James Clark, Scientific Editor, looks back on 2001

2001 has been another eventful and largely positive year for *Green Chemistry*. The journal has gone from strength to strength with a growing number of high-quality articles and an increasing number of subscribers. Of particular note was the recent announcement of the journals first official impact factor which at 2.11 ranks it alongside many well established and highly regarded chemistry and engineering journals—thanks to all who have made this possible. We continue to be very ambitious in our plans for the journal which we intend to remain *the* journal for innovative research in green chemical technology and for publicising relevant educational and industrial developments.

The year saw major conferences and events on green chemistry and related topics in India, Italy, England, Wales, Scotland, Ireland, USA, Japan, Korea, China and Spain. Highlights included the official opening of the new Australian Centre for Green Chemistry (*Green Chemistry*, 2001, G66), the IUPAC/OECD Green Chemistry education workshop, the start of a European ‘COST’ programme in Green Chemistry *(Green Chemistry*, 2001, G72) and the launch of the UK Faraday Partnership on Green Chemical Technology (*Green Chemistry*, 2001, G38). It is interesting to note that the year started and finished with significant events in India. January saw the first IUPAC international Symposium on Green Chemistry in Delhi reflecting the recognition of the importance of the movement in the developing countries (*Green Chemistry*, 2001, G18). At the end of December the National Renewable Energy Convention was held in Warangal. Renewable energy is a subject of widespread interest and has been a theme of several front section articles in *Green Chemistry* in 2001. A recent survey in the UK showed that almost everyone interviewed was aware of climate change and 74% said they were concerned about its effects. Almost three-quarters of the public associate the use of fossil fuel with an increased risk of climate change and there was high approval for renewable energy sources (http://www.rspb.org.uk/caffairs/default.asp). There has been some significant progress in the use of renewable fuels for transportation (*Green Chemistry*, 2001, G56 and G61) including the use of rapeseed oil for running some passenger and goods trains in Germany (http://www.prignitzer-eisenbahn.de/index.html). While these are exciting developments they also represent another illustration of where better assessment of their true environmental impacts and benefits are required—life cycle assessment and other metrics for new potentially greener processes and products will become increasingly important as green chemistry matures.

2001 also saw significant progress with green chemistry education. Here the IUPAC/OECD Green Chemistry Workshop held in Venice this year was especially significant (see http://helios.unive.it/inca/iupac workshop/). Some 30 resources ranging from books to web-based materials and from laboratory classes to theoretical workshops were identified at the meeting. Meanwhile in Japan the Green and Sustainable Chemistry network (GSCN) is now active in enlightening students, schoolchildren, teachers and academics on green and sustainable chemistry and the GSCN education group is preparing an introductory textbook for college students ‘Chemistry and Environment: and Introduction to Green Chemistry’. Developments in the UK include a new graduate course and new undergraduate courses start this year. While these educational developments for schools and Universities are commendable it is also important that we recognise the need for continuing education and awareness courses for those already practising the subject in teaching and in industry. It should also be recognised that a great deal of international co-ordination and co-operation is required if we are to achieve the rapid progress required at all educational levels.

For 2002 a number of major events are already planned including the next Gordon Research conference on Green Chemistry in Oxford, UK (see http://www.grc.uri.edu/grc_home.htm) and the 6th annual Green Chemistry and Engineering Conference in Washington, USA (http://www.epa.gov/opptintr/greenchemistry/ calendar.htm). We can also look forward to the first round of green chemistry awards from the GSCN in Japan and new network-type activities in Asia and in Europe.

We seek to publish a range of research and general interest articles in *Green Chemistry* that properly reflect the state-of-the-art in the rapidly developing world of green chemistry and technology—chemistry and engineering research and application, education, and including related topics such as energy issues and life cycle assessment. The journal has come a long way in its short lifetime. We need your help and support to maintain its pre-eminent position so as to help make the world a greener place. I wish you all a happy and sustainable 2002.

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Colin Raston, the new Chair of the Editorial Board, looks forward to 2002

It is an honour to start 2002 as Chair of the Editorial Board for *Green Chemistry*. My realisation of the importance of green chemistry evolved during a term as President of the Royal Australian Chemical Institute, and this led to involvement in debate and leadership in the field, as well as developing research initiatives. Green chemistry is the way ahead in developing more benign technologies, and ultimately sustainability for the benefit of future generations. The tragic events of 11 September 2001 have given way to optimism, and chemists can contribute to this through various avenues, in particular by looking to a brighter future by getting involved in green chemistry. *Green Chemistry* can play a pivotal role in facilitating this, providing the leading forum for reporting primary research in the field as well as news and views on green chemistry in the wider context.

Green Chemistry is now in its fourth year and has already stamped its success as a journal in the chemical sciences with an inaugural impact factor of 2.11. This is an amazing achievement and its success rests on the importance of the field and the determination of the Editorial team, the Board and International Advisory Board, those who have contributed research papers, Guest Editorials, news and views and more. In looking ahead much is being done to further enhance the journal. The signs are there, a high impact and a steady increase in quality and number of papers submitted. Interest in the field is rapidly increasing in the academic, government and industrial sectors, as well as in the public sector. The general enthusiasm for green chemistry in academia is particularly encouraging, both in research and undergraduate teaching programs. In this context the journal is interested in receiving manuscripts dealing with teaching initiates including new experiments for undergraduate laboratories. At the postgraduate level, research programs are flourishing, workshops are now commonplace, and there is an increasing number of conferences dedicated solely to green chemistry.

Chemistry departments may find that mounting lecture courses, and indeed degree programs in green chemistry, may be a way of stemming the tide of fewer students entering degree programs in chemicals sciences, as well as identifying green chemistry as a great career choice. The teaching of green chemistry has important implications in down stream research into sustainablity, as well as enhancing community perceptions about chemistry, and more.

The Editorial Board and the International Advisory Board are responsible for increasing the standing of *Green Chemistry*, for it to best serve the readers, those engaged in research through to teaching, industrial issues, debate, *etc*. We are looking for flexibility. The journal is a forum for providing primary research on green chemistry, as well as a forum for news and views, bringing together research highlights from other journals, conferences, industry, and government. All these are important in raising the awareness of green chemistry and are important for such a rapidly emerging discipline. If you feel you can make a contribution to the journal in any of these categories, we would like to hear from you.

Green chemistry covers a wide spectrum of chemistry linking into the biological sciences, for example in bio-catalysis associated with generating commodity chemicals from bio-mass, through to engineering, analytical methodology, mineral processing, and nano-technology. Research linking into the *12 Principles of Green Chemistry*, should be considered for publication in the journal. The more common areas of synthetic protocol and alternative reaction media do not cover the full spectrum of green chemistry, and may distort the perceptions as to what the important issues are. In addition to the *12 Principles of Green Chemistry*, originally mapped out by Anastas and Warener, there are now 12 more principles for consideration, reported in the last issue of the journal (Winterton, G73–74).

My vision for the journal is one of taking the issues of green chemistry to the fore. Green chemistry is the link to sustainability, and researchers in the field are the caretakers for the future. I welcome all new members to the Board and the International Advisory Board and I look forword to the challenges ahead.

Board members 2002

The following are the members of the Editorial and International Advisory Boards of *Green Chemistry* for 2002

CHAIR

Colin Raston completed a Ph.D. under the guidance of Professor Allan White, and after postdoctoral studies with Professor Michael Lappert at the University of Sussex, he was appointed Lecturer at the University of Western Australia (1981), then to Chairs of Chemistry at Griffith University (1988), and Monash University (1995), before his move early in 2001 to the University of Leeds where he holds the Chair of Inorganic Chemistry. His research interests cover aspects of main group, supramolecular and green chemistry, having helped to establish the Centre for Green Chemistry at Monash University.

SCIENTIFIC EDITOR

James Clark is a graduate of Kings College, London. Following postdoctoral research in Canada and in the UK he joined the academic staff at the University of York in 1979. He now holds the Chair of Industrial and Applied Chemistry at York where he heads the Clean Technology Centre including a large research group working on various aspects of green chemistry including clean synthesis, the replacement of hazardous substances including conventional acids and bases, and renewable feedstocks. He is also the founding director of the Green Chemistry Network which has over 500 members worldwide.

ASSOCIATE EDITOR, THE AMERICAS

James K. Bashkin was born in Iowa City in 1958, but spent most of his early years in Tucson, AZ. After attending the University of Arizona for a year, he transferred to the University of California at Irvine. After graduating in 1977, he went to Oxford to do his graduate work with Malcolm L. H. Green. He obtained a D.Phil. in organometallic chemistry in 1982, and then moved to R. H. Holm's group at Harvard, where he was an NIH postdoctoral fellow in bio-inorganic chemistry. He then took a position at Monsanto Corporate Research. During this time (1985–1991), he co-invented a solid-state reference electrode, a new green chemistry version of nucleophilic aromatic substitution, and catalytic drug candidates based on functional mimics of ribozymes. Through the efforts of many co-workers, the green chemistry was commercialized in Europe by Flexsys, a joint venture between Solutia and Akzo Nobel. He and co-inventor M. K. Stern shared Monsanto's Thomas and Hochwalt prize for this chemistry, and the team shared the Presidential Green Chemistry Challenge Award in 1998. From 1991–99 he was a member of the chemistry faculty at Washington University in St. Louis. In 1999, he returned to Monsanto (now Pharmacia Corporation), and also became Research Associate Professor at the University of Missouri, St. Louis.

ASSOCIATE EDITOR, THE AMERICAS

Terry Collins is the Thomas Lord Professor of Chemistry at Carnegie Mellon University and an Honorary Professor at the University of Auckland, New Zealand. He earned his B.Sc. (1974), M.Sc. (1975) and Ph.D. (1978) degrees from the University of Auckland in New Zealand where he worked with Warren R. Roper. After postdoctoral work at Stanford University with Jim Collman, he joined the faculty of Caltech in 1980 and the faculty of Carnegie Mellon University in 1987. Professor Collins' research awards include the 1998 Presidential Green Chemistry Challenge Award, the 1997 Award of the Society of Pure and Applied Coordination Chemistry of Japan, a Camille and Henry Dreyfus Teacher-Scholarship, an Alfred P. Sloan Foundation Fellowship, and the Lionel H. Briggs Memorial Prize of the University of Auckland. He has been a visiting professor at the University of Auckland and Osaka City University. He has written and lectured widely on the possibilities before chemists to develop vibrant new economies to promote sustainability. His research program is aimed at greening oxidation technologies and is currently focused primarily on the design of nontoxic catalysts for activating natural oxidants, especially hydrogen peroxide, for sustainable oxidations. His catalyst design work has overlapped with the design of molecular magnetic compounds.

Tracy Williamson received her B.A. in chemistry in 1985 from Hamilton College and her Ph.D. in physical organic chemistry in 1992 from the University of Delaware. Tracy currently is acting Chief of the Industrial Chemistry Branch in the Office of Pollution Prevention and Toxics at the U.S. Environmental Protection Agency. Responsibilities at EPA have included providing technical support to EPA's New and Existing Chemicals. She has also worked extensively on several green chemistry initiatives including grants programs aimed at providing support for basic research in the area of green chemistry and educational projects aimed at incorporating green chemistry concepts and examples into classical

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chemistry curricula, textbooks, and laboratory courses. Tracy is currently the Director of EPA's Green Chemistry Program. She is also very active in the American Chemical Society as a professional member and serves on the Board of the ACS Committee on Environmental Improvement.

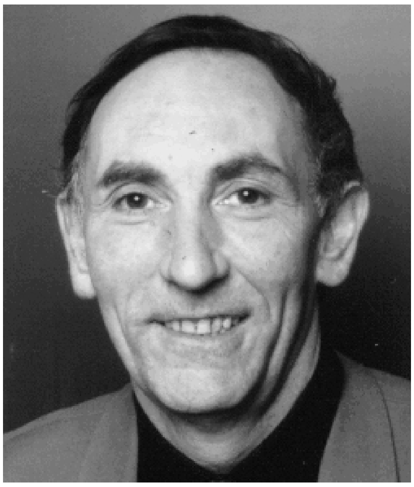
Pietro Tundo graduated at University of Bologna (1969), and following appointments at the Universities of Torino and Messina, he was appointed Full Professor of Organic Chemistry at Ca' Foscari University of Venice in 1989. He was the founder of the Interuniversity Consortium 'Chemistry for the Environment' (INCA: 1993) of which he is Director. He is chairman of the Working Party on 'Synthetic Pathways and Processes in Green Chemistry', under IUPAC Commission III/2, a member of the editorial committee of *Reactive & Functional Polymers*, *La Chimica e l'Industria* and of *Clean Products and Processes* and a member of the OECD Issue Team for the Sustainable Chemistry Program.

Makoto Misono received his Bachelor, Master, and Doctor's degree in engineering from the Unversity of Tokyo and started his academic career in 1966 at the University of Tokyo, where he became a full professor in 1983. Since he retired in 1999 with the Emeritus professorship, he has been a professor at Kogakuin University, a private technical university located in the center of Tokyo. He has studied heterogeneous catalysis for 40 years and is now more involved in various activities related to the environment and chemistry. He received awards from the Catalysis Society (1991), Petroleum Institute (1996), and Chemical Society of Japan (1987 and 2002) and also was a Ipatieff lecturer (1996/7) at Northwestern University, USA. Finally, he is Member, Science Council of Japan; Chairman, Steering Committee of Green Sustainable Chemistry Network, Japan; Chairman, Committee for Environment and Safety; and Representative, Forum for Green Chemistry, The Chemical Society of Japan.

Tony Barrett was educated at Imperial College in London (B.Sc. 1973, Ph.D. 1975) where he worked with Professor Sir Derek H. R. Barton, Nobel Laureate. He was appointed as Lecturer immediately following his Ph.D. studies and he continued research in South Kensington until 1983. In that year he was appointed a full professor of Chemistry at Northwestern University in Evanston, Illinois, USA. In 1990 he moved further west in the United States to become a full professor of Chemistry at Colorado State University. After nearly ten years research in the USA, he returned to Imperial College as Head of Organic Chemistry and subsequently Synthetic Chemistry, where he holds the position of *Glaxo Professor of Organic Chemistry* and *Director of the Wolfson Centre for Organic Chemistry in Medical Science*. Recently he was appointed *Sir Derek Barton Professor of Synthesis*.

Avelino Corma Canos was born in Moncófar, Spain, in 1951. He studied Chemistry at the Universidad de Valencia (1967–1973), and received his Ph.D. at the Universidad Complutense de Madrid in 1976. He is director of the Instituto de Tecnología Química (UPV-CSIC) at the Universidad Politécnica de Valencia since 1990. His current research field is zeolites as catalysts, covering aspects of synthesis, characterization and reactivity in acid-base and redox catalysis. Avelino Corma has written about 400 articles on these subjects in international journals, three books, and a number of reviews and book chapters. He has been a member of the Editorial Boards of *Microporous and Mesoporous Materials, Catalysis Review Science and Engineering*, *Catalysis Letters, Journal of Molecular Catalysis*, *Catalysis Technologies*, *Chemical Communications*, *Japanese Catalysis Surveys*, *Physical Chemistry Chemical Physics*, *Journal of Catalysis* and *Dalton Transactions*. He is co-author more than 45 patents, six of them being commercialised. He has been awarded with the DuPont Award on new materials (1995), the Spanish National Award 'Leonardo Torres Quevedo' on Technology Research (1995), Burdiñola (1997), Premio Iberdrola de Química, (1998) and F. Ciapetta award of the North American Catalyst Society (1998), Ipatieff Lecturer at Northwestern University 2000/01, 'Rey Jaime I' Award on New Technologies (2000), and the François Gault Lectureship (EFCATS) (2001).

Roger A. Sheldon has more than 20 years industrial experience with Shell (1969–1980) and DSM (1980-1990). In 1991 he was appointed Professor of Organic Chemistry & Catalysis at the Delft University of Technology in the Netherlands. His primary research interests are in the application of catalytic methods—homogeneous, heterogeneous and enzymatic—in organic synthesis. He is the author of three books on catalysis, one (with Jay Kochi) on catalytic oxidation, one on syngas chemistry and, more recently, one on chirotechnology. He is the recipient of the 1997 Paul Rylander Award of the Organic Reactions



and Catalysis Society. He developed the concepts of E factors and atom utilization for assessing the environmental impact of chemical processes. Recent achievements include the application of water soluble palladium complexes in the biphasic carbonylation of alcohols, hydrocarboxylation of olefins and CO/olefin copolymerizations. The application of biphasic catalysis, with water soluble complexes to other conversions, *e.g.* the catalytic oxidation of alcohols and olefins, is currently under investigation.

Robin D. Rogers was born in Ft. Lauderdale, FL in 1957 and moved to Alabama in 1960. He obtained both his B.S. in Chemistry (1978) and his Ph.D. in Chemistry (1982) at The University of Alabama and is currently a Professor of Chemistry and Director of the Center for Green Manufacturing at UA. He became a full Professor at Northern Illinois University in 1994, and in 1996, he returned to a full professorship at his alma mater. In 1998, he became the Director for The University of Alabama's Center for Green Manufacturing. Rogers holds three patents and has published over 480 papers on a diverse array of topics including structural chemistry, green separation science and technology, room temperature ionic liquids, aqueous biphasic separations, dissolved metal ion separations, environmental applications, pollution prevention, pollution remediation, design and synthesis of porous solids, radiochemistry, and environmental inorganic chemistry. Rogers has had an influential role in the expansion of interest and research in ionic liquid systems, his initial paper on ionic liquid/aqueous partitioning (*Chem. Commun.*, 1998, 1765) effectively kick-started interest in applying ionic liquids to clean separations. He has co-organized NATO ARW, and ACS symposia on Industrial Applications of Ionic Liquids. Rogers was the Editor of *Journal of Chemical Crystallography*, one of the Founding Editors of *Crystal Engineering*, and an Associate Editor for *Separation Science and Technology*. Recently Rogers was named Editor-in-Chief of the new ACS journal *Crystal Growth & Design* and serves on the Editorial Board of the ACS journal *Industrial and Engineering Chemistry Research*.

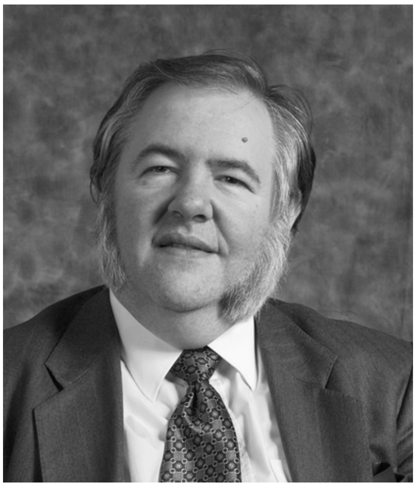
Adisa Azapagic is a Reader in Environmental Systems Engineering in the Department of Chemical and Process Engineering at the University of Surrey. She holds Dipl.-Ing. and MSc degrees in Environmental Chemical Engineering and a PhD in Environmental Technology. Dr Azapagic is also Programme Director for Engineering for the Environment. Her current research interests include System Modelling and Optimisation**,** Clean Technology**,** Pollution Prevention and Control, Life Cycle Assessment, Environmental Decision-making and Sustainable Development. She is a co-investigator on a number of research projects and has over 100 journal and conference publications and chapters in books.

Dennis L. Hjeresen received his M.S. in Neuroscience in 1982, and his Ph.D. in Neuroscience (minor in Ecology) in 1984 from the University of Washington in Seattle. His research career focused on biological effects of environmental pollutants and includes an extensive list of peer-reviewed publications and a history of professional service.

Dr. Hjeresen is currently Director of the Green Chemistry Institute based in Washington, D.C. He has a long history of creating pollution prevention programs and catalyzing partnerships. Dr. Hjeresen established Los Alamos as lead DOE laboratory for EPA Green Chemistry Programs. He has lectured and given presentations in this area all over the world and established significant international interest in green chemistry. He also serves as a member of the editorial board for the *Journal of Clean Products and Processes* and the advisory board of *the Journal of Environmental Science and Technology*. Dr. Hjeresen serves as secretary and chair of the organizing Committee of CHEMRAWN XIV World Congress on Green Chemistry. Dr. Hjeresen serves as a United States Delegation Member—Organization for Economic Cooperation and Development (OECD) Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology: Working Group on Research and Development in the Context of Sustainable Chemistry.

Dr. Hjeresen also serves as director of the US/China Water Resources Management Program for the White House and coordinates the activities of 11 USG agencies, the private sector and NGO's as they relate to water in China. This is a treaty level activity under the US/China Joint Commission Meeting on Science and Technology. Dr. Hjeresen has featured green chemistry as a key method for avoiding water pollution. He has worked in China with universities, industry and government to establish a national program and to promote US private sector opportunity. Dr. Hjeresen has worked to establish an international program for the Green Chemistry Institute and established international chapters in 13 countries.

Dr. Hjeresen was a key author of the Industrial Waste Reduction Program and the Environmental Management Science Program for DOE and has developed industrial and government partnerships in a number of areas. Dr. Hjeresen is currently serving as the Chair of the DOE Environmental Management Science Program Technical Program Committee. Dr. Hjeresen also serves on the DOE Strategic Laboratory Council, an advisory body to Senior DOE Management.



Kenneth R. Seddon started his academic career at Liverpool University where he graduated with his PhD in 1973. After Research Fellowships at Liverpool University and Oxford, he joined the University of Sussex as a Lecturer in Experimental Chemistry in 1982. In 1993, he was appointed to the Chair of Inorganic Chemistry at Queen’s University Belfast and is now also Director of the Queen’s University Ionic Liquids Laboratories (QUILL) Centre. It was in Oxford that his interest in his three main research areas (ionic liquids for green industrial applications, crystal engineering, and archaeological chemistry) had their roots. The principal aim of his work is to explore, develop and understand the role of ionic liquids as media for synthetic organic chemistry, such that current processes may be replaced by clean ones using ionic liquids.

Professor Seddon is currently European Editor of the ACS journal *Crystal Growth and Design*, an active editorial board member of *Green Chemistry*, and a member of the Research Committee of the newly formed Crystal Faraday Partnership for Green Chemistry.

Janet Scott was born in Durban, South Africa in 1964 and completed a B.Sc. degree at the University of Natal (Durban) in 1985. After a period as a Research Assistant at the Medical Research Council she obtained her B.Sc.(Hons) degree and Ph.D. at the University of Cape Town under the direction of Profs. Mino R. Caira and Luigi R. Nassimbeni.

From 1992 to 1995 she held the position of lecturer jointly in the Department of Chemistry and the Academic Development Programme at the University of Cape Town and in 1996 moved to Fine Chemicals Corporation (South Africa) as Research and Development Manager before relocating to Australia and Monash University (Melbourne) during 1999 where she currently holds the position of Deputy Director in the Centre for Green Chemistry.

Martyn Poliakoff began his academic career as an undergraduate at King’s College, Cambridge, obtaining his B.A. in 1969 and Ph.D. in 1973 under the supervision of J. J. Turner on the *Matrix Isolation of Large Molecules*. In 1972, he was appointed as a 1972-79 Research Officer in the Department of Inorganic Chemistry of the University of Newcastle upon Tyne. Promotion to Senior Research Officer followed in 1973 and then to a tenured position in 1975. In 1979, he was appointed to a Lectureship in the Department of Chemistry at the University of Nottingham. Promotion to Reader in Inorganic Chemistry and then to Professor of Chemistry followed in 1985 and 1991 respectively. In addition to his chair in Nottingham, Professor Poliakoff is an Honorary Professor of Chemistry at Moscow State University. From 1994–99, he held an EPSRC/Royal Academy of Engineering Clean Technology Fellowship at Nottingham.

Professor Poliakoff is a member of the Clean Technology Group in the School of Chemistry at Nottingham. His research interests involve chemical applications of supercritical fluids, with particular emphasis on green chemistry.

Joan F. Brennecke is Professor of Chemical Engineering at the University of Notre Dame, Indiana. Her research interests are in the areas of supercritical fluid technology and thermodynamics. Of particular interest is the use of supercritical carbon dioxide and supercritical water as environmentally benign solvents for extractions, separations and reactions. Current research projects investigate the solvent effect on reactions in supercritical fluids, use of spectroscopy and integral equation theory to determine the local environment around dissolved solutes, and measurement and modeling of high pressure phase behavior. Her group is also interested in experimental and theoretical studies of preferential solvation in liquid mixtures.

Michael Warhurst has worked for Friends of the Earth as a Safer Chemicals Campaigner since 1997, and his work focuses on chemicals policy in the EU and UK, and on the science of the health and environmental effects of chemicals. Dr Warhurst has a Degree in Biochemistry from the University of York, a PhD in the breakdown of chemicals by bacteria from the University of Glasgow and an MSc in Environmental Chemistry from the University of Edinburgh. From April 2002 Dr Warhurst will be working in

Brussels for WWF as Senior EU Toxics Policy Officer, continuing his involvement in EU chemicals policy.

Walter Leitner has since 1998 been supervisor of the central high pressure and large scale synthesis facilities of the Max-Planck-Institut für Kohlenforschung. Since April 2000 acting director of the Lehrstuhl for Chemie and Petrochemie at the RWTH, Aachen. His interests are: mechanisms and models in homogenous catalysis; oganometallic compounds as selective reagents and catalysts; CO_2-activation; and catalysis in supercritical CO_2.

Paul Anastas serves in the National Security and International Activities Division in the White House Office of Science and Technology Policy. His responsibilities include furthering the science and technology relationship between the U.S. and China. In addition to bilateral international activities, Dr. Anastas is responsible for furthering international public-private cooperation in areas of science for sustainability such as green chemistry. In the area of international water science and technology, Dr. Anastas coordinates the inter-agency working group to identify areas of cross-agency collaboration.

Prior to coming to OSTP in October of 1999, Dr. Anastas served as the Chief of the Industrial Chemistry Branch of the U.S. Environmental Protection Agency since 1989. During that period he was responsible for regulatory review of industrial chemicals under the Toxic Substances Control Act and the development of rules, policy and guidance. In 1991, he established the industry-government-university partnership Green Chemistry Program which was expanded to include basic research and the Presidential Green Chemistry Challenge Awards. Prior to joining the U.S. EPA, he worked as an industrial consultant to the chemical industry in the development of analytical and synthetic chemical methodologies.

Dr. Anastas is the author/editor of nine scientific and technical books including *Green Chemistry: Theory and Practice* which has been translated into five languages. He currently is a visiting Professor in the Chemistry Department at the University of Nottingham, U.K. and serves on the editorial board of the journal Environmental Science and Technology. Dr. Anastas received his M.A. and Ph.D. in Organic Chemistry from Brandeis University and his B.S. in Chemistry from the University of Massachusetts at Boston.

Mark Harmer works at DuPont Central Research & Development, at Wilmington, DE, USA. His interests include fluoropolymer nanocomposites and related materials.

Coming next issue

The next issue of *Green Chemistry* will be a Special Guest Editor issue on **IONIC LIQUIDS** – compiled by Professor Ken Seddon, Director of the Queen's University Ionic Liquid Laboratories (QUILL), based in

The following is a selection of the papers to be included:

Biocatalysis in ionic liquids
Professor Sheldon and colleagues in Delft, The Netherlands

Hydrogen sulfate- and tetrakis(hydrogensulfato)borate ionic liquids
Peter Wasserscheid and colleagues in Aachen, Germany

Epoxidation of electrophilic alkenes in ionic liquids
Valeria Conte and colleagues at Ferrara, Foffia and Pisa, Italy

Immobilization of ionic liquids on solid supports
Wolfgang Hölderich and colleagues in Aachen, Germany

The oxidation of alcohols in substituted imidazolium ionic liquids using ruthenoum catalysts
Tom Welton and Victoria Farmer from Imperial College, London

Solvation of small molecules in imidazolium ionic liquids: a simulation study
Ruth Lynden-Bell and colleagues at Queen's University, Belfast

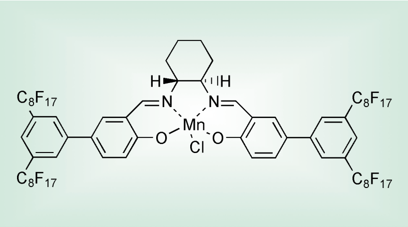
Study of the ligand and base effects on the enantioselective alkylation catalyzed by Pd(0)-phosphine complexes in [bmim][PF_6] ionic liquid
Stefan Toma and colleagues at Comenius University, Bratislava, Slovakia

On the solubilization of water with ethanol in hydrophobic hexafluorophosphate ionic liquids
Robin Rogers and colleagues at the University of Alabama, USA

Highlights

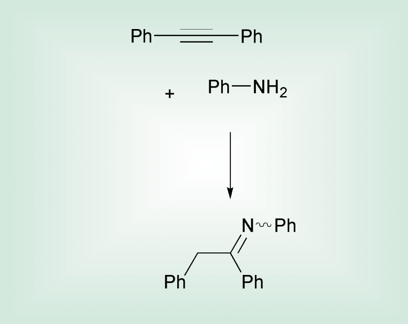
Fluorous phase-soluble catalysts

The development of fluorous phase-soluble catalysts is vital if the potential of fluorous biphasic solvent systems is to be realised. Reports of novel Mn–salen catalysts with fluorous phase solubility and excellent activity/selectivity have been reported by the group led by Gianluca Pozzi at the CNR centre in Milan, Italy, and the University of Milan (*Eur. J. Org. Chem.*, 2001, 4639). They have attached various *p*-aryl groups containing fluorous ponytails to "classical" Mn–salen complexes in order to design active and selective catalysts for epoxidation reactions. Activity was good, and selectivity was, in the best cases, equivalent to conventional systems. Reuse was also relatively good, and better than resin-bound Mn–salen systems.



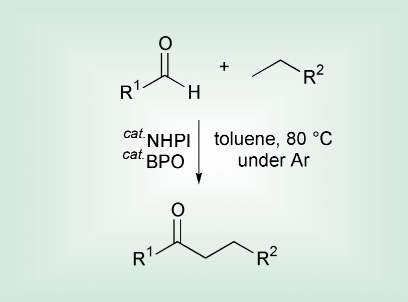
Addition of amines to alkynes

The addition of amines to alkynes represents a 100% atom efficient reaction. This can be achieved by Cp_2TiMe_2 catalysts, but only after prolonged reaction times, often requiring a few days. Igor Bytschkov and Sven Doye of the University of Hannover, Germany, have now shown that microwave heating can dramatically reduce the time required, and give excellent yields of addition product (*Eur. J. Org. Chem.*, 2001, 4411). They have found that using microwaves, that the reaction time could be reduced to 3 hours. A wide range of substrates can be efficiently converted in this manner.



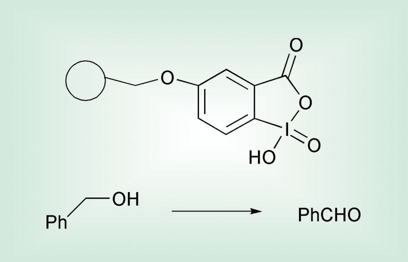
Addition of acyl radicals to alkenes

N-hydroxyphthalimide (NHPI) has been reported as a metal-free oxidation promoter, capable of promoting aerobic oxidation of hydrocarbons. Now Yasutaka Ishii and co-workers from Kansai University in Osaka, Japan, have shown that it can also function as a polarity reversal catalyst in the addition of acyl radicals to alkenes (*Chem. Commun.*, 2001, 2352). Their system effects the addition of aldehydes to alkenes by hydrogen abstraction, radical addition and then return of the hydrogen from the reduced NHPI. Dibenzoyl peroxide was used as initiator to oxidise the NHPI, and kick off the chain reaction. Good yields were obtained for a variety of additions.

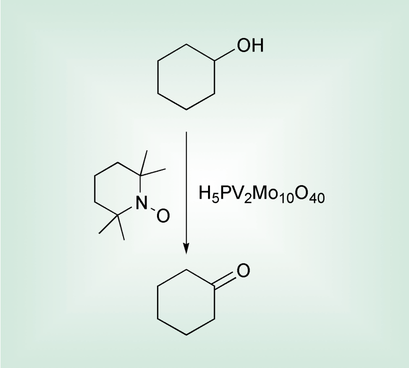


Oxidations

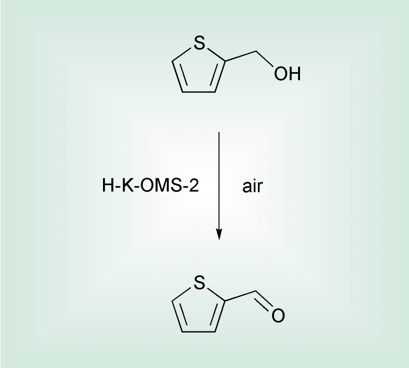
A metal-free oxidation system based on polymer-supported high-valent iodine complexes has been reported by Joerg Rademann and colleagues from the University of Tuebingen, Germany, and Schering in Berlin (*Angew. Chem., Int. Ed.*, 2001, **40,** 4395). Crosslinked polystyrene, functionalised with chloromethyl groups was functionalised with an iodine(V) reagent, which was then used to oxidise a range of alcohols to aldehydes in excellent yields. An unsaturated carbamate was cyclised. The supported reagent could be recycled readily using tetrabutylammonium oxone.



A second method for the oxidation of alcohols has been reported by Ronny Neumann and co-workers at the Weizmann Institute of Science in Israel in collaboration with DSM Research in the Netherlands (*J. Org. Chem.*, 2001, **66**, 8650). Their system involves the combination of TEMPO and a polyoxometallate as a catalytic system for the aerobic oxidation of primary and secondary alcohols. Excellent yields and selectivities are obtained for a range of primary and secondary alcohols, without overoxidation to acid. Water is the only by-product.



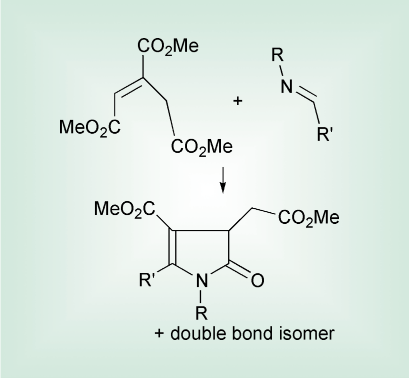
An alternative approach to alcohol oxidation has been reported by Steven Suib and colleagues at the University of Connecticut, USA (*Angew. Chem., Int. Ed.*, 2001, **40**, 4280). They have shown that octahedral molecular sieves can be produced in a simple reaction between potassium permanganate and manganese sulfate. These materials, when the potassium ions are partly replaced by protons, can catalyse the oxidation of



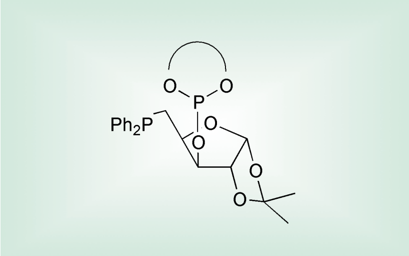
alcohols using air as oxidant. Yields for a range of alcohols were excellent, with even sensitive alcohols being efficiently converted.

Renewable resources

The group led by Hans Schaefer at the University of Muenster, Germany, has now described novel domino reactions of trimethyl aconitate, a renewable resource from sugar molasses or citric acid (*Angew. Chem, Int. Ed.*, 2001, **40**, 4212). They have shown that the reaction of trimethyl aconitate with imines proceeds *via* a sequence of reactions to give dihydropyrrolones, structures common in natural products. Yields are reasonable and reaction conditions are mild, allowing the construction of an important class of compounds in one step, with the generation of minimal quantities of waste.

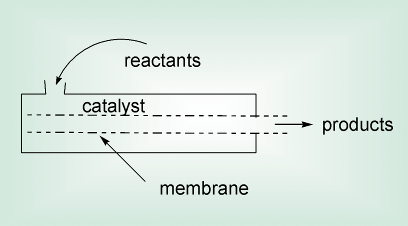


Aurora Ruiz and colleagues from the Universitat Rovili I Virgili in Tarragona, Spain, have developed chiral ligands based on D-xylose, which are excellent for hydrogenation reactions (*J. Org. Chem.*, 2001, **66**, 8364). The ligands are available *via* a two-step reaction, and are mixed phosphine–phosphite systems. These are used to coordinate Rh and the resultant complex gives very good enantioselectivities in the hydrogenation of methyl acetamidoacrylate and similar substrates.



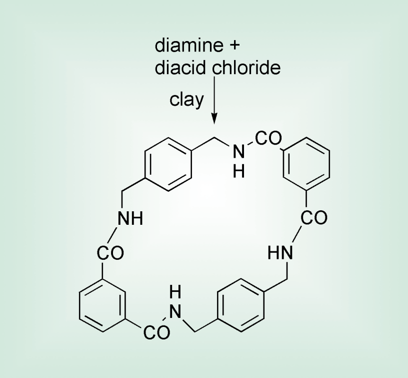
Membrane reactors

The use of membrane reactors allows various possibilities for continuous reactions with inherent separation of catalysts. Leo van den Broeke and his group at the Technical University of Eindhoven, The Netherlands, have developed a silica membrane reactor for continuous reactions in supercritical carbon dioxide (*Angew. Chem., Int. Ed.*, 2001, **40**, 4473). They used a microporous membrane to allow hydrogenation of butene with hydrogen to occur, with the reaction products (butane) being able to pass through the membrane, while the bulkier (homogeneous) catalyst was held up in the reactor.



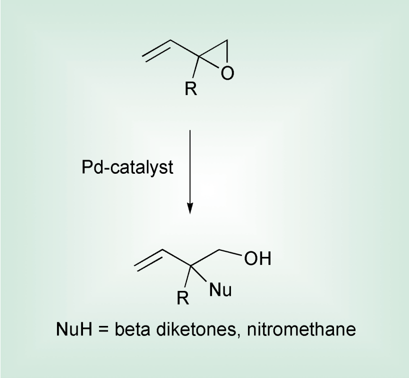
Macrocycle synthesis

Macrocycle synthesis is often plagued by low yields, and often requires inconvenient reaction protocols to achieve reasonable selectivity. Dimitrios Petridis and colleagues from the Institute of Materials Science in Athens, Greece, have published details of a simple solution to this problem for one class of compounds (*Angew. Chem., Int. Ed.*, 2001, **40**, 4286). They used the self-assembly of diamines inside a clay to set up a system whereby adjacent diamines could be acylated at both ends to give a macrocyclic tetraamide. The yields obtained were 60%, with homogeneous conditions giving different products.



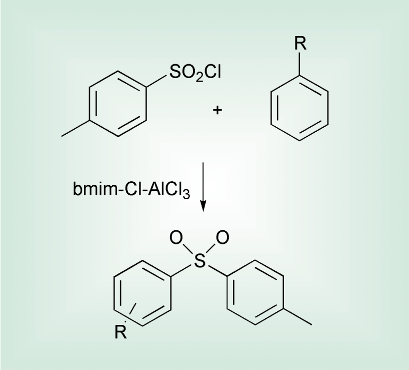
Nucleophilic addition

Addition reactions lie at the heart of clean synthetic methodology. Barry Trost and Chunhoi Jiang at Stanford University, USA, have now applied such a reaction type to the formation of quaternary centres (*J. Amer. Chem. Soc.*, 2001, **123**, 12907). Pushing the addition of nucleophiles to vinyl epoxides away from the generally favoured 1,4-addition towards a 1,2-addition will achieve this goal. While this can be done with H-bonding nucleophiles such as alcohols and amines, this paper is the first example of the use of a C-centred nucleophile in this reaction. Both beta-ketoesters and nitromethane were found to react efficiently in this way under Pd catalysis.

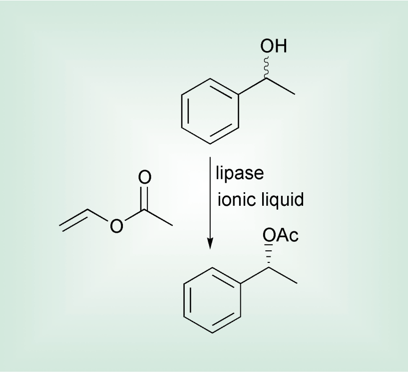


Ionic liquids

Ionic liquids continue to attract attention as solvents for Friedel–Crafts reactions. Manikrao Salunkhe and co-workers at the Institute of Science in Mumbai, India, have shown that sulfonylations can be readily achieved under very mild conditions (*J. Org. Chem.*, 2001, **66**, 8616). They have found that the reaction proceeds very readily in chloroaluminate ionic liquids, giving very good yields in short reaction times. They have also provided some interesting insights into the chemistry occurring under reaction conditions using *in-situ* ^{27}Al NMR techniques. It is nor clear whether the ionic liquid was recycled.

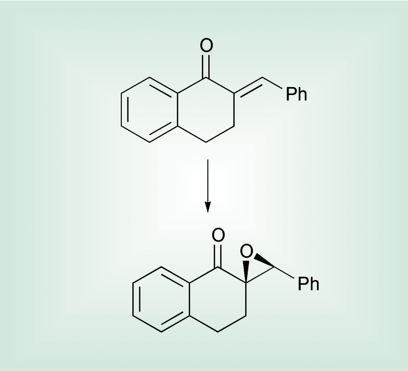


A second paper describes improvements to ionic liquid preparation which enhances their ability to promote lipase-catalysed reactions to occur. Seongsoon Park and Romas Kaslauskas of McGill University in Montreal, Canada, have shown that washing ionic liquids with sodium carbonate significantly enhances the activity of lipases in ionic liquids (*J. Org. Chem.*, 2001, **66**, 8395). They attribute this enhancement to the removal of acidic impurities or to the removal of traces of silver anion, left over from metathesis reactions. With these improvements they have shown that lipases will catalyse reactions very efficiently, allowing these reaction to occur in much more polar media than before.



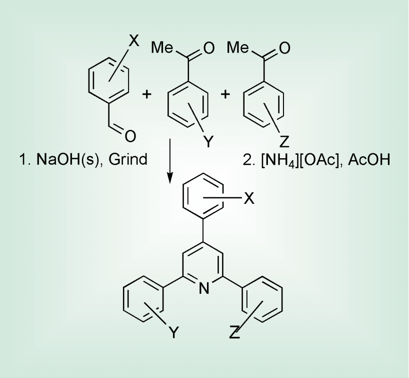
Polyamino acid catalysts

Polyamino acids are promising catalysts for various reaction types. In particular, the use of polyleucines has been shown to be effective catalysts for the enantioselective epoxidation of enones. Stan Roberts and colleagues at the University of Liverpool, UK, have now shown that poly(β-leucine) is an efficient catalyst for the epoxidation of chalcone under heterogeneous conditions (*Chem. Commun.,* 2001, 2330). While the new catalysts are no better than the best of the existing polyleucine catalysts, the structure activity relationships described may prove beneficial to developing newer better systems.



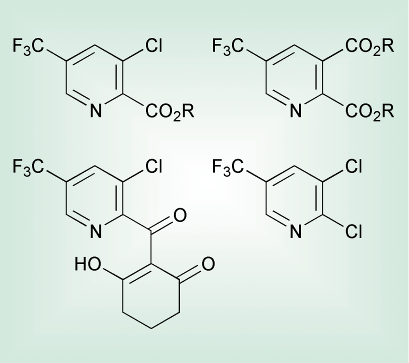
Solvent-free reactions

Colin Raston (University of Leeds, UK) and Gareth Cave (Monash University, Australia) describe a solventless route to pyridines (*J. Chem. Soc., Perkin 1*, 2001, 3258). This route revolves around the efficient tandem aldol reaction between a benzaldehyde and a ketone, followed by a subsequent Michael reaction with a second ketone in solvent-free conditions. The resultant diketone can then be condensed with ammonium acetate in acetic acid to give a range of pyridines.



Carbonylations

Palladium catalysed carbonylations are useful routes to a range of aromatic esters and acids. Yves Bessard and co-workers at the Department of Process Research at Lonza in Visp, Switzerland, have published their results on a process for the alkoxycarbonylation of chloropyridines (*Org. Proc. R+D*, 2001, **5**, 572). They give details of their work aimed at developing such reactions for the preparation of intermediates for agrochemicals. They show that such reactions can be used successfully, and give details of reactions carried out at > 100-g scale.



Permanganate green?

Potassium permanganate is not often thought of as green. However, an article by Nirmal Singh and Donald Lee of the Carus Chemical Company, USA, and the University of Regina, Canada, claims just that (*Org. Proc. R+D*, 2001, **5**, 599). They describe recent advances in the oxidation chemistry of potassium permanganate and, crucially, the development of a recycling method for the waste manganese dioxide, as well as a scheme for the return of the MnO_2, or on-site regeneration. This scheme is currently recycling several million pounds of waste MnO_2 annually.

Mini reviews

- H Groeger (*Chem, Eur J.,* 2001, **7** 5246) details advances in the development of utilisation of a series of chiral catalysts containing both Lewis basic sites and Lewis acidic sites for coordination / activation.

- Claudio Palomo *et al.* describe progress in the Aldol addition reaction, with significant focus of atom economy and environmental aspects (*Chem., Eur J.,* 2002, **8**, 36).

- Yolande de Miguel *et al.* describe recent developments in supported catalysts in synthetic organic *chemistry (J. Chem. Soc., Perkin Trans. 1*, 2001, 3085).

- Plato Magriotis discusses the first catalytic routes to beta lactams in a short review article in *Angew Chem., Int Ed.*, 2001, **40**, 4377.

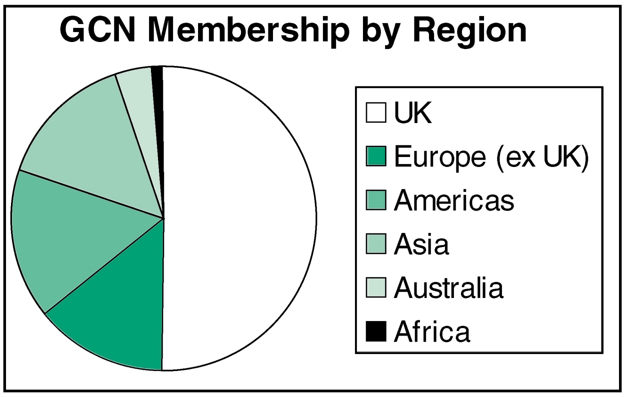
Green Chemistry Network 3 years old

Mike Lancaster, Director of the Green Chemistry Network, describes progress since the launch, especially the growth in international membership

GREEN CHEMISTRY NETWORK

The UK Green Chemistry Network (GCN), sponsored by the Royal Society of Chemistry reached its third birthday towards the end of 2001. The membership of the GCN has greatly expanded during this time, growing from a handful of UK-based academics, to over 500 members spread across the globe. It has been particularly encouraging to see the non-UK membership grow to the extent that 50% of (now over 500) members now reside outside the UK. This is a clear indication of the worldwide recognition of green chemistry and its importance to the chemical industry and beyond. The other interesting and welcome statistic regarding membership is the growth in members from industry. Although over the last three years some industrialists have needed to be convinced of the aims and motives behind the green chemistry movement, there is now wide acceptance. In the UK this is amply exemplified by industrial membership of the Government-funded CRYSTAL Faraday partnership for *A Greener Chemical Industry*. Whilst the number of individual company members and those associated through other network-type organisations exceeds academic institution members it is noteworthy that the main trade association, the Chemical Industries Association is heavily committed to the Partnership.

Last year saw the first residential course run by the GCN. The three-day intensive course on *Development of Sustainable Chemical Products & Processes* proved very popular with the pharmaceutical sector and highlighted the importance now placed on waste minimization at source by this sector. In general, the last two years has seen a very large growth in the number of courses available with a significant green chemistry or green technology element. Not least in this respect is the growing number of universities (in the UK and elsewhere) that now either have specific green chemistry modules or teach the principles as an underlying theme throughout the undergraduate course. As a consequence of this the availability of resource material is rapidly improving. A recent OECD / IUPAC workshop on *Green Chemistry Education*, held in Venice, set about trying to identify resource material currently available. Whilst not claiming to be comprehensive the working party had no difficulty in identifying several pages of material ranging from books and lecture courses on the web to tried and tested laboratory experiments. A full list of the resources identified can be found at http://helios.unive.it/inca/iupac.workshop/.



Whilst the GCN has a growing and dedicated membership from developing nations there is an urgent need for both educational resources and technology solutions to help ensure these countries avoid some of the past 'environmental' pitfalls experienced by the developing chemical industry in the west. One of the services the GCN offers to members is a helpdesk in which we help identify potential solutions to specific challenges or at least point people in the right direction. Overwhelmingly, requests to the help desk come from members in the developing nations. There is a real requirement and thirst for information on new technology, best practice and educational material. We do our bit to help, but there is a real need for an organised, concerted effort to make resource material and information on latest technology available. This is obviously a costly undertaking, particularly if translation of material is involved, but the urgent need to start was again recognised at the Venice conference.

For more information about the GCN and its activities see http://www.chemsoc.org/gcn

Perspective

Developing metal-mediated and catalyzed reactions in air and water

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Chao-Jun Li gives a personal perspective on research that won the 2001 Presidential Green Chemistry Challenge Award (academic category)

Introduction

The importance of carbanions in synthesis is exemplified by the Grignard and Wittig reactions. Although they are among the most versatile and useful reactions in organic chemistry, carbanion-based reactions are generally known to be very sensitive towards air and water. The required deviation from ambient conditions along with the commonly used methods for their generation leads to several fundamental drawbacks when the Principles of Green Chemistry[1] are applied (Fig. 1): (1) large volumes of anhydrous organic solvents are required which could potentially increase volatile organic emissions; (2) anhydrous conditions require excess drying agents which leads to unwanted waste; (3) anhydrous conditions also require the protection of functional groups such as hydroxy groups and carboxylic acids; (4) the requirement of inert gas atmosphere implies that the catalyst is prone to deactivation, which will increase the amount of heavy metal waste; (5) requirement of stoichiometric amounts of metals also leads to a large amount of metal waste; and (6) the general use of organic halides as the carbanion source will generate a stoichiometric amount of halide waste, as well as requiring multi-step synthesis of the halides.

Chao-Jun Li received a Ph.D at McGill University and did postdoctoral research at Stanford University. Since 1994, he has been at the Chemistry Department of Tulane University as an Assistant Professor, Associate Professor (1998), and Professor (2000–present). He received a National Science Foudnation's Early CAREER Award (1998), a Tulane's Eli Lilly Teaching Fellowship (1996), an Outstanding Young Scientist Award (Overseas) from the NFS of China (2000). He served as an International Co-coordinator for the Green Chemistry Workshop in China.

Project goal

To green carbanion-based reactions, with a focus on carbonyl additions (Barbier–Grignard type reactions), through stepwise elimination of all the auxiliary factors and evaluate their scope in synthesis (Fig. 1). The research was divided into two stages: (1) the factors below the scheme in Fig. 1 and (2) the factors above the scheme in Fig. 1.

Stage 1: Eliminating the requirements for inert atmosphere, anhydrous solvent and protection

Carbonyl allylation/allenylation/propargylation. Organometallic chemistry and transition-metal catalysis have traditionally been carried out in dry-boxes where the use of an inert gas atmosphere and the exclusion of moisture have been essential. However, Nature′s use of metals catalytically under ambient conditions of air and water have played key roles in various enzymatic reactions including biocatalysis, biodegradation, photosynthesis, nitrogen fixation, digestion, as well as in the

Green Context

It is unthinkable that Grignard and similar reactions could proceed in water. Decades of 'common knowledge' has made this idea ridiculous, meaning that synthetic chemists prepare anhydrous solvents regularly, generating large quantities of waste in the process, every time they attempt one of these reactions. This article challenges this accepted wisdom, and shows that it is indeed possible to carry out many of these reactions in water itself, leading to significant advances in the environmental performance of these reaction types. ***DJM***

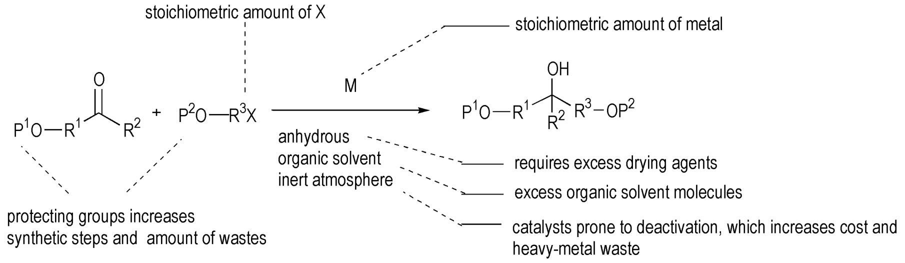
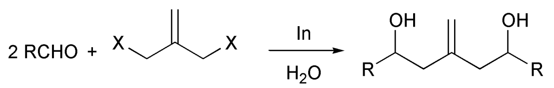


Fig. 1 Stepwise greening of Grignard-type reactions

evolution of bioorganisms. Since Wolinsky *et al.*[2] made an observation in 1977 that the allylation reaction of carbonyl compounds with allyl bromide mediated by zinc could be carried out in 95% ethanol and *tert*-butyl alcohol, metal-mediated Barbier–Grignard type carbonyl additions in aqueous media have received increased interest. Extensive research has been carried out by many groups on the allylation of carbonyl compounds in water,[3] in which one of the characteristics of these reactions is that they can also be carried out in air. Based upon my earlier work with T. H. Chan in the development of indium mediated allylation in water, my research group has recently developed various new synthetic methodologies.[4] They include generation of a trimethylenemethane dianion equivalent by a metal-mediated bisalkylation process [eqn. (1)],[5] alkylation of 1,3-dicarbonyl type compounds [eqn. (2)]),[6] a [3 + 2] cyclo-addition reaction to generate five-membered carbocycles [eqn. (3)],[7] a two-atom[8] as well as a one-atom[9] carbocycle-enlargement [eqn. (4)], a *gem*-allyl dianion equivalent [eqn. (5)],[10] and a synthesis of β-hydroxy esters [eqn. (6)][11] which were all developed in air and water. A mechanistic investigation of these reactions was also carried out[12] along with their application in the synthesis of three types of natural products: polyhydroxylated natural products [eqn. (7)],[13] medium-sized ring natural products,[14] and macrocyclic compounds.[15]



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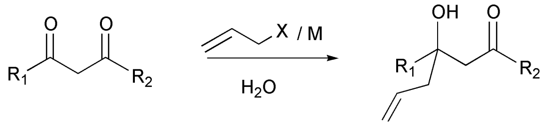

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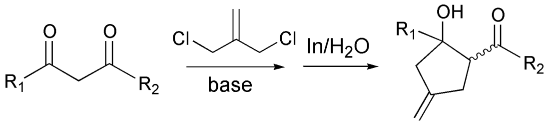

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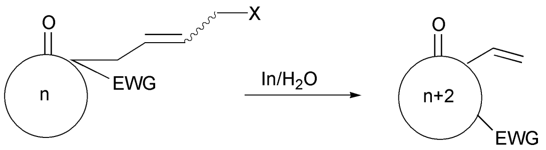

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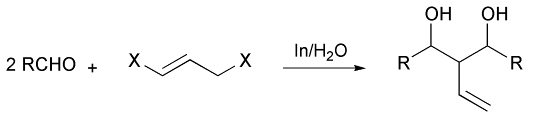

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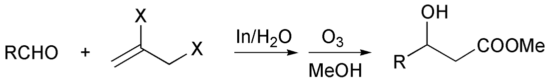

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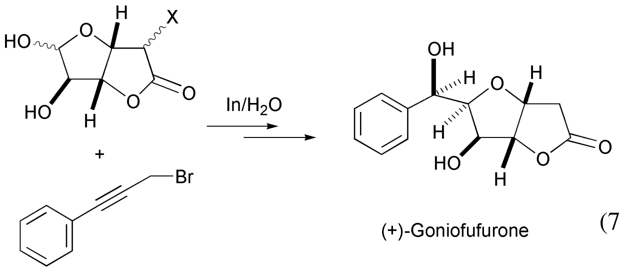
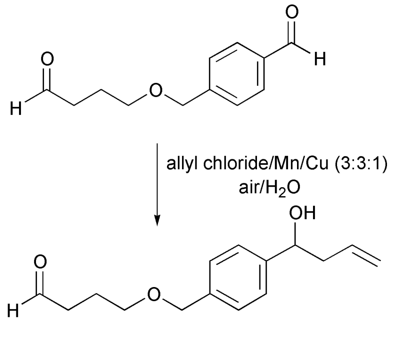


(+)-Goniofufurone (7)

Catalytic reactions in air/water. Early successes in developing aqueous Barbier–Grignard type reactions have been mostly limited to the use of organic halides involving an activated C–X bond (mainly allyl halides). An effort was thus made to extend the scope of the reactions by using transition metals to activate non-activated C–X bonds in air and water. Although a number of transition-metal catalyzed reactions are successful in aqueous media,[16] these catalyses are known to be very sensitive to air. Noting that the widely used Mn–Cu batteries operate in air and water, the combination of these two metals was examined for catalyzed C–C reactions in water. It was found that the combination of manganese and a catalytic amount of copper was a highly *regioselective* mediator for the allylation of aryl aldehydes in air and water [eqn. (8)].[17] An exclusive selectivity was also observed when both aliphatic and aromatic aldehyde functionalities were present in the same molecule. The reaction however is still limited to an allylation reaction. Additionally, in the presence of acetic acid or ammonium chloride, manganese and magnesium were found to effect pinacol-coupling reactions in water[18] and also proceeded selectively with aryl aldehydes.



(only allylation product)

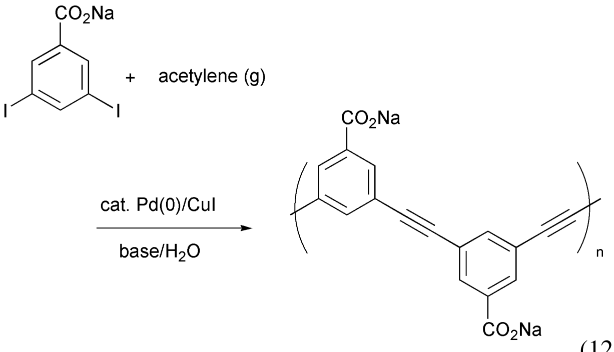
(8)

The use of a palladium catalyst was due to an effort in effecting coupling between carbonyls and organic halides involving a sp²-C–halogen bond in air and water. Palladium catalysts are known to be particularly effective in activating such bonds, which is the basis of many important synthetic reactions.[19] When iodobenzene was reacted with benzaldehyde and zinc together with a palladium catalyst in air and water, the desired carbonyl addition product was not generated, and instead a Ullmann-type phenyl–phenyl coupling product was obtained [eqn. (9)].[20] The palladium catalyst was also effective for Stille coupling, Sonigashira coupling and Suzuki coupling in air and water, although with lower conversions. The study also led to the development of a simple synthesis of unsymmetrical biaryls through palladium-catalyzed coupling of arylsilanes with aryl halides in air and water [eqn. (10)]. [21] On a different front, we have also developed a highly efficient aryl halide–acetylene gas coupling reaction catalyzed by palladium in water [eqn. (11)],[22] which has been used for the synthesis of various poly(arene ethylene) materials [eqn. (12)].[23]

$$\mathrm{ArI} \xrightarrow[\text{Zn/air/water}]{\text{cat. Pd/C}} \text{Ar-Ar} \qquad (9)$$

$$\mathrm{ArI} + \mathrm{Ar'Si(R)_nX_m} \xrightarrow[\text{air/water}]{\text{cat. Pd/C}} \text{Ar-Ar'} \qquad (10)$$

$$\mathrm{ArX} \;+\; \text{acetylene (g)} \xrightarrow[\text{base/H}_2\text{O}]{\text{cat. Pd(0)/CuI}} \mathrm{Ar{-}{\equiv}{-}Ar} \qquad (11)$$

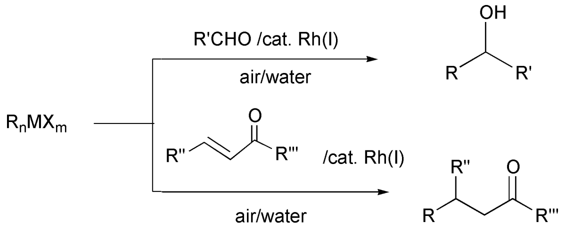


(12)

reversible hydrogel

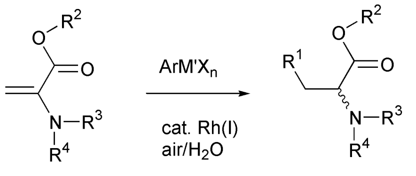
Although the use of palladium catalysts provided us with a way of activating organic halides involving a sp^2-C–halogen bond in air and water, further reaction of the transient organopalladium intermediate with aldehydes was not successful. Thus the remaining obstacle was the addition of the sp^2-C–M organometallic intermediate on to carbonyl groups. In order to choose a suitable organometallic reagent, the general requirement for the success of the desired reactions was that this reagent be stable in air and water. A variety of aryl and vinyl derivatives of metals including B, In, Si, Sn, Ge, Pb, As, Sb, and Bi, were tested.

A screening of various transition-metal catalysts available in our laboratory was carried out, $Rh_2(COD)_2Cl_2$ and $Rh(COD)_2BF_4$ [and to a lesser extent, $Ni(acac)_2$] were found to provide the desired aldehyde addition and conjugated addition products smoothly in air and water [eqn. (13)]. Except for organoarsenic and organoantimony reagents, aryl or vinyl derivatives of all the other metals (and metalloids) examined were able to generate the desired carbonyl addition and conjugated addition products with varied efficiencies. Among them, aryl and vinyl tin,[24] silicon,[25] boron,[26] lead,[27] and bismuth[28] derivatives were found to be the most effective. The corresponding indium and germanium reagents provided only low yields of the products. The conjugated additions were found to be highly selective—when either a mono- or di-substituted alkene was involved, the reaction proceeded rapidly whereas essentially no reaction was observed with tri-substituted derivatives. This led to a new synthesis of amino acids [eqn. (14)].[29] The success of both the carbonyl addition and the conjugated addition was found to be highly dependent upon both the metal and the substituents on the metal.[30]



R_nMX_m R= aryl or vinyl
M= B, In, Si, Sn, Ge, Pb, Bi
X= alkyl, aryl, halogen, hydroxyl, and alkoxyl

(13)



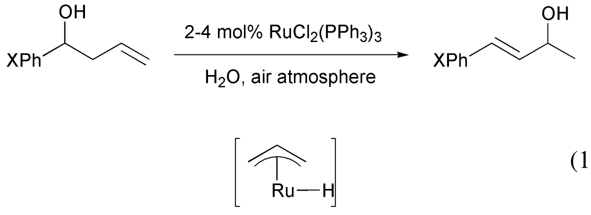
(14)

Stage 2: Eliminating the requirements of stoichiometric metals and organic halides

Reactions through electrochemistry. Although the above successes have overcome the major concerns related to carbanion reactions, the use of stoichiometric amounts of metal has the disadvantage of leading to a significant amount of metal waste. One way to overcome this is through the use of electricity as the electron source to regenerate the metal mediator so that only a catalytic amount of metal need be used. There has been extensive literature on the reductive generation of metals *via* electrochemistry[31] and various aqueous methodologies have provided the theoretical foundation for performing the desired electrochemistry-based reactions. However, the drawbacks to this method are the requirement to synthesize the organic halide and the generation of stoichiometric halide waste.

Reactions through C–H activation in air and water. The ultimate goal of our research is to eliminate all the concerns outlined in Fig. 1 (and carbanion-based reactions) and to obtain a theoretical 100% atom-efficiency.[32] To do this, we decided to develop related reactions through C–H activation[33] in air and water. The study of the stoichiometric reactions already provided us with the foundation for this ultimate endeavor.

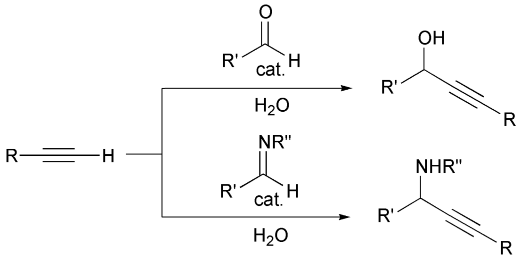
The first investigation was on the activation of sp^3 allylic C–H bonds by using ruthenium catalysts in air and water. Through the catalysis of $RuCl_2(PPh_3)_3$, allylic C–H bonds can be activated, and the functional groups of homoallyl alcohols are repositioned to give allyl alcohols [eqn. (15)].[34] Under the same reaction conditions, the functional groups of allyl alcohols also underwent allylic rearrangements. With a water-soluble ruthenium catalyst, a living catalytic system is possible in which the catalyst can be (in principle) recycled many times.[35] It still remains to be seen whether the organoruthenium intermediate resulting from the allylic C–H activation can be captured by carbonyls to form C–C bonds in air and water.



(15)

proposed intermediate

The second investigation is on the activation of sp C–H bonds in air and water. Our studies show an effective addition reaction of acetylenes to aldehydes in air and water *via* C–H activation [eqn. (16)],[36] and the reaction has been extended to other electrophiles. Also, significant progress has been made in the activation of sp^2 C–H bonds for related reactions in air and water.[37]



(16)

Conclusion and outlook

We have shown that it is possible to eliminate all the auxiliary factors in the classical carbanion-based reactions in a stepwise manner and to transform them into more atom-economical reactions. As Anastas and Warner pointed out that green chemistry is a journey rather than a conclusion,[1] the long-term objective of this endeavor is ultimately to develop C–H activation based C–C bond formations in air and water by using water-soluble catalysts.

In addition to the usual advantage of water being not flammable, explosive or toxic, water-soluble substrates can be used directly avoiding protection/deprotection of functional groups, thus saving many synthetic steps. In large industrial processes, isolation of the organic products can be performed by simple phase-separation (as shown by other aqueous catalysis).[38] The open-air feature offers convenience in the operations of chemical synthesis and catalyst recycling.

Acknowledgement

I wish to thank all the colleagues who have contributed to the field of Organic Reactions in Water. Particular acknowledgements are given to coworkers in my group whose names appear in the references. I am especially grateful to the support provided over many years by the National Science Foundation (Early CAREER Award), the NSF-EPA Joint Program for a Sustainable Environment, the Petroleum Research Fund administered by the American Chemical Society, the Louisiana Board of Regents, and Tulane University.

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Application of olefin metathesis in oleochemistry: an example of green chemistry

Review

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The metathesis of natural oils and fats and their derivatives is a clean catalytic reaction that can be considered as an example of green chemistry. Using this reaction, oleochemical feedstocks can be converted into valuable chemical products, directly or in only a few reaction steps. With the development of catalysts that are active and highly selective under mild reaction conditions, there are favourable perspectives for the application of the metathesis reaction in the oleochemical industry.

1. Introduction

In the twenty-first century, the availability of fossil organic feedstocks—both as energy sources and for the production of organic chemical raw materials—will gradually decrease. At the same time, the world population will grow, with an increasing demand for a higher average standard of living. Hence it is important to look for alternative feedstocks. These can be found in renewable natural resources, both for energy purposes as well as for raw materials for the chemical industry. In the latter case, much attention has already been given to making products from natural oils and fats in the oleochemical industry. Unlike petrochemicals, oleochemicals are derived from renewable resources, have good biodegradability and no net CO_2 production. Therefore, the use of renewable resources is an important component of green chemistry.

Natural fats and oils (composed predominantly of glyceryl esters of fatty acids) are important sources both for nutrition and as raw materials in the oleochemical industry. About 14% of the world production of fats and oils (annual production 103 million tonnes) is used in the oleochemical industry as starting material for a wide range of chemical products.[1] The most important are the long-chain vegetable oils, such as soybean oil, the new high-oleic-acid varieties of sunflower seed oil and rapeseed oil (all containing mainly unsaturated C_{18} fatty acids), and palm oil (containing both C_{16} and unsaturated C_{18} chains). Short- and medium-chain vegetable oils, such as coconut and palm kernel oil, consist mainly of lauric (C_{12}) and myristic (C_{14}) acid chains and are important sources for the production of cosmetics, detergents, soaps, emulsifiers, *etc*. Some other vegetable oils are the source of oleochemicals on a smaller scale. An example is castor oil (consisting of 85–95% ricinoleic acid, *i.e.*, 12-hydroxyoctadecenoic acid) that has a wide range of industrial uses. Animal fats (making up 19% of total commodity oils and fats[1]), such as tallow (a by-product of the meatpacking industry, containing 40% oleic acid) and lard, are also in demand as raw material, mainly because of their low price.

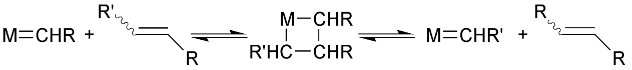
Fatty acid monoesters are usually obtained from the transesterification of natural oils and fats with a lower alcohol, *e.g.*, methanol, along with glycerol. More than 90% of all oleochemical reactions (conversion into fatty alcohols and fatty amines) of fatty acid esters is carried out at the carboxy function.[2] However, transformations by reactions of the carbon–carbon double bond, such as hydrogenation, epoxidation, ozonolysis and dimerization, are becoming increasingly important industrially. Here we will discuss another reaction of the carbon–carbon double bond, the olefin metathesis reaction.

Olefin metathesis is an important catalytic reaction in organic synthesis, in which olefins are converted into new products *via* the rupture and reformation of carbon–carbon double bonds;[3] eqn. (1).

$$2\ \mathrm{RCH{=}CHR'} \rightleftharpoons \mathrm{RCH{=}CHR} + \mathrm{R'CH{=}CHR'} \quad (\mathrm{R\ and\ R'} = \text{alkyl or H})$$

(1)

The key step in this process is the reaction between an olefin and a transition metal alkylidene (carbene) complex in a 2 + 2 fashion to generate an unstable metallacyclobutane intermediate. This intermediate can either revert to the starting material or open productively to afford a new metal carbene and produce a new olefin; eqn. (2). If this process is repeated often enough, eventually an equilibrium mixture of olefins will be obtained.



(2)

At the moment there are several applications of olefin metathesis in the petrochemical industry, such as the Phillips triolefin process, which produces polymerization-grade propene by cross-metathesis of ethene and 2-butene, and a process for the production of neohexene, an intermediate in the synthesis of musk perfume. A large-scale industrial process incorporating olefin metathesis is the Shell Higher Olefins Process (SHOP) for converting ethene to detergent-range alkenes. Moreover, several interesting polymeric materials are

Green Context

This century will see an increasing use of renewable natural resources both in the energy and chemical industries. New and improved chemistry will often be required to transform natural raw materials into useful products. Natural oils are an important source of raw materials for the oleochemicals industry and so far 14% of the world production of fats and oils are used for this purpose. In this paper olefin metathesis reactions are used to transform fats and oils *via* a clean catalytic route. ***JHC***

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commercially produced *via* the so-called ring-opening metathesis polymerization of different types of unsaturated cyclic monomers, including cyclooctene, norbornene and dicyclopentadiene.[3]

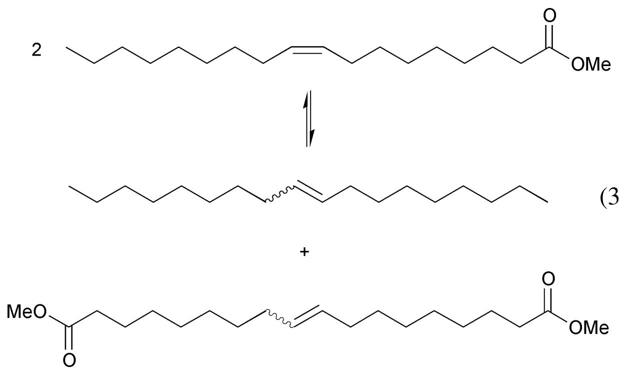
Unsaturated fatty acid esters and oils are very promising renewable and cheap feedstocks for metathesis, which makes the metathesis reaction of interest to the chemical industry by offering novel routes to new and existing products.

2. Metathesis of unsaturated fatty acid esters

Metathesis reactions of unsaturated fatty acid esters provide a convenient, environmentally benign and highly selective route to various chemical products, directly or in only a few reaction steps. Two main types of metathesis reactions are plausible: self-metathesis (between two identical olefin molecules) and cross-metathesis (between two different olefin molecules).

2.1. Self-metathesis

The first successful metathesis conversion in this area was the selective transformation by Boelhouwer and co-workers[4] of methyl oleate (methyl *cis*-9-octadecenoate), a readily accessible unsaturated ester of oleic acid, into equimolar amounts of 9-octadecene and dimethyl 9-octadecene-1,18-dioate; eqn. (3).

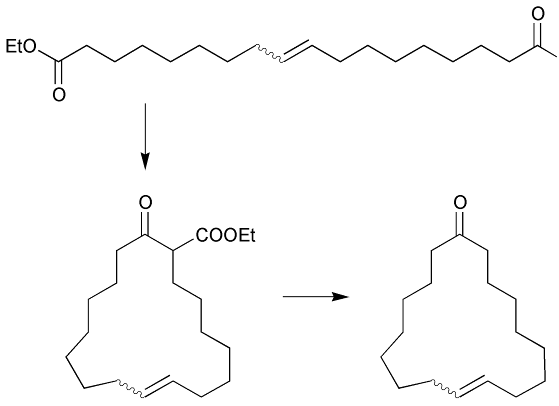


(3)

Using 1–2 mol% of a WCl_6/Me_4Sn catalyst system, equilibrium conversion was reached within 4 h at 70 °C. Because the free energy change in this type of reaction is virtually zero, the result at equilibrium is a random distribution of the alkylidene groups. Thus, starting with methyl oleate, the equilibrium mixture consists of 50 mol% of the starting material and 25 mol% of each of the two reaction products. As metathesis also brings about *cis–trans* isomerization (‘non-productive’ metathesis), the products as well as the starting material end up in their thermodynamic *trans*/*cis* equilibrium ratio, in which *trans* is favoured.

The above reaction demonstrates that, in the presence of a suitable catalyst, the metathesis of unsaturated fatty acid esters provides a convenient and selective route to unsaturated diesters and internal alkenes, both of which are useful intermediates in product synthesis. In other words, the metathesis of methyl oleate is characterized by a quantitative catalytic reaction with no by-products; *i.e.*, it is a 100% atom-efficient process.

Unsaturated diesters can be used for the production of useful chemical products such as macrocyclic compounds. For instance, the diester obtained by metathesis of ethyl oleate has been subjected to a Dieckmann condensation, followed by hydrolysis and decarboxylation, to give a *cis–trans* mixture of the unsaturated macrocyclic ketone 9-cycloheptadecen-1-one (**1**), whose *cis* form, *civetone*, is an attractive ingredient in musk perfumes, which otherwise can only be synthesized involving many steps giving poor yields;[5,6] eqn. (4).



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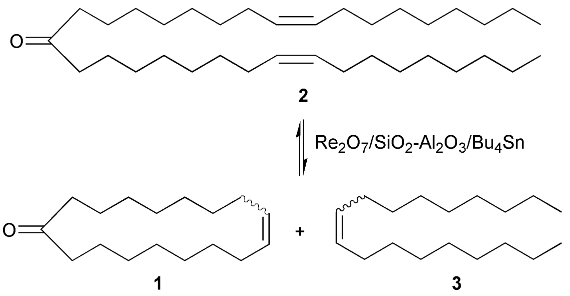
(4)

Moreover, unsaturated dicarboxylic esters and acids are interesting starting materials for the manufacture of unsaturated (vulcanizable) polyesters and polyamides.[7] On the other hand, the co-product 9-octadecene can, for example, be dimerized and hydrogenated to give 10,11-dioctyleicosane, a lube-oil-range hydrocarbon intermediate.[8]

Several catalyst systems, homogeneous as well as heterogeneous, have been developed since this first example for the metathesis of unsaturated fatty acid esters and related compounds; see Section 4.

For the metathesis of methyl oleate, a very pure substrate is required. We have demonstrated a convenient new synthetic route to civetone. In this route, methyl oleate is first converted *via* a Claisen condensation to the doubly unsaturated ketone oleon (9,26-pentatriacontadien-18-one) (**2**), which can be separated in pure form from the reaction mixture. Oleon is then converted into 9-octadecene (**3**) and a *cis–trans* mixture of 9-cycloheptadecen-1-one (**1**) *via* a ring-closing metathesis reaction; eqn. (5).

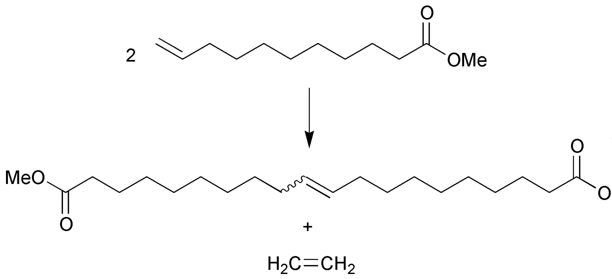


(5)

This reaction could be carried out at room temperature in the presence of a heterogeneous Re_2O_7-based catalyst.[9] Although the initial results gave a low overall yield, the development of new ruthenium metathesis catalysts (see Section 4) makes the ring-closing metathesis route to macrocyclic musks very promising, despite the fact that high dilution conditions are required to reduce the possibility of intermolecular metathesis reactions between oleon molecules.

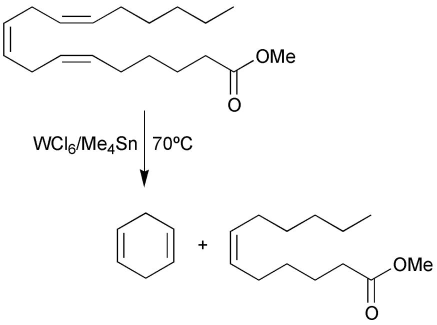
Many other unsaturated fatty acid methyl esters of the general formula $Me(CH_2)_nCH{=}CH(CH_2)_mCOOMe$ have been shown to undergo metathesis with high selectivity, such as methyl palmitoleate (methyl *cis*-9-hexadecenoate, $n = 5$, $m = 7$), methyl erucate (methyl *cis*-13-docosenoate, $n = 7$, $m = 11$), methyl petroselenate (methyl *cis*-6-octadecenoate, $n = 10$, $m = 4$) and methyl elaidate (the *trans* isomer of methyl oleate).[10]

Another example is the metathesis of ω-unsaturated fatty acid esters leading to an internally unsaturated long-chain dicarboxylic acid ester, *e.g.*, the metathesis of methyl 10-undecenoate, which can be obtained by pyrolysis of methyl ricinoleate (source *e.g.*, castor oil). The metathesis of methyl 10-undecenoate proceeds to completion when the volatile co-product ethene is removed during the reaction; eqn. (6).



(6)

Metathesis of esters of polyunsaturated fatty acids, such as methyl linoleate (methyl *cis,cis*-9,12-octadecadienoate) and methyl linolenate (methyl *cis,cis,cis*-9,12,15-octadecatrienoate) leads to a variety of reaction products. Three main sets of linear products are formed: polyenes, monocarboxylic esters and dicarboxylic esters. The product distribution at equilibrium corresponds to a random scrambling of alkylidene and carboxyalkylidene moieties leading to a 1 : 2 : 1 molar ratio of the three main types of reaction products. Moreover, 1,4-cyclohexadiene and cyclopolyenes are also formed, as a result of secondary intramolecular metathesis reactions,[11] as illustrated for methyl linolenate in eqn. (7).



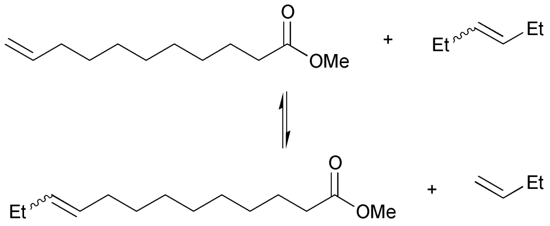
(7)

2.2. Cross-metathesis

Cross-metathesis of unsaturated fatty acid esters with a normal alkene is an elegant way of synthesizing more desirable homologues of these esters, and greatly extends the versatility of the metathesis reaction in the field of oleochemistry. From most industrial vegetable oil crops, predominantly fatty esters are obtained with chain lengths of 16–22 carbon atoms. These long-chain fatty acid esters can be shortened *via* cross-metathesis with a lower olefin to form less abundant medium-chain fatty acid esters, such as the highly-demanded detergent-range C_{12}–C_{14} acid esters. An example is the cross-metathesis of methyl oleate with 3-hexene, giving 3-dodecene and methyl 9-dodecenoate; eqn. (8) .[12–14] A large excess of 3-hexene can force the reaction to the product side and suppress self-metathesis of the ester.

With regard to their chain length, these middle-chain esters are quite similar to those derived from palm kernel and coconut oils. In addition, the C_{11}–C_{13} alkene co-products, with the double bond near the end of the chain, can be transformed into useful linear C_{12}–C_{14} alcohols by hydroformylation, or transformed into linear alkylbenzene sulfonates.

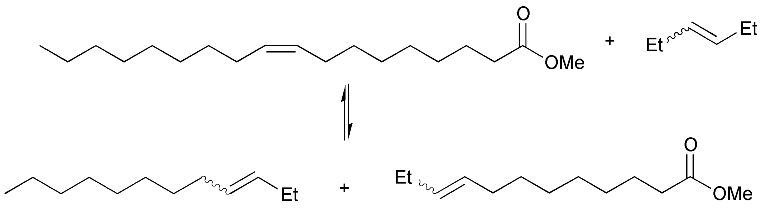
Instead of shortening the carbon chain of unsaturated esters, it is also possible to lengthen it, as illustrated for the cross-metathesis between methyl 10-undecenoate and 3-hexene in eqn. (9).



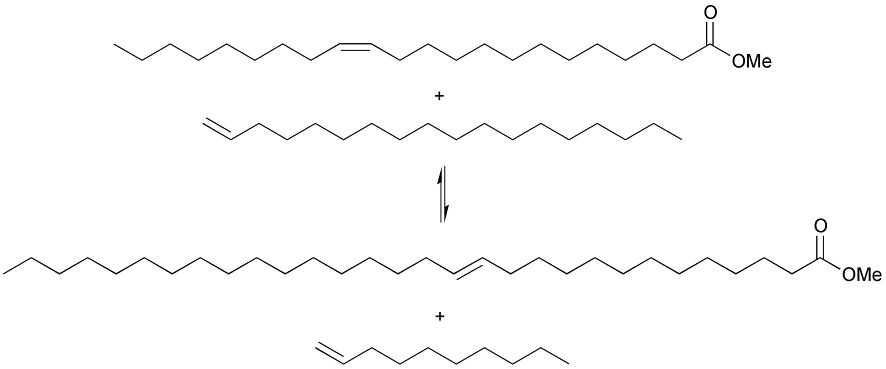
(9)

From a synthetic point of view, cross-metathesis reactions are very useful for the production of fine chemicals, which often are difficult to obtain by other means, or only after many reaction steps. An example is the synthesis of 1-triacontanol, $CH_3(CH_2)_{28}CH_2OH$, a plant growth stimulant. This synthesis was performed in a relatively simple two-step process by cross-metathesis of methyl erucate with 1-octadecene in the presence of a WCl_6/Me_4Sn catalyst, eqn. (10), followed by hydrogenation of the methyl 13-triacontenoate over a Cu/Zn catalyst at 280 °C and 250 bar.[15] However, in addition to the desired metathesis products of eqn. (10), the self-metathesis products of the starting materials as well as the two 'reverse' cross-metathesis products were also formed.

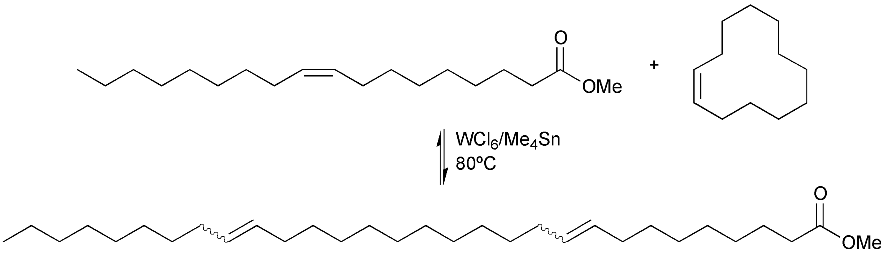
The synthesis of biologically active compounds such as insect pheromones is another example of organic synthesis *via* cross-metathesis. The use of such pheromones offers an effective, environmentally benign and selective pest control method. Thus, cross-metathesis of ethyl oleate with 5-decene



(8)



(10)



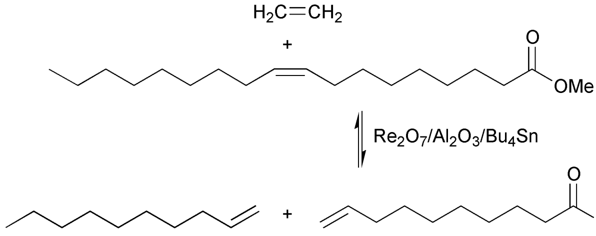
(11)

gives a *cis–trans* mixture of ethyl 9-tetradecenoate, an insect pheromone precursor.[16] Cross-metathesis of methyl *cis*-5-eicosenoate (obtained from meadowfoam oil) with excess 5-decene gave methyl *trans*-5-decenoate, which was transformed into an 83 : 17 mixture of *trans*-5-decenyl acetate and *trans*-5-decenol, the sex pheromone of the peach twig borer moth, a major pest in stone fruit orchards. The mixture was active in disrupting the mating cycle of the insects.[17] Other examples of organic synthesis *via* cross-metathesis are summarized elsewhere.[10,18,19]

Cross-metathesis of an unsaturated ester with a cyclic olefin leads to long-chain linear di-unsaturated esters. Thus, 1-triacontanol was also obtained by cross-metathesis between methyl oleate and cyclododecene, eqn. (11), followed by hydrogenation of the unsaturated ester product.[20]

2.3. Ethenolysis

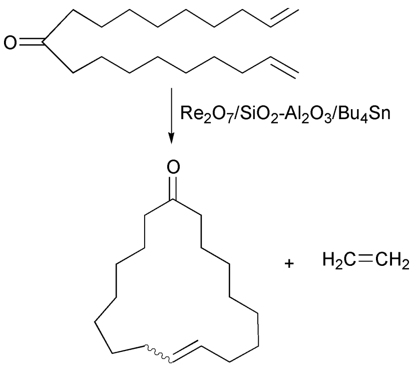
Cross-metathesis of an olefinic compound with ethene is denoted *ethenolysis*. Ethenolysis of unsaturated fatty acid esters allows the synthesis of shorter-chain ω-unsaturated esters, which have a wide range of applications. Excess ethene can easily be applied (*e.g.*, by using elevated ethene pressures) to suppress self-metathesis of the ester and to force the conversion to completion. Ethenolysis of methyl oleate produces methyl 9-decenoate and 1-decene;[21,22] eqn. (12).



(12)

Methyl 9-decenoate is the key intermediate in the synthesis of many chemical products. After hydrolysis and hydrogenation, it yields decanoic acid or decanol, substances used in the synthesis of lubricants and plasticizers. It can also be used to produce fragrances (*e.g.*, 9-decen-1-ol), pheromones (*e.g.*, 9-oxo-*trans*-2-decenoic acid, a honeybee pheromone, the queen substance), prostaglandins (*e.g.*, 9-oxodecanoic acid, a prostaglandin intermediate) *etc.*, which are easily isolated in pure form.[18,19] Methyl 9-decenoate is also the hypothetical source of many polymers and copolymers and can, for example, be converted into 10-aminodecanoic acid and then used for the production of nylon-10. Unsaturated polyesters were recently synthesized starting from some ω-unsaturated fatty acid esters that were obtained via ethenolysis of natural internally-unsaturated fatty acid methyl esters.[23]

Dimerization of methyl 9-decenoate to give 1,18-nonadecadien-10-one, followed by ring-closing metathesis under liberation of ethene, is another interesting route to give the macrocyclic musk civetone;[9] eqn. (13). With a rhenium-based catalyst, however, a low yield of 9-cycloheptadecen-1-one (*trans*/*cis* ratio 1 : 1) was obtained.



(13)

The same principle was recently applied using a ruthenium catalyst for the metathesis step. Dimerization of methyl 9-decenoate *via* a Ti-Claisen condensation, followed by ring-closing metathesis, gave a 17-membered ß-ketoester, which, after hydrolysis and decarboxylation, gave 9-cycloheptadecen-1-one. The overall isolated yield was 74% with the product having a *trans*/*cis* ratio of 3 : 1.[24] Unfortunately, in this type of synthesis there is little selectivity with respect to the configuration of the carbon–carbon double bond in the resulting product.

The co-product 1-decene of eqn. (12) is an important intermediate in organic syntheses, and has a variety of end uses in polymers, surfactants and lubricants.

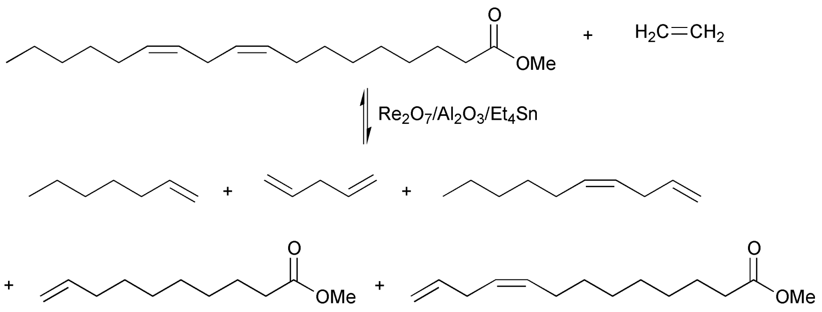
Ethenolysis of methyl erucate (the main component of high-erucic rapeseed oil and of Crambe oil) gives another ω-unsaturated ester, methyl 13-tetradecenoate, which potentially has applications that are analogous to those of methyl 9-decenoate.

Ethenolysis of polyunsaturated fatty acid esters at elevated ethene pressure leads to good yields of 1-heptene or 1-butene (from linoleic or linolenic esters, respectively), 1,4-pentadiene, 1,4-decadiene, methyl 9-decenoate and methyl 9,12-tridecadienoate. This reaction is illustrated for methyl linoleate in eqn. (14).[25]

3. Metathesis of natural oils and fats

A variety of unsaturated fatty oils may serve as easily obtainable and relatively inexpensive raw materials for the metathesis reaction. Metathesis of fatty oils that contain triglycerides of unsaturated long-chain fatty acids proceeds intramolecularly as well as intermolecularly, the latter reaction strongly predominating. Thus, in the presence of the catalyst system WCl_6/Me_4Sn, olive oil, which consists mainly of glyceryl trioleate (triolein), yields 9-octadecene and polymeric triglycerides (principally dimers and trimers);[19,26] eqn. (15).

Both drying and semidrying oils (such as linseed oil and soybean oil, respectively) are valuable raw materials for the manufacture of oil-based paint, printing ink, synthetic resins *etc.*[27] Metathesis of these oils (containing triglycerides of oleic, linoleic and linolenic acid) results in high-molecular-weight oils, so-called stand oils (*i.e.*, drying oils of increased viscosity). This process of molecular enlargement does not involve the consumption of double bonds. Therefore, these high-molecular-



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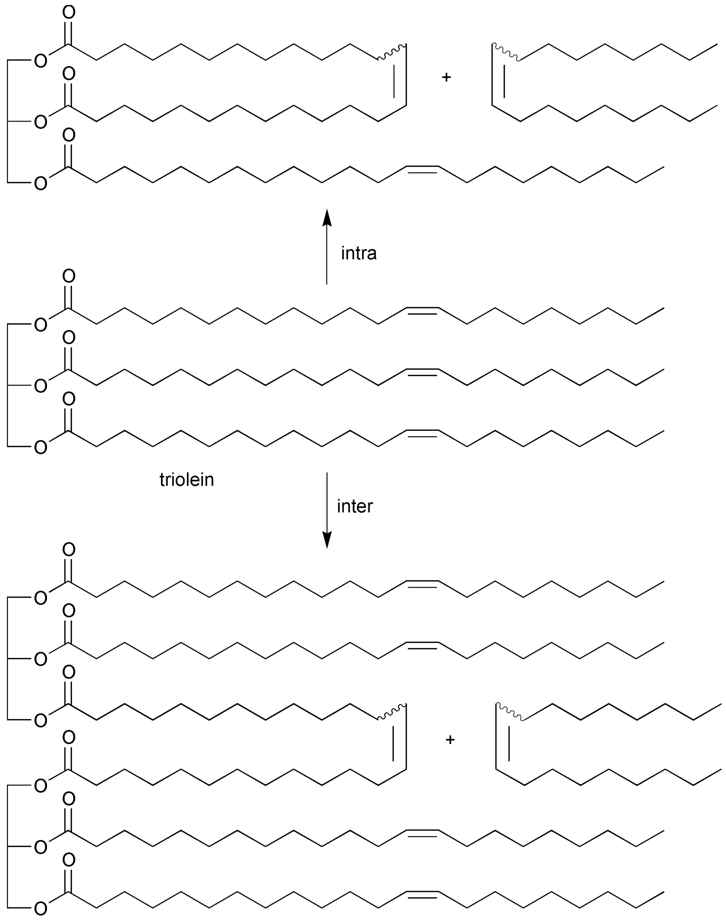


(15)

weight oils have drying properties that are more pronounced than those of thermally polymerized oils where the polymerization process has already considerably reduced the number of double bonds available for cross-linking during the drying process.[19] Thus, soybean oil that was metathesized in the presence of the WCl_6/Me_4Sn catalyst system and used as an additive at low concentrations dramatically decreased the drying time of soybean oil, of benefit for printing ink vehicles, *etc*.[28] The metathesis of a number of unsaturated vegetable oils in the presence of the ruthenium catalyst $Ru(=CHPh)Cl_2(PCy_3)_2$ was recently investigated.[29]

Cross-metathesis of distinct fatty oils (olive, soybean, rapeseed, cottonseed) consisting of long-chain unsaturated fatty acid triglycerides, with lower olefins allows, in principle, the transformation of natural fatty oils into fatty oils of lower molecular weight. An example is the production of tricaprin from olive oil by ethenolysis and subsequent hydrogenation; eqn. (16). As valuable co-products, corresponding amounts of terminal olefins are produced.

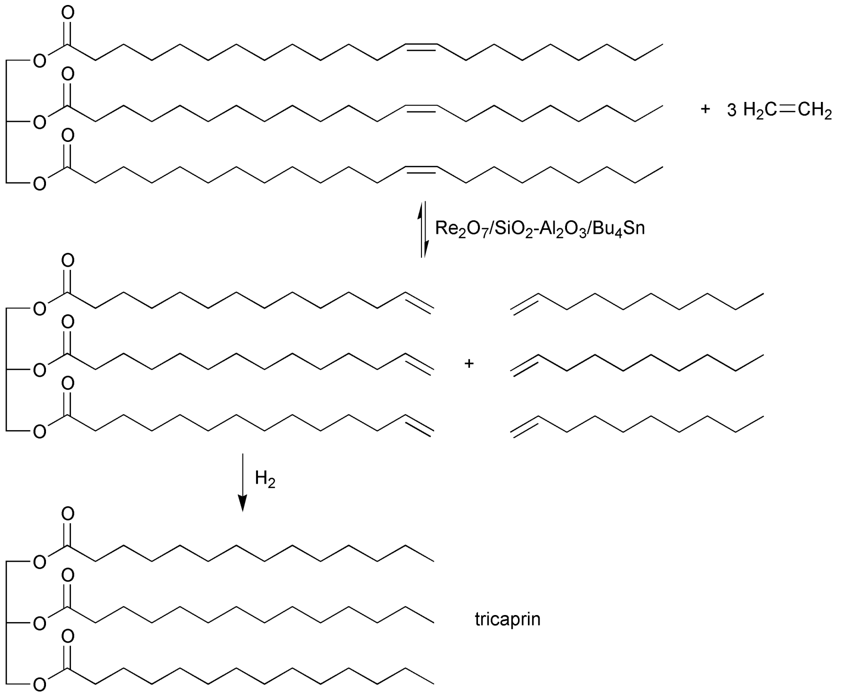
The ethenolysis of triolein into tridecenylglycerol proceeds, in the presence of a heterogeneous Re_2O_7-based catalyst, with high conversion at room temperature and an ethene pressure of 30 bar.[10]

4. Catalysts

Table 1 gives several examples of catalyst systems that are able to bring about the metathesis of oleic acid esters. The values reported for the turnover number (TON) are the effective TONs, this being the total number of substrate molecules converted to metathesis products per molecule of catalyst. Table 2 gives several examples of catalyst systems used for the metathesis of methyl 10-undecenoate. It follows that these metathesis reactions can proceed at room temperature. Moreover, although nearly all reactions mentioned in the Tables were performed in a solvent, a solvent is not always necessary; when a solvent is advantageous, an environmentally benign solvent such as pentane or heptane can be employed. The catalysts mentioned are also suited for cross-metathesis and ethenolysis reactions.

4.1. Homogeneous catalyst systems

Homogeneous metathesis catalysts generally consist of (i) a combination of a transition metal halide or oxo–halide with an alkylating co-catalyst; or (ii) a well-defined metal alkylidene (carbene) complex of a transition metal, such as Ru, Mo or W.



(16)

In the former case (*i.e.*, the classical catalysts), the active alkylidene species is generated from the alkyl groups on the co-catalyst, most probably via a double alkylation of the metal centre, followed by α-H-elimination. Functional groups, such as ester groups, in the substrate can, however, interfere with catalytic activity: they may bind to the active metal centre in competition with the carbon–carbon double bond and deactivate the catalyst, or they may react directly with the metal centre and destroy the active species.[10] Therefore, not all catalyst systems that are active for the metathesis of normal olefins are active for the metathesis of functionalized olefins.

Two-component catalyst systems, mainly $WOCl_4$ and WCl_6 in combination with a suitable co-catalyst, have been widely employed on a laboratory scale. These were the first catalyst systems developed for the metathesis of unsaturated fatty acid esters.[3,4] They are more sensitive to moisture and air, but less expensive and easier to handle than the metal–alkylidene complexes. However, their turnover numbers are low and a toxic co-catalyst is required.

First examples of metal–alkylidene catalysts that are active for metathesis of functionalized olefins were the complexes **I**[32] and **II**.[33] The bulkiness of imido and aryloxide ligands prevents, to some extent, the co-ordination of the functional group to the tungsten atom and probably slows down dimerization of these electron-deficient organometallic complexes to inactive complexes.[44] Next, attention was focused on ruthenium–alkylidene complexes. The well-defined ruthenium benzylidene complexes $Ru(=CH–CH=CPh_2)Cl_2(PCy_3)_2$[45] and $Ru(=CHPh)Cl_2(PCy_3)_2$,[46] developed by Grubbs and co-workers, are excellent functional-group-tolerant metathesis catalysts. Using the latter, we obtained 40% conversion of methyl oleate in 4 h at a substrate/catalyst molar ratio of 550, in dichloromethane,

Table 1 Examples of catalyst systems for the metathesis of (m)ethyl oleate

Catalyst	Ester/metal atom[a]	T/°C	t[b]/h	TON[c]	Ref.
Homogeneous systems					
WCl_6/Me_4Sn	75	110	2	38	26
$W(OC_6H_3Cl_2\text{-}2,6)_2Cl_4/Bu_4Pb$	50	85	0.5	25	30
$W(=CHCMe_3)NpCl(OAr)_2(OEt_2)$[d]	100	85	1	32	31
[W]$=CHCMe_3$ (see formula **I**)	300	25	2–3	150	32
[W]$=CHCMe_3$ (see formula **II**)	500	25	1	250	33
$Ru(=CH–CH=CPh_2)Cl_2(PCy_3)_2$	2 000	20	96	960	34
$Ru(=CHPh)Cl_2(PCy_3)_2$	5 500	20	48	2 500	35
$[Ru_2]=CHPh$ (**III**, R′ = CF_3)	550	40	1	225	36
$Ru(=CHPh)Cl_2(H_2IMes)(PCy_3)$ (**IV**)[e]	987 000	55	6	440 000	48
Heterogeneous systems					
$Re_2O_7/Al_2O_3/Et_4Sn$	60	20	2	3	18
$Re_2O_7/MoO_3/Al_2O_3/Et_4Sn$	60	20	2	30	18
$Re_2O_7/B_2O_3/Al_2O_3/Bu_4Sn$	120	20	2	50	37
$Re_2O_7/SiO_2–Al_2O_3/Bu_4Sn$	240	40	2	120	10
$Re_2O_7/B_2O_3/SiO_2–Al_2O_3/Bu_4Sn$[f]	480	20	2	160	38
$Re_2O_7/B_2O_3/SiO_2–Al_2O_3/Bu_4Sn$[g]	200	80	2	90	39
$CH_3ReO_3/SiO_2–Al_2O_3$	100	25	2	27	40
MoO_3/SiO_2/(CO, $h\nu$)/cyclopropane	250	50	0.17	25	41
MoO_3/SiO_2/(CO, laser)/cyclopropane	1 250	40	3	500	10

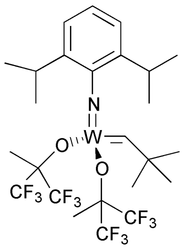
[a] Molar ratio. [b] t = Time to reach the highest conversion. [c] TON = Moles of substrate converted per mol of W, Ru, Re or Mo into reaction products. [d] Ar = $C_6H_3Ph_2$-2,6; Np = CH_2CMe_3. [e] No solvent. [f] Silica–alumina containing ~25wt% Al_2O_3. [g] Silica–alumina containing 60wt% Al_2O_3.

Table 2 Examples of catalyst systems for the metathesis of methyl 10-undecenoate

Catalyst	Ester/ metal atom	T/°C	t/h	TON	Ref.
WCl_6/Me_4Sn	75	110	10	67	26
WCl_6/Ph_2SiH_2	50	75	16	31	42
$Re_2O_7/B_2O_3/SiO_2–Al_2O_3/Bu_4Sn$	350	50	13	348	43
$Ru(=CHPh)Cl_2(PCy_3)_2$	4 000	50	2	3 120	23
$Ru(=CHPh)Cl_2(H_2IMes)(PCy_3)$ (**IV**)[a]	50 000	50	16	11 200	48

[a] No solvent.

with 96% selectivity, while with a higher substrate/catalyst ratio a TON as high as 2500 was obtained (see Table 1).[35] An advantage of homogeneous catalysts is that they can easily be modified by ligand design.



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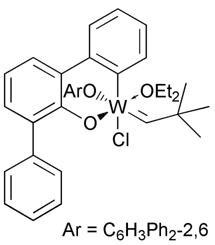

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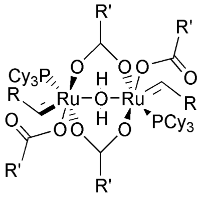
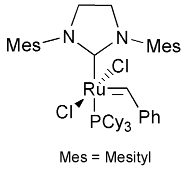


III

One aspect that is of interest is the stereoselective production of *cis* or *trans* isomers, *e.g.*, in the metathesis of methyl oleate where the *cis* isomer of the diester can be the desired product for further conversion to fine chemicals. We have recently synthesized a new family of dimeric ruthenium carbene complexes of the general formula $Ru_2(=CHR)_2(R'CO_2)_2(\mu\text{-}R'CO_2)_2(PCy_3)_2(\mu\text{-}H_2O)$ (**III**) (R = Ph or –CH=CPh$_2$; R′ = CF_3, C_2F_5) and these are active catalysts for the metathesis of methyl oleate[36] (Table 1). These systems show a very high selectivity (> 99.9%) as well as an increased product stereoselectivity compared with $Ru(=CHPh)Cl_2(PCy_3)_2$.

Recently, we obtained exciting results with a Grubbs ruthenium–carbene catalyst containing an N-heterocyclic carbene ligand, $Ru(=CHPh)Cl_2(H_2IMes)(PCy_3)$ (**IV**; H_2IMes = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene).[47] When using this complex as catalyst for the metathesis of methyl oleate, we obtained an extremely high TON of 440 000 and high selectivity at a reaction temperature of 55 °C after 6 h in the absence of a solvent.[48] Moreover, also for the metathesis of methyl 10-undecenoate, a very high TON of 11 200 was obtained. These figures justify industrial applications.†

Presently, attention has also focused on immobilizing homogeneous catalysts on a solid support. Immobilization of the ruthenium carbene complex $Ru(=CHPh)Cl_2(PCy_3)_2$ on a functionalized polystyrene support yielded a catalyst that was moderately active in the metathesis of methyl oleate.[50]



IV

4.2. Heterogeneous catalysts

In general, heterogeneous metathesis catalysts have the advantage that they are more favourable with respect to the separation of the catalyst from the reaction products, catalyst reuse and application in continuous processes.

For the metathesis of normal olefins, heterogeneous catalysts generally consist of a transition metal oxide or chloride supported on a high-surface-area inorganic oxide. Examples are Re_2O_7/Al_2O_3, MoO_3/SiO_2 and WO_3/SiO_2. These catalysts do not contain an alkylidene moiety in their original co-ordination sphere; the initiating metal carbene is formed from the catalyst and the olefin itself. A supported Re_2O_7 catalyst is particularly attractive because it is active and highly selective under mild reaction conditions (20–100 °C) and can be recovered easily. Unfortunately, these catalysts show no activity for the metathesis of functionalized olefins such as unsaturated acid esters. Therefore, a major step forward was the discovery that the metathesis of unsaturated acid esters can be brought about by the catalyst Re_2O_7/Al_2O_3 when promoted with a Me_4Sn cocatalyst.[51]

4.2.1. Rhenium catalysts[52].

Since the discovery of the active rhenium-based catalyst system $Re_2O_7/Al_2O_3/Me_4Sn$ for the metathesis of unsaturated acid esters, we could improve its catalytic performance by (i) the incorporation of a third metal oxide such as V_2O_5, MoO_3 or WO_3;[53] (ii) the use of a mixed oxide as the catalyst support, *e.g.*, $SiO_2–Al_2O_3$;[54] (iii) the treatment of the support with phosphate or borate;[10,37,55] or (iv) the use of other promoters, such as Et_4Sn, Bu_4Sn, Et_4Pb or Bu_4Pb.[18] The high selectivity (> 97%) encountered with these heterogeneous catalyst systems might not only be due to the low reaction temperature, but also to complexation of the ester group to the Brønsted acid sites on the support, preventing side reactions such as double bond shift. One of the most active combinations with supported rhenium oxide catalysts is the system $Re_2O_7/B_2O_3/SiO_2–Al_2O_3/Bu_4Sn$ (Table 1). Low rhenium contents are sufficient for the modified rhenium oxide catalysts.

Because the tin and lead compounds are toxic, attention has been given to promoters other than tetraalkyl-tin or -lead, *viz.* environmentally more benign alkyl-silyl and -germanium compounds. An example of such an active promoter is Bu_4Ge.[56]

The catalytic activity of (promoted) Re_2O_7/Al_2O_3 increases with increasing rhenium loading up to a loading of 18 wt% Re_2O_7. A positive correlation between the catalytic activity and the surface acidity (mainly the Brønsted acidity) has been observed.[57,58] The increasing activity of Re_2O_7/Al_2O_3 catalysts can be explained on the basis of the activity of the surface ReO_4 groups that have reacted with Lewis acid sites on the alumina and with the different aluminium-bonded OH groups during the preparation of the catalyst.[55] The most active sites arise from the reaction between ReO_4^- ions and the most acidic OH groups on the alumina surface, to form Al-bonded ReO_4 species. Such reactions are favoured only after the basic and neutral OH groups on the alumina have reacted to some extent.

On the other hand, when $SiO_2–Al_2O_3$ is used as the catalyst support, the specific catalytic activity decreases with increasing rhenium loading.[59] A high activity is obtained for a $SiO_2–Al_2O_3$ supported catalyst with an alumina content of about 25 wt%,

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† N.B. In a recent article it is stated that, for the fragrance and flavour industry, the utilization of noble metals such as ruthenium and/or sophisticated ligands, is only justified 'when the turnover number is higher than 1000 or even 10 000 depending on the cost of the target product'[49].

which has a high Brønsted acidity. This Brønsted acidity is due to two types of hydroxyl groups: hydroxyl groups attached to a Si atom and bridging hydroxyl groups attached to both a Si and an Al atom. At low rhenium loading ReO_4^- ions react preferentially with the bridging surface hydroxyl groups during calcination, resulting in electron-poor rhenium centres (ReO_4^- tetrahedra), the active site precursors. This might explain why Re_2O_7 supported on SiO_2–Al_2O_3 is already very active at low rhenium loading. At higher rhenium loading, the hydroxyl groups attached to a Si atom are also replaced, resulting in inactive rhenium centres of the type $\equiv$Si–O–ReO_3 (or rhenium clusters).

Likewise, the positive effect on the activity of the addition of other metal oxides, borate or phosphate, has been attributed to an increase of the Brønsted acidity of both the supports and their corresponding catalysts.

Rhenium-based systems are only active for the metathesis of functionalized olefins when promoted with an alkylating co-catalyst. The active catalytic sites generated by a R_4M (M = Sn, Pb, Ge, Si) co-catalyst may be intrinsically different from those present on the unpromoted catalyst. Based on ^{119}Sn Mössbauer and ^{13}C and ^{119}Sn MAS NMR experiments with the catalyst system Re_2O_7/SiO_2–Al_2O_3/R_4Sn, it has been proposed that these active sites are formed *via* a double alkylation involving one rhenium site, followed by α-H-abstraction leading to a rhenium–alkylidene species.[60,61]

4.2.2. Molybdenum catalysts. Only two of the many Mo-based heterogeneous metathesis catalyst systems have been reported to bring about the metathesis of functionalized olefins, *viz*. $MoCl_5/SiO_2/R_4Sn$ (R = Me, Et)[16] and MoO_3/SiO_2 (after a special treatment). MoO_3/SiO_2 that has been photoreduced at room temperature with an Hg lamp in a CO atmosphere and subsequently treated with cyclopropane is an active catalyst for the metathesis of unsaturated acid esters.[41] An alternative activation procedure, consisting of photoreduction of MoO_3/SiO_2 in CO with laser irradiation of 308 nm instead of an Hg lamp, followed by cyclopropane treatment, leads to a catalyst of even higher activity.[10,62]

4.2.3. Catalyst deactivation and regeneration. The activity of a rhenium-based catalyst in the metathesis of unsaturated esters is unavoidably limited by complexation of the ester group to the catalytically active site.[10] Moreover, there are many routes that lead to deactivation of the catalyst. Polar compounds such as H_2O or free acids, alcohols and peroxides, which might be present as an impurity in the substrate(s), can act as catalyst poisons. Other possible routes for the deactivation of rhenium-based catalysts include (i) reduction of the rhenium below its optimum oxidation state; (ii) adsorption of (polymeric) product molecules on the surface of the catalyst, blocking the active sites; or (iii) reductive elimination of the metallacyclobutane intermediate.[63] Even when the greatest care is taken, deactivation of the rhenium catalyst cannot be avoided; therefore, the turnover numbers obtained with these catalysts are not very high. The relatively low turnover numbers are to some extent compensated by the fact that, after deactivation, the catalyst can be regenerated via calcination at 500–550 °C, followed by further addition of promoter. However, there is a limit to the number of times that the catalyst can be regenerated in this way, due to accumulation of tin on the catalyst surface.[64]

The molybdenum-based catalysts deactivate faster than the rhenium-based ones. Studies concerning the stability of the catalyst during continuous metathesis of propene showed a loss of activity due to an intrinsic deactivation mechanism.[65]

Although rhenium is a precious metal, rhenium-based catalysts are preferable to molybdenum ones because their activation is simpler and regenerability is much better.

5. Perspectives

The metathesis of natural fats and oils and their derivatives is a clean catalytic reaction that can be considered as an example of green chemistry. Starting with renewable raw materials, valuable chemical products are directly, or in only a few reaction steps, obtainable with high selectivity under mild reaction conditions, while solventless operation is possible. Therefore, the metathesis reaction has good prospects as a contribution to a sustainable chemical industry provided that sufficient raw materials are available. In particular, metathesis has prospects for making products with a high added value, such as fine chemicals.

The solid rhenium oxide catalyst systems developed in our laboratory are already active at room temperature, can be easily separated from the reaction mixture and can be regenerated many times. After total deactivation the rhenium can be recovered relatively easily.

Recent findings demonstrate that new well-defined homogeneous ruthenium complexes are very effective as catalysts for the metathesis of unsaturated fatty acid esters and related compounds. Although they are still expensive and decompose irreversibly during the reaction, this is compensated by high turnover numbers.

In summary, metathesis of unsaturated fatty oils and their derivatives should now seriously be considered by the oleochemical industry as an interesting process awaiting application.

Acknowledgement

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Ring-opening polymerization of lactones catalyzed by ion-exchanged clay montmorillonite

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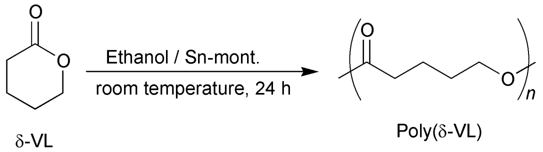
Tin ion-exchanged montmorillonite catalyzed the ring-opening polymerization of δ-valerolactone in a solvent free system. The polymerization proceeded in a living manner, giving rise to poly(δ-valerolactone)s with controlled molecular weights. Aluminium and iron ion-exchanged montmorillonites were also effective for the polymerization. Furthermore, the copolymerization of δ-valerolactone with γ-butyrolactone took place in the presence of the montmorillonite to produce the corresponding copolymers.

Introduction

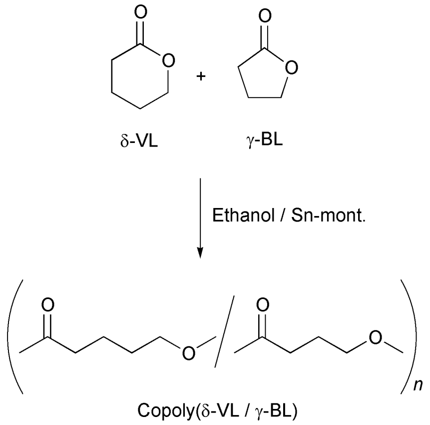
Clay montmorillonite is a layered silicate possessing ion-exchange ability. The acid property of montmorillonite can be easily altered by replacing interlayered cations in the montmorillonite without any change of the crystalline structure.[1] It has been reported that aluminium, iron and tin ion-exchanged montmorillonites are strongly acidic and efficient for several acid-catalyzed organic reactions, such as aldol and Michael reactions.[2,3]

Aliphatic polyesters are of great interest for their applications in the medical field as biodegradable surgical sutures or as a delivery medium for controlled release of drugs due to their biodegradable, biocompatible and permeable properties.[4] Recent development of living ring-opening polymerization of lactones has enabled us to obtain polyesters with controlled molecular weights and polydispersity ratios. One of the most useful methods to control ring-opening polymerization of lactones is 'activated monomer cationic polymerization', which was carried out using an acid catalyst and an alcohol initiator.[5] In this type of the ring-opening polymerization, Lewis or protic acids are used as a catalyst, which activates the lactone monomer. Then, the alcohol initiates the polymerization *via* ring-opening. Mesoporous zeolite has also been used as a solid acidic catalyst for the controlled polymerization of lactones.[6]

In this paper, we report that tin(IV) ion-exchanged montmorillonite (Sn-mont) is a novel, efficient solid catalyst for the ring-opening polymerization of δ-valerolactone (δ-VL) to produce poly(δ-VL), which takes place by a living mechanism (Scheme 1). Aluminium and iron ion-exchanged montmorillonites (Al-mont and Fe-mont, respectively) are also employed for the polymerization of δ-VL. Furthermore, we demonstrate herein the copolymerization of δ-VL with γ-butyrolactone (γ-BL) catalyzed by Sn-mont, giving rise to copoly(δ-VL/γ-BL) (Scheme 2).



Scheme 1 Ring-opening polymerization of δ-VL.



Scheme 2 Ring-opening copolymerization of δ-VL with γ-BL.

Results and discussion

The polymerization of δ-VL initiated with ethanol in the presence of various amounts of Sn-mont proceeded at room temperature without solvent and the monomer conversion was quantitative after 24 h to give poly(δ-VL) (Table 1). For example, when a mixture of δ-VL and ethanol at a mole ratio of 10 was stirred in the presence of Sn-mont (0.20 g) under argon, the polymerization proceeded to attain 98.4% monomer conversion in 24 h (Table 1, entry 2). After the reaction, Sn-mont was removed by filtration and the filtrate evaporated under reduced pressure to obtain the product poly(δ-VL). The structure of the

Green Context

The production of polymers represents a major class of chemical processes, and there are many opportunities for cleaner polymer synthesis. This contribution describes the use of a clay-based catalyst for a polymerisation leading to a polyester. The polymerisation proceeds smoothly, and a simple filtration is sufficient to recover the catalyst. This process means that separation of the catalyst is much more straightforward, leading to a simpler separation, and also opening up the possibility of better quality polymers, with the potential for reducing the amount of polymer required for a specific purpose. ***DJM***

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Table 1 Ring-opening polymerization of δ-VL initiated with ethanol in the presence of ion-exchanged montmorillonites[a]

			Before precipitation			After precipitation		
Entry	Montmorillonite	[δ-VL]$_0$/ [Ethanol]$_0$	Conversion[b] (%)	DP[b]	M_w/M_n[c]	Yield[d] (%)	DP[b]	M_w/M_n[c]
1	Sn-mont	5	97.6	6.2	1.22	86.8	7.7	1.17
2	Sn-mont	10	98.4	9.2	1.27	95.4	9.6	1.24
3	Sn-mont	15	98.6	11.5	1.24	96.1	12.3	1.24
4	Sn-mont	20	98.8	13.4	1.27	98.0	14.3	1.27
5	Al-mont	10	98.6	9.1	1.26	95.5	9.1	1.20
6	Fe-mont	10	98.6	9.0	1.29	96.6	9.1	1.24

[a] δ-VL; 0.50 mmol, montmorillonite; 0.20 g, at room temperature for 24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GPC analyses with chloroform as the eluent. [d] Cyclohexane insoluble fraction.

product was determined by its ^{1}H NMR spectrum ($CDCl_3$): δ 1.55–1.83 (m, $O{=}CCH_2CH_2CH_2C$, 4 H), 2.22–2.48 (m, $O{=}CCH_2$, 2 H), 3.98–4.23 (m, CH_2O, 2 H). In addition to these peaks due to the polymer chain, a set of small signals assignable to CH_3CH_2O (δ 1.26) and CH_2OH (δ 3.61) is observed. The relative intensity of these signals was 3 : 2, indicating that the polymerization was initiated by ethanol with incorporation of the ethoxy end group at the initiating site of the polymer chain. The degree of polymerization (DP), therefore, was calculated by the integrated ratio of the signal due to the methyl end group to the signals due to the polymer main chain. Furthermore, the molecular weight distribution (M_w/M_n) of the product was estimated by gel permeation chromatography (GPC) measurement with chloroform as the eluent. Fig. 1 illustrates the relationships of DP and M_w/M_n in terms of the monomer conversion. When 0.20 g of Sn-mont was used with 0.50 g of δ-VL the DP values (Fig. 1, ●) were proportional to the monomer conversions, and close to the calculated values. Furthermore, the M_w/M_n values (Fig. 1, ■) were < 1.25. These data indicate the living nature of the present polymerization process catalyzed by Sn-mont. An additional evidence of the living nature is given by a monomer-addition experiment (Fig. 2). When the same amount of monomer was added after the complete consumption of the first monomer at the final stage, the propagation still continued to give the polymer having a doubled DP value at the second final stage. The DP values obtained by using the smaller amount of the catalyst (0.025 g), however, were lower than the calculated values (Fig. 1, ○). The above data indicate that the use of 0.20 g of catalyst with 0.50 g of the monomer is more advantageous for the living polymerization process compared to the smaller amount of the catalyst (0.025 g). The following experiments, therefore, were carried out using 0.20 g of the catalyst and 0.50 g of monomer.

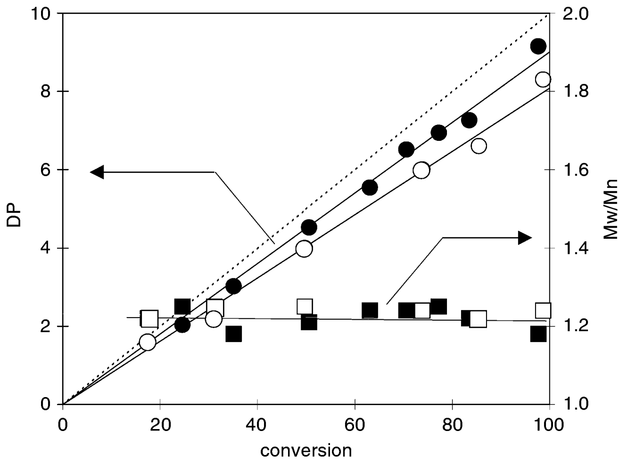

Fig. 1 DP and M_w/M_n values *vs.* monomer conversions in the polymerization of δ-VL; $[\delta\text{-VL}]_0/[\text{ethanol}]_0 = 10.0$: (● and ■) Sn-mont, 0.20 g, δ-VL, 0.50 g; (○ and □) Sn-mont, 0.025 g, δ-VL, 0.50 g. The dashed line represents the calculated DP value

The product polymer can be purified further by precipitation into cyclohexane. Some polymerization results are summarized in Table 1. When the ratios of monomer to initiator are < 10, the DP values of the product polymers are in good agreement with the calculated values (entries 1 and 2). With increasing the ratios of monomer to initiator than 10, the DP values become smaller than the calculated values (entries 3 and 4). These observations are probably due to the presence of the moisture in the polymerization system at the larger monomer/initiator ratios. Because the integrated ratios of the CH_3 peak to the CH_2OH peak were smaller than 3/2 in the ^{1}H NMR spectra of the polymers of entries 3 and 4, indicating that the polymerizations were initiated by not only ethanol but also water. Al-mont and Fe-mont were also effective as catalysts for the polymerization (entries 5 and 6).

After the polymerization, the Sn-mont catalyst was removed from the reaction mixture by filtration. The recovered Sn-mont was dried at 120 °C for 3 h under reduced pressure, and used as the catalyst again for the polymerization of δ-VL under the same conditions as above. The yields and DP values were comparable to those shown in Table 1. For example, when the polymerization was carried out using the recovered Sn-mont under the conditions as in entry 2, poly(δ-VL) was obtained in 96.6% yield. The DP and M_w/M_n values were 9.2 and 1.29, respectively. When the catalyst after the 2nd run was recovered further and used once more for the polymerization under the same conditions, poly(δ-VL) with DP = 9.2 and M_w/M_n = 1.28 was obtained in 98.9% yield. These experimental results indicate that the catalytic activity did not decrease for the 2nd and 3rd runs.

As an extension of the polymerization reaction catalyzed by Sn-mont, copolymerization of δ-VL with γ-BL was carried out under the conditions as used for the homopolymerization of δ-VL. It is well known that γ-BL on its own does not polymerize under such polymerization conditions. In fact, when the polymerization of γ-BL was performed in the presence of Sn-

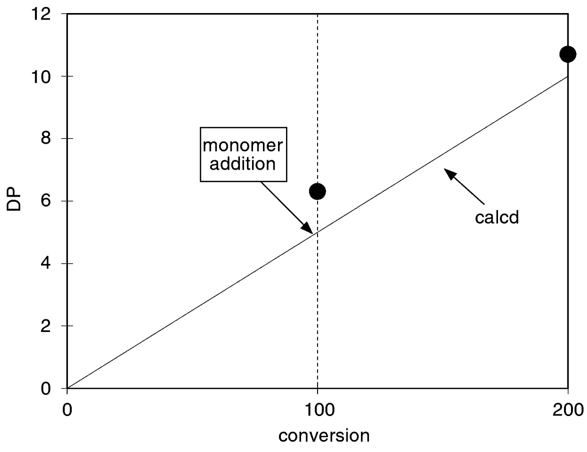

Fig. 2 DP values obtained in a monomer-addition experiment; $[\delta\text{-VL}]_0/[\text{ethanol}]_0 = 5.0$.

Table 2 Copolymerization of δ-VL with γ-BL initiated with ethanol in the presence of Sn-mont[a]

Entry	Feed ratio δ-VL : γ-BL	Temperature/°C	Time/h	Yield[b] (%)	DP[c]	M_w/M_n[d]	Composition[c] δ-VL : γ-BL
1	1 : 1	rt	3	49.3	6.6	1.33	1 : 0.19
2	1 : 5	rt	3	15.8	5.0	1.34	1 : 0.25
3	1 : 10	rt	3	6.7	3.9	1.29	1 : 0.34
4	1 : 10	rt	24	9.6	4.7	1.28	1 : 0.43
5	1 : 10	50	3	5.7	4.3	1.25	1 : 0.39
6[e]	0 : 1	rt	3	5.5	2.4	1.21	0 : 1

[a] δ-VL; 1.0 mmol, ethanol; 0.10 mmol, Sn-mont; 0.20 g. [b] Residual percentage after evaporation. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by GPC analyses with chloroform as the eluent. [e] γ-BL; 5.0 mmol, ethanol; 0.50 mmol, Sn-mont, 0.20 g.

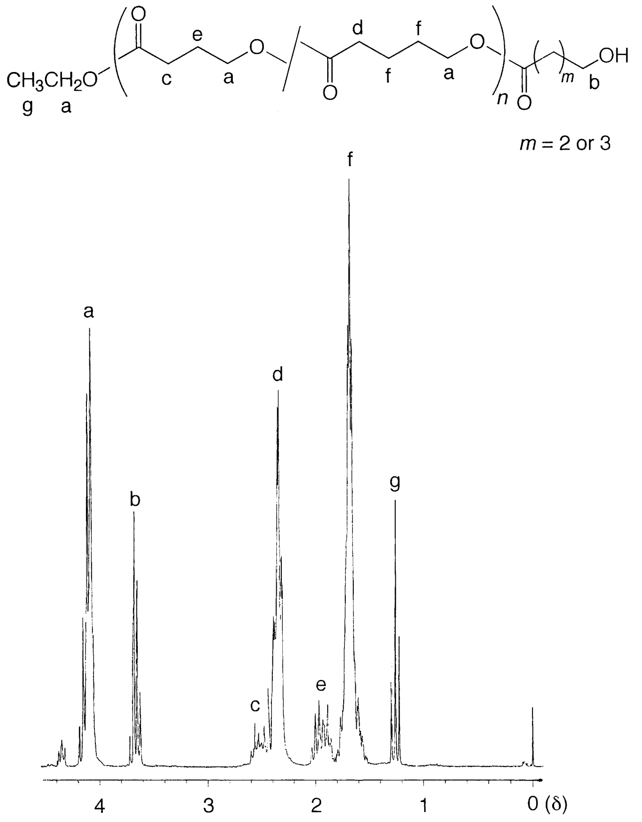

Fig. 3 ^{1}H NMR spectrum of the copolymer between δ-VL and γ-BL ($CDCl_3$).

mont, only an oligomeric product with low DP (2.4) was obtained in low yield (5.5%) (Table 2, entry 6). The copolymerization of δ-VL with γ-BL gave the corresponding copolymers consisting of δ-VL and γ-BL units. The structure of the copolymer was confirmed by ^{1}H NMR spectroscopy. As shown in Fig. 3, both the signals ascribed to δ-VL units (signals a, d, and f) and γ-BL units (a, c, and e) are observed, accompanied with the signals g and b due to CH_3CH_2O and CH_2OH of the end groups, respectively. The results of the copolymerization at various monomer feed ratios are shown in Table 2. The contents of γ-BL units in the copolymers are always less than the γ-BL ratios in the monomer feeds, attributed to the very low polymerizability of γ-BL. The yields and DP values decrease with increasing the γ-BL ratios in the monomer feeds (entries 1–3). Longer reaction times gave the copolymer with higher DP in higher yield (entry 4). A higher reaction temperature, however, was not effective for improving the DP and yield (entry 5).

In conclusion, we have found that ion-exchanged montmorillonites were effective as acidic catalysts for the ring-opening polymerization of δ-VL. The polymerization catalyzed by Sn-mont proceeded in a living manner to give poly(δ-VL)s with controlled molecular weights. Furthermore, copolymerization of γ-BL with δ-VL catalyzed by Sn-mont also took place, giving rise to the corresponding copolymers.

Experimental

Ion-exchanged montmorillonites were prepared according to the literature and dried at 120 °C for 3 h under reduced pressure (0.20 mmHg) prior to use.[7] Monomers, δ-VL and γ-BL, and the initiator ethanol were purified by distillation. NMR spectra were recorded on a Varian Mercury 200 spectrometer. GPC analyses were performed by using a Hitachi 655A-11 apparatus with a refractive index detector under the following conditions: Tosoh TSKgel G3000H$_{XL}$ column with chloroform as eluent at a flow rate of 1.0 mL min^{-1}.

Typical procedure

Under argon, to a suspension of δ-VL (0.50 g, 5.0 mmol) and Sn-mont (0.20 g) was added ethanol (0.023 g, 0.50 mmol) with stirring at room temperature to start the polymerization. After the solution was stirred for 24 h, the reaction mixture was diluted with chloroform and Sn-mont was separated by filtration. The chloroform solution was washed with aqueous sodium hydrogen carbonate and dried over sodium sulfate. The solution was evaporated and dried under reduced pressure to give a white polymeric material (0.52 g). The product was dissolved in chloroform and the solution poured into a large amount of cyclohexane to precipitate the polymer. The precipitate was isolated by decantation and dried *in vacuo* to give the purified polymer in 95.4%.

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Zero-valent metal accelerators for the dechlorination of pentachlorophenol (PCP) in subcritical water

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Preliminary trials with 0.5 mg pentachlorophenol (PCP) in the presence/absence of 50 mg of 325-mesh Ag^0/Fe^0 (2% w/w) granules, demonstrated that the extent of dechlorination increased with both increased reaction time (0.5–2 h) and increased temperature (200–350 °C) but that recoveries of products were incomplete. Whereas reaction (200 °C) in the absence of metal accelerator furnished only unreacted PCP after 2 h and a mixture of tetrachloro species and substrate (~ 50%) after 4 h of reaction, timed trials in the presence of Fe^0 or 2% (w/w) Ag^0/Fe^0 bimetallic mixture resulted in more extensive dechlorinations. Only sequential dechlorinations were observed for iron-based accelerators and the dechlorination route was consistent with relief of steric strain as the dominant influence that determined the decomposition products. There was no appreciable difference in the course of the dechlorinations between the Fe^0 and the 2% (w/w) Ag^0/Fe^0 bimetallic mixture but differences in the rates of reaction were evident. Dechlorinations with magnesium-based bimetallic accelerators were more extensive, more rapid and both concerted and stepwise reactions were observed. With 100 mg Pd^0/Mg^0, 63% of products consisted of phenol plus cyclohexanone and a further 9% was *o*-chlorophenol yet 13% were tetrachloro species. By contrast, an equal quantity of Mg^0 alone mediated only partial dechlorination. The dechlorinations represent a detoxification—the toxiforic chloro substituents of the substrate are reduced to innocuous chloride while the sacrificial Mg metal is oxidised to Mg^{2+}.

Introduction

Water, at ambient temperature and pressure (dielectric constant, ε ~80[1]), is extremely polar. Whereas increasing temperature decreases the dielectric constant appreciably, increasing pressures cause only modest increases in this parameter. The net effect is that under supercritical conditions [> 374 °C and > 22 MPa (220 bar)] the dielectric constant of the fluid is reduced to < 10 (similar to dichloromethane). The corrosivity of water at near critical conditions (higher density) has prompted researchers to systematically investigate water under subcritical conditions. Fortunately, the polarity of water can be decreased appreciably at relatively mild pressures (sufficient to maintain the liquid state) and temperatures in the range of 100–350 °C. Thus, ε = 27–29 for T = 250 °C and pressures of 5.1–25.3 MPa (51–253 bar). With these conditions, subcritical water resembles a polar organic solvent (for ethanol ε = 24 and for methanol ε = 33). Dechlorination rate limitations that result from the sparing solubilities of non-polar chlorinated substrates in water (at ambient conditions) can be overcome.

A popular approach to abiotic dehalogenations has been to mediate the reduction in aqueous media in the presence of a sacrificial metal in its elemental form. Zero-valent iron[2–9] and iron–palladium[10–12] bimetallic mixtures have become especially popular for this purpose. In anoxic aqueous media, free metal ions, chloride ion and hydrogen gas were produced by reaction at the surface of metal particles and protons were consumed. The process kinetics were dependent on solution pH, surface area of the metal particle, substrate concentration, buffer selection and solvent composition.[7] Dechlorination approximately followed first-order kinetics and rate coefficients tended to increase with time, that possibly resulted from an increased surface area of reactive metal due to cathodic depolarization and pitting.[4]

Based on the low concentration of chlorinated degradation products in the solution phase it was suggested that most of the substrate remained sorbed to the iron surface until complete dechlorination had been achieved.[6] Prolonged exposure of the Fe^0 or Pd^0/Fe^0 surface to a saturated solution of aqueous organochlorine compounds resulted in the growth of a hydroxylated iron oxide film that deactivated the Pd^0/Fe^0 surface. However, the activity of the metal surface was restored by washing with a dilute acid.[3,12,13]

The dehalogenated of aromatics with zero-valent metals have also been studied. Copper metal has been reported to dechlorinate DDT[14] and its derivatives. Catalytic hydroprocessing over molecular hydrogen that mediates the reduction of arylchlorine substituents to chloride at relatively low temperatures has been reported with Ni-, Pd-, Pt- and Rh-based catalysts.[15–20] The liquid phase catalytic hydrodechlorination of chlorophenols over Pt/C[21] and in the gas phase over Ni^0/SiO_2[22,23] and over Ni^0/zeolite[22] has also been examined. Hydrogen

Green Context

Dechlorination of heavily chlorinated aromatics is required for waste water treatment. Here a straightforward combination of Mg and subcritical water is used to effect an efficient destruction of these compounds using a relatively innocuous medium. ***DJM***

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treatment of HOArCl isomers in the range of 150–300 °C, yielded phenol as the only appreciable product.[22] Under these conditions, phenol was hydrogenated to cyclohexanol and cyclohexanone with benzene being formed at $T > 250$ °C. The continuous gas phase hydrodechlorination of pentachlorophenol (PCP) was studied in H_2 at 200–350 °C over 1.5 or 15.2% Ni/SiO_2 and Ni/zeolite.[23] With these conditions, dechlorination has been shown[22,24] to proceed *via* an electrophilic mechanism involving spillover hydrogen and associated chloroaromatic. There is persuasive evidence[25,26] for the co-existence of charged (H^+) and uncharged (H atoms) spillover hydrogen on silica where the former is considered to be the reactive specie in catalytic hydrodechlorination.

Analogous continuous dechlorinations have involved the use of steam or supercritical carbon dioxide. In the steam reforming process,[27] liquid substrate was merged with steam and pyrolysed over a commercial Ni catalyst [$Ni^0/CaAl_2O_4$ (23 wt%)] or 0.5% $Pt/\gamma\text{-}Al_2O_3$ at 600–800 °C. Aryl chloride was converted to $CO + H_2 + HCl$ in a steam reforming reaction and the CO plus water was transposed to CO_2 and hydrogen with a second water gas shift reaction. In another process, PCBs[28] or PCP[29] was merged with supercritical CO_2 and dechlorinated efficiently over (2% w/w) Ag^0/Fe^0 at ~450 °C. Decreases in the catalyst activity with time were restored to their original values with a methanol–water wash. Zero-valent iron and bimetallic mixtures have also been evaluated (in batch processes) for PCP[30,31] and for PCB[32,33] dechlorinations. For subcritical water, Hinz *et al.*[33] have proposed that the magnetite [$Fe(OH)_2$] formed by Fe^0 corrosion of water is converted thermally to Fe_3O_4 with the liberation of H_2.

The objectives of the current study were to evaluate selected zero-valent metals or bimetallic mixtures for their ability to accelerate the dechlorination of PCP in hot pressurised water. If differences were evident, it was anticipated that changes in the product distribution with time would provide insights into the mechanistic course of the dechlorination.

Experimental

Chemicals

Pentachlorophenol (PCP, nominally 99% pure), trichlorophenols (1,2,3-, 1,2,4-, 1,2,5-, 2,3,4-, 2,3,5-), dichlorophenols (2,3-, 2,4-, 2,5-, 2,6-, 3,4-, 3,5-) monochlorophenol (2-, 3-, and 4-) and phenol were purchased from Aldrich Chemical Co., Milwaukee, WI, USA). Tetrachlorophenols (2,3,4,5-, 2,3,4,6- and 2,3,5,6-) were purchased from Supelco, Bellefonte, PA, USA. Acids [HCl (15 M) and HNO_3 (17% v/v)], sodium bicarbonate and solvents (dichloromethane and acetone) were purchased from Fisher Scientific Co., Fair Lawn, NJ, USA. Copper powder (electrolytic grade, 40-100 mesh, nominally 99.5% purity), iron (40 mesh, 100 mesh or 325-mesh, nominally 99.5% purity), magnesium (~20-mesh), nickel (50–100 mesh, nominally 99.5% purity), zinc particles (100 mesh, nominally 99.9% purity), were purchased from Aldrich Chemical Co., or Alfa Aesar (Ward Hill, NJ, USA). Chemicals were ACS-Reagent grade (unless noted otherwise) and were used as received.

Dechlorinations

Timed trials were performed under static (no flow) conditions in 4 mL capacity stainless steel cells (64 mm long by 6.3 mm inner diameter, fitted with threaded (npt) screw-top end caps, Parker Hannifen Corp., Columbus, OH). Each reactor was partilly filled by adding 2.7 mL water (that had been purged with N_2 for 2 h) to 50 mg test accelerator that had been amended with 0.5 mg PCP (contained in 10 μL acetone). Each reactor was sealed immediately and added to a clamping device mounted on the circumference of a circular disk. The disk was mounted on a metal plate (that approximated the dimensions of the door of the gas chromatographic oven) and could be rotated to mix the contents of each reactor (in end over end fashion). For reactions at 200 °C, the oven door was opened and the loaded rack–metal plate assembly was substituted quickly into the oven that had been pre-heated to 250 °C. The oven set-point temperature was maintained at 250 °C until the oven temperature had increased to 190 °C then the temperature set-point of the chromatograph was lowered to the desired 200 °C. An analogous procedure was used for other experimental reaction temperatures. Companion trials in which a thermocouple extended into the aqueous reaction mixture had indicated that the interior cell temperature reached 190 °C after 4 min. The rack was rotated continuously (~30 revolutions min^{-1}) and timed trials were considered to have commenced as soon as the oven had returned to operating temperature. Upon completion of each timed trial, the reaction was stopped by cooling each sealed cell rapidly in cold running water.

Safety note

It is imperative to maintain sufficient headspace above the reaction mixture so that the internal pressure is governed by the steam/water equilibrium and excessive pressure is avoided. In the range 105–350 °C, the pressure for steam/water[1] ranges between 1.3 and 170 bar (~2500 psi) substantially below the 517 bar (7500 psi) pressure rating of the cells.

Reaction work up

The contents of each reactor was acidified with five drops of conc. HCl or HNO_3 then transferred to a 7 mL vial and extracted three sequential times with 1 mL CH_2Cl_2. The organic extracts were combined and supplemented with 0.3 mg 2-chloronaphthalene (in 10 μL acetone) that acted as an internal standard and analysed by GC-MS.

Ag^0 or Pd^0/metal^0 bimetallic mixture

The general preparations described by Zhang *et al.*[34] were followed. Ag^0/Fe^0 and Pd^0/Fe^0 were prepared from 325- or 100-mesh iron granules that had been washed copiously with 6 M HNO_3 and rinsed with distilled water. Sufficient aqueous $AgNO_3$ or K_2PdCl_6 to result in a 2% or 0.2–0.5% (w/w) surface coverage, respectively, of the iron, was added to the aqueous metal suspension that was gently mixed on a rotary evaporator for 12 h. Ag^0/Ni^0 was prepared in similar fashion by reaction of aqueous $AgNO_3$ [sufficient to provide a 2% (w/w) surface coverage] with aqueous suspension of pre-washed 50–100 mesh nickel granules during 12 h. For magnesium granules, the reaction with aqueous $AgNO_3$ or K_2PdCl_6 was more rapid and only 10 min were required.

Pd^0/Mg^0

Mg^0 (25 or 10 g of 12–50 mesh granules) was combined with ~50 mL H_2O in a 250 mL round bottom flask (RBF). An aqueous solution of K_2PdCl_6 (188 mg/~10 mL) was added and the flask was swirled vigorously under cold running water to mix the reagents. The reaction was exothermic and the supernatant liquid rapidly turned black. The RBF was maintained on the rotary evaporator to maximise mixing. After 10 min, the aqueous supernatant fraction was decanted off and discarded. The granules were washed (~30 mL) three times with water and a further three times with acetone. The solids were then dried under reduced pressure on the rotary evaporator and stored in a sealed jar.

Ag^0/Mg^0

In similar fashion, $AgNO_3$ (788 mg) dissolved in ~25 mL H_2O was combined with the 25 g Mg^0 granules suspended in ~50 mL H_2O and reacted for 10 min. An identical work up furnished the Ag^0/Mg^0 bimetallic mixture.

Gas chromatography–mass spectrometry

Chromatographic separations were performed on an Agilent Technologies model 5890 series II gas chromatograph fitted with a model 5970 mass selective detector and an autoinjector system. Injections were performed in the splitless mode into a DB-5 capillary column (30 m × 0.25 mm i.d. and 0.25 μm film thickness, J & W Scientific, Rancho Cordova, CA, USA) and eluted with helium (column head pressure, 10 psi). After an initial hold for 1 min at 40 °C, the column was ramped, at 10 °C min^{-1}, to 320 °C and held for a further 5 min prior to cooling. The temperature of the injector and transfer line were maintained at 300 and 280 °C, respectively. Quantitations were based on relative response factors of individual standards to the internal standard (2-chloronaphthalene). Similarly, the identification and quantitation of degradation products were based on comparisons of mass spectra and retention times of pure standards with those of the sample components (unless noted otherwise).

Chloride ion determination

Chloride ion in aqueous fractions of reaction mixtures that had been charged with 5 mg substrate were performed in triplicate or quadruplicate with a chloride ion selective electrode (Cole Parmer, Vernon Hills, IL, USA).

Results and discussion

Because water that was added to each reactor had been deaerated for 2 h with nitrogen prior to use it was anticipated that the dominant reactions would be hydrolytic rather than oxidative. For the preparation of bimetallic metal mixtures, it had been established previously that only traces of silver or palladium remained in the aqueous supernatant fraction after reaction with the Fe^0 or Mg^0. In preliminary ranging trials, it was also established that the presence of zero-valent metals did accelerate dechlorinations relative to companion runs that contained only PCP. However, neither the copper, zinc, nickel nor a 2% (w/w) Ag^0/Ni^0 bimetallic mixture were as efficient as iron metal (Fe^0) at mediating dechlorinations. As has been observed by others,[9,12] it was corroborated that a reduced particle size (325- *vs.* 100- *vs.* 40-mesh) of the Fe^0 granules did increase the rate/extent of PCP dechlorination in this medium as well.

Iron-based accelerators

Initial trials that were performed with 0.5 mg PCP (1.88 μmol) in the presence/absence of 50 mg of 325-mesh Ag^0/Fe^0 granules (~0.9 mmol), demonstrated that the extent of dechlorination increased with both increased reaction time (0.5–2 h) and increased temperature (200–350 °C). However, recoveries were incomplete (ranging from 20–27%) so that the values recorded in Table 1 represent the molar percent distribution among the products that could be determined by GC/MS with the extraction procedure. The low recoveries were repeatable and not surprising given the tendency[6,35] of chlorinated substrates to sorb strongly to metal surfaces and the probable formation of ring hydroxylation products that might not be detected with the recovery procedure. Chlorobenzenes and PCBs have been reported to form ring-hydroxylated products in subcritical H_2O. Dechlorinations also occurred in the absence of accelerator (Table 1) but were appreciably less extensive.

In a subsequent series of trials, the influences of bimetallic Ag^0/Fe^0 mixtures and Fe^0 on the dechlorination rates were compared. Dechlorinations of 0.5 mg PCP in the presence of 200 mg Ag^0/Fe^0 (Fig. 1A), 100 mg Ag^0/Fe^0 (Fig. 1B) or 100 mg Fe^0 (Fig. 1C) granules for up to 20 h were compared. In all cases, dechlorination reactions at 200 °C in this medium proceeded in stepwise fashion and none of the dechlorinations was complete in any of these timed trials. Monochloro species accumulated rapidly within the 200 mg trials (◆, Fig. 1A) and was virtually quantitative (>95%) within 3 h of reaction whereas the accumulation of monochloro analytes was somewhat slower for the treatments with 100 mg of the bimetallic mixture (Fig. 1B) and was maximized at 10 h. By contrast,

Table 1 Variations, with time or temperature, in the mean mol% distribution[a] of products for the dechlorination of 1.87 μmol PCP in the presence/absence of 50 mg of 2% (w/w) silver–iron bimetallic mixture (Ag^0/Fe^0) for 0.5–2 h at 200 °C or for 1 h at 200–350 °C

At 200 °C	Substrate	Tetra-Cl	Tri-Cl	Di-Cl	Mono-Cl	Phenol
PCP, no catalyst, 0.5 h	96	0.5	N.D.[b]	N.D.	N.D.	N.D.
Ag^0/Fe^0, 0.5 h (3 runs)	N.D.	4 ± 1	65 ± 3	27 ± 2	N.D.	N.D.
PCP, no catalyst, 1 h	78	17	3	N.D.	N.D.	N.D.
Ag^0/Fe^0,1 h (2 runs)	N.D.	N.D.	17 ± 1	59 ± 4	8 ± 2.0	3 ± 0.4
PCP, no catalyst, 1 h	77	17	4	N.D.[b]	N.D.	N.D.
Ag^0/Fe^0,1 h (2 runs)	N.D.	N.D.	19 ± 1	67 ± 4	9 ± 2	2 ± 0.4
PCP, no catalyst, 1.5 h	64	32	N.D.	N.D.	N.D.	N.D.
Ag^0/Fe^0, 1.5 h (3 runs)	N.D.	N.D.	1 ± 2	56 ± 2	32 ± 0.4	9 ± 0.5
PCP, no catalyst, 2 h	N.D.	40	54	N.D.	3	5
Ag^0/Fe^0, 2 h (3 runs)	N.D	N.D.	N.D.	42 ± 2	51 ± 2	1 ± 0.9
For 1 h	Substrate	Tetra-Cl	Tri-Cl	Di-Cl	Mono-Cl	Phenol
PCP, no catalyst, 200 °C	77	17	4	N.D.	N.D.	N.D.
Ag^0/Fe^0, 200 °C (2 runs)	N.D.	N.D.	22 ± 1	64 ± 4	9 ± 2	2 ± 0.4
PCP, no catalyst, 250 °C	66	5	15	N.D.	4	9
Ag^0/Fe^0, 250 °C (3 runs)	N.D.	3 ± 4	71 ± 5	17 ± 3	N.D.	N.D.
PCP, no catalyst, 300 °C	N.D.	1	33	1	3	52
Ag^0/Fe^0 1 h, 300 °C (3 runs)	N.D.	N.D.	7 ± 0.5	12 ± 0.1	12	48 ± 7
PCP, no catalyst, 350 °C	0.2	N.D.	0.2	2	32	46
Ag^0/Fe^0, 350 (3 runs)	N.D.	N.D.	N.D.	N.D.	10 ± 2	82 ± 2

[a] ± One relative standard deviation based on two or three replicate runs. [b] N.D. = none detected.

tetrachloro species (●, Fig. 1C) comprised >60% of the product mixture at 0.5 h for the Fe^0 accelerated reaction (Fig. 1C), but only traces of these compounds were observed in the 100 mg Ag^0/Fe^0mediated dechlorinations (Fig. 1B) and none was detected in 200 mg trials (Fig. 1A). Neither monochlorinated products nor phenol were detected in the Fe^0 catalysed dechlorinations but were the only components at later sampling times for the Ag^0/Fe^0 accelerated reaction. The fact that the Ag^0/Fe^0 mixture and Fe^0 continued to react after 5 and 10 h, respectively, seems to mitigate against complete accelerator inactivation at this time. It seems more likely that the rates of reaction for different substrates are appreciably different. Fig. 1 corroborates the observations of others[12] that the rates of zero-valent metal mediated dechlorinations are accelerated by the presence of multiple chlorine substituents.

Product speciation

Reaction at 200 °C in the absence of accelerator furnished only unreacted PCP after 2 h and a mixture of 2,3,4,5- and 2,3,5,6-tetrachlorophenol (10:1 ratio) and substrate (~50%) after 4 h of reaction. The dominant chloro-species that were accumulated with time in the iron-accelerated trials are summarised in Fig. 2. For short reaction periods (0.5–1.5 h) in the presence of Fe^0, one tetrachloro specie [2,3,4,5-tetrachlorophenol, (2,3,4,5-TeCP)] dominated the product distribution (~60% at 0.5 h). Two trichloro species [2,4,5- and 2,3,4-trichlorophenol (TCP)] were also present, in an approximate 2:1 ratio at the 0.5 h sampling time. Traces of 2,3,5-trichlorophenol were also observed and only at short reaction times. Whereas the quantity of 2,3,4-trichloro specie remained a minor component (~10%) of the product mixture, the 2,4,5-trichloro specie rapidly increased with time to dominate the mixture (~60%) at 3.5 h and only decreased gradually with longer reaction times to be replaced with 3,4-dichlorophenol (3,4-DCP). Post the initial *ortho*-dechlorination to form the 2,3,4,5- species, the second dechlorination occurred virtually exclusively at the *meta* position and resulted in the 2,4,5- and 2,3,4- species. The subsequent *o*-dechlorination resulted in the 3,4-dichloro product. One possible explanation for the selectivity might be that the interaction of the substrate PCP with the surface of the metal accelerator occurred predominantly *via* the π-electron system of the aromatic ring so that all the Cl substituents were accessible to the catalyst. The *ortho–para* directing character of the hydroxy substituent does not seem to explain the relatively high level of selectivity that is associated with the observed sequential dechlorination process. To the extent that aryl dechlorination is an electrophilic (E_1) process, dechlorination at the *o*- or *p*-positions would stabilize the intermediate cation and favour dechlorination at these sites. If resonance stabilization were the dominant influence the product distribution would be predicted to consist of 2,3,5-TCP, 2,3-DCP, 2,5-DCP and 3-MCP. As an alternative explanation,

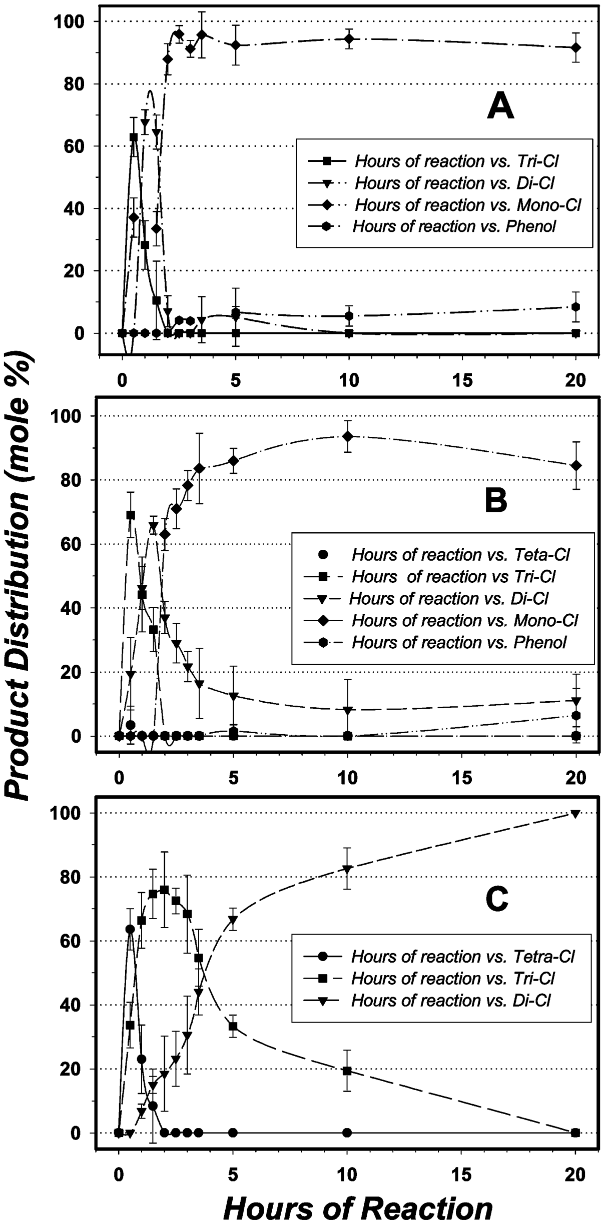

Fig. 1 Variations with time in the product distribution for the hydrolytic dechlorination of pentachlorophenol in the presence of A, 200 mg of Ag^0/Fe^0; B, 100 mg of Ag^0/Fe^0 or C, 100 mg of Fe^0.

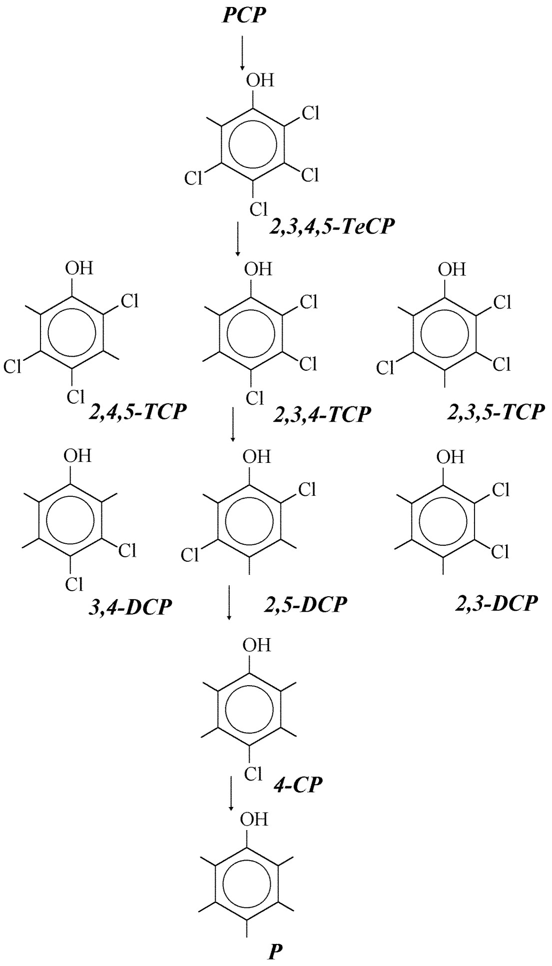

Fig. 2 Reaction pathway for the dechlorination of PCP mediated by Fe^0 or an Ag^0/Fe^0 bimetallic mixture.

the removal of bulky chlorine substituents from the ring would provide relief of steric strain. The initial loss of Cl from the C-2 or C-6 position (*ortho* to the hydroxy and a chlorine substituent) decreases steric strain and repulsion more than the loss of a *m*-Cl substituent. The loss of a second chlorine substituent occurs at a position with two nearest Cl neighbours and the loss of the third chlorine again occurs from the position that is *ortho* to the hydroxyl group.

For dechlorinations with an equivalent quantity (100 mg) of an Ag^0/Fe^0 mixture, only traces of 2,3,4,5-tetrachlorophenol were observed (0.5 h). Four trichlorophenols (2,3,4- and 2,4,5-) each accounted for ~20% and the 2,3,5- isomer accounted for ~10% of the products after 0.5 h of reaction. The 2,3,6- isomer was observed in only one of the replicate trials and only at the 0.5 h sampling time. Chlorinated phenols 2,3- (~8%) and 3,4-dichlorophenol (~25%) and 4-chlorophenol (~5%) accounted for the remainder of the products. Whereas trichloro species were absent at 2 h, the dichlorinated phenols persisted throughout much of the trial and the 4-chlorophenol dominated the products after 2 h. Phenol was only detected intermittently and only in the latter stages of the trial.

For reaction with 200 mg of 2% (w/w) Ag^0/Fe^0, (Table 2) lesser quantities of 2,4,5- (~28%), and traces of 2,3,5- (7%) and 2,3,4- (4%) were recovered from the reaction mixture at shorter reaction times (0.5 or 1 h). Dichlorinated species were more prevalent and more persistent with time. Small quantities of 2,3-dichloro (10%), and 2,5-dichloro (~10%) did not accumulate with time but the 3,4-dichloro species (initially ~40%) increased to 62% at 1.5 h then subsequently decreased gradually to 10% at 5 h. The only monochlorophenol to accumulate was the 4-chloro specie that had increased to 86% at 2.5 h and increased further to 92% at 20 h. The only other product detected at longer reaction times (>2 h) was phenol (3–8%). Seemingly, there was no appreciable difference in the course of the reaction for the Fe^0 and the 2% (w/w) Ag^0/Fe^0 bimetallic mixture but differences in the rates of dechlorination were clearly evident (Fig. 1).

Magnesium-based accelerators

Dechlorinations with magnesium-based accelerators were appreciably more extensive and more rapid. As with Fe^0, Mg^0 is known to hydrolyse water exothermically to form $Mg(OH)_2$ and H_2; a white powder was observed in all crude product mixtures but companion trials with the thermocouple did not detect any influence of the temperature of the reaction mixture on the dechlorinations. In the presence of excess K_2PdCl_6 (25 μmol), PCP (1.88 μmol) was dechlorinated quantitatively to phenol and cyclohexanol (Table 3). Increased quantities of Mg^0 (50 *vs.* 100 *vs.* 200 mg) in the reaction mixture favoured hydrogenation of the ring and subsequent reduction to cyclohexanol post dechlorination to phenol. However, the rates of formation of specific intermediates did not depend linearly as the quantity of added accelerator. By contrast, Mg^0 alone mediated only partial dechlorination to the 2,3,5,6- and 2,3,4,6-tetrachloro species and 2,3,4- and 2,3,5-trichlorophenol. A pre-formed bimetallic mixture (Pd^0/Mg^0) at 0.2% (w/w) loading or 2% (w/w) Ag^0/Mg^0 was less efficient than the co-addition of Mg^0 + K_2PdCl_6. Again, the extent of dechlorination was dependant on the

Table 2 Variations with time in the mean mol% distribution[a] for the dechlorination of pentachlorophenol (PCP, 1.87 μmol) at 200 °C, in the presence of 200 mg of a 2% (w/w) Ag^0/ Fe^0 bimetallic mixture

Time/h	2,3,4-TriCl	2,3,5-TriCl	2,4,5-TriCl	2,3-DiCl	2,5-DiCl	3,4-DiCl	4-Cl	Phenol
0.5	4 ± 1	7 ± 4	28 ± 11	10 ± 3	38 ± 7	6 ± 4	2 ± 3	N.D.[b]
1.0	2 ± 3	4 ± 4	21 ± 8	10 ± 10	22 ± 24	42 ± 21	N.D.	N.D.
1.5	N.D.	N.D.	8 ± 11	6 ± 8	13 ± 1	62 ± 13	12 ± 13	N.D.
2.0	N.D.	N.D.	N.D.	N.D.	N.D.	50 ± 7	50 ± 11	N.D.
2.5	N.D.	N.D.	N.D.	N.D.	5 ± 8	4 ± 8	86 ± 16	3 ± 2
3.0	N.D.	N.D.	N.D.	N.D.	8 ± 14	N.D.	90 ± 13	2 ± 4
3.5	N.D.	N.D.	N.D.	N.D.	N.D.	12 ± 17	82 ± 9	6 ± 9
5.0	N.D.	N.D.	N.D.	N.D.	N.D.	10 ± 9	82 ± 6	8 ± 3
10.0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	95 ± 3	5 ± 3
20.0	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	92 ± 5	8 ± 5

[a] ± One relative standard deviation based on two or three replicate runs. [b] N.D. = none detected.

Table 3 The mean mol% distribution[a] of products that resulted from 0.5–2 h of reaction, at 200 °C, of PCP (1.87 μmol) in the presence of magnesium-based accelerator

Treatment	PCP	Tetra-Cl[b]	Tri-Cl[c]	Di-Cl[d]	Mono-Cl[e]	Phenol	Cyclo-ol[f]	Cyclo-one[g]
50 mg Mg^0 + 25 μmol K_2PdCl_6, 1 h	N.D.	N.D.	N.D.	N.D.	N.D.	60 ± 6	40 ± 6	Trace
100 mg Mg^0 + 25 μmol K_2PdCl_6, 1 h	N.D.	N.D.	N.D.	N.D.	N.D.	15 ± 21	85 ± 21	N.D.
200 mg Mg^0 + 25 μmol K_2PdCl_6, 1 h	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	100	N.D.
50 mg Mg^0, 1 h	N.D.	69 ± 2	31 ± 0.1	N.D.	N.D.	N.D.	N.D.	N.D.
50 mg, Pd^0/Mg^0, (0.2% w/w), 1 h	N.D.	63 ± 2	21 ± 8	trace	4 ± 4	4 ± 5	N.D.	12 ± 4
100 mg, Pd^0/Mg^0, (0.2% w/w), 1 h	N.D.	13 ± 1	11 ± 1	4 ± 6	9 ± 2	38 ±1	N.D.	25 ± 5
50 mg Ag^0/Mg^0, (2% w/w), 1 h	16 ± 11	55 ± 4	26 ± 12	3 ± 4	N.D.	N.D.	N.D.	N.D.
100 mg Ag^0/Mg^0, (2% w/w) 1 h	N.D.	N.D.	7 ± 2	84 ± 4	7 ± 3	N.D.	N.D.	N.D.
25 mg Pd^0/Mg^0 (0.5% w/w), 0.5 h	10 ± 14	8 ± 2	2 ± 3	N.D.	1 ± 2	75 ± 35	N.D.	4 ± 5
50 mg Pd^o/Mg^o (0.5% w/w), 0.5 h	N.D.	N.D.	4 ± 5	N.D.	N.D.	83 ± 3	N.D.	12 ± 2
100 mg Pd^o/Mg^o (0.5% w/w), 0.5 h	N.D.	N.D.	N.D.	N.D.	1 ± 1	76 ± 5	N.D.	21 ± 4
25 mg Pd/Mg (0.5% w/w), 1 h	18 ± 23	36 ± 16	2 ± 2	Trace	3 ± 0.5	38 ± 5	N.D.	3 ± 0.5
50 mg Pd/Mg (0.5% w/w), 1 h	N.D.	0.3 ± 0.4	6 ± 8	N.D.	4 ±0.9	78 ± 5	N.D.	9 ± 2
100 mg Pd/Mg (0.5% w/w), 1 h	N.D.	N.D.	N.D.	N.D.	7 ± 7	86 ± 5	N.D.	8 ± 4
25 mg Pd^0/Mg^0 (0.5% w/w), 2 h	18 ± 23	36 ± 17	2 ± 2	Trace	3 ± 0.5	38 ± 5	N.D.	3 ± 0.5
50 mg Pd^0/Mg^0 (0.5% w/w), 2 h	N.D.	N.D.	N.D.	N.D.	6 ± 8	91 ± 13	N.D.	3 ± 5
100 mg Pd^0/Mg^0 (0.5% w/w), 2 h	N.D.	N.D.	N.D.	N.D.	N.D.	96 ± 6	N.D.	5 ± 7
50 mg Mg^0, 2 h	38 ± 9	52 ± 8	10 ± 14	N.D.	N.D.	N.D.	N.D.	N.D.

[a] ± One relative standard deviation based on two or three replicate runs. [b] 2,3,4,5-Tetrachlorophenol and 2,3,5,6-tetrachlorophenol. [c] 2,3,4-; 2,3,5- and 2,4,5-Trichlorophenol. [d] 2,3-; 2,5-; and 2,6-Dichlorophenol. [e] *o*-Chlorophenol and *p*-chlorophenol. [f] Cyclohexanol. [g] Cyclohexanone.

quantity of accelerator (50 *vs.* 100 mg) added to the reaction. For 50 mg Pd^0/Mg^0, 16% of the products were totally dechlorinated yet 63% were tetrachloro species indicating that this pre-formed accelerator mediated both concerted and stepwise dechlorinations. For 100 mg Pd^0/Mg^0, 63% of products consisted of phenol plus cyclohexanone and a further 9% was *o*-chloro phenol yet 13% were tetrachloro species. The Ag^0/Mg^0 bimetallic mixture, at 50 or 100 mg, proved to be less efficient than the Pd^0/Mg^0 mixture; only partial dechlorination was observed and this mixture was abandoned.

Increased reaction time (0.5 *vs.* 1.0 *vs.* 2.0 h) also increased the extent of dechlorination modestly however the effect was not monotonic. Substrate PCP was observed among the products at all three reaction times only for the 25 mg loading of 0.5% (w/w) accelerator. Increased loadings of accelerator were generally more efficient at mediating dechlorinations than extended reaction times.

Increased PCP loadings

In a final series of trials, 100 mg of Pd^0/Mg^0 were reacted with 5 mg (18.8 μmol) or 50 mg (187.7 μmol) of PCP for 1 h at 200 °C. In both cases, the principal product was phenol. Compared to the original PCP loading, phenol was found at 97 ± 10 mol% and 23 ± 1 mol% for low and high quantities of PCP, respectively. Additionally, several minor products were observed for both concentrations of PCP (Table 4). For 5 mg of substrate the products included cyclohexanone ($\sim$3 mol%), monochlorophenols ($\sim$4 mol%) represented mainly by *o*-Cl phenol, dichlorophenols ($\sim$2 mol%), trichlorophenols ($\sim$2 mol%), tetrachlorophenols ($\sim$3 mol%) and unreacted PCP ($\sim$4 mol%). Of the four dichlorophenols isomers, 2,3- and 3,4- were major products and only traces of 2,5- and 2,6-isomers were observed. For trichlorophenols, 2,3,4- and 2,3,5-isomers were major and traces of 2,3,6- and 2,4,5-isomers were observed. All three tetrachlorophenol isomers were observed with the 2,3,4,6-isomer as the most abundant. These distributions have been calculated relative to the 5 mg (18.8 μmol) of substrate PCP that were added to the reaction mixture. Thus, 111 ± 14 mol% of the substrate was accounted for among the products, 100 ± 12 mol% as non-chlorinated and a further 11 ± 2 mol% of partially dechlorinated materials.

At the higher substrate loading (187.7 μmol) the recovery of phenol (23 ± 1 mol%) was decreased; only an additional 14 ± 2 mol% of substrate was found in chlorinated materials, and the recovery of unreacted PCP was only 2 mol%. Lower recoveries for the higher loading might be explained by an exhausted accelerator and/or sorption of the substrate and products to the surface of the accelerator.

Efforts were also made to determine the chlorine balance at the termination of the Pd^0/Mg^0 trials at higher PCP loadings (5 or 50 mg). The crude reaction product mixtures were acidified with nitric acid) prior to extraction with organic solvent. The chlorine mass balance at the 5 mg substrate loading (Table 5) indicated incomplete release of chloride into the aqueous phase $\sim$20% and a further $\sim$5% was accounted for among the organochlorine products that had been quantified. It seems probable that at least a portion of the remainder consisted of smaller chlorinated fragments that were not extracted or detected by GC/MS. The highest substrate loading (187.7 μmol) proved to be similar. Again, $\sim$10% of the chlorine in the PCP substrate was detected as chloride and a further $\sim$10% was accounted for among the chlorinated organics fraction. Although strong acid has been employed for the extraction,[31] the recovery of chloride and/or of organochlorine products was insufficient to obtain mass balance for chlorine. In a companion trial, 5 mg (18.8 μmol) PCP was reacted with 100 mg of 325-mesh Fe^0. Despite a work up that included sufficient H$^+$ to solubilise the surfaces of the Fe^0 particles and to acidify the crude product mixture to pH $\sim$1, product recoveries were disappointingly low; only $\sim$12% of the chlorine was accounted for.

Table 4 Determinations of the mean[a] mol% recoveries of products post 1 h of reaction at 200 °C

Initial substrate loading	18.8 μmol	187.7 μmol
Cyclohexanone	3.2 ± 2.5	0.3 ± 0.2
Phenol	97 ± 10	23 ± 1
MCPs	3.8 ± 2.6	2.2 ± 0.5
DCPs	2.4 ± 2.1	4.2 ± 1.3
TCPs	1.6 ± 0.9	2.5 ± 1.0
TeCPs	2.9 ± 2.4	2.3 ± 2.4
Unreacted PCP	3.7 ± 3.4	2.3 ± 3.9

[a] Mean ± one relative standard deviation based on two or three replicate runs.

Table 5 Determinations of the mean[a] chlorine balance for zero-valent metal (100 mg) mediated dechlorinations with PCP (5 or 50 mg) substrate.

		Wt% of chlorine		
Accelerator/mg	Initial PCP mass[b]/mg	Cl$^-$ Ion	Organo-chlorine	PCP
Fe^0 (100 mg)	5	7 ± 2	6 ± 3	0
Pd^0/Mg^0 (50 mg)	5	20 ± 4	5 ± 4	0.1 ± 0.2
Pd^0/Mg^0 (100 mg)	5	21 ± 6	4 ± 2	3 ± 3
Pd^0/Mg^0 (50 mg)	50	10 ± 2	8 ± 5	2 ± 1
Pd^0/Mg^0 (100 mg)	50	11 ± 1	6 ± 2	5 ± 7

[a] ± One standard deviation based on three or four replicate determinations. [b] Reactions were performed for 1 h at 200 °C.

Mg^0-mediated dechlorinations

Mg^0-based accelerators followed a reaction course somewhat different from the Fe^0 mediated dechlorinations for which only stepwise dechlorinations had been observed. For bimetallic Pd^0/Mg^0, phenol was the major product yet with limited loadings of this accelerator, the other major products were tetrachloro species (Table 3). Based on the accumulation of limited quantities of partially dechlorinated compounds in the product mixture, Fig. 3 is proposed as a probable dechlorination scheme. All three tetrachloro species were present in a $\sim$2:1:1 ratio with the 2,3,4,6-isomer predominating. Two congeners dominated the trichloro fraction 2,3,5- and 2,4,5- ($\sim$5:4 ratio), two dichloro species (2,3- and 3,4- in approximately equal concentrations) dominated the dichloro fraction and two monochlorophenols *ortho* and *para* were present among the products in a $\sim$2:1 ratio. In addition to the dechlorination products isolated from Fe^0-mediated dechlorinations (Fig. 2), the remaining chlorinated products are similar to the distribution of products reported by Shin and Keane[23] (labelled with an * in Fig. 3) that included 2,3,5-TCP, 2,4,5-TCP and 2,5-DCP over Ni/zeolite and 2,3-DCP and 2-CP (but not 3,5-DCP) over Ni/SiO$_2$. Small quantities of cyclohexanone also accumulated in the presence of the pre-formed bimetallic mixture whereas a larger excess of K$_2$PdCl$_6$ together with Mg^0 resulted only in cyclohexanol. Mg^0 or Ag^0/Mg^0 were less efficient accelerators and caused only limited dechlorination. Although reaction conditions remain to be optimised, the results with Pd^0/Mg^0 in these trials are encouraging. Dechlorination in this case represents a detoxification in which the toxiforic chloro substituents of the substrate are reduced to innocuous chloride while the sacrificial Mg metal is oxidised to Mg^{2+}. The released Mg^{2+} ion is also considered to be innocuous. The reaction is

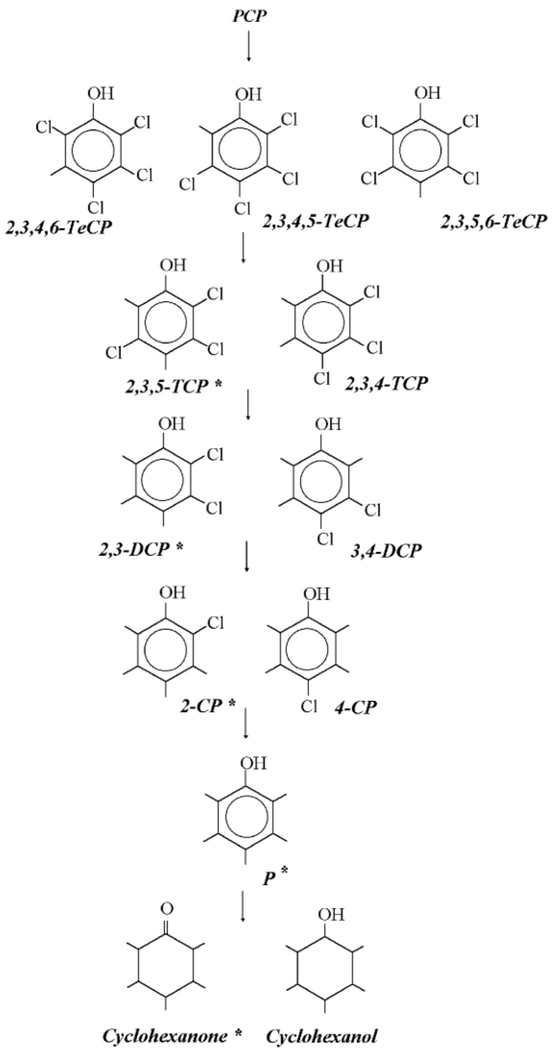

Fig. 3 Reaction pathway for the dechlorination of PCP mediated by Mg^0 or Pd^0/Mg^0 bimetallic mixture.

rapid and extensive at relatively low temperature and there does not appear to be any reason why other reducible substituents including other halogens or aryl-nitro group would not be behave similarly.

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Quaternary ammonium zinc- or tin-containing ionic liquids: water insensitive, recyclable catalysts for Diels–Alder reactions

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Synthetically important Diels–Alder reactions occur in high yield in novel Lewis acidic ambient temperature ionic liquids composed of choline chloride–MCl_2 (1:2) (M = Zn or Sn). The liquids are not moisture-sensitive and after separation of the products they can be reused with no noticeable drop in activity.

Introduction

In the search for cleaner technologies for chemical synthesis finding alternatives to toxic, volatile organic solvents is a particularly important goal. Room temperature ionic liquids have a number of properties which make them suitable alternatives to conventional solvents. They have very low vapour pressure and hence produce virtually no hazardous vapours; in addition they are non-explosive and thermally stable providing a relatively wide liquid range. Their polar nature means they are often immiscible with organic solvents and may therefore be used in biphasic systems. In principle this provides an easy separation of products from metal-containing catalysts and allows easy recycling of the ionic liquid phase for reuse of solvent and catalyst. The use of room temperature ionic liquids as solvents for synthesis and catalysis has recently been reviewed.[1]

Diels–Alder reactions are some of the most useful carbon–carbon bond forming reactions in organic chemistry[2] being used in the synthesis of many natural products and physiologically active molecules. Solvent effects on the rate and selectivity of Diels–Alder reactions are well established, notably use of water as a solvent leads to dramatic enhancements of rate and stereoselectivity.[3] Ionic liquids have also been used as solvents and as Lewis acid catalysts for Diels–Alder reactions. For example, the reaction between cyclopentadiene and ethyl or methyl acrylate gave a mixture of *endo* and *exo* products in a ratio of 6.7 : 1 in $[EtNH_3][NO_3]$.[4] The same reactions have been studied in a number of 1-alkyl-3-methylimidazolium salts (alkyl = Et or Bu) with rate and selectivity being dependent on the anion chosen with *endo* : *exo* selectivity up to 8 : 1 in the best case.[5] Chloroaluminate ionic liquids have been reported as both solvent and Lewis acid catalyst for Diels–Alder reactions.[6] Thus, cyclopentadiene and methyl acrylate reacted to give *endo* and *exo* cycloadducts in greater than 79% combined yield; the rate and *endo* : *exo* selectivity was dependent on the Lewis acidity of the ionic liquid. However, these ionic liquids are extremely sensitive to water and are corrosive to many materials because of the presence of aluminium chloride. Dialkylimidazolium bromide and trifluoroacetate are reported to catalyse Diels–Alder reactions of cyclopentadiene, however, the yields were rather low due to the weak Lewis acidity of the cations.[7]

We have now found that the combination of MCl_2 (M = Zn or Sn) with choline chloride, or related ammonium salts in a 2 : 1 ratio leads to a range of ionic liquids of different melting points and viscosities.[8] These are water insensitive, non-corrosive to steel, and have a wide range of applications,[9] for example electrochemical metal deposition, as solvents, and in certain cases as catalysts. In addition, they are relatively inexpensive compared with the imidazolium based ionic liquids. We report here the use of these choline chloride–MCl_2 (M = Zn or Sn) ionic liquids as solvents and catalysts for a number of Diels–Alder reactions and investigate the ease of separation of the products, reuse of the liquids and the effect of water on the reactions.

Results and discussion

The Diels–Alder reactions of a number of dienes (**1**) and dienophiles (**2**) were attempted using the choline chloride–MCl_2 (1 : 2) (M = Zn or Sn) ionic liquids as both solvent and catalyst and the results are shown in Table 1. In all cases isolated yields of about 90% or greater were obtained. Thus, 2,3-dimethylbutadiene (**1a**) reacts with acrolein (**2a**), methyl vinyl ketone (**2b**), or methacrolein (**2c**) in the zinc-containing ionic liquid (Table 1, entries 1, 3 and 4) to give products **3a–c**, respectively, which exist as single isomers. The reactions occur in 2 , 1 h and 5 h, respectively, whereas the uncatalysed reactions are reported to take at least 1000 times longer.[10] Isoprene (**1b**) reacts similarly with acrolein (entry 6) to give a 95:5 mixture of **4a** : **4b**. Cyclohexadiene (**1c**) reacts with acrolein, and cyclopentadiene (**1d**) reacts with methyl vinyl ketone or methyl acrylate (entries 7, 8 and 10) to give the corresponding Diels–Alder adducts **5**, **6a** and **6b**, respectively, with very high *endo* selectivity, typical of Lewis acid catalysed

Green Context

There is considerable interest in using ionic liquids as solvents and catalysts for organic reactions that normally require acid catalysts. Thus it is known that these are suitable media for Diels–Alder reactions but problems remain, notably moisture sensitivity, high cost and difficult extraction procedures. Here relatively inexpensive and water-insensitive ionic liquids with good activity in Diels–Alder reactions are described. ***JHC***

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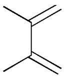
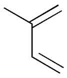
Table 1 Diels–Alder reactions in choline chloride–MCl_2 (1:2) ionic liquids[a]

Entry	Diene	Dienophile	Product	Ratio[c]	M	Time	Yield (%)
1	**1a**	**2a**	**3a**	—	Zn	2 h	91
2[b]	**1a**	**2a**	**3a**	—	Zn	2 h	91
3	**1a**	**2b**	**3b**	—	Zn	1 h	89
4	**1a**	**2c**	**3c**	—	Zn	5 h	91
5[b]	**1a**	**2c**	**3c**	—	Zn	5 h	91
6	**1b**	**2a**	**4ab**	95:5[d]	Zn	55 min	90
7	**1c**	**2a**	**5**	97:3	Zn	2 h	90
8	**1d**	**2b**	**6a**	96:4	Zn	8 min	94
9[b]	**1d**	**2b**	**6a**	92:8	Zn	8 min	86
10	**1d**	**2d**	**6b**	83:17	Zn	30 min	89
11	**1a**	**2a**	**3a**	—	Sn	20 h	85
12[b]	**1a**	**2a**	**3a**	—	Sn	20 h	89
13[b]	**1b**	**2a**	**4ab**	95:5[d]	Sn	24 h	88

[a] Reactions carried out at ambient temperature. [b] Reactions carried out in the presence of an equivalent amount of water to metal. [c] Refers to *endo*:*exo* ratio. [d] Refers to the ratio of **4a**:**4b**.

reactions. This indicates that the ionic liquid is acting as a catalyst and not just as a polar medium.


1a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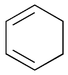
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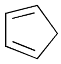
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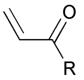
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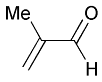
2b, R = Me
2d, R = OMe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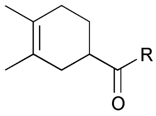
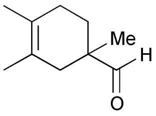
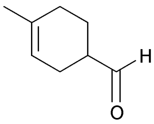
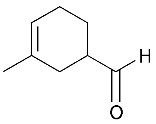

3a, R = H
3b, R = Me


3c


4a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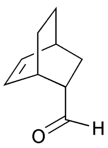
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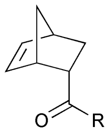
6a, R = Me
6b, R = OMe

The reactions catalysed by the zinc-containing ionic liquids are two phase reactions; the dienophile dissolves in the ionic liquid, however, the less polar diene forms a separate phase. At the end of the reaction the product also forms a separate phase on top of the ionic liquid and is therefore easily separated by decanting or removing by pipette; washing with a small amount of hexane, which then allows reuse of the ionic liquid catalyst. For example the reaction between **1a** and **2b** could be repeated at least five times with no noticeable drop in activity or yield.[11]

The use of heterogeneous zinc-containing catalysts for Diels–Alder reactions has been described. Cyclopentadiene and methyl vinyl ketone gave cyclo-adduct **6a** with high *endo* selectivity in 80 or 84% yield in the presence of Zn^{2+} ion-exchanged Zn^{2+}–K10 or Zn^{2+}–AlMCM-41, respectively, at 0 °C in 2 h.[12] In the zinc-containing ionic liquid, **6a** was formed in 94% yield and 96:4 *endo*:*exo* selectivity at room temperature in 8 min (entry 8). Similar results were found using 5 mol% ZnI_2 dissolved in a dialkylimidazolium ionic liquid,[5b] emphasising that the increased rate and selectivity are primarily due to the Lewis acidic zinc.

Since the reactions were biphasic and the ionic liquid is rather viscous at room temperature mechanical stirring was required to improve mass transport. Performing the reactions in an ultrasonic bath gave very similar results though no attempt was made to optimise the irradiation in the ultrasonic bath.

To show that the zinc-containing ionic liquid is unreactive to water some reactions were repeated in the presence of water. For example, the reaction between 2,3-dimethylbutadiene and acrolein in a mixture of zinc chloride–choline chloride–water (2:1:2 ratio) gave **3a** in 91% yield at room temperature in 2 h (entry 2) *i.e.* the same as in the anhydrous melt (entry 1) (compare also entries 4 and 5, 8 and 9). The most noticeable effect of the added water is to reduce the viscosity of the ionic liquid hence these reactions can be stirred magnetically. These results also suggest that traces of moisture absorbed by the hygroscopic ionic liquids should not affect their activity as Lewis acid catalysts for Diels–Alder reactions.

Having established catalytic activity with the zinc-containing ionic liquid we tested the less Lewis acidic tin-containing liquid. Reaction of **1a** with **2a** gave **3a** in 85% yield after 24 h (entry 11), hence the catalytic activity is somewhat less than for zinc for which the corresponding reaction took 2 h (entry 1). Similarly, reaction between **1b** and **2a** gave **4a** and **4b** in a 95:5 ratio and 88% combined yield (entry 13) almost identical to the result in the zinc-containing liquid (entry 6) though at a slower rate. As in the case of zinc, the reactions in the tin-containing liquid can be carried out in the presence of added water with no significant effect on the course of the reaction (compare entries 11 and 12).

Conclusion

We have demonstrated that the ionic liquids formed from choline chloride and MX_2 (M = Zn or Sn) in 1:2 ratio are effective media for some Diels–Alder reactions. In these cases the primary accelerating effect of the ionic liquids is due to their Lewis acidity. The liquid products are easily separated from the ionic liquid by decantation and washing with hexane, hence the liquids are easily recycled and can be reused at least five times. The liquids are not moisture sensitive which means that no specialist apparatus is required for their synthesis or use and aqueous work-up can be used if necessary. Further experiments to probe the effect of differently functionalised ammonium cations on catalysis and whether such groups survive recycling are under way.[11]

Experimental

General procedure for Diels–Alder reactions

A mixture of diene (12 mmol) and dienophile (12 mmol) in zinc chloride–choline chloride (2:1) (0.5 ml) ionic liquid was stirred mechanically (reaction time as given). Then the pure cyclo-adduct was pipetted off the top of the ionic liquid and the ionic liquid was washed with hexane (2 ml). For most of the reactions purification was not necessary and the products were analysed by ^1H NMR spectroscopy (**3a–c**) or gas chromatography (**4–6**), however, where appropriate, flash column chromatography was used for further purification. Ultrasound promoted reactions were carried out in a decon-FS100b bath.

Acknowledgement

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11 After use, if the ionic liquid is left for a prolonged period (a week or more) it becomes yellow which may be due to impurities left after the reaction. Mass spectrometric analysis of the ionic liquid after recycling suggests that the alcohol side chain of some of the ammonium cations may have reacted with the carbonyl starting material.

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A highly stereoselective synthesis of β-olivosides by glycosidations of 2-iodo-olivosyl fluoride using montmorillonite K-10 as an environmentally benign solid acid

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The novel and highly β-stereoselective glycosidations of a 2-iodo-olivosyl fluoride and alcohols using a heterogeneous and environmentally benign solid acid, montmorillonite K-10, have been developed to afford the corresponding 2-iodo-β-olivosides in high yields with high stereoselectivities.

Introduction

Highly effective, simple and environmentally benign glycosidations have attracted considerable attention in current synthetic organic chemistry related to both biomolecules and functional materials.[1] In this context, some of the challenges for the greening of the chemical glycosidations may include the use of a heterogeneous and reusable solid acid as the activator.[2] On the other hand, deoxy sugars frequently appear in the sugar components of bioactive substances.[3,4] Among them, olivoside, a typical 2-deoxy (2,6-dideoxy) glycoside, is one of the most common and important, and found in many biologically important natural products such as aureolic acids, angucyclines, avilamycins, concanamycins, venturicidins, *etc*.[3,4] However, the β-stereoselective glycosidation of 2-deoxy sugars has proved particularly difficult to achieve due to the anomeric effect and the lack of stereodirecting anchimeric assistance from the C-2 position.[1c,5,6] The most extensively developed strategy for the synthesis of 2-deoxy-β-glycosides utilizes donors with equatorial C-2 heteroatom substituents that are easily and reductively removed after the glycosidation event. However, most of these methods use a homogeneous Lewis acid as the activator which contaminates the reaction solvent and can not be reused. Furthermore, these homogeneous Lewis acids are volatile, corrosive and have an odor. In contrast, heterogeneous catalysts are easily handled due to their nonvolatile, noncorrosive and odorless properties.

We now report the new and highly stereoselective synthesis of β-olivosides by the glycosidations of 2-iodo-olivosyl fluoride and alcohols using a heterogeneous and environmentally friendly solid acid, montmorillonite K-10, as illustrated in Fig. 1.

Results and discussion

During our initial attempts of searching for a new activator, we examined the glycosidations of the 3,4-di-*O*-acetyl-2-iodo-β-D-olivosyl fluoride (**1**)[7,8] and cyclohexylmethanol (**2**) in CH_2Cl_2 using several heterogeneous solid acids such as montmorillonite K-10 (K-10),[9] Nafion-H®[10] and SO_4/ZrO_2,[11] all of which could be recovered from the reaction mixture by simple filtration and then reused. These results are summarized in Table 1. It was found that montmorillonite K-10, Nafion-H® and SO_4/ZrO_2 could activate the anomeric C–F bond of **1**,[12] and that montmorillonite K-10 was superior to the other solid acids with respect to both the chemical yield and stereoselectivity to give the corresponding 2-iodo-β-olivoside in moderate yield (entries 1–3 in Table 1).† Our attention next turned to the solvent and the dehydrating agent effect in this glycosidation. Therefore, we tested the glycosidations of **1** and **2** using montmorillonite K-10 in several solvents, CH_2Cl_2, CH_3CN or Et_2O, in the presence or absence of molecular sieves 5A (MS 5A).[13] Although CH_3CN was found to be superior to CH_2Cl_2 and Et_2O in the absence of MS 5A, a considerable amount of the corresponding 1-hydroxyolivose was generated as a result of the hydrolysis of **1** (entry 5 in Table 1). On the other hand, the glycosidation was best affected in the presence of MS 5A in CH_2Cl_2 (entry 6 in Table 1). Surprisingly, the glycosidations in the presence of MS 5A in

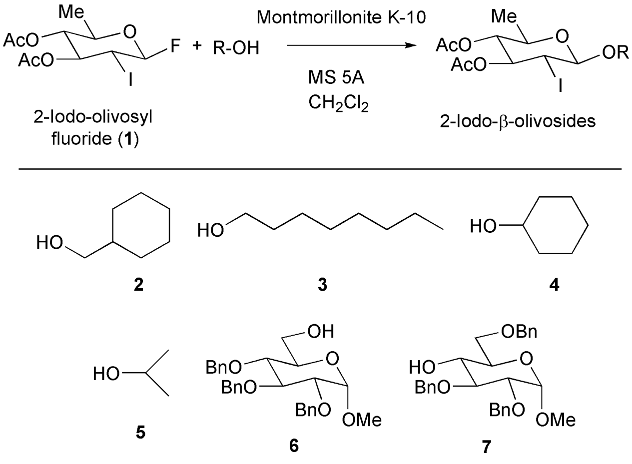


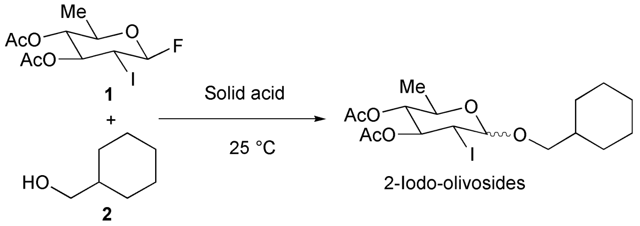
Fig. 1

Green Context

β-Olivosides are representative of a versatile class of compounds with applications in biological systems, and in materials chemistry. Synthesis of these by displacement of a fluoride leaving group by an incoming alcohol has been found to proceed very well in the presence of a cheap and simple clay catalyst. The reaction requires the presence of molecular sieves to avoid hydrolysis. Solvent effects on the reaction are dificult to understand, and currently the best system involves dichloromethane. *DJM*

DOI: 10.1039/b109172g

Table 1 Glycosidations of **1** and **2** by solid acids under several conditions[a]



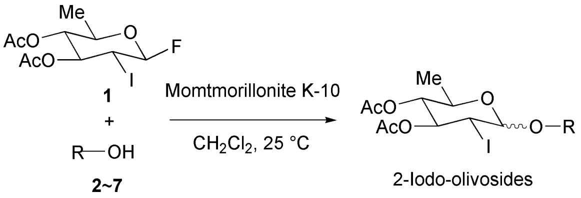
Entry	Solid acid (wt%)	MS (wt%)	Solvent	Time/h	Yield (%)[b]	α/β Ratio[c]
1	Nafion-H® (20)	—	CH_2Cl_2	5	56	10:90
2	SO_4/ZrO_2 (20)	—	CH_2Cl_2	5	19	10:90
3	K-10 (20)	—	CH_2Cl_2	5	65	5:95
4	K-10 (20)	—	Et_2O	5	11	31:69
5	K-10 (20)	—	MeCN	5	88	10:90
6	K-10 (20)	MS 5A (100)	CH_2Cl_2	5	90	8:92
7	K-10 (20)	MS 5A (100)	Et_2O	5	0	—
8	K-10 (20)	MS 5A (100)	MeCN	5	0	—
9	K-10 (50)	MS 5A (100)	CH_2Cl_2	5	93	9:91
10	K-10 (100)	MS 5A (100)	CH_2Cl_2	5	98	8:92
11	K-10 (50)	MS 5A (50)	CH_2Cl_2	20	95	9:91

[a] All reactions were carried out by use of 2.0 equiv. of **2** to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers. K-10: montmorillonite K-10.

CH_3CN and Et_2O did not proceed at all (entries 7 and 8 in Table 1). Furthermore, the use of 100 wt% montmorillonite K-10 and 100 wt% MS 5A significantly increased the chemical yield (entry 10 in Table 1). Thus, the glycosidation of **1** and **2** using 100 wt% montmorillonite K-10 in the presence of 100 wt% MS 5A in CH_2Cl_2 at 25 °C for 5 h proceeded effectively to afford the corresponding 2-iodo-olivoside, the precursor of olivoside, in 98% yield with 92:8 β-stereoselectivity. In addition, when half the amounts of montmorillonite K-10 and MS 5A were employed, a longer reaction time gave a similar result (entry 11 in Table 1). Thus, the glycosidation of **1** and **2** using 50 wt% montmorillonite K-10 in the presence of 50 wt% MS 5A in CH_2Cl_2 at 25 °C for 20 h yielded the corresponding 2-iodo-olivoside in 95% yield with 91:9 β-stereoselectivity.

To enhance the synthetic utility of this novel and simple reaction, glycosidations using other primary and secondary alcohols **3–7** were next examined. Based on the results shown in Table 2, all the glycosidations of **1** and **3–7**, as well as that of **2**, effectively proceeded under similar conditions to give the corresponding 2-iodo-β-olivosides in high yields with good to high stereoselectivities. It was noted that even the hindered carbohydrate glycosyl acceptor **7** smoothly reacted with **1** to produce the corresponding disaccharide in high yield with good β-stereoselectivity. Furthermore, a low reaction temperature was not required for obtaining good to high β-stereoselectivities. It was also confirmed that no epimerization at the anomeric center occurred during the glycosidation due to the mild reaction conditions. Finally, we tested the catalyst recycling. After filtration, washing with methanol and heating at 100 °C/1 mmHg for 12 h, a mixture of montmorillonite K-10 and MS 5A was reused two times showing moderate yields. Since the ease and effective conversion of the 2-iodo substituent in the glycosides into hydrogen using H_2 in the presence of Pd-C or Bu_3SnH is well known,[1c,5,6,8] the present novel method provides a significantly new way to stereoselectively synthesize β-olivosides.

Table 2 β-Stereoselective glycosidations of **1** and several alcohols[a]



Entry	Alcohol (ROH)	Wt% of K-10	Wt% of MS 5A	Time/h	Yield (%)[b]	α/β Ratio[c]
1	**2**	100	100	5	98	8:92
2	**2**	50	50	20	95	9:91
3	**3**	100	100	5	95	8:92
4	**3**	50	50	20	93	9:91
5	**4**	100	100	5	98	7:93
6	**4**	50	50	20	97	7:93
7	**5**	100	100	5	86	9:91
8	**5**	50	50	20	97	9:91
9	**6**	100	100	5	93	17:83
10	**6**	50	50	20	90	18:82
11	**7**	100	100	5	88	19:81
12	**7**	50	50	20	88	17:83

[a] All reactions were carried out by use of 2.0 equiv. of the alcohol to **1**. [b] Isolated yields after purification by column chromatography. [c] α:β Ratios were determined by ^1H NMR (270 MHz) spectroscopy and/or isolation of pure isomers.

Conclusions

In conclusion, we have presented a new and highly stereoselective synthesis of β-olivosides by the glycosidations of 2-iodo-olivosyl fluoride and alcohols using a heterogeneous and environmentally acceptable solid acid, montmorillonite K-10. The results including the simple and environmentally friendly protocol, high yield and stereoselectivity should find widespread application for the synthesis of biologically important natural products which possess β-olivoside as a sugar component.

Experimental

Typical procedure

To a stirred solution of 3,4-di-*O*-acetyl-2-iodo-β-D-olivosyl fluoride (**1**) (0.5 mmol) and an alcohol (1.0 mmol) in dry CH_2Cl_2 (5.0 ml) were added MS 5A (100 wt% to the glycosyl donor **1**) and montmorillonite K-10 (100 wt% to the glycosyl donor **1**). After stirring at 25 °C for 5 h, the mixture was filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the corresponding 2-iodo-olivosides which predominately contained the β-anomer. All 2-iodo-olivosides were purified by silica gel column chromatography and were fully characterized by spectroscopic means. The configurations of the anomeric centers were clearly confirmed by the coupling constants between H-1 and H-2 in the ^{1}H NMR analyses.

Acknowledgments

We thank the New Energy and Industrial Technology Development Organization (NEDO) and the Research Institute of Innovative Technology for the Earth (RITE) for financial support.

Notes and references

† Taking into account of the surface areas of the used montmorillonite K-10 and Nafion-H®, the activity of montmorillonite K-10 as an acid is comparable to that of Nafion-H®.

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7 2-Iodo-olivosyl fluoride (**1**) was stereoselectively prepared from 2-iodo-olivosyl acetate in two steps in 63% overall yield (i, NH_2NH_2 (aq.), MeOH–Et_2O, 25 °C, 0.5 h; ii. DAST, THF, −30 to 0 °C, 0.5 h). Also see ref. 8(a).

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9 Montmorillonite K-10 was purchased from Aldrich Chemical Company, Inc. and dried at 200 °C/1 mmHg for 12 h before use.

10 Nafion-H® was purchased from Wako Pure Chemical Industries, Ltd. as Nafion® NR-50 and dried at 25 °C/1 mmHg for 2 h before use.

11 SO_4/ZrO_2 was purchased from Wako Pure Chemical Industries, Ltd. and dried at 200 °C/1 mmHg for 12 h before use.

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13 We and the group of Mukaiyama found that MS 5A is superior to other MS such as MS 3A and MS 4A in glycosidations using a protic acid, see: refs. 2(f) and 12(b).

A green chemical method for the direct conversion of alcohol tetrahydropyranyl ethers into the corresponding acetates

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Alcohol tetrahydropyranyl ethers are readily converted into the corresponding acetates by the reaction with acetyl bromide in acetonitrile. Using various substituted acetyl chlorides with an equimolar amount of sodium iodide, tetrahydropyranyl ethers can be also transformed into the corresponding substituted acetates in high yields. This clean synthesis is a significant method for atom economy.

Introduction

A great number of protecting groups for the hydroxy function have been extensively explored in organic synthesis[1] and in these methods, acetates and substituted acetates are widely used as well as other type protecting groups, such as silyl ether, acetal, and alkyl ether types. In a series of studies[2] on the direct transformation of a protecting group of the hydroxy function into another, we have demonstrated that silyl ether, and alkyl ether protecting groups for hydroxy functions can be efficiently converted into the corresponding acetates in good yields under the influence of tin(II) bromide and acetyl bromide in dichloromethane.[3] These results suggested a one-step transformation of alcohol THP ethers into acetates. Some useful direct transformations into acetates from tetrahydropyranyl ethers under various reaction conditions, including acidic and basic conditions were reported.[4] We considered that a catalyst-free transformation that can be carried out stoichiometrically is very important as an environmentally benign reaction.

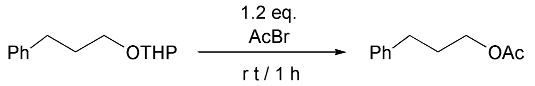
In this communication, we wish to report a novel and highly efficient and convenient method for the direct conversion of tetrahydropyranyl ethers into the corresponding acetates or substituted acetates in a one-pot procedure.

Results and discussion

Initially, we examined the reaction of the THP ether of 3-phenylpropanol with acetyl chloride in acetonitrile at room temperature. After the reaction mixture was stirred for 3 h at this temperature, usual work-up afforded 3-phenylpropyl acetate in 6% yield (Table 1, entry 1). On the other hand, when using acetyl bromide instead of acetyl chloride, the yield of the corresponding acetate improved dramatically (Table 1, entry 2). Therefore, we used acetyl bromide as the acyl halide. After a screening of various solvents, we found that acetonitrile as a solvent gave the desired acetate in the highest yield (entries 2–6).

Representative examples of this direct conversion of various alcohol THP ethers into the corresponding acetates are collected in Table 2. THP ethers of primary and secondary alcohols were transformed into the corresponding acetates in excellent yields (entries 1–5). In the case of the THP ether substrates having other functional groups such as a benzoate and benzyl ether, the THP ether moieties were transformed into the corresponding acetates selectively (entries 6 and 7). The bis-THP ether of an aliphatic 1,6-diol was readily converted into the corresponding bis-acetate in 98% yield (entry 8). Furthermore, phenolic THP ethers were also successfully transformed into the corresponding acetates in good yields (entries 9 and 10).

Table 1 The effect of solvent on the reaction of the THP ether of 3-phenylpropanol with acetyl chloride



Entry	Solvent	Yield[a] (%)
1	CH_3CN	6[b]
2	CH_3CN	99
3	CH_3CH_2CN	96
4	CH_3NO_2	97
5	$CH_3CO_2C_2H_5$	63
6	CH_2Cl_2	91

[a] Isolated yield of purified product. [b] AcCl was used and reacted for 3 h.

In order to explore the generality and scope of this reaction, we examined a reaction of the THP ether of 3-phenylpropanol with acetyl chloride. As mentioned above, when a reaction was performed with only acetyl chloride, the desired acetate was hardly obtained (Table 3, entry 1), while the yield was improved when sodium bromide or sodium iodide was used as an additive as shown in Table 3. It was found that an equimolar amount of sodium iodide was an excellent promoter in this one-step conversion into acetate, and that the corresponding acetate was obtained in 91% yield (entry 5). Next, we examined the reaction of the THP ether of 3-phenylpropanol with various substituted acetyl chlorides in the presence of an equimolar amount of sodium iodide. Successful results are shown in Table 4. Various

Green Context

While Green Chemistry teaches us to avoid protecting groups whenever possible, they remain important in many areas of organic synthesis. It is important therefore that we develop the most efficient and low-waste methods for protection and de-protection. Here the direct conversion of tetrahydropyranyl ethers to the corresponding acetates in one pot is described. No catalyst is required. The methodology is simple and inexpensive, operated under mild conditions and is very atom efficient. *JHC*

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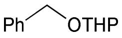
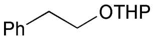
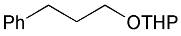
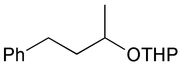
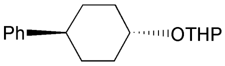
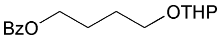
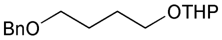
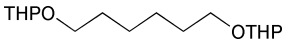
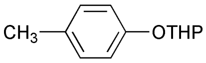
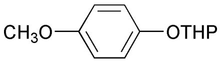
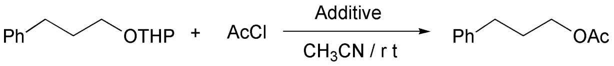
Table 2 Synthesis of various acetates from THP ethers

$$\mathrm{ROTHP} \xrightarrow[\mathrm{CH_3CN\,/\,r\,t\,/\,1\,h}]{\mathrm{AcBr}} \mathrm{ROAc}$$

Entry	ROTHP	Yield[a] (%)
1		91
2		92
3		99
4		95
5		98
6		99
7		90[b]
8		98[c]
9		85
10		85

[a] Isolated yield of purified product. [b] Reaction was carried out at 0 °C. [c] 2.4 equiv. of AcBr was used.

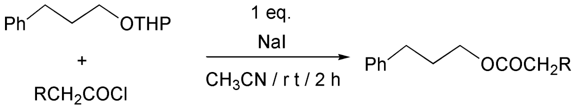
Table 3 The effect of additive on the reaction of the THP ether of 3-phenylpropanol with acetyl chloride



Entry	Additive (mol%)	Time/h	Yield[a] (%)
1	None	3	6
2	NaBr (100)	2	85
3	NaI (10)	3	75
4	NaI (50)	3	83
5	NaI (100)	2	91

[a] Isolated yield of purified product.

Table 4 Synthesis of substituted acetates from THP ethers



Entry	RCH_2COCl	Yield[a] (%)
1	CH_3COCl	91
2	$PhCH_2COCl$	97
3	$(CH_3)_3CCOCl$	92
4	$MeOCH_2COCl$	94
5	$PhOCH_2COCl$	92

[a] Isolated yield of purified product.

substituted acetyl chlorides tested worked well to afford the desired substituted acetates in high yields.

In summary, we have described a novel direct conversion of alcohol THP ethers into the corresponding acetates using only acetyl bromide without catalyst. In addition, THP ethers were readily converted into the corresponding substituted acetates in the presence of an equimolar amount of sodium iodide. Although the reaction with only acetyl chloride scarcely proceeded, we found that the corresponding acetate was obtained in good yields in the presence of an equimolar amount of sodium iodide. Hence THP ethers were readily converted into the corresponding substituted acetats. The procedure can be performed without any difficulty employing readily available chemicals, and the reaction proceeded smoothly at room temperature under very mild reaction conditions. Moreover, because the reagent is almost completely consumed, the reaction is expected to be extremely effective from the viewpoint of atom economy.

Experimental

Typical procedure for the direct conversion of alcohol THP ethers into the corresponding acetates

1-Tetrahydropyranyloxy-3-phenylpropane (66.8 mg, 0.30 mmol) was added to acetyl bromide (44.3 mg 0.36 mmol) in CH_3CN (1 ml) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature and quenched with phosphate buffer (pH 7). The organic materials were extracted with Et_2O and dried over anhydrous magnesium sulfate. The solvent was evaporated and 3-phenylpropyl acetate (52.9 mg, 99%) was isolated by thin-layer chromatography on silica gel (diethyl ether–hexane = 1:3). The product gave satisfactory ^1H NMR and IR spectra. IR: 3025, 2950, 1740, 1365, 1240, 1035, 745, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.96 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.69 (t, 2H, J 7.6 Hz, CH_2), 4.09 (t, 2H, J 6.4 Hz, CH_2), 7.17–7.31 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 20.95 (CH_3), 30.15 (CH_2), 32.16 (CH_2), 63.83 (CH_2), 125.98 (Ph), 128.37 (Ph), 128.42 (Ph), 141.18 (Ph), 171.16 (C=O).

Acknowledgements

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Transesterification of β-ketoesters with alcohols catalyzed by montmorillonite K-10

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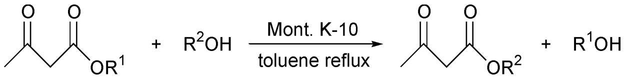
Montmorillonite K-10 is an efficient reusable catalyst for the transesterification of ethyl/methyl β-ketoesters with various alcohols in good yields. The main advantages of the catalyst are easy operation in the workup and a more economical and environmentally benign procedure.

Introduction

Transesterification is one of the established organic reactions that command numerous laboratory uses and industrial applications.[1,2] β-Ketoesters are of interest as chemical intermediates in the pharmaceutical, agrichemical, chemical and polymer industries.[3] Thus, a number of procedures for transesterification have been reported, which are catalyzed by a variety of protic or Lewis acids, organic or inorganic bases, enzymes or antibodies. However, it is well known that traditional acidic catalysts such as sulfuric acid, phosphoric acid and hydrochloric acid can cause severe environmental problems.[2] In addition most of the normal catalysts are not efficient for the transesterification of β-ketoesters so that various other catalysts have been applied to the reaction. Transesterification of β-ketoesters is catalyzed by DMAP[4] in good yield, but the application of this catalyst is limited owing to its toxicity, high price and requirement for high temperature. An efficient method of transesterification employing *tert*-butyl acetoacetate has been reported, but is restricted to *tert*-butyl esters, thus lacking generality.[5] Some other catalysts have been documented, such as sulfated tin oxide,[6] zeolites,[7] kaolinitic clay,[8] Mo-ZrO_2,[9] $FeSO_4$ and $CuSO_4$,[10] an yttria–zirconia based strong Lewis acid[11] and Envirocat EPZG^R.[12] However, they are not very satisfactory due to some drawbacks such as tedious workup, low selectivity, long reaction time, corrosivity, effluent pollution and non-recoverable catalysts.

The most important issue in the scientific community of chemistry is to develop economical and practical processes based on the idea of green chemistry. In recent years, solid acidic catalysts[13,14] such as montmorillonite clays and M_xO_y/SO_4^{2-} superacids have received considerable attention in different areas of organic synthesis because of their environmental compatibility, reusability, high selectivity, operational simplicity, non-corrosiveness and low cost. Among them, the application of montmorillonite clays has been extensively studied in many organic reactions.[15]

Montmorillonite K-10 is a type of acidic stratified silicate mineral with a three-layer structure with an ideal chemical formula of $(Al_{2-y}Mg_y)Si_4O_{10}(OH)_2{\cdot}nH_2O$. In montmorillonite clay one octahedral aluminate layer is sandwiched between two octahedral silicate layers. The interlayer cations are exchangeable, which allows alteration of the acidic nature of the material by a simple ion-exchange procedure. Both Brönsted and Lewis acidic catalytic sites are available, and its natural occurrence as well as its ion exchange properties make it a useful catalyst. Up to now, montmorillonite and in particular montmorillonite K-10, has been used as an efficient acidic catalyst for many organic transformations, such as substitution,[13] acetalization[16] *etc*. This prompted us to initiate a systematic investigation on montmorillonite K-10 catalyzed transesterification of β-ketoesters (Scheme 1) and herein we wish to disclose our results.



Scheme 1

Results and discussion

Montmorillonite K-10 was purchased from Aldrich. The catalyst has surface area of 220–270 $m^2\ g^{-1}$ and a bulk density of 300–370 g l^{-1}. The montmorillonite K-10 was activated at 120 °C over night prior to use.

In a typical experimental procedure, when the β-ketoesters were treated with alcohols in the presence of a catalytic amount of montmorillonite K-10 catalyst, the corresponding transesterified products were obtained in good to excellent yields. The results of transesterification are summarized in Table 1. After completion of the reaction, the reaction mixture was separated and the wet catalyst was washed with methanol and reused for three cycles after activation without significant loss of activity.

Spectroscopic[17] and kinetic[17–19] studies have indicated that the transacetoacetylation reaction proceeds *via* a mechanism in which acetylketene **2** is formed in the rate-limiting nuimolecular step (Scheme 2). One diketene free approach involves the

Green Context

Transesterification is an important synthetic transformation used in many sectors of the chemical industry. Traditional methods based on soluble or liquid acids and other reagents cause major problems in separation and product purification leading to relatively large volumes of waste. Here we see how a solid acidic clay can be effectively used instead of conventional acids giving very good product yields in the transesterification of β-keto esters—a particularly important reaction in pharmaceutical, agrochemical, polymer and other chemical industries. Reactions are carried out in a relatively benign hydrocarbon solvent. Separation is easy and the clay can be reused. *JHC*

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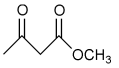
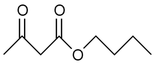
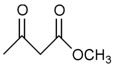
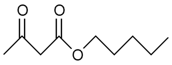
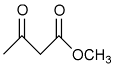
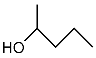
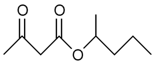
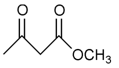
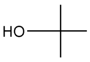
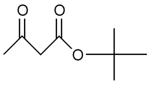
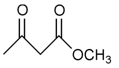
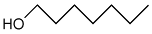
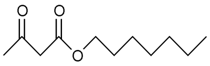
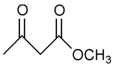
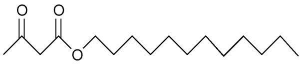
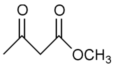
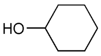
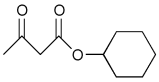
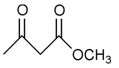
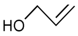
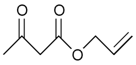
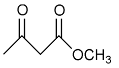
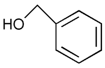
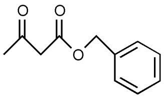
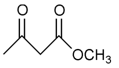
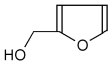
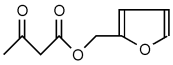
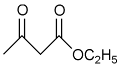
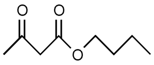
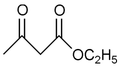
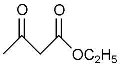
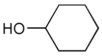
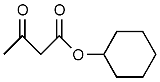
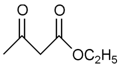
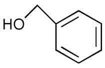
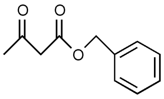
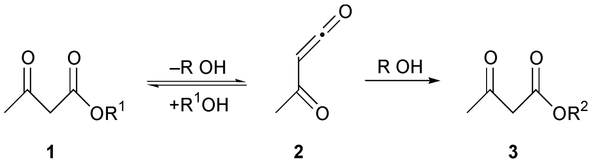
Table 1 Montmorillonite K-10 catalyzed transesterification of β-ketoesters

Entry	β-Ketoester	Alcohol	Time/h	Product	Yield[a] (%)
1			3.0		96
2			3.0		91
3			2.5		87
4			4.0		59
5			3.0		92
6			3.0		93
7			2.5		89
8			2.5		92
9			3.5		89
10			4.0		87
11			3.0		82
12			3.0		86
13			2.5		84
14			3.5		80

[a] Yields refer to isolated products.



Scheme 2

transesterification of the corresponding nucleophile with an appropriate acetoacetate (transacetoacetylation). We can use a variety of alcohols as nucleophiles to react with the acetylketene and the reactions are easily carried out under heating at 110 °C in toluene in the presence of montmorillonite K-10.

It is clear from Table 1 that the conversion from methyl/ethyl ketoesters to higher homologues appears to be efficient and practical through this procedure. The present procedure is quite general for a wide range of structurally varied alcohols such as open chain, cyclic and aromatic ones (entries 2, 7 and 9). The reaction proceeds smoothly with primary and secondary alcohols in excellent yields. As for *tert*-butyl alcohol (entry 4), which is often problematic in acid catalyzed reactions, a satisfactory outcome is realized by this reagent with a moderate yield of product.

It should be pointed out that transesterification of β-ketoesters with unsaturated alcohols is rather difficult as it is offset by facile decarboxylation rearrangment; however, using this method β-ketoesters underwent smooth reaction. It is importment to mention that the reaction appears to be specific only for the transesterification of β-ketoesters. Other esters such as α-ketoesters, γ-ketoesters as well as normal esters failed to undergo the reaction. The difference in the reactivity between β-ketoesters and other esters in transesterification is probably be due to the formation of acyl ketene intermediates in the former as proposed by Campbell and Lawrie.[19]

In summary, we have described a new and highly efficient procedure for the transesterification of β-ketoesters using an environmentally acceptable montmorillonite K-10 clay as catalyst. The obvious advantages of the catalyst are easy and simple operation in the workup in an inexpensive, non-toxic, non-corrosive, recyclable, more economical and environmentally friendly procedure. We believe this will present a better and more practical method to the existing methodologies and should find widespread application in academic and industrial fields.

Experimental

Liquid alcohols were purified by distillation prior to use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer

(KBr). ^{1}H NMR spectra were measured on a Bruker AC-80 (80 MHz), spectrometer using TMS as internal standard and $CDCl_3$ as solvent. MS were determined on a VG-7070E spectrometer (EI, 70 eV). The products were identified by IR, MS,^{1}H NMR spectra.

Typical procedure

A 1:1 mole ratio mixture of β-ketoester (5 mmol) and alcohol (5 mmol) together with the montmorillonite K-10 catalyst (0.1 g) and the solvent toluene was heated at 383 K in a round-bottomed flask with a distillation condensor to remove methanol or ethanol. The reaction was monitored by TLC. After completion, the reaction mixture was cooled, filtered and the filtrate was concentrated and chromatographed on silica gel using light petroleum and diethyl ether as eluent to afford the pure transesterified products.

Acknowledgment

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Solid-state synthesis of heterocyclic hydrazones using microwaves under catalyst-free conditions†

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The reactions of neat 5- or 8-oxobenzopyran-2-ones, **1–3**, with a variety of aromatic and heteroaromatic hydrazines, **4**, are accelerated upon irradiation in a household microwave oven in the absence of any catalyst, solid support or solvent. The approach provides an attractive and environmentally friendly pathway to several synthetically useful heterocyclic hydrazones.

Introduction

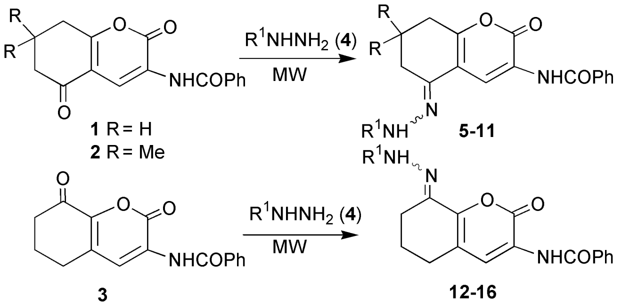
Microwave (MW) irradiation has been used for the rapid synthesis of a variety of compounds.[1] Chemical reactions are accelerated because of selective absorption of microwave energy by polar molecules, non-polar molecules being inert to the microwave dielectric loss. Among them, heterogeneous reactions facilitated by supported reagents on various mineral oxides have received special attention in recent years.[2] Relatively little attention is, however, paid to solventless reactions with neat reactants in the absence of a catalyst or solid support.[3]

Hydrazones are important synthons for several transformations[4a–d] and their syntheses from various precursors are well documented.[4a,b] Recently, hydrazones have been prepared from carbonyl compounds and hydrazine hydrate in ethylene glycol[5a] and toluene[5b] by the application of microwave irradiation while some others are synthesized in the presence of silica gel and sodium hydroxide.[6]

The synthetic efforts to this class of compounds have been previously directed for the selective design of the benzopyran-2-one ring at the positions 5 and 8 as well as for the new transformation into the corresponding quinoline derivatives.[7a–f] The conformational analysis has been accomplished for some of these derivatives *via* molecular modelling techniques based on experimentally determined NOE distance restraints in order to establish their structure in solution.[7a,d] These studies have been stimulated, in part, due to potentially significant biological activity associated with a variety of 2*H*-1-benzopyrans and quinolines.[7d] In general, heterocyclic systems encompassing pyran unit have found application as pharmaceuticals, agrochemicals, veterinary products, dyes or pigments.[7g] 5,6,7,8-Tetrahydro-2*H*-1-benzopyran-2-ones display a wide range of biological activities, such as anti-inflammatory, local anesthetic, platelet antiaggregating, analgesic, *etc*.[7h,i] Consequently, we believe an expeditious and selective transformation of such compounds under environmentally benign conditions is of importance.

Results and discussion

For the aforementioned reasons and in view of our general interest in the development of environmentally friendlier synthetic alternatives using microwaves,[2] we became interested in an expeditious synthesis of these compounds. We report here a general synthesis of several hydrazones **5–16**, whose earlier preparations required relatively strenuous reaction conditions namely heating substrates for several hours in the presence of an acidic catalyst.[7a–f] In all the reactions reported in this paper, we worked under solvent-free conditions utilizing neat starting materials, 2*H*-1-benzopyran-2-ones **1**,[8a,b] **2**,[8a,b] **3**[8c] and hydrazines, **4**, wherein the reactions are completed within minutes and in high yields (61–98%, Scheme 1, Table 1) using an unmodified household microwave oven. Interestingly, reactions proceeded well even when both the starting reactants were solids and the reaction temperature was maintained below the melting points of both components. Recently, some comments



Scheme 1

Green Context

Alternative energy sources and solvent free synthesis are key technologies in the green chemistry toolkit. In this article these are combined in the solid state synthesis of heterocyclic hydrazones in a household microwave oven. The reactions are fast and high-yielding. ***JHC***

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have been made on the preparation of phthalimides from solid reactants, phthalic anhydride and amino compounds[9a] with a specific MW effect being highlighted in the synthesis of fused pyrazoles.[9b] After the appearance of our report,[3b] we became aware of another investigation on conventional solid/solid organic reactions.[9c] In view of the unprecedented nature of this reaction, we examined the synthesis of the products **9**, **11** and **15** in detail by varying the amount of hydrazines and exposure time to microwaves. In contrast to commercial microwave devices available that provide adequate mixing and control of reaction temperature, an unmodified household MW oven is used in this study with no accurate temperature control. Consequently, we decided to measure the temperature of the alumina bath that housed the reaction vessel in the MW oven with a calibrated thermometer immediately after completion of the reaction. In a controlled experiment, concurrently, we also heated the lower melting reactant in a separate glass beaker to obtain visual information about the integrity of the solid materials upon exposure to microwaves.

For the synthesis of **11**, the starting benzopyran **2**[8a,b] (mp 179–179.5 °C) and 3-chloro-6-hydrazinopyridazine[10a] (mp 135–137 °C), were admixed in the ratio 1 : 2 (Table 1). When the reaction mixture was irradiated with microwaves for 5.5 min, the highest temperature in the alumina bath recorded was 120–122 °C. The reaction mixture remained solid and no reaction was observed. After heating for 6 min, however, the temperature of the bath reached 130–132 °C and the reaction mixture was completely in liquefied form affording hydrazone **11** in 85% isolated yield (see Table 1). The 3-chloro-6-hydrazinopyridazine kept in the same bath barely melted (~5% as estimated visually) at that temperature. With the critical temperature information in hand, we embarked on a comparative study and heated the above reaction mixture in the same proportions using a preheated oil-bath. Heating for 12 min at 133 °C gave a mixture (liquid with some suspended solid material). The NMR analysis revealed that the molar ratio between hydrazone **11** and starting benzopyran **2** was approximately 3.3 : 1. Prolonged heating of the reaction mixture for 1 h at 133 °C resulted in the formation of the liquid with no suspended solids. The work-up (as in general procedure) and NMR analysis revealed that the ratio between **11** and **2** in the isolated product was 92 : 8. Obviously, the unreacted benzopyran derivative was still present in high enough quantity to be separated together with the product **11**, while in the corresponding MW experiment, we observed complete conversion of the reactants to a single product (Table 1).

For the synthesis of hydrazone **8**, the effect of the increased amount of hydrazine was evaluated. The reactants, benzopyran **1**[8a,b] (mp 188–189 °C) and 3-chloro-6-hydrazinopyridazine[10a] (mp 135–137 °C), were admixed in the ratio 0.5 : 1.5 mmol and were subjected to microwave exposure for the same period (5.5 min) in the similar temperature range of 125–126 °C. The reaction mixture became a spongy brown mass with molten spots showing that melting had taken place followed by the formation and the separation of the solid product **8**. The 3-chloro-6-hydrazinopyridazine kept in the same alumina bath barely melted (2–3% as estimated visually) at that temperature. Additional experiments with increased exposure time to microwaves (alumina bath temperature being ~133 °C) resulted in the development of fumes and a darkened reaction mixture with hydrazone **8** being detected by TLC. In a separate experiment, we irradiated in the same bath 3-chloro-6-hydrazinopyridazine and benzopyran **1** (in different beakers) and both remained practically unchanged (pyridazine derivative slightly melted). The repetition of the above experiments with the ratio of the starting compounds, benzopyran **2** : 3-chloro-6-hydrazinopyridazine being 1 : 2, resulted in a spongy brown mass that afforded the product **8** in 62% isolated yield (Table 1). Even extended irradiation for up to 7 min (~135 °C) with this ratio (1 : 2) resulted in no observable decomposition of the reaction mixture. With two successive irradiations of the same reaction mixture (5 min each, bath temperature ~150 °C), no violent decomposition was observed. These experiments indicate the importance of the correct ratio of the reactants; higher amounts of hydrazine are detrimental as demonstrated in the uncontrollable reaction when the reactants are in the ratio 1 : 3. A comparative study was performed using a preheated oil-bath at 128 °C for 20 min. The NMR analysis after the work-up (as in the general procedure) revealed that the molar ratio between hydrazone **8** and starting benzopyran **1** was approximately 2.6 : 1.

For the synthesis of **15** starting from **3**[8c] (mp 248–250 °C) and 4-nitrophenylhydrazine[10b] (mp ~157 °C with decomposition) we performed an experiment with the reactants in the ratio 1 : 2.6, respectively. The commercially obtained hydrazine derivative, however, contained 10–15% of water for stabilization and as such slightly melted at 130 °C. Upon MW irradiation for 5.5 min (120–122 °C), the reaction mixture was completely melted while the 4-nitrophenylhydrazine in the second beaker was only barely melted. NMR analysis of crude mixture showed no presence of the benzopyran derivative **3**, and the work-up resulted in hydrazone **15** in 94% yield. On the other hand, heating the same reaction mixture for 1 h at 128 °C in an oil-bath resulted in a mixture of product **15** and starting **3** in the ratio 4.3 : 1, as discerned from ^1H NMR spectrum of the crude reaction mixture. The reaction mixture at the end of this heating period was solid. This comparative study of the reactions taking place in an oil-bath in the absence of MW heating revealed a substantial rate enhancement for reactions conducted under MW irradiation conditions, presumably due to the increase in polarity after change from the solid to the liquid phase.[9a] Such bimolecular reactions[2d,e] will show a polarity enhancement as a result of the ensuing intermediate transition state and consequently may display a pronounced microwave effect.[9b] Further, the reactions could be visibly monitored since no reaction occurs without formation of a melt. This methodology allows for performing rapid syntheses of a variety of hydrazones below the melting points of the participating starting materials. This could be explained by lowering of the melting point by the formation of the eutectic.[11] Consequently, such methodology seems to be especially useful when starting from substrates, which decompose at the normal melting point.

An adequate temperature control of the reaction, however, is strongly recommended. The temperature of the alumina bath upon MW heating for a specific period is dependent on the moisture (water) content of alumina. As an example, dried and desiccated alumina due to the diminished water content may heat up to 20 °C lower than the alumina in a bath stored in the laboratory atmosphere. The consequence of the lower tem-

Table 1 Solvent-free preparation of hydrazones, **5**–**16**, using microwaves

Starting benzopyran	Hydrazine **4** (R^1, mmol)	React. time/min	Product (yield, %)[a]
1	Ph (1.2)	6	**5** (83)
1	2,5-$F_2C_6H_3$ (3.0)	8	**6** (69)
1	3-$CF_3C_6H_4$ (1.5)	8	**7** (75)
1	6-Chloropyridazin-3-yl (2.0–3.0)	5.5	**8** (62)
2	Ph (2.0)	8	**9** (61)
2	3-$CF_3C_6H_4$ (3.0)	10	**10** (62)
2	6-Chloropyridazin-3-yl (2.0)	6	**11** (85)
3	Ph (3.0)	3	**12** (95)
3	3-$CF_3C_6H_4$ (1.5)	8	**13** (92)
3	Pyridin-2-yl (3.0)	5	**14** (65)
3	4-$NO_2C_6H_4$ (~2.6)[b]	9	**15** (98)
3	2,5-$F_2C_6H_3$ (3.0)	8	**16** (96)

[a] Yield of pure product. [b] Reagent contains 10–15% of water for stabilization.

perature may influence the outcome of the reaction; solid reactants may not melt and no reaction may be observed.

Conclusion

In conclusion, we have developed an expeditious, easy-to-handle and environmentally friendlier approach to the synthesis of a variety of non-easily-available hydrazones using microwave irradiation that can be extended to other systems.

Experimental

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with the Bruker Avance DPX 300 and Varian VXR-300 Unity Plus spectrometers in DMSO-d_6, using TMS as an internal standard. The coupling constants (J) are given in Hz. IR spectra were obtained with a Perkin Elmer Spectrum 1000 spectrophotometer. Mass spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Thin-layer chromatography was carried out on Fluka silica gel TLC-cards. The starting benzopyran-2-ones, **1–3**, and 3-chloro-6-hydrazinopyridazine were prepared as described in the literature.[8,10a] All other reagents and solvents were used as received from commercial suppliers. An unmodified household microwave oven operating at 2450 MHz was used at its full power, 650 W, for all the experiments.

General procedure for the synthesis of hydrazones 5–16

A neat mixture of benzopyran derivative **1–3** (1 mmol) and hydrazine **4** (1.2–3 mmol; see Table 1) in a 10 mL glass beaker was thoroughly mixed for about 5 min, then it was placed in an alumina bath inside the household microwave oven and irradiated. The maximum temperature reached in the alumina after 10 min was about 150 °C. After cooling, methanol (~4 mL) was added to the mixture and the separated solid was filtered off and washed with a small amount of methanol. The products were crystallized from appropriate solvents for elemental analysis. The details of reaction conditions and yields are provided in the Table 1.

Analytical and spectroscopic data of products 5–16

***N*-(5,6,7,8-Tetrahydro-2-oxo-5-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (5)**. Mp 213–216 °C (DMF–MeOH); lit.[7c] 217–220 °C.

***N*-[5-(2,5-Difluorophenyl)hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (6)**. Mp 248–249 °C, decomp. (DMF–MeOH); IR$_{max}$/cm^{-1} 1628, 1665, 1706; ^{1}H NMR, δ 1.94 (2H, m, 7-CH$_2$), 2.71 (4 H, m, 6-CH$_2$, 8-CH$_2$), 6.59 (1H, m, C_6H_3), 7.21 (2H, m, C_6H_3), 7.58 (3H, m, COPh), 7.96 (2H, m, COPh), 8.67 (1H, s, 4-H), 9.00 (1H, s, NH), 9.62 (1H, s, NH); ^{13}C NMR (50 °C), δ 19.2, 22.9, 26.1, 101.0 (dd, J_1 29, J_2 3.7 Hz), 104.4 (dd, J_1 25, J_2 7.3 Hz), 112.2, 115.8 (dd, J_1 20.7, J_2 10.5 Hz), 122.9, 125.2, 127.4, 128.4 131.9, 133.5, 135.5 (dd, J_1 11, J_2 11 Hz), 143.5, 145.9 (dd, J_1 238, J_2 2.3 Hz), 157.8, 158.1, 158.9 (dd, J_1 237 Hz, J_2 1.8 Hz), 165.6; MS, m/z 409 (M$^+$, 14%), 105 (100). Anal. Calc. for $C_{22}H_{17}N_3O_3F_2$: C, 64.54; H, 4.19; N, 10.26. Found: C, 64.67; H, 4.13; N, 10.19%.

***N*-[5,6,7,8-Tetrahydro-2-oxo-5-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (7)**. Mp 222–223 °C (DMF–MeOH); IR$_{max}$/cm^{-1} 1598, 1639, 1675, 1699; ^{1}H NMR, δ 1.97 (2H, m, 7-CH$_2$), 2.63 (2H, m) and 2.71 (2H, m) (6-CH$_2$, 8-CH$_2$), 7.06 (1H, m, C_6H_4), 7.46 (3H, m, C_6H_4), 7.58 (3H, m, COPh), 7.96 (2H, m, COPh), 8.69 (1H, s, 4-H), 9.57 (1H, s, NH), 9.68 (1H, s, NH); ^{13}C NMR, δ 19.3, 23.0, 26.2, 108.6 (q, J 3.7 Hz), 112.6, 114.7 (q, J 3.7 Hz), 115.7, 123.0, 124.4 (q, J 272 Hz), 125.0, 127.6, 128.6, 129.8 (q, J 31 Hz), 130.0, 132.1, 133.6, 139.5, 146.4, 156.9, 158.3, 165.8; MS, m/z 441 (M$^+$, 21%), 105 (100). Anal. Calc. for $C_{23}H_{18}N_3O_3F_3$: C, 62.58; H, 4.11; N, 9.52. Found: C, 62.71; H, 3.97; N, 9.27%.

***N*-[5,6,7,8-Tetrahydro-2-oxo-5-(6-chloropyridazin-3-yl)-hydrazono-2*H*-1-benzopyran-3-yl]benzamide (8)**. Mp 287–290 °C (DMF–MeOH); lit.[7c] 287–290 °C.

***N*-(5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (9)**. Mp 223–226 °C, decomp. (DMF–MeOH); lit.[7c] 241–242 °C, decomp.

***N*-[5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (10)**. Mp 221–223 °C (DMF); IR$_{max}$/cm^{-1} 1599, 1618, 1642, 1667, 1720; ^{1}H NMR, δ 1.10 (6H, s, 2Me), 2.61 (2H, s, CH$_2$), 7.06 (1H, m, C_6H_4), 7.47 (3H, m, C_6H_4), 7.59 (3H, m, COPh), 7.96 (2H, m, COPh), 8.69 (1H, s, 4-H), 9.59 (1H, s, NH), 9.76 (1H, s, NH), (one CH$_2$ group is overlapped with DMSO-d_6); ^{13}C NMR, δ 28.0, 30.4, 36.4, 38.9, 108.7 (q, J 4 Hz), 111.9, 112.9, 114.8 (q, J 4 Hz), 115.7, 122.9, 124.4 (q, J 272 Hz), 124.7, 127.5, 128.5, 129.8 (q, J 31 Hz), 130.0, 132.0, 133.6, 138.8, 146.4, 155.4, 158.6, 165.7; MS, m/z 469 (M$^+$, 75%), 105 (100). Anal. Calc. for $C_{25}H_{22}N_3O_3F_3$: C, 63.96; H, 4.72; N, 8.95. Found: C, 63.81; H, 4.68; N, 8.79%.

***N*-[5,6,7,8-Tetrahydro-7,7-dimethyl-2-oxo-5-(6-chloropyridazin-3-yl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (11)**. Mp 259–261 °C (DMF–MeOH); lit.[7a] 260–263 °C.

***N*-(5,6,7,8-Tetrahydro-2-oxo-8-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (12)**. Mp 258–262 °C (DMF–MeOH); lit.[7f] 257–260 °C.

***N*-[5,6,7,8-Tetrahydro-2-oxo-8-(3-trifluoromethyl)phenylhydrazono-2*H*-1-benzopyran-3-yl]benzamide (13)**. Mp 113–114.5 °C (DMF–MeOH); IR$_{max}$/cm^{-1} 1581, 1597, 1617, 1633, 1676, 1707; ^{1}H NMR, δ 1.90 (2H, m, 6-CH$_2$), 2.64 (4H, m, 5-CH$_2$, 7-CH$_2$), 7.13 (1H, m, C_6H_4), 7.55 (6H, m, C_6H_4, COPh), 7.94 (2H, m, COPh), 8.08 (1H, s, 4-H), 9.56 (1H, s, NH), 9.95 (1H, s, NH); ^{13}C NMR (50 °C), δ 20.1, 23.9, 25.6, 109.1 (q, J 4 Hz), 115.6 (q, J 4 Hz), 116.5, 117.3, 123.7, 124.7 (q, J 272 Hz), 127.3, 128.4, 129.0, 129.7 (q, J 31 Hz), 129.9, 132.0, 133.4, 135.5, 145.7, 146.2, 158.2, 165.5; MS, m/z 441 (M$^+$, 36%), 105 (100). HRMS: Calc. for $C_{23}H_{18}N_3O_3F_3$ 441.1300. Found: 441.1316.

***N*-[5,6,7,8-Tetrahydro-2-oxo-8-(pyridin-2-yl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (14)**. Mp 226–229 °C (DMF–MeOH); IR$_{max}$/cm^{-1} 1575, 1591, 1633, 1673, 1699; ^{1}H NMR, δ 1.86 (2H, m, 6-CH$_2$), 2.61 (2H, m) and 2.69 (2H, 2m) (5-CH$_2$, 7-CH$_2$), 6.85 (1H, ddd, J_1 7.3, J_2 4.9, J_3 1.0 Hz, 5′-H), 7.30 (1H, ddd, J_1 8.4, J_2 1.0, J_3 0.9 Hz, 3′-H), 7.59 (3H, m, COPh), 7.71 (1H, ddd, J_1 8.4, J_2 7.3, J_3 1.9 Hz, 4′-H), 7.94 (2H, m, COPh), 8.08 (1H, s, 4-H), 8.17 (1H, ddd, J_1 4.9, J_2 1.9, J_3 0.9 Hz, 6′-H), 9.56 (1H, s, NH), 10.11 (1H, s, NH); ^{13}C NMR, δ 20.2, 23.8, 25.7, 107.1, 115.8, 117.5, 123.9, 127.3, 128.4, 128.8, 131.9, 133.4, 136.2, 137.8, 146.1, 147.4, 156.9, 158.2, 165.5; MS, m/z 374 (M$^+$, 56), 105 (100%). Anal. Calc. for

$C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.10; H, 4.81; N, 14.72%.

***N*-[5,6,7,8-Tetrahydro-2-oxo-8-(4-nitrophenyl)hydrazono-2*H*-1-benzopyran-3-yl]benzamide (15)**. Mp 290 °C (DMSO); IR_{max}/cm^{-1} 1594, 1668, 1715; ^1H NMR, δ 1.91 (2H, m, 6-CH_2), 2.64 (2H, m) and 2.70 (2H, m) (5-CH_2, 7-CH_2), 7.37 (2H, dd, J_1 9.4, J_2 0.7 Hz, C_6H_4), 7.58 (3H, m, COPh), 7.94 (2H, m, COPh), 8.09 (1H, s, 4-H), 8.17 (2H, dd, J_1 9.4, J_2 0.7 Hz, C_6H_4), 9.47 (1H, s, NH), 10.35 (1H, s, NH); ^{13}C NMR, δ 20.2, 24.4, 25.8, 112.5, 119.0, 124.6, 125.9, 127.6, 128.6, 128.9, 132.2, 133.4, 138.8, 139.3, 145.7, 150.6, 158.1, 165.7; MS, *m*/*z* 418 (M^+, 32%), 105 (100). Anal. Calc. for $C_{22}H_{18}N_4O_5$: C, 63.15; H, 4.34; N, 13.39. Found: C, 63.11; H, 4.19; N, 13.46%.

***N*-[5,6,7,8-Tetrahydro-2-oxo-8-(2,5-difluorophenyl)-hydrazono-2*H*-1-benzopyran-3-yl]benzamide (16)**. Mp 238–239 °C (DMSO); IR_{max}/cm^{-1} 1631, 1671, 1701; ^1H NMR, δ 1.87 (2H, m, 6-CH_2), 2.62 (2H, m) and 2.72 (2H, m) (5-CH_2, 7-CH_2), 6.66 (1H, m, C_6H_3), 7.23 (2H, m, C_6H_3), 7.58 (3H, m, COPh), 7.94 (2H, m, COPh), 8.09 (1H, s, 4-H), 9.26 (1H, s, NH), 9.58 (1H, s, NH); ^{13}C NMR, δ 20.3, 24.1, 25.8, 101.7 (dd, J_1 30, J_2 3.3 Hz), 105.6 (dd, J_1 24, J_2 7 Hz), 116.4 (dd, J_1 21, J_2 10 Hz), 118.5, 124.5, 127.6, 128.7, 129.2, 132.3, 133.5, 134.9 (dd, J_1 11, J_2 11 Hz), 138.9, 145.9, 146.2 (dd, J_1 238, J_2 2 Hz), 158.3, 159.0 (dd, J_1 238, J_2 2 Hz), 165.8; MS, *m*/*z* 409 (M^+, 53%), 105 (100). Anal. Calc. for $C_{22}H_{17}N_3O_3F_2$: C, 64.54; H, 4.19; N, 10.26. Found: C, 64.66; H, 4.03; N, 10.32%.

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Grignard type reaction *via* C–H bond activation in water

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A Grignard-type reaction of phenylacetylene with aldehydes was developed *via* alkynyl C–H activation under aqueous conditions catalyzed by a bimetallic Ru–In system in water.

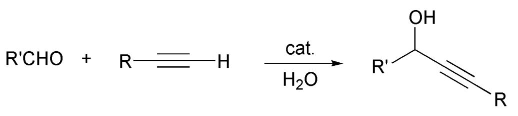
Recently, carbon–carbon bond formation based upon C–H bond activation has attracted considerable interest.[1] The direct addition of terminal alkynes to aldehydes was reported by using stoichiometric amounts of Sn(II)[2] or Zn(II)[3] together with amine to generate the acetylenic alcohols. On the other hand, the direct alkynyl C–H activation has been succeeded by using several catalysts,[4] among which the use of ruthenium-based catalysts are particularly effective.[5] These catalysts have been used successfully in adding terminal alkynes to nucleophiles such as electron deficient alkenes and alkynes.[6] Herein we wish to report that by using a bimetallic Ru–In catalytic system, phenylacetylene were added to aldehydes *via* C–H activation to give Grignard-type nucleophilic addition products in water (Scheme 1). Previously, a Ru–In catalytic system has been used by Trost *et al.* for addition of allenols to unsaturated compounds using propargyl alcohols as a synthon.[7]

At the beginning of the research, a variety of catalysts (such as Rh, Ru, Pd, and Ni) were examined for such a goal without success. A key observation of those investigations was that while the alkynes were converted into a range of products, the aldehyde did not participate in the reaction. Therefore, it was postulated that a water-tolerant Lewis acid catalyst[8] is required to activate the carbonyl. Subsequently, reactions between phenylacetylene and benzaldehyde were carried out by using various bi-catalyst systems: with one to catalyze the overall reaction and the other to activate the carbonyl. Among a variety of bi-catalytic systems, it was found that the desired addition product was formed by using $RuCl_3$–$In(NO_3)_3$ in water (Table 1, entry 1),[9] although the conversion was very low (<5%). Subsequently, conditions were optimized for forming the desired product (Table 1). The experiments demonstrated that the combination of a catalytic amount of $RuCl_3$ and a catalytic amount of indium salts such as $In(OAc)_3$, $In(OTf)_3$, and $In(NO_3)_3$ showed catalytic activity, and the best yield of the desired product was obtained with $RuCl_3$–$In(OAc)_3$. Interestingly enough, no catalytic activity was observed with a combination of $RuCl_3$–$InCl_3$ (entry 6). The combination of $RuCl_2(PPh_3)_3$–$In(OAc)_3$ was also effective but it provided a decreased yield of the desired product. Similar results were found with the use of a combination of $RuCl_3$–$Zn(OAc)_2$ which was also effective but resulted in a lower conversion. The desired conversion was enhanced by increasing the amount of either $RuCl_3$ or $In(OAc)_3$. Decreasing the amount of the ruthenium or indium catalysts resulted in a longer reaction time to achieve the same conversion. Although it is not essential for the reaction to proceed, the presence of an amine base increases conversion of the addition reaction considerably. A survey of a variety of amine bases revealed that morpholine is the best in providing the highest conversion. The use of 5% aqueous K_2CO_3 (wt%) instead of water alone further improved the reaction (entry 4).

Table 1 Conditions on catalyzed addition of phenylacetylene to benzaldehye in aqueous media

Entry	$RuCl_3$ (0.05 equiv.) + additives (equiv.)	Solvent	Conversion (%)[a]
1	$In(NO_3)_3$ (0.1)/—	H_2O	<5
2	$In(NO_3)_3$ (0.1)/morpholine (0.5)	H_2O	23
3	$In(NO_3)_3$ (0.1)/morpholine (0.5)	5% aq. K_2CO_3	35
4	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. K_2CO_3	85 (57)
5	$In(OTf)_3$ (0.1)/morpholine (0.5)	5% aq. K_2CO_3	60
6	$InCl_3$ (0.1)/morpholine (0.5)	5% aq. K_2CO_3	Trace
7	$In(OAc)_3$ (0.1)/pyrrolidine (0.5)	5% aq. K_2CO_3	50
8	$In(OAc)_3$ (0.1)/piperidine (0.5)	5% aq. K_2CO_3	45
9	$In(OAc)_3$ (0.1)/triethylamine (0.5)	5% aq. K_2CO_3	35
10	$In(OAc)_3$ (0.1)/pyridine (0.5)	5% aq. K_2CO_3	20
11	$In(OAc)_3$ (0.1)/morpholine (0.5)	1% aq. K_2CO_3	70
12	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. $KHCO_3$	50
13	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. Cs_2CO_3	60
14	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. Na_2CO_3	80 (45)
15	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. $NaHCO_3$	50
16	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. KOAc	55
17	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. KF	60
18	$In(OAc)_3$ (0.1)/morpholine (0.5)	5% aq. K_2CO_3	90 (62)[b]

[a] Conversion was based on ^1H NMR measurement of disappearance of the starting materials (partial polymerization of phenylacetylene was observed in each case); isolated yield in parenthesis. [b] At 100 °C.



Scheme 1

A broad range of substituted aromatic aldehydes and aliphatic aldehyde without α-hyrdogen were examined *via* this catalytic process to afford the corresponding phenylacetyenic alcohol (Table 2). The presence of an electron-withdrawing trifluoromethyl group significantly increased the yield of the reaction whereas a cyano group decreased the yield of the

Green Context

The idea of carrying out Grignard-like reactions in water seems counterintuitive, but could be a useful addition to synthetic methodology, as it would preclude the use of flammable organic solvents, and also avoid the wasteful process of drying them. This paper describes the development of a system which allows such reaction to occur using bimetallic Ru–In systems. ***DJM***

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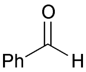
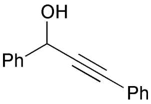
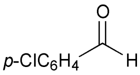
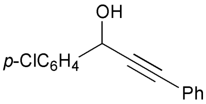
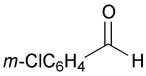
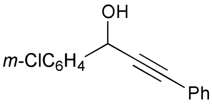
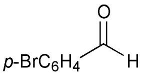
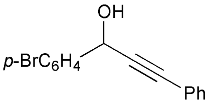
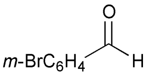
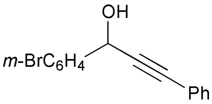
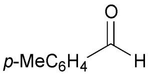
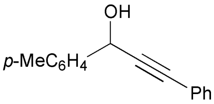
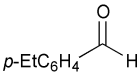
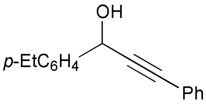
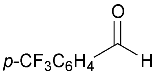
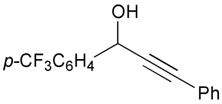
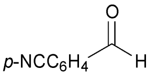
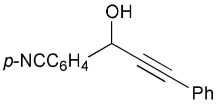
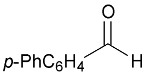
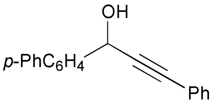
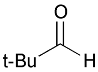
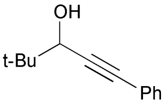
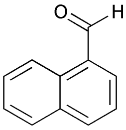
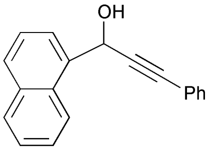
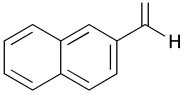
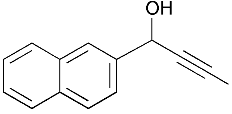
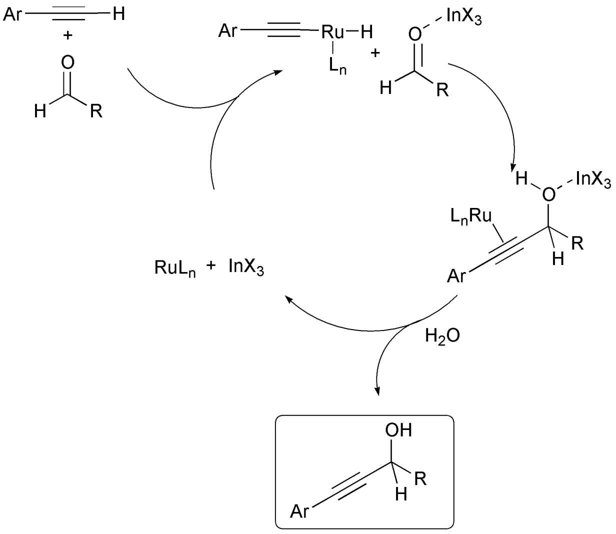
Table 2 Grignard-type reaction *via* C–H activation in water

Entry	Aldehyde	Conditions	Product	Yield (%)
1		80 °C/48 h		57
2		95 °C/24 h		52
3		95 °C/24 h		40
4		95 °C/24 h		60
5		95 °C/24 h		51
6		80 °C/24 h		46
7		95 °C/48 h		41
8		70 °C/48 h		94
9		60 °C/48 h		27
10		95 °C/48 h		42
11		60 °C/24 h		38
12		85 °C/48 h		47
13		85 °C/48 h		62

desired products. The moderate yields in most cases were due to the oligamerization and polymerization of phenylacetylene.

The exact reason behind the success of the reaction is still under investigation. Alkynylmetallic reagents such as Cu(I)[10] and Ag(I),[11] which are stable in water, are too stable to participate in nucleophilic carbon–oxygen double bond addition reactions. Unlike previous alkyne–aldehyde additions,[2] the generation of an alkynyl carbanion is unlikely due to the large pK_a difference between the terminal acetylene and the solvent water.[12] A tentative mechanism was proposed which involves the simultaneous activation of C–H bond of alkyne by the ruthenium catalyst and the aldehyde carbonyl by indium ion. The ruthenium intermediate then underwent Grignard-type addition followed by an *in situ* hydrolysis in water to give the desired carbonyl addition product and regenerated the ruthenium and indium catalysts to catalyze further reactions (Scheme 2).



Scheme 2

In conclusion, the Grignard-type reaction of phenylacetylene with aldehydes *via* C–H activation has been developed under aqueous conditions. The scope, mechanism, asymmetric, and synthetic applications of this reaction are under investigation.[13]

Acknowledgment

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13 *Typical experimental procedure*: to a mixture of ruthenium trichloride (5 mol%), indium acetate (10 mol%), benzaldehyde (5 mmol), and morpholine (2.5 mmol) in 10 mL of aqueous potassium carbonate (5

wt%), phenylacetylene (15 mmol) was added with stirring under an inert atmosphere of nitrogen. After continuous stirring at room temperature for 10 min, the mixture was heated at 80 °C and stirred. Stirring was continued until no further increase of the reaction product as monitored by ^{1}H NMR. The reaction mixture was poured into water, acidified with dilute HCl, and extracted with diethyl ether or methylene chloride. A usual work-up generated a crude material. After flash column chromatography on silica gel with 1 : 20 EtOAc–hexane as eluent, the product was isolated. *Characterization of products*: most products are known compounds except entries 7, 8, 10, 13. All new compounds have been characterized by ^{1}H and ^{13}C NMR, IR, MS or elemental analysis.

Adsorption and separation of cations on silica gel chemically modified by homogeneous and heterogeneous routes with the ethylenimine anchored on thiol modified silica gel

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Ethyleneimine (etn) has been covalently bonded onto silica gel *via* homogeneous (SiSN1) and heterogeneous (SiSN2) routes. Both synthesised silica gel surfaces have been applied to adsorb divalent cations from aqueous solution at room temperature. The series of isotherms of adsorption were adjusted to a modified Langmuir equation, after collecting the data from the solid/MCl_2 solution (M = Co, Ni, Cu, Pb and Hg) interfaces. The maximum adsorption were 1.08, 1.20, 1.70, 1.34 and 4.02 mmol g^{-1} for SiSN1 and 0.72, 1.74, 1.91, 2.19 and 2.89 mmol g^{-1} for SiSN2, for a the sequence of divalent cations: Co, Ni, Cu, Pb and Hg, respectively. Columns loaded with immobilised silica show resolutions (R) for separating metal ion couples: $R_{Co–Ni} = 0.22$, $R_{Co–Pb} = 0.76$, $R_{Co–Cu} = 1.12$, : $R_{Co–Hg} = 2.06$, $R_{Ni–Pb} = 0.50$, $R_{Ni–Cu} = 1.17$, $R_{Ni–Hg} = 2.38$, $R_{Pb–Cu} = 0.33$, $R_{Pb–Hg} = 1.83$ and $R_{Cu–Hg} = 1.60$ for the SiSN1 surface. The sequence: $R_{Co–Ni} = 1.10$, $R_{Co–Pb} = 1.44$, $R_{Co–Cu} = 1.63$, : $R_{Co–Hg} = 2.26$, $R_{Ni–Pb} = 0.08$, $R_{Ni–Cu} = 0.33$, $R_{Ni–Hg} = 1.40$, $R_{Pb–Cu} = 0.38$, $R_{Pb–Hg} = 1.82$ and $R_{Cu–Hg} = 1.55$ was determined for SiSN2.

Introduction

Inorganic oxides such as silica gel have received great attention not only due to their surface reactivity, but also to their ability in immobilising organic molecules onto the surface.[1] The importance of the evolution of this field of investigation in the last three decades reflects in significant review articles.[2,3] Thus, the active silanol groups dispersed on silica gel, has a great ability for attaching with a myriad of different pendant functional organosilyl groups, to give some organic characteristics to the precursor inorganic support.[4–6] Another feature related to these surfaces is the property of the functional groups already anchored onto silica for reacting with an active molecule to enlarge the original organic chain. On the other hand, these organofuntionalized surfaces are resistant to removal from the surface by organic solvents or water, as well as having high thermal resistance.[3,5] Once the compounds are immobilised, the resultant new silica can be applied in many academic and technological areas, such as catalysis for enzymatic reactions,[7,8] for heterogeneous catalyst,[9,10] biotechnology processes,[11–13] cation preconcentration,[14,15] agrochemical preconcentration,[16] cation separation processes[17,18] and development of agrochemicals with controlled released properties.[19,20]

The use of chemically modified silica gel containing a variety of chelating groups on a pendant organic chain can be designed for the adsorption and preconcentration of metal ions from aqueous and non-aqueous solutions. In a simple process, a packed column with organofuntionalized material can be effectively employed in a reliable process for preconcentration of the metal ions before analysis[21,22]

Sulfur donor atoms covalently attached on pendant chains anchored on a silica surface showed a particularly high chemical selectivity for mercury ions. This procedure can be used to remove and/or preconcentrate this species and, in such an operation, the main objective is to determine this high toxic contaminant. For direct determination of heavy metals in aquatic environments, a number of well-developed sensitive methods are available, including atomic spectroscopy. However, this technique shows systematic interference from the presence of other simple water constituents. For this reason, a preconcentration and/or separation step is often necessary before quantifying the desired analytes.[23] The preparation of solid adsorbents, to be applied for removal of these contaminants from waste effluent streams, is one of the major goals of green chemistry.[24]

Applications designed to improve analytical determinations and to improve the environment by metal removal have recently emerged. For instance, some of these are employed to eliminate and/or separate traces of toxic metals from waste waters,[23–26] and relevant aspects of interest appear for monitoring river water and a diversity of other sources of natural waters.[24]

This present investigation deals with cyclic ethyleneimine covalently attached onto silica gel by exploring homogeneous and heterogeneous synthesis methods. The main interest in these resulting modified silicas is related to their high selectivity toward divalent mercury, which is normally found in combination with lead in some Brazilian rivers.[27] Copper, nickel, cobalt and other metals are pollutant components from various sources, mainly from textile industries.[28] The adsorption and separation of a range of these cations from aqueous solution are now reported.

Green Context

Organically modified porous inorganic oxides are attracting considerable interest as hybrid materials for catalysis and reagents. High site loadings, adsorption capacities and good material stabilities are valuable properties that can extend the range of applications for such materials. Here we see the utilisation of organically modified porous silicas for analytical determinations and metal trapping. The materials reported have excellent capacity for mercury and other metals. They are significantly more efficient than other materials. ***JHC***

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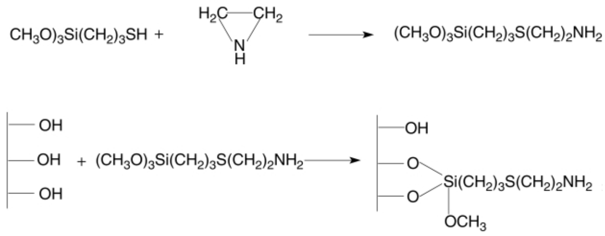
Experimental

Chemicals

The silylating agent 3-mercaptopropyltrimethoxysilane (mpts) (Aldrich) was used without previous purification. The silica gel (Aldrich), with particle size 70–230 mesh, average pore diameter 60 Å and pore volume 0.75 $m^3\ g^{-1}$, was treated and activated by heating at 423 K for 10 h in vacuum and held under a nitrogen atmosphere, as before.[1] Ethylenimine was synthesised following a described procedure, by reacting 2-aminoethyl hydrogen sulfate (Aldrich) in hot alkaline medium.[29,30] Solutions of all divalent cations were prepared from reagent grade salts.

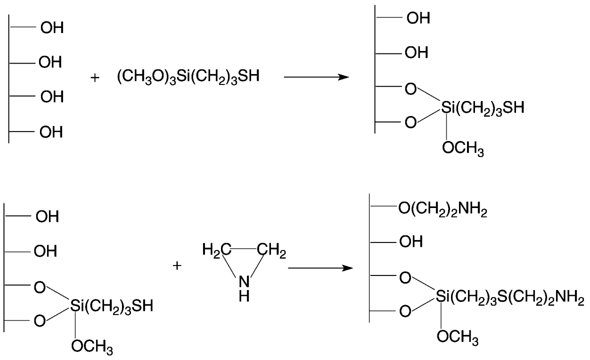
Synthesis

Ethylenimine (eth) was covalently bonded to the precursor mpts through two distinct routes: The homogeneous method consisted of reacting 5.5 cm^3 (29.0 mmol) of mpts with 6.0 cm^3 (116.0 mmol) of etn under reflux at 323 K. The resulting compound, 3-trimethoxypropylthioethylamine (mptt), was allowed to react with 5.0 g of activated silica in dry xylene at 343 K. The final product, denoted SiSN1, was washed and dried[30] (eqn. (1)).



(1)

The heterogeneous method consisted of reacting 15.0 cm^3 (84.0 mmol) of mpts with 40.0 g of activated silica gel suspended in 15.0 cm^3 of dry xylene. A sample of 5.0 g of the obtained product, denoted Sil-SH, was then reacted with 2.0 cm^3 (38.8 mmol) of liquid etn, which was added under a nitrogen atmosphere, to form the product SiSN2,[30] as shown in eqn. (2).



(2)

Adsorption

Adsorption isotherms were obtained using the batchwise method,[31,32] which consisted in suspending a series of 50.0 mg samples of the modified silica in 20.0 cm^3 of aqueous solutions, containing each cation at several different concentrations, varying from 0 to 50.0 mmol dm^{-3}. The solutions were mechanically stirred for 4 h at 298 ± 1 K and the solid was separated by centrifugation and dried at 313 K. The metal concentration adsorbed was determined by sampling the supernatant, which was complexometrically titrated with EDTA, using convenient indicators[33] for cobalt, nickel and copper. The other cations, lead and mercury, were determined by using ICP-AES with a Perkin Elmer model 3000 DV instrument.

Separation

The ability for separating the cations was followed using a glass column with 0.50 cm internal diameter packed with 1.00 g of the immobilised SiSN*x* (x = 1, 2) silicas. To this column 80.0 cm^3 of a mixture of divalent metal chloride solutions 0.50 mmol dm^{-3} each of copper, nickel, cobalt, lead or mercury was percolated through the solid bed with a flow rate of 8.33×10^{-3} $cm^3\ s^{-1}$. Passing 2.0 cm^3 aliquots of Clark/Lubs buffer solution at four distinct pH values, 4.0, 3.0, 2.0 and 1.0,[14] eluted the adsorbed cations. The amount of metal ions recovered was determined using ICP-AES.

The amounts of nitrogen and sulfur anchored on silica were determined through the Kjeldhal method and by using a Perkin Elmer model 2400 Elemental Analyser, respectively.[19]

Results and dicussion

Although the process of ethylenimine molecule immobilisation onto the silica gel surface leads to the same final product, distinct amounts of anchored pendant groups were obtained through the homogeneous and heterogeneous routes. Based on nitrogen analysis for the SiSN1 silica, the homogeneous method gave 1.74 mmol of ethylenimine anchored onto the surface. However, the SiSN2 silica obtained by the heterogeneous route, showed ethylenimine bonded not only on sulfur groups of Sil-SH precursor, but also on the silanol groups of the surface.[30] Sulfur analysis showed the presence of 0.78 mmol of this element on the SiSN2 surface, with an amount of nitrogen of 1.73 mmol in the same surface. These values indicate that 0.95 mmol of ethylenimine reacted directly with silanol groups of the surface.

The molecules anchored onto silica, containing sulfur and amino groups on pendant chains, permit the interaction of this support with a great range of cations, due to the presence of distinct basic centres. The sulfur basic centres present an effectiveness in interacting with softer acids than do nitrogen basic centres. This combination increases the interaction with various cations, being favourable for interactions with mercury. However, both basic centres can bond cations, simultaneously. Based on structural features presented by the pendant groups attached to the inorganic backbone, it is expected that sulfur atoms can chelate soft cations. By contrast, hard cations are chelated preferentially by nitrogen atoms, with the possibility of also using both centres, as shown in Fig. 1.

The ability of these surfaces to bind cations from aqueous solution was evaluated by measuring the sorption isotherms for divalent cations such as copper, nickel, cobalt, lead and mercury. Under equilibrium conditions, the exchange processes in the solid/liquid interface can be characterised by the numbers of moles adsorbed (N_f) per gram of support. This value was calculated from the initial number of moles of cation (n_i) and that (n_s) at the equilibrium condition for a given mass (m) of the support in grams, by applying eqn. (3):

$$N_f = (n_i - n_s)/m \qquad (3)$$

Profiles of the adsorption isotherms for all the cations in water are represented in Figs. 2 and 3. The number of moles adsorbed *versus* the number of moles at equilibrium (n_s) per volume of solution is illustrated for all cations. A simple observation is related to the maximum adsorption values, which are distinguishable for all these cations. For the series of isotherms, the data reveal that the adsorption process conforms

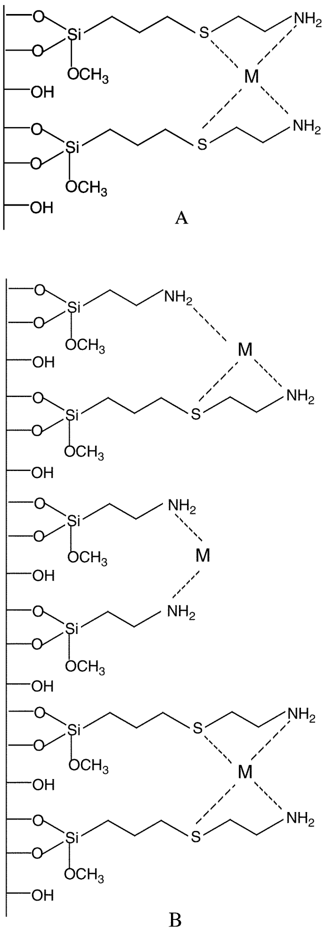


Fig. 1 Proposed scheme for interaction of metal ions with anchored surfaces when chelated with SiSN1 (A) and SiSN2 groups (B).

to the Langmuir model (eqn. (4)), as proposed for a series of systems.[1,3]

$$C_s/N_f = C_s/N_s + (1/N_s b) \quad (4)$$

For this expression, C_s is the concentration of the solution in equilibrium (mol dm^{-3}), N_f is concentration of cations adsorbed on the surface (mol g^{-1}), N_s is the maximum cation adsorbed on surface (mol g^{-1}), which depends on the number of adsorption sites, and b is a constant. All these adsorption studies were based on the linearised form of the adsorption isotherm derived from C_s/N_f as a function of C_s. From these data, the maximum retention capacity (N_s) was determined for each cation-matrix interaction through application of the modified Langmuir equation, where N_s and b were obtained from the curved and linear coefficients of the isotherm.

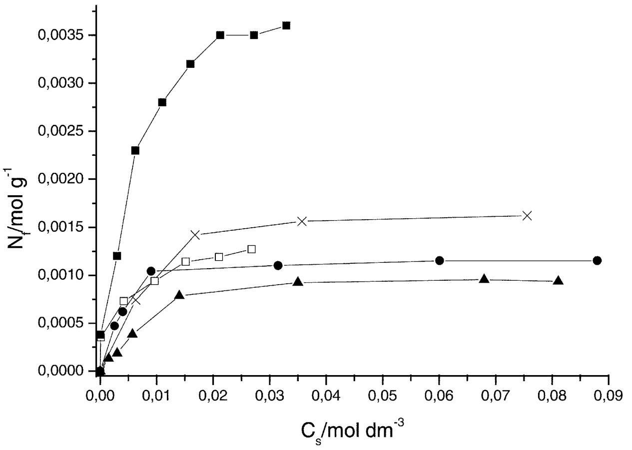


Fig. 2 Adsorption isotherms of divalent cations for the SiSN1 surface at 298 ± 1 K: Hg (■), Pb (□), Cu (×), Ni (●), Co (▲).

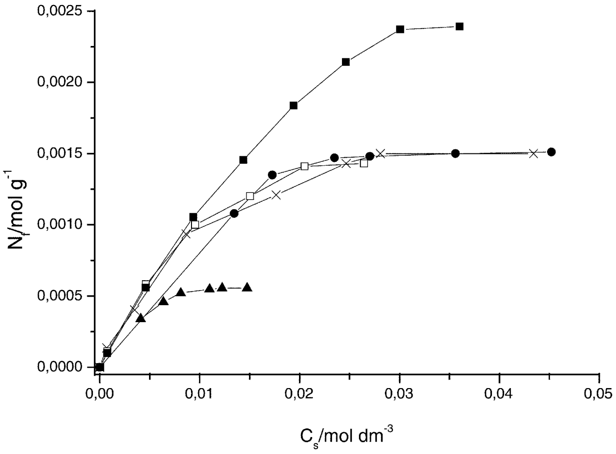


Fig. 3 Adsorption isotherms of divalent cations for the SiSN2 surface at 298 ± 1 K: Hg(■), Pb (□), Cu (×), Ni (●), Co (▲).

Data calculated by applying the Langmuir equation (eqn. (4)) are listed in Table 1 and show that the adsorption followed the sequence Hg ≫ Cu > Pb > Ni > Co and Hg > Pb > Cu > Ni > Co, for SiSN1 and SiSN2, respectively.

The interactive effect of mercury on the SiNS1 surface is much more effective than for other cations. A similar order was observed for the other anchored surface, SiNS2, but with weaker interactions. This fact reflects the lower amount of sulfur in SiSN2 than in SiSN1, even though, in both cases, the binding with mercury is significant, confirming the high affinity between sulfur molecules and mercury. This process clearly reveals the high affinity soft acid–soft base interaction, with the preference for sulfur–mercury interactions.

By comparing both anchored surfaces in relation to the cation interaction process, the data showed that the presence of a higher sulfur content on the SiSN1 surface caused an increase in affinity for cobalt and mercury. This same behaviour was not observed for lead, in spite of its soft acid characteristics. This fact could probably be associated with steric hindrance due to the increase in the number of pendant chains on the SiSN1 surface. On the other hand, the results obtained with nickel and copper cations showed a decrease in binding on the SiSN1 surface, as a consequence of an enhancement in hard acid properties. Moreover, as the presence of a hard amine base on SiSN2 increases, then the pendant chains on the surface favour the interaction with copper and nickel.

The separation ability of these surfaces was obtained for five cations through the percolation of solutions containing mixtures of two of them in separate experiments. The pH is one of the most important factors in controlling the extraction of these cations at the surface.[15,18] The ability to separate the cations at different pH values is illustrated in Figs. 4–7 for both surfaces. When a column is loaded, the cations can be removed under distinct conditions: (i) cobalt at pH 3, (ii) lead, nickel and copper at pH 2 and (iii) mercury at pH 1 for the SiSN1 surface. The same behaviour was observed for the SiSN2 surface in

Table 1 The maximum retention capacity on SiSN1 (N1) and SiSN2 (N2) surfaces for divalent cations (M^{2+})

M^{2+}	N1/mmol g^{-1}	N2/mmol g^{-1}
Hg	4.02	2.89
Pb	1.34	2.19
Cu	1.70	1.91
Ni	1.20	1.74
Co	1.08	0.72

removing cobalt at pH 3, nickel and lead at pH 2 and mercury at pH 1.

To confirm the ability of these surfaces to separate cations, the resolution was calculated by considering the separation of the column, using eqn. (5),

$$N_f = (n_i - n_s)/m \tag{5}$$

where ΔV is the difference in volume between two successive peaks obtained by eluting the analytes and w is the base width measured in volume units[15,18] The aliquot of concentration as a function of eluent volume was plotted and the values obtained were employed to calculate the resolution of these surfaces for separating these cations. These resolutions are listed in Table 2.

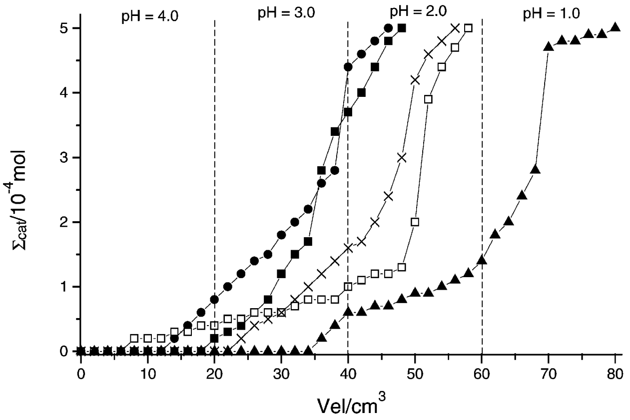


Fig. 4 Extraction of divalent cations in a column packed with SiSN1: Hg (■), Pb (□), Cu (×), Ni (●), Co (▲). The amount (Σ_{cat}) was obtained by elution with variable amounts (V_{el}) of aqueous solutions varying in pH.

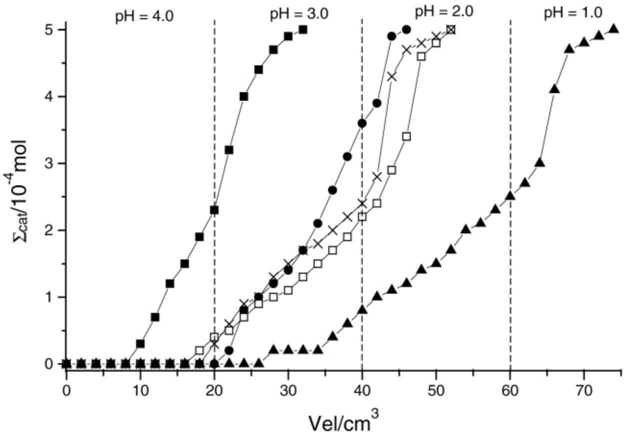


Fig. 5 Extraction of divalent cations in a column packed with SiSN2: Hg (■), Pb (□), Cu (×), Ni (●), Co (▲). The amount (Σ_{cat}) was obtained by elution with variable amounts (V_{el}) of aqueous solutions varying in pH.

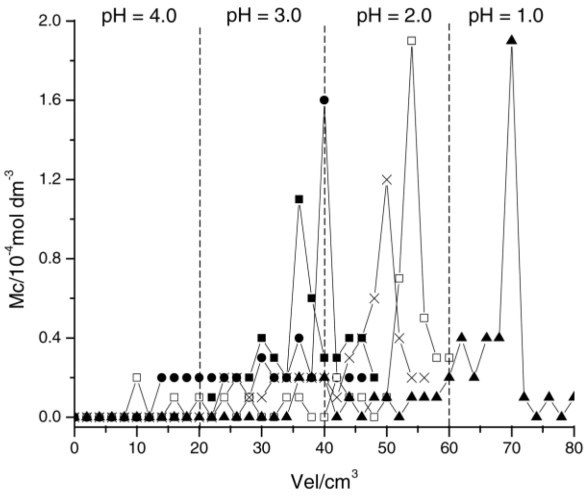


Fig. 6 Separation of divalent cations in a column packed with SiSN1: Hg (■), Pb (□), Cu (×), Ni (●), Co (▲). The uptake cation concentration (M_c) was obtained by elution with variable amounts (V_{el}) of aqueous solutions with decreasing pH values for the homogeneous (Hom) and heterogeneous (Het) immobilization routes.

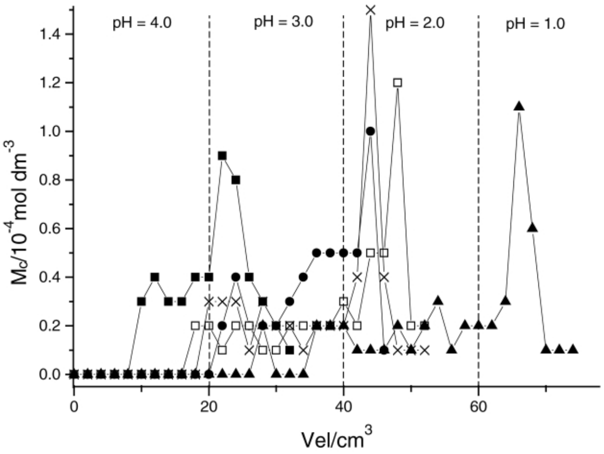


Fig. 7 Separation of divalent cations in a column packed with SiSN2: Hg (■), Pb (□), Cu (×), Ni (●), Co (▲). The uptake cation concentration (M_c) was obtained by elution with variable amounts (V_{el}) of aqueous solutions with decreasing pH values.

The results with SiSN1 showed that cobalt is quickly eluted while mercury is more strongly retained, eluting at low pH. The other cations were almost eluted together. However, mercury was completely isolated from the mixture of these cations. Lead, copper, nickel and cobalt cations did not present an effective separation. Cobalt and nickel are eluted together, but this couple is well separated from other cations. Lead and copper are eluted together as well, although these cations also show an effective separation from the other cations.

The SiSN2 surface data showed that cobalt was quickly eluted while mercury needs a large amount of the eluent at low pH, similar to the SiSN1 surface. There are differences between the surfaces with respect to the separations. Mercury and cobalt are well separated from mixtures, however, the remaining three cations did not present an effective separation on SiSN2.

In summary, both surfaces present a high affinity for mercury and low affinity for cobalt. This fact permits an excellent separation of mercury from other cations, and these surfaces may be useful in separating divalent cations, mainly mercury. The characteristics of these matrices showed their ability to adsorb and separate toxic elements. These abilities can be explored for applications in clean technologies, reinforcing the importance of developments in basic sciences for green chemistry.

Table 2 Column resolutions for SiSN1 ($R1$) and SiSN2 ($R2$) surfaces for successive couples of eluted cations (Ma–Mb)

Ma–Mb	*R*1	*R*2
Co–Ni	0.22	1.10
Co–Pb	0.76	1.44
Co–Cu	1.12	1.63
Co–Hg	2.06	2.26
Ni–Pb	0.50	0.08
Ni–Cu	1.17	0.33
Ni–Hg	2.38	1.40
Pb–Cu	0.33	0.38
Pb–Hg	1.83	1.82
Cu–Hg	1.60	1.55

Conclusion

Surfaces chemically modified with ethyleneimine by either homogeneous or heterogeneous processes present a high affinity for divalent mercury, due to presence of one basic sulfur centre in the pendant chains anchored on the silica surface. These surfaces also present useful adsorption behavior for copper, lead, nickel and cobalt due to the presence of a basic nitrogen atom centre. Both surfaces presented a high ability for separating mercury from cation mixtures. SiNS1 and SiNS2 are good separating matrices for copper and lead, and cobalt from other cations, respectively. Nickel did not show good separation on the SiSN1 surface, but was eluted together with copper and lead. For the SiSN2 surface nickel was eluted very closely with cobalt. The high selectivity in bonding mercury suggests that these materials may be useful for removal of this toxic heavy metal ion from waste waters.

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A greener approach to cotton dyeings with excellent wash fastness

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Attempts were made to find a more environmentally friendly method of dyeing cotton as an alternative to standard reactive dyeing processes that require high levels of water, salt and alkali and produce high levels of effluent contamination. It was intended that the new method would not compromise the excellent wash fastness levels typical of reactive dyed cotton. By employing a pre-treatment method, salt and alkali could be completely eliminated from the dyeing process and, in comparison with standard reactive dyeing processes, the time taken for the dyeing process to be completed could be significantly reduced and the volume of water required could be halved. The dyeings secured using the pre-treatment method had wash fastness values equal to those observed for the standard reactive dyeings.

Introduction

Cotton and other cellulosics comprise over 40% of world textile consumption. Colour can be imparted to cellulosic fibres using several different classes of dye, with reactive dyes finding greatest use with over 50% of world consumption.[1] Reactive dyes are desirable because of their excellent wash fastness, which arises from a covalent bond formed between dye and fibre.

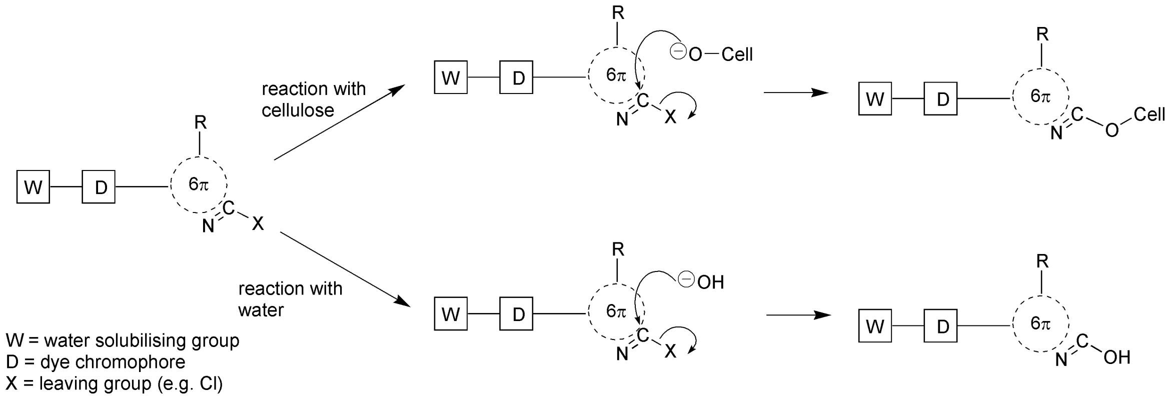
However, the reactive dyeing process can be expensive and time-consuming, needing significantly high salt and alkali concentrations. Electrolyte is needed in the dyeing process to overcome the long-range repulsion forces operating between slightly negatively charged fibre and negatively charged dye molecules (as a result of water-solubilising sulfonic acid groups). Without salt addition, adsorption of dye to fibre will not occur, and with dyes such as reactive dyes, which are very soluble in water, a high amount of salt is required in the dyeing process. The salt remains at the end of the dyeing process and is very difficult and expensive to remove from the effluent.

Alkali is required in reactive dyeing to achieve a pH of around 11 in order to generate sufficient cellulosate anions (cell–O$^-$) for fixation; the neutral species (cell–OH) is not sufficiently nucleophilic for reaction between dye and fibre to occur. Alkali must be neutralised at the end of dyeing, the product of which is additional cost and an increased salt concentration in the effluent. In addition, up to 40% of the dyestuff may hydrolyse in the dyeing process. This hydrolysed dye is highly substantive to the fibre, but is unfixed and requires extensive wash-off in order to achieve the characteristic very high fastness to washing (Schemes 1 and 2). This wash-off and subsequent effluent treatment to remove the resultant colour pollution can account for up to 50% of the total cost of reactive dyeing.[2]

The high level of salt and alkali used in reactive dyeing causes a high level of pollution, particularly to fresh water, the

Green Context

A high proportion of textiles used in the world are made of cotton or other cellulose materials. Many textiles are dyed using reactive dyes because of their greater stability on washing. Unfortunately standard reactive dyeing procedures require high levels of water, salt and alkali which lead to very large volumes of effluent. Here it is shown how a fabric pre-treatment method can lead to complete elimination of salt and alkali, lower water volumes and reduced process times. Thus several green chemistry reductions (waste, energy, raw materials) are achieved in this very important area of industrial chemistry. *JHC*



Scheme 1 Reaction of reactive dyes *via* a nucleophilic substitution mechanism.

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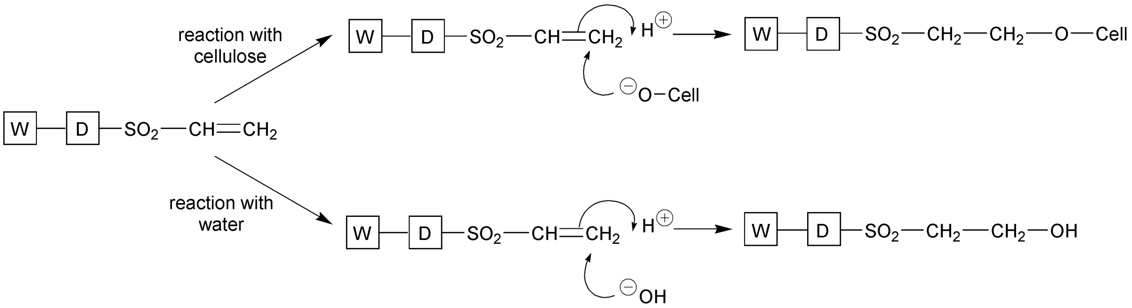


Scheme 2 Reaction of reactive dyes *via* a Michael addition mechanism.

wash-off process requires high volumes of water and energy, and the whole process is very time-consuming. The purpose of this work was to determine whether a greener alternative to reactive dyeing could be used successfully without compromising the desirable attributes of reactive dyes on cotton.

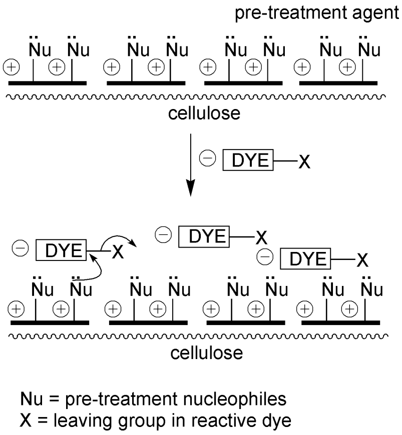
Experimental

General structure of pre-treatment agent

It was postulated that incorporation of nucleophilic sites within a polymer, which could then be applied to cotton, could enable reactive dyeing to be carried out in a more efficient manner at neutral pH values.

The pre-treatment agent employed is a developmental polymer and as such specific details of its structure cannot be disclosed. In general, it has a plurality of cationic centres and a plurality of nucleophilic centres and is a copolymer of at least one cationic monomer and another monomer including a nucleophilic group. The nucleophilic centres are strong nucleophiles and as such have high reactivity with the dye. Generally, the degree of cationicity is at least one cationic, particularly quaternary ammonium, centre per 500 g mol^{-1}, with a maximum of one per 150 g mol^{-1}. The polymer has at least one nucleophilic centre per five monomer residues with an upper limit of one nucleophilic centre per monomer residue. The polymer has a molecular weight in the region of 10000–30000 g mol^{-1}.

The pre-treatment agent is highly substantive to cellulosic fibre. Once the agent has been adsorbed onto the cotton reactive dye is introduced, the anionic dye molecules are attracted to the cationic sites in the polymer through ionic association, enabling adsorption of the dye without the need for adding salt. Free primary amino groups in the polymer provide extremely reactive nucleophilic sites for reaction with reactive dyes, they are much more reactive than the hydroxyl groups in cotton, so no addition of alkali is required as fixation occurs at neutral pH. The mechanism of how the pre-treatment agent works is shown schematically in Scheme 3. In addition, it is proposed that at neutral pH that hydrolysis of the reactive dye will be minimised, thus only minimal wash-off should be required as most of the dye applied is fixed to the fibre.



Scheme 3 Pre-treatment of cotton and dyeing with reactive dyes.

Materials

The dyes used in the study, their Colour Index generic name, maker and chemical constitution are shown in Table 1. The respective dye maker generously supplied samples of each of the dyes. Bleached, scoured, fluorescent brightener free, woven cotton (150 g m^{-2}) was supplied by Whaley's, Bradford, UK. Uniqema supplied the development pre-treatment agent. All other chemicals were of general laboratory grade.

Dyeing by pre-treatment method

Cotton samples were pre-treated, dyed and washed-off in sealed stainless steel dyepots of 300 cm^3 capacity, housed in a laboratory-scale *Roaches Pyrotec S* dyeing machine. At the end of dyeing the samples were removed and dried in the open air. The method used for each of the dyes shown in Table 1 is displayed graphically in Fig. 1.

Table 1 Reactive dyes used

Commercial name	C. I. Generic name	Dye maker	Reactive group
Procion Yellow H-EXL	C. I. Reactive Yellow 138:1	DyStar	Monochlorotriazine
Procion Brilliant Red H-EGXL	C. I. Reactive Red 231		
Procion Blue H-EXL	C. I. Reactive Blue 198		
Remazol Yellow RR	None ascribed	DyStar	Sulfatoethylsulfone
Remazol Red RR	None ascribed		
Remazol Blue RR	None ascribed		
Cibacron Yellow F-3R	C. I. Reactive Orange 91	Ciba	Monofluorotriazine
Cibacron Red F-B	C. I. Reactive Red 184		
Cibacron Blue F-R	C. I. Reactive Blue 182		

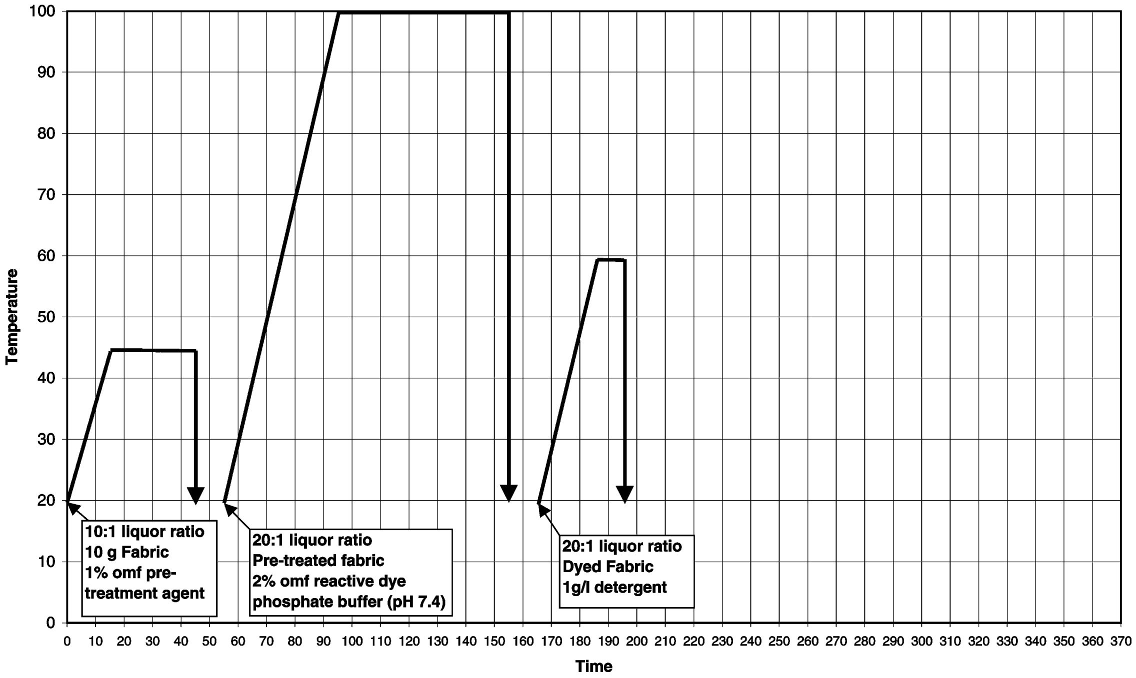


Fig. 1 Method of pre-treatment and application of reactive dyes to cotton.

Dyeing by standard method

For comparison purposes, standard dyeings were carried out on cotton that had not been pre-treated following the dye manufacturer's recommendations.

Cotton samples were dyed and washed-off in sealed stainless steel dyepots of 300 cm^3 capacity, housed in a laboratory-scale *Roaches Pyrotec S* dyeing machine. At the end of dyeing the samples were removed and dried in the open air. The method used for *Remazol RR* reactive dyes[3] is displayed graphically in Fig. 2, the method used for *Procion H-EXL* reactive dyes[4] is displayed graphically in Fig. 3 and the method used for *Cibacron F* reactive dyes[5] is displayed graphically in Fig. 4.

Wash fastness testing

Samples were subjected to the ISO 105 : C06/C2S wash test (60 °C) using SDC multifibre fabric as adjacent.[6] The samples were washed five times using the same piece of multifibre strip for each washing. After washing the samples were visually assessed using grey scales according to the ISO 105 : A02 and ISO 105 : A03 test protocols[6] to determine the degree of washdown and cross staining, respectively. The grey scale ranges from 5 for no shade change (or no stain on the adjacent fibres) down to 1 for a severe shade change (or staining), with half points in between.

Colour measurement

The samples were measured using a *Match-Rite*™ colour spectrophotometer attached to a personal computer. From the reflectance values at the $\lambda_{\max}$ of the dyeings (R), the colour strength (K/S) of the sample was calculated using the Kubelka–Munk equation [eqn. (1)].[7]

$$\mathrm{K/S} = \frac{(1-\mathrm{R})^2}{2\mathrm{R}} \qquad (1)$$

Results and discussion

Colorimetric analysis of dyed samples

The K/S values calculated from the colorimetric data for the reactive dyes applied using the standard method and for the reactive dyes applied using the pre-treatment method are shown in Table 2. It was observed that the K/S values secured using the pre-treatment method were higher for all dyes used in comparison with the standard dyeings. It was not an intention of the work to achieve colour strength values in excess of the standard, only to equal. Nevertheless, this is advantageous, as less dye would need to be applied using the pre-treatment system to achieve a specific K/S value, hence reducing the cost and reducing the concentration of dye in the effluent. It is proposed that this result was achieved because less dye is hydrolysed and more of the dye applied fixes to the cotton. In theory if up to 40% of the dye applied using a standard method is hydrolysed, then a 2% omf application of dye could result in a 1.2% omf dyeing, whereas using the pre-treatment method a 2% omf dyeing is theoretically possible if no hydrolysis occurs.

Visual inspection of the samples showed only very slight variations in shade between dye type when comparing colour differences between standard and pre-treated dyeings. *Remazol RR* and *Cibacron F* pre-treated dyeings were effectively identical in shade to the standard dyeings (taking into account the differences in strength). The *Procion H-EXL* dyeings were a little duller than the standard.

Wash fastness assessment

The wash fastness results for the standard and pre-treated dyeings are given in Table 3. It was observed after one wash that all the dyeings produced using the various processes displayed excellent wash fastness, the dyeings exhibited similar levels of colour loss, inferring that the pre-treatment process secured dyeings for which the dye was adequately fixed. A lack of staining of adjacent fabric, particularly in the first wash,

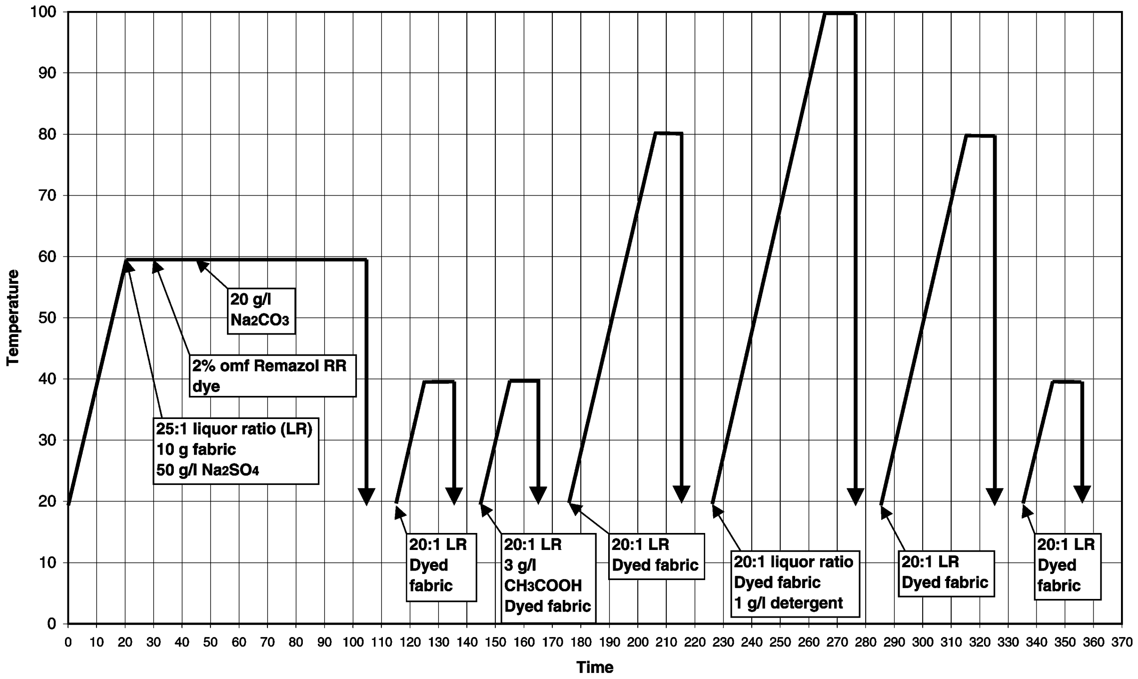


Fig. 2 Method of application of *Remazol RR* reactive dyes to cotton (Michael addition fixation mechanism).

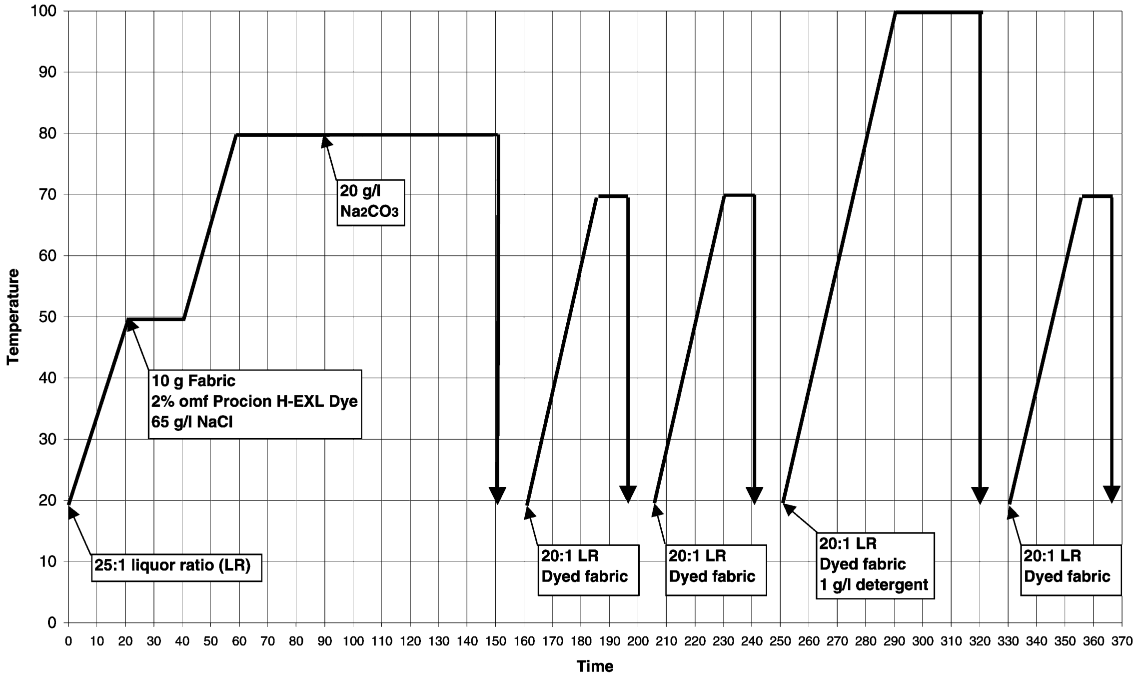


Fig. 3 Method of application of *Procion H-EXL* reactive dyes to cotton (nucleophilic substitution fixation mechanism).

indicated that extensive wash-off of unfixed dye was not required with the pre-treatment method.

After five washes, although the wash fastness levels in general were very good to excellent for all dyeings, in some cases the wash fastness of the dyeings using the pre-treatment method were slightly superior to those secured with the conventional systems. In the conventional dyeing processes a long wash-off procedure was used and it is proposed that this contributed to the inferior wash fastness. It is suggested that, in the case of conventionally dyed cotton, a small amount of dye-fibre bond cleavage occurs as a result of the wash-off stages and, particularly, the five-wash fastness tests. It is known that the dye–fibre bond formed using vinylsulfone reactive dyes on cotton is more alkali-sensitive than that derived from mono-halotriazine dyes,[8] and this would explain the *Remazol RR* dyeings having slightly inferior wash fastness to the *Procion H-EXL* and *Cibacron F* dyeings. The cotton adjacent picks up the small amount of loose colour that is generated, the stain becoming quite noticeable after five washes; in addition, the colour strength of the dyeing is reduced. With the pre-treatment method, the long wash-off method is negated, thus slightly reducing the cumulative dye-fibre bond cleavage.

Comparison of the different dyeing processes

A summary of the differences in the dyeing processes used is given in Table 4. It was observed that the pre-treatment method vastly reduced the total time of the dyeing operation. The standard reactive dyeing processes were between 295 and 365 min in duration, whereas the pre-treatment method was completed in 195 min.

Table 2 *K*/*S* values for reactive dyes applied to cottonby standard methods and by the pre-treatment method

Dye	% omf	Standard /PT	*K*/*S*
Remazol Yellow RR	2	Standard	3.81
	2	PT	4.73
Remazol Red RR	2	Standard	8.55
	2	PT	8.73
Remazol Blue RR	2	Standard	6.53
	2	PT	6.75
Procion Yellow H-EXL	2	Standard	10.23
	2	PT	10.49
Procion Brilliant Red H-EGXL	2	Standard	8.30
	2	PT	8.79
Procion Blue H-EXL	2	Standard	6.20
	2	PT	6.78
Cibacron Yellow F-3R	2	Standard	5.18
	2	PT	5.26
Cibacron Red F-B	2	Standard	5.47
	2	PT	6.33
Cibacron Blue F-R	2	Standard	4.38
	2	PT	4.67

Water consumption is highly significant from an environmental and cost point of view and dyeing processes that can reduce the volume of water used are desirable. The amount of water used is calculated using eqn. (2) by a summation of the

$$\text{volume water used (l (kg fibre)}^{-1}\text{)} = \text{LR (dyeing)} + \text{LR(pretreatment)} + \text{LR(washoff 1)} + \text{LR(washoff 2)} + \ldots \quad (2)$$

water used in each separate process; where the liquor ratio (LR) is given as a ratio of liquor to fibre, *e.g.* a 25 : 1 liquor ratio is 25 l of water per kg of fibre used.

Each of the standard reactive dyeing processes (Fig. 2–4) used over 100 l of water per kg of fabric dyed, with most of the water consumed in the wash-off processes, however, the pre-treatment method (Fig. 1) consumed less than half the volume, with only 50 l of water per kg of fabric used.

A high amount of salt (up to 1.6 kg per kg of fabric dyed) and alkali (0.5 kg Na_2CO_3 per kg of fabric) was consumed in the standard reactive dyeing processes, but by employing the pre-treatment method both salt and alkali were completely eliminated from the dyeing process.

Table 3 Wash fastness grey scale ratings of standard reactive dyeings and pre-treated reactive dyeings on cotton following ISO 105:C06/C2S wash tests[a]

Dye	Standard /PT	Washes	S	D	C	N	P	A	W
Remazol Yellow RR	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Remazol Red RR	Standard	1	4/5	5	5	5	5	5	5
		5	4	5	4	4/5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Remazol Blue RR	Standard	1	4/5	5	5	5	5	5	5
		5	4	5	4	4/5	5	5	5
	PT	1	4/5	5	5	5	5	5	5
		5	4	5	4/5	5	5	5	5
Procion Yellow H-EXL	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Procion Brilliant Red H-EGXL	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Procion Blue H-EXL	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	4/5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Cibacron Yellow F-3R	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
Cibacron Red F-B	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	4/5	5	5	5	5	5	5
Cibacron Blue F-R	Standard	1	5	5	5	5	5	5	5
		5	4/5	5	4/5	5	5	5	5
	PT	1	5	5	5	5	5	5	5
		5	5	5	5	5	5	5	5

[a] S Shade change, staining to D diacetate, C cotton, N nylon, P polyester, A acrylic, W wool.

Table 4 Comparison of different systems employed

Procedure	Time/min	Water/l (kg fabric)$^{-1}$	NaCl/g (kg fabric)$^{-1}$	Na_2SO_4/g (kg fabric)$^{-1}$	Na_2CO_3/g (kg fabric)$^{-1}$	Other chemicals/g (kg fabric)$^{-1}$
Remazol RR	355	145	0	1250	500	Acetic acid (60), detergent (20)
Procion H-EXL	365	105	1625	0	500	Detergent (20)
Cibacron F	295	125	0	1500	500	Acetic acid (60), detergent (20)
Pre-treatment	195	50	0	0	0	Pre-treatment (10), phosphate buffer (120), detergent (20)

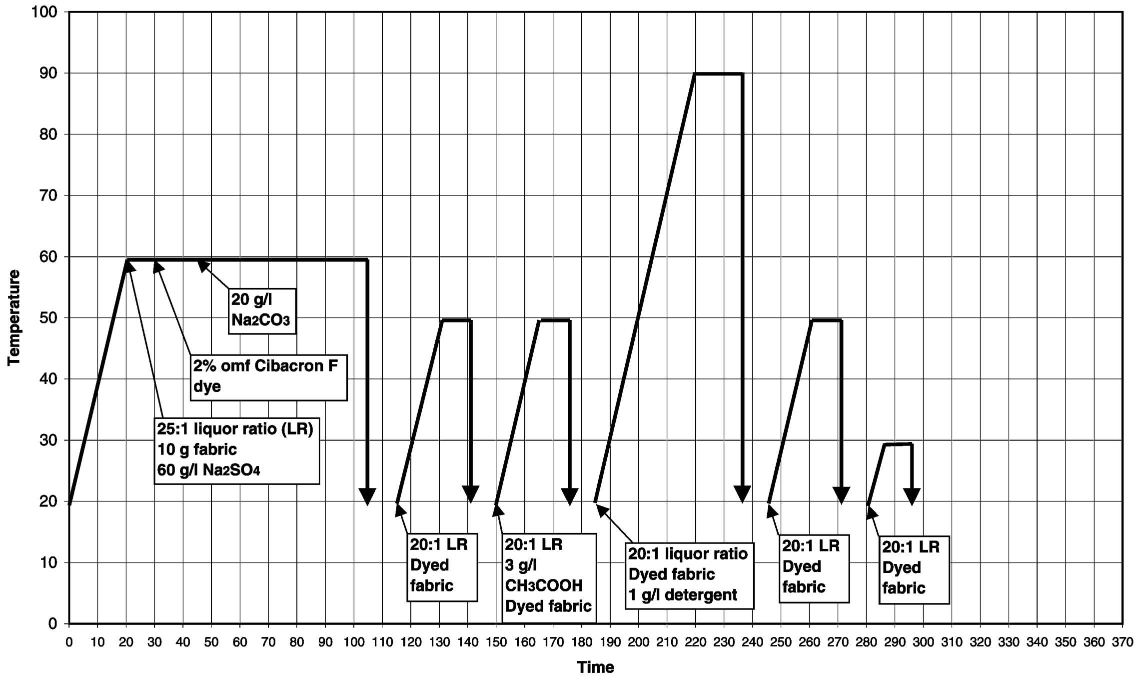


Fig. 4 Method of application of *Cibacron F* reactive dyes to cotton (nucleophilic substitution fixation mechanism).

Considering the other chemicals used in the dyeing processes, the pre-treatment agent was applied in relatively low concentration and it is suggested that it would have high exhaustion values, hence, its presence in the effluent would be expected to be in extremely low concentrations. In addition, the agent is polymeric and as such poses minimal environmental impact. It is noted that in the pre-treatment method 120 g of phosphate buffer per kg of fabric is used. This was for a laboratory situation and it is hoped that the process can be developed so that on a larger scale the neutral pH of tap water would negate the need for a buffer, certainly, it is hoped that the system would be as efficient in a pH range of 6–8.

Conclusions

It has been demonstrated that dyeings on cotton with excellent wash fastness can be achieved using alternative methods to the standard reactive dyeing processes. Employing the pre-treatment method may significantly reduce the time taken for the dyeing process to be completed and halve the volume of water required. In addition, the salt and alkali used in the dyeing process is negated.

Dyeings secured using the pre-treatment method had higher colour strength values than the standard dyeings and it was proposed that this was because more dye fixed to the cotton as hydrolysis was minimal. In addition, only minimal wash-off was required. Visual inspection of the samples showed only very slight variations in shade between dye type when comparing colour difference between standard and pre-treated dyeings.

The pre-treatment method did not negatively affect the wash fastness of the dyeings over initial and repeated washing; the results being equal, if not slightly superior, to those secured using the standard methods.

It could be concluded that the pre-treatment system provided a much ‘greener’ alternative to achieving wash fast dyeings on cotton.

Acknowledgements

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Esterification of carboxylic acids with alcohols catalyzed by polyaniline salts

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Polyaniline salts such as polyaniline hydrochloride, sulfate, nitrate, phosphate and *p*-toluenesulfonate are used as catalysts in the esterification of carboxylic acids with alcohols. The activity, recovery, reusability and handling of the catalysts are found to be good. This process is being reported for the first time.

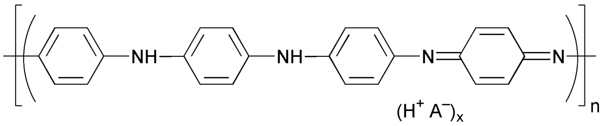
Introduction

In view of environmental mandates, there is a global effort to replace conventional catalysts by eco-friendly catalysts. The replacement of current chemical processing with more environmentally benign alternatives is an increasingly attractive subject.[1] Esterification is one of the most fundamental and important reactions in organic synthesis (see ref. 2 and references cited therein). Esters are useful in a wide variety of industrial applications, such as coatings, adhesives, resins, fragrances, perfumes, plasticizers *etc*. Although several methods have been explored and developed,[2] most of them are not suitable to meet the stringent specifications which are being applied in the chemical industry. The most acceptable method of preparing an ester is to react an acid with an alcohol in the presence of a catalyst.

The catalysts employed in the esterification reaction of carboxylic acids with alcohols include mineral acids,[3,4] anhydrous magnesium sulfate and catalytic amounts of sulfuric acid,[5] tosyl chloride, pyridine,[6] boron trifluoride etherate alcohol,[7] titanium salts,[8] tin salts,[9] hafnium salts[10,11] aluminium phosphate molecular sieve,[12] NaX and NaY zeolites,[13] polymer protected reagent,[14] graphite bisulfite,[15] diorgano tin dichloride,[16] Filtrol-24, Amberlyst-15, sulfated zirconia,[17] and ion exchange resin.[18,19]

Results and discussion

Recent advances in the field of electrically conducting polymers have led to a variety of materials with significant potential applications. Electrically conducting polymers form a unique class of materials, offering the possibility of controlled electrical conductivity combined with their good processing characteristics, low cost and stability. Among them, polyaniline is one of the most interesting materials because of its moderately high conductivity upon doping with acids, well behaved electrochemistry, easy preparation, possible processability and good environmental stability (see ref. 20 and references cited therein). In this work, the application of polyaniline in catalysis was attempted. Polyaniline salts such as polyaniline hydrochloride, sulfate, nitrate, phosphate and *p*-toluenesulfonate were prepared by chemical oxidative polymerization of aniline by ammonium persulfate in the presence of acid.[21] The structure of polyaniline salt is generally represented as shown below.



$H^+ A^-$ = HCl, HNO_3, H_2SO_4, H_3PO_4, $CH_3(C_6H_4)SO_3H$

We first investigated the esterification of lauric acid with different amounts of methanol. The esterification of lauric acid (1 g) and different amounts of methanol (1, 2, 3, 4 and 5 ml) was carried out in a 10 ml round bottom flask with 150 mg of polyaniline sulfate powder. The reaction mixture was refluxed at 70 °C for 20 h. The reaction mixture was filtered and washed with chloroform to recover the catalyst. The chloroform solvent and unreacted methanol were evaporated off. The compound was loaded onto a column containing silica gel of finer than 200 mesh and eluted with 20 : 80 chloroform–hexane (400 ml). The solvent mixture was recovered to obtain the pure ester (Table 1). More than 3 ml of methanol gave the ester quantitatively, but the use of 1 ml of methanol gave the corresponding ester in low yield.

We investigated the catalytic activities of various polyaniline salts which promote the reaction of lauric acid with methanol at reflux. The esterification of lauric acid (1 g, 5 mmol) and

Table 1 Direct esterification of lauric acid and methanol catalyzed by polyaniline sulfate salt

Entry	Amount of methanol/ml	Yield (%)
1	1	55
2	2	90
3	3	92
4	4	99
5	5	99

Green Context

Esterifications are important reaction types which often rely on the use of homogeneous acids. This contribution describes the use of a polymeric salt of a strong acid and a weak base which is shown to be an easily recoverable and effective catalyst for the esterification of lauric acid. While reaction times are moderate, the catalyst can be recovered and reused readily, making product isolation and catalyst reuse simple. ***DJM***

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methanol (4 ml, 98.7 mmol) was carried out with 150 mg (15 wt% based on the amount of the acid) of polyaniline salt powder. The reaction mixture was refluxed at 70 °C for 20 h. Five different catalysts were employed in esterification. Polyaniline hydrochloride, sulfate, nitrate, *p*-toluene sulfonate gave esters in good yield, whereas the polyaniline phosphate gave the corresponding ester in low yield (Table 2). This is due the low strength of phosphoric acid when compared to the other acids.

Table 2 Direct esterification of lauric acid and methanol using polyaniline salt catalysts

Entry	Polyaniline salt	Yield of ester (%)
1	Polyaniline hydrochloride	99
2	Polyaniline sulfate	99
3	Polyaniline nitrate	99
4	Polyaniline phosphate	75
5	Polyaniline *p*-toluene sulfonate	99

To explore the generality and scope of the polyaniline salt catalyzed esterification, we examined the reaction of various structurally diverse alcohols with carboxylic acids (Table 3).

Table 3 Direct esterification of carboxylic acids and alcohols catalyzed by polyaniline sulfate salt[a]

Entry	Acid	Alcohol	Yield of ester (%)
1	Lauric acid	Methanol	99
2	Lauric acid	Ethanol	98
3	Lauric acid	Propanol	98
4	Lauric acid	Butanol	98
5	Lauric acid	1-Decanol	98
6	Lauric acid	Isopropyl alcohol	26
7	Lauric acid	*tert*-Butyl alcohol	11
8	Caprylic acid	Methanol	95
9	Caproic acid	Methanol	99
10	Myristic acid	Methanol	98
11	Stearic acid	Methanol	99
12	11-Bromoundecanoic acid	Methanol	99
13	Cinnamic acid	Methanol	99
14	Phenoxyacetic acid	Methanol	85
15	Naproxen	Methanol	81
16	Acetic acid	Menthol	57

[a] The products were analyzed by ^{1}H NMR spectra and authenticity of the products was established.

The esterification of carboxylic acid (1 g) and alcohol (4 ml) was carried out with 200 mg of polyaniline sulfate salt as catalyst. The reaction mixture was refluxed at 70 °C for 24 h. The esters of aliphatic carboxylic acids with aliphatic alcohols gave quantitative yields. The yield of the esters was found to decrease (99, 26 and 11%) in going from primary, to secondary to tertiary alcohols, respectively. Phenoxyacetic acid (α-substituted acid) gave the ester in 85% yield while cinnamic acid (α,β-unsaturated acid) gave a 99% yield of ester. Menthyl acetate (57%) was prepared in the same configuration using menthol (chiral alcohol) and acetic acid. The methyl ester of Naproxen (81%) was obtained in the same configuration from Naproxen (chiral acid) and methanol.

Reusability of catalyst was checked by the esterification of lauric acid with methanol catalyzed by polyaniline sulfate salt and resulted in a stoichiometric yield (99%). The experiment was repeated nine times with the same filtered catalyst and it gave the corresponding ester in the same high yield (99%). After completing ten cycles, the catalyst, polyaniline sulfate salt was recovered and characterized. The results for the used polyaniline sulfate salt catalyst were found to be essentially the same as that of the polyaniline sulfate salt prepared originally (Table 4).

Table 4 Comparison of polyaniline sulfate salt used ten times as catalyst in the esterification reaction with that of fresh polyaniline sulfate salt

	Polyaniline sulfate salt	
Properties	Fresh[a]	Used as catalyst
Amount of acid present in the polyaniline sulfate salt (%)	25.3	24.7
Pellet density/g cm^{-3}	1.20	1.18
Particle size/μm	10–100	1–90
Conductivity/S cm^{-1}	4	5

[a] Ref. 21.

The esterification reaction has been carried out using monoaliphatic carboxylic acids, α-substituted acid, α,β-unsaturated acid; primary, secondary and tertiary alcohols; chiral alcohols and chiral acids. The advantages of polyaniline salt catalysts over the conventional catalyst are: (i) preparation of polyaniline salts through a simple synthetic route, (ii) various types of polyaniline salts can be synthesized, (iii) the amount of acid in the polyaniline chain can be varied, (iv) quick regeneration of the catalyst, and (vi) better reusability of the catalyst.

Conclusion

Polyaniline salts are used as catalysts in the esterification of carboxylic acids with alcohols. Preparation and handling of the catalyst are easy. This catalyst can be easily separated and reused, there is no acidic waste and catalyst life time can be maximized. Polyaniline salts are environmental-friendly. However, esterification reactions take longer (20 h) and also require higher amount of catalyst (15 wt%) to obtain the ester in quantitative yield. Work is in progress to modify the polyaniline system and thereby increase the efficiency of the catalyst. The use of polyaniline salts as catalysts in organic transformations may open up future work in the catalysis field.

Experimental

In a typical experiment, esterification of lauric acid (1 g) and methanol (4 ml) was carried out in a 10 ml round bottom flask with 200 mg of polyaniline sulfate powder. The reaction mixture was refluxed at 70 °C for 24 h. The reaction mixture was filtered and washed with chloroform to recover the catalyst. The chloroform solvent and unreacted methanol were evaporated off. The compound was loaded a column containing silica gel of finer than 200 mesh and eluted with 20:80 chloroform–hexane (400 ml). The solvent mixture was recovered to obtain the pure ester.

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KF/natural phosphate as an efficient catalyst for synthesis of 2′-hydroxychalcones and flavanones

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Potassium fluoride supported on natural phosphate has a strong basic activity which can be efficiently used to promote the Claisen–Schmidt reaction of 2′-hydroxyacetophenones with benzaldehydes.

Introduction

The use of heterogeneous catalysts under solvent-free conditions represents a potentially valuable and clean route to a range of organic products.[1,2] The use of naturally-occurring minerals as catalysts or catalyst supports has been a particularly useful area of research; in particular, many catalysts based on clay minerals have found use in such systems, especially Montmorillonite K10, and related acid treated clays.[3] Few basic catalysts have been utilised in such a way, one example being KF/alumina,[4] which has been used to catalyse a number of reactions, with the Henry reaction being catalysed by hydrotalcites in the absence of solvent, but in an excess of nitroalkane.[5]

We now report results based on the naturally occurring material natural phosphate (NP). This mineral, brought from the region of Khouribgra in Morocco, belongs to the mineralogical family of phosphocalcic apatite. NP has been exploited in many synthetic applications and both basic and acid activity has been demonstrated. Thus NP alone, or doped with mineral salts, has been used to promote many reactions: Knoevenagel reaction,[6] nitrile hydration,[7] α-hydroxyphosphonate synthesis,[8] Michael addition,[9] dipolar cycloaddition,[10] and acyclonucleoside synthesis.[11]

The preparation of the KF/NP material involves a simple evaporation of potassium fluoride solution in the presence of NP. Such a process has been used for the production of KF/Al_2O_3,[12] as well as KF/ZnO and KF/$AlPO_4$.[13] The latter two are useful catalysts for the Michael reaction[13] and low temperature butene isomerisation,[14] respectively. While their structures have not been thoroughly investigated, Zhu and Xu indicate that there is an interaction of KF with the AlPO4 support.[14] KF/Al_2O_3 is the most thoroughly studied and it is well established that the structure is a complex mixture of various tetra- and hexa-fluoroaluminates, as a result of extensive reaction between the components.[12]

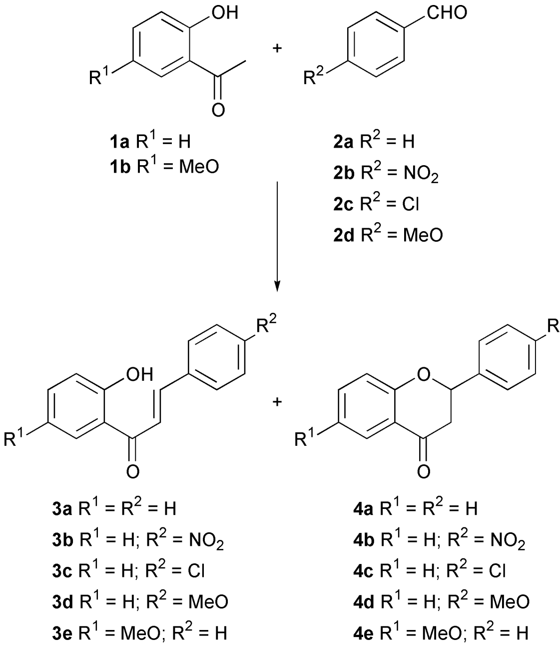
We now present results on the synthesis and use of KF/NP, which indicate that some structural reorganisation does take place in the preparation of KF/NP, and that the resultant material is an efficient base catalyst.

The catalyst is evaluated in the condensation reaction of 2’-hydroxyacetophenones **1** with aromatic aldehydes **2**, leading to chalcones **3** and flavanones **4** (Scheme 1), compounds of interest pharmacologically, especially in the areas related to anti-oxidant activity.[15–19] Such a reaction has been investigated using heterogeneous catalysts before, with interesting results.[20–24]

Results and discussion

Preparation and characterisation of KF/NP catalysts

The catalysts were prepared by addition of NP to a solution of KF in water. Ratios of NP : KF were varied on a mass basis from



Scheme 1 Condensation of aldehydes and 2′-hydroxyacetophenones, giving chalcones and flavanones.

Green Context

Solvent, used for reaction mixtures and purification, is often the largest contributor to chemical waste for a given process. Eliminating solvent is therefore a frequent goal in green chemistry, but it is a goal that is not easily achieved. Here, the authors describe a solvent-free system for the condensation of 2′-hydroxyacetophenones with aromatic aldehydes to give chalcones and flavonones, using a solid catalyst derived from KF and the mineral 'natural phosphate'. The reactions products are of interest, for example as antioxidants. Yields and conversion are excellent, and catalyst recycle is demonstrated. ***JKB***

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2 : 1 to 16 : 1. Evaporation of water gave the catalysts, designated by the codes KF/NP-*r* where $r = 2–16$, and represents the mass ratio of NP : KF. The catalysts were all grey powders, the colour of NP itself.

The analysis of the material is illustrated by KF/NP-8, the most active of the catalysts. X-Ray diffraction of KF/NP-8 gives a diffraction pattern almost identical to that of NP itself. Peak positions and intensities are essentially unaltered, except for a minor reduction in intensity. This result indicates that the crystalline structure of the support remains essentially unaltered in the catalyst, and also indicates that no crystalline KF phase is present. Thus the KF is well dispersed throughout the material. Interestingly, the surface areas of NP and KF/NP-8, as measured by nitrogen adsorption, indicate an increase in surface area and pore volume on supporting KF. The surface area of NP is measured as 1.4 $m^2 g^{-1}$ (*i.e.* below the 2 $m^2 g^{-1}$ limit of the instrument) and the pore volume is 0.05 $cm^3 g^{-1}$, values which are consistent with a crystalline solid, something which is confirmed by the typical type II isotherm (according to the BDDT classification) displayed by the material. On supporting the KF, the surface area increases to 8.9 $m^2 g^{-1}$, and the pore volume to 0.128 $cm^3 g^{-1}$. Again the isotherm is of the same form. Supporting metal salts on solids will typically reduce the surface area of the material, whereas in this case the surface area has increased significantly, although it is still very low compared to solids such as alumina, clay and silica, which typically have surface areas of > 100 $m^2 g^{-1}$. Changes in the IR spectrum of the two materials are relatively minor, the major change being the presence of some additional H-bonded water at 3250 cm^{-1} and at 1636–1675 cm^{-1} for the supported material. Scanning electron micrograph images indicate that the morphology of the particles has altered significantly as a consequence of supporting KF onto NP, indicating that some significant change has taken place. Specifically, the particle size has reduced somewhat, but the shape has remained similar.

From the above it appears that supporting KF on NP causes the formation of a more open structure which incorporates KF in such a way that crystalline KF is not formed in significant quantities. However, it appears that the basic structure of the NP is not destroyed, indicating a less profound interaction of KF with NP than is the case with alumina. Further investigations into these reactions are planned.

The use of KF/NP as catalyst for the condensation of 2′-hydroxyacetophenones with benzaldehydes was investigated. This reaction produces chalcones and flavanones, both of which are of interest in a variety of applications, including their wide range of biological activities. Reactions were carried out under a variety of conditions, which were designed to optimise the system in a general way. The results generated indicate that KF/NP is a highly effective, general catalyst, based on inexpensive raw materials, which can work under solvent free conditions.

The reaction of 2′-hydroxyacetophenone **1a** with benzaldehyde **2a** was chosen to optimise the reaction conditions. 10 mmol of each reactant was added to a flask, heated to reaction temperature and the catalyst then added. Initially, the effect of temperature was analysed, with reactions being sluggish at 150 °C, but significantly quicker at 180 °C. Further optimisation was thus carried out at the latter temperature, in the absence of solvent. The influence of the mass of catalyst was investigated, and it was found that for 10 mmol of reactants, 1 g of KF/NP-4 was optimal (Table 1). Conversion increased up to this amount and then decreased significantly. While the increase is not dramatic from 0.25 g to 1 g catalyst, it was decided to continue optimisation with 1 g of catalyst.

During these reactions, it was noted that the degree of conversion of benzaldehyde was significantly higher than that of the acetophenone component, and that the formation of benzoic acid was noted, probably due to simple oxidation of benzaldehyde under the basic conditions of the reaction. Thus, prolonged reaction times (up to 12 h) failed to improve yields and conversion of the acetophenone. Such behaviour was also noted by Climent *et al.*[20] in this reaction using hydrotalcite catalysts. It was thus decided to add the benzaldehyde stepwise in an attempt to limit this side reaction. Thus half the benzaldehyde was added at the start of the reaction, and half after 55 min. Results are shown in Table 2.

Table 1 Influence of catalyst mass on the condensation of 2′-hydroxyacetophenone **1a** with benzaldehyde **2a** (10 mmol of each reactant)

	Conversion of 2′-hydroxyacetophenone **1a** (%)			
Time/h	0.25 g KF/NP-4	0.5 g KF/NP-4	1 g KF/NP-4	2 g KF/NP-4
1	21	20	29	15
2	25	30	40	28
4	40	46	56	32

Table 2 Influence of a two step addition of benzaldehyde on conversion of acetophenone **1a**

	Conversion of **1a** (%)	
Time/h	Two-stage addition	One-stage addition
0.5	20	—
1	50	29
2	87	40
3	88	—
4	88	56

It is clear that the stepwise addition of benzaldehyde dramatically enhances the conversion and reduces substantially the amount of oxidation to benzoic acid. Addition of benzaldehyde after 30 min resulted in a lower performance enhancement (76 rather than 88% conversion). Separate experiments show that, perhaps surprisingly, the addition of benzoic acid at the start of reaction does not reduce the rate of reaction, and thus appears not to be a catalyst poison.

Using this two-step addition protocol, we then studied the influence of the ratio NP : KF. The ratio was varied from 2 to 16, and the resultant catalysts evaluated. It was found that the catalyst with KF/NP-8 was the best catalyst, giving 95% conversion after 4 h reaction time (Table 3).

Having ascertained the optimum conditions and reaction procedure, we investigated the scope of the reaction with a range of reactants, and the results are shown in Table 4 below.

Table 3 Influence of mass ratio NP : KF on conversion

	Conversion of **1a** (%)			
Time/h	KF/NP-2	KF/NP-4	KF/NP-8	KF/NP-16
1	40	50	67	20
2	64	87	90	26
4	68	88	95	40

Table 4 Results obtained with a range of reactants

					Yield (%)	
R^1	R^2	Run	Time/h	Conversion of **1** (%)	**3**	**4**
H	H	a	1	67	30	35
			2	90	30	58
H	NO_2	b	1	77	37	39
			2	98	44	54
H	Cl	c	1	66	26	30
			2	91	23	54
H	OCH_3	d	1	65	29	36
			2	91	35	52
OCH_3	H	e	1	50	16	34
			2	54	16	36

It can be seen from Table 4 that for all aldehydes, the conversion is excellent. The only example where conversion is lower is for the 4-methoxyacetophenone, where the early stages of reaction proceed relatively rapidly, but the reaction does not proceed much beyond 50% conversion. The ratio of chalcone : flavanone varies from 0.42 in example c to 0.81 in example b after 2 h reaction time. While the exact reasons for this behaviour are not clear, studies of the formation of the chalcone,[25] its conversion to flavanone[26] and the adsorptive behaviours of both flavanones and chalcones on different solids[27] indicate that there are many subtle inter-relationships in the detailed mechanism, even in solution, which are further complicated by the presence of a solid catalyst.

Several solid catalysts have been investigated in the Claisen–Schmidt reaction. Barium oxides have shown some promise[23,28] but are relatively toxic, and are thus unattractive for environmentally benign processing. Quaternary ammonium hydroxides supported on MCM-41 have also shown promise[29] in this reaction, giving 65% conversion after 8 hours at 130 °C for the unsubstituted benzaldehyde and acetophenone. The combination of natural phosphate, water and a phase transfer catalyst, benzyltriethylammonium chloride has been shown to be very efficient for the same reaction of unsubstituted benzaldehyde and acetophenone.[30] Neither of the two catalyst systems above have been applied to the 2′-hydroxyacetophenone system. The main work which has been published on the 2′-hydroxyacetophenone/benzaldehydes system was carried out by Climent *et al.*[20] They compared a range of catalysts and several differently substituted reactants. A comparison of their results with those reported in this study is given in Table 5.

Table 5 Comparison of literature results for the reaction of substituted benzaldehydes **2** and acetophenones **1** after 1 h reaction time

Catalyst	Conversion of acetophenone **1a** (%)
KF/NP-8[a]	67
Zeolite X-NaCs	1
Sepiolite Cs	2
Hydrotalcite HY-102	12
Hydrotalcite C-13	78
Hydrotalcite C-14	60
MgO	40

[a] Result presented in this paper; all other results are from ref. 20.

As can be seen, the KF/NP system gives a somewhat lower conversion than hydrotalcite C-13 after 1 h reaction time, but significantly outperforms all the other catalysts studied. Indeed, the final conversion achieved by the hydrotalcite C-13 reaches 84% after 2 h reaction time, while KF/NP-8 has achieved 90% by this stage, and 95% after 4 h. Thus, KF/NP-8 appears to be the most efficient catalyst for this reaction.

Reuse studies were performed by filtering the catalyst from the reaction mixture after 2 h, washing briefly with dichloromethane, and allowing to dry at room temperature. The catalyst was then added to a fresh batch of reagents. It was found that a slightly higher yield of products (95%) was obtained upon first reuse, then activity dropped somewhat (70% after 2 h, but 90% after 4 h). One more reuse led to a low conversion (30% after 4 h). At this stage, a thorough wash with acetone (until washings were colourless) and reactivation at 150 °C for 4 h was sufficient to restore activity to that of the fresh catalyst. Selectivity was not affected.

Extending the comparison to a wider range of substrates illustrates that the KF/NP-8 catalyst is consistently efficient, and is less affected by substituent effects than the hydrotalcite[20] (Table 6).

Thus it can be seen that KF/NP catalysts represent a very active and versatile class of catalysts for the Claisen–Schmidt reaction of 2′-substituted acetophenones.

Table 6 Comparison of literature results for the reaction of acetophenone **1a** with benzaldehyde **2a** after 1 h reaction time

Conversion of **1** (%)			Yield (%)[a]			
			3		**4**	
C-13	KF/NP-8	Run[b]	C-13	KF/NP-8	C13	KF/NP-8
78(84)	67(90)	a	50	30(30)	28	35(58)
61	77(98)	b	16	37(44)	45	39(54)
35	66(91)	c	27	26(23)	8	20(54)
17	65(91)	d	7	29(35)	10	36(52)
23	50(54)	e	16	16(16)	7	34(36)

[a] Figures in parenthesis indicate conversion or yield respectively after 2 h (where available). [b] See Table 4

Experimental

Natural phosphate was prepared using the following procedure: Natural phosphate (NP) comes from an extracted ore in the region of Khouribga (Morocco). The fraction of 100–400 μm is isolated, washed with water, calcined at 900 °C for 2 h, sieved (63–125 μm) and conserved at 150 °C or in a desiccator.

Deionised water was used throughout. Potassium fluoride, the aldehydes and acetophenones were all obtained from Aldrich. The aldehydes were purified by distillation under reduced pressure before use. The other chemicals were used as received.

GC analysis was carried out using a Hewlett–Packard 6890 GC with autosampler, fitted with a DB-5 capillary column, using nitrogen as carrier gas.

Surface area and pore size analysis were carried out on a Micromeritics ASAP2010 instrument using nitrogen as adsorbent. Surface areas were calculated using the BET equation. SEM images were taken on a Hitachi S-2400 microscope. X-Ray diffraction was carried out on a Philips 1050 using Cu-Kα radiation. IR spectra were obtained using a diffuse reflectance accessory on a Bruker Equinox 55 instrument. Samples were prepared by dilution (10%) in KBr and preheated to 150 °C under vacuum before analysis.

Preparation of KF/NP-8

Natural phosphate (8 g) was added to a solution of KF (1.00 g) in water (100 ml). The mixture is stirred at room temperature for 30 min, then water is removed on a rotary evaporator under reduced pressure at a bath temperature of 60 °C. The solid obtained is then dried under vacuum at 150 °C for 2 h.

Condensation of acetophenones with benzaldehydes

A mixture of the acetophenone (10 mmol), the aldehyde (5 mmol) and *n*-tetradecane (0.60 g) was heated to 180 °C on an oil-bath. After the reaction temperature was reached, the catalyst (1 g) was added. After 55 min, a further quantity of aldehyde (5 mmol) was added and the reaction continued. Samples were taken at appropriate intervals for GC analysis using *n*-tetradecane as internal standard. Isolation of products is achieved by washing with small quantities of dichloromethane. Confirmation of product identity was achieved by GC-MS, and comparison with authentic samples.

Conclusions

The preparation of a series of catalysts based on natural phosphate and potassium fluoride has been described. Supporting KF on natural phosphate leads to an increased surface area and a more open structure, but does not appear to change the crystalline structure of the support significantly. The catalysts are shown to be very active in the Claisen–Schmidt reaction of various substituted benzaldehydes with substituted acetophenones. The conversions and yield of product obtained are excellent for a range of substrates, and demonstrate that the catalystsare both highly active and versatile.

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Selective synthesis of fluorinated ethers by addition reaction of alcohols to fluorinated olefins in water

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The green process for the preparation of fluorinated ether by the addition reaction of 2,2,2-trifluoroethanol to fluorinated olefins was examined. The selective synthesis of fluorinated ether was achieved by increasing the amount of the proton source in the reaction. The reaction with water as the proton source was a particularly environmentally friendly process, because a highly selective synthesis was achieved by means of a completely organic solvent-free procedure. Also, it allowed for a simple work-up, and a scaling up was easily performed.

Introduction

We have developed hydrogen-containing fluorinated ethers (HFEs) as alternatives to chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs).[1] HFEs have almost zero ozone depleting potential (ODP) due to the absence of a chlorine atom in the molecules.[2] As well, some HFEs have low global warming potential, and are expected to act as environmentally friendly alternatives.

There are many methods of preparing fluorinated ethers. The typical methods are as follows: (i) fluorination of the ether compound by F_2 gas,[3,4] (ii) fluorination of the ether compound by metal fluoride,[5] (iii) electro-chemical fluorination of the ether compound,[6] (iv) addition reaction of alcohol to fluorinated olefin under basic conditions,[7] and (v) nucleophilic reaction of fluorinated alkoxide.[8–12] Of these reactions, the addition reaction of alcohols to fluorinated olefins is the most convenient method to prepare HFEs from industrially available alcohols and fluorinated olefins.

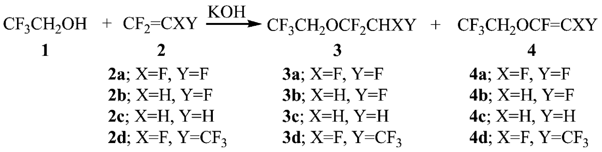
Many addition reactions of alcohols to fluorinated olefins have previously been reported.[13–21] In these reports, the reactions were carried out with or without the organic solvent, and unsaturated ether might be formed besides fluorinated ether. In some reports, the reaction mixture was treated with bromine, and then distilled to remove the unsaturated ether.[13,17] The removal of the unsaturated ether is easily performed, but the waste of the brominated compound is unavoidable and the production of the unsaturated ether lowers the yield of the saturated ether. In this paper, we investigated the addition reaction of 2,2,2-trifluoroethanol to fluorinated olefins, and achieved the selective synthesis of saturated ether. In addition, the mechanism for the production of unsaturated ether is discussed.

Results and discussion

Addition reactions of 2,2,2-trifluoroethanol to fluorinated olefins

The addition reactions of 2,2,2-trifluoroethanol **1** to fluorinated olefins **2** were carried out (Scheme 1, Table 1). In these reactions, potassium hydroxide was employed as a basic catalyst.

At first, the ratio of saturated ether **3** and unsaturated ether **4** was estimated in the addition reactions without the solvent or in 1,4-dioxane. In the addition reactions with tetrafluoroethylene **2a**, **3a** was obtained as the only product (Table 1, entries 1 and 2). In the reactions with trifluoroethylene **2b**, vinylidene fluoride **2c** or hexafluoropropene **2d**, not only **3** but also **4** was obtained (Table 1, entries 3, 4, 7, 8, 11 and 12). In the reactions to **2d**, some components with high molecular weight were detected by GC-MS. It was considered that these compounds were formed by the addition reaction of **1** to **4d**,[22] and the generation of these compounds lowered the yield of **3d**. In the reaction to **2b** or **2d** using an excess amount of **1** as the solvent, the yield and the selectivity of **3** were higher than that without the solvent or in 1,4-dioxane (Table 1, entries 5 and 13). Under the same conditions, the reaction to **2c** did not proceed efficiently, because a high pressure of **2c** was necessary (Table 1, entry 9). In the reaction to **2b**, **2c** or **2d**, the reactions were carried out in water. In any of these cases, the yield and the



$$\underset{\mathbf{1}}{CF_3CH_2OH} + \underset{\mathbf{2}}{CF_2{=}CXY} \xrightarrow{KOH} \underset{\mathbf{3}}{CF_3CH_2OCF_2CHXY} + \underset{\mathbf{4}}{CF_3CH_2OCF{=}CXY}$$

2a; X=F, Y=F	**3a**; X=F, Y=F	**4a**; X=F, Y=F
2b; X=H, Y=F	**3b**; X=H, Y=F	**4b**; X=H, Y=F
2c; X=H, Y=H	**3c**; X=H, Y=H	**4c**; X=H, Y=H
2d; X=F, Y=CF_3	**3d**; X=F, Y=CF_3	**4d**; X=F, Y=CF_3

Scheme 1 Addition reactions of 2,2,2-trifluoroethanol **1** to fluorinated olefins.

Green Context

Hydrogen-containing fluorinated ethers may contribute towards the development of replacements for CFCs. Some of these molecules look to be well-suited to such a role, and new cleaner methods for their synthesis are required. This paper describes an aqueous route to the products, which involves a selective high-yielding addition reaction carried out in water, with the product being isolated by direct distillation. Such an approach involves mild conditions and little waste. ***DJM***

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Table 1 Addition reactions of 2,2,2-trifluoroethanol **1** to fluorinated olefins[a]

Entry	**2**	Solvent	Temp./°C	Time/h	Yield (%)[b] **3**	**4**
1	CF_2=CF_2 (**2a**)	None	70	24	90	0
2	CF_2=CF_2 (**2a**)	1,4-Dioxane	70	0.5	99	0
3	CF_2=CHF (**2b**)	None	70	24	75	9[g]
4	CF_2=CHF (**2b**)	1,4-Dioxane	70	0.5	58	42[g]
5[c]	CF_2=CHF (**2b**)	**1**	70	24	81	8
6[d]	CF_2=CHF (**2b**)	H_2O	70	24	85	1
7[e]	CF_2=CH_2 (**2c**)	None	70	24	46	44
8	CF_2=CH_2 (**2c**)	1,4-Dioxane	70	0.5	16	83
9[c]	CF_2=CH_2 (**2c**)	**1**	70	24	22	13
10[d]	CF_2=CH_2 (**2c**)	H_2O	70	24	81	3
11	CF_2=$CFCF_3$ (**2d**)	None	25	24	70	18[g]
12	CF_2=$CFCF_3$ (**2d**)	1,4-Dioxane	25	0.5	69	29[g]
13[c]	CF_2=$CFCF_3$ (**2d**)	**1**	25	24	84	0
14[d]	CF_2=$CFCF_3$ (**2d**)	H_2O	25	24	83	3
15[df]	CF_2=$CFCF_3$ (**2d**)	H_2O	25	24	92	1

[a] *Reaction conditions*: **1** (1.0 mmol), **2** (7.5 mmol), solvent (none or 1.0 ml), KOH (1.0 mmol). [b] Yields were determined by NMR and based on **1**. [c] **1** (3.0 mmol), **2** (1.0 mmol). Yield was based on **2**. [d] H_2O (0.1 ml). [e] $CH_3COOCH_2CF_3$ was obtained in 6% yield..[14] [f] KOH (0.2 mmol). [g] Mixture of *cis* and *trans* isomers.

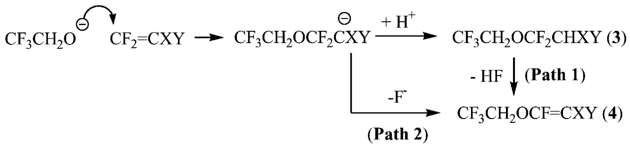
selectivity of **3** were quite high (Table 1, entries 6, 10 and 14). By using a smaller amount of potassium hydroxide, the yield and the selectivity of **3d** were further improved (Table 1, entry 15). The reactions of other fluorinated alcohols to hexafluoropropene were examined briefly. For $CF_3CF_2CH_2OH$ or $(CF_3)_2CHOH$, high yield and selectivity were also obtained.

In the reactions to any fluorinated olefins, the use of an excess amount of alcohol or water as the solvent was effective for the selective synthesis of the saturated ether. However, when using an excess amount of the alcohol as the solvent, only some fluorinated olefins reacted efficiently, and it was necessary to isolate the product from the solvent. The reaction in water is a completely organic solvent-free procedure, and a simple work-up can be performed. The fluorinated ether can be extracted easily after the reaction, because the layer of fluorinated ether and the aqueous layer can be separated.

Mechanism for production of unsaturated ether

To authenticate the solvent effect, the mechanism for the production of unsaturated ether **4** was examined. There are two plausible mechanisms for the production of **4**. One is the dehydrofluorination of **3** (Scheme 2, path 1), while the other is the elimination of fluoride anion from the carbanion intermediate (Scheme 2, path 2).

To clarify the contribution of path 1, the stabilities of saturated ethers under the basic conditions were observed (Table 2). The conditions were as follows: a mixture of **3** (1.0 mmol), **1** (1.0 mmol) and potassium hydroxide (1.0 mmol) was stirred. **3b** was recovered quantitatively and no unsaturated ether was detected (Table 2, entries 1 and 2). **3c** was recovered in 95% yield, but no **4c** was detected (Table 2, entry 3). It was presumed that the 5% loss of **3c** was due to the hydrolysis of $CH_3COOCH_2CF_3$ formed by the decomposition of **3c**. For **3d** in 1,4-dioxane, **3d** was recovered with only 72% yield, and the reaction mixture contained a small amount of **4d** and some components with high molecular weight (Table 2, entry 6).



Scheme 2 Mechanism for production of unsaturated ether.

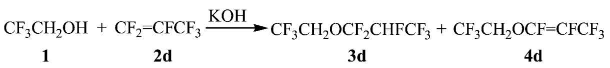
Table 2 Stabilities of saturated ethers under basic conditions

Entry	$CF_3CH_2OCF_2CHXY$ (**3**)	Solvent	Time/ h	Temp./ °C	Recovery of **3** (%)
1	$CF_3CH_2OCF_2CH_2F$ (**3b**)	None	24	70	100
2	$CF_3CH_2OCF_2CH_2F$ (**3b**)	1,4-Dioxane	0.5	70	100
3	$CF_3CH_2OCF_2CH_3$ (**3c**)	None	24	70	95
4	$CF_3CH_2OCF_2CH_3$ (**3c**)	1,4-Dioxane	0.5	70	100
5	$CF_3CH_2OCF_2CHFCF_3$ (**3d**)	None	24	25	100
6	$CF_3CH_2OCF_2CHFCF_3$ (**3d**)	1,4-Dioxane	0.5	25	72
7	$CF_3CH_2OCF_2CHFCF_3$ (**3d**)	H_2O	24	25	100

However, **3d** was recovered quantitatively in the case of no solvent or in water (Table 2, entries 5 and 7).

From these results regarding the stabilities of the saturated ethers, only in the addition reaction of **1** to **2d** in 1,4-dioxane, would unsaturated ether be formed *via* both paths 1 and 2, but in the other reactions, path 2 is the exclusive mechanism. Thus, path 2 must be effectively avoided for the selective synthesis of saturated ethers; this was achieved by increasing the amount of the proton source such as water or alcohol in the reaction.

Scaling up



Scheme 3 Scaling up addition reactions of 2,2,2-trifluoroethanol to hexafluoropropene.

It was confirmed that the addition reaction in water was remarkably effective for the selective synthesis of saturated ethers. In industrial production, this type of reaction could be carried out by feeding the gas of fluorinated olefin to the mixture of the alcohol, the basic catalyst and the solvent during the reaction, because this procedure does not require a large apparatus. The addition reaction of **1** to **2d** was then carried out by means of this procedure (Scheme 3, Table 3). To quantify the effect of water in this procedure, reactions without the solvent or in 1,4-dioxane were also carried out. In the latter cases, **3d** was obtained in only a fair yield, and **4d** and some components with high molecular weight were also obtained (Table 3, entries 1

Table 3 Scaling up addition reactions of 2,2,2-trifluoroethanol to hexafluoropropene

Entry	**1**/mol	KOH/ mol	Solvent[a]	Pressure of **2d**/MPa	Temp./ °C	Time/ h	Yield (%)[b] **3d**	**4d**
1	0.5	0.2	None	< 0.3	20	1	73	21
2	0.1	0.1	1,4-Dioxane	< 0.3	20	0.5	58	8
3	0.1	0.1	H_2O	0.5	70	7	97	< 1
4	0.3	0.1	H_2O	0.5	20	2	96	< 1

[a] Solvent (50 ml). [b] Yields were determined by NMR.

and 2). In using water as the solvent, **3d** was obtained in an almost quantitative yield (Table 3, entries 3 and 4). Although water works as a poor solvent and prevents fluorinated olefin from being dissolved to alcohol, the reaction rate could be accelerated by increasing the ratio of **1** to water.

Experimental

General

All organic reagents and solvents were purified prior to use. Fluorinated olefins were used without purification. KOH was based on 86% purity. ^{1}H and ^{19}F NMR were measured using a JNM-LA300 instrument (JEOL, 300 MHz) and employing TMS and $CFCl_3$ as an internal standard and $CDCl_3$ as a solvent. MS spectra were measured using the Hewlett-Packard 5790 series system equipped with a jet separator for the 5890A GC. HRMS spectra were measured using Hitachi M-80B.

Typical procedure for the addition reaction

2,2,2-Trifluoroethanol (1.0 mmol), potassium hydroxide (0.1 mmol) and the solvent were placed in a stainless-steel reactor equipped with a stop valve (volume: 10 ml). After cooling the reactor with liquid N_2, fluorinated olefin (7.5 mmol) was introduced to the reactor with a vacuum line and stirred. Products were transferred from the reaction mixture and fractionated through traps at −60, −114 and −196 °C with a vacuum line. The saturated ether and the unsaturated ether were trapped at −114 °C. The structures of the products were determined by ^{1}H, ^{19}F and MS spectra. The ratio of the products was determined by ^{1}H and ^{19}F NMR spectra.

The synthesis of **3a–d**,[18] **4a**,[23] **4b**[24] and **4c**[25] have previously been reported. However, the spectroscopic data for **4c** have not been reported, while **4d** is a new compound.

Preparation of unsaturated ethers

Sodium 2,2,2-trifluoroethoxide (1.0 mmol) and dried diglyme (1.0 ml) were placed in a stainless-steel rector equipped with a stop valve (volume: 10 ml). After cooling with liquid N_2, fluorinated olefin (2.0 mmol) was introduced to the reactor with a vacuum line. The reactor was warmed to ambient temperature and stirred for 24 h. Products were transferred from the reaction mixture and fractionated through traps at −60, −114 and −196 °C with a vacuum line. The unsaturated ether was trapped at −114 °C. The structures of the products were determined by ^{1}H, ^{19}F NMR and MS spectra.

1-Fluoro-1-(2,2,2-trifluoroethoxy)ethene 4c

This compound was prepared from vinylidene fluoride: yield 81%.

δ_H ($CDCl_3$, 300 MHz, Me_4Si) 3.55 (d of d, 1H, J = 4.7, 39.6 Hz), 3.83 (d of d, 1H, J = 4.7, 5.5 Hz), 4.19 (q, 2H, J = 7.9 Hz), δ_F($CDCl_3$, 282 MHz, $CFCl_3$) −74.6 (d of t, 3F, J = 1.2, 7.9 Hz), −84.1 (d of d of q, 1F, J = 1.2, 5.5, 39.6 Hz). MS: *m*/*z*, 144 (M^+), 83 ($CF_3CH_2^+$), 45 (CH_2CF^+), 42, 33.

1,1,1,2,3-pentafluoro-3-(2,2,2-trifluoroethoxy)-2-propene 4d

This compound was prepared from hexafluoropropene: yield 70% (*cis*/*trans* = 33/67).

***cis*-Isomer**. δ_H ($CDCl_3$, 300 MHz, Me_4Si) 4.39 (q, 2H, J = 7.9 Hz), δ_F ($CDCl_3$, 282 MHz, $CFCl_3$) −68.1 (complex, partially resolved, d of d, 3F, J = 9.8, 12.8 Hz), −74.8 (t of q, 3F, J = 1.8, 7.9 Hz), −97.6 (d of q, 1F, J = 20.5, 9.8 Hz), −181.6 (d of q, 1F, J = 20.5, 12.8 Hz).

***trans*-Isomer**. δ_H ($CDCl_3$, 300 MHz, Me_4Si) 4.31 (q, 2H, J = 7.9 Hz), δ_F ($CDCl_3$, 282 MHz, $CFCl_3$) –68.1 (d of d, 3F, J = 12.8, 22.0 Hz), −75.2 (t, 3F, J = 7.9 Hz), −113.0 (d of q, 1F, J = 121.5, 22.0 Hz), −188.4 (d of q, 1F, J = 121.5, 12.8 Hz).

***cis* and *trans*-Isomers**. HRMS (ES): calc. for $C_5H_2F_8O$, 229.9978; found, 229.9963. MS: *m*/*z*, 230 (M^+), 211 (M − F), 83 ($CF_3CH_2^+$), 69 (CF_3^+), 33.

Typical procedure for evaluation of stability of saturated ether

Saturated ether (1.0 mmol), 2,2,2-trifluoroethanol (1.0 mmol), potassium hydroxide (0.1 mmol) and the solvent were placed in a stainless-steel rector equipped with a stop valve (volume: 10 ml) and stirred. Products were transferred from the reaction mixture and fractionated through traps at −60, −114 and −196 °C with a vacuum line. The saturated ether was trapped at −114 °C.

Typical procedure for scaling up reaction

2,2,2-Trifluoroethanol (0.1 mol), potassium hydroxide (0.1 mol) and the solvent (50 ml) were placed in a stainless-steel reactor (volume: 250 ml). After cooling the reactor with liquid N_2, the reactor was warmed up to ambient temperature. Hexafluoropropene was introduced to the reactor and fed continuously during the reaction. The pressure of the hexafluoropropene was kept constant, and the temperature was controlled by cooling the reactor. After stopping the consumption of hexafluoropropene, the organic layer was extracted. The ratio of the products was determined by ^{1}H and ^{19}F NMR spectra.

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22 The highest *m*/*z* of some components with high molecular weight were 311 or 310 by GC-MS. It was suspected that the peak (*m*/*z*: 311) was derived from the fragment ion $[M - F]^{\cdot+}$ peak of $(CF_3CH_2O)_2CFCHFCF_3$ or $CF_3CH_2OCHFCF(OCH_2CF_3)CF_3$, and the peak (*m*/*z*: 310) was derived from the molecular ion peak of $(CF_3CH_2O)_2C{=}CFCF_3$ or $CF_3CH_2OCF{=}C(OCH_2CF_3)CF_3$.
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Pd-catalysed coupling reactions in supercritical carbon dioxide and under solventless conditions

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The homocoupling of iodoarenes catalysed by $Pd(OCOCF_3)_2/P(2\text{-furyl})_3$ occurs best in $scCO_2$ and under solventless reaction conditions, and provides an attractive alternative to previously reported procedures. A comparison of the results in these cases suggests interesting preferential solvation effects are occurring in $scCO_2$. Each of the methods investigated has advantages and disadvantages which need to be carefully considered before the method of choice is determined.

Introduction

New methods of carbon–carbon bond formation such as those catalysed by transition metals are of great importance to synthetic chemists owing to their versatility and power in assembling complex and often synthetically challenging carbon frameworks. However, they are generally carried out in conventional solvents such as *N*,*N*-dimethylformamide which can limit their attractiveness from the environmental point of view.[1] Notable exceptions to this are the use of environmentally acceptable alternative solvents such as water (although this has limitations resulting from the relative insolubility of organic compounds in such a reaction medium)[2] and ionic liquids.[3,4] Our initial interest in this area was to develop methods to allow such reactions to be carried out in supercritical CO_2 ($scCO_2$)[5] which also has promise as an environmentally benign reaction medium, however in the course of these studies we have also found it necessary to investigate reactions in the absence of solvent, which is another alternative green technology rapidly emerging in importance.[6] Our results reported in this paper demonstrate striking similarities between these two methods, and allow a comparison of the techniques which is of increasing importance when deciding on which particular methodology has the most green potential.[7]

We have recently reported methods which enable Heck, Suzuki and Stille reactions to be efficiently carried out in $scCO_2$ using simple commercially available reagents.[8] This relied on the known enhanced solubility of fluorinated palladium sources (*e.g.* $Pd(OCOCF_3)_2$ and $Pd(F_6\text{-acac})_2$) over those more conventionally used (*e.g.* $Pd(OAc)_2$), and the use of more lipophilic phosphine ligands (*e.g.* PBu_3, PCy_3, $P(2\text{-furyl})_3$ (TFP)) which also have enhanced solubility in $scCO_2$ compared to the more conventional PPh_3. In the course of this work, we encountered an important and mechanistically interesting Pd-catalysed biaryl formation as a side reaction which would appear to be particularly facile in $scCO_2$. This forms the basis of the results described in this paper.

Results

In the course of our studies on Pd-catalysed reactions in $scCO_2$, we decided to investigate the use of acrolein as the alkene component in the Heck coupling reaction with iodobenzene, as it is known to be particularly poor, and we hoped that switching to an unusual reaction medium such as $scCO_2$ might improve the efficiency of such a reaction. We were disappointed to find that the proposed Heck reaction was unsuccessful, but instead were intrigued to find that the major product was biphenyl, arising from the oxidative coupling of iodobenzene. It was possible to optimise this reaction further by carrying it out in the absence of acrolein, to give biphenyl in 95% isolated yield (Table 1, entry 1).

A survey of the literature revealed that similar reactions had been reported before, although they generally required the presence of additives such as tetra-*n*-butylammonium bromide (TBAB),[9] Zn/H_2O with Pd/C,[10] the use of palladacycle catalysts[11] or $Pd(OAc)_2$ often at temperatures much higher than the ones we were using (140 *cf.* 75 °C) requiring polar (and generally toxic) solvents such as DMF and DMA.[12,13] This latter observation is intriguing in that it is this reaction which bears most similarity to our work, yet is reported not to proceed in non-polar solvents such as *p*-xylene, which would be expected to be most similar to $scCO_2$ in terms of its solvent properties, particularly when compared to DMF. Indeed, on repeating our reaction in toluene, which is often considered to be a good model solvent for $scCO_2$, we observed only traces of the coupling product (Table 1, entry 2). This poses some important questions regarding the role solvent, particularly $scCO_2$, plays in these processes, and general assumptions often made regarding such reactions. We therefore decided to investigate the reaction in more detail to compare its efficiency in $scCO_2$, in toluene as a representative non-polar solvent, with and without the presence of TBAB for comparison with earlier work,[9] and under solventless conditions.[14] Initial results compared the coupling reaction of iodobenzene, and are summarised in Table 1.

Green Context

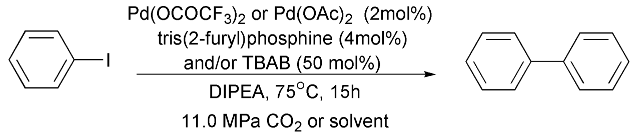
The choice of solvent can play a critical role in the development of a clean process. Here, a comparison of a range of solvents is carried out, with emphasis on $scCO_2$ and solvent-free conditions. Interestingly, there are many similarities between these two media, the reasons for which are discussed using the coupling reaction of iodoaromatics.

DJM

It can be seen that there is a dramatic difference between reactions carried out in $scCO_2$ and toluene as already discussed. In the presence of TBAB the reaction in toluene is now significantly better (Table 1, entry 3), but note that $Pd(OCOCF_3)_2$ is significantly better than $Pd(OAc)_2$ (Table 1, entry 4), a factor not previously noted. Isolated yields tend to be lower in these reactions due to problems removing tetrabutylammonium residues (Table 1, entry 3).[9] It is also interesting to note that use of both TFP and TBAB in toluene in the same reaction results in suppressing the reaction totally. Note also that the solventless reaction proceeds well without addition of TBAB, although not quite as well as for $scCO_2$. In all cases where significant reaction is observed, a red colouration indicative of oxidation of the diisopropylethylamine (DIPEA) is observed which is consistent with the proposed mechanism in previous reports.[9,12]

We then investigated the coupling of functionalised iodoarenes to determine the effect of substitutents on the efficiency of the reaction (Table 2). These results show that the reaction is generally favoured by electron donating groups (CH_3, OCH_3), but in the presence of strong electron withdrawing groups (NO_2, CO_2CH_3), yields of the biaryl products are lower due to reductive deiodination which is now a serious side reaction, as is also often the case with alternative procedures.[9–13] In general, observations are similar to those for iodobenzene in that reactions are most efficient in $scCO_2$, but also work well in the absence of solvent. In toluene, conversions are low, but can be significantly improved by addition of TBAB. In the case of 4-iodonitrobenzene, reactions in $scCO_2$ and toluene proceed to completion even in the absence of TBAB, however the extent of reduction is significantly lower in toluene if TBAB is present. Importantly, for the solventless reaction, a very low conversion

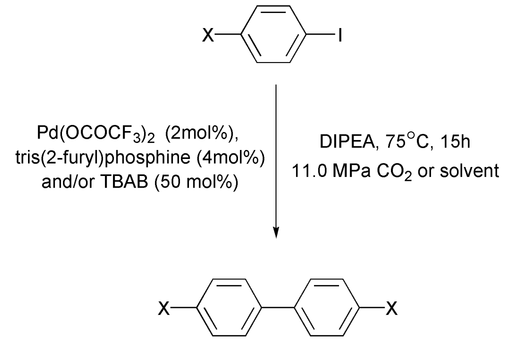
Table 1 Homocoupling of iodobenzene under various reaction conditions



Entry[a]	Catalyst	Ligand	Additive	Solvent	Conversion[b] (%)	Yield[c] (%)
1	$Pd(OCOCF_3)_2$	TFP	—	$ScCO_2$	>95	95
2	$Pd(OCOCF_3)_2$	TFP	—	Toluene	12	n.d.
3	$Pd(OCOCF_3)_2$	—	TBAB	Toluene	90	66
4	$Pd(OCOCH_3)_2$	—	TBAB	Toluene	18	n.d.
5	$Pd(OCOCH_3)_2$	TFP	TBAB	Toluene	0	n.d.
6	$Pd(OCOCF_3)_2$	TFP	—	Solventless	76	n.d.

[a] Reactions were carried out at 75 °C using $Pd(OCOCF_3)_2$ or $Pd(OAc)_2$ (2 mol%) and DIPEA (1.6 equiv.), with TFP (4 mol%) and/or TBAB (50 mol%) as required. [b] Determined by ^1H NMR. [c] n.d. = Not determined.

Table 2 Homocoupling of substituted iodobenzenes under various reaction conditions



Entry[a]	X	Ligand	Additive	Solvent	Conversion[b] (%)	Yield[c] (%)
1	CH_3	TFP	—	$ScCO_2$	>95	87
2	CH_3	TFP	—	Toluene	11	n.d.
3	CH_3	—	TBAB	Toluene	36	n.d.
4	CH_3	TFP	—	Solventless	72	n.d.
5	OCH_3	TFP	—	$ScCO_2$	>95	82
6	OCH_3	TFP	—	Toluene	16	n.d.
7	OCH_3	—	TBAB	Toluene	27	n.d.
8	OCH_3	TFP	—	Solventless	83	80
9	NO_2	TFP	—	$ScCO_2$	>95	44 (1:1)
10	NO_2	TFP	—	Toluene	>95	24 (1:2)
11	NO_2	—	TBAB	Toluene	95	n.d. (7:3)
12	NO_2	TFP	—	Solventless	<5	n.d.
13	CO_2CH_3	TFP	—	$ScCO_2$	>95	46 (1:1)
14	1-Iodonaphthalene	TFP	—	$ScCO_2$	15	n.d.(1:1)
15	1-Iodonaphthalene	TFP	—	Toluene	11	n.d.(1:4)
16	1-Iodonaphthalene	—	TBAB	Toluene	39	n.d.(1:3)
17	1-Iodonaphthalene	TFP	—	Solventless	28	n.d.

[a] Reactions were carried out at 75 °C using $Pd(OCOCF_3)_2$ (2 mol%), DIPEA (1.6 equiv.), with TFP (4 mol%) and/or TBAB (50 mol%) as required. [b] Determined by ^1H NMR. [c] n.d. = Not determined; values in parenthesis are ratio of biaryl formation to reductive deiodination.

is obtained in this case presumably due to the high melting point of 4-iodonitrobenzene (175–177 °C),[15a] and its low solubility in the neat reaction mixture (Table 2, entry 12). This contrasts sharply with the high conversion observed in $scCO_2$ (Table 2, entry 9) in which the 4-iodonitrobenzene would be expected to have at least some solubility. Attempted coupling of 1-iodonaphthalene was poor under all conditions but proceeded best in toluene in the presence of TBAB (Table 2, entry 16). The poor conversion of the reaction in $scCO_2$ can be readily explained, as a definite liquid layer was visible in the bottom of the reaction vessel under typical reaction conditions, consistent with the known low solubility of polycyclic aromatics in this medium.[16]

Discussion

The results show that the homocoupling of iodoarenes to form biphenyl derivatives can be an efficient process under a variety of conditions.[17] One of the most striking aspects of these results is the similarity between solventless reaction conditions and those obtained in $scCO_2$, which contrast sharply with those obtained in a non-polar solvent such as toluene. Previous results from our group have demonstrated related effects, where double bond migration following an intramolecular Heck reaction is significantly suppressed in $scCO_2$ and under solventless conditions when compared to reactions in conventional solvents such as toluene and acetonitrile.[14] Concern that reactions in $scCO_2$ could be occurring neat in the bottom of the reactor were addressed by carrying out studies in high pressure view cells. Small traces of liquid can be seen in some cases around the side of the vessels, and solid products precipitate out as they are formed, but the vast majority of reagents in the initial period of the reaction are in a homogeneous phase with the CO_2 unless otherwise stated. The difference in results observed in some cases between neat and $scCO_2$ reactions (*cf.* entries 1 and 4, 9 and 12, 14 and 17, Table 2), and analogy with our previously reported homogeneous Pd-catalysed coupling reactions,[8,14] also strongly suggest the reactions are occurring in the supercritical phase. The possibility that these reactions may be occurring neat cannot be totally discounted, but if this were to be the case, the reactions reported here would represent further examples of carbon dioxide accelerated solventless reactions, which are fascinating themselves.[18] However a more likely explanation to account for the similarity of the results obtained in $scCO_2$ and under solventless can be obtained by considering the nature of reactions in $scCO_2$ in more detail.

A common problem when using $scCO_2$ as a reaction medium is that because of its generally weak solvent power, we are often working at the borderline of solubility. Whilst many of the catalyst systems we have devised have high solubility in $scCO_2$,[8,14] the $Pd(OCOCF_3)_2/P(2\text{-furyl})_3$ system is somewhat borderline, with small traces of solid being visible. The base (DIPEA) is totally miscible with the $scCO_2$.[19] However some of the reagents we are using have a finite solubility in *pure* $scCO_2$, significantly less than the typical concentrations of our reactions. For example, iodobenzene has a solubility of approximately 1.8 mg ml^{-1} in $scCO_2$ at 80 °C, 107 bar[18] and other more polar arenes (*e.g.* 4-iodonitrobenzene) are likely to be significantly less soluble. We are typically working at a concentration of 18 mg ml^{-1} iodobenzene with 25 mg ml^{-1} of DIPEA. The $Pd(OCOCF_3)_2$ catalyst is essentially insoluble in $scCO_2$ on its own, but rapidly dissolves in the presence of phosphine and base. It is thus the solubility of the combination of reagents which make up the reaction mixture which is important in determining whether a reaction is homogeneous and likely to proceed effectively. In order to improve the solvent power of $scCO_2$, co-solvents are often added such as MeOH, MeCN and toluene, and these can dramatically enhance the solvent power of the medium. However, reagents will also act as cosolvents, and in the case of this reaction, the amine, the phosphine and aromatic substrate will all help each other to dissolve in the $scCO_2$ medium. As a result, it would be expected that there would be preferential interaction between these reagents than with the CO_2 solvent. Indeed, such effects are well established for supercritical fluids[20] where local concentrations of cosolvents around substrates can be as high as 10 times the bulk values, particularly near the critical point. Although we are working at temperatures significantly higher than the critical point of CO_2 (31.1 °C), it is important to realise that for a given pressure, solvent power generally decreases with increasing temperature as the solvent density decreases. Hence factors which can enhance the solubility of reagents are still very important under the conditions we are working.

In light of these considerations, it is possible to suggest why these reactions in $scCO_2$ resemble those of solventless conditions more closely than those in non-polar solvents. If preferential solvation is occurring, then the reaction is most likely to be taking place in areas of exaggerated reagent concentration. This effectively forms a region similar in composition to a solventless reaction mixture, resulting in a similar product distribution. In a conventional non-polar solvent such as toluene, such an effect would not be expected as the individual organic reagents are all independently miscible with the solvent. It would also be expected that the solventless reaction mixture would be significantly more polar than toluene, particularly as organic salts are produced during the reaction. This may account for the similarity with reactions conducted in more polar solvents.[12,13]

The relative efficiencies of the different reaction media are worthy of comment. In general, reactions in $scCO_2$ are cleanest and easiest to purify, but require high-pressure apparatus. Reactions in toluene require the addition of TBAB for best conversions, which results in more complex purification procedures, lower isolated yields and significant waste. The solventless procedures are attractive, particularly on a small scale, although limitations with high melting reagents such as 4-iodonitrobenzene can be problematic, as may be efficient mixing and control of exotherms for larger scale processes. Reaction work-up and purification may require the use of solvents, as is also the case for reactions in $scCO_2$.[21] As with many aspects of green chemistry, the final choice of conditions will be determined by a variety of factors depending on the particular reaction. Comparative studies help identify potential advantages and disadvantages of the competing technologies, and will be crucial in assessing their relative impact in the green chemistry arena.

In summary, we have shown that the coupling reaction between iodoarenes occurs best in $scCO_2$ and under solventless reaction conditions, and provides an attractive alternative to previously reported procedures. The similarity between the results in these cases suggest interesting preferential solvation effects are occurring in $scCO_2$. Each of the methods investigated has advantages and disadvantages which need to be carefully considered before the method of choice is determined.

Experimental

Typical procedure

CAUTION: *As with all reactions under high pressure, appropriate safety precautions must be taken.* Iodobenzene (0.200 ml, 1.78 mmol), diisopropylethylamine (0.500 ml, 2.87 mmol), palladium trifluoroacetate (11.9 mg, 0.0356 mmol) and tris-2-furylphosphine (16.6 mg, 0.0712 mmol) were added in the order described to a 20.0 ml high-pressure reaction vessel, which was sealed and connected to a CO_2 supply (an Isco 260D controllable syringe pump with a cooled head).[5,8] The vessel was charged with CO_2 until a pressure of 48 bar was obtained and heated at 80 °C to a stabilised pressure of 71 bar. More CO_2 was added to obtain a pressure of 109 bar (11.0 MPa) and the reactants left to stir under these conditions for 15 h. The stirrer and temperature controls were then switched off, CO_2 gradually released into the solvent trap (40.0 ml), the vessel disconnected and allowed to cool. The apparatus was cleaned with dichloromethane (4 × 1.00 ml) and the washings directed into the solvent trap. The contents of the solvent trap were combined with the dark red solids obtained from the reactor vessel, and the resulting organic phase washed with aqueous saturated ammonium chloride (3 × 20.0 ml), dried with $MgSO_4$, concentrated and purified [flash silica (40 g); hexane eluent] to give biphenyl (204 mg, 95%) as colourless needles, mp 69–71 °C (from light petroleum bp 40–60 °C, lit.[15b] 69–72 °C).

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Efficient solvent-free Thorpe reactions

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Solvent-free intermolecular and intramolecular Thorpe reactions proceeded efficiently to give acyclic and cyclic enamines, respectively. In the latter case, the reaction products were obtained as colorless crystalline powders just by washing of the reaction mixture with water.

Introduction

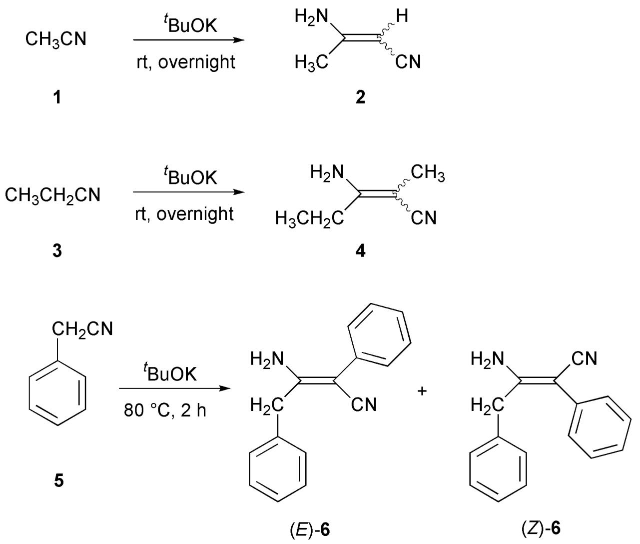
A solvent-free organic reaction is an important synthetic procedure from the view point of green and sustainable chemistry. We have been developing various solvent-free organic reactions.[1] Recently, we found that the intermolecular dimerization of nitriles and intramolecular cyclization of dinitriles, which are known as Thorpe reactions,[2] proceed very efficiently under solvent-free conditions. When the reaction product is a solid, it can be isolated just by washing the reaction mixture with water. The solvent-free procedure in Thorpe reactions is valuable not only for ecological and economical reasons but also for simplicity in procedure and for the high yields of the products. In addition, the reaction mechanism of the solvent-free Thorpe reaction was clarified by monitoring of the reaction by IR spectral measurement in the solid state.

Results and discussion

Intermolecular Thorpe reactions

For example, after a mixture of acetonitrile (**1**) and a 1.4 molar amounts of powdered ^{t}BuOK was kept at room temperature overnight, water was added to the reaction mixture and the product extracted with ether. Distillation using Kugelrohr apparatus of the residue left after evaporation of the solvent gave a 1 : 1 mixture of (*E*)- and (*Z*)-enamines (**2**) in 48% yield (Scheme 1). The same treatment of propionitrile (**3**) with powdered ^{t}BuOK gave a 1 : 1 mixture of (*E*)- and (*Z*)-enamines (**4**) in 65% yield. Solvent-free Thorpe reaction of benzylcyanide (**5**) at 80 °C was completed within 3 h to give a 4 : 1 mixture of (*E*)- and (*Z*)-enamines (**6**) in 73% yield. For both **2** and **4**, the ratio of (*E*)- and (*Z*)-isomers was determined to be 1 : 1 by ^{1}H NMR spectroscopy, although the correlation between the spectral data and the isomerism is not clear. In the case of **6**, however, the (*E*) : (*Z*) ratio was determined to be 4 : 1 by ^{1}H NMR spectroscopy and the spectrum which shows normal CH_2 absorption was assigned to the (*E*)-**6** isomer. The (*Z*)-**6** isomer showed CH_2 protons at relatively higher magnetic fields due to a shielding effect by the phenyl ring. The formation of the sterically more favorable (*E*)-**6** isomer as a major product is resonable. In the Thorpe reactions of **1**, **3** and **5** reported in 1942, products had been identified as imines instead of enamines and no (*E*), (*Z*) assignment had been described.[3] In 1959, the enamine structure **2** was assigned to the Thorpe reaction product.[4]

The solvent-free procedure can be applied to cross-Thorpe reactions (Scheme 2). A mixture of powdered *p*-methylbenzonitrile (**7b**), two molar amounts of **1** and two molar amounts of powdered ^{t}BuOK was heated at 80 °C for 2 h and kept at room temperature overnight. To the reaction mixture, water was added and the product extracted with ether. From the ether solution, **8b** was obtained by distillation in 74% yield. In this reaction, the product was obtained only as the (*E*)-isomer. In the solvent-free cross-reaction, self-condensation reaction of **1** did



Scheme 1

Green Context

The avoidance of volatile organic solvents is one of the major targets of green chemistry. While there is considerable and worthwhile research effort going into the design and application of alternative solvents it is worth remembering that the fundamentals of green chemistry teach us to seek to avoid auxiliaries, including solvents, in chemical manufacturing processes. Here we see a good example of how some important organic reactions can be efficiently accomplished without any solvent. Various solvent free reactions of nitriles are described. The reaction procedure is simple and the product yields are good. There is however still room for improvement since quite large amounts of conventional strong base are required and in some cases, an organic solvent is used to extract the product at the end of the reaction.

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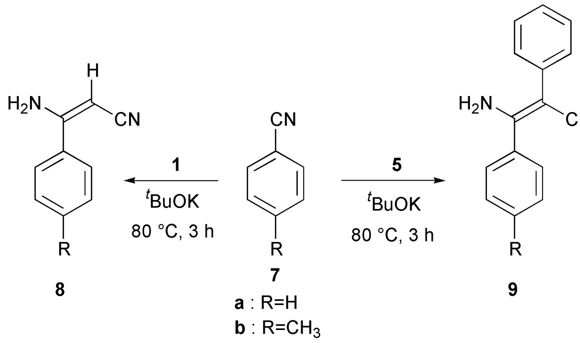


Scheme 2

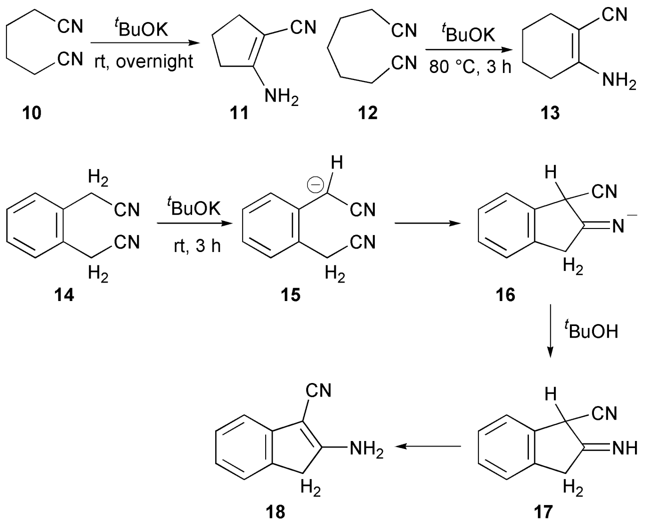
not occur. On the other hand, the cross-reaction of **7b** and **1** under reflux in toluene and in THF for 1 day gave **8b** in 52 and 34% yields, respectively.

The cross-condensation of benzonitrile (**7a**) with **1** under solvent-free conditions gave **8a** in 70% yield. The same cross-condensation of **7a** and **7b** with **5** gave **9a** and **9b** in 70 and 62% yields, respectively. In all reactions, no (*Z*)-isomer was produced.

Intramolecular Thorpe reactions

After a mixture of powdered adiponitrile (**10**) and 0.60 molar amount of powdered ^{t}BuOK was kept at room temperature for 3 h, the reaction mixture was washed with water to give the cyclization product (**11**) as a white crystalline powder in 74% yield (Scheme 3). It has been reported that the Thorpe reaction of **10** is very sensitive to the reaction conditions. For example, the reaction under homogeneous conditions using a catalytic amount of ^{t}BuONa in ^{t}BuOH gave mostly a dimeric product in 67–76% yield, however, the reaction under heterogeneous conditions using an equimolar amount of ^{t}BuONa in toluene gave **11** in 85% yield.[5] The heterogeneous reaction of **10** in toluene corresponds to the solvent-free reaction which gives **11** as the sole product. By the same solvent-free procedure, pimelonitrile (**12**) and *o*-di(cyanomethyl)benzene (**14**) gave **13** and **18** as white crystalline powders in 83 and 97% yields, respectively. It has been reported that the Thorpe reaction of **14** in EtOH containing EtONa gives **18** in a quantitative yield.[6]

Until recently the products of all nitrile cyclizations by the Thorpe reaction had been formulated as imines. In 1955, Hammer and Hines pointed out that the product from adiponitrile (**10**) was better described as the enamine (**11**). By the same idea, the cyclization product of **14** can be described as the enamine (**18**) which is derived from the initially formed imine (**17**) through the mechanism shown in Scheme 3. In order to clarify the mechanism, the intramolecular Thorpe reaction of **14** under solvent-free conditions was monitored by measurement of IR spectra in Nujol mulls (Fig. 1). As the reaction proceeds, the CN absorption of **14** at 2250 cm^{-1} decreases and a new CN absorption of the intermediate (**17**) arises at 2143 cm^{-1}. As **17** is converted into **18** by a proton migration, the CN absorption of **17** at 2143 cm^{-1} disappears, and only the CN absorption of **18** at 2189 cm^{-1} remains.



Scheme 3

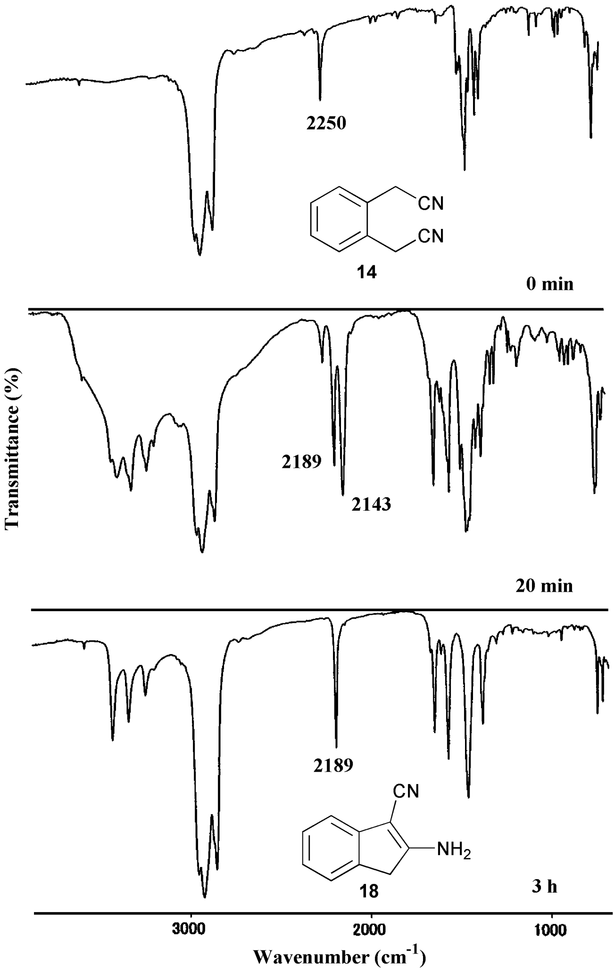


Fig. 1 Monitoring of the Thorpe reaction of **14** to **18** *via* **17** by IR spectral measurement in Nujol mulls.

Experimental

General procedures

All ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$.

Intermolecular Thorpe reactions of acetonitrile (1), propionitrile (3) and benzylcyanide (5)

A mixture of nitrile (0.10 mol) and ^{t}BuOK (0.14 mol) was kept at room temperature overnight. In the case of **5**, reaction was carried out at 80 °C for 2 h. Water was added to the reaction mixture and the product extracted with diethyl ether. Distillation using Kugelrohr apparatus of the residue left after evaporation of the solvent of the dried ether solution gave the enaminonitrile condensation product as an oil in the yield indicated in Table 1. The (*E*) : (*Z*) ratios were determined by ^{1}H NMR spectra.

Table 1 Solvent-free intermolecular Thorpe reactions

	Reaction conditions		Product		
Nitrile	Temperature	Time		Yield (%)	(*E*):(*Z*) ratio[a]
1	rt	overnight	**2**	48	1 : 1
3	rt	overnight	**4**	65	1 : 1
5	80 °C	2 h	**6**	73	4 : 1

[a] The ratios were determined by ^{1}H NMR measurements.

2 (1 : 1 (*E*),(*Z*) mixture): 48% yield; IR (neat) 1600, 1647, 2181, 3253, 3353, 3419 cm^{-1}. The IR spectrum was identical to that reported for **2**.[4] ^{1}H NMR (400 MHz) one isomer: δ 1.92 (s, 3 H, CH_3), 3.82 (s, 1 H, =CH), 4.64 (br s, 2 H, NH_2); the other isomer: δ 2.10 (s, 3 H, CH_3), 4.12 (s, 1 H, =CH), 4.28 (br s, 2 H, NH_2). **4** (1:1 (*E*),(*Z*) mixture): 65% yield; IR (neat) 1613, 1641, 2182, 3232, 3361, 3457 cm^{-1}. The IR spectrum was identical to that reported for **4**.[7] ^{1}H NMR (300 MHz) one isomer: δ 1.19 (t, J = 7.6 Hz, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.44 (q, J = 7.6 Hz, 2 H, CH_2), 4.04 (br s, 2 H, NH_2); the other isomer: 1.23 (t, J = 7.6 Hz, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.21 (q, J = 7.6 Hz, 2 H, CH_2), 4.31 (br s, 2 H, NH_2). **6** (4 : 1 (*E*),(*Z*) mixture): 73% yield; IR (neat) 1583, 1626, 2180, 3234, 3346, 3467 cm^{-1}. The IR spectrum was identical to that reported for **6**.[3] ^{1}H NMR (300 MHz) (*E*)-isomer: δ 3.96 (s, 2 H, CH_2), 4.51 (br s, 2 H, NH_2), 7.25–7.44 (m, 10 H, ArH); (*Z*)-isomer: δ 3.70 (s, 2 H, CH_2), 4.69 (br s, 2 H, NH_2), 7.25–7.44 (m, 10 H, ArH).

Cross-Thorpe reactions of benzonitrile (7a) and *p*-methylbenzonitrile (7b) with acetonitrile (1) and benzylcyanide (5)

A mixture of two different nitriles A and B (0.10 mol each) and powdered ^{t}BuOK (0.28 mol) was heated at 80 °C for 3 h and then kept at room temperature overnight. Water was added to the reaction mixture and the product extracted with ether. Hexane was added to the ether solution and kept at room temperature to give the cross-Thorpe reaction product as crystals in the yields indicated below.

8a: 70% yield; mp 89–90 °C; IR (Nujol) 1588, 1628, 2180, 3351, 3442 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.25 (s, 1 H, =CH), 4.94 (br s, 2 H, NH_2), 7.41–7.51 (m, 5 H, ArH); ^{13}C NMR (100 MHz) δ 63.8, 119.4, 126.0, 129.0, 130.9, 135.4, 161.4. **8b**: 52% yield; mp 107–108 °C; IR (Nujol) 1588, 1641, 2182, 3243, 3341, 3430 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.39 (s, 3 H, CH_3), 4.24 (s, 1 H, =CH), 4.89 (br s, 2 H, NH_2), 7.43 (t, J = 8.2 Hz, 2 H, ArH), 7.39 (d, J = 8.2 Hz, 2 H, ArH); ^{13}C NMR (100 MHz) δ 21.3, 63.0, 119.6, 125.8, 129.6, 132.4, 141.3, 161.5. **9a**: 70% yield; mp 147–148 °C; IR (Nujol) 1556, 1619, 2176, 3201, 3303, 3345, 3467 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.78 (br s, 2 H, NH_2), 7.28–7.50 (m, 8 H, ArH), 7.69–7.72 (m, 2 H, ArH); ^{13}C NMR (75 MHz) δ 81.1, 122.4, 127.2, 127.9, 128.4, 128.6, 129.2, 133.8, 135.8, 157.1. **9b**: 62% yield; mp 135–136 °C; IR (Nujol) 1555, 1606, 2182, 3389, 3492 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.41 (s, 3 H, CH_3), 4.73 (br s, 2 H, NH_2), 7.27–7.31 (m, 3 H, ArH), 7.43 (t, J = 7.9 Hz, 2 H, ArH), 7.54 (d, J = 8.0 Hz, 2 H, ArH), 7.60 (t, J = 8.1 Hz, 2 H, ArH); ^{13}C NMR (100 MHz) δ 21.4, 81.6, 122.3, 127.3, 127.9, 128.6, 129.4, 129.5, 133.1, 134.1, 140.9, 157.0.

Intramolecular Thorpe reactions of adiponitrile (10), pimelonitrile (12) and *o*-di(cyanomethyl)benzene (14)

A mixture of adiponitrile (**10**) (2.16 g, 20 mmol) and powdered ^{t}BuOK (3.16 g, 24 mmol) was kept at room temperature overnight. The crystalline solid formed by addition of water to the reaction mixture was filtered off and recrystallized from MeOH to give the cyclization product (**11**) (1.60 g) in 74% yield as a colorless crystalline powder: mp 147–148 °C (lit.,[5] mp 147–148 °C); IR (Nujol) 1608, 1644, 2182, 3235, 3352, 3427 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.89–1.96 (m, 2 H, CH_2), 2.46 (t, J = 7.9 Hz, 2 H, CH_2), 2.54 (t, J = 7.0 Hz, 2 H, CH_2), 4.43 (br s, 2 H, NH_2).

A mixture of pimelonitrile (**12**) (1.22 g, 10 mmol) and powdered ^{t}BuOK (1.58 g, 12 mmol) was kept at 80 °C for 3 h and then at room temperature overnight. Water was added to the reaction mixture and the product extracted with ether. Recrystallization of the crystalline solid left after evaporation of the solvent of the ether solution from MeOH gave **13** as colorless crystals (1.01 g, 83% yield): mp 94 °C; IR (Nujol) 1604, 1643, 2172, 3225, 3346, 3436 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.56–1.72 (m, 4 H, CH_2), 2.10–2.21 (m, 4 H, CH_2), 4.21 (br s, 2 H, NH_2).

A mixture of *o*-di(cyanomethyl)benzene (**14**) (1.56 g, 10 mmol) and ^{t}BuOK (0.75 g, 6.0 mmol) was ground using an agate mortar and pestle for 5 min, and the mixture was kept at room temperature for 3 h. Washing the reaction mixture with water gave the cyclization product (**18**) (1.51 g, 97% yield): mp 192–193 °C (lit.,[6] 193 °C); IR (Nujol) 1567, 1645, 2189, 3244, 3339, 3426 cm^{-1}; ^{1}H NMR (300 MHz) δ 3.56 (s, 2 H, CH_2), 5.12 (br s, 2 H, NH_2), 7.03 (t, J = 7.3 Hz, 1 H, ArH), 7.16–7.28 (m, 3 H, ArH).

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Improved synthesis of the Ni(II) complex of the Schiff base of (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]benzophenone and glycine

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The environmental impact of a known synthesis of the Ni complex of the Schiff base of (*S*)-2-[*N*-(*N′*-benzylprolyl)amino]benzophenone and glycine was decreased by optimisation of the ratio the starting materials; a new starting material, $Ni(NO_3)_2 \cdot 6NH_3$, was evaluated as a nickel source.

For the preparation of non-coded and/or selectively labelled α-amino acids, several chiral glycine and alanine synthons are manufactured and marketed in bulk quantities. The most important are Seebach′s[1] and Oppolzer′s[2] derivatives and O′Donnell′s achiral synthon,[3] for stereospecific alkylation for which an efficient chiral catalyst has been recently developed.[4] Ni(II) complexes of Schiff bases of (*S*)-2-[*N*-(*N′*-benzylprolyl)-amino]benzophenone (BPB) and α-amino acids achieve high asymmetric induction for the synthesis of α-amino acids[5] at ambient temperature. The chiral auxilliary BPB is regenerated but excess nickel in the waste water is a potential environmental problem.

The complexes were developed as artificial analogs of pyridoxal 5′-phosphate (PLP)-dependent enzymes.[6] The central sodium atom of a PLP-dependent enzyme was replaced by nickel in order to form a more stable compound. In spite of the inexpensive and reliable application of these complexes, the fate of the nickel used in their preparation should be carefully controlled. Energy-consuming procedures used for removal of nickel from waste water might significantly increase the cost of α-amino acids production. Nickel from the complexes is easily regenerated when a mixture of an amino acid and nickel chloride (after acidic hydrolysis) is separated on a cation-exchanger. A large amount of metal remains in the methanolic waste solution after preparation of the complexes, due to a two-fold excess of $Ni(NO_3)_2 \cdot 6H_2O$ used in a standard protocol.[7–9] This excess is necessary in order to shift the equilibrium towards complex formation.

Previous attempts to substitute nickel nitrate with nickel acetate, which bears four molecules of water in the internal coordination sphere instead of six in the nitrate, did not shift the equilibrium towards complex formation.[10]

In this work the successful synthetic application of near stoichiometric amounts of $Ni(NO_3)_2 \cdot 6H_2O$ or anhydrous $Ni(NO_3)_2 \cdot 6NH_3$†, minimising amount of Ni^{2+} need to be recovered from waste water, is described (Scheme 1).

Results and discussion

In this work a two-fold excess of glycine instead of five-fold[7–9] was used in order to reduce the amount of nickel chelating amino acid in the waste water.

Experiments did not support the initial hypothesis that anhydrous $Ni(NO_3)_2 \cdot 6NH_3$ would shift the equilibrium towards complex formation. Observed yields of complex formation starting from $Ni(NO_3)_2 \cdot 6H_2O$ were 5–13% higher than the corresponding yields starting from $Ni(NO_3)_2 \cdot 6NH_3$ (Table 1).

When a two-fold excess of any nickel salt was used solid precipitate appeared in the reaction mixture after 90 min. With lower excesses of nickel salts no precipitates were observed. Formation of the precipitate is probably responsible for lower yields of the complexes when using a two-fold excess of a nickel salt compared with 1.2-fold. This may be due to absorbtion of BPB by precipitated nickel oxide/hydroxide. Work-up of the homogeneous reaction mixtures obtained with lower excesses of nickel salts is better suited to scale-up as no separation and processing of solid nickel-containing waste is necessery.

Application of the Ni(II) complex of the Schiff base of BPB and glycine for asymmetric synthesis of α-amino acids often does not require separation of the complex from unreacted BPB (see, for example, ref. 9). In such cases, in spite of lower yields of the complexes, a 1.05-fold excess of nickel salt might be the best ratio. This will decrease the amount of nickel circulating in the process.

Synthesis of more sterically hindered complexes derived from α-monosubstituted glycines (*e.g.* proteinogenic α-amino acids) is in progress in order to test the new ratio of the starting compounds under more challenging conditions.

Green Context

The preparation of speciality α-amino acids requires the large-scale manufacture of various chiral glycine and alanine synthons. Nickel complexes have been shown to be particularly effective in achieving high asymmetric induction for the synthesis of α-amino acids but nickel contaminated waste waters present an environmental problem. Here the synthesis of the nickel complex is optimised including the use of a new nickel source. The net result is a reduction in the environmental impact of the process. *JHC*

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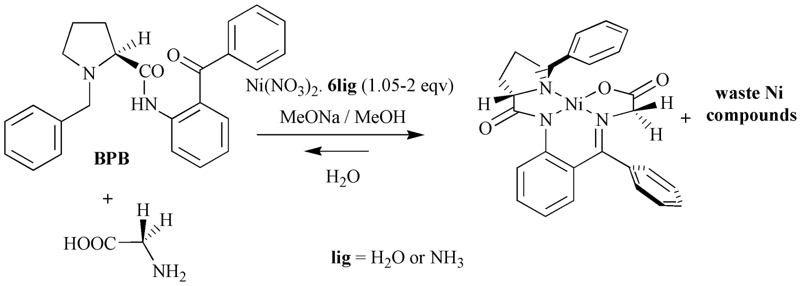

Scheme 1

Table 1 Yields of the Ni(II) complex of Schiff base of BPB and glycine depending on excess of nickel salts

Excess of the nickel salt	2	1.2	1.05
Yield of the complex starting from $Ni(NO_3)_2{\cdot}6NH_3$ (%)	64	78	67
Yield of the complex starting from $Ni(NO_3)_2{\cdot}6H_2O$ (%)	77	88	71

Experimental

General procedure for the synthesis of the glycine complex

2.5 M MeONa/MeOH (8 ml, 20 mmol) was added to a stirred suspension of BPB (500 mg, 1.3 mmol), glycine (195 mg, 2.6 mmol) and the corresponding amount of a nickel salt (Table 1) in dry MeOH (4 ml) under argon at 55 °C. The volume of the reaction mixture was then adjusted to 15 ml with dry MeOH. After stirring at 55 °C for 90 min, the mixture was poured into 10% aqueous citric acid (100 ml), stirred and the resulting precipitate was filtered off and dried in air. The dry precipitate was purified by column chromatography using silica gel (Merck 40/63) eluted with chloroform.‡ Yields of complex formation are given in the Table 1. ^{1}H and ^{13}C NMR data have been reported previously.[11]

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Notes and references

† $Ni(NO_3)_2{\cdot}6NH_3$ for this work was prepared by bubbling NH_3 gas through a cold methanolic solution of $Ni(NO_3)_2{\cdot}6H_2O$ and filtering off the resulting precipitate. Aqueous ammonia may be also used instead of NH_3 gas, in this case the content of water in the internal coordinational sphere of $Ni(NO_3)_2{\cdot}6NH_3$ will be higher.

‡ As chloroform is known to be a human carcinogen, for preparative applications a gradient elution using $CH_2Cl_2 \rightarrow CH_2Cl_2$–$Me_2CO$ = 7 : 1 or toluene → toluene–Me_2CO = 2 : 1 is strongly recommended.

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