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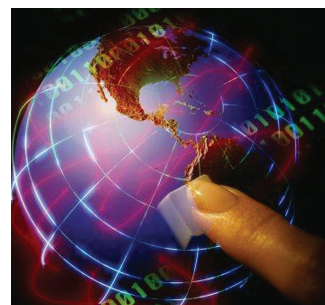
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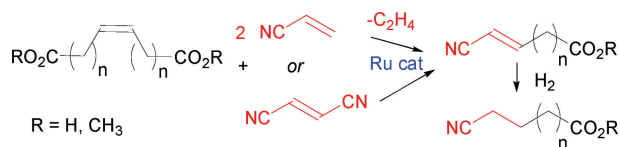
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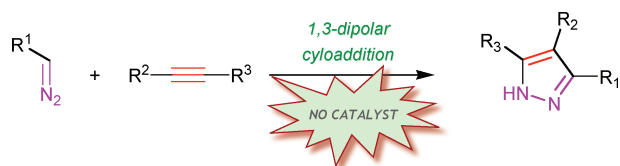
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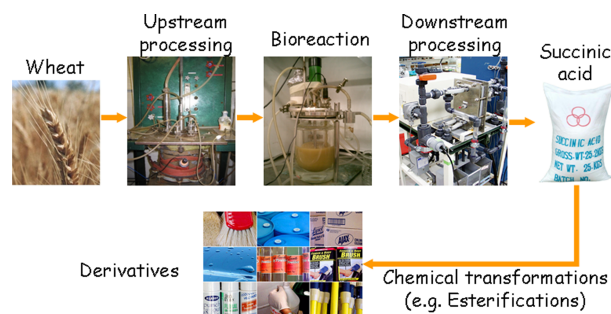
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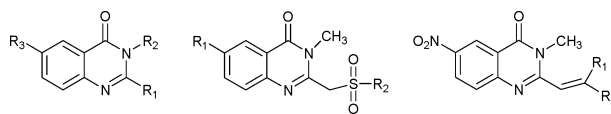
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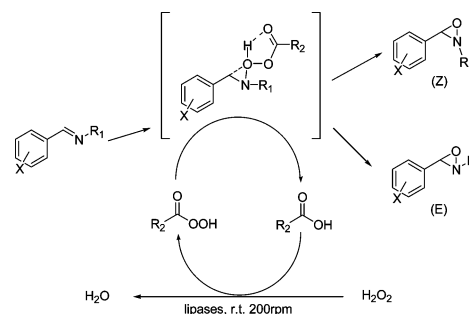
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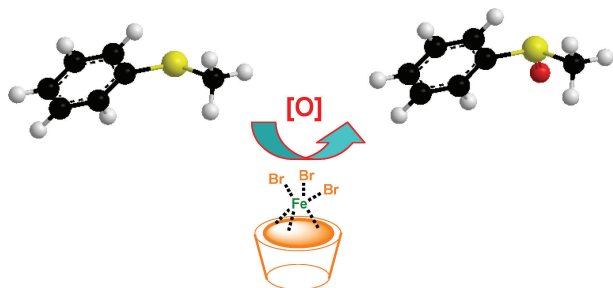
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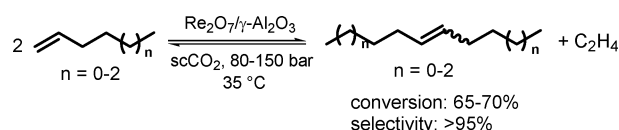
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Chemistry Innovation

The mission of Chemistry Innovation is 'Driving the Innovation Agenda for the Chemistry-Using Industries', and we see sustainable technologies as a key part of that agenda. Within Chemistry Innovation, the Sustainable Technologies priority is focused on using innovation to solve sustainability issues in society in general and specifically within downstream industry sectors.

Just over a year ago Chemistry Innovation launched the online update of the Sustainable Technologies Roadmap (www.chemistryinnovation.co.uk/roadmap/sustainable/roadmap). It sets out to explain the potential, scope and business opportunities for sustainable technologies to as wide an audience as possible. The roadmap describes the main trends and drivers encouraging the use of more sustainable approaches in the chemical and chemical using industries, the current and future needs of many user industries, and information on emerging sustainable technologies. One of the most useful sections is the library of over 100 case studies of sustainable products, processes and services. These are categorised by industry sector, technology and problem solved.

Academics can get a wider understanding of industry needs for new solutions to sustainability issues, see how technologies are being used today and find new research ideas. Our academic colleagues also tell us that it is a great source of teaching material. Industrial users can find out more about their downstream customer's needs, as well as explanations of the current limits and capabilities of sustainable technologies, and practical examples of successful commercial exploitation of sustainability thinking.

Other groups are developing roadmaps for the chemistry using industries that are producing important strategic research agendas for required technologies; including the IChemE Roadmap launched in 2007, the SusChem strategic research agenda, and the current RSC exercise (www.rsc.org/roadmap). Our roadmap is more focused on understanding the needs of industry and the business potential of meeting these needs in a sustainable way.

Our plan is for the roadmap to be a living resource that grows organically over time, to become a valuable resource for everyone interested in sustainability in the chemistry-using industries. In the last year, over 60 updates and edits have been made, and we are keen to add more. To do that we need the help of the community. *Green Chemistry* readers can contribute to this project in several ways. Every page of the roadmap website has a feedback button through which you can send us comments, corrections, and suggestions for new material. We are always looking for additional case studies highlighting the successful commercial exploitation of sustainable technologies. If you have been involved in a success story, or know of one, please get in touch. *Green Chemistry* authors can also provide summaries of their work or short critical reviews of a technology area with links to more detailed *Green Chemistry* articles.

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www.chemistryinnovation.co.uk/roadmap/sustainable/roadmap

Renewable materials as precursors of linear nitrile-acid derivatives *via* cross-metathesis of fatty esters and acids with acrylonitrile and fumaronitrile†

Raluca Malacea,[a] Cédric Fischmeister,[a] Christian Bruneau,*[a] Jean-Luc Dubois,[b] Jean-Luc Couturier[b] and Pierre H. Dixneuf*[a]

The cross-metathesis of fatty acids and esters, as renewable raw materials, with acrylonitrile and fumaronitrile is presented. The cross-metathesis reactions of both terminal and internal double bond containing compounds were performed using a ruthenium catalyst and led to bifunctional nitrile-esters or nitrile-acids with high conversions. The tandem ruthenium catalysed cross-metathesis and hydrogenation provide precursors of aminoacid monomers for the production of polyamides from renewable resources.

Alkene metathesis catalysis[1] has brought revolutions in synthetic methodologies, by introducing an elegant way to make C–C bonds and significantly reducing steps in complex architecture synthesis,[2] molecular material design[3] and polymer science.[4] It has recently contributed to the development of green processes,[5] including metathesis of fatty esters.[6]

Alkene cross-metathesis[7] especially has the potential to give added value to renewable materials, leading selectively to unsaturated functional molecules. Plant oils and fats constitute excellent renewable materials, as precursors of functional industrial intermediates[8] as demonstrated with the cross-metathesis of fatty esters with acrylic esters offering a direct access to industry relevant unsaturated diesters.[9]

The cross metathesis of acrylonitrile and unsaturated acids or esters, associated with the hydrogenation of both the C=C and CN bonds, constitutes a challenge and a potential strategic way to generate from renewables linear aminoacid monomers useful for the production of polyamides (Scheme 1).
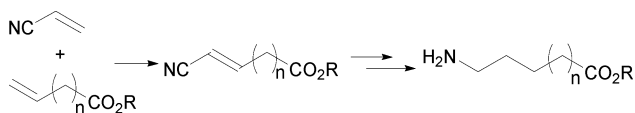
Scheme 1 Synthesis of aminoacids and esters from renewable materials.

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† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b816917a

We have thus considered the transformation *via* cross-metathesis, with acrylonitrile, of two unsaturated acids and their esters arising from renewable resources: the C11 ester **1** obtained from castor oil and its related carboxylic acid **2**, and the C18 diester **3** and diacid **4** obtained *via* biotransformation or self-metathesis of oleic acid. (Scheme 2). Until now, cross-metathesis of alkenes with acrylonitrile has been studied only in some rare examples. The first example of cross metathesis of terminal olefins with acrylonitrile was described by Crowe and Goldberg,[10] in the presence of the Schrock catalyst Mo(=CHCMe$_2$Ph)(NAr)(OC–Me(CF$_3$)$_2$), Ar = 2,6-diisopropylphenyl, affording moderate yields. Since then, ruthenium catalysts have been used to perform cross-metathesis more efficiently with acrylonitrile of organic substrates with an alkene chain.[11] To our knowledge, only one example of cross metathesis between acrylonitrile and an internal double bond containing olefin was described by Blechert, using the second generation Grubbs catalyst and copper chloride as an additive.[12]
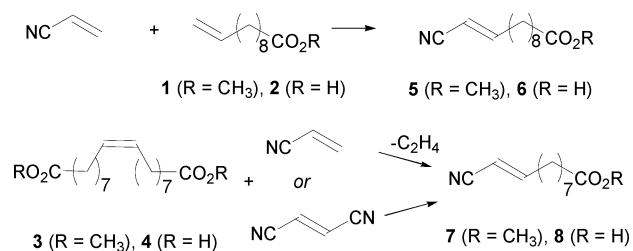
Scheme 2 Synthesis of nitrile-acids and -esters **5–8** *via* cross-metathesis with acrylonitrile.

We now report that the ruthenium catalyzed cross-metathesis of acrylonitrile or fumaronitrile with fatty ester and acid **1** and **2**, and internal C=C bond containing derivatives **3** and **4** leads to bifunctional nitrile-esters or acids **5–8**, precursors of C12 and C11 linear aminoacids (Scheme 2). The synthesis of saturated nitrile esters by a tandem metathesis/hydrogenation sequence using the residual metathesis ruthenium as the hydrogenation catalyst is also presented.

Cross-metathesis of acrylonitrile with the unsaturated ester 1 and acid 2

The cross-metathesis of the unsaturated monoester **1** with an excess of acrylonitrile (2 equiv.) was performed in toluene at 100 °C with the Grubbs **I** and Hoveyda **II** catalysts to give the

Table 1 Cross-metathesis of **1** with acrylonitrile[a]

Entry	1 (equiv.)	Acrylonitrile (equiv.)	Cat. (mol%)	t (h)	Conv[c] (%)[c]	Z/E[d]
1	1	2	**I** (5)	2	72	3.5/1
2	1	2	**I** (1)	2	43	3.8/1
3	1	2	**II** (5)	1	96 (86)[e]	2.6/1
4	1	2	**II** (1)	1	95	3.0/1
5[b]	1	2	**II** (1)	1	86	2.9/1

[a] [**1**] = 0.05M, toluene, 100 °C. [b] [**1**] = 0.1M, toluene, 100 °C. [c] Determined by gas chromatography. [d] Determined by gas chromatography. [e] Isolated yield.

C12 nitrile ester **5** as a mixture of *Z* (major) and *E* isomers (Fig. 1, Table 1). The Hoveyda catalyst **II** was found to be the most efficient, allowing better conversion with low catalyst loading (1%). It is important to note that increasing the reagents concentration resulted in lower conversion (Table 1, entry 5).
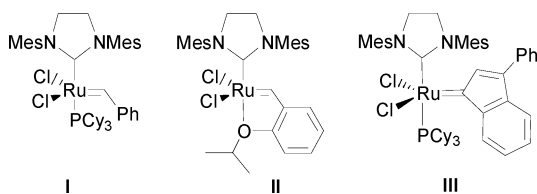
Fig. 1 Ruthenium based olefin metathesis catalysts.

The possibility to synthesize saturated nitrile-esters from renewable oils by tandem cross-metathesis/hydrogenation catalysis was investigated. Thus, the crude reaction mixture, obtained after cross metathesis using 1 mol% of **II** (Table 1, entry 4) and containing residual ruthenium catalyst, was concentrated, transferred to an autoclave, and hydrogenated without additional catalyst under 10 bar of H$_2$ to quantitatively give a single compound **9** (Scheme 3). This reaction provides an example of two consecutive catalytic reactions using only one starting ruthenium alkene metathesis catalyst *in situ* transformed into a hydrogenation catalyst.[13]
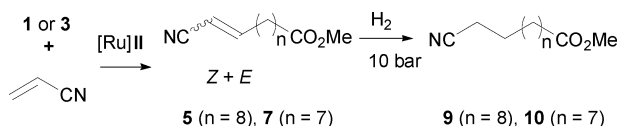
Scheme 3 Tandem cross-metathesis/hydrogenation.

The question of the relative easiness and efficiency of cross-metathesis of unsaturated ester *versus* its carboxylic acid was studied. The similar cross metathesis reaction was performed starting with acid **2** (Scheme 4). In order to monitor the reaction by gas chromatography, the crude products were esterified with DMF-dimethylacetal. Both catalysts **I** and **II** were evaluated for the transformation of **2** into **6** under the conditions previously described for the transformation of **1**. Catalyst **II** (1 mol%, toluene) showed the best performances giving 90% conversion in 1 h at 100 °C, the *Z* isomer being the major one (*Z/E* = 3.2/1) (Scheme 4). These experiments demonstrate that cross-metathesis using catalyst **II** is not significantly affected by the presence of an acidic functionality and that linear unsaturated acids such as **2** can now be considered as direct starting materials
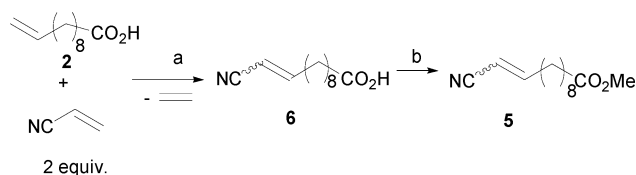
Scheme 4 Cross-metathesis of **2** followed by esterification. a: **I** or **II** (1 mol%), [**2**] = 0.05 M, toluene 100 °C. b: DMF-dimethylacetal, pyridine, 100 °C, 1 h.

leading to bifunctional nitrile-acids, precursors of aminoacids. The catalytic activity of **I** was significantly inhibited by the acidic functionality since the conversion only reached 23% *versus* 43% for the cross-metathesis of **1**.

Cross metathesis of the diester 3 and diacid 4 with acrylonitrile

The cross-metathesis with acrylonitrile of the symmetrical C18 diester **3** as a potential source of C11 nitrile-ester **7** was attempted (Scheme 5).
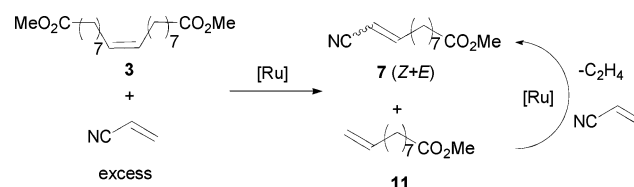
Scheme 5 Cross metathesis of diester **3** with acrylonitrile.

As summarised in Table 2, catalysts **I**, **II**, and **III** promoted the synthesis of the unsaturated nitrile-esters **7**. Catalyst **II** was again the most efficient one, when the diester **3** was reacted with 4 equivalents of acrylonitrile in toluene at 100 °C for 1 h, but using 5 mol% of catalyst (Table 2, entries 2 and 4). Compound **7** was obtained as a mixture of *Z* (major) and *E* isomers. When the conversion was not complete, as observed with **I** and **III**, large amounts of the monoester **11** (Scheme 5) were formed (Table 2, entries 1,3). Longer reaction times did not improve the conversion suggesting a rapid deactivation of the catalyst during the first hour of reaction.[14] Attempts to run the reaction in acrylonitrile as solvent at 60 °C were not successful and the starting diester **3** was recovered, and an increasing of reagent concentration led to conversion decreasing (entries 2 and 7,8). The above results show that the cross-metathesis with acrylonitrile of linear olefins containing an internal double bond

Table 2 Cross-metathesis of **3** with acrylonitrile[a]

Entry	Catalyst (mol%)	t/h	T/°C	Conv. (%)	Z/E	7/11
1	**I** (5)	2	100	75	2.8/1	2.9/1
2	**II** (5)	1	100	99	2.6/1	20.7/1
3	**III** (5)	2	100	61	2.8/1	2.1/1
4	**II** (1)	1	100	68	2.8/1	3.4/1
5[b]	**I** (5)	19	60	—	—	—
6[b]	**II** (5)	19	60	—	—	—
7[c]	**II** (5)	3	100	86.5	2.9/1	12/1
8[d]	**II** (5)	3	100	64	3.2/1	4.3/1

[a] **3** (1 mmol), acrylonitrile (4 mmol), 20 ml toluene [**3**] = 0.05 M. [b] **3** (1 mmol), 20 ml acrylonitrile. [c] [**3**] = 0.1 M. [d] [**3**] = 0.25 M.

can be efficiently achieved, as it was also observed for the cross metathesis with acrylic esters.[9]

The crude reaction mixture of the nitrile-ester **7** was also hydrogenated under 10 bars of H$_2$, using the residual ruthenium complex as the hydrogenation catalyst precursor. This tandem metathesis/hydrogenation led to the quantitative formation of the saturated nitrile-ester **10** (Scheme 3).

The direct cross-metathesis of the diacid **4** with acrylonitrile was attempted using 5 mol% of **II** in toluene at 100 °C for 1 h (Scheme 6). The crude product was directly esterified by treatment with DMF-dimethylacetal at 100 °C for 1 h to observe 90% conversion of **4** and the formation of **7** ($Z/E = 2.4$) and **11**, with a **7/11** ratio = 23/1. Thus, the cross-metathesis with acrylonitrile of internal CH=CH bond containing derivatives can be performed analogously for the diacid as for the diester using 5 mol% of catalyst **II**.
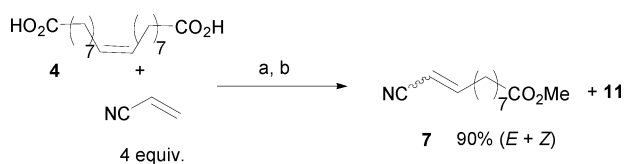
Scheme 6 a: **II** (5 mol%), toluene 100 °C. b: DMF-Dimethylacetal, pyridine, 100 °C, 1 h.

For cross-metathesis of ester **1** and acid **2** no self-metathesis product was observed, likely due to the profitable excess of acrylonitrile.

Cross metathesis of diester 3 with fumaronitrile

Several attempts were made using fumaronitrile instead of acrylonitrile as a source of unsaturated nitrile for the cross metathesis with the diester **3** (Scheme 7). Using only 1% molar of ruthenium complex **II** and two equivalents of fumaronitrile the conversion reached 50% in 2 h but with higher catalyst loading (5 mol%) the nitrile ester **7** was obtained in 92% isolated yield. (Table 3, entries 2,3)

Scheme 7 Cross-metathesis of diester **3** with fumaronitrile.

Table 3 Cross-metathesis of **3** with fumaronitrile[a]

Entry	Catalyst (mol%)	Conv (%)[b]
1	**I** (1)	11
2	**II** (1)	50
3	**II** (5)	97 (92)[c]
4	**III** (1)	18

[a] **3** (1 mmol), fumaronitrile (2 mmol), 20 ml toluene, 100 °C, 2 h.
[b] Determined by gas chromatography. [c] Isolated yield.

Cross metathesis of acrylonitrile with methyl oleate 12

The methyl oleate **12** which presents an analogy with diester **3** for its internal double bond, was reacted with 2 or 4 equivalents of acrylonitrile in toluene at 100 °C for 2 h with 5 mol% of ruthenium catalyst **II**. This reaction proceeded with full conversion of methyl oleate leading to a mixture of the expected unsaturated nitrile **13** and nitrile ester **7** in equal proportions, each of them being present in the reaction as a mixture of two E and Z isomers (Scheme 8).
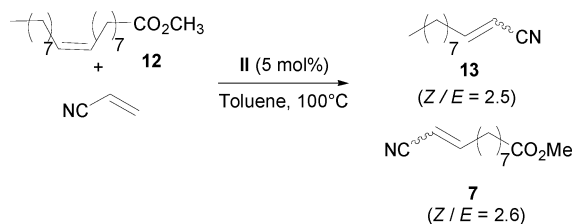
Scheme 8 Cross-metathesis of methyl oleate with acrylonitrile.

The analogous reaction was performed using fumaronitrile instead of acrylonitrile (Scheme 9). The reaction of **12** with one or two equivalents of fumaronitrile in the presence of 5 mol% of ruthenium complex **II** in toluene at 100 °C for 2 h also proceeded quantitatively providing **7** and **13** as a mixture of E and Z isomers, in equal proportion.
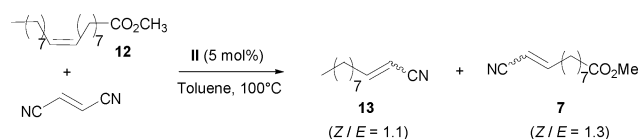
Scheme 9 Cross-metathesis of methyl oleate with fumaronitrile.

In conclusion, the above results show that the cross-metathesis of both terminal and internal unsaturated esters and acids with acrylonitrile, and even fumaronitrile, can be efficiently and selectively performed using the Hoveyda catalyst **II**, without isomerisation of initial substrates and products. These plant oil derivatives have now become valuable sources of bifunctional nitrile-acid derivatives. This catalytic cross-metathesis reaction, which can be coupled with hydrogenation, offers potential applications for the formation of a variety of bifunctional nitrogen containing compounds from renewable raw materials including aminoacids, the precursors of polyamides.

Experimental

General procedure for the cross-metathesis reactions.

Cross metathesis of C18 diester 3 with acrylonitrile

In a Schlenck tube under argon, 340 mg (1 mmol) of **3** and 212 mg (4 mmol, 4 equiv.) of acrylonitrile were dissolved in 20 mL of toluene before addition of 5 mol% of **II** and tetradecane (10 mol%) as the gas chromatography internal standard. The reaction mixture was then heated at 100 °C. Samples of the reaction mixture were taken at different times under argon atmosphere and then analyzed by GC analysis. Purification by column chromatography using petroleum ether/diethyl ether

(9/1 and 8/2 v/v) as the eluent yielded 190 mg (86%) of **5** obtained as a colourless oil.

Acknowledgements

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Synthesis of pyrazoles through catalyst-free cycloaddition of diazo compounds to alkynes†

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The synthesis of pyrazoles *via* 1,3-dipolar cycloaddition of diazo compounds to alkynes proceeds easily by heating. With α-diazocarbonyl substrates the reactions are conducted under solvent-free conditions affording the pyrazole products in high yields without any work up or purification.

The pyrazole motif is found in many biologically active molecules with a broad range of applications in the pharmaceutical industry (Viagra,[1] Celebrex[2]) as well as in the agrochemical field (*e.g.* Tebufenpyrad insecticide[3]).[4] Thus, various processes have been reported for the synthesis of these heterocycles. The most employed strategy involves the reaction of hydrazines with 1,3-difunctional substrates: 1,3-dicarbonyl compounds,[5] or ynones.[6] However, the formation of regioisomeric mixtures of pyrazole is frequently observed. Thus, during the last years new paths have emerged, as exemplified by the synthesis of pyrazoles through domino C–N coupling/hydroamidation of enynes,[7] and aza-cyclisation of elaborated substrates.[8,9] Nevertheless, the scope of these methods is hindered by the multistep sequences required for the preparation of the starting materials and/or by the use of reagents affording notable amounts of side-products. Thus, there is still a need for a straightforward and "greener" approach to pyrazoles. In this connection, the cycloaddition between alkynes and 1,3-dipoles provides a direct access to pyrazoles.[10,11] While the use of electron-rich diazo compounds as dipoles is well-known and can be conducted under thermal conditions,[12] the development of efficient processes for the reaction with electron-deficient diazo carbonyl molecules required special efforts.[13] In 2004, Li realised a breakthrough by reporting the first intermolecular cycloaddition of various α-diazocarbonyl molecules to electron-poor alkynes catalysed by indium(III) chloride in water.[14] More recently, Ready extended the scope of the reaction to a wide range of alkynes by using copper acetylides in THF,[15] while other developments involved zeolite NaY as promoter in CH_2Cl_2,[16] and microwave-assisted reaction with the alkyne as solvent.[17] During our research, we now found that the 1,3-dipolar cycloaddition of diazo compounds to alkynes did not need any special promoter

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Table 1 1,3-Dipolar cycloaddition of ethyl diazo carboxylate to electron-deficient alkynes under solvent-free conditions[a]

Entry	R	$T/°C$	Time/h	Conversion (%)[b]
1	H	20	8	100
2	CO_2Et	20	8	60
3	H	80	0.5	100 (95)
4	CO_2Et	80	1	100 (95)

[a] Reactions were performed on a 1 mmol scale. Position of the NH in the product is assigned arbitrarily. [b] Yields are given in parentheses.

or medium, and could be simply conducted under thermal conditions with various partners.
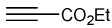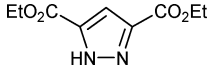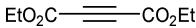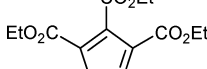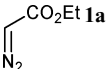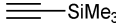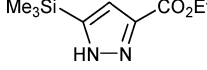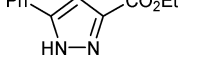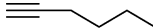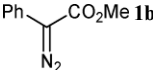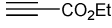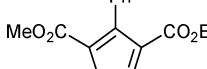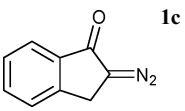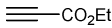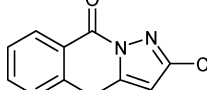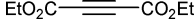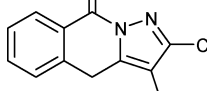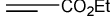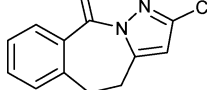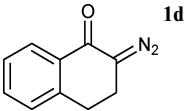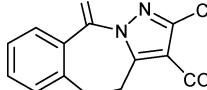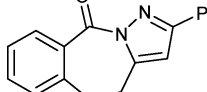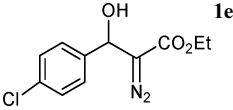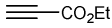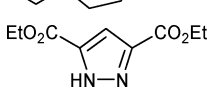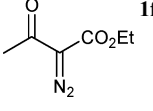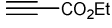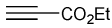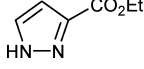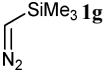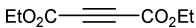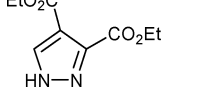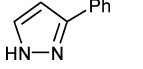
Diazocompounds are generally difficult to prepare and handle as they are potentially explosive. In contrast, when these molecules are α-substituted with an electron-withdrawing group (diazocarbonyl, diazoacetate), they are highly stable even at high temperatures and can be handled without any particular precaution.[18] Thus, our investigations started by reacting 1 mmol of ethyl diazoacetate with 1.1 mmol of ethyl propiolate (both liquids) under neat conditions.[19] The solution slowly turned into a very viscous mixture, and after 8 h, ^{1}H NMR monitoring revealed that the consumption of the diazo substrate was complete and that the pyrazole, resulting from a 1,3-dipolar cycloaddition followed by a 1,3-hydrogen shift, was formed. Evaporation of the small excess of alkyne afforded the expected product, as confirmed by comparison with literature data[20] (Table 1, entry 1). As a further experiment, the internal alkyne diethyl acetylenedicarboxylate was assessed and showed only 60% conversion after 8 h. However, by heating the medium to 80 °C, the reaction was significantly accelerated and completed within 0.5 and 1 h for ethyl propiolate and acetylene dicarboxylate, respectively (entries 3 and 4). In both cases, after evaporation of the reagent in excess, the pyrazoles were obtained with excellent purity and in excellent yields (95% each).

Having in hand an easy and clean protocol (neat, at 80 °C) for the synthesis of functionalised pyrazoles, the reaction was then extended to other alkynes and diazo compounds. It is worth to note that, in order to get the products easily and neatly, the reactions were performed with 1.1 equivalents of the most volatile of the two reagents used (diazo molecule or alkyne, according to their respective b.p.). Results are presented in Table 2.

Table 2 1,3-Dipolar cycloaddition of diazo compounds to alkynes under solvent-free conditions[a]

Entry	Diazo compound	Alkyne	Pyrazole	Time/h	Yield (%)
1		≡—CO$_2$Et	EtO$_2$C—pyrazole—CO$_2$Et (HN—N)	0.5	95
2		EtO$_2$C—≡—CO$_2$Et	CO$_2$Et, EtO$_2$C, CO$_2$Et pyrazole (HN—N)	1	95
3	CO$_2$Et **1a** (N$_2$)	≡—SiMe$_3$	Me$_3$Si—pyrazole—CO$_2$Et (HN—N)	24	90
4		≡—Ph	Ph—pyrazole—CO$_2$Et (HN—N)	48	93
5		≡—(propyl)	—	48	—
6[b]	Ph, CO$_2$Me **1b** (N$_2$)	≡—CO$_2$Et	MeO$_2$C—pyrazole(Ph)—CO$_2$Et (HN—N)	16	60
7	**1c** (indanone-diazo)	≡—CO$_2$Et	tricyclic pyrazole—CO$_2$Et	2.5	90
8		EtO$_2$C—≡—CO$_2$Et	tricyclic pyrazole—CO$_2$Et, CO$_2$Et	2.5	85
9	**1d** (tetralone-diazo)	≡—CO$_2$Et	tetracyclic pyrazole—CO$_2$Et	4	88
10		EtO$_2$C—≡—CO$_2$Et	tetracyclic pyrazole—CO$_2$Et, CO$_2$Et	4	85
11[b]		≡—Ph	tetracyclic pyrazole—Ph	48	40
12[b]	OH, CO$_2$Et **1e** (Cl-phenyl, N$_2$)	≡—CO$_2$Et	EtO$_2$C—pyrazole—CO$_2$Et (HN—N)	1	86
13	**1f** (O, CO$_2$Et, N$_2$)	≡—CO$_2$Et	—	48	—
14[c,d]		≡—CO$_2$Et	pyrazole—CO$_2$Et (HN—N)	0.5	93
15[c,d]	SiMe$_3$ **1g** (N$_2$)	EtO$_2$C—≡—CO$_2$Et	EtO$_2$C—pyrazole—CO$_2$Et (HN—N)	0.5	86
16[c]		≡—Ph	pyrazole—Ph (HN—N)	5	87

[a] Reactions were performed on a 1 mmol scale with 1.1 eq. of the most volatile reagent, neat, at 80 °C. [b] Product was purified through column chromatography. [c] Trimethylsilyl diazomethane was used as a 2 M solution in hexane. [d] Reaction was performed at 20 °C.

With ethyl diazoacetate as the dipole (entries 1–5), we were delighted to see that even the poorly reactive trimethylsilyl acetylene and phenyl acetylene reacted very well, albeit in 24 and 48 h, respectively, to afford the corresponding products with a yield >90% (entries 3 and 4). However, hexyne did not undergo any transformation, even after 48 h (entry 5).

Assessment of other α-diazocarbonyl molecules **1b–d** (derived from phenyl acetate, 1-indanone and α-tetralone, respectively) also gave very good results affording more structurally complex pyrazoles. As previously reported by Li,[14] during the reaction between **1b** and ethyl propiolate the cycloaddition occurred followed by 1,5-aryl and 1,3-hydrogen shifts to afford the 3,4,5-trisubstituted pyrazole in 60% yield (entry 6). With cyclic compounds **1c–d** the reaction with electron-poor dipolarophiles took place easily in 2.5–4 h (80 °C, neat) and polyfunctionalised tricyclic compounds were obtained in excellent 85–90% yields (entries 7–10), while phenyl acetylene also reacted with **1d** albeit sluggishly (40% yield, entry 11). In the course of this reaction with diazo-indanone and -tetralone, a ring expansion occurred for which a putative mechanism is proposed (Scheme 1).
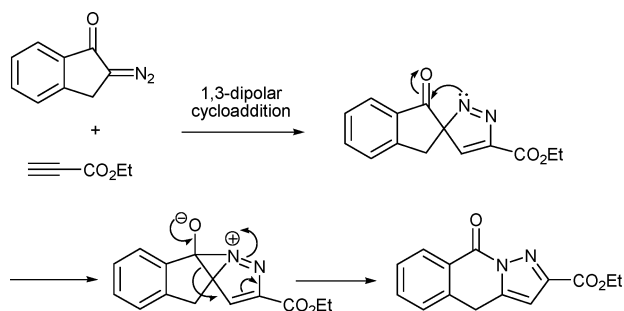
Scheme 1 Putative mechanism for the reaction of diazo indanone with ethyl propiolate.

Interestingly, β-hydroxy-α-diazocarboxylate **1e** can also be used, but the obtained pyrazole is the same as that afforded with simple ethyl diazoacetate (entry 1), and is accompanied with an equivalent of 4-chlorobenzaldehyde (entry 12). As previously suggested, a retro-aldol reaction may occur after the cycloaddition step to afford the more stable pyrazole with release of a benzaldehyde molecule.[14] However, the use of α,α-dicarbonyl compound **1f** as the dipole did not afford any pyrazole and it slowly decomposed in the reaction medium.

Interestingly, these reaction conditions are also very efficient with trimethylsilyl diazomethane **1g**, a stable analogue of diazomethane. It is important to note that, in this case, conditions were slightly modified since trimethylsilyl diazomethane is commercialised as a concentrated solution (2 M in hexane). The reaction with activated alkynes was complete within only 0.5 h at room temperature (entries 14 and 15) but required 5 h at 80 °C with phenyl acetylene (entry 16). For all these three reactions, a 1,5-TMS shift followed by desilylation occurred, without any aqueous work up, and the pyrazoles were recovered after hexane evaporation in excellent yields (>86%).

Finally, to assess the preparative effectiveness of our protocol we scaled up the process (17-fold): by reacting 2 grams of ethyl diazoacetate with 1.1 equivalent of ethyl propiolate at 80 °C, full conversion also occurred after 0.5 h. As for previous examples, the slight excess of alkyne was removed *in vacuo*, and the product was obtained in 96% yield (still with very good purity).

To summarize, a simple and "clean" process has been set up for the one-step synthesis of pyrazoles. Conditions are very simple: various diazo compounds and alkynes (even without an electron-withdrawing group) react through a 1,3-dipolar cycloaddition without any promoter or special medium. The reaction affords pyrazoles in excellent yields and purity, often without any other work up than distilling the small excess of the lightest reagent. Moreover, this attractive protocol is also efficient on a multigram scale, and is promising for industrial applications.

Acknowledgements

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Solventless microwave assisted protocol for synthesis of arylalkylpiperazines using Cs-base†

Alain Gamal Giuglio-Tonolo, Thierry Terme and Patrice Vanelle

A series of some arylalkylpiperazines was prepared in good yields under microwave irradiation in dry media conditions using CsOH with high chemo- and regioselectivity.

Introduction

Synthesis of arylalkylpiperazines is obviously an important task in modern medicinal chemistry. Some of them constitute an essential part of a large number of biologically active compounds. For example, some derivatives, containing amidoalkyl or amidoaryl groups, possess central nervous system depressant activity, present excellent 5-HT$_2$ receptor antagonism and 5-HT$_{1A}$ receptor agonism, or display D$_2$ and 5-HT$_{1A}$ receptor affinity.[1]

The synthetic approaches to tertiary aliphatic amines from secondary amines include reductive amination[2] and direct *N*-alkylation.[3] The nucleophilic attack of alkyl halides by secondary amines in the presence of base is useful for the preparation of tertiary amines, but the reaction requires long reaction times and gives a mixture of secondary and tertiary amines. Furthermore, reaction times of *N*-alkylation of arylpiperazines with primary alkyl halides, which is an important synthetic method to obtain the corresponding arylalkylpiperazines, range between 4 and 26 h.[4] In recent years, microwave irradiation has become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as promoting new reactions.[5] Moreover, when carrying out a reaction in a microwave oven, the use of a solvent can be avoided, allowing eco-friendly synthesis and offering several advantages, such as to reduce the risk of explosion and easier work-up.[6]

As a part of our program directed toward the preparation of new derivatives with potential CNS activities,[7] we developed a method to synthesize arylalkylpiperazine moieties as synthetic intermediates involving an eco-friendly method for the chemoselective preparation of tertiary amine corresponding to alkylsubstituted arylpiperazines (Scheme 1).

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R$_1$ = 3,4-Cl; 2-OCH$_3$; 2,5-CH$_3$; 2-CF$_3$ or 4-F
R$_2$ = OH; CO$_2$Et or CN

Scheme 1

Results and discussion

We initially studied the microwave-assisted coupling of 3,4-(dichlorophenyl)piperazine **1** with 4-chlorobutanol **2a** using a solventless procedure (Scheme 2).
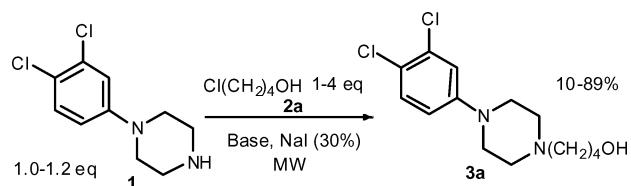
Scheme 2

The first attempts to prepare **3a** using **1** in slight excess (1.2 eq) to reduce overalkylations with **2a** (1 eq) were unsuccessful (10–19%). The reactants were adsorbed on the surface of the additive (Al$_2$O$_3$/base in 4:1 ratio) in large excess and a base, such as NaHCO$_3$, K$_2$CO$_3$ or KOH, was employed. As expected, direct *N*-monoalkylation techniques using bases like NaHCO$_3$ or K$_2$CO$_3$ and a large excess of **2a** (2 eq) gave, after optimization, moderate yields (40 and 48%, respectively) because of overalkylations. The volatility of **2a** and the basic properties of **1** in the reaction mixture can induce a lower yield. In the last few years, Cs-base promoted synthetic protocols have been widely applied to the formation of a variety of carbon-hetero atom bond forming reactions.[8–10] Recently, an elegant methodology for direct amination reactions promoted by CsOH·H$_2$O with the use of DMF has been reported.[8] However, this report is limited to alkylation of primary alkyl amines which can be rapidly converted to the secondary amine under the classical heating method in moderate to good yields. With the aim of efficiently synthesizing substituted arylpiperazines, S$_N$2 alkylation using monohydrate CsOH or Cs(CO$_3$)$_2$ as base under microwave irradiation was investigated (Scheme 2, Table 1).

We demonstrate that arylalkylpiperazine **3a** can be obtained in good yield, using a Cs-base as base under microwave irradiation without solvent. These conditions reaction exhibited enhanced chemoselectivities in amine alkylation compared to the previously reported protocols. The multimode reactor used was an ETHOS Synth Lab station (Ethos start, Milestone Inc.).

Table 1 Solventless *N*-alkylation under microwave irradiation

Entry[a]	Base (eq)	Reaction conditions	Yield[b] (**3a**)
1	CsOH·H₂O (1 eq)	200 W; 50 °C; 2 × 15 min[d]	64%
2	Cs₂CO₃ (1.2 eq)	150 W; 50 °C; 30 min	63%
3	CsOH·H₂O (2 eq)	200 W; 50 °C; 2 × 15 min[d]	79%
4	CsOH (2 eq)[c]	200 W; 50 °C; 3 × 15 min[d]	89%

[a] All the reactions are performed using amine **1** (1 eq: 4 mmol) with haloalkane **2a** (4 eq) in the presence of 30% NaI and 0.8 g of dessicant (MgSO₄). [b] % Yield relative to amine **1**. [c] CsOH·H₂O was dried at 120 °C for 24h. [d] Pulse irradiation (with 90 s intervals).

Scheme 3

90 s intervals were needed between pulse irradiation because the sensitivity of the products to heating. Furthermore, monohydrate CsOH (Table 1, entry 1 and 3) was found to be superior. Cesium bicarbonate (Table 1, entry 2) gave lower conversions, presumably due to decreased basicity and solubility. However, when CsOH is strictly dried, the yield increased to 89%. Moreover, NaI is used to facilitate the reaction by a halogen exchange activation. This methodology exhibits several advantages over the conventional heating by reducing the reaction time, improving the reaction yield and also by eliminating the side reactions. With this general procedure for the synthesis of **3a** (Table 1, entry 4) in hand, we then investigated direct *N*-monoalkylation using a variety of arylpiperazines and haloalkanes (Table 2, Scheme 3). In order to apply this new procedure to a series of arylpiperazines with various haloalkanes, we have modified some parameters, such as the power of the microwave oven, reaction time, temperature and quantity of haloalkane (3–5 eq), due to the physico-chemical properties of the used haloalkane. After monitoring by TLC, the optimized yields are reported in Table 2. For the haloalkanes **2c** and **2d**, the optimization seems to be haloalkane-dependent whatever amine is used.

As shown in Table 2, various functionalized primary chloro or bromoalkane derivatives were efficiently coupled with various arylpiperazines generating the corresponding tertiary amines. This methodology can be applied with alcohol, ester or nitrile derivatives. As expected, the reactions still exhibited high yields. In order to show the advantage of the use of a microwave reactor, we realized the preparation of compound **5b** under the same experimental conditions without microwave irradiation but using an oil bath for heating instead. Only 21% yield of compound **5b** was isolated after 18 h *versus* 96% yield after 4 × 20 min, under microwave irradiation. Mono-*N*-alkylation was then applicable with the use of a range of different arylpiperazines, offering similar trends. In all entries (Table 2), very little or no overalkylation was detected. This chemoselectivity can be explain by analogy with the mechanism proposed by K. W. Jung and coworkers,[10] a strong affinity of the tertiary amine for the cesium cation reduces the nucleophilicity of the tertiary amine and produce a sterically hindered complex.
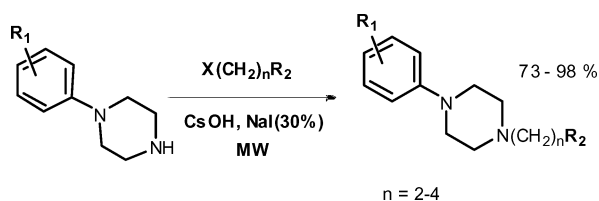
Conclusion

In order to obtain antipsychotic precursors, we developed a synthetic method of arylalkylpiperazines under microwave irradiation in "dry" media conditions including Cs(OH) as base to promote chemo- and regioselectively the *N*-alkylation. Thanks to this approach, substituted arylpiperazine derivatives of pharmacological interest were obtained in good yields. This simple and convenient methodology corresponds to a "green chemistry" approach which has been widely adopted to meet the fundamental scientific challenges of protecting human health and the environment. Currently, efforts are underway to extend this procedure to the synthesis of cyclic tertiary amines from primary amines by di-*N*-alkylation.

Table 2 CsOH-promoted *N*-alkylation using various secondary amines and haloalkanes

Amine (quantity)	R₁	Haloalkane (equivalent)	X	n	R₂	Reaction conditions	Yield[a] (product)[b]
1 (4 mmol)	3,4-Cl	**2a** (4 eq)	Cl	4	OH	200 W; 60 °C; 3 × 15 min[c]	89% (**3a**)
4 (4 mmol)	2-OCH₃	**2a** (4 eq)	Cl	4	OH	150 W; 55 °C; 4 × 15 min[c]	90% (**5a**)
6 (2 mmol)	4-F	**2a** (4 eq)	Cl	4	OH	200 W; 60 °C; 3 min	95% (**7a**)
1 (4 mmol)	3,4-Cl	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 9 min	90% (**3b**)
4 (4 mmol)	2-OCH₃	**2b** (3 eq)	Cl	3	CN	150 W; 60 °C; 4 × 20 min[c]	96% (**5b**)
6 (2 mmol)	4-F	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 5 min	86% (**7b**)
8 (4 mmol)	2,5-CH₃	**2b** (3 eq)	Cl	3	CN	200 W; 60 °C; 3 × 15 min[c]	73% (**9b**)
1 (2 mmol)	3,4-Cl	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	82% (**3c**)
6 (2 mmol)	4-F	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	88% (**7c**)
8 (2 mmol)	2,5-CH₃	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	74% (**9c**)
10 (2 mmol)	3-CF₃·HCl	**2c** (5 eq)[d]	Br	2	CN	100 W; 50 °C; 4 × 5 min[c]	86% (**11c**)
1 (2 mmol)	3,4-Cl	**2d** (3 eq)	Cl	3	CO₂Et	150 W; 50 °C; 4 × 4 min[c]	98% (**3d**)
6 (2 mmol)	4-F	**2d** (3 eq)	Cl	3	CO₂Et	150 W; 50 °C; 4 × 4 min[c]	95% (**7d**)
8 (2 mmol)	2,5-CH₃	**2d** (3 eq)	Cl	3	CO₂Et	150 W; 50 °C; 4 × 4 min[c]	97% (**9d**)
10 (2 mmol)	3-CF₃·HCl	**2d** (3 eq)	Cl	3	CO₂Et	150 W; 50 °C; 4 × 4 min[c]	97% (**11d**)

[a] All the reactions are performed using 1 equivalent of arylpiperazine with corresponding haloalkane in the presence of 30% NaI and 0.8 g of dessicant (MgSO₄), promoted by dried CsOH. [b] NMR and mass spectra of all synthesized products are in accordance with the literature.[11] [c] Pulse irradiation (with 90 s intervals). [d] No NaI was added in the reaction mixture containing bromohaloalkane **2c**.

Experimental

General procedure

To a mixture of arylpiperazine (1 eq), sodium iodide (0.3 eq), magnesium sulfate (0.8 g) and cesium hydroxide (2 eq) was added 4-haloalkane (3–5 eq). The reaction mixture was stirred and irradiated in a microwave oven (Ethos start) for an appropriate time and temperature. After being cooled down, the mixture was then taken up in 1 N NaOH and then extracted with AcOEt (3 × 30 mL). The organic layers were washed with water (2 × 30 mL), with brine (30 mL) and dried over anhydrous sodium sulfate. Concentration of the solvent under reduced pressure and drying in a oven under reduced pressure afforded the desired alkylarylpiperazine.

For the reactions carried out with 4-chorobutanol **2a**, the corresponding desired product was isolated and separated to secondary products by chromatographic column with AcOEt/*n*-hexane as eluent. For example: 4-[4-(3,4-dichlorophenyl)piperazin-1-yl]butan-1-ol **3a** NMR ^{1}H (200 MHz, CDCl$_3$) 7.26 (d, J = 9.0 Hz, 1H), 6.95 (d, J = 2.9 Hz, 1H), 6.69–6.75 (dd, J = 9.0 and 2.8 Hz, 1H), 3.64–3.56 (m, 2H), 3.47–3.41 (m, 1H), 3.27–3.22 (m, 4H), 2.74–2.69 (m, 4H), 2.50–2.55 (m, 2H), 1.72–1.63 (m, 4H); NMR ^{13}C (50 MHz, CDCl$_3$) 150.7, 132.7, 130.4, 122.0, 117.1, 115.2, 70.6, 58.3, 52.8, 48.6, 27.7, 23.6; HRMS (EI): calc. for C$_{14}$H$_{20}$N$_2$OCl$_2$ (M$^+$) 303.1025, found 303.1023.

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Mechanically activated synthesis of 1,3,5-triaryl-2-pyrazolines by high speed ball milling†

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An efficient mechanically activated solvent-free synthesis of 1,3,5-triaryl-2-pyrazolines from chalcones and phenylhydrazines using high speed ball milling is described. This method has notable advantages in terms of good yield, short reaction time and neat conditions.

Pyrazoline derivatives have been found to possess a broad spectrum of biological activities[1] including antibacterial, antifungal, anti-inflammatory, antiamoebic, and antidepressant activity. Among various pyrazoline derivatives, 1,3,5-triaryl-2-pyrazolines seem to be the most frequently studied pyrazoline type compounds. A variety of methods have been reported for the preparation of this class of compounds. One of the most commonly used methods is the cyclization of chalcones with phenylhydrazines or phenylhydrazine hydrochlorides. Many of these procedures use AcOH,[2] HCl,[3] Et$_3$N,[4] C$_5$H$_5$N,[5] Ba(OH)$_2$[6] or NaOH[7] as the reagent or catalyst, most of these require high temperature or long times to complete the reaction. Other methods, including using ultrasound irradiation and microwave-assisted synthesis, have been reported with various yields.[8]

In recent years solvent-free chemical synthesis has developed into a powerful methodology as it reduces the toxic waste produced and therefore becomes less harmful to the environment. Mechanically activated solvent-free reactions are reactions conducted by grinding or ball milling without solvent. High speed ball milling (HSBM) is an attractive mechanically activated method that has started to gain attention. It has often been used for milling minerals into fine particles and for the preparation and modification of inorganic solids.[9] In the field of synthetic organic chemistry, it has also found many applications,[10] such as Heck-type cross-couplings,[11] asymmetric Aldol reactions,[12] Baylis–Hillman reactions,[13] reduction of esters,[14] synthesis of fluoroaromatic compounds,[15] protection of diamines, anthranilic acid, diols and polyols,[16] and so on. However, the application of HSBM on the cyclization of chalcones with phenylhydrazines has not been reported. It is known that NaHSO$_4$ is an efficient reagent which can be used for different functional group transformations under heterogeneous conditions.[17] The stability and cheapness, low toxicity, heterogeneous nature of the reactions, high yields of the products and short reaction times are the notable advantages

which have attracted more attention of organic chemists. Herein, we wish to report an efficient method for the synthesis of 1,3,5-triaryl-2-pyrazolines in the presence of NaHSO$_4$·H$_2$O by HSBM.

Initial research was focused on the synthesis of 1,3,5-triphenyl-2-pyrazoline from chalcone and phenylhydrazine. The HSBM experiments were conducted in a AGO-2 planetary-centrifugal mill (acceleration: 60 g; volume of one drum: 35 mL; diameter of stainless steel ball: 5 mm; weight of balls: 75 g). To prevent "overheating" of the reaction mixture, a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5 min pause was specified. This cycle can be repeated until the reaction is completed. Different feed ratios of the reaction were tested to find the optimized conditions. As shown in Table 1, chalcone/phenylhydrazine/NaHSO$_4$·H$_2$O = 1:2:0.2 was determined to be the more suitable system to obtain the desired products with good yield (Table 1, Entry 2). When the amount of phenylhydrazine increased to three times that of chalcone, the yields did not improve significantly (Table 1, Entry 3). Higher yields could be obtained by employing more NaHSO$_4$·H$_2$O (Table 1, Entries 4, 5), but more catalyst could not increase the yield obviously. While using the lower amounts of catalyst, longer reaction times were usually used, and only the relatively lower yields were obtained (Table 1, Entry 6). In addition, when silica gel or the catalyst was absent in this reaction, the yield declined sharply (Table 1, Entries 7, 8). It was supposed that the silica gel might act as the grinding-aid agent or absorbent in this reaction.

Table 1 Effect of reaction condition on synthesis of 1,3,5-triphenyl-2-pyrazoline[a]

Entry	Chalcone/phenylhydrazine/NaHSO$_4$·H$_2$O	Time (min)	Yield (%)[b]
1	1:1:0.2	5	76
2	1:2:0.2	5	93
3	1:3:0.2	5	94
4	1:2:0.3	5	95
5	1:2:0.5	5	96
6	1:2:0.05	15	67
7	1:2:0	15	10
8	1:2:0.2[c]	15	40

[a] For a typical experimental procedure, see ref. 18. [b] Based on chalcone. [c] Not using silica gel.

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† Electronic supplementary information (ESI) available: Experimental details and characterisation data. See DOI: 10.1039/b816788e

Table 2 The recovery and reuse of the phenylhydrazine[a]

Entry	Phenylhydrazine (new + recovered) (g)	Time (min)	Recovered phenylhydrazine (g)/ recovered yield (%)	Yield (%)[b]
1	2.2 + 0	5	1.05/95.5	95
2	1.15 + 1.05	5	1.00/91.1	93
3	1.2 + 1.00	5	0.94/85.5	91

Table 3 Synthesis of 1,3,5-triaryl-2-pyrazolines catalyzed by $NaHSO_4 \cdot H_2O$ under HSBM conditions[a]

Entry	Ar_1	Ar_2	Ar_3	Product	Time (min)	Yield (%)[b]
1	C_6H_5	C_6H_5	C_6H_5	**3a**	5	87[c]
2	C_6H_5	C_6H_5	$4\text{-}ClC_6H_4$	**3b**	5	91
3	$4\text{-}ClC_6H_4$	C_6H_5	C_6H_5	**3c**	5	92
4	$4\text{-}ClC_6H_4$	C_6H_5	$4\text{-}ClC_6H_4$	**3d**	5	90
5	C_6H_5	$4\text{-}ClC_6H_4$	C_6H_5	**3e**	5	90
6	C_6H_5	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	**3f**	15	89
7	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5	**3g**	5	92
8	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	**3h**	5	91
9	$4\text{-}CH_3OC_6H_4$	$4\text{-}ClC_6H_4$	C_6H_5	**3i**	5	90
10	C_6H_5	$4\text{-}CH_3OC_6H_4$	C_6H_5	**3j**	5	92
11	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	C_6H_5	**3k**	5	93
12	$3\text{-}O_2NC_6H_4$	C_6H_5	C_6H_5	**3l**	15	85
13	C_6H_5	$4\text{-}O_2NC_6H_4$	C_6H_5	**3m**	15	82

[a] Substrate 1 (10 mmol), substrate 2 (20 mmol) and $NaHSO_4 \cdot H_2O$ (2 mmol) in silica gel (10 g) was used. [b] Based on chalcone. [c] Yield after four cycles.

Meanwhile, the recovery and reuse of the phenylhydrazine was investigated. Chalcone (2.1 g, 10 mmol), phenylhydrazine (2.2 g, 20 mmol), $NaHSO_4 \cdot H_2O$ (0.28 g, 2 mmol) and silica gel (10 g, 200–300 mesh) were reacted under similar conditions. After completion, the product of 1,3,5-triaryl-2-pyrazoline was firstly obtained by column chromatography (petroleum ether:EtOAc = 5:1), then the phenylhydrazine was attained (petroleum ether:EtOAc = 3:1). The recovered phenylhydrazine together with the new phenylhydrazine was used in the next reaction. The results are summarized in Table 2. It was found that the excess phenylhydrazine can be recovered and reused without obvious effect on the yield.

On the basis of the above results, to extend the scope and generality of this method, several structurally diverse chalcones and phenylhydrazines were cyclized to give 1,3,5-triaryl-2-pyrazolines by HSBM. The results are listed in Table 3. It could be seen that the reactions proceeded well with all the substrates, but substrates with electron-donating groups were generally more reactive than those with electron-withdrawing groups.

In a typical experiment, after the reaction was completed, $NaHSO_4 \cdot H_2O$ with silica gel was collected and dried to be regenerated. The reusability of the catalyst was examined and resulted in 92, 92, 90 and 87% yield over four recycles (Table 3, Entries 1).

Next, we attempted to prepare other types of 2-pyrazolines under the above optimum conditions. When α,β-unsaturated ketone (10 mmol), phenylhydrazine or thiosemicarbazide (20 mmol), $NaHSO_4 \cdot H_2O$ (2 mmol) and silica gel (10 g)

were used, the corresponding 2-pyrazolines (**3n**, **3o**, **3p**) were obtained in 80%, 76% and 62% yield, respectively (Scheme 1). However, when chalcone was examined with acyl hydrazides such as benzoylhydrazide and acethydrazide, we only got the corresponding hydrazones but not the target products, although the reaction time was extended to 25 min. This may be attributed
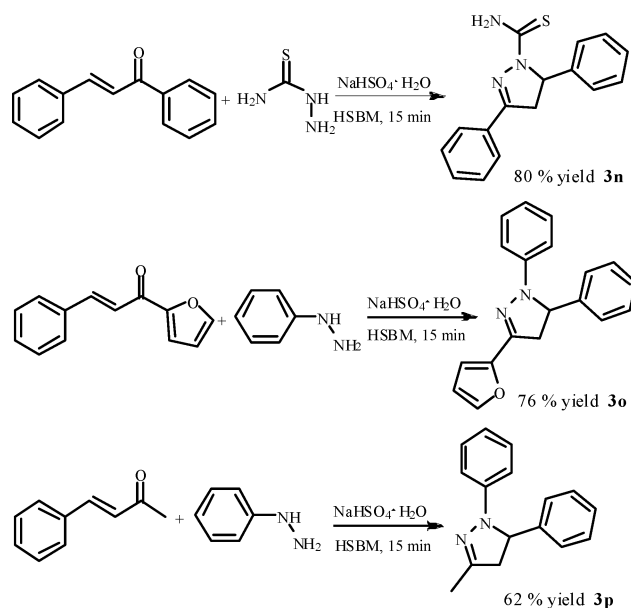
Scheme 1

to the strong electron-donating effect of acyl groups in acyl hydrazides. Preparation of 1-acyl-2-pyrazolines using other catalysts by HSBM is now under investigation.

In conclusion, we have developed an efficient and comparatively green strategy for the synthesis of 1,3,5-triaryl-2-pyrazoline by HSBM. Good yield, short reaction times and neat conditions are the notable advantages of this method. Besides, catalyst recovery and reusability is another feature of this procedure. We believe that this method has provided a better scope of the synthesis of 1,3,5-triaryl-2-pyrazolines and will be a more practical alternative to the existing methods for other organic reactions.

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18 Typical procedure: the following components were added to the reaction vessels: chalcone (2.1 g, 10 mmol), phenylhydrazine (2.2 g, 20 mmol), NaHSO$_4$·H$_2$O (0.28 g, 2 mmol), silica gel (10 g, 200–300 mesh). Then, stainless steel balls were added and the vessel was closed with lid and gasket. The ball mill was then run at a milling cycle with a rotational speed of 1290 rpm for 5 min followed by a 5 min pause. During the pause, a mixture example was taken out and dissolved in dichloromethane to monitor the progress of the reaction using TLC. This cycle was repeated until the reaction was completed. All the reaction mixture was washed off the vessel using EtOAc (20 ml) and then was filtered. The filtrate was dried (MgSO$_4$) and evaporated. The crude product was purified by column chromatography to provide 1,3,5-triphenyl-2-pyrazoline.

Ethyl lactate as a tunable solvent for the synthesis of aryl aldimines†

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Ethyl L-lactate can be tuned with a cosolvent to create polarity conditions ideal for synthesizing aryl aldimines that crystallize directly out of solution within minutes under ambient conditions in excellent yields and requiring no further purification.

Imines (Fig. 1) are intermediates in many reactions of both enzymatic and pharmaceutical interest. Traditional syntheses often involve the use of toxic solvents such as methylene chloride[1] or refluxing in petroleum-based solvents such as toluene as azeotroping agents.[2] Some recent imine syntheses have successfully used more benign solvents or conditions but still require recrystallization or other work up procedures, which negate some of the benefits of the green synthesis itself.[3–8] Here, we describe a greener synthesis of aryl aldimines using ethyl L-lactate as the solvent. Water was used as a cosolvent to optimize solvent polarity and induce rapid formation of product. The imines crystallized directly out of solution in high purity and yield, requiring no further purification. Ethyl lactate is unusual in that it is miscible with water as well as nonpolar organic solvents. Thus, a broad range of solvent polarity is accessible by simply "tuning" ethyl lactate with a cosolvent to create ideal conditions for rapid product formation. In addition, ethyl lactate is approved by the FDA as a food additive, is derived from renewable resources, and is biodegradable. Polarity adjustment by using a cosolvent is a standard technique for optimizing recrystallizations but we could find no instances of this same logic applied to reaction conditions. "Solvent tuning" is typically used in reference to supercritical fluids, when cosolvents are added to affect parameters like equilibria.[9] As far as we can find, this communication is the first example of ethyl lactate polarity tuning under ambient conditions to optimize reaction purity, yield, and speed.

Fig. 1 General synthesis of aryl aldimines.

Recently, several environmentally friendly syntheses of aryl aldimines have been reported: the sonication of ethanolic solutions containing silica as a catalyst,[8] solventless grinding

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with catalyst followed by recrystallization,[5] aqueous suspension followed by recrystallization,[6] aqueous suspension with vigorous mechanical stirring for ≥2 h,[7] solid phase grinding followed by vacuum removal of water at 80 °C,[3] and clay-catalyzed microwave synthesis followed by dichloromethane extraction.[4] In most of these syntheses, recrystallization or extraction was required to further purify or isolate the desired imine. Some methods also required catalysts or heat and nearly all required stirring. In contrast, our method required no catalyst, stirring, or further purification of the product imine. Nor was evidence of starting materials or solvents apparent in spectroscopic analyses.

The imines prepared are useful in a variety of applications. Salicylideneanilines show activity against tuberculosis,[15] a leading causes of infectious death. Cinnamylidene imines are useful intermediates in the preparation of β-lactam antibacterial compounds[16] and have been shown to greatly accelerate photodegradation of polyethylene, which could have favorable environmental consequences.[17]

To demonstrate the versatility of this solvent tuning technique for generating aryl aldimines, a variety of aryl aldehydes and aryl amines containing both activating and deactivating substituents were examined (Table 1). We found no need for catalysts or external energy for the reactions except the example with *p*-nitrobenzaldehyde (**a**). The literature data that we used for comparison are the best sources we could find where yields and some measure of purity, usually melting point, were reported. Full spectroscopic characterization of products is included in the ESI.† Only one example (**a**) required heat due to solubility problems with the *p*-nitrobenzaldehyde, but the reaction was complete within three minutes, compared to 24 h of continuous heat in the literature method.

All reactions were first run in pure ethyl L-lactate. Reactions that took more than ten minutes were tuned with water to reduce reaction time. The % EL values in Table 1 reflect the best combination of crystal quality and reaction speed. While we did not examine the mechanistic aspects of this reaction, we surmise water exerted its effect by one or both of the following routes: (1) water stabilized the carbinolamine intermediate, which accelerated the reaction or (2) the obvious insolubility of the imine product made it apparent when the reaction was complete, thus, excess time was not wasted to ensure reaction completion.

The synthesis of cinnamylidine aniline (**j**) is representative of the procedure. Briefly, 10 mmol aniline was dissolved in 5 mL 80% ethyl L-lactate in water (v/v) followed by addition of 10 mmol cinnamaldehyde. The reaction mixture was swirled until homogeneous and then allowed to sit undisturbed at room temperature for four minutes, when crystal formation

Table 1 Aryl aldimines synthesized using ethyl lactate (EL) polarity tuned with water. *Literature values for comparison are in italics with the reference cited in the % yield column*

	Solvent (% EL)	Ar$_1$	Ar$_2$	Time^a (*Lit.*)	mp °C (*Lit.*)	%Yield(*Lit.*)
a	100	p-CH$_3$O-C$_6$H$_4$	p-NO$_2$-C$_6$H$_4$	1–3 min^b (*24 h, Δ*)	133–134 (*134*)	94 (*100*)[3]
b	100	p-CH$_3$O-C$_6$H$_4$	p-Cl-C$_6$H$_4$	0.5–1 min (*6 h*)	127–129 (*124–125*)	93 (*100*)[3]
c	95	p-CH$_3$O-C$_6$H$_4$	C$_6$H$_5$CH=CH	0.5–1.5 min (*2 h*)	119–120 (*116–119*)	96 (*88*)[10]
d	90	p-CH$_3$O-C$_6$H$_4$	p-CH$_3$O-C$_6$H$_4$	1–3 min (*5–10 min*) (*nr*)	144 (*nr*)^c (*142*)	93 (*>99*)[8] (*nr*)[11]
e	100	p-CH$_3$-C$_6$H$_4$	p-Cl-C$_6$H$_4$	1–2 min (*6 h*)	124–125 (*125*)	96 (*100*)[6]
f	100	p-CH$_3$-C$_6$H$_4$	p-HO-C$_6$H$_4$	1–2 min (*2 h*)	217–220 (*215*)	90 (*100*)[3]
g	80	p-CH$_3$-C$_6$H$_4$	o-HO-C$_6$H$_4$	2–4 min (*>10 min*)	94 (*95–96*)	97 (*90*)[12]
h	90	Ph	p-Cl-C$_6$H$_4$	4–6 min (*2 h*)	63–64 (*58–61*)	95 (*97*)[6]
i	90	Ph	p-Br-C$_6$H$_4$	3–5 min (*1 h*)	71–72 (*71–74*)	99 (*86*)[6]
j	80	Ph	C$_6$H$_5$CH=CH	2–4 min (*5–10 min*) (*10–30 min*) (*nr*)	108–109 (*nr*) (*nr*) (*109*)	98 (*85*)[8] (*89*)[5] (*nr*)[13]
k	90	Ph	p-HO-C$_6$H$_4$	5–7 min (*30 min*) (*3 min*)	193–194 (*50–53*) (*195*)	>99 (*94*)[6] (*95*)[4]
l	100	p-Br-C$_6$H$_4$	p-Cl-C$_6$H$_4$	1–2 min	119–120	96
m	70	p-Br-C$_6$H$_4$	Ph	3–5 min (*30 min*)	66–68 (*62–65*)	93 (*98*)[6]
n	80	p-Br-C$_6$H$_4$	o-HO-C$_6$H$_4$	2–3 min (*nr*)	111 (*112*)	96 (*nr*)[11]
o	80	p-Cl-C$_6$H$_4$	p-Cl-C$_6$H$_4$	2–3 min (*30 min*)	110–111 (*110–113*)	97 (*87*)[6]
p	80	p-Cl-C$_6$H$_4$	C$_6$H$_5$CH=CH	1–2 min	105	97
q	90	p-Cl-C$_6$H$_4$	o-HO-C$_6$H$_4$	6–10 min (*nr*)	104 (*101–102*)	96 (*nr*)[14]

^{a} Beginning to end of crystallization. ^{b} Gentle heat. ^{c} nr = not reported.

was complete. Crystals were chilled, rinsed with cold brine and vacuum filtered, washed with cold water, and allowed to air dry. Some of the hydroxyl-containing imines had to be desiccated to completely remove water, especially when humidity was high. All melting points and spectroscopic data† were acquired on the crude imines. However, these imines can be recrystallized from ethyl lactate or low molecular weight alcohols.

While most reactions we tested occurred in either pure ethyl lactate or an ethyl lactate–water combination, we did find instances where a nonpolar cosolvent was necessary. For example, the synthesis of the imine between *p*-anisidine and *p*-phenylbenzaldehyde (not shown) required a 20% ethyl lactate : 80% *d*-limonene solvent system. The reaction was complete within seconds and resulted in a 99% yield. However, the product formed was not crystalline and required further purification. We are examining alternative green ways to tune ethyl lactate in the less polar direction to optimize such reactions. In addition, we are examining the utility of this technique for imines from aliphatic amines and/or aldehydes and have had promising preliminary results with benzylamines.

In conclusion, we have developed an effective, green synthesis for a variety of aryl imines using ethyl lactate as a versatile solvent that can be polarity tuned by adding a cosolvent. The reactions are complete within minutes at room temperature and the products are pure enough to avoid the necessity for recrystallization or other solvent-intensive isolation or purification procedures. No metals or hazardous auxiliaries were used at any point in the procedure.

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A green chemical approach for the *N*-alkylation of aldoximes to form nitrones in organized aqueous media and their *in situ* cycloaddition with olefins†

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Aldoximes react with α,β-unsaturated carbonyl and sulfonyl compounds in organized aqueous media (nanoreactor system) using dodecylbenzenesulfonic acid (DBSA) as surfactant to generate *N*-alkylated nitrones, which undergo intermolecular cycloaddition in the same pot with maleimides to give the desired cycloadduct in absence of any organic solvent and catalyst. Divinyl sulfone was successfully used for both *N*-alkylation and intramolecular cycloaddition, affording only one cycloadduct. This is a new example of green chemistry and provides a new aspect of reactions in water.

Introduction

The concept of green chemistry[1] and its application[2] in synthetic chemistry, has emerged as a major solution for the development of cleaner and more benign chemical processes. Various methodologies and routes have been developed for this purpose. Use of water as a solvent[3] is undoubtedly the best alternative as there will be no use of hazardous and toxic organic solvents and no need for vigorous drying of the solvents. The problem of insolubility and hydrolytic decomposition of many organic compounds in water may be solved by the use of a surfactant, which in water forms an organized medium.[4] The border between the homogeneous (solution phase) and heterogeneous phases consists of micellar, reverse micellar, microheterogeneous, colloidal phases *etc.* During the course of surfactant catalyzed reactions, the organized medium acts as a nanoreactor,[5] which solubilizes and conforms hydrophobic organic compounds into its hydrophobic cores and thus protects water labile substances from decomposition.[6] Although different research groups have developed various types of reactions in aqueous media,[3,4] the preparation of nitrones by *N*-alkylation of aldoximes[7] in water appears to be the first example of this type of useful reaction, attempted so far. In the course of developing efficient organic reactions in water, our group earlier reported a one-pot process for nitrone formation in water, followed by its intermolecular cycloaddition to form isoxazolidines.[4b] Recently, we also reported stereoselective synthesis of chiral oxepanes and pyrans through intramolecular nitrone cycloaddition in organized aqueous media.[4c] These studies led us to investigate

the formation of nitrones through *N*-alkylation of oximes in organized aqueous media.

Nitrones are well-known 1,3-dipoles in thermal cycloaddition reactions with multiple bond systems to provide different heterocyclic five membered ring systems.[8] Various uses and reactions of nitrones are well established.[9] There are many standard routes for the formation of nitrones.[10] Most of them include anhydrous conditions or dehydrative agents. For example, one of the most convenient methods of nitrone generation is the reaction of oximes with various alkylating agents or dipolarophiles.[11] When oximes are *N*-alkylated in this process, the formed nitrones have different functionalities and can take part in various types of reactions leading to the synthesis of biologically active natural products.[11a,12] Cycloaddition reaction with externally added dipolarophiles is the most common reaction of the formed nitrones. However, most of the processes use anhydrous conditions, toxic organic solvents and different catalysts (non-green process), along with high temperature and long reaction times.

Results and discussion

Intermolecular pathway

We hereby report for the first time the formation of nitrone through the *N*-alkylation of aldoximes in water and its subsequent cycloaddition (Table 1). Aldoximes react with α,β-unsaturated carbonyl and sulfonyl compounds to give *N*-alkylated nitrones in moderate to good yields, which then undergo intermolecular cycloaddition with maleimide to give the desired cycloadduct. We used dodecylbenzenesulfonic acid (DBSA) as surfactant to form the desired organized media. Dynamic light scattering (DLS), *i.e.* a particle size analyzer study,[5a] proved the formation of the nanoreactor system (Fig. 1). We also obtained the optical micrograph of the aqueous media containing DBSA as surfactant (Fig. 2).

The applicability of the resultant *N*-alkylated nitrone, such as its reaction with some dipolarophiles through intermolecular

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† Electronic supplementary information (ESI) available: NMR spectra of all the cycloaddition products and synthetic procedures of the reactants. CCDC reference number 686184. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b812290c
‡ Deceased.

Table 1 Surfactant-catalyzed conjugate additions of oximes to α,β-unsaturated carbonyl and sulfonyl compounds and intermolecular nitrone cycloaddition with various *N*-substituted maleimides in organised aqueous media

1a–g: R_1 = Ph, 3-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, (*E*)-C$_6$H$_4$CH=CH, CH$_3$CH$_2$CH$_2$, 2-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$
2a: R_2 = H, X = CO$_2$Et; **2b:** R_2 = Ph, X = COPh; **2c:** R_2 = H, X = SO$_2$Ph
3a–c: R_3 = Ph, Me, CH$_2$CH$_2$CH$_3$
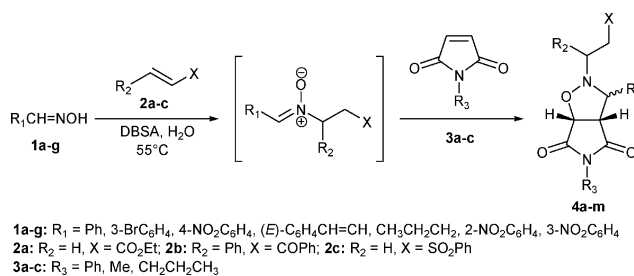
Entry	Oximes	R_1	Acceptors	Maleimide	Time/h	Product[a] (Yield) (%)	Product[b] (*exo*:*endo*)
1	**1a**	Ph	**2a**	**3a**	20	**4a** (58)	100:0
2	**1a**	Ph	**2b**	**3a**	20	**4b** (68)	60:40
3	**1b**	3-BrC$_6$H$_4$	**2a**	**3b**	26	**4c** (55)	100:0
4	**1b**	3-BrC$_6$H$_4$	**2b**	**3b**	26	**4d** (68)	59:41
5	**1c**	4-NO$_2$C$_6$H$_4$	**2a**	**3a**	28	**4e** (53)	100:0
6	**1c**	4-NO$_2$C$_6$H$_4$	**2b**	**3a**	28	**4f** (66)	77:23
7	**1d**	(*E*)-PhCH=CH	**2a**	**3a**	22	**4g** (57)	100:0
8	**1e**	n-C$_3$H$_7$	**2a**	**3a**	22	**4h** (70)	100:0
9	**1e**	n-C$_3$H$_7$	**2b**	**3a**	20	**4i** (75)	100:0
10	**1f**	2-NO$_2$C$_6$H$_4$	**2b**	**3a**	30	**4j** (55)	59:41
11	**1g**	3-NO$_2$C$_6$H$_4$	**2a**	**3c**	26	**4k** (58)	68:32
12	**1a**	Ph	**2c**	**3b**	25	**4l** (53)	100:0
13	**1c**	4-NO$_2$C$_6$H$_4$	**2c**	**3a**	32	**4m** (52)	100:0

[a] after purification by column chromatography. [b] *exo*:*endo* ratio is determined by ^{1}H and ^{13}C spectra.
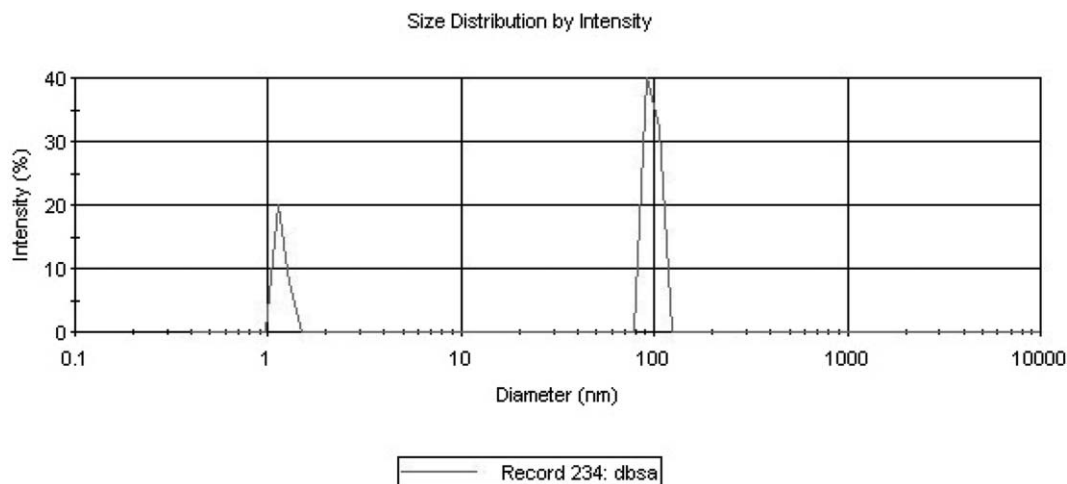
Fig. 1 Dynamic light scattering (DLS) data of the organised media using DBSA as surfactant.
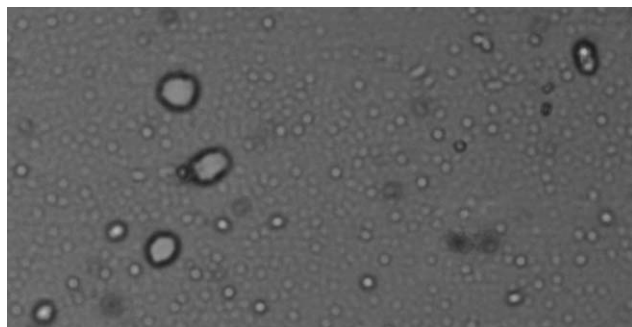
Fig. 2 Optical micrograph of the aqueous media containing DBSA as surfactant.

nitrone cycloaddition, has not been investigated much except for some reports in organic solvents.[11b,13] Kanemasa *et al.* have reported[7] *N*-alkylation of aldoximes in organic solvents such as benzene, dichloromethane and toluene in the presence of Lewis acid catalysts like ZnI$_2$ and BF$_3$.OEt$_2$ and the subsequent intermolecular cycloaddition with maleimides. In many cases, they had to reflux the hazardous organic solvents for many hours to get a good yield.

The present unique and safe approach for the preparation of nitrones by *N*-alkylation of aldoximes and their *in situ* intermolecular cycloaddition with various maleimides provides important cycloaddition products. As a part of our process we prepared seven aldoximes (**1a–g**; see ESI†). The aldoximes

Table 2 Effect of surfactants in the nitrone formation and intermolecular cycloaddition reaction in water

Entry	A	Time/h	Yield (%)
1	Surfactant DBSA	26	55
2	—	> 50	nil
3	Surfactant CTAB	> 50	10–15
4	Surfactant SDS	> 50	5–10
5	Surfactant Tween 80	> 50	not detected
6	Toluene-4-sulfonic acid	> 50	-do-
7	Toluene-4-sulfonic acid + Surfactant CTAB	> 50	25

Table 3 Reaction of oximes with divinyl sulfones

a-e: R_1 = Ph, 3-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, (E)-C$_6$H$_4$CH=CH, CH$_3$CH$_2$CH$_2$

Entry	Oxime	Time/h	Product	Yield[a] (%)
1	**1a**	16	**6a**	57
2	**1b**	17	**6b**	55
3	**1c**	20	**6c**	52
4	**1d**	17	**6d**	53
5	**1e**	15	**6e**	53

[a] after purification by column chromatography.

were successfully reacted with α,β-unsaturated carbonyl compounds in presence of the surfactant in aqueous media to give *N*-alkylated nitrones in moderate to good yield (Table 1). We used ethyl acrylate and *trans*-chalcone as α,β-unsaturated carbonyl compounds and phenyl vinyl sulfone as α,β-unsaturated sulfonyl compound for this purpose. The progress of the reaction was monitored by TLC. Between ethyl acrylate and *trans*-chalcone, formation of the *N*-alkylated nitrone was better with the former, possibly due to the absence of any substituent at the β-position.

As the conjugate addition step of aldoximes to α,β-unsaturated carbonyl compounds towards formation of *N*-alkylated nitrones was found to be a slow process, *N*-substituted maleimide was added directly to the reaction mixture after formation of nitrone (~70%) to drive the equilibrium towards the end product.

We selected the reaction of 3-bromobenzaldoxime (**1b**) with ethyl acrylate (**2a**) and subsequent intermolecular cycloaddition with *N*-methylmaleimide (**3b**) as a model reaction (Table 2). We performed this reaction in various conditions including the use of different types of surfactants *i.e.* cationic, anionic, nonionic and acidic surfactants. Excellent results were obtained by using acidic surfactant DBSA. Yields were not good with cationic (CTAB), anionic (SDS) or nonionic (Tween 80) surfactants. There were no reactions in neat conditions or in water without surfactant. So it was evident that acidic surfactants had a prominent role in the *N*-alkylation of aldoximes towards the formation of the cycloadducts.

To confirm whether any non-surfactant type acid can promote nitrone formation under this condition, we carried out the reaction using a non-surfactant acid (toluene-4-sulfonic acid). As no product could be detected, the role of surfactant was established. The reaction also occurred in much lower yield when toluene-4-sulfonic acid was used in conjunction with a non-acidic surfactant (CTAB). Thus, the dual role of DBSA in ensuring the success of the reaction is established.

Moderate to excellent yields (52–75%) were obtained (Table 1) in this reaction. We observed that the nature of the alkyl or aryl components present in the aldoxime moiety influenced the course of the reaction. Generally electron donating substituents gave better results by enhancing the nucleophilicity of the oxime nitrogen atom and thus promoting the Michael addition (or ene-like step). It was also found that the majority of the aldoximes afforded a single product (*exo*) with ethyl acrylate (**2a**) but a mixture of diastereomers with *trans*-chalcone (**2b**). Only the aliphatic aldoxime, butyraldehyde oxime (**1e**) produced solely the *exo* product with both the nucleophiles. The structures of the products were deduced on the basis of analytical and spectroscopic data. For example, the relative configurations among the three methine protons (3-H, 3a-H, and 6a-H) of **4c** were deduced by COSY and NOESY. From NOESY, it was evident that the 3a-H and 6a-H methine protons are in *cis* orientation, whereas 3-H is *trans* to 6a-H *i.e. trans* to 3a-H also. These results confirmed the *exo* structure. Exclusive or predominant formation of *exo* product in most of the reactions (Table 1) can be rationalised, as *endo* approach is sterically hindered. The minor *endo* adducts were not separated and the diastereomeric ratio was determined by NMR spectroscopy.

Intramolecular pathway

Aldoximes reacted with divinyl sulfone (**5**), a 1,4-diene, *via* a tandem process involving an *N*-(4-alkenyl) nitrone intermediate and gave rise to a bridged-ring product (**6**). Although the intermediate *N*-(4-alkenyl) nitrones can undergo cycloaddition in two different ways to yield the cycloadduct (**6**) or (**7**), we got only **6a–e**. The reaction of various aldoximes with divinyl sulfone afforded only one product each, *i.e.* 8-aryl/alkyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide exclusively. Though Grigg *et al.* had reported[14] the formation of two types of bridged-ring products in boiling xylene, we found only one in good yield (Table 3). Here also, the nucleophilicity of the oxime nitrogen atom controls the rate of the reaction by regulating the Michael addition step. We observed that the greater the electron-density on the oxime nitrogen atom, greater is the yield of the product. The structure of the product was deduced from spectroscopic and analytical data and confirmed from X-ray crystal structure[15] determination (Fig. 3).

Conclusions

In conclusion, we have demonstrated a useful and 'green' approach to the preparation of nitrones through the *N*-alkylation of aldoximes in organized aqueous media and subsequent intermolecular or intramolecular cycloaddition reactions in the
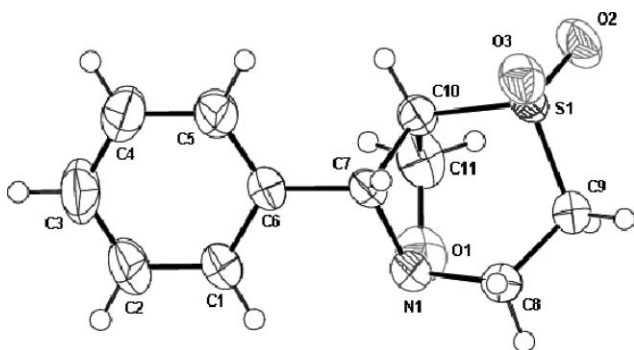
Fig. 3 X-Ray structure of the compound **6a**.

same pot. This process leads to the formation of only one product in most of the cases. This concept of a nanoreactor, formed in the organized aqueous media, could be applicable to various other types of reactions.

Experimental

General

Some reagents were obtained from commercial sources and used without purification. The solvents used were of technical grade, and freshly distilled prior to use. [1]H (300 MHz, 600 MHz) and ^{13}C (75 MHz, 150 MHz) NMR spectra were recorded using CDCl$_3$ as solvent and tetramethyl silane (TMS) as internal standard on Bruker DPX 300 MHz and Bruker DRX 600 MHz NMR instruments at ambient temperature. Chemical shifts are stated in parts per million in δ scales. COSY and NOESY experiments have been carried out in order to assign the ^{1}H spectra completely. Infrared spectra were recorded on a JASCO-FT-IR Model-410. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. IR spectra were measured using a KBr pellet or in neat condition. Mass spectra were measured mostly in ESIMS (+) and some in EIMS mode. DI-EIMS were recorded on a GCMS-Shimadzu-QP5050A and ESIMS were done on a Waters® Micromass® Q-TOF micro™ Mass Spectrometer. X-Ray crystallographic data of single crystals were collected on Bruker Kappa Apex II with Mo-Kα radiation ($\lambda = 0.71073$ Å). Dynamic light scattering (DLS) was performed by Malvern Instruments (Model: Nano ZS 80). Optical micrograph was taken at 10x magnification in a Nikon ECLIPSE (Model: E200) microscope. The surfactants used were dodecyl benzene sulfonic acid (DBSA), cetyl trimethyl ammonium bromide (CTAB), sodium dodecyl sulfate (SDS) and polyoxyethylene(20) sorbitan monooleate (Tween 80). TLC was performed on pre-coated plates (0.25 nm, silica gel 60 F$_{254}$). Organic extracts were dried over anhydrous sodium sulfate. Column chromatography and flash chromatography were carried out using commercial-grade silica gel (100–200 mesh or 230–400 mesh). PS and EA stand for petroleum spirit (60–80 °C) and ethyl acetate, respectively.

Experimental procedure for *N*-alkylation of aldoximes and subsequent cycloaddition reaction in organized aqueous media

An aromatic or aliphatic aldoxime (0.5 mmol) and an α,β-unsaturated carbonyl compound (0.5 mmol, 1.0 equiv.) were

added successively to a solution of the surfactant (DBSA, 0.05 mmol) in H$_2$O (2 mL) at room temperature in a 25 mL round-bottom flask. The reaction was sonicated§ for 10 minutes, then stirred at 55 °C and monitored by TLC. After satisfactory formation of the *N*-alkylated nitrone, *N*-alkyl or aryl maleimide (0.6 mmol) was added and the stirring of the reaction mixture was continued at that temperature. After stirring at that temperature for the period of time listed in Table 1, the product was extracted with ethyl acetate. Then it was washed with brine, dried over Na$_2$SO$_4$, and concentrated in rotavapor. The crude product was then purified by silica gel column chromatography.

3-(4,6-Dioxo-3,5-diphenyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4a)

Grayish solid; yield 58% (eluent PS-EA, 4:1); mp. 145 °C; only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.20 (t, $J = 7.1$ Hz, 3H), 2.51–2.62 (m, 2H), 2.85–3.03 (m, 2H), 3.84 (dd, $J = 3.3$, 7.3 Hz, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 4.37 (bs, 1H), 5.07 (d, $J = 7.3$ Hz, 1H), 7.31–7.50 (m, 10H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 14.1 (CH$_3$), 33.1 (CH$_2$), 53.7 (CH$_2$), 60.4 (CH$_2$), 68.4 (CH), 75.8 (CH), 79.1 (CH), 126.3 (Ar-CH), 128.2 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 129.3 (Ar-CH), 131.3 (C), 171.8 (C), 172.3 (C), 174.3 (C); IR (KBr) ν_{max}: 3449, 2915, 1713, 1497, 1389, 1324, 1193, 1070 cm^{-1}; ESIMS (*m/z*): 395 (M$^+$ + 1), 417 (M$^+$ + 23). Elemental analysis for C$_{22}$H$_{22}$N$_2$O$_5$: Calcd. C, 66.99; H, 5.62; N, 7.10. Found: C, 67.13; H, 5.73; N, 6.97.

2-(3-Oxo-1,3-diphenyl-propyl)-3,5-diphenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4b)

Yellowish sticky liquid; yield 68%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo*:*endo* = 60:40; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.23 (dd, $J = 4.9$, 17.5 Hz, 1H), 3.53 (dd, $J = 6.6$, 16.9 Hz, 1H), 3.58 (t, $J = 8.1$ Hz, 2H), 3.85 (d, $J = 8.7$ Hz, 1H), 4.04–4.14 (m, 2H), 4.27 (t, $J = 8.5$ Hz, 1H), 4.59–4.68 (m, 2H), 4.84 (t, $J = 5.6$ Hz, 1H), 4.94 (d, $J = 7.3$ Hz, 1H), 5.26 (d, $J = 8.2$ Hz, 1H), 6.65–6.68 (m, 1H), 7.08 (d-like, $J = 6.8$ Hz, 2H), 7.18–7.54 (m, 32H), 7.97 (t-like, $J = 8.0$ Hz, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 42.4 (CH$_2$), 43.7 (CH$_2$), 53.5 (CH), 54.1 (CH), 61.0 (CH), 64.0 (CH), 68.5 (CH), 69.0 (CH), 75.5 (CH), 78.0 (CH), 125.9 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.0 (Ar-CH), 128.1 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 130.1 (Ar-CH), 130.8 (Ar-CH), 131.2 (Ar-CH), 132.8 (Ar-CH), 133.0 (Ar-CH), 133.2 (Ar-CH), 134.6 (C), 135.3 (C), 136.8 (C), 137.0 (C), 171.6 (C), 171.9 (C), 172.7 (C), 174.2 (C), 197.8 (C); IR (neat) ν_{max}: 3492, 3062, 3028, 2923, 2342, 1958, 1785, 1722, 1684, 1597, 1496, 1451, 1381, 1288, 1205 cm^{-1}; EIMS (*m/z*): 502(M$^+$). Elemental analysis for C$_{32}$H$_{26}$N$_2$O$_4$: Calcd. C, 76.48; H, 5.21; N, 5.57. Found: C, 76.39; H, 5.33; N, 5.66.

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§ It is well-known that sonication favors the formation of organized media and so we did it to obtain a shorter reaction time and better result.

3-[3-(3-Bromo-phenyl)-5-methyl-4,6-dioxo-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4c)

Yellow solid; yield 55% (eluent PS-EA, 4:1); mpt. 140°C; only *exo* product is formed; confirmed by COSY and NOESY; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 2.68 (t, J = 6.9 Hz, 2H), 2.80–2.89 (m, 1H), 2.97 (s, 3H), 3.06–3.16 (m, 1H), 3.70 (t, J = 7.9 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 4.89 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.33 (s, 1H), 7.46 (d, J = 7.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): 14.1 (CH$_3$), 24.8 (CH$_3$), 32.8 (CH$_2$), 51.0 (CH$_2$), 54.1 (CH), 60.5 (CH$_2$), 72.5 (CH), 76.2 (CH), 122.9 (q), 126.3 (Ar-CH), 130.3 (Ar-CH), 130.7 (Ar-CH), 132.0 (Ar-CH), 135.8 (C), 171.7 (C), 172.6 (C), 174.8 (C); IR (KBr) ν_{max}: 2986, 1786, 1731, 1707, 1564, 1437, 1385, 1322, 1290, 1180, 1131, 1070, 1045, 983, 856, 781 cm^{-1}; ESIMS (m/z): 433, 435 (M$^+$ + Na$^+$ for [79]Br, [81]Br). Elemental analysis for C$_{17}$H$_{19}$BrN$_2$O$_5$: Calcd. C, 49.65; H, 4.66; N, 6.81. Found: C, 49.56; H, 4.78; N, 6.77.

3-(3-Bromo-phenyl)-5-methyl-2-(3-oxo-1,3-diphenyl-propyl)-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4d)

Yellowish white solid; yield 68% (eluent PS-EA, 4:1); mpt. 134 °C; mixture of diastereomers; *exo*:*endo* = 59:41; further separation by column chromatography failed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.75 (s, 3H), 2.89 (s, 3H), 3.26 (dd, J = 5.7, 17.6 Hz, 1H), 3.41 (t, J = 8.0 Hz, 1H), 3.58 (dd, J = 7.0, 16.9 Hz, 1H), 3.68 (d, J = 8.6 Hz, 1H), 3.92–4.05 (m, 3H), 4.36 (d, J = 9.0 Hz, 1H), 4.49 (t, J = 6.7 Hz, 1H), 4.74 (q, J = 5.9 Hz, 2H), 5.02 (d, J = 7.7 Hz, 1H), 6.99–7.03 (m, 3H), 7.17–7.33 (m, 15H), 7.44–7.48 (m, 7H), 7.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): 24.4 (CH$_3$), 24.6 (CH$_3$), 42.5 (CH$_2$), 43.0 (CH$_2$), 53.5 (CH), 54.3 (CH), 60.9 (CH), 64.3 (CH), 67.2 (CH), 69.1 (CH), 75.4 (CH), 77.2 (CH), 122.1 (q), 122.8 (q), 126.2 (Ar-CH), 127.8 (Ar-CH), 128.0 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 128.4 (Ar-CH), 129.6 (Ar-CH), 130.0 (Ar-CH), 130.3 (Ar-CH), 130.6 (Ar-CH), 130.8 (Ar-CH), 131.0 (Ar-CH), 131.9 (Ar-CH), 133.0 (Ar-CH), 133.1 (Ar-CH), 134.4 (C), 135.4 (C), 136.6 (C), 136.9 (C), 137.3 (C), 139.5 (C), 172.3 (C), 172.7 (C), 173.9 (C), 174.9 (C), 197.5 (C), 197.6 (C); IR (KBr) ν_{max}: 3482, 3065, 1786, 1714, 1596, 1431, 1380, 1286, 1219, 1145, 1051, 996, 791, 749, 693 cm^{-1}; ESIMS (m/z): 541, 543 (M$^+$ + 23 for [79]Br, [81]Br). Elemental analysis for C$_{27}$H$_{23}$BrN$_2$O$_4$: Calcd. C, 62.44; H, 4.46; N, 5.39. Found: C, 62.36; H, 4.38; N, 5.50.

3-[3-(4-Nitro-phenyl)-4,6-dioxo-5-phenyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4e)

Brownish sticky liquid; yield 53%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.22 (t, J = 7.1 Hz, 3H), 2.65 (t, J = 6.7 Hz, 2H), 2.97 (t, J = 6.7 Hz, 2H), 3.80 (dd, J = 4, 7.4 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.45 (bs, 1H), 5.09 (d, J = 7.4 Hz, 1H), 7.31–7.34 (m, 2H), 7.42–7.54 (m, 3H), 7.62 (d, J = 8.6 Hz, 2H), 8.28 (d, J = 8.7 Hz, 2H). ^{13}C NMR (CDCl$_3$, 150 MHz): δ 14.1 (CH$_3$), 32.9 (CH$_2$), 60.7 (CH$_2$), 75.9 (CH), 124.2 (Ar-CH), 126.2 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 129.4 (Ar-CH), 131.0 (C), 148.1 (C), 171.5 (C), 173.7 (C). IR (neat) ν_{max}: 3381, 3078, 2926, 2855, 2453, 1788, 1722, 1599, 1521, 1383, 1348, 1195, 1108, 1015, 853, 754,

693 cm^{-1}; ESIMS (m/z): 462 (M$^+$ + 23), 494 (M$^+$ + 23 + MeOH). Elemental analysis for C$_{22}$H$_{21}$N$_3$O$_7$: Calcd. C, 60.13; H, 4.82; N, 9.56. Found: C, 60.25; H, 4.72; N, 9.69.

3-(4-Nitro-phenyl)-2-(3-oxo-1,3-diphenyl-propyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4f)

Yellowish orange solid; yield 66%; (eluent PS-EA, 4:1); mp. 192°C; mixture of diastereomers; *exo*:*endo* = 77:23; ^{1}H NMR (CDCl$_3$, 600 MHz): δ 3.35 (dd, J = 5.4, 16.8 Hz, 2H), 3.66 (t, J = 8.1 Hz, 2H), 3.94 (d, J = 8.4 Hz, 2H), 4.25 (dd, J = 8.4, 16.8 Hz, 1H), 4.28 (t, J = 8.4 Hz, 1H), 4.58 (dd, J = 5.4, 8.4 Hz, 2H), 4.98 (d, J = 7.5 Hz, 2H), 6.79 (d, J = 8.1 Hz, 1H), 7.00–7.02 (m, 3H), 7.22–7.24 (m, 4H), 7.31–7.58 (m, 22H), 8.03 (d, J = 8.4 Hz, 4H), 8.27 (d, J = 8.4 Hz, 4H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 42.0 (CH$_2$), 43.8 (CH$_2$), 53.7 (CH), 54.2 (CH), 61.3 (CH), 64.5 (CH), 67.6 (CH), 69.1 (CH), 75.4 (CH), 77.8 (CH), 123.4 (Ar-CH), 124.2 (Ar-CH), 125.6 (Ar-CH), 125.8 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.2 (Ar-CH), 130.1 (Ar-CH), 130.9 (C), 133.3 (Ar-CH), 133.4 (Ar-CH), 134.0 (C), 136.6 (C), 137.0 (C), 139.8 (C), 140.6 (C), 142.6 (C), 147.5 (C), 148.1 (C), 171.1 (C), 171.6 (C), 172.3 (C), 173.6 (C), 197.8 (2C, C); IR (KBr) ν_{max}: 3449, 3065, 1723, 1685, 1598, 1521, 1496, 1449, 1385, 1348, 1205 cm^{-1}; ESIMS (m/z): 570 (M$^+$ + 23). Elemental analysis for C$_{32}$H$_{25}$N$_3$O$_6$: Calcd. C, 70.19; H, 4.60; N, 7.67. Found: C, 70.28; H, 4.52; N, 7.80.

3-(4,6-Dioxo-5-phenyl-3-styryl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4g)

Brown liquid; yield 57%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.22 (t, J = 7.1 Hz, 3H), 2.60–2.73 (m, 2H), 2.84–2.92 (m, 1H), 3.29–3.39 (m, 1H), 3.62 (t, J = 8.3 Hz, 1H), 3.76 (t, J = 7.5 Hz, 1H), 4.07–4.16 (m, 2H), 4.98 (d, J = 7.3 Hz, 1H), 5.99 (dd, J = 8.9, 15.8 Hz, 1H), 6.77 (d, J = 15.8 Hz, 2H), 7.29–7.50 (m, 5H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 14.2 (CH$_3$), 33.0 (CH$_2$), 50.7 (CH$_2$), 52.8 (CH), 60.5 (CH$_2$), 72.3 (CH), 75.7 (CH), 121.2 (Ar-CH), 126.3 (Ar-CH), 127.0 (Ar-CH), 128.5 (Ar-CH), 128.6 (Ar-CH), 128.9 (Ar-CH), 129.2 (Ar-CH), 129.3 (Ar-CH), 131.4 (C), 135.8 (C), 137.0 (Ar-CH), 172.0 (C), 172.4 (C), 173.9 (C); IR (neat) ν_{max}: 2982, 1720, 1597, 1497, 1450, 1383, 1193, 1094, 1028, 969, 860, 754, 693 cm^{-1}; ESIMS (m/z): 443 (M$^+$ + 23). Elemental analysis for C$_{24}$H$_{24}$N$_2$O$_5$: Calcd. C, 68.56; H, 5.75; N, 6.66. Found: C, 68.69; H, 5.86; N, 6.79.

3-(4,6-Dioxo-5-phenyl-3-propyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl)-propionic acid ethyl ester (4h)

Brownish orange sticky liquid; yield 70%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.0 (t, J = 6.8 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.52–1.73 (m, 4H), 2.66 (t, J = 6.9 Hz, 2H), 3.00–3.09 (m, 1H), 3.14–3.24 (m, 1H), 3.41 (bs, 1H), 3.54 (dd, J = 3.5, 7.5 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.90 (d, J = 7.5 Hz, 1H), 7.29–7.50 (m, 9H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 13.9 (CH$_3$), 14.1 (CH$_3$), 19.3 (CH$_2$), 29.8 (CH$_2$), 33.2 (CH$_2$), 51.0 (CH$_2$), 54.3 (CH), 60.5 (CH$_2$), 69.7 (CH), 76.3 (CH), 126.1 (Ar-CH), 126.3 (Ar-CH), 128.8 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 131.4 (C), 171.8 (C), 174.8 (C);

IR (neat) ν_{max}: 3489, 2961, 2935, 2873, 1784, 1724, 1597, 1498, 1456, 1382, 1189, 1061, 1028, 858, 736, 692 cm^{-1}; ESIMS (m/z): 383 (M$^+$ + 23), 415 (M$^+$ + 23 + MeOH). Elemental analysis for $C_{19}H_{24}N_2O_5$: Calcd. C, 63.32; H, 6.71; N, 7.77. Found: C, 63.22; H, 6.63; N, 7.62.

2-(3-Oxo-1,3-diphenyl-propyl)-5-phenyl-3-propyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4i)

Yellowish orange sticky liquid; yield 75%; (eluent PS-EA, 4:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 0.68 (t, J = 6.7 Hz, 3H), 0.87–0.97 (m, 2H), 1.32–1.42 (m, 2H), 3.54 (d, J = 8.1 Hz, 1H), 3.64 (dd, J = 9.5, 17.3 Hz, 1H), 3.74–3.78 (m, 1H), 3.97 (dd, J = 3.0, 17.3 Hz, 1H), 4.51 (dd, J = 3.0, 9.0 Hz, 1H), 5.04 (d, J = 8.1 Hz, 1H), 7.20–7.27 (m, 5H), 7.33–7.41 (m, 3H), 7.45–7.60 (m, 6H), 7.83 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 13.3 (CH$_3$), 19.3 (CH$_2$), 37.7 (CH$_2$), 44.4 (CH$_2$), 54.9 (CH), 65.2 (CH), 67.5 (CH), 78.7 (CH), 126.3 (Ar-CH), 126.5 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 129.1 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 131.4 (C), 133.0 (Ar-CH), 136.9 (C), 139.3 (C), 173.8 (C), 175.4 (C), 197.5 (C); IR (neat) ν_{max}: 3064, 3029, 2960, 2874, 1785, 1720, 1683, 1596, 1496, 1453, 1380, 1189, 1078, 858, 750, 690 cm^{-1}; ESIMS (m/z): 491 (M$^+$ + 23), 523 (M$^+$ + 23 + MeOH). Elemental analysis for $C_{29}H_{28}N_2O_4$: Calcd. C, 74.34; H, 6.02; N, 5.98. Found: C, 74.42; H, 5.96; N, 6.09.

3-(2-Nitro-phenyl)-2-(3-oxo-1,3-diphenyl-propyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4j)

Brownish red sticky liquid; yield 55%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo:endo* = 59:41; 1H NMR (CDCl$_3$, 300 MHz): δ 3.29–3.41 (m, 2H), 4.06–4.09 (m, 1H), 4.14–4.17 (m, 1H), 4.24 (dd, J = 8.4, 16.8 Hz, 2H), 4.38 (t, J = 8.4 Hz, 1H), 4.55 (t, J = 6.8 Hz, 1H), 4.81 (t, J = 5.4 Hz, 1H), 4.98 (d, J = 7.2 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H), 5.22 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 6.4 Hz, 4H), 7.08–7.39 (m, 17H), 7.48 (t, J = 7.1 Hz, 6H), 7.55–7.68 (m, 6H), 7.94 (d, J = 7.1 Hz, 1H), 8.03 (d, J = 7.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 150 MHz): 41.7 (CH$_2$), 41.8 (CH$_2$), 52.8 (CH), 53.2 (CH), 61.2 (CH), 63.4 (CH), 64.0 (CH), 66.3 (CH), 75.2 (CH), 76.7 (CH), 125.2 (Ar-CH), 125.2 (Ar-CH), 125.8 (Ar-CH), 126.0 (Ar-CH), 127.3 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-CH), 128.7 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 128.9 (Ar-CH), 129.0 (Ar-CH), 129.0 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 129.7 (Ar-CH), 131.0 (Ar-CH), 131.1 (C), 131.4 (C), 133.3 (C), 133.4 (Ar-CH), 133.4 (C), 133.7 (C), 134.0 (Ar-CH), 136.5 (C), 137.1 (C), 140.1 (C), 148.5 (C), 149.2 (C), 171.6 (C), 172.0 (C), 173.3 (C), 173.9 (C), 197.9 (C), 198.1 (C); IR (neat) ν_{max}: 1721, 1680, 1593, 1526, 1494, 1380, 1202, 750 cm^{-1}; ESIMS (m/z): 570 (M$^+$ + 23). Elemental analysis for $C_{32}H_{25}N_3O_6$: Calcd. C, 70.19; H, 4.60; N, 7.67. Found: C, 70.32; H, 4.53; N, 7.56.

3-[3-(3-Nitro-phenyl)-4,6-dioxo-5-propyl-hexahydro-pyrrolo[3,4-d]isoxazol-2-yl]-propionic acid ethyl ester (4k)

Brownish red sticky liquid; yield 58%; (eluent PS-EA, 4:1); mixture of diastereomers; *exo:endo* = 68:32; 1H NMR (CDCl$_3$, 300 MHz): δ 0.80–0.94 (m, 9H), 1.25 (t, J = 7.1 Hz, 3H), 1.49–1.63 (m, 4H), 2.66–2.75 (m, 3H), 2.80–2.99 (m, 3H), 3.09–3.16 (m, 2H), 3.37–3.51 (m, 4H), 3.56 (dd, J = 2.9, 8.2 Hz, 1H), 3.75 (t, J = 7.9 Hz, 1H), 4.09–4.13 (m, 4H), 4.32 (dd, J = 5.6, 7.9 Hz, 1H), 4.78 (d, J = 8.2 Hz, 1H), 4.83 (s, 1H), 4.92 (d, J = 7.3 Hz, 1H), 5.27 (d-like, 1H), 6.77 (d, J = 9.6 Hz, 1H), 7.57–7.65 (m, 2H), 7.74 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.31 (s, 1H); ^{13}C NMR (CDCl$_3$, 150 MHz): δ 11.0 (CH$_3$), 11.2 (CH$_3$), 14.1 (CH$_3$), 21.1 (CH$_2$), 21.9 (CH$_2$), 32.6 (CH$_2$), 39.3 (CH$_2$), 40.7 (CH$_2$), 48.9 (CH), 51.0 (CH$_2$), 53.8 (CH), 55.7 (CH), 60.7 (CH$_2$), 62.4 (CH), 67.8 (CH), 72.2 (CH), 76.0 (CH), 87.1 (CH), 122.1 (Ar-CH), 122.8 (Ar-CH), 123.3 (Ar-CH), 123.9 (Ar-CH), 129.8 (Ar-CH), 129.9 (Ar-CH), 133.1 (Ar-CH), 133.9 (Ar-CH), 135.7 (C), 139.7 (C), 147.6 (C), 148.3 (C), 167.2 (C), 171.7 (C), 172.1 (C), 172.6 (C), 174.6 (C), 177.0 (C); ESIMS (m/z): 428 (M$^+$ + Na+). Elemental analysis for $C_{19}H_{23}N_3O_7$: Calcd. C, 56.29; H, 5.72; N, 10.37. Found: C, 56.41; H, 5.85; N, 10.45.

2-(2-Benzenesulfonyl-ethyl)-5-methyl-3-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4l)

Yellowish orange amorphous solid; yield 53%; (eluent PS-EA, 3:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.92 (s, 3H), 3.37–3.39 (m, 2H), 3.65 (dd, J = 3.2, 7.2 Hz, 1H), 3.71–3.84 (m, 2H), 4.79 (t-like, 1H), 5.04 (d, J = 7.2 Hz, 1H), 7.24–7.26 (m, 3H), 7.35–7.38 (m, 5H), 7.51–7.67 (m, 1H), 7.81 (d, J = 7.4 Hz, 1H). ^{13}C NMR (CDCl$_3$, 150 MHz): δ 25.2 (CH$_3$), 34.4 (CH$_2$), 54.2 (CH), 54.3 (CH$_2$), 66.8 (CH), 79.8 (CH), 127.3 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 129.0 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 133.8 (Ar-CH), 135.0 (C), 139.3 (C), 174.8 (C). IR (KBr) ν_{max}: 3454, 2938, 1709, 1439, 1382, 1289, 1141, 1047 cm^{-1}. ESIMS (m/z): 423 (M$^+$ + 23). Elemental analysis for $C_{20}H_{20}N_2O_5S$: Calcd. C, 59.99; H, 5.03; N, 7.00. Found: C, 60.08; H, 4.96; N, 6.88.

2-(2-Benzenesulfonyl-ethyl)-3-(4-nitro-phenyl)-5-phenyl-tetrahydro-pyrrolo[3,4-d]isoxazole-4,6-dione (4m)

Yellow sticky liquid; yield 52%; (eluent PS-EA, 3:1); only *exo* product is formed; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.04–3.16 (m, 2H), 3.38–3.53 (m, 2H), 3.80 (dd, J = 3.5, 6.9 Hz, 1H), 4.43 (bs, 1H), 5.00 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.7 Hz, 2H), 7.45–7.68 (m, 8H), 7.85 (d, J = 7.7 Hz, 2H), 8.28 (d, J = 8.0 Hz, 2H). ^{13}C NMR (CDCl$_3$, 150 MHz): δ 49.1 (CH$_2$), 54.2 (CH$_2$), 56.8 (CH), 66.3 (CH), 75.9 (CH), 124.1 (Ar-CH), 124.3 (Ar-CH), 126.2 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 128.9 (Ar-CH), 129.2 (Ar-CH), 129.4 (Ar-CH), 130.9 (Ar-CH), 134.0 (Ar-CH), 139.2 (C), 142.5 (C), 147.8 (C), 148.2 (C), 173.3 (C). IR (neat) ν_{max}: 3489, 3068, 1721, 1601, 1520, 1447, 1383, 1348, 1308, 1195, 1146, 1083 cm^{-1}. ESIMS (m/z): 508 (M$^+$ + 1), 530 (M$^+$ + 23). Elemental analysis for $C_{25}H_{21}N_3O_7S$: Calcd. C, 59.16; H, 4.17; N, 8.28. Found: C, 59.30; H, 4.26; N, 8.37.

Experimental procedure for intramolecular nitrone cycloaddition reaction in aqueous media

An aromatic or aliphatic aldoxime (0.5 mmol) and divinyl sulfone (0.5 mmol, 1.0 equiv) were added successively to a

solution of surfactant (DBSA, 0.05 mmol) in H_2O (2 mL) at room temperature in a 25 mL round-bottom flask. The reaction was sonicated for 10 minutes and then stirred at 55 °C. After stirring at that temperature for the period of time listed in Table 3, the product was extracted with ethyl acetate. Then it was washed with brine, dried over Na_2SO_4, and concentrated in rotavapor. The crude product was then purified by silica gel column chromatography.

8-Phenyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6a)

Colorless needles; m.p. 170 °C; yield 57%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04–3.16 (m, 1H), 3.36–3.48 (m, 2H), 3.74–3.90 (m, 3H), 4.50 (d, $J = 9.0$ Hz, 1H), 5.15 (s, 1H), 7.29–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.4 (CH_2), 68.1 (CH_2), 69.1 (CH), 70.5 (CH), 125.5 (Ar-CH), 128.1 (Ar-CH), 128.8 (Ar-CH), 136.3 (C). IR (KBr) v_{max}: 3433, 2998, 2945, 1607, 1453, 1304, 1224, 1169, 1121, 1083 cm^{-1}. ESIMS (m/z): 240 ($M^+ + 1$), 262 ($M^+ + 23$). Elemental analysis for $C_{11}H_{13}NO_3S$: Calcd. C, 55.21; H, 5.48; N, 5.85. Found: C, 55.33; H, 5.52; N, 5.92. Melting point and ^{1}H spectra are literature consistent.[14c]

8-(3-Bromo-phenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6b)

Yellowish white solid; yield 55%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.06–3.17 (m, 1H), 3.42 (d-like, $J = 9.0$ Hz, 2H), 3.76–3.92 (m, 3H), 4.51 (d, $J = 9.0$ Hz, 1H), 5.12 (s, 1H), 7.23–7.28 (m, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.65 (s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.4 (CH_2), 68.1 (CH_2), 69.0 (CH), 70.0 (CH), 123.1 (C), 124.2 (Ar-CH), 128.9 (Ar-CH), 130.4 (Ar-CH), 131.4 (Ar-CH), 138.5 (C). IR (KBr) v_{max}: 3418, 2962, 2896, 1567, 1471, 1419, 1316, 1223, 1161, 1120 cm^{-1}. ESIMS (m/z): 341 ($M^+ + 23$). Elemental analysis for $C_{11}H_{12}BrNO_3S$: Calcd. C, 41.52; H, 3.80; N, 4.40. Found: C, 41.69; H, 3.88; N, 4.28.

8-(4-Nitro-phenyl)-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6c)

Off white solid; m.p. 240 °C; yield 52%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13–3.17 (m, 1H), 3.40–3.55 (m, 2H), 3.78–3.94 (m, 3H), 4.55 (d, $J = 9.8$ Hz, 1H), 5.24 (s, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 8.26 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 45.9 (CH_2), 53.3 (CH_2), 68.2 (CH_2), 68.9 (CH), 70.2 (CH), 124.1 (Ar-CH), 126.9 (Ar-CH), 143.2 (C), 147.8 (C). IR (KBr) v_{max}: 3423, 3111, 2948, 1601, 1514, 1347, 1320, 1230, 1121, 1020 cm^{-1}. ESIMS (m/z): 285 ($M^+ + 1$), 307 ($M^+ + 23$). Elemental analysis for $C_{11}H_{12}N_2O_5S$: Calcd. C, 46.47; H, 4.25; N, 9.85. Found: C, 46.32; H, 4.33; N, 9.94. Melting point and ^{1}H spectra are literature consistent.[14c]

8-Styryl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6d)

Off white solid; m.p. 194 °C; yield 53%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03–3.07 (m, 1H), 3.36–3.44 (m, 2H), 3.70–3.79 (m, 2H), 4.15 (dd, $J = 5.8, 9.7$ Hz, 1H), 4.54 (d, $J = 9.7$ Hz, 1H), 4.72 (d, $J = 5.0$ Hz, 1H), 6.01 (dd, $J = 5.3$,

16.0 Hz, 1H), 6.78 (dd, $J = 1.0, 16.0$ Hz, 1H), 7.27–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.1, 53.4, 67.7, 68.8, 69.6, 123.3, 126.7, 128.5, 128.8, 129.0, 133.3, 135.7. IR (neat) v_{max}: 2980, 1493, 1447, 1326, 1284, 1211, 1119, 965 cm^{-1}. ESIMS (m/z): 288 ($M^+ + 23$). Elemental analysis for $C_{13}H_{15}NO_3S$: Calcd. C, 58.85; H, 5.70; N, 5.28. Found: C, 59.01; H, 5.83; N, 5.40.

8-Propyl-7-oxa-4-thia-1-aza-bicyclo[3.2.1]octane 4,4-dioxide (6e)

Off white solid; m.p. 115 °C; yield 53%; (eluent PS-EA, 3:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, $J = 7.0$ Hz, 3H), 1.29–1.56 (m, 4H), 2.99–3.05 (m, 1H), 3.24–3.34 (m, 2H), 3.61–3.65 (m, 2H), 3.90 (t, $J = 6.7$ Hz, 1H), 4.14 (dd, $J = 6.0, 9.8$ Hz, 1H), 4.48 (d, $J = 9.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5 (CH_3), 19.2 (CH_2), 33.7 (CH_2), 45.8 (CH_2), 53.5 (CH_2), 66.8 (CH), 68.7 (CH & CH_2). IR (neat) v_{max}: 3434, 2949, 2871, 1455, 1325, 1282, 1195, 1121, 963 cm^{-1}. ESIMS (m/z): 206 ($M^+ + 1$), 228 ($M^+ + 23$). Elemental analysis for $C_8H_{15}NO_3S$: Calcd. C, 46.81; H, 7.37; N, 6.82. Found: C, 46.69; H, 7.49; N, 6.99.

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15 Crystal data of compound **6a**: $C_{11}H_{13}NO_3S$, FW = 239.28, monoclinic, space group P21/c, a = 17.1392 (5) Å, b = 6.0512 (2) Å, c = 10.9857 (4) Å, β = 93.007 (2)°, V = 1137.79 (7) Å^3, Z = 4, T = 296 (2) K, d_{calcd} = 1.397 g cm^{-3}, F (000) = 504. Diffraction data were measured with Mo K$_\alpha$ (λ = 0.71073 Å) radiation at 296 K using a Bruker Kappa Apex 2 CCD system. A total of 2660 unique reflections were measured (θ_{max} = 30.87 °). Data analyses were carried out with the Difference Vectors program. The structures were solved by direct methods using the SHELXS-97[16] program. Refinements were carried out with a full matrix least squares method against F^2 using SHELXL-97.[17] Non-hydrogen atoms were refined with anisotropic thermal parameters. The final R value was $R1$ = 0.0456 and w$R2$ = 0.1500 with $I > 2\sigma(I)$. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre with reference numbers CCDC 686184.

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Properties and applications of biodegradable transparent and photoluminescent cellulose films prepared *via* a green process

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Cellulose was dissolved rapidly in 7 wt% NaOH/12 wt% urea aqueous solution pre-cooled to −12 °C within 2 min to obtain its solution, which is a "green" process. A series of regenerated cellulose (RC) films were prepared from the cellulose solution *via* a simple and low-cost method to evaluate their structure and properties as packaging and functional materials. The cellulose films were treated successfully with fluorescent dyes and photoluminescent (PL) pigments to fabricate, for the first time, novel PL materials, which exhibited strong fluorescence and long after-glow emission. The results from CP/MAS ^{13}C NMR spectra, X-ray diffraction and tensile testing confirmed that the transparent RC films possessed an homogenous structure, excellent optical transmittance (90% at 800 nm), as well as good tensile strength. Moreover, the drawing process could significantly improve their tensile strength, which reached 138 MPa. In addition, the biodegradation tests revealed that the RC films could be biodegraded completely. This work provided a non-toxic solvent system for the preparation of the packaging films and PL materials. This process is promising on a large scale and will maintain clean air in the production environment.

Introduction

Commercial products prepared from synthetic polymers have been used actively for nearly 70 years to provide great benefits to modern society. However, they also pose serious environmental threats and their raw materials are naturally limited.[1] The waste from these polymer-based products are non-biodegradable, resulting in "white pollution", and damaging to wild-life, leading to calls from the "green" movements to return to biologically based (renewable) polymers.[2,3] Cellulose is the most abundant natural polymer on earth, and it will become the main chemical resource in the future.[4,5] It is considered to be an almost inexhaustible source of raw material for the increasing demand for environmentally friendly and biocompatible products.[6] However, the full potential of cellulose has not yet been exploited because of the lack of an environmental-friendly method and the limited number of common solvents that readily dissolve cellulose.[7] Cellophane prepared through the viscose route is transparent, lustrous, durable, flexible, and impervious to air, grease, germs, and dirt.[8] However, this method produces serious pollution (CS_2). In recent years, the "green" comprehensive utilization of cellulose resources has drawn much attention from governments and researchers.[7,9] Thus, new and powerful organic solvents, such as *N*-methylmorpholine-*N*-oxide (NMMO)[4,10] and ionic liquids,[7,9,11–13] have been developed to be used for the preparation of the regenerated cellulose films and fibers. In 2004, D. Klemm won the Anselme Payen Award for his exceptional

achievements in the development of new materials based on cellulose, and in 2005, R. D. Rogers won the US Presidential Green Chemistry Challenge Awards for his great contributions to cellulose dissolution in ionic liquids. Clearly, the regenerated cellulose films and fibers prepared from "green" processes have great importance for a sustainable development. Today, cellulose offers great opportunities in the field of edible and packaging films as well as biodegradable materials, because of its low cost and biodegradability, promising an environmental solution to the plastic waste issue.[14–18]

In our laboratory, a new solvent for cellulose, 7 wt% NaOH/12 wt% urea aqueous solution pre-cooled to −12 °C, has been developed to rapidly dissolve cellulose within 2 min.[19,20] Interestingly, the quick dissolution of cellulose arises as a result of a dynamic self-assembly process among solvent molecules (NaOH, urea and water) and cellulose macromolecules through the formation of new hydrogen bonding networks at low temperatures.[21] The main advantage of this method is its rapid dissolution, relative simplicity and cost-effectiveness, and it is an environmentally friendly process. Moreover, a series of regenerated cellulose products such as novel cellulose fibers,[22–24] functional fibers,[25] separation materials[26,27] and aerogels[28] have been fabricated successfully from the cellulose dope. However, the preparation and properties of the cellulose transparent and photoluminescent (PL) films have been never published. It is noted that biodegradable transparent films such as packaging films, as well as fluorescence, phosphorescence and long after-glow materials have large practical and potential applications in many fields.[29–32] Faced with the serious pollution produced by non-biodegradable films, we aim at developing a new pathway for the preparation of transparent and functional films with

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Table 1 Physical properties of the RC films and commercial cellophane

Sample	$M_\eta \times 10^{-4}$/g.mol^{-1}		χ_c/%
	Cellulose samples	RC films	
RC-13	13.1	12.3	47
RC-11	11.1	10.5	46
RC-9	9.2	9.0	46
RC-7	7.8	7.6	44
RC-6	6.3	6.0	44
RC-4	4.8	4.5	51
RC-3	3.1	2.9	52
Cellophane	—	4.5	45

biodegradability *via* a "greener" process on a large scale. In this work, we prepared transparent regenerated cellulose (RC) films and PL materials from the cellulose solution in the NaOH/urea aqueous system. Their structure and properties were investigated to evaluate the desirability of their applications in the packaging and functional materials fields.

Experimental

Materials

The cellulose samples (cotton linter pulps) were supplied by Hubei Chemical Fiber Co. Ltd. (Xiangfan, China), coded as C-6, C-7, C-9, C-11 and C-13, respectively. The weight-average molecular weight (M_w) of C-9 was determined by light scattering to be 9.2×10^4.[33] The cellulose samples with low molecular weight were prepared from the C-9 cellulose by acid hydrolysis according to ref. 33, and were coded as C-3 and C-4, respectively. Their viscosity-average molecular weights (M_η) measured with viscometry are summarized in Table 1. The commercial cellophane was also supplied by Hubei Chemical Fiber Co. Ltd. The fluorescent dyes including Fluorescein, Acridine Orange and Rhodamine B were purchased from commercial sources in China. Two kinds of commercial photoluminescent pigments (PL: PLB-7C and PLO-8C) were alkaline earth aluminates [MAl$_2$O$_4$:Eu^{2+} (M: Ca, Sr)], and their average particle size was 55–65 μm for PLB-7C and 25–35 μm for PLO-8C. They were supplied by Dalian Luminglight Co., Ltd., and are non-toxic to the environment. All other chemical reagents were purchased from commercial sources in China, and were of analytical grade.

Preparation of cellulose films

A mixture of NaOH and urea in distilled water (7:12:81 by weight) was pre-cooled to −12.6 °C. An appropriate amount of cellulose was added immediately into the solution with vigorous stirring for 2 min to obtain a 4% cellulose solution. Fig. 1 shows the pictures of the dissolution process of cellulose in laboratory (top) and in a dissolution tank of 1000 L capacity (bottom, Jiangsu Long-Ma Green Fibers Co. Ltd). The cellulose could be dissolved completely in the solvent within 2 min on a typical laboratory scale and within 5 min on a large scale. The cellulose solution prepared in the laboratory was subjected to centrifugation at 166.66 Hz (10 000 rpm) for 10 min at 10 °C for degasification. The resulting transparent solution
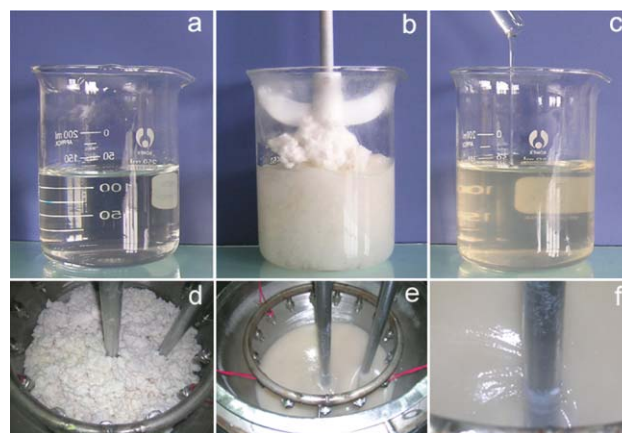
Fig. 1 (Top) Photographs of the dissolution process of cellulose in a beaker of 250 mL capacity: (a) 7% NaOH/12% urea (w/w) aqueous solution; (b) cellulose in the solvent pre-cooled to −12.5 °C and stirring at the start of the dissolution process; (c) transparent cellulose solution obtained by stirring for 2 min. (Bottom) Photographs of the cellulose solution in a dissolution tank of 1000 L capacity (Jiangsu Long-Ma Green Fibers Co. Ltd), in which all chemical reagents were of industrial grade: (d) cotton linter pulp; (e) cellulose solution dissolved in the solvent pre-cooled to −12.5 °C after stirring for 3 min; (f) transparent cellulose solution obtained by stirring for 5 min.

was immediately cast on a glass plate to give a thickness of 250 μm for a gel sheet, and then immersed into a coagulation bath with 5 wt% H$_2$SO$_4$ for 5 min at 25 °C to coagulate and regenerate. The resulting films were washed with running water and then with deionized water. The wet films were fixed on a glass plate to prevent shrinkage, and finally were air-dried at ambient temperature to obtain transparent regenerated cellulose films, coded as RC. The RC films prepared from the cellulose samples with M_η ranging from 13.1×10^4 to 3.1×10^4 were coded as RC-13, RC-11, RC-9, RC-7, RC-6, RC-4, and RC-3, respectively. To test the effects of the drawing process, the RC films were prepared as follows. The never-dried RC-7 film was cut into strips of approximately 20 cm length (l_0) and 4 cm width, and was then clamped in a manual stretching device and elongated slowly to the desired length (l_i). The drawn film remained at the drawing state for 8 h to be air-dried at room temperature. Then the drawing ratio (λ) was calculated by: $\lambda = l_i/l_0$.

To fabricate the fluorescent films, the never-dried films (RC-7) were immersed in a container with 0.1% fluorescent dye aqueous solutions and left for 1 h. They were then washed with deionized water and then dried at ambient temperature. The fluorescent films prepared from Fluorescein, Acridine Orange, and Rhodamine B were coded as RC-F1, RC-F2 and RC-F3, respectively.

To fabricate the luminescent films, the PLB-7C and PLO-8C pigments were mixed, separately, with the cellulose solution ($M_\eta = 7.8 \times 10^4$). The resultant mixture was degassed, and then immediately cast on a glass plate to give a thickness of 250 μm for a gel sheet. The cellulose gel sheet was immersed into a coagulation bath with 5 wt% H$_2$SO$_4$ for 5 min at 25 °C to coagulate and regenerate. The PL composite films were washed with running water and then with deionized water. The wet films were fixed on glass plates to prevent shrinkage, and finally were air-dried at ambient temperature. The PL luminescent films

prepared from PLB-7C and PLO-8C were coded as RC-F4 and RC-F5, respectively. The ratio of pigments to cellulose in the resulting composite films is 10 wt%.

Characterizations

The viscosity-average molecular weights (M_η) of the cellulose samples and RC films in the 4.6 wt%LiOH/15 wt%urea aqueous solution were determined using a Ubbelohde viscometer at 25 °C, and were calculated from intrinsic viscosity [η] by the Mark–Houwink equation.[32] The sulfur contents in the cellulose films were measured with an elemental analyzer (Heraeus Co., Germany). Solid-state ^{13}C NMR spectra of the cellulose films were recorded on an Infinity Plus-400 spectrometer (Varian, Inc., USA; magnetic field = 9.4 T; ^{13}C frequency = 100 MHz) equipped with a cross polarization/magic angle spinning (CP/MAS) unit. Wide-angle X-ray diffraction (WAXD) was measured with an X-ray diffractometer (D/MAX-1200, Rigaku Denki Co. Ltd., Japan). The X-ray radiation used was Ni-filtered CuK with a wavelength of 1.5406 Å. The samples were mounted on a solid circular holder, and the proportional counter detector was set to collect data at a rate of $2\theta = 1°$ min^{-1} over the 2θ range from 4 to 40°. The crystallinity (χ_c) values of cellulose samples were calculated from the X-ray diffraction patterns according to the usual method.[34] Scanning electron micrographs (SEM) of the RC, RC-3 and RC-13 films were taken on a Hitachi S-570 scanning electron microscope with 20 kV accelerating voltage and at a magnification of 3000. The SEM observation of F-2, F-3, F-4 and F-5 was carried out with a Hitachi X-650 microscope (Mountain View, CA, Japan).

Optical transmittance (T_r) of the films was measured with a UV–vis spectrometer (Shimadzu UV-160A, Japan) at a wavelength of 800 nm. The thickness of the RC films has been controlled to be about 20 µm, which was measured with a thickness gauge (W-1.0 Teclock Co., Japan), and that of the commercial cellophane was 17 µm. The excitation spectra and emission spectra of the films were measured on a fluorescence spectrophotometer (F-4500, Hitachi). The after-glow spectrum of the films was also measured on the same fluorescence spectrophotometer after excitation with 365 nm radiation for 10 min.

The tensile strength (σ_b) and the elongation at breaking (ε_b) of the films were measured on a universal testing machine (CMT6503, Shenzhen SANS Test Machine Co. Ltd., Shenzhen, China) according to ISO 527–3, 1995 (E) at a speed of 5 mm min^{-1}. Biodegradation tests was performed as follows. Eight test films (15×15 cm^2) enclosed in a nylon mesh netting (2×2 mm^2 mesh size) were buried about 20 cm beneath natural soil in an 80 L barrel. The average values of the temperature, moisture, and pH of the soil were 30 °C, 20%, and 6.8, respectively. From 3 to 30 days of burying, the degraded films and fragments were taken out one after another, rinsed with water, and then vacuum-dried at room temperature for 3 days before the characterizations. The weight loss, w_{loss} (%), of the film degraded in soil at 10-day intervals was measured. The half-life $t_{1/2}$ and degradation rate constant k were obtained from double-logarithmic plots of weight loss against the burying period in soil (t) by the equations in ref. 35.

Results and discussion

"Green" process of preparation

As shown in Fig. 1, cellulose could be dissolved rapidly in 7 wt% NaOH/12 wt% urea aqueous system pre-cooled to −12 °C to obtain transparent cellulose solution. This is the most rapid dissolution (less than 5 min) of native cellulose on both laboratory and industry scale that has ever been reported. The formation of regenerated cellulose films is a physical process, mainly related to the diffusion between non-solvent and solvent in the cellulose solution, leading to the regeneration of the gel sheet, followed by drying. In this system, NaOH and urea are nontoxic and inexpensive. It is noted that there was no evaporation of any chemical agents during dissolution of cellulose at low temperature, thus maintaining clean air in the environment during production on a large scale (Fig. 1, bottom). The byproducts could be easily separated and recycled to be reutilized. The byproducts in the coagulation bath are mainly Na$_2$SO$_4$ and urea, which can be separated easily by using flash evaporation, and then crystallization because of the large difference in the solubility between Na$_2$SO$_4$ and urea. Therefore, this pathway is a real "green" technology, because it is non-polluting, and it is easy to recycle the byproducts. Furthermore there is no evaporation of the chemical agents during the process.

The cellulose solution is relatively stable at 0–5 °C.[36] The M_η values of the original cellulose samples and the RC films prepared from them are summarized in Table 1. The results indicated that no obvious degradation of cellulose occurred in the dissolution and regeneration processes. It is worth noting that the sulfur content in all RC films was determined to be essentially zero (below the detection limit), whereas that of the commercial cellophane from the viscose route was about 0.02 wt%.

Morphology and structure of RC films

Fig. 2 shows the SEM images of the RC films and the commercial cellophane. All of the RC films displayed highly uniform and dense surface and cross-section. The thicknesses of the RC films and commercial cellophane were determined
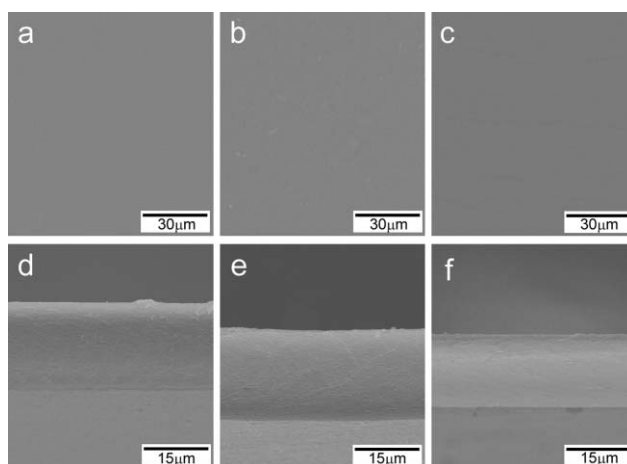
Fig. 2 SEM images of (a, b, c) surface and (d, e, f) cross-section for RC films and commercial cellophane: a, d, RC-13; b, e, RC-3; c, f, cellophane.

by SEM to be 21 and 17 μm, respectively, in agreement with the values measured with a thickness gauge. The agreement suggested structural homogeneity of the films from the interior to the surface, indicating a good architecture of the cellulose macromolecules. Fig. 3 shows the CP/MAS ^{13}C NMR spectra of original cellulose, commercial cellophane and RC films. The spectrum of the RC films exhibited four main peaks at 105.6, 88.0, 75.2 (76.8, 73.5) ppm, corresponding to C1, C4, C5 (C3, C2), respectively, as well as the peak for C6 at 63.0 ppm, assigned to the cellulose II structure. The results strongly indicated that the native cellulose could be dissolved completely in the present solvent system. Moreover, it was confirmed that the cellulose solution did transform into regenerated cellulose II when the cellulose gel was regenerated in the coagulation bath. The intensities of the C4 signal at around 88 ppm and its shoulder peak at 84.0 ppm depend on the status of carbons located in either the crystalline or amorphous regions, respectively.[37] For the RC films, the C4 peaks located at 88.0 ppm shifted to higher magnetic field than the native cellulose (89.3 ppm), and the intensity was significantly lower, suggesting a decrease in the crystallinity. The intensity of the shoulder peak of C4 for the RC film, which is related to the degree of anisotropy,[38] was lower than that of the cellophane, indicating a relatively low orientation of RC because of the preparation on the laboratory scale without drawing. The X-ray diffraction patterns of the RC films and commercial cellophane are shown in Fig. 4. There were three peaks at $2\theta = 11.8°$, $19.9°$, and $21.6°$, corresponding to the (110), (1$\bar{1}$0), and (200) planes, respectively, which are attributed to the typical cellulose II crystalline form.[20] The χ_c values of the RC films were smaller to that of cotton linter pulp (68%), as a result of the rearrangement of the cellulose macromolecules during dissolution and regeneration.

Fig. 4 X-ray diffraction of (a) original cellulose (cotton linter pulp), (b) RC films (RC-7) and (c) commercial cellophane.

Properties of RC films

Fig. 5 shows the M_η dependencies of the tensile strength (σ_b) and the elongation at breaking (ε_b) of the RC films. The measurements gave the mechanical properties, with errors, of $\Delta\sigma_b = \pm 4$–5 MPa and $\Delta\varepsilon_b = \pm 0.8$–1.5%. The RC films having low M_η, such as RC-3, were brittle. However, with an increase of M_η, the ε_b value of RC films increased, and that for RC-13 having M_η of 11.1×10^4 reached 9.3%. Moreover, the σ_b value for the RC films also increased from 62 MPa to achieve 106 MPa with increasing M_η on the whole. However, the σ_b value for the RC films decreased with M_η as high as 1.31×10^5, due to the incomplete dissolution of cellulose with higher M_η. Interestingly, the σ_b value of the RC films hardly changed in the range of M_η from 7.0×10^4 to 1.31×10^5. The σ_b values of cellophane having M_η of 4.5×10^4 were about 80 MPa, slightly higher than that of the RC films with the same M_η (about 75 MPa from the curve in Fig. 5). The ε_b values (8%) of cellophane were much higher than that of the RC films with the same M_η (about 4.1% from the curve in Fig. 5). The explanation for this difference is that the orientation of the commercial cellophane has been enhanced through the drawing process in industrial production, leading to the increases in strength and elongation. The Young's modulus

Fig. 3 The CP/MAS ^{13}C NMR spectra of (a) cellulose (cotton linter pulp), (b) commercial cellophane and (c) RC films (RC-7).
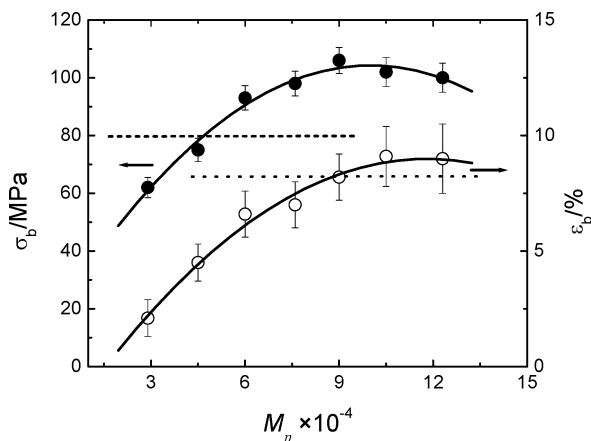
Fig. 5 Dependence of the tensile strength (σ_b, ●) and elongation at break (ε_b, ○) of the RC films on M_η. '---' and '····' represent σ_b and ε_b of cellophane, respectively.

value (not shown) of the RC films increased from 3500 to 5000 MPa with an increase of M_η, and was higher than that of the commercial cellophane (about 3000 MPa).

In order to investigate the influence of the drawing orientation on the mechanical properties, we performed the drawing experiments for RC films on a laboratory drawing machine. Fig. 6 shows the dependence of the σ_b and ε_b value of RC-9 on the drawing ratio (λ). With an increase of drawing ratio from 1.00 to 1.05, the σ_b values of the RC-9 films increased significantly from 106 to 138 MPa. At the same time, the ε_b value of the RC films slightly decreased. During the drawing process, the cellulose molecular chains oriented uniaxially along the drawing direction, leading to the enhancement of the strength of the RC films. It is anticipated that their mechanical properties would be improved significantly by the orientation *via* the drawing process in an industrial production setting and will be much higher than that of the commercial cellophane.
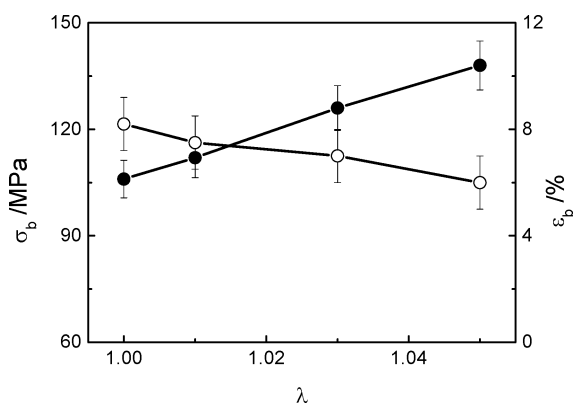
Fig. 6 Dependence of the tensile strength (σ_b, ●) and elongation at break (ε_b, ○) of RC-9 on the drawing ratio (λ).

One of the main strong points of the commercial cellophane is its transparence. The optical transmittance (T_r) of commercial cellophane is 85%, indicating remarkable homogeneity of the cellophane. As shown in Fig. 7a, the T_r values of most of the RC films were about 90%, which were higher than that of cellophane. The RC films were transparent and colorless, rather than yellow like cellophane due to the existence of a small quantity of sulfur in cellophane. The deceased T_r values of the RC-11 and

RC-13 films were as a result of some cellulose being dissolved incompletely with M_η above 13.1×10^4. The photograph of the RC-7 film (Fig. 7b) revealed that these RC films possessed good optical transmittance. This indicated that the RC films prepared from cellulose solution in the NaOH/urea aqueous system can be used as transparent packaging materials because of the bio-based, transparent, colorless and biodegradable properties. Therefore, the RC films as a utility wrap can be used on a variety of products including food, textiles, tobacco, and drugs. Also, RC films can be used for making artificial flowers and bandages for surgical dressings.[8]

PL composite films

To develop applications of these films as anti-counterfeiting packaging and functional materials, a series of PL films have been fabricated by blending cellulose with fluorescent dyes and PL pigments, respectively. Fig. 8 (top) shows the fluorescence image of the composite films (Fig. 8b–f). Compared with the pure RC films (RC-7, Fig. 8a), the composite films (RC-F1 to RC-F5) appeared as brilliant outlook colors (yellow-green to blue-green), owing to the emission from the fluorescent dyes and PL pigments in the cellulose matrix. The emission spectra of these fluorescent films are shown in Fig. 8 (bottom). Here, for the first time, we have prepared successfully PL cellulose films with different fluorescence colours. Fig. 9 shows the SEM images of surface for RC-F2 (a), RC-F3 (b), RC-F4 (c) and RC-F5 (d). The RC-F2 and RC-F3 films exhibited a highly uniform and dense surface, indicating that a good compatibility

Fig. 7 (a) Dependence of T_r (%, 800 nm) of the RC films (○) on M_η, with comparison of cellophane (- - -) and (b) photographs of the RC-7 film packaging a flower.
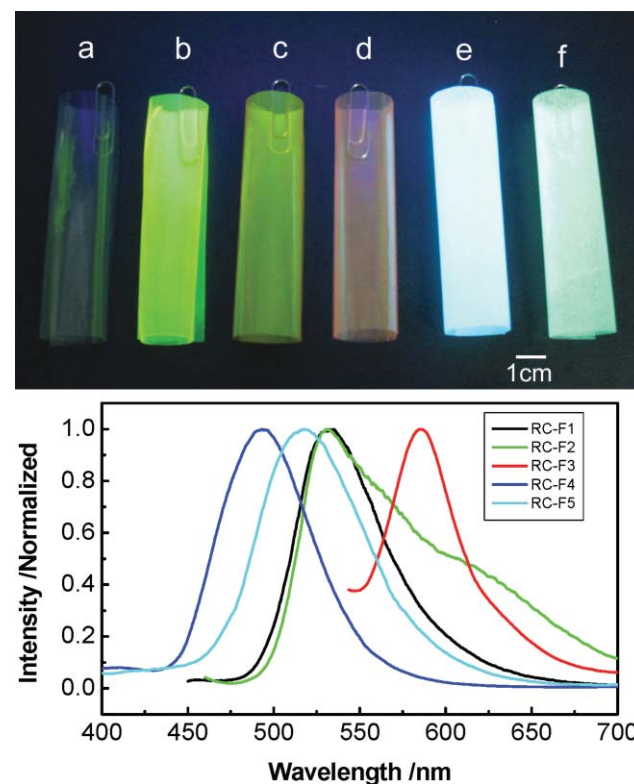
Fig. 8 Fluorescence images (top) of (b–f) RC composite films and (a) RC films excited by a UV lamp at 302 nm: a, RC-7; b, RC-F1; c, RC-F2; d, RC-F3; e, RC-F4; f, RC-F5; and emission spectra (bottom) of the composite films.
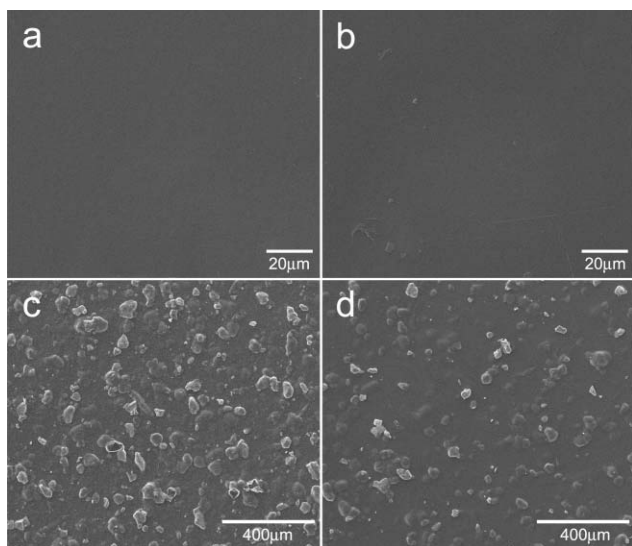
Fig. 9 SEM images of surface for RC-F2 (a), RC-F3 (b), RC-F4 (c) and RC-F5 (d).

existed between cellulose and the components. Fluorescent dyes (such as Fluorescein, Acridine Orange, and Rhodamine B) which are typically conjugated organic molecules, were bound strongly with the cellulose matrix, leading to the compact structure of the RC-F1 to RC-F3 films. The surface of the RC-F4 and RC-F5 films exhibited the well-dispersed PL pigments, as shown in Fig. 9c and d. The PL particles of alkaline earth aluminates were embedded in cellulose matrix, suggesting a strong interaction between PL pigments and cellulose. These PL films have the ability of absorption in the near UV/blue region and emission in the visible part of the spectrum, so they can be widely used in the field of luminescence and display. In addition, the stress–strain (σ–ε) curves of the composite films are shown in Fig. 10. The results indicated that the addition of fluorescent dyes hardly changed the mechanical properties of the films. Compared with pure RC-7, RC-F4 and RC-F5 blended with 10% inorganic PL pigments exhibited a decrease in ε_b, but the σ_b values of the composite films slightly increased on the whole. The results support the presence of strong interactions between cellulose and the dyes or pigments in the composite films.
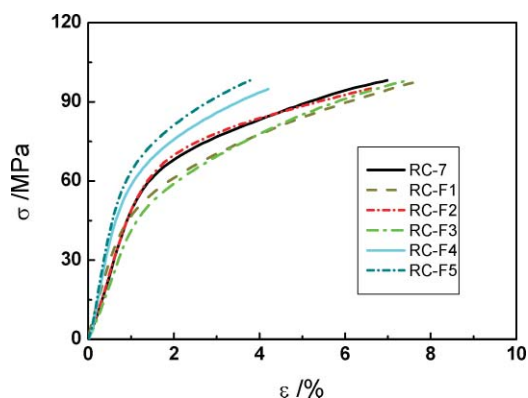
Fig. 10 σ–ε curves of the PL composite films and pure RC film.

Fig. 11 (right) shows the after-glow photographs of the RC-F4 and RC-F5 after being irradiated by 365 nm UV light for
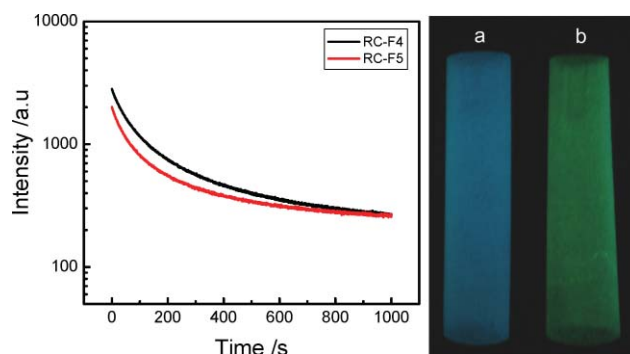
Fig. 11 After-glow decay curve (left) and photograph (right) of after-glow of luminescent films: a, RC-F4; b, RC-F5. Samples were irradiated by 365 nm UV light for 10 min before measurement (at time of 5 s).

10 min. The PL pigments also offer the advantages of a short activation period, a long after-glow, and high brightness. The luminescent films exhibited long-lasting emission. The decay curve in the spectral integral intensity of the luminescent films after irradiation is shown in Fig. 11 (left). The decay process of the long-lasting phosphorescence can be divided into two parts: the fast process and the slow process. The decay time is mainly determined by the slow part. It is believed that the luminescent films are a new type of long after-glow PL films. They can absorb light (sunlight, fluorescent, incandescent, *etc.*) for about 10–15 min and then emit a visible light for more than 10 h in the dark. Moreover, they are free of radioactive and toxic materials and are chemically stable. Therefore, the novel PL films can be used to make PL signs, photos, *etc.*, which can be widely used in the field of information technology, anti-counterfeiting techniques and functional packaging.

Biodegradation properties

SEM photographs of the RC-7 film biodegraded in the soil for 3 days (a), 6 days (b), and 9 days (c) are shown in Fig. 12 (left). A porous structure with fungal mycelia on the surface of the decayed film was observed. It indicated that the biodegradation of the films was caused by the microorganisms, and this process occurred gradually. After having been buried in the soil for
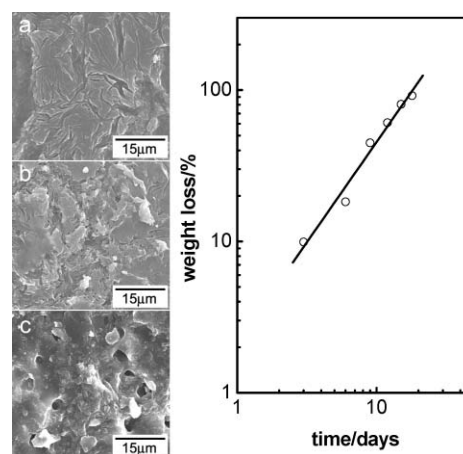
Fig. 12 SEM images (left) of RC-7 surface degraded for (a) 3 days, (b) 6 days, and (c) 9 days; and degradation time dependence of weight loss for RC-7 in soil at 30 °C (right).

9 days, only broken fragments of the films were observed; and after 1 month, no fragments of the films were found in the soil. The results suggested that the microorganisms in the soil directly attacked and metabolized the cellulose films, and the films were completely biodegradable.

The changes of physical properties of the RC films with biodegradation time have been investigated. The M_η values (not shown) of the RC-7 films decreased from 7.6×10^4 (original) to 4.3×10^4 after degradation for 9 days in the soil at 30 °C. However, the M_η values of the films stored in our laboratory for more than 1 year practically remained unchanged. It suggested that molecular chains of the cellulose are broken down by microorganism in the soil. Fig. 12 (right) shows the course of weight loss against degradation time for the films buried in the soil. The values of biodegradation rate constants k and half-life ($t_{1/2}$) of the films have been calculated to be 1.32 and 11 days, respectively. After 9 days of decay, the microorganisms in the soil have reduced the M_η by 31% with 44% weight loss for the film. The extrapolations of the plots shown in Fig. 12 (right) indicated that after 20 days these films were almost completely decomposed into CO_2 and water by the microorganisms in the soil.[35] Compared to the commercial products prepared from synthetic polymers, the cellulose based photoluminescent materials are safe and biodegradable after being used, and the fabrication method is a simple and "green" process. Moreover, both photoluminescent materials prepared from synthetic and natural polymers, respectively, by blending with dyes and pigments have luminescent properties. Thus, these attractive RC films will have promising applications because of the renewable supply of raw materials, "green" process, and complete biodegradability.

Conclusion

Transparent RC and photoluminescent composite films were prepared successfully from cellulose solution in the NaOH/urea aqueous system pre-cooled to −12 °C. It was a real green process for the production of the cellulosic packaging and functional materials from renewable raw materials *via* an environmentally friendly technology. The results revealed that the RC films exhibited structural homogeneity, excellent optical transmittance and good tensile strength. Moreover, their mechanical properties could be improved significantly by the drawing process. For the first time, novel fluorescent and long after-glow PL films have been prepared by blending cellulose with fluorescent dyes and PL pigments, respectively. The strong interaction between cellulose and the dyes or pigments existed in the composite films. The PL films could absorb light for several minutes and then emit a visible light for more than 10 h in the dark, indicating good PL properties. The films were safe and stable, as well as biodegradable. This work provided a new pathway for producing cellulose and its composite films, which will find wide applications in the fields of packaging, anti-counterfeiting techniques and functional materials.

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A potential ionic liquid for CO_2-separating gas membranes: selection and gas solubility studies

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The production of hydrogen from fossil fuels by steam reforming/water gas shift can be enhanced by separating the reaction byproduct, CO_2, within the reactor as it is produced. Such a separation-enhanced reaction not only has higher conversion efficiency, but can also be considered a greener process which produces high-purity hydrogen with little CO_2 contamination. Supported ionic liquid membranes may be able to achieve this separation task since they are known to have high CO_2 and low H_2 solubilities. In this study, the 1-alkyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl)imide family of ionic liquids has been selected for this purpose, based on limited literature data. The solubilities of major reaction gases, namely CO_2, H_2, CO, and CH_4, in 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide are compared to one another. In addition, the solubilities of CO_2 and H_2 in 1-ethyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl)imide are compared. The results indicate, from a thermodynamic point of view, the possibility of using this family of ionic liquids as separation membranes with practical CO_2/H_2 selectivities.

Introduction

Supported liquid membranes are solid porous membranes whose pores are impregnated with liquids. The solute molecules dissolve into the membrane at the feed/membrane interface. The dissolved species diffuse through the membrane and desorb at the opposite membrane surface. Supported liquid membranes are promising because they not only combine the processes of extraction and stripping, but also significantly reduce the necessary amount of solvent compared to conventional solvent extraction processes. However, supported liquid membranes with conventional liquids deteriorate with time because the membrane liquids eventually evaporate. This evaporation also necessitates a minimum membrane thickness, which restricts net flux through the membrane.[1] In addition, the membrane being used to purify a certain fluid, contaminates it at the same time by evaporating and "bleeding" into the stream. However, ionic liquids (ILs) are greener solvents which have a number of unique properties that provide distinctive advantages over conventional liquids used in supported liquid membranes. Ionic liquids are organic salts that are liquid at room temperature. They consist of an organic cation such as quaternary ammonium, imidazolium, pyridinium, or pyrrolidinium ions combined with either an organic or an inorganic anion of usually smaller size and more symmetrical shape such as Cl^-, Br^-, I^-, $AlCl_4^-$, BF_4^-,

PF_6^-, $ROSO_3^-$, or Tf_2N^-. Most ionic liquids have insignificant volatility at room temperature and high surface tension, which together ensure minimal evaporation or displacement loss from the support, thus minimizing gas stream contamination and ionic liquid loss. Because of this, together with their high thermal stability and chemical stability under oxygen-lean conditions, and their high solvation power for some gases such as CO_2, SO_2, and N_2O, ionic liquids provide opportunities to develop new gas separation/enrichment technologies. This is a largely undeveloped field for the potential commercial application of ionic liquids.

Research has started only recently in the exploration of supported ionic liquid membranes (SILM) for gas separation and enrichment.[1–14] The majority of studies in this field focus on the separation and purification of natural gas from the contaminating acid gases,[5–8] and removal of CO_2 and SO_2 from stack gases.[9–13] Much less activity is documented in the literature on the idea of using ionic liquids to separate H_2. An experimental study by Gan *et al.*[1] showed H_2/CO separation factors up to a maximum of 4.3 tested with four members of the bis(trifluoromethylsulfonyl)imide ([Tf_2N]) ionic liquid family. With hydrogen purification in mind, Yokozeki and Shiflett[14] recently used an equation of state model to predict very high CO_2/H_2 separation selectivities (about 30–300) using [bmim][PF_6].

In this study, the idea of using a separation-enhanced SILM reactor in the production of hydrogen from fossil fuel is investigated from a thermodynamic perspective. Based on available literature data, two potential ionic liquids suitable for this task, *i.e.* permeating CO_2 better than H_2, are proposed. An experimental approach is then used to obtain binary phase behaviour data of relevant gases in these ionic liquids. The

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solubility data[15,16] of CO_2, CO, CH_4, and H_2 are then compared and the feasibility of using the [Tf_2N] family of ionic liquids for gas separation is discussed on a purely thermodynamic basis.

Selection of a suitable ionic liquid

The main reactions of concern in the production of hydrogen from fossil fuels, for example from natural gas, are the following:

$$CH_4 + H_2O \leftrightarrow CO + 3H_2 \quad \text{steam reforming}$$

$$CO + H_2O \leftrightarrow CO_2 + H_2 \quad \text{water gas shift}$$
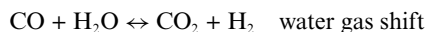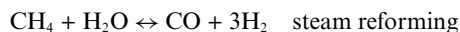
By removing either CO_2 or H_2 from the reaction mixture, the equilibrium can be shifted to the product side. This can effectively lower the reaction temperature and offer higher conversion, as well as improve the purity of the product.[17] In addition to these advantages, the combination of separation and reaction into one unit can result in lower investment costs. However, for economic viability, costs of the ionic liquids should be much lower than at present.

CO_2 separation is a flexible technique that can be used not only in carbon-free hydrogen production from natural gas, but also in coal and biomass gasification plants or in electricity generation. With such reactions in mind, the following criteria were taken into account for selecting an ionic liquid intended to be used in a CO_2-separating SILM:

1. High CO_2 solubility and low H_2 solubility for optimal separation.

2. Manageable viscosity (too high a viscosity hinders mass transfer).

3. High thermal stability to withstand reaction temperatures.

Each aspect will be considered in the following sections.

Solubility

At the time that this project was commenced, ionic liquid gas solubility data were severely lacking in literature. The data available were mostly in the form of Henry's constants at very low gas concentrations and pressures, a highly idealized case ($k_H = \lim_{x \to 0} P/x$, where k_H is Henry's constant, P is pressure, and x is the concentration of gas in the ionic liquid). But due to the absence of more suitable data, Henry's constant was chosen as the comparison index of solubility for the selection of a potential gas-separating ionic liquid.

Compared to many other gases, the Henry's constants are very low for CO_2 in ionic liquids, indicating high solubilities. The CO_2 solubility is particularly high in ionic liquids based on the imidazolium cation. However, it is the anion of the ionic liquid that has the dominant effect on the interaction with CO_2, with the cation playing a secondary role.[18] In Table 1, Henry's constants are given for CO_2, CO, and H_2 in various ionic liquids found in literature.[19–23] It is seen that the family of ionic liquids with the [Tf_2N] anions have among the lowest Henry's constants for both CO_2 and CO. The three-digit-valued Henry's constants for H_2 show that hydrogen solubility at atmospheric conditions is much lower than the corresponding solubility of CO_2 and somewhat lower than for CO.

Table 1 Henry's Law constants for CO_2, CO, and H_2 at atmospheric conditions in various ionic liquids found in literature

Ionic liquid	k_H for CO_2, MPa[a,b,c]	k_H for CO, MPa[d]	k_H for H_2, MPa[e]
[emim][BF_4]	—	667	—
[bmim][BF_4]	5.65	337	580
[hmim][BF_4]	—	161	570
[bmim][PF_6]	6.18	327	660
[bmim][CF_3SO_3]	$3.7 < k_H < 6.18$	—	—
[emim][Tf_2N]	3.56	118	—
[bmim][Tf_2N]	3.7	95	450
[hmim][Tf_2N]	3.5	76	—
[omim][Tf_2N]	$k_H < 3.5$	—	—
[bmmim][Tf_2N]	—	—	380
[bmim][methide]	$3.5 < k_H < 3.7$	—	—
[bmim][SbF_6]	—	201	490
[bmim][CF_3CO_2]	—	191	490

[a] Cadena *et al.*[19] [b] Baltus *et al.*[20] [c] Aki *et al.*[21] [d] Ohlin *et al.*[22] [e] Dyson *et al.*[23]

Thermal stability

An ionic liquid is only suitable for a separation-enhanced membrane reactor if it can withstand the temperatures involved in the reaction. Separation-enhanced water gas shift of gas from a coal gasifier requires temperatures of at least 150 °C.

Ionic liquids are generally considered to have high thermal stability. Stability is found to be more dependent upon the anion than the cation. The onset of thermal decomposition appears to decrease as the anion hydrophilicity increases.[24] The stability also increases with increasing anion size.[25] With respect to the cation, it is known that the thermal stability of imidazolium-based ionic liquids increase with increased alkyl substitution, as long as linear alkyl groups are used; however, the alkyl chain length doesn't have a large effect.[26,27] Ionic liquids based on imidazolium cations and fluoride containing anions, in general, show even higher thermal stability.[27,28] Ionic liquids that are stable at much higher temperatures are the dicationic ionic liquids. They exhibit much higher thermal stability, with onset temperatures ranging from 330 to over 400 °C.[29]

There is evidence that for some imidazolium salts, the thermal decomposition temperature in an oxidizing atmosphere (O_2) is not significantly different than in an inert atmosphere (N_2). However, some imidazolium salts, such as those containing the [PF_6] anion, have been shown[25] to decompose at lower temperatures in the presence of O_2. The effect of typical impurities, such as water or chloride, on the thermal stability of ionic liquids seems to be insignificant.[30]

The vast majority of thermal stability data available in literature are obtained by fast ThermoGravimetric Analysis (TGA) scans collected under an atmosphere of nitrogen. These data do not imply a *long-term* thermal stability below the given temperature.[30] In Table 2, the onset temperatures for thermal decomposition are given for some ionic liquids.[25,31,32] Since these temperatures are based on the TGA method, they are probably higher than the long-term degradation temperatures. They can, however, be used to compare the thermal stability of different ionic liquids. As discussed above, ionic liquids with the [Tf_2N] anion show high thermal stability. In addition, the presence of air

Table 2 Onset temperatures for thermal decomposition for various ionic liquids found in literature

Ionic liquid	Onset temperatures for thermal decomposition (°C)[a,b,c]
[bmim][Cl]	264
[bmim][Br]	273
[bmim][DCA]	300
[emim][BF$_4$]	412
[bmim][[BF$_4$]	361
[bmmim][BF$_4$]	380
[bmim][methide]	413
[bmim][CF$_3$SO$_3$]	392
[emim][PF$_6$]	375
[bmim][PF$_6$]	349
[bmmim][PF$_6$]	373
[emim][Tf$_2$N]	440/455
[pmim][Tf$_2$N]	452
[bmim][Tf$_2$N]	422
[pmmim][Tf$_2$N]	462

[a] Huddleston et al.[31] [b] Fredlake et al.[25] [c] Camper et al.[32]

is rather insignificant on the thermal degradation of the [Tf$_2$N] ionic liquids as compared to a pure nitrogen atmosphere.[30]

Viscosity

The viscosity of the ionic liquid is also an important criterion when selecting an ionic liquid to use as a membrane. A high viscosity leads to low mass transfer. The viscosities of most of the ionic liquids are relatively high compared with those of common organic solvents. Organic solvents typically have room temperature viscosities ranging from 0.2 to 10 cP, while ILs display a broad range of room temperature viscosities from 10 to greater than 10^5 cP.[33] In addition to electrostatic attraction between the cations and anions and the tendency to form hydrogen bonds, the viscosity of ionic liquids is generally influenced by van der Waals interactions. The geometry and molar mass of the anions strongly influence the viscosity; increasing size and increasing symmetry of the anions cause an increase in viscosity.[24,34] The degree of freedom of the anion also has an effect on viscosity, as does its shape. With focus on the anion, low polarizability, high degrees of freedom, good charge distribution, and a somewhat flat shape contribute to lowering the viscosity of ionic liquids.[34] Fluorination of the alkyl chain in the anion also leads to lower viscosity, due to the better charge distribution and lower polarizability for the fluorinated anions, *i.e.* this makes a contribution to reducing the strength of cohesive forces, including Coulombic interactions, van der Waals interactions, and hydrogen bonding, thus lowering the viscosity.[24,34] On the cation side, the viscosity generally increases with increasing length of the alkyl side due to the increase of van der Waals interactions.[34] Branching of the alkyl side chain in 1-alkyl-3-methylimidazolium salts always reduces viscosity.[24] Table 3 shows the viscosities for some ionic liquids.[31,34] The [Tf$_2$N] family seems to exhibit the most workable viscosities.

Choice of ionic liquid

Examining the above-mentioned considerations among the various ionic liquids for which a reasonable amount of information was already available, the choice of the ionic family to be

Table 3 Viscosity of various ionic liquids at 25 °C

Ionic liquid	Viscosity at 25 °C (cP)[a,b]
[hmim][Cl]	716
[emim][BF$_4$]	43/38
[bmim][BF$_4$]	233
[hmim][BF$_4$]	314 (at 20 °C)
[bmim][PF$_6$]	450
[hmim][PF$_6$]	585
[bmim][CF$_3$CO$_2$]	73
[emim][Tf$_2$N]	28
[bmim][Tf$_2$N]	52
[emmim][Tf$_2$N]	88
[bmmim][Tf$_2$N]	97

[a] Huddleston et al.[31] [b] Zhou et al.[33]

considered as a possible CO$_2$-separating membrane is rather straightforward. The [Tf$_2$N] family of ionic liquids shows very low Henry's constants for CO$_2$, suggesting that this gas may also have high solubilities in the ionic liquid at higher pressures. However, the solubilities of H$_2$ in this family of liquids are also higher than in other ionic liquids. This difference is, however, small compared to the much higher solubility differences of CO$_2$ in the different ionic liquids. In other words, the ratios of CO$_2$/H$_2$ solubilities are expected to be higher in the [Tf$_2$N] family. In addition, the greater thermal stabilities and lower viscosities of this family make it stand out further as the most promising class of ionic liquids for further consideration. It is also of great significance that the [Tf$_2$N] ionic liquids are mostly water immiscible, a characteristic of utter significance for membrane stability in a reaction involving steam. In addition, the thermal stability of the imidazolium [Tf$_2$N] ionic liquids seems to be unaffected by the presence of air, as compared to an inert N$_2$ atmosphere.[31]

However, the choice of the specific member of this family is less obvious. A larger alkyl side chain is favoured for higher CO$_2$ solubility. However, a larger alkyl side chain also increases H$_2$ solubility. On the other hand, smaller members of the [Tf$_2$N] family are preferred for their higher thermal stability and lower viscosity. For this reason, two different members of the [Tf$_2$N] family have been selected in order to offer a greater range of physical properties which may be of concern for making ionic liquid impregnated membranes, rather than simply concentrating on solubility concerns alone. The two selected ionic liquids are [emim][Tf$_2$N] and [bmim][Tf$_2$N]. The molecular structures of these two ILs are shown on Fig. 1.

Procedure

Binary phase behaviour experiments were carried out for the various reaction gases in the selected ionic liquids in a so-called Cailletet apparatus, which allows the measurement of phase equilibrium according to the synthetic method within temperatures and pressures up to 450 K and 15 MPa, respectively. The equilibrium cell used for the measurements is a glass tube with variable pressure imposed by mercury. A mixture with fixed overall composition of the components is sealed within this tube and kept at constant temperature using thermostat fluid which circulates around the tube. At any desired temperature, the pressure is varied until the disappearance of
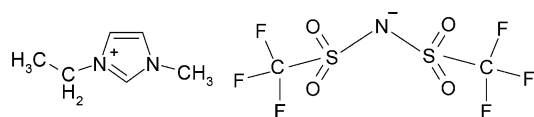
1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
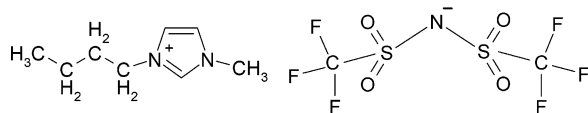
1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide

Fig. 1 Molecular structures of [emim][Tf$_2$N] and [bmim][Tf$_2$N].

the last bubble of vapour is observed visually, as the mixture is continuously stirred. The accuracies of measurement are within 0.02 K for temperature, 0.003 MPa for pressure, and 0.001 for molar fraction. Details of the experimental apparatus and procedure are given elsewhere.[35] The phase behaviour of the binary systems CO$_2$ + [emim][Tf$_2$N], CO$_2$ + [bmim][Tf$_2$N], H$_2$ + [emim][Tf$_2$N], H$_2$ + [bmim][Tf$_2$N], CH$_4$ + [bmim][Tf$_2$N], and CO + [bmim][Tf$_2$N] were measured.[15,16,36,37]

Results and discussion

Solubility of CO$_2$

Fig. 2 shows the solubility of CO$_2$ in [emim][Tf$_2$N] at various temperatures in the form of bubble point curves for a number of isotherms.[36] The nonlinearity of the curves indicate that extrapolating available Henry's constant data to higher gas concentrations can be seriously misleading and erroneous. Therefore, it is absolutely necessary to measure gas solubilities in ionic liquids over the range of concentrations and pressures of concern.
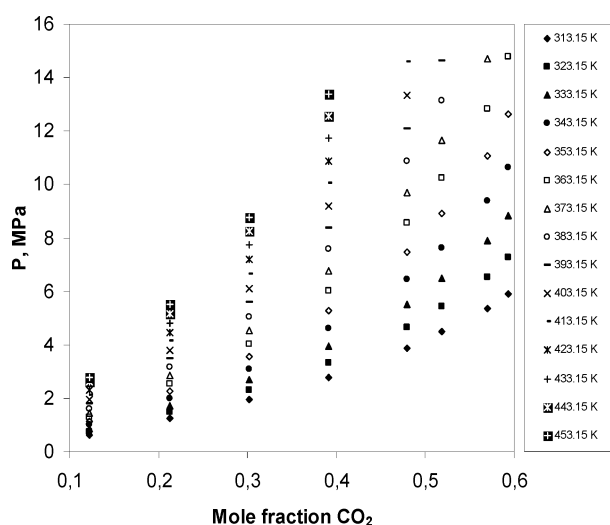
Fig. 2 Experimental pressure–composition data for binary mixtures of CO$_2$ + [emim][Tf$_2$N] at different temperatures. Data taken from Schilderman *et al.*[36]

As expected for a gas dissolving in a liquid, Fig. 2 shows that CO$_2$ solubility increases with decreasing temperature and

increasing pressure. However, it is the large quantities of CO$_2$ that can be dissolved in this IL, for example, up to 60 mole percent at 333 K and pressures of about 9MPa which makes such a binary system particularly interesting.[36] This is even higher than commonly investigated 1-alkyl-3-methylimidazolium ionic liquids, such as, for example [emim][PF$_6$], sharing the same cation but having a differing anion, as shown in Fig. 3. At the same temperature of 333 K, similar CO$_2$ solution capacity can only be obtained at pressures of about 75 bar for the ionic liquid [emim][PF$_6$].[38] Increasing the size of the alkyl side chain to butyl allows for even higher CO$_2$ solubility than [emim][Tf$_2$N]. For example, at conditions of 333K and 9MPa, up to approximately 62 mole percent CO$_2$ can be dissolved in [bmim][Tf$_2$N].[15] The trends and slopes of the CO$_2$ solubility curves are very similar to those of [emim][Tf$_2$N], however, the curves of [bmim][Tf$_2$N] are shifted slightly to the right relative to those of [emim][Tf$_2$N].
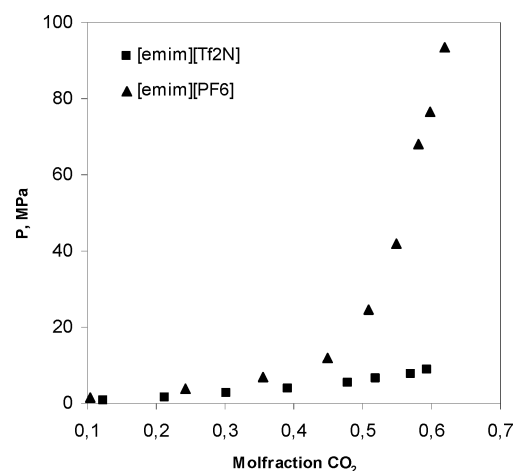
Fig. 3 Comparison of the solubilities of CO$_2$ in [emim][Tf$_2$N] and [emim][PF$_6$] at 333.15 K (data taken from Shariati and Peters[38] and Schilderman *et al.*[36]).

At low concentrations and low pressures, carbon dioxide shows very high solubility enhancement with small increases in pressure. However, with increased CO$_2$ concentrations the P–x curve steeps upwards, indicating that little CO$_2$ can be further dissolved with increasing pressure (Fig. 2). There is a chance that the bubble point curve will bend back down at extremely high pressures to meet the dew point curve but it is more likely that it will simply continue upward to infinitely high pressures. Due to practical limitations, dewpoint measurements were not feasible in the Cailletet apparatus. Other researchers' attempts at measuring dew point curves in ionic liquids, have indicated immeasurably small IL concentrations. Brennecke and coworkers[39] indicated that the solubility of [bmim][PF$_6$] in CO$_2$ is less than 5×10^{-7} in mole fraction at 40 °C and 138 bars. A binary mixture of [bmim][PF$_6$] with 97 mol% CO$_2$ showed the existence of two phases even up to a pressure of 3100 bars at 40 °C. Brennecke and coworkers[39] state that such diverging behaviour of binary mixtures of CO$_2$ and an IL, with an immiscibility gap even up to extremely high pressures, is very unusual for a mixture of CO$_2$ in a liquid, *i.e.*, normally when a large amount of CO$_2$ dissolves in the liquid phase at low pressures, the system shows a simple phase envelope with a mixture critical point at moderate pressures. However, according

to phase behavior principles, this kind of behavior is not unusual, although indeed, it is not so commonly observed. According to the classification of Scott and Van Konynenburg,[40] such systems of CO_2 + IL most likely have Type III behavior (although Types IV and V should not be excluded as possibilities).[18]

Solubility measurements, spectroscopic studies, X-ray diffraction studies, and molecular simulations have shown that CO_2 solubility depends primarily on the strength of interactions of CO_2 with the anion.[21,41] The anions and cations of ionic liquids form ion pairs due to strong Coloumbic interactions that keep them closely associated, even in systems diluted with CO_2. Therefore, IL molecules are considered to be highly asymmetric neutral ion pairs with large dipole moments as a result of the charge distribution over the ion pair.[42] On the other hand, CO_2 molecules have quadrupole moments. So it is the interactions between CO_2 molecules and IL anions that are of primary importance in solubility. Although it is known that CO_2 reacts with the anion of some organometallic compounds to produce carboxylic acids, no evidence has been found for such reactions in ionic liquids. The particularly high solubility in the [Tf_2N] ionic liquids, can be attributed to the CO_2-philic nature of the fluoroalkyl groups.[21] In fact, fluorination is a proven technique of increasing the CO_2-philicity of molecules, although the exact reasons for this are still the subject of active debate in literature.[43,44] For example, Raveendran and Wallen,[44] using quantum chemical calculations, and Kazarian et al.,[45] using in situ ATR-IR studies, both suggested the existence of a specific interaction between the fluorine atoms and CO_2, with fluorine atoms acting as weak Lewis bases. Baltus et al.[20] attributed the higher solubilities to steric constraints. They argued that the larger-sized Tf_2N anions, compared to most other anions, lead to weaker cation–anion interactions, thus increasing the interactions between the ionic liquid and CO_2 and increasing the free volume. Recently, Brennecke and coworkers[43] suggested that the good CO_2 solubility in [Tf_2N] anion-based ILs could be due to a combination of fluorination and the presence of S=O groups. This was based on ab initio calculations which implied that the S=O group could be used to increase CO_2-philicity of molecules due to Lewis base–Lewis acid interactions with the carbon atom of CO_2.

Possibility of separation

The solubility of hydrogen is low in both of the ionic liquids selected in this study, even at high pressures. For example, at a temperature of 453 K the maximum amount of hydrogen that dissolved in [emim][Tf_2N] and [bmim][Tf_2N] at a pressure of 9MPa was only about 6 mole% and 7 mole%, respectively.[37] Hydrogen solubility increased with increasing pressure and the variation was rather linear in this family of ILs. CO and CH_4 solubilities were much less than those of CO_2, but higher than H_2. Fig. 4 shows, for example, a descriptive compilation of solubilities of CO_2, H_2, CO, and CH_4 in [bmim][Tf_2N] on a single graph.[15,16,37] This figure illustrates that the solubility of hydrogen is one order of magnitude lower than the corresponding solubility of CO_2 in [bmim][Tf_2N]. A ratio of CO_2/H_2 up to 15 has been observed within the operating condition limits of the experimental apparatus. This ratio may be higher at other conditions. The hypothesis of
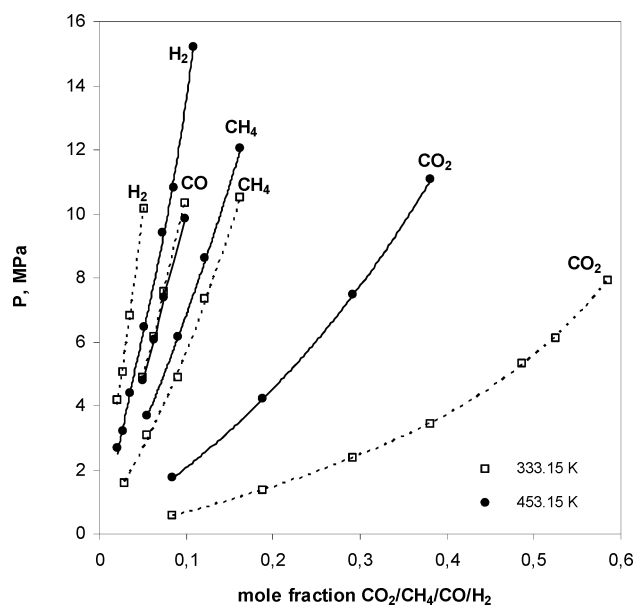
Fig. 4 Comparison of the solubilities of CO_2, CH_4, CO and H_2 in the ionic liquid [bmim][Tf_2N] at 333.15 K and 453.15 K (data taken from Raeissi and Peters[15,16,37]).

the possibility of gas separation using such ionic liquids is confirmed by comparing the above-mentioned selectivity to that of typical polymeric membranes for the separation of CO_2 from H_2. For example, polysulfone and cellulose acetate membranes were reported to have CO_2/H_2 selectivities of 0.5 and 2.0, respectively.[46] However, the highest reported CO_2/H_2 selectivity is 10 for water saturated hydrophilic polymers such as cellulose acetate.[47,48] There are also a few examples of facilitated transport membranes with high CO_2/H_2 selectivities. Way and Hapke[49] reported CO_2/H_2 selectivities of 6.8 using ionomeric membranes consisting of films of poly(perfluorosulfonate) with a monoprotonated ethylenediamine counterion. Pellegrino and co-workers[50] reported pressure dependent CO_2/H_2 selectivities of 20 to 55 for a poly(perfluorosulfonate)-ethylenediamine membrane gelled with water.[48] Quinn et al. showed that salt hydrate membranes of tetramethylammoniumfluoride tetrahydrate/poly(trimethylsilylpropyne) exhibit CO_2/H_2 selectivities as high as 360 at low feed partial pressures of CO_2 and about 30 at higher pressures.[48] However, in industrial processes for the recovery of H_2, it is important to retain the recovered H_2 at feed pressures to avoid the cost of its repressurization.

It should be recognised that the CO_2/H_2 selectivities presented in this work are simply the values of CO_2 solubility in the pure ionic liquid to the value of H_2 solubility in the pure ionic liquid. In real ternary systems, the presence of H_2 can affect the solubility of CO_2 in the ionic liquid and vice versa. For example, Hert et al.[51] observed increased O_2 and CH_4 solubility in [hmim][Tf_2N] in the presence of CO_2. Their results also showed a decreased solubility of CO_2 in the ionic liquid when either O_2 or CH_4 was present, relative to pure CO_2 gas. Therefore, the actual selectivities in real multicomponent systems are expected to be somewhat different than the ones presented here, and thus remain to be investigated for more accurate conclusions.

Fig. 4 also emphasises the strong dependence of the solubility ratio on both pressure and temperature. In the conditions

studied, typical CO_2/H_2 values ranged from approximately 5 to 15 depending on operating conditions. Hence, optimization on pressure and temperature is necessary for good ionic liquid membrane performance. Although not shown, [emim][Tf_2N] also has quite a similar graph but CO_2 and H_2 solubilities are lower compared to [bmim][Tf_2N].

The shapes of the solubility curves are also worth some discussion. While the CO_2 solubility curves exhibit the concave behaviour typical of CO_2 in ionic liquids,[18] H_2, CH_4, and CO have a much more linear behaviour (Figs. 2 and 4). This particular difference in shape of solubility curves can further benefit the separation process. If the H_2 curve were also to have a concave behaviour similar to the CO_2 curve, then the solubility differences of H_2 and CO_2 would not be as great as they are with the actual curves presented in Fig. 4.

Whereas most systems show a decrease in gas solubility upon increasing temperature, hydrogen exhibits the opposite trend in [emim][Tf_2N] and [bmim][Tf_2N] as can be seen, for example, in Fig. 5.[37] Since CO_2 solubility decreases at higher temperatures while H_2 solubility shows an increase as temperature is increased, the maximum separation of these two gases is achieved by operating at the lowest possible reaction temperatures. Operating at lower temperatures will also increase membrane life.
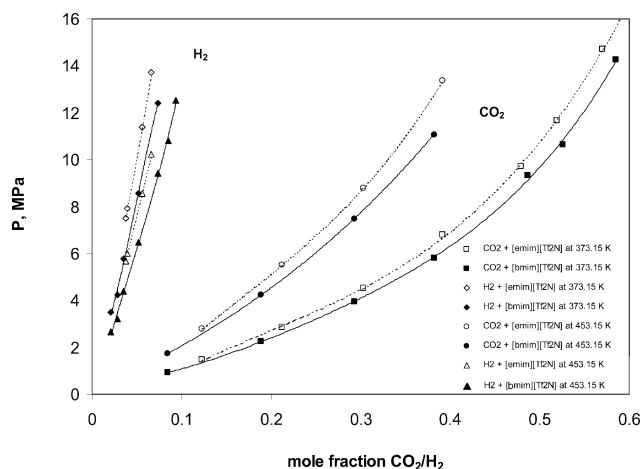
Fig. 5 Comparison of relative solubilities of CO_2 and H_2 in [bmim][Tf_2N] and [emim][Tf_2N] at two different temperatures (data taken from Schilderman *et al.*,[36] and Raeissi and Peters[15,37]).

Comparison of [emim][Tf_2N] and [bmim][Tf_2N]

Fig. 5 compares gas solubilities between the two ionic liquids [emim][Tf_2N] and [bmim][Tf_2N] at two different temperatures. Similar trends are observed at other temperatures as well. It is evident that the size of the alkyl side chain of the cation does indeed affect solubility, however, the effect is not as pronounced as the substitution of the anion, as discussed above. CO_2 solubility increases with increasing alkyl chain length at all pressures. Aki and coworkers[21] explained this based on the decreasing densities of imidazolium-based ILs with increasing alkyl chain length. The greater free volume in ILs with longer alkyl chains allows for more CO_2 to dissolve. Baltus *et al.*[20] argued that as the length of the carbon chain increases, steric constraints decrease the strength of the ionic interaction between

the imidazolium cation and the Tf_2N anion. The weaker cation–anion interactions can strengthen the interaction between the cation and CO_2, leading to an increased CO_2 solubility. As Fig. 5 shows, the differences are more distinct at higher CO_2 concentrations and higher pressures. In fact an almost linear relationship seems to exist between the alkyl chain length and the solubility of CO_2 in the [Tf_2N] ILs. This is seen in Fig. 6.[15]
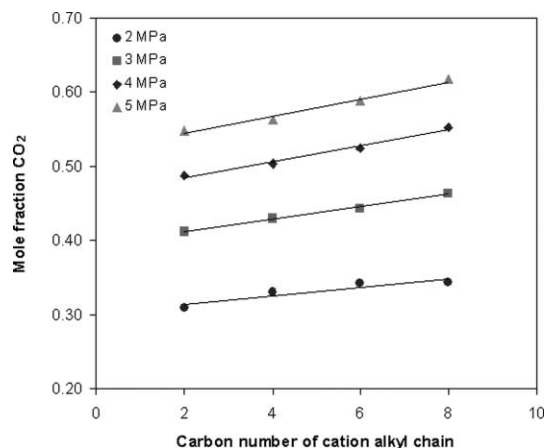
Fig. 6 The effect of alkyl chain length on the solubility of CO_2 in [$C_n$mim][Tf_2N] at 313.15 K and various pressures.[15] The data at carbon numbers 2, 4, 6, and 8 are from ref. 36, 15, 21, and 21, respectively.

Even though results have indicated a better solubility of CO_2 in [bmim][Tf_2N], and thus a better membrane yield as compared to [emim][Tf_2N], one cannot make the conclusion that [bmim][Tf_2N] is the better ionic liquid for the membrane. The ratio of CO_2/H_2 solubility is also of utmost importance in establishing separation selectivities. Fig. 5 assists in the comparison of these ratios for both [bmim][Tf_2N] and [emim][Tf_2N] at two different temperatures. For example, at a temperature of 373.15 K and a pressure of 10 MPa, the solubility ratios of CO_2/H_2 are 8.6 and 9.8 in [bmim][Tf_2N] and [emim][Tf_2N], respectively. So while [bmim][Tf_2N] is the superior ionic liquid regarding yield, [emim][Tf_2N] has the advantage when it comes to selectivity. In addition, [emim][Tf_2N] has a considerably lower viscosity and a slightly higher thermal stability, which should also be considered when making the final selection.

Conclusions

A literature survey through the limited data available on solubility of gases in various ionic liquids, together with other considerations, namely suitable viscosity and high thermal stability, has led us to suggest the [$C_n$mim][Tf_2N] family as potential ionic liquids for CO_2 separation in the coal-gasification process. Two members of this family, namely [emim][Tf_2N] and [bmim][Tf_2N], were selected for phase behaviour measurements. The solubilities of CO_2 and H_2 in both [emim][Tf_2N] and [bmim][Tf_2N] were determined[15,36,37] using a synthetic phase equilibrium measurement technique. The solubilities of CH_4 and CO in [bmim][Tf_2N] were measured as well.[16,37]

The experimental results indicated that CO_2 solubility is strongly dependent on temperature and pressure, decreasing with temperature and probably having an economically optimum mid-range pressure. The results obtained have confirmed

the expectations of very high CO_2 solubility in [bmim][Tf$_2$N] and [emim][Tf$_2$N], reaching values up to 60 molar percent, and possibly even higher. Such CO_2 solubilities are considerably higher than in the other commonly investigated ionic liquids.

Hydrogen solubilities, on the other hand, are an order of magnitude lower than CO_2 solubilities. The pressure–composition curves of hydrogen are also more steep and linear. This indicates that increases in pressure will cause little additional H_2 to dissolve while it can result in much greater CO_2 dissolution. The temperature dependence of hydrogen solubility is the reverse of CO_2, meaning hydrogen dissolves better by increasing temperature. Therefore, to obtain the best possible membrane efficiency, temperatures should be kept as low as possible. Methane and carbon monoxide solubilities in [bmim][Tf$_2$N] fall in between those of H_2 and CO_2, and they have a rather linear relationship with pressure.

CO_2/H_2 ratios of up to 15 (and possibly even higher) confirm the possibility, from a thermodynamic point of view, of using the [Tf$_2$N]-anion-based family of ionic liquids as supported ionic liquid membranes for the selective separation of CO_2 from H_2. A comparison of the two selected ionic liquids, [bmim][Tf$_2$N] and [emim][Tf$_2$N], reveals that CO_2 dissolves better in [bmim][Tf$_2$N]. However, H_2 also shows the same preference of solution in [bmim][Tf$_2$N]. This better solubility, in fact, goes as far as reducing the CO_2/H_2 ratio in [bmim][Tf$_2$N] to values lower than in [emim][Tf$_2$N]. The overall result is that [bmim][Tf$_2$N] will have the higher solubility yield of CO_2 but a lower separation selectivity as compared to [emim][Tf$_2$N].

Abbreviations

The following abbreviations have been used for various cations and anions of ionic liquids:

Cation

1-ethyl-3-methylimidazolium	[emim]
1-*n*-butyl-3-methylimidazolium	[bmim]
1-*n*-hexyl-3-methylimidazolium	[hmim]
1-*n*-octyl-3-methylimidazolium	[omim]
1-alkyl-3-methylimidazoleum	[C$_n$mim]
1-butyl-2,3-dimethylimidazolium	[bmmim]
2,3-dimethyl-1-propylimidazolium	[pmmim]
1-*n*-hexyl-3-methylpyridinium	[hmpy]

Anions

hexafluorophosphate	[PF$_6$]
tetrafluoroborate	[BF$_4$]
bis(trifluoromethylsulfonyl)imide	[Tf$_2$N]
trifluoromethanesulfonate	[CF$_3$SO$_3$]
dicyanamide	[DCA]
(trifluoromethylsulfonyl)methide	[methide]

Acknowledgements

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Chemical transformations of succinic acid recovered from fermentation broths by a novel direct vacuum distillation-crystallisation method

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A novel alternative methodology (direct crystallisation) to the traditional calcium precipitation to obtain succinic acid (SA) from defined and wheat-based fermentation broths is reported. SA crystals were successfully recovered from fermentation broths (FB) using this method. A higher SA crystal purity (95%) and yield (70%) were obtained in the direct crystallisation method compared to a slightly modified traditional calcium precipitation method (90% and 24%, respectively). Chemical transformations (e.g. esterifications) to high-added value derivatives of both recovered SA crystals were then investigated using a range of solid acids including our acidic tunable mesoporous carbonaceous materials denoted as Starbon® acids. Results showed that SA crystals could be successfully converted into mono- and diesters in high yields and selectivities employing solid acids regardless of the reaction conditions. The order of reactivity was found to be: pure SA crystals > SA crystals from defined FB > FB SA crystals. Results demonstrate that SA can be effectively purified from actual fermentation broths, showing the importance of integrating the fermentation and downstream processing to optimise the fermentative production of SA and its chemical transformations to produce high-added value derivatives.

Introduction

Succinic acid (1,4-butanedioic acid, SA) is a potential intermediate for the production of many high-added value end-products including polymers, surfactants, solvents, detergents and flavours and fragrances.[1] SA is a metabolite of the Krebs cycle, a respiratory process involving the breakdown of carbohydrates. The use of fermentation technology for the production of succinic acid as a potential industrial chemical feedstock has been the subject of intensive development over the last decade and the commercial production of bio-succinic acid has recently been announced by DSM and Roquette,[2] with further development planned by Bio-amber.[3]

In nature, SA is the direct *in vivo* precursor that accounts for up to 70% of the propionic acid formed in the rumen of cows.[4] Most SA producing micro-organisms have actually been isolated from bovine rumen. Two main approaches that have been pursued as strain selection strategies are the isolation of rumen bacteria from natural sources and metabolic engineering of mutant strains. *Escherichia coli* mutants,[5,6] *Anaerobiospirillum succiniciproducens*,[4,7] *Actinobacillus succinogenes*,[8–11] and *Mannheimia succiniciproducens*[12,13] are four of the most promising species reported in the literature for succinic acid production.

Downstream processing refers to isolation, purification and sterilisation of potential end products. It is estimated to account for about 80% of the overall production cost.[14] Efficient separation of high purity SA from by-products such as acetic, formic, and pyruvic acids is desirable for the process to be economically viable. Various recovery techniques including crystallisation,[15,16] extraction,[17–19] adsorption[17,20] and electrodialysis with bipolar membranes[7,21,22] have been reported.

Crystallisation is the conventional method for the recovery of organic acids from fermentation broths. Datta *et al.* developed a calcium precipitation method to recover SA from fermentation broth produced by *Anaerobiospirillum succiniciproducens*.[15] This method is based on successive crystallisation processes, acidification, followed by ion exchange resins. Although SA crystals with purity up to 94.2% were obtained, the main disadvantage of the process was the formation of undesirable waste residues such as calcium sulfate (gypsum).[15] Both environmental and economic concerns also arise in the handling and disposal of solid wastes and slurries.

The high purity of SA crystals makes them very attractive to undergo chemical transformations as starting materials. SA was ranked among the top platform chemicals, strengthened by a recent report by the US Department of Energy.[23] Platform molecules, also known as building blocks, are molecules with multiple functional groups that possess the potential to be transformed into new families of useful molecules, including commodity and speciality chemicals.[24] In this regard, esterifications are one of the most useful transformations for organic acids, especially for a dicarboxylic acid since the diester can be used as an intermediate in the manufacture of polymers.[1]

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Traditional esterification methods are unselective, use soluble mineral acids that have to be separated at the end of the reaction, and lead to hazardous waste.[25] Thus, selective and recyclable solid acids will be a great advantage in this reaction.

We have recently reported the preparation of a novel family of tunable mesoporous carbonaceous materials (Starbon® acids) that can be employed as catalysts in the esterification of organic acids (including succinic acid) to mono- and diesters in aqueous ethanol.[26–28] Preliminary results showed that the Starbon® acids based on Starbons® prepared at different temperatures exhibited an optimum of catalytic activity, with sharply reduced activities below or above this maximum, providing quantitative conversions of starting material after 4–5 h of reaction.[24,26–28] Starbon® acids also provided higher conversions than any other commercially available solid acid employed in the reaction. Interestingly, a substrate-dependent maximum of catalytic activity under conventional heating was also observed.[26]

The use of microwave irradiation can also speed up the rates of reactions from hours to minutes, especially those promoted by materials/reagents/solvents with the ability to convert microwave energy into heat at a given frequency and temperature (*e.g.* ethanol).[29] In this regard, the use of polar solvents including ethanol or water may have an important effect in the conversion of SA in the esterification reaction.

In this study, we report the development of two processes (modified calcium precipitation, Process I, and direct crystallisation, Process II) for the effective separation and purification of an SA-enriched fermentation broth (FB) and a comparison of the activities of pure SA crystals and FB SA crystals in the esterification of succinic acid using various solid acids as catalysts both under conventional heating and microwave irradiation.

Materials and methods

Chemicals, micro-organism and growth conditions

All chemicals employed in this study were obtained from Sigma–Aldrich and Fisher Scientific, except where otherwise specified. Sulfated zirconia was gratefully donated by MEL Chemicals, Manchester (www.zrchem.com). Zeolites (beta-25 and ZSM-5) were purchased from Zeolyst Inc. and activated at 500 °C prior to their use. *A. succinogenes* (ATCC 55618) was obtained from the American Type Culture Collection (ATCC, Manassasa, VA, USA). An inoculum was prepared by incubating *A. succinogenes* cells from cryopreservation vial in 100 mL Duran bottles containing 50 mL of trypticase soya broth (TSB; Fluka, BioChemika, Buchs, Switzerland) at 30 °C (recommended ATCC cultivation procedure) on a rotary shaker of 100 rpm for 48 hours.

Defined fermentation broths

Four synthetic fermentation broths (solutions A, B, C and D) were prepared with compositions listed in Table 1. Solution A was a mixture of organic acids consisting of acetic, formic, pyruvic and succinic acids and their concentrations were based on the typical *A. succinogenes* fermentations.[9–11] Solution B was an aqueous solution consisting of various sodium salts

Table 1 Compositions of defined fermentation broths A, B, C and D

Solution	A	C
Component	Concentration (g/L)	Concentration (g/L)
Pyruvic acid	5	5
Acetic acid	5	5
Formic acid	5	5
Succinic acid	51.6	45.1
Glycine	0	1
Biomass	0	1
Flour hydrolysate[a]	0	30 mL

Solution	B	D
Component	Concentration (g/L)	Concentration (g/L)
Sodium pyruvate	6.25	5
Sodium acetate	6.8	5
Sodium formate	7.4	5
Sodium succinate	68.6	50

[a] Flour hydrolysate is a wheat-based fermentation feedstock as reported in a previous publication.[8]

(acetate, formate, pyruvate and succinate) with equivalent acid concentrations as in Solution A. The concentrations of organic acids in Solution C were similar to Solution A, except 1 g/L of glycine and 1 g/L cell biomass were added into Solution C to mimic the composition of practical fermentation broth produced by *A. succinogenes*. Solutions A, B and C were separately tested in Process I and similarly, Solutions A and D were individually used in Process II. In all cases, 100 mL of fermentation broth was used for the recovery of succinic acid crystals.

Fermentation broths produced by *A. succinogenes*

The inoculation procedure and batch fermentation conditions for the semi-defined and wheat-derived fermentations were described in a previous publication.[9] Two batches of bacterial fermentations were conducted at 37 °C with a working volume of 0.6 L semi-defined and wheat-derived media separately in a 1.8 L bench-top bioreactor (Electrolab 351, Tewkesbury, UK). The semi-defined medium (L^{-1}) comprised of: 51 g glucose; 10 g yeast extract (Fisher BioReagents, Fisher Scientific, Loughborough, UK); 1.16 g NaH$_2$PO$_4$·H$_2$O; 0.31 g Na$_2$HPO$_4$; 1.0 g NaCl; 0.2 g MgCl$_2$·6H$_2$O; 0.2 g CaCl$_2$·2H$_2$O; 1 μg B$_{12}$ vitamin; 20 μg biotin; 20 μg folic acid; 50 μg thiamine; 50 μg riboflavin; 50 μg niacin; 50 μg pantothenate; 50 μg *p*-aminobenzoate; 50 μg lipoic acid; 100 μg B$_6$ vitamin, 30 g MgCO$_3$ and 1 mL silicone antifoam.

The wheat-derived medium used in this study was generated from a soft wheat variety (*Consort*), harvested in 2003 and supplied by Fisher Seed and Grain Limited (Cranswick, East Yorkshire, UK). The composition of wheat-derived medium comprised of 150 mL flour hydrolysate containing around 200 g L^{-1} glucose and 200 mL gluten autolysate containing 1.2 g/L free amino nitrogen (FAN). The detailed procedure for preparing the wheat-derived medium has been described in a previous publication.[11] Prior to autoclaving, 2 g L^{-1} MgCO$_3$

was also added to the medium as a neutral pH buffer for the fermentation. The pH was automatically controlled at 6.6–6.8 with the addition of 10 M NaOH solution. The broth was sparged with 0.5 vvm CO_2 and agitated at 300 rpm. The inoculum size for the batch fermentation was 8.3% v/v. The two resultant fermentation broths are denoted as Fermentation Broth I (containing 35.3 g L^{-1} SA from semi-defined medium) and Fermentation Broth II (35.7 g L^{-1} SA from wheat-derived medium).

Downstream process for SA recovery

The fermentation broth (100 mL) was centrifuged for 15 minutes at 4,000 rpm and 20 °C to separate the cell biomass. The supernatant was further filtrated through Whatman No.1 paper in order to separate the trace solid residues. Activated carbon (12.5% w/v) was mixed with the filtrate for 12 h to remove the organic impurities that contributed to the dark brown colour of the broth. The suspension was then filtered and the clear fermentation broth obtained was further treated using

either Process I or Process II to remove the by-products and salts.

Modified calcium precipitation method (Process I). The pH of the clear fermentation broth (Fig. 1A; Filtrate II) was adjusted to around 13.5 by the addition of calcium hydroxide (20% w/w) and the mixture in Universal bottles was placed on a shaker at 200 rpm at 39 °C for 20 h. Calcium succinate solids were slurried with distilled water in a ratio of 33% (w/w) and an excess of sulfuric acid (H_2SO_4) was added to form calcium sulfate. The addition of sulfuric acid was stopped when the pH decreased to around 2.5 and the precipitate of calcium sulfate was removed *via* filtration. The filter cake was washed twice with distilled water to remove the SA remnants. The filtrate was vacuum distilled at 60 °C for 12 h to eliminate residual volatile carboxylic acids, such as acetic, formic and pyruvic acids. The solution was concentrated to around 20% of its original volume and the crystallisation of SA was carried out at 4 °C for 24 h. The final slurry was filtrated through Whatman No. 1 paper and the SA crystals were dried at 40 °C for 12 h. The purity and
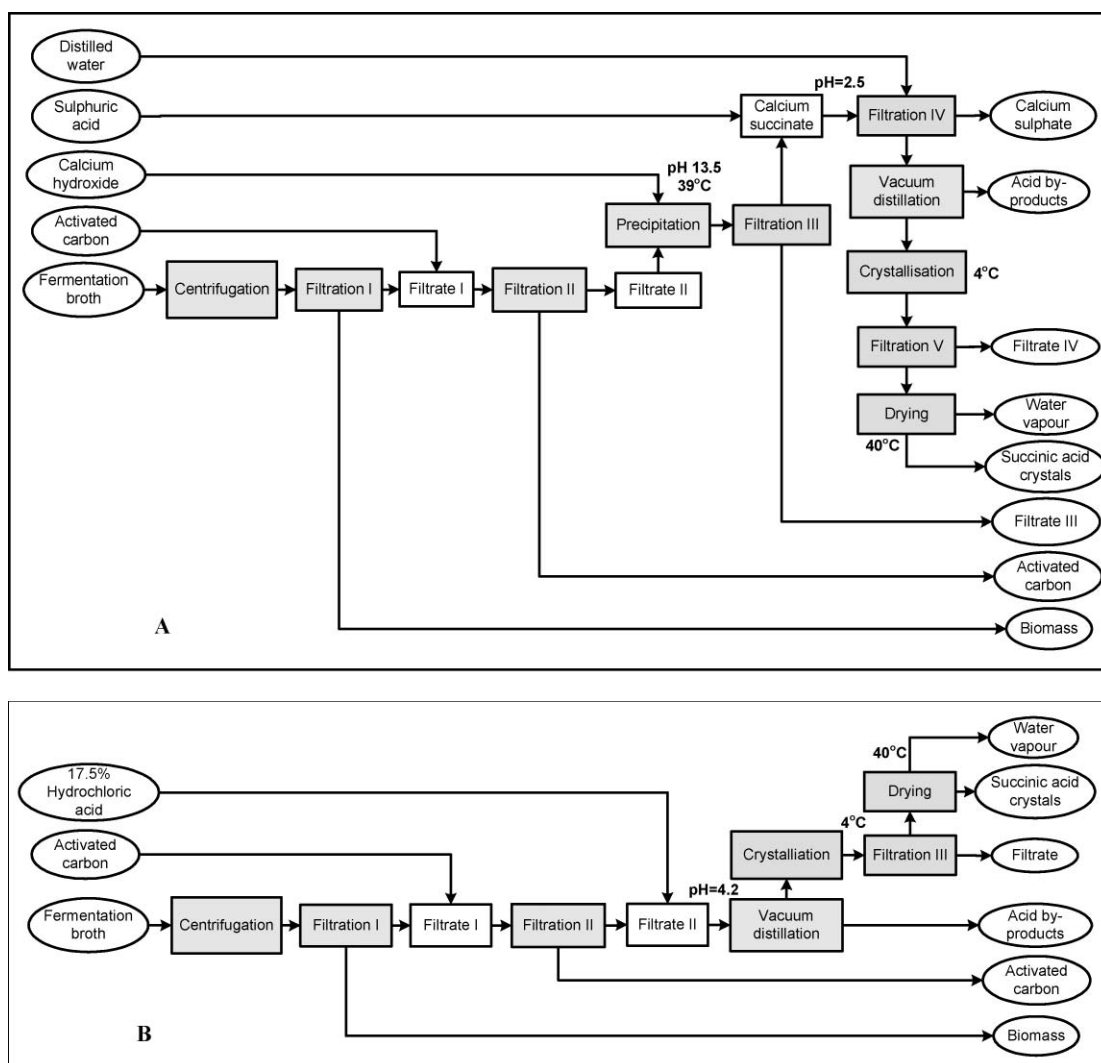
Fig. 1 Schematic diagrams of two recovery processes of SA crystals (A) modified calcium precipitation method (Process I) and (B) direct crystallisation method (Process II).

purification yield of the recovery process are defined as follows (eqn (1) and (2)):

Purity (%) =

$$\frac{\text{SA concentration in crystals recovered (g/L)}}{\text{Total acid concentrations in crystals recovered (g/L)}} \times 100 \quad (1)$$

Yield (%) =

$$\frac{\text{Dry weight of SA in crystals recovered (g)}}{\text{Initial dry weight of SA in the fermentation broth (g)}} \times 100 \quad (2)$$

Direct crystallisation method (Process II). The pH of the aqueous fermentation broth (Fig. 1B; Filtrate II) was adjusted to 4.2 by addition of 17.5% (v/v) hydrochloric acid. It was then followed by vacuum distillation and crystallisation as described in Process I for the recovery of SA crystals.

Materials preparation and catalytic experiments

Starbon®-400 preparation method comprises of three key stages as previously reported,[24,27] namely gelatinisation, solvent exchanging and drying and carbonisation under nitrogen at 400 °C. As-prepared Starbon®-400 was then suspended in H_2SO_4 99% purity (10 mL acid g^{-1} material) and heated for 4 h at 80 °C. After sulfonation, samples were subsequently washed with distilled water until the washings were neutralised, extracted with toluene (4 h in boiling toluene) and water (3 h, 80 °C) and finally oven dried (100 °C) overnight before being tested in the catalytic reaction. The SO_3H loading of the sulfonated Starbon®-400 (Starbon®-400-SO_3H) was *ca.* 0.5 mmol g^{-1}.[26,28] The choice of the Starbon®-400 as catalyst in the reaction was supported by reported results that the optimum catalytic activity in the esterification of SA was obtained using this particular solid acid.[26] Sulfonated DARCO® was prepared from commercial microporous DARCO® in a similar way to that of the reported Starbon®-400-SO_3H. The other solid acids (sulfated zirconia and zeolites) were used as purchased.

A typical catalytic test run under conventional heating was performed as follows: 1 mmol SA crystals, 30 mmol EtOH (2.4 mL) and 50 mmol water (0.9 mL) were added to a round bottom flask with 0.1 g solid acid, increasing the temperature to 80 °C. Samples were withdrawn periodically from the reaction mixture and the mixture was left reacting for 12 hours. The same quantities of starting materials and catalysts (see above) were used in the esterification run under microwave irradiation aiming to compare the results. The reaction mixture was placed in a microwave tube and microwaved for 15–30 min at maximum power output (300 W). The temperature reached (90–120 °C) was variable depending on the reaction conditions.

Analytical techniques

Concentrations of SA, acetic acid, formic acid and pyruvic acid were determined by high performance liquid chromatography (HPLC) as previously described.[11] All samples were analysed at least in triplicate to ensure consistent results. Calculations were generally based on the average values of the individual readings taken.

Diffuse reflectance infrared Fourier transform spectra (DRIFTS) were recorded on a Brüker EQUINOX-55 in-

strument equipped with a liquid N_2 cooled MCT detector. Resolution was 2 cm^{-1} and 1024 scans were averaged to obtain the spectra in the 4000–600 cm^{-1} range. Spectra were recorded using KBr as reference. The samples for DRIFTS studies were prepared by mechanically grinding all reactants to a fine powder (sample/KBr 1/1000 ratio).

Microwave experiments were carried out in a CEM–DISCOVER model with PC control and monitored by sampling aliquots of reaction mixture. Experiments were conducted in a closed vessel (pressure controlled) under continuous stirring. The microwave method was generally power controlled, where the samples were irradiated with the maximum power output to achieve various temperatures (90–120 °C), depending on the reaction conditions and catalyst.

The products obtained in the esterification of SA were analysed by gas chromatography (GC) using an Agilent 6890 N GC model equipped with a 7683B series autosampler, fitted with a DB-5 capillary column and an FID detector. They were also identified and their structures confirmed by gas chromatography-mass spectrometry (GC-MS). Response factors of the reaction products (mainly mono- and diethyl succinate, although increasing quantities of other by-products including esters from acetic, lactic and pyruvic acids were observed when decreasing the purity of the crystals) were determined with respect to SA from GC analysis using known compounds in calibration mixtures of specified compositions.

Results and discussion

Table 2 shows the pK_a values and solubility of common carboxylic acids found in *A. succinogenes* fermentation. Therefore, the adjustment of pH to 4.2 with HCl (Fig. 1B) could selectively crystallise SA as its solubility in water at 20 °C is only 5.8–6.8 wt% and the other acid by-products (*e.g.* acetic, formic and pyruvic acids) are water miscible at this temperature. For the recovery of SA in solution, two methodologies were proposed: a modification of the traditional calcium precipitation and a novel direct crystallisation method (Fig. 1).

The traditional methodology of calcium succinate crystallisation (Fig. 1A, Process I) is effective at removing proteins, sugars and other by-products including calcium salts. However, it is neither rapid nor energy efficient due to the potential loss of succinic acid with other by-products.[30] Also, the formation of gypsums and solid wastes causes additional handling and materials disposal costs.

Compared to that, our proposed direct crystallisation method (Fig. 1B, Process II), employing a simple and environmentally benign vacuum distillation and crystallisation methodology

Table 2 The pK_a values and the solubilities in water 20 °C of common organic acids produced in *A. succinogenes* fermentation

Acid	pK_a		Solubility in water at 20 °C	Melting point (°C)
	pK_1	pK_2		
Succinic	5.6	4.2	5.8–6.8% (wt)	188
Acetic	4.8	—	Fully miscible	16.5
Pyruvic	2.9	—	Miscible	11.8
Formic	3.8	—	Miscible	8.6

Table 3 Compositions of actual fermentation broths

Recovery process	Fermentation medium	Fermentation broth	Concentration (g L^{-1})			
			Acetic acid	Formic acid	Pyruvic acid	Succinic acid
I	Semi-defined	I	8.1	6.3	1.0	35.3
II	Wheat-derived	II	16.9	9.4	4.1	35.7

(employed as the final steps of recovery in Processes I and II), allowed the isolation of highly pure SA crystals in a similar way to that reported by Song *et al.*[13] This methodology was employed to increase the SA concentration (5-fold) as well as to remove the residual volatile organic acids (Table 3). As the final step of purification process, the crystallisation was carried out at 4 °C and colourless SA crystals were obtained after drying. The feasibility and effectiveness of the two proposed methodologies will be evaluated in the recovery of SA from both synthetic and actual fermentation broths.

Succinic acid recovery from synthetic fermentation broths

Table 4 presents a summary of the purity and yield of SA crystals recovered from synthetic fermentation broths (Solutions A to D) in Processes I and II. Overall, the purity of the recovered SA crystals was relatively high (89–97%). However, the crystal yields obtained by means of Process I were very low (20–27%) compared to those obtained in Process II (60–75%). Moreover, the recovery of SA crystals from solution C (containing complex components including flour hydrolysate and cell biomass) resulted in lower yields compared to Solutions A and B, as shown in Table 4 (20% *versus* 27 and 26%, respectively). This was likely due to the complex nature of flour hydrolysate and cell biomass. Significant amounts of SA were lost in the filtrate (Filtrate III; Fig. 1A), explaining the low yield obtained in Process I. These results also imply the calcium precipitation method was not the most appropriate to recover SA crystals with high purity and yield.

A significant improvement in the recovery of SA crystals was obtained using the direct crystallisation method (Process II) as compared to the modified calcium precipitation method (Process I). As shown in Table 4, SA recovery yield was more than double, resulting high crystal purity (over 90%). The highest purity and yield were achieved using Solution D in Process II (97% and 75%, respectively), implying Process II was a more effective method for SA recovery from synthetic fermentation broths due to a significant reduction of steps in the methodology.

Table 4 Summary of SA crystals recovered in Processes I and II. An initial volume of 100 mL was used for all solutions and fermentation broths

Process	Solution	Initial succinic acid concentration (g L^{-1})	Purity (%)	Yield (%)
I	A	51.6	93	27
I	B	41.2	89	26
I	C	45.1	90	20
I	Fermentation Broth I	35.3	30	13
II	A	51.6	90	61
II	D	50.1	97	75
II	Fermentation Broth II	35.7	45	28

Succinic acid recovery from fermentation broth produced by *A. succinogenes*

We then moved on to study the SA crystals recovery from actual fermentation broths. Table 4 shows the purity and yield of SA crystals obtained from actual fermentation broths produced by *A. succinogenes*.

The initial SA concentration in Fermentation Broth I was 35.3 g/L but only 13 g of SA crystals per L were isolated using the modified calcium precipitation method (Process I). We believe the activated carbon added to remove some of the impurities and by-products (that give the crystals a dark-brown colour) absorbed up to 27% SA from the solution. Despite the removal of such impurities, the purity of the recovered SA crystals was poor (30%, Table 4).

Compared to Process I, both purity and recovery yield were improved due to a simplification in the number of steps involved in Process II. The purity of the crystals was considerably increased (up to 45%, Table 4). Still, a substantial loss of SA (~11%) was observed as only 28 g/L SA were recovered out of the initial 35.7 g/L SA in Fermentation Broth II.

Esterifications of recovered SA crystals

Esterifications under conventional heating

Esterification reactions of the various SA crystals were then carried out to investigate the effect of the crystal purity on the rate of reaction. We have previously reported the esterification of pure SA in aqueous ethanol using solid acids as catalysts.[26–28] Under optimised conditions, Starbon®-400 acid provided quantitative conversion of pure SA within 5 h of reaction with a complete selectivity to the diester (diethyl succinate, DIES). The other solid acid catalysts (including the DARCO® sulfonated analogue) exhibited poor activities in the aqueous esterification (Table 5).

Table 5 Catalytic activity comparison (conversion and selectivity) of different materials in the esterification of pure SA in aqueous ethanol

Catalyst	Conversion$_{max}$ (mol%)	t (h)	Products	Selectivity$_{max}$ (mol%)	t (h)
Sulfated zirconia	>99	24	Monoester	50	23
			Diester	**45**	**23**
β-25	>95	14	Monoester	35	14
			Diester	**70**^{a}	**24**^{a}
DARCO®-SO$_3$H	>99	12	Monoester	52	10
			Diester	**90**	**19**
Starbon®-400-SO$_3$H	>99	5	Monoester	35	1.5
			Diester	**90**	**6**

^{a} Reaction not completed.

A comparison of the activities of the various solid acids in the esterification using pure and recovered SA crystals is shown in Fig. 2. Starbon®-400 acid was particularly active and selective in the esterification, with remarkably improved activities as compared to other commercial solid acids employed in the reaction (*e.g.* sulfated zirconia, zeolites). This water-tolerant acidic carbonaceous material was able to provide moderate to very good conversions of SA with very good selectivities to the diester (Fig. 2). The difference in selectivity to 100 mainly corresponds to monoester (monoethyl succinate). Of interest was also the decrease in conversion and selectivity to DIES with a decrease in the purity of the crystals (from pure to recovered SA crystals from the actual fermentation broth). The presence of impurities gave increasing quantities of by-products thus decreasing the selectivity to DIES.

Microwave-assisted esterifications

Microwave-assisted reactions were conducted to compare the activities of the solid acids to those obtained under conventional heating. The effect of the power, the time of reaction and the quantity of catalyst were investigated. The optimised reaction conditions are shown in Fig. 3. Time of microwave reaction was found to be the critical parameter in the reaction, doubling the activity and selectivity to DIES in the systems from 15 to 30 min (DIES starts building up from the monoester). An increase in the power output (from 100 to 300 W) increased the conversion and selectivity to DIES as expected, so 300 W (maximum power output, 140 °C max. temperature reached) was selected as the optimised power (Fig. 3). Increasing quantities of catalyst (from 0.01 to 0.1 g) improved the conversion in

the systems, but a further increase in catalyst amount (0.2 g) did not remarkably improve the conversion or selectivity in the systems, so 0.1 g catalyst was set as optimum. Under the optimised reaction conditions, Starbon®-400-SO$_3$H material exhibited almost quantitative conversion of recovered SA with a high selectivity to DIES after 15 min microwave irradiation. Interestingly, a small decrease in the rate of reaction was observed when decreasing the purity of SA compared to that of the esterifications run under conventional heating. This microwave protocol afforded comparable and even improved activities and selectivities in shorter times of reaction (15–30 min) compared to the conventional heating experiments.

Catalysts reuse

The solid acid catalysts were also reused in the esterification reaction. Results are shown in Fig. 4 for Starbon® acid. As previously reported, all materials were reusable in the esterification reaction.[24,26–28] In particular, Starbon®-400-SO$_3$H was reusable in the esterification up to five reuses, preserving most of its initial activity (Fig. 4). Nevertheless, an increasing loss in activity was found when decreasing the purity of the SA crystals (from pure to recovered SA from actual fermentation broth) in both esterifications run under conventional heating and microwave irradiation.

Diffuse reflectance Fourier-tranform infrared spectra (DRIFTS) of reused solid acids were recorded to further check the reasons for the partial deactivation in the materials when recovered SA was employed as substrate. Results are presented in Fig. 5 for sulfonated Starbon®-400. DRIFTS of reused Starbon® acid exhibited clear differences compared to the parent
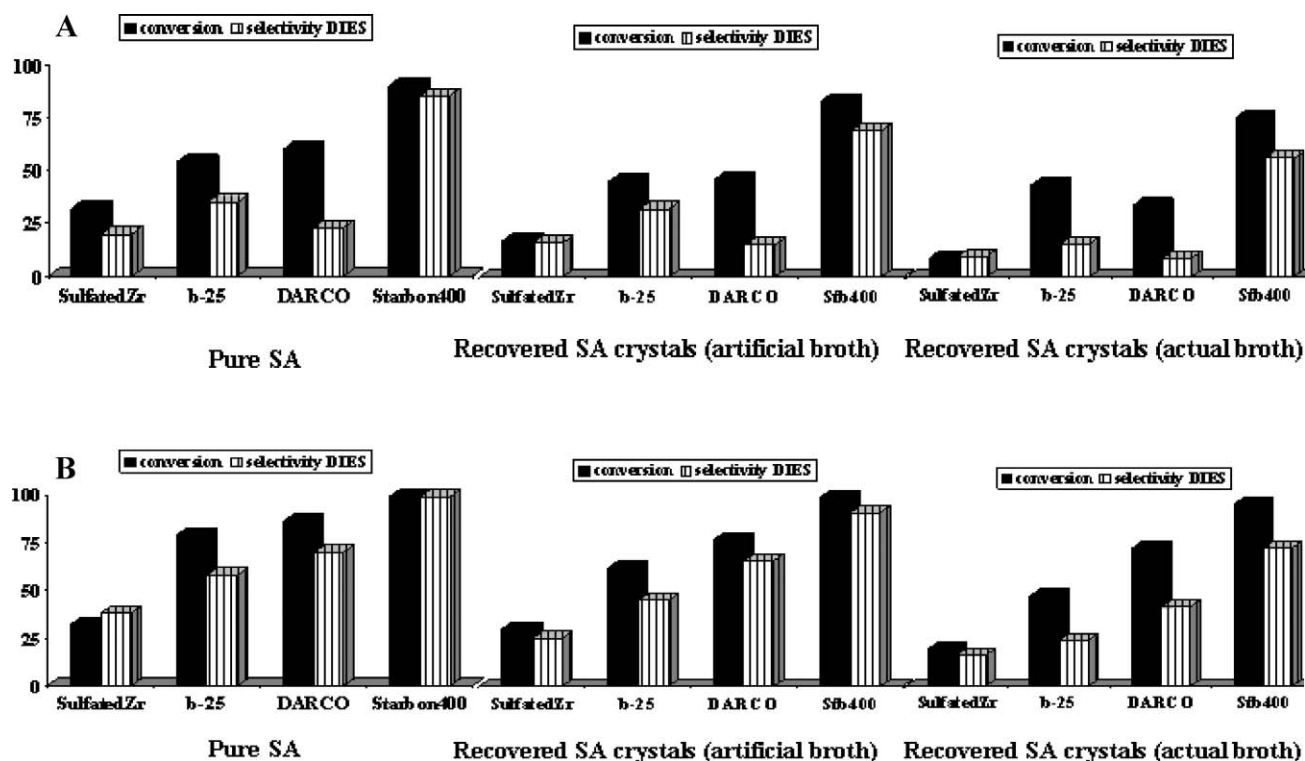
Fig. 2 Comparison of the activities of solid acid catalysts after (A) 4 h and (B) 12 h in the esterification of pure and recovered SA crystals in aqueous ethanol under conventional heating. *Reaction conditions*: 1 mmol SA, 30 mmol EtOH, 50 mmol H$_2$O, 0.1 catalyst, 80 °C, 4 or 12 h reaction.
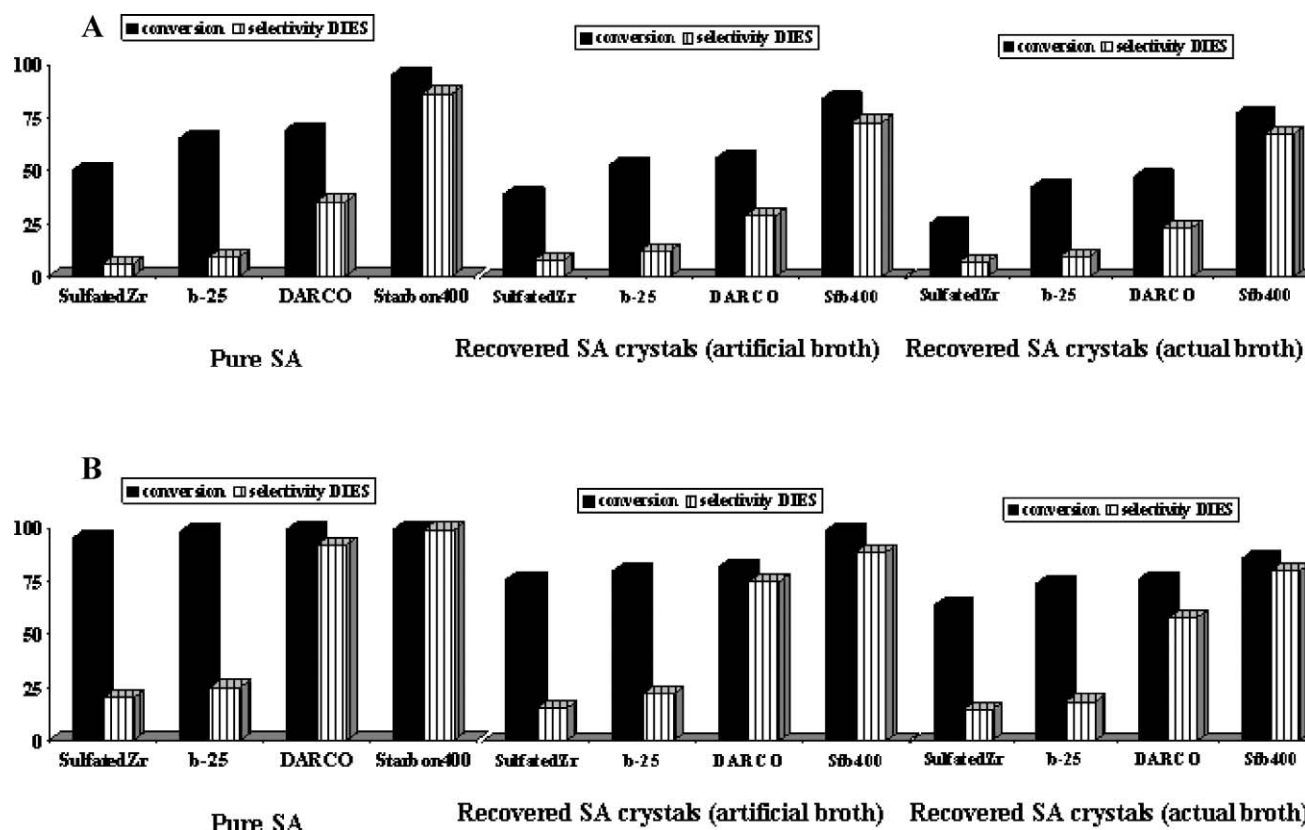
Fig. 3 Optimised microwave conditions (A) 15 min and (B) 30 min microwave irradiation in the esterification of recovered SA in aqueous ethanol using different solid acids. *Reaction conditions*: 1 mmol SA, 30 mmol EtOH, 50 mmol H_2O, 0.1 catalyst, 300 W (130–140 °C maximum temperature reached), 15 or 30 min microwave irradiation.
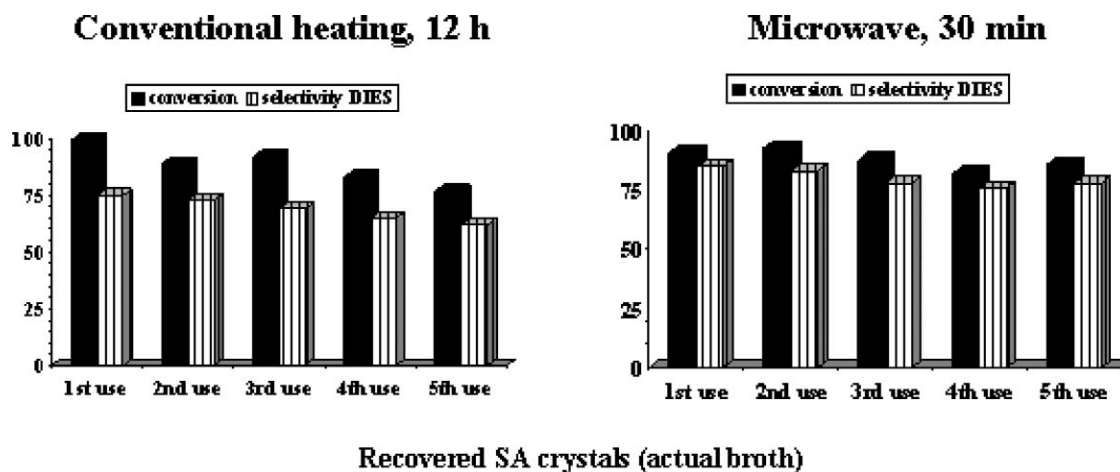
Fig. 4 Reuse of Starbon®-400-SO_3H in the esterification of recovered SA in aqueous ethanol under conventional heating (12 h, left) and microwave irradiation (30 min, right).

sulfonated and non-sulfonated materials. Bands appearing in the 1200–600 cm⁻¹ range, correlated to SO_3H groups in different environments,[31] did not significantly change after the esterification reaction. This indicates that there is no evidence of by-products and impurities present in SA crystals (*e.g.* aminoacids or peptides) directly reacting/bonding with/to SO_3H groups. However, the significant changes in the 1710 cm⁻¹ band (due to C=O$_{str}$) and 1600–1500 cm⁻¹ range (C=C$_{str}$, C–H$_{def}$) point to

the adsorption and/or deposition of organic compounds on the catalyst surface. The strong adsorption of these organic compounds, that can only be removed at temperatures higher than 200 °C, may be the reason of the loss in activity of the solid acids and the reduced reusability when impurities are present in SA crystals (Fig. 4). We also believe the slight decrease in activity and reusability of the microwave experiments compared to those of conventional heating can be attributed to a lower
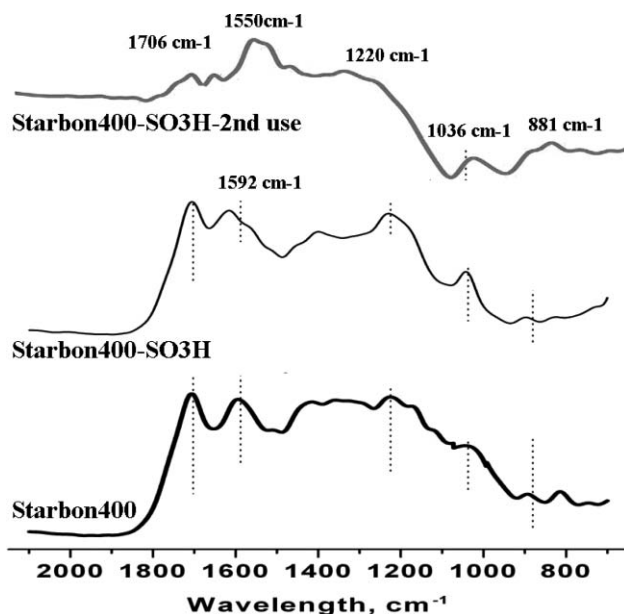
Fig. 5 DRIFTS spectra of parent Starbon®-400 and Starbon®-400-SO₃H materials compared to the 2nd use Starbon®-400-SO₃H (1st reuse) in the esterification reaction of SA in aqueous ethanol.

adsorption/deactivation of the catalysts due to shorter times of reaction in microwave irradiation (15–30 min) compared to longer conventional heating experiments (4–12 h).

Conclusions

A simple, effective and environmentally friendly direct crystallisation process (*via* vacuum distillation and crystallisation) has been developed for the recovery of SA crystals with high purity from fermentation broths. Compared to the traditional crystallisation method, the purity and recovery yield of SA crystals improved by 50% and 87%, respectively, using an actual fermentation broth produced by *A. succinogenes*. Recovered SA crystals were tested as starting materials in the esterification of SA in aqueous ethanol using a range of solid acid catalysts under both conventional heating and microwave irradiation and results were compared with those of pure SA. The solid acids afforded moderate to very good conversions of SA and selectivities to diester. Starbon®-400-SO₃H is the most active and selective catalyst in the reaction, with almost quantitative conversion and selectivity to the diester after 6–8 h. The microwave protocol improved the conventional heating results, providing quantitative conversions and selectivities within 30 min of reaction.

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Microwave-assisted synthesis in aqueous medium of new quinazoline derivatives as anticancer agent precursors

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Fast and eco-friendly microwave-irradiated reactions permitting the "green synthesis" of new 2-substituted quinazoline derivatives in aqueous medium *via* S-alkylation or $S_{RN}1$ reaction from 2-chloromethyl-3-methylquinazolin-4(3H)-one derivatives with different benzenesulfinic acids and nitronate anions, are reported herein.

Introduction

Within the last few years, green chemistry has become a major interest for the chemistry community.[1] The investigations and applications of green chemistry principles have led to the development of cleaner and more benign chemical processes, many new technologies being developed each year.[2]

In most chemical processes, major adverse effects towards the environment are due mainly to the consumption of energy for heating. To overcome this problem it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, to facilitate chemical reactions. At the same time, water can undoubtedly be considered as the cleanest solvent available for chemists.

Recently, the combination of these two prominent green chemistry principles, "microwaves" and "water", has become very popular and received substantial interest.[3]

On the other hand, quinazoline derivatives have shown a remarkable activity as antitubercular, anti-fungal, antimalarial and anticancer agents.[4] Indeed, quinazoline derivatives have been shown to be efficient and highly selective inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) *via* a competitive mechanism with the binding of ATP. These compounds are of potential interest as anticancer drugs, because EGFR is known to be over-expressed in many clinical cancers, and its overexpression is associated with poor prognosis.[5]

Characterization of molecules which are likely to interact with the EGFR and to inhibit selectively this tyrosine kinase activity, such as gefitinib (Iressa®) or erlofitinib (Tarceva®), has given rise to important hopes for both patients and clinitians (Scheme 1).

The growing medicinal importance of these heterocycles perpetuates to provide strong international effort for the development of synthetic methods for their preparation.

We have recently developed a new microwave-assisted method for synthesizing compounds in water.[6] The biological activity of the quinazoline derivatives led us to develop the synthesis of new

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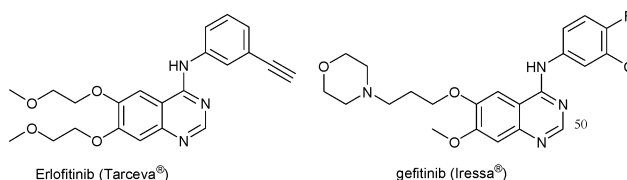
Scheme 1

2-subtituted quinazolines, under microwave irradiation, in aqueous medium. Substituents were selected with different electronic and solubility characteristics, with the aim of investigating the substituent effects at the 2-position.

Results and discussion

The majority of synthetic routes to 2-substituted quinazolin-4(3H)-ones is based on Niementowski's reaction, which involves the fusion (130–150 °C) of anthranilic acid analogues with amides, proceeding *via* an *o*-amidobenzamide intermediate.[7] The reaction yield in such conditions is variable and sometimes, complicated mixtures of carbonaceous compounds and impurities are formed, requiring a purification step with chromatography column.

For the above mentioned reasons, we studied extensively the synthesis of 2-chloromethylquinazolin-4(3H)-one **2** under microwave irradiation by various methods.

Conventional synthesis of **2** involves two steps, condensation of 2-aminobenzonitrile with an excess of chloroacetylchloride, affording 2-chloro-*N*-(2-cyanophenyl)acetamide **1**,[8] followed by Radziszewski's reaction using UHP (urea hydrogen peroxide) as a mild, safe and non-hazardous oxidizing agent, leading to 2-chloromethylquinazolin-4(3H)-one **2**.[9]

We initialy started by conducting the first step in both classical and microwave-assisted conditions (Scheme 2).

Scheme 2

In classical conditions, the product **1** is obtained in 54% yield after 3 h reaction time, whereas under microwave irradiation, the same product is isolated in 98% yield after only 4 minutes reaction time. We then compared classical conditions *versus* microwave-assisted conditions toward a second reaction step.

In classical conditions (30 h at 84 °C), the derivative **2** is obtained in 55% yield, and under microwave irradiation (1.5 h reaction time at 70 °C, measured by an infrared detector), the same product **2** is prepared in 78% yield (Scheme 3).
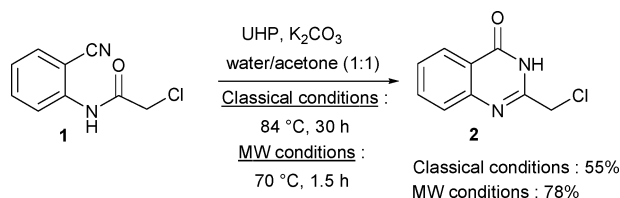
Scheme 3

Recently in the literature,[10] another method described the one pot solvent-free synthesis of **2**, from 2-aminobenzamide and 2-chloroacetic acid, under microwave irradiation (Scheme 4). This method consists in the fusion of 2-chloroacetic acid with 2-aminobenzamide. After several tests, we could not isolate the desired compound, using this method.

Scheme 4
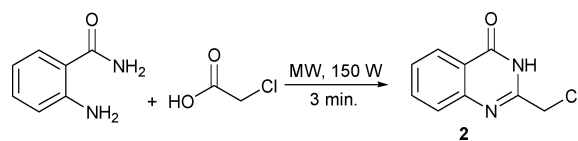
From the same 2-aminobenzamide, reacting with an excess of chloroacetylchloride under microwave irradiation, we formed the intermediate *N*-(2-aminophenyl)-2-chloroacetamide. The crude product was isolated and directly engaged in a cyclization, with K$_2$CO$_3$ in water, under microwave irradiation, leading to the expected product **2**, as shown in Scheme 5.

Scheme 5
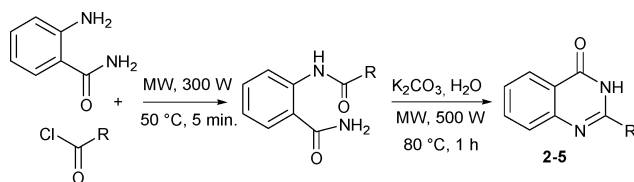
This method was generalized with various acid chlorides, enabling us to obtain compounds **2–5** in good yields (Table 1).

The 2-chloromethylquinazolin-4(3*H*)-one **2** can be methylated by using dimethylsulfate (DMS) in a water/THF (1:1) mixture and then, nitrated using the HNO$_3$–H$_2$SO$_4$ mixture, leading to 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7** in 63% global yield (Scheme 6).

Aiming at avoiding the last nitration step, we investigated another synthetic procedure for the preparation of 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one **7**, starting from the 2-amino-5-nitrobenzonitrile. Unfortunately, the yields we

Table 1 Reactions of 2-aminobenzamide with various acid chlorides

N°	Product	Yield
2		87
3		81
4		83
5		72
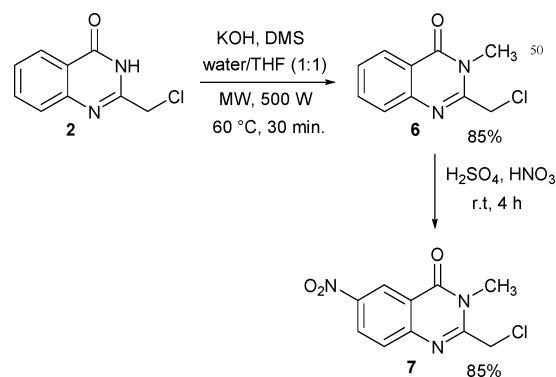
Scheme 6

obtained, were appreciably lower than those previously observed (Scheme 7). However, this method permitted us to confirm the position of the nitro group on the quinazoline ring, firstly determined by NMR study.

Scheme 7
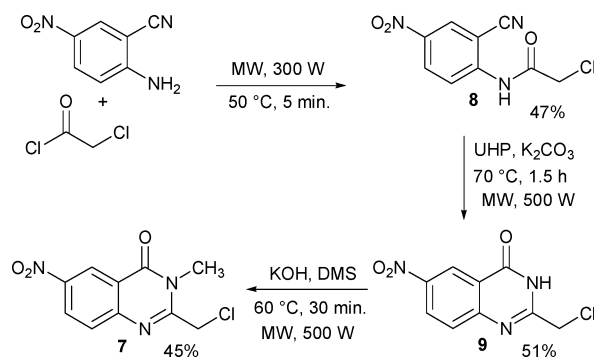
Recently, we described a "green chemistry procedure" allowing the substitution of a chloride atom by a sulfone group.[6] This

ecofriendly methodology in aqueous phase using microwave technology to ensure respect of the environment, was developed for the preparation of new 2-substituted quinazolines (Table 2). Experimentaly, a simple addition of both 2-chloromethyl-3-

Table 2 Reactions of 2-chloromethyl-3-methyl quinazolin-4(3H)-one derivatives **6**, **7** with benzenesulfinic acid anions **10a–j**[a]

Anion	Product	Yield $R_1 = H$	Yield $R_1 = NO_2$
10a	**11a-12a**	68	95
10b	**11b-12b**	71	91
10c	**11c-12c**	66	71
10d	**11d-12d**	67	67
10e	**11e-12e**	67	69
10f	**11f-12f**	60	63
10g	**11g-12g**	—	75
10h	**11h-12h**	—	59
10i	**11i-12i**	57	—
10j	**11j-12j**	54	—

[a] Microwave instrumentation: the temperature was measured by an infrared detector, and the microwave pulsed power was regulated by the software of terminal 320 for Ethos start, Milestone Inc. Reaction conditions: 1 h, microwave power 300 W, 100 °C.

methylquinazolin-4(3H)-one derivatives **6**, **7** and the sodium salt of benzenesulfinic acid **10a–j** in an aqueous solution gave the corresponding S-alkylated product **11a–j** and **12a–j** in high yields (Scheme 8).

Scheme 8
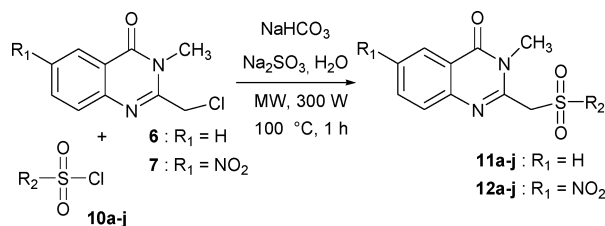
When the same reaction was carried out under classical conditions (24 h, 100 °C), 2-chloromethyl-3-methyl quinazolin-4(3H)-one **6** reacted with the benzenesulfonyl chloride, leading to the same product **11a**, with a lower yield (70%).

The above results show the activation of the S-alkylation reaction by microwave heating.

In order to extend the chemical variability in position 2, we applied the microwave technology to the $S_{RN}1$ reaction in the quinazoline series. Thus, compound **7** was treated with 2-nitropropane anion **13a** to afford the ethylenic derivative **15a** as shown in Scheme 9.

Scheme 9
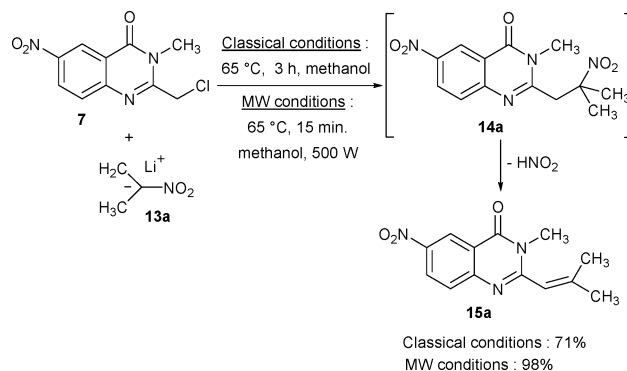
The C-alkylated product **14a** was not isolated because the nitrous acid elimination is very rapid in basic medium, due to the acidity of the methylene protons.
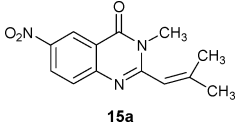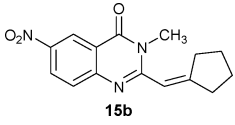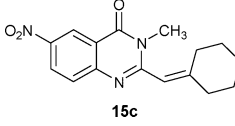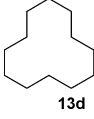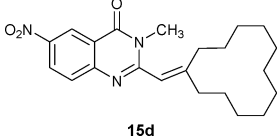
The best reaction yield (98%) of **15a** was obtained when the reaction was carried out under 500 W microwave power, during 15 minutes, in methanol using 3 equivalents of 2-nitropropane anion **13a**. The electron transfer mechanism was confirmed by complete inhibition studies.[11]

From these interesting results, we sought to generalize this $S_{RN}1$ reaction in the quinazoline series to various nitronate anions **13b–d** (Table 3).

It was described that the thermal effects and specific effects induced by the microwave field can be observed for polar mechanisms when the polarity is increased during the reaction, from the ground state (GS) towards the transition state (TS).[12]

We recently observed that the TS for S-alkylation reaction (S_N2 mechanism) involves loose ion pairs as a charge delocalised

Table 3 Reactions of 2-chloromethyl-3-methylquinazolin-4(3*H*)-one derivatives **7** with several nitronate anions **13a–d**[a]

Anion	Product	Yield
13a	**15a**	98
13b	**15b**	97
13c	**15c**	95
13d	**15d**	93

[a] Microwave instrumentation: the temperature was measured by an infrared detector, and the microwave pulsed power was regulated by the software of terminal 320 for Ethos start, Milestone Inc. Reaction conditions: 15 min, microwave power 500 W, 65 °C.

(soft) anion,[6] whereas the GS involves a neutral electrophile and tighter ion pair. During the course of the reaction, ionic dissociation is increased and that way, polarity is enhanced from GS to TS. Thus, a favourable microwave effect can be observed. It is the same for the $S_{RN}1$ reactions using charged species such as the nitroalkane lithium salts and radicals or radical anions derived from **7**.

All the quinazoline derivatives obtained are to be screened for their antitumor activity. Their cytotoxicity is under evaluation in triplicate on colon adenocarcinoma cell line (HT29 and SW620) and vulvar epidermoid carcinoma cell line (A431), in order to evaluate the activity of the prepared 2-substituted quinazolines on the EGFR signaling.

Conclusion

In the present study, we have investigated the preparation of new anticancer agent precursors in a quinazoline series. Using dedicated microwave irradiation in aqueous medium, the Niementowski reaction could be easily and rapidly performed, affording the intermediate 2-chloromethyl-6-nitroquinazolin-4(3*H*)-one **9** in very good yield. This compound served as a substrate for the synthesis of several new quinazolines, bearing various substituents in position 2. The present synthetic method is a simple, efficient, inexpensive and green approach for the preparation of 2-substituted quinazolines *via* S-alkylation or $S_{RN}1$ reactions in aqueous medium.

These new quinazoline derivatives could be employed as intermediates in the synthesis of more complex quinazolines,

properly substituted in position 4, as potential inhibitors of the EGFR.

Experimental

General experimental

Melting points were determined on a Büchi B-540 and are uncorrected. Elemental analyses were performed by the Micro-analyses center of the University of Aix-Marseille 3, France. Both ^{1}H and ^{13}C NMR spectra were determined on a Bruker ARX 200 spectrometer. The ^{1}H chemical shifts are reported as ppm downfield from tetramethylsilane (Me$_4$Si), and the ^{13}C chemical shifts were referenced to the solvent peak: CDCl$_3$ (76.9 ppm) or DMSO-d_6 (39.5 ppm). Solvents were dried by conventional methods. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC were performed on 5 cm × 10 cm aluminium plates coated with silica gel 60F-254 (Merck) in an appropriate solvent.

Microwave instrumentation

Multimode reactors. ETHOS Synth Lab station and MicroSYNTH Lab terminal 1024 (Ethos start, Milestone Inc.). The multimode microwave has a twin magnetron (2 × 800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During experiments, time, temperature and power were measured with the "easy WAVE" software package. The temperature was measured throughout the reaction and evaluated by an infrared detector or an optical fiber (ATC-FO 300).

In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (amount of reactants and temperature) using a thermostated oil bath. The temperature was measured by the insertion of a Quick digital thermometer into the reaction mixture and the rate of the temperature rise was adjusted to be the same as measured under microwave irradiation.

Experimental procedure

2-Chloro-*N*-(2-cyanophenyl)acetamide 1

Classical method.[8]

Microwave method. To a solution of 2-aminobenzonitrile (5 g, 42.2 mmol) in pyridine (10.2 mL, 126.7 mmol), chloroacetylchloride (5.7 mL, 71.8 mmol) diluted in DMF (48 mL) was added dropwise at 0 °C. The reaction mixture was irradiated in a microwave oven at 40 °C, for 4 min. at a power of 150 W. After cooling, 100 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 8.05 g (98%) of white solid, mp 116 °C (Lit.[8] 115–116 °C). δ_H (200 MHz; CDCl$_3$) 4.26 (s, 2H, CH$_2$Cl), 7.21–7.28 (m, 1H, H ar), 7.59–7.67 (m, 2H, H ar), 8.38 (d, *J* = 8.8 Hz, 1H, H ar), 8.86 (bs, 1H, NH). δ_C (50 MHz; CDCl$_3$) 42.9, 102.9, 115.8, 121.1, 125.1, 132.4, 134.2, 139.3, 164.3.

2-Chloromethylquinazolin-4(3*H*)-one 2

To a mixture of **1** (5.76 g, 29.6 mmol) and acetone/H_2O (v/v 1:1, 160 mL) was added K_2CO_3 (0.8 g, 5.8 mmol) and UHP (5.6 g, 59.2 mmol). The reaction mixture was irradiated in a microwave oven at 70 °C, for 1.5 h at a power of 500 W. After cooling, 100 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 4.49 g (78%) of white solid, mp 249–250 °C (Lit.[9] 247–248 °C). δ_H (200 MHz; DMSO-d_6) 4.55 (s, 2H, CH$_2$Cl), 7,51–7.58 (m, 1H, H ar), 7.68 (d, J = 8.1 Hz, 1H, H ar), 7.80–7.87 (m, 1H, H ar), 8.12 (d, J = 8.1 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 43.4, 121.4, 126.0, 127.4, 134.8, 148.4, 152.5, 161.7.

General procedure for the synthesis of 2-chloromethylquinazolin-4(3*H*)-one 2–5, from 2-aminobenzamide, *via* the corresponding 2-amidobenzamide derivatives

First step: a mixture of 2-aminobenzamide (1 g, 7.40 mmol) and corresponding acid chloride derivative (6 eq) was irradiated in a microwave oven at 50 °C, for 5 min. at a power of 300 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). A white solid was obtained and directly engaged in the second step.

Second step: a mixture of the corresponding intermediate compound and K_2CO_3 (0.5 eq) in water (40 mL), was irradiated in a microwave oven at 80 °C for 1 h at a power of 500 W. After cooling, 60 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave the expected compound **2–5**.

2-Methylquinazolin-4(3*H*)-one 3

Light yellow solid, mp 230–231 °C, (Lit.[13] 229–230 °C). δ_H (200 MHz; CDCl$_3$) 2.26 (s, 3H, CH$_3$), 7.43–7.62 (m, 2H, H ar), 7.66–7.82 (m, 1H, H ar) 8.24 (d, J = 8.1 Hz, 1H, H ar), 11.09 (bs, 1H, NH). δ_C (50 MHz; CDCl$_3$) 24.1,126.9, 128.9, 130.0, 131.9, 135.0, 147.8, 154.5, 163.2.

2-(2-Nitrophenyl)quinazolin-4(3*H*)-one 4

Light yellow solid, mp 212 °C, (Lit.[14] 210–212 °C). δ_H (200 MHz; DMSO-d_6) 7.49–7.61 (m, 2H, H ar), 7.65 (d, J = 8.4 Hz, 1H, H ar) 7.81–7.95 (m, 4H, H ar), 8.21 (t, J = 8.1 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 121.1, 124.4, 125.9, 127.0, 127.2, 129.2, 131.3, 131.7, 134.1, 134.7, 147.5, 148.5, 151.6, 161.5.

2-Phenylquinazolin-4(3*H*)-one 5

Light yellow solid, mp 241 °C, (Lit.[13] 241–242 °C). δ_H (200 MHz; CDCl$_3$) 7.48–7.60 (m, 4H, H ar), 7.78–7.91 (m, 2H, H ar), 8.24–8.35 (m, 3H, H ar). δ_C (50 MHz; CDCl$_3$) 120.8, 126.4, 126.8, 127.5, 127.5, 127.9, 129.0, 129.0, 131.7, 132.7, 134.9, 149.4, 151.8, 163.8.

2-Chloromethyl-3-methylquinazolin-4(3*H*)-one 6

2-Chloromethylquinazolin-4(3*H*)-one **2** (1.56 g, 8.02 mmol), dimethyl sulfate (1.52 ml, 16.04 mmol) and potassium hydroxide (0.78 g, 13.9 mmol) were intimately mixed in a solution THF/H_2O (v/v 1:1, 40 mL). The reaction mixture was irradiated in a microwave oven, at 60 °C, for 30 min. at a power of 500 W. After cooling, 60 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). The product was recrystallized from 2-propanol gave 1.43 g (85%) of yellow solid, mp 185 °C (Lit.[15] 182 °C), δ_H (200 MHz; CDCl$_3$) 3.77 (s, 3H, N-CH$_3$), 4.65 (s, 2H, CH$_2$Cl), 7,48–7.56 (m, 1H, H ar), 7.66–7.81 (m, 2H, H ar), 8.29 (dd, J = 2.4 Hz, J = 8.2 Hz, 1H, H ar). δ_C (50 MHz; CDCl$_3$) 30.7, 44.4, 120.8, 126.9, 127.4, 134.4, 146.6, 151.6, 162.1.

The same method was used to prepare compound **7** from **9**, by methylation.

2-Chloromethyl-3-methyl-6-nitroquinazolin-4(3*H*)-one 7

To a solution of 2-chloromethyl-3-methylquinazolin-4(3*H*)-one **6** (1.18 g, 5.65 mmol) in concentrated sulfuric acid (12.7 mL), fuming nitric acid (1.3 mL) was added dropwise at 0 °C. The reaction mixture was stirred at the room temperature for 4 h, poured into crushed ice (100 mL). A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). Recrystallization from 2-propanol gave 1.22 g (85%) of yellow solid, mp 178–179 °C, (Found: C, 47.05; H, 3.24; N, 16.90. C$_{10}$H$_8$ClN$_3$O$_3$ requires C, 47.35; H, 3.18; N, 16.57%). δ_H (200 MHz; CDCl$_3$) 3.80 (s, 3H, N-CH$_3$), 4.66 (s, 2H, CH$_2$Cl), 7.82 (d, J = 9.1 Hz, 1H, H ar), 8.55 (dd, J = 2.5, J = 9.1 Hz, 1H, H ar), 9.15 (d, J = 2.5 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 31.1, 44.1, 121.0, 123.6, 128.5, 129.2, 146.3, 150.6, 154.8, 161.1.

2-Chloro-*N*-(2-cyano-4-nitrophenyl)acetamide 8

A mixture of 2-amino-5-nitrobenzonitrile (1 g, 6.13 mmol) and corresponding acid chloride (6 eq) was irradiated in a microwave oven at 50 °C, for 5 min. at a power of 300 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in vacuum drying oven (dessicator cabinet). A brown solid was obtained in 47% yield and directly engaged in the second step, mp 159 °C (Lit.[16] 157–159 °C).

2-Chloromethyl-6-nitroquinazolin-4(3*H*)-one 9

To a mixture of 2-chloro-*N*-(2-cyano-4-nitrophenyl)acetamide **8** (0.5 g, 2.08 mmol) and acetone/H_2O (v/v 1:1, 20 mL) was added K_2CO_3 (0.06 g, 0.42 mmol) and UHP (0.4 g, 4.16 mmol). The reaction mixture was irradiated in a microwave oven at 70 °C, for 1.5 h at a power of 500 W. After cooling, 50 mL of water were added. A precipitate appeared and was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). The product required was recrystallized from 2-propanol gave 0.25 g (51%) of yellow solid, mp 235 °C, (Found: C, 44.81; H, 2.61; N, 17.64. C$_9$H$_6$ClN$_3$O$_3$ requires C, 45.11; H, 2.52; N, 17.54%). δ_H (200 MHz; DMSO-d_6) 4.61 (s, 2H, CH$_2$Cl), 7.89 (d, J = 8.9 Hz, 1H, H ar), 8.57 (dd, J = 2.7,

J = 8.9 Hz, 1H, H ar), 8.81 (d, J = 2.7 Hz, 1H, H ar) δ_C (50 MHz; DMSO-d_6) 43.4, 121.9, 122.4, 129.0, 129.5, 145.8, 152.9, 156.5, 161.3.

General procedure for the synthesis of the sulfonylmethyl-quinazolin-4(3H)-one derivatives (11a–j and 12a–j)

The sodium salts were commercially available or prepared as previously described.[17]

Conventional conditions. To a solution of benzenesulfonyl chloride (2 eq), NaHCO₃ (0.34 g, 1.92 mmol), Na₂SO₃ (2 eq) in water (30 mL) at 100 °C, was added 2-chloromethyl-3-methylquinazolin-4(3H)-one **6** (0.2 g, 0.96 mmol). The reaction mixture was heated at 100 °C for 24 h and filtered. The precipitate was filtered, washed with 3 × 20 mL of water and dried in a low pressure drying oven. The product required **11a** was recrystallized from 2-propanol.

Microwave irradiation conditions. To a solution of substituted sulfonyl chloride (2 eq), NaHCO₃ (2 eq), Na₂SO₃ (2 eq) in water (30 mL) was added 2-chloromethyl-3-methylquinazolin-4(3H)-one **6** (0.2 g, 0.96 mmol) or 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3H)-one **7** (0.2 g, 0.79 mmol). The reaction mixture was irradiated in a microwave oven, at 100 °C, for 1 h at a power of 300 W. The precipitate was filtered, washed with water (3 × 20 mL) and dried in a vacuum drying oven (dessicator cabinet). The product required was recrystallized from 2-propanol.

3-Methyl-2-(phenylsulfonylmethyl)quinazolin-4(3H)-one 11a

White solid, mp 186 °C, (Found: C, 61.19; H, 4.47; N, 8.93. C₁₆H₁₄N₂O₃S requires C, 61.13; H, 4.49; N, 8.91%). δ_H (200 MHz; CDCl₃) 3.85 (s, 3H, CH₃), 4.72 (s, 2H, CH₂), 7.34 (d, J = 8.3 Hz, 1H, H ar), 7.45–7.56 (m, 3H, H ar), 7.64–7.73 (m, 2H, H ar), 7.84 (m, 2H, H ar), 8.26 (dd, J = 2.3 Hz, J = 8.3 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 32.0, 62.1, 120.7, 127.0, 127.1, 127.7, 128.7, 129.2, 134.2, 134.3, 138.0, 146.2, 146.3, 162.0.

3-Methyl-2-(tosylmethyl)quinazolin-4(3H)-one 11b

White solid, mp 178 °C, (Found: C, 62.15; H, 5.00; N, 8.54. C₁₇H₁₆N₂O₃S requires C, 62.18; H, 4.91; N, 8.53%). δ_H (200 MHz; CDCl₃) 2.44 (s, 3H, CH₃), 3.83 (s, 3H, CH₃), 4.69 (s, 2H, CH₂), 7.30 (d, J = 8.5 Hz, 2H, H ar), 7.38 (d, J = 8.5 Hz, 1H, H ar), 7.44–7.54 (m, 1H, H ar), 7.65–7.74 (m, 3H, H ar), 8.27 (dd, J = 2.4 Hz, J = 8.5 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 21.3, 32.1, 62.0, 120.6, 126.8, 127.0, 127.8, 128.8, 129.8, 134.4, 135.2, 145.6, 146.0, 146.6, 161.8.

2-[(4-Chlorophenylsulfonyl)methyl]-3-methylquinazolin-4(3H)-one 11c

White solid, mp 207 °C, (Found: C, 55.03; H, 3.72; N, 7.98. C₁₆H₁₃ClN₂O₃S requires C, 55.09; H, 3.76; N, 8.03%). δ_H (200 MHz; CDCl₃) 3.84 (s, 3H, CH₃), 4.67 (s, 2H, CH₂), 7.29 (d, J = 8.4 Hz, 1H, H ar), 7.44–7.54 (m, 3H, H ar), 7.65–7.75 (m, 3H, H ar), 8.26 (dd, J = 2.2 Hz, J = 8.4 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 32.0, 61.9, 120.6, 126.8, 127.0, 127.9, 129.4, 130.3, 134.5, 136.4, 141.3, 146.0, 146.2, 161.8.

2-[(4-Fluorophenylsulfonyl)methyl]-3-methylquinazolin-4(3H)-one 11d

White solid, mp 184 °C, (Found: C, 57.88; H, 3.96; N, 8.43. C₁₆H₁₃FN₂O₃S requires C, 57.82; H, 3.94; N, 8.43%). δ_H (200 MHz; CDCl₃) 3.84 (s, 3H, CH₃), 4.67 (s, 2H, CH₂), 7.12–7.21 (m, 2H, H ar), 7.28 (d, J = 8.9 Hz, 1H, H ar), 7.45–7.53 (m, 1H, H ar), 7.64–7.72 (m, 1H, H ar), 7.76–7.84 (m, 2H, H ar), 8.26 (dd, J = 2.1 Hz, J = 8.9 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 32.0, 62.0, 116.6, 120.6, 120.7, 126.9, 127.0, 127.9, 131.7, 131.9, 133.9, 134.5, 146.1, 146.3, 161.9, 163.7, 166.3.

2-[(4-Bromophenylsulfonyl)methyl]-3-methylquinazolin-4(3H)-one 11e

White solid, mp 217 °C, (Found: C, 48.46; H, 3.28; N, 6.83. C₁₆H₁₃BrN₂O₃S requires C, 48.87; H, 3.33; N, 7.12%). δ_H (200 MHz; CDCl₃) 3.84 (s, 3H, CH₃), 4.66 (s, 2H, CH₂), 7.29 (d, J = 8.2 Hz, 1H, H ar), 7.46–7.55 (m, 1H, H ar), 7.64–7.74 (m, 5H, H ar), 8.26 (dd, J = 2.9 Hz, J = 8.2 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 32.0, 62.0, 120.7, 126.9, 128.0, 129.9, 130.3, 132.4, 134.5, 135.3, 137.0, 146.1, 146.2, 162.0.

3-Methyl-2-[(4-nitrophenylsulfonyl)methyl]quinazolin-4(3H)-one 11f

White solid, mp 273 °C, (Found: C, 53.54; H, 3.61; N, 11.32. C₁₆H₁₃N₃O₅S requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; DMSO-d_6) 3.68 (s, 3H, CH₃), 5.32 (s, 2H, CH₂), 7.32 (d, J = 8.5 Hz, 1H, H ar), 7.49–7.56 (m, 1H, H ar), 7.72–7.80 (m, 1H, H ar), 8.11 (d, J = 8.5 Hz, 1H, H ar), 8.19 (d, J = 9.1 Hz, 2H, H ar), 8.41 (d, J = 9.1 Hz, 2H, H ar). δ_C (50 MHz; DMSO-d_6) 31.8, 60.2, 120.6, 124.7, 126.8, 127.2, 128.1, 131.0, 135.1, 144.7, 146.5, 147.7, 151.2, 161.6.

3-Methyl-2-[(3-nitrophenylsulfonyl)methyl]quinazolin-4(3H)-one 11i

White solid, mp 233 °C, (Found: C, 53.52; H, 3.65; N, 11.58. C₁₆H₁₃N₃O₅S requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; CDCl₃) 3.86 (s, 3H, CH₃), 4.74 (s, 2H, CH₂), 7.18 (d, J = 8.7 Hz, 1H, H ar), 7.46–7.54 (m, 1H, H ar), 7.62–7.75 (m, 2H, H ar), 8.06–8.15 (m, 1H, H ar), 8.27 (dd, J = 2.3 Hz, J = 8.7 Hz, 1H, H ar), 8.50–8.55 (m, 1H, H ar), 8.71 (m, 1H, H ar). δ_C (50 MHz; CDCl₃) 31.9, 61.6, 120.7, 124.5, 126.7, 127.2, 128.1, 128.7, 130.3, 134.4, 134.6, 140.0, 145.8, 146.0, 148.3, 161.7.

3-Methyl-2-[(thiophen-2-ylsulfonyl)methyl]quinazolin-4(3H)-one 11j

White solid, mp 189 °C, (Found: C, 52.55; H, 3.86; N, 8.70. C₁₄H₁₂N₂O₃S₂ requires C, 52.48; H, 3.78; N, 8.74%). δ_H (200 MHz; CDCl₃) 3.84 (s, 3H, CH₃), 4.83 (s, 2H, CH₂), 7.12–7.16 (m, 1H, H ar), 7.43–7.55 (m, 2H, H ar), 7.66–7.76 (m, 3H, H ar), 8.28 (d, J = 8.6 Hz, 1H, H ar). δ_C (50 MHz; CDCl₃) 32.0, 63.0, 120.6, 127.0, 127.8, 128.0, 134.4, 135.4, 135.8, 138.4, 146.2, 146.3, 161.8.

3-Methyl-6-nitro-2-(phenylsulfonylmethyl)quinazolin-4(3H)-one 12a

Yellow solid, mp 202 °C, (Found: C, 53.17; H, 3.71; N, 11.70. $C_{16}H_{13}N_3O_5S$ requires C, 53.48; H, 3.65; N, 11.69%). δ_H (200 MHz; CDCl$_3$) 3.87 (s, 3H, CH$_3$), 4.71 (s, 2H, CH$_2$), 7.41 (d, J = 8.9 Hz, 1H, H ar), 7.51–7.58 (m, 2H, H ar), 7.67–7.74 (m, 1H, H ar), 7.82–7.86 (m, 2H, H ar), 8.44 (dd, J = 2.1 Hz, J = 8.9 Hz, 1H, H ar), 9.10 (d, J = 2.1 Hz, 1H, H ar). δ_C (50 MHz; CDCl$_3$) 32.4, 62.2, 120.8, 123.7, 128.4, 128.7, 129.3, 134.6, 137.9, 146.1, 149.8, 150.1, 154.2, 160.8.

3-Methyl-6-nitro-2-(tosylmethyl)quinazolin-4(3H)-one 12b

Yellow solid, mp 241 °C, (Found: C, 54.51; H, 4.07; N, 11.28. $C_{17}H_{15}N_3O_5S$ requires C, 54.68; H, 4.05; N, 11.25%). δ_H (200 MHz; DMSO-d_6) 2.46 (s, 3H, CH$_3$), 3.87 (s, 3H, CH$_3$), 4.72 (s, 2H, CH$_2$), 7.34 (d, J = 8.9 Hz, 2H, H ar), 7.53 (d, J = 9.3 Hz, 1H, H ar), 7.73 (d, J = 8.9 Hz, 2H, H ar), 8.48 (dd, 1H, J = 2.3 Hz, J = 9.3 Hz, 1H, H ar), 9.11 (d, J = 2.3 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 21.6, 32.3, 61.2, 120.5, 122.9, 128.9, 129.1, 130.1, 136.2, 145.5, 145.9, 150.5, 151.6, 161.0.

2-[(4-Chlorophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3H)-one 12c

Yellow solid, mp 260 °C, (Found: C, 48.49; H, 3.07; N, 10.52. $C_{16}H_{12}ClN_3O_5S$ requires C, 48.80; H, 3.07; N, 10.67%). δ_H (200 MHz; DMSO-d_6) 3.71 (s, 3H, CH$_3$), 5.29 (s, 2H, CH$_2$), 7.56 (d, J = 9.4 Hz, 1H, H ar), 7.70 (d, J = 8.3 Hz, 2H, H ar), 7.93 (d, J = 8.3 Hz, 2H, H ar), 8.52 (dd, J = 2.8 Hz, J = 9.4 Hz, 1H, H ar), 8.80 (d, J = 2.8 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.7, 120.6, 122.7, 129.0, 129.7, 131.1, 137.8, 139.9, 146.0, 150.4, 151.6, 161.0.

2-[(4-Fluorophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3H)-one 12d

Yellow solid, mp 234 °C, (Found: C, 50.69; H, 3.26; N, 10.91. $C_{16}H_{12}FN_3O_5S$ requires C, 50.93; H, 3.21; N, 11.14%). δ_H (200 MHz; DMSO-d_6) 3.69 (s, 3H, CH$_3$), 5.24 (s, 2H, CH$_2$), 7.42 (d, J = 9.1 Hz, 1H, H ar), 7.52 (d, J = 9.6 Hz, 2H, H ar), 7.95 (m, 2H, H ar), 8.49 (dd, J = 2.4 Hz, J = 9.1 Hz, 1H, H ar), 8.77 (d, J = 2.4 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 31.9, 60.5, 116.5, 120.2, 122.6, 128.7, 132.1, 134.9, 145.6, 150.1, 151.3, 160.7, 165.5.

2-[(4-Bromophenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3H)-one 12e

Yellow solid, mp 247 °C, (Found: C, 43.65; H, 2.69; N, 9.27. $C_{16}H_{12}BrN_3O_5S$ requires C, 43.85; H, 2.76; N, 9.59%). δ_H (200 MHz; DMSO-d_6) 3.71 (s, 3H, CH$_3$), 5.28 (s, 2H, CH$_2$), 7.57 (d, J = 9.1 Hz, 1H, H ar), 7.85 (m, 4H, H ar), 8.53 (dd, J = 3.0 Hz, J = 9.1 Hz, 1H, H ar), 8.80 (d, J = 3.0 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.7, 120.6, 122.9, 129.0, 131.1, 132.7, 137.3, 139.9, 146.0, 150.4, 151.6, 161.0.

3-Methyl-6-nitro-2-[(4-nitrophenylsulfonyl)methyl] quinazolin-4(3H)-one 12f

Yellow solid, mp 244 °C, (Found: C, 47.26; H, 2.91; N, 13.47. $C_{16}H_{12}N_4O_7S$ requires C, 47.53; H, 2.99; N, 13.86%). δ_H (200 MHz; DMSO-d_6) 3.70 (s, 3H, CH$_3$), 5.46 (s, 2H, CH$_2$), 7.52 (d, J = 8.6 Hz, 1H, H ar), 8.22 (d, J = 8.9 Hz, 2H, H ar), 8.42 (d, J = 8.9 Hz, 2H, H ar), 8.47 (dd, J = 2.5 Hz, J = 8.6 Hz, 1H, H ar), 8.77 (d, J = 2.5 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.3, 60.2, 120.7, 123.0, 124.7, 129.1, 129.3, 131.1, 144.5, 146.1, 150.3, 151.3, 151.5, 161.0.

2-[(4-methoxyphenylsulfonyl)methyl]-3-methyl-6-nitro quinazolin-4(3H)-one 12g

Yellow solid, mp 217 °C, (Found: C, 52.38; H, 3.94; N, 10.46 $C_{17}H_{15}N_3O_6S$ requires C, 52.44; H, 3.88; N, 10.79%). δ_H (200 MHz; DMSO-d_6) 3.68 (s, 3H, CH$_3$), 3.85 (s, 3H, CH$_3$) 5.15 (s, 2H, CH$_2$), 7.11 (d, J = 8.7 Hz, 2H, H ar), 7.58 (d, J = 8.9 Hz, 1H, H ar), 7.80 (d, J = 8.7 Hz, 2H, H ar), 8.51 (dd, J = 2.6 Hz, J = 8.9 Hz, 1H, H ar), 8.79 (d, J = 2.6 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.0, 56.0, 61.1, 114.5, 120.2, 122.7, 128.6, 128.8, 130.1, 131.0, 145.6, 150.2, 151.5, 160.7, 163.9.

3-Methyl-6-nitro-2-[(2-nitrophenylsulfonyl)methyl] quinazolin-4(3H)-one 12h

Yellow solid, mp 232 °C, (Found: C, 47.79; H, 2.96; N, 13.46. $C_{16}H_{12}N_4O_7S$ requires C, 47.53; H, 2.99; N, 13.86%). δ_H (200 MHz; DMSO-d_6) 3.72 (s, 3H, CH$_3$), 5.50 (s, 2H, CH$_2$), 7.47 (d, J = 9.2 Hz, 1H, H ar), 7.85–7.92 (m, 1H, H ar), 7.98–8.11 (m, 3H, H ar), 8.48 (dd, J = 2.6 Hz, J = 9.2 Hz, 1H, H ar), 8.80 (d, J = 2.6 Hz, 1H, H ar). δ_C (50 MHz; DMSO-d_6) 32.1, 61.4, 120.4, 122.6, 125.1, 128.7, 130.7, 132.7, 133.1, 136.5, 145.7, 148.8, 150.1, 150.9, 155.0, 160.7.

General procedure for the synthesis of the 6-nitroquinazolin-4(3H)-one derivatives (15a–d)

The lithium salts were prepared as previously described.[18]

Classical conditions. To a solution of lithium salt of nitronate anion 13a (3 eq) in methanol (20 mL) was added 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3H)-one 7 (0.2 g, 0.79 mmol). The reaction mixture was heated (oil bath), to 65 °C, for 3 h. After evaporation of methanol, the residue was dissolved in ethyl acetate and washed with water (3 × 30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. Then, the product 15a was recrystallized from 2-propanol and dried in a vacuum drying oven (dessicator cabinet).

Microwave conditions. To a solution of lithium salt of nitronate anion 13a–d (3 eq) in methanol (20 mL) was added 2-chloromethyl-3-methyl-6-nitroquinazolin-4(3H)-one 7 (0.2 g, 0.79 mmol). The reaction mixture was irradiated in a microwave oven, at 65 °C, for 15 min. at a power of 500 W. After evaporation of methanol, the residue was dissolved in ethyl acetate and washed with water (3 × 30 mL). The organic layer was dried over magnesium sulfate and the solvent was removed under vacuum. Then, the corresponding product 15a–d was recrystallized from

2-propanol and dried in a vacuum drying oven (dessicator cabinet).

3-Methyl-2-(2-methylprop-1-enyl)-6-nitroquinazolin-4(3*H*)-one 15a

Yellow solid, mp 145 °C, (Found: C, 60.13; H, 5.01; N, 16.17. $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%). δ_H (200 MHz; CDCl$_3$) 2.06 (s, 3H, CH$_3$), 2.10 (s, 3H, CH$_3$), 3.63 (s, 3H, CH$_3$), 6.18 (s, 1H, CH), 7.76 (d, J = 8.8 Hz, 1H, H ar), 8.48 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H, H ar), 9.13 (d, J = 2.8 Hz, 1H, Har). δ_C (50 MHz; CDCl$_3$) 20.7, 27.1, 31.7, 117.4, 120.1, 123.6, 128.1, 128.5, 145.4, 150.7, 151.3, 156.2, 161.4.

2-(Cyclopentylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15b

Yellow solid, mp 175 °C, (Found: C, 62.98; H, 5.35; N, 14.68. $C_{15}H_{15}N_3O_3$ requires C, 63.15; H, 5.30; N, 14.73%). δ_H (200 MHz; CDCl$_3$) 1.80 (m, 4H, 2CH$_2$), 2.63 (t, J = 7.4 Hz, 2H, CH$_2$), 2.94 (t, J = 7.4 Hz, 2H, CH$_2$), 3.66 (s, 3H, CH$_3$), 6.40 (s, 1H, CH), 7.73 (d, J = 9.1 Hz, 1H, H ar), 8.46 (dd, J = 2.8 Hz, J = 9.1 Hz, 1H, H ar), 9.12 (d, J = 2.8 Hz, 1H, H ar). δ_C (50 MHz; CDCl$_3$) 25.5, 26.5, 31.1, 33.5, 36.9, 111.8, 119.7, 123.7, 128.0, 128.4, 145.0, 151.6, 156.0, 161.5, 167.3.

2-(Cyclohexylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15c

Yellow solid, mp 154 °C, (Found: C, 63.92; H, 5.79; N, 14.03. $C_{16}H_{17}N_3O_3$ requires C, 64.20; H, 5.72; N, 14.04%). δ_H (200 MHz; CDCl$_3$) 1.67 (m, 6H, 3CH$_2$), 2.39 (t, J = 6.3 Hz, 2H, CH$_2$), 2.59 (t, J = 6.3 Hz, 2H, CH$_2$), 3.64 (s, 3H, CH$_3$), 6.10 (s, 1H, CH), 7.77 (d, J = 9.5 Hz, 1H, H ar), 8.48 (dd, J = 2.6 Hz, J = 9.5 Hz, 1H, H ar), 9.14 (d, J = 2.6 Hz, 1H, H ar). δ_C (50 MHz; CDCl$_3$) 26.1, 26.5, 31.1, 33.5, 36.9, 111.8, 119.7, 123.7, 128.0, 128.4, 145.0, 151.6, 156.0, 161.5, 167.3.

2-(Cyclododecylidenemethyl)-3-methyl-6-nitroquinazolin-4(3*H*)-one 15d

Yellow solid, mp 130 °C, (Found: C, 68.56; H, 7.76; N, 10.83. $C_{22}H_{29}N_3O_3$ requires C, 68.90; H, 7.62; N, 10.96%). δ_H (200 MHz; CDCl$_3$) 1.35 (m, 14H, 7CH$_2$), 1.57 (m, 2H, CH$_2$), 1.73 (m, 2H, CH$_2$), 2.38 (t, J = 6.3 Hz, 2H, CH$_2$), 2.56 (t, J = 6.3 Hz, 2H, CH$_2$), 3.64 (s, 3H, CH$_3$), 6.26 (s, 1H, CH), 7.75 (d, J = 8.4 Hz, 1H, H ar), 8.49 (dd, J = 2.5 Hz, J = 8.4 Hz, 1H, H ar), 9.14 (d, J = 2.5 Hz, 1H, H ar). δ_C (50 MHz; CDCl$_3$) 22.5, 23.2, 23.9, 24.1, 24.4, 24.5, 24.6, 24.7, 24.9, 29.9, 31.9, 33.2, 117.9, 120.2, 123.6, 128.1, 128.7, 145.3, 151.5, 156.5, 156.8, 161.5.

Acknowledgements

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Chemo-enzymatic synthesis of N-alkyloxaziridines mediated by lipases and urea-hydrogen peroxide†

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Chemo-enzymatic oxidation of various N-alkylimines mediated by lipases produced the corresponding *E*- or a mixture of *E*- and *Z*-N-oxaziridines with moderate to very high yields (>99%) and good to excellent selectivities (70–100%) within 30 min to 6 h in various organic solvents at room temperature (25 °C) with urea-hydrogen peroxide (UHP) or aqueous hydrogen peroxide (AHP). The *E/Z* isomer ratio was critically dependent on the stereo-electronic nature of the substituents in the N-alkylimines. The influence of organic solvents, acyl donor and lipase mass was evaluated in these reactions.

Introduction

The evolution of environmentally acceptable organic synthesis is ever present in chemistry today. The most promising approaches to "Green Synthesis" involve the replacement of conventional methods employing toxic/hazardous stoichiometric reagents with biocatalytic processes using enzymes and whole cells.[1,2] and the utilization of nonvolatile and recyclable reaction media[3] Oxaziridines were firstly reported in the late 1950s.[4] They constitute a class of three-membered heterocycles, which have received attention as potential antitumour agents[5,6] and analogues of penicillin.[7,8] Davis and co-workers reported that N-sulfonyloxaziridines are able to oxidise nucleophilic substrates in the same way as peracids.[9] The reactivity of oxaziridines is generally dependent on the nature of the substituent linked to the N-atom of the cycle.[10] They can be readily prepared from Schiff bases, through a number of methods including oxidation in the presence of transition metals, oxidizing agents such as Oxone,[11] or a urea-hydrogen peroxide (UHP)/maleic anhydride system,[12] oxidation with hydrogen peroxide or molecular oxygen and treatment with sulfonic peracids or in a nitrile/hydrogen peroxide system.[13] Until now, the most used method to form oxaziridines involves the oxidation of an imine with a peracid such as *m*-chloroperbenzoic acid (MCPBA).[14]

An alternative method to prepare peroxyacids in the presence of a small amount of free fatty acids mediated by lipases was first described by Björkling[15] in the early 1990s. The peracid, which transfers oxygen to the double bonds, is formed *in situ* from hydrogen peroxide and the corresponding fatty acid. Recent papers have described the preparation of peracids by lipases with hydrogen peroxide and fatty acids.[16,17]

Lipases are versatile catalysts as they catalyze many types of reactions, such as esterification, amidation, transesterification of esters, and oxidation of cyclic ketones to produce lactone

(Baeyer–Villiger oxidation)[18] along with perhydrolysis reactions. Recent applications of lipases include the production of food additives, chiral intermediates and pharmaceutical products.[19] The use of lipases in an organic medium makes many synthetic reactions that do not occur in the natural media of these enzymes possible.[20]

Moreover, the enzyme is among the most important factors determining the overall cost of the process.[21]

Herein, peracids, prepared using a method mediated by three different lipases with UHP (18%) and/or AHP (30%) as oxidizing agents at room temperature, were used in the oxidation of the C=N bonds of a series of N-alkylimines in order to obtain various N-oxaziridines. Other parameters include the influence of organic solvents, acyl donors, lipase mass and substituent effects on the N-alkylimines. N-alkyloxaziridines were obtained in moderated to high product yields under mild conditions (Scheme 1).

1, **13** R₁ = -2-ethyl-hexyl,	X = 4-H	
2, **14** R₁ = -2-ethyl-hexyl,	X = 4-OH	
3, **15** R₁ = -2-ethyl-hexyl,	X = 4-CH₃	
4, **16** R₁ = -2-ethyl-hexyl,	X = 4-OCH₃	
5, **17** R₁ = -2-ethyl-hexyl,	X = 4-F	
6, **18** R₁ = -2-ethyl-hexyl,	X = 2,4-Cl	
7, **19** R₁ = -2-ethyl-hexyl,	X = 2-N(CH₃)₃	
8, **20** R₁ = -2-ethyl-hexyl,	X = 2,4,5-OCH₃	
9, **21** R₁ = -CH(CH₃)Ph,	X = H	
10, **22** R₁ = -tert-butyl,	X = H	
11, **23** R₁ = -sec-butyl,	X = H	
12, **24** R₁ = -n-butyl,	X = H	
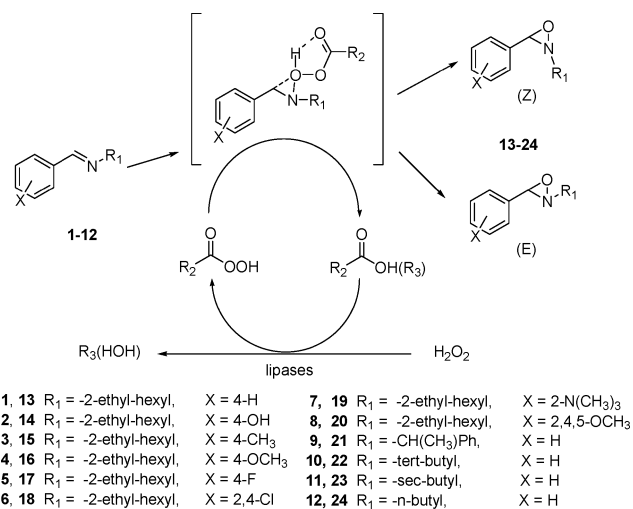
$R_2 = CH_3(CH_2)_6-, CH_3(CH_2)_{10}-, CH_3(CH_2)_{12}-, CH_3(CH_2)_{14}-, C_6H_5-, CH_3CH_2-$

$R_3 = CH_3CH_2-$

Scheme 1

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Results and discussion

Oxidant effects

Firstly, the effect of the peroxy donor on the formation of the N-oxaziridine **13** was evaluated. In this study AHP (30%) or UHP (18%) were used in acetonitrile as the organic solvent and in the presence of octanoic acid and lipase from *Candida antarctica* (CAL-B–Novozymes), which was immobilised in an anionic resin as the biocatalyst. The results are shown in Fig. 1.
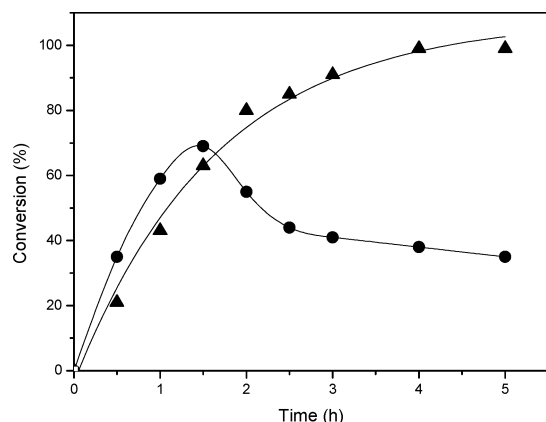
Fig. 1 Peroxy donor effects on the formation of N-oxaziridine **13** carried out in UHP (18%) (▲) or APH (30%) (●) under the reaction conditions: acetonitrile (5 mL), CAL-B (25 mg), octanoic acid (1 mmol), r.t., and 200 rpm.

The conversion to **13** was faster using AHP than UHP during the first 3 h of reaction, forming the product in 70% and 60% conversion degrees, respectively. Using UHP, the conversion to **13** continued to increase, reaching at the equilibrium a maximum of 96% after 5 h of reaction. However, using AHP, a decrease in the conversion was observed after 3 h of reaction; reaching values lower than 10%. Through the GC analysis benzaldehyde was detected as one of the hydrolysis products by comparison with a standard sample. After 5 h of reaction, the undesirable product benzaldehyde was formed in 40% conversion. This problem was minimised by using periodic addition of AHP (0.1 mmol/h), whereby the imine hydrolysis degree decreased but was still higher than 15%. Another drawback is that AHP can denature the lipase due to its high toxicity level.[22]

However, using UHP benzaldehyde was only formed at conversions of <2%. Similar results were obtained by Kraïem *et al.* for the synthesis of oxaziridines with a trichloroacetonitrile-hydrogen peroxide system.[10] Thus, to minimise side reactions and the formation of hydrolysis products, urea-hydrogen peroxide was used to replace aqueous hydrogen peroxide in the subsequent experiments. This reactant is easy to handle and has low toxicity levels. Using UHP good conversions were also achieved in the chemo-enzymatic epoxidation of (+)-3-carene.[23]

Solvent effects

In another study, two other commercially available enzymes were screened in the formation of N-oxaziridine **13** in various organic solvents. Besides CAL-B, lipases from *Pseudomonas* sp. (Amano, PSL) and *Rhizopus oryzae* (Amano, ROL) were also

Table 1 Solvent effects on the chemo-enzymatic formation of N-oxaziridine 13 using different lipases[a]

Solvent	Log P^e	Lipase Conversion (%)[b]		
		CAL-B	PSL	ROL
Ethanol	−0.31	26[c]	n.d.[d]	n.d.
Acetonitrile	−0.33	91	16	8
Diethyl ether	0.83	26	<5	10
MTBE[f]	1.43	76	<5	<5
Dichloromethane	1.50	60	23	<5
Chloroform	2.00	61	10	<5
Toluene	2.50	60	<5	<5
Hexane	3.50	73	<5	<5

[a] UHP (0.4 mmol) as a peroxide donor, 25 mg of lipases (250 U CAL-B, 750 U PSL and 3750 U ROL), octanoic acid (1 mmol) and 5 mL of organic solvents. [b] Evaluated by GC from the crude *E*/*Z* isomer mixture, 3 h of reaction, r.t., 200 rpm. [c] In 24 h. [d] n.d.—not detected. [e] Log *P*—octanol–water partition coefficient.[24] [f] MTBE = methyl *tert*-butyl ether.

employed using UHP as the peroxy donor and octanoic acid as the acyl donor. These lipases (PSL and ROL) were employed in native form. The results for the degrees of conversion to the N-oxaziridines **13** are given in Table 1.

These data indicated that there is not a linear relationship between the N-oxaziridine conversion degrees and the organic solvent polarity (expressed as log *P* values).[24] Using CAL-B the highest conversion degrees were obtained when acetonitrile, methyl *tert*-butyl ether (MTBE) and hexane were the organic solvents, these being 91%, 76% and 73% respectively. Using dichloromethane, chloroform and toluene the conversion degrees were 60–61%. Another interesting result was obtained using ethanol, forming the product in 26% conversion in 24 h of reaction. However, using PSL the highest degrees of conversion to N-oxaziridine **13** were 23% and 16% using dichloromethane and acetonitrile, respectively. Using PSL and ROL in diethyl ether, toluene or hexane, lower values were obtained, these being 10% or only <5%. The reactions carried out in diethyl ether did not give good conversions, probably due to the low solubility of UHP in this medium. In this study CAL-B was the best biocatalyst, regardless of the organic solvent, forming the product **13** in the range of 26% to 91% conversion. Even though the unit values for PSL and ROL were higher than that for CAL-B, they proved not to be suitable catalysts for this oxidation reaction, probably due to the fact that they were used in a free form and their activities were considerably effected by the presence of hydrogen peroxide. Thus, based on the results given above CAL-B was selected for use in all subsequent experiments.

Amount of CAL-B

In another study, the influence of the amount of CAL-B on the conversion of N-oxaziridine **13** was evaluated, in the range of 0–150 mg (0–1500 U). The results are presented in Fig. 2, which show that the conversion to **13** increased up to 25 mg (250U) CAL-B, and from this value onwards it can be observed that there is a plateau with a conversion degree of 93% (~2.1×10^{-3} mmol.min^{-1}). Thus, this lipase mass was used in the subsequent experiments.
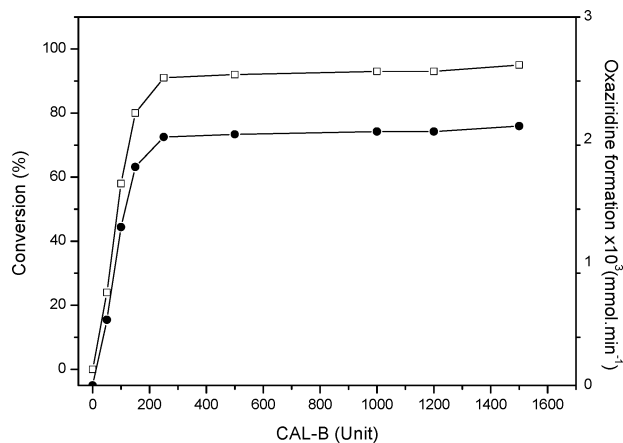
Fig. 2 Influence of CAL-B units on the chemo-enzymatic oxidation of N-benzyliden-2-ethylhexylamine **1** with UHP as peroxide donor. (●) Oxaziridine formation (×10³ mmol min⁻¹) and (■) Conversion (%). Reaction conditions as given in Fig. 1.

Amount and type of acyl donor

The chemo-enzymatic formation of oxaziridines involves basically two steps. Firstly, the enzymatic formation of peracids by the carboxylic acids or esters and hydrogen peroxide, followed by the attack of the double bond C=N of an imine on the electrophilic oxygen of the peracid, resulting in an oxazirane ring (Scheme 1). Thus, in this study the acyl donor content and type (carboxylic acid or an ester) were evaluated in the conversion of the corresponding oxaziridine **13**, using CAL-B as the biocatalyst. The results are shown in Table 2.

The results show that the conversion into oxaziridine **13** was dependent on the structure of the acyl donor. The conversion rates were similar using octanoic, lauric, myristic and palmitic acids. These results are in agreement with those reported by Moreira *et al*.[23] The enzymatic step involves the stabilisation of the tetrahedral intermediate acyl-enzyme which was dependent on the chain length.[25] In the reaction using benzoic acid as the acyl donor, no product was formed. Using ethyl acetate the oxaziridine **13** was obtained in reasonable conversion (53%). However, the formation of by-products such as benzaldehyde

Table 2 Influence of the acyl donor chain length on the chemo-enzymatic formation of oxaziridine **13**[a]

Acyl donor[b]	Conversion (%)[c]			
	Time (h)			
	0.5	1	3	Rate × 10³ (mmol min⁻¹)
Octanoic acid	20	43	90	2.00
Lauric acid	27	50	75	1.67
Myristic acid	18	38	70	1.56
Palmitic acid	15	40	69	1.53
Acetic acid	n.d.[d]	7	16	0.36
Benzoic acid	n.d.	n.d.	n.d.	0
Ethyl acetate	3	28	53	1.18

[a] UHP (0.4 mmol) as a peroxide donor and 25 mg of CAL-B. [b] Acyl donor (1 mmol). [c] Evaluated by GC from the crude *E*/*Z* mixture, r.t., 200 rpm. [d] n.d.—not detected.

was detected by GC analysis after 3 h of reaction. The formation rate of oxaziridine **13** as a function of the amount of octanoic acid is shown in Fig. 3. These data show that the conversion was dependent on the acyl donor reaching ~1.7 × 10⁻³ mmol min⁻¹ using 2 mmol of octanoic acid. Furthermore, under these conditions, the product was easily recovered.
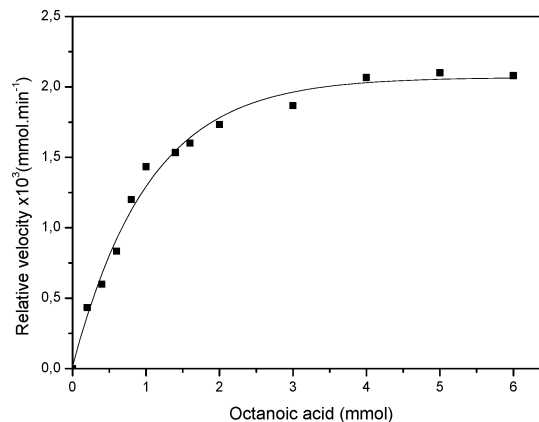
Fig. 3 Influence of octanoic acid on the chemo-enzymatic oxidation of N-benzyliden-2-ethylhexylamine **1** with UHP as peroxide donor. Reaction conditions as given in Fig. 1.

Substituent effects on the phenyl ring and nitrogen

After optimising the parameters described above, a series of N-alkylimines was tested for the formation of oxaziridines. The results given in Table 3 show the high efficiency (entries 1–6) and a 100% selectivity (entry 10) for this oxidation system, after 1 h of reaction. Substrates with electron donating and withdrawing groups on the aromatic ring had a pronounced effect on the conversion to the products. For example, in the presence of 4-OH (entry 2), 4-CH₃ (entry 3), 4-OCH₃ (entry 4) and 4-N(CH₃)₂ (entry 5), the conversion degrees were in the range of 87–95%. These values are similar to that obtained under the same reaction conditions for substrate **1**, which was 91% after 3 h of reaction. However, in the presence of 2,4,5-OCH₃ groups, the conversion was >99% after only 20 min of reaction, showing the strong influence of this substituent on the formation of oxaziridine **18**. The *E*:*Z* ratio remained almost constant regardless of the nature of the electron donating or withdrawing groups (around 70:30%). Using substrates with electron withdrawing groups such as, 4-F (entry 7) and 2,4-Cl (entry 8), lower degrees of conversion to products were observed, these being 50% and 35%, respectively.

The influence of some substituents linked to the nitrogen was then evaluated (compounds **9–12**). In general, good degrees of conversion to the corresponding N-oxaziridines **21–24** were obtained, these being in the range of 40–70%. However, the most interesting feature was that for substrate **10**, with a bulky *tert*-butyl substituent on the nitrogen, only the *E*-oxaziridine isomer was formed. These results are in agreement with those reported by Mohajer[11] *et al*. for the oxidation of substrate **10** and N-naphthyliden-methylamine with Oxone, achieving 100% of *E*-isomer and 86% of *Z*-2-methyl-3-1-naphthyloxaziridine, respectively. For substrates **9**, **11** and **12** the *E*:*Z* ratio remained

Table 3 Chemo-enzymatic oxidation of N-alkylimines **1–12** mediated by CAL-B[a]

N.	Alkylimine	Oxaziridine	Conv (%)[b]	E:Z[c]	δH (ppm)[d]
1		13	43	65:35	4.47 (E) 5.25 (Z)
2		14	87	70:30	4.37 (E) 5.19 (Z)
3		15	90	75:25	4.44 (E) 5.21 (Z)
4		16	95	75:25	4.40 (E) 5.17 (Z)
5		17	88	70:30	4.42 (E) 5.11 (Z)
6		18	>99[e]	75:25	3.95 (E) 5.27 (Z)
7		19	50	71:29	4.45 (E) 5.23 (Z)
8		20	35	80:20	4.91 (E) 5.39 (Z)
9		21	65	80:20	4.59 (E) 5.04 (Z)
10		22	60	100:0	4.68 (E)
11		23	70	80:20	4.48 (E) 5.14 (Z)
12		24	40	70:30	4.47 (E) 5.12 (Z)

[a] Reaction conditions are given in the text. [b] Conversions determined by GC in a 1 h reaction. [c] Determined by ^{1}H NMR and GC. [d] The chemical shifts of the oxaziridine ring hydrogen. [e] 20 minutes reaction.

almost constant, with a predominance of the E-isomer (around 70–80%), as previously observed for substrates **1–8**.

The results show that the E- and Z-oxaziridines can be formed from anti-imines according to a concerted mechanism (similar to that of epoxidation by peracids) under mild conditions forming the corresponding products in good conversions and with excellent selectivity depending on the substrate structure.

Conclusions

In conclusion, we have developed a highly efficient chemo-enzymatic system for the oxidation of N-alkylimines, mediated by lipases, in comparison to traditional methodologies, *e.g.* MCPBA epoxidation. The advantages of this method are the use of mild conditions (room temperature and neutral pH) and the absence of strong oxidants such as Oxone or peracetic acid.

The use of UHP minimised the side reactions due to the absence of water, and the conversion was dependent on the type of organic solvent and acyl donor. Also, the conversion degrees and E:Z ratios were found to be strongly dependent on the substrate structure. No oxidation product was detected in the blank experiments, that is, in the absence of lipases.

Experimental

General

All chemicals are commercially available and were used without purification. All solvents were analytical grade and were dried by storing over activated 3 Å molecular sieves before use. The lipolytic enzyme preparations from *Rhizopus oryzae* (Amano—150 U/mg) and *Pseudomonas* sp. (Amano—30,000 U/g) were donated by Amano Pharmaceutical Co. and lipase from

Candida antarctica B absorbed on a macroporous resin (Novozym 435—10,000 PLU/g) was donated by Novozymes Inc.[28]

The reaction progress was measured by GC on a Shimadzu GC14B instrument equipped with a Shimadzu CBP-5 column using H_2 as the carrier gas, with the flame ionization detector set at 280 °C, an injector set at 270 °C, and a column temperature range of 70–250 °C (10 °C/min). The characterization of the products was performed by spectroscopic analysis on a Perkin Elmer FTIR 16PC, [1]H (400 MHz) and [13]C (100 MHz) nuclear magnetic resonance on a Varian EM360L spectrometer, using CDCl₃ as solvent.

General procedure for the oxidation of N-alkylimines

The starting N-alkylimines (**1–12**) were prepared by conventional methods reported in the literature[26] with yields in the range of 82–97%. All N-alkylimines were obtained as single geometrical *E*-isomer.[27] The chemo-enzymatic reaction for the preparation of N-alkyl oxaziridine was carried out using 0.4 mmol of N-alkylimines, 0–6.0 mmol of the different acyl donors, lipases with different masses or unit values, and a peroxide donor (AHP 30% or UHP 18%) at room temperature and at 200 rpm. The mixture was washed with distilled water and then with dichloromethane to remove UHP. The crude products (**13–24**) were purified using a small column of SiO₂ to obtain separately the *E* and *Z* isomers, using hexane:ethyl acetate (9:1). The organic solvent was evaporated under reduced pressure at 40 °C to give the pure product which was weighed to obtain the corresponding yields. The products formed were fully characterised by ^{1}H and ^{13}C NMR and IR spectroscopies.

The IR and NMR spectroscopy data for compounds **21–24** were compared with those reported in the literature.[10,11] The data for compounds **13–20**, including both isomers, are described below.

2-Ethyl-hexylamine-3-phenyl oxaziridine (14). (*E*)-isomer: yellow oil (26%, 25 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.41–7.37 (5H, m, Ph), 4.47 (1H, s), 2.86–2.75 (2H, m), 1.71 (1H, m), 1.36–1.26 (8H, m), 0.89 (3H, s), 0.87 (3H, s).; ^{13}C NMR (CDCl₃) δ$_c$ 130.2, 130.1, 128.7, 127.8, 128.6, 80.9, 65.6, 39.5, 34.3, 31.8, 31.2, 29.3, 29.1, 29.0, 25.0, 14.3, 11.0. IR (ZnSe window): cm⁻¹ 2924, 1633,1549, 1459, 1370, 1270, 731.

(*Z*)-isomer: colourless oil (10%, 11 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.41–7.37 (5H, m, Ph), 5.25 (1H, s), 2.84–2.73 (2H, m), 1.70 (1H, m), 1.39–1.26 (8H, m), 0.89 (3H, s), 0.87 (3H, s).; ^{13}C NMR (CDCl₃) δ$_c$ 133.1, 130.2, 128.7, 127.8, 79.9, 63.4, 42.8, 39.5, 34.2, 31.8, 24.4, 23.2, 22.8, 14.1, 11.0. IR(ZnSe window): cm⁻¹ 2962, 1653,1423, 1375, 1297, 756.

2-Ethyl-hexylamine-3-4-hydroxy phenyl oxaziridine (15). (*E*)-isomer: pale brown oil (15%, 15 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.51 (2H, d, Ph), 6.73 (2H, d), 4.37 (1H, s), 3.45 (2H, m), 1.65 (1H, m), 1.29–1.19 (8H, m), 0.86–0.83 (6H, s), ^{13}C NMR (CDCl₃) δ$_c$ 153.6, 129.9, 119.9, 114.2, 77.2, 62.1, 33.1, 30.4, 26.6, 23.2, 21.8, 12.3, 8.6. IR (ZnSe window): cm⁻¹ 2960, 1620,1509, 1459, 1300, 1292, 728.

(*Z*)-isomer: pale brown oil (15%, 15 mg) ^{1}H NMR (CDCl₃): δ$_h$ 8.02 (2H, d, Ph), 6,74 (2H, d), 5.19 (1H, s), 3.64 (2H, m), 1.59 (1H, m), 1.27–1.11 (8H, m), 0.78–0.71 (6H, s), ^{13}C NMR

(CDCl₃) δ$_c$ 158.5, 129.9, 115.2, 114.0, 78.3, 66.1, 36.1, 32.4, 29.9, 28.4, 21.2, 12.3, 8.61. IR (ZnSe window): cm⁻¹ 2979, 1618, 1519, 1400, 1372, 1268, 730.

2-Ethyl-hexylamine-3-4-methyl phenyl oxaziridine (16). (*E*)-isomer: colourless oil (38.4%, 38 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.76 (2H,d), 7.18 (2H, d), 4.44 (1H, s), 2.75–2.73 (m, 2H), 2.33(s, 3H), 1.62, (1H, m), 1.43–0.86 (14H, m). ^{13}C NMR (CDCl₃) δ$_c$ 136.1, 130.1, 127.3, 125.8, 78.9, 63.7, 37.1, 35.1, 29.9, 27.2, 23.0, 20.7, 12.3, IR (ZnSe window): cm⁻¹ 2890, 1620, 1471, 1374, 1305, 1162, 810.

(*Z*)-isomer: light yellow oil (15%, 15 mg) ^{1}H NMR (CDCl₃): δ$_h$ 8.13 (2H,d), 7.75 (2H, d), 5.21 (1H, s), 2.73 (m, 2H), 2.33 (s, 3H), 1.62–1.28 (8H, m), 0.87–0.86 (6H, s). ^{13}C NMR (CDCl₃) δ$_c$ 137.6, 128.1, 127.4, 125.8, 77.5, 63.5, 36.9, 29.6, 26.5, 23.0, 21.1, 12.2. IR(ZnSe window): cm⁻¹ 2926, 1622, 1460, 1386, 1216, 818.

2-Ethyl-hexylamine-3-4-methoxy phenyl oxaziridine (17). (*E*)-isomer: yellow oil (66%, 70 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.31 (2H, d), 6.90 (2H, d), 4.40(1H, s), 3.76 (3H, s), 2.77–2.70 (2H, m), 1.66 (1H, m), 1.26 (8H, m), 0.89–0.84 (6H, m). ^{13}C NMR (CDCl₃) δ$_c$ 159.4, 129.1, 127.2, 112.1, 78.7, 63.7, 53.5, 36,1, 29.8, 28.3, 23.1, 21.7, 12.3. IR(ZnSe window): cm⁻¹ 2929, 1592, 1577, 1506, 1450, 1309, 1257, 1160, 1022, 829.

(*Z*)-isomer: light yellow oil (23%, 25 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.81 (2H, d), 6.96 (2H, d), 5.17(1H, s), 3.76 (3H, s), 2.77–2.70 (2H, m), 1.65 (1H, m), 1.35–1.25 (8H, m), 0.89–0.84 (6H, m). ^{13}C NMR (CDCl₃) δ$_c$ 153.4, 130.2, 129.1, 125.2, 112.1, 77.6, 63.6, 53,8, 37,0, 29.8, 29.7, 23.1, 21.7, 12.3. IR(ZnSe window): cm⁻¹ 2928, 1603,1570, 1448, 1451, 1313, 1238, 1156, 1026, 829.

2-Ethyl-hexylamine-3-4-N,N-dimethyl phenyl oxaziridine (18). (*E*)-isomer: dark yellow oil (42.5%, 47 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.61(d. 2H), 6.69 (2H, d), 4.42 (1H, s), 3.48–3.45 (2H, m), 2.99 (6H, s), 1.67(1H, m), 1.30(8H, m), 0.90–0.88(6H, s). ^{13}C NMR (CDCl₃) δ$_c$ 157.4, 126.3, 116.0, 111.2, 72.2, 62.8, 40.0, 34.8, 31.8, 29.3, 25.2, 22.8, 14.3, 11.0. IR(ZnSe window): cm⁻¹ 2959, 1600, 1535, 1480, 1374, 1332, 1292, 1237, 1165, 1113, 849, 721, 630.

(*Z*)-isomer: pale brown oil (27%, 30 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.61(d. 2H), 6.69 (2H, d), 5.11(1H, s), 3.46–3.44 (2H, m), 2.99(6H, s), 1.78 (1H, m), 1.44 (8H, m), 0.92 (6H, m). ^{13}C NMR (CDCl₃) δ$_c$ 157.4, 126.3, 116.0, 111.2, 70.2, 62.3, 40.10, 34.8, 31.8, 29.3, 25.2, 22.8, 14.3, 11.1. IR(ZnSe window): cm⁻¹ 2960, 1600, 1459, 1377, 1332, 1289, 1167, 1101, 852, 757, 724, 627.

2-Ethyl-hexylamine-3-2,4,5-trimethoxy phenyl oxaziridine (19). (*E*)-isomer: orange oil (46%, 60 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.72 (1H s), 6.47 (1H, s), 3.99 (1H, s), 3.95 (3H, s), 3.90 (3H, s), 3.83 (3H, s), 2.29(2H, m), 1.59 (1H, m) 1.28–1.27(8H, m),0.88 (6H, m); ^{13}C NMR (CDCl₃) δ$_c$ 151.8, 142.4, 111.7, 96.8, 70.9, 56.5, 36.9, 29.3, 29.1, 25.1, 23.7, 14.3, 10.6. IR(ZnSe window): cm⁻¹ 2980, 1607, 1507, 1459, 1408, 1285, 1224, 1122, 1029, 876.

(*Z*)-isomer: dark orange oil (29%, 38 mg) ^{1}H NMR (CDCl₃): δ$_h$ 7.66 (1H s), 6.43 (1H, s), 5.27 (1H, s), 3.90 (3H, s), 3.85 (3H, s), 3.80 (3H, s), 2.25 (2H, m), 1.55(1H, m), 1.26 (8H, m), 0.81(6H, m); ^{13}C NMR (CDCl₃) δ$_c$ 151.8, 142.5, 109.2, 99.9, 70.9, 56.4, 56.3, 36.9, 34.4, 30.3, 29.3, 28.6, 25.1, 22.8, 14.2, 10.6. IR(ZnSe window): cm⁻¹ 2962, 1608, 1460, 1378, 1332, 1285, 1165, 1100, 848, 757, 722, 618.

2-Ethyl-hexylamine-3-4-fluoro phenyl oxaziridine (20). (*E*)-isomer: colourless oil (28%, 28 mg) ^{1}H NMR (CDCl₃): δ_h 7.38 (2H, m), 7.04 (2H, m), 4.45 (1H, s), 2.82–2.72 (2H, m), 1.62 (1H, m), 1.43–0.81 (14H, m). ^{13}C NMR (CDCl₃) δ_c 165.3, 155.42, 132.9, 132.8, 131.4, 129.7, 115.6, 80.0, 62.5, 39.1, 31.8, 31.7, 24.8, 23.2, 14.3, 11.0. IR (ZnSe window): cm⁻¹ 2932, 1603, 1541, 1480, 1260, 1104, 829, 610.

(*Z*)-isomer: colourless oil (13%, 13 mg) ^{1}H NMR (CDCl₃): δ_h 7.55 (2H, d), 7.15 (2H, d), 5.23 (1H, s), 2.93–2.78 (2H, m), 1.85–1.82 (1H, m), 1.60–0.89 (14H, m). ^{13}C NMR (CDCl₃) δ_c 162.8, 155.4, 162.8, 132.8, 131.5, 131.1, 115.8, 77.6, 62.5, 39.1, 34.3, 31.6, 29.2, 25.0, 14.3, 10.6. IR(ZnSe window): cm⁻¹ 2932, 1603, 1541, 1480, 1260, 1104, 829, 610.

2-Ethyl-hexylamine-3-2,4-dichloro phenyl oxaziridine (21). (*E*)-isomer: white solid (mp 118 °C, 33%, 40 mg) ^{1}H NMR (CDCl₃): δ_h 7.44–7.30 (3H, m), 4.91 (1H, s), 2.93–2.70 (2H, m), 1.64 (1H, m), 1.28–1.26 (8H, m), 0.86 (6H, m). ^{13}C NMR (CDCl₃) δ_c 134.2, 133.4, 129.3, 127.5, 126.1, 125.4, 75.2, 63.7, 37.4, 30.0, 27.4, 23.3, 21.4, 21.0, 12.1, 9.7. IR(KBr): cm⁻¹ 2960, 1608, 1469, 1390, 1258, 1140, 1080, 829, 818.

(*Z*)-isomer: light green oil (12.5%, 15 mg) ^{1}H NMR (CDCl₃): δ_h 7.74–7.61 (3H, m), 5.39 (1H, s), 2.95–2.73 (2H, m), 1.61 (1H, m), 1.28 (2H, m), 1.28–0.87 (14H, m). ^{13}C NMR (CDCl₃) δ_c 134.2, 133.4, 129.3, 129.2, 127.5, 126.0, 75.2, 63.7, 37.4, 32.2, 30.1, 27.4, 23.2, 21.4, 12.3, 9.8. IR (ZnSe window): cm⁻¹ 2930, 1690, 1503, 1459, 1285, 810.

Acknowledgements

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27 (*a*) Isolated yields of imines: (**1**) 82%, (**2**) 84%, (**3**) 90%, (**4**) 89%, (**5**) 95%, (**6**) 88%, (**7**) 97%, (**8**) 92%, (**9**) 92%, (**10**) 90%, (**11**) 96%, (**12**) 97%, (**13**) 88%; (*b*) Determined by ^{1}H-NMR, the signals of *E*-isomer are in a range of δ_H 8.10–8.25 ppm. See reference 26.
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Novel ((3Z,5Z)-3,5-bis(phenylimino)-1,2-dithiolan-4-yl) and 3H-[1,2]dithiolo[3,4-b]quinolin-4(9H)-one heterocycles: an effective and facile green route†

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Two new sulfur heterocycle systems containing a 1,2-dithiole group, have been synthesized and characterized by IR, ^{1}H NMR and single crystal X-ray crystallography. Optimum conditions for these closed-ring reactions have been studied and the possible reaction mechanism has been explored. A simple, fast, inexpensive and clean green synthesis route has been described here. The anti-cancer activity of these compounds was evaluated in terms of cell growth inhibition against human liver cancer cells HepG2.

Introduction

Over recent years great efforts have been made in the field of green chemistry to adopt methods and processes that use less toxic chemicals, produce smaller amounts of by-products and use less energy.[1] As part of this green concept, toxic and flammable organic solvents are replaced by alternative non-toxic and non-flammable media or the reactions are carried out without the use of any organic solvent, and the classical sources of heating are replaced or reactions carried out at ambient temperature.[2] Organic reactions under solvent-free conditions have attracted significant attention[3] for the advantages they offer in terms of green chemistry.[4] Among various chemical methods, ultrasonic treatment has been suggested as a promising technique since it possesses various advantages.[5] The ultrasonic method is a fast continuous extrusion process with a residence time of a few seconds. The process may not require the use of any chemical agent and does not generate byproducts. It is an energy efficient environmentally friendly physical process. In fact, ultrasonic techniques have been employed for the synthesis of cycloadditions,[6] methanofullerene derivatives,[7] selective nitration of phenols,[8a] and Suzuki cross-coupling reactions,[8b] etc.[9,10] To contribute to the development of environmentally benign organic chemistry, we are focusing our research on the replacement of the volatile common organic reaction media and we are interested in the use of solvent-free conditions and ultrasonic methods.

In the field of biological research, cancer prevention and controlling remains an important topic. Since the 1990's it has been discovered that 1,2-dithiole derivatives may be used as new anti-cancer drugs,[11,12] there has been great interest in the research of the anti-cancer activity of 1,2-dithiole derivatives and their related compounds.[13] 1,2-Dithiole derivatives have a gene-repairing function and are capable of repairing damaged DNA.[14,15] These compounds are very effective in preventing and controlling liver, breast and lung cancers.[16,17] They may also prevent the formation of tumors because of their unique electronic structure, and thus induce cancer resistance in the human body.[18,19]

Quinolone derivatives also exhibit impressive biological activity[20] and have been extensively investigated as antidiabetic,[21] anticancer,[22,23] and antiviral[24] agents. Some fluoroquinolone compounds, such as norfloxacin,[25] ciprofloxacin,[26] and levofloxacin,[27] have been developed and clinically used for the treatment of various infectious diseases. These compounds seem to exert their antitumor effect through inhibition of tubulin polymerization involving binding to the colchicine binding site of tubulin.[28] The quantitative structure–activity relationships of a variety of antimitotic quinolones have been reported by Weigt.[29] Quinolone derivatives are known as broad-range drugs and have a different anticancer mechanism to 1,2-dithiole. Taking advantage of the concept of bioisosterism, the novel 3H-[1,2]dithiolo[3,4-b]quinolin-4(9H)-one compounds containing a quinolone group and a 1,2-dithiole ring were designed and synthesized in order to search for a new drug with higher bioactivity.

In this paper, we describe the solvent-free synthesis and structure of two new classes of 1,2-dithiole derivatives: ((3Z,5Z)-3,5-bis(phenylimino)-1,2-dithiolan-4-yl) (**1**) and 3H-[1,2]dithiolo[3,4-b]quinolin-4(9H)-one (**2**) (Scheme 1). The in vitro anti-tumor tests of the two new classes of compounds are also reported. The results demonstrate that the compound ((3Z,5Z)-3,5-bis (phenylimino)-1,2-dithiolan-4-yl)(4-fluorophenyl)methanone exhibits excellent anti-cancer activity and is, potentially, a novel anti-tumor medicine.

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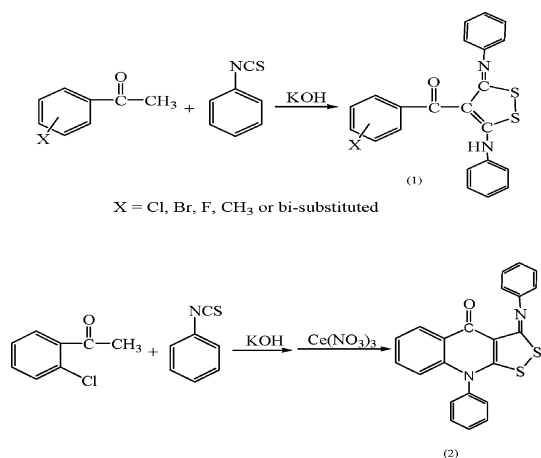
Scheme 1

Result and discussion

Synthesis and crystal structure

By reacting 1-(2,4-dichlorophenyl)ethanone with 1-isothio-cyanatobenzene under basic conditions, two different products were isolated. Crystal structure determinations carried out on both products reveal that they are ((3Z,5Z)-3,5-bis(phenylimino)-1,2-dithiolan-4-yl)(2,4-dichlorophenyl) methanone (**1e**) and (3Z)-7-chloro-9-phenyl-3-(phenylimino)-3H-[1,2]dithiolo [3,4-b]quinolin-4(9H)-one (**2e**). Thus, we have found the a method to synthesize compound (**1**) and (**2**) derivatives. Fig. 1 and 2 show the molecular structures of compounds (**1**) (**1e**, **1h**, **1i**) and (**2**) (**2e**), respectively.‡ In order to expediently compare

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‡ *Crystal data*: **1e**, $C_{22}H_{14}Cl_2N_2OS_2$, $Mr = 457.37$, Triclinic, space group *P-1*, $a = 10.084(2)$ Å, $b = 10.331(2)$ Å, $c = 10.414(2)$ Å, $\alpha = 87.60(3)°$, $\beta = 10.331(2)°$, $\gamma = 78.10(3)°$, $V = 1058.1(4)$ Å^3, $Z = 2$, $T = 293$(K), $\rho_{cald} = 1.436$ mg m^{-3}, $\mu = 0.520$ mm^{-1}, F(000) = 468. Intensity data were collected on a Bruker XSCANS system. The structure was solved by direct methods. There were 4872 measured reflections of which 4604 reflections ($R_{int} = 0.0464$) were independent and all are included in the refinement. $R_1 = 0.0668$, $wR_2 = 0.1577$ for 263 observed reflections with $I \geq 2\sigma(I)$, and $R_1 = 0.1616$, $wR_2 = 0.2053$, GOOF = 0.965 for all data. *Crystal data*: **1h**, $C_{22}H_{13}Cl_2FN_2OS_2$, $Mr = 475.36$, Triclinic, space group *P-1*, $a = 9.896(2)$ Å, $b = 10.256(2)$ Å, $c = 11.128(2)$ Å, $\alpha = 89.64(3)°$, $\beta = 73.71(3)°$, $\gamma = 82.42(3)°$, $V = 1074.0(4)$ Å^3, $Z = 2$, $T = 293$(K), $\rho_{cald} = 1.470$ mg m^{-3}, $\mu = 0.522$ mm^{-1}, F(000) = 484. Intensity data were collected on Bruker XSCANS system. The structure was solved by direct methods. There were 4867 measured reflections of which 4592 reflections ($R_{int} = 0.0286$) were independent and all are included in the refinement. $R_1 = 0.0482$, $wR_2 = 0.1297$ for 271 observed reflections with $I \geq 2\sigma(I)$, and $R_1 = 0.0736$, $wR_2 = 0.1461$, GOOF = 1.034 for all data. *Crystal data*: **1i**, $C_{23}H_{17}BrN_2OS_2$, $Mr = 481.42$, Triclinic, space group *P-1*, $a = 6.3729(13)$ Å, $b = 12.941(3)$ Å, $c = 13.413(3)$ Å, $\alpha = 108.64(3)°$, $\beta = 96.27(3)°$, $\gamma = 96.96(3)°$, $V = 1027.5(4)$ Å^3, $Z = 2$, $T = 293$(K), $\rho_{cald} = 1.556$ mg m^{-3}, $\mu = 2.221$ mm^{-1}, F(000) = 488. Intensity data were collected on a Bruker XSCANS system. The structure was solved by direct methods. There were 4243 measured reflections of which 3546 reflections ($R_{int} = 0.021$) were independent and all are included in the refinement. $R_1 = 0.0938$, $wR_2 = 0.2734$ for 261 observed reflections with $I \geq 2\sigma(I)$, and $R_1 = 0.1304$, $wR_2 = 0.3077$, GOOF = 1.035 for all data. *Crystal data*: **2e**, $C_{22}H_{13}ClN_2OS_2$, $Mr = 420.91$, Monoclinic, space group P2(1)/c, $a = 11.497(2)$ Å, $b = 7.5370(15)$ Å, $c = 22.384(5)$ Å, $\beta = 103.64(3)°$, $V = 1884.9(7)$ Å^3, $Z = 4$, $T = 293$(K), $\rho_{cald} = 1.483$ mg m^{-3}, $\mu = 0.440$ mm^{-1}, F(000) = 864. Intensity data were collected on a Bruker XSCANS system. The structure was solved by direct methods. There were 4160 measured reflections of which 3966 reflections

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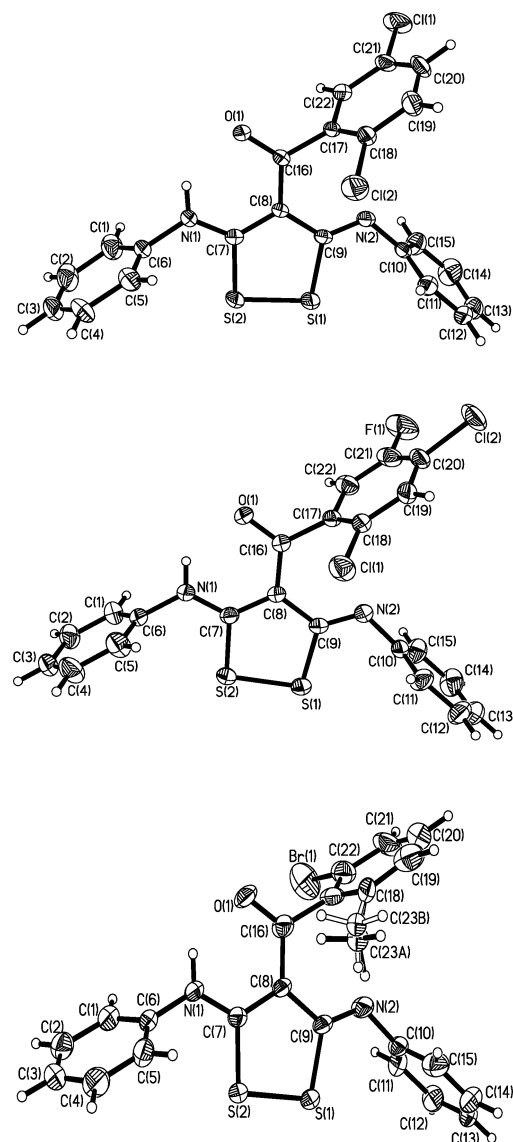
Fig. 1 Molecular structure of compound (**1**) (top, **1e**; middle, **1h**, bottom, **1i**) with the atomic numbering scheme.

Fig. 1 and 2, we have chosen a similar numbering system in these four crystal structures.

Compounds **1e**, **1h** and **1i** are isomorphous and isostructural, they all have the same triclinic crystal system and *P*$\bar{1}$ space group, and the unit cells all consist of two monomeric units. Compound **2e** has the monoclinic crystal system and $P2_1/c$ space group, $Z = 4$. The bond lengths and angles of three phenyl rings in these four structures are normal. The S(1)–S(2) bond lengths of 2.070(2) Å **1e**, 2.074(1) Å **1h** and 2.066 (3) Å **1i** are all slightly longer than that of 2.062(2) Å for **2e**. The bond angles in the 1,2-dithiole ring are also slightly different between compounds **1** and **2** (See Table 1). In compounds **1**, the 1,2-dithiole ring and three conjoint atoms C(6), N(1) and N(2) all lie in the same plane, with the largest atom deviation 0.052 Å for **1e**, 0.047 Å

($R_{int} = 0.0332$) were independent and all are included in the refinement. $R_1 = 0.0536$, $wR_2 = 0.1404$ for 253 observed reflections with $I \geq 2\sigma(I)$, and $R_1 = 0.1159$, $wR_2 = 0.1700$, GOOF = 1.013 for all data.

Table 1 Selected band (Å) and angle (°)

	1e	1h	1i	2e
S(1)–C(9)	1.804(4)	1.798(2)	1.788(6)	1.815(3)
S(1)–S(2)	2.070(2)	2.074(1)	2.066(3)	2.062 (2)
S(2)–C(7)	1.747(4)	1.751(2)	1.736(6)	1.745(3)
O(1)–C(16)	1.233(5)	1.241(3)	1.234(9)	1.235(4)
N(1)–C(7)	1.323(5)	1.336(3)	1.327(8)	1.358(4)
N(1)–C(6)	1.437(5)	1.436(3)	1.433(9)	1.456(3)
N(2)–C(9)	1.270(5)	1.269(3)	1.271(1)	1.277(4)
N(2)–C(10)	1.418(5)	1.421(3)	1.421(9)	1.409(4)
C(7)–C(8)	1.399(6)	1.401(3)	1.428(9)	1.384(4)
C(8)–C(9)	1.446(5)	1.463(3)	1.461(9)	1.455(5)
C(9)–S(1)–S(2)	96.46(2)	96.36(8)	96.8(2)	97.28(1)
C(7)–S(2)–S(1)	95.11(2)	95.43(8)	95.3(2)	94.38(1)
C(7)–N(1)–C(6)	124.0(4)	123.74(2)	125.3(6)	118.8(2)
C(9)–N(2)–C(10)	119.8(4)	119.7(2)	120.1(6)	126.2(3)
N(1)–C(7)–C(8)	126.3(4)	126.0(2)	124.7(6)	124.6(3)
N(1)–C(7)–S(2)	115.7(3)	116.06(2)	116.8(5)	116.3(2)
C(8)–C(7)–S(2)	118.0(3)	117.92(2)	118.4(5)	119.1(3)
C(7)–C(8)–C(9)	117.2(4)	116.9(2)	115.3(5)	117.5(3)
N(2)–C(9)–C(8)	127.0(4)	126.4(2)	125.4(6)	124.5(3)
N(2)–C(9)–S(1)	120.0(3)	120.31(2)	120.6(5)	123.8(3)
C(8)–C(9)–S(1)	113.0(3)	113.35(2)	114.0(5)	111.6(2)
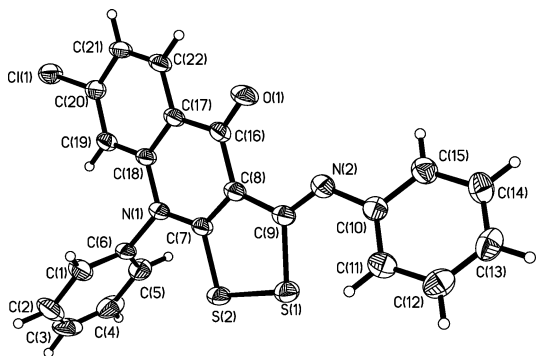
Fig. 2 Molecular structure of compound (**2e**) with the atomic numbering scheme.

for **1h**, and 0.055 Å for **1i**, respectively. For compound **2e**, the atoms in the 1,2-dithiole ring and quinoline ring neatly define a plane, with the largest atom deviation being 0.145 Å for C(20), and the dihedral angles between the two phenyl rings and above the plane are 85.85° and 33.30°, respectively.

Further investigation revealed that ((3Z,5Z)-3,5-bis(phenylimino)-1,2-dithiolan-4-yl) derivatives (**1**) could be synthesized directly in very high yields simply using air as oxidant under basic conditions. In addition, it was discovered in our experiments that although 3H-[1,2]dithiolo[3,4-b] quinolin-4(9H)-one derivatives (**2**) may be directly obtained by making 1-(2-chlorophenyl)ethanone or 1-(2-bromophenyl) ethanone react with 1-isothiocyanatobenzene in one-pot, compound (**2**) can also be obtained from compound (**1**). The latter, catalyzed by cerous nitrate, can undergo ring closing to turn into (**2**). From this we infer that the possible reaction mechanism may be as shown in Scheme 2.

From the possible reaction mechanism in Scheme 2 it can be seen that an oxidative cyclization occurs as step (6). Other oxidants, such as H₂O₂ and MnO₂, did not give the expected results and we thus suggest that the mild oxidation by oxygen in the air is most efficacious for the closed-ring reaction. In this way, we have synthesized ten ((3Z,5Z)-3,5-bis(phenyl-imino)-
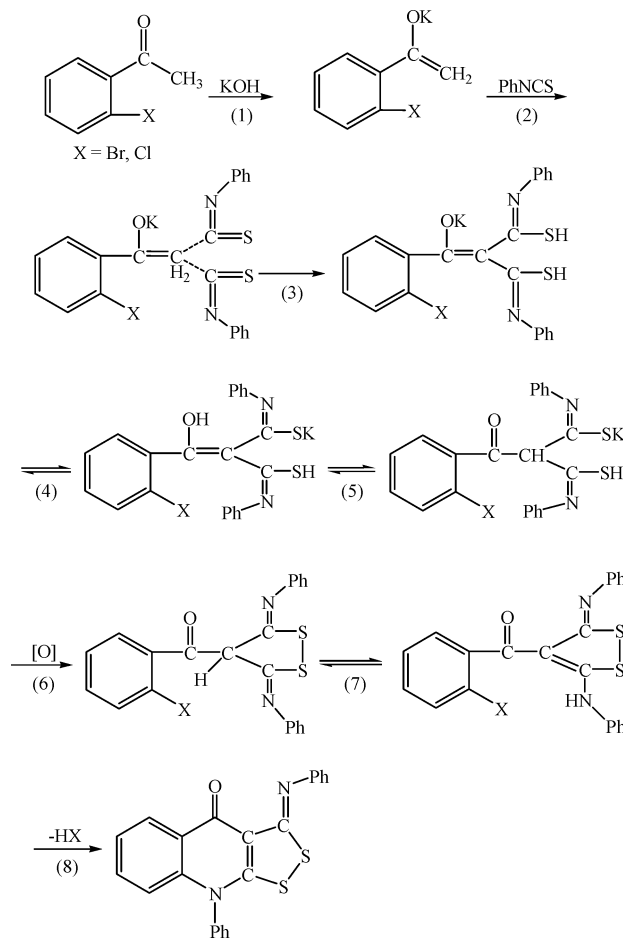
Scheme 2

1,2-dithiolan-4-yl) compounds **1a**–**1j** and five 3H-[1,2]dithiolo [3,4-b]quinolin-4(9H)-one compounds (**2a**, **2e**, **2f**, **2h** and **2i**), and their structures were characterized by elemental analysis, IR and ¹H NMR spectroscopy, and **1e**, **1h**, **1i** and **2e** were also characterized by X-ray diffraction.

We have initially optimized the reaction conditions by studying the influence of the solvent, the alkalinity and reaction temperature as well as the various 1-(substituted-phenyl)ethanone for compounds (**1**), and the results of the effects of the solvent are reported in Table 2. It can be seen from the Table 2 that the choice of solvent is of great importance. Dioxane as solvent gave the best yield. An absolutely anhydrous solvent improves the yield and reduces by-products. In addition, the presence and concentration of base has a dominating effect; potassium hydroxide, due to its high solubility in dioxane, gave high yields.

The synthesis of 3H-[1,2]dithiolo[3,4-b] quinolin-4(9H)-one derivatives (**2**) using a catalyst was also studied. It could be shown that (**2**) could be obtained by the catalyzed reaction of compounds (**1**) with HX (X = Br,Cl) being eliminated. By examining the effects of different catalysts it can be seen from Table 3 that the choice of anion has little effect on the reactions but that the cation is critical. The trivalent cerium and yttrium ions lead to acceptable reaction rates while the quadrivalent cerium and bivalent Cu and Pb do not catalyse the reaction. Trivalent Fe ion is a catalyst but the reaction rate is low. The

Table 2 The effects of solvent for synthesis compounds (**1**)

Solvent	Yield(%)	Solvent	Yield(%)
1,4-Dioxane	91.5	Cyclohexane	40.0
Tetrahydrofuran	71.0	Petroleum ether	25.9
Ethyl ether	65.5	Pyridine	45.8
Ethanol	0	Benzene	42.4
Methanol	0	Toluene	40.7
Water	0	n-Hexane	35.5
DMF	12.7	Ethyl acetate	0

Table 3 The effects of catalyst to the reaction

Catalyst	Yield(%)	Catalyst	Yield(%)
$Ce(NO_3)_3$	63.0	$CuCl_2$	0
$Ce(NO_3)_4$	0	$FeCl_3$	15
$CeCl_3$	59.0	H_2O_2	0
$GdCl_3$	56.3	$Pb(NO_3)_4$	0
$NaNO_3$	4.6	air	4.3

mechanism of the catalysis by Ce^{3+}, Yb^{3+} and Fe^{3+} is not yet clear. Additionally, by adopting the "one-pot approach" in which the 1-(2-chlorophenyl) ethanone or 1-(2-bromophenyl) ethanone derivatives react with 1-isothio-cyanatobenzene, together with potassium hydroxide and cerous nitrate, (**2**) can also be obtained directly. Table 4 shows the effect of different 1-(substituted-phenyl)ethanones and the yields obtained. Table 5 shows the obtained compounds (**2**) and yields.

Ultrasonic treatment can produce a localized and transient high temperature and pressure as high as ~5000 K and ~300 atm,[30] respectively. Chemical effects may be induced by ultrasonic techniques through direct formation of cavitation micro-bubbles. Considering 1-isothio-cyanatobenzene was liquid and some 1-(substitutedphenyl)ethanone derivatives also were liquid, solvent-free conditions might be realized by ultrasound. With this idea in mind, we mixed 1-(2-chlorophenyl) ethanone and 1-isothio-cyanatobenzene with solid KOH under ultrasonic conditions using ultrasonic instrument JCX-600G, and allowed them to react for 10 minutes, the compound (**1a**) could be obtained with 96% yield. Hence, an effective and facile green route to synthesize these novel (3Z,5Z)-3,5-bis(phenyl-imino)-1,2-dithiolan-4-yl) (**1**) and 3H-[1,2]dithiolo[3,4-b]quinolin-4(9H)-one (**2**) derivative heterocycle systems were formed. If the 1-(substituted-phenyl)ethanone was liquid, we first mixed 0.01 mol of 1-(substituted-phenyl)ethanone and 0.02 mol 1-isothiocyanato-benzene in a 50 mL round bottomed flask with stirring. We then added milled solid KOH in small amounts. The ultrasonic reaction lasted 10–15 minutes, the reactants were fully changed to a dope or light-yellow solid. We let the obtained products (dopes or light-yellow solid) dry in air for more than 24 hours under room temperature; or 8–10 hours at temperature 60–70 °C. The yellow solid was obtained by washing the above products with water several times. If the 1-(substituted-phenyl)ethanone was solid, we first ground it with solid KOH together, then added it to liquid 1-isothiocyanato-benzene with stirring. The other processes were the same as above. Yellow single crystals, suitable for X-ray measurements, were obtained by recrystallization from acetic ether. The compounds (**1**),

3,5-bis(phenylamino) 1,2-dithiole derivatives, are stable in the solid state and in all organic solvents tested. We have only repeated the synthesis of compounds (**1a**), (**1b**), (**1e**), (**1f**) and (**1j**) using ultrasonic reaction conditions to compare with the general method, and found (**1a**), (**1b**) and (**1j**) had an improved yield, but (**1e**) and (**1f**) did not. Table 6 shows the comparative results of the two different synthesis methods at room temperature.

Using solvent-free synthesis, the compounds (**2**) are more easily obtained in one-pot. If the 1-(2-chlorophenyl) ethanone or 1-(2-bromophenyl) ethanone derivatives were liquid, they were first mixed with 1-isothiocyanato-benzene in a 50 mL round bottomed flask in 1:2 molar ratio, then 4 mole ratio of solid KOH and a little metal K were added. The ultrasonic reactions lasted 30 minutes. The products were dissolved in water and aqueous $Ce(NO_3)_3$ added while stirring. The yellow precipitation formed was isolated by filtration and recrystallized from acetic ether. The pure compounds (**2**) could be obtained in satisfying yield. Although the compounds (**2**) were stable in air, they all decompose before their melting point.

Up to now, we have only been able to synthesise the compounds (**1**) when electron-withdrawing groups, such as chlorine or bromine, are attached to the benzene ring of the 1-(substituted-phenyl)ethanone. Using these 1-(substituted-phenyl) ethanones, the reaction and product isolation are facile. However, if the benzene ring of the 1-(substituted-phenyl)ethanone have an –NO_2 substituent, the reaction proceeds very rapidly but numerous by-products are formed and product isolation becomes difficult. As an exception, the reaction of acetyl pyridine is very fast and product isolation easy. So far, we have not obtained compound (**1**) when there are electron contributing groups such as alkyl or alkoxy attached to the benzene ring of the acetophenone. We are continuing to explore further variations of this reaction.

Biological results

The basic 1,2-dithiole structure in both classes of compounds (**1**) and (**2**) suggested that these compounds might exhibit anti-cancer activity. Thus, samples of some compounds (**1**) and (**2**) were given to the anti-cancer medicine laboratory of the China Pharmaceutical University for further research. Adopting the MTT (methyl thiazolyl tetrazolium) method for the *in vitro* research of antitumor drugs, experiments were carried out to examine anti-cancer activity against human liver cancer cells (HepG2 and SMMC-7721). The preliminary *in vitro* anti-tumor tests show that the compounds (**1**) have good anti-cancer activity and are potentially a new group of anti-tumor medicines, the IC_{50} values of compounds (**1c**) and (**1d**) are about 1.36 μM and 0.984 μM on HepG2, which is lower than that of the positive control drug, gambogic acid (about 1.55 μM). But, neither (**1**) nor (**2**) is effective against human liver cancer cells SMMC-7721. Table 7 list the results of 13 compounds which were compared with the positive control drug, gambogic acid on HepG2 (IC_{50} = half inhibition concentration of drug).

Compounds (**1d**), (**1h**) and (**2d**), having a fluorin substituent on the phenyl ring, showed strong HepG2 inhibitory activity ($IC_{50} < 10^{-5}$M). Substituents at the *para*- position of the phenyl ring seem to be more effective than those at the *ortho*-position.

Table 4 Products and yields from the different 1-(substituted-phenyl)ethanones
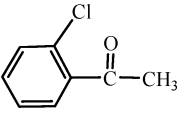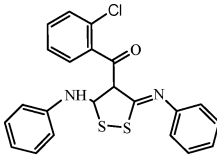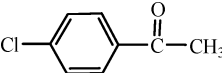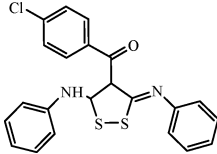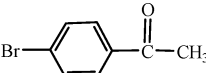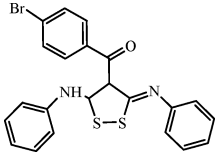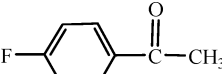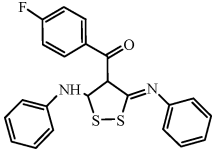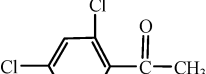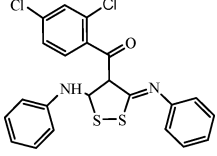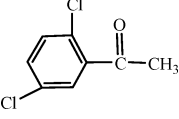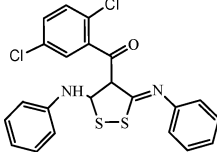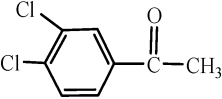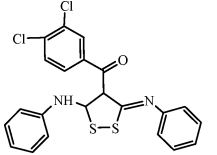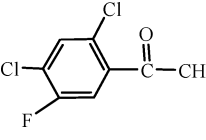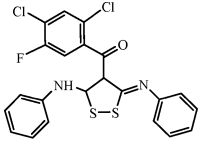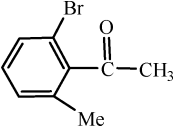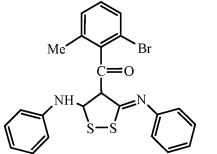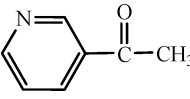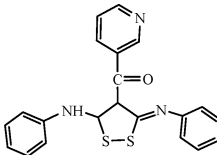
Entry	Starting Materials	Products	Mp (°C)	Yield (%)
1a			171	73.0
1b			149	91.5
1c			155	93.0
1d			145	56.0
1e			165	73.5
1f			174	75.0
1g			171	95.0
1h			169	78.5
1i			173	71.0
1j			146	91.5

Table 5 Products and yields for compounds (**2**)
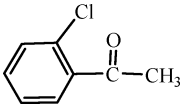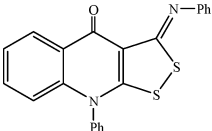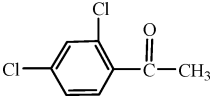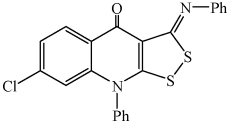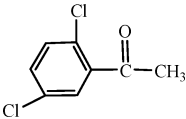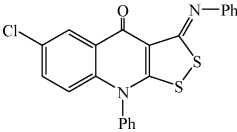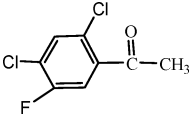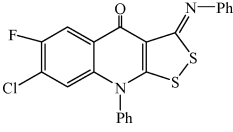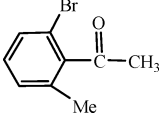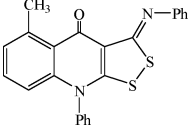
Entry	Starting Materials	Products	Mp (°C)	Yield (%)
2a			254	50.0
2e			275	63.0
2f			271	60.0
2h			289	70.5
2i			261	85.5

Table 6 The comparing result of general and ultrasonic treatment

Entry	Condition	Reaction time	Yield%
1a	Dioxane	6 hour	73.0
	Solvent-free	10 minutes	96.0
1b	Dioxane	6 hour	91.5
	Solvent-free	10 minutes	88.0
1e	Dioxane	6 hour	73.5
	Solvent-free	15 minutes	68.0
1f	Dioxane	6 hour	75.0
	Solvent-free	15 minutes	65.0
1j	Dioxane	6 hour	91.5
	Solvent-free	15 minutes	86.0

Table 7 The inhibition effects of tested drugs on *in vitro* growth of HepG-2[a]

	Concentration			
Entry	10^{-5} M	10^{-6} M	10^{-7} M	IC$_{50}$[b]
1a	14.51%	6.32%	4.75%	nd
1b	50.54%	29.46%	8.85%	1.02×10^{-5} M
1c	62.72%	53.54%	2.22%	1.36×10^{-6} M
1d	83.65%	59.75%	16.04%	9.84×10^{-7} M
1e	11.94%	6.40%	3.20%	nd
1f	11.36%	10.07%	0.03%	nd
1g	19.10%	6.88%	0.31%	nd
1h	23.11%	16.43%	14.14%	9.1×10^{-5} M
1i	9.63%	8.10%	5.15%	nd
1j	50.72%	26.20%	8.04%	1.00×10^{-5} M
2a	10.91%	3.65%	3.33%	3.11×10^{-4} M
2c	14.45%	5.07%	3.15%	nd
2d	11.68%	10.70%	2.46%	1.66×10^{-4} M
GA[c]	93.96%	69.89%	0.8%	1.55×10^{-6} M

[a] nd = not determined. [b] IC$_{50}$ = half inhibition concentration of drug. [c] GA = gambogic acid.

However, multi-substituted compounds showed decreased anti-cancer activity, and compounds (**1e**), (**1f**), (**1g**) and (**1i**) lacked anticancer activity against HepG2. The reason for these results is not clear. In order to understand the relationship of the anti-cancer activity of a drug with time, further tests on the *in vitro* growth of HepG-2 over longer time periods were carried out. Table S18 in the ESI† lists the results. Our results demonstrated that the extent of inhibition depends on both the length of reaction time and the concentration of compounds applied. The compound (**1d**) is given as an example: at 48 h, when the concentration of (**1d**) is increased from 10^{-7} M to 10^{-4} M, the inhibitory rate reaches to 93.69% from 16.04%; at 12h, if the concentration of (**1d**) is increased from 10^{-7} M to 10^{-4} M, the inhibitory rate reaches 71.55% from 10.37%. It is suggested

there exists the obvious relationship between inhibitory rate, time and concentration.[31]

Conclusions

In summary, we have discovered two new closed-ring reactions and developed a convenient, solvent-free and environmentally

benign one-pot method for the synthesis of various substituted (3Z,5Z)-3,5-bis(phenylimino)-1,2-dithiolan-4-yl) (**1**) and 3*H*-[1,2]dithiolo [3,4-*b*]quinolin-4(9*H*)-one (**2**) derivatives. Starting from commercially available 1-isothiocyanatobenzene and 1-(substituted- phenyl) ethanone derivatives, a range of pharmaceutically relevant compounds (**1**) or (**2**) are obtained selectively. The compounds (**2**), 3*H*-[1,2]dithiolo [3,4-*b*]quinolin-4(9*H*)-ones, are a new class of heterocyclic systems. The reported ultrasonic method is shown to be very flexible; the reaction conditions can be easily controlled to obtain (**1**) or (**2**) in most cases. Mild reaction conditions, high yield, simple purification, short reaction period and the stability and cheapness of the reagents are features of this new procedure. The work-up procedure is simple and green: the all steps reaction processes are carried out in water or under solvent free conditions, washing of the reaction mixture is with water and all the steps of the reaction are carried out at ambient temperature. All of these features make this synthesis a promising method in industrial applications. Moreover, extrapolation of this method to the application to the methylene cyanide, [CH$_2$(CN)$_2$], malonic ester, [CH$_2$(COOR)$_2$], or other compounds containing active α-H is currently under investigation. Additionally, the preliminary experimental results indicate that ((3Z,5Z)-3,5-bis (phenylimino)-1,2-dithiolan-4-yl)(4-fluorophenyl)methanone is an anti-cancer medicine of great potential. Of those compounds, the most potent HepG2 inhibitors were those (**1d**, **1h** and **2d**) having a fluorin substituent on the phenyl ring. The substituents at the *para*- position of the phenyl ring exhibited greater anti-cancer activity than those at the *ortho*- or *meta*-positions. Further design and chemical modifications to synthesis compounds (**1**) containing a fluorine atom are in progress.

Experimental

Because all compounds reported in this manuscript were synthesized by a general method, and not all by a solvent-free method, we should first introduce the general synthesis procedure below.

General procedure for (3Z,5Z)-3,5-bis(phenyl-imino)-1,2-dithiolan-4-yl) derivatives (**1a–1j**): 0.01 mol of acetophenone (or its derivative) in 20 mL of dioxane was placed in a 50 mL round bottomed flask. 0.02 mol (1.12 g) of KOH was then added while stirring at room temperature. 0.02 mol 1-isothiocyanatobenzene was then added dropwise over three hours. The reaction was stirred for a further six hours, and a yellow precipitate formed. The precipitate was then filtered, washed with diethyl ether and dried in air. Yellow single crystals, suitable for X-ray measurements, were obtained by recrystallization from a mixture of acetic ether:cyclohexane (1:3). Compounds **1** are stable in the solid state and in all organic solvents tested.

The example for synthesis of (3Z)-7-chloro-9-phenyl-3-(phenylimino)-3*H*-[1,2]dithiolo[3,4-*b*]quinolin-4(9*H*)-one **2e** is given to illustrate the general procedure for compounds (**2a**, **2e**, **2f**, **2h** and **2i**). To a 50 mL flask 0.01 mol of 1-(2,4-dichloro-phenyl)ethanone in 20 mL of anhydrous dioxane was added. Then 0.04 mol (1.75 g) KOH and a little metal K was added while stirring and the mixture refluxed for 10 min. 1-isothio-cyanatobenzene (0.02 mol) was then added dropwise over three hours. The reaction was stirred for a further six hours,

during which a light yellow precipitate formed. The precipitation was filtered, washed with diethyl ether, dissolved in water and Ce(NO$_3$)$_3$ aq. added while stirring. The precipitation was isolated by filtration. Yellow single crystals suitable for X-ray measurements were obtained from a mixture of acetic ether:petroleum ether (1:2).

Representative experimental procedure for compounds (**1a**) under solvent-free conditions was as follows. The ultrasonic treatment was conducted with an Ultrasonic Generator JCX-600G (100 kHz, 600 W, Shangdong Ultrasonic Co. Ltd., China) in a temperature controlled container, in which a 50 mL flask is placed in a water bath and ultrasonically treated from underneath. At ambient temperature, the mixture of 0.01 mol of 1-(2-chlorophenyl)ethanone and 0.02 mol 1-isothiocyanatobenzene was put into the above flask, then the milled solid KOH (0.02 mol) was added in the flask. The ultrasonic reaction was carried out for 10 minutes, the reactants were changed to a light-yellow solid. We let the obtained light-yellow solid dry in air for more than 24 hours under room temperature. The yellow solid (**1a**) was obtained by washing with water several times.

The original IR and ^{1}H NMR spectral data, elemental analysis for compounds (**1**) and (**2**), crystal data for compounds **1e**, **1h**, **1i** and **2e**, MTT (methyl thiazolyl tetrazolium) methods and the experiments of the anti-cancer activity against the human liver cancer cells, *etc.* are given in the ESI.† CCDC-652764 for compound **1e**, CCDC-652761 for compound **1h**, CCDC-652762 for compound **1i**, and CCDC-652763 for compound **2e**, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data-request/cif.

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The development of an environmentally benign sulfide oxidation procedure and its assessment by green chemistry metrics

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Different Iron (III) species were used as catalysts in sulfoxidation reactions giving excellent yields and high chemoselectivity. Among the iron (III) species, the best one was a solid β-cyclodextrin-FeBr$_3$ complex. Sulfoxidation takes place with high chemoselectivity in the presence of other groups such as isothiocyanate. Good results were obtained when these reactions were analyzed using green chemistry metrics.

Introduction

Sulfoxides and other organosulfur compounds are important synthetic intermediates in organic chemistry[1] and are valuable in the preparation of biologically and pharmaceutically relevant materials.[2] One of the oxidation reactions found in pharmaceutical research and production is that of a sulfide to a sulfoxide, which is achieved with a very wide variety of reagents.[3] When there are several different functional groups present in a molecule as in esomeprazole,[4] a sulfoxide-containing drug, chemoselective transformations are of great significance. This has often been difficult in sulfoxidation chemistry because oxidations of other functional groups can take place simultaneously.[5] Furthermore, sulfoxides can undergo overoxidation to sulfones and therefore it is important that the catalyst has a low reactivity towards the sulfoxides.[6]

In view of the general and continuous interest in the oxidation of sulfides[7] and particularly in the development of synthetic methods for the selective conversion of sulfides into sulfoxides,[8] we are currently involved in the study of reaction methodologies to achieve chemoselective sulfoxidation reactions.[9]

From a study of different combinations of metallic bromides and/or metallic nitrates it was concluded that combinations of iron salts formed an excellent catalytic system for the oxidation of sulfides to sulfoxides (Scheme 1).[10] Electrochemical studies in the presence of iron salts lead one to propose that the reaction occurs within the coordination sphere of the metal where the substrate is activated to be oxidized by the bromine generated from the Fe^{III} bromide and the nitric acid. The water molecules and/or the oxygen present in the system subsequently oxygenated the substrate. Selectivity fails whenever this metal was absent.[11]

In a previous paper,[12] we have reported on the synthesis, characterization and catalytic activity of several cyclodextrins-FeBr$_3$ (CD-Fe) complexes. We found that cyclodextrin complexes have a very good catalytic activity in sulfoxidation

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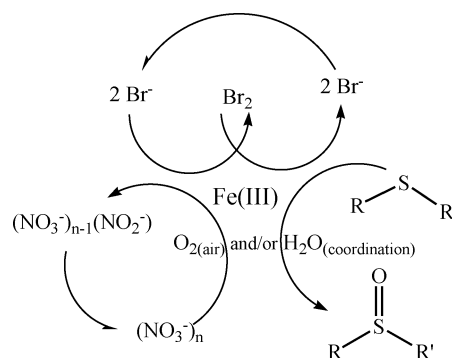
Scheme 1 Redox mediators in catalytic and selective oxidation of sulfide.

reactions and it was shown that several sulfides give sulfoxides with excellent yields in the presence of a catalytic amount of [Fe(NO$_3$)$_3$·9H$_2$O] as oxidant. Furthermore, these complexes can be re-used several times. These reactions were performed by recycling the solid CD-Fe complexes while the substrate, iron(III) nitrate and the organic solvent were renewed.[12b]

Based on previous studies using catalysts containing FeBr$_3$ stabilized by complexation with DMSO or with different cyclodextrins we considered it of interest to explore the scope of their use in the chemoselective synthesis of sulfoxides. Complexes with cyclodextrins are of particular interest because of the possibility of inducing enantiomeric excess.

We report here that substrates such as 4-(methylthio)-phenylisothiocyanate **1**; 4-(methylthio)benzoic acid **2**; 4-(methylthio)acetophenone, **3**; 2-(methylthio)benzoic acid **5**; 2-(methylthio)bromo benzene **6** and 2-(methylthio) benzaldehyde **7** are oxidized with very high chemoselectivity and in excellent yields (Scheme 2). It should be noted that highly oxidizable functions such as isothiocyanate or aldehyde remain unchanged under the reaction conditions used.

Green chemistry was introduced with the aim to overcome health and environmental problems at the source by developing cleaner chemical processes for the chemical industry through the design of innovative and environmentally benign chemical reactions.[13–15] We have analyzed the results in terms of reported green metric parameters and we demonstrate that the

X =	4-NCS	1	1a
	4-COOH	2	2a
	4-C(O)CH₃	3	3a
	2-NCS	4	--
	2-COOH	5	5a
	2-Br	6	6a
	2-CHO	7	7a
	4-NH₂	8	--
	2-NH₂	9	--
	4-NCO	10	--
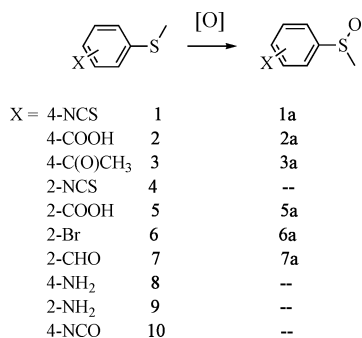
Scheme 2

methodology proposed for the oxidation of sulfides fulfill several of the green chemistry principles since the oxidant is oxygen from the air, the reactions are highly selective producing a minimum amount of waste and the catalyst is a non-contaminating metal.

Results and discussion

Compound **1**, 4-(methylthio)phenylisothiocyanate, was oxidized with high yield and chemoselectivity using FeBr₃ free or in the form of complexes. As can be observed in Table 1, we have obtained 4-(methylsulfinyl) phenylisothiocyanate **1a** with excellent yields using FeBr₃, the β-CD complex or the DMSO complex. Although all the reactions gave almost quantitative yield, the amount of isolated product is not the same because the work-up is in some cases more complicated than in others. No efforts were done to optimize the isolation procedures. The best reaction conditions are those involving the β-CD complex as catalyst and Fe(NO₃)₃ in catalytic amount as oxidation promoter, Table 1 entry 3, because the catalyst is easily eliminated from the system by filtration and can be reused. The FeBr₃ and its DMSO complex are completely soluble in the reaction system and difficult to separate from the reaction products without an important loss of the product of interest and consequently a decrease in the isolated product. For this reason, although FeBr₃ appears as a more efficient catalyst since less reaction time is required, its use is not recommended

because complete elimination of the catalyst from the product could not be achieved without significant loss of the product of interest. Entries 2 and 4 in Table 1 show that without the catalyst the yield is very low or there is no reaction. Decreasing the amount of the nitrate (compare entries 1 and 3 in Table 1) did not result in a significant change in the yield of **1a**. When HNO₃ was used the product of interest was obtained with very good yield, Table 1 entry 7. It is remarkable that functions such as the isothiocyanate group, that can react with nucleophiles and with electrophiles or can isomerize to thiocyanate,[16] survive under the reaction conditions and remain unchanged. This is very important because isothiocyanates are useful intermediates in organic synthesis,[17] and they are also interesting for their biological activities.[18]

The sulfoxidation reaction was also very efficient in the presence of *ortho* and *para* carboxylic acid groups since 4-(methylthio)benzoic acid **2** and 2-(methylthio)benzoic acid **5** gave the expected products. The results are summarized in Table 2.

Excellent yield of 4-(methylsulfinyl)benzoic acid **2a** was obtained in most of the used conditions, Table 2 entries 1, 3 and 5. Nevertheless, in the absence of a catalyst, Table 2 entries 2 and 4, the sulfoxidation did not take place. The *ortho* derivative is significantly more reactive than the *para* derivative under all conditions and it is even reactive in the absence of the catalyst (compare runs 2 with 7 and 4 with 9 in Table 2).

Under the same reaction conditions used for **1** and **2**, 4-(methylthio)acetophenone **3** was oxidized on the sulfur almost quantitatively, although somewhat more slowly, compare for instance run 1 in Table 3 with run 1 in Table 2.

In order to determine the importance of the group position, we carried out the reaction with 2-(methylthio)phenyl isothiocyanate **4** (Table 1, entries 9–13), with 2-(methylthio) benzoic acid **5** (Table 2, entries 7–10), with 2-(methylthio) bromobenzene **6** (Table 4, entries 1–3) and with 2-(methylthio)benzaldehyde **7** (Table 4, entries 4–6).

For substituents –COOH, Br and –COH the reactivity of the *o*-substituted compounds is significantly higher than that of the *p*-substituted derivatives.[12b,19] Contrasting with that, in the case

Table 1 Oxidation reactions of *x*-(methylthio)phenylisothiocyanate to *x*-(methylsulfinyl)phenylisothiocyanate[a]

Entry	*x*-	Oxidant (%)	Catalyst[b]	Time[c]	% Substrate[d]	% Yield[e]
1	4-	Fe(NO₃)₃ (10)	β-CD-Fe	3.0	0	93
2	4-	Fe(NO₃)₃ (10)	—	3.6	75[f]	25[f]
3	4-	Fe(NO₃)₃ (5)	β-CD-Fe	6.0	0	96
4	4-	Fe(NO₃)₃ (5)	—	6.0	87[f]	13[f]
5	4-	Fe(NO₃)₃ (10)	FeBr₃	2.5	0	90
6	4-	Fe(NO₃)₃ (10)	DMSO-Fe	5.5	0	95
7	4-	HNO₃ (13)	FeBr₃	2.5	0	100
8	4-	HNO₃ (13)	—	5.5	50[f]	50[f]
9	2-	Fe(NO₃)₃ (10)	β-CD-Fe	20.0	62	38[g]
10	2-	Fe(NO₃)₃ (10)	—	20.0	100	N.R.[h]
11	2-	HNO₃ (13)	FeBr₃	20.0	100	N.R.
12	2-	HNO₃ (13)	—	8.5	100	N.R.
13	2-	Fe(NO₃)₃ (10)	DMSO-Fe	20.0	70	30[g]

[a] Solvent acetonitrile, oxidant Fe(NO₃)₃·9H₂O or nitric acid, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. [b] Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr₃; DMSO-Fe = (FeBr₃)₂(DMSO)₃. [c] Reaction time in hours. [d] Percent substrate recovered. [e] Percent yield of oxidation products after isolation and purification. [f] Percent yield of product and/or substrate determined by ¹H NMR analysis of the raw reaction products. [g] Unidentified products, percent conversion of substrate. [h] N.R. = no reaction.

Table 2 Oxidation reaction of x-(methylthio)benzoic acid to x-(methylsulfinyl)benzoic acid[a]

Entry	x-	Oxidant (%)	Catalyst[b]	Time[c]	% Substrate[d]	% Yield[e]
1	4-	Fe(NO$_3$)$_3$ (10)	β-CD-Fe	4.0	0	100
2	4-	Fe(NO$_3$)$_3$ (10)	—	19.0	100	N.R.[f]
3	4-	HNO$_3$ (13)	FeBr$_3$	2.5	0	100
4	4-	HNO$_3$ (13)	—	22.0	100	N.R.
5	4-	Fe(NO$_3$)$_3$ (10)	DMSO-Fe	2.0	0	95
6	2-	Fe(NO$_3$)$_3$ (10)	β-CD-Fe	2.0	0	100
7	2-	Fe(NO$_3$)$_3$ (10)	—	20.0	30	70
8	2-	HNO$_3$ (13)	FeBr$_3$	1.0	0	100
9	2-	HNO$_3$ (13)	—	20.0	66	44[g]
10	2-	Fe(NO$_3$)$_3$ (10)	DMSO-Fe	1.5	0	93

[a] Solvent acetonitrile, oxidant Fe(NO$_3$)$_3$·9H$_2$O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. [b] Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr$_3$; DMSO-Fe = (FeBr$_3$)$_2$(DMSO)$_3$. [c] Reaction time in hours. [d] Percent substrate recovered. [e] Percent yield of oxidation products after isolation and purification. [f] N.R. = no reaction. [g] Percent yield of product and/or substrate determined by ^{1}H NMR analysis of the raw reaction products.

Table 3 Oxidation reaction of 4-(methylthio)acetophenone to 4-(methylsulfinyl)acetophenone[a]

Entry	Oxidant (%)	Catalyst[b]	Time[c]	% Substrate[d]	% Yield[e]
1	Fe(NO$_3$)$_3$ (10)	β-CD-Fe	6.0	0	100
2	Fe(NO$_3$)$_3$ (10)	—	22.5	92[f]	8[f]
3	HNO$_3$ (13)	FeBr$_3$	2.5	0	100
4	HNO$_3$ (13)	—	22.5	78[f]	22[f]
5	Fe(NO$_3$)$_3$ (10)	DMSO-Fe	3.0	0	95

[a] Solvent acetonitrile, oxidant Fe(NO$_3$)$_3$·9H$_2$O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. [b] Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr$_3$; DMSO-Fe = (FeBr$_3$)$_2$(DMSO)$_3$. [c] Reaction time in hours. [d] Percent substrate recovered. [e] Percent yield of oxidation products after isolation and purification. [f] Percent yield of product and/or substrate determined by ^{1}H NMR analysis of the raw reaction products.

Table 4 Oxidation reaction of 2-(methylthio)bromobenzene **6** and 2-(methylthio)benzaldehyde **7**[a]

Entry	Substrate	Oxidant (%)	Catalyst[b]	Time[c]	% Substrate[d]	% Yield[e]
1	**6**	Fe(NO$_3$)$_3$ (10)	β-CD-Fe	3.0	0	92
2	**6**	Fe(NO$_3$)$_3$ (10)	—	3.0	100[f]	N.R.[g]
3	**6**	HNO$_3$ (13)	FeBr$_3$	2.8	0	100[h]
4	**7**	Fe(NO$_3$)$_3$ (10)	β-CD-Fe	3.0	0	100
5	**7**	Fe(NO$_3$)$_3$ (10)	—	3.0	95[f]	5[f]
6	**7**	HNO$_3$ (13)	FeBr$_3$	6.7	0	100[h]

[a] Solvent acetonitrile, oxidant Fe(NO$_3$)$_3$·9H$_2$O, ratio substrate : catalyst 1.00 : 0.05 mol, at room temperature with stirring, under air but in a closed system. [b] Catalysts: β-CD-Fe = complex (β-cyclodextrin)FeBr$_3$. [c] Reaction time in hours. [d] Percent substrate recovered. [e] Percent yield of oxidation products after isolation and purification. [f] Percent yield of product and/or substrate determined by ^{1}H NMR analysis of the raw reaction products. [g] N.R. = no reaction. [h] Without purification.

of the isothiocyanate derivatives the *p*-substituted compound reacts very well but the *o*-substituted derivatives do not react at all or give other products (see Table 1, runs 9–13). Mechanistic studies are currently being done in our laboratory in order to understand the substituent effect.

In previous work, we reported that substrates such as 4-(methylthio) benzaldehyde; 4-(methylthio)benzylalcohol; 2-(methylthio)benzothiazole; 2-(benzylthio)benzothiazole were oxidized with very high chemoselectivity and in excellent yields.[19] It should be noted that highly oxidizable functions such as benzaldehyde, benzylic alcohol, benzylic methylene and heterocyclic sulfur or nitrogen atoms remained unchanged under the reaction conditions.

Compounds 4-(methylthio)aniline **8**, 2-(methylthio)aniline **9** and 4-(methylthio)phenylisocyanate **10** were not completely consumed after 50 hours, and a complex mixture of products was obtained. We think that the reason for this is that the amino group reacts faster than the sulfur group with nitrogen oxides formed in the reaction medium and consumes irreversibly those species which are needed to initiate the oxidation process. These reactions are currently under investigation in our laboratory and will be a matter for future publications.

The reaction conditions used in the present work meets several green chemistry principles since a catalytic amount of oxidant is used, in fact the real oxidant is oxygen,[20] the catalyst is a non-contaminating metal and the reactions are carried out at room temperature under normal pressure.

The definitions of green chemistry related terms,[21] as well as the green metrics are frequently revised in modern literature.[22] It is generally agreed that metrics must be clearly defined, simple, measurable and objective rather than subjective. Some of the most commonly used metric are the environmental factor based

on molecular weight (E_{mw}), atom economy (*AE*), mass intensity (*MI*), reaction mass efficiency (*RME*), the environmental impact factor based on mass (E_m) and the carbon efficiency (*CE*).[23] The reactions reported here meet several of the green chemistry principles with very satisfactory green metrics.

Atom economy (*AE*), mass intensity (*MI*), reaction mass efficiency (*RME*) and the carbon efficiency (*CE*) have been proposed in the last decade as a measure of environmental sustainability in terms of minimisation theoretical waste amount.[22b] *AE* was introduced by Trost[24] and is a theoretical measure of the chemical and environmental efficiency of a chemical reaction based on stoichiometric equation; it does not consider solvents, possible excess of reagents, formation of unwanted products, *etc.* *MI* takes into account the yield, stoichiometry, the solvent and the reactant used in the reaction. *RME* is a more sophisticated measure of *greenness* which allows for the effect of yield and the excess or catalytic amount of reactants used, but it does not account for solvent use. Finally, *CE* is the percentage of carbon in the reactants that remain in the final product, this parameter is not very important here because the oxidation does not involve carbon, it mainly reflects the yield of the reactions. In an ideal situation % *AE* ≈ 100, *MI* ≈ 1, % *RME* ≈ 100, % *CE* ≈ 100.

In Table 5 the green metrics calculated for our reaction mixtures are summarized. The results show that our reactions have an excellent *CE*; which in this case is equal to the yield because all carbon atoms of the reactant are present in the product. In the same direction, the high yields, the catalytic amounts of oxidant and the use of catalyst produce very good values of *RME*. On the other hand, the *MI* values obtained are acceptable since not much solvent is used. It is important to remark that this reaction can be carried out with much less solvent than the amount used which results in a significant improvement of the *MI* parameter. In fact, we carry out one reaction using substrate 4-(methylthio)benzaldehyde and only 0.6 mL of solvent and the product was obtained with excellent yield and the *MI* value was 4.04. Since 4-(methylthio)benzaldehyde is liquid at room temperature, the reaction was also done without any solvent and the yield obtained was excellent. The *MI* value was 1.2 in this case, thus very close to the ideal value. The reason why we used more solvent in all the other reactions is because that was needed to take samples and determine the time needed for completion.

Experimental

The ^{1}H NMR spectra were carried out in a 400 MHz Bruker Avance II spectrometer. The chromatograms were carried out in a GC-14B Shimadzu chromatograph and mass spectra in MS-GC CQ5050 Shimadzu GC-Mass Spectrometer.

The solvents used, Fe(NO$_3$)$_3$·9H$_2$O and FeBr$_3$, were analytical grade commercially available samples and used as received. Cyclodextrin-FeBr$_3$ and DMSO-FeBr$_3$ complexes were prepared as described in previous papers.[12a,25] Substrates 4-(methylthio)phenylisothiocyanate **1**; 4-(methylthio)benzoic acid **2**; 4-(methylthio)acetophenone, **3**; 2-(methylthio)phenyl isothiocyanate **4**; 2-(methylthio)benzoic acid **5**; 2-(methylthio) bromobenzene **6**; 2-(methylthio)benzaldehyde **7**; 4-(methylthio)-aniline **8**, 2-(methylthio)aniline **9** and 4-(methylthio)phenylisocyanate **10** were obtained from commercial suppliers. The products were characterized by the ^{1}H NMR spectra and/or by MS-GC.

General procedure

All reactions were carried out in a closed reaction tube, 165 mL, with magnetic stirring at room temperature. The volume of the reaction vessel is important because it must have enough oxygen for the oxidation reaction. The molar ratios substrate : catalyst : nitrate were 1.00 : 0.05 : 0.10 or 0.13. In a typical procedure, the substrate (1 mmol) was dissolved in acetonitrile (2.6 mL) and the iron complex (0.05 mmol) and the iron (III) nitrate (0.10 mmol) or nitric acid (0.13 mmol) were added.

Table 5 Green metrics calculated for the sulfoxidation reactions[a]

Substrate	% Yield (Table;Entry)	MI[b]	% RME	% CE	% AE
1	93 (1;1)	12.46[c]	77.20[c]	93	92.50
1	96 (1;3)	11.94[c]	87.08[c]	96	92.50
1	90 (1;5)	12.93	70.34	90	92.50
1	95 (1;6)	12.39	67.17	95	92.50
1	100 (1;7)	11.50	87.81	100	92.50
2	100 (2;1)	12.31[c]	82.01[c]	100	92.01
2	100 (2;3)	12.24	87.05	100	92.01
2	95 (2;5)	13.28	65.91	95	92.01
3	100 (3;1)	12.43[c]	81.85[c]	100	91.93
3	100 (3;3)	12.37	86.93	100	91.93
3	95 (3;5)	13.33	65.59	95	91.93
5	100 (2;6)	12.31[c]	82.01[c]	100	92.01
5	100 (2;8)	12.24	87.05	100	92.01
5	93 (2;10)	13.48	64.42	93	92.01
6	92 (4;1)	11.42[c]	77.69[c]	92	93.19
6	100 (4;3)	10.45	88.88	100	93.19
7	100 (4;4)	13.39[c]	80.63[c]	100	91.31
7	100 (4;6)	13.31	85.99	100	91.31

[a] MI: mass intensity. % RME: percentage reaction mass efficiency. % CE: percentage carbon efficiency. % AE: percentage atom economy. [b] The solvent used in the purification step was not considered in the calculations. [c] The amount of catalyst was not used in the calculations because it is recoverable by filtration and it can be reused.[12b]

The reactions were analyzed from time to time by thin layer chromatography or by GC in order to determine the time of the total consumption of the substrate. Under the same reaction conditions, the total reaction time depended on the sulfide. The reactions with cyclodextrin complexes are heterogeneous since complexes are solid, not soluble in this system. Once the reaction was over, diverse isolation and/or purification methods were used. In all cases 10 mL of CH_2Cl_2 were added, the solution was filtered and the solid washed several times with CH_2Cl_2. The organic layer was separated and washed with distilled water (3 × 10 mL) to remove any inorganic residue. Then, it was dried with $MgSO_4$ and the solvent was evaporated and recovered for further use. The residue was analysed by different chromatographic and spectroscopic methods. In some cases after filtration, the products were purified by column chromatography on silica gel 60 (70–230 mesh ASTM). All reactions were conducted in duplicate. In no case were sulfones detected.

Reactants and products characterization

4-(Methylthio)phenylisothiocyanate 1. δ_H (400 MHz, CDCl₃, Me₄Si) 2.48 (3H, s, -CH₃) and 7.10–7.22 (4H, m, ArH). *m/z* 181(M⁺, 100%), 166(91), 135(12), 122(20), 108(35), 90(8), 69(8), 50(10).

4-(Methylsulfinyl)phenylisothiocyanate 1a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.73 (3H, s, -CH₃) and 7.35–7.67 (4H, m, ArH). *m/z* 197(M⁺, 23%), 182(100), 166(51), 150(22), 134(15), 108(21), 90(8), 69(6), 50(12).

4-(Methylthio)benzoic acid 2. δ_H (400 MHz, CDCl₃, Me₄Si) 2.54 (3H, s, -CH₃) and 7.31–7.94 (4H, m, ArH). *m/z* 168(M⁺, 100%), 151(43), 135(7), 123(12), 108(5), 105(5), 69(11), 45(20).

4-(Methylsulfinyl)benzoic acid 2a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.84 (3H, s, -CH₃) and 7.76–8.20 (4H, m, Ar). *m/z* 184(M⁺, 2%), 168(27), 153(21), 152(100), 151(82), 123(20), 108(11), 97(12), 77(19), 65(12), 45(28).

4-(Methylthio)acetophenone 3. δ_H (400 MHz, CDCl₃, Me₄Si) 2.52 (3H, s, -CH₃), 2.57 (3H, s, -CH₃) and 7.25–7.88(4H; m; ArH). *m/z* 166(M⁺, 77%), 151(100), 123(31), 108(17), 79(21), 45(37).

4-(Methylsulfinyl)acetophenone 3a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.61 (3H, s, -CH₃), 2.73 (3H, s, -CH₃) and 7.48–8.06 (4H; m; ArH).[26] *m/z* 182(M⁺, 59%), 167(100), 162(42), 153(10), 152(81), 151(80), 139(20), 123(19), 121(15), 108(12), 91(7), 76(18), 63(13), 45(24), 43(31).

2-(Methylthio)phenylisothiocyanate 4. δ_H (400 MHz, CDCl₃, Me₄Si) 2.51 (3H, s, -CH₃) and 7.12–7.30 (4H, m, ArH).

2-(Methylthio)benzoic acid 5. δ_H (400 MHz, CDCl₃, Me₄Si) 2.50 (3H, s, -CH₃) and 7.20–8.16 (4H, m, ArH). *m/z* 168(M⁺, 100%), 153(47), 135(20), 122(60), 121(53), 108(13), 105(23), 97(11), 69(18), 45(40).

2-(Methylsulfinyl)benzoic acid 5a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.90 (3H, s, -CH₃) and 7.59–8.10 (4H, m, ArH). *m/z* 166(27%), 136(100), 121(1), 108(42), 92(3), 82(9), 69(15), 50(6).

2-(Methylthio)bromobenzene 6. δ_H (400 MHz, CDCl₃, Me₄Si) 2.43 (3H, s, -CH₃) and 6.81–7.69 (4H; m; ArH).

2-(Methylsulfinyl)bromobenzene 6a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.83 (3H, s, -CH₃) and 7.37–7.98 (4H, m, ArH).[27]

2-(Methylthio)benzaldehyde 7. δ_H (400 MHz, CDCl₃, Me₄Si) 2.45 (3H, s, -CH₃), 7.25–7.77 (4H, m, ArH) and 10.91 (1H, s, CHO).

2-(Methylsulfinyl)benzaldehyde 7a. δ_H (400 MHz, CDCl₃, Me₄Si) 2.75 (3H, s, -CH₃), 7.67–8.26 (4H, m, ArH) and 9.98 (1H, s, CHO). *m/z* 168(M⁺, 28%), 153(28), 152(100), 123(18), 109(10).

4-(Methylthio)aniline 8. δ_H (400 MHz, CDCl₃, Me₄Si) 2.43 (3H, s, -CH₃) and 6.63–7.21 (4H, m, ArH).

2-(Methylthio)aniline 9. δ_H (400 MHz, CDCl₃, Me₄Si) 2.39 (3H, s, -CH₃) and 6.74–7.45 (4H, m, ArH).

4-(Methylthio)phenylisocyanate 10. δ_H (400 MHz, CDCl₃, Me₄Si) 2.48 (3H, s, -CH₃) and 7.02–7.22 (4H, m, ArH).

Green metric calculations

The green metrics were calculated using the procedures reported in the literature.[22b] They are defined as follows:

$$\text{Mass intensity (MI)} = \frac{\text{Total mass used in a process or process step (g)}}{\text{Mass of product (g)}}$$

$$\text{Reaction mass efficiency (RME)} = \frac{\sum \text{mass of products}}{\sum \text{mass of reactants}} \times 100$$

$$\text{Carbon efficiency (CE)} = \frac{\text{N}^\circ \text{ of moles of product } x \text{ N}^\circ \text{ of carbons in product}}{\sum (\text{N}^\circ \text{ of moles of reactant } x \text{ N}^\circ \text{ of carbons in reactant})} \times 100$$

$$\text{Atom economy (AE)} = \frac{\text{molecular weight of product}}{\sum \text{molecular weight of reactant}} \times 100$$

An example of a typical calculation follows

4-(Methylthio)phenylisothiocyanate (0.181 g, 1 mmol, FW 181.28) reacts with the iron (III) nitrate nonahydrate (0.040 g, 0.10 mmol, FW 404.00) and molecular oxygen (0.016 g, 0.5 mmol, FW 32.0) in the presence of iron complex (0.068 g, 0.05 mmol, FW 1369.17) in acetonitrile (2.6 mL, 2.044 g) to give 4-(methylsulfinyl)phenylisothiocyanate (FW 197.28) isolated in 93% yield (0.93 mmol, 0.183 g). The amount of catalyst was not used in the calculations because it is recoverable by filtration and it can be reused. For *AE*, reagents in catalytic quantities and catalysts are not considered in the calculation.

Mass intensity = (0.181 + 0.040 + 2.044 + 0.016)/0.183 = 12.46 g/g

Reaction mass efficiency = [0.183/(0.181 + 0.040+ 0.016)] × 100 = 77.2%

Atom Economy = (197.28/181.28 + 32.00) × 100 = 92.5%

Carbon efficiency = (0.93 × 8)/(1 × 8) = 93%

Conclusions

It can be concluded that FeBr$_3$ and its complexes with cy-clodextrin or DMSO are excellent catalysts for chemoselective sulfoxidation reactions. The cyclodextrin complex is the best because it not only gave very good yields of products but it was easily handled under normal laboratory conditions. It could be easily isolated after the reaction and eventually re-used, this cannot be made with FeBr$_3$ or with its DMSO complex because they are soluble in the reaction media. Besides, the isolation of the reaction products was very simple when cyclodextrin complexes were used as catalyst. All these reactions are achieved in the presence of a catalytic amount of nitrate and the oxygen from the air is the oxidant agent. From the green chemistry point of view, the reactions reported here follow several of its principles and they have very good green metrics. It is also important to remark that the reactions take place a room temperature and under normal pressure.

In summary, we report herein a green and efficient method for the selective oxidation of sulfides to sulfoxides under very mild heterogeneous conditions with high yields and excellent chemoselectivity in the presence of other reactive groups such as *p*-isothiocyanate, *o*- and *p*-carboxylic acid, *p*-acetyl, *o*-bromo and *o*-aldehyde.

Acknowledgements

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The metathesis of α-olefins over supported Re-catalysts in supercritical CO₂

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At 35 °C, in the presence of supercritical carbon dioxide (80–150 bar) as a solvent, α-olefins (RCH=CH₂, R = C4–C6) undergo highly selective self-metathesis catalyzed by supported Re-oxide (7%). To the best of our knowledge, this is the first procedure for the metathesis of alkenes, in which heterogeneous catalysts are combined with the use of dense CO₂. The intrinsic eco-compatibility and the unique physicochemical properties of this medium offer both environmental and synthetic advantages: not only conventional toxic solvents (*e.g. n*-heptane and toluene) can be replaced, but the reaction is faster. For instance, after 2 h, the average conversion of 1-octene is 67% and 40% in scCO₂ and *n*-heptane, respectively. The product of self-methatesis, 7-tetradecene, can be isolated in yields up to 68%. At 90 bar, the reaction is rather sensitive to the mole fraction of the olefin (in scCO₂); though, the enhancement of the pressure (and the density) of the supercritical medium does not induce significant effects on either the rate or the selectivity of the process. The nature of the catalytic support also greatly affects the reaction outcome: Re-oxide shows good activity if dispersed over γ-Al₂O₃, while silica-based systems are ineffective.

Introduction

The olefin metathesis reaction is a powerful, elegant, clean, and atom economical means of constructing complex carbon frameworks.[1] As such it has undergone tremendous development since its discovery in the 1950s,[2] culminating in the Nobel Prize in Chemistry awarded to Chauvin, Grubbs, and Schrock in 2005. The applications of the reaction span from petrochemistry (*e.g.* in the synthesis of linear higher olefins and of propene), to polymer chemistry (*e.g.* polynorbornene and poly(dicyclopentadiene) *via* ring-opening-metathesis polymerization), to fine chemistry. The metathesis of alkenes represents the archetype green chemistry reaction for clean syntheses with reduced emissions of hazardous wastes to the environment.[3] In this context, the increasing demand for safer and more efficient synthetic procedures has spurred research towards new homogeneous catalysts able to operate under milder conditions, to improve the reaction selectivity, and to extend the synthetic scope of the metathetic process in general.[4] Excellent examples were designed by Grubbs *et al.*,[3–5] based on Ru- and Mo-carbene complexes capable of tolerating a variety of polar and protic groups for the ring-closing metathesis (RCM) of functionalized dienes to produce valuable cyclic intermediates.

Further improvements of the synthetic potential, scope, and eco-compatibility of the metathesis lie, in our opinion, in the use of alternative safer and *greener* solvents able to replace conventional media, typically hydrocarbons (hexane and toluene)

or light chlorinated compounds (dichloromethane and carbon tetrachloride).[3,6] This is a largely unexplored area: only a few recent patents and papers report on the application of dense CO₂ or ionic liquids as solvents for RCM and ROMP (ring opening metathesis polymerization) processes,[7,8] using either Grubbs catalysts or transition metal salts [RuCl₃, Ru(H₂O)₆(tos)₂, and WCl₆/Ph₄Sn].

Compressed CO₂ as a solvent is perfectly suited for metathesis applications, especially if combined with the use of heterogeneous catalysts. First of all its solvating power towards alkenes is high.[9] Secondly, dense carbon dioxide is very efficient at penetrating meso- and micro-porous supports used for solid catalysts, thanks to its low viscosity (η) and high diffusivity (D) (0.01–0.03 mPa s and ~0.07 × 10⁻⁶ m² s⁻¹, respectively).[10] In both its liquid and supercritical states, CO₂ as a solvent/carrier, can therefore improve the mass transfer (and the reaction rate) for a variety of different processes catalysed by solid materials. Examples are alkylations,[8–11] etherifications and esterifications,[12] hydrogenations and hydroformylations,[13,14] and oxidations[15] carried out either in batch or in continuous-flow conditions, in the presence of zeolites, supported acids, metals on polysiloxane-based Deloxan or Amberlyst resins, on MCM solids, and on alumina and silica.

Yet, to the best of our knowledge, the combined use of heterogeneous catalysts and CO₂ solvent has not been investigated for the metathesis of olefins. This observation in conjunction with our long-standing interest for green synthetic methods using CO₂ and its derivatives,[16] have inspired the present work. We report that in the presence of Re₂O₇ supported on γ-Al₂O₃, not only the self-metathesis of α-olefins occurs efficiently in supercritical carbon dioxide (scCO₂), but the reaction also takes place faster than in classic media (*n*-heptane and toluene). The properties of scCO₂ increase the overall efficiency and sustainability of the transformation.

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Results

Catalysts

The heterogeneous catalysts for the metathesis of olefins are usually transition metal oxides such as Re_2O_7 and MoO_3 supported on several inorganic matrices (SiO_2, Al_2O_3, ZrO_2 and TiO_2).[1,17] The catalytic systems used in this study were based on Re_2O_7 supported on both γ-Al_2O_3 (from Puralox Condea and from Alfa-Aesar), and SiO_2 (from Aldrich). These were prepared by a conventional impregnation technique,[18] using commercial ammonium perrhenate (NH_4ReO_4) as the precursor of the active phase. Each sample was calcined in dry air at 550 °C, and immediately before use, it was activated in dry N_2 at the same temperature (details in the Experimental section). Four different catalysts were obtained: three of them were supported on two different aluminas, while the fourth specimen was dispersed on SiO_2. They were labelled as Re-A$_1$, Re-A$_2$, Re-A$_3$, and Re-S, respectively. The final metal content (by weight) was determined by optical ICP, and it ranged from 6.4 to 7.0%. The catalysts on γ-Al_2O_3 (Re-A$_1$, Re-A$_2$, and Re-A$_3$) were also characterised by TEM. Catalyst characteristics are listed in Table 1.

Self-metathesis of 1-octene in conventional solvents (method A) and in supercritical CO$_2$ (method B)

Method A. The reaction of 1-octene (**1a**)—chosen as a model for α-olefins—was carried out under conventional liquid-phase conditions, by adjusting an existing procedure.[17] In a 25 mL round-bottomed flask, the catalyst (0.56 g, 7%) was activated at 550 °C; then, at 35 °C, a 5×10^{-1} M solution (10 mL) of 1-octene (5 mmol) in *n*-heptane or toluene, was introduced and kept magnetically stirred for 2 hours. After this time, ~70% conversion of 1-octene was reached, that corresponded to the equilibrium composition of metathesis products: between 70 and 80% as reported elsewhere for 1-octene.[18] The molar ratio **1a**:Re was 23.7. All operations (catalyst activation, transfer of the solution, and reaction step) were carried out under a N_2 atmosphere.[19] The course of the reaction was monitored by GC-MS.

Method B. The metathesis of 1-octene was then performed in dense CO_2. In order to compare the results of methods A and B, identical amounts of the olefin **1a** and the catalyst (5 mmol of 1-octene; molar ratio **1a**:Re = 23.7) were used in both cases. The reaction was run for 2 h, sufficient to reach the equilibrium composition of metathesis products in this case also, as indicated by the fact that conversion did not increase further for longer

reaction times. Preliminary experiments showed that at 35 °C in a 30 mL autoclave, a homogeneous solution of **1a** (5 mmol) in CO_2 was obtained at pressure $\geq$ 80 bar.[20] A first set of tests was then executed at 90 bar where the CO_2 density (0.66 g/mL) was very similar to that of *n*-heptane (0.67 g/mL).[21] Since previous methodologies were not available, the entire apparatus needed to be arranged. A Schlenk system was assembled to perform multiple operations under an inert (N_2) atmosphere. In particular: i) the high-temperature activation of the catalyst in a glass flask;[22] ii) the charging of the catalyst and of the reactant olefin in a stainless-steel reactor (a 30 mL autoclave); iii) the reaction step in the autoclave, at CO_2 pressures $\geq$ 90 bar. Fig. 1 shows a schematic diagram of the system.

In all cases, regardless of the solvent used, the formation of the expected product of self-metathesis (7-tetradecene, **2a**) was accompanied by different co-products which were identified as isomers of 1-octene (2-, 3-, and 4-octene) and linear olefins C_9–C_{13} (Scheme 1).
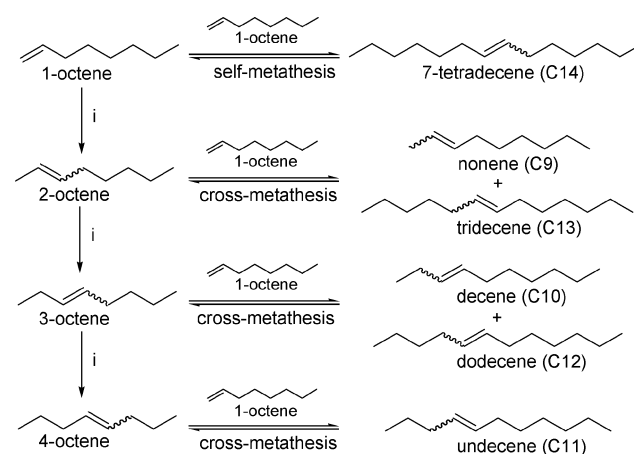
Scheme 1 Self- and cross-metathesis reactions were catalysed by supported Re_2O_7. The isomerization (i) of 1-octene was promoted by the support (γ-Al_2O_3 or SiO_2) alone.

This behaviour was in line with that already reported for the metathesis of α-olefins carried out in the liquid phase.[17,18,23] In particular, the isomerisation reaction could occur either due to the acidic sites of the support,[22b] or by an addition–elimination sequence mediated by a metal-hydride species as observed elsewhere for Ru.[24] Higher internal olefins (C_9–C_{13}) derived from the cross-metathesis of the reagent **1a** and of its isomers.[25]

Table 1 Re_2O_7 supported catalysts

	Precursor	Re (wt%)[a]	Support			Cat. label	Particle size (nm)[c]
			Type	S_A [m^2/g][b]	Source		
1	NH$_4$ReO$_4$	6.8	γ-Al$_2$O$_3$	257	Puralox-Condea	Re-A$_1$	<1
2	NH$_4$ReO$_4$	7.0	γ-Al$_2$O$_3$	200	Alfa-Aesar	Re-A$_2$	<1
3	NH$_4$ReO$_4$	6.4	γ-Al$_2$O$_3$	257	Puralox-Condea	Re-A$_3$	<1
4	NH$_4$ReO$_4$	6.7	SiO$_2$	550	Aldrich	Re-S	

[a] The metal content was determined by optical ICP. [b] Surface area of the support. (Typically, the S_A for metathesis catalysts is $\geq$ 200 m^2/g; ref. 1). [c] Determined by TEM.

Table 2 Self-metathesis of 1-octene in different solvents using supported Re_2O_7 catalysts[a]

| Entry | Cat. | Solvent[b] | X_{1a}[c] ($\times 10^{-2}$) (mol:mol) | Conv.'n (%, GC)[d] | Products (%, GC) | | | Selectivity (%)[h] | Y (%)[i] |
					Iso[e]	C_9–C_{13}[f]	2a[g]		
1	Re-A$_1$	n-Heptane	7.3	67	1	4	62	92	62
2	Re-A$_2$			46	1	1	44	96	
3	Re-S			1	1	—	—		
4	Re-A$_1$		1.1	40	1	1	38	95	
5	Re-A$_1$	Toluene	5.4	65	1	2	62	95	
6	Re-S			<1	<1				
7	Re-A$_1$		1.1	36	1	1	34	95	
8	Re-A$_1$	scCO$_2$	1.1	71	1	2	68	97	67
9	Re-A$_2$			37	1	2	32	86	
10	Re-S			<1	<1				

[a] All reactions were carried out at 35 °C for 2 hours, using 1-octene (5 mmol) and the catalyst (0.56 g) in the molar ratio olefin:Re = 23.7. [b] n-Heptane and toluene: 10 mL of a 5×10^{-1} M solution of **1a**; scCO$_2$: 90 bar (V = 30 mL, d = 0.66 g/mL). [c] X_{1a} = mole fraction of 1-octene in the 1-octene/solvent solution. [d] The reaction conversion (% by GC) was referred to all metathesis (olefins C_9–C_{14}) and isomerization compounds (Scheme 2). [e] Total amount (% by GC) of isomerization by-products (2-, 3- and 4-octene). [f] Total amount (% by GC) of products of the cross-metathesis reaction (olefins C_9–C_{13}). [g] Total amount (% by GC) of 7-tetradecene: geometric isomers *trans*/*cis* were in ratio 3.8–4.0. [h] Selectivity towards the product of self-metathesis: [C_{14} (Area%, GC)/conversion (%)] × 100. [i] Isolated yields of crude **2a**.
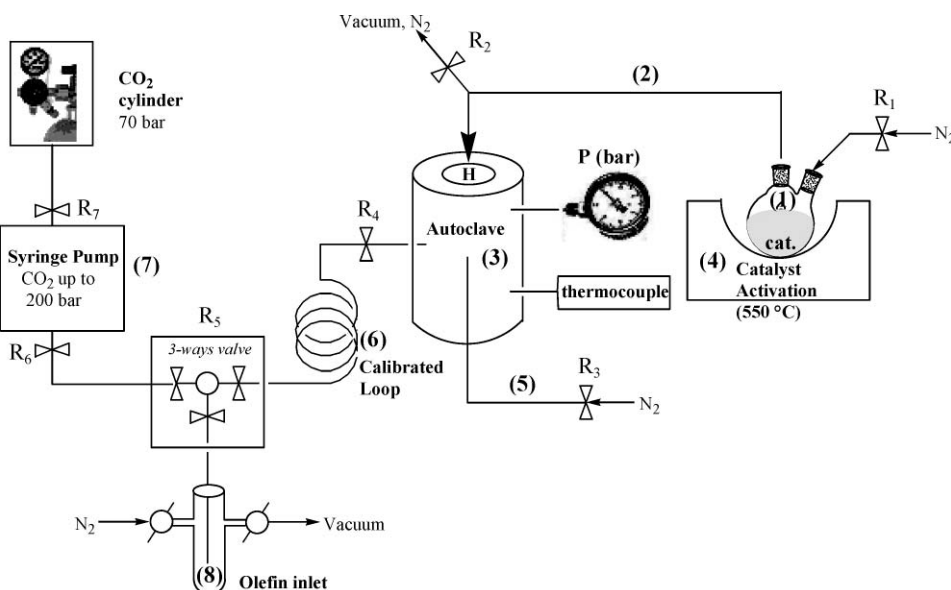
Fig. 1 Schematic diagram of the apparatus used to carry out the metathesis of olefins in dense CO$_2$.

Table 2 reports the results of the self-metathesis of 1-octene using different solvents and different catalysts. Iso, C_9–C_{13}, and C_{14} refer to the amounts (by GC) of isomerization products (total of 2-, 3-, and 4-octene), of cross-metathesis compounds (total of C_9–C_{13}), and of 7-tetradecene (total of *cis*/*trans* isomers), respectively. The reaction selectivity refers only to the formation of the self-metathesis product (**2a**).

The first significant aspect, never previously reported, was that scCO$_2$ could act as a solvent for the metathesis of 1-octene catalyzed by supported Re-oxide (entries 7–9). Other features emerging from Table 2, were: i) regardless of the solvent, only catalysts prepared from γ-Al$_2$O$_3$ were active for the transformation (entries 1, 2, 4, 5, 7 and 8); ii) the influence of the support was rather similar in the three tested solvents. In particular, the best system was Re-A$_1$ (on alumina Puralox, S_A = 257 m^2/g), which allowed, after 2 h, conversions of 67, 65, and 71%, in n-heptane, toluene, and scCO$_2$, respectively

(entries 1, 5 and 8). The reaction conversions were lower on Re-A$_2$ (on alumina Alfa-Aesar, S_A = 200 m^2/g): 46 and 37% in n-heptane and scCO$_2$ (entries 2 and 9). The silica-supported catalyst was not active at all (entries 3, 6 and 10); iii) finally, the selectivity towards the product of self-metathesis (7-tetradecene) was always very high (up to 96%). This compound (**2a**) was isolated from mixtures of reactions carried out in the presence of both n-heptane and scCO$_2$ solvents (conditions of entries 1 and 7): yields of crude 7-tetradecene (98% pure by GC) were 62% (305 mg) and 67% (340 mg), respectively.

Finally, two recycling experiments were performed using the Re-A$_2$ catalyst. After the reaction was carried out in the presence of scCO$_2$ (Table 2), Re-A$_2$ was filtered, dried under vacuum, and re-activated according to the procedure described above (N$_2$, 550 °C, 1.5 h). The catalyst was then re-used under the conditions of entry 9 (CO$_2$, 90 bar, Table 2). This cycle (activation/reaction) was repeated once more. The two reactions gave results in line

with the previous one (entry 9): the conversions were 39 and 33%, respectively, and the selectivity for 7-tetradecene was 99% in both cases. The catalyst recycle was not further investigated.[26]

An issue of the reactions shown in Table 2 relates to the concentration of 1-octene in the different solvents: it is readily apparent that the reactant was significantly more concentrated in *n*-heptane and toluene (0.54 M) than in CO_2 (0.17 M). While the molar concentration is a convenient parameter to compare kinetic profiles in liquid solvents, it is not suitable for supercritical solvents as it does not take into account pressure and the related significant solvation effects. The mole fraction of 1-octene **1a** $\{X_{1a} = [1a]/([1a] + [solvent])\}$ appeared like a more appropriate parameter for a coherent comparison. In fact, in the experiments of Table 2, X_{1a} was also much larger in *n*-heptane and toluene (7.3×10^{-2} and 5.4×10^{-2} respectively) than in dense CO_2 (1.1×10^{-2}). Therefore, the metathesis was carried out in *n*-heptane and toluene with the same mole fraction of 1-octene $X_{1a} = 1.1 \times 10^{-2}$ as in $scCO_2$ (entries 4 and 7), using Re-A$_1$ as the catalyst. All else being equal, the conversion in these instances after 2 h were significantly lower (40% and 36% respectively, entries 4 and 7) with respect to the reaction in dense CO_2 (71%, entry 8). This indicated that the metathesis reaction was faster in the supercritical medium than in liquid solvents.

To further investigate the dilution effect, two more reactions were carried out in $scCO_2$ (90 bar, 35 °C), using more diluted solutions of the substrate. With respect to the above described conditions (method B), in the new experiments, the amount of olefin was decreased to 3.7 and 2.5 mmoles, which corresponded to mole fractions (X_{1a}) of 0.5×10^{-2} and 0.8×10^{-2}, respectively. The quantity of the catalyst (Re-A$_1$) was also reduced to 0.42 and 0.28 g, in order to keep the molar ratio olefin:Re constant at 23.7 (method B). The results are illustrated in Fig. 2, where the conversion and the selectivity of the reaction, are plotted against the mole fraction of the olefin. To complete the view, the figure also includes the case of entry 8 of Table 2.
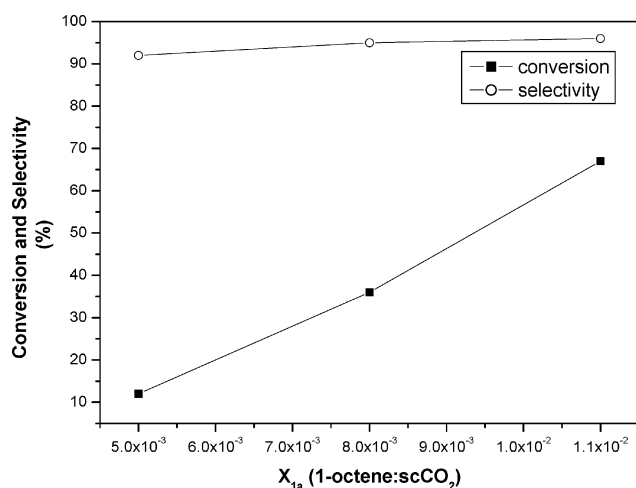
Fig. 2 Conversion of 1-octene and self-metathesis selectivity after 2 hours of reaction in $scCO_2$.

The overall effect of dilution was to decrease the rate of the process: when the mole fraction X_{1a} was halved (from 1.1×10^{-2} to 0.5×10^{-2}), the conversion of 1-octene dropped considerably from 71 to 12% (■ line in Fig. 2). By contrast,

the self-metathesis selectivity (92–97%, ○ line in Fig. 2) was not appreciably modified by the change of X_{1a}. This behaviour was similar to that observed in the presence of *n*-heptane and toluene as solvents (compare entries 1 and 4 , and 5 and 7 of Table 2).

The effect of the CO_2 pressure

The solvating ability of supercritical carbon dioxide can be controlled by adjusting density and viscosity through small variations of pressure and temperature.[27] This behaviour allows one to fine-tune the solvent power of $scCO_2$, and can be exploited to improve the performance of several processes.[8,25]

A set of experiments were devised to investigate the effect of the CO_2 pressure under the conditions set up for the metathesis on solid catalysts. The above-described method B (35 °C; 5 mmol of **1a**; molar ratio **1a**:Re = 23.7, 2 h), was used to carry out the reaction of 1-octene at 80, 120 and 150 bar, in the presence of Re-A$_1$ as the catalyst. The results are shown in Fig. 3, where the conversion and the selectivity of the process are plotted against the CO_2 pressure. To complete the view, the figure also includes the data obtained at 90 bar (entry 8, Table 2). At the different pressures, the values of the density of CO_2 are indicated in parenthesis.
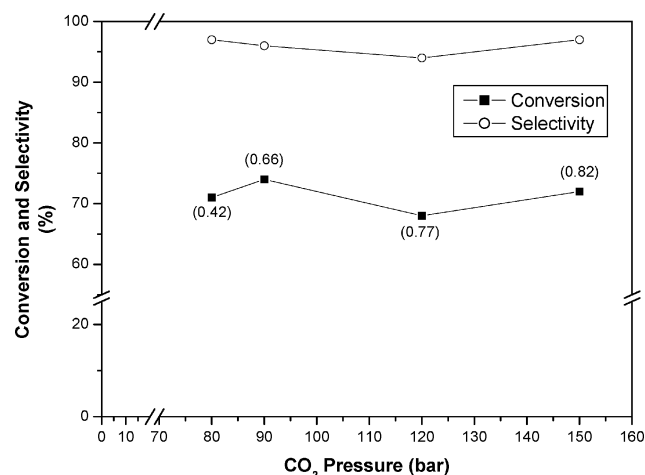
Fig. 3 The self-metathesis of 1-octene: conversion and selectivity as a function of the CO_2 pressure. The values of the CO_2 density (taken from ref. 21) are shown in parenthesis.

The change of the CO_2 pressure in the range from 80 to 150 bar did not affect the reaction outcome: both the conversion of 1-octene and the self-metathesis selectivity remained substantially constant at nearly 70% and 95%, respectively. It should be promptly noted that this behaviour implied an apparent incongruity. In fact, since the increase of the pressure (and of the density) of the supercritical medium entailed a decrease of the mole fraction of the olefin (80 bar: $X_{1a} = 1.7 \times 10^{-2}$; 150 bar: $X_{1a} = 0.9 \times 10^{-2}$), a significant drop of the reaction conversion would have been expected (compare Tables 2 and Fig. 1). A comment is offered in the Discussion section.

The effect of the catalyst amount

In the presence of $scCO_2$, the influence of the catalyst amount on the metathesis of 1-octene, was studied using the Re-A$_3$

Table 3 The effect of the catalyst amount on the self-metathesis of 1-octene carried out in scCO$_2$ (35 °C, 90 bar)[a]

Entry	Catalyst	1a:Re[b] (mol:mol)	t (h)	Conv.'n (%)[c]	Sel. (%)[c]	TOF × 10^{-2} (mol/mol min)[d]
1	Re-A$_3$	47.4	2	39	85	15
2	Re-A$_3$	23.7	2	71	96	14
3	Re-A$_3$	15.8	2	82	94	11
4	Re-A$_3$	11.8	2	81	93	8
5	Re-A$_3$	11.8	1	64	94	13

[a] All reactions were carried out following the general procedure described as method B. [b] **1a**:Re was the molar ratio 1-octene:Re. [c] The reaction conversion and the self-metathesis selectivity were defined as reported in Table 2. [d] TOF: mole of converted olefin per mole of Re per minute.

sample (Table 1). According to the method B (see above), five subsequent experiments were performed by setting the molar ratio **1a**:Re at 47.4, 23.7, 15.8, and 11.8, respectively. Other parameters such as temperature and pressure (35 °C and 90 bar) and the olefin amount (5 mmol) were not altered. Results are reported in Table 3.

After 2 hours of reaction, doubling the amount of catalyst increased the conversion from 39 to 71% (**1a**:Re ratio was halved from 47.4 to 23.7; entries 1–2). Further increments of the catalyst amount (**1a**:Re at 15.8 and 11.8, respectively) produced only a moderate change: the substrate conversion reached a substantially constant value slightly over 80% (entries 3–4), that did not increase further for longer reaction times.

This behaviour along with the calculated turnover frequency (TOF: moles of converted olefin per mole of Re per minute), suggested that a ratio **1a**:Re in the range of 23.7–15.6 allowed the metathesis of 1-octene to achieve equilibrium in the first 120 min. If a higher amount of catalyst was used (**1a**:Re of 11.8), a lower specific activity resulted (entry 4, TOF = 8 min^{-1}): under these conditions, the equilibrium was perhaps reached more quickly. The last experiment corroborated this hypothesis. Operating at the highest catalyst loading (**1a**:Re of 11.8), the conversion was 64% after only 1 hour, and the corresponding TOF went up to 13 min^{-1} (entry 5), in line with the values obtained in the previous reactions (TOF = 14–15, entries 1–2). The self-metathesis selectivity was at the same high level (93–96%) reported in Tables 2 and 3 and Fig. 2 and 3, except for the lower catalyst amount (**1a**:Re of 47.4): in this case, the selectivity dropped to 85% (entry 1), due to the onset of the isomerization reaction whose products summed to 7% (by GC).

The self-metathesis of 1-hexene and 1-heptene in scCO$_2$

In the presence of the Re-A$_3$ catalyst, the metathesis of other α-olefins such as 1-hexene and 1-heptene (**1b** and **1c**, respectively), was investigated in supercritical carbon dioxide as the solvent (Scheme 2).

Scheme 2
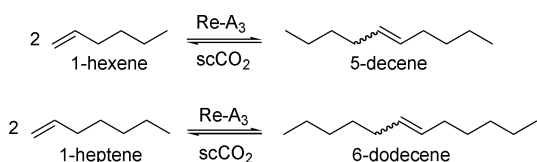
The reaction conditions were those of entry 8 in Table 2. Both reactions proceeded very similarly to that of 1-octene (Table 4). At 35 °C (90 bar), after 2 hours, conversions were

Table 4 The self-metathesis of 1-hexene and 1-heptene carried out in scCO$_2$ (35 °C, 90 bar)[a]

Entry	Catalyst	Substrate	Conv.'n (%)[b]	Products (%, GC)[c]			Sel. (%)[d]
				Iso	Cross	Self	
1	Re-A$_3$	1-Hexene	64	1	2	61	95
2	Re-A$_3$	1-Heptene	67	2	2	63	94

[a] All reactions were carried out for 2 hours, at 35 °C, in the presence of Re-A$_3$ as the catalyst. Experiments were run under the conditions of entry 8 in Table 2, by using a mixture of α-olefin (5 mmol) and the catalyst (0.56 g) in the molar ratio olefin:Re = 23.7. [b] The reaction conversion was determined by GC. [c] Products. Iso: total amount of isomers of 1-hexene (2- and 3-hexene, entry 1) and of 1-heptene (2- and 3-heptene, entry 2); Cross: total amount of products of cross-metathesis of 1-hexene (olefins C$_7$–C$_9$, entry 1) and of 1-heptene (olefins C$_8$–C$_{11}$, entry 2); Self: amount of the product of self-metathesis of 1-hexene (5-decene, entry 1) and of 1-heptene (6-dodecene, entry 2). [d] The selectivity was defined towards the product of self-metathesis. Entry 1: [C$_{10}$ (Area%, GC)/conversion (%)] × 100; entry 2: [C$_{12}$ (Area%, GC)/conversion (%)] × 100.

64 and 67% for 1-hexene and 1-heptene, respectively. The self-metathesis selectivity was 94 and 95%, and the structures of the corresponding products (5-decene and 6-dodecene) were assigned by GC-MS and by comparison to authentic samples.

Reproducibility

A total of nearly 120 experiments were carried out (including reactions, not here reported, to evaluate conversions *vs.* time, and to reproduce results of Tables 2 and 3 and Fig. 2 and 3) during the examination of the metathesis of 1-octene in both scCO$_2$ and conventional liquid solvents. Both the conversion and the self-metathesis selectivity (determined by GC-MS) were reproducible within a range of ±5%. It should be mentioned however, that 15 out of the total number of the tests showed a conversion less than 10%, and most of these unsuccessful trials (12) were observed in *n*-heptane.[28] Presently, no clear reasons account for this behaviour.

Discussion

CO$_2$ as a solvent for metathesis

Although the use of scCO$_2$ as a metathesis solvent in place of traditional organic solvents, represents an improvement towards greening the process, by itself it is not necessarily an innovation. It becomes such only when scCO$_2$ contributes to enhance other aspects of the chemical transformation as well, particularly if it

makes the reaction faster compared to traditional conditions, or if it overcomes a technological barrier towards more efficient operation.

One such instance where scCO$_2$ has a significant advantage over traditional solvents is when it is used to overcome the mass transfer limitations associated with heterogeneous catalysis. This is exemplified by the present case where Re-based solid catalysts, prepared by impregnation of Re on commercial alumina supports, were shown to be active for the metathesis of olefins when combined with the use of compressed CO$_2$ as a solvent (Table 2). ScCO$_2$ promoted the self-metathesis of 1-octene over these supported Re catalysts with higher conversion compared to conventional liquid solvents. The properties of the supercritical medium account for this behaviour. For one, the gas-like diffusivity and viscosity and the liquid-like density of scCO$_2$, as well as the elimination of interphases, result in a significant improvement of the mass transfer. In addition, peculiar solvation phenomena are known to take place. These can be described as local density enhancements (LDEs), whereby the density as well as the composition of the local environment around the solute molecules are modified, with respect to the bulk of the supercritical solvent.[8,11]

The outcome of the self-metathesis is sensitive to the concentration of the olefin solution: the more diluted the substrate, the lower the conversion (Fig. 2). However, when the pressure (*i.e.* the density) of CO$_2$ is increased in the range of 80–150 bar, thereby diluting the reactant olefin, the expected drop of conversion is not observed (Fig. 3). Different aspects can account for this apparent inconsistency. On one side, the enhancement of the pressure may have a beneficial influence: in dense CO$_2$, it is often reported that kinetic profiles, yields, and selectivity of a variety of reactions, are improved by increasing the density of the medium.[8,11,25] On the other hand, by operating at high pressure in a closed system, the equilibrium is different from an open system due to the release of stoichiometric amounts of ethylene that could prove disadvantageous for a reaction such as metathesis. However, being the total pressure almost exclusively determined by the CO$_2$, the release of ethylene and the equilibrium should not be affected.[7b,29] In the case investigated here, these opposite effects seem counterbalanced in such a way that the final pressure (and density) of the supercritical solvent does not affect the macroscopic outcome of the process.

The influence of the catalyst

The most significant aspect deals with the nature of the supports (γ-Al$_2$O$_3$ and silica). It is generally agreed that the monomeric tetrahedral structure of ReO$_4^-$, is stabilized over the alumina surface: the metal centre forms three equivalent Re=O moieties and a Re–O–Al bond with an acidic OH group on the support.[18,30] Although the nature of this last interaction is not fully understood, a high surface area (S_A) of the solid alumina is crucial to increase the dispersion of the active phase and to improve the catalytic performance.[31] This reason may account for the behaviour reported in Table 2: in the presence of both scCO$_2$ and *n*-heptane as a solvent, the Re-A$_1$ sample supported on a γ-Al$_2$O$_3$ of 257 m^2/g, allows a higher conversion with respect to the Re-A$_2$ catalyst prepared on a γ-Al$_2$O$_3$ of 200 m^2/g. However, definite conclusions on metal dispersion

and particle size cannot be drawn yet. The TEM analysis of Re-A$_1$ and Re-A$_2$ shows the γ-phase in the shape of grains of 5–6 nm, while the Re-oxide particles are not clearly distinguishable, their size being less than 1 nm. Onaka *et al.* have reported a similar result.[18]

Silica possesses a lower surface acidity with respect to alumina.[32] This difference is claimed to explain the generally poorer activity of silica-supported Re-oxide in the metathesis of olefins.[33] An example is the metathesis of 1-butene which is reported to take place at temperatures not below 75 °C, in the presence of a Re$_2$O$_7$/SiO$_2$ (6%) catalyst.[34] The results of Table 2 can be discussed on a similar basis: plausibly, the Re-S sample (on silica) is not effective for the reaction of 1-octene, because of the low reaction temperature (35 °C).

As far as the amount of the catalyst, Table 3 suggests that in the presence of a relatively low metal loading (7%),[35] a convenient olefin:Re molar ratio is in the range of 20–25. Under these conditions, in supercritical CO$_2$ (90 bar, 35 °C, $d = 0.66$ g/mL), the substrate conversion reaches an equilibrium value of ~ 70% after the first 120 min of reaction.

Conclusions

This paper describes the first example of self-metathesis of α-olefins (1-hexene, 1-heptene, and 1-octene) catalysed by heterogeneous Re-based catalysts, in the presence of supercritical carbon dioxide as the solvent. Although an additional "compression" energy (and costs) must be provided with respect to traditional solvent systems, in the present case, beyond the environmentally benign character of scCO$_2$, a remarkable improvement of the reaction outcome is observed: for example, at 35 °C, the self-metathesis of 1-octene proceeds with a conversion over 30% higher on average in the supercritical medium than in a conventional solvent such as *n*-heptane. A performance possibly due to the increase of the mass transfer promoted by dense CO$_2$. The reaction of 1-octene is also plausibly affected by the enhancement of the pressure of CO$_2$, through opposite actions: on one hand, a beneficial solvation/mass transfer effect may operate; on the other, disadvantages may derive from the dilution of the substrate. The final result is that in the range of 80–150 bar, both the conversion and the self-metathesis selectivity show no appreciable variations.

The most significant influence of the catalysts, deals with the nature of their support. In the presence of γ-Al$_2$O$_3$, the catalytic systems are active, and their performance seems improved by the increase in the surface area of the solid matrix. By contrast, if Re-oxide is dispersed over the less acidic silica (with respect to alumina), no reaction takes place at all. This behaviour is observed in both scCO$_2$ and *n*-heptane solvents.

Overall, scCO$_2$ appears as a viable alternative for the replacement of liquid solvents ordinarily used in the metathesis of olefins. Not only the sustainability of the process is improved, but the novelty of this finding opens a new perspective in a field which is still largely unexplored.

Experimental

General. α-Olefins **1a-c** were ACS grade and were employed without further purification. Conventional liquid solvents

(*n*-heptane and toluene), were either used as such or purified through known methods.[36] Ammonium perrhenate (NH_4ReO_4, ≥99%) was from Aldrich. γ-Al_2O_3 was from two different sources: Puralox-Condea and Alfa-Aesar. These solids had a surface area (S_A) of 257 and 200 m^2/g, respectively. Silica was from Aldrich (S_A = 550 m^2/g). GC-MS (70 eV) analyses were run using a HP5/MS capillary column (30 m). The gaseous N_2 used throughout the activation of catalysts and the general procedure for the reaction (see below), was of an R-grade and it was further purified by Drierite®/13X filters (Aldrich). Wherever used, water was of milli-Q grade. CO_2 was of a SFC/SFE grade (purity 99.998%). ^{1}H NMR spectra were recorded on a 300 MHz spectrometer, using $CDCl_3$ as solvent.

The preparation of catalysts

All catalysts were prepared by a wet-impregnation technique described in the literature.[5c,37] A 25 mL round bottomed flask was charged with an aqueous solution (1.7×10^{-1} M, 12 mL) of NH_4ReO_4 (555 mg, 2.1 mmol) and with the chosen support (γ-Al_2O_3 or silica; 5 g). The slurry was kept under magnetic stirring for 1 hour at rt, and then dried under vacuum (50 °C, 36 mbar). The solid residue was further wetted with water (8 mL), stirred for 15 min at rt, and finally, dried again (50 °C, 2 mbar). The solid sample was placed in a tubular quartz reactor and calcined in a stream of dried air (~80 mL/min). The final calcination temperature (550 °C) was reached through a ramp of 10 °C/min, and it was kept for 4 hours. Three catalysts were supported on two different aluminas, while a fourth specimen was dispersed on SiO_2. They were labelled as Re-A_1, Re-A_2, Re-A_3, and Re-S, respectively.

The characterization of catalysts

Systems Re-A_1, Re-A_2 and Re-A_3 were characterized by optical ICP and TEM. In order to perform ICP analyses, solid samples were digested through the following procedure: a Teflon-lined autoclave (200 mL) was charged with the catalyst (0.05 g), water (5 mL), aq HF (40%, 1.5 mL), and a mixture of aq HCl/HNO_3 (3:1 v/v; 3 mL). The autoclave was then closed with a Teflon-lined cap, and heated in a microwave digestion rotor (MDS 2000) at 170 °C, for 1 hour. After being cooled to rt, the clear solution was transferred into a volumetric flask and diluted with water to 50 mL. Then, ICP analyses were carried out at 197.248 nm (power of 1400 W). In the three catalytic samples, the Re content was of 6.8, 7.0 and 6.4, respectively (Table 1).

TEM analysis was carried out with a JEM 3010 (JEOL) electron microscope operating at 300 kV, point to point resolution at Scherer defocus of 0.17 nm. A suspension of the catalytic sample (20 mg) in *i*-propanol was sonicated for 5 min. Then, an aliquot (5 μL) was poured on a copper grid coated with amorphous carbon. At rt, once *i*-propanol was evaporated, the sample was ready for the analysis.

TEM measures showed the presence of grains of γ-Al_2O_3 with an average size of 5–6 nm. Instead, the particles of Re-oxide were not clearly visible, their dimensions being lower than 1 nm. Fig. 4 shows the TEM images of the ReA_1 catalyst.
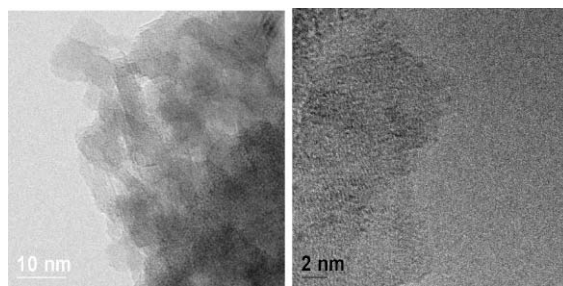
Fig. 4 TEM images of the ReA_1 catalyst.

General procedures for the metathesis of 1-octene

Two procedures (methods A and B) were used. In both cases, since heterogeneous catalysts for the metathesis of alkenes were extremely sensitive to air and humidity, all operations required a strictly inert atmosphere.

Method A. This method was devised for reactions performed with conventional liquid solvents (*n*-heptane and toluene). The catalyst, Re_2O_7 supported on γ-Al_2O_3 or on SiO_2 (0.56 g, 7%), was charged in a 25 mL 3-necked round bottomed flask, equipped with two stopcocks and a screw-thread adapter capped with a rubber septum. A magnetic stirring bar was hung on the top of the adapter, by a small external magnet.[38] At rt, three N_2/vacuum cycles were performed, and the system was kept under a N_2 stream of 50 mL/min. The flask was placed in an electric oven and heated up to 550 °C. This temperature was reached through a ramp of 10 °C/min, and it was maintained for 1.5 hours. The heating operation was checked by a thermocouple positioned on the bottom of the flask.

During the activation step, the colour of the catalyst showed some peculiar changes: the white powder (initially charged in the flask) turned to a gray tonality around 400 °C, then a black colour was persistent at 550 °C. After 1 h at this temperature, the powder began to fade until a pale yellow solid was obtained at the end of the heating time. This was the final colour of the catalyst used in the reaction.

After cooling at rt, the flask was thermostated at 35°C, and the stirring bar was released over the solid catalyst. A solution of 1-octene in *n*-heptane (Table 2: 5×10^{-1} M, 10 mL; Table 3: 0.7×10^{-1} M, 70 mL) was degassed, transferred over the activated catalyst, and kept under a static N_2 atmosphere.[39] The suspension was magnetically stirred (450 rpm) for 2 hours, cooled to rt, and finally vented. An aliquot (0.5 mL) of the final mixture was centrifuged and analysed by GC-MS.

Method B. Method B was specifically conceived for the use of dense CO_2 as the solvent. Fig. 1 illustrates the apparatus specifically designed to the scope.

SAFETY WARNING

Operators of high pressure equipment should take proper precautions to minimize the risks of personal injury.[40]

The catalytic activation was carried out under conditions identical to those above-described for method A, with one difference: the flask (**1**) was connected to a glass adapter (**2**) sealed at the autoclave top aperture (**H**), by a rubber conic ring. In this way, the N_2 stream coming out from the flask, was

conveyed directly in the autoclave (**3**) throughout the activation step. Once this operation was concluded, at rt, the flask was rotated along the axis of the adapter (**2**), to let the catalyst slide in the autoclave. Thanks to a supplementary gas line (**5**), the N_2 flow was enhanced up to 150 mL/min, the adapter (**2**) was rapidly removed, and the reactor was finally closed. The reactant olefin (1-octene, 0.56 g, 5 mmoles), preliminary charged in a 4 mL vial (**8**), was degassed under vacuum and loaded in a 1 mL calibrated loop (**6**). From here, the olefin was transferred in the autoclave under a CO_2 stream generated through a syringe pump (ISCO 260D, **7**). Unless otherwise specified, the molar ratio 1-octene:Re was 23.7. The reactor was pressurized at approximately 60 bar and electrically heated at the desired temperature (35 °C). The final pressure (80–150 bar) was reached by slowly adding the remaining CO_2. The mixture was magnetically stirred at ~500 rpm and its visual inspection was possible thanks to two sapphire windows assembled on both head and bottom of the autoclave. The reaction was allowed to proceed for 2 h. Then, after cooling at rt, CO_2 was slowly vented by bubbling it into a 5 mL vial of acetone. The content of the reactor was washed with additional acetone (5 mL), and the combined organic solutions were analyzed by GC-MS.

Fig. 5 exemplifies a typical GC-MS obtained for the self-metathesis of 1-octene catalyzed by Re_2O_7/γ-Al_2O_3 (7%, ReA$_1$ in Table 2 of the Result section), in the presence of dense CO_2 (90 bar, 35 °C, $d = 0.66$ g/mL) as solvent. Reaction conditions are those of entry 8 in Table 2.

Isolation and characterisation of 7-tetradecene. Since heterogeneous catalysts for the metathesis of alkenes are rather delicate systems, the mass balance of the reaction was never evaluated by addition of internal standards. However, using both method A and B, the product of self-metathesis of 1-octene (7-tetradecene) was obtained in yields of 62–68%, which well-matched conversions measured by GC-MS. Product **2a** was simply isolated by filtration of the catalyst and removal of the unreacted 1-octene under vacuum (50 °C/200 mbar). The
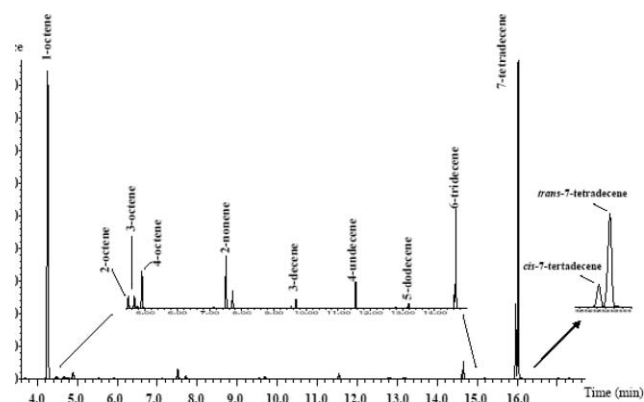
Fig. 5 GC-MS of the self-metathesis of 1-octene in dense CO_2. Enlargements are reported to detail *cis/trans* isomers of 7-tetradecene and products coming from isomerization and cross-metathesis reactions.

crude product was obtained as a pale-yellow liquid and it was characterized as such.

7-Tetradecene. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 5.40 (2H, m), 1.99 (4H, m), 1.29 (16H, m), 0.90 (6H, t, $J = 6.7$ Hz). In the *cis/trans* mixture, vinylic hydrogens were centered at $\delta = 5.35$ for the *cis* isomer, and at $\delta = 5.38$ for the *trans* compound.[18] The structure was also assigned by comparison with an authentic commercial sample (Aldrich # 227560).

***trans*-7-Tetradecene.** GC-MS (relative intensity, 70 eV) m/z: 196 ([M]$^+$, 24%), 111 (21), 98 ([M – (CH$_2$)$_7$]$^+$, 18), 97 (50), 85 (12), 84 ([M – (CH$_2$)$_8$]$^+$, 35), 83 (72), 82 (14), 71 (23), 70 ([M – (CH$_2$)$_9$]$^+$, 63), 69 (100), 68 (12), 67 (21), 57 (43), 56 ([M – (CH$_2$)$_{10}$]$^+$, 58), 55 (90), 54 (24). Database Wiley: Ref. 33342, *match quality* 97%.[41]

***cis*-7-Tetradecene.** GC-MS (relative intensity, 70 eV) m/z: 196 ([M]$^+$, 20%), 111 (21), 98 ([M – (CH$_2$)$_7$]$^+$, 16), 97 (50), 85 (12), 84 ([M – (CH$_2$)$_8$]$^+$, 34), 83 (68), 82 (16), 81 (11), 71 (24), 70 ([M – (CH$_2$)$_9$]$^+$, 67), 69 (99), 68 (13), 67 (25), 57 (47), 56 ([M – (CH$_2$)$_{10}$]$^+$, 66), 55 (100), 54 (23). Database Wiley: Ref. 33341, *match quality* 96%.[41]

Table 5 MS characterization of the reaction products of 1-octene

Compound	GC-MS (relative intensity, 70 eV)	Match quality (%) (*Ref. Wiley*)
1-Octene	m/z: 112 ([M]$^+$, 11%), 84 ([M – (CH$_2$)$_2$]$^+$, 23), 83 (39), 71 (12), 70 ([M – (CH$_2$)$_3$]$^+$, 88), 69 (50), 57 (16), 56 ([M – (CH$_2$)$_4$]$^+$, 86), 55 (100), 54 (11), 53 (10)	91 (*116372*)
2-Octene	m/z: 112 ([M]$^+$, 40%), 84 ([M – (CH$_2$)$_2$]$^+$, 10), 83 (21), 70 ([M – (CH$_2$)$_3$]$^+$, 53), 69 (29), 57 (18), 56 ([M – (CH$_2$)$_4$]$^+$, 53), 55 (100), 54 (10)	91 (*3597*)
3-Octene	m/z: 112 ([M]$^+$, 39%), 83 (19), 70 ([M – (CH$_2$)$_3$]$^+$, 55), 69 (32), 57 (19), 56 ([M – (CH$_2$)$_4$]$^+$, 52), 55 (100), 53 (10)	64 (*3598*)
4-Octene	m/z: 112 ([M]$^+$, 41%), 84 ([M – (CH$_2$)$_2$]$^+$, 11), 83 (19), 70 ([M – (CH$_2$)$_3$]$^+$, 53), 69 (35), 57 (20), 56 ([M – (CH$_2$)$_4$]$^+$, 55), 55 (100), 54 (10)	80 (*116369*)
2-Nonene	m/z: 126 ([M]$^+$, 33%), 97 (17), 84 ([M – (CH$_2$)$_3$]$^+$, 15), 83 (13), 70 ([M – (CH$_2$)$_4$]$^+$, 42), 69 (38), 57 (11), 56 ([M – (CH$_2$)$_5$]$^+$, 61), 55 (100), 54 (11)	83 (*6385*)
3-Decene	m/z: 140 ([M]$^+$, 5%), 111 (14), 98 ([M – (CH$_2$)$_3$]$^+$, 13), 97 (32), 84 ([M – (CH$_2$)$_4$]$^+$, 26), 83 (39), 82 (11), 71 (10), 70 ([M – (CH$_2$)$_5$]$^+$, 90), 69 (70), 68 (11), 67 (12), 57 (62), 56 ([M – (CH$_2$)$_6$]$^+$, 100), 55 (89), 54 (13), 53 (10)	—
4-Undecene	m/z: 154 ([M]$^+$, 32%), 97 (20), 84 ([M – (CH$_2$)$_5$]$^+$, 23), 83 (35), 71 (10), 70 ([M – (CH$_2$)$_6$]$^+$, 53), 69 (76), 67 (16), 57 (22), 56 ([M – (CH$_2$)$_7$]$^+$, 59), 55 (100), 54 (14)	94 (*15562*)
5-Dodecene	m/z: 168 ([M]$^+$, 33%), 111 (11), 98 ([M – (CH$_2$)$_5$]$^+$, 12), 97 (29), 84 ([M – (CH$_2$)$_6$]$^+$, 26), 83 (45), 82 (10), 71 (12), 70 ([M – (CH$_2$)$_7$]$^+$, 53), 69 (79), 67 (15), 57 (28), 56 ([M – (CH$_2$)$_8$]$^+$, 56), 55 (100), 54 (17)	97 (*21249*)
6-Tridecene	m/z: 182 ([M]$^+$, 44%), 111 (18), 98 ([M – (CH$_2$)$_6$]$^+$, 15), 97 (43), 84 ([M – (CH$_2$)$_7$]$^+$, 30), 83 (61), 82 (12), 71 (18), 70 ([M – (CH$_2$)$_8$]$^+$, 59), 69 (100), 67 (17), 57 (34), 56 ([M – (CH$_2$)$_9$]$^+$, 54), 55 (82), 54 (19)	—

Products of isomerization of 1-octene and of cross-metathesis.
These compounds (see Fig. 5) were identified by GC-MS analyses, and their structures were assigned by comparison to standard products included in the Wiley Library of Mass spectral data.[41] Table 5 reports molecular ions, the main fragmentation pattern, and the match quality obtained for each compound.

Self-metathesis of 1-hexene and 1-heptene

Method B was used also to carry out the self-metathesis of 1-hexene and 1-heptene (Table 5). The olefin amounts were of 5 mmol in both cases (0.42 and 0.49 g for 1-hexene and 1-heptene, respectively) and the molar ratio olefin:Re was of 23.7. Both products were not isolated: their structures were assigned by GC-MS and by comparison to an authentic commercial sample (5-decene: Aldrich # 110485).

5-Decene. Compared to an authentic commercial sample from Aldrich Chemical Co. GC-MS (relative intensity, 70 eV) m/z: 140 ([M]$^+$, 35%), 97 (17), 84 ([M − (CH$_2$)$_4$]$^+$, 13), 83 (15), 70 ([M − (CH$_2$)$_5$]$^+$, 38), 69 (46), 67 (10), 57 (11), 56 ([M − (CH$_2$)$_6$]$^+$, 46), 55 (100), 54 (10). Database Wiley: Ref. 10399, *match quality* 90%.[41]

6-Dodecene. Recognized by comparison of its physical data with those in the literature.[42] GC-MS (relative intensity, 70 eV) m/z: 168 ([M]$^+$, 35%), 111 (11), 98 ([M − (CH$_2$)$_5$]$^+$, 11), 97 (30), 84 ([M − (CH$_2$)$_6$]$^+$, 26), 83 (43), 71, (13), 70 ([M − (CH$_2$)$_7$]$^+$, 56), 69 (100), 67 (15), 57 (30), 56 ([M − (CH$_2$)$_8$]$^+$, 53), 55 (82), 54 (18). Database Wiley: Rif. 21247, *match quality* 96%.[41]

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Assessing photochemistry as a green synthetic method. Carbon–carbon bond forming reactions†

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Introduction

Concern for the ecological effects of the production of chemicals is increasing. Consequently, there is a growing interest for the quantitative evaluation of the ecological potential in chemical processes.[1] A reliable assessment would involve a complete life cycle analysis that takes into account all of the processes involved, from the environmental cost of the starting material to the persistence of the commercialized product, clearly a demanding job. Several methods that obtain a reasonable evaluation through a much easier procedure have been reported, though.[2,3] Obviously, such methods have been conceived for industrial processes, where the environmental effect really matters. On the other hand, it is desirable that the variety of new synthetic procedures that are continuously offered by the literature are as soon as possible evaluated from the environmental aspect, in order that one may understand whether a new method is promising from this point of view.

As a matter of fact, many new processes are claimed to be environmentally preferable when published. Even a casual observation shows, however, that at the best only the key idea of the methods presented is environmentally friendly. As an example the introduction of a new catalyst that gives a better yield, but then little or no attention is given to the factors that actually determine the environmental cost of each of the operations involved, including the preparation of the catalyst and the manipulations required for its proper performance, such as the anhydrification and/or deoxygenation of the solvent, the various operations for synthesis, work up and purification of the products, the recovery and/or the appropriate treatment of by-products, solvents and so on. Therefore we feel that environmental evaluations should be carried out as often as possible for every new method proposed in literature, obviously through a rather simple method, not through a complete life cycle analysis. Although this may result in an inappropriate assessment in absolute terms, a relative ranking can be obtained so that the most environmentally advantageous methods are identified as early as possible and/or environmentally troublesome aspects are identified, so that improvements are devised and introduced. The environmental evaluation of

experiments in teaching laboratories should also be carried out.[4]

An ideally clean chemical process should use energy from a renewable source, such as solar light, and convert harmless chemicals into the desired products, avoiding the co-production of waste.[5] This is exactly what happens in photosynthesis, where renewable reagents (water and carbon dioxide) are converted into useful chemicals by drawing energy from solar light.[6] Unfortunately, no man-made process approaching this result is available. The structural complexity of solar light receptors used by green plants in photosynthesis cannot be easily reproduced in artificial systems, although active research in this direction continues and is leading to a considerable advancement.[7]

On the other hand, a variety of artificial synthetic methods where the photon is used as a chemical reagent have been reported. These have no direct connection with processes occurring in nature, but still are appealing for the mild conditions used when employing light rather than a chemical reagent for activating the starting material. To simplify, photons play the same role as activating reagents and/or catalysts in organic synthesis, promoting the reaction by introducing alternative paths so that it occurs in the cold under mild conditions. Furthermore, contrary to chemical activating agents, light leaves no spent reagent or residue in the reaction mixture and this usually makes work-up simpler.[8]

Thus, it seems possible that photochemical reactions are environmentally advantageous. This concept dates back to the work of Giacomo Ciamician a century ago. He suggested that photochemistry, where a clean reagent such as light is substituted for aggressive chemical reagents or elevated temperature and pressure, offered a way to a 'cleaner' path for chemical syntheses.[9,10] Ciamician used solar light, which is obviously the best solution from the environmental point of view. Nowadays a large number of photochemical reactions are known,[11] although these have generally been carried out by using lamps. This is mainly because it is much easier to do explorative studies by using a constant and well defined light source, but most such reactions could be easily brought out by solar irradiation, as indeed demonstrated by several recent studies.[12]

Photochemistry is deemed one of the most important, but also 'one of the most neglected techniques available to green chemistry'.[13] However, although the observations above suggest that photochemistry *may* be a green method, this point has not been systematically explored up to now. It thus seems appropriate to assess whether, or in which cases, or under which conditions, photochemical reactions are *really* green. A convenient way of assessing the environmental value of such methods

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would involve comparing a set of reactions that could be carried out both under photochemical and under thermal activation. In recent years, a range of procedures for the photoinduced generation of carbon–carbon bonds *via* alkylation,[14] acylation[14] and arylation reactions[15] have been developed in the submitters' laboratory that closely duplicate thermal methods, including modern catalytic procedures that certainly can be considered 'green'.

A number of such synthetic methods could be grouped in photochemical/thermal pairs of synthetic methods starting from, and arriving at, the same compounds, or a close analogue. Within each pair, the course of the reaction was quite similar, and in most cases involved the generation of the same active intermediate either by thermal or by photochemical means, so that the comparison was also justified from the mechanistic point of view.[16] In several cases the quantum yield of the photoreactions has been measured and found to be >0.1, thus ensuring preparative interest. Some of the compounds synthesized have practical use (see *e.g.* estragole). Finally, the importance of forming carbon–carbon bonds in synthesis need not be stressed, and the evolution of new methods under mild conditions is continuous in this field. Restricting the choice to reactions developed in the submitters' laboratory is limiting with respect to the literature, but allowed us to elaborate the synthetic procedures and make new experiments under 'greener' conditions when suggested by the environmental analysis.

On the basis of the above considerations, it appeared worthwhile to carry out an environmental assessment on such reaction pairs. Among the methods proposed[2,3] in the literature, we selected the EATOS (**E**nvironmental **A**ssessment **T**ool for **O**rganic **S**ynthesis)[17] method for the assessment because it takes into account a reasonably large number of characteristics for justifying the expectation that a sensible conclusion is reached and yet requires only easily available data as entries. The comparison has been carried out by using a dedicated software, developed by Eissen and Metzger.[17]

This program evaluates the chemical processes through four indices. Two of these are referred to the *quantity* of the chemicals used up.

• S^{-1}, the mass index, corresponding to the quantity of input chemicals (reagents, solvent, catalyst and auxiliary materials) used in order to obtain one gram of desired product.

• E, the environmental factor, corresponding to the total amount of waste generated when producing one gram of product. The term waste includes both by-products and input reagents that are not used or recovered during the process.

In addition, two environmental parameters are calculated, where the environmental *quality* is assessed:

• $E_{in} = S^{-1} \times Q_{in}$, where the amount of chemicals used in the process is multiplied by factor Q_{in}, which takes into account the environmental and social cost involved in the production of each of such chemicals (based upon parameters such as risk phrases, transport information and cost).

• $E_{out} = E \times Q_{out}$, where Q_{out} represents the potential damage on the ecosystem by the chemicals produced (based upon ecological parameters and acute and chronic toxicity).

The four indices are obtained by adding the individually calculated contributions by reagents, solvents, catalysts and auxiliary products. Furthermore, the system calculates the

economical index, that is the cost incurred for the production of 1 kilogram of product (expressed in € per kilogram of the desired product).

The EATOS assessment obtained in this way takes into account the economical and environmental value of the chemicals used in the procedures compared.[18] Clearly, in order to establish whether these and related photoreactions really represent a viable environmentally friendly alternative it is further required that the cost of the photons emitted by the lamp is evaluated, or that the shift to the use of solar light is considered. The EATOS procedure does not take into account the energy used and this aspect is excluded from the present study. A second part of this work is planned and will be focused on comparing the environmental cost of producing and using light[19] with respect to other activation methods through appropriate experiments and a detailed life cycle analysis, taking into account the role of low-consumption lamps, solar irradiation and reactor design (also using light sources different from arcs, such as lasers or LEDs).

Results

The mode of operation and indications about the choice of the inputs for carrying out an assessment through the EATOS software are explained in the original literature.[17] The data introduced and the results obtained are reported in full as ESI.† From the results, three EATOS parameters were chosen as the most representative ones, *viz*. E_{in}, E_{out}, €/kg and are reported in the main text. In fact the first two assess the environmental potential with regard both to the quantity and to the quality of the input or output chemicals, while the importance of the price is obvious. The data in Tables 1–8 are broken down in separated contributions due to the different categories of the chemicals involved, *viz*. (where applicable): starting reagents; solvent; catalyst; coupled products (products different from the desired one); auxiliary materials (used either during the reaction or during the work up). In this way, one may judge which element contributes more to the overall assessment.

Alkylation reactions

Hydrocarbons represent the most abundant starting materials in organic chemistry. Therefore, the direct functionalization of non activated C–H bonds, in particular for the formation of C–C bonds, is a process of obvious significance for the exploitation of such a largely available and cheap feed for the synthesis of valuable fine chemicals. However, this usually requires harsh conditions. An appealing reaction is the alkylation of electrophilic alkenes by alkanes, a 100% atom economy reaction where the reagents are completely incorporated into the products. The process can be carried out *via* radicals and the key radical intermediates can be produced from the alkane either by thermolysis[20] (a process that has found only a sparse attention in the literature) or, under mild conditions, by hydrogen abstraction by a photocatalyst (Scheme 1, eq. 1 and 2).[21]

The two methods are compared in Table 1 and through the histogram in Fig. 1 for the case of the alkylation of methyl acrylate by cyclohexane (for complete data, see ESI†). The environmental parameters and the price are listed and

Table 1 Environmental parameters calculated for reactions (1) and (2)

	Reaction 1, Δ			Reaction 2, hν		
	E_{in}	E_{out}	€/kg	E_{in}	E_{out}	€/Kg
Reagents	7.0	2.8	53	13.4	10.3	87.0
Solvents	112[a]	119[a]	857[a]	426	284	2150
Catalyst	—	—	—	1.40	0.50	195
Total value of parameters	119	122	910	441	295	2430

[a] Excess cyclohexane was considered as solvent.
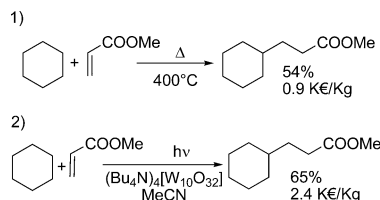
Scheme 1 Thermal (1) and *photoinduced* (2) alkylation of methyl acrylate by cyclohexane.
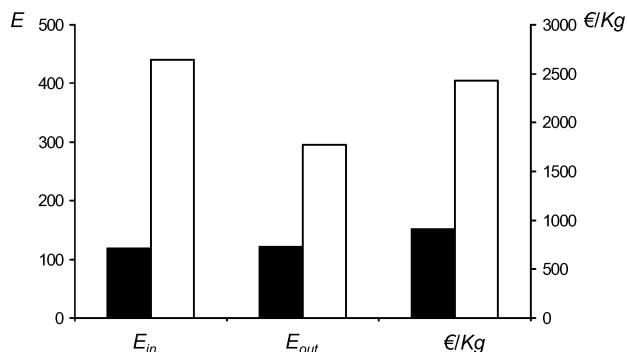
Fig. 1 Comparison between the environmental and economical cost of the thermal (eq. (1), filled bars) and photochemical (eq. (2), open bars) syntheses of 3-cyclohexyl-methylpropanoate.

subdivided into the contributions due to reagents, solvent and (where applicable) catalyst. The thermal alkylation involves flash pyrolysis of cyclohexane (in large excess) at 400 °C in the presence of the unsaturated ester.[20] If only the fraction of cyclohexane participating into the reaction is considered as a reagent, and the excess cyclohexane is considered as solvent, this accounts for by far the largest single contribution to all of the indices: for all of the cases >95%.

The photochemical process is carried out at room temperature and makes use of a photocatalyst, tetrabutylammonium decatungstate.[21] This gives only a small contribution to the indices as does the limited excess of cyclohexane used. However, the irradiation is conveniently carried out by using a rather dilute solution. A polar and (obviously) non hydrogen-donating solvent gives the best results, as is the case for acetonitrile used in the original work. This choice involves a heavy environmental contribution, however, amounting to 97% or more of the overall values. The considerable environmental impact of acetonitrile has been evidenced in an exhaustive work that describes all issues related to the choice of an organic solvent in green reactions.[22] Through the combined use of two different types of software (see ref. 3 for details), the authors showed that alkanes (such as

cyclohexane), alcohols or aqueous mixtures should be preferred to dioxane, tetrahydrofuran or acetonitrile, in order to minimize the environmental impact of a chemical process.

In our case, the use of neat acetonitrile limits the 'green' characteristics of the photochemical process, making it three to four times worse than the thermal process in the environmental indices and nearly three times as expensive. This, of course, in the hypothesis that all of the solvent is used up. If the solvent is recovered, as it would be reasonable if the two processes were seriously considered for industrial application, the preference for the thermal reaction in the indices would be reduced to a factor of two, and the photochemically obtained product would come out much cheaper. If a more environment-friendly solvent is chosen (preliminary attempts suggest that viable alternatives to acetonitrile exist, *e.g.* dimethyl carbonate) the photochemical reaction becomes comparable also for the environmental indices.

The comparison of alkylation reactions can be further extended to the more commonly used method *via* alkyl halides, where alkyl radicals are accessed by homolytic cleavage of C–Br and C–I bonds. In this case one more step is involved and the environmental effect is strongly dependent on the reagents used for carrying out the radical chain process (see Scheme 2).
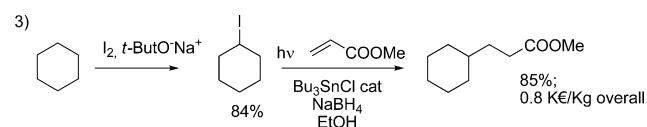
Scheme 2 Synthesis of 3-cyclohexyl-methylpropanoate by homolytic cleavage of C–I bond.

The overall process, iodination of cyclohexane[23] and alkylation of methyl acrylate by the latter by using tributyltin chloride in a catalytic amount (this is regenerated by sodium

Table 2 Calculated parameters of reaction (3) (see Scheme 2 for details)

Reaction 3, hν	E_{in}	E_{out}	€/kg
Reagents	15.3	34.6	631
Coupled products	—	3.6	–
Solvents	9.1	13.7	90
Auxiliaries[a]	2.1	4.0	30
Catalyst	0.80	2.6	65
Total value of parameters	**27.3**	**58.5**	**816**

[a] Referred to the synthesis of iodocyclohexane.
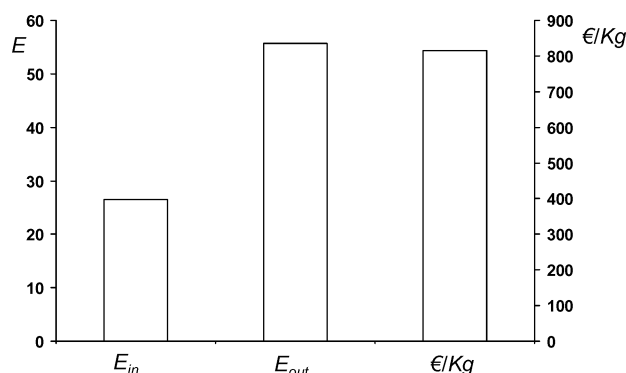
Fig. 2 Environmental and economical cost of the two-steps synthesis of methyl 3-cyclohexylpropanoate (eq. (3)).

borohydride) receives good environmental marks[24] (with the caveat that the EATOS assessment does not fully take into account the fact that a more elaborate starting material, an alkyl iodide rather than an alkane, is used). The reaction could be furthermore improved; for example, Ryu has recently reported a photoinduced Giese free-tin alkylation, that involves NaBH₃CN as radical generator.[25] In the three cases discussed up to now the purification of the product has not been taken into account. In fact, in some cases there are no sufficient details on this point in the literature. At any rate it seems reasonable that distillation is equally effective in the three cases and thus the ranking remains the same.

On the other hand, examination of the related synthesis of 3-cyclohexylcyclohexanone from 2-cyclohexenone by two alternative procedures, the photochemical alkylation by using directly cyclohexane[26] and the thermal alkylation with iodocyclohexane[27] shows that the former gives a result similar to the other photochemical synthesis according to equation 2, but the latter, if carried out as reported by using [(PhCOO)₂, AlCl₃] as the activator gets poor marks, mainly due to the dichloromethane used in the work up. An improvement of the environmental impact of this process would be represented by using triethyborane instead of aluminium chloride. However, this leads to a less selective reaction, where a product arising from solvent addition is also formed. Unfortunately, the use of benzophenone instead of decatungstate as photocatalyst leads to formation of several secondary photoproducts (*e.g.* benzopinacol) and makes purification by distillation inconvenient. Thus, isolation of the product by column chromatography was preferred, as indeed was the case also for the thermal synthesis. Since this led to no difference, we did not take into account the purification step, except for the previous extraction by
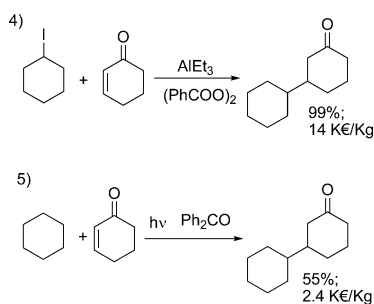
dichloromethane/aqueous hydrochloric acid that was required in the thermal method (see ESI†).

Acylation reactions

The intermolecular attack of acyl radicals onto C–C double bonds provides a useful method for the synthesis of asymmetrical ketones. These aliphatic radicals behave as nucleophiles and add efficiently to electron poor alkenes and alkynes.

As for thermal methods, acyl radicals are easily generated by group transfer reaction from acyl selenides[28] or by addition of alkyl radicals to carbon monoxide under pressure.[28] A photochemical alternative has been also documented and involves formation of acyl radicals by photochemical hydrogen atom cleavage of the C–H bond in aldehydes, provided that a non reactive solvent such as benzene is used, although the yield of acylated products is unsatisfactory in most cases.[29] Better results have been obtained using benzophenone as photocatalyst for the generation of the radicals.[28] However, as in the previous case, under such conditions degradation products from benzophenone (such as benzopinacol) are generated, which makes purification of the desired product a time consuming procedure. An improved acylation procedure has been developed, based again on tetrabutylammonium decatungstate (TBADT) as the photocatalyst, which is used in a small amount and easily separated after the reaction.[14] Under these conditions, good yields of the acylated products are obtained from olefins and aldehydes in equimolar amounts.[30] A representative example of this procedure has been compared with a thermal alternative
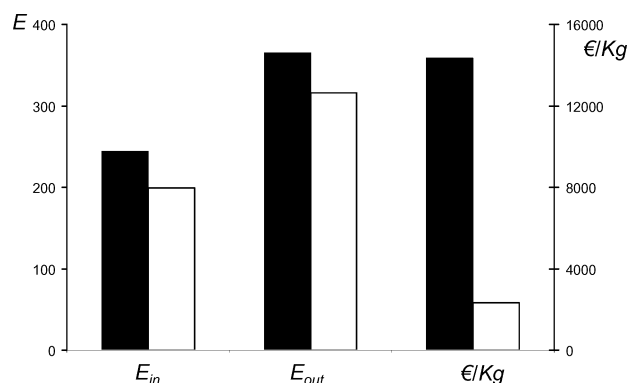
Fig. 3 Comparison between environmental and economical parameters for the thermal (eq. (4), filled bars) and photochemical (eq. (5), open bars) alkylation of 2-cyclohexenone.

Scheme 3 Thermal (4) and *photochemical* (5) alkylation of 2-cyclohexenone.

Table 3 Environmental parameters calculated for the synthesis of 3-cyclohexylcyclohexanone according to equations (4) and (5)

	Reaction 4, Δ			Reaction 5, hv		
	E_{in}	E_{out}	€/Kg	E_{in}	E_{out}	€/kg
Reagents	49.7	109	12800	*5.50*	–	*1085*
Solvents	140	120	1223	*192[a]*	*307[a]*	*1206[a]*
Catalyst	15	10.9	185	*1.8*	*9.4[b]*	*95*
Coupled products	—	1.30	—	–	–	–
Auxiliaries (isolation)	39.8	124	146	–	—	—
Total value of parameters	244	365	14360	*212*	*316*	*1608*

[a] Excess cyclohexane was considered as solvent; [b] Referred to photodegradation of benzophenone.

Table 4 Calculated parameters for reactions (6) and (7)

	Reaction 6, Δ			Reaction 7, hv		
	E_{in}	E_{out}	€/Kg	E_{in}	E_{out}	€/kg
Reagents	571	1000	6610	*4.90*	*2.20*	*74*
Solvents	2340	3200	7800	*206*	*165*	*1248*
Catalyst	—	—	16	*1.4*	*0.70*	*286*
Coupled products	—	2.5		—	—	—
Total value of parameters	2910	4200	14400	*212*	*168*	*1610*

Scheme 4 reactions (6), (7), (8)
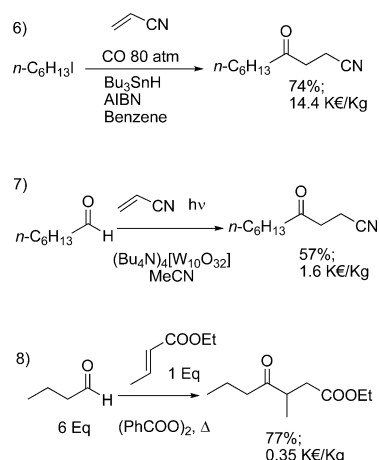
Scheme 4 Thermal (6, 8) and *photochemical* (7) pathways in acylation process.
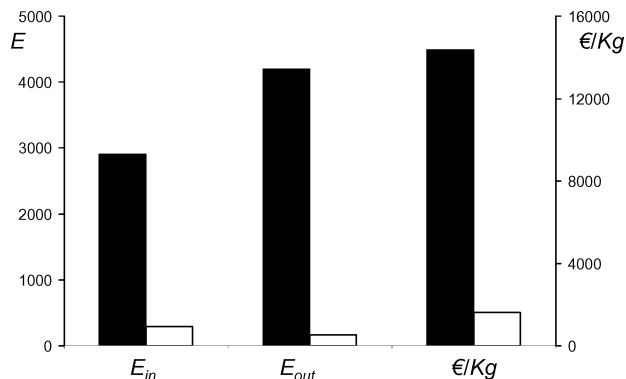
Fig. 4 Comparison between thermal (eq. (6), filled bars) and photochemical (eq. (7), open bars) preparation of 4-ketodecanitrile.

Fig. 5 Environmental and economical parameters calculated for the synthesis of 4-keto-3-methyl ethylheptanoate (see eq. (8) for details).

Table 5 Calculated parameters for reaction (8)

Reaction 8, Δ	E_{in}	E_{out}	€/kg
Reagents	7.4	14.9	314
Coupled products	—	—	—
Catalyst	0.90	0.20	9
Auxiliaries (reaction)	6.8	6.70	31
Total value of parameters	15.1	21.8	354

involving addition of alkyl radicals onto carbon monoxide[31] for the case of 4-ketodecanenitrile. Noteworthy, in this case the environmental and economical cost of the thermal reaction is larger than that of the photochemical alternative, even if the purification step is not taken into account (this involves treatment of the crude product with a KF solution for removing the organo-tin derivatives and column chromatography for the thermal reaction, bulb to bulb distillation of the raw photolyzate in the case of the photochemical alternative).

In fact, the thermal synthesis turns out to be environmentally unsafe and quite expensive, due to the use of a large amount of tributyltin hydride and of benzene (highly toxic, $Q_{out} = 7!$) as the solvent (of course the latter would be immediately substituted by any industry considering this procedure). A toxic solvent, but not as dramatically so, such as MeCN, gives the main contribution to the photochemical reaction that performs much better. On the other hand, the long known (1956) thermal version of the acylation by aldehydes, which is performed by using the aldehydes neat as the solvent (equation 8), however, and is initiated by benzoyl peroxide[32] turns out as the best method in terms of green chemistry. It is important to note that calculation of these green methods includes the work up procedure too, although the limitation remains of the use of such a large excess of a rather unstable compound such as an aldehyde.

Arylation reactions

The formation of an aryl-carbon bond is efficiently obtained by electrophilic alkylation, the well known Friedel–Craft reaction. From the environmental point of view, this procedure is less advantageous because of the large amount of aluminium trichloride used for generating carbon-centered electrophiles and because of the moderate regioselectivity, leading often to product mixtures. An alternative is represented by nucleophilic substitution, although this process is of limited application because only electron-poor aryl halides react efficiently with carbon based nucleophiles.

Table 6 Environmental parameters calculated for the thermal (9) and the *photochemical* (10) synthesis of estragole

|	Reaction 9, Δ			Reaction 10, hν		
	E_{in}	E_{out}	€/kg	E_{in}	E_{out}	€/kg
Reagents	18.9	4.0	9250	*47.5*	*55.6*	*21530*
Coupled products	—	18.7	—	—	0.80	—
Catalyst	1.50	0.20	5930	—	—	—
Solvents	51.0	41.0	95.0	*216*	*151*	*1014*
Auxiliaries (reaction)	11.0	26.0	5460	—	—	—
Auxiliaries (isolation)	72.0	72.0	490	*81.3*	*271*	*277*
Total value of parameters	155	161	21300	*345 (254)[a]*	*478 (207)[a]*	*22800 (22500)[a]*

[a] Liquid–liquid extraction with CH_2Cl_2 has not been taken into account, see text.

Conversely, a variety of processes involving catalysis by transition metal complexes, in particular of Pd, Ni and Fe have been introduced to overcome this shortcoming and make nucleophilic substitution a wide scope procedure. In these transformations, a formal aromatic nucleophilic substitution between an aromatic halide (usually iodide and bromide) or sulfonate and a carbon based nucleophile (generally an organometallic species) occurs, affording the desired product. There is no doubt about the efficiency and versatility of these procedures, but some difficulties remain. With regard to the cost of the reaction, the use of expensive catalysts certainly represents a limitation, as is the use of aryl iodides, not always easily available. These processes are being successfully extended to the cheaper and more easily available chlorides,[33] however, and an example of these procedures has been examined below. On the other hand, the use of aggressive and toxic organometallic species such as organotin derivatives involves several problems from the environmental point of view.

Photochemical methods have also been developed. In particular, the photoinduced ArS_N1 reaction based on the photogeneration of phenyl cations and their reaction with neutral π nucleophiles such as alkenes or (hetero)aromatic rivals thermal methods and is complementary to them, since it performs well with electron rich aryl chlorides. Notice further that the photochemical procedure avoids the use (and the required recovery) of toxic organometallic derivatives.

As a first example, a palladium catalyzed[34] and a photochemical[35] procedure are compared in Scheme 5 for the allylation of aromatics, where both gave good yields. In the case of estragole, a natural occurring allylphenol of practical significance in the pharmaceutical and cosmetics industry,[36]
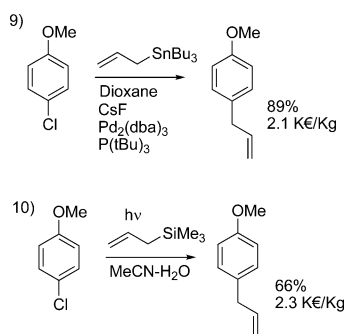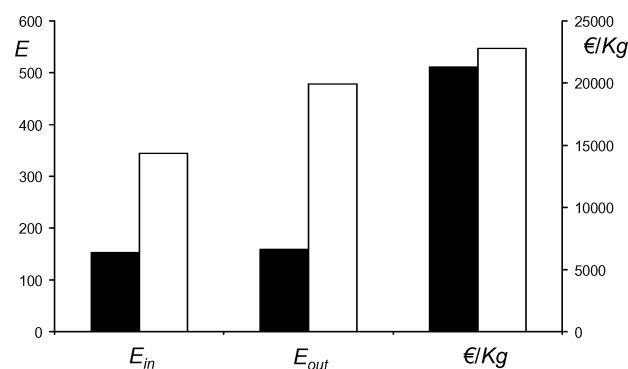
Fig. 6 Comparison between environmental and economical parameters for thermal (eq. (9), filled bars) and photochemical (eq. (10), open bars) synthesis of estragole.

the two methods were assessed and found to have comparable environmental indices. The solvent gives the main contribution in the photochemical synthesis, the auxiliary agents employed to remove catalyst and tin derivatives (ethyl acetate, silica gel, indicated in Table 6 as "Auxiliaries-isolation") the main one in the thermal reaction. In addition, the cost of the two processes is similar and has to be mainly imputed to the Pd-catalyst and to the base used (cesium fluoride, indicated in Table 6 as "Auxiliaries") in the case of thermal pathway and to the large excess of allyltrimethylsilane (10 times as much as 4-chloroanisole) for the photochemical process.

On the other hand, the photochemical procedure involves a simple liquid–liquid extraction of the photolyzed solution with dichloromethane, which is a bad choice from the environmental point of view. However, later studies in the submitters' laboratory[37] demonstrated that when the irradiation was carried out in an acetonitrile/water mixture, the products could be easily purified by direct evaporation of the solvent and bulb to bulb distillation of the crude mixture. Introducing this change would strongly improve the environmental evaluation.

A further application of the above strategies has been found in the arylation of arenes (Scheme 6) and of alkynes (Scheme 7). These are synthetically appealing reactions, but it is difficult to find in the literature thermal and photochemical procedures that are exactly comparable. It was deemed appropriate to compare procedures that lead to the same product from different starting materials (see *e.g.* 2-iodo- and 2-chloroanisole in Scheme 6). This is taken into account in the environmental

Scheme 5 Thermal (9) and *photochemical* (10) synthesis of estragole.

Table 7 Environmental parameters calculated for the synthesis of 2,4,6-trimethyl-2′methoxybiphenyl according to Scheme 6

	Reaction 11, Δ			Reaction 12, hν			Reaction 13, hν		
	E_{in}	E_{out}	€/kg	E_{in}	E_{out}	€/kg	E_{in}	E_{out}	€/kg
Reagents	10.9	7.50	20100	25.1	61.4	2040	15.7	19.5	633
Solvents	28.7	28.7	295	739	384	63050	210	193	879
Catalyst	0.40	0.60	2630	—	—	—	—	—	—
Coupled products	—	—	—	2.40	0.70	38	—	8.60	—
Auxiliaries (Isolation)	12.9	24.4	4340						
Total value of parameters	52.9	62.0	27300	766	446	65100	226	221	1510
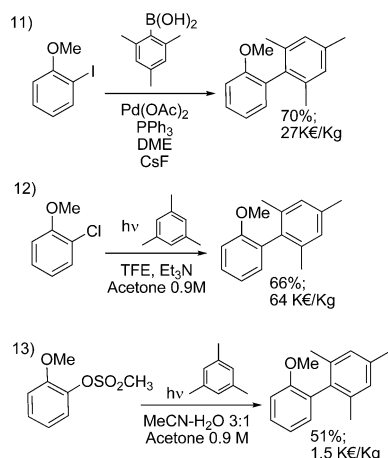
Scheme 6 Thermal (11) and *photochemical* (12, 13) synthesis of 2-methoxy-2′,4′,6′-trimethyl- biphenyl.
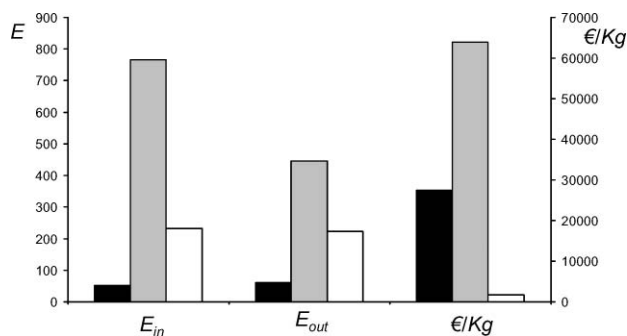
Fig. 7 Comparison between thermal (eq. (11), filled bars) and photochemical (eq. (12), shaded, and eq. (13), open bars) synthesis to 2-methoxy-2′,4′,6′-trimethylbiphenyl.

evaluation and has no major effect on the result in the reaction considered, see ESI.† The thermal arylation considered has been carried out under Pd catalysis (eq. (11)).[38] A photochemical alternative is shown in eq. (12).[39] The latter is clearly the worst choice for the synthesis considered, but once again the poor performance depends exclusively on the choice of the solvent (2,2,2-trifluoroethanol) used in the exploratory study. Therefore, some optimization was pursued and it was found that irradiation of the mesylate in a MeCN-H$_2$O 3:1 solvent mixture (eq. (13)) was a better choice.[40] This gave a reasonable yield and cut down strongly the environmental indices. This also made the price much lower than that of the thermal process, where the price is determined mainly by the reagents, in particular by the highly reactive nucleophile mesityl boronic acid. On the contrary, the photochemical synthesis makes use of non activated (and thus cheaper) aromatic hydrocarbon mesitylene as the nucleophile. Here, the environmental and economical index is dominated, even with the less expensive choice of eq. (13), by the contribution by the solvent typical of the "high dilution conditions" of photochemical processes and not by the reagent. The purification of the final products has been carried out by column chromatography in all of these syntheses and this step has not been considered into the calculations.

Finally, the synthesis of phenylalkynes from aryl halides and alkynes has been considered by comparing the catalytic (Sonogashira reaction)[41] and the photochemical[42] method. The latter got markedly worse marks with the environmental parameters in this case. As it appears from Table 8, the largest contribution to the parameters calculated for the catalytic reaction is given by methylene chloride used in the isolation procedure, while in the photochemical pathway it is the solvent that accounts for more than 90% of the total environmental indices. Furthermore, the calculated price evidences that using an excess of such an

Table 8 Environmental parameters calculated for the thermal (eq. (14)) and photochemical (eq. (15)) synthesis of 1-(4-methoxy)phenylhexyne

	Reaction 14, Δ			Reaction 15, hν		
	E_{in}	E_{out}	€/kg	E_{in}	E_{out}	€/kg
Reagents	6.20	—	693	33.6	44.3	7940
Solvents	23.3	26.7	344	715	1670	60100
Auxiliaries (reaction)	—	—	—	3.0	2.0	20
Auxiliaries (isolation)	583	608	711	—	—	—
Catalyst	3.40	2.20	15100	—	—	—
Coupled products	—	2.10	—	—	7.40	—
Total value of parameters	231	641	16800	752	1720	68100
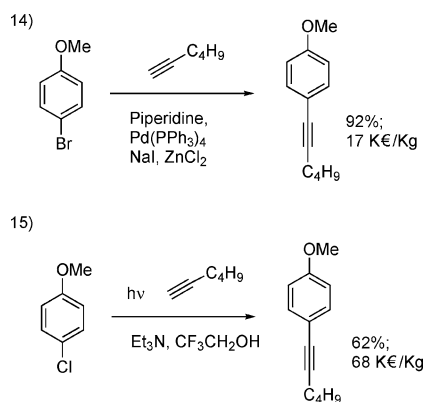
Scheme 7 Catalyzed (14) and *photoinduced* (15) synthesis of 1-(4-methoxy)phenylhexyne.

Fig. 8 Comparison between thermal (eq. (14), filled bars) and photochemical (eq. (15), open bars), synthesis of 1-(4-methoxy)phenylhexyne.

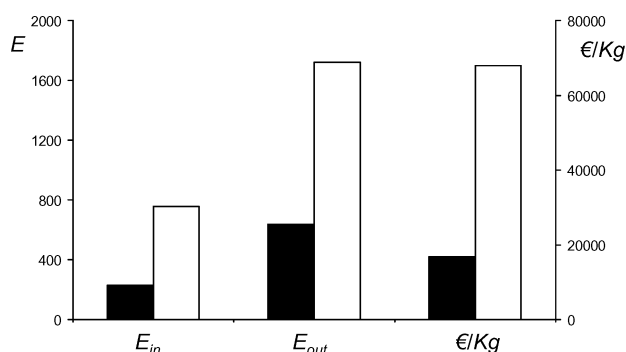expensive reagent as 1-hexyne and an expensive solvent such as TFE disfavors the photochemical synthesis. Clearly, this is a point that should be attended to, should a scaling up of the process be considered, by optimizing the recovery and recycling (or the choice) of the solvent and by limiting the excess of the reagent. As in the previous case, the final purification step has not been included into calculations for these Sonogashira-like reactions, because column chromatography has been used in all of the cases.

Discussion

The key results from this work are gathered in Table 9.

In Table 9, the values E_{in} and E_{out}, which, as mentioned, take into account not only the quantity of chemicals introduced/formed, but also the degree of the damage to environment these cause, are reported along with the calculated cost of production. In the cost column is also indicated which component gives the largest contribution (generally 90% or more), be it the solvent (S), the reagent(s) (R), the catalyst (C), or the auxiliaries (A). These are accompanied by the indication of the same parameters omitting the contribution by the solvent (whether the reaction solvent or that used in the work up). It is apparent that the values are now much lower and somewhat more realistic (although the use of prices taken from commercial catalogues for reagents are still too high). Obviously, when the

Table 9 Environmental parameters for reactions (1)–(15)

Reaction	E_{in}	$E*_{in}$ [a]	E_{out}	$E*_{out}$ [b]	€/kg [c]	€* [d]
1, Δ	119	7	122	2.8	910	53
2, hν	*441*	*13.4*	*295*	*10.3*	*2430[(S)]*	*87*
3, hν	*27.3*	*15.3*	*58.5*	*34.6*	*816[(R)]*	*631*
4, Δ	244	50	365	109	14360[(R)+(A)]	12800
5, hν	*199*	*5.5*	*315*	—	*2390*	*1085*
6, Δ	2910	570	4200	1000	14400	6610
7, hν	*212*	*4.9*	*168*	*2.2*	*1610*	*74*
8, Δ	15.1	7.4	21.8	14.9	354[(R)]	314
9, Δ	155	18.9	161	4.0	21300[(R)+ (C)+(A)]	9250
10, hν	*345*	*47.5*	*478*	*55.6*	*23000[(R)]*	*21530*
11, Δ	52.9	10.9	62.0	7.5	27300 [(R)]	20160
12, hν	*766*	*25.1*	*446*	*61.4*	*65100[(S)]*	*2040*
13, hν	*226*	*15.7*	*221*	*19.5*	*1510[(R)+(S)]*	*633*
14, Δ	231	6.2	641	—	16800[(C)+(R)]	693
15, hν	*752*	*33.6*	*1724*	*44.3*	*68100[(S)]*	*7940*

[a] $E*_{in}$, $E*_{out}$. Contribution of the reagents to the E_{in} index and E_{out} index, excluding solvent and auxiliaries. [b] $E*_{in}$, $E*_{out}$. Contribution of the reagents to the E_{in} index and E_{out} index, excluding solvent and auxiliaries. [c] The superscript indicates which component gives the main contribution to the overall value (see text). [d] €* Contribution of reagents to the calculated cost, excluding solvent and auxiliaries.

main contribution is given by reagents or catalysts the indices remain high.

Some comments may be appropriate. Perhaps the first one is the large difference between explorative research and industrial application of reactions. The target of research work remains discovering new reactions that are selective and give a good yield. The exclusive concentration on this target may lead (or hopefully used to lead) to using benzene or chloroform as solvents for the work up. Even if such excesses are avoided, this attitude is dramatically opposed to the main principle of green chemistry, which requires that consideration of the environmental aspects is a main concern *from the start*, and thus the environmentally less hazardous choices should be introduced already when planning the synthesis. At the very least, when some step of a new process involves environmentally unsuitable conditions, the report should be accompanied by some explorative work aimed at uncovering safer conditions.

A second note refers to the different role of the various entries considered in the assessment of the reactions considered, which, as mentioned, are explorative studies. As observed above, by far the main contribution to the indices is in most cases given by the reaction solvent and by the solvent or auxiliaries used in the product purification, due to a less thoughtful choice of such solvent, not taking into account the environmental factor (this has only recently begun to be considered by photochemistry practitioners). This is lamentable but should, in principle, be easier to correct, by making a different choice of the solvents, than changing the reagent, the catalyst or the conditions. Alternatively, it should be possible to plan a rational recovery and reuse of such solvent, in particular when a scale-up of the reaction is required (although this is no trivial question and may turn out to be excessively energy demanding).[22,43] As any experimentalist well knows, neither of these operations is straightforward and more time might be devoted to settle satisfactorily these problems than to optimizing the yields.

Nevertheless, it seems that when the main problem is the solvent, strong improvements should be possible and the price of the products should become closer to that of reagents, catalysts and chemicals other than the solvents.

As for the target of the present contribution, *viz* the comparison of photochemical *vs* thermal reactions, the result is varied, and quite often there is at least one thermal alternative that has better environmental indices than the photochemical reaction and, particularly, is less expensive. However, it is important to notice that in virtually all of the photochemical processes the main contribution is given by the solvent, and since this *has* at any rate to be recovered, it is sensible to consider the indices omitting the solvent contribution (see the quantities marked with an asterisk in Table 9). In this case, the advantage of thermal in comparison to photochemical methods is reduced, and quite often the photochemical alternative becomes the most convenient.

It seems reasonable to conclude that the use of a large amount of solvent–dilute conditions are usually required for a clean process. This limitation may be relieved by using flow microreactors, as recently reported.[44] From what can be judged from the few cases studied, the use of higher concentration (needed to improve the absorption of the light flux in the micrometric scales) leads to an efficient reaction with a short residence time. In addition, the occurring of secondary photoreactions is prevented.[45] One cannot deny that the propensity of the practitioners of photochemistry to use solvents that are known as convenient (= inert) for photochemical reactions, but are environmentally non acceptable, is generally the main stumbling block for obtaining environmentally friendly photochemical reactions. This fact, along with the considerable engineering problems associated with setting up a photochemical reactor, which is often custom-made and scarcely versatile, may limit consideration of such processes by the industry.[46] Both attention to the environmental indices, particularly with regard to the solvent, in the early stage of synthetic planning and an improved offer of photochemical reactors are required for making photochemistry more largely used in industry and for taking advantage of the interesting possibilities this method undoubtedly offers.

Indeed, as even a cursory examination such as that presented above reveals some clear potentialities of photochemical methods. These are the use of less activated/functionalized (and thus less expensive) starting materials, the use of milder reaction conditions and the avoidance of often labile and expensive catalysts. When one considers the environmental indices, a characteristics that is immediately apparent is the optimal atom economy that characterizes some of the photochemical processes presented above, most of which leads to the *total* inclusion of the atoms in the starting materials into the products (see examples 2, 5 and 7) or involve a small loss (a molecule of hydrochloric acid in examples 10 and 12). This fortunate situation must pay dividends, provided that the reactions are carried out appropriately.

Certainly, choosing a method depends also on other factors, such as the scale of the production, the experience in the group, the availability of convenient reactors, which may delay the choice of a photochemical synthesis for reactions in a (relatively) large scale. Recent contributions from several laboratories

have confronted the problem of scaling-up photoreactions and in some cases simple devices were found to give good results.[12b,47,48]

Furthermore, photochemistry allows for an unparalleled versatility, in terms of choice of the temperature but also of other parameters, *e.g.* when reaction in a geometrically precise location is desired, *e.g.* in solid phase synthesis. Let us consider the fragmentation of 1,2,4-oxadiazole-4-oxides to give useful synthetic intermediates such as nitrosocarbonyls as an example of clean reaction. These have been obtained both thermally and photochemically (see Scheme 8) and have been efficiently trapped by dienes or by alkenes to give the hetero Diels–Alder or ene adducts, respectively. The thermal reaction took place at 130 °C or above, depending on the substrate structure,[49] while the photochemical reaction was carried out at room temperature by using solar light or UV irradiation.[50] The trapping products were obtained in an almost quantitative yield by both methods. The choice will thus be done on the basis of practical considerations, such as the volatility and the thermal stability of the trap or the experimental arrangement. For example, when the 1,2,4-oxadiazole-4-oxide is linked to a Wang resin, the best choice is the photochemical method due to the milder conditions used that avoid evaporation of the reagents.[51]
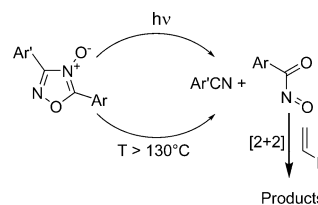
Scheme 8 Thermal and photochemical generation of nitrosocarbonyls dipoles.

As mentioned in the introduction, the use of a "clean" reagent as photon is *per se* no guarantee that a green process is obtained. The choice of the solvent (and those generally preferred by photochemistry practitioners are unsuitable) and of the other experimental parameters has a great importance. Furthermore, the use of an artificial light source such as mercury or xenon arc involves a large energy consumption, since the conversion into light is inefficient. The last point will be considered in a forthcoming study (notice however that a considerable improvement of this point comes from the use of LEDs; as a further advantage, these are available with a short λ range emission, allowing to choice the best match between source and reagent absorption).[52] From the present work, it can be concluded that the large amount of photochemical syntheses reported in the literature, and in particular the C–C bond forming reactions discussed here, require further elaboration for being considered satisfactory from the environmental point of view. However, the changes to be made are identified by the EATOS analysis and once that these are applied the environment-friendly character of these reactions becomes apparent. This suggest that photochemistry can indeed acquire a more important role in green chemistry.

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Immobilised *Burkholderia cepacia* lipase in dry organic solvents and ionic liquids: A comparison

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Lipase PS from *Burkholderia cepacia* in its free, commercial form (BCL-PS), immobilised in a sol–gel (BCLxero) and as a CLEA (BCL-CLEA) was tested in dry organic solvents, ionic liquids and their mixtures. Utilising the acylations of secondary alcohols **1–3** the influence of the enzyme preparation on its activity and enantioselectivity was studied. BCL-CLEA displays higher activity (initial rates) than BCLxero for all substrates in the ILs but loses its activity rapidly. Thus, BCLxero is suitable for kinetic resolution in ILs and in their mixtures with organic solvents. It is not possible to label one IL better than the other without taking the nature of the substrate into account. In neat solvents, the nature of the solvent affects enantioselectivity (*E*) only when furyl-substituted alcohol **2** serves as a substrate while variation in *E* is more evident for reactions in solvent mixtures.

Introduction

Ionic liquids (IL) and enzymes, as well as their application, were both described long ago but it has taken until recently before the potential of combining them was recognised. They have been thoroughly reviewed as separate subjects and in combination.[1–10] Using enzymes in ionic liquids many new applications of biocatalysis have came about. However, to fully appreciate the possibilities of applying enzymes in ionic liquids, the parameters influencing the behaviour of enzymes in ILs need to be understood. One of the parameters which has, to date, virtually not been systematically investigated, is the influence of the enzyme preparation on its stability in different dry ILs or IL/organic solvent mixtures.[5]

One of the enzymes best studied in ILs is *Burkholderia cepacia* lipase (BCL), also known as *Pseudomonas cepacia* lipase and lipase PS or lipase PS "Amano" SD.[11–20] Here we report on the application of three different BCL forms, the commercial free enzyme powder from Amano which is sold diluted with dextrin, a cryoprotector,[21] BCL encapsulated inside a sol–gel[22] and BCL cross-linked as a CLEA.[23] These forms of BCL are utilised in different, often used ILs and in IL/organic solvent mixtures for the enantioselective acylation of diverse racemic alcohols. A water miscible ionic liquid (IL) with a hydrophilic anion [EMIM][BF$_4$] and water immiscible ionic liquids with hydrophobic anions [EMIM][Tf$_2$N] and [BMIM][PF$_6$] were chosen. These ILs are thoroughly characterized (Table 1), and display hydrogen bond donor abilities similar to those of

alcohols while their nucleophilicities are much lower and entirely anion dependent, *i.e.*, the ILs are unique as solvents showing high polarity and low nucleophilicity.[24–26] The cations are both modestly hydrophilic. Although it is well-known that [BF$_4$] and [PF$_6$] can release HF this is not the case when they are used under dry conditions, as described here.[9,16,25] Both [EMIM] and [BMIM] were recently assessed for their ecotoxicity and fall into a similar range as most organic solvents.[27,28] The advantage of using these ILs lies therefore mainly in the fact that they are non-volatile and that a lot of previous work has been performed in them. This allows a systematic comparison of the different immobilisation techniques.

As test reactions, the kinetic resolution of aromatic alcohol **1**, heteroaromatic alcohol **2** and *N*-acylated amino alcohol **3** were investigated (Scheme 1). In addition, the potential side reaction, hydrolysis of the acetate products **4–6** due to residual water in the enzymatic reaction mixture, was explored. This side reaction causes the release of acetic acid, reduces the yield, affects enantiopurities and is normally neglected. The significance of this side reaction is often ignored although ample evidence of its importance is available.[29–34] Esterification of the acid was previously proposed as the continuous source of water.[35]

In an earlier study we could already demonstrate that there is a significant difference in behaviour between the BCL preparations, and that depending on the substrate (**1–3**), different organic solvents should be employed.[36] The commercial BCL (BCL-PS) is in essence dextrin, containing 3% free enzyme. The encapsulated enzyme is prepared with the sol–gel technique, utilising both MTMS (methyltrimethoxysilane) and TMOS (tetramethoxysilane) as precursors for the sol–gel.[36,37] The initially obtained aquagel is lyophilised to obtain the xerogel which is then ready to be used as a catalyst. The final preparation (BCLxero) is the enzyme encapsulated in reverse phase silica in which part of the capsules will be broken due to the drying process. The cross linked BCL (BCL-CLEA) is prepared

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Table 1 Properties of dry ILs: log P (logarithm for the partition coefficient of an IL between 1-octanol and water), E_T^N (Reichardt's normalized polarity scale) and viscosity (25 °C)

Ionic liquid	log P^{24}	$E_T^{N\,24}$	Viscosity [cP][25]	Water content [ppm][a]	Water solubility[26]
[EMIM][BF$_4$]	−3.53	0.697	43	986	yes
[EMIM][Tf$_2$N]	−1.18	0.661	28	45	no
[BMIM][PF$_6$]	−2.06	0.670	450	486	no
Toluene	2.8	—	—	77	no
DIPE	1.9	0.546	—	321	no
TBME	1.35	—	—	622	no

[a] Determined by Karl Fisher titration.
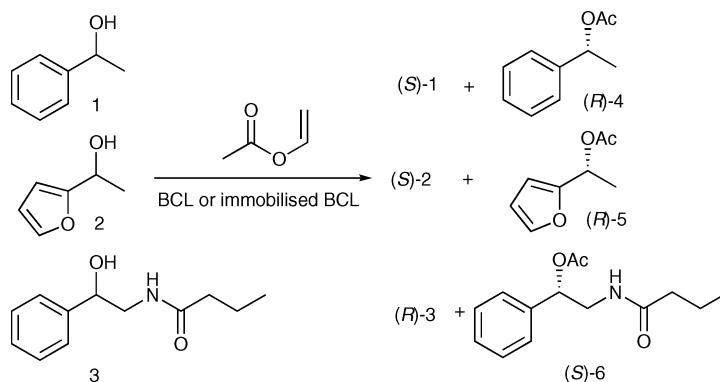
Scheme 1 Kinetic resolution of three different alcohols catalysed by different BCL preparations, performed in organic solvents, ILs and IL/organic solvent mixtures.

according to standard methodology.[36,38] While the BCLxero had the same or lower activity than BCL-PS in organic solvents the BCL-CLEA had higher activity (Tables 2 and 3).[36] On the other hand BCLxero proved more stable in organic solvents than BCL-CLEA. We here describe the behaviour of the BCL preparations in three different ILs and in their mixtures with selected organic cosolvents with three different substrates (1–3). To make direct comparison of the results possible, the protein content was kept as 100 mg ml⁻¹ BCLxero and BCL-PS, on one hand, and as 50 mg ml⁻¹ for BCL-CLEA and BCL-PS, on the other hand.

Results and discussion

Racemates 1–3 were first subjected to acylation with vinyl acetate in toluene, DIPE and TBME as well as in [EMIM][Tf$_2$N], [EMIM][BF$_4$] and [BMIM][PF$_6$] in the presence of the BCLxero and BCL-CLEA (Table 2). Toluene for 1, DIPE for 2 and TBME for 3 were previously best detected for the acylation in the presence of BCLxero and BCL-CLEA.[36] On the other hand, the ILs were chosen as best for the previous acylation of 3 with lipase PS-C II (BCL preparation on Toyonite from Amano[16]).[39] Activities in the table are given as initial rates measured by

Table 2 Acylation of 1–3 (0.1 M) with vinyl acetate (0.2 M) in organic solvents and in ionic liquids in the presence of BCLxero and BCL-CLEA at room temperature

			BCLxero[a]		BCL-CLEA[b]	
Entry	Substrate	Solvent	v_0^c	Conv. [%][d]/E	v_0^c	Conv. [%][d]/E
1	1	Toluene	1.42 ± 0.02	50/>200	7.0 ± 0.9	50/>200
2	1	Toluene	—	—	3.86 ± 0.25[e]	46/>200
3	1	[EMIM][Tf$_2$N]	0.31 ± 0.01	30/>200	0.32 ± 0.01	5/>200
4	1	[EMIM][BF$_4$]	0.19 ± 0.01	23/>200	1.65 ± 0.07	24/>200
5	1	[BMIM][PF$_6$]	0.41 ± 0.01	34/>200	1.1 ± 0.1	18/>200
6	2	DIPE	1.47 ± 0.02	51/131	30.1 ± 0.4	53/58
7	2	[EMIM][Tf$_2$N]	0.90 ± 0.01	28/38	0.17 ± 0.01	3/—
8	2	[EMIM][BF$_4$]	0.15 ± 0.02	23/46	2.28 ± 0.25	34/40
9	2	[BMIM][PF$_6$]	0.27 ± 0.04	41/78	1.34 ± 0.38	21/49
10	3	TBME	1.54 ± 0.03	49/>200	6.7 ± 0.3	49/>200
11	3	[EMIM][Tf$_2$N]	0.03 ± 0.01	5/>200	0.06 ± 0.01	1/>200
12	3	[EMIM][BF$_4$]	0.04 ± 0.01	5/>200	1.91 ± 0.01	17/—
13	3	[BMIM][PF$_6$]	0.08 ± 0.01	13/>200	0.67 ± 0.07	10/>200

[a] Based on 100 mg of BCL-PS powder. [b] Based on 50 mg of BCL-PS powder. [c] μmol min⁻¹ g⁻¹. [d] Conversion after 24 h/E. [e] CLEA prepared by adding bovine serum albumin.

Table 3 Acylation of **1–3** (0.1 M) with vinyl acetate in organic solvents and the mixtures of IL:organic solvent (1:2) in the presence of BCL-PS at room temperature

Entry	Substrate	Solvent	Phases	BCL-PS	t [h]	c [%]	E	v_0 [μmol min^{-1} g^{-1}]
1	**1**	Toluene	1	50 mg [a]	24	49	>200	3.4 ± 0.2
2	**1**	[EMIM][NTf$_2$]:toluene	2	50 mg [a]	48	17	>200	0.13 ± 0.01
3	**1**	[EMIM][BF$_4$]:toluene	2	50 mg [a]	24	47	>200	1.15 ± 0.01
4	**1**	[BMIM][PF$_6$]:toluene	2	50 mg [a]	48	49	>200	0.79 ± 0.01
5	**2**	DIPE	1	50 mg [a]	24	51	131	3.8 ± 0.2
6	**2**	[EMIM][NTf$_2$]:DIPE	2	50 mg [a]	48	30	51	0.26 ± 0.004
7	**2**	[EMIM][BF$_4$]:DIPE	2	50 mg [a]	24	51	134	1.27 ± 0.01
8	**2**	[BMIM][PF$_6$]:DIPE	2	50 mg [a]	24	50	77	0.79 ± 0.01
9	**3**	TBME	1	50 mg [a]	48	33	14	2.38 ± 0.03
10	**3**	[EMIM][BF$_4$]:TBME	2	50 mg [a]	48	23	50	0.84 ± 0.001
11	**3**	[BMIM][PF$_6$]:TBME	2	50 mg [a]	48	48	70	0.79 ± 0.001
12	**3**	[EMIM][NTf$_2$]:TBME	2	50 mg [a]	48	24	>200	0.16 ± 0.004
13	**1**	Toluene	1	100 mg [b]	24	50	>200	2.7 ± 0.3
14	**1**	[EMIM][NTf$_2$]:toluene	2	100 mg [b]	48	17	51	0.084 ± 0.002
15	**1**	[EMIM][BF$_4$]:toluene	2	100 mg [b]	24	50	>200	0.57 ± 0.001
16	**1**	[BMIM][PF$_6$]:toluene	2	100 mg [b]	48	50	>200	0.46 ± 0.01
17	**2**	DIPE	1	100 mg [b]	24	50	115	3.5 ± 0.2
18	**2**	[EMIM][NTf$_2$]:DIPE	2	100 mg [b]	48	45	88	0.21 ± 0.001
19	**2**	[EMIM][BF$_4$]:DIPE	2	100 mg [b]	6	50	115	1.54 ± 0.01
20	**2**	[BMIM][PF$_6$]:DIPE	2	100 mg [b]	24	47	196	0.43 ± 0.001
21	**3**	TBME	1	100 mg [b]	24	25	30	1.69 ± 0.05
22	**3**	[EMIM][BF$_4$]:TBME	2	100 mg [b]	24	33	50	0.41 ± 0.01
23	**3**	[BMIM][PF$_6$]:TBME	2	100 mg [b]	48	16	15	0.067 ± 0.001
24	**3**	[EMIM][NTf$_2$]:TBME	2	100 mg [b]	48	30	30	0.12 ± 0.003

[a] Corresponds to protein in BCL-CLEA. [b] Corresponds to protein in BCLxero.

μmol min^{-1} g^{-1} of the original BCL-PS used to prepare the xero gel or the CLEA, thus allowing direct comparison. The results clearly indicate that initial rates in the organic solvents (entries 1, 6 and 10) are always higher than those in the studied ILs. The acylation in organic solvents proceeds smoothly close to 50% conversion in a highly enantioselective manner while in the ILs there is a tendency for the progress of the acylation to cease. Finally, the acylation of **3** in the ILs with both BCL preparations practically stops at early stages (entries 11–13). The BCL-CLEA displays higher initial rates than the BCLxero for all substrates in [EMIM][BF$_4$] and in [BMIM][PF$_6$] (entries 4, 5, 8, 9, 12 and 13). Diffusion limitations can be proposed as a reason for apparent low activities of the BCLxero. However, diffusion limitation should be most evident in the viscose [EMIM][Tf$_2$N] rather than in [EMIM][BF$_4$] or [BMIM][PF$_6$] (Table 1). This is not the case ruling out the influence of diffusion on the reaction rates of BCLxero (Table 2, compare entries 3, 4, 5 and 7, 8, 9). It can therefore be concluded that all three ILs have a negative effect on the initial activity of BCLxero. For the more active BCL-CLEA the diffusion limitations do become evident in the same examples explaining the relatively low initial rate of BCL-CLEA in [EMIM][Tf$_2$N]. But as with BCLxero all ILs seem to have a negative influence on the initial rates of BCL-CLEA. Poor reactivity was reported earlier for the BCL-PS preparation in ILs.[12]

While the initial rates of BCLxero are significantly lower than those of BCL-CLEA the overall conversion in the IL with BCLxero is much better for the acylation of **1** and **2**. Indeed, with BCLxero conversions continue to increase toward 50% conversion with time. In contrast BCL-CLEA seems to loose its activity rather rapidly and even with high initial rates the reactions tend to stop at low conversions (entries 3, 4, 8, 9, 12, 13,

Table 2). This loss of activity might be due to the earlier described acetaldehyde-oligomer formation induced by ILs when vinyl acetate is used as an acyl donor.[17,40] Free BCL-PS was also previously shown to loose its activity in [BMIM][PF$_6$] and other *N,N*-dialkyl imidazolium ion based ILs.[12] The stabilisation of BCL *via* immobilisation on the ceramic Toyonite carriers for the use in ILs has earlier been described.[16,17,39] The results described here indicate that the xerogel can also protect BCL against deactivation, while cross-linking does not provide this stabilisation. Consequently BCLxero is the BCL preparation of choice in IL.

No clear trend as to which IL is the best can be deduced from Table 2. It seems that, much like the organic solvents, there is a "best IL" for each of the three substrates. Thus it can be said that with the organic solvent of choice for each substrate the enzyme preparations always perform better than with the IL of choice.

For kinetic resolutions of racemates, enantioselectivity (measured by the enantiomer ratio E) is often a more important parameter than reactivity. In the case of **2**, considerable solvent effects on enantioselectivity are evident when either BCLxero or BCL-CLEA was used (entries 6–9 Table 2). As for the activity, the enzyme enantioselectivity is highly dependent on the substrate. For this substrate [BMIM][PF$_6$] is the IL of choice. The excellent enantioselectivity for the acylations of **1** and **3** was not affected by the solvents used (entries 1–5 and 10–13, Table 2).

In our previous work for the acylation of **3** with lipase PS–C II, activities and enantioselectivities were enhanced when TBME was added to [EMIM][Tf$_2$N] and [EMIM][BF$_4$].[39] Accordingly, toluene, DIPE and TBME were mixed with the ILs studied here, and the acylation of **1–3** in the respective mixtures was investigated using all three BCL preparations, BCL-PS, BCLxero and

Table 4 Acylation of **1–3** (0.1 M) with vinyl acetate (0.2M) in the mixture of IL:organic solvent in the presence of BCLxero (based on 100 mg of the original BCL-PS powder) at room temperature

Entry	Substrate	Solvent system	Phases	Conv.[a] [%]	ee[b] [%]/E	v_0 [μmol min^{-1} g^{-1}]
1	**1**	[EMIM][Tf$_2$N]:toluene (2:1)	1	40/49	98/>200	0.24 ± 0.05
2	**1**	[EMIM][Tf$_2$N]:toluene (1:1)	2	22/34	>99/>200	0.14 ± 0.001
3	**1**	[EMIM][Tf$_2$N]:toluene (1:2)	2	45/49	>99/>200	0.98 ± 0.08
4	**1**	[EMIM][Tf$_2$N]:toluene (1:3)	2	—/30	>99/>200	0.25 ± 0.001
5	**1**	[EMIM][BF$_4$]:toluene (2:1)	1	33/45	99/>200	0.40 ± 0.02
6	**1**	[EMIM][BF$_4$]:toluene (1:1)	2	43/48	99/>200	0.60 ± 0.12
7	**1**	[EMIM][BF$_4$]:toluene (1:2)	2	39/47	99/>200	0.35 ± 0.03
8	**1**	[EMIM][BF$_4$]:toluene (1:3)	2	29/40	>99/>200	0.28 ± 0.001
9	**1**	[BMIM][PF$_6$]:toluene (2:1)	1	37/47	99/>200	0.84 ± 0.01
10	**1**	[BMIM][PF$_6$]:toluene (1:2)	2	46/50	99/>200	0.72 ± 0.05
11	**2**	[EMIM][Tf$_2$N]:DIPE (1:2)	2	51/54	85/66	0.71 ± 0.04
12	**2**	[EMIM][BF$_4$]:DIPE (2:1)	2	51/—	91/66	1.19 ± 0.14
13	**2**	[EMIM][BF$_4$]:DIPE (1:2)	2	54/—	87/61	2.19 ± 0.09
14	**2**	[BMIM][PF$_6$]:DIPE (2:1)	2	51/—	87/42	1.48 ± 0.16
15	**2**	[BMIM][PF$_6$]:DIPE (1:2)	2	34/33	96/60	0.68 ± 0.04
16	**3**[c]	[EMIM][Tf$_2$N]:TBME (2:1)	1	10/18	>99/>200	0.12 ± 0.01
17	**3**[c]	[EMIM][Tf$_2$N]:TBME (1:2)	2	26/37	97/126	0.31 ± 0.01
18	**3**[c]	[EMIM][BF$_4$]:TBME (2:1)	1	32/42	96/71	0.46 ± 0.01
19	**3**[c]	[EMIM][BF$_4$]:TBME (1:2)	2	28/37	96/89	0.30 ± 0.02
20	**3**[c]	[BMIM][PF$_6$]:TBME (2:1)	1	5/5	>99/—	0.15 ± 0.04
21	**3**[c]	[BMIM][PF$_6$]:TBME (1:2)	2	41/44	97/102	1.06 ± 0.11

[a] Conversion after 24 h/48 h. [b] ee for the formed ester product at the conversion after 48 h. [c] Reaction temperature 48 °C.

Table 5 Acylation of **1–3** (0.1 M) with vinyl acetate (0.2 M) in the mixture of an IL and an organic solvent in the presence of BCL-CLEA (based on 50 mg of the original BCL-PS powder) at room temperature

Entry	Substrate	Solvent system	Phases	Conv.[a] [%]	ee[b] [%]/E	v_0 [μmol min^{-1} g^{-1}]
1	**1**	[EMIM][Tf$_2$N]:toluene (2:1)	1	11/19	>99/>200	1.21 ± 0.62
2	**1**	[EMIM][Tf$_2$N]:toluene (1:2)	2	10/18	>99/>200	1.57 ± 0.47
3	**1**	[EMIM][BF$_4$]:toluene (2:1)	1	41/49	98/>200	5.83 ± 1.44
4	**1**	[EMIM][BF$_4$]:toluene (1:2)	2	41/48	>99/>200	6.60 ± 0.71
5	**1**[c]	[EMIM][BF$_4$]:toluene (1:2)	2	32/43	>99/>200	1.98 ± 0.36
6	**1**	[BMIM][PF$_6$]:toluene (2:1)	1	15/28	>99/>200	1.80 ± 0.36
7	**1**	[BMIM][PF$_6$]:toluene (1:2)	2	20/32	>99/>200	1.90 ± 0.41
8	**2**	[EMIM][Tf$_2$N]:DIPE (1:2)	2	19/31	95/49	1.80 ± 0.18
9	**2**	[EMIM][BF$_4$]:DIPE (2:1)	2	34/46	92/57	3.57 ± 0.26
10	**2**	[EMIM][BF$_4$]:DIPE (1:2)	2	40/50	93/79	4.82 ± 0.15
11	**2**	[BMIM][PF$_6$]:DIPE (2:1)	2	18/36	96/79	0.54 ± 0.13
12	**2**	[BMIM][PF$_6$]:DIPE (1:2)	2	33/47	94/78	2.57 ± 0.42
13	**3**[d]	[EMIM][Tf$_2$N]:TBME (1:2)	2	4/7	>99/—	0.35 ± 0.04
14	**3**[d]	[EMIM][BF$_4$]:TBME (2:1)	1	19/29	95/43	0.54 ± 0.13
15	**3**[d]	[EMIM][BF$_4$]:TBME (1:2)	2	22/33	95/55	1.69 ± 0.40
16	**3**[d]	[BMIM][PF$_6$]:TBME (2:1)	1	29/40	95/73	3.14 ± 0.38
17	**3**[d]	[BMIM][PF$_6$]:TBME (1:2)	2	31/41	96/105	3.29 ± 0.38

[a] Conversion after 24 h/48 h. [b] ee for the formed ester product at the conversion after 48 h. [c] CLEA prepared by adding bovine serum albumin. [d] Reaction temperature 48 °C.

BCL-CLEA (Tables 3–5). The addition of an organic solvent lowers the viscosity of an IL.[41] Another important factor is that the organic solvents used are not in all proportions soluble in the ILs and separation into two phases may take place as given in the tables.

All BCL preparations display the highest initial rates in the pure organic solvent. Mixtures of ILs with organic solvents slow down the reaction in most cases, independent of the fact whether it is a mono- or biphasic mixture.

For substrate **1** BCL-PS clearly performs best in toluene, and only in [EMIM][BF$_4$]:toluene 1:2 mixture equal enantioselectivity and close to 50% conversions after 24 h were observed (Table 3, entries 1, 3, 13, 15). In IL organic solvent mixtures BCLxero always displays lower activities for this substrate than in toluene, but keeps excellent enantioselectivity (Table 2 entry 1 and Table 4 entries 1–10). For BCL-CLEA the activity towards **1** also uniformly drops in IL organic solvent mixtures compared to the pure organic solvent, while excellent enantioselectivities are maintained (Table 2 entry 1 and Table 5 entries 1–7).

For substrate **2** BCL-PS again performs best in the organic solvent and in [EMIM][BF$_4$]:DIPE 1:2 mixture while in the other IL:DIPE mixtures lower activity and enantioselectivity are observed (Table 3). In contrast BCLxero displays practically the same (51–54%) conversion toward **2**, independent of the solvent system (Table 4, entries 11–14), the mixture [BMIM][PF$_6$]:DIPE (1:2) being an exception (entry 15). However, the

enantioselectivity in IL:DIPE mixtures is always lower than in pure DIPE (Table 2 entry 6 and Table 4 entries 11–15). BCL-CLEA is less active and less enantioselective toward **2** when used in IL:DIPE mixtures compared to its use in pure DIPE (Table 2 entry 6 and Table 5 entries 8–12).

In the case of substrate **3**, BCLxero and BCL-CLEA have the highest activity and enantioselectivity in TBME (compare Table 2 entry 10 with Tables 4 and 5). This is not the case for BCL-PS. Here improved enantioselectivity can be observed in some cases in IL:TBME mixtures (Table 3, entries 9–12 and 21–24). In this case hydrolysis by the water in the enzyme may complicate the interpretation of the observed results as will be discussed below. However, the initial rates are always highest in the pure organic solvent.

Thus, no clear trend-line can be deduced as to which reaction medium should be used, mono- or biphasic. Instead it seems that for each substrate the best solvent (mixture) has to be found separately.

We then studied the hydrolysis of the produced enantiopure esters (*R*)-**4**, (*R*)-**5** and (*S*)-**6** with the residual water in the system with the two most successful BCL preparations, BCL-PS and BCLxero. The potential of hydrolysis for the produced ester in the acylation of **1–3** can be seen in such experiments while the real proportion of the hydrolysis during the acylation cannot be determined. Moreover, the proportion in the acylation is certainly much less that the data in Table 6 suggest because the concentration of the hydrolysable ester is initially zero and the substrate alcohol (**1–3**) then competes with water as a nucleophile. In the case of all the substrates, the presence of BCLxero causes considerably less hydrolysis than BCL-PS (Table 6). The hydrolysis of (*S*)-**6** in the solvent mixture is an exception (entry 6). In this case, the hydrolysable ester is butanoate rather than acetate and the reaction takes place at an elevated temperature. Another observation is that hydrolysis is always more significant in the solvent mixture than in a neat organic solvent. This might be explained by the relatively high water content (986 ppm) of [EMIM][BF$_4$] and by its water miscibility. However, the same amount of water from the IL is present in all the solvent mixtures (entries 2, 4 and 6), and accordingly the water contents of the organic solvents (77 ppm for toluene, 321 ppm for DIPE and 622 ppm for TBME) make the difference. BCLxero in toluene and in the solvent mixture caused practically no hydrolysis in the case of (*R*)-**4** (entries 1 and 2) while considerable hydrolysis by the residue water was observed in the case of (*S*)-**6** in the solvent mixture (entry 6). While the acylation of **3** in TBME with vinyl acetate

and BCLxero proceeded smoothly without clear indications about hydrolysis of the produced (*S*)-**6** (Table 2, entry 10), the hydrolysis in [EMIM][BF$_4$] (1:2) (Table 4, entry 19) evidently caused the observed difficulties in leading the acylation reaction to 50% conversion and variations in *E* values with time.

Conclusions

The present work indicates that the nature of the BCL preparation (native BCL-PS, BCLxero and BCL-CLEA in the present work) on its activity is one of the crucial variables when enzymes are used to catalyse organic reactions in the presence of ILs. When these enzyme preparations were applied to the acylation of three different aromatic secondary alcohols (**1–3**) in the most commonly used ionic liquids ([EMIM][Tf$_2$N], [EMIM][BF$_4$] and [BMIM][PF$_6$]) in biocatalysis it was shown that the ILs have a negative influence on the initial rates (activities) of the enzyme preparations compared to the reactions in selected organic solvents or in their mixtures with an IL. While BCL-CLEA displays higher activity (initial rates) than BCLxero for all substrates in the ILs it loses its activity rapidly. In organic solvents and in the ILs, the nature of the solvent affects *E* only with **2** serving as the substrate while *E* > 200 is evident with **1** and **3**. This work reveals that it is not enough to consider activities of the BCL preparations to find the one with highest stability against an IL. Rather the overall conversion and possible side reactions, the tendency for hydrolysis of the ester produced in particular, needs to be taken into consideration. Contrary to earlier results,[42] it is not possible to label one IL better than the other without taking the nature of the substrate and the ester produced into account. Overall, the results show that BCLxero is a good choice, especially in cases where the produced ester is an activated ester and thus susceptible to hydrolysis as a side reaction.

Experimental

Materials

Lipase PS "Amano" SD (BCL-PS, from *Burkholderia cepacia*) was purchased from Amano Pharmaceuticals Co., Ltd (Nagoya, Japan). 1-Phenylethanol (98%) and 2-amino-1-phenylethanol (98%) were products of Aldrich and 1-(2-furyl)ethanol (>97%) was from Fluka. Amide **3** was prepared by the reaction of 2-amino-1-phenylethanol with butanoic anhydride (0.95 eqv.). (*R*)-**4**, (*R*)- **5** and (*S*)-**6** were available from our

Table 6 Conversion (%) after 24 h in the hydrolysis of enantiopure esters **4–6** (0.05 M) by the residual water in the enzyme preparation and the solvent system at room temperature

Entry	Substrate	Solvent	log *P*	Conv. [%] by BCL-PS[a]	Conv. [%] by BCLxero[b]
1	(*S*)-**4**	Toluene	2.8	4	1
2	(*S*)-**4**	[EMIM][BF$_4$]:toluene (1:2)		27	2
3	(*S*)-**5**	DIPE	1.9	20	10
4	(*S*)-**5**	[EMIM][BF$_4$]:DIPE (1:2)		22	26
5	(*R*)-**6**[c]	TBME	1.35	86	16
6	(*R*)-**6**[c]	[EMIM][BF$_4$]:TBME (1:2)		35	45

[a] 100 mg mL^{-1} of BCL-PS. [b] BCLxero based on 100 mg mL^{-1} of BCL-PS. [c] Butanoate instead of acetate; reaction temperature 48 °C.

previous work.[36] Methyltrimethoxysilane (MTMS, Aldrich, >99%), tetramethoxysilane (TMOS, Fluka, >99%) and glutaraldehyde (Fluka, 25% in water) were used as supplied. [EMIM][Tf$_2$N], [EMIM][BF$_4$] and [BMIM][PF$_6$] were prepared by the methods described in the literature.[36,39] Ethyl bromide (>99%), 1-methylimidazole (>99%), 1-chlorobutane (>99.5%), LiNTf$_2$ (>99%) and sodium fluoroborate (>98%) were products of Fluka. HPF$_6$ (60% in H$_2$O) was from Aldrich. Vinyl acetate and the solvents were of the highest grade from Aldrich, J.T. Baker and Lab-Scan Ltd. Water contents of the neat solvents were measured by Karl Fischer titration and were: toluene 77 ppm, TBME 622 ppm, DIPE 321 ppm, [EMIM][Tf$_2$N] 45 ppm, [EMIM][BF$_4$] 986 ppm and [BMIM][PF$_6$] 486 ppm.

Analysis

The progress of the reactions was followed by taking samples (50 μL) at intervals and extracting the products into toluene, TBME or DIPE accordingly to organic solvent in the reaction. The samples were derivatized with propionic anhydride in the presence of 4,4-dimethylaminopyridine (DMAP, 1% in pyridine) to achieve a good baseline separation and analyzed by GC equipped with Chrompack CP-Chirasil-DEX CB column (25 m × 0.25 mm) and Chrompack CP-Chirasil-L-valine column. The determination of E was based on equation $E = \ln[(1 - c)(1 - ee_S)]/\ln[(1 - c)(1 + ee_S)]$ with $c = ee_S/(ee_S + ee_P)$ using linear regression (E as the slope of the line $\ln[(1 - c)(1 - ee_S)]$ versus $\ln[(1 - c)(1 + ee_S)]$). The protein content of lipase PS-SD powder was determined using bicinchoninic acid assay using bovine serum albumin as the standard protein.

Encapsulation of BCL in a sol–gel matrix

The sol–gel precursor was prepared according to a literature method.[36,37] Acidic water (1.38 mL, pH= 2.85 by HCl) was added to a mixture of MTMS (2.1 g, 15.4 mmol), TMOS (9.08 g, 58.5 mmol) and distilled water (10.4 mL) and the mixture was stirred until it was homogenous. The formed methanol was removed by evaporizing in a rotary evaporator until the odours of MTMS, TMOS and MeOH were not detectable any longer. The mixture was cooled to 0 °C and water was added until the total volume corresponded to the initial MTMS/TMOS volume. The sol precursor was used immediately for the encapsulation of BCL. BCL-PS powder (containing 3% protein, 100 mg) was dissolved in KH$_2$PO$_4$-buffer (200 μL, 0.1 M, pH = 7.0). The sol precursor mixture (200 μL) was added and the mixture was stirred magnetically until homogenous, followed by the removal of the stirring bar. The mixture gelled (1–2 min) and the gel was aged at 4 °C for 24 h followed by lyophilization at 0.2 atm for 4 h. The formed xerogel was stored at 4 °C and used as a pellet.

Preparation of BCL-CLEA

The preparation of CLEA was based on a literature method.[36,38] BCL-PS powder (containing 3% protein, 50 mg) in KH$_2$PO$_4$ buffer (1 mL, 0.1 M, pH = 7) was added dropwise to saturated (NH$_4$)$_2$SO$_4$ (9 mL) at 4 °C. Glutaraldehyde (377 μL, 100 mM, 25% in water) was added and the mixture was stirred at 4 °C for 5 h. The suspension was diluted with 3 mL of the

buffer and centrifugated. The pellet was washed two times with the buffer (3 mL) and once with acetonitrile (3 mL). After centrifugation, the obtained CLEA was dried in vacuum and stored at 4 °C. When BSA was used, it was added in KH$_2$PO$_4$ buffer together with BCL-PS.

Enzymatic acylation

For enzymatic acylation, an organic solvent (1 mL) or the mixture of ionic liquid, solvent (1 mL) and vinyl acetate (0.2 M) were added to one of the lipase preparations (for BCLxero corresbonds to 100 mg and for BCL-CLEA 50 mg of original BCL-PS powder; with BCL-PS both 50 and 100 mg were used) and the addition of a substrate (0.1 M) started the reaction. The reactions were shaken at room temperature (23 °C) for the reactions of **1** and **2** and at 48 °C for the reaction of **3**.

Acknowledgements

Notes and references

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The enantioselective cyanosilylation of aldehydes on a chiral VO(Salen) complex encapsulated in SBA-16

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A solid catalyst for enantioselective cyanosilylation of aldehydes was prepared by encapsulating a chiral vanadyl Salen complex [VO(Salen)] in the nanocage of SBA-16. After encapsulation, the pore entrance size of SBA-16 was finely tuned through a silylation method to confine the metal complex in the nanocage and allow the free diffusion of the reactants and products during the catalytic process. For the enantioselective cyanosilylation of benzyldehyde, the enantioselectivity of the solid catalyst can achieve as high as 90%. When alkanes such as pentane, hexane and heptane were used as solvents, VO(Salen) confined in the nanocage of SBA-16 exhibits higher enantioselectivity than its homogeneous counterpart. In halogenated alkanes, the enantioselectivity of VO(Salen) confined in the nanocage of SBA-16 is lower than that of the homogeneous catalyst. The different solvent effect for the solid catalyst from the homogeneous counterpart is probably due to the altered microenvironment of VO(Salen) encapsulated in the nanocage.

Introduction

The enantioselective cyanosilylation of carbonyl compounds represents an effective approach for the synthesis of optically active cyanohydrins, which are versatile building blocks for the preparation of chiral compounds such as amino alcohols, amino acids and hydroxyl acids.[1] Great efforts have been devoted for the development of efficient catalysts for asymmetric cyanosilylation, such as chiral metal complexes[2–15] and organocatalyst.[16–19] Heterogeneous asymmetric catalysis has attracted much research attention recently because it provides a green process for the production of chiral compounds.[20,21] Compared with the homogeneous process, only limited works are related to the heterogeneous asymmetric cyanosilylation. VO(Salen) complex, an efficient catalyst for asymmetric cyanosilylation, has been immobilized on silica, MCM-41, active carbon and single-walled carbon nanotubes *via* a covalent linkage.[22–27] Unfortunately, in most cases, the immobilized catalyst usually exhibited lower enantioselectivity and activity than its homogeneous counterpart.

Among versatile methods for immobilization of chiral catalysts onto solid supports, the encapsulation is one of the most promising strategies because it can keep the properties of chiral catalyst by simply confining the catalyst in a solid matrix. Mesoporous silicas with ordered pore arrangement, high surface area and rigid framework, are an ideal porous matrix for entrapment of large metal complexes. The nanopore of the mesoporous silicas accommodating chiral catalysts can be regarded as a nanoreactor for asymmetric synthesis. The properties of

the nanoreactor could be finely modified to meet the requirements of a given reaction, such as the surface hydrophobicity/hydrophilicity, surface polarity, and electrostatic properties. The asymmetric catalysis in the nanoreactor is promising and provides opportunities to develop more efficient asymmetric synthetic systems based on the solid chiral catalysts.[28]

In our previous work, Co(Salen) and Ru-TsDPEN metal complexes were successfully confined in the nanocages of SBA-16 by reducing the pore entrance size through a silylation method.[29] Since there are no covalent linkage and other strong interactions between the Co(Salen) complex and the surface of the nanocage, the Co(Salen) in the nanocage keeps its properties as much as possible. The encapsulated catalyst shows similar enantioselectivity to the homogeneous counterpart and displays much higher activity in the hydrolytic kinetic resolution of propylene epoxide than its homogeneous counterpart especially at high substrate/catalyst ratios. The high activity is due to the enhanced cooperative activation effect by the nanocage of mesoporous materials.[30]

In this work, a chiral VO(Salen) complex was confined in the nanocage of SBA-16 for the enantioselective cyanosilylation of aldehyde. Under the optimized conditions, the ee value can reach as high as 90% on the solid catalyst for the cyanosilylation of benzaldehyde. The catalytic activity highly depends on the pore entrance size of the solid catalysts. The influence of the solvent on the catalytic performance of the solid and homogeneous catalyst was investigated. The results reflect that the VO(Salen) complex confined in the nanocage of SBA-16 has a different microenvironment from that in the homogeneous system.

Results and discussion

Tuning the pore entrance size of SBA-16 by silylation

For accommodation of the metal complex, the pore entrance size of SBA-16 should be larger than the molecular size of

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metal complex in order to introduce the metal complex into the nanocages of SBA-16. However, confining the metal complex within the nanocages requires a pore entrance size smaller than the molecular size of the metal complex. Therefore, the pore entrance size of SBA-16 with encapsulated metal complex should be reduced to be small enough to prevent the escape of the metal complex from the cavity and large enough to permit the free diffusion of the reactants and products (Scheme 1). Among various methods of reducing the pore entrance size of mesoporous silicas, silylation is one of the most convenient and controllable ways because the silylation occurs under relatively mild conditions,[31,32] which is very important to protect the confined metal complex in the nanocage from decomposition.

Propyltrimethoxysilane (C3), octyltrimethoxysilane (C8), dodecyltrimethoxysilane (C12), and a mixture of C8 and C12 organosilane with different molar ratios were used as silylating reagents to tailor the pore entrance size of SBA-16. The N_2 sorption isotherms of SBA-16 and the silylated SBA-16 samples are displayed in Fig. 1. Similar to the parent SBA-16 with cage-like pore structure, the sorption isotherms of SBA-16-C3, SBA-16-C8, SBA-16-C8-C12(3/1) and SBA-16-C8-C12(1/3) [3/1 and 1/3 mean the molar ratios of octyltrimethoxysilane (C8) to dodecyltrimethoxysilane (C12), see Experimental section] exhibit typical type IV isotherm patterns with a H2 hysteresis loop. Compared with the parent SBA-16, the hysteresis loops of these samples shift to lower relative pressure, suggesting that the
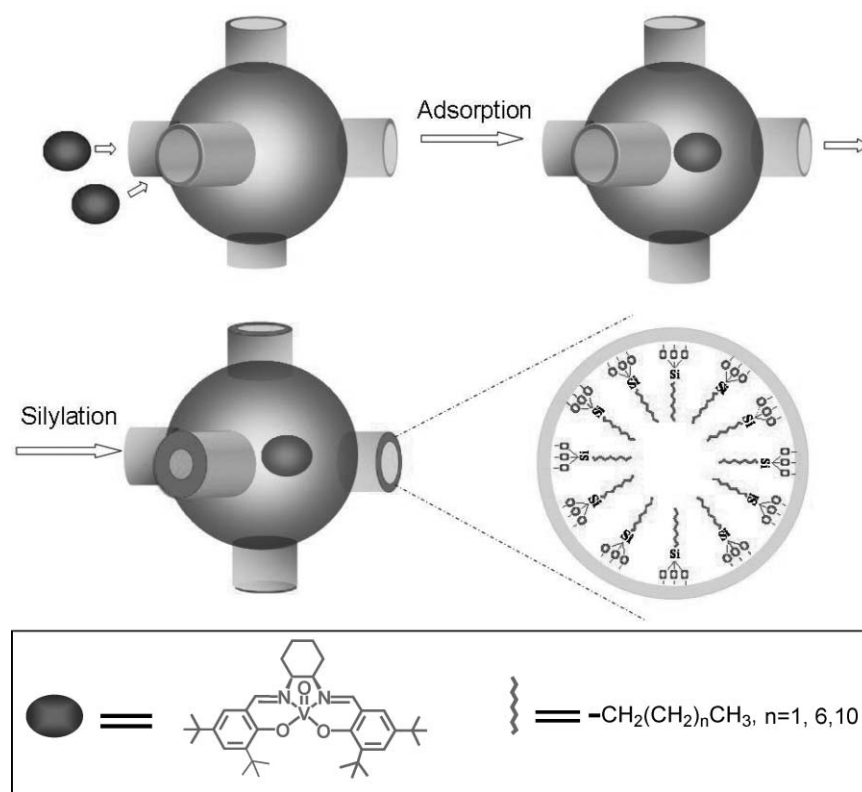
Scheme 1 Schematic description for encapsulating a chiral VO(Salen) complex in the nanocages through the silylation method.
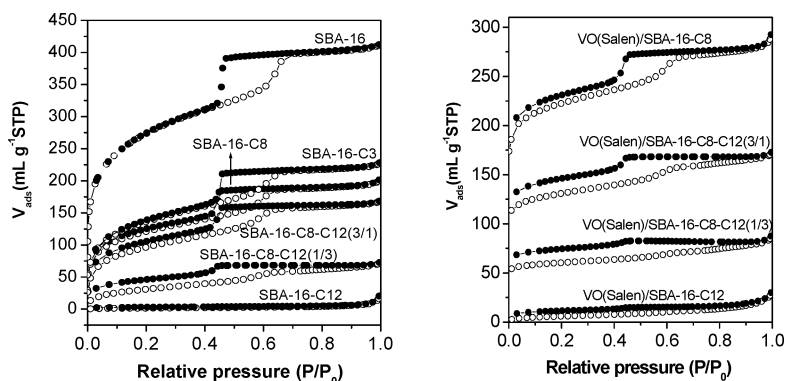
Fig. 1 N_2 sorption isotherms of SBA-16, silylated SBA-16 and solid catalysts, VO(Salen)/SBA-16-C8, offset vertically by 150; VO(Salen)/SBA-16-C8-C12(3/1), by 100; VO(Salen)/SBA-16-C8-C12(3/1), by 50.

Table 1 Physical parameters of SBA-16, the silylated SBA-16 samples and the solid catalyst

Samples	S^a (m^2/g)	V^b (cm^3/g)	Cage size ^{c} (nm)	Decrease in cage size (nm)^d
SBA-16	959	0.64	6.0	—
SBA-16-C3	487	0.35	5.6	0.4
SBA-16-C8	428	0.31	5.2	0.8
SBA-16-C8-C12(3/1)	346	0.26	5.1	0.9
SBA-16-C8-C12(1/3)	126	0.17	4.9	1.1
SBA-16-C12	19	0.05	—	—
VO(Salen)/SBA-16-C8	236	0.21	5.0	1.0
VO(Salen)/SBA-16-C8-C12(3/1)	115	0.11	4.7	1.3
VO(Salen)/SBA-16-C8-C12(1/3)	39	0.06	4.6	1.4
VO(Salen)/SBA-16-C8-C12(1/3)	22	0.05	—	—

^{a} BET surface area. ^{b} Single point pore volume calculated at relative pressure P/P_0 of 0.99. ^{c} BJH method from adsorption branch. ^{d} The decreased value of cage diameter, compared with the cage size of SBA-16.

cage size is reduced by silylation. When C12 silane was used as the silylating reagent, the pore entrance of SBA-16 was blocked, as evidenced by the fact that there was only a little amount of N$_2$ adsorption.

The physical parameters of these samples are summarized in Table 1. The surface area, pore volume and cage size of the silylated SBA-16 decrease with the increase of the carbon chain length of the organosilane. The surface area, pore volume and cage size of SBA-16-C8-C12(1/3) silylated with higher C12/C8 molar ratio are smaller than those of SBA-16-C8-C12(3/1). SBA-16-C12 exhibits very low surface area and pore volume because of the blockage of the pore entrance.

The adsorption of the probe molecules from solution into the cages of SBA-16 is a reliable method to estimate the pore entrance size of SBA-16 smaller or larger than the molecular size of the probe molecule.[29] In this paper, Co(II)(Salen) (similar molecular size to VO(Salen)) was employed as the probe molecule and UV-vis spectroscopy was used to monitor the concentration of the probe molecules before and after the adsorption with the silylated SBA-16 samples. If the concentration of the probe molecule in the solution decreases after the adsorption, the pore entrance size of the silylated SBA-16 is not smaller than the probe molecule and vice versa. The UV-vis spectra of Co(Salen) in dichloromethane before and after adsorption with SBA-16-C3, SBA-16-C8, SBA-16-C8-C12(3/1), SBA-16-C8-C12(1/3) and SBA-16-C12 are presented in Fig. 2. After adsorption with SBA-16-C3, the intensities of the UV-vis bands decreased sharply compared with those of the original solution. This means that the pore entrance size of SBA-16-C3 is larger than the molecular size of Co(Salen). When the solution was adsorbed with SBA-16-C8, SBA-16-C8-C12(3/1), SBA-16-C8-C12(1/3) and SBA-16-C12, the intensities of the characteristic band of Co(Salen) remained almost the same, indicating that the pore entrance size of the above samples is small enough to prevent Co(Salen) from diffusion into the cage of SBA-16.

Encapsulation of VO(Salen) in the nanocages of SBA-16

From the above results, we can see that the pore entrance size of SBA-16-C8, SBA-16-C8-C12(3/1), SBA-16-C8-C12(1/3) and SBA-16-C12 is smaller than the molecular size of Co(Salen). Accordingly, VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1), VO(Salen)/SBA-16-C8-
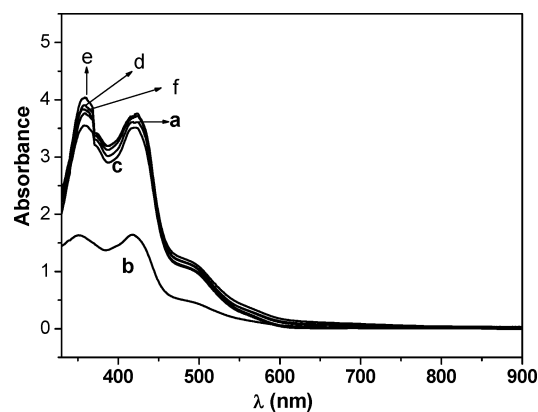

Fig. 2 UV-vis spectra of Co(II)(Salen) solution before and after adsorption with SBA-16 and silylated SBA-16: (a) Co(II)(Salen) solution before adsorption; (b) after adsorption with SBA-16-C3; (c) after adsorption with SBA-16-C8; (d) after adsorption with SBA-16-C8-C12(3/1); (e) after adsorption with SBA-16-C8-C12(1/3); (f) after adsorption with SBA-16-C12.

C12(1/3) and VO(Salen)/SBA-16-C12 were prepared using C8, a mixture of C8/C12 with a molar ratio of 3/1, a mixture of C8/C12 with a molar ratio of 1/3, and C12 organosilane as silylating agent, respectively. The sorption isotherms and the physical parameters of these solid catalysts are also displayed in Fig. 1 and Table 1, respectively. The solid catalysts VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1) and VO(Salen)/SBA-16-C8-C12(1/3) still exhibit a typical type IV isotherm pattern with H2 hysteresis loops similar to that of the parent SBA-16. This indicates that the solid catalysts still have the mesoporous cagelike structure. VO(Salen)/SBA-16-C12 shows a little amount of N$_2$ sorption due to the blockage of the pore entrance. The mesoporous structure of VO(Salen)/SBA-16-C8 was also confirmed by TEM (Fig. 3). The (100) projection corresponding to a cubic *Im3m* structure was observed clearly. This indicates that the mesoporous structure of SBA-16 is maintained after the encapsulation of VO(Salen).

Compared with SBA-16-C8, SBA-16-C8-C12(3/1) and SBA-16-C8-C12(1/3), the surface area, pore volume and cage size of VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1) and VO(Salen)/SBA-16-C8-C12(1/3) and VO(Salen)/SBA-16-C12 decrease, confirming the accommodation of VO(Salen) complex in the nanocages of SBA-16. For these three solid catalysts,
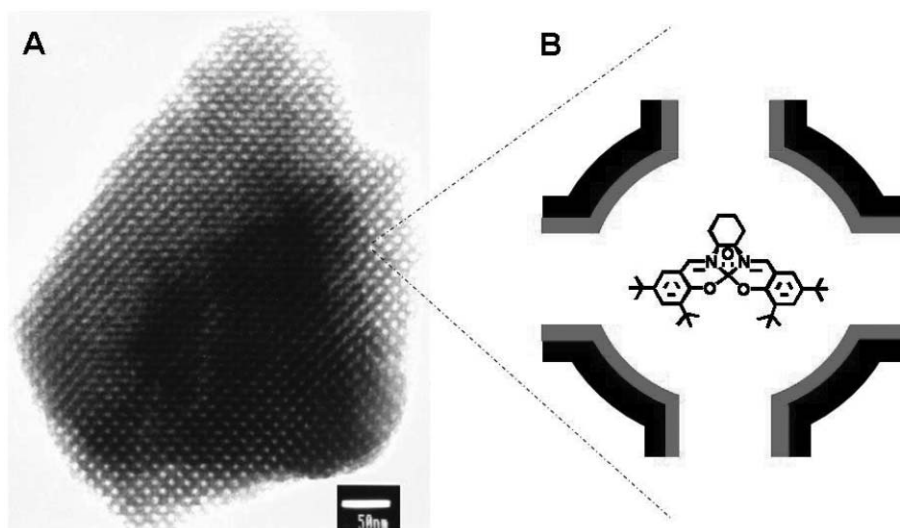
Fig. 3 TEM image of VO(Salen)/SBA-16-C8 (A) and schematic description of VO(Salen) complex confined in the nanocages of SBA-16 (B).

the cage size decreases in the order of VO(Salen)/SBA-16-C8 > VO(Salen)/SBA-16-C8-C12(3/1) > VO(Salen)/SBA-16-C8-C12(1/3) > VO(Salen)/SBA-16-C12. The pore entrance size probably also decreases in a similar order. From ICP analysis, the V contents in the solid catalysts are 0.030 wt%, 0.025 wt%, 0.042 wt% and 0.040 wt% for VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1) and VO(Salen)/SBA-16-C8-C12(1/3) and VO(Salen)/SBA-16-C12, respectively.

VO(Salen)/SBA-16-C8 is chosen as a model catalyst for characterization (Fig. 4). The FT-IR spectrum of SBA-16 exhibits a sharp peak at 3740 cm^{-1} and a broad band in the range of $3200~3700$ cm^{-1} (Fig. 4A). The absorbance peak at 3740 cm^{-1} is attributed to the stretching vibration of the isolated silanol groups (not the hydrogen-bonded silanol groups). The broad absorbance band in the range of $3200~3700$ cm^{-1} is ascribed to the vibration of the hydrogen-bonded silanol groups. In the FT-IR spectra of SBA-16-C8 and VO(Salen)/SBA-16-C8, the intense peak at 3740 cm^{-1} disappeared, and the intensity of the broad band in the range of $3200~3700$ cm^{-1} also decreased dramatically. The above results indicate that a portion of silanol groups is consumed due to the silylation reaction. The

presence of a peak at 3700 cm^{-1} is due to the silanols that are inaccessible to the silylating reagent.[33] The peaks in the range of $2800~3000$ cm^{-1} and at 1462 cm^{-1} in the FT-IR spectra of SBA-16-C8 and VO(Salen)/SBA-16-C8 can be assigned to C–H stretching vibrations and C–H bending vibration (Fig. 4B), confirming the successful silylation. Compared with the FT-IR spectra of SBA-16 and SBA-16-C8, two new peaks at 1531 and 1613 cm^{-1} in the FT-IR spectrum of VO(Salen)/SBA-16-C8 are the characteristic peaks of metal Salen complex, which could be assigned to the stretching vibrations of C=N and C=C after coordination with metal, respectively.[34] This confirms that VO(Salen) complexes are successfully encapsulated in the nanocages of SBA-16.

UV-vis spectroscopy was also employed to characterize VO(Salen)/SBA-16-C8 (Fig. 5). The UV-vis spectrum of VO(Salen) in dichloromethane shows three bands at 264 (π–π* transition of phenyl ring on Salen ligand), 385 (charge transfer transition of ligand to metal) and 625 nm (d–d transition). Similar to the UV-vis spectrum of VO(Salen) in solution, the diffuse reflectance UV-vis spectrum of VO(Salen)/SBA-16-C8 displays three bands, which are not observed in the UV-vis spectrum of SBA-16-C8. This further confirms that VO(Salen) is encapsulated in the nanocages of SBA-16. For VO(Salen) encapsulated in SBA-16, the band at 385 nm shifts to 365 nm
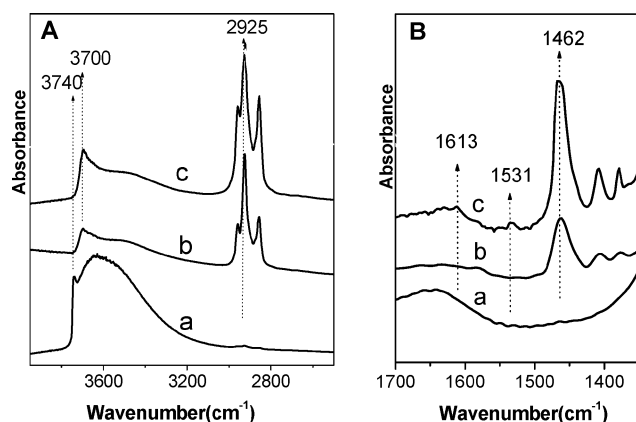

Fig. 4 FT-IR spectra of SBA-16, silylated SBA-16 and the solid catalysts: (a) SBA-16; (b) SBA-16-C8; (c) VO(Salen)/SBA-16-C8.
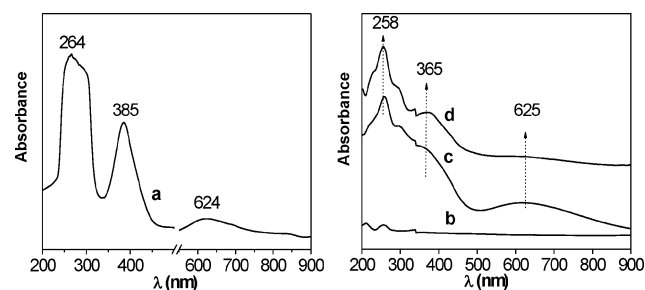

Fig. 5 UV-vis spectra of VO(Salen) in dichloromethane, silylated SBA-16 and the solid catalysts (diffuse reflectance): (a) VO(Salen) in dichloromethane; (b) SBA-16-C8; (c) VO(Salen)/SBA-16-C8; (d) VO(Salen)/SBA-16-C8 catalyst after being used 6 times.

because of the weak interactions between VO(Salen) complex and the wall of SBA-16.

Asymmetric cyanosilylation of aldehydes

The results of asymmetric cyanosilylation of benzaldehyde with VO(Salen) complex catalyst and the solid catalysts are summarized in Table 2. At room temperature, VO(Salen) complex catalyst shows 89% conversion with 85% enantisoselectivity in 18 hours. Under the same conditions, VO(Salen)/SBA-16 catalyst [synthesized by adsorption of VO(Salen) into SBA-16 without the subsequent silylation procedure] shows almost no activity for the cyanosilylation of benzaldehyde. The solid catalyst VO(Salen)/SBA-16-C8 affords 80% conversion with 80% enantioslectivity, which is nearly comparable to its homogeneous counterpart. As far as we know, this is the best result for the immobilized VO(Salen) in the cyanosilylation of benzaldehyde. This result further confirms that VO(Salen) complex can be successfully encapsulated in the nanocage of SBA-16 after reducing the pore entrance size through the silylation method, and the VO(Salen) complex confined in the nanocage of SBA-16 can keep most of its catalytic performance. When the reaction temperature is decreased to −20 °C, the enantioslectivity of VO(Salen)/SBA-16-C8 can approach 90% (Table 2, entry 5). The catalytic activity dramatically decreases to 47%, which is much lower than the homogeneous VO(Salen) catalyst (70%, Table 2, entry 2). The decrease in catalytic activity suggests that the diffusion barrier for the solid catalyst is increased because of the slow movement of the reactant and product at low temperature.

Similar to VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1), VO(Salen)/SBA-16-C8-C12(1/3) and VO(Salen)/SBA-16-C12 can also catalyze the cyanosilylation of benzaldehyde with almost the same enantioselectivity (Table 3). In order to compare the activity of the solid catalysts, the reaction kinetics was investigated (Fig. 6). The TOF for the
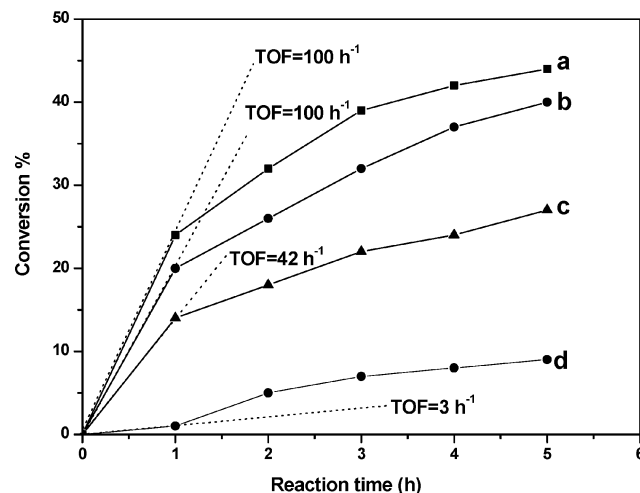

Fig. 6 Kinetic plots of the benzaldehyde cyanosilylation over solid catalysts: (a) VO(Salen)/SBA-16-C8; (b) VO(Salen)/SBA-16-C8-C12(3/1); (c) VO(Salen)/SBA-16-C8-C12(1/3); (d) VO(Salen)/SBA-16-C12. TOF calculated is based on the initial 1 hour. For VO(Salen)/SBA-16-C8, VO(Salen) is 0.24 mol% equivalent to benzaldehyde; for other catalytsts, their weight are the same as that of VO(Salen)/SBA-16-C8, TMSCN is 1.2 molar equivalent to benzaldehyde, CHCl$_3$ as solvent.

Table 2 Results of the enantioselective cyanosilylation of benzaldehyde on VO(Salen) and the solid catalysts[a]

Entry	Catalysts	Temperature (°C)	Time (h)	Conv.[b] (%)	Ee[c] (%)
1	VO(Salen)	20	18	89	85
2	VO(Salen)	−20	30	70	94
3	VO(Salen)/SBA-16	20	30	Trace	—
4	VO(Salen)/SBA-16-C8	20	30	80	80
5	VO(Salen)/SBA-16-C8	−20	30	47	90

[a] VO(Salen) is 0.24 mol% equivalent to benzaldehyde; TMSCN is 1.2 molar equivalent to benzaldehyde, CHCl$_3$ as a solvent. [b] GC analysis, p-nitrobenzene is used as the internal standard compound. [c] Ee values are based on GC analysis of O-acetyl cyanohydirn, which is the derived from cyanohydrin trimethylsilyl ethers in the presence of Sc(OTf)$_3$ and acetic anhydride (see ref. 39).

Table 3 Results of the enantioselective cyanosilylation of benzaldehyde on the solid catalyst with different pore entrance size [a]

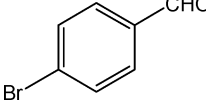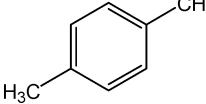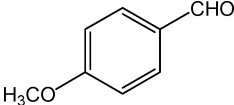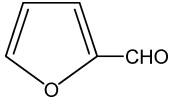| Entry	Catalysts	Conv.[b] (%)	Ee (%)	TOF[c] (h^{-1})
1	VO(Salen)/SBA-16-C8	80	80	100
2	VO(Salen)/SBA-16-C8-C12(3/1)	76	79	100
3	VO(Salen)/SBA-16-C8-C12(1/3)	57	78	42
4	VO(Salen)/SBA-16-C12	14	76	3
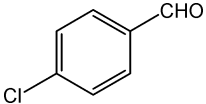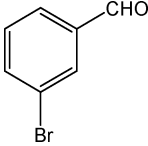
[a] VO(Salen) is 0.24 mol% equivalent to benzaldehyde for VO(Salen)/SBA-16-C8. For other catalytsts, their weight are the same as that of VO(Salen)/SBA-16-C8. TMSCN is 1.2 molar equivalent to benzaldehyde, CHCl$_3$ as solvent. [b] GC analysis, p-nitrobenzene is used as an internal standard compound. [c] TOF calculated is based on the initial one hour.

four catalysts is quite different and it decreases in the order of VO(Salen)/SBA-16-C8 $\cong$ VO(Salen)/SBA-16-C8-C12(3/1) > VO(Salen)/SBA-16-C8-C12(1/3) > VO(Salen)/SBA-16-C12 (Table 3). The different activity of VO(Salen) confined in the host material which was modified using different kinds of silane precursors may be due to the different pore entrance size. The large pore entrance size favors the fast diffusion of reactants and products and the small pore entrance size will make the diffusion of reactions and products through the porous matrix difficult. This may suggest that pore entrance size modification is the key factor for obtaining efficient solid catalyst by the entrapment method.

VO(Salen) confined in the nanocage will have a different microenviroment from the homogeneous counterpart because of the surrounding rigid pore wall of SBA-16. In an attempt to optimize the performance of the solid catalyst and investigate the influence of the rigid pore wall on the catalytic performance of the solid catalyst, the cyanosilylation of benzaldehyde was performed in different solvents. Table 4 gives the results for the cyanosilylion of benzaldehyde on homogeneous catalyst and heterogeneous catalysts. For the homogeneous catalyst, CH_2Cl_2 and THF are the best solvents in view of enantioselectivity (87%). Using $CHCl_3$ and CH_2ClCH_2Cl as solvents, 85% and 84% enantioselectivty can be obtained, respectively. While a moderate enantioselectivity (70%) was obtained in dimethyl ether solvent. For the solid catalyst, VO(Salen)/SBA-16-C8, $CHCl_3$ was found to be the best solvent, in which 80% enantioselectivity can be obtained. When the solvent was changed to CH_2Cl_2 and THF, the enantioselectivity decreased to 69% and 74%, respectively, which was lower than that of the homogeneous catalyst. In the cases of dimethyl ether, much lower enantioselectivity (29%) than the homogeneous system was observed. Interestingly, when pentane, hexane and heptane are used as solvents (Table 4, entries 6~8), the solid catalyst exhibits higher enantioselectivity than VO(Salen) catalyst. Obviously, the VO(Salen) catalyst and VO(Salen)/SBA-16-C8 show different solvent effects. The chiral induction capability of VO(Salen) catalyst confined in the nanocage seems to be more sensitive to solvent than VO(Salen) catalyst in the homogeneous system. The differences may be due to the altered microenvironment of VO(Salen) encapsulated in the nanocage.[35] Carefully screening of the reaction solvent and modification of the microenvironment of the pore surface are crucial to obtain high enantioselectivity for the asymmetric reaction occurring in the nanocage.

The substrate scope of asymmetric cyanosilylation was investigated under optimized conditions using VO(Salen)/SBA-16-C8 as a model catalyst (Table 5). Most aromatic aldehydes can be efficiently converted to the corresponding product with high enantioselectivity (80~87% ee) on VO(Salen)/SBA-16-C8. However, the catalytic activity varies depending on the substrate. Higher catalytic activity was observed for Cl- and Br-substituted benzaldehyde. Furfural shows the lowest activity.

Table 5 Results of the asymmetric cyanosilylation of other aldehydes on the solid catalyst VO(Salen)/SBA-16-C8[a]

Entry	Substrates	Conv. (%)[b]	Ee (%)
1		89	86
2		82	80
3		85	87
4		67	84
5		60	84
6		45	82

[a] VO(Salen), 0.24 mol% equiv. to benzaldehyde; TMSCN, 1.2 mol equiv. to benzaldehyde; reaction time, 30 hours; 0 °C. $CHCl_3$ as a solvent. [b] Based on GC integral area.

Table 4 Results of the enantioselective cyanosilylation of benzaldehyde on VO(Salen) and the solid catalysts in different solvents[a]

Entry	Solvent	VO(Salen)		VO(Salen)/SBA-16-C8	
		Ee (%)	Conv. (%)	Ee (%)	Conv. (%)
1	CH_2Cl_2	87	91	69	77
2	$CHCl_3$	85	89	80	80
3	CH_2ClCH_2Cl	84	73	67	64
4	THF	87	21	74	13
5	Dimethyl ether	70	55	29	60
6	Pentane	69	81	75	27
7	Hexane	71	82	76	27
8	Heptane	66	83	73	23

[a] VO(Salen), 0.24 mol% equiv. to benzaldehyde; TMSCN, 1.2 mol equiv. to benzaldehyde; reaction temperature, 20 °C; reaction time, 18 hours for homogeneous catalyst, 30 hours for the solid catalyst.

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Table 6 Results of the entantioselective cyanosilylation of benzalde-hyde on VO(Salen)/SBA-16-C8 catalyst for six cycles[a]

Entry	Cycles	Time (h)	Conv. (%)	Ee (%)
1	Run1	30	58	88
2	Run2	30	55	86
3	Run3	30	52	84
4	Run4	30	48	79
5	Run5	36	55	78
6	Run6	40	54	80

[a] VO(Salen), 0.24 mol% equiv. to benzaldehyde; TMSCN, 1.2 mol equiv. to benzaldehyde; reaction temperature, 0 °C.

The influence of the substrate on the catalytic activity needs further investigation.

To determine the heterogeneity of the reaction, the activity of the filtrate was tested. The solid catalyst was filtrated out after the conversion reached 42%. The solution was continually stirred. After 24 hours, the conversion is about 43%. This indicates that the filtrate shows almost no catalytic activity, further confirming that the catalytic reaction mainly takes place in the nanocages of SBA-16 instead of in the solution. ICP analysis of vanadium content in the filtrate after the first run is only 0.132 ppm, this is partly due to the leaching of VO(Salen) and partly due to the loss of the catalyst with fine particles in the filtration. In order to test the stability of the solid catalyst, six sequential asymmetric cyanosilylations of benzaldehyde in trichloromethane were investigated. The reaction results are summarized in Table 6. The used solid catalyst was recovered by a simple filtration, and washed thoroughly with trichloromethane. No obvious loss of catalytic activity and enantioselectivity was observed for the first three cycles of reaction. The loss of catalytic activity and enantioselectivity was observed for the fourth cycle. The solid catalyst after 6 cycles was characterized by UV-vis spectroscopy (Fig. 5d). The solid catalyst shows almost the same UV-vis spectrum to the fresh catalyst, indicating that VO(Salen) complexes are still encapsulated in the nanocage of SBA-16 even for 6 reaction cycles. Therefore, the deactivation of the solid catalyst may be due to the loss of solid catalyst during the recycle process.

Conclusions

A chiral VO(Salen) complex was encapsulated in the nanocages of SBA-16 by reducing the pore entrance size through silylation with different organosilane precursor. A VO(Salen) complex encapsulated in the nanocage of SBA-16 is efficient for the asymmetric cyanosilylation of aldehydes and shows ee values as high as 90%. VO(Salen) encapsulated in the nanocage of SBA-16 is more sensitive to the solvent than the homogeneous counterpart, probably because of the altered microenvironment of VO(Salen) encapsulated in the nanocage.

Experimental

Reagents and materials

Pluronic P123 copolymer ($EO_{20}PO_{70}EO_{20}$), pluronic copolymer F127 ($EO_{106}PO_{70}EO_{106}$), propyltrimethoxysilane, octyltrimethoxysilane, dodecyltrimethoxysilane were purchased from Sigma Company. Scandium (III) trifluoromethanesulfonate ($Sc(OTf)_3$, 95%) was purchased from Acros Company. 4-Chlorobenzaldehyde and 3-bromobenzaldehyde (>97%) were obtained from Alfa Aesar Company. Benzaldehyde, 4-methylbenzaldehyde, 2-furaldehyde and acetic anhydride were purchased from Shanghai Chemical Reagent Company of the Chinese Medicine Group.

(R,R)-N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine,[36] vanadyl Salen complex [VO(Salen)],[11] trimethylsilyl cyanide (TMSCN) and mesoporous cagelike material SBA-16 were synthesized according to the literature.[37,38]

Tuning the pore entrance size of SBA-16 by silylation and determining the pore entrance size by adsorption

1.5 mL of dry toluene was added to 1.0 g of SBA-16 (evacuated at 125 °C for 6 h), followed by the addition of 1.25 mL of anhydrous pyridine and 5 mmol of silylating reagent or a mixture of different silylating reagents. After refluxing for 24 h under Ar atmosphere, the resulting solid was isolated by a rapid filtration, washed thoroughly with toluene and the mixture of CH_2Cl_2 and diethyl ether and dried under vacuum. When the silylating reagents are propyltrimethoxysilane (C3), octyltrimethoxysilane (C8), the mixture of octyltrimethoxysilane and dodecyltrimethoxysilane with molar ratio of 3:1, the mixture of octyltrimethoxysilane and dodecyltrimethoxysilane with molar ratio of 1:3, and dodecyltrimethoxysilane (C12), the resultant materials are designated as SBA-16-C3, SBA-16-C8, SBA-16-C8-C12(3/1), SBA-16-C8-C12(1/3) and SBA-16-C12, respectively.

The adsorption experiment is as follows: 0.08 g of the organically modified SBA-16 (SBA-16-C3, SBA-16-C8 and SBA-16-C12) was dispersed in 3.8 mL of chloroform containing 1.33×10^{-6} mmol of Co(Salen). After stirring for 6 hours, the liquid was isolated by filtration and measured with a UV-vis spectrophotometer.

Synthesis of the solid catalysts

A typical synthesis procedure for the heterogeneous catalysts is as follows: 1.0 g of SBA-16 (evacuated at 125 °C for 6 h) was dispersed in 5 mL of CH_2Cl_2 containing 0.15 g of VO(Salen). After stirring at refluxing temperature for 24 h under an Ar atmosphere, CH_2Cl_2 was removed by evaporation. The resultant solid was added to a mixture containing 1.5 mL of dry toluene, 1.25 mL of anhydrous pyridine and 5 mmol of silylating reagent or the mixture of silylating reagents. After refluxing for 24 h under Ar atmosphere, the resulting solid was isolated by filtration and thoroughly washed with toluene, CH_2Cl_2 and THF. Then the solid product was dried under vacuum. When the silylating reagents are propyltrimethoxysilane (C3), octyltrimethoxysilane (C8), the mixture of octyltrimethoxysilane and dodecyltrimethoxysilane with molar ratio of 3:1, the mixture of octyltrimethoxysilane and dodecyltrimethoxysilane with molar ratio of 1:3, and dodecyltrimethoxysilane (C12), the resultant solid catalysts are designated as VO(Salen)/SBA-16-C3, VO(Salen)/SBA-16-C8, VO(Salen)/SBA-16-C8-C12(3/1), VO(Salen)/SBA-16-C8-C12(1/3) and VO(Salen)/SBA-16-C12, respectively.

General procedure for the enantioselective cyanosilylation of aldehydes

An heterogeneous catalyst was added in 0.8 mL of dry chloroform followed by the addition of 0.4 mmol of aldehyde under an Ar atmosphere. After the suspension was stirred for 2 min, 0.48 mmol of TMSCN was added. The reaction mixture was stirred for the desired time interval. 8 µL of reaction mixture was taken out and diluted with chloroform. The liquid obtained by centrifugation was analyzed with GC to measure the conversion (nitrobenzene as internal standard). The product trimethylsilyl ethers of cyanohydrin was further derived with Ac_2O in the presence of $Sc(OTf)_3$ to form O-trimethylsilyl cyanohydrin.[39] The enantioselectivity of O-trimethylsilyl cyanohydrin was measured using GC with a chiral column (HP-Chiral19091G-B213 capillary column).

Recycling the solid catalyst: after reaction, the solid catalyst was separated by filtration and washed thoroughly with chloroform. The solid catalyst was treated in ethanol at 90 °C under air for the regeneration of the catalyst. After 6 hours, the catalyst was isolated, dried under vacuum and used in the next catalytic reaction.

To determine the heterogeneity of the reaction, the reaction was stopped after 20 hours (20 °C), and the solid catalyst was removed. The filtrate isolated by filtration was continuingly stirred under Ar atmosphere for another 24 hours. The filtrate was analyzed with GC to measure the conversion.

Characterization

N_2 sorption was carried out on a Micromeritics ASAP 2020 volumetric adsorption analyzer after the samples were outgassed at 393 K for 6 h. UV-vis spectra were recorded on a JASCOV-550 UV-vis spectrophotometer using dichloromethane as the reference. Diffuse-reflectance UV-vis spectra were also recorded on the same spectrophotometer using $BaSO_4$ as the reference. FT-IR spectra were collected on a Thermo-Nicolet Nexus 470 infrared spectrometer after the sample was outgassed at 513 K for 4 hours. Vanadium contents were analyzed quantitatively on an atomic adsorption spectroscopy Plasmaspec-II (Leeman). TEM micrographs were taken using JEM-2010 transmission electron microscopy at an acceleration voltage of 120 kV.

Acknowledgements

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Structure-sensitive biodiesel synthesis over MgO nanocrystals†

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Size-controlled MgO nanocrystals were synthesised *via* a simple sol-gel method and their bulk and surface properties characterised by powder XRD, HRTEM and XPS. Small, cubic MgO single crystals, generated by low temperature processing, expose weakly basic (100) surfaces. High temperature annealing transforms these into large, stepped cuboidal nanoparticles of periclase MgO which terminate in more basic (110) and (111) surfaces. The size dependent evolution of surface electronic structure correlates directly with the associated catalytic activity of these MgO nanocrystals towards glyceryl tributyrate transesterification, revealing a pronounced structural preference for (110) and (111) facets.

A Introduction

The use of heterogeneous catalysts for the synthesis of the renewable diesel-substitute biodiesel has many advantages over the homogeneous routes currently favoured by industry.[1] Contaminated waste, soap formation and emulsification of the products, caused by using liquid acid and bases such as H_2SO_4 and NaOH, can be virtually eliminated through the use of solid catalytic materials. The latter can be easily separated from the reaction mixture and offer the possibility of continuous processing *via* flow reactors, resulting in a more economic and less energy intensive manufacturing regime.[2]

Solid base catalysts, such as alkaline earth oxides,[3] hydrotalcites,[4] alkali-doped mesoporous silicas[5] and resins,[6] and even dolomitic rock,[7] have shown great promise for biodiesel production. In contrast their solid acid counterparts are generally less active, and require higher reaction temperatures and larger volumes of solvents to achieve the same biodiesel yield.[8] Recent research also suggests that the efficacy of solid base catalysts in triglyceride transesterification is favoured by stronger basic sites at the catalyst surface.[9] Unfortunately the effects of basicity on catalytic activity remain poorly understood, hampering material optimisation and commercial exploitation. Current experimental approaches to determining basicity are semi-quantitative and unreliable, with base titration being subject to solvent effects and indicator structure, and acid probe molecules often decomposing on adsorption at strong base sites or at high temperature.[10] Alkaline earth oxide catalysts are very sensitive to their preparation route,[11] however, to date there is no simple way to characterise their surface basicity which is intimately linked to their reactivity in solid base catalysed transesterifications.

In order to improve our understanding of factors influencing solid base catalysts for biodiesel synthesis, we have applied a simple spectroscopic method for the quantitative determination of surface basicity, independent of adsorption probes, to systematically explore the relationship between the activity of MgO nanocrystals and their basicity. Glyceryl tributyrate transesterification, a plant oil triglyceride analog, was performed over a series of MgO catalysts, with carefully tuned crystallite sizes, which it was hoped would facilitate control over their surface morphology and corresponding basicity.[12] This provides a simple means to examine structure-sensitivity in solid base catalysed transesterification.[13]

B Experimental

Material preparation

A family of oxide catalysts were prepared from a methoxide precursor adapting the method described by Utamapanya *et al.*[14] Briefly, a 10 wt% solution of magnesium methoxide in methanol was prepared by dissolving Mg ribbon (Aldrich, ≥99.5%) in methanol under N_2. The methoxide solution was hydrolyzed overnight in the presence of toluene and the resulting sol transferred to an autoclave, pressurized to 100 psi N_2. Slow heating to 265 °C led to the creation of a supercritical atmosphere, after which the autoclave was vented. The resulting white powder was dried in an oven at 120 °C for 2 h and calcined at 300 °C (5 °C/min) for 5 h under a 10 mL/min flow of helium gas. The final product, labelled NanoMgO, was divided into individual batches which were calcined at temperatures between 400 and 700 °C (indicated by NanoMgO-XXX) in the same manner as described above.

Material characterisation

Surface area determination by N_2 adsorption-desorption at −196 °C was performed on a Quantachrome Nova 1200 porosimeter. Surface areas were calculated using the

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† Electronic supplementary information (ESI) available: HRTEM of MgO nanocrystal series. See DOI: 10.1039/b814357a

Brunauer-Emmet-Teller (BET) method over a P/P$_0$ range where a linear relationship was maintained. X-ray diffraction (XRD) powder patterns were collected on a Bruker D8 advance X-ray diffractometer fitted with a Lynx eye high-speed strip detector and a Cu Kα (1.5418 Å) radiation source. Samples were scanned over a 2θ range of 10–90 ° with a 0.02° step size and a scan speed of 0.04 s/step. Transmission electron microscopy (TEM) images were collected on a 200 keV JEOL 2200 FS ultra high resolution Field Emission Transmission Electron Microscope, fitted with Cs Aberration Correctors, allowing a resolution down to 1 Å. X-ray photoelectron spectroscopy (XPS) and Auger electron spectroscopy (AES) were performed on a Kratos AXIS HSi X-ray photoelectron spectrometer. The incident radiation was monochromatic Al K$_α$ X-rays (1486.6 eV) and an analyzer pass energy of 40 eV was used.

Transesterification reaction

Transesterification reactions were performed on a Radleys carousel at 60 °C. Individual reaction tubes were charged with glyceryl tributyrate (0.01 mol, Aldrich, 98%) in methanol (12.5 mL), with dihexyl ether (0.0025 mol, Aldrich, 97%) as an internal standard. Reactions were performed in air with 50 mg of catalyst. Compositional analysis of periodically withdrawn, quenched aliquots was performed on a Varian CP-3800 gas chromatograph, fitted with a VF-1 capillary column (film thickness 0.25 μm, i.d. 0.32 mm, length 30 m). Initial rates were calculated from the linear portion of the conversion profile during the first 60 min of the reaction. Turn over frequencies (TOFs) were determined as initial rate of conversion per gram of catalyst per square meter of available active surface.

C Results and discussion

Surface area analysis and characterisation by XRD and TEM of the syntheised MgO nanocrystals, (Table 1), reveals a progressive fall in surface area with increasing calcination temperature, associated with the formation of larger crystallites.

This particle sintering is accompanied by a phase transition from the Mg(OH)(OCH$_3$) precursor (2θ = 12°, 2θ = 32–39°) to the pure periclase form of MgO at 300 °C. Diffraction patterns for the MgO nanoparticles (Fig. 1) quantify this growth process, with crystallite dimensions calculated employing the Scherrer equation. These volume-averaged particle sizes are in good agreement with those from transmission electron microscopy. Peaks corresponding to higher index planes (111) and (311)

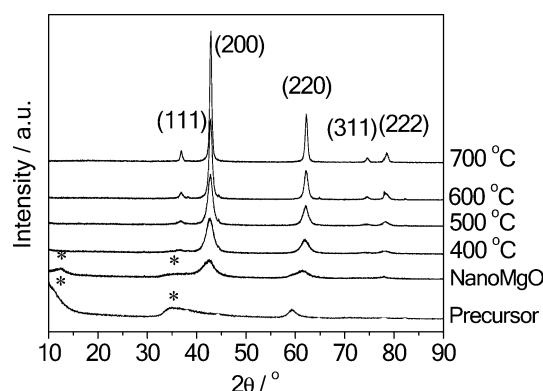**Fig. 1** Powder XRD patterns of MgO precursor Mg(OH)(OCH$_3$), and parent and calcined NanoMgO samples. Indexed reflections correspond to periclase MgO (JCPDS file 87–0653). Mg(OH)(OCH$_3$) phase is denotated by * (JCPDS file 22–1788).

planes are visible above 500 °C, again indicative of large crystallites.

More detailed TEM analysis (see ESI†) shows the parent NanoMgO consists of small randomly aligned crystallites dispersed in an amorphous medium. These cubic shaped domains appear free of obvious defects and low index (100) terraces dominate. Calcination eliminates the amorphous phase, resulting in increasingly large cuboidal crystals.

In the NanoMgO-500 sample (see ESI†), erosion of the cubic structure is observed close to the crystallite boundaries and in the case of NanoMgO-700 (Fig. 2) it is possible to see steps and corner sites. Both (111) and (110) planes are present in NanoMgO-500 and NanoMgO-700. The emergence of these surface symmetries is consistent with degradation of the MgO cubic nanoparticles during calcination. The experimentally observed surface terminations for (111) and (110) facets suggest that such restructuring should expose more defective,
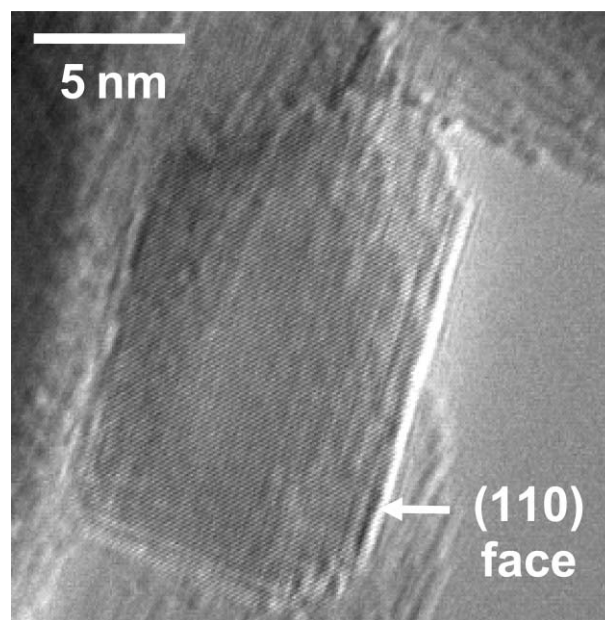
Table 1 MgO catalyst surface areas and crystallite sizes determined by XRD and TEM

Sample[a]	S.A[b]/m² g⁻¹	Crystallite size (XRD)/nm	Crystallite size (TEM)/nm
NanoMgO	580	2.8	1–3
NanoMgO-400	360	5.1	—
NanoMgO-500	250	7.3	5–6
NanoMgO-600	140	10.8	—
NanoMgO-700	80	16.5	14–18

[a] NanoMgO-XXX: parent annealed at specified temperature for 5 h.
[b] Surface areas determined by BET method.

Fig. 2 Transmission electron micrograph of NanoMgO-700 showing (110) surfaces.

electron-donating O^{2-} centers, postulated as superbasic sites in solid base catalysis.

Computational modelling of MgO surfaces also predicts that such defect centers are energetically favoured over (110) and (111) facets.[15] It is thought that thermal treatment of MgO leads to defect migration from the bulk of crystallites to their surfaces, particularly to corners and steps, creating additional low coordinate sites.[16] Such defects can trap electrons at the crystallite surface,[17] and the synergy between these phenomena may account for the enhanced reactivity of oxide catalysts. In fact, both electronic structure modeling,[18] and chemical titrants, such as BF_3,[10] predict that lower coordinate corner and step sites possess higher base strengths.

Our surface sensitive X-ray photoelectron and Auger electron spectroscopy measurements confirm this hypothesis. Fig. 3A and B show representative O 1 s XP and O KLL Auger spectra for the small NanoMgO, and larger, more defective NanoMgO-700 samples. XPS reveals the presence of two distinct chemical environments in the parent NanoMgO, corresponding to the oxide and residual surface methoxide from the precursor. These contributions are also reflected in the more complex Auger spectra, which have been carefully fitted against reference materials. NanoMg-700 exhibits similar surface species, although both O 1 s components shift to higher binding energy and the surface oxide contribution is enhanced *versus* carbonate or hydroxyl.[19]
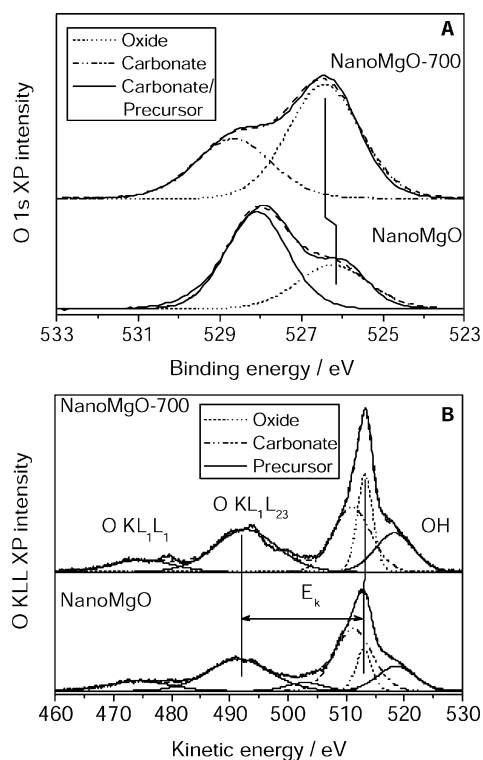
Fig. 3 A) O 1 s XP spectra and B) Auger O KLL regions of NanoMgO and NanoMgO-700.

Due to the complexity of surface oxygen environments, the absolute core level and Auger photoelectron energies are hard to interpret directly. However insight into the electronic properties of the surface oxide can be obtained by combining this information into the Auger parameter (α), defined as:

$$\alpha = \text{Kinetic energy (Auger)} + \text{Binding energy (photoemission)}$$

where the transitions share a common core level. An *increase* in α relative to gaseous H_2O ($\alpha = 1038.5$ eV[20]), and a corresponding *decrease* in the oxide O $KL_{23}L_{23}$ and O KL_1L_{23} Auger separation (ΔE_k), are indicative of increasing surface polarisability,[21] and thus provide a quantitative measure of Lewis basicity. Fig. 4 shows the variation in these spectroscopic parameters as a function of MgO nanoparticle size. α and ΔE_k both predict an increase in MgO surface base strength accompanying crystallite growth and the transformation from regular (100) to stepped (110) facets. Sintering crystallites beyond 10 nm had no additional impact on their preferred morphology or surface termination, and this is mirrored by the plateau evident in their polarisability.
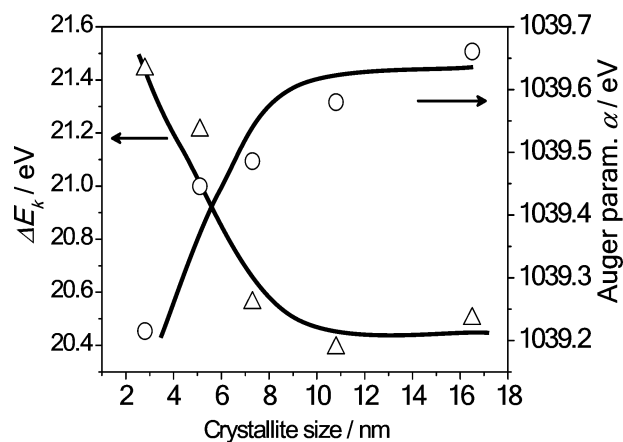

Fig. 4 Oxide O KLL Auger peak energy difference ($\triangle$) and oxygen Auger parameter ($\bigcirc$) for the oxide component of the nanocrystalline MgO catalysts as a function of nanocrystallite size.

The impact of tuning MgO nanocrystallite size and surface termination, and thus basicity, upon the resulting catalytic reactivity was assessed towards the transesterification of glyceryl tributyrate. This is a short chain model of the saturated triglycerides typically used to produce commercial biodiesel from palm oil. Glyceryl tributyrate conversion varied between 60 and 80% over 24 h, increasing with mean particle size, before passing through a maximum for diameters around 5 nm. The precursor material, $Mg(OH)(OCH_3)$, and commercial samples of $Mg(OH)_2$ and $MgCO_3$, were found to be essentially inactive for the transesterification of tributyrin. Any traces of these surface species therefore have no influence on the observed transesterification behaviour. Fig. 5 provides deeper insight into the relationship between catalyst structure and performance, showing turnover frequencies (initial rates normalized to the total MgO surface area) as a function of the surface polarisability determined by XPS.

This data reveals a striking linear correspondence between the catalytic activity and surface basicity of MgO nanoparticles. The link between these parameters is particularly remarkable given that catalyst basicity is determined spectroscopically *in vacuo*. We are currently investigating whether this methodology can be extended to trends in other solid base materials.
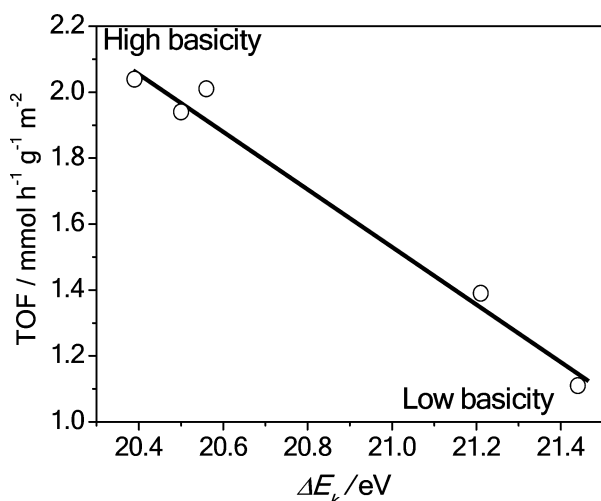
Fig. 5 Surface area normalised turnover frequency for glyceryl tributyrate conversion as a function of surface polarisability.

However, we feel care may be required when correlating transesterification activity for more basic alkaline earth oxides such as BaO which may show appreciable solubility in methanol.[22]

In summary, Auger parameter measurements allow the development of a non-invasive method to quantify the surface basicity, and thereby rationalise the catalytic activity of MgO nanoparticles in triglyceride transesterification. The combination of atomic resolution TEM and surface sensitive photoelectron spectroscopies identifies low coordination MgO surfaces as the most active for the mild conversion of tributyrin to methyl butyrate. This discovery is particularly significant since it paves the way to rapid screening of new MgO formulations for practical biodiesel synthesis.

Conclusions

A series of size-controlled MgO nanoparticles have been synthesised *via* thermal treatment of a parent nanocrystalline $Mg(OH)(OCH_3)$ precursor. Small (<8 nm) MgO nanoparticles terminate in high coordination (100) facets, and exhibit both weak polarisability and poor activity. Calcination drives restructuring to expose lower coordination stepped (111) and (110) surface planes, which exhibit strong polarisability and good performance in the transesterification of glyceryl tributyrate to methyl butyrate under mild conditions. The utility of XPS for rapidly screening the basicity of solid oxide catalysts has also been demonstrated, and its importance as a valuable tool in the catalytic chemists' armoury for optimising biodiesel manufacture exemplified.

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Homocoupling reaction of terminal alkynes catalyzed by a reusable cationic 2,2′-bipyridyl palladium(II)/CuI system in water†

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A cationic 2,2′-bipyridyl palladium(II)/CuI system was proven to be a reusable and highly efficient catalyst for the homocoupling of terminal alkynes at room temperature using water as a solvent in the presence of TBAB under aerobic conditions. For aromatic terminal alkynes, the reaction was performed either with or without I_2 as an oxidant; the addition of I_2 was required when aliphatic terminal alkynes were used as a substrate for the homocoupling reaction. In the presence of 0.0001–1 mol% palladium catalyst and 1 mol% CuI, a variety of terminal alkynes were homocoupled in good to excellent yields. The water-soluble catalytic system was separated from the organic products by extraction and the residual aqueous solution showed activity for reuse for several cycles without a significant decrease in activity.

Introduction

The homocoupling of terminal alkynes is a straightforward method for the synthesis of buta-1,3-diynes,[1] which are important building blocks in the organic synthesis of natural products,[2] pharmaceuticals,[3] organic/inorganic composites,[4] and polymers.[5] Since Rossi's group used a palladium/CuI catalytic system to catalyze the homocoupling of terminal alkynes,[6] this method has attracted a great deal of interest due to its mildness and wide-ranging substituent tolerance. Recent efforts have brought about the development of several mild and efficient palladium complexes/CuI catalytic systems in the presence of bases and oxidants in organic solvents such as NMP,[7] CH_3CN,[8] DMSO,[9] DMF,[10] THF,[11] amines[12] or CH_2Cl_2[13] for the homocoupling reaction of terminal alkynes. On the other hand, porous glass and silica gel supported palladium have also been used as heterogeneous catalysts for the synthesis of buta-1,3-diynes.[14–15]

To date, most of the terminal alkyne homocoupling reactions catalyzed by Pd/CuI systems have been carried out in organic solvents. There are no previous reports, to the best of our knowledge, of the use of water as a solvent for the homocoupling reaction of terminal alkynes catalyzed by palladium complexes. Although the reaction rates of the organic reaction in water may be slower than those in organic solvents, the advantages of the employment of water as a solvent are numerous: not only is it cheap, nontoxic, and inflammable, but it also has the feature that the catalyst may be easily separated from the organic products if the catalyst is water-soluble, leading to the possibility of reuse of the catalyst; therefore, the discovery of a catalytic

system that can achieve these purposes is highly desirable. We have recently reported that a reusable cationic 2,2′-bipyridyl palladium(II) complex catalyzed the Suzuki–Miyaura[16] and Hiyama[17] reactions in water under aerobic conditions. In this paper, we report the homocoupling reaction of terminal alkynes at room temperature in water catalyzed by a highly efficient cationic 2,2′-bipyridyl palladium(II)/CuI catalytic system, and demonstrate that catalyst activity is retained for further cycles after the separation of the residual aqueous solution from the organic products, which makes this homocoupling reaction greener (Scheme 1).
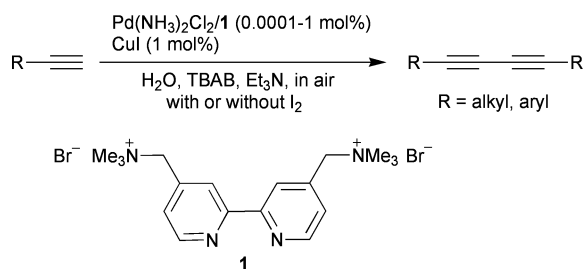
Scheme 1 Homocoupling of terminal alkynes in water.

Experimental

General

Chemicals were purchased from commercial suppliers and were used without further purification. With the exception of phenylacetylene, the aromatic terminal alkynes[18] and cationic 2,2′-bipyridyl ligand[16,17] were prepared according to the published procedures. Melting points were recorded using melting point apparatus and were uncorrected. All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C on a Varian 200 NMR spectrometer. GC analysis was performed on a SHIMADZU GC-14B equipped with a fused silica capillary column.

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Typical procedure for the homocoupling of a terminal alkyne

A 20 mL reactor was charged with CuI (1.9 mg, 0.01 mmol), TBAB (161.2 mg, 0.5 mmol), H_2O (2 mL), and Et_3N (0.42 mL, 3.0 mmol). The mixture was stirred at room temperature for 5 min, leading to a clear solution. Then, the aqueous solution of catalyst (1 mL, different concentrations for various substrate/catalyst ratios), I_2 (253.8 mg, 1.0 mmol), and alkyne (1.0 mmol) were added and the reaction mixture was stirred at room temperature. When the reaction was completed, the aqueous solution was extracted with hexane or EtOAc and the organic phase was washed with saturated $Na_2S_2O_3$ aqueous solution. The organic layer was then dried over $MgSO_4$ and the solvent was removed under vacuum. Column chromatography on silica gel afforded the desired product.

Typical procedure for the reuse of the catalytic aqueous solution

The reaction was conducted following the previous procedure under the reaction conditions shown in Table 4 (see later). After the reaction, the aqueous reaction mixture was washed with hexane under vigorous stirring three times, then the combined upper organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. Column chromatography on silica gel afforded the homocoupling product. The residual aqueous solution was then charged with Et_3N and terminal alkyne for the next reaction. In the case of 1-octyne, the addition of I_2 was required in each cycle.

1,4-Diphenyl buta-1,3-diyne (3a). White solid. Mp 86–87 °C (lit.[12a] 86–87 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 7.31–7.35 (m, 6H), 7.53 (d, J = 7.3 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 73.9 (2C), 81 (2C), 121.8 (2C), 128.4 (4C), 129.1 (2C), 132.5 (4C).

1,4-Bis(*o*-methylphenyl)buta-1,3-diyne (3b). White solid.[19] Mp 72–74 °C. ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 2.49 (s, 6H), 7.11–7.23 (m, 6H), 7.50 (d, J = 7.4 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 20.7 (2C), 77.6 (2C), 81.2 (2C), 121.7 (2C), 125.6 (2C), 129.0 (2C), 129.5 (2C), 132.9 (2C), 141.5 (2C). HRMS calcd for $C_{18}H_{14}$, 230.1096; found, 230.1093.

1,4-Bis(*m*-methylphenyl)buta-1,3-diyne (3c). White solid.[20] Mp 68–70 °C. ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 2.34 (s, 6H), 7.19–7.23 (m, 4H), 7.32–7.35 (m, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 21.2 (2C), 73.7 (2C), 81.6 (2C), 121.7 (2C), 128.3 (2C), 129.6 (2C), 130.1 (2C), 132.9 (2C), 138.1 (2C). HRMS calcd for $C_{18}H_{14}$, 230.1096; found, 230.1092.

1,4-Bis(*p*-methylphenyl)buta-1,3-diyne (3d). White solid. Mp 137–138 °C (lit.[8b] 138–140 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 2.35 (s, 6H), 7.12 (d, J = 8.1 Hz, 4H), 7.40 (d, J = 8.1 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 21.6 (2C), 73.5 (2C), 81.5 (2C), 118.8 (2C), 129.2 (4C), 132.4 (4C), 139.4 (2C).

1,4-Bis(*o*-methoxyphenyl)buta-1,3-diyne (3e). Yellow solid. Mp 138–140 °C (lit.[21] 138 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 3.88 (s, 6H), 6.84–6.93 (m, 4H), 7.28 (dd, J = 1.6, 7.8 Hz, 2H), 7.46 (dd, J = 1.6, 7.8 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 55.7 (2C), 77.9 (2C), 78.6 (2C), 110.6 (2C), 111.2 (2C), 120.4 (2C), 130.4 (2C), 134.2 (2C), 161.2 (2C).

1,4-Bis(*m*-methoxyphenyl)buta-1,3-diyne (3f). Yellow solid. Mp 92–93 °C (lit.[22] 92–93 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 3.81 (s, 6H), 6.90–7.29 (m, 8H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 55.3 (2C), 73.7 (2C), 81.5 (2C), 116.0 (2C), 117.1 (2C), 122.7 (2C), 125.0 (2C), 129.5 (2C), 159.3 (2C).

1,4-Bis(*p*-methoxyphenyl)buta-1,3-diyne (3g). White solid. Mp 141–142 °C (lit.[8b] 140–142 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 3.82 (s, 6H), 6.85 (d, J = 8.7 Hz, 4H), 7.46 (d, J = 8.7 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 55.3 (2C), 73.0 (2C), 81.2 (2C), 113.9 (4C), 114.1 (4C), 134.0 (2C), 160.2 (2C).

1,4-Bis(*p*-fluorophenyl)buta-1,3-diyne (3h). White solid. Mp 187–189 °C (lit.[23] 190–191 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 7.04 (dd, J = 8.6 Hz, J_{H-F} = 8.6 Hz, 4H), 7.51 (dd, J_{H-F} = 2.2 Hz, J = 8.6 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 73.6 (2C), 80.4 (2C), 115.9 (d, J_{C-F} = 22.2 Hz, 4C), 117.9 (d, J_{C-F} = 3.8 Hz, 2C), 134.5 (d, J_{C-F} = 8.4 Hz, 4C), 163.0 (d, J_{C-F} = 250.3 Hz, 2C).

1,4-Bis(*o*-chlorophenyl)buta-1,3-diyne (3i). Yellow solid. Mp 138–140 °C (lit.[24] 139.5–140 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 7.24 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.59 (d, J = 7.3 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 78.4 (2C), 79.4 (2C), 121.8 (2C), 126.5 (2C), 129.4 (2C), 130.2 (2C), 134.3 (2C), 136.9 (2C).

1,4-Bis(*p*-benzoic acid ethyl ester)buta-1,3-diyne (3j). Pale yellow solid. Mp 165–167 °C. ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 1.40 (t, J = 7.2 Hz, 6H), 4.39 (q, J = 7.2 Hz, 4H), 7.59 (d, J = 8.1 Hz, 4H), 8.03 (d, J = 8.1 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 14.3 (2C), 61.3 (2C), 76.2 (2C), 81.9 (2C), 126.0 (2C), 129.5 (4C), 130.9 (2C), 132.4 (4C), 165.7 (2C). Found: C, 76.33; H, 5.27. Calcd. for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24.

1,4-Bis(*p*-acetylphenyl)buta-1,3-diyne (3k). Blue solid. Mp 178–180 °C. ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 2.62 (s, 6H), 7.62 (d, J = 8.3 Hz, 4H), 7.94 (d, J = 8.3 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 26.6 (2C), 76.5 (2C), 81.9 (2C), 126.1 (2C), 128.2 (4C), 132.6 (4C), 137.0 (2C), 196.8 (2C). HRMS calcd for $C_{20}H_{14}O_2$, 286.0994; found, 286.0998.

1,4-Dinaphthyl-1,3-butadiyne (3l). Yellow solid. Mp 177–180 °C (lit.[25] 177–180 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 7.43–7.68 (m, 6H), 7.82–7.92 (m, 6H), 8.44 (d, J = 8.0 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 78.7 (2C), 81.0 (2C), 119.5 (2C), 125.2 (2C), 126.1 (2C), 126.7 (2C), 127.2 (2C), 128.4 (2C), 129.7 (2C), 132.0 (2C), 133.1 (2C), 133.9 (2C).

Hexadeca-7,9-diyne (3m). Light brown oil,[26] ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 0.89 (t, J = 6.8 Hz, 6H), 1.26–1.56 (m, 16H), 2.25 (t, J = 6.8 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 14.0 (2C), 19.2 (2C), 22.5 (2C), 28.4 (2C), 28.5 (2C), 31.3 (2C), 65.3 (2C), 77.5 (2C).

Tetracosa-11,13-diyne (3n). Light brown oil.[11a] ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 0.88 (t, J = 6.2 Hz, 6H), 1.26–1.55 (m, 32 H), 2.24 (t, J = 6.8 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 14.1 (2C), 19.2 (2C), 22.7 (2C), 28.4 (C), 28.9 (2C), 29.1 (2C), 29.3 (2C), 29.5 (2C), 29.6 (2C), 31.9 (2C), 65.3 (2C), 77.4 (2C).

1,4-Bis(cyclohex-1-enyl)buta-1,3-diyne (3o). Light brown solid. Mp 63–66 °C (lit.[8b] 63–65 °C). ^{1}H NMR (CDCl$_3$,

200 MHz) δ = 1.58–1.61 (m, 8H), 2.10–2.18 (m, 8H), 6.25 (t, J = 4.0 Hz, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 21.3 (2C), 22.2 (2C), 25.9 (2C), 28.7 (2C), 71.6 (2C), 82.7 (2C), 119.9 (2C), 138.0 (2C).

Dicyclohexyl-1-buta-1,3-diyne (3p). Yellow solid. Mp 97–98 °C (lit.[27] 100–102 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 0.83–0.88 (m, 4H), 1.23–1.82 (m, 16H), 2.34–2.45 (m, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 24.5 (4C), 25.8 (2C), 29.6 (2C), 32.3 (4C), 65.2 (2C), 81.9 (2C).

1,6-Diphenoxy-2,4-hexadiyne (3q). Yellow solid. Mp 77–79 °C (lit.[28] 79 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 4.72 (s, 4H), 6.91–7.00 (m, 6H), 7.29 (t, J = 7.2 Hz, 4H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ = 56.1 (2C), 71.0 (2C), 74.7 (2C), 114.8 (4C), 121.7 (2C), 129.5 (4C), 157.3 (2C).

2,7-Dimethyl octa-3,5-diyne-2,7-diol (3r). Light brown solid. Mp 131–132 °C (lit.[10b] 131–133 °C). ^{1}H NMR (CDCl$_3$, 200 MHz) δ = 1.54 (s, 12H), 2.04 (s, 2H); ^{13}C NMR (CDCl$_3$, 50 NHz) δ = 31.1 (4C), 65.6 (2C), 66.3 (2C), 84.0 (2C).

Results and discussion

The cationic 2,2′-bipyridy palladium(II) aqueous solution can be prepared by mixing equimolar amounts of Pd(NH$_3$)$_2$Cl$_2$ and **1** in water directly. The catalyst is stable in water and can be stored under air. As shown in Table 1, our initial goal was to optimize the reaction conditions for the Pd(NH$_3$)$_2$/**1**/CuI (1 mol%)-catalyzed homocoupling of phenylacetylene (**2a**) in water at room temperature under air. The results showed that the addition of 0.5 equiv TBAB provided a much higher yield than reaction in the absence of TBAB (Entries 1 and 2). When the amount of Et$_3$N was increased to 3 equiv, the homocoupling reaction was completed in 6 h (Entry 3). As for the employment of a co-catalyst, we found that the addition of 1 mol% CuI gave the best result (Entries 3–6). For comparison, the reaction was also conducted in the absence of ligand **1**, which revealed the importance of the ligand: in this case, 1,4-diphenyl buta-1,3-diyne (**3a**) was obtained in only a 60% yield (Entry 7). Importantly, the use of 1 equiv iodine as an

oxidant was considered superior, as it gave the target compound in the same yield as that obtained under the conditions of entry 3, but in a significantly shorter reaction time (Entry 8). Further experiments revealed a significant dependence of the homocoupling reaction on the nature of the base. Other organic and inorganic bases were also employed in this reaction, and we found that the use of diisopropylamine and Bu$_3$N afforded the product in moderate yields (Entries 10 and 11), whereas the inorganic bases gave only trace amounts of **3a** (Entries 12 and 13).

Under the optimized reaction conditions, the homocoupling reactions of various aromatic terminal alkynes (**2a–2l**) were examined (Table 2). The addition of I$_2$ as an oxidant greatly reduced the reaction time when a catalyst loading of 0.1 mol% was used, although a 76% yield of product **3a** was found in the absence of I$_2$ with a longer reaction time (Entries 1 and 2). Further reducing the catalyst loading to 0.01 mol%, an 80% GC yield was found after 48 h when the reaction was conducted in 20 mmol scale (Entry 3). The homocoupling of ethynyltoluenes (**2b–d**) using 0.01 mol% catalyst gave moderate to high yields (Entries 4, 6 and 7). The lower yield for the homocoupling of 2-ethynyltoluene (**2b**) was probably due to the steric effect of the methyl group located at the *ortho*-position. The employment of ethynylanisoles (**2e–g**) led to similar results to those of ethynyltoluenes (Entries 9–11 and 13). For the homocoupling of 3-ethynylanisole (**2f**) in the presence of 0.001 mol% Pd, an excellent result was obtained and the turnover number (TON) of this reaction was found to be up to 82,000 when **2f** was used in 10 mmol scale (Entry 12). With higher catalyst loading (1 mol%), mono-substituted phenylacetylenes, for example, **2c** and **2e**, were also coupled in the absence of I$_2$ to give the corresponding products in good yields (Entries 5 and 8). Aromatic alkynes with halogen substitution, **2h** and **2i**, were coupled with 0.1 mol% catalyst loading to afford the corresponding diynes **3h** and **3i** in 77 and 79% isolated yields, respectively (Entries 14 and 15). Similarly, **2j** was homocoupled efficiently using a very low catalyst loading (Entry 16). Homocoupling of **2k** and **2l** in the presence of 1 mol% of catalyst led to the formation of **3k** and **3l** in air without the addition of I$_2$ (Entries 16 and 17).
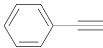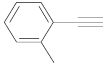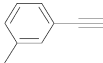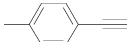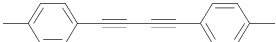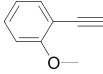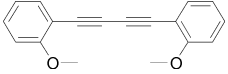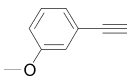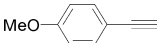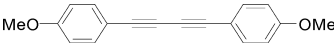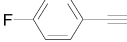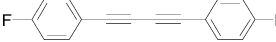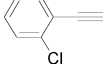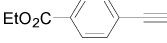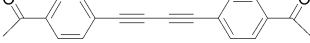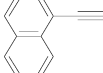
Next, the scope of this homocoupling reaction of aliphatic terminal alkynes in water was evaluated (Table 3). Contrary to that of aromatic terminal alkynes, the homocoupling of aliphatic terminal alkynes gave <10% GC yields in the absence of I$_2$. However, 1-octyne (**2m**) was converted to hexadeca-7,9-diyne (**3m**) very efficiently at room temperature, giving a 99% yield in the presence of 1 equiv I$_2$, even with 0.001 mol% catalyst loading (Entries 1 and 2). Further reducing the catalyst loading to 0.0001 mol% resulted in the formation of **3m** in a 43% yield, corresponding to a TON of 430,000, along with 20% of 1-iodo-1-octyne (Entry 3), which was not observed when Pd was employed at 0.001 mol% in Entry 2. This undesired product could be separated easily during purification by column chromatography. The formation of 1-iodo-1-octyne is understandable because the use of CuI is fixed to 1 mol% in all cases. The molar ratio of CuI to Pd is 10,000 in the case of Entry 3; therefore, the alkynylcuprate(I) formed in large excess has the chance to react with I$_2$, giving the by-product. Terminal alkynes **2o** and **2p** were also homocoupled to afford the corresponding products **3o** and **3p** in good to high yields at very low catalyst

Table 1 Homocoupling of phenylacetylene **2a** in water under different conditions[a]

Entry	Base (eq)	CuI (mol%)	Oxidant (eq)	t (h)	Yield (%)[b]
1[c]	Et$_3$N (2)	1.0	—	48	25
2	Et$_3$N (2)	1.0	—	48	83
3	Et$_3$N (3)	1.0	—	6	99 (94)
4	Et$_3$N (3)	—	—	6	5
5	Et$_3$N (3)	0.5	—	6	71
6	Et$_3$N (3)	2.0	—	6	84
7[d]	Et$_3$N (3)	1.0	—	6	60
8	Et$_3$N (3)	1.0	I$_2$ (1)	3	99 (94)
9	Et$_3$N (3)	1.0	I$_2$ (0.5)	3	54
10	iPr$_2$NH (3)	1.0	I$_2$ (1)	3	54
11	Bu$_3$N (3)	1.0	I$_2$ (1)	3	44
12	NaOAc (3)	1.0	I$_2$ (1)	3	8
13	KOAc (3)	1.0	I$_2$ (1)	3	3

[a] Reaction conditions: phenylacetylene **2a** (1.0 mmol), Pd(NH$_3$)$_2$Cl$_2$/**1** (1 mol%), TBAB (0.5 mmol), and H$_2$O (3 mL) at room temperature under air. [b] GC yields. Isolated yields are given in parentheses. [c] In the absence of TBAB. [d] In the absence of ligand **1**.

Table 2 Homocoupling of terminal aryl alkynes in water at room temperature under air[a]

Entry	Alkyne		Pd/1 (mol%)	Product		t (h)	Yield (%)[b]	TON
1[c]		2a	0.1		3a	48	76	760
2		2a	0.1		3a	12	98 (93)	980
3[d]		2a	0.01		3a	48	80 (78)	8000
4		2b	0.01		3b	48	43 (37)	4300
5[c]		2c	1		3c	18	80 (72)	80
6		2c	0.01		3c	48	87 (85)	8700
7		2d	0.01		3d	48	75 (71)	7500
8[c]		2e	1		3e	48	96 (88)	96
9		2e	0.1		3e	24	99 (93)	990
10		2e	0.01		3e	72	48 (42)	4800
11		2f	0.01		3f	48	99 (88)	9900
12[e]		2f	0.001		3f	72	82 (77)	82000
13		2g	0.01		3g	72	— (86)	8600
14		2h	0.1		3h	48	— (77)	770
15		2i	0.1		3i	48	— (79)	790
16		2j	0.01		3j	48	— (56)	5600
17[c]		2k	1		3k	24	— (71)	71
18[c]		2l	1		3l	48	— (32)	32

[a] Reaction conditions: terminal alkyne (1.0 mmol), TBAB (0.5 mmol), I$_2$ (1 mmol) and H$_2$O (3 mL) at room temperature under air. [b] GC yields. Isolated yields are given in parentheses. [c] In the absence of I$_2$. [d] 20 mmol of terminal alkyne was used. [e] 10 mmol of terminal alkyne was used.

loading (0.001 mol%, Entries 7 and 9). **2q** and **2r** showed slower reaction rates, and so higher catalyst loadings (0.1 and 1 mol%, respectively) were applied (Entries 10 and 11).
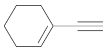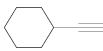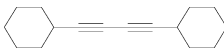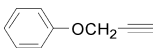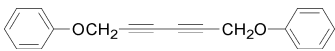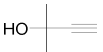
The reusability of the residual aqueous solution is important from practical and industrial utilization viewpoints. Phenylacetylene (**2a**) and 1-octyne (**2m**) were used as representative examples in experiments to test the reusability. As shown in Table 4, homocoupling of **2a** with 1 mol% catalyst loading in the absence of I$_2$ led to the formation of **3a** in 99% GC yield in 6 h. After the completion of the first cycle, hexane was used to extract the organic product and the remaining aqueous solution was recharged with base and **2a** for the second cycle. It was found that the residual aqueous solution could be reused several times with only a slight decrease in activity (Entry 1). In the case of **2m**,

a lower catalyst loading (0.1 mol%) was employed in the presence of 1 equiv I$_2$ (Entry 2). The reuse runs proceeded smoothly for each cycle, indicating that the use of this catalytic system may meet the targets of green chemistry.

Conclusion

In conclusion, we have developed a reusable and highly efficient water-soluble cationic 2,2′-bipyridyl palladium(II)/CuI catalytic system for the homocoupling of terminal alkynes in water under aerobic conditions. The reaction could be performed either in the presence or absence of I$_2$ as an oxidant for the homocoupling of aromatic terminal alkynes; for aliphatic terminal alkynes, the addition of I$_2$ as an oxidant was required.

Table 3 Homocoupling of terminal alkyl alkynes in water at room temperature under air[a]

Entry	Alkyne		Pd/1 (mol%)	Product		t (h)	Yield (%)[b]	TON
1	CH₃(CH₂)₄H₂C—	2m	0.01	CH₃(CH₂)₄H₂C———CH₂(CH₂)₄CH₃	3m	24	99	9900
2		2m	0.001		3m	48	99 (93)	99000
3[c, d]		2m	0.0001		3m	72	43 (40)	430000
4	CH₃(CH₂)₈H₂C—	2n	0.1	CH₃(CH₂)₈H₂C———CH₂(CH₂)₈CH₃	3n	12	98	980
5		2n	0.01		3n	48	83 (75)	8300
6		2o	0.01		3o	24	99 (88)	9900
7		2o	0.001		3o	48	80 (73)	80000
8		2p	0.01		3p	24	95 (83)	9500
9		2p	0.001		3p	48	49 (44)	49000
10	⬡—OCH₂—	2q	0.1	⬡—OCH₂———CH₂O—⬡	3q	48	— (42)	420
11	HO————	2r	1	HO————————OH	3r	48	— (81)	81

[a] Reaction conditions: terminal alkyne (1.0 mmol), TBAB (0.5 mmol), I₂ (1 mmol) and H₂O (3 mL) at room temperature under air. [b] GC yields. Isolated yields are given in parentheses. [c] 10 mmol of terminal alkyne was used. [d] 20% GC yield of 1-iodo-1-octyne was found.

Table 4 Reuse studies of Pd/1/CuI catalyzed homocoupling of terminal alkynes[a]

Entry	Alkyne		Pd/1 (mol%)	t (h)	Yield (%)[b]			
					1st cycle	2nd cycle	3rd cycle	4th cycle
1[c]	Phenylacetylene	2a	1	6	99 (94)	96 (92)	87 (85)	81 (77)
2[d]	1-Octyne	2m	0.1	12	99 (93)	99 (94)	86 (82)	82 (78)

[a] Reaction conditions: alkyne (1 mmol), CuI (1 mol%), TBAB (0.5 mmol), I₂ (1 mmol), Et₃N (3 mmol), and H₂O (3 mL) under air. [b] GC yields. Isolated yields are given in parentheses. [c] In the absence of I₂. [d] I₂ (1 mmol) and Et₃N (3 mmol) were added in each cycle.

This green procedure using water as the solvent enables the reuse of the catalytic system and has potential for use in industrial applications. Further studies on the applicability of this system in other organic syntheses are under investigation.

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Simple and efficient methods for selective preparation of α-mono or α,α-dichloro ketones and β-ketoesters by using DCDMH

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New processes that can selectively prepare α-mono or α,α-dichloro ketones and β-ketoesters using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) are reported. Using silica gel as the catalyst and methanol as the solvent and heating for 1 h under reflux, α-monochlorinated products were selectively obtained in 86–98% yield. However using a deep eutectic solvent (choline chloride: *p*-TsOH = 1:1) as the solvent and stirring for 45 min at room temperature, α,α-dichlorinated products were selectively obtained in 86–95% yield.

Introductions

Chlorinated organic compounds constitute an important class of intermediates as they can be converted into other functional molecules by simple chemical transformation.[1] α-Chlorinated ketones and β-ketoesters are among the most versatile intermediates used for medicine and agriculture, and their high reactivity makes them react with a large number of nucleophiles to provide a variety of useful compounds.[2] The previous methods to preparing the chlorinated organic compounds were based on molecular chlorine, some ammonium chlorides or *N*-chlorosuccinimide (NCS).[3] The novel methods of halogenating with high selectivity that satisfy the requirements of green chemistry have attracted a lot of attention.[4] However, developing selective monochlorination reactions or selective dichlorination reactions remains a challenge since these reactions in many cases always result in a mixture of mono- and dichlorinated products.[5] There are some excellent methods that have been reported to solve this challenge. M. Marigo *et al.* used NCS to prepare chlorinated ketones with high regioselectivity and stereoselectivity.[6] Wang *et al.* also used NCS to chlorinate ketones and accomplish high selectivity.[7] H. M. Meshram *et al.* used Amberlyst-15 as catalyst and obtained excellent results with high selectivity.[8] Recently, B. Sreedhar *et al.* also published a novel method to prepare chlorinated ketones rapidly with high selectivity.[9]

1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) is a disinfecting agent and bleaching agent that has been extensively used as a disinfectant for industrial and domestic water.[10] In contrast to common disinfectants, DCDMH does not have the odor of chlorine and is barely irritating to human beings.[11] Additionally, DCDMH can be used as a novel bactericide, so is also expected to be widely used for fruit storage.[12] Compared with *N*-chlorosuccinimide (NCS), a readily available N–Cl reagent that is widely used as electrophilic chlorinating agent, DCDMH is a widely used industrial product and is much cheaper. For example, the price of DCDMH was about three times lower than the price of NCS in 2006, according to the product catalogue of Alfa Aesar.[13] Z. Xu *et al.*[14] used DCDMH to chlorinate acetophenones in methanol, and the yields were good. Although DCDMH is cheap, Xu's process would produce much sewage containing *p*-toluenesulfonic acid, which was used as catalyst, so is not favorable for industry. We wish to discuss and develop a new process that can reduce the acid sewage while maintaining high selectivity.

Results and discussion

In order to reduce the acid sewage while retaining high selectivity, we tried various catalysts and found that when silica gel was added to the mixture of acetophenone **1a**, methanol and DCDMH, the chlorination took place quickly under reflux and only the α-chlorinated product was obtained easily (Scheme 1 and Table 1). So we used silica gel to substitute *p*-TsOH as the catalyst in the process. After that, we chose **1a** as the test substrate to optimize the reaction conditions (Table 1). When 1 g silica gel was added to the reaction mixture, a pure solid of **2a** was obtained in 95% yield; when 0.1 g silica gel was added, the yield of **2a** was increased to 97% (Table 1–Entry 2). So it seems that the larger amount of silica gel added to the reaction mixture was not so helpful to the process. When DCDMH was replaced by NCS under similar conditions, the conversion of acetophenone determined by GC was declined to 70%. When the process was without silica gel or was not heated at reflux but only at 40 °C,
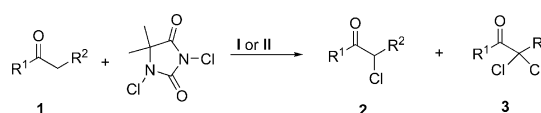
I: SiO₂,MeOH,reflux,1h; Yield: **2a~2l**(86~98%)

II: DES, rt, 45 min.; Yield: **3a~3l**(86~95%)

1a: R¹=phenyl, R²=H

1b: R¹=*p*-Cl-phenyl, R²=H

1c: R¹=*p*-Br-phenyl, R²=H

1d: R¹=*p*-Me-phenyl, R²=H

1e: R¹=*p*-NO₂-phenyl, R²=H

1f: R¹=*m*-NO₂-phenyl, R²=H

1g: R¹=4'-Br-biphenyl, R²=H

1h: R¹=*p*-OMe-phenyl, R²=H

1i: R¹=Me, R²= -COOEt

1j: R¹=benzoyl, R²= -COOEt

1k: R¹=*p*-NO₂-benzoyl, R²= -COOEt

1l: R¹= *t*-butyl, R²=H

Scheme 1

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Table 1 Conditions of the α-chlorination of acetophenone with DCDMH using silica gel[a]

Entry	SiO₂/g	Solvent	Temperature/°C	Product	Yield (%)
1	1	methanol	reflux	solid (m.p. 51–52 °C)	95[b]
2	0.1	methanol	reflux	solid (m.p. 51–52 °C)	97[b,e]
3	0	methanol	reflux	oil	80[c]
4	0.1	methanol	40	oil	66[c]
5	0.1	acetonitrile	reflux	oil	(29 + 8)[d]

[a] All reactions were run with 10 mmol of acetophenone using 7.5 mmol of DCDMH for 1 h. [b] Isolated yield. [c] A mixture of α-monochloroacetophenone and acetophenone was obtained and the conversion of acetophenone was determined by GC. [d] A mixture of α-mono-, α,α-dichloroacetophenone and acetophenone was obtained and the ratio determined by GC was 29:8:63. [e] Using NCS to replace DCDMH with the same conditions, a mixture of α-monochloroacetophenone and acetophenone was obtained; their ratio determined by GC was 70:30.

the conversion of **1a** that was determined by GC declined and a mixture of α-monochloroacetophenone and acetophenone was obtained (Table 1-Entry 3 and 4). When acetonitrile was used as solvent, replacing methanol, the conversion of **1a** determined by GC declined obviously and the dichlorinated product was found. So we thought silica gel as the catalyst and methanol as the solvent were necessary and helpful for the reaction rate and selectivity.
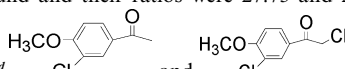
The process involving 10 mmol of **1a**, 7.5 mmol of DCDMH and 0.1 g of silica gel was heated at reflux for 1 hour to offer
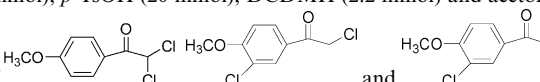
the product is, perhaps, the best reaction conditions without *p*-TsOH (Table 1–Entry 2). After that, we chose **1b**, **1c** and **1d** as the tested substrate and the selectivity, reaction rate and yields were good (Table 2). High purity products **2b**–**2d** were directly obtained even without any further purification. The conversion of α-monochlorination of **1e** was almost 100%, but among the products 73% was obtained in the form of the α-monochlorinated ketal (Table 2–Entry 5). The case of **1f** was similar (Table 2–Entry 6). Research into ketals is in progress. The reaction of **1g** did not take place, as the substrate hardly

Table 2 α-Chlorinations of ketones and β-ketoesters with DCDMH

Entry	Substrate	Product	Isolated yield (%)	mp/°C
1[a]	1a	2a	97	51–52 (lit: 51–52[15])
2[a]	1b	2b	98	99–101 (lit: 101–101.5[16])
3[a]	1c	2c	93	114–116 (lit: 113.5–115[17])
4[a]	1d	2d	92	52–54 (lit: 54.5–55[18])
5[a]	1e	2e	(27 + 73)[b]	—
6[a]	1f	2f	(28 + 72)[b]	—
7[a]	1g	2g	0[c]	—
8[a]	1h	2h	—[d]	—
9[a]	1i	2i	88 **2i** and methyl ester[e]	—
10[a]	1j	2j	86 **2j** and methyl ester[e]	—
11[a]	1k	2k	88 **2k** and methyl ester[e]	—
12[a]	1l	2l	—[f]	—
13[g]	1a	3a	95	oil (lit: 19–20.5[20])
13[g]	1b	3b	94	56–58 (lit: 58–59[20])
15[g]	1c	3c	96	59–61 (lit: 61–62[20])
16[g]	1d	3d	94	52–54 (lit: 54–56[21])
17[h]	1e	3e	86	oil (lit: 26.8–27.8[20])
18[h]	1f	3f	89	50–51 (lit: 52.5–54[20])
19[h]	1g	3g	93	138–140
20[g]	1h	3h	—[i]	—
21[g]	1i	3i	94	—
22[g]	1j	3j	92	—
23[g]	1k	3k	92	—
24[g]	1l	3l	88	50–51 (lit: 50–51[22])

[a] Substrate (10 mmol), methanol (10 ml), DCDMH (7.5 mmol), silica gel (0.1 g), reflux for 1 hour. [b] The α-monochloroketones and the α-monochlorinated ketals as products were found and their ratios were 27:73 and 28:72. [c] The substrate hardly resolved in the methanol and

the process of chlorination did not take place. [d] (structure) and (structure) were found as the products. The ratio of the two products determined by ¹H NMR was 4:1. [e] Ester exchange reaction took place in the process. The conversion of substrates was complete and the yields of the products, which include methyl ester and ethyl ester, were determined by ¹H NMR. The ratio of methyl ester:ethyl ester = 1:5. [f] A mixture of α-chloropinacolone and α,α-dichloropinacolone was obtained and the ratio of the compounds determined by ¹H NMR was 2.7:1. [g] Substrate (10 mmol), choline chloride (20 mmol), *p*-TsOH (20 mmol), DCDMH (11 mmol) and acetonitrile (0.5 ml). The mixture and DES were stirred at room temperature for 45 minutes. [h] Substrate (2 mmol), choline chloride (20 mmol), *p*-TsOH (20 mmol), DCDMH (2.2 mmol) and acetonitrile (0.5 ml).

The mixture and DES were stirred at room temperature for 45 minutes. [i] (structure), (structure) and (structure) were found in the products and the ratio of three compounds determined by ¹H NMR was 1:3:3.

dissolved in the solvent. Substrates with a strong electron-donating group, such as **1h**, were also chlorinated on the benzene ring, and a mixture of 3-chloro-4-methoxyacetophenone and α,3-dichloro-4-methoxyacetophenone was obtained after work-up. β-Ketoesters, such as **1i**, **1j** and **1k**, were completely transferred to the products but the ester exchange reaction took place in the process. Some chlorinated methyl esters were found among chlorinated ethyl esters. In the case of aliphatic ketone pinacolone **1l**, a mixture of α-chloropinacolone and α,α-dichloropinacolone was obtained and the ratio of the compounds determined by ^{1}H NMR was 2.7:1. It seems the selectivity of our methods declined slightly when an aliphatic ketone (pinacolone) was used as the substrate. In short, this process of α-monochlorination of some acetophenones and β-ketoesters was rapid with high selectivity and much greener than the previous method using DCDMH.

We tried to use the same process of silica gel and methanol to prepare dichlorinated acetophenones. When the reaction time was prolonged from 1 hour to 3 hours and the amount of DCDMH was increased from 7.5 mmol to 11 mmol, a mixture of α-monochloroacetophenone and α,α-dichloroacetophenone was obtained, the ratio determined by GC was 68:32. So a novel and rapid method of preparing α,α-dichlorinated ketones needed to be developed. Deep eutectic solvents (DES) formed between choline chloride and acids are thought to be versatile alternatives to ionic liquids and have been shown to be good solvents for many reactions.[19] Herein, we tried to use a DES to accomplish the dichlorinating process.

Firstly, to prepare a proper DES we tried some ratios of two compounds in the mixture such as hydantoin with TsOH, hydantoin with choline chloride, hydantoin with ZnCl$_2$, hydantoin with FeCl$_3$, hydantoin with AlCl$_3$, urea with FeCl$_3$, urea with AlCl$_3$ and urea with TsOH. After heating, the mixture turned into sticky liquid but the liquid easily became solid again at room temperature. After obtaining many negative results, we found only the mixture of choline chloride and p-TsOH could be transferred to DES easily and the ratio of these two substances was 1:1.

So we used this new DES to prepare α,α-dichlorinated acetophenones. After that, we chose **1a** as the test substrate to optimize the reaction condition (Table 3). When the ratio of DES and **1a** was 1:10, the conversion of **1a** to α,α-dichlorination was 56% (Table 3–Entry 1). When the ratio was decreased to 2:1, the conversion was increased to 86% (Table 3–Entry 3). After that, we tried to add a little acetonitrile to speed up the reaction and the conversion of **1a** was complete after stirring the reaction mixture for 0.75 hour (Table 3–Entry 5).

We found that the mixture of substrate (10 mmol), choline chloride (20 mmol), p-TsOH (20 mmol), DCDMH (11 mmol), acetonitrile (0.5 ml) being stirred at room temperature for 45 minutes was a good reaction condition for selective preparation of α,α-dichloroacetophenones, and the yield of **3a** was 95% (Table 2–Entry 13). The amount of DES made the products easy to be extracted by an organic solvent such as MTBE and made the DES easy to be reused to reduce the usage of p-TsOH. We reused DES five times and the yield of **3a** did not decline obviously. After that, the other substrates were tested and the yields of the products were also high (Table 2). High purity α,α-dichlorinated products **3a**–**3f** were directly obtained. For the solid substrates, such as **1g**, that hardly dissolved in the DES, we reduced the amount of the substrate (Table 2–Entries 17–19). As for **1h**, 3-chloro-4-methoxyacetophenone and α,3-dichloro-4-methoxyacetophenone were also found with the product **3h**, and the ratio of these three compounds determined by ^{1}H NMR was 3:3:1. The yields of the tested β-ketoesters, such as **1i**, **1j** and **1k**, were also good (Table 2–Entries 21–23). In the case of aliphatic ketone **1l**, α,α-dichloropinacolone **3l** as a pure and white solid was obtained in 88% yield.

As mentioned above, when acetonitrile, which is without a hydroxyl group, was used as solvent, replacing methanol, in the process that used silica gel as catalyst, the reaction did not take place so rapidly and without high selectivity (Table 1-Entry 5). It seems the hydroxyl in the solvent is maybe helpful and necessary for the reaction. To prove this, a DES formed from p-TsOH and tributylmethylammonium chloride (1:1) that is without hydroxyl was used in the process of preparing α,α-dichlorinated acetophenone, and the yield of product declined to 56%. This perhaps also points to the necessity of the hydroxyl in the solvent.

NCS as a good chlorinating agent catalyzed by acid functionalized silica has been reported.[23] In our process catalyzed by silica gel without acid, when DCDMH was replaced by NCS, the conversion of acetophenone declined, as mentioned above. In our process, it seems that NCS was not more efficient than DCDMH. Samant *et al.*[24] suggested the mechanism of keto-enol tautomerism in the process of the bromination of substituted acetophenones using NBS and we thought the mechanism of our processes was possibly similar to the one that Samant *et al.* mentioned.

Conclusions

We used DCDMH, which is cheap and clean, as a chlorination reagent to prepare chlorinated acetophenones and β-ketoesters

Table 3 Conditions of α,α-dichlorination of **1a** with DCDMH in DES[a]

Entry	Choline chloride: p-TsOH:**1a**/mmol	Reaction time/h	Acetonitrile/ml	Conversion of **1a** (%)[b]
1	1:1:10	1	0	56
2	1:1:1	1	0	69
3	2:2:1	1	0	86
4	2:2:1	1	0.5	100
5	2:2:1	0.75	0.5	100

[a] **1a** was 10 mmol, DCDMH was 11 mmol and the reaction mixture was stirred in room temperature. [b] The conversion of **1a** was determined by GC.

rapidly and with high selectivity. These two processes can easily offer α-monochlorinated acetophenones and β-ketoesters or α,α-dichlorinated acetophenones and β-ketoesters with high selectivity; and these two processes, that are greener than the previous methods, using DCDMH are easy to scale up in industry.

Experimental

Typical procedure for preparation of α-chloroacetophenone (2a)

Silica gel (0.1 g) and DCDMH (1.48 g, 7.5 mmol) were added into a mixture of **1a** (1.2 g, 10 mmol) and methanol (10 ml) in a flask equipped with a magnetic stirring bar. The solution was heated at reflux for 1 hour and then was cooled to room temperature. After the mixture was filtered, solvent was distilled under reduced pressure and MTBE (20 ml) was added to the residue. The MTBE layer was washed twice by water (20 ml) and was dried over MgSO$_4$. After that, the organic layer was filtered and solvent was removed under reduced pressure. The product was obtained as a white solid (1.5 g, 97% yield). mp: 51–52 °C (lit: 51–52 °C).[15] ^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.72 (s, 2H, CH$_2$Cl), 7.51 (t, J = 7.8 Hz, 2H, ArH), 7.63 (t, J = 7.4 Hz, 1H, ArH), 7.96–7.98 (m, 2H, ArH).[25]

Typical procedure for preparation of α,α-dichloroacetophenone (3a)

A mixture of choline chloride (2.8 g, 20 mmol) and TsOH (3.4 g, 20 mmol) was added into a flask with a magnetic stirring bar under N$_2$ atmosphere. The flask was heated in an oil bath at 100 °C for 40 minutes and then was cooled to room temperature slowly. When the mixture was heated, there was a little HCl released from the mixture. After cooling down, the colourless DES was prepared in the flask. **1a** (1.2 g, 10 mmol), acetonitrile (0.5 ml) and DCDMH (2.2 g, 11 mmol) were added into the flask and the mixture was stirred for 45 minutes at room temperature. MTBE (30 ml) was added slowly to extract the product and the MTBE layer was separated from the flask carefully. The organic layer was washed twice by water (30 ml) and was dried over MgSO$_4$. After that, the organic layer was filtered and solvent was removed under reduced pressure. The product was obtained as light yellow oil (1.8 g, 95% yield, 98% GC area purity). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.69 (s, 1H, CHCl$_2$), 7.52 (t, J = 7.8 Hz, 2H, ArH), 7.65 (t, J = 7.4 Hz, 1H, ArH), 8.08–8.10 (m, 2H, ArH).[26]

Preparation of α,α-dichloromethyl-4′-bromobiphenyl ketone (3g)

The reaction was carried out as described in typical procedure for preparation of α,α-dichloroacetophenone (**3a**). 0.55 g (2 mmol) of methyl 4′-bromobiphenyl ketone **1g** was used to give a white solid **3g**: 0.65 g (yield 93%). mp: 138–140 °C. A white crystal was obtained by recrystallation from methanol. mp: 144–145 °C (methanol).^{1}H NMR (CDCl$_3$, 500 MHz) δ: 6.70 (s, 1H, CHCl$_2$), 7.52 (d, J = 8.5 Hz, 2H, ArH), 7.64 (d, J = 8.5 Hz, 2H, ArH), 7.72 (d, J = 8.5 Hz, 2H, ArH), 8.20 (d, J = 8.5 Hz, 2H, ArH). ^{13}C NMR (CDCl$_3$, 500 MHz) δ: 67.9 (CHCl$_2$), 123.2 (ArCBr), 127.3 (ArCH), 128.9 (ArCH), 129.3 (ArCH), 130.5 (ArCH), 132.3 (ArCH), 138.3 (ArCH), 146.0 (ArCH), 185.5 (CO). Element Analysis: found: C, 48.71%; H, 2.70%. Calculated for C$_{14}$H$_9$BrCl$_2$O (344.03): C, 48.83%; H, 2.62%.

Acknowledgements

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The Baeyer–Villiger oxidation of ketones with bis(trimethylsilyl) peroxide in the presence of ionic liquids as the solvent and catalyst

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A new method for lactone synthesis with bis(trimethylsilyl) peroxide as the oxidant and ionic liquids as solvents is reported. We propose two possibilities for the Baeyer–Villiger reaction course. The first of these is based on simply exchanging dichloromethane, the classical solvent for Baeyer–Villiger oxidation, for the ionic liquid bmimNTf$_2$, which results in increased product yields. The second possibility is the elimination of the Baeyer–Villiger reaction catalyst and use of 1-butyl-3-methylimidazolium trifluoromethanesulfonate as both the solvent and catalyst. This method gives lactones in high yields with the possibility of ionic liquid recycling.

Introduction

The Baeyer–Villiger (BV) reaction is based on the formation of esters and lactones by the oxidation of ketones with peroxide derivatives.[1] It is still one of the most important reactions in organic chemistry, with a large range of possible applications, including the synthesis of antibiotics, steroids, pheromones, and monomers for polymerization.[2]

A large variety of new reaction systems *e.g.* oxidant/catalyst, are constantly under investigation.[3] The most commonly used oxidants in this process are organic peracids and hydrogen peroxide. Occasionally, the bis(trimethylsilyl) derivative of hydrogen peroxide is used. With this interesting oxidant, the oxidation occurs specifically at the carbonyl function and carbon–carbon double bonds are not affected.[4] Furthermore, bis(trimethylsilyl) peroxide is readily accessible, and is known as a masked form of 100% hydrogen peroxide. The silyl group attached to the oxygen atoms possesses high nucleophilicity with respect to the oxygen atoms in the parent hydrogen peroxide.[5] This easily handled reagent also has reasonable thermal stability.

Bis(trimethylsilyl) peroxide can be used as the oxidant in the BV reaction together with an acidic catalyst, such as BF$_3$*OEt$_2$.[4] In 1979, an interesting variation of the BV reaction was introduced, which showed that the bis(trimethylsilyl) derivative of Caro's acid, namely, bis(trimethylsilyl) peroxomonosulfate, exhibits remarkable reactivity.[6] Additionally, it was found that bis(trimethylsilyl) peroxide, when combined with trimethylsilyl trifluoromethanesulfonate as a catalyst, is useful for the BV-type reaction of a range of ketones.[7] Nevertheless, these methods suffer from several disadvantages including the use of SO$_3$ or unstable silyl ester as additional reagent and cryogenic reaction temperatures (–78, –30 °C).

Currently, the solvents that are used in BV reactions include dichloromethane, chloroform, and acetonitrile, which can easily

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evaporate and catch fire. Recently, ionic liquids (ILs) have been described as one of the most promising new reaction mediums—green alternatives to volatile organic solvents.[8] There is little information in the literature about successful synthesis approaches employing ionic liquids as solvents in BV oxidations.[9] Herein, we present a new approach to lactones synthesis involving the application of bis(trimethylsilyl) peroxide as an oxidant and ionic liquids as solvents that provides additional efficiency to the reaction.
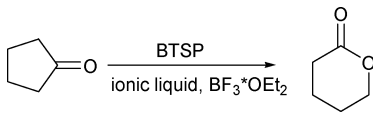
Results and discussion

We propose two possible methods for the BV reaction with bis(trimethylsilyl) peroxide (BTSP): simple replacement of the classical solvent with an ionic liquid, or elimination of the catalyst and use of an ionic liquid as both the solvent and catalyst.

Ionic liquids as solvents for the Baeyer–Villiger oxidation

It is known from the literature that the treatment of ketones with BTSP and a Lewis acid such as SnCl$_4$ or BF$_2$*OEt$_2$ in dichloromethane at room temperature affords esters in fair to excellent yields.[4] We tested the possibility of obtaining lactones by simply changing the solvent in this reaction system. We chose four ionic liquids as solvents for our study: 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide (bmimNTf$_2$), 1-butyl-3-methylimidazolium tetrafluoroborate (bmimBF$_4$), 1-butyl-3-methylimidazolium hydrogensulfate (bmimHSO$_4$) and 1-butyl-3-methylimidazolium trifluoro methanesulfonate (bmimOTf). In Table 1, we present the results of the reaction of cyclopentanone as a model reactant with BTSP, where BF$_3$*OEt$_2$ was used as a catalyst. For comparison, the same reactions were carried out in dichloromethane. In all reactions carried out in ionic liquids, higher or similar yields compared to CH$_2$Cl$_2$ were obtained. The most effective were bmimOTf and bmimNTf$_2$. Most likely, bmimNTf$_2$ which is highly hydrophobic liquid provides anhydrous reaction conditions, so that the hydrolysis of the lactones to their

Table 1 Oxidation of cyclopentanone (0.5 mmol) with BTSP (1 mmol) in the presence of BF$_3$*OEt$_2$ (1 mmol) with ionic liquids as the solvent at room temperature. The reaction time is 5 h

Entry	Solvent	Yield of δ-valerolactone [%][a]
1	bmimNTf$_2$	95 (89)
2	bmimHSO$_4$	80
3	bmimBF$_4$	78
4	bmimOTf	99
5	CH$_2$Cl$_2$	73 (68)

[a] Yields determined by GC; isolated yields in parenthesis.

Table 2 Oxidation of ketones (0.5 mmol) with BTSP (1 mmol) in the presence of a catalyst (1 mmol) at room temperature. The reaction time is 5 h

Entry	Catalyst	Yield of δ-valerolactone [%][a]		Yield of ε-caprolactone [%][a]	
		bmimNTf$_2$	CH$_2$Cl$_2$	bmimNTf$_2$	CH$_2$Cl$_2$
1	AlCl$_3$	87	55	88	74
2	SnCl$_4$	94	90	98 (90)	92 (84)
3	BF$_3$*OEt$_2$	95 (89)	73 (68)	88	60 (52)

[a] Yields determined by GC; isolated yields in parenthesis.

corresponding hydroxyacids is not possible. BmimOTf is hydrophilic and we will comment on its behavior in the next paragraph. We obtained similar results using other well known Lewis catalysts such as AlCl$_3$, and SnCl$_4$ while carrying out the reaction in bmimNTf$_2$ (Table 2).

It is important to note that two of the ILs used in this study are based on BF$_4$$^-$ and HSO$_4$$^-$ anions and are known Brønsted acids. Acidic ionic liquids have recently been widely used as task-specific substances—dual solvents and catalysts.[8] We had hoped that these ILs could replace the acidic catalyst required for the BV reaction. Unfortunately, this was not possible, as no BV reaction occurred in the absence of Lewis acids.

It is known that peroxy compounds can easily decompose in the presence of various reagents *e.g.* acids.[10] Therefore, we tested the stability of BTSP by stirring it in ionic liquids at room temperature. After 5 hours the concentration of BTSP was checked by iodometric titration (Table 3). In the case of acidic ionic liquids, 65–84% of the peroxide was decomposed. This could be the reason why the BV reaction does not proceed in acidic ionic liquids without an extra catalyst. Perhaps, the BV reaction rate is moderate and the decomposition of peroxide is faster. The addition of a catalyst, such as BF$_3$*OEt$_2$, to this system probably promotes a very fast BV reaction (Table 1, entry 2, 3). BmimNTf$_2$, bmimOTf and CH$_2$Cl$_2$ practically do not decompose BTSP. Our results show that it is possible to replace the classical solvent of the BV reaction with BTSP (dichloromethane) and replace it with an ionic liquid such as bmimNTf$_2$.

Table 3 Stability test of BTSP in ionic liquids at room temperature

Entry	Ionic liquid	Decomposition of BTSP [%][a]
1	bmimHSO$_4$	84
2	bmimBF$_4$	65
3	bmimNTf$_2$	10
4	bmimOTf	10
5	CH$_2$Cl$_2$	6

[a] The concentration of BTSP was determined by iodometric titration after 5 h.

BmimOTf as solvent and catalyst for the Baeyer–Villiger oxidation

We have found an interesting behavior of ionic liquid containing the trifluoromethanesulfonate anion OTf $^-$. The oxidation of ketones with BTSP and bmimOTf as the solvent proceeds very efficiently without any additional catalysts. In fact, cyclic ketones are readily oxidized to their corresponding lactones in high yields (72–91%) under mild conditions (Table 4) within a short time.

Camphor could be oxidized in high yield and selectivity to give only 6% of the regioisomer (Table 4, entry 8). In case of norcamphor only one isomer was found (entry 9).
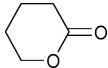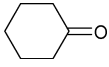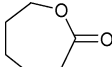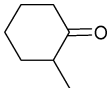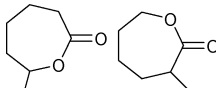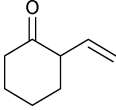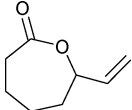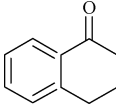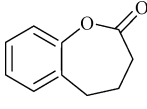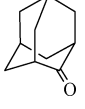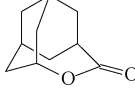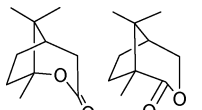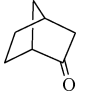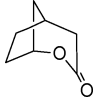
The process is very selective for the oxidation of ketones possessing double bonds in their structures. Such systems can be oxidized with our method without any protection of the carbon–carbon double bound (Table 4, entry 5).

We suggest that the anion in the ionic liquid, OTf $^-$, has an influence on the reaction course. To confirm this thesis, an additional oxidation was made with NaOTf present. In Table 4 entry 2, the formation of δ-valerolactone, with NaOTf as a catalyst in dichloromethane without any additional Lewis acid catalyst, was observed. Additionally, the reaction does not proceed in bmimNTf$_2$ without a catalyst. Based on these facts, we can state that bmimOTf works in the reaction as both the catalyst and solvent, and we propose the mechanism of the reaction in Scheme 1. First, the trimethylsilyl peroxy anion attacks the carbonyl group and the Criegee adduct **2** is formed in-parallel with the new ester **1**, which is involved in the rearrangement of **3** to the final e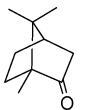ster and the stable hexamethylsiloxane **4**. With bmimNTf$_2$ alone the reaction does not proceed because, in terms of mechanistic consideration,
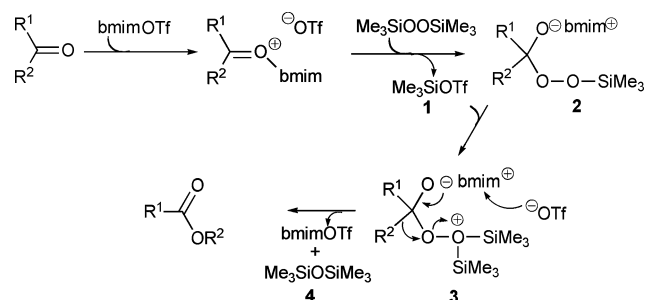
Scheme 1 Proposal for the mechanism of the Baeyer–Villiger oxidation of ketones by BTSP in the presence of bmimOTf as the solvent and catalyst.

Table 4   Oxidation of ketones (0.5 mmol) with BTSP (1 mmol) in the presence of bmimOTf (2 ml) as the solvent and catalyst

Entry	Ketone	Lactone	Time [h]	Temp. [°C]	Yield [%][a]
1			1	25	98 (91)
2			2	25	95 (89)
3			2[b]	25	94
			2.5	25	78 (72)
4		20%	2	25	96 (91)
5			8	40	94 (89)
6			10	40	41[c]
7			24	40	(87)
8		6	15	40	(89)
9			8	25	99 (90)

[a] Yields determined by GC; isolated yields in parenthesis. [b] Reaction carried out in CH$_2$Cl$_2$ as a solvent (2 ml) and NaOTf (1.1 mmol) as a catalyst. [c] Yield determined by HPLC.

during this process the creation of adequate ester **1** (which seems to be the key-step) is not possible.

A slightly similar phenomenon was observed by Noyori and his coworkers.[7] They found that BV oxidation of ketonic substrates is achievable with the use of bis(trimethylsilyl) peroxide and a catalytic amount of trimethylsilyl trifluoro methanesulfonate in dichloromethane. In this system, to achieve a 58% yield of δ-valerolactone, the reaction mixture was stirred at −78 °C for l h and then at −30 to −20 °C for 8 h. To achieve a 76% yield of ε-caprolactone, the reaction was conducted at −78 °C for 6 h and then at −40 °C for 1 h. The authors suggested that the high stability of hexamethylsiloxane is the driving force of this reaction.

At the end of our study, the ionic liquid were recovered and reused for further reactions, which gave almost identical

Table 5   Recycling of bmimOTf in the oxidation of cyclopentanone at room temperature. The reaction time is 2 h

Recycle of IL	Yield [%][a]
fresh, non-recycled IL	95
first	95
second	95
third	95
fourth	94
fifth	93

[a] Yields determined by GC.

results. In Table 5, 4 recycles of bmimOTf for the oxidation of cyclopentanone is shown.

Experimental

Materials

Ionic liquids: bmimOTf, bmimHSO$_4$ (Merck), ketones and AlCl$_3$, SnCl$_4$, BF$_3$*OEt$_2$, NaOTf (Acros Organics) were commercial materials; bmimBF$_4$, bmimNTf$_2$[11] and BTSP[12] were prepared according to standard procedures.

Typical procedure for BV oxidation in the presence of Lewis acids

BTSP (1.0 mmol) was added to a solution of ketone (0.5 mmol) and Lewis acid (1.0 mmol) in ionic liquid (2 ml) and stirred under the nitrogen atmosphere at room temperature for 5 hours. The progress of the reaction was monitored by GC. After this time the post-reaction mixture was extracted with diethyl ether (6 × 5 ml). The organic layer was washed with 5 ml of 10% of a water solution of NaHCO$_3$, dried over anhydrous MgSO$_4$, filtered, and concentrated in a vacuum. The yields of lactones after the purification by column chromatography with hexane:ethyl acetate (4:1) as an eluent were for δ-valerolactone 68–89%; for ε-caprolactone 52–90%. The same procedure was used for the reactions carried out in the presence of Lewis acids in dichloromethane as solvent.

Typical procedure for BV oxidation in bmimOTf as the solvent and catalyst

BTSP (1.0 mmol) was added to a solution of ketone (0.5 mmol) in bmimOTf (2 ml) and stirred under the nitrogen atmosphere at room temperature to 40 °C for 1 to 24 hours (depending on the reaction rate). The progress of the reaction was monitored by GC. After this time, insoluble in bmimOTf by-product, hexamethylsiloxane, can be isolated by decantation. Next, the post-reaction mixture was extracted with diethyl ether (6 × 5 ml). The organic layer was washed with 5 ml of 10% of a water solution of NaHCO$_3$, dried over anhydrous MgSO$_4$, filtered, and concentrated in a vacuum. The yields of lactones after the purification by column chromatography with hexane:ethyl acetate (4:1) as an eluent were 72–91%.

Recycling of bmimOTf

For the experiments where bmimOTf was recycled, four times of the amount of reactants described above, were used. After BV reaction, bmimOTf was purified for recycling tests by extractions of post-reaction mixture with diethyl ether (6 × 5 ml). Next, bmimOTf was concentrated and dried in a vacuum (60 °C, 12 h).

Stability of BTSP

A solution of 0.2 g BTSP in 2 ml IL was stirred for 5 h at room temperature. After this time the content of BTSP was determined by iodometric titration.

Analysis

All products were characterized by comparison of their NMR spectra with authentic samples. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz in CDCl$_3$ (Varian Unity Inova plus, internal TMS). GC analysis was performed using PerkinElmer chromatograph and decane as the external standard; HPLC was performed by liquid chromatograph (Alliance, Waters 2690 system) with a 2 × 150 mm column (Nova-Pak Silica, 60A, 4 µm); the solvent system included hexane/2-propanol (95/5 v/v, flow rate 0.25 ml/min).

Conclusions

In summary, we have reported an efficient method for lactones synthesis that utilizes bis(trimethylsilyl) peroxide as the oxidant in environmentally attractive ionic liquids. First we proposed the utilization of bmimNTf$_2$ as the solvent and SnCl$_4$ as a catalyst. This method yielded results that are comparable to the literature with dichloromethane as the solvent. Neverless, substantial benefit is gained from elimination of the classical solvent for the oxidation process, not only by the minimization of solvent waste but also by improving work safety.

Our second study is based on the utilization of bmimOTf as both the solvent and catalyst. This new method seems to be very attractive, since it gives lactones in high yields. The simplicity of the methodology, ease of the product isolation, high yields, mild conditions and possibility of IL recycling could result in significant progress towards greener processes for the manufacture of lactones.

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Comparative study of the *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide chemical and electrochemical syntheses†

Agustín Palma, Jorge Cárdenas and Bernardo A. Frontana-Uribe*

In order to show the advantages and limitations of organic electrosynthesis in the total synthesis of a natural product, one of the promising green chemistry techniques in organic chemistry, the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide (**3**) was undertaken. Chemical and electrochemical routes that use the same intermediates were used to carry out the syntheses. Four reactions were compared from a green chemistry point of view in the synthesis of **3**: (a) alcohol to aldehyde oxidation, (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction. All the electrolyses were carried out in non-divided cells at a constant current. The electrochemical method in the oxidation reaction of alcohols and the carboxylic acid amidation gave better yields (95% and 67%, respectively) than the corresponding chemical reactions. The Horner–Emmons reaction gave the same yields in both techniques (80–85%); however, the electrochemical method was more environmentally friendly, due to the fact that the base used was electrogenerated, avoiding corrosive and sensitive base manipulation. Finally, the electrochemical Wittig reaction was unsuccessful in the different experimental conditions attempted, and only the chemical method produced the target product. This study demonstrated that organic electrochemistry can be a reliable method for the synthesis of important intermediates, but not all electrochemical reactions can compete with the already well-established methods of organic chemistry.

Introduction

Unsaturated *N*-isobutylamides such as spilanthol **1** and α-sanshoöl **2** are natural products found in plants of *Echinacea*,[1] *Salmea*,[2] *Spilanthes*,[3] and *Asarum* species[4] from the *Compositae*, *Piperaceae*, and *Rutaceae* families.[5] These compounds have anaesthetic,[6,7] anti-inflammatory,[8] potent mosquito larvicidal,[9] cannabinoid type-2 (CB2) receptor antagonistic,[10] insecticidal,[3,11] and antihelmitic[12] properties. Low stability of the natural unsaturated *N*-isobutyl-amides has been reported;[13] therefore, derivatives were required that are better suited to the environmental conditions. In addition, in order to carry out further studies of the biological activity, it is necessary to obtain these products in larger quantities than those isolated from natural sources. *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide **3** was chemically prepared in our laboratories several years ago.[14] Our preliminary studies using the *Artemia salina* biological test[15] showed that this compound was more stable than natural products **1** and **2**, and 74 times more active. Compound **3** has also been prepared by hydrogenation of natural unsaturated *N*-isobutylamides and it has been applied to flavor mixtures due to its organoleptic properties.[16]

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† Electronic supplementary information (ESI) available: [1]H, ^{13}C spectra of the prepared compounds. See DOI: 10.1039/b815745f
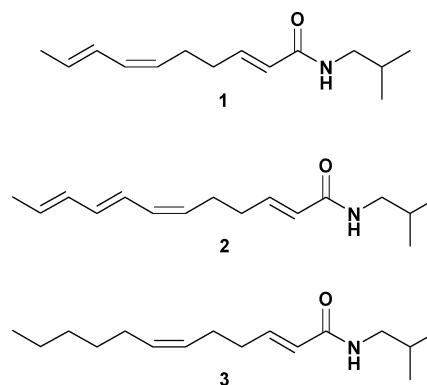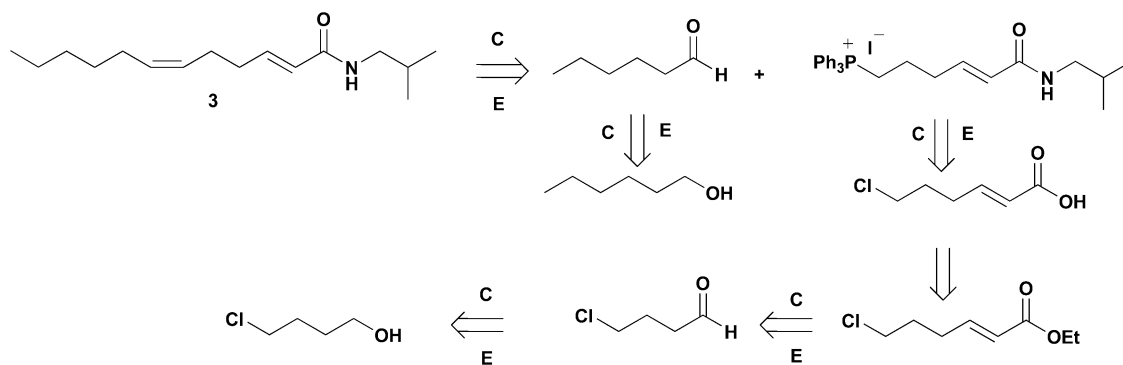

Fig. 1 *N*-isobutyl-amides with biological activity.

Organic chemistry generally uses specific methods for the synthesis of natural products such as enzymatic, photochemical and organometallic catalytic processes.[17] One of the methods that has not been widely used in organic chemistry is organic electrosynthesis, and it is rare to find a report that describes electrochemical steps in a total synthesis.[18] Synthetic organic electrochemistry nowadays offers many electrochemical versions for almost all types of classical chemical reactions.[19] The use of organic electrochemistry opens a non-traditional way of synthesizing molecules[19a,19b,20] and has important characteristics that make it attractive for synthetic green chemistry applications.[21] In organic electrosynthesis the electron becomes a reactant, thus, its use opens the possibility of replacing toxic

**Scheme 1** Retrosynthetic analysis of compound **3**. C: chemical reaction, E: electrochemical reaction.

redox reagents, using catalytic quantities of expensive redox mediators *via* electroregenerating reactions, electrogenerating *in situ* stoichiometric amounts of dangerous reagents, using ionic liquids which are the conducting media and solvents in electrochemistry, and opens the possibility of following the reactions by electroanalytical techniques. These features are in agreement with some of the basic principles of green chemistry.

Therefore, in this contribution the synthetic route previously used[14] for the synthesis of compound **3** was optimized and compared from the green chemistry point of view, using both electrochemical (E) and chemical (C) synthetic routes. The retrosynthetic pathway depicted in Scheme 1 was followed for the synthesis of this compound. In this strategy, the most important intermediates can be obtained by organic electrochemistry and by classical organic chemistry reactions, a fact that allowed us to compare both methodologies. Four reactions were evaluated during the synthesis of **3**: (a) alcohol to aldehyde oxidation, (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction.

Results and discussion

Oxidation of alcohols (4) to aldehydes (5)

The first intermediate required in the synthesis of compound **3** is the 4-chlorobutaldehyde (**5a**); hexanal (**5b**) was used later in the synthesis route. Both aldehydes were obtained from the oxidation of their corresponding alcohols (**4a** and **4b**). Among the classical methodologies for this oxidation (PCC,[22] DMSO/(COCl)$_2$,[23] Dess–Martin,[24] TPAP[25]), the reaction with PCC[26] was chosen for the chemical comparison because nowadays it is frequently used.[27] The reaction of PCC with alcohols **4a** and **4b** gave the corresponding aldehydes in 55% and 57% yields, respectively (Scheme 2). The work-up of this reaction requires a high quantity of anhydrous ether and the final mixture is a very viscous brown tar, which made isolation of the aldehydes
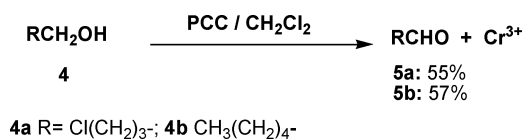
difficult. In addition, the use of chromium salt requires a special treatment for the residual wastewaters due to its toxicity.
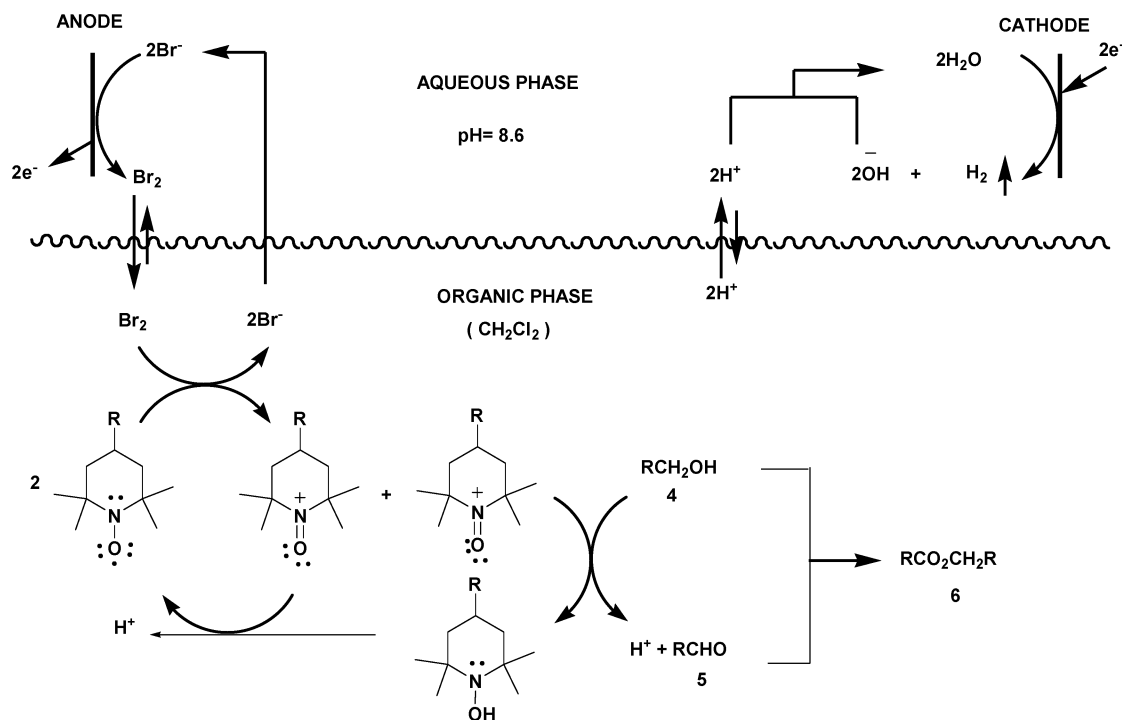
Direct electrochemical oxidation of alcohols requires a very high positive potential and the reaction is not selective.[28] Therefore, an indirect electrochemical reaction allowed us to carry out the oxidation at lower potential values, with a higher rate of reaction and higher selectivity.[29] This methodology requires a regenerable redox catalyst (mediator) that is used to transport electrons between the electrode and the compound to be oxidized. The selective electrochemical oxidation of alcohols to aldehydes was carried out by means of the electrocatalytic reaction with radical 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) as a redox catalyst (1% mol) by a double mediator electrochemical reaction (Scheme 3).[30,31]

In this reaction the primary oxidant, a halogen, was obtained by electrochemically oxidizing chloride or bromide ions, which are regenerated during the reaction. When chlorine was used (Table 1, entries 1–3), aldehyde production was very low and, even in the presence of a mixture of bromide and chloride ions or at higher temperatures, the yield did not substantially increase.[32] Better results were obtained when bromine was used as the primary oxidant (Table 1, entries 4–9). At 25 °C, the yield of the isolated aldehyde was lower; thus, all the other reactions were carried out at 0 °C. Three TEMPO derivatives were studied demonstrating that TEMPO and TEMPO-4-OBz were the better mediators for the reaction. Due to the higher cost of TEMPO-4-OBz, TEMPO was selected as the mediator in the macroelectrolysis. When the alcohol was added to the electrolysis cell at the beginning of the reaction, aldehyde **5a** was produced in high yields (94%). The ester (**6**) was observed as a secondary product, and its quantity depended on the alcohol used. Thus, when **4a** was electrolyzed only traces of **6a** were observed; when **4b** was used, 28% of ester was produced. Consequently, it was decided to add the alcohol in three portions during the electrolysis of **4b**, observing an improvement in the production of aldehyde **5b** reaching a 95% yield (Table 1, entry 9). An additional advantage of the electrochemical method is its self-indicator end of reaction property; the reaction became orange due to the presence of bromine when the alcohol was almost totally consumed. The fact that the reaction was carried out in a biphasic system led to easier isolation of the final products, since they accumulated in the organic layer. Nevertheless, it is not possible to use electron-rich aromatic rings or unsaturated alcohols since they suffer halogenation during the oxidation.[33]

Scheme 2 Chemical oxidation of alcohols **4a** and **4b** using PCC reagent.

Table 1 Indirect electrooxidation of alcohols **4a** and **4b** using the TEMPO double mediator system[a]

Exp.	Alcohol	X-TEMPO	Temperature/°C	Primary oxidant		Products (%)[b]		
				NaCl/M	KBr/M	**4**	**5**	**6**
1	4-Chlorobutanal (**4a**)	X = H	0	0.85	0.0	87	13	T[d]
2	**4a**	X = H	0	0.85	0.01	80	20	T[d]
3	**4a**	X = H	25	0.85	0.01	94	6	T[d]
4	**4a**	X = H	0	0	1.46	6	94	T[d]
5	**4a**	X = H	25	0	1.46	75	10	15
6	**4a**	X = 4-Oxo	0	0	1.46	100	—	—
7	**4a**	X = 4-OBz	0	0	1.46	7	93	0
8	1-Hexanol (**4b**)	X = H	0	0	1.46	5	67	28
9	**4b**[c]	X = H	0	0	1.46	T[d]	95	5

[a] Carried out using 10 mmol of alcohols **4**, 0.1 mmol of TEMPO (1% mol) derivatives in CH_2Cl_2 (50 mL) and aqueous solution (100 mL) of the halogen salt. The pH was adjusted to 8.6 by saturation with $NaHCO_3$. The reaction was stopped after the passage of 2.3 F mol^{-1} at a current density of 70 mA cm^{-2} using a carbon anode (12 cm^2) and a Ti cathode (12 cm^2). [b] Determined from the reaction mixture by ^{1}H NMR. [c] The alcohol was added in three parts during the reaction. [d] Traces.


Scheme 3 General mechanism of the indirect electrooxidation of alcohols using the TEMPO($^+$)/TEMPO($\cdot$) and Br_2/Br^- double mediator biphasic system.

When the yields obtained for the selective oxidation of alcohols to aldehydes are compared using the chemical (55–57%) and the electrochemical (94–95%) methods, the latter one is more advantageous. From an environmental and safety point of view, the electrochemical method is superior, because the use of toxic metals (Cr^{VI}) is avoided, catalytic quantities of mediator are used, the bromine used in the reaction is stoichiometrically electrogenerated and is never manipulated and, finally, hydrogen is generated as the final product together with the aldehyde. Practical advantages such as selective oxidation to aldehydes, the use of distilled solvents in biphasic aqueous-organic media instead of pure dry solvents, the easiness of separation of the products of reaction (concentrated in the organic layer), self-

monitoring of the end of reaction and shorter reaction times make the electrocatalytic method a truly attractive alternative.

Synthesis of the ethyl-6-chloro-2(*E*)-hexenoate (9) *via* a Horner–Emmons reaction

The second reaction to be compared was the production of the α,β-(*E*)-unsaturated ester (**9**) using the Horner–Emmons reaction,[34] a variant of the classical Wittig methodology,[35] which uses an aldehyde and the triethyl phosphonoacetate carbanion (**8**). The chemical version was attempted with NaH, which is a base typically used in this reaction, and the previously obtained 4-chlorobutanal (**5a**) (Scheme 4).[36]
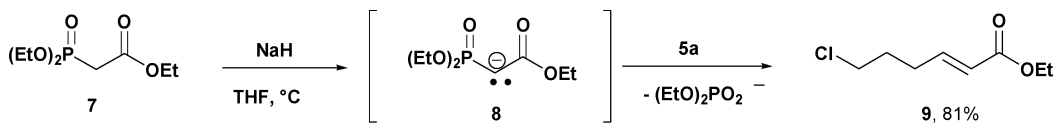
Scheme 4 Chemical synthesis of compound **9** using a Horner–Emmons reaction.

The chemical reaction produced a yield (81%), which is in agreement with the data reported in literature.[36] As a limitation, during the course of the reaction the mineral oil used for the stabilization and conservation of NaH turned very viscous, impeding the magnetic stirring of the reaction. Because NaH is very sensitive fresh base is always required. The corrosive properties of this compound also impose special manipulation precautions such as an inert atmosphere and dry solvents.

The electrochemical Horner–Emmons reaction was carried out using the galvanostatic non-divided cell with a sacrificial anode methodology for the electrogeneration of triethyl phosphonoacetate carbanion (**8**).[37] This method does not use a strong base, since the cathode plays the role of base when it reduces to hydrogen the acidic protons of triethyl phosphonoacetate (Scheme 5). The electrochemical cell filled with the electrolytic solution (Et₄NBF₄, 0.03 M dissolved in DMF) was fitted with concentric electrodes using a Pt electrode as the cathode and an Mg rod as the anode. Aldehyde and triethyl phosphonoacetate were added at the beginning of the electrolysis. The Mg²⁺ ions produced at the anode stabilized the carbanion, a fact that permits the reaction to be carried out at lower reduction potentials decreasing the energy required for the transformation.[37] Moreover, by using a non-divided cell and a sacrificial electrode, we were able to use a lower quantity of the supporting electrolyte; the ionic species electrogenerated during the reaction favors the conductivity of the medium.

Aldehyde **5a** was added at the beginning of the electrolysis in order to favor its reaction with the triethyl phosphonoacetate carbanion as soon as the latter is formed. During electrolysis, small bubbles could be observed on the cathode surface. After reaction work-up and column separation ethyl-6-chloro-2(*E*)-

hexenoate **9** was obtained in 84% yield. The reaction was stereospecific because the *Z* isomer was never detected by ¹H NMR in the reaction mixture. The chemical and electrochemical yields were practically the same but the electrochemical methodology is safer since it eliminates the use and manipulation of a strong, corrosive, and sensitive base. The use of a galvanostatic non-divided cell assures simplicity, a fact that is appreciated by the organic chemist. Reports in the literature mention that the Horner–Emmons reaction carried out in a divided cell[38] typically has a 60% yield; therefore, the reaction in a non-separated cell fitted with a sacrificial anode, as used in this study, is more efficient. When acetonitrile was used as solvent or aluminium as the sacrificial anode, the reaction did not work efficiently.

Synthesis of the *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

Saponification of ester **9** with LiOH/THF[39] and further acidification yielded 88% of carboxylic acid **10**. The amidation of carboxylic acid **10** requires its activation, which was carried out using the acyloxytriphenylphosphonium ion **11** (P^V), generated chemically and electrochemically by oxidizing triphenylphosphine (P^III). In the chemical version Fröyen's methodology was used.[40] The reaction consisted of oxidizing Ph₃P with *N*-bromo- or *N*-chlorosuccinimide (NBS or NCS) in the presence of the carboxylic acid producing **11** *in situ*.[41] Later on, the amine was gradually added until two equivalents were reached. This chemical synthesis of **12** gave us, after several attempts, an optimized yield of 27% (Scheme 6). Other final products of the reaction were: oxidant (NBS) and the corresponding reduced product, triphenylphosphine, its oxide, and the remaining starting material. This mixture is complicated to purify and requires
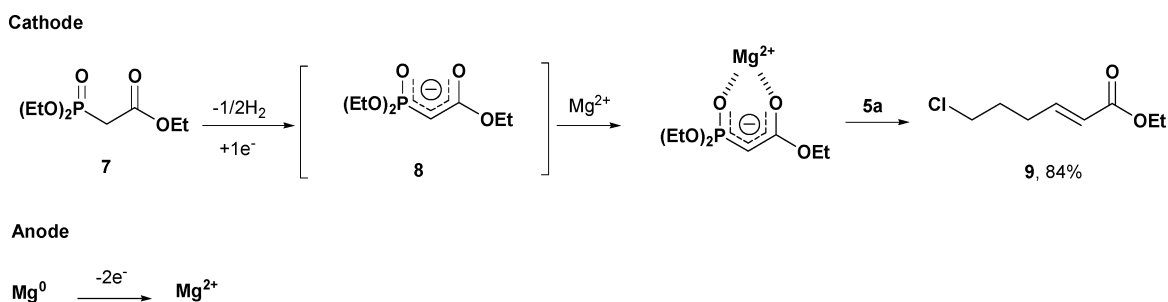
Scheme 5 Proposed mechanism for the electrosynthesis of α,β-(*E*)-unsaturated ester **9**. Pt cathode, +1e⁻, charge = 1 F mol⁻¹, current density = 2 mA cm⁻², 0.03 M Et₄NBF₄ in DMF; Mg rod as sacrificial anode in undivided cell.
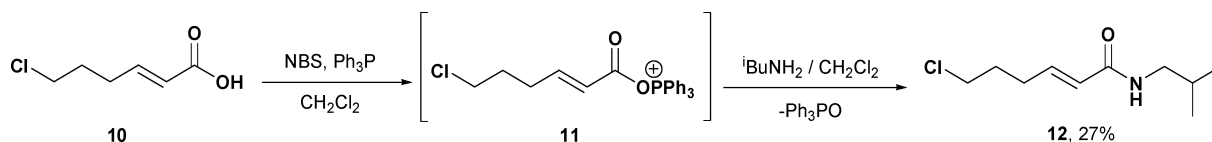
Scheme 6 Chemical amidation of **10** using Fröyen's methodology.

large quantities of solvent for the column chromatography separation.

The electrochemical process takes advantage of the redox properties or the organophosphorus compounds which can be exploited in electrosynthesis.[42] Thus, phosphonium ions can be electrogenerated directly at the anode and activate carboxylic acids generating their derivatives in a redox-substitution reaction. In this reaction, the typical behavior of triphenylphosphine as a nucleophile is changed to an electrophile by an electrochemical umpolung process, which is very useful in electrosynthetic procedures.[20a] Triphenylphosphine showed an anodic peak at 1.3 V *vs.* Ag/AgCl[43] that increased its current value with the addition of aliquots of carboxylic acid **10** (Fig. 2). This increment in current is provoked by the fast consumption of the cation-radical of the triphenylphosphine by the nucleophilic attack of the carboxylic acid generating **11**, a reaction that favors the electrochemical step.[44] In this way, the possibility of producing the acyloxytriphenylphosphonium ion **11** by oxidation of triphenylphosphine in the presence of **11** was demonstrated. Isobutylamine and carboxylic acid **10** were electrochemically inactive in the experimental conditions used.

The macroelectrolysis was carried out in a galvanostatic non-divided cell using platinum electrodes in CH_2Cl_2 using 2,6-lutidinium perchlorate ($LutClO_4$) as a supporting electrolyte. At the anode the triphenylphosphine is oxidized, whereas at the cathode, the supporting electrolyte is reduced to hydrogen and the corresponding base (Scheme 7). This base traps the protons liberated during the amidation process, maintaining a neutral media during the process.[45]

After several electrolyses (Table 2), the best conditions were 32 °C (CH_2Cl_2 boils at 34 °C in Mexico City), low current density values (1.31 mA cm^{-2}), and the addition of the amine in three portions during the electrolysis (Table 2, entry 5). In this way, the electrochemical reaction yield (67%) was 2.5 times the yield obtained by means of a chemical reaction. Since the anode replaces the oxidizing agent, the separation of the reaction mixture is easier to carry out. A minor inconvenience of the electrochemical reaction is the use of $LutClO_4$, which is not commercial but can be very easily prepared and purified (see the Experimental).

Table 2 Electrochemical amidation of 6-chloro-2(*E*)-hexenoic acid (**10**) using as electrogenerated acyloxytriphenylphosphonium ion[a]

Exp.	Temperature/°C	Current density/ mA cm^{-2}	Amine added	Yield (%)[b]
1	20	1.31	At the beginning	5
2	32	1.31	At the beginning	24
3	32	1.31	At the end	32
4	32	2.28	At the end	37
5	32	1.31	In three parts	67

[a] Platinum anode (13.7 cm^2), platinum cathode (24.4 cm^2), charge consumed: 2.4 F mol^{-1} of acid (**7**) 1 mM, Ph$_3$P 2 mM, ^{i}BuNH$_2$ 4 mM, supporting electrolyte: $LutClO_4$ (2 mM) in CH_2Cl_2 (35 mL). [b] Yield corresponding to isolated product.
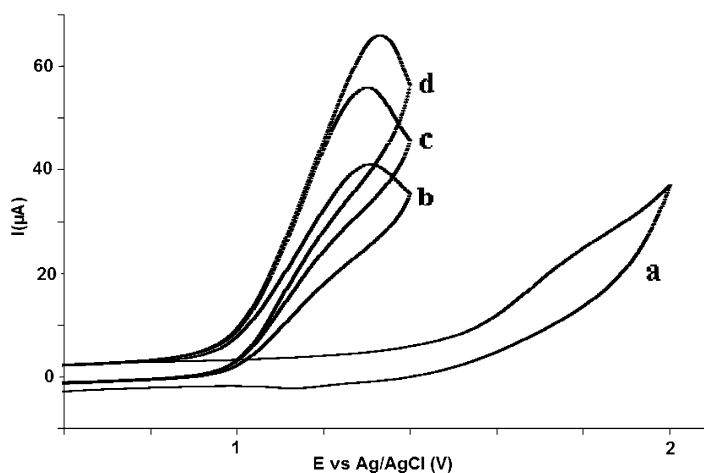
Fig. 2 Cyclic voltammetry using a Pt disk (1 mm diam.) as a working electrode, a Pt wire as an auxiliary electrode and Ag/AgCl as a reference electrode at 50 mV s^{-1}. (a) Supporting electrolyte, $LutClO_4$ 0.1M in CH_2Cl_2; (b) triphenylphosphine, 5 mM; (c) as (b) plus 6-chloro-2(*E*)-hexenoic acid (**10**) 5 mM; (d) as (b) plus 6-chloro-2(*E*)-hexenoic acid (**10**) 10 mM.
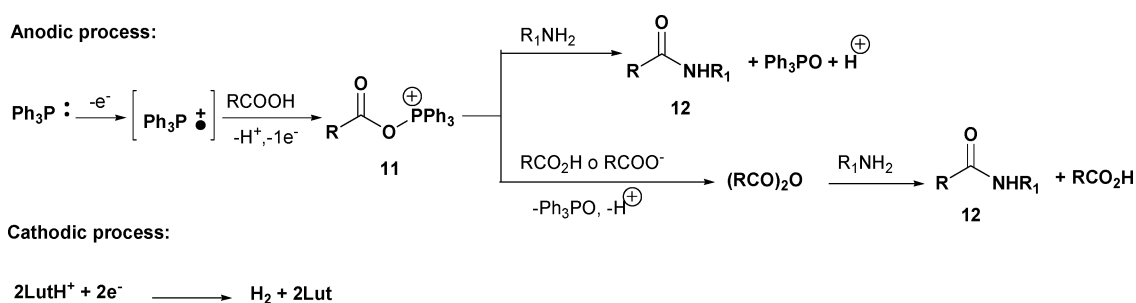
Scheme 7 Proposed mechanism for amide electrosynthesis *via* an electrogenerated acyloxytriphenylphosphonium ion.
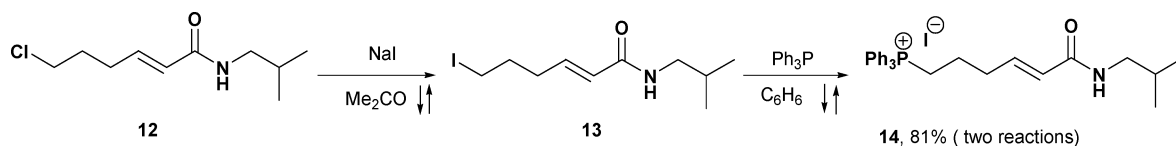
Scheme 8   Preparation of the Wittig salt **14**.
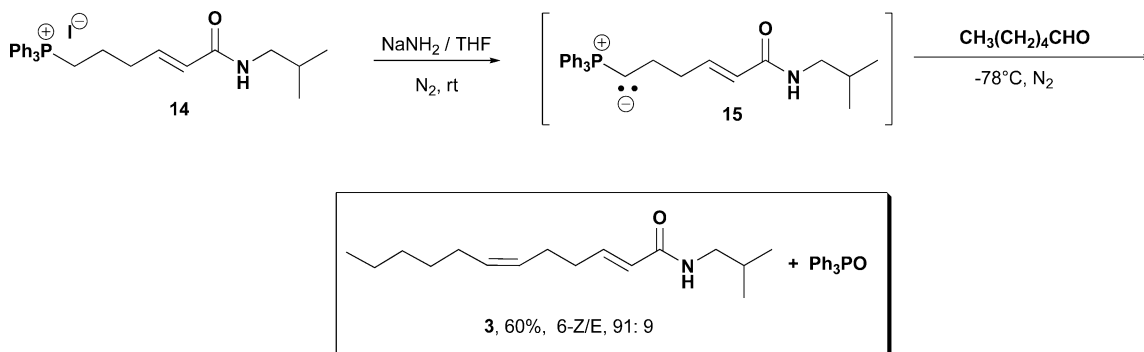
Scheme 9   Synthesis of compound **3** using a Wittig reaction.

Preparation of *N*-isobutyl-(2*E*, 6*Z*)-dodecadienamide (3) *via* a Wittig reaction

With compound **12** in hand a Wittig reaction was attempted to generate target compound **3**. In order to perform the reaction, the corresponding Wittig salt of compound **12** was produced substituting the chlorine atom with an iodine atom using the Finkelstein method.[46] This generated compound **13** quantitatively (Scheme 8), and it was used without purification. Later on, the reaction of **13** with Ph_3P in benzene produced 81% of the Wittig salt **14**.

The stereoselective Wittig reaction[35] of **14** with hexanal (**5b**), obtained in a previous step, was the fourth reaction compared during the synthetic route of the target compound **3**. The *Z* alkene is required in the final product because the biological activity depends on the stereochemistry of this double bond.[5,47] This stereochemistry is favored when the reaction mixture is free of the salts generated during the ylide production.[48] The chemical reaction was performed using sodium amide as the strong base in THF, generating the phosphorous ylide (**15**) (Scheme 9). Efficient mixing of the reaction was needed to generate the ylide, therefore the reaction was carried out inside an essay tube closed with a septum and was ultrasonically stirred. Once ylide was formed and the salts were separated, it was reacted at −78 °C with the hexanal diluted in THF. After work-up, compound **3** was obtained in a 60% yield and ^{13}C NMR showed a ratio *Z*/*E* 91 : 9 for the C-6 double bond.

The electrochemical Wittig reaction requires electrogeneration of the corresponding ylide **15**. Two different approaches were attempted: (a) a direct electroreduction of the protons next to the phosphonium group and (b) the use of an electrogenerated base (EGB). The cyclic voltammetry of salt **14** demonstrated the possibility of using the first approach (Fig. 3). Salt **14** showed a reduction peak on Pt electrode at −1.95 V *vs.* Ag/AgCl in a system containing ACN/Bu_4NBr 0.1 M. This peak could be attributed to the reduction of the protons next to the phosphonium group. Hexanal in the same analysis media did
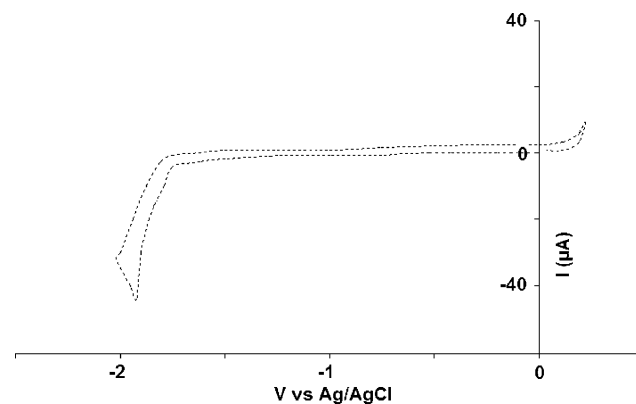
Fig. 3   Cyclic voltammetry of the Wittig salt **14** (6 mM) in Bu_4NBr 0.1 M/ACN, WE: Pt, AE: Pt, RE: Ag/AgCl, $v = 100$ mV s^{-1}.

not show any cathodic signal. When hexanal was added to the solution containing salt **14**, a slight increment in the current of **14** was observed. With this analytical background the preparative direct reduction of **14** was carried out using the same electrolyte in the presence of hexanal with a divided cell and a platinum cathode. The electrochemical reaction produced a mixture of compounds and the NMR analysis of the major components showed products corresponding to the cleavage of the P–C bond and Ph_3P (Scheme 10).[49] After the negative results of the direct reduction, we decided to use the second approach, which involved the electrogeneration of a base at the cathode.
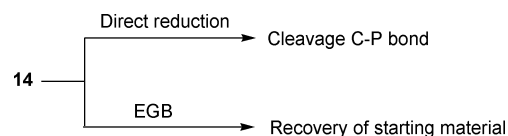
Scheme 10   Cathodic behavior of salt **14** using direct electroreduction and electrogenerated base.

The use of electrogenerated bases has been widely discussed in the electrosynthetic literature[50] and the most common pro-bases used in Wittig reactions were essayed in our experiments. Azobenzene,[51] trityl,[52] and hexamethyldisilazane[53] were used as pro-bases using the described experimental procedures in an electrolysis divided cell. Using one equivalent or an excess of pro-base and one equivalent of salt **14**, in all our attempts we never observed the typical intense red color of the ylide **15** and the starting material was recovered without change. Stronger bases such as acetonitrilate (ACN⁻) can be electrogenerated,[54] but they require higher reduction potential values that provoke the direct reduction of **14** promoting the C–P bond cleavage.

In this synthetic step, only the chemical Wittig reaction was able to produce the final compound **3** in a 60% yield. Despite the fact that cyclic voltammetry showed that salt **14** was electroreducible, the induced reaction was not useful for the ylide synthesis and the same result was obtained when an EGB was used.

Conclusions

In this work the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide **3** was carried out both by a chemical and an electrochemical methodology, comparing the different green chemistry aspects of four reactions: (a) alcohol oxidation to aldehydes (PCC *vs.* TEMPO), (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction (Scheme 11). The electrochemical route did not work for the Wittig reaction. The overall yield of amide **12** (the first three steps of the synthesis) is 10% by the chemical route and 46% by the electrochemical pathway. Until here, the electrosynthetic pathway is clearly superior to the chemical one not only in terms of performance (yield) but also in being more environmentally friendly. It is also important to remark that in a total synthesis scheme, electrosynthetic methods are complementary to currently used chemical methods since not all the electrochemical reactions are efficient. Thus, combining the best electrochemical/chemical reactions a global yield of 22% can be reached, instead of a very low 5% by the chemical route. A synthetic organic chemist can easily carry out the electrochemical reactions used in the synthetic route, due to the fact that they are carried out at a constant current and in a non-divided cell. Thus, no sophisticated equipment was required, the major obstacle perceived by chemists when the methodology is selected. A convenient choice of the synthetic methodology using the best chemical or electrochemical methodologies, can improve substantially the total synthesis yield of organic compounds, keeping a green chemistry philosophy along the synthetic route.

Experimental

General

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. THF was stirred in sodium for 2 h in an ultrasonic bath and distilled. DMF was dried over phosphorus pentoxide and distilled at reduced pressure. CH_2Cl_2 was dried with CaH_2 at reflux for 3 h and distilled. Et_4NBF_4 was dried at night in an Alberhaldren apparatus before use. $LutClO_4$, was prepared by adding 70% $HClO_4$ (164 g) dropwise to 2,6-lutidine (110 g) at 0 °C. The crystals were filtered, recrystallized from AcOEt–EtOH, dried under reduced pressure at room temperature, and stored in a desiccator. Prior to its use $LutClO_4$ was dried in an Alberhadren apparatus. Other supporting electrolytes were obtained from commercial sources and were dried under reduced pressure at 100 °C in the same apparatus.

Melting points were determined on a Fisher-Johns apparatus. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were measured with a Varian Unity (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane in CDCl₃; J values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; t, triplet; m, multiplet; bs, broad signal. MS were recorded on a JEOL JMS-AX 505HA spectrometer by electron impact (EI). UV spectra were recorded in a Shimadzu U-160 spectrophotometer. Infrared spectra were recorded in film technique using a Nicolet Magna 750 spectrophotometer. The cyclic voltammetry and the preparative electrolysis were performed with EG & G PAR potentiostat Model 273A. The cyclic voltammetry was performed on a vitreous carbon disk electrode (3 mm diameter) using an Ag/AgCl reference electrode and a platinum wire as a counter-electrode. Platinum cylindrical gauze and titanium plate were used as cathodes in the preparative electrolysis, while magnesium rod, platinum cylindrical gauze and carbon plate were used as anodes. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck Silica gel 60 F₂₅₄). Column chromatography was performed on silica gel (Macherey-Nagel 230–400 mesh).

Chemical oxidation of alcohols 4a and b to aldehydes

In a round bottom-flask fitted with a reflux condenser PCC (89.6 g, 0.415 mol) and anhydrous CH_2Cl_2 (450 mL) were added. The alcohol **4** (0.277 mol) dissolved in anhydrous CH_2Cl_2 was slowly added. The mixture was magnetically stirred during 2.5 h at room temperature. Later, anhydrous diethylether (500 mL) was added to the reaction mixture. Black insoluble residue was washed with more anhydrous diethylether. The organic solution was passed through a short florisil® column followed by removal of solvent at reduced pressure. The aldehyde was purified by distillation at reduced pressure.

4-Chlorobutyraldehyde (5a). Colorless oil, bp. 77 °C (38 mm Hg) 16 g, 55%. IR (film, ν/cm⁻¹): 2710, CHO; 1715, CO. ¹H NMR: 2.10 (q, 2H, $CH_2CH_2CH_2$, J = 6.9), 2.67 (td, 2H, CH_2CHO, J = 6.9, 0.9), 3.6 (t, 2H, CH_2Cl, J = 6.3), 9.8 (t, 1H, **CHO**, J = 0.9). EI-MS m/z (rel. int. %): [M + 2]⁺ 92(4), [M]⁺ 90(12), 55(53), 42(81), 31(100).

Hexanal (5b). colorless oil, bp. 63–65 °C (60 mm Hg) 15.2 g, 57%. IR (film, ν/cm⁻¹): 2700, CHO; 1736, CO. ¹H NMR: 0.9 (t, 3H, CH₃, J = 6.9), 1.66–1.31 (m, 6H, 3CH₂), 2.42 (td, 2H, CH_2CHO, J = 7.5, 2.0), 9.77 (t, 1H, **CHO**, J = 2.0). EI-MS m/z (rel. int. %): [M]⁺ 100(1), 77(20), 56(83), 44(100), 41(72).
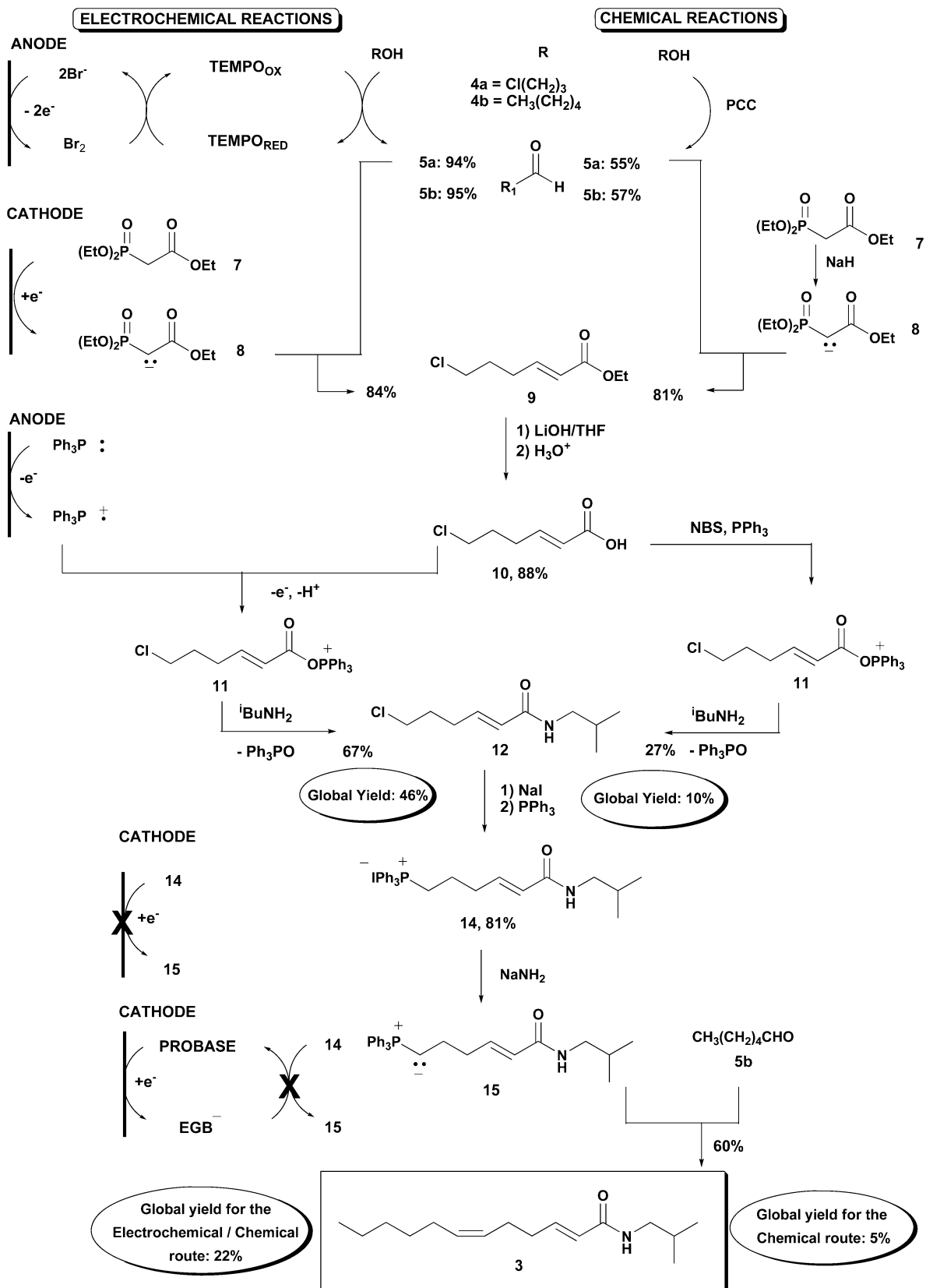
Scheme 11 Summary of the electrochemical (left) and chemical (right) routes used for the synthesis of *N*-isobutyl-(2*E*, 6*Z*)-dodecadienamide **3**.

Electrooxidation of alcohols 4a and b to aldehydes

Alcohol (10 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (15.6 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (50 mL) in an electrolysis vessel. To this solution was added aqueous NaCl or NaBr (100 mL) saturated with $NaHCO_3$. Into the upper layer (aqueous) of the resulting biphasic mixture the electrodes were immersed in a parallel disposition: a centered carbon electrode (6 cm^2) was used as anode and two titanium electrodes (6 cm^2) behaved as the cathodes. The mixture was electrolyzed under a constant current of 70 mA cm^{-2} with a moderate stirring. The electrolysis was stopped when 2.3 F mol^{-1} of electricity were passed and organic phase was separated from aqueous phase using a separation funnel. The organic layer was purified with successive washes with 10% HCl (20 mL) containing NaI (0.25 g), 10% sodium thiosulfate (20 mL) and brine (20 mL). After that, the CH_2Cl_2 layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was analyzed by ^1H NMR in order to quantify the aldehyde. The product was purified by distillation at reduced pressure in a Kugelrohr. 4-Chlorobutaldehyde (**5a**) 0.96 g, 94%; hexanal (**5b**) 0.91 g, 95%.

Chemical synthesis of ethyl-6-chloro-2-*E*-hexenoate (9)

In a dry N_2 purged round flask, NaH was added (60% dispersion in mineral oil, 0.483 g, 11.96 mmol) in dry THF (15 mL). Triethylphosphonoacetate **7** (2.7 g, 11.96 mmol) dissolved in dry THF (5 mL) was added dropwise at 0 °C. This addition was carried out over 30 min and later the mixture was stirred for 1.5 h at the same temperature. After this time, a solution of **5a** (1.27 g, 11.96 mmol) in dry THF (5 mL) was added dropwise at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and was stirred for 2 h at this temperature. The solvent was evaporated and the resulting residue was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried; evaporated and resulting oil was purified by column chromatography (hexane-EtOAc 95 : 5) to give **9** as oil (2.11 g, 81%). IR (film, v/cm^{-1}): 1720, C=O; 1656, C=C. UV λ_{max}/nm (ε/L mol^{-1} cm^{-1}) (MeOH): 209 (246). ^1H NMR: 1.26 (t, 3H, CH_3, $J = 7.2$), 1.80–1.96 (m, 2H, CH_2), 2.30–2.40 (m, 2H, allylic-CH_2), 3.52 (t, 2H, CH_2Cl, $J = 6.4$), 4.16 (q, 2H, OCH_2, $J = 7.2$), 5.84 (d, 1H, CHCO, $J = 15.6$), 6.89 (dt, 1H, $CH_2CH=CH$, $J = 15.6$, 6.9). ^{13}C NMR: 14.2, 29.1, 30.6, 43.9, 60.2, 122.4, 146.8, 166.0. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 178 (17), $[M]^+$ 176 (45), 150 (11), 148 (38), 131 (100), 99 (62), 67 (26), 55 (20), 41 (26), 33 (34), 29 (17).

Electrochemical synthesis of ethyl-6-chloro-2-*E*-hexenoate (9)

Into a previously N_2 purged (5 min) one-compartment cell, equipped with a concentric cylindrical Pt gauze as cathode (15 cm^2) and the magnesium rod as anode (12 cm^2), a solution containing anhydrous DMF (30 mL), the aldehyde **5a** (0.2 mol L^{-1}), Et_4NBF_4 (0.03 mol L^{-1}) and triethyphosphonoacetate **7** (0.1 mol L^{-1}) were added. The mixture was magnetically stirred under nitrogen and electrolyzed with 1 F mol^{-1} of electricity at constant current (2 mA cm^{-2}), the solution was maintained in the electrolysis cell for 0.5 h at room temperature under inert atmosphere. Lately, saturated NH_4Cl solution (50 mL) was added to the mixture reaction and extracted repeatedly with

diethylether (3 × 25 mL). The organic fraction was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated by means of a rotatory evaporator. The product was purified by column chromatography (hexane–EtOAc, 95 : 5). The product was obtained as colorless oil (0.45 g, 84%).

Preparation of 6-chloro-(2*E*)-hexenoic acid (10)

To a solution of ester **9** (2.72 g, 15.45 mmol) dissolved in THF (20 mL) was added a solution of $LiOH \cdot H_2O$ in water (10 mL, 0.71 g, 17 mmol). The resulting mixture was stirred at room temperature for 22 h. THF was evaporated, and then to the residue was added 10% $NaHCO_3$ solution (3 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 15 mL), acidulated with 10% HCl until pH 4 and extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were put together, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. The residue was purified by crystallization from hexane to give **10** (2.02 g, 88%) as white crystals (mp 36–37 °C). IR (KBr, v/cm^{-1}): 2966 broad, O–H; 1697, C=O; 1655, C=C. UV λ_{max}/nm (EtOH): 207.2. ^1H NMR: 1.96 (q, 2H, H-5, $J = 6.9$), 2.42 (c, 2H, H-4 $J = 6.9$), 3.56 (t, 2H, H-6, $J = 6.3$), 5.9 (dt, 1H, H-2, $J = 15.6$, 1.5), 7.06 (dt, 1H, H-3, $J = 15.6$, 6.9). ^{13}C NMR: 29.3, 30.5, 43.8, 121.8, 149.9, 171.8. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 150 (4.5) $[M]^+$ 148, 99 (100).

Chemical synthesis of *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

To a stirred solution of triphenylphosphine (0.67 g, 2.55 mmol) and acid **10** (0.37 g, 2.5 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C, was added *N*-bromosuccinimide (NBS, 0.5 g, 2.8 mmol) in one portion. The mixture was stirred for 20 min letting it slowly reach room temperature. Isobutylamine (0.52 mL, 5.25 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature in inert atmosphere (N_2). Next, to the mixture was added CH_2Cl_2 (20 mL) and it was washed in an extraction funnel with water (15 mL), 10% HCl (15 mL), saturated $NaHCO_3$ (15 mL), and finally with brine (15 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by column chromatography (hexane–AcOEt, 4 : 2) and crystallized from diethylether–hexane to give **12** (0.137 g, 27%) as white solid (mp 56–57 °C). IR (KBr, v/cm^{-1}): 3297, NH; 3084, H–C=C; 2800–2990 C–H; 1668, CH=CH; 1625, CO. UV λ_{max}/nm (EtOH): 210.4. ^1H NMR: 0.93 (d, 6H, CH_3, $J = 6.6$ Hz), 1.88–1.74 (m, 1H, CH), 1.93 (q, 2H, CH_2 **CH_2**CH_2, $J = 7.8$ Hz), 2.35 (c, 2H, **CH_2**CH=CH, $J = 7.2$ Hz), 3.15 (t, 2H, CH_2N, $J = 6.9$), 3.55 (t, 2H, CH_2Cl, $J = 6.6$), 5.58 (s, broad, 1H, NH), 5.84 (dt, 1H, CH=**CH**CO, $J = 15.3$, 1.5 Hz), 6.80 (dt, 1H, **CH**–CH=C, $J = 15.3$, 6.9 Hz). ^{13}C NMR: 20.07, 28.5, 28.9, 30.85, 44.0, 46.8, 124.8, 142.3, 165.6. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 205 (6.5), $[M]^+$ 203 (19.3), 190 (3.3), 188 (10), 162 (4), 150 (5.6), 148 (17.1), 133 (33), 131 (100), 60 (12.1).

Electrochemical synthesis of *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

A solution of triphenylphosphine (0.524 g, 2 mmol), acid **10** (0.15 g, 1 mmol), ^{i}BuNH$_2$ (0.15 mL, 1.5 mmol, added in three parts during the electrolysis) and LutClO$_4$ (0.41 g, 2 mmol)

in dry deoxygenated (N_2) CH_2Cl_2 (35 mL) was placed in the electrolysis cell equipped with a two concentric cylindrical Pt gauze electrodes (15 cm^2 and 10 cm^2). The mixture was electrolyzed at 32 °C under N_2 atmosphere and at 1.31 mA cm^{-2} until 2.4 F mol^{-1} with respect to the acid **10** had passed. The solution was washed with 10% HCl (15 mL), brine (15 mL), 10% $NaHCO_3$ (15 mL) and finally with brine (15 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by column chromatography (hexane–EtOAc, 4 : 2) and crystallized from diethylether–hexane to give **12** as a white solid (0.136 g, 67%).

Synthesis of Wittig salt (14)

A mixture of anhydrous NaI (previously dried in the rotary evaporator under house vacuum for 2 h at 80 °C, 32 g, 213 mmol), anhydrous acetone (250 mL) and chloro compound **12** was heated to reflux for 18 h. The reaction mixture was cooled and the precipitate was filtered out. The solid residue was washed with acetone and the acetone washes were put together with the filtrate. This solution was evaporated in the rotary evaporator under reduced pressure. The organic mixture was dissolved in ethyl acetate and was washed with brine and sodium thiosulfate solution (5%) to decolorize. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. This crude product **13** was used without purification in the next step.

In a 250 mL round-bottom flask equipped with reflux condenser was dissolved triphenylphosphine (25.7 g, 98.2 mmol) in benzene (75 mL). Compound **13** was added to the solution and was heated to reflux for 24 h. After this time, the reaction was cooled down at 10 °C and the Wittig salt was separated by filtration. The solid was washed with hexane and then recrystallized from ethanol–EtOAc producing **14** (43.6 g, 81% yield) as white crystals (mp 187–188 °C). IR (KBr, ν, cm^{-1}): 1706, C=O; 1655, C=C. ^{1}H NMR: 0.92 (d, 6H, $3CH_3$, $J = 6.6$), 1.7–2.0 (m, 3H, $CH_2CH_2CH_2$, CH), 2.5–2.7 (m, 2H, $CCH_2CH=C$), 3.1 (t, 2H, $NHCH_2$, $J = 6.6$), 3.4–3.6 (m, 2H, CH_2P), 6.4 (d, 1H, $CH_2CH=CHCO$, $J = 15$), 6.6 (dt, 1H, $CH_2CH=CH$), 7.5 (s, 1H, NH), 7.6–8.0 (m, 15H, H aromatics). ^{13}C NMR: 19.9, 28.1, 31.3, 31.6, 46.5, 46.7, 118.2, 127.3, 130.2, 133.7, 134.9, 139.2, 166.4.

Preparation of N-isobutyl-(2E,6Z)-dodecadienamide (3)

The dry Wittig salt **14** (1.2 g, 2.14 mmol) and an excess of commercial $NaNH_2$ powder (0.34 g, 8.6 mmol) were transferred to a dry test tube. The tube was previously closed with a septum and parafilm® and was N_2 purged. THF was added *via* syringe to prepare 0.2 mol L^{-1} solution of **14**. This reaction mixture was ultrasonically stirred in N_2 atmosphere for 20 min. During this time the ylide was formed and the solution took a brick red color. The N_2 line was removed and the tube was centrifuged to sediment the salts. The supernatant solution containing the salt-free ylide was transferred *via* a cannula to a dry round-bottom flask at −78 °C. To this solution was slowly added hexanal (0.204 g, 2.02 mmol) dissolved in dry THF (11 mL). The reaction mixture was stirred for 15 min at −78 °C and then the mixture was allowed to reach room temperature. After an hour at this temperature, water was added and three extractions with

diethylether were carried out. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. The residue was purified by column chromatography (hexane–AcOEt, 4 : 1) to give **3** as yellow oil (307 mg, 60%). IR (film, $ν/cm^{-1}$): 3288, NH; 3082, 309, H–C≡C; 2850–2960, CH_3, CH_2, CHO; 1670, C=C; 1632, CO. UV $λ_{max}$./nm: 212.5. ^{1}H NMR: 0.88–0.93 (m, 9H, $3CH_3$), 1.4–1.6 (m, 6H, $CH_3CH_2CH_2CH_2$), 1.8 (m, 1H, CH, $J = 6.9$ Hz), 2.0 (c, 2H, $CH_2CH_2CH=CH$, $J = 6.6$ Hz), 2.1–2.3 (m, 4H, $CH=CHCH_2CH_2CH=CH$), 3.1 (t, 2H, $NHCH_2CH_2$, $J = 6.6$ Hz), 5.3–5.5 (m, 2H, CH=CH, *Z* isomer), 5.85 (dt, 1H, $CH=CHCO$, $J = 15.3, 1.2$ Hz), 6.09 (s, NH), 6.81 (dt, 1H, $CH_2CH=CHCO$, $J = 15.3, 6.3$ Hz). ^{13}C NMR: 13.9, 20.0, 22.4, 25.9, 27.1, 28.4, 29.1, 31.3, 32.1, 46.8, 123.9, 127.9, 131.0, 143.5, 166.1. EI-MS, m/z (rel. int. %): 251 (32) $[M]^+$, 179 (59), 141 (100), 69 (85), 55 (57), 41 (44). HRMS FAB$^+$ m/z requires $C_{16}H_{30}NO$ $[M − H]^+$ 252.2327, found 252.2324.
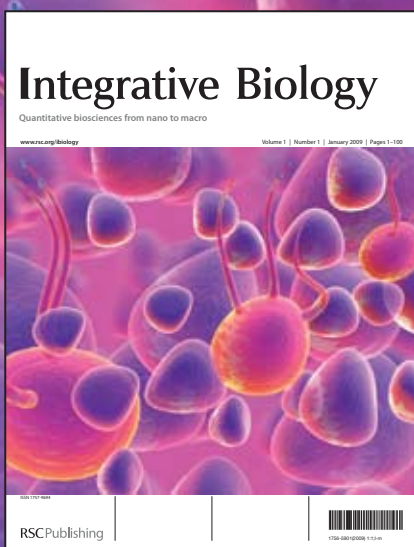
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