

Environmentally Benign Solvents in Organic Synthesis: Current Topics

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Abstract: Organic solvents are extensively used in organic synthesis and for this reason they are a matter of much concern due to characteristics such as: high flammability, volatility, hazardness, and toxicity. Thus the search for environmentally benign substitutes for organic solvents has recently gained more attention in view of the increasing importance of Green Chemistry.

In this review, recent developments in the fields of supercritical fluids, ionic liquids, low melting polymers (especially PEG), perfluorinated solvents and water in many types of organic reactions will be disclosed.

INTRODUCTION

When planning an organic reaction, one of the major concerns to chemists is the choice of solvent and this is not without a reason. Solvents play essential roles in chemical processes not only serving to put reactants into contact by dissolution but also affecting rates, chemo-, regio- and stereoselectivities of the reactions. Solvents are also used in the later stages of a reaction, which means extraction and purification of the products.

The most used organic solvents comprise hydrocarbons (including halogenated and aromatic hydrocarbons), ethers and alcohols. Despite the usefulness and importance of these compounds in organic reactions they undoubtedly have a detrimental impact on the environment. Some intrinsic characteristics of most organic solvents are their high flammability and volatility, their hazardness and toxicity. Each year millions of tons of solvents are discharged into the atmosphere by industries worldwide. As a result there has been an increase in air pollution and the global climate is continuously changing.

Until most recently, organic solvents were the most common and perhaps the only choices of solvents among chemists. This scenario has been substantially changed during the last decade or so due to the intensive research towards environmentally benign substitutes for volatile and toxic organic solvents. Now chemists have to deal with the challenge of reducing the environmental impact of the processes without losing their efficiency by using the so-called green solvents under the concepts of Green Chemistry, which has emerged as an important area of chemistry and has achieved outstanding progresses towards the development of green reaction processes [1].

A green solvent must ideally have a high boiling point, a low vapor pressure, be non-toxic, dissolve a great range of organic compounds, be inexpensive and of course be recyclable. All these things put together tend to narrow the possibilities of finding a compound or a class of compounds

that can effectively be called a green solvent. However, many efforts from research groups all around the world have enabled the appearance of some good alternatives for organic solvents, which include: supercritical fluids, ionic liquids, low melting polymers, perfluorinated solvents and water.

The aim of this article is to discuss the advantages and limitations as well as to highlight the most recent developments achieved in each of these fields. Most of these processes have been separately reviewed and will be adequately referenced along the following sections. Due to space limitation it was not possible to cover everything in each area but emphasis was given to works that in our opinion brought some novelty to the field [2].

ALTERNATIVE SOLVENTS IN ORGANIC SYNTHESIS

1. Water

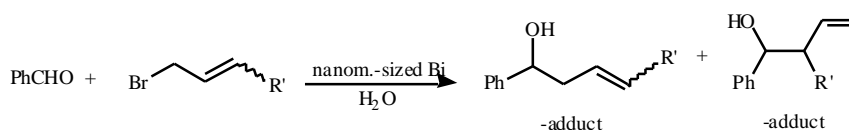
Water is perhaps one of the greener solvents one can imagine in terms of costs, availability, safety and environmental impact. But because of the low solubility of most organic compounds in it and its great reactivity towards some organic compounds (e.g., organometallics), the use of water as solvent was limited to hydrolysis reactions until the pioneering works of Breslow [3] and Grieco [4] in the early 1980s. Since then, many striking examples have appeared in the literature showing that water has unique properties as a solvent that can sometimes lead to surprising results. For instance, the rates and stereoselectivities of many types of organic reactions can be dramatically enhanced in water due to solvophobic effects. The use of organic cosolvents or surfactants helps to increase the solubility of nonpolar reactants in water by disrupting the strong hydrogen-bond network of pure water [5]. The discovery that Lewis acids, especially some metal triflates, can efficiently catalyze reactions in water also contributed to popularize it as solvent in organic reactions [6].

Many interesting examples of organic reactions in water have appeared recently in the literature, from which we selected a few representative of the great potential of water as solvent [7]. For those readers seeking a broader understanding of organic reactions in water, recent reviews by Engberts and Blandamer [8] and by Lindström [5] are recommended.

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Table 1. Allylation of carbonyl compounds mediated by nanometer-sized bismuth in H₂O.

Entry	R ¹	R ²	Yield (%) / Time (h)		
			Bi Nanotube	Bi nanopart.	reg. Bi
1	Ph	H	100/1	92/15	46/24
2	<i>p</i> -NO ₂ C ₆ H ₄	H	99/4	82/2	9/24
3	<i>p</i> -MeC ₆ H ₄	H	36/7	85/2	6/24
4	¹³ C ₆ H ₁₃	H	99/6	99/1.5	46/24
5	CH ₃ CH(OH)	CH ₃	95/45	92/1	82/24
6	CH ₃ CH ₂	CH ₃	90/5	---	80/24
7	Ph	CH ₃	66/2	---	2/24

**Scheme 1.**

1.1 Metal-Catalyzed Reaction

1.1.1 Allylation of Carbonyl Compounds

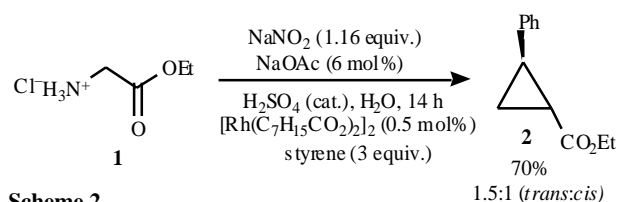
Metal-mediated allylation of carbonyl compounds in aqueous media represents an important carbon-carbon bond forming reaction in organic synthesis [9]. Xu *et al.* [10] studied the allylation of carbonyl compounds mediated by nanometer-sized bismuth in water. Both Bi nanotubes and *in situ* generated Bi nanoparticles dramatically enhanced the yield of the corresponding homoallylic alcohols and shortened the reaction times as compared to regular bismuth. However, some differences in the results were found in these two kinds of nanometer-sized bismuth. Some selected examples are shown in Table 1.

p-Nitrobenzaldehyde was smoothly allylated in both methodologies whereas a mixture of the homoallylic alcohol and the *N*-allylated product was obtained in very low yield when regular Bi was used (entry 2). When an electron-donating group is attached to the aromatic ring, Bi nanoparticles showed much better results (entry 3). In contrast, Bi nanoparticles were unable to mediate the allylation of ketones (entries 6 and 7) except for 3-hydroxybutan-2-one (entry 5) in which case the bismuth atom would assist the formation of a chelate between the hydroxyl and the carbonyl groups, thus facilitating the reaction.

The reaction was also found to be regioselective (Scheme 1). In the allylation of ethyl-4-bromocrotonate, the -adduct was exclusively obtained in both conditions. However, in the allylation of crotyl bromide, the -adduct was obtained with high selectivity (greater than 95%) by *in situ* Bi nanoparticles while the reaction mediated by Bi nanotubes favored the -adduct (~2.6:1).

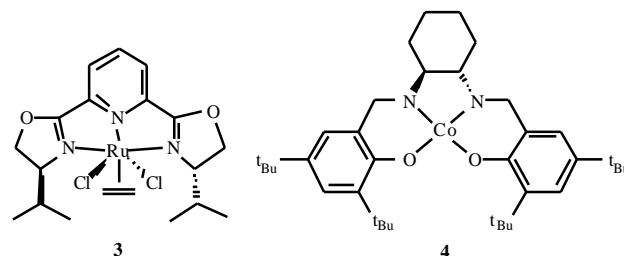
1.1.2 Cyclopropanation of Olefins

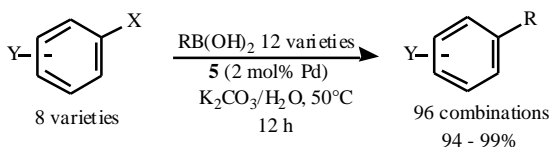
Wurz and Charette [11] reported the *in situ* generation of ethyl diazoacetate in water and its reaction with styrene to form a cyclopropane derivative (Scheme 2). Other alkenes were investigated and in most cases the yields of the

**Scheme 2.**

products were comparable to those obtained in CH₂Cl₂. Higher yields were obtained with hydrophobic rhodium catalysts, Rh(II) octanoate being the most efficient catalyst. The authors claimed that the success of this reaction might possibly result from its biphasic nature in which the hydrophobic catalyst migrates into the alkene substrate leading to a high effective concentration of alkene. Upon diffusion of the diazo compound into the organic phase, cyclopropanes are formed preferentially.

The asymmetric cyclopropanation was also investigated using the ruthenium(II)-based catalyst (**3**) and the Co(II)-type catalyst (**4**) (Fig. (1)). In the case of catalyst (**3**), excellent diastereoselectivities (19-24:1, *trans/cis*) and enantioselectivities (83-90% ee) were obtained, which are comparable to those obtained in CH₂Cl₂, but the yields were not as good (31-46% vs. 40-74% in CH₂Cl₂). Catalyst (**4**) gave higher yields of products (60-80%) but the diastereo- and enantioselectivities were much lower (1.5-2:1, *trans/cis* and 22-47% ee for the *trans* isomer). These results were comparable to those obtained using THF.

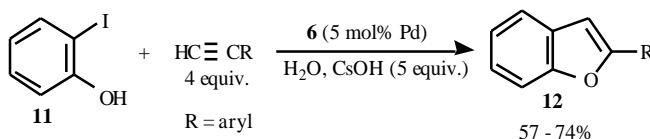
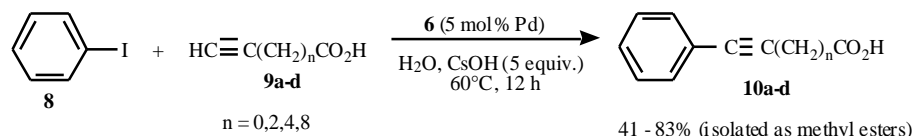
**Fig. (1).** Catalysts for the asymmetric cyclopropanation in water.



Scheme 3.

1.1.3 Catalysis by Resin-Supported Palladium Complexes

Uozumi *et al.* [12-15] designed a series of amphiphilic resin-supported palladium complexes which have been able to combine the advantages of both homogeneous and heterogeneous catalysts in one system and have proved to be very effective in aqueous medium. These catalysts incorporate a palladium complex immobilized by coordination with a phosphine ligand anchored on an amphiphilic PS-PEG resin (Fig. (2)).



Scheme 4.

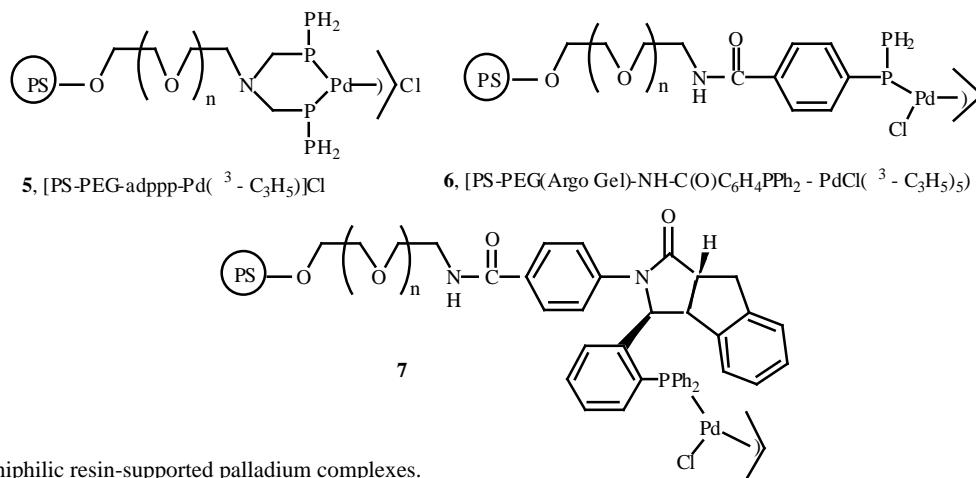


Fig. (2). Amphiphilic resin-supported palladium complexes.

For instance, compound (5) was successfully employed in the Suzuki-Miyaura cross-coupling of aryl halides with arylboronic acids (Scheme 3) [12]. This reaction is an extremely versatile methodology for the generation of new carbon-carbon bonds and is employed most successfully in the synthesis of biaryls [16]. Furthermore, it has gained prominence in recent years because of the availability of functionally substituted boronic acids, which are environmentally safer than most other organometallics [17]. However, it suffers from a number of drawbacks such as catalyst loss into the product, catalyst decomposition and poor reagent solubilities.

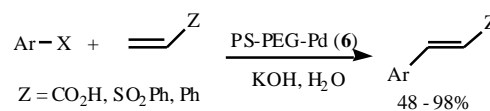
In the present case, almost quantitative yields of coupling products could be obtained in aqueous potassium carbonate at 50°C for 12 h. Easy separation of the products from the

resin catalyst was achieved by simple filtration followed by washing with ether. The recovered catalyst could be reused twice with no loss of catalytic activity. A library of 96 compounds was easily obtained by combination of 8 varieties of aromatic halides and 12 varieties of aryl- or vinylboronic acids. This methodology showed a wide functional group tolerance in the aromatic rings, including carbonyls and hydroxyls.

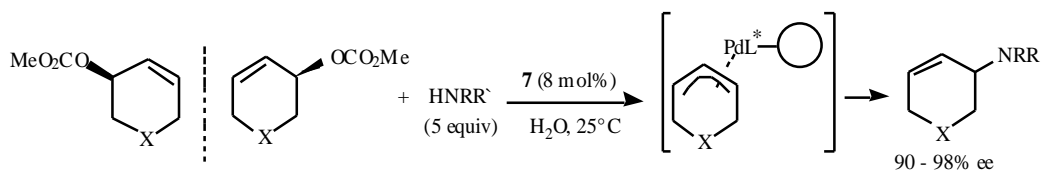
Compound (6) was used as catalyst in the Sonogashira coupling [18] of iodobenzene with alkynes in water under copper-free conditions [13] (Scheme 4). By using this protocol, a one-step preparation of benzofurans was achieved in water via coupling of 2-iodophenol (11) and terminal alkynes (Scheme 4).

The vinylation of aryl halides catalyzed by palladium complexes, commonly called Heck reaction, has received

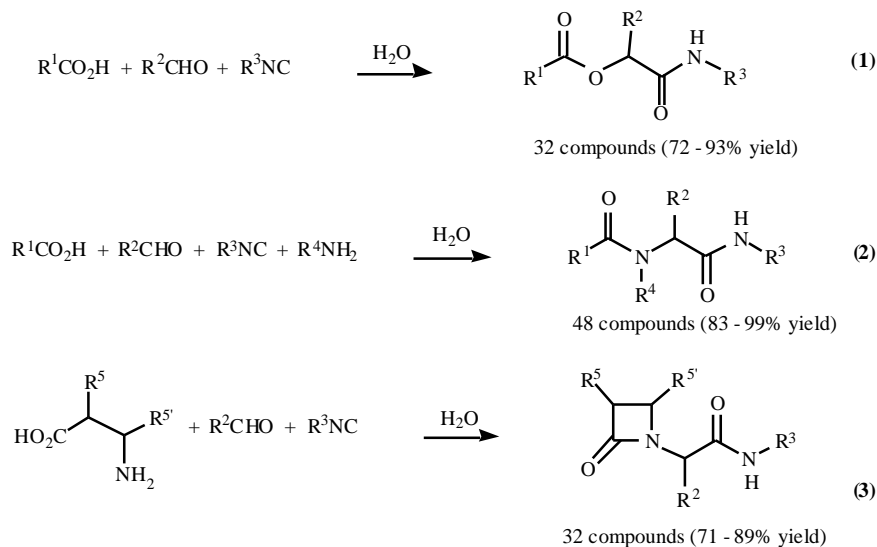
increasing attention because of its enormous synthetic potential for generating carbon-carbon bonds and its tolerance towards a wide range of functional groups [19]. The reaction is usually carried out in polar solvents such as DMF, DMSO and CH₃CN. The reaction in aqueous medium of various aryl halides and alkenes was also efficiently achieved using compound (6) [14] (Scheme 5). Good yields of the products were obtained in the presence of 10 mol% Pd of catalyst (6) and 3 equiv. of NaOH. The catalyst resin was



Scheme 5.



Scheme 6.



Scheme 7.

recovered and successively subjected to other series of reactions under the same conditions, affording the products with an average yield of 92% after 5 continuous runs. More recently, Heck reactions in water catalyzed by an oxime-derived palladacycle [20] and in ionic liquid accelerated by microwave heating [21] were reported.

Compound (7) was recently used in the asymmetric amination of cycloalkenyl esters forming optically active cyclic allylamines with high enantioselectivities (up to 98% ee) [15] (Scheme 6). Noteworthy is that complex (7) showed no catalytic activity at 25°C when the reactions were carried out in CH₂Cl₂ and also when the phosphine moiety lacks PS-PEG supports. The authors suggested that a significant reactivity is achieved into the polystyrene matrix in water in which the hydrophobic organic substrate might diffuse. No loss of stereoselectivity or catalytic activity was observed after the third use of the recovered catalyst without any additional charge of palladium.

1.2 Multicomponent Reactions (MCRs)

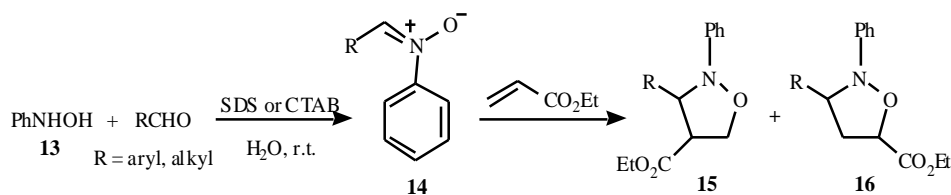
In multicomponent reactions (MCRs), three or more components react in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amounts of solvents, and expensive purification techniques [22]. For these reasons, they have received increasing attention recently. Pirrung and Sarma [23] demonstrated that Passerini [24] and Ugi [25] reactions can be extremely accelerated in

water (nearly 300-fold) as compared to organic solvents [26]. For instance, they created a library of 32 Passerini reaction products (Scheme 7, eq. 1) and 48 Ugi reaction products (Scheme 7, eq. 2). The reactions were complete in 3-6 h at 25°C (3 h for Ugi reactions) and the products were easily isolated by filtration or extraction in high yields and purities. Use of α -aminoacids in the Ugi reaction produced a library of 32 β -lactams in high yields (Scheme 7, eq. 3).

1.3 Surfactant-Catalyzed Reactions

Chatterjee *et al.* [27] reported the surfactant-catalyzed formation of nitrones, by dehydration of phenyl hydroxylamine in the presence of several aldehydes, and then cycloaddition reaction in a single pot with ethylacrylate in aqueous medium (Scheme 8). Both anionic (sodium dodecylsulphate, SDS) and cationic (cetyltrimethylammonium bromide, CTAB) surfactants were investigated and the latter showed better results presumably due to stronger binding of the CTAB to the substrate.

The reactions were carried out under sonication (5 min) and stirring (16-76 h) and the yields were good (71-91%) except when 2,5-dimethoxy benzaldehyde was used (27-38%). In most cases, except for *p*-OMe, control of regioselectivity favors the *trans* substituted product (16) as the major isomer. In contrast, cycloaddition of nitrones in organic solvents leads to a mixture of the four possible isomers (15:16 = 2:1).



Scheme 8.

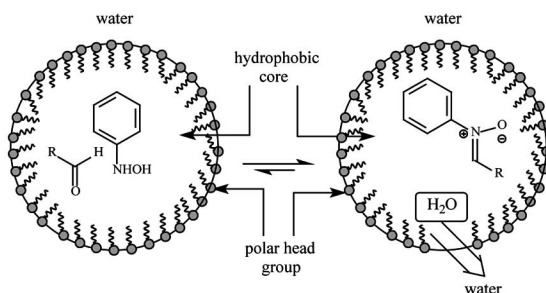
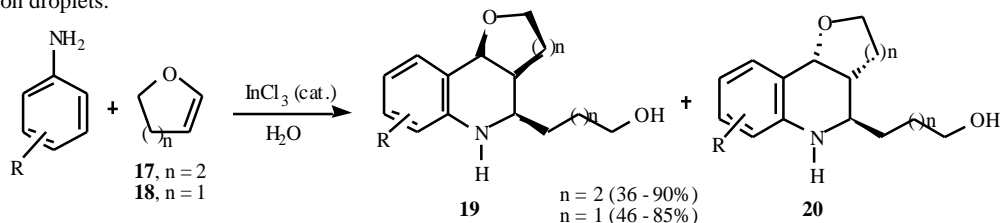


Fig. (3). Emulsion droplets.



Scheme 9.

R = H, CH₃, OH, OCH₃, halogen, CN, PhNH

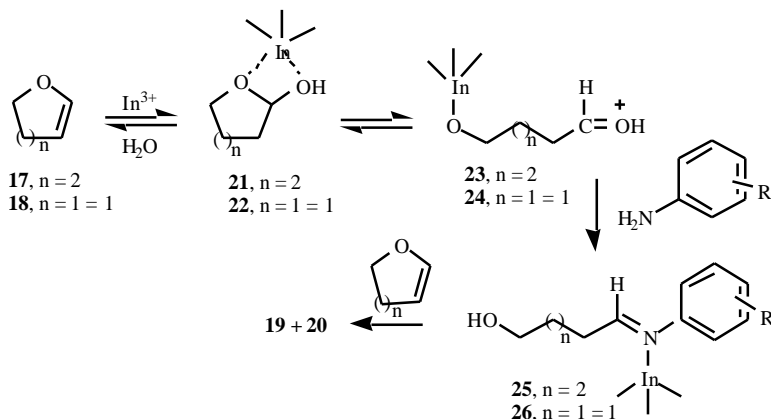
The proposed model for the dehydration reaction in the presence of a surfactant is shown in Fig. (3). The driving force for the reaction is the ejection of water molecules from the hydrophobic interior of the emulsion droplets that are formed. These emulsion droplets were confirmed by optical microscopy.

Other examples of surfactant-catalyzed reactions in water have been published which show a good level of enhancement both in yields or selectivities as compared to common organic solvents [28].

1.4 Domino Reactions

Tetrahydroquinoline derivatives were efficiently prepared via a novel domino coupling of aniline derivatives and cyclic enol ethers, catalyzed by indium(III) chloride in water [29] (Scheme 9).

Several aniline derivatives were screened in the reaction with compounds (17) and (18). Faster reaction rates and enhanced *cis* selectivities were observed for dihydrofuran (18) in comparison to dihydropyran (17). The reaction times could be shortened by increasing the reaction temperature to 50-60°C. Another important feature is that anilines bearing electron-donating groups were more reactive than ones bearing electron-withdrawing groups.



Scheme 10.

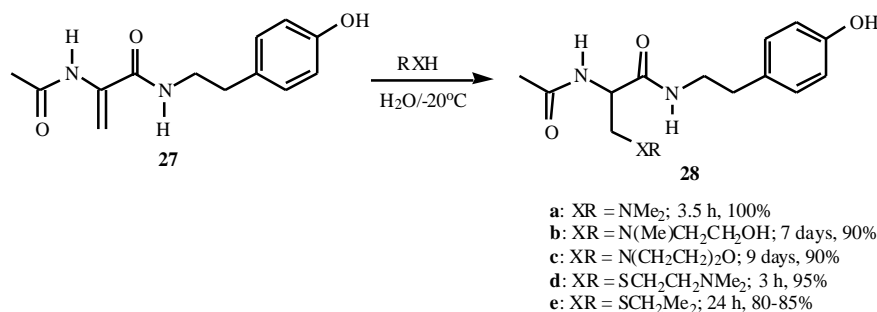
Based on experimental evidences, the proposed mechanism for this domino reaction involves the direct intermediacy of water (Scheme 10). The cyclic enol ethers (17) and (18) react with water in the presence of a Lewis acid to give (21) or (22), respectively. These substrates then undergo facile ring opening in the presence of indium(III) ion to give (23) and (24), which react with aniline to give the indium-coordinated imines (25) and (26). The next step is an aza-Diels-Alder reaction of imines (25) and (26) with (17) or (18) to generate the tetrahydroquinoline derivatives.

1.5 Michael Additions

Naidu *et al.* [30] described for the first time that Michael additions of amine and sulfur nucleophiles to various acrylamides could be successfully carried out in frozen water (-20°C). Under this condition, the chemoselectivity was enhanced and unwanted side reactions were minimized. Representative examples are shown in Scheme 11. The Michael adducts were obtained in high yields although in some cases the reaction required several days for completion.

2. Ionic Liquids

Undoubtedly, ionic liquids (ILs) have been the most explored source of alternative solvent in organic reactions lately, as confirmed by the incredible amount of works in the



Scheme 11.

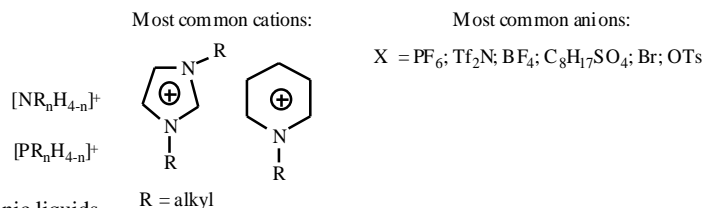


Fig. (4). Main classes of ionic liquids.

literature regarding this topic. Indeed, several reviews and books about ILs have been recently published [31]. So, the readers must refer to these references for an in-depth discussion about their properties. In this review, a brief introduction will be given followed by some examples of how these compounds can be useful for organic chemists focusing on the most recent advances in the area.

The great interest for such compounds relies on the fact that they possess several attractive properties such as negligible vapor pressure, chemical and thermal stability, nonflammability, high ionic conductivity, wide electrochemical potential window and moreover the ability to act as catalysts. In contrast to conventional solvents that are constituted of molecules, ionic liquids consist of ions and are liquid at room temperature (RTILs) or have a low melting point (generally below 100°C). This ionic character allows them to potentially behave in a very different manner when used as solvents as compared to conventional molecular liquids.

A huge amount of different ionic liquids can be envisioned by the simple combination of different anions and cations. Despite their great potential, most are yet to be discovered and so far only a few types of cations and anions comprise most ionic liquids (Fig. (4)). ILs based on 1,3-dialkylimidazolium cations are by far the most used.

By changing the anion or alkyl chain of the cation, one can vary physical properties such as the hydrophobicity, viscosity, density, and solvation of the ionic liquid system. For this reason they have been referred to as “designer solvents” [32]. ILs can be easily separated from the organic products of a reaction but this process usually requires extraction with a non polar organic solvent. Their high viscosities make stirring and homogenization of the reaction medium difficult, which causes slow dissolution of solids. Other drawbacks are their higher costs as compared to most organic solvents and also little is known about their toxicity.

ILs are not only restricted to simple substitutes to organic solvents as reaction media for organic reactions. In some cases they can act as reagents or catalysts (task-specific ILs) and as media for immobilizing catalysts or inducing chirality. The following sections will present a brief

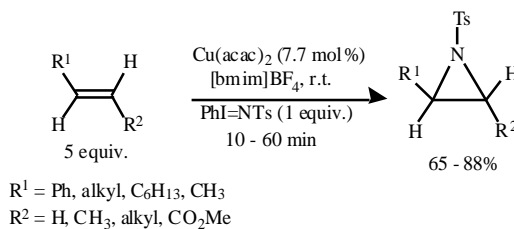
overview of some interesting techniques that help make ionic liquids even more popular.

2.1 Immobilized Reactions

One major advantage of ionic liquids is their ability to immobilize polar or ionic compounds that can act as catalysts in organic reactions. Thus, at the end of a reaction these compounds can be separated from the reagents and products and recovered unchanged in the ionic liquid phase, being reused in subsequent runs. Some recent representative examples are disclosed in this section [33].

2.1.1 Synthesis of Aziridines

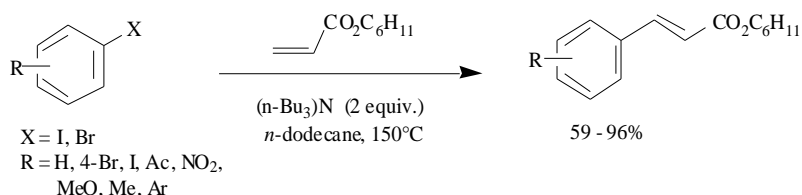
Aziridines are important building blocks for the synthesis of a wide range of nitrogen containing compounds [34]. Kantam *et al.* [35] reported the aziridination of olefins using a recyclable system in which the catalyst, Cu(acac)₂, was immobilized in [bmim]BF₄ or [bmim]PF₆ ionic liquids in the presence of a nitrogen donor (PhI=NTs) (Scheme 12). Both aromatic and aliphatic olefins furnished good yields of aziridines and no reaction occurred in the absence of the catalyst. The authors pointed out that except for cyclohexene the reactions were faster than the earlier reported methods using conventional solvents such as acetonitrile, being complete within minutes (the completion of the reactions is indicated by the dissolution of PhI=NTs in the ionic liquid). This might indicate that ionic liquid is not only a convenient medium for this reaction but also accelerates it. Furthermore, recovery of the ionic liquid phase containing the catalyst was easily accomplished by simple extraction of the products with ether. This catalytic system could then be reused for five cycles without loss in activity.



Scheme 12.

2.1.2 Mizoroki-Heck Reaction

As already mentioned, the Mizoroki-Heck coupling is one of the most important reactions to construct carbon-carbon bonds [19]. Due to the formation of Pd clusters, which leads to a decrease in the catalytic activity of the catalyst, heterogeneous catalysts are preferable although they can be less reactive compared to homogeneous catalysts. To achieve recyclability and reactivity, a homogeneous catalyst can be immobilized in a solid support. In this respect, Hagiwara *et al* [36] reported the Mizoroki-Heck reaction in which palladium acetate is supported on amorphous silica with the aid of an ionic liquid, [bmim]PF₆. Several aryl halides were examined in the reaction with cyclohexyl acrylate (Scheme 13).



Scheme 13.

According to the authors, the advantages of this immobilization are that it stabilizes the Pd catalyst, it is cheap and, also, accumulation of Pd on silica facilitates the catalytic reaction. The immobilization process involves a suspension of spherical amorphous silica in a solution of Pd(OAc)₂ in [bmim]PF₆ and THF, which is evaporated to dryness to afford a powdery and free-flowing immobilized catalyst. Based on experimental evidences, it was suggested that the solution of Pd(OAc)₂ in an ionic liquid exists in the pores of silica (Fig. (5)).

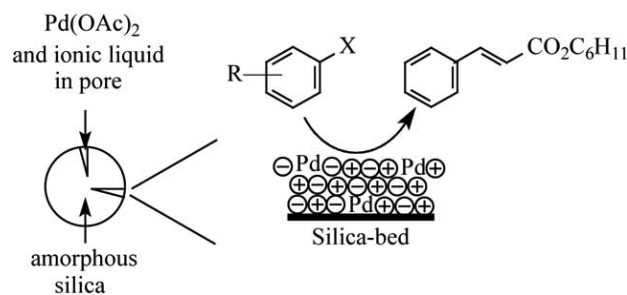


Fig. (5). Mizoroki-Heck reaction in amorphous silica.

The optimized conditions involved the use of hydrocarbon solvents to prevent removal of the ionic liquid

layer from the silica, *n*-dodecane being the best. Besides, the most efficient base was tri-*n*-butylamine and the reactions were carried out at 150°C. The catalyst could be reused but it was observed a decrease in the catalytic activity after the third cycle. To circumvent this problem, the catalyst had to be washed with an aqueous solution of NaOH to retrieve its catalytic activity. The level of leaching (0.24% Pd) reasonably compares to other heterogeneous catalysts supported on solids [37].

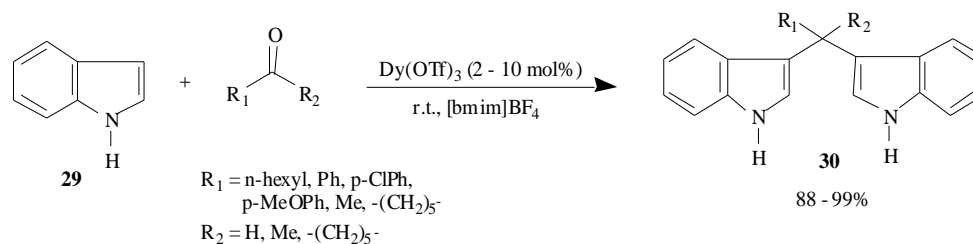
2.1.3 Electrophilic Substitutions of Indole

3-Substituted indole derivatives are versatile intermediates in organic synthesis [38], due to the feasibility of their 3-position for electrophilic substitution. Mi *et al.*

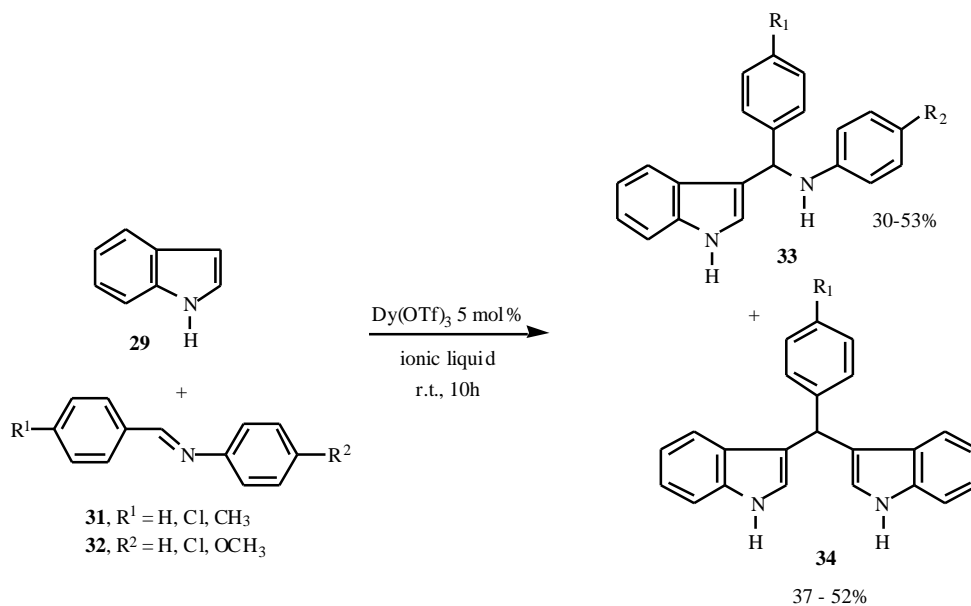
[39] reported the reaction of indole with aldehydes/ketones (Scheme 14) and imines (Scheme 15) in ionic liquids, using immobilized dysprosium triflate (Dy(OTf)₃) as the catalyst. In the absence of the catalyst the reactions did not occur. Among the ionic liquids tested, [bmim]BF₄ gave the highest yields for carbonyl compounds whereas [bupy]BF₄ worked better for imines. The bisindolyl products were smoothly obtained at room temperature after short reaction times, the reactions being considerably faster compared to those realized in aqueous media, although bisindolyl methane by-products (**34**) were formed in the reactions with imines along with the desired secondary indolyl amines (Scheme 15). The ratio of the products (**33:34**) was influenced by the structure of the ionic liquids. After extraction of the products with ether the catalytic system could be reused for 6 cycles without loss of activity.

2.1.4 Synthesis of Imines

Imines or Schiff bases are important intermediates in organic synthesis [40]. The formation of these compounds from the reaction of aldehydes and primary amines is usually carried out in ethereal or chlorinated organic solvents, but recently there have been some reports of *in situ* formation of imines in ionic liquids with their subsequent use in organic reactions [41]. Andrade *et al.* [42] reported the use of molecular sieves in ionic liquids as an efficient and

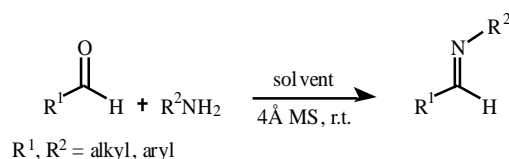


Scheme 14.



Scheme 15.

Table 2. Synthesis of imines in ionic liquids.



Solvent	4Å MS	Time (min)	Yield (%)
CH_2Cl_2	Yes	30 – 180	83 – 94
[bmim]PF ₆	Yes	15 – 120	88 – 98
[bmim]PF ₆	No	25 – 330	91 – 97
[bmim]BF ₄	Yes	15 – 180	80 – 95
[bmim]BF ₄	No	10 – 80	91 – 93

recyclable medium for the synthesis and isolation of several imines (Table 2).

Aliphatic, aromatic and heteroaromatic amines and aldehydes were investigated. The reactions were run at room temperature and the crude imines were obtained in excellent yields in all cases, after extraction with ether, without the need for purification. It was observed that the use of 4Å molecular sieves as water scavenger had little effect in the yields but lowered the reaction times in [bmim]PF₆ as compared to the reactions run in CH_2Cl_2 . In [bmim]BF₄ no effect of this kind was observed, probably due to the differences in solubility of water in these two ionic liquids and the formation of different polarity regions [43]. After extraction of the products, the remaining system containing the ionic liquid and molecular sieves could be recovered and reused up to five times without loss in activity.

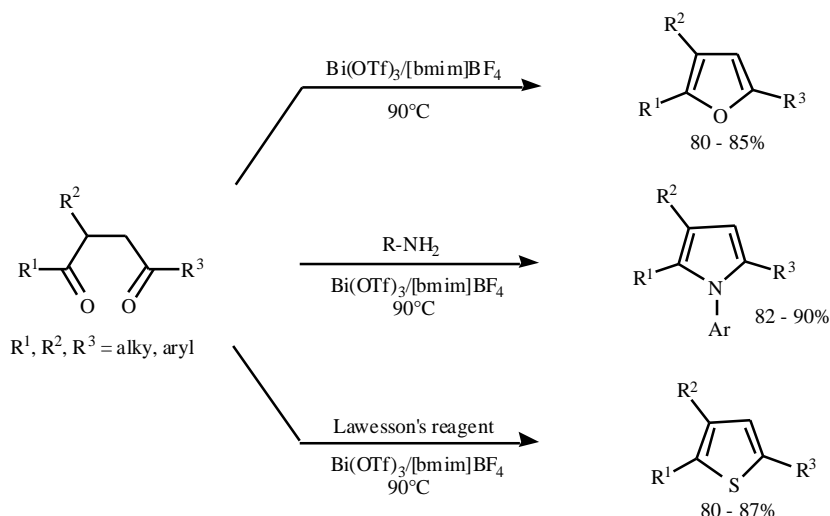
2.1.5 Synthesis of Heterocycles

Yadav *et al.* [44] described a novel and recyclable catalytic system based on $Bi(OTf)_3$ (5 mol%) immobilized in [bmim]BF₄ for the synthesis of furan, pyrrole and thiophene

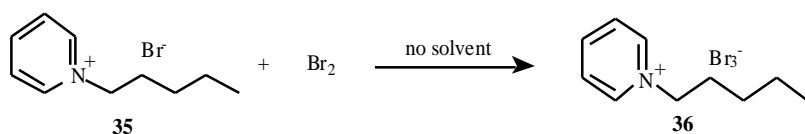
derivatives from 1,4-dicarbonyl compounds (Scheme 16). Various substituted 1,4-diketones underwent smooth cyclization affording the corresponding heterocycles in very good yields under mild conditions. It was observed that no cyclization occurred in the ionic liquid alone in the absence of the catalyst. The products were easily isolated by extraction with ether and the remaining catalytic system could be recovered and recycled in at least four subsequent reactions with a slight decrease in the yield (from 87% in the first cycle to 76% in the fourth cycle). This method proved to be very useful for using a cheap and easily prepared metal triflate and for avoiding strong acidic conditions, which could lead to decomposition of the heterocycles.

2.2 Task-Specific Ionic Liquids

Task-specific ionic liquids (TSILs) may be defined as ionic liquids in which a functional group is covalently tethered to the cation or anion (or both) of the IL [31n]. These ILs can then act as reagents or catalysts in organic reactions and some selected examples are shown below.



Scheme 16.



Scheme 17.

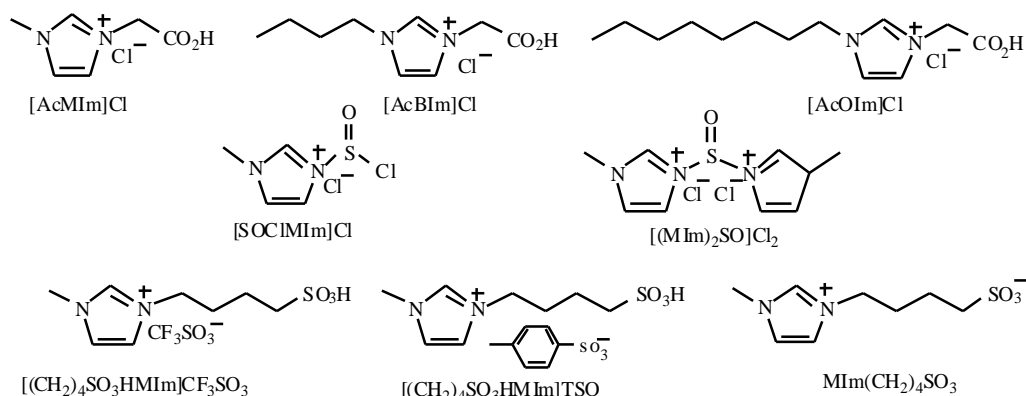


Fig. (6). Functional ILs used in acetalization reactions.

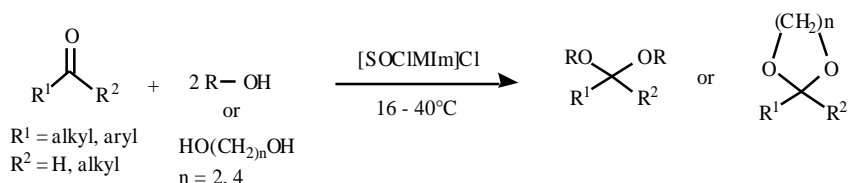
2.2.1 Bromination Reactions

Salazar and Dorta [45] reported the synthesis of pentylpyridinium tribromide (**36**) (Scheme 17), which is a proton free RTIL bromine analogue that does not have any measurable vapor pressure, and its use as a bromination reagent for ketones, aromatics, alkenes and alkynes. Compound (**36**) does not lose bromine even after prolonged heating at 70°C under high vacuum, which is very important because it eliminates toxic bromine vapors. After the reactions, compound (**35**) could be recovered and recycled with another equivalent of bromine to afford (**36**). The selectivities and yields of the reactions were very good. For instance, bromination of phenol at room temperature within 20 min gave exclusively *p*-bromophenol in 93% yield. Also, alkenes and alkynes were selectively dibrominated by (**36**). *E* alkenes gave exclusively the *trans* disubstituted compound whereas *Z* alkenes gave the *cis* isomers.

2.2.2 Acetalization of Carbonyls

The protection of carbonyl groups of aldehydes and ketones as acetals is very common in organic synthesis [46]. To achieve this goal in a green process, Li *et al.* [47] reported the synthesis and use of several acid functional ionic liquids based on $-\text{CO}_2\text{H}$, $-\text{SOCl}$ and $-\text{SO}_3\text{H}$, with two adjacent acid sites, including the N^+ in the imidazolium (Fig. (6)).

The authors observed that these two acid sites have a synergistic effect that might be the key factor for the high catalytic activity. Among the ionic liquids studied, $[\text{SOCIMIm}]\text{Cl}$ gave the best results in terms of conversion and selectivity in the model reaction between butyraldehyde and isoamyl alcohol and was further used in other acetalization reactions (Scheme 18). All reactions were performed at $16\text{--}40^\circ\text{C}$ for 2-23 h. Good results were obtained only in the reactions of ethanediol with aliphatic or aromatic



Scheme 18.

aldehydes (80-90% conversion) and ketones (70-98% conversion) except for cyclopentanone (44.5% conv.). When other alcohols such as butanediol, methanol and ethanol were used the results were not as good, which is a limitation of this process. The products were isolated by simple decantation and the catalytic activity of the IL was maintained after three cycles showing its great stability in the presence of water, which is formed during the reaction.

2.2.3 Hydrosilylation of Olefins

The development of a fluorous IL with characteristics of both conventional ILs and fluorous solvents (see section 4) was reported by van den Broeke et al. [48]. The idea was to design an IL capable of dissolving more efficiently apolar substrates so that it could be used in fluorous biphasic catalyst recycling. The air-stable imidazolium borate IL [bmim]B{C₆H₄(SiMe₂CH₂CH₂C₆F₁₃)-*p*}₄ (**37**) (Fig. (7)) was prepared by metathesis of [bmim]I and Na[B{C₆H₄(SiMe₂CH₂CH₂C₆F₁₃)-*p*]₄ in CH₂Cl₂. It is insoluble in water and very soluble in polar and to some extent in apolar organic solvents and its polarity is comparable to that of acetone and ether.

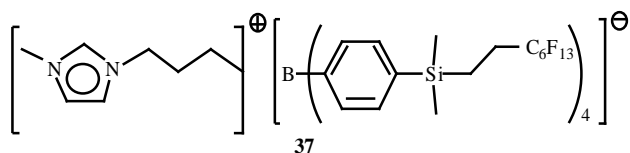
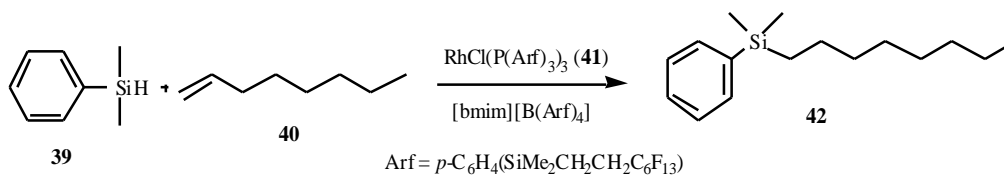
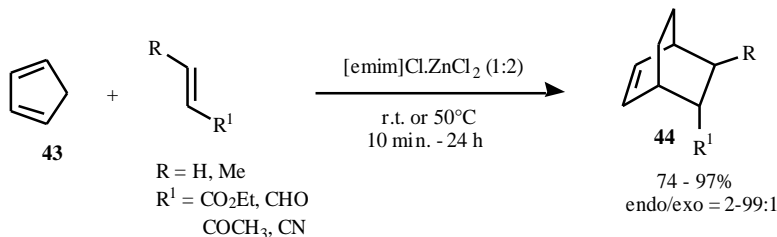


Fig. (7). A fluorous RTIL.

To verify the ability of (**37**) to function as a catalyst immobilization medium, rhodium-catalyzed hydrosilylation of 1-octene was studied. Common ILs such as [bmim]BF₄ and [bmim]PF₆ are not able to immobilize the catalyst



Scheme 19.



Scheme 20.

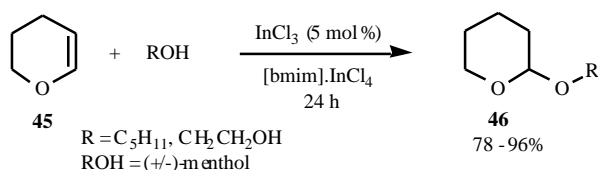
because it has a higher affinity for the organic phase rather than for the ionic phase. Whereas Wilkinson's catalyst ([RhCl(PPh₃)₃], **38**) was insoluble in (**37**), a fluorous derivative of (**38**) was conveniently soluble. Using (**41**), dimethylphenyloctylsilane (**42**) was obtained, with selective addition at C-1 of the alkene (Scheme 19).

The turnover number (TON) was significantly higher than corresponding values for the conventional system under monophasic conditions [49] and, according to the authors, this was at that time the most efficient combination for recycling of a Wilkinson-type catalyst in the hydrosilylation of olefins.

2.3 Lewis Acid-Containing Ionic Liquids

Another advantage associated with the use of ILs is that they can possess acidic properties when a Lewis acid is incorporated in their structures. The most common example of this class of ILs are the chloroaluminates [50], with composition AlCl₃.MCl, where M is the cation. These ILs are versatile agents because their nature can be easily altered from basic (M in excess) to acidic (AlCl₃ in excess) by manipulating their composition [51]. Several examples of their applications are known [52]. However, they are extremely reactive and moisture-sensitive reagents requiring strictly anhydrous manipulation, limiting their application as recyclable reaction media. Other ILs based on AuCl₃ [53], CuCl [54], UCl₆ [55], NbF₅ and TaF₅ [56] have also been reported.

Recently, some milder alternatives have been proposed which are air- and moisture-stable. For instance, organozincates were prepared and used in Diels-Alder reactions [57]. As for chloroaluminates, the Lewis acidity and the catalytic activity of Zn-containing ILs were dependent on the content of ZnCl₂ used. Better results were attained using a 1:2 molar ratio of [emim]Cl.ZnCl₂ (Scheme 20). After



Scheme 21.

extraction of the products with ether, followed by CHCl₃, the IL was almost quantitatively recovered and could be reused five times without loss in activity or yield. According to the authors, the reaction rate and *endo* selectivity were found to be far superior to those observed in traditional reaction media.

Other important members of this class of ILs are the organoindates [58, 59]. Dupont *et al.* [59] reported the synthesis of [bmim]InCl₄ and its use in tetrahydropyranylation of alcohols (Scheme 21). In this case, a 1:1 mixture of [bmim]Cl and InCl₃ was used and the resulting IL showed neutral properties. Therefore, the protection of the alcohols were carried out in the presence of InCl₃ (5 mol%). [bmim]InCl₄ was soluble in polar solvents such as dichloromethane, acetone and acetonitrile but almost insoluble in light alkanes and ether. Its solubility in water was around 15% wt% at room temperature. An interesting

property of this IL is its higher density and lower viscosity compared to other ILs. The authors pointed out that this might facilitate stirring and product separation. The yields of the *O*-protected alcohols were high and the recovered ionic liquid phase could be reused at least 4 times with reproducing results.

2.4 Chiral Ionic Liquids

Despite the ever increasing number of different known ionic liquids, only a few chiral ILs have been reported [60]. Some representative examples are shown in Fig. (8). Chiral ILs can be particularly attractive if one considers their potential applications to chiral discrimination, including asymmetric syntheses and optical resolution of racemates. Due to their high degree of organization one can expect a significant transfer of chirality in these solvents [31f]. Most reports deal with the synthesis and properties of the new ILs and only a few deal with their application in organic reactions. For instance, a chiral IL derived from a chiral vanadyl salen complex (57, Fig. (9)) was synthesized and used as catalyst in the cyanosilylation of benzaldehyde in conventional ionic liquids [61] (Table 3). The reactions showed good conversions except for [bmim]BF₄ and the cyanohydrin was obtained in low to modest *ee*'s.

The transfer of chirality of a chiral IL was also reported in the asymmetric Baylis-Hillman reaction [62] between

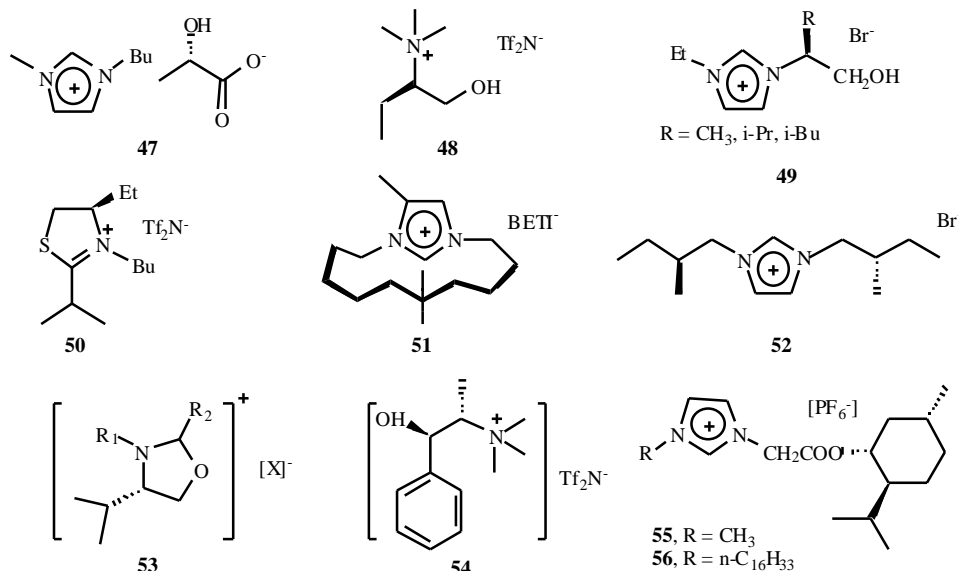
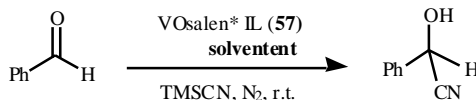
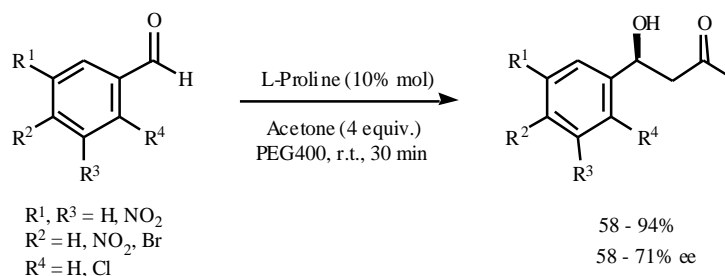


Fig. (8). Chiral ILs.

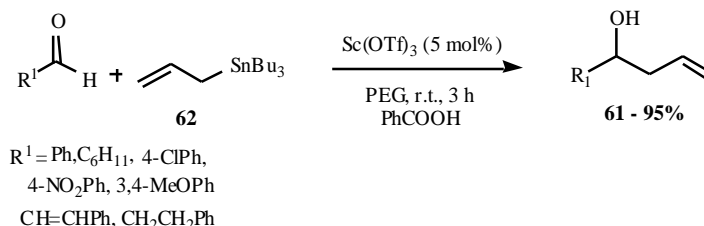
Table 3. Cyanosilylation of aldehydes in the presence of a chiral IL.



Entry	Solvent	Time (h)	Conversion (%)	ee (%)
1	[bmim]PF ₆	3	88	57
2	[bmim]Cl	24	95	41
3	[bmim]BF ₄	24	16	20



Scheme 24.



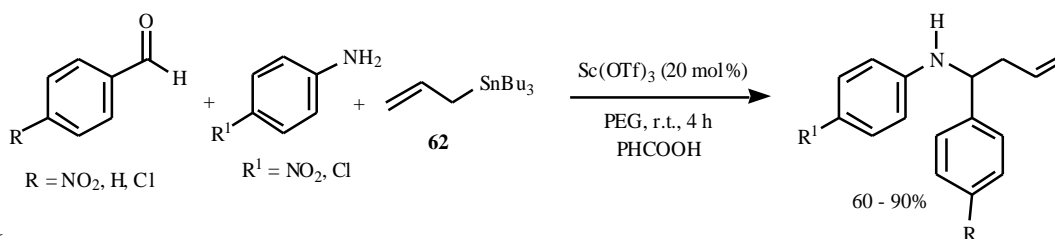
Scheme 25.

is relatively recent and it is usually used in low molecular weights (< 2000) because it is either liquid at room temperature or has a low melting point. Although less popular, PEG is commercially available and is much cheaper than ionic liquids but unlike the latter its properties can not be easily tuned. One of the major drawbacks in its use in organic reactions that also applies to ionic liquids is the inconvenience of using organic solvents to extract the products, even though scCO_2 (see section 5) can also be used in both cases.

Probably due to the higher popularity of other alternative solvents, especially ionic liquids, there are only a few examples in the literature that uses PEG as solvent in organic reactions, which will be disclosed in this review. To the best of our knowledge this is the first review describing the use of PEG as solvent in organic reactions.

3.1 Asymmetric Aldol Reaction

-Hydroxy carbonyl compounds are important intermediates in organic synthesis and the aldol reaction is one of the most efficient processes to obtain these compounds [70]. Chiral catalysts enable the efficient obtention of enantioenriched compounds. L-proline has gained attention recently for being environmentally friendly due to its nonmetallic character. In this respect, Chandrasekhar *et al.* [71] used PEG400 as solvent in the asymmetric aldol reaction between aromatic aldehydes and acetone using L-proline as chiral catalyst (Scheme 24). The aldol adducts were obtained in good yields and moderate enantioselectivities.



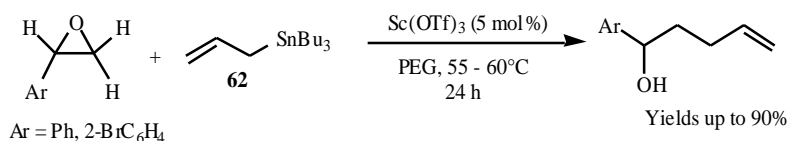
Scheme 26.

The use of aliphatic aldehydes (butyraldehyde and cyclohexanal) also gave good yields (90% and 65%, respectively) in greater enantiomeric excesses (71% and 84%, respectively), but the reaction times were increased (120 - 180 min). The aldol product was easily separated by stirring with anhydrous ether for 5 minutes, followed by decantation of the ether layer. This process was repeated twice. The remained PEG + L-proline system was reused for several runs without loss of activity of either the catalyst or the solvent. For instance, the reaction between *p*-nitrobenzaldehyde and acetone gave yields up to 94% and ee's up to 71% after 10 runs.

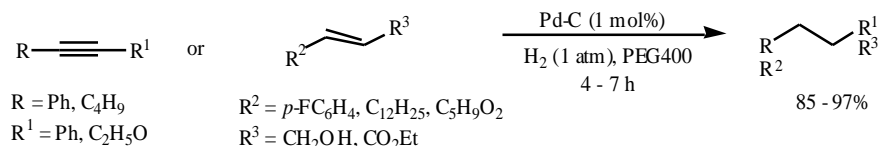
3.2 Allylation of Aldehydes, Aldimines and Ring Opening of Terminal Aromatic Epoxides

Lewis acid catalyzed allylation of aldehydes and aldimines represents an important carbon-carbon bond forming reaction in organic synthesis [72]. Choudary *et al.* [73] used scandium triflate as catalyst (5 mol%) in the allylation of aldehydes/amines and in the ring opening of epoxides in PEG as a recyclable solvent, furnishing the corresponding homoallylic alcohols (Scheme 25), homoallylic amines (Scheme 26) and bishomoallylic alcohols (Scheme 27), respectively, in high yields.

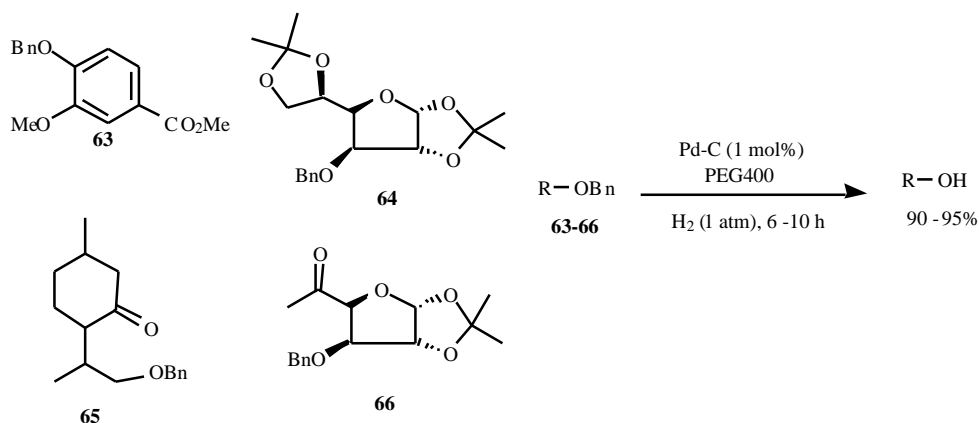
The authors pointed out that the PEG-scandium triflate catalytic system displays higher activity over the allylation reactions performed in aqueous medium under similar conditions [74]. Addition of water decreases the Lewis acidity of scandium triflate significantly, thus remarkably retarding the allylation reactions [75]. Furthermore, in water the system could be recycled only twice.



Scheme 27.



Scheme 28.



Scheme 29.

In the allylation of aldehydes and in the one-pot synthesis of homoallylic amines, when 1 equivalent of benzoic acid was employed as an additive the reaction times decreased. At completion of the reactions, the mixture was extracted with dry ether and the catalytic system could be reused for several times (8 cycles).

In the synthesis of bishomoallylic alcohols from terminal epoxides (Scheme 27), the regiochemistry of the ring opening of oxiranes was completely controlled with good yields using PEG as solvent. In traditional synthesis of bishomoallylic alcohols both regioisomers are present [76].

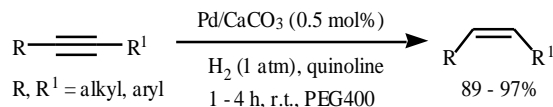
3.3 Hydrogenation and Hydrogenolysis

Chandrasekhar *et al.* [77] reported the use of PEG400 as the most efficient solvent system for complete hydrogenation (Scheme 28) and hydrogenolysis (Scheme 29) of various functionalities, virtually at room temperature and atmospheric pressure. Saturated compounds were obtained in high yields in both cases.

At the end of the reaction, dry ether was added, the mixture was stirred for 5 min and the reaction was allowed to settle for another 5 min. Cooling of the contents in an acetone dry ice bath led to precipitation of solid PEG and catalyst. The organic phase was then removed by simple decantation. By using this protocol, the solvent (PEG) and catalyst (Pd/C) could be recycled and reused with retention of efficiency and activity over four runs.

The same authors reported a practical and efficient protocol for the partial reduction of triple bonds to *cis*-

olefins using Lindlar's catalyst in PEG400 [78] (Scheme 30). The solvent and the catalyst could be reused for 3-5 times without significant loss in activity or yields. The reactions proved to be regioselective in that hydrogenation sensitive groups such as benzyloxy and olefin survived to the conditions employed. According to the authors, the efficiency of the sequence can be attributed to the high solubility of hydrogen in PEG compared to conventional solvents. Furthermore, Pd is efficiently retained in PEG by solidification during extraction of the products with ether.

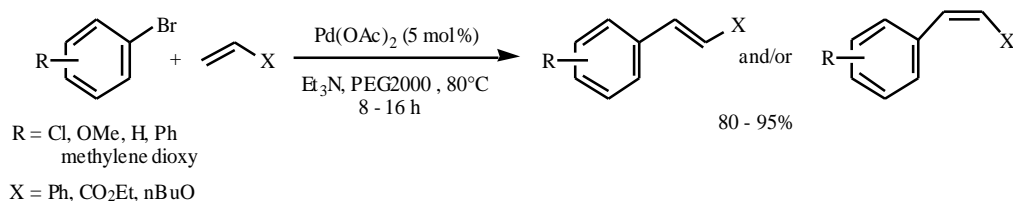


Scheme 30.

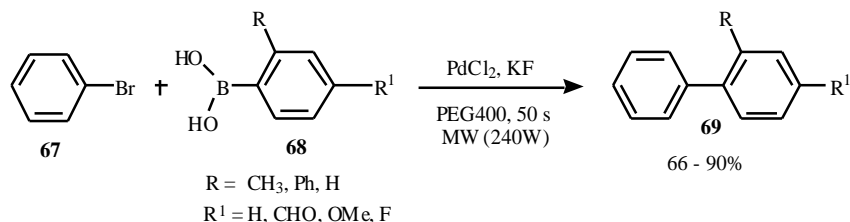
3.4 Heck Reaction

As already mentioned, the Heck reaction is an important process in C-C bond formation [19]. Chandrasekhar *et al.* [79] reported the application of PEG having molecular weight 2000 (or lower) as an efficient solvent for Heck reaction (Scheme 31). At the end of the reaction, the mixture was allowed to cool to room temperature, diluted with dry ether, and cooled to 0°C to precipitate out PEG and Pd(OAc)₂ that were reused for 4 runs without loss in yields, regio- and stereoselectivities.

In Heck reactions with electron-rich olefins, it was observed that the *E* isomer was majoritary, whereas when



Scheme 31.



Scheme 32.

electron-deficient olefins were employed only a single isomer was formed. In both cases, the products were easily obtained in high yields. The stereo- and regioselectivities were different from those with conventional organic solvents and ionic liquid media. For comparison, in organic solvents mixtures of products were obtained with varying ratios [80] and when ionic liquids were used some different results were observed [81]. It was postulated that PEG not only acts as an efficient solvent medium but also as a phase transfer catalyst for smooth C-C bond formation.

3.5 Suzuki Cross Coupling Reaction [16]

Nambodiri and Varma [82] reported the preparation of various substituted biaryls from substituted aromatic bromides and aromatic boronic acids in PEG400 using microwave for a few seconds (Scheme 32). The reaction could also be conducted in 15 minutes using an alternative-heating medium (oil-bath at 100°C) with similar yields.

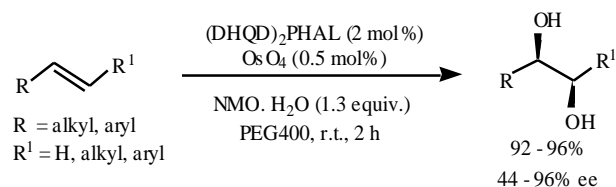
Potassium fluoride is the most convenient base for this reaction because the use of other bases required water as cosolvent for their dissolution which not only reduces the solubility of the aromatic bromide but also increases the self condensation of boronic acids. The system was recycled with good yields for 3 runs and yields were higher for aromatic rings bearing electron-withdrawing groups.

3.6 Asymmetric Dihydroxylation of Olefins

The osmium-catalyzed asymmetric dihydroxylation of olefins using cinchona alkaloids-derived ligands is recognized as a very efficient method for the preparation of a wide range of enantiomerically pure vicinal diols [83].

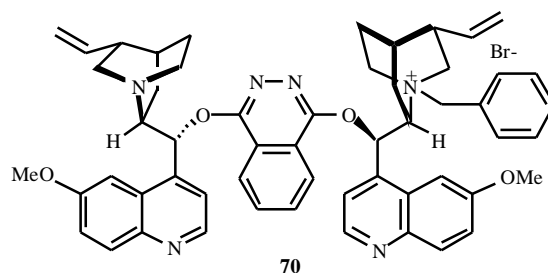
Chandrasekhar *et al.* [84] were the first to report the asymmetric dihydroxylation of olefins in PEG400 as a recoverable and reusable system in which the reactions are rapid (2 h) and high yielding, using very low concentrations of OsO₄ (0.5 mol%) (Scheme 33). For instance, using *trans*-stilbene as substrate, the product was obtained in 94% ee and 95% chemical yield. For comparison, the dihydroxylation of a substrate with an internal double bond usually requires a longer reaction period (up to 24 h) and addition of methane sulfonamide. The enantioselectivities were high (> 90% ee) in all but one case (1-tetradecene).

After extraction with ether and isolation of the products, the recyclability of the catalysts was tested and it was observed that no further addition of OsO₄ was necessary for the reaction to occur even after 5 runs. In contrast, to keep the high ee values, an extra amount of the ligand (0.25-0.5 mol%/run) had to be added. Thus it was suggested that PEG works as a natural encapsulation medium for OsO₄ and for the ligand to some extent.

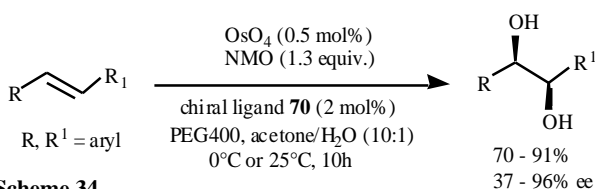


Scheme 33.

More recently, Jiang *et al.* [85] reported the synthesis of the mono-quaternized bis-*cinchona* alkaloid ligand (**70**) (Fig. (10)) and its use in asymmetric dihydroxylations of olefins in PEG400 using osmium tetroxide (Scheme 34). NMO was used as co-oxidant in the asymmetric dihydroxylations giving products in high yields (70-91%) and high enantioselectivities (78-95% ee).

Fig. (10). Bis-*cinchona* alkaloid ligand.

The ligand combines ionic character and high polarity which renders it a greater recyclability. The authors found out that the enantioselectivity was increased by slow addition of the olefins during a period of 10 h in a mixture of



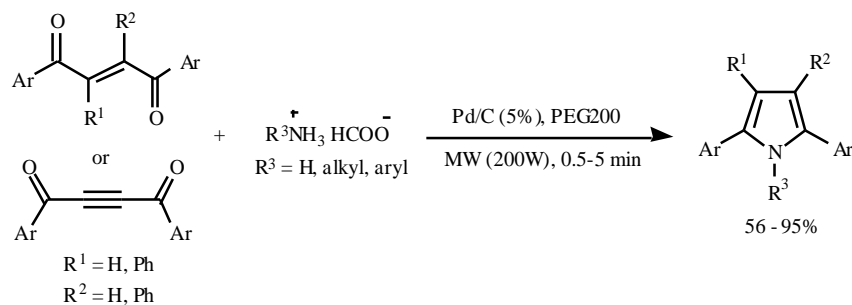
Scheme 34.

acetone/ H_2O (10:1) combined with PEG as the medium, at low temperatures (0°C). Both the solvent and the catalysts could be recycled five times without any further addition of OsO_4 and ligand. The yields and enantioselectivities were about the same after the third run but dropped a little after the fifth run. The same reactions were realized in the ionic liquid $[\text{bmim}]\text{PF}_6$ with similar results. When the reactions were finished, the product was extracted with ether. The authors pointed out that leaching of the OsO_4 and the chiral catalyst was inevitable during extraction of the diol product with ether, because the ligand can dissolve in ether to some extent and bring out some osmium by complexation.

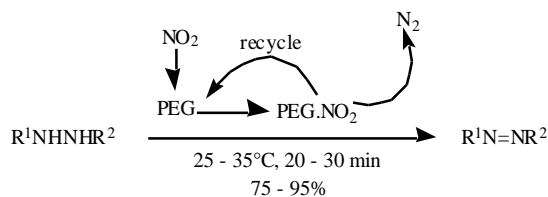
3.7 Synthesis of Polyarylpyrroles

Rao *et al.* [86] described the synthesis of several pyrrole derivatives with multiple aryl substituents in a one-pot reaction from ynediones and enediones using ammonium and alkylammonium formates in the presence of palladium, PEG200 as solvent and microwave promoted reactions (Scheme 35).

To achieve the one-pot synthesis of 2,5-diaryl-1-*H*-pyrroles from enediones, first the enediones were reduced to 1,4-diones in the initial transformation via palladium catalyzed transfer hydrogenation followed by amination-cyclization by utilizing *in situ* generated ammonia in a domino fashion. The one-pot synthesis of 2,5-disubstituted pyrroles from ynediones was achieved by a complete

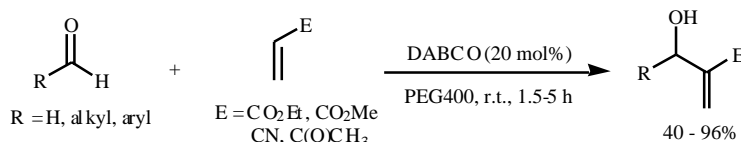


Scheme 35.



$\text{R}^1 = 4\text{-F-Ph, 3-Cl-Ph, 4-Br-Ph, 4-Me-Ph, CO}_2\text{CH}_2\text{CCl}_3, \text{CO}_2\text{Et, CO}_2\text{Me, 4-OMe-Ph-NC}_2\text{O}_2$
 $\text{R}^2 = \text{Ph, 4-Me-Ph, CO}_2\text{CH}_2\text{CCl}_3, 4\text{-Cl-Ph, 4-NO}_2\text{-Ph}$

Scheme 36.



Scheme 37.

hydrogenation followed by an amination-cyclization reaction. It appears that the reactivity of ynediones towards the formation of pyrrole derivatives is similar to enediones.

The reactions under microwave conditions were very fast. For comparison, the formation of 2,5-diphenyl-1-*H*-pyrrole was complete in 30 s whereas in refluxing methanol it required 30 min. Furthermore, the yields of the pyrrole derivatives with electron donating groups were comparatively better under the conditions employed in this study.

3.8 Synthesis of Azo Compounds

Qiao *et al.* [87] reported selective oxidation reactions of hydrazo, hydrazide semicarbazides and urazole derivatives to furnish azo compounds under mild conditions using the complex $\text{PEG}\cdot\text{NO}_2$, which is an efficient, clean and moderate oxidant (Scheme 36). PEG400 is able to absorb NO_2 (up to 97% absorption) forming $\text{PEG}\cdot\text{NO}_2$, which liberates NO_2 gradually in the course of the reaction with other organic compounds. PEG could be recovered and recycled after the oxidation process by dehydration under reduced pressure.

The ideal temperature was found to be $25\text{-}35^\circ\text{C}$ and in the absence of PEG the reaction of NO_2 proceeded vigorously at 0°C , but gave low yields of azo compounds with aromatic nitration being a side reaction. Using gas-chromatography the tail gas was analyzed and found to be composed of N_2 and NO in a ratio of 296:1, thus showing a very little secondary pollution.

3.9 Baylis-Hillman Reactions

Chandrasekhar *et al.* [88] reported that Baylis-Hillman reactions [62] of various unreactive aldehydes with activated olefins proceeded very fast using PEG400 as a recyclable solvent medium (Scheme 37). The original conditions for

this reaction suffer from very long reaction times (up to a week for 50% conversion), low yields and high concentration of catalyst. In contrast, when performed in PEG the reactions were complete within a few hours at room temperature, using only 20 mol% of DABCO and the Baylis-Hillman adducts were obtained in very good yields by simple extraction with ether. The remaining reaction medium consisting of PEG and DABCO could be reused 4 times without the need to add more DABCO, but extended reaction times were necessary after each run to obtain similar yields of the products (24 h in the fourth run for a yield of 89%). Aromatic, aliphatic and even conjugated aldehydes were used and the reaction of *p*-methoxybenzaldehyde with methyl acrylate was the only case in which the yield was low (40%).

4. PERFLUORINATED (FLUOROUS) SOLVENTS

The term fluoruous was firstly introduced by Horváth and Rábai [89] analogously to aqueous or aqueous medium. More recently, fluoruous compounds (and many other terms in fluoruous chemistry) were defined by Gladysz and Curran [90] as being compounds that are highly fluorinated and based upon sp^3 -hybridized carbons. Fluoruous (perfluorinated) solvents as perfluoroalkenes, perfluoralkyl ethers and perfluoroalkylamines are generally chemically benign and environmentally-friendly for being non-toxic (unlike the freons), nonflammable, thermally stable, recyclable, and for their high ability to dissolve oxygen gas, which is an advantage used in medical technology. In fluoruous solvents or fluids the fluorine atoms replace the hydrogens (C-F bond) [91].

Fluoruous fluids have very unusual properties, such as high density and high stability (due mainly to the stability of the C-F bond), low solvent strength, and extremely low solubility in water and organic solvent [92], although they are miscible at higher temperature. The poor solubility of fluorinated solvents can be explained based on their low surface tensions, low intermolecular interactions, high densities and low dielectric constants.

Fluoruous phase reactions have a slightly different green approach in comparison to other alternative solvents. For instance, supercritical fluids and ionic liquids can be seen basically as solvent replacement systems. Although fluoruous phase systems are solvents, they are not simply solvent replacements. Due to their extremely nonpolar characteristics they are not suitable for most organic reactions and tend to be used in conjunction with a traditional organic solvent (or some sort of immiscible solvent) to form a biphasic system [2].

In fluoruous biphasic system (FBS) a highly fluoruous soluble reagent/catalyst resides in the fluoruous phase whereas the starting materials are dissolved in an immiscible solvent phase, which can be either an organic solvent, water or a non-organic solvent [93]. These two distinct layers are made homogeneous upon heating and the reactants are put into contact and the reaction takes place. The layers separate again when the temperature is lowered and the products remain in the organic layer while the catalyst or any unreacted fluoruous reagent stays in the fluoruous phase. This allows an easy separation of products and recycling of the catalysts, without the need for using organic solvents for

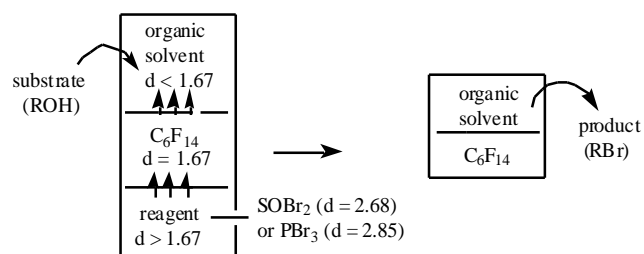
extraction. Overall FBS combines the advantages of a single-phase system with the convenience of biphasic product separation [94].

For these reasons, the fluoruous biphasic system shows appealing general feature, such as employment of non-toxic, reusable perfluorocarbons and easy separation of catalyst from reactants and products. However, the manufacture of these fluoruous solvents is not so simple generally requiring the use of huge amounts of high volatile organic solvents and toxic reagents such as fluorine gas and HF.

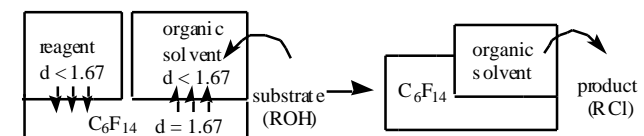
In 2002, an issue of *Tetrahedron (Tetrahedron Symposium-In-Print)* was entirely devoted to fluoruous chemistry and for this reason this review will focus on more recent examples of fluoruous techniques, especially those involving FBS.

4.1 Chlorination and Bromination of Alcohols

Ryu *et al.* [95] reported the bromination of alkenes and the dealkylation of aromatic ethers and Nakamura *et al.* [96] reported the chlorination and bromination of alcohols using a new and interesting method which they called Phase-Vanishing (PV) reactions. PV is based upon the density of three layers: organic (top), fluoruous (middle) and organic and inorganic (bottom). Heavier reagents ($d > 1.67$) are transported from the bottom layer to the top layer ($d < 1.67$) through the fluoruous layer (C_6F_{14} , $d = 1.67$) (Scheme 38). This technique was further extended to lighter reagents with the introduction of a triphasic U-tube system in which a lower fluoruous phase serves as a phase-screen to separate the upper reagent and organic phases ($d < 1.67$) (Scheme 39). The reagent is transported through the fluoruous phase to react with the substrate in the organic phase and vanishes as it is consumed.



Scheme 38.

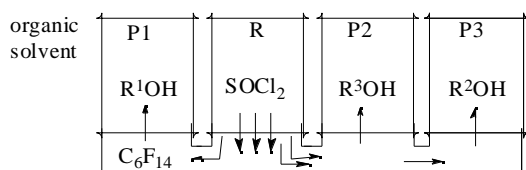
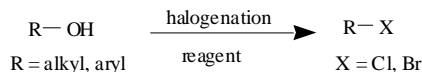
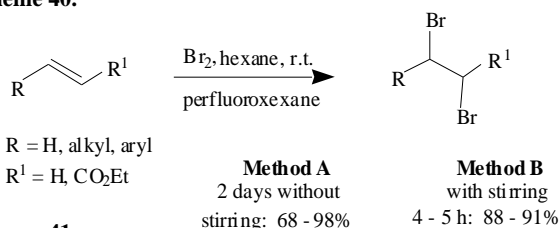


Scheme 39.

The bromination of alcohols was investigated by the PV method using thionyl bromide ($d = 2.68$) and phosphorus tribromide ($d = 2.85$) as heavier reagents whereas the chlorination reactions were realized in the triphasic U-tube system using thionyl chloride ($d = 1.63$) and phosphorus trichloride ($d = 1.57$) as lighter reagents. In both cases, perfluorohexane (C_6F_{14}) was used as the fluoruous solvent and toluene as the organic solvent (Table 4).

Table 4. Halogenation of alcohols in fluoruous systems.

Entry	Halogenation reagent	Method	Time (h)	Yield (%)
1	SOBr ₂	PV	6-22	50-99
2	PBr ₃	PV	12-24	34-96
3	SOCl ₂	U-tube	4-20	80-98
4	PCl ₃	U-tube	12-50	28-86

**Scheme 40.****Scheme 41.**

The isolation of the products was very simple (decantation of the toluene layer) and the alkyl halides were obtained in good yields especially with SOBr₂ (entry 1) and SOCl₂ (entry 3). PCl₃ was also effective but in some cases the yields were low (entry 4).

Next, a parallel synthesis using the triphasic U-tube system was developed using a multislit apparatus in which the fluoruous phase acts as a phase-screen layer (Scheme 40). Each toluene solution of three different alcohols was added to the fluoruous phase (C₆F₁₄) from each slit (P1-P3), and thionyl chloride was floated on the slit R. SOCl₂ was then transported through the fluoruous layer into the reactant layer of each slit (P1-P3). The reactions were complete in 24 h and the corresponding chlorides were obtained in good yields (70-99%) without any contamination.

The brominations of alkenes were carried out using bromine as the bottom layer, perfluorohexane as the fluoruous solvent and hexane as the upper layer (Scheme 41). Both

cyclic and aliphatic alkenes underwent bromination to give the corresponding dibromides in good yields. The completion of the reaction could be easily monitored by the disappearance of the bromine phase (2 days without stirring or 4-5 h with gentle stirring). Cyclic alkenes gave only the *trans*-1,2-dibromides while disubstituted aliphatic alkenes gave a mixture of stereoisomers.

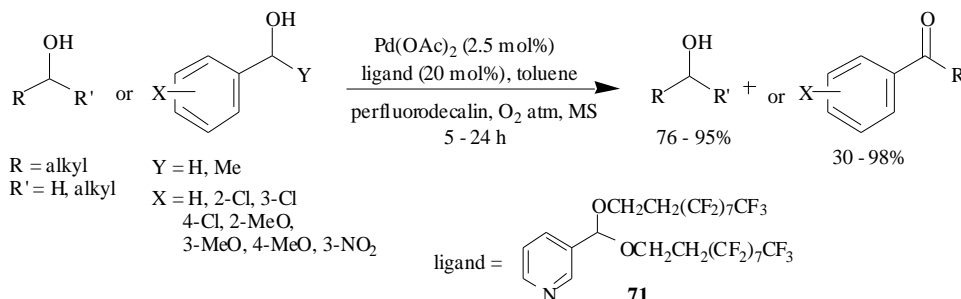
The authors pointed out that reagent transportation and extrusion of organic products were superior for fluoruous media as compared to water or acetonitrile. These two solvents also create a three-phase system with bromine and hexane and were much less effective in the bromination of cyclohexene. For comparison, the reaction in water required stirring and furnished the product in 54% yield (3% without stirring) whereas when acetonitrile was used a great amount of the product dissolved in it.

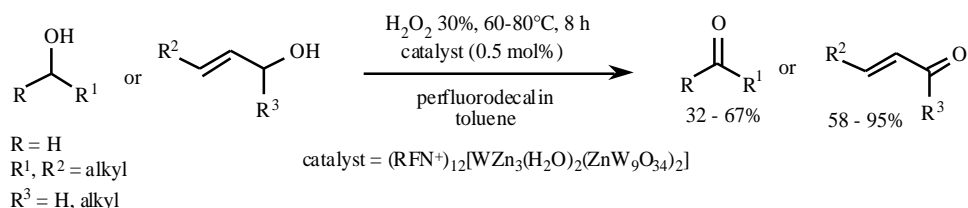
The highly exothermic demethylation of aromatic ethers was accomplished using boron tribromide as the heavier layer. In this case, water and acetonitrile were not considered as phase screens because BBr₃ is highly moisture sensitive. The ethers were dissolved in CH₂Cl₂ and the triphasic system was kept overnight at room temperature. The corresponding phenols were obtained in 76-98% yield.

4.2 Oxidation Reactions

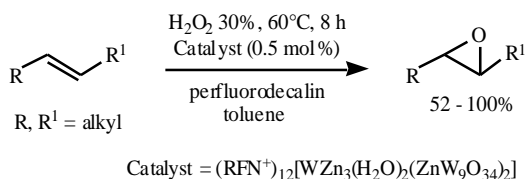
Nishimura *et al.* [97] used a fluoruous biphasic system (FBS) composed of toluene and perfluorodecalin in the oxidation of various benzylic and aliphatic alcohols (Scheme 42). The fluoruous phase containing the active palladium species was easily separated and could be reused 5 times without significant loss of catalytic activity.

Four different perfluoroalkylated-pyridine derivatives were prepared and used to evaluate the Pd(OAc)₂-catalyzed oxidation of alcohols. The best ligand in the oxidation of alcohols was prepared by a simple one-step acetalization of a

**Scheme 42.**



Scheme 43.



Scheme 44.

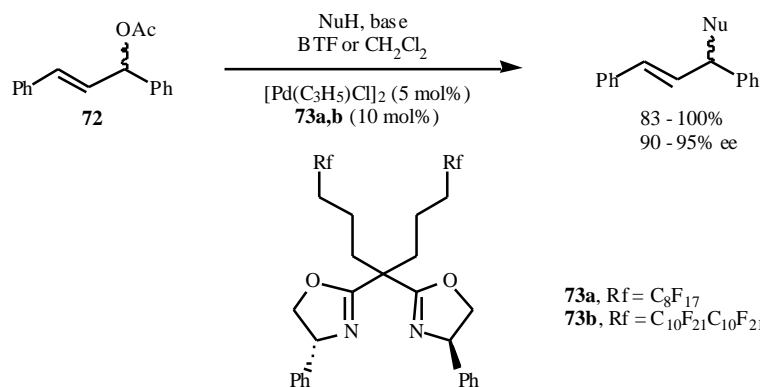
pyridine derivative (**71**, Scheme 42). In the oxidation of aliphatic alcohols a longer reaction time was generally required.

Maayan *et al.* [98] reported the oxidation of aliphatic alcohols and alkenols (Scheme 43) and the formation of epoxides (Scheme 44) using fluorosoluble biphasic catalysis. The oxidation with aqueous hydrogen peroxide was performed using perfluorinated quaternary ammonium salts of polyoxometalates as catalysts (0.5 mol%) where the polyanions are [WZnM₂(H₂O)₂(ZnW₉O₃₄)₂]¹²⁻ with M = Mn(II), Zn(II) and the cationic species is [CF₃(CF₂)₇(CH₂)₃]₃N⁺ or (R_FN⁺).

In this fluorosoluble biphasic catalysis, the fluorosoluble layer was a perfluorodecalin and as the organic layer was used ethyl acetate or toluene, which are insoluble in the fluorosoluble phase at room temperature, but dissolves in it at 60°C. The products were smoothly obtained in moderate to good yields in all cases and after separation of the fluorosoluble phase (which contains the catalyst) it could be reused three more times without significant loss in activity.

4.3 Asymmetric Allylic Alkylation

Bayardon and Sinou [99] reported the use of fluorosoluble chiral bisoxazolines (**73a,b**) in the asymmetric palladium-catalyzed alkylation of the allylic substrate (**72**) (Scheme 45). The products were obtained in high yields and enantioselectivities either in CH₂Cl₂ or in benzotrifluoride



Scheme 45.

(BTF). These results are comparable to those obtained using non-fluorinated bisoxazolines in usual organic solvents [100].

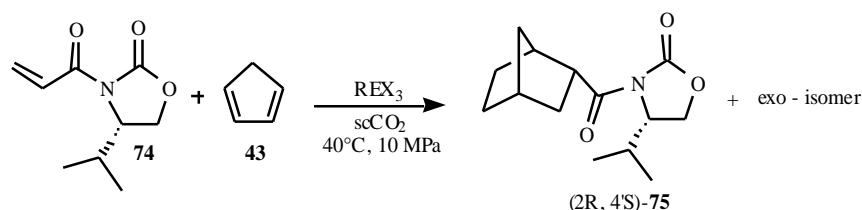
All attempts to recycle the palladium catalyst using a two-phase system CH₂Cl₂-FC-72 were unsuccessful, due to precipitation of black palladium. However, after evaporation of CH₂Cl₂ and extraction of the residue with FC-72, the ligand was recovered in 70% yield after evaporation of the fluorosoluble solvent and was reused in a new alkylation reaction with similar results.

5. SUPERCRITICAL FLUIDS

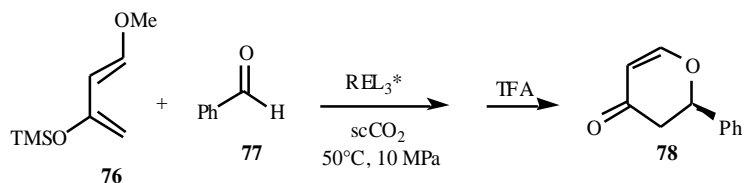
A supercritical fluid (SCF) is defined as a substance above its critical temperature (T_c) and critical pressure (P_c). The properties of an SCF lie between those of its liquid and gas phases. These properties can be specifically tuned by varying the pressure and the temperature.

The most popular SCF is carbon dioxide (scCO₂). The critical point of CO₂ is at 73 atm and 31.1°C, which are conditions easily achieved in the laboratory. Other supercritical solvents are not as useful due to the somewhat forcing conditions to achieve the critical point. For example, water has a critical point of 218 atm and 374°C. However, some recent examples of reactions in this medium have been reported [101].

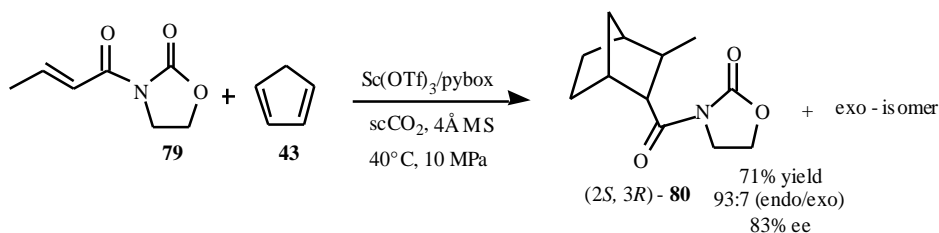
The advantages related to the use of scCO₂ are numerous and were clearly addressed in a recent article [102]: CO₂ is non-flammable and less toxic than most organic solvents; it is relatively inert towards reactive compounds and is a natural, unregulated solvent, with high availability; it can be easily removed by depressurization, which renders it an easy separation from the products of a reaction. Other advantages include high gas solubility, weak solvation, high diffusion rates and good mass transfer. Furthermore, the selectivity of a reaction can be dramatically changed when conducted in a supercritical fluid as compared to traditional organic solvents.



Scheme 46.



Scheme 47.



Scheme 48.

Some disadvantages associated with the use of scCO_2 as solvent are: it is reactive towards powerful nucleophiles; specialized and expensive equipment is needed to achieve critical conditions; also, CO_2 has low dielectric constant, which can imply poor solvent power. Another drawback is that CO_2 behaves like a hydrocarbon solvent and for this reason reactants and/or catalysts are often not very soluble in it.

Recent reviews describing the use of supercritical fluids in catalysis (homogeneous [103], heterogeneous [104] and biocatalysis [105]) and disclosing some of their applications [106] have been published. Also of great importance are the reviews of Oakes *et al.* [107], which deals with the use of SCFs in synthetic organic chemistry, and that of Prajapati *et al.* [108] which describes the applications of SCFs in carbon-carbon bond formation. The present review will focus on literature examples from 2003 which were not cited in the above mentioned reviews.

5.1 Asymmetric Diels-Alder Reaction

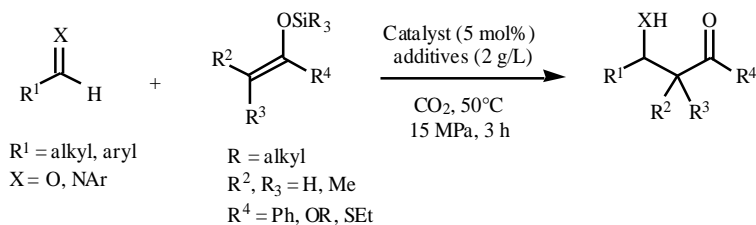
Fukusawa *et al.* [109] described the use of scCO_2 in asymmetric Diels-Alder reactions catalyzed by rare earths complexes. In this work, Evans' acryloyl oxazolidinone (**74**) was reacted with cyclopentadiene (**43**) in scCO_2 in the presence of a catalytic amount (10 mol%) of rare earths salts (REX_3) (Scheme 46).

The catalyzed reaction in scCO_2 proceeded smoothly and more quickly than in CH_2Cl_2 to give mainly the *endo* product in high yield with moderate to good diastereoselectivities. For comparison, $\text{La}(\text{OTf})_3$ gave 59-62% de of the adduct in 84% yield in scCO_2 , while it gave 38-42% de in 92% yield in CH_2Cl_2 . When the reaction was carried out without a solvent, the diastereoselectivity was lower (42% de) than that in

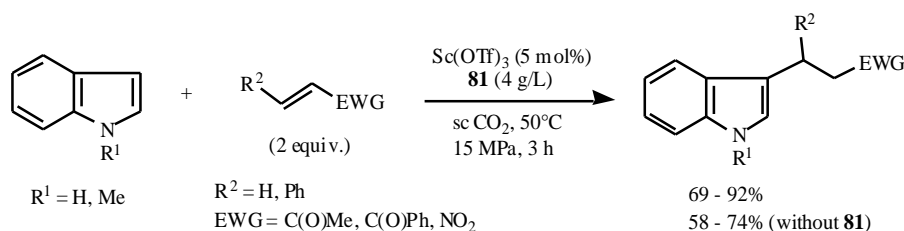
scCO_2 demonstrating the improvement in diastereoselectivity when scCO_2 was used as solvent. Almost the same selectivity was obtained when a stoichiometric amount of $\text{La}(\text{OTf})_3$ was used indicating that only dissolved $\text{La}(\text{OTf})_3$ could work as a catalyst. It was observed that the reaction diastereoselectivity was almost independent on the CO_2 density, but the de value was higher in the near critical region (40°C , 7.8 MPa).

Next, the rare earth-catalyzed reaction between Danishefsky's diene (**76**) and benzaldehyde (**77**) was investigated using chiral ligands as catalysts (Scheme 47). The yield of the product was significantly improved as compared to the reaction in CH_2Cl_2 (67% vs. 22%) using (+)- $\text{Eu}(\text{hfc})_3$ but the enantioselectivity was still low though it was increased (22% vs. 12% ee). The reaction did not proceed in the absence of a catalyst. The use of (+)- $\text{Yb}(\text{hfc})_3$ and (+)- $\text{Sc}(\text{hfc})_3$ improved the enantioselectivity to 35-38% ee. The use of other chiral ligands such as pybox gave poor results either in CH_2Cl_2 or in scCO_2 .

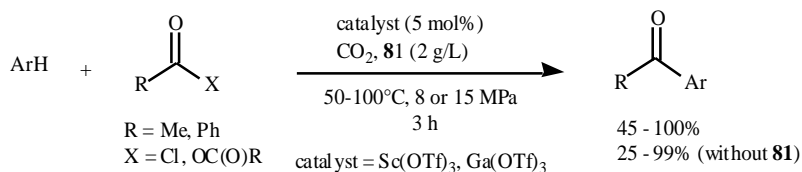
In the same study, a remarkable result was obtained when 3-crotonyl-2-oxazolidinone (**79**) was reacted with cyclopentadiene (**43**) using pybox as chiral catalyst (Scheme 48). The value of ee% of compound (**80**) was as high in scCO_2 as in CH_2Cl_2 even though in the former the reaction was carried out at a higher temperature (40°C vs. 0°C). The combination of $\text{Sc}(\text{OTf})_3$ and pybox afforded the *endo*-($2S, 3R$)-**80**-product (*endo/exo* = 93:7) in good yield with high enantioselectivity (83% ee). Noteworthy is the tremendous reduction in the reaction time in scCO_2 (0.5 h vs. 18 h in CH_2Cl_2 for completion). In this respect, a recent detailed physical-chemical study was published in which the reaction rate measured in scCO_2 for the Diels-Alder reaction between 9-hydroxymethylanthracene and *N*-ethylmaleimide

Table 5. Aldol and Mannich reactions in the CO₂ – PEG/fluorosurfactant system.

Entry	X	Pressure (MPa)	Catalyst	Additive	Yield (%)
1	OH	8	Sc(OTf) ₃	PEG(OMe) ₂	48-96
2	OH	8	Sc(OTf) ₃	81	87-99
3	NAr	15	Yb(OTf) ₃	PEG	63-89
4	NAr	15	Yb(OTf) ₃	81	61-97



Scheme 49.



Scheme 50.

was 25 times faster than that measured in acetonitrile [110]. This acceleration is attributed to strong solvophobic interactions.

It was also observed that higher enantioselectivities were achieved when 4Å molecular sieves were used. The authors claimed that the sieves might promote coordination of the oxazolidinone group to the scandium metal center. Another observation is that the enantioselectivity was almost independent on the CO₂ pressure (density).

5.2 Reactions in scCO₂ Using Additives

To overcome the problem of low solubility of reactants in CO₂, Komoto and Kobayashi [111] reported the use of PEG derivatives and perfluoroalkanes as surfactants in several organic reactions in scCO₂. These compounds facilitate the formation of emulsions in which substrates and catalysts are concentrated and therefore the reactions can proceed faster.

For instance, the CO₂-PEG system was effective for scandium-catalyzed aldol reactions and ytterbium-catalyzed Mannich reactions (Table 5). Various aldehydes/imines and silicon enolates derived from esters, thioesters and a ketone were reacted and the corresponding aldol/Mannich products were obtained in good yields. In all cases studied, the *anti* isomer was slightly favored (1.2-3:1). Better yields were obtained when 1-dodecyloxy-4-heptafluorooctylbenzene (**81**) was used as additive. It was also observed that the length of the perfluoroalkyl chains of the catalysts and the

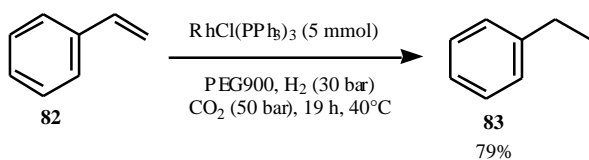
surfactants influenced the yield of the products, i.e. the longer the alkyl chains were the lower the yields.

Other factors that had a direct influence on the yields were the CO₂ pressure, the concentration of the additives and the average molecular weight of PEG. In the Mannich reactions, the highest yields were obtained at 15 MPa using PEG400 or perfluoroalkane (**81**) whereas in the aldol reactions better results were attained at 8 MPa using PEG(OMe)500 or perfluoroalkane (**81**). In both reactions the ideal concentration of the additives was 2 g/L. Fluorosurfactant (**81**) was recovered quantitatively from the reaction mixture by simple extraction with a fluorosolvent (FC-72) and the Lewis acid catalyst was also recovered and reused without loss of activity. These same reactions were also performed in water with very good results [7c,d,k].

The CO₂-fluorosurfactant system was also successfully applied to the Friedel-Crafts alkylation of indoles and to the acylation of aromatic compounds. In this system, alkylated indoles were obtained in higher yields as compared to the same reactions without the fluorosurfactant or with PEGs (Scheme 49).

In the acylation reactions, either acid anhydrides or acyl chlorides worked well to give the corresponding aromatic ketones (Scheme 50). Acetylation and benzylation products were obtained in good yields.

The combination of PEG and scCO₂ for biphasic catalysis was applied to the RhCl(PPh₃)₃-catalyzed



Scheme 51.

hydrogenation of styrene to ethyl benzene without the use of volatile or halogenated solvents [112] (Scheme 51). Homogeneous catalyzed hydrogenation could be performed in the molten PEG ($M_n = 900$), followed by extraction of the product with scCO_2 . The PEG phase which contains the catalyst could be used repeatedly for hydrogenation without addition of further catalyst or PEG.

CONCLUDING REMARKS

The achievement of green reaction media has posed many challenges to the scientific community and the methodologies and techniques presented herein clearly demonstrate the enormous potential and benefits of the concepts of Green Chemistry when applied to organic synthesis. Many options are available now and each one has its own peculiarities with advantages and drawbacks. The choice for one specific green solvent in which to carry out an organic reaction will depend on economical aspects as well as on the intrinsic characteristics of a given reaction and/or solvent. With the growing efforts of researchers in this area, industries worldwide are already investing in green technologies, thus contributing to reduce the harmful effects of conventional organic solvents on the environment. We believe that the concepts discussed in this review are undoubtedly having a huge impact on the way one thinks about chemistry nowadays and for the future many new issues will come.

ACKNOWLEDGEMENT

We wish to specially acknowledge all the researchers whose work is described in this review for their contribution to the development of green reaction media as a way of reducing the use of toxic and volatile organic solvents.

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