

Cite this: *Chem. Commun.*, 2011, **47**, 6208–6227

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FEATURE ARTICLE

Glycerol and derived solvents: new sustainable reaction media for organic synthesis**Alba E. Díaz-Álvarez, Javier Francos, Beatriz Lastra-Barreira, Pascale Crochet and Victorio Cadierno****Received 31st January 2011, Accepted 4th March 2011*

DOI: 10.1039/c1cc10620a

The rapid growth of the biodiesel industry has led to a large surplus of its major byproduct, *i.e.* glycerol, for which new applications need to be found. Research efforts in this area have focused mainly on the development of processes for converting glycerol into value-added chemicals and its reforming for hydrogen production, but recently, in line with the increasing interest in the use of alternative greener solvents, an innovative way to revalorize glycerol and some of its derivatives has seen the light, *i.e.* their use as environmentally friendly reaction media for synthetic organic chemistry. The aim of the present *Feature Article* is to provide a comprehensive overview on the developments reached in this field.

Introduction

Petroleum is the main energy source in the world, but its availability is limited and the search for new renewable energy sources is of prime interest.¹ Biodiesel, composed of long-chain monoalkyl esters of fatty acids derived from vegetable oils or animal fats, is the most realistic alternative to effectively reduce our current dependence on fossil fuels for transportation in the short-term.² Production of biodiesel is a relatively simple process that involves the catalytic transesterification

of triglycerides with a short-chain aliphatic alcohol, typically methanol, under basic conditions (Scheme 1).² One major concern regarding the biodiesel production is the formation of glycerol (glycerine or 1,2,3-propanetriol) as a by-product (~10% by weight). In this sense, according to recent estimates,³ world production of glycerol could have reached 1.2 million tonnes in 2010 and will grow in coming years due to the increasing demand for biodiesel.⁴

There are over 2000 established uses for glycerol as a high-valued starting material in the drug, food, beverage, chemicals and synthetic materials industries (see Fig. 1).⁵ It is used in cosmetics, toiletries, sweeteners, softening agents, cough syrups, surface coatings, paints and many other products. However, the large surplus of glycerol generated by the biodiesel industry has recently led to a collapse in the

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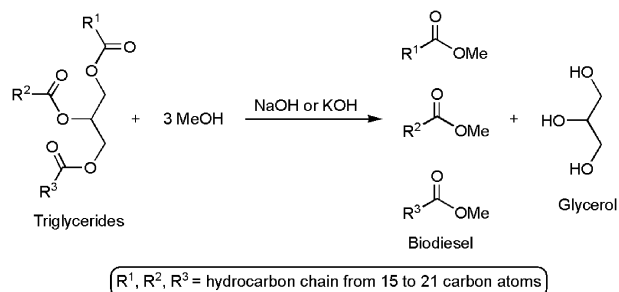
**Alba E. Díaz-Álvarez**

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development of new catalytic transformations in water and glycerol.

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Scheme 1 Overall reaction for production of biodiesel.

prices, which has been accompanied by a growing imbalance in the supply/demand of this chemical. The current inability of the market to absorb all the glycerol produced in the biodiesel plants makes this renewable chemical become a mere waste. This scenario could have negative implications on the economic viability of many biorefineries in the near future, and also on the environment due to an improper disposal of glycerol. Consequently, new applications for this polyol as a low-cost raw material need to be developed and/or the existing ones need to be expanded.⁶



Beatriz Lastra-Barreira

Beatriz Lastra-Barreira received his BSc in Chemistry from the University of Oviedo (Spain) in 2006. She is currently a PhD student working under the supervision of Dr P. Crochet. In 2008 she conducted a two-month stay in the group of Prof. D. Bourissou (Université Paul Sabatier, France). Her thesis is focused on the design of new water-soluble ruthenium complexes and their catalytic applications.



Pascale Crochet

Pascale Crochet studied chemistry at the University of Rennes I (France) and obtained her PhD in 1996 under the supervision of Prof. P. H. Dixneuf and B. Demerseman. After a two-year post-doctoral stay in the group of Prof. M. A. Esteruelas (University of Zaragoza, Spain) and one year as an Assistant Professor at the "National High School of Physics and Chemistry" of Bordeaux (France), she moved in 1999 to the

University of Oviedo where she is currently an Associate Professor of Inorganic Chemistry. Her research interests deal with the design and synthetic applications of organometallic complexes, with a particular focus on hydrosoluble ruthenium catalysts.

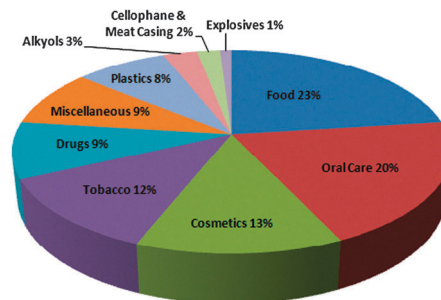


Fig. 1 The market of glycerol (industrial sectors and volumes).

Today, most of the efforts in this area are focusing on the development of procedures to convert this highly functionalized molecule into value-added chemicals that have either been previously prepared from petrochemical sources or suffered from environmental problems during their preparation. Several comprehensive review articles covering the current state-of-the-art have already appeared in the literature, and they are recommended to readers seeking a broader knowledge on this topic.^{3,6,7} Glycerol reforming for hydrogen production,⁸ and its transformation into fuel additives,⁹ are also extremely active areas of research. However, in order to absorb all the surpluses, new uses requiring large volumes of glycerol would be highly welcomed.

Reaction solvents are used in huge amounts and are one of the most important constituents in any chemical process. Synthetic organic chemistry is traditionally carried out in solution to facilitate the intimate contact of reactants and catalysts. Although any liquid may be potentially used as a solvent, the most widely employed in both academia and industry are the hydrocarbons (including halogenated and aromatic ones), ethers and alcohols derived from fossil fuels. However, despite the obvious usefulness of these organic solvents, problems associated with their volatility, flammability and toxicity, as well as their increasing prices, advise against their use.



Victorio Cadierno

Victorio Cadierno studied chemistry at the University of Oviedo and obtained his PhD degree in 1996 working under the supervision of Prof. J. Gimeno. He then joined the group of Prof. J. P. Majoral at the LCC-CNRS (Toulouse, France) for a two-year post-doctoral stay. Thereafter, he returned to the University of Oviedo where he is currently an Associate Professor of Inorganic Chemistry. In 2002 he was awarded with the Spanish Royal Society of

Chemistry (RSEQ) Young Investigator Award. His current research interests cover the development of catalytic transformations in green reaction media, being co-author of more than 110 publications.

In recent years, safety and environmental concerns have been increasingly recognized by the chemical community worldwide, and the twelve principles of the so-called “Green Chemistry” are nowadays considered as an essential driving force in the quest for sustainable chemical processes.¹⁰ Solvents are a key component in making a process “green” and, consequently, one of the major challenges for today’s chemists is to move away from the classical volatile organic solvents.¹¹ An ideal “green” solvent should have a high boiling point, a low vapour pressure, be non-toxic, be able to dissolve a great range of compounds, be inexpensive and, of course, be recyclable. Although the universal green solvent for all situations does not exist, several alternatives have been evaluated during the last years (water, ionic liquids, supercritical fluids, perfluorinated solvents, *etc.*).¹² Among them, water appears to be the superior choice since it satisfies the aforementioned considerations almost completely. Indeed, it is now well-accepted that water is a reliable alternative to the petroleum-based solvents, a wide variety of highly efficient and selective synthetic protocols conducted in aqueous media being already available for practical uses.¹³

As water, glycerol and some of its most direct derivatives meet the requirements needed to be considered as green solvents. In fact, their use as alternative media for organic reactions has emerged as a promising new field of research, which opens a new way to revalorize this waste generated by the biodiesel industry. The aim of the present *Feature Article* is to provide a comprehensive overview on the developments reached in this field. In particular, after a few brief comments on the main properties of these new solvent systems, their applications in synthetic organic chemistry, catalysis and biocatalysis will be discussed in detail. At this point, we must note that a recent, non-comprehensive and complementary, article highlighting the utility of glycerol as solvent in different areas has already appeared.¹⁴ In addition, although a large number of glycerol transformations take place in the absence of any added solvent,^{6,7} only selected examples where glycerol is simultaneously used as a solvent and as a reagent are included here.

Solvent properties of glycerol and its derivatives

Glycerol

In pure form, glycerol is a sweet-tasting, colourless, odourless, viscous liquid which possesses a unique combination of physical and chemical properties (some key data are collected in Table 1).⁶ Thus, like water, glycerol is highly polar, biodegradable, immiscible with hydrocarbons and ethers (adequate therefore for biphasic catalysis and for product isolation by liquid–liquid extraction), able to form strong hydrogen bonds and to dissolve inorganic compounds (salts, acids, bases and transition metal complexes). It is also virtually non-toxic and non-flammable. Moreover, in comparison with water, it presents the advantage to dissolve organic compounds usually insoluble in water. Another interesting features of glycerol are (i) its high boiling point, which enables the development of high-temperature organic reactions in a technically easier way (the use of autoclaves or sealed tubes is

Table 1 Some physicochemical properties and toxicity data of glycerol

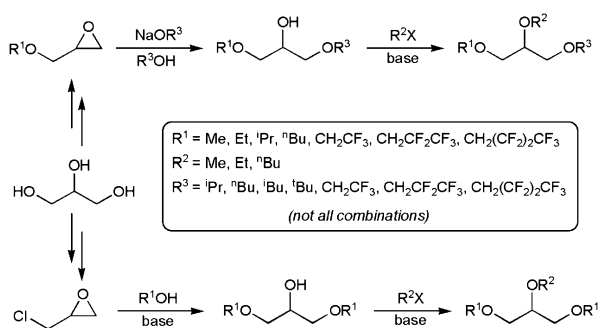
Melting point	17.8 °C
Boiling point	290 °C
Viscosity (20 °C)	1200 cP
Vapour pressure (20 °C)	< 1 mm Hg
Density (20 °C)	1.26 g cm ⁻³
Flash point	160 °C (closed cup)
Autoignition temperature	400 °C
Critical temperature	492.2 °C
Critical pressure	42.5 atm
Dielectric constant (25 °C)	44.38
Dipole moment (30–50 °C)	2.68 D
LD ₅₀ (oral-rat)	12 600 mg kg ⁻¹
LD ₅₀ (dermal-rabbit)	> 10 000 mg kg ⁻¹
LC ₅₀ (rat-1 h)	570 mg m ⁻³

not needed) and the isolation of the final reaction products through a simple distillation process, (ii) its low vapor pressure and (iii) its high dielectric constant, all these properties facilitating its use as a suitable solvent for microwave-assisted reactions.¹⁵ However, despite all these considerations, problems associated with its high viscosity, which could provoke poor substrate diffusion in the medium, and the presence of three reactive and metal-coordinating hydroxyl groups should be taken into account prior to its utilization as solvent for a particular reaction.

For its part, crude glycerol generated in biodiesel plants is an impure material in which, depending on the feedstock and production process employed, glycerol accounts for 65–85 wt% of the total.¹⁶ Methanol and soaps are the major impurities contained in crude glycerol. The presence of methanol is due to the fact that biodiesel producers use excess of methanol to drive the chemical transesterification to completion, while soaps originate from the reaction of free fatty acids present in the starting materials and the base employed as a catalyst. In addition to methanol and soaps, water, inorganic salts and unreacted mono-, di- and triglycerides are also present in varying proportions. Crude glycerol usually appears as a cloudy dark-brown liquid with a high pH value (11–12) and, unrefined, has only a marginal value. Purifying crude glycerol is expensive and requires energy,⁶ so the possibility of developing large-scale synthetic processes using crude glycerol as the solvent would be highly appreciated.

Glycerol-based ethers, esters and carbonates

The drawbacks outlined above for using glycerol as a solvent can be overcome by the synthesis of a glycerol-based family of solvents whose properties can be tailored, tuned and adjusted according to the requirements of each reaction. The presence of three reactive hydroxyl groups makes glycerol an excellent platform for chemical modification, giving the opportunity to produce unlimited glycerol derivatives that can potentially be used as solvents. In this context, following classical synthetic routes García and Mayoral have prepared a family of alkyl glycerol ethers, consisting of over sixty 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes, both symmetrically and unsymmetrically substituted at terminal positions, and evaluated their possible role as substitutive solvents through measurements of their physico-chemical properties (Scheme 2).¹⁷ Nearly 400 experimental data were collected for these species and

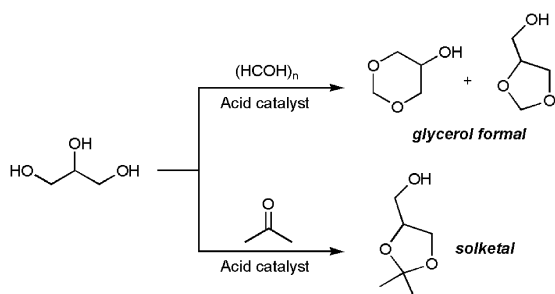


Scheme 2 Synthetic routes to symmetrical and unsymmetrical alkyl glycerol ethers.

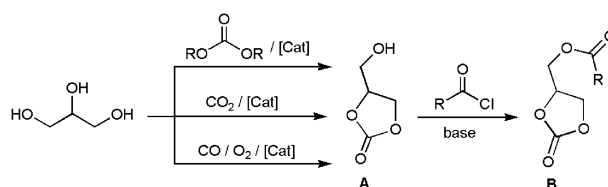
compared with analogous properties of common organic solvents. The molecular diversity of the derivatives prepared results in significant variations of polarity, viscosity, hydrogen bond ability and hydrophobicity, while maintaining in all cases a high boiling point and low toxicity. Similarly, a variety of mono-, di-, and tri-esters are also accessible from glycerol through catalytic esterification or transesterification reactions.¹⁸ Among them, triacetin (glycerol triacetate) is the most popular representative due to its industrial applications in cosmetics and as fuel additive. As the reader will see below, this oily liquid has also found usefulness as a combined solvent and acyl donor in some catalytic and biocatalytic transformations.

Glycerol can also be easily transformed into high valued cyclic acetals and ketals by reaction with carbonyl compounds.¹⁹ For example, acid-catalyzed direct acetalization of glycerol with formaldehyde gives the well-known “glycerol formal”, which is composed of a mixture of 5-hydroxy-1,3-dioxane and 4-hydroxymethyl-1,3-dioxolane in *ca.* 60 : 40 ratio (Scheme 3).²⁰ Like glycerol, glycerol formal is a viscous colorless liquid of high boiling point, which finds applications as a low-toxic solvent in different areas (injectable preparations, paints, plastifying agents, insecticide delivery systems, *etc.*). Note that, unlike glycerol, glycerol formal is completely miscible with ethers and acetone.

Through a related condensation reaction with acetone, solketal (2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane) is also accessible.²¹ As in the precedent case, the low toxicity of solketal has allowed its use as a solvent in several large-scale applications. Moreover, its polarity and hydrophobicity parameters have been determined, pointing out that its polarity lies between those of acetonitrile and ethanol, whereas its hydrophobicity is halfway between those of ethanol and 2-propanol.



Scheme 3 Synthesis of glycerol formal and solketal.



Scheme 4 Preparation and derivatization of glycerol carbonate.

The hydrogen bond ability ($\alpha = 0.81$) of solketal is typical for an aliphatic alcohol.^{21c}

Organic carbonates are becoming widely recognized as solvents for green organic synthesis due to their high biodegradability and low toxicity.²² In this context, glycerol carbonate **A** is a readily available compound that can be prepared by direct carbonation of glycerol with CO_2 ,²³ by metal-catalyzed oxidative carbonylation of glycerol,²⁴ or by catalytic transesterification with other carbonates (dimethyl, diethyl or propylene carbonate) or urea (Scheme 4).²⁵ In addition, derivatization of glycerol carbonate with carboxylic acid chlorides allows the access to high-boiling carbonates **B** which are useful solvents for reactions under fine vacuum conditions at elevated temperatures.²⁶

Despite the potential utility of all these glycerol-based ethers, esters and carbonates as solvents in organic synthesis, one should keep in mind that they contain reactive functional groups and, even if they tolerate a broad range of experimental conditions and reagents, may not be suitable solvents for any type of reactions.

Glycerol-based ionic liquids and deep eutectic solvents

As already commented, ionic liquids (ILs), salts having a melting point below 100 °C, are receiving considerable attention as potential alternatives to conventional molecular organic solvents.²⁷ An ionic liquid generally consists of a large nitrogen-containing organic cation and a smaller inorganic anion. The cation/anion asymmetry reduces the lattice energy of the crystalline structure and results in a low melting point salt. Many ionic liquids are highly polar and non-coordinating, ideal for catalytic reactions, many are immiscible with water, saturated hydrocarbons, dialkyl ethers, and a number of common organic solvents, thus providing flexibility for reaction and separation schemes. In addition, by selecting anions and cations, ILs can be easily tuned to provide a specific melting point, viscosity, volatility, density, hydrophobicity, miscibility, *etc.* for specific chemical systems. However, despite all these promising properties, widespread application of ILs in process chemistry is still hampered by doubts generally related to their high cost, and possible biodegradability and toxicological concerns.²⁸

Although their green and sustainable nature is also doubtful, some glycerol-based ILs have seen the light in recent years. In this context, Bellina and Chiappe *et al.* have recently described the preparation of a series of task-specific ILs based on glycerylimidazolium cations (**C** and **D** in Fig. 2) by reaction of 1-chloropropanediol, a compound readily obtainable from glycerol,²⁹ with the appropriate imidazolic base and subsequent alkylation of the resulting 3-(1*H*-imidazol-1-yl)propane-1,2-diol with chloroalkanes, bromoalkanes or alkyl mesylates.³⁰

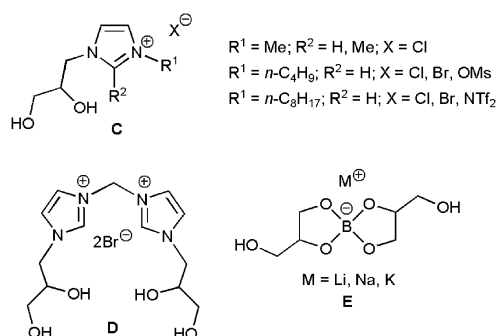


Fig. 2 Structure of some glycerol-based ionic liquids.

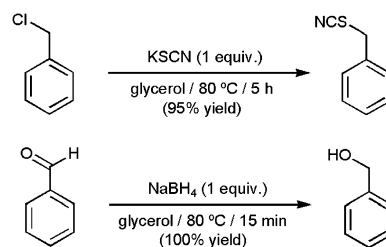
Alternatively, some (glycerol)borate-based ILs **E** have also been prepared by neutralization of bis(glycerol)boric acid, generated by treatment of boric acid with glycerol in refluxing toluene, with alkali hydroxides.³¹ All these species are potential solvents for developing selective synthetic organic reactions.

On the other hand, the so-called deep eutectic solvents (DESs) are eutectic mixtures of a solid ammonium salt and a hydrogen-bond donor which, like the more classical ILs, often have melting points below room temperature, low vapor pressure, high thermal stability and are usually water-miscible.³² DESs are readily prepared from low-cost starting materials, typically by mixing choline chloride (ChCl) or ethylammonium chloride with an organic hydrogen-bond donor such as acetamide, urea, malonic acid, *etc.* Compared to ILs, DESs have the advantage of being in general non-toxic and biodegradable. In addition, the solvent properties of these eutectic mixtures, in which both anions and cations as well as neutral molecules are present, differ considerably from those of ILs since, in addition to the electrostatic solvation, substrates can also establish a hydrogen-bond network with the solvent.³³ Glycerol is known to form eutectic mixtures with quaternary ammonium salts, a property that has been exploited for the purification of biodiesel.³⁴ Quite recently, the physical properties of DESs resulting from mixing choline chloride with glycerol have been quantified and it was shown that they can circumvent some of the difficulties of using glycerol as a solvent.³⁵ Thus, by adding ChCl to glycerol there is a marked reduction in the viscosity (from 1200 to 400 cP by adding 30 mol% of ChCl) and density (from 1.26 to 1.18 g cm⁻³ by adding 30 mol% of ChCl). This is due to the 3D intermolecular H-bond interactions in glycerol that are broken up on addition of ChCl, resulting in a less ordered system. Several polarity parameters (E^N_T , α , β and π^*)³⁶ were also measured, the data obtained suggesting that the relative polarity of these systems is similar to the classical imidazolium-based ILs.

Although the ability of DESs to serve as solvents in the field of synthetic organic chemistry has not been adequately explored,³⁷ as the reader will see below, glycerol eutectics have already found some applications in biocatalysis.

Organic synthesis without transition metals

First examples demonstrating the utility of glycerol as solvent for synthetic organic chemistry were described by Wolfson and co-workers, who successfully accomplished the nucleophilic substitution of benzyl chloride with potassium thiocyanate,



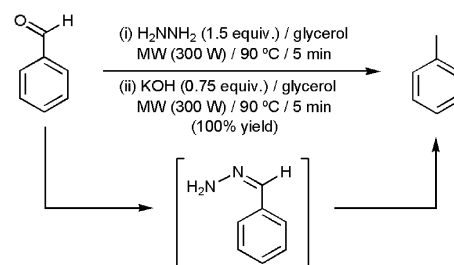
Scheme 5 Nucleophilic substitution and reduction reactions in glycerol.

and the reduction of benzaldehyde with sodium borohydride, in this “green” medium (Scheme 5).³⁸ Reactions performed at 80 °C with stoichiometric amounts of KSCN and NaBH₄ delivered the desired benzyl thiocyanate and alcohol, respectively, in excellent yields and short times. Further studies by the same group showed that other carbonyl compounds (aldehydes, ketones and β -ketoesters) can be selectively reduced in glycerol with NaBH₄.³⁹ In general, reactions proceeded efficiently at room temperature with one equivalent of NaBH₄, affording the final alcohols in good yields after quenching the reaction mixtures with diluted acid and extraction with diethyl ether. Interestingly, almost quantitative conversion of ethyl acetoacetate into ethyl 3-hydroxybutyrate could be reached using only 0.25 equiv. of NaBH₄, *i.e.* the stoichiometrically correct amount of reductant based on hydride. Note that these atom-economical conditions are rarely found in the literature.

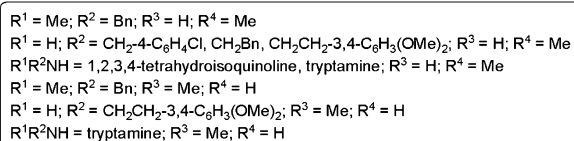
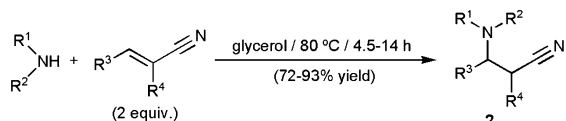
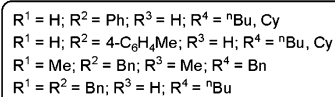
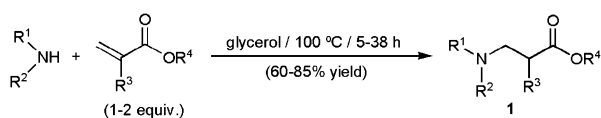
As a solvent, glycerol also allowed the reduction of benzaldehyde to toluene with hydrazine under basic conditions, *via* the Wolff–Kishner reaction.³⁹ Taking advantage of the high dielectric constant and boiling point of glycerol, the process was conveniently performed using microwave irradiation heating (Scheme 6).

After these pioneering works, many other useful synthetic protocols in glycerol have been developed. Thus, Gu and Jérôme have demonstrated that glycerol is an efficient promoting medium for the catalyst-free aza-Michael addition of amines to α,β -unsaturated carbonyl compounds and nitriles (Scheme 7).⁴⁰ Reactions performed at 80–100 °C afforded the corresponding mono-adducts **1–2** in good yields after extraction of the crude mixtures with ethyl acetate, and subsequent chromatographic work-up. In addition, the recovered glycerol phase could be reused, with the yields obtained after three consecutive runs being comparable to those reached in fresh glycerol.

Remarkably, classical organic solvents, such as toluene, DMF, DMSO or 1,2-dichloroethane, were completely ineffective for these reactions, and only trace amounts of **1–2** were



Scheme 6 Wolff–Kishner reduction of benzaldehyde in glycerol.

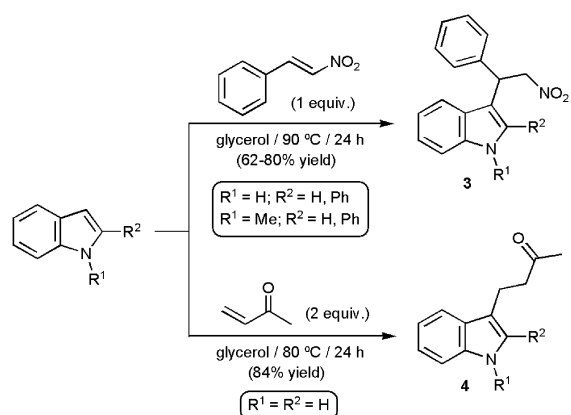


Scheme 7 Catalyst-free aza-Michael reactions in glycerol.

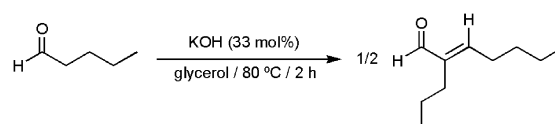
formed in water or under solvent-free conditions. A similar trend was also observed when studying the Michael addition of indoles to β -nitrostyrene and 3-buten-2-one, in which only the use of glycerol (or water) afforded the desired products **3–4** in good yields without the assistance of any Brønsted or Lewis acid catalyst (Scheme 8).^{40,41}

Although reasons behind the promoting effect of glycerol in these addition reactions are not entirely clear, it is suspected that the strong hydrogen bond network of glycerol might be responsible, similarly to the well-known accelerating effect exerted by water in many organic reactions. However, at present it cannot be totally ruled out that the presence of trace amounts of impurities (acidic or basic derivatives) can act as a possible catalyst.¹⁴

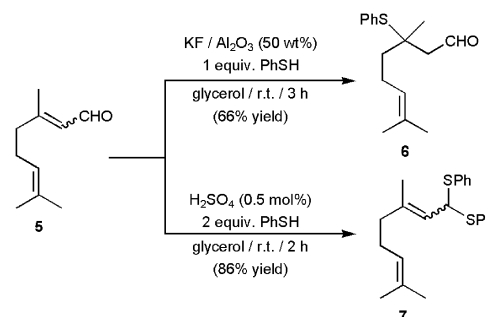
Importantly, the Michael-type addition reactions depicted in Schemes 7 and 8 also proceeded efficiently in technical grade glycerol,⁴⁰ which is much more appealing from the viewpoint of Green Chemistry since purification of crude glycerol from biodiesel production is a costly and energy consuming process.⁶ In this context, we must note that crude glycerol, generated from various vegetable oil sources, was also



Scheme 8 Catalyst-free Friedel-Crafts alkylations of indoles in glycerol.



Scheme 9 Base-catalyzed aldol condensation of *n*-valeraldehyde.

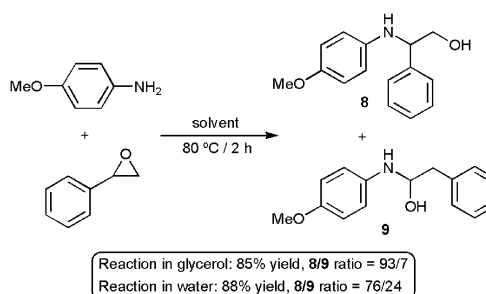


Scheme 10 Addition of thiophenol to citral in glycerol.

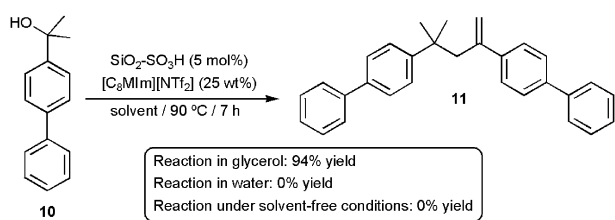
successfully employed by Wolfson's group as a green solvent in the KOH-catalyzed aldol condensation of *n*-valeraldehyde (Scheme 9). However, for this particular reaction lower conversions compared to that reached in pure glycerol were observed (31–43% vs. 52%).⁴²

Michael addition of thiophenol to citral **5** was also studied in glycerol (Scheme 10).⁴³ In the absence of any catalyst a mixture of two products, **6** and **7**, resulting from the conjugated 1,4- or double 1,2-addition, respectively, of PhSH to the enal unit was obtained. However, the selectivity of the process could be finely tuned by using an appropriate acid or base catalyst. Thus, over basic KF/Al₂O₃, the reaction was oriented towards the formation of the 1,4-adduct **6**, whereas in the presence of H₂SO₄ the 1,2-addition product **7** was exclusively generated. In the presence of KF/Al₂O₃, other aliphatic and aromatic thiols were selectively added to citral, and related electron-poor alkenes, in glycerol. Note that the catalyst and solvent could be effectively recycled after extraction of the reaction products with diethyl ether.

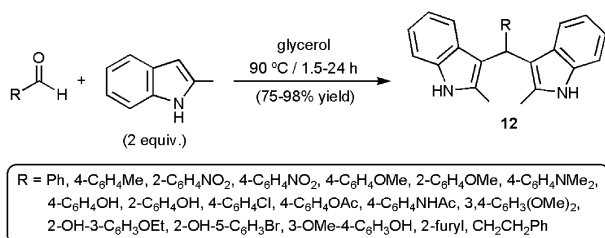
Glycerol was also an excellent promoting medium for the ring-opening of styrene oxide with *p*-anisidine (Scheme 11).⁴⁰ In this case no catalysts were needed to reach a good selectivity. Indeed, it was remarkably higher to that observed when the reaction was performed in aqueous medium under identical conditions (**8/9** ratio = 93/7 vs. 76/24). Good results were also observed in the acid-catalyzed dehydrative dimerization of



Scheme 11 Ring-opening of styrene oxide with *p*-anisidine.



Scheme 12 Acid-catalyzed dehydrative dimerization of alcohol **10**.



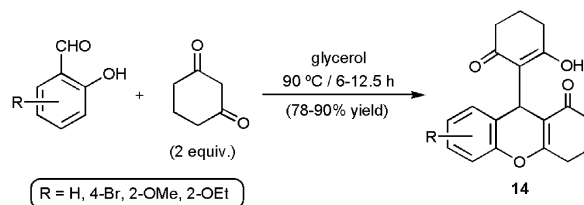
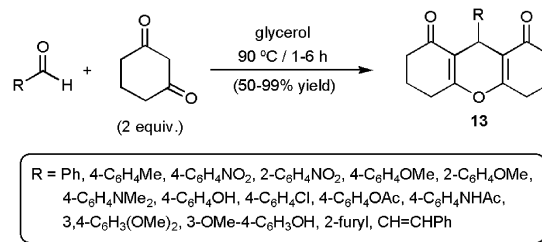
Scheme 13 Catalyst-free synthesis of bis(indolyl)methanes in glycerol.

alcohol **10**, where only the use of glycerol led to the formation of the desired product **11** (Scheme 12).⁴⁰

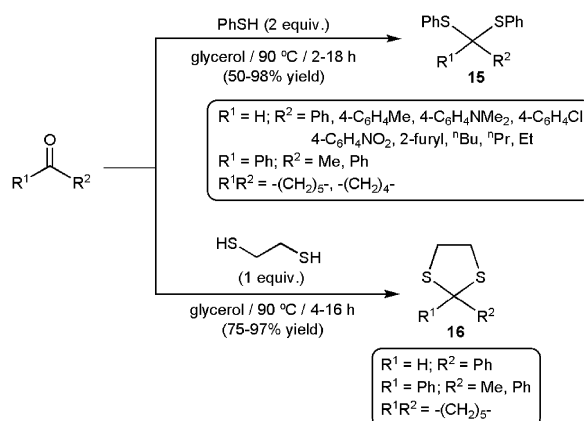
In the context of a broad study, Gu and co-workers have demonstrated that glycerol is an advantageous solvent for the electrophilic activation of aldehydes.⁴⁴ Thus, as shown in Scheme 13, several bis(indolyl)methane derivatives **12** could be efficiently synthesized by a thermal reaction between 2-methylindole and aldehydes, without using any acid catalyst. Aromatic, heteroaromatic and aliphatic aldehydes, including the acid-sensitive furfural and 4-dimethylaminobenzaldehyde, were tolerated and the process could be satisfactorily extended to other indole derivatives (1-methylindole, 2-phenylindole, 2-methyl-5-methoxyindole, 1-methyl-2-phenylindole or indole itself).⁴⁵ The only limitation was found in the reactions with ketones, which were completely inoperative in the process. For comparative purposes, the suitability of other solvents, such as toluene, DMF, DMSO, *n*-butyl acetate, *n*-butanol, ethylene glycol, polyethylene glycol (PEG-400) and water, in these catalyst-free coupling reactions was evaluated under the same experimental conditions. In all cases, the desired products were obtained either in a trace amount or in a significantly lower yield than in glycerol. Moreover, taking advantage of the insolubility of bis(indolyl)methanes **12** in glycerol, at the end of the reaction, they could be easily isolated by simple filtration.

Glycerol also promoted the condensation of aromatic, heteroaromatic and α,β -unsaturated aldehydes with 1,3-cyclohexanedione to generate selectively the corresponding xanthene-1,8(2*H*)-diones **13**, or the isomeric 1-oxo-hexahydroxanthenes **14** if salicylaldehydes are used as starting materials, reactions that are conventionally carried out using acid catalysts (Scheme 14).⁴⁴

Thioacetals are useful carbonyl protecting groups in organic synthesis due to their inherent stability towards ordinary acidic and basic conditions.⁴⁶ As in the precedent transformations, thioacetalization reactions usually require the assistance of protic or Lewis acids. However, taking advantage of the activating effect of glycerol towards C=O bonds, an appealing



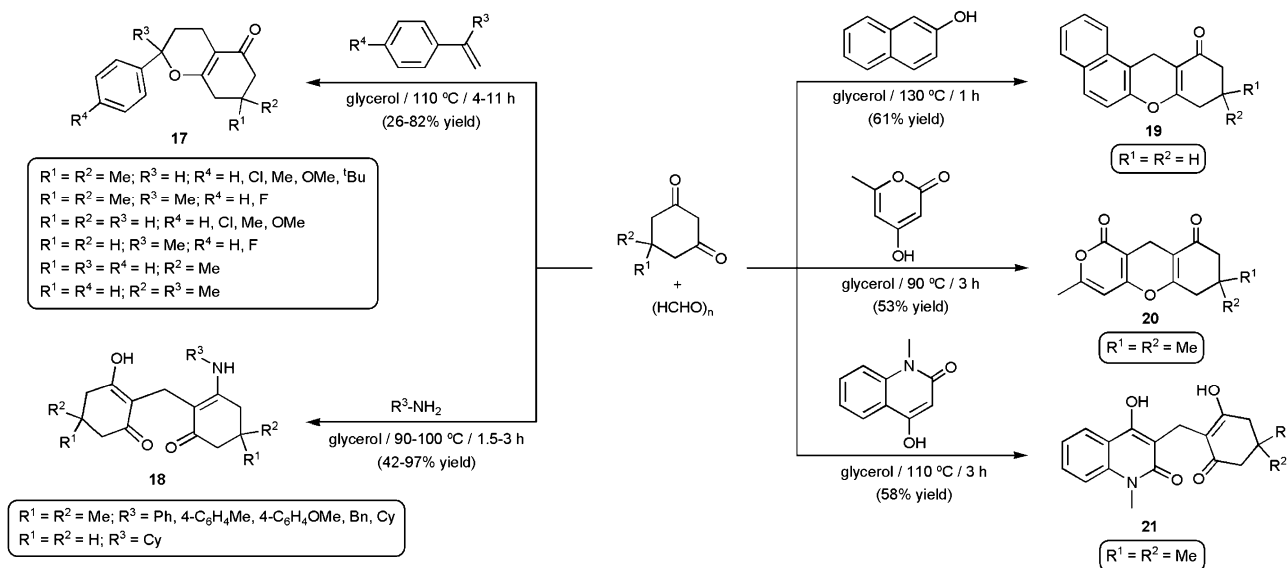
Scheme 14 Catalyst-free condensations of aldehydes with 1,3-cyclohexanedione in glycerol.



Scheme 15 Thioacetalization of carbonyl compounds in glycerol.

and general catalyst-free thioacetalization protocol has been recently described using glycerol as solvent.⁴⁷ Thus, as shown in Scheme 15, several aldehydes and ketones could be successfully thioacetylated with benzenethiol or 1,2-ethanedithiol just by heating in glycerol at 90 °C. The resulting thioacetals **15–16** were isolated in good yields after extraction of the crude reaction mixtures with hexanes, and subsequent chromatographic purification. In addition, glycerol could be reused for further thioacetalizations maintaining its good level of efficiency after four consecutive runs.

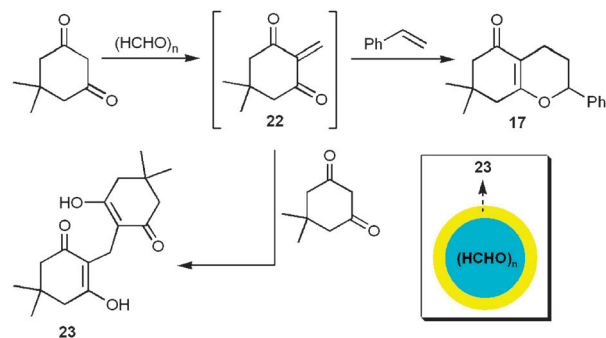
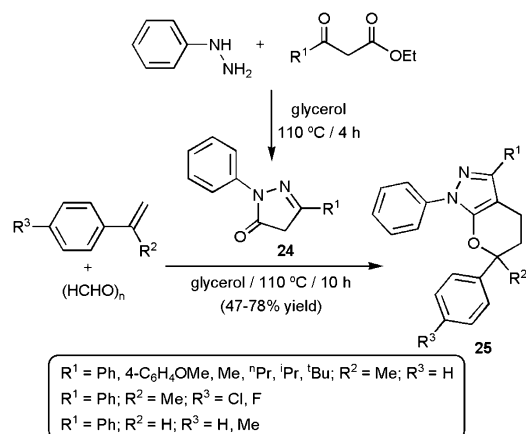
Multicomponent reactions (MCRs), in which three or more reactants are combined in a single chemical step, comply with most of the requirements for an ideal organic synthesis (structural complexity from readily available starting materials, atom economy, operational simplicity, resource effectivity, *etc.*).⁴⁸ In this context, glycerol also proved to be a convenient platform to perform this type of transformations. In particular, many substrates, such as styrenes, primary amines, 2-naphthol, 4-hydroxy-6-methyl-2-pyrone and 4-hydroxy-1-methyl-2-quinolone, could be readily assembled with 1,3-cyclohexanedione and formaldehyde in glycerol, under catalyst-free conditions, to afford the elaborated polycyclic compounds **17–21** in moderate to high yields (Scheme 16).⁴⁹ In



Scheme 16 Multicomponent reactions of 1,3-cyclohexanediones and formaldehyde in glycerol.

these MCRs, glycerol not only showed a significant beneficial effect on the reaction yields compared to more classical organic solvents (toluene, nitromethane, DMF or DMSO) and water, but also allowed easy separation of the products **17–21** by means of extraction with ethyl acetate.

The reaction of styrene with dimedone and paraformaldehyde was studied in great detail and the positive effect of glycerol could be attributed to two factors: (i) a restricted formation of the oxo-diene intermediate **22** (Scheme 17), resulting from the initial Knoevenagel condensation between dimedone and formaldehyde, and (ii) the enhancing effect of glycerol on the rate of the subsequent hetero-Diels–Alder reaction of **22** with styrene due to its polar character. In this sense, during the reaction, the authors observed the formation of a thin shell, mainly composed of the insoluble by-product **23** generated at the beginning of the reaction, on the surface of solid paraformaldehyde (NMR analysis).⁴⁹ This coating of paraformaldehyde by **23** in glycerol, not observed when water and other organic compounds were used as solvents, inhibits its decomposition and controls the formation of the key intermediate **22**. Thus, **22** is formed gradually and it is immediately consumed in the Diels–Alder step without time to evolve into **23**, the major reaction product observed using other solvents.

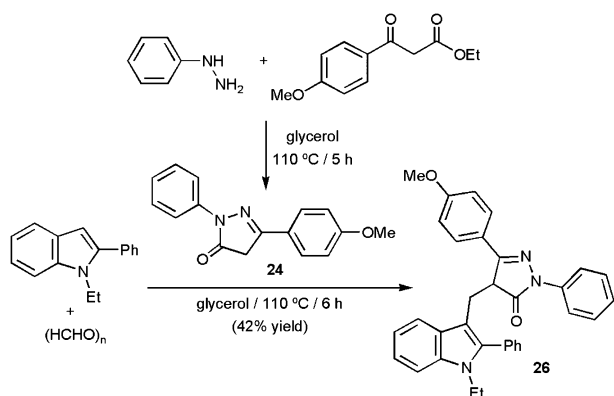
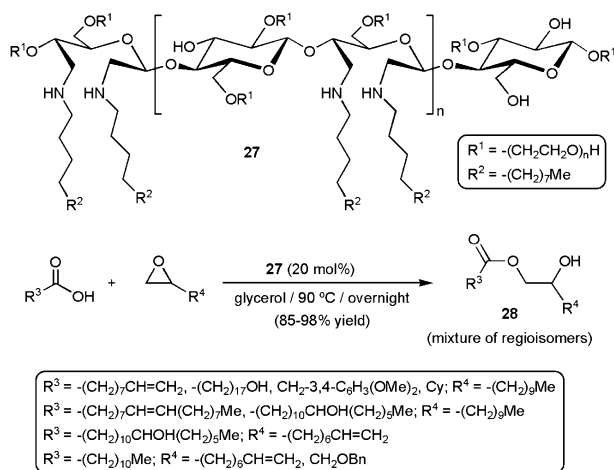
Scheme 17 Reaction pathway involved in the formation of **17**.

Scheme 18 Four-component two-step sequential reactions in glycerol.

The utility of glycerol in MCRs was further demonstrated in the preparation of the polyheterocycles **25** through a one-pot two-step sequential coupling of phenylhydrazine, β -keto esters, formaldehyde and styrenes (Scheme 18).⁵⁰ In the first step a 1,3-disubstituted 5-pyrazolone **24** is selectively formed by condensation between phenylhydrazine and the β -keto ester. Subsequent addition of the styrene derivative and paraformaldehyde to the reaction mixture generates **25** through a tandem Knoevenagel/hetero-Diels–Alder reaction.

A related sequential transformation involving the coupling of phenylhydrazine, a β -keto ester, formaldehyde and 1-ethyl-2-phenylindole in glycerol has also been described, the process allowing the preparation of the highly functionalized indole derivative **26** in 42% yield (Scheme 19).⁵⁰

Using the aminopolysaccharide **27** as a surfactant-combined basic catalyst, chemoselective ring-opening of epoxides with carboxylic acids to afford the corresponding esters **28** could be achieved in glycerol (Scheme 20).⁵¹ Remarkably, the use of conventional basic catalysts, such as ZnO, K_2CO_3 or secondary amines, resulted in lower reaction rates and selectivities since

Scheme 19 Synthesis of the functionalized indole **26**.

Scheme 20 Catalytic ring-opening of epoxides with carboxylic acids.

formation of ethers, derived from the ring-opening of the epoxides with glycerol, as by-products was observed. Apparently, the aminopolysaccharide **27** favours a better diffusion of the organic reactants in glycerol, limiting also the reactivity of this polyol. In addition, the emulsions formed in glycerol were found to be unstable. Thus, after centrifugation, the reaction media rapidly became biphasic, which allowed easy separation of the reaction products without assistance of any organic solvent. This particular property of glycerol also enabled the homogeneous catalyst **27** to be recycled up to ten times without any change in activity or selectivity. The versatility of the aminopolysaccharide **27** as catalyst was further demonstrated by conducting successfully other classical base-catalyzed reactions in glycerol, such as the Knoevenagel condensation of benzaldehyde with malononitrile, the Henry condensation of benzaldehyde with nitroethane or the Michael addition of nitroethane to 2-cyclohexen-1-one.⁵¹

Selective ring-opening reactions of epoxides with carboxylic acids were also performed in glycerol using poly(propylene)-imine (PPI) dendrimers, decorated on the surface with glyceryl moieties, as basic catalysts (as a representative example the 2nd generation of these functionalized PPI dendrimers **29** is given in Fig. 3).⁵² Owing to the presence of glyceryl units surrounding the PPI core, the dendritic catalysts were successfully immobilized in glycerol, which also facilitated the separation of the products **28** and a convenient dendrimer-recycling.

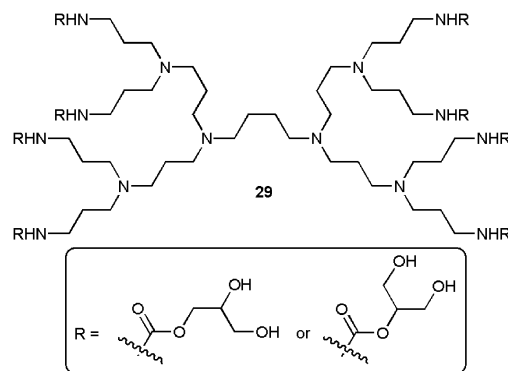
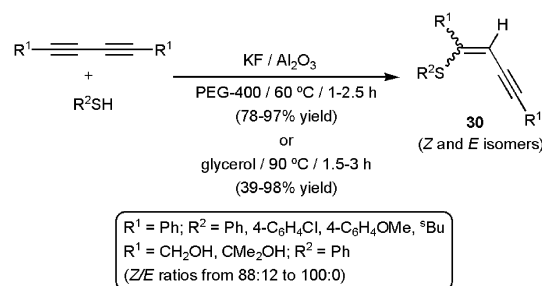


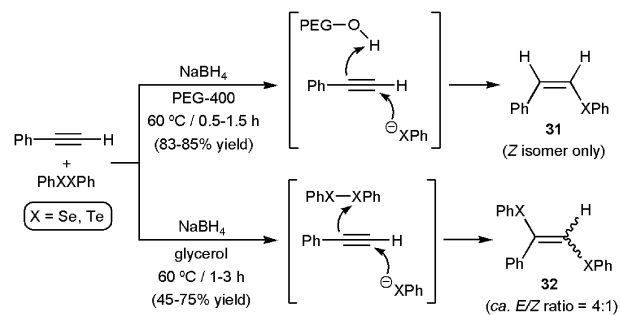
Fig. 3 PPI dendrimer used in the catalytic ring-opening of epoxides.



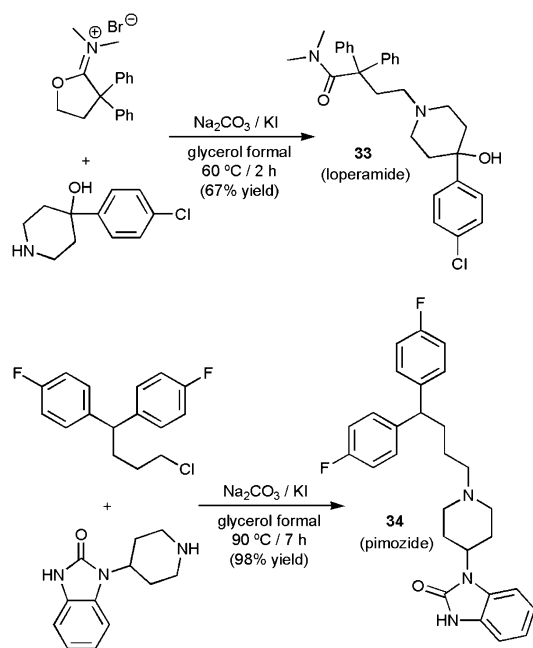
Scheme 21 Hydrothiolation of 1,3-butadiynes in PEG-400 and glycerol.

A green and general protocol for the synthesis of thio-butenynes **30** in glycerol, through the heterogeneous KF/Al₂O₃-catalyzed hydrothiolation of disubstituted 1,3-butadiynes, was developed by Perin and co-workers (Scheme 21).⁵³ However, we must note that, for this particular transformation, the use of polyethylene glycol (PEG-400) resulted more advantageous since higher yields at lower temperatures (60 vs. 90 °C) were in general reached. Formation of *Z*-isomers was preferential in both media and the solvent/catalyst systems could be reused up to three times with comparable activities and *Z*-selectivities.

PEG-400 and glycerol were similarly employed as recyclable solvents for hydrohalcogenation reactions of phenylacetylene (Scheme 22).⁵⁴ The nucleophilic species of selenium and tellurium were in this case generated *in situ* from the corresponding diphenyl dichalcogenide and NaBH₄ at 60 °C. Interestingly, while the reactions conducted in PEG-400 afforded selectively the corresponding (*Z*)-β-phenylchalcostyrenes **31**, the formation of a mixture of the *E* and *Z* isomers of the dichalcogenated



Scheme 22 Hydrohalcogenation reactions of phenylacetylene.

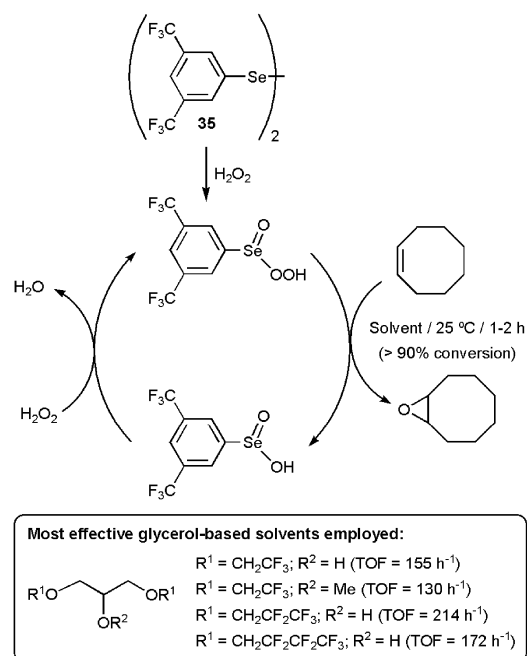


Scheme 23 Synthesis of loperamide and pimozone in glycerol formal.

alkenes **32** was observed when glycerol was used as solvent. The lower solubility of the starting materials in glycerol *vs.* PEG-400 was evoked to explain the different reactivities observed.

Recent years have also seen the use of different glycerol derivatives as green solvents in synthetic organic chemistry. In this context, improved processes for the preparation of the antiarrhythmic and antipsychotic drugs loperamide **33** and pimozone **34**, respectively, have been patented using glycerol formal (Scheme 23).⁵⁵ This inert solvent conveniently replaces the methyl isobutyl ketone employed in the most classical preparations. In addition, glycerol formal exhibits a superior technical performance than methyl isobutyl ketone as evidenced by the lower equivalents of base required (1.1 *vs.* 1.6–2.6 equiv. of Na_2CO_3), the reduced temperature regime (60–90 *vs.* 120 °C), the shorter reaction times (2–7 *vs.* 15–65 h), and the possibility of carrying out an aqueous work-up, thus simplifying the isolation and purification of the products.

Within a broad comparative study, a family of 13 common solvents and 18 glycerol-based ethers (1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes) were evaluated as suitable reaction media for cyclooctene epoxidation with H_2O_2 using bis[3,5-bis(trifluoromethyl)phenyl]diselenide **35** (1 mol%) as a catalyst (Scheme 24).⁵⁶ Although the best results were achieved in 2,2,2-trifluoroethanol (TOF = 491 h^{-1}), the use of some glycerol-based ethers bearing fluorinated alkyl chains also allowed fast conversions (TOF = 130–214 h^{-1}). Indeed, some of them performed better than dichloromethane (TOF = 153 h^{-1}), which is one of the most commonly used solvents in these epoxidation reactions. As in the case of 2,2,2-trifluoroethanol, the activating properties towards H_2O_2 *via* hydrogen bonding have been evoked to explain the beneficial effect of these new reaction media. The range of applicability of this catalytic transformation was successfully extended to the epoxidation of the more challenging olefin cyclohexene.⁵⁷

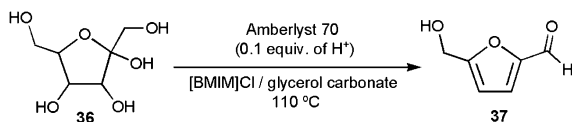


Scheme 24 Epoxidation of cyclooctene in glycerol-derived solvents.

It is also important to note that recycling of the catalytically active phase, *i.e.* fluorinated solvent + selenium catalyst, was possible through distillation of the cyclohexene oxide from the reaction mixture.

Ionic liquids (ILs) are widely used in carbohydrate chemistry owing to their unique ability to dissolve a large number of mono-, oligo- and polysaccharides.⁵⁸ In this context, their use as solvents for the acid-catalyzed dehydration of fructose **36** to 5-hydroxymethylfurfural **37** (HMF), a useful synthetic intermediate in the preparation of a wide range of fine chemicals, has been extensively investigated in recent years.⁵⁹ However, the high prices and toxicity of ILs are major obstacles to the practical application of these methodologies at the productive scale. As a possible solution, Jérôme and co-workers have demonstrated that ILs can be partially substituted by inexpensive and safe glycerol carbonate.⁶⁰ Thus, as shown in Table 2, using the acidic ion-exchange resin Amberlyst 70 as a catalyst, up to 80 wt% of 1-butyl-3-methyl imidazolium chloride ([BMIM]Cl) could be replaced by glycerol carbonate without a dramatic effect on the HMF yield (entries 1–4). The glycerol carbonate content could be further increased from 80 to 90 wt% working under biphasic (entry 6 *vs.* 5) or more diluted conditions (entry 7 *vs.* 5), the use of a biphasic media ([BMIM]Cl/glycerol acetate–methyl isobutyl ketone) allowing also the effective separation of **37** since it selectively dissolves in the methyl isobutyl ketone phase. Similar studies were also performed with pure and crude glycerol instead of glycerol carbonate.⁶⁰ However, in these cases only 35 wt% of [BMIM]Cl could be effectively replaced since side reactions between glycerol and **37** occur at higher glycerol contents.

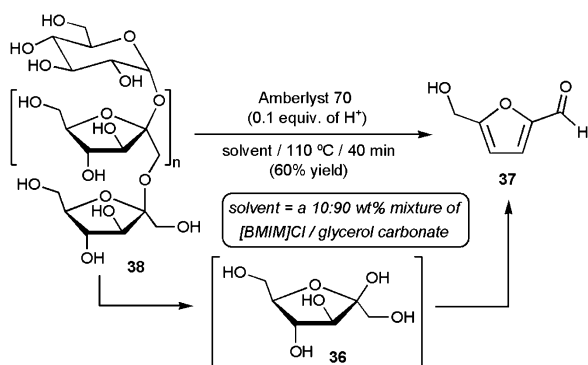
Using Amberlyst 70 as catalyst, direct production of HMF **37** in a [BMIM]Cl/glycerol carbonate mixture (10 : 90 wt%) could be achieved starting from inulin **38**, a natural polysaccharide extracted from chicory or dahlia tubers (Scheme 25).⁶⁰

Table 2 Acid-catalyzed dehydration of fructose in [BMIM]Cl/glycerol carbonate mixtures^a

Entry	[BMIM]Cl/glycerol carbonate (wt% ratio)	<i>t</i> /min	Yield (%)
1	100 : 0	15	95
2	65 : 35	35	98
3	50 : 50	30	91
4	20 : 80	25	75
5	10 : 90	20	60
6 ^b	10 : 90	30	70
7 ^c	10 : 90	40	72
8	0 : 100	20	10

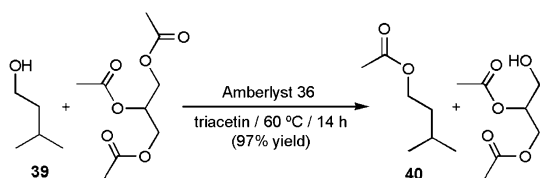
^a Reactions performed at 110 °C using 1 g of fructose, 2.5 g of the [BMIM]Cl/glycerol carbonate mixture and Amberlyst 70 (0.1 equiv. H⁺). ^b Reaction performed in the presence of methyl isobutyl ketone.

^c Reaction performed starting from 0.5 g of fructose dissolved in 2.5 g of the [BMIM]Cl/glycerol carbonate mixture.

**Scheme 25** Acid-catalyzed production of HMF from inulin.

As proposed by the authors, the residual water contained in the acidic resin (54–59 wt%) is able to promote the initial hydrolysis of **38** to fructose **36**, which subsequently undergoes the acid-catalyzed dehydration reaction.

Finally, an efficient and green synthesis of isoamyl acetate **40**, an industrially relevant food additive because of its characteristic banana flavor, has been described by transesterification of isoamyl alcohol **39** employing Amberlyst 36 as a catalyst, and triacetin (glycerol triacetate) as both an acyl donor and a solvent (Scheme 26).⁶¹ The use of triacetin enabled easy isolation of the product by simple extraction with petroleum ether, as well as separation and recycling of the heterogeneous catalyst by filtration. Experiments conducted in a domestic microwave oven also revealed the compatibility of

**Scheme 26** Transesterification of isoamyl alcohol in triacetin.

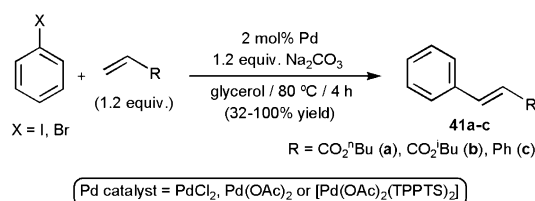
this transesterification process with MW heating (a 100-fold increase in the reaction rate was observed).

Transition-metal catalyzed reactions

Early attempts to use glycerol as solvent for metal-catalyzed reactions were reported in 1968 by Tarama and Funabiki, who studied the partial reduction of butadiene into butene in a glycerol/methanol solvent mixture (1 : 1 v/v).⁶² Unfortunately, the hydrogenation process, performed at 20 °C and promoted by pentacyanocobaltate(II) generated *in situ* from CoCl₂ and an excess of KCN, proceeded with lower rates and selectivities than in H₂O. Thus, while 1-butene was almost the only isomer generated in water, an approximately 50/40/10 ratio of 1-butene/*cis*-2-butene/*trans*-2-butene was obtained in glycerol/MeOH.

Despite this early interest, glycerol has only been recognized as a useful solvent for catalysis in very recent years. In this sense, works by Wolfson and co-workers in 2007 demonstrated that glycerol is a suitable medium for Heck-type C–C couplings.^{38,63} In particular, using the cross-coupling between iodobenzene and *n*-butyl acrylate as model reaction, they evaluated the catalytic activities of several palladium species in pure glycerol (Scheme 27). Best results were obtained using PdCl₂, Pd(OAc)₂ and [Pd(OAc)₂(TPPTS)₂] (TPPTS = tris(3-sulfophenyl)phosphine trisodium salt), associated with Na₂CO₃, which led to the selective formation of *n*-butyl cinnamate **41a** in 32–100% yield after 4 h at 80 °C. Worthy of note, this chemical transformation could be considerably accelerated under microwave irradiation. Thus, using a domestic MW oven with a temperature rise from 26 to 117 °C, [Pd(OAc)₂(TPPTS)₂] as a catalyst and Na₂CO₃ as a base, **41a** could be generated in 93% yield after only 10 min of irradiation.

The Heck coupling of iodobenzene was also operative with *i*-butyl acrylate and styrene, furnishing *i*-butyl cinnamate **41b** and stilbene **41c**, respectively, in high yields. Alternatively, bromobenzene could also be employed as starting material, although in this case, as usually observed in Heck reactions, the efficiency of the process was significantly reduced.⁶³ Interestingly, these catalytic reactions were compatible with the use of crude glycerol as solvent, albeit slightly lower conversions than in pure glycerol were in general reached.⁴² This decrease in activity has been attributed to the presence of fatty acid salts in the solvent, impurities presumably able to deactivate the catalytically active species. However, it is important to note that, when crude glycerol was used as solvent, addition of a base was not required since basic residues present in the solvent are sufficient to generate the catalytically active Pd(0) species.

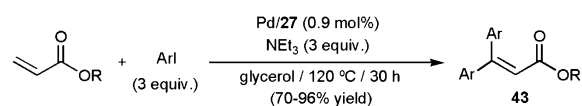
**Scheme 27** Heck-type reactions performed in glycerol.

Related cross-coupling reactions between ethyl acrylate and iodobenzene have also been investigated by Bellina and co-workers employing the glycerol-based ionic liquids **C** as solvents (Fig. 2).³⁰ Reactions performed at 100 °C in the presence of 5 mol% of PdCl₂ and NaOAc (1.1 equiv.) delivered the desired ethyl cinnamate in variable yields after 1 h (3–87%). In general, better results were obtained on increasing the length of the alkyl chain in the cation, that is, on increasing the lipophilicity of the solvent. Unfortunately, reuse of these IL systems was not very encouraging due to the considerable loss of activity after the first recycling.

In contrast to classical monoarylation processes, which have found widespread applications in organic synthesis, efficient β,β-diarylations of alkenes remain scarce.⁶⁴ Such a double C–C couplings are generally favoured at high temperatures, hence glycerol can be particularly adequate for such transformations. Accordingly, Jérôme and co-workers have recently reported the high yield synthesis of a variety of diaryl alkenes **43** through the diarylation of acrylates with iodoarenes in this medium (Scheme 28).⁶⁵ Reactions promoted by palladium nanoparticles stabilized over the aminopolysaccharide **27** (see Scheme 20) and triethylamine were carried out in the presence of 3 equivalents of the corresponding aryl iodides at 120 °C for 30 h. Interestingly, under these experimental conditions no monoarylated derivatives were detected in the crude reaction mixtures, although small amounts (<10%) of biphenyls, typical homo-coupling side-products in Heck-type reactions, were produced. It is also noteworthy that diaryl alkenes **43** showed a good stability in glycerol, which contrasts favorably with their behavior in aqueous media, where the ester moieties are prone to undergo partial hydrolysis making difficult their isolation in good yields.⁶⁶

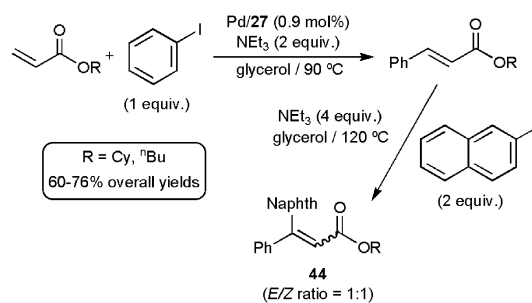
The catalytic system Pd/**27** is also suitable for performing the selective monoarylation of acrylates, just by decreasing the quantity of aryl iodide (1 vs. 3 equiv.) and the temperature (90 vs. 120 °C) employed. Taking advantage of this behavior, a convenient synthetic route to unsymmetrical diarylated alkenes **44** could be developed through the sequential Heck couplings of acrylates, first with iodobenzene at 90 °C, and then with 2-iodonaphthalene at 120 °C (Scheme 29).⁶⁵ Concerning the isolation of the products, the best results were achieved by extracting **43–44** from the glycerolic medium with scCO₂, since the use of classical organic solvents led to concomitant extraction of the Pd/AP catalyst.

The feasibility of Suzuki-type processes in glycerol has also been demonstrated using the coupling between iodobenzene and phenyl boronic acid as model reaction (Scheme 30).⁶³ The behavior of different palladium catalysts was evaluated in this transformation, finding that Pd(OAc)₂ and [Pd(OAc)₂(TPPTS)₂] presented the highest activities, whereas the best recyclability

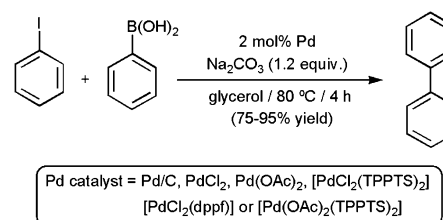


R = Cy; Ar = Ph, 2-naphthyl, 2,4-C₆H₃(OMe)₂, 2-Me-5-C₆H₃NO₂, 2-Me-5-C₆H₃NH₂
R = ⁿBu; Ar = Ph, 2-naphthyl, 2,4-C₆H₃(OMe)₂

Scheme 28 β,β-diarylation of acrylate derivatives in glycerol.



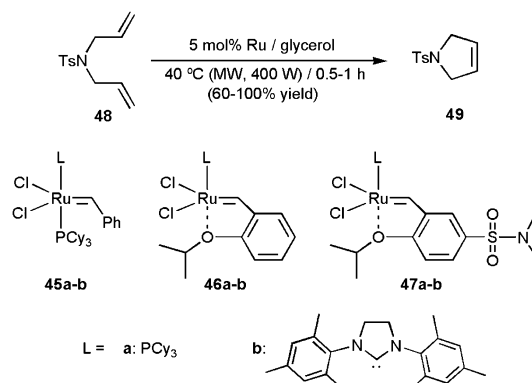
Scheme 29 Unsymmetrical β,β-diarylations of acrylates in glycerol.



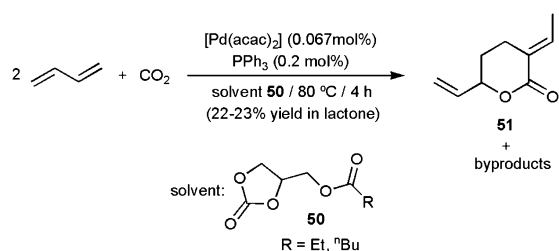
Scheme 30 Biphenyl synthesis through Suzuki coupling in glycerol.

(up to three consecutive runs without loss of activity) was provided by [PdCl₂(dppf)] (dppf = 1,1'-bis(diphenylphosphino)ferrocene).

Olefin metathesis is one of the most powerful tools presently available to generate new C–C bonds,⁶⁷ with recent efforts in this area being focused on the development of environmentally friendly procedures to perform this type of transformations. In this context, a wide variety of elaborated water-soluble metal-catalysts have been designed to realize these processes in aqueous media.⁶⁸ The higher capacity offered by glycerol to dissolve transition-metal complexes has been recently exploited by Colacino and co-workers to develop ring closing metathesis (RCM) reactions in this green medium using classical ruthenium-carbenes.⁶⁹ In particular, they explored the efficiency of the first and second generations of Grubbs (**45a–b**), Hoveyda–Grubbs (**46a–b**) and Zhan (**47a–b**) catalysts in the RCM of *N,N*-diallyltosylamine **48** (Scheme 31). By performing the reactions at 40 °C under MW-irradiation with a ruthenium loading of 5 mol%, all the catalysts checked proved to be active, with the most soluble one **47b** showing the best performance (complete conversion after



Scheme 31 Catalytic RCM of *N,N*-diallyltosylamine in glycerol.



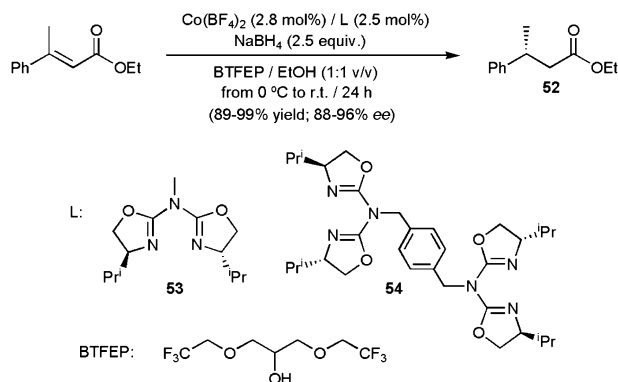
Scheme 32 Pd-catalyzed telomerization of butadiene with CO_2 .

30 min of irradiation). The low solubility of *N*-tosyl-2,5-dihydro-1*H*-pyrrole **49** in glycerol allowed its isolation by simple extraction with diethyl ether. In addition, after lyophilization to remove traces of water and Et_2O , the glycerolic phase containing the Ru catalyst could be reused in two further catalytic cycles without a significant loss of activity.

The potential of glycerol carbonate esters **50** to act as solvents for catalytic C–C bond forming reactions was evaluated in the Pd-catalyzed telomerization of butadiene with carbon dioxide to form the δ -lactone **51** (Scheme 32).²⁶ Control on the selectivity of this reaction towards **51**, a valuable intermediate in organic synthesis,⁷⁰ is a challenging task since several side reactions can occur, *i.e.* dimerization and oligomerization of butadiene, formation of acyclic acids and esters, *etc.* In this sense, although somewhat worse yields and selectivities were observed using carbonate esters **50** when compared with results obtained in lighter carbonates (ethylene-, propylene- and butylene-carbonate), only the use of these high-boiling point solvents allowed total separation of the product by distillation in a semi-technical scale, and the reuse of the catalytic system.

In addition to the early attempts made by Tarama and Funabiki to perform hydrogenations in a glycerolic medium,⁶² Wolfson and co-workers also investigated the hydrogenation of styrene into ethylbenzene in neat glycerol using $[\text{RhCl}(\text{TPPTS})_3]$ or Pd/C as the catalyst (10 bar of H_2 , 80 °C).³⁸ Addition of Pluronic, a non-ionic surfactant, was necessary to compensate for the poor solubility of styrene in the medium, but even so the catalytic activities remained moderate. The same authors equally explored the hydrogenation of carbonyl compounds in glycerol (10 bar of H_2 , 60 °C).³⁹ Moderate yields on the reduced alcohols were reached with Pd/C (52–60%), while molecular rhodium or ruthenium precursors appeared to be almost inactive. The poor catalytic performances, inferior than those observed in methanol or toluene, were ascribed to the low solubility of hydrogen gas in glycerol. Note that, the use of the chiral ruthenium catalyst $[\text{RuCl}(\eta^6\text{-}p\text{-cymene})\{(S)\text{-BINAP}\}][\text{Cl}]$ (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) in the hydrogenation of ethyl acetoacetate induced a high enantioselectivity (99% ee, with *(S)*-ethyl-3-hydroxybutyrate as the major enantiomer), albeit with a very disappointing yield (7%).³⁹ Despite its limited potential, this reaction merits to be highlighted since it stands as the first example of an asymmetric metal-catalyzed process carried out in glycerolic media.⁷¹

More recently, high enantioselectivities, combined with excellent yields, have been described for the Co(II)-catalyzed

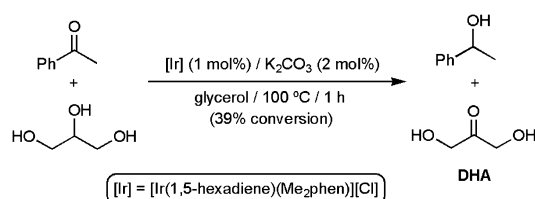


Scheme 33 Co(II)-catalyzed enantioselective C=C reduction by NaBH_4 .

reduction of (*E*)-ethyl-3-phenylbut-2-enoate into (*R*)-ethyl-3-phenylbutanoate **52** by NaBH_4 , using chiral azabis(oxazoline) ligands **53–54** and a mixture of the glycerol-based ether BTFEP (1,3-bis(2,2,2-trifluoroethoxy)propan-2-ol) and ethanol as solvent (Scheme 33).⁷² When compared with its homologue **53**, ligand **54** conferred a higher stability to the resulting catalytic system, thus leading to a better conversion, selectivity and recyclability. Interestingly, the catalytic performances of these cobalt(II)/azabis(oxazoline) systems in BTFEP/EtOH surpassed by far those achieved using the ionic liquid $[\text{BMIM}][\text{PF}_6]$ as solvent.

In the last few decades, metal-catalyzed transfer hydrogenation (TH) reactions from 2-propanol to unsaturated compounds have emerged as an efficient reduction method of organic substrates such as ketones, aldehydes, imines and olefins.⁷³ Like 2-propanol, glycerol can also act as a solvent and hydrogen donor in TH reactions. Interest in TH processes from glycerol relates also with the concomitant formation of dihydroxyacetone (DHA), the expected oxidized form of glycerol,⁷⁴ due to the industrial relevance of this chemical.⁷⁵ The first report on TH in glycerol, published by Crotti and co-workers in 2009, examined the reduction of acetophenone by the iridium(I) derivatives $[\text{Ir}(1,5\text{-hexadiene})(\text{N-N})][\text{Cl}]$ (N–N = 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4phen), 4,7-dimethyl-1,10-phenanthroline (Me_2phen), 4,4'-dimethyl-2,2'-bipyridine (Me_2bipy), 2,2'-bipyridine (bipy)).⁷⁶

The highest rate was achieved by employing $[\text{Ir}(1,5\text{-hexadiene})(\text{Me}_2\text{phen})][\text{Cl}]$ associated with K_2CO_3 at 100 °C, but conversion in 1-phenylethanol was quite modest (39%) (Scheme 34). In addition, authors observed the gradual decomposition of DHA, probably favoured by the presence of a base and the high temperature employed. In order to minimize the DHA decomposition, Crotti and co-workers also explored the ability of the iridium(I) complex **55** (Fig. 4),



Scheme 34 Transfer hydrogenation of acetophenone in glycerol.

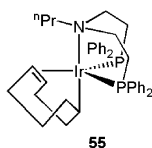


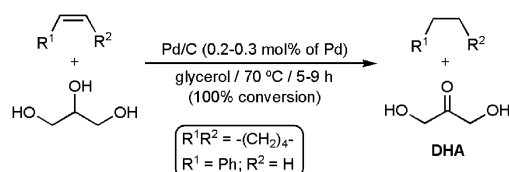
Fig. 4 Structure of the iridium(I) complex **55**.

previously described as an efficient catalyst for TH reactions under base-free conditions in isopropanolic media,⁷⁷ to promote the reduction of acetophenone in glycerol.⁷⁸ Unfortunately, **55** turned out to be almost inactive (yields <8%). In contrast, when benzaldehyde, a more reactive substrate, was used as starting material it could be reduced to benzyl alcohol under these base-free conditions, albeit with moderate conversion (up to 46%). Once again, despite the absence of a base, DHA still underwent degradation, with its final proportion being well below than that of benzyl alcohol (12–24% vs. 18–46%).⁷⁸

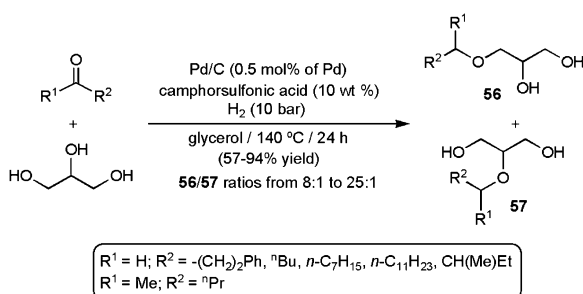
The hydrogen transfer from glycerol to benzaldehyde was also explored using a catalytic system composed of the ruthenium dimer $[\{\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-}p\text{-cymene})\}_2]$ and KOH (1 mol% of Ru, 12 mol% of base).⁷⁹ Both conventional heating (70 °C) and MW irradiation (domestic oven, 900 W) led to moderate yields in benzyl alcohol (33–45%), and complete transformation of benzaldehyde could only be achieved by increasing the ruthenium loading to 25 mol%.^{79a}

Reduction of olefins through TH processes in glycerol proved to be more satisfactory than reduction of carbonyl compounds. Thus, palladium supported on carbon (0.2–0.3 mol% Pd) was found to hydrogenate quantitatively cyclohexene or styrene after 5–9 hours of heating at 70 °C in pure glycerol (Scheme 35).^{79a} However, we must note that bulky olefins (*i.e.* stilbene and 1,1-diphenyl ethylene) and linear aliphatic alkenes (*i.e.* 1-hexene and 1-octene) were only partially reduced through this methodology (7–35% yields).⁸⁰

The reductive etherification of glycerol with carbonyl compounds depicted in Scheme 36 is another example of a catalytic process in which the glycerol acts both as a solvent



Scheme 35 Pd-catalyzed transfer hydrogenation of olefins in glycerol.

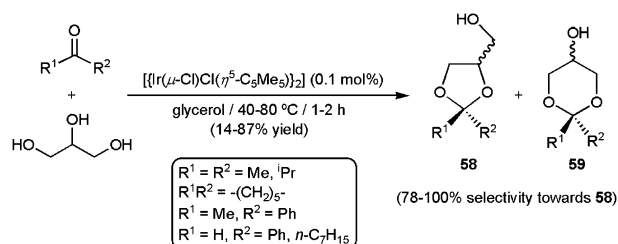


Scheme 36 Reductive etherification of glycerol.

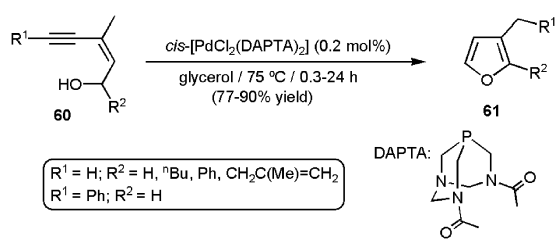
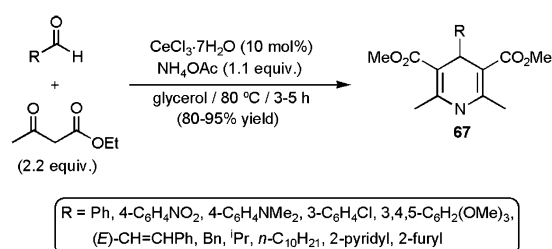
and reagent. This coupling between an aldehyde (or a ketone) and glycerol, promoted by Pd/C and camphorsulfonic acid under H₂ atmosphere, offers an easy entry to glycerol monoethers **56–57**.⁸¹ Interestingly, despite the similar pK_a values of the different hydroxyl groups in glycerol, 1-*O*-alkylation occurred preferentially, thus generating ethers **56** as the major reaction products. This high selectivity is specific to glycerol since related etherification reactions of 1,2-propanediol, a diol with both primary and secondary hydroxyl functions, gave rise to 1 : 1 mixtures of the two possible regioisomers, *i.e.* 1-*O*-alkyl and 2-*O*-alkyl ethers. Concerning the mechanism of these catalytic reactions, the authors demonstrated that 5- and 6-membered cyclic acetals are first formed from the starting aldehyde and glycerol, and then they are reduced with hydrogen to generate the final acyclic ethers.

Glycerol-based acetals and ketals are valuable chemical intermediates,⁸² and the development of efficient and selective routes of access is of particular interest. Glycerol acetalization can be promoted by conventional acid catalysts, however such procedures are environmentally unfriendly due to extensive salt formation, and they suffer from a lack of selectivity towards the two possible regioisomers, *i.e.* the five-membered cyclic acetal (1,3-dioxolane **58**) and the six-membered one (1,3-dioxane **59**). In contrast, it has been recently demonstrated that the iridium dimer $[\{\text{Ir}(\mu\text{-Cl})\text{Cl}(\eta^5\text{-C}_5\text{Me}_5)\}_2]$ catalyzes the glycerol acetalization with acetone in good yield (75%) and excellent selectivity (98%) towards the corresponding 1,3-dioxolane **58** (Scheme 37).⁸³ Comparable results were also obtained with cyclohexanone, but the involvement of more sterically hindered ketones resulted in a drop of the conversion (only 14% for R¹ = R² = ^{*i*}Pr). The acetalization with acetophenone, an unsymmetrical ketone, exhibited once again a good regioselectivity (96% of **58**), but a total lack of diastereoselectivity (*cis/trans* ratio = 1 : 1). As expected, aldehydes showed higher reactivity than ketones (yields up to 87%), albeit with a slightly lower regioselectivity (78–82%).

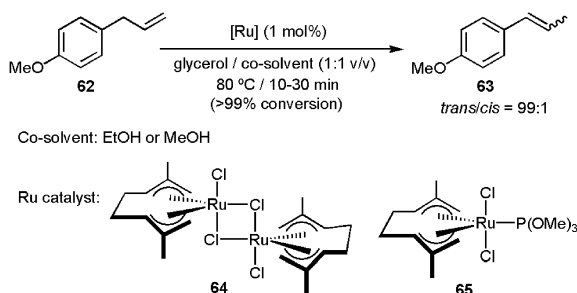
Cycloisomerization of (*Z*)-enynols represents an appealing route for the construction of furan rings due to its atom-economical nature.⁸⁴ However, despite its synthetic interest, efforts devoted to develop this process in a green media have been scarce.⁸⁵ Recently, the heteroannulation of (*Z*)-2-en-4-yn-1-ol derivatives **60** into furans **61** has been conveniently performed in glycerol using the hydrophilic palladium(II) catalyst *cis*-[PdCl₂(DAPTA)₂] (Scheme 38).⁸⁶ Although slightly higher activities were observed in aqueous medium, catalyst recycling after extraction of the product with diethyl ether was much more effective in glycerol. Thus, while the



Scheme 37 Ir-catalyzed glycerol acetalization with carbonyl compounds.

Scheme 38 Palladium-catalyzed cycloisomerization of (*Z*)-enynols.

Scheme 41 Hantzsch synthesis of pyridines in glycerol.

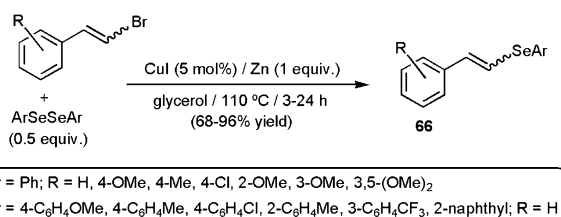


Scheme 39 Ru-catalyzed isomerization of estragole into anethole.

performances of the aqueous solution decreased rapidly, allowing only five consecutive runs, the catalytic behavior of the glycerolic phase was maintained during 17 runs, leading to cumulative TON values up to 8190, which are the highest reported up to date for this catalytic transformation.

trans-Anethole **63** is a relevant compound with important applications in the cosmetic industries and as a food and beverage additive. According to current food regulatory instructions, the *cis*-anethole content is limited to 1% for human uses due to its toxicity and organoleptic properties. Hence, the search for highly *trans*-selective formation of anethole represents a challenge for synthetic chemists. In this context, a green protocol based on the isomerization of estragole **62** into anethole has been designed in glycerolic media employing different ruthenium(IV) catalysts (Scheme 39).⁸⁷ Best results were accomplished with the dimeric precursor **64** and the mononuclear derivative **65** in glycerol/EtOH or glycerol/MeOH mixtures which allowed full conversions in short times and, most importantly, with high *trans*-selectivities (99%). Similar results were also obtained using water/MeOH or water/EtOH solvent systems, but catalyst recycling was again more effective from the glycerolic mixtures.

Coupling reactions of vinyl bromides with diaryl diselenides have also been studied using glycerol as the reaction medium (Scheme 40).⁸⁸ Seleniations proceeded efficiently in the



Scheme 40 Copper(I)-catalyzed seleniation of vinyl bromides in glycerol.

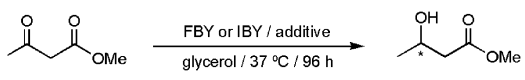
presence of 5 mol% of CuI and zinc dust, and were operative with several diaryl diselenides and a variety of substituted aromatic vinyl bromides, with *cis*- or *trans*-disposition on the C=C bond. Interestingly, the stereochemistry of the starting products was mainly retained in the final vinyl selenides **66**. Following a similar methodology, phenyl styryl telluride has been synthesized from diphenyl ditelluride. We note also that the catalytic system could be recovered, after extraction of the products with ethyl acetate, and reused 4 times with only a slight decrease in the activity.

In recent years, considerable attention has been paid to the synthesis of 1,4-dihydropyridines owing to their significant biological activities.⁸⁹ One of the most reliable methodologies is the Hantzsch reaction, a one-pot three-component process, which involves the coupling between an aldehyde, two equivalents of a β -ketoester and an ammonium salt. In this context, Narsaiah and Nagaiah have recently developed a procedure to prepare Hantzsch pyridines in glycerol.⁹⁰ Thus, as shown in Scheme 41, using 10 mol% of CeCl₃ as a catalyst, a variety of electron-rich or electron deficient aromatic-, heteroaromatic- or aliphatic-aldehydes were efficiently transformed into 1,4-dihydropyridines **67** by coupling with ethyl acetoacetate and ammonium acetate.

Biocatalysis

Biocatalysis plays an important role within the Green Chemistry context, since it usually provides highly chemo- regio- and stereoselective synthetic routes under mild conditions.⁹¹ Although the natural solvent for enzymes is water, the hydrophobic character of most of the organic compounds has made almost mandatory the use of partly or fully nonaqueous environments. However, it is well-documented that enzymes are denatured in the presence of organic solvents, and that the specific catalytic activities of enzymes that are stable in organic media are generally lower than those in aqueous systems.⁹² In this sense, the ability of glycerol to mimic the effect of water preserving enzyme structure,⁹² makes this solvent an appropriate candidate for biocatalysis.

In 2006, Wolfson and co-workers reported the first biocatalytic transformation in pure glycerol, accomplishing successfully the asymmetric reduction of methyl acetoacetate with both free (FBY) and immobilized (IBY; alginate beads) baker's yeast.⁹³ As illustrated in Table 3, IBY showed a higher catalytic activity than FBY, while the enantioselectivity of the product, (*S*)-methyl 3-hydroxybutyrate, was very high (>95% ee) with both catalysts (entry 1). The higher performance of IBY was attributed to the presence of residual water, which

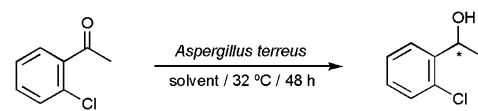
Table 3 Enantioselective reduction of methyl acetoacetate with baker's yeast in glycerol^d


Entry	Additive	FBY (%)	ee (%)	IBY (%)	ee (%)
1	None	61	> 99 (<i>S</i>)	87	> 99 (<i>S</i>)
2	Water ^b	73	97 (<i>S</i>)	94	97 (<i>S</i>)
3	Glucose	71	> 99 (<i>S</i>)	96	> 99 (<i>S</i>)
4	Sucrose	75	> 99 (<i>S</i>)	99	> 99 (<i>S</i>)
5	Ethanol	67	95 (<i>S</i>)	90	> 99 (<i>S</i>)

^a Reactions performed at 37 °C for 96 h using 1 g of substrate, 50 mL of glycerol, 10 g of FBY or 50 g of IBY (generated from 10 g of FBY) and 5 g of additive. ^b 5 wt%.

remained inside the IBY beads during their preparation. In accord with this, the addition of 5 wt% of water to glycerol increased the activity without changing significantly the enantioselectivity (entry 2 vs. 1). Addition of various hydrogen sources, such as glucose (entry 3), sucrose (entry 4) or ethanol (entry 5), equally increased the activity (up to 99% conversion), while keeping the high enantioselectivity. Using IBY as the catalyst and sucrose as the additive, good results were also obtained in the asymmetric reduction of ethyl acetoacetate, *i.e.* 99% conversion after 48 h with > 99% ee. However, we must note that, under the same reaction conditions, the activity of IBY towards the aliphatic prochiral ketones 2-octanone and 2-butanone was much lower (up to 22% conversion after 96 h with > 97% ee).⁹³

Remarkably, although higher activities were observed when these reduction reactions were performed in aqueous medium, the use of glycerol as solvent enabled a more efficient product extraction, since glycerol does not form emulsions with the extracting solvent (ethyl acetate, diethyl ether, *n*-hexane and dichloromethane were evaluated).^{93,94}

Table 4 Influence of organic co-solvents in the asymmetric bioreduction of 2'-chloroacetophenone^d


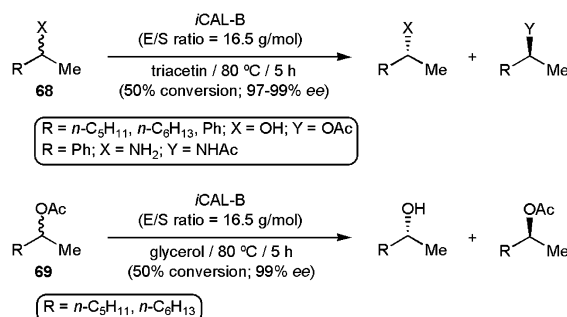
Entry	Solvent	Yield (%)	ee (%)
1	PBS	24	65 (<i>S</i>)
2	PBS–glycerol (9 : 1)	49	92 (<i>S</i>)
3	PBS–glycerol (4 : 1)	44	> 99 (<i>S</i>)
4	PBS–DMSO (9 : 1)	51	> 99 (<i>S</i>)
5	PBS–DMSO (4 : 1)	10	> 99 (<i>S</i>)
6	PBS–acetonitrile (9 : 1)	9	> 99 (<i>S</i>)
7	PBS–acetonitrile (4 : 1)	—	—
8	PBS–toluene (9 : 1)	4	—
9	PBS–toluene (4 : 1)	< 1	—
10	PBS–diethyl ether (9 : 1)	4	—
11	PBS–diethyl ether (4 : 1)	3	—
12	PBS–THF (9 : 1)	2	—
13	PBS–THF (4 : 1)	2	—

^a Reactions performed at 32 °C for 48 h using 3.0 g of fungal cells, 20 μL of substrate and 50 mL of solvent. PBS = phosphate buffer solution (Na₂HPO₄/KH₂PO₄; pH 7).

Studies by Andrade and co-workers have also demonstrated the utility of glycerol as co-solvent for biocatalytic transformations in aqueous solution. Thus, in the enantioselective bioreduction of 2'-chloroacetophenone by cells of *Aspergillus terreus* in phosphate buffer solution (pH 7), they observed remarkable yield and enantioselectivity improvements by adding variable amounts of glycerol (entries 2 and 3 vs. 1 in Table 4).⁹⁵ As shown in Table 4, such improvements were in general not observed using other water–organic solvent mixtures (entries 4–13). Three factors have been evoked to explain the beneficial effect of glycerol in this reaction: (i) it improves the solubility of the substrate, (ii) unlike the other organic solvents, it generates a homogeneous medium in combination with water that avoids mass transfer limitations facilitating the enzyme–substrate interactions, and (iii) it stabilizes the protein native structure and prevents its denaturation, thus preserving the enzymatic activity. We note that similar positive results were obtained in the bioreduction of other *ortho*-, *meta*- and *para*-substituted halo-acetophenones (F, Cl, Br).⁹⁵ In addition, the synthetic utility of the process was confirmed by performing the catalytic reactions at a preparative scale, which delivered the desired optically active alcohols in high isolated yields (up to 80% with 95–99% ee).

The higher ability of glycerol vs. water to dissolve organic compounds has also been exploited to facilitate the hydrolytic kinetic resolution of racemic styrene oxide at high substrate concentrations.⁹⁶ Thus, using the recombinant *Pichia pastoris* yeast which expresses the epoxide hydrolase gene of *Rhodotorula glutinis* as the biocatalyst, enantiopure (*S*)-styrene oxide (98% ee) could be obtained in 41% yield (maximum yield = 50%) from 1.8 M racemic styrene oxide, after 24 h at 4 °C, by adding 40% (v/v) of the surfactant Tween 20 and 5% (v/v) of glycerol to the KH₂PO₄ buffer (pH 8.0). Note that, in the absence of glycerol, the recombinant cells only catalyzed the kinetic resolution efficiently at concentrations below 1.3 M (0.526 M in the absence of both Tween 20 and glycerol).

The utility of triacetin as green solvent and acyl donor for lipase-catalyzed kinetic resolution of racemates has also been recently demonstrated by Dlugy and Wolfson.⁹⁷ Thus, as shown in Scheme 42, they successfully performed the kinetic resolution of representative secondary alcohols and amines **68** in triacetin using *Candida antarctica* lipase B immobilized on acrylic resin (*i*CAL-B). Full conversions (50%) and excellent enantioselectivities (97–99% ee) were in all cases reached at 80 °C employing an enzyme to substrate (E/S) ratio of 16.5 g mol⁻¹. In the course of the alcoholysis process, glycerol

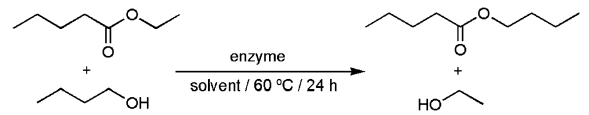
**Scheme 42** Kinetic resolutions using triacetin and glycerol.

diacetate, glycerol monoacetate and glycerol are formed as by-products. However, their high solubility in triacetin allowed the easy separation of the desired alcohol (or amine) and ester (or amide) enantiomers from the crude reaction mixture by simple extraction with diethyl ether. In the same work, efficient kinetic resolution of 2-heptyl acetate and 2-octyl acetate racemates **69** could also be achieved using glycerol as the solvent and acyl-acceptor (Scheme 42).⁹⁷ The effective resolution of a racemic mixture of 2-pentyl acetate with *i*CAL-B in glycerol was similarly achieved.³⁸

Triacetin was also employed as solvent and acyl donor in the transesterification of isoamyl alcohol **39** into isoamyl acetate **40** (see Scheme 26).⁹⁸ Both free (CAL-B) and immobilized *Candida antarctica* lipase B (*i*CAL-B) were able to promote efficiently the transesterification process, with the latter showing a higher efficiency (73% of conversion after 5 h at 80 °C). At the end of the reaction, **40** could be easily separated from the reaction mixture by extraction with petroleum ether, and the immobilized lipase was recovered by simple filtration and re-used three additional times without significant loss of its efficiency.

Deep eutectic solvents (DESs) have recently emerged as promising reaction media for biocatalysis.⁹⁹ In this context, using the transesterification of ethyl valerate with 1-butanol as model reaction, the activities of selected lipases in different DESs based on choline chloride (ChCl) or ethylammonium chloride (EAC) mixtures with the organic hydrogen-bond donors acetamide (Acet), urea (U), malonic acid (MA), ethylene glycol (EG) or glycerol (Gly) were evaluated by Kazlauskas and co-workers.¹⁰⁰ As shown in Table 5, all the enzymes tested showed similar or higher activities to that shown in toluene (entry 9) when the glycerol-based deep eutectic mixture ChCl:Gly (entry 3) was used as solvent

Table 5 Lipase-catalyzed transesterification of ethyl valerate with 1-butanol in DESs and toluene^a

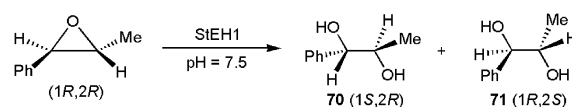


Entry	Solvent	<i>i</i> CAL-B ^b	CAL-B ^b	CAL-A ^{b,c}	PCL ^{b,d}
1	ChCl:Acet	23	96	0.5	0.0
2	ChCl:EG	11 (99)	32 (93)	3.0	0.2
3	ChCl:Gly	96	96	70	22
4	ChCl:MA	30	58	0.7	0.0
5	ChCl:U	93	99	1.6	0.8
6	EAC:Acet	63	92	2.7	0.0
7	EAC:EG	23 (54)	33 (79)	20	0.0
8	EAC:Gly	93	91	2.1	0.5
9	Toluene	92	92	76	5.0

^a Reactions performed at 60 °C for 24 h using 40 mM ethyl valerate, 400 mM 1-butanol and 10 mg cm⁻³ of the corresponding enzyme.

^b Percentage conversions of ethyl valerate to butyl valerate are given (%). Number in parentheses is the percentage conversion including the side reaction with the ethylene glycol component of the deep eutectic solvent. No side reactions were observed in the rest of the cases.

^c CAL-A = lyophilized *Candida antarctica* lipase A. ^d PCL = lyophilized *Pseudomonas cepacia* lipase (recently reclassified as *Burkholderia cepacia*).



Scheme 43 StEH1-catalyzed hydrolysis of (1*R*,2*R*)-2-methylstyrene oxide.

(*i*CAL-B and CAL-B showed also a remarkable activity in EAC:Gly; entry 8). Remarkably, contrary to the case of ethylene glycol (entries 2 and 7), competence of glycerol with 1-butanol in the transesterification process was not observed. In addition, after incubation of *i*CAL-B in either toluene or ChCl:Gly for 18 h at 60 °C, its activity dropped by 12% in toluene, compared to that observed before incubation, and only by 5% in ChCl:Gly, thus demonstrating the higher long-term stability of the enzyme in this alternative reaction medium.^{100c} *i*CAL-B-catalyzed aminolysis of ethyl valerate with 1-butylamine could also be conveniently performed in ChCl:Gly with a rate and conversion similar again to that reached in toluene.^{100a,b}

The deep eutectic mixture ChCl:Gly can also be used as a suitable co-solvent for biocatalytic transformations in aqueous solution. In this sense, the rate of esterase-catalyzed hydrolysis of *p*-nitrophenol acetate in BES buffer (*N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid and its sodium salt) increased moderately upon addition of 10 vol% of ChCl:Gly (three-fold increase for pig liver esterase and *Rhizopus oryzae* esterase and a 25% increase for *Pseudomonas fluorescens* esterase), while an impressive 20-fold increase in conversion was observed in the EHAD1-catalyzed hydrolysis of styrene oxide (EHAD1 = epoxide hydrolase AD1 from *Agrobacterium radiobacter*).¹⁰⁰ The effect of ChCl:Gly in the catalytic hydrolysis of (1*S*,2*S*)- and (1*R*,2*R*)-2-methylstyrene oxide was also evaluated using the *Solanum tuberosum* epoxide hydrolase 1 (StEH1).¹⁰¹ In this case, enzyme function was not significantly affected by the presence of the glycerol-based DES. However, it is of note that it was able to enhance the regioselectivity of the hydrolysis of the (1*R*,2*R*) enantiomer, favouring the epoxide ring opening at the benzylic carbon, as compared to the phosphate buffer-only system (**70/71** ratio = 2.33 vs. 1.35; Scheme 43). Unfortunately, no explanation was given for this solvent-effect on the regioselectivity.

Conclusions

This *Feature Article* has outlined the utilization of glycerol and some of its derivatives as green reaction solvents for synthetic organic chemistry, an emerging research field that has as main objective the valorization of a waste generated by the biodiesel industry. The current availability of glycerol on a large scale and at a low cost, combined with its intrinsic properties, *i.e.* no toxicity, no flammability, obtaining from renewable sources and biodegradability, makes it an ideal candidate to develop greener synthetic processes. However, despite all these considerations, problems associated with its high viscosity, which could provoke poor substrate diffusion in the medium, and the presence of three reactive and metal-coordinating hydroxyl groups should be taken into account prior to its utilization as solvent for a particular reaction. Extraction of

highly polar reaction products from glycerol is also a problem that needs to be solved prior to practical uses.

Solvent properties of glycerol can be tailored, tuned and adjusted according to the requirements of each reaction by chemical modification of its structure, thus allowing to overcome some of the above-mentioned drawbacks. However, synthetic routes must be improved since most of the glycerol-based solvents presently available are synthesized through very costly processes.

In summary, although much effort has to be made in the future to extend the use of these alternative solvent systems, the numerous publications appeared in the last five years reveal that this field is of major interest to the chemical community, and the authors hope that this comprehensive account will stimulate further work.

Acknowledgements

Financial support from the Spanish MICINN (Projects CTQ2006-08485/BQU, CTQ2010-14796/BQU and CSD2007-00006) is gratefully acknowledged. B.L.-B. thanks FICYT of Asturias (PCTI-Severo Ochoa program) and J.F. thanks MEC of Spain and the European Social Fund (FPU program) for the award of PhD grants.

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