

Glycerol as a sustainable solvent for green chemistry

Yanlong Gu^{*a} and François Jérôme^{*b}

Received 25th January 2010, Accepted 7th April 2010

First published as an Advance Article on the web 11th June 2010

DOI: 10.1039/c001628d

Glycerol, an organic waste generated by the biodiesel industry, has been recently proposed as a valuable green solvent. This review summarizes the advantages, disadvantages and potential uses of glycerol as a green solvent for catalysis, organic synthesis, separations and materials chemistry. In particular, through selected examples we show here that glycerol may combine the advantages of water (low toxicity, low price, large availability, renewability) and ionic liquids (high boiling point, low vapour pressure, low solubility in scCO_2). More generally, all these reported works contribute to increase the portfolio of available green solvents and afford innovative solutions to the substitution of the conventionally used volatile organic solvents.

1. Introduction

Most organic reactions occur in a liquid phase. The solvent not only allows a better contact between reactants, stabilises or destabilises intermediates and/or transition states but also determines the choice of work up procedures and recycling or disposal strategies. Taking into account the impact of chemical processes on the environment, the search for innovative concepts for the substitution of volatile organic solvents has become a

tremendous challenge in academia and industry.¹ According to the twelve principles of green chemistry, a green solvent should meet numerous criteria such as low toxicity, non-flammability, non-mutagenicity, non-volatility and widespread availability among others. Moreover these green solvents have to be cheap and easy to handle and recycle.²

In the past decade, water,³ ionic liquids,⁴ polyethylene glycol,⁵ supercritical fluids⁶ (particularly supercritical carbon dioxide (scCO_2)⁷) and perfluorinated solvents⁸ appeared as the most promising approaches for current solvent innovation. Although fascinating results have been reported, use of these solvents is still subject to strict limitations such as high cost equipment for scCO_2 ,⁹ or high prices and lack of data about the toxicity and bio-compatibility for ionic liquids,¹⁰ or product separation for aqueous-based processes.¹¹ In other words, a universal green solvent doesn't exist and for this reason, the scientific community is continuously searching for new sustainable media in order to widen their use in catalytic and organic processes.

^aInstitute of Physical Chemistry and Industrial Catalysis, Hubei Key Laboratory of Material Chemistry and Service Failure, Huazhong University of Science and Technology, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology (HUST), 1037 Luoyu road, Hongshan District, Wuhan, 430074, China. E-mail: klgyl@hust.edu.cn; Fax: (0)86-(0)27-87 54 45 32

^bLaboratoire de Catalyse en Chimie Organique, Université de Poitiers/CNRS, 40 avenue du recteur, Pineau, 86022, Poitiers, France. E-mail: francois.jerome@univ-poitiers.fr



Yanlong Gu

Yanlong Gu obtained his PhD degree in 2005 from Lanzhou Institute of Chemical Physics, Chinese Academy of Science, China (with Prof. Y. Deng). He then accepted a post-doctoral position at the University of Tokyo, Japan (with Prof. Shū Kobayashi). After one year, he joined the group of Joël Barrault at the Université de Poitiers, France. Since September 2008, he is a professor in the School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan, P.R. China. His research interests include value-added conversions of biomass and development of synthetic methodologies by using green solvent systems.



François Jérôme

François Jérôme received his PhD degree in chemistry from the University of Burgundy (France, with Prof. R. Guilard) in 2000. He then moved to the University of California, Davis (USA with Prof. K. M. Smith) as a post-doctoral fellow. Next, he moved back to France for a second postdoctoral position at the University of Rennes 1 (with Prof. P. H. Dixneuf). In 2002, he joined the CNRS as a permanent researcher in the Laboratoire de Catalyse en Chimie Organique located at the University of Poitiers in France. His current research interests concern the development of new catalytic systems for the selective conversion of renewable raw materials.

Nowadays, most solvents are prepared from fossil oil reserves. With the predicted disappearance of oils, interest in utilization of biomass-derived solvents has grown.¹² So far, many naturally available products, such as soy methyl ester,¹³ lactate ester,¹⁴ D-limonene¹⁵ and polyhydroxyalkanoates¹⁶ among others have been proposed as safer solvents for catalysis, organic reactions or separations. Many others have also been used as precursors for the synthesis of potentially safer green solvents, for example, bio-based ionic liquids.¹⁷ As compared to the traditional petrochemical-derived solvents, these biomass-based solvents exhibit many advantages such as biodegradability, low vapor pressure and high boiling point which perfectly fit with the different international legislations pushing forward the reduction of volatile organic compounds (VOCs) in the atmosphere. If these biomass-derived solvents are attractive from the viewpoint of green chemistry, it is also noteworthy that their broad utilization in industry requires them to be cost profitable which represents a prerequisite for their viable utilization.

In this context, the possible use of glycerol as a solvent for catalysis or organic chemistry has become of particular interest. This topic is mainly boosted by the rapid emergence of biodiesel on the market. Indeed, glycerol is the main co-product of the vegetable oil industry and new applications are now strongly researched for this natural polyol.¹⁸ Most efforts in this area focus on conversions of glycerol to higher value-added chemicals and some comprehensive reviews have already summarized this work.¹⁹ Although promising works have been reported, other methods that are capable of economically utilizing glycerol waste have also to be considered. In particular, the utilization of glycerol as a solvent or as a precursor for the synthesis of biomass-based solvents has recently emerged in the literature as a feasible and promising approach. Even if this topic does not aim to consume glycerol as a reactant, it is noteworthy that the direct use of glycerol as a solvent offers an indisputable economically and environmentally viable application for this natural polyol. In this review, we report the most recent advances regarding the utilization of glycerol as a green solvent and we summarize here the main advantages and limitations arising from the development of this topic. It should be noted that although some glycerol derivatives, such as glycerol formal,²⁰ glycerol carbonate,²¹ glycerol ethers²² and others,²³ have also been proposed as potential green solvents, these solvents will not be discussed here mainly due to their preparations involving either the use of petrochemicals or complex transformative steps.

2. Solvent properties of glycerol

In its pure form, glycerol is a sweet-tasting, clear, colorless, odorless and viscous liquid. Because it is a trihydric alcohol, glycerol is a polar protic solvent with a dielectric constant of 42.5 (at 25 °C) which is intermediate between that of water (78.5) and an ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm]PF₆, 11.4). Glycerol is completely soluble in water and short chain alcohols, sparingly soluble in many common organic solvents (ethyl acetate, dichloromethane, diethyl ether, etc...), and is insoluble in hydrocarbons. At low temperatures (<17.8 °C), glycerol forms crystals. Its specific density is 1.26 and its molecular weight is 92.09.

Prior to using glycerol as a potentially safer solvent, some specific points have to be taken into consideration in order to maximize as much as possible its solvent properties:

(1) **Solubility:** Like polar solvents such as water, DMSO and DMF, glycerol is able to facilitate dissolution of inorganic salts, acids, bases, enzymes and many transition metal complexes. Furthermore, it also dissolves organic compounds that are poorly miscible in water. Many hydrophobic solvents, such as ethers and hydrocarbons, are immiscible in glycerol. This enables the reaction products to be removed by simple liquid–liquid phase extraction.

(2) **Volatility and boiling point:** As mentioned above, glycerol is nonvolatile under normal atmospheric pressure and has a high boiling point (290 °C), thus making distillation of the reaction products a feasible separation technique. Moreover, taking advantage of its high boiling point, reactions in glycerol can be carried out at high temperatures, thus allowing acceleration of the reaction, or making possible reactions that do not proceed in low boiling point solvents.

(3) **Safety:** Data about the toxicity and environmental compatibility have to be collected before utilization of a green solvent on a large scale. In this context, glycerol has a clear advantage compared with most organic solvents. Indeed, glycerol is a non-toxic (LD 50 (oral rat) = 12600 mg/Kg), biodegradable and non-flammable solvent for which no special handling precautions or storage is required. In particular, the low toxicity of glycerol also allows its use as a solvent in the synthesis of pharmaceutically active ingredients, in which the toxicity and residue of solvents have to be carefully controlled.

(4) **Availability:** To be viable, a green solvent has to be cheap and available on a large scale. Glycerol meets these criteria since it is available on a large scale from the vegetable oil industry. For instance, the production of glycerol reached 1.5 Mt in 2009. Glycerol is also very cheap (0.50 €/Kg for pharmaceutical grade (99.9%) and 0.15€/Kg for the technical grade (80%)) and, sometimes, even cheaper than water.

Despite these clear advantages, the possible use of glycerol as a solvent also requires chemists to overcome a few obstacles such as:

(1) The high viscosity of glycerol that can induce important mass transfer problems. Fortunately, at temperatures higher than 60 °C, glycerol is much less viscous. Therefore, reactions involving glycerol as solvent have to proceed at temperatures higher than 60 °C. Otherwise, a fluidifying co-solvent has to be used.

(2) The chemical reactivity of hydroxyl groups which can lead to the formation of side products. In particular, the three hydroxyl groups of glycerol are reactive in extremely acidic or basic conditions. Therefore, glycerol has to be used as a solvent in a chemically inert environment for the hydroxyl groups to remain intact.

(3) The coordinating properties of glycerol which may induce some problems when transition metal complex catalysts are used in this solvent. In particular, deactivation of organometallic complexes might occur in glycerol.

Taking into account these advantages and disadvantages, research dealing with the possible use of glycerol as a solvent is no longer a simple transfer of a known method from a conventional solvent system to glycerol. Therefore, innovative

solutions have to be thought of in order to maximize the advantages of glycerol. Although it seems very difficult, after a few years of exploration, researchers involved in this field have developed some successful examples that not only have demonstrated the feasibility and the necessity of using glycerol as a solvent, but have also contributed to the emergence of promising methods especially in the field of organic synthesis, catalysis, separations and materials chemistry. Now, we will show what glycerol as a solvent contributes to current chemistry.

3. Performance of glycerol solvent

3.1. Glycerol as a solvent for organic transformations

Replacing volatile organic solvents used in organic transformations with a new and environmentally benign medium is one of the most effective methods to minimize generation of VOCs.²⁴ Although glycerol has been used as a reaction solvent since the middle of the last century,²⁵ it was generally not considered as a necessary solvent by researchers. This tendency mainly stemmed from (i) the high viscosity of glycerol that causes mass transfer and handling problems during the work-up procedure; and (ii) high cost. Indeed, at that time, supply of fatty oils was not extensive like today, and, at this period, glycerol available on the market was produced from propylene. As compared to other available organic solvents, industrial chemical processes yielding glycerol were not competitive enough to allow the emergence of glycerol as a solvent. Therefore, during this period, glycerol was considered as an expensive and inadequate solvent for organic synthesis. With the rapid emergence of vegetable oils for non-food applications, availability of glycerol has dramatically increased since 1996 while its price continuously decreased to 0.50€/Kg (for pharmaceutical grade (99.9%) in 2010, thus now making glycerol an attractive new class of green solvent.

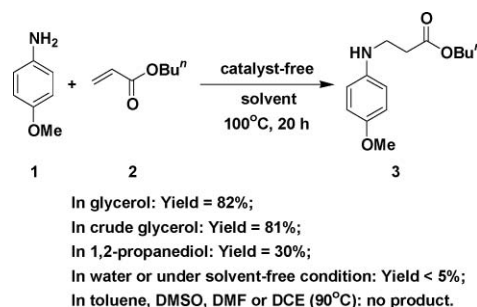
In 2006, Wolfson's group²⁶ in Israel reported the first example for the use of glycerol as a green reaction solvent, and since then, the number of publications dealing with the possible use of glycerol as a sustainable solvent for catalysis and organic chemistry has significantly increased, thus showing the actual interest of the scientific community for this medium. In this part, we will mainly discuss the effects of using glycerol as a reaction solvent on organic transformations.

3.1.1. Glycerol as a promoting solvent for organic synthesis.

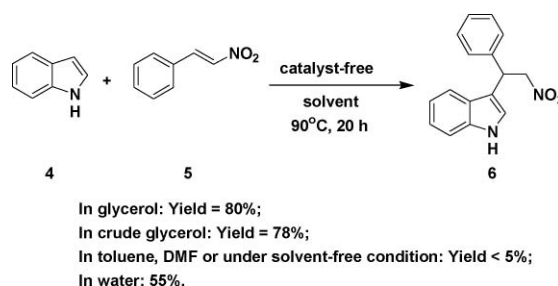
In order to check whether or not a chemical can be used as a green solvent in organic synthesis, four issues have to be demonstrated: (i) greenness, (ii) availability and price; (iii) feasibility of using the targeted liquid as a solvent, and (iv) necessity of using this chemical as a solvent. The green aspects, availability and price of glycerol, have already been demonstrated in detail above. So, now the problem is how to demonstrate the feasibility and necessity of using glycerol as a green solvent. In the first stage of this topic, researchers mainly focused on the second issue and have demonstrated the feasibility of using glycerol as a possible solvent for organic reactions. Initially, the best methods consisted of replacing conventional organic solvents by glycerol and to observe what happened. In this context, Wolfson and co-workers examined many organic reactions, including Heck, Suzuki and hydrogenation reactions using glycerol as a solvent. They showed that these catalytic reactions

proceeded well in glycerol and high yields can be obtained, thus showing that glycerol can, in these cases, replace the traditional volatile organic solvents.²⁷ In these reactions, glycerol was found to be stable and capable of facilitating isolation of the reaction products (by liquid–liquid phase extraction with ethers or esters). Although good yields have been obtained by using glycerol as a solvent, no real advantage, in terms of reaction selectivity or catalyst activity, has been highlighted. Nevertheless, the work of the Wolfson's group is very important and clearly demonstrates, for the first time, the feasibility of using glycerol as a solvent, thus opening new routes in the search for safer organic solvents.

In 2008, Gu and Jérôme reported that glycerol may offer remarkable advantages over conventional or known innovative solvent systems, thus demonstrating the next issue, *i.e.* the necessity of using glycerol as a solvent. In particular, Gu and Jérôme reported that an aza-Michael reaction between *p*-anisidine (**1**) and *n*-butyl acrylate (**2**) can successfully proceed under catalyst-free conditions using glycerol as a sole solvent.²⁸ Remarkably, while high yield (>80%) has been obtained either in pure glycerol or in technical grade glycerol (contains 80% of glycerol, ~15% of water and ~5% of free fatty acid salts, furnished by Valagro) under standard conditions (100 °C and 20 h), only a trace amount of product has been obtained in water or under solvent-free conditions. Many organic solvents such as toluene, DMF, DMSO and 1,2-dichloroethane were all ineffective for this reaction (Scheme 1). A similar trend has been observed in the Michael addition of indole (**4**) to nitrostyrene (**5**), in which only glycerol was found to be capable of affording the desired product in *ca.* 80% yield under catalyst-free conditions (Scheme 2). Furthermore, product isolation and recycling of glycerol were conveniently achieved by means of liquid–liquid phase extractions with ethyl acetate. These results



Scheme 1 Aza-Michael reaction of *p*-anisidine in different solvent systems.



Scheme 2 Michael reaction of indole in different solvent systems.

not only demonstrated the necessity of using glycerol as a promoting medium for organic reactions, but also avoided the use of catalyst, thus simplifying the work-up procedure and consequently increasing the greenness of the synthetic method. Note that in the case of technical grade glycerol, the presence of residual free fatty acid salts may play the role of catalyst, thus allowing the reaction to proceed better than in neat water.

In the electrophilic activations of aromatic aldehydes with indoles or 1,3-cyclohexanediones, glycerol has also been proved to be an advantageous solvent. These reactions are generally carried out in the presence of acid catalysts. Under optimized conditions (90 °C and 3 h), 95% yield was obtained in glycerol from 4-nitrobenzaldehyde (**7**) and 2-methylindole (**8**) without assistance of any catalyst (Scheme 3). Other solvent systems, such as toluene, DMF, DMSO, *n*-butyl acetate, *n*-butanol and water were also examined and, in all cases, the targeted product has been obtained either in a trace amount or in a significantly lower yield than in glycerol (Scheme 3).²⁹ Interestingly, the products formed are insoluble in glycerol. Therefore, at the end of the reaction, the reaction products were conveniently isolated by filtration after dilution in water (Fig. 1). Advantages of glycerol for this reaction include (i) the non-assistance of acid catalysts, which not only simplifies the work-up procedure and minimizes the generation of waste, but also allows the use of acid-sensitive substrates; (ii) easy separation of the reaction products; and (iii) no volatile organic solvent was used. However, this method has shortcomings: (i) for products that cannot precipitate in glycerol, organic solvents have to be used in order to extract them, and (ii) the use of glycerol as the solvent doesn't work for some less-reactive substrates and, in these cases, addition of a Lewis acid such as CeCl₃·7H₂O, was necessary to improve the reaction yield.³⁰

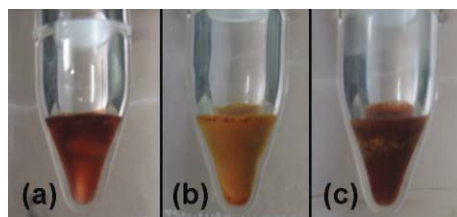
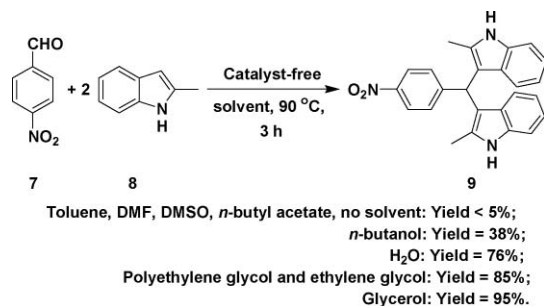
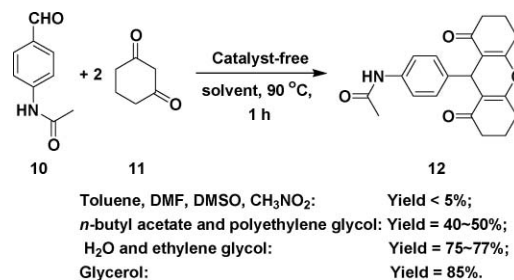


Fig. 1 Progress of the reaction between (**7**) and (**8**) in glycerol (a: beginning of the reaction; b: during the reaction; c: the end of the reaction) (from F. He, P. Li, Y. Gu, G. Li, *Green Chem.* **2009**, *11*, 1767–1773; DOI: 10.1039/b916015a; reproduced with permission of The Royal Society of Chemistry).



Scheme 3 Reaction between 4-nitrobenzaldehyde and 2-methylindole in different solvent systems and under catalyst-free conditions.

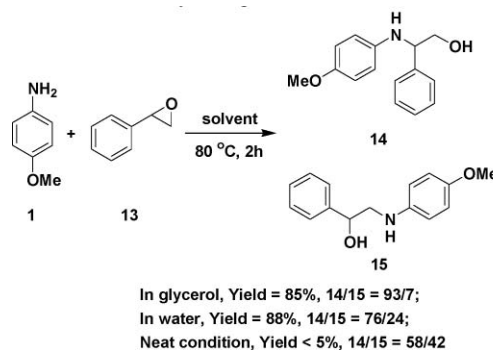
As depicted in Scheme 4, glycerol can also promote the reaction of 4-acetamidobenzaldehyde (**10**) with 1,3-cyclohexanedione (**11**). As described above, this reaction can proceed in glycerol without assistance of any acid catalyst as is generally the case for such reaction.²⁹ Although glycerol has been proven to be capable of promoting many organic reactions, no information is available, today, concerning the reasons behind these promising results. This point definitely deserves further investigations. In the literature, a similar trend has been observed using water as a solvent and many efforts have been made to better understand the mechanism of water in organic reactions.³¹ The methods and strategies in this area should help us to understand the glycerol system since both water and glycerol are characterized by a strong hydrogen bond network.



Scheme 4 Reaction between 4-acetamidobenzaldehyde and 1,3-cyclohexanedione in different solvent systems under catalyst-free conditions.

3.1.2. Glycerol as a solvent for enhancing reaction selectivity.

When a reaction is performed in a liquid phase, the solvent can exhibit not only a beneficial effect on the reaction rate but can also dramatically impact the reaction selectivity. Therefore, effect of a solvent on the reaction selectivity is another means to demonstrate the importance of the considered solvent. In this context, promising results for glycerol as a solvent have also been obtained in some reactions. For example, ring-opening of *p*-anisidine (**1**) with styrene oxide (**13**), which is generally catalyzed by Lewis or Brønsted acids, can be performed in the absence of catalyst either in glycerol or in water. Interestingly, under identical conditions, the regioselectivity obtained in glycerol is higher than that in water (Scheme 5).²⁸ Even if there is no explanation yet for this change of selectivity, this result shows that glycerol can indeed also affect the reaction selectivity.



Scheme 5 Ring-opening of styrene oxide by *p*-anisidine.

Continuing their efforts, Gu and co-workers have recently developed a novel three-component reaction involving styrene, paraformaldehyde and dimedone in glycerol.³² In this study, utilization of glycerol as a solvent has been found to be crucial for a close control of the reaction selectivity. As shown in Scheme 6, this reaction proceeds through a tandem Knoevenagel/hetero-Diels Alder sequence. In order to achieve this reaction with a maximum of selectivity, the Knoevenagel reaction has to be the rate-determining step while the hetero-Diels Alder reaction has to proceed quickly. Interestingly, only a small amount of product was obtained either in the presence of conventional solvents such as water, toluene, nitromethane or under solvent-free conditions due to the lack of selectivity. Indeed, in these cases, an important formation of a by-product **20** has been observed (Scheme 6). Remarkably, when this reaction was conducted in glycerol, the reaction selectivity was drastically improved and the desired product (**18**) was obtained with 68% yield. Interestingly, a large amount of white solid was formed during the reaction using glycerol as the solvent, whereas in nitromethane and in toluene a transparent mixture was obtained at the end of the reaction (Fig. 2). NMR analysis revealed that the white solid observed in glycerol was mainly composed of paraformaldehyde and the by-product **20**. It has been also found that paraformaldehyde decomposed quickly in glycerol in the absence of dimedone in contrast to toluene for which many hours were necessary in order to decompose paraformaldehyde. This result shows that (i) glycerol is a preferable solvent for the decomposition of paraformaldehyde compared with toluene; and (ii) the greater stability of paraformaldehyde in glycerol is due to the presence of dimedone. In order to shed light on the detailed mechanism, many factors were then considered, and finally it was found that generation of the by-product **20** was actually the key. The by-product **20** is a solid (melting point =

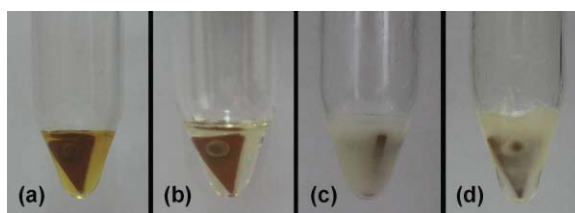


Fig. 2 Progress of the reaction of styrene, paraformaldehyde and dimedone in glycerol without any catalyst ((a): at the end of the reaction in nitromethane; (b): at the end of the reaction in toluene; (c): at the beginning of the reaction in glycerol; (d): at the end of the reaction in glycerol). (From M. Li, C. Chen, F. He, Y. Gu, *Adv. Synth. Catal.* **2010**, 352, 519–530, DOI: 10.1002/adsc.200900770, Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

192 °C) insoluble in glycerol. As illustrated in Fig. 3, it has been found that **20** tended to be piled up on the surface of solid paraformaldehyde. This deposition resulted in the formation of a thin layer of **20** on the surface of the paraformaldehyde sphere, which prevented the degradation of paraformaldehyde by glycerol. This coating of paraformaldehyde by **20** observed in glycerol significantly inhibited its decomposition, thus favoring the formation of intermediate **19**. Glycerol is not only able to affect the Knoevenagel reaction, but is also capable of enhancing the rate of the hetero-Diels Alder reaction because it is a polar protic solvent. By these synergistic effects, the three-component reaction can proceed in glycerol with greater selectivity than in other systems.

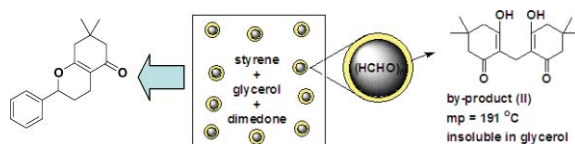
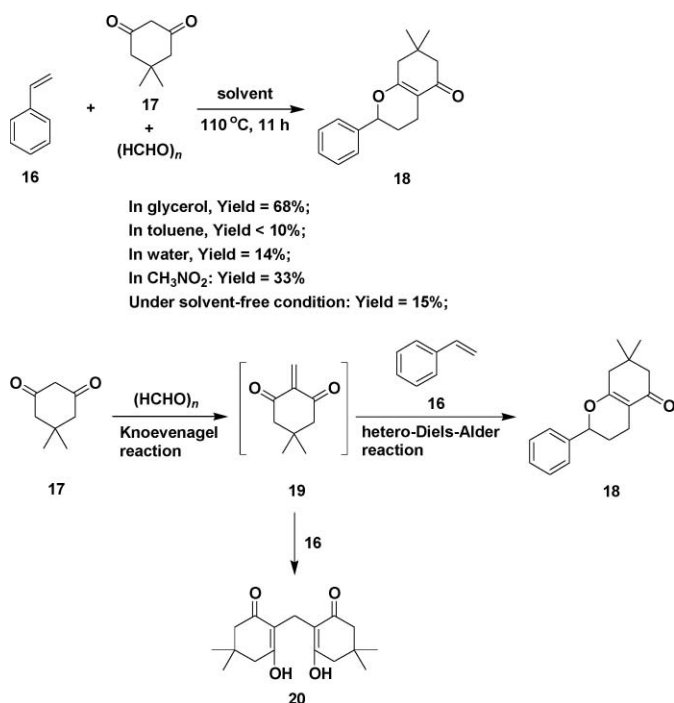


Fig. 3 Imagined procedure for the stabilization of paraformaldehyde in glycerol. (From M. Li, C. Chen, F. He, Y. Gu, *Adv. Synth. Catal.* **2010**, 352, 519–530, DOI: 10.1002/adsc.200900770, Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

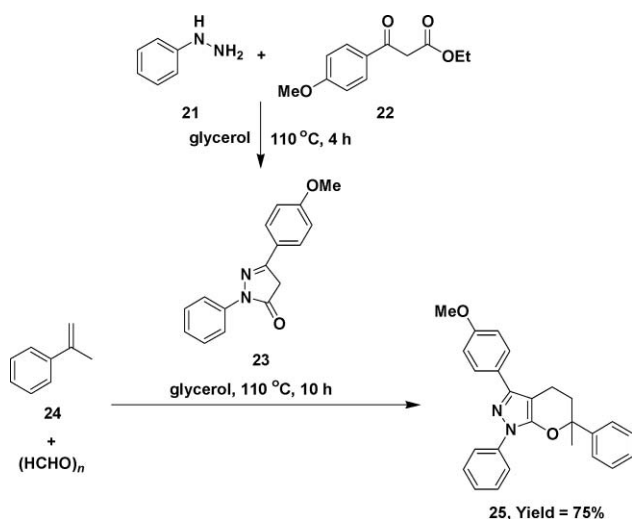


Scheme 6 Three-component reaction involving styrene, paraformaldehyde and dimedone and its reaction pathway.

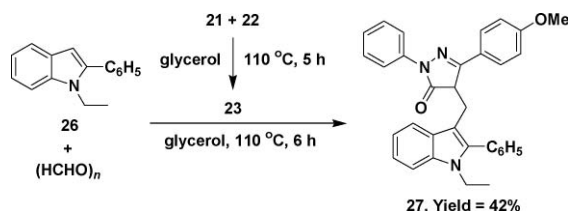
In fact, many substrates, including 1,3-dicarbonyl compounds, 1,3-disubstituted 5-pyrazolones, 2-naphthol and barbituric acid derivatives can be used in the presence of formaldehyde and styrene to establish versatile three-component reactions (MCRs).³³

More recently, glycerol has been used as a unique solvent to establish a new one-pot two-step sequential reaction involving arylhydrazines, β -ketone esters, formaldehyde and styrenes.³⁴ As shown in Scheme 7, in the first step of the reaction, phenylhydrazine (**21**) and ethyl 4-methoxybenzoate (**22**) were heated at 110 °C in glycerol for 4 h. In this step, 1,3-diphenyl-5-pyrazolone (**23**) was formed exclusively. Then, paraformaldehyde and α -methylstyrene (**24**) were added into the reaction vial, and the mixture was stirred at 110 °C for 10 h. According to this procedure, the desired product (**25**) was obtained with good yields (75%).

Proceeding on the same line, another one-pot sequential reaction involving this time indoles, arylhydrazine, β -ketone esters and paraformaldehyde has been successfully developed in glycerol (Scheme 8).³⁴ Although examples using glycerol as a solvent for designing new reactions are not popular at this



Scheme 7 One-pot sequential reaction involving phenylhydrazine, ethyl 4-methoxybenzoylacetate, α -methylstyrene and paraformaldehyde in glycerol.

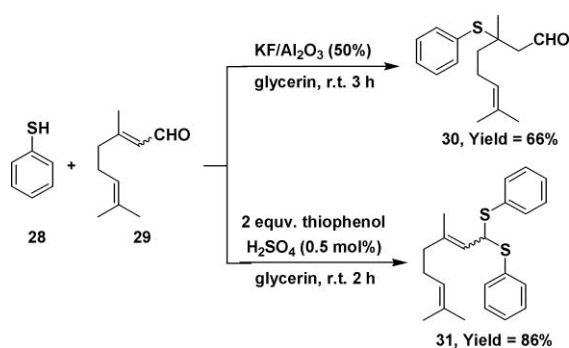


Scheme 8 One-pot sequential reaction involving phenylhydrazine, ethyl 4-methoxybenzoylacetate, 1-ethyl-2-phenylindole and paraformaldehyde in glycerol.

stage, the two examples discussed here, clearly demonstrate that glycerol can indeed be used as a useful medium for maximizing the synthetic efficiency.

Combining a catalyst with glycerol as the solvent is also a great means to closely tune the selectivity of a reaction. In this context, reactions between thiophenol (**28**) and α,β -unsaturated compounds have been investigated in technical grade glycerol (80%). In this context, it has been found that a mixture of two products resulting from the 1,4- and 1,2-addition of thiophenol to citral (**29**) were obtained. The reaction selectivity can be adjusted in the presence of an acid or a basic catalyst. For example, over basic $\text{KF}/\text{Al}_2\text{O}_3$ solid catalyst, the reaction was mainly driven towards the 1,4-addition whereas using an acid catalyst such as sulfuric acid, the 1,2-addition was exclusively observed, thus opening new routes for the design of selective processes in glycerol (Scheme 9).³⁵

3.1.3. Glycerol as a solvent for biocatalysis. Because of its unique properties such as low toxicity and high affinity for hydrophilic compounds, glycerol has also been proposed as a solvent for bio-catalysis. Wolfson and co-workers have reported that a Baker's yeast catalyzed reduction of prochiral ketones can be conveniently performed in glycerol.²⁶ More recently, Andrade and co-workers³⁶ observed a clear yield improvement when glycerol was used as a co-solvent in the bioreductions of 2'-chloroacetophenone (**32**) by *Aspergillus terreus*. As shown in Scheme 10, when comparing the results with those obtained in aqueous or other aqueous-organic media, utilization of glycerol



Scheme 9 Addition of thiophenol to citral in glycerol in the presence of catalyst.

Solvent	Concentration of product (%)	ee (%)
PBS	24	65 (S)
PBS-glycerol (9/1)	49	92 (S)
PBS-glycerol (4/1)	44	> 99 (S)
PBS-DMSO (9/1)	50	> 99 (S)
PBS-DMSO (4/1)	10	> 99 (S)
PBS-CH ₃ CN (9/1)	9	> 99 (S)
PBS-toluene (9/1)	4	-

PBS: Phosphate buffer solution [$\text{Na}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$ buffer (pH 7)].

Scheme 10 Influence of co-solvents on the bioreduction of 2'-chloroacetophenone (**32**).

as a co-solvent increased the reaction yield while keeping high enantioselectivity. Note that high isolated yields of the desired chiral benzyl alcohols have been also successfully achieved at a preparative scale, thus showing the potential of glycerol for biocatalysis.

Despite these promising results, clear explanations on the beneficial impact of glycerol on the reaction selectivity are still missing at this stage. Therefore, much effort is needed in order to shed light on this point.

3.1.4. Glycerol as a solvent to facilitate isolation of the reaction products. As already described above, glycerol is capable of dissolving many polar organic compounds, while being immiscible with non-polar solvents. This property is actually very similar to that of water and most ionic liquids. Water and ionic liquids have been extensively used for facilitating isolation of the reaction products. However, many ionic liquids were proved to be toxic and suffer from many problems, such as poor bio-compatibility, generation of organic and inorganic wastes and high cost. Compared with water, glycerol has the unique advantage to dissolve more hydrophobic substrates. On the basis of these properties, it would not be unreasonable to expect that, like water and ionic liquids, glycerol could also allow a convenient isolation of the reaction products. Some above-described examples have already highlighted the beneficial effect of glycerol for the product isolation. In these cases, reaction products have been easily isolated either by liquid-liquid phase extraction with a non polar solvent²⁸ or by filtration after precipitation of the reaction products upon addition of a small amount of water.²⁹ Recently, Wolfson and co-workers

investigated the Baker's yeast catalyzed asymmetric reduction of methyl acetoacetate in aqueous glycerol. Interestingly, authors found that the product extraction yields were affected by the concentration of glycerol in the aqueous solution.³⁷ As illustrated in Fig. 4, the highest extraction yields have been obtained in mixtures containing 25–75 wt% of glycerol in water. In these mixtures, the extraction yields were increased by ~15% when compared with neat glycerol or neat water. This synergistic effect can be explained by the formation of strong interactions between glycerol and water, which decreased solubility of the reaction product in the aqueous glycerol phase. A similar effect has been observed for the extraction of 2-butanol from an aqueous solution of glycerol with diethyl ether. Whereas the extraction yield of 1 g of 2-butanol dissolved in 50 mL of water or glycerol by 2 × 40 mL of diethyl ether was 20% and 26% respectively, extraction of 2-butanol from a 50 wt% aqueous solution of glycerol resulted in a significant increase of the extraction yield to 50%. Note that recovery of 2-butanol can also be achieved by distillation. However, although 2-butanol has a relatively low boiling point, it is difficult to distil it from water since it forms an azeotropic mixture. In glycerol, it is not the case and 2-butanol can be easily and conveniently isolated by distillation. It should be noted that this method is only applicable to low boiling point derivatives, otherwise the economical viability of the distillation process is dramatically decreased.

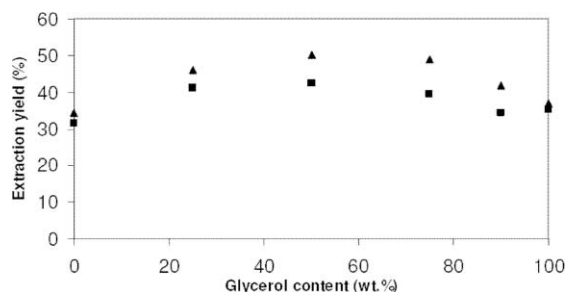


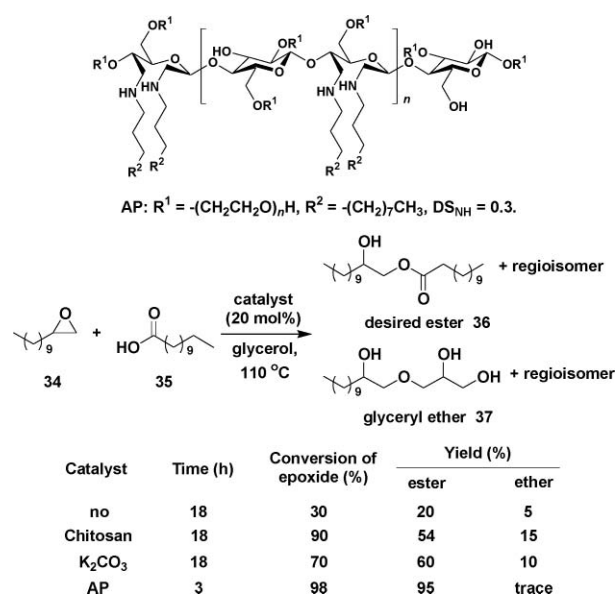
Fig. 4 Extraction yields of methyl acetoacetate from water and glycerol mixtures. Extraction conditions: 50 mL of solvent, 2 extraction steps with 40 mL of extractive solvent, 1 g of methyl acetoacetate, RT. Closed triangles: extraction yield with diethyl ether. Closed squares: extraction yield with dichloromethane (from A. Wolfson, N. Haddad, C. Dlugy, D. Tavor, Y. Shotland, *Org. Commun.* **2008**, 1:2, 9–16, reproduced with permission of ACG publications).

3.1.5. Glycerol as a solvent for catalyst design and recycling.

Within the framework of green chemistry, homogeneous catalyst recovery is an important topic and, in this context, solvents are of prime importance. For example, some solvents, such as water, ionic liquid and PEGs, have been used to immobilize homogeneous catalysts, which offers a feasible and an efficient method for recycling the homogeneous catalysts. These strategies mainly rely on the better solubility of the targeted homogeneous catalyst in the water or ionic liquids phases than in the extraction organic solvents. As described above, glycerol also has a great ability to dissolve ionic species. Therefore, glycerol also appears as a possible solvent for the immobilization of polar homogeneous catalysts. In this context, Silveira and co-workers investigated the catalytic formation of bisindoly methane in glycerol over

CeCl₃ Lewis acid. In particular, they showed that, at the end of the reaction, the reaction products can be selectively extracted from the glycerol/CeCl₃ mixture by liquid phase extraction with ethyl acetate, thus allowing a convenient recycling of both CeCl₃ and glycerol.³⁰ Owing to the capacity of glycerol to dissolve organometallic complexes, non-ionic species can also be recycled in glycerol. For example, Wolfson and co-workers recently reported a hydrogenation reaction catalyzed by the [Ru(*p*-cumene)Cl₂]₂ complex using glycerol both as solvent and as hydrogen donor.³⁸ Although this Ru complex catalyst is not ionized in glycerol, its recycling after extraction of the reaction products with diethyl ether was found possible.

Even if utilization of glycerol as a safe solvent for catalysis clearly offers promising advantages, these glycerol-based processes still have shortcomings such as (i) the insolubility of strongly hydrophobic substrates in glycerol and (ii) the possible generation of side-products owing to the high reactivity of glycerol towards various electrophiles. These points could be found in an example reported by Jérôme and co-workers who investigated the base-catalyzed ring opening of fatty epoxide (**34**) with fatty acid (**35**) in glycerol (Scheme 11).³⁹ When this reaction is catalyzed by commonly used basic catalysts such as chitosan (a naturally available basic polysaccharide), ZnO, K₂CO₃ or a silica-supported secondary amines, the reaction rate is rather low since complete conversion is achieved within 18 h of reaction. In this case, the reaction medium is biphasic since both reactants are not miscible in the catalytic glycerol phase. Therefore, the catalytic process only took place at the glycerol-oil interface resulting in a very low reaction rate. Moreover, under basic conditions, the ring opening of the fatty epoxide with glycerol has also been observed leading to the formation of glycerol ethers as side products (10–15%, Scheme 11).



Scheme 11 Ring-opening of epoxide with carboxylic acid in glycerol.

In order to overcome these two problems, authors investigated the efficiency of the so-called surfactant-combined catalyst (SCC) in glycerol. Inspired by micellar catalysis in water, these SCC were expected to (1) favor the dissolution of the fatty

reactants in glycerol owing to their surfactant properties and (2) inhibit the reactivity of glycerol owing to the formation of catalytic hydrophobic pockets. In this context, dodecylamine chains have been grafted over hydroxyethylcellulose yielding the corresponding aminopolysaccharide (AP). The structure of this AP is highly interesting owing firstly to its amphiphilic properties and secondly because the hydrophobic core is surrounded by amino moieties which can act as a basic catalyst.

Interestingly, as observed in water, authors found that this amphiphilic AP was able to emulsify the reaction medium resulting in a spectacular increase of the reaction rate (Fig. 5, Scheme 11). Indeed, under the same conditions, completion of the reaction has been observed within only 3 h vs. 18 h for non amphiphilic basic catalyst. Moreover, in the presence of the AP catalyst, the catalytic process was much more selective since formation of glycerol ethers was no longer observed. This particular selectivity obtained with the amphiphilic AP was attributed to the presence of hydrophobic areas close to the amino catalytic sites which prevent the diffusion of glycerol.

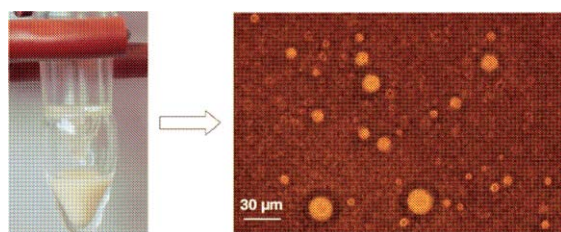


Fig. 5 Emulsion obtained in glycerol from AP and a solution of 1,2-epoxydodecane (detected by phase contrast microscopy) (from A. Karam, N. Villandier, M. Delample, C. K. Koerkamp, J.-P. Douliez, R. Granet, P. Krausz, J. Barrault, F. Jérôme, *Chem. Eur. J.* **2008**, *14*, 10196–10200, DOI: 10.1002/chem.200801495, Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).

Interestingly, authors found that emulsion formed in glycerol was much less stable than those formed in water. Consequently, after centrifugation of the crude mixture at the end of the reaction, the reaction medium rapidly became biphasic allowing a direct and selective extraction of the reaction products from the glycerol catalytic phase without assistance of any organic solvent as it is generally the case in water. Taking into account this remarkable advantage of glycerol over water, the AP catalyst has been successfully recycled 10 times without obvious drop of catalytic activity, thus providing a suitable solution for the recycling of homogeneous catalysts (Fig. 6).

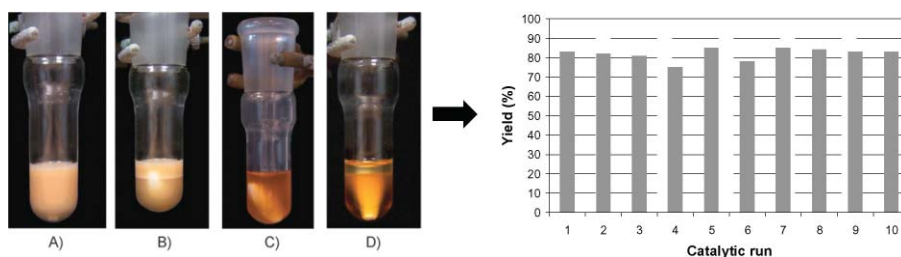


Fig. 6 Emulsion behavior of AP in A) water during the reaction (70% yield after 8 h at 90 °C), B) in water after centrifugation at the end of the reaction, C) in glycerol during the reaction, D) in glycerol after centrifugation at the end of the reaction, and on the left side recycling experiments (from A. Karam, N. Villandier, M. Delample, C. K. Koerkamp, J.-P. Douliez, R. Granet, P. Krausz, J. Barrault, F. Jérôme, *Chem. Eur. J.* **2008**, *14*, 10196–10200, DOI: 10.1002/chem.200801495, Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission).

If this method afforded good tools for the recycling of a homogeneous catalyst, it is also clear that this approach closely relies on the solubility of the reaction products in the glycerol phase. Therefore, when the reaction products are soluble in the glycerol phase, an extraction solvent is needed. In this context, Jérôme and co-workers showed that the reaction products can be selectively and cleanly extracted from the glycerol phase with supercritical carbon dioxide (scCO₂), thus avoiding the traditional assistance of petrochemically-derived volatile organic solvents.⁴⁰

In their work, authors investigated the catalytic β,β -diarylation of acrylate derivatives in glycerol. The diarylation of acrylate derivatives generally occurs at a higher temperature (120–140 °C) than the monoarylation step. Therefore, these reactions are generally carried out in high boiling point solvents such as DMF⁴¹ and ionic liquids⁴² or under pressure.⁴³ Within the framework of green chemistry, Najera and co-workers investigated the β,β -diarylation of acrylate derivatives in water.⁴⁴ Although this work indisputably offered a greener route to the synthesis of disubstituted acrylate derivatives, this method was only applicable to the *tert*-butylacrylate. Indeed, in water, authors pointed out that other acrylate derivatives are partially hydrolyzed making isolation of the disubstituted alkenes with good yield difficult.



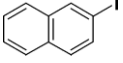
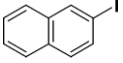
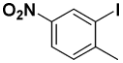
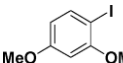
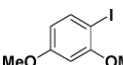
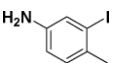
Whereas this reaction is generally catalyzed under an inert atmosphere by expensive phosphine or carbene palladium complexes, authors have shown that the β,β -diarylation of acrylates can be conveniently achieved in glycerol in the presence of air-stable palladium nanoparticles (average particle size = 6 nm). These palladium nanoparticles were stabilized over the above-described sugar-based surfactant (Pd/AP).

Interestingly, at 120 °C and in the presence of 0.9 mol% of palladium, the Pd/AP cleanly afforded a wide range of β,β -diarylated products with good to excellent yields (Table 1). Note that, in accordance with most of the previous work on the diarylation of alkenes, this catalytic process was found to be efficient mainly with aryl iodides. Indeed, utilization of aryl bromides or chlorides unfortunately slowed down the reaction rate to unacceptable levels.

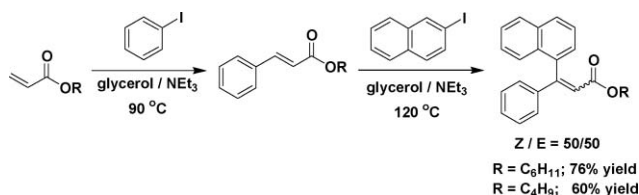
By an adjustment of the reaction temperature, authors were also able to control the mono- and diarylation step of alkenes, thus offering a convenient route to the unsymmetrical diarylated alkenes (Scheme 12).

If glycerol afforded an environmentally friendlier route to the β,β -diarylation of acrylates, extraction of the reaction products

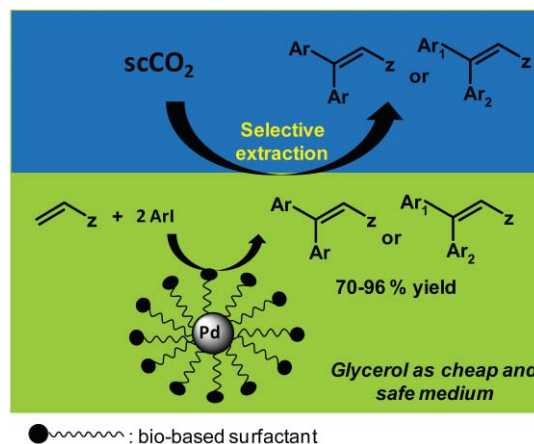
Table 1 β,β -Diarylation of acrylate derivatives in glycerol

Entry	R	ArI	Yield (%) ^a
1	Cyclohexyl		92
2	Butyl		95
3	Cyclohexyl		96
4	Butyl		70
5	Cyclohexyl		85
6 ^b	Butyl		80
7 ^b	Cyclohexyl		86
8	Cyclohexyl		93

^a Isolated yield after 30 h of reaction, 3 eq of aryl iodides and triethylamine were used. ^b Reaction performed at 80 °C.

**Scheme 12** Unsymmetrical β,β -diarylation of acrylate derivatives in glycerol.

from the glycerol phase was found to be rather difficult mainly because of their solubility in glycerol. As in the case of ionic liquids, glycerol is a high boiling point solvent and its removal by distillation is not conceivable. Therefore, assistance of an extraction solvent was found to be necessary to recover the products of the reaction. Among all tested extraction solvents, authors found that $scCO_2$ was by far the most efficient solvent to selectively extract the β,β -diarylated products from the glycerol-Pd/AP phase (Fig. 7). Indeed, other tested solvents such as dichloromethane, ethyl acetate, toluene, among others led to the concomitant extraction of the reaction products with the Pd/AP catalyst, thus involving further purification steps. Interestingly, at 50 °C, 250 bar and with a $scCO_2$ flow of 40 g min^{-1} , the β,β -diarylated products have been cleanly and selectively recovered with a molar purity of 93% (extraction efficiency = 80%; the Pd/AP remained in the glycerol phase), thus offering (1) a simple work-up procedure and (2) an alternative to the extensive

**Fig. 7** Pictures of the extracted β,β -diarylated alkenes with $scCO_2$.

utilization of volatile organic solvent. The solubility of glycerol in CO_2 under high pressure has been estimated thanks to the equation of Chrastil⁴⁵ which correlates the solubility of solids and liquids in supercritical gases with the densities of the gas. In the reported conditions, it has been found that the solubility of glycerol in $scCO_2$ was 40 times lower than that of water (0.06 Kg. m^{-3} for glycerol vs. 2.39 Kg. m^{-3} for water).

Note that this process has been successfully scaled up and up to 9 g of β,β -diarylated acrylate were successfully recovered according to this strategy.

Even if the $scCO_2$ allowed a selective and convenient extraction of the reaction products from the glycerol/Pd-AP phase, the recycling of the Pd-AP catalyst was difficult mainly because of the accumulation of salts in the glycerol phase (unavoidable side products of the Heck reaction). Nevertheless, as observed in ionic liquids and polyethylene glycol, this work offers new tools for the design of greener processes and on the basis of this concept salt-free reactions might be applied such as hydrogenation reactions for example.

3.2. Glycerol as a solvent for separation

If the above-described results clearly highlight the contribution of glycerol as a medium for organic transformations and catalysis, glycerol has also been successfully used in separation processes. Bioethanol is an important bio-fuel, generated by a fermentation process, which can be used as an alternative fuel to gasoline. However, purification of bioethanol by conventional distillation is not easy since water forms an azeotrope with ethanol at atmospheric pressure. Consequently, using this separation technique, only ethanol with an alcoholic degree of 95.5 can be obtained. To reach the specification that allows its direct addition to gasoline, ethanol must be dehydrated to at least 99.3 wt%, which means that the azeotrope must be eliminated. Nowadays, the most commonly used processes for ethanol dehydration consists of (1) adsorption over molecular sieves or (2) azeotropic distillation with cyclohexane or (3) extractive distillation with monoethyleneglycol. In the typical case of extractive distillation, the sustainability of this process is not satisfactory yet mainly because monoethyleneglycol is derived from fossil oils. In order to solve this problem, the search for an alternative biochemical that can replace monoethyleneglycol

has become an important topic. Recently, Dias and co-workers have proposed an elegant method consisting of the replacement of monoethyleneglycol by glycerol for the extractive distillation production of anhydrous ethanol.⁴⁶ Conventional extractive distillation uses two distillation columns in order to separate the binary azeotrope ethanol–water. The first one is called an extractive column and provides pure ethanol on the top of the column. The second one is called a recovery column where water is separated from monoethyleneglycol by distillation. As shown in Fig. 8, with the configuration reported by Dias, there is no need to use the second distillation column.

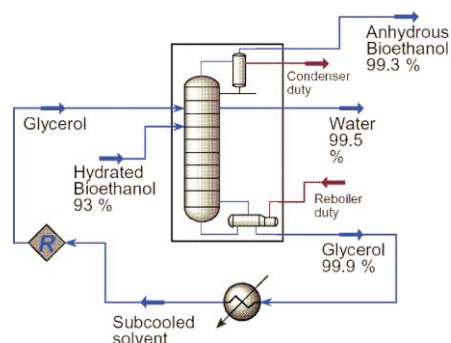


Fig. 8 Configuration of extractive distillation for the purification of bioethanol with glycerol (reproduced from ref. 46).

Indeed, the anhydrous bioethanol is directly collected on the top of the column and glycerol and water are separated at the bottom. Using this process, ethanol, water and glycerol were all recovered with more than 99% purity. Simulations carried out with software Hysys showed that both glycerol and the proposed column configuration have a great potential to be used in the industry since yield, energy and solvent consumption are similar to or even lower than those usually found in the industrial bioethanol production processes.

3.3. Glycerol as a solvent for materials chemistry

It is well known that solvent also plays a major role in the preparation of materials. Green solvents, such as scCO_2 and ionic liquids have been widely used in material preparations. Utilization of glycerol as a green solvent for the preparation of materials has not been well recognized yet. However, glycerol meets two important criteria: (i) like ionic liquids, glycerol exhibits a high boiling point and a low vapor pressure allowing the material synthesis to be performed at a high temperature; and (ii) excellent solubility of many inorganic and polar organic precursors in glycerol.

Preparation of metal particles is one of the most important topics, and many methods have been developed. Among all reported methods that have been well recognized, utilization of polyol represents an elegant strategy. This process is based on the heating of a suitable inorganic/organic metallic salt in a polyol, which acts both as a solvent and as a reducing reagent. Polyols with high boiling points, such as ethylene glycol and diethylene glycol, are generally employed. Because glycerol contains one secondary and two primary hydroxyl groups, it would not be unreasonable to expect that glycerol is also able to reduce some metallic salts. Glycerol has a higher boiling point

(290 °C) than ethylene glycol (197 °C) and hence it can work at higher reaction temperatures than is tolerable for ethylene glycol. Although preparation of metal particles in glycerol is reasonable, particular attention has to be paid to the possible decomposition of glycerol under high temperature. In 2002, Sinha and Sharma reported the first example for the preparation of metal particles in glycerol.⁴⁷ In particular, by heating $\text{Cu}(\text{OH})_2$, CuO and $\text{Cu}(\text{OAc})_2$ under atmospheric conditions in glycerol at a temperature below 240 °C, they successfully obtained some copper particles. By means of physicochemical characterizations, it has been confirmed that the obtained metallic copper particles are crystalline with purities higher than 99%. All metallic copper particles obtained by this process are generally spherical and have a narrow size distribution. The average diameters of crystallites obtained from $\text{Cu}(\text{OH})_2$, CuO , $\text{Cu}(\text{OAc})_2$ are 3.5 μm , 1 μm and 5.6 μm , respectively. With an analogous process, metallic silver particles, with uniform particle morphology and high yield, have also been prepared in glycerol using silver nitrate as the precursor.⁴⁸ Compared with the other polyol processes involving for instance ethylene glycol, the total incubation period for the precipitation of metallic silver particles is much shorter, probably due to the higher reductive properties of glycerol. It should be noted that in glycerol, the average particle size of silver particles can be controlled, to some extent, by adjusting the molar ratio silver nitrate precursor/glycerol. Interestingly, the metal particles produced in glycerol are covered by a thin organic layer that might prevent the particle aggregation and oxidation. Note that glycerol has also been involved in the preparation of MnO_2 nanoparticles (from KMnO_4 as precursor). However, in this case, water was used as the solvent, and glycerol acted only as a reducing reagent.⁴⁹

4. Conclusion and perspective

The background and some aspects regarding the utilization of glycerol as a green solvent were summarized in this review. Strategies dealing with the possible use of glycerol as a solvent not only opens a new way to valorize this organic waste generated by the biodiesel industry, but also offers many new opportunities to current solvent innovations. Particularly, intrinsic properties of glycerol, such as low toxicity, good biodegradability, low vapor pressure, large availability and easy handling and storage, offer complementary advantages to the usual reported green solvents. In view of the following facts: (1) the environmentally benign properties of glycerol, (2) the low price of glycerol and (3) the beneficial effect of glycerol on reaction rates and selectivity, it is not an exaggeration to conclude that glycerol is, no doubt, a qualified green solvent.

The low solubility of glycerol with usual volatile organic solvents also offers good means to extract products from the glycerol phase. In particular, as in the case of ionic liquids, the low solubility of glycerol in scCO_2 offers new tools for (1) performing catalysis in a cheap and sustainable medium and (2) selectively and cleanly extracting the reaction products from glycerol. Remarkably, this last example shows that glycerol may combine advantages of water (low price, non toxicity) and ionic liquid (high boiling point, low solubility in scCO_2).

Despite these promising features, much effort has to be made in the future to extend the use of glycerol as a green solvent.

Until now, reasons behind the promoting effect of glycerol are still undiscovered. As in the case of water and ionic liquids, elucidation of this aspect will take years. In a first approximation, we may suspect that, as in the case of water, the strong hydrogen bond network of glycerol might be responsible for this rate enhancement. However, this kind of “magic solvent effect” might also be explained by the presence of impurities in glycerol. Indeed, industrially produced glycerol contains 10 to 20 wt% of water and free fatty acid salts (5%) are also present. Therefore, even if the beneficial effect of glycerol on reaction rate and selectivity had mainly been collected in pharmaceutical grade glycerol (99.9%), we cannot totally rule out that the presence of trace amounts of acidic or basic derivatives can act as a possible catalyst.

Within the framework of green chemistry, the possible and direct utilization of technical grade glycerol (80%) as a green solvent is even more desirable and successful examples are still scarce. Indeed, even if pharmaceutical grade glycerol (99.9%) is very cheap, purification of technical grade glycerol (80%) is an energy-consuming process, thus affecting the whole environmental impact of all glycerol-based processes. Therefore, in our view, many efforts have to be directed towards the possible use of technical grade glycerol as a solvent. In this case, because of the important presence of impurities, attention has to be paid (1) to the design of the reaction and (2) to the choice of substrates. It should also be noted that the recent progress on the hydrolysis and alcoholysis of vegetable oils over solid catalysts will definitely contribute to an increase in the purity of the industrially produced glycerol.

From all above-presented results, it is clear that this new topic raises now several questions: is it possible to use glycerol to design a continuous biphasic reaction system for catalysis? Is it possible to use glycerol instead of water in the field of phase-transfer catalysis? As a polar solvent with a high boiling point, glycerol also has to face a problem that many ionic liquids are suffering *i.e.* how to remove polar compounds from glycerol? This is an important issue that needs to be addressed. In this context, are the industrial processes for water purification applicable for glycerol? To answer all these questions, we have to, firstly think more about the nature and the potential capacity of glycerol, and secondly, to investigate further the use of glycerol as a solvent.

Despite these questions, using glycerol as a solvent clearly offers new tools in the search of innovative solutions for the progressive replacement of volatile organic solvents by greener alternatives. More generally, this new topic largely contributes to widen the portfolio of the available green solvents, and to the best of our knowledge, glycerol is the only green solvent like water that can combine a low price with a low toxicity. In this context, we are fully convinced that glycerol has all the features to become a central green solvent not only in catalysis or organic chemistry but also in materials chemistry and in biology.

Acknowledgements

YG thanks the National Natural Science Foundation of China for the financial support (20903042). YG is also grateful for Ms. Ping Liang and all the other staff members in the Analytical and Testing Center of HUST, for their supportive and constant

contributions to our works. The program for new Century Excellent Talents in the University of China (NCET-10-0383) and Chutian Scholar Program of the Hubei provincial government are also acknowledged by YG. FJ is grateful to the CNRS and the French Ministry of Research for financial supports and all PhD students who contributed to the development of this topic are also strongly acknowledged. YG and FJ are also grateful to Joël Barrault for fruitful discussions.

Notes and references

- 1 F. M. Kerton, *Alternative Solvents for Green Chemistry*, RSC Green Chemistry Series, Series Editors: J. Clark, 2009.
- 2 C. Capello, U. Fisher and K. Kungerbühler, *Green Chem.*, 2007, **9**, 927–934.
- 3 C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82.
- 4 N. V. Plechkova and K. R. Seddon, *Chem. Soc. Rev.*, 2008, **37**, 123–150.
- 5 J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64–82.
- 6 J. F. Brennecke, *Chem. Ind.*, 1996, 831–834.
- 7 C. A. Eckert, B. L. Knutson and P. G. Debenedetti, *Nature*, 1996, **383**, 313–318.
- 8 I. T. Horváth, *Acc. Chem. Res.*, 1998, **31**, 641–650.
- 9 J. M. DeSimone, C. Hill and W. Tumas, (Ed.), *Green Chemistry Using Liquid and Supercritical Carbon Dioxide*, 2003, Oxford University Press, USA.
- 10 (a) R. D. Rogers, K. R. Seddon, (Ed.) *Ionic Liquids as Green Solvents progress and prospect*, ACS Pub., 2003; (b) D. Coleman and N. Gathergood, *Chem. Soc. Rev.*, 2010, **39**, 600.
- 11 M. N. William, (Ed.) *Green Solvents for Chemistry-Perspectives and Practice*, 2003, Oxford University Press, USA.
- 12 R. Rinaldi and F. Schüth, *ChemSusChem*, 2009, **2**, 1096–1107.
- 13 S. Salehpour and M. A. Dube, *Green Chem.*, 2008, **10**, 321–326.
- 14 S. Aparicio and R. Alcalde, *Green Chem.*, 2009, **11**, 65–78.
- 15 M. Virost, V. Tomao, C. Ginies, F. Visinoni and F. Chemat, *J. Chromatogr. A*, 2008, **1196–1197**, 147–152.
- 16 C. S. K. Reddy, R. Ghai, Rashmi and V. C. Kalia, *Bioresour. Technol.*, 2003, **87**, 137–146.
- 17 G. Imperato, B. Koenig and C. Chiappe, *Eur. J. Org. Chem.*, 2007, 1049–1058.
- 18 M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi and C. D. Pina, *Angew. Chem., Int. Ed.*, 2007, **46**, 4434–4440.
- 19 (a) F. Jérôme, Y. Pouilloux and J. Barrault, *ChemSusChem*, 2008, **1**, 586–613; (b) C.-H. Zhou, J. N. Beltrami, Y. X. Fan and G. Q. Lu, *Chem. Soc. Rev.*, 2008, **37**(3), 527; (c) M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi and C. Della Pina, *Angew. Chem., Int. Ed.*, 2007, **46**, 4434; (d) A. Behr, J. Eilting, K. Irawadi, J. Leschinski and F. Lindner, *Green Chem.*, 2008, **10**, 13; (e) M. Pagliaro, M. Rossi, *The Future of Glycerol: New Usages for a Versatile Raw Material*, 2008, RSC Publishing, Cambridge, UK.
- 20 C. C. Estevez, N. B. Ferrer, B. J. Castells, B. B. Echeverria, *PCT Int. Appl.*, 2008, WO 2008080601.
- 21 (a) D. Hérault, A. Eggers, A. Strube, J. Reinhardt, *Ger. Offen.*, 2002, DE 10110855; (b) M. Notari, F. Rivetti, *PCT Int. Appl.*, 2004, WO 2004052874.
- 22 H. García-Marín, J. C. van der Toorn, J. A. Mayoral, J. I. García and I. W. C. E. Arends, *Green Chem.*, 2009, **11**, 1605–1609.
- 23 (a) F. Bellina, A. Bertoli, B. Melai, S. Scalesse, F. Signori and C. Chiappe, *Green Chem.*, 2009, **11**, 622–629; (b) A. Wolfson, D. Saidkarimov, C. Dlugy and D. Tavor, *Green Chem. Lett. Rev.*, 2009, **2**, 107–110; (c) O. Aschenbrenner, S. Supasitmongkol, M. Taylor and P. Styring, *Green Chem.*, 2009, **11**, 1217–1221.
- 24 (a) W. Leitner, *Green Chem.*, 2007, **9**, 923; (b) W. Leitner, *Green Chem.*, 2009, **11**, 603.
- 25 L. W. Clark, *J. Am. Chem. Soc.*, 1955, **77**, 6191–6192.
- 26 A. Wolfson, C. Dlugy, D. Tavor, J. Blumenfeld and Y. Shotland, *Tetrahedron: Asymmetry*, 2006, **17**, 2043–2045.
- 27 A. Wolfson and C. Dlugy, *Chem. Pap.*, 2007, **61**, 228–232.
- 28 Y. Gu, J. Barrault and F. Jérôme, *Adv. Synth. Catal.*, 2008, **350**, 2007–2012.
- 29 F. He, P. Li, Y. Gu and G. Li, *Green Chem.*, 2009, **11**, 1767–1773.

- 30 C. C. Silveira, S. R. Mendes, F. M. Líbero, E. J. Lenardão and G. Perin, *Tetrahedron Lett.*, 2009, **50**, 6060–6063.
- 31 C.-J. Li, T.-H. Chan, *Comprehensive organic reactions in aqueous media*, 2e, John Wiley & Sons, Inc., 2007.
- 32 M. Li, C. Chen, F. He and Y. Gu, *Adv. Synth. Catal.*, 2010, **352**, 519.
- 33 (a) Y. Gu, R. De Sousa, G. Frapper, C. Bachmann, J. Barrault and F. Jérôme, *Green Chem.*, 2009, **11**, 1968–1972; (b) Y. Gu, J. Barrault and F. Jérôme, *Adv. Synth. Catal.*, 2009, **351**, 3269–3278.
- 34 J.-N. Tan, M. Li and Y. Gu, *Green Chem.*, 2010, **12**, 908–914.
- 35 E. J. Lenardão, D. O. Trecha, P. da C. Ferreira, R. G. Jacob and G. Perin, *J. Braz. Chem. Soc.*, 2009, **20**.
- 36 L. H. Andrade, L. Piovan and M. D. Pasquini, *Tetrahedron: Asymmetry*, 2009, **20**, 1521–1525.
- 37 A. Wolfson, N. Haddad, C. Dlugy, D. Tavor and Y. Shotland, *Org. Commun.*, 2008, **1**, 9–16.
- 38 A. Wolfson, C. Dlugy, Y. Shotland and D. Tavor, *Tetrahedron Lett.*, 2009, **50**, 5951–5953.
- 39 A. Karam, N. Villandier, M. Delample, C. K. Koerkamp, J.-P. Douliez, R. Granet, P. Krausz, J. Barrault and F. Jérôme, *Chem.–Eur. J.*, 2008, **14**, 10196–10200.
- 40 M. Delample, N. Villandier, J.-P. Douliez, S. Camy, J.-S. Condoret, Y. Pouilloux, J. Barrault and F. Jérôme, *Green Chem.*, 2010, **12**, 804–808.
- 41 (a) A. Svennebring, P. Nilsson and M. Larhed, *J. Org. Chem.*, 2004, **69**, 3345–3349; (b) M. Moreno-Mañas, M. Perez and R. Pleixats, *Tetrahedron Lett.*, 1996, **37**(41), 7449–7452.
- 42 (a) G. Zou, W. Huang, Y. Xiao and J. Tang, *New J. Chem.*, 2006, **30**, 803–809; (b) S. B. Park and H. Alper, *Org. Lett.*, 2003, **5**(18), 3209–3212; (c) V. Calò, A. Nacci, A. Monopoli, L. Lopez and A. Di Cosmo, *Tetrahedron*, 2001, **57**, 6071–6077.
- 43 T. Sugihara, M. Takebayashi and C. Kanedo, *Tetrahedron Lett.*, 1995, **36**(31), 5547–5550.
- 44 (a) L. Botella and C. Najera, *J. Org. Chem.*, 2005, **70**, 4360–4369; (b) L. Botella and C. Najera, *Tetrahedron Lett.*, 2004, **45**, 1833–1836.
- 45 J. Chrastil, *J. Phys. Chem.*, 1982, **86**(15), 3016–3021.
- 46 M. O. S. Dias, F. A. D. Mateus, M. R. W. Maciel, R. M. Filho, C. E. V. Rossell, *Anhydrous bioethanol production in one side stream distillation column using bioglycerol as solvent*. V Workshop Internacional Brasil-Japão em Biocombustível, Meio Ambiente e Novos Produtos da Biomassa, 29 a 01 de novembro de 2007.
- 47 A. Sinha and B. P. Sharma, *Mater. Res. Bull.*, 2002, **37**, 407–416.
- 48 A. Sinha and B. P. Sharma, *Bull. Mater. Sci.*, 2005, **28**, 213–217.
- 49 V. Subramanian, H. Zhu and B. Wei, *Chem. Phys. Lett.*, 2008, **453**, 242–249.