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Review

Glycerol-based solvents in organic synthesis

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ABSTRACT

Representative glycerol-based solvents were employed as green reaction mediums for various organic reactions. It was found that the solubility of the substrate in the solvent, which depends on solvent polarity, is the main factor that affects reaction performance. In addition, the effect of solvent polarity on product solubility in the reaction solvent determined the effectiveness of product separation by extraction with glycerol immiscible solvent.

KEYWORDS: glycerol, glycerol derivatives, green solvent, catalysis, Suzuki cross-coupling

1. INTRODUCTION

The search for more environment-friendly routes of chemical synthesis has expanded considerably in recent years [1-3]. As organic reactions proceed mainly in solvents that help bring the reactants and catalysts together and that assist in the transfer of momentum, heat and mass; using green solvents in organic synthesis is among the methods with the most potential to decrease the environmental impact of a chemical process. Moreover, in addition to the nature of each solvent, i.e., its chemical, physical, and biological properties, which define how it can benefit the environment and make it more attractive as a reaction medium, a green solvent is also one that enables easy and simple product separation and catalyst recycling.

During the last two decades, a variety of green systems with different alternative solvents have been reported in the literature [1-3]. Among them four main solvent systems are recognized as green reaction mediums: water [4], ionic liquids [5, 6], fluorous solvents [7, 8], and supercritical fluids [9, 10]. Moreover, it is also recognized that no single green solvent can fulfill the requirements for all organic reactions - each of the existing green reaction mediums comes with its particular advantages and disadvantages.

Several years ago, we reported for the first time, on the use of glycerol as a sustainable reaction medium in both catalytic and non-catalytic organic syntheses [11]. Since then, glycerol has been successfully employed as a green solvent in a wide variety of organic reactions and synthesis methodologies, and in some examples it was simultaneously used as solvent and reactant [12, 13]. In addition, in different systems, glycerol enhanced reaction activity and selectivity and tolerated easy product isolation and catalyst recycling. Besides its high boiling point, low vapor pressure, thermal stability, and recyclability, the primary advantage of glycerol over most of the above-mentioned green solvents is its renewable origin, which makes it non-toxic, non-irritant, and biodegradable. Moreover, as glycerol is a by-product of simple and relatively non-hazardous oil and fat transesterification in oleochemical and bio-diesel production, the available amounts of glycerol are continuously increasing while its price is decreasing.

Yet despite glycerol's promise as a sustainable solvent for liquid phase organic syntheses, the low solubility of highly hydrophobic compounds and gases in glycerol limits its utilization. However, those limitations can be overcome by using

glycerol derivatives, thereby tailoring the polarity of the solvent while preserving its sustainable nature [14, 15].

The current mini-review will discuss the scope and limitations of employing glycerol-based solvents in organic transformations. Both solvent characteristics and reaction parameters, such as catalytic performance, product isolation, and catalyst recycling, will be discussed using several representative chemo- and bio-catalytic reactions.

2. Synthesis and characteristics of glycerol-derivatives

Glycerol offers a very versatile opportunity to produce unlimited derivatives by eliminating or exchanging its three hydroxyl groups (Figure 1). The elimination of each hydroxyl group of glycerol by hydrogenolysis yields either 1,3- or 1,2-propanediol, which are both less polar and less viscous molecules than glycerol [16]. Furthermore, each hydroxyl group of glycerol or of the two synthesized propanediols, alone or together, can be transferred into various ether [17] or ester groups [18]. For example, glycidyl ethers were employed in various epoxide ring opening reactions to produce ethers such as 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxypropanes [18].

Replacing part or all of glycerol's functional groups would thus yield a variety of solvents with different properties. However, the first requirement is that the derivatives produced would still be 'green solvents,' i.e., non-volatile, non-hazardous, biodegradable, etc., a classification that necessarily also takes into account their production processes, which require the addition of extra materials and energy. Glycerol derivatives such as 1,2-propanediol, 1,3-propanediol, glycerol di- or triacetate (di- and triacetin), and glycerol diglycidyl ether fit this criteria as expressed by their high normal boiling points and relatively low toxicities, e.g. LD_{50} (Table 1).

As previously mentioned, a solvent should facilitate the combination of reactants and catalysts, and as such, it should be able to dissolve solids, liquids, and gases. On the other hand, reaction product solubility in the reaction medium and solvent nature also dictate separation technique. The nature of a solvent, in terms of its microscopic and macroscopic properties, is difficult to represent with a single parameter. However, as reaction performance and product isolation procedure are mainly dependent on the relative solubilities of reactants, catalysts, and products in the reaction solvent, solvent polarity can be used as a representative measurement for solvent comparison.

Various empirical and theoretical methods, representing solvent physical and chemical properties, intermolecular forces, and solute-solvent interactions, can be used to calculate solvent polarity [19]. One of the primary methods

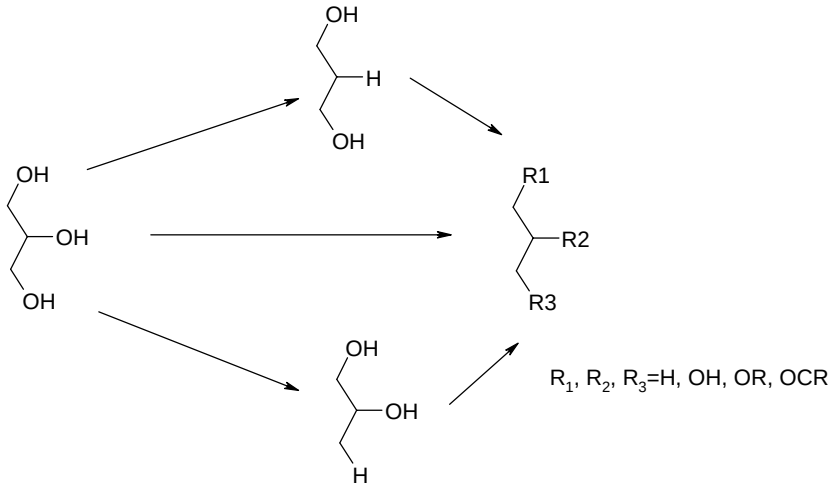


Figure 1. Synthesis of glycerol-based solvents.

Table 1. Physico-chemical properties of representative commercially available glycerol-based solvents.

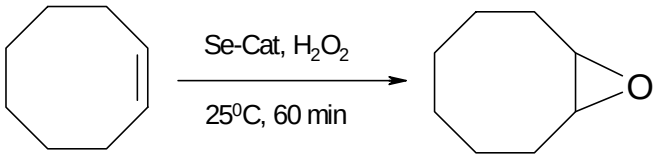
Entry	Solvent	Normal Boiling Point (°C)	LD_{50} (mg/Kg)	LogP
1	Glycerol	290	12,600	-4.15
2	1,2-Propanediol	187.6	20,000	-0.92
3	1,3-Propanediol	214	15,000	-1.00
4	Glycerol diacetate (Diacetin)	260	8,500	-0.64
5	Glycerol triacetate (Triacetin)	259	3,000	0.25
6	Glycerol tributyrate	307.5	3,200	3.31
7	Glycerol diglycidyl ether	341.4	n.a.	n.a.

for measuring polarity is the partition coefficient, a ratio of the concentrations of un-ionized compound between water and octanol as determined by spectroscopic analysis. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called log P. As illustrated in Table 1, exchanging the hydroxyl groups of glycerol with more hydrophobic organic groups, such as ether or ester, or eliminating them altogether, decreased solvent polarity, as expressed by the increase in log P of the solvent. Hence, we expect the increase in the solvent polarity to also increase the solubility of more hydrophobic organic molecules in solution.

3. Organic reactions in glycerol-based solvents

The first example of an organic reaction in a glycerol-based solvent was reported by Héctor García-Marín *et al.* [14], who synthesized eighteen glycerol-based ethers and tested the effects of their polarities on the performance of selenium-catalyzed epoxidation of cyclooctene with hydrogen peroxide as an oxidant (Figure 2). It was found that the conversions were, in some cases, comparable to those obtained with standard organic solvents such as dichloromethane, and while in other cases the conversions were even better. In addition, derivative polarity was shown to affect the reaction conversion, and derivatives that had high hydrogen bond donor but low hydrogen bond acceptor (Lewis basicity) abilities were superior. Moreover, the reaction also proceeded in the absence of catalysts, yielding almost complete cyclooctene conversions at moderate reaction temperatures.

We recently used commercially available glycerol derivatives as solvents in representative organic reactions with homogeneous and heterogeneous chemo- and biocatalysts [15]. The first example was the catalyst-free nucleophilic substitution of benzyl halides with different salts using glycerol, 1,2-propanediol, or di- or triacetin as representative glycerol-based solvents representing a broad range of polarities. The substitution reactions proceeded smoothly under mild conditions, using benzyl chloride and benzyl bromide with sodium acetate or ammonium acetate [15]. As expected, the reaction with benzyl bromide, the more active benzyl halide, was faster. In addition, the reaction with ammonium acetate yielded more product than that with sodium acetate, probably as the former is more soluble in organic solvents. Solvent polarity also affected reaction performance (Table 2). Increasing the polarity increased the benzyl acetate yield, probably because the reaction requires the salt to be split into ions, a phenomenon that increases in a more polar solvent. It can also explain the negligible reaction in di- or triacetin, which are the most hydrophobic of the four selected glycerol derivatives (Table 2, entries 3 and 4). Solvent polarity also affected the product extraction yield, which was tested by adding neat benzyl acetate to the four representative glycerol derivatives followed by its extraction with petroleum ether. Increasing the solvent polarity increased the extraction yield of the product, which was relatively hydrophobic, and therefore, it dissolved better in the more hydrophobic petroleum ether.



2,2,2-trifluoroethanol: conversion=100%
1,3-bis(2,2,3,3,3-pentafluoropropoxy)-2-propanol: conversion=90%

Figure 2. Selenium-catalyzed epoxidation of cyclooctene with hydrogen peroxide in glycerol-based solvents [15].

Table 2. Nucleophilic substitution of benzyl chloride and ammonium acetate in representative glycerol-based solvents [14][a].

Entry	Solvent	LogP	Product yield (%)	Product extraction yield (%)[b]
1	Glycerol	-4.15	100	94
2	1,2-Propanediol	-0.92	18.6	85
3	Diacetin	-0.64	2	45
4	Triacetin	0.25	0	23

[a]Reaction conditions: 0.7 mmol benzyl chloride, 0.77 mmol salt, 5 mL solvent, 80°C, 1 h.
[b]Extraction conditions: R.T., 0.5 g neat phenyl acetate, 5 mL petroleum ether.

Another non-catalytic reaction that was tested in glycerol or 1,2-propanediol was the azo-Michael reaction between *p*-anisidine and *n*-butyl acrylate (Figure 3, [20]). Replacing glycerol with 1,2-propanediol tremendously lowered the reaction conversion, but a negligible reaction was detected in other polar solvents like water, DMSO, or DMF. These results may be attributed not only to the polarity of the solvent, but also to the presence of hydroxyl groups or to the structure of glycerol and 1,2-propanediol.

The same four representative glycerol derivatives, glycerol, 1,2-propanediol, or di- or triacetin, were also used in the Suzuki cross-coupling of iodobenzene and phenylboronic acid (Figure 4, [15]). Coupling reactions, whose inventors were recently awarded the Nobel Prize in chemistry, are an important class of organic transformations. The Suzuki reaction is an excellent example of the power of a solvent in organic reactions as it involves hydrophobic halobenzene, more hydrophilic phenylboronic acid, a soluble palladium metal catalyst, and an inorganic base as the co-catalyst [21]. The results illustrate the effect of glycerol-based solvent polarity on catalytic performance (Table 3). On the one hand, glycerol, the most polar solvent of the four that were tested, easily dissolved phenylboronic acid, palladium salts, and inorganic base, but the solubility of iodobenzene in glycerol was limited. On the other hand, decreasing solvent polarity increased the dissolution of the more hydrophobic reactant, iodobenzene, and decreased the solubility of the base. This phenomenon is probably the reason why the yield of the reaction product, biphenyl, was highest in 1,2-propanediol, which has an average polarity that facilitates the optimal dissolution of all reaction components (Table 3, entry 2).

When bio-catalysts are employed, besides the solubility of the substrates or the bio-catalysts in the reaction mixture and the contribution of the solvents to product separation and catalyst recycling, the effect of the solvent on enzyme conformation or on microorganism cell vitality may affect catalytic performance and thus should also be considered. Therefore, we examined the effect of glycerol derivatives as reaction mediums on the activity, enantioselectivity, and the viability

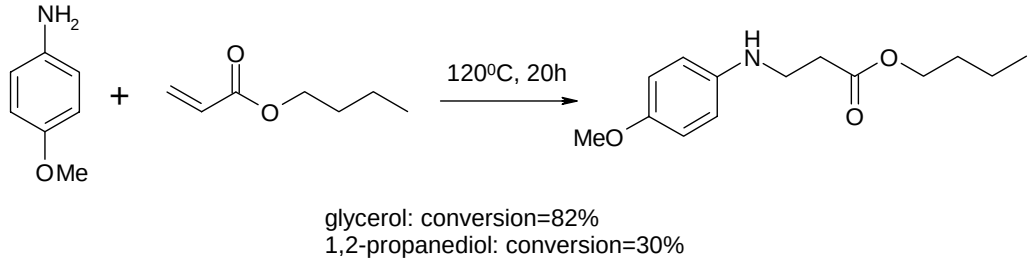


Figure 3. Catalyst-free aza-Michael reaction in glycerol-based solvents [20].

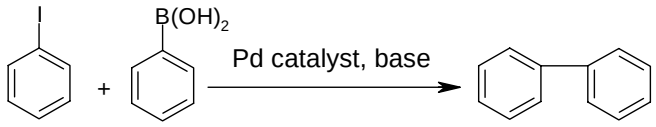


Figure 4. Suzuki cross-coupling of halobenzene and phenylboronic acid.

Table 3. Suzuki cross-coupling of iodobenzene and phenylboronic acid in representative glycerol-based solvents[a]. Reprinted from Wolfson, A. *et al*. 2010, Green Chem. Lett. and Rev., Accepted, with permission from Taylor & Francis Group. http://www.tandfonline.com.

Entry	Solvent	LogP	Product yield (%) 5%Pd/C	Product yield (%) $Pd(OAc)_2$	Product extraction yield (%)[b]
1	Glycerol	-4.15	95	90	100
2	1,2-Propanediol	-0.92	100	100	81
3	Diacetin	-0.64	83	79	87
4	Triacetin	0.25	73	70	95

[a]Reaction conditions: 0.7 mmol iodobenzene, 0.84 mmol phenylboronic acid, 10 μmol palladium, 0.77 mmol sodium carbonate, 5 mL solvent, 80°C, 2.5 h, [b]Extraction conditions: R.T., 0.5 g biphenyl, 5 mL petroleum ether.

of baker's yeast in the asymmetric reduction of ethyl acetoacetate or 2-heptanone (Table 4, [15]). As illustrated in Table 4, while cell viability in the more polar derivatives, glycerol and the propanediols, was zero after exposure to the solvents for several minutes (entries 2-5), the more hydrophobic ester and ether derivatives, glycerol triacetate or glycerol tributyrate, only slightly decreased yeast cell viability after 5 min exposure to the solvent (entries 6-8). Cell viability in glycerol triacetate after 12 h exposure (entry 6) was high and comparable to that in water (entry 1). It is well-known that a polar organic solvent like glycerol can decrease cell viability by imposing a high osmotic pressure on the cells that eventually causes them to burst. On the other hand, hydrophobic organic solvents may dissolve the cell membrane. However, it is worth mentioning that although the cells may be dead when exposed to organic solvents, the cell enzymes can still be active as was previously reported for the same reaction in glycerol [22, 23].

The solubility of either the ethyl acetoacetate or 2-heptanone reagent increased as the polarity of the solvent decreased, but while 2-heptanone has very low solubility in water or glycerol, ethyl acetoacetate dissolved fairly in all tested solvents. Hence, both the solubility of the substrate and the viability of the cells and of the enzymes in the solvents are expected to affect catalytic performance. As illustrated in Table 4, no products were detected in either of the propanediols (entries 3

Table 4. Asymmetric reduction of ethyl acetoacetate and 2-hepatnone in water and glycerol derivatives [14][a].

Entry	LogP	Solvent	Yeast Viability*10^{-3}		Ethyl acetoacetate[a]		2-Heptanone[b]	
			5 min (CFU/mL)	12 h	Conv. (%)	Ee (%)	Conv. (%)	Ee (%)
1	-	Water	3000	3000	74	>99	20	>99
2	-4.15	Glycerol	0	0	45	>99	8.8	97
3	-0.92	1,2-Propanediol	0	0	0	0	0	0
4	-1.00	1,3-Propanediol	0	0	0	0	0	0
5	-0.64	Diacetin	0	0	0	0	0	0
6	0.25	Triacetin	2000	2000	52	97	30	97
7	3.31	Glycerol tributyrate	2100	0	50	98	-	-
8	n.a.	Glycerol diglycidyl ether	1050	0	54	97	-	-

[a]Reaction conditions: 35 mL solvent, 16 g IBY, 5 mmol ethyl acetoacetate, 3.5 g glucose, 37°C, 48 h.
[b]5 mmol 2-heptanone, 72 h.

and 4) or in glycerol di-acetate (diacetine, entry 5), a finding that may be attributed to damage to the enzymes or to the co-factors in these solvents that prevented the reaction. On the other hand, both substrates were active in asymmetric reduction in glycerol, though the yields of the detected products were lower than in water, probably due to cell death and to the high viscosity of glycerol. The enantioselective reduction of ethyl acetoacetate in the more hydrophobic glycerol derivatives glycerol triacetate (entry 6), glycerol tributyrate (entry 7), or glycerol diglycidyl ether (entry 8) was also lower than in water (entry 1) but higher than in glycerol, most likely due to the higher viability of the cells and the enzymes in those solvents. In addition, in all the tested reactions enantioselectivity was very high.

Finally, the effect of solvent polarity on the reaction conversion can be seen mainly in the asymmetric reduction of 2-heptanone, which has poor solubility in either water (entry 1) or glycerol (entry 2) and higher solubility in glycerol triacetate (entry 6). This is probably the reason for the relatively high conversion of 2-heptanone in glycerol, even relative to the same reaction in water.

4. Glycerol derivates as solvents and reactants

In the above-mentioned reactions, glycerol derivatives were used as sustainable reaction mediums, enabling the dissolution of both reactants and catalysts and facilitating easy separation of the products and recycling of the catalysts. However, glycerol and glycerol triacetate were also simultaneously employed as solvent and reactant in several organic transformations. One such system is the catalytic transfer-hydrogenation of various unsaturated organic compounds in glycerol (Figure 5, [24-26]). Not only was glycerol used as solvent and hydrogen donor, its oxidation yielded dihydroxyacetone, a valuable intermediate in the production of many chemicals [27, 28]. Glycerol was also successfully employed as solvent and resolving agent in the lipase catalyzed kinetic resolution of several ester racemates (Figure 6a, [29]). In contrast, glycerol triacetate (triacetin) was used as solvent and resolving agent in the opposite reaction, the kinetic resolution of alcohol racemates (Figure 6b, [29]). Both reactions achieved high product yields and enantioselectivity. In addition, using glycerol or triacetin as the solvent for kinetic resolution also allowed for easy product isolation.

Glycerol and triacetin were also used as solvent and as acyl donor or acceptor in various transesterification reactions using homogeneous and heterogeneous bases, acids, and lipase (Table 5, Figure 7). The acid catalyzed transesterification of

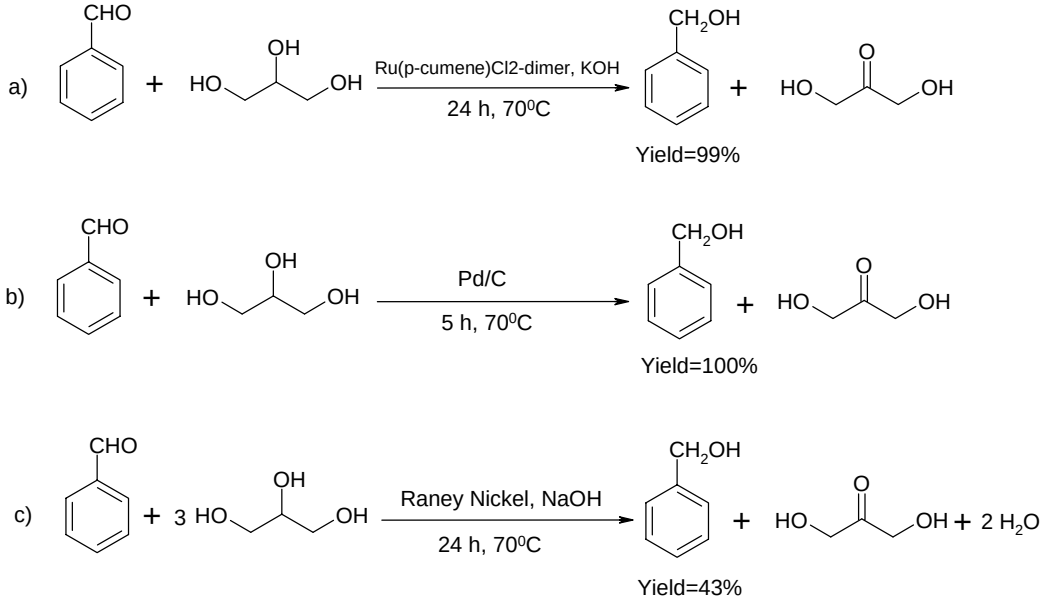


Figure 5. Transfer-hydrogenations of unsaturated organic compounds in glycerol [24].

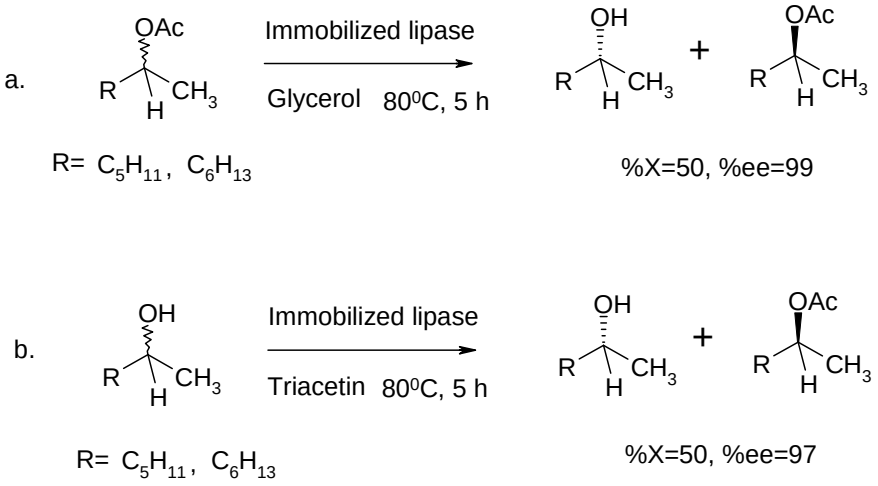


Figure 6. Lipase catalyzed kinetic resolution in glycerol-based solvents [29].

benzyl acetate to benzyl alcohol in glycerol was first tested with both sulfuric acid and immobilized sulfuric acid (Amberlyst-36) as representative homogeneous and heterogeneous acid catalysts, respectively (Table 5, entries 1 and 2, [30]). The same reaction was also successfully run with a representative homogeneous or heterogeneous base, NaOH or MgO, respectively (entries 3 and 4). Finally, immobilized *Candida Antarctica* (I-CAL-B) lipase was used as the representative bio-catalyst in the transesterification of both benzyl acetate and amyl acetate in glycerol (entries 5 and 6). All the reactions achieved high yields, and the products were easily extracted with glycerol immiscible solvents while the catalysts were successfully reused.

Likewise, both Amberlyst-36 [31] and free and immobilized CAL-B [32] were successfully employed as catalysts in the transesterification of isoamyl alcohol to produce isoamyl acetate, one

Table 5. Transesterification in glycerol-based solvents[a].

Entry	Substrate	Solvent	Catalyst	Conversion (%)
1	Benzyl acetate	Glycerol	H_2SO_4	57
2	Benzyl acetate	Glycerol	Amberlyst-36	27
3	Benzyl acetate	Glycerol	NaOH	96
4	Benzyl acetate	Glycerol	MgO	68
5	Benzyl acetate	Glycerol	I-CAL-B	40
6	Amyl alcohol	Triacetin	I-CAL-B	70
7	Isoamyl alcohol	Triacetin	Amberlyst-36	78
8[b]	Isoamyl alcohol	Triacetin	CAL-B	45
9	Isoamyl alcohol	Triacetin	I-CAL-B	67

[a]Reaction conditions: 5 g solvent, 0.1 g substrate, 0.01 g catalyst, 70°C, 5h.
[b]Reaction conditions: 5 g solvent, 0.1 g substrate, 0.1 g catalyst, 60°C, 7h.

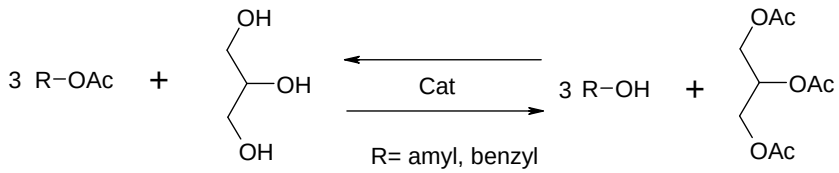


Figure 7. Transesterification of esters in glycerol-based solvents.

Table 6. Recycling of immobilized CAL-B and triacetin[a]. Reprinted from Wolfson, A. *et al*. 2009, Bioprocess and Biosystems Eng., 33, 363, with kind permission of Springer Science + Business Media.

Entry	Procedure	Conversion (%)
1	First cycle.	73
2	Second cycle of the catalyst, fresh triacetin.	71
3	Third cycle of the catalyst, fresh triacetin.	71
4	Forth cycle of the catalyst, fresh triacetin.	69
5	Second cycle of the catalyst and triacetin.	70
6	Second cycle of the catalyst and triacetin[b]	50

[a]Reaction conditions: 10 g triacetin, 1 g isoamyl alcohol, 0.1 g immobilized CAL-B, 80°C, 5 h. Catalyst separation by filtration and product extraction by petroleum ether, [b]Recycling of the catalyst and the triacetin after extraction of the product without prior isolation of the catalyst.

of the most widely used short-chain esters in the food industries because of its characteristic banana flavor [33] (Table 5, entries 7-9).

Finally, separation of the product and recycling of the catalyst are also important from environmental and economical points of view. The recycling of I-CAL-B as catalyst in the transesterification of isoamyl alcohol to isoamyl acetate in triacetin was tested and summarized in Table 6. Running the reaction with I-CAL-B for 5 h with an enzyme to fresh isoamyl alcohol ratio of 8.8 g/mol at 80°C resulted in high product yield (Table 6, entry 1).

After the first reaction cycle, the catalyst was filtrated and added to a fresh mixture of isoamyl alcohol in triacetin, and the reaction was run again under similar conditions. As illustrated in Table 6, three cycles of catalyst re-use resulted in only negligible change in reaction conversion (entries 2-4), revealing that little or no catalyst was lost or deactivated during the reaction. Yet because triacetin acted simultaneously as solvent and as acyl donor, triacetin must be recycled together with the heterogeneous catalyst. This requirement was also tested by filtration of the catalyst at the end of the first reaction cycle, extraction of the product and of the residual substrate, and addition of the used catalyst plus some fresh isoamyl alcohol to the used triacetin (Table 6, entry 5). The subsequent reaction resulted in a similar isoamyl alcohol conversion, showing that triacetin recycling is also possible. Finally, extraction of the product from the reaction mixture with the catalyst after the first reaction cycle to avoid catalyst filtration and the addition of fresh isoamyl alcohol to the re-used reaction mixture was also tested (entry 6). The lower conversion of isoamyl alcohol was probably due to partial damage to the immobilized lipase by the petroleum ether during product extraction.

CONCLUSIONS

In conclusion, glycerol derivatives can be successfully employed as green reaction mediums for various representative organic transformations. Both reaction performance and product separation as well as catalyst recycling were affected by the type and the polarity of the solvent in all reactions. It would appear that substrate solubility was the main determinant of reaction activity while the product solubility in the solvent determined the effectiveness of its extraction.

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