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A readily scalable methodology for the synthesis of non-symmetric glyceryl diethers by a tandem acid/base catalyzed process.

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KEYWORDS Heterogeneous acid catalysis, glycerol, glyceryl ethers, green solvent.

ABSTRACT: A useful optimized synthetic methodology has been designed for the obtaining of non-symmetric glyceryl diethers from epichlorohydrin. A tandem process combining a cheap, heterogeneous and fully recoverable acid catalyst and alkaline hydroxide is used for the synthesis of a variety of glycerol-derived ethers bearing different alkyl substituents in 1 and 3 positions. Different heterogeneous acid catalysts have been tested for the reaction of epichlorohydrin with several alcohols, the best results being obtained with readily available recoverable and inexpensive Montmorillonite-K10 and Nafion® NR50. For the second reaction step potassium hydroxide is used. In all the cases, good yields of the desired glyceryl diethers are obtained in smooth reaction conditions, always with total conversion of epichlorohydrin and without the need of intermediate purification. Scale up of the tandem process has been carried out with good results.

INTRODUCTION

Green Chemistry focusses on the production of chemicals improving the sustainability and safety of the synthetic processes, reducing the generation of by-products and minimizing risks.[1] One of the outstanding aspects related to Green Chemistry is the development of green solvents, able to substitute conventional ones, which have a non-renewable origin, and usually present negative features, such as volatility, flammability and toxicity.

In the last decades, different families of neoteric solvents have arisen such as bio-based solvents, fluorinated solvents, ionic liquids, deep eutectic solvents, supercritical fluids, gasexpanded liquids, switchable solvents, etc.[2-6] Bio-based solvents are attracting a great attention due to their chemical similarity with conventional organic solvents, and their favorable features, mainly their bio-based origin, biodegradability and low toxicity.[7] Among the different proposals, glycerol and its derivatives such as esters, ethers, carbonates and ketals present very interesting properties.[8] These compounds have been used as solvents and additives in cleaning, cosmetic, food and pharmaceutical industry.[9-13]

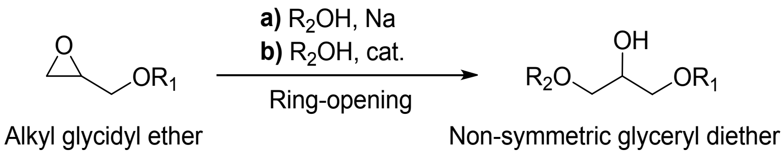
The use of glycerol itself or its derivatives as solvents is supported by the readily availability of glycerol as it appears to be the concomitant product in the biodiesel preparation from vegetable oils.[14] Thus valorization of glycerol has attracted a great attention both in academic and industrial fields.[15,16]

Glyceryl ethers stand out with respect to other glycerol derivatives due to their chemical stability, especially to oxidation,[17] their tunable physical-chemical properties, mainly polarity, viscosity and interfacial characteristics, as a function of their substituents,[18,19] their low volatility and flammability, interesting hydrotropy,[20,21] and low acute ecotoxicity.[22-24]

Different synthetic procedures for the obtaining of glyceryl ethers have been proposed using glycerol as starting material, including substitutions, alkylations, etherifications with alcohol or alkenes, telomerization reactions, etc.[25] However, controlling product selectivity results in a quite difficult task. In that case, an alternative approach is the use of building blocks such as glycidol, epichlorohydrin, glycerol carbonate or solketal.

The use of glycidol and epichlorohydrin has been preferred for the synthesis of mono- and symmetric diethers derived from glycerol, respectively. Different alkylating agents have been used such as dimethyl sulfate,[26] or alkoxides coming from the reaction of an alcohol with metallic sodium.[18] Recently, some systematic studies have been published for the catalyzed synthesis of monoethers,[27-29] and symmetric diethers.[30] In spite of the utility of non-symmetric glyceryl diethers as extraction agents of hydrophobic natural compounds much less interest has been displayed on the synthesis,.[21]

For the obtaining of non-symmetric glyceryl diethers, the ring-opening reaction of different commercial alkyl glycidyl ethers with an alcohol has been described. This synthesis is thus limited by the commercial availability of the starting glycidyl ether. Two different approaches have been envisaged for the ring-opening reaction (Scheme1): Alkoxide opening reaction, that involves a previous reaction of the alcohol with metallic sodium,[18] and acid catalyzed ring-opening reaction using several Lewis acids such as $FeCl_3$,[31] $(ZrO(OTf)_2)$,[32] I_2/poli(4-vinylpyridinium),[33] $V^{IV}(tpp)(OTf)_2$,[34] or $Sn^{IV}(tpp)(OTf)_2$.[35]



Scheme 1. Previous approaches for the synthesis of non-symmetric diethers.

In this work we present a tandem process for the synthesis of non-symmetric glyceryl diethers starting from epichlorohydrin and several alcohols as reagents using readily available and recoverable heterogeneous acid catalysts and developing an easily scalable methodology.

EXPERIMENTAL SECTION

General

Gas chromatography was carried out in a Hewlett Packard 7890 Series II Gas Chromatograph using a column of phenyl silicone 5.5% (Zebron ZB-5HT Inferno 30 m x 0.25 mm x 0.25 µm), Helium as carrier gas, and equipped with a flame ionization detector (FID).

^{1}H-, ^{13}C-, and ^{19}F-NMR spectra (DMSO-d_6, δ ppm, J Hz) were obtained using a Bruker AV-400 instrument with TMS as standard.

Mass Spectroscopy was carried out in a Bruker MicroTof-Q spectrometer, by electrospray ionization.

Boiling points were determined using differential scanning calorimetric (DSC) analysis in a TA Instruments DSC-Q20, calibrated with indium, using micropore aluminum pans, in a range of 298–673K, at atmospheric pressure. Boiling points were determined using onset temperature.

Density, sound propagation speed and Molar Volume. Density and sound propagation speed were determined simultaneously using an Anton Paar DSA 5000 M, with an internal Peltier thermostat at ±0.001 K. After appropriate calibration, the sample was introduced into a U-shaped glass tube and the density obtained from its frequency of vibration with an uncertainty of ±5 × 10−3 kg m^{-3}. Correction due to the kinematic viscosity of the liquid was performed automatically. The sound propagation speed of the sample was calculated with an uncertainty of ±0.1 m s^{-1} by passing sound waves through the cell. The Molar Volume (in $cm^3 \cdot mol^{-1}$) was calculated using the mass molecular and density data using the equation:

$$V_m = \frac{M_m}{\rho}$$

Viscosity. Three Ubbelohde viscometers with suspended ball level and intermediate flow time were used so as to cover the entire range of experimental values (instruments 50103/0c, 50110/I and 50111/Ia, with constants, k, of 0.002835, 0.01029 and 0.04957 mm^2 s−2 respectively). The viscometers were placed in a thermostatted bath. Flow time was measured at least three times with differences not greater than ±0.3 s. Viscosities were determined (in centistokes cSt) with an uncertainty of 0.6% using equation:

$$\nu = k(t - \Delta_{HC})$$

where ν is the kinematic viscosity, k the viscometer constant, t the average flow time (in seconds) and Δ_{HC} the kinetic energy correction. Dynamic viscosity values (in centipoises cP) were calculated using measured kinematic viscosity and density data.

Surface tension. A Lauda TVT-2 drop volume tensiometer was used to obtain the surface tension of solvents at a fixed temperature with a relative uncertainty not worse than 0.5%. A Lauda E-200 thermostat allowed the sample temperature to be maintained within ±0.01 K.

In all cases, the temperature was recorded using a ΑΣΛ digital thermometer with a Pt sensor, with a resolution of 0.001° and uncertainty of ±0.01 K.

Boiling points. Boiling points were determined using the onset temperature of Differential Scanning Calorimetric (DSC) analysis in a TA Instruments DSC-Q20, calibrated with indium, using micropore aluminum pans at atmospheric pressure.

Flash points. Flash points were calculated using the T.E.S.T. EPA software (Toxicity Estimation Software Tool) Version 4.2.1, which has a large compounds database, using the Consensus Method in all cases.

Refractive index. An Abbe ZUZI 315 refractometer with controlled temperature and a sodium lamp was used to measure refractive indices with an uncertainty of ±0.0001.

Molar Refractivity. The molar refractivity (in $cm^3 \cdot mol^{-1}$) was calculated using the measured refractive index and molar volume values according to the equation:

$$R_m = \frac{(n_D^2 - 1)}{(n_D^2 + 2)} \cdot V_m$$

Hidrophobicity. The ΔLogP298 values were calculated using the T.E.S.T. EPA software (Toxicity Estimation Software Tool) Version 4.2.1, starting from groups contribution theory.

Polarity. The dielectric permittivity was measured using a WTW (DM01) dipolemeter (Kahlsico) at 2 MHz. One thermostatted cylindrical condenser was used to cover the full range of experimental data (cell DFL2 for the range of 1-7), being calibrated previously with high purity reference liquids. The relative uncertainty in the dielectric values is estimated to be better than 0.05%. Finally, with the dielectric constant and other experimental data, an average dipole moment <μ2>1/2 was calculated for every liquid (in Debye) using the Onsager equation

Nafion ® NR50, Amberlyst 15, Dowex 50WX2, Montmorillonite K10-H^+, epichlorohydrin and 2,3-dihydrobenzofuran were purchased from Sigma–Aldrich. Methanol, ethanol, isopropanol and potassium hydroxide were purchased from Scharlab. Butanol and 2,2,2-trifluoroethanol were purchased from Alfa Aesar.

Methanol and ethanol were dried and distilled over calcium hydride prior to use. The rest of alcohols were used without any further purification. The potassium hydroxide purity was determined by titration using potassium hydrogen phtalate as titrating agent.

Synthesis of 1-chloro-3-alkoxypropan-2-ol ***[R.0.Cl]***

The appropriate amount of alcohol ROH (15:1 mol with respect to epichlorohydrin), the catalyst (5 or 10 % mol with respect to epichlorohydrin), and 2,3-dihydrobenzofuran as internal standard (15% w/w with respect to epichlorohydrin) were placed into a round bottomed flask.

Catalysts functionalization: Nafion ® NR50 0.8 mmol H^+g^{-1}, Amberlyst 15:: 4.6 mmol H^+g^{-1}; Dowex 50WX2: 4.5 mmol H^+g^{-1}; Montmorillonite: 0.59 mmol H^+g^{-1} .

The reaction was stirred and heated at 65 °C under argon. Then, epichlorohydrin (4.35 mmol, 0.35 mL) was added. The reaction was monitored at different times by extracting samples that were filtered previous to injection in GC. After total consumption of epichlorohydrin, the catalyst was filtered off and washed with methanol previous to recovery and the solvent was removed under vacuum distillation. The product was used in the second reaction without any further purification.

Reactions were scaled up in order to obtain 1 mol of product using a 2L thermostated glass reactor with mechanical stirring (Figure 6). 7.5 mol of alcohol, 5% mol of the catalyst were place on the glass reactor and heated at 65ºC. 1 mol of epichlorohydrin was added dropwise using an addition funnel. Once epichlorohydrin was consumed, the bulk of the reaction was collected in a 2L Erlenmeyer, the catalyst was filtered off and the solvent was removed under vacuum distillation.

Synthesis of non-symmetric 1,3-dialkoxypropan-2-ol ***[R.0.R´]***

Potassium hydroxide (120% with respect to epichlorohydrin) was dissolved in the desired alcohol R'OH (15:1 mol with respect to epichlorohydrin), then the product of the first reaction was added dropwise. After total consumption of [**R.0.Cl**] and the disappearance of the glycidyl ether intermediate, the excess of KOH was neutralized with HCl 0.3M, then filtered off and the alcohol was removed under vacuum distillation.

Reactions were scaled up in order to obtain 1 mol of product using a 2L thermostated glass reactor with mechanical stirring (Figure 6). 1.2 mol of KOH were dissolved in 7.5 mol of alcohol while heating at 65ºC. Then the crude of the reaction of the synthesis of R.0.Cl was added dropwise using an addition funnel. When the reaction ended, HCl 0.3M was added until neutralization, reaction crude was collected in a 2L Erlenmeyer, KCl was filtered off and the solvent was removed under vacuum distillation.

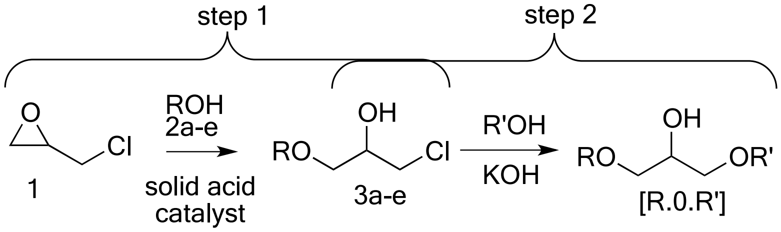
Pure (>99% GC) non-symmetric glyceryl diethers were finally obtained after a vacuum distillation.

Conversions and yields were determined by GC and checked by ^{1}H-NMR at the end of reaction. All the products were identified and characterized by ^{1}H-, ^{13}C-, and ^{19}F-NMR, and by HRMS. Boiling points were determined by DSC measurements.

Full characterization of products is gathered in the Supporting Information.

RESULTS AND DISCUSSION

The synthesis of non-symmetric glycerol-derived diethers **[R.0.R']** has been envisaged by a tandem process starting from epichlorohydrin (Scheme 2). In the first step the acid catalyzed opening of the oxirane ring has been considered, in order to achieve the synthesis of several 1-chloro-3-alkoxypropan-2-ol derivatives **[R.0.Cl]**. Subsequently, S_N2 substitution of chlorine by the corresponding alkoxide would provide the desired diethers [**R.0.R'**]. This reaction pathway was selected in order to prevent the formation of symmetric glyceryl ethers due to simultaneous SN_2 substitution and epoxide ring opening. This fact it has been previously described when epichlorohydrin is reacted with an alcohol in a basic media.[36]

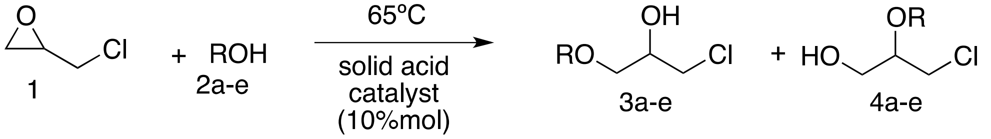


2a MeOH	2d ^{i}PrOH
2b EtOH	2e TFE (2,2,2-trifluoroethanol)
2c BuOH	

Scheme 2. Proposal of a tandem process for the synthesis of non-symmetric glyceryl diethers [**R.0.R'**].

Several solid acid catalysts have been tested in the reaction of epichlorohydrin (**1**) with five alcohols (methanol **2a**, ethanol **2b,** butanol **2c**, isopropanol **2d** and 2,2,2-trifluoroethanol **2e**). Namely, two sulfonic resins (Dowex® 50WX2 and Amberlyst® 15), a perfluoro sulfonic resin, Nafion® NR50, and a natural clay, Montmorillonite K10-H^+ were selected and tested using initially 10% mol of catalyst and 65 °C as reaction temperature (Scheme 3).

Results were analyzed by GC and the two isomers **3** and **4** were observed, although **3** was the major product in all the cases.



ROH: MeOH,EtOH, BuOH, ^{i}PrOH, TFE

Scheme 3. Reaction of epichlorohydrin **1** and several alcohols **2a-e** using acid catalysis.

In the case of using the sulfonic resins, Dowex® 50WX2 and Amberlyst 15, long reaction times (24 h) were needed in order to achieve maximum epichlorohydrin conversions, and in all the cases moderate yields of the desired products were obtained (Figure 1). In the case of 2,2,2-trifluoroethanol (**2e**), only a yield of 10% was reached due to the lower nucleophilicity of this alcohol.

As it can be seen, better results were obtained when using Amberlyst 15, a higher crosslinked resin and thus with a more rigid structure than Dowex® 50WX2. With these two catalysts, a decrease both in conversion and yields were observed from methanol to butanol. As the nature of the acid sites was equal in both catalysts, this fact revealed a problem in the accessibility to the sulfonic sites due to an insufficient swelling of the resin in less polar alcohols such as isopropanol or butanol.

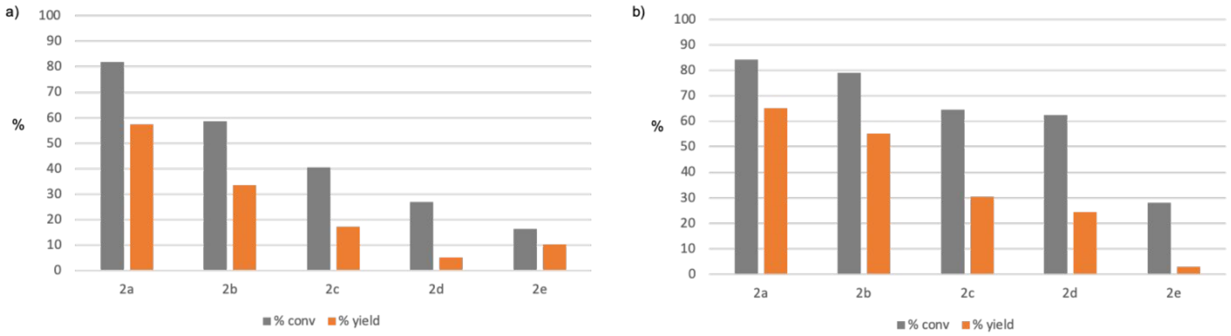
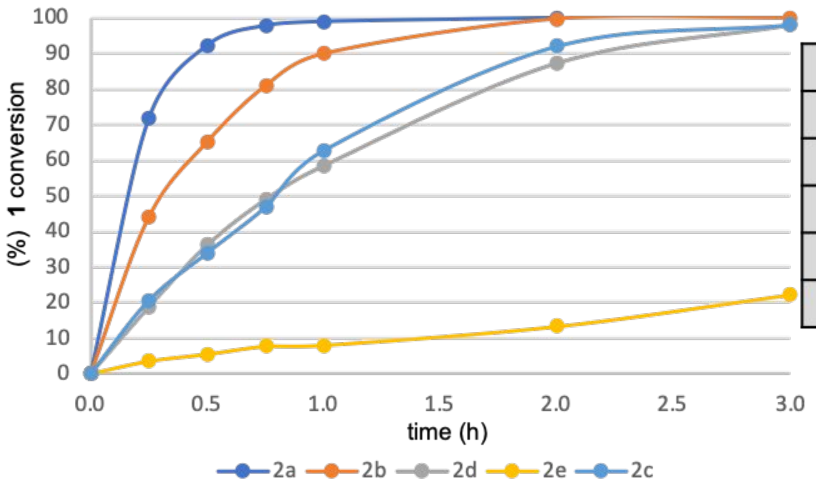


Figure 1. Epichlorohydrin conversion and **3a-e** yields in the reactions catalyzed by a) Dowex® 50WX2 and b) Amberlyst 15 (10% mol of catalyst, 65 °C and 24 hours reaction time).

A similar behavior was observed in the case of using Nafion® NR50 (Figure 2), although in this case, the stronger acidity of the acid sites provided total conversion of epichlorohydrin in shorter times, together with excellent yields towards 1-chloro-3-alkoxypropan-2-ols (**3a-d**). Again, reaction with trifluoroethanol (**2e**) proceeded with very low conversion and lower selectivity toward the desired product (**3e**).



product	yield (%) (time)
3a	98.9 (2h)
3b	97.4 (2h)
3c	92.5 (3h)
3d	93.0 (3h)
3e	6.9 (3h)

Figure 2. Epichlorohydrin conversions and product yields in the reactions catalyzed by Nafion® NR50 (10% mol of catalyst, 65 °C).

In the case of using Montmorillonite K10-H^+, both epichlorohydrin (**1**) conversion and **3a-e** product yield were closely related to the nucleophilicity of the starting alcohol (Table 1). Thus, the best results were obtained using isopropanol and butanol and again the use of trifluoroethanol provided low yields of the product **3e**. Ratios of regioisomers **3/4** in between 13:1 for methanol and 60:1 for isopropanol were observed, which represents less than a 7% yield of isomer **4** in the worst of the cases.

Table 1. Epichlorohydrin (**1**) conversion and product yields (**3**) in the reactions catalyzed by Montmorillonite K10-H^+. (10% mol of catalyst, 65 °C and 24 hours reaction time).

	Time (h)				
	0.25	**0.5**	**1**	**2**	**3**

2a	**1** conv. (%)	35	54	75	91	95
	3a yield (%)	25	41	64	77	84
2b	**1** conv. (%)	39	72	93	99	99
	3b yield (%)	37	62	84	88	89
2c	**1** conv. (%)	96	98	100	--	--
	3c yield (%)	85	88	88	--	--
2d	**1** conv. (%)	77	96	100	--	--
	3d yield (%)	76	94	98	--	--
2e	**1** conv. (%)	29	49	60	80	--
	3e yield (%)	13	20	24	34	--

*Reaction conditions: 10% mol of catalyst and 65 °C.

When comparing the activity of Nafion® NR50 and Montmorillonite K10-H^+ at short reaction time (0.25 h) (Figure 3) the different trend in the catalyst behavior is clear. Thus, Nafion® NR50 should be selected for the obtaining of **3a** or **3b**. A better swelling of the resin in methanol and ethanol favors the accessibility of epichlorohydrin to the stronger perfluoro sulfonic acid sites giving rise to 99% yield of **3a** in only one hour and 97% of **3b** in two hours. While Montmorillonite K10-H^+ will be preferable when **3c** or **3d** are the objective, thus 88% and 98% yields are obtained respectively in one hour.

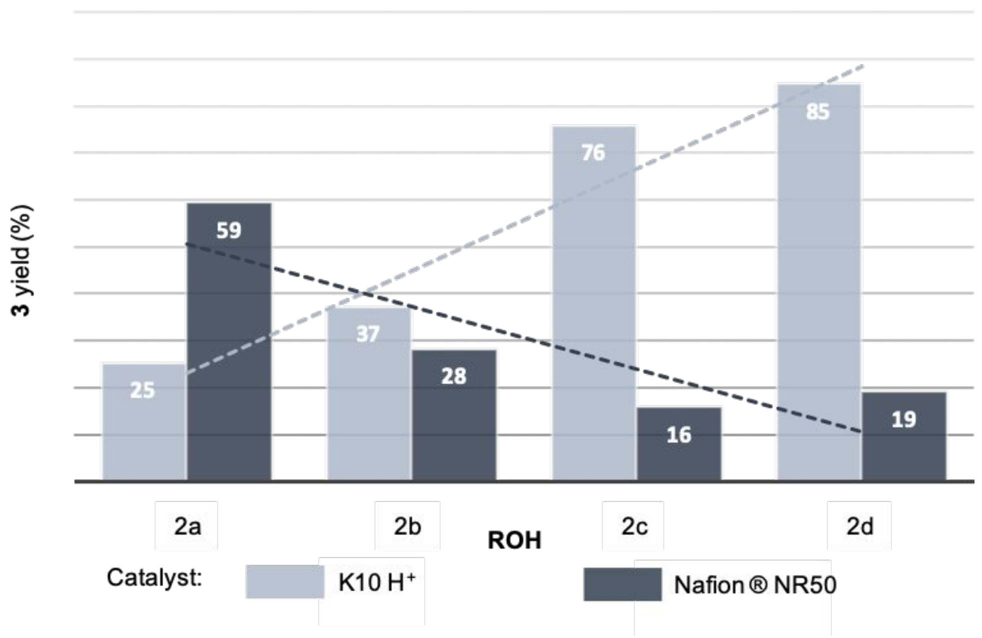


Figure 3. Comparison of **3** yields in the reaction of epichlorohydrin (**1**) with different alcohols (**2a-e**) at 0.25 h reaction time catalyzed by Nafion® NR50 and Montmorillonite K10-H$^+$.

An optimization of the amount of catalyst has been also envisaged. The synthesis of **3** was carried out using 5% mol of catalyst (Figure 4). Nafion® NR50 was selected for the reaction with methanol (**2a**) and ethanol (**2b**), and Montmorillonite K10-H$^+$ was used as catalyst with butanol (**2c**) and isopropanol (**2d**). In all the cases the reaction rates were slightly slowdown, although this effect was more pronounced in the reactions catalyzed by Nafion® NR50. Nevertheless, total conversion of epichlorohydrin and good yields of the product **3** were achieved, thus demonstrating that 5% mol of catalyst is enough to carry out this reaction.

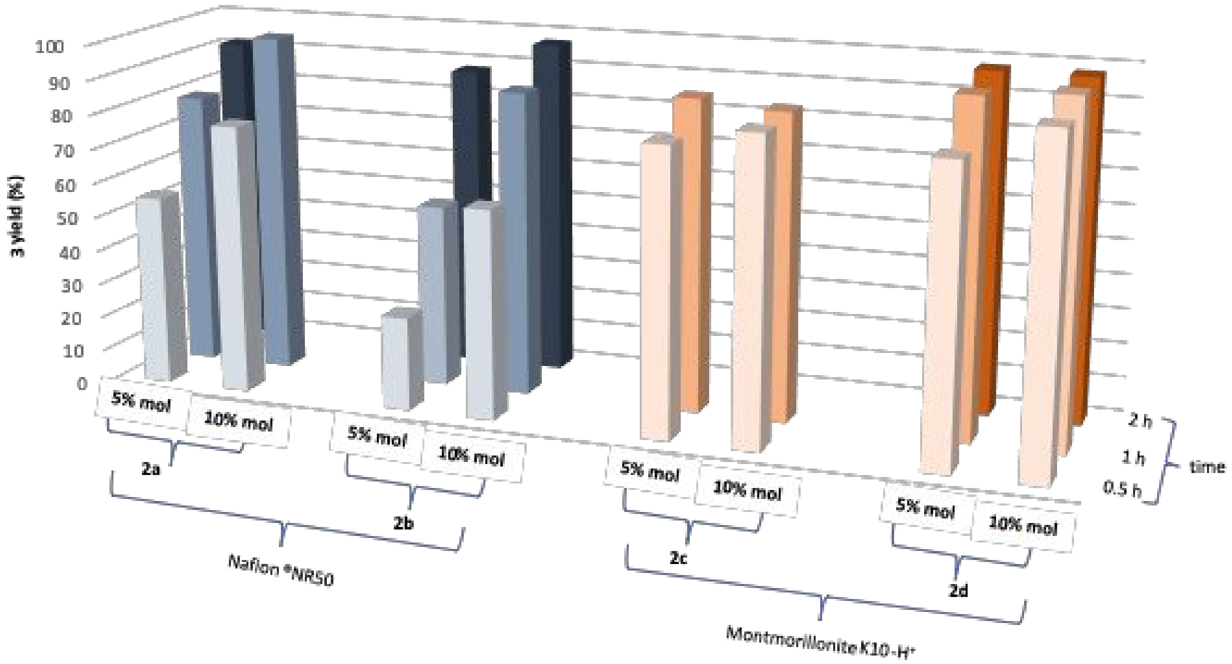


Figure 4. Influence of the amount of catalyst in **3** yields in the reaction of epichlorohydrin (**1**) with different alcohols (**2a-d**) catalyzed by Nafion® NR50 and Montmorillonite K10-H+.

The possibility of recovering the catalyst was also studied. Thus, as a proof of concept Nafion NR50 was tested in the reaction of epichlorohydrin with methanol (**2a**) and Montmorillonite K10-H+ in the reaction of epichlorohydrin with butanol **(2d)**. In both cases, the catalysts were fully recoverable up to five consecutive runs without any loss of activity. (Figure 5).

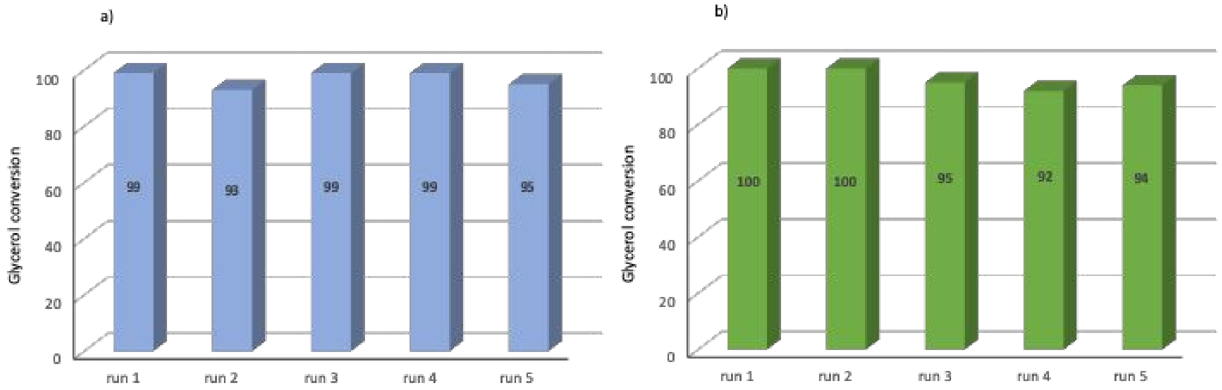
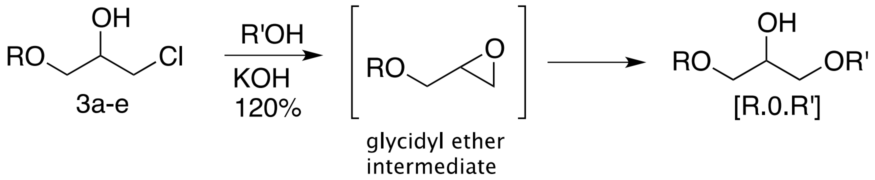


Figure 5. Study of the catalyst recoverability in the reaction of epichlorohydrin (**1**) with a) **2a** catalyzed by Nafion® NR50 and b) **2c** catalyzed by Montmorillonite K10-H^+. (reaction conditions: 65°C, 2 h reaction time, 5% mol of catalyst, 15:1 molar ratio alcohol (**2**)/epichlorohydrin)

Finally, a scale-up to 1 mol of the reaction was carried out in a 2L reactor (Figure 6**)**. As reactor volume was a limiting parameter, the ratio alcohol 2/ epichlorohydrin 1 was reduced to 7.5:1. In all the cases, the same results of yields and selectivity at the same reaction times were observed, thus demonstrating the viability of this process for the production of R0Cl (**3**) intermediates in an hectogram scale.

Figure 6. Experimental set up for the synthesis of 1 mol scale of **3** in a 2 L reactor. (reaction conditions: 5% mol of catalyst, 7.5:1 molar ratio alcohol (**2**)/epichlorohydrin, 65°C)

After catalyst filtration and the evaporation of the excess of alcohol **2** and without any further purification, the product of the first reaction **[R.0.Cl]** was used in the second step in which the S_N2 substitution of chlorine was carried out (Scheme 4).



Scheme 4. Second step reaction for the synthesis of non-symmetric glyceryl diethers **[R.0.R']**.

For this reaction, optimized conditions previously reported for the synthesis of glycerol derived monoethers[28] and symmetric diethers[36] were applied (65°C and 120% mol of base). Thus, stoichiometric amount of base is necessary for chlorine substitution and 20% mol of base is the optimal amount for subsequent ring opening reaction. Reactants **3a-d** rapidly disappeared forming the corresponding glycidyl ether (Scheme 4) that underwent the ring-opening reaction to produce the desired glyceryl diether **[R.0.R']**. It is worth mentioning that the reactions proceeded with total conversion of **3** and the glycidyl ether intermediate and total selectivity towards the desired product **[R.0.R']**, although reaction time strongly depended on the nature of the alcohol (R'OH). Thus, the reaction proceeded in less than 2 hours with butanol (**2c**), whereas 6 hours were needed when using isopropanol (**2d**) and 72 hours in the case of trifluoroethanol (**2e**). In the case of the synthesis of trifluoroethoxy derivatives, it is necessary to introduce this substituent in the second step in order to achieve the best yields.

This synthetic methodology was successfully applied for the synthesis of eleven different non-symmetric glyceryl diethers

(Figure 7) both at 5 mmol scale and 1 mol scale using the previously described system (Figure 6).

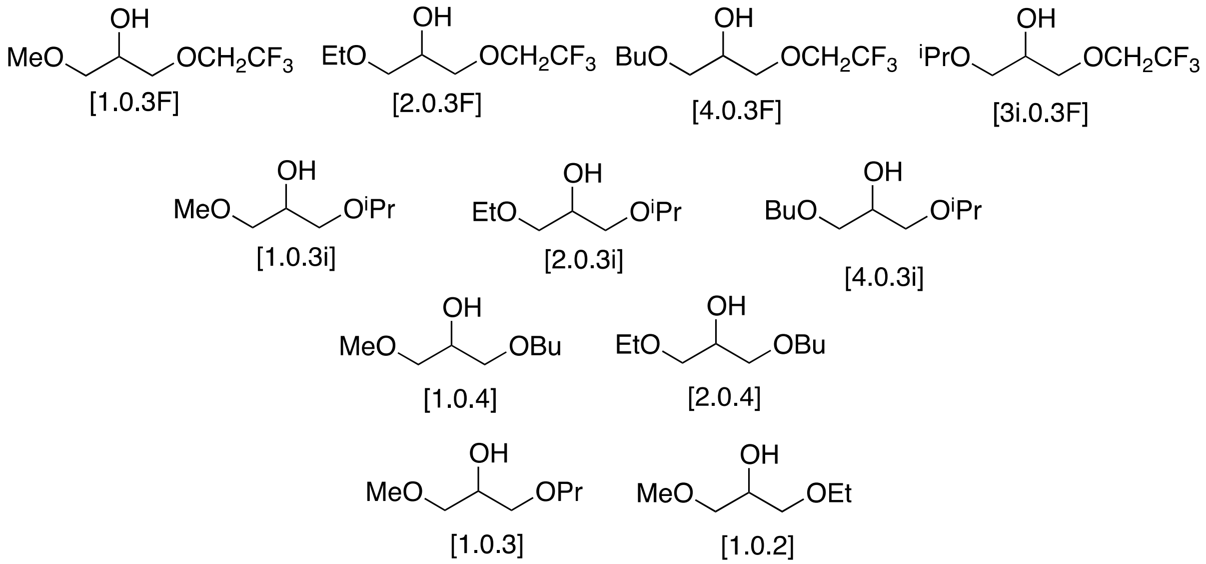


Figure 7. Structures of the non-symmetric glyceryl diethers synthetized in this work.

The most relevant physical-chemical properties of these compounds were determined in order to evaluate their applicability as renewable solvents. The ranges of values of these properties measured at 25 °C are gathered in Table 2 together with the ones of other glycerol-derivatives: monoethers (**R00**), symmetric diethers (**R0R**), triethers (**RRR**) and R00-DES (all the values for R0R’are gathered in the supplementary information). In general, these new bio-solvents are low viscous protic solvents presenting densities, refractivities and surface tensions similar to those of other conventional solvents. They are non-volatile solvents and their boiling points are lower than those of other glycerol derivatives, in the range of 180-220 °C. For this reason, their Flash Points are moderated, being "combustible liquids" (but not "flammable liquids") according to the EPA and OSHA classifications. Their polarity (E_T^N, ε, etc.) is moderated, presenting a wide range of values of hydrophobicity, and some of them are water miscible. It is worth mentioning that the presence of fluorine atoms notably modifies the properties, increasing mainly the viscosity and the polarity.

Table 2. Ranges of values of main physical-chemical properties of different glyceryl ethers.

	Glycerol	**R00**[28]	**R0R**[36]	**R0R′**	**RRR**	**R00-DES**[37]
Density (g·cm^{-3})	1.26	0.95-1.36	0.88-1.56	**0.90-1.35**	0.82-1.30	1.05-1.30
Viscosity (cP)	1200	40-110	3-20	**3-7**	1-3	>130
Surface Tension (mN·m^{-1})	63.4	25-40	19-30	**24-30**	22-29	30-50
Boiling Point (°C)	290	200-290	170-350	**180-220**	150-240	n.d.
Flash Point (°C)	160	80-125	58-180	**55-100**	30-90	n.d.
Sound speed (m·s^{-1})	1964	1200-1550	800-1370	**1200-1300**	980-1300	1450-2000
Refraction Index	1.47	1.38-1.45	1.32-1.44	**1.39-1.43**	1.35-1.42	1.42-1.55
Permittivity (ε)	46	8-25	3-14	**5-12**	4-14	n.d.
Polarity (E_T^N)	0.81	0.62-0.78	0.36-0.72	**0.43-0.56**	0.14-0.20	0.69-0.85
H-Bond Donor (α)	0.91	0.55-1.11	0.21-1.10	**0.32-0.78**	0.11-0.58	0.41-0.76

K-T Parameter (π*)	1.05	0.59-0.87	0.42-0.73	**0.58-0.72**	0.52-0.70	0.55-1.28
Hidrophobicity (logP)	-1.4	(-1)-2	(-0.6)-6	**(-0.2)-2**	(-0.2)-3	n.d.

A 2D-map can be a powerful tool for choosing the most suitable solvent for a solvent's application or to replace a conventional non-renewable solvent. Thus we have gathered the most relevant properties of glycerol derived solvents and conventional solvents in two plots (notation for conventional solvents is gathered in S.I.). The first one represents viscosity vs volatility (boiling points), two important operational properties (Figure 8), and the second one hydrophobicity (ΔLogP98) vs surface tension, two interesting parameters influencing in solvation processes (Figure 9).

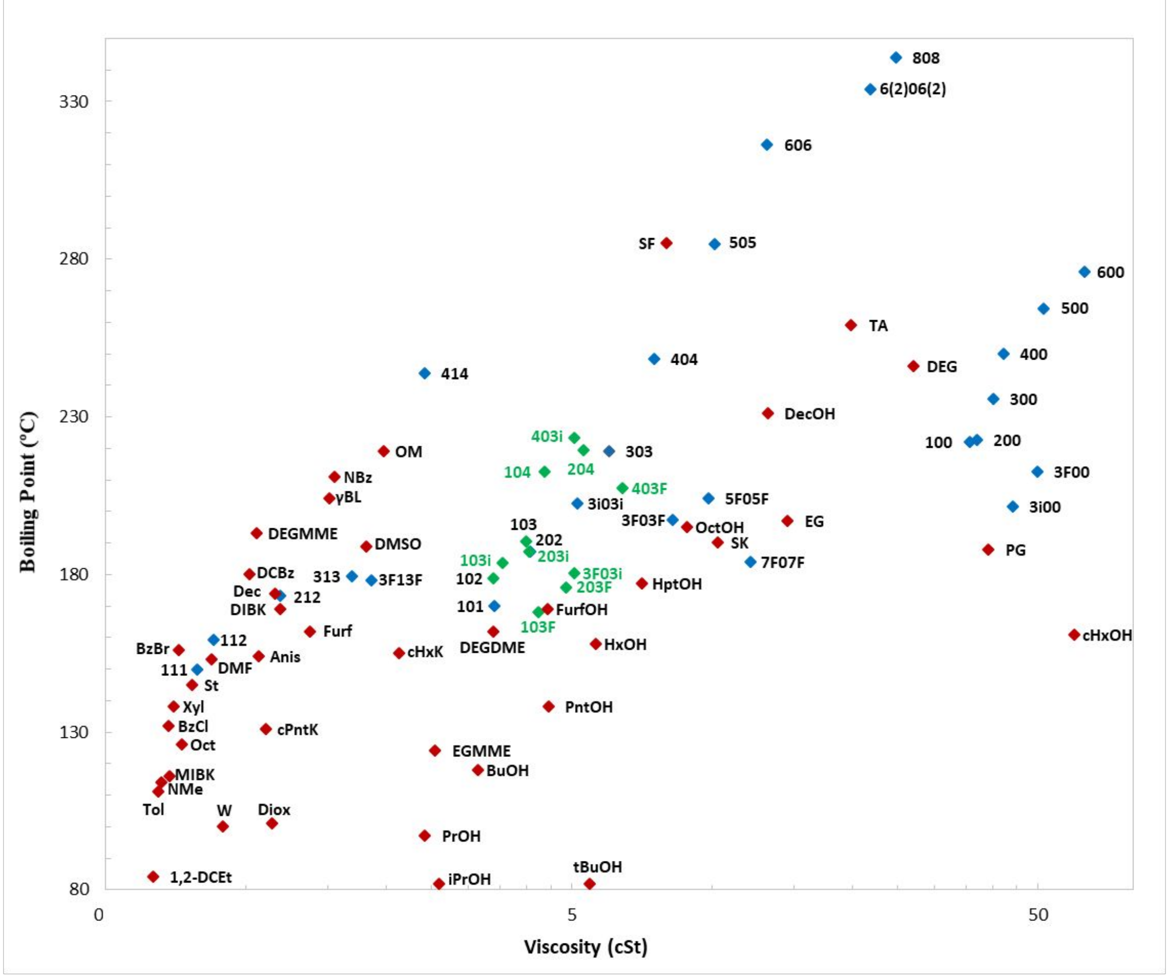


Figure 8. 2D-Map of viscosity vs volatility (boiling points) for a selection of glycerol derived solvents (in blue), including the non-symmetric diethers synthetized in this work (in green), and several conventional solvents (in red).

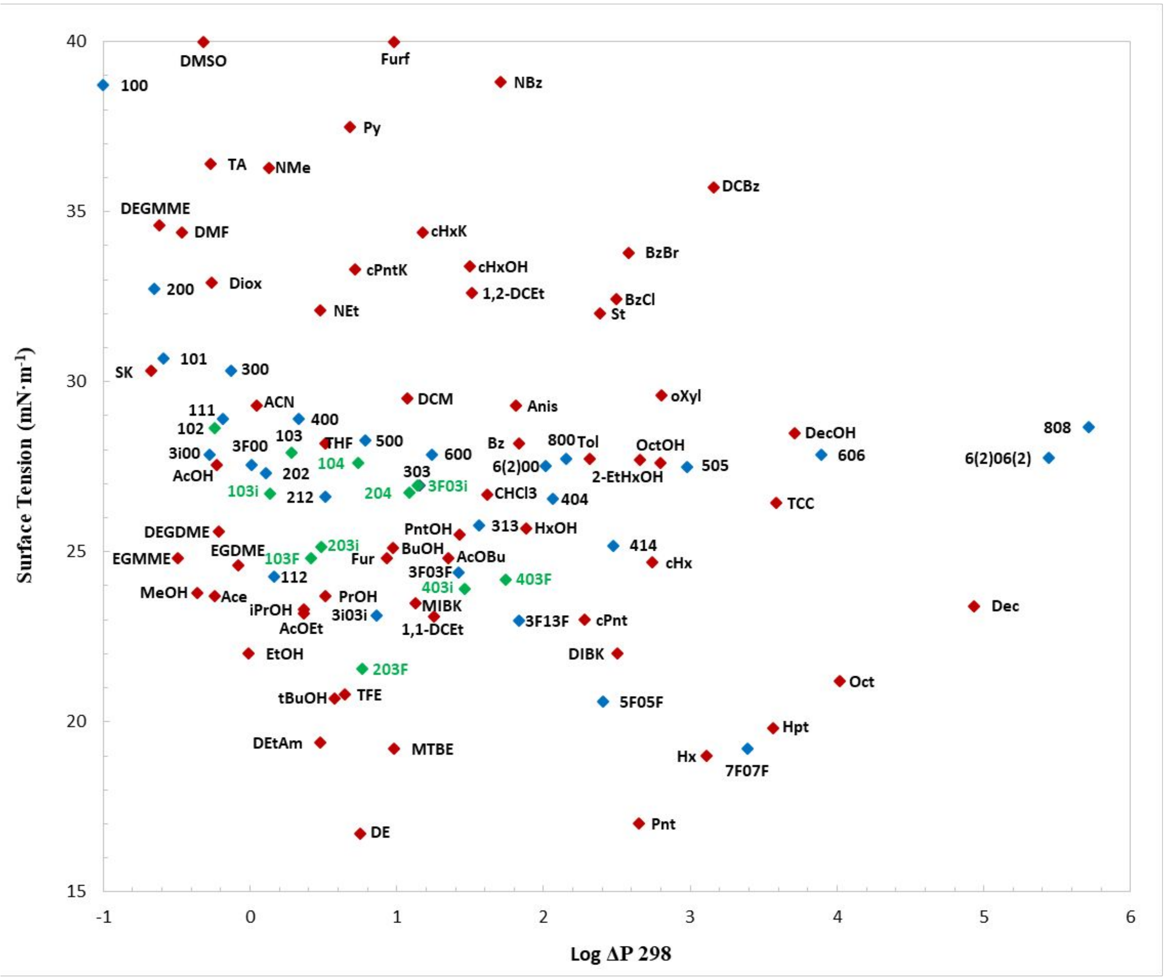


Figure 9. 2D-Map of the hydrophobicity (ΔLogP98) vs surface tension for a selection of glycerol derived solvents (in blue), including the non-symmetric diethers synthetized in this work (in green), and several conventional solvents (in red).

As it can be seen, physical-chemical properties of non-symmetric glyceryl diethers are very similar to those of symmetric glyceryl diethers, being both protic solvents similar to some conventional solvents in terms of polarity and surface tension, but with higher boiling points, that is safer solvents for some applications and thus possible renewable alternative solvents.

The main added value for non-symmetric glyceryl diether is the possibility of fine tuning their properties for a specific applications. For example, if we need solvent with properties in between symmetric [2.0.2] and [4.0.4], solvents such as [2.0.4], [2.0.3], [2.0.3i] and [2.0.3F], provide a fine adjust of viscosity, surface tension, polarity, etc.

CONCLUSIONS

We have applied a simple and scalable methodology for the obtaining of non-symmetric glyceryl diethers. The use of a tandem process facilitates the work up and provides excellent yields of the diethers [R.0.R’]. In the first step, Nafion®NR50 and Montmorillonite are preferred as heterogeneous acid catalysts for ring opening reaction of epichlorohydrin while an alkaline hydroxide is used in the second step. Up to eleven different compounds have been obtained in an hectogram scale using this methodology. The values of their physical-chemical properties evidences that a fine tuning of boiling points, polarity, viscosity or surface tension can be achieved by adjusting the nature of the substituents. 2D plots evidence the usefulness of these glycerol derived solvents as possible substituents of conventional hazardous solvents in specific applications.

ASSOCIATE CONTENT

Supporting information contents:

Products characterization; product and [R.0.Cl] intermediates description; Products physical chemical properties and Key of the 2D-maps.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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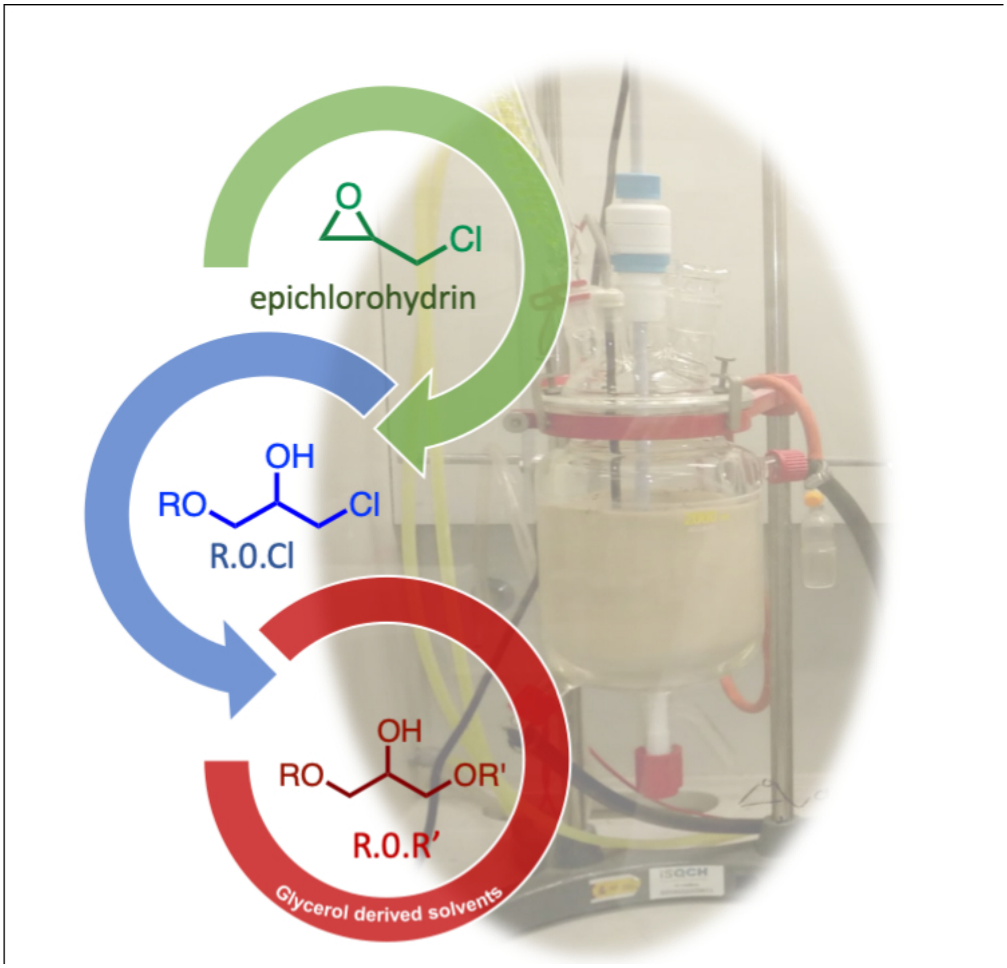

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