Glycerol Ether Synthesis: A Bench Test for Green Chemistry Concepts and Technologies

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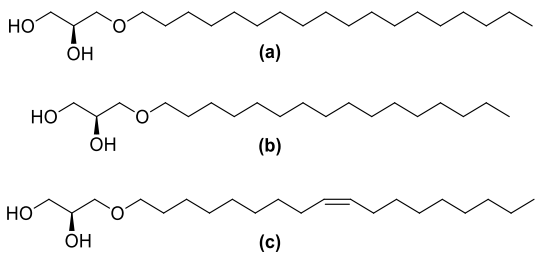
Content

1. Introduction: properties and potential applications of glycerol ethers

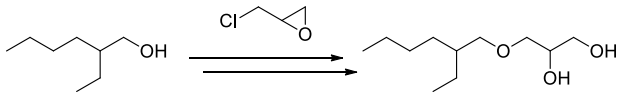
Naturally occuring, glycerol ethers are generally pure enantiomers and batylic, chimylic, selachylic alcohols (Scheme 1) are the major ones which can be found in lipid membranes.[1,2,3] Glycerol ethers, and specifically the mono-alkylated ones, have already found applications in several industrial domains and can be considered as among one of the most promising areas for glycerol valorization into products for fine and specialty chemistry.[4]



Scheme 1. Most common glycerol mono-ethers found in nature: **(a)** (*S*)-batylic alcohol ((*S*)-3-*O*-octadecyloxy-1,2-propanediol), **(b)** (*S*)-chimylic alcohol ((S)-hexadecyloxy-1,2-propanediol) et **(c)** (*S*)-selachylic alcohol ((*S*,*Z*)-3-(9-octadecenyloxy)propane-1,2-diol).

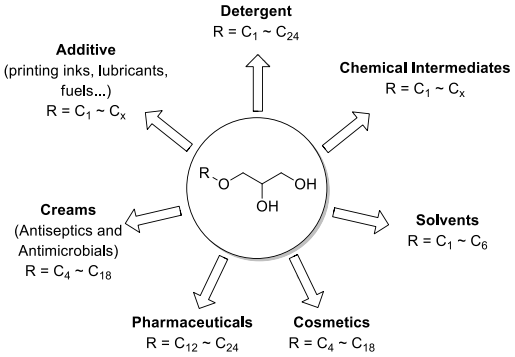
The synthesis of glycerol ethers was earlier studied in order to modify the hydrophilic (glycerol, diglycerol, triglycerol) and hydrophobic parts (branched or linear chains) allowing the possibility to develop a large class of compounds with useful biological and physical properties.[5] Several studies have demonstrated their original surfactant properties compared to classical nonionic surfactants such as polyethylene glycols (PEGs) synthesized from petrochemicals.[6,7,8,9,10,11] For example, Aubry recently defined hydrotropic properties for some short alkylated chain glycerol mono-ethers (GMEs).[12] These compounds also possess some original biological properties such as immunostimulating,[13] antimicrobial,[14,15,16] and antitumor activity[17,18,19] or can be used in equine anesthesia.[20] This class of compound is also present as additives in the pharmaceutical domain, as they allow the transport of active substances through the skin,[21] lipid membrane[22] and hemato-encephalic barrier.[23,24,25] They can be found in dermatological preparations[26,27,28] for the treatment of allergic diseases, especially asthma,[29] as they have activity towards mycobacteria.[30,31,32,33,34] Cosmetics[35,36] also use GMEs, specifically in the composition of deodorants,[37,38] hair dyes,[39] shampoos[40,41] and creams for the skin.[42,43]

One of the most widespread molecules used in skin creams is 3-[(2-ethylhexyl)oxy]-1,2-propanediol which is also known as SENSIVA® SC50. This compound is industrially synthesized from epichlorohydrin (ECH) by SCHÜLKE & MAYR (Scheme 2).[44] The KAO company produces glycerol isostearyl ether which is commercialized as PENETOL GE-IS.[45] GMEs are also used as emulsifiers[46] and in liquid detergent compositions.[47,48,49] They are present in the formulation of inks,[50,51] herbicides,[52] polymers,[53,54] and lubricants.[55] Furthermore, glycerol diethers increase performance as fuel additives.[56,57] Finally, this class of compound can also be used as intermediates in the preparation of chemicals or materials for example 1,3-dioxolan-2-ones,[58] urethanes,[59] hydrogels[60] and ionic surfactants.[61,62,63,64,65,66,67,68,69]



Scheme 2. 3-[(2-ethylhexyl)oxy]-1,2-propanediol (Sensiva® SC50), prepared from epichlorhydrin

Most of the literature data refer to studies concerning applications of GMEs. Numerous patents over the last twenty years, about (3355 et 2378 ppour 20 ans)3147 records,[70] show how these compounds can be used as substitutes for polyethylene and polypropylene glycol derivatives which are widely-used industrially. In fact, the latter have environmental side effects so glyme and diglyme solvents must be substituted.[71]



Scheme 3. Applications of Glycerol Mono-Ethers

Despite the numerous potential application domains (Scheme 3), poor data are available concerning GMEs production as well as their demand. This could be due to two reasons. First, even though the synthesis of GMEs has been described since the end of the 19th century significant scientific and economic interest appeared only in the last 5 years. Second, the chemical and physical properties of glycerol make the synthesis of ether derivatives difficult and often not acceptable either from an economic or ecological point of view. In fact, the three alcohol functions have similar pKa and reactivity. In addition, the extremely hydrophilic character of this substrate makes reactions with many organic (hydrophobic) reagents difficult

and sometimes impossible. For glycerol ether synthesis, problems of selectivity (primary versus secondary ethers, formation of mono- versus di- or tri-ethers) are significant. In many cases, the conversion is low. On the other hand, glycerol is nowadays one of the few pure bio-sourced chemicals available on a large scale (about 3 million tons in 2012) at a relatively low price.

Many reviews dealing with potential applications of glycerol derivatives have been published over the last few years.[72,73,74,75,76,77,78,79,80,81,82] These very useful general articles show the wide interest in this type of molecule but only a few of them describe some of the new synthetic pathways for glycerol ether synthesis. However, this review focusses on the synthesis of glycerol ethers and the difficulties encountered. Moreover, preparation of these target molecules, i.e. glycerol ethers, was also the occasion for testing the most recent concepts and technologies, especially the sustainable ones. In fact, as soon as green (renewable) starting material began to be used, then clean and safe synthesis appeared the obvious and necessary option.

The potential and specific difficulties in the synthesis of glycerol alkyl or aryl ethers have been the opportunity for chemists both in academic and industrial laboratories to put the modern concepts of green chemistry to the test. These concepts such as “Life Cycle Analysis”, “Atom economy”, and “The Twelve Principles of the Green Chemistry and of the Chemical Engineering” appeared at the end of the 1990’s and the beginning of 2000 and were associated with many types of synthetic methods and strategies. On a single set of similar molecules (glycerol ethers), syntheses using already well-known technologies, and many new ones, could be compared not only in terms of yields and selectivity (chemio-, regio- and even stereo-selectivity) but also sustainability.[83]

The first obvious valorization strategy involves the transformation of glycerol (the starting material) into already known chemical intermediates, such as epichlorohydrin, glycidol,

chloropropane diol, and acrolein, etc. This is sometimes already done on an industrial scale. Furthermore, these intermediates can be readily transformed into other derivatives including glycerol ethers using well-documented industrial processes. However, these strategies obviously suffer from the high toxicity of such intermediates.

In order to improve regio- and chemio-selectivity, a strategy including protection-deprotection steps starting from glycerol was suggested. Efficient reactions were obtained but these additional steps limit the interest of these synthetic pathways in terms of cost and sustainability. Nevertheless, intermediates such as glycerol carbonate and glycerol acetal which are already used as solvents and in other applications may prove to be a valuable option. In fact, if such chemicals found large-scale application their use as advanced intermediates would be of economic interest.

Alkylation of alcohol in basic conditions via the Williamson synthesis is still an efficient strategy but suffers from poor atom economy and difficult reaction conditions (toxicity of solvents and reagents, salts production). Therefore, not surprisingly, catalysis was the main technological tool used in order to obtain efficient and selective alkylation or arylation which could be acceptable both in terms of economy and ecology. Most of the different types of catalyst were used for aryl or alkyl ethers of glycerol synthesis. Catalysis using Brønsted or Lewis acids, in solution or supported on organic, inorganic or hybrid material have been widely tested. Shape selectivity obtained with specific materials has also been observed and used. Phase-Transfer Catalysis including solid-liquid or liquid-liquid processes, has been used in order to overcome some of the limitations of the Williamson synthesis (*vide supra*). Catalysis by transition metal complexes or supported-metal catalysts is the most used and probably the most successful, at least in terms of selectivity and conversion. These catalysts were applied to alkoxy-

telomerization reactions with butadiene, reductive alkylation, and dehydrogenative alkylation and thus they could be evaluated and compared. The very recent concept of a "hydrogen-borrowing catalyst" for reactions combining oxidation and reduction to form CO bonds was applied to glycerol ether synthesis. In a few cases, biocatalysis was also used as a tool for the synthesis of glycerol ethers.

Finally, many new activation technologies such as microwave, ultrasound and new solvents, such as super-critical CO_2 (sc-CO_2); room temperature ionic liquids and new (greener) reagents were also tested in association with different types of catalysis.

All the discussed technologies in this review have both advantages and drawbacks. Moreover, many economic parameters are difficult to determine and problems may be encountered during the industrial developments and are also difficult to predict. Nevertheless, this article will present a panorama of the chemistry applied to a challenging and important subject of glycerol ether synthesis at the beginning of the 21st century.

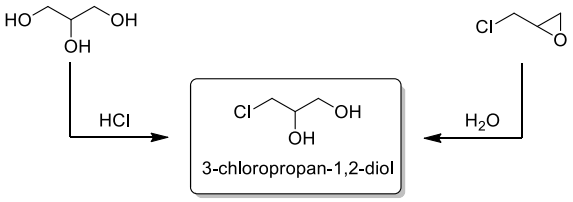
2. Glycerol ether synthesis from already existing industrial building blocks

There are two ways to replace fossil raw materials by renewable bio-sourced starting material. The first requires the transformation of the available bio-sourced molecule into a (simpler) known building block then integrate it into the existing synthetic pathway toward the desired active molecules. The second strategy uses the available bio-sourced starting material and an original synthetic pathway (and sometimes new equipment) in order to obtain a molecule with a similar or different structure but exhibiting the desired properties. Most of the so-called "bio-refineries" are based on the first strategy which is obviously less of a risk from an economic point of view. The second chapter of this review deals with this particular strategy.

2.1. From 3-chloro-1,2-propanediol as starting material

Among the available starting materials, 3-chloro-1,2-propanediol (3-MCPD) could be used to synthesize GMEs. This compound is also identified as one of the chemical contaminants known as chloropropanols. It is a contaminant of polyamine flocculants used in the removal of color, turbidity, and organic compounds from dye wastewater.[84] It can come from the transformation of foodstuffs containing acid-hydrolyzed vegetable protein. This compound is also an intermediate in the manufacture of dyes, used as a solvent for cellulose acetate, or to lower the freezing point of dynamite. Toxicological studies concerning this compound highlight a carcinogenic effect in rats, producing tumors in males in the testes, mammary glands and also kidney tumors in both sexes.[85,86] 3-MCPD is also responsible for male infertility[87,88,89] and has been identified as neurotoxic.[90,91]

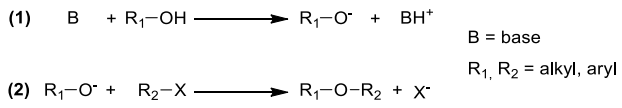
The main pathways to synthesize this building block involve the transformation of glycerol,[92] epichlorohydrin[93] and allyl chloride or alcohol. For each, different procedures are reported. For example, to prepare 3-MCPD, glycerol could be mixed with hydrochloric acid[87,88,89] or ECH could be hydrolyzed (Scheme 4).[90,91] The first one seems of particular interest due to the possibility of using bio-sourced glycerol as starting material.



Scheme 4. 3-chloro-1,2-propanediol synthesis

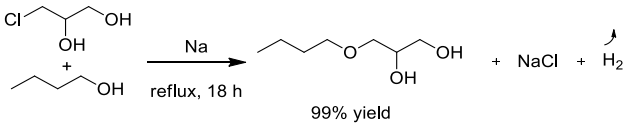
Ethers can be prepared under Williamson conditions,[94] *via* an S_N2-type reaction between an alkoxide and 3-MCPD (Scheme 5). The presence of a stoichiometric amount of a strong base allows the formation of an alkoxide (eq. 1), which then substitutes the halide to form the

corresponding ether (eq. 2). Alcohol could be used as solvent for this reaction. Otherwise, aprotic polar solvents are generally used such as DMF or DMSO. The effectiveness of this pathway for ether synthesis allowed its adaptation to glycerol derivatives, despite an often low atom economy. From our knowledge, monoglycerol ether was firstly synthesized from sodium ethoxide and 3-chloro-1,2-propanediol by Reboul in 1860,[95] only 9 years after the discovery of the Williamson synthesis of ether.



Scheme 5. General scheme of the Williamson reaction

In 1930, Davies reported the preparation of GME from 3-chloro-1,2-propanediol starting material in an excess of alcohol and sodium (Scheme 6).[96] Under these conditions, limitations were observed when long chain alcohols such as stearic alcohol where used, probably due to a lack of miscibility between the two reagents. Improvements were proposed by Stegerhoek and Verbade by the substitution of chloride by iodide, and in the case of stearyl alcohols the desired product was formed although with a low yield.[97]



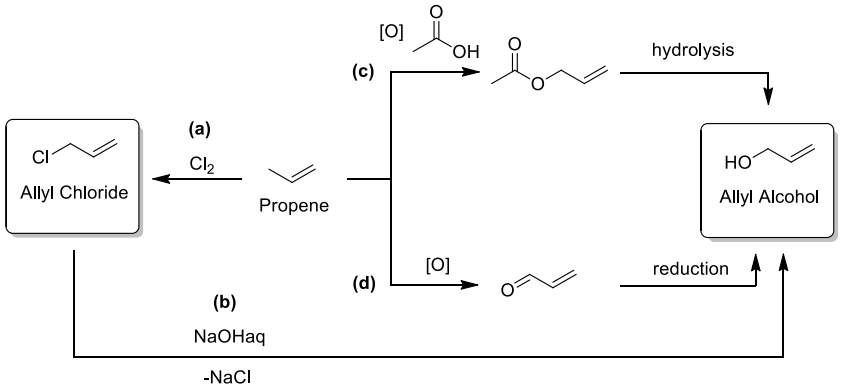
Scheme 6. Butanol etherification with 3-chloro-1,2-propanediol

The afore-mentioned Williamson-type reactions lead to a stoichiometric quantity of salts and an atom economy of 80% in this particular case. Although this strategy and starting material have historical interest, there are several drawbacks. Firstly, the high toxicity of the starting

material (carcinogenic, reprotoxic and neurotoxic), and secondly, for long alkyl chains, the use of dipolar aprotic solvents is required inducing a very bad E factor.[83]

2.2. From allyl halides or allyl alcohols as starting materials

Each year, several hundred thousand tons of allyl chloride and allyl alcohol are produced even though both compounds are mutagenic and toxic.[98,99] Allyl chloride is an alkylating agent which could be used in pharmaceuticals or the agrochemical industry.[100] It is formed by the selective chlorination of the methyl group of propylene at 500°C (Scheme 7, path a). The main production of allyl chloride is dedicated to the preparation of ECH.

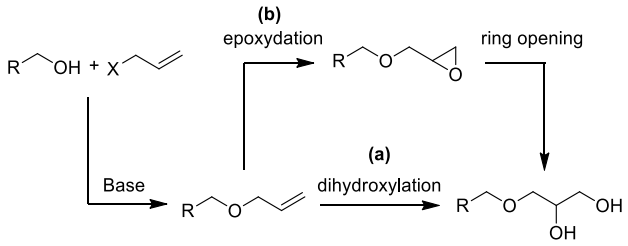


Scheme 7. Main pathways to synthesize allyl chloride and allyl alcohol

Allyl alcohol is an intermediate in the production of diols (1,4-butanediol). The Rh-catalyzed hydroformylation of allyl alcohol to 4-hydroxybutanal, first developed by Kuraray and Daicel Chemical Industries, is then followed by a hydrogenation step.[101] Allyl alcohol is also used in many applications such as water treatment and glass adhesion, plasticizers, and resins for coatings.[100] It is classically prepared from the hydrolysis of allyl chloride in the presence of a base (Scheme 7, path b). During this reaction, stoichiometric quantities of salts are produced. The direct oxidation of propene in acetic acid with a palladium catalyst under an oxygen atmosphere is also an industrial pathway. The allyl acetate obtained is then hydrolyzed to allyl

alcohol and acetic acid which could be recycled (Scheme 7, path c). Another industrial approach consists in the oxidation of propylene forming acrolein which is then reduced in the presence of aluminum isopropylate (Scheme 7, path d). The gas-phase isomerization of propylene oxide to allyl alcohol was developed in the presence of basic Li_3PO_4 at high temperature (Arco Chemical Technology).[102] The production of acrolein from glycerol over an acid catalyst in the liquid phase (sulfuric or phosphoric acid derivatives) or gas-phase (supported or non-supported tungsten, zeolite, etc) has recently been reported as an example of glycerol valorization.[103,104]

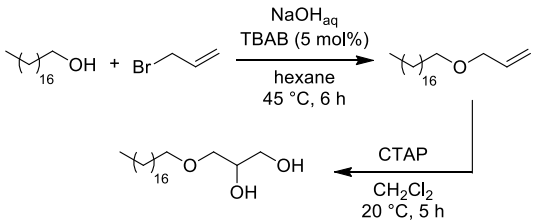
Allyl halides were used early on in the synthesis of glycerol ethers. Allyl ethers are the intermediates obtained by a Williamson-type reaction between a fatty alcohol and an allyl halide. The direct dihydroxylation of the olefin affords the desired GME (Scheme 8, a).[26,27,28,105,106] Epoxidation of the olefin with hydrogen peroxide is an alternative (Scheme 8, b).[107] However, for this pathway, one additional step is needed. From the epoxide, the access to GME is well described (see section later), but the epoxidation of this family of substrates is rarely mentioned in the literature.



Scheme 8. Pathways for the formation of GMEs from allyl ethers

Subbarao developed an allyl ether synthesis in basic medium *via* phase-transfer catalysis.[108] The second step involved the oxidation of the olefin to 1-*O*-alkylglycerol in the presence of cetyltrimethylammonium permanganate (CTAP, Scheme 9). It also involved the dihydroxylation of the allyl ether intermediate with hydrogen peroxide.

In order to avoid the formation of stoichiometric quantities of salts, the direct etherification of allyl alcohol was investigated by dehydration reactions in the presence of a metal (palladium, platinum, ruthenium)[109] or in acidic medium (HCl).[110] The catalytic dehydrative allylation to alcohols by a cationic ruthenium complex give a yield up to 90% at low temperature (70°C) with neither additives or solvents. The allyl glycidyl ether was obtained with 87% of yield and 98% ee in the presence of dichloromethane. From the literature data, these strategies have not been directly applied to GME synthesis.



Scheme 9. Synthesis of 1-*O*-stearylglyceryl ether from allyl bromide

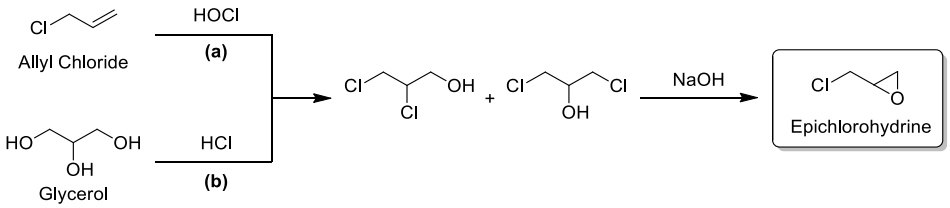
The above dihydroxylation step has been widely studied in organic chemistry. Besides the classic oxidative reagents (H_2O_2-formic acid, and peracid, etc.[111]), homogeneous or heterogeneous osmium catalysts are among the most efficient.[112,113,114] The osmium-catalyzed dihydroxylation conditions developed by Sharpless[115,116] are also well-documented including the synthesis of enantiopure ethers.[117,118,119]

The synthesis of GME via an allyl ether presents several distinct advantages. Firstly, although obtained from petro-sourced propene, the allyl substrates are widely available and economically interesting. In addition, literature data show that all the different steps could result in high yields and *via* a catalytic process. ~~In fact,~~ On the opposite of Williamson synthesis of ethers, the association of dehydration and catalytic dihydroxylation may lead to a synthesis with an almost optimal atom economy (only one molecule of water is formed as by-product) and even to the preparation of enantiopure GME. Unfortunately, the use of chlorinated solvents generated safety

problems, waste production and unacceptable E factor. Moreover, catalytic hydroxylation uses osmium complexes as catalyst which may limit industrial applications even for pharmaceuticals.

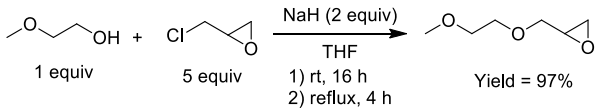
2.3. From ECH as starting material

ECH is an important building block in the chemical industry and more than 1.5 million tons were produced in 2012 with an annual increase of 4.8%.[120] It is used in the manufacture of epoxy resins for surface coatings, castings, laminates and adhesives, as well as specialty resins for water treatment, paper treatment (for example, tea bags) and ion exchange type II resins. ECH is also used as a raw material for the manufacture of diverse glycerol (glycerin) and glycidol derivatives used as plasticizers, stabilizers, solvents, dyestuff intermediates, surface active agents and pharmaceuticals, and as intermediates for further synthesis.[121,122,123] However, like many alkylating agents, ECH is toxic and is also identified as a CMR (cytotoxic, mutagenic, reprotoxic) product.[124] It was mostly prepared from allyl halide and hypochlorous acid which afforded 2,3-dichloropropan-1-ol and 1,3-dichloropropan-2-ol. The second step consists of the treatment of the intermediate with sodium or calcium hydroxide (Scheme 10, (a)). In 2012 in Asia, Solvay developed a new industrial process (Epicerol®) with a production capacity of 100 000 tons/year. From glycerol with hydrochloric acid, the dichloride intermediates are transformed into epoxide using an inorganic base (Scheme 10, (b)).[47,48,49]

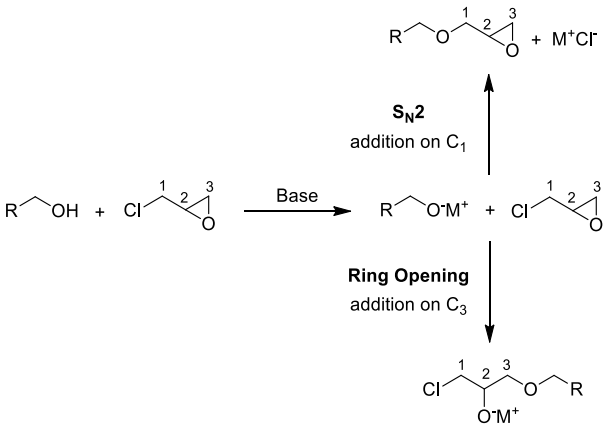


Scheme 10. Main synthetic routes to ECH

The etherification of ECH with a fatty alcohol or a phenol in basic conditions (with NaOH,[125,126] K_2CO_3,[127] NaH,[128] or tertiary amines[129] for phenols) has been widely described in the preparation of glycidol ether precursors of GME. In spite of the necessity to add one step with the opening of the epoxide, this strategy is in fact the sole industrially used one to prepare glycerol ethers, and specifically 3-[(2-ethylhexyl)oxy]-1,2-propanediol (Sensiva® SC50). This is also used to prepare functionalized glycerol ethers. However, ECH and the base should often be added in excess in order to reach a good isolated yield (Scheme 11).[121,122,123] Moreover, 1-chloro-3-alkyloxypropan-2-ol derivatives could be formed as by-products during the competitive ring-opening of the epoxide on the C3 position (Scheme 12). Taking into account the toxicity of the chloride derivatives, one additional step to form the epoxide is often realized before the hydrolysis into glycerol ether.



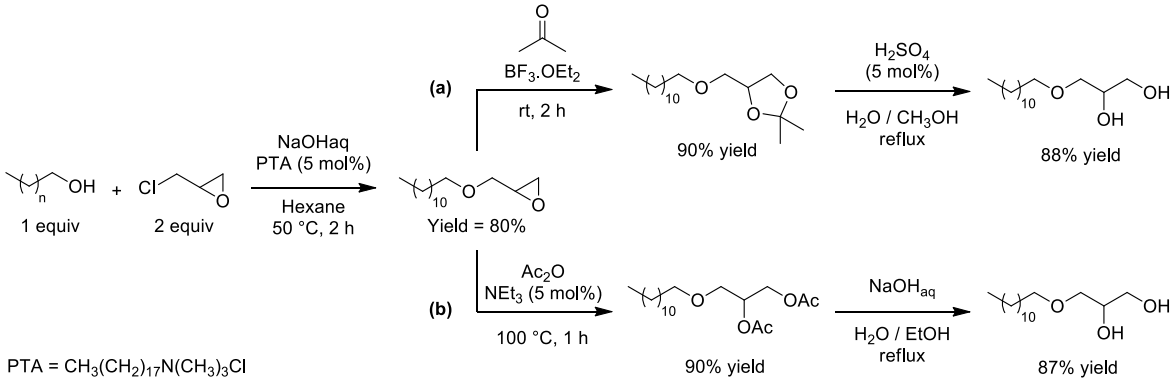
Scheme 11. Glycidol ether synthesis from epichlorohydrin



Scheme 12. Addition of an alcohol on ECH using two competitive reactions

From these observations, modifications were made on the reaction conditions to improve yield and selectivity for glycidol ether with the use of microwaves and phase-transfer catalysis.[130,131,132] For example, this combination[133,134] allowed the formation of only the 1,2-epoxy-3-phenoxypropane resulting from the addition on the C1 carbon, with a high yield (90%). This is three times higher than with the same conditions under classical heating.[135]

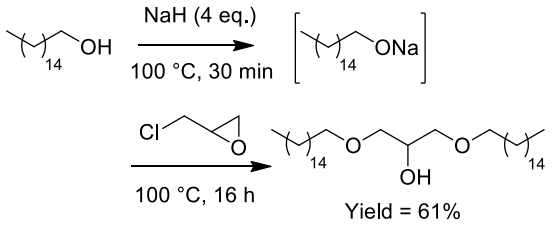
Two alternative processes in three steps were developed by the group of Takaishi and Urata in 1988.[136] The glycidol ether was prepared in phase-transfer catalysis conditions. Then, the GME was prepared using two different pathways. The first proposed the formation of the ketal intermediate by reaction of the glycidol ether with acetone in the presence of boron trifluoride. The last step is acidic hydrolysis to obtain the GME with a global yield of 88% (Scheme 13 (a)). The other route proposes the ring-opening of the epoxide in the presence of acetic anhydride and a tertiary amine. After hydrolysis, the corresponding glycerol ethers were obtained in 87% yields (Scheme 13, (b)). In these reactions, high yield and selectivity are obtained but an additional step is required and a large amount of salts and organic byproducts are produced.



Scheme 13. Multi-step synthesis of 1-*O*-docecylglyceryl ether from ECH from two pathways (a and b)

The 1,3-dialkylglycerol ethers synthetic pathways (or their sulfate derivatives) are mainly reported from epichlorohydrin and a fatty alcohol in Williamson conditions (Scheme

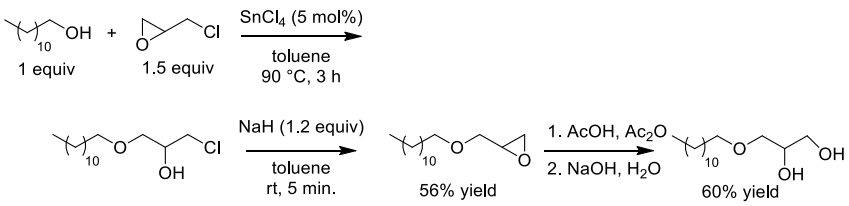
14).[137,138,139,140] These compounds are directly used as surfactants,[141] solvents[142] or as intermediates for the preparation of ionic surfactants, for example phospholipids.[143,144,145]



Scheme 14. Synthesis of 1,3-(bis)hexadecyloxy-propan-2-ol from epichlorohydrin

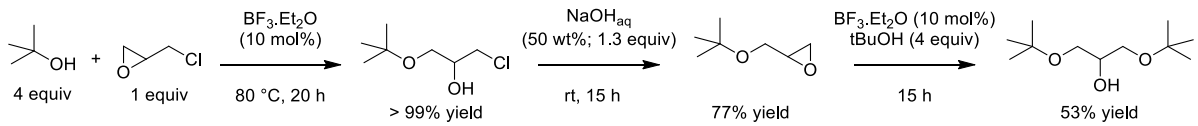
To our knowledge, no catalytic process described the synthesis of this class of products.

In acidic conditions, the preparation of GME was also described by etherification of ECH. In this case, the addition of the alcohol is generally realized on the C1 position of the epoxide *via* Brønsted[146] or Lewis[147] acid catalysis, where the major product obtained is a chlorohydrin intermediate. An epoxidation step is then done in basic medium, in order to avoid chloride derivatives in the final product (Scheme 15).[148]



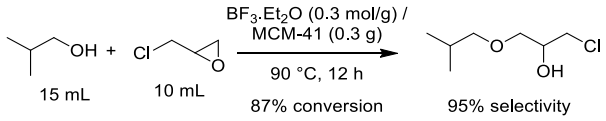
Scheme 15. Reaction with ECH with alcohol in acidic conditions

Canoira recently proposed a three-step synthesis of 1,3-di-*tert*-butoxypropan-2-ol using the following approach (Scheme 16).[149]



Scheme 16. Synthesis of 1,3-di-*tert*-butoxypropan-2-ol from ECH

Finally, some researchers described the use of heterogeneous acid catalyst.[150,151] Zhou supported boron trifluoride on MCM-41 and SiO_2 which were used for the reaction between isobutanol and ECH. Conversions were improved to 87% in addition to 95% selectivity for the desired product (Scheme 17) by increasing the quantity of $BF_3.Et_2O$ to 0.3 mol per gram of MCM-41. The authors observed a drop in catalytic activity through leaching into the different solvents and no recycling of the catalyst seemed possible. Therefore, the practical interest in using this heterogeneous catalyst is somewhat limited.



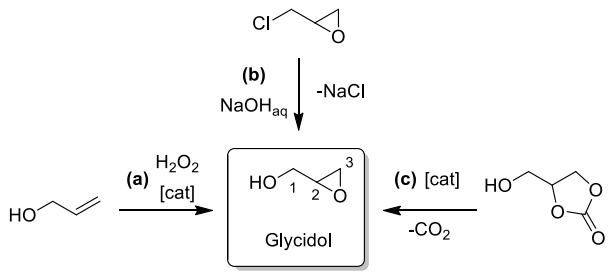
Scheme 17. Synthesis of 1-*iso*butoxy-3-chloropropanol from ECH *via* heterogeneous catalysis

Although the Solvay process[152] gives access to bio-sourced ECH, its use as starting material requires several steps including a Williamson-type reaction and salt formation. Curiously, no example using a recyclable organic scavenger, like in the BASIL^{TM}-process[153] was found during our literature search. In fact, this could be a solution for one of the drawbacks of this strategy i.e. the formation of salts and therefore an atom economy lower than 80%. In order to improve the selectivity and avoid the formation of toxic chloro-derivatives, an additional step needs to be introduced. Moreover, the high toxicity of this intermediate is probably the main drawback of these syntheses. Indeed, solvent and waste are generally contaminated by these highly toxic compounds. This makes the waste treatment complex and costly.

2.4. From glycidol as starting material

Glycidol or 2,3-epoxy-1-propanol is used for the production of functionalized epoxides in order to synthesize molecules of interest in pharmaceutical industries. It is also used as a

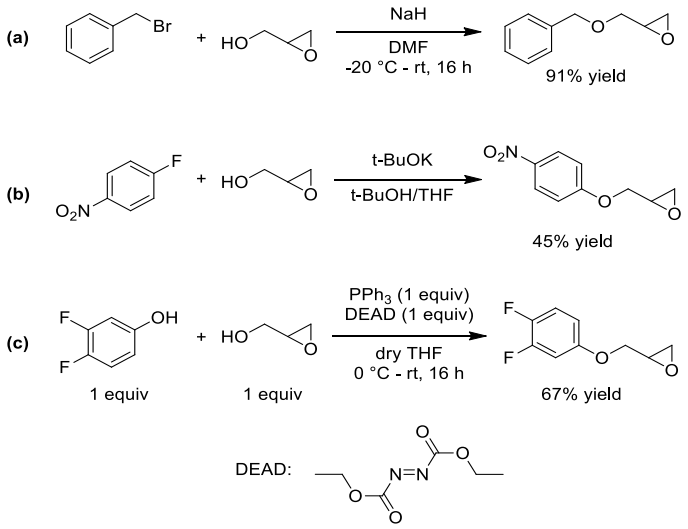
stabilizer in the manufacture of polymers and production of natural oils.[154] However, this compound is toxic, an irritant and classified as a carcinogenic substance.[155] This synthon, 2,3-epoxy-1-propanol, was obtained from epoxidation of allylic alcohol[156] in the presence of hydrogen peroxide with homogeneous or heterogeneous catalysts such as vanadium, tungsten or titanium[157] complexes (Scheme 18, a). Diethyl tartrate with titanium allows the preparation of enantiopure glycidol.[158] Enantiopure ether-containing terminal epoxides could be also obtained by kinetic resolution using a Jacobsen catalyst.[159] Another synthetic pathway consists in the hydrolysis of ECH in the presence of an inorganic base (Scheme 18, b).[160] However, other alternatives coming from bio-sourced molecules such as glycerol carbonate have recently been developed by removing a carbon dioxide molecule (Scheme 18, c).[161,162,163,164]



Scheme 18. Main synthetic pathways to glycidol

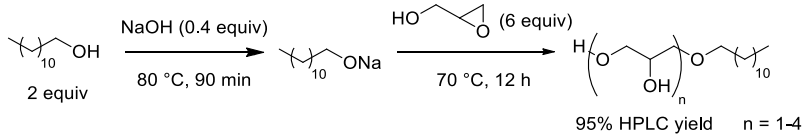
The Williamson-type conditions were applied for the synthesis of glycidol ether as a precursor of GME by the nucleophilic substitution of alkyl bromide under basic conditions (Scheme 19, a).[165] Similar conditions could also be applied for the reaction between the tosylated glycidol and an alcohol. These conditions allowed the retention of the configuration of the chiral center of the epoxide.[166,167] Few or no reaction on the electrophilic carbons of the epoxide were observed in these conditions.

Aromatic nucleophilic substitution (SN_{Ar}) *via* a Meisenheimer intermediate of an aryl halide and glycidol was studied in basic conditions (Scheme 19, b).[168] However, this strategy is limited to aromatic compounds bearing an electron-withdrawing group. The Mitsunobu conditions were also applied for the synthesis of pharmaceuticals products.[169] For example, Liu described the synthesis of arylethers in the presence of triphenylphosphine (PPh_3) and ethyl azodicarboxylate (DEAD) (Scheme 19, c).[170]



Scheme 19. Nucleophilic substitution of benzyl bromide with glycidol (a); aromatic nucleophilic substitution of 1-fluoro-4-nitrobenzene with glycidol (b); preparation of a glycidyl ether by a Mitsunobu reaction (c)

Conversely, the addition of an alcohol on the C_3-position of glycidol was investigated to form GMEs *via* a ring-opening reaction in basic conditions.[171] However, a side reaction was often observed leading to the formation of polyglycerol ethers.[172,173,174,175,176] Sakanishi therefore proposed the synthesis of polyglycol ethers with 1 to 4 glycol units at 80°C in the presence of dodecyl alcohol and sodium hydroxide (Scheme 20).[177]



Scheme 20. Direct synthesis of GME from glycidol

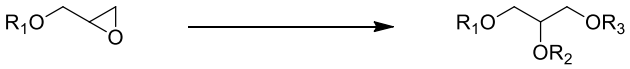
To limit or control the formation of polyglycerols, Lewis acids[178] such as titanium (Ti^{IV})[179], tin (Sn^{IV})[180] or aluminium derivatives (DIBAL)[181] or a strong Brønsted acid could be added.[182,183]

2.5. The glycerol ethers via hydrolysis of epoxide

The use of glycidol as starting material for the synthesis of GMEs required ring-opening of the epoxide later. This hydrolysis into vicinal diols is also required when using ECH or allyl ether followed by epoxidation and has been widely studied.[184,185] Both Lewis acids[186,187,188,189] including vanadium, tin and erbium catalysts and Brønsted[190] acids could catalyze such a transformation in a heterogeneous or homogeneous process. In basic conditions with an S_N2 mechanism, the nucleophile will attack the least hindered carbon. Due to the low solubility of glycidol ethers in aqueous solution, the ring-opening may be more easily realized *via* the formation of ketal intermediates in organic solvents, before their hydrolysis, thus avoiding polymerization reactions.[191]

Table 1 presents most of the methods proposed for epoxide hydrolysis and formation of GME. However, as can be seen from this table, difficulties are often encountered in doing such apparently simple transformations for a large number of these methods. In fact, on the one hand, acid catalyzed ring-opening leads to oligomerization and on the other hand, the base-catalyzed reaction induces the formation of a large amount of waste.

Table 1. Ring-opening synthetic route of glycidyl ether



	R_1	Solvent	T.°C	Cond. / Cat.	R_2	R_3	Y. %	Ref.
1	iPr	ROH	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	R	>94	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	R	>85	189
			65	I_2/P(4-VP)	H	R	70	186
		H_2O/CH_3CN	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	H	99	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	H	90	189
			65	I_2/Poly-(4-VP)	H	H	82	186
		AcOH	reflux	$V^{IV}(tpp)(OTf)_2$	H	Ac	98	190
			65	I_2/Poly-(4-VP)	H	Ac	82	186
2	Bu	H_2O	200	1.5 MPa	H	H	95	202
			100	-	H	H	97	198
3	2-ethylhexyl	H_2O	250	5 MPa	H	H	98	201
		IEW	280	8MPa	H	H	-	200
		$AcOH/H_2SO_4$	95	NaOH/MeOH	H	H	78	196
4	$C_{16}H_{33}$	THF/CH_2Cl_2	80	$Bu_4NTFA/TFAA$	$COCF_3$	$COCF_3$	96	197
5	$C_{18}H_{37}$	AcOH / BuOH	130	Aq.NaOH	H	Ac	75	192
6	Ph	ROH	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	R	>93	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	R	>85	189
			reflux	$Er(OTf)_3$	H	R	>59	187
			65	I_2/P(4-VP)	H	R	>67	186
		H_2O/CH_3CN	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	H	99	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	H	92	189
			65	I_2/Poly-(4-VP)	H	H	94	186

		AcOH	reflux	$V^{IV}(tpp)(OTf)_2$	H	Ac	98	189
			65	I_2/Poly-(4-VP)	H	Ac	86	186
7	Allyl	ROH	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	R	>97	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	R	>95	189
			25	$Er(OTf)_3$	H	R	>70	187
			65	I_2/P(4-VP)	H	R	>75	186
		H_2O/CH_3CN	reflux	$Sn^{IV}(tpp)(OTf)_2$	H	H	96	188
			reflux	$V^{IV}(tpp)(OTf)_2$	H	H	96	189
			65	I_2/Poly-(4-VP)	H	H	76	186
		AcOH	reflux	$V^{IV}(tpp)(OTf)_2$	H	Ac	98	189
			65	I_2/Poly-(4-VP)	H	Ac	85	186

Takaishi proposed two alternatives routes with ketal or acetate as intermediates (scheme 13), and in 1994, Goto described the ring-opening of glycidol ether by the reaction of sodium hydroxide and acetic acid followed by the hydrolysis of the mono-acetate in basic media. Although the ring-opening is catalyzed, the diol is obtained together with a stoichiometric amount of sodium acetate inducing a low atom economy (70-80% depending on the chain length).[192] Similar conditions are also reported with different bases (organic and inorganic) and acetylating agent. In all cases, the hydrolysis of acetylated intermediates allowed GME to be isolated with yields up to 90%.[193],[194] The direct hydrolysis of glycidol ethers in diols in aqueous solution of aliphatic carboxylic salts at high temperature has also been patented. This method is obviously better from an atom economy point of view even if reaction conditions are relatively harsh.[195] In 2011, Beilfuss described the synthesis of GME from epoxide derivatives using formic acid as protecting group and sulfuric acid as catalyst. Ethyl hexyl GME was obtained after hydrolysis in basic media together with the formation of sodium formate without the

purification of intermediates in 78% yield.[196] A mixture of trifluoroacetic anhydride (TFAA) and tetrabutylammonium trifluoroacetate (nBu$_4$NTFA) was used by Stawinski[197] to transform the oxirane into the corresponding bis(trifluoroacetate) derivative in 92% yield. The deprotection step was realized with pyridine in methanol at room temperature with an overall yield of 86%. Despite the efficiency of these processes, the difficult purification of GME and the production of large amounts of waste (low atom economy and selectivity) are significant limitations for large scale development. In fact, the acid catalyzed hydrolysis leads to the formation of polyglycerols as by-products and the basic treatment of intermediate esters produces saline wastes.

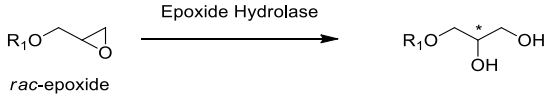
Alternative conditions for the hydrolysis of epoxide were proposed with water as solvent at high temperature[198,199] or under high pressure[200,201] without the presence of catalyst or the formation of by-products. In 2009, Saito reported the hydrolysis of glycidol ether at 200°C and 15 bars.[202] This process was also adapted to a continuous flow reactor in even harsher conditions (99% conversion within 10 min at 250°C). The hydrolysis of glycidyl ethers under hydrothermal conditions has been done with excellent conversion and high selectivity (>90%) within several minutes without catalyst. This "greener" high temperature reaction presents some advantages such as easy separation of the desired product after depressurization and cooling down (biphasic system).

2.6. Enantioselective synthesis of GMEs

Bio-catalysis is an efficient tool for the preparation of enantiomerically pure GMEs and is often one of the greener pathways for the hydrolysis of oxiranes. For example, Shöning used the hydrolase enzyme expressed from microorganisms to convert homoallylic or 3-(triethoxysilyl)-propyl glycidol ethers into corresponding glycerol ethers in mild conditions by kinetic resolution, i.e. 24h at pH 7 and at 30°C with yields from 64 to 91%.[203] Kotik et *al*. described the route to

enantiopure GMEs by kinetic resolution of epoxide derivatives using epoxide hydrolase which was selective for *S*- and *R*-configuration. However, the selectivities (selectivity factor) are relatively low (Table 2, Entries 1-6)[204] compared to that obtained using a Jacobsen catalyst. The epoxide hydrolase, Aspergillus Niger, showed a relatively high enantioselectivity (*E*-value is about 30) for the hydrolysis of racemic *tert*-butyl glycidyl ether to (*S*)-3-tert-butoxy-1,2-propanediol (Table 2, Entry 7).[205] Unfortunately, the hydrolysis of *rac*-allyl glycidyl ether presents only a moderate conversion and no enzyme has been found to differentiate the enantiomers (Table 2, Entry 8). The E-value observed in the case of glycidyl ether is lower than that observed for 1-phenylpropene oxide (E-value >200) or styrene oxide derivatives (E-value > 60). Further investigation is being done to find the synthetic potential of epoxide hydrolase, especially to improve selectivity for glycidyl ether.

Table 2. Data obtained for the enzymatic hydrolytic kinetic resolution ~~hydrolysis~~ of racemic epoxides using various epoxide hydrolases.

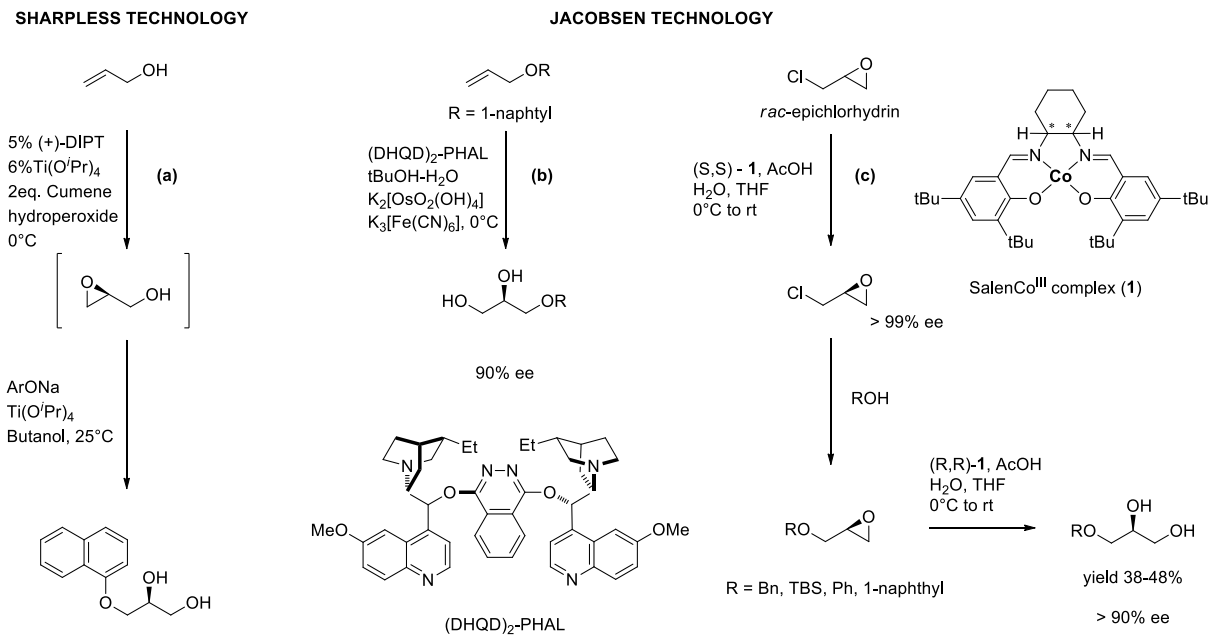


Ent.	Subs.	R_1	Enzyme	Abs. configuration		Conv.	E-value
				epoxide	diol		
1	*rac*	Bz	*Kau2 (E. coli)*	S	S	-	n.d.
2	*rac*	Bz	*Kau8 (E. coli)*	R	S	-	1.8
3	*rac*	Bz	*Rhodoturula mucilaginosa*	R	S	60	7-8
4	*rac*	Bz	*Rhodococcus fascians*	S	R	55	3-4
5	*rac*	^{t}Bu	*Kau2 (E. coli)*	S	S	-	1.03
6	*rac*	^{t}Bu	*Kau8 (E. coli)*	R	S	-	10
7	*rac*	^{t}Bu	*Aspergillus Niger*	R	S	56	28-32

8	*rac*	Allyl	*Cryptococcus laurentii*	n.d.	n.d	60	3

During the redaction of this part of our review, we observed that most syntheses of enantiopure GME are done with pathways using "already existing industrial building blocks" particularly kinetic resolution of epoxide (asymmetric organometallic catalysis) or by direct dihydroxylation of allylic ether. Powerful methodologies have been developed for direct asymmetric epoxidation of allyl alcohol using di-isopropyl tartrate and Ti^{IV} complex and chiral glycidol could be obtained in high yield and selectivity (Scheme 21, a).[180] Unfortunately, only substrates with a hydroxyl functional group could be used and the difficulty of selectively opening the epoxide makes the use of this tool relatively limited. The ring-opening reaction occurred in the presence of alcoholate derivatives inducing the formation of enantiopure glycidyl ether. Moreover, the asymmetric dihydroxylation of allyl ether using ligand-accelerated catalysis such as hydroquinidine 1,4-phtalazinediyl ether $(DHQD)_2$-PHAL or hydroquinidine p-chlorobenzoate using *N*-methylmorpholine *N*-oxide (NMO)[118] or potassium ferricyanide as oxidant[117,118], respectively, present good enantioselectivities to give the corresponding diol (Scheme 21, b). Beller et *al*. observed the dihydroxylation of olefins, especially allyl phenyl ether, with the same catalyst and with a moderate enantioselectivity of 67% using air as a cost-effective oxidant.[119]

Starting from racemic ECH as substrate, the preparation of enantio-enriched epoxide was envisaged using a chiral Salen-Co^{III} complex done by Jacobsen technology in water media. The ring-opening was done using the same catalyst in acidic media to obtain the 1-chloro-2,3-propanediol in 99%ee (Scheme 21, c).[159]



Scheme 21. Asymmetric epoxidation of allylic alcohol *via* Sharpless technology (a) and hydrolytic kinetic resolution of ECH *via* Jacobsen technology (b, c).

The ethers of glycidol are found as intermediates in numerous syntheses of complex molecules and may be used to form GME by electrophilic or nucleophilic processes. Hydrolysis can also be done at high temperature, high pressure and even supercritical conditions or with enzymatic processes. In addition, catalytic kinetic resolution allows the formation of enantiopure GME although access to the glycidyl ether *via* such strategies seems limited to very high value molecules. Finally the strategy implying glycidol as key intermediate is of large interest if 1,3-diethers are the target molecules. ~~However, a new approach using protected glycidol into 1,2-*O*-isopropylidene glycol or glycerol carbonate as intermediate may lead to an interesting process for the synthesis of GMEs from both economic and ecological points of view.~~

3. Glycerol ether synthesis using protection-deprotection strategy

~~However,~~ A new approach using 1,2-*O*-isopropylidene glycol or glycerol carbonate as intermediates may lead to an interesting process for the synthesis of GMEs from both economic

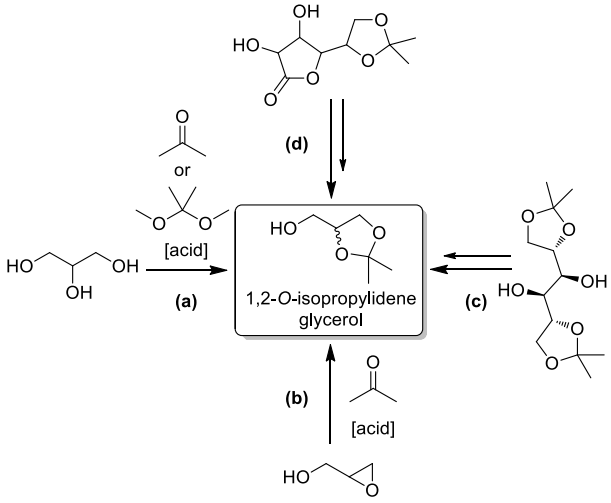
and ecological points of view. Use of a protecting step is one of the main tools in the chemistry of polyols and sugars. Nevertheless, it is doubtful that a strategy involving two additional stages could be interesting from economic or ecological points of view. In fact, the 8th principle of green chemistry is especially dedicated to limiting the number of derivatives.[206,207] Nevertheless, some protected glycerols could be produced as solvents or fuel additives on a large scale, and then the economic factor becomes less significant. This is particularly the case for glycerol acetonide and glycerol carbonate.

3.1. 1,2-*O*-isopropylidene glycol as starting material

1,2-*O*-isopropylidene glycol or (2,2-dimethyl-1,3-dioxolan-4-yl)methanol is often known as solketal. Mota et al.[208] have recently shown that this compound improved the octane number and reduced gum formation in gasoline. Glycerol acetonide has 3 oxygen atoms corresponding to 36% of its weight. This compound is a good platform for an oxygenated gasoline additive, especially in Brazil, where the major part of the gasoline comes from catalytic cracking. In some case, glycerol acetals reduce the pour point and the viscosity of esters of fatty acids.[209] The synthon, 1,2-*O*-isopropylidene glycol, is classified as a polar solvent and represents an alternative to others labeled as toxic and hazardous substances.

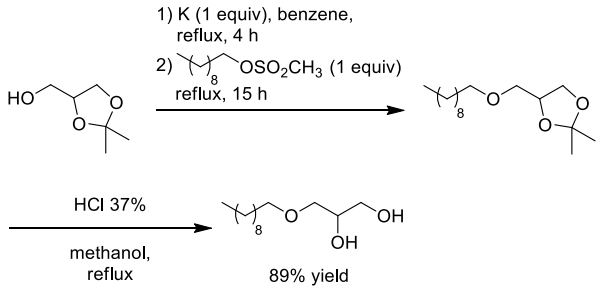
Glycerol acetonide was first prepared by Fischer[210] in 1895 from acetone and glycerol in the presence of hydrogen chloride. Due to safety constraints and the risk of an explosive reaction, a safer alternative was proposed by Newman and Renoll 50 years later.[211] These procedures involve the reaction of acetone with glycerol with an acidic Brønsted catalyst such as *p*-toluene-4-sulfonic acid (Scheme 22, a) or by a trans-acetalisation of the 2,2-dimethoxypropane[212,213]. The condensation of acetone with glycidol in the presence of erbium,[214] ruthenium[215] or iron[216] catalysts was also done to obtain glycerol acetonide compound in high

yield (Scheme 22, b). The oxidation and reduction steps of 1,2:5,6-di-*O*-isopropylidene-D-mannitol in the presence of lead^{IV} acetate[217] or sodium periodate[218,219] and sodium tetrahydroborate give the desired compound with high stereochemistry (Scheme 21, c) and with a yield of 86% and 88%, respectively. The use of sugar derivatives such as 5,6-isopropylidene-gulonic acid-γ-lactone is also reported (Scheme 21, d).[220]



Scheme 22. Synthetic routes of solketal

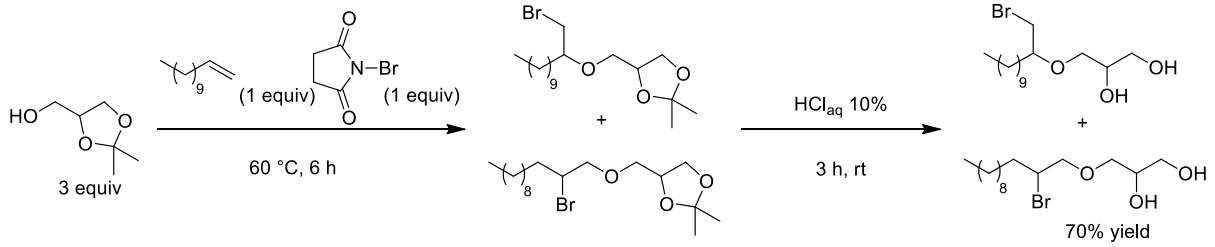
Glycerol acetonide was notably used as starting material for the synthesis of 1-*O*-glycerylether in basic media from alkyl halides. Alkyl 1-*O*-glyceryl ether having a long chain up to C_{16} carbon has been used in the presence of alkyl iodide and sodium naphthalene under reflux for 48 hours giving a moderate yield of 30%.[221] Other examples have been described using alkyl[222,223] unsaturated alkyl[224] or benzyl groups.[225] The synthesis of glycerol ethers was also done using tosyl[226,227,228] or mesyl[229,230,231,232] groups. The acidic hydrolysis of the acetal group allowed the formation of the desired products as shown in scheme 23. A poor atom economy (72%) and the required elimination of the bromide for most of the potential applications make this strategy of little interest from ecological point of view.



Scheme 23. Etherification of 1,2-*O*-isopropylidene glycerol with decylmesylate

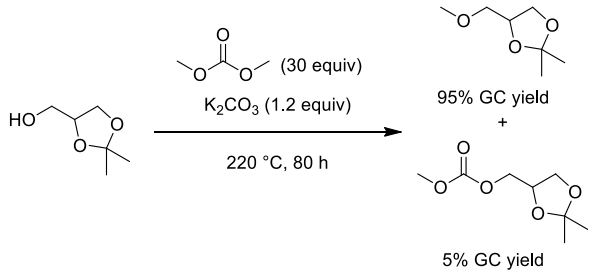
The above conditions were improved with the use of a phase transfer catalyst such as tetrabutylammonium bromide (TBAB) and an aqueous solution of potassium hydroxide (33%) in order to reduce the reaction time. Moreover, such modifications avoid the use of potassium and benzene and dramatically increase the safety of the process.

Singh also described a new synthetic route to β-bromoglycerol ether by a co-halogenating reaction of α-olefins in the presence of *N*-bromosuccinimide and glycerol acetonide (Scheme 24).[233] A regio- and stereoisomeric mixture was obtained. The ~~authors proposed~~ mechanism proposed by the authors was the formation of a cyclic bromonium ion followed by the nucleophilic addition of a hydroxyl group belonging to solketal molecule. A possible excess of HBr in the system might catalyze the reaction.



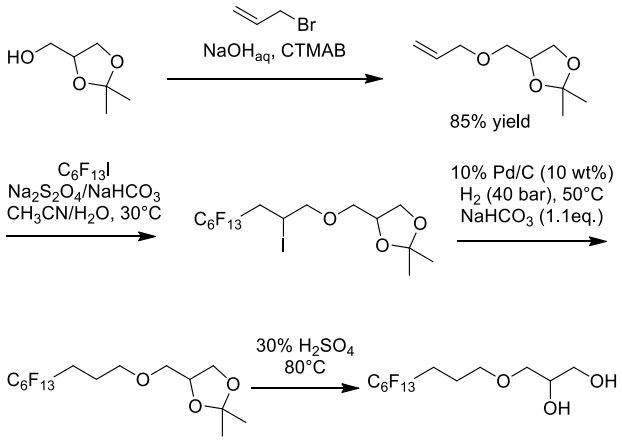
Scheme 24. Synthesis of *β*-bromo-glyceryl ethers by co-halogenation

The etherification of glycerol acetonide in the presence of dialkylcarbonate and potassium carbonate as catalyst at high temperature was described by Selva *et al*.[234] The main advantages of these conditions are the use of dimethylcarbonate (DMC), well-known to be non-toxic and a weak base, without additive or solvent (Scheme 25) This point is of utmost importance because conversely of dimethyl carbonate most of the methylating agent (methyl iodide , dimethyl sulfate ..) are known to be CMR. However, the main drawbacks are the large excess of DMC and the high temperature required. Only an efficient recycling of the excess of dimethyl carbonate could make this method of practical interest. Unfortunately the conversion of DMC is not indicated in this article therefore the E factor could not be evaluated. The hydrolysis of an isopropylidene moiety is generally realized in acidic aqueous solution[235] but other systems can also be used such as a mixture of trifluoroacetic acid and triethyl borate in a fluorous organic solvent such as 2,2,2-trifluoroethanol.[236]



Scheme 25. Etherification of solketal with dimethyl carbonate

The corresponding 3-*O*-allyl ether was obtained by the reaction of glycerol acetonide with allyl bromide in aqueous solution in the presence of a phase transfer catalyst (Scheme 26).[237] The perfluoroalkylation, following by the reduction and hydrolysis steps lead to the formation of the desired compound in 40% overall yield.



Scheme 26. Perfluoroalkyl GME synthesis

Atom economy in this particular case is only 61% but this is mainly due to the use polyfluoroalkyl iodide; the protecting group represents only a small part of the waste.

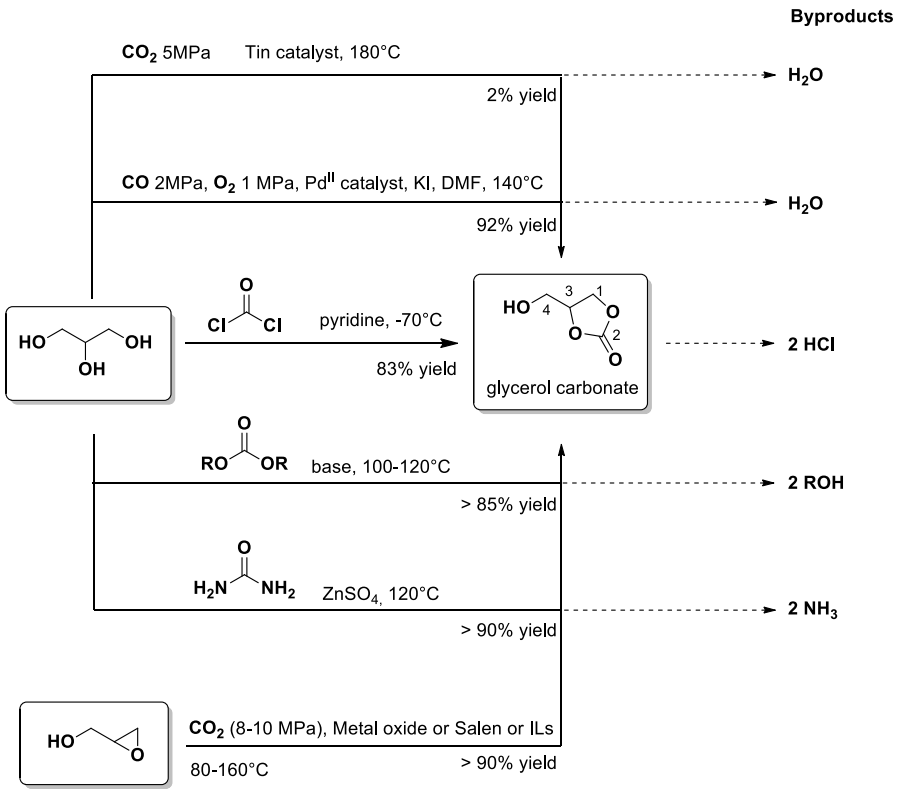
Using glycerol acetonide has several advantages. Firstly, it is readily available even on an industrial scale. Second, it can be prepared and used as a chiral building block starting from cheap sugar derivatives. Third, and in contrast to glycerol, this compound is soluble in most organic solvents. The last point is important when the introduction of a long (hydrophobic) alkyl chain is necessary. Finally, its hydrolysis is easy even if water soluble acetone seems difficult to recycle.

3.2. From glycerol carbonate as starting material

4-Hydroxymethyl-1,3-dioxolan-2-one or glycerol carbonate is considered in chemical synthesis as a bio-sourced platform[238] for the preparation of higher value added products. Glycerol carbonate is available on a large scale and sold by several companies such as Huntsman and Ube Industries. This substrate has three electrophilic centers (C_2 carbon from the carbonyl function and two alkylene carbons C_1 and C_3 from the 1,3-dioxoloan-2-one cycle) and a nucleophilic center. Thus, glycerol carbonate reacts differently depending on the experimental

conditions and the reactants engaged in the reaction. This compound also exhibits low toxicity and is biodegradable. Glycerol carbonate has recently been used in various applications, for example, as an additive in batteries, a bio-sourced solvent[239] or a monomer for the preparation of polymers or starting material for the synthesis of surfactants in cosmetic and detergent formulations.

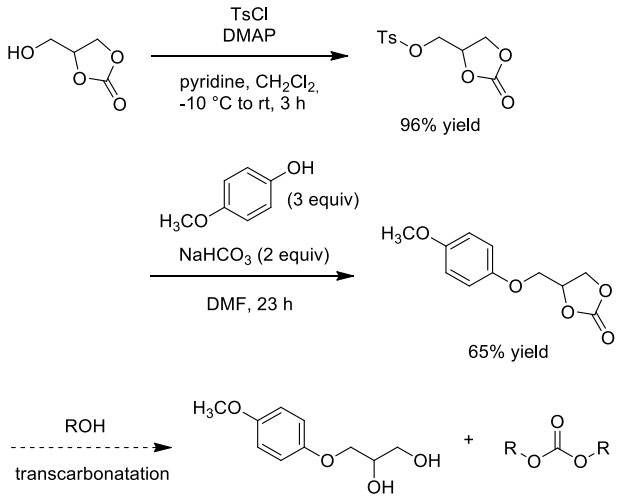
The preparation of glycerol carbonate directly from glycerol is at present the objective of intensive scientific research, and a review has summarized the different reaction pathways.[240] The direct carbonation of glycerol with carbon dioxide is an interesting route especially in terms of atom economy (scheme 27). Nevertheless, only very poor conversion and yield are obtained.[241,242,243] An alternative method is the oxidative carbonylation of glycerol with carbon monoxide in the presence of molecular oxygen.[244] The formation of glycerol carbonate with toxic phosgene[245] or, by using a more acceptable route from a safety point of view, by transcarbonation with alkyl or alkylene carbonates[246,247] or urea[248,249,250,251] has also been extensively studied. A final possibility is the insertion of CO_2 on glycidol with good yield and atom economy, except that glycidol is toxic.[252,253]



Scheme 27. Glycerol carbonate synthesis pathways

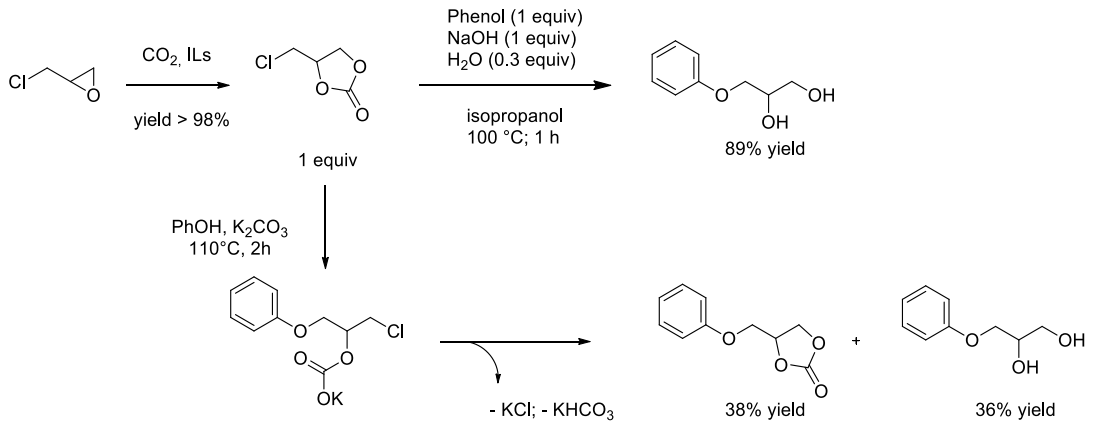
Glycerol carbonate has the potential of being used in many applications as a solvent or building block. It can either be produced by using efficient technologies but dangerous or toxic reagents (carbon monoxide, phosgene or glycidol) or safe reagents such as dialkyl carbonate or urea, but unfortunately in an exchange reaction with excess of reagent and low atom economy.

A few reports deal with the formation of 1-*O*-alkylglycerol ethers from glycerol carbonate. The activation of the latter by a tosyl group allows the formation of GME in the presence of alcohols or phenols (Scheme 28).[254]



Scheme 28. Tosylation of glycerol carbonate followed by etherification

Kuran[255] reported the reaction of phenol with 4-chloromethyl-1,3-dioxolan-2-one in basic medium. This cyclic intermediate was obtained by the addition of CO_2 to ECH in the presence of ionic liquids (scheme 29).[256,257,258] When sodium hydroxide is used, the major product formed is glycerol phenylether. The author explains this result by the reaction of 4-chloromethyl-1,3-dioxolan-2-one with a phenoxide anion at a temperature higher than 90°C. Below this temperature (60°C), a competitive reaction takes place between phenoxide and hydroxide anions and glycerine was formed as the main product. Using a weak base such as potassium carbonate, 4-phenoxymethyl-1,3-dioxolan-2-one and 3-phenoxypropan-1,2-diol were obtained in an equimolar ratio.

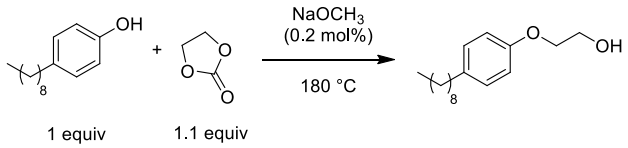


Scheme 29. Etherification of 4-(chloromethyl)-1,3-dioxolan-2-one by nucleophilic substitution

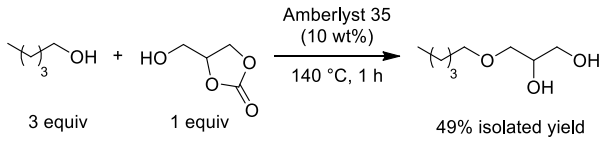
The direct etherification of glycerol carbonate with an alcohol is difficult because of the competitive transcarbonation reaction. Phenols, considered as soft nucleophiles, can react selectively with cyclic alkylene carbonate[259] leading to the formation of ethers and the release of carbon dioxide.[260] Nava described such a transformation from ethylene carbonate and phenols with sodium methoxide with high conversion of phenol derivatives (Scheme 30).[261] However, when alkyl alcohols were used in similar conditions, the transcarbonation product was observed. The only example described in the literature is a patent which describes the preparation of glyceryl ether from the carbonate and a fatty alcohol such as lauryl alcohol using KOH as catalyst at 70°C with 89% yield.[262]

On the contrary to a base-catalysed process, the use of an acid-catalysed reaction seems much more selective toward *O*-alkylation compared to transcarbonation. In another patent, our group described the synthesis of GME from glycerol carbonate and short alkyl alcohols (between 5 and 10 carbons) in the presence of heterogeneous acid resin catalysts such as Amberlyst 35. When using a short chain alcohol such as pentanol, the conversion was complete and the desired 1-*O*-pentylglycerol ether was obtained with 49% yield (Scheme 31).[263] Unfortunately, this procedure cannot be applied to alkyl alcohols with long chains due to the formation of the corresponding

dialkyl carbonate.

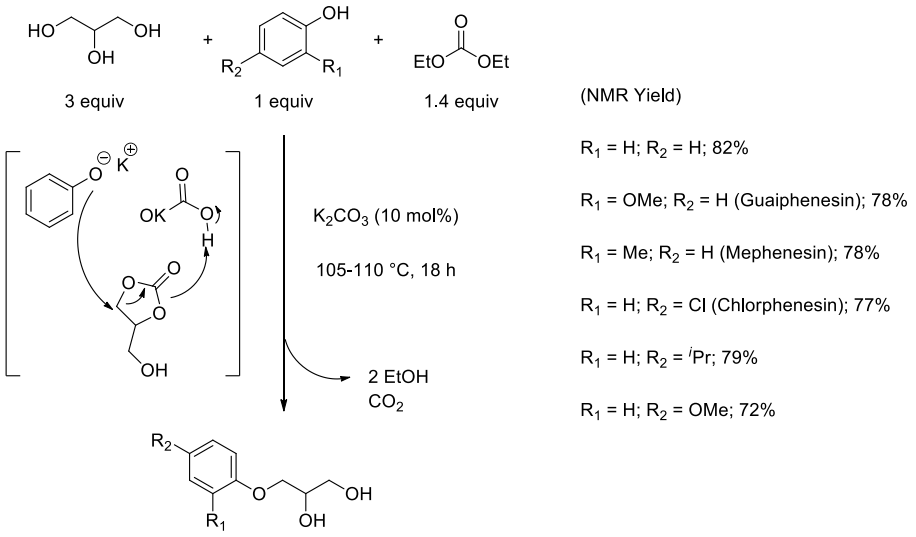


Scheme 30. Etherification of nonyl-phenol with ethylene carbonate



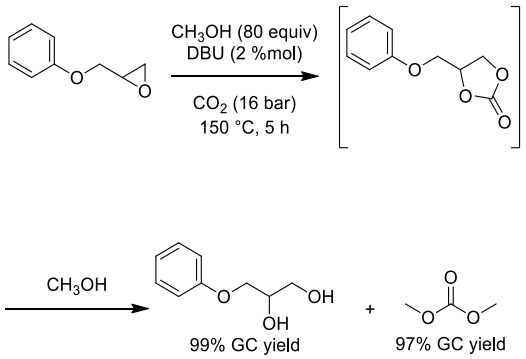
Scheme 31. Etherification of glycerol carbonate with an alcohol and a basic or an acid catalyst

Recently, Truscello[264] described a multi-component approach for the preparation of glyceryl aryl ethers. Some of these compounds are known for their biological activities such as guaiphenesin, mephenesin or chlorophenesin.[265,266] Glyceryl aryl ethers are also used as intermediates for the preparation of drugs and pharmaceuticals. For example, methocarbamol is used as a muscle relaxant, whereas mephenoxalone is used as a tranquillizer.[267] To prepare aryl ethers, phenol was mixed with an excess of glycerol and diethyl carbonate in the presence of a catalytic amount of potassium carbonate at 105-110 °C for 18 h. Under these conditions, several racemic glyceryl aryl ethers were obtained in fair to good yields (Scheme 32). The authors propose that the glycerol carbonate is formed as the intermediate, followed by nucleophilic addition of the phenolate anion on the less sterically-hindered alkylene carbon. Thus, the corresponding glyceryl ether is formed by the ring-opening of the cyclic carbonate with the release of CO_2.



Scheme 32. One-pot synthesis of aryloxypropanediols by *in situ* formation of glycerol carbonate; proposed mechanism by *in situ* formation of glycerol carbonate followed by nucleophilic addition.

Ring-opening is often done *via* the formation of the corresponding carbonate. This pathway is industrially used to prepare dimethyl carbonate (DMC) from ethylene oxide using basic catalysis.[268,269,270,271] We suppose the first step to be the reaction between the epoxide and carbon dioxide, then the trans-esterification step in the presence of methanol leads to the corresponding diol and DMC as by-product.[272,273] Although this byproduct (i.e. dialkyl carbonate) results in a very poor atom economy, the dialkyl carbonates are well-known as safe solvents with low toxicity and may be valorized.[274,275] Moreover, the cyclo-addition of carbon dioxide on epoxides was studied in ionic liquids,[276] or under microwave,[277] with homogeneous or heterogeneous catalysts.[278] Kishimoto reported a one-step methodology with the addition of methanol in a mixture of glycidol ether and 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) under CO_2 pressure (16 bar) (Scheme 33).[279] After optimization, the GME and DMC were obtained in good yields and selectivities.



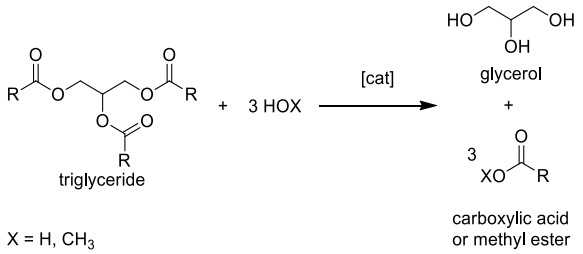
Scheme 33. Glycidyl ether opening with carbon dioxide and methanol

The use of glycerol carbonate as intermediate for glycerol ether synthesis is very efficient in the case of soft nucleophiles such as phenol but much less in the case of aliphatic alcohol. In fact, in this particular case, the Williamson-type synthesis is still the most efficient method even if few examples of base and acid catalysis are described (mainly in patents). Although the use of CO_2 as reagent or solvent is of special interest, most of the glycerol ether synthesis having glycerol carbonate as starting material exhibit poor atom economy and often require organic solvent which induce bad E factor. The interest of this strategy is closely dependent on the future development of the glycerol carbonate itself which also requires a more efficient and cleaner synthetic pathway.

4. From glycerol by a direct one-step synthesis

4.1. Glycerol preparation pathways, industrial availability and safety

Glycerol is today widely available as a by-product of the vegetable oil industry (Scheme 34) and only a small part is obtained from fossil C3 chemistry.[72-82] The methanolysis of vegetable oils to fatty acid methyl esters (FAMEs), the so-called biodiesel, was supported and developed in particular by the European Union governments to blend petro-based diesel fuels with FAMEs.



Scheme 34. Synthesis of glycerol from vegetable oil

New reports concerning the supply/demand for glycerol were recently published.[280] In 2011, the total supply of crude glycerol was around 2.9 million metric tons. Glycerol arising from the biodiesel industry represented two-thirds of the total world production, whereas the other industrial sources, mainly fatty acid and alcohol production, manufacture of soaps, etc., contribute to the last third.[280]

With the predicted depletion of petroleum oil reserves and the increase in petrol price, an unprecedented development in the early 2000s of the biodiesel industry led to an overproduction of glycerol and the traditional markets of glycerol were not able to absorb all this oversupply.[281] New applications for this polyol were therefore needed to favor and support the development of the vegetable oil industry and in particular the biodiesel activity.[72-82] The supply of glycerol increases every year and it is estimated that it will exceed 3 million metric tons in 2014, with a growth rate of 2.5% per year (Figure 1).

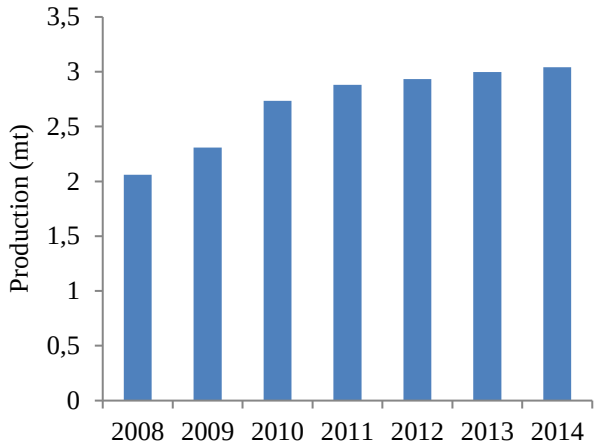


Figure 1. World supply of crude glycerol from 2008-2011 and estimated production for 2012-2014 (cf YR)

80 to 90% of crude glycerol can be refined to produce a high-quality raw material in order to be valorized for industrial applications. Thus, in reviews, many new chemical transformations using glycerol as starting material have been described such as reductions, oxidations, dehydrations, esterifications, carbonations, acetalisations, gasification and oligomerization reactions using heterogeneous or homogeneous catalysis. As a consequence, some of these new processes were recently adapted to an industrial scale, such as the production of ECH[282] or 1,2-propanediol.[283]

Since the reports in the late 2000s giving some glycerol market data, new projections indicate, however, that development of the biodiesel activity should slow down in the next few years. This is linked to political and economic reasons, as biodiesel activity will continue as long as it is supported by proactive policies, especially in the European Union. Ethical and environmental reasons are also being discussed, due to the competition between the biodiesel industry and food industry (food for human consumption) which is still under debate, as well as the footprint of this activity on the land and atmosphere (greenhouse gas emissions). In the future, the development

of the second generation of biofuels from lignocellulosic biomass will also be in competition with the biodiesel obtained from vegetable oil.[280] However, recent growth in the demand for refined glycerol caused by new applications (such as ECH and 1,2-propanediol production and its use as an antifreeze agent instead of glycol ethers) may increase market demand in the next few years. Thus, the availability and prices of glycerol could be a key issue. In fact, some studies show that the supply/demand balance for refined glycerol should be in equilibrium in 2014.[280]

The high-tonnage glycerol-based processes will thus have to overcome the aforementioned socio-economic issues. The development of alternative processes using glycerol as raw material for the production of higher value added products in the lower-tonnage processes for fine chemistry and cosmetics could thus be a very interesting solution, such as the preparation of alkyl- and aryl- glycerol ethers directly from glycerol. Moreover, these products retain all the specific functions of glycerol.

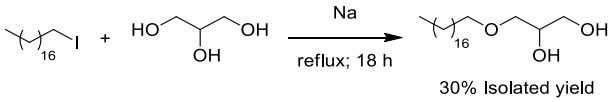
4.2. Williamson-type synthesis of glycerol ethers

The preparation of glyceryl ethers directly from glycerol is a challenge. The presence of three hydroxyl groups with a similar pKa is a source of difficulty in terms of selectivity. Moreover, glycerol is a hydrophilic molecule, thus its interaction and miscibility with non-polar organic substrates are weak. Finally, its high viscosity may cause mass transfer and stirring problems.

4.2.1. In basic conditions, by nucleophilic substitution

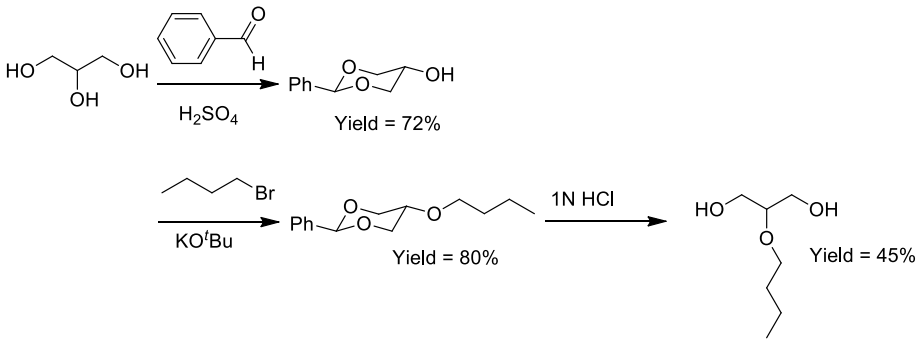
The direct etherification of glycerol was described by Stegerhoek and Verbade in Williamson-type conditions.[97] A primary monoglycerol ether could be obtained by mixing 1-iodooctadecane and glycerol with sodium. The desired product is obtained in only 30% isolated yield (Scheme 35) because of similar reactivity of the three hydroxyl groups leading to other

etherification reactions. Practical interest of this reaction is also limited by the low atom economy (70%).



Scheme 35. Glycerol etherification by nucleophilic substitution with 1-iodooctadecane

The selective synthesis of 2-alkyloxy-1,3-propanediol was reported from glycerol including a protection-deprotection sequence. After the formation of the six-membered acetal by reaction with benzaldehyde,[284] the alkylation step is generally performed in basic medium,[285] followed by a deprotection in acidic conditions.[286,287]

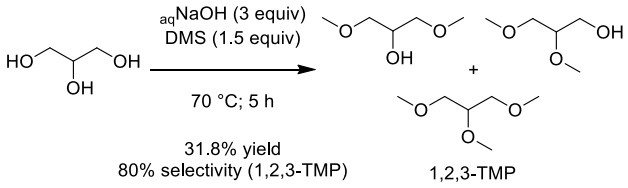


Scheme 36. Synthesis of 2-alkyloxy-1,3-propanediol

This family of compounds was synthesized for polymer applications. [288,289,290] They are also intermediates to prepare molecules of biological interest.[291,292,293,294,295,296,297,298]

Basic conditions were also used to form the triether derivative. For example, the triallylation of glycerol with allyl bromide in basic media was done in two steps in order to etherify the three positions.[299] Methylation of glycerol with dimethyl sulfate and sodium hydroxide was also developed.[300,301] Recently, Chang described the synthesis of a mixture of mono-, di- and

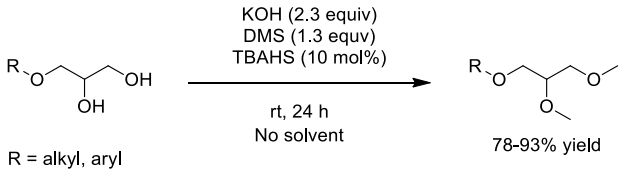
trimethylated glycerol used as fuel additives following this strategy. For 1,2,3-trimethoxypropane (1,2,3-TMP), a moderate yield and selectivity were obtained (Scheme 37).[302]



Scheme 37. Methylation of glycerol using dimethylsulfate and NaOH

With the same molecular formula as diglyme, which is identified as reprotoxic,[303] 1,2,3-TMP could also be a potential new non-protic solvent. Thus, several approaches have been evaluated to selectively prepare this compound. For example, phase-transfer catalysis with tetrabutylammonium hydrogenosulfate using potassium hydroxide and DMS as alkylating agent gave good yield and selectivity.[304,305] 1,2,3-TMP was purified by distillation and isolated in 78% yield with no traces of dimethyl sulfate or dimethylated glycerol. However, this process also produced a stoichiometric amount of salts and atom economy is only 42%. Traces of dimethyl sulfate make also the toxic wastes difficult to treat.

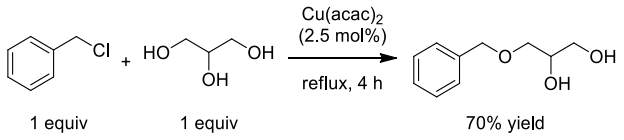
Toxicological tests have been done on pure 1,2,3-TMP following OCDE guidelines.[306] The results revealed that it has a low acute toxicity, and no skin sensitization, mutagenicity or ecotoxicity in an aquatic environment. The flash point was measured at 45.5 °C. This compound has also been used as solvent for the reduction of organic functions. In particular, a new process for the reduction of nitriles to amines in 2-methyltetrahydrofurane and in 1,2,3-TMP was developed, using tetramethyldisiloxane in association with copper triflate ($Cu(OTf)_2$). Similar conditions were adapted for the preparation of 1-alkoxy-2,3-dimethoxypropanes and 1-aryloxy-2,3-dimethoxypropane from GME as potential new non-protic solvents (Scheme 38).[305,307]



Scheme 38. Synthesis of 1-alkoxy- and 1-aryloxy-2,3-dimethoxy-propanes by phase-transfer catalysis.

4.2.2. Benzylation of glycerol

The benzylation of alcohols with benzyl halides in milder conditions than the Williamson ones is an interesting choice to protect hydroxyl groups since no strong bases are required.[308] For example, monobenzylation of diols was studied by Sauvé with Ag_2O and benzylbromide. With this methodology, monobenzylated products were obtained with good isolated yields. However, with unsymmetrical diols, such as 1,2-propanediol or glycerol, the selectivity between primary and secondary monobenzylated products was low. An inseparable mixture of mono-benzylated derivatives was obtained in a 2:1 ratio, respectively.[309] Interestingly, the formation of an ether bond could be obtained from alcohol and benzyl chloride in the presence of a copper catalyst, although the catalyst loading is still relatively high. Sirkecioglu[310] also described a solvent-free methodology with glycerol and benzyl chloride (Scheme 39).



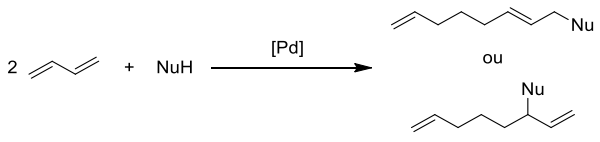
Scheme 39. Benzylation of glycerol with benzyl chloride catalyzed by $Cu(acac)_2$

When a high yield is the main target, a very effective monobenzylation of 1,2-propanediol was described with an excess of silver carbonate and benzyl bromide at room temperature.[311] In the case of diols, 80% of the primary ether was isolated. The two previous examples are

representative of the two approaches. The one with silver carbonate is looking for performance and high yield independently of the cost or waste production and was almost the only one developed in academic laboratories during the second part of the 20th Century. The second second one with copper, looking for a cleaner process, could be a somewhat less selective method. Obviously, both approaches have a scientific interest. Nevertheless, from our point of view, only the catalytic version has the potential for an industrial application. Comparison of the atom economy for these two methods illustrates clearly the advantage of the second one (45% for the first one and 83% for the catalytic reaction).

4.3. Catalytic *O*-telomerization with 1,3-dienes

Since the discovery of telomerisation in 1967 by Smutny[312] and Takahashi,[313] the reaction between 1,3-dienes and protic nucleophiles has allowed the formation of many products with diverse applications.[314] During this transformation, a butadiene or *taxogen* is dimerized or oligomerized by the addition of a nucleophile or *telogen*. All nucleophiles containing an acidic proton can be considered as a *telogen*. This reaction is generally catalyzed by a transition metal catalyst such as nickel or platinum complexes. Nevertheless, homogeneous palladium complexes are the most efficient and are widely studied. A mixture of linear or branched products (i.e. telomers) is obtained at the end of the reaction. The major isomers have the *E* configuration. The atom economy of this reaction is 100% without the formation of salts (Scheme 40). Unfortunately, the oligomerization of butadiene cannot be avoided and increases the E factors.



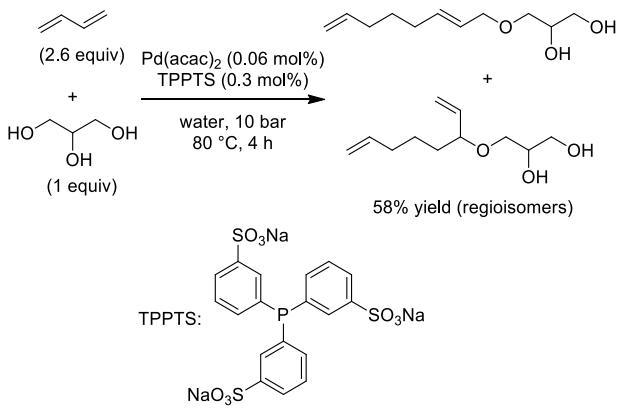
Scheme 40. General scheme of the telomerization reaction

Recently, the telomerization of polyols with butadiene was investigated in order to control the selectivity towards the mono-alkylated products or monotelomers. For the alkylation of ethylene glycol, a biphasic media (aqueous/butadiene phases) was used by Behr in 2003.[315,316] This reaction was later extended to glycerol by several research groups.

The poor miscibility of glycerol with alkene makes homogeneous catalysis difficult and generally requires a complex mixture of solvent (PEG, etc.). Therefore, a biphasic phase system involving a polar phase (glycerol or water) and a non-polar phase (butadiene or alkene) is generally preferred. In this section, only gas/liquid and gas/liquid/liquid processes will be described. Mass transfer issues have rarely (if at all) been studied but it could be assumed that this specific problem could be treated similarly to the well-known hydroformylation process (i.e. interface and /or supported aqueous phase catalysis). In addition, the chemioselectivity is high and the addition of a dimer is generally much more favorable. Therefore, the hydrophobic/hydrophilic balance is well-controlled from a mechanistic point of view. Secondly, the presence of a ramification induces a low melting point and the double bond makes the biodegradability easier.

4.3.1. Biphasic catalysis with water soluble catalyst

A biphasic system was adapted to glycerol by Behr,[317] using $Pd(acac)_2$ and triphenylphosphinetrisulfonate (TPPTS) as ligand. The hydrosoluble catalytic $Pd(acac)_2$/TPPTS system allows the monoetherification of the glycerol into the corresponding glycerol monoether, which migrates in the organic phase preventing the second alkylation from occurring (Scheme 41). The ratio between both isomers is not mentioned in this particular case but the steric hindrance of the glycerol moiety seems to facilitate the addition on the terminal carbon, increasing the selectivity towards the primary glyceryl ether.



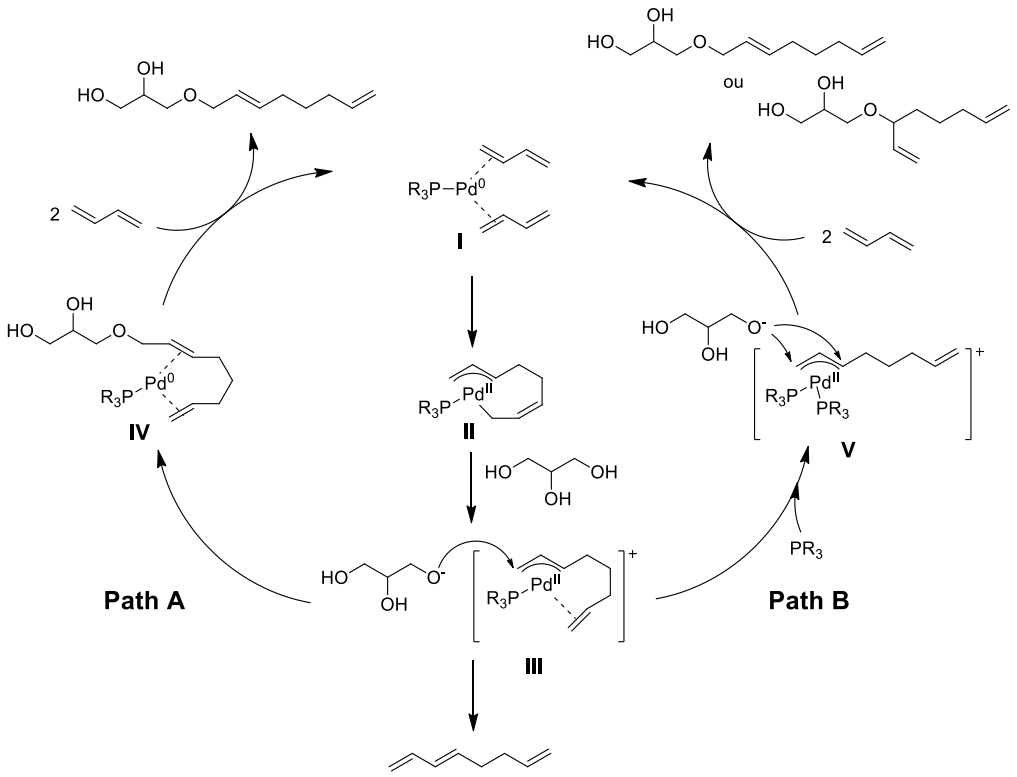
Scheme 41. Telomerization of glycerol in biphasic media

At the end of the reaction, the aqueous phase containing the catalytic system was recycled 5 times. The yield decreased dramatically after the third run. The turnover number (TON) was 990 and the turnover frequency (TOF) 248 h^{-1}. The total TON was 3300 after the fifth recycling. The monoalkylated glycerol was synthesized with a good selectivity (>95%) in this biphasic system. The only by-products detected were butadiene dimers and vinyl octanol which were detected in 1-2% yields. A "one pot" two-step telomerization-hydrogenation procedure was reported by Okutsu[318] in order to synthesize saturated glyceryl monoethers. The monooctyl glycerol ether was obtained in 55% yield and the reaction mixture also contained 22% of the dioctyl glycerol ether as well as unreacted glycerol. The regioisomers were obtained in a linear/branched product ratio of 84/16.

Weckhuysen[319] evaluated several catalytic systems associating a palladium source and a triphenylphosphine in a solvent-free glycerol/butadiene system. The best selectivity for glyceryl monoethers was obtained in the presence of a catalytic amount of tris(*ortho*-methoxyphenyl)phosphine (TOMPP). The highest yield of 92% for the desired products was obtained when the butadiene/glycerol molar ratio was 4, with a TON of 2626 and a TOF of 3418

h^{-1}. The by-products formed, resulting from the telomerization of butadiene with water, represented less than 5%.

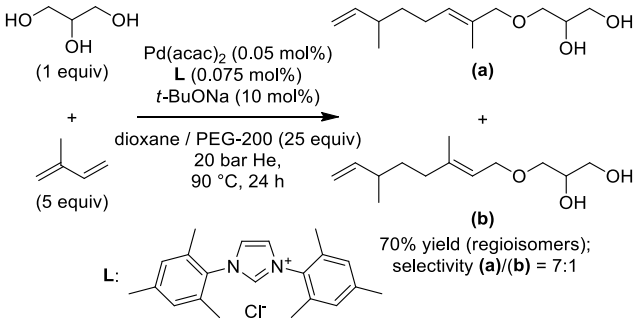
Two mechanisms have been proposed for the palladium-catalyzed telomerization depending on the nature of the catalyst and the substrate: the bisallyl monopalladium pathway described by Jolly[320,321] and the bisallyl dipalladium route proposed by Keim.[322] The former mechanism or closed one as shown by Beller[323,324] seems more accurate when the nucleophile is an alcohol or a polyol. In the specific case of glycerol telomerization with butadiene, Weckhuysen proposed the mechanism[325] given in (Scheme 42). The first step consists of the oxidative addition of two molecules of 1,3-butadiene to form the palladium complex **II** which is protonated by the glycerol (intermediate **III**). On the one hand, pathway **A**, the glycerolate attack on the C1 position of the 1,3-diene, gives complex **IV** which is thermodynamically more stable. The β-elimination of hydrogen from the C4 position of the protonated species will allow the formation of 1,3,7-octatriene as a side-product. With an excess of phosphine, the addition of the alkoxide can occur either at the C1 or C3 position of the protonated species to afford the linear or branched product. The attack at the C3 position leads to the branched product, which is electronically favored.



Scheme 42. Proposed mechanism for the telomerization of glycerol with 1,3-butadiene

Weckhuysen studied the above reaction with other polyols such as propanediols or butanediols.[326,327] Behr pursued these studies in monophasic or in biphasic media[328,329] to increase the selectivity for the GMEs and finally developed a continuous flow process.[330,331,332] The influence of the different parameters on the selectivity of the reaction under aqueous biphasic conditions was also investigated by Castanet.[333] Alternative catalytic systems have also been described for this reaction. Carbene-palladium complexes[334] were used for the telomerization of glycerol with isoprene (Scheme 43).[335] A base (*t*-BuONa) is necessary for the activation of the ligand and the polyethylene glycol (PEG-200) must be in a homogeneous phase in the reactor. A mixture of regioisomers is obtained under these conditions and ~~telomerization of~~ polyethylene glycol also reacts with butadiene ~~also observed~~. In this reaction, the atom

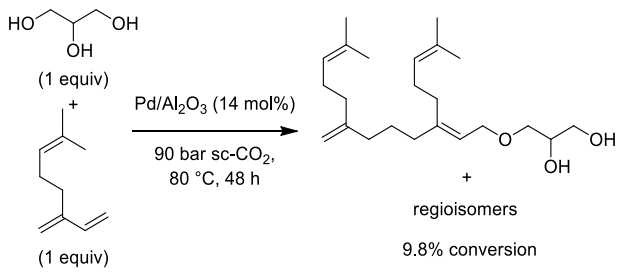
economy is perfect (100%!) but a careful evaluation of all the by-products formed has to be performed.



Scheme 43. Telomerization of glycerol with isoprene

4.3.2. With heterogeneous catalysis

If homogeneous catalysis has an advantage in terms of efficiency, heterogeneous catalysis is often preferred from an industrial point of view. Two recents reports by Bogel-Łukasik described the telomerization of glycerol with 1,3-dienes in the presence of a heterogeneous catalyst Pd/Al_2O_3. The reaction is done with a terpene, β-myrcene, and a stoichiometric quantity of glycerol in sc-CO_2.[336,337] Results are promising since the selectivity is good for the monoalkylated products although the conversion is low (Scheme 44).[336] The catalytic system seems easier to separate and recycle although no data is mentioned on this point. However, the lower activity could be ascribed either to mass transfer difficulties or to a lower reactivity of the myrcene. Nevertheless, this approach is interesting. In fact, the use of myrcene gives access to much longer hydrophobic chains (20 carbon atoms) and 100% bio-sourced surfactants.



Scheme 44. Heterogeneous catalysis for the telomerization of glycerol

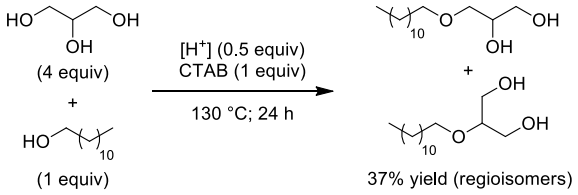
4. 4. Glycerol ether synthesis *via* acid catalysis

The reaction of alcohols or alkenes with glycerol in acidic conditions has been widely studied over the last ten years due to the accessibility of the substrates as well as the ease of the catalyzed procedures. The major part of the published research reports the alkylation of the three hydroxyls to prepare additives for fuels. Nevertheless, several studies also described conditions to selectively prepare GMEs. Furthermore, a large part of the literature data is dedicated to the elaboration of heterogeneous catalysts. In fact, the nature and structure of the catalyst are well studied. According to the shape selectivity concept, the distribution of active sites has a primordial role in the conversion and selectivity of the considered transformations.

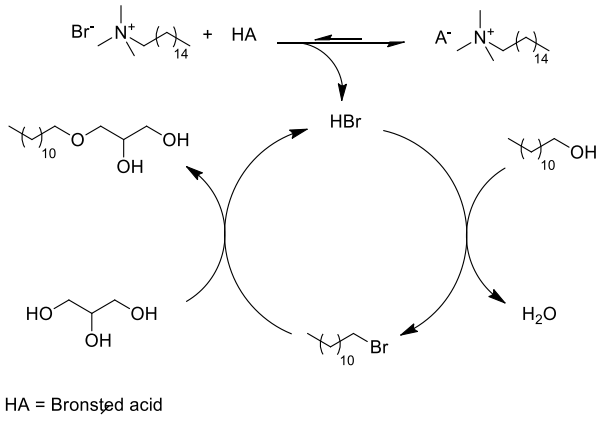
In the 1990s, the etherification of activated alcohols in acidic media with glycols or glycerol was described in order to functionalize bioactive molecules (antitumor agents, for example) in order to increase their solubility in water.[338,339] Clearly, the specific aim of these studies is related to selectivity, but ecological concepts also have to be considered. Their interest as additives for fuels was ~~only~~ reported later from aliphatic alcohols by a homogeneous or heterogeneous acid catalysis.[340,341]

4.4.1. Dehydration and etherification by homogeneous acid catalysis

Only a few reports describe the direct etherification of glycerol with an alcohol using a homogeneous acid catalyst, probably due to the easy formation of symmetrical ethers. Jérôme recently studied the direct etherification of 1-dodecanol with glycerol with a phase-transfer catalyst (cetyltrimethylammonium bromide (CTAB)) and a homogeneous or heterogeneous acid (Scheme 45).[342] In this transformation, the intermediate is 1-bromododecane obtained by reaction between the alcohol and the *in situ* formed hydrogen bromide. The addition of 10 mol% of 1-bomodecane increases the yield of glycerol dodecylether to 60% and no salts are formed during the reaction. Scheme 46 shows the proposed mechanism.



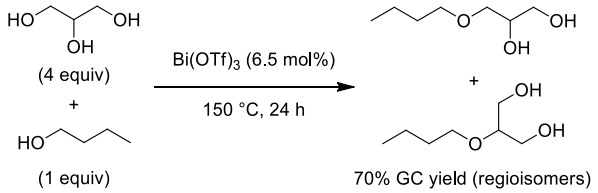
Scheme 45. Homogeneous acid catalyzed etherification of glycerol with 1-dodecanol



Scheme 46. Proposed mechanism

Lewis acids were evaluated by the same group for the etherification of short chain alcohols.[343] Best results were observed with metal triflates and especially with bismuth triflate ($Bi(OTf)_3$). For example, the reaction of butanol with glycerol afforded the corresponding glyceryl

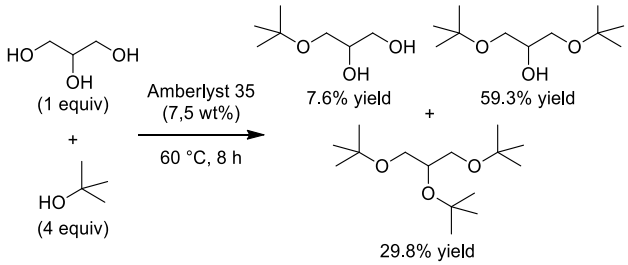
monoethers in 70% yield obtained as a mixture of regioisomers. Nevertheless, the yield decreases with the increase of chain length: 50% from pentanol and 32% from hexanol (Scheme 47). The formation of triflic acid by the *in situ* glycerolysis of the catalyst seems explain the good selectivity for the monoalkylated products.



Scheme 47. Catalytic homogeneous etherification of glycerol by $Bi(OTf)_3$

4.4.2. Dehydration and etherification by heterogeneous acid catalysis

From this pioneer work, the Mravec group was probably one of the first to develop the solvent-free etherification of glycerol with *tert*-butanol in the presence of a resin or a zeolite as catalyst (Scheme 48).[344,345,346] The three hydroxyl groups of glycerol will react with the carbocation obtained by the elimination of water from *tert*-butanol in acidic media. The glycerol tri-alkyl ether was evaluated as an additive for fuels.[347] In this study, the authors show that the activity of the resin was linked to the size of the pore, the level of acid function and the degree of ~~reticulation~~ cross-linking. The best results were obtained with Amberlyst 35 dry (A35), in order to avoid the inhibiting effect of water on the catalytic activity of ion-exchange resins.

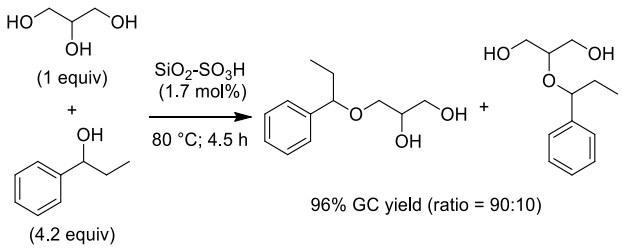


Scheme 48. Etherification of glycerol with *tert*-butanol by acid catalysis.

From the above studies, numerous data were reported concerning the direct etherification of glycerol with alcohols,[348] and especially *tert*-butanol for fuel applications. Thereby, the nature and structure of heterogeneous catalysts (resins,[349,350] zeolites,[351,352] heteropolyacids,[353] and sulfated carbon)[354,355,356] were studied. Amberlyst 15 (A15) resin gave the best results and a mixture of mono-, di- and triether (in a molar ratio of 54/41/1, respectively) was obtained with 95% conversion of glycerol at 70 °C. Studies have been done to calculate the kinetic parameters[357] of this transformation and evaluate the glycerol etherification with *tert*-butyl alcohol catalyzed by A15 under reactive distillation.[358] With zeolite catalysts, even if the reaction temperature had to be higher (90° to 110 °C), they were better in terms of stability and activity for producing high amounts of *di*-tertiary butyl (DTBG) and *tri*-tertiary butyl glycerol ether (TTBG). With a Nano-beta (N-BEA) zeolite catalyst, above 95% conversion of glycerol was observed with more than 45% and 54% selectivity towards DTBG and TTBG. The association of catalyst resin and zeolite in a flow reactor shows a synergetic effect which has a great potential for the etherification of glycerol.[359] With heteropolyacids, the conversion decreased to a value close to 30% but the selectivity for the monoether was higher (90%). Finally, comparable results with resins were obtained with sulfonated carbons prepared from sugar cane bagasse. The industrial development of glycerol etherification with *tert*-butyl alcohols in the presence of resins is feasible with high conversion of glycerol. The main difficulties are associated with the separation process, in which the authors have mentioned the necessity to recycle the monoether by-product and separate the water and *tert*-butyl alcohol which formed an azeotrope.[360] The difference of solubility of the mono- and di-butyl ethers in sc-CO_2 could be a solution.[361]

Several research groups have retained the strategy of acidic catalysis to prepare GMEs with a good selectivity but by using less reactive substrates than tertiary alcohols. For example, Barrault

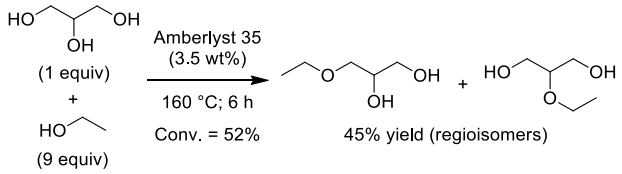
and Jérôme described the etherification of activated alcohols (benzylic, allylic, and propargylic, etc.) with glycerol and acid catalysts.[362] The best results afforded a mixture of regioisomers in 96% yield with sulfonic functionalized silica catalysts (SiO_2-SO_3H, Scheme 48). Moreover, the recyclability of the catalytic system was demonstrated by running the reaction 5 times with the same catalyst without altering the monoether yield. The authors explained the results by a strong affinity of the heterogeneous catalyst for glycerol and benzylic alcohols leading to a higher reaction rate (Scheme 49). However, these conditions were inefficient when dodecanol was used instead of benzylic alcohols. The synthesis of GMEs was also reported in this study by the cleavage of benzylether with the same catalytic system. The glycerol etherification in acidic medium with benzyl alcohols was also reported with zeolites[363] or with acid based polysaccharides Starbon® by Clark. [364]



Scheme 49. Etherification of glycerol with benzyl alcohol

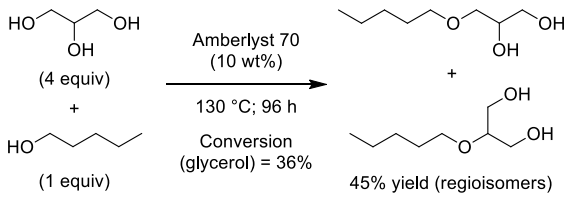
The reaction of aliphatic primary alcohols with glycerol is difficult. In fact, the formation of the carbocation is the limiting step and the difference of polarity between glycerol and fatty alcohols induces miscibility issues. Fajula developed reactions with ethanol.[365] The most active catalysts have the highest affinity with glycerol such as Amberlyst type resins. At 160°C, the GMEs were obtained in 52% yield with 90% selectivity. A large excess of ethanol was necessary as a large quantity of diethyl ether was formed as co-product of the reaction (Scheme 50). A silica-supported tungstophosphoric catalyst ($H_3PO_{40}W_{12}/SiO_2$) was used by Hou[366] to realize the

same chemical transformation. At the same temperature (160°C), 97% of glycerol was converted to monoethers with 62% selectivity. The formation of diethylether was not mentioned in this study. Melero[367] also studied the influence of the different parameters in the catalyzed etherification by a sulfonated mesostructured silica.



Scheme 50. Etherification of glycerol with ethanol by acid catalysis

Jérôme developed the Amberlyst 70 (A70) catalyzed etherification of glycerol with 1-pentanol.[368] The desired GMEs were obtained as a mixture of regioisomers in 45% yield after a long reaction time (96 h) at 130°C (Scheme 51). Under these conditions, the authors also observed the formation of diglycerol and dipentyl ether. With the increase of chain length, this process becomes even less efficient because of mass transfer or miscibility problems. When the reaction is done with 1-dodecanol, the major products observed are diglycerol and didodecyl ether.



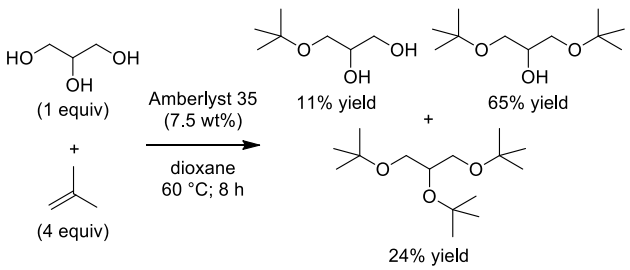
Scheme 51. Etherification of glycerol with 1-pentanol by heterogeneous acid catalysis

Recently, Frusteri have studied the utilization of a permselective membrane coupled with a batch reactor in which the etherification of glycerol with butanol were catalyzed by Amberlyst A15.[369] When looking at the atom economy of the acid catalyzed formation of glycerol ether with alcohol as alkylating agent, the interest of such approach seems very high. Nevertheless, side

reactions such as symmetrical ether formation (both from the alkylating agent and glycerol itself) are generally difficult if not impossible to avoid. ~~This reactions had also a relatively small domain of application , mainly to the substrates able to form stable carbocation. On the opposite when di or even trialkyl ether of glycerol are the target molecules these strategy seems the more efficient so far.~~

4.4.3. Addition of glycerol on alkenes

The addition of glycerol on alkenes, especially isobutene in order to prepare the corresponding *tert*-butyl ethers, was also reported in articles and patents with homogeneous or heterogeneous catalysts.[370,371] The nature and structure of the catalysts (Lewis acids,[372] Brønsted acids,[373,374] zeolites,[375] sulfonated zeolites,[376,377] acidic resins,[378,379] sulfonated mesostructured carbons,[380] heteropolyacids and ionic liquids,[381] and sulfonated aerogels,[382] silica etc.) and the experimental parameters,[383,384,385] notably to develop an industrial process,[386] were evaluated. For example, Mravec compared the activity of 1) acid Amberlyst resin-type catalysts with 2) large pore H-Beta or H-Y zeolites and with 3) *para*-toluenesulfonic acid in the etherification of glycerol with isobutene (Scheme 52). The author found that, depending on the catalyst, the selectivity of the etherification changed i.e. the major product was the tri-alkylated product with Amberlyst 35, whereas the dialkylated products were the second most important. The authors hypothesized that the pore size plays a role in the selectivity towards the formation of poly-alkylated glycerol. ~~These results could be explained by the size of the pores which prevent additional etherification by steric hindrance~~ The solvent is also important for the reaction and the best compromise was to use dioxane albeit its known toxicity which solubilized the substrates without inhibiting the active sites of the catalyst.



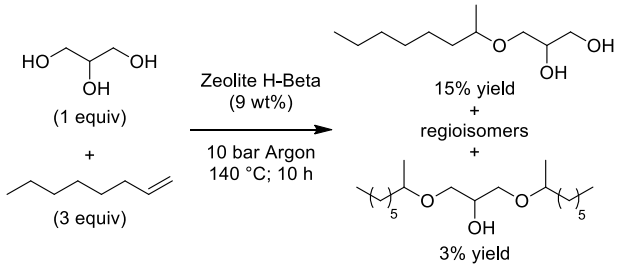
Scheme 52. Heterogeneous acid catalyzed etherification of glycerol with isobutene

Recently, Yang[387] developed a new catalyst synthesized by the sulfonation of partially-carbonized peanut shell for the etherification of glycerol with isobutene. After 2 hours at 70°C with a molar ratio of 4:1 isobutene/glycerol and 6% weight of catalyst, the glycerol was totally converted and a mixture of dialkylated and trialkylated products was obtained in 92% yield. In the same reaction, Zhang[388] treated zeolites with citric acid or nitric acid. The use of these catalysts allowed the formation of a mixture of di- and tri-alkylated products. To explain these results, the authors suggest that the acidic treatment could be responsible for partial dealumination of the zeolites, a decrease of the number of acidic sites (1.35 mmol/g for a treated zeolite H-Y compared to 3.76 mmol/g for non-treated ones) and a limited increase of the specific surface area (817 m^2/g compared to 754 m^2/g). Modification of the pore size as well as the strong Brønsted acid sites at the catalyst surface was also observed.

The modification of H-β zeolites by doping with rare-earth metals was described by Yang.[389] The best results were obtained with zeolites enriched with neodymium (Nd), which possess a higher number of strong Brønsted acid sites (732 µmol/g) than standard zeolites (571 µmol/g).

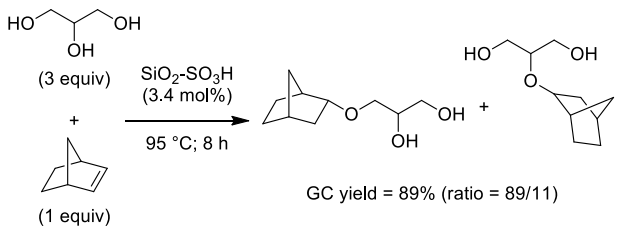
The selective preparation of GMEs from long carbon chain olefins was studied by Weckhuysen. The etherification of 1-octene with glycerol was realized with diverse catalysts such as Amberlyst 70, *para*-toluenesulfonic acid and several zeolites.[390] The reaction with an H-β zeolite afforded a moderate conversion of glycerol (19%) and a selectivity of 81% (Scheme

53). The major product was the branched monoether. The conversion and selectivity of the reaction are linked to numerous factors such as the hydrophilic/hydrophobic balance and the 3D structure of the catalyst (pore diameter and volume). In addition, different by-products were observed such as the dehydration or oligomerisation products of glycerol and octene. Although conversion and selectivities are generally lower, this approach was considered as a complementary route to the telomerization of glycerol with butadiene.[391] Following the reaction on the microscopic scale gave information concerning the relatively low conversion of the glycerol.[392] On the one hand, the authors mentioned a deactivation of the catalyst with the formation of by-products (olefin oligomerization) which are deposited on its surface. On the other hand, the difference of reactivity observed for 1,2-propylene glycol and glycerol is due to the difference in adsorption, *i.e.* in the center of the zeolite particle for glycerol and on the external surface for glycols.



Scheme 53. Etherification of glycerol with 1-octene by zeolites

Gu *et al.* studied the addition of glycerol on cyclic alkenes catalyzed by sulfonic acid supported on silica (Scheme 54).[362] The corresponding monoethers were obtained in good yields without the formation of by-products.



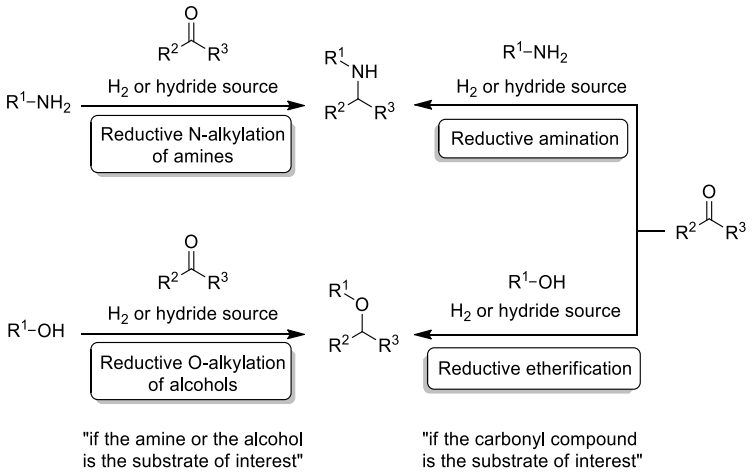
Scheme 54. Addition of glycerol on norbornene under acidic conditions

Formation of the monoglyceryl ether by addition of glycerol onto alkenes mediated by an acidic catalysis has many advantages in terms of cost and sustainability. In fact, alkenes are available on a large scale and at low prices. Moreover, for this reaction, the theoretical atom economy is perfect although E factor may be relatively bad taking into account the oligomerization of the alken difficult to avoid. In addition, many solid acid catalysts were proven to be efficient in different conditions in many cases with an easy separation and recyclability. However, the selectivity could be controlled only at relatively low conversion, especially if the monoether is the target molecule. This difficulty could be attributed once again to the poor miscibility of the fatty alkene and glycerol. Conversely, when the target molecule is the tri or the di-alkylated glycerol, for example for the preparation of oxygenated fuel additives, the use of such strategy appears even more efficient that the previous one's which use alcohol as alkylation agent. The other drawback of this strategy is linked to the use of petro-sourced mono-alkenes. Curiously, few or no articles deal with the use of bio-sourced alkenes such as terpenes or unsaturated fatty acids.

4.5. Reductive alkylation of glycerol

By analogy with the reductive alkylation of amine, though in this case mainly called "reductive amination", the reductive alkylation of alcohol refers to the reaction of an alcohol with a carbonyl function in the presence of a reducing agent. As the outcome is the formation of

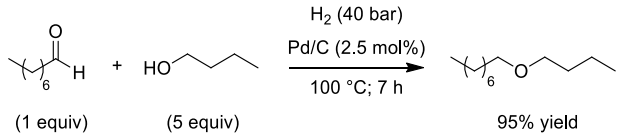
an ether, this reaction is sometimes referred to as “reductive etherification”. In this review, both “reductive alkylation” and “reductive etherification” terms will be used depending on the substrate of interest (Scheme 55).



Scheme 55. Reductive alkylation: analogy between amines and alcohols

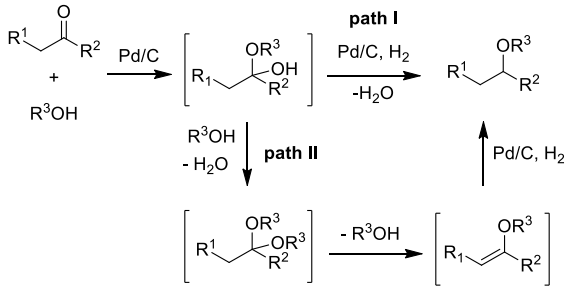
The reductive alkylation process finds its roots in the Eschweiler-Clarke[393,394] reaction in which amines are (per)methylated with formaldehyde in the presence of excess formic acid but also in the Leuckart[395,396] reaction which involves the preparation of amines through the reductive amination of aldehydes or ketones in the presence of ammonium formate. Although reductive amination has attracted much attention throughout the 20th century, it was not until 1995 that the first example of direct reductive alkylation of an alcohol was reported. In fact, inspired by pioneer work describing the condensation of alcohols to carbonyl compounds,[397] the hydrogenolysis of acetals with Rh/Al_2O_3[398] and the reduction of lactones[399] in the presence of PtO_2 and a stoichiometric amount of HCl or $HClO_4$, a general method was described for the preparation of ethers by reductive alkylation of primary or secondary alcohols with aldehydes or ketones using Pd on charcoal.[400] The reaction is done with a heterogeneous catalyst and requires relatively harsh conditions (100 °C and 40 bar of hydrogen pressure) and a large excess of one of

the reactants (alcohol or carbonyl compound). A range of alkyl-alkyl-ethers was prepared using primary or secondary alcohols with moderate to excellent isolated yields (50-95%) (Scheme 56).



Scheme 56. Formation of ether by reductive alkylation of alcohol

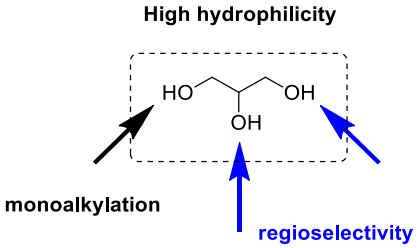
One of the key features of the above method is that the only by-product is water inducing high atom economy; the use of recyclable heterogeneous catalyst is also an important point for sustainability of such chemical transformation. The authors also proposed a mechanism to account for the formation of the ether which is that the condensation of the alcohol to the carbonyl compound, probably activated by the presence of Pd/C, could first produce a hemi-ketal that would be reduced *in situ* by hydrogenolysis to form the corresponding ethers (Scheme 56, path I). The mechanism was studied in detail by Marecot[401] who confirmed the crucial role of Pd/C on the activation of the carbonyl compound. He showed that the reaction could also proceed through the formation of a ketal, followed by its dehydration, catalyzed by the acidity of the support, to form an enol ether which is finally hydrogenated to give the corresponding ether (Scheme 57, path II).



Scheme 57. Proposed mechanisms for the reductive alkylation of alcohols

Further studies were carried out by Gooβen[402] and Mallinson[403] who showed that the reductive alkylation of alcohols could also be catalyzed by various catalysts such as Pt/C and Pd/SiO_2, respectively. More notably, Kita[404] developed a process working under a continuous flow of hydrogen and using an azeotropic removal of water that makes this method more amenable to large scale production.

The direct functionalization of glycerol through reductive *O*-alkylation represents a real challenge in terms of selectivity due to the presence of primary and secondary hydroxyl groups and the possibility of forming stable ketals and mono-, di- or tri-ethers. For the preparation of glycerol-based amphiphilic molecules, the formation of the monoether is highly desirable as it usually offers an adequate, and tunable, hydrophilic/lipophilic balance for targeted applications such as detergents. Thus, the incorporation of long alkyl chains makes the problem even more complex because these substrates are not miscible with highly hydrophilic glycerol (Scheme 58).

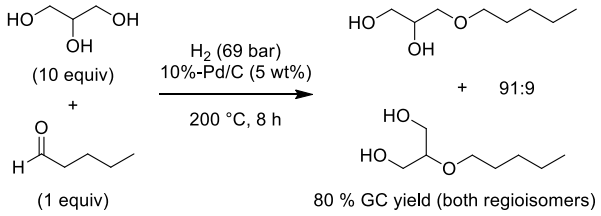


Scheme 58. Challenges for the reductive monoalkylation of glycerol

4.5.1. With aldehydes or ketones as alkylating agents

The reductive alkylation of polyols, including glycerol, has been described in several patents. However, very high temperature and hydrogen pressure are often required and low selectivities are usually observed for the desired GMEs.[405,406,407,408,409] For example, Tulchinsky *et al.*[410] described the etherification of glycerol with a small range of aldehydes (C4 to C7) at 200 °C under 1000 psi (69 bar) of hydrogen. Using valeraldehyde, a mixture of 1-*O*-pentylglycerol and

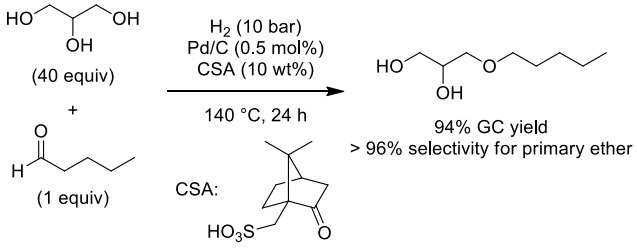
2-*O*-pentylglycerol was obtained with 80 % gas chromatographic (GC) yield and 91:9 ratio in favor of the 1-*O*-alkylglycerol regioisomer (Scheme 59). It should be noted that a large excess of glycerol (10 equiv) was necessary to ensure high selectivity towards the formation of monoethers.



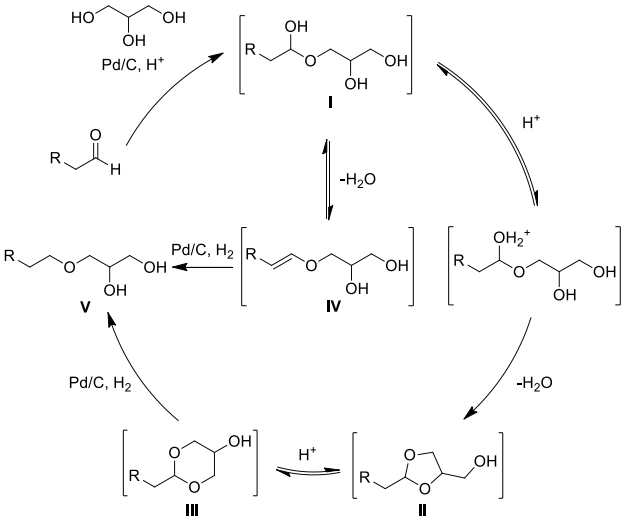
Scheme 59. Etherification of glycerol with Pd/C

At the same time, milder conditions were developed by Lemaire *et al.* for the reductive alkylation of glycerol with aldehydes or ketones.[411,412,413] The association of Pd/C and a Brønsted acid allowed the reaction to proceed at only 140 °C under 10 bars of hydrogen. The use of 0.5 mol% of Pd/C and 10 wt% of camphorsulfonic acid (CSA) as a co-catalyst afforded the 1-*O*-alkyl GMEs with both high yields and selectivities. For example, the reductive alkylation of glycerol (40 equiv) with valeraldehyde (1 equiv) gave the corresponding 1-*O*-pentylglycerol with 94 % GC yield and > 96 % selectivity for the primary ether (Scheme 60). The authors also observed a decrease in both the yield and selectivity with an increase in the length of the aldehyde chain. They explained the excellent selectivity towards the monoether at the primary position of glycerol by the presence of the Brønsted acid co-catalyst, which has a crucial role in the mechanism.[414] First, the condensation of glycerol with the carbonyl compound could lead to the formation of a hemi-ketal **I**. Under acidic conditions, this intermediate could cyclize to give the corresponding 5-membered **II** and 6-membered **III** glycerol acetals. Both acetals are in equilibrium under such conditions and the selective hydrogenolysis of these intermediates would form the desired glycerol monoether **V**. However, an alternative mechanism involving the

formation of an enol ether **IV** and its subsequent hydrogenation cannot be ruled out when using enolizable aldehydes or ketones (Scheme 61).



Scheme 60. Etherification of glycerol with Pd/C and a co-catalyst

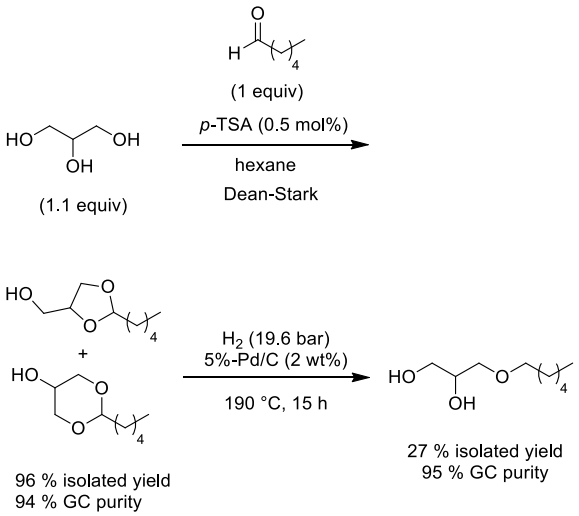


Scheme 61. Proposed mechanism for the reductive alkylation of glycerol under acidic conditions

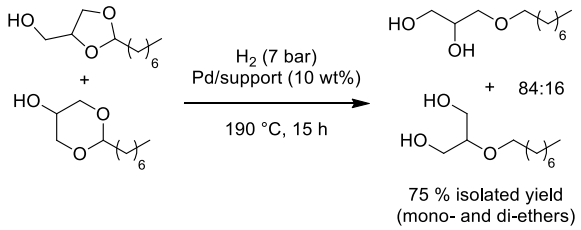
Olken and Tulchinsky further developed the reductive alkylation of glycerol using a range of palladium catalysts deposited on mesoporous acidic carbon supports.[415] For the alkylation of glycerol with valeraldehyde, the authors showed that the combined GC yield of all the glycerol ethers (monoethers and diethers) could reach 93 % using a 2.5 wt%-Pd/mesoporousC (10 wt%) catalyst. The selectivity of pentyl GMEs usually reached > 90 % but could be improved to > 95 % by incorporating Ni or La (2.5 or 5 wt%) during the preparation of the catalysts. However, this

improvement of selectivity was accompanied by a decrease of combined GC yield due the presence of glycerol acetal intermediates.

For selectivity reasons or convenience, it is sometimes interesting to prepare, and possibly isolate, the 5- and/or 6-membered glycerol acetals prior to the reduction step. As early as 1994, Nakagawa prepared a mixture of 5- and 6-membered hexylglycerol acetals through the condensation of glycerol (1.1 equiv) with hexanal (1 equiv) in a Dean-Stark apparatus and obtained a mixture of regioisomers (unknown ratio) with 96 % isolated yield and 94 % GC purity.[416] The mixture was subjected to hydrogenolysis at 190 °C under 19.6 bars of hydrogen in the presence of Pd/C to give a 7:3 mixture of GMEs and diethers. Finally, distillation gave the desired 1-*O*-hexylglycerol with 27 % yield and 95 % GC purity (Scheme 61). The system was further improved using a mesoporous aluminosilicate-supported palladium catalyst under 7 bars of hydrogen at 190 °C.[417] Under these conditions, a mixture of octylglycerol acetals (unknown ratio) gave a 94:6 mixture of mono- and di-octylglycerol ethers with 75 % yield. GC analysis revealed an 84:16 mixture of 1-*O*- and 2-*O*-octylglycerol (Scheme 62).



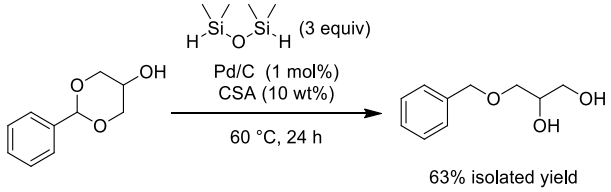
Scheme 62. Reduction of glycerol acetal to glycerol ether by catalytic hydrogenation



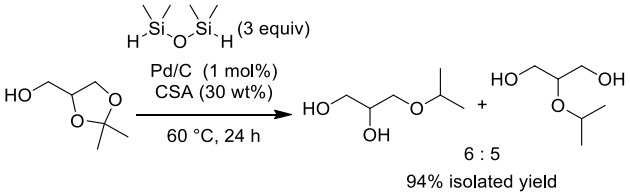
Scheme 63. Reduction of glycerol acetals with Pd/mesoporous aluminosilicate

The reduction of C-O bond of acetals using hydrides such as aluminum or boron hydrides ($LiAlH_4$,[418] DIBAL-H,[419] $NaBH_3CN$,[420] BH_3[421]) or hydrosilanes (Et_3SiH,[422] $PhSiH_3$[423]) is also quite well-documented. However, these reagents have several drawbacks such as their price, low tolerance to air and moisture, incompatibility with some functions, the formation of pyrophoric gas, production of saline by-products, the need to work under dry conditions and in some cases the use of Lewis acids in stoichiometric amount. In this context, hydrosiloxanes, which are available from the silicon industry, have recently found applications as safe reductants.[424] For example, 1,1,3,3-tetramethyldisiloxane (TMDS) has been used for the reduction of glycerol acetals to give the corresponding GMEs. The cleavage of symmetrical 6-membered benzaldehyde glycerol acetal with TMDS (3 equiv; 6 equiv of hydride/substrate) in the presence of Pd/C (1 mol%) and CSA (10 wt%) gave the corresponding 1-*O*-benzylglycerol with 63% isolated yield (Scheme 64).[425] Moreover, unsymmetrical substrates such as solketal could also be reduced under these conditions resulting in the corresponding isopropylglycerol with 94 % isolated yield. However, almost no selectivity was observed for the cleavage of the primary or secondary C-O bond since the product was isolated as a 6:5 mixture of regioisomers (Scheme 65). Interestingly, the reduction of a 1:1 mixture of 5- and 6-membered pentylglycerol acetals under the same conditions gave a 7:3 mixture of 1-*O*-pentyl and 2-*O*-pentylglycerol with 87 % isolated yield (Scheme 66). Since the ring-opening of the 6-membered acetal could only give 1-

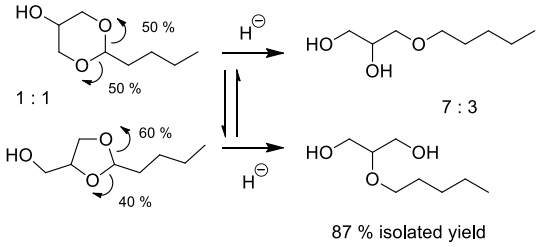
O-pentylglycerol, this result indicates that the 5-membered acetal was reduced with 60% selectivity for the primary C-O bond and 40% selectivity for the secondary C-O bond.



Scheme 64. Reduction of acetal to glycerol ether using TMDS-Pd/C-CSA



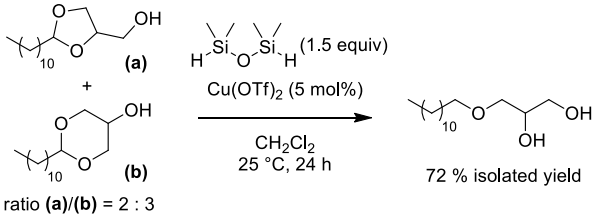
Scheme 65. Cleavage of solketal with TMDS-Pd/C-CSA



Scheme 66. Selectivity in the ring-opening of glycerol acetals with TMDS

Another method has also been developed by Lemaire *et al.* using TMDS and copper triflate ($Cu(OTf)_2$).[426] A 2:3 mixture of 5- and 6-membered dodecylglycerol acetals was treated with TMDS (0.6 equiv; 1.2 equiv of hydride/substrate) and $Cu(OTf)_2$ (1 mol%) to give 1-*O*-dodecylglycerol with 72 % isolated yield (Scheme 66). Even if the reduction of glycerol acetals with hydrides does not seem competitive, notably in terms of atom-economy, compared to the reductive alkylation of glycerol using hydrogen (only 20% in case of the reduction of solketal

scheme 64), this method still remains a good alternative for substrates bearing aromatic rings or other functions that could be reduced under these conditions. In fact, when using hydrides such as TMDS, the reagent, solvent and catalyst are relatively expensive and lead to silicon-based waste. However, these methods do not require the use of a large excess of glycerol. Besides this, the direct reductive alkylation of glycerol using aldehydes also has its own limitations. Albeit that good isolated yields and high selectivities were reached, the development of this reductive alkylation route for the preparation of GMEs on an industrial scale is compromising due to the high cost and relatively low accessibility of (fatty)-aldehydes.

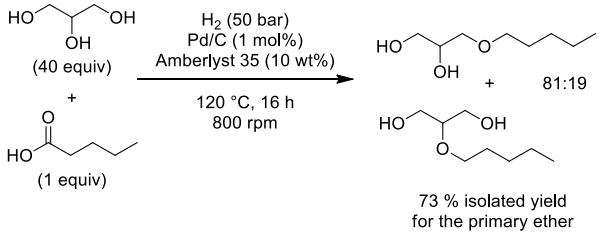


Scheme 67. Reduction of glycerol acetals with TMDS-$Cu(OTf)_2$

4.5.2. With carboxylic acids or esters as alkylating agent

In 2012, a solvent-free reductive alkylation method of glycerol using carboxylic acids as alkylating agent was described for the first time.[427] These compounds are usually cheaper and more easily available on an industrial scale than their aldehyde equivalents. Moreover, many of them could be obtained from bio-resources, especially fatty acids. For example, the reductive alkylation of glycerol (in large excess) with valeric acid at 120 °C under 50 bars of hydrogen gave an 81:19 mixture of 1-*O*-pentyl-glycerol and 2-*O*-pentylglycerol. The former has been isolated by column chromatography with 73 % isolated yield (Scheme 68).[428] It should be noted that in this case, CSA which is expensive and soluble in glycerol, was advantageously replaced by Amberlyst 35 as a heterogeneous acid co-catalyst. The mixture of heterogeneous catalysts

(Pd/C and Amberlyst 35) was recovered by filtration and recycled 3 times without significant loss of yield or selectivity towards the desired GMEs.

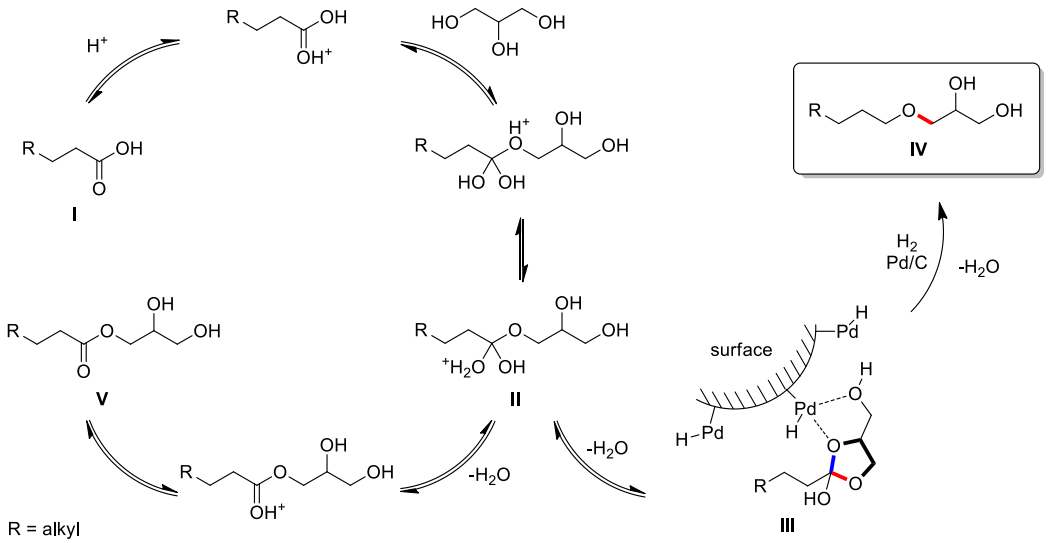


Scheme 68. Reductive alkylation of glycerol using carboxylic acids

It is important to point out that the trend of a decrease of yield with increasing chain length is similar to the reductive alkylation of aldehyde. However, the reaction conditions for reductive alkylation using carboxylic acids are somewhat harsher (higher glycerol/substrate ratio, higher hydrogen pressure and temperature) than the same reaction with aldehydes. As a result, the regioselectivity towards the primary ether is lower and the percentage of secondary ether could reach up to 20%.

The application of the above conditions to a wide range of carboxylic acids and polyols gave a large panel of amphiphilic compounds with various physicochemical properties. Lemaire *et al.*[428] proposed a mechanism based on the reactivity of various substrates such as 1-propanol, 1,2-propanediol and 1,3-propanediol. First, carboxylic acid **I** is activated by Amberlyst 35 which favors the addition of glycerol to give intermediate **II** after prototropy. Then, this intermediate could undergo an intramolecular cyclization to give a 5-membered hemi-*ortho* ester. The coordination of the free hydroxyl group of the glycerol moiety onto the palladium surface would give a 5-membered palladacycle **III**. The authors claimed that the formation of this complex is responsible for the selective hydrogenolysis of the secondary C-O bond (Scheme 69, bond in

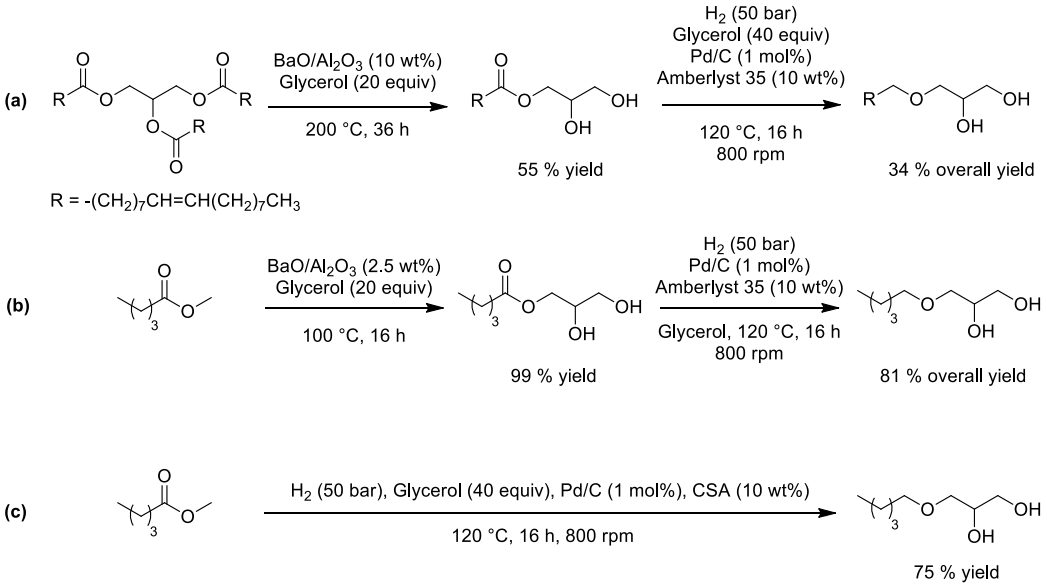
blue in **III**) rather than the primary one (Scheme 69, bond in red in **III**). This leads to the formation of the primary glycerol monoether **IV** as the major isomer.



Scheme 69. Proposed mechanism for the reductive alkylation carboxylic acids with glycerol

It should be noted that intermediate **II** could be dehydrated to the corresponding monoglyceride **V**. The formation of this glycerol ester is reversible and therefore rehydration is possible to reform the intermediate **II**. This proposition is reinforced by the results obtained for the reductive alkylation of 1,3-propanediol and 1,2-propanediol. For the former, the formation of the corresponding ether was observed with 6% yield, the rest being the ester. For the latter, 80% of ethers were formed with almost no selectivity for primary/secondary ether. These results suggest the formation of a 5-membered hemi-*ortho* ester and the potential role of the free hydroxyl in the selectivity. Based on this hypothesis, the same group developed a two-step synthesis of GMEs from triglycerides or from (fatty acid)-methyl esters.[429] These substrates were first transesterified at high temperature with a large excess of glycerol (20 equiv) in the presence of a catalytic amount of alumina-supported barium oxide (BaO/Al_2O_3). The corresponding monoglycerides were isolated and submitted to the optimized conditions (previously developed

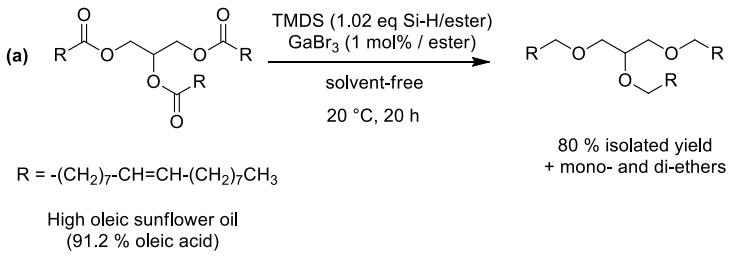
when using carboxylic acids) to give the corresponding GMEs with moderate to good yields (Scheme 70, a and b). The authors also showed that the direct reductive alkylation of glycerol using methyl esters as alkylation agents was laborious under heterogeneous conditions, partly due to their low solubility in the glycerol phase. The replacement of Amberlyst 35 by CSA, which is soluble in glycerol, significantly improved the isolated yields of the corresponding GMEs (Scheme 70, c).



Scheme 70. Synthesis of GMEs from triglycerides or (fatty acid)-methyl esters

The results presented above highlight the fact that the reduction of esters to ethers using hydrogen as a clean reductant under specific conditions is feasible. It is also important to note that the examples of ester to ether reduction are relatively rare and are usually carried out using hydrosilanes or hydrosiloxanes in the presence of indium,[430] titanium,[431] gallium[432] or iron catalysts.[433] In the context of triether of glycerol synthesis, Biermann and Metzger[434] recently showed that high oleic sunflower oil could be directly reduced to the corresponding glyceryl trioleyl ether using TMDS as reductant. The reaction was carried out under solvent-free conditions in the presence of $GaBr_3$ (1 mol%/ester function) and gave 80% of the fully-reduced

product (Scheme 71). These trialkylglycerol ethers are of potential interest for cosmetic or lubricant applications as they exhibit lower melting point and viscosity compared to the corresponding triglycerides.



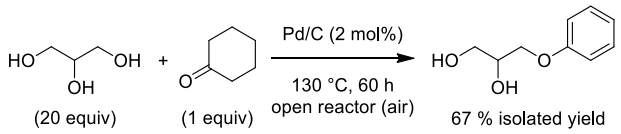
Scheme 71. Direct reduction of high oleic sunflower oil

To conclude, the direct access of glycerol ethers through reductive alkylation of glycerol using (fatty) aldehydes, esters or carboxylic acids usually gives excellent selectivities towards the primary alcohol and the formation of monoethers. It also offers an excellent atom economy pathway as 2 molecules of water are the only by-products of the reaction. However, the need for a high pressure of hydrogen (7-200bars) and specialized equipment might discourage chemists from using these methods for cost and/or safety reasons.

4.6. Aryl ether synthesis by dehydrogenative alkylation of cyclic ketone

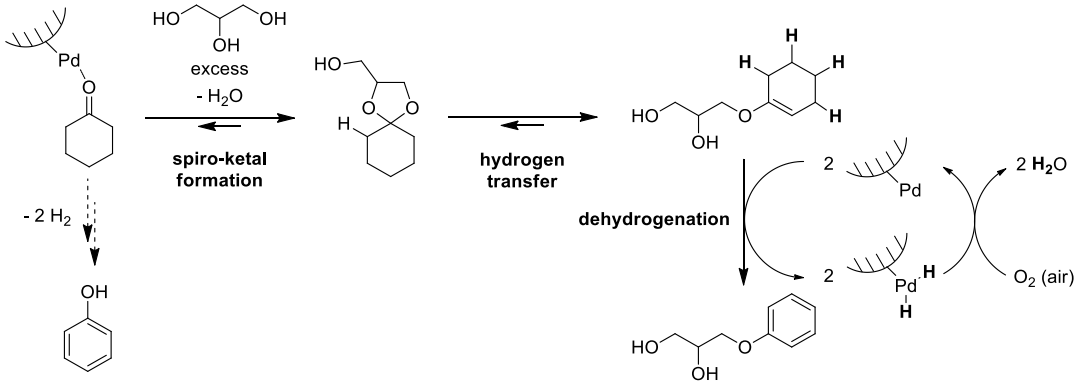
Inspired by pioneering work,[435,436,437,438] Stahl achieved a significant breakthrough in 2011 with the discovery of an aerobic dehydrogenation method of substituted cyclohexanones for the preparation of phenols.[439] This discovery recently led to a renewal of interest in the preparation of aromatic compounds such as anilines and aromatic ethers, from non-aromatic substrates and the corresponding amines and alcohols. For example, Li's group reported an original approach to aryl ethers in which the aromatic moiety is created through the condensation of an alcohol with a 2-cyclohexenone, followed by oxidative aromatization under an oxygen atmosphere.[440] A similar strategy was developed using cyclohexanone derivatives as non-aromatic precursors.[441] More

importantly, they showed that glycerol could be arylated using heterogeneous and solvent-free conditions. Treatment of glycerol (20 equiv) with cyclohexanone (1 equiv) at 130 °C for 60 h in the presence of Pd/C (2 mol%) gave the corresponding 1-*O*-phenylglycerol with 67 % isolated yield (Scheme 72).



Scheme 72. Preparation of glycerol phenyl ether from glycerol and cyclohexanone

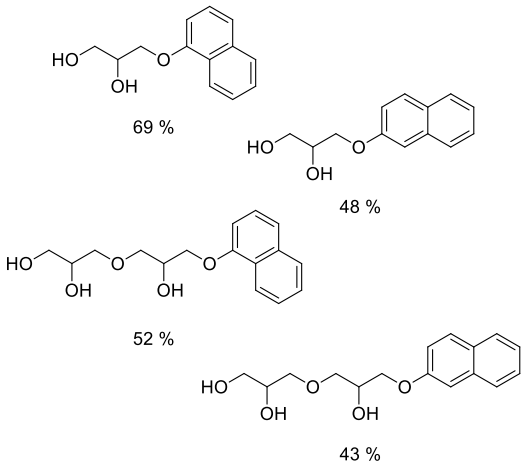
Further studies[442] led the authors to propose the following mechanism. First, the addition of glycerol to cyclohexanone generates a spiro-ketal that undergoes a hydrogen transfer to give the enol ether. This intermediate is then dehydrogenated over a Pd/C heterogeneous catalyst under aerobic conditions to give the corresponding aryl ether (Scheme 73). The ketal intermediate was identified by GCMS analysis.



Scheme 73. Proposed mechanism for the dehydrogenative arylation of glycerol with cyclohexanone under aerobic conditions

The scope of the above reaction was then extended to the preparation of other glycerol derivatives. For example, treatment of glycerol (5 equiv) with α- or β-tetralone (1 equiv) in a sealed tube at 150 °C for 60 h in the presence of Pd/C (1 mol%) gave the corresponding

naphthylglycerol ethers with 69 and 48 % isolated yields, respectively. The application of the same conditions to diglycerol gave the corresponding aryldiglycerol ethers with 52 and 43 % isolated yields (Scheme 74).



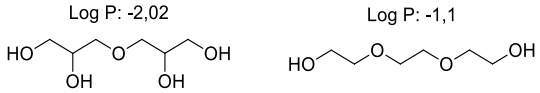
Scheme 74. Preparation of naphthyl(di)glycerol from (di)glycerol (isolated yields)

The interest in 1-phenyl glycerol ether was evaluated recently by Aubry[12] and they observed that this compound was not amphiphilic enough to lead to self-associative phenomena or co-solubilization of oil and water. Nevertheless, these studies need to be widened to cover to other compounds of this family. Although limited to specific aryl derivatives with no known applications for the moment, this new approach possesses almost all the characteristics required for sustainability i.e. high atom economy, hydrogen as the only by-product (or water if the reaction is carried out under oxygen), use of heterogeneous catalysis and no solvent.

5. Glycerol oligomerisation: properties and application of di-, tri- and poly- glycerol

In the previous chapters, attention has been paid to accessing GMEs through the incorporation and/or modification of the hydrophobic chain. The aim of this section is to describe the main routes that have been developed for the preparation of polyglycerol ethers in recent years, with the wish to highlight the progress that has been made in a context of eco-friendly chemistry. We

focus on the modification of the hydrophilic part, *i.e.* on the preparation of di-, tri-, tetra-glycerols or other polyglycerols. The interest for polyglycerols has significantly grown in recent years due to their potential to replace petrochemical-based glycol ethers. The latter are still widely used in industry as a coalescent in paints, solvents, inks or in cleaning formulations.[160] However, some of them are toxic such as short ethylene glycols that have been classified as CMR due to their reprotoxicity. Hence, there is an urgent need to find alternatives, preferably bio-based ones if possible, with similar physicochemical properties and reduced toxicity (Scheme 75).



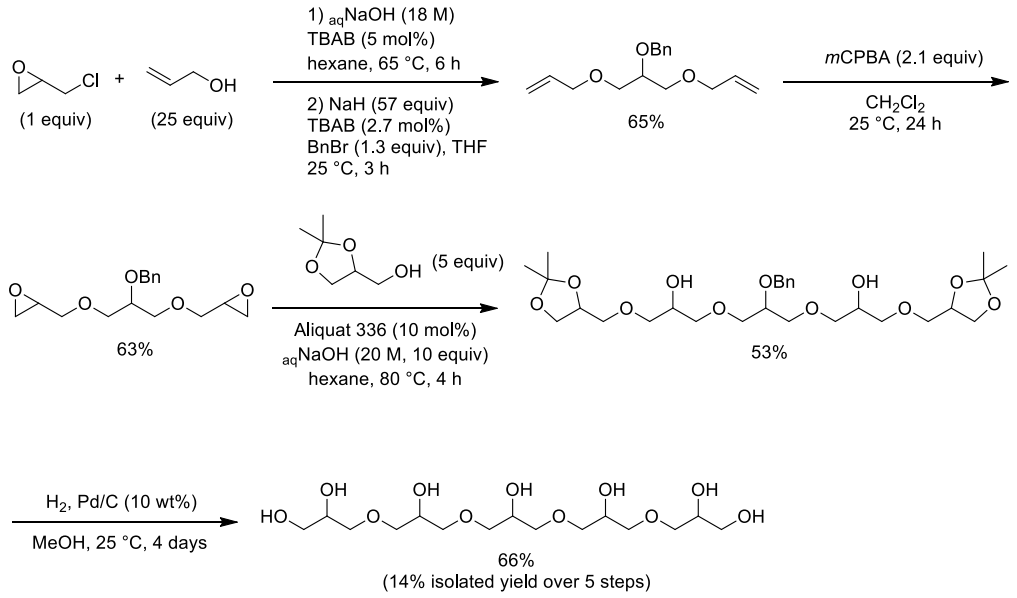
Scheme 75. Diglycerol **(a)** as potential substitute for triethylene glycol **(b)**

The possibility to control the length and degree of branching of the polyglycerols allows access to various hydrophilic heads with tunable physicochemical properties. Some of these compounds have already found applications in cosmetics,[443] lubricants, plasticizers, dispersants, surfactants,[444,172-176] and polymers[445] used in food-processing,[446] medicinal[447] and pharmaceutical[448] industries. The preparation of polyglycerols was recently described in reviews or book chapters mainly dedicated to the catalytic systems used[449] or to the formation of short oligomers such as di-, tri- or tetraglycerol.[450]

5.1. Industrial synthesis of polyglycerols

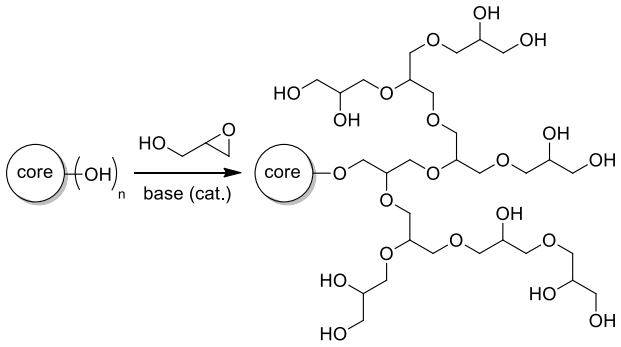
Historically, the objective of polyglycerol synthesis was to control the structure of the hydrophilic part for surfactant applications and so obtain the desired oligomers with the best yields and selectivities. In this context, multi-step syntheses were widely used with

protection/deprotection strategies, and chemicals such as allyl ethers, ECH, glycidol or 1,2-*O*-isopropylidene glycol.[451] For example, Plusquellec and Rollin prepared a range of polyglycerols using multi-step chemistry.[452] Treatment of ECH with an excess of allylic alcohol under phase-transfer conditions and subsequent benzylation led to the formation of 2-*O*-benzyl-1,3-*O*-bis-allylglycerol with 65% yield over two steps. Epoxidation of the terminal double bonds with *m*CPBA and subsequent ring-opening with solketal gave an intermediate that finally undergoes hydrogenolysis to give pentaglycerol with 14% isolated yield over 5 steps (Scheme 76).



Scheme 76. Preparation of linear pentaglycerol from ECH and allylic alcohol

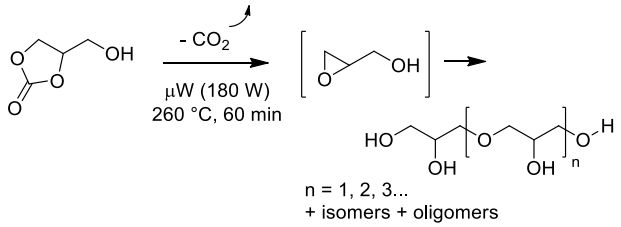
The above approach has also been successively applied to anionic[172-176,453,454,455] and cationic[172-176,456] polymerization of glycidol for the preparation of highly-branched polymers with molecular weights ranging from 1,000 to 30,000 g.mol^{-1} (Scheme 77).



Scheme 77. Highly branched polyglycerol by anionic polymerization of glycidol

These spectacular multistep syntheses are good examples of the power of modern organic synthesis but also of the practical limitations because of the very low atom economy (less than 5% for the reaction described in scheme 75). Moreover, E factor should be even worse regarding reagents and solvents required for these syntheses.

More recently, the context of eco-responsible chemistry has driven the development of new etherification processes such as the formation of polyglycerols from glycerol carbonate under microwave irradiation in which glycidol is formed *in-situ* by decarboxylation of the reactant (Scheme 78).[457] These authors have shown that the molecular size dispersion was relatively similar to that of polyglycerols obtained under basic conditions.



Scheme 78. Polyglycerols from glycerol carbonate.

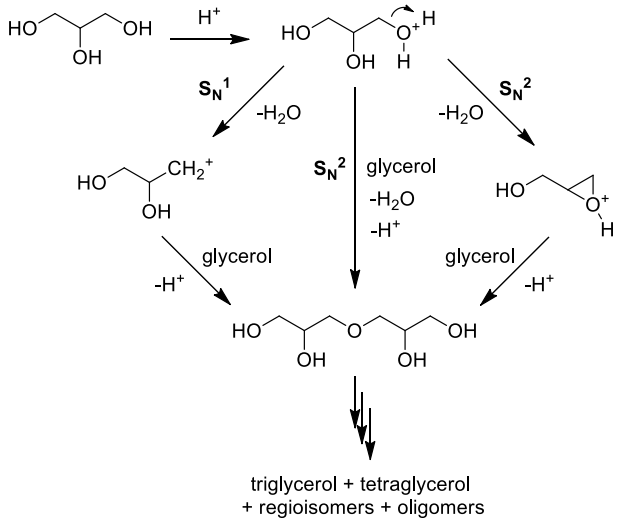
5.2. Polyglycerols by direct glycerol oligomerization

The control of the degree of polymerization and regioselectivity (linear, branched, cyclic polymers) in order to form a well-defined oligomer are the main difficulties encountered in the

direct oligomerization of glycerol. In this context, the nature and structure of the catalysts developed often play a crucial role for such approaches. Finally, separation methods for polyglycerol fractions have also been carefully studied.[458,459,460,461]

5.2.1. By homogeneous acidic or basic catalysis

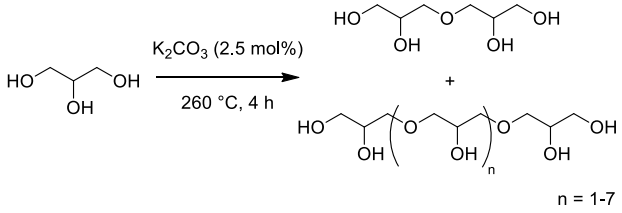
The direct polymerization of glycerol through homogeneous acidic or basic catalytic processes has been the subject of numerous studies. Similar to the acidic etherification of glycerol with alcohols, an S_N1 mechanism is commonly assumed. The protonation of a primary hydroxyl group could form a primary carbocation that reacts with another molecule of glycerol to give the corresponding diglycerol (Scheme 79). Nevertheless, this mechanism seems unlikely because the formation of a (very reactive) primary cation would lead to a significant proportion of α,β-diglycerol whereas in many cases the α,α-diglycerol is mainly obtained. Although, with a high concentration of glycerol (solvent-free conditions), an S_N2 mechanism via either direct hydronium substitution or formation of an epoxide cannot be ruled out. However, as the oligomerization of glycerol is usually conducted at elevated temperature, the product distribution probably results from a combination of all these mechanisms.



Scheme 79. Oligomerization of glycerol under acidic conditions

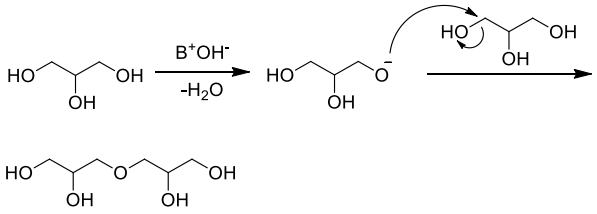
Polymerization is usually not selective when using Brönsted acids such as sulfuric[462,463,464] or phosphoric acid.[465] These acidic conditions lead to the production of large quantities of dehydration products such as acrolein along with some rearrangement of reactive glycidol or acrolein products that are difficult to identify. Moreover, these processes do not produce well-defined polyglycerol fractions.

The polymerization of glycerol could also be carried out using homogeneous basic catalysts that are soluble in glycerol. They are mainly found among alkaline hydroxides or carbonates.[466] For example, Garti[467] showed that potassium carbonate (K_2CO_3), although far less basic than potassium hydroxide, was the most efficient catalyst for such polymerization due to its improved solubility in the glycerol phase at high temperatures. However, the oligomerization was also not selective under these conditions and a complex mixture of di- and polyglycerols was recovered (Scheme 80).



Scheme 80. Polymerization of glycerol using K_2CO_3

Under basic conditions, the etherification tends to follow an S_N2 mechanism. The interaction of a base (BOH) with glycerol forms a glycerolate anion that reacts on another glycerol to form diglycerol with elimination of water (Scheme 81). This type of mechanism could only be considered at high temperature (260°C) due to the poor leaving group.



Scheme 81. Oligomerization of glycerol by basic catalysis

Other bases such as $CsHCO_3$[468] or Na_2CO_3[469] have also been used but once again the length of polyglycerols could not be controlled under these conditions. Another example is when Khayoon reported the etherification of glycerol to diglycerol using 2 wt% of lithium hydroxide (LiOH).[470] This base allowed complete conversion of glycerol in 6 hours at 240 °C but the selectivity towards diglycerol was only 33%. The use of homogeneous catalysts was progressively abandoned in favor of heterogeneous ones that have better eco-compatible profiles.

5.2.2. By heterogeneous acidic and basic catalysis

The use of heterogeneous catalysts is part of the objective to develop more environmentally-friendly processes. Not only can these catalysts be recovered, recycled and re-used, but they also improve the selectivity thanks to their 3D structures by blocking the formation of high molecular weight polymers.

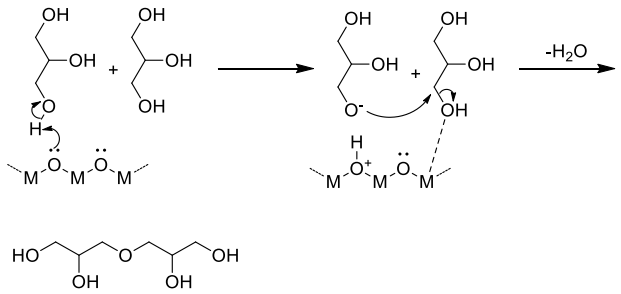
Several solid acid catalysts have been used for the oligomerization of glycerol such as the ion-exchange resin Amberlyst 16 (by Barrault[469]) or an ion-exchange perfluorinated polymer type Nafion® NM-112 (by Richter[471]). For the latter, the linear diglycerol ether has been obtained with 85% selectivity at 90% conversion of glycerol when using 0.5 to 5 wt% of catalyst under reduced pressure (2 mbar) at 160°C. Similarly to the acidic etherification of glycerol with alcohols, the suggested mechanism is that the protonation of a primary hydroxyl group could form a primary carbocation that reacts with another molecule of glycerol to give the corresponding diglycerol. The excellent selectivity obtained could be explained by the

development of a “falling-film” type reactor that was especially designed for this reaction. In this reactor, glycerol boils at the bottom and condenses at the top, and then drops down a catalyst foil where it oligomerizes. The diglycerol and higher oligomers produced concentrate at the bottom because they cannot be vaporized under the selected temperature and pressure and therefore cannot be oligomerized further. Excessive polymerization is thus avoided.[472]

Acidic zeolites have also been used for the oligomerization of glycerol. The main advantage lies in the intrinsic structure of such catalysts in which the pore size plays a crucial role in blocking the formation of high molecular weight polymers. For example, zeolite β has been tested and gave encouraging results.[469] The same authors also tested a mesoporous silica MCM-41.[469] Finally, montmorillonite saponite-type acid clays have also been studied.[473] At 250°C, 6% linear diglycerin was obtained with 78% of unconverted glycerin.

The oligomerization of glycerol has also been studied with heterogeneous basic catalysts. The Weckhuysen group showed that the reaction could be carried out with several alkaline metal oxides such as MgO, CaO, SrO and BaO.[474,475] It was shown that the conversion of glycerol was closely related to the basicity of the catalyst but also to the strength of Lewis acid sites that facilitate the elimination of the hydroxyl group. A conversion of 80% was obtained after 20 hours at 220 °C with barium oxide (BaO) and similar results were obtained with calcium oxide (CaO) which has both Lewis basic and acid sites (Scheme 81). No difference of selectivity was observed when comparing the different catalysts, and the quantity of triglycerol increased with the glycerol conversion at the expense of the diglycerol. The authors’ observation was that the isomer distribution of the diglycerol formed changed with reaction time.

Torres prepared and tested mixed Mg-Al metallic oxides derived from hydrotalcites for the aforementioned transformation.[476] A conversion of 50% of glycerol was obtained and diglycerol was isolated with 43% yield after 24 hours at 220 °C.



Scheme 82. Oligomerization of glycerol by basic catalysis with Lewis acid sites

Other groups are also interested in the study of heterogeneous basic catalysts (such as X, Y or β zeolites) exchanged with alkaline ions. Good selectivities were obtained for the formation of linear diglycerol at low conversion.[477] The influence of the basicity of the alkaline ions and the 3D structure of the zeolite was demonstrated in these studies. Basic mesoporous materials derived from silica and alumino-silicates incorporated with different alkaline elements such as Li, Cs, La, Na and Mg have also been described for the oligomerization of glycerol.[478,479] In these studies, the best results were obtained with cerium-doped materials. Unfortunately, these catalysts were found to be unstable and some leaching of cerium species was observed. Finally, other systems were recently developed to achieve good selectivities for only one type of oligomer at high glycerol conversion. To reach that goal, focus was put on the design of the catalysts and their stability at high temperatures. For example, hydrotalcite (lamellar double structure ($Mg_6Al_2(OH)_{16}CO_3.4H_2O$)[480]) were described by Abdullah.[481] In another study by the same group, clays like LiOH-doped montmorillonite[482,483] K-10 proved to be very efficient at low loading (2 wt%) and diglycerol was obtained with 53% selectivity at 98% conversion after 12 hours at 240 °C.[484]

For both strategies *i.e.* acid- and base-catalyzed, yields and selectivity may be considered as satisfactory. Nevertheless, there is still debate about both the acid- and base-catalyzed mechanisms. The proposed acid-catalyzed mechanism implies the formation of a primary cation in the presence of a secondary alcohol. Therefore, formation of glycidol as intermediate could not be ruled out. This point is important taking into account the toxicity of this intermediate. The base-catalyzed mechanism requires the substitution of a hydroxyl group which is only possible at high temperature (>240°C). However, glycerol is not stable at this temperature and may lead to acrolein or glycidol. These mechanistic issues are important especially if traces of toxic intermediate are to be avoided in industrial processes.

Similarly to the synthesis of 1-*O*-alkyl glycerol ethers, the selective preparation of a well-defined fraction of polyglycerol directly from glycerol is still the subject of intense research. The use of heterogeneous catalysts and solvent-free conditions allows the development of a cleaner process but also to reach better selectivities for the desired products. In addition, reactor design, use of milder conditions and understanding reaction mechanisms will play a key role in the development of efficient, economic and environmentally-friendly processes.

6. Conclusion

~~To conclude, as soon as we started the redaction of this review, we understood that the question "Which technology will lead to the most efficient synthesis of glycerol ethers from both an economical and ecological point of view?" cannot be answered with only technological data. After many discussions,~~ Several outcomes emerge from reviewing the chemical and industrial literature dealing with glycerol ether synthesis and manufacturing From the analysis of the numerous methods used for the preparation of the glycerol ethers, the advantages and drawbacks

could be highlighted for each strategy. Theoretical atom economy is a useful concept as is the ratio of bio-sourced starting material integrated in the final molecule. Unfortunately, other information such as practical atom economy and E factors, and the possibility of recycling are scarce or inaccessible. This should be considered as a limitation of the present analysis. It will be necessary to wait until examples of successes (and failures) of industrial attempts in order to confirm or reject any prediction. The significant effort of chemists to determine life cycles assessment (LCA),[485,486] cumulative energy demand (CED)[487] and the environment, health and safety (EHS)[488] aspects of the main synthetic building blocks will doubtless lead to usable tools but only in the future. Nevertheless, for the moment, we could compare the atom economy in several cases for which the target molecules are the same. For many others, we could only make a qualitative assessment which would be, all the same, very useful.

The first approach, and probably the most advanced from an industrial point of view, requires the synthesis of an intermediate, a "platform" which already has several industrial applications. The most important molecule in this case is ECH which is produced on a very large scale and (recently) accessible from bio-sourced glycerol. This strategy is advantageous because little or no new equipment is required. Several "bio-refineries" have been developed using this approach where the biomass is transformed into small building blocks which the oil industry then uses in traditional synthetic routes toward more elaborated molecules. In fact, this approach is already successful but sustainable chemistry not only requires the use of renewable material (7^{th} principle of the green chemistry) but also less dangerous chemicals and processes (4^{th}, 5^{th}, 6^{th} and 12^{th} principles). Moreover, ECH is a highly reactive (and toxic) reagent. It could easily be transformed into ether in the presence of a base but with the production of a large amount of salt which would contribute to a low atom economy (2^{nd} principle).

The second approach, i.e. the use of protective groups such as in glycerol carbonate or glycerol acetonide, eliminates several specific problems of glycerol functionalization but appears even more uncertain for increased development of glycerol ether synthesis. On the one hand, the protection of two hydroxyl groups increases the solubility of the glycerol derivative and the miscibility with a hydrophobic reagent. Furthermore, the problem of selectivity is also reduced. On the other hand, this strategy requires two additional synthetic steps (protection and deprotection) which decrease both the overall yield and atom economy (8^{th} principle of green chemistry). Such a highly efficient method could be considered only if the protected derivatives are produced on a very large scale for other applications (energy, for example) and are then available at a low price. This is not the case for the moment.

Finally, the use of glycerol as starting material is the most interesting even if alkylation using base and electrophilic alkylhalides (Williamson-type syntheses) gives rise to only poor (regio- and chemio-) selectivities and also exhibits low atom economy. Therefore, it is not surprising that catalysis (9^{th} principle of green chemistry) offers the most attractive solutions. The simplest is acid catalysis and many clever and useful methods have been published where the selectivity is controlled and the catalyst recovered.

Several materials have been specifically created or developed for the etherification of glycerol using aliphatic alcohols of alkenes. In these reactions, theoretically only water or no byproducts are produced as a byproduct. Selectivity for the mono-etherification of glycerol may be achieved but, unfortunately, the reaction of alkyl cation with glycerol may not be the only reaction to occur and oligomerization of alkene as well as formation of symmetrical ethers are competitive reactions. ~~dissymmetrical dehydration of the glycerol and aliphatic alcohol may not be the only reaction. Therefore, large proportions of symmetrical aliphatic ethers are often~~

~~obtained.~~ Selectivity is rarely given in most articles but it appears to be the main limitation of acid catalysis in the synthesis of glycerol ethers. However, this limitation is much smaller in the case of specific substitution, such as benzyl or *tert*-butyl groups. This approach was also proved to be especially efficient if di or tri-alkylated ethers of glycerol are the target molecules.

Good regio- and chemio-selectivity can be obtained using homogeneous palladium catalysis for the telomerization of butadiene using glycerol as the nucleophile. The theoretical atom economy is 100% in this particular case. This method seems even more interesting because the catalyst loading can be very low. The process could also profit from the immiscibility of glycerol with alkene in order to obtain an easy separation of the catalyst using a liquid/liquid separation system. Examples of such processes already exist on a large scale[489] and the only drawback we could find is (for the moment) the non-bio-sourced butadiene.

A similar analysis, i.e. theoretical atom economy of 100%, could be made for heterogeneous catalysis with good selectivity and efficiency when performing reductive alkylation of glycerol with aldehyde and where the only by-product is water. The catalyst could be recycled but alkyl aldehydes are not (for the moment) bio-sourced. However, bio-sourced carboxylic acids could be used for the reductive alkylation of glycerol but with lower selectivity and harsher conditions of temperature and pressure. The mixture of the two solid catalysts (sulfonic resin and palladium on charcoal) could be recycled as well as glycerol. This is particularly important because a large excess of this product is required to ensure good selectivity for the monoalkylation. This new reaction together with the butadiene oligomerization may be considered as the best candidates and discrimination between them may be determined by a chemical engineering study. The possibility of recycling and process intensification may be the key parameters in the final choice for potential industrialization.

One of the specific problems we encountered is connected to the comparative evolution of the price of bio-sourced and petro-sourced raw materials. In fact, about ten years ago, the fast expansion of the production of fatty acid esters as bio-diesel required the valorization of glycerol from an economic point of view. The slowing down of production growth of first generation bio-fuel makes the use of glycerol less justified. Moreover, the use of shale gas is probably going to delay the famous "oil peak" at a date much further way than what was planned only a few years earlier. Nevertheless, as can already be seen, the price of oil will not return to the level of the nineties. This is probably due to the more expensive (and often more polluting) technologies required for the extraction of unconventional hydrocarbons.

Global warming has already had climate, economic and social effects which will affect the development of any fossil raw materials and favor use of renewable starting materials. It is easy to see that prices of raw materials for chemistry are submitted to contradictory evolutions. However, the fact that the Earth will be inhabited by more than 9 billion human beings in a few decades makes the use of renewable raw materials a medium-term absolute necessity.

The evolution in the regulations in the use of chemicals is also a significant source of uncertainty for the orientation of the choice of an optimal synthetic pathway. These regulations sometimes appear limiting to innovation but the tendency to limit the use of potentially dangerous or toxic chemicals is still very important. In fact, due to recent pollution problems, such as the scattering of endocrine disruptors or massive air pollution in big cities, people now consider the sciences and chemistry in particular as suspicious. As a consequence, politicians have increased the control and the limitations. These are particularly true in the areas of speciality chemicals used in laundry, agrochemicals, and paint, etc. where the trend seems to be

for the extension of the regulations based on the most restrictive. Unfortunately, certain chemical operations have been relocated to countries with less strict regulations.

Finally, predicting the evolution of technologies, even for a short period, is something out of our expertise. Over the last ten years, most technologies having advantages from a sustainability point of view have been tested for glycerol ether synthesis, and not surprisingly all catalyses (from homogeneous to heterogeneous) offered the most attractive solutions. Biotransformation is nevertheless almost not represented. This may be the missing link because every year researchers claim that new chemical building blocks can be produced from biomass or by using biotransformation. One of the most spectacular may be the production of succinic acid by fermentation at a price similar or even lower than the chemical process.[490,491] In the case of glycerol ethers, there is, to the best of our knowledge, no publication devoted to this type of synthesis. Nevertheless, intensive research is being done on etherase for the degradation of lignin or toxic ethers like dioxin.[492,493,494]

~~From all the above limitations, our analysis may be (and should be) discussed.~~ It is important to note that alkyl ether is probably one of the molecules which has led to the most synthesis research in the academic world (> 1200 articles in the last 10 years) but even more in industry (> 2000 patents for the same period). This strong effort and hard competition are part of a general evolution resulting from economic, ecological and social demands and which have already produced new concepts, new technologies, new starting materials, and even new industrial competitors that altogether may be considered as an “industrial revolution”.

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Marc Sutter was born in 1986 in Strasbourg, France. He received his master degree in chemistry in 2009 at the University of Strasbourg. Then he joined the research group of Prof. Marc Lemaire in Lyon. He received his Ph. D. degree from the University of Lyon 1 in 2013 for work on new access routes to glyceryl ethers with the collaboration of Sofiprotéol. He is currently a chemical Engineer at Solvay in the Research and Innovation Center of Lyon.

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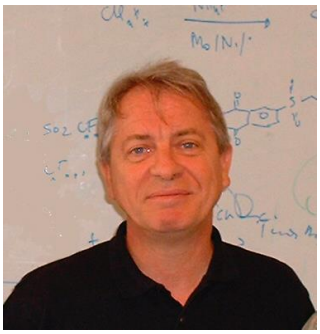
Nicolas Duguet was born in 1980 in Normandy, France. He graduated from Institut National des Sciences Appliquées de Rouen in 2003 and received his Ph.D. degree from the University of Rouen, France in 2006 under the supervision of Dr. Jacques Maddaluno working on chiral lithium amides. As part of his Ph.D. studies he spent some time working in collaboration with Pr. Kiyoshi Tomioka in Kyoto University, Japan. In 2007, he joined the group of Dr. Andrew D. Smith at the University of St Andrews, Scotland, UK as a postdoctoral fellow (Leverhulme Trust) where he stayed for two years developing novel organocatalytic methodologies using N-heterocyclic carbenes. He moved back to France in 2009 for second postdoc in medicinal chemistry at the University of Orléans under the guidance of Pr. Sylvain Routier. In 2010, he was appointed assistant professor in the group of Pr. Marc Lemaire at the University of Lyon. His current research is focused on the development of green and sustainable methodologies.

Yann Raoul was born in 1974 in Paris, France. He graduated from Université de Picardie Jules Verne in 1998 and received his Ph.D. degree from the University of Hull (UK) in 2001 under the supervision of Dr. Grahame Mackenzie and with the support of Croda Universal, in the field of lipid chemistry on the synthesis of nervonic acid derivatives. In 2001, he joined the group of Dr. Mike Hird at the University of Hull (UK) as a postdoctoral fellow where he stayed for two years working on the synthesis and properties of achiral and racemic materials with bent molecular structures. He moved to Italy in 2003 for a Marie Curie postdoctoral fellowship in medicinal chemistry with Molteni Farmaceutici, Firenze. In 2004, he joined Croda Chemicals Europe, Leek (UK) as a research chemist in the field of lipid chemistry for health applications. He then joined the Sofiproteol group, the financial and industrial actor of the french vegetable oil and protein industry, in 2008 and its subsidiairy Oleon Novance in 2013, now as R&D department head for organic synthesis & analysis to develop specialty products from natural oils & fats through sustainable technologies.

Estelle Métay, CNRS research associate at the University of Claude Bernard Lyon 1, in the CASYEN Laboratory. She is graduated from the University of Nantes and defended her PhD at the university of Paris XII in 2005 (Prof. J. Y. Nédélec), working on the synthesis of medium ring benzolactones. She spent 14 months as a postdoctoral researcher at the Purdue University (Prof E.-I. Negishi). She joined the Marc Lemaire's group in 2007. Her main research interests concern the organic and organometallic catalysis applied to green chemistry. One part concerns the development of new safer and cleaner reagents for the reduction of different organic functions. Another part is dedicated to the valorization of bio-sources derivatives to prepare as for example surfactants. She earned her HDR in 2012. She is co-author of 47 publications and patents.



Professor Marc Lemaire started his career as technician at the Roussel UCLAF research centre (Romainville) then at the Delallande research centre (Rueil-Malmaison). Thanks to the evening courses at University (CNAM) he obtained a master degree in organic chemistry at CNAM Paris then a PhD degree at the Paris VI University (Dir J.P. Guetté). He spent 18 months as postdoctoral fellow at the University of Groningen, Netherland (Dir R.M. Kellogg). He obtained an assistant professor position at the CNAM in 1982. He was appointed as professor at the University of Lyon in 1989, 2°class, then 1°class and exceptional class. During the last 20 years, he created a new laboratory at the Lyon 1 University (Catalysis and Organic Synthesis), he was successively Director of the master of catalysis and physical chemistry (8 years) and then director of the organic synthesis master (5 years). He was director of the UMR 5181 (fine organic chemistry) from 1998 to 2004. He was appointed at the national committee of CNRS section 12 then 16 and on national committee of Universities section 32, member of the board of the SFC (organic chemistry division) and of the CA of the SFC. He was one of the coordinator of the green chemistry network of the CNRS. He was a member of the scientific committee of the "Institute de chimie séparative" of Marcoule and of the scientific committee of the Society MINAKEM. He has been appointed senior member of the "Institut Universtaire de France". He also managed industrial research projects and is now co-director of the International Laboratory on Malagasy Biodiversity Valorization at Antananarivo Madagascar. He is the author of more than 350 scientific articles and 64 original patents. He has presented 145 national and international conferences, h factor = 48 (2014).

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