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Synthesis of Biomass-Derived Ethers for Use as Fuels and Lubricants

ChemSusChem Review for Special Issue on Sustainable Organic Synthesis

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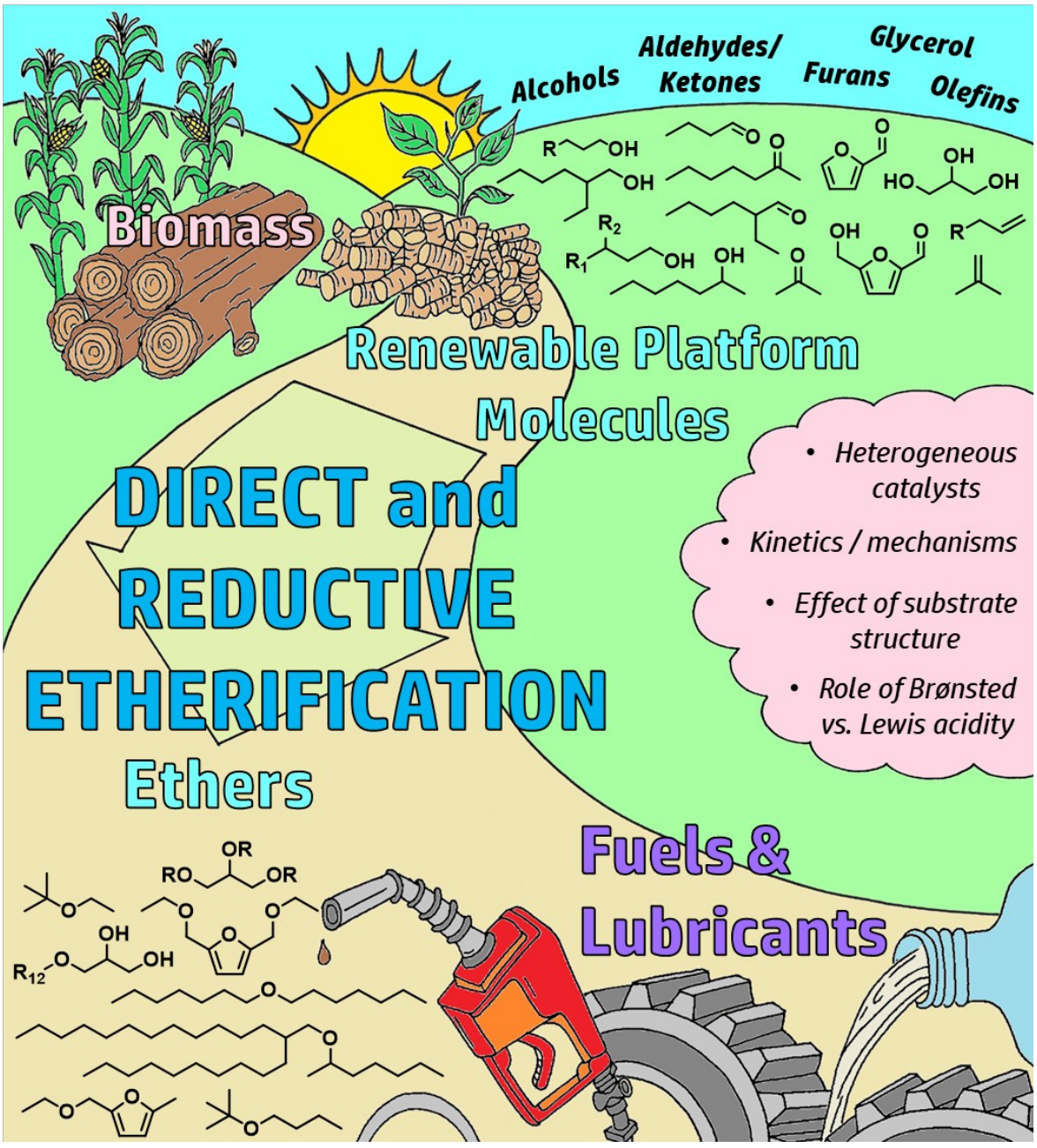
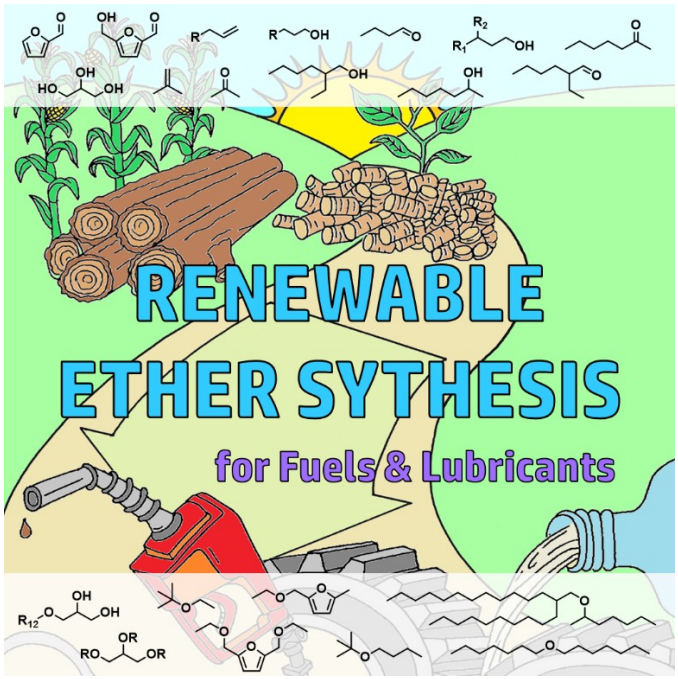
Frontispiece Image:



Smaller Graphical Abstract for Table of Contents: “Into the Ether”



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General Outline:

Author Biographies and Photos:

Julie Rorrer received her bachelor's degree in Chemical Engineering from Arizona State University in 2014. She is currently a PhD candidate in chemical engineering at the University of California, Berkeley as a National Science Foundation Graduate Fellow. Her research is focused on the heterogeneous catalytic conversion of renewable platform molecules into fuels and specialty chemicals.

Alexis T. Bell received his S.B. and Sc.D. degrees in chemical engineering from the Massachusetts Institute of Technology and then joined the faculty of the Department of Chemical and Biomolecular Engineering at the University of California, Berkeley, in 1967, where he currently holds the position of the Dow Professor of Sustainable Chemistry. Since 1975 he has also been a senior faculty scientist at Lawrence Berkeley National Laboratory. His research is devoted to fundamental studies of the structure−function relationships for heterogeneous catalysts and the application of such catalysts in a variety of contexts, including synthesis of fuels and chemicals from CO and H_2, conversion of biomass to fuels and chemicals, electrochemical splitting of water, and reduction of CO_2. These efforts have involved both experimental and theoretical studies. His work has received extensive recognition, and he is a member of the National Academy of Engineering, the National Academy of Sciences, and the American Academy of Arts and Sciences.

F. Dean Toste received his B.Sc. and M.Sc. from the University of Toronto and completed his Ph.D. studies at Stanford University under the guidance Professor Barry Trost. After a post-doctoral appointment with Professor Robert Grubbs at the California Institute of Technology, he took an Assistant Professorship at the University of California, Berkeley in 2002. In 2006, he was promoted to Associate Professor and is currently Gerald E. K. Branch Distinguished Professor of Chemistry.

Abstract

Ethers synthesized from biomass-derived compounds have exceptional properties as fuels, lubricants, and specialty chemicals, and can serve as replacements for petroleum-derived products. Recent efforts have identified heterogeneous catalysts for the selective synthesis of ethers from alcohols, aldehydes, ketones, furans, esters, olefins, carboxylic acids, and other molecules derived from biomass. This review highlights the scope of etherification reactions and provides insights into the choice of catalysts and reaction conditions best suited for producing targeted ethers from the available starting materials. We start by noting the properties of ethers for specific applications and then discussing the methods by which synthons for ether synthesis can be obtained from biomass. We then summarize progress made on the synthesis of ethers via direct etherification of alcohols; reductive etherification of alcohols with aldehydes or ketones; etherification of furanic compounds, esters, and carboxylic acids; and the addition of alcohols to olefins. Next, we discuss the mechanisms of these reactions and catalyst properties required to promote them with the goal of understanding how reaction conditions can be tuned to optimize catalyst activity and selectivity towards desired ethers. We close by examining the tradeoffs between catalyst selectivity, activity, stability, and reaction conditions required to achieve the most economically and environmentally favorable routes to biomass-derived ethers.

1. Introduction

The increasing global consumption of petroleum-derived fuels and chemicals has resulted in rapid generation of atmospheric CO_2, the accumulation of which has adverse effects on the global climate.[1] One strategy for lowering the overall emission of CO_2 from the combustion of petroleum-derived fuels and lubricants is to replace them with similar products derived from renewable sources.[2] This approach has the potential to be both environmentally responsible and economical, particularly if policy changes incentivize the use of non-fossil energy resources in the future.[1,2] An attractive feedstock for producing sustainable fuels and specialty chemicals is lignocellulosic biomass, because it does not compete with food feedstocks and would otherwise be considered waste.[3]

There have been many recent developments in the production of fuels and specialty chemicals from biomass.[2,4–6] Various catalytic pathways involving condensation, reduction, acetalization, and dehydration have been identified for producing liquid fuels from biomass-derived platform chemicals.[6–8] Ethers have emerged as a class of molecules with excellent properties that can be used to meet the growing demands for gasoline additives,[9–12] cetane enhancers for diesel fuel,[13–15] automotive lubricants,[16,17] and other valuable products.[18–20]

What makes ethers attractive for meeting these applications is that they can be produced from biomass-derived carbohydrates and triglycerides with a minimum consumption of molecular hydrogen, unlike the synthesis of fuels from the hydrogenation of furan-containing condensation products or aldol condensation products derived from biomass. This latter characteristic is important since currently nearly all hydrogen is produced by steam reforming of methane, a process that produces a mole of fossil-based CO_2 per four moles of H_2.

Our objective is to review recent reports of ether synthesis from biomass-derived platform molecules and understand how heterogeneous catalysts promote these reactions. To this end, we examine the roles of Brønsted and Lewis acid sites on the reaction mechanism and the role of substrate composition and structure. Our ultimate aim is to identify the combination of catalyst properties required to achieve high ether selectivity for a specified class of synthons. Meeting this objective is not easy since etherification can occur by direct etherification of alcohols and reductive etherification alcohols with aldehydes, furans, ketones, carboxylic acids, esters, and olefins. The etherification of glycerol is also discussed briefly, since several recent reviews have discussed glycerol conversion to ethers,[21,22] solketal,[23,24] acrolein,[25–29] propylene glycol,[30] polymers,[31,32] propanediols,[33,34] glycerol oxidation products,[35] fuel additives,[22,36] and other value-added products.[31,36–38] Williamson ether synthesis and other homogeneous routes are not discussed, since these processes require catalyst separation and produce salts.[19,39] Instead, we focus exclusively on the use of heterogeneous catalysts due to their ease of separation from products.

We begin by discussing the fuel and lubricant properties of ethers obtained by the etherification of biomass-derived platform molecules, and the methods for sourcing these molecules from biomass. This is followed by a discussion of ether formation via direct etherification of alcohols, reductive etherification of alcohols and carbonyl compounds, and etherification of olefins with alcohols. Through this discussion, we describe the reaction conditions and catalyst properties required for selective ether synthesis, and specifically discuss the role of cooperative effects between Brønsted and Lewis acid sites in controlling ether selectivity. Finally, we offer a roadmap for producing targeted ethers from available starting materials in high selectivity by utilizing knowledge of the effects of reactant structure, catalyst properties, and reaction conditions.

2. Applications and Fuel and Lubricant Properties of Biomass-Derived Ethers

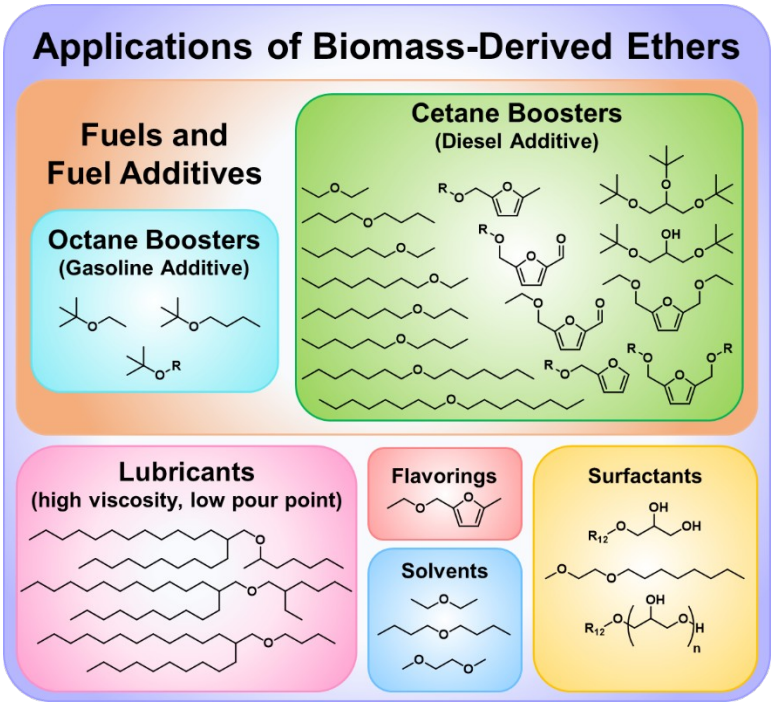


Figure 1: *Applications of selected biomass-derived ethers.*

Table 1: Representative linear alkyl ethers and selected diesel fuel properties.

Ether	Blending Cetane Number [BCN]	Blending Cloud Point [BCP °C]	Blending Cold Filter Plugging Point [BCFPP °C]
di-methyl-ether	55-66[40]		
di-ethyl-ether	>125[40]		
di-n-butyl ether	85[13]	-20[13]	-13[13]
di-n-pentyl ether	109[13]	-22[13]	-20[13]
di-n-hexyl ether	117[13]	-7[13]	-5[13]
di-n-heptyl ether	117[13]	-7[13]	-5[13]
di-n-octyl ether	118[13], 119[41]	-17[13,41]	-15[13,41]
Methyl-octyl ether	89 [14]		
Ethyl-octyl ether	100[13], 98[14]		
n-butyl-hexyl ether	94[13]		
n-heptyl propyl ether	94[13]		
Reference: diesel fuel	48–51 [14,41]	-2 to 5[41]	-4 to 3 [41]

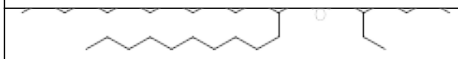
Table 2: Comparison of Lubricant Properties of PAO and C_{32} Ether (Ref. [16])							
	KV100 [cSt]	KV40 [cSt]	VI	PP °C	DSC oxidation onset T [8C]	TGA Noack [wt.%]	CCS [cP]
 11-(((2-ethylhexyl)oxy)methyl)tricosane	3.5[16]	12.0[16]	145[16]	-36[16]	206[16]	5.1[16]	769[16]
Reference: Poly-Alpha-Olefins (PAO)	4.0[16]	17.8[16]	126[16]	-75[16]	221[16]	18.8[16]	1276 [16]

Figure 1 shows some example structures of ethers synthesized from biomass-derived molecules that have properties making them suitable as diesel fuels, cetane boosters, octane boosters, automotive lubricants, and other products. Ethers that could serve as diesel are shown in **Table 1**. Symmetrical, linear ethers such as di-n-hexyl ether and di-n-octyl ether have high energy density and high cetane numbers, which allows for decreased ignition delay in diesel vehicles.[13,15,42,43] Addition of di-ethyl ether to ethanol biodiesel blends also reduces the ignition delay, exhaust gas oxygen, smoke emissions, and particulate matter.[44] Linear asymmetrical ethers such as ethyl-octyl ether and butyl-hexyl ether also have high cetane numbers and can be added to diesel blends.[13,14]

For use as gasoline additives, shorter chain branched ethers are suitable due to their high octane numbers.[10] The increased substitution of the ether results in a higher ignition delay, allowing the fuel to be used in gasoline engines, which operate at high compression ratios. An example is ethyl-*tert*-butyl ether (ETBE), which has an octane number of 112.[9] Not only can ETBE be produced from renewable sources, but it also has a higher boiling point, a lower flash point, lower blending Reid vapor pressure, and lower solubility in water than methyl-*tert*-butyl ether.[9,45] Over the years, the global consumption of ETBE for use in gasoline has increased as ETBE has excellent gasoline additive properties but has reduced environmental toxicity and improved biodegradability compared to MTBE, is less soluble in water, and utilizes renewable ethanol.[9,36,46]

Mono-ethers and di-ethers derived from furans such as 5-(ethoxymethyl)furfural-2-carboxaldehyde (EMF) and 2,5-bis(ethoxymethyl)furan (BEMF) have excellent cetane

numbers and can be added to diesel or used as a drop-in fuel.[47–49] EMF has an energy density of 8.7 kWh L^{-1}, comparable to gasoline (8.8 kWh L^{-1}) and diesel (9.7 kWh L^{-1}), and superior to that of ethanol (6.1 kWh L^{-1}).[48]

Ethers derived from biomass also have the potential to replace petroleum-derived automotive lubricants.[16,50,51] Transportation vehicles consume almost 30% of energy produced today, and of that, approximately one third is lost due to friction and wear.[52,53] This gives rise to a global demand for lubricants of around 35 million tonnes per year, with automotive lubricants accounting for about 15% of the total lubricant consumption.[54] The performance of automotive lubricants is judged by a number of criteria, including the kinematic viscosity at 40 °C and 100 °C, (KV100 and KV40, respectively), the viscosity index (VI), the pour point (PP), the oxidation stability (DSC onset T), the volatility (TGA Noack), and the cold-cranking simulator viscosity (CCS). The current synthetic automotive lubricant consists of poly-alpha-olefins (PAO), which are derived from petroleum via the oligomerization of α-olefins.[55,56] However, as shown in **Table 2**, recent reports have shown that branched ethers such as 11-(((2-ethylhexyl)oxy)methyl)tricosane have comparable lubricant properties, and can be synthesized from renewable sources.[16] Branches in the alkyl portions of ethers lower the pour point and raise the viscosity of the ether, enhancing the lubricant properties.[16,57] Other ethers such as alkylated di-phenyl ether and glycerol ethers have excellent lubricant properties.[58,59] Glycerol ethers and poly-ethers also have applications as surfactants[18,60] and fuel additives.[22] Monododecyl polyglyceryl ether (MAGEn) and multidodecyl polyglyceryl ethers produced from the etherification of glycerol with dodecanol have excellent surfactant properties.[60] Other monoether glyceryl ethers have been shown to have pharmaceutical applications such as anti-inflammatory, antibacterial, anti-tumor, and antifungal properties.[61–63] Di- and tri-*tert*-

butyl ethers are soluble in diesel fuel, and can be added as oxygenates to decrease the viscosity and cloud points.[64–67]

One of the important considerations in utilizing ethers as fuels and lubricants is their propensity to form peroxides. There is a delicate balance with peroxide formation, because some peroxide formation is beneficial for ignition properties of the fuel, but too much peroxide formation can lead to stability and safety concerns. The peroxide number is a measure of a tendency for a material to form peroxides.[68,69] Compounds are classified based upon their peroxide numbers in order to ensure safe handling. For example, diethyl ether is classified as a group B compound for peroxide formation, meaning it must be discarded or used after one year of storage.[69] On the other hand, MTBE forms peroxides more slowly than tetrahydrofuran (THF), 2-methyl-THF, and 2,5-dimethyl furan.[69] Another important consideration is the fact that the addition of oxygenates to fuel blends also impacts the exhaust emissions, lowering carbon monoxide emissions and other unregulated emissions such as benzene and 1,3-butadiene.[70] A review by Di Nicola et al. provides greater detail about emissions from ethers and organic carbonate fuel additives.[70]

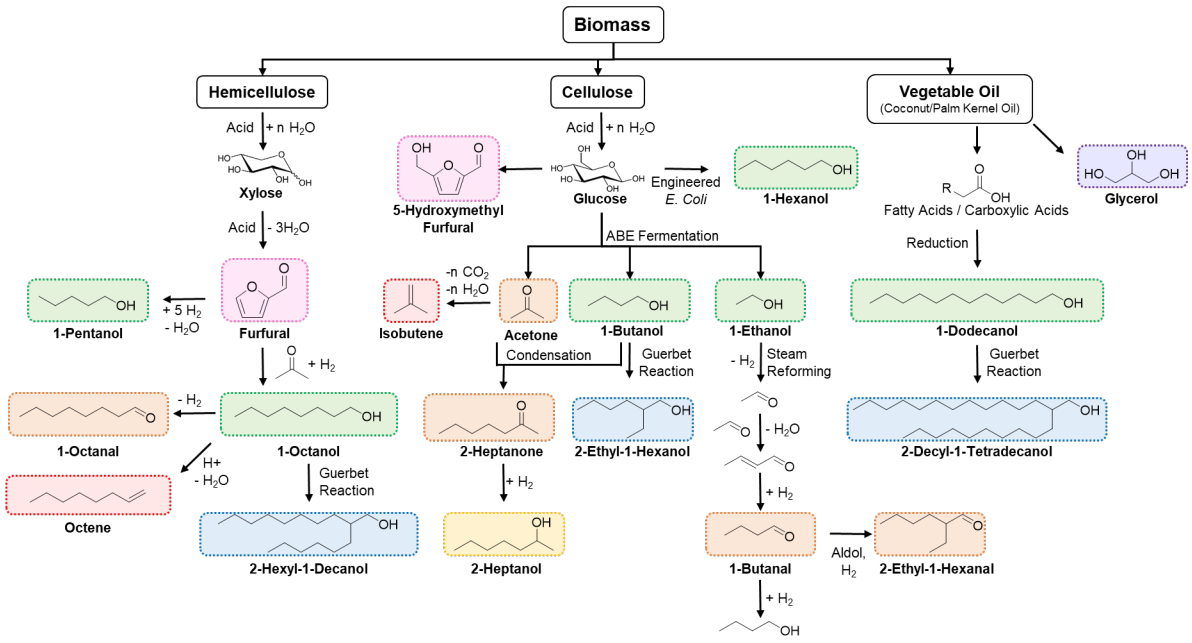
3. Platform Molecules from Biomass-Derived Feedstocks

A variety of synthons derived from the carbohydrate fraction of biomass can be used to produce ethers. These include aldehydes, ketones, alcohols, and furans. **Scheme 1** illustrates pathways for producing these synthons starting from C_5 and C_6 sugars. Recent investigations of ABE fermentation of glucose using *clostridium acetobutylicum* have shown that a mixture of butanol, acetone, and ethanol can be produced with the molar ratio of 6:3:1.[71,72] These products can be further upgraded to afford higher carbon number alcohols and ketones, such as 2-pentanone, 2-heptanone, 4-heptanone, 6-undecanone, methyl isobutyl ketone (MIBK), and others.[7,73,74] Some of these same compounds can be

prepared from furfural and 5-hydroxymethyl furfural (HMF) by the dehydration of xylose and glucose, respectively.[75–77]

Condensation of furfural with acetone in the presence of hydrogen produces 1-octanol.[78] Other linear alcohols such as 1-hexanol and 1-dodecanol can be accessed from glucose via engineered *Escherichia coli*[79] and via hydrolysis of triglycerides and fatty acids,[73] respectively. Furfural can be converted to 1-pentanol via hydrogenation to furfuryl alcohol, followed by hydrolysis to produce levulinic acid, which can then be hydrogenated to form 1-pentanol.[80,81] The carbon number of linear alcohols can be further increased via the Guerbet pathway, which affords branched alcohols such as 2-ethyl-1-hexanol, 2-hexyl-1-decanol, 2-decyl-1-tetradecanol, and others.[82] Olefins derived from biomass are also useful synthons for producing ethers. For example, isobutene can be selectively formed from acetone or ethanol over zinc oxide dispersed on zirconia in the presence of water,[83,84] or via fermentation of biomass-derived sugars.[85] Other olefins such as octene, decene, and 2-ethyl hexene can be prepared via unimolecular dehydration of biomass-derived alcohols.

Glycerol is another abundant and inexpensive biomass-derived platform chemical obtained as a byproduct of biodiesel production. Sources of triglycerides for the generation of biodiesel include various vegetable oils, waste oil products, and algae.[4,5]



***Scheme 1**: Overview of processes for deriving alcohols, aldehydes, ketones, and furans from biomass-derived feedstocks.*

4. Synthesis of Ethers from Biomass-Derived Platform Chemicals

A number of different pathways are available for obtaining biomass-derived synthons for the production of ethers, as shown in **Scheme 1**. The choice of synthetic pathway depends on the composition of the feedstock and the desired final product and selectivity. In this section, we discuss the scope of direct etherification of alcohols, the reductive etherification of alcohols with aldehydes, ketones, esters, and carboxylic acids in the presence of hydrogen, direct and reductive etherification of furanic compounds, and the etherification of olefins by reaction with alcohols. For each of these methods, we examine the reaction mechanism and the activity and selectivity of known catalysts, and discuss adjustments that can be made to the reaction conditions in order to obtain the maximum product yield.

4.1 Direct Etherification of Alcohols

Direct Etherification of Linear and Branched Alcohols

Direct etherification of alcohols over a solid-acid catalyst involves the bimolecular dehydration of two alcohols in the absence of a reducing agent to produce ether and water, as shown by the solid green arrow in **Figure 2a**. Solid-acid catalyzed etherification of alcohols in the liquid phase enables the production of ethers in a single phase, and can be performed in the presence of either a solvent, or using the alcohol as the solvent itself. One of the advantages of the latter approach is that it eliminates the need for solvent separation. Various polymeric resins, metal oxides, and other solid acid catalysts are effective for the direct etherification of linear alcohols. The competing reaction in the presence of an acid catalyst is unimolecular dehydration of the alcohol to form an olefin, a product that is thermodynamically favored over ether formation at elevated temperatures. For example, **Figure 2b** shows that the unimolecular dehydration of 1-dodecanol is thermodynamically favored over formation of di-dodecyl ether at temperatures above ~ 350 K.[86] Other linear and branched alcohols such as 1-hexanol, 2-hexanol, and 3-hexanol follow the same trend of increasing thermodynamic preference for unimolecular dehydration with increasing temperature.[87] Olefins are not desired in fuel and lubricant blends because they tend to form gums.[88] Moreover, as shown in **Figure 2a**, primary olefins can rehydrate to form secondary alcohols, which can result in the formation of branched ethers, which change fuel properties such as the cetane number.[89] Olefins can also oligomerize to form larger olefins and coke, resulting in catalyst deactivation. Other challenges with direct etherification are associated with the inhibiting effects of water and ether on reaction rates and ether selectivity.[86,90]

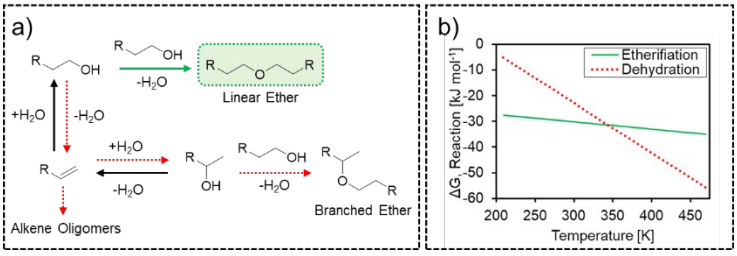


Figure 2: *a) Reaction pathway for acid catalyzed direct etherification of alcohols (solid green arrow) and side product formation (dashed red arrows), b) Gibbs free energies of formation for 1-dodecanol etherification (green, solid) and unimolecular dehydration (red, dashed).*

To achieve high ether selectivity, the catalyst must either operate at temperatures below the temperature at which unimolecular dehydration becomes thermodynamically preferred, or have an intrinsic selectivity for etherification versus dehydration. The most desirable catalyst has high activity (turnover number), low activation energy for etherification, high selectivity for etherification, high thermal stability, and reusability. **Table 3** lists a number of heterogeneous catalysts and reaction conditions that are effective for the direct liquid-phase etherification of linear alcohols to symmetrical ethers. The reported solid-acid catalysts employed for direct etherification include Brønsted acid catalysts, Lewis acid catalysts, and catalysts with both Brønsted and Lewis acid sites. Among these are acidic resins, metal oxides, and other solid-acid catalysts. The desired acid strength for etherification is not clearly defined, with some studies suggesting that etherification requires high acid site density and low acid strength,[13] and others suggesting that acid strength only affects rates but not selectivity.[91] Published studies suggest that bimolecular etherification of alcohols requires that two alcohol molecules interact favorably with one another. This condition can be achieved either by using a catalyst with strong acid sites located within large pores that provide a high local concentration of alcohol, or by using a catalyst with two proximate active sites for adsorption of both alcohols.

Table 3: Synthesis of symmetrical ethers via direct etherification of aliphatic alcohols catalyzed by solid acids.

Entry	Reactant	Catalyst	Temperature [K]	Selectivity to di-Ether	Turnover Number [$r_{0,\ ether,\ eq.}$ (mol/(h eq H^+)]	E_A, Etherification [kJ/ mol]	E_A, Dehydration [kJ/mol]	Ref.
1	1-pentanol	Amberlyst 70	423	98	2.7	114.7±5.4		[92]
2	1-pentanol	NR50	423	98	6.5	109.3±3.4		
3	1-pentanol	H-BEA 25	423	89	1.5	121.2±1.7		
4	1-pentanol	Amberlyst 36	423	86	3.9	110.1±2.1		
			393	92	0.4			
5	1-pentanol	CT- 224	423	97	3.1	119.1±4.3		
			393	97	0.2			
6	1-pentanol	DL-H/03	423	96	3.2	110.6±2.6		

7	1-pentanol	DL-I/03	423	83	3.4	113.4±6.5		
8	1-pentanol	Dow 50	423	98	2.7	114.7±1.5		
			393	100	0.3			
9	1-hexanol	Amberlyst 70	423	97.7		108 ±7		[93]
10	1-hexanol	Amberlyst 70	463	86.9				
11	1-hexanol	Nafion NR50	423	97.9		118 ±6		
12	1-hexanol	Nafion NR50	463	93.4				
13	1-hexanol	Zeolite H-BEA-25	463	88.8		148 ±11		
14	1-hexanol	Amberlyst 70	423–463 K			125 ± 3*,121 ± 3**		[94]
15	1-octanol	Zeolite BEA SiO_2:Al_2O_3 75:1	390-430 K			149.8		[95]
16	1-hexanol	WO_x/ZrO_2	393	>99	1.3	127 ± 1	157 ± 13	[96]
17	4-methyl-1-pentanol	WO_x/ZrO_2	393	>99	1.2	127 ± 3	158 ± 10	
18	3-methyl-1-pentanol	WO_x/ZrO_2	393	87	1.0	127 ± 1	155 ± 1	
19	2-methyl-1-pentanol	WO_x/ZrO_2	393	<1		133 ± 11	124 ± 2	
20	2-hexanol	WO_x/ZrO_2	393	<1		127 ± 10	114 ± 5	
21	2-methyl-2-pentanol	WO_x/ZrO_2	393	<1		--	100 ± 12	
22	1-heptanol	WO_x/ZrO_2	393	>99	1.2	127 ± 2	155 ± 11	
23	1-octanol	WO_x/ZrO_2	393	>99	1.4	126 ± 3	154 ± 1	
24	1-nonanol	WO_x/ZrO_2	393	>99	1.6	127 ± 1	155 ± 7	
25	1-decanol	WO_x/ZrO_2	393	>99	1.6	126 ± 12	155 ± 11	
26	1-undecanol	WO_x/ZrO_2	393	>99	1.5	126 ± 4	154 ± 5	
27	1-dodecanol	WO_x/ZrO_2	393	94	1.4	127 ± 7	155 ± 10	[96] [86]
28	1-dodecanol	Amberlyst 70	393	97	0.7			[86]
29	1-dodecanol	Nafion NR50	393	98	1.9			
30	1-dodecanol	Zeolite BEA	393	61	0.2			
31	1-dodecanol	Amberlyst 15	393	46	0.1			
32	1-dodecanol	Amberlyst 36	393	65	0.3			
33	1-hexanol	η-Alumina	523	61 ± 3				[13]
34	1-heptanol	η-Alumina	523	71 ± 3				
35	1-octanol	η-Alumina	523	65 ± 3				
36	1-nonanol	η-Alumina	523	73 ± 1				
37	1-decanol	η-Alumina	523	66 ± 3				
38	1-dodecanol	η-Alumina	548	50 ± 6				
*Fit using a Langmuir-Hinshelwood model, ** Fit using a modified Eley-Rideal model								

Brønsted acid catalysts involve proton donor sites. Polymeric resins such as Amberlyst and Nafion contain Brønsted-acidic H atoms attached to sulfonic acid groups. Amberlyst 70 is a macroporous sulfonic styrene-di-vinyl benzene (DVB) resin catalyst with a surface area of 36 m^2 g^{-1} and an acid site concentration of 3 eq H^+ kg^{-1}.[97] Nafion NR-50 is a sulfonated Brønsted-acidic catalyst that has a fluorinated backbone, as shown in **Figure 3b**. Amberlyst 70 and Nafion NR-50 stand out as active and selective Brønsted acid catalysts for the direct etherification of linear primary alcohols 1-octanol, 1-hexanol, and 1-pentanol.[92–94] **Table 3**, entries 1-2, 5-6, 8-9, and 11, show that Amberlyst 70, Nafion NR-50, as well as resins Purolite CT-224, Amberlyst DL-H/03, and Dow 50 are highly selective for the synthesis of symmetrical ethers from linear alcohols at 423 K, which is above the critical

temperature at which unimolecular dehydration is thermodynamically favored. Nevertheless, as the temperature increases, the rates increase but the ether selectivity decreases for many of the catalysts.[13,86,93]

Polymeric resins are limited by intraparticle mass transfer, thermal stability, and ease of regeneration. For example, Amberlyst 70 and Nafion NR50 are unstable above 463 K,[92,98] and other resins such as Amberlyst 15 are even less thermally stable and are not recommended for use above 393 K. Moreover, regeneration of resin catalysts requires solvents and separation processes that consume energy and generate additional waste.

In a study of octanol etherification over gel-type and macroreticular polymeric resins, the best selectivity to di-n-octyl ether was observed for catalysts with a low degree of crosslinking.[41] Resins with low crosslinking degree (Amberlyst 39 and Amberlyst 70) were also found to be more selective for the etherification of 1-hexanol and 1-pentanol than catalysts with higher degrees of crosslinking with DVB.[99] As shown in **Figure 3a**, a high degree of DVB crosslinking (pink) results in more confined pore volumes and thus less accessibility to the active sites by long chain alcohols. Solvent effects on polymer swelling are also important, as they introduce mass transfer limitations due to variation in the number of accessible acid sites with time.[100] Cooley et al. have examined the microscopic and bulk swelling behavior of Nafion in mixtures of water and ethanol using small angle X-ray diffraction and optical microscopy.[101] While the microscopic swelling decreased with increasing ethanol content, the bulk swelling increased dramatically with increasing ethanol content. The authors concluded that the ethanol plasticizes the fluorocarbon matrix in Nafion, which allows the ionic material to form numerous smaller clusters compared to membranes swollen solely with water.[101] A lower degree of crosslinking generally results in greater swelling of the resins, and as a result, improved accessibility of the active centers for etherification.

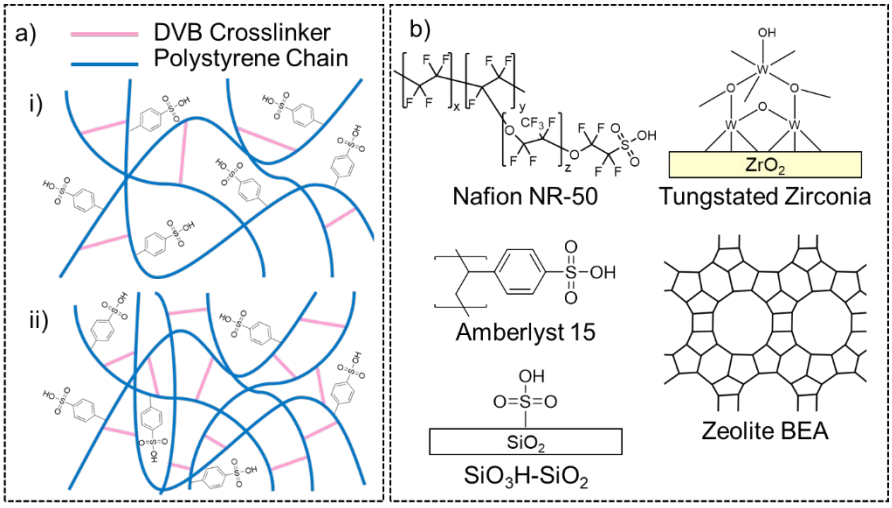


***Figure 3**: a) Sulfonated polystyrene resin catalysts with low (i) and high (ii) crosslinking degree, b) Solid-acid catalysts of interest for etherification and dehydration.*

Zeolites, such as H-BEA pictured in **Figure 3b**, are also strong acids, but have superior thermal stability to resins, and can be regenerated easily by calcination. The Brønsted acid site in zeolites is generated when a silicon atom (4^+) in the framework structure is replaced by an aluminum atom (3^+), requiring a proton to balance the charge; thus, the higher the Al/Si ratio, the higher the Brønsted acid site density. However, zeolites tend to catalyze undesired side reactions, such as unimolecular dehydration, more rapidly than etherification, and produce coke, which results in catalyst deactivation.[102] **Table 3** shows that the selectivity to di-dodecyl ether for dodecanol etherification over H-BEA at 393 K is only 61%, compared to 97% and 98% for Amberlyst 70 and Nafion NR-50, respectively. Moreover, while Amberlyst 70, Nafion NR-50, and tungstated zirconia exhibit similar activation energies for 1-hexanol etherification (108 - 127 kJ mol^{-1}) the activation energy for the H-BEA-25 is significantly higher (148 ± 11 kJ mol^{-1}).[93,94,96] A study of HUSY suggests that its higher surface hydrophilicity leads to the retention of a portion of the byproduct water inside the pores, thereby reducing its etherification activity at low temperatures.[42,103] If high reaction temperatures and ease of catalyst regeneration are

desired at the expense of selectivity, then zeolites such as H-BEA could be employed as solid Brønsted acids.

Another class of solid acids are Lewis-acidic catalysts such as zirconia, alumina, silica, and aluminosilicates. At 393 K, Lewis-acidic zirconia, gamma-alumina, mesostructured silica, and mesostructured aluminosilicate, have all been shown to be inactive for the liquid phase etherification of 1-dodecanol.[86] While η-alumina has been shown to be active for etherification of C_6-C_{12} linear alcohols at 523 K (**Table 3**, entries 33-38), it is not highly selective.[13] We have shown that tungstated zirconia, a solid acid catalyst containing both Brønsted and Lewis acid sites, promotes the direct etherification of primary linear alcohols ranging from hexanol to dodecanol, with ether selectivities of over 94% at 393 K.[86,96] Tungstated zirconia is also highly active. The turnover frequency (TOF) normalized per Brønsted acid site at 393 K for 1-hexanol etherification sites is 1.3 s^{-1}, which is significantly higher than the TOFs for the etherification of 1-pentanol over Amberlyst 70, Nafion NR50, Zeolite HBEA 25, Amberlyst 36, CT-224, DL-H/03, DL-I/03, and Dow 50 (0-0.4 s^{-1}) at the same temperature and reactant concentration.[92] We hypothesize that tungstated zirconia is an effective catalyst for the etherification of alcohols because Brønsted and Lewis acid sites on the surface of the catalyst work cooperatively to promote bimolecular etherification over unimolecular dehydration, as illustrated in **Figure 4**.[86] In contrast to acidic resins, tungstated zirconia exhibits high thermal stability and facile catalyst regeneration, making it an excellent choice of catalyst for the synthesis of symmetrical linear ethers.

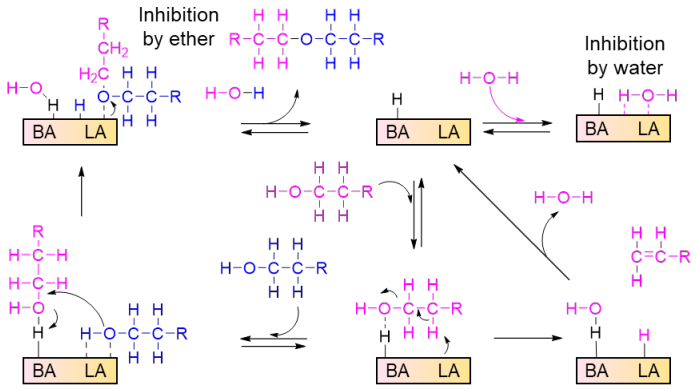


***Figure 4**: Mechanism of direct etherification and dehydration of linear alcohols over cooperative Brønsted (BA) and Lewis (LA) acid sites of tungstated zirconia (adapted from [86]).*

In addition to forming linear symmetrical ethers, direct etherification of alcohols can be used to synthesize asymmetrical ethers such as ethyl-octyl ether. As shown in **Table 4**, Amberlyst 121, Dowex 50Wx2, and CT244 are most selective for producing ethyl-octyl ether from equimolar feed ratios of ethanol and octanol,[14,104] although symmetrical ethers are still formed. As shown in **Table 3**, the alkyl chain length of the alcohols does not have a significant effect on the ether selectivity nor the activation energies for etherification and dehydration over tungstated zirconia (entries 22-27) and Amberlyst 70 (entries 1, 9, and 28). Because of the negligible changes in kinetics with increasing linear alcohol length, mixtures of linear alcohols couple in a nearly statistical manner. Our recent study of alcohol etherification over tungstated zirconia has shown that equimolar mixtures of 1-hexanol, 1-heptanol, 1-octanol, 1-nonanol, 1-decanol, 1-undecanol, and 1-dodecanol produce a nearly statistical distribution of C_{12}-C_{24} ethers at 393 K.[96] In another study, Walsh et al. have demonstrated that short-chain (C_1-C_5) alcohols couple to form a nearly statistical distribution of ethers over Nafion SAC-13 and Purolite CT-175 in the presence of supercritical CO_2.[105] Thus, the cross-coupling of alcohols is desirable for producing mixtures of ethers for diesel blends, but not when pure asymmetrical ether products are desired because homocoupling of alcohols will also occur.

Table 4: Synthesis of ethyl-octyl ether via direct etherification of ethanol and octanol catalyzed by solid acids.

Entry	Mol. Octanol: Ethanol	Catalyst	Temperature [K]	Selectivity to Ethyl Octyl Ether	Ref.
1	1:1	Amb 15	423	17.1*	[104]
2	1:1	Amb 35	423	15.2*	
3	1:1	Amb 16	423	21.9*	
4	1:1	Amb 36	423	20.6*	
5	1:1	Amb 39	423	35.1*	
6	1:1	Amb 70	423	42.8*	
7	1:1	CT 244	423	39.3*	
8	1:1	Amb 31	423	36.8*	
9	1:1	Dowex 50Wx4-50	423	40.8*	
10	1:1	Amb 121	423	45.7*	
11	1:1	Amb 121	423	30.3 from EtOH, 69.0 from Octanol	[14]
12	1:1	Amb 70	423	25.5 from EtOH, 69.4 from Octanol	
13	1:1	CT244	423	26.2 from EtOH, 72.4 from Octanol	
14	1:1	Dowex 50Wx2	423	26.1 from EtOH, 73.7 from Octanol	

*(Moles of ethanol reacted to form ethyl octyl ether + moles of octanol reacted to form ethyl octyl ether)/moles of ethanol and octanol reacted*100%

The synthesis of ethyl-hexyl ether and ethyl-octyl ether has also been investigated using diethyl carbonate as an ethylating agent, where two moles of alcohols are added to one mole of diethyl carbonate to produce two moles of asymmetrical ethers, one mole of H_2O, and one mole of CO_2.[106–108] Carbonates such as dimethyl and diethyl carbonate are now considered “green reagents” because they be prepared from the catalytic oxidative carbonylation of methanol or ethanol with CO_2 rather than from phosgene.[12,109] But, Tejero et al. compared ethyl-octyl ether synthesis via etherification of octanol with diethyl carbonate and via direct etherification of ethanol and octanol, and concluded that direct etherification was the most effective method of producing ethyl-octyl-ether over acidic ion-exchange resins.[107] The authors found that at long reaction times, the yields of ethyl-octyl ether were similar for the two synthesis methods, but at early reaction times, direct etherification of ethanol and octanol resulted in higher rates of ethyl-octyl ether formation. Furthermore, they suggest that direct etherification is preferable to etherification of alcohol with a carbonate because it does not produce CO_2.[107]

Direct etherification of branched alcohols in the absence of solvent has also been investigated over tungstated zirconia. Our studies concluded that primary alcohols with

carbon branches at least three carbons away from hydroxyl group are highly selective to ether formation, but as the carbon branch approaches the alpha and beta carbons of the alcohol, the selectivity to ether drastically drops, as shown in **Table 3** (entries 16-21) and illustrated in **Figure 5**.[96] Other studies have also shown that substituted alcohols, such as 2-butanol, readily undergo unimolecular dehydration over tungsten oxide catalysts, while etherification is negligible.[110]

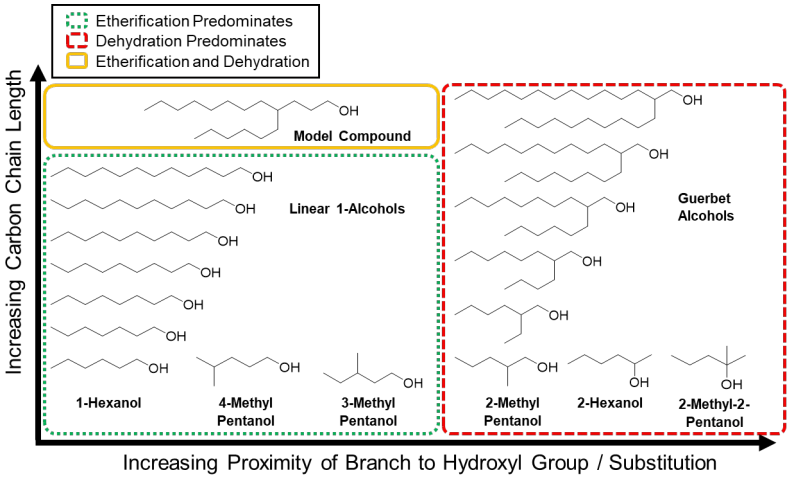


***Figure 5**: Various alcohols and their tendencies to undergo etherification or dehydration over tungstated zirconia at 393 K from ref.[96]*

In our previous study of the kinetics and mechanism of etherification and dehydration over tungstated zirconia, measurements of kinetic isotope effects revealed that the rate-limiting step for unimolecular dehydration is the cleavage of a β-carbon hydrogen bond of the alcohol.[86] Kinetic isotope studies of ethanol dehydration over γ-Al_2O_3 have also suggested that this is the rate-limiting step.[111,112] The addition of alkyl branches to the alpha and beta carbons of the alcohol enhances the stability of the carbocation intermediate involved in the unimolecular dehydration, thereby promoting olefin formation. This evidence, coupled with the fact that activation barriers for dehydration decrease with increasing substitution of the alcohol,[86,112] suggests that direct

etherification is limited to primary alcohols with no branches or with branches located a sufficient distance from the hydroxyl group.

Measurements of the kinetics of ethanol dehydration and etherification in the gas phase have also revealed important considerations concerning the inhibition by ethanol-water dimers, as well as more complicated dimer and trimer species.[90,111,113–115] The inhibition by water was observed for primary linear alcohol etherification over tungstated zirconia, as shown in **Figure 4**;[86] but, it was also observed for 1-octanol etherification over BEA,[95] and for 1-pentanol etherification over Amberlyst 70.[97] The removal of water is thus an important consideration for improving selectivity towards ethers across a variety of catalysts, particularly if the reaction is operated in a batch process at high conversions. In this connection, we note that Tejero et al. have found that water removal during the etherification of 1-pentanol over Purolite CT-244 by distillation improved ether selectivity.[116]

Ether selectivity can also be improved by eliminating both external and internal mass transfer limitations. In addition to considering the molecular size of adsorbing species and swelling of pore sizes caused by alcohols and solvent (if the solvent is different than the alcohol), external mass transfer can be improved by operating at high stirring rates, whereas small particle sizes reduce the effects of internal mass transfer. Improper mixing hinders bimolecular interactions of alcohols, especially for alcohols with long chain lengths, such as 4-hexyl-dodecanol (**Figure 5**), resulting in a decreased selectivity with increasing chain length due to external mass-transfer limitations.[13,96]

The preceding discussion suggests that catalysts with both large pore volumes and small particle sizes enable selective ether synthesis via direct etherification from a wide variety of alcohols. Consistent with this conclusion, a recent study of ethanol dehydration

over the metal organic framework MOF UIO-66, which contains nodes in the form of a Zr_6O_8 cluster, demonstrated that the catalyst exhibits 100% selectivity to diethyl ether at 473-523 K.[114] The authors suggest that the key to achieving high ether selectivity is the breaking of node-linker bonds, which forms defect sites proximate to open sites that facilitate effective bond formation between the alcohols. The authors found that the rate of etherification was three times greater for MOF UiO-66 (200 nm particle diameter) than for MOF UiO-67 (800 nm particle diameter), suggesting that transport limitations in the pores are significant.[114] In practice, though, this catalyst may not be suitable for selective ether formation because while vacancy sites produce more catalytically active sites, they contribute to a loss of crystallinity and, thus, stability.[114]

In summary, in order to achieve high yields of ethers from alcohols via direct etherification, a balance must be struck between catalyst selectivity, activity, and thermal stability. Moreover, the reactor in which etherification is carried out must be well mixed and water produced by the reaction should be separated from the reactant mixture. Catalysts with confined spaces such as zeolites and resins with a high degree of crosslinking exhibit lower selectivity to ether, suggesting that pore confinement isolates alcohols and facilitates unimolecular dehydration. Achieving a high local concentration of alcohols at the catalyst surface is necessary to promote biomolecular etherification. This can be achieved either using Brønsted acid catalysts with large pores that swell up in the presence of the solvent, such as Amberlyst 70, or through adsorption of alcohols onto catalysts containing proximate Brønsted and Lewis acid sites that facilitate the cross-coupling reaction, as occurs for tungstated zirconia. Still, the method of direct etherification is only applicable for producing symmetrical ethers from linear alcohols or blends of asymmetrical and symmetrical ethers from a feed composed of a mixture of linear alcohols. If high selectivities of linear asymmetrical ethers or ethers with branches

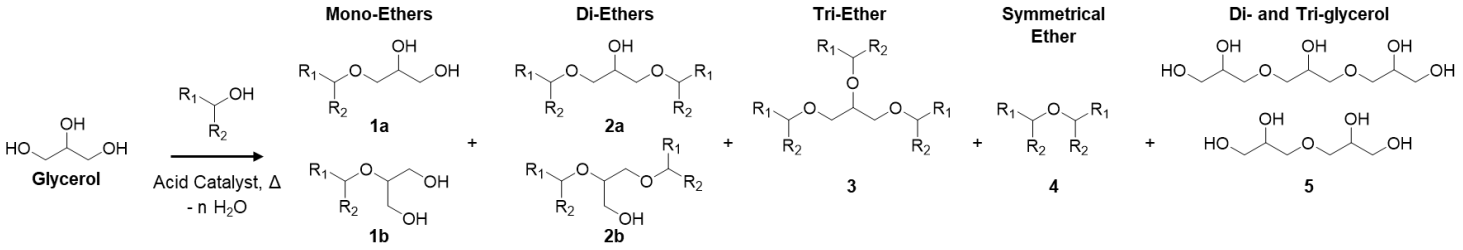
closer than three carbons away from the hydroxyl group are desired, the method of reductive etherification of an alcohol and an aldehyde or ketone is preferred. This method is discussed in **Section 4.2**.

Synthesis of mono-, di-, and tri- ethers via the direct etherification of glycerol and polyols with alcohols

Glycerol is an inexpensive byproduct of biodiesel production, and has emerged as an attractive platform molecule for the production of fuels and specialty chemicals. The valorization of glycerol through acetalization, dehydration to acrolein, conversion to 1,3-propanediol, and other methods has been studied and reviewed extensively; therefore, we will only highlight a few examples of glycerol valorization to fuels and lubricants via direct etherification using solid-acid catalysts.

Brønsted acid catalysts such as Amberlyst 70, Amberlyst 15, Amberlyst 35, sulfated zirconia, sulfonated silica, and zeolite H-BEA are effective for catalyzing the etherification of glycerol with a variety of alcohols in the liquid phase.[18,61,117–122] **Table 5** illustrates a number of examples of solid-acid catalyzed direct etherification of glycerol with alcohols. In general, the major product for the mono-ether is **1a**, whereas **1b** is the minor product formed by the more sterically difficult etherification of the middle hydroxyl group of the glycerol. Similarly, **2b** is the minor product for the di-ethers. The tri-ether **(3)** is a result of etherification of each of the hydroxyl groups of glycerol with alcohols. The bimolecular etherification of two alcohols (**4**) as well as the oligomerization of glycerol (**5**) also occurs. Notably, in the case of ethanol etherification with glycerol, the side reaction of diethyl ether formation did not have a significant effect on the rates of formation of the desired products.[123] In order to maximize yields of mono-, di-, and tri-glycerol ethers, it is important to consider the effects of the catalyst properties, alcohol structure, temperature, and water removal in order to optimize the kinetics.

Table 5: Scope of some ethers that can be produced from the direct etherification of glycerol with alcohols.



Entry	Catalyst	Temp. [K]	Time [h]	Alcohol [A]	Glycerol:A [mol]	Conversion [%]		Yield [%]					Ref
						Glycerol	Alcohol	1a + 1b	2a +2b	3	4	5	
1	Amberlyst 70 (10 wt%)	403	24	1-dodecanol	1	57	0	0	-	-	-	25	[18]
2	Amberlyst 70 (10 wt%)	403	24	1-dodecanol	4	36	5	5	-	-	-	25	[18]
3	Amberlyst 70 (10 wt%)	403	24	1-butanol	4	17	26	26	-	-	-	4	[18]
4	Amberlyst 70 (10 wt%)	403	24	1-pentanol	4	13	22	22	-	-	-	4	[18]
5	Amberlyst 70 (10 wt%)	403	24	1-hexanol	4	11	13	13	-	-	-	4	[18]
6	Amberlyst 70 (10 wt%)	403	24	1-octanol	4	36	5	5	-	-	-	6	[18]
7	SiO_2–SO_3H (1.7 mol%)	353	7	1-phenylpropan-1-ol	1	88	NA	76	12	-	NA	-	[61]
8	SiO_2–SO_3H (1.7 mol%)	353	48	1-dodecanol	NA	0	0	-	-	-	-	-	[61]
9	SiO_2–SO_3H (2.5 mol%)	353	39	oct-2-en-1-ol	NA	NA	NA	61	-	-	-	-	[61]
10	SiO_2–SO_3H (1.7 mol%)	353	19	benzyl alcohol	NA	NA	NA	76	-	-	-	-	[61]
11	Amberlyst 35	383	2	benzyl alcohol	~0.33	100	NA	~40	~20	~2	~30	-	[117]
12	K-10 montmorillonite	383	2	benzyl alcohol	~0.33	100	NA	~40	~3	~0	~55	-	[117]
13	Zeolite Beta	383	2	benzyl alcohol	~0.33	100	NA	~55	~2	~0	~40	-	[117]
14	Sulfated Zirconia	413	6	benzyl alcohol	1	NA	~70	~25	~25		~20	-	[118]
15	Amberlyst 15 (1.2 wt%)	343	6	*tert*-butanol	4	NA	NA	36.6 [b]	13.7 [b]	0	4.9[a,b]	-	[119]
16	Amberlyst 15	343	6	isobutanol	0.25	100	NA	8.3	60.4	31.3			[120]
17	Amberlyst 15	343	6	*tert*-butanol	0.25	78.9	NA	56.5	21.9	0.4			[121]
18	Amberlyst 15	343	6	1-butanol	0.25	0	NA	0	0	0	-	-	[122]
19	Amberlyst 15	433	6	1-butanol	0.25	85.1	NA	70.0	0.4	0.09	-	-	[122]
20	Amberlyst 15	393	6	ethanol	~0.1	0	NA	-	-	-	-	-	[123]
21	Amberlyst 15	413	6	ethanol	~0.1	0	NA	-	-	-	-	-	[123]
22	Amberlyst 15	433	6	ethanol	~0.1	32	NA	32	0	0	-	-	[123]
23	DBSA	403	24	1-dodecanol	4	26	72	10	9	-	62	-	[18]

[a] selectivity to isobutene, [b] product distribution (wt%), with remainder 28.6 wt% *tert*-butanol and 6.4 wt% glycerol

To synthesize mono-, di-, and tri- ethers of glycerol with linear alcohols, one must consider the tradeoff between etherification activity and selectivity. For the etherification of glycerol with ethanol over Amberlyst 15 shown in **Table 5**, entries 20-22, no reaction occurred below 433 K.[123] While this reaction is highly selective to the mono-ether, the catalyst is not reusable, as Amberlyst 15 is unstable above 393 K. Similarly, the etherification of glycerol with butanol over Amberlyst 15 is active at 433 K, reaching a

mono-ether yield of up to 70% at a glycerol conversion of 85.1%, but is not active at 343 K, as shown in **Table 5**, entries 18-19.[122] Therefore, for these reactions, it is recommended that a more thermally stable catalyst such as Amberlyst 70 or a metal oxide is used, since high temperatures are required.

For the synthesis of glycerol ethers using alcohols such as 1-dodecanol and 1-octanol, there are additional challenges due to mass transfer limitations introduced by the poor solubility of long chain alcohols in glycerol. As shown in **Table 5**, entry 8, a temperature of 353 K is insufficient for etherification of dodecanol with glycerol over sulfonated silica, a catalyst that is active under the same conditions for the etherification of glycerol with benzyl alcohol to produce mono-ether (entry 10).[61] Adding a surfactant promotes etherification of glycerol with long-chain alcohols such as dodecanol in the liquid phase to improve solubility. For example, Jérôme et al. have used dodecylbenzene sulfonic acid (DBSA) to enable emulsification of the reaction medium, which resulted in yields of monododecyl glycerol ethers of 30% at 403 K, as shown in **Table 5**, entry 23.[18] De Campo et al. have also demonstrated that using a well-tuned amphiphilic copolymer PSt-PSSA, a surfactant acid catalyst grafted on silica, significantly increased ether formation from dodecanol and glycerol by facilitating better contact between the two reactants.[60]

Amberlyst 70 and sulfonic acid supported on silica are effective for the synthesis of mono-ethers from linear and benzyl alcohols, as demonstrated by **Table 5**, entries 2-7, 9, and 10.[18,61] Amberlyst 15 is effective for producing di- and tri-ethers from the reaction of glycerol with isobutanol to produce diesel additives, as demonstrated by **Table 5** entry 16. [120] If high yields of di- and tri-ethers are desired, the water must be removed during the synthesis to increase the conversion. Frusteri et al. used a membrane to selectively remove water and shift the equilibrium of the reaction towards the formation of poly-ethers for the etherification of glycerol with *tert*-butyl alcohol[119,121] as well as butanol.[122]

De Campo et al. have also used a water removal process to increase selectivity of alkyl-poly-gylceryl ether (AGEM) during the etherification of dodecanol and glycerol over sulfonated silica catalysts, leading to yields of AGEM > 80 % at 423 K.[60]

The effectiveness of strong solid Brønsted acids for glycerol etherification reactions depends on several catalyst properties including hydrophilicity, accessibility, and thermal and mechanical stability. In a study of glycerol etherification with ethanol over solid acid catalysts, Fajula et al. suggested that the hydrophobicity of the catalyst is an important factor in determining etherification activity. The authors found that strongly hydrophobic catalysts were less effective for glycerol etherification because they were unable to allow for the adsorption of glycerol; however, hydrophilic catalysts that adsorb glycerol too strongly also resulted in lower etherification rates.[123] For example, Nafion NR50, a hydrophobic strong Brønsted-acidic fluorinated sulfonated polystyrene resin, did not catalyze the etherification of glycerol but it did catalyze bimolecular etherification of the alcohol.[123] The authors also studied the etherification of glycerol with ethanol over a series of zeolites with varying silica to alumina ratios and found that there is a tradeoff between the silica to alumina ratio and the etherification activity. As the aluminum content was increased, a higher density of acid sites were generated, which contributed to an increase in the etherification rate; however, the surface also became more polar, thus decreasing the glycerol etherification rate due to the increased hydrophobicity. The authors found that a compromise could be achieved with zeolites with intermediate aluminum contents (Si/Al ratios around 25), which were the most effective for glycerol etherification. Amberlyst resins 15 and 35 were also effective for glycerol etherification at 433 K, with selectivities towards mono-ethoxy glyceryl ethers of 100% and 90% (remainder di-ethers) at glycerol conversions of 32% and 52%, respectively. While the zeolites were found to be active at 473 K and are more thermally stable, they also

exhibited lower selectivity. The tradeoff between selectivity and thermal stability of the catalyst is thus a concern for direct etherification of glycerol, as well as for primary alcohols as discussed earlier, since higher temperatures not only increase rates of alcohol but also catalyze the unimolecular dehydration of alcohols to olefins, especially for substituted alcohols like isobutanol, 2-propanol, and for Guerbet alcohols.

The accessibility of acid sites also plays a fundamental role in promoting catalyst activity, as it has been found that catalysts with larger pore volumes are more active.[119] The kinetics of glycerol etherification with alcohols depends greatly on the reactant concentration and temperature. For example, Frusteri et al. found that the molar ratio of alcohol to glycerol for *tert*-butanol etherification with glycerol over Amberlyst 15 does not affect the product distribution.[119] However, Jaworski et al. reported that for the etherification of benzyl alcohol with glycerol over sulfated zirconia, mono-ether and di-ether formation rates were first order in benzyl alcohol concentration, but benzyl alcohol self-condensation was second order with respect to benzyl alcohol.[118] They also found that benzyl-alcohol self-condensation had a higher activation energy than mono- and di-ether formation, suggesting an explanation for the higher selectivity towards cross-etherification at lower temperatures.[118]

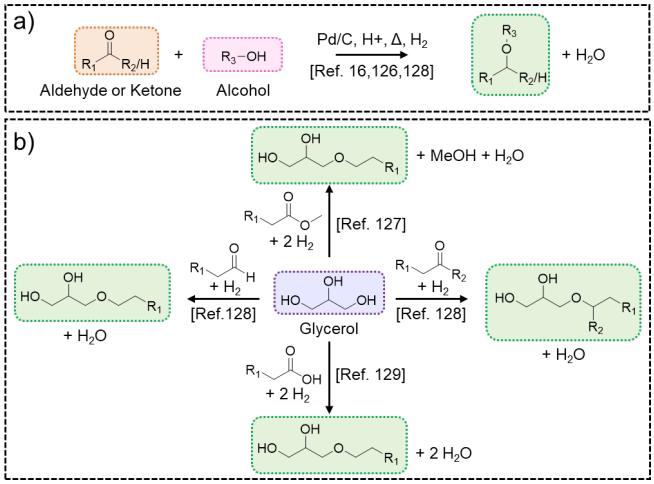
Several approaches can be considered to address the tradeoff between activity and selectivity that occurs with increasing temperature of etherification. Batch reactors coupled with water permselective membranes can enhance ether selectivity by removing water. As temperature is increased, membrane effectiveness increases, but unimolecular dehydration of alcohols also increases.[122] Therefore, developing stable membrane separators that are effective at lower temperatures could improve ether selectivity. Further modification of the acid-base properties of the catalysts could also enable tuning of product distributions for glycerol etherification. For example, Weckhuysen et al. have

found that the rates of etherification of glycerol to produce di- and tri-glycerols over CaO, SrO, and BaO at 533 K increase with increasing basicity of the catalyst.[124] Understanding the role of Lewis acidity and basicity could enable the development of catalysts that optimize glycerol adsorption and reaction to form ethers.[125]

4.2 Reductive Etherification of Alcohols with Aldehydes, Ketones, Esters, and Carboxylic Acids

Asymmetrical ethers with and without branching are desirable as cetane boosters and as automotive lubricant base oils. As noted above, direct etherification of a branched alcohol and a linear alcohol is ineffective for the synthesis of asymmetrical branched ethers, because substituted alcohols and alcohols with carbon chain branches on the alpha and beta carbons readily undergo dehydration. This method is also relatively ineffective for the synthesis of asymmetrical linear ethers because the alcohols will self-couple to generate symmetrical ethers. Reductive etherification of alcohols with aldehydes and ketones provides an alternative approach for producing high yields of symmetrical and asymmetrical ethers with a variety of structures and degrees of carbon chain branches.[16,19,126]

Scheme 2a shows a general scheme for the reductive etherification of a carbonyl compound with an alcohol to produce an asymmetrical ether. The overall reductive etherification reaction of an alcohol with an aldehyde or ketone to produce an ether and water occurs in the presence of H_2, a catalyst for H_2 activation, such as carbon-supported palladium, and an acid catalyst.



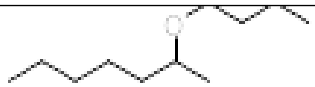
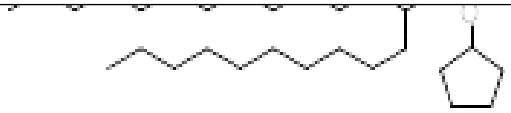
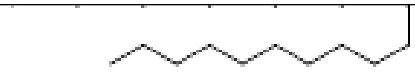
Scheme 2: *a) Reductive etherification of carbonyl compounds with alcohols, b) Reductive etherification of glycerol with aldehydes, ketones, carboxylic acids, and fatty acid methyl esters.*

The heterogeneously catalyzed reductive etherification of aldehydes and ketones with an alcohol allows for flexibility in the choice of both reactants, enabling the utilization of biomass-derived alcohols with carbon chain branches produced via the Guerbet reaction, as well as carbonyl compounds obtained from a variety of biomass sources, as shown in **Scheme 1**. This method is therefore suitable for the selective synthesis of symmetrical or asymmetrical primary or secondary ethers. Reductive etherification of carbonyl compounds can also be performed with polyols such as glycerol,[127–129] to produce surfactants, fuel additives, and other value-added products. Drawbacks of the reductive etherification synthesis involve the requirement of hydrogen, and the use of precious metal catalysts. In addition, there are some limitations to the scope of aldehydes for the synthesis; for example, the carbonyl group of an aromatic aldehyde can reduce rapidly, thereby reducing the extent of etherification.[19]

We have recently demonstrated that a wide variety of ethers suitable for use as fuels and lubricants can be synthesized from biomass-derived platform molecules.[16] Representative ethers prepared with high yields are shown in **Table 6**. These reactions were carried out at 393 K using a combination of Pd/C and H_2, and silica-supported 4-

ethylbenzenesulfonic acid (EBSA/SiO_2). In order to utilize Guerbet alcohols, four equivalents of aldehyde or ketone were required per equivalent of alcohol.[16] Amberlyst 15 was also an effective acid catalyst for this reaction. Unlike direct etherification, this method enabled the use of substituted alcohols and Guerbet alcohols, since dehydration of the alcohols to olefins is not observed. Thus, carbonyl compounds and alcohols can be selected independently to produce either symmetrical or asymmetrical ethers.

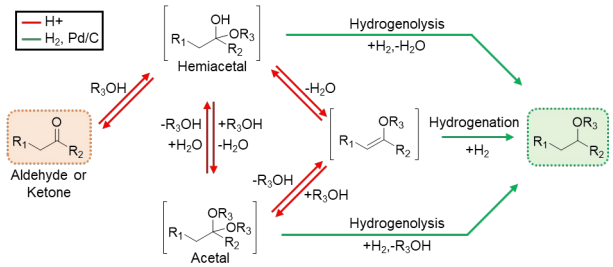
Table 6: Conversion of biomass-derived carbonyl compounds and alcohols to ethers from Ref. [16]

Entry	**Carbonyl (C)**	**Alcohol (A)**	**Mol C:A**	**Ether**	**%Yield / (% Conversion of Limiting Substrate)**
1	2-heptanone	butanol	1:4		88 / (100)
2	2-ethyl-hexanal	butanol	1:4		85 / (100)
3	2-heptanone	2-decyl-tetradecanol	4:1		91 / (100)
4	butanal	2-decyl-tetradecanol	4:1		88 / (97)
5	isobutanal	2-decyl-tetradecanol	4:1		86 / (100)
6	cyclopentanone	2-decyl-tetradecanol	4:1		87 / (100)
7	8-pentadecanone	2-hexyl-decanol	4:1		88 / (93)
8	octanal	2-decyl-tetradecanol	4:1		59 / (94)
9	2-ethyl-hexanal	2-decyl-tetradecanol	4:1		51 / (79)

Reagents and conditions: carbonyl compound (2 or 8 mmol), alcohol (2 or 8 mmol), 5% Pd/C (2.5 mol%), EBSA/SiO_2 (entries 1-2: 2.5 mol%, entries 3,5,6: 10 mol%, entries 4,5,8,9: 5 mol%), 393 K, 150 psi H_2, 5 h.

The mechanism of reductive etherification is not known, but it has been proposed to proceed via hemiacetal or acetal intermediates, as shown in **Scheme 3**.[16,19,126] The first

step is the acid-catalyzed activation of the carbonyl group, which is followed by addition of an alcohol to form the hemiacetal or acetal intermediate. These intermediates can undergo hydrogenolysis to form ether directly, or undergo a two-step process of acid-catalyzed dehydration or loss of alcohol followed by hydrogenation over Pd/C.

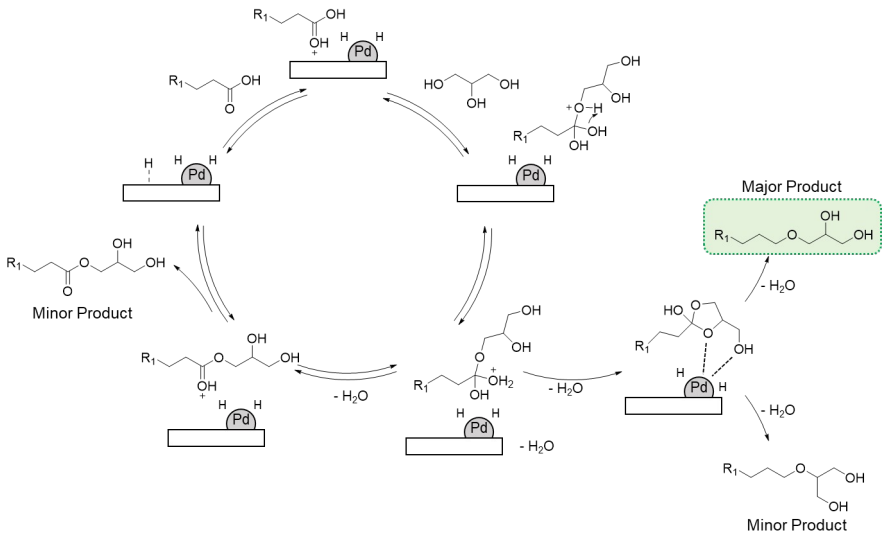


Scheme 3: *Reaction pathway for the reductive etherification of aldehydes or ketones with alcohols proposed by Fujii et al.*[126]

In addition to the synthesis of lubricant-range ethers from biomass-derived alcohols, reductive etherification has been employed for the synthesis of glycerol ethers, as shown in **Scheme 2b**. Lemaire et al. have prepared glycerol ethers selectively via the reductive etherification of glycerol with aldehydes,[128] ketones,[128] carboxylic acids[129], methyl esters, and triglycerides.[127] These reactions were performed with a combination of carbon-supported palladium, H_2, and an acid catalyst.[127–129]

The mechanism for glycerol etherification with a carboxylic acid in the presence of molecular hydrogen proposed by Lemaire et al. is shown in **Scheme 4**. The major product is shown in green. Minor products involve the ether formed from the middle hydroxyl group, as well as the unreduced ester. The proposed mechanism for etherification of glycerol with the methyl ester proceeds similarly except that the hydroxy group is replaced with a methoxy group.[127] Lemaire et al. have also demonstrated that glycerol ethers can be produced from the reductive etherification of triglycerides directly with glycerol in a two-step process.[127] First, glycerol and triolein are esterified using 10 wt%

BaO/Al_2O_3 at 473 K, followed by reduction in 50 bar H_2, with 10 wt% Amberlyst 15, and 1 mol% Pd/C at 393 K, resulting in an isolated yield of 34% of the mono-ether.[127]

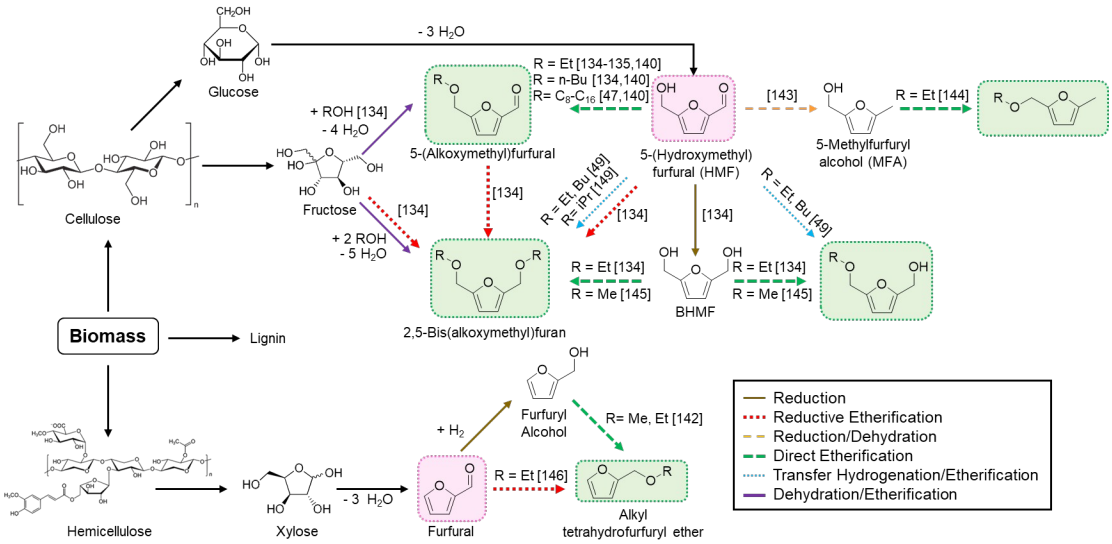


Scheme 4*: Mechanism of glycerol etherification with carboxylic acid (adapted from ref. [129])*

4.3 Synthesis of Ethers from Furanics via Direct and Reductive Etherification

Furfural and other furanic compounds have emerged as a class of useful platform molecules that can be readily produced from biomass via the dehydration of sugars derived from cellulose and hemicellulose or synthesized directly from biomass feedstocks.[75,76,130,131] Ethers obtained from these platform molecules, such as alkoxymethyl furfural, can be used as biofuels and specialty chemicals.[75,132][133] Both direct and reductive etherification have been employed to upgrade these synthons to furanyl ethers. Etherification of furans with alcohols presents challenges similar to those for the direct etherification of alcohols in terms of activity and selectivity. Undesired side reactions such as the unimolecular and bimolecular dehydration of alcohols make the task of synthesizing asymmetrical ethers challenging. In addition, there is a tradeoff between reaction rate and selectivity for producing ethers, as increasing temperature improves total product yield

but decreases selectivity for direct etherification.[134] Several recent efforts by our group and others to produce ethers from both direct and reductive etherification of furfural, furfuryl alcohol, and 5-hydroxyl-methyl furfural (HMF) are shown in the **Scheme 5**. Below, we discuss recent efforts to synthesize furanyl ethers via direct etherification of furanyl alcohols with linear alcohols, reductive etherification of furans with alcohols, and transfer hydrogenation/etherification reactions.



***Scheme 5**: Synthesis of furanyl ethers via direct and reductive etherification of biomass-derived platform molecules. References are noted in the brackets.*

Direct Etherification of Ethanol and HMF

The direct etherification of furfuryl alcohol, HMF, and 2,5-bis(hydroxymethyl)furan (BHMF) with linear alcohols is represented in **Scheme 5** by the dashed green lines. One reaction of particular interest is the direct etherification of HMF with ethanol to produce 5-(ethoxymethyl)furan-2-carbaldehyde (EMF) and ethyl levulinate (EL).[134–139] Both products can serve as platform molecules for the synthesis of fuels and, hence, understanding which reaction conditions favor either EMF or EL production would enable the proper choice of reaction conditions to make one of these two products. **Table 7** summarizes the

effectiveness of solid-acid catalysts for selective production of EMF or EL and compares the yields with those obtained using sulfuric acid.

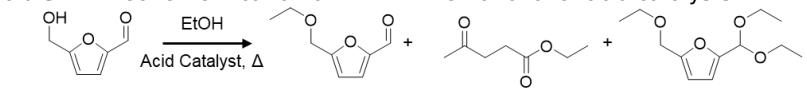
In a study of the etherification of HMF with ethanol, Lanzafame et al. suggested that the presence of Brønsted versus Lewis acid sites on the catalyst surface are required to selectively produce EMF or EL. They achieved EMF yields of 76% and EL yields of 23% at 100 % conversion of HMF for the direct etherification of HMF with ethanol over Z-SBA-15 for 5 hours at 413 K.[135] Under the same reaction conditions but using Amberlyst 15 as the catalyst, they observed a >99% yield of EL at 100% conversion of HMF.[135] In fact, they found that purely Brønsted-acidic catalysts, such as H_2SO_4, Amberlyst 15, and Al-MCM-41 (Si/Al = 25), favored formation of EL. However, introduction of Lewis acid sites, such as Zr^{4+} into SBA-15 (Z-SBA-15) or extra-framework isolated Al^{3+} sites in Al-MCM-41 (Si/Al = 50), resulted in higher selectivity to EMF.[135]

Our group and others have shown that high selectivities towards EMF can be achieved using the Brønsted acid catalyst Amberlyst 15. We observed EMF yields of over 55% from the etherification of HMF and ethanol at 348 K for 24 h.[134] Similarly, Xu et al. have observed EMF yields of over 62% for the etherification of HMF and ethanol at 363 K for 2 h.[138] Ether formation is favored at lower temperatures, which means that in order to produce EMF in high yields, longer reaction times and lower temperatures are preferred, and under these conditions, Lewis acid sites are not needed to produce EMF selectively. Amberlyst 15 is an excellent candidate for carrying out reactions at lower temperatures, because it is thermally stable up to 393 K, and does not degrade like the sulfonated functionalized ion-exchange resin NKG-9, which was selective for EMF synthesis from HMF and ethanol but decomposed during the reaction.[136]

In addition to ethanol, direct etherification of HMF over solid acid catalysts has been achieved with other alcohols, such as butanol[134,140] and C_8-C_{16} alcohols.[47,140] For example, Iborra et al. have investigated the cross-etherification of C_8-C_{18} n-alcohols with HMF to produce asymmetrical ethers for applications as biodegradable surfactants over zeolites H-BEA, HY, H-MOR, H-MFI, ITQ-2, and MCM-41 at 373 K. This work identified H-BEA as an effective catalyst, enabling the attainment of ether yields over 92%.[47]

HMF can also undergo self-etherification to produce 5,5′-oxy(bis-methylene)-2-furaldehyde (OBMF), a useful precursor for the synthesis of crown ethers, polyurathanes, polyamides, and other polymers.[141] Sn-montmorillonite gave almost complete conversion of HMF with 98% selectivity to OBMF using non-polar aprotic dicholoroethane as a solvent at 373 K.[141]

Table 7: Direct etherification of HMF with ethanol over acid catalysts



5-hydroxymethyl-furfural **(HMF)** | 5-(ethoxymethyl) furan-2-carbaldehyde **(EMF)** | ethyl levulinate **(EL)** | 5-(ethoxymethyl)-furfural diethylacetal **(EMFDEA)**

Catalyst	Temperature [K]	Time [h]	HMF:ROH [mol]*	HMF Conversion [%] EMF	EMF yield [%]	EL yield [%]	EMFDEA yield [%]	DE yield [%]	Ref.
Z-SBA-15	413	5	~1:23	100	76	23		-	[135]
Al-MCM-41 (Si/Al 50)	413	5	~1:23	100	68	10		13	[135]
SZ-SBA-15	413	5	~1:23	100	62	35		-	[135]
Al-MCM-41 (Si/Al 25)	413	5	~1:23	100	37	47		12	[135]
Amberlyst 15	413	5	~1:23	100	-	>99		-	[135]
SBA-15	413	5	~1:23	75	-	-		54	[135]
Al-MCM-41 (Si/Al 75)	413	5	~1:23	61	-	-		19	[135]
H_2SO_4	413	5	~1:23	100	3	96		-	[135]
H_2SO_4 (5 mol%)	348	24	~1:43		81	16			[134]
Dowex DR2030 (5 mol%)	348	24	~1:43		57	8	33		[134]
Amberlyst 15 (5 mol%)	348	24	~1:43		55	8	31		[134]
Dowex50WX8 (5 mol%)	348	24	~1:43		45	9	28		[134]
Silica sulfuric acid (5 mol %)	348	24	~1:43		36	7	25		[134]
Amberlite IR120 (5 mol %)	348	24	~1:43		33	7	14		[134]
NKG-9	343	24	~1:86	100	82.8				[136]
HY-Zeolite	343	24	~1:86	10	8.5				[136]

Al-TUD-1 (Si/Al 21)	413	24	~1:57	97	70	11	3		[139]
Al-TUD-1(4)-at (acid treated)	413	42	~1:57	88	81	6			[139]
H-ZSM-5	413	24	~1:139	~100	~80	~5			[137]
H-MOR	413	24	~1:139	~100	~80	~5			[137]
SO_3H-SBA-15-D	413	24	~1:139	~100	~10	~75			[137]
Amberlyst 15	363	2	~1:10	25.5	62.5	5.2			[138]
$H_4SiW_{12}O_{40}$	363	2	~1:10	89.4	85.3	5.4			[138]
40 wt.% HSiW/MCM-41	363	2	~1:10	80.1	85.8	4.6			[138]
HMF: 5-hydroxymethylfurfural; EMF: 5-(ethoxymethyl)furan-2-carbaldehyde; EL: ethyl 4-oxopentanoate or ethyl levulinate; DE: 1,1-dietoxy ethane, EMFDEA: 5-(ethoxymethyl)- furfural diethylacetal. *Ethanol is used as both the reactant and solvent.									

Direct Etherification of Furfural and Methyl Furfural with Ethanol

The direct etherification of furfural with ethanol or methanol to produce alkyl-tetra-hydrofurfuryl ether can also be achieved over solid acid catalysts. Zhou et al. have demonstrated that H-MFI (Si/Al 25) was effective in the etherification of furfuryl alcohol with methanol and ethanol, obtaining selectivities to methyl furfural ether (MFE) and ethyl furfuryl ether (EFE) of 58.9% and 44.8%, respectively at 298 K for 24 h using methanol or ethanol as the solvent.[142]

Methyl furfuryl alcohol (MFA) can be produced from HMF via selective hydrogenation over a Ru–MoO_x/C catalyst.[143] The etherification of MFA with ethanol to produce 2-(ethoxymethyl)-5-methylfuran (EMMF) was achieved over Amberlyst 15. Recent work in our group has demonstrated EMMF selectivities and yields of over 98% over Amberlyst 15 at 298 K.[144] Amberlyst 15 was also effective for the direct etherification of other alcohols such as butanol and other furans such as BHMF. It was proposed that the high selectivity towards asymmetrical ethers is achieved through the formation of a solvation shell of polar C_1-C_4 alcohols that form around the active site of the catalyst, enhancing the cross-coupling reaction, shown in **Figure 6**.[144]

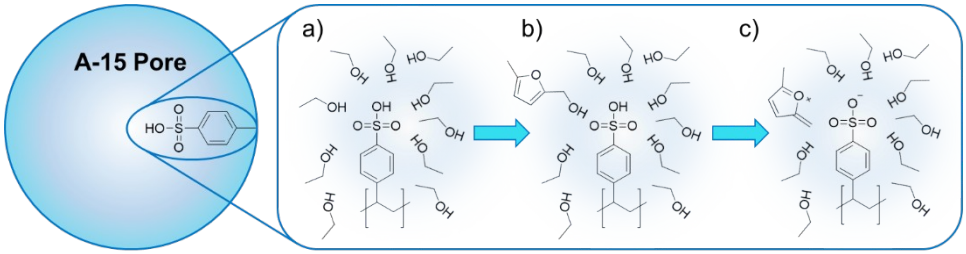


Figure 6: *Formation of the reactive intermediate in a solvation shell inside a pore of Amberlyst 15 for the etherification of methyl furfural with ethanol (adapted from ref [144]).*

Direct Etherification of BHMF

Amberlyst 15 and zeolites are effective for the direct etherification of furan compounds with alcohols. For the direct etherification of BHMF with ethanol, yields of up to 80% 2,5-bis(ethoxymethyl)furan and 6% (5-(ethoxymethyl)furan-2-yl)methanol were achieved using 5 mol% catalyst loading of Amberlyst 15, at 313 K for 16 h.[134] Etherification of BMMF and BHMF with methanol is also highly selective over zeolites. Zhang et al. achieved ether selectivities of over 95% over 1.5% Sn-ZSM-5 at 338 K.[145] The authors suggest that the main and side reactions, such as furan ring opening and polymerization, are dictated by pore structure as well as synergistic effects between Brønsted and Lewis acidity.[145]

Reductive Etherification of HMF, Furfural, Alkoxy-Methyl-Furfural, and Levulinic Acid with Alcohols

The cross-etherification of alcohols is limited by the tendency for branched alcohols, such as isopropanol, to undergo unimolecular dehydration, as discussed in **Section 4.1**. One way to suppress this side reaction and improve the selectivity to cross-etherification products is to employ reductive etherification. Some examples of reductive etherification routes to producing ethers from furans are illustrated in **Scheme 5** by the dotted red lines. We have employed reductive etherification for the production of 2,5-bis-(alkoxymethyl)furan via the reaction of HMF with ethanol and butanol. Yields of the di-

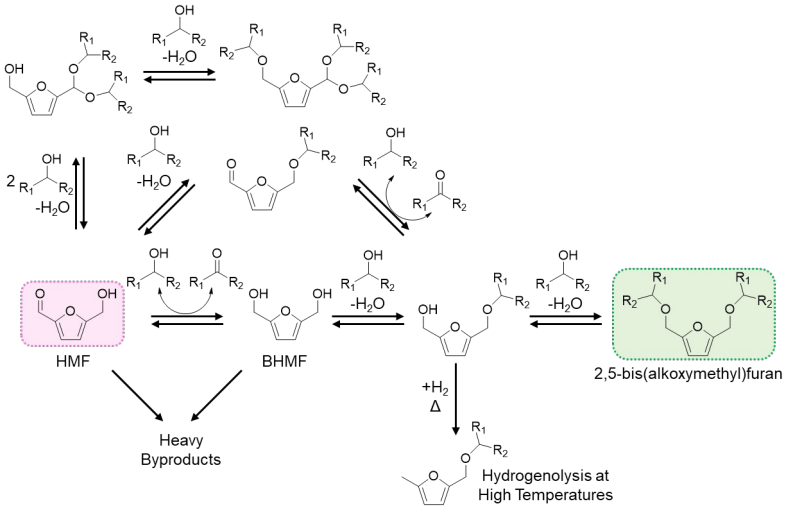
ether (2,5,-bis(ethoxymethyl)furan)) of up to 59%, with 7% of the mono-ether (5-(ethoxymethyl)furan-2-yl)methanol),) and 1% 2-(diethoxymethyl)-5-(ethoxymethyl)furan, were produced using 5 mol% Amberlyst 15, 1 mol% Pt/alumina, at 348 K for 24 h in the presence of 200 psi H_2.[134] Wu et al. have demonstrated that Pd supported on TiO_2, Al_2O_2, SiO_2, and active carbon are also effective for the reductive etherification of furfural with ethanol at 333 K with 0.3 MPa of H_2.[146] Yields of up to 81% of furfuryl ethyl ether (FEE) were obtained over 0.7 wt% Pd/C with minor formation of 2-(diethoxymethyl)furan (4%), furfuryl alcohol (10%), and tetrahydrofurfuryl alcohol (3%).[146] The authors suggested that palladium hydride, formed *in situ*, catalyzes the formation of the key intermediate, 2-(diethoxymethyl)furan.[146] They also suggested that the key to achieving a high yield of ether is the balance between the proton-donating ability and hydrogenolysis activity of palladium hydride, which requires tuning of the Pd loading, hydrogen pressure, and reaction temperature.[146]

Reductive etherification of alcohols with levulinic acid or ethyl levulinate can also be employed for the synthesis of sustainable non-VOC solvents or biofuels.[147,148] Recent efforts have demonstrated that methanol, ethanol, n-butanol, and n-heptanol can undergo reductive etherification with levulinic acid to produce alkyl 4-alkoxypentanoates (4-alkoxyvalerates) in 54−77% yield under hydrogen at 473 – 493 K and 1000 psig in the presence of a Pd/C catalyst.[147] The addition of acidity has also shown to improve the yield and selectivity of ethyl-4-ethoxypentanoate (EEP) by reductive etherification of ethanol with ethyl levulinate at 413 K, as introducing zeolite beta as a co-catalyst with Pd/SiO_2-Carbon enabled the attainment of EEP yields of 93% at 100% conversion of ethyl levulinate.[148]

Etherification via Transfer Hydrogenation for the Synthesis of Furanyl Ethers

Transfer hydrogenation etherification has also emerged as a method of synthesizing furanyl ethers. A few illustrations of this means of HMF etherification are presented in **Scheme 5** by the dotted blue lines. In this case, the alcohol serves as both the solvent, reactant, and hydrogen transfer agent. Vlachos et al. have demonstrated that Lewis acidic Sn-BEA and Zr-BEA are effective catalysts for the transfer hydrogenation and etherification of HMF with 2-propanol and 2-butanol at 453 K. Yields of over 80% of 2,5,-bis(isopropoxylmethyl)furan were reported.[149] Vlachos et al. proposed a mechanism and reaction pathway for the formation of 2,5-bis(alkoxymethyl)furan from HMF via direct etherification and etherification via transfer hydrogenation using isopropanol.[149] This reaction pathway is shown more generally for alcohols in **Scheme 6.** HMF is first converted to BHMF via transfer hydrogenation by an alcohol. The BHMF then undergoes direct etherification with another alcohol molecule to produce the mono-ether, and a second etherification with another alcohol molecule to produce the di-ether.[149] The proposed rate limiting step is the Meerwein-Ponndorf-Verley (MPV) conversion of HMF to BHMF via hydrogen transfer from the alcohol. Roman-Leshkov et al. have also identified Lewis acid zeolites as effective catalysts for the coupled transfer hydrogenation and etherification of HMF with ethanol and butanol at 393 K for 24 h and pressures of 791 kPa in a 100 mL stainless steel Parr reactor.[49] The authors found that Sn-BEA showed the highest stability and selectivity for etherification, whereas Hf-BEA and Zr-BEA appeared to be more active for the MPV reduction. Hard Lewis-acid centers, such as Zn and Sn, were found to be particularly effective in stabilizing the transition state of the rate-limiting hydride transfer step, whereas the weaker Lewis acid centers, such as Ti and Ta were less effective in catalyzing hydrogen transfer.[49] Primary alcohols are less likely to donate a hydrogen, as 2-butanol is more effective than 1-butanol.[49] Thus for the etherification of substituted alcohols with furans, hydrogen transfer reductive etherification is an attractive

option. Still, it is important to note that etherification via transfer reductive hydrogenation is typically done in a batch reactor to support the hydrogen transfer step, which can limit the process scalability and increase the concentration of water in the vessel, thus inhibiting both the transfer hydrogenation and etherification reactions.[49]



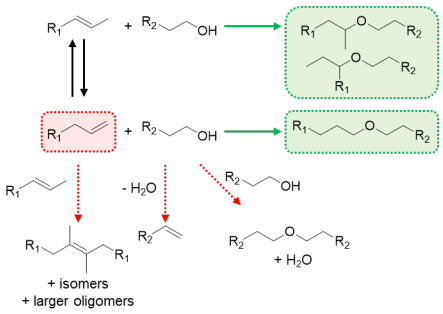
Scheme 6: *Reaction of sequential catalytic transfer hydrogenation and etherification of HMF to 2,5-bis(alkoxymethyl)furan with alcohol (ethanol, 1-butanol, isopropanol) catalyzed by Sn-Beta (adapted from ref. [149])*

4.4 Etherification by Alcohol Addition to an Olefin

Branched ethers produced by the addition of an alcohol to an olefin, such as methyl-*tert*-butyl ether (MTBE), ethyl-*tert*-butyl ether (ETBE), *tert*-amyl methyl ether (TAME), and *tert*-amyl-ethyl ether (TAEE), are useful fuel additives that can be generated from biomass-derived molecules. During the direct etherification of *tert*-butanol with linear alcohols, *tert*-butanol tends to favor dehydration to isobutene, producing water, thereby reducing ether selectivity. The reaction of an alcohol and an olefin to yield an ether is stoichiometric; however, there are many challenges to the synthesis of ethers by the addition of an alcohol to an olefin. These include reactor design, side product formation,

and product inhibition. This section discusses these challenges and identifies how the yield of the desired ether products can be improved.

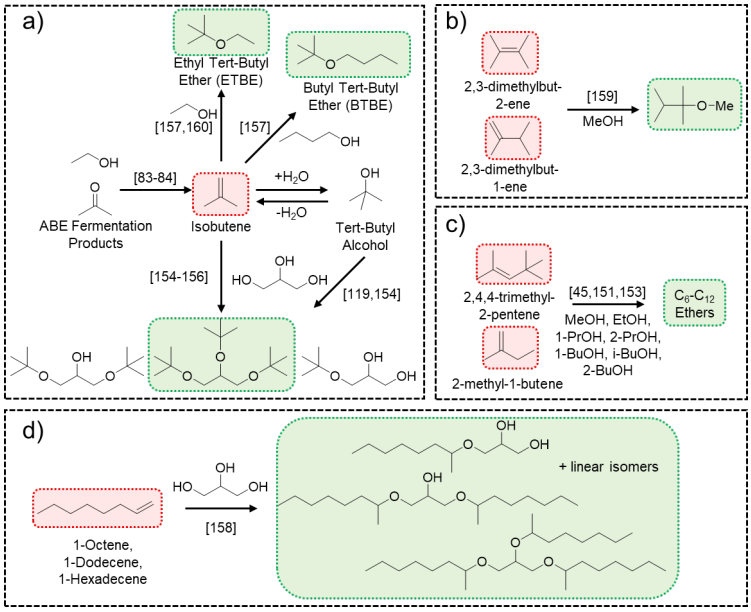
One key challenge in the reaction of olefins with alcohols is the fact that for gaseous olefins, such as isobutene, the reaction cannot be performed in a single phase. For example, the formation of methyl *tert*-butyl ether is often completed in a two-step process: isobutanol is first dehydrated over a silica-alumina catalyst at 498 K, then reacted with isobutene over Amberlyst 15 at 323 K, achieving a yield of MTBE and MIBE of approximately 28% with a MTBE:MIBE ratio of 11.7:1.[150] Not only is the ether selectivity fairly low, but the second step involves either bubbling a gas through liquid, which introduces mass transfer limitations, or operating at elevated pressure in order to keep all reactants in the liquid phase.[151]



Scheme 7: *Reaction pathway and side product formation for the etherification of primary alcohols with linear olefins.*

The formation of side products is also a key concern, since isomerization and dimerization of olefins, as well as alcohol dehydration, adversely affect selectivity to the desired ethers. **Scheme 7** provides an overview of the reaction pathway and side products formed from the addition of primary alcohols to linear olefins. In the presence of an acid catalyst, olefins can undergo oligomerization, producing higher carbon-number products that can further oligomerize and contribute to coke formation and, hence, catalyst deactivation. In addition, alcohols can undergo unimolecular dehydration to form

olefins or direct etherification to form symmetrical ethers. When olefins are reacted with glycerol or polyols, the polymerization of the alcohols to poly-ethers is also a concern. As shown in **Scheme 7**, primary olefins can readily isomerize to form secondary olefins,[151] which can also react with alcohol to produce a variety of ether products depending on which side of the double bond the alcohol adds to. Karinen et al. have found that as the temperature increases from 333 to 353 K, the ratio of olefin isomerization to etherification increases for reactions of methanol, ethanol, 1-propanol, 1-butanol, 2-butanol, and isobutanol with 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene over Amberlyst 15.[151] Other authors have suggested that isobutene dimerization over Amberlyst 35 and Purolite CT275 increases with increasing temperature and increasing olefin to alcohol ratio.[152] For side reactions involving alcohol dehydration, the production of water presents additional challenges. Water can readily react with 1,1-disubstituted olefins to form tertiary alcohol, [11,151,153] and thereby inhibit active sites on the catalyst, decreasing rates of both isomerization and etherification.[45,151,154]



***Scheme 8**: Scope of ether formation reactions via alcohol addition to olefins catalyzed by Amberlyst 35 and other catalysts. References are noted in the brackets.*

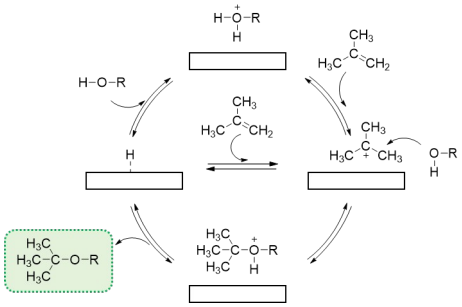
The challenges noted above can be surmounted in several ways in order to control product selectivity. These include the choice of catalyst, the ratio of olefins to alcohols, the choice of alcohol and olefin structures, the temperature, and water removal. **Scheme 8** shows some sample reactions of olefins with alcohols to produce useful ether products. Amberlyst 35 is an effective catalyst for producing asymmetrical ethers from a variety of alcohols and olefins.[67,154,155] As shown in **Figure 8a**, glycerol can be reacted with isobutene to form mono-, di-, and tri-*tert*-butyl ethers. Bajus et al. have reported yields of di- and tri- ethers from glycerol of up to 89% at 100% conversion of glycerol at 333 K[154] and demonstrated that Amberlyst 35 is highly selective for the etherification of isobutene with ethylene glycol compared with para-toluene sulfonic acid and large-pore zeolites H-Y and H-BEA.[156] Krause et al. have found that for the etherification of glycerol with isobutene over Amberlyst 35, optimal selectivity towards ethers was achieved with an isobutene to glycerol molar ratio of 3:1 at 353 K.[155] By controlling the reaction conditions, it is possible to tune the distribution of ethers to match desired fuel blends, thus avoiding costly separations. As mentioned in Section 2, di- and tri-*tert*-butyl glyceryl ethers are preferred for diesel blends due to their solubility in diesel fuel and their properties such as viscosity and cloud points.[64–67] Mravec et al. found that the highest yields of di- and tri-*tert*-butyl glyceryl ethers were achieved over Amberlyst 35.[156] While glycerol conversion was highest over zeolite HBEA, the reaction to form tri-*tert*-butyl glycerol ether was sterically hindered, thus the selectivity was low.[156]

The reaction of isobutene with ethanol or butanol produces ethyl-*tert*-butyl ether (ETBE) and butyl-*tert*-butyl ether (BTBE), respectively, as shown in **Scheme 8a**. Tejero et al. found Amberlyst 35 to be the most effective catalyst for this reaction compared to Amberlyst 16, Amberlyst 39, Amberlyst 46, Amberlyst 70, and Purolite CT-275, at temperatures between 315 and 353 K.[157] Amberlyst 35 was also effective for the

etherification of 2-methyl-1-butene and 2,4,4-trimethyl-1-pentene with various C_1-C_4 alcohols between 333 – 353 K in the liquid phase (**Scheme 8c**)[151] and for the etherification of C_8-olefins with methanol in the liquid phase between 323 – 363 K (**Scheme 8d**).[153]

Tejero et al. suggest that Amberlyst 35 is the most promising catalyst because of its strong acidity and rigid polymer backbone, which enhance the reaction rate.[157] However, according to Weckhuysen et al., catalyst hydrophilicity and pore structure are the most critical catalyst properties for achieving high ether selectivity.[158] While Bajus et al. suggest that H-BEA is not effective for etherification reactions of olefins and alcohols, Weckhuysen et al. have reported H-BEA to be more selective for the etherification of glycerol and other glycols with 1-octene, 1-dodecene, and 1-hexadene compared to Amberlyst 70, p-TSA, H-Y, USY, and H-MFI. Using H-BEA, selectivities towards mono- and di-octyl ethers from glycols such as ethylene glycol and 1,2-propylene glycol of up to 85-95% were achieved at glycol conversions between 15-20% at temperatures between 393 – 413 K.[158] Silica-supported sulfated zirconia, Amberlyst 16W, and Amberlyst 15 have also been employed as catalysts for the reactions of C_6 olefins with methanol (**Scheme 8b**)[159], etherification of isoamylenes (2-methyl-1-butene, and 2-methyl-2-butene) with methanol, ethanol, and n-propanol (**Scheme 8c**),[45] and isobutene with butanol (**Scheme 8a**),[160] respectively, for temperatures between 333 and 353 K. While zeolites introduce pore volume constraints, they are thermally stable above 423 K, unlike Amberlyst 35 and Amberlyst 16. Still, the majority of alcohol additions to olefins are performed between 323 and 363 K, which is well within the range of thermal stability of resin catalysts. The catalysts that are effective for the etherification of olefins with alcohols contain large pore volumes or no pores, and have high acid capacities, suggesting that Amberlyst 35 is a promising candidate for these reactions.

The ratio of alcohol to olefin strongly affects the kinetics of the reaction. Scurrell et al. have observed that the kinetics of etherification varies with the ratio of reactants.[161] For the reaction of isobutene with methanol or n-butanol over Amberlyst 15, at lower isobutene to alcohol ratios, the rate of etherification is zero order in alcohol and first order in olefin, whereas at higher alcohol to isobutene ratios, the reaction is first order in alcohol and zero order in olefin. These observations suggest that when the surface is saturated with alcohol, the rate-limiting step is the protonation of the olefin by the solvated proton, and when the surface is saturated with olefins coordinated to the sulfonic acid groups, the rate limiting step is the interaction of the olefin with the alcohol.[161]



Scheme 9: *Proposed mechanism for the etherification of isobutene with linear alcohols (top pathway shows how alcohol can be protonated and then donate a hydrogen to the olefin).*

Scheme 9 shows a proposed mechanism for the reaction of isobutene with an alcohol and demonstrates how solvated alcohols can assist in the protonation of the olefin. In the general mechanism suggested by Tretbar et al., the olefin is first protonated by the acid site, leaving a stabilized carbocation intermediate, which then accepts electrons from the oxygen of the alcohol, forming a protonated ether, which, in turn, desorbs in the final step to form the asymmetrical ether.[160] The upper pathway in **Scheme 9** shows how the alcohol can be protonated by the acid site and then proceed to readily donate an acidic hydrogen to the olefin. For this mechanism, the rate-limiting step would be protonation of the olefin, resulting in a first order dependence of the rate of etherification on the olefin

concentration. This conclusion is consistent with the observation that the reaction is first order in olefin and zero order in alcohol at low isobutene to alcohol ratios.[45,150,161]

The alcohol structure also affects the mechanism for the addition of an alcohol to an olefin. Fattore et al. have suggested that when isobutene is reacted with higher alcohols, the reactivity order is related to the alcohol basicity, which dictates the proton transfer ability of the ROH_2^+.[162] Therefore, in the case where the alcohol to olefin ratio is greater than or equal to one, the alcohol acts as a solvent. Krause et al. have shown that etherification and dehydration rates increase with decreasing alcohol polarity and with increasing carbon number of the alcohol, owing to the acidity and Mulliken charges of the oxygen atom of the alcohol.[151] Scurrell et al. also point out that the higher reactivity of n-butanol over methanol for etherification of tertiary olefins over Amberlyst 15 reflects the higher acidity of the proton on n-butanol than on methanol.[161,163] The authors suggest that the excess of alcohol breaks up the network of hydrogen-bonded sulfonic acid groups, which aids in solvating and, hence, dissociating the proton.[161] By contrast, Linnekoski et al. found that methanol, ethanol, and 1-propanol affect the rate of olefin isomerization but not the etherification rate for alcohol addition to isoamylenes.[45] This trend was explained by the fact that 2-methyl-1-butene isomerizes to 2-methyl-2-butene more rapidly in the presence of more acidic protons caused by more basic alcohols. The more substituted olefin, 2-methyl-2-butene, is more stable and thus less reactive for etherification, so the effects of increased acid strength cancel each other out, resulting in no net change in the etherification rate. The solvation effects of alcohols are consistent with the mechanism proposed in **Scheme 9**, in which the rate-limiting step for etherification is the protonation of the olefin.

In addition to the choice of alcohol, the choice of olefin also contributes to the reaction kinetics. The more volatile the olefin, the more pressure must be applied to

maintain a liquid phase reaction. Generally, the longer the chain length, the lower the volatility. The selection of isomer also affects the reaction rate, because the olefin isomers which are thermodynamically favored at equilibrium have a lower reactivity for etherification. Selecting less substituted olefins can increase etherification rates, although isomerization is likely to occur. Krause et al. found that etherification rates of olefins with methanol were lower for olefins with longer carbon chains (C_8) compared to shorter chains (C_5).[153] In addition, they found that the equilibrium between 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene was affected by steric hindrance, which is another concern when selecting an olefin for this reaction.[153]

Temperature has a clear effect on ether selectivity. As discussed earlier, the optimal temperatures for etherification of olefins with alcohols is between 323 – 363 K.[45,151,153,154,156,157,159,160] The tradeoffs between catalyst activity and selectivity are critical in optimizing for ether formation. In a prospective study by Bringue et al., the equilibrium conversion, selectivity, and yield was optimized using a combination of experimental and numerical multi-objective optimization in order to determine conditions most favorable for the liquid phase etherification of isobutene and isoamylene by addition of ethanol over Amberlyst 35.[11] This study concluded that the optimal experimental conditions for maximizing the simultaneous production of ETBE and TAEE occurred for molar alcohol to olefin ratios of 0.9, C_4 to C_5 olefins ratios of 0.5, and at a temperature of 323 K.[11]

In summary, the reaction of alcohols with olefins produces asymmetrical ethers with a high degree of branching for use as fuel additives. Under the right conditions, high yields of mono- di- and tri- ethers of glycerol with olefins as well as cross coupling of mono-alcohols with olefins can be achieved. While this method of producing ethers could be employed to produce symmetrical linear ethers, the tendency for olefins to undergo isomerization and oligomerization suggests that direct etherification of alcohols is more

appropriate for obtaining high selectivities towards linear symmetrical ethers. Thus, this reaction is best employed when the olefin is highly substituted and the desired product is an asymmetrical ether.

5. The Role of Cooperative Brønsted and Lewis Acidity in Selective Ether Synthesis

Recent studies of alcohol etherification and dehydration over solid acids have indicated that by tuning the strength and ratio of Brønsted and Lewis acid sites on the surface of the catalyst, the selectivity of the reaction can be adjusted. As mentioned in **Section 4.1**, our group has proposed that cooperative effects between Brønsted and Lewis acid sites on tungstated zirconia promote the biomolecular etherification of dodecanol to form di-dodecyl ether.[86] Hammond et al. have suggested that bifunctional Brønsted and Lewis acidic zeolites facilitate the production of butoxymethyl furan via the etherification of furfural and 2-butanol.[164] The authors found that a bifunctional H-BEA containing 2 wt% Sn and 0.5 wt% Al gave high ether selectivity, >75%, and exhibited excellent stability. By contrast, monofunctional analogues or physical mixtures of the analogues were less selective and stable.[164] Zhang et al. also found that Sn-MFI was effective for the etherification of 2,5-bis(hydroxymethyl)furan (BHMF) with methanol to produce 2,5-Bis(methoxymethyl)furan (BMMF), achieving a selectivity of 95%. The authors found that BMMF formation increased with increasing Lewis acidity of the catalyst.[145]

Several studies have shown that the ratio of Brønsted to Lewis acid sites on the surface of a catalyst can be tuned to adjust the product distribution for glycerol dehydration reactions. Wang et al. studied the dehydration of glycerol to acrolein over Al/H-ZSM5 zeolite catalysts, and suggested that a cooperative effect between Brønsted and Lewis acid sites on the surface of the catalyst is responsible for the high acrolein selectivity. [165] Sievers et al. studied the role of Lewis and Brønsted acid sites in the

dehydration of glycerol over niobia, and concluded that a higher ratio of Brønsted acid sites to Lewis acid sites results in higher acrolein selectivity, whereas a larger ratio of Lewis acid sites to Brønsted acid sites results in higher selectivity towards hydroxyacetone.[166] Cooperative effects between Brønsted and Lewis acid sites on Sn-Beta have also been proposed for ethanol dehydration. For example, Greeley et al. have proposed a concerted transition state involving both the Lewis acidic Sn center and an adjacent weakly Brønsted-acidic framework silanol group.[115]

Because there is precedent for the role of Brønsted and Lewis acidity in controlling etherification and dehydration selectivity over metal oxides, the investigation of tuning Brønsted and Lewis acid sites by varying the ratio of Brønsted to Lewis acid sites, changing the strength of Lewis acid centers by varying the metal cations, and changing the density of Brønsted acid sites, is a promising avenue for future improvement of ether selectivity that is not afforded by Brønsted acidic polymeric resins.

6. Conclusions and Outlook

We have shown that ethers suitable for use as fuels, lubricants, and specialty chemicals can be synthesized from a variety of biomass-derived platform molecules through direct and reductive etherification of alcohols, aldehydes, ketones, esters, carboxylic acids, and olefins. The best strategy for synthesizing ethers from biomass-derived compounds using heterogeneous catalysts depends on the structure of the reactants and the properties of the catalyst. In this review, we have outlined the advantages and disadvantages to various methods of producing ethers from renewable sources. Here we summarize the recommended synthesis routes for producing a particular type of ethers from a defined set of reactants.

Symmetrical ethers can be formed from linear alcohols via direct etherification over a solid acid, using the reactant alcohol as the solvent, at low temperatures, and with minimal side product formation. If there are carbon chain branches on the alcohol, direct etherification is still viable as long as the branches are at least three carbons away from the hydroxyl group of the alcohol. If mixtures of symmetrical and asymmetrical linear ethers are desired, direct etherification of a mixture of linear alcohols is a viable synthetic route. However, if purely asymmetrical ethers are desired, we recommend reductive etherification of an alcohol and an aldehyde or ketone in the presence of a solid acid catalyst and a hydrogenation catalyst, such as Pd/C. This method enables selective synthesis of asymmetrical or symmetrical ethers from alcohols with a significantly larger range of structures including branched alcohols, such as those produced from the Guerbet reaction, to create lubricant-range molecules, as well as 2° and 3° alcohols for use as diesel and gasoline additives. Reductive etherification can also be used to prepare ethers via the reaction of alcohols with esters and carboxylic acids, and both direct and reductive etherification can also be employed for the valorization of glycerol and polyols for the synthesis of fuel additives and specialty chemicals.

Fuel additives can also be produced via direct, reductive, and transfer hydrogenation etherification of furfural and furans derived from biomass. For these methods, we discussed the reaction pathways and conditions for selective synthesis of the desired ethers based upon recent developments in the literature. Amberlyst 15 and zeolites stand out as selective catalysts for the direct etherification of ethanol with hydroxymethyl furfural. Amberlyst 15 is also an effective catalyst for the etherification of furfural or methyl furfural with ethanol and for the direct etherification of BHMF with alcohols. Low temperatures and longer reaction times are preferred for these reactions. Reductive etherification of furans enables enhanced selectivity towards cross-

etherification by limiting homocoupling of alcohols and can be achieved using a combination of an acid catalyst, Pd/C, and H_2 for reduction. For the etherification of substituted alcohols with furans, transfer hydrogenation etherification is also a viable option, as the alcohol can be used as both the reducing agent and the reactant, eliminating the need to supply molecular hydrogen.

The addition of an alcohol to an olefin is another method of producing ethers. The selectivity to ether via this reaction depends on avoidance of alcohol dehydration. This can be achieved by operating at temperatures between 323 and 363 K and using Amberlyst 35 as a catalyst. This synthesis method is most effective for the etherification of alcohols with highly substituted olefins, such as the synthesis of ethyl-*tert*-butyl ether.

Brønsted acidic resins with large pores that swell in the presence of solvent such as Amberlyst 70 are effective in promoting etherification of alcohols by increasing the concentration of alcohol around the active site. A high local concentration of alcohol can also be achieved using bifunctional catalysts that contain proximate adsorption sites for alcohols, such as the Brønsted and Lewis acid sites on tungstated zirconia. Future directions in employing tandem catalysts, tuning pore sizes, and identifying the site requirements for side reactions could enable finer enhancements of selectivity for both direct and reductive etherification reactions. Another promising approach, particularly for the synthesis of asymmetrical ethers via direct etherification, is the use of so-called “heterogenized” homogeneous acid catalysts. For example, the homogeneous cationic ruthenium−hydride complex $[(C_6H_6)(PCy_3)(CO)RuH]^+BF_4^-$ is known to catalyze the selective etherification of two different alcohols to form asymmetrical substituted ethers with a large scope of substrates and without the need for reactive reagents or protecting groups.[167] Developing heterogeneous catalysts that enable selective asymmetrical ether synthesis without the need for reductive etherification could lower costs associated with

operating under hydrogen pressure, and would allow more flexibility in the choice of alcohol substrates.

The removal of water is also a major consideration in the synthesis of ethers, as water inhibits active sites for etherification, thus lowering the etherification rate and selectivity. Investigation into water removal with membranes and reactive distillation with recirculation is a physical method of improving ether yields. Further investigation into tuning feed ratios for direct and reductive etherification may also elucidate pathways towards producing blends of ethers for fuel and lubricant applications. Moving forward, investigation of multi-step processes for synthesizing ethers directly from biomass will be necessary to provide further insights into developing industrially-relevant processes for synthesizing renewable ethers. Overall, these recent efforts to synthesize ethers from renewable sources using sustainable heterogeneous catalysis provide a vast scope of pathways towards utilizing biomass-derived platform molecules, and have the potential to enable the production of fuels, lubricants, and specialty chemicals which can replace petroleum-derived products at low cost and with reduced adverse environmental effects.

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