

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/87712/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Davies, Thomas E., Kondrat, Simon A., Nowicka, Ewa , Graham, James J., Apperley, David C., Taylor, Stuart H. and Graham, Andrew E. 2015. Dehydrative etherification reactions of glycerol with alcohols catalyzed by recyclable nanoporous aluminosilicates: telescoped routes to glyceryl ethers. *ACS Sustainable Chemistry & Engineering* 4 (3) , pp. 835-843. 10.1021/acssuschemeng.5b00894

Publishers page: <http://dx.doi.org/10.1021/acssuschemeng.5b00894>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Dehydrative Etherification Reactions of Glycerol with Alcohols Catalyzed by Recyclable Nanoporous Aluminosilicates: Telescoped Routes to Glyceryl Ethers

*Thomas E. Davies^a, Simon A. Kondrat^b, Ewa Nowicka^b, James J. Graham^c, David C. Apperley^d,
Stuart H. Taylor^b and Andrew E. Graham^{c*}*

^a Stephenson Institute for Renewable Energy, Department of Chemistry, University of Liverpool,
L69 7ZD, UK

^b Cardiff Catalysis Institute, School of Chemistry, Main Building, Park Place, Cardiff University,
Cardiff, CF10 3AT, UK;

^c School of Applied Sciences, University of South Wales, CF37 4AT, UK;

^d EPSRC Solid-State NMR Service, Department of Chemistry, Durham University, DH1 3LE, UK;

*Corresponding author. Email: andrew.graham@southwales.ac.uk

KEYWORDS: nanoporous aluminosilicates: evaporation-induced self-assembly: glycerol:
dehydrative etherification: heterogeneous catalysis: telescoped reaction protocols.

ABSTRACT: Catalytic strategies for the efficient transformation of abundant sustainable bioderived molecules, like glycerol, into higher value more useful products is an important research goal. In this study, we demonstrate that atom efficient dehydrative etherification reactions of glycerol with

activated alcohols are effectively catalyzed by nanoporous aluminosilicate materials in dimethylcarbonate (DMC) to produce the corresponding 1-substituted glyceryl ethers in high yield. By carrying out the reaction in acetone, it is possible to capitalize on the ability of these materials to catalyze the corresponding acetalization reaction allowing for the development of novel, telescoped acetalization-dehydrative etherification reaction sequences to selectively produce protected solketal derivatives. These materials also catalyze the telescoped reaction of glycerol with *tert*-butanol (TBA) in acetone to produce the corresponding solketal mono *tert*-butyl ether product in high yield, providing a potential route to convert glycerol directly into a useful and sustainable fuel additive.

INTRODUCTION

The development of renewable feedstocks, and in particular, feedstocks derived from biorenewable sources, has emerged as a vibrant and rich research area for the production of commodity chemicals and clean fuels. Glycerol is one such non-toxic, biorenewable and cheap feedstock candidate that is widely produced as a by-product in biodiesel production and soap manufacturing, and by the fermentation of biomass.^{1,2} Glycerol is therefore considered to be an ideal candidate as a highly flexible feedstock chemical, given its biosustainable production, its rich chemical functionality, and biodegradability. It is therefore not surprising that processes for the valorization of glycerol have attracted considerable recent interest.³⁻⁶ Amongst the many appealing strategies currently being explored are the transformation of biomass derived glycerol into oxygenated compounds by acetalization, esterification and etherification reactions for use as fuel additives or for improving engine performance.⁷⁻¹⁰ Established processes for the etherification of glycerol, which employ alkenes as the alkylating agent, have a number of disadvantages, in that the alkene component can be relatively expensive and the reaction can display poor selectivity producing a mixture of mono-, di- and tri-ethers.¹¹ Furthermore, a number of secondary reactions, such as alkene oligomerization, may also reduce the yield of the desired ether products and impact on overall atom

efficiency.¹² This has led to interest in alternative etherification strategies with reduced environmental impact that employ alcohols in a dehydrative etherification approach.¹³⁻¹⁸ In contrast to the classical Williamson ether synthesis, which utilize organohalide compounds and strongly basic conditions for the generation of the requisite alkoxide intermediate, dehydrative etherification reactions proceed under essentially neutral conditions, and do not suffer from limitations imposed by competing elimination reactions or the use of halogenated hydrocarbon starting materials.

An additional area of interest for glycerol valorization has been as a starting material for the synthesis of complex organic structures which contain a functionalized glycerol moiety within the core architecture. A diverse array of compounds feature this motif, including marine natural products with cytotoxic activity, phospholipids involved with both metal chelation and cellular signaling pathways, advanced intermediates in the synthesis of pharmaceutically active compounds and amphiphilic polymers for the formation of polymeric micelles.¹⁹⁻²³ In general, glycerol does not lend itself well as a starting material for the synthesis of the protected 1-substituted glyceryl ethers required as intermediates in these synthetic sequences, unless protecting group strategies are employed to differentiate the chemically similar hydroxyl groups and improve solubility. Thus, the requisite-protected mono-glyceryl ethers are typically accessed by a relatively inefficient three-step process involving initial acetalization, followed by etherification with a halogenated hydrocarbon followed by acetal hydrolysis.²⁰⁻²³ This has led to the development of alternative synthetic strategies which derive the desired functionalized glycerol moiety from either carbohydrates or highly reactive and toxic epoxide starting materials, such as epichlorohydrin or glycidol.^{24,25}

We recently reported a protocol for the dehydrative etherification of alkyl alcohols and diols with activated alcohols catalyzed by nanoporous aluminosilicate materials to give the corresponding ether products in high yield and with excellent selectivity.²⁶ As part of our ongoing studies to develop novel reaction strategies,²⁷⁻³² we have extended our work in this area to consider protocols for the reaction of glycerol with activated and unactivated alcohols under aluminosilicate catalysis to provide the

corresponding 1-substituted glyceryl ethers. This can be achieved either by direct reaction of glycerol with the alcohol component to provide unprotected glyceryl ethers which are useful synthetic intermediates, or by novel, telescoped acetalization-dehydrative etherification protocols which provide direct and rapid access to protected ether products which are also of interest as potentially useful fuel additives.

RESULTS AND DISCUSSION

A range of silicate (S-1) and aluminosilicate materials (Al-5-(3.00), Al-13-(3.18) and Al-54-(3.06)) displaying varying amounts of aluminum (Si/Al ratio 5:1, 13:1 and 54:1 respectively) and the borosilicate material (B-13-(3.54)) were synthesized using our previously reported evaporation induced self-assembly (EISA) procedure,^{26,27} and characterized using a range of standard techniques (Table 1 and pages S4-S9 supplementary information). All of these silicate materials displayed the expected large surface areas and narrow pore size distributions (Table 1), and the mesoporous nature of the Al-13-(3.18) material was further confirmed by TEM, which displayed sponge-like structures typical of amorphous materials (Figure 1).

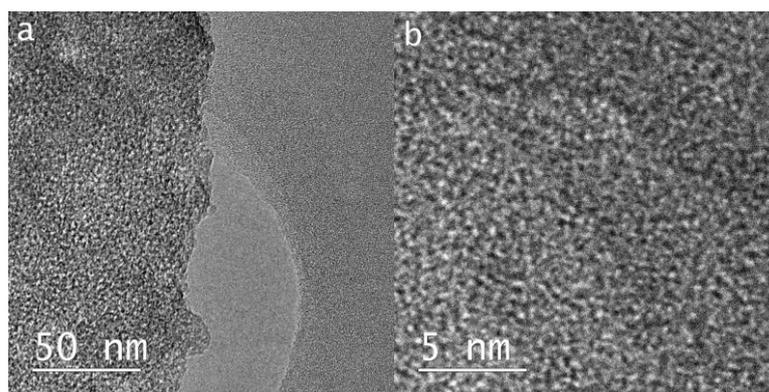


Figure 1. Transmission electron micrographs of calcined Al-13-(3.18) a) 120kX and b) 1200kX

The disordered mesoporous nature of these materials was also confirmed by the XRD patterns obtained for this sample, which displayed a broad peak at low angles ($2\theta \sim 2.5^\circ$) of moderate intensity (S-6 Supplementary Information). Samples synthesized by this modified EISA procedure produced

materials with a significantly larger pore size and exhibited higher acidity than the smaller pore materials produced using our original EISA method.²⁸⁻³⁰

Table 1. Nanoporous Silicate Physical Properties.

Catalyst	Si/Al Gel Composition	Si/Al (EDX) ^a	BET Surface Area (m ² g ⁻¹) ^b	Acidity (μmol g ⁻¹) ^c	Pore Width (nm) ^d
S-1-(3.42)	-	-	914	130	3.42
Al-13-(3.18)	13	14	980	530	3.18
Al-5-(3.00)	5	5	1542	214	3.00
Al-54-(3.06)	54	56	1230	400	3.06
B-13-(3.54)	13	-	1095	590	3.54
Zeolite Y-5	5	3	763	300	1.11
ZSM-5-30	30	19	405	1450	0.82
Amberlyst TM -15	-	-	45 ^e	4600 ^e	24 ^e

^a Determined by energy dispersive X-ray (EDX) analysis. ^b Obtained by the Brunauer–Emmett–Teller (BET) method. ^c Determined by temperature programmed desorption (TPD) analysis. ^d Determined by the non-linear density function theory (NLDFIT) method. ^e Literature values: see reference [33].

Our initial studies built on our previous experience in this area employing the aluminosilicate material Al-13-(3.18) to catalyze the reactions of a two-fold excess of glycerol with *para*-methoxybenzyl alcohol (PMBA) **1a** in dimethyl carbonate (DMC) (Table 2). Disappointingly, reactions carried out at reflux temperatures gave only low conversions to the desired 1-functionalized PMB ether **2a** even after protracted reaction times (entry 1). Conversions were much improved, however, by employing higher temperatures and carrying out the transformation in sealed reaction vessels. Under these modified conditions, high conversions to the desired PMB ether were achieved with the expected high selectivity for the 1-PMB ether **2a** over the isomeric 2-PMB ether **3a** (entry 2). In addition to the isomeric ethers **2a** and **3a**, small quantities of the self-condensation product **4a** were also observed in these reactions. We next examined the ability of a range of silicate materials,

of this reaction, and further highlights the efficiency of the nanoporous silicate materials. This product presumably arises due to the high acidity of AmberlystTM-15 which is sufficient to catalyze the hydrolysis of DMC to produce methanol, which subsequently reacts with PMBA to give the methyl ether product. The quantity of 4-methoxybenzyl methyl ether present was unaffected by pre-drying the AmberlystTM-15 catalyst, and suggests that it is the water generated during the dehydrative etherification reaction which is responsible for DMC hydrolysis, and subsequent methanol generation. No 4-methoxybenzyl methyl ether was observed in the corresponding reactions catalyzed by zeolites or nanoporous aluminosilicates, presumably due to the much lower acidity of these materials. In line with previous reports and our own observations,^{26,27} the silicate material S-1-(3.42) displayed little catalytic activity, and in this case starting materials were again recovered unchanged (entry 9).

We next addressed strategies for improving selectivity by minimizing the formation of the dimeric ether **4a**. We have previously demonstrated that this can be achieved by ensuring that only low concentrations of the activated alcohol are present in the reaction mixture by slow addition of the activated alcohol as a dilute solution.²⁶ Since this was not possible in these reactions, we employed increased quantities of glycerol (Table 3, entry 2). While this approach was successful in minimizing dimer formation, it also led to significant catalyst aggregation in the early stages of the reaction due to the polar nature of glycerol, resulting in capricious catalyst activity marked by slower reactions and decreased product formation (entry 2). In an attempt to overcome the deleterious effects of high glycerol loadings, we next assessed the potential of employing other polar solvents with a view to reducing catalyst aggregation. Disappointingly, reactions carried out in acetonitrile gave significantly poorer conversions (entry 3), as did reactions in methanol. The use of chloroform did partially ameliorate the aggregation issue, but provided overall yields of **2a** and product distributions comparable to reactions carried out in DMC (entry 4). We determined that the benefits of pursuing

chloroform as a solvent in these reactions were not sufficient to justify using a material with such a poor environmental profile.

Table 3: Optimisation of Reaction Conditions^a

$$\text{HO-CH}_2\text{-CH(OH)-CH}_2\text{-OH} \xrightarrow[100\text{ }^\circ\text{C, ROH}]{\text{Al-13-(3.18) (50 mg)}} \text{HO-CH}_2\text{-CH(OH)-CH}_2\text{-OR} + \text{HO-CH}_2\text{-CH(OR)-CH}_2\text{-OH} + \text{R-O-R}$$

2a-d
3a-d
4a-d

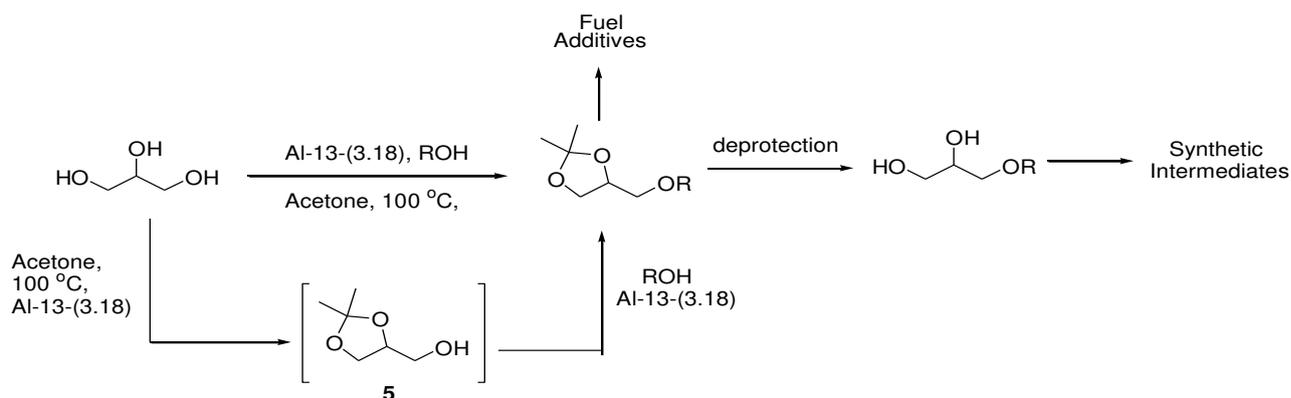
Entry	Alcohol	Glycerol:ROH ratio	Solvent	Time (h)	Selectivity 2:3:4 (%) ^b	Conversion (%) ^b
1	PMBA	2:1	DMC	4	90:6:4	85
2	PMBA	4:1	DMC	5	95:5:0	70
3	PMBA	4:1	CH ₃ CN	4	81:19:0	40
4	PMBA	4:1	CHCl ₃	4	95:5:0	75
5	DMDPM	2:1	DMC	1	92:7:1	95 ^c
6	DMDPM	2:1	CHCl ₃	1	85:6:9	90 ^c
7	DMBA	2:1	DMC	1	88:9:0	92
8	DMBA	2:1	CHCl ₃	1	100:0:0	12
9	DPM	2:1	DMC	4	98:2:0	40 ^c
10	DPM	2:1	CHCl ₃	4	75:5:20	41 ^c

^a Experimental conditions: The catalyst (50 mg) was added to a solution of the specified alcohol (1 mmol) and glycerol in the specified solvent (3 mL) in a sealed reaction vessel and heated to 100 °C. ^b Determined by ¹H NMR and GC–MS analysis of the crude reaction mixture. ^c ¹H NMR analysis in DMSO-d₆.

We next extended our studies to consider the reaction of glycerol with a range of activated alcohols to produce the corresponding mono-ether glyceryl derivatives bearing commonly employed protecting groups.³⁴ Our initial reactions, employing a two-fold excess of glycerol over 4,4'-dimethoxybenzhydrol (DMDPM) **1b** in DMC, proceeded rapidly to provide high yields of the 1-DMDPM ether **2b** again with excellent selectivity over the 2-DMDPM ether **3b** (entry 5). In this case, only low yields of the dimeric ether **4b** were observed, which may reflect the reported ability of this material to act as an alkylating species in its own right. Similarly, reactions of the activated alcohol 3,4-dimethoxybenzyl alcohol (DMBA) **1c** provided high yields of the desired ether product **2c** again with minimal formation of the dimeric ether (entry 7). Reactions of the less activated

diphenylmethanol (DPM) **1d** proceeded more slowly, and gave only moderate yields of **2d** (entry 9). Reactions carried out with alcohols **1b-1d** under similar conditions in chloroform displayed no significant improvements over DMC, highlighting the effectiveness of DMC as a sustainable and less toxic alternative to commonly employed halogenated solvents.³⁵

An alternative strategy that could effectively address both the issues encountered with the formation of the dimeric ether product, and hence improve selectivity for the 1-alkylated ether products, is to reduce the polarity of glycerol by selective protection of one or more of the hydroxyl groups. This is a widely employed but relatively inefficient strategy, where the protected glyceryl derivative is first synthesized and isolated, and then reacted with an alkylating agent in a separate reaction.²⁰⁻²³ In contrast to this two-step approach, we identified strategies where the protection step and the dehydrative etherification reaction are achieved in a telescoped sequence either in a one-pot, sequential protocol or alternatively, by a one-pot tandem reaction sequence (**Scheme 1**). This strategy is highly attractive, not only because of its improved efficiency, but also due to the potential improvements in the selectivity of the etherification reaction which is beneficial in the synthesis of synthetic building blocks for further elaboration into complex glycerol derivatives. Furthermore, it also allows access to glycerol derivatives with significantly reduced polarity and physical properties more suited to application as fuel additives.



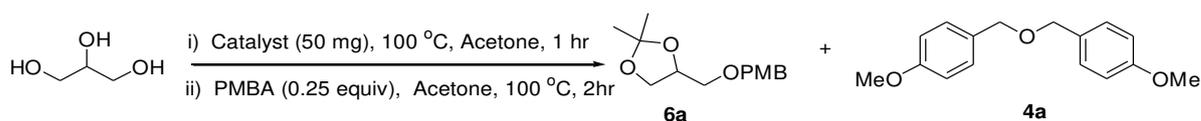
Scheme 1: Telescoped Sequential and Tandem Reaction Sequences

There has been considerable interest in the development of reaction sequences where multiple synthetic transformations are achieved without the isolation and purification of intermediates, as they offer potential savings and improved efficiency due to the reduction in the number of synthetic steps, the elimination of work-up procedures and the subsequent reduction in the quantity of solvents employed, and the overall improvement in atom efficiency.³⁶⁻³⁹ Examples of telescoped catalytic processes, however, in which one catalyst is responsible for catalyzing two distinctly different reactions, are somewhat less common.^{28,40-43} We have previously demonstrated that our nanoporous aluminosilicate materials are highly efficient catalyst for the direct conversion of carbonyl compounds to acetals in the presence of alcohols and diols without the requirement for an additional dehydrating agent.⁴⁴ We reasoned that it should be possible to extend our studies to develop a tandem acetalization-dehydrative etherification process that did not require prior synthesis and isolation of the protected glycerol component. A significant benefit of this streamlined approach is that the efficiency of the sequence is considerably improved, as the acetal is generated *in situ* and does not require prior synthesis and purification. This strategy also capitalizes on the benefits of our direct dehydrative etherification chemistry which avoids the use of traditional etherification conditions employing halogenated alkylating agents under strongly basic conditions.

We identified the isopropylidene group as a suitable protecting group strategy, employing acetone both as a solvent and as an acetalization reagent. An additional benefit of this strategy is that it selectively forms the 5-membered dioxolane product solketal **5**, produced from selective reaction of the 1- and 2-hydroxy groups of glycerol,^{7,44} rather than the isomeric 6-membered dioxane, which would provide enhanced selectivity for 1-protected ether products in the subsequent etherification reaction. We initially considered a telescoped, sequential protocol, as we reasoned that this strategy should provide the optimal outcome in terms of overall yield and selectivity, as it initially forms the protected glycerol intermediate solketal **5** produced *in situ*, which is then selectively converted into the mono-ether product on addition of the activated alcohol component.

Our initial reactions employed an excess of glycerol over PMBA, as it has been demonstrated that these protecting group reactions are typically most efficient when carried out with an excess of the solketal/glycerol component.^{19,20,23} Furthermore, carrying out the reaction in the presence of an excess of solketal also has the added benefit of minimizing the formation of the self-condensation product **4a**. We began our studies in this area by rescreening our nanoporous silicate materials to assess the efficacy of these catalysts to promote both the acetalisation and dehydrative etherification reactions of glycerol in acetone (Table 4).

Table 4: Telescoped, Sequential Acetalization-Etherification Reactions of Glycerol with PMBA^a



Entry	Catalyst	Conversion of 5 to 6a (%) ^b
1	Al-13-(3.18)	88
2	Al-5-(3.00)	80
3	Al-54-(3.06)	78
4	ZSM-5-30	50
5	Amberlyst TM -15	39 ^c

^a Experimental conditions: The catalyst (50 mg) was added to a solution of glycerol (4 mmol) in acetone (3 mL) in a sealed reaction vessel and heated to 100 °C for 1 hour before the addition of PMBA (1 mmol). ^b Determined by ¹H NMR and GC analysis of the crude reaction mixture. ^c Reaction gave 4-methyl-3-penten-2-one as the major product.

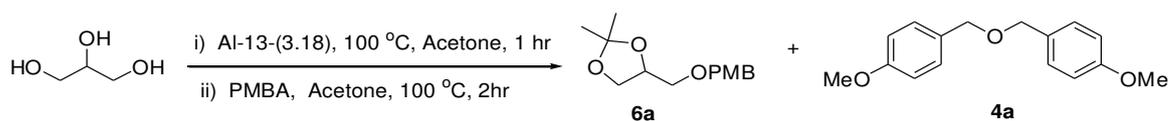
These initial reactions confirmed the high efficiency of all of these catalysts to promote the formation of solketal **5** directly from acetone and glycerol, which proceeded to give quantitative conversions in very short reaction times, and with the expected selectivity for the dioxolane product. Importantly, no catalyst aggregation occurred in these reactions. PMBA was then added to the reaction, followed by heating to promote the etherification reaction. Gratifyingly, GC-MS, GC and ¹H NMR analysis of the crude reaction mixtures employing our aluminosilicate materials after two

hours confirmed the presence of high yields of the desired protected solketal derivative **6a** (Table 4, entries 1-3) with only trace quantities of the dimeric ether species **4a**. In order to confirm the high selectivity for the formation of the 1-protected PMB ether product over the 2-protected ether product **3a**, the crude reaction mixture from the reaction employing Al-13-(3.18) was treated with dilute acid to remove the isopropylidene protecting group. ¹H NMR and GC–MS analysis of the crude reaction mixture confirmed the formation of the 1-PMB ether product **2a** with excellent selectivity (>98%) over the corresponding 2-PMB ether **2b**. Reactions employing ZSM-5-30 also proceeded to give good conversions to **6a**, however, trace quantities of the expected aldol product, formed by self condensation of acetone, were detected by both GC–MS and ¹H NMR analysis (entry 4). AmberlystTM-15 gave only moderate conversions to **6a**, however, in line with literature reports,⁴⁵ this highly acidic material was very effective in promoting the aldol condensation of acetone to give the aldol by-product as the major product (entry 5).

We also investigated the corresponding sequential reactions in the presence of both stoichiometric and excess quantities of the alkylating agent under similar reaction conditions (Table 5). While this approach also proved successful for the formation of **6a**, overall conversions at stoichiometric or near stoichiometric ratios were significantly limited by the formation of the dimeric ether product **4a** (entries 2-4). Acceptable yields of **6a** were achieved, however, employing a four-fold excess of PMBA to compensate for the material consumed in the unproductive dimerization reaction (entry 5). We also investigated the potential for catalyst recovery and recycling using this telescoped, sequential protocol as a representative example. We have previously demonstrated that it is beneficial to subject the catalyst recovered from dehydrative etherification reactions to a short recalcination step in order to achieve consistent results. This process restores full catalytic activity without significantly changing the physical properties of the material even after multiple recalcination steps.²⁶ We were highly gratified to observe that the recovered, recalcined, Al-13-(3.18) material displayed near

identical activity to the fresh material for the formation of the 1-PMB ether **6a** in the sequential reaction protocol (Table 5, entry 6).

Table 5: Optimisation of Telescoped, Sequential Acetalization-Etherification Reactions of Glycerol with PMBA^a

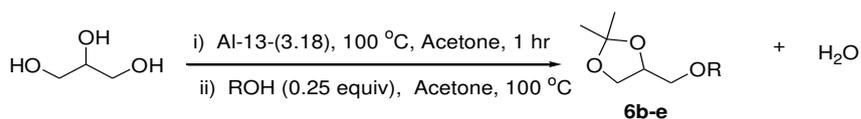


Entry	Glycerol:PMBA ratio	Selectivity 6a:4a (%) ^b	Conversion of 5 to 6a (%) ^b
1	4:1	>98:2	88
2	1:1	65:35	60
3	1:2	50:50	55
4	1:2	50:50	52 ^c
5	1:4	20:80	70
6	4:1	>98:2	86 ^c

^a Experimental conditions: The catalyst (50 mg) was added to a solution of glycerol in acetone (3 mL) in a sealed reaction vessel and heated to 100 °C for 1 hour before the addition of PMBA. ^b Determined by ¹H NMR and GC analysis of the crude reaction mixture. ^c Recycled catalyst.

We subsequently extended our studies to consider the reactions of a number of activated alcohols with glycerol to produce the corresponding ether derivatives exhibiting commonly employed alcohol protecting group strategies. We were highly gratified to observe that the sequential acetalization-dehydrative etherification reactions of DMDPM **1b**, DMBA **1c** and DPM **1d** all proceeded rapidly to give excellent yields of the corresponding mono protected solketal derivatives (Table 6, entries 1-4). In the case of benzyl alcohol (BA) **1e** (entry 5), little or no ether product was observed even after extended reaction times, which is presumably due to the relatively low reaction temperatures employed here.¹⁶

Table 6: Telescoped, Sequential Acetalization-Etherification Reactions of Glycerol with Activated Alcohols^a

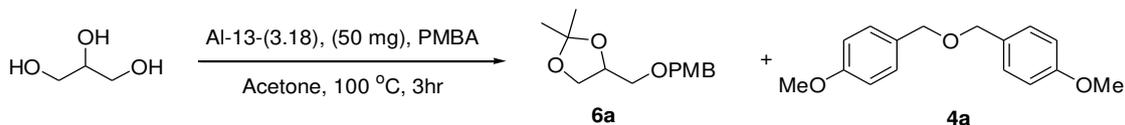


Entry	Alcohol	Time (h)	Yield 6b-6e (%) ^b
1	DMDPM	2	78
2	DMBA	3	72
3	DMBA	2	69 ^c
4	DPM	2	68
5	BA	4	<10

^a Experimental conditions: The catalyst (50 mg) was added to a solution of glycerol (4 mmol) in acetone (3 mL) in a sealed reaction vessel and heated to 100 °C for 1 hour before the addition of the activated alcohol (1 mmol). ^b Isolated yields. ^c Recycled catalyst.

The tandem variant of this telescoped process, in which all of the reagents are present at the start of the reaction, was also successful employing PMBA with an excess of glycerol, and provided moderate conversions to **6a** (Table 7; entries 1 and 2). In this case, the competing dimerization reaction proved to be more problematic than in the corresponding sequential reactions, and impacted on overall yields of **6a** by consuming PMBA. In this case, the addition of an excess of PMBA led to the formation of significant quantities of **4a** without significantly improving overall yields of **6a** (entries 3 and 4).

Table 7: Telescoped Tandem Acetalization-Etherification Reactions of Glycerol with PMBA^a



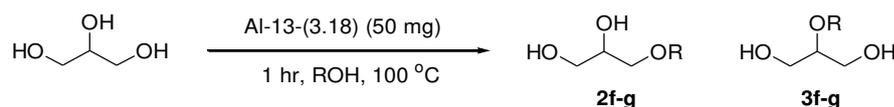
Entry	Glycerol:PMBA ratio	Conversion of 5 to 6a (%) ^b
1	4:1	65
2	2:1	45
3	1:2	52
4	1:3	60

^a Experimental conditions: The catalyst (50 mg) was added to a solution of glycerol and PMBA in acetone (3 mL) in a sealed reaction vessel and heated to 100 °C for 3 hours. ^b Determined by ¹H NMR and GC analysis of the crude reaction mixture.

Finally, we considered the reactions of glycerol with unactivated alcohols, such as *tert*-butanol (TBA) (**1f**) and 1-butanol **1g**. The formation of di- and tri-alkyl ether products derived from glycerol and alkenes under heterogeneous catalysis has proved to be a vibrant research area^{10-12,16-18} for the synthesis of potentially useful oxygenated fuel additives. These studies have demonstrated that macroreticular ion exchange resins, such as Amberlyst-35, are highly efficient promoters of this reaction, while zeolites, such as H-Y and Z-beta, are unsuitable due to their small pore size.¹⁸ Furthermore, reactions employing TBA as the alkylating agent generally produce poor yields of the mono-ether product **2f**, which is unsuitable for use as a fuel additive owing to its high water solubility. These poor yields are due to deactivation of the catalyst by water produced in the etherification reaction.¹⁸ To improve the miscibility of glycerol mono-ether products it is necessary to protect the remaining free alcohol functionalities, and for example, a crude mixture of glycerol, solketal and the corresponding mono *tert*-butyl ether **2f** derived from solketal, has been demonstrated to perform as an efficient octane booster when added to gasoline.⁴⁶ It occurred to us that a variant of our telescoped acetalization-etherification protocols may provide an attractive approach for the synthesis of these *tert*-butyl protected materials, given the demonstrated efficiency of the acetalization reaction and the ability to perform the sequence in a one-pot manner.

We began these studies by rescreening our silicate materials to assess the efficacy of these catalysts for the dehydrative etherification reactions of glycerol in an excess of TBA, and monitoring product formation by ^1H NMR and GC–MS analysis (Table 8).⁴⁷

Table 8: Nanoporous Silicate-Mediated Reactions of Glycerol with Unactivated Alcohols^a



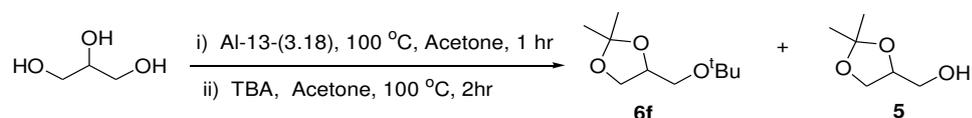
Entry	Alcohol	Catalyst	Selectivity 2:3 (%)	Conversion (%) ^b	Product
1	TBA	Al-13-(3.18)	>98:2	35	2f
2	TBA	Al-5-(3.00)	>98:2	30	2f
3	TBA	Al-54-(3.06)	>98:2	32	2f
4	TBA	Al-13-(3.18)	>98:2	68 ^c	2f
5	TBA	B-13-(3.54)	-	<5	2f
6	TBA	No Catalyst	-	<5	-
7	1-Butanol	Al-13-(3.18)	-	<10 ^d	2g

^a Experimental conditions: The catalyst (50 mg) was added to a solution of glycerol (100 mg) in the specified solvent (3 mL) in a sealed reaction vessel and heated to 100 °C. ^b Determined by ^1H NMR analysis of the crude reaction mixture. ^c An additional 25 mg portion of catalyst was added after 1 hr and the reaction continued for an additional 1 hour. ^d Reaction at 120 °C.

Gratifyingly, all of the aluminosilicate materials performed well, and provided moderate yields of **2f** (entries 1-3) after one hour with the expected high selectivity for the mono-ether product.¹³ Extending reaction times led to no significant increase in the yield of ether, presumably due to deactivation of the catalyst. Improved yields could be achieved if an additional portion of catalyst was added (entry 4), and under these modified conditions, respectable yields of the mono-ether product **2f** were achieved. It is noteworthy that at higher conversions, small quantities of the di- and tri-ether products (<5%) were observed by GC–MS analysis. While the requirement to use comparatively high catalyst loadings to achieve acceptable yields is at first sight undesirable, the complete recyclability of the aluminosilicate material employed in these reactions ameliorates this limitation. As previously, the

use of the borosilicate material B-13-(3.54) (entry 5) or indeed no catalyst (entry 6), produced no ether products, and starting materials were recovered unchanged. We also investigated the use of primary alcohols in the etherification reaction employing 1-butanol **1g** as a model alkylating reagent. Under our standard conditions or at slightly elevated reaction temperatures, no significant quantity of ether product **2g** were observed (entry 7) by GC-MS or ¹H NMR analysis, which is again presumably due to the relatively low reaction temperatures employed here.^{3,16}

Finally, we investigated the opportunity to develop a one-pot protocol by carrying out the etherification reaction in acetone under our standard telescoped reaction conditions (**Scheme 2**). The addition of an excess of TBA to an acetone solution of solketal, led to the formation of a 2:1 mixture of solketal and ether product **6f** as determined by ¹H NMR, GC and GC-MS analysis. In addition, small quantities of the mono-ether product **2f** were observed, presumably due either to hydrolysis of **6f**, or by hydrolysis of solketal followed by dehydrative etherification of the resulting free glycerol.



Scheme 2: Telescoped, Sequential Reactions of Glycerol with TBA

In conclusion, the high aluminum containing nanoporous aluminosilicate material Al-13-(3.18) is a highly effective catalyst for the dehydrative etherification reactions of glycerol in DMC, providing direct access to protected 1-substituted ethers from activated alcohols. In order to overcome issues with catalyst aggregation at high glycerol loadings, acetone was employed as solvent which allowed us to extend our studies to successfully develop telescoped acetalization-dehydrative etherification protocols applying either a sequential or tandem approach. This strategy avoids the prior isolation and purification of the intermediate solketal product by carrying out both the acetalization and dehydrative etherification reactions in one reaction vessel. Furthermore, in addition to achieving higher and more consistent yields of ether products, this approach allows for improved selectivity in

the etherification reaction, and provides a simple, efficient and effective synthetic strategy for the generation of advanced intermediates useful for the synthesis of a range of complex glycerol derivatives. This telescoped approach is also effective for the etherification of glycerol employing the unactivated alcohol TBA, and directly provides direct access to the mono *tert*-butyl ether of solketal which is a potentially useful and bio-sustainable fuel additive.

EXPERIMENTAL SECTION

Catalyst Preparation.

A typical preparation for the synthesis of the aluminosilicate AS-13-(3.18) catalyst is as follows:^{26,27} cetyltrimethylammonium bromide (4.0 g, 11 mmol) was dissolved in a solution of hydrochloric acid (2.5 mL, 0.1 M), ethanol (17.5 mL) and water (22.5 mL). Tetraethyl orthosilicate (25 mL, 112 mmol) was then added and the mixture stirred for 10 minutes at 40 °C. The solution was cooled to room temperature and aluminum nitrate nonahydrate (3.35 g, 8.95 mmol) was added in one portion. The mixture was stirred for 20 minutes and then left to age at room temperature for 24 hours. The resultant orange solid was crushed into a fine powder and calcined in air at 550 °C for 6 hours to remove the organic template to give a fine white powder. All materials were stored at 120 °C for at least 12 hours prior to use.

General Procedure for the Direct Dehydrative Etherification of Glycerol with PMBA.

The aluminosilicate catalyst Al-13-(3.18) (50 mg) was added to a solution of glycerol (184 mg, 2.0 mmol) and PMBA (138 mg, 1 mmol) in DMC (3 mL) and the reaction heated to 100 °C with vigorous stirring. On completion of the reaction, the catalyst was removed by filtration through a Celite plug which was washed with dimethyl carbonate (2 × 2 mL), and the combined solvents were removed under reduced pressure to afford the crude product as a colorless oil that was purified by column chromatography (hexane → 30% diethyl ether:hexane);²³ ¹H NMR (400 MHz; CDCl₃) δ = 7.25 (2H,

d, $J = 9.0$ Hz), 7.00 (2H, d, $J = 9.0$ Hz), 4.50 (2H, s), 3.50-3.85 (8H, m); ^{13}C NMR (100 MHz; CDCl_3) $\delta = 159.3, 129.7, 129.5, 113.9, 73.2, 71.4, 70.8, 64.0, 55.3$; ν_{max} (film)/ cm^{-1} (neat) 3401, 2934, 1613, 1513, 1302, 1248 and 1174; MS (EI) m/z 212 (M)⁺.

General Procedure for the Sequential Acetalization-Dehydrative Etherification of Glycerol with PMBA.

The aluminosilicate catalyst Al-13-(3.18) (50 mg) was added to a solution of glycerol (368 mg, 4.0 mmol) in acetone (3 mL) and the reaction heated to 100 °C with vigorous stirring. After one hour, the reaction mixture was cooled to room temperature and PMBA (138 mg, 1 mmol) was added, and the reaction reheated to 100 °C with vigorous stirring for an additional 2 hours. On completion of the reaction, the catalyst was removed by filtration through a Celite plug which was washed with dimethyl carbonate (2×2 mL), and the combined solvents were removed under reduced pressure to afford the product as a colorless oil. This crude product was dissolved in methanol (3 mL) and treated with H_2SO_4 (50 μL , 1M solution) at room temperature for four hours.⁴⁷ Removal of the solvent under reduced pressure gave the crude product as colorless oil with spectroscopic data identical to that above.

General Procedure for the Dehydrative Etherification of Glycerol with *tert*-Butanol.

The aluminosilicate catalyst Al-13-(3.18) (50 mg) was added to a solution of glycerol (100 mg, 1.09 mmol) in *tert*-butanol (3 mL) and the reaction heated to 100 °C with vigorous stirring for 1 hour. At this time, the reaction was cooled to room temperature and an additional quantity of catalyst (25 mg) was added and the reaction reheated to 100 °C with vigorous stirring for an additional hour. On completion of the reaction, the catalyst was removed by filtration through a Celite plug which was

washed with dimethyl carbonate (2 × 2 mL), and the combined solvents were removed under reduced pressure to afford the crude product as a colorless oil.⁴⁸

ASSOCIATED CONTENT

Supplementary Information

General methods, experimental procedures, catalyst characterization methods, catalyst characterization data and spectroscopic data for ether products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*Email: andrew.graham@southwales.ac.uk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

The authors thank Rob Clowes at the Centre for Materials Discovery, Liverpool University for XRD analysis. The authors thank the EPSRC UK National Solid-state NMR Service at Durham University for solid-state NMR spectra, the EPSRC UK National Mass Spectrometry Facility (NMSF) at Swansea University for high resolution mass spectra. UK Catalysis Hub is kindly thanked for resources and support provided via our membership of the UK Catalysis Hub Consortium and funded by EPSRC (portfolio grants EP/K014706/1, EP/K014668/1, EP/K014854/1 and EP/K014714/1).

REFERENCES

- (1) Morrison, L. R. Glycerol, Kirk-Othmer Encyclopedia of Chemical Technology, John Wiley & Sons, Inc., New York, 2001.
- (2) Wang, Z. Z. J.; Zhuge, J.; Fang, H.; Prior, B. A. Glycerol production by microbial fermentation: a review. *Biotechnol. Adv.* **2001**, *19*, 201–223.
- (3) Sutter, M.; Da Silva, E.; Duguet, N.; Raoul, Y.; Méta y. E.; LeMaire, M. Glycerol Ether Synthesis: A bench test for green chemistry concepts and technologies. *Chem. Rev.* **2015**, *115*, 8609–8651.
- (4) Zhou, C.-H.; Beltramini, J. N.; Fan Y.-X.; Lu, G. Q. Chemoselective catalytic conversion of glycerol as a biorenewable source to valuable commodity chemicals. *Chem. Soc. Rev.* **2008**, *37*, 527–549.
- (5) Papanikolaou, S.; Fakas, S.; Fick, M.; Chevalot, I.; Galiotou-Panayotou, M.; Komaitis, M.; Marc I.; Aggelis, G. Biotechnological valorization of raw glycerol discharged after bio-diesel (fatty acid methyl esters) manufacturing process: production of 1,3-propanediol citric acid and single cell oil. *Biomass Bioenerg.* **2008**, *32*, 60–71.
- (6) Pagliaro, M.; Cirimuina, R.; Kimura, H.; Rossi, M.; Pina, C. D. From glycerol to value added products. *Angew. Chem. Int. Ed.* **2007**, *46*, 4434–4440.
- (7) Deutsch, J.; Martin, A.; Lieske, H. Investigations on heterogeneously catalysed condensations of glycerol to cyclic acetals. *J. Catal.* **2007**, *245*, 428–435.
- (8) Mota, C. J. A.; da Silva, C. X. A.; Rosenbach, Jr. N.; Costa, J.; da Silva, F. Glycerin derivatives as fuel additives: the addition of glycerol/acetone ketal (solketal) to gasolines. *Energy Fuels* **2010**, *24*, 2733–2736

- (9) Huber, G. W.; Iborra, S.; Corma, A. Synthesis of transportation fuels from biomass: chemistry, catalysis and engineering. *Chem. Rev.* **2006**, *106*, 4044–4098.
- (10) Izquierdo J. F.; Montiel, M.; Palés, I.; Outón, P. R.; Galán, M.; Jutglar, L.; Villarrubia, M.; Izquierdo, M.; Hermo, M. P.; Ariza X. Fuel additives from glycerol etherification with light olefins: state of the art. *Renew. Sust. Energ. Rev.* **2012**, *16*, 6717–6724.
- (11) Di Serio, M.; Casale, L.; Tesser, R.; Santacesaria, E. New process for the production of glycerol tert-butyl ethers. *Energy Fuels* **2010**, *24*, 4668–4672.
- (12) Klepáčová, K.; Mravec, D.; Kaszonyi, A.; Bajus, M. Etherification of glycerol and ethylene glycol by isobutylene. *Appl. Catal. A* **2007**, *328*, 1–13.
- (13) Karine, R. S.; Krause, A. O. I. New biocomponents from glycerol. *Appl. Catal. A* **2006**, *306*, 128–131.
- (14) Corma, A.; Renz, M. A general method for the preparation of ethers using water-resistant solid Lewis acids. *Angew. Chem. Int. Ed.* **2007**, *46*, 298–300.
- (15) Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. Dehydration reactions in water. Brønsted acid-surfactant-combined catalyst for ester, ether, thioether, and dithioacetal formation in water. *J. Am. Chem. Soc.* **2002**, *124*, 11971–11978.
- (16) Nandiwale, K. Y.; Patil, S. E.; Bokade, V. V. Glycerol etherification using n-butanol to produce oxygenated additives for biodiesel fuel over H-beta zeolite catalysts. *Energy Technol.* **2014**, *2*, 446–452.
- (17) Pico, M. P.; Rosas, J. M.; Rodríguez, S.; Santos, A.; Romero, A. Glycerol etherification over acid ion exchange resins: effect of catalyst concentration and reusability. *J Chem. Technol. Biotechnol.* **2013**, *88*, 2027–2038.

- (18) Klepáčová, K.; Mravec, D.; Bajus, M. tert-Butylation of glycerol catalysed by ion-exchange resins. *Appl. Catal. A* **2005**, *294*, 141–147.
- (19) Pack, D. W.; Chen, G.; Maloney, K. M.; Chen, C.-T.; Arnold, F. H. A metal-chelating lipid for 2D protein crystallization *via* coordination of surface histidines. *J. Am. Chem. Soc.* **1997**, *119*, 2479–2487.
- (20) Johns, M. K.; Yin, M.-X.; Conway, S. J.; Robinson, D. E. T. E.; Wong, L. S.-M.; Bamert, R.; Wettenhalle, R. E. H.; Holmes, A. B. Synthesis and biological evaluation of a novel cardiolipin affinity matrix. *Org. Biomol. Chem.* **2009**, *7*, 3691–3697.
- (21) Jiang, G.; Xu, Y.; Falguières, T.; Gruenberg, J.; Prestwich, G. D. Concise synthesis of ether analogues of lysobisphosphatidic acid. *Org. Lett.* **2005**, *7*, 3837–3840.
- (22) Feng, L.; Manabe, K.; Shope, J. C.; Widmer, S.; DeWald, D. B.; Prestwich, G. D. A real-time fluorogenic phospholipase A₂ assay for biochemical and cellular activity measurements. *Chem. Biol.* **2002**, *9*, 795–803.
- (23) Qin, D.; Byun, H.-S.; Bittman, R. Synthesis of plasmalogen *via* 2,3-bis-*O*-(4'-methoxybenzyl)-*sn*-glycerol. *J. Am. Chem. Soc.* **1999**, *121*, 662–668.
- (24) Walker, L. F.; Bourghida, A.; Connolly, S.; Wills, M. Synthesis of 2,5-dihydrofurans *via* alkylidene carbene insertion reactions. *J. Chem. Soc., Perkin Trans. 1* **2002**, 965–981.
- (25) Cassel, S.; Debaig, C.; Benvegna, T.; Chaimbault, P.; Lafosse, M.; Plusquellec, D.; Rollin, P. Original synthesis of linear, branched and cyclic oligoglycerol standards. *Eur. J. Org. Chem.* **2001**, 875–896.

- (26) Davies, T. E.; Kean, J. R.; Apperley, D. C.; Taylor S. H.; Graham, A. E. Nanoporous aluminosilicate-mediated synthesis of ethers by a dehydrative etherification approach. *ACS Sustain. Chem. Eng.* **2014**, *2*, 860–866.
- (27) Davies, T. E.; Kondrat, S. A.; Nowicka, E.; Kean, J. L.; Harris, C. M.; Socci, J. M.; Apperley, D. C.; Taylor, S. H.; Graham, A. E. Nanoporous aluminosilicate-mediated Meinwald rearrangement of epoxides. *Appl. Catal. A* **2015**, *493*, 17–24.
- (28) Kubczyk, T. M.; Williams, S. M.; Kean, J. R.; Davies, T. E.; Taylor S. H.; Graham, A. E. Nanoporous aluminosilicate catalyzed Friedel–Crafts alkylation reactions of indoles with aldehydes and acetals. *Green Chem.* **2011**, *13*, 2320–2325.
- (29) Robinson, M. W. C.; Davies, A. M.; Mabbett, I.; Davies, T. E.; Apperley, D. C.; Taylor, S. H.; Graham, A. E. Synthesis of nanoporous aluminosilicate materials and their application as highly selective heterogeneous catalysts for the synthesis of β -amino alcohols. *J. Mol. Catal. A: Chem.* **2010**, *329*, 57–63.
- (30) Robinson, M. W. C.; Davies, A. M.; Mabbett, I.; Apperley, D. C.; Taylor, S. H.; Graham, A. E. Synthesis and catalytic activity of nanoporous aluminosilicate materials. *J. Mol. Catal. A: Chem.* **2009**, *314*, 10–14.
- (31) Bethell, D.; Graham, A. E.; Heer, J. P.; Markopoulou, O.; Page, P. C. B.; Park, B. K. Reactivity and selectivity in the oxidation of aryl methyl sulfides and sulfoxides by hydrogen-peroxide mediated by acetonitrile. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2161–2162.
- (32) Page, P. C. B.; Graham, A. E.; Park, B. K. A convenient preparation of symmetrical and unsymmetrical 1,2-diketones – application to fluorinated phenytoin synthesis. *Tetrahedron* **1992**, *48*, 7265–7274.

- (33) Neves, P.; Lima, S.; Pillinger, M.; Rocha, S. M.; Rocha, J.; Valente, A. A. Conversion of furfuryl alcohol to ethyl levulinate using porous aluminosilicate catalysts. *Catalysis Today* **2013**, *218–219*, 76–84.
- (34) Wuts, P. G. M.; Green, T. W. *Protective Groups in Organic Synthesis*; John Wiley and Sons, New York, 2006.
- (35) Ferrer, B.; Alvaro, M.; Garcia H.; Application of dimethyl carbonate as solvent and reagent, in: *Green Solvents 1: Properties and Applications in Chemistry*, ed A. M. Inamuddin, Springer, 2012.
- (36) Tietze, L. F. Domino reactions in organic synthesis. *Chem. Rev.* **1996**, *96*, 115–136.
- (37) Phillips, D. J.; Pillinger, K. S.; Wei, L.; Taylor, A. E.; Graham, A. E. Diol desymmetrization as an approach to the synthesis of unsymmetrical dienyl diesters. *Tetrahedron* **2007**, *63*, 10528–10533.
- (38) Bagley, M. C.; Lin, V.; Phillips, D. J.; Graham, A. E. Barium manganate in microwave-assisted oxidation reactions: synthesis of lactones by oxidative cyclization of diols. *Tetrahedron Lett.* **2009**, *50*, 6823–6825.
- (39) Phillips, D. J.; Graham, A. E. *In situ* generation of ylides for tandem oxidation-olefination reactions of unactivated diols. *Synlett* **2008**, 649–652.
- (40) Louie, J.; Bielawski, C. W.; Grubbs, R. H. Tandem catalysis: the sequential mediation of olefin metathesis, hydrogenation, and hydrogen transfer with single-component Ru complexes. *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.
- (41) Bielawski, C. W.; Louie, J.; Grubbs, R. H. Tandem catalysis: three mechanistically distinct reactions from a single ruthenium complex. *J. Am. Chem. Soc.* **2000**, *122*, 12872–12873.

- (42) Chen, J.; Otera, J. Parallel differentiated recognition of ketones and acetals. *Angew. Chem. Int. Ed.* **1998**, *37*, 91–93.
- (43) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. New tandem catalysis: preparation of cyclic enol ethers through a ruthenium-catalyzed ring-closing metathesis–olefin isomerization sequence. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391.
- (44) Yip, L.; Kubczyk, T. M.; Davies, T. E.; Taylor S. H.; Apperley, D. C.; Graham, A. E. Nanoporous aluminosilicate mediated transacetalization reactions: application in glycerol valorization. *Catal. Sci. Technol.* **2012**, *2*, 2258–2263.
- (45) Xu, Q.; Yang, Z.; Yin, D.; Zhang, F. Synthesis of chalcones by a novel sulfonic acid from bamboo. *Catal. Commun.* **2008**, *9*, 1579–1582.
- (46) Wessendorf, R.; Graf, W. Verfahren zur herstellung von polyolalkylethern. European Patent EP0718270 A2, June 26, 1996.
- (47) De Medeiros, F.E.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans 1* **1991**, 2725–2730.
- (48) Jamróz, M. E.; Jarosz, M.; Witowska-Jarosz, J.; Bednarek, E.; Tęcza, W.; Jamróz, M. H.; Dobrowolski, J. C.; Kijéński, J. Mono-, di-, and tri-*tert*-butyl ethers of glycerol: a molecular spectroscopic study. *Spectrochim. Acta A* **2007**, *67*, 980–988.

For Table of Contents Use Only

Dehydrative Etherification Reactions of Glycerol with Alcohols Catalyzed by Recyclable Nanoporous Aluminosilicates: Telescoped Routes to Glyceryl Ethers

Thomas E. Davies^a, Simon A. Kondrat^b, Ewa Nowicka^b, James J. Graham^c, David. C. Apperley^d,
Stuart. H. Taylor^b and Andrew E. Graham^{c*}

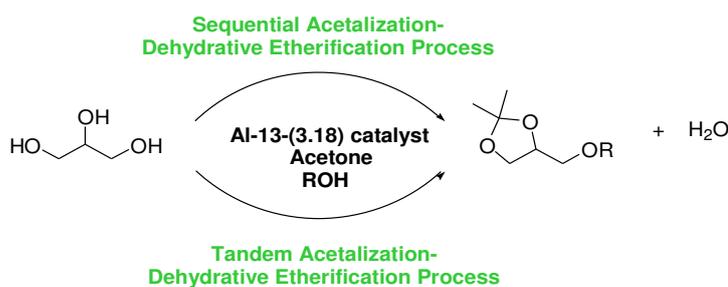
^a Stephenson Institute for Renewable Energy, Department of Chemistry, University of Liverpool, L69 7ZD, UK.

^b Cardiff Catalysis Institute, School of Chemistry, Main Building, Park Place, Cardiff University, Cardiff, CF10 3AT, UK.

^c School of Applied Sciences, University of South Wales, CF37 4AT, UK.

^d EPSRC Solid-State NMR Service, Department of Chemistry, Durham University, DH1 3LE, UK.

*Corresponding author. Email: andrew.graham@southwales.ac.uk



Recyclable nanoporous aluminosilicate materials efficiently catalyze the formation of 1-glyceryl ethers from alcohols in novel, telescoped acetalization-dehydrative etherification reactions.