

# The Continuous Acid-Catalyzed Dehydration of Alcohols in Supercritical Fluids: A New Approach to the Cleaner Synthesis of Acetals, Ketals, and Ethers with High Selectivity

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**Abstract:** We report a new continuous method for forming ethers, acetals and ketals using solid acid catalysts, DELOXAN ASP or AMBERLYST 15, and supercritical fluid solvents. In the case of ether formation, we observe a high selectivity for linear alkyl ethers with little rearrangement to give branched ethers. Such rearrangement is common in conventional syntheses. Our approach is effective for a range of *n*-alcohols up to *n*-octanol and also for the secondary alcohol 2-propanol. In the reaction of phenol with an alkylating agent, the continuous reaction can be tuned to give preferential O- or C-alkylation with up to 49% O-alkylation with supercritical propene. We also investigate the synthesis of a range of cyclic ethers and show an improved method for the synthesis of THF from 1,4-butanediol under very mild conditions.

## Introduction

In recent years there has been an increasing interest in environmentally more sustainable chemical processes.<sup>1,2</sup> This has led to increased research into the use of supercritical fluids (SCFs),<sup>3–5</sup> especially carbon dioxide, scCO<sub>2</sub>, as an environmentally benign and economically feasible reaction medium for heterogeneously catalyzed reactions.<sup>3,4,6</sup>

SCFs are gases heated above their critical temperature ( $T_C$ ) and compressed above their critical pressure ( $P_C$ ).<sup>7,8</sup> CO<sub>2</sub> has a critical point close to ambient temperature ( $T_C = 31.3$  °C,  $P_C = 72.9$  atm)<sup>4</sup> and is nonflammable, nontoxic, and inexpensive. With extremely low viscosity and good thermal and mass transport properties, SCFs are attractive solvents for continuous reactions. Moreover, their properties can be tuned within certain limits by adjusting pressure and temperature (and hence the density). In a continuous flow reactor, such parameters can be adjusted independently, giving very precise control over reaction conditions. Furthermore, continuous reactors are generally smaller and safer than batch reactors with equivalent production capacity.<sup>9</sup>

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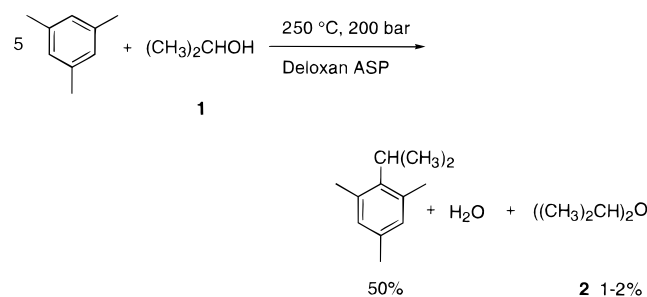
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## Scheme 1



We have previously reported<sup>10,11</sup> how SCFs, particularly scCO<sub>2</sub>, can be used for the continuous hydrogenation of a wide range of organic substrates using a fixed-bed reactor packed with a supported noble metal catalyst (e.g. Pt, Pd, etc.). This supercritical process combines cleaner processing with very high conversions and high product selectivities. More recently, with slightly modified equipment, we have carried out selective Friedel–Crafts alkylation reactions using solid acid catalysts and alcohols as the alkylating agents.<sup>12</sup> In some of these alkylation reactions, we observed small amounts of ethers as byproducts, formed by condensation of two molecules of the alcohol, Scheme 1. It was this observation which prompted the study of etherification in scCO<sub>2</sub>, reported here.

**Acid-Catalyzed Reactions in the Supercritical Phase.** A greater number of fundamental catalytic organic reactions are promoted by acid than all other catalytic reactions added together.<sup>13,14</sup> Solid acid catalysts such as clays, zeolites and even

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graphite are commonly used in such reactions, but rapid catalyst deactivation and a lack of selectivity has meant that such catalysts are far from ideal. In this paper, we describe the use of solid acid catalysts for the continuous conversion of alcohols to linear and branched ethers, to cyclic ethers, to aryl ethers and to acetals and ketals in good yields with high selectivities.

Although the first report of an acid catalyzed reaction in an SCF was over fifty years ago,<sup>15</sup> it is only in the last 10 years that the number of papers on the subject has grown substantially.<sup>16–22</sup> Eckert<sup>16</sup> has reported Friedel–Crafts alkylation of phenol in near critical water, with the water itself acting as the acid catalyst. There are a number of reports<sup>23,24</sup> of the oligomerization of supercritical isopentane or isobutane over a solid zeolite catalyst, with the supercritical reactant also acting as the solvent. This method is attractive because heterogeneous catalysts provide an environmentally and economically acceptable alternative to conventional homogeneous catalysts such as H<sub>2</sub>SO<sub>4</sub> and HF.<sup>13</sup> Furthermore, the catalyst lifetime can, in many cases, be dramatically improved under supercritical conditions, due to reduced coking.<sup>25,26</sup> Long chain ester formation from the acid-catalyzed reaction of oleic acid with methanol in scCO<sub>2</sub> has also been reported.<sup>18,19</sup> Very recent work by Subramaniam,<sup>27</sup> on the oligomerization of butane/1-butene, has shown that, using scCO<sub>2</sub> as a solvent (rather than supercritical isobutane/1-butene), reactions can be performed at lower temperatures, with greater selectivity for C<sub>8</sub> oligomers, although coking is a major problem at subcritical temperatures with respect to reactants<sup>28</sup> (~50 °C). Fortunately, however, catalyst coking is not a serious problem in the reactions reported in this paper.

**Ether synthesis.** There are a variety of methods for synthesizing ethers, all of which can encounter problems on scale-up. The most widely used method, the Williamson ether synthesis,<sup>29</sup> in which an alkyl halide is reacted with an alkoxide or a phenoxide, is generally high-yielding and clean, with a salt (e.g., NaCl) as a byproduct. However, it is far from an ideal synthetic route because the most common methods of preparing alkyl halides (e.g., alcohol substitution or the addition of hydrogen halides or phosphorus polyhalides to alkenes) generate large amounts of halogenated waste and solid salts. The reaction of alcohols with inorganic esters (e.g., dimethyl sulfate) also gives ethers, but the process again involves the disposal of aqueous effluent containing large amounts of inorganic salts. A recent communication by Strauss et al.<sup>30</sup> described a new method for the formation of symmetrical ethers from alcohols by use of

the corresponding alkyl bromide as a promoter. Although ethers were formed in good yield, reaction times were up to 24 h in some cases. Halogenated waste was still produced, albeit in much reduced amounts, and this might cause problems on scale-up.

One of the most cost-effective and atom efficient processes for ether formation is the dehydration of alcohols with an acid catalyst.<sup>31–34</sup> However, this reaction often leads to a mixture of products because the intermediate carbocation can rearrange from the primary to the secondary and thence to the tertiary position. In addition, the use of homogeneous acid catalysts, such as H<sub>2</sub>SO<sub>4</sub>, requires a final separation step to recover or neutralize the acid. Therefore, these reactions are usually carried out in a batch or semi-batch reactor, and the long contact time between catalyst and starting materials often leads to further isomerization.

**Supercritical Etherification.** There are a few reports of supercritical etherification. In 1995 Antal<sup>35</sup> reported acid-catalyzed formation of *t*-BuOEt from EtOH and *t*-BuOH at high temperature and pressure. The reported yields and selectivities were good, and interestingly, the ether could only be formed from the reaction of EtOH with *t*-BuOH, but not from EtOH and isobutene. Dehydration of alcohols to ethers and alkenes in supercritical water (scH<sub>2</sub>O) has been studied by a number of authors;<sup>17,20,36–41</sup> all report good yields and high selectivities. Some of the most important work in this area has been done by Antal et al. They report the formation of Et<sub>2</sub>O from EtOH in scH<sub>2</sub>O,<sup>20</sup> as well as a number of other acid-catalyzed dehydrations.<sup>39–41</sup> Finally, work by Richter and Vogel<sup>42</sup> reports the batch dehydration and cyclization of 1,4-butanediol in scH<sub>2</sub>O, at >374 °C to give tetrahydrofuran (THF) in quantitative yield.

In this paper, we describe a *continuous* and selective general route to ethers, using scCO<sub>2</sub> as the solvent. We begin by describing the reactor and then outline how it can be used to generate cyclic ethers from diols. Particular attention is paid to the cyclization of 1,4-butanediol to give THF. We then investigate the condensation of a range of primary alcohols to give linear ethers and show that relatively little isomerization to branched products occurs. Finally we describe O-alkylation versus C-alkylation selectivities in the reaction of phenol with *i*-PrOH or propene.

## Experimental Section

**Safety Hazard. CAUTION!** The experiments described in this paper involve the use of relatively high pressures and require equipment with

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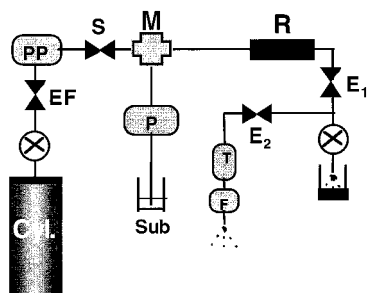
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**Figure 1.** Schematic view of the apparatus used for etherification. The parts are labeled as follows (alphabetically): *Cyl*, cylinder of gas (CO<sub>2</sub>, propane or propene); *EF*, excess flow cut-out valves; *E<sub>1</sub>* and *E<sub>2</sub>*, two expansion valves for pressure reduction and flow control; *F*, flow meter; *M*, mixer; *P*, HPLC pump (0.3–20.0 mL/min, Gilson model 303); *PP*, pneumatic pump 20–200 atm (module PM 101, NWA GmbH); *Prod*, product(s); *R*, reactor made from 316 stainless steel tubing (9 mm i.d.), length 152 mm or 304 mm (10 mL or 20 mL volume respectively), containing the solid catalyst; *S*, regulator which determines the system pressure; *Sub*, organic substrate; *T*, trap for any droplets inadvertently carried through with the gas (CO<sub>2</sub>, propane or propene).

the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meets the necessary safety requirements. The components described below work well, but they are not necessarily the only equipment of this type available nor the most suitable for the purpose.

Figure 1 shows the apparatus used in these experiments, which is similar to that used for hydrogenations<sup>11</sup> but without an H<sub>2</sub> supply. The gaseous solvent (CO<sub>2</sub>, propane, or propene) is pressurized using the pneumatic pump, PP, and then reduced to system pressure across valve S. The solvent enters the mixing area, M, where it meets the organic substrate, the mixture then passes through the reactor, R, containing the catalyst. After the fluid passes through the reactor, the pressure is dropped stepwise to separate the product(s) from the fluid using an expansion module (PE 103, NWA GmbH). In this module, the expansion valve E<sub>2</sub> controls the flow rate of the exhaust gases. Additionally, a flow meter, F, measures the flow rate of the fluid, which is typically set to 0.65 L/min of gas at 1 atm and 20 °C, corresponding to 1.06 g of CO<sub>2</sub>/min. The organic products are recovered free of any solvent and thus they can immediately be analyzed by NMR (Bruker DPX 300), GC (Philips PU 4500), or GC–MS (Shimadzu QP-5000) without further workup.

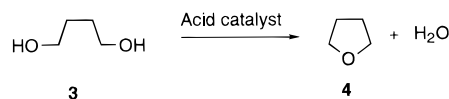
R is heated by three cartridge-heaters in an aluminum block, which encases the reactor. The heaters are thermostatically controlled by a thermocouple reading the temperature of the catalyst bed. Two additional thermocouples are used to monitor the system, one reading the temperature of the Al heating block and the other in the fluid stream at the end of the reactor. For all of the reactions described in this paper, the temperature quoted is that of the catalyst bed.

We have used two types of solid acid catalyst in the experiments described here. DELOXAN ASP catalyst (Degussa-Huls AG, Frankfurt, Germany) has in the past been found<sup>12</sup> to be a reliable and convenient catalyst for use in our continuous flow reactor. During the course of our study, we have also found that AMBERLYST resin-based acid catalysts (Rohm and Haas Co.) can also be effective. All reactions described in this paper were run with commercially available substrates (Aldrich, Fluka, Acros). The apparatus used in these experiments gave a high degree of reproducibility.

## Results and Discussion

**Cyclic Ether Formation. Synthesis of Tetrahydrofuran (4) from 1,4-Butanediol (3).** Our preliminary investigations into ether formation have been carried out using the cyclization of 1,4-butanediol, **3**, to THF, **4**, as a model reaction, because it is both facile and clean and has no unwanted byproducts (see Scheme 2). Furthermore, the cyclization of **3** is also a significant industrial route to **4**, with more than 50% of **3** produced annually

## Scheme 2



**Table 1.** Effect of Reactor Conditions on the Conversion of **3** into **4** in scCO<sub>2</sub><sup>a</sup>

	temperature (°C)	pressure (atm)	flow rate of <b>3</b> (mL/min)	product	
				<b>4</b> (%) <sup>b</sup>	<b>3</b> (%)
varying <i>T</i>	100	100	0.5	63	37
	125	100	0.5	96	4
	150	100	0.5	100	0
	175	100	0.5	100	0
	200	100	0.5	100	0
varying <i>P</i>	100	125	0.5	69	31
	100	150	0.5	79	21
	100	175	0.5	81	19
	100	200	0.5	87	13
	150	60–200	0.5	100	0
varying flow rate of <b>3</b>	150	100	0.5	100	0
	150	100	1.0	100	0
	150	100	2.0	98	2
	150	100	3.0	93	7

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst; 10 mL reactor; flow rate of CO<sub>2</sub> 0.65 L/min. <sup>b</sup> In all tables presented in this paper the symbol (%) next to a numerical identifier refers to the percentage yield of that particular product, as found upon analysis of the material collected.

in USA being used in the manufacture of THF.<sup>14</sup> Conventionally, **3** is passed through a hot tube in the presence of H<sub>2</sub>SO<sub>4</sub> or H<sub>3</sub>PO<sub>4</sub> at 100 atm and 300 °C, with **4** being generated in 90–100% yield in a continuous process.

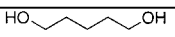


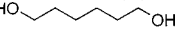


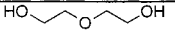


For our experiments **3** (mp 16 °C) was first dissolved in a small amount of MeOH, (25 g **3** in 10 mL) to ensure that **3** did not solidify in any of the pipework. The cyclization of **3** in scCO<sub>2</sub> is highly successful. Flow rates of up to 1.0 mL/min of **3** can be maintained for up to 15 h over the same catalyst with no loss of activity. Table 1 shows the effect of temperature and pressure on the yield of **4**. Thus, increasing the reactor temperature from 100 to 125 °C at 100 atm results in a 33% increase in the yield of **4**, and increasing it to 150 °C gives full conversion. At 150 °C, varying the pressure inside the reactor had no effect on conversion, even at only 60 atm (below the critical pressure of CO<sub>2</sub>).<sup>43</sup> However, at 100 °C, a clear relationship between reactor pressure and yield can be seen, with an 18% increase in conversion when the pressure was raised from 100 to 200 atm. Such an effect is to be expected, considering that, in fixed bed flow reactors and under these conditions, an increase in pressure, at constant temperature, increases the residence time of the substrate over the catalyst. It should be noted that under steady state conditions the weight hourly space velocity of material passing through our apparatus will remain the same irrespective of the system pressure. However, the residence time over the catalyst will be affected by pressure because of the high compressibility of the supercritical fluid.

**Etherification of 1,5-Pentanediol (5) and 1,6-Hexanediol (8).** **5** and **8** can be dehydrated with very high selectivity for tetrahydropyran, **6**, and the oxepane ring, **9**, respectively (see Table 2). This is a striking result since one would generally expect the rearranged 2-alkyltetrahydrofurans, **7** and **10**, to

(43) 60 atm is above the vapor pressure of CO<sub>2</sub> at room temperature. Thus, under these conditions liquid CO<sub>2</sub> will mix with the reactant(s) in the cool part of the apparatus upstream of the reactor. This CO<sub>2</sub>/reactant mixture is likely to have lower viscosity than the pure reactants themselves.



**Table 2.** Formation of Cyclic Ethers from  $\alpha,\omega$ -diols in  $scCO_2^a$ 

Substrate	T (°C)	Products <sup>1</sup>	
	200		
<b>5</b>		<b>6 (%)</b> 86	<b>7 (%)</b> 1
	150		
<b>8</b>		<b>9 (%)</b> 28	<b>10 (%)</b> 3
<b>8</b> <sup>2</sup> + MeOH	200	MeO(CH <sub>2</sub> ) <sub>6</sub> OH	MeO(CH <sub>2</sub> ) <sub>6</sub> OMe
1:3		<b>11 (%)</b> 65	<b>12 (%)</b> 6
	330		
<b>13</b>		<b>14 (%)</b> 95	<b>15 (%)</b> 5

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst; 10 mL reactor; 200 atm pressure; flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min. <sup>1</sup> All material not accounted for was recovered as unreacted starting material. <sup>2</sup> Yields based on **8** consumed.

predominate.<sup>29</sup> **5** and **8** are both solids at room temperature and thus were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (25 g in 30 mL) for these reactions.

By contrast, quite a different reaction is observed when **8** is dissolved in MeOH rather than CH<sub>2</sub>Cl<sub>2</sub>. The reaction of **8** with excess MeOH gives high selectivity for the linear monomethyl ether product **11**. Possibly the preferential formation of **11**, rather than **12**, is due to **8** being more polar than **11**.  $scCO_2$  is a relatively nonpolar solvent, comparable to cyclohexane. In such a medium, polar species, such as the reactants, intermediates, and catalyst in our reactor, will be forced together with an increased chance of reaction. Such effects are well documented and have been used to achieve high ortho selectivity in the Friedel–Crafts alkylation of phenol.<sup>44</sup> Clark and co-workers<sup>45</sup> have reported a similar solvent effect in the base-catalyzed Knoevenagel condensation, where the choice of solvent has a marked effect on the rate of reaction, with a general order: cyclohexane > toluene > 1,2-dichloroethane > chlorobenzene. It therefore seems likely that the more polar diol, **8**, is preferentially adsorbed onto the ionic catalyst surface and thus reacts readily, whereas the less polar mono-ether, **11**, is resistant to further etherification.<sup>46,47</sup> Hydrogen bonding between **8** and MeOH may also be an important factor in these reactions.

Unfortunately, we were unable to establish whether Me<sub>2</sub>O was formed in our reactor since it is too volatile (bp –24.8 °C) to be trapped in the recovery system. Thus, formation of Me<sub>2</sub>O may be occurring in this reaction, and in the others discussed below, where MeOH is used as a reactant under acidic conditions.<sup>48,49</sup> However, MeOH is detected in large quantities

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





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**Table 3.** Continuous Formation of Acetals and Ketals in  $scCO_2^a$ 

Substrates	T (°C)	Products <sup>1</sup>
 <b>16</b> <sup>2</sup>	150	 <b>18 (%)</b> 61
 <b>17</b>		
 <b>16</b> <sup>2</sup>	100	 <b>20 (%)</b> 89
 <b>19</b>		

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst, 10 mL reactor; 200 atm; flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min.

<sup>1</sup> All material not accounted for was recovered as unreacted starting material. <sup>2</sup> Yields based on **16** consumed; ratio of **16:17** or **19** was 1:2, respectively.

in the NMR spectra of our product samples, which suggests that, if Me<sub>2</sub>OH forms at all, it is not formed in sufficient quantities to deplete MeOH significantly as a potential reactant in these experiments.

**Di(ethylene Glycol) (13) and Ethylene Glycol (16).** **13** gave a surprisingly clean and high-yielding reaction with excellent selectivity for 1,4-dioxane **14**. However, the formation of small quantities of acetal, **15**, as a side product prompted us to investigate the supercritical formation of acetals and ketals, see below. By contrast, the reaction of ethylene glycol, **16**, gave only decomposition products, probably resulting from partial dehydration and rearrangement of **16** to acetaldehyde. The product mixture would then be further complicated by the reaction of the acetaldehyde with **16** to give an acetal. Clearly, the failure to form the first ether linkage (i.e., **16** is not converted to **13**) is the reason **16** does not cyclize cleanly.

**Acetals and Ketals.** The most widely used method for generating acetals and ketals is the reaction of alcohols with aldehydes or ketones under acidic conditions, with removal of water. This is precisely the route used in our supercritical reactor. Thus, we have studied the reaction of **16** with acetone, **17**, and benzaldehyde, **19**, as simple examples of ketal and acetal formation respectively (Table 3).

Usually, a major problem associated with acetal and ketal synthesis is that the reaction is an equilibrium process; H<sub>2</sub>O must be removed to drive the equilibrium toward products.<sup>50</sup> However, the yields in our reactor are remarkably high, probably for two reasons. First, the relatively low solubility of H<sub>2</sub>O in  $scCO_2$ , compared to that of the starting materials and organic products,<sup>51,52</sup> means that H<sub>2</sub>O is effectively removed from the reactant/product mixture, thus driving the equilibrium toward products. Second, a number of studies have shown that high pressure favors the formation of ketals, and to a lesser extent of acetals, from the reaction of alcohols with carbonyl compounds. Indeed, it has been claimed that this is a general effect in all bimolecular acid-catalyzed reactions, due to the negative volume of activation experienced by reactions proceeding via an ionic intermediate.<sup>53,54</sup>

**Reaction of Primary Alcohols.** Table 4 shows that a range of *n*-alkyl ethers can be selectively formed in good yield from

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the corresponding *n*-alcohols over the DELOXAN ASP catalyst in scCO<sub>2</sub>. For all alcohols, the yields in a 20 mL reactor were significantly higher than those in a 10 mL vessel, with little effect on selectivity.

Poor yields were obtained for *n*-octanol, **30**, which is dehydrated readily under these conditions to give octene, probably as a result of the reduced solubility of long chain alcohols in scCO<sub>2</sub>.<sup>51</sup> The reaction between *n*-BuOH, **24**, and MeOH is interesting because, even when a 2.5:1 excess of MeOH is used, *n*-Bu<sub>2</sub>O, **25**, and *n*-BuOMe, **33**, are produced in *comparable amounts*, rather than the expected large excess of **33**. This suggests either that MeOH must be forming its corresponding cation *less readily* than **24** or that **33** may possibly be formed via trans-etherification of Me<sub>2</sub>O with **24**.

In all of the reactions of *n*-alcohols, we observed some alkene production, resulting from the competing dehydration process, with significant amounts only occurring when high temperatures were used (typically above 200 °C in the 10 mL reactor). Usually the predominant olefin product is the corresponding 2-alkene, although some 1-alkene is observed. Production of these olefins causes the yield of, and the selectivity for, the *n*-ether to fall because Markovnikov protonation of the olefin will result in formation of a secondary carbocation, leading to branched ethers. For this reason, it is important to maintain a balanced temperature. Pressure effects in these reactions are similar to those already observed for the formation of cyclic ethers, acetals, and ketals and is likely to be due to the same reasons (i.e., longer residence time and the negative volume of activation for bimolecular reactions).

**Origin of the High Selectivity for *n*-Ethers: Solvent Effects.** To establish whether scCO<sub>2</sub> itself affects the selectivity, a number of experiments were carried out in supercritical propane (scPropane; *T*<sub>C</sub> = 96.6 °C, *P*<sub>C</sub> = 41.9 atm).<sup>4</sup> The results, Table 5, suggest that scCO<sub>2</sub> is a better solvent than scPropane for these reactions, although it is not yet clear why. Possibly, the ether products are more soluble in scCO<sub>2</sub> than in scPropane and, thus are more efficiently separated from H<sub>2</sub>O, thereby avoiding a back reaction.<sup>51</sup> It should be noted that in a flow reactor it is difficult to make precise comparisons between two supercritical fluids because some of the reaction parameters will usually be different. For example, at 200 °C and 200 atm the density of CO<sub>2</sub> (0.2629 g/mL) is lower than that of propane (0.3145 g/mL) at the same temperature and pressure.<sup>55</sup> To match the fluid densities inside the reactor, the pressure during the scPropane experiment could be lowered, but this might decrease the residence time of the reactants inside the reactor, making a quantitative comparison between CO<sub>2</sub> and propane more difficult.

The supercritical solvent appears to play a definite role in determining the yield, but not the selectivity. Thus when *n*-PrOH, **21**, was passed over the catalyst in the flow reactor at 200 °C and 200 atm *without any supercritical fluid*, it gave predominantly the *n*-Pr<sub>2</sub>O, although in a yield (7% **22**:4% **23**) much lower than that with scCO<sub>2</sub>. Similarly, when *n*-hexanol, **27**, was refluxed (~156 °C) over DELOXAN ASP in the absence of any solvent (but with the possibility of H<sub>2</sub>O venting off), *n*-hexyl ether, **28**, (12.5% after 2 h) was formed much more slowly than in our flow reactor, but with only 1% of the branched ether, **29**. This selectivity is similar to that obtained in the flow reactor.

**Effect of Catalyst. Comparison of DELOXAN ASP with AMBERLYST 15.** DELOXAN ASP was used as the catalyst

**Table 4.** Continuous Formation of Acyclic Ethers in scCO<sub>2</sub><sup>a</sup>

substrate	<i>T</i> (°C)	reactor size (mL)	products <sup>b,c</sup>		
			( <i>n</i> -Pr) <sub>2</sub> O <b>22</b> (%)	<i>n</i> -PrO <i>i</i> -Pr <b>23</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -PrOH <b>21</b>	200	10	29	4	5
	150	20	60	8	10
substrate			( <i>n</i> -Bu) <sub>2</sub> O <b>25</b> (%)	<i>n</i> -BuOs-Bu <b>26</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -BuOH <b>24</b>	200	10	33	1	5
substrate			( <i>n</i> -C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> O <b>28</b> (%)	<i>n</i> -C <sub>6</sub> H <sub>13</sub> Os-C <sub>6</sub> H <sub>13</sub> <b>29</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -C <sub>6</sub> H <sub>13</sub> OH <b>27</b>	200	10	34	1	11
	150	20	54	8	16
substrate			( <i>n</i> -C <sub>8</sub> H <sub>15</sub> ) <sub>2</sub> O <b>31</b> (%)	<i>n</i> -C <sub>8</sub> H <sub>15</sub> Os-C <sub>8</sub> H <sub>15</sub> <b>32</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -C <sub>8</sub> H <sub>15</sub> OH <b>30</b>	150	10	14	0	10
	200	10	0	0	95
substrate			( <i>n</i> -Bu) <sub>2</sub> O <b>25</b> (%)	<i>n</i> -BuOs-Bu <b>26</b> (%)	<i>n</i> -Bu-O-Me <b>33</b> (%)
<i>n</i> -BuOH + MeOH <b>24</b> <sup>d</sup>	200	10	24	1	27
			1:2.5		
substrate			( <i>n</i> -Bu) <sub>2</sub> O <b>25</b> (%)	<i>n</i> -BuO <i>n</i> -Pr <b>34</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -BuOH + <i>n</i> -PrOH <b>24</b> <sup>e</sup> + <b>21</b>	200	10	20	28	9
			1:1.2		
substrate			( <i>n</i> -Pr) <sub>2</sub> O <b>22</b> (%)	<i>n</i> -PrO <i>i</i> -Pr <b>23</b> (%)	alkene/rearranged alcohol (%)
<i>n</i> -PrOH + <i>i</i> -PrOH <b>21</b> <sup>f</sup> + <b>1</b>	150	20	12	41	7
			1:1.2		
substrate			PhCH <sub>2</sub> OMe <b>36</b> (%)	<i>p</i> -PhCH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH <b>37</b> (%)	
PhCH <sub>2</sub> O + MeOH <b>35</b> <sup>g</sup>	200	10	84	7	
			1:2.5		
substrate			(Ph(CH <sub>2</sub> ) <sub>2</sub> ) <sub>2</sub> O <b>39</b> (%)	Ph(CH <sub>2</sub> ) <sub>2</sub> -O-CH(CH <sub>3</sub> )Ph <b>40</b> (%)	
Ph(CH <sub>2</sub> ) <sub>2</sub> OH <b>38</b>	200	10	58	2	
substrate			( <i>i</i> -Bu) <sub>2</sub> O <b>42</b> (%)	<i>i</i> -BuO <i>t</i> -Bu <b>43</b> (%)	alkene/rearranged alcohol (%)
<i>i</i> -BuOH <b>41</b>	200	10	8	5	5
substrate			(CH <sub>2</sub> =CHCH <sub>2</sub> ) <sub>2</sub> O <b>45</b> (%)	CH <sub>2</sub> =CHCH <sub>2</sub> -CH(CH <sub>3</sub> )CHO <b>46</b> (%)	
CH <sub>2</sub> =CHCH <sub>2</sub> OH <b>44</b>	60	10	1	0	
	120	10	9	1 <sup>h</sup>	

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst; 200 atm; flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min. <sup>b</sup> All material not accounted for was recovered as unreacted starting material. <sup>c</sup> Yields of volatile alkenes (propene, butene, etc.) were calculated by mass balance. <sup>d</sup> Yields based on **24** consumed; 5% alkene/rearranged alcohol products also formed. <sup>e</sup> Yields based on **24** consumed, yield of **22** (formed as a result of self-condensation of **21**) was 13%, based on **21** consumed, 4% mixed branched ether products also formed. <sup>f</sup> Yields based on **21** consumed; yield of **2** (formed as a result of self-condensation of **1**) was 6%, based on **1** consumed. <sup>g</sup> Yields based on **35** consumed. <sup>h</sup> 2% propionaldehyde **47** also formed.

**Table 5.** Comparison of scCO<sub>2</sub> and scPropane as Solvents for Etherification<sup>a</sup>

substrate	<i>T</i> (°C)	solvent	products <sup>b,c</sup>		
			( <i>n</i> -Bu) <sub>2</sub> O <b>25</b> (%)	<i>n</i> -BuOs-Bu <b>26</b> (%)	alkene/ rearranged alcohol (%)
<i>n</i> -BuOH <b>24</b>	200	scCO <sub>2</sub>	33	1	5
	200	scPropane	24	2	5

substrate	solvent	products <sup>b,c</sup>			
		( <i>n</i> -C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> O <b>28</b> (%)	<i>n</i> -C <sub>6</sub> H <sub>13</sub> Os- C <sub>6</sub> H <sub>13</sub> <b>29</b> (%)	alkene/ rearranged alcohol (%)	
<i>n</i> -C <sub>6</sub> H <sub>13</sub> OH <b>27</b>	150	scCO <sub>2</sub>	14	0	10
	150	scPropane	3	0	0

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst; 200 atm; flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min. <sup>b</sup> All material not accounted for was recovered as unreacted starting material. <sup>c</sup> Yields of butene were calculated by mass balance.

**Table 6.** Comparison of DELOXAN ASP and AMBERLYST 15 as Catalysts for Etherification<sup>a</sup>

substrate	<i>T</i> (°C)	catalyst	products <sup>b,c</sup>		
			( <i>n</i> -Pr) <sub>2</sub> O <b>22</b> (%)	<i>n</i> -PrOi-Pr <b>23</b> (%)	alkene/ rearranged alcohol (%)
<i>n</i> -PrOH <b>21</b>	200	DELOXAN ASP	29	4	5
	175	AMBERLYST 15	42	3	1

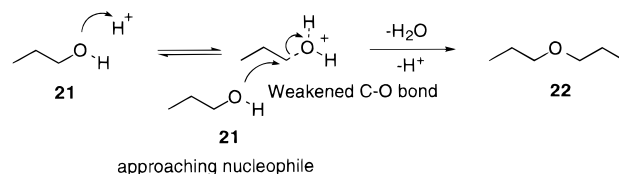
substrate	<i>T</i> (°C)	catalyst	products <sup>b,c</sup>		
			( <i>n</i> -Bu) <sub>2</sub> O <b>25</b> (%)	<i>n</i> -BuOs-Bu <b>26</b> (%)	alkene/ rearranged alcohol (%)
<i>n</i> -BuOH <b>24</b>	200	DELOXAN ASP	33	1	5
	175	AMBERLYST 15	47	6	2

<sup>a</sup> Other reaction conditions: 200 atm, 10 mL reactor, flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min. <sup>b</sup> All material not accounted for was recovered as unreacted starting material. <sup>c</sup> Yields of propene and butene were calculated by mass balance.

in all of the reactions listed in Tables 1–5 and has been found to be an excellent catalyst, mainly due to its thermal stability and high acidity. Table 6 summarizes the results of experiments carried out to compare the ion-exchange resin AMBERLYST 15 with DELOXAN.

It can be seen from Table 6 that there are only small differences between the product yields obtained with the two catalysts. AMBERLYST 15 is an excellent catalyst for these reactions, although it is not as thermally stable as DELOXAN ASP. Whereas DELOXAN ASP performs well at temperatures up to 350 °C, AMBERLYST 15 rapidly deactivates above 225 °C. Furthermore, large quantities of alkenes were produced above 175 °C with AMBERLYST 15, at least 25 °C lower than that for DELOXAN ASP.

Although it is clear that DELOXAN ASP itself is not having any specific effect on the linear/branched ratio, it is still possible that the acid strength of the two catalysts is the controlling influence on the selectivities. Theoretical studies by Sandré et al on the condensation of MeOH to Me<sub>2</sub>O in a zeolite pore concluded that the transition state involved direct condensation of two molecules of MeOH, with the zeolite acting only as an acidic medium.<sup>56</sup> Interaction between the zeolite surface and a

**Scheme 3****Table 7.** Effect of Flow Rate of *n*-PrOH, **21**, on Linear/Branched Selectivity of the Etherification<sup>a</sup>

flow rate of <b>21</b> (mL/min)	products <sup>b,c</sup>				propene (%)
	( <i>n</i> -Pr) <sub>2</sub> O <b>22</b> (%)	<i>n</i> -PrOi-Pr <b>23</b> (%)	<i>i</i> -PrOH <b>1</b> (%)		
0.2	38	5.0	2.0		5.2
0.5	28	4.0	1.0		5.1
1.0	15	2.3	0.5		4.8
2.0	15	2.0	0.3		4.9
3.0	12	2.0	0.2		4.8
5.0	9	1.5	0.1		4.7

<sup>a</sup> Other reaction conditions: DELOXAN ASP catalyst; 200 °C; 200 atm; 10 mL reactor, flow rates of CO<sub>2</sub> 0.65 L/min. <sup>b</sup> All material not accounted for was recovered as unreacted starting material. <sup>c</sup> Yields of propene were calculated by mass balance.

molecule of MeOH weakened, and therefore polarized, the C–O bond and thus promoted nucleophilic attack from a second MeOH molecule (see Scheme 3). If such a mechanism were in operation in our reactor it would lead to predominantly *n*-ether products.

**Effect of Alcohol Flow Rate on Linear/Branched Selectivities.** Makarova et al.<sup>57</sup> observed that the concentration of alcohol around the acidic sites of the catalyst was crucial in determining the selectivity for *n*-ethers in the dehydration of *n*-BuOH, **24**, over zeolites. They found that reducing the concentration of **24** in their reactor dramatically increased the ratio of butene and mixed ethers to *n*-ethers in the product mixture. By contrast, Table 7 shows that there is little or no difference in selectivity for linear ether formation when the flow rate, and hence the concentration, of **21** is varied in our reactor (with a constant flow rate of scCO<sub>2</sub>). The increasing yield of *i*-PrOH, **1**, with decreasing flow rate suggests that the concentration of **21** may be a limiting factor at the very lowest flow rates; the cation is still rearranging, but there is insufficient **21** to react with the cation so that it is re-attacked by H<sub>2</sub>O, giving **1**.

All of our reactions show that, under these conditions, there is a clear preference for formation of *n*-terminal products over their branched analogues. Products resulting from the rearrangement of the intermediate cation to a more stable secondary position are only seen in very low yield. The literature suggests that rearrangement of an intermediate cation can be avoided by using a strong acid catalyst. Work by Olah<sup>58</sup> on cyclic ether formation suggests that an exceptionally strong acid will favor formation of *n*-terminal products because strong acids can stabilize the protonated alcohol intermediate, allowing approach of the nucleophile prior to H<sub>2</sub>O elimination. In this context we suggest that the high selectivity for linear ethers reported by Strauss et al in their process<sup>30</sup> may be due to the presence of HBr, a strong acid catalyst. Possibly, the use of relatively nonpolar solvents (e.g., scCO<sub>2</sub>) also increases ionic interactions between polar molecules and hence the effective strength of

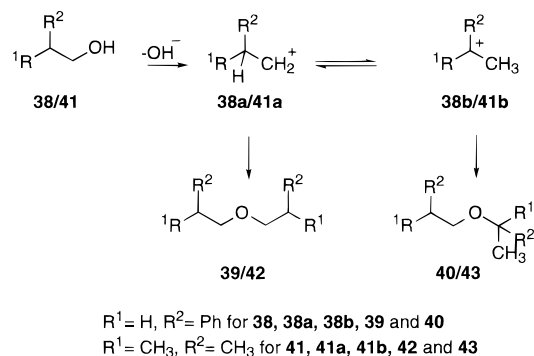
(56) Sandré, E.; Payne, M. C.; Gale, J. D. *Chem. Commun.* **1998**, 2445.

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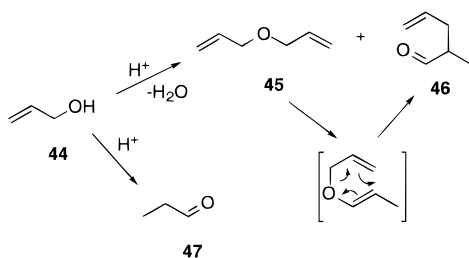
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## Scheme 4



## Scheme 5



the acid/substrate interaction.<sup>45,59,60</sup> Finally, although we observe no carbonate species resulting from reaction of  $\text{CO}_2$  with the alcohol in the product mixture, we cannot rule out the formation of such species as transient intermediates in the reactions carried out in  $\text{scCO}_2$ .

**2-Phenyl-1-ethanol (38) and Isobutanol (41).** Table 4 also shows that there is a high selectivity (12:1) for the *n*-terminal product, **39**, in the etherification of **38**. This selectivity is striking because the rearranged benzylic cation, **38b**, is stabilized by the adjacent aromatic ring and thus is much more stable than the secondary cation, **38a**, and hence, rapid rearrangement would be expected under normal reaction conditions, see Scheme 4.

Tertiary cations are, in turn, more stable than benzylic cations, and this may explain why *i*-BuOH (2-methylpropanol), **41**, gave a much lower (8:5) *n*-ether selectivity, with rapid formation of the rearranged *tert*-butyl cation, **41b**, and consequent formation of ether **43**, see Table 4 and Scheme 4.

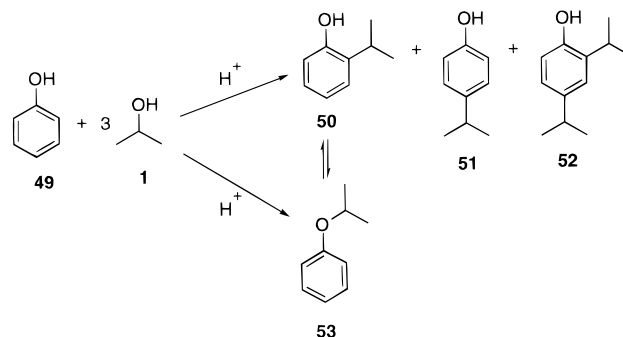
**Allyl Alcohol (44).** Table 4 shows that the etherification of **44** was an unsuccessful reaction, even in  $\text{scCO}_2$ . In this reaction, propanal, **47**, is formed by a simple rearrangement of the double bond. The other aldehyde product, **46**, arises from rearrangement of one of the double bonds in the ether, **45**, followed by a Claisen-type sigmatropic rearrangement (see Scheme 5).

**Reaction of Secondary Alcohols.** *i*-PrOH, **1**, is the only secondary alcohol that can be dehydrated to give an ether in our system (29% yield at 200 °C). Even so, propene was the major reaction product (56%). At temperatures above 200 °C, propene was formed in >80% yield, with a corresponding decrease in the yield of ether **2**. Surprisingly, the yield of **2** also decreased when a 20 mL reactor was used, instead of 10 mL, under identical conditions. Reaction of longer chain secondary alcohols, such as *s*-pentanol, **48**, gave exclusively alkenes with no evidence for any ether formation, even at reduced temperatures. Clearly, secondary alcohols, apart from **1**, cannot be etherified effectively in our system due to the ease with which they dehydrate.

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## Scheme 6



**Aryl Ethers.** We have previously reported that the Friedel-Crafts alkylation of mesitylene and anisole can be carried out with **1** in our flow reactor.<sup>12</sup> When phenol, **49**, is used as the substrate, competing etherification and alkylation reaction should occur, as shown in Scheme 6. Conventionally, selective etherification of phenol (O-alkylation) can be difficult to achieve. Although many authors have studied such reactions,<sup>48,49,61-72</sup> there is still a degree of confusion over exactly which factors favor O-alkylation versus C-alkylation. Although it is agreed that increasing reaction temperatures favor C-alkylation because of the thermodynamics of the process, the role of the catalyst is much less clearly defined. It has been claimed that the presence of strongly acidic sites on metal oxides, phosphates, and sulfates favors O-alkylation and, conversely, that weakly acidic sites favor C-alkylation. Zeolites also seem to have a similar effect, although Marczewski<sup>64</sup> has observed that strong acid sites on zeolite USHY favor both O- and C-alkylation to give cresols, while weak acid sites give only O-alkylation. More recently<sup>61</sup> a high potassium content (3%) in sulfates has been claimed to give aryl ethers in excellent yields and selectivities (>90%).

We have studied the alkylation of **49** with **1** in  $\text{scCO}_2$ , and with  $\text{scPropene}$ , at a variety of temperatures and pressures. When **1** was used as the alkylating agent, a 3:1 molar excess of **1:49** was used. When  $\text{scPropene}$  acting both as solvent and reagent was used, a 230:1 excess of propene was present. The results (Table 8 and Figure 2) indicate that reaction conditions can be manipulated to give a good degree of selectivity for etherification over Friedel-Crafts alkylation.

When **1** was used as the alkylating agent, the yield of *i*-PrOPh **53** reached a maximum of 32% at 160 °C and 160 atm. At this point the combined total of the Friedel-Crafts products **50**, **51**, and **52** was 13%. At 200 °C the yield of **53** is very low, and the dialkylated product predominates. In the Friedel-Crafts alkylation process, there is a high degree of selectivity for ortho-

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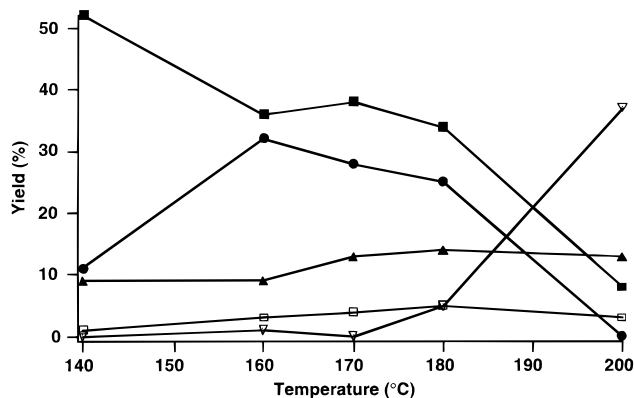
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**Table 8.** Effect of Reaction Conditions on the Alkylation/Etherification of Phenol in scCO<sub>2</sub> and scPropene<sup>a</sup>

temperature (°C)	pressure (atm)	products <sup>b,c</sup>				
		49 (%)	50 (%)	51 (%)	52 (%)	53 (%)
140 <sup>1</sup>	140	52	9	1	0	11
160 <sup>1</sup>	160	36	9	3	1	32
170 <sup>1</sup>	160	38	13	4	3	28
180 <sup>1</sup>	160	34	14	5	5	25
200 <sup>1</sup>	160	8	13	3	37	0
160 <sup>2</sup>	160	21	5	1	0	56
200 <sup>2</sup>	200	10	7	4	0	59

<sup>a</sup> Other reaction conditions: **49** dissolved in THF (10 g in 25 mL); DELOXAN ASP catalyst; 10 mL reactor; flow rates – CO<sub>2</sub> 0.65 L/min, substrate 0.5 mL/min; **49:1** = 3:1. <sup>b</sup> CO<sub>2</sub> used as supercritical solvent. <sup>c</sup> Propene used as supercritical solvent and reagent.



**Figure 2.** Plot showing the variation in isolated product yields with temperature in the reaction of **49** with **1**. The points are labeled as follows: (■) Phenol, **49**, (▲) 2-*i*-propylphenol, **50**, (□) 4-*i*-propylphenol, **51**, (▽) 2,4-di-*i*-propylphenol, **52**, (●) phenyl-*i*-propyl ether, **53**. DELOXAN ASP catalyst, 10 mL reactor, flow rates – CO<sub>2</sub> 0.65 L/min.

alkylation, **50**, over *para*-alkylation, **51**, (14% *ortho* vs 5% *para* at 180 °C, 160 atm), possibly because **50** is produced by either rearrangement of **53** or by ring alkylation via a complex between the alkylating agent and the hydroxyl group of phenol.<sup>44</sup>

We observed a greater degree of selectivity for etherification over alkylation when the experiment was repeated using scPropene (scPropene;  $T_C = 91.6$  °C,  $P_C = 45.4$  atm)<sup>4</sup> as both alkylating agent and supercritical solvent and with THF as a cosolvent for phenol. O/C-alkylation selectivities were as high as 9:1 at 160 °C, 160 atm (compared to 2.5:1 when **1** was the alkylating agent under otherwise identical conditions). The highest yield of **53** (59%) was achieved at 200 °C and 200 atm in scPropene. We tentatively offer two rationalizations for this phenomenon:

1. When the reaction was carried out in scPropene, the ratio of propene/phenol was calculated to be 230:1. The ether **53** is

the kinetic product, and it is likely that, at such high propene concentrations relative to **49**, **53** rapidly forms as soon as the polar, and therefore reactive, phenol enters the reactor. As the less polar ether product **53** passes down through the reactor, the large excess of propene molecules may coordinate to, and hence block, active sites on the catalyst surface, thus preventing possible rearrangement of **53** to **50**.

2. It can be assumed that the polarity of the two reaction systems PhOH/*i*-PrOH/scCO<sub>2</sub> and PhOH/THF/scPropene will differ significantly. It is likely that the solubility of **53** in the scPropene/THF mixture will be greater since THF itself is an ether, and thus its affinity for the catalyst will also be reduced, resulting in less rearrangement.

## Conclusions

We have reported the first examples of continuous etherification in scCO<sub>2</sub>. Our results show that CO<sub>2</sub> can provide significant advantages in these heterogeneous, acid-catalyzed reactions over a wide range of temperatures and pressures. In addition to the well documented benefits of reduced coking,<sup>25–28</sup> we believe that the use of a nonpolar medium, such as scCO<sub>2</sub>, may promote reaction by increasing the interaction of polar species, such as the alcohols, reaction intermediates, and the catalyst surface. Furthermore, using scCO<sub>2</sub> as the solvent for ether formation will encourage the phase separation of H<sub>2</sub>O, which appears to reduce back reaction via rehydration of the product.

Our results underline the advantages of continuous reactors in supercritical fluids. As in hydrogenation<sup>10,11</sup> and Friedel–Crafts alkylation,<sup>12</sup> relatively small reactors can give excellent throughput of materials. At the same time, the relatively small volume of the reactor reduces the problems of working at high pressures, compared to batch reactors of similar capacity. Moreover, scale-up of flow reactors is generally simpler than for batch processes, and it should be possible to scale-up many of the reactions reported here to industrially usable levels. Currently, work is in progress in our laboratory to extend the use of such fixed-bed reactors to other continuous reactions under supercritical conditions (e.g., dehydrogenation and hydroformylation).

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