VIP **Etherification**

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A General Method for the Preparation of Ethers Using Water-Resistant Solid Lewis Acids**

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Ethers are fundamental compounds in organic chemistry, and the search for simple efficient preparation methods is a matter of general interest. The Williamson reaction, discovered in 1850, is still the best general method for the preparation of symmetrical and unsymmetrical ethers.[1,2] This method involves the treatment of a halide with an alkoxide or aryloxide ion prepared from an alcohol or phenol. However, the Williamson reaction is not applied industrially in many cases because the starting halide compounds are not easily available or they are too expensive. Furthermore, it should also be considered that the use of the starting halides together with the production of waste products is environmentally less desirable than producing the ethers from the corresponding alcohols, provided that a general and efficient procedure is found.

Brønsted acids can catalyze the formation of ethers when starting from two alcohol molecules, and this synthetic strategy is particularly useful for the preparation of symmetrical lower alkyl ethers. For instance, diethyl ether can be prepared by vapor-phase dehydration of ethanol in a fixed-bed reactor using alumina catalyst.[3,4] Many studies in homogeneous phases have been carried out with sulfuric acid.[5] In these cases, the hydroxy group is converted into a better leaving group, namely ROH_2^+ or $ROSO_2OH$,[6] and the formation of the ether may occur by a S_N1 or S_N2 pathway.

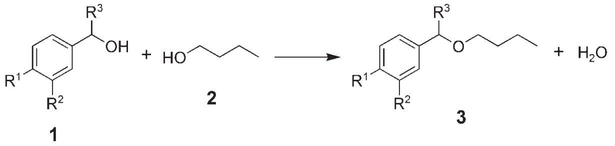
Both types of procedures to prepare ether, that is, the Williamson reaction and alcohol dehydration, are limited to primary ethers. Low yields are observed with secondary alcohols, and especially tertiary alcohols and halides tend to give elimination reactions.[7,8] Recently, a very efficient and comprehensive method for the synthesis of ethers was developed by Shintou and Mukaiyama,[9,10] involving a new type of oxidation–reduction condensation, wherein one alcohol is mixed successively with *n*BuLi, Ph_2PCl, and tetrafluoro-1,4-benzoquinone (fluoranil) and then treated with the second alcohol. The reaction proceeds smoothly to afford the corresponding symmetrical and unsymmetrical ethers in good to high yields and has been demonstrated for a broad scope of substrates. Despite the procedure being an elegant one from an organic chemist's point of view, the reactants used can restrict its use in practice. Therefore, the search for new efficient etherification methods is still an interesting and current research topic.

In contrast to Brønsted acids, little is known about the possibilities of Lewis acids as etherification catalysts,[11] probably due to the sensibility of conventional Lewis acids such as BF_3 or $AlCl_3$ to the water produced in the reaction that deactivates or decomposes them.

Herein, we show that by introducing single, isolated Lewis acid sites in the framework of molecular sieves, water-stable Lewis acid catalysts are attained that are active and selective for the production of a large number of ethers. We then show that these Lewis acid catalysts can be used in cascade-type reactions to produce ethers of interest as fragrances, starting from commercial aldehydes and alcohols with remarkably high yields and selectivities. We prepared Sn-, Ti-, and Zr-containing catalysts in which the metal is located in framework positions of Beta zeolite and mesoporous MCM-41 following published procedures.[12–18]

When the etherification of a lower alkyl alcohol such as 1-butanol (**2**, Table 1) with *para*-methoxybenzyl alcohol (**1a**) is carried out using *para*-toluenesulfonic acid as catalyst, benzene has to be introduced as solvent to carry on the azeotropic distillation of the water formed and allow the reaction to proceed further.[19] However, in our case working with an excess of 1-butanol and using Sn-Beta or Sn-MCM-41 catalysts, the removal of the water formed was not necessary for the reaction to be completed.[20] Furthermore, owing to the nature of the catalyst, the workup is very simple and 1-butanol (**2**) can be easily recovered and recycled. Therefore, the catalyst is collected by filtration and the excess of alcohol **2** is distilled off (see Experimental Section). In Table 2, it can be seen that this method provides the desired ether **3a** in high

Table 1: Etherification of 1-butanol (**2**) with *para*-methoxybenzyl alcohols (**1**).



R^1	R^2	R^3	Alcohol	Ether
OMe	H	H	**1a**	**3a**
OMe	H	Me	**1b**	**3b**
OH	OMe	H	**1c**	**3c**
OH	OEt	H	**1d**	**3d**
OMe	OMe	H	**1e**	**3e**

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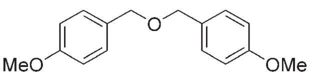
yield and with high selectivity (Table 2, entry 1), with the dimer **4a** (formed from two molecules of alcohol **1a**) being produced in very low amounts. Two blank experiments were performed with 1) an all-silica Beta zeolite and 2) a silica Beta zeolite impregnated with SnO_2. Ether formation was not observed in either case, confirming that the catalytic activity must be related to the isolated Sn Lewis acid sites present within the zeolite framework. Similar results were obtained with Sn- and Zr-Beta catalysts, while Ti-Beta gave much lower yields.

Table 2: Etherification of different alcohols with 1-butanol (**2**) employing Sn-Beta or Sn-MCM-41 as catalysts.

Entry	Alcohol	Catalyst	*t* [h]	Conv. [%][a]	Selectivity [%] ether **3**	dimer **4**
1	**1a**	Sn-Beta	4	97 (71)	98	2
2	**1a**	Sn-MCM-41	4	92 (60)	95	5
3	**1b**	Sn-Beta	0.5	99	97	2
4	**1b**	Sn-MCM-41	0.5	99	99	1
5	**1c**	Sn-Beta	7	23 (5)	100	0
6	**1c**	Sn-MCM-41	4	100 (90)	100	0
7	**1d**	Sn-Beta	6	64 (14)	100	0
8	**1d**	Sn-MCM-41	6	98 (58)	98	0
9	**1e**	Sn-Beta	6	64 (20)	100	0
10	**1e**	Sn-MCM-41	6	85 (44)	96	3

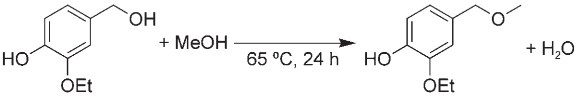
[a] Values in parentheses indicate the conversions after a reaction time of 1 h.



4a

Alcohols with additional substituents at the aromatic ring (see Table 1) can be more difficult to react with Sn-Beta as the diffusion of the reactant alcohol and ether within the channels of the Beta structure (6.5–7.6 Å) can be hindered. In such a case, a catalyst with a mesoporous structure (pore diameter ≈ 35 Å), namely Sn-MCM-41,[21] can be successfully used instead. When alcohol **1a**, which can diffuse in the channels of both Sn-MCM-41 and Sn-Beta, is treated with the former catalyst, the reaction proceeds slower than with Sn-Beta although full conversion is still achieved (see Table 2, entries 1 and 2). These results show a lower intrinsic activity of Sn-MCM-41 with respect to Sn-Beta for etherification, as also occurs with other Lewis acid catalyzed reactions.[22,23] Thus, by selecting the appropriate Sn-molecular sieve catalyst a large variety of alcohols can be etherified with excellent conversions and selectivities (see Table 2).

From an industrial point of view, alcohol **1d** is an important precursor for fragrance ethers. When it is reacted with methanol, the corresponding ether is formed, that is, 3-ethoxy-4-hydroxybenzyl methyl ether, commercialized as Methyl Diantilis [Eq. (1)].[24] Methyl Diantilis is a substitute for isoeugenol and has found use in shampoos and fine fragrances. Interestingly, in the original patent the ethyl, *n*-propyl, and isopropyl ethers of alcohol **1d** have also been described, all of which have different odor notes with good tenacity.[25] The patent reported a synthesis of the ether starting with alcohol **1d** in methanol as solvent in the presence of sodium hydrogen sulfate, with ether **3d** isolated in 56% yield. It was further stated that the other ethers were also obtained by this procedure, however, the yields obtained were not reported.

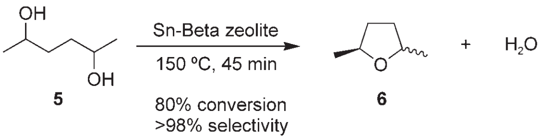


(1)

1 Methyl Diantilis

The synthesis of this series of ethers was an interesting challenge for our mild etherification method, as in the case of fragrance compounds the formation of by-products even in small amounts can condition the overall olfactory performance. Results show that for many of these ethers, by optimizing the reaction conditions no by-products could be detected by gas chromatography, with 100% yield of the desired product observed (see Supporting Information). After a simple workup, that is, removal of the catalyst by filtration and evaporation of the remaining alkyl alcohol, all products were obtained in pure, solvent-free form and were characterized by ^1H and ^{13}C NMR spectroscopy (see Supporting Information).

The Sn-Beta catalyst can also be employed with less-activated substrates. However, in these cases the reaction conditions have to be adjusted with, for example, the reaction temperature raised to 150 °C. At this temperature, 80% of 2,5-hexanediol (**5**) is converted into 2,5-dimethyltetrahydrofuran (**6**) with excellent selectivity within 45 min [Eq. (2)]. The only products observed were the two possible diastereomers of the furan **6**.

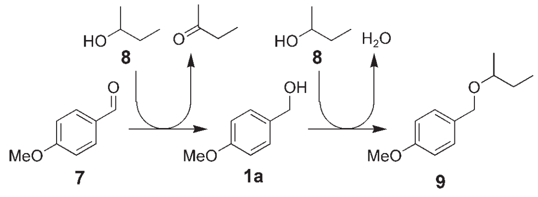


(2)

Ether **9** (Table 3) has a fruity pear odor and is a potential fragrance compound.[26] However, for the commercial success of a fragrance, besides an attractive odor, the cost of the product is an important variable. The starting alcohol **1a** is obtained industrially from the corresponding aldehyde **7**.[27] Thus, the commercial process involves a first step in which the aldehyde is reduced to the corresponding alcohol, which leads to some loss of product and produces undesired products that have to be distilled off. Therefore, we thought that it would be conceptually interesting and industrially relevant if the global process could be performed in one pot through a cascade reaction, starting from the aldehyde **7** and ending up with the desired product **9** with high yields and selectivities.

The idea was to convert aldehyde **7** into alcohol **1a** through a Meerwein–Ponndorf–Verley reaction with 2-butanol (**8**) and to etherify the intermediary alcohol **1a** with 2-butanol (**8**) present in excess, all in a cascade reaction. Again, the workup was very simple, as the catalyst (either Sn- or Zr-Beta) was removed at the end by filtration and the solvent (including butanone) was evaporated. The selectivity for the one-pot process is very high, and the desired ether **9** was the

Table 3: Cascade reaction for the synthesis of ether **9**.[a]



Catalyst (mass [mg])	*t* [h]	Total conversion [%]	Overall selectivity [%]
Sn-Beta (50)	8	71	100
Sn-Beta (100)	24	99	99
Zr-Beta (50)	8	100	100

[a] Alcohol **1a** is produced in the first step by a Meerwein–Ponndorf–Verley reduction (reaction temperature: 100 °C).

only product observed (see Table 3). In this case, the dimer **4a** could not be detected owing to the low concentration of the intermediary alcohol **1a** during the reaction, as it rapidly reacts on the catalyst to give the corresponding ether **9** (see Supporting Information). With both catalysts, that is, Zr- and Sn-Beta, the desired fragrance was obtained in 98 % yield, with the Zr catalyst being more active for the global process.

In conclusion, Sn- and Zr-containing silicate molecular sieves are very active and selective catalysts for synthesizing a large variety of ethers from the corresponding alcohols without requiring the removal of water. As a result, a new process for producing ethers of interest in the fine chemicals industry has been developed with these catalysts, starting from one commercial aldehyde and one alcohol, through a cascade reaction that involves a Meerwein–Ponndorf–Verley reduction of the aldehyde followed by etherification of the alcohol.

Experimental Section

Sn-Beta,[15] Zr-Beta,[15] and Sn-MCM-41[21] were prepared following published procedures. X-ray diffraction studies and N_2 adsorption isotherms confirmed the good quality of the samples. Atomic adsorption spectroscopy indicated that the silicon/metal ratios were 107 (Sn-Beta), 134 (Zr-Beta), and 25 (Sn-MCM-41).

General procedure for the etherification reaction starting from two alcohols: Sn-Beta zeolite catalyst (50 mg) was added to a solution of *para*-methoxybenzyl alcohol **1a** (4 mmol) in 1-butanol (**2**; 3 g), and the reaction mixture was heated to 100 °C. Aliquots were withdrawn periodically, and the progress of the reaction was monitored by gas chromatography (HP5 column, 15 m × 0.32 mm, 5-μm film, using a suitable temperature program). The products were identified and characterized by GC-MS and ^{1}H NMR spectroscopy (see Supporting Information).

2,5-Dimethyltetrahydrofurane (**6**): 2,5-Hexanediol (**5**; 1.00 g, 8.53 mmol) and Sn-Beta (100 mg) were introduced into a 25-mL flask, and the flask was placed in a Kugelrohr distillation apparatus. The reaction mixture was heated for 45 min at 150 °C, during which time almost all the liquid distilled. A mainly solid material (zeolite Beta catalyst, 134 mg) was recovered from the flask, as well as a distillate (938 mg), which was analyzed by GC and GC-MS. The only compounds detected were 2,5-hexanediol (**5**) and 2,5-dimethyltetrahydrofuran (**6**, two diastereomers) in 20:80 ratio.

General procedure for the cascade etherification reaction starting from an aldehyde: Sn- or Zr-Beta zeolite catalyst (50 mg or 100 mg) was added to a solution of *para*-methoxybenzaldehyde (**7**; 1.1 mmol) in 2-butanol (**8**; 3 g), and the reaction mixture was heated to 100 °C.

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