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COMMUNICATION

Direct synthesis of unsymmetrical ethers from alcohols catalyzed by titanium cation-exchanged montmorillonite†

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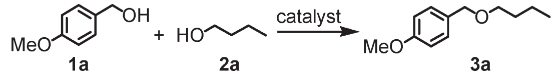
Titanium-exchanged montmorillonite (Ti^{4+}-mont) was found to act as an efficient heterogeneous catalyst for the etherification of a wide range of alcohols under mild reaction conditions. Ti^{4+}-mont was reusable with retention of high efficiency and applicable to scale-up reaction conditions.

Ethers are essential compounds in organic chemistry, serving as solvents and important precursors for polymers and fragrances.[1] The Williamson ether synthesis has been widely used for the preparation of symmetrical and unsymmetrical ethers.[2] However, this method generally requires the preparation of organohalides by the treatment of alcohols with environmentally harmful phosphorous halides, followed by their substitution with alkoxides under strong basic conditions, which results in the generation of large amounts of waste. Alternatively, the direct synthesis of ethers through dehydrative etherification of alcohols has attracted much attention because of its advantages, such as easy work-up procedures, low costs and the formation of water as the only by-product.[3,4] Many homogeneous catalysts such as Brønsted acid or Lewis acid based transition metals have been reported in the etherification of alcohols.[3] However, these systems have some drawbacks including their deactivation through the decomposition by water formed during the reaction, the necessity of neutralization after the reaction, and difficulties in catalyst recovery and reuse. Heterogeneous catalysts have been developed to overcome these problems, but the reported heterogeneous catalysts have been mostly applied to the synthesis of symmetrical ethers, and heterogeneous catalysts for the synthesis of unsymmetrical ethers are still rare.[4] Therefore, the direct synthesis of a wide range of unsymmetrical ethers derived from various combinations of alcohols using heterogeneous catalysts is still a challenge.

Recently, we demonstrated that titanium cation-exchanged montmorillonite (Ti^{4+}-mont) acted as an efficient solid acid catalyst for many environmentally benign reactions where the titanium oxide species sandwiched in the layers exhibited high catalytic activity for the acetalization of carbonyl compounds, the deprotection of acetals and the esterification of carboxylic acids.[5] Herein, Ti^{4+}-mont was also found to be effective as a reusable catalyst in the direct synthesis of unsymmetrical ethers from different classes of alcohols under mild reaction conditions. This catalyst system provided several improvements over reported solid acids in the scope of substrates and reaction temperatures.

Ti^{4+}-mont was prepared according to our previous report.[5a] The loading of Ti in Ti^{4+}-mont was 3.25 wt% from elemental analysis. A mixture of *p*-methoxybenzyl alcohol (**1a**) and *n*-butanol (**2a**) was stirred in the presence of Ti^{4+}-mont at 30 °C in an Ar atmosphere for 4 h. **1a** was converted to the desired unsymmetrical ether **3a** in 90% yield with >99% selectivity without the production of symmetric ethers. Among the various acid catalysts tested, Ti^{4+}-mont showed the highest catalytic activity. Commercially available acid catalysts of montmorillonite K-10, H-USY and H-Y resulted in low yields of **3a** (Table 1, entries 2–4), and other solid acids and a homogeneous Brønsted acid of *p*-toluenesulfonic acid barely worked as catalysts (Table 1, entries 5–8). The use of parent Na^{+}-mont in place of Ti^{4+}-mont did not promote the etherification, suggesting that the titanium species within layers of the montmorillonite was an active Brønsted acid species (Table 1, entry 9).[6] At 50%

Table 1 Etherification of *p*-methoxybenzyl alcohol and *n*-butanol[a]



Entry	Catalyst	Yield (%)[b]
1	Ti^{4+}-mont	90
2	Montmorillonite K-10	38
3	H-USY	20
4	H-Y	15
5	Nafion-H NR50	5
6	H-ZSM-5	4
7	H-mordenite	2
8	*p*-Toluenesulfonic acid[c]	4
9	Na^{+}-mont	0

[a] Reaction conditions: catalyst (0.1 g), *p*-methoxybenzyl alcohol (1 mmol), *n*-butanol (3 mL), 30 °C, Ar atmosphere, 4 h. [b] Determined by GC using an internal standard technique. [c] 10 mol%.

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[b] *Research Center for Solar Energy Chemistry, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan*

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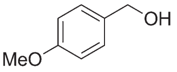
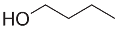
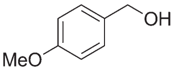
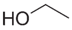
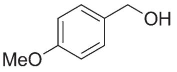
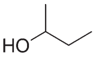
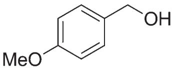
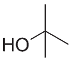
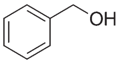
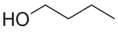
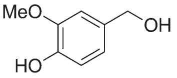
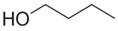
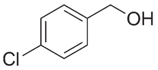
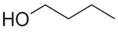
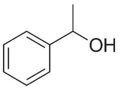
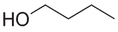
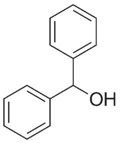
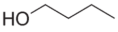
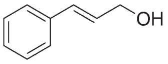
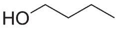
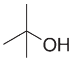
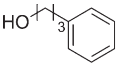
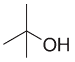
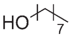
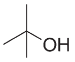
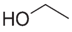
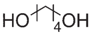
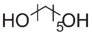
Table 2 Etherification of different classes of alcohols by Ti^{4+}-mont[a]

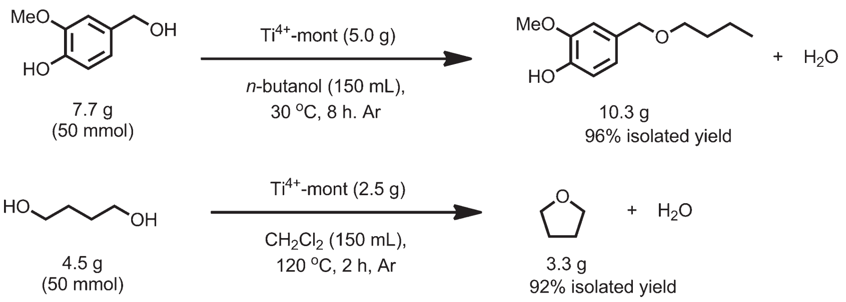
$$\underset{\mathbf{1}}{\text{R–OH}} + \underset{\mathbf{2}}{\text{R'–OH}} \xrightarrow{\text{Ti}^{4+}\text{-mont}} \underset{\mathbf{3}}{\text{R–O–R'}}$$

Entry	R–OH	R′–OH	R–O–R′	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	**3a**	6	99 (92)
2[c]				6	97
3[d]				6	97
4[e]				6	96
5[f]	 **1a**	 **2b**	**3b**	8	98 (95)
6	 **1a**	 **2c**	**3c**	20	80 (65)
7	 **1a**	 **1h**	**3d**	30	74 (61)
8[g]	 **1b**	 **2a**	**3e**	10	99 (91)
9	 **1c**	 **2a**	**3h**	5	99 (98)
10[g]	 **1d**	 **2a**	**3j**	30	98 (95)
11[f]	 **1e**	 **2a**	**3f**	15	91 (85)
12	 **1f**	 **2a**	**3g**	20	98 (98)
13[f]	 **1g**	 **2a**	**3i**	8	99 (97)
14[f]	 **1h**	 **2d**	**3k**	10	87 (81)
15[f]	 **1h**	 **2e**	**3l**	10	82
16[h]	 **1h**	 **2a**	**3m**	10	73
17[i]	 **1i**		**3n**	1.5	96
18[j]	 **1j**		**3o**	12	98

[a] Reaction conditions: Ti^{4+}-mont (0.1 g), **1** (1 mmol), **2** (3 mL), 30 °C, Ar atmosphere. [b] Determined by GC using an internal standard technique. Values in parentheses are isolated yields. [c] Reuse 1. [d] Reuse 2. [e] Reuse 3. [f] 60 °C. [g] 120 °C. [h] 100 °C. [i] Ti^{4+}-mont (0.05 g), CH_2Cl_2 (5 mL), 120 °C. [j] Ti^{4+}-mont (0.05 g), CH_2Cl_2 (5 mL), 140 °C.

conversion of **1a**, Ti^{4+}-mont was removed from the reaction mixture by filtration, and further treatment of the resulting filtrate under similar reaction conditions did not afford any products. This confirmed that Ti^{4+}-mont performed as a heterogeneous catalyst in the etherification.

The substrate scope of Ti^{4+}-mont for the synthesis of unsymmetrical ethers derived from diverse combinations of alcohols is exemplified in Table 2. **1a** could react with secondary and tertiary alcohols, as well as primary ones, giving the corresponding unsymmetrical ethers in high yields (Table 2, entries 1 and 5–7).[8] The etherification of various primary benzylic alcohols with **2a** afforded excellent yields of unsymmetrical ethers (Table 2, entries 8–10), even in the case of chlorobenzyl alcohol with an electron-withdrawing group at the *para*-position which is known to be less reactive (Table 2, entry 10).[4a] Ti^{4+}-mont was also effective in the etherification of secondary benzylic alcohols. For example, 1-phenylethanol (**1e**) was selectively converted to the corresponding ether without any formation of



Scheme 1 Etherifications using Ti^{4+}-mont under scale-up reaction conditions.

Table 3 NH3-TPD measurement of Ti^{4+}-mont

Temp. range of NH_3 desorption Amounts of partial acid sites (mmol g^{-1})	25–100 °C 0.06	100–200 °C 0.02	200–300 °C 0.10	300–400 °C 0.05	400–500 °C 0.03
Ti^{4+}-mont (treatment temp.)	Ti^{4+}-mont (100)	Ti^{4+}-mont (200)	Ti^{4+}-mont (300)	Ti^{4+}-mont (400)	Ti^{4+}-mont (500)
Yield of **3a** (%)[a]	trace	3	71	84	90
TON[b]	<1	4	66	26	17

[a] Reaction conditions: Ti^{4+}-mont (0.1 g), *p*-methoxybenzyl alcohol (1 mmol), *n*-butanol (3 mL), 30 °C, Ar atmosphere, 4 h. [b] TON of Ti^{4+}-mont(X) = [the amount of **3a** using Ti^{4+}-mont(X) − the amount of **3a** using Ti^{4+}-mont(X − 100)]/the amount of partial acid sites of Ti^{4+}-mont(X).

styrene as a by-product through the intramolecular dehydration of **1e** (Table 2, entry 11). The present Ti^{4+}-mont-catalyzed etherification could be extended to the preparation of aliphatic unsymmetrical ethers from non-activated aliphatic alcohols (Table 2, entries 14–16). For example, ethyl *tert*-butyl ether, which is an effective fuel additive in gasoline reforming, was obtained in high yield from *tert*-butanol and ethanol (Table 2, entry 16). The catalytic activity of Ti^{4+}-mont in the synthesis of aliphatic ethers was found to be outstanding compared to other solid acids which showed low activity under similar reaction conditions.[9] Moreover, Ti^{4+}-mont was applicable to the intramolecular etherification of diols. 1,4-Butanediol and 1,5-pentanediol were successfully converted into the corresponding cyclic ethers with excellent selectivity (Table 2, entries 17 and 18). The high efficiency of Ti^{4+}-mont was also demonstrated under preparative-scale reaction conditions in these inter- and intra-molecular etherifications of alcohols. For example, 7.7 g of vanillyl alcohol (50 mmol) smoothly reacted with 1-butanol at 30 °C to give 10.3 g (96% isolated yield) of vanillyl butyl ether, commonly used in fragrances and warming agents (Scheme 1). These above etherifications were achieved without requiring the removal of water, indicating that Ti^{4+}-mont was water-compatible. A further advantage of this solid catalytic system was its reusability. The Ti^{4+}-mont catalyst was easily recoverable and reusable without loss of its high activity (Table 2, entries 2–4).

To investigate the high catalytic activity of Ti^{4+}-mont, the acidity of Ti^{4+}-mont was measured by NH_3-TPD (temperature programmed desorption) at different temperatures (Table 3).[10] The maximum number of acid sites was present in the range of 200–300 °C.[11] The acid sites of Ti^{4+}-mont were poisoned by the adsorption of NH_3 and then the acid sites were partially regenerated by the desorption of NH_3 at different temperatures. As shown in Table 3, Ti^{4+}-mont treated at 300 °C [Ti^{4+}-mont(300)] could promote the etherification of **1a** with **2a** to give **3a** in 71% yield, while use of Ti^{4+}-mont(100) and Ti^{4+}-mont(200) gave extremely low yields,[12] revealing that the acid sites of Ti^{4+}-mont generated during the desorption of NH_3 in the range of 200 °C to 300 °C were extremely effective in the etherification. The calculation of turnover numbers also showed the high efficiency of the acid sites generated during the above treatment (Table 3). From these results, the high catalytic activity of Ti^{4+}-mont may be due to having the largest amount of acid sites with suitable acid strengths for the etherification. Similar phenomena of proper acid strengths were observed in other solid acids.[13]

In conclusion, Ti^{4+}-mont acted as a highly efficient heterogeneous Brønsted acid catalyst in the etherification of various unsymmetrical ethers from different classes of alcohols under mild conditions. Moreover, Ti^{4+}-mont was also separable and reusable and maintained its high activity and selectivity without requiring the removal of water. We also found that the acid sites generated during desorption of NH_3 in the range of 200 °C to 300 °C were quite effective in the etherification.

Acknowledgements

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3 For representative examples of homogeneous catalysts for etherification of alcohols, see: (*a*) S. Kim, K. N. Chung and S. Yang, *J. Org. Chem.*, 1987, **52**, 3917; (*b*) L. Karas and W. J. Piel, in *Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, 4th edn, 1992, vol. 9 pp. 860–876; (*c*) P. Salehi, N. Iranpoor and F. K. Behbahani, *Tetrahedron*, 1998, **54**, 943; (*d*) G. V. M. Sharma and A. K. Mahalingam, *J. Org. Chem.*, 1999, **64**, 8943; (*e*) A. Kawada, K. Yasuda, H. Abe and T. Harayama, *Chem. Pharm. Bull.*, 2002, **50**, 380; (*f*) K. J. Miller and M. M. Abu-Omar, *Eur. J. Org. Chem.*, 2003, 1294; (*g*) Y. Liu, R. Hua, H.-B. Sun and X. Qiu, *Organometallics*, 2005, **24**, 2819; (*h*) T. Shibata, R. Fujiwara and Y. Ueno, *Synlett*, 2005, **1**, 152; (*i*) A. Prades, R. Corberán, M. Poyatos and E. Peris, *Chem.–Eur. J.*, 2008, **14**, 11474.

4 Reported solid catalysts act not as Brønsted acids but as Lewis acids. See $AlPW_{12}O_{40}$: Reactions of benzylic or allylic alcohols with primary or secondary alcohols under reflux conditions: (*a*) H. Firouzabadi, N. Iranpoor and A. A. Jafari, *J. Mol. Catal. A: Chem.*, 2005, **227**, 97; . Sn- and Zr-containing silicate molecular sieve: Reaction of benzylic alcohols with primary aliphatic alcohols at 100 °C: (*b*) A. Corma and M. Renz, *Angew. Chem., Int. Ed.*, 2007, **46**, 298; . $Cs_{2.5}H_{0.5}PW_{12}O_{40}/ZrO_2$: The synthesis of ethers derived from combinations of *p*-methoxybenzyl alcohols with aliphatic alcohols at 65 °C and diphenyl methanol with aliphatic alcohols at 120 °C, respectively: (*c*) K. T. V. Rao, P. S. N. Rao, P. S. Sai Prasad and N. Lingaiah, *Catal. Commun.*, 2009, **10**, 1394.

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6 It is known that 2,6-lutidine can interact with Brønsted acid sites but cannot react with Lewis acid sites due to steric hindrance.[7] The Ti^{4+}-mont-catalyzed etherification of alcohols was inhibited by the addition of 2,6-lutidine, showing that the active species of Ti^{4+}-mont were Brønsted acid sites in the etherification.

7 A. Corma, *Chem. Rev.*, 1995, **95**, 559.

8 In the Ti^{4+}-mont-catalyzed etherifications, trace amounts of symmetrical ethers from aliphaticalcohols (**2**) were formed as by-products.

9 The yields of **3m** in the etherification of **1h** with **2a** were as follows: montmorillonite K-10, 36%; *p*-toluenesulfonic acid, 18%; H-Y, 5%.

10 The measurement of desorbed NH_3 was carried out at different temperatures where higher NH_3 desorption temperatures corresponded to stronger acid sites; see the following reference: P. Berteau and B. Delmon, *Catal. Today*, 1989, **5**, 121.

11 The total amount of acid sites in Ti^{4+}-mont was 0.26 mmol g^{-1}, which corresponded to the amount of NH_3 in the whole range of NH_3 desorption temperatures (25–500 °C).

12 The catalytic activity of Ti^{4+}-mont(500) was very similar to that of the fresh Ti^{4+}-mont catalyst, showing that the total active acid sites of fresh Ti^{4+}-mont in the etherification corresponded to that of Ti^{4+}-mont(500).

13 See ESI†.