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Mesoporous aluminosilicate promoted protection and deprotection of carbonyl compounds

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Abstract—Mesoporous aluminosilicates are efficient heterogeneous catalysts for both the formation and hydrolysis of a range of acetals under mild conditions and in short reaction times.

The protection of carbonyl functions as acetals and their subsequent deprotection is an important strategy in multi-stage synthesis.[1] The use of acetals as protecting groups has been employed widely and typically utilizes acid catalysts such as *para*-toluene sulfonic acid (PTSA) or boron trifluoride diethyl etherate in the presence of a dehydrating agent such as trimethyl orthoformate.[2] Numerous attempts to improve the atom efficiency of this process have been investigated and a number of strategies, such as the use of Lewis acid catalysts, solvent-free conditions and ionic liquids have been reported.[3] These processes, however, still require dehydrating agents, high temperatures or azeotropic removal of water. The application of heterogeneous catalysis offers a number of attractive advantages such as low toxicity, ease of separation from the reaction mixture and reduction in the amount of waste products. Solid acid catalysts such as Keggin-type heteropoly acids, zeolites, clays and SO_3H-functionalized silica have all previously been utilized. Although these protocols are effective, they are limited to either the formation of cyclic acetals or require extended reaction times.[4] Mesoporous silicates, such as MCM-41, have found applications as adsorbents, dehydrating agents, solid supports and as an acid catalyst in a number of synthetic transformations.[5] Indeed, the potential for mesoporous silicates to act as efficient, re-usable acetalization catalysts has been demonstrated. Silicate MCM-41 promotes acetalization reactions in methanol without the requirement for additional dehydrating agents, however, this protocol requires protracted reaction times or elevated temperatures to obtain high yields.[6] Attempts to increase the activity of the catalyst by incorporating metals, such as aluminium, into the mesoporous framework has led to the production of the corresponding Al-MCM-41 materials, which also catalyze the acetalization of carbonyl compounds.[7] These studies, however, investigated the reactions of only a limited range of carbonyl compounds and also required the presence of trimethyl orthoformate.[7a] In an attempt to produce efficient, heterogeneous acetalization catalysts, we synthesized a number of mesoporous aluminosilicates containing varying Si/Al ratios and assessed their ability to catalyze the acetalization of a range of carbonyl compounds.

The mesoporous silicate and aluminosilicate catalysts used in this study were synthesized using a modified literature procedure,[8] and their ability to catalyze the formation of benzaldehyde dimethyl acetal in the presence and absence of trimethyl orthoformate was assessed. Reactions utilizing these catalysts in the presence of an excess of trimethyl orthoformate produced the acetal product in agreement with literature reports.[7a] It was found, however, that a number of these materials catalyzed acetal formation directly from benzaldehyde and methanol to varying degrees. The highest catalytic activity was displayed by the material having a silicon/aluminium ratio = 14 as measured by EDX analysis and this catalyst was used in all subsequent reactions. Acetalization appears to be efficient for a range of carbonyl compounds, which are readily transformed into

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Keywords: Acetalization; Acetal hydrolysis; Heterogeneous catalysis; Mesoporous aluminosilicates.

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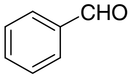
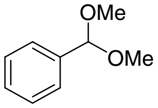
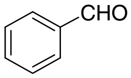
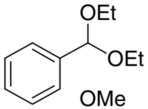
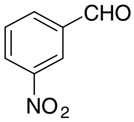
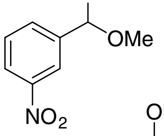
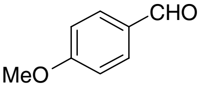
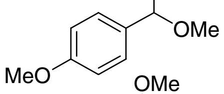
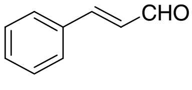
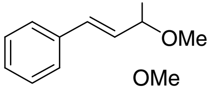
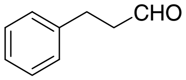
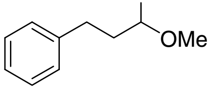
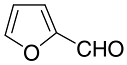
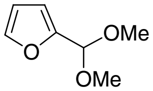
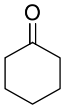
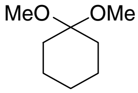
Table 1. Mesoporous aluminosilicate promoted acetalization of carbonyl compounds

Entry	Carbonyl compound	Time (h)	Product[a]	Yield[b] (%)
1		4		87[c]
2		5		95[d]
3		6		92
4		1		98[d]
5		3.5		98[c,d]
6		4		92
7		1		63[d]
8		6		25[d]

[a] Reaction in 10 mL of alcohol solvent at 50 °C utilizing 50 mg of catalyst.

[b] All compounds gave satisfactory spectroscopic data.

[c] At room temperature.

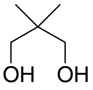
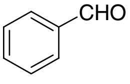
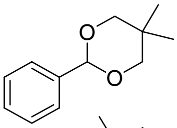
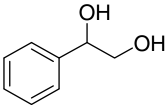
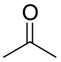
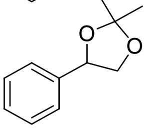
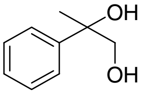
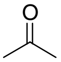
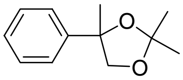
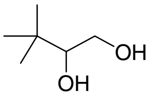
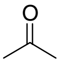
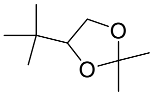
[d] Crude ^{1}H spectra gave >95% purity.

dimethyl and diethyl acetals in high yields from methanol and ethanol, respectively (Table 1). The reaction of cyclohexanone, however, resulted in a low isolated yield of the dimethyl ketal even though NMR analysis of the crude reaction mixture indicated complete consumption of the starting material. This may be due to the ketal product being adsorbed onto the aluminosilicate.[9] Attempts to remove the product by washing did not lead to improved isolated yields. Significantly, reactions utilizing our plain silicate gave no acetal product under these conditions even after protracted reaction times.

Our attention was next turned to the formation of cyclic acetals. Due to the elevated boiling points of the diols used, these transformations were carried out in the presence of a volatile co-solvent, such as dichloromethane utilizing a small excess of the diol. Disappointingly, under these conditions the reaction of benzaldehyde with 1,2-ethane and 1,3-propane diols resulted in low isolated yields even after protracted reaction times at reflux temperatures. Gratifyingly, however, reactions involving 2,2-dimethylpropane-1,3-diol proceeded readily to give the corresponding cyclic acetal in high yield and this protocol was found to be effective for a small range of 1,2-diols, which typically did not require further purification (Table 2). These studies demonstrate the high efficiency and wide synthetic utility of mesoporous aluminosilicate materials as catalysts for acetal formation.

The corresponding deprotection reactions of acetals is achieved by a variety of methods such as aqueous acid hydrolysis, the use of Lewis acid catalysts, under neutral conditions utilizing metal salts or organic promoters, or under basic conditions using ceric ammonium nitrate. These techniques, while useful, suffer from limitations including harsh reaction conditions leading to the decomposition of sensitive acetals or products, protracted reaction times or tedious work-up procedures.[10] Heterogeneous catalysts such as K-10 Montmorillonite, silica supported γ-PCC, silica supported perchloric acid and Matgrieve have proved to be extremely useful. As with all methods employing heterogeneous reagents, the process is operationally straightforward and the reagent is easily removed by filtration.[11] It is surprising therefore that there appears to be no reports to date of aluminosilicates being employed for the corresponding hydrolysis reactions of acetals and ketals. We therefore next studied the ability of our materials to catalyze the hydrolysis of benzaldehyde dimethyl acetal and were gratified to find that the reaction proceeded rapidly in refluxing aqueous acetone. Several acetals underwent rapid hydrolysis under these conditions to produce the corresponding carbonyl compound in high yields with-

Table 2. Mesoporous aluminosilicate promoted formation of cyclic acetals

Entry	Diol	Carbonyl compound	Product	Yield[a] (%)
1				80[b,c]
2				97[d]
3				96[d]
4				80[d]

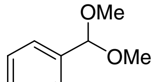
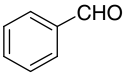
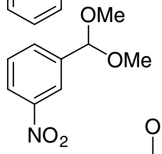
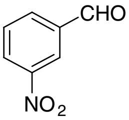
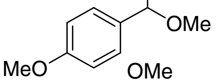
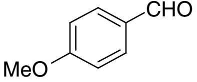
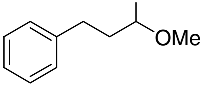
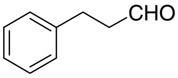
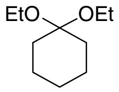
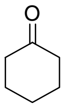
[a] All compounds gave satisfactory spectroscopic data.

[b] In refluxing CH_2Cl_2 using 1 equiv of diol and carbonyl compound and 50 mg of catalyst for 6 h.

[c] Isolated yield after column chromatography.

[d] Reactions in refluxing acetone using 50 mg of catalyst for 6 h.

Table 3. Mesoporous aluminosilicate promoted acetal hydrolysis

Entry	Acetal[a]	Time (h)	Product	Yield[b] (%)
1		0.5		87
2		2		98
3		0.5		99
4		3		90[c]
5		2		85

[a] Acetals were used as supplied or synthesized according to literature procedures.[3]

[b] All compounds gave satisfactory spectroscopic data.

[c] Yield after column chromatography.

out the requirement for chromatographic purification (Table 3).

In conclusion, we have demonstrated that mesoporous aluminosilicates are highly efficient catalysts for the synthesis of both cyclic and acyclic acetals from a range of carbonyl compounds in high yields and in short reaction times. The synthesis of dimethyl and diethyl acetals proceeds without the requirement for inert or anhydrous reaction conditions, co-solvents, high temperatures or additional dehydrating agents directly from the corresponding alcohols. The synthesis of cyclic acetals is also achieved in high yields and amply demonstrates the generality of the process. We have also shown that mesoporous aluminosilicates are highly efficient catalysts for the hydrolysis of acetals in high yields and in short reaction times. The facile synthesis of these materials, their benign nature, potential for re-use, their ease of handling and the simplified reaction and isolation procedures make them a highly attractive alternative to current methodologies.

Typical experimental procedure for the synthesis of acyclic acetals: Benzaldehyde (106 mg, 1 mmol) was dissolved in methanol (10 mL) at room temperature. The catalyst (50 mg) was added and the reaction mixture stirred at room temperature and monitored by TLC. Upon completion of the reaction, the catalyst was removed by filtration through a Celite plug, which was washed with dichloromethane (2 × 5 mL), and the combined solvents removed under reduced pressure. Purification by column chromatography (ethyl acetate/hexane 1:3) gave the product *benzaldehyde dimethyl acetal* (132 mg, 87%) as a colourless oil.

Typical experimental procedure for the synthesis of cyclic acetals: Benzaldehyde (112 mg, 1.06 mmol) and 2,2-dimethylpropane-1,3-diol (212 mg, 2.03 mmol) were dissolved in dichloromethane (10 mL) at room temperature. The catalyst (50 mg) was added and the reaction mixture stirred at 45 °C for 6 h. After this time, the reaction mixture was cooled to room temperature and the catalyst was removed by filtration through a Celite plug, which was washed with dichloromethane (2 × 5 mL), and the combined solvents removed under reduced pressure. Purification by column chromatography (ethyl acetate:hexane 1:4) gave the product *5,5-dimethyl-2-phenyl-[1,3]-dioxane* (160 mg, 80%) as a colourless oil; ^{1}H NMR (400 MHz; $CDCl_3$) $\delta = 7.45$–7.40 (m, 2H), 7.32–7.23 (m, 3H), 5.30 (s, 1H), 3.67 (d, 2H, $J = 11$ Hz), 3.56 (d, 2H, $J = 11$ Hz), 1.22 (s, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) $\delta = 130.1$, 129.3, 128.5, 126.6, 102.2, 78.1, 23.5, 22.3; MS (EI) *m/z* 192 (M^+); HRMS (EI) calculated for $C_{12}H_{17}O_2$ ($M+H^+$), 193.1223, found ($M+H^+$) 193.1223.

Typical experimental procedure for the synthesis of [1,3]-dioxolanes: 1-Phenylethane-1,2-diol (135 mg, 0.98 mmol) was dissolved in acetone (5 mL). The catalyst (50 mg) was added and the reaction mixture stirred at 55 °C for 6 h. After this time, the reaction mixture was cooled to room temperature. The catalyst was removed by filtration through a Celite plug, which was washed with dichloromethane (2 × 5 mL), and the combined solvents removed under reduced pressure to give the product *2,2-dimethyl-4-phenyl-*[*1,3*]*-dioxolane* (166 mg, 97%) as a colourless oil; ^{1}H NMR (400 MHz; $CDCl_3$) $\delta = 7.44$–7.31 (m, 5H), 5.10 (dd, 1H, $J = 6$ and 2 Hz), 4.33 (dd, 1H, $J = 6$ and 2 Hz), 3.74 (t, 1H, $J = 8$ Hz), 1.20 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) $\delta = 129.2$, 128.9, 126.3, 110.2, 77.8, 72.3, 27.0, 26.7; MS (CI–NH_3) *m/z* 197 ($M+NH_4{}^+$); HRMS (EI) calculated for $C_{11}H_{15}O_2$ ($M+H^+$), 179.1067, found ($M+H^+$) 179.1068.

Typical procedure for the hydrolysis of acetals: Benzaldehyde dimethyl acetal (152 mg, 1 mmol) and water (42 mg, 2.3 mmol) were dissolved in acetone (5 mL) at room temperature. The catalyst (25 mg) was added and the reaction mixture stirred at 55 °C for 30 min. After this time, the reaction mixture was cooled to room temperature. The catalyst was removed by filtration through a Celite plug, which was washed with dichloromethane (2 × 5 mL). The combined solvents were removed under reduced pressure to yield the product *benzaldehyde* (93 mg, 87%) as a colourless oil.

Acknowledgements

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8. Catalyst preparation (Si/Al = 14): The cetyltrimethylammonium bromide template (4.0 g, 11 mmol) was dissolved in a solution of hydrochloric acid (2.5 mL, 0.1 M) and ethanol (17.5 mL). Tetraethylorthosilicate (25 mL, 112 mmol) was then added and the mixture stirred for 10 min at 40 °C. The solution was cooled to room temperature and aluminium nitrate nonahydrate (3.35 g, 8.95 mmol) was added in one portion. The mixture was stirred for 20 min and then left to age at room temperature for 1 week. The resultant orange solid was crushed into a fine powder, dried overnight at 90 °C and then calcined in air at 550 °C for 12 h to remove the organic template. The resulting white aluminosilicate catalyst was characterized by EDX, MAS-NMR (^{27}Al and ^{29}Si) and XRD. Surface area measurements and pore size distribution were obtained from BET experiments.
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