Titanium silicate molecular sieve, TS-1, catalysed C–C bond formation in Mukaiyama type aldol reactions

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The titanium silicate molecular sieve, TS-1, efficiently catalyses the formation of carbon–carbon bond in the Mukaiyama type aldol reaction of silyl enol ethers and aldehydes forming β-hydroxy esters/aldols in high yields under heterogeneous and ambient reaction conditions.

The Mukaiyama[1] type reactions between silyl enol ethers and aldehyde/ketal, a facile method for C–C bond formation, are promoted by Lewis acids both in stoichiometric or catalytic[2–5] amounts under homogeneous reaction conditions at subambient temperatures. Kawai *et al.*[6] have compared the catalytic activity and selectivity of various conventional solid acid catalysts, (*e.g.* SiO_2–Al_2O_3, clays such as montmorillonite, Nafion-117, CaY *etc.*) in aldol condensation reactions. Al-montmorillonite was found to be quite active and selective. However, like homogeneous systems, these heterogeneous reactions were also carried out at low temperatures (0 to −95 °C).

Now, we demonstrate for the first time the use of titanium silicate molecular sieve, TS-1, as an efficient, environmentally safe, heterogeneous catalyst in Mukaiyama type reactions involving silyl enol ethers and aldehydes to produce β-hydroxy esters in good to very good yields at room temperature or at 60–80 °C. TS-1 is a MFI type titanium silicate molecular sieve, which is a well known oxidation catalyst[7–9] using dilute hydrogen peroxide. In the present communication, we have successfully explored the use of TS-1 in efficiently catalysing the above mentioned C–C bond formation. The results are compared with other zeolites and related solid catalysts.

The TS-1 and other catalysts were prepared and thoroughly characterized according to conventional known procedures. The details about their crystallographic pore structure have been compiled and published recently.[10] The catalysts were calcined and activated at 500 °C for 6–8 h in flowing air before use. In a typical reaction, the catalyst (300 mg) was added to a mixture of silyl enol ether (10 mmol) and an aldehyde **1**–**8** (10 mmol) in *dry* THF (10 ml), in a magnetically stirred glass batch reactor. The reactions were carried out at room temperature (25–27 °C) unless stated otherwise. The progress of the reaction was monitored by TLC, and after completion of the reaction, the catalyst was filtered off and the products were separated by flash chromatography† followed by their characterization by ^1H NMR and IR spectroscopic and mass spectrometric methods.

Table 1 shows that TS-1 (entries 1–11), *vis-a-vis* other solid catalysts (entries 14–22), is quite an efficient catalyst for the condensation of silyl enol ether with various aldehydes (entries 1–8) to produce corresponding β-hydroxy esters in good yields (Scheme 1). Cyclic and aromatic aldehydes exhibited good reactivity. Although, aldehyde **6** was also quite reactive, **7** (with a long chain) and **8** (with a branched chain) gave relatively lower yields (67–70%) compared to **1**–**5**. Entry 10 shows that as-synthesized TS-1 (with pores filled with organic template) was less active compared to its organic-free calcined form (with free pores, entry 2). However, 2-nitrobenzaldehyde (entry 9) gave 70% yield indicating that the external surface may also be active in this reaction. Entries 2, 11 and 12 show that while THF and CH_2Cl_2 are good solvents for this reaction using TS-1 catalyst, $MeNO_2$ seems to lower the yields. Interestingly, when water was added along with the solvent (THF) the reaction occurred to a significant extent (entry 13, Table 1). The absence of any significant optical rotation in the product suggests the formation of a racemic mixture.

Having ascertained the efficacy of TS-1 as a heterogeneous catalyst in the aldol reactions involving an open-chain silyl enol ether **2a** (Scheme 1), the methodology was extended to cyclic silyl enol ethers *viz.* 1-trimethylsilyloxycyclohexene **2b** (Scheme 1). Interestingly, a facile reaction was observed under reflux conditions (80 °C) when the reaction was performed in THF to which an equal volume of water has been added. In the absence of water using dry THF or CH_2Cl_2 as solvent, no reaction was observed (Table 2). A significant finding was the preferred formation of *syn*-aldol stereoisomer in all the cases except one (Table 2, entry 1). It is worth noting that, in general, the *anti*-aldol is the preferred isomer under the Mukaiyama aldol reaction conditions and only under specialized conditions involving homogeneous catalysis has *syn*-selectivity for the aldol been achieved.[1,3] Although the catalyst could be reused

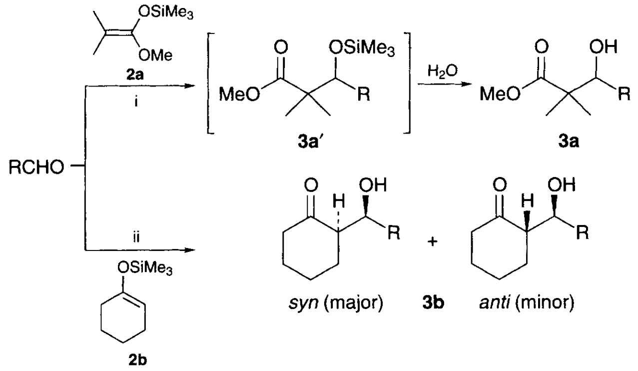
Table 1 Reaction of methyl trimethylsilyl dimethylketene acetal **2a** with aldehydes catalysed by different molecular sieves

Entry	RCHO	Catalyst	*T*/°C	Product yield[a] (%)
1	benzaldehyde **1**	TS-1[b]	room temp.	85
2	4-nitrobenzaldehyde **2**	TS-1	room temp.	90
3	4-cyanobenzaldehyde **3**	TS-1	60	82
4	4-methoxybenzaldehyde **4**	TS-1	room temp.	85
5	furfuraldehyde **5**	TS-1	60	85
6	propionaldehyde **6**	TS-1	room temp.	70
7	octylaldehyde **7**	TS-1	60	85
8	isobutyraldehyde **8**	TS-1	room temp.	67
9	2-nitrobenzaldehyde **9**	TS-1	room temp.	70
10	**2**	TS-1[c]	room temp.	40
11	**2**	TS-1[d]	room temp.	90
12	**2**	TS-1[e]	room temp.	75
13	**2**	TS-1[f]	room temp.	70
14	**2**	VS-1	60	10
15	**2**	SnS-1	60	25
16	**2**	[Sn]MTW	60	15
17	**2**	Beta	60	20
18	**2**	Re-Y	60	50
19	**2**	La-Y	60	37
20	**2**	Na-Y	60	0
21	**2**	H-ZSM-5	60	0
22	**2**	—	60	0

[a] Isolated yield of the product. [b] TS-1:[9] Si/Ti (molar ratio) = 32; VS-1:[13] Si/V = 86; and SnS-1:[14] Si/Sn = 67; all these three catalysts possess MFI (ZSM-5) topology, were completely free from Al and Na. The raw materials tetraethylorthosilicate and tetrapropylammonium hydroxide (Aldrich) used to prepare these material were also free from such impurities (Al < 0.1 ppm, Na ≈ 4 ppm). [Sn]MTW:[15] a tin-silicate analogue of zeolite ZSM-12 with MTW topology, Si/Sn = 78; Beta:[16] Si/Al 60; Y: Si/Al = 2.4 (Na, La and Re forms)‡ and H-ZSM-5:[17] Si/Al = 33. [c] As-synthesised, uncalcined. [d] Solvent, dichloromethane. [e] Solvent, nitromethane. [f] Solvent, THF–water (1 : 1 m/m).

(with reduced activity) after filtration and washing, the original catalytic activity of TS-1 can be restored only after calcination at *ca.* 450 °C in air for 6–8 h.

In the complete absence of water TS-1 exhibits 'neutral, oxophilic Lewis acid' sites[11] while the possibility of Brønsted acid sites has been suggested[12] in the presence of H_2O_2 only. However, our experimental results, where no H_2O_2 is used, would indicate that neither the Lewis acidity (facile reaction in the presence of water) nor the Brønsted acidity (no dehydration of aldols into olefinic compounds as well as the absence of any reaction on H-ZSM-5, Table 1, entry 21) is playing a prominent role in the catalysis. The key step in such reactions involving silyl enol ethers and aldehydes is the activation of enolic oxygen followed by the migration of double bond thus facilitating the formation of a nucleophilic moiety at the β-carbon position leading to the condensation. Apparently, the Ti^{4+} in TS-1 with its d^0 configuration offers oxophilic sites to the oxygen of the reacting species, probably giving rise to a favourable six-membered transition state similar to the one proposed by Mukaiyama *et al.*[1] leading to the aldol. Further, the successful isolation of the intermediate **3a′** (Scheme 1) (characterised by ^1H NMR) prior to its hydrolysis clearly indicates that TS-1 activates the enolic oxygen of O–Si bond leading to its cleavage.



Scheme 1 *Reagents and conditions*: i, THF, TS-1, room temp., 8 h; ii, THF–H_2O, TS-1, 80 °C, 5 h

Table 2 Reaction of 1-trimethylsilyloxycyclohex-1-ene with aldehydes over TS-1[a]

Entry	RCHO	Yield[b] (%)	*syn* : *anti*[c]
1	benzaldehyde **1**	68	49 : 51
2	4-nitrobenzaldehyde **2**	81	58 : 42
3	4-cyanobenzaldehyde **3**	84	60 : 40
4	furfuraldehyde **5**	69	60 : 40
5	isobutyraldehyde **8**	58	71 : 29

[a] TS-1, calcined: 20% m/m on **2b**; *T* = 80 °C; [b] Isolated after chromatographic purification. [c] *syn* : *anti* ratios have been determined by ^1H NMR (200 MHz).

In conclusion, we have demonstrated the first non-oxidative, efficient catalytic use of titanium silicate molecular sieve, TS-1, in Mukaiyama type aldol reactions involving C–C bond formation between silyl enol ethers and aldehydes to produce corresponding β-hydroxy esters in good to very good isolated yields at room temperature or under reflux conditions.

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Footnotes

† Flash chromatography: silica gel with mesh size between 230 and 350 to provide better separation of components.

‡ Na-Y was obtained from UCIL, Bombay; Re-Y and La-Y were obtained by conventional ion-exchange of Na-Y zeolite.

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