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# Spontaneous aldol and Michael additions of simple enoxytrimethylsilanes in DMSO

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## Abstract

Activation of simple trimethylsilyl ketene acetals by dipolar aprotic solvents has been evidenced, allowing efficient solvent assisted aldol and Michael additions under extremely simple, mild and metal free conditions. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Mukaiyama reaction; aldol addition; Michael additions; enoxysilanes; solvent effect.

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Since the initial report of Mukaiyama, the use of enoxysilanes as latent enolates in aldol additions attained an impressive level of sophistication. Efficient catalytic processes are now available that afford high control of both diastereo- and enantioselectivity.<sup>1</sup>

The Mukaiyama reaction is classically promoted by a Lewis acid (or a trityl salt<sup>2</sup>) which initiates the enoxysilane addition through the electrophilic activation of the aldehyde. Facial discrimination of the carbonyl group also depends on this chelation in the asymmetric version of the reaction. The exact mechanistic pathway has been shown to be complex.<sup>3</sup>

Alternatively, the latent enolate can also be subject to activation, either through nucleophilic cleavage of the O–Si bond (upon action of a fluoride salt<sup>4</sup> or a phosphine<sup>5</sup>), or via Lewis base coordination to the silicon atom. In the later strategy developed by Denmark,<sup>6</sup> the presence of highly electronegative chlorides on the silicon atom of the enoxysilane ensures a strong chelation (essential for a significant level of asymmetric induction with a chiral promoter), while giving rise in some cases to a concurrent uncatalysed reaction pathway.<sup>7</sup>

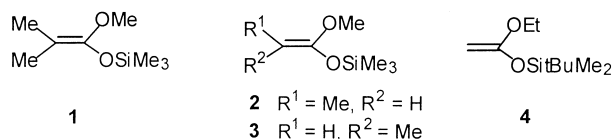
Strictly unpromoted enoxysilane additions have also been described. All the reported examples are based on an unusual substitution pattern that renders the enolsilane appropriately electrophilic.<sup>8</sup> The rate acceleration resulting from incorporation of the silicon atom within a four-membered ring have been studied by Myers<sup>9</sup> and Denmark.<sup>10</sup> Highly efficient and diastereoselective uncatalysed additions of such silacyclobutyl ketene acetals rely on the coordination of the

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aldehyde oxygen to the silicon atom. For this, the strong Lewis acidity due to the angle strain introduced by the four-membered ring is necessary. Smooth addition of dimethyl(trifloxy)silyl enol ethers generated in situ to various nucleophiles have been shown to occur diastereoselectively in the absence of any external promoter.<sup>11</sup> The thermal aldolisation of dimethylsilyl enol ethers and  $\alpha$ -dimethylsilyl esters was also reported to proceed slowly upon gentle heating in DMF, albeit without appreciable stereoselectivity.<sup>12</sup>

We wish to report here that trivial trimethylsilyl ketene acetals can also readily participate in spontaneous addition reactions. While screening for new catalysts we incidentally found that highly dipolar aprotic media have a profound rate accelerating effect on aldolisation with enoxy-trimethylsilanes.<sup>13</sup> Thus, enoxysilane **1** adds to benzaldehyde at room temperature to furnish the trimethylsilyl ether of the expected aldol product in 70–80% yield after one day, when solvents such as DMA, DMF or DMSO are employed. Interested by this finding we further optimised the reaction conditions. DMSO was chosen for its stronger ability to promote the reaction.<sup>14</sup> Concentration of the reaction medium to 1 M increased the reaction rate. Strict exclusion of moisture was critical for optimum efficiency, though the reaction tolerates traces of water (70% yield after one day in DMSO containing water in 0.5% volume). Thus, treatment of benzaldehyde with a slight excess of trimethylsilyl ketene acetal **1** during one day at room temperature in freshly distilled DMSO, and in the presence of activated 4 Å molecular sieves, gives silyl ether of the desired adduct nearly quantitatively. Desilylation followed by filtration over silica gel affords pure aldol in 95% yield. It is worth noting that the same reaction has been reported to require heating at 150°C (neat) for 18 h to furnish 81% yield in the expected aldolisation product.<sup>15</sup>



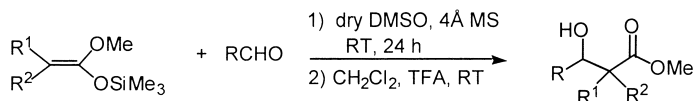
The mildness of our reaction conditions clearly originates from the strong coordinating capacity of DMSO, and is likely to proceed through an activation of the enoxysilane by chelation of the silicon atom. This interpretation is supported by the fact that the more hindered *t*-butyl-dimethylsilyl ketene acetal **4** failed to react with benzaldehyde under similar conditions.

We then generalised our study to other electrophiles. Silyl ketene acetal **1** smoothly reacts with various aromatic and conjugated aldehydes (Table 1, entries 1–4). Addition to aliphatic derivatives occurs less efficiently but still furnishes the aldol compound in a synthetically useful fashion (Table 1, entries 5 and 6). Michael additions also readily operate in DMSO with different enones to afford high yields of 1,4-adducts (Table 2, entries 1–3).

These reaction conditions are also applicable to other silyl ketene acetals such as **2**.<sup>16</sup> While addition to various aldehydes occurs in a comparable fashion (Table 1, entries 7–10), a slight drop in reactivity towards enones was noticed (Table 2, entries 4 and 5).<sup>17</sup>

Use of monosubstituted enoxysilanes allowed us to address the stereochemical outcome of these spontaneous aldolisations (Table 1, entries 7 and 11). Addition of this *E* silyl ketene acetal to benzaldehyde proceeds with a slight diastereoselectivity in favour of the *syn* adduct (d.r. 60/40), similarly to what was reported for the original  $\text{TiCl}_4$  catalysed Mukaiyama reaction.<sup>18</sup> The *Z* isomer **3** gives a 66/43 d.r. in favour of the same *syn* adduct. These observations suggest the intervention of an acyclic transition state as generally admitted for the Lewis acid mediated reaction.<sup>19</sup>

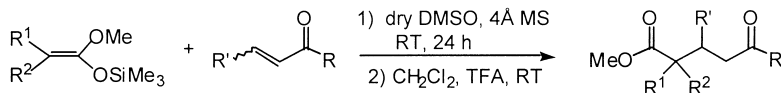
Table 1



Entry	Aldehyde	Ketene acetal		<i>syn</i> / <i>anti</i>	Isolated yield
		R <sup>1</sup>	R <sup>2</sup>		
1	benzaldehyde	Me	Me		95
2	<i>p</i> -methoxybenzaldehyde	Me	Me		89 <sup>(a)</sup>
3	2-naphtaldehyde	Me	Me		81
4	cinnamaldehyde	Me	Me		90 (1,2:1,4 83/17) <sup>(a)</sup>
5	hydrocinnamaldehyde	Me	Me		47
6	cyclohexanecarboxaldehyde	Me	Me		35
7	benzaldehyde	Me	H	60 / 40	88
8	2-naphtaldehyde	Me	H	62 / 38	73
9	cinnamaldehyde	Me	H	53 / 47	88 (1,2:1,4 100/0) <sup>(a)</sup>
10	hydrocinnamaldehyde	Me	H	58 / 42	22
11	benzaldehyde	H	Me	66 / 34	86

a) TBAF supported on SiO<sub>2</sub> in THF was used for desilylation.

Table 2



Entry	Enone	Ketene acetal		<i>syn</i> / <i>anti</i>	Isolated yield
		R <sup>1</sup>	R <sup>2</sup>		
1	chalcone	Me	Me		97
2	cyclohexenone	Me	Me		81
3	cyclopentenone	Me	Me		95
4	chalcone	Me	H	60 / 40	74
5	cyclopentenone	Me	H	50 / 50	62

In conclusion, we have found new conditions for aldolisations and Michael additions of trimethylsilyl enoxysilanes. These efficient solvent assisted reactions can simply be carried out at low cost and without the necessity of any metallic derivatives.

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