

## SILICON DIRECTED DIASTEREO- AND ENANTIOSELECTIVE MUKAIYAMA MICHAEL TANDEM ALDOL CONDENSATION: A NOVEL STRATEGY FOR SIX MEMBERED RING CYCLISATION\*

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**Abstract:** Silicon directed diastereo- and enantioselective conjugate addition of enolsilanes to  $\alpha,\beta$ -unsaturated ketones are reported which undergo subsequent intramolecular cyclization on treatment with aqueous  $\text{HBF}_4$  to furnish aldol adducts. Depending on the substituents, the aldol adducts undergo dehydration to give substituted  $\alpha,\beta$ -unsaturated cyclohexenones.

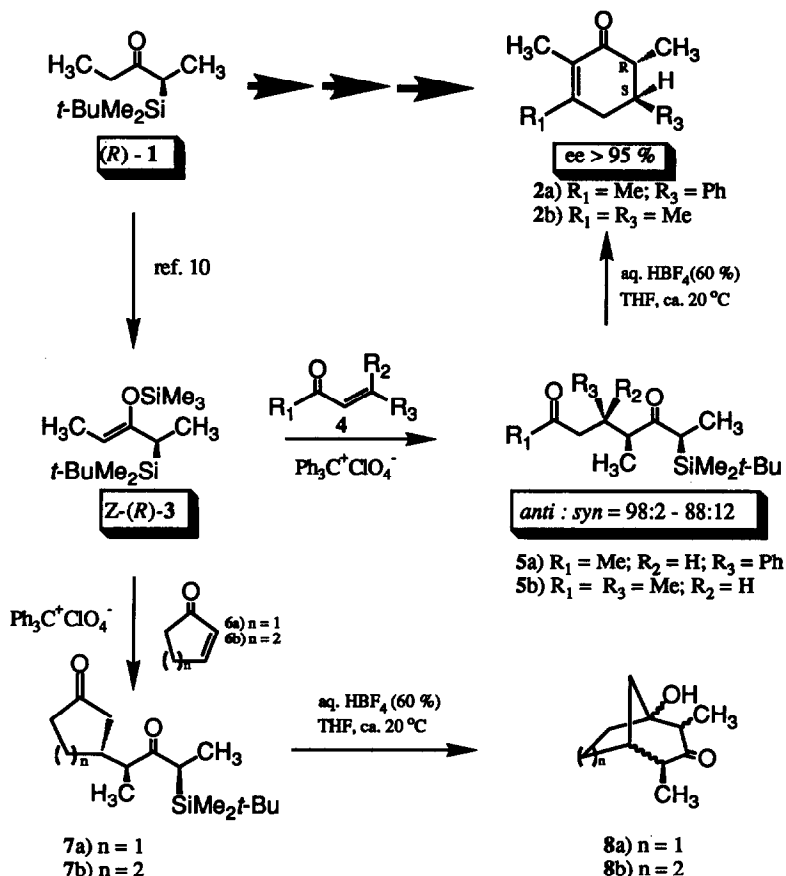
The conjugate addition of active methylene components to  $\alpha,\beta$ -unsaturated carbonyl compounds is one of the most widely utilized C-C bond forming reactions <sup>1</sup> and has growing synthetic applications <sup>2</sup>. In the last few years several modifications of Michael reaction have been reported<sup>3,4</sup>. Enders and coworkers <sup>5</sup> have demonstrated a remarkable success in the diastereo- and enantioselective Michael addition of hydrazone enolates to  $\alpha,\beta$ -unsaturated esters, however, the conjugate addition of ketone enolates to enones has met with limited success. We would like to report herein, a new silicon directed diastereo- and enantioselective Mukaiyama - Michael reaction of enolsilanes with enones. Enolsilanes derived from  $\alpha$ -silylated ketones, which are easily available from dialkylketones by asymmetric  $\alpha$ -C-silylation <sup>6</sup> or from methyl alkyl ketones through silylation followed by alkylation <sup>7</sup> using the (-)-(S)-Amino-2-Methoxymethyl Pyrrolidine (SAMP) or RAMP hydrazone method, <sup>8</sup> have been employed as chiral methylene components in highly diastereo- and enantioselective aldol reactions <sup>9</sup> and  $\alpha$ -hydroxylation of dialkyl ketones <sup>10</sup>. This encouraged us to further investigate a related reaction, the silicon directed asymmetric Michael addition of enolsilanes to enones.

As shown in the Scheme, 2-(*R*)-*t*-butyldimethylsilylpentan-3-one [(*R*) - 1 ] was first transformed into its corresponding trimethylsilyl enol ether using Kuwajima's method <sup>11</sup> (Z : E = 99:1) and was allowed to react with enones in the presence of a catalytic amount of trityl perchlorate (5 mole %). Michael reaction proceeded smoothly at -78 °C to give the corresponding silicon substituted 1,5-dicarbonyl compounds 5 a,b and 7 a,b in good yields and selectivity (Table -I). No 1,2-addition product was detected. Attempted removal of the silicon substituents from 5 a,b and 7 a,b with aq.  $\text{HBF}_4$  (60%) in THF lead to an interesting regioselective intramolecular aldol reaction. In the case of 5 a,b, the resultant aldol products undergo dehydration under acidic conditions to give  $\alpha,\beta$ -unsaturated cyclic enones (2 a,b) (Table II, entries 1 and 2), whereas treatment of 7 a,b under similar conditions afforded the  $\beta$ -hydroxyketones (8 a,b) in high yields (Table II, entries 3 and 4).

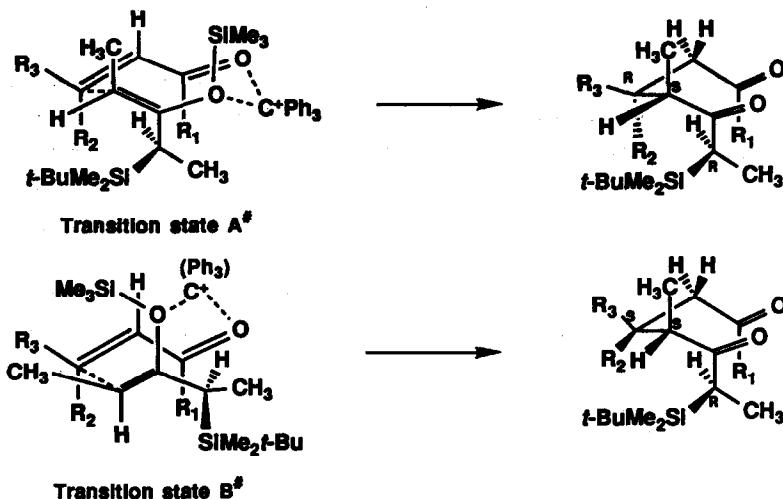
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Scheme 1



The enantiomeric excesses of the major diastereomers were determined by  $^1\text{H}$  NMR using  $\text{Eu}(\text{hfc})_3$  as a chiral shift reagent. The assignment of absolute configurations are based on the assumption that the enone approaches the enolsilanes **Z-(R)-3** from the opposite face of the bulky silyl group in the chair type transition state **A<sup>‡</sup>**. Similar approaches of electrophiles to enolsilanes have previously been used to explain the stereochemical outcome in an aldol reaction<sup>9</sup> or in the oxidation of enolsilanes by *m*-CPBA<sup>10</sup>. The lower selectivity observed with cyclohexenone may be due to the significant contribution from the twisted chair transition state **B<sup>‡</sup>** or the inability of the enolate to distinguish between the two faces of the cyclohexenone.

Table I : Michael addition of enolsilanes to enones<sup>a</sup>

entry	enones			product	yield (%)	<i>anti</i> : <i>syn</i> <sup>b</sup>
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>			
1.	Me	H	Ph	5a	81	98 : 2 <sup>c</sup>
2.	Me	H	Me	5b	82	88 : 12 <sup>c</sup>
3.	-(CH <sub>2</sub> ) <sub>2</sub> -	H		7a	72	87 : 13 <sup>c</sup>
4.	-(CH <sub>2</sub> ) <sub>3</sub> -	H		7b	79	55 : 45

Table II : Intramolecular Aldol Condensation of 1,5-Dicarbonyl Compounds Catalyzed by HBF<sub>4</sub>.<sup>a</sup>

entry	diketones	product	yield (%)	<i>anti</i> : <i>syn</i> <sup>b</sup>
1.	5a	2a	63	90 : 10 <sup>c</sup>
2.	5b	2b	65	80 : 20 <sup>c</sup>
3.	7a	8a	75	— <sup>d</sup>
4.	7b	8b	71	— <sup>d</sup>

a) All new compounds showed satisfactory i.r.; <sup>1</sup>H NMR; <sup>13</sup>C NMR; Mass Spectra and analytical data. b) *anti* : *syn* ratios were determined by <sup>1</sup>H NMR and <sup>13</sup>C NMR using Heathcock's method<sup>4</sup>. c) In each case (±)racemic compounds 5a,b; 7a,b; 2a,b were prepared using (±) **1** for comparison and determination of % ee using Eu(hfc)<sub>3</sub> as chiral shift reagent on a 100 MHz NMR; error ± 5%. d) The *anti* : *syn* ratios as well as % ee could not be determined accurately.

A typical experimental procedure for the reaction of enolsilanes with  $\alpha,\beta$ -unsaturated ketones is as follows: A mixture of  $\alpha,\beta$ -unsaturated ketone (5 mmol) and trityl perchlorate (0.25 mmol, 5 mol %) in dry dichloromethane (10 mL) was stirred at -78 °C and 2-(*S*)-*t*-butyldimethylsilyl-3-trimethylsiloxy pent-3-ene (enolsilanes, 5.5 mmol) was added dropwise. After stirring for ca. 1 h, aq. NaHCO<sub>3</sub> was

added and the mixture was extracted with dichloromethane (3 X 20 mL). The combined organic extracts were washed with brine (20 mL), dried ( $\text{MgSO}_4$ ) and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel to give 1,5-diketones in good yields (63-75%). The diketone (2 mmol) was treated with aq.  $\text{HBF}_4$  (1 mL) in THF (5 mL) at ca. 20 °C for 24 - 48 h. The reaction mixture was then diluted with 20 mL of  $\text{CH}_2\text{Cl}_2$  and washed with water (10 mL), 10 % aq.  $\text{NaHCO}_3$  (2 X 10 mL), brine (10 mL), dried ( $\text{MgSO}_4$ ) and the solvent was evaporated under reduced pressure to afford high yields of cyclic enones or  $\beta$ -hydroxyketones (Table II).

In summary, we have found a very simple method to construct substituted six membered cyclic enones and bicyclic  $\beta$ -hydroxyketones, which are important building units in many natural products. The application of this new strategy is under investigation for the synthesis of several chiral pheromones of ghost moth, swift moth, drugstore beetle and cigarette beetle<sup>12</sup>.

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