# Lewis Acid Promoted Ene-like Reactions of Enol Ethers with Aldehydes[1]

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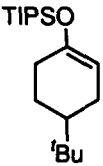Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan
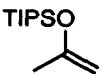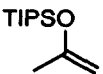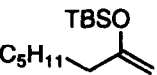
*Abstract:* Use of organoaluminum reagents induces ene-like reactions of enol silyl ethers with aldehydes, and enols having bulky silyl groups selectively afforded *syn* adducts.

Ene reactions[2] of carbonyl compounds have been widely used for selective carbon-carbon bond formation. We recently reported stereoselective ene reactions of 2-(alkylthio)allyl silyl ethers with a wide range of aldehydes.[3] In connection with our previous findings, our interest was next focused to the reactivity of enol ethers as ene substrates. Although reactions of enol silyl ethers with aldehydes have been well recognized as Mukaiyama aldol reaction,[4] several ene-like reactions of enol ethers have also been reported by us[5] and others.[6] This paper describes ene-like reactions of enol ethers with aldehydes and their stereochemical results.



(Scheme 1)
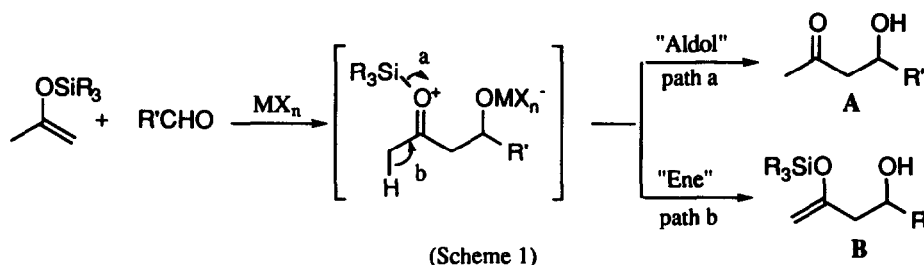
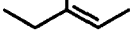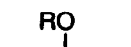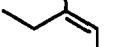Several investigations (see Table) disclosed synthetically useful results to favor the ene-like reaction as follows. (1) Although most of Lewis acids effect aldol reactions between 1-trimethylsiloxycyclohexene **1a** and aldehydes, use of organoaluminum reagents has proven of great advantage to induce the ene-like reaction (entry 1).[7] In addition to Me$_2$AlCl, Et$_2$AlI and Me$_3$Al are also effective. (2) The bulkiness of the silyl group is crucial to control the reaction course; bulkier silyl groups seem to disfavor the cleavage of O-Si bond , which leads to selective formation of products of type **B** (entries 2-6). Alkyl enol ethers are also employable as good ene substrates (entries 7,8). (3) Use of non-polar solvent such as toluene or hexane also facilitates the ene type reaction. In the presence of Me$_2$AlCl, for example, the reaction of **1c** with benzaldehyde in CH$_2$Cl$_2$ afforded only the aldol product **A** (95% yield), whereas the ene adduct **B** was obtained in 75 % yield along with the aldol

Table. Reactions of Enol Ethers with Aldehydes[a]

| entry | Ene Substrate | | R' | Lewis Acid | Yield (%)[b] of Ene Adduct | syn : anti[c] |
|---|---|---|---|---|---|---|
| 1 | | 1a (R =TMS) | $C_6H_{13}$ | $Me_2AlCl$ | 36[d] | 78 : 22 |
| 2 | | 1b (R = TES) | $C_6H_{13}$ | $Me_2AlCl$ | 89 | 64 : 36 |
| 3 | | 1c (R = TIPS) | $C_6H_{13}$ | $Me_2AlCl$ | 95 | 63 : 37 |
| 4 | | 1c | $CH_3CH=CH$ | $Me_2AlCl$ | 58 | 59 : 41[e] |
| 5 | | 1c | $C_6H_5$ | $Et_2AlI$ | 89[f] | 34 : 66 |
| 6 | | 1d (R = TBDPS) | $C_6H_{13}$ | $Me_2AlCl$ | 73 | 76 : 24 |
| 7 | | 1e (R = Me) | $C_6H_{13}$ | $Me_2AlCl$ | 91 | 12 : 88 |
| 8 | | 1e | $C_6H_5$ | $Me_2AlCl$ | 92[f] | 34 : 66 |
| 9 | | 2 | $C_6H_{13}$ | $Me_2AlCl$ | 72 (47:34:10:9)[e] | |
| 10 | | 3 | $C_6H_{13}$ | $Me_2AlCl$ | 84 | |
| 11 | | 3 | $C_6H_5$ | $Me_3Al$ | 88[f] | |
| 12 | $C_5H_{11}$ | 4 | $C_6H_{13}$ | $Et_2AlI$ | 76[g,h] | |
| 13 | | Z-5a (R = TBS) | $C_3H_7$ | $Et_2AlI$ | 86[h] | 76 : 24 |
| 14 | | Z-5b (R = TBDPS) | $C_3H_7$ | $Et_2AlI$ | 81[h] | 91 : 9 |
| 15 | | Z-5b | $(CH_3)_2CH$ | $Et_2AlI$ | 75[h] | 83 : 17 |
| 16 | | E-5a (R = TBS) | $C_3H_7$ | $Et_2AlI$ | 82[h] | 51 : 49 |
| 17 | | E-5b (R = TBDPS) | $C_3H_7$ | $Et_2AlI$ | 62[h] | 94 : 6 |
| 18 | | E-5b | $(CH_3)_2CH$ | $Et_2AlI$ | 43[h] | 88 : 12 |

[a]Reactions were performed in $CH_2Cl_2$ at -78 °C. [b]Isolated yield. [c]Determined by $^1H$-NMR or GC. [d]Aldol product was obtained in 46% yield. [e]Stereochemistry is not determined.
[f]The reaction was performed in toluene. [g]The ratio of geometrical isomers (Z : E) was 91 : 9.
[h]The reaction was performed in hexane.

product (18%) by using toluene as the solvent. Further, the reaction mode could be controlled almost completely by performing the reaction in toluene using $Et_2AlI$ (entry 5).

To determine the mechanism either concerted or stepwise, the reaction of 4-$^t$butyl-1-siloxycyclohexene 2 was attempted. A concerted process involving selective abstraction of an axial $\alpha'$-hydrogen should produce only two diastereomers among possible four isomers, but the results of entry 9 suggest a stepwise mechanism.[5b)]

Further, it should be worthy to note this methodology allows a highly chemoselective transformation. The following two results represent typical examples.
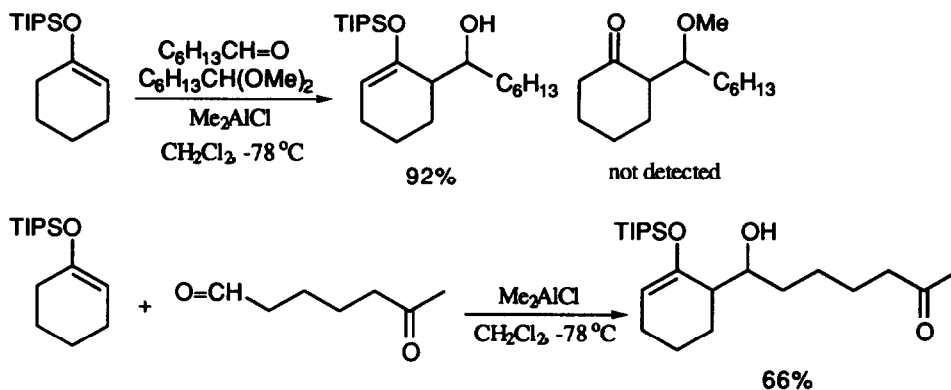


In the reactions with heptanal, enol silyl ethers **1a-d** afforded the *syn* adducts[8)] with moderate selectivity. On the contrary, methyl enol ether **1e** showed *anti* selectivity (entries 7, 8).

Acyclic enol ethers revealed much interesting results: Both *Z*- and *E*-enol ethers of diethyl ketone (**5a,b**) preferentially afforded *syn* adducts, and the selectivity increased with the bulkiness of the silyl group (entries 14, 15, 17, 18). Simple application of open chain transition state models[9)] may account for the results of *Z*-silyl enol
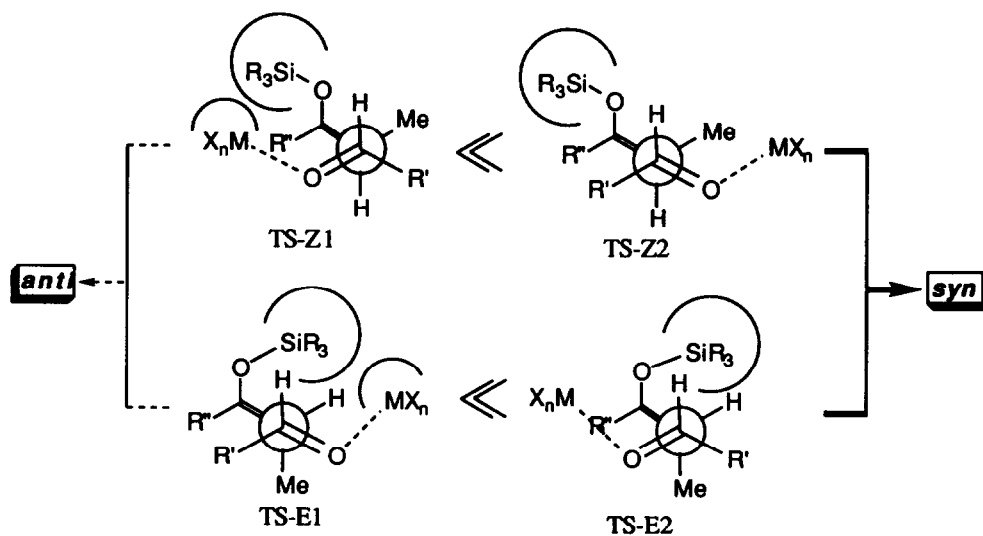


(Fig 1)

ethers, but not those of *E*-enol ethers.

Taking the effect of the bulkiness of the silyl group into account, the observed *syn* selectivity may be explained by assuming transition states shown in Fig 1, in which the silyl group locates differently depending on the enol geometry.[10] To these enols, an aldehyde approaches so as to situate the hydrogen at the more hindered silyl ether side.

Among these four transition states, the steric repulsion between the bulky silyl group and the Lewis acid which coordinates *anti* to the alkyl group of the aldehyde, disfavors TS-Z1 and TS-E1. Consequently, the reactions preferentially proceed through TS-Z2 and TS-E2 to afford the *syn* addition products.

In summary, the present methodology provides an alternative transformation of enol ethers with aldehydes. We are currently investigating scopes of the these reactions in more details.

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