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# HIGHLY THREO-SELECTIVE ENE-REACTION OF 2-(ALKYLTHIO)ALLYL SILYL ETHERS WITH ALDEHYDES [1]

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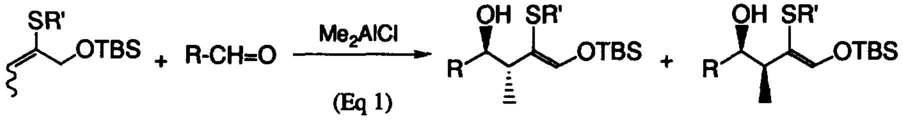
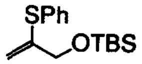
Abstract: Under the influence of $Me_2AlCl$, ene-reaction of 2-(alkylthio)allyl silyl ethers readily proceeds with a wide range of aldehydes to afford the corresponding γ-hydroxy carbonyl compounds as their enol silyl ethers with high threo-preference as well as excellent (Z)-selectivity.

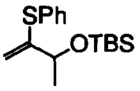
Ene-reactions with carbonyl compounds have constituted a powerful methodology for selective carbon-carbon bond formation. Fixed transition states involved in these reactions have often brought about a high degree of stereocontrol on the resulting products.[2] These transformations are often employed with great success in intramolecular version, but synthetic utility as well as applicable range generally diminishes in intermolecular cases due to the following drawback: Usual olefins only react with active enophiles such as formaldehyde or glyoxal derivatives,[3] whereas highly activated olefins such as enol silyl ethers preferably undergo the aldol reaction under similar reaction conditions.[4] In order to develop intermolecular reactions of general applicability, we have attempted to find suitably reactive olefins appropriate for the reaction with usual aldehydes. Due to an activation of allylic hydrogen, allyl silyl ethers seemed to be nucleophiles of choice, and 2-(alkylthio)-allyl silyl ethers **1**[5] could be employed as effective nucleophiles for the present purposes. Thus, on treating a vinyl sulfide **1a** or **1b** with aldehydes in the presence of $Me_2AlCl$ (1.1equiv), the corresponding enol silyl ethers of γ-hydroxy aldehydes or ketones were obtained in good yields. The reaction took place readily with various kinds of aldehydes, including aliphatic, aromatic, and α, β-unsaturated ones in methylene chloride or toluene at ambient temperature (Eq 1).



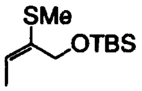
(Eq 1)



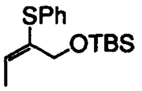
**1a**



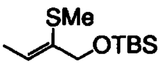
**1b**



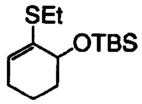
**1c-E**



**1d-E**



**1c-Z**



**1e**

Two types of remarkable stereocontrol have been observed in this reaction. One is concerned with the olefin geometry of the reaction products: The (Z)-isomers[6] of enol silyl ethers were obtained exclusively both from **1a** and **1b**. Such selectivity seems to be characteristic for allylic ethers because a similar reaction of 2-(phenylthio)-1-nonene[7] with benzaldehyde gave a mixture of (Z)- and (*E*)-isomers. Further, the reactions with (*E*)-2-(alkylthio)crotyl silyl ethers proceeded in a highly stereocontrolled manner: Treatment of **1c-E** or **1d-E**

## The Ene Reaction with 2-(Alkylthio)allyl Silyl Ethers

| Ene / Aldehyde | Yield(%) of the Product [a] (Threo:Erythro) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1a | 1b | 1c-E | 1d-E | 1c-Z | 1d-Z | 1e |
| $C_6H_5$-CH=O | 96 | 98 | 81(>99:<1) [b] | 86(94:6) [b] | 92(78:22) [b]<br>60(50:50) [c] | 0 | 95(>99:<1) |
| $CH_3CH$=CH·CH=O | 78 | *trace* | 60(>99:<1) [c] | | | | |
| $C_6H_{13}$-CH=O | 88 [b] | 78 [b] | 86(78:22)<br>83(92:8) [e] | 84(59:41) | 89(60:40) | 88(64:36) [b,d] | 92(87:13) [c] |
| *c*-$C_6H_{11}$-CH=O | | | 80(95:5) | | | | |

a) The reactions were performed as follows. To a mixture of 2-(alkylthio)allyl silyl ether (0.50 mmol) and an aldehyde (0.50 mmol) in $CH_2Cl_2$ (2 ml) was added 1M hexane solution of $Me_2AlCl$ (0.55 ml) at -40°C. After stirring for 1-20 hours, a mixture of triethylamine (0.25 ml) and water (0.50 ml) was added, and the product was obtained by purification with column chromatography.

b) The reaction was performed at -23°C. c) The reaction was performed in toluene.

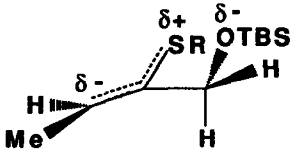
d) The (E)-threo isomer was also formed in this case [6]. (Z)-threo : (E)-threo : (Z)-erythro = 42 : 22 : 36.

e) The reaction was performed at -78°C in toluene.

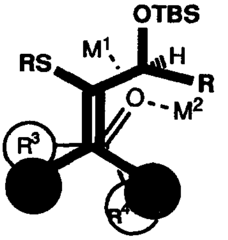
with benzaldehyde under similar reaction conditions afforded the corresponding threo isomer with an excellent selectivity.[8] Especially, complete diastereocontrol has been achieved in the reaction of **1c-E** and **1e** with an aromatic and α, β-unsaturated aldehyde, and formation of the erythro-isomer could not be detected in the reaction mixture both by NMR and GLC analyses.

Interestingly, **1c-Z** also gave the threo-isomer predominantly, but the degree of stereo-selection became much lower. The olefin **1d-Z** did not react with benzaldehyde under the present reaction conditions, but gave the corresponding adduct with an aliphatic aldehyde. Results are shown in the Table.

Selective formation of (*Z*)-olefins suggests a certain attractive interaction works between SR and OTBS group. A dipole interaction between an electron-deficient sulfur and an electron-rich oxygen (Fig 1) might be responsible for such an attracting effect.



(Fig 1)



|  | R¹ | R² | R³ | R⁴ | M¹ | M² |
|---|---|---|---|---|---|---|
| TS-E1 | H | $CH_3$ | R | H | $AlX_3$ | - |
| TS-E2 | H | $CH_3$ | H | R | - | $AlX_3$ |
| TS-Z1 | $CH_3$ | H | H | R | - | $AlX_3$ |
| TS-Z2 | $CH_3$ | H | R | H | $AlX_3$ | - |

$R^2\ \mathrm{I}\ R^4 \gg R^1\ \mathrm{I}\ R^3$

(Fig 2)

Remarkably high threo-control observed in this ene reaction may be explained as shown in Fig 2, and the reactions of (*E*)- and (*Z*)-enes may proceed through TS-E1 or TS-E2 and TS-Z1 or TS-Z2, respectively (Fig 2).[9] Among these reaction pathways, severe steric repulsion between R and methyl groups greatly disfavors the TS-E2 and TS-Z2, and both enes afford threo-(Z)-adducts as major products. More detailed examination of these transition states may provide support for a generally much larger steric repulsion between the two right-side substituents $R^2$ and $R^4$ than the left-side ones $R^1$ and $R^3$. If R is more bulky than methyl, thermodynamic stabilities of the TS's are expected to be in the following order: TS-E1 > TS-Z1 > TS-Z2 > TS-E2.

Consequently, the reaction with (*E*)-enes preferentially proceeds through TS-E1 to yield threo-adducts, whereas lower threo-selectivity results in the reaction of (Z)-enes.

An excellent threo-selectivity as well as a wide range of applicability may make the present method very useful. Various types of synthetic transformation are feasible by using these ene adducts. For example, hydrolysis, alkylation, and a subsequent removal of sulfur group have readily provided a variety of γ-hydroxy carbonyl compounds.

In addition, the ene-reaction products can be directly converted to the corresponding β-hydroxy ester with retention of threo configuration through ozonolysis and a subsequent treatment with m-CPBA in ethanol.

We are currently investigating scope of this type of reaction in more detail, and application to an enantioselective ene reaction.

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