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Desulfurizative Titanation of Allyl Sulfides. Regio and Diastereoselective Preparation of Homoallyl Alcohols

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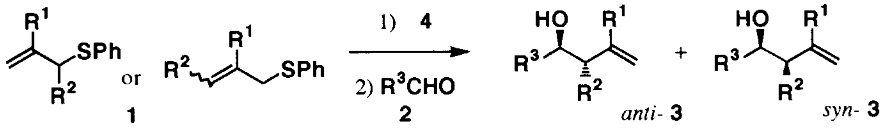
Abstract: The successive treatments of allyl sulfides with the low-valent organotitanium species, prepared by the reaction of titanocene dichloride with 2 equiv. of butyllithium, and aldehydes gave the homoallyl alcohols with high regio and diastereoselectivity in good yields.

Since the alkylation of allylic α-thiocarbanions and following reductive desulfurization constitute a useful method for the preparation of olefins, a variety of reducing agents have been developed for this purpose.1) Although the desulfurizative metallation which affords reactive organometallic compounds is synthetically useful for further transformation, only a few methods for such desulfurization are known. Cohen and co-workers showed that substituted allyllithiums were prepared by the treatment of allyl sulfides with lithium 1-(dimethylamino)naphthalenide.2) As for the desulfurizative stannylation, Ueno *et al.* reported that allylstannanes were obtained by the SH' reaction of allyl sulfides with tributyltin hydride.3) We also reported the desulfurizative stannylation4) and germylation5) of allyl sulfides utilizing tributylstannyllithium and triethylgermyllithium, respectively. We have further investigated the desulfurizative metallation which affords reactive allylmetal reagents using various low-valent metal species as reducing agents. In this communication, we describe the desulfurization of allyl sulfides **1** with low-valent titanium species, and the reaction of the resulting allyltitanium reagents with aldehydes **2** (Eq. 1).

$$Cp_2TiCl_2 \xrightarrow{2\ BuLi} \text{" }Cp_2Ti\text{ "}\ \underset{}{\mathbf{4}}$$



(1)

Although the desulfurization of organosulfur compounds such as alkenyl sulfides, aryl sulfides, and thioacetals with the low-valent titanium species formed by the reduction of titanium(IV) chloride with lithium aluminum hydride was investigated by Mukaiyama and co-workers,6) the isolated products of these reactions were corresponding hydrocarbons and the details including the reaction intermediate have not yet been elucidated. Therefore we examined the preparation of low-valent titanium species **4** by the reaction of titanocene dichloride with two molar equivalents of butyllithium and its use as a desulfurization agent.

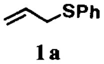
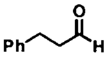
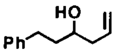
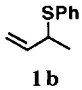
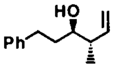
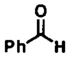
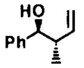
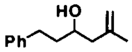
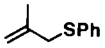
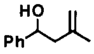
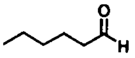
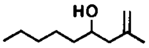
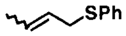
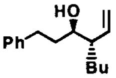
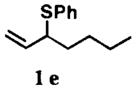
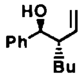
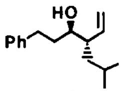
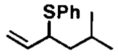
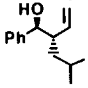
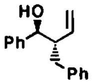
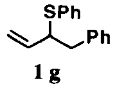
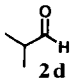
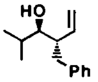
When 3-phenylthio-4-phenyl-1-butene (**1g**) was treated with **4** at -78 °C and then 0 °C for 15 min each, the corresponding terminal olefin, 4-phenyl-1-butene, was isolated in 46% yield as sole desulfurization product after aqueous work-up. It is reasonable to assume that the reaction proceeds *via* the allyltitanium reagent **5** formed by the oxidative addition of allyl sulfide to the divalent titanium species **4**. Then we studied the reaction of various substituted allyl sulfides with **4** followed by the treatment with aldehydes and found that the homoallyl alcohols **3** were produced in good yields (Table 1). Sato *et al.* reported the similar oxidative addition of crotyl halides to the low-valent titanium species prepared by the reaction of titanocene dichloride with isopropylmagnesium bromide in the presence of dienes$^{7)}$ and subsequent reaction with aldehydes.$^{8)}$ Although this reaction would be mechanistically similar to the present transformation, it is of interest that the allyl sulfide **1g** was not reduced with such a reagent.

The typical experimental procedure is as follows; to a THF (3 ml) suspension of titanocene dichloride (249 mg, 1 mmol) was added a hexane solution of butyllithium (1.2 ml, 2 mmol) at -78 °C. After 1h, a THF (2 ml) solution of 4-phenyl-3-phenylthio-1-butene (**1g**) (120 mg, 0.5 mmol) was added to the reaction mixture and stirring was continued for 15 min at the same temperature and then at 0 °C for 15 min. Benzaldehyde (**2b**) (66 mg, 0.6 mmol) in THF (1 ml) was added, and the reaction mixture was further stirred for 30 min. The reaction was quenched by addition of water, and the resulting insoluble materials were filtered off. The organic materials were extracted with ether, and the extract was dried over Na_2SO_4. After removal of solvent, the residue was purified by silica-gel chromatography (hexane : AcOEt = 9 : 1) and 2-benzyl-1-phenyl-3-buten-1-ol (**3g-1**) (88 mg) was isolated in 74% yield.

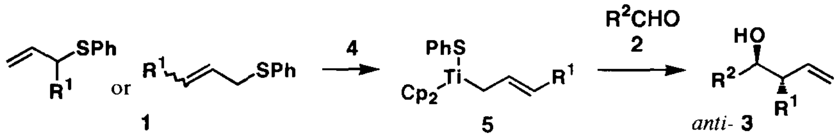
In all the cases examined, the homoallyl alcohols with a terminal olefin moiety **3** were the only isolated products in the present reaction, and the formation of another regioisomers was not observed. It was also found that the reactions of 3-phenylthio-1-butene (**1b**) and 1-phenylthio-2-butene (**1d**) with benzaldehyde (**2b**) gave the same product (**3b-2**) with the same diastereoselectivity, in which the *anti*-isomer$^{9)}$ was predominated (runs 3 and 8). Furthermore, the NMR spectra of the homoallyl alcohols **3** obtained from allyl sulfides **1e**, **f**, and **g** which have an α-substituent other than methyl group showed that they consisted of single diastereoisomers, though their stereochemistries were uncertain. Schlosser and Fujita reported the diastereoselective synthesis of several homoallyl alcohols.$^{10)}$ The methine protons α to hydroxyl group of *syn*-isomers of these alcohols are found further downfield than those of *anti*-isomers, and they noted that the vinylidene signals of *syn*-isomers appear at slightly higher field. Then we prepared the epimers **3'** by the Mitsunobu reaction$^{11)}$ of **3** to study their NMR spectra. The α-methine protons of **3'** appeared at slightly lower field and their vinylidene signals appeared at higher field than those of **3** without exception.$^{12)}$ These facts suggest that the products of present reaction have *anti*-configuration.

The reactions of allyltitanium reagents with aldehydes were well studied$^{13)}$, and it was reported that high *anti*-selectivity is observed in the reaction of crotyltitanium reagents bearing various ligands.$^{14)}$ The *anti*-selectivity is explained by assuming the preferential formation of *E* -isomer of crotyltitanium reagent and the six-membered cyclic transition state having a chair geometry. The addition of allyltitanium reagent prepared from the allyllithiums stabilized by α-heteroatoms to aldehydes also affords *anti*-alcohols.$^{15)}$ It was also reported that *anti*-homoallyl alcohols are preferentially formed by the reaction of aldehydes with allylzirconium reagents formed by the treatment of allylic Grignard reagents with zirconium halides$^{16)}$ or the reaction of allylic ethers with the zirconocene equivalent.$^{17)}$ Therefore, the observed regio and diastereoselectivity in the present reaction strongly supports the intermediary of the primary allyltitanium reagent with *E*-configuration **5** (Eq. 2).

Table 1. The Desulfurizative Titanation of Allyl Sulfides and the Subsequent Reaction with Aldehydes.[a]

Run	Allyl Sulfide **1**	Aldehyde **2**	Product	Yield[b] %	*anti* : *syn* [c]
1	 **1a**	 **2a**	 **3a-1**	84	-
2	 **1b**	**2a**	 **3b-1**	69	97 : 3
3		 **2b**	 **3b-2**	60	97 : 3
4		**2a**	 **3c-1**	82	-
5	 **1c**	**2b**	 **3c-2**	84	-
6		 **2c**	 **3c-3**	76	-
7	 **1d**	**2a**	**3b-1**	77	97 : 3
8		**2b**	**3b-2**	86	97 : 3
9		**2a**	 **3e-1**	69	100 : 0[d]
10	 **1e**	**2b**	 **3e-2**	70	100 : 0[d]
11		**2a**	 **3f-1**	67	100 : 0[d]
12	 **1f**	**2b**	 **3f-2**	73	100 : 0[d]
13		**2b**	 **3g-1**	74	100 : 0[d]
14	 **1g**	 **2d**	 **3g-2**	72	100 : 0[d]

a) All reactions were performed with a similar procedure as described in the text. b) The structures of these compounds were supported by IR and NMR spectra. c) Determined by NMR spectrum. d) The *syn*-isomer could not be detected by NMR spectrum.



(2)

The present desulfurizative titanation possesses advantages over other transformations of allyl sulfides to allylmetal species that allyltitanium reagents react with aldehydes without any promotors to give the corresponding homoallyl alcohols with high regio and diastereoselectivity. Since the alkylation of allyl sulfides is easily performed using various alkylating agents, the present reaction provides a useful synthetic tool for the construction of *anti*-homoallyl alcohols.

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