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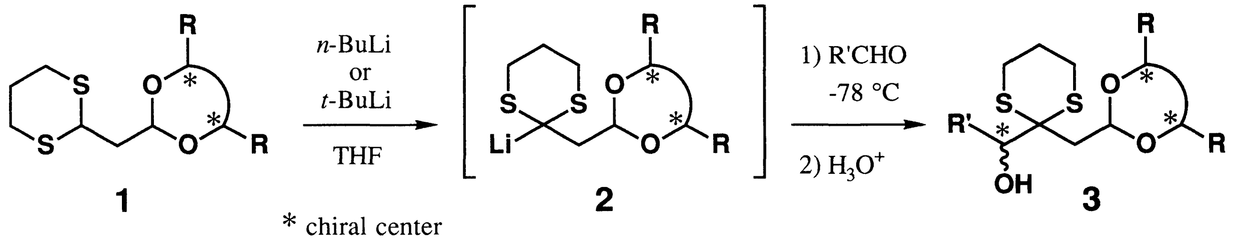
Stereochemical Studies of Chiral Nonconjugated Carbanions. Asymmetric Alkylation of Aldehydes with Sulfur-Substituted Carbanions of Chiral α-(1,3-Dithian-2-yl) Acetals

Hidenori CHIKASHITA,* Tsutomu YUASA, and Kazuyoshi ITOH
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Suita, Osaka 564

A new type of asymmetric induction based on the nucleophilic addition of sulfur-substituted nonconjugated carbanions produced from a variety of chiral α-(1,3-dithian-2-yl) acetals to achiral aldehydes was studied. The reaction with the carbanion of the chiral acetal derived from (4*R*,5*R*)-3,6-diethyl-3,6-dimethoxy-4,5-octanediol showed the best stereoselectivity (*ds*=2.4:1-6.3:1) producing a chiral secondary-alcohol center.

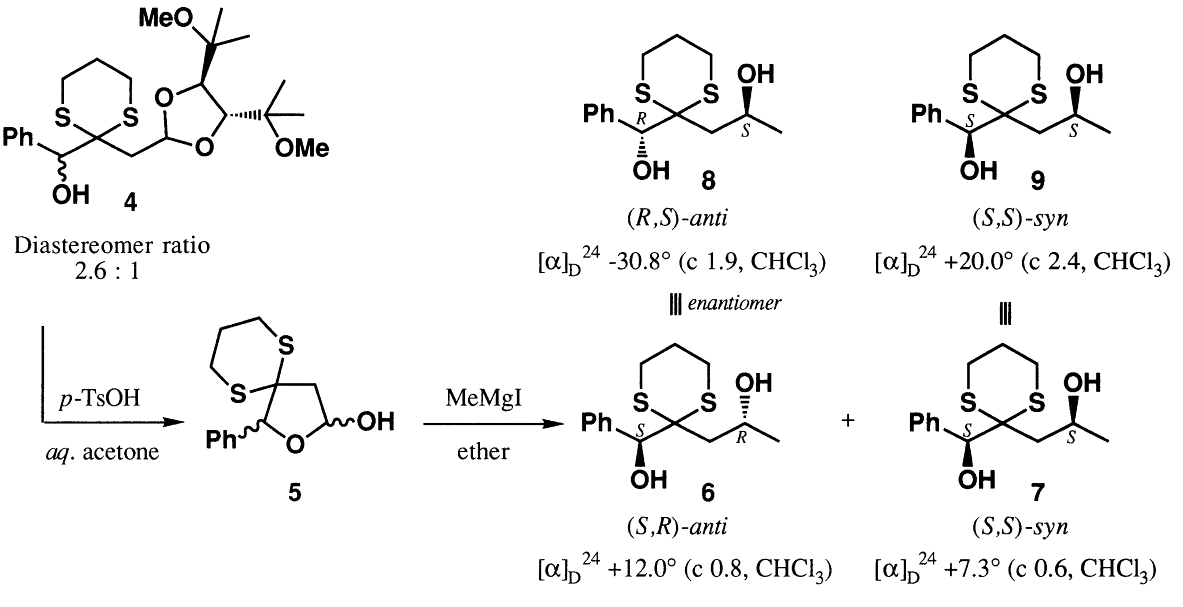
The alkylation of carbonyls with carbon nucleophiles is one of the simplest, fundamental, and essential reactions in organic synthesis. This type of reaction has been widely extended to a variety of recent asymmetric synthesis by employing chiral carbonyls1) or chiral carbon nucleophiles, and many of these reactions show promise in synthesizing chiral alcohols with a high degree of stereochemical and stereoselective control. Asymmetric reaction with chiral carbon nucleophiles can be fundamentally classified into either a reaction of carbonyls with chiral conjugated carbanions (*e.g.*, asymmetric aldol reaction with chiral enolates)2) or a reaction of carbonyls with chiral nonconjugated carbanions (*e.g.*, the reaction with chiral, nitrogen-substituted, nonconjugated carbanions).3) The asymmetric induction based on the former type of reaction has been extensively developed in recent years and has emerged to the level that would allow general access to a high degree of stereoselective control.2) However, the latter type of asymmetric reaction has not widely been advanced yet, and up to now, no method has allowed general access to control of the remote chiral center. In this paper, we wish to report our initial results for a new method based on this concept by employing the reaction of aldehydes with the sulfur-substituted nonconjugated carbanion **2** produced from chiral α-(1,3-dithian-2-yl) acetal **1**, producing the chiral secondary alcohol **3** (Scheme 1).4)



Scheme 1.

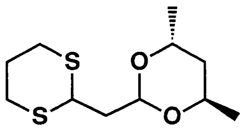
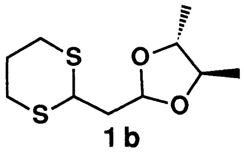
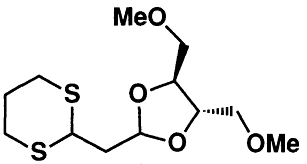
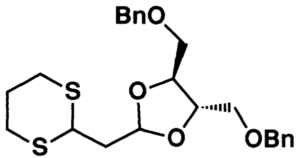
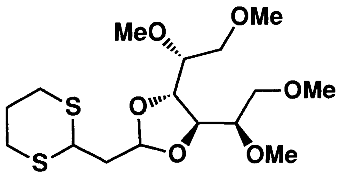
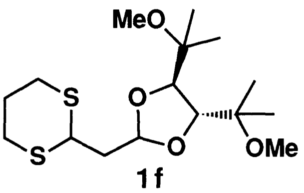
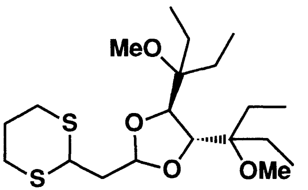
We started the present work by examining the reaction of aldehydes with carbanions **2a**,**b** of the chiral acetals **1a**,**b** derived from commercially available (2*R*,4*R*)-pentanediol and (2*R*,3*R*)-butanediol, respectively.5) The results are summarized in Table 1 (Entries 1-8). Although the reaction of the dioxolane-type chiral acetal **1b** with aldehydes showed no stereoselection (Entries 6-8), the reaction of the dioxane-type chiral acetal **1a** with several different aldehydes except for pivalaldehyde brought 1,6-asymmetric induction producing the corresponding diastereomeric mixture of the alcohol **3a** with the ratio of 1.3:1-3.0:1 (Entries 1-5). We next tried the synthesis and use of different types of chiral acetals **1c**-**e** containing two or more alkoxy groups on the chiral dioxolane-substituents which might be efficient to fix their carbanion configurations by chelation to Li^+. In contrast to the case of **1b**, a series of reactions with **1c**-**e** in THF produced a 1,6-asymmetric induction with various degrees of stereoselectivity depending on the structure of the chiral substituents on the dioxolane ring (Table 1). Especially, good results (3.0:1-4.7:1) were realized in each reaction of the α,β-unsaturated aldehyde, 2-butenal, with **1c**-**e** (Entries 13, 20, 26). It should be noted that the addition of HMPA to the reaction system dropped the selectivity to a high degree to give a 1:1 diastereomeric mixture of the corresponding product alcohols (Entries 14, 21). On the other hand, although the yield was not high, the reaction of **1c** with 2-butenal in ether solvent afforded higher selectivity than a similar reaction in THF (Entry 15). These results show that the chelation effect of the alkoxy groups on chiral substituents of the dioxolane ring and the chelation structure play an important role for inducing stereoselectivity in the present 1,6-asymmetric induction.

We presumed that the steric bulkiness of the two chiral substituents in the acetal moiety might be important in the transition state for controlling the stereoselection in addition to their chelation effects. Thus, the reaction of the chiral acetals **1f**,**g** with aldehydes was finally demonstrated with the results summarized in Table 1 (Entries 27-36).6) The stereoselectivity of the reaction with **1f** was at almost the same level as that of **1e** (Entries 27-31). However, the reaction of **1g** afforded the best selectivity in the present study to give the corresponding alcohols with a diastereomeric ratio of 2.4-6.3 (Entries 32-36), indicating the reasonability of our presumption. The low yields of the reactions with **1g** when compared with the reactions with **1f** is probably due to high steric hindrance in the reaction of **1g** with *t*-BuLi or the reaction of the anion of **1g** with aldehydes because all reactions of **1f** and **1g** were carried out in the same reaction conditions. The stereochemistry of the reaction with **1f** was representatively determined by the transformation of **4** into the 1,4-diols **6** and **7** (Scheme 2).7) The treatment of **4** with *p*-TsOH in aqueous acetone followed by the alkylation of resulting lactol **5** with MeMgI gave the easily



Scheme 2.

Table 1. Asymmetric Alkylation of Aldehydes with Chiral α-(1,3-Dithian-2-yl) Acetals[a,b)]

Entry	Chiral acetal[c)]	Aldehyde (R'CHO)	Yield/ %[d)]	Diastereomer ratio[e)]
1	 **1a**	n-C_3H_7CHO	64	3.0 : 1
2		$(CH_3)_2CHCHO$	61	2.3 : 1
3		$(CH_3)_3CCHO$	85	1.0 : 1
4		C_6H_5CHO	54	1.3 : 1
5		$CH_3CH{=}CHCHO$	46	1.4 : 1
6	 **1b**	n-$C_7H_{15}CHO$	63	1.0 : 1
7		$(CH_3)_3CCHO$	62	1.0 : 1
8		C_6H_5CHO	51	1.0 : 1
9	 **1c**	n-C_3H_7CHO	72	1.9 : 1
10		$(CH_3)_2CHCHO$	71	1.4 : 1
11		$(CH_3)_3CCHO$	74	1.0 : 1
12		C_6H_5CHO	83	1.5 : 1
13		$CH_3CH{=}CHCHO$	91	3.0 : 1
14		"	32	1.0 : 1[f)]
15		"	22	5.3 : 1[g)]
16	 **1d**	n-C_3H_7CHO	81	1.8 : 1
17		$(CH_3)_2CHCHO$	72	2.1 : 1
18		$(CH_3)_3CCHO$	77	1.3 : 1
19		C_6H_5CHO	80	1.4 : 1
20		$CH_3CH{=}CHCHO$	86	3.4 : 1
21		"	32	1.0 : 1[f)]
22	 **1e**	n-C_3H_7CHO	72	3.0 : 1
23		$(CH_3)_2CHCHO$	81	2.7 : 1
24		$(CH_3)_3CCHO$	85	1.8 : 1
25		C_6H_5CHO	75	2.3 : 1
26		$CH_3CH{=}CHCHO$	83	4.7 : 1
27	 **1f**	n-C_3H_7CHO	74	2.8 : 1
28		$(CH_3)_2CHCHO$	72	2.2 : 1
29		$(CH_3)_3CCHO$	86	1.8 : 1
30		C_6H_5CHO	85	2.6 : 1
31		$CH_3CH{=}CHCHO$	92	4.6 : 1
32	 **1g**	n-C_3H_7CHO	32	4.0 : 1
33		$(CH_3)_2CHCHO$	27	3.1 : 1
34		$(CH_3)_3CCHO$	31	2.4 : 1
35		C_6H_5CHO	26	3.4 : 1
36		$CH_3CH{=}CHCHO$	23	6.3 : 1

a) Reactions were carried out with excess amount of aldehydes (2.1-2.6 equiv.) in THF at -78 °C for 30 min unless otherwise noted. b) Yields are not optimized. c) The anions were prepared by metallation of **1a**-**g** with *n*-BuLi or *t*-BuLi in THF. d) Yield of isolated, pure diastereomeric mixture. e) Determined by 400 MHz ^1H-NMR analysis. f) Reaction in the presence of 3 equiv. of HMPA. g) Reaction in ether at -78 °C.

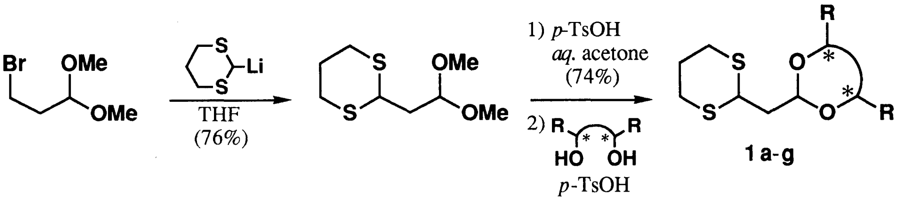
separable mixture of **6** and **7**. We have already reported the synthesis of optically pure **8** and **9** together with their specific rotations.[4] Since ^{1}H NMR data of **6** and **7** obtained in this study were in full accord with those of **8** and **9**, respectively, the stereochemistry of **6** and **7** were proved to be (*S*,*R*)-*anti* and (*S*,*S*)-*syn*, respectively, based on the comparison of specific rotations.[8] The absolute configuration at the hydroxylated carbon of the major diastereoisomer of **4** could be thus established to be *S* (Scheme 2).

In summary, we have disclosed the potential possibility of a new type of asymmetric carbonyl addition of sulfur-substituted, nonconjugated carbanions produced from the chiral acetal **1**. Among these reactions, which induced an 1,6-asymmetric induction with varying degrees of stereoselectivity depending on the structure of the chiral acetal moiety, a series of reactions of an α,β-unsaturated aldehyde with **1c**-**g** and the reactions of **1g** were found to afford fairly high stereoselectivity. From the present results, although the mechanistic aspect of inducing the stereoselection is not clear yet, it would be suggested that chelation ability and steric bulkiness of the substituents at the chiral acetal unit play an important and essential role in inducing the present stereoselectivity.

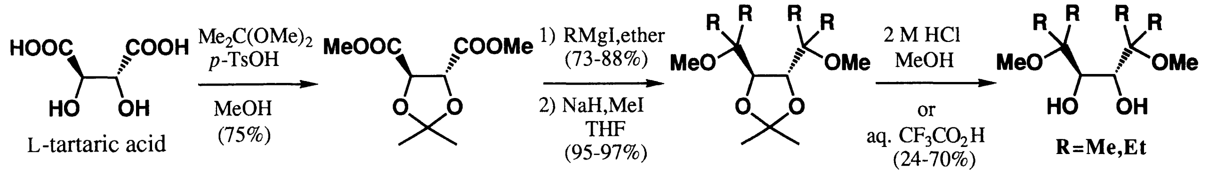
Further study on the scope and limitations as well as synthetic application of the method are now in progress.

References

1) For reviews, see: E. L. Eliel, "Asymmetric Synthesis," ed by J. D. Morrison, Academic, New York (1983), Vol. 2, pp. 125-156; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, **23**, 556 (1984); G. J. McGarvey, M. Kimura, T. Oh, and J. M. Williams, *J. Carbohydr. Chem.*, **3**, 125 (1984); T. Oishi and T. Nakata, *Acc. Chem. Res.*, **17**, 338 (1984); S. Masamune, W. Choy, J. S. Peterson, and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, **24**, 1 (1985); J. Jurczack, S. Pikul, and T. Bauer, *Tetrahedron* , **42**, 447 (1986).
2) For recent papers, see: M. P. Bonner and E. R. Thornton, *J. Am. Chem. Soc.*, **113**, 1299 (1991); S. E. Denmark and B. R. Henke, *J. Am. Chem. Soc.*, **113**, 2177 (1991); M. N. Stormes and E. R. Thornton, *J. Org. Chem.*, **56**, 2489 (1991); and references cited therein.
3) W. H. Pearson and A. C. Lindbeck, *J. Am. Chem. Soc.*, **113**, 8546 (1991); and references cited therein.
4) We have already reported the 1,4-asymmetric induction based on a similar concept by employing a different type of chiral, sulfur-substituted, nonconjugated carbanion: H. Chikashita, H. Yasuda, Y. Kimura, and K. Itoh, *Chem. Lett.*, **1992**, 195.
5) Chiral acetals **1a**-**g** were prepared according to the following sequence:



6) The (3*R*,4*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol and the (4*R*,5*R*)-3,6-dimethoxy-3,6-diethyl-4,5-octanediol needed for the synthesis of **1e**,**g** were prepared from L-tartaric acid according to the following sequence:



7) Stereochemistry of other reactions in the present study has not been established yet.
8) The ee values of **6** and **7** were estimated to be 39% and 37%, respectively, which were comparable to the estimated value (44% ee) from the diastereomer ratio of **4** (2.6:1).

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