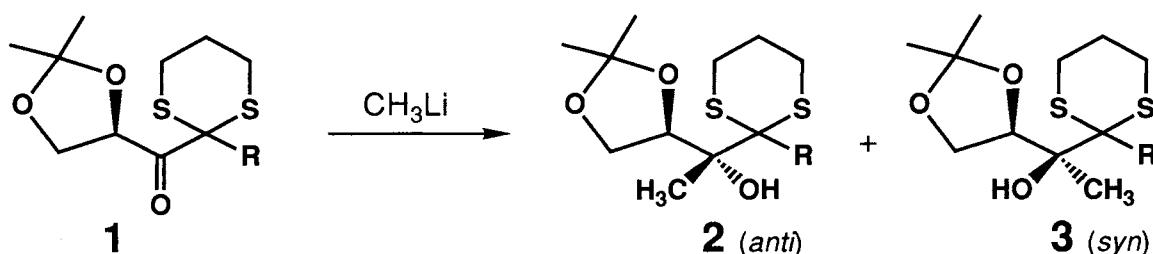


Highly Diastereoselective Addition of Methylolithium to Chiral α,β -Dialkoxy Ketones
and Its Application to the Stereocontrolled Asymmetric Synthesis of
Highly Substituted Tetrahydrofurans

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The nucleophilic addition of methylolithium to chiral α,β -dialkoxy 1,3-dithian-2-yl ketones in ether gave the corresponding Cram type of *anti* isomers in excellent diastereoselectivity. The method was applied to the stereocontrolled synthesis of optically active and highly substituted tetrahydrofurans.

1,2-Asymmetric induction based on nucleophilic addition to chiral alkoxy aldehydes and ketones is a topic of modern synthetic organic chemistry and continues to receive great interest.¹⁾ Especially, chiral α -alkoxy and α,β -dialkoxy aldehydes have been frequently used for the synthesis of many useful chiral synthons and natural products. Among these, an extensively studied substrate as an α,β -dialkoxy aldehyde is 1,2-*O*-isopropylidene-D-glyceraldehyde or its enantiomer.²⁾ However, the study and synthetic application of 1,2-asymmetric induction based on the addition of carbon nucleophiles to analogous ketones is rare^{1,2)} and has not been advanced yet,³⁾ although the stereochemistry of chelation- and nonchelation-controlled reactions with chiral α -alkoxy ketones has been well known to be generally *anti* which should be explained by Cram's cyclic α -chelation model or Felkin's nonchelation model.^{1,4)} In this paper, we wish to report that the chiral α,β -dialkoxy 1,3-dithian-2-yl ketones **1** show exceptionally excellent diastereofacial preference in the nucleophilic addition of methylolithium to give the Cram type of *anti* isomers **2** (Scheme 1). We will also describe an application of this method to the stereocontrolled asymmetric synthesis of highly substituted tetrahydrofurans.



Scheme 1.

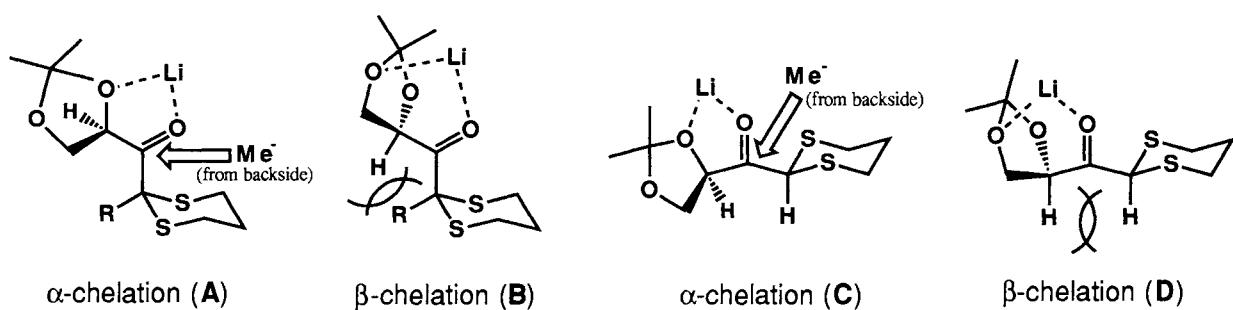
As can be seen in Table 1, the treatment of 1,3-dithian-2-yl ketone **1a** with MeLi in THF at -78 °C gave a mixture of *anti* and *syn* isomers, **2a** and **3a**, in good yield with high stereoselectivity (Entry 1). The addition of HMPA to this reaction dropped the selectivity to a high extent, showing that the origin of the selectivity is based on a chelation-controlled transition state (Entry 2). While the reaction with MeLi in dichloromethane or ether was

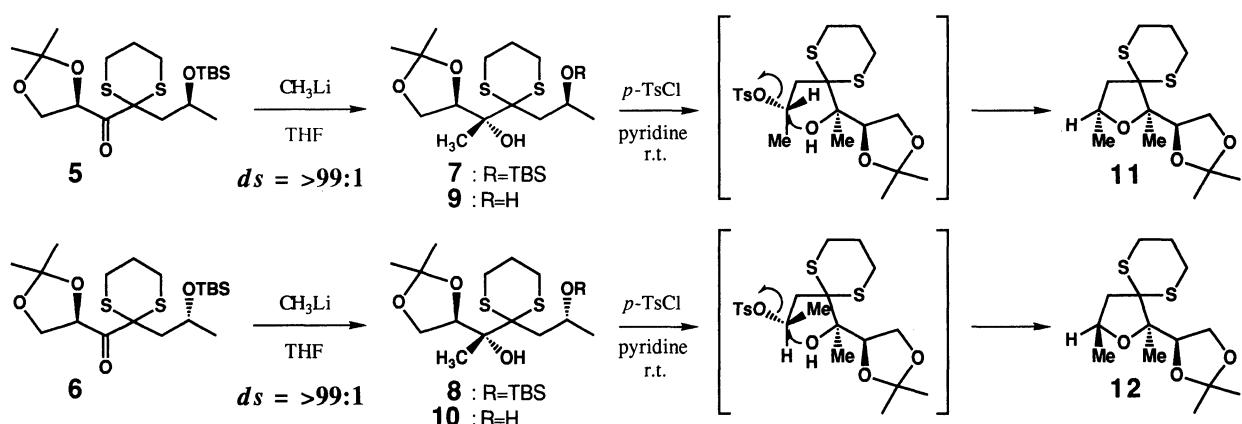
Table 1. Diastereoselective Addition of MeLi to α -Chiral 1,3-Dithian-2-yl Ketones **1**^{a)}

Entry	Substrate	R	Solvent (additive)	Isolated yield/ %	Selectivity ^{b)} 2 : 3
1	1a	H	THF	62	5 : 1
2	1a	H	THF (HMPA)	71	2 : 1
3	1a	H	CH ₂ Cl ₂	51	14 : 1
4	1a	H	Ether	60	14 : 1
5	1a	H	Ether ^{c)}	84	4 : 1
6	1b	CH ₃	Ether	50	>99 : 1
7	1c	n-C ₄ H ₉	Ether	98	>99 : 1
8	1d	n-C ₉ H ₁₉	Ether	62	>99 : 1
9	1e	Ph	Ether	70	>99 : 1
10	1f	CH ₂ =CHCH ₂	Ether	84	>99 : 1

a) The reactions were carried out with 2 equiv. of MeLi at -40 °C for 7-10 h. b) Determined by 400 MHz ¹H NMR analysis. c) Reaction with 2 equiv. of MeMgI at -78 °C for 4 h.

found to show higher stereoselectivity (Entries 3 and 4), the use of MeMgI in ether afforded only moderate selectivity (Entry 5). It is noteworthy that the presence of substituent R at the 2-position on the dithiane ring markedly enhanced the selectivity, and the structure of R and reaction temperature (-78-0 °C) did not significantly affect the stereoselectivity of the reaction, indicating the existence of very tight chelation structure. Thus, the reaction of a series of 2-substituted-1,3-dithian-2-yl ketones **1b-f** with MeLi in ether at -40 °C gave, in all cases, only the corresponding *anti* isomers **2b-f** (Entries 6-10).^{5,6)} Considering these observations, the origin of the present high diastereoselectivity and its stereochemistry can be best explained by the tight α -chelation transition states **A** and **C**. In the transition states for the reaction of **1b-f**, the α,β -dialkoxy carbonyl moiety is presumed to occupy an axial position of the dithiane ring and the carbonyl group is presumed to be directed inside the dithiane ring for minimizing 1,3-diaxial interactions. The methylation in **A** should occur from the *si*-face because the very crowded *re*-face is highly protected from the methylation by both of carbonyl substituents. On the other hand, in the transition states for the reaction of **1a**, the α,β -dialkoxy carbonyl moiety should occupy an equatorial position of the dithiane ring and the methylation in **C** would occur with *si*-facial selectivity. In striking contrast to **A** and **C**, there is a strong steric repulsion between the substituent R and the α -hydrogen or a 1,3-steric repulsion between two α -hydrogens in the β -chelation transition states **B** and **D**. The remarkably high





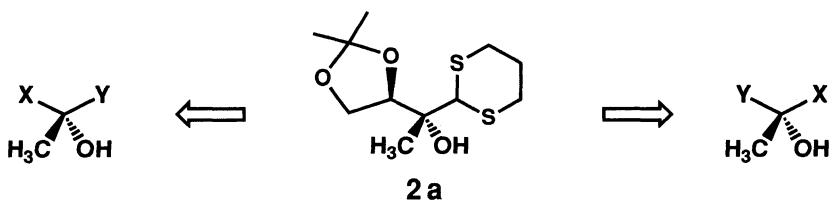
Scheme 2.

selectivity in the reaction of **1b-f** is well understood based on large energy gap between **A** and **B** and high efficiency of protecting the *re*-face from the methylation in **A**.

The *anti* preference of the present reaction was further demonstrated by alkylating the ketones **5** and **6**⁷⁾ which possess an additional chiral alkoxy group on substituent R of the dithioacetal group. The reaction of these ketones with MeLi in ether at -78 °C led to the corresponding 2,3-*anti* tetraol derivatives **7** and **8** as the sole products in 91% and 98% yield, respectively (Scheme 2).⁵⁾ Hydrolysis of the *tert*-butyldimethylsilyl group of **7** and **8** with aqueous *n*-Bu₃N⁺F⁻ quantitatively afforded 1,4-diols **9** and **10**, respectively. The stereochemistry of these products could be easily redetermined after their transformations into tetrahydrofurans **11** and **12** by a new method based on the stereoselective one-step cyclodehydration (Scheme 2). The treatment of **9** and **10** with 5 equiv. of *p*-TsCl in pyridine at room temperature for 48 h cleanly gave the tetrahydrofurans **11** and **12** in 80% and 83% yield, respectively without epimerization and racemization.⁸⁾ The relative stereochemistry of these tetrahydrofurans was easily assigned based on the NOE-measurements.⁹⁾ Since the cyclization should proceed via an S_N2 type mechanism with complete inversion of configuration at the tosyloxylated secondary carbon, the 2,3-stereochemistry of **7** and **8** was thus established to be *anti*.

In summary, the dithioacetal group was efficiently utilized as a stereocontrolling auxiliary in the Cram type of 1,2-asymmetric induction based on the nucleophilic addition of methylolithium to α -chiral α,β -dialkoxy ketones in order to construct a chiral quaternary center. As demonstrated in Scheme 2, the present method is expandable to the stereocontrolled construction of optically active, multifunctional and highly substituted tetrahydrofurans by following the novel function of the dithioacetal group.¹⁰⁾

It should be expected that the multi-functional chiral tertiary alcohols **2** could be a useful chiral synthon for the synthesis of a variety of compounds with chiral tertiary-alcohol centers including natural products because of the ready convertibility of both the terminal dihydroxyl and dithioacetal groups to a variety of functionalities by known methods. For example, as illustrated in Scheme 3, since both the terminal dihydroxyl and dithioacetal



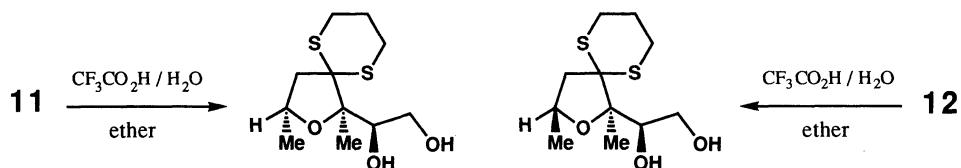
Scheme 3.

groups are convertible to either functionality **X** (e.g. CHO) or **Y** (e.g. COOR), **2a** can be regarded to be a reversible chiral synthon for both enantiomers with respect to the chiral quaternary center.

Further study on the scope and limitations as well as applications of the method are now under investigation.

References

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- 3) Nucleophilic hydride addition to α,β -dialkoxy ketones including the present type of α,β -dialkoxy 1,3-dithian-2-yl ketones **1** has been known to give *syn*-triol derivatives: K. Mead and T. L. Macdonald, *J. Org. Chem.*, **50**, 422 (1985); H. Chikashita, T. Nikaya, H. Uemura, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 2121 (1989).
- 4) W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, **21**, 1031 (1980) and references cited therein.
- 5) Stereochemistry of the products was directly determined by 400 MHz ^1H NMR analysis. For example, see: B. Landmann and R. W. Hoffmann, *Chem. Ber.*, **120**, 331 (1987).
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- 7) These compounds were easily prepared as optically pure forms from (1,3-dithian-2-yl)acetone and 1,2-*O*-isopropylidene-D-glyceraldehyde via the asymmetric reduction of the former ketone with bakers' yeast: H. Chikashita, E. Kittaka, Y. Kimura, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 833 (1989).
- 8) Specific rotations (in chloroform) of compounds prepared in the present study are as follows: **2a**, $[\alpha]^{28}\text{D}$ +7.55 (c 1.26); **2b**, $[\alpha]^{27}\text{D}$ +7.86 (c 1.12); **2c**, $[\alpha]^{28}\text{D}$ +5.39 (c 1.31); **2d**, $[\alpha]^{28}\text{D}$ +5.83 (c 1.21); **2e**, $[\alpha]^{34}\text{D}$ +6.84 (c 1.14); **2f**, $[\alpha]^{27}\text{D}$ 6.30 (c 1.35); **7**, $[\alpha]^{23}\text{D}$ 16.89 (c 1.72); **8**, $[\alpha]^{25}\text{D}$ -12.24 (c 1.31); **9**, $[\alpha]^{24}\text{D}$ +17.99 (c 1.25); **10**, $[\alpha]^{23}\text{D}$ -8.67 (c 1.27); **11**, $[\alpha]^{24}\text{D}$ -25.44 (c 1.24); **12**, $[\alpha]^{23}\text{D}$ +22.50 (c 1.11).
- 9) The NOE-measurements were carried out with the following diol derivatives which were easily obtained by the hydrolysis of **11** and **12**:



- 10) A new stereocontrolled route to *trans*-2,5-disubstituted tetrahydrofurans based on the highly stereoselective one-step cyclodehydration of a similar 1,4-diol consisting of two secondary hydroxyl groups has been studied: H. Chikashita, Y. Yasuda, Y. Kimura, and K. Ito, *Chem. Lett.*, in press.

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