Tetrahedron Letters, Vol.31, No.38, pp 5479-5482, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

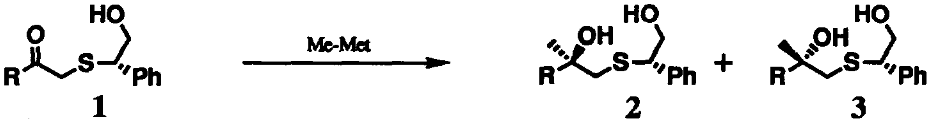
EITHER DIASTEREOFACIAL DIFFERENTIATION IN THE REACTION OF CHIRAL THIOMETHYLKETONES WITH APPROPRIATE ORGANOMETALLICS

Tamotsu FUJISAWA,* Isao TAKEMURA, and Yutaka UKAJI
Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan

Summary: Introduction of sulfur atom instead of oxygen into α-position to ketone was found to be crucial for efficient diastereofacial differentiation; *i.e.*, either diastereomer of tertiary alcohol could be obtained by the reaction of organometallics to chiral thiomethylketones derived from (*S*)-2-mercapto-2-phenylethanol and α-halo ketones. For example, MeLi attacked from *si*-face, while Me_2Zn preferred *re*-facial attack. In addition, both enantiomers of 1,2-*O*-isopropylidene-2-methyl-1,2,5-pentanetriol, a key intermediate for the synthesis of frontalin, were successfully synthesized utilizing the present method.

Recently, many approaches to the asymmetric carbon-carbon bond formation have been widely studied and various useful methods have been developed.1) Being concerned with this problem, we have studied on designing chiral carbonyl compounds which produce respectively both two enantiomers by the reaction with appropriately selected organometallics, and reported that stereocontrolled addition reaction of organometallics to chiral ketones possessing two hetero atoms, such as nitrogen and oxygen, in neighborhood of carbonyl group.2) Unfortunately in the case of α-amino ketones, removal of chiral auxiliary required rather drastic conditions,2b) and in the reaction of alkoxymethylketones with aliphatic ketone moiety, the stereoselectivity was not satisfactorily high.2c) Among the coordinatable heteroatoms, sulfur atom has been known to possess unique affinities to metals. For example, the nucleophilic addition reaction of metallic reagents to α-thio carbonyl compounds was reported to give different stereoselection from that to α-alkoxy carbonyl compounds.3) The coordination state of sulfur containing organometallics are varied depending on the structure of substrates.4) Furthermore, in 1,3-oxathiane ring system, the coordination ability of oxygen is known to be superior to that of sulfur.5,6) In order to design the more efficient substrate for the either diastereoselection in acyclic precursors, sulfur functional group instead of oxygen was next planed to be utilized. In this paper, we wish to report highly diastereofacial differentiating reaction of organometallics to ketones possessing sulfur functional group at α-position to furnish both isomers stereoselectively.

The addition reaction of MeLi to thiomethylketone **1a** ($[\alpha]_D^{23}$ -6.3° (c 0.4, $CHCl_3$)), prepared from α-bromoacetophenone and (*S*)-2-mercapto-2-phenylethanol,7) in Et_2O occurred predominantly from *si*-face to give the corresponding *R*-tertiary alcohol **2a**. The diastereomeric ratio of the addition products was determined to be 76 to 24 by HPLC analysis (Entry 1). When THF was used as a solvent, the addition product could not be



a R = Ph **b** R = $Me_2C{=}CH(CH_2)_2$ **c** R = $PhCH_2O(CH_2)_3$

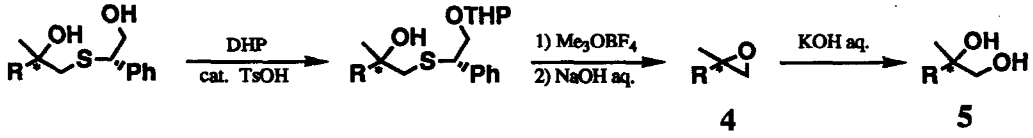
Table 1. Reaction of chiral thiomethylketones **1** with organometallic reagents.

Entry		R	Me-Met	Solvent	Temp/°C	Yield/%	**2** : **3**[a)]
1	**a**	Ph	MeLi[b)]	Et$_2$O	-78→-60	51	76 : 24
2			MeLi[b)]	toluene	-78→ rt	73	85 : 15
3			MeLi[b)]	toluene	-100→-78	90	90 : 10
4			MeMgBr[b)]	Et$_2$O-THF	-50→ 0	41	17 : 83
5			Me$_2$Zn[c)]	Et$_2$O	-20 → 0	60	8 : 92
6	**b**	Me$_2$C=CH(CH$_2$)$_2$	MeLi[b)]	toluene	-100→ rt	96	90 : 10
7			Me$_2$Zn[c)]	Et$_2$O	-30 → rt	98	5 : 95
8	**c**	PhCH$_2$O(CH$_2$)$_3$	MeLi[b)]	toluene	-105→ rt	76	90 : 10
9			Me$_2$Zn[c)]	Et$_2$O	-15 → rt	65	34 : 66

a) The ratios were determined by HPLC (Finepak SIL). b) The molar ratio of Me-Met to **1** was 2.6 - 3.0. c) The molar ratio of Me$_2$Zn to **1** was 10 - 11.

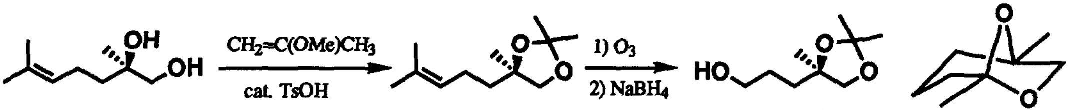
obtained and 95% of **1a** was recovered. In less polar solvent, toluene, the stereoselectivity was higher than that in Et$_2$O (Entry 2). Especially higher selectivity in the reaction with MeLi was realized at lower temperatures in toluene (Entry 3). In sharp contrast, the use of MeMgBr in Et$_2$O-THF resulted in stereochemical reversal to give the corresponding *S*-thiomethylalcohol **3a** by *re*-facial attack (Entry 4). In other solvents such as THF, Et$_2$O, DME, CH$_2$Cl$_2$, or toluene at lower temperatures, the reaction with MeMgBr showed lower selectivity. Although the reaction of thiomethylketone **1a** with MeTi(O^{i}Pr)$_3$ did not proceed, Me$_2$Zn, prepared from MeMgBr and ZnCl$_2$ *in situ*,[8)] was found to give the highest selectivity in favor of **3a** (Entry 5).[9)] In the case of aliphatic ketone **1b** ($[\alpha]_D^{23}$ +153° (c 0.3, MeOH)), either diastereofacial differentiation could be also realized depending on the kind of organometallics used; *i.e.*, the reaction of **1b** with MeLi and Me$_2$Zn gave *R*-tertiary alcohol **2b** and *S*-alcohol **3b** in a highly stereoselective manner, respectively (Entries 6 and 7). Thus designing thiomethylketone **1** instead of alkoxylmethylketone derived (*R*, *R*)-2,4-pentanediol[2c)] resulted in successful stereoselection. Furthermore, in order to investigate the influence of the other coordinatable heteroatom to the stereochemical course, the reaction of thiomethylketone **1c** ($[\alpha]_D^{23}$ +99° (c 0.4, MeOH)), possessing the other ethereal oxygen in a molecule, was examined. While MeLi reacted stereoselectively (Entry 8), the ethereal oxygen was found to affect the direction of the nucleophilic attack of Me$_2$Zn to give *S*-alcohol **3c** with low selectivity (Entry 9). These results are listed in Table 1.

The absolute configurations of the chiral center newly formed in the thiomethylalcohols were determined by the conversion to the corresponding optically active epoxides **4** by the protection of primary alcohols (54 - 70%), followed by the treatment with Me$_3$OBF$_4$ and 5% aq. NaOH solution to remove the chiral auxiliary (70 - 90%). In the case of thiomethylalcohol **2a**, the stereochemistry was determined as *R* by the comparison of optical rotation of the corresponding epoxide **4a** ($[\alpha]_D^{23}$ -2.7° (c 0.7, acetone)) derived from a 88 : 12 mixture of **2a** : **3a** with that of an authentic sample.[2b)] The thiomethylalcohol **3b** was determined to be *S* configuration after the transformation of a 12 : 88 mixture of **2b** and **3b** into 2,6-dimethyl-5-heptene-1,2-diol **5b** ($[\alpha]_D^{23}$ -7.4° (c 0.3,



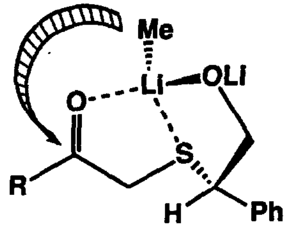
$CHCl_3$))2c) *via* the epoxide **4b** followed by the treatment with 0.3 N aq. KOH solution. Further in the case of thiomethylalcohol **2c**, the configuration was confirmed to be *R* by the conversion to the corresponding epoxide **4c** obtained from a 90 : 10 mixture of **2c** and **3c** and the following transformation into 2-methyl-1,2,5-pentanetriol **5c** ($[\alpha]_D^{23}$ +0.9° (c 0.4, MeOH))10) by hydrolysis and hydrogenolysis.

Frontalin is known as the aggregation pheromone of the southern pine bark beetle, *Dendroctonus frontalis*, and of the western pine bark beetle, *Dendroctonus brevicomis*, and 1,2-*O*-isopropylidene-2-methyl-1,2,5-pentanetriol **6** was reported to be a key intermediate for the synthesis of frontalin.11) The optically pure *R*-diol ***R*-5b**12) obtained by the present reaction was easily converted into ***R*-6** ($[\alpha]_D^{23}$ +1.5° (c 0.4, acetone)) by acetonization (86%) and ozonolysis (70%).13) The antipode ***S*-6** ($[\alpha]_D^{23}$ -1.3° (c 0.6, acetone)) was also synthesized from **3b** *via* ***S*-5b**. The absolute configurations of tertiary alcohols in **2b** and **3b** were also confirmed by the comparison of specific rotation of **6**.11)



***R*-5b** ***R*-6** **(+)-frontalin**

Although the detailed mechanism of the present reaction remains to be studied, the stereoselection might be elucidated by the difference of the coordination ability, especially the coordination number of organometallics; *i.e.*, organolithium reagent shapes tetrahedral four coordination structure **7**, while organozinc reagent constructs six coordinated octahedral structure **8**14) in which the three hetero atoms of thiomethylketone are located on the same plane. The attack of the alkyl group onto the carbonyl carbon occurred from less hindered side to avoid the steric interaction, respectively. In the reaction of **1c** with Me_2Zn, coordination of oxygen attached with benzyl group to much Lewis acidic zinc metal, might alter the chelation like **8** resulting in lower selectivity.



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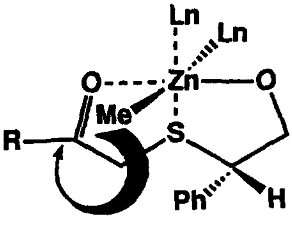

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As described above, the present method provides a useful way for the selective synthesis for either enantiomer of tertiary alcohol starting from a same chiral carbonyl compound by the suitable choice of organometallic reagents.17)

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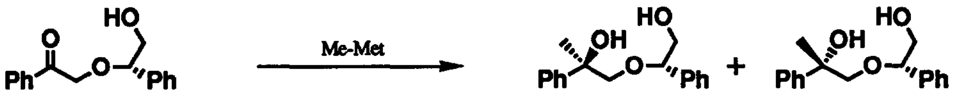

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MeLi	(toluene)	58 : 42
Me_2Zn	(Et_2O)	8 : 92

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17) The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

(Received in Japan 15 June 1990)