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Diastereoselective Addition of Organometallics to α-Keto Esters Bearing *chiro*-Inositol Derivatives as Chiral Auxiliaries

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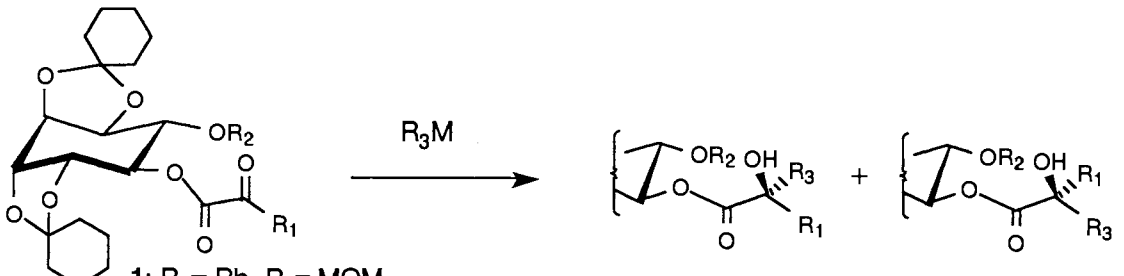
The nucleophilic addition of organometallics to α-keto esters derived from (1L)-1,2:5,6-di-*O*-cyclohexylidene-3-*t*-butyldimethylsilyl-*chiro*-inositol afforded the corresponding α-hydroxy esters of high diastereomeric excess (up to 98% de). Grignard reagents attacked from *re*-face, while organolithium reagents preferred *si*-face attack.

Diastereoselective addition of organometallics to α-keto carboxylic acid derivatives, which constitutes a significant reaction for the synthesis of optically active α-hydroxy acid derivatives,[1] has been extensively investigated.[2] While highly diastereoselective addition to chiral α-keto amides bearing (*S*)-proline[3] and C_2 symmetric pyrrolidine derivatives[4] as chiral auxiliaries was reported, no remarkable stereoselectivity was achieved with α-keto ester derivatives except for a few reports.[5] Furthermore, obtaining both diastereomers of high stereochemical purity from a single substrate by proper choice of the reagents is a challenging goal in asymmetric synthesis.[6]

We reported, in a previous paper,[7] that K-Selectride reduced α-keto ester bearing chiral inositol derivative (2) to give α-hydroxy ester with excellent diastereofacial selectivity, and addition of 18-Crown-6 led to dramatic reversal in the selectivity. In this paper we wish to report highly diastereoselective addition of organometallics to 2 and the reversal in diastereoselectivity observed by use of either Grignard reagent or organolithium reagent.

The starting α-keto esters 1, 2, and 3 were prepared starting from L-quebrachitol[7,8] (1L-(-)-2-*O*-methyl-*chiro*-inositol), a naturally abundant optically active inositol. In the first place, addition of organometallics to 1, bearing a methoxymethyl (MOM) ether, was studied, and the results are shown in Table 1. Addition of MeMgI



1; R_1= Ph, R_2= MOM
2; R_1= Ph, R_2= TBDMS
3; R_1= Me, R_2= TBDMS

4a **4b**

Table 1. Reaction of α-keto ester with organometallics

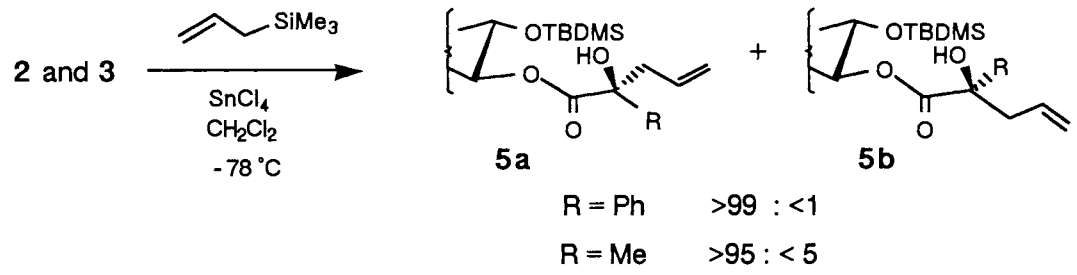
Entry	Keto ester	Organometallics[a)]	Solvent	Temp / °C	Yield/%	**4a : 4b**
1	**1**	MeMgI	THF	0	90	70 : 30
2	**1**	MeMgI	Toluene	-72	89	56 : 44
3	**1**	MeLi	Toluene	-72	84	42 : 58
4	**2**	MeMgI	Toluene	-72	88	98 : 2
5	**2**	MeMgI	Et_2O	0	87	95 : 5
6	**2**	MeMgI	Et_2O-HMPA	0	75	87 : 13
7	**2**	MeLi	Toluene	-90	84	10 : 90
8	**2**	MeLi	THF	-70	73	20 : 80
9	**3**	PhMgBr	THF	0	83	93 : 7
10	**3**	PhMgBr	Toluene	0	89	82 : 18
11	**3**	PhMgBr	Et_2O	0	90	80 : 20
12	**3**	TolMgBr	THF	0	85	99 : 1[b)]
13	**3**	TolMgBr	Toluene	0	87	92 : 8[b)]
14	**3**	TolMgBr	Et_2O	0	90	71 : 29[b)]

a) 1.2-1.5 equiv. of the reagents were employed. b) Absolute configuration of the chiral center newly formed was reasoned by analogy to the reaction of PhMgBr.

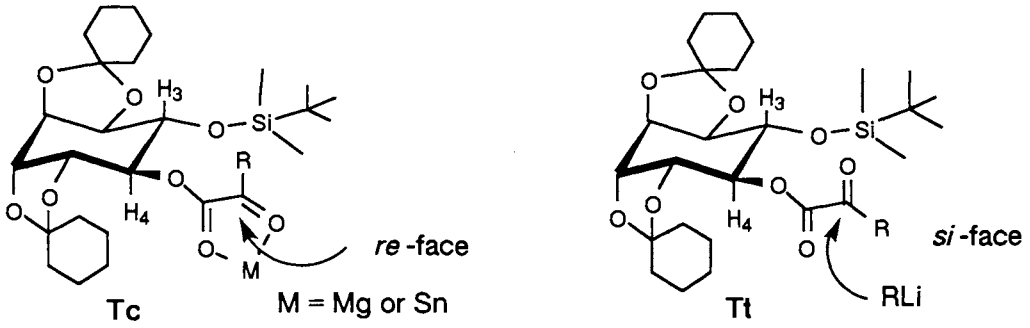
to **1** in THF exhibited moderate selectivity (Entry 1). The reaction with MeLi showed no selectivity (Entry 3). In order to enhance the bulkiness of the ether vicinal to α-keto ester moiety, *t*-butyldimethylsilyl (TBDMS) derivative **2** was next employed. Treatment of **2** with MeMgI in toluene at -72 °C afforded **4a** predominantly in 96% de (Entry 4). In sharp contrast, MeLi in toluene afforded the opposite diastereoisomer **4b** preferentially (Entry 7). The diastereofacial selectivity was estimated by the integral of 270 MHz ^{1}H NMR. The absolute configuration of the chiral center newly formed was determined by optical rotation of the α-hydroxy acid obtained by saponification of the ester.[9)]

Next the additions of Grignard reagents to a methyl ketone **3** were examined. Prominent solvent effects were observed and THF showed the best results. Addition of PhMgBr produced a 93/7 mixture of diastereomers (Entry 9), and almost complete stereoselection was achieved with *p*-tolylMgBr (Entry 12).

Finally, Lewis acid promoted additions of allylsilane to **2** and **3** were investigated.[3,10)] Treatment of **2** with allyltrimethylsilane (1.2 equiv.) in the presence of $SnCl_4$ (1.1 equiv.) in CH_2Cl_2 at -78°C for 1 h afforded a homoallyl alcohol (**5a**) exclusively in 92% yield; HPLC analysis showed the selectivity was more than 99:1.[11)] Neither **5a** nor **5b** was obtained by use of other Lewis acids such as $TiCl_4$ and BF_3·OEt_2. Addition to **3** also proceeded with excellent diastereoselectivity.[12)]



In the present study, the attack of the Grignard reagents and allylsilane took place from *re*-face preferentially, while that of the organolithium reagent from *si*-face. Although the exact conformation of **2** is not clear, large $J_{H\text{-}3,H\text{-}4}$ value (11.1 Hz) observed in ^1H NMR[13] suggests that both silyloxy and α-keto ester substituents occupy equatorial positions. The bulky TBDMS group hence worked more effectively as a stereo controlling element than the MOM ether. The high diastereoselectivity observed with the Grignard reagent can be rationalized in terms of the chelation model with *s-cis* conformation (**Tc**) depicted below, in which the TBDMS group effectively hindered the attack from the *si*-face of the ketone. The identical facial selectivity in the addition of allylsilane promoted by $SnCl_4$, which is a Lewis acid with strong coordinating ability, supports this mechanism. In contrast, the stereochemical outcome in the addition with organolithium reagent can be explained by the non-chelation model with *s-trans* conformation (**Tt**).



In conclusion, cyclitols have proved to be effective as chiral auxiliaries in the addition of carbon nucleophiles. Other asymmetric synthesis employing cyclitols as chiral auxiliaries are under progress in our laboratory.

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9) (*S*)-2-Hydroxy-2-phenylpropionic acid obtained by hydrolysis of the ester in Entry 4 of Table 1; $[\alpha]_D^{22}$ +35 ° (c 0.58, EtOH), (lit. $[\alpha]_D^{10.5}$ +37.7 ° (c 3.5, EtOH)).[14]

10) Diastereoselective allylation of allyltrimethylsilane to α-keto esters by means of $TiCl_4$ and with moderate selectivity; I. Ojima, Y. Miyazaki, and M. Kumagai, *J. Chem. Soc., Chem. Commun.*, **1976**, 927.

11) (S)-2-Hydroxy-2-phenyl-4-pentenoic acid obtained by hydrolysis; $[\alpha]_D^{22}$ +28 ° (c 0.8, $CHCl_3$), (lit. $[\alpha]_D^{22}$ +29 ° (c 1, $CHCl_3$)).[15]

12) Estimated by 270 MHz ^1H NMR and ^{13}C NMR. Absolute configuration was estimated by analogy to the reaction of **2**.

13) ^1H NMR of **2** (270 MHz, $CDCl_3$) δ= 0.05 (3H, s, CH_3), 0.13 (3H, s, CH_3), 0.87 (9H, s, $C(CH_3)_3$), 1.41-1.84 (20H, m, $(CH_2)_{10}$), 3.71 (1H, dd, $J_{2,3}$=7.0 Hz, $J_{3,4}$=11.1 Hz, H-3), 4.22 (1H, dd, $J_{1,2}$=6.1 Hz, H2), 4.30 (1H, dd, $J_{4,5}$=8.6 Hz, $J_{5,6}$=6.0 Hz, H-5), 4.46 (1H, dd, $J_{1,6}$=3.4 Hz, H-1), 4.50 (1H, dd, H-6), 5.23 (1H, dd, H-4), 7.47-7.53 (2H, m, aromatic), 7.62-7.68 (1H, m, aromatic), 8.10-8.14 (2H, m, aromatic).

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