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1,3-Asymmetric Induction in the Reaction of Organometallics to β-Hydroxy Ketones and β-Silyloxy Ketones

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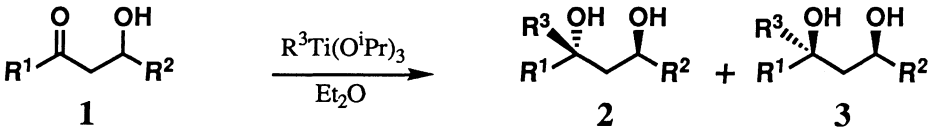
High level of 1,3-asymmetric induction was realized in the reaction between β-hydroxy ketones and triisopropoxytitanium reagents to give *anti*-1,3-diols possessing tertiary alcohols. To the contrary, *syn*-1,3-diols were obtained by the addition reaction of organometallics to β-*t*-butyldimethylsilyloxy ketones.

The stereoselective construction of oxygen functionalized molecules is an important current topic in organic chemistry and a wide variety of highly selective reactions relevant to the synthesis of polyoxy natural products have been developed.[1] Especially 1,3-diol is one of the most important constituents of polyoxy compounds and several methods for stereoselective construction of 1,3-diols were studied by 1,3-asymmetric induction in the reduction of β-hydroxy ketones[2] and carbon-carbon bond forming reaction of β-alkoxy aldehydes.[3-5] With regard to construction of 1,3-diols containing tertiary alcohols, however, only a few methods have been reported.[6] We describe here the selective 1,3-asymmetric induction in the nucleophilic addition of organometallics to β-hydroxy ketones and β-silyloxy ketones to give 1,3-diols stereoselectively.

First, the nucleophilic reaction of 3-hydroxy-1,3-diphenyl-1-propanone (**1A**) with various organometallics was examined. MeLi and MeMgBr reacted with **1A** to give *anti*-1,3-diol **2a** and *syn*-diol **3a** in a ratio of 79 : 21 and 32 : 68, respectively.[7] Considerable *anti*-selectivity was realized utilizing titanium reagents; *i.e.*, β-hydroxy ketone **1A** reacted with $MeTiCl_3$ in ether to give *anti*-1,3-diol **2a** with high stereoselectivity (**2a** : **3a** = 97 : 3, 78%). Further, almost complete stereoselection (**2a** : **3a** = >99 : <1) was accomplished in the reaction with $MeTi(O^iPr)_3$ prepared from MeLi and $ClTi(O^iPr)_3$ *in situ* (Entry 2).[8] The reaction with LiCl-free $MeTi(O^iPr)_3$, isolated by distillation,[9] also showed excellent selection (Entry 3). Main by-product in the reaction with $MeTi(O^iPr)_3$ was α, β-unsaturated ketone, 1,3-diphenyl-2-propen-1-one. The addition of LiI appeared to enhance the yield of *anti*-1,3-diol **2a** (Entry 1). Then, the reaction of triisopropoxytitanium reagents with several β-hydroxy ketones was examined and *anti*-1,3-diols **2** were obtained stereoselectively as shown in the Table 1. Especially, in the reaction of β-hydroxy ketones possessing phenyl group in the position of R^1 or R^2, excellent



1 **2** **3**

A; $R^1 = R^2$ = Ph,
B; R^1 = *n*-Pr, R^2 = Ph,
C; $R^1 = PhCH_2CH_2$, R^2 = *c*-Hex

a; $R^1 = R^2$ = Ph, R^3 = Me,
b; R^1 = *n*-Pr, R^2 = Ph, R^3 = Me
c; $R^1 = PhCH_2CH_2$, R^2 = *c*-Hex, R^3 = Me,
d; $R^1 = R^2$ = Ph, R^3 = *n*-Bu

Table 1. Reaction of β-hydroxy ketones **1** with R^3 $Ti(O^iPr)_3$[a,b]

Entry	1	R^1	R^2	R^3	Additive[c]	Temp/°C	Products	Yield/%	2 : 3
1	**A**	Ph	Ph	Me	LiI	-78 - -20	**a**	69	99 : 1[d]
2					---	-78 - -35	**a**	59	>99 : <1[d]
3					---	-78 - -20	**a**	53	98 : 2[d]
4	**B**	*n*-Pr	Ph	Me	LiI	-78 - -30	**b**	54	>99 : <1[d]
5					---	-78 - -40	**b**	41	92 : 8[d]
6	**C**	$PhCH_2CH_2$	*c*-Hex	Me	LiI	-78 - -30	**c**	76	79 : 21[d]
7					---	-78 - -40	**c**	76	74 : 26[d]
8					---	-78 - 0	**c**	61	57 : 43[d]
9	**A**	Ph	Ph	*n*-Bu	LiI	-78 - r.t	**d**	51	>99 : <1[e]

a) The molar ratio of $R^3Ti(O^iPr)_3$ to β-hydroxy ketone **1** was 5.0 except for Entries 5 and 8 (Entry 5, 3.0; Entry 8, 6.0). b) $R^3Ti(O^iPr)_3$ was prepared from R^3Li and $ClTi(O^iPr)_3$ *in situ* except for Entries 3, 5, and 8. (Entries 3, 5, and 8; Distilled $MeTi(O^iPr)_3$ was used.) c) The molar ratio of additive to β-hydroxy ketone was 5.0. d) The ratio was determined by HPLC (Finepak SIL). e) The ratio was determined by capillary GLC (SE-30).

level of asymmetric induction was realized (Entries 1, 4, and 9). The presence of lithium salt enhanced the stereoselectivity and yields especially in the reaction of **1C** (Entries 6-8).

On the other hand, in order to prepare *syn*-1,3-diols, the addition reaction of organometallics to β-hydroxy ketones after the protection of the hydroxyl group as silyl ether was next investigated.[10] When 1,3-diphenyl-3-(*t*-butyldimethylsilyloxy)-1-propanone (**4A**) was reacted with MeLi, excellent *syn*-stereoselection (**5a** : **6a** = 4 : 96) was accomplished (Entry 1). Further, the reaction with Grignard and titanium reagents also gave *syn*-alcohol **6a** with high selectivity (Entries 2-4). Stereoselective synthesis of several *syn*-1,3-diols from β-silyloxy ketones **4** was examined, and the corresponding *syn*-tertiary alcohols **6** were obtained with good selectivity (Entries 5-9) as listed in the Table 2. In general, the reaction with alkyllithium realized better selectivity than that with Grignard reagent. The obtained *syn*-alcohols **6** were easily deprotected by HF into *syn*-1,3-diols **3**.

Diastereomers of the obtained 1,3-diols **2** and **3** could be separated by TLC on silica gel. X-Ray crystallographic analysis of the single crystal of **3a** determined the configuration to be *syn* as depicted in Fig. 1,[11] and the relative configuration of **2a** was consequently determined to be *anti*.[12a] The ^1H NMR spectrum of **2b** was in good agreement with that of the authentic sample obtained by the hydrogenation of *anti*-3-methyl-1-phenyl-5-hexyn-1,3-diol, which was synthesized from 4-hydroxy-4-phenyl-2-butanone and allenylboronic acid.[6a,12b] Further, the configuration of **2d** and **3d** was presumed to be *anti* and *syn*, respectively, by the comparison of their chemical shifts of methine protons (-CH(OH)-) with those in **2a** and **3a**; *i.e.*, methine protons of *syn*-isomers appeared at lower fields than those of *anti*-isomers.[12c]

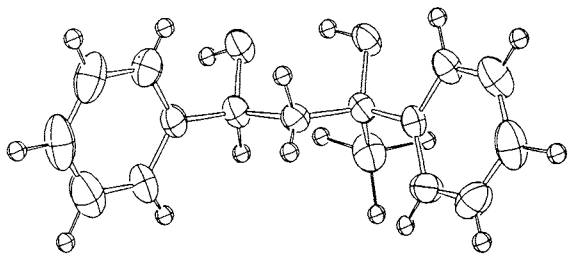
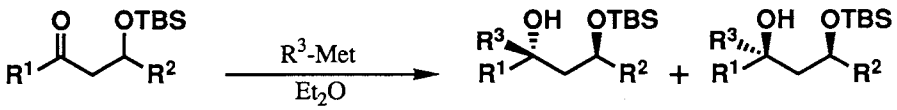


Fig. 1.



4 5 6

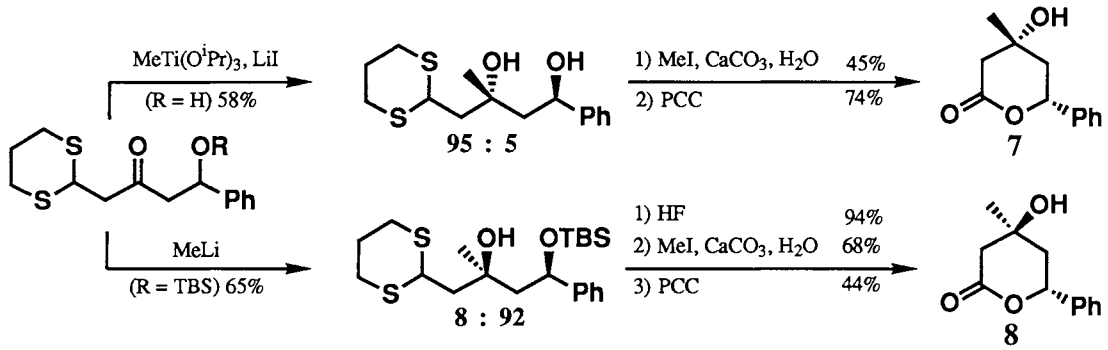
(TBS = ^{t}BuMe$_2$Si)

Table 2. The addition reaction of β-silyloxy ketones **4** with organometallics

Entry	4	R^1	R^2	R^3-Met[a]	Temp/°C	Products	Yield/%	5 : 6[b]
1	A	Ph	Ph	MeLi	-78 - -68	a	86	4 : 96
2				MeMgBr	-78 - -35	a	90	2 : 98
3				$MeTiCl_3$	-78 - 0	a	70	6 : 94
4				$MeTi(O^iPr)_3$[c]	r.t.	a	49	14 : 86
5	B	*n*-Pr	Ph	MeLi	-78	b	88	14 : 86
6				MeMgBr	-78 - -48	b	66	18 : 82
7	C	$PhCH_2CH_2$	*n*-Hex	MeLi	-78 - -65	c	79	18 : 82
8				MeMgBr	-78 - -20	c	80	24 : 76
9	A	Ph	Ph	*n*-BuLi	-78	d	71	17 : 83

a) Ratio of R^3-Met to β-silyloxy ketone was 1.2 - 1.9 except for Entry 4 (Entry 4; 3.0). b) Ratio was determined by HPLC (Finepak SIL). c) Distilled $MeTi(O^iPr)_3$ was used without solvent.

β-Hydroxy-δ-valerolactone, structurally analogous to compactin lactone, is a potent competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.[13] By utilizing the present procedure for the synthesis of *anti*- and *syn*-1,3-diols, stereoselective synthesis of both diastereomers of substituted β-hydroxy-δ-valerolactones **7** and **8** from β–hydroxy ketone was demonstrated (Scheme 1). The configuration of the obtained lactone **8** was identified with the authentic sample derived from 4-(bromoacetoxy)-4-phenyl-2-butanone and SmI_2.[6b,14]



Scheme 1.

Since β-hydroxy ketone is readily available by aldol reaction,[15] this reaction provides unique and singularly efficient entries into synthesis of polyoxy natural products containing tertiary alcohols.

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12) a) **2a**; oil, ^1H NMR (CCl_4) δ 1.31(3H, s, $C\underline{H}_3$), 4.24(1H, dd, J=6, 7 Hz, -C<u>H</u>(OH)-). **3a**; crystal, mp 86-88 °C (toluene), ^1H NMR (CCl_4) δ 1.63(3H, s, $C\underline{H}_3$), 4.99(1H, dd, J=4, 10 Hz, -C<u>H</u>(OH)-). We found that the previous assignment of the relative configuration of **2a** and **3a** in lit[16] was reverse each other; b) **2b**; ^1H NMR (CCl_4) δ 1.10(3H, s, $C\underline{H}_3$). **3b**; δ 1.30(3H, s, $C\underline{H}_3$); c) **2d**; ^1H NMR (CCl_4) δ 4.26(1H, m, -C<u>H</u>(OH)-). **3d**; δ 4.93(1H, m, -C<u>H</u>(OH)-).

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14) **7**; ^1H NMR (CCl_4) δ 1.50(3H, s, $C\underline{H}_3$), 5.24(1H, dd, J=6, 9 Hz, PhC<u>H</u>O-). **8;** δ 1.40(3H, s, $C\underline{H}_3$), 5.70(1H, dd, J=4, 11 Hz, PhC<u>H</u>O-).

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