CHEMISTRY LETTERS, pp. 2045-2048, 1989.

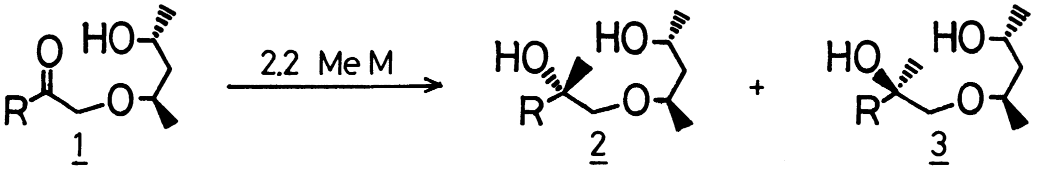
Diastereofacial Controlled Addition Reaction of Alkoxymethylketones Modified by (2*R*,4*R*)-2,4-Pentanediol with Organometallics

Tamotsu FUJISAWA,* Toshiyuki WATAI, Takeshi SUGIYAMA, and Yutaka UKAJI
Chemistry Department of Resources, Mie University, Tsu, Mie 514

Oxygen functionalized chiral alkoxymethylketone, derived from (2*R*,4*R*)-2,4-pentanediol, provided an efficient chiral environment in the reaction with organometallics which resulted in the either stereoselection depending on metal used; *i.e.*, the reactions with MeLi and MeTi(O^{i}Pr)$_3$ selectively furnished the corresponding (*S*)- and (*R*)-tertiary alcohols, respectively.

Asymmetric carbon-carbon formation by the reaction of carbonyl compounds with organometallics have been one of the most important problems in asymmetric synthesis.[1] In the nucleophilic addition reaction of organometallics, if a few chiral functional groups were adequately located in the neighborhood of ketone, the stereoselection for either face of carbonyl group is expected to be accomplished by choosing appropriate organometallics. Concerned with this problem, we have already studied the diastereodifferentiating reaction of organometallics to chiral α-ketoenamines and α-aminoketones derived from (*S*)-2-methoxymethylpyrrolidine, which possesses nitrogen and oxygen as coordinatable heteroatoms.[2] Developing another efficient substrate built up by oxygen functional groups, where either stereoselection would take place, we describe here a stereoselective reaction of organometallics with chiral alkoxymethylketones **1** which possess different kinds of oxygen functional groups.

Chiral alkoxymethylketones 1 were prepared from (2*R*,4*R*)-2,4-pentanediol,[3] which is easily available and a useful chiral auxiliary.[4] First, the reaction of α-alkoxyacetophenone **1a** with 2.2 molar amounts of MeLi in Et$_2$O was investigated. After hydrolysis, the corresponding (*S*)- and (*R*)-tertiary alcohols **2a** and **3a** were obtained in a ratio of 6 : 1 (Entry 1). Unfortunately, MeMgBr reacted with **1a** not selectively (Entry 4). It was found that use of titanium reagents realized reversal of diastereoselection to afford (*R*)-alcohol **3a** selectively (Entries 5 and 6).



1 2 3

R= a; Ph, b; p-Tol, c; α-Nap, d; Ph(CH$_2$)$_4$, e; (CH$_3$)$_2$C=CH(CH$_2$)$_2$

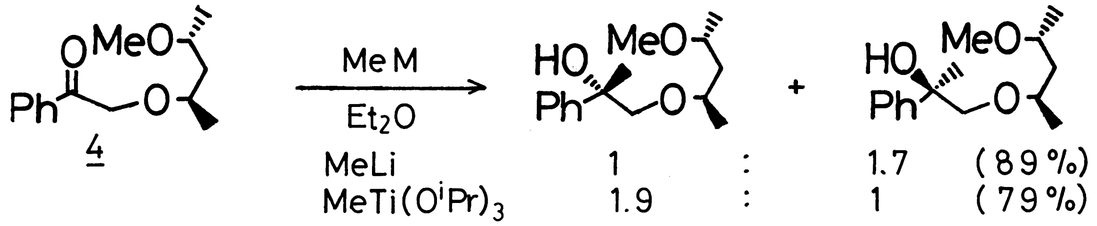
Table 1. Reaction of α-alkoxyacetophenone **1a** with organometallics[a]

Entry	MeM	Solvent	Total yield/%	Ratio of **2a** : **3a**[b]
1	MeLi	Et_2O	85	6 : 1
2		THF	18	3 : 1
3		toluene	72	3 : 1
4	MeMgBr	Et_2O	68	1 : 1.1
5	$MeTiCl_3$	Et_2O	47	1 : 5
6	Me_2TiCl_2	Et_2O	79	1 : 5
7	$MeTi(O^iPr)_3$	Et_2O	83	1 : 7
8		THF	78	1 : 7
9		CH_2Cl_2	4	1 : 3

a) The reaction was performed using 2.2 molar amounts of organometallics at -78 °C - r.t. b) The diastereomeric ratio was determined by capillary GLC (FFAP).

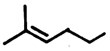
Especially in the case of $MeTi(O^iPr)_3$, higher stereoselection was accomplished to produce **2a** and **3a** in a 1 : 7 ratio (Entry 7). Ether was a superior solvent to other solvents such as THF in the reaction of MeLi (Entries 1 - 3) and $MeTi(O^iPr)_3$ (Entries 7 - 9). These results are summarized in Table 1.

In order to confirm the influence of a hydroxyl group in **1a** on the stereoselection, the control experiment on methylation of the corresponding methyl ether of **1a** was performed for comparison. However, the reaction of the methyl ether **4** with MeLi and $MeTi(O^iPr)_3$ proceeded in a poor selective manner, and the role of a hydroxyl group moiety on the stereochemical course appeared to be crucial.



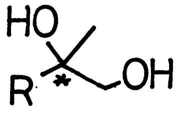
Diastereodifferentiating reaction of various alkoxymethylketones **1** using MeLi and $MeTi(O^iPr)_3$ was examined. As shown in Table 2, in all cases (*S*)-tertiary alcohols **2** were selectively obtained when MeLi was used as organometallics. On the other hand, the reaction of $MeTi(O^iPr)_3$ afforded (*R*)-alcohols **3** selectively, and thus this method appeared to be general. The remarkable features of these reactions were noted: a) The reactions of aromatic ketones **1b,c** proceeded in higher stereoselectivity (Entries 4 - 7). b) The presence of one molar amount of lithium trifluoromethanesulfonate (LiOTf) improved the stereoselection in the reaction of MeLi with especially aliphatic ketones **1d,e** (Entries 2, 9, and 12).[5] c) Although $MeTi(O^iPr)_3$ was prepared *in situ* from $ClTi(O^iPr)_3$ and MeLi in general reaction, the addition reaction of isolated $MeTi(O^iPr)_3$,[6] free from LiCl, surprisingly occurred not selectively; *e.g.*, the treatment of isolated $MeTi(O^iPr)_3$ with **1d** or **1e** afforded a 1 : 1.1 mixture of **2d** and **3d**, or **2e** and **3e**, respectively.

Table 2. Diastereodifferentiating reaction of alkoxymethylketones **1** in Et_2O

Entry	**1**	R	MeM	Temp/ °C	Total yield/%	Ratio of **2** : **3**
1	**a**	Ph	MeLi	-78 - r.t.	85	6 : $1^{a)}$
2			$MeLi^{b)}$	-110	74	7 : $1^{a)}$
3			$MeTi(O^iPr)_3{}^{c)}$	-78 - r.t.	83	1 : $7^{a)}$
4	**b**	*p*-Tol	MeLi	-78	80	27 : $1^{d)}$
5			$MeTi(O^iPr)_3{}^{c)}$	-78 - r.t.	86	1 : $6^{d)}$
6	**c**	α-Nap	MeLi	-78 - -60	68	12 : $1^{d)}$
7			$MeTi(O^iPr)_3{}^{c)}$	-78 - r.t.	60	1 : $15^{d)}$
8	**d**	$Ph(CH_2)_4$	MeLi	-78 - -35	79	4 : $1^{e)}$
9			$MeLi^{b)}$	-110	41	7 : $1^{e)}$
10			$MeTi(O^iPr)_3{}^{c)}$	-78 - r.t.	76	1 : $6^{e)}$
11	**e**		MeLi	-78	67	1.4 : $1^{f)}$
12			$MeLi^{b)}$	-110 - -78	92	4 : $1^{f)}$
13			$MeTi(O^iPr)_3{}^{c)}$	-78 - r.t.	59	1 : $7^{f)}$

a) The ratio was determined by capillary GLC (FFAP). b) LiOTf was added. c) $MeTi(O^iPr)_3$ was prepared from $ClTi(O^iPr)_3$ and MeLi *in situ* . d) The ratio was determined by capillary GLC (SE-30). e) The ratio was determined by HPLC (Finepak-SIL). f) The ratio was determined by HPLC (Finepak-SIL) after the conversion to the corresponding mono-*O*-benzoate.

The obtained tertiary alcohols **2** and **3** were able to be converted to the corresponding chiral 1,2-diols **5** through PCC oxidation and retro-Michael reaction.[4,7] The absolute configuration of tertiary carbon attached to the hydroxyl group of **2a**,**b** was determined to be *S* by the comparison with the authentic samples of **5a**,**b**.[8] Furthermore, in ^1H NMR spectra, all the differences of the chemical shifts between methylene protons H_A and H_B adjacent to the ether oxygen atom (Fig. 1) were 0.09 - 0.36 ppm larger for **3a**-**e** than those for **2a**-**e**, respectively.



5

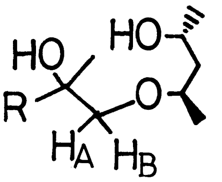


Fig. 1.

The factor of this either selection is not clear but might be the result from different coordination number of organometallics as previously reported;[2b] *i.e.*, the coordination number of lithium is four and that of titanium is six. The role of lithium salts might be the activation of carbonyl group to make the nucleophilic addition proceed at lower temperature or the alternation of the degree of aggregation.[5]

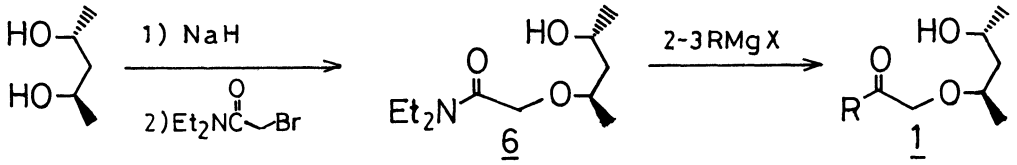
In most asymmetric synthesis, only one of the two epimeric isomers was obtained, and the selective preparation of both isomers from a single starting material has been strongly desired.[9] The present reaction provides a useful solution for the synthesis of both enantiomers utilizing the different coordinating ability of organometallics.[11]

References

1) "Asymmetric Synthesis" ed by J. D. Morrison, Academic Press. Inc., New York (1983-1985).

2) a) T. Fujisawa, M. Watanabe, and T. Sato, Chem. Lett., 1984, 2055; b) T. Fujisawa, M. Funabora, Y. Ukaji, and T. Sato, ibid., 1988, 59.

3) Chiral alkoxymethylketones **1** were prepared by the reaction of chiral alkoxyacetamide **6**, obtained from (2*R*,4*R*)-2,4-pentanediol and *N*,*N*-diethyl 2-bromoacetamide, with Grignard reagents.



4) H. Yamamoto and A. Mori, Yuki Gosei Kagaku Kyokai Shi, 45, 944 (1987); T. Sugimura, T. Futagawa, and A. Tai, Tetrahedron Lett., 29, 5775 (1988).

5) The remarkable effects of lithium salts in organolithium reaction and lithium enolate reaction were reported; J. K. Whitesell, A. Bhattacharya, and K. Henke, J. Chem. Soc., Chem. Commun., 1982, 988; D. Seebach, Angew. Chem., Int. Ed. Engl., 27, 1624 (1988).

6) M. T. Reetz, J. Westermann, and R. Steinbach, Chem. Ber., 118, 1421 (1985).

7) The specific rotations ($[\alpha]_D^{23}$) were +10.7°(c 0.64, $CHCl_3$) (**5b**, from **2b**/**3b** = 27/1), -3.0°(c 0.48, $CHCl_3$) (**5c**, from **2c**/**3c** = 1/11), -0.4°(c 1.05, EtOH) (**5d**, from **2d**/**3d** = 4/1), and -6.7°(c 0.39, $CHCl_3$) (**5e**, from **2e**/**3e** = 4/1).

8) The authentic diols (*R*)-**5a** ($[\alpha]_D^{23}$ -5.8°(c 0.17, EtOH)) and (*R*)-**5b** ($[\alpha]_D^{23}$ -13.8° (c 1.32, $CHCl_3$) were prepared by $LiAlH_4$ reduction of (*R*)-(-)-methyl atrolactate[10] and (*R*)-(-)-*p*-methylatrolactic acid, respectively. Although the optical rotation of **5a** (from **2a**/**3a** = 6/1) did not exhibit constant value because of a few amounts of unremovable contaminant, the analysis of the corresponding mono-1-*O*-MTPA ester revealed that the optical purity of the diol was 74% ee and the configuration was *S*.

9) T. Fujisawa and Y. Ukaji, Yuki Gosei Kagaku Kyokai Shi, 47, 186 (1989).

10) E. L. Eliel and J. P. Freeman, J. Am. Chem. Soc., 74, 923 (1952); S. Mitsui and S. Imaizumi, Nippon Kagaku Zasshi, 86, 219 (1965);

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

(Received August 8, 1989)