Magnesium Bromide Diethyl Etherate Mediated Highly Diastereoselective Aldol Reaction between an Aldehyde and a Silyl Enol Ether

Hidehiko Fujisawa, Yasuhiro Sasaki, and Teruaki Mukaiyama*
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjyukuku,Tokyo 162-8601

(Received November 22, 2000; CL-001062)

High yield and excellent diastereoselectivity in the formation of methyl (2*R*,3*R*,5*R*,6*S*)-2,6-dibenzyloxy-7-(*t*-butyldimethylsiloxy)-3-hydroxy-5-(4-methoxybenzyloxy)-4,4-dimethylheptanoate **3** and methyl (2*R*,3*R*,4*S*)-2,4-dibenzyloxy-3-hydroxypentanoate **7** are achieved by aldol reaction between (*Z*)-2-benzyloxy-1-methoxy-1-(trimethylsiloxy)ethene **1** and chiral alkoxy aldehydes using three equivalents of $MgBr_2 \cdot OEt_2$. The following mechanism of the above aldol reaction proposes that $MgBr_2 \cdot OEt_2$ activated both chiral alkoxy aldehydes and silyl enolate, that is, magnesiumu enolate, formed by transmetalation from silyl enolate and $MgBr_2 \cdot OEt_2$, reacted with $MgBr_2 \cdot OEt_2$-chelated alkoxy aldehydes via the six-membered cyclic transition state.

Stereoselective synthesis of chiral polyhydroxylated acyclic compounds is one of the important topics in modern organic synthesis. Aldol reactions between carbonyl compounds and several silyl enolates bearing a protected hydroxy group at α-position are useful tools for the synthesis of diol units with two carbon extension.[1] Based on this method, stereoselective aldol reaction between **1**, derived from methyl 2-benzyloxyacetate, and optically active trialkoxy aldehyde **2** was employed as a key step in preparing chiral polyoxy ester **3**,[2] in our synthesis of the B ring system of Taxol which possessed a 2,3,5,6-*anti*,*anti*,*anti* relative configuration. It was reported briefly from our Laboratory that **3** was obtained in high yield with excellent diastereoselectivity by the $MgBr_2 \cdot OEt_2$-mediated aldol reaction. Here, we would like to describe a characteristic feature of $MgBr_2 \cdot OEt_2$-mediated aldol reaction between chiral alkoxy aldehydes and α-alkoxy silyl ketene acetals.

While working on the above mentioned aldol reactions between **1** and **2**, it was found that the desired aldol adduct **3** was obtained in poor yields when typical Lewis acids such as $TiCl_4$ or $SnCl_4$ were used. It was supposed that these results were attributed to the strong coordinations of Lewis acids to the aldehydes bearing oxygenated functional groups to deactive the Lewis acids. At the same time, silyl enolates bearing benzyloxy group at α-position decreased their nucleophilic ability in comparision with the reactivity of the enolates not bearing benzyloxy group. After screening various Lewis acids, it was interestingly found that the desired diastereomer was selectively formed by using $MgBr_2 \cdot OEt_2$. Of the four possible diastereomeric aldol products, only two diastereomers **3** and **4** were obtained under the present reaction conditions while the other two diastereomers 2,3-*anti*,3,5-*syn*,5,6-*anti* and 2,3,5-*syn*,*syn*,5,6-*anti* isomers were not detected. Formation of diastereomers **3** and **4** is explained by considering a selective attack of enolate **1** from *si* face of aldehyde **2**, that is, the coordination of aldehyde **2** to $MgBr_2 \cdot OEt_2$ caused to inhibit *re* face attack of the enolate, and thus the 3,5-*anti* isomer is expected to form selectively.

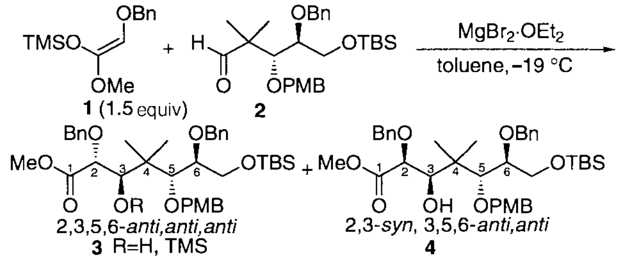

Table 1.

Entry	$MgBr_2 \cdot OEt_2$ /equiv	Time /min	Yield[a] **3** /%	Yield[a] **4** /%	Ratio **3** : **4**	Recovered **2**[a] /%
1	6.0	30	94	2.3	41 : 1	-
2	3.0	45	95	2.3	41 : 1	-
3	2.0	70	79	2.8	28 : 1	13
4	1.5	70	54	2.3	24 : 1	44

[a] Isolated yields.

After carefull optimization of reaction conditions, the best result (97%, **3**:**4**=41:1) was obtained when reactions were carried out at –19 °C using $MgBr_2 \cdot OEt_2$ whose amount exceeded the combined quantity of aldehyde plus silyl enolate[3] (Table 1, entry 2). The high reactivity and selectivity in the present experiment suggested that $MgBr_2 \cdot OEt_2$ activated not only aldehyde as a Lewis acid but also the silyl enolate forming the corresponding magnesium enolate by metal exchange under the reaction conditions. Although several metal salts such as $TiCl_4$, and Bu_2BOTf were already known to be able to form the corresponding metal enolates by metal exchange with silyl enolate,[4] this type of transmetalation with magnesium salts has not been reported to the best of our knowledge.[5]

In order to examine the above mentioned transmetalation, silyl enolate **1** was treated with $MgBr_2 \cdot OEt_2$ in toluene-d_8 at room temperature and the formation of trimethylsilyl bromide was observed by ^1H NMR measurement.[6] This indicated that the magnesium enolate was formed readily and it behaved as a nucleophile in the formation of aldols.

Further, there are two factors to achieve the excellent diastereoselectivity: that is, a) formyl face selectivity by the chelation control of $MgBr_2 \cdot OEt_2$,[7] and b) stereoselectivity via the six membered cyclic transition state[8] involving magnesium enolate. It was assumed that the high diastereoselectivity in the present aldol reaction using $MgBr_2 \cdot OEt_2$ would be performed by the concurrent effect of a) and b). By this combined effect, aldol reaction using $MgBr_2 \cdot OEt_2$ was expected to afford the aldols in higher yields and diastereoselectivity compared with the cases obtained by using conventional Lewis acids or metal enolates.

To verify the above assumption, the double facial diastereoselectivity in the $MgBr_2 \cdot OEt_2$-mediated aldol reaction of chiral *O*-benzyl lactaldehyde **5** was examined and compared to the results with that of the reactions using other Lewis acids and silyl or other metal enolates.[9] Then, it was found that high yield and excellent diastereoselectivity were achieved only when

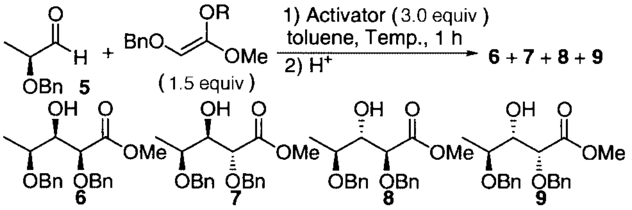

Table 2.

Entry	R	Activator	Temp. /°C	Yield[a] /%	Product distribution[b] 6 : 7 : 8 : 9
1	TMS	$MgBr_2 \cdot OEt_2$	-78	82	5 : 90 : 0 : 5
2	TMS	$MgBr_2 \cdot OEt_2$	-45	97	1 : 98 : 0 : 1
3[c]	TMS	$MgBr_2 \cdot OEt_2$	-45	93	3 : 95 : 0 : 2
4	TMS	$MgBr_2 \cdot OEt_2$	-19	91	7 : 90 : 1 : 2
5	TMS	$MgBr_2 \cdot OEt_2$	r.t.	80	16 : 62 : 20 : 2
6[d]	TMS	$MgBr_2 \cdot OEt_2$	-78	93	56 : 40 : 0 : 4
7	TMS	MgI_2	-45	trace	
8	TMS	$MgCl_2$	-45	9	23 : 45 : 25 : 7
9	TMS	$Mg(OTf)_2$	-45	9	23 : 49 : 16 : 12
10	TMS	$Mg(ClO_4)_2$	-45	42	5 : 84 : 3 : 8
11	TMS	$SnCl_4$	-78	42	26 : 35 : 18 : 21
12	TMS	$BF_3 \cdot OEt_2$	-78	53	18 : 16 : 29 : 37
13	TMS	$AlCl_3$	-78	43	27 : 20 : 30 : 23
14	TMS	$TiCl_4$	-78	33	20 : 54 : 14 : 12
15	TMS	$ZnCl_2$	-78	44	4 : 88 : 4 : 4
16[e]	Li	-	-78	18	4 : 21 : 39 : 36
17[e]	MgBr	-	-78	7	9 : 14 : 26 : 51

[a] Isolated yields. [b] Ratios were determined by 500-MHz ^{1}H NMR analysis. [c] 1.0 equiv of $MgBr_2 \cdot OEt_2$ was used. [d] Dichloromethane was used as a solvent. [e] Tetrahydofuran was used as a solvent.

$MgBr_2 \cdot OEt_2$ was used. Lewis acidity was not the main factor to control the efficiency and selectivity of the present aldol reaction, since $MgCl_2$, $Mg(OTf)_2$, $Mg(ClO_4)_2$, or MgI_2 did not promote effectively the aldol reaction as $MgBr_2 \cdot OEt_2$ did. In order to clarify the difference between $MgBr_2 \cdot OEt_2$ and other magnesium salts, silyl enolate **1** was treated with MgI_2, $MgCl_2$, $Mg(OTf)_2$, or $Mg(ClO_4)_2$ in benzene-d_6 at room temperature, and the formation of trimethylsilyl bromide was not observed in each case by ^{1}H NMR measurements. These results implied that the magnesium enolates were not formed by transmetalation between **1** and magnesium salts except $MgBr_2 \cdot OEt_2$. That is, magnesium salts worked like common Lewis acids to activate only the aldehydes and not the silyl enolate except $MgBr_2 \cdot OEt_2$, and therefore, the aldol reaction gave the adducts only in low yields.

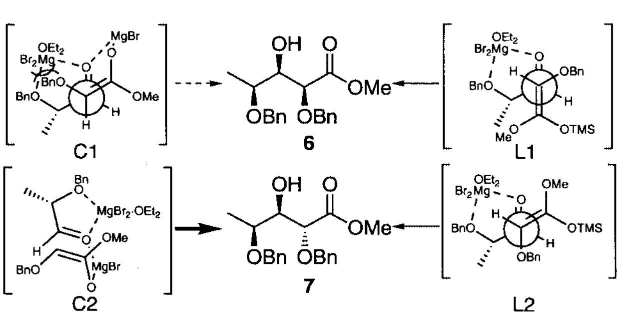

Figure 1.

The 2,3-*anti* selectivity was further examined with regard to the reaction using *Z* silyl enolate **1**[10] whose configuration was determined by NOE measurement. The results are listed in Table 2 and assembly of transition state models by using $MgBr_2 \cdot OEt_2$ are shown in Figure 1. The intermediates L1 and L2 are the open transition state models[11] activated by $MgBr_2 \cdot OEt_2$ whereas the intermediates C1 and C2 are the models organized by the concurrent effects of a) and b). When $MgBr_2 \cdot OEt_2$ worked only as a Lewis acid, it was not possible to differentiate the two transition states L1 and L2 which resulted in the formation of a mixture of two diastereo isomers **6** and **7**. That is, the reaction would have proceeded in parallel via L1 and L2, and the mixture of diastereomers **6** and **7** was formed without perfect preference. With respect to the C1 and C2, the latter should be dominant to C1 because of the steric hindrance of C1; thus, the diastereomer **7** should be obtained via C2. The result shown in Table 2 shows the ratio of the products **7** and **6** goes up to 98:1 indicating that the aldol reaction would procced via the transition state C2.

Magnesium halides mediated aldol reactions were reported by some groups[7] using the magnesium salts simply as Lewis acids. Among those reported examples, Corey et al. recently reported on the magnesium iodide mediated aldol reaction with interesting double-face selectivity in the total synthesis of lactacystin.[12] It is noted that, the results described here suggest a novel and efficient highly diastereoselective aldol reactions which are promoted by the double activation of aldehyde and silyl ethers with $MgBr_2 \cdot OEt_2$

This work was supported by Grant-in-aid for Scientific Research the Ministry of Education, Science, Sports and Culture.

References

1 W. H. Pearson and M. C. Cheng, *J. Org. Chem.*, **52**, 3176 (1987); T. Mukaiyama, H. Uchiro, I. Shiina, and S. Kobayashi, *Chem. Lett.*, **1990**, 1019; T. Mukaiyama, I. Shiina, and S. Kobayashi, *Chem. Lett.*, **1991**, 1901; D. A. Evans and S. L. Bender, *Tetrahedron Lett*, **27**, 799 (1986); T. K. Jones, S. G. Mills, R. A. Reamer, D. Askin, R. Desmond, R. P. Volante, and I. Shinkai, *J. Am. Chem. Soc.*, **111**, 1157 (1989).

2 I. Shiina, J. Shibata, Y. Imai, R. Ibuka, H. Fujisawa, I. Hachiya, and T. Mukaiyama, *Chem. Lett.*, **1999**, 1145.

3 $MgBr_2 \cdot OEt_2$ purchased from Aldrich Chemical Company, Inc. was used. (And other magnesium salts such as $MgBr_2$, $MgCl_2$, MgI_2, $Mg(OTf)_2$ and $Mg(ClO_4)_2$ failed to promote this reaction.)

4 I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, **18**, 181 (1985); M. Sodeoka, K. Ohrai, and M. Shibasaki, *J. Org. Chem.*, **60**, 2648 (1995).

5 G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4464 (1968).

6 The metyl group of the generated Me_3SiBr was detected, and disappearance of **1** was observed by ^{1}H NMR measurements. It was unable to observe directly the magnesium enolate formed from **1** probably because of aggregation of the formed magnesium enolate and their decomposition.

7 K. Takai and C. H. Heathcock, *J. Org. Chem.*, **50**, 3247 (1985); J. Uenishi, H. Tomozane, and M. Yamato, *Tetrahedron Lett*, **26**, 3467 (1985); A. Bernardi, S. Cardani, L. Colombo, G. Poli, G. Schimperna, and C. Scolastico, *J. Org. Chem.*, **52**, 888 (1987).

8 S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991); Y. Li, M. N. Paddon-Row, and K. N. Houk, *J. Org. Chem.*, **55**, 481 (1990).

9 M. M. Mader and J. C. Edel, *J. Org. Chem.*, **63**, 2761 (1998).

10 M. Terada, J. H. Gu, D. C. Deka, K. Mikami, and T. Nakai, *Chem. Lett.*, **1992**, 29.

11 C. H. Heathcock, S. K. Davidsen, K. T. Hug, and L. A. Flippin, *J. Org. Chem.*, **51**, 3027 (1986).

12 E. J. Corey, W. Li, and G. A. Reichard, *J. Am. Chem. Soc.*, **120**, 2330 (1998).