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

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High yield and excellent diastereoselectivity in the formation of methyl (2R,3R,5R,6S)-2,6-dibenzylxoy-5-(4-butylidemethylsiloxy)-3-hydroxy-5-(4-methoxybenzylxoy)-4,4-dimethylpentanoate 3 and methyl (2R,3R,4S)-2,4-dibenzylxoy-3-hydroxypentanoate 7 are achieved by aldol reaction between (Z)-2-benzylxoy-1-methoxy-1-(trimethylsiloxy)ethene 1 and chiral alkoxy aldehydes using three equivalents of MgBr₂·OEt₂. The following mechanism of the above aldol reaction proposes that MgBr₂·OEt₂ activated both chiral alkoxy aldehydes and silyl enolate, that is, magnesium enolate, formed by transmetallation from silyl enolate and MgBr₂·OEt₂, reacted with MgBr₂·OEt₂-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. Based on this method, stereoselective aldol reaction between 1, derived from methyl 2-benzylxoyacetate, and optically active trialkoxy aldehyde 2 was employed as a key step in preparing chiral polony ester 3, 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 MgBr₂·OEt₂-mediated aldol reaction. Here, we would like to describe a characteristic feature of MgBr₂·OEt₂-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 TiCl₄ or SnCl₄ 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 deactivate the Lewis acids. At the same time, silyl enolates bearing benzoxyl group at α-position decreased their nucleophilic ability in comparison with the reactivity of the enolates not bearing benzoxyl group. After screening various Lewis acids, it was interestingly found that the desired diastereomer was selectively formed by using MgBr₂·OEt₂. 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-anit,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 MgBr₂·OEt₂ caused to inhibit re face attack of the enolate, and thus the 3,5-anti isomer is expected to form selectively.

After careful optimization of reaction conditions, the best result (97%, 3:4=41:1) was obtained when reactions were carried out at -19 °C using MgBr₂·OEt₂ whose amount exceeded the combined quantity of aldehyde plus silyl enolate (Table 1, entry 2). The high reactivity and selectivity in the present experiment suggested that MgBr₂·OEt₂ 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 TiCl₄ and Bu₄NBF₄ were already known to be able to form the corresponding metal enolates by metal exchange with silyl enolate, this type of transmetallation with magnesium salts has not been reported to the best of our knowledge.

In order to examine the above mentioned transmetallation, silyl enolate 1 was treated with MgBr₂·OEt₂ in toluene-d₈ at room temperature and the formation of trimethylsilyl bromide was observed by ¹H NMR measurement. This indicated that the magnesium enolate was formed readily and it behaved as a nucleophile in the formation of aldos.

Further, there are two factors to achieve the excellent diastereoselectivity: that is, a) formyl face selectivity by the chelation control of MgBr₂·OEt₂, and b) stereoselectivity via the six membered cyclic transition state involving magnesium enolate. It was assumed that the high diastereoselectivity in the present aldol reaction using MgBr₂·OEt₂ would be performed by the concurrent effect of a) and b). By this combined effect, aldol reaction using MgBr₂·OEt₂ was expected to afford the aldos in higher yields and diastereoselectivity compared with the case obtained by using conventional Lewis acids or metal enolates.

To verify the above assumption, the double facial diastereoselectivity in the MgBr₂·OEt₂-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. Then, it was found that high yield and excellent diastereoselectivity were achieved only when

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>MgBr₂·OEt₂ (equiv)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Ratio 3:4</th>
<th>Recovered (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>6.0</td>
<td>30</td>
<td>94</td>
<td>2.3</td>
<td>41:1</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>45</td>
<td>95</td>
<td>2.3</td>
<td>41:1</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>70</td>
<td>79</td>
<td>2.8</td>
<td>28:1</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>70</td>
<td>54</td>
<td>2.3</td>
<td>24:1</td>
</tr>
</tbody>
</table>

*Isolated yields.
MgBr₂-ΟEt₂ was used. Lewis acidity was not the main factor to control the efficiency and selectivity of the present aldol reaction, since MgCl₂, Mg(Ott)₂, MgCl₂O₄, or Mg₂ did not promote effectively the aldol reaction as MgBr₂-ΟEt₂ did. In order to clarify the difference between MgBr₂-ΟEt₂ and other magnesium salts, silyl enolate 1 was treated with MgCl₂, MgCl₂O₄, Mg(Ott)₂, or Mg₂Cl₂ in benzene-d₆, at room temperature, and the formation of trimethylsilyl bromide was not observed in each case by ¹H NMR measurements. These results implied that the magnesium enolates were formed by transmetallation between 1 and magnesium salts except MgBr₂-ΟEt₂. That is, magnesium salts worked like common Lewis acids to activate only the aldehydes and not the silyl enolate except MgBr₂-ΟEt₂, and therefore, the aldol reaction gave the adducts only in low yields.

The 2,3-anti selectivity was further examined with regard to the reaction using Z silyl enolate 10 whose configuration was determined by NOE measurement. The results are listed in Table 2 and assembly of transition state models by using MgBr₂-ΟEt₂ are shown in Figure 1. The intermediates L1 and L2 are the open transition state models 11 activated by MgBr₂-ΟEt₂, whereas the intermediates C1 and C2 are the model organized by the concurrent effects of a) and b). When MgBr₂-ΟEt₂ 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 diastereoisomers 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 proceed via the transition state C2.

Magnesium halides mediated aldol reactions were reported by some groups7 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 lactacycin.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 MgBr₂-ΟEt₂.

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References
3. MgBr₂-ΟEt₂ purchased from Aldrich Chemical Company, Inc. was used. (And other magnesium salts such as MgCl₂, Mg₂Cl₂, Mg(Ott)₂ and MgCl₂O₄ failed to promote this reaction.)
6. The methyl group of the generated Me₂SiBr was detected, and disappearance of 1 was observed by ¹H 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.