Boron-Mediated Double Aldol Reaction of Carboxylic Esters

Atsushi Abiko,*[,†] Ji-Feng Liu,[‡] Dana C. Buske,[‡]
Satoshi Moriyama,[†] and Satoru Masamune*[,‡]

Venture Laboratory, Kyoto Institute of Technology
Matsugasaki, Sakyo-ku
Kyoto 606-8585, Japan
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts, 02139

Received April 30, 1999

Recently, we have found that carboxylic esters undergo boron-mediated aldol reactions.[1] Indeed, chiral propionate esters **1** and **2** achieve high stereoselectivities in the construction of *anti*- and *syn*-β-hydroxy-α-methyl carbonyl systems.[2,3] An extension of this investigation would naturally include an acetate aldol reaction utilizing a chiral ester. In our investigation, we have unexpectedly found that (i) an aldol reaction with an acetate ester, such as ester **3** (Figure 1), proceeds to provide bis-aldol products via a double aldol reaction and (ii) these products serve as the starting materials for the synthesis of chiral triols of C_3 symmetry, compounds which may prove highly valuable in asymmetric synthesis. Herein we summarize these unprecedented findings.

From our previous work with the propionate esters **1** and **2**, we had empirically determined that the reaction conditions necessary to provide mono-aldol product in high yield are the use of 2 equiv of dialkylboron triflate and 2.4 equiv of trialkylamine. However, the reaction of ester **3** under the same reaction conditions proceeded in an unusual manner to afford a substantial amount of unexpected bis-aldol products **5**, along with the expected mono-aldol product **4** (Scheme 1).

Efforts to optimize a variety of reaction parameters led to the establishment of conditions for almost exclusive formation of **5** (**4**:**5** $\leq$ 5:95). Treatment of **3**, under the conditions specified in Scheme 2 (i and ii), provided bis-aldol products in over 95% yield with a diastereomer ratio of **5a-A**:**5a-B**:**5a-C** = 90:8:2. The fourth possible isomer was not detected. Bis-aldol product **5a-A**, obtained as a pure crystalline compound, has been fully characterized by NMR as well as X-ray crystallography.[4] The structure of **5a-B**, isolated as a mixture with **5a-A**, was proved by reduction of the mixture of acetonides **6a-A** and **6a-B** (91:9) to produce a single alcohol **7a-A** with 82% ee. The third isomer was determined to be **5a-C** by NMR analysis of the corresponding acetonide **6a-C** (H5: δ 2.56, t, J = 2.7 Hz).

The double aldol reaction should proceed in a stepwise manner (Scheme 2) since mono-aldol **4a-A** was the major product when the reaction was maintained at −78 °C (**4a-A**:**4a-B** = 88:12). The auxiliary-controlled first aldol reaction produced two diastereomeric mono-aldolates whose stereochemistry corresponds to **4a-A** and **4a-B** at position 3. Since **4a-A** and **5a-A** (and also **4a-B** and **5a-B**) have the same configuration at position 3, each pair of compounds is derived from the intermediate mono-aldolate with the same configuration.[5] However, the mono-aldolates' structures (not the same as the dicyclohexylboron derivative of **4a**, see **14** in Scheme 5) are still unknown.

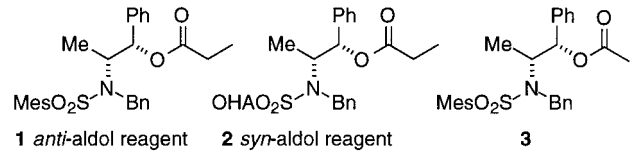
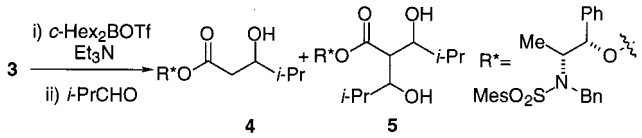
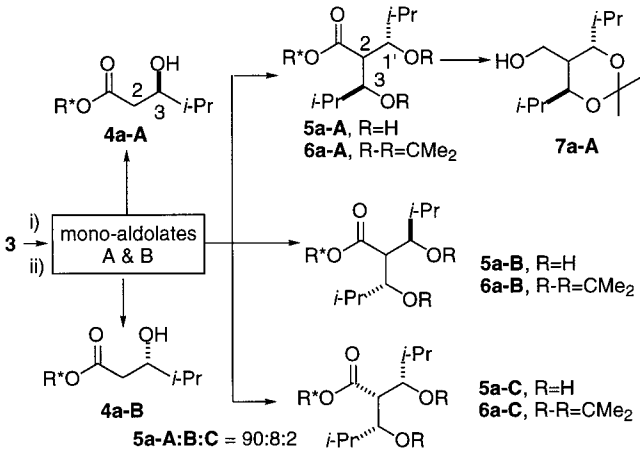


Figure 1. Carboxylic ester reagents.

Scheme 1

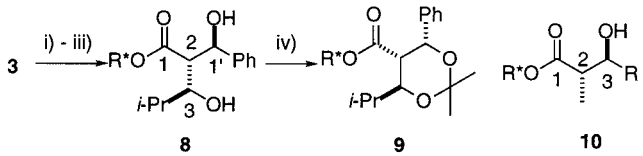


Scheme 2[a]



[a] Conditions: (i) *c*-Hex$_2$BOTf (2.5 equiv), Et$_3$N (3.0 equiv), −78 °C, 15 min; (ii) *i*-PrCHO (3.0 equiv), −78 °C, 10 min, then room temperature, 30 min, 95%. Note for nomenclature: 1, 2, 3, ... refers to structures; a, b, c, ... refers to aldehydes; A, B, C, ... refers to stereoisomers.

Scheme 3[a]



[a] Conditions: (i) *c*-Hex$_2$BOTf (2.5 equiv), Et$_3$N (3 equiv), −78 °C, 15 min; (ii) *i*-PrCHO (1.0 equiv) −78−0 °C, 10 min; (iii) PhCHO (1.5 equiv), 0 °C, room temperature, 30 min, 63%; (iv) Me$_2$C(OMe)$_2$, PPTS, 100%.

To elucidate the pathway of the second aldol reaction, the enolate of **3** was treated with two different aldehydes in a stepwise manner (Scheme 3). The stereochemistry of positions 2 and 1′ of the major product **8**, determined as its acetonide **9**, was proved to be the same as that of *anti*-aldol product **10** (obtained from an *E(O)*-enolate of propionate **1**) at positions 2 and 3. Thus, **8** (and also **5a-A**) must have been formed from an *E(O)*-enolate of the mono-aldolate, rather than a *Z(O)*-enolate.[5]

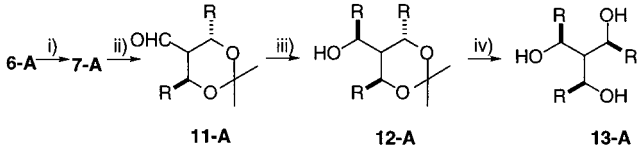
The utility of the bis-aldol products **5** has been demonstrated by the synthesis of chiral triols of C_3 symmetry (Scheme 4). Compounds of C_3 symmetry have attracted much attention as valuable ligands for asymmetric catalysts.[6] Among the class of

† Kyoto Institute of Technology.
‡ Massachusetts Institute of Technology.

(1) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590.
(2) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.
(3) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873.
(4) X-ray data in Supporting Information.
(5) **5a-C** is possibly produced from both diastereomers of the mono-aldolate. For a detailed discussion of the stereochemistry of the double aldol reaction and information to support a cyclic transition state involving an *E*(O)-enolate, see the Supporting Information.
(6) (a) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248. (b) Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139 and references therein.

10.1021/ja9914184 CCC: $18.00
Published on Web 07/14/1999

Scheme 4[a]



[a] **a**: R = *i*-Pr; **b**: R = Et; **c**: R = Ph. Conditions: (i) $LiAlH_4$, THF; (ii) PDC, CH_2Cl_2; (iii) RMgX, THF; (iv) TFA, MeOH. **a**: (i) 99%, (ii) 95%, (iii) 65%, 97:3 (**7a-A**, 35%), (iv) 96%; **b**: (i) 95%, (ii) 95%, (iii) 98%, >99:1, (iv) 93%; **c**: (i) 94%, (ii) 95%, (iii) 92%, 95:5, (iv) 99%.

chiral C_3 symmetric ligands, chiral triols have not been studied adequately, presumably because of the limited availability of these materials.[7] Starting with the two preexisting stereocenters (positions 3 and 1′) in **5-A**, introduction of a third carbinol at position 1 produces the chiral C_3 symmetric triols (**13-A**s). Thus, alcohol **7-A**[8] was oxidized to aldehyde **11-A** by PDC.[9] Stereoselective introduction of the third substituent via a Grignard reaction gave alcohol **12-A**, with >95:5 selectivity.[10] Acidic hydrolysis of the acetonide group in **12-A** provided the chiral C_3 symmetric triols **13-A**. The existence of C_3 symmetry in **13-A** was easily ascertained by ^1H and ^{13}C NMR analyses.

Finally, we should emphasize unique features of the boron-mediated aldol reaction of carboxylic esters and the unusual behavior of the boron-containing intermediate.

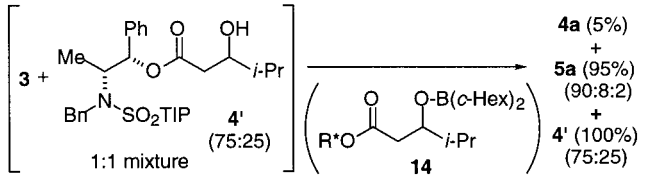
(1) While double aldol reactions proceed with an acetate ester as the enolate source, this double aldol reaction does *not* occur with other carbonyl compounds such as methyl ketones, acetate thioesters, and propionate esters, exemplified by **1** and **2**.

(2) When acetate ester **3** was enolized with *less* than 2 equiv of dialkylboron triflate, both bis-aldol products **5** and recovered starting material were obtained. Therefore, the formation of bis-aldol products is not solely due to the ratio of the excess dialkylboron triflate to ester.

(3) When the enolate of *ent*-**3** (enantiomer of **3**, 1 equiv), prepared with *c*-Hex_2BOTf (2 equiv) and Et_3N (2.5 equiv), was mixed with *S*-phenyl thioacetate (1 equiv), no enolization of *S*-phenyl thioacetate occurred. This result is in contrast to the same experiment with acetophenone in place of *ent*-**3**, in which the aldol product of the thioester was obtained in ~50% yield. Thus, the ester *ent*-**3** somehow renders the second equivalent of *c*-Hex_2BOTf unreactive. Indeed, 2 equiv of boron triflate are necessary for the ester aldol reaction, since the extent of enolization of ester *ent*-**3** with 1.0 and 1.5 equiv of boron triflate was 47 and 73%, respectively. These results demonstrate that the stoichiometry of the enolization of the carboxylic ester with boron triflate is 1:2. The "second equivalent of boron triflate" is neither free boron triflate nor an equilibrium form of boron triflate. These findings were totally unexpected!

(4) Subjection of an equimolar mixture of **3** and **4′** (ds = 75:25) under the optimized double aldol reaction conditions afforded **5a**s in the same ratio as shown in Scheme 2, while **4′** was recovered unchanged, quantitatively (Scheme 5).[11] This result

Scheme 5



implies that **14**, the dicyclohexylboron derivative of **4′** (and also that of **4a**), is not a precursor of the double aldol reaction and thus is clearly distinct from the mono-aldolate species in Scheme 2.[12]

It is now a distinct possibility that two kinds of boron species are involved in the boron-mediated aldol reaction of carbonyl compounds. The first boron species exists with ketones and thioesters and leads to the single aldol reaction, since boron can only chelate with the carbonyl group to form a 1:1 complex. The second boron species[13] exists with acetate esters, in which coordination to the extra oxygen atom forms a 2:1 complex which leads to the double aldol reaction. We are currently investigating the structure of this boron−ester complex.[14]

In conclusion, we have discovered the unprecedented double aldol reaction of acetate esters and have identified unique features of the enolization of carboxylic esters with boron triflate and amine. The bis-aldol products obtained were utilized in the synthesis of chiral C_3 symmetric triols. Further studies on the application of these C_3 triols as chiral ligands are in progress in our laboratories.

Acknowledgment. A.A. was supported by a grant from the Ministry of Education, Science, Sports and Culture of Japan (Grant-in-Aid 10640578). S.M. was supported by a grant from NIH (CA48175). D.C.B. was supported in part by a National Cancer Institute training grant (CA09112) and a fellowship from Boehringer-Ingelheim Pharmaceuticals, Inc. We are grateful to Dr. W. M. Davis for assistance in obtaining the X-ray structure of **5a-A**.

Supporting Information Available: Further discussion regarding the transition state and stereoselectivity of the double aldol reaction, experimental procedures, and spectral data for all compounds, and X-ray structural information for **5a-A** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9914184

(7) Lütjens, H.; Wahl, G.; Möller, F.; Knochel, P.; Sundermeyer, J. *Organometallics* **1997**, *16*, 5869.

(8) The reaction with EtCHO produced **5b-A**:**5b-B**:**5b-C** = 89:3:8 in 95% yield, from which **5b-A** of 94% de was obtained by chromatography. In the subsequent step, diastereomerically pure acetonide **6b-A** was isolated by recrystallization. The reaction with PhCHO produced **5c-A**:**5c-B**:**5c-C** = 85:1:14 in 97% yield, from which **5c-A** was isolated by recrystallization. For characterization and determination of the absolute stereochemistry of **5b-A** and **5c-A**, see the Supporting Information.

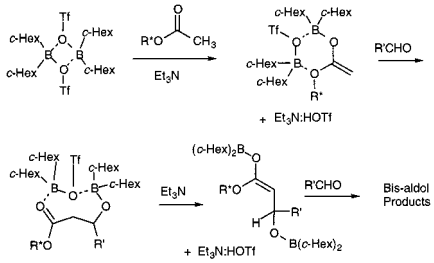
(9) For oxidation of **7c-A**, pyridinium chlorochromate was used instead of pyridinium dichromate.

(10) With *i*-PrMgCl, reduction product **7a-A** was obtained in 35% yield.

(11) Compare with: Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

(12) Only this mono-aldolate species is responsible for the double aldol reaction. This species seems to be rather labile and readily decomposed, thus allowing for the formation of mono-aldol products. Indeed, when the aldehyde was added rapidly, a significant amount of the mono-aldol product **4** was formed.

(13) The oligomeric form of boron triflate, with a dimeric diboradioxetane structure, may be responsible for the enolization of carboxylic esters. See, Ooi, T.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 8105.



(14) It is not clear that the boron species described in ref 13 is incorporated in the aldol reaction of propionate esters in general. The failure of the double aldol reaction for propionate ester **1** and **2** very likely be attributed to the steric reason.