

Reaction of Titanate-Type Aldehyde Enolate with Ketones To Provide 3-Hydroxyaldehydes

Kentaro Yachi, Hiroshi Shinokubo, and Koichiro Oshima*

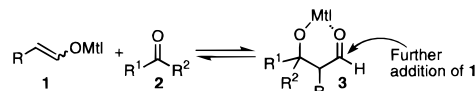
Department of Material Chemistry
Graduate School of Engineering, Kyoto University
Sakyo-ku, Yoshida, Kyoto 606-8501, Japan

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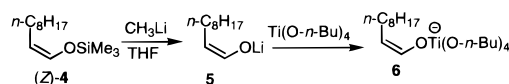
The aldol-type reaction is a classic organic reaction and one of the most versatile synthetic tools for carbon–carbon bond formation; it is, therefore, widely used in organic synthesis.¹ Many types of highly stereo- and enantioselective aldol-type reactions have been developed. However, most of them involve reaction between the carbonyl compounds and the enolates derived from a ketone, ester, or amide. Only a few reports have been published on the cross-aldol reaction between an aldehyde enolate (RCH=CHO⁻, **1**) and another aldehyde, **2** (R² = H), to provide a 3-hydroxyaldehyde **3**,² although the term “aldol” (i.e., aldehyde alcohol) originally meant hydroxyaldehyde. Moreover, very little is known about the aldol reaction of an aldehyde enolate with a ketone (R¹, R² ≠ H). Formation of a hydroxyaldehyde from an aldehyde enolate **1** with a ketone is a thermodynamically very unfavorable process in comparison with the reaction of a ketone enolate with an aldehyde.³ In the former case, a proton abstraction from the ketone by the aldehyde enolate to provide the ketone enolate could be a troublesome problem. Additionally, the aldehyde moiety of the product **3** seemed to be more reactive than the starting ketone **2**, and it should provide a complex mixture derived from further addition of an enolate **1** to aldol adduct **3** (Scheme 1). The choice of metal for the aldehyde enolate and its ligands could be essential for the successful cross-aldol reaction of aldehyde enolate. Herein, we disclose the cross-aldol reaction of aldehyde enolate with an aldehyde or ketone using an organotitanium reagent.⁴

We examined the effect of titanium alkoxide on lithium enolate **5**, which was derived from silyl enolate (*Z*)-**4** (*Z/E* = >99/<1).⁵ Treatment of **4** with methyllithium in THF provided **5**, which was further converted into titanium ate-complex **6** (Scheme 2).^{6–8} Addition of 2-methylpropanal afforded the expected aldol adduct

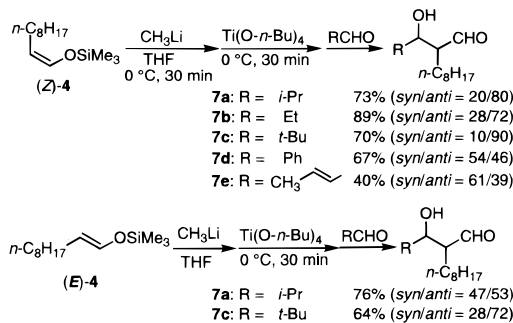
Scheme 1



Scheme 2



Scheme 3



7a in 73% yield without any byproducts after aqueous workup. Without titanium alkoxide, the reaction of **5** with 2-methylpropanal afforded a complex mixture containing a trace amount of **7a**. Therefore, addition of Ti(O-*n*-Bu)₄ dramatically improved the yield of the adduct. The use of (*E*)-**4** (*Z/E* = <1/>99) provided **7a** in almost the same yield, while the stereoselectivity was lowered. The use of Ti(O-*i*-Pr)₄ was less effective than Ti(O-*n*-Bu)₄, and the yield of **7a** was somewhat decreased (62%).⁹ The results of this cross-aldol reaction using titanium alkoxide are summarized in Scheme 3.

Next, we focused on the aldol reaction of various aldehyde enolates with ketones. The representative results of the reaction with titanate enolates **6**, **8**, and **9** are summarized in Table 1.^{10,11} A unique steric effect was observed in the reaction of enolate **6** with ketones.¹² Ethyl methyl ketone and cycloheptanone did not give any adducts, and decanal was recovered in both cases (entries

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(3) Ab initio calculation (RHF/6-31G) showed that the formation of 3-hydroxyaldehyde ((CH₃)₂C(OH)CH₂CHO) from acetone and acetaldehyde is far more unfavorable than that of 3-hydroxyketone (CH₃CH(OH)CH₂COCH₃). The formation energy of the latter is -10.455 kcal/mol, whereas that of the former is 21.155 kcal/mol.

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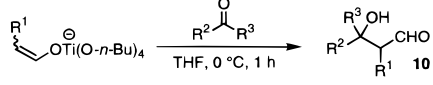
(8) Trapping experiment of titanium enolate **6** prepared from (*Z*)-**4** with Me₃SiCl afforded the starting silyl enolate (*Z*)-**4** (*Z/E* = >99/<1) in quantitative yield. From this result, no isomerization of enolates **5** and **6** occurred during the transmetalation step.

(9) The use of ClTi(O-*n*-Bu)₃ in place of Ti(O-*n*-Bu)₄ was not effective, and **7a** was obtained in reduced yield (47%, *syn/anti* = 70/30) upon treatment with 2-methylpropanal.

(10) The reaction of titanate enolate prepared from 2-ethyl-1-trimethylsilyloxy-1-butene with ketones provided no aldol adduct.

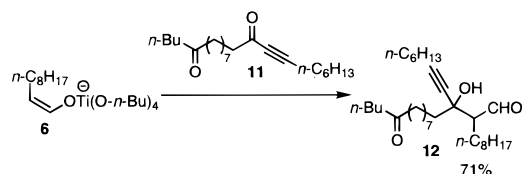
(11) In the absence of Ti(O-*n*-Bu)₄, no trace of **10** could be observed in the reaction mixture, and complex products were formed.

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Table 1. Cross-Aldol Reaction of Aldehyde Enolates with Ketones


entry	enolate R ¹	ketone		yield (%)	isomeric ratio
		R ²	R ³		
1	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	CH ₃	CH ₃	53	
2	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	Et	CH ₃	nr ^a	
3	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	-(CH ₂) ₅ -		56	
4	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	-(CH ₂) ₆ -		nr ^a	
5	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	-(CH ₂) ₄ -		35	
6	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	-(CH ₂) ₃ -		91	
7	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	HC≡C-	CH ₃	85	59/41 ^b
8	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	PhC≡C-	CH ₃	86	52/48 ^b
9	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	<i>n</i> -BuC≡C-	CH ₃	81	55/45 ^b
10	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	Me ₃ SiC≡C-	<i>n</i> -C ₇ H ₁₅	74	51/49 ^b
11	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	CH ₂ Cl	CH ₂ Cl	91	
12	<i>n</i> -C ₈ H ₁₇ ((<i>Z</i>)- 6)	CCl ₃	CH ₃	72	>99/1 ^c
13	<i>n</i> -C ₈ H ₁₇ ((<i>E</i>)- 6)	CCl ₃	CH ₃	75	>99/1 ^c
14	H (8)	CH ₃	CH ₃	34	
15	H (8)	-(CH ₂) ₃ -		75	
16	H (8)	CH ₂ Cl	CH ₂ Cl	95	
17	H (8)	HC≡C-	CH ₃	52	
18	CH ₂ =CH- (9) ^d	CH ₂ Cl	CH ₂ Cl	67	

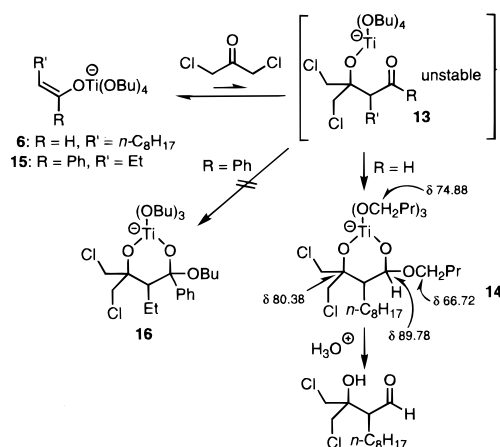
^a No reaction. Decanal was quantitatively recovered after aqueous workup. ^b The stereochemistry of the adduct is not determined. ^c *Anti*/*syn*. ^d *Z/E* = 87/13.

Scheme 4

2 and 4), although the steric bulkiness of ethyl methyl ketone or cycloheptanone seems to be not so large as that of acetone or cyclohexanone. The use of alkynes provided the corresponding hydroxyaldehydes in good yields. Cyclobutanone or α -halogenated ketones were also very reactive, affording the adducts in good yields. In the case of 1,1,1-trichloroacetone, the *anti* isomer was exclusively obtained regardless of geometry of enolate **6** (entries 12 and 13).¹³ The abstraction of an acetylenic proton of 3-butyne-2-one with this titanium enolate did not occur. Thus, the basicity of the titanate enolate might not be so strong. The titanate dienolate **9** prepared from 1-trimethylsiloxy-1,3-butadiene reacted with 1,3-dichloroacetone at the 2-position exclusively, and no adduct derived from the attack at the 4-position was obtained (entry 18). It is worth noting that a chemoselective addition of the enolate **6** to the acetylenic ketone moiety was achieved in the reaction with diketone **11** (Scheme 4).

We are tempted to assume the following reaction mechanism for this cross-aldol reaction of aldehyde enolate (Scheme 5). The

(13) This stereochemical outcome might indicate that this reaction proceeds under thermodynamic control.

Scheme 5

initial adduct **13** might be unstable since the titanate species should have little ability to form a chelated intermediate. Therefore, the adduct **13** might collapse easily to enolate and ketone by retro-aldol reaction, and the formation of the adduct at equilibrium would be unfavorable. However, migratory addition of butoxide on the titanium to the aldehyde moiety in **13** to form a cyclic titanate, **14**, would shift the equilibrium to the product. Additionally, the aldehyde moiety could be temporarily protected from a further attack of enolate.^{14,15} The formation of **14** was ascertained by ¹³C NMR examination. No signal assigned to the carbonyl carbon of **13** could be detected. It was anticipated that migration of butoxy group to **16** would not take place in the reaction of ketone enolate (*R* ≠ H) because of its steric hindrance. In fact, the reaction of the titanate-type ketone enolate **15** provided no aldol adduct, and phenyl propyl ketone was quantitatively recovered. The use of titanium enolate (*n*-C₈H₁₇CH=CHOTi(OBu)₃) derived from **5** and ClTi(OBu)₃ instead of **6** afforded the aldol adduct in decreased yield (52%), along with some unidentified byproducts. Therefore, it seems to be important for a smooth migration of butoxide to carbonyl to use titanate species. This is the first example of the reaction between a ketone and an aldehyde enolate to our best knowledge. Further efforts to improve the stereoselectivity and to extend the scope of this reaction are currently underway.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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