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A highly effective aldol reaction mediated by $Ti(O\text{-}n\text{-}Bu)_4/t\text{-}BuOK$ combined reagent

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Abstract

A combined reagent derived from $Ti(O\text{-}n\text{-}Bu)_4$ and KO-*t*-Bu (1:1) has proved to be very effective for the self-aldol addition and also for the cross-aldol condensation between aldehyde and α,β-unsaturated aldehyde such as 2-alkenal or 2-alkynal. © 2000 Elsevier Science Ltd. All rights reserved.

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The aldol addition is a classic organic reaction and a versatile synthetic tool for carbon–carbon bond formation.[1] Since the aldol-type condensation reaction was first discovered by Wurtz from the acid-catalyzed self-condensation reaction of acetaldehyde, much attention has been paid to perfecting this reaction either in yield or in selectivity.[2] Many successful examples using transition metal enolates as well as main group metal enolates have been reported in the recent literature.[3] However, the aldol addition still has some drawbacks which have to be solved. Under either basic or acidic conditions, the problems incurred in the aldol reactions are: (1) the further side reactions of the aldol-type product with enolate; (2) the elimination of the hydroxy group resulting in the formation of α,β-unsaturated aldehyde which further gives side-reactions such as 1,4-Michael addition;[4] and (3) Tishchenko side-reaction.[5] Thus, there is a need for developing a new simple procedure by which β-hydroxy aldehyde can be synthesized directly from aldehyde in high yield.

Recently, we found that the addition of $Ti(O\text{-}n\text{-}Bu)_4$ to lithium enolate, derived from silyl enolate ($RCH{=}CHOSiMe_3$) and methyllithium, dramatically improved the yields of β-hydroxyaldehyde in the cross-aldol reactions.[6] Then it occurred to us that the use of a combination of a base and $Ti(O\text{-}n\text{-}Bu)_4$ in the self-aldol reaction would provide aldehyde alcohol (aldol adduct) effectively. This was indeed the case, and treatment of aldehyde with a $Ti(O\text{-}n\text{-}Bu)_4/t\text{-}BuOK$[7,8] reagent afforded the corresponding aldol product in excellent yield. For instance, heptanal (**1a**,

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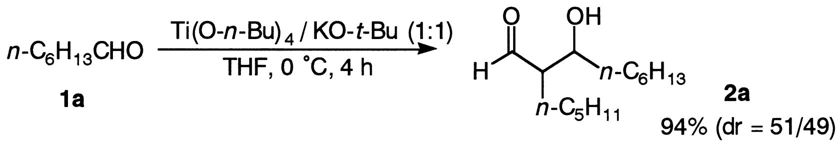
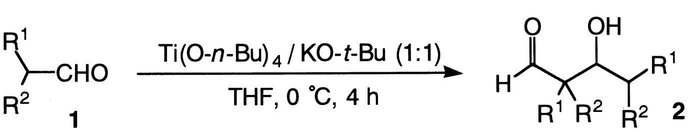
2.0 mmol) gave 3-hydroxy-2-pentylnonanal (**2a**) in 94% yield upon treatment with a mixture of Ti(O-*n*-Bu)$_4$ (2.0 mmol) and *t*-BuOK (2.0 mmol) in THF at 0°C for 4 h (Scheme 1).[9] Other representative results are shown in Table 1.



Scheme 1.

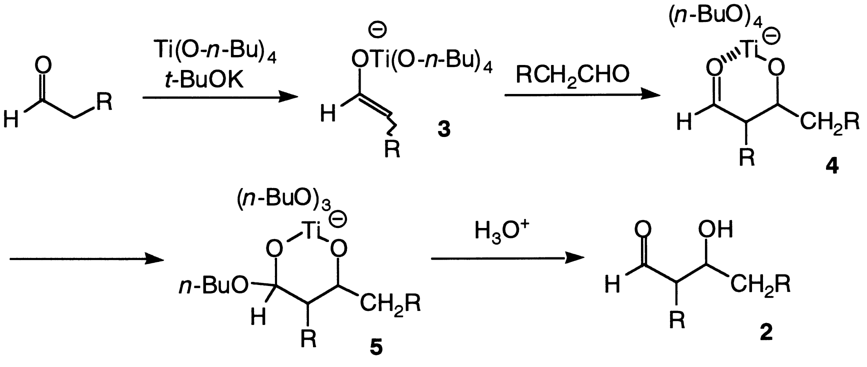
Table 1
Ti(O-*n*-Bu)$_4$/KO-*t*-Bu-induced self-aldol addition



entry		R^1	R^2	product	yield (dr)[a]
1	**1b**	n-C_3H_7	H	**2b**	97% (50/50)
2	**1c**	n-C_8H_{17}	H	**2c**	99% (50/50)
3	**1d**	$(CH_3)_2CH$	H	**2d**	85% (80/20)
4	**1e**	$PhCH_2$	H	**2e**	96% (50/50)
5	**1f**	CH_3	CH_3	**2f**	87%[b]

a The yield and dr(diastereomer ratio) were determined by ^1H NMR .
b The reaction time is 8 h .

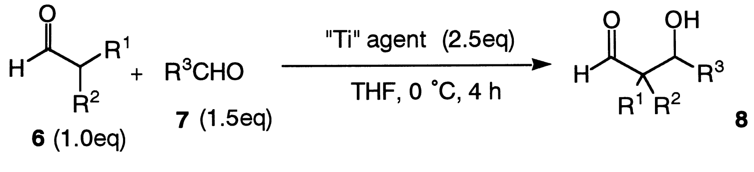
In general, base-catalyzed self-addition of aldehydes to form β-hydroxy aldehyde is successful under mild conditions, but only with relatively low molecular weight aldehydes. However, not only pentanal but also heptanal and decanal provided the self-addition adducts in excellent yields without contamination by α,β-unsaturated aldehydes by means of this new Ti(O-*n*-Bu)$_4$/*t*-BuOK system. The molar ratio of Ti(O-*n*-Bu)$_4$/*t*-BuOK played a critical role for the successful reaction. The use of the reagent generated from Ti(O-*n*-Bu)$_4$/*t*-BuOK = 2/1 afforded no aldol adducts in the reaction of **1a**. The yield of **2a** dropped to 60% and unidentified complex compounds were obtained as by-products with the reagent (Ti(O-*n*-Bu)$_4$/*t*-BuOK = 1/2). The reaction mechanism might be as follows. The combined base Ti$^-$(O-*n*-Bu)$_4$(O-*t*-Bu)K$^+$ abstracts α-hydrogen of the aldehyde to give titanium enolate **3**. An addition of this enolate to a second molecule of the aldehyde would afford adduct **4**. The excellent yield of β-hydroxy aldehyde could be attributed to the stabilization of the cyclic chelated intermediate **5** which could be formed through the migratory addition of *n*-butoxide on the titanium to the aldehyde moiety of aldol product **4** as in the previous reaction between aldehyde silyl enolate and other aldehydes (Scheme 2).



Scheme 2.

Then, the cross-aldol addition reactions between two different aldehydes were examined. The aldehydes, such as benzaldehyde (entries 1–3 in Table 2), cinnamaldehyde (entries 4 and 5), and 2-octynal (entries 6–11) which do not have an acidic α-hydrogen were used as the second component. For example, treatment of a mixture of hexanal (1.0 mmol) and 2-octynal (1.5 mmol) with a mixture of Ti(O-*n*-Bu)$_4$ (2.5 mmol) and *t*-BuOK (2.5 mmol) in THF at 0°C for 4 h gave **8g** in 91% yield. The results are summarized in Table 2.[10]

Table 2
Ti(O-*n*-Bu)$_4$/*t*-BuOK-induced cross-aldol reaction



Entry	R^1	R^2	R^3	Product	Yield(dr)^a
1	*n*-C$_3$H$_7$	H	Ph	**8a**	97%(57/43)
2	*n*-C$_5$H$_{11}$	H	Ph	**8b**	97%(56/44)
3	*n*-C$_8$H$_{17}$	H	Ph	**8c**	99%(62/38)
4	*n*-C$_3$H$_7$	H	PhCH=CH-	**8d**	86%(55/45)
5	*n*-C$_5$H$_{11}$	H	PhCH=CH-	**8e**	81%(50/50)
6	*n*-C$_3$H$_7$	H	*n*-C$_5$H$_{11}$C≡C-	**8f**	93%(54/46)
7	*n*-C$_5$H$_{11}$	H	*n*-C$_5$H$_{11}$C≡C-	**8g**	91%(50/50)
8	*n*-C$_8$H$_{17}$	H	*n*-C$_5$H$_{11}$C≡C-	**8h**	90%(50/50)
9	(CH$_3$)$_2$CH	H	*n*-C$_5$H$_{11}$C≡C-	**8i**	89%(53/47)
10	PhCH$_2$	H	*n*-C$_5$H$_{11}$C≡C-	**8j**	99%(51/49)
11	CH$_3$	CH$_3$	*n*-C$_5$H$_{11}$C≡C-	**8k**	99%

a The yields and diastereomer ratios were determined by NMR.
The products were purified through silica gel column chromatography.

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7. Synthesis of α,β-unsaturated carbonyl compounds by titanium tetraalkoxide ($Ti(O\text{-}i\text{-}Pr)_4$ or $Ti(O\text{-}n\text{-}Bu)_4$) induced aldol condensation has been reported. See: Mahrwald, R.; Schick, H. *Synthesis* **1990**, 592–594.
8. The combination of $Ti(O\text{-}i\text{-}Pr)_4/t\text{-}BuOK$ gave almost the same yields of aldol adducts as $Ti(O\text{-}n\text{-}Bu)_4/t\text{-}BuOK$. The use of $Al(O\text{-}i\text{-}Pr)_3$ in place of $Ti(O\text{-}n\text{-}Bu)_4$ resulted in 80% recovery of heptanal along with an unidentified complex mixture. The reaction of heptanal with a combined system ($Ti(O\text{-}n\text{-}Bu)_4/LDA$) afforded the aldol adduct in only 50% yield.
9. The general experimental procedure is exemplified by the reaction of heptanal: $Ti(O\text{-}n\text{-}Bu)_4$ (0.680 g, 2.0 mmol) and KO-*t*-Bu (0.224 g, 2.0 mmol) were dissolved in 5 ml of dry THF under argon at room temperature. After being stirred for 10 min the solution turned clear. Then the solution was cooled to 0°C and heptanal (0.228 g, 2.0 mmol) was added and the resulting mixture was stirred for 4 h at 0°C. Then, the reaction mixture was worked up by quenching with 1N HCl aqueous solution and the aqueous layer was extracted three times with ethyl acetate:hexane (1:3). The combined organic layers were washed with brine, dried and filtered with Na_2SO_4, concentrated in vacuo affording product **1** in 94% yield after silica-gel column purification.
10. The cross-aldol reaction between aldehyde and 2-alkynal could not give a satisfactory result under ordinary conditions because of the high reactivity of 2-alkynal and its aldol adduct. In fact, treatment of a mixture of heptanal and 2-octynal with *t*-BuOK alone in THF at 0°C provided a complex mixture. Thus, titanium alkoxide could play a critical role for the successful reaction.