Enolate Formation from α-Iodoaldehydes and α-Iodoketones by Means of Allylsilane−Titanium Tetrachloride and Its Application to an Aldol Reaction

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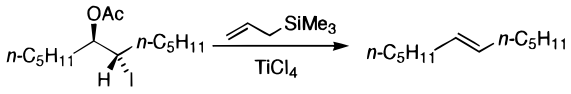
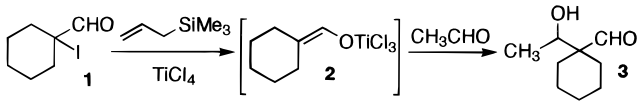
The renaissance that has occurred in the study of the aldol-type reaction in the last two decades has been mainly due to the development of methods for the formation and use of preformed enolates.[1] Despite extensive work on the aldol-type reaction between the various metal enolates, derived from ketones, esters, or amides, and aldehydes, only a few reports have been published on the cross-aldol reaction between enolates generated from an aldehyde (R^1CH_2CHO) and another aldehyde (R^2CHO).[2] Mixed aldol reactions between two different aldehydes generally give mixtures when each aldehyde can function both as an enolate precursor and electrophilic component.[3] Another problem encountered in mixed aldol reactions is a formation of a complex mixture derived from further reaction of the aldol adduct ($R^2CH(OH)CHR^1CHO$) with the enolate ($R^1CH{=}C(H)O^-$). To solve these problems, it is desirable to have a facile route to enolates from aldehydes under mild reaction conditions.

Recently, we have reported that treatment of vicinal methoxyiodoalkanes or acetoxyiodoalkanes with an allylsilane−titanium tetrachloride system provided alkenes stereospecifically (Scheme 1).[4] The elimination of iodide and the methoxy or acetoxy groups proceeded in anti fashion. The coordination of oxygen of the methoxy or acetoxy group to titanium tetrachloride would facilitate the attack of allyltrimethylsilane on the iodine atom. It then occurred to us that, if α-iodoaldehyde[5] should behave as vicinal methoxyiodoalkanes, treatment of α-iodocarbonyl compounds with an allylsilane−titanium tetrachloride system would provide an expeditious route to titanium enolates.[6] We have indeed found that sequential treatment of a solution of α-iodoaldehydes and allyltrimethylsilane with titanium tetrachloride and acetaldehyde provided β-hydroxy aldehydes[7] in good yields (Scheme 2).

Scheme 1



Scheme 2



We examined the reaction of 1-iodocyclohexanecarbaldehyde (**1**) with acetaldehyde with several Lewis acids such as $TiCl_4$, Cp_2TiCl_2, $(i\text{-PrO})_2TiCl_2$, $TiCl_3$, $ZrCl_4$, $SnCl_4$, $AlCl_3$, BCl_3, and $La(OTf)_3$ in combination with allyltrimethylsilane. Among them, only titanium tetrachloride gave an aldol adduct, 1-(1-hydroxyethyl)cyclohexanecarbaldehyde (**3**) in good yield via titanium enolate **2**. The representative results are summarized in Table 1.

It was expected that allylation of the aldehyde moiety would compete with trichlorotitanium enolate formation upon treatment of a less hindered α-iodoaldehyde such as 2-iododecanal (**6**) with allyltrimethylsilane−$TiCl_4$. In fact, treatment of **6** with allyltrimethylsilane−$TiCl_4$ followed by quenching with methanol provided a mixture of decanal (**7**) and 4-hydroxy-5-iodo-1-tridecene (**8**) (Scheme 3). To optimize the conditions for enolate formation, the reaction was performed under several reaction conditions in which the solvent and temperature were varied. For example, an addition of $TiCl_4$ (1.0 mmol) to a solution of **6** (1.0 mmol) and allyltrimethylsilane (2.0 mmol) in toluene at −78 °C provided a mixture of decanal (**7**, 44%) and **8** (17%). In contrast, use of dichloromethane as a solvent at −78 °C has proved to be the best condition to give decanal in 80% yield along with a trace amount of **8**.

The allylation of the aldol adduct also could compete with enolate formation and cause a problem in that the

(1) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.4, pp 99−131. Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.6, pp 181−238. Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.7, pp 239−275. Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.8 pp 277−299. Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.9, pp 301−319.

(2) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.5, pp 133−179. Heathcock, C. H. *Modern Synthetic Methods*; Sheffold, R., Ed.; Springer-Verlag: Berlin, 1992; p 1; Heathcock, C. H. *Aldrichmica Acta* **1990**, *23*, 99. Very recently, aldol reaction between two different aldehydes in the presence of $TiCl_4$ and a base has been reported. Mahrwald, R.; Costisella, B.; Grü ndogan, B. *Tetrahedron Lett.* **1997**, *38*, 4543. This method, however, could be applied only to the synthesis of 3-hydroxyaldehydes following Lieben's rule.[3]

(3) Lieben, A. *Monatsh. Chem.* **1901**, *22*, 289.

(4) Yachi, K.; Maeda, K.; Shinokubo, H.; Oshima, K. Tetrahedron Lett. **1997**, *38*, 5161. Maeda, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1997**, *62*, 6429.

(5) α-Iodoaldehydes were prepared from silyl enolates of the corresponding aldehydes with I_2 and aqueous $NaHCO_3$ in ether. Details are available in the Supporting Information section.

(6) (a) Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343. (c) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4134. (d) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211. (e) Morris, J.; Wishka, D. G.; Luke, G. P.; Judge, T. M.; Gammill, R. B. *Tetrahedron* **1997**, *53*, 11211. (f) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (g) Toshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727. (h) Baker, R. K.; Rupprecht, K. M.; Armistead, D. M.; Boger, J.; Frankshun, R. A.; Hodges, P. J.; Hoogsteen, K.; Pisano, J. M.; Witzel, B. E. *Tetrahedron Lett.* **1998**, *39*, 229. (i) Mahrwald, R.; Gündogan, B. *J. Am. Chem. Soc.* **1998**, *120*, 413. (j) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

(7) For synthesis of β-hydroxyaldehyde by other methods, see (a) Reduction of β-hydroxyamide: Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1903. (b) Enzymatic method: Bianchi, D.; Cesti, P.; Golini, P. *Tetrahedron* **1982**, *45*, 869.

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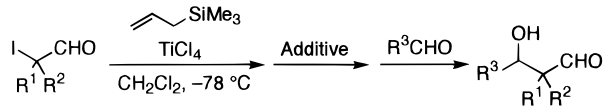
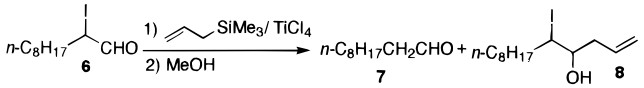
Table 1. Aldol Reaction of Trichlorotitanium Enolates Derived from α-Iodoaldehydes



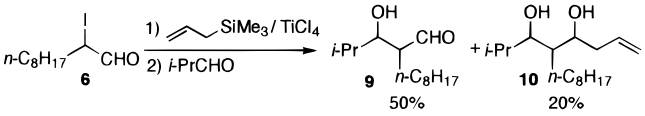
entry	α-iodoaldehyde R¹	α-iodoaldehyde R²		aldehyde R³	additive	reaction temp. time	adduct yield(%)
1	−(CH₂)₅−		**1**	Et	−	−78 °C 1 h	85
2			**1**	*i*-Pr	−	0 °C 1 h	87
3			**1**	Ph	−	0 °C 1 h	75
4	Et	Et	**4**	*i*-Pr	−	0 °C 1 h	75
5	*n*-C_9H_{19}	Me	**5**	*i*-Pr	−	0 °C 1 h	79[a]
6	*n*-C_8H_{17}	H	**6**	*i*-Pr	−	−78 °C 1 h	50[b]
7			**6**	*i*-Pr	Ti(O-*n*-Bu)₄	−78 °C 1 h	68[c]
8			**6**	Et	Ti(O-*n*-Bu)₄	−78 °C 1 h	55[d]
9			**6**	*n*-$C_3H_7CH{=}CH$	Ti(O-*n*-Bu)₄	−78 °C 1 h	44[e]

[a] Isomeric ratio = 75/25. [b] syn/anti = 50/50. [c] syn/anti = 64/36. [d] syn/anti = 80/20. [e] syn/anti = 90/10.

Scheme 3



Scheme 4



aldol adduct is not obtained as a single product. Thus, treatment of 2-iododecanal **6** with allylsilane−$TiCl_4$ in dichloromethane followed by an addition of 2-methylpropanal afforded 3,5-dihydroxy-2-methyl-4-octyl-7-octene (**10**) in 20% yield along with the desired aldol adduct (**9**, 50%, Scheme 4). The formation of **10** could be suppressed by an addition of titanium tetrabutoxide[8] (equimolar amount for $TiCl_4$) prior to an addition of 2-methylpropanal to provide **9** (syn/anti = 64/36) in 68% yield without contamination by **10** (Table 1, entry 7). The addition of Ti(O-*n*-Bu)₄ was also effective in the case of other aldehydes (Table 1, entries 8 and 9). In contrast, in the case of α,α-dialkyl substituted α-iodoacetaldehydes (**1**, **4**, and **5**, entries 1−5), the addition of titanium tetrabutoxide was not required since aldol adducts were obtained in good yields without contamination by further allylated products.

Then we applied our new method to the aldol-type reaction between an enolate from α-iodoketone and carbonyl compounds.[9,10] The use of α-iodoketones instead of α-iodoaldehydes gave the corresponding *β*-hydroxy ketones in good yields. The results are shown in Table 2.

The formation of trichlorotitanium enolate was ascertained by the examination of the ^1H NMR spectrum of a $CDCl_3$ solution of 3-iodo-4-heptanone, allyltrimethylsilane, and $TiCl_4$. ((*E*/*Z* = 13/87), *δ* 0.96 (t, *J* = 7.4 Hz, 2.61H), 0.97 (t, *J* = 7.1 Hz, 0.39H), 1.04 (t, *J* = 7.5 Hz, 3H), 1.27 (tq, *J* = 7.2, 7.5 Hz, 2H), 2.04 (dq, *J* = 7.8, 7.1 Hz, 0.26H), 2.27−2.41 (m, 3.74H), 4.85 (t, *J* = 7.4 Hz, 0.87H), 5.57 (t, *J* = 7.8 Hz, 0.13H)). The spectrum data was almost identical with the reported data[6a] for $CH_3CH_2C(OTiCl_3){=}CHCH_3$.

Table 2. Aldol Reaction of Trichlorotitanium Enolates Derived from α-Iodoketones

entry	α-iodoketone	carbonyl compounds	adduct yield (%)	anti/syn
1		CH_3CHO	98	19/81
2		PhCHO	96	20/80
3		*i*-PrCHO	86	30/70
4		CH_3COCH_3	92	
5	*n*-$C_5H_{11}COCH_2I$	CH_3CHO	66	
6	*n*-$C_4H_9CH(I)COCH_3$	CH_3CHO	87	20/80
7		CH_3CHO	69	39/61

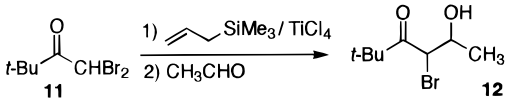
Experimental Section

General Procedure for Enolate Formation from α-Iodoaldehydes. To a solution of titanium tetrachloride (1.0 mmol) in dichloromethane (7 mL) at −78 °C was added a mixture of α-iodocyclohexanecarbaldehyde (**1**, 238 mg, 1.0 mmol) and allyltrimethylsilane (0.24 mL, 1.5 mmol) in dichloromethane (2 mL), and the mixture was stirred for 10 min at −78 °C. Propanal (0.14 mL, 2.0 mmol) was added to the resulting red solution at −78 °C, and the reaction mixture was stirred for 1 h at −78 °C. Extractive workup followed by silica gel column purification afforded 1-(1-hydroxypropyl)cyclohexanecarbaldehyde (145 mg, 0.85 mmol) in 85% yield: IR (neat) 3380, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 0.96 (t, *J* = 7.2 Hz, 3H), 1.08−1.47 (m, 6H), 1.47−1.82 (m, 5H), 1.94−2.03 (m, 1H), 2.03−2.12 (m, 1H), 3.40 (dd, *J* = 10.7, 2.3 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$) *δ* 11.01, 22.31, 22.43, 24.61, 25.53, 27.73, 28.33, 54.02, 78.35, 208.85.

(8) Titanium tetraisopropoxide and titanium tetraphenoxide were not so effective as titanium tetrabutoxide. Although the role of titanium tetrabutoxide is not clear at this stage, we are tempted to assume that the bulky butoxy group on titanium in the aldol adduct *β*-titanoxyaldehyde would inhibit the attack of allylsilane on the aldehyde moiety. The protection of the aldehyde group by a bulky aluminum complex from an attack of a nucleophile has been reported, see: Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131. Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091. Saito, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 2928. Ooi, T.; Miura, T.; Kondo, Y.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 3947.

(9) For a reductive formation of enolate from α-iodoketone with various organometallic compounds, see: Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463.

(10) The use of ethyl iodoacetate, 3-bromo-4-heptanone, and 2,2-dibromo-3-heptanone in this system would not give any aldol adducts, and the starting halocarbonyl compounds were recovered quantitatively. The reaction of 1,1-dibromo-3,3-dimethyl-2-butanone (**11**) provided 4-bromo-5-hydroxy-2,2-dimethyl-3-hexanone (**12**) in 41% yield along with the recovered starting material **11** (50%) upon treatment with allylsilane−$TiCl_4$ followed by an addition of acetaldehyde.



Anal. Found: C, 70.33; H, 10.73%. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%.

Aldol Reaction in the Presence of Titanium Tetrabutoxide. To a solution of titanium tetrachloride (1.0 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added a mixture of 2-iododecanal (**6**, 282 mg, 1.0 mmol) and allyltrimethylsilane (0.24 mL, 1.5 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred for 10 min. Titanium tetrabutoxide (1.0 mL, 1.0 M CH_2Cl_2 solution, 1.0 mmol) was added, and the mixture was stirred for 10 min at −78 °C. Then, 2-methylpropanal (0.18 mL, 2.0 mmol) was added, and the whole was stirred for 1 h. Extractive workup followed by silica gel column purification afforded 2-(1-hydroxy-2-methylpropyl)decanal (syn/anti = 6/4, 146 mg, 0.64 mmol) in 64% yield: IR (neat) 3400, 1721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 1.8H), 0.91 (d, J = 6.9 Hz, 1.2H), 0.94 (d, J = 6.9 Hz, 1.2H), 0.96 (d, J = 6.6 Hz, 1.8H), 1.14−1.46 (m, 12H), 1.49−1.86 (m, 3.6H), 1.95−2.07 (m, 0.4H), 2.38−2.48 (m, 1H), 3.54 (dd, J = 6.0, 5.7 Hz, 0.4H), 3.65 (dd, J = 7.1, 4.7 Hz, 0.6H), 9.72 (d, J = 2.4 Hz, 0.6H), 9.73 (d, J = 2.7 Hz, 0.4H); ^{13}C NMR ($CDCl_3$) δ 13.95, 16.62, 17.72, 19.28, 19.48, 22.52, 23.74, 26.58, 26.94, 27.74, 29.13, 29.23, 29.28, 29.63, 29.82, 30.91, 31.18, 31.74, 54.58, 54.84, 75.83, 76.47, 205.80, 206.27. Anal. Found: C, 73.56; H, 12.43%. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36%.

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Supporting Information Available: Experimental procedures and compound characterization data (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Additions and Corrections

Vol. 60, 1995

Joseph J. P. Zhou, Boyu Zhong, and Richard B. Silverman*. An Improved Procedure for the Synthesis of Substituted β-Hydroxynitriles.

Page 2262. All of the analytical data for compound **4e** and those for **4f** should be switched. Also, a ^1H NMR peak at δ 1.11 (s, 9 H) should be added to the ^1H NMR data for **4f**. The diastereomeric ratio for compound **4d** was found to be 4:1 *anti*:*syn* (not one pure compound as implied); the data for the major compound was reported. Also, a ^{13}C NMR peak at δ 126.3 should be added to the ^{13}C NMR data for **4d**. We thank Professor Paul Carlier (Hong Kong University of Science and Technology) for notifying us of these oversights.

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M. A. Carr, P. E. Creviston, D. R. Hutchison, J. H. Kennedy, V. V. Khau, T. J. Kress,* M. R. Leanna, J. D. Marshall, Michael J. Martinelli,* B. C. Peterson, D. L. Varie,* and J. P. Wepsiec. Synthetic Studies Towards the Partial Ergot Alkaloid LY228729, a Potent 5HT1a Receptor Agonist.

Page 8640, column 2, ref 4 should read as follows: Nichols, D. E.; Robinson, J. M.; Li, G. S.; Cassady, J. M.; Floss, H. G. *Org. Prep. Proc. Int.* **1977**, *9*, 277−280.

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Mark. A. Blaskovich, Ghotas Evindar, Nicholas G. W. Rose, Scott Wilkinson, Yue Luo, and Gilles A. Lajoie*. Stereoselective Synthesis of *Threo* and *Erythro* β-Hydroxy and β-Disubstituted-β-Hydroxy α-Amino Acids.

Page 3635, Table 4. The heading "ketone substrate" should be moved to column 3 and placed above R^1.

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