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Highly Stereoselective Coupling Reaction of Acrolein or Vinyl Ketone with Aldehydes

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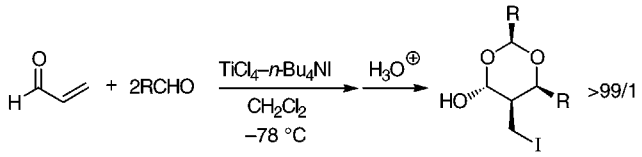
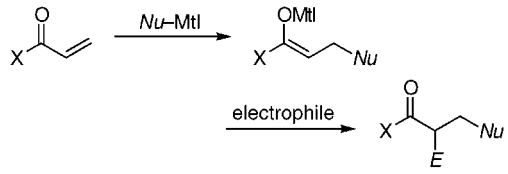
ABSTRACT



Treatment of acrolein with a $TiCl_4$–*n*-Bu_4NI mixed reagent in the presence of 2 equiv of aldehydes provided 4-hydroxy-1,3-dioxane derivatives in good yields with high stereoselectivities. The use of vinyl ketones instead of acrolein afforded aldol-type adducts with high syn selectivities.

The conjugate addition reaction of various nucleophiles to α,β-unsaturated compounds such as 1,2-enones has been extensively explored, and it has been recognized as a powerful route for enolate formation.[1] Then, the sequential reaction of the resulting enolate with electrophiles provides organic chemists an extremely effective methodology for construction of the carbon framework of organic molecules (Scheme 1).[2] With regard to acrolein, however, few examples

Scheme 1



of conjugate addition to acrolein are described in the literature.[3] Moreover, trapping of the resulting enolate with carbon electrophiles such as carbonyl compounds has been quite limited. In most cases, 1,2-addition of nucleophiles to acrolein is the predominant reaction. In addition, if 1,4-addition to acrolein occurs, reaction of the resulting enolate with acrolein could readily cause polymerization of acrolein because of its high reactivity. Herein we wish to report that a $TiCl_4$−*n*-Bu_4NI[4] system mediates formation of an enolate from acrolein and the subsequent trapping of the resulting titanium enolate[5] with aldehydes affords 3-hydroxy-aldehydes and their derivatives with high stereoselectivities.

Treatment of tetrabutylammonium iodide with $TiCl_4$ in dichloromethane at 0 °C provided a dark-red solution. After

(1) (a) *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press: New York, 1994. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 1.1, pp 1−67. (c) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 1.2 pp 69−137. (d) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 1.3, pp 139−168.

(2) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847−876. (d) Taylor, R. J. K. *Synthesis* **1985**, 364−392. (c) Noyori, R.; Suzuki, M. *Chemtracts−Org. Chem.* **1990**, *3*, 173−197. (d) Hulce, M.; Chapdelaine, M. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 1.6, pp 237−268.

(3) Examples of conjugate addition to acrolein: (a) Alexakis, A.; Chuit, C.; Commerçon-Bourgain, M.; Foulon, J. P.; Jarbi, N.; Mangeney, P.; Normant, J. F. *Pure Appl. Chem.* **1984**, *56*, 91−98. (b) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574−1575.

(4) (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *39*, 4767. (b) Yachi, K.; Maeda, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 5161.

(5) (a) *Organotitanium and Organozirconium Reagents*; Ferreri, C., Palumbo, G., Caputo, R., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

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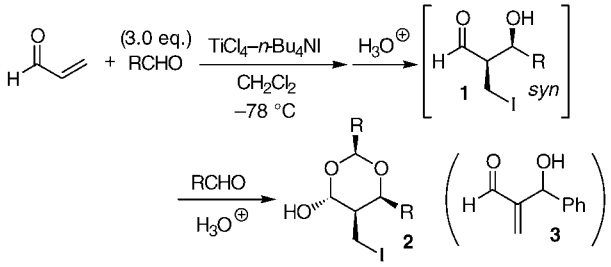
being stirred for 10 min, an addition of an excess amount of 2-methylpropanal (3.0 equiv) followed by acrolein (1.0 equiv) at −78 °C afforded a cyclic hemiacetal **2a** in 68% yield (based on the amount of acrolein employed) as a single stereoisomer.[6,7] This cyclic hemiacetal could be generated from the initial aldol adduct **1** and another molecule of 2-methylpropanal (Scheme 2). Interestingly, no polymerization of acrolein could be observed in this reaction. The use of a reduced amount of 2-methylpropanal (1.0 mmol per 1.0 mmol of acrolein) also resulted in formation of the cyclic hemiacetal **2a** in 32% yield along with a small amount of aldol adduct **1a** (10%).[8] Therefore, it is desirable to use more than 2 equiv of aldehydes. The reaction with aliphatic aldehydes such as cyclohexanecarbaldehyde, decanal, or dihydrocinnamaldehyde also gave the corresponding cyclic hemiacetal **2** in good yield with high stereoselectivity. On the other hand, the use of benzaldehyde afforded a complex mixture containing a trace amount of **2**. Baylis−Hillman-type adduct **3** could only be isolated in 29% yield. The adduct **3** was presumably formed by elimination of hydrogen iodide from the initial adduct **1**.

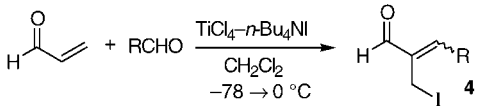
Scheme 2



RCHO	Product	Yield (%)	Selectivity
i-PrCHO	**2a**	68%	>99/1
c-C_6H_{11}CHO	**2b**	68%	>99/1
n-C_6H_{13}CHO	**2c**	74%	>99/1
$PhCH_2CHO$	**2d**	64%	>99/1

In this reaction, the reaction temperature is critical to determine the distribution of the product. Whereas the reaction at −78 °C gave hemiacetal **2** exclusively, warming the reaction mixture to 0 °C prior to quenching with saturated aqueous ammonium chloride provided the corresponding dehydration products **4** (Scheme 3).

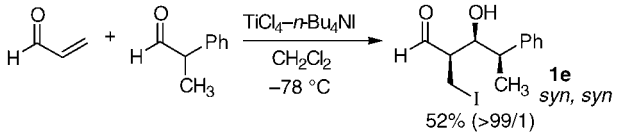
Scheme 3



4a: R = *i*-Pr 51% (*E*/*Z* = 46/54)
4b: R = *c*-C_6H_{11} 57% (*E*/*Z* = 34/66)

A high level of diastereofacial selectivity was achieved in the reaction of acrolein with 2-phenylpropanal (Scheme 4). The 3-hydroxyaldehyde **1e** was obtained as a single diastereomer instead of the cyclic hemiacetal **2** due to the steric bulkiness of 2-phenylpropanal. The stereochemical outcome could be explained by the Felkin−Anh model.[9]

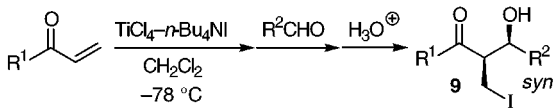
Scheme 4



52% (>99/1)

Next, the reaction of vinyl ketone was examined. Treatment of phenyl vinyl ketone with titanium tetrachloride−tetrabutylammonium iodide at −78 °C and subsequent addition of aldehydes also provided the corresponding aldol-type adducts **9** in good yields (Scheme 5).[10] *syn*-3-Hydroxy ketones **9** were obtained with high stereoselectivities as in the case of acrolein. For instance, an addition of benzalde-

Scheme 5



R^1	R^2	Product	Yield (%)	Selectivity
Ph	Ph	**9a**	89%	>99/1
Ph	*n*-C_9H_{19}	**9b**	73%	>99/1
Ph	CH_3	**9c**	96%	>99/1
Ph	*i*-Pr	**9d**	70%	89/11
Ph	Et_2CH	**9e**	79%	96/4
n-C_5H_{11}	Ph	**9f**	75%	94/6
n-C_5H_{11}	*n*-C_6H_{13}	**9g**	71%	94/6

(6) Experimental procedure is as follows. To a solution of $TiCl_4$ (2.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of *n*-Bu_4NI (2.0 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After being stirred for 10 min at 0 °C, a resulting dark-red solution was cooled to −78 °C, and 2-methylpropanal (3.0 mmol) and acrolein (1.0 mmol) were added. The mixture was stirred for 30 min at −78 °C, and then the whole mixture was poured into saturated aqueous ammonium chloride. Extractive workup and purification by silica gel column chromatography afforded 4-hydroxy-2,6-diisopropyl-5-iodomethyl-1,3-dioxane (**2a**, 0.22 g) in 68% yield.

(7) The stereochemical assignment of this aldol adduct was performed as follows. Reduction of **2a** with $NaBH_4$ followed by *n*-Bu_3SnH provided 2,4-dimethyl-1,3-pentanediol as a single isomer (>99/1). This product was identical with authentic *syn*-diol. The assignment of relative stereochemistry of another isopropyl group was based on NOE experiment. The anomeric stereocenter was assumed taking account of the anomeric effect.

(8) Some attempts to obtain 3-hydroxyaldehyde **1** as a major product were not successful.

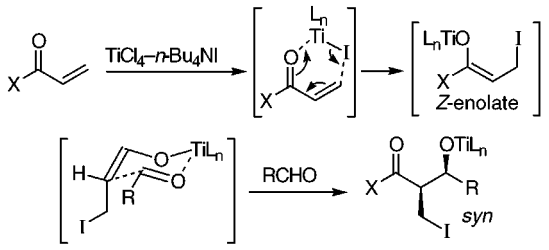
(9) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(10) The reaction of α,β-unsaturated ketone with Et_2AlI has been reported. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274−278.

hyde or acetaldehyde afforded syn adduct **9a** or **9c** in 89% or 96% yield, respectively.

Selective formation of the syn isomer might be explained as follows (Scheme 6): (1) the selective generation of

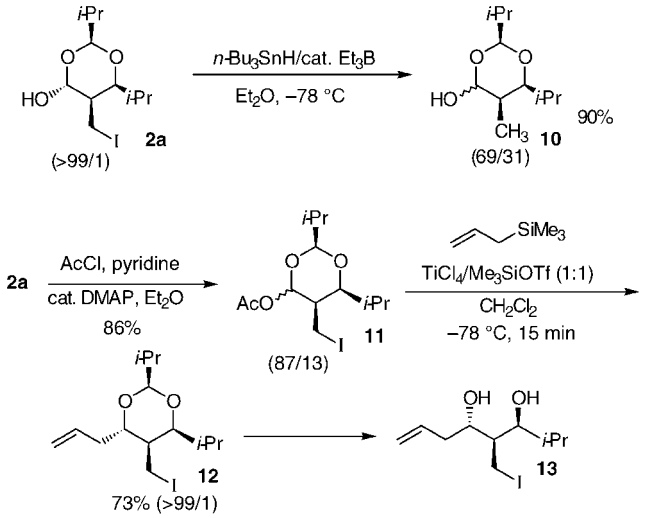
Scheme 6



Z-enolate from acrolein or phenyl vinyl ketone by the action of the combination of $TiCl_4-n$-Bu_4NI and (2) aldol addition of (*Z*)-titanium enolate to aldehyde through a rigid six-membered transition state.

Finally, the cyclic hemiacetal **2** obtained in our reaction turned out to be an useful intermediate in organic synthesis. Reduction by tin hydride of iodine in **2a** provided methyl-substituted acetal **10** in almost quantitative yield (Scheme 7).[11] Several groups have developed the synthetic use of the cyclic hemiacetal for construction of stereocontrolled 1,3-diol systems.[12] The cyclic hemiacetal **2** also proved to be a good substrate for further carbon−carbon bond formation reaction. For example, allylation of acetylated cyclic hemiacetal **11** with allyltrimethylsilane in the presence of Lewis

Scheme 7



acids afforded tetrasubstituted 1,3-dioxane **12** as a single isomer in good yield that was further deacetalized to 1,3-diol **13** (Scheme 7).[13]

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Supporting Information Available: General procedures and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990934W

(11) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.

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(13) The use of $TiCl_4$-Me_3SiOTf mixed reagent[14] as a Lewis acid afforded the best result. The reaction using only $TiCl_4$ gave a complex mixture containing a small amount of the allylated product, and no reaction occurred in the case of Me_3SiOTf.

(14) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727−8730.