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A STEREOCONTROLLED SYNTHESIS OF 2-METHYL-2-ALKENENITRILES FROM
C-METHYL-C,N-BIS(TRIMETHYLSILYL)KETENIMINE AND ALDEHYDES
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A stereocontrolled synthesis of 2-methyl-2-alkenenitriles is achieved via the diastereoselective aldol type reaction of C-methyl-C,N-bis(trimethylsilyl)ketenimine with aldehydes in the presence of a mixture of TiCl<sub>4</sub> and Ti( $O^{-i}Pr$ )<sub>4</sub>.

Of many carbonyl olefination for the synthesis of 2-alkenenitriles, (Z)-selective routes have been almost established in both  $\operatorname{acidic}^{1, 2}$  and  $\operatorname{basic}^{3}$  conditions. On the contrary, (Z)-stereoselection in 2-substituted 2-alkenenitriles synthesis is not established completely.<sup>4</sup> Although few examples of Wittig-Horner type reactions are reported,<sup>5, 6</sup> the effective cyclic phospholene and phosphoramide require the tedious procedures for preparation. Related to our concern exploiting new condensation reagents, we describe a successful stereoselective synthesis of 2-methyl-2-alkenenitriles ( $\mathfrak{Z}$ ) resulting from the diastereoselective formation of 2 in the reaction of C-methyl-C,N-bis(trimethylsilyl)ketenimine ( $\mathfrak{L}$ ) with aldehydes activated by a mixture of TiCl<sub>4</sub> and Ti(O-<sup>i</sup>Pr)<sub>4</sub>.

Although ketenimine (1) gave smoothly 3 in one pot reactions with aldehydes by the assistance of MgBr<sub>2</sub> or BF<sub>3</sub>·Et<sub>2</sub>O at room temperature, stereochemistry of 3 could not be controlled. A well-known activating agent, TiCl<sub>4</sub><sup>7</sup> catalyzed to



form  $2^{8}$  at -78°C. However, yields and diastereoselectivity in the reaction depended on the type of aldehydes. A disappointing result was obtained in the case of cyclohexanecarbaldehyde [29% yield of 2e,  $(2R^*, 3R^*)/(2R^*, 3S^*) = 20/80$ ] compared with the case of benzaldehyde [78% yield of 2e,  $(2R^*, 3R^*)/(2R^*, 3S^*)$ = 43/57].

The result suggests a certain balance between Lewis acidity and an induced nucleophilicity of 1 in the addition step. Thus, a modified titanium reagent which was composed of TiCl<sub>4</sub> and Ti( $0-i^{i}$ Pr)<sub>4</sub> brought about a remarkable improvement in both yield and diastereoselectivity of 2.<sup>8,9</sup> The latter changed remarkably with the proportion of  $Ti(0-^{i}Pr)_{4}$ . The results obtained by the reaction of 1with nonanal in the presence of various types of Lewis acid are summarized in The best (2R<sup>\*</sup>, 3R<sup>\*</sup>)-selectivity was attained by using a mixture of Table 1.  $TiCl_4/Ti(O-^{i}Pr)_4 = 1/3$ , which would form a mixed ligand titanium compound,  $TiCl(O-^{i}Pr)_3$  by disproportionation.<sup>11</sup> An analogously modified titanium reagent  $[TiCl_4/Ti(0-CEt_3)_4 = 1/3]$  afforded a slight predominance of  $(2R^*, 3S^*)$ -2a (entry 9) in Table 1).

Since the stereospecificity in the transformation of 2a to 3a is wellestablished,  $^9$ ,  $^{10}$  the completion of diastereoselective synthesis of 2 discloses a stereoselective synthetic route to 3 in two stages. Various types of aldehydes were conducted in the analogous conditions in order to clarify the scope and limitations of this carbonyl olefination. A drastic contrast in the stereoselectivity was observed, which related to the substituents on the  $\alpha$ -carbon

Entry	Lewis acids	Conditions	Yield	રેક્ષ (%) <sup>a)</sup> <sub>E/Z</sub> b)
1	MgBr <sub>2</sub>	$Et_2O/C_6H_6 = 9/4$ , r.t., 20h	99	69/31
2	BF <sub>3</sub> Et <sub>2</sub> O	$CH_2Cl_2$ , -78°C, 3h $\rightarrow$ r.t., 2h	42	43/57
3	TiCl <sub>4</sub>	$CH_2Cl_2$ , -78°C, 1h $\rightarrow$ -35°C, 3h <sup>c</sup> )	62	66/34
4	$\operatorname{TiCl}_4/\operatorname{Ti}(0-^i\operatorname{Pr})_4 = 2/1$	CH <sub>2</sub> Cl <sub>2</sub> , -78°C, 5h <sup>c)</sup>	80	15/85
5	$\operatorname{TiCl}_4/\operatorname{Ti}(0-^i\operatorname{Pr})_4 = 1/1$	CH <sub>2</sub> C1 <sub>2</sub> , -78°C, 5h <sup>c)</sup>	86	8/92
6	$\operatorname{TiCl}_4/\operatorname{Ti}(0-^{i}\operatorname{Pr})_4 = 1/2$	CH <sub>2</sub> C1 <sub>2</sub> , -78°C, 5h <sup>c)</sup>	76	7/93
7	$\operatorname{TiCl}_{4}/\operatorname{Ti}(0-^{i}\operatorname{Pr})_{4} = 1/3$	CH <sub>2</sub> Cl <sub>2</sub> , -78°C, 5h <sup>C)</sup>	78	3/97
8	$TiCl_4/Ti(0-^{i}Pr)_4 = 1/11$	CH <sub>2</sub> Cl <sub>2</sub> , -78°C, 5h <sup>C)</sup>	66	17/83
9	$TiCl_4/Ti(0-CEt_3)_4 = 1/3$	$CH_2Cl_2, -78^{\circ}C, 5h^{\circ}$	96	56/44

Table 1. Effect of Lewis acid in the reaction of 1 with nonanal.

a) Isolated yields.
b) Determined by GLC (PEG-20M).
c) Crude 2a obtained by quenching the mixture with aqueous sodium carbonate was immediately decomposed in the presence of an equivalent of boron trifluoride etherate at room temperature.

of formyl group and the ratio of  $TiCl_4$  and  $Ti(0-iPr)_4$ . Nonbrached aldehydes lead to (2)-3 (entries 1, 2, and 4 in Table 2), whereas branched ones at  $\alpha$ -carbon to (E)-3 selectively (entries 5, 7, and 9 in Table 2) in the case of  $TiCl_4/$  $Ti(O-iPr)_4 = 1/3$ . Decreased ratio of  $Ti(O-iPr)_4$  brought about the opposite selectivity for monosubstituted aldehydes at  $\alpha$ -carbon (entries 6 and 8 in Table 2) selectivity for disubstituted one (entry 10 in Table 2). and same Since the elimination condition of 2 is identical in all cases, the results reflect the diastereoselective discrimination forming 2.

A remarkable influence of the substituent in aldehydes and the ratio of TiCl, and  $Ti(O_{-}^{\nu}Pr)_{A}$  suggests that aggregation of 1 and aldehydes around the titanium atom would play an important role to control a stereochemical course in the Thus, organotitanium compounds  $4^{12, 13}$  may be a major species addition step. Reaction of 4 with the aldehyde via four-membered in the reaction conditions. cyclic transition state 5 would afford the observed  $(2R^*, 3R^*)$ -2. On the other hand, reaction of 4 through six-membered cyclic transition state 6 with minimal steric repulsion is expected to lead to  $(2R^*, 3S^*)$ -2. The choice of the preferable path would depend on the environment around the titanium atom. The results in Table 2 are consistent with this conception.

Entry	Aldehydes	Yield	⋧ (%) <sup>b)</sup> <sub>E/Z</sub> c)	Entry	Aldehydes	Yield	ξ (%) <sup>b)</sup> ε/Ζ <sup>c)</sup>
1	Nonanal	78	3/97	5		66	90/10
	D		01 (70	6		58	15/85 <sup>d)</sup>
2	PhCH <sub>2</sub> CH <sub>2</sub> -CHO	96	21/79	7	7	69	90/10
3	Ph-CHO	97	27/73	8	СНО	59	10/90 <sup>d)</sup>
4	PhCH=CH-CHO	78	10/90	9	tan Du Ollo	53	83/17 <sup>e)</sup>
				10	<i>ver</i> -bu-ChO	54	88/12 <sup>d) e)</sup>

Table 2. Carbonyl olefination by the reaction of  $1.^{a}$ 

a) Aldehydes (2  $\sim$  3 mmol) and 1.5  $\sim$  2 equivalents of 1 were added successively to a dichloromethane solution of 0.5 equivalents of titanium tetrachloride and 1.5 equivalents of titanium tetraisopropoxide at -78°C. The solution and 1.5 equivalents of titalium tetraisoproposide at 278 C. The solution was stirred for 5h at -78°C and quenched with aqueous sodium carbonate. Obtained crude 2 were conducted immediately in a dichloromethane solution of an equivalent of boron trifluoride etherate.
b) Isolated yields. c) Determined by GLC (PEG-20M).
d) TiCl<sub>4</sub>/Ti(O-*i*Pr)<sub>4</sub> = 1/1 was used. e) Temperature was raised up to r.t..



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8. All these compounds were isolated by column chromatography (hexane/AcOEt
   = 20/1) and showed correct values of analyses and corresponding i.r. and
   <sup>1</sup>H n.m.r. spectra except 2g. <sup>1</sup>H N.m.r. data in CDCl_3 of 2g are shown.
   (2R^*, 3S^*) - 2c; \delta 0.29 (9H, s), 1.05 (3H, s), 2.20 (1H, OH, d, J=3.3 Hz),
                    4.53 (1H, d, J=3.3 Hz), and 6.1 (5H, br.s).
   (2R^*, 3R^*)-2c; \delta 0.19 (9H, s), 1.25 (3H, s), 2.9 \vee 3.1 (1H, OH, br.),
                    4.86 (1H, s), and 6.1 (5H, br.s).
9. The ratio of both diastereomers in 2 was deduced from the isomer ratio of 3
   obtained by the stereospecific \beta-elimination of Me<sub>3</sub>SiOH from 2. The
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- isolated diastereomer,  $(2R^*, 3R^*)$ -2a was specifically transformed to Z-3a or E-3a in the presence of an equivalent of BF<sub>3</sub>. Et<sub>2</sub>O or KH, respectively.
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