CHEMISTRY LETTERS, pp. 97-100, 1983. © The Chemical Society of Japan 1983

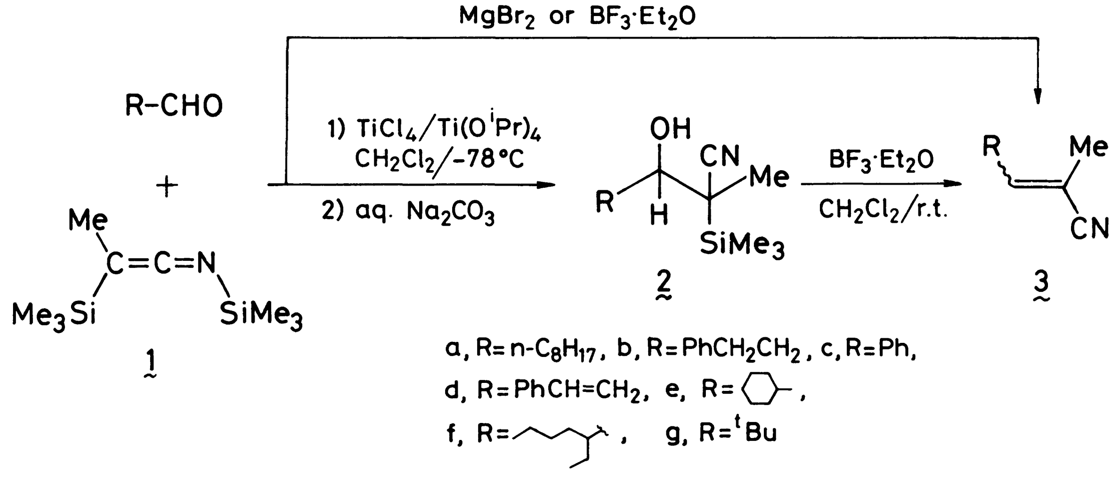
A STEREOCONTROLLED SYNTHESIS OF 2-METHYL-2-ALKENENITRILES FROM C-METHYL-C,N-BIS(TRIMETHYLSILYL)KETENIMINE AND ALDEHYDES

Hisashi OKADA, Isamu MATSUDA,* and Yusuke IZUMI
Department of Synthetic Chemistry, Faculty of Engineering,
Nagoya University, Chikusa, Nagoya 464

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 $TiCl_4$ and $Ti(O\text{-}^{i}Pr)_4$.

Of many carbonyl olefination for the synthesis of 2-alkenenitriles, (*Z*)-selective routes have been almost established in both acidic[1, 2] and basic[3] conditions. On the contrary, (*Z*)-stereoselection in 2-substituted 2-alkenenitriles synthesis is not established completely.[4] Although few examples of Wittig-Horner type reactions are reported,[5, 6] 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 (**3**) resulting from the diastereoselective formation of **2** in the reaction of C-methyl-C,N-bis(trimethylsilyl)ketenimine (**1**) with aldehydes activated by a mixture of $TiCl_4$ and $Ti(O\text{-}^{i}Pr)_4$.

Although ketenimine (**1**) gave smoothly **3** in one pot reactions with aldehydes by the assistance of $MgBr_2$ or $BF_3 \cdot Et_2O$ at room temperature, stereochemistry of **3** could not be controlled. A well-known activating agent, $TiCl_4$ [7] 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 **2c**, $(2R^*,3R^*)/(2R^*,3S^*)$ = 20/80] compared with the case of benzaldehyde [78% yield of **2c**, $(2R^*,3R^*)/(2R^*,3S^*)$ = 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 $TiCl_4$ and $Ti(O\text{-}^{i}Pr)_4$ brought about a remarkable improvement in both yield and diastereoselectivity of **2**.[8, 9] The latter changed remarkably with the proportion of $Ti(O\text{-}^{i}Pr)_4$. The results obtained by the reaction of **1** with nonanal in the presence of various types of Lewis acid are summarized in Table 1. The best $(2R^*,3R^*)$-selectivity was attained by using a mixture of $TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 1/3, which would form a mixed ligand titanium compound, $TiCl(O\text{-}^{i}Pr)_3$ by disproportionation.[11] An analogously modified titanium reagent [$TiCl_4/Ti(O\text{-}CEt_3)_4$ = 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 well-established,[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 α-carbon

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

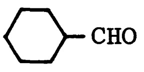
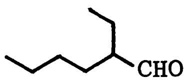
Entry	Lewis acids	Conditions	**3a** Yield (%)[a)]	**3a** *E*/*Z*[b)]
1	$MgBr_2$	Et_2O/C_6H_6 = 9/4, r.t., 20h	99	69/31
2	$BF_3\ Et_2O$	CH_2Cl_2, -78°C, 3h → r.t., 2h	42	43/57
3	$TiCl_4$	CH_2Cl_2, -78°C, 1h → -35°C, 3h[c)]	62	66/34
4	$TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 2/1	CH_2Cl_2, -78°C, 5h[c)]	80	15/85
5	$TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 1/1	CH_2Cl_2, -78°C, 5h[c)]	86	8/92
6	$TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 1/2	CH_2Cl_2, -78°C, 5h[c)]	76	7/93
7	$TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 1/3	CH_2Cl_2, -78°C, 5h[c)]	78	3/97
8	$TiCl_4/Ti(O\text{-}^{i}Pr)_4$ = 1/11	CH_2Cl_2, -78°C, 5h[c)]	66	17/83
9	$TiCl_4/Ti(O\text{-}CEt_3)_4$ = 1/3	CH_2Cl_2, -78°C, 5h[c)]	96	56/44

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(O-^{i}Pr)$_4$. Nonbrached aldehydes lead to (Z)-**3** (entries 1, 2, and 4 in Table 2), whereas branched ones at α-carbon to (E)-**3** selectively (entries 5, 7, and 9 in Table 2) in the case of $TiCl_4$/Ti(O-^{i}Pr)$_4$ = 1/3. Decreased ratio of Ti(O-^{i}Pr)$_4$ brought about the opposite selectivity for monosubstituted aldehydes at α-carbon (entries 6 and 8 in Table 2) and same selectivity for disubstituted one (entry 10 in Table 2). 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 $TiCl_4$ and Ti(O-^{i}Pr)$_4$ suggests that aggregation of **1** and aldehydes around the titanium atom would play an important role to control a stereochemical course in the addition step. Thus, organotitanium compounds **4** [12, 13] may be a major species in the reaction conditions. Reaction of **4** with the aldehyde via four-membered 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.

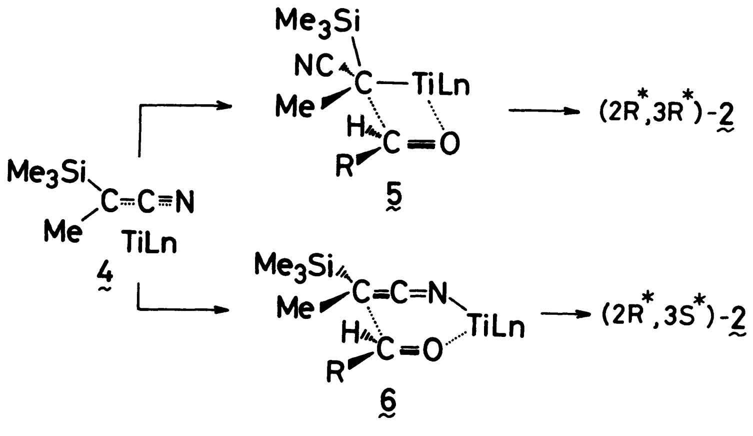
Table 2. Carbonyl olefination by the reaction of **1**.a)

Entry	Aldehydes	**3**		Entry	Aldehydes	**3**	
		Yield (%)b)	E/Zc)			Yield (%)b)	E/Zc)
1	Nonanal	78	3/97	5		66	90/10
				6		58	15/85d)
2	$PhCH_2CH_2$-CHO	96	21/79	7		69	90/10
3	Ph-CHO	97	27/73	8		59	10/90d)
				9	*ter*-Bu-CHO	53	83/17e)
4	PhCH=CH-CHO	78	10/90	10		54	88/12d) e)

a) Aldehydes (2 ∿ 3 mmol) and 1.5 ∿ 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 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) $TiCl_4$/Ti(O-iPr)$_4$ = 1/1 was used. e) Temperature was raised up to r.t..



Acknowledgment: The authors thank Shinetsu Chemical Co. for a gift of Me_3SiCl.

REFERENCES

1. Y. Sato and Y. Niinomi, *J. Chem. Soc. Chem. Commun.*, 56 (1982).
2. I. Matsuda, H. Okada, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, in press.
3. R. Haruta, M. Ishiguro, K. Furuta, A. Mori, N. Ikeda, and H. Yamamoto, *Chem. Lett.*, 1093 (1982).
4. W. S. Wadsworth, Jr., *Organic Reactions*, 25, 73 (1977).
5. A. Redjel and J. Seyden-Penne, *Tetrahedron Lett.*, 1733 (1974).
6. B. Deshamps, J. Lampin, F. Mathey, and J. Seyden-Penne, *Tetrahedron Lett.*, 1137 (1977).
7. a) T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, 16, 617 (1977).
   b) K. Yamamoto, Y. Tomo, and S. Suzuki, *Tetrahedron Lett.*, 21, 2861 (1980).
   c) I. Matsuda and Y. Izumi, *Tetrahedron Lett.*, 22, 805 (1981).
8. All these compounds were isolated by column chromatography (hexane/AcOEt = 20/1) and showed correct values of analyses and corresponding i.r. and ^{1}H n.m.r. spectra except **2g**. ^{1}H N.m.r. data in $CDCl_3$ of **2c** are shown.
   (2R*,3S*)-**2c**; δ 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**; δ 0.19 (9H, s), 1.25 (3H, s), 2.9 $\sim$ 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 β-elimination of Me_3SiOH from **2**. The isolated diastereomer, (2R*,3R*)-**2a** was specifically transformed to *Z*-**3a** or *E*-**3a** in the presence of an equivalent of $BF_3 \cdot Et_2O$ or KH, respectively.
10. P. F. Hudrlik and D. Peterson, *Tetrahedron Lett.*, 1173 (1974), *J. Am. Chem. Soc.*, 97, 1464 (1975).
11. C. Dijkgraaf and J. P. G. Rousseau, *Spectrochem. Acta*, 24A, 1213 (1968).
12. L. Willer and D. Seebach, *Helv. Chim. Acta*, 65, 1085 (1982).
13. M. Leetz and R. Peter, *Tetrahedron Lett.*, 22, 4691 (1981).

(Received November 13, 1982)