Lewis Base Catalyzed Aldol Reaction of Trimethylsilyl Enolates with Aldehydes

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 65th birthday

A new *Lewis* base catalyzed aldol reaction of trimethylsilyl enolates with aldehydes is established in DMF or pyridine solvent by using a *Lewis* base such as lithium diphenylamide (*Tables 4* and *5*) or lithium 2-pyrrolidone (*Tables 6–8*). The effect of solvent suggests that this reaction proceeds *via* the pentacoordinated hypervalent silicate generated by the coordination of the above *Lewis* base to a trimethylsilyl enolate. Successive coordination of the solvent to the thus-formed pentacoordinated silicate leads to an active enolate intermediate having hexacoordinated silicate, which, in turn, attacks carbonyl compounds to form the desired aldols (*Scheme 5*).

1. Introduction. – The aldol reaction is one of the most important tools for C–C bond-formation and is frequently employed in synthetic organic chemistry (for reviews, see [1]). Reactions involving silyl enolates, aldol donors, have become very popular since the crossed aldol reaction between silyl enolates and aldehydes promoted by *Lewis* acids was reported from our laboratory [2], and they are frequently employed in the construction of C-skeletons. There are also reaction patterns of silyl enolates with aldehydes without using any *Lewis* acids. For example, reactions *via* metal enolates formed by transmetallation of silyl enolates with various metal salts including its original MeLi [3] to the recent transition metal catalysts [4], and also those *via* enolate anions generated by nucleophilic cleavage of the O–Si bond with a fluoride ion [5] or phosphines [6]. Reactions of silyl enolates such as trichlorosilyl enolates [7], dimethyl(trifloxy)silyl enolates [8], enoxysilacyclobutanes [9], and dimethylsilyl enolates [10] that readily form hypervalent silicates with acceptor aldehydes were shown to proceed even in the absence of catalysts. Moreover, reactions of silyl ketene acetals with aldehydes were carried out in H_2O [11], DMSO, DMF, and DME [12], and under high pressure [13]. Recently, several methods to activate silyl enolate by using *Lewis* bases were established: *Denmark* and *Stavenger* introduced a *Lewis* base-catalyzed aldol reaction of trichlorosilyl enolates with aldehydes by using phosphoramides [7], and *Hosomi* and co-workers reported a reaction by using a combination of dimethylsilyl enolate and $CaCl_2$ in aqueous DMF [14]. In these *Lewis* base catalyzed aldol reactions, several silyl enolates with an enhanced *Lewis* acidic Si-atom interacted with *Lewis* bases more readily. Now, to activate simple and popular silyl enolates such as trimethylsilyl enolates, exploration of newer *Lewis* base catalysts was planned. In this paper, we would like to describe a new catalytic aldol reaction of trimethylsilyl enolates with aldehydes by using the *Lewis* base catalysts lithium diphenylamide ($LiNPh_2$) [15] and lithium 2-pyrrolidone [16].

2. Results and Discussion. – 2.1. *Activation of Trimethylsilyl Enolate by Lithium Amide.* Lithium amides derived from the hindered amines, *e.g.*, lithium diisopropylamide (LDA), were known to behave as strong bases with low nucleophilicity and were often employed in the formation of enolates from carbonyl compounds, or of lithiated C-skeletons. Conventionally, such amides were employed only as *Brønsted* bases and have never been used as the *Lewis* bases to generate an active trimethylsilyl enolate having a hypervalent silicate.

Aldol reaction of a trimethylsilyl enolate derived from methyl isopropionate with benzaldehyde (PhCHO) was tried in THF by using 1.4 equiv. of the lithium amide as an activator. The reaction then proceeded to afford the aldol adduct in 24% yield, suggesting that the amides would be able to promote the above aldol reaction (*Table 1*, *Entry 2*). Next, the effect of various lithium amides was screened to establish an effective lithium amide mediated aldol reaction under the above conditions by taking the reaction of trimethylsilyl enolate derived from methyl isopropionate with PhCHO as a model reaction. Of all lithium amides screened lithium diphenylamide ($LiNPh_2$) turned out to be most effective, as shown in *Table 1*.

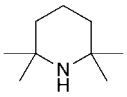
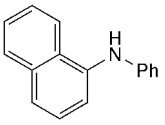
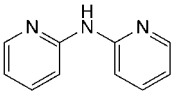
Then, the following control experiments were tried to clarify the effect of $LiNPh_2$ on this reaction (*Scheme 1*). When lithium enolate generated from trimethylsilyl enolate and MeLi were allowed to react under the above conditions, the aldol adduct was obtained in low yield. Since the application of $LiNPh_2$ alone did not generate the lithium enolate, it was noted that the above lithium enolate was not the key intermediate of this reaction. Also, the reaction did not take place when 1.5 equiv. of weakly basic Ph_2NH were used in place of the above $LiNPh_2$; therefore, it is noted that Ph_2NH itself is not a promoter of the aldol reaction.

Thereafter, $LiNPh_2$ was chosen as one of the catalysts of the present aldol reaction.

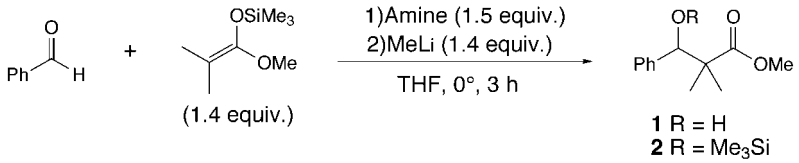
2.2. *Catalytic Aldol Reaction with $LiNPh_2$ as* Lewis *Base.* Next, several catalytic aldol reactions were tried by using $LiNPh_2$ as the *Lewis* base. When the above reaction was carried out in THF solvent with 20 mol-% of $LiNPh_2$, aldol adduct was obtained in 15% yield. This indicated that a stoichiometric amount of $LiNPh_2$ was required for the completion of the reaction. The aldol adducts thus formed after quenching were a mixture of aldol (R = H, **1**) and *O*-silyl ether (R = Me_3Si (TMS), **2**), which suggested the existence of both lithium aldolate and *O*-silyl ether. In addition, it was noted in all cases that the amount of *O*-silyl ether formed was less than that of the aldol in THF irrespective of the kind of lithium amide employed (*Table 1*). To establish a catalytic aldol reaction, the aldol adduct should be transformed to its *O*-silyl ether rapidly. Lithium aldolate was formed along with silyl amide, and it showed that a catalytic aldol reaction did not take place under the above conditions. The silyl amide was regarded as a silylating reagent, and silylation of the lithium aldolate by the thus-formed silyl amide was expected to afford *O*-silyl ether along with the regeneration of lithium amide when suitable reaction conditions were chosen (*Scheme 2*).

Since it was assumed that solvents influenced the silyl transfer of silyl amide to the lithium aldolate [1a][17], various solvents were further screened to obtain higher yields and higher *O*-silyl ether to aldol ratios (*Table 1*). It was found that DMF (H/TMS 1:35) and pyridine (H/TMS 1:6) were excellent solvents to afford the aldol adducts in

Table 1. *Lithium Amide Mediated Aldol Reaction of Trimethylsilyl Enolate and Benzaldehyde*[a])

Entry	Amine	Yield[b])/%	SMR[c])/%	**1/2**
1	Et_2NH	35	6	3:1
2	$(i\text{-}Pr)_2NH$	24	3	2:1
3		35	8	2:1
4		67	18	4:1
5	$(Me_3Si)_2NH$	trace	17	3:1
6	$BnNH_2$	62	5	9:5
7	Ph_2NH	81	n.d.	2:1
8	$(4\text{-}MeOC_6H_4)NH_2$	66	trace	6:5
9	$(4\text{-}MeOC_6H_4)_2NH$	62	5	3:2
10		58	trace	8:5
11		58	18	3:2
12	$Me_2N(CH_2)_2NHMe$	70	10	7:5

[a])



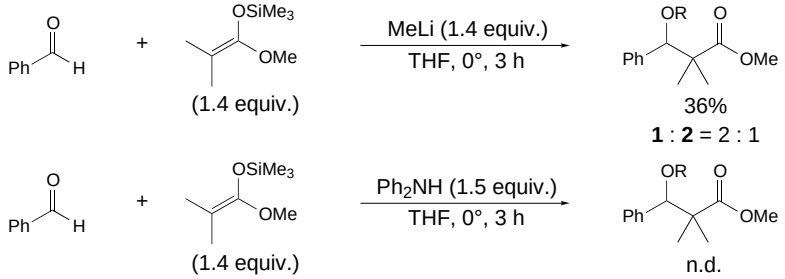
[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [c]) Starting material recovered.

quantitative yields (*Table 2*). The possibility to establish a catalytic cycle was suggested because the major product in these reactions was *O*-silyl ether.

Recently, *Génisson* and *Gorrichon* reported that the aldol reaction of this combination proceeded 'spontaneously' in DMSO, DME, and DMF at room temperature [12]. To examine the effect of $LiNPh_2$ catalyst on the present reaction, the conditions under which the reaction did not proceed in those solvents alone were examined. As a result, the reaction proceeded neither in DMF at the temperatures below $-45°$ nor in pyridine at $0°$ (*Table 3*).

Then, the same reaction was tried by adding 5 mol-% of $LiNPh_2$ in DMF at $-45°$, and the desired aldol was obtained in 80% yield along with 18% of the starting material. Likewise, the aldol adduct was obtained in quantitative yield when the reaction was carried out at $0°$ with 20 mol-% of $LiNPh_2$ in pyridine (*Scheme 3*).

Scheme 1



Scheme 2

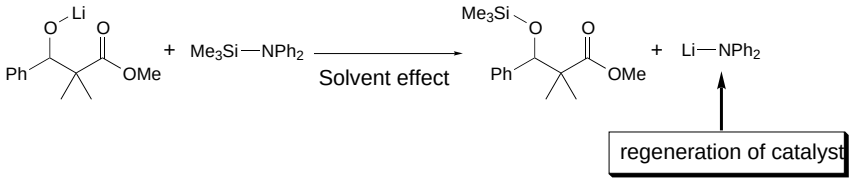
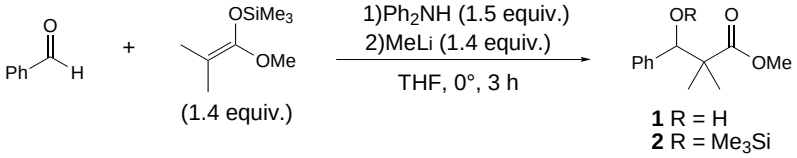


Table 2. *Effect of Solvent on the $LiNPh_2$-Mediated Aldol Reaction of Trimethylsilyl Enolate and Benzaldehyde*[a])

Entry	Solvent	Yield[b])/%	**1/2**
1	THF	81	2 : 1
2	Et_2O	n.d.	–
3	CH_2Cl_2	6	5 : 7
4	Toluene	7	1 : 12
5	Hexane	n.d.	–
6	MeCN	47	1 : 9
7	DMF	96	1 : 35
8	Pyridine	quant	1 : 6

[a])

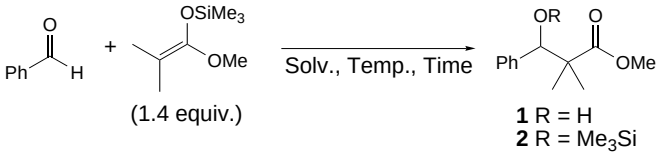


[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard.

Table 3. *Effect of Solvent and Temperature on the Spontaneous Aldol Reaction of Trimethylsilyl Enolate and Benzaldehyde*[a])

Entry	Solvent	Temp./°	Time/h	Yield[b])/%
1	DMF	0	1	84
2	DMF	– 19	1	43
3	DMF	– 45	1	trace
4	Pyridine	0	4	n.d.

[a])



[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard.

Apparently, these results indicated that $LiNPh_2$ did behave as an effective catalyst in promoting the present aldol reaction in DMF or pyridine.

2.3. *$LiNPh_2$-Catalyzed Aldol Reaction between Trimethylsilyl Enolate and Aldehydes.* Taking these results into consideration, reactions with other aldehydes were tried, and the results are summarized in *Table 4*. Here, a trimethylsilyl enolate derived from methyl isopropionate reacted smoothly with various aromatic aldehydes to afford the corresponding aldols in high yields. Either aromatic aldehydes, which have an electron-withdrawing group such as 4-nitrobenzaldehyde, or aliphatic aldehydes also afforded the desired aldol adducts in moderate yields. When a conjugated aldehyde was used, 1,2- and 1,4-addition reactions took place simultaneously in DMF, while the aldol adduct was exclusively formed in high yield without accompanying 1,4-adduct in pyridine.

Next, the $LiNPh_2$-catalyzed aldol reaction with several silyl enolates was studied (*Table 5*). In the first place, enolates generated either from *S*-ethyl ethanethioate or

Scheme 3

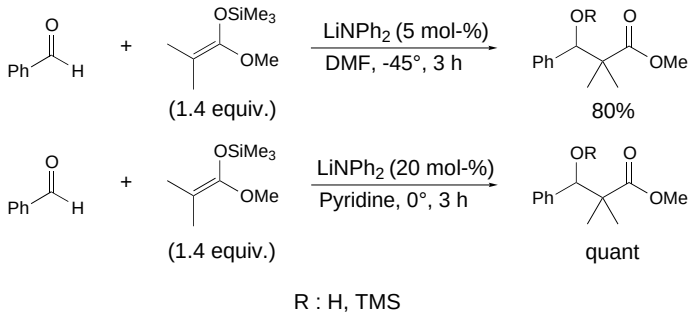
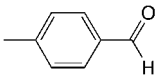
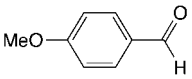
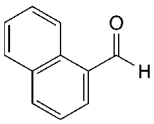
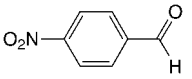
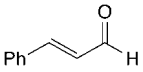
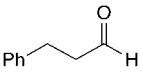
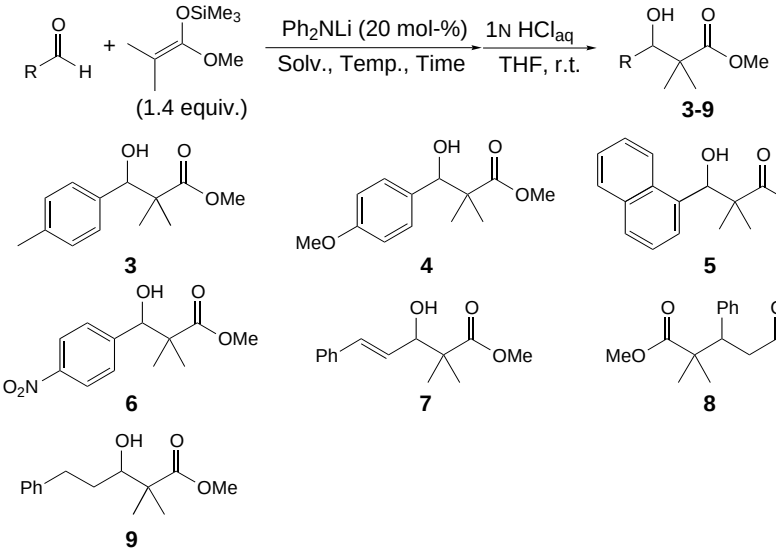


Table 4. *$LiNPh_2$ Catalyzed Aldol Reaction of Trimethylsilyl Enolate and Aldehydes*[a])

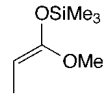
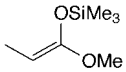
Entry	Aldehyde	Solv.	Temp./°	Time/h	Product	Yield[b])/%
1		DMF	– 45	1	**3**	96
2		Pyridine	0	7	**3**	98
3		DMF	– 45	1	**4**	98
4		Pyridine	0	1	**4**	97
5		DMF	– 45	1	**5**	97
6		Pyridine	0	6	**5**	95
7		DMF	– 45	1	**6**	70[c])
8		DMF	– 45	1	**7**, **8**	99 (12 : 1)[c])[d])
9		Pyridine	0	6	**7**, **8**	96 (100 : 0)[c])[d])
10		DMF	– 45	2	9	60

[a])

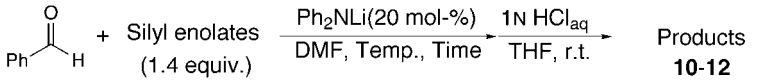


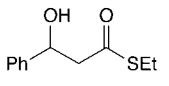
[b]) Isolated yield. [c]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [d]) In parentheses, the ratio **7**/**8**.

Table 5. *$LiNPh_2$ Catalyzed Aldol Reaction of Trimethylsilyl Enolate and Benzaldehyde*[a])

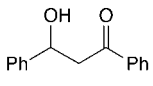
Entry	Silyl enolate	Temp./°	Time/h	Product	Yield[b])/%	*syn*/*anti*
1		– 45	2	**10**	95	–
2		– 45	5	**11**	93[c])	–
3		0	5	**11**	8[c])	–
4	 (*E*):(*Z*) 5:1	– 45	5	**12**	41	1.9 : 1
5	 (*E*):(*Z*) 1:9	– 45	5	**12**	79	2.7 : 1

[a])





10



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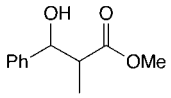

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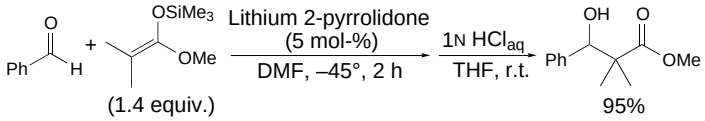
[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [c]) Isolated yield.

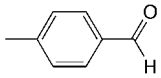
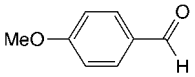
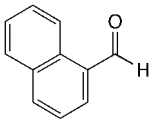
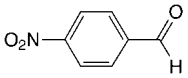
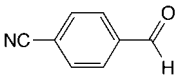
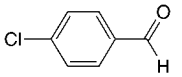
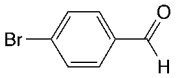
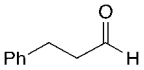
Scheme 4



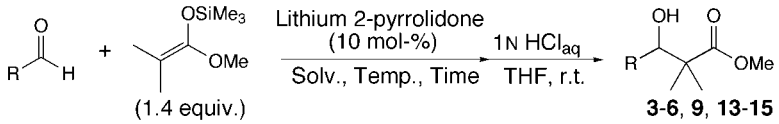
acetophenone were allowed to react with PhCHO in the presence of a catalytic amount of $LiNPh_2$, and the corresponding aldol adducts were obtained in good yields (*Entries 1* and *2*). Further, it was observed that the silyl enolate derived from methyl propionate gave aldols with moderate *syn*-diastereoselectivity irrespective of the geometry of the two isomeric silyl enolates (*Entries 4* and *5*).

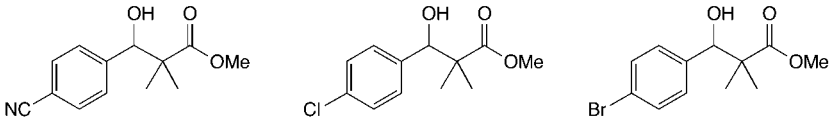
2.4. *Lithium 2-Pyrrolidone-Catalyzed Aldol Reaction between Trimethylsilyl Enolates and Aldehydes.* It turned out that $LiNPh_2$ is an effective *Lewis* base catalyst for the aldol reaction of several trimethylsilyl enolates with various aldehydes in DMF

Table 6. *Lithium 2-Pyrrolidone Catalyzed Aldol Reaction of Trimethylsilyl Enolate and Aldehydes*[a])

Entry	Aldehyde	Solv.	Temp./°	Time/h	Product	Yield[b])/%
1		DMF	– 45	1.5	**3**	95
2		Pyridine	0	3	**3**	93
3		DMF	– 45	2	**4**	92
4		Pyridine	0	3	**4**	95
5		DMF	– 45	4	**5**	91[c])
6		Pyridine	0	5	**5**	83[c])
7		DMF	– 45 → r.t.	3 d	**6**	57
8		DMF	– 45	3	**13**	78
9		Pyridine	0	5	**13**	89
10		DMF	– 45	2	**14**	87
11		Pyridine	0	30	**14**	82
12		DMF	– 45	3	**15**	92
13		Pyridine	0	30	**15**	88
14		DMF	– 45	4	**9**	55[c])

[a])

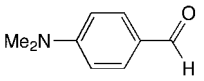
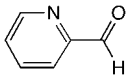
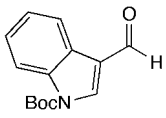




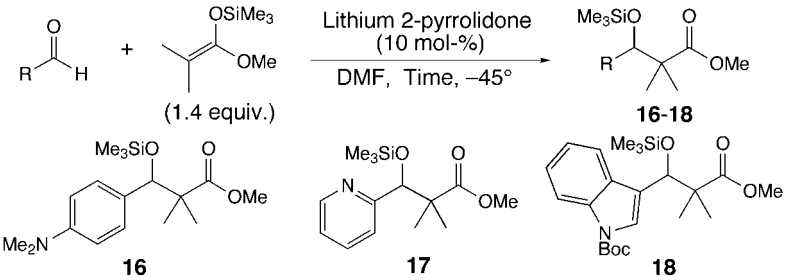
13 **14** **15**

[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [c]) Isolated yields.

Table 7. *Lithium 2-Pyrrolidone Catalyzed Aldol Reaction of Trimethylsilyl Enolate and Aldehydes with Basic Part*[a])

Entry	Aldehyde	Time/h	Product	Yield[b])/%
1		1	**16**	97
2		2	**17**	91
3		3	**18**	97[c])

[a])

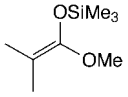
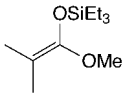
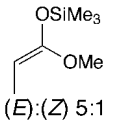
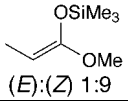


[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [c]) Isolated yield.

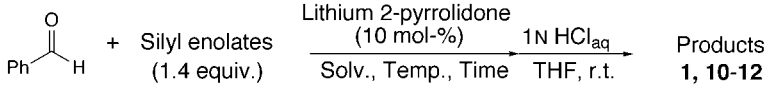
or pyridine. The above catalyst, however, has some problems in separating it from the resulting reaction mixture. Having as a goal the activation of a simple and popular silyl enolate such as trimethylsilyl enolate, another *Lewis* base catalyst that could be easily removed from an organic layer by simple extraction with H_2O was considered. Then, our attention was focused on a lactam such as 2-pyrrolidone as a precursor of the catalyst. It is not only easy to dissolve in H_2O, it is readily available, inexpensive, and the pK_a value of the N–H bond is relatively close to that of Ph_2NH measured in DMSO [18]. Thus, a catalytic aldol reaction of trimethylsilyl enolates with aldehydes was tried in the presence of a catalytic amount of lithium 2-pyrrolidone.

When trimethylsilyl enolate derived from methyl isopropionate and PhCHO was allowed to react in the presence of a stoichiometric amount of lithium 2-pyrrolidone in THF at 0°, the aldol adduct was obtained in only 39% yield. On the other hand, the above reaction proceeded smoothly by using a catalytic amount of lithium 2-pyrrolidone in DMF or pyridine. That is, the reaction was carried out by adding 5 mol-% of lithium 2-pyrrolidone either at $-45°$ in DMF or at 0° in pyridine, and the desired aldol was obtained in 95% yield in DMF (*Scheme 4*) or 78% yield in pyridine.

Table 8. *Lithium 2-Pyrrolidone Catalyzed Aldol Reaction of Silyl Enolates and Benzaldehyde*[a])

Entry	Silyl enolates	Solv.	Temp./°	Time/h	Product	Yield[b])/%	*syn*/*anti*
1		DMF	– 45	2	**10**	95	–
2		DMF	– 45	3	**11**	77	–
3		DMF	– 45	2	**1**	95[c])	–
4		DMF	– 45	3	**1**	trace	–
5	 (*E*):(*Z*) 5:1	DMF	– 45	3	**12**	42	63 : 37
6		DMF	0	3	**12**	50	62 : 38
7		Pyridine	– 19 → 0	18	**12**	4	62 : 38
8	 (*E*):(*Z*) 1:9	DMF	– 45	3	**12**	88	73 : 27
9		DMF	0	3	**12**	95	71 : 29
10		Pyridine	– 19 → 0	18	**12**	70	71 : 29

[a])



[b]) Yields were determined by ^{1}H-NMR analysis (270 MHz) with 1,1,2,2-tetrachloroethane as an internal standard. [c]) 5 mol-% of lithium 2-pyrrolidone was used.

These results indicated that the lithium 2-pyrrolidone as the *Lewis* base did catalyze the aldol reaction of trimethylsilyl enolates with aldehydes in DMF or pyridine.

The scope of acceptor aldehydes was further examined by using 10 mol-% of lithium 2-pyrrolidone in DMF or pyridine (*Table 6*). Trimethylsilyl enolate derived from methyl isopropionate smoothly reacted with various aromatic aldehydes to afford the corresponding aldols in high yields. Either aromatic aldehydes, which have an electron-withdrawing group such as 4-nitrobenzaldehyde, or aliphatic aldehydes also afforded the aldol adducts in moderate yields. Thus, the lithium 2-pyrrolidone, like $LiNPh_2$, behaved as an effective catalyst in aldol reaction.

Lewis base catalyzed reaction exhibits its full power in aldol reaction especially when aldehydes having basic functions are used. To show the utility of this *Lewis* base catalyzed aldol reaction, trimethylsilyl enolates generated from methyl isopropionate and aldehydes having basic functions were allowed to react in DMF at – 45°

in the presence of 10 mol-% of lithium 2-pyrrolidone. The reaction proceeded smoothly, and the corresponding aldol adducts were obtained in high yields (*Table 7*).

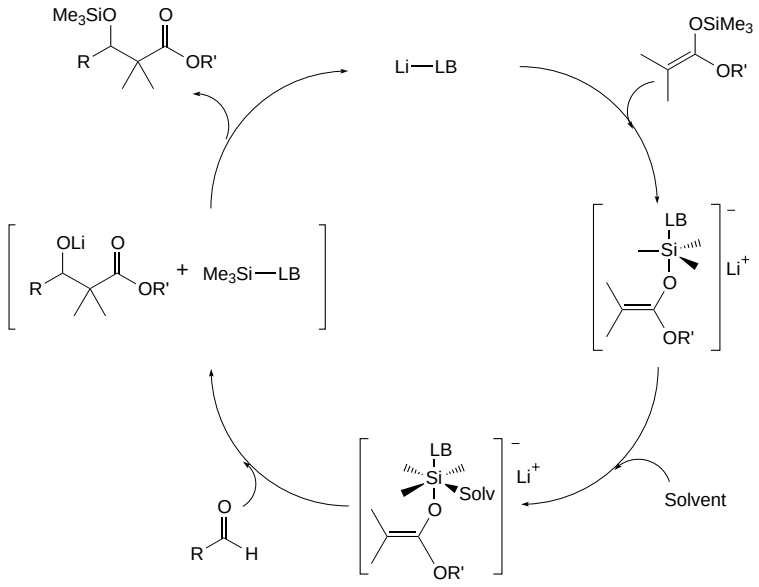
Several silyl enolates were further employed in this lithium 2-pyrrolildone-catalyzed aldol reaction (*Table 8*). In the first place, enolates prepared from *S*-ethyl ethanethioate or acetophenone were employed, and the corresponding aldol adducts were obtained in good yields (*Entries 1* and *2*). On the other hand, only a trace amount of the desired aldol was detected when a bulkier silyl derivative such as triethylsilyl enolate derived from methyl isopropionate was employed (*Entry 4*) in place of the above-mentioned trimethylsilyl enolate (*Entry 3*). Since the reactivity of this aldol was strongly influenced by the bulkiness of the silyl group of the enolate, the reaction was assumed to proceed *via* activation of trimethylsilyl enolates by coordination of the lithium 2-pyrrolidone catalyst to the Si-atom of the enolate [12]. In addition, the reaction would proceed mostly *via* acyclic transition states, since the silyl enolate derived from methyl propionate was observed to give aldols with moderate *syn*-diastereoselectivity irrespective of the geometry of the two isomeric silyl enolates (*Entries 4–9*). Thus, the reaction was shown to proceed mostly *via* acyclic transition states [10].

It should be noted that the solvent also plays an important role in this aldol reaction. Nucleophilicity of the amide anion was amplified by coordination of a *Lewis* basic solvent such as DMF or pyridine to the lithium ion and resulted in both acceleration of the aldol reaction and the silylation of the aldolate. To supplement the solvent effect, the aldol reaction of trimethylsilyl enolate of methyl isopropionate with PhCHO and 5 mol-% of lithium 2-pyrrolidone was performed in pyridine or substituted pyridines such as 4-picoline, 2-picoline, and 2,6-lutidine, to give yields of 54%, 18%, and trace, respectively. These results show that the reactivity diminished remarkably when bulky substituents were present around the N-atom of the solvent; therefore, it is noted that the coordination of the solvent to the Si-atom plays an important role in this reaction. Since this reaction in pyridine at 0° did not take place in the absence of catalyst, the mechanism of the reaction can be explained as follows: in the first place, lithium 2-pyrrolidone coordinates to the Si-atom of trimethylsilyl enolates to form a pentacoordinated hypervalent silicate; the solvent further coordinates to the Si-atom of thus-formed pentacoordinated silicate to produce a hexacoordinated hypervalent silicate. The reactivity of the enolate, therefore, increased enough for it to attack the aldehyde, forming the desired aldol *via* acyclic transition states. Subsequent silylation of lithium aldolate by the thus-formed silyl amide afforded *O*-silyl ether along with the regeneration of lithium amide to establish a catalytic cycle (*Scheme 5*).

3. Conclusions. – In summary, a new *Lewis* base catalyzed aldol reaction of trimethylsilyl enolates with aldehydes was established by using *Lewis* bases such as $LiNPh_2$ or lithium 2-pyrrolidone in DMF or pyridine solvent.

This work was supported by *Grant-in-aid for Scientific Research* from the *Ministry of Education, Science, Sports and Culture*, Japan. We thank Mr. *H. Kitagawa* and Miss *S. Miki*, *Meiji Seika Kaisha, Ltd.* for mass-spectrometry analysis.

Scheme 5



LB: diphenylamide or pyrrolidone

Experimental Part

General. All reactions were carried out under an Ar atmosphere in dried glassware. DMF was dried with P_2O_5 and then distilled from CaH_2 under reduced pressure and dried (molecular sieves (4 Å)). Pyridine was distilled from P_2O_5 and dried (KOH). All reagents were purchased from *Tokyo Kasei Kogyo*, *Kanto Chemical*, or *Aldrich Chemical*. Column chromatography (CC): silica gel *60* (*Merck*) or *Wakogel B5F*. M.p.: *Yanaco MP-S3* micro melting-point apparatus. IR Spectra: *Horiba FT300* infrared spectrometer; in cm^{-1}. NMR Spectra: *JEOL JNM-EX270L* spectrometer; $CDCl_3$ solns., with $SiMe_4$ and $CHCl_3$ as internal standard; δ in ppm, J in Hz. High-resolution (HR) MS: *JEOL JMS-700* mass spectrometer with 4-nitrobenzyl alcohol and glycerol as matrix. Elemental analysis: *Yanaco MT-6 CHN CORDER*.

General Procedure for the $LiNPh_2$ Catalyzed Aldol Reaction. To a soln. of Ph_2NH (71.6 mg, 0.42 mmol) in THF (1.5 ml) was added MeLi in Et_2O (1.14M, 0.29 ml, 0.30 mmol) at 0° and was stirred for 30 min. After evaporation of the solvent, DMF (2.0 ml) was added. To the soln. were successively added a soln. of a silyl enolate (2.4 mmol) in DMF (1.0 ml) and a soln. of aldehyde (1.6 mmol) in DMF (1.2 ml) at −45°. The mixture was stirred for an appropriate time at −45°, and then sat. aq. NH_4Cl was added. The mixture was extracted with Et_2O. After evaporation of the solvent, the residue was dissolved in a mixture of HCl (1.0M, 1.5 ml) and THF (6 ml). The mixture was stirred for 30 min, extracted with Et_2O, and the org. layer was washed with brine and dried (Na_2SO_4). After filtration of the mixture and evaporation of the solvent, the crude product was purified by CC to afford corresponding aldol. Products and yields were as reported in the text.

Methyl 3-Hydroxy-2,2-dimethyl-3-phenylpropionate (**1**) [19]. White powder. M.p. 67.1°. IR (neat): 3394, 2985, 1704, 1450, 1281, 1149, 1049. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.11 (*s*, 3 H); 1.14 (*s*, 3 H); 3.12 (*d*, J = 4.1, 1 H); 3.72 (*s*, 3 H); 4.90 (*d*, J = 4.0, 1 H); 7.22–7.47 (*m*, 5 H). ^{13}C-NMR (67.8 MHz, $CDCl_3$): 19.0; 23.0; 47.7; 52.1; 78.6; 127.6; 127.7; 139.9; 178.2.

Methyl 2,2-Dimethyl-3-phenyl-3-(trimethylsiloxy)-3-phenylpropionate (**2**) [20]. Colorless oil. IR (neat): 2947, 1736, 1458, 1257, 1134, 1095. ^{1}H-NMR (270 MHz, $CDCl_3$): −0.05 (*s*, 9 H); 0.99 (*s*, 3 H); 1.12 (*s*, 3 H); 3.67

(*s*, 3 H); 4.97 (*s*, 1 H); 7.49–7.64 (*m*, 5 H). ^{13}C-NMR (67.8 MHz, $CDCl_3$): −0.08; 19.1; 23.0; 49.0; 51.6; 79.2; 127.6; 127.7; 140.8; 177.3.

Methyl 3-Hydroxy-2,2-dimethyl-3-(4-methylphenyl)propionate (**3**). White powder. M.p. 70.0°. IR (neat): 3502, 2950, 1730. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.08 (*s*, 3 H); 1.12 (*s*, 3 H); 2.32 (*s*, 1 H); 3.05 (*s*, 1 H); 3.69 (*s*, 3 H); 4.83 (*s*, 1 H); 7.09–7.18 (*m*, 4 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 19.0; 21.0; 22.8; 47.7; 51.9; 78.4; 127.4; 128.3; 137.0; 137.2; 178.1. Anal. calc. for $C_{13}H_{18}O_3$: C 70.24, H 8.16; found: C 70.05, H 8.17.

Methyl 3-Hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropionate (**4**) [19] [20]. White powder. M.p. 81.2°. IR (neat): 3502, 2985, 1720. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.07 (*s*, 3 H); 1.12 (*s*, 3 H); 3.05 (*s*, 1 H); 3.70 (*s*, 3 H); 3.78 (*s*, 3 H); 4.83 (*s*, 1 H); 6.83 (*m*, 2 H); 7.20 (*m*, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 18.9; 22.8; 47.7; 51.9; 55.1; 78.1; 113.0; 128.6; 132.1; 159.0; 178.1.

Methyl 3-Hydroxy-2,2-dimethyl-3-(naphthalen-1-yl)propionate (**5**). Colorless oil. IR (neat): 3471, 2946, 1720. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.07 (*s*, 3 H); 1.24 (*s*, 3 H); 3.72 (*s*, 3 H); 5.92 (*s*, 1 H); 7.42–7.51 (*m*, 3 H); 7.65–7.68 (*m*, 1 H); 7.77–7.86 (*m*, 2 H); 8.13–8.16 (*m*, 1 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 18.9; 23.7; 48.7; 52.1; 73.0; 123.7; 124.9; 125.2; 125.7; 125.7; 128.2; 128.7; 131.7; 133.4; 136.2; 178.4. HR-MS: 258.1259 ($C_{16}H_{18}O_3^+$, M^+; calc. 258.1256).

Methyl 3-Hydroxy-2,2-dimethyl-3-(4-nitrophenyl)propionate (**6**). White crystals. M.p. 114.5°. IR (neat): 3517, 2985, 1712, 1519. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.13 (*s*, 3 H); 1.15 (*s*, 3 H); 3.74 (*s*, 3 H); 5.01 (*s*, 1 H); 7.41–7.62 (*m*, 2 H); 8.09–8.32 (*m*, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 19.2; 22.7; 47.6; 52.3; 77.7; 122.9; 128.6; 147.3; 147.6; 177.7. HR-MS: 254.1029 ($C_{12}H_{16}NO_5^+$, $[M+H]^+$; calc. 254.1028).

*Methyl (*E*)-3-Hydroxy-2,2-dimethyl-5-phenylpent-4-enoate* (**7**) [4c]. Colorless oil. IR (neat): 3409, 2970, 1720, 1458, 1265, 1134, 971, 748, 702. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.23 (*s*, 3 H); 1.24 (*s*, 3 H); 2.75–2.89 (br. *s*, 1 H); 3.72 (*s*, 3 H); 4.29–4.44 (*m*, 1 H); 6.21 (*dd*, J = 7.1, 15.8, 1 H); 6.64 (*d*, J = 15.8, 1 H); 7.23–7.40 (*m*, 5 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 20.0; 22.8; 47.2; 52.1; 77.8; 126.5; 127.4; 127.8; 128.5; 132.9; 136.5; 177.9.

Methyl 2,2-Dimethyl-3-phenyl-5-oxopentanoate (**8**). Colorless oil. IR (neat): 3464, 1712. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.10 (*s*, 3 H); 1.16 (*s*, 3 H); 2.69 (*ddd*, J = 1.3, 4.3, 16.8, 1 H); 2.98 (*ddd*, J = 2.6, 10.9, 16.8, 1 H); 3.62 (*dd*, J = 4.3, 10.9, 1 H); 3.66 (*s*, 3 H); 7.16–7.32 (*m*, 5 H); 9.53 (*dd*, J = 1.3, 2.6, 1 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 21.3; 24.3; 44.8; 46.1; 46.7; 51.9; 127.3; 128.2; 129.4; 139.0; 177.3; 201.3. HR-MS: 235.1335 ($C_{14}H_{19}O_3^+$, $[M+H]^+$; calc. 235.1334).

Methyl 3-Hydroxy-2,2-dimethyl-5-phenylpentanoate (**9**) [4c]. Colorless oil. IR (neat): 3465, 2939, 1720. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.16 (*s*, 3 H); 1.18 (*s*, 3 H); 1.53–1.81 (*m*, 2 H); 2.51 (*s*, 1 H); 2.59–2.70 (*m*, 1 H); 2.90–3.00 (*m*, 1 H); 3.60–3.67 (*m*, 1 H); 3.68 (*s*, 3 H); 7.15–7.31 (*m*, 5 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 20.3; 22.4; 32.8; 33.6; 47.1; 51.9; 76.0; 125.8; 128.4; 128.5; 142.1; 178.2.

S-*Ethyl 3-Hydroxy-3-phenylpropanethioate* (**10**) [21]. Colorless oil. IR (neat): 3502, 3425, 2970, 2924, 1682. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.25 (*t*, J = 7, 3 H); 2.84–3.04 (*m*, 4 H); 3.11–3.17 (br. *s*, 1 H); 5.12–5.21 (*m*, 1 H); 7.23–7.40 (*m*, 1 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$):14.6; 23.5; 52.5; 70.8; 125.5; 127.7; 128.4; 142.2; 198.7.

3-Hydroxy-1,3-diphenylpropan-1-one (**11**) [19]. Colorless oil. IR (neat): 3548, 3425, 1673. ^{1}H-NMR (270 MHz, $CDCl_3$): 3.37 (*d*, J = 6, 2 H); 5.34 (*t*, J = 6, 1 H); 7.29–7.58 (*m*, 8 H); 7.81–8.12 (*m*, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 47.4; 70.0; 125.7; 127.7; 128.1; 128.6; 128.7; 133.6; 136.5; 142.9; 200.2.

Methyl 3-Hydroxy-2-methyl-3-phenylpropionate (**12**) [19]. syn-*Isomer:* Colorless oil. IR (neat): 3518, 3425,2978, 1728, 1443, 1188, 1049. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.12 (*d*, J = 7, 3 H); 2.62–3.09 (br *s*, 1 H); 2.79 (*dq*, J = 4, 7, 1 H); 3.66 (*s*, 3 H); 5.09 (*d*, J = 4, 1 H); 7.21–7.43 (*m*, 5 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 10.7; 46.4; 51.8; 73.6; 125.9; 127.5; 128.2; 141.4; 176.1. anti-*Isomer:* White powder. M.p. 48.0°. IR (neat): 3502, 2970, 1728, 1450, 1180, 1041. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.00 (*d*, J = 7, 3 H); 2.63–3.20 (br. *s*, 1 H); 2.82 (*dq*, J = 7, 8, 1 H); 3.72 (*s*, 3 H); 4.74 (*d*, J = 8, 1 H); 7.25–7.43 (*m*, 5 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 14.4; 47.1; 51.9; 76.4; 126.6; 128.1; 128.5; 141.5; 176.2.

Methyl 3-(4-Cyanophenyl)-3-hydroxy-2,2-dimethylpropionate (**13**) [20]. White powder. M.p. 96.0°. IR (neat): 3479, 2985, 2229, 1728. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.09 (*s*, 3 H); 1.13 (*s*, 3 H); 3.59–3.68 (*m*, 1 H); 3.71 (*s*, 3 H); 4.95 (*d*, J = 4.3, 1 H); 7.38–7.48 (*m*, 2 H); 7.55–7.66 (*m*, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 19.1; 22.3; 47.6; 52.1; 77.5; 111.2; 118.6; 128.3; 131.3; 145.5; 177.5.

Methyl 3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethylpropionate (**14**). White powder. M.p. 63.2°. IR (neat): 3471, 2978, 1720. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.08 (*s*, 3 H); 1.12 (*s*, 3 H); 3.21 (*s*, 1 H); 3.71 (*s*, 3 H); 4.85 (*s*, 1 H); 7.18–7.36 (*m*, 4 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 19.0; 22.8; 47.6; 52.1; 77.9; 127.9; 129.0; 133.5; 138.4; 178.0. Anal. calc. for $C_{12}H_{15}ClO_3$: C 59.39, H 6.23; found: C 59.29, H 6.22.

Methyl 3-(4-Bromophenyl)-3-hydroxy-2,2-dimethylpropionate (**15**). White powder. M.p. 70.8°. IR (neat): 3471, 3410, 2978, 1705. ^{1}H-NMR (270 MHz, $CDCl_3$): 1.07 (*s*, 3 H); 1.11 (*s*, 3 H); 3.24–3.44 (br. *s*, 1 H); 3.70

(*s*, 3 H); 4.82 (*s*, 1 H); 7.14–7.17 (*m*, 2 H); 7.42–7.45 (*m*, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 19.0; 22.7; 47.5; 52.1; 77.8; 121.5; 129.3; 130.8; 138.9; 177.9. Anal. calc. for $C_{12}H_{15}BrO_3$: C 50.19, H 5.27; found: C 50.15, H 5.27.

Methyl 3-[4-(Dimethylamino)phenyl]-2,2-dimethyl-3-(trimethylsilyloxy)propionate (**16**) [19]. White powder. M.p. 80.1°. IR (neat): 2978, 1728, 1612, 1519, 1458, 1349, 1250, 1073. ^{1}H-NMR (270 MHz, $CDCl_3$): −0.07 (*s*, 9 H); 1.00 (*s*, 3 H); 1.09 (*s*, 3 H); 2.91 (*s*, 6 H); 3.65 (*s*, 3 H); 4.87 (*s*, 1 H); 6.59 (*d*, $J = 8.7$, 2 H); 7.31 (*d*, $J = 8.7$, 2 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): −0.1; 18.8; 21.9; 40.5; 49.2; 51.5; 79.0; 111.3; 128.4; 128.5; 149.8; 177.6.

Methyl 2,2-Dimethyl-3-(pyridin-2-yl)-3-(trimethylsilyloxy)propionate (**17**). Colorless oil. IR (neat): 3626, 3186, 2993, 1728. ^{1}H-NMR (270 MHz, $CDCl_3$): −0.04 (*s*, 9 H); 0.98 (*s*, 3 H); 1.12 (*s*, 3 H); 3.65 (*s*, 3 H); 5.06 (*s*, 1 H); 7.07–7.17 (*m*, 1 H); 7.34–7.44 (*m*, 1 H); 7.56–7.70 (*m*, 1 H); 8.40–8.49 (*m*, 1 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): 0.0; 20.2; 21.0; 48.7; 51.7; 79.8; 122.1; 135.6; 147.8; 161.1; 176.6. Anal. calc. for $C_{14}H_{23}NO_3Si$: C 59.75, H 8.24, N 4.96; found: C 59.64, H 8.25, N 4.97.

*Methyl 3-[1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl]-2,2-dimethyl-3-(trimethylsiloxy)propionate* (**18**). Colorless oil. IR (neat): 2978, 1736, 1458, 1373, 1257, 1149, 1280, 856, 756. ^{1}H-NMR (270 MHz, $CDCl_3$): −0.04 (*s*, 9 H); 1.09 (*s*, 3 H); 1.25 (*s*, 3 H); 1.68 (*s*, 9 H); 3.67 (*s*, 3 H), 5.26 (*s*, 1 H); 7.12–7.37 (*m*, 2 H); 7.43 (*s*, 1 H); 7.68–7.84 (*m*, 1 H); 7.99–8.22 (*m*, 1 H). ^{13}C-NMR (68.7 MHz, $CDCl_3$): −0.2; 19.9; 21.9; 28.2; 49.7; 51.7; 74.1; 83.7; 114.9; 120.8; 121.5; 122.3; 124.0; 129.9; 135.2; 149.7; 168.1; 177.2. HR-MS: 419.2120 ($C_{22}H_{33}O_5NSi^+$, M^+; calc. 419.2128).

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