Lewis Base-Promoted Aldol Reaction of Dimethylsilyl Enolates in Aqueous Dimethylformamide: Use of Calcium Chloride as a Lewis Base Catalyst

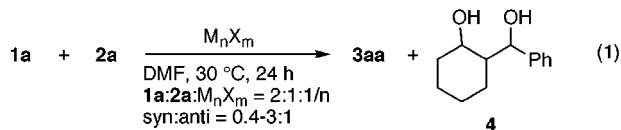Katsukiyo Miura, Takahiro Nakagawa, and Akira Hosomi*

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The aldol reactions of silyl enolates have been widely utilized for highly efficient and stereoselective C−C bond formation.[1] A variety of reagents, particularly Lewis acids, are known to promote the nucleophilic process.[2] Recently, water-stable Lewis acids such as lanthanide triflates, which enable the aldol reactions in aqueous solvent or pure water, have received much attention in relation to the development of economical and environmentally benign synthetic methods.[3] Fluoride ion and other Lewis bases also accelerate the aldol reactions by nucleophilic activation of silyl enolates;[4,5] however, the base-catalyzed system has not yet been utilized in aqueous media to the best of our knowledge. We herein disclose that $CaCl_2$ works as a Lewis base to promote the aldol reaction of dimethylsilyl (DMS) enolates even in the presence of water.[6]

The uncatalyzed reaction of benzaldehyde (**2a**) with DMS enolate **1a** (2 equiv) at 30 °C for 24 h gave aldol adduct **3aa** in 43% yield.[7] Addition of an equimolar amount of $CaCl_2$ completed the aldol reaction in 2 h to achieve a quantitative yield of **3aa**. A catalytic amount of $CaCl_2$ and a small excess of **1a** were enough to attain high reaction efficiency (entry 1 in Table 1). In contrast to the result with **1a**, cyclohexanone TMS enolate was quite insensitive to **2a** under similar conditions. As shown in Table 1, the $CaCl_2$-catalyzed system was applicable to α,β-unsaturated and aliphatic aldehydes. DMS enolate **1b** showed slightly higher reactivity than **1a**.

Encouraged by the initial results with $CaCl_2$, we examined the aldol reaction using other alkali earth and alkali metal salts. As a result, some metal salts proved to be effective promoters (eq 1).

Table 1. $CaCl_2$-Promoted Aldol Reaction of DMS Enolates[a]

1a: $R^1, R^2 = (CH_2)_4$ **2a**: R = Ph
1b: $R^1 = Ph, R^2 = Me$ **2b**: R = (E)-PhCH=CH
   2c: R = $Ph(CH_2)_2$

entry	enolate	aldehyde	product	yield/%[b]	syn:anti[b]
1	**1a**	**2a**	**3aa**	90 (82)	45:55 (47:53)
2	**1a**	**2b**	**3ab**	92 (79)	50:50 (51:49)
3	**1a**	**2c**	**3ac**	65 (75)	40:60 (39:61)
4	**1b**	**2a**	**3ba**	98 (82)	53:47 (52:48)
5	**1b**	**2b**	**3bb**	99 (85)	42:58 (42:58)
6	**1b**	**2c**	**3bc**	90 (79)	53:47 (54:46)

[a] Conditions: **1** (1.00 mmol), **2** (0.50 mmol), $CaCl_2$ (0.125 mmol), DMF (1 mL), 30 °C, 24 h. [b] The result with a small excess of **1** (0.60 mmol) and a half amount of DMF (0.5 mL) is shown in parentheses.

yield of **3aa** were as follows: $CaCl_2$, 95; LiCl, 98; Bu_4NCl, 67; $CaBr_2$, 54; $MgBr_2$, 54; LiBr, 52; Bu_4NBr, 25; CaI_2, 32;[10] LiI, 34;[10] NaI, 35; KI, 34; Bu_4NI, 40; LiOTf, 17; none, 20. Thus, the reaction efficiency varied with the salts used to a great extent. These results indicate that the rate-acceleration does not originate from the increased polarity of the reaction medium,[11] and the counteranion plays a crucial role in promoting the aldol reaction. The rate-accelerating ability of metal salt increased with increasing intrinsic nucleophilicity of the counteranion: $TfO^- < I^- \leq Br^- < Cl^-$.[12]

Judging from the low Lewis acidity of $CaCl_2$[13] and the rate-accelerating ability of other metal salts, in the present $CaCl_2$-catalyzed system, the chloride ion would work as a Lewis base to activate DMS enolates.[4,5] This deduction is supported by the rate-accelerating effect of Bu_4NCl and the insensitivity of cyclohexanone TMS enolate. In the Bu_4NCl-promoted reaction (eq 1), the activation of **2a** is not likely. The latter result is attributable to the steric bulkiness around the silicon atom, which would interfere with attack of the chloride ion.

In our previous work on the base-catalyzed Mannich-type reaction of DMS enolates,[6] we have found that the reactivity of **1a** to N-tosylimine **5** is much higher than that to **2a** under the basic conditions (entry 1 in Table 2). To confirm the role of $CaCl_2$, we examined a competitive reaction of **1a** with **2a** versus **5** in the $CaCl_2$-catalyzed system (entry 2). As a result, the Mannich-type reaction with **5** smoothly proceeded in preference to the aldol reaction with **2a**. In contrast, the competitive reaction with $TiCl_4$, a typical Lewis acid, gave aldol adduct **3aa** exclusively (entry 3). These observations clearly indicate that $CaCl_2$ acts as a Lewis base.

The $CaCl_2$-promoted reaction was strongly affected by the solvent used (eq 2). The aldol reaction of **1a** with **2a** smoothly proceeded in DMSO, while the use of THF, which hardly dissolved $CaCl_2$,

The LiCl- and NaCl-promoted reactions of **2a** with **1a** for 24 h gave **3aa** in high yields; however, shortening the reaction time revealed that the rate-accelerating ability of NaCl was much lower than that of $CaCl_2$ (36% yield of **3aa** after 2 h). The low activity of NaCl would come from the lower solubility to DMF. Interestingly, in the case of Na_2CO_3, a certain amount of diol **4** was formed by the tandem aldol−reduction reaction.[8] To gain a mechanistic insight into the present reaction, Bu_4NCl was used instead of a metal salt. The chloride also accelerated the aldol reaction of **1a**.

We further investigated the rate-accelerating ability of metal and tetrabutylammonium salts very soluble to DMF. When the reaction of **1a** with **2a** was performed in DMF solution with a certain ion strength ($I = 1.0-1.1$) at 30 °C for 3 h,[9] the salt examined and the

Table 2. Competitive Reaction of **1a**[a]

| entry	conditions[b]	yield/%	
		3aa	**6**
1[c]	H$_2$O (0.6), i-Pr$_2$NH (0.024), DMF, −78 °C, 24 h	0	90
2	CaCl$_2$ (1.0), DMF, 30 °C, 24 h	10	88
3	TiCl$_4$ (1.0), CH$_2$Cl$_2$, −78 °C, 2 h	quant.	trace

[a] **1a** (0.50 mmol), **1a**:**2a**:**5** (molar ratio) = 1:1:1. [b] The molar ratio to **1a** is shown in parentheses. [c] See ref 6.

Table 3. Aldol Reaction of Aqueous Aldehydes in DMF[a]

entry			1:2:CaCl$_2$[b]	product	yield/%[c,d]	syn:anti
1	**1a**	**2d** (R =H)	1:2:1	**3ad**	78[e] (58)	
2	**1b**	**2d**	1:2:0.13	**3bd**	99 (30)	
3	**1c**	**2d**	1:2:1	**3cd**	77[e,f]	
4	**1d**	**2d**	1:2:1	**3dd**	83	
5	**1a**	**2e** (R = PhCO)	1.2:1:1[g]	**3ae**	72 (71)	52:48[h]
6	**1b**	**2e**	1:0.5:0.5	**3be**	93 (73)	73:27
7	**1a**	**2f** (R = Cl$_3$C)	1:0.5:0.5	**3af**	48 (28)	88:12
8	**1b**	**2f**	1:0.5:0.5	**3bf**	89 (41)	91:9

[a] Unless otherwise noted, all reactions were performed with **1** (1.00 mmol) in DMF (1.5 mL in entries 1−4 or 1 mL in entries 5−8) at 30 °C for 24 h. [b] Molar ratio. [c] Based on **1** in entries 1−4 or **2** in entries 5−8. [d] The result without CaCl$_2$ is shown in parentheses. [e] At 0 °C. [f] Cis:trans = 63:37. [g] With 0.60 mmol of **1a**. [h] The relative configuration was not assigned.

resulted in a low conversion of **2a**. The homogeneous reaction in MeOH gave dehydrated 2:1 adduct **7** as a major product. Surpris-
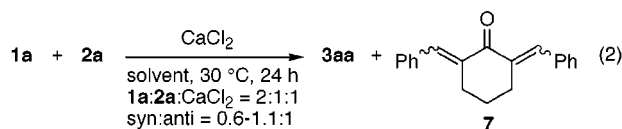

Solvent, Yield of **3aa** (**7**): DMSO, 81; THF, 26; MeOH, trace (78); H$_2$O, 70; H$_2$O-DMF (1:1), 73; none, 41

ingly, water was an effective solvent although the substrates did not dissolve well in water.[14,15] A control experiment without solvent proved the utility of water. Aqueous DMF (H$_2$O−DMF 1:1) was also available for the CaCl$_2$-promoted system.

The above results induced us to apply the CaCl$_2$-promoted system to the aldol reaction of aqueous aldehydes. We first investigated hydroxymethylation reaction with a 37% aqueous solution of HCHO (**2d**).[3b,16] The uncatalyzed reaction of **1a** with **2d** (2 equiv) in DMF at 30 °C for 24 h gave adduct **3ad** in 58% yield (entry 1 in Table 3). In the presence of CaCl$_2$, the yield increased to 71%. NaCl and MgCl$_2$ had similar effects on the reaction efficiency. Lowering the reaction temperature to 0 °C slightly improved the yield (entry 1). The use of water as solvent brought a low yield of **3ad**. DMS enolate **1b** showed higher reactivity to **2d** to give a quantitative yield of **3bd** even in the presence of a catalytic amount of CaCl$_2$ (entry 2). Without CaCl$_2$, the yield of **3bd** dropped to 30%. The hydroxymethylation of DMS enolate **1c** and its regioisomer **1d**

proceeded in a regiospecific manner (entries 3−4). The present system could be successfully utilized for the aldol reactions with phenylglyoxal monohydrate (**2e**) and chloral monohydrate (**2f**) (entries 5−8).
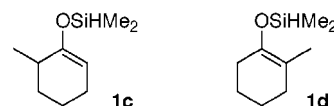
In summary, we have revealed that CaCl$_2$ is an effective Lewis base catalyst for the aldol reaction of DMS enolates. The present study shows the first example that the Lewis base activation of silyl enolates, as well as the Lewis acid activation of aldehydes, is valuable for the aqueous aldol reaction of silyl enolates.

Supporting Information Available: Experimental details and spectroscopy data of DMS enolates and unknown aldol adducts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org..

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(15) The use of Bu$_4$NCl (0.5 equiv) in combination with CaCl$_2$ improved the yield of **3aa** to 88%.
(16) The commercially available HCHO solution including 5−10% of MeOH as a stabilizer was used.

JA017218L