Metal Chloride-Promoted Aldol Reaction of α-Dimethylsilylesters with Aldehydes, Ketones, and α-Enones

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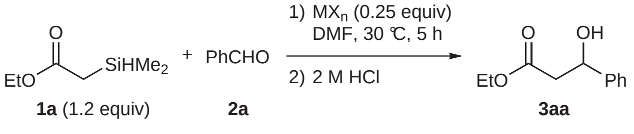
Abstract: In the presence of a catalytic amount of LiCl, α-dimethylsilylesters (α-DMS-esters) **1** smoothly reacted with various aldehydes at 30 °C to give aldols in good to high yields. On the other hand, the aldol reaction with ketones was effectively promoted by $MgCl_2$ rather than by LiCl. α-Enones also underwent the metal chloride-promoted addition of **1** at the carbonyl carbon or β-carbon.

Key words: aldehydes, aldol reactions, ketones, Michael additions, α-silylesters

The Mukaiyama-aldol reactions of silyl enolates provide regio- and stereoselective methods for C–C bond formation and functionalization.[1] Since the pioneering work by Mukaiyama et al.,[2] Lewis acid catalysts have frequently been used for the synthetically valuable transformations. It is also well known that fluoride ion sources work as Lewis base catalysts to promote the aldol reaction via nucleophilic activation of silyl enolates.[3] In recent years, however, much attention has been focused on the development of other Lewis base-catalyzed systems.[1,4,5] In this context, we have reported that the aldol reaction of dimethylsilyl enolates derived from ketones is accelerated by chloride ion sources such as alkali and alkali earth metal chlorides.[6,7] The known Lewis base-catalyzed systems including the fluoride ion-catalyzed ones are useful for the reaction with aldehydes, while there are few successful examples of the use of ketones as electrophiles.[8,9] We herein disclose that α-dimethylsilylesters (α-DMS-esters) work as enolate equivalents under catalysis by metal chlorides to achieve an efficient aldol reaction of simple ketones and α-enones as well as aldehydes.[10]

Initially, the reaction of ethyl DMS-acetate (**1a**) with benzaldehyde (**2a**) was selected to examine the catalytic activity of metal salts and Bu_4NCl.[11] As previously reported by us,[11a] **1a** reacted spontaneously with **2a** in DMF (30 °C, 5 h). An acidic, desilylative work-up followed by purification by silica gel column chromatography gave β-hydroxyester **3aa** in 61% yield. A catalytic amount of $MgCl_2$, LiCl, or $CaCl_2$ effectively promoted the aldol reaction under the same conditions. Particularly, the use of LiCl achieved a quantitative yield of **3aa**. In contrast, Bu_4NCl, LiBr, and LiOTf showed lower catalytic activity than these metal chlorides.



MX$_n$, yield (%): none, 61; LiCl, 95; $MgCl_2$, 82; $CaCl_2$, 81; Bu_4NCl, 68; LiBr, 70; LiOTf, 69.

Scheme 1

Under catalysis by LiCl, α-DMS-ester **1a** added smoothly to aromatic and aliphatic aldehydes **2a**–**h** to afford the corresponding β-hydroxyesters **3aa**–**ah** in good to high yields (entries 1–8 in Table 1).[12] The aldol reaction with **2c** took place only at the aldehyde carbonyl (entry 3). In the case of chiral aldehyde **2g**, moderate *syn* (Cram-type) selectivity was observed (entry 7). The stereochemical outcome with β-alkoxyaldehyde **2h** (dr = 57:43) indicates that the present reaction system is not suitable for chelation control (entry 8). The use of hydroxy-substituted benzaldehydes **2i**–**j** resulted in low yields of **3ai**–**aj** even when an increased amount of **1a** was employed (entries 9, 10). The aldol reaction of **2i** competed with the reduction of **2i** to 2-hydroxybenzyl alcohol (**4**). Such a side reaction was not observed with **2j**, and an increased amount of LiCl improved the yield of **3aj**. In these cases, the acidic hydroxy groups of **2i**,**j** would cause the protodesilylation of **1a**. The DMS ether thus formed from **2i** would be converted into **4** by intramolecular hydride transfer (Scheme 2). α-DMS-esters **1b**,**c**, substituted at the α-carbon, showed similar reactivities to aldehydes as did **1a** (entries 11–20). Unfortunately, the reaction of **1b** proceeded with low diastereoselectivity.

Unlike benzaldehyde, cyclohexanone (**5a**) never underwent the addition of **1a** in the absence of a promoter (30 °C, 24 h, Scheme 3). An equimolar amount of LiCl or $CaCl_2$ induced the aldol reaction; however, the rate-accelerating ability was not high enough to realize a successful aldol reaction. In contrast, $MgCl_2$ was found to be an effective promoter. The use of a catalytic amount of $MgCl_2$ resulted in a lower yield of the desired product **6aa**. The rate-accelerating abilities of Bu_4NCl and $Mg(OTf)_2$ were rather low.

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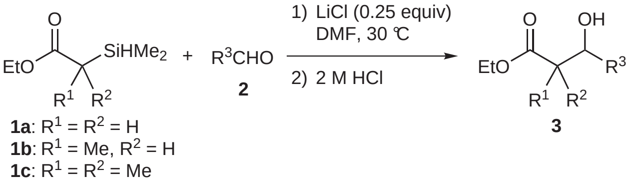
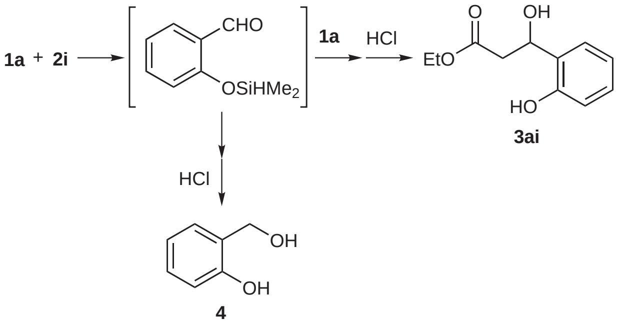
Table 1 LiCl-Catalyzed Addition of α-DMS Esters to Aldehydes[a]



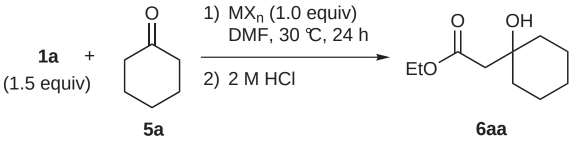
Entry	1	Aldehyde 2	R^3	3	Yield (%)[b] (*syn*:*anti*)
1	**1a**	**2a**	Ph	**3aa**	95
2	**1a**	**2b**	4-MeO-C_6H_4	**3ab**	96
3	**1a**	**2c**	4-MeC(O)-C_6H_4	**3ac**	77
4	**1a**	**2d**	(*E*)-PhCH=CH	**3ad**	95
5	**1a**	**2e**	$Ph(CH_2)_2$	**3ae**	79
6	**1a**	**2f**	*i*-Pr	**3af**	89
7	**1a**	**2g**	MeCH(Ph)	**3ag**	68 (74:26)
8	**1a**	**2h**	$MeCH(OBn)CH_2$	**3ah**	76 (57:43)[c]
9	**1a**	**2i**	2-HO-C_6H_4	**3ai**	51,[d,e] 66[e,f]
10	**1a**	**2j**	4-HO-C_6H_4	**3aj**	40,[e] 83[e,f]
11	**1b**	**2a**	Ph	**3ba**	97 (69:31)
12	**1b**	**2d**	(*E*)-PhCH=CH	**3bd**	98 (56:44)
13	**1b**	**2e**	$Ph(CH_2)_2$	**3be**	75 (54:46)
14	**1b**	**2f**	*i*-Pr	**3bf**	92 (53:47)
15	**1b**	**2j**	4-HO-C_6H_4	**3bj**	75[e,f] (63:31)
16	**1c**	**2a**	Ph	**3ca**	97
17	**1c**	**2d**	(*E*)-PhCH=CH	**3cd**	95
18	**1c**	**2e**	$Ph(CH_2)_2$	**3ce**	77
19	**1c**	**2f**	*i*-Pr	**3cf**	86
20	**1c**	**2j**	4-HO-C_6H_4	**3cj**	77[e,f]

[a] Unless otherwise noted, all reactions were performed with **1** (0.60 mmol), **2** (0.50 mmol), and LiCl (0.13 mmol) in DMF (1 mL) at 30 °C for 5 h. For general procedure, see ref. 12.
[b] Isolated yield.
[c] The relative configuration was not determined.
[d] Alcohol **4** was obtained in 44% yield.
[e] With 2.0 equiv of **1a**.
[f] With 1.0 equiv of LiCl.

The $MgCl_2$-promoted aldol reaction of **1a** was applicable to both aromatic and aliphatic ketones (entries 1–5 in Table 2). The reaction with ketone **5e** required slightly higher temperature for its complete conversion (entry 5). 4-*tert*-Butylcyclohexanone (**5g**) underwent equatorial attack of **1a** preferentially (Scheme 4).[13] The present reaction stands in sharp contrast with the TBAF-catalyzed reaction of ethyl trimethylsilylacetate with simple ketones, which causes deprotonative silylation to ketone trimethylsilyl enolates.[10] The presence of a hydroxy group in the substrate lowered the reaction efficiency (entry 6). The aldol reaction with 1,3-dicarbonyl compounds such as 2,4-pentanedione and ethyl 3-oxobutanoate did not occur at all. These results are probably due to the deprotonation of the activated methylene by **1a**, which not only consumes **1a** but also reduces the electrophilicity of the carbonyl carbon.



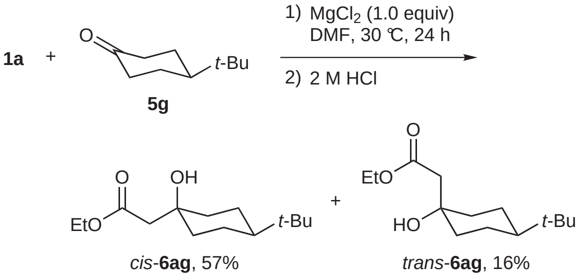
Scheme 2



MX_n, yield (%): none, 0; LiCl, 35; $MgCl_2$, 88; $MgCl_2$*, 59; $CaCl_2$, 35; Bu_4NCl, <5; $MgBr_2$, 29; $Mg(OTf)_2$, 13.
*0.25 equiv of $MgCl_2$ was used.

Scheme 3

α-DMS-ester **1b** as well as **1a** reacted smoothly with ketones **5a**,**b** to give the corresponding aldols in high yields (entries 7, 8). The reaction with **5b** resulted in low diastereoselectivity. Sterically demanding DMS-ester **1c** was less reactive to ketones (entries 9, 10). The products derived from **1c** were easily decomposed by the acidic work up. A neutral aqueous work up provided silyl ethers **7c** in moderate yields.

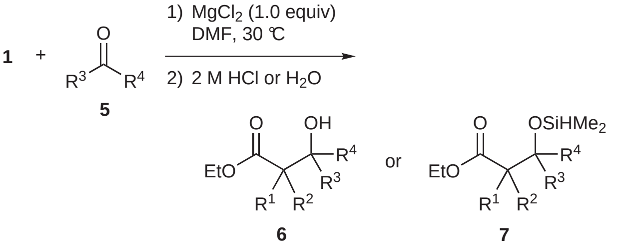


cis-**6ag**, 57% *trans*-**6ag**, 16%

Scheme 4

We further examined the reaction of **1a** with α-enones **8** (Table 3). The $MgCl_2$-promoed reaction of **1a** with chalcone (**8a**) gave aldol **9aa** in high yield (entry 1). The corresponding Michael adduct was not formed at all. The use of $CaCl_2$ instead of $MgCl_2$ led to a slightly higher yield of

Table 2 $MgCl_2$-Promoted Addition of α-DMS Esters to Ketones[a]



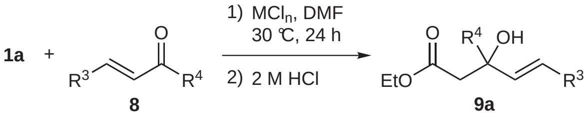
Entry	1		Ketone **5**		**6**	Yield (%)[b]
			R^3	R^4		
1	**1a**	**5a**	$(CH_2)_5$		**6aa**	88
2	**1a**	**5b**	Ph	Me	**6ab**	90
3	**1a**	**5c**	Ph	Et	**6ac**	93
4	**1a**	**5d**	4-MeO-C_6H_4	Me	**6ad**	96
5	**1a**	**5e**	*n*-$C_{11}H_{23}$	Me	**6ae**	59, 95[c]
6	**1a**	**5f**	$HO(CH_2)_3$	Me	**6af**	25
7	**1b**	**5a**	$(CH_2)_5$		**6ba**	91
8	**1b**	**5b**	Ph	Me	**6bb**	88[d]
9	**1c**	**5a**	$(CH_2)_5$		**7ca**	50
10	**1c**	**5b**	Ph	Me	**7cb**	57

[a] Unless otherwise noted, all reactions were carried out with **1** (0.75 mmol), **5** (0.50 mmol), and $MgCl_2$ (0.50 mmol) in DMF (1.0 mL) at 30 °C for 24 h. The reaction mixture was treated with 2 M HCl (1 mL in entries 1–8) or H_2O (1 mL in entries 9 and 10) for 5 min.
[b] Isolated yield.
[c] At 50 °C.
[d] Diastereomeric ratio = 45:55.

9aa, while LiCl was less effective than $MgCl_2$ and $CaCl_2$ (entries 2 and 3). Other α-enones **8b–d** also underwent the $CaCl_2$-promoted aldol reaction to give **9ab–9ad** in moderate to good yields (entries 4–6). With the aid of Lewis acids and bases, silyl enolates and α-silylesters react with α-enones generally at the β-carbon in a conjugate manner.[14–16] The present reaction of **1a** provided a novel example of the aldol reaction with α-enones.[9,17] Unfortunately, α-enone **8e**, bearing a *tert*-butyl group on the carbonyl carbon, was unreactive to **1a** (entry 7).

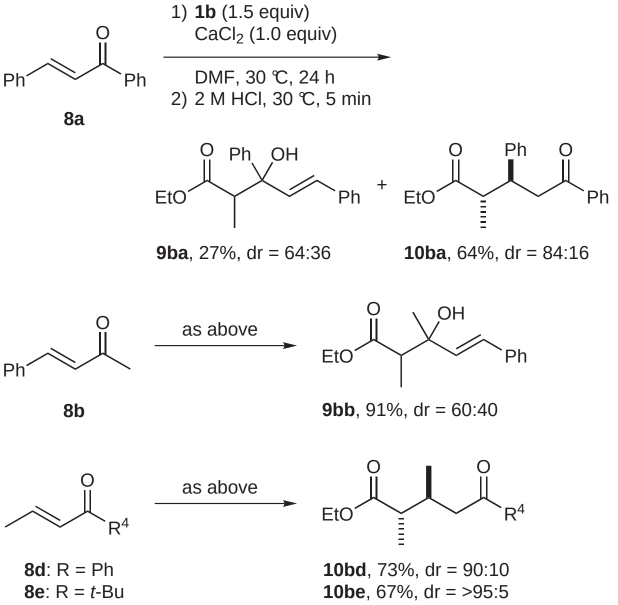
The chemoselectivity of the $CaCl_2$-promoted reaction of **1b** heavily depended on the α-enone used (Scheme 5). The reaction with **8a** gave a mixture of aldol **9ba** and the Michael adduct **10ba** in high yield. α-Enone **8b** underwent only the aldol reaction leading to **9bb**. In contrast, the use of **8d**,**e** afforded only **10bd**,**be** with high *anti*-selectivity. These results indicate that a bulky group on the carbonyl carbon of **8** and a small group on the β-carbon induce the Michael reaction rather than the aldol reaction.

Table 3 Addition of α-DMS Ester **1a** with α-Enones[a]



Entry	MCl_n		α-Enone **8**		**9a**	Yield (%)[b]
			R^3	R^4		
1	$MgCl_2$	**8a**	Ph	Ph	**9aa**	89
2	$CaCl_2$	**8a**	Ph	Ph	**9aa**	92
3	LiCl	**8a**	Ph	Ph	**9aa**	77[c]
4	$CaCl_2$	**8b**	Ph	Me	**9ab**	55[c]
5	$CaCl_2$	**8c**	H	Me	**9ac**	60
6	$CaCl_2$	**8d**	Me	Ph	**9ad**	78
7	$CaCl_2$	**8e**	Me	*t*-Bu	**9ae**	0[c]

[a] Unless otherwise noted, all reactions were carried out with **1** (0.75 mmol), **5** (0.50 mmol), and $MgCl_2$ (0.50 mmol) in DMF (1.0 mL) at 30 °C for 24 h. The reaction mixture was treated with 2 M HCl (1 mL in entries 1–8) or H_2O (1 mL in entries 9 and 10) for 5 min.
[b] Isolated yield.
[c] Yields of the recovered **8**: 20% (entry 3), 39% (entry 4), and >90% (entry 7).



Scheme 5

To gain mechanistic insight, we carried out the metal chloride-catalyzed reactions of ethyl trimethylsilylacetate and ethyl diisopropylsilylacetate with **2a** and **5a**. As a result, these α-silylesters bearing a sterically more crowded silicon center were found to be much less reactive than **1a**. The difference in reactivity suggests that the present reaction should include nucleophilic activation of α-DMS-esters as the key step. The less catalytic activities of metal bromides and triflates also lead to the same mechanistic aspect because a chloride ion (a hard base) has higher silaphilicity than bromide and triflate ions (softer bases).[18] We attempted to observe the active species generated from LiCl and **1a** by ^1H NMR and ^{13}C NMR analyses.

However, the signals of **1a** did not shift in the presence of LiCl. The present reaction may involve reversible formation of a transient active species such as a chloride ion bound silicate.

The low rate-accelerating ability of Bu_4NCl (Scheme 1 and Scheme 3) suggests that the metal ion of a metal chloride also plays an important role for the present reaction. In addition, the fact that $MgCl_2$ promotes the aldol reaction with **5a** more effectively than LiCl and $CaCl_2$ seems to signify the role of the magnesium ion as Lewis acid. When simple ketones are used as electrophiles, simultaneous activation of both **1** and ketones may be required for a successful aldol reaction to compensate their low electrophilicity.[19]

In conclusion, we have demonstrated that α-DMS-esters **1** work as stable enolate equivalents in the presence of inexpensive, disposable metal chlorides such as LiCl, $MgCl_2$, and $CaCl_2$. The aldol reaction of **1** proceeds efficiently under very mild conditions and it is applicable to a variety of aldehydes and ketones. The reaction mechanism would involve nucleophilic activation of **1** by a chloride ion although the participation of metal ions in promoting the present reaction is also important.

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Under N_2 atmosphere, *n*-BuLi (1.61 M in hexane, 62 mL, 100 mmol) was added to a solution of *i*-Pr_2NH (14 mL, 100 mmol) in THF (100 mL) over 5 min at 0 °C. After 10 min, the mixture was cooled to –78 °C. Then, EtOAc (9.3 mL, 95 mmol) was added to the solution of LDA over 5 min. After 2 h, the reaction mixture was treated with chlorodimethylsilane (12.2 mL, 110 mmol) and gradually warmed to r.t. over 12 h. The resultant mixture was diluted with dry pentane (50 mL) and filtered through Celite®. After evaporation of the filtrate, the residual oil was diluted with dry pentane (50 mL) again, filtered through Celite®, and evaporated. Purification of the crude product by distillation gave **1a** (9.2 g, 63 mmol) in 66% yield.
Compound **1a**: bp 58–60 °C (180 Torr). IR (neat): 1669 (C=O), 1253, 1205 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.20 (d, *J* = 3.6 Hz, 6 H), 1.23 (t, *J* = 6.9 Hz, 3 H), 1.96 (d, *J* = 3.3 Hz, 2 H), 4.06 (sept, d, *J* = 3.6, 3.3 Hz, 1 H), 4.10 (q, *J* = 6.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = –4.36 ($CH_3 \times 2$), 14.09 (CH_3), 24.08 (CH_2), 59.91 (CH_2), 172.54 (C). Anal. Calcd for $C_6H_{14}O_2Si$ (%): C, 49.53; H, 9.69. Found: C, 49.27; H, 9.65.

(12) **General Procedure for the Aldol Reaction of 1 with Aldehydes 2**
Under the atmosphere, dry LiCl (5.5 mg, 0.13 mmol) was added to a two-necked, round-bottomed flask (10 mL), which was connected with a nitrogen balloon. After introduction of nitrogen, DMF (1.0 mL) was added to the flask. The mixture was warmed to 30 °C under stirring. After 10 min, **2** (0.50 mmol) and **1** (0.60 mmol) were added to the mixture. After being stirred for 5 h, the reaction mixture was treated with 2 M aq HCl (1 mL) for 5 min and neutralized with sat. aq $NaHCO_3$. The aqueous mixture was extracted with EtOAc (3 × 10 mL). The extract was dried over Na_2SO_4 and evaporated. The crude product was purified by silica gel column chromatography.

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(19) As shown in Table 3, the reaction of **1a** with **8a** proceeded efficiently irrespective of the metal chloride used. This observation may be due to higher coordinating ability (Lewis basicity) of α-enones, which allows carbonyl activation even with less Lewis acidic metal ions. For the coordinating ability of α-enones, see ref. 17a.