Selected Paper

Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in Anhydrous or Water-Containing *N*,*N*-Dimethylformamide

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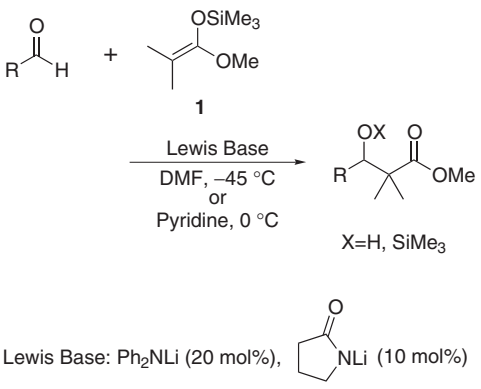
Lithium acetate (AcOLi)-catalyzed aldol reactions between trimethylsilyl enolates and aldehydes proceed smoothly in anhydrous DMF or pyridine to afford the corresponding aldols in good to high yields under weakly-basic conditions (Tables 1–5). This catalytic aldol reaction is performed smoothly also by using other metal carboxylates that are easily prepared in situ by treating carboxylic acids with lithium carbonate (Li_2CO_3) (Table 2, Scheme 5). In order to show the effect of mild and readily-available AcOLi catalyst, the aldol reaction in water-containing DMF was studied in detail. AcOLi and various metal carboxylates behaved as effective Lewis base catalysts in aldol reactions between trimethylsilyl enolate and aldehydes in DMF–H_2O (50:1) (Tables 6, 7). One of the most characteristic points of the above reaction that took place in water-containing DMF is that the aldehydes having a free amide and a hydroxy or even a carboxyl group reacted smoothly and afforded the desired aldols **29**–**31** in moderate to high yields (Table 8, Entries 12–15). Trimethylsilyl enolates derived from carboxylic esters behaved similarly as excellent nucleophiles in the above reaction. This is the first example of Lewis base-catalyzed aldol reactions to afford the desired aldol adducts even when silyl enolates derived from carboxylic esters were used in a water-containing organic solvent.

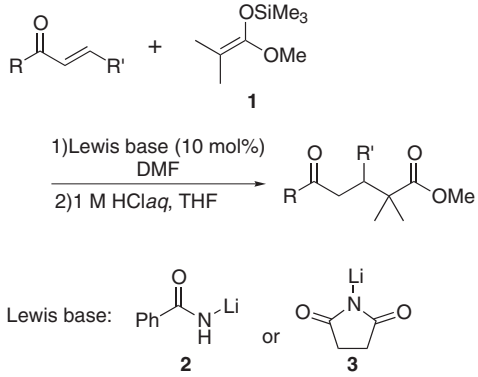
After a crossed aldol reaction between aldehydes and silyl enolates promoted by Lewis acids such as titanium tetrachloride was reported from our laboratory,[1] silyl enolates have been recognized as convenient and useful nucleophiles and are employed frequently in the construction of carbon skeletons. In recent years, activation of silyl enolates under neutral or non-acidic conditions has intensively been studied: for example, Denmark et al.[2] and Hosomi and co-workers[3] reported methods that used silyl enolates having an enhanced Lewis acidic silicon atom which interacted with Lewis bases more easily. Another example may be found in our earlier paper, where a new method for base-catalyzed aldol reaction between silyl enolates and aldehydes was introduced: that is, simple and commonly-employed trimethylsilyl (TMS) enolates reacted smoothly with aldehydes to afford the corresponding aldols in the presence of lithium diphenylamide or lithium pyrrolidone as a Lewis base catalyst in a *N*,*N*-dimethylformamide (DMF) or pyridine solvent (Scheme 1).[4]



Scheme 1. Lewis base-catalyzed aldol reaction between aldehyde and trimethylsilyl enolate.

Next, the use of lithium acetate (AcOLi), a milder and readily-available Lewis base, was examined in place of the above-mentioned lithium salts by considering the following evidence: that is, lithium benzamide **2** or lithium succimide **3** was effectively used in Michael reaction between TMS enolates and α,β-unsaturated carbonyl compounds (Scheme 2).[5]

It is interesting to note that the TMS enolate was activated by a nucleophilic attack of lithium succimide **3** to its silicon atom, although the pK_a value of N–H bond of the succimide was



Scheme 2. Lewis base-catalyzed Michael reaction between ketene silyl acetals and α,β-unsaturated carbonyl compounds.

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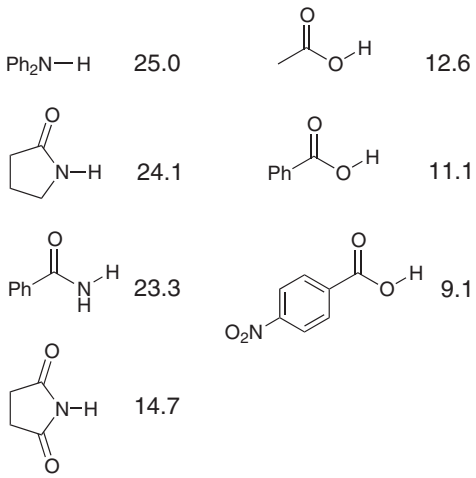
much lower than that of diphenylamine or pyrrolidone.[6] In order to examine the possibility of employing lithium carboxylates as catalysts in the above reactions, we tried carboxylic acids such as acetic acid because the pK_a values of their O–H bonds are relatively close to that of the N–H bond of the succimide.[6] Further, they have advantages in easy availability and low price (Scheme 3).

Next, in order to show the usefulness of a mild and readily available AcOLi catalyst, the aldol reaction in water-containing DMF using the above catalyst was tried. The acetate anion behaved as an effective catalyst in water at low temperatures; however, the corresponding anions were not generated in water from lithium diphenylamide or pyrrolidone. Therefore, no catalytic reaction took place under the above conditions. In this paper, we would like to report on the lithium acetate (AcOLi)-catalyzed aldol reaction between TMS enolates and aldehydes in DMF, pyridine, or DMF–H_2O (50:1) that afforded the corresponding aldols in high yields.[7]



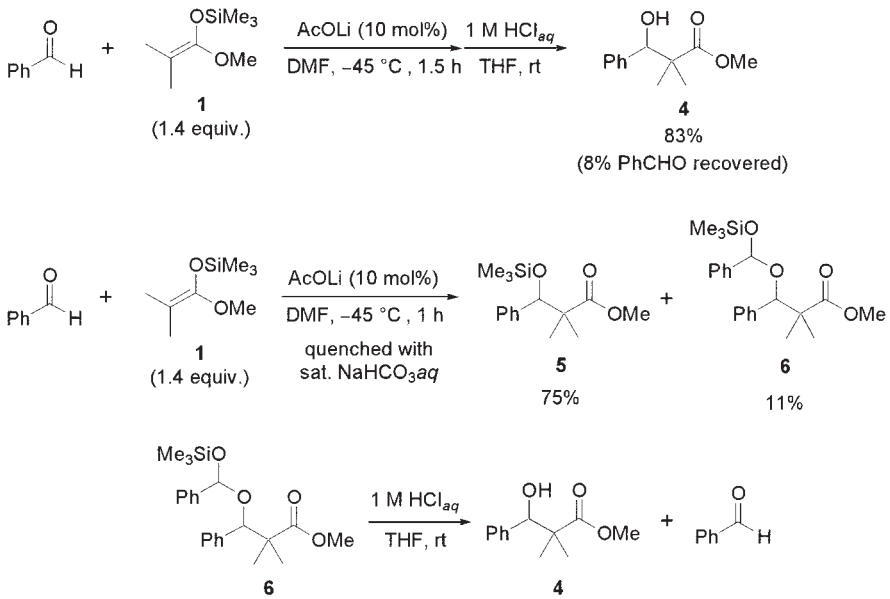
Scheme 3. pK_a values of acidic hydrogens in dimethyl sulfoxide.

Results and Discussion

Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in *N*,*N*-Dimethylformamide or Pyridine. In the first place, the reaction of benzaldehyde and TMS enolate derived from methyl isobutyrate **1** was tried in the presence of 10 mol% of AcOLi at −45 °C in DMF for 1.5 h; its completion was confirmed by TLC. In the above reaction, aldol adduct **4** was obtained in 83% yield and a small amount of aldehyde was recovered after the usual work up, in which a crude mixture was treated with 1 M HCl in THF. After the above reaction mixture was quenched under basic conditions, careful work up revealed that silyl acetal **6** was produced together with **5**, which was easily converted to aldol **4** and aldehyde on treatment with 1 M HCl (Scheme 4).[8]

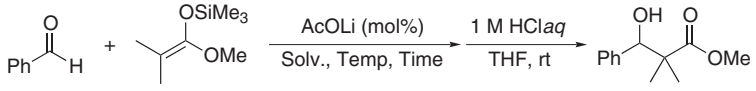
After screening the conditions of the above reaction (see Table 1), we noted that the amounts of catalyst did not influence the yields of **6** and that the aldol adducts were obtained in good yields (Entries 1, 2). Since AcOLi is a weak nucleophile, the reaction did not take place at 0 °C in pyridine, whereas it proceeded smoothly by using a catalytic amount of lithium diphenylamide or lithium pyrrolidone.[4] On the other hand, the corresponding aldol was obtained in high yield when the reaction was carried out at 70 °C in pyridine (Entry 4). In the absence of the catalyst, the aldol adduct was obtained in poor yield even when the reaction mixture was heated at 70 °C in pyridine (Entry 5). These results show that AcOLi behaved as an effective Lewis base catalyst in the present aldol reaction.

Next, the usefulness of several metal carboxylate catalysts in the present reaction was examined (see Table 2). Although potassium and sodium acetates also catalyzed this reaction, the yield of **4** slightly decreased and the amount of **6** increased (Entries 1, 2). The catalytic effects of metal carboxylates were found to be dependent on their nucleophilic abilities: that is, the aldol adduct **4** was obtained in good yields when lithium benzoates having an electron-donating group were used, while the use of lithium 4-nitrobenzoates gave **4** in only 37% yield



Scheme 4. AcOLi-catalyzed aldol reaction between TMS enolate **1** and benzaldehyde in DMF.

Table 1. Screening of the AcOLi-Catalyzed Reaction Conditions between Silyl Enolate **1** and Benzaldehyde

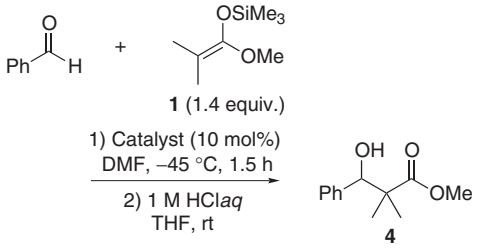


1 (1.4 equiv.) **4**

Entry	AcOLi/mol%	Solv.	Temp/°C	Time/h	Yield[a)]/%
1	20	DMF	−45	1	79
2	5	DMF	−45	1	74
3	10	Pyridine	rt	4.5	81
4	10	Pyridine	70	1.5	95
5	0	Pyridine	70	2	14

a) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Table 2. Screening of Various Catalysts



Entry	Catalyst	Yield[a)]/%
1	AcONa	75
2	AcOK	77
3	4-$Me_2NC_6H_4COOLi$	83
4	4-$MeOC_6H_4COOLi$	81
5	PhCOOLi	77
6	4-$NO_2C_6H_4COOLi$	37
7	*i*-PrCOOLi	90
8	*t*-PrCOOLi	94
9	**2**	91
10[b)]	**3**	66
11	Potassium phthalimide	68

a) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. b) Reaction was carried out for 3 h.

(Entries 3, 4, and 6). We observed that **4** was obtained in high yield when lithium pivalate (*t*-BuCOOLi) was employed as a catalyst (Entry 8). On the other hand, **4** was obtained in moderate yield and the amount of **6** increased when either lithium succimide **3** or potassium phthalimide was used as a catalyst (Entries 10, 11). The imides were also shown to work as effective Lewis base catalysts in Michael-[5] and Mannich-type[9] reactions. The desired **4** was also obtained in good yield when lithium benzamide **2** was used (Entry 9).

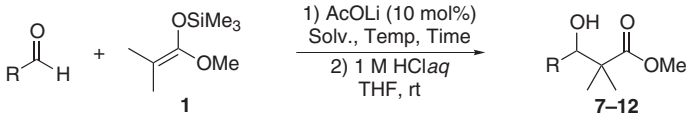
Next, the reactions of TMS enolate **1** with various carbonyl compounds were tried by using 10 mol% of AcOLi in DMF or pyridine (see Table 3). Aromatic aldehydes having an electron-donating group reacted smoothly to afford the desired aldols in high yields (Entries 1–4), whereas aromatic aldehydes having an electron-withdrawing group and an aliphatic aldehyde such as 3-phenylpropionaldehyde in DMF gave the corresponding aldols in moderate yields. Here, silyl acetals were formed by a subsequent reaction of the desired aldols **9**–**11** with aldehydes. The aromatic aldehydes gave the aldol adducts in good to high yields when the reactions were carried out in pyridine at 70 °C (Entries 4, 6, and 8) or by using *t*-BuCOOLi (Entries 5, 7) as a catalyst. An aromatic ketone such as ethyl benzoyformate reacted smoothly with **1** to give the corresponding silyl ether **12** at 0 °C, even under the conditions of desilylation (Entry 11).

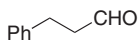
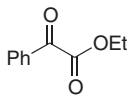
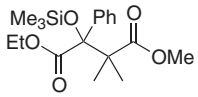
This Lewis base-catalyzed reaction has a remarkable advantage of forming aldols even in the cases of using aldehydes that have basic functions in the same molecules: that is, the reactions proceeded smoothly at −45 °C in DMF to afford the corresponding aldols in high yields (Table 4, Entries 1–4).

The AcOLi-catalyzed aldol reaction was further examined by using several other silyl enolates (see Table 5). When enolates generated from *S*-ethyl and *S*-*t*-butyl ethanethioates were employed, the aldol adducts were obtained in high yields (Entries 1, 2) while enolates generated from acetophenone and *S*-*t*-butyl isobutanethioate were not effectively activated at −45 °C even when *t*-BuCOOLi was used. However, the latter reactions proceeded smoothly at 0 °C to afford the aldol adducts in good yields (Entries 5, 6). The aldol adduct was obtained only in 4% yield when the sterically-hindered triethylsilyl enolate derived from methyl isobutyrate was employed in place of the above TMS enolate **1** (Entry 8). This result indicated that the reaction proceeded via the activation of TMS enolate by forming a hypervalent silicate between AcOLi and silicon atom of the enolate.[4c] Further, the aldol adducts were obtained in high yields with moderate *syn*-diastereoselectivity when silyl enolates derived from *S*-ethyl and *S*-*t*-butyl propanethioate, propiophenone and methyl propionate were used. The enolates derived from methyl propionate gave the corresponding *syn*-aldols with moderate selectivity, irrespective of the geometry of the two isomeric enolates (Entries 3, 4, 7, and 9–12).

Though the preparation of previously reported Lewis bases such as lithium diphenylamide or lithium pyrrolidone needed strong bases such as alkyllithium,[4c] this catalytic aldol reaction was successfully performed by using various lithium carboxylates that were easily prepared in situ by treating carboxylic acids with lithium carbonate (Li_2CO_3). For example, the aldol reaction of 4-methoxybenzaldehyde with silyl enolate **1** gave the aldol adduct **7** in 92% yield by using 10 mol% of lithium isobutyrate prepared from isobutyric acid and Li_2CO_3 in DMF (Scheme 5).[10]

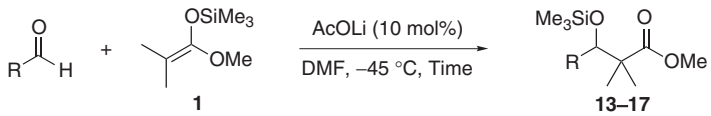
Table 3. AcOLi-Catalyzed Aldol Reaction between Various Carbonyl Compounds and TMS Enolate **1**

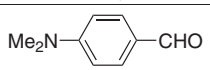
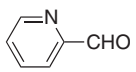
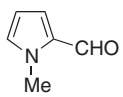
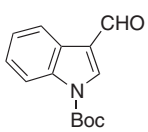
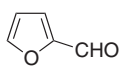


Entry	Carbonyl compound	Solv.	Temp/°C	Time/h	Product	Yield[a]/%
1	4-$MeOC_6H_4CHO$	DMF	–45	1	**7**	94[b]
2	4-$MeOC_6H_4CHO$	Pyridine	rt	2	**7**	96[b]
3	4-MeC_6H_4CHO	DMF	–45	2	**8**	84
4	4-MeC_6H_4CHO	Pyridine	70	2	**8**	98
5	4-ClC_6H_4CHO	DMF	–45	3	**9**	63 (72)
6	4-ClC_6H_4CHO	Pyridine	70	4.5	**9**	93
7	4-$NO_2C_6H_4CHO$	DMF	–45 → rt	2 d	**10**	69 (73)
8	4-$NO_2C_6H_4CHO$	Pyridine	70	3	**10**	82
9		DMF	–45	2	**11**	65[b] (58[b])
10		Pyridine	70	4.5	**11**	54[b]
11		DMF	0	3	 **12**	84[b]

a) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses were yields by using *t*-BuCOOLi as a catalyst. b) Isolated yields.

Table 4. Aldol Reaction Using Various Aldehydes



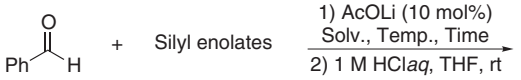
Entry	Aldehyde	Time/h	Product	Yield[a]/%
1[b]		1	**13**	99
2		1.5	**14**	84
3		1.5	**15**	98[c]
4		2.5	**16**	99
5		1	**17**	90

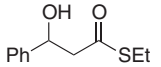
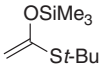
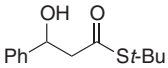
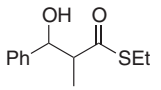
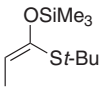
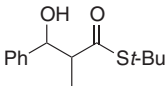
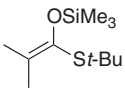
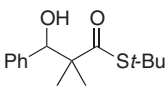
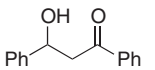
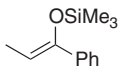
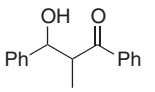
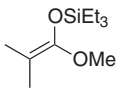
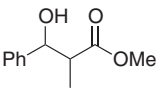
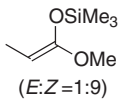
a) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. b) 5 mol% of AcOLi was used. c) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,3,5-trimethylbenzene as an internal standard.

Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in *N*,*N*-Dimethylformamide Containing Water. The aldol reactions in water or water-containing organic solvents have attracted much attention in a sense related to economical and environmentally-benign synthetic methods. Although several methods of aldol reactions using silyl enolates in water or water-containing organic solvents have been reported,[11–13] there are few methods that used silyl enolates derived from carboxylic esters, due to their extreme sensitivities toward water. Among the few reported reactions, one was carried out in emulsified spheres using surfactants[11] and the other example showed that the reaction proceeded by restrictive use of highly reactive acceptor aldehydes.[13b]

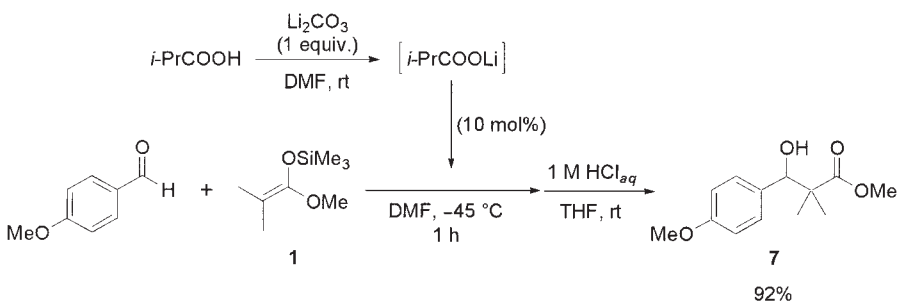
In the first place, reaction of benzaldehyde and TMS enolate

Table 5. Aldol Reaction Using Various Silyl Enolates



Entry	Silyl enolates	Solv.	Temp/°C	Time/h	Products		Yield[a]/%	*syn*:*anti*[b]
1		DMF	–45	2		**18**	91	—
2		DMF	–45	1		**19**	97	—
3		DMF	–45	1		**20**	83	63:37
4		DMF	–45	1.5		**21**	74 (76)	74:26 (72:28)
5		DMF	0	3		**22**	86	—
6		DMF	0	2		**23**	85 (84)	—
7		DMF	0 ⟶ rt	6		**24**	87	63:37
8		DMF	–45	1.5	**4**		4	—
9		DMF	–45	3		**25**	87	64:36
10	(*E*:*Z* =5:1)	Pyridine	70	2			86	61:39
11		DMF	–45	3	**25**		79	73:27
12	(*E*:*Z* =1:9)	Pyridine	70	2	**25**		94	65:35

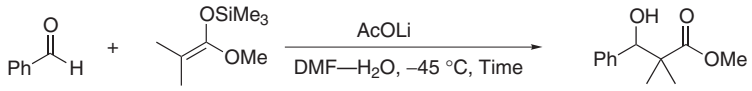
a) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses were yields by using *t*-BuCOOLi as a catalyst. b) Determined by ^{1}H NMR analysis (270 MHz). Numbers in parentheses was a ratio by using *t*-BuCOOLi as a catalyst.



Scheme 5. Aldol reaction by using *i*-PrCOOLi prepared from *i*-PrCOOH and lithium carbonate.

derived from methyl isobutyrate **1** was tried in the presence of 10 mol% of AcOLi at −45 °C in DMF–H_2O (10:1). The aldol adduct **4** was obtained in 71% yield without producing **6** (Table 6, Entry 1). The reaction conditions were then even more carefully screened so as to improve the yield (see Table 6). The aldol adduct **4** was afforded in good yield when the volume ratio of DMF and water was changed from 10:1 to 50:1 (Entry 6). Finally, the corresponding aldol **4** was obtained in high yield when the reaction was carried out by using two equivalents of **1** in DMF–H_2O (50:1) (Entry 13). In the absence

Table 6. Screening of the AcOLi-Catalyzed Reaction Conditions between Silyl Enolate **1** and Benzaldehyde in DMF Containing H_2O[a)]

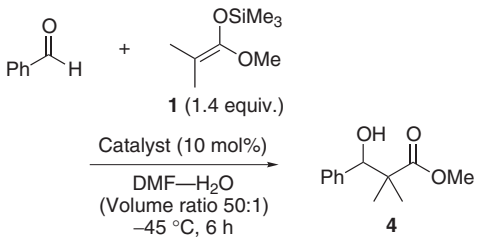


1 **4**

Entry	**1**/equiv.	AcOLi/mol%	DMF–H_2O/Volume ratio	Time/h	Yield[b)]/%
1	1.4	10	10:1	15	71
2[c)]	1.4	10	10:1	15	67
3	1.4	20	10:1	15	77
4	2	10	10:1	15	71
5	1.4	10	20:1	15	78
6	1.4	10	50:1	14	88
7	1.4	10	50:1	3	80
8	1.4	10	50:1	1	79
9	1.4	20	50:1	3	82
10	2	10	50:1	3	90
11	2	20	10:1	3	51
12	2	10	20:1	4	65
13	2	10	50:1	6	96
14	2	0	50:1	6	17

a) All reactions were carried out by using benzaldehyde (0.4 mmol) in DMF (3 mL) and corresponding volume ratio of H_2O. b) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. c) Reaction was carried out at −20 °C.

Table 7. Screening of Various Catalysts[a)]



4

Entry	Catalyst	Yield[b)]/%
1	$AcONa \cdot 3H_2O$	96
2	4-$MeOC_6H_4COOLi$	87
3[c)]	PhCOOLi	94
4	4-$NO_2C_6H_4COOLi$	42
5	*i*-PrCOOLi	99
6	*t*-BuCOOLi	95[d)]

a) All reactions were carried out using benzaldehyde (0.4 mmol) in DMF (3 mL) and H_2O (0.06 mL). b) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. c) Reaction was carried out for 6.5 h. d) Isolated yield.

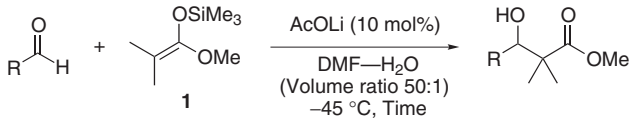
of the catalyst, on the other hand, the adduct was obtained only in 17% yield under the same conditions, indicating that AcOLi behaved as an effective Lewis base catalyst in the above aldol reaction (Entry 14).

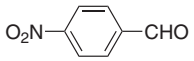
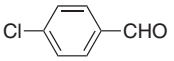
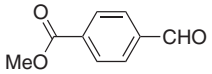
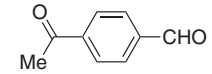
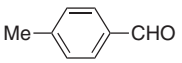
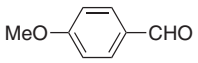
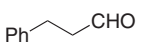
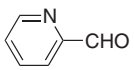
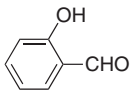
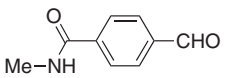
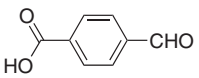
The effect of several metal carboxylates was further examined (see Table 7). Since an acetate anion seemed to have worked as an effective catalyst in water at low temperatures, sodium acetate trihydrate was considered also to catalyze the above reaction effectively to afford **4** in high yield (Entry 1). Further, it is noted that the effects of catalyts in water-containing DMF are similar to those in anhydrous DMF: i.e., the aldol reaction proceeded smoothly when various lithium carboxylates were employed as catalysts and **4** was afforded in high yield, except in the case of using lithium 4-nitrobenzoate, where the yield was only in 42% (Entries 2–6).

The reactions of TMS enolate **1** with various aldehydes were further tried and the aldol adducts were obtained in high yields (see Table 8). It is remarkable that both aromatic aldehydes having electron-withdrawing groups and an aliphatic aldehyde, 3-phenypropionaldehyde, reacted smoothly to afford the desired aldols in high yields (Entries 1, 2, and 9). 2-Pyridinecarboxaldehyde also afforded the aldol adduct in high yield, whereas this reaction was known not to proceed when Lewis acids were used (Entry 11). One of the most characteristic points of the present reaction in water-containing DMF is that the aldehydes having free amide, hydroxy, or even carboxylic functions reacted smoothly to afford the desired aldols in moderate to high yields (Entries 12–15).

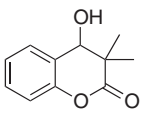
The AcOLi catalyzed aldol reaction in water-containing DMF was further examined by using several other silyl enolates (see Table 9). When enolates generated from *S*-ethyl and *S*-*t*-butyl ethanethioates were employed, only trace amounts of the aldol adducts were obtained because of their preferential protonation of silyl enolates by water (Entries 1, 2). On the other hand, the above reactions proceeded smoothly to afford the aldol adducts in moderate to good yields when enolates derived from *S*-*t*-butyl propanethioate or *S*-*t*-butyl 2-methylpropane-1-thioate were used (Entries 3, 4). The silyl enolates derived from acetophenone and propiophenone preferentially afforded the protonated products by water in the case when benzaldehyde was used, while the aldol adduct **33** was obtained in good yield when 4-nitrobenzaldehyde was used (Entries 5–7). Further, it is noted that the *syn*-diastereoselectivity of the present reaction in water-containing DMF decreased in comparison with that in anhydrous DMF, except when the enolate derived from propio-

Table 8. Aldol Reactions Using Various Aldehydes in DMF Containing H_2O[a)]



Entry	Aldehyde	Time/h	Product	Yield[b)]/%
1		3	**10**	97[c)]
2		3	**9**	94
3		3	**26**	99
4		3	**27**	93[c)]
5		6	**8**	80
6		16	**8**	78
7		6	**7**	67 (68)
8		17	**7**	62
9		6	**11**	79[c)]
10		18	**11**	84[c)]
11		2.5	**28**	97
12[d)]		6	**29**	89
13[d)]		14	**29**	84
14		3	**30**	92[c)]
15[e)]		24	**31**	52

a) All reactions were carried out using aldehyde (0.4 mmol) and **1** (0.8 mmol) in DMF (3 mL) and H_2O (0.06 mL). b) Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. Numbers in parentheses was a yield using *t*-BuCOOLi as a catalyst. c) Isolated yield. d) Product was isolated as a chromanone **32** by PTLC. e) Reaction temperature was gradually warmed up to rt.



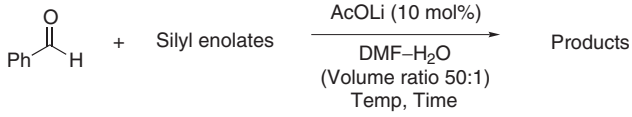
32

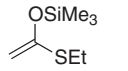
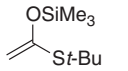
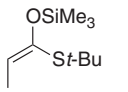
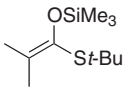
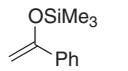
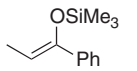
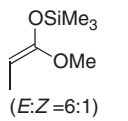
phenone was used (Entries 3, 7, and 8).

Mechanism for AcOLi-Catalyzed Aldol Reaction between Aldehyde and TMS Enolate in Anhydrous or Water-Containing DMF. The present AcOLi-catalyzed aldol reaction in anhydrous DMF or pyridine is assumed to proceed by a pathway similar to that of previously reported Lewis base-catalyzed aldol reactions[4c] (see Scheme 6): that is, AcOLi and the solvent coordinated to silyl enolates and the reaction proceeded via a hexacoodinated hypervalent silicate **34** to afford lithium aldolate **36**. Subsequent silylation of **36** by thus-formed trimethylsilyl acetate **35** afforded *O*-silyl, while AcOLi was regenerated (Cycle A). An alternative catalytic cycle in producing silyl acetals can also be assumed if AcOLi was used as a catalyst (Cycle B): that is, 1:2 adduct **37** formed from enolate and aldehyde was partially produced along with **36**. Since trimethylsilyl acetate **35** is a more powerful silylating reagent compared with *N*-trimethylsilyl-diphenylamine or -pyrrolidone employed in the previously reported Lewis base catalyzed aldol reactions,[4c] **35** partially silylated **37** to afford silyl acetals and then AcOLi was regenerated. Actually, silyl acetal **6** was produced along with silyl ether **5** when lithium aldolate **38** in DMF was treated with **35** in the presence of benzaldehyde at −45 °C, although **5** was a single product when *N*-trimethylsilyl pyrrolidone was used under the same reaction conditions (Scheme 7).

The amount of silyl acetal decreased when the reaction was carried out at 70 °C in pyridine (Table 1, Entry 4) or when lithium pivalate (*t*-BuCOOLi) was employed as a catalyst (Table 2, Entry 8). The results are explained by considering that silylation of **36** by **35** at high temperature proceeded rapidly before **37** is produced or that no silylation of **37** took place due to the steric hindrance between both bulky **37** and silylating reagent, trimethylsilyl pivalate. Further, aromatic aldehydes hav-

Table 9. Aldol Reaction Using Various Silyl Enolates in DMF Containing H_2O[a)]



Entry	Silyl enolates	Temp/°C	Time/h	Products	Yield[b)]/%	*syn*:*anti*[c)]
1		–45 → rt	24	**18**	0	—
2		–45	6	**19**	4	—
3		–45	6	**21**	61 (61)	55:45 (55:45)
4		0	5	**22**	83	—
5		0 → rt	24	**23**	0	—
6[d)]		–45 → rt	5	**33**	86[e)]	—
7		0 → rt	6	**24**	39	78:22
8	 (*E*:*Z* =6:1)	–45	6	**25**	65	51:49

a) All reactions were carried out using benzaldehyde (0.4 mmol) and silyl enolate (0.8 mmol) in DMF (3 mL) and H_2O (0.06 mL). b) Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. A numbers in parentheses was a yield using *t*-BuCOOLi as a catalyst. c) Determined by ^{1}H NMR analysis (270 MHz). Numbers in parentheses was a ratio by using *t*-BuCOOLi as a catalyst. d) 4-Nitrobenzaldehyde was used as a substrate. e) Isolated yield.

ing an electron-withdrawing group and an aliphatic aldehyde such as 3-phenylpropionaldehyde in a DMF solvent gave the corresponding aldols in moderate yields along with silyl acetals formed from the desired aldols (Table 3, Entries 5, 7, and 9). These results show the increase in the amount of **37** either when more electrophilic aldehydes such as aromatic aldehydes having an electron-withdrawing group were used or when less-hindered **37** derived from 3-phenylpropionaldehyde was formed.

The reaction was considered to proceed mostly via acyclic transition states since the silyl enolate derived from methyl propionate gave the corresponding aldols with moderate *syn*-diastereoselectivities irrespective of the geometries of the two isomeric silyl enolates (Table 5, Entries 9–12). The *syn*-diastereoselectivity of *E*-enolate was lower than that of *Z*-enolate because of the steric hindrance between hexacoodinated hypervalent silicate of *E*-enolate and pheny group of benzaldehyde in the acyclic transition states; therefore, *syn*-aldol is formed more preferentially from *Z*-enolate (Fig. 1).

The assumed catalytic cycle of the AcOLi-catalyzed aldol reaction in water-containing DMF is illustrated in Scheme 8. The same reaction pattern may be conceivable until the lithium aldolate **36** is formed via a hexacoodinated hypervalent silicate **34** under non-aqueous conditions. Such lithium aldolate **36** and silyl acetate **35** are rapidly hydrolyzed to produce lithium hydroxide and acetic acid in water-containing DMF. Subsequent neutralization affords lithium acetate, to establish a catalytic cycle.

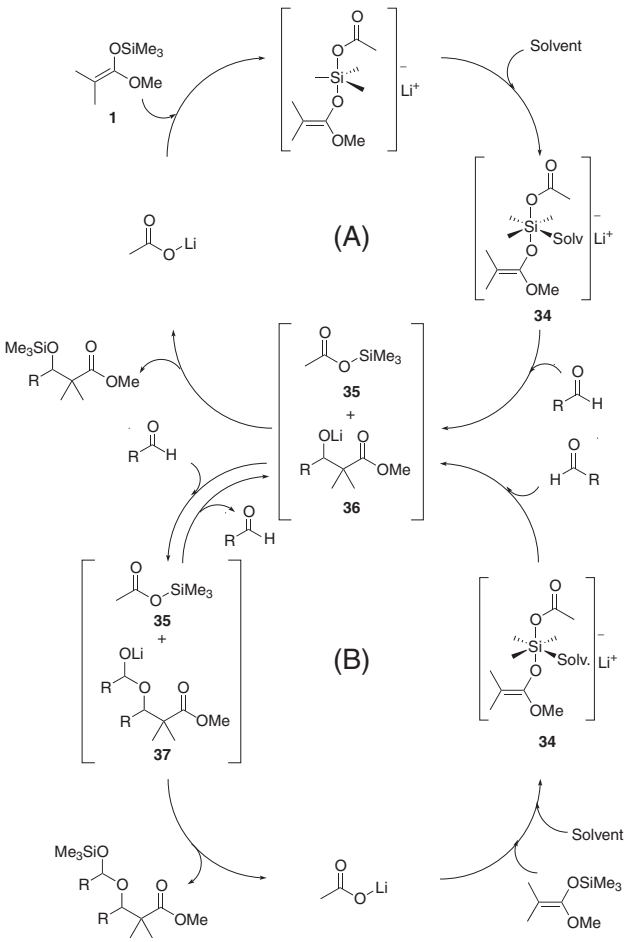
Under non-aqueous conditions, the initially formed lithium aldolate **36** was converted into its TMS ether by the reaction with trimethylsilyl acetate **35** along with the regeneration of the catalyst. Aromatic aldehydes having electron-withdrawing groups and 3-phenypropionaldehyde afforded silyl acetals, co-products, via the reaction with **36**; therefore, the yields of the desired aldols became moderate under non-aqueous conditions (Table 3, Entries 5, 7, and 9). In the presence of water, on the other hand, lithium aldolates were rapidly hydrolyzed and the formation of the above-mentioned silyl acetals was restrained. Thus, the formation of the desired aldols in high yield was dependent on the electrophilicities of the starting aldehydes (Table 8, Entries 1, 2, and 9).

Further, the *syn*-diastereoselectivity of the present reaction in water-containing DMF decreased compared with that in anhydrous DMF, except for the case when the enolate derived from propiophenone was used (Table 9, Entries 3, 7, and 8). This indicates that water is involved in the diastereoselection step. Most probably, a rapid isomerization of the produced lithium aldolate occurred at 0 °C before the silylated product was formed with trimethlysilyl acatate **35** when enolate derived

from propiophenone was used in anhydrous DMF. Thus, the *syn*-diastereoselectivity of the desired aldol becomes lower than that in water-containing DMF.

Conclusion

Lithium acetate (AcOLi)-catalyzed aldol reactions between TMS enolates and aldehydes under weakly basic conditions in anhydrous or water-containing DMF and pyridine were established. Various metal carboxylates such as lithium pivalate (*t*-BuCOOLi) are effective as catalysts. This is the first example of a Lewis base-catalyzed aldol reaction which afforded aldol adducts even when silyl enolates derived from carboxylic esters were used in a water-containing organic solvent. This method is quite practical and thus is applicable to the synthesis of various aldols, since its reaction conditions are not strictly anhydrous and the reaction proceeds smoothly by using a mild and readily-available Lewis base catalyst.



Scheme 6. Assumed catalytic cycle of AcOLi-catalyzed aldol reaction in anhydrous DMF or pyridine.

Experimental

General. All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and are not corrected. Infrared (IR) spectra were recorded on a Perkin Elmer SPECTRUM 1000 or a Horiba FT300 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM EX270L (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on an EX270L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane,

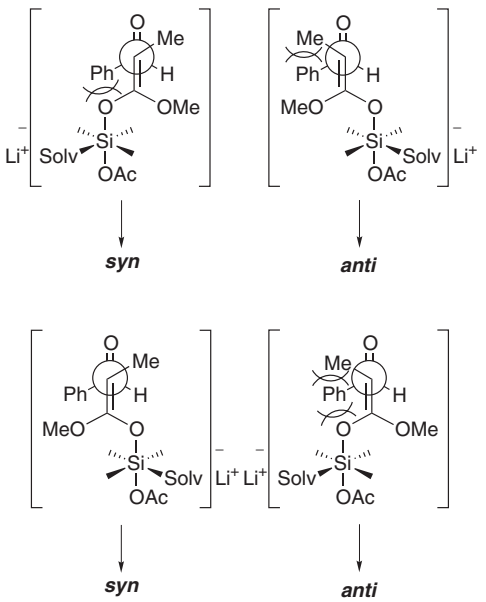
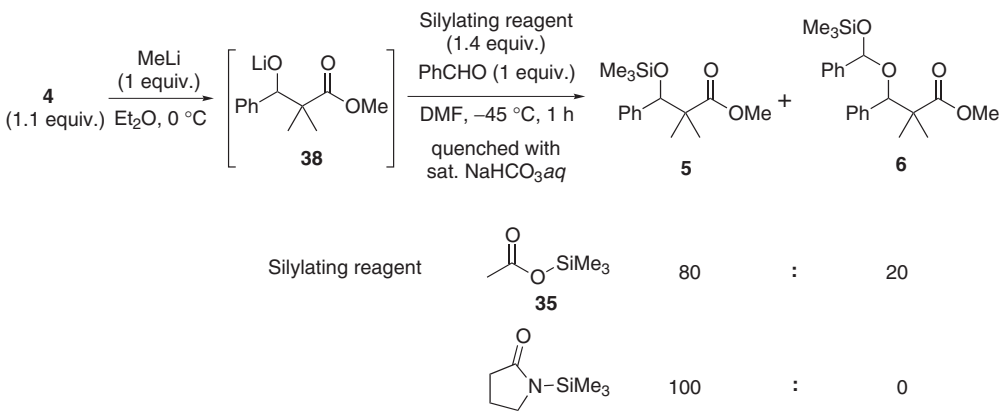
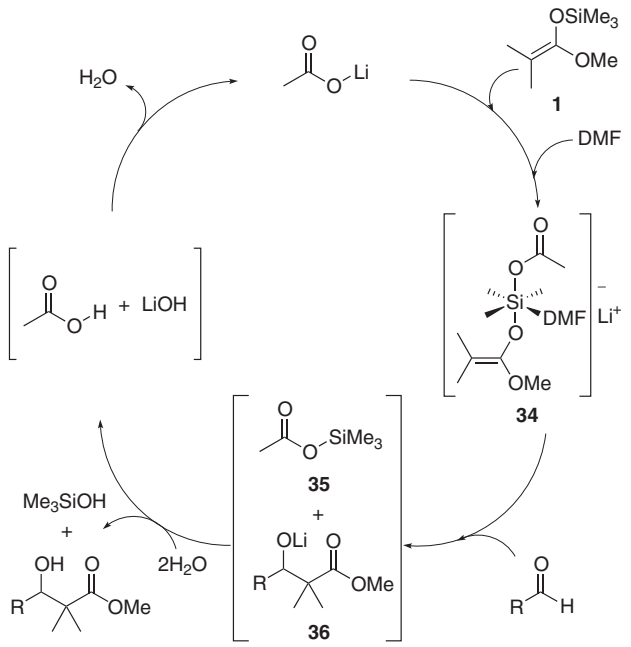


Fig. 1. Difference of reactivity between *E*- and *Z*-enolate.



Scheme 7. Silylation of lithium aldolate **38** in the co-existence of benzaldehyde.



Scheme 8. Assumed catalytic cycle of AcOLi-catalyzed aldol reaction in water-containing DMF.

with the solvent resonance as the internal standard ($CDCl_3$; $\delta = 77.0$, C_6D_6; $\delta = 128.0$, DMSO-d_6; $\delta = 39.5$). High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX102A. Elemental analyses were conducted using a Yanaco MT-5 CHN Corder. Analytical TLC was performed on Merck preparative TLC plates (silica gel 60 GF254, 0.25 mm). Column chromatography was carried out on Merck silica gel 60 (0.063–0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. Reactions in anhydrous DMF or pyridine were carried out under an argon 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). Reactions in water-containing DMF were carried out using DMF purchased from Tokyo Kasei Kogyo and purified water purchased from Kokusan Chemical, without further purifications. Lithium acetate and lithium benzoate were purchased from Wako Pure Chemical Industries. Sodium and potassium acetate and sodium acetate trihydrate were purchased from Kokusan Chemical. Other Lewis base catalysts were prepared from corresponding precursors and *n*-BuLi in THF at 0 °C. After the solvent had been removed under reduced pressure, the residue was used without further purification. Lithium isobutyrate was prepared from isobutyric acid and Li_2CO_3 in DMF at room temperature overnight; we used the solution after decantation in the reaction of Scheme 5. All reagents were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Kokusan Chemical, Wako Pure Chemical Industries or Aldrich Chemical. Aldehydes were used after purification by distillation or recrystallizaion. Silyl enolates and *N*-trimethylsilyl pyrrolidone were prepared by usual methods. 4-(*N*-Mehtylcarbamoyl)benzaldehyde was prepared following literature procedures.[14]

General Procedure for Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in *N*,*N*-Dimethylformamide. To a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.5 mL) were added successively a solution of silyl enolate (0.56 mmol) in DMF (1.0 mL) and a solution of aldehyde (0.4 mmol) in DMF (1.5 mL) at an appropriate temperature. The mixture was stirred for an appropriate time at the same temperature, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O and the residue was dissolved in a mixture of HCl (1.0 M, 0.5 mL) and THF (5 mL) after evaporation of the solvent. The mixture was stirred for 30 min and was extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding aldol. Products and yields are as reported in the text.

Methyl 3-Hydroxy-2,2-dimethyl-3-phenylpropionate (4).[4c,13c] White powder; mp 67.1 °C; IR (neat, cm^{-1}) 3394, 2985, 1704, 1450, 1281, 1149, 1049; ^1H NMR (270 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.14 (s, 3H), 3.12 (d, $J = 4.1$ Hz, 1H), 3.72 (s, 3H), 4.90 (d, $J = 4.0$ Hz, 1H), 7.22–7.47 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 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-trimethylsiloxypropionate (5).[4c] The material obtained by quenching the reaction with saturated aqueous $NaHCO_3$ was purified by column chromatography on silica gel (deactivated by 10 wt % of water, hexane/ethyl acetate = 20/1). Colorless oil; IR (neat, cm^{-1}) 2947, 1736, 1458, 1257, 1134, 1095; ^1H NMR (270 MHz, $CDCl_3$) δ −0.05 (s, 9H), 0.99 (s, 3H), 1.12 (s, 3H), 3.67 (s, 3H), 4.97 (s, 1H), 7.49–7.64 (m, 5H), ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.08, 19.1, 23.0, 49.0, 51.6, 79.2, 127.6, 127.7, 140.8, 177.3.

Methyl 2,2-Dimethyl-3-phenyl-3-[phenyl(trimethylsilanyloxy)methoxy]propionate (6). The material obtained by quenching the reaction with saturated aqueous $NaHCO_3$ and ^1H NMR of crude mixture was found to be a diastereomixture (major:minor = 65:35). The crude mixture was purified by column chromatography on silica gel (deactivated by 10 wt % of water, hexane/ethyl acetate = 20/1). Pure **6** was partially obtained as a diastereomixture (major isomer of crude mixture:minor isomer of crude mixture = 26:74). Colorless oil; IR (neat, cm^{-1}) 2962, 2900, 1736, 1450, 1257, 1126, 1041, 879, 856; ^1H NMR (270 MHz, C_6D_6) δ 0.01 (s, 6.66H), 0.05 (s, 2.34H), 1.05 (s, 2.22H), 1.17(s, 0.78H), 1.35 (s, 2.2H), 1.48 (s, 0.78H), 3.35 (s, 2.22H), 3.51 (s, 0.78H), 4.97 (s, 0.74H), 5.43 (s, 0.26H), 5.63 (s, 0.26H), 5.87 (s, 0.74H), 7.11–7.25 (m, 5.56H), 7.38–7.44 (m, 2.22H), 7.50–7.55 (m, 2.22H); ^{13}C NMR (68 MHz, C_6D_6) (major isomer of crude mixture) δ 0.49, 20.9, 21.7, 48.3, 51.6, 81.5, 95.0, 126.5, 127.7, 128.1, 128.6, 129.1, 138.3, 142.4, 176.1; (minor isomer of crude mixture) δ 0.52, 19.5, 22.8, 48.5, 51.5, 84.5, 99.3, 126.7, 127.6, 128.3, 128.6, 128.9, 139.2, 141.9, 176.4; Anal. Calcd for $C_{22}H_{30}O_4Si$: C, 68.36; H, 7.82%. Found: C, 68.23; H, 7.80%.

Methyl 3-Hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropionate (7).[4c] White powder; mp 81.2 °C; IR (neat, cm^{-1}) 3502, 2985, 1720; ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.12 (s, 3H), 3.05 (s, 1H), 3.70 (s, 3H), 3.78 (s, 3H), 4.83 (s, 1H), 6.83 (m, 2H), 7.20 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 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-3-(4-methylphenyl)-2,2-dimethylpropionate (8).[4c] White powder; mp 70.0 °C; IR (neat, cm^{-1}) 3502, 2950, 1730; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.12 (s, 3H), 2.32 (s, 1H), 3.05 (s, 1H), 3.69 (s, 3H), 4.83 (s, 1H), 7.09–7.18 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.0, 21.0, 22.8, 47.7, 51.9, 78.4, 127.4, 128.3, 137.0, 137.2, 178.1.

Methyl 3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethylpropionate (9).[4c] White powder; mp 63.2 °C; IR (neat, cm^{-1}) 3471, 2978, 1720; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.12 (s, 3H), 3.21 (s, 1H), 3.71 (s, 3H), 4.85 (s, 1H), 7.18–7.36 (m, 4H);

^{13}C NMR (68 MHz, $CDCl_3$) δ 19.0, 22.8, 47.6, 52.1, 77.9, 127.9, 129.0, 133.5, 138.4, 178.0.

Methyl 3-Hydroxy-2,2-dimethyl-3-(4-nitrophenyl)propionate (10).[4c] White crystals; mp 114.5 °C; IR (neat, cm^{-1}) 3517, 2985, 1712, 1519; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.15 (s, 3H), 3.74 (s, 3H), 5.01 (s, 1H), 7.41–7.62 (m, 2H), 8.09–8.32 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.2, 22.7, 47.6, 52.3, 77.7, 122.9, 128.6, 147.3, 147.6, 177.7.

Methyl 3-Hydroxy-2,2-dimethyl-5-phenylpentanoate (11).[4c] Colorless oil; IR (neat, cm^{-1}) 3465, 2939, 1720; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.18 (s, 3H), 1.53–1.81 (m, 2H), 2.51 (s, 1H), 2.59–2.70 (m, 1H), 2.90–3.00 (m, 1H), 3.60–3.67 (m, 1H), 3.68 (s, 3H), 7.15–7.31 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.3, 22.4, 32.8, 33.6, 47.1, 51.9, 76.0, 125.8, 128.4, 128.5, 142.1, 178.2.

Methyl 3-Ethoxycarbonyl-2,2-dimethyl-3-phenyl-3-trimethylsiloxypropionate (12). Colorless oil; IR (neat, cm^{-1}) 2939, 1736, 1250, 1142; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.21 (s, 3H), 1.27 (s, 3H), 1.37 (t, $J = 7.0$ Hz, 3H), 3.62 (s, 3H), 4.22–4.41 (m, 2H), 7.23–7.25 (m, 3H), 7.53–7.56 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 2.3, 14.2, 21.8, 23.0, 51.6, 52.7, 61.6, 81.2, 127.1, 127.4, 127.6, 138.8, 172.3, 175.9; HRMS (FAB+) calcd for $C_{18}H_{28}LiO_5Si^+$ $[M + Li]^+$ 359.1861, found m/z 359.1867.

Methyl 3-(4-Dimethylaminophenyl)-2,2-dimethyl-3-trimethylsiloxypropionate (13).[4c] White powder; mp 80.1 °C; IR (neat, cm^{-1}) 2978, 1728, 1612, 1519, 1458, 1349, 1250, 1073; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.07 (s, 9H), 1.00 (s, 3H), 1.09 (s, 3H), 2.91 (s, 6H), 3.65 (s, 3H), 4.87 (s, 1H), 6.59 (d, $J = 8.7$ Hz, 2H), 7.31 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −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-(2-pyridyl)-3-trimethylsiloxypropionate (14).[4c] Colorless oil; IR (neat, cm^{-1}) 3626, 3186, 2993, 1728; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.04 (s, 9H), 0.98 (s, 3H), 1.12 (s, 3H), 3.65 (s, 3H), 5.06 (s, 1H), 7.07–7.17 (m, 1H), 7.34–7.44 (m, 1H), 7.56–7.70 (m, 1H), 8.40–8.49 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 0.0, 20.2, 21.0, 48.7, 51.7, 79.8, 122.1, 135.6, 147.8, 161.1, 176.6.

Methyl 2,2-Dimethyl-3-(1-methyl-2-pyrrolyl)-3-trimethylsiloxypropionate (15). Colorless oil; IR (neat, cm^{-1}) 2947, 1736, 1257, 1072, 879, 849; ^{1}H NMR (270 MHz, C_6D_6) δ 0.05 (s, 9H), 1.09 (s, 3H), 1.50 (s, 3H), 3.10 (s, 3H), 3.53 (s, 3H), 5.24 (s, 1H), 6.25 (dd, $J = 2.4$, 3.5 Hz, 1H), 6.29–6.31 (m, 2H); ^{13}C NMR (68 MHz, C_6D_6) δ 0.1, 19.5, 22.5, 34.6, 50.0, 51.5, 73.4, 107.6, 109.9, 122.5, 131.3, 176.8; HRMS (FAB+) calcd for $C_{14}H_{25}NO_3Si^+$ $[M]^+$ 283.1604, found m/z 283.1621.

Methyl 3-(1-*t*-Butoxycarbonyl-3-indolyl)-2,2-dimethyl-3-trimethylsiloxypropionate (16).[4c] Colorless oil; IR (neat, cm^{-1}) 2978, 1736, 1458, 1373, 1257, 1149, 1280, 856, 756; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.04 (s, 9H), 1.09 (s, 3H), 1.25 (s, 3H), 1.68 (s, 9H), 3.67 (s, 3H), 5.26 (s, 1H), 7.12–7.37 (m, 2H), 7.43 (s, 1H), 7.68–7.84 (m, 1H), 7.99–8.22 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −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.

Methyl 3-(2-Furyl)-2,2-dimethyl-3-trimethylsiloxypropionate (17).[15] Colorless oil; IR (neat, cm^{-1}) 2962, 1736, 1257, 1142, 1088, 864; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.02 (s, 9H), 1.02 (s, 3H), 1.21 (s, 3H), 3.66 (s, 3H), 4.99 (s, 1H), 6.18 (d, $J =$ 2.7 Hz, 1H), 6.29 (dd, $J = 1.9$, 3.2 Hz, 1H), 7.32 (t, $J = 0.8$ Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ −0.3, 19.6, 21.3, 48.6, 51.8, 73.4, 107.8, 109.8, 141.4, 154.2, 176.6; HRMS (FAB+) calcd for $C_{13}H_{22}NaO_4Si^+$ $[M + Na]^+$ 293.1181, found m/z 293.1191.

***S*-Ethyl 3-Hydroxy-3-phenylpropanethioate (18).**[4c,16] Colorless oil; IR (neat, cm^{-1}) 3502, 3425, 2970, 2924, 1682; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, $J = 7.0$ Hz, 3H), 2.84–3.04 (m, 4H), 3.11–3.17 (brs, 1H), 5.12–5.21 (m, 1H), 7.23–7.40 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.6, 23.5, 52.5, 70.8, 125.5, 127.7, 128.4, 142.2, 198.7.

***S*-*t*-Butyl 3-Hydroxy-3-phenylpropanethioate (19).**[16] Colorless oil; IR (neat, cm^{-1}) 3487, 3356, 2962, 2916, 1674, 1041; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.78–2.95 (m, 2H), 3.20 (brs, 1H), 5.15 (dd, $J = 4.1$, 8.6 Hz, 1H) 7.24–7.36 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.6, 48.5, 52.6, 70.7, 125.4, 127.5, 128.2, 142.0, 199.6.

***S*-Ethyl 3-Hydroxy-2-methyl-3-phenylpropanethioate (20).**[16] *syn* Isomer: Colorless oil; IR (neat, cm^{-1}) 3494, 3363, 2970, 2924, 1674, 964; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16 (d, $J = 7.0$ Hz, 3H), 1.22 (t, $J = 7.6$ Hz, 3H), 2.87 (q, $J = 7.6$ Hz, 2H), 2.90 (dq, $J = 4.1$, 7.0 Hz, 2H), 2.90 (brs, 1H), 5.10 (d, $J = 4.1$ Hz, 1H) 7.24–7.34 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.4, 14.6, 23.3, 54.9, 73.7, 125.9, 127.4, 128.1, 141.0, 203.9. *anti* Isomer: Colorless oil; IR (neat, cm^{-1}) 3464, 3332, 2962, 2931, 1674, 964; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.02 (d, $J = 7.3$ Hz, 3H), 1.26 (t, $J = 7.6$ Hz, 3H), 2.69 (brs, 1H), 2.92 (q, $J = 7.6$ Hz, 2H), 3.00 (dq, $J = 7.0$, 8.4 Hz, 2H), 4.81 (d, $J = 8.4$ Hz, 1H) 7.28–7.40 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.6, 15.5, 23.3, 55.4, 76.6, 126.6, 128.1, 128.5, 141.6, 203.7.

***S*-*t*-Butyl 3-Hydroxy-2-methyl-3-phenylpropanethioate (21).**[17] *syn* Isomer: Colorless oil; IR (neat, cm^{-1}) 3340, 2924, 1666, 1458, 957; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (d, $J = 7.0$ Hz, 3H), 1.43 (s, 9H), 2.76–2.85 (m, 1H), 2.99 (brs, 1H), 5.07 (d, $J = 3.8$ Hz, 1H) 7.24–7.34 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 11.5, 29.7, 48.3, 55.0, 73.8, 126.0, 127.3, 128.1, 141.1, 204.9. *anti* Isomer: Colorless oil; IR (neat, cm^{-1}) 3379, 2962, 2916, 1674, 1458, 957; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (d, $J =$ 7.0 Hz, 3H), 1.46 (s, 9H), 2.79 (d, $J = 4.3$ Hz, 1H), 2.88 (dq, $J = 0.8$, 7.0 Hz, 1H), 4.77 (dd, $J = 3.0$, 7.8 Hz, 1H) 7.27–7.38 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.6, 29.8, 48.4, 55.6, 76.6, 126.5, 127.9, 128.3, 141.6, 204.3.

***S*-*t*-Butyl 3-Hydroxy-2,2-dimethyl-3-phenylpropanethioate (22).**[18] White crystals; mp 69.0 °C; IR (neat, cm^{-1}) 3587, 3471, 2924, 1651, 941; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.47 (s, 9H), 3.14 (d, $J = 4.1$ Hz, 1H), 4.89 (d, $J = 3.5$ Hz, 1H) 7.29–7.32 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.4, 23.7, 29.7, 47.8, 54.8, 79.0, 127.6, 127.7, 139.9, 208.5; Anal. Calcd for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32%. Found: C, 67.24; H, 8.17%.

3-Hydroxy-1,3-diphenyl-1-propanone (23).[4c,13c–e] Colorless oil; IR (neat, cm^{-1}) 3548, 3425, 1673; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.37 (d, $J = 6.0$ Hz, 2H), 5.34 (t, $J = 6.0$ Hz, 1H), 7.29–7.58 (m, 8H), 7.81–8.12 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 47.4, 70.0, 125.7, 127.7, 128.1, 128.6, 128.7, 133.6, 136.5, 142.9, 200.2.

3-Hydroxy-2-methyl-1,3-diphenyl-1-propanone (24).[13c–e] (*syn*/*anti* = 63/37) Colorless oil; IR (neat, cm^{-1}) 3510, 3417, 3047, 1674; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.05 (d, $J = 7.0$ Hz, 1.11H), 1.19 (d, $J = 7.3$ Hz, 1.89H), 3.07 (brs, 0.37H), 3.65 (brs, 0.63H), 3.69 (dq, $J = 3.2$, 7.3 Hz, 1.26H), 3.83 (dq, $J = 7.7$, 7.7 Hz, 0.74H), 4.98 (d, $J = 8.1$ Hz, 0.37H), 5.23 (d, $J = 3.2$ Hz, 0.63H), 7.22–7.60 (m, 8H), 7.90–7.98 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) *syn* isomer: δ 11.3, 47.0, 73.0, 125.9, 127.1, 128.1, 128.3, 128.6, 133.4, 135.4, 141.6, 205.5; *anti* Isomer: δ 15.8, 47.8, 76.7, 126.6, 127.8, 128.3, 128.5, 133.2, 136.5, 142.0, 204.6.

Methyl 3-Hydroxy-2-methyl-3-phenylpropionate (25).[4c,13b]

syn Isomer: Colorless oil; IR (neat, cm^{-1}) 3518, 3425, 2978, 1728, 1443, 1188, 1049; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (d, $J = 7.0$ Hz, 3H), 2.62–3.09 (brs, 1H), 2.79 (dq, $J = 4.0$, 7.0 Hz, 1H), 3.66 (s, 3H), 5.09 (d, $J = 4.0$ Hz, 1H), 7.21–7.43 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 10.7, 46.4, 51.8, 73.6, 125.9, 127.5, 128.2, 141.4, 176.1. *anti* Isomer: White powder; mp 48.0 °C; IR (neat, cm^{-1}) 3502, 2970, 1728, 1450, 1180, 1041; ^1H NMR (270 MHz, $CDCl_3$) δ 1.00 (d, $J = 7.0$ Hz, 3H), 2.63–3.20 (brs, 1H), 2.82 (dq, $J = 7.0$, 8.0 Hz, 1H), 3.72 (s, 3H), 4.74 (d, $J = 8.0$ Hz, 1H), 7.25–7.43 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.4, 47.1, 51.9, 76.4, 126.6, 128.1, 128.5, 141.5, 176.2.

General Procedure for Lithium Acetate-Catalyzed Aldol Reaction between Aldehyde and Trimethylsilyl Enolate in Dimethylformamide Containing Water. To a stirred solution of AcOLi (2.6 mg, 0.04 mmol) in DMF (0.5 mL) and H_2O (0.06 mL) were added successively a solution of aldehyde (0.4 mmol) in DMF (1.5 mL) and a solution of silyl enolate (0.8 mmol) in DMF (1.0 mL) at an appropriate temperature. The mixture was stirred for an appropriate time at the same temperature, and then quenched with 1.0 M HCl. The mixture was extracted with Et_2O and the organic layer was washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by preparative TLC to give the corresponding aldol. Products and yields are as reported in the text.

Methyl 4-(1-Hydroxy-2-methoxycarbonyl-2-methylpropyl)-benzoate (26). White crystals; mp 97.0 °C; IR (neat, cm^{-1}) 3502, 2931, 1720, 1286; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.14 (s, 3H), 3.23 (d, $J = 4.1$ Hz, 1H), 3.73 (s, 3H), 3.92 (s, 3H), 4.95 (d, $J = 4.1$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 8.00 (dd, $J = 1.9$, 6.8 Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.1, 22.7, 47.6, 52.08, 52.14, 78.0, 127.4, 128.8, 129.2, 145.0, 166.7, 177.6; Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81%. Found: C, 62.89; H, 6.72%.

Methyl 3-(4-Acetylphenyl)-3-hydroxy-2,2-dimethylpropionate (27). White powder; mp 83.3 °C; IR (neat, cm^{-1}) 3518, 3471, 2931, 1728, 1682, 1265; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.12 (s, 3H), 2.58 (s, 3H), 3.26 (brs, 1H), 3.71 (s, 3H), 4.94 (s, 1H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.89 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.2, 22.9, 26.7, 47.7, 52.3, 78.1, 127.6, 127.7, 136.3, 145.2, 177.7, 197.7; Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%. Found: C, 67.13; H, 7.32%.

Methyl 3-Hydroxy-2,2-dimethyl-3-(2-pyridyl)propionate (28).[13b] Colorless oil; IR (neat, cm^{-1}) 3494, 2985, 2947, 1466, 1265, 1142, 1057, 764; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.17 (s, 3H), 3.73 (s, 3H), 4.71 (d, $J = 6.2$ Hz, 1H), 4.96 (d, $J = 4.1$ Hz, 1H), 7.18 (d, $J = 8.1$ Hz, 2H), 7.23 (dt, $J = 1.1$, 4.9 Hz, 1H), 7.66 (dt, $J = 1.9$, 7.6 Hz, 1H), 8.55 (dd, $J = 1.1$, 3.8 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.8, 20.9, 48.4, 51.9, 76.9, 122.0, 122.7, 136.0, 147.9, 158.1, 176.9.

Methyl 3-Hydroxy-3-(2-hydroxyphenyl)-2,2-dimethylpropionate (29). This material was obtained by column chromatography on silica gel (deactivated by 10 wt % of water, hexane/ethyl acetate = 4/1). White powder; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.24 (s, 3H), 3.74 (s, 3H), 4.37 (brs, 1H), 5.12 (s, 1H), 6.77–6.91 (m, 3H), 7.14–7.21 (m, 1H), 8.50 (brs, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.0, 22.8, 48.8, 52.5, 80.4, 117.4, 118.8, 121.5, 129.1, 129.5, 156.4, 178.6. This compound is unstable and mostly converted to **32** by column chromatography on silica gel. The product was isolated quantitatively as **32** by PTLC.

4-Hydroxy-3,3-dimethyl-2-chromanone (32).[19] White crystals; mp 102.2 °C; IR (neat, cm^{-1}) 3386, 1759; ^1H NMR (270 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.41 (s, 3H), 1.91 (brs, 1H), 4.94 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 7.18 (dt, $J = 0.8$, 7.6 Hz, 1H), 7.34–7.38 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.8, 22.6, 43.5, 74.1, 116.5, 124.2, 124.6, 127.8, 130.2, 150.4, 172.4.

Methyl 3-Hydroxy-2,2-dimethyl-3-[4-(mehtylcarbamoyl)-phenyl]propionate (30). White crystals; mp 151.7 °C; IR (KBr, cm^{-1}) 3541, 2569, 2484, 1713, 1659, 1435, 1165; ^1H NMR (270 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.13 (s, 3H), 3.02 (d, $J = 4.9$ Hz, 3H) 3.25 (d, $J = 4.1$ Hz, 1H), 3.73 (s, 3H), 4.94 (d, $J = 3.2$ Hz, 1H), 6.12 (brs, 1H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.3, 22.6, 26.8, 47.7, 52.1, 77.9, 126.1, 127.5, 133.5, 143.4, 168.0, 177.7; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28%. Found: C, 63.25; H, 7.14; N, 5.13%.

4-(1-Hydroxy-2-methoxycarbonyl-2-methylpropyl)benzoic Acid (31). White crystals; mp 167.2 °C; IR (KBr, cm^{-1}) 3390, 3284, 2947, 1731, 1633, 1505; ^1H NMR (270 MHz, DMSO-d_6) δ 0.92 (s, 3H), 1.03 (s, 3H), 3.59 (s, 3H), 4.86 (d, $J = 4.3$ Hz, 1H), 5.73 (d, $J = 4.3$ Hz, 1H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.87 (d, $J = 8.1$ Hz, 2H), 12.91 (brs, 1H); ^{13}C NMR (68 MHz, DMSO-d_6) δ 19.9, 21.6, 47.9, 51.8, 76.5, 127.7, 128.6, 129.7, 146.9, 167.3, 176.2; Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39%. Found: C, 61.66; H, 6.62%.

3-Hydroxy-3-(4-nitrophenyl)-1-phenylpropane-1-one (33).[20] White crystals; mp 112.9 °C; IR (neat, cm^{-1}) 3703, 1674, 1520, 1342; ^1H NMR (270 MHz, $CDCl_3$) δ 3.29–3.46 (m, 2H), 3.93 (brs, 1H), 5.46 (dd, $J = 4.1$, 8.1 Hz, 1H), 7.45–7.50 (m, 2H), 7.59–7.64 (m, 3H), 7.93–7.960 (m, 2H), 8.20–8.23 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 47.0, 69.2, 123.7, 126.4, 128.0, 128.8, 133.9, 136.0, 147.2, 150.0, 199.3.

Silylation of Lithium Aldolate 38 in Co-Existence of Benzaldehyde (Scheme 7). To a solution of **4** (0.22 mmol) in Et_2O (1 mL) was added MeLi in Et_2O (0.2 mmol) at 0 °C. This mixture was stirred for 30 min. After evaporation of the solvent, DMF (0.5 mL) was added. To the solution were then successively added a solution of benzaldehyde (0.2 mmol) in DMF (1.0 mL) and a corresponding silylating reagent (0.28 mmol) at −45 °C. The reaction mixture was stirred for 1 h at −45 °C, and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with ether; the organic layer was washed with brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the product ratio (**5**:**6**) was determined by ^1H NMR spectra of the crude product.

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