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Organotin Perchlorates as Gentle Lewis Acid Catalysts in Mukaiyama Reaction

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Abstract: Organotin perchlorates catalyze Mukaiyama reaction of ketene silyl acetal in highly chemoselective but uncommon manners. The competition reaction between aldehyde and acetal leads to exclusive formation of the aldehyde aldols leaving the acetal counterpart intact, an unusual outcome in terms of reaction under acidic conditions. α-Enals react with ketene silyl acetal in preference to the corresponding alkanal. In the competition between electronically different aldehydes, an electron-donating group increases the reactivity of aldehyde while the reverse is true with an electron-withdrawing group. These are opposite to the reactivity order in nucleophilic addition to free carbonyls. In contrast to ketene silyl acetal, enol silyl ethers derived from ketones are not activated by organotin perchlorates. Thus, these two enol silyl ethers can be discriminated from each other. A disilyl enol ether derived from a keto ester undergoes the electrophilic attack by aldehyde and α-enone exclusively on the ester function. The catalytic activities of $TBSClO_4$ which should be formed if organotin perchlorates underwent transmetallation with ketene silyl acetal or silyl ether of the aldolate, are totally different from those of organotin perchlorates, indicating that the organotin species work as real active species. The reaction is interpreted in terms of the SN2 mechanism where the initial coordination of carbonyl group with organotin perchlorates plays a key role. The remarkable selectivitities are ascribed to the weak acidity of the catalysts. The reactivities of the complexed carbonyls are completely different from those of free carbonyls. © 1997 Elsevier Science Ltd.

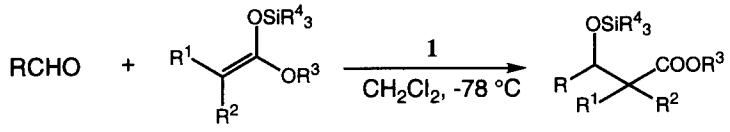
INTRODUCTION

Organotin compounds exhibit Lewis acidity[1] but, in general, it is not strong enough to trigger synthetically useful reactions.[2] However, if their acidity is increased they would serve as versatile catalysts which work under mild conditions due to their stability in the open atmosphere and easiness to handle. We have been working on organotin chemistry along this line. One of such strategies is to make use of associated organotin templates involving multi-reaction sites.[3] A substrate and a reagent are activated by coordination with different tin atoms. These tin atoms are located closely to each other so that the substrate and reagent could interact directly on the tin template to facilitate the reaction through entropy gain. Another way for this purpose is to attach electronegative groups on the tin atom. We disclosed that incorporation of the triflate groups on tin led to a unique Lewis acid which enabled various types of differentiation between carbonyls and acetals.[4] More recently, attachment of the perfluorophenyl group also was found to successfully increase the acidity.[5] The present study stemmed from the expectation that the highly electron-withdrawing perchlorate group would create new organotin Lewis acid catalysts of synthetic promise. This is indeed the case. We report here that organotin perchlorates induce uncommon chemoselectivities in aldol and Michael reactions of enol silyl ethers (Mukaiyama reaction).

RESULTS AND DISCUSSION

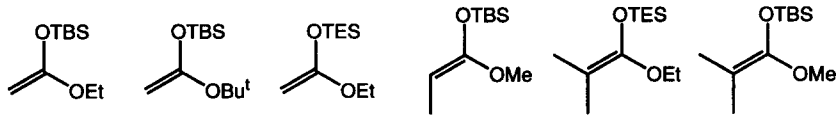
Mukaiyama-Aldol Reaction of Ketene Silyl Acetal. We employed two organotin perchlorates, Bu_3SnClO_4 (**1a**) and $Bu_2Sn(ClO_4)_2$ (**1b**), in this study. These compounds were most conveniently prepared according to Lambert's method.[6] Bu_3SnH or Bu_2SnH_2 was treated with 1 equiv. or 2 equiv. of Ph_3CClO_4 in dichloromethane and the resulting solution was used in situ for the Mukaiyama reaction. The solution contains

Table 1. Organotin Perchlorate-Catalyzed Mukaiyama-Aldol Reaction of Ketene Silyl Acetal.



3 **2** **4**

entry	1	2	3	yield (%) of **4**
1	**1a**	**2a**	**3a**	**4aa** 89
2	**1b**	**2a**	**3a**	**4aa** 92
3	**1a**	**2a**	**3b**	**4ab** 80
4	**1b**	**2a**	**3b**	**4ab** 89
5	**1a**	**2a**	**3c**	**4ac** 82
6	**1a**	**2a**	**3d**	**4ad** 86
7	**1a**	**2b**	**3a**	**4ba** 45
8	**1a**	**2c**	**3a**	**4ca** 52
9	**1a**	**2d**	**3a**	**4da** 90
10	**1b**	**2d**	**3a**	**4da** 91
11	**1a**	**2d**	**3b**	**4db** 81
12	**1b**	**2d**	**3b**	**4db** 87
13	**1a**	**2e**	**3a**	**4ea** 85
14	**1b**	**2e**	**3a**	**4ea** 86
15	**1a**	**2e**	**3b**	**4eb** 69
16	**1b**	**2e**	**3b**	**4eb** 73
17	**1a**	**2e**	**3c**	**4ec** 83
18	**1a**	**2e**	**3d**	**4ed** 60
19	**1a**	**2f**	**3a**	**4fa** 88



2a **2b** **2c** **2d** **2e** **2f**

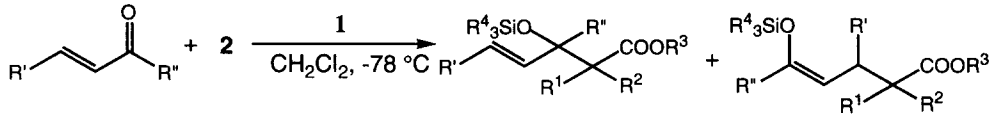
PhCHO (**3a**) *n*-C_7H_{15}CHO (**3b**) 4-$MeOC_6H_4$CHO (**3c**) 4-NCC_6H_4CHO (**3d**)

Ph_3CH but this has no influence on the reaction. This is the safest way to arrive at **1** because the perchlorates are always manipulated in solution. We have no data on physical and chemical properties of the solid organotin perchlorates although metal perchlorates are explosive on some occasions. Anyway, we have encountered no troubles so far in the present method.

As expected, both **1a** and **1b** catalyzed reaction of ketene silyl acetals **2** with aldehydes **3** (Table 1); no significant difference was observed between these two catalysts. Unsubstituted, monosubstituted, and disubstituted ketene silyl acetals reacted quite smoothly, and both aromatic and aliphatic aldehydes were employable.

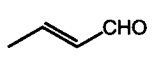
When α-enals were used as substrates, 1,2- and 1,4-additions competed (Table 2). Unsubstituted ketene silyl acetal **2a** favored the 1,2-addition (entries 1-3) while the 1,4-addition predominated with disubstituted one **2e** (entries 11,12). Virtually, no selectivity was observed with monosubstituted reagent **2d** (entries 6-8). By contrast, α-enone **6** always underwent exclusive 1,4-addition irrespective of nucleophiles (entries 4,5,9,10,13).

Table 2. Organotin Perchlorate-Catalyzed Mukaiyama Reaction of α-Enal and -Enone.

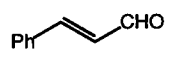


5 or 6 **7** **8**

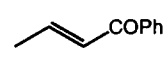
entry	1	2	5 or 6	Yield (%) 7		8		7:8
1	**1a**	**2a**	**5a**	**7aa**	81	**8aa**	6	93:7
2	**1b**	**2a**	**5a**	**7aa**	84	**8aa**	10	89:11
3	**1a**	**2a**	**5b**	**7ab**	83		0	100:0
4	**1a**	**2a**	**6**		0	**8ac**	78	0:100
5	**1b**	**2a**	**6**		0	**8ac**	66	0:100
6	**1a**	**2d**	**5a**	**7da**	38	**8da**	47	45:55
7	**1b**	**2d**	**5a**	**7da**	36	**8da**	47	43:57
8	**1a**	**2d**	**5b**	**7db**	45	**8db**	48	48:52
9	**1a**	**2d**	**6**		0	**8dc**	77	0:100
10	**1b**	**2d**	**6**		0	**8dc**	77	0:100
11	**1a**	**2e**	**5a**	**7ea**	17	**8ea**	73	19:81
12	**1a**	**2e**	**5b**	**7eb**	19	**8eb**	70	21:79
13	**1a**	**2e**	**6**		0	**8ec**	40	0:100



5a



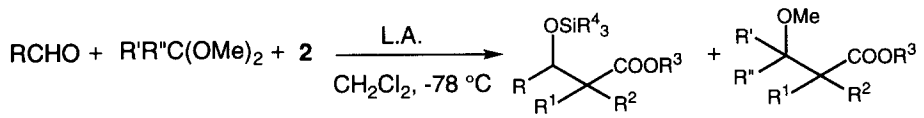
5b



6

Competition between Aldehyde and Acetal. Although it is rather difficult to differentiate between the carbonyl functions and their acetals in Lewis acid-promoted reactions, there appeared some selective reactions. Trimethylsilyl triflate induced the Mukaiyama-aldol reaction of enol silyl ethers with acetals but not with carbonyls[7] and alkyltitanium chlorides reacted with an acetal in the presence of a ketone.[8] These results are easy to explain in terms of the facile formation of the oxocarbocation intermediate from acetal under acidic conditions. The reversal of this chemoselectivity is of synthetic interest. Previously, we disclosed unique chemoselectivities in Mukaiyama-aldol reaction by dibutyltin bis(triflate) (DBTT).[4a] Smooth reaction occurred with aldehydes and ketals while ketones and acetals of aldehydes failed to react under the same reaction conditions. DBTT also differentiated various carbonyls and acetals in dithiane and dithiolane synthesis from thiostannanes.[9] Mukaiyama et al. also reported the reversed selectivity in Mukaiyama-aldol reaction catalyzed by TBSCl-$InCl_3$.[10] Now, we have found that **1** give rise to the perfect preference for aldehydes over acetals in Mukaiyama-aldol reaction of ketene silyl acetals (Table 3).[11] In the competition reaction between aldehyde and acetal, no products were formed at all from acetals **9** which are prone to generate the carbocation. The control data with conventional Lewis acids are given in entries 3-7 and 12. Except DBTT, all failed to give the high chemoselectivity. Notably, $TiCl_4$ having the strongest acidity preferred the acetal and the upon decreasing the acidity, the aldehyde is getting more favored. Apparently, organotin perchlorates are not acidic enough to generate the oxocarbocation and the reaction proceeds via SN2 mechanism. This is consistent with the fact that **1** cannot induce reaction with less nucleophilic enol silyl ethers derived from ketone (*vide infra*).

Table 3. Competition between Aldehyde and Acetal in Mukaiyama Reaction of Ketene Silyl Acetal.



3 **9** **4** **10**

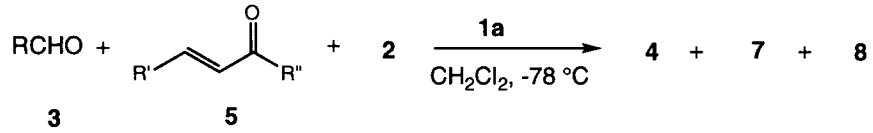
entry	L.A.	2	3	9	L.A.:2:3:9	Yield (%) 4	10	4:10
1	**1a**	**2a**	**3a**	**9a**	0.1:1.5:1.0:1.0	94	0	100:0
2	**1b**	**2a**	**3a**	**9a**	0.1:1.5:1.0:1.0	84	0	100:0
3	$Bu_2Sn(OTf)_2$	**2a**	**3a**	**9a**	0.1:1.0:1.0:1.0	62	0	100:0
4	$TiCl_4$	**2a**	**3a**	**9a**	1.0:1.0:1.0:1.0	12	26	32:68
5	$SnCl_4$	**2a**	**3a**	**9a**	0.1:1.0:1.0:1.0	34	5	87:13
6	Ph_3CClO_4	**2a**	**3a**	**9a**	0.1:1.0:1.0:1.0	44	8	85:15
7	TMSOTf	**2a**	**3a**	**9a**	0.1:1.0:1.0:1.0	70	9	89:11
8	**1a**	**2a**	**3a**	**9b**	0.1:1.5:1.0:1.0	89	0	100:0
9	**1b**	**2a**	**3a**	**9b**	0.1:1.5:1.0:1.0	82	0	100:0
10	**1a**	**2a**	**3b**	**9a**	0.1:1.5:1.0:1.0	78	0	100:0
11	**1a**	**2a**	**3b**	**9c**	0.1:1.0:1.0:1.0	64	0	100:0
12	TMSOTf	**2a**	**3b**	**9c**	0.1:1.0:1.0:1.0	48	23	68:32
13	**1a**	**2d**	**3a**	**9a**	0.1:1.0:1.0:1.0	87	0	100:0
14	**1a**	**2d**	**3b**	**9a**	0.1:1.5:1.0:1.0	67	0	100:0
15	**1a**	**2e**	**3a**	**9a**	0.1:1.5:1.0:1.0	85	0	100:0

9a $PhCH(OMe)_2$ **9b** $PhC(OMe)_2CH_3$ **9c** $n\text{-}C_7H_{15}C(OMe)_2CH_3$

Competition between Aldehyde and α-Enal. Because of the prevalence of nucleophilic addition towards carbonyls in organic synthesis, differentiation between different carbonyl functions is highly desired.[9] In general, incorporation of electron-donating group on carbonyl decreases the electrophilicity of the carbonyl carbon. An α,β-unsaturated group also reduces the reactivity of the carbonyl group through the delocalization of π-electrons and, hence, α-enones and -enals are less reactive than the corresponding alkanones and alkanals. The reversal of the reactivity between these carbonyl groups is difficult and finds only a few precedent examples. Reetz disclosed that $CH_3Ti(OiPr)_3$ reacted with α-enone and -enal faster than the corresponding aliphatic ketone and aldehyde.[12] He explained this selectivity in terms of the more increased steric hindrance of aliphatic carbonyls. Markó et al. reported the analogous selectivity for the addition of thallium ate complexes to a mixture of enone and ketone; α-enones and acetophenones reacted preferentially over aliphatic ketones (selectivity 5:1~75:1).[13] In this case, the initial electron transfer from the ate complex to the carbonyls was suggested. Nakai et al. put forth the Lewis acid promoted protocol.[14] In $Eu(fod)_3$-catalyzed Mukaiyama reaction of acetals, α-enones were much more reactive than the corresponding saturated ketone. This was interpreted in terms of stronger coordinating ability and, hence, more effective activation of the α-enones. It seems that such differentiation is more difficult between aldehyde pairs because of their higher reactivitites. Herein, we describe the high preference of α-enals over aldehyde by virtue of organotin perchlorate catalyst.[15]

As shown in Table 4, exposure of an equimolar mixture of **3** and **5** to **2** in the presence of catalytic **1a** resulted in the preferential or exclusive formation of **7** and **8** derived form **5** except one case (entry 4). Aliphatic aldehyde **3b** was most inactive and thus led to the exclusive formation of **7** (and **8**) (entries 2, 6). Benzaldehyde was a little more reactive to result in the decreased selectivities (entries 1, 5). An electron-withdrawing group on the aromatic ring reduced the reactivity of the benzaldehyde derivative leading to the perfect selectivity (entry 3) while an electron-donating group increased the reactivity giving rise to the outcome opposite to the others (entry 4). Dimethyl-substituted ketene silyl acetal **2e** also exhibited the preference for α-enal but gave the Michael adduct predominantely (entry 7).

Table 4. Competition between Aldehyde and α-Enal in Mukaiyama Reaction of Ketene Silyl Acetal.

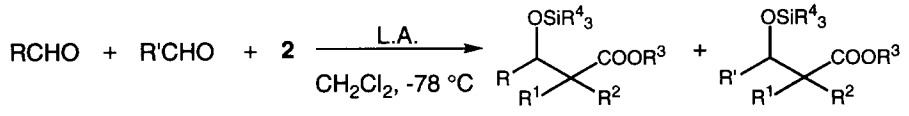


3 **5**

entry	2	3	5	Yield (%) 4	7	8	4:(7 + 8)
1	**2a**	**3a**	**5b**	7	77	0	8:92
2	**2a**	**3b**	**5b**	0	81	0	0:100
3	**2a**	**3d**	**5b**	0	78	0	0:100
4	**2a**	**3c**	**5b**	52	33	0	61:39
5	**2a**	**3a**	**5a**	16	62	4	20:80
6	**2a**	**3b**	**5a**	0	69	4	0:100
7	**2e**	**3a**	**5b**	3	12	64	4:96

To further shed light on the electronic effect of the substituent on the carbonyl reactivity, we conducted competition reaction between different aldehydes (Table 5). In the competition between benzaldehyde (**3a**) and octanal (**3b**), **3a** was the winner in the **1a**-catalyzed reaction (entry 1) indicative of higher reactivity of the aromatic aldehyde than the aliphatic counterpart. Incorporation of an electron-donating group increased the reactivity (entry 6) while an electron-withdrawing group decreased it (entry 7). Quite naturally, combination of both groups resulted in the perfect bias (entry 8). The analogous selectivity held with dimethyl-substituted ketene silyl acetal **2e** (entries 11-13). The results revealed in Table 4 and 5 imply that the reactivity of the carbonyl groups, when they are complexed, is quite different from that of free carbonyls. The relative reactivity can be interpreted in terms of coordinating ability of carbonyls. As described by Denmark[16] and Nakai,[14] the coordination of aromatic and α,β-unsaturated aldehydes is more facilitated than aliphatic aldehydes by stabilization of the electron-deficient carbonyl carbon through the extended conjugation. The electron-donating group also induces the stronger coordination due to the increased basicity of the carbonyl oxygen. However, it should be noted that strong Lewis acids such as $TiCl_4$ and $SnCl_4$, failed to detect the subtle differences between the aldehydes (Table 5, entries 3-5, 10). Both carbonyls are activated to a comparative extent. On the other hand, the use of **1a** even in the 2 equivalent amount gave rise to the high selectivities (entries 2, 9). Apparently, the subtle difference in the carbonyl reactivity can be detected only with gentle Lewis acids.

Table 5. Competition between Aldehydes in Mukaiyama Reaction of Ketene Silyl Acetal.

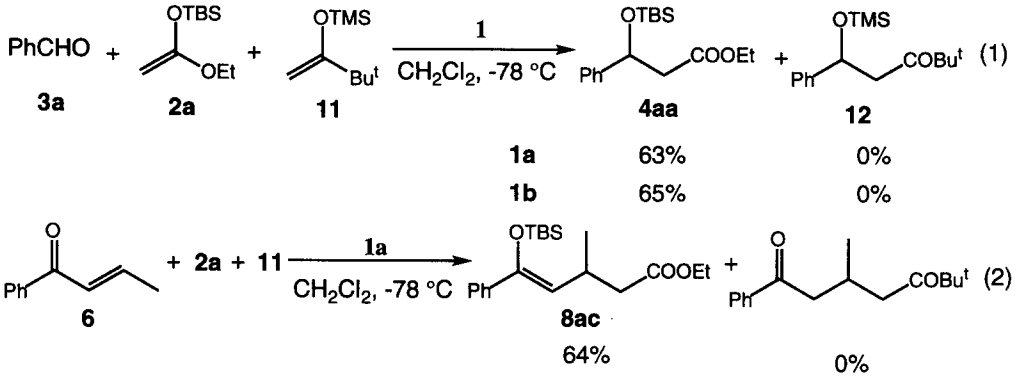


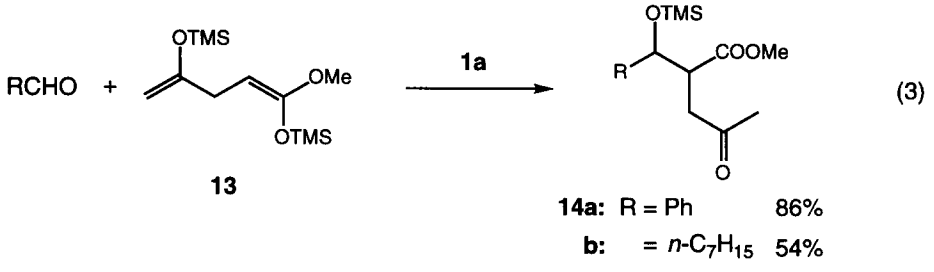
3 **3'**

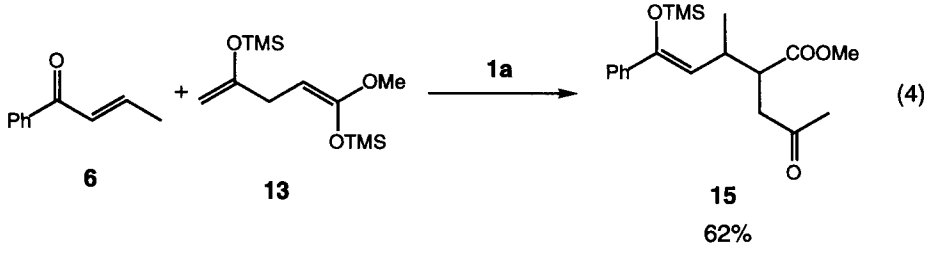
					Yield (%)		
entry	L.A. (equiv)	2	3	3'	4	4'	4:4'
1	**1a** (0.1)	**2a**	**3a**	**3b**	59	8	88:12
2	**1a** (2.0)	**2a**	**3a**	**3b**	52	16	76:24
3	$TiCl_4$ (1.0)	**2a**	**3a**	**3b**	23	42	35:65
4	$TiCl_4$ (2.0)	**2a**	**3a**	**3b**	26	34	43:57
5	$SnCl_4$ (0.1)	**2a**	**3a**	**3b**	23	21	52:48
6	**1a** (0.1)	**2a**	**3a**	**3c**	5	80	6:94
7	**1a** (0.1)	**2a**	**3a**	**3d**	71	4	95:5
8	**1a** (0.1)	**2a**	**3c**	**3d**	88	0	100:0
9	**1a** (2.0)	**2a**	**3c**	**3d**	84	0	100:0
10	$TiCl_4$ (2.0)	**2a**	**3c**	**3d**	34	23	60:40
11	**1a** (0.1)	**2e**	**3a**	**3b**	57	6	90:10
12	**1a** (0.1)	**2e**	**3a**	**3c**	4	70	5:95
13	**1a** (0.1)	**2e**	**3a**	**3d**	60	12	83:17

Differentiation of Enol Silyl Ethers Derived from Ester and Ketone. In sharp contrast to enol silyl ethers derived from esters (ketene silyl acetals), those derived from ketones have been found not to undergo organotin perchlorate-catalyzed Mukaiyama reactions. Thus, competition between **2a** and **11** towards **3a** or **6** led to the exclusive formation of **4aa** or **8ac** that resulted from the reaction of **2a**; no products from **11** were

detected (eqs. 1 and 2). The synthetic significance of this remarkable discrimination was highlighted by the intramolecular versions (eqs. 3 and 4). Disilyl enol ether **13** derived from methyl 4-oxopentanoate reacted with aldehyde and α-enone on the ester function exclusively. Notably, the C2 position is mono-substituted while the C5 is at the terminal, yet the reaction occurred only at C2. Apparently, the innate reactivity of ketene silyl acetal function overcome the steric demand. The enhanced nucleophilic character of the β,β-dialkoxyvinyl moiety in comparison with the β-monoalkoxy analog is reasonable, yet the differentiation between these two functions would not be achievable without gentle Lewis acids.

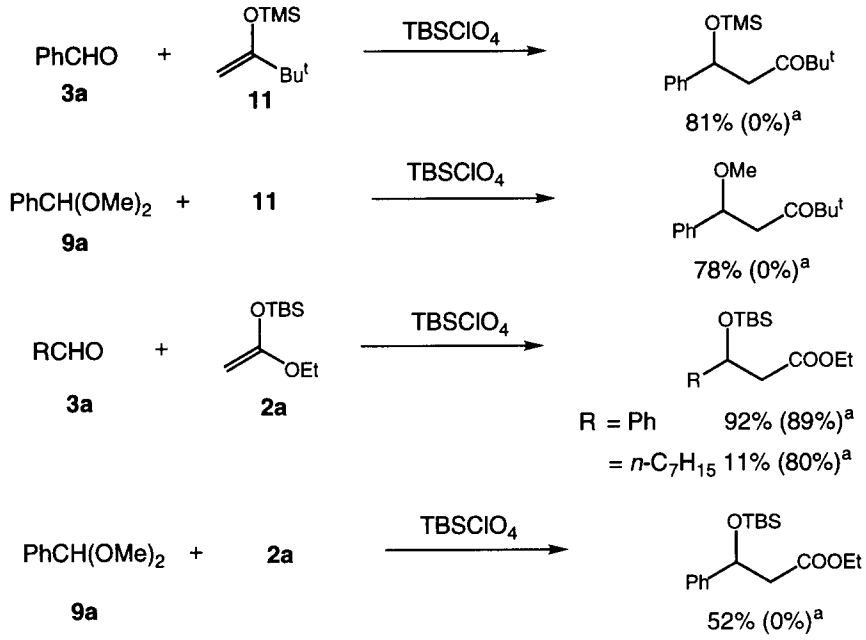






Concluding Remarks. In the Lewis acid-catalyzed aldol reaction of ketene silyl acetal, it is important to sort out the real active catalyst species because of possible transmetallation of ketene silyl acetal[17] or the silyl ether of aldolate formed[18] with Lewis acid, by which a new silyl Lewis acid should emerge. To check the possibility of the direct transmetallation between ketene silyl acetal and **1a**, the following experiment was carried out. First, **1a** (0.1 equiv) and **2a** (1.3 equiv) was stirred at -78 ℃ for 1.5 h, and then **3a** (1.0 equiv) was added to this solution. After 2 h, an 89% yield of **4aa** was obtained, indicating no virtual change from the reaction under the standard conditions (initial mixing of **1a** and **3a** followed by addition of **2a**). The possibility of both

transmetallation processes was more unambiguously ruled out by the reaction with $TBSClO_4$ that was supposed to be formed if the transmetallation had occurred. As depicted in Scheme 1, the $TBSClO_4$ catalyst exhibited totally different features from **1**. It smoothly catalyzed aldol reaction of enol silyl ether derived from pinacolone **11** with aldehyde and acetal in contrast to the complete ineffectiveness of the organotin perchlorates. On the other hand, octanal which can be activated by **1a** reacted sluggishly with **2a** in the presence of $TBSClO_4$. Reaction of acetal **9a** with **2a** was also effected by $TBSClO_4$. It follows from these results that $TBSClO_4$ did not play any role in the organotin perchlorate-catalyzed reaction.



[a]Yields in the **1a**-catalyzed reaction are given in parentheses.

Scheme 1.

The reactivities revealed in this study is totally in accord with the SN2 mechanism. The preference of aldehyde over acetal is the typical example. Organotin perchlorates are not acidic enough to generate the carbocation and the coordination with carbonyl is the crucial step. The importance of this step is reflected on the preferred reaction of α-enals to saturated aldehydes. The SN2 mechanism also enables differentiation between enol silyl ethers derived from esters and ketones. The former ethers are more nucleophilic so that the reaction is triggered by **1** while the latter ones are not nucleophilic enough to be activated by **1**. Detection of the subtle differences requires to invoke the weak catalytic activities. Hence, the usefulness of gentle Lewis acids for designing highly chemoselective reactions will receive more attention.

EXPERIMENTAL SECTION

Reaction of 2 with 3 (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of Ph_3CClO_4 (34.2 mg, 0.1 mmol) was added Bu_3SnH (30.6 mg, 0.105 mmol) at room temperature. In the meantime, the yellow color disappeared. The solution was stirred for 1 h to form **1a**. To the resulting solution were added a CH_2Cl_2

solution (2 mL) of **3a** (106 mg, 1 mmol) and then **2a** (242 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) at -78°C. After 2 h, the reaction mixture was subjected to aqueous workup and column chromatography on silica gel (1:3 CH_2Cl_2-hexane) of the crude product afforded **4aa**[19] (274 mg, 89%): ^{1}H NMR ($CDCl_3$) δ -0.13 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.89 (s, 9H, t-Bu), 1.25 (t, 3H, J=7.1Hz, CH_3), 2.53, 2.71 (ABX, 2H, J_{AB}=14.6, J_{AX}=4.0, J_{BX}=9.4Hz, CH_2), 4.17 (q, 2H, J=7.1Hz, CH_2), 5.17-5.21 (m, 1H, CH), 7.29-7.40 (m, $5H_{arom}$). The other reactions were carried out analogously.

4ab: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H, CH_3), 0.06 (s, 3H, CH_3), 0.86 (s, 9H, t-Bu), 0.88 (t, 3H, J=6.5Hz, CH_3), 1.25 (t, 3H, J=7.1Hz, CH_3), 1.27-1.49 (m, 12H, $6CH_2$), 2.40-2.43 (m, 2H, CH_2), 4.08-4.15 (m, 3H, CH, CH_2). This compound was confirmed by desilylation to give the known alcohol.[20]

4ac: ^{1}H NMR ($CDCl_3$) δ -0.19 (s, 3H, CH_3), -0.01 (s, 3H, CH_3), 0.83 (s, 9H, t-Bu), 1.25 (t, 3H, J=7.1Hz, CH_3), 2.50, 2.73 (ABX, 2H, J_{AB}=14.4, J_{AX}=4.3, J_{BX}=9.3Hz, CH_2), 3.79 (s, 3H, OCH_3), 4.10 (q, 2H, J=7.1Hz, CH_2), 5.08-5.11 (m, 1H, CH), 6.84 (m, $2H_{arom}$), 7.25 (m, $2H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[21]

4ad: ^{1}H NMR ($CDCl_3$) δ -0.16 (s, 3H, CH_3), -0.01 (s, 3H, CH_3), 0.84 (s, 9H, t-Bu), 1.24 (t, 3H, J=7.1Hz, CH_3), 2.52, 2.69 (ABX, 2H, J_{AB}=14.8, J_{AX}=4.5, J_{BX}=8.7Hz, CH_2), 4.10 (q, 2H, J=7.1Hz, CH_2), 5.16-5.20 (m, 1H, CH), 7.41 (m, $2H_{arom}$), 7.62 (m, $2H_{arom}$); HRMS calcd for $C_{18}H_{28}NO_3Si$ (M^+ + 1) 334.1838, found 334.1855.

4ba: ^{1}H NMR ($CDCl_3$) δ -0.19 (s, 3H, CH_3), 0.04 (s, 3H, CH_3), 0.85 (s, 9H, t-Bu), 1.42 (s, 9H, t-Bu), 2.46, 2.66 (ABX, 2H, J_{AB}=14.9, J_{AX}=4.3, J_{BX}=8.7Hz, CH_2), 5.08-5.13 (m, 1H, CH), 7.24-7.35 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[22]

4ca: ^{1}H NMR ($CDCl_3$) δ 0.47 (q, 6H, J=7.8Hz, $3CH_2$), 0.85 (t, 9H, J=7.8Hz, $3CH_3$), 1.24 (t, 3H, J=7.1Hz, CH_3), 2.55, 2.74 (ABX, 2H, J_{AB}=14.7, J_{AX}=4.4, J_{BX}=9.9Hz, CH_2), 4.10 (q, 2H, J=7.1Hz, CH_2), 5.14-5.18 (m, 1H, CH), 7.25-7.38 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[23]

4da: ^{1}H NMR ($CDCl_3$) δ -0.30 (s, 3H, CH_3), -0.02 (s, 3H, CH_3), 0.80 (s, 9H, t-Bu), 0.84 (d, 3H, J=7.1Hz, CH_3), 2.61-2.68 (m, 1H, CH), 3.57 (s, 3H, OCH_3), 4.69 (d, 1H, J=9.3Hz, CH), 7.23-7.31 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[24]

4db: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H, CH_3), 0.05 (s, 3H, CH_3), 0.86 (s, 9H, t-Bu), 0.88 (t, 3H, J=6.5Hz, CH_3), 1.10 (d, 3H, J=7.1Hz, CH_3), 1.26-1.47 (m, 12H, $6CH_2$), 2.61-2.66 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 4.00-4.02 (m, 1H, CH); HRMS calcd for $C_{18}H_{39}O_3Si$ (M^+ + 1) 331.2668, found 331.2633.

4ea: ^{1}H NMR ($CDCl_3$) δ 0.45 (q, 6H, J=7.8Hz, $3CH_2$), 0.83 (t, 9H, J=7.8Hz, $3CH_3$), 0.96 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.24 (t, 3H, J=7.1Hz, CH_3), 4.13 (q, 2H, J=7.1Hz, CH_2), 5.00 (s, 1H, CH), 7.23-7.28 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[25]

4eb: ^{1}H NMR ($CDCl_3$) δ 0.59 (q, 6H, J=7.8Hz, $3CH_2$), 0.86 (t, 3H, J=6.5Hz, CH_3), 0.95 (t, 9H, J=7.8Hz, $3CH_3$), 1.05 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.17-1.42 (m, 15H, $6CH_2$, CH_3), 3.85-3.89 (m, 1H, CH), 4.10 (q, 2H, J=7.1Hz, CH_2); HRMS calcd for $C_{20}H_{43}O_3Si$ (M^+ + 1) 359.2981, found 359.3024.

4ec: ^{1}H NMR ($CDCl_3$) δ 0.45 (q, 6H, J=7.8Hz, $3CH_2$), 0.83 (t, 9H, J=7.8Hz, $3CH_3$), 0.95 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.26 (t, 3H, J=7.1Hz, CH_3), 3.80 (s, 3H, OCH_3), 4.09 (q, 2H, J=7.1Hz, CH_2), 4.95 (s, 1H, CH), 6.81 (m, $2H_{arom}$), 7.20 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[26]

4ed: ^{1}H NMR ($CDCl_3$) δ 0.45 (q, 6H, J=7.8 Hz, $3CH_2$), 0.84 (t, 9H, J=7.8, 3 CH_3), 0.96 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.25 (t, 3H, J=7.1 Hz, CH_3), 4.11 (q, 2H, J=7.1 Hz, CH_2), 5.05 (s, 1H, CH), 7.41 (m, $2H_{arom}$), 7.60 (m, $2H_{arom}$); HRMS calcd for $C_{20}H_{32}NO_3Si$ (M^+ + 1) 362.2155, found 362.2188.

4fa: ^{1}H NMR ($CDCl_3$) δ -0.35 (s, 3H, CH_3), -0.01 (s, 3H, CH_3), 0.87 (s, 9H, t-Bu), 0.98 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.96 (s, 1H, CH), 7.27 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[27]

Reaction of 2 with 5 or 6 (Typical Procedure). To a CH_2Cl_2 solution (0.5 mL) of **1a** (0.1 mmol) were added a CH_2Cl_2 solution (2 mL) of **5a** (70 mg, 1 mmol) and subsequently **2a** (263 mg, 1.3 mmol) in CH_2Cl_2 (2 mL) at -78°C. After 2 h, the reaction mixture was subjected to aqueous workup and column chromatography on silica gel (1:20 EtOAc-hexane) of the crude product afforded **7aa** (221 mg, 81%):[28] ^{1}H-NMR ($CDCl_3$) δ 0.01 (s, 3H, CH_3), 0.02 (s, 3H, CH_3), 0.84 (s, 9H, t-Bu), 1.24 (t, 3H, J=7.1Hz, CH_3), 1.65 (d, 3H, J=5.8Hz, CH_3), 2.38, 2.49 (ABX, 2H, J_{AB}=14.3, J_{AX}=5.2, J_{BX}=8.2Hz, CH_2), 4.12 (q, 2H, J=7.1Hz, CH_2), 4.51-4.53 (m, 1H, CH), 5.44-5.47 (m, 1H, CH), 5.58-5.65 (m, 1H, CH); **8aa** (17 mg, 6%):[28] ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H, $2CH_3$), 0.89 (s, 9H, t-Bu), 1.02 (d, 3H, J=6.8Hz, CH_3), 1.24 (t, 3H, J=7.1Hz, CH_3), 2.24 (d, 2H, J=6.4Hz, CH_2), 2.52-2.62 (m, 1H, CH), 4.10 (q, 2H, J=7.1Hz, CH_2), 4.89 (dd, 1H, J=12.1, 8.8Hz, CH), 6.27 (d, 1H, J=12.1Hz, CH). The other reactions were conducted analogously.

7ab:[29] ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), 0.89 (s, 9H, t-Bu), 1.26 (t, 3H, J=7.1Hz, CH_3), 2.51, 2.62 (ABX, 2H, J_{AB}=14.4, J_{AX}=5.2, J_{BX}=7.7Hz, CH_2), 4.13 (q, 2H, J=7.1Hz, CH_2), 4.76-4.78 (m, 1H, CH), 6.19 (dd, 1H, J=15.8, 7.0Hz, CH), 6.57 (d, 1H, J=15.8Hz, CH), 7.24-7.38 (m, $5H_{arom}$).

7da:[28] ^{1}H NMR ($CDCl_3$) δ -0.02 (s, 6H, $2CH_3$), 0.83 (s, 9H, t-Bu), 1.00 (d, 3H, J=7.0Hz, CH_3), 1.66 (d, 3H, J=6.9Hz, CH_3), 2.46-2.52 (m, 1H, CH), 3.63 (s, 3H, OCH_3), 4.14-4.18 (m, 1H, CH), 5.25-5.35 (m, 1H, CH), 5.56-5.63 (m, 1H, CH).

7db:[30] ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 6H, $2CH_3$), 0.87 (s, 9H, t-Bu), 1.08 (d, 3H, J=7.0 Hz, CH_3), 2.60-2.67 (m, 1H, CH), 3.65 (s, 3H, OCH_3), 4.38-4.43 (m, 1H, CH), 6.06 (dd, 1H, J=15.9, 7.0 Hz, CH), 6.53 (d, 1H, J=15.9 Hz, CH), 7.30-7.40 (m, $5H_{arom}$);

7ea: ^{1}H NMR ($CDCl_3$) δ 0.53 (q, 6H, J=7.8 Hz, $3CH_2$), 0.92 (t, 9H, J=7.8 Hz, $3CH_3$), 1.03 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.24 (t, 3H, J=7.1 Hz, CH_3), 1.68 (d, 3H, J=6.1Hz, CH_3), 4.10 (q, 2H, J=7.1Hz, CH_2), 4.24 (d, 1H, J=8.1Hz, CH), 5.39 (dd, 1H, J=15.3, 8.1Hz, CH), 5.55-5.62 (m, 1H, CH); HRMS calcd for $C_{16}H_{33}O_3Si$ (M^+ + 1) 301.2199, found 301.2205.

7eb: ^{1}H NMR ($CDCl_3$) δ 0.58 (q, 6H, J=7.8Hz, $3CH_2$), 0.93 (t, 9H, J=7.8Hz, $3CH_3$), 1.10 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.26 (t, 3H, J=7.1Hz, CH_3), 4.15 (q, 2H, J=7.1Hz, CH_2), 4.49 (d, 1H, J=7.9Hz, CH), 6.14 (dd, 1H, J= 15.9, 7.9Hz, CH), 6.50 (d, 1H, J=15.9Hz, CH), 7.25-7.39 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known alcohol.[31]

8ac:[17] ^{1}H NMR ($CDCl_3$) δ -0.16 (s, 3H, CH_3), -0.14 (s, 3H, CH_3), 0.89 (s, 9H, t-Bu), 0.99 (d, 3H, J=6.8Hz, CH_3), 1.16 (t, 3H, J=7.1Hz, CH_3), 2.16-2.19 (m, 2H, CH_2), 3.05-3.16 (m, 1H, CH), 4.03 (q, 2H, J=7.1Hz, CH_2), 4.83 (d, 1H, J=9.6Hz, CH), 7.29-7.40 (m, $5H_{arom}$).

8da:[28] ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H, $2CH_3$), 0.90 (s, 9H, t-Bu), 0.97 (d, 3H, J=6.5Hz, CH_3), 1.09 (d, 3H, J=6.5Hz, CH_3), 2.23-2.36 (m, 2H, 2CH), 3.63 (s, 3H, OCH_3), 4.74-4.92 (m, 1H, CH), 6.23 (d, 1H, J=11.8Hz, CH).

8db:[32] ^{1}H NMR ($CDCl_3$) δ 0.96 (d, 3H, J=7.0Hz, CH_3), 2.68-2.89 (m, 3H, CH, CH_2), 3.39-3.45 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 7.16-7.34 (m, $5H_{arom}$), 9.54 (s, 1H, CHO).

8dc:[33] ^{1}H NMR ($CDCl_3$) δ -0.01 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), 0.98 (s, 9H, t-Bu), 1.10 (d, 3H, J=6.8Hz, CH_3), 1.18 (d, 3H, J=6.8Hz, CH_3), 2.35-2.50 (m, 1H, CH), 2.67-2.76 (m, 1H, CH), 3.68 (s, 3H, OCH_3), 4.87 (d, 1H, J=10.9Hz, CH), 7.35-7.49 (m, $5H_{arom}$).

8ea: ^{1}H NMR ($CDCl_3$) δ 0.66 (q, 6H, J=7.8Hz, $3CH_2$), 0.92 (d, 3H, J=7.2Hz, CH_3), 0.98 (t, 9H, J=7.7Hz, $3CH_3$), 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.25 (t, 3H, J=7.1Hz, CH_3), 2.34-2.40 (m, 1H, CH), 4.11 (q,

2H, J=7.1Hz, CH_2), 4.87 (dd, 1H, J=11.8, 9.8Hz, CH), 6.27(d, 1H, J=11.8Hz, CH): HRMS calcd for $C_{16}H_{33}O_3Si$ (M^+ + 1) 301.2199, found 301.2197.

8eb: ^{1}H NMR ($CDCl_3$) δ 0.64 (q, 6H, J=7.8Hz, $3CH_2$), 0.95 (t, 9H, J=7.8Hz, $3CH_3$), 1.07 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.20 (t, 3H, J=7.1Hz, CH_3), 3.50 (d, 1H, J=10.7Hz, CH), 4.04 (q, 2H, J=7.1Hz, CH_2), 5.43 (dd, 1H, J=11.7, 10.7Hz, CH), 6.32 (d, 1H, J=11.7Hz, CH), 7.14-7.28 (m, $5H_{arom}$). This compound was confirmed by desilylation to give the known aldehyde.[34]

8ec:[17] ^{1}H NMR ($CDCl_3$) δ 0.62 (q, 6H, J=7.8Hz, $3CH_2$), 0.92 (t, 9H, J=7.8Hz, $3CH_3$), 0.96 (d, 3H, J=6.7Hz, CH_3), 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.15 (t, 3H, J=7.1Hz, CH_3), 2.67-2.73 (m, 1H, CH), 3.95-4.10 (m, 2H, CH_2), 4.93 (d, 1H, J=11.2Hz, CH), 7.26-7.39 (m, $5H_{arom}$).

Competition reaction (General Procedure). To a CH_2Cl_2 solution (1 mL) of **1a** (0.1 mmol) were added a mixture of electrophiles (1.0 mmol each) in CH_2Cl_2 (3 mL) and subsequently **2** (1.5 mmol) in CH_2Cl_2 (2 mL) at -78°C. After 2 h, aqueous workup and evaporation afforded a crude product that was analyzed by GLC.

Competition Reaction of Enol Silyl Ethers Derived from Ester and Ketone (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of **1a** (0.1 mmol) were added a CH_2Cl_2 solution (2 mL) of **3a** (106 mg, 1.0 mmol) at -78°C. Then, **2a** (202 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) and **11** (174 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) were added. The solution was stirred for 3 h. Aqueous workup and evaporation afforded a crude product that was analyzed by GLC.

Preparation of 13 (two stereoisomers). To a THF solution (90 mL) of diisopropylamine (11.2 g, 110 mmol) was added BuLi (1.6 M hexane solution, 69 mL, 110 mmol) at 0°C. The solution was cooled to -78°C and methyl β-acetylpropionate (6.5 g, 50 mmol) was added. The reaction mixture was stirred at -78°C for 1 h and trimethylsilyl chloride (15.1 g, 140 mmol) was added rapidly. After stirring for 1 h at room temperature, the reaction mixture was filtered and then THF was evaporated. The residue was dissolved in 150 mL of pentane and the salt precipitated was removed by filtration. After evaporation, the residue was distilled under reduced pressure (69-73 °C/3 mmHg) to give **13** (4.80 g, 35%, 7:3 *E/Z* mixture). ^{1}H NMR ($CDCl_3$) δ 0.19 (major) and 0.20 (minor) (each s, 9H, $3CH_3$), 0.21 (major) and 0.22 (minor) (each, s, 9H, $3CH_3$), 2.68 (d, 2H, J=7.1Hz, CH_2), 3.51 (minor) and 3.52 (major) (each s, 3H, OCH_3), 3.56 (t, 1H, J=7.1Hz, CH), 4.03 (minor) and 4.05 (major) (each s, 1H, CH), 4.11 (minor) and 4.13 (major) (each s, 1H, CH).

Reaction of 13 with Aldehyde. To a CH_2Cl_2 solution (1 mL) of **1a** (0.1 mmol) were added a CH_2Cl_2 solution (2 mL) of **3a** (106 mg, 1.0 mmol) and then **13** (329 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) at -78°C. After 2 h, 2-(hydroxymethyl)pyridine (33 mg, 0.3 mmol) and pyridine (0.1 mL) were added. The resulting mixture was diluted with hexane (60 mL) and washed with aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (1:8 EtOAc-hexane) to give **14a** (266 mg, 86%). ^{1}H NMR ($CDCl_3$) δ -0.02 (s, 9H, $3CH_3$), 2.03 (s, 3H, CH_3), 2.32, 2.69 (ABX, 2H, J_{AB}=17.8, J_{AX}=3.6, J_{BX}=10.6Hz, CH_2), 3.21-3.28 (m, 1H, CH), 3.70 (s, 3H, OCH_3), 4.84 (d, 1H, J=7.7Hz, CH), 7.24-7.34 (m, $5H_{arom}$): HRMS calcd for $C_{16}H_{25}O_4Si$ (M^+ + 1) 309.1522, found 309.1500. The other reaction was carried out analogously to afford **14b** which was confirmed as the corresponding alcohol after desilylation: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=6.2Hz, CH_3), 1.24-1.80 (m, 12H, $6CH_2$), 2.18 (s, 3H, CH_3), 2.75-2.83 (m, 1H, CH), 2.92-3.08 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.97-4.05 (m, 1H, CH); HRMS calcd for $C_{14}H_{25}O_3$ (M^+ - OH) 241.1804, found 241.1804.

Reaction of 13 with 6. The reaction was carried out analogously as described above employing **6** (146 mg, 1.0 mmol) in place of **13** to give **15** (216 mg, 62%). This compound was confirmed as follows: **15** was treated with Bu_4NF (178 mg, 0.68 mmol) and THF (3 mL) at room temperature for 1 h. Aqueous $NaHCO_3$ was added to this solution, and the mixture was extracted with ethyl acetate. The organic layer was dried and

evaporated. The residue was chromatographed on silica gel (1:6 EtOAc-hexane) to give 6-benzoyl-4-methoxycarbonyl-5-methyl-2-hexanone: ^{1}H NMR ($CDCl_3$) δ 0.99 (d, 3H, J=6.8Hz, CH_3), 2.18 (s, 3H, CH_3), 2.49-3.14 (m, 6H, 2CH, $2CH_2$), 3.68 (s, 3H, OCH_3), 7.28-7.60 (m, $5H_{arom}$): HRMS calcd for $C_{16}H_{21}O_4$ (M^+ + 1) 277.1440, found 277.1487.

Mukaiyama reaction catalyzed by $TBSClO_4$ was carried out in the same way as organotin perchlorate-catalyzed reaction.

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