Unusual Preference for Ketone and Reversal of Chemoselectivity in Lewis Acid-Catalyzed Aldol Reaction of Ketene Silyl Acetal

Jian-xie Chen, Katsumasa Sakamoto, Akihiro Orita, and Junzo Otera*

Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan

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Ketene silyl acetals undergo facile reaction with ketones in the presence of a Lewis acid such as $(C_6F_5)_2SnBr_2$, TMSOTf, or $Sc(OTf)_3$. This unique reactivity allows ketones to react in preference to aldehydes or acetals in competitive aldol-type reactions. Upon treatment with keto aldehydes or keto acetals, ketene silyl acetals provide single products derived from the exclusive reaction with the ketonic function. Particularly noteworthy is the discrimination of ketones from aldehydes in naked forms. It has been proved that such bias results from the differentiated recognition of ketone and aldehyde carbonyls. The ternary system consisting of ketene silyl acetal, carbonyl, and an appropriate Lewis acid is crucial for achieving the effective differentiation.

The nucleophilic addition to carbonyl substrates is one of the most important chemical transformations, and the differentiation between carbonyl functions in the competition reaction is highly useful in organic synthesis. Basically, carbonyl functions possess different reactivities, and thus one reacts faster than the other to some extent, yet the highly selective differentiation is rather difficult to achieve.[1] Reversal of such innate reactivity is more intriguing and challenging but extremely difficult. The protection-dependent method is most commonly invoked to this end: a more reactive function is selectively protected initially, and subsequently the remaining less-reactive naked function undergoes selective nucleophilic addition.[2] We alternatively advanced the activation−deactivation method: aldehyde and ketone are transformed to the corresponding acetal and ketal, and then in situ treatment of the mixture with silyl nucleophile in the presence of organotin triflate catalyst results in preferential reaction of the ketal, leaving the acetal unchanged.[3] The intramolecular version based on the neighboring group participation was also put forth by treating keto aldehyde substrates with disilyl enol ethers of keto esters.[4] In addition to these protective methods, the direct differentiation of α,*β*-unsaturated ketones[5] or aldehydes[6] from the corresponding saturated ketones or aldehydes, respectively, was realized. Nevertheless, the discrimination of ketone from aldehyde *in naked form*, the most important and fundamental combination, has still remained to be established although Molander et al. made reference to one example of exclusive reaction of 2-heptanone in the presence of octanal in the context of their neighboring group participation protocol.[4a]

Another synthetic challenge is the differentiation between ketone and acetal in Lewis acid-promoted reactions, yet this type of differentiation is not exercised with much ease. Under acidic conditions normally employed, acetals are supposed to be more reactive than the carbonyl counterparts due to their facile capability of carbocation formation. Nevertheless, only a limited number of successful examples along this line were reported, that is, TMSOTf (trimethylsilyl triflate)-catalyzed aldol reaction of enol silyl ethers[7] and methylation with CH_3TiCl_3.[8] On the contrary, the reversed selectivity has appeared more recently. Under the catalysis of $Bu_2Sn(OTf)_2$, silyl nucleophiles reacted preferentially with aldehyde acetals over the parent aldehydes.[3] This catalyst gave rise to the analogous selectivities in the synthesis of dithianes and dithiolanes from thiostannanes.[9] Further examples were put forth with (TBS)Cl−$InCl_3$ ((TBS)Cl = *tert*-butyldimethylsilyl chloride),[10] organotin perchlorates,[11] and a bidentate organoaluminum compound.[12]

In this paper we report an intense preference of ketene silyl acetals for ketone that leads to the extremely high level of chemoselectivity in the competition with aldehyde or acetal.[13]

Results and Discussion

The facile reactions of ketene silyl acetals **1** (Chart 1) with ketones are exemplified in Table 1. The reactions of acetophenone (**2a**) catalyzed by bis(pentafluorophenyl)tin dihalides were quenched in 1 h (entries 1 and 2), yet thin layer chromatography (TLC) monitoring exhibited the complete disappearance of the ketone after 10

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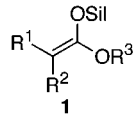
Chart 1



1

1a: $R^1 = R^2 = H$; $R^3 = Et$; Sil = $^tBuMe_2Si$
b: $R^1 = H$; $R^2 = R^3 = Me$; Sil = $^tBuMe_2Si$
c: $R^1 = H$; $R^2 = Me$; $R^3 = Et$; Sil = Et_3Si
d: $R^1 = R^2 = Me$; $R^3 = Et$; Sil = Et_3Sil

2

2a: R^1 = Ph; R^2 = Me
b: R^1 = 4-$MeOC_6H_4$; R^2 = Me
c: R^1 = 2,4-$(MeO)_2C_6H_3$; R^2 = Me
d: $R^1 = C_2H_5$; R^2 = Me
e: $R^1 = n$-C_4H_9; R^2 = Me
f: R^1, $R^2 = (CH_2)_5$
g: R^1 = 4-$NO_2C_6H_4$; R^2 = Me

RCHO

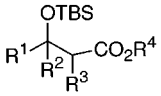
3

3a: R = n-C_5H_{11}
b: R = n-C_7H_{15}
c: R = Ph
d: R = 4-$MeOC_6H_4$
e: R = 4-NCC_6H_4
f: R = PhCH=CH

$R^1R^2C(OMe)_2$

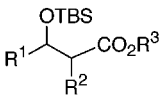
4

4a: R^1 = Ph; R^2 = H
b: $R^1 = n$-C_7H_{15}; R^2 = H
c: $R^1 = n$-C_6H_{13}; R^2 = Me
d: R^1 = R^2 = Me



5

5aa: R^1 = Ph; R^2 = Me; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
ab: R^1 = 4-$MeOC_6H_4$; R^2 = Me; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
ac: R^1 = 2,4-$(MeO)_2C_6H_3$; R^2 = Me; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
ad: $R^1 = C_2H_5$; R^2 = Me; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
ae: $R^1 = n$-C_4H_9; R^2 = Me; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
af: R^1, $R^2 = (CH_2)_5$; R^3 = H; R^4 = Et; Sil = $^tBuMe_2Si$
ag: R^1 = 4-$NO_2C_6H_4$; R^2 = Me; R^4 = Et; Sil = $^tBuMe_2Si$
ba: R^1 = Ph; $R^2 = R^3 = R^4$ = Me; Sil = $^tBuMe_2Si$
ca: R^1 = Ph; $R^2 = R^3$ = Me; R^4 = Et; Sil = Et_3Si



6

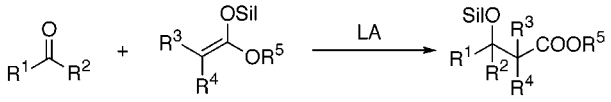
6aa: $R^1 = n$-C_5H_{11}; R^2 = H; R^3 = Et
ab: $R^1 = n$-C_7H_{15} R^2 = H; R^3 = Et
ac: R^1 = Ph; R^2 = H; R^3 = Et
ad: R^1 = 4-$MeOC_6H_4$; R^2 = H; R^3 = Et
ae: R^1 = 4-NCC_6H_4; R^2 = H; R^3 = Et
af: $R^1 = C_6H_5CH$=CH; R^2 = H; R^3 = Et
bb: $R^1 = n$-C_7H_{15}; $R^2 = R^3$ = Me

min, indicative of extremely rapid reaction. Other Lewis acids such as TMSOTf, $Sc(OTf)_3$, Bu_3SnClO_4, $TrClO_4$, and BF_3OEt_2 afforded good to excellent yields (entries 3−7), whereas stronger Lewis acids such as tin and titanium tetrahalides failed to give satisfactory yields (entries 8−10). Other ketones also reacted smoothly (entries 11−15) except an aromatic ketone bearing an electron-withdrawing *para*-substituent (entry 16). Monomethyl-substituted ketene silyl acetals **1b** and **1c** reacted as well (entries 17 and 18), but no reaction occurred with dimethyl compound **1d** (entry 19).

The high reactivity of ketene silyl acetal toward ketone mentioned above stands in sharp contrast to the sluggish reaction of **1a** with octanal catalyzed by $(C_6F_5)_2SnBr_2$,[14]

(14) Chen, J.; Sakamoto, K.; Orita, A.; Otera, J. *Synlett* **1996**, 877.

Table 1. Reaction of Ketene Silyl Acetal with Ketone[a]



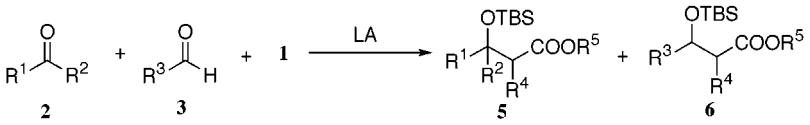
2 + **1** → **5** (LA)

entry	1	2	LA	reacn time/h	yield[b]/%	
1	**1a**	**2a**	$(C_6F_5)_2SnBr_2$	1	**5aa**	92
2			$(C_6F_5)_2SnCl_2$	1	**5aa**	93[c]
3			TMSOTf	3	**5aa**	86
4			$Sc(OTf)_3$	3	**5aa**	88
5			Bu_3SnClO_4	4	**5aa**	88[c]
6			$TrClO_4$	4	**5aa**	93
7			BF_3OEt_2[d]	4	**5aa**	76[f]
8			$SnCl_4$	4	**5aa**	53[c]
9			$SnBr_4$	4	**5aa**	43[c]
10			$TiCl_4$[d]	4	**5aa**	48[c,e]
11		**2b**	$(C_6F_5)_2SnBr_2$	1	**5ab**	89
12		**2c**	$(C_6F_5)_2SnBr_2$	1	**5ac**	92
13		**2d**	$(C_6F_5)_2SnBr_2$	1	**5ad**	87
14		**2e**	$(C_6F_5)_2SnBr_2$	1	**5ae**	87
15		**2f**	$(C_6F_5)_2SnBr_2$	1	**5af**	93
16		**2g**	$(C_6F_5)_2SnBr_2$	8	**5ag**	63
17	**1d**	**2a**	$(C_6F_5)_2SnBr_2$	3.5	**5ba**	86
18	**1c**	**2a**	$(C_6F_5)_2SnBr_2$	4	**5ca**	87
19	**1d**	**2a**	$(C_6F_5)_2SnBr_2$	3.5	−	−

[a] Reaction conditions: **1**:**2**:LA = 1.3:1.0:0.1; CH_2Cl_2; −78 °C. [b] Isolated yield. [c] GLC yield. [d] A 1 equiv amount of LA was used. [e] A hydroxy ester, not a silyl ether, was obtained. [f] A mixture of hydroxy ester (66%) and silyl ether (10%).

and thus we expected the preference for ketone in competition with aldehyde. This is indeed the case as shown in Table 2. An equimolar mixture of acetophenone (**2a**) and hexanal (**3a**) was exposed to ketene silyl acetal **1a** in the presence of $(C_6F_5)_2SnBr_2$ (10 mol %) in dichloromethane at −78 °C. Aldolates **5aa** and **6aa** formed in 91:9 ratio (entry 1). Other Lewis acids gave rise to the similar tendency (entries 3−7), although the selectivity varied to a considerable extent. Apparently, $(C_6F_5)_2SnX_2$, TMSOTf, and $Sc(OTf)_3$ gave satisfactory results with respect to both yield and the selectivity. Electron-donating substituents on the phenyl ring increased the reactivity of aromatic ketones (compare entries 9 and 10 with entry 8). Even an aliphatic ketone and cyclohexanone experienced the strong bias in favor of the ketones (entries 11 and 12). Notably, GLC analysis of the reaction mixture exhibited no peaks other than those attributable to the carbonyl substrates and aldol products. The amount of the starting materials remaining after the reaction are also given in the last columns in the table. The clean reaction unambiguously indicates that the high selectivity was not the consequence of the consumption of an aldehyde component by undesired side reactions but resulted from the differentiated recognition between the ketone and aldehyde carbonyl functions. It should be noted, however, that the TMSOTf-catalyzed reaction is somewhat different. Under the standard conditions in this study, Lewis acids were charged in the reaction flask first (see footnote *a* in Table 2). However, the standard method in the reaction between **2a** and **3a** with TMSOTf afforded an 84% yield of the trioxane derived from **3a** together with the ketone aldolate. Accordingly, this catalyst was added last (see footnote *c*), yet a 52% yield of the trioxane emerged on the basis of ^1H NMR analysis. Thus, it is not certain in this case whether the bias in favor of the ketone was induced by the parallel recognition only or by concomitant contribution of the aldehyde

Table 2. Competition Reaciton between Ketone and Aldehyde[a]



2 3 5 6

					yield[b]/%					recovery[b]/%	
					5		6				
entry	1	2	3	LA					5:6	2	3
1	**1a**	**2a**	**3a**	$(C_6F_5)_2SnBr_2$	**5aa**	75	**6aa**	7	91:9		
2				$(C_6F_5)_2SnCl_2$	**5aa**	70	**6aa**	11	86:14		
3				TMSOTf[c]	**5aa**	90	**6aa**	12	88:12		
4				$Sc(OTf)_3$[c]	**5aa**	72	**6aa**	6	92:8		
5				Bu_3SnClO_4	**5aa**	41	**6aa**	17	70:30		
6				$SnCl_4$	**5aa**	26	**6aa**	6	81:19		
7				$TrClO_4$	**5aa**	55	**6aa**	27	67:33		
8		**2a**	**3b**	$(C_6F_5)_2SnBr_2$	**5aa**	72	**6ab**	8	90:10	16	88
9		**2b**	**3b**	$(C_6F_5)_2SnBr_2$	**5ab**	85[d]	**6ab**	5[d]	94:6	0	84
10		**2c**	**3b**	$(C_6F_5)_2SnBr_2$	**5ac**	86[d]	**6ab**	4[d]	94:6	0	93
11		**2e**	**3b**	$(C_6F_5)_2SnBr_2$	**5ae**	68[d]	**6ab**	9[d]	88:12	21	76
12		**2f**	**3b**	$(C_6F_5)_2SnBr_2$	**5af**	72	**6ab**	3	96:4	16	88
13		**2a**	**3c**	$(C_6F_5)_2SnBr_2$	**5aa**	27[d]	**6ac**	62[d]	30:70		
14		**2a**	**3c**	TMSOTf[c]	**5aa**	30[d]	**6ac**	64[d]	22:68		
15		**2a**	**3c**	$Sc(OTf)_3$[c]	**5aa**	43[d]	**6ac**	51[d]	46:54		
16		**2e**	**3c**	$(C_6F_5)_2SnBr_2$	**5ae**	19[d]	**6ac**	75[d]	20:80		
17		**2f**	**3c**	$(C_6F_5)_2SnBr_2$	**5af**	29	**6ac**	55	35:65		
18		**2cd**	**3e**	$(C_6F_5)_2SnBr_2$	**5ac**	57	**6ae**	28	67:33		
19	**1b**	**2a**	**3b**	$(C_6F_5)_2SnBr_2$	**5ba**	46	**6bb**	10	82:18	32	43

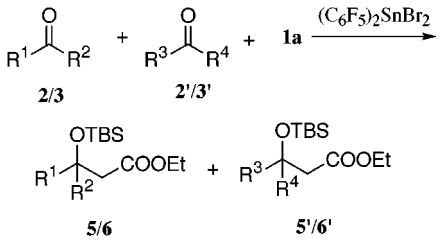
[a] Reaction conditions **1**:**2**:**3**:LA = 1.3:1.0:1.0:0.1; CH_2Cl_2; 3 h; order of addition: LA **2**, **3**, and **1**. [b] Determined by GLC (*n*-$C_{15}H_{32}$ as an internal standard). [c] Order of addition: **2**, **3**, **1**, and LA. [d] *n*-$C_{16}H_{34}$ as an internal standard.

consumption. An exception to the preference for ketone arose with benzaldehyde (**3c**) that reacted more preferentially than ketones (entries 13−17) although the strong electron-withdrawing *para*-cyano group reduced the reactivity (entry 18). Employment of methyl-substituted ketene silyl acetal **1b** induced the preferential uptake of ketone as well but to a slightly lower degree (entry 19).

The above results lead to the following order for the reactivity of the carbonyls: aromatic aldehyde > aromatic ketone > aliphatic ketone > aliphatic aldehyde. Moreover, the electron-donating substituents increase the reactivity while the electron-withdrawing groups exert the opposite influence. Accordingly, the differentiation can be expected between ketones or aldehydes, respectively. The results obtained with $(C_6F_5)_2SnBr_2$ are accommodated in Table 3. The low selectivities emerged between 2-hexanone (**2e**) and acetophenone (**2a**) or cyclohexanone (**2f**) (entries 1 and 2), but a complete bias was exercised between electron-rich (**2b**) and -deficient (**2g**) aromatic ketones (entry 3). By contrast, the differentiation between aldehydes was brought under perfect or nearly perfect control (entries 4−8).

The competition between ketone and acetal gave rise to the intensified distinction (Table 4). In addition to the Lewis acids that were effective for the ketone−aldehyde discrimination (entries 1−3), even Bu_3SnClO_4 and $TrClO_4$ that had given the poor ketone/aldehyde selectivity led to the perfect outcomes (entries 4 and 5). Notably, the acetal remained unchanged completely (see footnote *c* in Table 4), indicative of the clean recognition. BF_3OEt_2 also induced an excellent selectivity (entry 6). However, $SnCl_4$ furnished virtually no products (entry 7), and $TiCl_4$ resulted in the reversed selectivity (entry 8). The generality of the ketone preference was exemplified by using a variety of substrate arrays (entries 9−15). As in the ketone vs aldehyde competition, benzaldehyde (**3c**) was most reactive and thus predominated over its dimethyl

Table 3. Competition Reaction between Ketones or Aldehydes[a]



2/3 2′/3′ 5/6 5′/6′

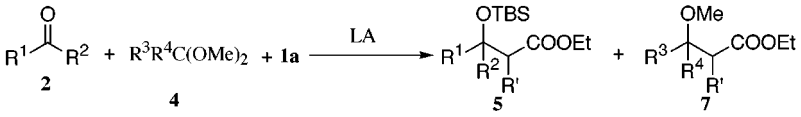
			yield[b]/%				
			5/6		5′/6		
entry	2/3	2/3					5:5′ or 6:6′
1	**2a**	**2e**	**5aa**	40	**5ae**	23	63:37
2	**2f**	**2e**	**5af**	54	**5ae**	24	69:31
3	**2b**	**2g**	**5ab**	87	**5ag**	0	100:0
4	**3c**	**3b**	**6ac**	88	**6ab**	3	97:3
5	**3d**	**3b**	**6ad**	96	**6ab**	3	97:3
6	**3f**	**3b**	**6af**	76	**6ab**	2	97:3
7	**3c**	**3e**	**6ac**	81	**6ae**	0	100:0
8	**3d**	**3e**	**6ad**	99	**6ae**	0	100:0

[a] Reaction conditions: **1a**:**2**(**3**):**2′**(**3′**):$(C_6F_5)_2SnBr_2$ = 1.3:1.0:1.0:0.1; CH_2Cl_2; −78 °C; 3 h. [b] Determined by GLC.

acetal counterpart **4a** (entries 16 and 17). Particularly noteworthy is the aldehyde preference obtained with TMSOTf. The totally opposite selectivity was reported for the competition between aldehyde and acetal in the TMSOTf-catalyzed aldol reaction of 1-(trimethylsiloxy-)cyclohexene.[7] Moreover, the ketone substrate did not react with enol silyl ethers derived from ketones with this catalyst. Apparently, the unusual reactivity for ketone along with the inertness toward acetal in our reaction is unique to the ketene silyl acetals.

The reversal of reactivity was highlighted by intramolecular versions (Scheme 1). The reaction of keto aldehydes **8**−**11** with **1a** (1.3 or 1.5 equiv) catalyzed by

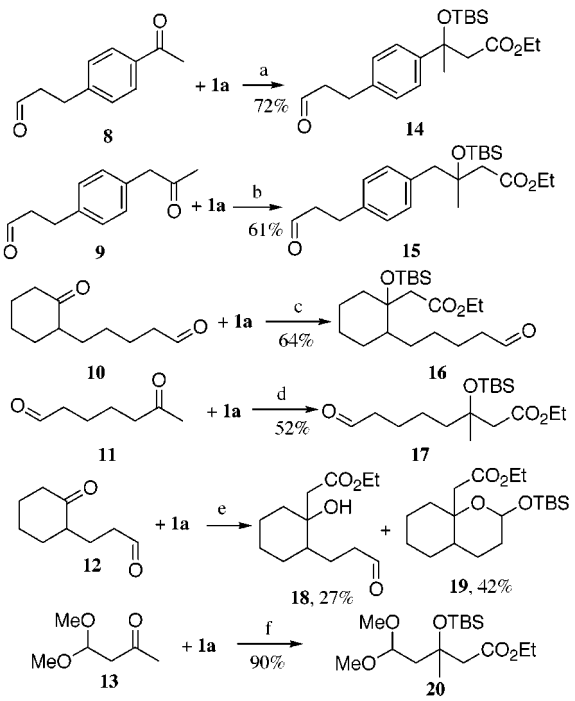
Table 4. Competition Reaction between Ketone and Acetal[a]



				yield[b]/%			
				5		7	
entry	2	4					5:7
1	**2a**	**4a**	$(C_6F_5)_2SnBr_2$	**5aa**	91	0[c]	100:0
2	**2a**	**4a**	TMSOTf[d]	**5aa**	91	0	100:0
3	**2a**	**4a**	$Sc(OTf)_3$[d]	**5aa**	91	0	100:0
4	**2a**	**4a**	Bu_3SnClO_4	**5aa**	81	0	100:0
5	**2a**	**4a**	$TrClO_4$	**5aa**	67	0	100:0
6	**2a**	**4a**	BF_3OEt_2[d,e]	**5aa**[f]	95	3	97:3
7	**2a**	**4a**	$SnCl_4$[d,e]	**5aa**[g]	1	3	–
8	**2a**	**4a**	$TiCl_4$[d,e]	**5aa**[h]	19	52	27:73
9	**2a**	**4b**	$(C_6F_5)_2SnBr_2$	**5aa**	96	0	100:0
10	**2a**	**4c**	$(C_6F_5)_2SnBr_2$	**5aa**	93	0	100:0
11	**2a**	**4d**	$(C_6F_5)_2SnBr_2$	**5aa**	95	0	100:0
12	**2d**	**4a**	$(C_6F_5)_2SnBr_2$	**5ad**	81	0	100:0
13	**2d**	**4d**	$(C_6F_5)_2SnBr_2$	**5ad**	88	0	100:0
14	**2f**	**4a**	$(C_6F_5)_2SnBr_2$	**5aa**	87	0	100:0
15	**2f**	**4c**	$(C_6F_5)_2SnBr_2$	**5af**	79	0	100:0
16	**3c**	**4a**	$(C_6F_5)_2SnBr_2$	**6ac**	92	0	100:0
17	**3c**	**4a**	TMSOTf[d]	**6ac**	70	9	89:11

[a] Reaction conditions: **1a**:**2**:**4**:LA = 1.3:1.0:1.0:0.05; CH_2Cl_2; −78 °C, 3 h; order of addition, LA **2**, **4**, and **1**. [b] Determined by GLC. [c] ^1H NMR showed that **4a** (97%) remained unchanged. [d] Order of addition: **2**, **4**, **1**, and LA (0.1 equiv). [e] A 1 equiv amount of LA was used. [f] A mixture of hydroxy ester (81%) and silyl ether (14%). [g] A hydroxy ester. [h] A mixture of hydroxy ester (16%) and silyl ether (3%).

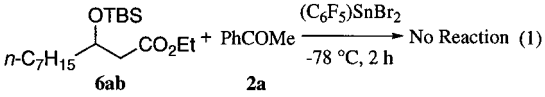
Scheme 1



[a] Reaction conditions: (a) **8**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.3:0.1; CH_2Cl_2, -78 °C; 4 h. (b) **10**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.4:0.3; CH_2Cl_2, -78 °C; 4 h. (c) **12**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.5:0.1; CH_2Cl_2, -78 °C; 6 h. (d) **14**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.5:0.1; CH_2Cl_2, -78 °C; 3.5 h. (e) **16**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.4:0.1; CH_2Cl_2, -78 °C; 1.5 h. (f) **19**:**1a**:$(C_6F_5)_2SnBr_2$ = 1.0:1.3:0.1; CH_2Cl_2, -78 °C; 3 h.

$(C_6F_5)_2SnBr_2$ (0.1 equiv), after isolation by column chromatography, furnished single products **14**−**17** that were derived from exclusive reaction of the ketonic function. However, **12** afforded **18** and **19**, the latter being derived from intramolecular cyclization of the silyl ether of initially formed **18**. The exclusive attack on the ketone moiety was also exemplified with keto acetal **13**.

Previously, the neighboring group participation was invoked for the preferential capture of a ketonic function of keto aldehyde substrates by enol silyl ethers in TMSOTf-catalyzed reaction. Namely, TMSOTf initially coordinates with aldehyde, and the ketonic oxygen attacks intramolecularly this activated aldehyde carbonyl so that the ketonic function is turned to be activated.[4] With a view to check if this sort of mechanism operates or not in our reaction, the aldolate **6ab** derived from octanal was exposed to acetophenone (**2a**) in the presence of a catalytic amount of $(C_6F_5)_2SnBr_2$ (eq 1). No reaction

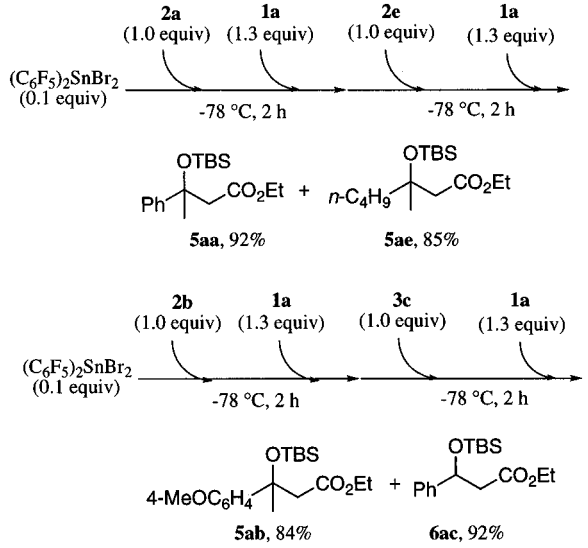


occurred under the standard conditions. Apparently, the ketone aldolate was not produced by the exchange reaction with the aldehyde aldolate. Moreover, the reaction of **12** in Scheme 1 unambiguously reflects the initial attack on the ketonic function that was followed by the intramolecular addition of the resulting silyl ether to the remaining aldehyde carbonyl. The failure of the intramolecular cyclization with substrates **8** and **9** also rules out the possibility for the Molander-type neighboring group participation on account of intervention of the planar phenyl ring that prevents the two carbonyls from interacting with each other.

It is of great significance to know if $(C_6F_5)_2SnBr_2$ works as a real active catalyst or not, because ketene silyl acetals often react with Lewis acids rather easily.[15] Furthermore, transmetalation between the siloxy aldolate and Lewis acid may possibly generate the silyl Lewis acid that could function as a catalyst if the aldol

(15) For example: Inaba, S.-I.; Ojima, I. *Tetrahedron Lett.* **1977**, 2009. Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 785. Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3347. Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 2951.

Scheme 2



reaction is slower.[16] However, the latter case is not true in our reaction because of the following reasons. The products were always the silyl ethers, and no β-hydroxy esters were detected, indicative of no possibility of the transmetalation. In addition, (TBS)Br ((TBS)Br = *tert*-butyldimethylsilyl bromide) that would be supposed to result from the transmetalation, if occurred, proved not to catalyze the Mukaiyama−aldol reaction at all.

On the other hand, $(C_6F_5)_2SnBr_2$ was found to react at room temperature with ketene silyl acetal to some extent to give α-stannyl ester and (TBS)Br. However, the effectiveness of $(C_6F_5)_2SnBr_2$ in our aldol reaction is apparent from the observations that follow. Namely, initial mixing of $(C_6F_5)_2SnBr_2$ (0.1 equiv) with **1a** (1.3 equiv) at room temperature for 5 h followed by addition of **2a** (1.0 equiv) at −78 °C led to a sharp decrease of the yield of **5aa** (10%), suggesting decomposition of the catalyst. The rate of the decomposition, however, was much slower at −78 °C: treatment of $(C_6F_5)_2SnBr_2$ with **1a** at −78 °C for 5 h followed by addition of **2a** furnished **5aa** in 64% yield. Under the standard conditions where $(C_6F_5)_2SnBr_2$, **2a**, and **1a** were mixed in this order at one time at −78 °C, no virtual decomposition of the catalyst occurred to give a 92% yield of **5aa**. These results imply that $(C_6F_5)_2SnBr_2$ works as its form and the aldol reaction proceeds much faster at −78 °C than the decomposition reaction.

The reactions shown in Scheme 2 lend further support. A dichloromethane solution of $(C_6F_5)_2SnBr_2$ (0.1 equiv), **2a** (1.0 equiv), and **1a** (1.3 equiv) was stirred at −78 °C for 2 h, and then 2-hexanone (**3c**) (1.0 equiv) and **1a** (1.3 equiv) were added to this reaction mixture. After 2 h at −78 °C, both desired aldolates **5aa** and **5ae** were obtained in 92 and 85% yields, respectively. Addition of benzaldehyde (**3c**) in place of 2-hexanone in the second reaction furnished the analogous outcome (84 and 92% yields). The catalyst no doubt survived the first reaction.

To get further mechanistic insight into the unusual ketone preference, the coordination of carbonyls with $(C_6F_5)_2SnBr_2$ was studied by ^{13}C NMR according to Nakai's method (Table 5).[5b] The low-field shift of $\delta_{C=O}$ ($\Delta\delta_i$) induced by mixing of acetophenone or propanal with the tin catalyst in 5:1 ratio was measured. Then, an equimolar amount of each solution was mixed, and the low-field shifts for the carbonyl signals relative to the free carbonyls ($\Delta\delta_m$) were recorded.[17] The relative coordinating ability was assessed according to eq 2. Apparently, the ketone coordination prevails, a reasonable outcome in terms of the higher basicity of ketone carbonyl oxygen than the aldehyde counterpart. This is also consistent with the precedent notion that revealed the parallelism between the coordinating ability of carbonyl and its reactivity in Lewis acid-promoted reactions.[5b,6,18,19] However, we point out that this is not enough to account for the present unusual ketone preference. An enol silyl ether derived from acetophenone reacted with hexanal smoothly but not with ketones at all,[14] and, hence, the ketone preference is unique to ketene silyl acetals. Notably, Yamamoto et al. disclosed that ketene silyl acetal reacted with aldehyde more smoothly than with ketone in the absence of Lewis acid under high pressure.[20] It follows therefore that the Lewis acids play a crucial role for the ketone preference. They should be acidic enough to trigger the reaction but moderate to detect the subtle difference between carbonyls. Obviously, the unique selectivity can be attained only when ketone, ketene silyl acetal, and Lewis acid are orchestrated, yet all attempted NMR studies to elucidate the emsenble of this ternary system have failed so far.

Table 5. ^{13}C NMR of Carbonyl−$(C_6F_5)_2SnBr_2$ System in CH_2Cl_2

	$\delta_{C=O}$/ppm	
	free	in the presence of $(C_6F_5)_2SnBr_2$
PhCOMe	197.6	198.4 ($\Delta\delta_i = 0.8$)[a]
C_2H_5CHO	202.7	204.6 ($\Delta\delta_i = 2.0$)[a]
PhCOMeC_2H_5CHO		198.9 ($\Delta\delta_m = 1.3$)[b] complexation 81%
		204.0 ($\Delta\delta_m = 1.3$)[b] complexation 33%

[a] Carbonyl:$(C_6F_5)_2SnBr_2$ = 5:1. [b] PhCOMe:C_2H_5CHO:$(C_6F_5)_2SnBr_2$ = 5:5:2.

$$\%\text{Complexation} = [\Delta\delta_m/2\Delta\delta_i] \times 100 \qquad (2)$$

In summary, ketene silyl acetals undergo facile reaction with ketones in the presence of an appropriate Lewis acid. This unique reactivity enables otherwise difficult-to-achieve discriminations of ketones from aldehydes or acetals in the naked forms in the aldol-type reactions. The simplicity and versatility of the present method will broaden the scope of synthetic utilities of the carbonyl addition protocol.

(16) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327.

(17) NMR spectra were measured in dry CH_2Cl_2 solution with an external $CDCl_3$ lock. Employment of $CDCl_3$ is not suitable due to contamination of H_2O. The catalyst concentration much higher than those employed in the standard reactions (1×10^{-2} mol/L) was inevitable in the NMR study (7×10^{-1} mol/L) because the acceptor property of the tin catalyst is so weak that, otherwise, no appreciable shifts of the signals could be detected. The measurements were carried out at 20 °C due to the high viscosity or freezing of the solution at lower temperatures. It is noted, however, that the ketone preference virtually holds even at room temperature despite a slightly lower selectivity (for example, 78:22 in the competition between **2a** and **3b**).

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(20) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Tetrahedron Lett.* **1984**, *25*, 1075.

Experimental Section

Ketene silyl acetals were prepared according to the literature method.[21] Preparation of $(C_6F_5)_2SnBr_2$,[14] $(C_6F_5)_2SnCl_2$,[22] and Bu_3SnClO_4[11] was described in the literature. Other Lewis acids and keto acetal **13** were commercially available. The preparation of keto aldehydes **8**−**12** is described in Supporting Information.

Reaction of Ketene Silyl Acetal with Ketone (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (61 mg, 0.1 mmol) were added a CH_2Cl_2 solution (1 mL) of **2a** (120 mg, 1 mmol) followed by ketene silyl **1a** (263 mg, 1.3 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The reaction was monitored by TLC. The solution was stirred at the same temperature for 1 h, and water (2 mL) was added. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried over Na_2SO_4. After the solvent was evaporated, the crude product was chromatographed on silica gel (EtOAc/hexane: 1/20) to give **5aa** (292 mg, 92%): ^{1}H NMR ($CDCl_3$) δ −0.11 (s, 3H), 0.08 (s, 3H), 0.93 (s, 9H), 1.09 (t, 3H, J = 7.1 Hz), 1.83 (s, 3H), 2.69, 2.82 (AB, 2H, J_{AB} = 13.4 Hz), 3.95 (q, 2H, J = 7.1 Hz), 7.23−7.34 (m, 3H), 7.44−7.49 (m, 2H). This compound was confirmed by desilylation to give the known alcohol.[23] The other reactions were carried out analogously.

Compound 5ab. ^{1}H NMR ($CDCl_3$) δ −0.14 (s, 3H), 0.05 (s, 3H), 0.91 (s, 9H), 1.11 (t, 3H, J = 7.1 Hz), 1.81 (s, 3H), 2.66, 2.79 (AB, 2H, J_{AB} = 13.5 Hz), 3.80 (s, 3H), 3.98 (q, 2H, J = 7.1 Hz), 6.83 (d, 2H, J = 9.0 Hz), 7.37 (d, 2H, J = 9.0 Hz). This compound was confirmed by desilylation to give the known alcohol.[24]

Compound 5ac. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.19 (s, 3H), 0.96 (s, 9H), 1.04 (t, 3H, J = 7.1 Hz), 1.74 (s, 3H), 2.83, 3.20 (AB, 2H, J_{AB} = 13.7 Hz), 3.79 (s, 6H), 3.92 (q, 2H, J = 7.1 Hz), 6.43−6.49 (m, 2H), 7.52 (d, 1H, J = 8.2 Hz). This compound was confirmed by desilylation to give the alcohol: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.1 Hz), 1.60 (s, 3H), 2.82, 3.23 (AB, 2H, J_{AB} = 15.0 Hz), 3.79 (s, 3H), 3.83 (s, 3H), 3.99 (q, 2H, J = 7.1 Hz), 4.51 (s, 1H), 6.47 (m, 2H), 7.47 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.96, 27.63, 45.16, 55.21, 60.21, 72.29, 99.12, 103.76, 126.41, 127.32, 156.79, 159.93, 172.78. HRMS. Calcd for $C_{14}H_{21}O_5$ (M^+ + H): 269.1389. Found: 269.1348. Anal. Calcd for $C_{14}H_{21}O_5$: C, 62.67; H, 7.51. Found: C, 62.80; H, 7.38.

Compound 5ad. ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.85 (s, 9H), 0.90 (t, 3H, J = 7.5 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.34 (s, 3H), 1.55−1.65 (m, 2H), 2.45 (s, 2H), 4.09 (q, 2H, J = 7.1 Hz). This compound was confirmed by desilylation to give the known alcohol.[25]

Compound 5ae. ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.84 (s, 9H), 0.90 (t, 3H, J = 7.5 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.22−1.36 (m, 4H), 1.34 (s, 3H), 1.53−1.62 (m, 2H), 2.45 (s, 2H), 4.10 (q, 2H, J = 7.1 Hz). This compound was confirmed by desilylation to give the known alcohol.[26]

Compound 5af. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.86 (s, 9H), 1.25 (t, 3H, J = 7.1 Hz), 1.32−1.80 (m, 10H), 2.50 (s, 2H), 4.12(q, 2H, J = 7.1 Hz). This compound was confirmed by desilylation to give the known alcohol.[26]

Compound 5ag. ^{1}H NMR ($CDCl_3$) δ −0.03 (s, 3H), 0.16 (s, 3H), 0.94 (s, 9H), 1.08 (t, 3H, J = 7.1 Hz), 1.81 (s, 3H), 2.76, 2.85 (AB, 2H, J_{AB} = 14.2 Hz), 3.95 (q, 2H, J = 7.1 Hz), 7.60−7.66 (m, 2H), 8.16−8.21 (m, 2H). This compound was confirmed by desilylation to give the known alcohol.[27]

Compound 5ba (9:1 Diastereomer). ^{1}H NMR ($CDCl_3$) δ −0.34 (−0.20) (s, 3H), −0.05 (0.04) (s, 3H), 0.85 (1.09) (d, 3H, J = 7.1 Hz), 0.88 (0.95) (s, 9H), 1.74 (1.60) (s, 3H), 2.91 (2.79) (q, 2H, J = 7.1 Hz), 3.63 (3.43) (s, 3H), 7.20−7.48 (m, 5H). These compounds were confirmed by desilylation to give the known alcohols.[28]

Compound 5ca (4:1 Diastereomer). ^{1}H NMR ($CDCl_3$) δ 0.38−0.55 (m, 6H), 0.80−0.99 (m, 12H), 1.26 (t, 3H, J = 7.1 Hz), 1.75 (1.74) (s, 3H), 2.85 (2.78) (q, 2H, J = 7.1 Hz), 4.09 (3.82) (q, 2H, J = 7.1 Hz), 7.20−7.48 (m, 5H). These compounds were confirmed by desilylation to give the known alcohols.[28]

Competition Reaction between Ketone and Aldehyde with Ketene Silyl Acetal (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (31 mg, 0.05 mmol) was added a CH_2Cl_2 solution (2 mL) of **2a** (60 mg, 0.5 mmol) and **3a** (50 mg, 0.5 mmol) at −78 °C followed by **1a** (131 mg, 0.65 mmol) in CH_2Cl_2 (2 mL). After 3 h, aqueous workup followed by evaporation afforded a crude product. *n*-$C_{15}H_{32}$ or *n*-$C_{16}H_{34}$ (0.25 mmol) as an internal standard was added to this product that was then analyzed by GLC. The authentic samples of **6** were prepared according to the previously reported method.[11] The other reactions were carried out analogously.

Competition Reaction between Ketones or Aldehydes with Ketene Silyl Acetal (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (31 mg, 0.05 mmol) was added a CH_2Cl_2 solution (2 mL) of **2a** (60 mg, 0.5 mmol) and **2e** (50 mg, 0.5 mmol) at −78 °C followed by **1a** (131 mg, 0.65 mmol) in CH_2Cl_2 (2 mL). After 3 h, aqueous workup followed by evaporation afforded a crude product. *n*-$C_{16}H_{34}$ (0.25 mmol) was added to this product that was then analyzed by GLC. The other reactions were carried out analogously.

Competition Reaction between Ketone and Acetal with Ketene Silyl Acetal (Typical Procedure). To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (31 mg, 0.05 mmol) was added a CH_2Cl_2 solution (2 mL) of **2a** (120 mg, 1.0 mmol) and **4a** (152 mg, 1.0 mmol) at −78 °C followed by **1a** (263 mg, 1.3 mmol) in CH_2Cl_2 (2 mL). After 3 h, aqueous workup followed by evaporation afforded a crude product. *n*-$C_{16}H_{34}$ (0.25 mmol) was added to this product that was then analyzed by GLC. The other reactions were carried out analogously.

Reaction of Keto Aldehyde with Ketene Silyl Acetal. To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (61 mg, 0.1 mmol) was added a CH_2Cl_2 solution (2 mL) of **8** (176 mg, 1.0 mmol) at −78 °C followed by ketene silyl acetal **1a** (263 mg, 1.3 mmol) in CH_2Cl_2 (2 mL). After 4 h, aqueous workup followed by column chromatography on silica gel (EtOAc/hexane: 1/10) to give **14** (272 mg, 72%): ^{1}H NMR ($CDCl_3$) δ −0.11 (s, 3H), 0.07 (s, 3H), 0.92 (s, 9H), 1.09 (t, 3H, J = 7.1 Hz), 1.79 (s, 3H), 2.66, 2.77 (AB, 2H, J_{AB} = 13.6 Hz), 2.76 (t, 2H, J = 7.4 Hz), 2.94 (t, 2H, J = 7.4 Hz), 3.96 (q, 2H, J = 7.1 Hz), 7.13 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 8.2 Hz), 9.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −2.54, −2.06, 13.98, 18.32, 25.92, 27.63, 28.42, 45.16, 51.01, 60.02, 75.48, 125.58, 127.64, 138.68, 145.53, 170.24, 201.61; HRMS. Calcd for $C_{20}H_{31}O_4Si$ ($M^+ - CH_3$): 363.1992. Found: 363.2003. Anal. Calcd for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05. Found: C, 66.70; H, 9.21.

Compound 15. ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz), 1.33 (s, 3H), 2.37, 2.46 (AB, 2H, J_{AB} = 13.8 Hz), 2.76 (t, 2H, J = 7.5 Hz), 2.93 (t, 2H, J = 7.5 Hz), 2.87, 3.01 (AB, 2H, J_{AB} = 13.1 Hz), 4.16 (q, 2H, J = 7.1 Hz), 7.09 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 9.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −2.07, −2.04, 14.16, 18.11, 25.79, 27.72, 45.29, 46.38, 48.08, 60.15, 75.06, 127.66, 131.09, 135.92, 138.16, 171.06, 201.67. HRMS. Calcd for $C_{22}H_{37}O_4Si$ (M^+ + H): 393.2461. Found: 393.2425. Anal. Calcd for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.78; H, 9.41.

Compound 16. ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.24 (t, 3H, J = 7.1 Hz), 1.10−1.75 (m, 15H), 2.35,

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2.84 (AB, 2H, J_{AB} = 13.0 Hz), 2.40 (t, 2H, J = 7.4 Hz), 4.09 (q, 2H, J = 7.1 Hz), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −2.16, −1.76, 14.20, 18.74, 21.70, 22.43, 25.68, 26.02, 26.69, 26.93, 29.21, 38.01, 43.56, 43.92, 46.28, 60.23, 76.63, 170.74, 202.81. HRMS. Calcd for $C_{20}H_{37}O_4Si$ ($M^+ - CH_3$): 369.2461. Found: 369.2450. Anal. Calcd for $C_{21}H_{40}O_4Si$: C, 65.58; H, 10.48. Found: C, 65.88; H, 10.44.

Compound 17. ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.83 (s, 9H), 1.25 (t, 3H, J = 7.1 Hz), 1.33 (s, 3H), 1.32−1.68 (m, 6H), 2.41−2.47 (m, 4H), 4.09 (q, 2H, J = 7.1 Hz), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −2.11, −2.06, 14.18, 18.12, 22.44, 23.69, 25.73, 28.01, 42.35, 43.85, 46.84, 60.15, 74.49, 171.02, 202.64. HRMS. Calcd for $C_{16}H_{31}O_4Si$ ($M^+ - CH_3$): 315.1992. Found: 315.1967.

Compound 18. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.1 Hz), 1.40−2.54 (m, 15H), 4.05 (br, 1H), 4.13−4.19 (m, 2H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.10, 21.87, 25.00, 27.83, 34.22, 38.92, 42.08, 45.11, 49.84, 60.44, 92.16, 170.84, 202.27. HRMS. Calcd for $C_{13}H_{21}O_3$ ($M^+ - OH$): 225.1491. Found: 225.1523.

Compound 19. ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 1.23 (t, 3H, J = 7.1 Hz), 1.20−1.83 (m, 13H), 2.51, 2.90 (AB, 2H, J_{AB} = 13.4 Hz), 4.09 (q, 2H, J = 7.1 Hz), 5.03 (dd, 1H, J = 2.6, 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ −5.34, −4.08, 14.18, 17.98, 21.10, 23.31, 23.44, 25.76, 28.24, 32.82, 37.45, 43.94, 59.99, 77.11, 91.53, 171.20. HRMS. Calcd: for $C_{19}H_{37}O_4Si$ ($M^+ + H$) 357.2461. Found: 357.2455.

Compound 20. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.85 (s, 9H), 1.24 (t, 3H, J = 7.1 Hz), 1.41 (s, 3H), 1.87, 2.03 (ABX, 2H, J_{AB} = 14.2, J_{AX} = 4.3, J_{BX} = 5.7 Hz), 2.49, 2.55 (AB, 2H, J_{AB} = 14.5 Hz), 3.28 (s, 6H), 4.09 (q, 2H, J = 7.1 Hz), 4.60 (dd, 1H, J = 4.3, 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ −2.13, 14.13, 18.04, 25.70, 28.49, 44.51, 46.98, 52.48, 59.96, 73.10, 102.02, 170.80. HRMS. Calcd for $C_{15}H_{31}O_4Si$ ($M^+ - OCH_3$): 303.1992. Found: 303.1953. Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 57.45; H, 10.24. Found: C, 57.02; H, 9.89.

Reaction of 2a with 6ab. To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (61 mg, 0.1 mmol) was added a CH_2Cl_2 solution (1 mL) of **2a** (120 mg, 1 mmol) followed by **6ab** (330 mg, 1.0 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The solution was stirred at the same temperature for 3 h. After aqueous workup followed by evaporation, the residue was analyzed by GLC that showed no reaction occurred.

Reaction of 2a with 1a followed by Reaction of 2e with 1a. To a CH_2Cl_2 solution (1 mL) of $(C_6F_5)_2SnBr_2$ (61 mg, 0.1 mmol) was added a CH_2Cl_2 solution (1 mL) of **2a** (120 mg, 1 mmol) followed by ketene silyl acetal **1a** (263 mg, 1.3 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The solution was stirred at the same temperature for 2 h. Then a CH_2Cl_2 solution of **2e** (72 mg, 1 mmol) and a solution of **1a** (263 mg, 1.3 mmol) were added to the reaction mixture. The reaction mixture was stirred at −78 °C for 2 h. Aqueous workup followed by evaporation afforded a mixture of the crude products. *n*-$C_{16}H_{34}$ (0.5 mmol) was added to this mixture that was then analyzed by GLC.

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Supporting Information Available: Text describing experimental and spectroscopic data for compounds **8**−**12** and figures shown; ^{1}H and ^{13}C NMR spectra of compounds **5aa**−**ca**, **8**, **9**, and **17**−**19** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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