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Reaction of the Acetals with TESOTf−Base Combination; Speculation of the Intermediates and Efficient Mixed Acetal Formation

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Abstract: We report here unexpected highly chemoselective deprotection of the acetals from aldehydes. Treatment of acetal compounds from aldehydes with TESOTf-2,6-lutidine or TESOTf-2,4,6-collidine in CH_2Cl_2 at 0 °C followed by H_2O workup at the same temperature caused the conversion of the acetal functions to aldehyde functions. The reaction had generality and was applied to many acetal compounds. Study using various bases revealed the reaction and reached the best combination of TESOTf−base. It was very mild and highly chemoselective and proceeded under weakly basic conditions. Then, many functional groups such as allyl alcohol, silyl ether, acetate, methyl ether, triphenylmethyl (Tr) ether, 1,3-dithiolane, methyl ester, and *tert*-butyl ester could survive under these conditions. Furthermore, this methodology could selectively deprotect the acetals in the presence of ketals as the most characteristic feature, although this chemoselectivity is difficult to achieve by other previously reported methods. A detailed study of the reaction including MS and NMR studies revealed the reaction mechanism for determining the structures of the intermediates, pyridinium-type salts. These intermediates had a weak electrophilicity and were successfully applied to the efficient formation of the mixed acetals in high yields.

Discovery of new chemical species sometimes opens a new field of chemistry. In this article we report such an example using the new salts obtained from the unprecedented deprotection of acetals.

Acetal functions are recognized as good protecting groups of carbonyl functions and widely used in synthetic organic chemistry. They are tolerant under neutral and basic conditions. The acidic conditions are usually used for their deprotection, and under these conditions, the acetals from ketone functions (ketals in this text) are usually deprotected more easily than the acetals from aldehyde functions (acetals in this text) due to the stability of the cation intermediates.[1] Although new methods, such as the reactions using a catalytic amount of a transition metal or Lewis acid reagents,[2a−c] phosphorus[2d,e] or silicon reagents,[2f,g] or DDQ or CAN reagents,[2h−j] have already been developed, the development of a mild and chemoselective deprotection method is strongly desirable. Recently, we found a novel chemical transformation in which acetals can be chemoselectively deprotected in the presence of ketals.[3] This was an unprecedented result, because ketals are usually deprotected faster than acetals by the reported procedures.[1,2,4] In our reactions, the starting acetals were first changed to very polar intermediates, and then the corresponding aldehydes were produced after treatment with H_2O. After the initial communication, we investigated the structures of the polar intermediates and determined them as pyridinium-type salts. We then used the intermediates for the novel formation of mixed acetals. We now present the full details of these reactions using new chemical species, speculation of their intermediates, and the application for an efficient mixed acetal formation (Scheme 1).

Deprotection of the Acetals by TESOTf−2,6-Lutidine or TESOTf−2,4,6-Collidine

Process of the Discovery: For our synthetic study of scyphostatin,[5] we intended the triethylsilylation of the *tert*-

(1) (a) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 297−329. (b) Hanson, J. R. In *Protecting Groups in Organic Synthesis*; Blackwell Science, Inc: Malden, MA, 1999; pp 37−43. (c) Kocienski, P. J. *Protecting Groups*; George Thieme Verlag: Stuttgart, 1994; pp 156−170.

(2) For selected recent examples on deacetalization, see: (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989−8999. (b) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A.; Sindona, G.; Bartoli, G. *J. Org. Chem.* **2002**, *67*, 9093−9095. (c) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027−1030. (d) Eash, K. J.; Pulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399−8401. (e) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207−3209. (f) Kaur, G.; Trehan, A.; Trehan, S. *J. Org. Chem.* **1998**, *63*, 2365−2366. (g) Marcantoni, E.; Nobili, F. *J. Org. Chem.* **1997**, *62*, 4183−4184. (h) Johnstone, C.; Kerr, W. J.; Scott, J. S. *Chem. Commun.* **1996**, 341−342. (i) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. H. *J. Org. Chem.* **1986**, *51*, 404−407. (j) Balme, G.; Goré, J. *J. Org. Chem.* **1983**, *48*, 3336−3338.

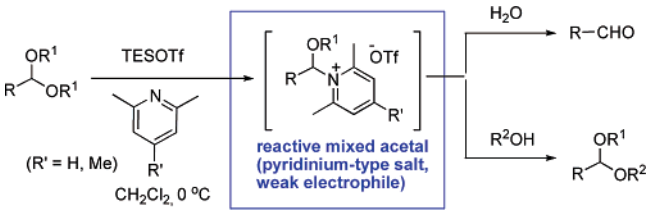
(3) Fujioka, H.; Sawama, Y.; Murata, N.; Okitsu, T.; Kubo, O.; Matsuda, S.; Kita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11800−11801.

(4) (a) Deslongchamps, P.; Dory, Y. L.; Li, S. *Tetrahedron* **2000**, *56*, 3533−3537. (b) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581−603.

(5) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825−4828. The manuscript for asymmetric total synthesis of scyphostatin is in preparation.

10.1021/ja060328d CCC: $33.50

Scheme 1



Scheme 2

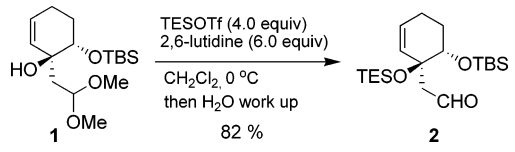
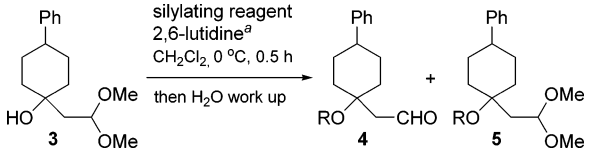


Table 1. Examination of the Reaction of **3** with Various Silylating Reagents



entry	silylating reagent (equiv)	R	yield (%)	4:5	product
1	TESOTf (4.0)	TES	98	100:0	**4a**
2	TMSOTf (2.0)	TMS	100	100:0	**4b**
3	TESCl (4.0)[b]		n.r.		
4	TMSCl (4.0)[b]	TMS	90	0:100	**5b**
5	TBDMSOTf (4.0)	TBDMS	87	0:100	**5c**

[a] Equivalent of 2,6-lutidine is 1.5 times to silylating reagent. [b] Reaction was carried out at room temperature for 24 h.

alcohol of cyclohexene alcohol **1** with an acetal from an aldehyde. When the reaction was carried out using triethylsilyl trifluoromethanesulfonate (TESOTf) (4.0 equiv) and 2,6-lutidine (6.0 equiv), the silylated aldehyde **2** was obtained in good yield under mild conditions (0 °C) (Scheme 2). This was an unexpected result, because the deprotection of acetals from aldehydes usually needs rather drastic acidic conditions. This fact suggested that the reaction proceeds through an unusual process. We then studied the reaction in detail.

Reactions of Various Acetals: Hydroxyl dimethyl acetal **3** was used as the substrate for this detailed study. Table 1 shows the combinations of the various silylating reagents and 2,6-lutidine.[6] The combination of TESOTf and 2,6-lutidine also produced the triethylsilylated aldehyde **4a** (R = TES) at 0 °C for 0.5 h. This fact showed that the reaction condition had the generality for the deprotection of acetals from aldehydes (entry 1). The use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) also caused the hydrolysis of the acetal and produced trimethylsilylated aldehyde **4b** (R = TMS) (entry 2).[7] In this case, 2.0 equiv of TMSOTf and 3.0 equiv of 2,6-lutidine were

(6) For a review of TMSOTf, see: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Göts, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle. T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1−26. For TESOTf, see: (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscger, U. *J. Org. Chem.* **1985**, *50*, 2095−2105. (b) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156−157.

(7) We regret our oversight in not locating and for not citing in our communication the reports that the combination of TMSOTf−2,6-lutidine caused the transformation of an acetal into an aldehyde in a natural product synthesis; Meert, C.; Wang, J.; De Clercq, P. J. *Tetrahedron Lett.* **1997**, *38*, 2179−2182. Wang, J.; De Clercq, P. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1749−1752.

Scheme 3

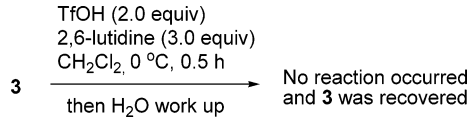
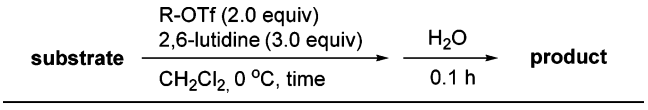
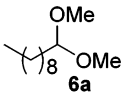
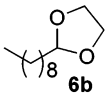
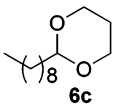
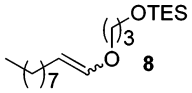


Table 2. Examination Using the Compounds with Only Acetal Functional Group



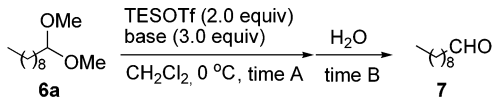
entry	substrate	R	time (h)	product	yield (%)
1	 **6a**	TES	0.5	 **7**	81
2		TMS	0.5		83
3	 **6b**	TES	0.5	**7**	75
4		TMS	0.5	**7**	79
5	 **6c**	TES	6.0	 **8**	86
6		TMS	3.0	**7**	72
7	 **9**	TES	6.0	**10**	trace
8		TMS	1.0	 **10**	79

enough to complete the reaction. It showed that TMSOTf was more reactive than TESOTf. However, no reaction occurred by TESCl, and for the silyl chloride or more bulky *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), only the silylated acetals **5** (R = TMS or TBDMS) were obtained. With these silylating reagents no deprotection of the acetal function afforded **4** (entries 3−5).

The reaction was not promoted by trifluoromethanesulfonic acid (TfOH), though it was formed by the reaction of the hydroxyl group and TESOTf or TMSOTf. This was ascertained by the fact that no reaction occurred by the addition of TfOH in place of TMSOTf (Scheme 3).

Two silylating reagents, TESOTf and TMSOTf, which were effective for the deprotection of the dimethyl acetal from an aldehyde having a hydroxyl group, were next examined using compounds with only the acetal functional group (Table 2). Although two reagents were similarly effective with the dimethyl acetals **6a** and the dioxolane **6b** to give the aldehyde **7** (entries 1−4), a difference was observed in the reactions of the dioxane **6c**. Thus, TMSOTf gave the deprotected aldehyde **7**, though it required a longer reaction time (entry 6), whereas TESOTf gave the enol silyl ether **8** in good yield (entry 5). The remarkable feature and the most interesting difference between the two reagents were exemplified in the reactions of the ketal **9**. Although TMSOTf produced the deprotected ketone **10** in 1 h via enol ether intermediate (TLC) (entry 8), TESOTf did not work well and the formation of only a trace amount of **10** was observed even after 6 h and starting material **9** was recovered (entry 7). These results, especially those of entries 3 and 7, suggested that the combination of TESOTf−2,6-lutidine could realize the unprecedented chemoselective deprotection of acetals in the presence of ketals (vide infra).

Table 3. Study of Various Bases for Deprotection of Acetal **6a**



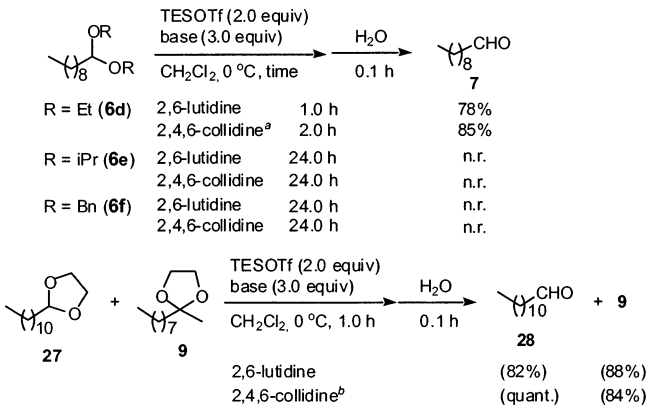
entry	base	time A / B (h)	yield (%)
1	none	-	complex mix.
2	pyridine	0.5 / 24.0	*high polar compound*
3	2-picoline	0.5 / 24.0	*high polar compound*
4	2,6-lutidine	0.5 / 0.1	81
5	2,4-lutidine	0.5 / 24.0	*high polar compound*
6	2,4,6-collidine	0.5 / 0.5	97
7	4-DMAP	24.0 / -	n.r.

To clarify the effect of base, various types of aromatic bases were next examined using the acetal **6a**, which has only the acetal function (Table 3). The reactions were carried out under the combination of TESOTf (2.0 equiv)−base (3.0 equiv). The nonbase condition proved that the base is necessary (entry 1). An interesting tendency was observed that depended on the type of base. Pyridine and 2-picoline formed very stable polar compounds, which were not transformed into **7** even by a long H_2O workup (24 h) (entries 2, 3). On the other hand, 2,6-lutidine, which has one more methyl group at the C6 position of 2-picoline, gave the deprotected aldehyde **7** in good yield for short H_2O treatment (0.1 h) (entry 4). These facts showed that the bulkiness of the base was very important for promoting this transformation. In fact, 2,4-lutidine, which is a regioisomer of 2,6-lutidine, with the bulkiness of its C2- and C6-positions being smaller than that of 2,6-lutidine, afforded a very stable polar compound, which was not transformed into **7** even by a long H_2O workup (24 h) (entry 5). This shows that the success of the reaction needs the appropriate bulkiness of the bases. Two bases were next examined. As expected, 2,4,6-collidine, which has one more C4-methyl group than 2,6-lutidine, afforded the deprotected aldehyde **7** in excellent yield, though the polar compound is more stable than that from 2,6-lutidine and a slightly longer H_2O workup (0.5 h) was necessary (entry 6). On the contrary, 4-(dimethylamino)pyridine (4-DMAP) did not work at all, and no reaction occurred (entry 7). The reason for this result is still unclear.

The reactivity of the combination of TESOTf−2,6-lutidine was next examined in various acetals. Table 4 shows the results of the various acetals. The aromatic acetal **11**, α,*β*-unsaturated acetal **13**, and acetal **15** next to the secondary carbon center also could be deprotected in good yields (entries 1−3). This reaction is very mild, and many functional groups such as acetate **17a**, methyl ether **17b**, triphenylmethyl (Tr) ether **17c**, 1,3-dithiolane **19**, methyl ester **21a**, and *tert*-butyl ester **21b** could survive under these conditions (entries 4−9). The compounds **23** and **25** having a hydroxyl function needed more reagents (entries 10 and 11). Among the acetals in Table 4, the compounds which gave rather low yields of products were treated with TESOTf−2,4,6-collidine, and better yields were obtained (entries 2, 3, 7, 11, and 12).

High Chemoselectivity: The rate-determining step of the transformation of acetals to carbonyl compounds is the cleavage step of the C−O bond of the acetals. The stabilities of the oxonium ions formed by the cleavage of the C−O bond of the acetals would then affect the reaction rate. Namely, acetals

Scheme 4



[a]TESOTf (3.0 equiv) and 2,4,6-collidine (4.0 equiv) were added.
[b]TESOTf (2.5 equiv) and 2,4,6-collidine (3.5 equiv) were added.

producing more stable oxonium ions (ketals) are more easily deprotected than those producing the less stable oxonium ions (acetals).[4] In fact, for example, Kreevoy et al. reported that the relative rate of hydrolysis of the ketal, $(CH_3)_2C(OEt)_2$, is 1.83 $\times 10^7$ times that of the acetal, $CH_2(OEt)_2$.[8] As mentioned above, it is widely recognized that ketals are deprotected much faster than acetals. On the other hand, our method, which deprotects acetals faster than the ketals, was unprecedented. Therefore, the results in Table 2, especially when the acetal in entry 3 is deprotected faster than ketal in entry 7 by TESOTf−2,6-lutidine, were in contrast to those found by the reported methods.

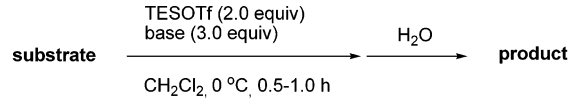
The high chemoselectivity of the TESOTf−2,6-lutidine combination was apparent from the following experiments. Among the three acyclic acetals **6d**−**f** examined, only the diethyl acetal **6d** was deprotected to give the aldehyde **7**, whereas other acetals, i.e., diisopropyl acetal **6e** and dibenzyl acetal **6f**, were not affected at all under the stated condition (Scheme 4). The same tendency was observed using 2,4,6-collidine. This fact and the results in Table 2 (entries 3 and 7) showed that a steric factor was very important in these reactions. This was also featured by the treatment of a 1:1 mixture of the acetal **27** and ketal **9**. Thus, the mixture afforded 82% of the aldehyde **28** from the acetal **27** with the recovered ketal **9** using 2,6-ludidine. The use of 2,4,6-collidine also afforded the quantitative yield of **28** and recovered **9**.

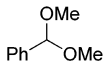
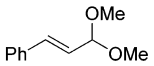
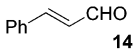
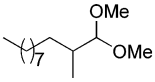
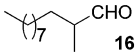
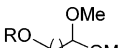
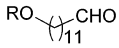
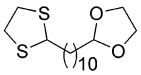
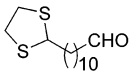
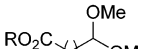
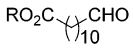
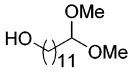
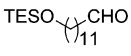
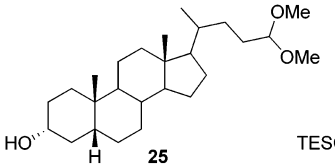
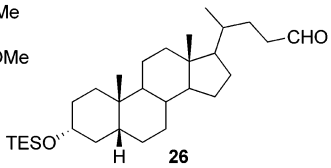
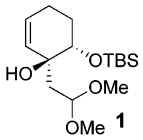
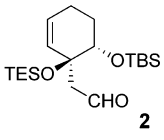
Furthermore, compound **29** having acetal and ketal units in the molecule was examined (Table 5). Our method selectively gave the ketal aldehyde **30** in good yield (entries 1, 2), whereas other representative methods such as the aq. *p*-TsOH or TMSI treatment did not produce any deacetalized product **30** (entries 3 and 4).[9,10]

Table 6 shows the results from the acetals having an acetal and a ketal unit together. In every entry, the major product was the one obtained by the selective acetal deprotection. In the cases of entries 4 and 5, the substrates had an additional hydroxyl function, and the TES-ether aldehyde ketals were obtained as major products. For the rather low yields of products (entries 2

(8) Kreevoy, M. M.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5590−5595. See also: Bunton, C. A.; De Wolfe, R. H. *J. Org. Chem.* **1965**, *30*, 1371−1375.
(9) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, 4175−4178.
(10) For examples in which aliphatic ketals are selectively deprotected in the presence of aliphatic acetals, see: (a) entry 8 of Table 1 in ref 2g. (b) Ukaji, Y.; Koumoto, N.; Fujisawa, T. *Chem. Lett.* **1989**, 1623−1626.

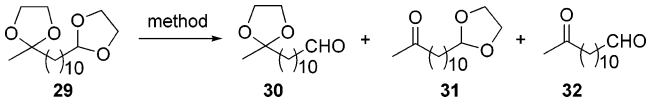
Table 4. Mild Deprotection of Various Acetals



entry	substrate	product	yield (%) 2,6-lutidine	yield (%) 2,4,6-collidine
1	 **11**	Ph-CHO **12**	92	
2	 **13**	 **14**	75	92
3	 **15**	 **16**	82	quant.[a]
4	R = Ac (**17a**)		90	
5	 R = Me (**17b**)	 **18a-c**	93	
6	R = Tr (**17c**)		92	
7	 **19**	 **20**	85	90[a]
8	 R = Me (**21a**)	 **22a,b**	91	
9	R = tBu (**21b**)		74	
10	 **23**	 **24**	95[a]	
11	 **25**	 **26**	83[a]	95[b]
12	 **1**	 **2**	82[b]	93[b]

[a] TESOTf (3.0 equiv) and base (4.0 equiv) were used. [b] TESOTf (4.0 equiv) and base (6.0 equiv) were used.

Table 5. Comparison of Our Method with Other Methods



29 **30** **31** **32**

entry	method (equiv)	condition	yield (%)	30:31:32
1	TESOTf (2.0) 2,6-lutidine (3.0)	CH_2Cl_2, 0 °C 1 h, then H_2O	79	100:0:0
2	TESOTf (2.0) 2,4,6-collidine (3.0)	CH_2Cl_2, 0 °C 1 h, then H_2O	83[a]	100:0:0
3	*p*-TsOH (1.0)	acetone/H_2O = 1:1, rt, 3.5 h	80	0:90:10
4	TMSI (1.0)	CH_2Cl_2, 0 °C 1 h	94	0:77:23

[a] Based on recovered starting material.

and 3), the use of 2,4,6-collidine tended to give the desired products in higher yields.

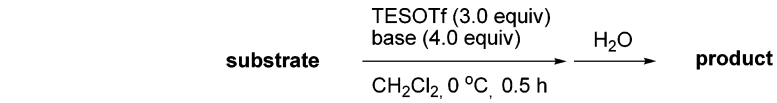
Reaction and Speculation of the Intermediate

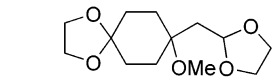
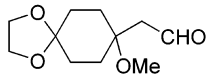
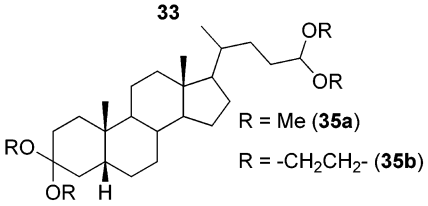
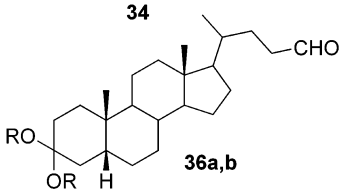
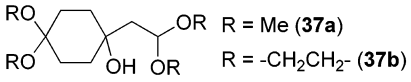
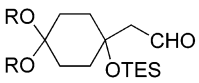
Discussion about the Reaction Mechanism and Chemoselectivity: Generally, trialkylsilyltriflate works on acetals such as a Lewis acid and can easily transform them into oxonium ions, which are strong electrophiles. It then works as an efficient catalyst for nucleophilic addition toward the acetal (Scheme 5, route a).[6] On the other hand, the attack of water on the oxonium ions can produce a carbonyl compound (route b). However TfOH is simultaneously produced in route b, and the reaction mixture becomes strongly acidic which results in moderate yields of the products (for example, see Scheme 6).

In fact, Trehan et al. reported that the deprotection of the acetal by TMSOTf gave the product in moderate yields.[11] Our result, entry 1 of Table 3, also showed that the use of TESOTf only produced poor results. On the other hand, as mentioned above, the combination of TESOTf−2,6-lutidine could deprotect acetals from aldehydes in good yields (for the benzaldehyde dimethyl acetal result, see Table 4, entry 1) (Scheme 6). Since the reaction proceeds under weakly basic conditions, many acid-labile functional groups could tolerate the reaction. Furthermore, highly polar compounds were first formed, and an H_2O workup

(11) See: Kaur, G.; Trehan, A.; Trehan, S. *J. Org. Chem.* **1998**, *63*, 3, 2365−2366, ref 9.

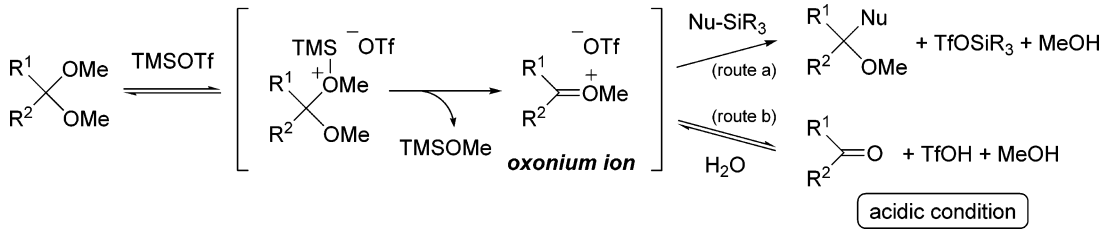
Table 6. Chemoselective Deprotection of Substrates Having Acetal and Ketal Units



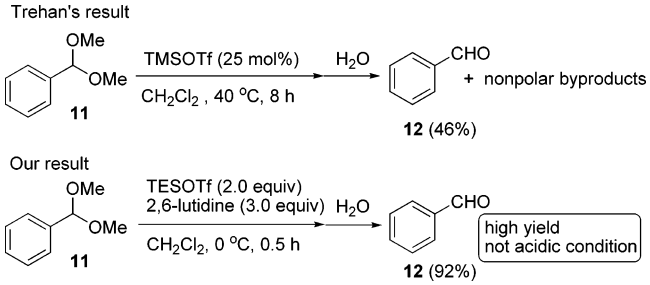
entry	substrate	product	yield (%) 2,6-lutidine	yield (%) 2,4,6-collidine
1[a]	 **33**	 **34**	86	
2	 R = Me (**35a**)	 **36a,b**	63	84
3	R = -CH_2CH_2- (**35b**)		50	63
4	 R = Me (**37a**)	 **38a,b**	82	
5	R = -CH_2CH_2- (**37b**)		87	

[a] TESOTf (2.0 equiv) and base (3.0 equiv) were used.

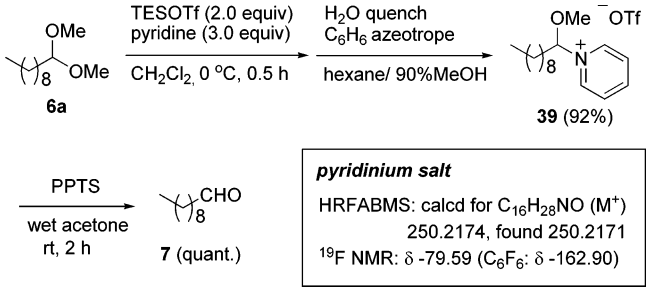
Scheme 5



Scheme 6



Scheme 7

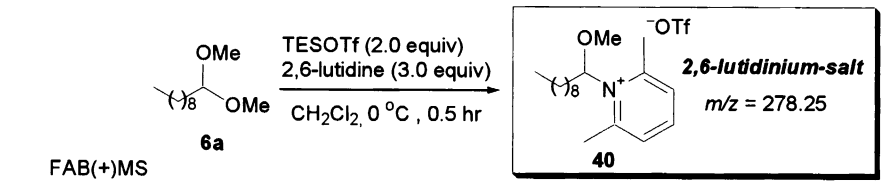


was necessary to produce the deprotected carbonyl compounds. These facts showed the unusual reaction path and new reaction intermediate.

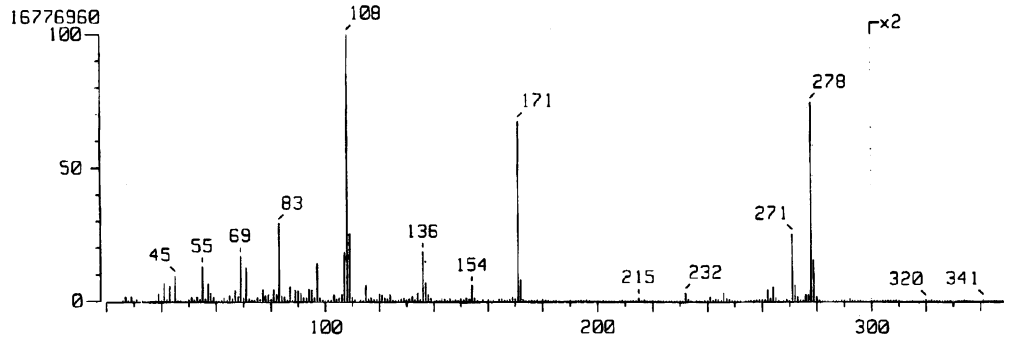
The Reaction Mechanism and the Structure of the Polar Compounds (NMR and MS Studies). The polar compound from the reaction of the acetal **6a** and pyridine (Table 3, entry 2) was first isolated. Thus, azeotropic distillation of the reaction mixture with benzene in vacuo removed CH_2Cl_2, H_2O, and pyridine to give the residue, which was dissolved in hexane/MeOH (1:9). The hexane layer containing the less polar component was removed, and evaporation of the MeOH layer afforded the polar compound **39** (Scheme 7). Its ^{1}H NMR spectrum showed the presence of three aromatic protons (δ: 9.10, 8.61, 8.18), an acetal proton (δ: 6.03), and one methoxy proton (δ: 3.50). Its ^{19}F NMR showed the presence of a fluorine atom (δ: −79.59). The high-resolution FABMS of **39** showed that its composition formula was $C_{16}H_{28}NO$. Aqueous acidic treatment of **39** gave the deprotected aldehyde **7** in quantitative yield. Therefore, we determined that the polar compound **39** was a pyridinium salt.

Based on the consideration of the result using pyridine, we postulated that the polar compound in the 2,6-lutidine reaction was similar to the lutidinium salt. As expected, the FABMS of the reaction mixture showed the M^+ peak of the 2,6-lutidinium salt **40** at 278 *m*/*z* (Scheme 8). An ^{1}H NMR spectrum of the reaction is shown in Figure 1. Chart A is the ^{1}H NMR chart of 2,6-lutidine. Chart B is the ^{1}H NMR chart of the acetal **6a**. Chart C is the ^{1}H NMR chart of the reaction mixture obtained by the treatment of **6a** with TESOTf (2.0 equiv) and 2,6-lutidine (3.0 equiv). The characteristic acetal proton around δ 6.0 ppm suggested the N,O-acetal structure and no proton from an aldehyde were observed in Chart C. However, the H_2O workup of the mixture resulted in the disappearance of the proton around δ 6.0 ppm and the formation of the new proton of an aldehyde around δ 9.75 ppm (Chart D). Additionally, similar reaction

Scheme 8. Study on the Reaction Intermediate **40** by FAB(+)MS



FAB(+)MS



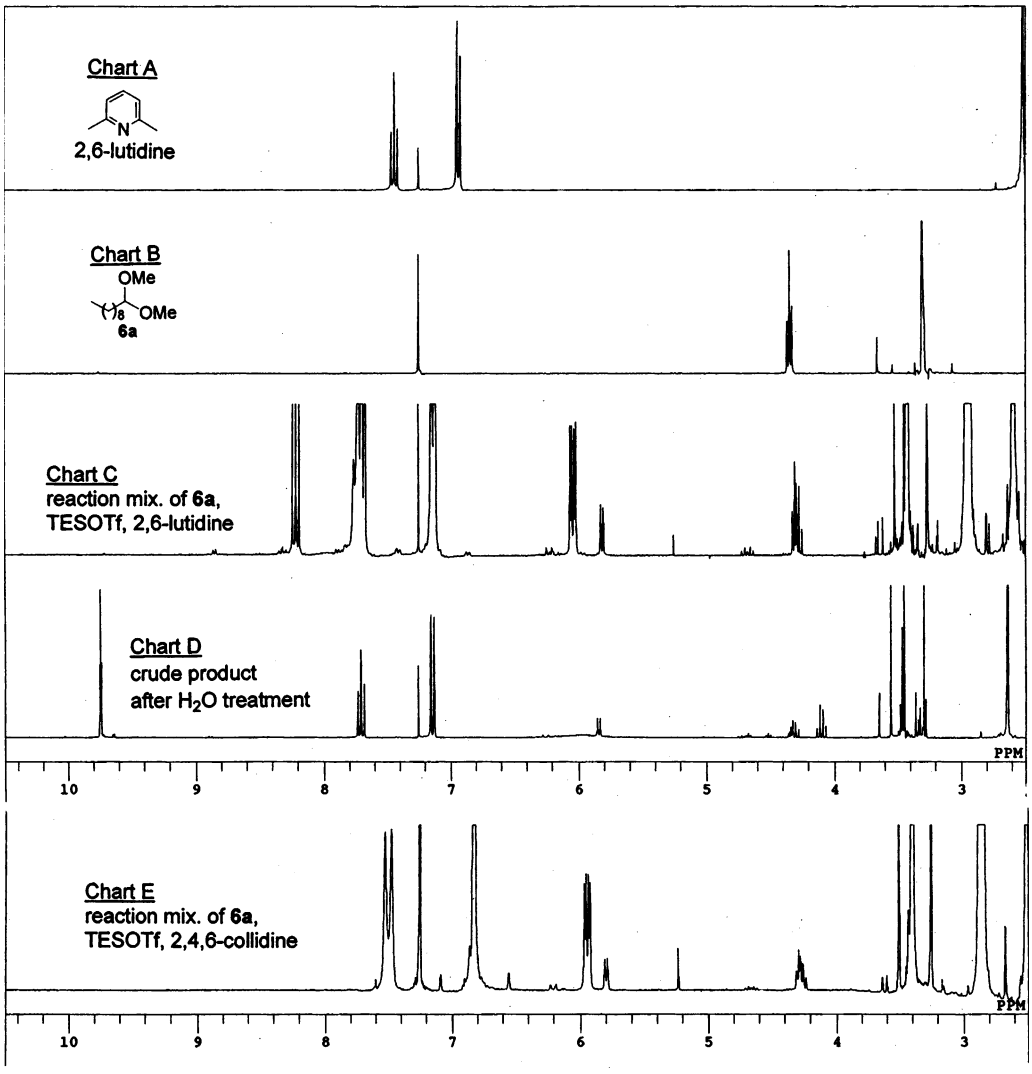
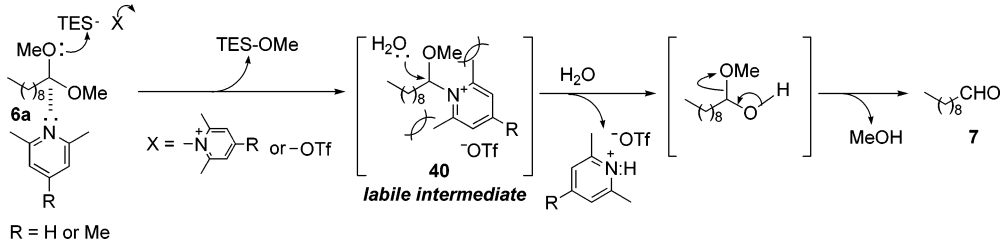


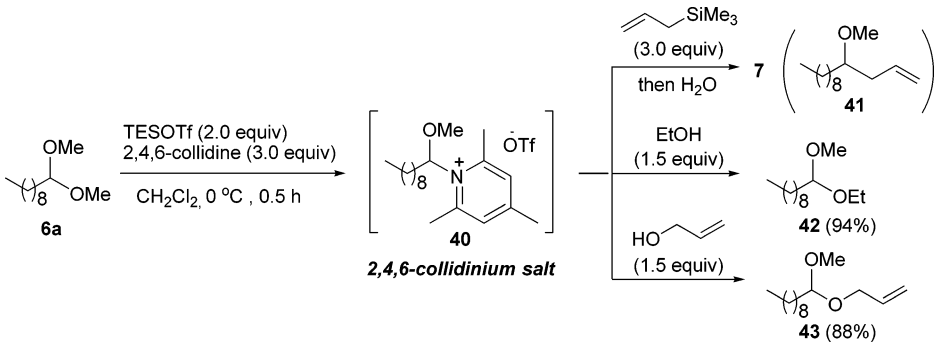
Figure 1. Study on the reaction mechanism by ^{1}H NMR.

intermediates were also observed for the reaction under TESOTf–2,4,6-collidine conditions. Chart E is the ^{1}H NMR chart of the reaction mixture obtained by the treatment of **6a** with TESOTf (2.0 equiv) and 2,4,6-collidine (3.0 equiv), and not 2,6-lutidine. In this case, the peak due to the N,O-acetal also newly appeared around 6.0 ppm, and Chart E is very similar to Chart C. Although Roush et al. succeeded in the intramolecular trans-acetalization of MOM ether under identical conditions and

Scheme 9



Scheme 10



they reported that their transacetalization was activated by TfOH,[12] in our case, TfOH is not effective (see Scheme 3). Therefore, we consider that our genuine species are different from theirs.[13] This conclusion also proved to be possible from the observation that the intermediates worked as good precursors for the efficient mixed acetal formation (see next chapter).

Based on this study, a plausible reaction mechanism is shown in Scheme 9. Thus the attack of 2,6-lutidine or 2,4,6-collidine on the acetal function activated by a Lewis acid resulted in the formation of the pyridinium-type salt **40** close to the pyridinium salt **39**. However, the stability of **40** was completely different from **39**. **40** was a very unstable compound because of the steric hindrance of the 2,6-dimethyl groups of 2,6-lutidine or 2,4,6-collidine and very reactive with water. Easy cleavage of the C−N bond followed by attack of H_2O then afforded the deprotected aldehyde **7**. At the same time, excess 2,6-lutidine or 2,4,6-collidine could capture the simultaneously formed trifluoromethanesulfonic acid. The reactions then proceeded under weakly basic conditions.

Efficient Mixed Acetal Formation: The properties of the collidinium salt converted to nucleophiles were examined. The reaction process was as follows. After the disappearance of **6a** on TLC by treatment with TESOTf (2.0 equiv)−2,4,6-collidine (3.0 equiv), 3.0 equiv of the nucleophile were added to the mixture. The use of allyltrimethylsilane,[14] a very popular nucleophile for oxonium ions, did not give the allylated product **41**, and an aldehyde **7** was obtained after H_2O workup, whereas the use of EtOH and allyl alcohol, stronger nucleophiles than the allyltrimethylsilane, gave the mixed acetals **42** and **43** in high yields (Scheme 10). These results meant that the collidinium salts have a very weak electrophilicity and only strong nucleophiles, such as water and alcohols, can react with the salts.

Although several studies are reported for the preparation of mixed acetals, most of them use an acid catalyst. Therefore, the yields of the desired mixed acetals are moderate due to the over-reaction. On the other hand, our method proceeds under weakly basic conditions and is quite good for making mixed acetals such as **42** and **43**. We then applied the method to the other mixed acetals, which were obtained in moderate yields in the previous studies (Scheme 11). Thus, the treatment of dimethyl acetal **44** with TESOTf and 2,4,6-collidine followed by the addition of geraniol gave the mixed acetal **45** in 87% yield, whereas the yield of the previous report was 57%.[15] For the same procedure, the mixed acetal **47** was obtained from **46** in 91% yield (the reported yield was 81%).[16] Although the dimethyl acetal **48** has acid-sensitive functional groups, the better yield of 79% than the reported yield of 67%[17] was obtained to give the mixed acetal **49**.

These results show that our method for the mixed acetal synthesis is very mild and superior to the previous methods.

Conclusion

We have developed a new deprotection method of acetals from aldehydes via pyridinium-type intermediates. The method is very sensitive to the steric morphology of the acetals and can produce the unprecedented, unexpected, and remarkably high chemoselective deprotection method. This methodology can selectively deprotect the acetals in the presence of ketals, although this chemoselectivity is difficult to achieve by other previously reported methods. A detailed study of the method using various bases and spectroscopic examination of the

(12) For the intramolecular transacetalization of MOM ether under identical conditions, see: (a) Durharm, T. B.; Blanchard, N.; Savall, B. M.; Powell, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2004**, *126*, 9307−9317. (b) Powell, N. A.; Roush, W. R. *Org. Lett.* **2001**, *3*, 453−456.

(13) TESOTf from ACROS ORGANICS was used in our experiments. When the reaction of **6a** was conducted by the all-distilled reagents (TESOTf, 2,4,6-collidine, and CH_2Cl_2), the same result was obtained. This fact shows that the reaction is not catalyzed by trace amounts of TfOH.

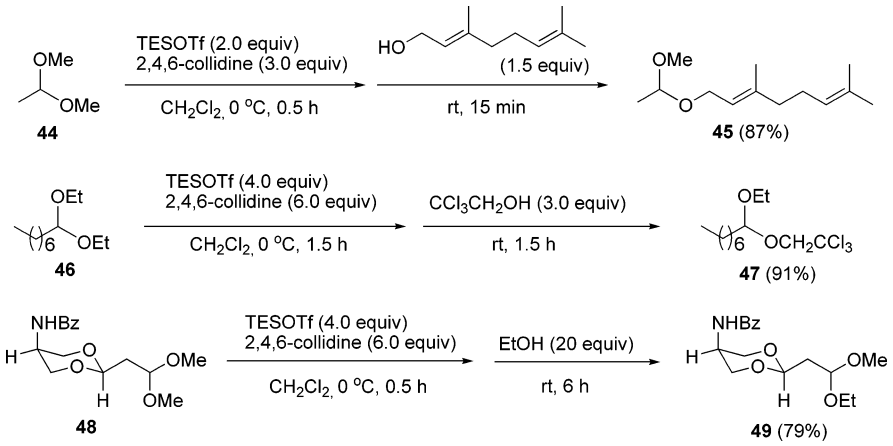
(14) For the reaction of allyltrimethylsilane and acetals mediated by TMSOTf, see: Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71−74.

(15) Baeckstrom, P.; Li, L. *Tetrahedron* **1991**, *47*, 6521−6532.

(16) Isidor, J. L.; Carlson, R. M. *J. Org. Chem.* **1973**, *38*, 554−556.

(17) Bi, L.; Zhao, M.; Wang, C.; Peng, S. *Eur. J. Org. Chem.* **2000**, 2669−2676.

Scheme 11



reaction revealed the reaction mechanism for determining the structures of the intermediates. These intermediates had a weak electrophilicity and were successfully applied to the efficient formation of the mixed acetals in high yields. The reaction is a new one via new intermediates, and its further application in synthetic organic chemistry is under investigation.

Experimental Section

General Reaction Procedure Using TESOTf−2,6-Lutidine (or 2,4,6-Collidine): First, 2,6-lutidine (or 2,4,6-collidine) (3.0 equiv for the compounds having only acetal function and 4.0 equiv for the compounds having hydroxyl and acetal functions) and, second, TESOTf (2.0 equiv for the compounds having only acetal function and 3.0 equiv for the compounds having hydroxyl and acetal functions) were added to a solution of an acetal in CH_2Cl_2 (0.1 M solution) at 0 °C under N_2 gas. The mixture was stirred at the same temperature. After checking for the disappearance of an acetal on TLC, H_2O was added to the resulting mixture and stirred. Disappearance of the polar component was ascertained by TLC. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography to produce the aldehyde.

Deprotection Reaction of 29 with TESOTf−2,6-lutidine, *p*-TsOH, and TMSI (Table 5). A. TESOTf−2,6-Lutidine: 2,6-Lutidine (55 μL, 0.48 mmol) and TESOTf (72 μL, 0.32 mmol) were added to a solution of **29** (48.0 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C under N_2 gas. The mixture was stirred for 1 h at the same temperature. After the disappearance of **29** was checked on TLC, H_2O was added to the resulting mixture and stirred. The disappearance of the polar component was ascertained by TLC. All procedures were done at 0 °C. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography using hexanes−Et_2O (7:1) to give **30** (32.5 mg, 79%).

B. *p*-TsOH: *p*-TsOH (5.8 mg, 0.03 mmol) was added to a solution of **29** (19.3 mg, 0.03 mmol) in acetone−H_2O (1:1)(0.6 mL), and the resulting mixture was stirred at rt for 3.5 h. After checking for the disappearance of **29** on TLC, sat. $NaHCO_3$ aq. was added to the mixture at 0 °C. The resulting solution was evaporated to remove the acetone in vacuo. The mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography using hexanes−Et_2O (2:1) to give a mixture of **31** and **32** (13.2 mg, 80%, the ratio of **31** and **32** was determined by ^{1}H NMR).

C. TMSI: TMSI (29 μL, 0.20 mmol) was added to a solution of **29** (60.6 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C under N_2 gas. The resulting mixture was stirred at 0 °C for 1 h. After checking for the disappearance of **29** on TLC, sat. $NaHCO_3$ aq. and sat. $Na_2S_2O_3$ aq. were successively added to the mixture at 0 °C. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography using hexanes−Et_2O (2:1) to give a mixture of **31** and **32** (46.9 mg, 94%, the ratio of **31** and **32** was determined by ^{1}H NMR).

Pyridinium Salt 39 and Its Hydrolysis in Scheme 7: Pyridine (60 μL, 0.74 mmol) was added to a solution of **6a** (50.2 mg, 0.25 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C under N_2. After the solution was stirred for 5 min, TESOTf (112 μL, 0.50 mmol) was dropwise added. The mixture was stirred at 0 °C. After the disappearance of **6a** (TLC check), the reaction was quenched by the addition of H_2O. The mixture was then evaporated in vacuo. The residue was further coevaporated with benzene. The residue was diluted with hexane−MeOH (1:9). The MeOH layer was dried over Na_2SO_4 and evaporated in vacuo to give **39** (89.4 mg, 92%). PPTS (2.5 mg, 0.01 mmol) was added to a solution of **39** (56.6 mg, 0.14 mmol) in acetone−H_2O (v/v = 1/1, 2.0 mL). The mixture was stirred for 2 h. The solution was poured into sat. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography using hexane−CH_2Cl_2 (3:2) as the eluent to give **7** (21.8 mg, quant). **1-(1-Methoxydecyl)pyridinium Trifluoromethanesulfonate (39):** Colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.10 (d, J = 5.4 Hz, 2H), 8.61 (t, J = 7.8 Hz, 1H), 8.18 (dd, J = 7.8, 5.4 Hz, 2H), 6.03 (t, J = 5.1 Hz, 1H), 3.50 (s, 3H) 1.94 (m, 2H), 1.23 (m, 14H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.0 (2C), 141.0, 128.7(2C), 102.0, 58.5, 38.0, 31.7, 29.3, 29.2, 29.1, 28.8, 24.1, 22.6, 14.0; ^{19}F NMR ($CDCl_3$) δ −79.59 (C_6F_6 as internal standard). HRFABMS: calcd for $C_{16}H_{28}NO$ (M^+), 250.2171; found, 250.2174.

Experiment in Scheme 8: 2,6-Lutidine (40 μL, 0.34 mmol) was added to a solution of **4a** (25.0 mg, 0.11 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C under N_2. After the solution was stirred for 5 min, TESOTf (52 μL, 0.23 mmol) was dropwise added. The mixture was stirred for 30 min. The solution was directly measured by FAB(+)MS.

General Procedure for the Synthesis of Mixed Acetals. 2,4,6-Colldine (3.0 equiv) and TESOTf (2.0 equiv) were added to a solution of an acetal in CH_2Cl_2 (0.1 M solution) at 0 °C under N_2. The mixture was stirred at the same temperature. After checking for the disappearance of the acetal by TLC, an alcohol (1.5 equiv) was added to the resulting mixture and stirred at rt. Disappearance of the polar component was ascertained by TLC. The mixture was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by flash SiO_2 column chromatography to give the mixed acetal.

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Supporting Information Available: Full experimental details including the physical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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