

## Trimethylsilyl Trifluoromethanesulfonate Promoted Chemoselective Reactions of Acyclic Acetals in the Presence of Cyclic Acetals

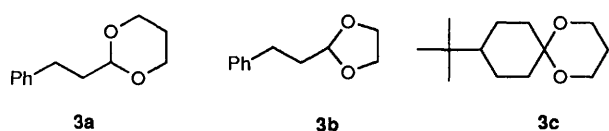
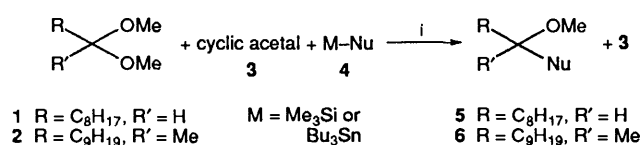
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Trimethylsilyl trifluoromethanesulfonate promoted chemoselective reactions of acyclic acetals with allyltrimethylsilane, allyltributyltin, a silyl enol ether, tributyltin hydride, trimethylsilyl azide and trimethylsilyl cyanide have been achieved in the presence of cyclic acetals.

The reaction of carbonyl compounds or their synthetic equivalents with nucleophiles is of great importance in organic synthesis and discrimination between carbonyl compounds and/or their synthetic equivalents has received a great deal of recent attention.<sup>1</sup> Acetals are of synthetic importance because they are both carbonyl equivalents<sup>2</sup> as well as carbonyl protecting groups.<sup>3</sup> Murata *et al.* reported that acetals activated by trimethylsilyl trifluoromethanesulfonate (TMSOTf) reacted selectively with silyl enol ethers in the presence of aldehydes and ketones.<sup>4</sup> Sato *et al.* found that ketone acetals were more reactive than aldehyde acetals in organotin trifluoromethanesulfonate promoted reactions with silyl enol ethers.<sup>5</sup> The cleavage of cyclic acetals activated by Lewis acids such as titanium tetrachloride<sup>6</sup> and TMSOTf<sup>7</sup> is well-known to proceed under mild conditions. Despite the high reactivity of the cyclic acetal group toward Lewis acids, we have found that acyclic acetals are much more reactive than cyclic acetals in TMSOTf promoted reactions, indicating that the reactivity of acetals depends critically on whether they are cyclic or acyclic.

The chemoselective allylation of acyclic acetals in the presence of cyclic acetals was initially carried out with allyltrimethylsilane and titanium tetrachloride. When an equimolar mixture of **1** and **3b** was treated with an equimolar mixture of allyltrimethylsilane and titanium tetrachloride in dichloromethane at  $-78\text{ }^{\circ}\text{C}$  for 2 h, **5** was isolated in 72% yield along with **3b** (17%), hydrocinnamaldehyde (49%), nonyl aldehyde (4%) and the allylated product of **3b** (6%) (Scheme 1).

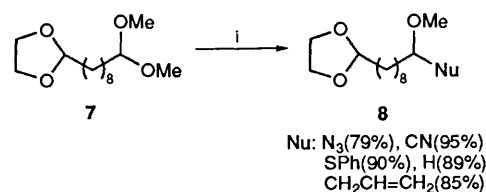


Scheme 1 Reagents and conditions: i, TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>,  $-78\text{ }^{\circ}\text{C}$

A similar result was obtained with boron trifluoride–diethyl ether. Furthermore, the use of titanium tetrachloride and boron trifluoride–diethyl ether as a catalyst (0.3 equiv.) was not effective, mainly leading to recovery of the starting acetals. When the reaction was carried out in the presence of TMSOTf (0.3 equiv.) under the same conditions, the allylation reaction occurred selectively with **1**, and **3b** was recovered unchanged. The reaction required 10 h for completion. Table 1 summarizes our experimental results and illustrates the scope and the

applicability of the present method. The use of allyltributyltin as the nucleophile gave similar results. Although the reaction occurred almost instantly, it required a stoichiometric amount of TMSOTf, suggesting that the tributyltin trifluoromethanesulfonate being formed in the reaction did not effectively activate the acetals. The discrimination between **1** or **2** and **3** was also achieved by using a silyl enol ether, trimethylsilyl azide, or trimethylsilyl cyanide as the nucleophile under similar conditions. The possibility of selective reduction of acyclic acetals in the presence of cyclic acetals was studied and initial attempts with triethylsilane failed owing to relatively weak nucleophilicity of triethylsilane. The problem was solved by using tributyltin hydride. Thus, the reaction of an equimolar mixture of **1** and **3a** with tributyltin hydride (1.1 equiv.) and TMSOTf (1.1 equiv.) in dichloromethane at  $-78\text{ }^{\circ}\text{C}$  for 5 min gave **5** in 94% yield along with the recovery of **3a**.

The results obtained from intermolecular competition experiments have been applied to the chemoselective reactions of **7** bearing an acyclic and a cyclic acetal group. As shown in Scheme 2, the acyclic acetal group reacted selectively with




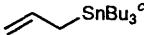
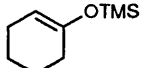
Scheme 2 Reagents and conditions: i, MNu, TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>,  $-78\text{ }^{\circ}\text{C}$  (MNu = Me<sub>3</sub>SiN<sub>3</sub>, Me<sub>3</sub>SiCN, Me<sub>3</sub>SiSPh, Bu<sub>3</sub>SnH, Bu<sub>3</sub>SnCH<sub>2</sub>CH=CH<sub>2</sub>)

allyltributyltin, tributyltin hydride, trimethylsilyl azide and trimethylsilyl cyanide, demonstrating the effectiveness of the present method for discriminating between an acyclic and a cyclic acetal group.

### Experimental

**General Procedure for the Chemoselective Reaction of Acyclic Acetal 1 in the presence of Cyclic Acetal 3a.**—To a stirred solution of compound **1** (188 mg, 1.0 mmol) and **3a** (192 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 cm<sup>3</sup>) were successively added allyltrimethylsilane (126 mg, 1.1 mmol) and TMSOTf (67 mg, 0.30 mmol) at  $-78\text{ }^{\circ}\text{C}$  under nitrogen. The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 h and then saturated aqueous K<sub>2</sub>CO<sub>3</sub> (3 cm<sup>3</sup>) was added to it to quench the TMSOTf. The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 cm<sup>3</sup>), washed with water (20 cm<sup>3</sup>) and then dried over MgSO<sub>4</sub>. The crude mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel using ethyl acetate–hexane as eluent (1:20, v/v) to give **5** (179 mg, 90%) and **3a** (182 mg, 95%).

**Table 1** Chemoselective reaction of acyclic acetals in the presence of cyclic acetals<sup>a</sup>

Nucleophile	Acyclic acetal	Cyclic acetal	Time	Product (yield, %) <sup>b</sup>
	1	3a	10 h	5 (90) 3a (95)
	2	3a	10 h	6 (84) 3a (97)
	2	3b	10 h	6 (66) 3b (92) 2 (26)
	2	3a	5 min	6 (98) 3a (97)
	2	3c	5 min	6 (97) 3c (95)
	1	3b	5 min	5 (95) 3b (96)
	1	3a	20 min	5 (87) 3a (96)
	2	3b	5 min	6 (85) 3b (90)
	1	3c	20 min	5 (88) 3c (94)
TMSN <sub>3</sub>	1	3a	20 min	5 (99) 3a (95)
	1	3b	20 min	5 (95) 3b (95)
TMSCN	1	3b	20 min	5 (90) 3b (90)
TMSSPh	1	3b	1 h	5 (98) 3b (95)
Bu <sub>3</sub> SnH <sup>c</sup>	1	3a	5 min	5 (94) 3a (95)
	2	3c	5 min	6 (94) 3c (97)
	2	3b	5 min	6 (97) 3b (91)

<sup>a</sup> The reaction was carried out in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. <sup>b</sup> The yield refers to the isolated yield. <sup>c</sup> 1.1 Equiv. of TMSOTf was used.

Compound 5:  $\delta_{\text{H}}$ (200 MHz; CCl<sub>4</sub>-C<sub>6</sub>D<sub>6</sub>; J/Hz) 0.8 (t, 3 H, J 6.8), 1.1 and 1.3 (m, 14 H), 2.0 and 2.1 (m, 2 H), 3.0 (m, 1 H), 3.1 (s, 3 H), 4.8 and 4.9 (m, 2 H) and 5.5 and 5.7 (m, 1 H).

**General Procedure for the Preparation of Cyclic Acetal 8 from 7.**—To a stirred solution of acetal 7 (260 mg, 1.0 mmol) and trimethylsilyl azide (127 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 cm<sup>3</sup>) was added TMSOTf (67 mg, 0.30 mmol) at -78 °C under nitrogen. After 5 min at -78 °C, the reaction mixture was allowed to warm to -50 °C and quenched by addition of silica gel (200 mg). The resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 cm<sup>3</sup>), washed with water (20 cm<sup>3</sup>) and then dried over MgSO<sub>4</sub>. A crude mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel using ethyl

acetate-hexane as eluent (1:10, v/v) to give  $\alpha$ -alkoxyalkyl azide 8 (214 mg, 79%),  $\delta_{\text{H}}$ (200 MHz; CCl<sub>4</sub>-C<sub>6</sub>D<sub>6</sub>; J/Hz) 1.1 and 1.3 (m, 12 H), 1.4 and 1.6 (m, 4 H), 3.3 (s, 3 H), 3.6 and 3.7 (m, 4 H), 4.0 (t, 1 H, J 5.7) and 4.6 (t, 1 H, J 4.3).

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