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COMMUNICATION

Direct conversion of acetals to esters with high regioselectivity *via* *O*,*P*-acetals†

Tomohiro Maegawa, Kazuki Otake, Akihiro Goto and Hiromichi Fujioka*

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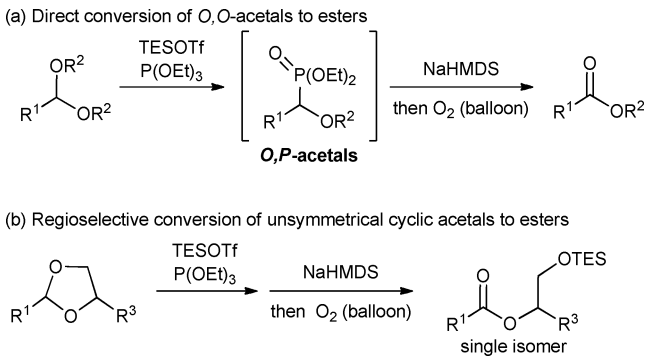
A new direct conversion of *O*,*O*-acetals to esters *via* *O*,*P*-acetal intermediates was developed. The regioselective cleavage of unsymmetrical cyclic acetals occurred to give the more crowded esters as single isomers.

O,*O*-Acetals are often used as a protecting group for carbonyl functions.[1] They can also be converted into other functional groups. For example, there have been many reports of the direct conversion of *O*,*O*-acetals to esters,[2] but most of them required a transition metal catalyst or peroxide. In this communication, we describe the new and efficient one-pot conversion of *O*,*O*-acetals to esters. The reaction is quite regioselective and unsymmetrical cyclic acetals can afford single esters (Scheme 1).



Scheme 1 Oxidation of *O*,*O*-acetals to esters *via* *O*,*P*-acetals.

Recently, we demonstrated the formation of pyridinium intermediates (*N*,*O*-acetals) from *O*,*O*-acetals and pyridines, and investigated their reactivity.[3] As an extension of this study, we also studied the reactivity of phosphonium intermediates (*O*,*P*-acetals) using phosphines instead of pyridines and developed the efficient nucleophilic substitution of *O*,*P*-acetals from P(*o*-tol)$_3$.[4] During the course of our study, we found the novel conversion of *O*,*O*-acetals to esters in one-pot *via* *O*,*P*-acetal intermediates.

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Osaka, 565-0871, Japan. E-mail: fujioka@phs.osaka-u.ac.jp; Fax: +8168798229; Tel: +8168798225

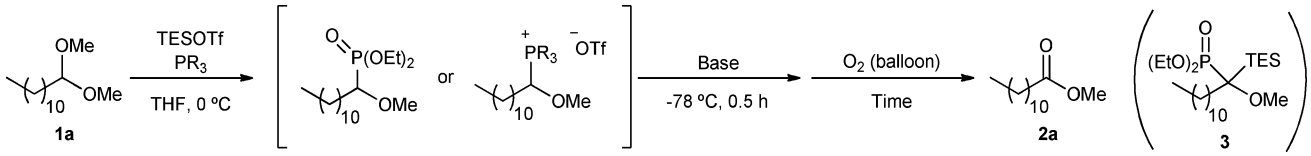
† Electronic supplementary information (ESI) available: Experimental details and the charts of ^{1}H, ^{13}C and ^{31}P NMR. See DOI: 10.1039/c1ob05687e

When *O*,*P*-acetal from P(OEt)$_3$ was treated with *n*-BuLi, the yield of the desired ester **2a** was low (entry 1).[5] The *O*,*P*-acetal was not converted to the ester at all in the case of NaH and *t*-BuOK (entries 2 and 3). On the other hand, when LiHMDS, NaHMDS and KHMDS were used, the reactions smoothly proceeded and the desired ester **2a** was obtained in good yields after a 2 h reaction (entries 4–6). Since a slight amount of a side product **3** was obtained in these reactions due to the reaction of the *O*,*P*-acetal anion and TESOTf, 3 eq. of Et$_3$N was added in order to quench TESOTf after the formation of the *O*,*P*-acetal (entry 7). Consequently, the yield was improved to 83% and the side product **3** was not detected. *O*,*P*-acetals from PPh$_3$ and P(*o*-tol)$_3$ were not effective for this phosphonate oxygenation.

With the optimal reaction conditions (Table 1, entry 7), various *O*,*O*-acetals were converted to the corresponding esters *via* the *O*,*P*-acetals. As shown in Table 2, not only aliphatic dimethyl and diethyl acetals, but also diisopropyl acetal were converted to esters in good yields (entries 1–3). Aromatic acetals **1d–1f** also gave the corresponding esters in good to excellent yields (entries 4–6). For the cyclic acetals **1g** and **1h**, the silylated esters **2g** and **2h** were obtained in good yields (entries 7 and 8).

Next, we planned the regioselective synthesis of esters from unsymmetrical cyclic acetals obtained from unsymmetrical 1,2-diols and aldehydes. We have reported the highly chemoselective transformation of acetals in the presence of ketals in combination with TESOTf and 2,4,6-collidine.[3a–c,f,h] This excellent selectivity is attributed to the discrimination of the steric environment by TESOTf, which selectively coordinates to the less hindered oxygen atom. We then expected the regioselective opening of the unsymmetrical cyclic acetals in combination with P(OEt)$_3$ and TESOTf. The resulting *O*,*P*-acetals would be converted to esters as a single regioisomer connecting to the more hindered hydroxyl group (Scheme 2). Although there are now a number of methods for the conversion of unsymmetrical cyclic acetals to esters, satisfactory results have not yet been obtained.[2] For example, the reaction of an unsymmetrical cyclic acetal **4a** using oxidating reagents, *t*-BuOOH-VO(OAc)$_2$[2h] and DMDO,[2m] gave isomeric mixtures in 70 : 30 and 89 : 11, respectively. To our delight, the ring-opening reaction of **4a** proceeded regioselectively and gave the corresponding ester **5a** as a single isomer under our reaction conditions though the yield was 18% (Table 3, entry 1).[6] While an increase in NaHMDS did not have a significant influence on the yield of **5a** (entry 2), the addition of 15-crown-5 substantially improved the yield (entry 3).[7] The reaction

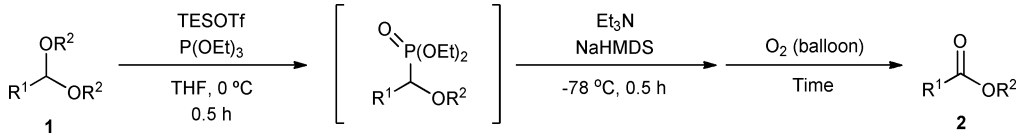
Table 1 Oxygenation of *O*,*P*-acetals[a]

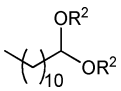
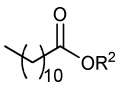
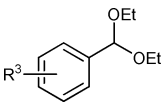
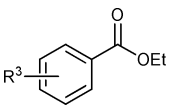
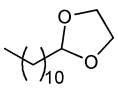
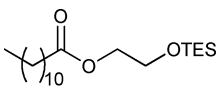
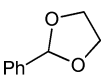
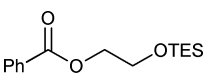


Entry	PR_3	Base	Time (h)	Yield (%)
1	$P(OEt)_3$	*n*-BuLi	3	8
2		NaH	5	—[b]
3		*t*-BuOK	5	—[b]
4		LiHMDS	2	75
5		NaHMDS	2	79
6		KHMDS	2	78
7[c]		NaHMDS	2	83

[a] The reaction conditions: To a solution of **1a** (1.0 eq.) and PR_3 (3.0 eq.) in THF (0.2 M) was added TESOTf (2.0 eq.) at 0 °C, and the solution was stirred for 0.5 h under a N_2 atmosphere. Then the reaction mixture was cooled to −78 °C and base (3.0 eq.) was added. After being stirred for 0.5 h, N_2 was replaced with O_2. [b] *O*,*P*-acetal was not converted to ester at all. [c] 3.0 eq. of Et_3N was added before the addition of NaHMDS.

Table 2 Oxidation of acetals to esters *via* *O*,*P*-acetals



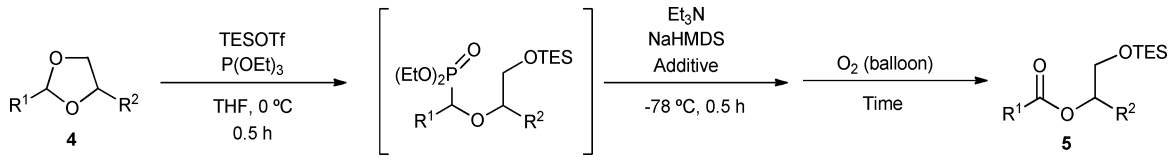
Entry	Substrate		Time (h)	Product		Yield (%)
1		R^2 = Me (**1a**)	2		R^2 = Me (**2a**)	83
2		R^2 = Et (**1b**)	3		R^2 = Et (**2b**)	79
3		R^2 = *i*-Pr (**1c**)	2		R^2 = *i*-Pr (**2c**)	83
4		R^3 = *p*-Me (**1d**)	2		R^3 = *p*-Me (**2d**)	75
5		R^3 = *p*-Br (**1e**)	1		R^3 = *p*-Br (**2e**)	90
6		R^3 = *o*-MeO (**1f**)	4		R^3 = *o*-MeO (**2f**)	70
7	 **1g**		2	 **2g**		86
8	 **1h**		2	 **2h**		84

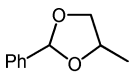
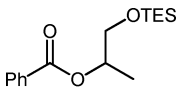
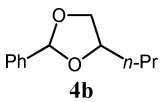
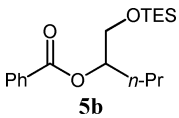
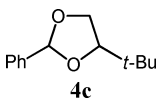
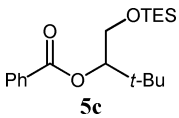
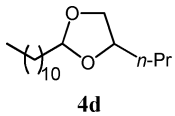
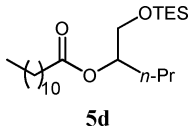
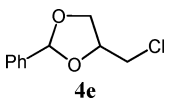
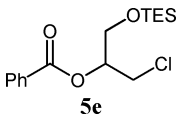
Scheme 2 Oxygenation of unsymmetrical cyclic acetal to ester *via* regioselective formation of *O*,*P*-acetal.

of other unsymmetrical acetals also afforded the corresponding esters in good yields (entries 4–6). However, the reaction of **5e**resulted in a low yield because the elimination reaction occurred concomitantly (entry 7).

In summary, we have developed a method for the direct conversion of *O*,*O*-acetals to esters *via* *O*,*P*-acetal intermediates. The feature of our reaction is the highly regioselective formation of more crowded esters from unsymmetrical cyclic acetals.

Table 3 Oxidation of unsymmetrical acetals to esters *via O*,*P*-acetals



Entry	Substrate[a]	Additive	Time (h)	Product	Yield (%)
1	 **4a**	None	2	 **5a**	18
2[b]		None	2		23
3		15-crown-5	2		75
4	 **4b**	15-crown-5	6	 **5b**	70
5	 **4c**	15-crown-5	6	 **5c**	70
6	 **4d**	15-crown-5	2	 **5d**	78
7	 **4e**	15-crown-5	6	 **5e**	34

[a] A mixture of isomers (**4a**; *cis* : *trans* = 5 : 4 **4b**; *cis* : *trans* = 1 : 1 **4c**; *cis* : *trans* = 2 : 1 **4d**; *cis* : *trans* = 4 : 1 **4e**; *cis* : *trans* = 5 : 4) was used. [b] 5.0 eq. of NaHMDS was used.

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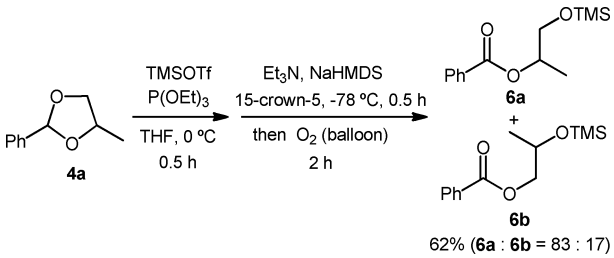
6 No other regioisomer was detected, and the *O*,*P*-acetal remained in the reaction.

7 For the regioselective oxygenation of unsymmetrical cyclic acetals, the choice of the silyltriflate is critical. When we examined the oxidation reaction with TMSOTf instead of TESOTf, the regioselectivity decreased.



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