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One-step chemoselective conversion of tetrahydropyranyl ethers to silyl-protected alcohols†

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Aluminium trichloride catalyses the expeditious direct conversion of tetrahydropyranyl ethers to silyl ethers. This one-step transformation is chemoselective *versus* deprotection of the acetal and hydrosilylation of unsaturated carbon–carbon bonds, and can also be applied to linear acetals. A possible mechanism is tentatively proposed.

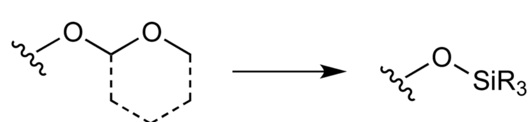
Introduction

The replacement of one protecting group with another, a common process in the synthesis of polyfunctional molecules, usually requires two separate steps: deprotection and re-protection.[1] One-step conversion of one protecting group to another, when possible, saves time, material, and energy.

Hydroxyl-protecting groups have been extensively explored and are generally classified as giving rise to alkyl ethers, silyl ethers, acetals, or esters; among the most popular are those producing silyl ethers[2] (–SiR_3) or acetals (tetrahydropyranyl (THP), ethoxyethyl (EE), methoxymethyl (MOM), *etc.*). A number of methods are now available for direct conversions among the various types,[3] yet only a couple concern the formation of silyl ethers from the widely used cyclic acetal (THP) ether.[1,4] Kim *et al.*[5] transformed THP ethers into *tert*-butyldimethylsilyl (TBDMS) ethers by treatment with TBDMSOTf and dimethyl sulfide in dichloromethane. Using Ph_3P instead of Me_2S afforded just slightly decreased yields, but pyridine and Et_3N were ineffective. Primary and secondary alkyl or benzylic THP ethers responded well, yielding the corresponding TBDMS ethers in high yields under very mild conditions (−50 °C), but allylic and tertiary alkyl THP ethers were less responsive. Oriyama[6] later reported that a mixture of trialkylsilyl trifluoromethanesulfonate and triethylamine converts THP ethers to the corresponding trialkylsilyl ethers at room temperature. Better yields were obtained with phenolic ethers than with aliphatic ethers, conversion of only primary and secondary examples of the latter being reported. The desired conversion also resulted from $Sn(OTf)_2$-catalysed reduction of THP ethers with a trialkylsilane, at least in the case of simple primary and secondary protected alcohols.

Despite their usefulness, both the above methods suffer from drawbacks (the use of noxious dimethylsulfide, or Lewis acid containing toxic tin, or competitive *O*-silylation of free hydroxyls by silyltriflate donors) and both afford unsatisfactory yields for sterically demanding aliphatic substrates. There is clearly a need for a "greener" and more generally applicable method.

$AlCl_3$ is one of the most powerful Lewis acids, and is also probably the most commonly used[7] in synthetic laboratories and in the chemical industry as a catalyst for Friedel–Crafts reactions, polymerizations, acetal cleavage,[8] and the hydrosilylation[9] of unsaturated carbon–carbon bonds. Here we report the use of aluminum trichloride catalyst for the expedient, direct conversion of acetals into silyl ethers. In addition to being effective with primary, secondary, and tertiary alkyl THP ethers, and for a wide range of different silyl protecting groups (including some of the more commonly employed), this reaction is applicable to substrates with unprotected functional groups that are known to be reactive under $AlCl_3/R_3SiH$ conditions, including alkenes and alkynes. It can be also applied to linear acetals (Scheme 1).



Scheme 1 Direct conversion of acetals to silyl ethers.

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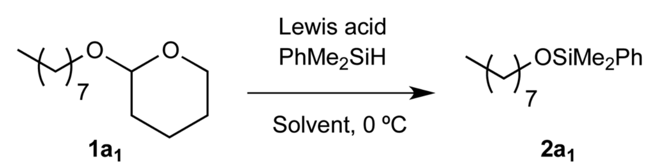
Results and discussion

Optimization of reaction conditions

With Oriyama's[6] $Sn(OTf)_2$-catalysed reaction in mind, we initiated our study by screening a representative set of Lewis acids. We chose the conversion of 1-(2-tetrahydropyranyloxy)octane (**1a$_1$**) to 1-(dimethylphenylsilyloxy)octane (**2a$_1$**) as the model reaction (Table 1). Silane and catalyst (5 mol%) were mixed in CH_2Cl_2 at 0 °C, and the acetal was then added.[10] As expected, $Sn(OTf)_2$ worked well for this simple THP-protected substrate, giving a yield of 81% (Table 1, entry 1). The titanium-based Lewis acids $CpTiCl_2$ and $Ti(iOPr)_2$ had no effect, while $TiCl_4$ led to decomposition of the starting material in less than 1 h (entries 2–4). $BF_3 \cdot Et_2O$ produced a complex mixture, and $InCl_3$ afforded but a poor yield, the main product being deprotected octanol (**3a**) (entries 5 and 6). $FeCl_3$ gave a better yield (60%, entry 7), though inferior to that of $Sn(OTf)_2$; and $EtAlCl_2$ yet a better (74%, entry 8), but required a reaction time of 8 h. Finally, with $AlCl_3$ an excellent 91% yield was obtained in just half an hour (entry 9), and we proceeded to optimize the experimental conditions for this catalyst.

Decreasing the concentration of $AlCl_3$ to 2.5 mol% slowed the reaction and lowered the yield (entry 10), while increasing it to 10 mol% favoured deprotection over the desired conversion (entry 11). At this point we also noticed that the absence of water was critical for avoiding THP cleavage, and dried solvent and freshly sublimated $AlCl_3$ were accordingly used in all subsequent experiments. Trials with alternative solvents identified none better than dichloromethane: the reaction was slightly slower in toluene, and failed to occur to any detectable extent in the coordinating solvents THF and DMF (entries 12–14).

Table 1 Optimization of Lewis acid and reaction conditions



Entry	Lewis acid	mol%	Time (h)	Solvent	Yield[a] (%)
1	$Sn(OTf)_2$	5	2	CH_2Cl_2	81
2	$CpTiCl_2$	5	5	CH_2Cl_2	—
3	$Ti(iOPr)_2$	5	5	CH_2Cl_2	—
4	$TiCl_4$	5	1	CH_2Cl_2	Decomp.
5	$BF_3 \cdot Et_2O$	5	2	CH_2Cl_2	10
6	$InCl_3$	5	2	CH_2Cl_2	19[b]
7	$FeCl_3$	5	2	CH_2Cl_2	60
8	$EtAlCl_2$	5	8	CH_2Cl_2	74
9	$AlCl_3$	5	0.5	CH_2Cl_2	91
10	$AlCl_3$	2.5	1	CH_2Cl_2	82
11	$AlCl_3$	10	0.5	CH_2Cl_2	50[b]
12	$AlCl_3$	5	2	Toluene	85
13	$AlCl_3$	5	5	THF	—
14	$AlCl_3$	5	5	DMF	—

[a] Isolated yield after column chromatography. [b] Deprotected octanol (**3a**) was also obtained.

Scope, chemoselectivity and limitations

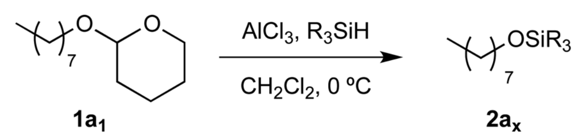
To evaluate the scope of the reaction on the silyl side we ran the reactions of 1-(2-tetrahydropyranyloxy)octane (**1a$_1$**) with an assortment of commercially available silanes (Table 2). Direct conversion proceeded smoothly in all cases, regardless of the steric and/or electronic properties of the silane: although slightly longer reaction times (1 h) were needed for silanes that were bulky (entries 7, 9 and 10) or oxygenated (entries 3 and 8), the yield of the silyl ether **2a$_x$** was always excellent. From among all the silanes tested, $PhMe_2SiH$ was selected for use thereafter in view of its excellent yield, easy visualization by TLC, and low cost.

To evaluate the scope of the reaction we tested a collection of THP ethers that included different functional groups (Tables 3, 4).

Primary, secondary and even tertiary alkyl acetals (**1*x*$_1$**) were all converted to the corresponding dimethylphenylsilyl ethers **2*x*$_1$** in short time and excellent yields, as were allylic, benzylic and propargylic acetals, although an extra equivalent of hydrosilane was required for sterically demanding substrates, entries 6 and 8.

Of particular note, the reaction was compatible with halide, alkene, alkyne and aromatic functional groups, being completely chemoselective for conversion of the protecting group despite these same experimental conditions having been shown to effect the regio- and stereoselective hydrosilylation of alkenes and alkynes.[9] Substrates with free hydroxyl groups were more problematic under standard conditions ($PhMe_2SiH$, $AlCl_3$, CH_2Cl_2, 0 °C), the THP-monoprotected 1,7-heptanediol **1k$_1$** evolved within minutes to deprotected 1,7-heptanediol (**3k**) instead of giving the desired 7-(phenyldimethylsilyloxy)-1-heptanol (**2k$_1$**); see Table 4, entry 1. The use of the bulky silane iPr_3SiH in toluene allowed useful yields of the corresponding silyl ether to be obtained – 58% in the case of 7-(triisopropylsilyloxy)-1-heptanol (**2k$_6$**)[11] (entry 2) and 70% in that of the bispropargylic substrate 4-(triisopropylsilyloxy)-but-2-yn-1-ol (**2l$_6$**) (entry 3). In this last case the

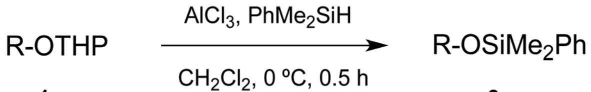
Table 2 Hydrosilane screening



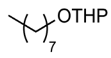
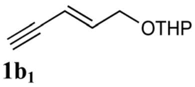
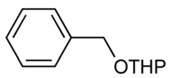
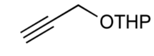
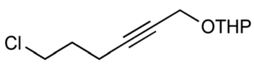
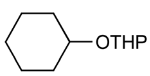
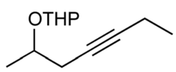
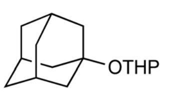
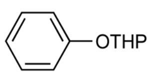
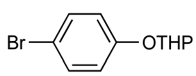
Entry	R_3SiH	Time (h)	Product number	Yield[a] (%)
1	$PhMe_2SiH$	0.5	**2a$_1$**	91
2	$BnMe_2SiH$	0.5	**2a$_2$**	89
3	$(EtO)Me_2SiH$	1	**2a$_3$**	80
4	$tBuMe_2SiH$	0.5	**2a$_4$**	83
5	Ph_3SiH	0.5	**2a$_5$**	79
6	Et_3SiH	0.5	**2a$_6$**	86
7	iPr_3SiH	1	**2a$_7$**	93
8	$(EtO)_3SiH$	1	**2a$_8$**	78
9	tBu_2MeSiH	1	**2a$_9$**	80
10	tBu_3SiH	1	**2a$_{10}$**	79

[a] Isolated yield after column chromatography.

Table 3 Scope of the reaction for THP ethers with no unprotected hydroxyl groups

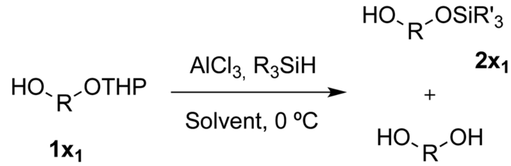


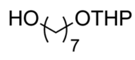
1x₁ → **2x₁**

Entry	R–OTHP	Product number	Yield[a,b] (%)
1	 **$1a_1$**	**$2a_1$**	91
2	 **$1b_1$**	**$2b_1$**	90
3	 **$1c_1$**	**$2c_1$**	89
4	 **$1d_1$**	**$2d_1$**	88
5	 **$1e_1$**	**$2e_1$**	85
6	 **$1f_1$**	**$2f_1$**	80[c]
7	 **$1g_1$**	**$2g_1$**	81
8	 **$1h_1$**	**$2h_1$**	80[c]
9	 **$1i_1$**	**$2i_1$**	97
10	 **$1j_1$**	**$2j_1$**	81

[a] Isolated yield after column chromatography. [b] Standard conditions: 0.05 eq. of $AlCl_3$, 1.25 eq. of $PhMe_2SiH$, 0.5 h. [c] 2.00 eq. of $PhMe_2SiH$, 1.25 eq. of $PhMe_2SiH$, 0.5 h.

Table 4 Optimization of chemoselectivity for THP ethers with unprotected hydroxyl groups



Entry	HO–R–OTHP	R_3SiH	Solvent	Product[a] (%)
1	 **$1k_1$**	$PhMe_2SiH$	CH_2Cl_2	**3k** (100)
2		iPr_3SiH	Toluene	**$2k_6$** (58)[b]
3	 **$1l_1$**	iPr_3SiH	Toluene	**$2l_6$** (70)

[a] Isolated yield after column chromatography. [b] 1,7-Heptanediol (**3k**) was also obtained.

final reaction mixture showed no traces of silane alcoholysis, reduction of the alcohol,[12] hydrosilylation of the alkyne, or cleavage of the acetal.

Finally, to explore the possible extension of the method to linear acetals, we subjected the methoxymethyl ether (MOM) **$1a_2$** and the ethoxyethyl ether (EE) **$1a_3$** to the standard conditions (Table 5). In these cases the desired product, silyl ether **$2a_1$**, was accompanied by the alkyl ethers **$4a_x$** due to the alternative cleavage of the acetals, the **$4a_x$** : **$2a_1$** ratio being greater for the α-substituted acetal **$1a_3$** (27%) than for the α-unsubstituted **$1a_2$** (16%) (Table 5, entries 2 and 3). In both cases the global yield of **$2a_1$** and **$4a_x$** exceeded 90%.

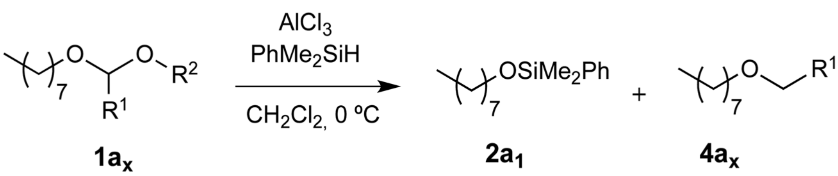
Mechanism

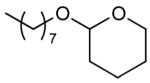
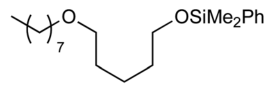
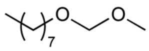
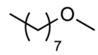
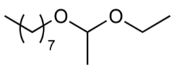
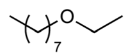
On the basis of the above experimental evidence, the tentative mechanism shown in Scheme 2 is proposed. Since pre-mixing of catalyst and silane seems to be critical for the efficiency of the reaction, the activation of the silane by aluminium through hydride abstraction appears to be a key step.[13] Following that, two pathways are possible (Routes A and B), corresponding to the two ways in which the reactive silyl-aluminium species can coordinate to the acetal oxygen atoms to form the six-membered cyclic transition structure of a concerted mechanism[14] in which charge pushing by one of the oxygens drives cleavage of the other acetal bond. Cleavage releases a silyl ether (**$2a_1$** or **$6a_x$**) and a carbocation (**I** or **II**) that subsequently evolves to compound **$5a_x$** or **$4a_x$**.[15] For THP ethers only Route A proceed well, Route B requiring the opening of the pyrane ring; but for the linear acetals both pathways may proceed well, leading to the observed mixtures of compounds **$2a_1$** and **$4a_x$**.

Conclusions

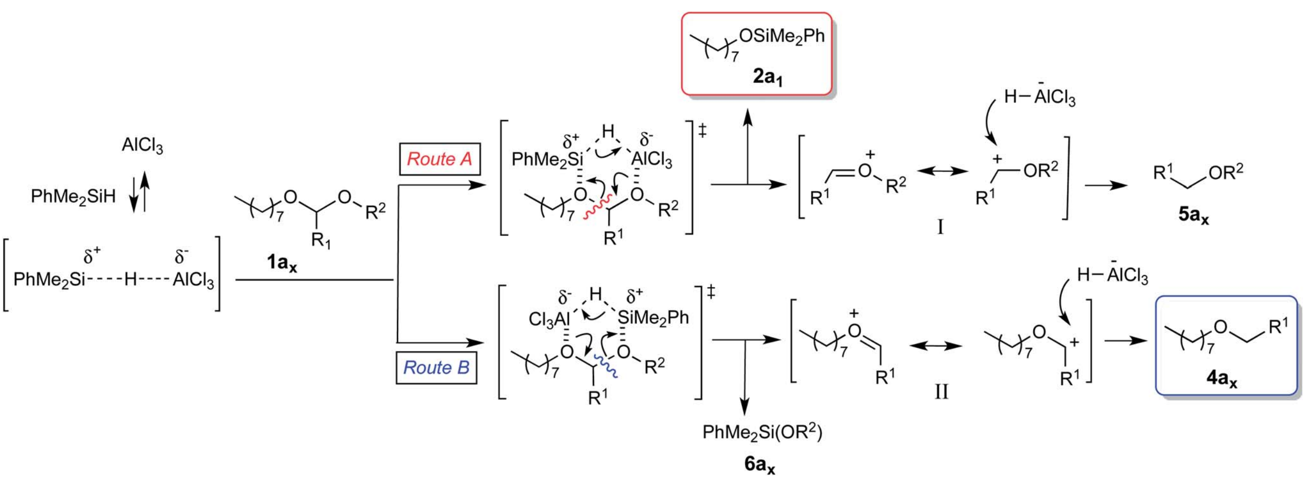
Summing up, we have developed an expedient procedure for the direct transformation of tetrahydropyranyl-protected alcohols into the corresponding silyl ethers by their reaction with hydrosilanes in the presence of catalytic amounts of $AlCl_3$. The advantages of this protocol – mild reaction conditions, short reaction times, applicability to a variety of substrates (including tertiary alcohols), high yield, and total chemoselectivity even in

Table 5 Extension to linear acetals



Entry	Substrate	$2a_1$ (%)	$4a_x$ (%)	Total yield[a] (%)
1	 **$1a_1$ (OTHP)** $R^1 + R^2 = -(CH_2)_4-$	91	 **$4a_1$** (0)	91
2	 **$1a_2$ (OMOM)** $R^1 = H$; $R^2 = Me$	78	 **$4a_2$** (15)	93
3	 **$1a_3$ (OEE)** $R^1 = Me$; $R^2 = Et$	68	 **$4a_3$** (25)	93

[a] Isolated yield after column chromatography.



Scheme 2 Tentative reaction mechanism.

the presence of free hydroxyls or unsaturated functional groups – make it an attractive and useful addition to the present methodological armamentarium.

Acknowledgements

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10 Pre-mixing of catalyst and silane was critical for the success of the reaction, since direct mixture of the three reagents led mainly to the free alcohol.

11 A small amount of 1,7-heptanediol (**3k**) was also obtained.

12 The system $HSiR_3/B(C_6F_5)_3$ has been used for both the silanolysis and the reduction of alcohols: (*a*) J. M. Blackwell, K. L. Foster, V. H. Beck and W. E. Piers, *J. Org. Chem.*, 1999, **64**, 4887–4892; (*b*) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 6179–6186.

13 Silyl cation formation has been reviewed in: J. B. Lambert, L. Kania and S. Zhang, *Chem. Rev.*, 1995, **95**, 1191–1201.

14 Piers has proposed a sequential mechanism for Lewis-acid-catalysed silanolysis of alcohols (see ref. 12), but in our case $AlCl_3$ is not able to promote the *O*-silylation of a free hydroxyl group.

15 The non-detection of dimethyl ether ($\mathbf{5a_2}$) and diethyl ether ($\mathbf{5a_3}$) is attributed to their extreme volatility. The alcoxysilanes $\mathbf{6a}_x$ were possibly eliminated during the working-up of the reaction.