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Reductive deprotection of silyl groups with Wilkinson's catalyst/catechol borane

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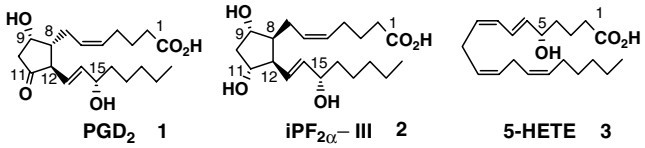
Abstract—Traditionally silyl groups are deprotected with acids and fluorides. These methods are, however, less discriminating when multi-silyl groups are present in the same molecule, resulting in lower yields of the desired products. The manipulation of these functions during the total synthesis of natural products, for example, prostaglandins and isoprostanes, requires the selective protection and deprotection of these groups.

We are reporting here on a mild, selective and efficient method for the reductive deprotection of silyl groups using Wilkinson's catalyst/catechol borane or catechol borane alone.

Silyl groups are used as hydroxyl-group protecting agents in organic synthesis.[1] Deprotection of the silyl ethers can be effected by using acidic conditions or a fluoride source such as tetrabutylammonium fluoride (TBAF) and sometimes by hydrogenolysis.[2–4] However, deprotection using acid and TBAF often results in poor selectivity when compounds with polyhydroxy functions (e.g., Scheme 1) carry one or more silyl protecting groups (vide infra). Also, in the case of TBAF, undesired silyl transfer often occurs.[5,6] Furthermore, use of acidic reagents and TBAF requires a work-up and purification step resulting in somewhat lower yields.

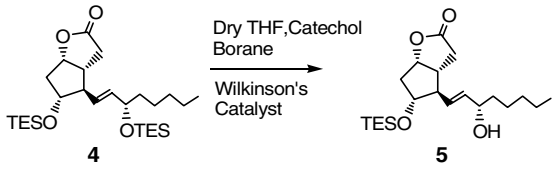
We are reporting here a general method by which hydroxy silyl protecting groups such as triethyl silyl (TES), tri-*n*-butyl silyl (TBS) and triisopropyl silyl (TIPS) are removed by a reductive process involving catechol borane (CB) and Wilkinson's catalyst. Scheme 2 illustrates the process. Aside from the unique selectivity of the deprotection process (Table 1), a great advantage of this procedure is that no aqueous work-up is required.



Scheme 1. Eicosanoids.

The examples we selected in Table 1 illustrate the specific and general applicability of this method.

A typical procedure is as follows: To a solution of the substrate (0.115–0.3 mmol) in dry THF (0.4–1.4 ml) was added Wilkinson's catalyst (3–9 mol %). The reaction mixture was cooled to 0 °C and then catechol borane (3–9 equiv) was slowly added under a nitrogen atmosphere. The ice bath was removed after 10 min



Scheme 2. Reductive deprotection of silyl group by Wilkinson's catalyst and catechol borane.

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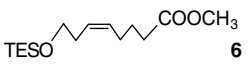
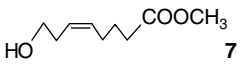
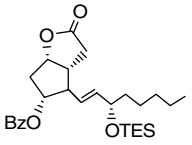
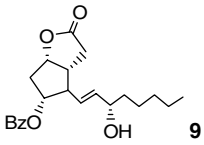
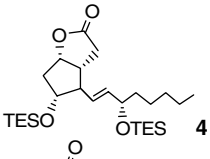
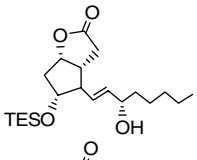
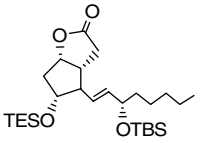
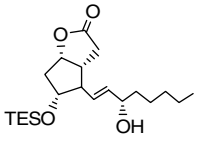
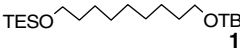
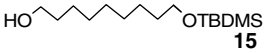
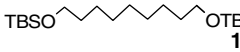
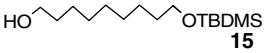
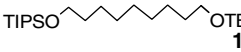
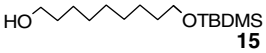
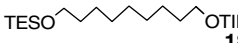
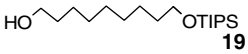
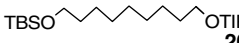
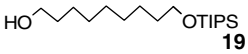
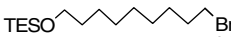
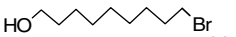
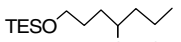
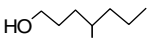
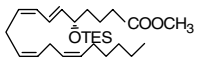
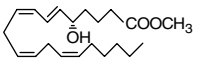
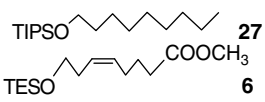
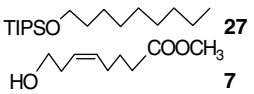
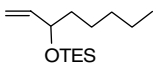
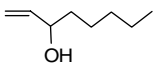
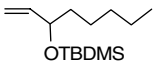
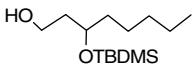
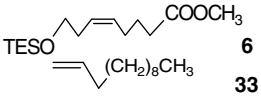
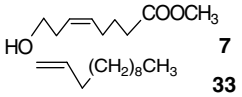
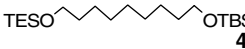
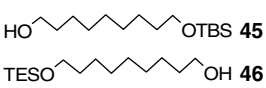
Table 1. Desilylation of silyl groups using Wilkinson's catalyst/catechol borane

Entry #	Substrate	Product	Catechol borane equivalents	Wilkinson's catalyst (mol %)	Reaction time (h)	Isolated yields (%)
1	 **6**	 **7**	3 9 3	3 8 —	16 04 70	90 91 80[a]
2	 **8**	 **9**	6	6	18	91[13]
3	 **4**	 **5**	6	6	16	93
4	 **12**	 **13**	6	6	22	92
5	 **14**	 **15**	3 3 9	3 — 9	09 34 06	95 90 96
6	 **16**	 **15**	3 6	3 —	18 48	95 92
7	 **17**	 **15**	9	9	48	90
8	 **18**	 **19**	3	3	10	90
9	 **20**	 **19**	3	3	18	90
10	 **21**	 **22**	6	6	09	91
11	 **23**	 **24**	5	5	3	91[b]
12	 **25**	 **26**	6	6	18	89
13	 **27** **6**	 **27** **7**	3	3	16	90
14	 **29**	 **30**	3	3	15	65[c]
15	 **31**	 **32**	3	3	12	85
16	 **6** **33**	 **7** **33**	3	3	16	91
17	 **44**	 **45** **46**	3	3	8	72[d] 18[d]

[a] 10% starting material recovered. Some impurities developed over time. 80% isolated yield.
[b] 80% conversion.
[c] Product is low boiling and volatile.
[d] Ratio determined by NMR.

and stirring continued until the disappearance of the starting material. The reaction mixture was passed through a silica column and the product isolated. Proton and ^{13}C NMR confirm the identity of the products.

As can be seen from Table 1, the reductive deprotection of TES, TBS and TIPS proceeds in high yield and can also occur without Wilkinson's catalyst albeit at a much reduced reaction rate. For example in entry 1 the reaction proceeds four times faster with the catalyst than without it. The use of a higher percentage of the catalyst and borane shortens the reaction time further. The reactions are clean. Two byproducts (**40** and **41**) containing the silyl moiety were isolated and identified. A control experiment in which substrate **16** (entry 6) was treated with Wilkinson's catalyst 7 mol % (without catechol borane) for 40 h, the starting material was recovered in 97% yields.

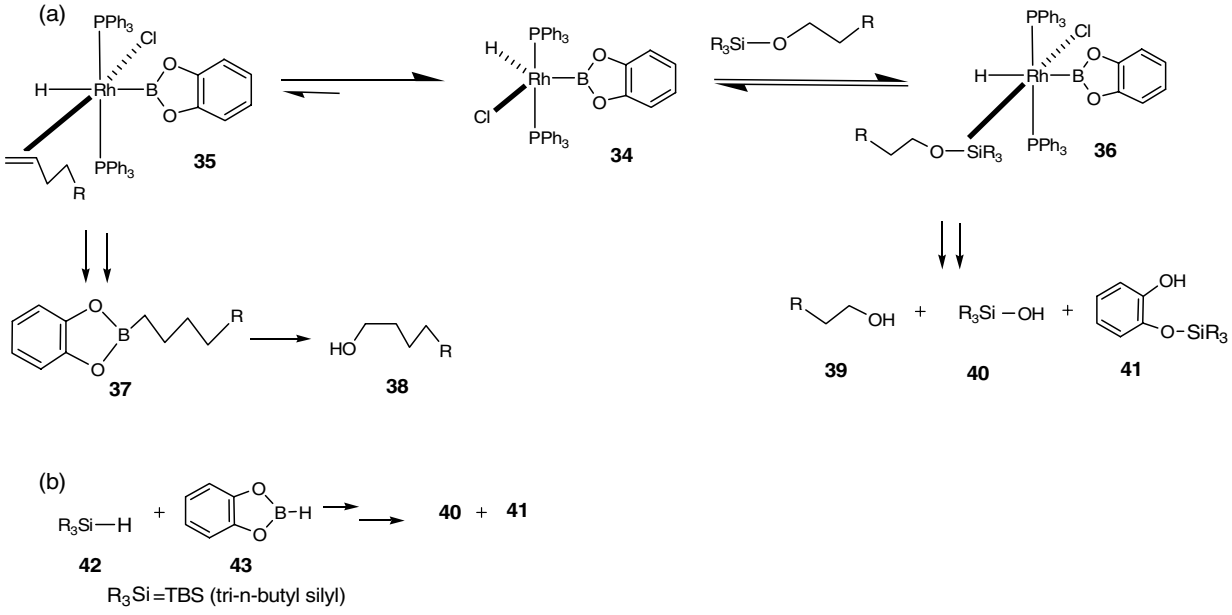
For the method to be useful and to suit our purpose in the total synthesis of eicosanoids, we needed to be able to selectively deprotect different silyl groups. Entries 5, 8 and 11 show that TES can be removed in the presence of TBS, TIPS and *tert*-butyldimethylsilyl (TBDMS) groups. Likewise, TBS entries 9 and 6 are selectively deprotected in the presence of TIPS and TBDMS; also, TIPS can be reductively deprotected in the presence of TBDMS. Whereas the TES protecting group can easily be removed with acid, the yields drop when multi-silyl and multi-functional groups are present (e.g., entry 2). Entry 11 shows that TES can be removed in the presence of TBS. The selectivity is not as good when TES and TBS are on primary carbons (e.g., entry 17). In all the cases studied, the TBDMS group is resistant to deprotection by this procedure.

Very importantly all these reductive deprotections can be accomplished in the presence of double bonds whether trans, cis or primary. Entries 1–4 and 12–16 show that olefins are unaffected by the deprotection procedure. Also, halogens (entry 10) and esters (entries 1 and 12) are unaffected by the deprotection.

Stable silyl protection groups such as TBDMS and *tert*-butyldiphenylsilyl (TBDPS),[4] although extremely useful, are also more difficult to remove, sometimes resulting in lower yields. Also in molecules such as **8**, acid and basic deprotection conditions result in substantial partial elimination of the silyloxy group to yield the α,β-unsaturated derivative.

Entry 2 is especially interesting as it shows the exclusive deprotection of a secondary TES at C-15, leaving intact the secondary TES on carbon 11 (Scheme 2). (The carbon numbers are based on the full prostaglandin molecule, Scheme 1.) Such selectivity, which could be very handy in the synthesis of prostaglandins,[7] could be of a steric nature and related to the substrate itself.[12] The orientation of the side chain at C-12, which is *beta* as opposed to the other three substituents in the 5-membered ring at C-8, C-9 and C-11, which are all *alpha*, may result in better accessibility of the silyloxy group at C-15 to the catalyst. This interpretation of the results is supported by the experiment in entry 4 in which complete selectivity for deprotection of the bulkier TBS at C-15 is observed.

Entry 12 is noteworthy as the deprotection of the silyl group occurs in high yield in the presence of two isolated double bonds and one conjugated diene. Our previous experience shows that deprotection of the silyl group in **25**, if done with fluoride, results in substantial lactonization and reduced yields. Equally, acid deprotection results in a low yield due in large part to lactonization and also to the formation of several byproducts. In this case the yield of the desired product **26** is around



Scheme 3. Interaction of silyl groups with Wilkinson's catalyst–catechol borane complex **34**.

30%. The deprotection of 5-hydroxy-eicosatetraenoic acid (5-HETE) by the procedure described here is an important result since 5-HETE **3** is the natural substrate for 5-hydroxy eicosanoid dehydrogenase (5-HEDH)[8] and its total synthesis is constantly required. This deprotection procedure can improve our overall yields by ~50%.

As mentioned above, the TBDMS group in entries 5, 6 and 7 is resistant to reductive deprotection. We found it very interesting that in entries such as 1–4 and 12–16, in which there is a double bond, hydroboration did not occur. The experimental conditions used in Table 1 are the most commonly used for effecting hydroboration.[9] Since the time scale for the two reactions, silyl deprotection and hydroboration, are also comparable, one would have expected some hydroboration to occur in entries 14 and 16. To ascertain that the hydroboration process can occur under our reaction conditions we subjected **29** and **31** (entries 14 and 15) to identical reductive desilylation procedures. As can be seen, the silyl deprotection of the TES occurred very efficiently. Also the hydroboration of **31** proceeded smoothly and the hydroboration product **32** was isolated in 90% yield.

To probe this point further, we performed the experiment in entry 16. It was designed to allow an equimolar mixture of a primary olefin **33** and a separate TES derivative **6** to compete for the catalyst. As can be seen, the TES group was removed in excellent yield and the primary olefin **33** was recovered unchanged.

It has been reported[10,11] in studies of the Wilkinson-catalyzed hydroboration of olefins that an intermediate such as **34** (Scheme 3a) is formed, which then complexes with an olefin to result in a boronate derivative **37**, which is subsequently oxidized to afford alcohol **38**.

In order to explain the lack of hydroboration, one assumption can be, using the published hydroboration complex **34,** that the silyl derivative complexes with the borane rhodium derivative **36** and does so more efficiently than complexation with the olefin. One must also assume that at the end of the catalysis cycle the catalyst is in a form which cannot be used for hydroboration. On the assumption that one of the primary products formed in this reduction is the silane, we added commercial TBS silane **42** and catechol borane in dry THF and observed the formation of **40** and **41** (Scheme 3b). We are attempting to clarify some aspects of the mechanism of the desilylation reaction in the presence of olefins.

Acknowledgments

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12. An interesting suggestion by the reviewer that the selective deprotection in entries 2, 3 and 4 at C-15 may be due to the allylic nature of the silyl ether is worth considering.
13. Spectroscopic data of substrate **9** in Table 1: ^{1}H NMR (400 MHz, $CDCl_3$): 0.806 (t, 3H), 1.181–1.267 (m, 5H), 1.341–1.525 (m, 4H), 2.139–2.189 (m, 1H), 2.423–2.683 (m, 2H), 2.70–2.827 (m, 2H), 4.979–4.995 (m, 1H), 4.979–5.010 (m, 1H), 5.157–5.20 (m, 1H), 5.485–5.611 (m, 2H), 7.193–7.393 (m, 2H), 7.479–7.498 (t, 1H), 7.912–7.932 (d, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 9.75, 18.29, 20.71, 27.40, 30.6, 32.95, 33.30, 38.44, 49.70, 67.93, 74.79, 78.99, 124.07, 124.26, 125.35, 129.08, 132.11, 161.82, 172.15.