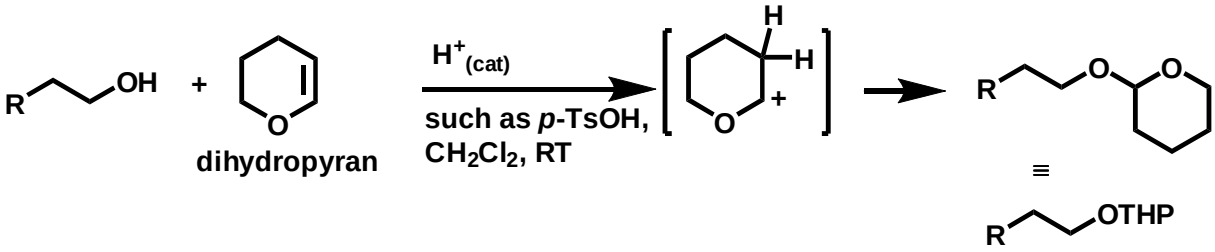
Alcohol Protecting Groups

It has been presented in 59-331/333 that alcohols can be protected from much of their reactivity by temporarily converted into a simple derivative, most often a type of ether. A reaction that is normally incompatible with the alcohol can then be done on some other part of the molecule, and the end, the alcohol can be recovered by 'deprotection' of the protecting group. The one protecting group that you were given in 59-331 is the OTHP group, which is a type of acetal…

1) **OTHP/OMOM Protecting Group**



The OTHP protecting group is stable to many reagents that would normally consume an alcohol. These include..

i) Bases such as NaH, KO^tBu, LDA, LiTMP

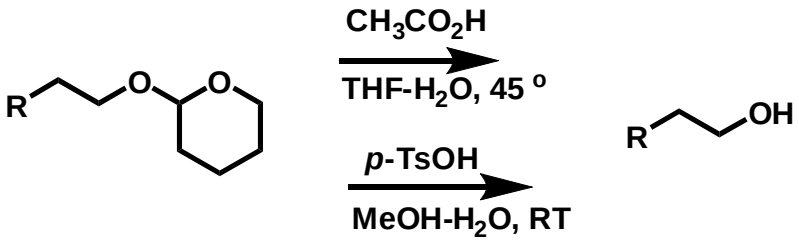
ii) Nucleophiles such as $NaOCH_3$, X^-, lithium enolates, RLi (organilithiums), RMgBr (Grignards), $Ph_3P{=}CH_2$ (Wittig reagents)

iii) Reductants such as H_2 and Ni^o or Pd^o, Na/NH_3, $NaBH_4$, $LiAlH_4$, DIBAL-H ($^iBu_2AlH$)

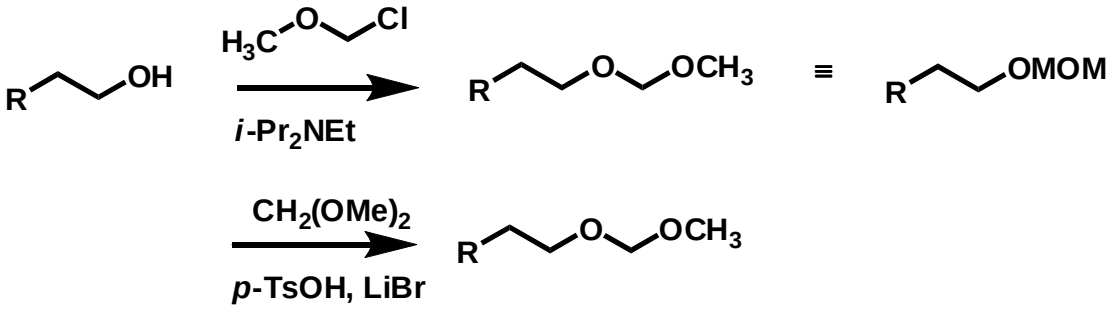
iv) Oxidants such as OsO_4, PCC/PDC, Swern, H_2O_2

-note that ozone (O_3) does react

When it is desired to recover the alcohol, normally this is done via some combination of H^+ and H_2O, taking advantage of the acid sensitivity of acetals.



If you have taken alternative courses, you may be aware of other acetals that are very similar to the OTHP, such as the OMOM protecting group.



Two sets of reagents have been given because chloromethyl methyl ether works really well, but the reagent is a carcinogen.

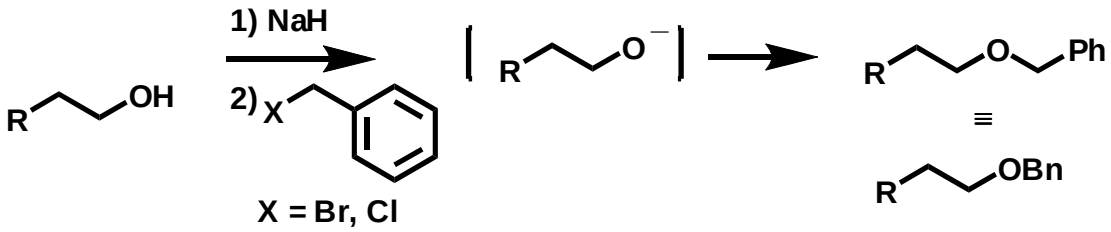
In any event, the OMOM protecting group is stable and unstable to a similar set of reagents as the OTHP. It also cleaves under acidic conditions, but the cleavage is slightly slower, so selectivity is possible. On the other hand, if there were protecting groups that were cleaved under completely different types of conditions, this selectivity business would be a lot easier. A selection of those protecting groups will be covered here.

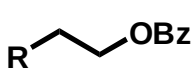
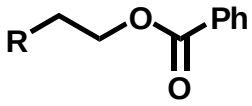
It is also worth mentioning that there are many other protecting groups that are slight variations on the same theme. One example is the ethoxyethyl group

ethoxyethyl

2) **Benzyl (OBn) Protecting Group**

A benzyl ether is a common and readily prepared protecting group for alcohols, with a conceptually or chemically distinct (we'll call this *orthogonal*) way of deprotecting. Since benzyl halides are wonderful substrates for S_N2 reactions, by far the most common way of making them is from the alkoxide derived from the alcohol.

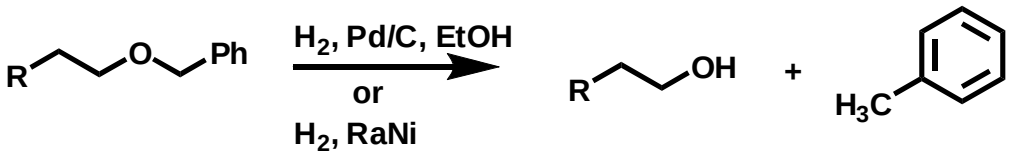


Note: Don't confuse this with  **which is** 

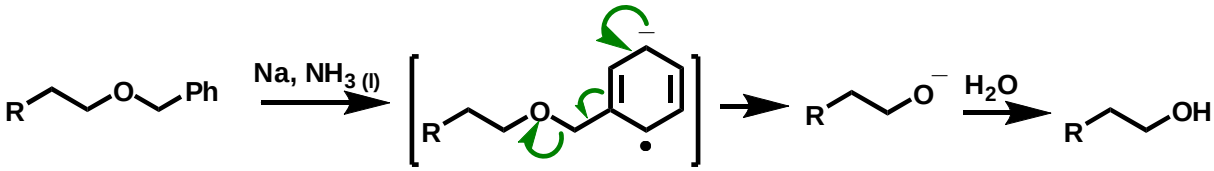
The O-benzyl group is stable to many of the same reagents as the OTHP, with the exception of a couple (highlighted below). Furthermore, it is *far* more stable to acid that the OMOM or OTHP group. Yes, very, very strong acids will cleave the OBn, traditional things like pH = 1 cause no problems, whereas the OTHP and OMOM deprotect.

On the other hand, under conventional hydrogenation conditions, benzyl ethers tend to do a C-O bond hydrogenolysis, and this is a very gentle way to do its deprotection. This is due to the fact the

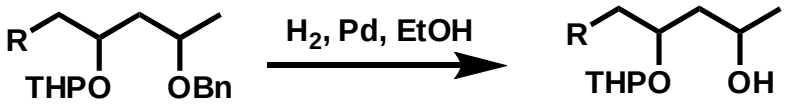
benzyl substrate are excellent for oxidative addition reactions of Pd^{o} or Ni^{o}. Of course, one has to look out for any C=C or CΞC bonds elsewhere in the molecule, since they can hydrogenate competitively.



Alternatively, benzyl ethers are also unstable to Birch reduction conditions (Na, $NH_{3(l)}$). This is a much less used method of deprotection, but *can* be used. With respect to both hydrogenolysis and Birch conditions, the OMOM and OTHP groups are generally stable.

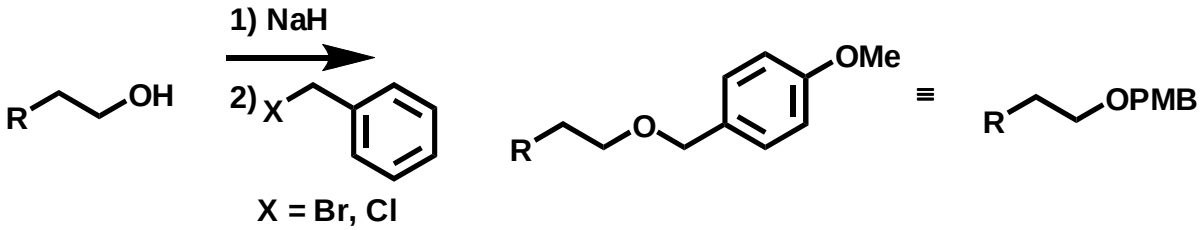


So an example of a selective deprotection is as follows.

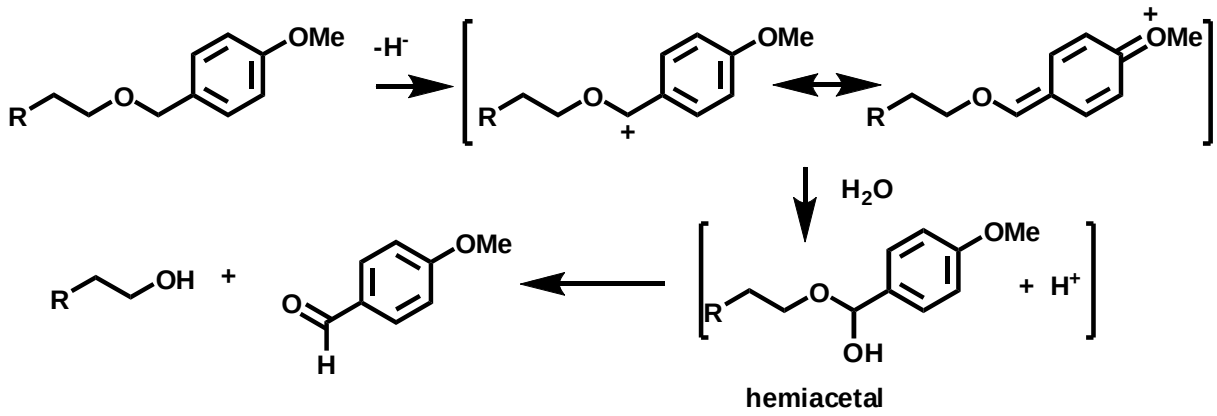


3) *p*-Methoxybenzyl Protecting Group (R-OPMB)

The OPMB protecting group looks a lot like a normal benzyl ether, but with a catch. Certainly though, since it's also a type of benzyl ether, it is usually put on just like a benzyl ether.

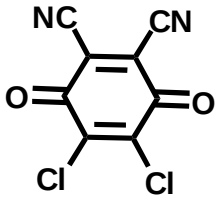


The reactivity of this group to most things is just like a benzyl ether (including potential deprotection by H_2, Pd), but there is more electron donation now, to particularly stabilize a carbocation at the benzylic site. If a reagent can be found to abstract H^- (*hydride*), it can be deprotected with H_2O. In principle a simple benzyl ether could do this, but they are much *less* reactive so that they are generally stable (or at least the PMB can be taken off first)



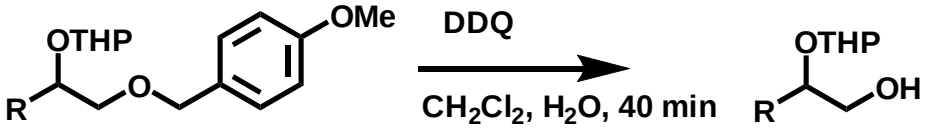
The most common reagents to do this hydride abstraction are:

i) DDQ



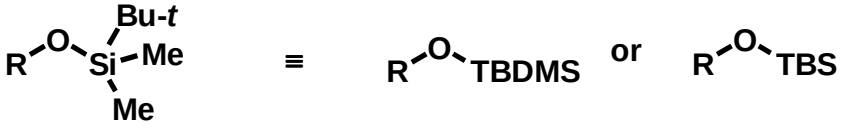
DDQ

ii) Ph_3C^+ BF_4^- (commonly called trityl cation)

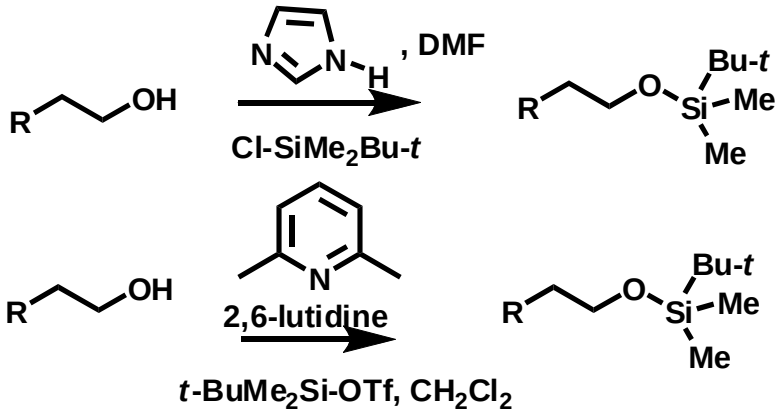


4) *tert*-Butyldimethylsilyl Ethers (R-OTBDMS or **R-OTBS)**

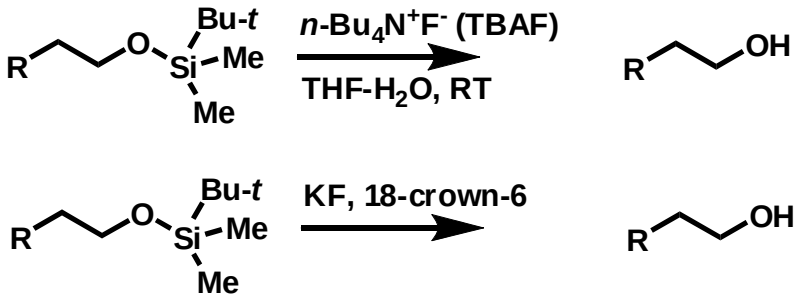
A completely different mode of deprotection is available if we leave the idea of using R-O-CR_3 as the alcohol protecting group, and go to R-O-SiR_3. Certainly the protecting group R-O-$SiMe_3$ is known, and easy to make, but in this case the Si-O is too susceptible to H_2O, and usually doesn't survive things like an aqueous workup of a reaction, or chromatography. On the other hand, these silyl ethers get more stable if there are groups bulkier than methyl on silicon, and many such as R-O-$SiEt_3$ and R-O-$Si(^iPr)_3$ (also known as R-O-TIPS) as known. By far, the most commonly employed case has one of the methyl group of TMS replaced by a *tert*-butyl group.



The normal preparation uses imidazole as base and DMF as solvent. Otherwise, more conventional bases and solvents can be used, but a more reactive replacement for TBDMS-Cl must be used as a silylating reagent.



The deprotection of TBDMS ethers has a special feature. Certainly strong acids (pH 2) or strong bases (pH >12) will remove silicon, but silicon has a tremendous affinity for fluoride ion that almost nothing else has. As a result, a good F^- source (particularly TBAF, *n*-$Bu_4N^+F^-$) will cleave the Si-O bond and affect pretty much nothing else. This is normally highly selective.

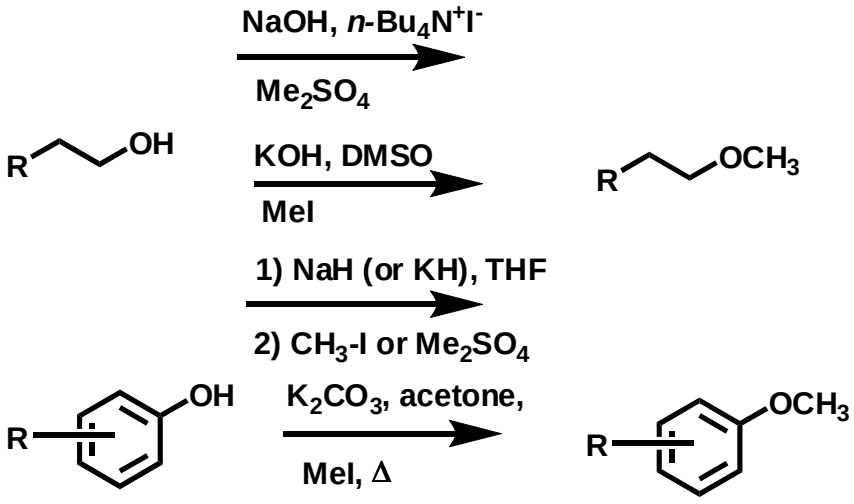


The deprotection can be called "S_N2-like"; I'd be interested in speculation as to why this term is used.

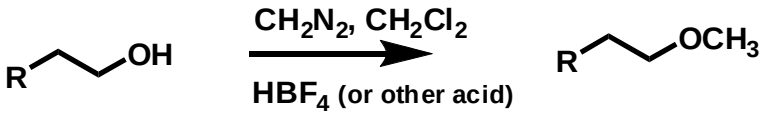
Once again, there are many useable variations on this protecting group, such the *tert*-butyldiphenylsilyl group (TBDPS) and the triisopropylsilyl group (TIPS). These are more stable to acid than the TBDMS, but also cleaved by F^-.

5) Methyl Ethers (R-OMe)

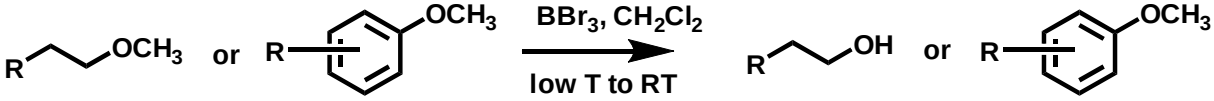
Methyl ethers have been left last for a reason. For most of the methods it is *the* most robust of the protecting group, and in most instances it is the 'last' group to come off. It is normally made by the Williamson ether synthesis (involving an S_N2 reaction of the alkoxide); the base employed vaies with the substrate. Note for phenols, a weaker base can be used.



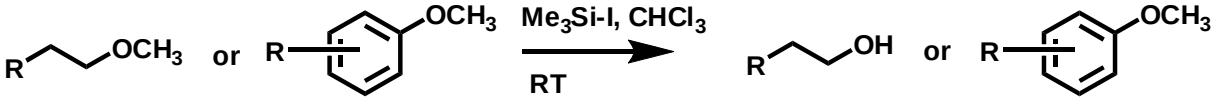
Or a specialty protocol that doesn't use a base per se.



These groups are stable to pretty much everything that has been discussed until this point. For deprotection, generally a *very* strong acid is required, with a counterion that is nucleophilic (HBr, HI). In practice, the (very strong) Lewis acid analogue is the one used synthetically. The most common version is using BBr_3:

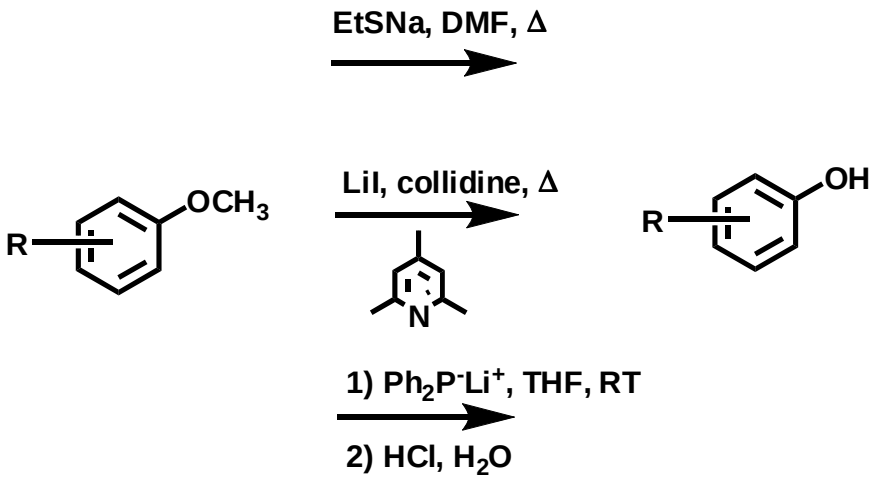


The second most common reagents is Me_3Si-I (TMSI):



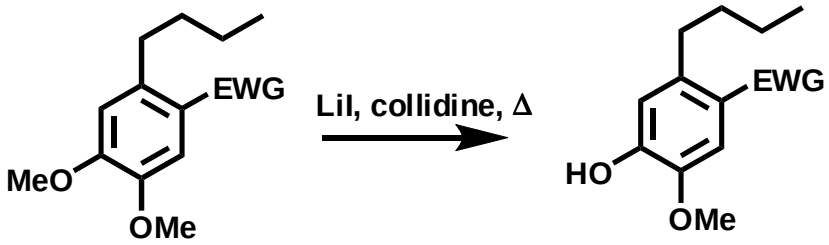
The 'problem' with this is, that these very aggressive conditions cleave pretty much ***all*** other protecting groups.

For phenols only, there is an option stemming from the fact that phenoxide ion (the alkoxide derived from phenol) is a leaving group, albeit a mediocre one. In these case, therefore, there is often success employing reagents that are really good nucleophiles. Some examples are below:



Therefore, in general the methyl ethers can be cleaved more rapidly than ethers that aren't as good at S_N2 reactions (ethyl, cyclohexyl ether, but *not* benzyl or allyl ethers).

It does mean that the presence of an electron withdrawing group on a benzene can be taken advantage of…



This is mainly in introduction to selective protective group chemistry. For a far more extensive version, with some really useful reactivity tables, see the Greene and Wuts books:
Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis"* 2nd Ed. (1991), 4th Ed. (2007)-my office; 3rd Ed (1999) Dr. Eichhorn's office