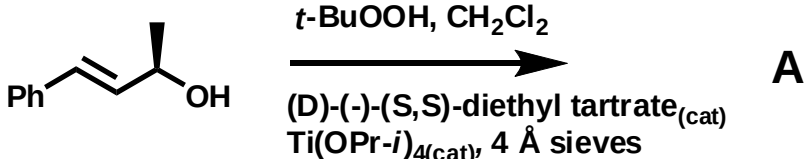
UNIVERSITY OF WINDSOR
CHEMISTRY AND BIOCHEMISTRY

Chemistry 59-531/431 **Dec. 14, 2012**
Final Examination **Time:3 hours**

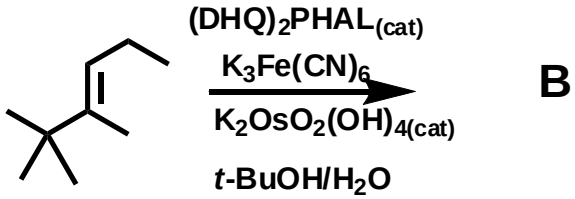
Answer all questions in the exam booklet.

1. Do any ten (10) 'letters'. (45 marks) Provide the major reaction product in each of the following transformations. Include stereochemical (relative and or absolute) information where it is relevant. I do wish you to show any intermediates that could be isolated. Mechanisms are not necessary, but showing your work may be a help. A warning, though…if you do the 1st letter of a series, you must do them all (i.e. you *can't* do **C** but not **D** / **E** or **I** but not **J).**

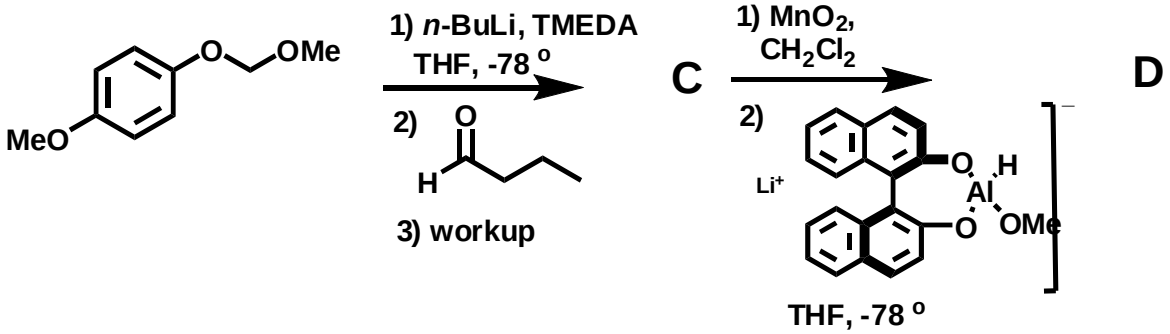
a) Material enantiomerically pure.



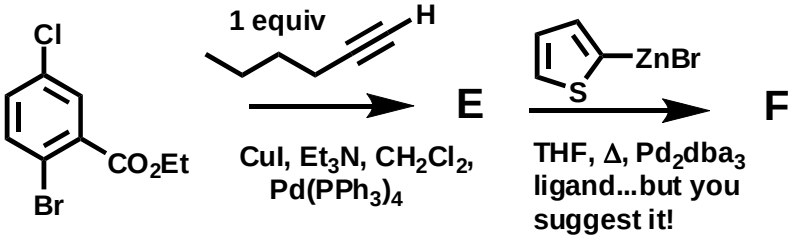
b) Stereochemical aspects are critical



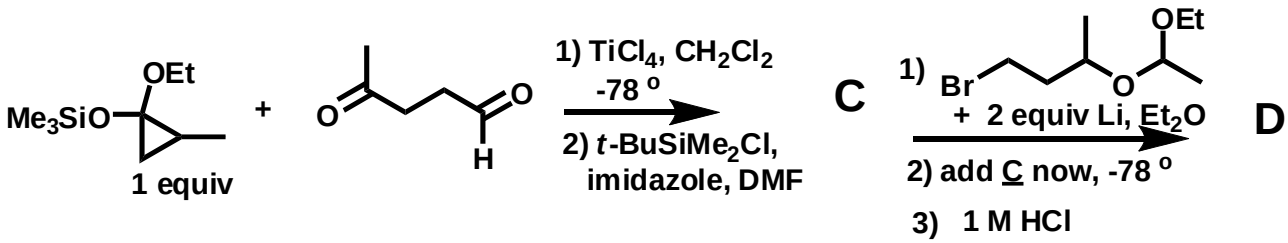
c) Stereochemical aspects are critical in the final step



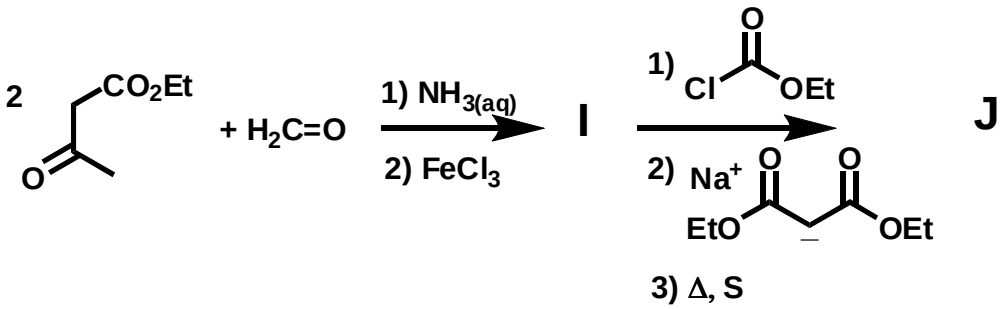
d).



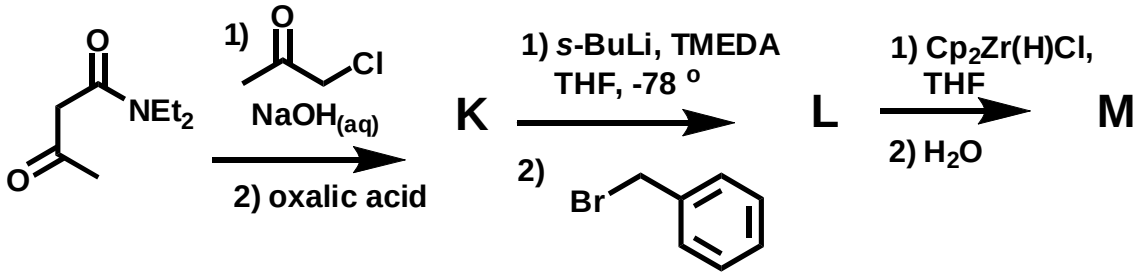
e)



f)

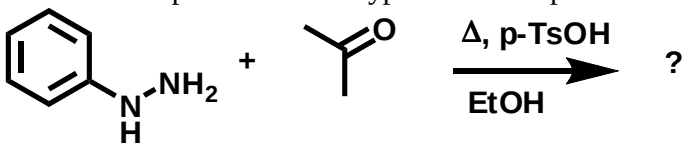


g)



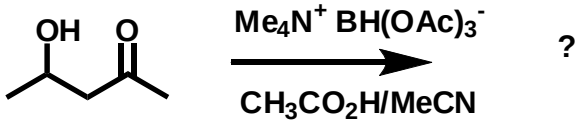
2. (**Total 30 marks**)

a) Give the complete mechanism of the following Fischer synthesis. You do not need to show the individual steps of an imine-type formation portion.

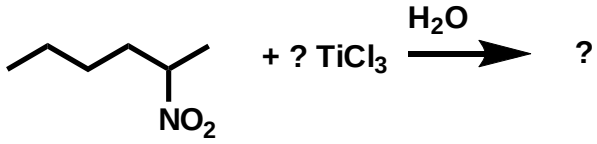


b) **Do *either* i) *or* ii) (but not both) and iii) (10 marks each).**

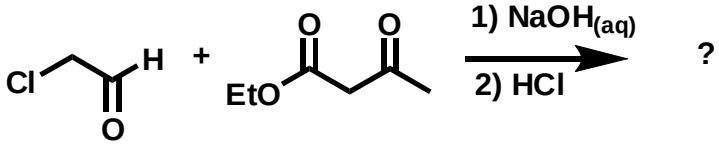
i) Show the mechanism of the highly diastereoselective reduction of a β-hydroxy ketone using the indicated borohydride reagent. Include the more and less favoured transition states of the reduction, and (of course) indicate the favoured diastereomer.



ii) Give a plausible mechanism for the NEF reaction. Once again, you need not show the discrete steps of hydrolysis of any imine-type intermediate to the carbonyl. The correct stoichiometry of the reaction should be implied in your answer.



iii) Propose a reasonable mechanism for the following Feist-Benary synthesis.

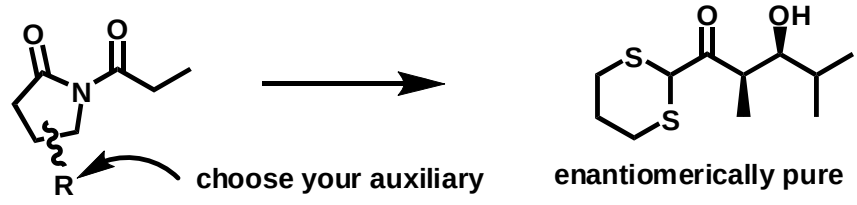


3. Do any five (5) of the following.

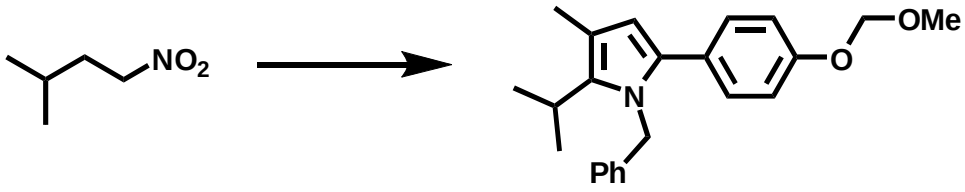
Show by equation how you would prepare the illustrated below from the given starting material. You may use any other reagents which you deem fit, as long as they are chemically stable. Show all reagents, conditions, and isolable intermediates; show the structures of all acronyms used (at least once), other than for solvents. Mechanisms are not necessary, but may be a help. (**Total 50 marks**)

a) Product to be enantiomerically pure.

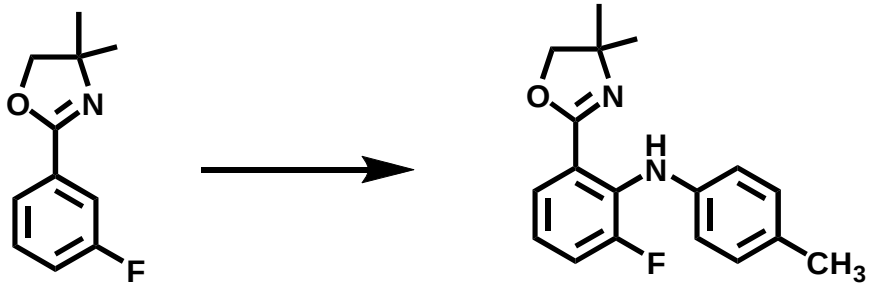
b)



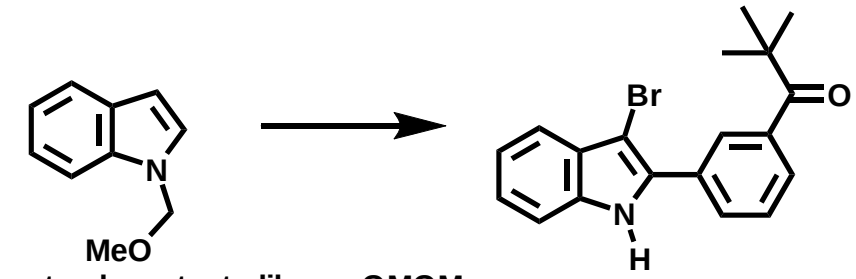
c)



d)

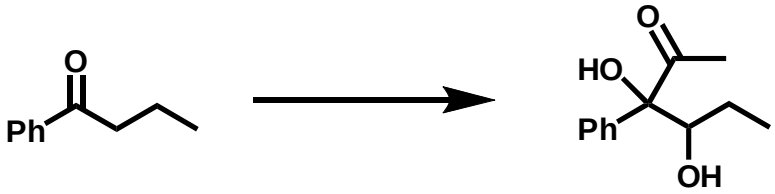


e)

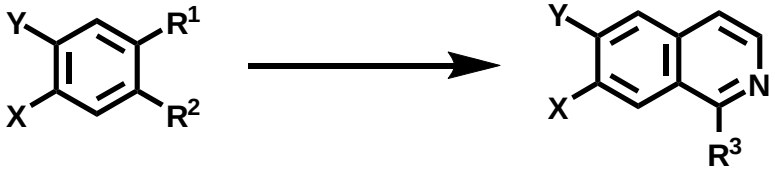


note: deprotects like an OMOM

f)



Bonus: Here's your chance to be creative. Generate your own isoquinoline synthesis from a benzene with an existing single simple R^1 or R^2 substituent. Give reasonable reagents and conditions, and what the nature of X and Y *need to be* or *would help the reaction* (and you tell me which). Also if R^3 or R^4 in the product needs to be something other than H, tell me that too.



Assorted Cheat-sheet info

Baldwin's Rules for Ring Closure

For tetrahedral substrates:

a) 3- to 7- exo-tet favoured
b) 5- to 6- endo-tet disfavoured

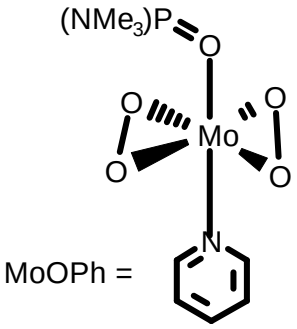
For trigonal substrates

a) 3- to 7- exo-trig favoured
b) 3- to 5- endo-trig disfavoured
c) 6- to 7- endo-trig favoured

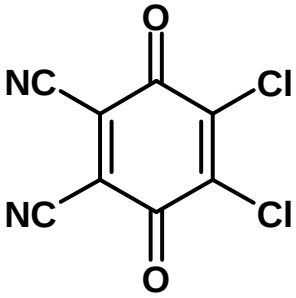
For digonal substrates

a) 3- to 4- exo-dig disfavoured
b) 5- to 7- exo-dig favoured
c) 3- to 7- endo-dig favoured

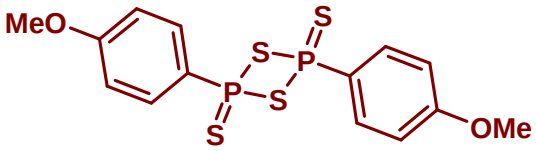
The structure of MoOPh is:



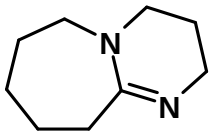
The structure of DDQ is



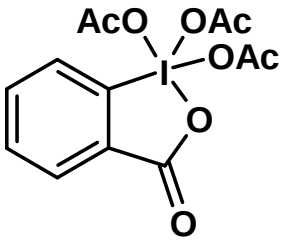
The structure of Laweson's reagent is



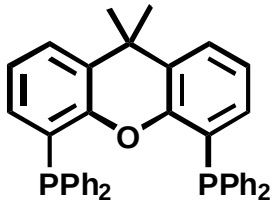
DBU (diazabicycloundecane) is



DMP (Dess-Martin periodinane) is



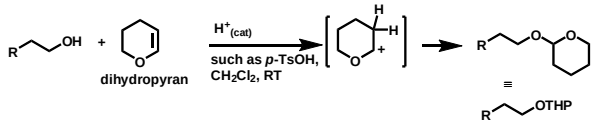
The structure of xantphos is



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…

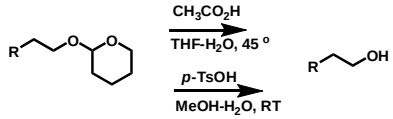
1) **OTHP/OMOM Protecting Group**



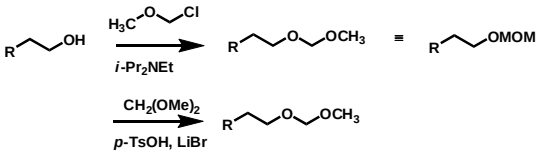
The OTHP protecting group is stable to many reagents that would normally consume an alcohol. These include..

i) Bases such as NaH, KO^{t}Bu, 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 ($^i Bu_2AlH$)
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.



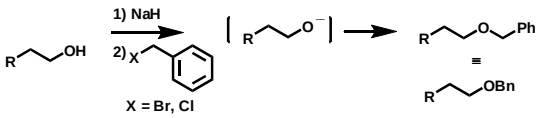
If you have taken alternative courses, you may be aware of other acetals that are very similar to the OTHP, such as the OMOM protecting group.



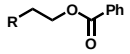
Two sets of reagents have been given because chloromethyl methyl ether works really well, but the reagent is a carcinogen.
In any event, the OMOM protecting group is stable and unstable to a similar set of reagents as the OTHP. It also cleaves under acidic conditions, but the cleavage is slightly slower, 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.

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

A benzyl ether is a common and readily prepared protecting group for alcohols, with a conceptually 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.

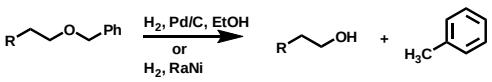


Note: Don't confuse this with 

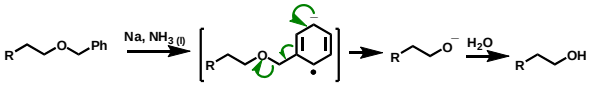
which is 

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 stronger 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.

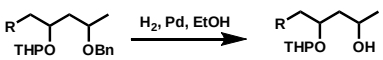
On the other hand, under conventional hydrogenation conditions, benzyl ethers tend to do a C-O bond hydrogenolysis, and this is a very gentle way to do its deprotection. This is due to the fact the benzyl substrate are excellent for oxidative addition reactions of Pd^o or Ni^o



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.

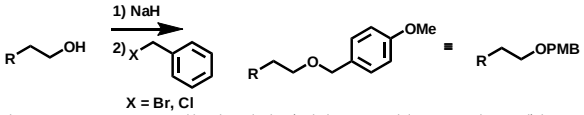


So an example of a selective deprotection is as follows.

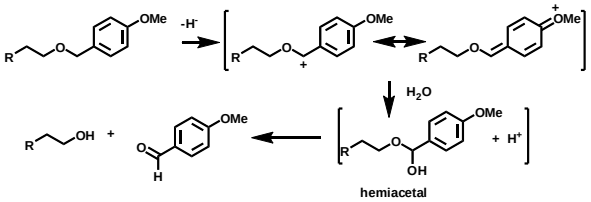


3) ***p*-Methoxybenzyl Protecting Group (R-OPMB)**

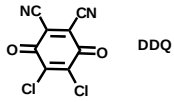
The OPMB protecting group looks a lot like a normal benzyl ether, but with a catch. Certainly though, since it's also a type of benzyl ether, it is usually put on just like a benzyl ether.



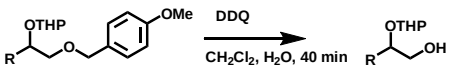
The reactivity in most was is just like a benzyl ether (including potential deprotection by H_2, Pd), but there is more electron donation now, to particularly stabilize a carbocation at the benzylic site. If a reagent can be found to abstract H^- (*hydride*), it can be deprotected with H_2O. In principle 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:

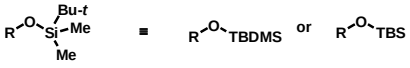
i) DDQ 

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

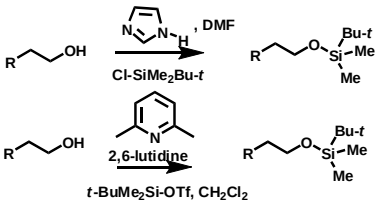


4) ***tert*-Butyldimethylsilyl Ethers (R-OTBDMS or R-OTBS)**

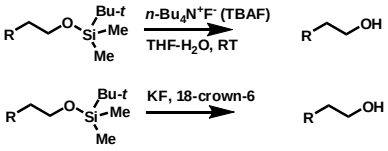
A completely different mode of deprotection is available if we leave the idea of using R-O-CR_3 as the alcohol protecting group, and go to R-O-SiR_3. Certainly the protecting group R-O-$SiMe_3$ is known, and easy to make, but in this case the Si-O is too susceptible to H_2O, and usually doesn't survive 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.



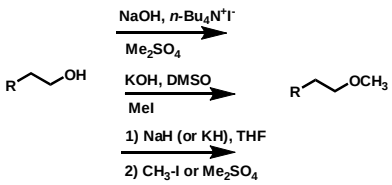
The deprotection of TBDMS ethers has a special feature. Certainly strong acids (pH 2) or strong bases (pH >12) will remove silicon, but silicon has a tremendous affinity for fluoride ion that almost nothing else has. As a result, a good F^- source (particularly TBAF, *n*-$Bu_4N^+F^-$) will cleave the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

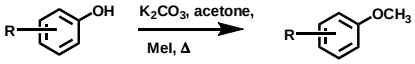


The deprotection can be called "S_N2-like"; I'd be interested in speculation as to why this term is used.

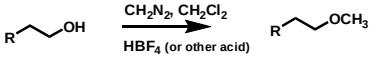
5) Methyl Ethers (R-OMe)

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 (and S_N2 reaction of the alkoxide); the base employed vaies with the substrate. Note for phenols, a weaker base can be used.

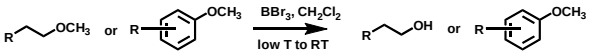




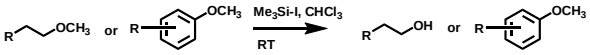
Or a specialty protocol that doesn't use a base per se.



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 use synthetically. The most common version is using BBr_3:

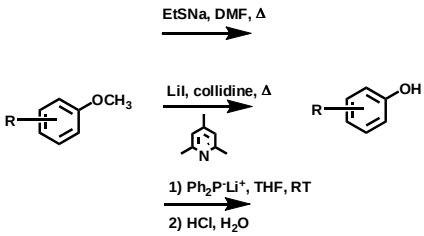


The second most common reagents is Me_3Si-I (TMSI):



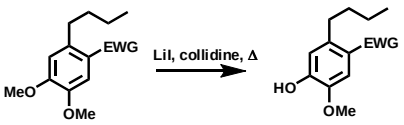
The 'problem' with this is, that these very aggressive conditions cleave pretty much ***all*** other protecting groups.

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 reacts (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, see 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