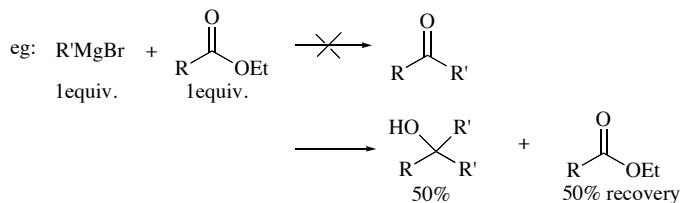
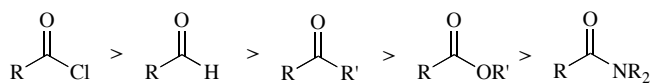
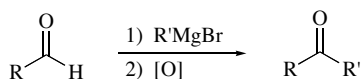


## Tips for taking exams in 852

## 1) Know the relative reactivity of carbonyl compounds

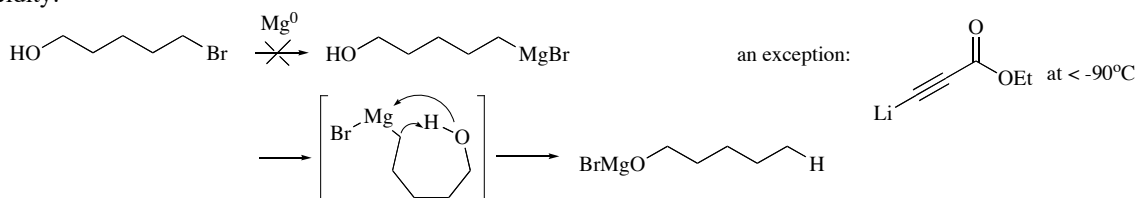


Use a 2 steps procedure:

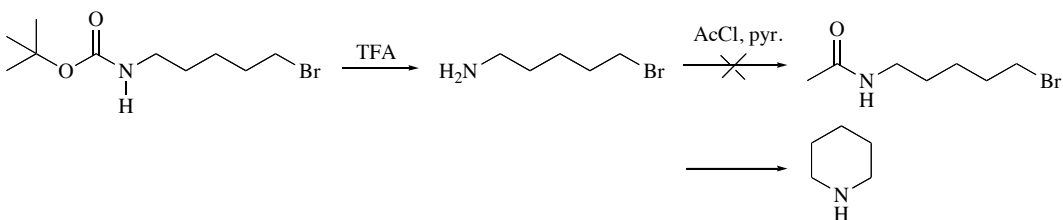
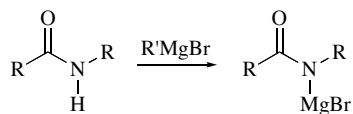
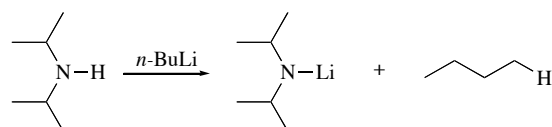


## 2) Beware of creating molecules that react with themselves.

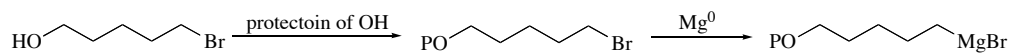
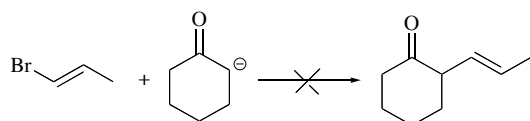
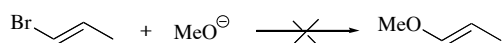
acidity:



This is also true for N-H bonds.



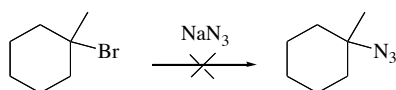
Solution:

3)  $\text{S}_{\text{N}}2$  reactions will not work with a leaving group on an  $\text{sp}^2$  carbon

Substitution on  $sp^2$  – carbons requires a multi-step process that begins with an oxidative addition usually with a transition metal. The synthetic chemist has access to both stoichiometric and catalytic versions of this process.



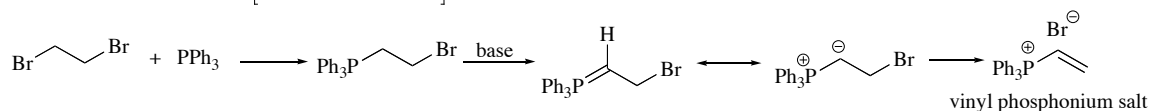
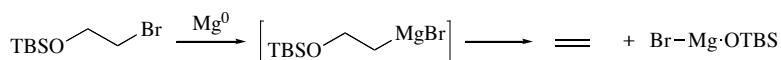
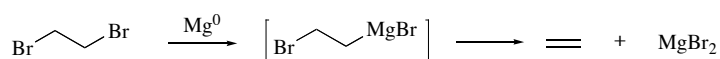
4)  $S_N2$  reactions in general don't work with leaving groups on a  $3^\circ$ -carbon



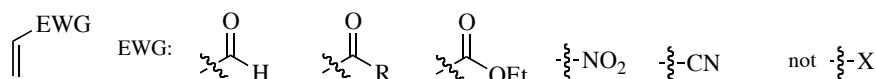
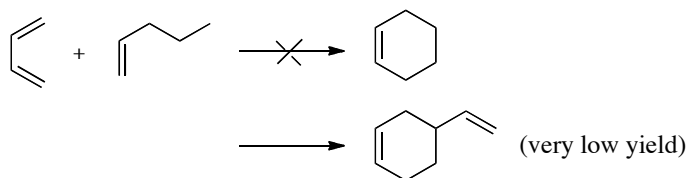
5) Know the structures (or acronyms) of reagents and catalysts for reactions of greatest importance. Use the correct enantiomer of the reagent or catalyst when a predictive model exists.

eg: Evans aldol reaction; Sharpless asymmetric epoxidation; Sharpless asymmetric dihydroxylation.

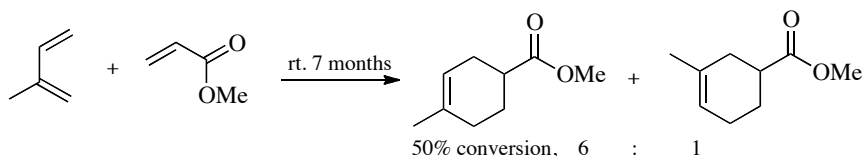
6) Beware that organometallic reagents will fragment if a leaving group is in the  $\beta$ -position.



7) Diels-Alder reactions require electron poor dienophiles



even with EWG, the D.A reaction can be slow.

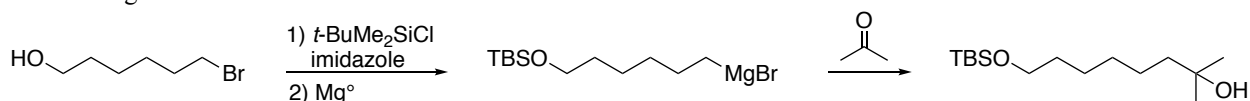


This reaction is complete in a few hours at  $150^\circ\text{C}$ ;

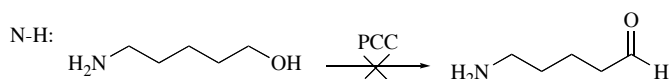
Lewis acid can accelerate this reaction at room temperature and lead to complete conversion.

8) Employ protecting groups when needed

a. From organometallics:

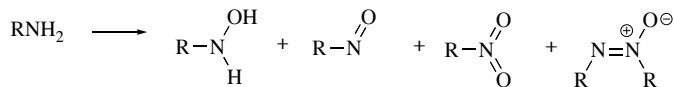


b. From oxidation (N-H bonds can be oxidized just like O-H bonds)

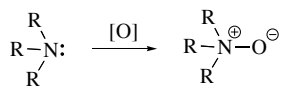


this won't work for 2 reasons:

1.  $\text{NH}_2$  can be oxidized.
2. the amino group would react with aldehyde.

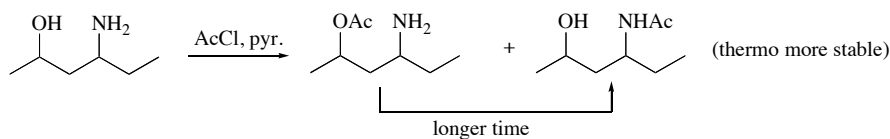


Solution: protect the  $\text{NH}_2$  as amide

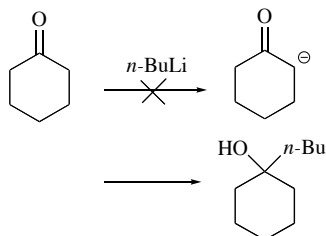


Solution: use  $\text{R}-\text{N}(\text{R}')\text{R}''-\text{BF}_3$  or reduce it back to  $3^\circ$  amine

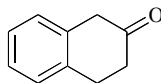
c. In nucleophilic addition



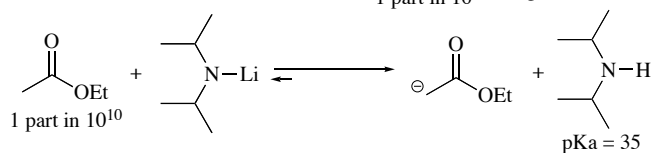
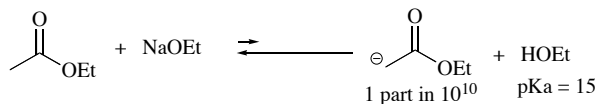
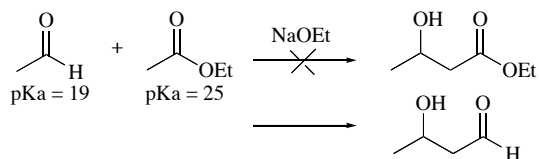
9) Be aware of the basicity vs nucleophilicity

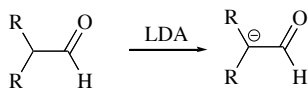
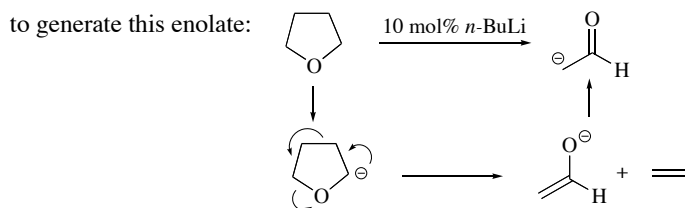
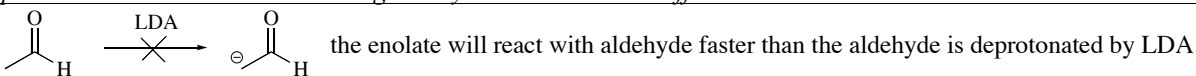


An exception is  $\beta$ -tetalone which can be deprotonated with organolithiums and Grignard reagents.



10) Be aware of the relative acidity of reagents and substrates

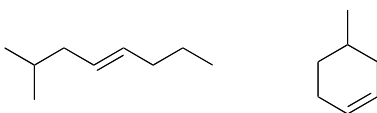




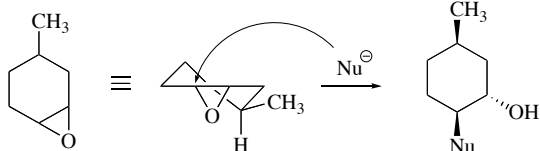
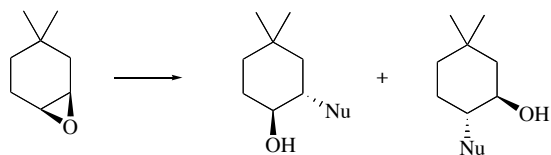
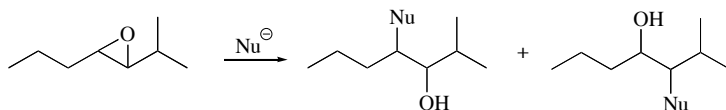
The stoichiometric generation of an enolate from an  $\alpha$ -branched aldehyde can be accomplished in some cases. It is best to avoid deprotonation of an aldehyde with LDA.

11) Understand limits of regioselectivity. If you are using a method that gives a mixture of regioisomers, redesign the synthesis. At the very beginning a synthesis, such a non-selective reaction can be used if the regioisomers are separated and if the starting material is inexpensive. Late in the synthesis this should not be used since the wrong diastereomer normally can't be recycled. For an example of a reaction that gives a mixture of products that can be used near the end of a synthesis, see TIP #12.

You should assume that there is no known chemical reaction that is regioselective with the following olefins:

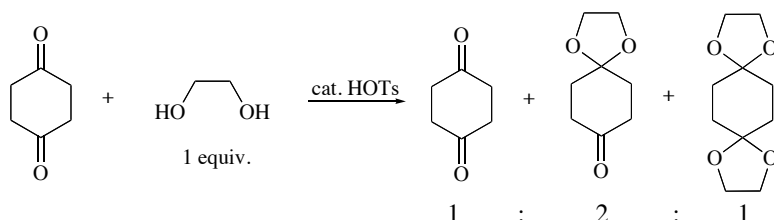


Nucleophilic opening of the following epoxides will give two regioisomers.

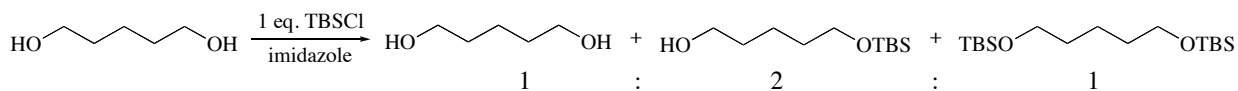


Epoxide opening in a 6-membered ring can be regioselective. This opening occurs in a trans-diaxial manner from the half-chair that has the substituent pseudo-equatorial.

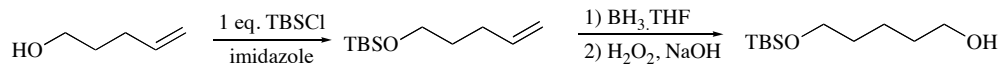
12) The desymmetrization of difunctional molecule should be assumed to be unselective and give statistical mixtures.



This type of unselective desymmetrization should be avoided when possible but can be used either at the beginning or the end of the synthesis since the undesired products can be recycled. Where possible a desymmetrization should be avoided if a selective method to the same molecule exists.

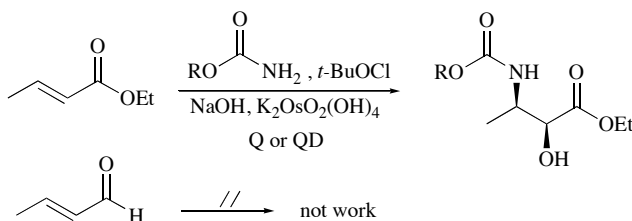


Solution:

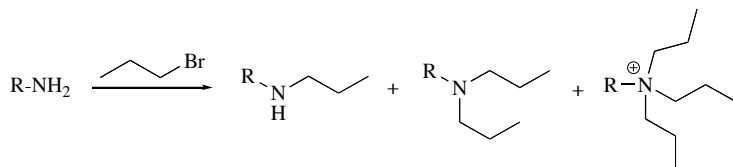


13) Be aware of compatibility of reagents and conditions with the substrates.

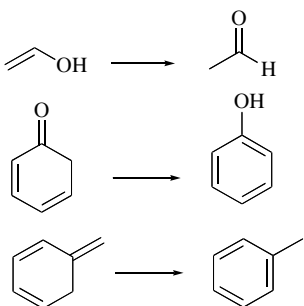
- a. The Sharpless asymmetric aminohydroxylation works well with  $\alpha,\beta$ -unsaturated esters. The oxidizing conditions of this reactions would not be compatible with aldehydes, which are easily oxidized.



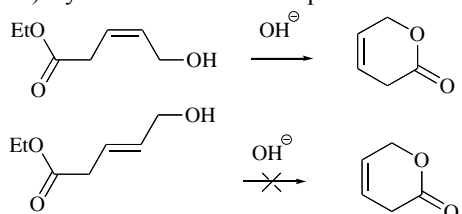
- b. In alkylation of amines, the 2° or 3° amine products are nearly as reactive as the starting amine and thus mixtures of products are obtained.



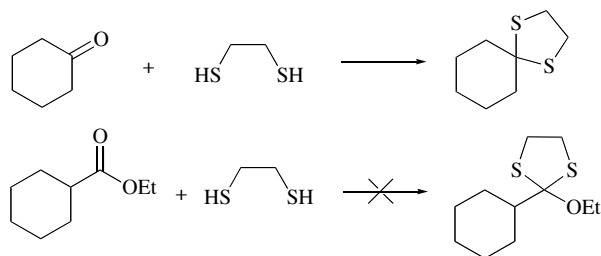
14) Be aware of tautomers: vinyl alcohol does not exist.



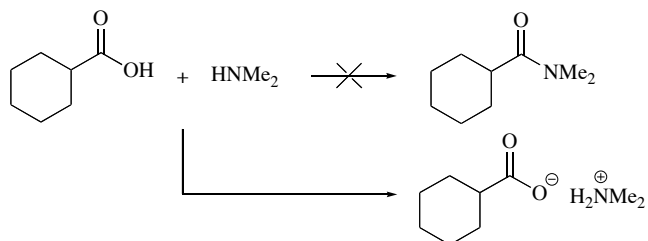
15) Cyclization reactions require double-bonds to have the correct geometry.



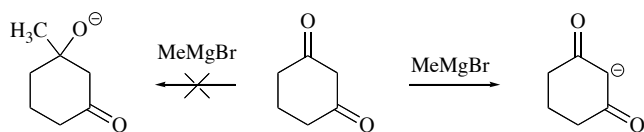
16) Diols and dithiols can be used to protect aldehydes and ketones but not esters and amides.



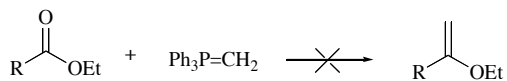
17) Amides can't be made by reacting amines with carboxylic acids. Salt formation will be the only outcome.



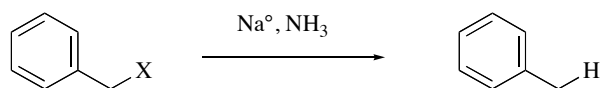
18) Organolithiums and other organometallic reagents will enolize active methylene compounds.



19) Wittig reactions and Horner-Wadsworth-Emmons reaction do not work on esters or amides.

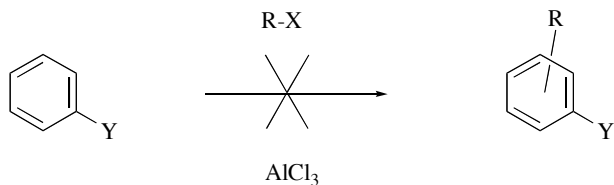


20) Birch reduction conditions for compounds containing a benzylic heteroatom substituent will first reduce the benzylic-heteroatom bond.



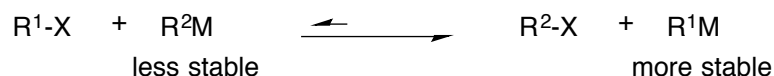
X = halogen, OR, NR<sup>1</sup>R<sup>2</sup>

21) Both Friedel-Crafts alkylations and acylations will fail on deactivated arenes.



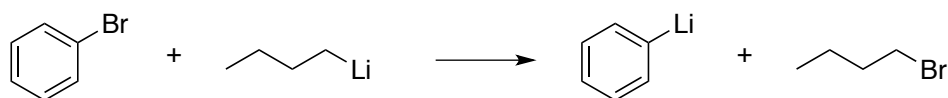
Y = ester, amides, aldehyde, nitrile, nitro, ketone, sulfonyl, etc.

22) Metal-Halogen exchange reactions are in equilibrium and are only useful when the new carbanion is much more stable than the starting carbanion.

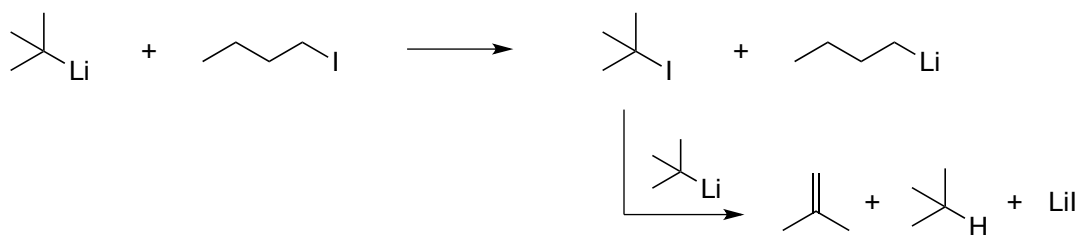


Exchange is useful only between two different classes of carbanions and then from a higher energy class to a lower energy class. Example:  $\text{sp}^3$  to  $\text{sp}^2$  carbanion.

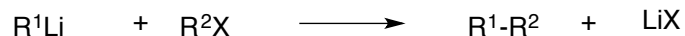
$\text{sp}^3$ carbanions	$\text{sp}^2$ carbanions	$\text{sp}$ carbanions
Class I	Class II	Class III
pKa ~ 45-50	pKa ~ 35-40	pKa ~ 15-25



Exchange between  $\text{sp}^3$  carbanions is only useful from higher energy  $3^\circ$  carbanions to lower energy  $1^\circ$  carbanions and even then only with iodides. A second equivalent of the  $3^\circ$  carbanion is needed.

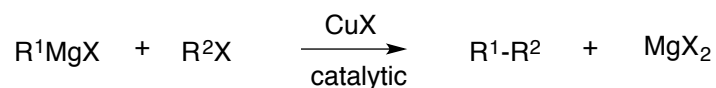


23) Grignards and Organolithiums do not couple well with alkyl halides or sulfonates.



This reaction is useful only for methyl iodide, allyl halides and benzyl halides.

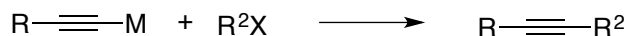
The reaction can be extended to the Grignard coupling with 1° bromides and iodides if a catalytic amount of a copper (I) salt is added.



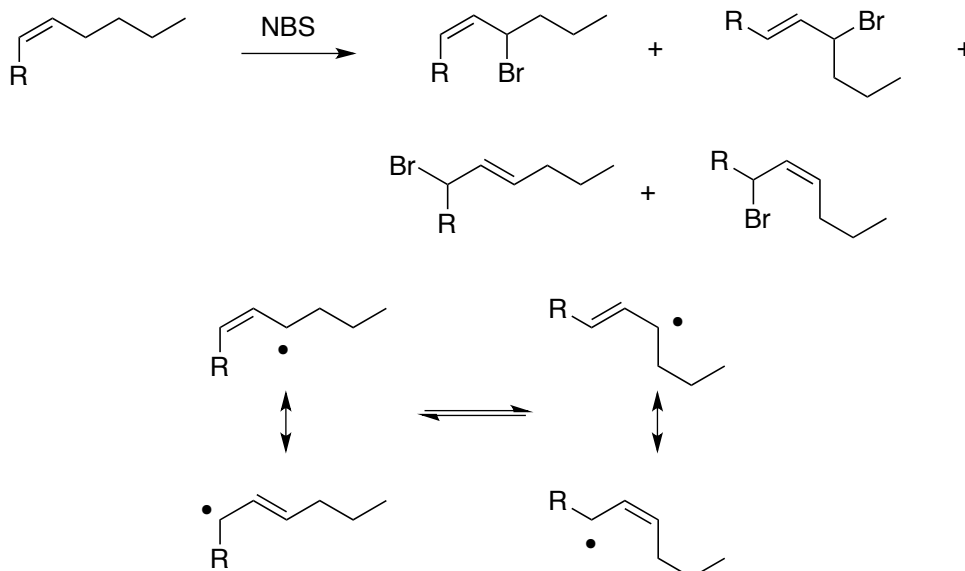
The reaction can be extended to the organolithium coupling with 1° bromides and iodides if the organolithium is first stoichiometrically converted to an organocuprate.



Acetylide anions will react with methyl iodides, allyl halides, benzyl halides and 1° bromides and iodides



24) Free radical bromination of alkenes can lead to regioisomeric allylic bromides and loss of stereochemistry of the alkene.





25) Metallation reactions are useful when the new carbanion is much more stable than the starting carbanion.



Metallation is normally only useful between two different classes of carbanions and then from a higher energy class to a lower energy class.

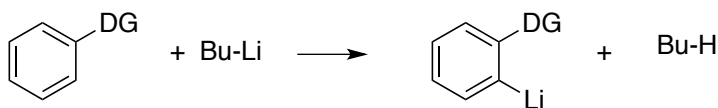
$sp^3$ carbanions	$sp^2$ carbanions	$sp$ carbanions
Class I	Class II	Class III
pKa ~ 45-50	pKa ~ 35-40	pKa ~ 15-25

This reaction is very clean when regiochemistry is not an issue and there is a big difference in anion stability

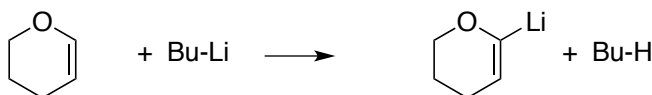


EtMgBr can also be used

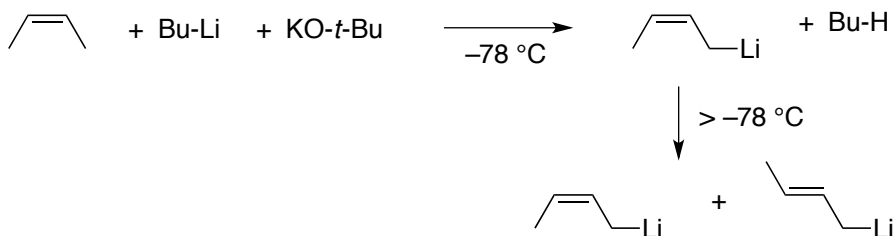
When regioisomers are possible, metallation can be controlled by the introduction of groups which direct metallation to the ortho position on benzene rings or the  $\alpha$ -position on enol ethers.



DG = OMe, OMOM, CONR<sub>2</sub>, etc.



Selective deprotonation on a  $sp^3$  carbon over a  $sp^2$  carbon is observed in alkenes due to the extra stability of the allylic anion. The stereochemistry of the alkene can be retained at low temperatures.



26) After you finish the exam, count the carbons in your product, also double-check the stereochemistry before handing in the exam.