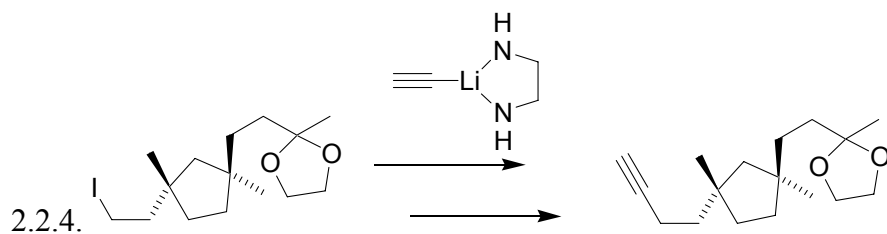
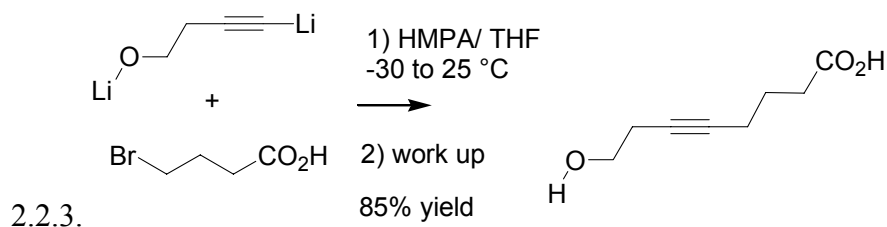


2.2. R' more than 5 carbon atoms long produce solubility problems under the specific reaction conditions given above.

2.2.1. Add THF as a cosolvent with NH₃. This improves the solubility of longer chains, resulting in better yields.

2.2.2. Other solvents: DMF, HMPA, DMSO (neat or with THF as a cosolvent)



2.3. The synthon, HC%C(-) does not translate to real reagents as simple as HC%CM, (M is a metal)

2.3.1.1. The lithium salt chelated to EDA as above is sometime employed.

2.3.1.1.1. However, for some substrates this reagent is rather inactive.

2.3.1.1.2. There are two other solutions.

2.3.1.2. R₃SiC%CM works well, where M is MgX, Li, or Na.

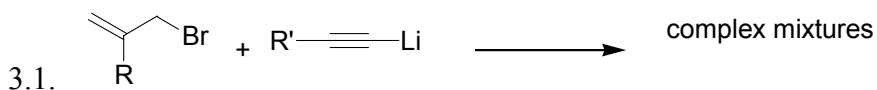
2.3.1.3. Another solution is to deprotonate acetylene gas in great excess.

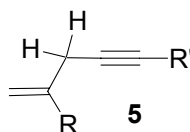
2.3.1.3.1. The salt MC%CM is stable and not very soluble. An excess of HC≡CH avoids double deprotonation.

2.3.1.3.2. Midland, M.; McLoughlin, J. I.; Ralph T. Werley, J.

"Preparation And Use Of Lithium Acetylide: 1-Methyl-2-Ethynyl-Endo-3,3-Dimethyl-2-Norbornanol" *Organic Synthesis, Coll.Vol.* 8, 391.

3. Scope limitations of alkynide homologation.

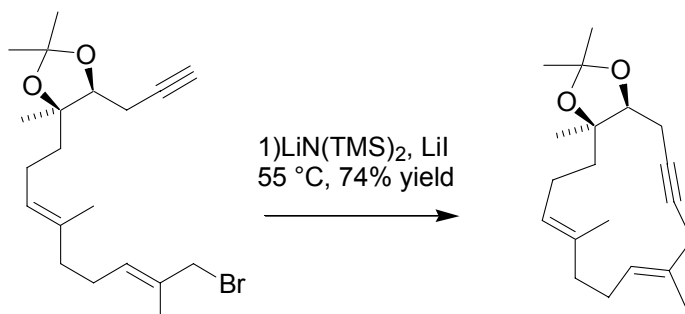




3.2. Because the protons in product 5. are acidic enough to make another electrophile and alkyl ate.

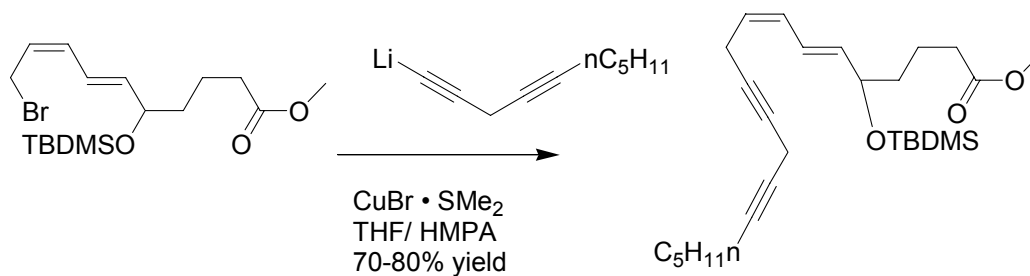
3.2.1. This sort of multiple addition is always a concern when working with strong bases. The question is: can the base/nucleophile react with the product in any way?

3.2.2. LiI suppress the tendency of the base to abstract these protons.

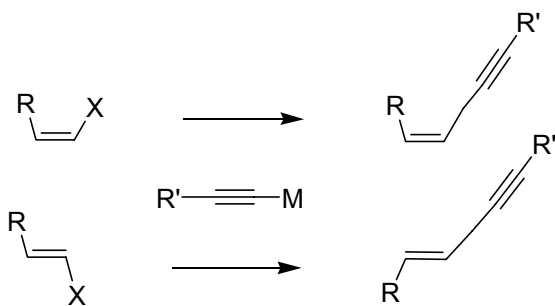


3.2.3.

3.2.4. Another way to decrease the basicity of alkynides is via their copper I salts.

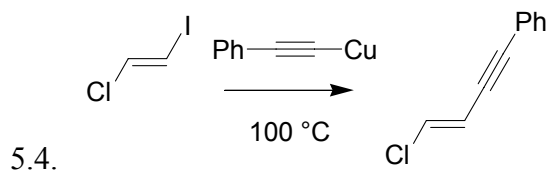
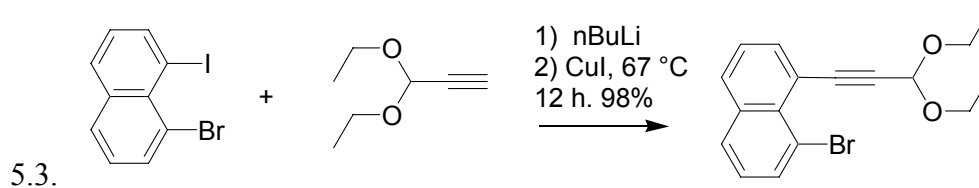
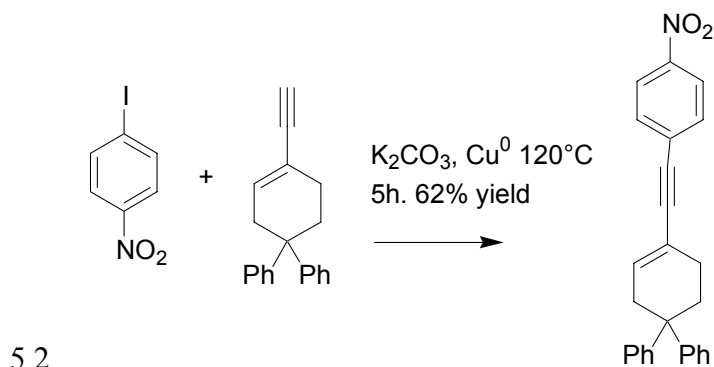
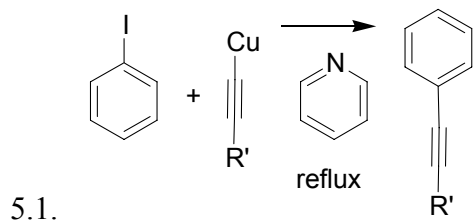


4. More esoteric metals than those in the first row need to be used.



4.1. Totally different class of reaction mechanism than S_N2 .

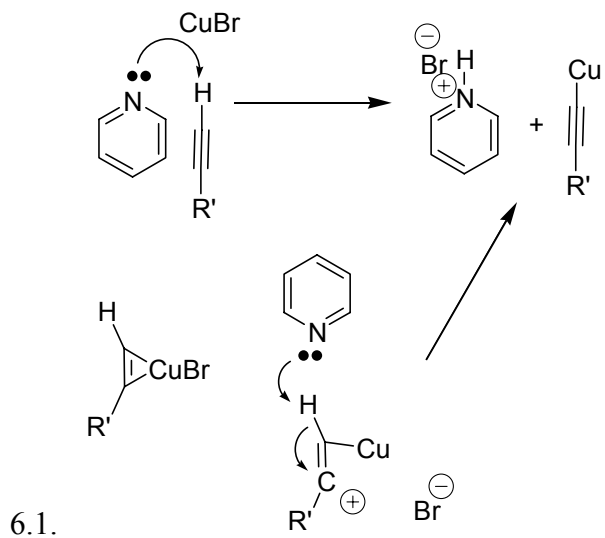
5. **Castro-Stevens reaction:**



5.4.1. Substitution rate: $I > Br > Cl$ selectively.

5.4.2. Stereocontrol!

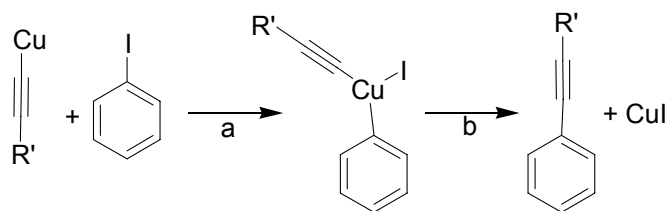
6. Mechanism:



6.2. Normally pyridine would not deprotonate the alkyne.

6.2.1. Cu alkynide salt is a thermodynamic sink.

6.2.2. Cu chelates with triple bond.



6.3.

6.3.1. reaction *a* is oxidative insertion

6.3.1.1. The oxidation state of Cu increases by 2. (I \rightarrow III)

6.3.2. reaction *b* is reductive elimination

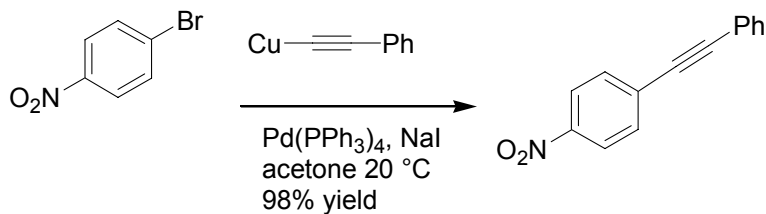
6.3.2.1. The oxidation state of Cu decreases by 2. (III \rightarrow I)

7. Castro-Stevens reactions require high temperature.

7.1. Transition state is high in energy compared to the starting materials.

7.2. The transformation would benefit from a metal that performs oxidative insertion easier.

8. Enter Pd(0)

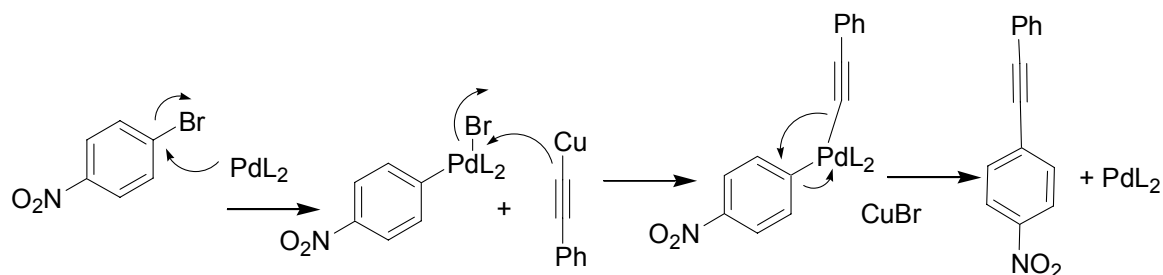


8.1.

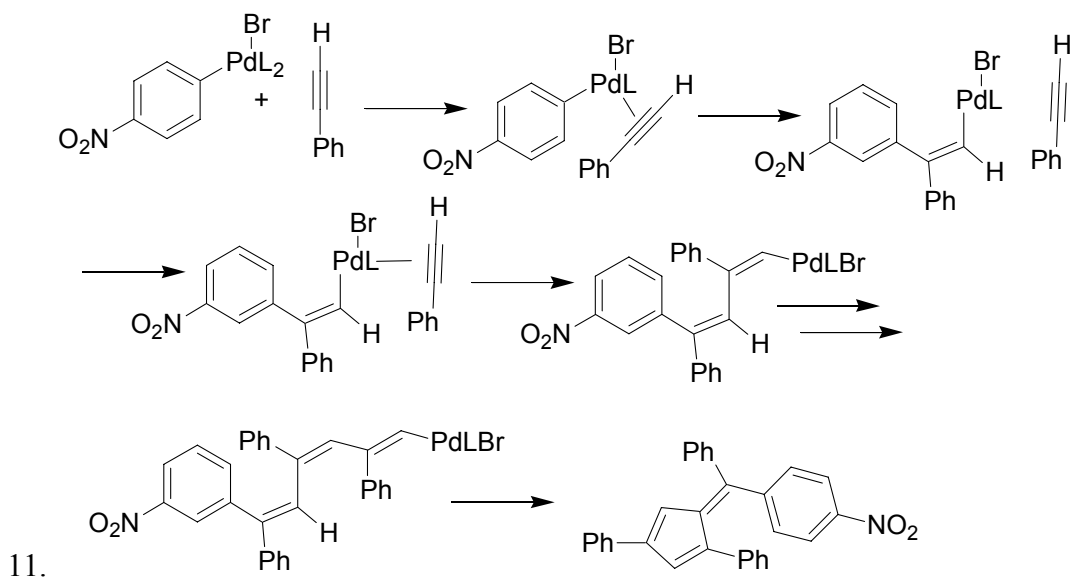
8.2. Sonogishira coupling

8.3. more facile than Castro-Stevens

9. Mechanism



10.

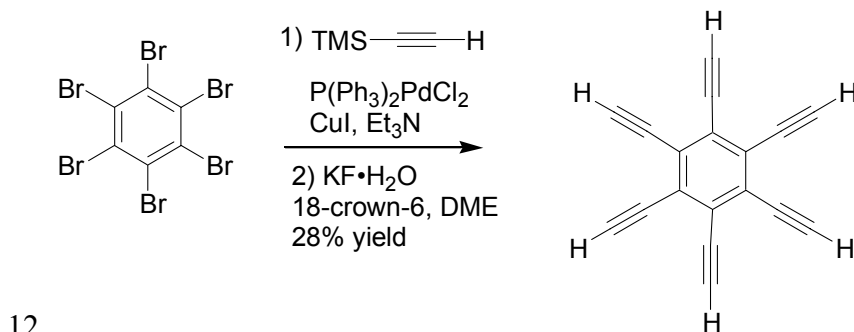


11.1. In the absence of Cu(I) the Cu alkynide does not form.

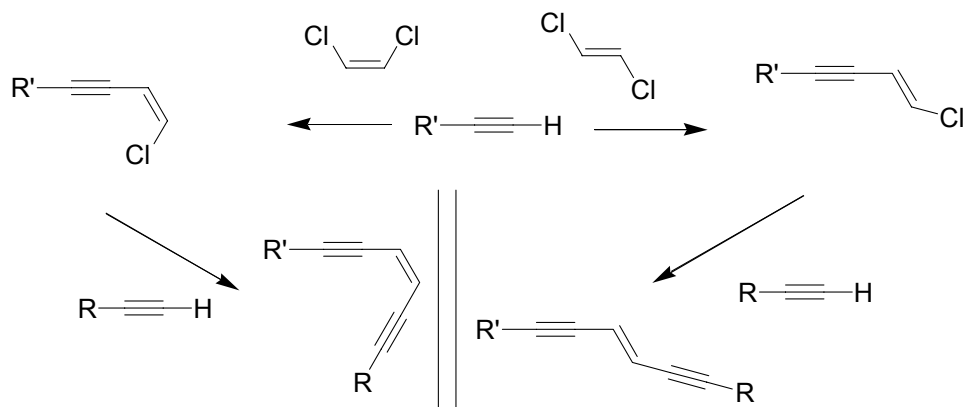
11.1.1. In the last step above PdLH is eliminated.

11.1.2. A base take this back to Pd(0)

11.1.3. $\text{PdLHBr} + \text{base} \rightarrow \text{Pd}(0) + \text{baseH}^{(+)}\text{Br}^{(-)}$

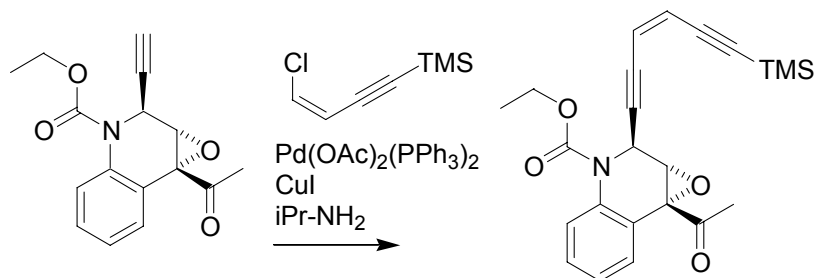


13. Stereocontrol



13.2. Stereocontrol is possible with substrates that do not interfere with catalysis.

- 13.2.1. Avoid substrates bearing the S atom unless it is highly oxidized eg. $\text{RSO}_2\text{R}'$ or $\text{R-SO}_3\text{R}'$.

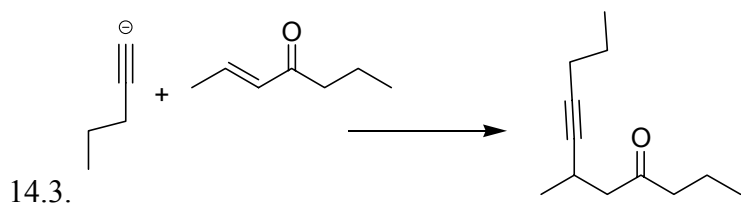


- 13.2.2. A host of functionality is compatible.

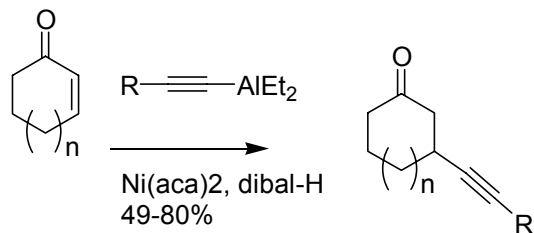
14. Michael Addition

- 14.1. 1,4-addition via cuprate reagents was discussed in class.

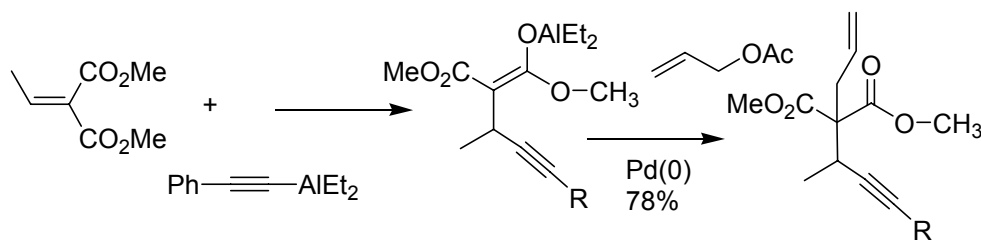
- 14.2. Unfortunately the corresponding reaction with alkynes is not as straight forward.



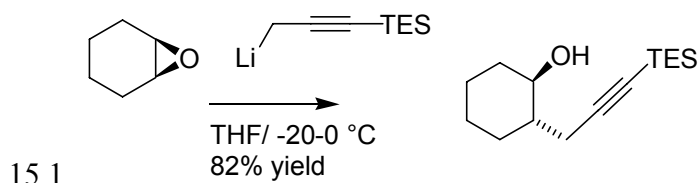
- 14.3.1. The above reaction does not work with Cu alkynides.



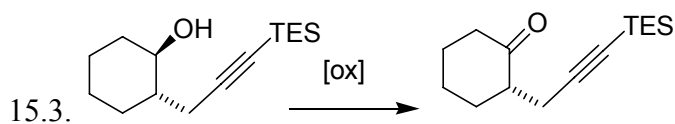
- 14.4. $n=0,1$ $\text{R}=\text{nBu, tBu, TMS}$



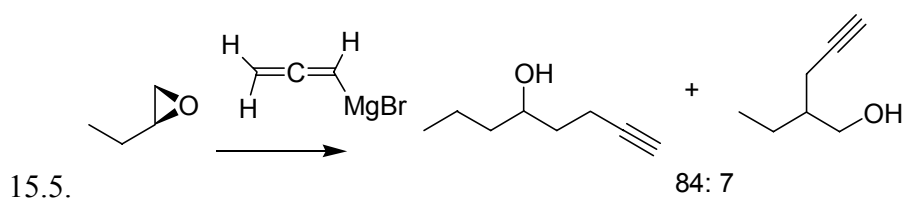
15. Open epoxides to make C-C bonds



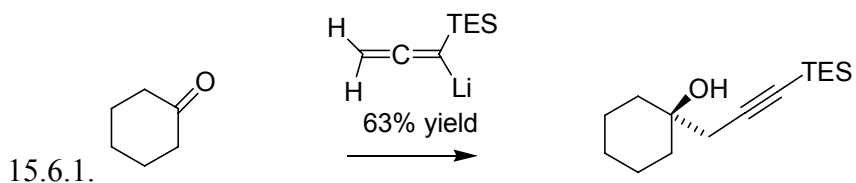
15.2. notice the stereochemistry above!



15.4. After oxidation you have accomplished a net 1,3-addition. Compare this to the 1,4-addition (Michael).



15.6. 1,2-addition (below) is an easy reaction

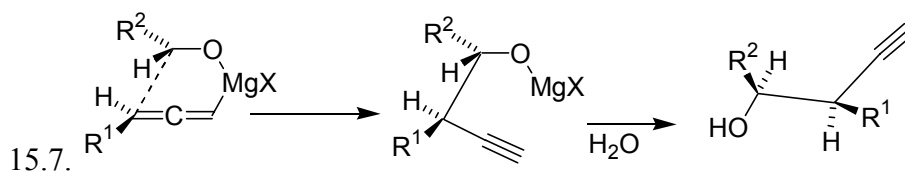


15.6.2. 1,2-addition is usually favored, even when the ketone or aldehyde is α,β -unsaturated.

15.6.3. Stereoselectivity in 1,2-additions of organoallene

15.6.4. Relies on the ability of the metal to chelate to the ketone or aldehyde in the transition state.

15.6.5. Li, Mg, Zn, Al, B, Ti and other can accomplish this.

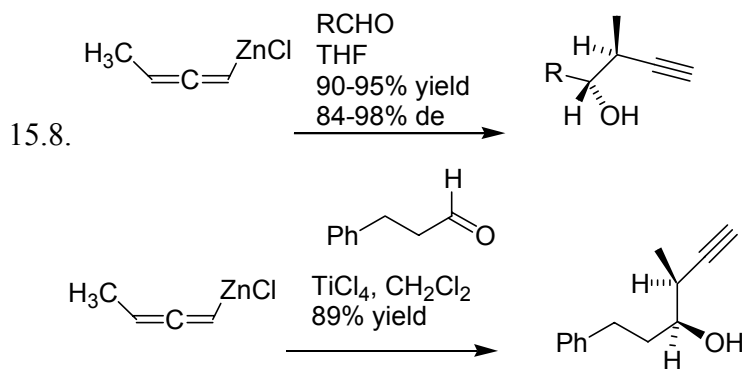


15.7.1. R=Me, 76:24 syn:anti

15.7.2. R=Et, 82:18 syn:anti

15.7.3. R=iPr, 90:10 syn:anti

15.7.4. R=tBu, 95:5 syn:anti

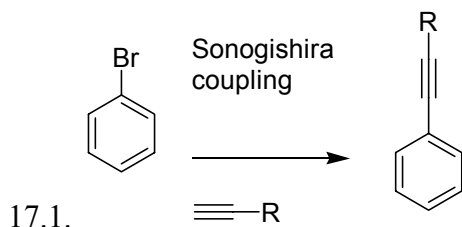


15.8.1. again syn product is major 3.1:1

16. HOW ARE YOU GOING TO REMEMBER THIS INFO? Are you going to remember the definition of syn and anti?

16.1. MY ADVICE: Go back to the transition state and figure it out!

17. Leaving groups attached to sp^2 carbon atoms can be used to form $\text{Csp}^2\text{-Csp}^2$ bonds.



17.1.1. The synthetic challenge to using this method in a complex context centers on the ability to make the alkyne and install the leaving group on the sp^2 carbon atom.

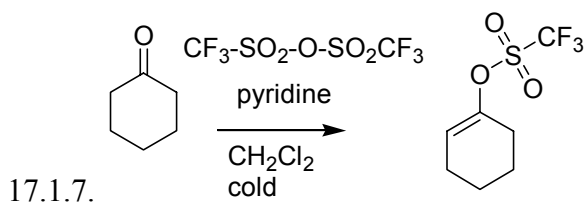
17.1.2. We have discussed ways to make alkynes.

17.1.3. The terminal alkynes can be used as a central unit in the homologation of carbon chains.

17.1.4. Versatility in the coupling partner with the sp^2 carbon atoms would increase the scope of the synthetic method outlined above.

17.1.5. Ketones (carbonyl groups) are versatile intermediates in the construction of complex organic compounds.

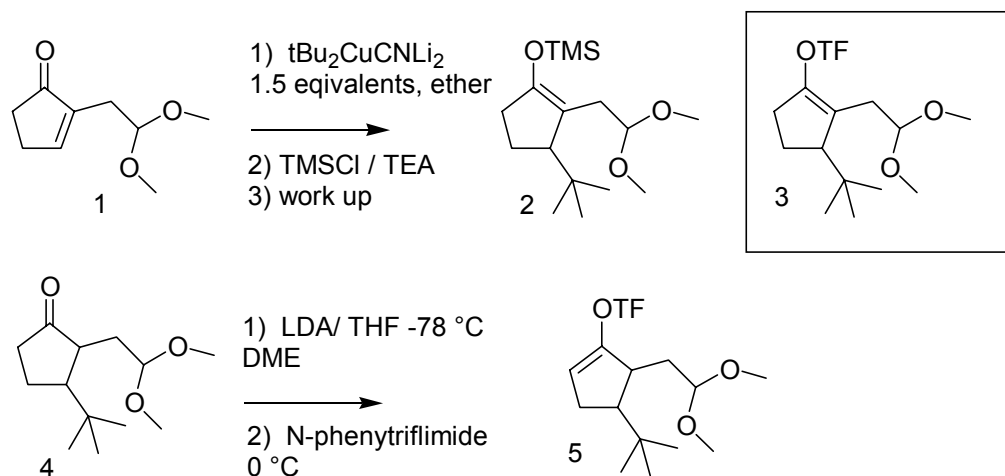
17.1.6. More on this topic latter.



17.2. Ketones with α -protons can be converted to enol trifluoromethylsulfonic esters (enol triflates)

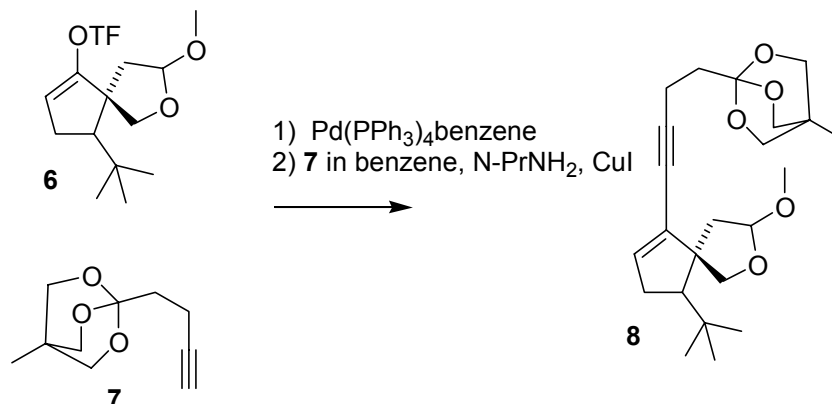
17.2.1. Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. "Chemical transformations induced by triflic anhydride." *Tetrahedron* **2000**, *56*, 3077-3119.

17.2.1.1. article is available online



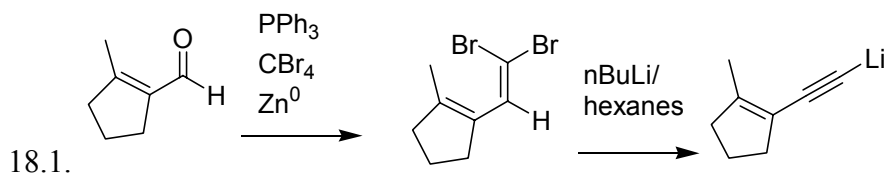
17.2.1.2. $\text{N-phenyltriflimide}$ can be used to trap enolates kinetically. Thus triflates **3** or **5** are available in this manner. Corey, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 649-651.

17.2.1.3. Now the leaving group on the sp^2 carbon is SO_3CF_3 . Why should this leaving group be so good?

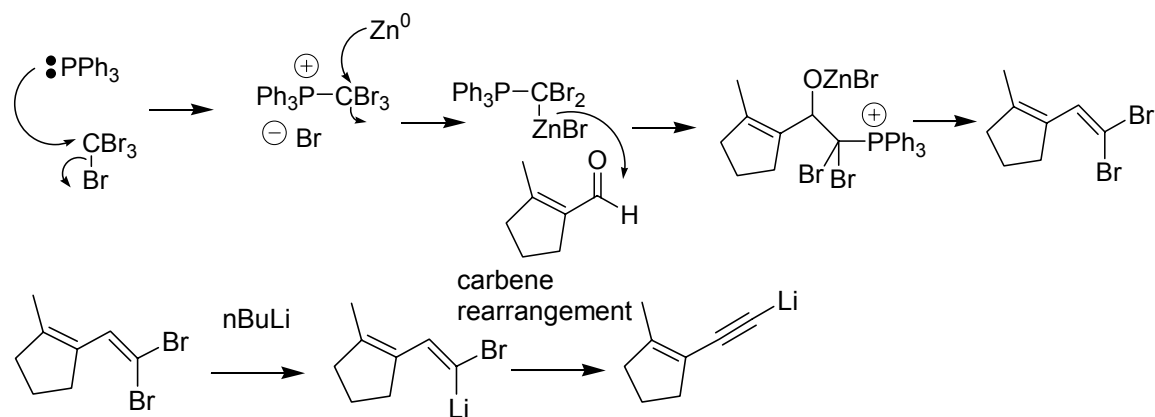


17.2.1.4. **7** imports oxygen-atom functionality in the carboxylic acid oxidation state Protected from organic anions

18. Functional group manipulation of the aldehyde to the alkyne.

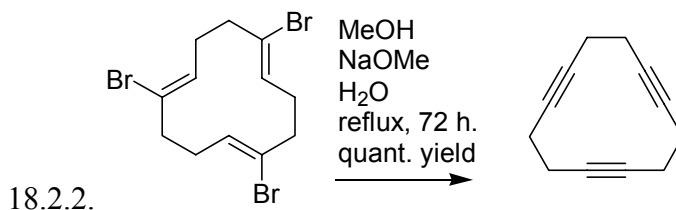
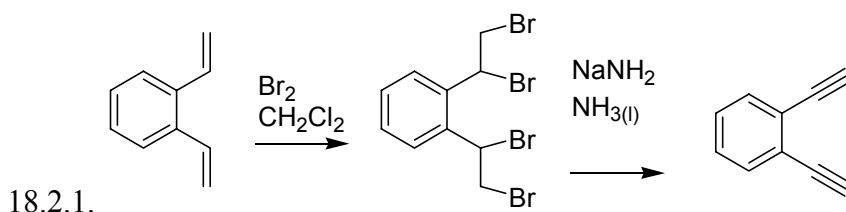


18.1.1. This is another way to generate alkyne synthons. Mechanism:



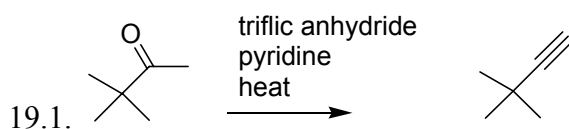
18.1.2. Okamura, et. al. *J. Am. Chem. Soc.* **1991**, *113*, 3873-3881.

18.2. Functional group manipulation of the alkene to the alkyne.



19. Functional group manipulation of the acetyl group to the terminal alkyne.

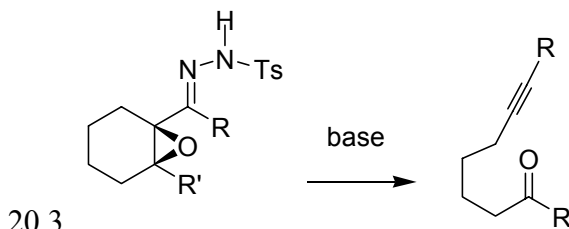
Tetrahedron **2000**, 56, 3077



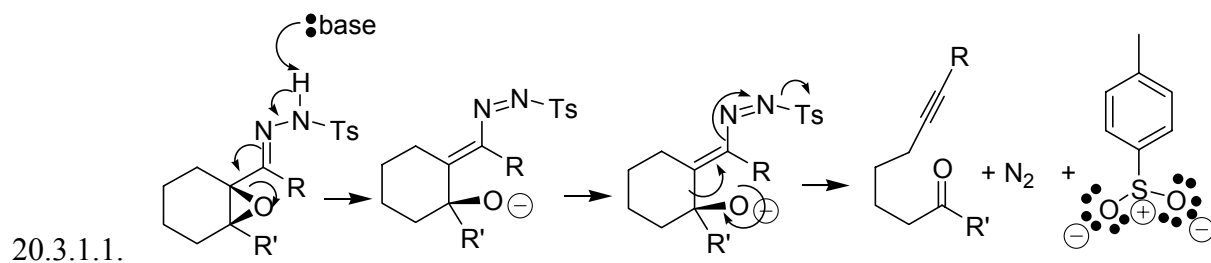
20. Alkynes via Fragmentation reactions.

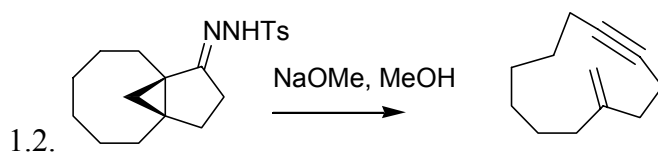
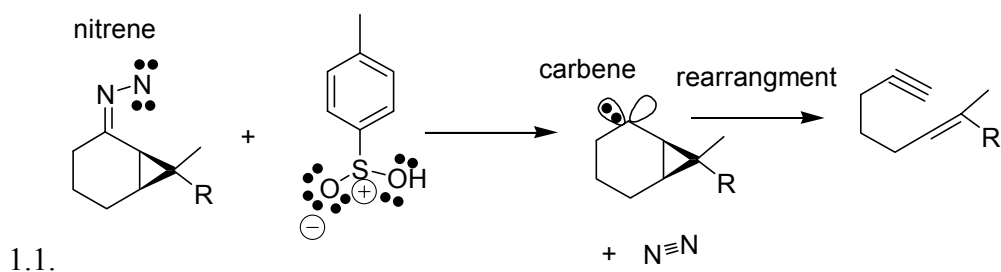
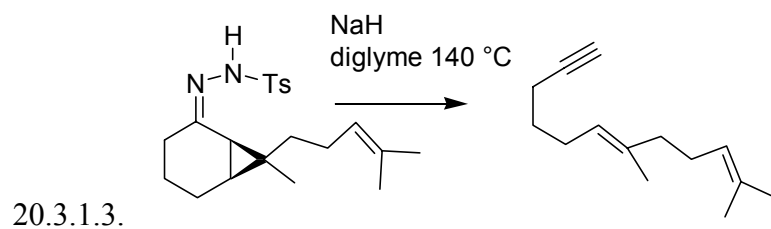
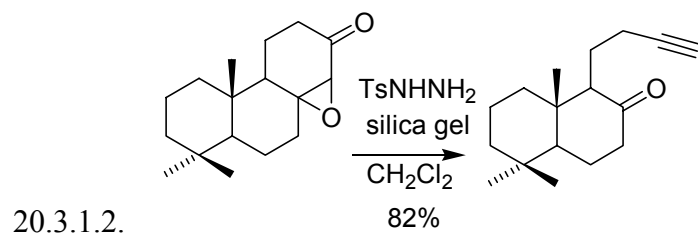
20.1. Eschenmoser fragmentation

20.2. NOTE, the 1,6 versus the 1,5 functional group positioning of these fragmentations versus the 3,3-sigmatropic rearrangement.



20.3.1. Mechanism





1.2.1. If you were going to make a ring containing a triple bond this is one way to do it.