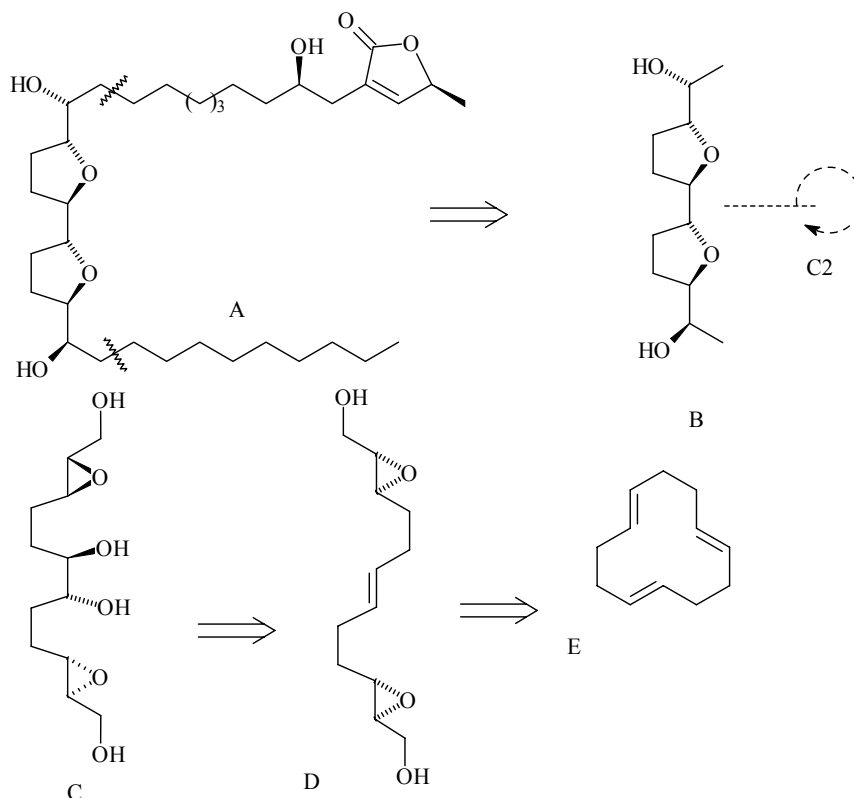


Epoxides of allylic alcohols, Important Synthetic Intermediates.

1. We have discussed some asymmetric reagents that oxidize alkenes and allylic alcohols.

1.1. In general epoxides are useful synthetic intermediates because they can be stereoselectively homologated by nucleophilic ring opening reactions. Let's consider the synthetic chemical issues in the following synthesis.



2. "Synthesis of (+)-parviflorin" Hoyer, T.R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801-1802.

2.1.1. Natural product source: annonaceous acetogenin, annonacea is a family of tropical trees

2.1.1.1. Bioactive: selectivity against certain human tumor cells.

2.1.2. Molecular Complexity

2.1.2.1. Oxygen based functionality at different levels of oxidation

2.1.2.2. The complex chirotopic environment.

2.1.2.3. The remote chirality in the δ -lactone-another mini-synthesis.

3. Pause here and talk about the logic of asymmetric synthesis and the problem remote chirality creates

3.1.1. Chemists use the stereochemistry at one position to determine stereochemistry at another.

3.1.2. This process is difficult and sometimes impossible when the interactions are far away from each other.

3.2. This is a retrosynthetic analysis based on the pseudo-symmetry of the bis-THF acetogenin as a simplifying principle.

3.2.1. Retrosynthesis from A to B gets us to a C₂ symmetric bis THF derivative.

3.2.1.1. Compounds can possess C₂ symmetry and still be chiral.

3.2.1.2. This compound is chiral.

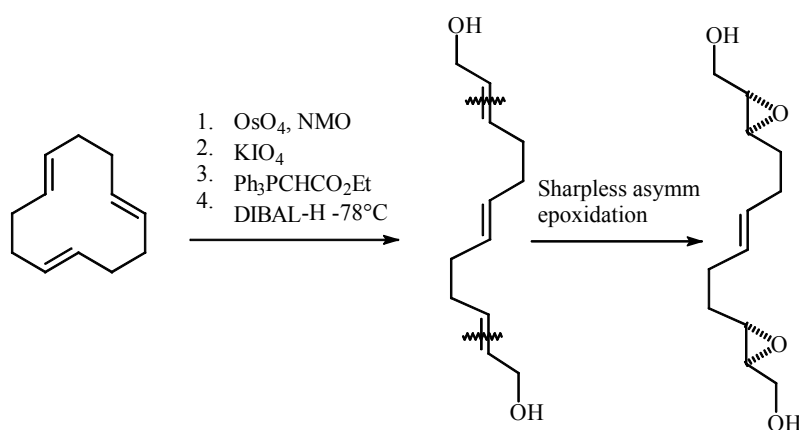
3.2.1.3. C₂ symmetric bis THF arises from the chiral C₂ bis-epoxide via Payne rearrangement.

3.2.2. The central chiral diols came from asymmetric hydroxylation.

3.2.3. Asymmetric epoxidation provides the initial asymmetry in the molecule.

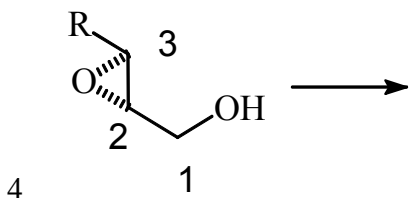
3.2.4. We have discussed sp² carbon stereocontrol to sp³ stereocontrol.

3.3. The authors of this paper obviously think structures like triene E are less complex than the chiral polyols. Because E was their starting point.



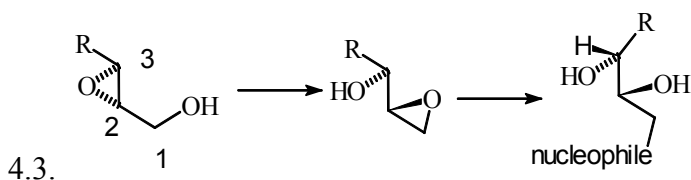
3.4.

3.4.1. After the epoxidation of the bis-allylic alcohol we are left with a very interesting electrophile. Let's leave the synthesis at this point and discuss these in general.



4.1. One can treat these compounds with a nucleophile and can work conditions out to get nucleophilic substitution either at C1, C2 or C3!

4.2. C1 substitution-Payne Rearrangement

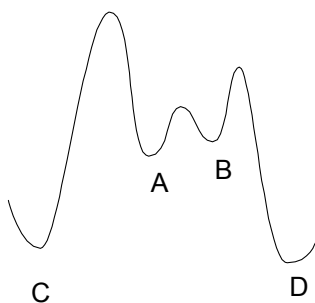


4.4. the material converts to the more reactive epoxide

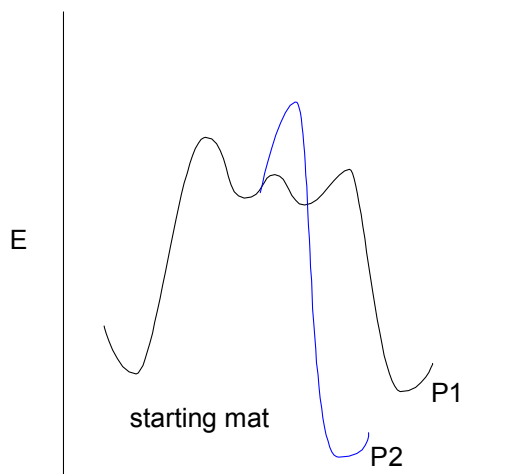
4.4.1. 1° vs. 2° epoxide

4.4.2. Curtin-Hammett principle

Curtin-Hammett Principle. When two conformations, tautomers, or isomers of a starting material are in rapid equilibrium (compared to rate of a reaction), then the product ratio is independent of the ratio of the starting species. Conversely, the product ratio gives no information about which conformation, tautomer or isomer was present in the starting material. In other words, just because you can see it doesn't mean that it is the reactive species.



4.4.3. Even though A is the major conformer in solution (lower energy than B), the major kinetic product is D, which comes from the minor conformer B.

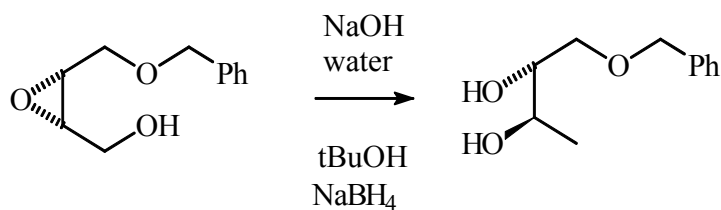


4.4.4. Rxn Coordinate

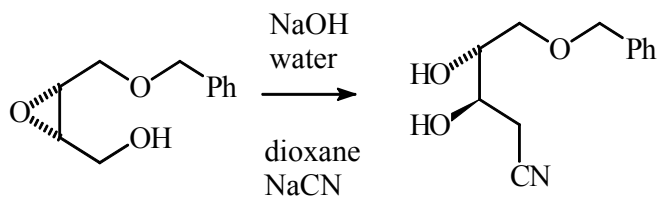
4.4.5. The barrier between intermediate and product determines the product instead of the relative energies of the intermediates.

4.4.6. The epoxide that is less hindered reacts because the barrier between it and ring opened product is lower.

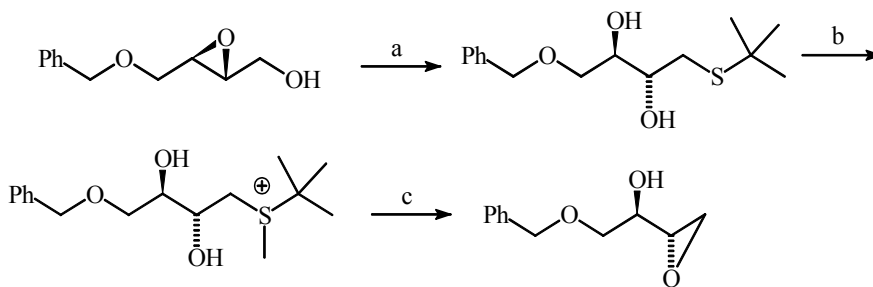
4.5. Examples



4.5.1.



4.5.2.



4.5.3.

4.5.3.1. a. OH⁻, water, tBuOH, tBuSH

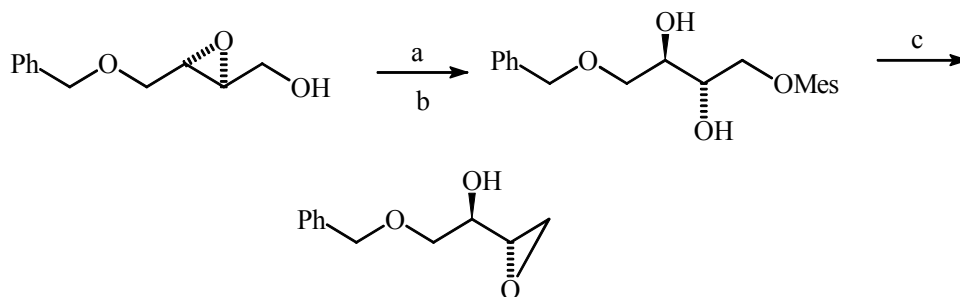
4.5.3.2. b. Me₃O⁺ BF₃⁻

4.5.3.3. c. NaH, CH₂Cl₂

4.5.3.4. In the above example we succeeded in moving the oxirane one carbon over and inverting the central carbon.

5. Examples simple transformations of 3-hydroxymethyl-oxiranes.

5.1. The H⁺ catalyzed ring opening of the epoxide.



5.2.

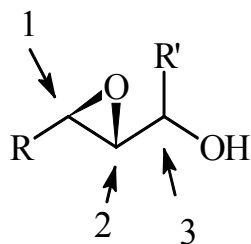
5.2.1. a) MsCl

5.2.2. b) HClO₄, water

5.2.3. c) K₂CO₃, water

5.2.3.1. Compare the **starting material** here to the **starting material** on the preceding page. They are enantiomers. Yet the products are the same.

5.2.3.2. Had we started from identical materials we could have made the enantiomers just by operating stereoselectively on these materials.

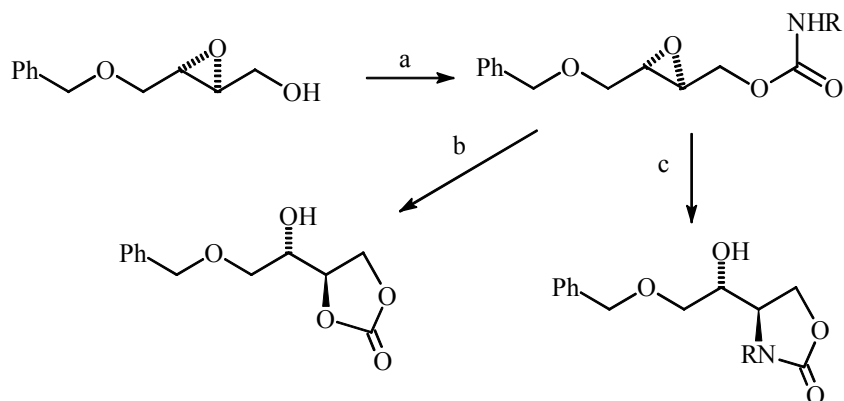


6.

6.1. We have been talking about the selective breakage of these C-O bonds

6.2. Substitution at C3 might involve activating the OH directly to S_N2.

7. Stereospecific substitution at C2.



7.1.

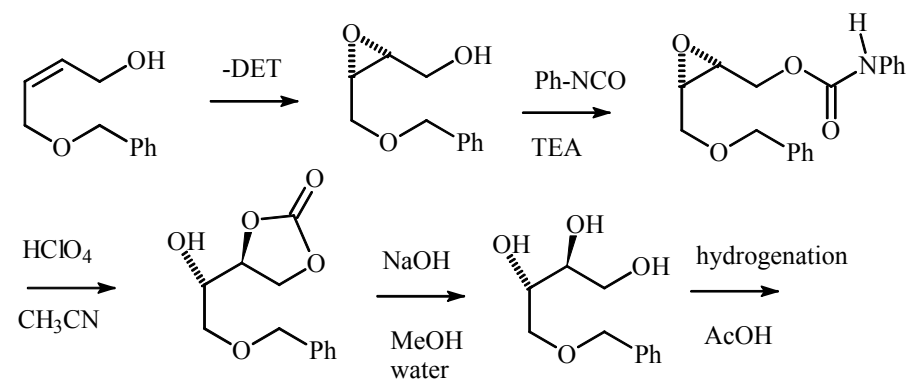
7.1.1. a) R-N=C=O

7.1.2. b) +H₃O(aq)

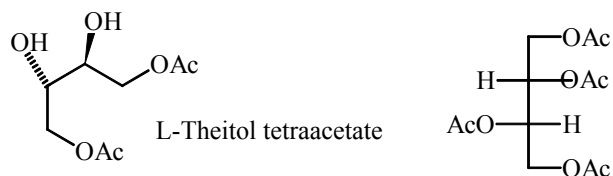
7.1.3. c) -OH(aq)

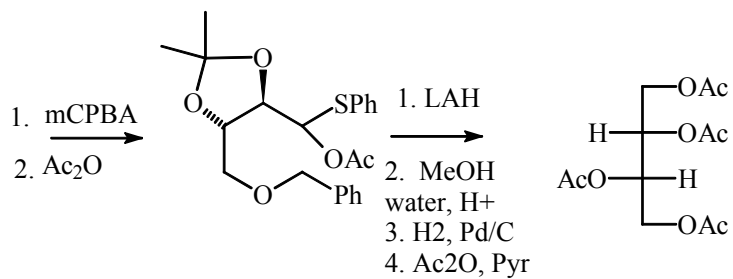
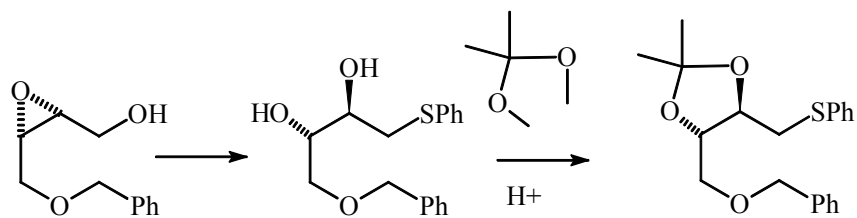
8. The method above is employed in the synthesis of molecules as complex as carbohydrates.

8.1. Sharpless and Masamune

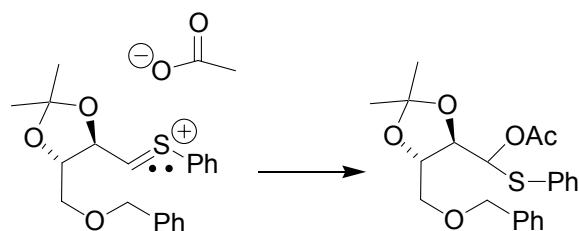
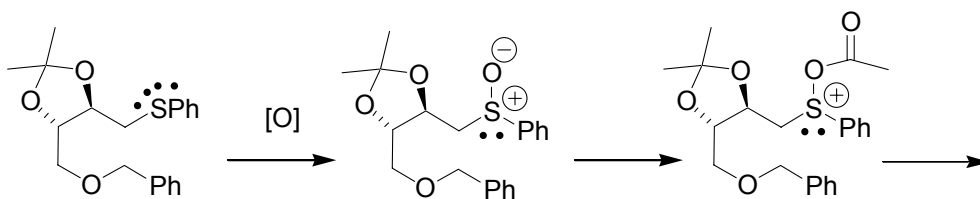


8.2.





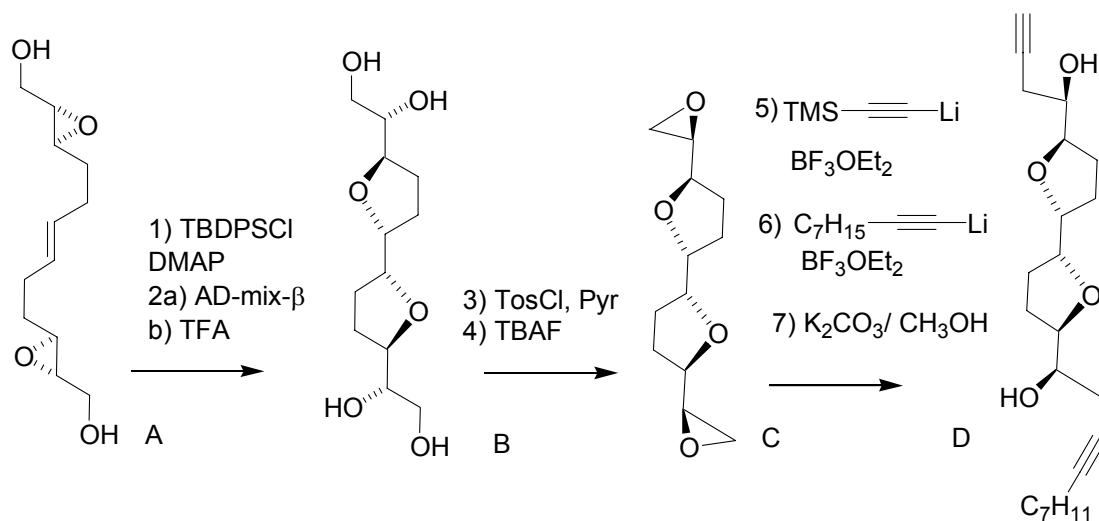
8.3.



8.4.

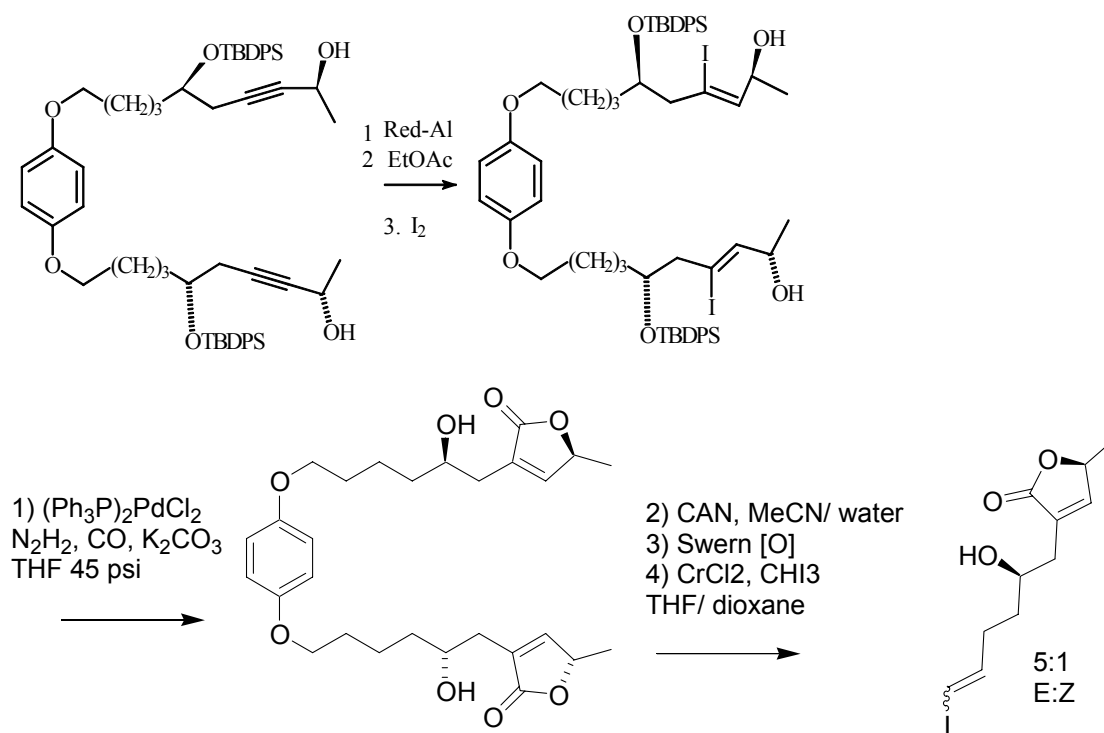
8.4.1. Oxidation via Pummerer intermediate.

9. Back to (+)-parviflorin



9.1. This is kid stuff we have seen it before.

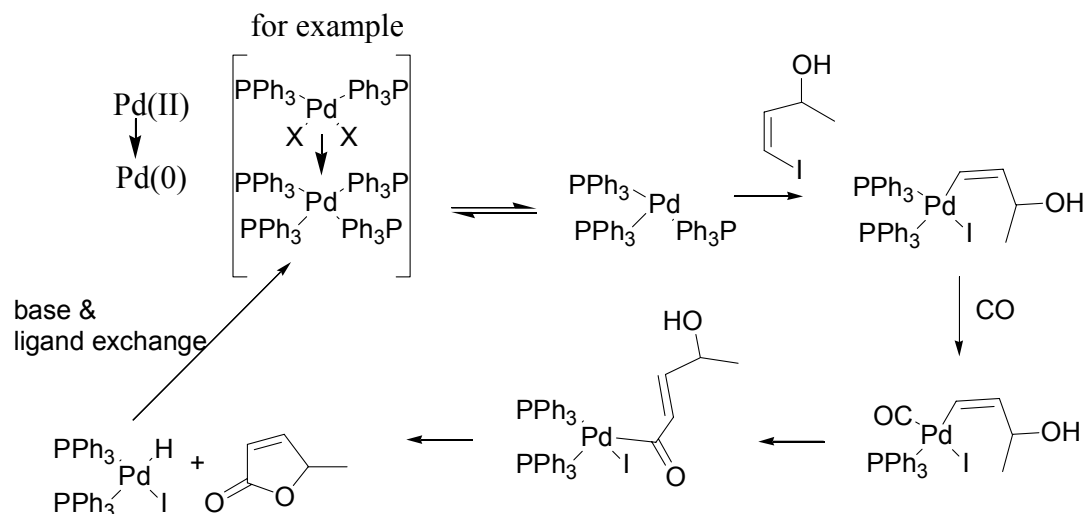
10. Red-Al = sodium *bis*(2-methoxy)ethoxyaluminiumhydride



11. Synthesis of lactones by palladium catalyzed carbonylation of haloalcohols Stille, J. et. al. *J. Am. Chem. Soc.* **1980**, *102*, 4193.

11.1. Mechanism of step one.

11.2.



11.3. Four coordinate species in Pd(0) are coordinatively saturated. These materials must lose a ligand for further transformations involving the Pd center.

11.4. Stereochemistry of oxidative insertion proceeds with inversion at sp³ carbon atoms and retention at sp² carbon atoms.

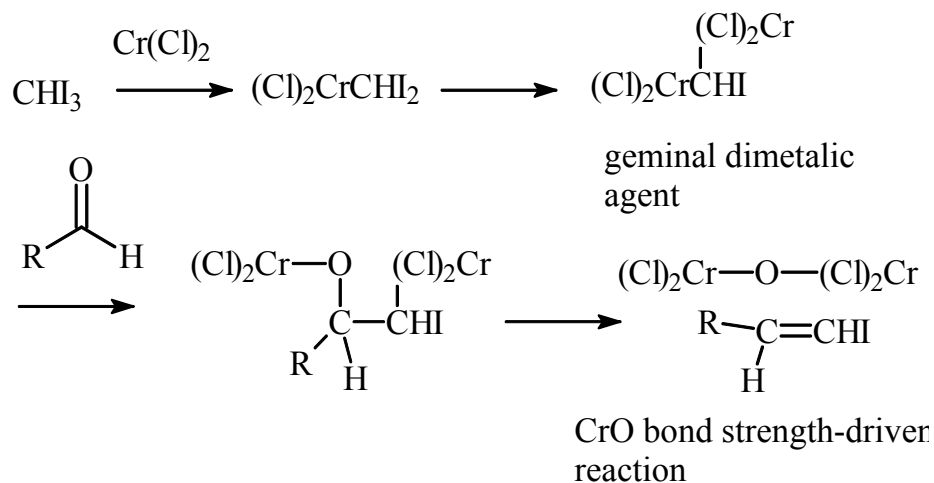
11.4.1. Can you identify the oxidative insertion step above?

12. (NH₄)₂Ce(IV)(NO₃)₆ wants to get an electron to fill the 5p shell. Strong 1 electron oxidizing agent.

12.1. *Synthesis*. **1985**, 641.

13. Takai's chromous chloride procedure

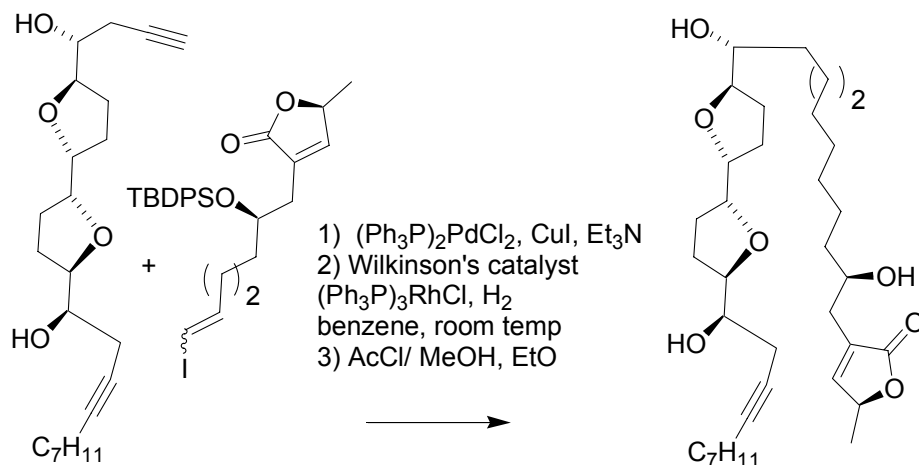
13.1. *J. Am. Chem. Soc.* **1986**, 108, 7408-7410.



Only works with aldehydes, not ketones.

14. Joining the two pieces together.

- 14.1. enyne synthesis
- 14.2. Terminal alkynes will couple directly with ArX or vinyl X or alkene X
- 14.3. CuI catalyzes this process w/base and allows the reaction to at room temp.
- 14.4. See Trost and Fleming vol 3 pg. 530-544 section
 - 14.4.1. We have discussed these kinds of reactions.



15. In general if you want to form the $\text{C}=\text{C}-\text{C}=\text{C}$ sigma bond, you want to use a transition-metal protocol. Especially if you want to do it in the presence of a lot of heteratomic functionality.