$$\longrightarrow \left[Ph_3\overset{\oplus}{P} - \overset{\ominus}{CH} - OCH_3 \right] \longrightarrow$$

(structures: cyclohexanone $= O$; enol ether cyclohexylidene $= CH-OCH_3$) $\xrightarrow{H_3O^{\oplus}_{(aq)}}$ (cyclohexyl-CHO)
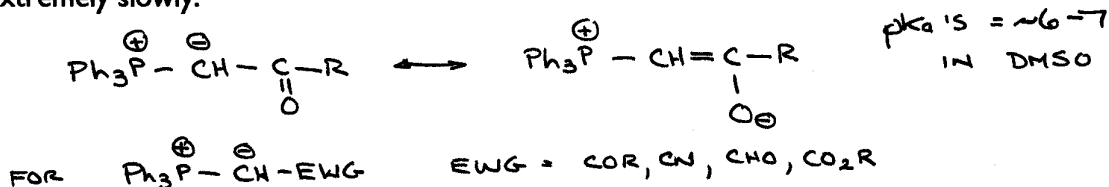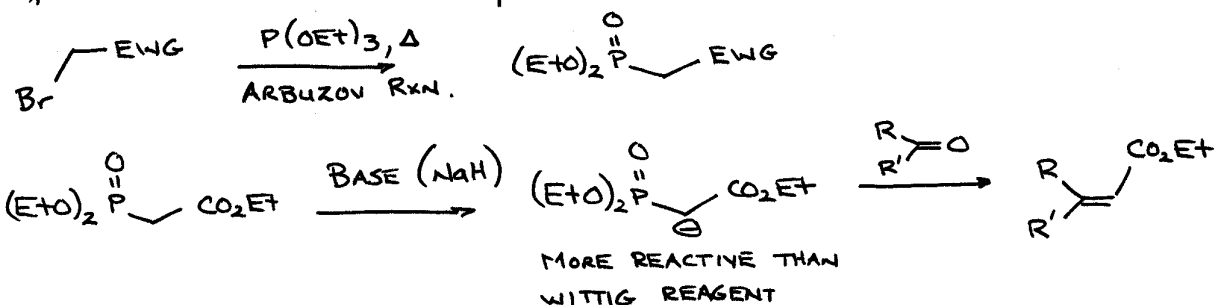
ENOL ETHER

ONE CARBON EXTENSION OF CARBONYL
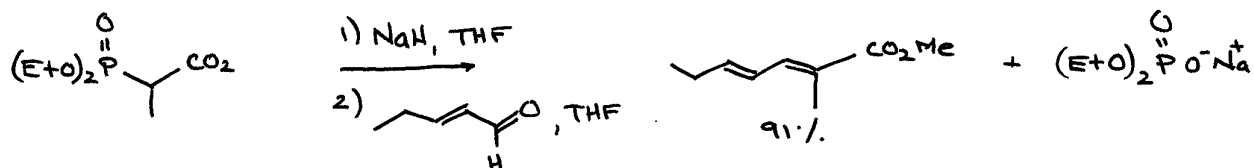
Problem-Reactivity:

There is a problem with reactivity if the phosphorus ylide has an electron withdrawing group. These ylides are much more stable; so stable that they are not very reactive with carbonyl compounds. They will in general still react with aldehydes (slowly), but ketones only extremely slowly.

$$Ph_3\overset{\oplus}{P} - \overset{\ominus}{CH} - \underset{O}{\overset{||}{C}} - R \quad \longleftrightarrow \quad Ph_3\overset{\oplus}{P} - CH = \underset{\underset{\ominus}{O}}{\overset{}{C}} - R$$

$pKa's = \sim6 - 7$ IN DMSO

FOR $Ph_3\overset{\oplus}{P} - \overset{\ominus}{CH} - EWG$ EWG = COR, CN, CHO, CO_2R

As a result, a modification has been made to the Wittig to make them more reactive. This uses phosphonate esters rather than phosphonium salts. Deprotonation of these esters now give anionic species (as opposed to zwitterions), and as a result they are much more reactive. These react quite rapidly with both aldehydes and ketones, and is an extremely common way to prepare α,β-unsaturated esters and related compounds.

$$Br\overset{\frown}{}EWG \xrightarrow[\text{ARBUZOV RXN.}]{P(OEt)_3, \Delta} (EtO)_2\overset{O}{\overset{||}{P}}\overset{\frown}{}EWG$$

$$(EtO)_2\overset{O}{\overset{||}{P}}\overset{\frown}{}CO_2Et \xrightarrow{BASE (NaH)} (EtO)_2\overset{O}{\overset{||}{P}}\overset{\frown}{\underset{\ominus}{}}CO_2Et \xrightarrow{\overset{R}{\underset{R'}{}}=O} \overset{R}{\underset{R'}{}}\overset{CO_2Et}{}$$

MORE REACTIVE THAN WITTIG REAGENT

This modification is a named reaction on it's own; unfortunately, few people can agree on which two of the names 'Wadsworth', 'Horner' and 'Emmons' to use. For the sake of diplomacy, I'm calling it the **Horner-Wadsworth-Emmons reaction.**

$$(EtO)_2\overset{O}{\overset{||}{P}}\overset{\frown}{}CO_2 \xrightarrow[\text{2) } \overset{\frown}{}\overset{O}{}, THF]{\text{1) NaH, THF}} \overset{\frown}{}CO_2Me + (EtO)_2\overset{O}{\overset{||}{P}}O^-Na^+$$

91%

Protection of Alcohols

Recall sometime earlier that we discussed the protection of aldehydes and ketones as acetals, so they wouldn't react with bases or nucleophiles when it wasn't desired.

Alcohols have a similar problem. Let's say you wanted to make a Grignard reagent with an alcohol function in it. It would never work in the most straightforward way, because the Grignard reagent, once formed, would deprotonate the alcohol, and the 'alkyl anion' activity would be killed.

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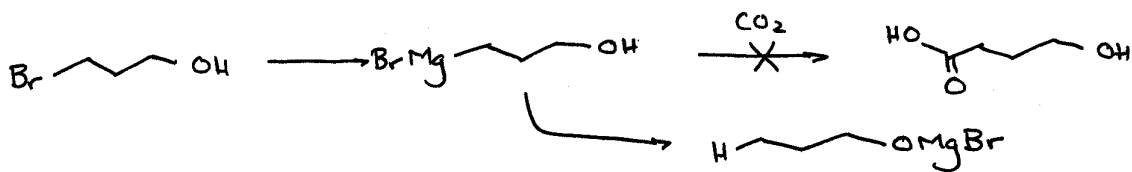
The most common way of getting around this and related problems is to protect the alcohol as some type of ether, from which the alcohol could easily be regenerated later. There are many versions of this, but one of the easiest is protection as the tetrahydropyranyl ether (THP ether), which is actually a type of **acetal**.

These are made by adding dihydropyan and a catalytic amount of acid to the alcohol. The resultant R-OTHP ether (or acetal) is stable to Grignard reagents, LiAlH$_4$, and many oxidizing reagents (as long as there's <u>no acid present</u>). Regeneration of the alcohol function is easily done by adding aqueous acid.
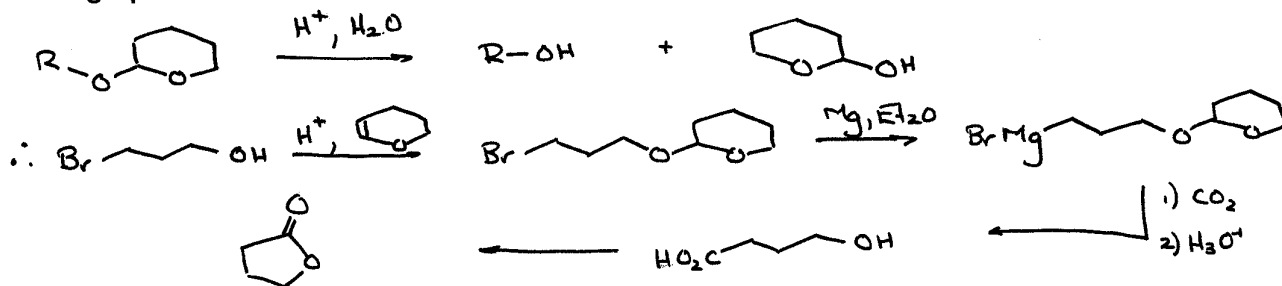
It is also worthy of note that the formation of protecting groups of alcohols is faster for the less hindered alcohols (1° > 2° > 3°). As a result, it is often possible to selectively protect one alcohol in the presence of another. This can be very useful.
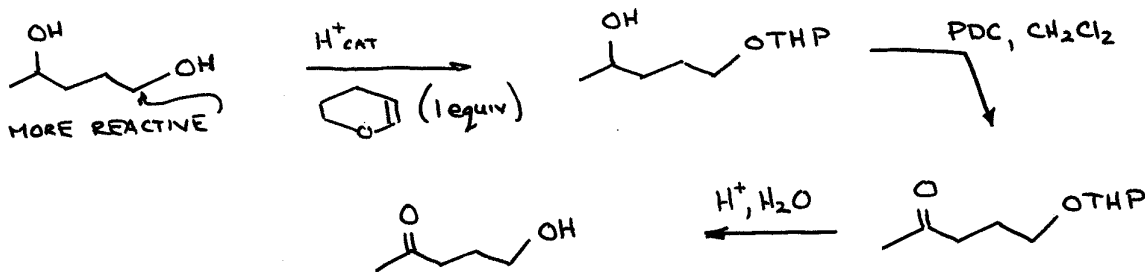
There are many, many protecting groups, to the point where there are books devoted to this subject exclusively. We will leave it at this point.

Diels-Alder Reaction   ([4+2] Cycloadditions)

The Diels-Alder reaction is a reaction that occurs between a **conjugated diene** and an alkene (or an alkyne), which are called **dienophiles**. It is simply done by taking the two and heating them up in an inert solvent. Benzene and toluene are very common for this, although, many, many other solvents have been used often.
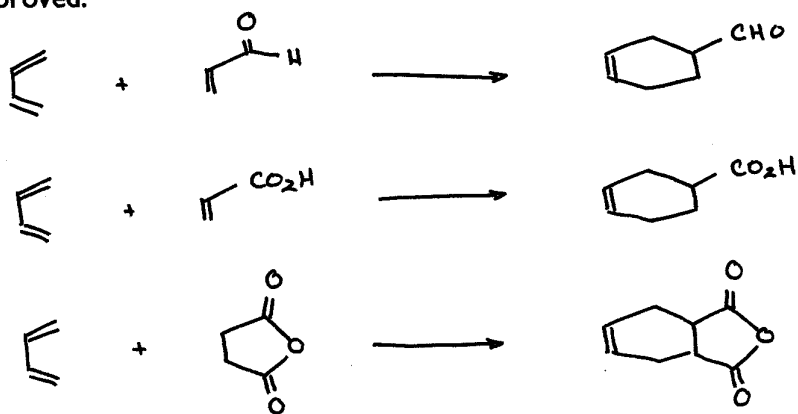
The prototype of the reaction is:

DIENE   DIENOPHILE

General Considerations
The Dienophile:

As a dienophile, ethene itself is very poor, and rarely reacts. When electron withdrawing groups (usually -M groups) are conjugated to the C=C however, the reactivity is much improved.

Alkynes are also quite respectable dienophiles, providing -M groups are conjugated here, too. Dimethyl acetylenedicarboxylate (DMAD) is a very common dienophile.
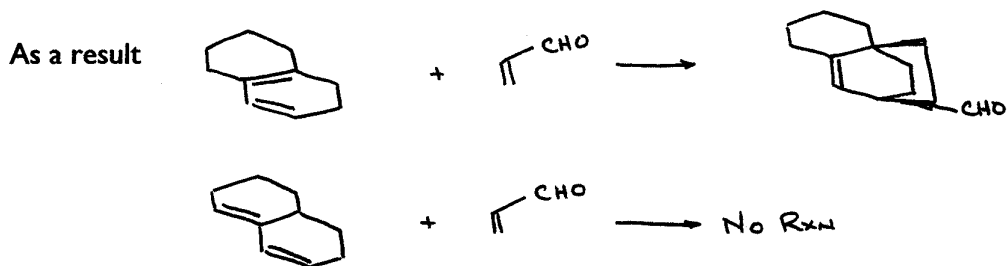

DIMETHYL ACETYLENEDICARBOXYLATE

The Diene:

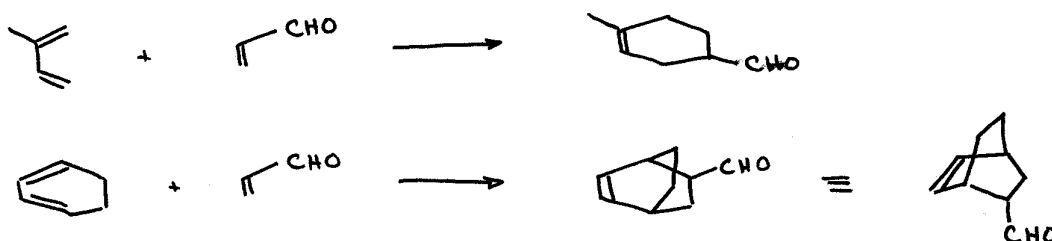There are two absolute requirements for dienes to be reactive in Diels-Alder reactions. They are:

-the diene 'must' be conjugated
-the diene must be able to attain an s-cis conformation

S-CIS   S-trans

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As a result
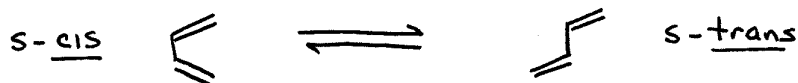
This is because the ends of the diene must be close enough together to react with the ends of the dienophile simultaneously.

The diene can be linear or cyclic

Butadiene (the unsubstituted case) is reactive enough to enter into a Diels-Alder, and is used commonly. The addition of electron donating groups (+I and +M), however, increases the reactivity of the diene by making it more electron rich.
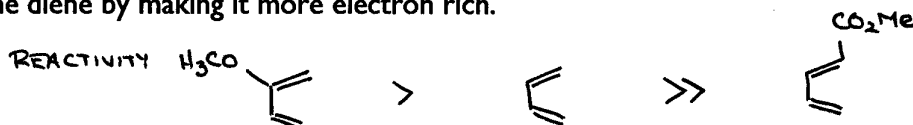

The diene is susceptible to steric hindrance.

Aromatic compounds are generally not useful as Diels-Alder dienes. Disrupting the aromaticity to enter into the reaction simply has too great an energetic cost. There is one noteworthy exception, furan, which *is* a decent Diels-Alder diene. It is "less aromatic" than other aromatic compounds.
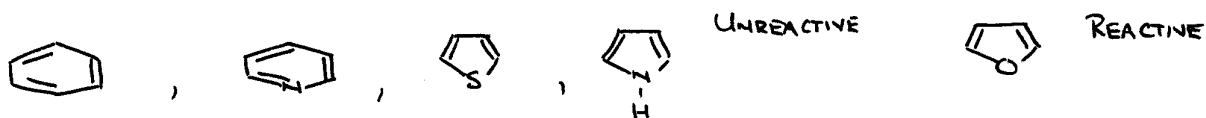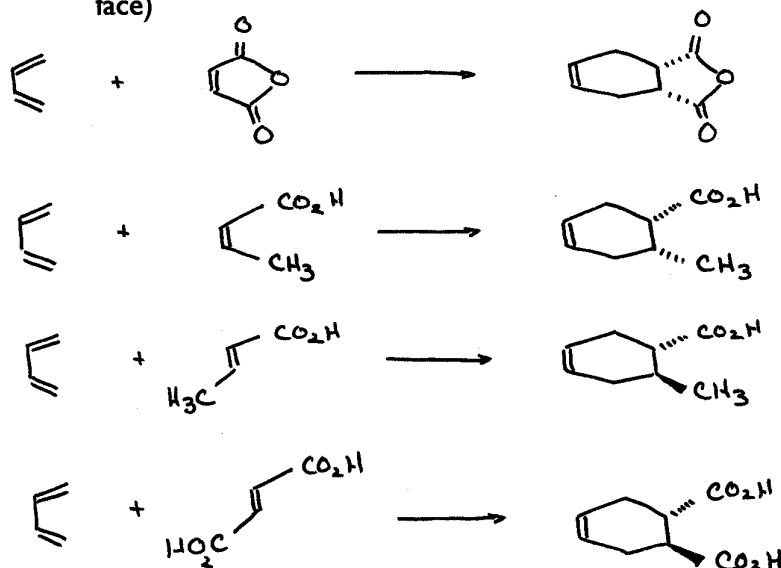

Other commonly used dienes:

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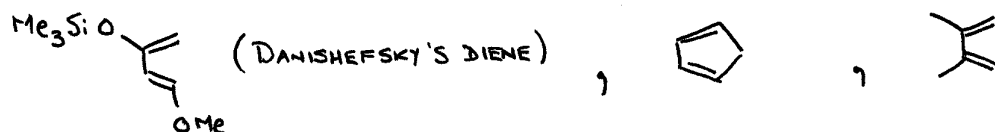
Stereochemistry/Regiochemistry

This can considered from several perspectives.

1) As we've already discussed, the diene must be able to attain an *s-cis* conformation. It doesn't have to be the ground state; it just has to be accessible.

2) With respect to the dienophile, the reaction is stereospecifically *syn* (addn to same face)

3) Endo versus exo addition
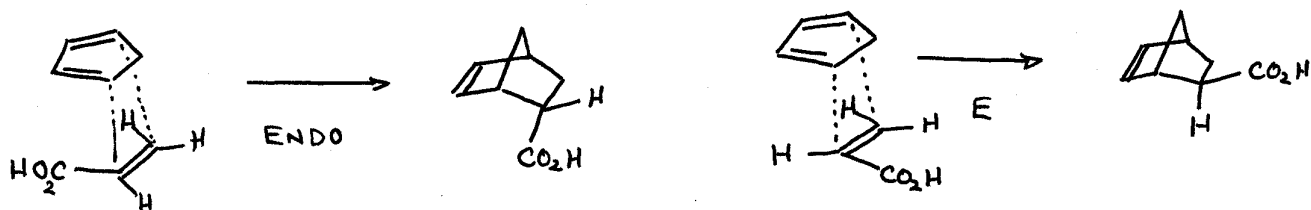
The majority of the time, the _endo_ product is the kinetic one, and it is usually obtained. Note however, that the Diels-Alder reaction is reversible, and if high T and extended reaction times are used, the reaction may end up under thermodynamic control. Then all bets are off on endo vs. exo.

4) Ortho/Para Rule
When an unsymmetrical diene and an unsymmetrical dienophile add, two possible regiochemical results may be obtained.

Case A- 1-substituted dienes

MOSTLY

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