

## ■ Organic Synthesis II: Selectivity & Control. Handout 2.1

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- **Regioselectivity: a recap**
- **Reacting the less reactive:** kinetic and thermodynamic approaches  
Trianions (and last in, first out)
- **Protecting groups for oxygen:** Silyl ethers  
Benzyl Ethers  
Acetal and Ketals  
Carbohydrates and protecting groups  
Selective cleavage of benzylidene acetals  
THP and butanediactal protecting groups
- **Case studies in protection:** Synthesis of a segment of Epothilone, a complex natural product  
The synthesis of specifically functionalized carbohydrates
- **Synthetic Planning:** Reactivity and control provide synthetic 'guidelines'
- **Books & other resources:**
  1. Organic Synthesis: The Disconnection Approach (Warren & Wyatt, Wiley, 2nd Ed., 2008)
  2. Classics in total synthesis (Nicolaou & Sorensen, Wiley, 1996).
  3. Protecting groups (Kocienski, 3rd Ed., Thieme, 2003)

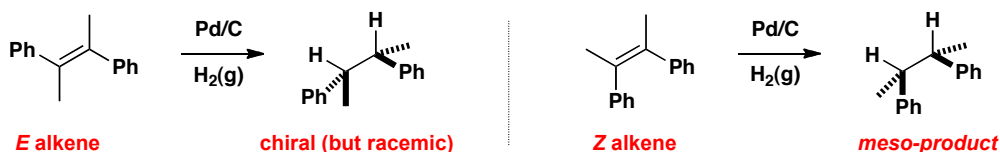
## ■ Organic Synthesis II: Selectivity & Control. Handout 2.2

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- **Synthetic Planning:** Reactivity and control provide synthetic 'guidelines'
- **Two group disconnections:** Two approaches to Mesembrine  
(i) intramolecular Mannich & MVK Michael addition  
(ii) Birch Reduction & Cope rearrangement route
- **Pattern Recognition:** The Diels Alder reaction  
Guanacastepene and a masked D-A disconnection  
The intramolecular Diels Alder reaction: Indanomycin  
Hetero-Diels Alder reactions: Carpanone
- **Two directional synthesis** Total synthesis through bi-directional synthesis
- **Pharmaceuticals** Commercial-scale synthesis of Crixivan
- **Pericyclic cascades** Colombiasin total synthesis  
Vinca alkaloid total synthesis
- **Books & other resources:**
  1. Organic Synthesis: The Disconnection Approach (Warren & Wyatt, Wiley, 2nd Ed., 2008)
  2. Classics in total synthesis (Nicolaou & Sorensen, Wiley, 1996).
  3. Protecting groups (Kocienski, 3rd Ed., Thieme, 2003)

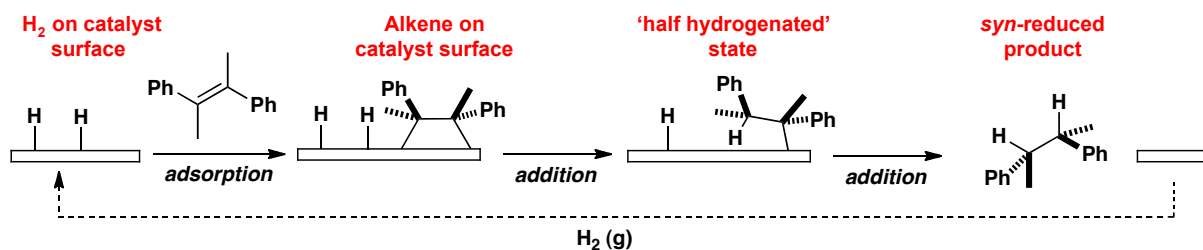
## Hydrogenation: metallic catalyst+hydrogen

- Reductions of alkenes: usually Pd metal on carbon support (and H<sub>2</sub> gas)



Generally: overall stereospecific *syn*-addition of hydrogen across the alkene  
Pd, Pt, Ru, Rh can all be used in hydrogenation processes

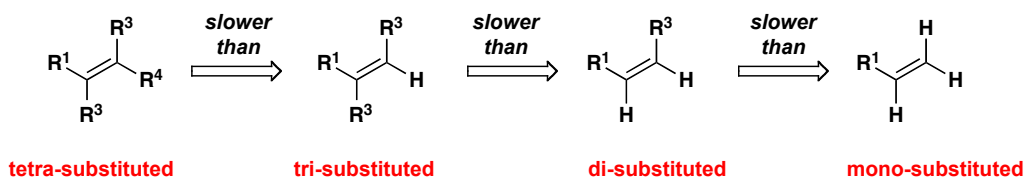
- Mechanisms of 'heterogeneous' hydrogenation are complex



Substrate binds to catalyst surface from one face leading to overall *syn*-hydrogenation

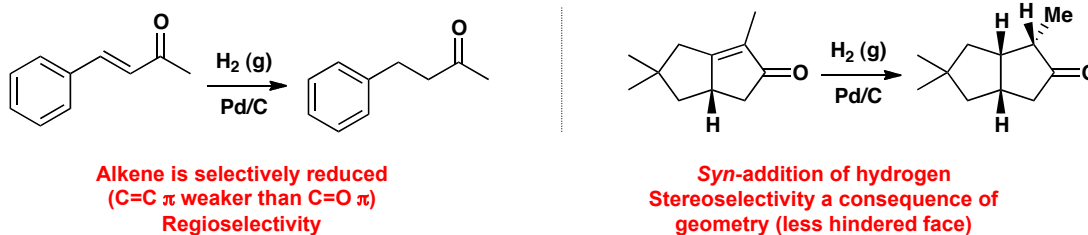
## Hydrogenation: metallic catalyst+hydrogen

- More substituted alkenes are reduced more slowly



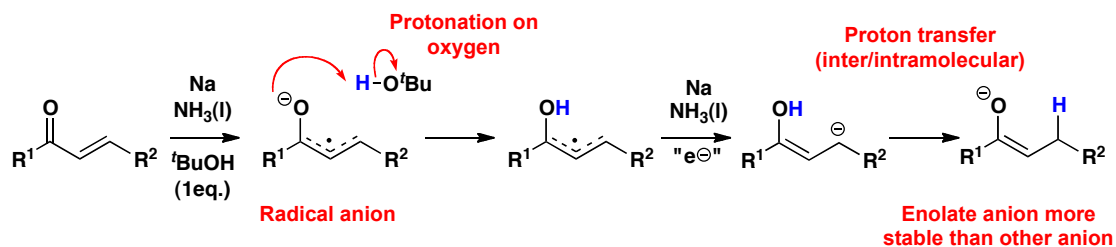
This can be attributed to steric hindrance to adsorption onto the catalyst surface

- We can also achieve selectivity in hydrogenation

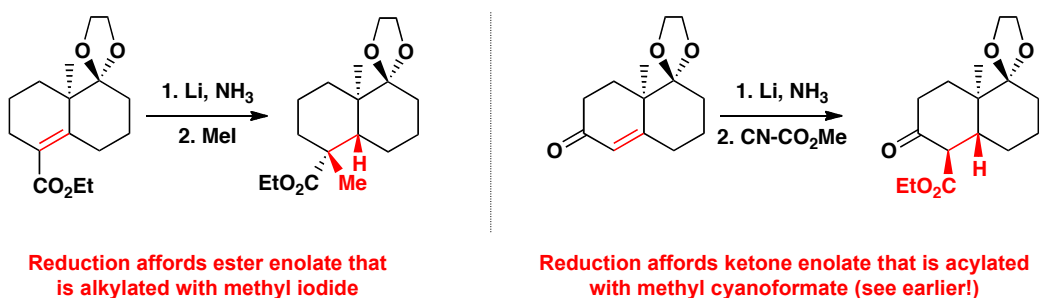


## ■ Birch-type reduction of $\alpha,\beta$ unsaturated ketones

- Birch-type reductions of  $\alpha,\beta$  unsaturated ketones give enolates as intermediates

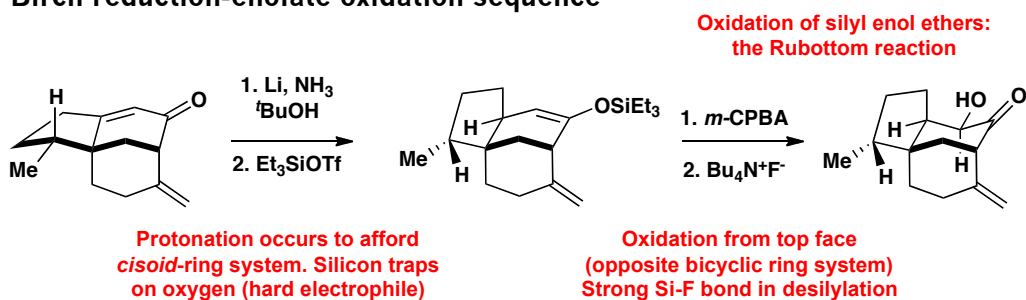


- These enolates can be used as reactive intermediates in ‘tandem’ reaction sequences

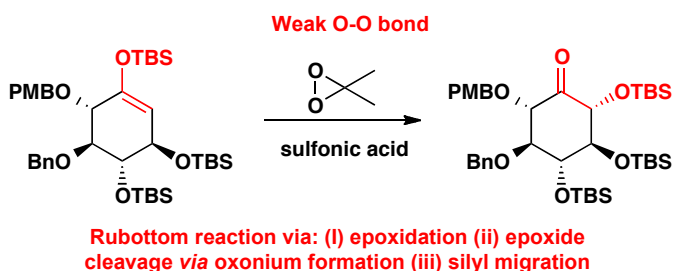
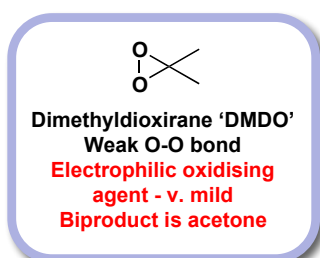


## ■ Oxidation of enolates and enol ethers (electron rich alkenes)

- Birch reduction-enolate oxidation sequence



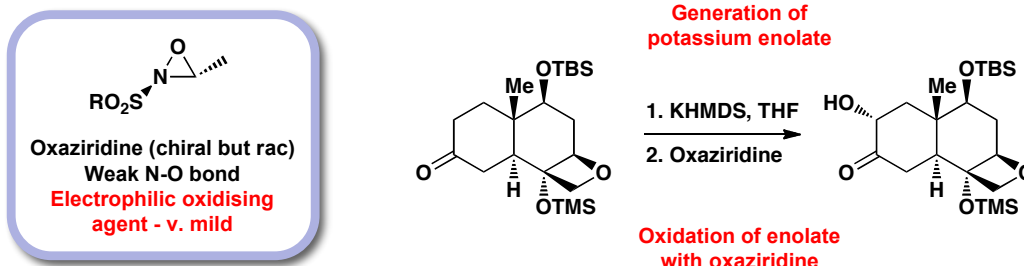
- Dioxiranes are alternative oxidizing agents for these materials



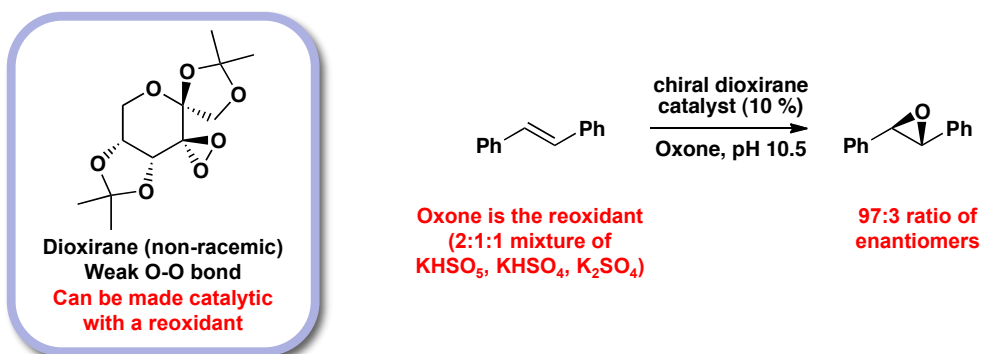
‘Protecting groups’: TBS = tert-butyl dimethylsilyl, Bn = benzyl  
PMB = *para*-methoxybenzyl (see later in the course)

## ■ Oxidation of enolates and enol ethers (electron rich alkenes)

- Oxaziridines can be used to perform similar transformations

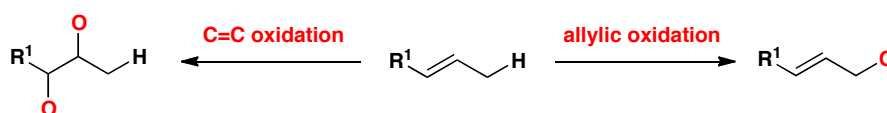


- Stereochemical information can be transmitted with chiral dioxiranes

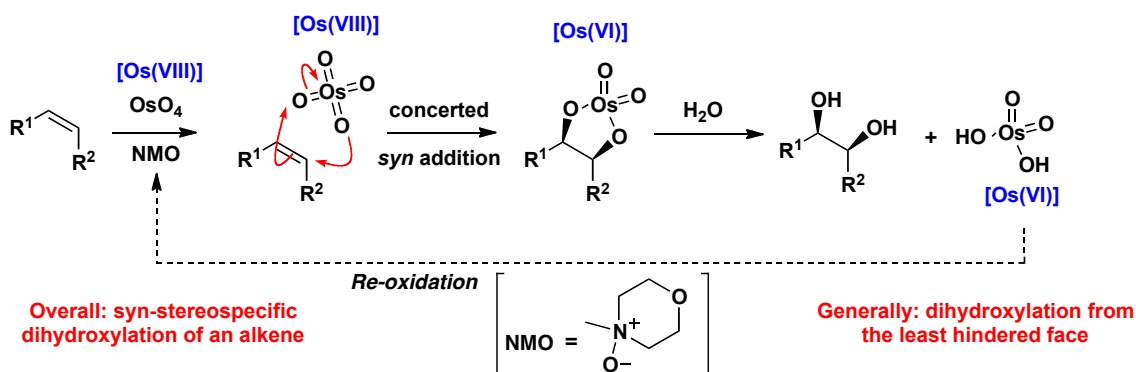


## ■ Selective oxidations of alkenes

- For alkenes there are essentially two modes of oxidation:



- C=C oxidations: Recap -  $\text{OsO}_4$  oxidation of alkenes

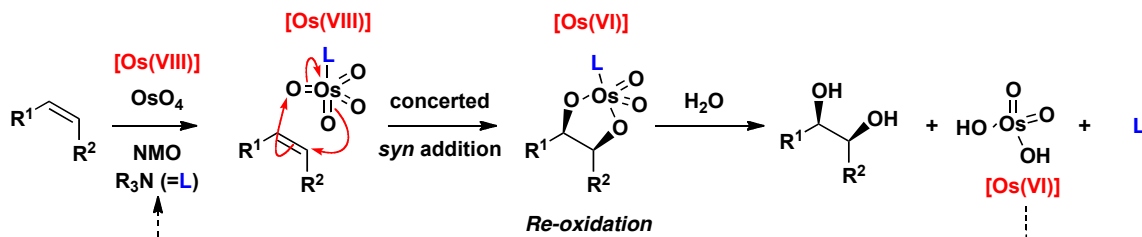


Compare with Woodward and Prevost methods for dihydroxylation

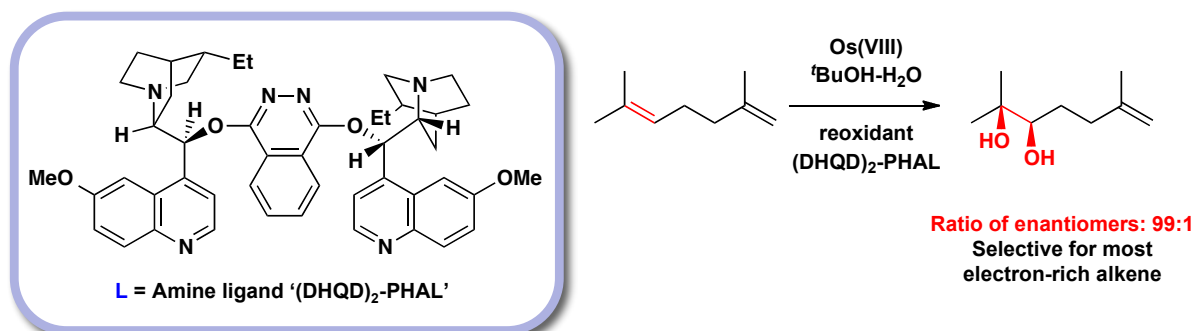
(see Dr E. Anderson Course HT 2011)

## ■ Selective oxidations of alkenes

- The dihydroxylation reaction is accelerated by amines (catalysis)

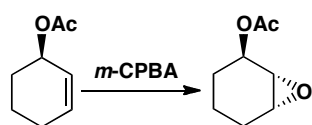


- We can transfer chirality from the amine to permit asymmetric dihydroxylation

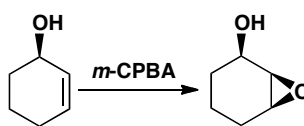


## ■ Recap: allylic alcohol alkene oxidations (see Dr Anderson course, HT 2011)

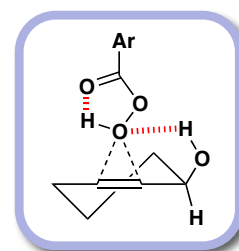
- Allylic epoxidation: *m*-CPBA-mediated



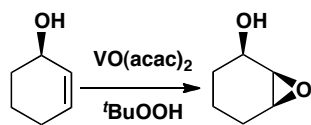
**Major diastereoisomer**  
Sterics: least hindered face is oxidized



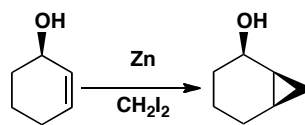
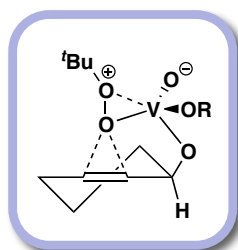
**Major diastereoisomer**  
Intramolecular H-bond stabilizes TS and directs oxidation



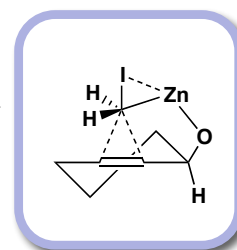
- Allylic functionalization: Vanadium and Zinc mediated process



**Major diastereoisomer**  
Alcohol-directed epoxidation

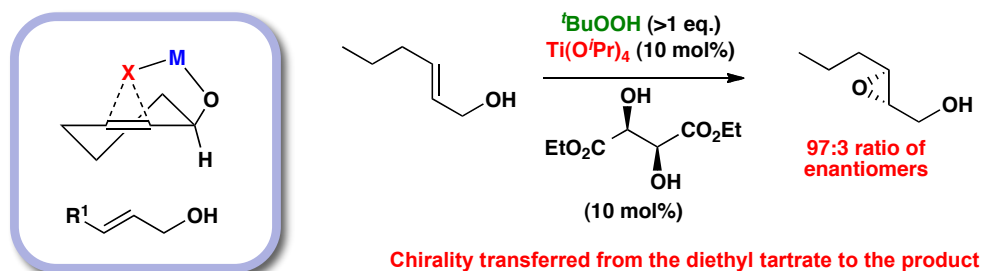


**Major diastereoisomer**  
Hydroxyl-directed cyclopropanation

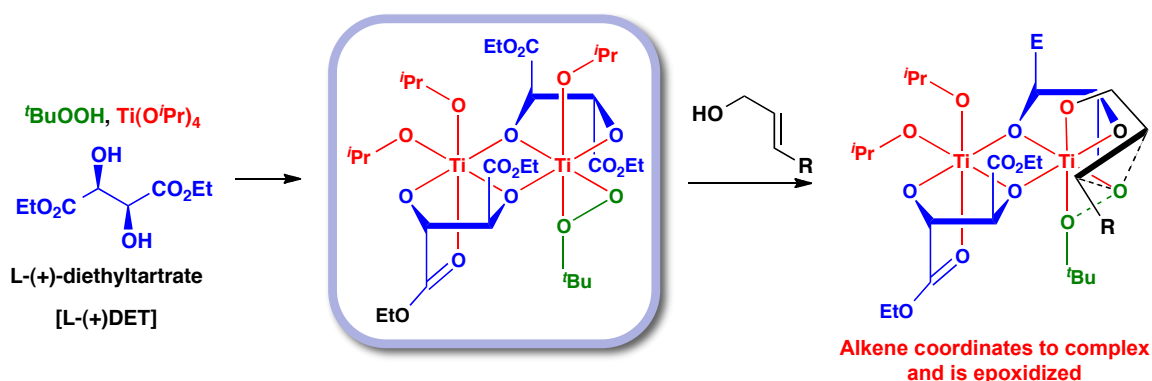


## Allylic alcohol reactions: Sharpless asymmetric epoxidation

- Reactions directed by the allylic alcohol are faster & more selective

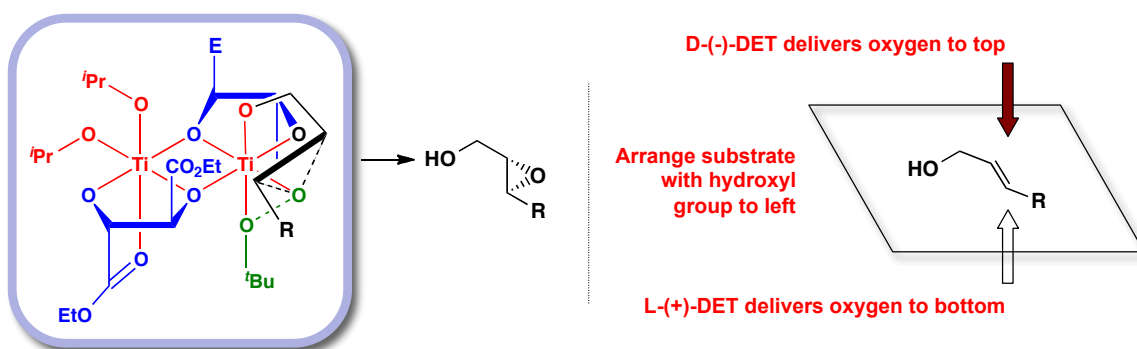


- The complex formed by the reagents is, well.....complex

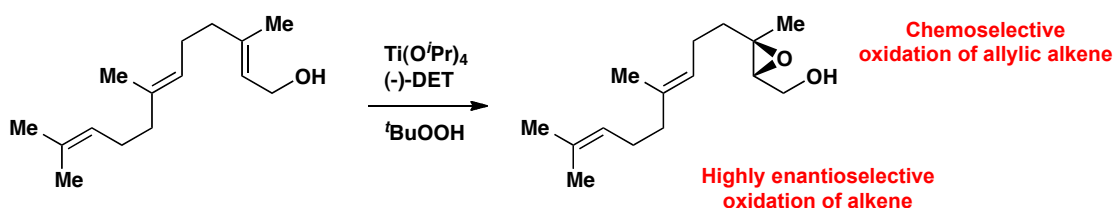


## Allylic alcohol reactions: Sharpless asymmetric epoxidation

- Luckily there is a mnemonic to work out which enantiomer is produced

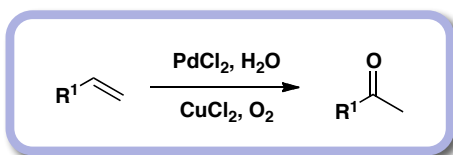


- Examples:



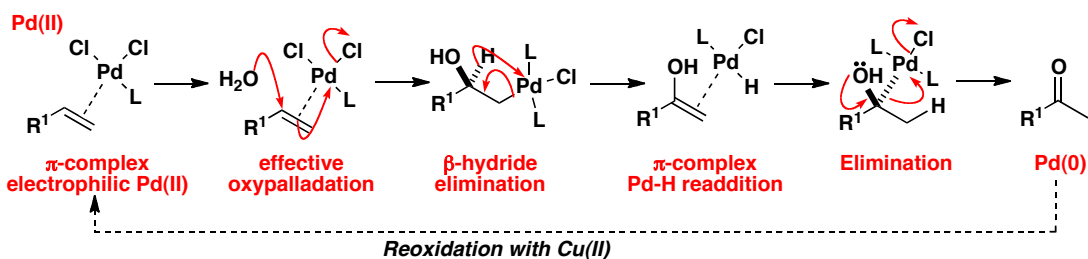
## Wacker Oxidation

- Mild method for oxidation of terminal alkenes



Generally gives this regiochemistry of oxidation

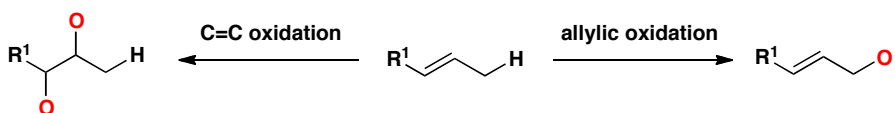
- Generalized mechanism:



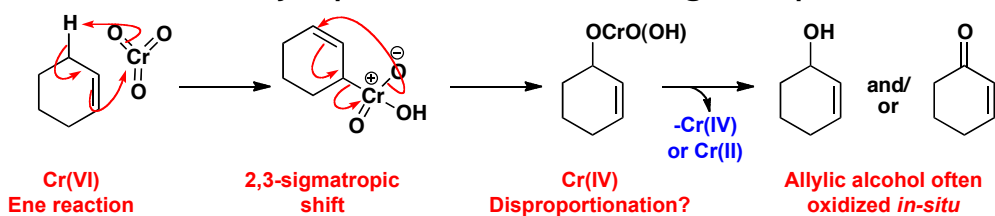
Attack of nucleophile (in this case  $\text{H}_2\text{O}$ ) is regioselective for the most substituted position  
Probably a consequence of charge stabilization in the TS (compare with attack of water on bromonium ions) but also a preference to put the bulky Pd in the least hindered position

## Oxidation of the allylic position

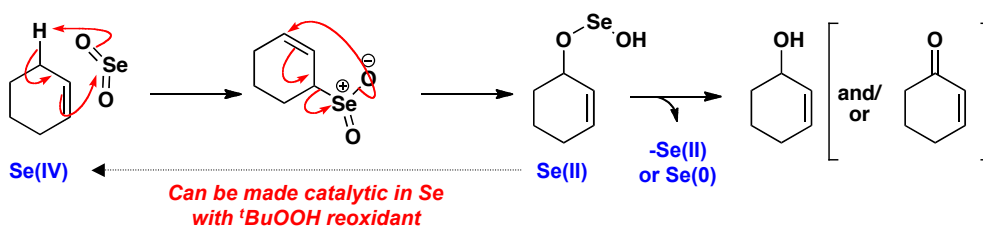
- The second of our two modes of reactivity:



- Oxidation in the allylic position is often a rearrangement process

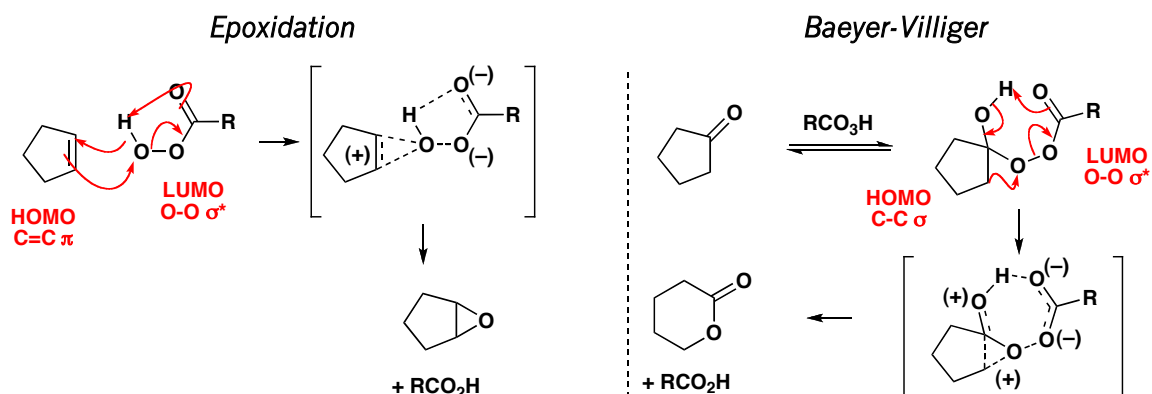


- Selenium dioxide can also be used: 'Riley Oxidation'



## Chemoselectivity in Oxidation

### Epoxidation vs Baeyer-Villiger: a comparison



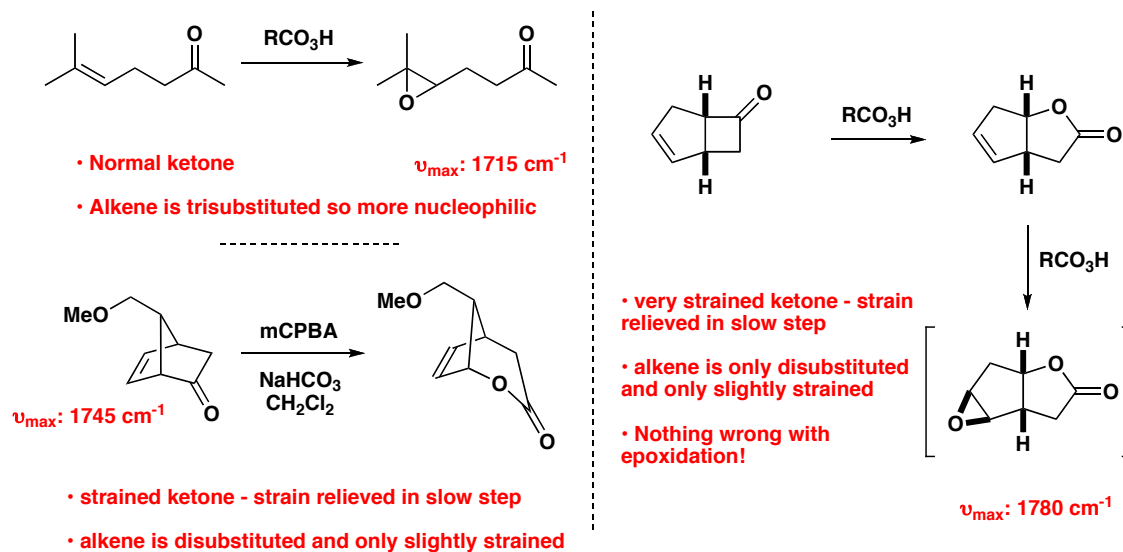
*Comparison: Though epoxidation is electrophilic attack on an alkene and Baeyer-Villiger rearrangement is nucleophilic attack on a C=O group, the slow steps both use the O-O  $\sigma^*$  as the LUMO*

*CF<sub>3</sub>CO<sub>3</sub>H is the best peroxy acid for both reactions.*

*So difficult to achieve chemoselectivity by choice of reagent*

## Oxidation: Epoxidation vs Baeyer-Villiger

### A delicate balance - take each case on its merits!

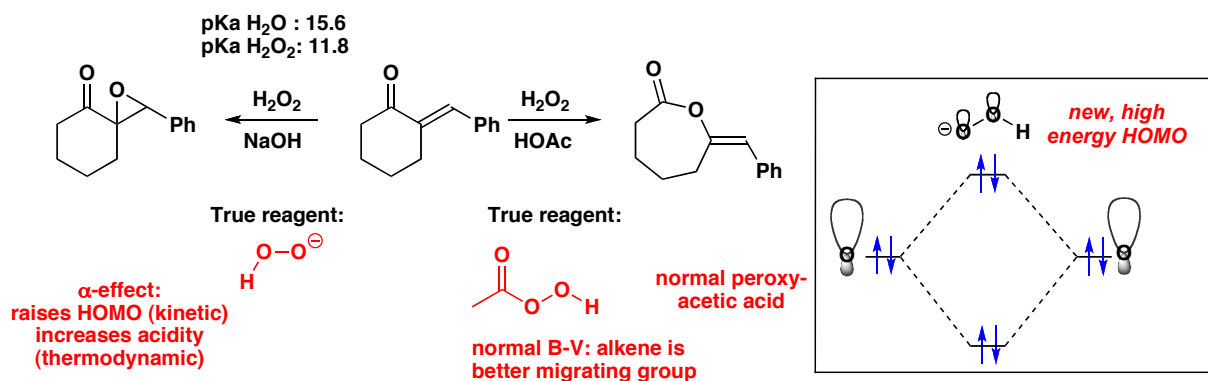


*Note regioselectivity in Baeyer-Villiger oxidation: more substituted carbon atom migrates with retention of configuration*

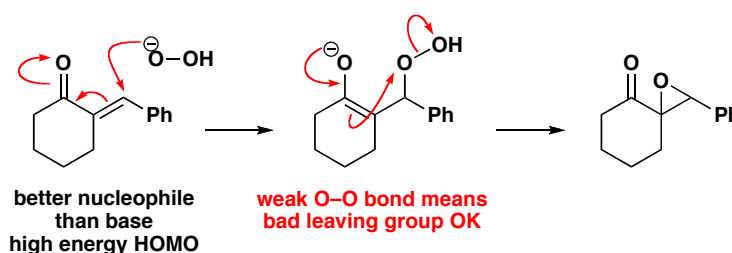


## ■ Oxidation: Epoxidation vs Baeyer-Villiger of conjugated enones

### ■ Chemo-selectivity and regioselectivity

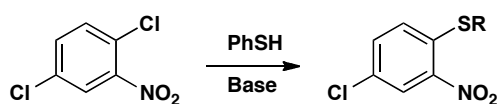


### ■ Mechanism:

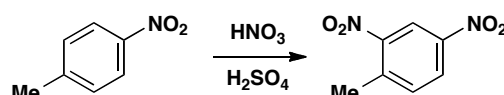


## ■ Regioselectivity: recapitulation of previous examples

### ■ Generation of functionalized aromatic compounds

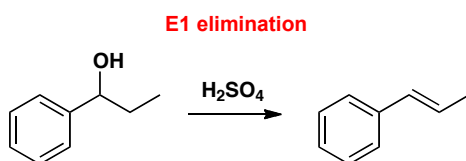


Only the *ortho*-leaving group is substituted

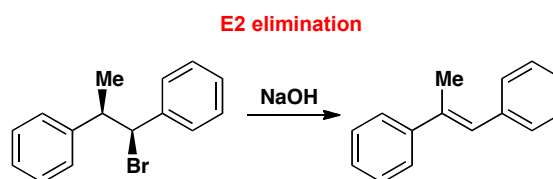


Combination of directing effects lead to specific nitration

### ■ Elimination processes



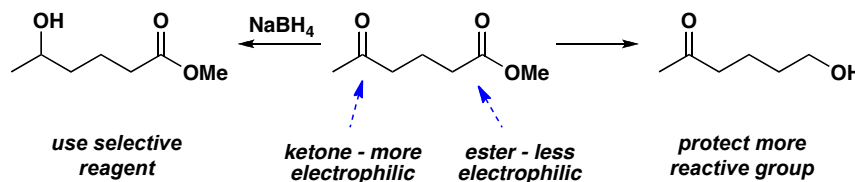
This geometry is the major product: consequence of lower TS energy (consider steric effects in intermediate cation & relate to TS energy)



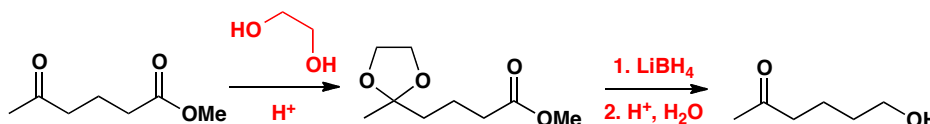
This geometry is the major product: H and Br must be antiperiplanar. This reaction is stereospecific

■ **Complex materials are polyfunctional: selectivity?**

- Functional groups may have the same type of reactivity:



- How do we access a kinetically less reactive functional group?



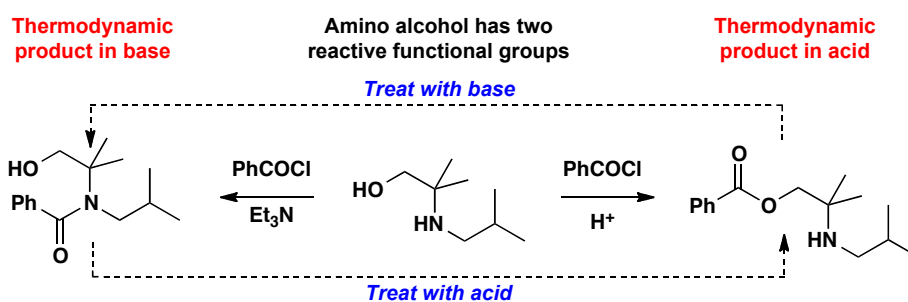
Ketone more electrophilic than ester: exploit in temporary blocking group formation

Ester now only electrophilic group. Can be reduced selectively, and then blocking group can be removed to regenerate ketone

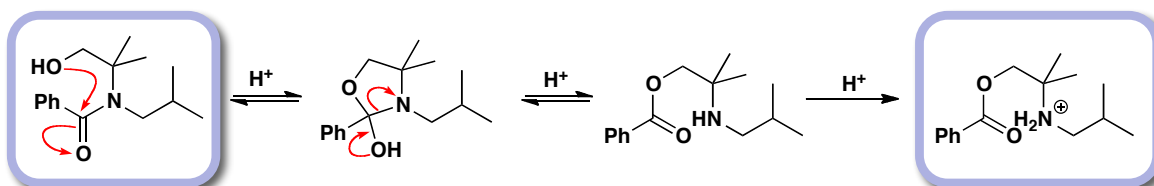
The use of 'protecting groups' can allow us to perform selective transformations but they add length and complexity to many synthetic routes (we have to put them on and then take them off too!)

■ **Reacting the less reactive group**

- Functional group reactivity can be a thermodynamic or kinetic phenomenon



- The most stable product predominates under the reaction conditions

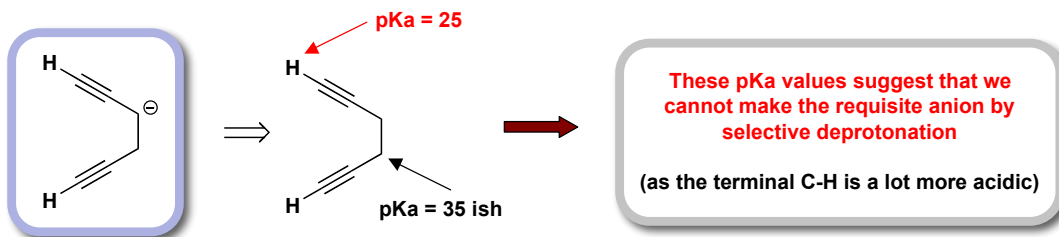


Amides are thermodynamically more stable than esters: predominates in base

Basic nitrogen is protonated in acid: unable to function as nucleophile

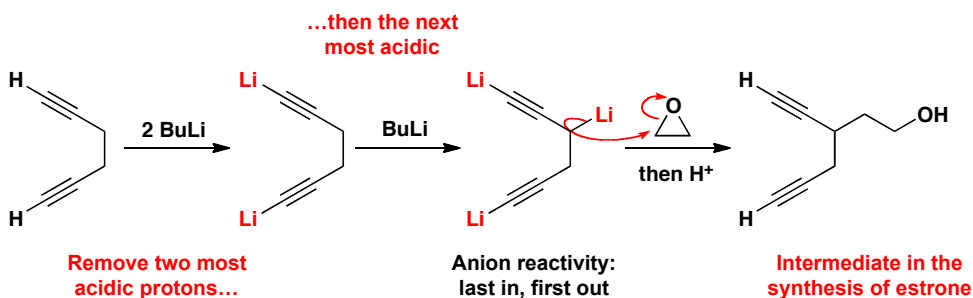
## ■ Reacting the 'less' reactive group

### ■ Accessing challenging patterns of reactivity



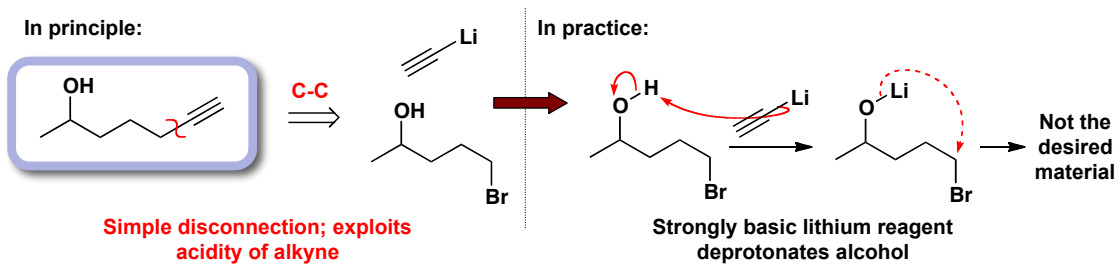
How do we access an anion like this?

### ■ A solution: make a tri-anion to allow access to the less reactive position



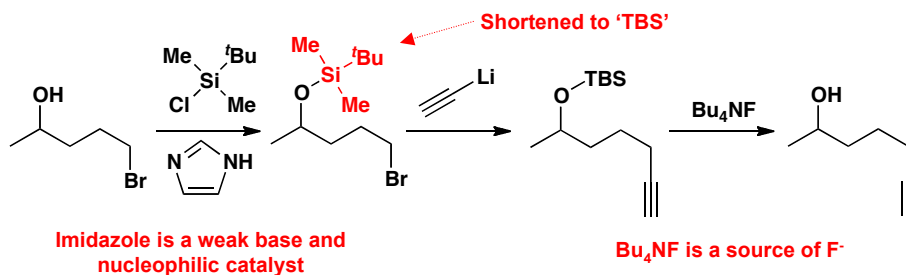
## ■ Protecting groups for oxygen

### ■ Blocking groups allow access to the less reactive functional group



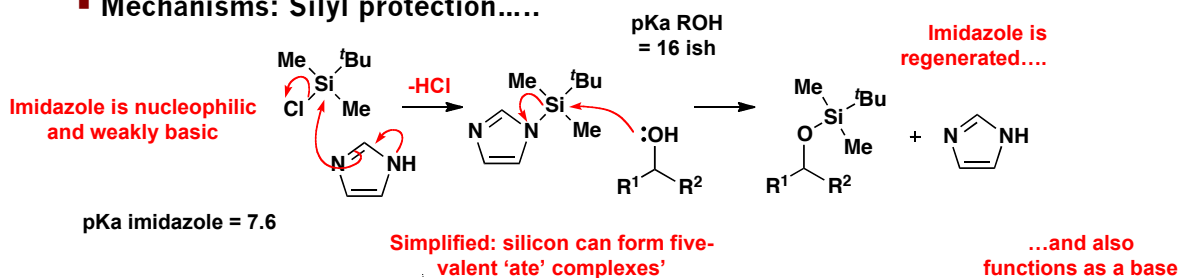
A solution is to use a protecting group to block the reactivity of the alcohol functional group

### ■ Silyl ethers are effective and versatile protecting groups for alcohols

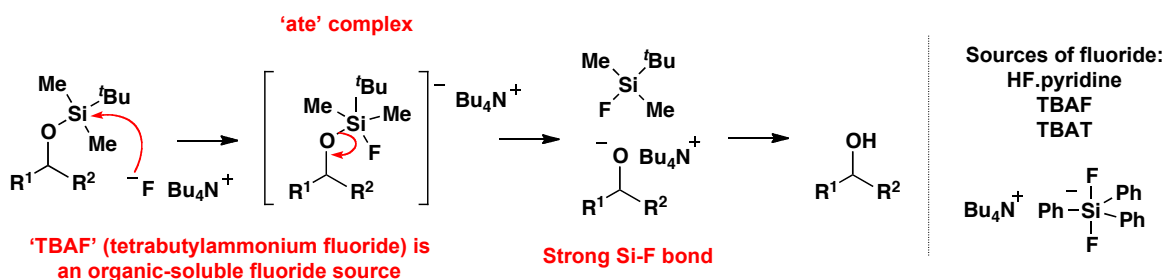


## Protecting groups for oxygen

### Mechanisms: Silyl protection.....



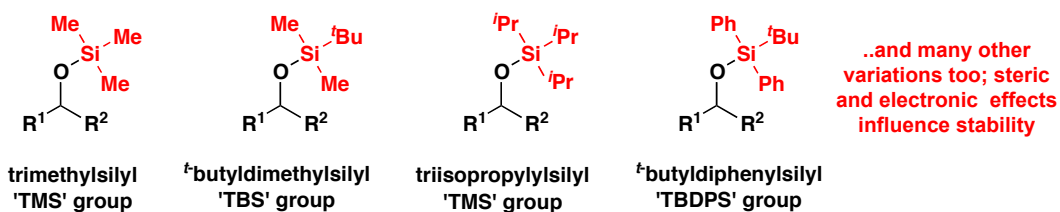
### .....and deprotection: Si-F is a strong bond (142kcal mol<sup>-1</sup>; Si-O 112kcal mol<sup>-1</sup>)



Silyl ethers are generally removed by treatment with fluoride or under acidic conditions but can also be hydrolysed under basic condition (sodium hydroxide)

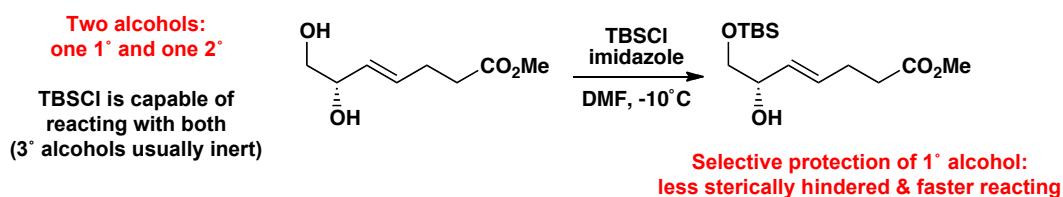
## Protecting groups for oxygen

### Different groups on the silicon change the nature of the group:



acid	1	20000	700000	5000000	Rates (1/k <sub>rel</sub> ) [bigger = slower]
base/F-	1	20000	100000	20000	

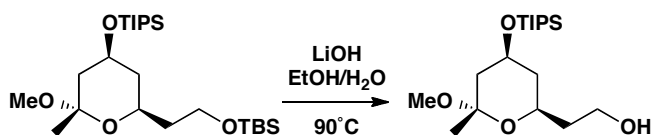
### Exploiting the different steric environments of alcohols; selectivity in protection



Similar selectivity for hydrolysis reactions too: 1° hydrolysed faster than 2°

## Protecting groups for oxygen

### ...and selectivity in deprotection

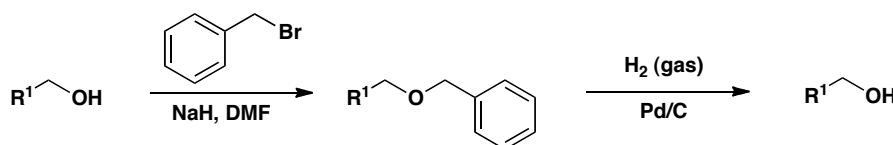


Selective removal of 1° TBS group rather than 2° TIPS group

Silyl ethers are generally stable to weak acid and base, and oxidizing and reducing conditions (except TMS: very labile!)

They are removed with strong acids (inc. Lewis acids), strong base and fluoride

### Benzyl ethers: alternative protecting groups for oxygen



Made by the classical Williamson ether synthesis

Removed by hydrogenation Pd common, but Ru, Rh, Pt also

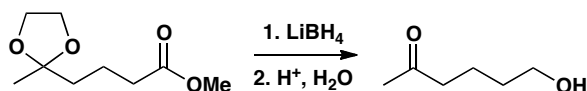
Generally stable to acids, bases and fluoride

Orthogonal to silyl ethers

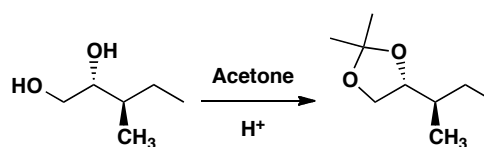
It is important to recognize that protecting groups are a (somewhat) necessary evil which can help or hinder efficiency in synthesis. Their use must be considered in the overall strategic approach to a synthesis

## Protecting groups for oxygen: acetals and ketals

### Acetals can be used to protect ketones or to protect diols



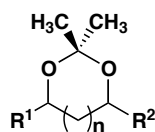
Ketone masked as an acetal to allow for reduction of less reactive functional group



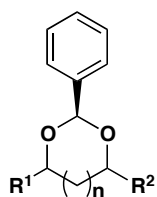
Protect diol as a ketal with acetone and acid

### Acetal groups you are likely to come across

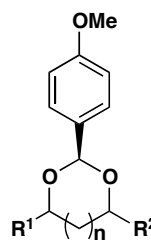
Generally  $n = 0, 1$   
For 1,2 and 1,3 diols



'acetonide'

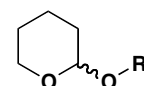


'benzylidene'



'p-methoxy benzylidene'

For alcohols

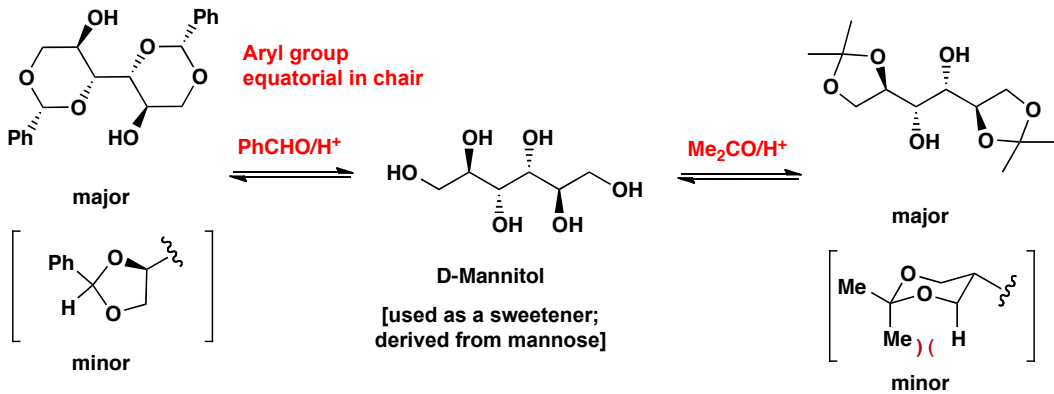


Tetrahydropyranyl 'THP'

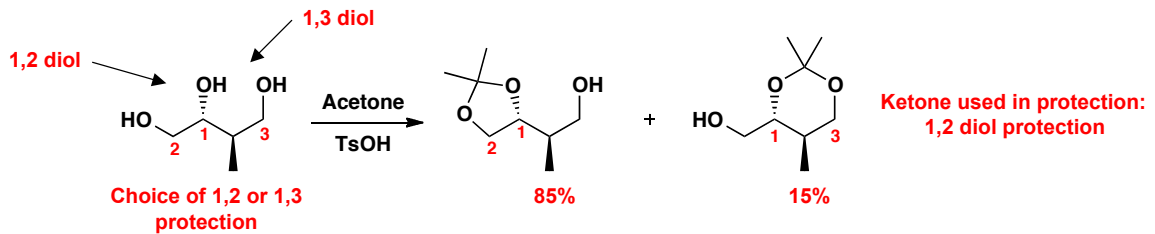
Reminder: acetals are generally made and hydrolysed under acidic conditions

## Protecting groups for oxygen: acetals and ketals

- Under thermodynamic control aldehydes select for 1,3-diols; ketones for 1,2 diols

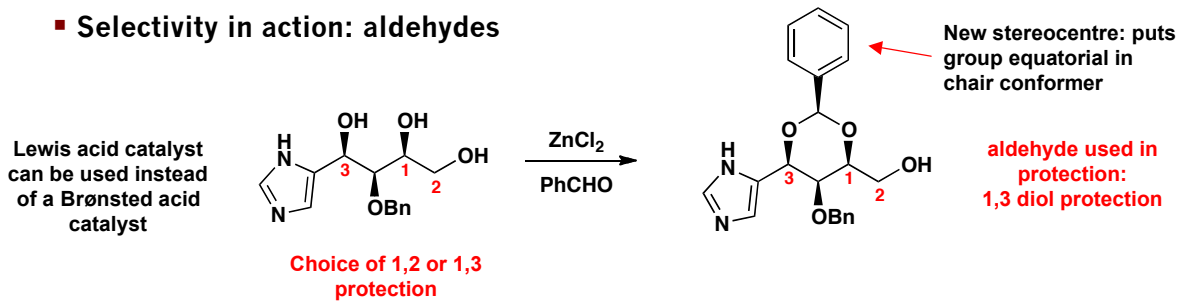


- Selectivity in action: ketones

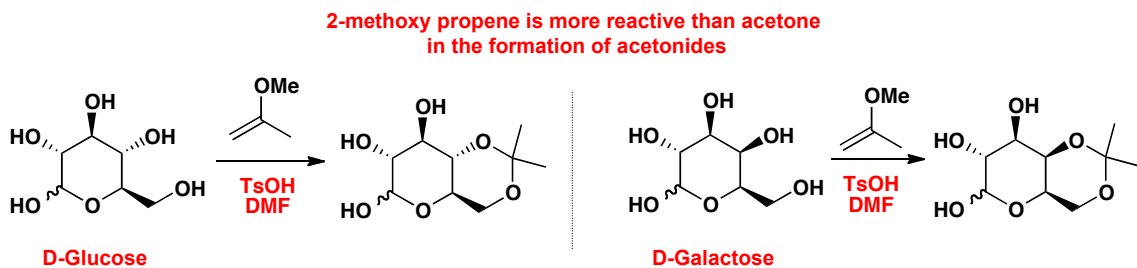


## Protecting groups for oxygen: acetals and ketals

- Selectivity in action: aldehydes



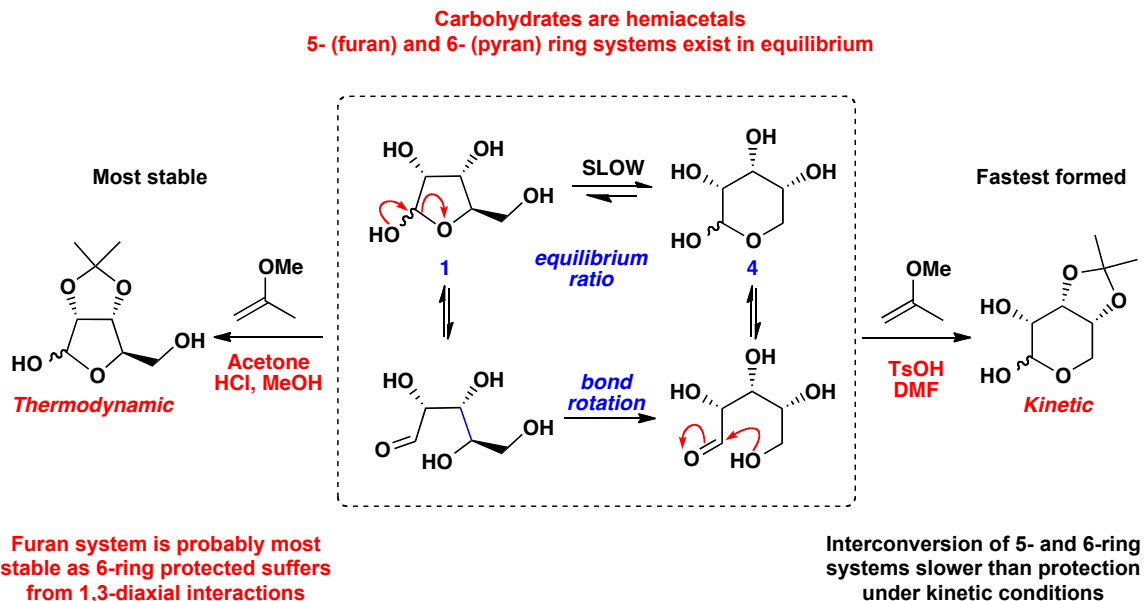
- Acetals and ketals can be made under kinetic control too:



Ketone selects 1,3 diol: the 1° alcohol is the most nucleophilic and reaction occurs there first  
 This selectivity relies on preventing equilibration to thermodynamic products

## Protecting groups for oxygen: acetals and ketals

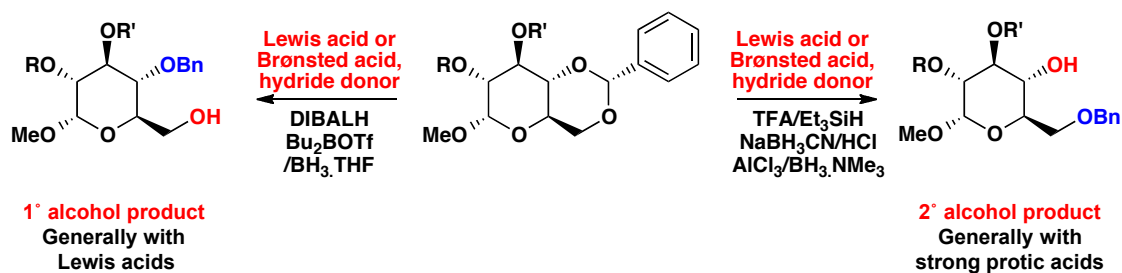
- kinetic and thermodynamic control can affect carbohydrate ring size



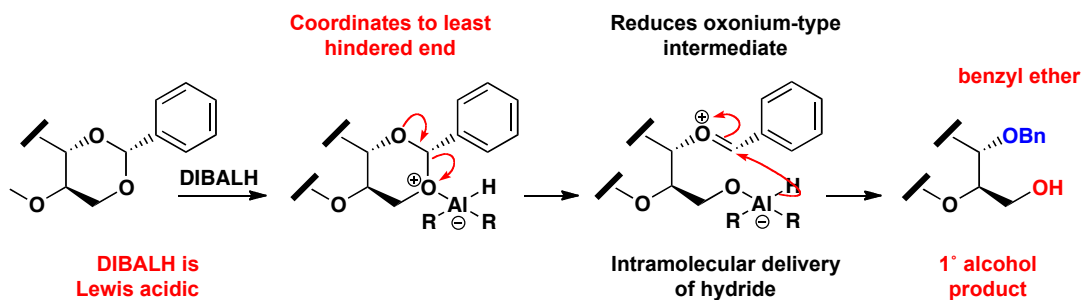
Very difficult to protect diequatorial diols with acetals using the groups we have seen so far

## Protecting groups for oxygen

- Benzylidene acetals can be regioselectively cleaved

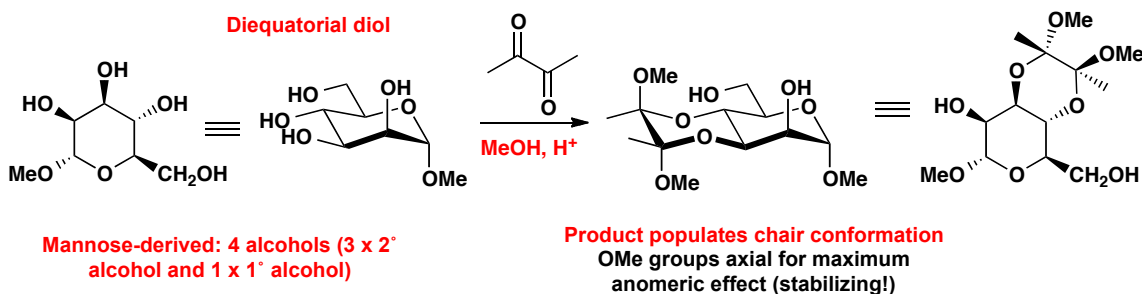


- Mechanism with Lewis acid

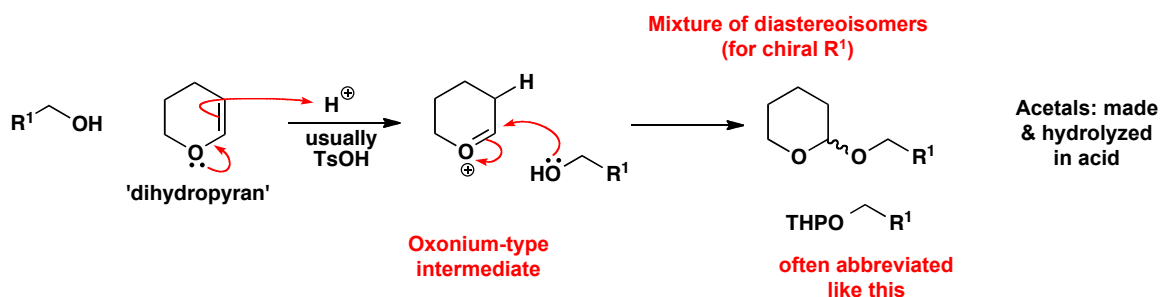


## Protecting groups for oxygen: acetals and ketals

- A special sort of ketal can be used for *trans*-diols

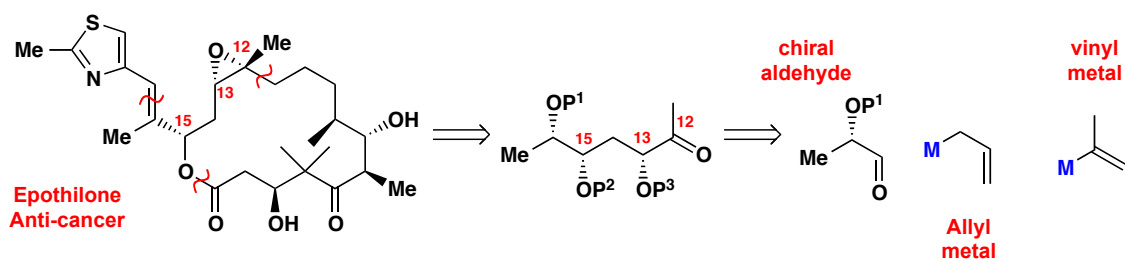


- The tetrahydropyranyl (THP) group is an acetal protecting group for alcohols

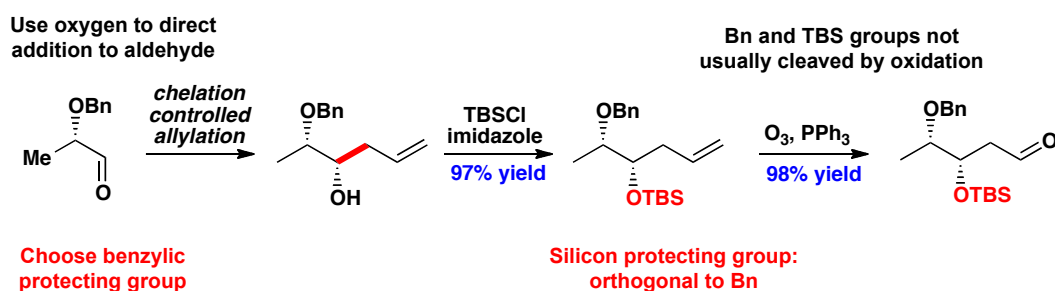


## Protecting groups: Case study I

- A fragment of a complex natural product: Epothilone



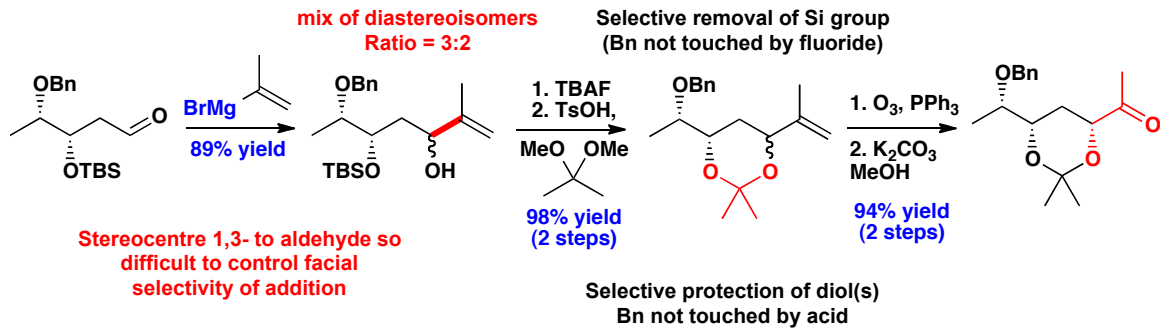
- Synthesis exploits orthogonal protecting group strategy



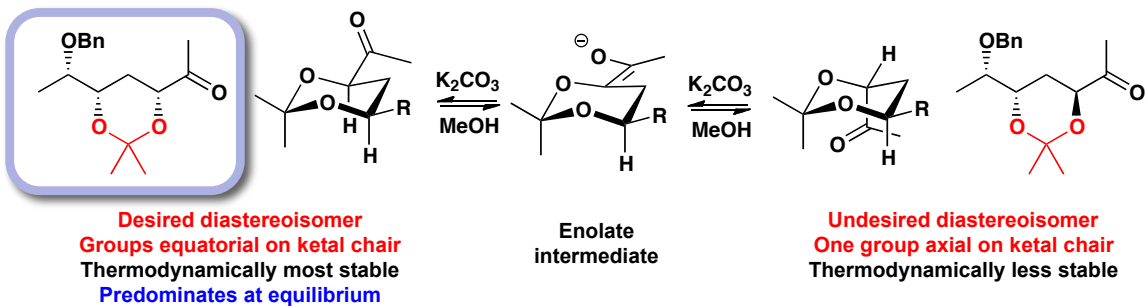


## Protecting groups: Case study I

### A fragment of a complex natural product: Epothilone

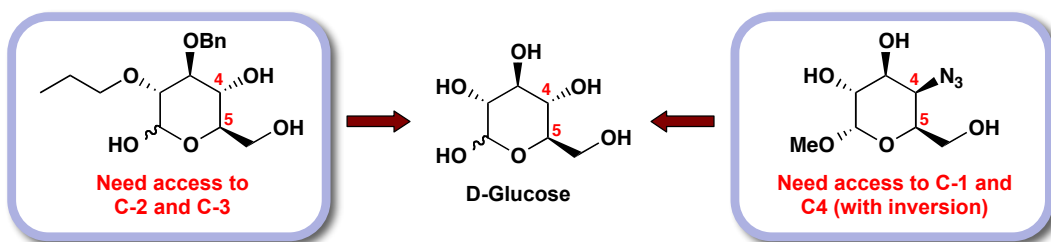


### Protecting groups are not always spectators: final step epimerization

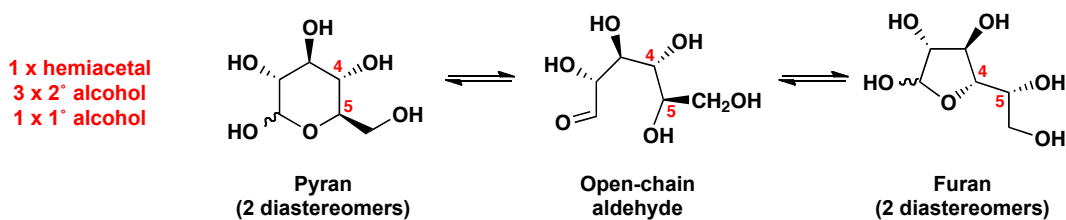


## Protecting groups: Case study II

### Carbohydrate targets often require access to specific functional groups



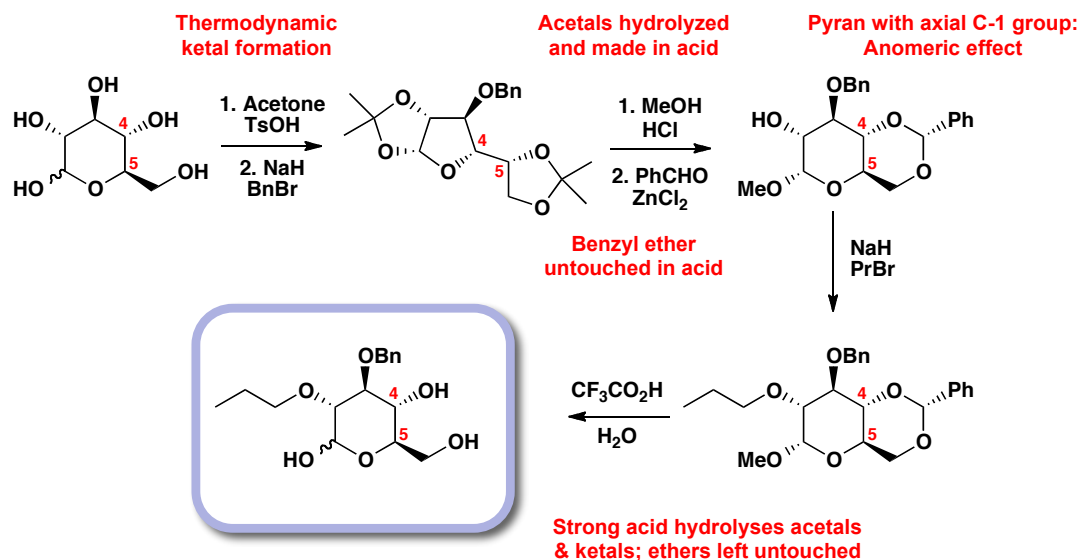
### D-Glucose is a polyfunctional material



Must consider the position of these equilibria in carbohydrate manipulations

## Protecting groups: Case study II

- Carbohydrate targets: examples of chronic protection!



This is an extreme example of the use of protecting groups: we should aim to minimize their use through the application of chemoselective transformations where possible.

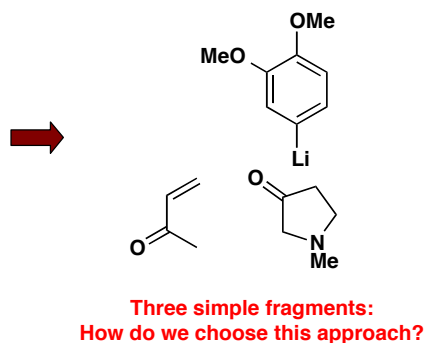
## Synthetic planning, reactivity and control

- How do we approach the synthesis of complex materials?



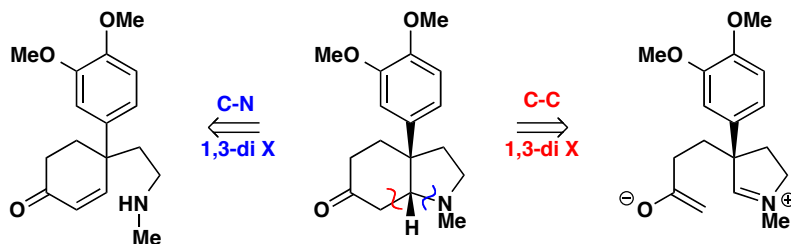
- The basics of synthetic planning: some 'guidelines' to consider

- Use **two-group** disconnections
- Disconnect at **branch points**
- Disconnect **rings** from chains
- Disconnect to **recognisable starting materials**
- Use **symmetry elements** if possible
- Analyse **oxidation states** and potential FGIs
- Chemoselectivity** is key to efficiency

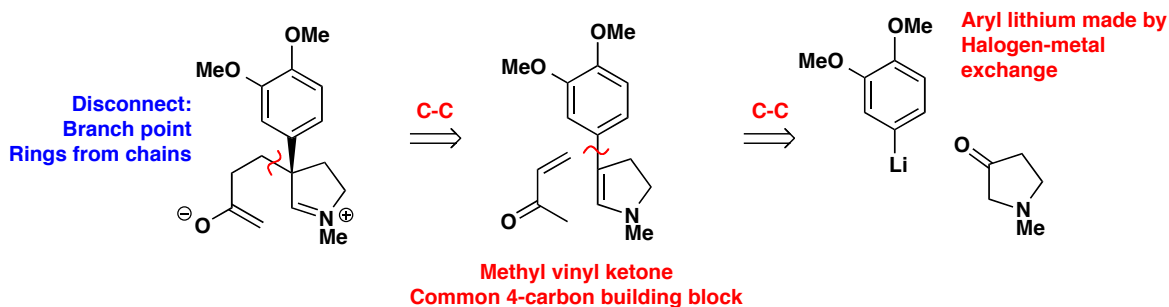


▪ Look for two-group disconnections

▪ Case study I: Mesembrine; two obvious two-group disconnections

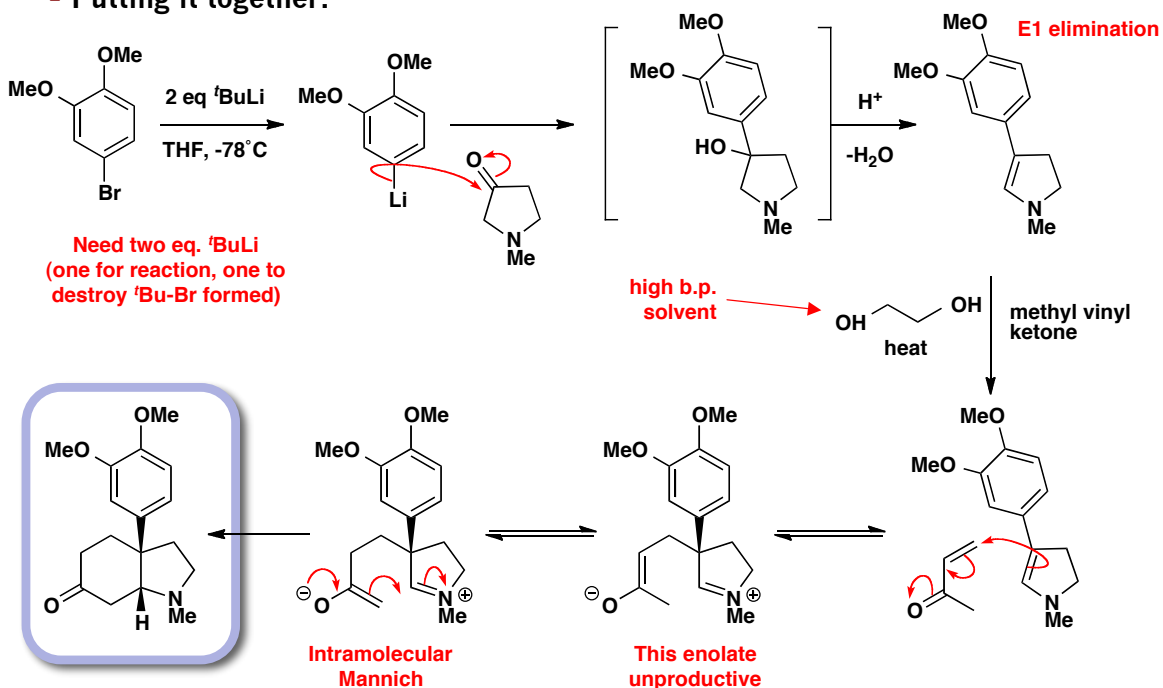


▪ Both disconnections are viable: examine C-C disconnection first



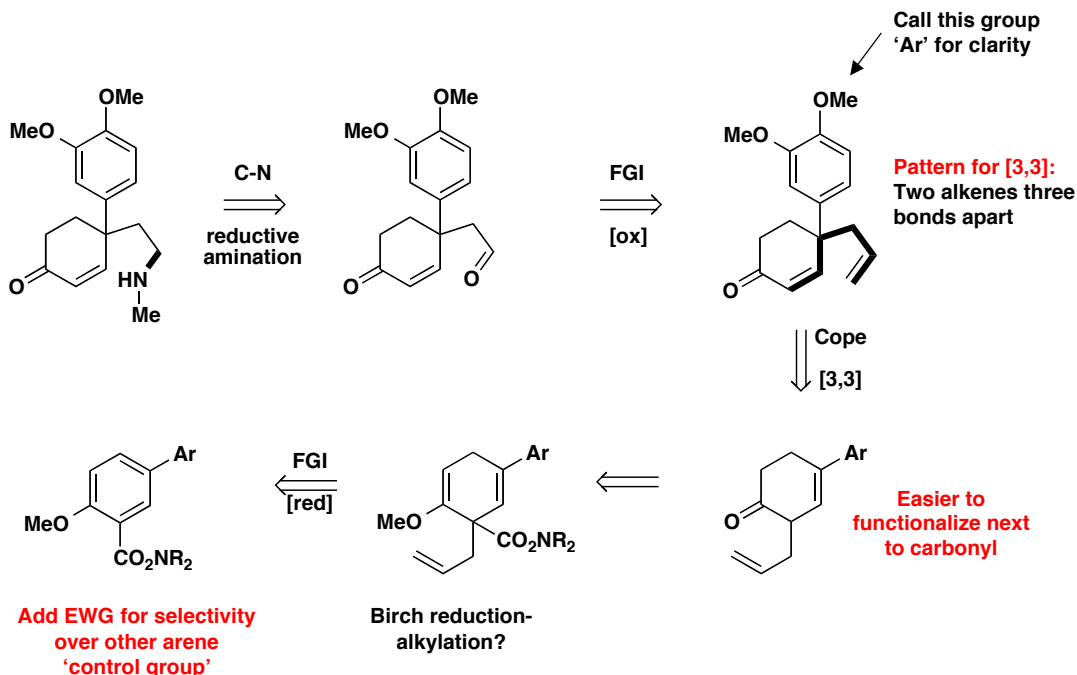
▪ Look for two-group disconnections

▪ Putting it together:



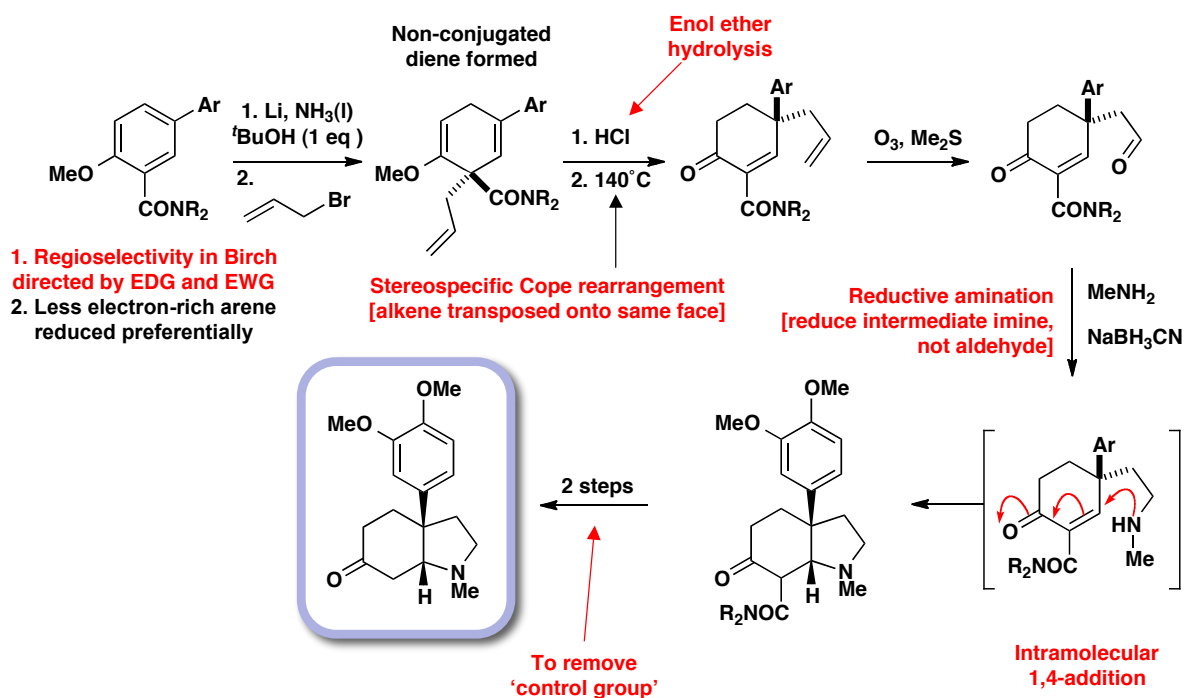
## Look for two-group disconnections

### Mesembrine disconnection II (more complex!)



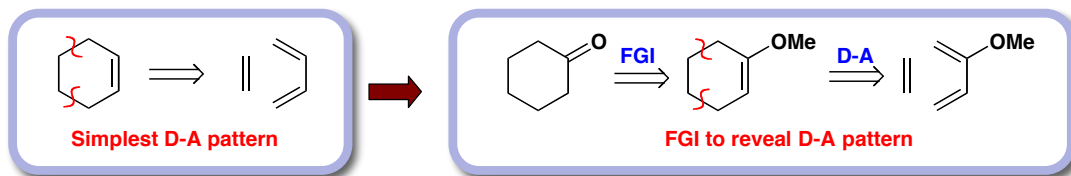
## Look for two-group disconnections

### Mesembrine final steps:



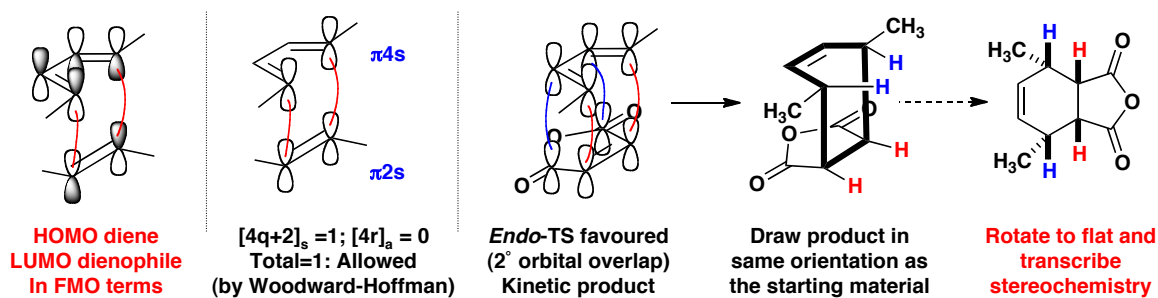
## Pattern recognition: the Diels-Alder reaction

- Simplest pattern: 6-ring containing an alkene



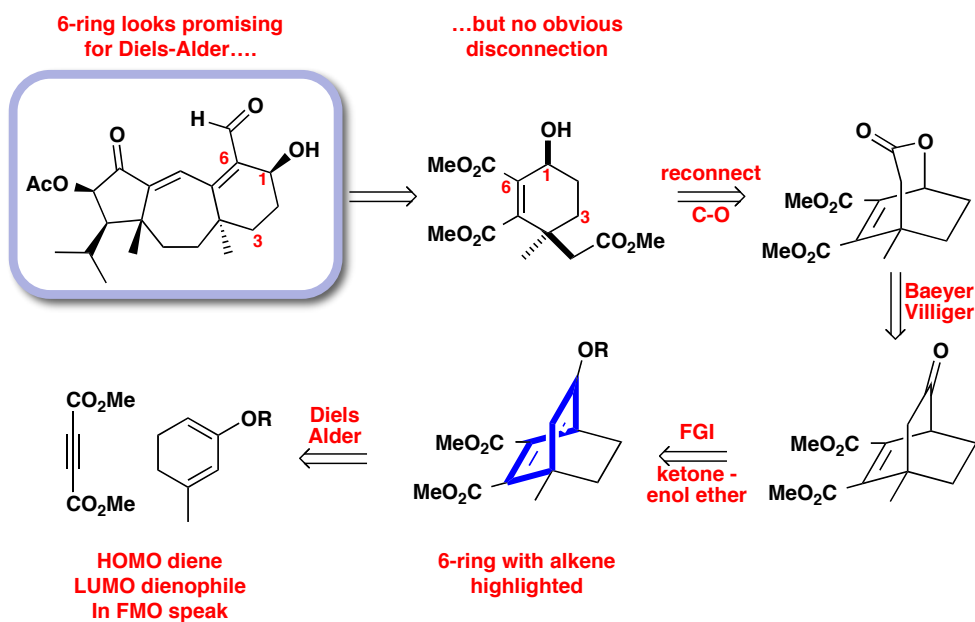
Remember: we generally need EDG on the diene and EWG on the dienophile to accelerate the reaction (this lowers the HOMO-LUMO gap, in the FMO treatment)

- and don't forget models for the actual reaction:



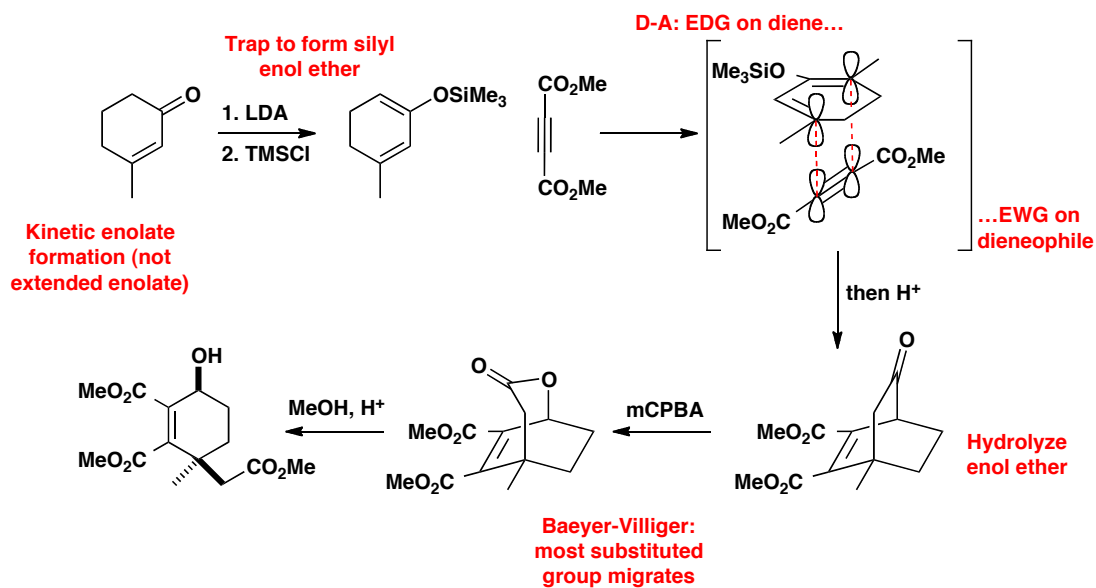
## Pattern recognition: the Diels-Alder reaction

- Complex natural product example disconnection: Guanacastepene



## ■ Pattern recognition: the Diels-Alder reaction

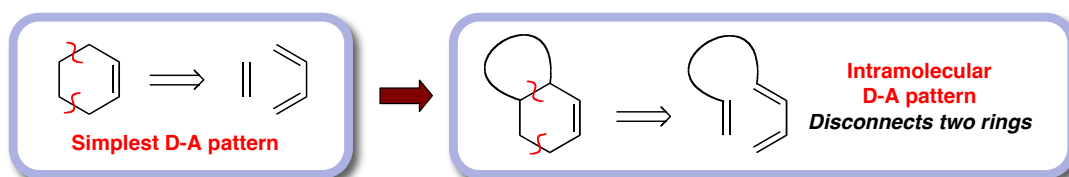
### ■ ...and the actual synthesis:



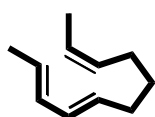
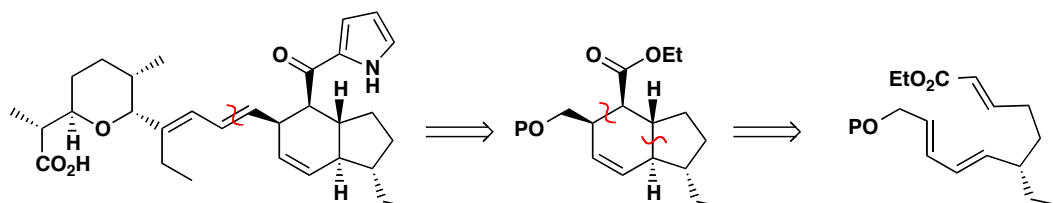
Note: the six membered ring that we start with is not the one that ends up in the product (as a consequence of the oxidative cleavage in the B-V reaction)

## ■ Pattern recognition: the Diels-Alder reaction

### ■ Intramolecular Diels-Alder



### ■ Example: Indanomycin (an antibiotic ionophore)

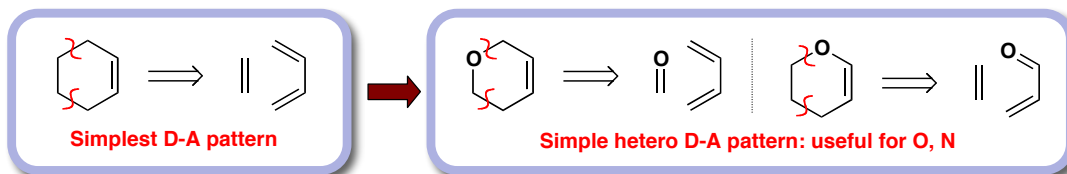


1. Electronics: best with EDG on diene and EWG on dienophile (or *vice versa*; an 'inverse electron demand' Diels Alder)
2. Stereochemistry: alkene geometry is key (stereospecific)
3. *Endo* vs *exo*: must consider length of 'tether'
4. Intramolecular better than intermolecular (and so the 'rules' are less stringent for substituent effects)

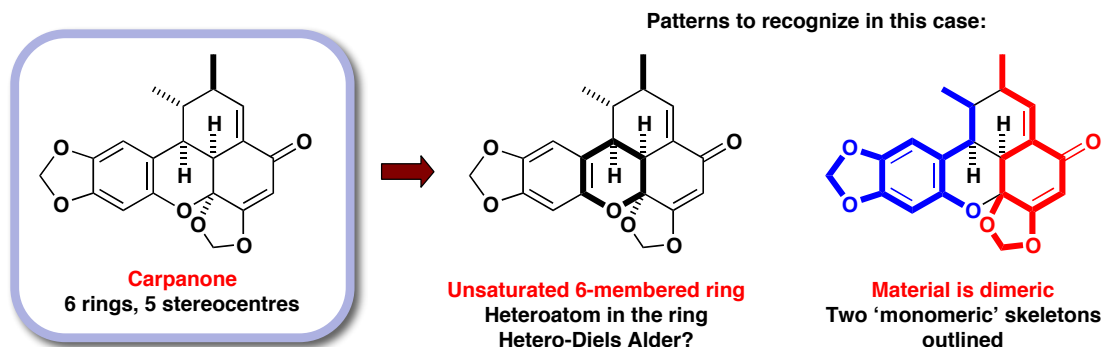


## ■ Symmetry and the Diels-Alder reaction

- Extension of the simple D-A pattern: hetero Diels-Alder reactions

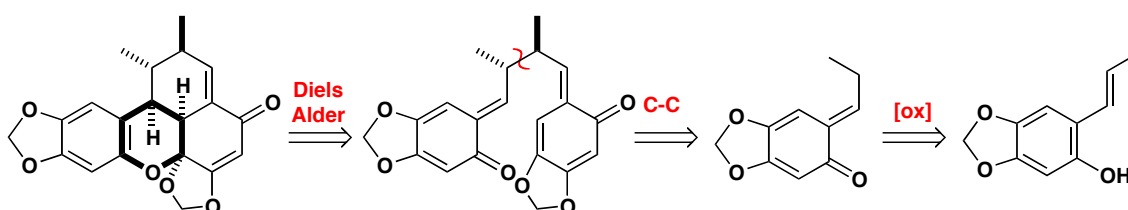


- How symmetry can help (I): Carpanone

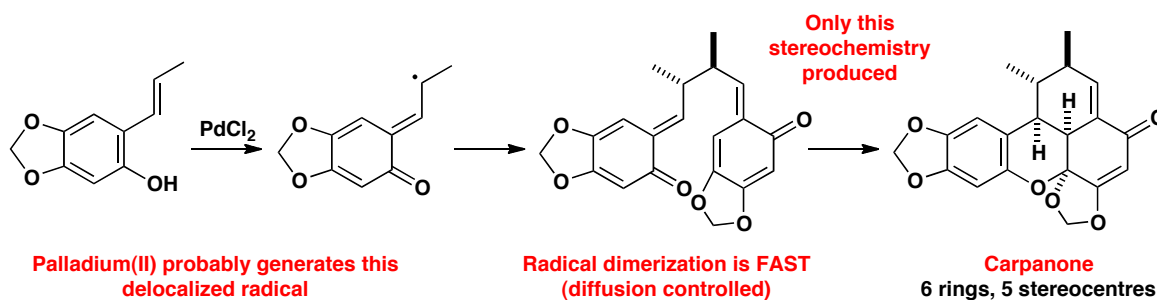


## ■ Symmetry and the Diels-Alder reaction

- Disconnection:



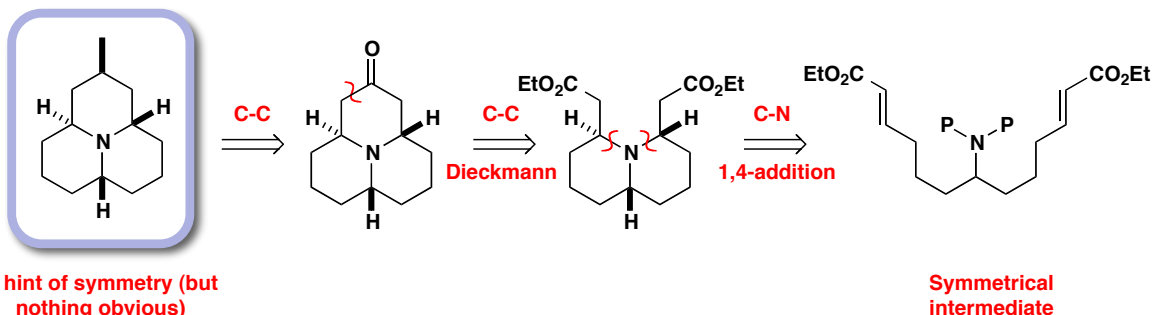
- Synthesis: one step (!)



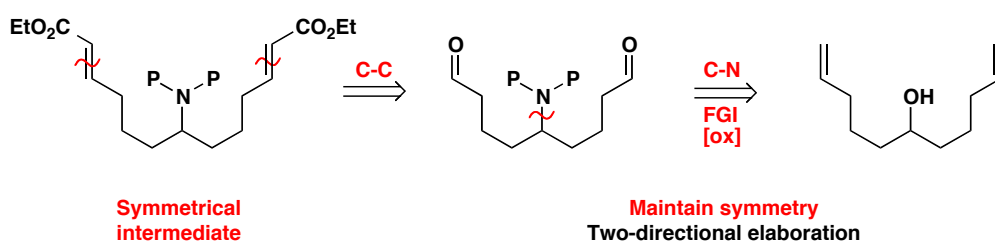


## ■ Symmetry as an aid to disconnection

### ■ Symmetry & 'two directional' synthesis

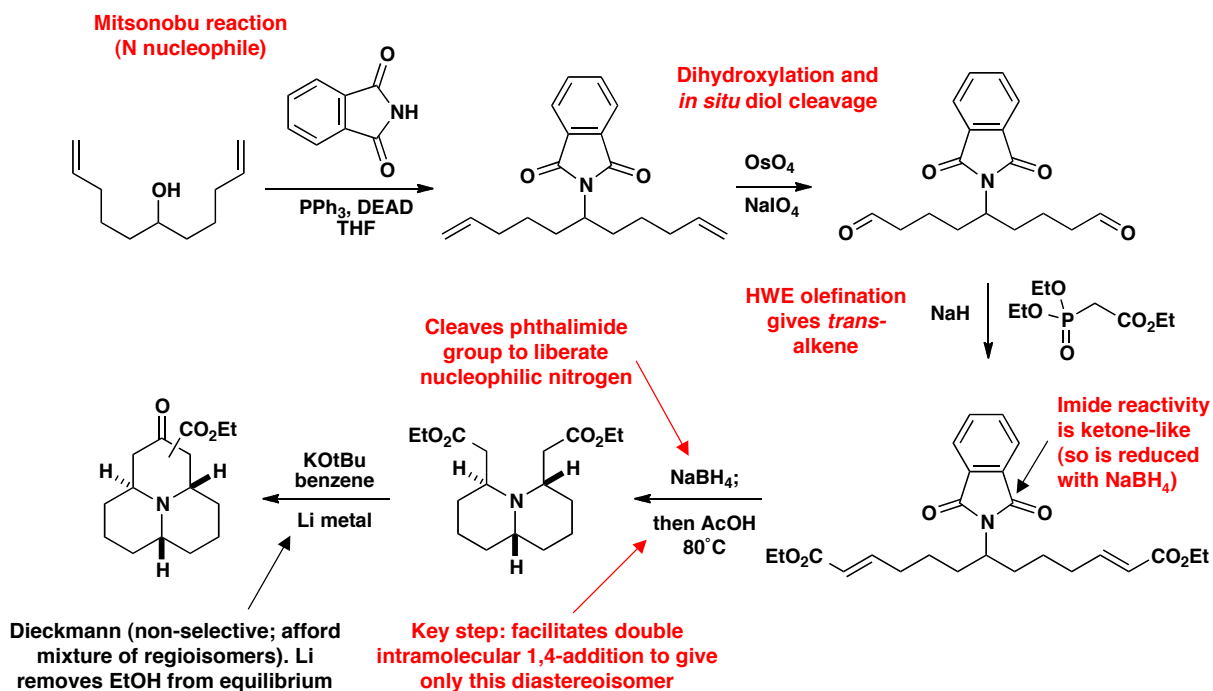


### ■ Disconnection of starting material



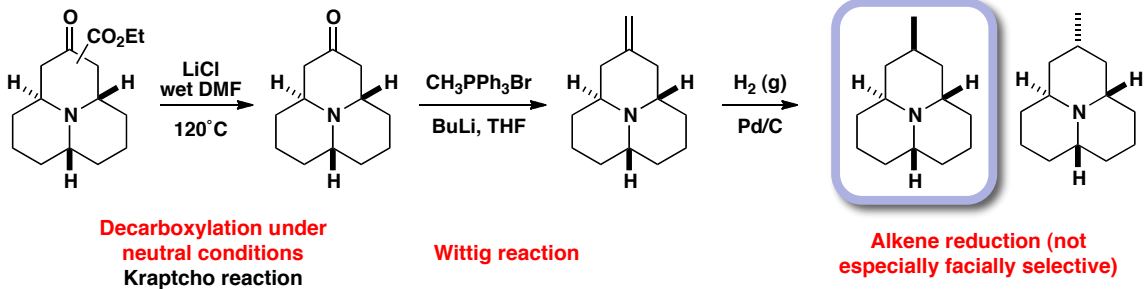
## ■ Symmetry as an aid to disconnection

### ■ Total synthesis (I): requires a desymmetrization

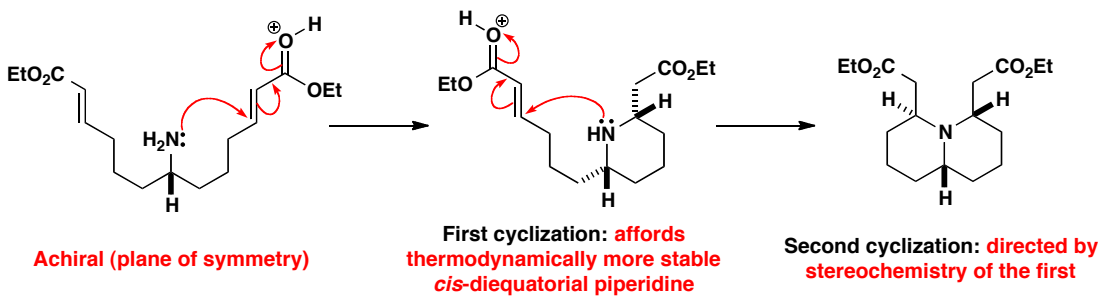


## ■ Symmetry as an aid to disconnection

### ■ Completion of the total synthesis:

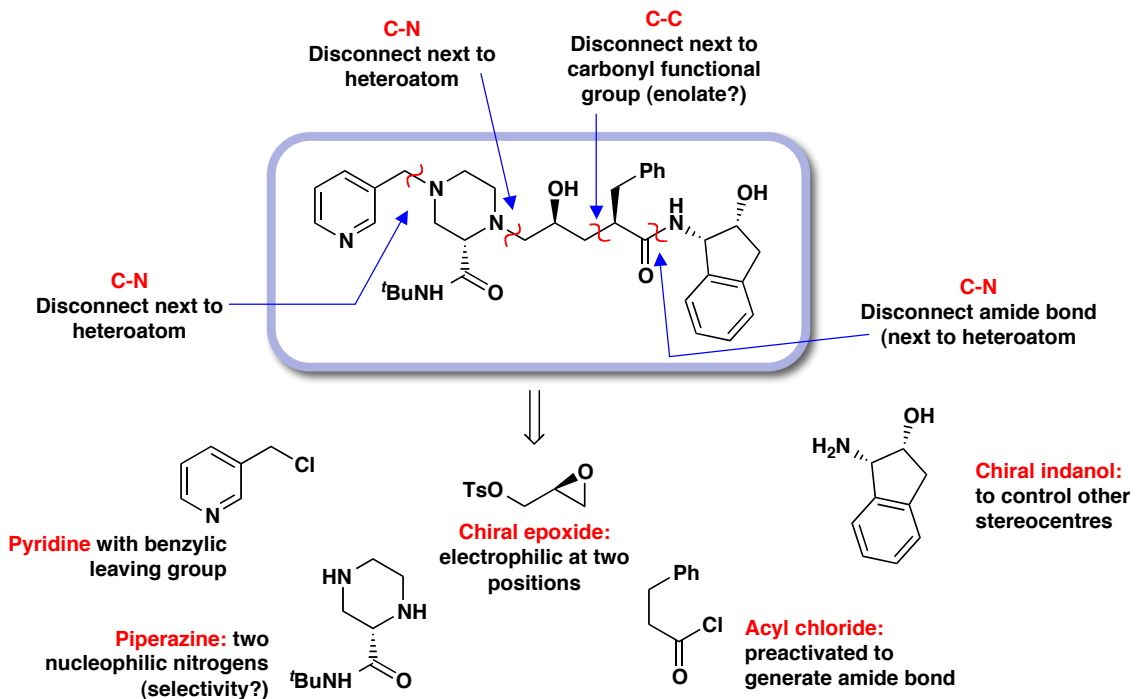


### ■ Review key diastereoselective step



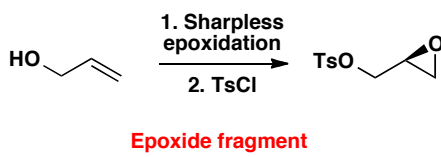
## ■ Crixivan: HIV protease inhibitor (Merck)

### ■ Patient requires ca. 1 kilo per year: very large scale, efficient synthesis required

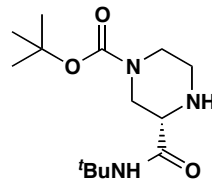


## ■ Crixivan: Fragment Syntheses

### ■ Epoxide



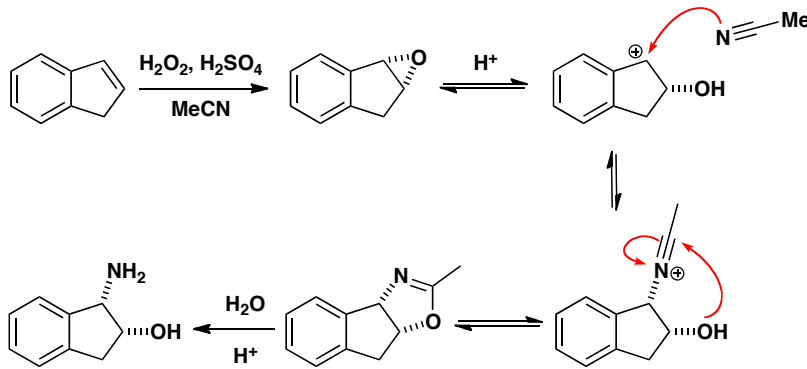
### ■ Piperazine



Protected piperazine  
(one nucleophilic nitrogen)

Made by asymmetric  
hydrogenation

### ■ Indanol



Made racemically by the  
Ritter reaction

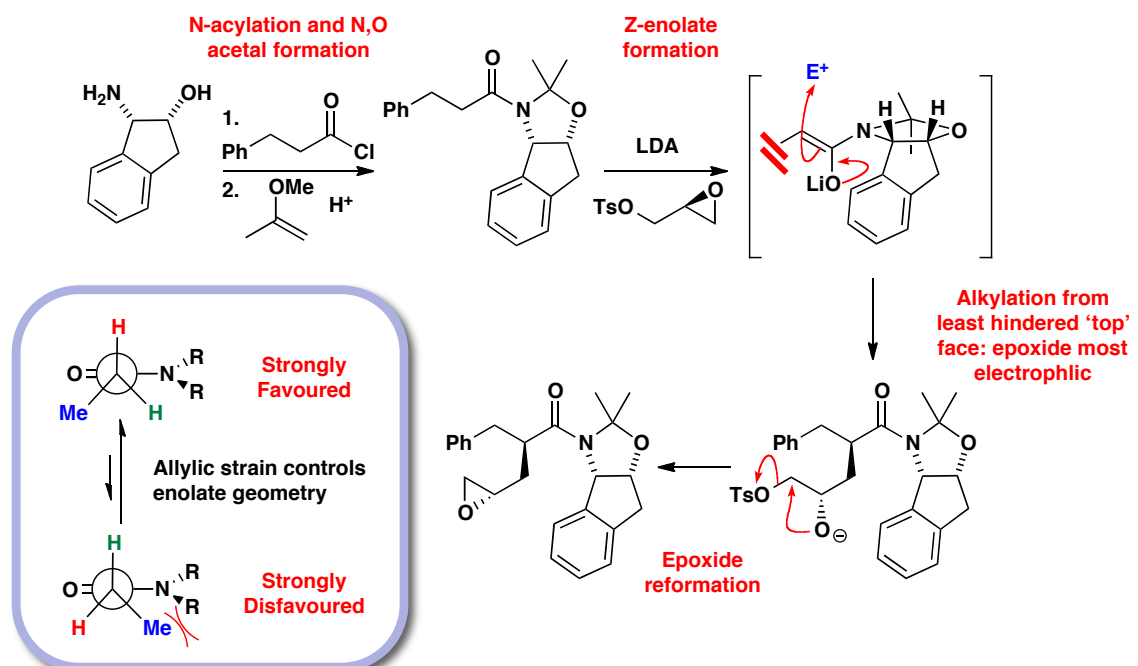
Only *cis* stereochemistry  
through reversibility (and  
thermodynamic stability of  
fused tricyclic system)

Can be resolved to give  
access to a single  
enantiomer

Indanol fragment

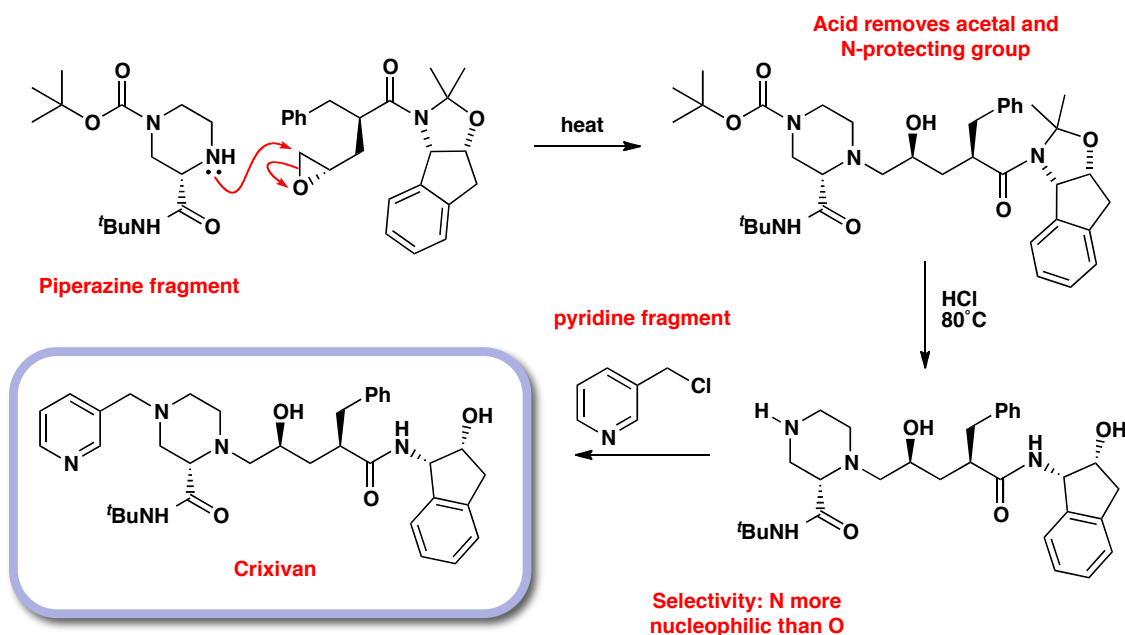
## ■ Crixivan: Fragment Assembly

### ■ Diastereoselective alkylation is a key step



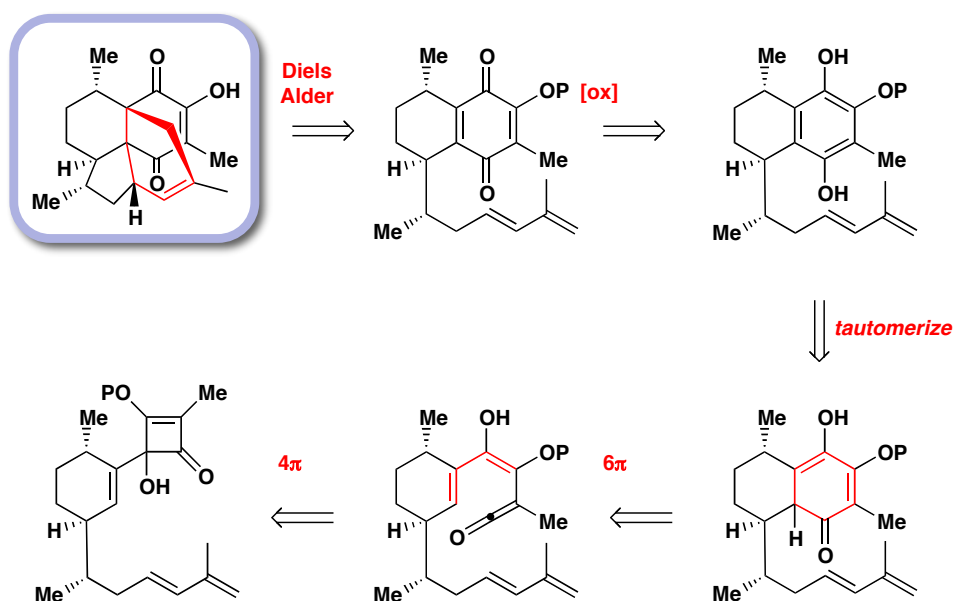
## ■ Crixivan: Fragment Assembly

### ■ Final steps.....



## ■ Cascade processes and complexity generating reactions

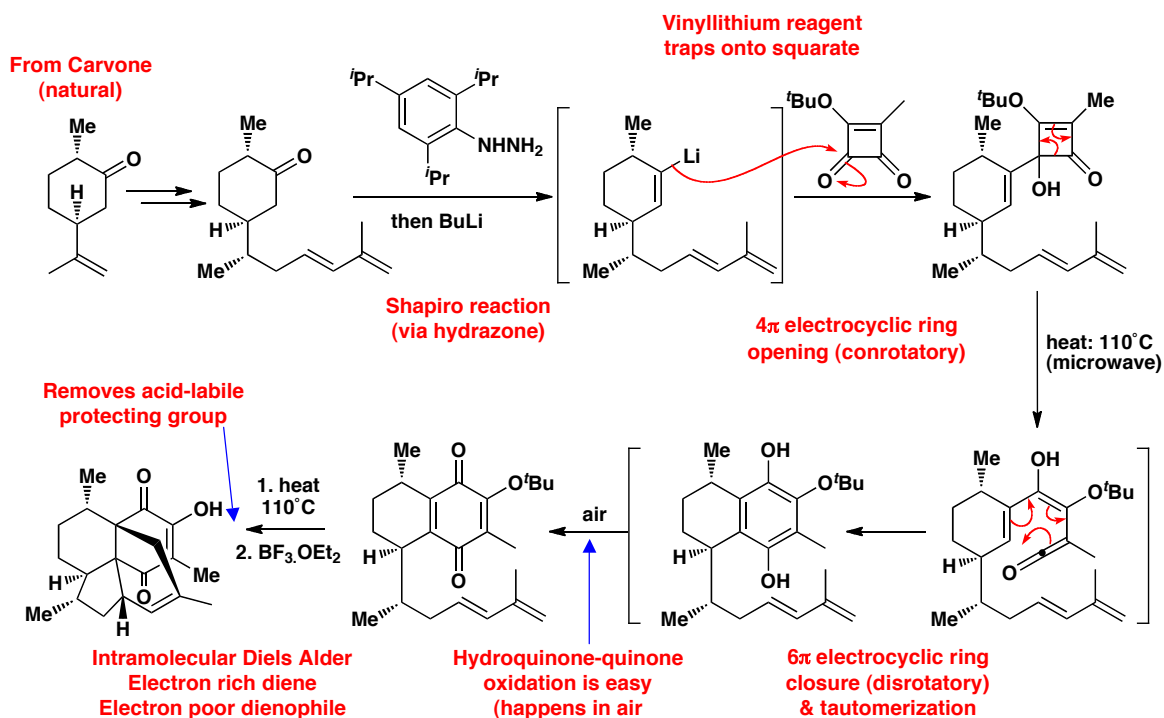
### ■ Cascade processes offer a rapid entry into complex structures



Can we accomplish several of these steps in one operation? (a 'cascade' reaction)

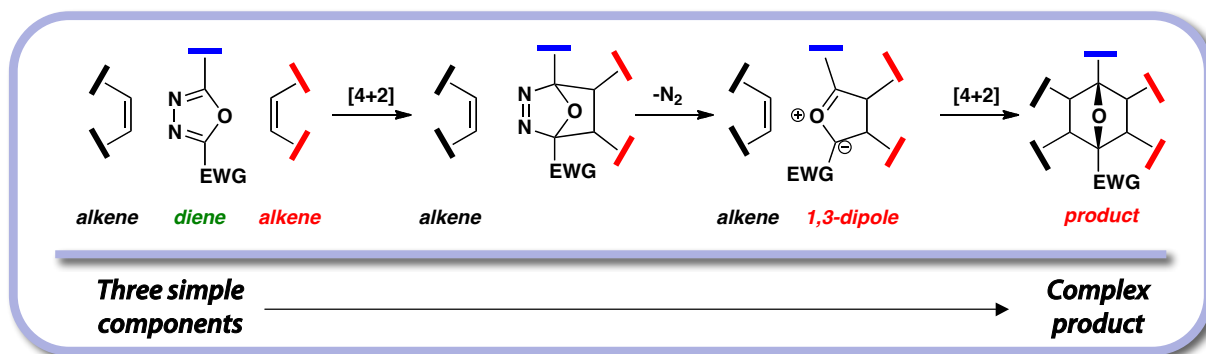
## ■ A Cascade process: synthesis of Colombiasin

- Electrocyclic cascades offer short sequences to complex materials

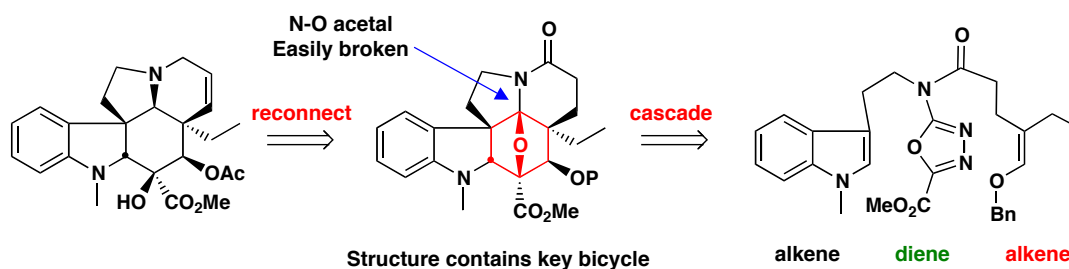


## ■ Pericyclic cascades II

- Pericyclic cascades offer short sequences to complex materials

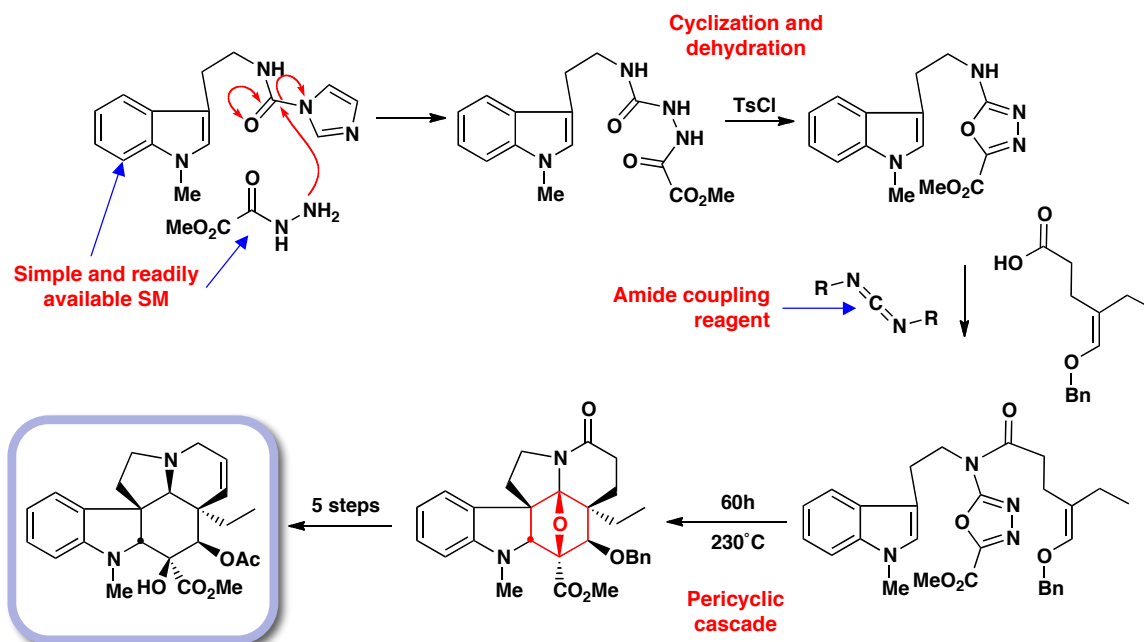


- Application in synthesis: vinca alkaloids



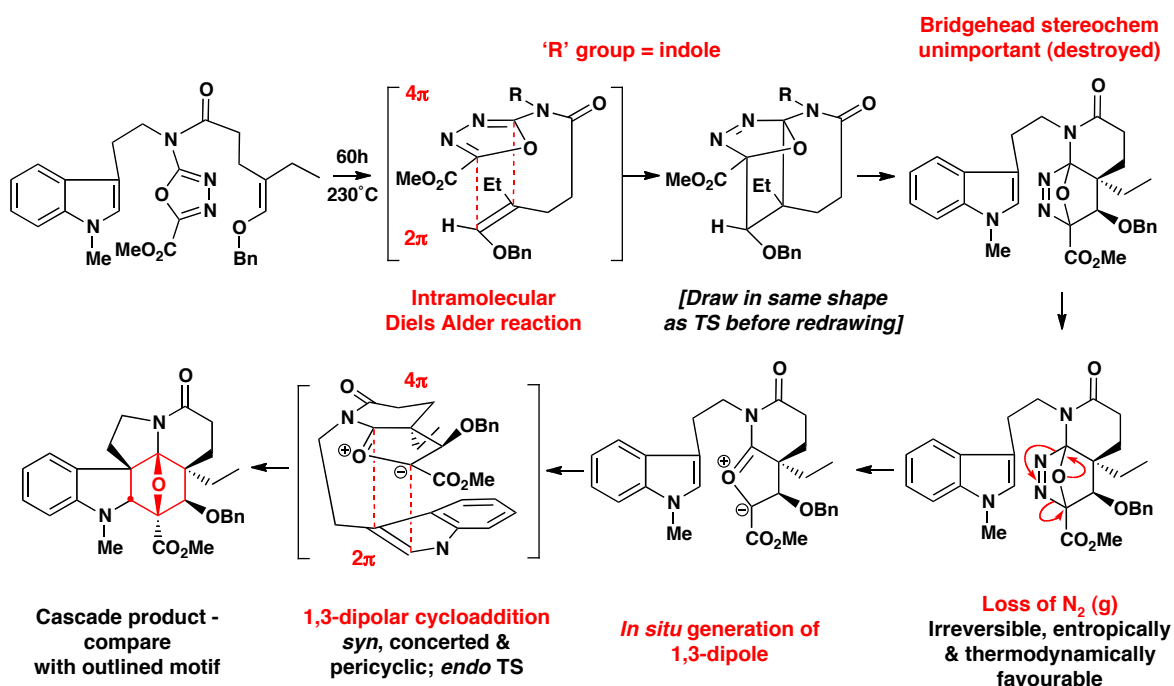
## Pericyclic cascades II

### Synthesis of vindorosine



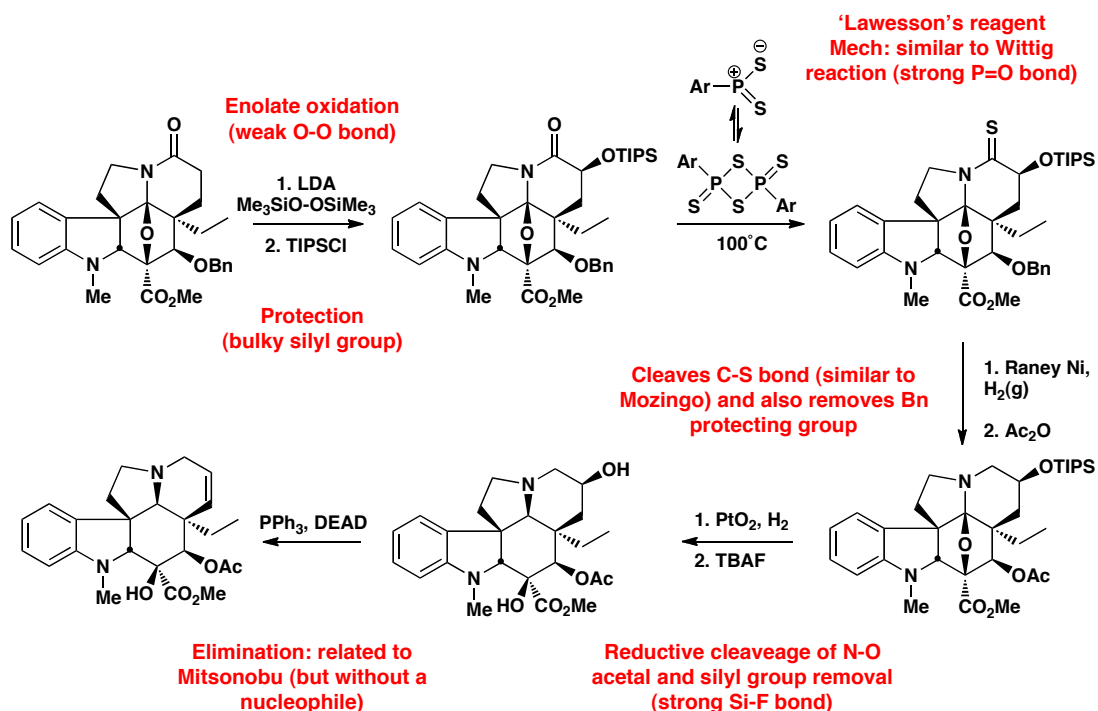
## Pericyclic cascades II

### Synthesis of Vindorosine: examination of the pericyclic cascade



## Pericyclic cascades II

### Synthesis of Vindorosine: completion of the synthesis



## Organic Synthesis II: 'Questions'

### Representative questions

This is a new course and hence there are no 'current' exam questions that relate specifically to this course (and the exclusion of any other). However, much of the material is what I would class as core material that will crop up across a range of examination questions.

As such, the attached questions (or in some cases parts of them) are representative of what you should expect:

Sample paper, Q 2, 5, 6  
2010: 1A, Q 4, 8  
2009: 1A Q 6, 7, 8  
2008: Q 8  
2007: Q 6, 7