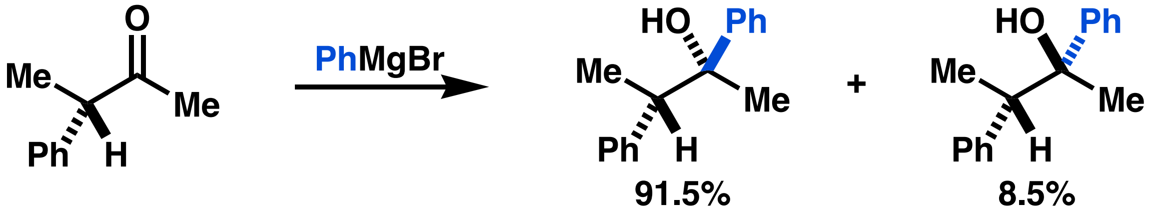
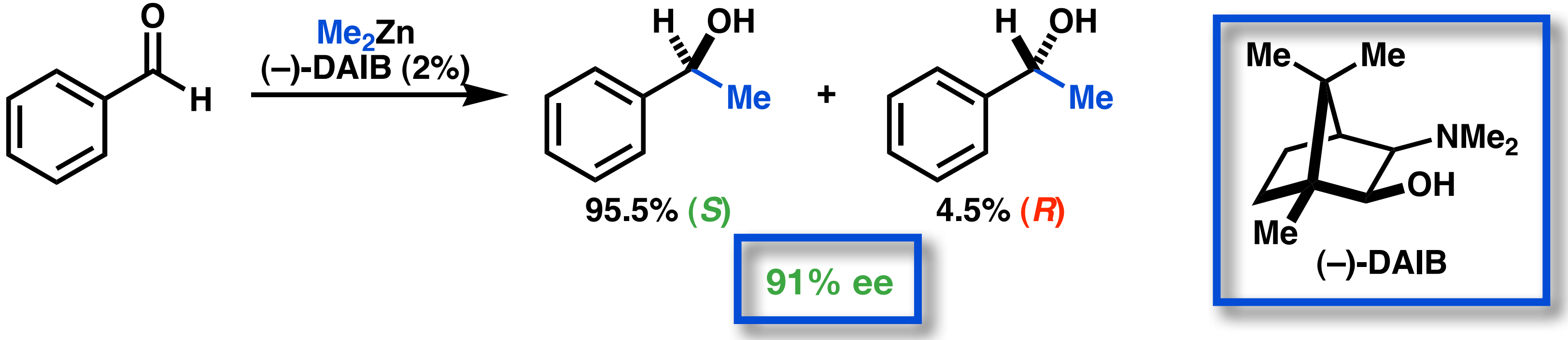
Stereoselectivity in organic synthesis

- **Stereospecific reactions** - a reaction where the mechanism means the stereochemistry of the starting material determines the stereochemistry of the product; there is no choice! *e.g.* S_N2 reactions
- **Stereoselective reactions** - a reaction where one stereoisomer of a product is formed preferentially over another. The mechanism does not prevent the formation of two or more stereoisomers but one predominates.
- **Diastereoselective reactions** - a stereogenic centre is introduced into a molecule in such a way that diastereoisomers are produced in unequal amounts



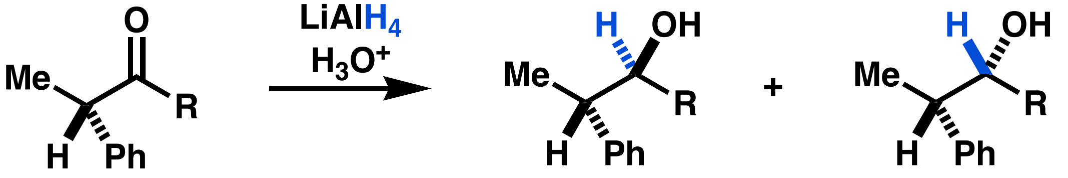
- **Enantioselective reactions** - a reaction that produces two enantiomers of a product in unequal amounts



Stereoselective reactions

Nucleophilic addition to C=O

- Reaction of a nucleophile with a chiral substrate gives **two** possible diastereoisomers
- Reaction is **stereoselective** if one diastereoisomer predominates

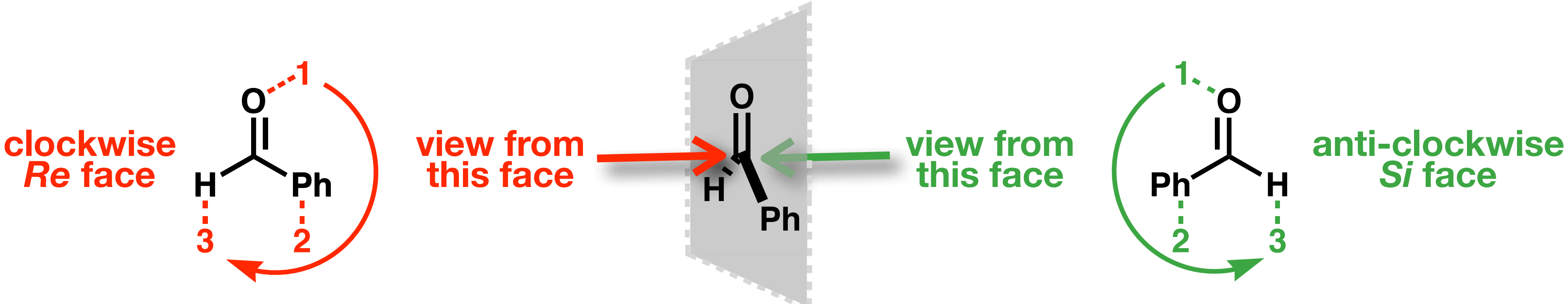


R = Me 25% : 75% (50% de)
R = *t*-Bu 2% : 98% (96% de)

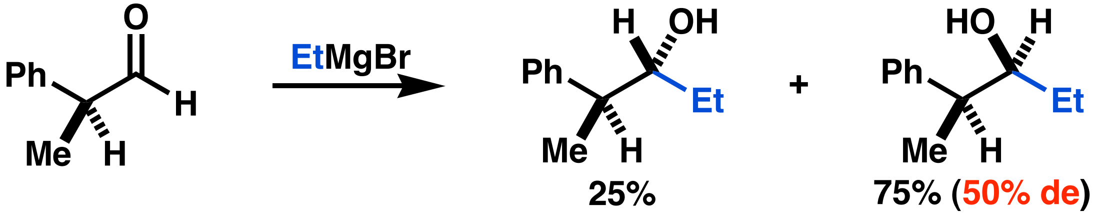
$$\boxed{\%\ \text{de} = \text{diastereisomeric excess} = \frac{[\textit{major}] - [\textit{minor}]}{[\textit{major}] + [\textit{minor}]} = \%\textit{major} - \%\textit{minor}}$$

Prochiral Nomenclature

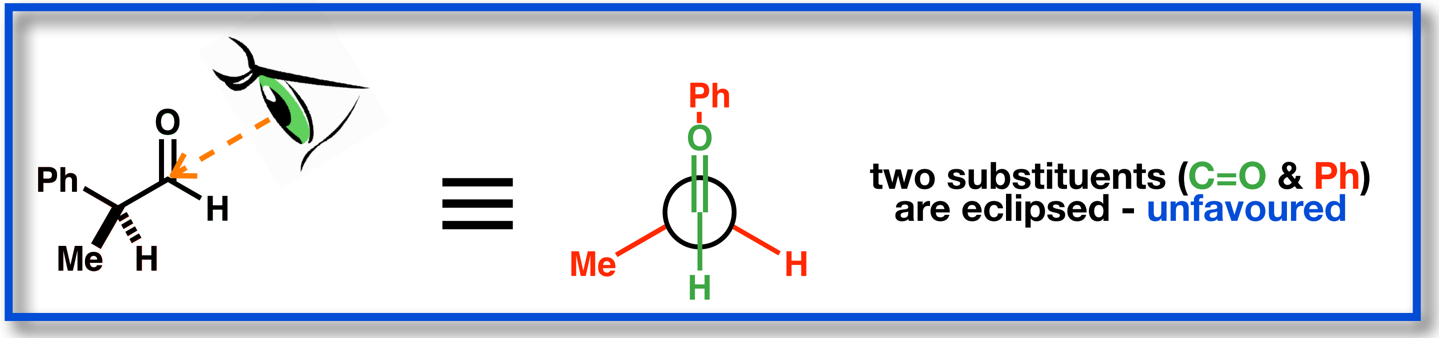
- Trigonal carbons that are not stereogenic centres but can be made into them are **prochiral**
- Each face can be assigned a label based on the CIP rules
- If the molecule is chiral (as above) the faces are said to be **diastereotopic**
- If the molecule is achiral (as below) the faces are **enantiotopic**



Felkin-Ahn model

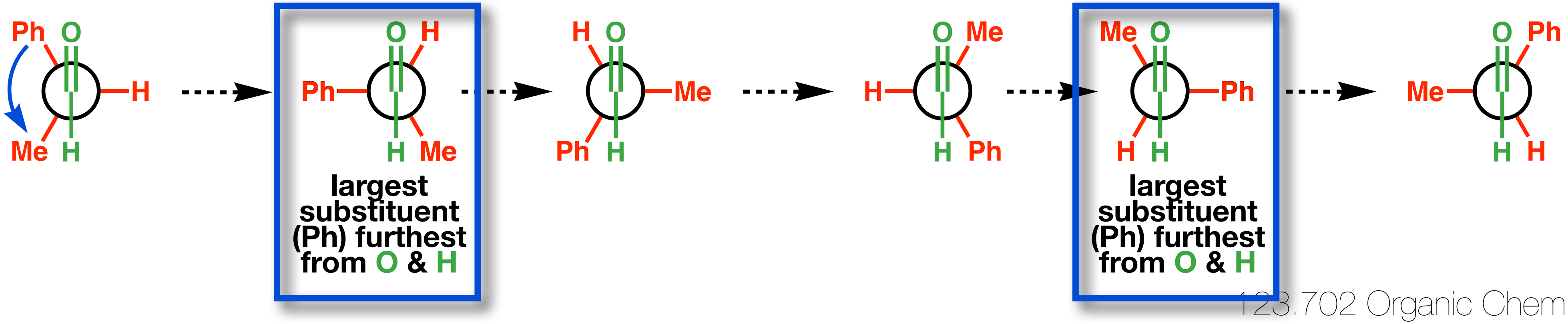


- The diastereoselectivity can be explained and predicted *via* the **Felkin-Ahn model**
- It is all to do with the conformation of the molecule...
- Easiest to understand if we look at the **Newman projection** of the starting material



two substituents (C=O & Ph) are eclipsed - unfavoured

- Rotate around central bond so that substituents are staggered
- Continue to **rotate** around central bond and find 6 possible conformations
- Two favoured as largest substituent (Ph) furthest from O & H

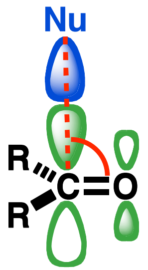


largest substituent (Ph) furthest from O & H

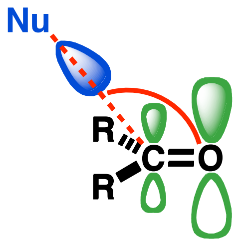
largest substituent (Ph) furthest from O & H

Felkin-Ahn model II

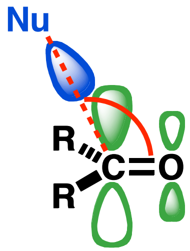
- Nucleophiles attack the carbonyl group along the **Bürghi-Dunitz** angle of ~107°



maximum overlap with π* - nucleophile attacks at 90° to C=O

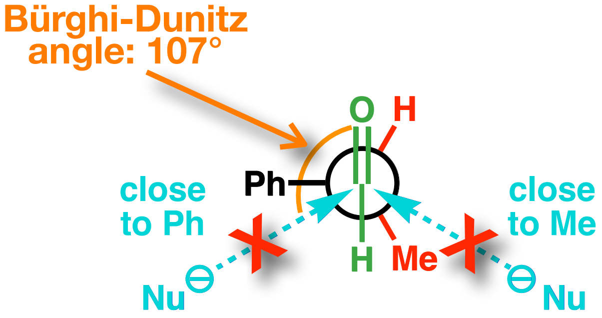


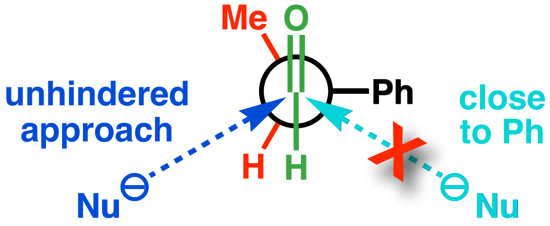
repulsion from full π orbital - nucleophile attacks from obtuse angle



compromise, nucleophile attacks π* orbital at angle of 107°

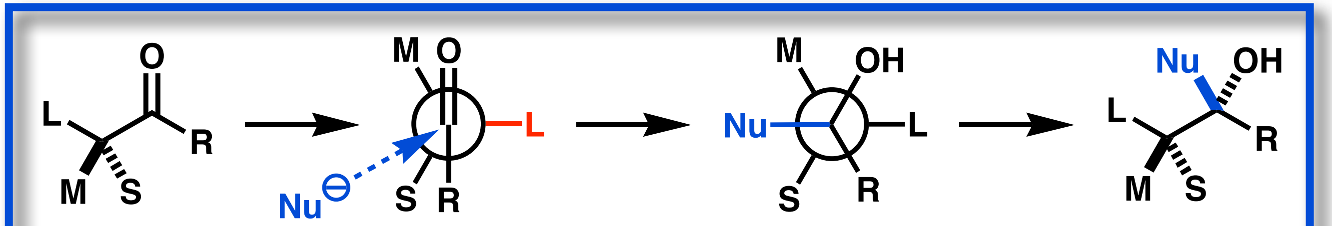
- As a result of the Bürghi-Dunitz (107°) angle there are four possible trajectories for the nucleophile to approach the most stable conformations
- Three are **disfavoured** due to steric hindrance of **Ph** or **Me**
- Therefore, only one diastereoisomer is favoured





- Favoured approach passed smallest substituent (H) when molecule in most stable conformation

Felkin-Ahn model IV

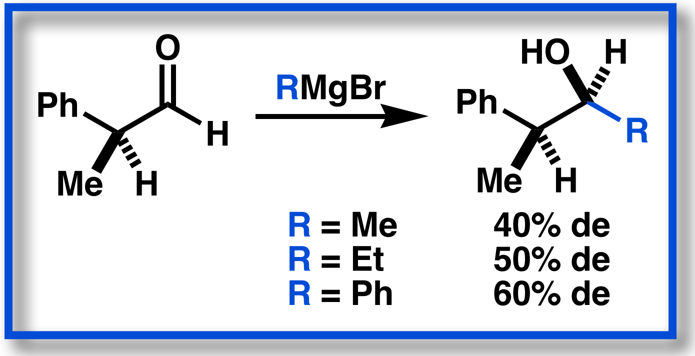


L = large group, M = medium group, S = small group

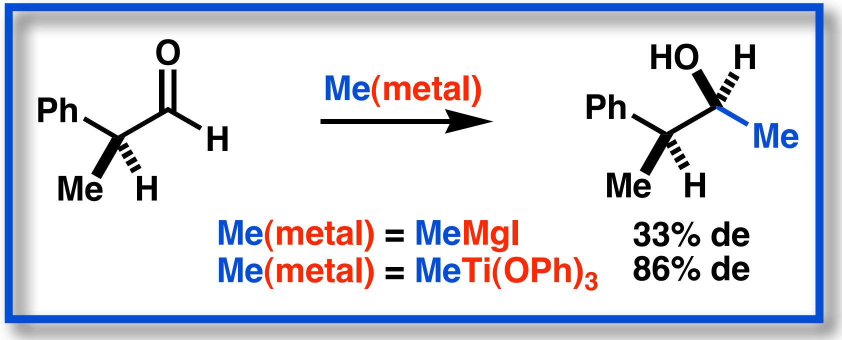
- To explain or predict the stereoselectivity of nuclophilic addition to a carbonyl group with an adjacent stereogenic centre, use the Felkin-Ahn model
- Draw Newman projection with the largest substituent (**L**) perpendicular to the C=O
- Nucleophile (**Nu**) will attack along the Bürghi-Dunitz trajectory passed the least sterically demanding (smallest, **S**) substituent
- Draw the Newman projection of the product
- Redraw the molecule in the normal representation

- Whilst the Felkin-Ahn model predicts the orientation of attack, it does not give any information about the degree of selectivity
- Many factors can affect this...

Diastereoselective addition to carbonyl group



R = Me	40% de
R = Et	50% de
R = Ph	60% de

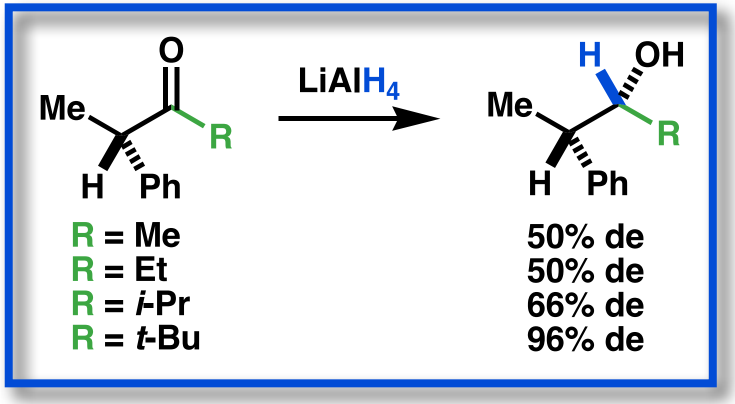


Me(metal) = MeMgI	33% de
Me(metal) = $MeTi(OPh)_3$	86% de

- The size of the nucleophile greatly effects the diastereoselectivity of addition
- Larger nucleophiles generally give rise to greater diastereoselectivities
- Choice of metal effects the selectivity as well, although this may just be a steric effect

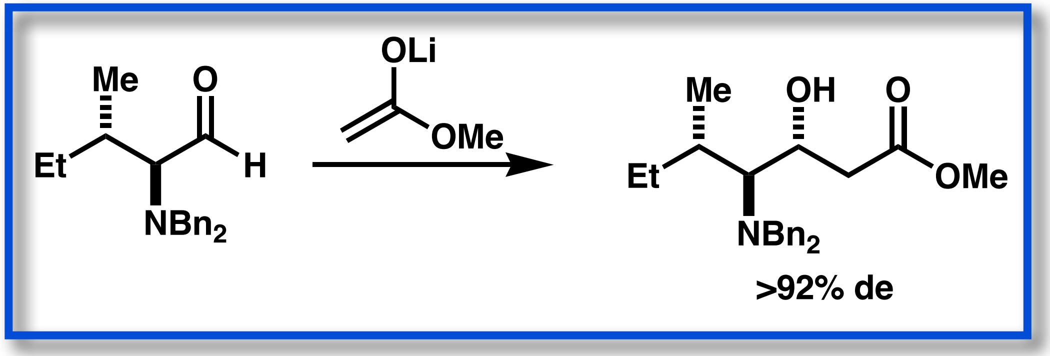
- The size of substituents on the substrate will also effect the diastereoselectivity
- Again, larger groups result in greater selectivity

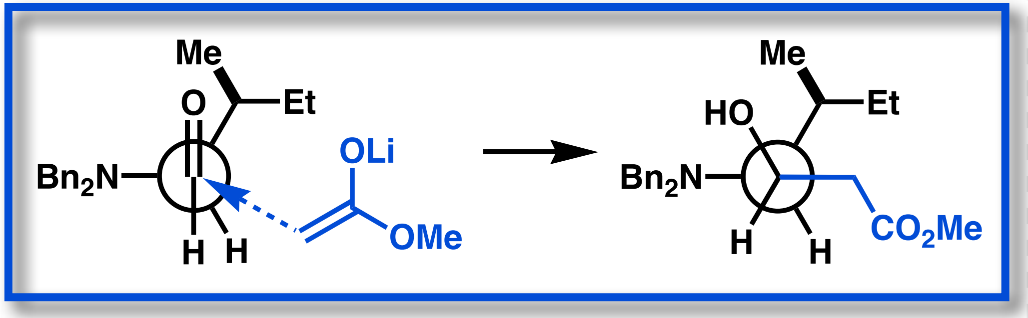
- Should be noted that larger substituents normally result in a slower rate of reaction



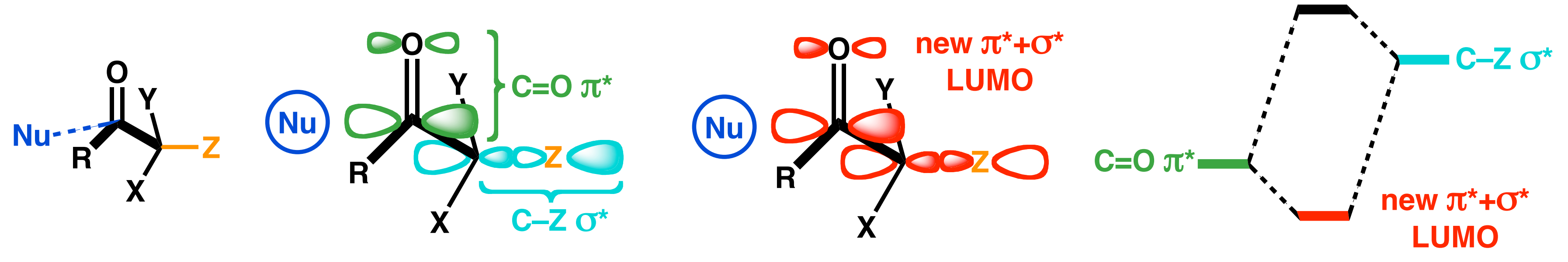
R = Me	50% de
R = Et	50% de
R = *i*-Pr	66% de
R = *t*-Bu	96% de

Effect of electronegative atoms





- It is hard to justify the excellent selectivity observed above using simple sterics
- The **Bn$_2$N** group must be perpendicular to C=O but a second factor must explain why the selectivity is so high (& the reaction much faster than previous examples)
- There is an **electronic** effect



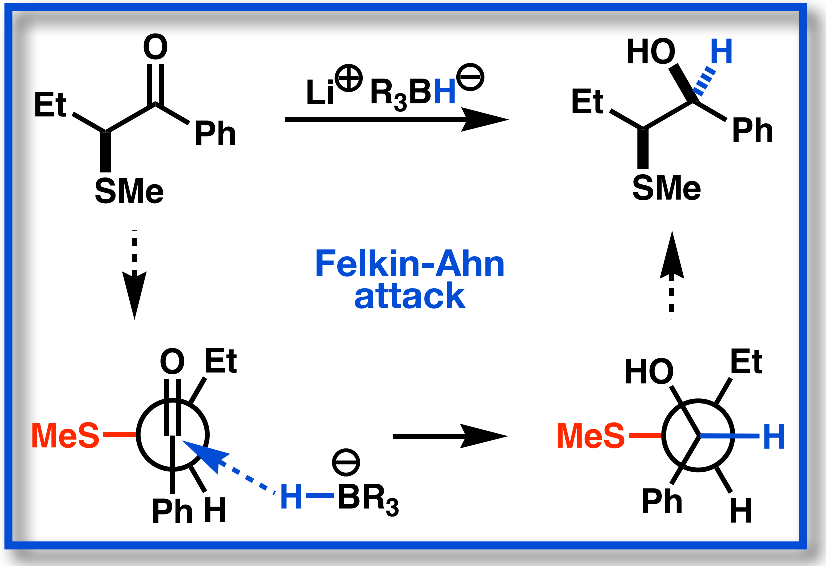
Z = electro-negative group

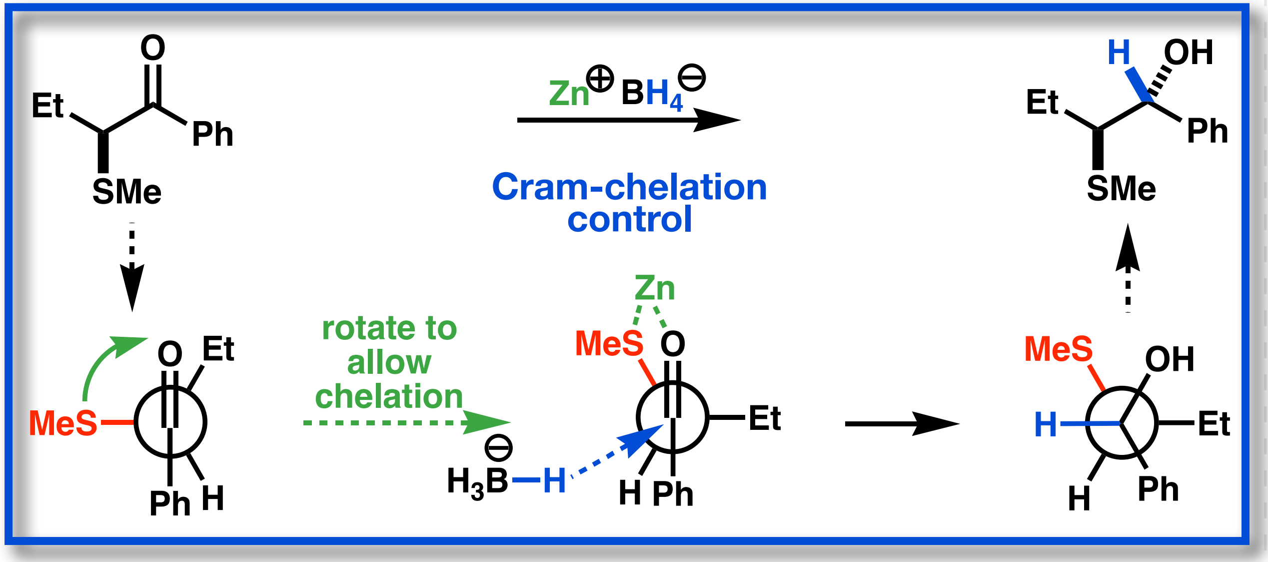
nucleophile interacts with π* orbital

new low energy orbital formed from C=O & C-Z anti-bonding orbitals favours nucleophilic attack at carbonyl

- When an **electronegative** group is perpendicular to the C=O it is possible to get an overlap of the **π* orbital** and the **σ* orbital**
- Overlap results in a new, lower energy orbital, more susceptible to nucleophilic attack
- Thus if electronegative group perpendicular, **C=O is more reactive**

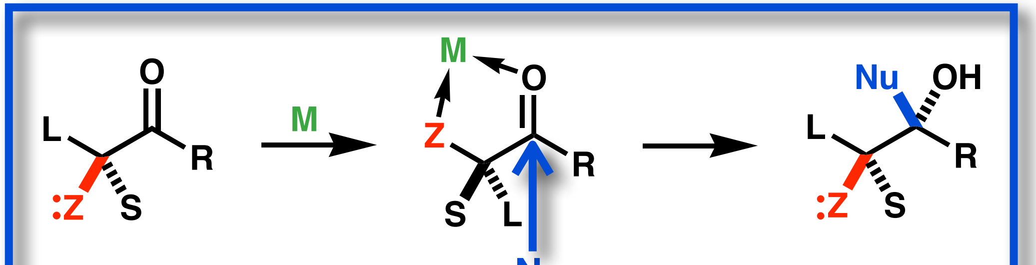
Effect of electronegative atoms II





- A good example of the previous effect is shown on the left hand-side
- But as always, chemistry not that simple...
- If heteroatom (**Z**) is capable of coordination and...
  a metal capable of chelating 2 heteroatoms is present we observe **chelation control**
- **Metal** chelates carbonyl and heteroatom together
- This fixes conformation
- Such reactions invariably occur with greater selectivity
- Reactions are considerably faster
- The chelating metal acts as a Lewis acid and activates the carbonyl group to attack
- As shown, **chelation** can reverse selectivity!

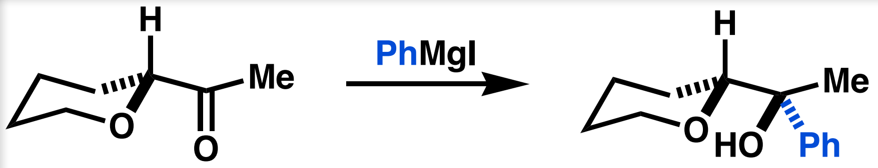
Chelation control



Nucleophile attacks
from least hindered face

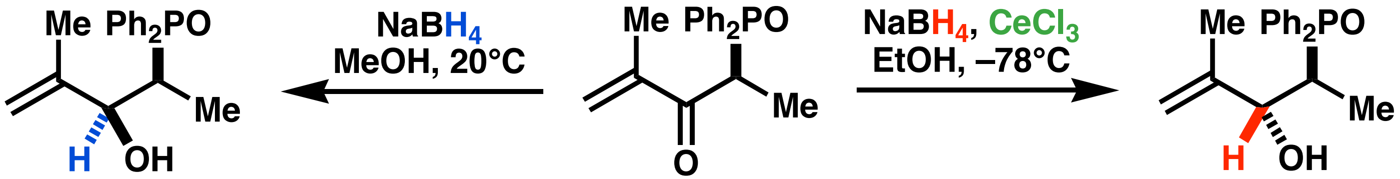
Z = heteroatom capable of coordination; M = metal
capable of coordinating to more than one heteroatom

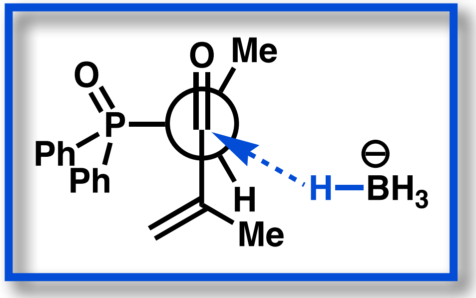
- Chelation controlled additions are easy to predict
- Normally do not need to draw Newman projection (yippee!)
- Simple example shown below

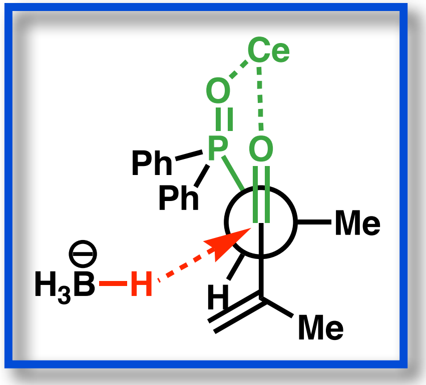


96% de

Chelation control II

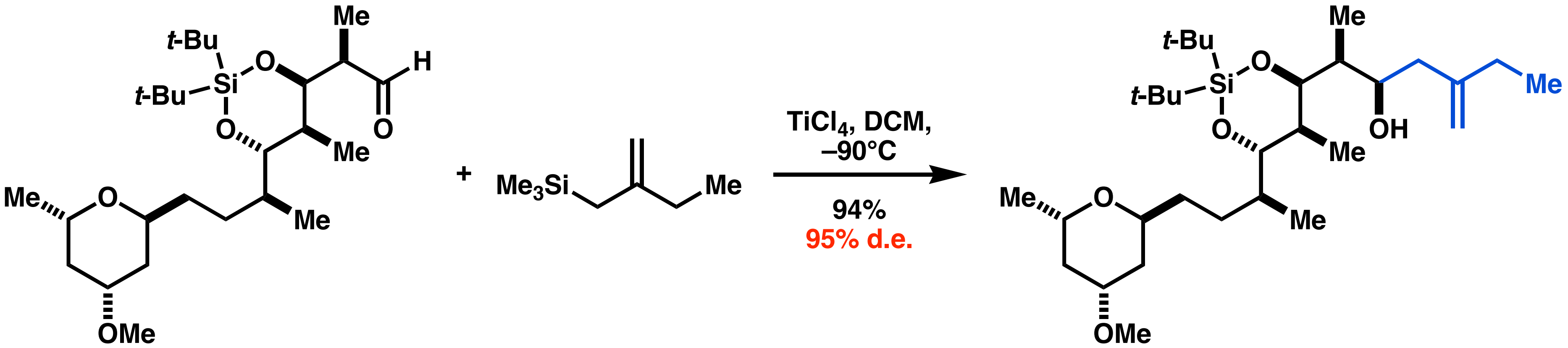


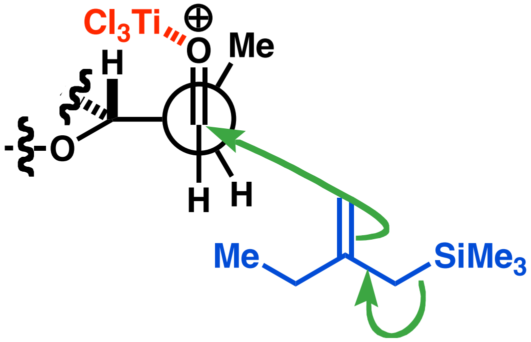


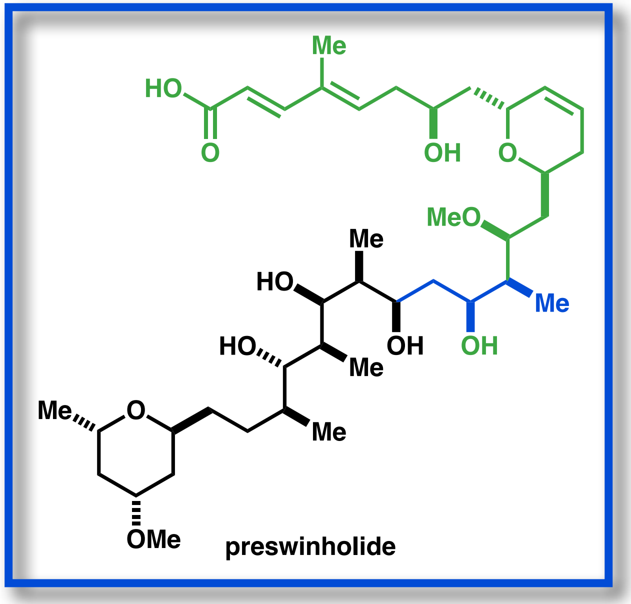


- Example shows normal Felkin-Ahn selectivity gives one diastereoisomer
- Electronegative and bulky phosphorus group in perpendicular position
- Chelation control gives **opposite** diastereoisomer
- Chelation can occur through 6-membered ring
- Lower temperature typical of activated, chelated carbonyl

Felkin-Ahn control in total synthesis



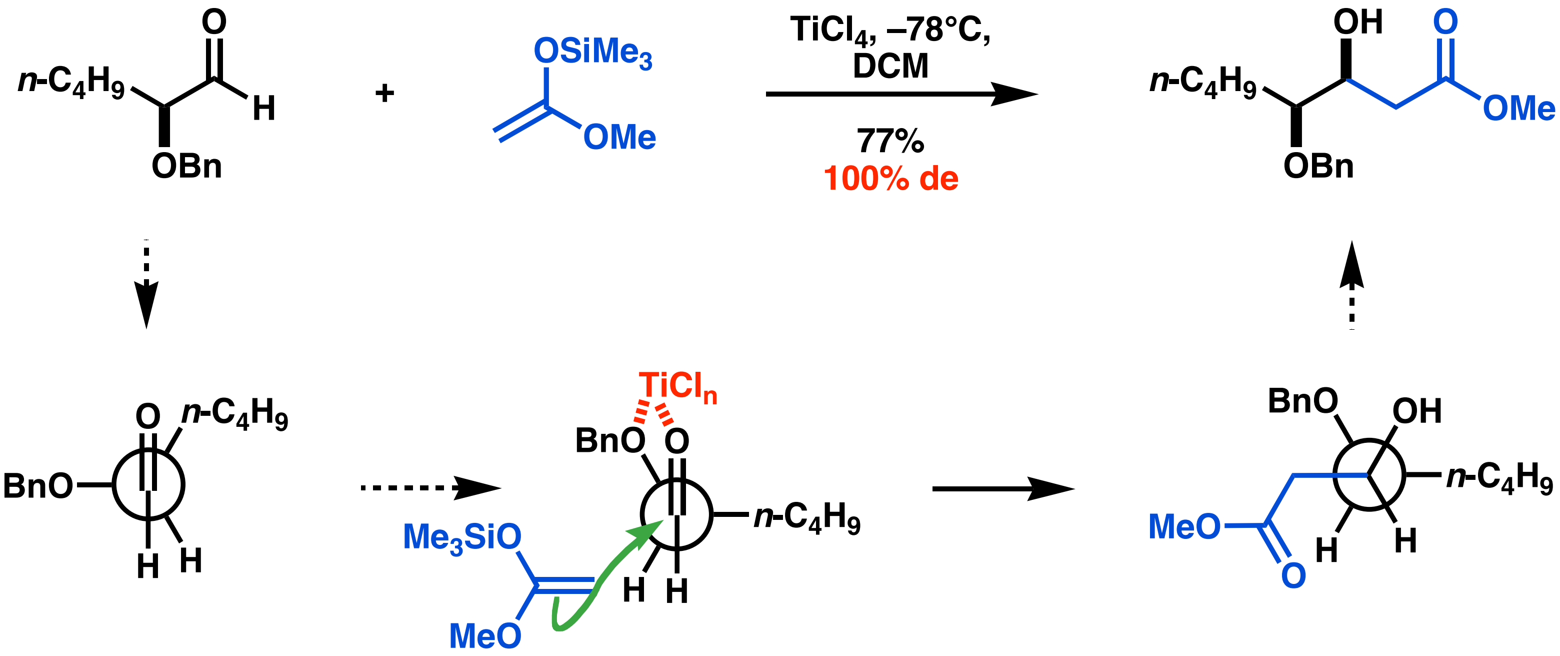




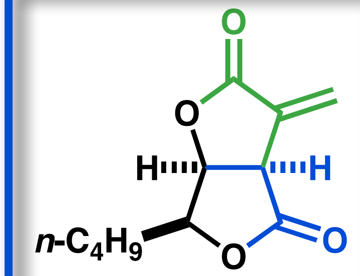
preswinholide

- An example of the Sakurai reaction from the synthesis of preswinholide A
- Preswinholide A is effectively the monomer of swinholide A (the dimer), a compound displaying potent cytotoxic activity that was isolated from a Red Sea sponge
- Ian Paterson, Richard A. Ward, Julian D. Smith, John G. Cumming and Kap-Sun Yeung, *Tetrahedron*, **1995**, *51*, 9437

Chelation control in total synthesis



- An example of the Mukaiyama aldol reaction
- Comes from the synthesis of canadensolide, a fungicidal agent
- Yung-Son Hon & Cheng-Han Hsieh, *Tetrahderon*, **2006**, *62*, 9713



canadensolide