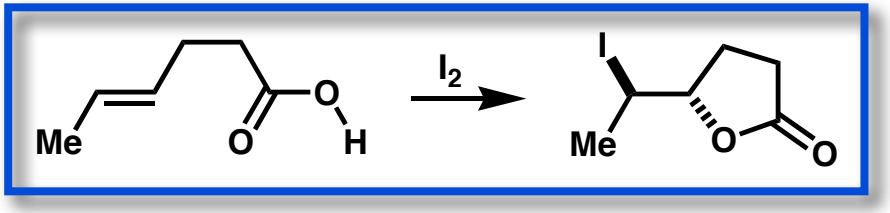
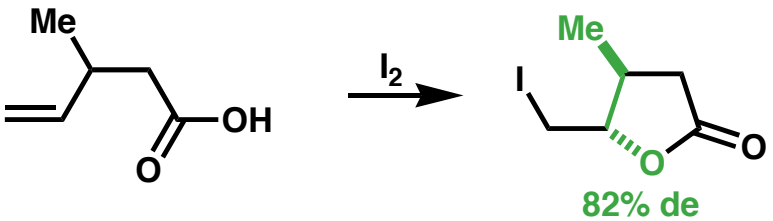
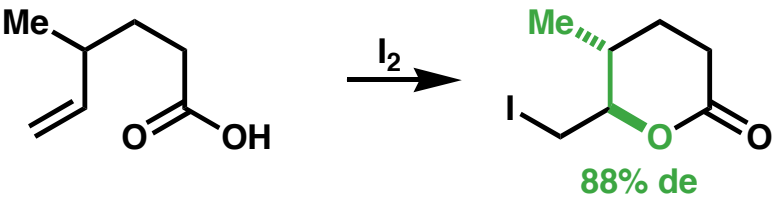
Stereoselective reactions of alkenes



- Earlier, we saw that **stereospecific** reactions can produce single diastereoisomers
- If there is a pre-existing stereogenic centre reactions can be **stereoselective**
- In other words, the faces of the alkene are **diastereotopic**

- Following two examples show highly diastereoselective iodolactonisations

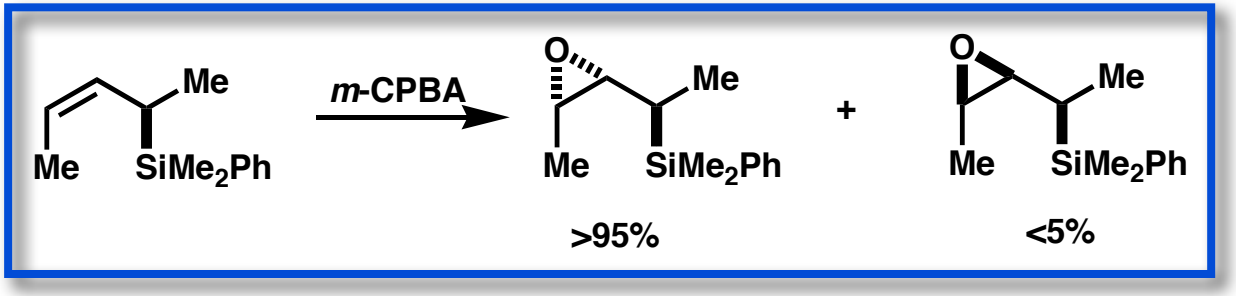




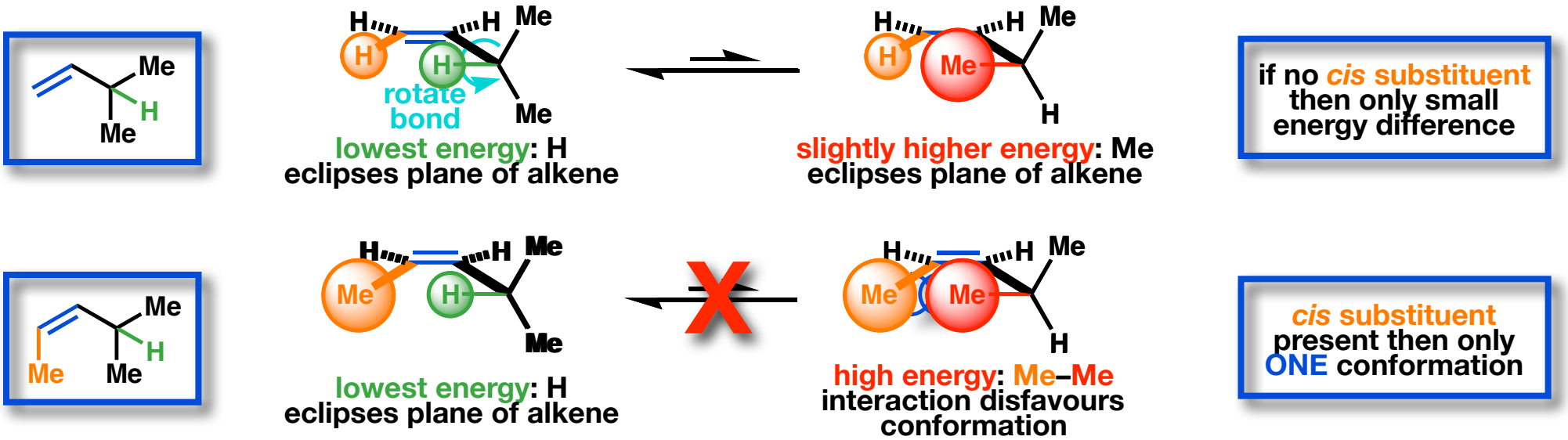
- These cyclisations are probably under **thermodynamic control**
- This means the reactions are reversible and equilibrate
- Therefore the product is the most **stable** compound

- If the reactions are under **kinetic control** we have to look at other factors and need to look at **conformation** again...

Stereoselective reactions of alkenes II



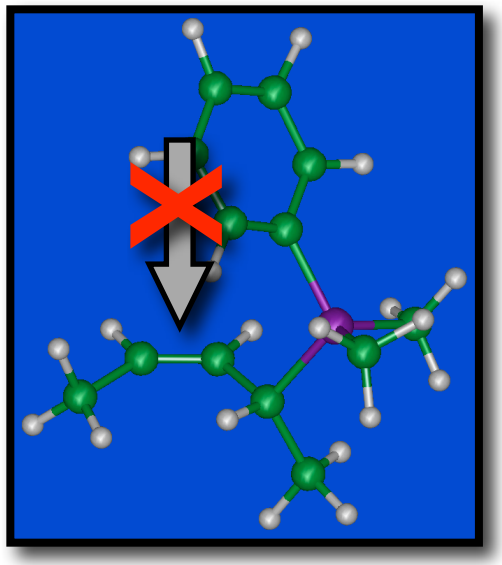
- Two diastereoisomers formed as a result of attack from the two diastereotopic faces
- Look at possible conformations...
- Arguably the lowest energy conformations have greatest separation of substituents



- The control of conformation by the interaction of methyl group and stereocentre is called **allylic strain** or **A$^{(1,3)}$ strain**

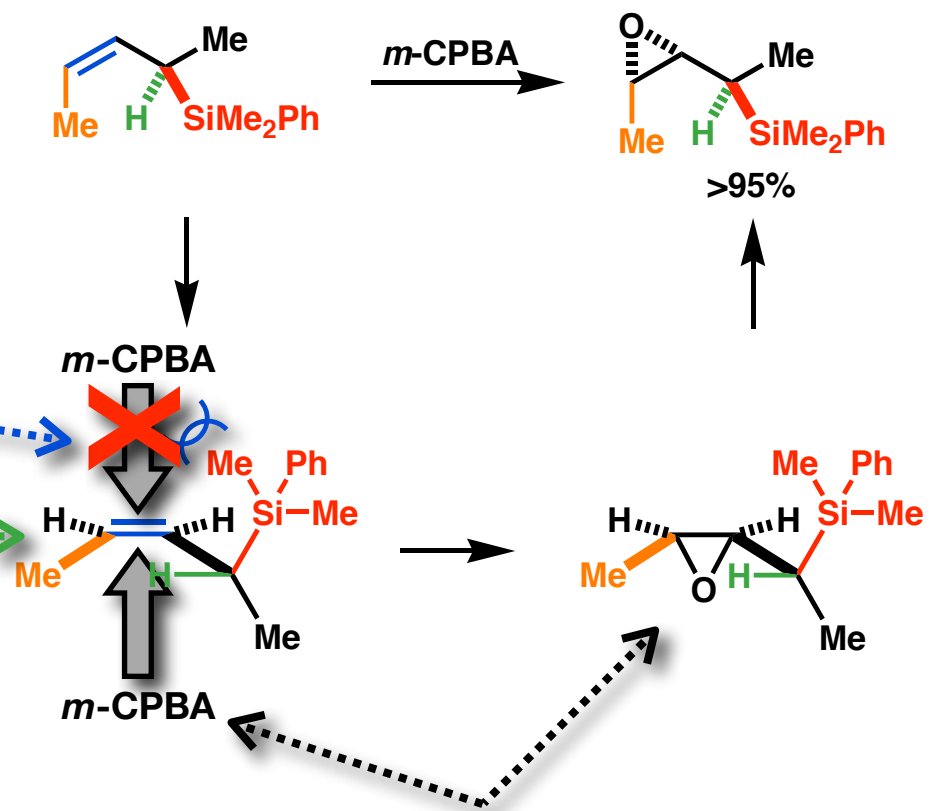
Stereoselective reactions of alkenes III

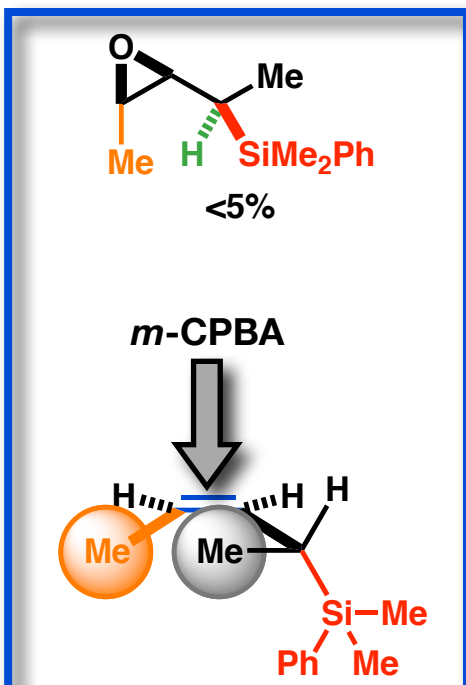
- Apply this knowledge to the real system...



silyl group blocks approach

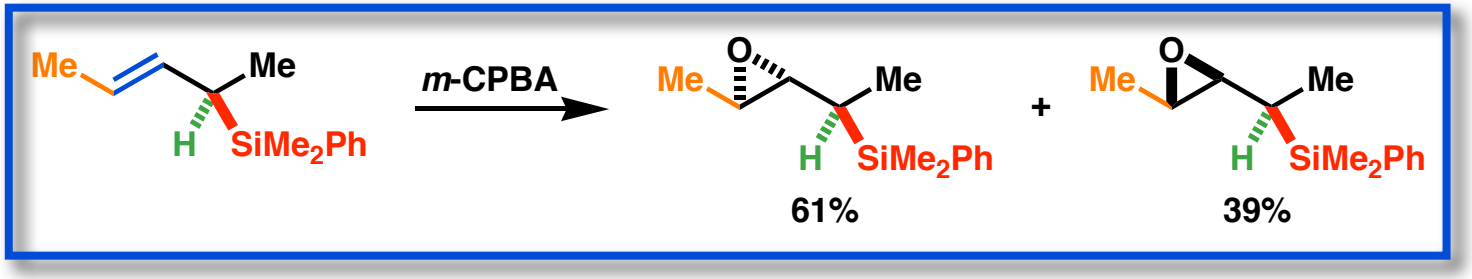
lowest energy conformation



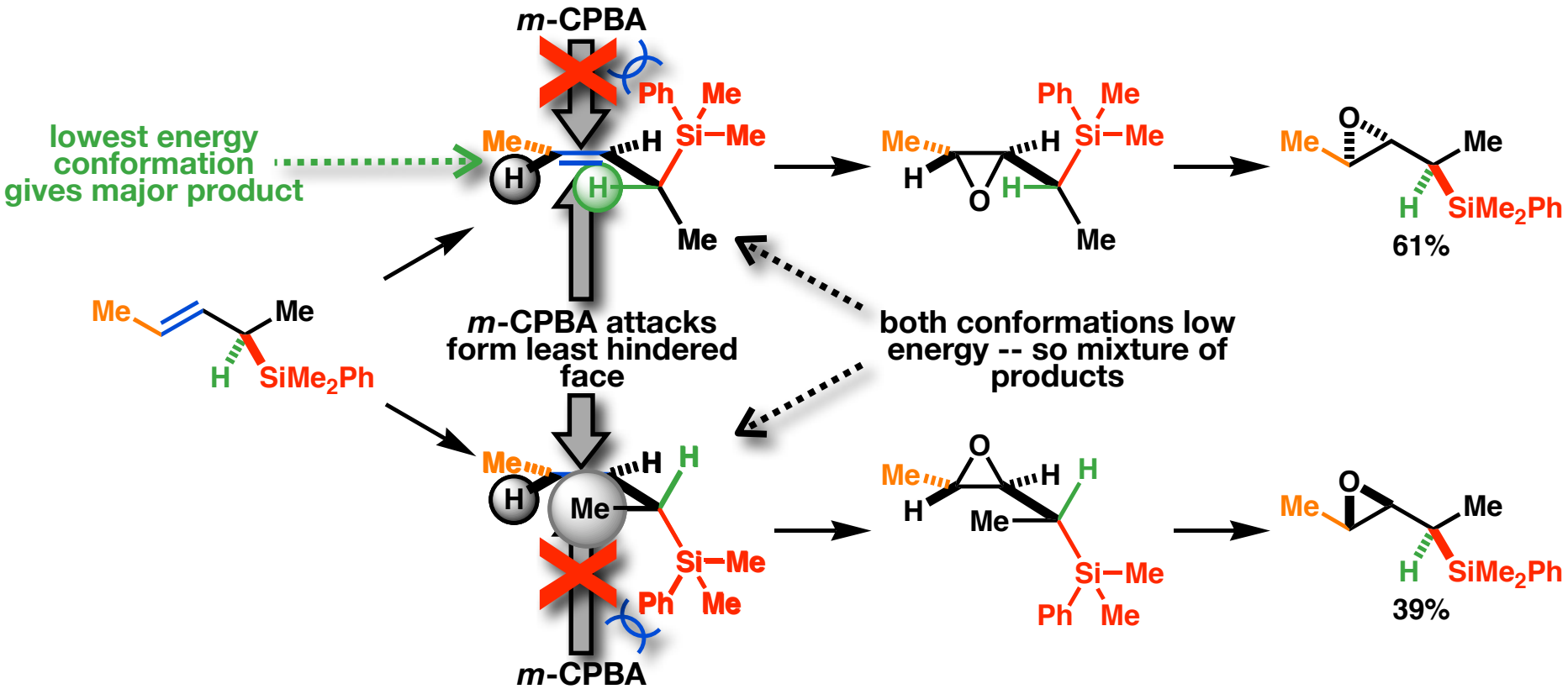


formation of minor diastereoisomer results from *m*-CPBA approaching alkene in above conformation or approaching passed the silyl group

Importance of $A^{(1,3)}$ strain

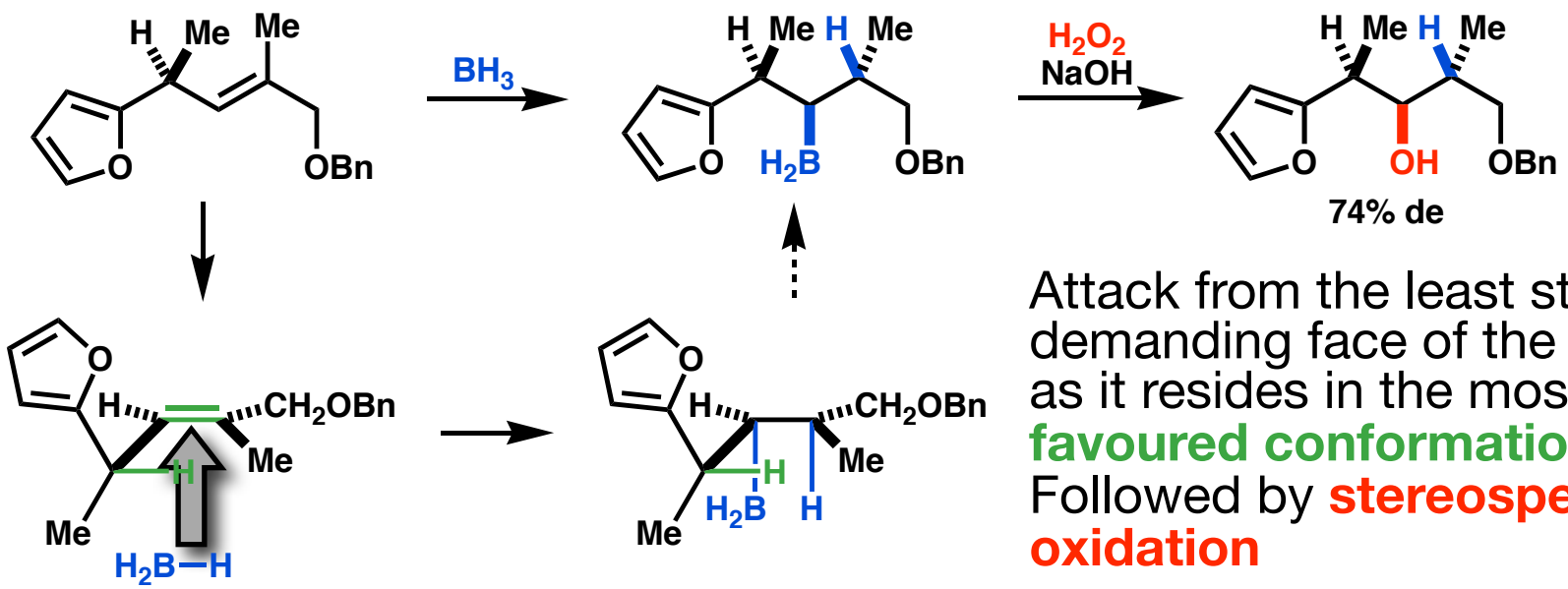


- The importance of a *cis*-substituent is made clear by the reduced stereoselectivity
- This is explained as follows...

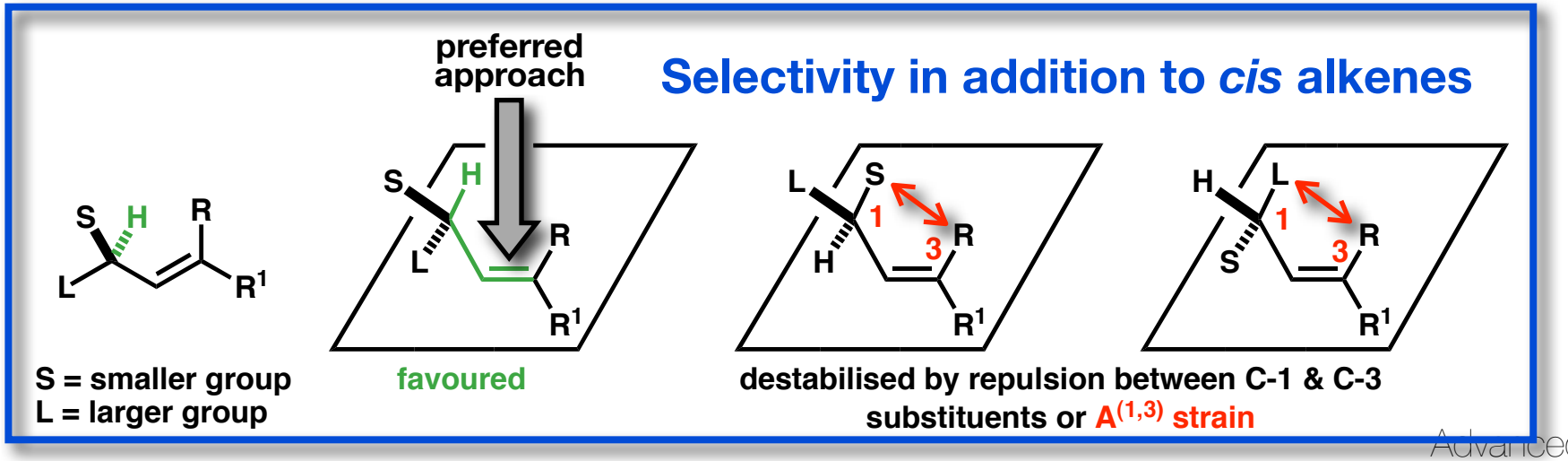


Other reactions...

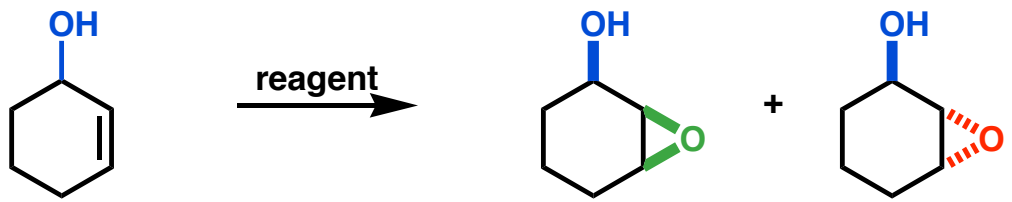
- Epoxidation is not the only stereoselective reaction of alkenes
- Below is an example of **hydroboration**, a useful reaction that you should be familiar with...



Attack from the least sterically demanding face of the alkene as it resides in the most **favoured conformation**. Followed by **stereospecific oxidation**

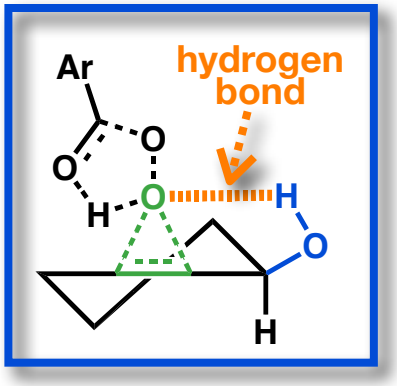


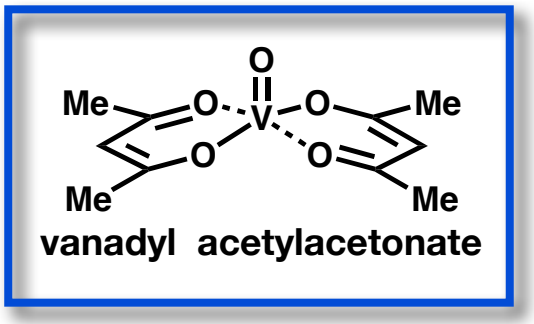
Directed epoxidation

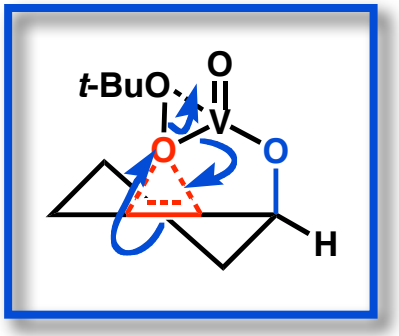


reagent:	*syn*		*anti*
m-CPBA	92	:	8
t-BuO_2H, $VO(acac)_2$	98	:	2

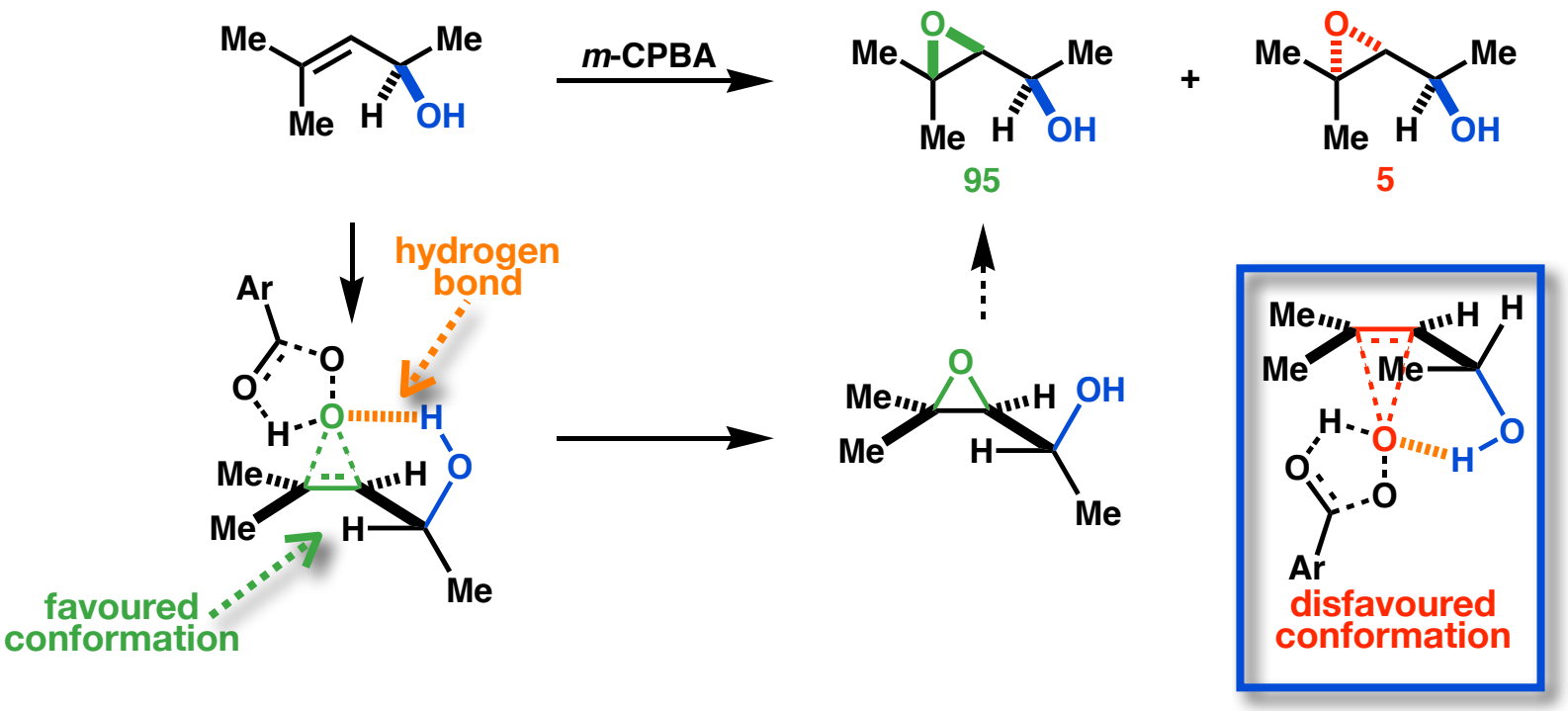
- A **hydroxyl** group can reverse normal selectivity and **direct** epoxidation
- Epoxidation with a peracid, such as *m*-CPBA, is directed by **hydrogen bonding** and favours attack from the same face as hydroxyl group
- The reaction with a vanadyl reagent results in higher stereoselectivity as it bonds / chelates to the oxygen





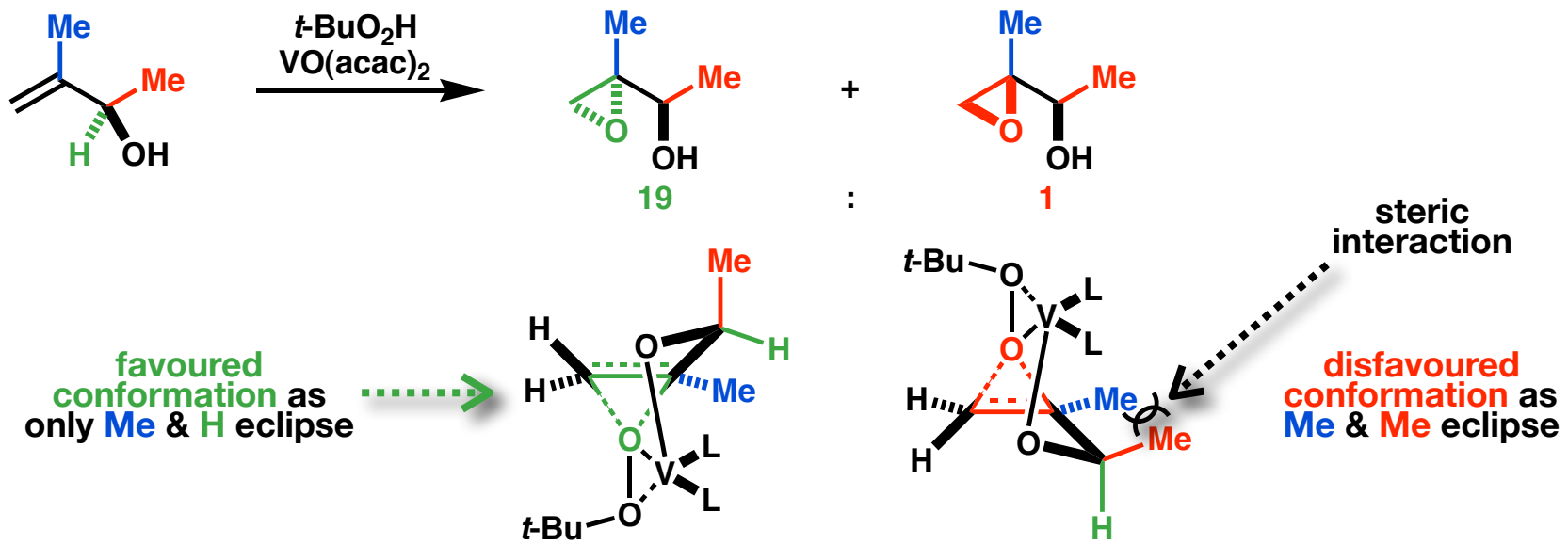


Directed epoxidation in acyclic systems

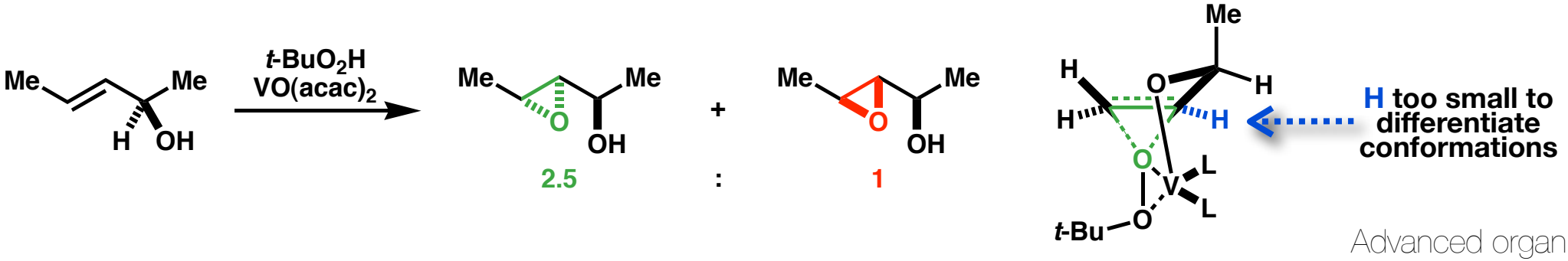


- Hydroxyl group can direct epoxidation in acyclic compounds as well
- Once again, major product formed from the most stable conformation
- Thus the *cis* methyl group is very important
- The minor product is formed either *via* non-directed attack or *via* the less favoured conformation

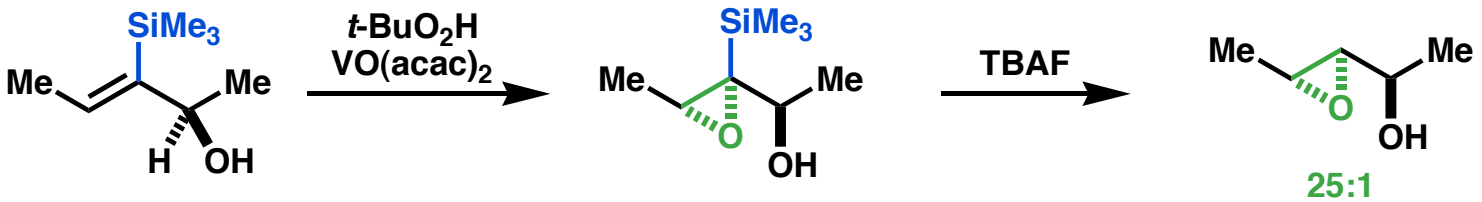
Directed epoxidation: effect of C-2 substituent



- The presence of a substituent in the C-2 position (**Me**) facilitates a highly diastereoselective reaction
- The preferred conformation minimises the interaction between the two **Me** (& **Me**) groups
- With C-2 substituent (**H**) there is little energy difference between conformations
- Therefore, get low selectivity

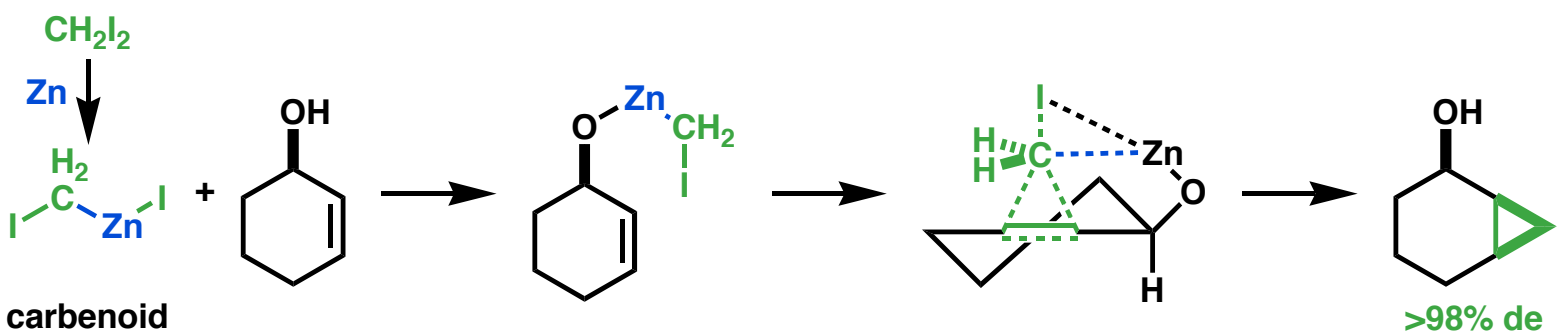


Directed reactions

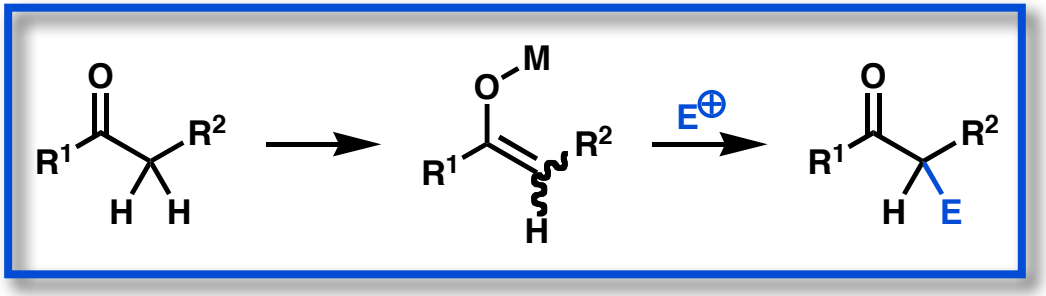


- It is possible to form the desired allylic epoxide in a highly selective manner by utilising a **temporary blocking** group
- The silyl group causes one conformation to predominate & can be removed at end
- As silyl group bigger than methyl reaction more selective

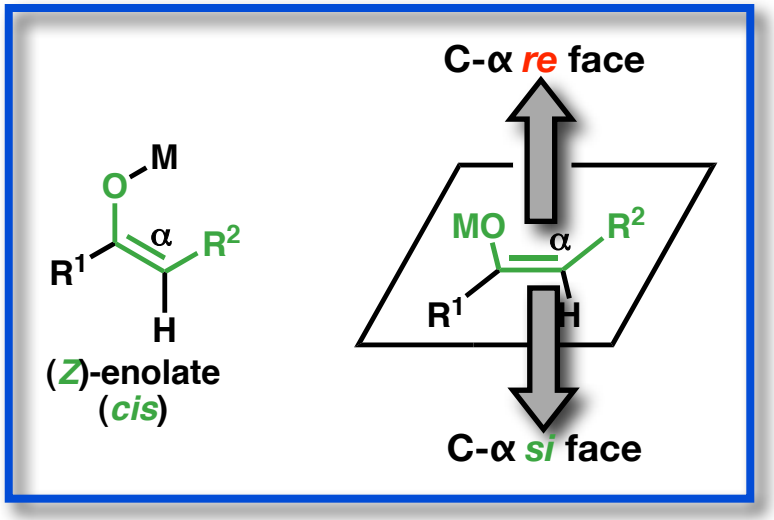
- Other diastereoselective reactions of alkenes can be controlled by a directing group
- Below is an example of cyclopropanation by the Simmons-Smith reagent

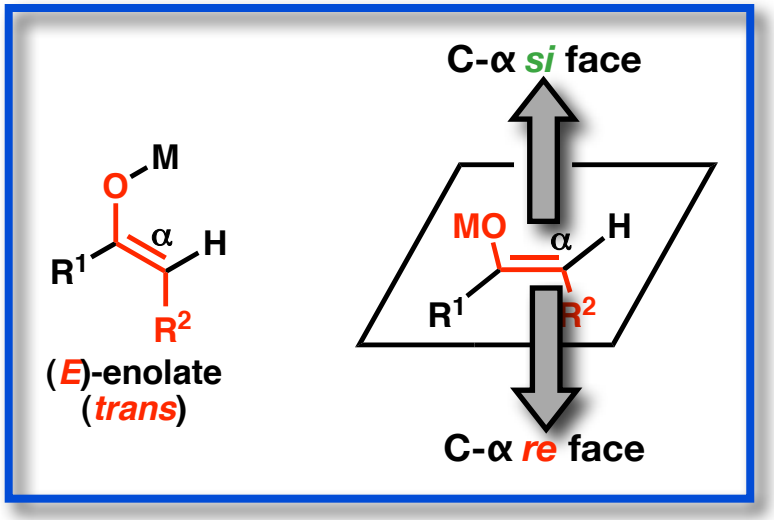


Stereoselective reactions of enolates



- The stereoselectivity of reactions of **enolates** is dependent on:
- Presence of stereogenic centres on **R¹**, **R²** or **E** (obviously!)
- Frequently on the **geometry** of the enolate (but not always)

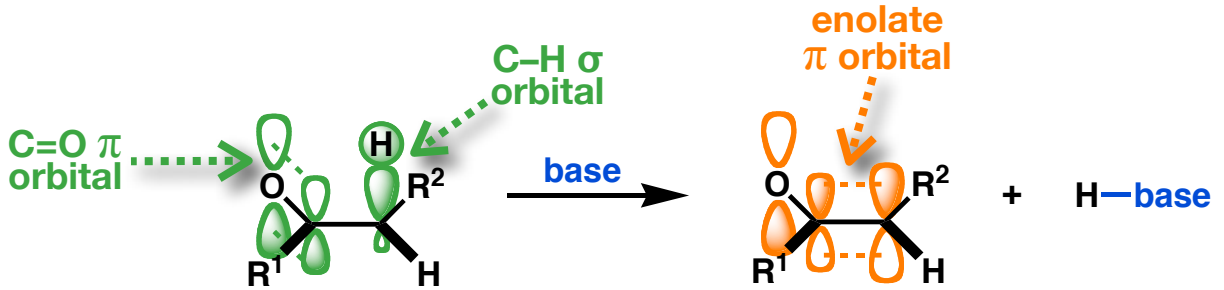




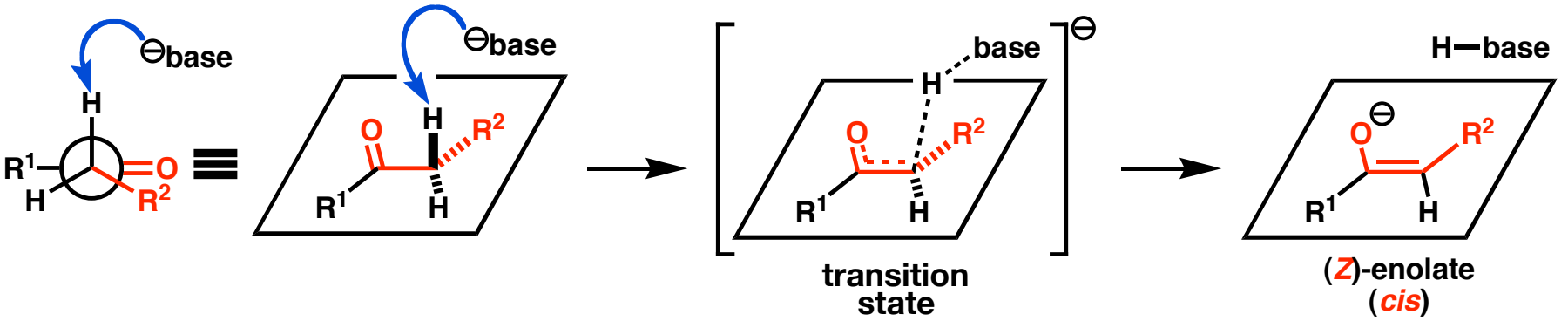
- Use terms ***cis*** and ***trans*** with relation to O–M to avoid confusion

Enolate formation and geometry

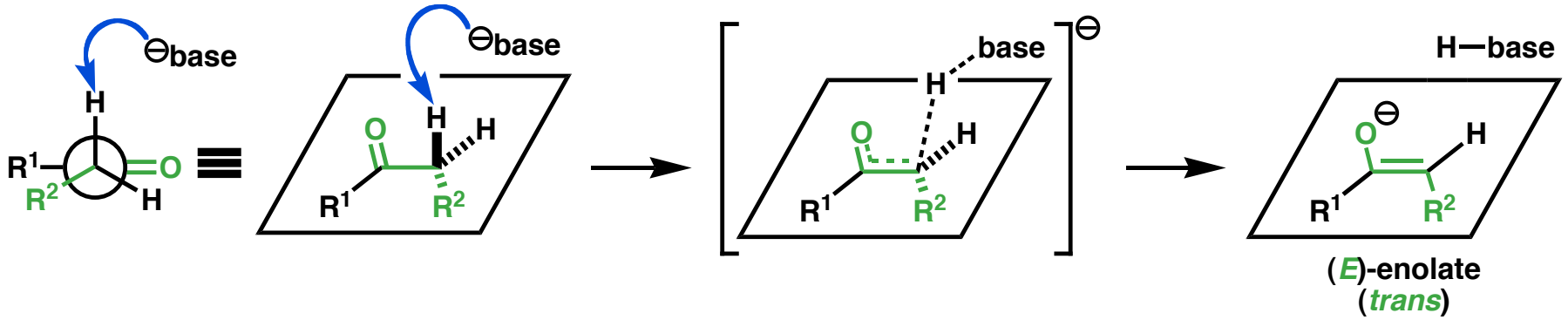
- Enolate normally formed by **deprotonation**
- This is favoured when the C–H bond is perpendicular to C=O bond as this allows σ orbital to overlap π orbital
- σ C–H orbital ultimately becomes p orbital at C-α of the enolate p bond



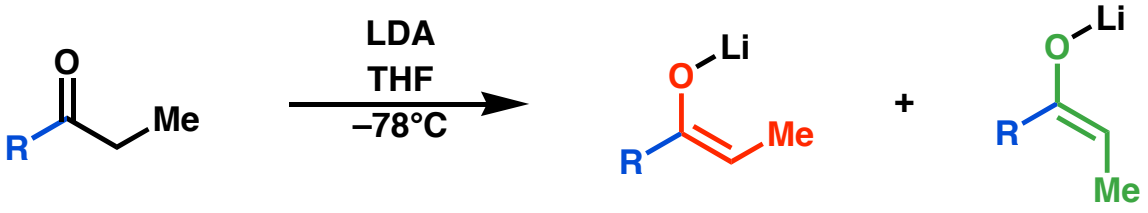
- Two possible conformations which allow this
- First is given below and results in the formation of ***cis* enolate**
- Initial conformation (Newman projection) similar to transition state
- Little steric interaction between **R**[1] and **R**[2]



Enolate formation and geometry II



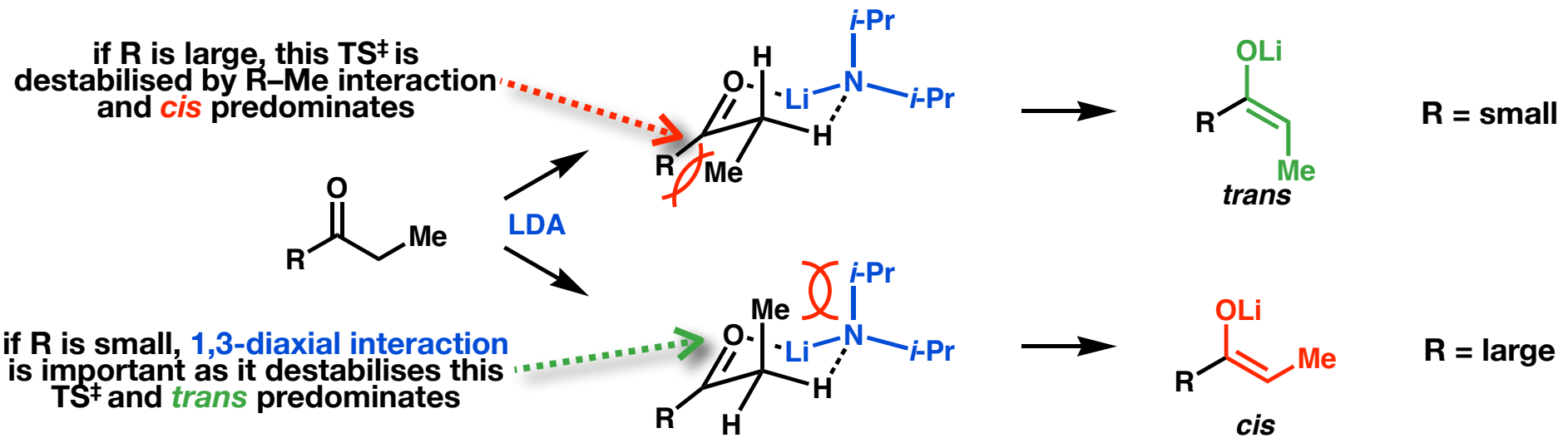
- Second conformation that places C–H perpendicular to C=O gives ***trans*-enolate**
- Only differs by relative position of **R^1** and **R^2**
- The steric interaction of **R^1** and **R^2** results in the ***cis*-enolate** normally predominating
- As results below demonstrate stereoselectivity is influenced by the size of R^1



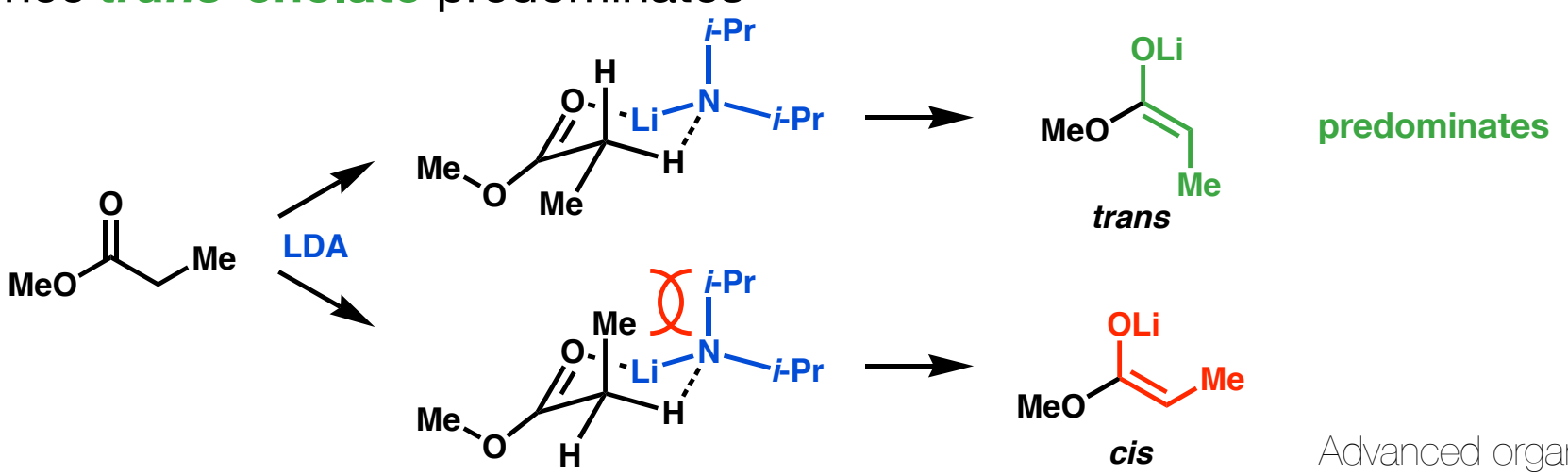
R =	*cis*		*trans*
Et	30	:	70
i-Pr	60	:	40
t-Bu	>98	:	<2
OMe	5	:	95
NEt_2	>97	:	<3

Enolate formation and geometry III

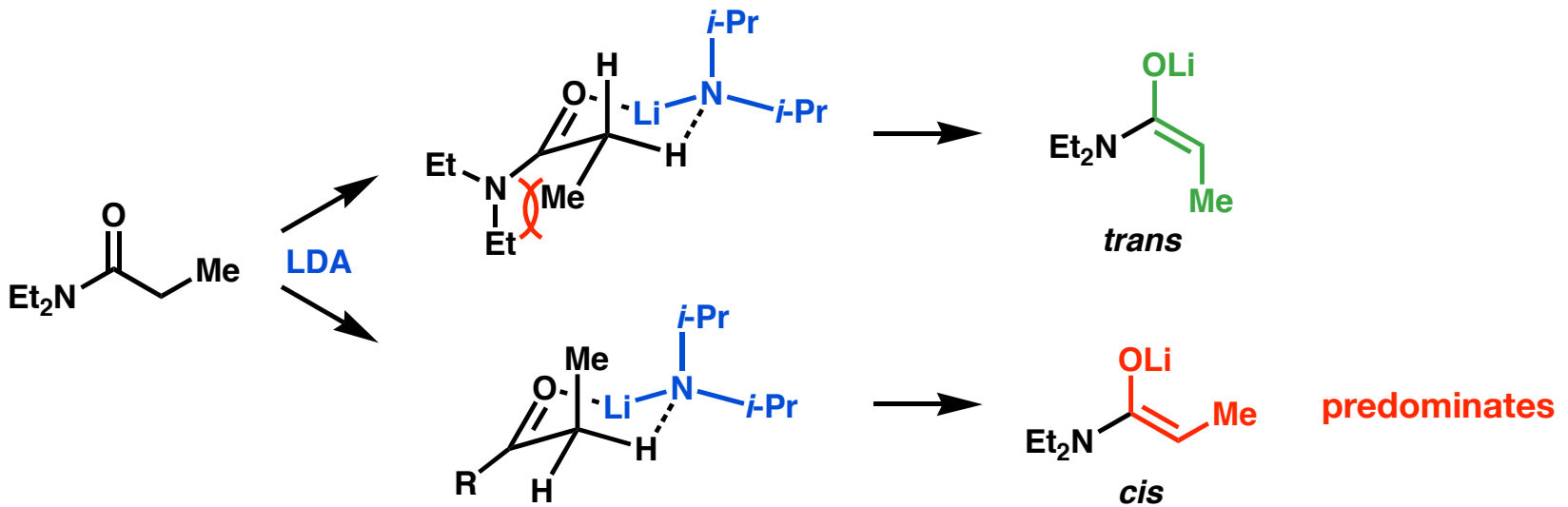
- Previous table shows that stereoselectivity of enolate formation not always obvious
- In ketones ***trans*-enolate** favoured if **R¹** is small but ***cis*-enolate** if **R¹** is large
- Can explain this with transition state (again...)



- With esters the **R** *vs* **OMe** interaction is alleviated and 1,3-diaxial interaction controls geometry - hence ***trans*-enolate** predominates

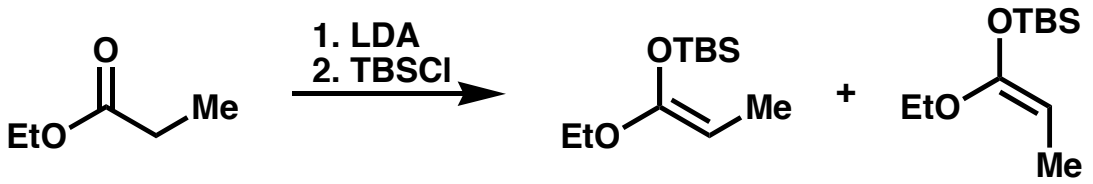


Enolate formation and geometry IV



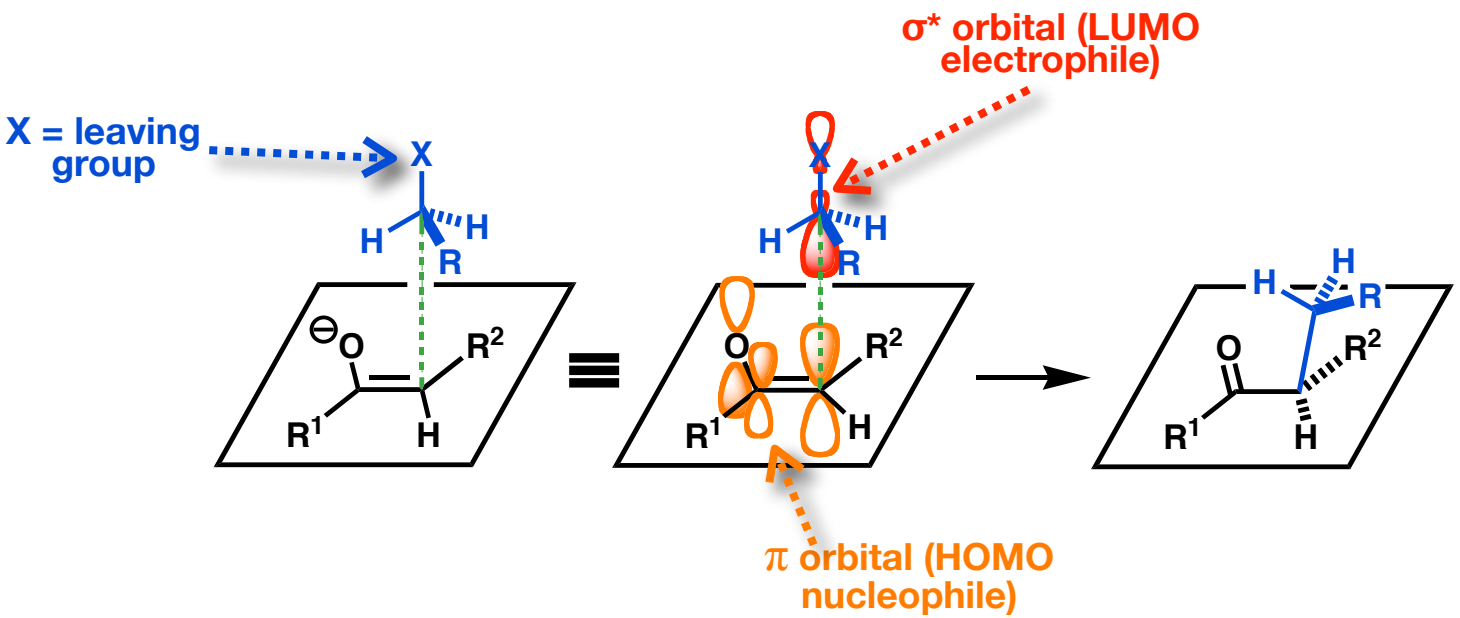
- Amides invariably give the ***cis*-enolate**; remember restricted rotation of C–N bond

- The previous arguments are good generalisations, many factors effect geometry
- Use of the additive **HMPA** (hexamethylphosphoric triamide) reduces coordination and favours the thermodynamically more stable enolate



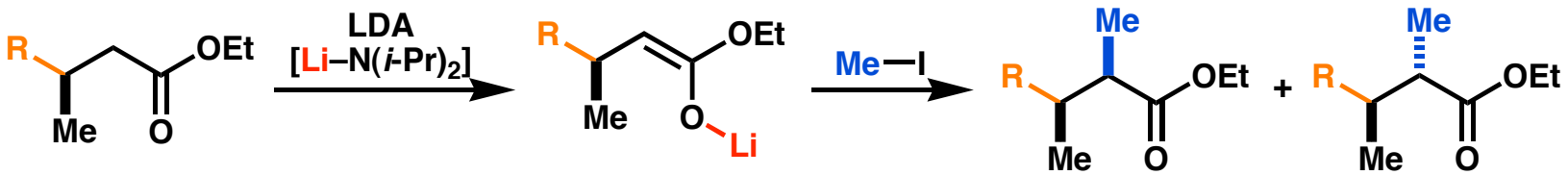
	cis	*trans*
THF	6	94
THF / HMPA	82	18

Addition of an electrophile to an enolate



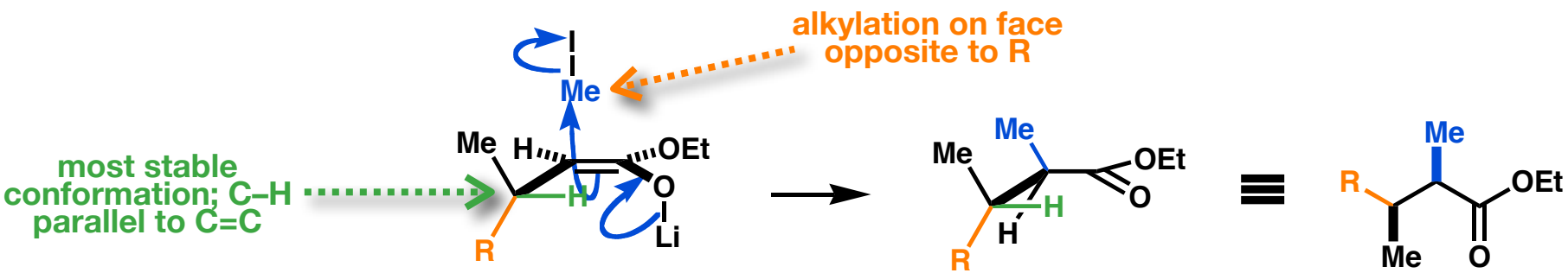
- Finally, need to know the trajectory of approach of the enolate and electrophile
- Reaction is the overlap of the **enolate HOMO** and **electrophile LUMO**
- Therefore, new bond is formed more or less perpendicular to carbonyl group
- Above is simple S_N2 with **X** = leaving group

Enolate alkylation



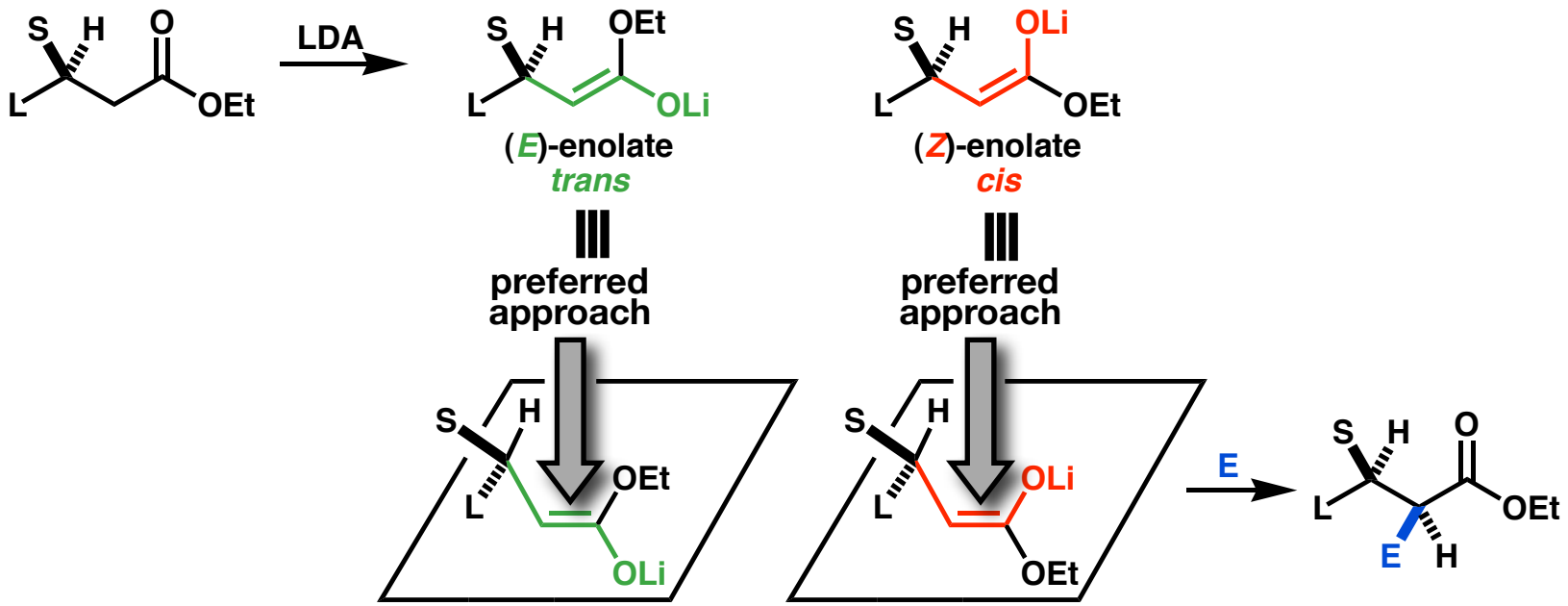
	syn	:	*anti*
R = Ph	77	:	23
R = Bu	83	:	27
R = $SiMe_2Ph$	95	:	5

- Simple alkylation of a chiral enolate can be very diastereoselective
- As we have a ***cis*-enolate** diastereoselectivity can be explained in an analogous fashion to simple alkenes *via* **$A^{(1,3)}$ strain**
- Larger the substituent, **R**, greater the selectivity

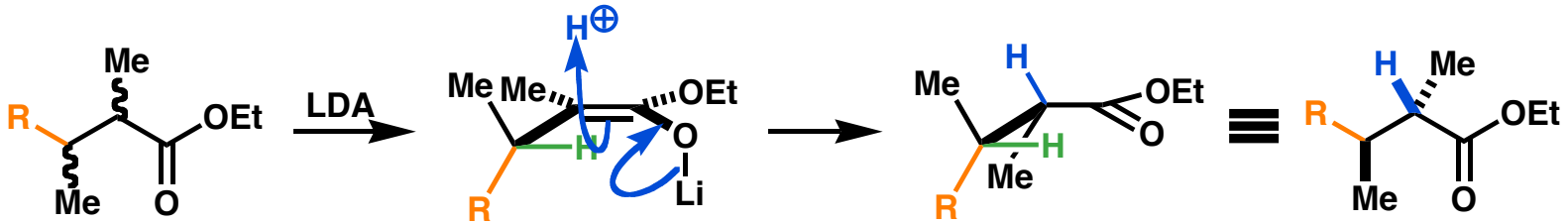


- **Note:** minor diastereoisomer probably arises from electrophile passing by **R** group
- Therefore, size does matter...

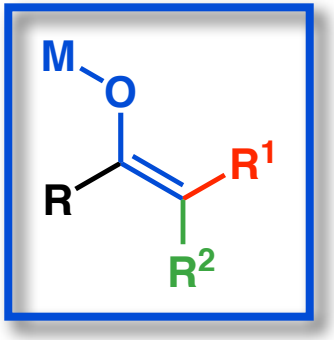
Enolate alkylation II



- In this example enolate geometry is not important - both are *cis*-alkenes
- Therefore, selectivity the same in both cases
- If we want to reverse selectivity, change the electrophile to H
- This route far less selective as H is small so less interaction with substituents

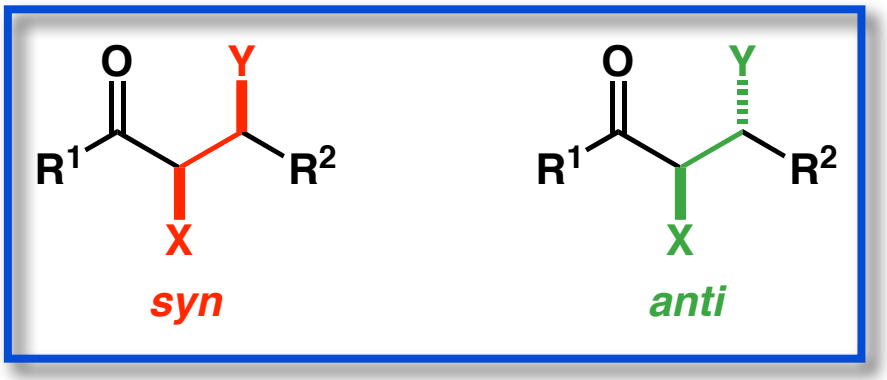


Nomenclature (again!!)



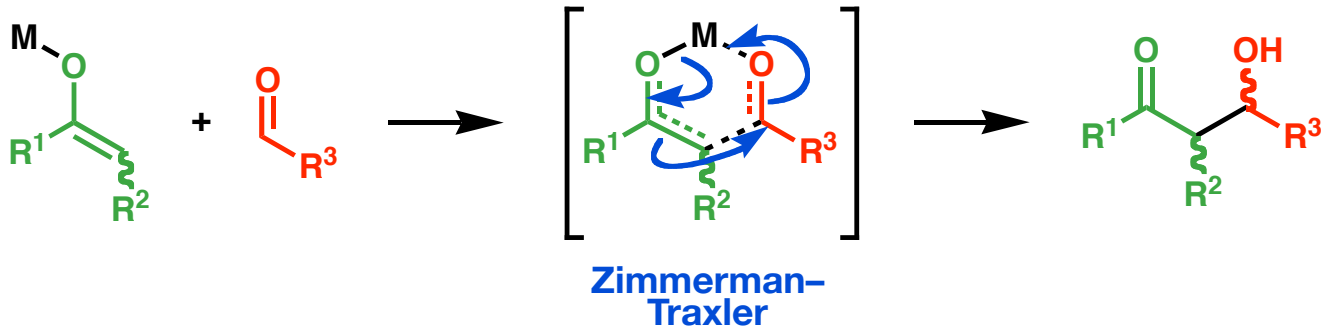
- You may have noticed some annoying changes nomenclature!
- With ester enolates the *E* / *Z* nomenclature changes depending on the nature of M (if we use the Cahn-Ingold-Prelog rules)

- As a result we will classify enolates as ***cis*** or ***trans*** with respect to **O–M**
  R^1 = ***cis***
  R^2 = ***trans***

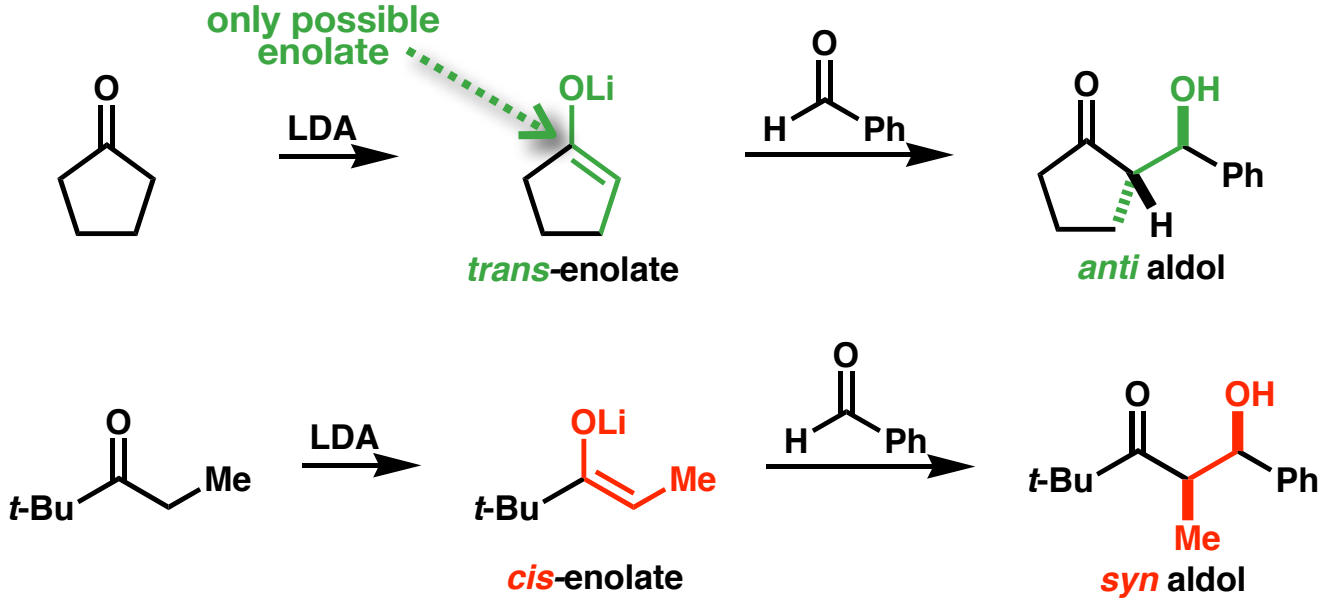


- ***Syn*** and ***anti*** in the aldol reaction refer to relative stereochemistry of enolate substituent **X** and hydroxyl group (or equivalent) **Y**

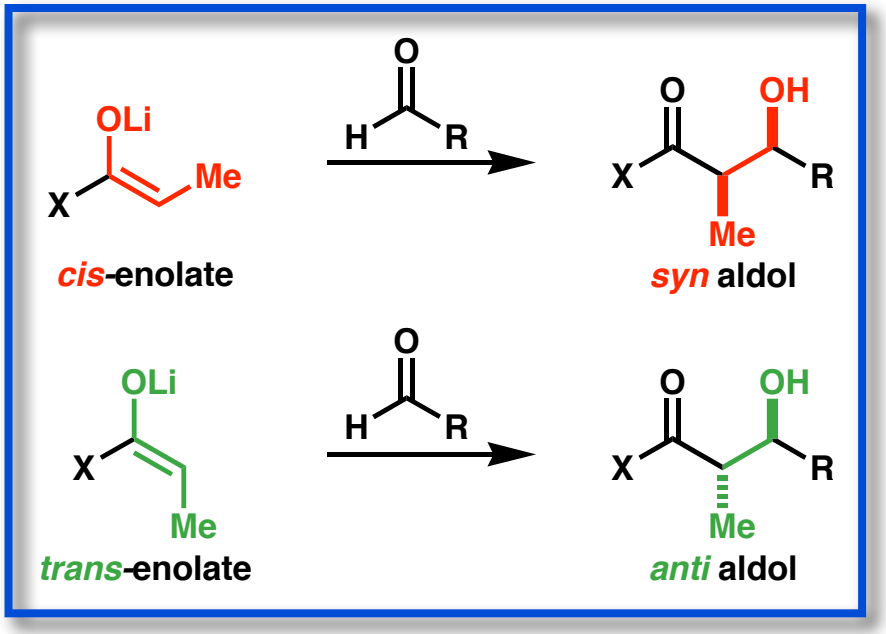
The aldol reaction



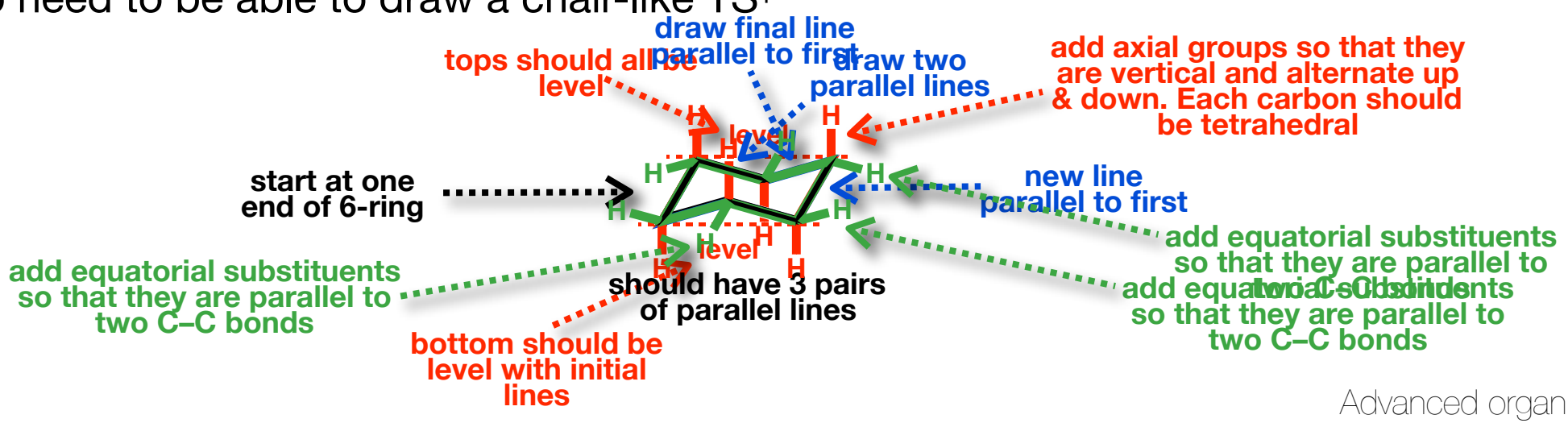
- The **aldol reaction** is a valuable C–C forming reaction
- In addition it can form two new stereogenic centres in a **diastereoselective** manner
- Most aldol reactions take place *via* a highly order transition state know as the **Zimmerman–Traxler** transition state
- It will not come as much surprise that this is a 6-membered, chair-like transition state
- Interestingly, enolate geometry effects **diastereoselectivity**



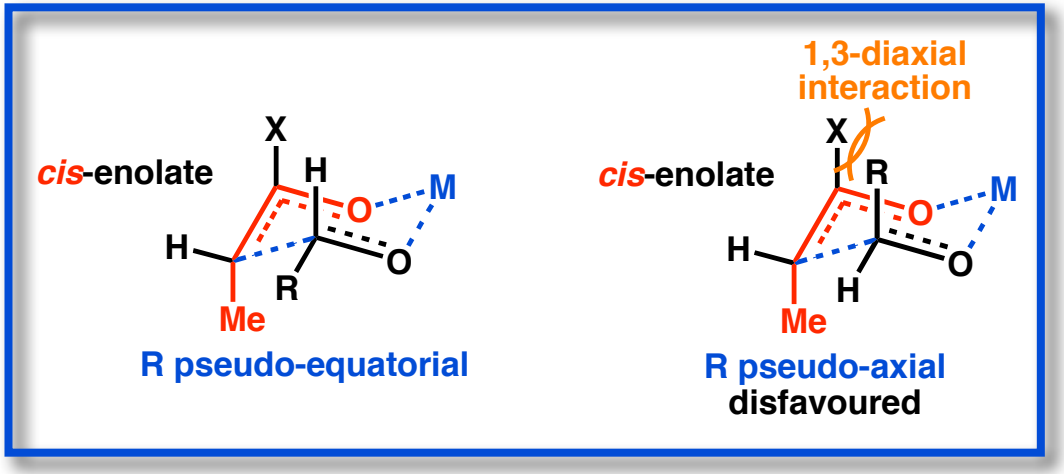
The aldol reaction II



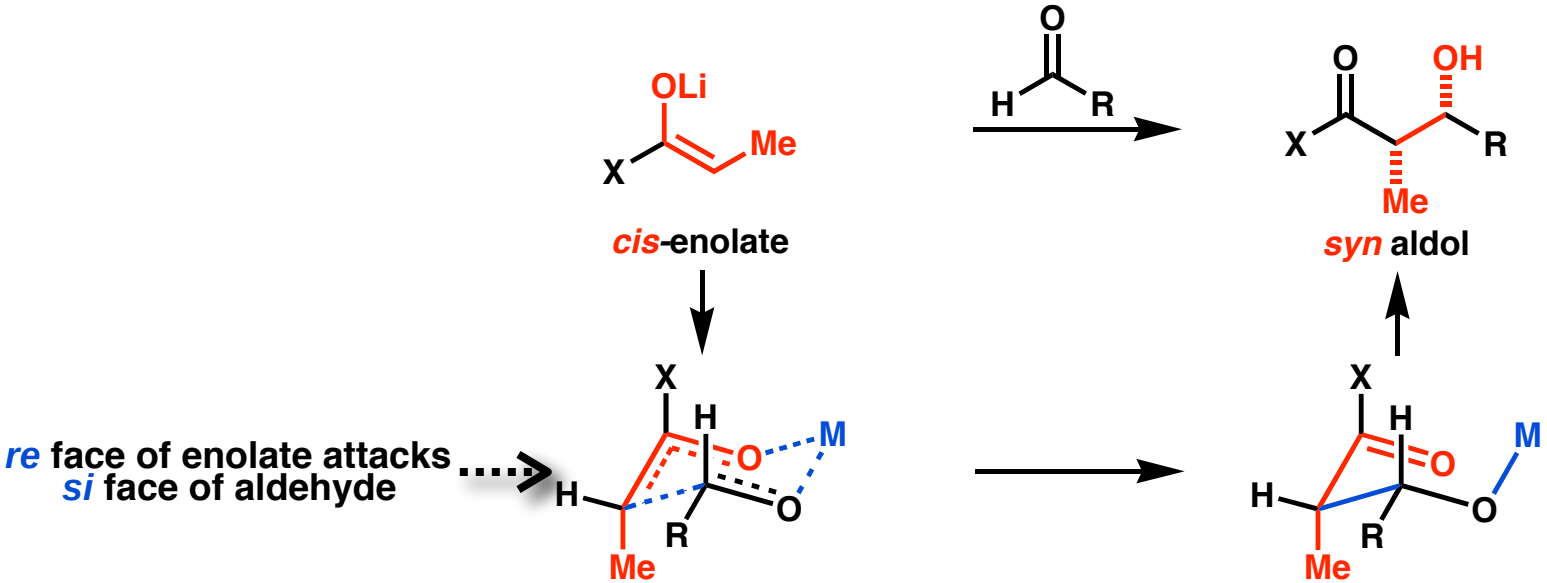
- Generally speaking the above guideline sums up aldol chemistry!
- To understand why this happens we need to examine Zimmerman-Traxler TS‡
- So need to be able to draw a chair-like TS‡

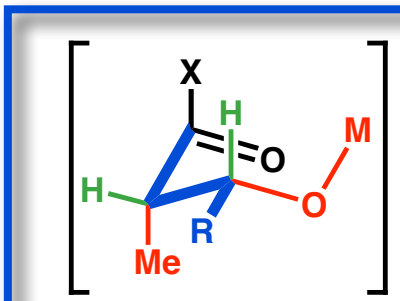


Zimmerman-Traxler transition state



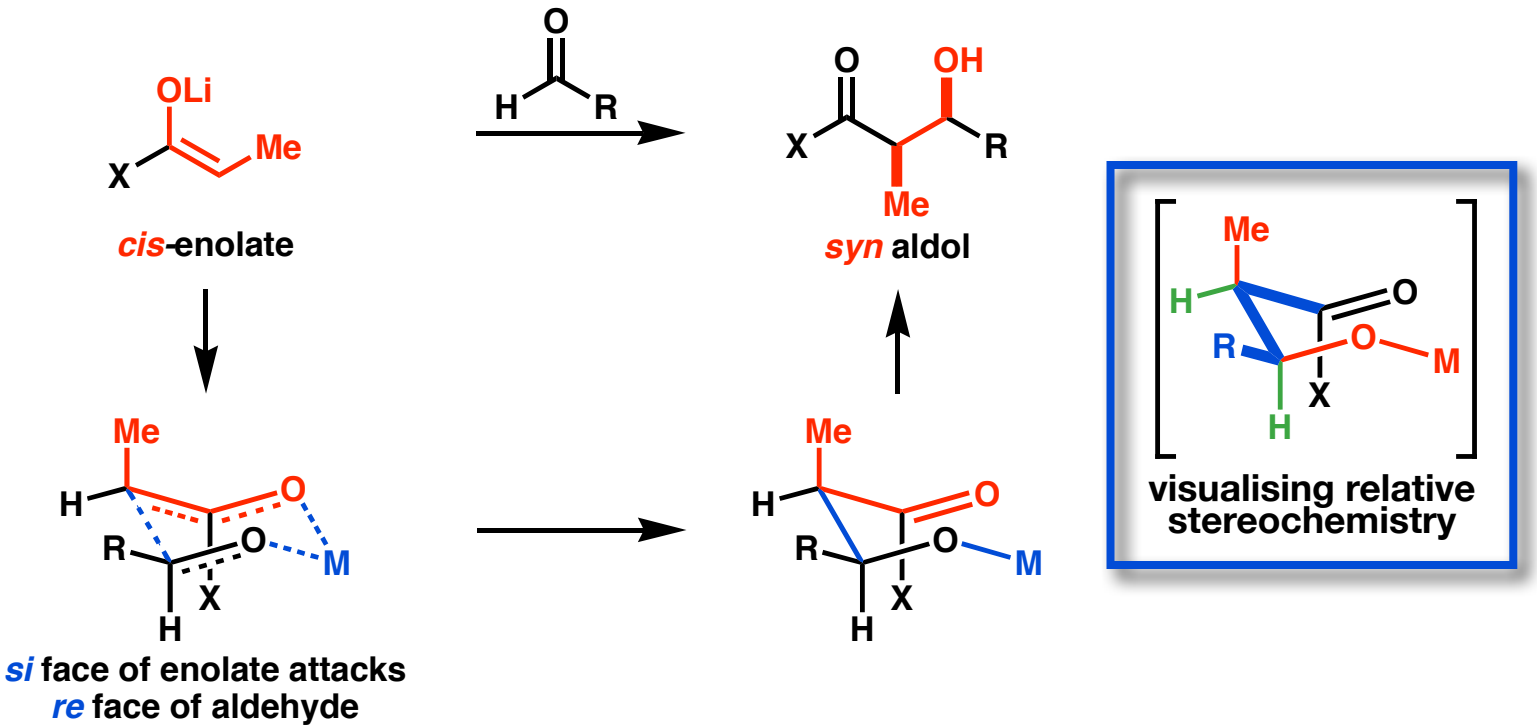
- We only have one choice in the aldol reaction - the orientation of the aldehyde
- Enolate substituents are fixed due to the double bond
- Aldehyde substituent is **pseudo-equatorial** to avoid **1,3-diaxial interactions**





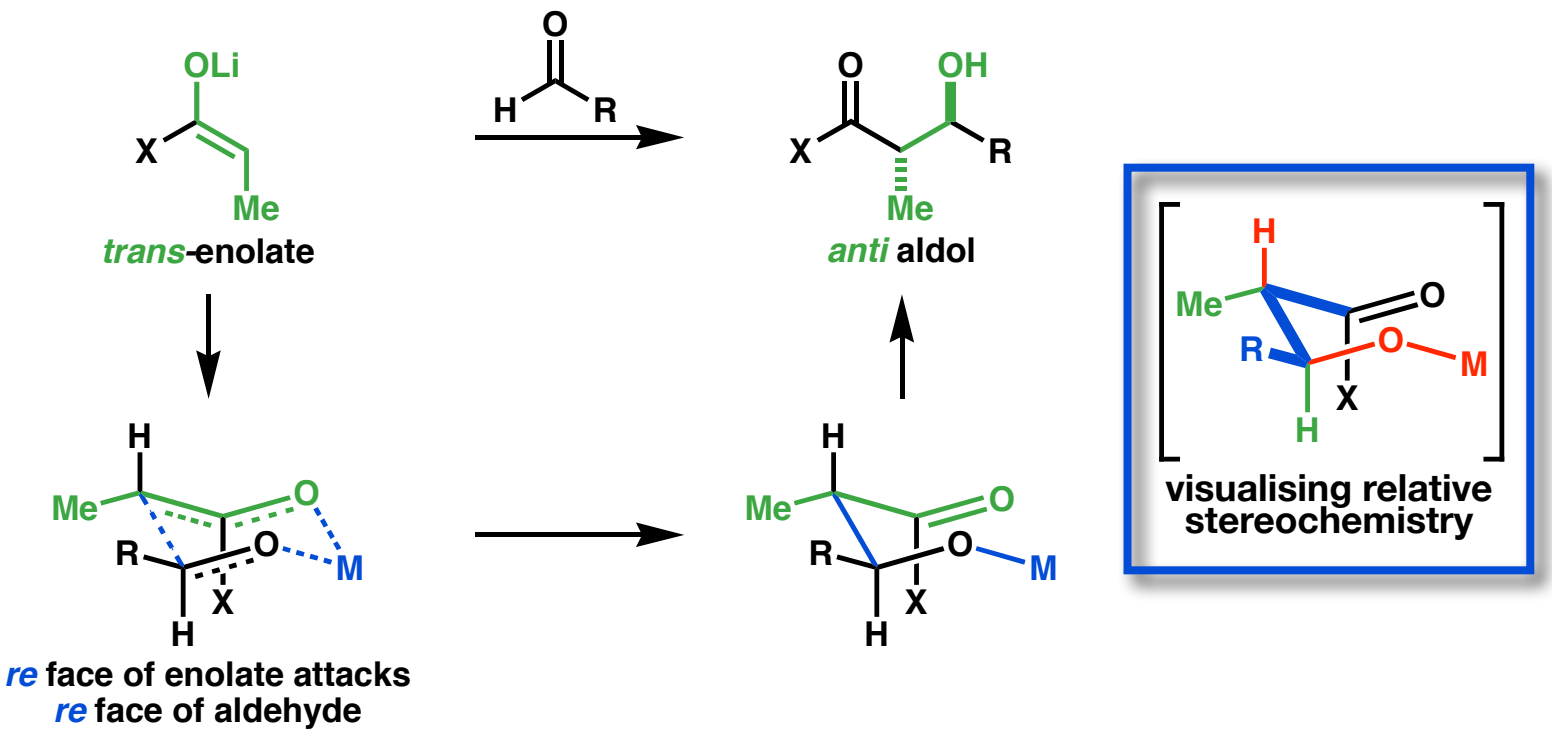
to 'see' relative stereochemistry consider S as plane and see which groups are above and which below

Zimmerman-Traxler transition state II



- Attack *via* the enantiomeric transition state (*re* face of aldehyde) gives the enantiomeric aldol product
- This differs only by the absolute stereochemistry - the relative stereochemistry is the same

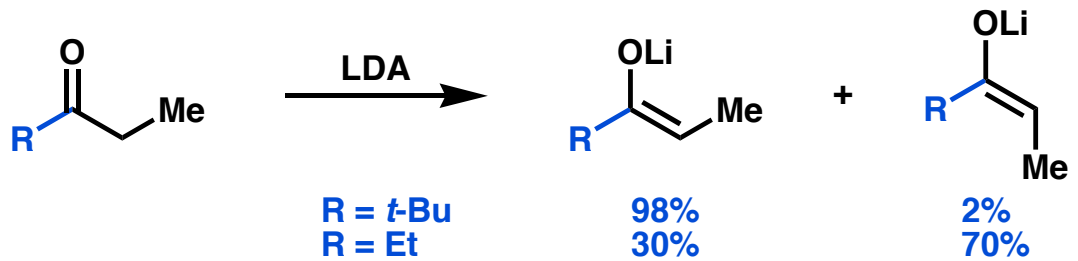
Zimmerman-Traxler transition state III



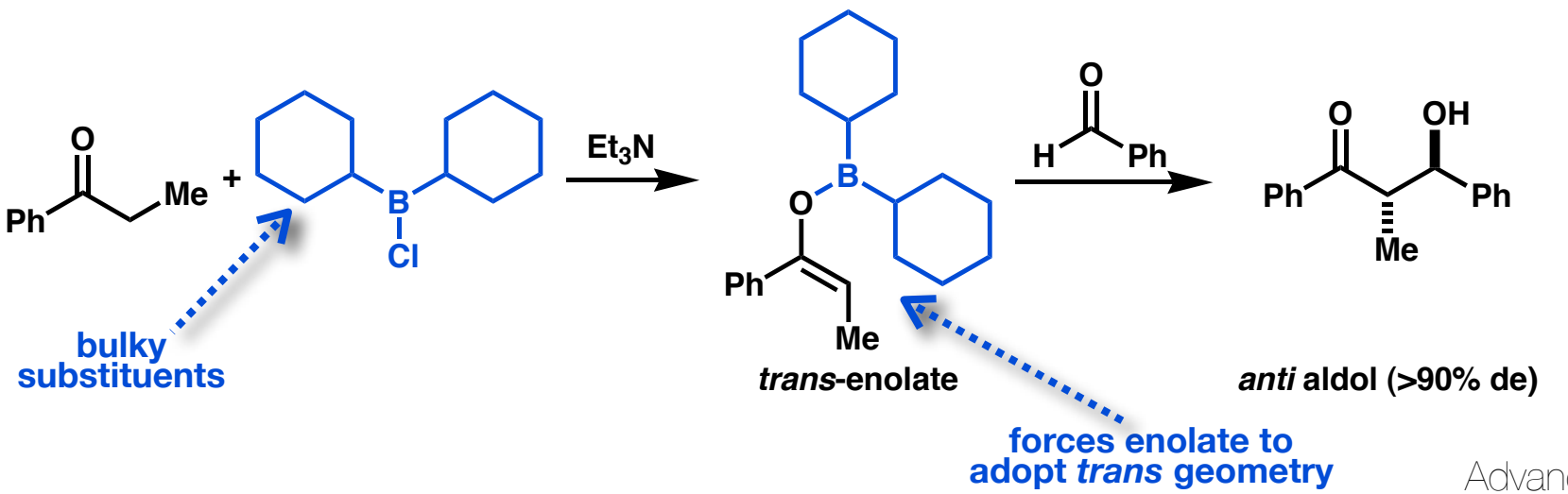
- The opposite stereochemistry of enolate gives opposite relative stereochemistry
- Once again the enolate has no choice where the methyl group is placed

Enolisation and the aldol reaction

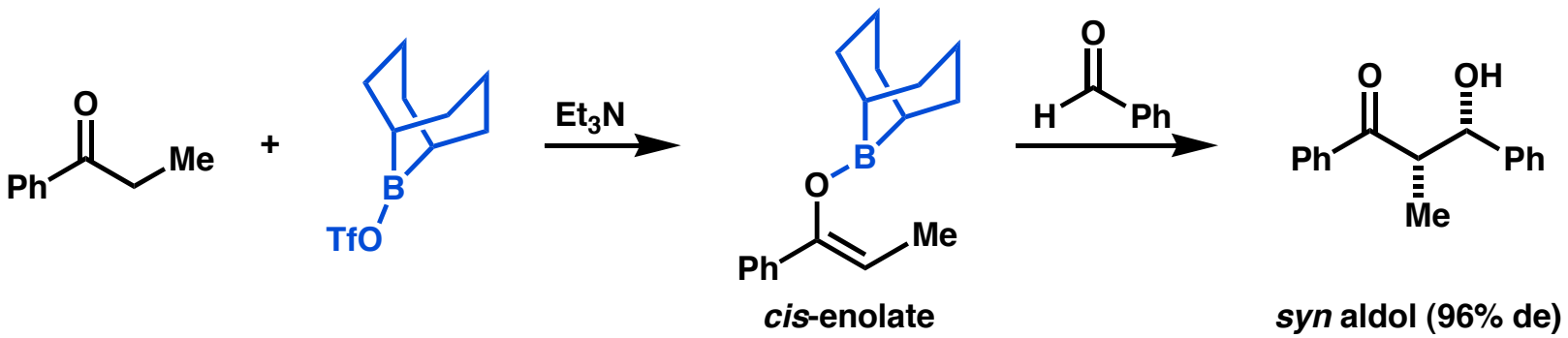
- Hopefully, all the previous discussion highlights that selective enolisation is essential for diastereoselective aldol reaction
- Each **geometry** of enolate gives a different **relative** stereochemistry
- With the **lithium** enolates of ketones the size of the non-enolised substituent, **R**, is important



- With **boron** enolates we can select the geometry by altering the boron reagent used



Enolisation and the aldol reaction II



- 9-BBN (9-borabicyclononane) looks bulky
- But most of it is ‘tied-back’ behind boron thus allowing formation of the *cis*-enolate