ΔΜΠΣ Ιατρικής Χημείας και Χημικής Βιολογίας

Οργανική Σύνθεση Φαρμάκων
- Ασύμμετρη Σύνθεση -

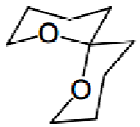
Διαλέξεις

Επικ. Καθ. Γ. Ρασσιά

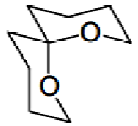
Τμήμα Χημείας
Πανεπιστήμιο Πατρών

Σπουδαιότητα χειρομορφίας στη φύση

olive fly sex pheromones

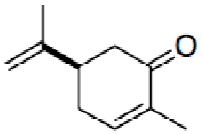


attracts Males

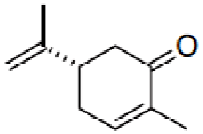


attracts Females

Carvone

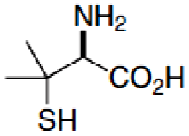


spearmint odor

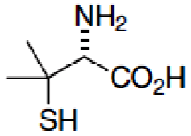


caraway

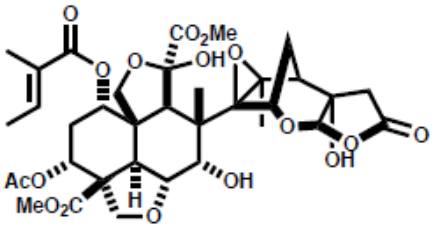
Penicillamine



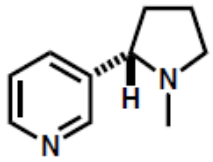
antidote for Pb, Au, Hg



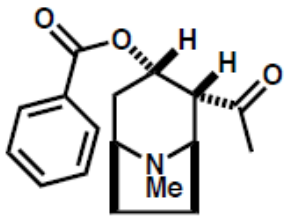
can cause optic atrophy => blindness



azadiractin
anti-feedant



(*S*)-3-(1-methylpyrrolidin-2-yl)pyridine
nicotine
toxin / stimulant

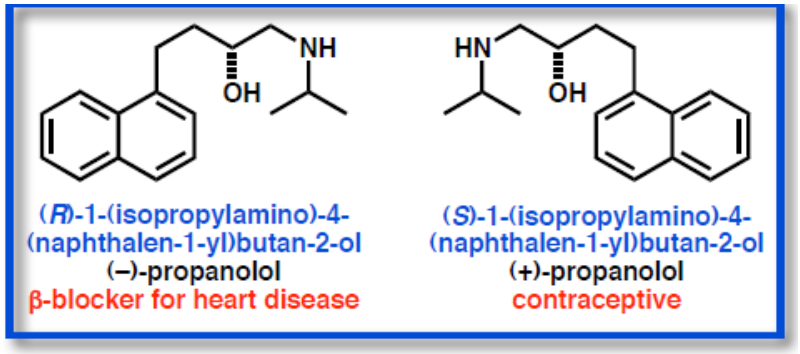


(1*R*,2*R*,3*S*,5*S*)-2-acetyl-8-methyl-8-aza-bicyclo[3.2.1]octan-3-yl benzoate
cocaine
stimulant

Η φύση συνθέτει πολλά χειρόμορφα μόρια, κάποια απλά και άλλα εξαιρετικά πολύπλοκα.

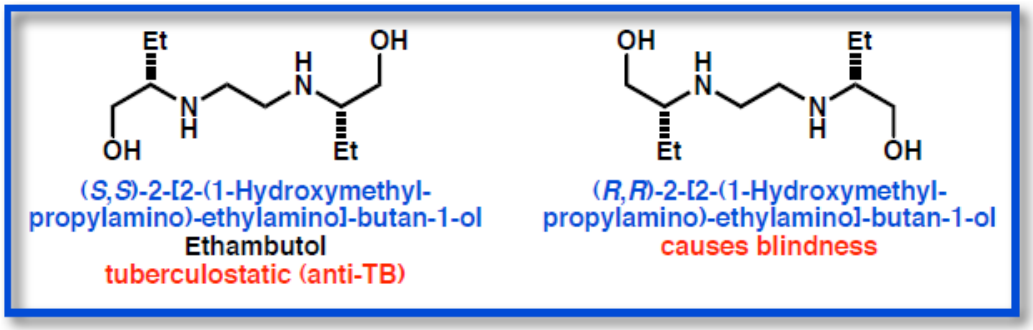
Σε πολλές περιπτώσεις συνθέτει και τα δύο εναντιομερή ή όλα τα πιθανά διαστεροισομερή ενός συστήματος αλλά το καθένα για διαφορετικό σκοπό.

Σπουδαιότητα ασύμμετρης σύνθεσης



(*R*)-1-(isopropylamino)-4-(naphthalen-1-yl)butan-2-ol
(–)-propanolol
β-blocker for heart disease

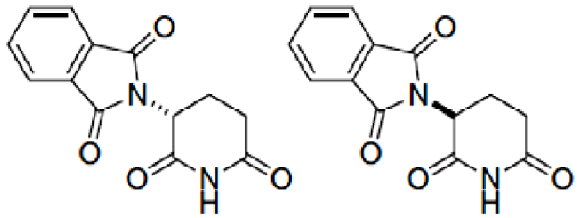
(*S*)-1-(isopropylamino)-4-(naphthalen-1-yl)butan-2-ol
(+)-propanolol
contraceptive



(*S,S*)-2-[2-(1-Hydroxymethyl-propylamino)-ethylamino]-butan-1-ol
Ethambutol
tuberculostatic (anti-TB)

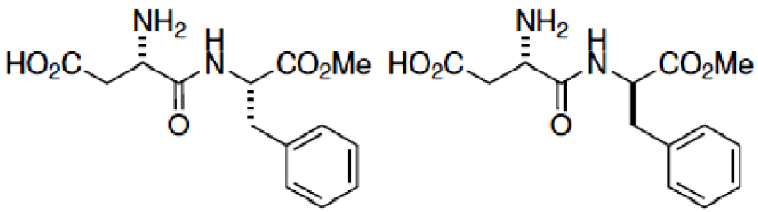
(*R,R*)-2-[2-(1-Hydroxymethyl-propylamino)-ethylamino]-butan-1-ol
causes blindness

Thalidomide



sedative, hypnotic teratogenic

Aspartame
(Nutrasweet)

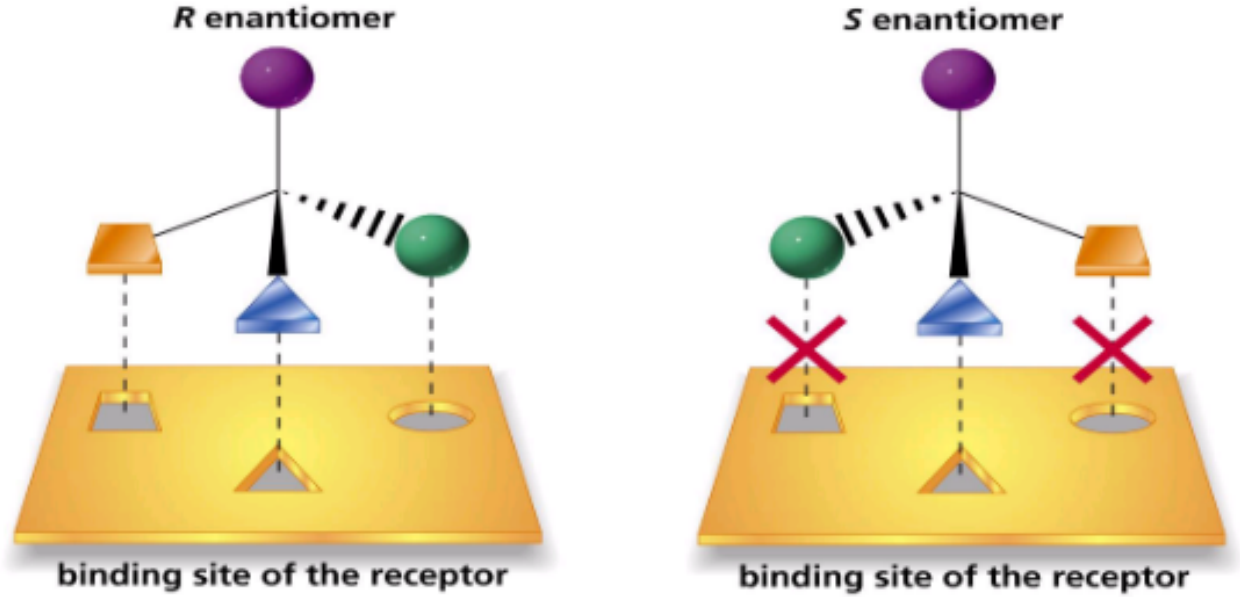


sweet bitter

Γενικά αποφεύγονται μείγματα εναντιο/διαστερεο-ισομερών ουσιών ως φάρμακα διότι συνήθως αλληλεπιδρούν διαφορετικά με τους χειρόμορφους βιολογικούς στόχους

Η παρασκευή ενός εναντιο/διαστερο-μερούς επιτυγχάνεται μέσω της ασύμμετρης σύνθεσης όπου μια αλληλουχία αντιδράσεων δημιουργεί επιλεκτικά ένα νέο χειρομορφικό στοιχείο με συγκεκριμένη διάταξη των υποκαταστατών στο χώρο.

Σπουδαιότητα χειρομορφίας βιολογικά συστήματα

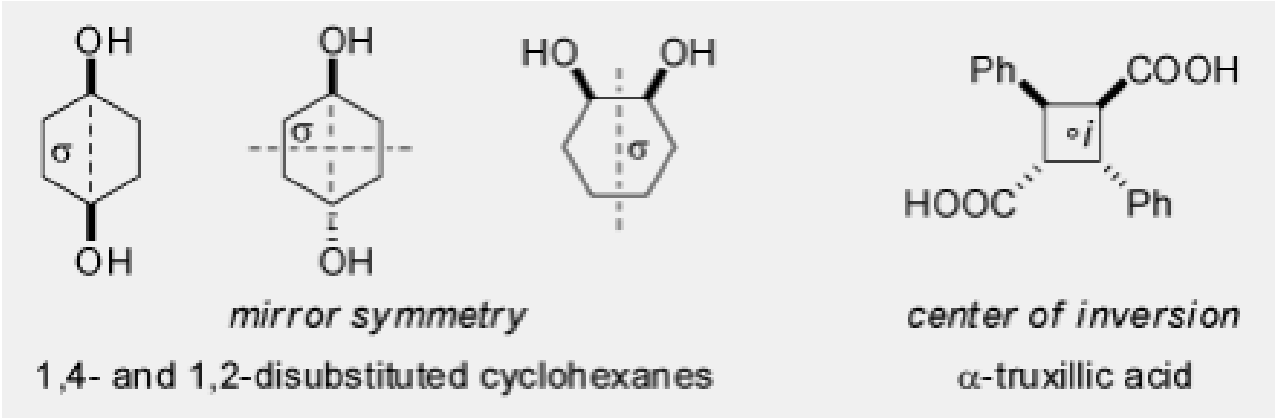


Τα εναντιομερή έχουν ίδιες φυσικοχημικές ιδιότητες και αντιδρούν πανομοιότυπα με μη-χειρόμορφα μόρια. Διαφέρουν μόνο στον τρόπο που αλληλεπιδρούν-αντιδρούν με άλλα χειρόμορφα μόρια και την κατεύθυνση που στρέφουν το επίπεδα πολωμένο φως

Συμμετρία και οπτική ενεργότητα

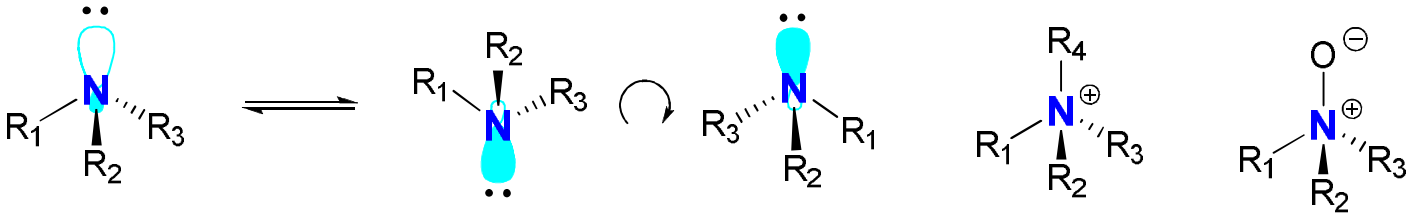
Ένα μόριο είναι χειρόμορφο ή οπτικά ενεργό όταν δεν είναι δυνατή η ταύτισή του μέσω απλών περιστροφών με το κατοπτρικό του είδωλο

Συμπεραίνεται ότι μόρια που η δομή τους εμπεριέχει στοιχεία συμμετρίας (κέντρο αντιστροφής, επίπεδο ή άξονα συμμετρίας) δεν είναι οπτικά ενεργά / χειρόμορφα.



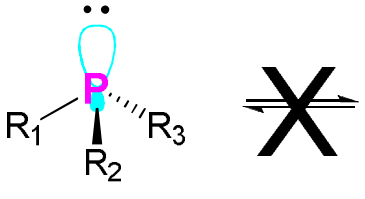
Όπως βλέπετε, η ύπαρξη ενός στερεογονικού κέντρου σε ένα μόριο δεν είναι απαραίτητη συνθήκη που το καθιστά χειρόμορφο

N,P,S ως στερεογονικά κέντρα

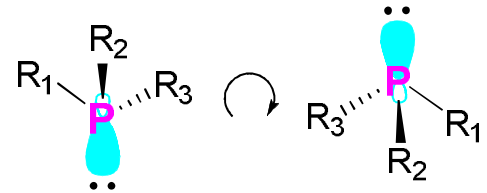


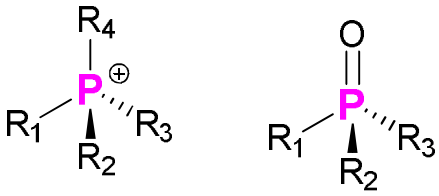
not chiral because in rapid interconversion with enantiomer

chiral



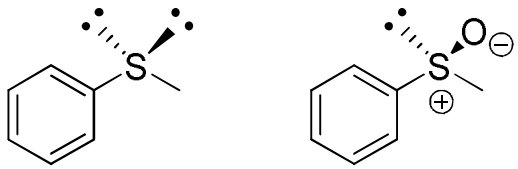
chiral



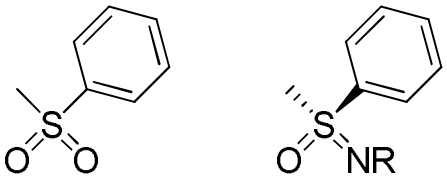


chiral

Also case for sulfur



not chiral

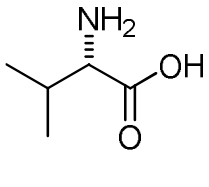


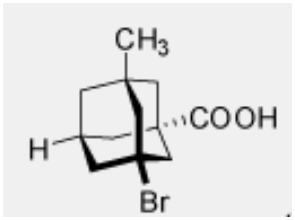
not chiral

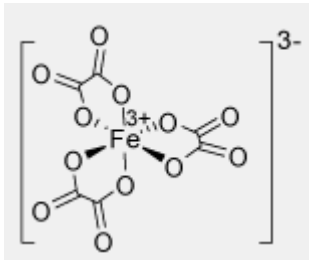
Χειρομορφικά στοιχεία

Η χειρομορφία ή οπτική ενεργότητα οφείλεται στην ύπαρξη (τουλάχιστον ενός) χειρομορφικού (στερεογονικού) στοιχείου (αντίστοιχα με εκείνα της συμμετρίας). Η χειρομορφία είναι προϊόν «κλειδώματος» υποκαταστατών ενός μορίου στον χώρο είτε λόγω ισχυρών δεσμών είτε λόγω διαμόρφωσης

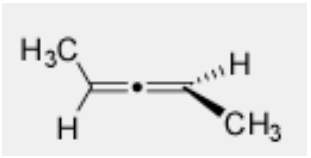
Κέντρο

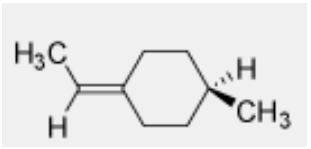




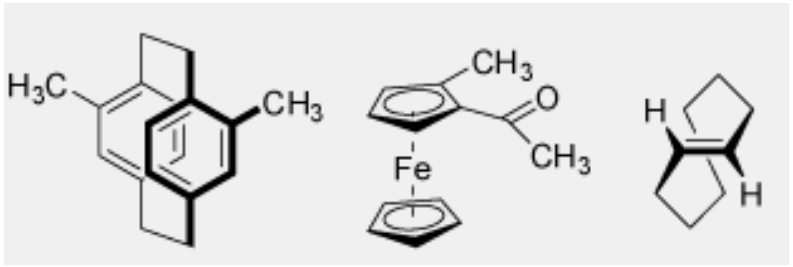


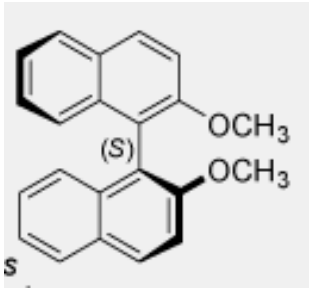
Άξονας



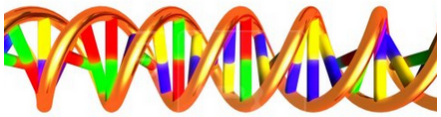


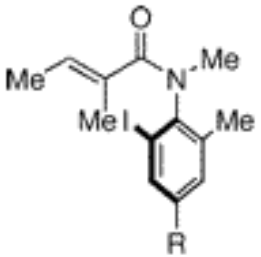
Επίπεδο



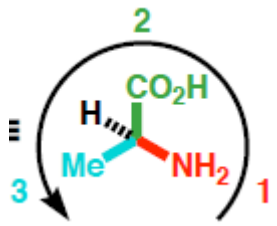


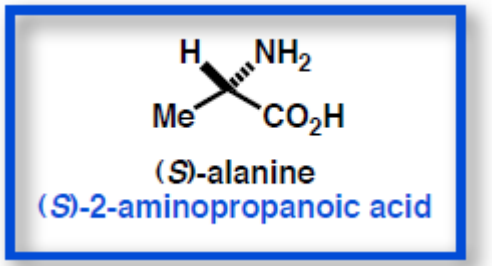
Έλικα (σπείρα)



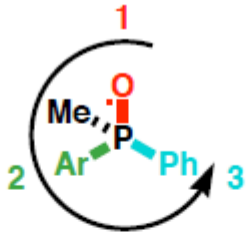


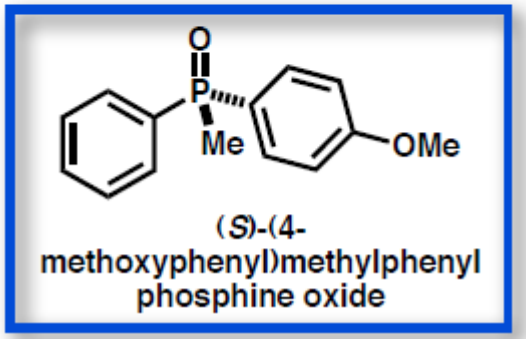
Προσδιορισμός στερεοχημείας R/S για χειρόμορφο κέντρο



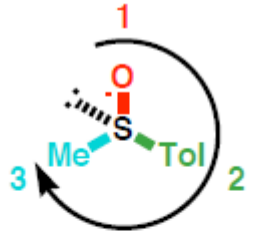


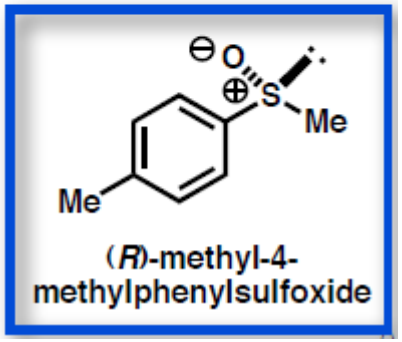
(*S*)-alanine
(*S*)-2-aminopropanoic acid





(*S*)-(4-methoxyphenyl)methylphenyl phosphine oxide





(*R*)-methyl-4-methylphenylsulfoxide

Cahn-Ingold-Prelog system

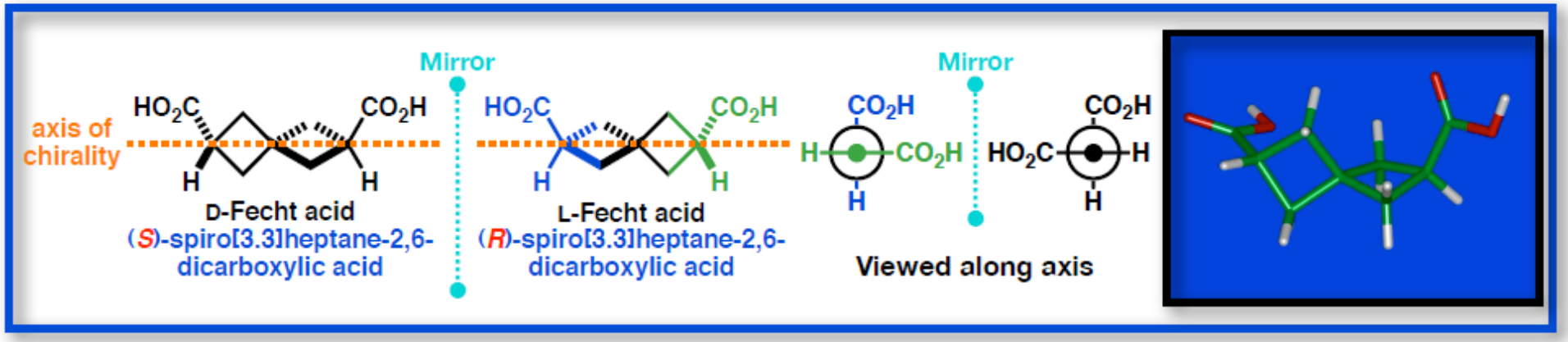
Δίδεται προτεραιότητα στους υποκαταστάτες με βάση τον μαζικό τους αριθμό

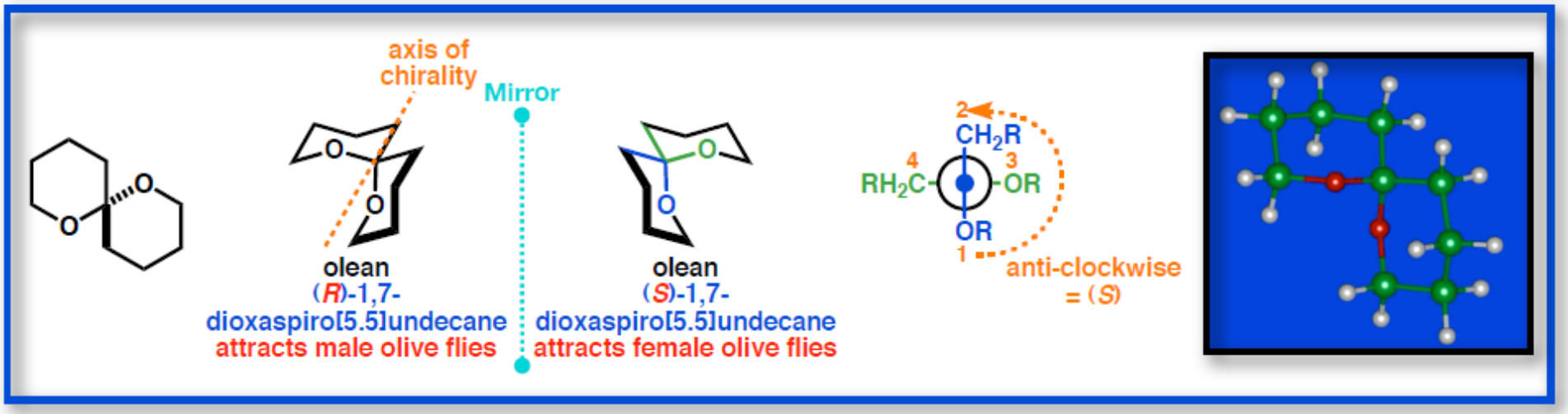
Τοποθέτηση του υποκαταστάτη με τη μικρότερη προτεραιότητα πίσω από το επίπεδο
Καθορισμός φοράς τόξου που σχηματίζεται από τον υποκαταστάτη με τη μεγαλύτερη προτεραιότητα προς εκείνον με τη μικρότερη

Προσδιορισμός στερεοχημείας R/S για χειρόμορφο άξονα

Axial chirality - Nonplanar arrangement of four groups about an axis

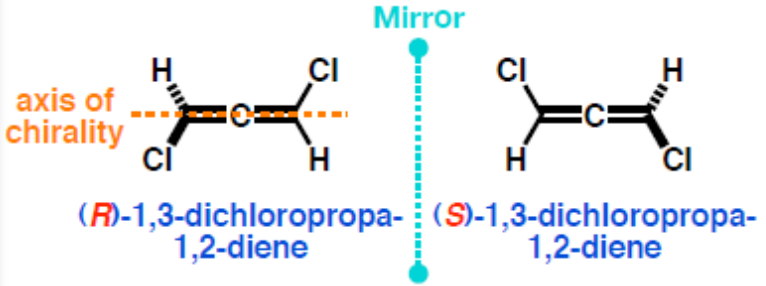
Spiro-compounds





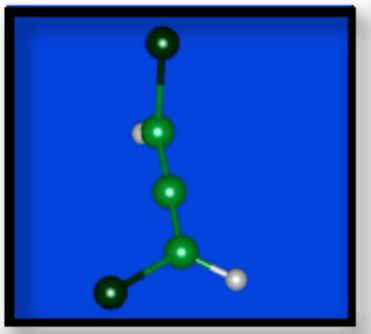
Προσδιορισμός στερεοχημείας R/S για χειρόμορφο άξονα

Allenes



(*R*)-1,3-dichloropropa-1,2-diene

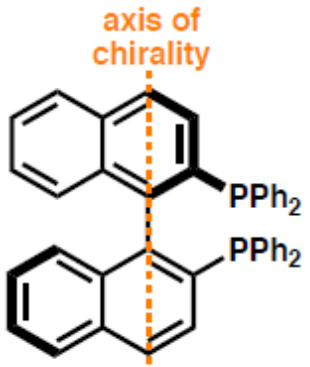
(*S*)-1,3-dichloropropa-1,2-diene



Axial chirality and atropisomerism

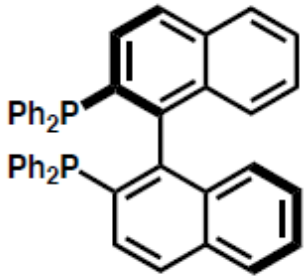
Atropisomers - stereoisomers resulting from restricted rotation about a single bond

Mostly commonly found in hindered biaryls



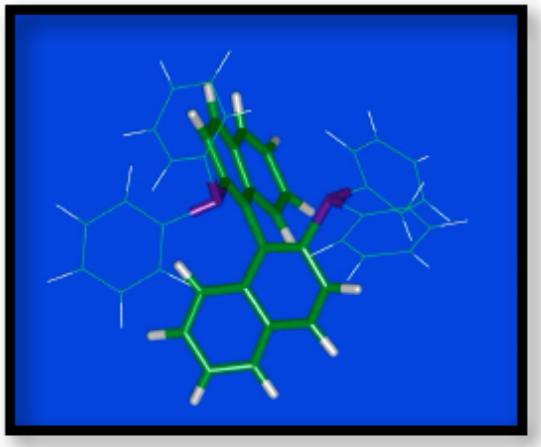
(*R*)-(+)-BINAP

(*R*)-2-(diphenylphosphino)-1-(2-(diphenylphosphino)naphthalen-1-yl)naphthalene



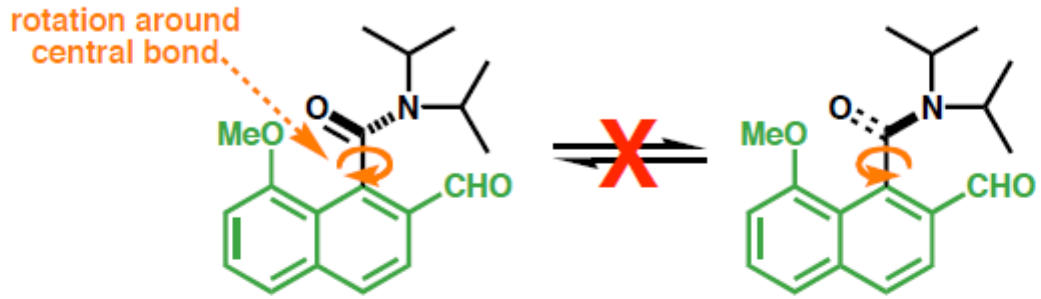
(*S*)-(-)-BINAP

(*S*)-2-(diphenylphosphino)-1-(2-(diphenylphosphino)naphthalen-1-yl)naphthalene

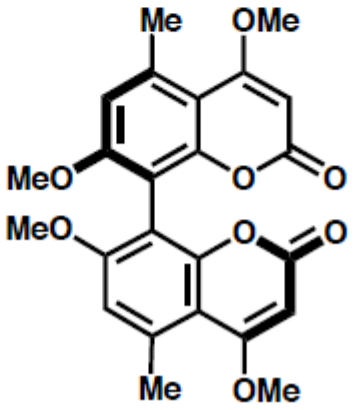


Ατροποϊσομερή

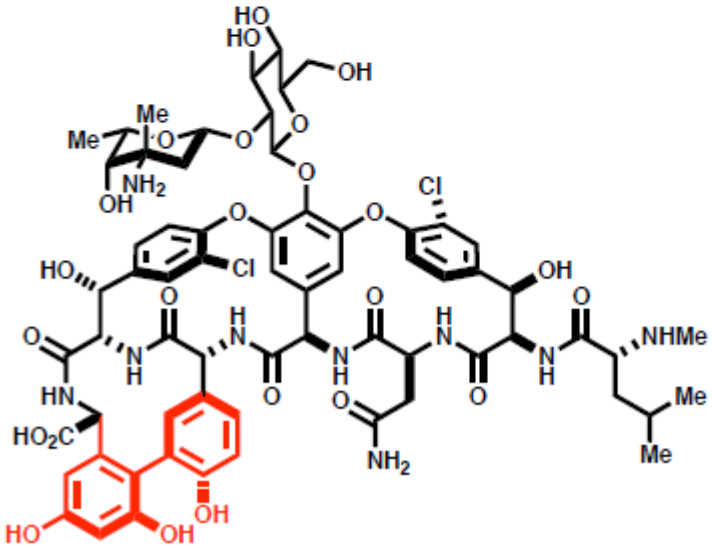
- Atropisomerism is not just found in biaryl compounds
- Any molecule in which rotation is restricted sufficiently to allow isolation of each isomer can be chiral...



- Atropisomerism is found in nature
- Vancomycin is an anti-bacterial
- Kotanin is from rice mold



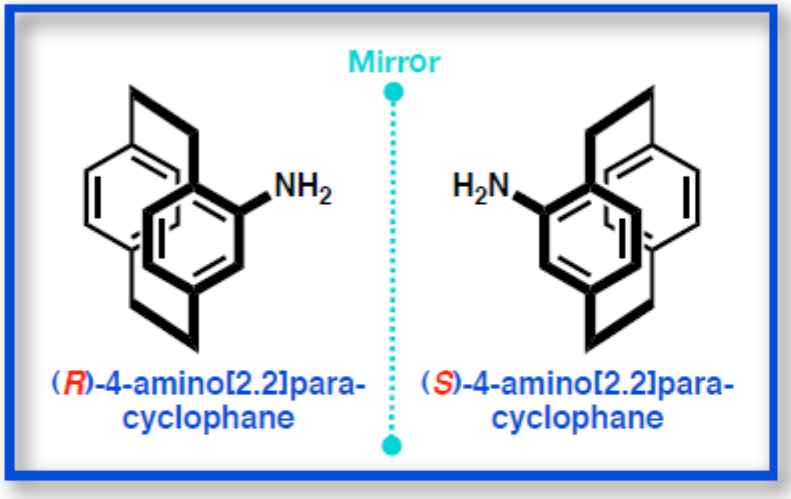
kotanin

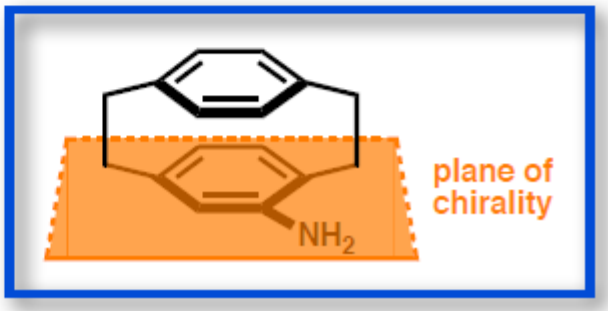


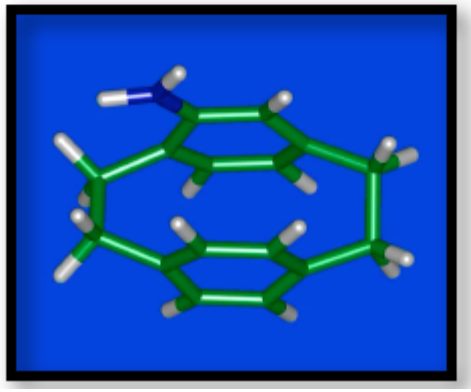
Vancomycin

Προσδιορισμός στερεοχημείας R/S για χειρόμορφο επίπεδο

- **Planar chirality** - chirality resulting from the arrangement of out-of-plane groups with respect to a plane, called the chiral plane
- In [2.2]paracyclophane the more substituted benzene ring is considered the chiral plane

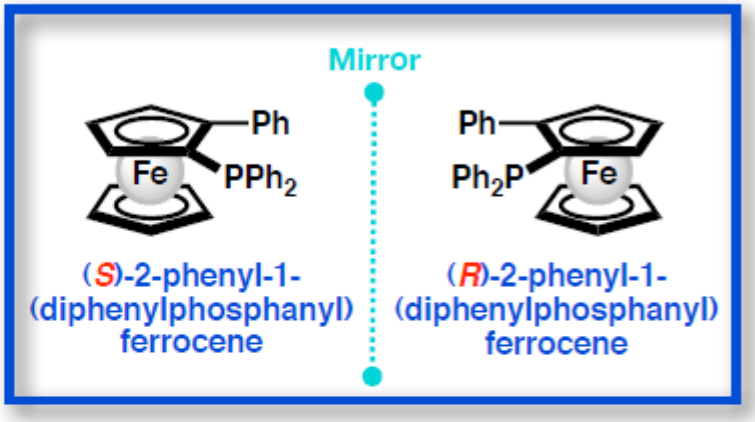


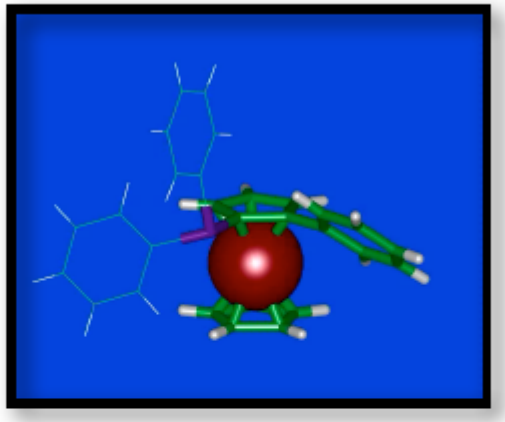




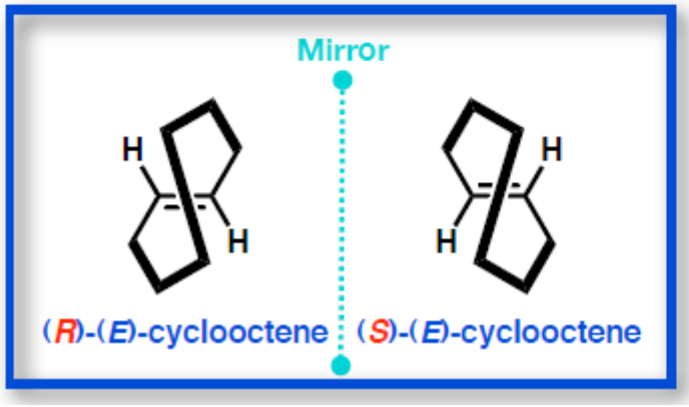
Προσδιορισμός στερεοχημείας R/S για χειρόμορφο επίπεδο

- Probably the most important planar chiral compounds are ferrocene derivatives
- These have found considerable use in enantioselective catalysis



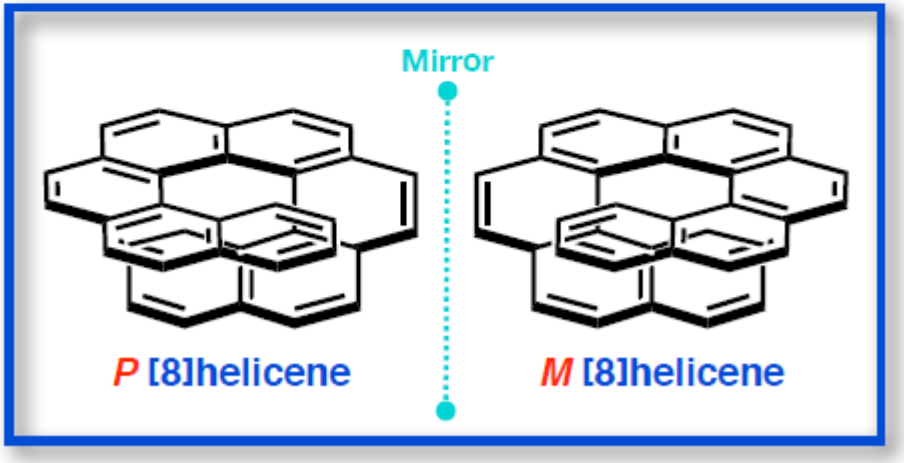


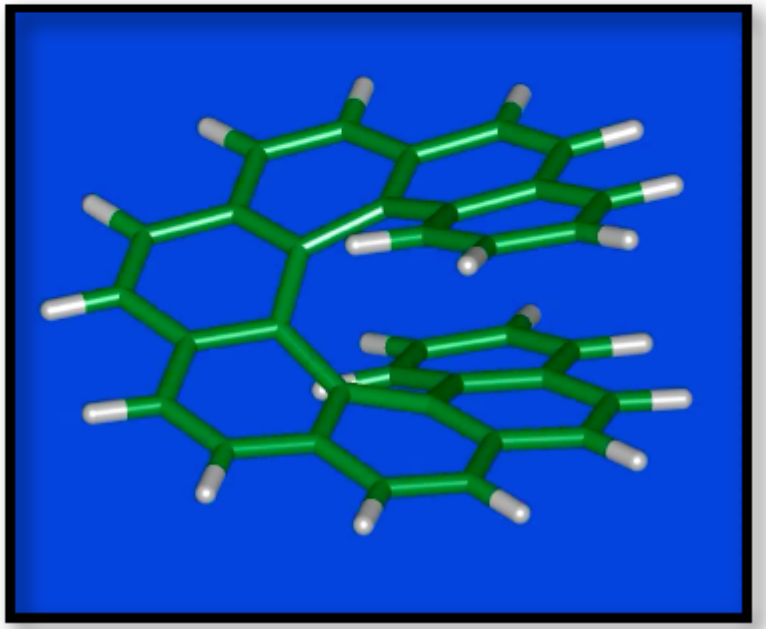
- An interesting example of planar chirality is found in some (*E*)-cycloalkenes



Προσδιορισμός στερεοχημείας M/P για χειρόμορφη έλικα

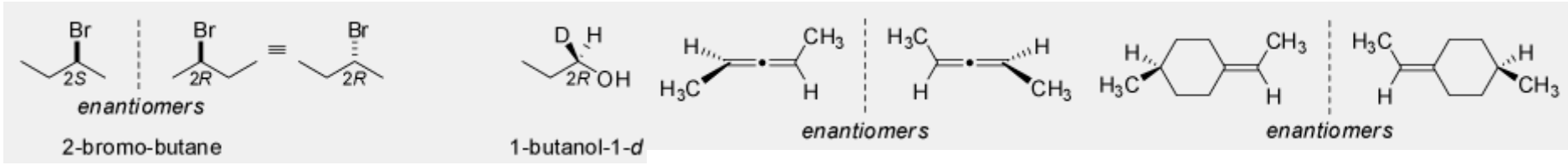
- Molecules that twist like a helix, propeller or screw
- Right-handed helix is denoted *P* (clockwise as you travel away from viewer)
- Interestingly, [8]helicene racemises (1:1 mixture of enantiomers) readily at 293°C!

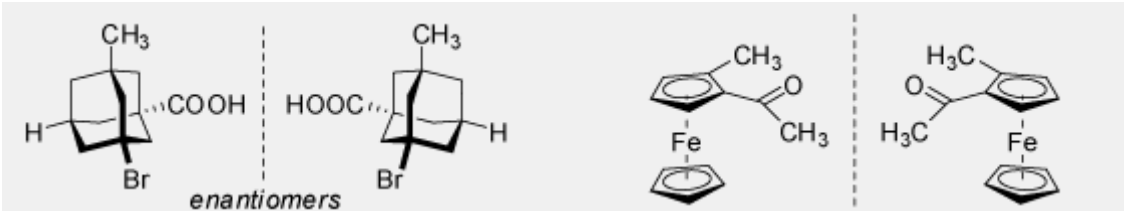


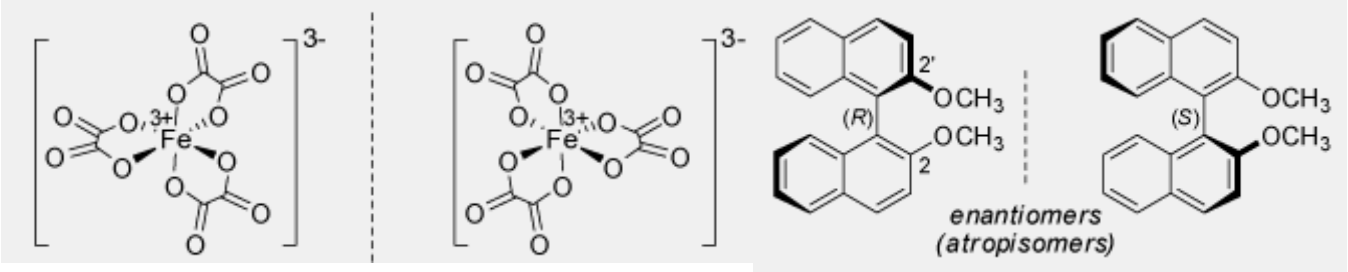


Εναντιομερή

Εναντιομερή είναι τα ζεύγη ενώσεων που έχουν σχέση αντικειμένου-ειδώλου. δηλ. η διάταξη των υποκαταστατών που σχετίζονται με ένα ή περισσότερα στερεογονικά στοιχεία, είναι αντεστραμμένη.





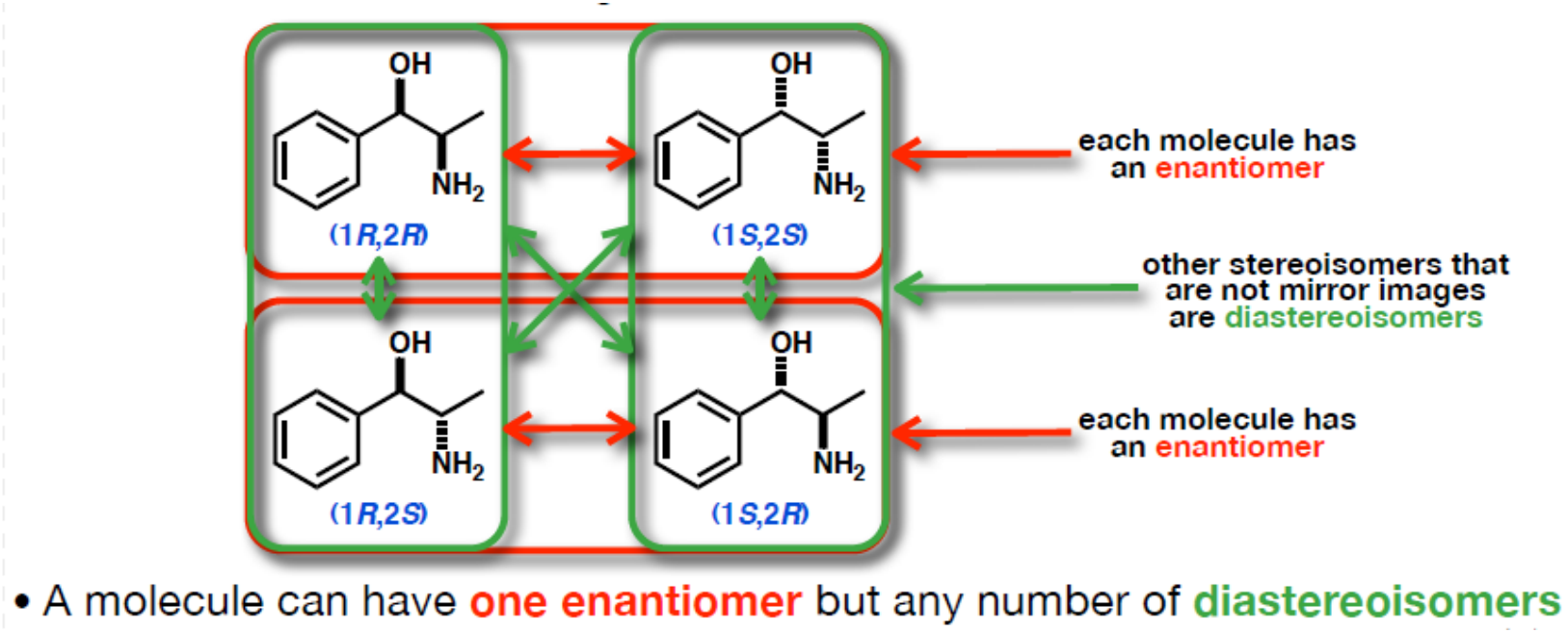


Διαστεροϊσομερή

Όταν υπάρχουν περισσότερα από ένα στερεογονικά στοιχεία προκύπτουν συγγενικές ενώσεις που διαφέρουν κατά την διάταξη των υποκαταστατών στο χώρο.

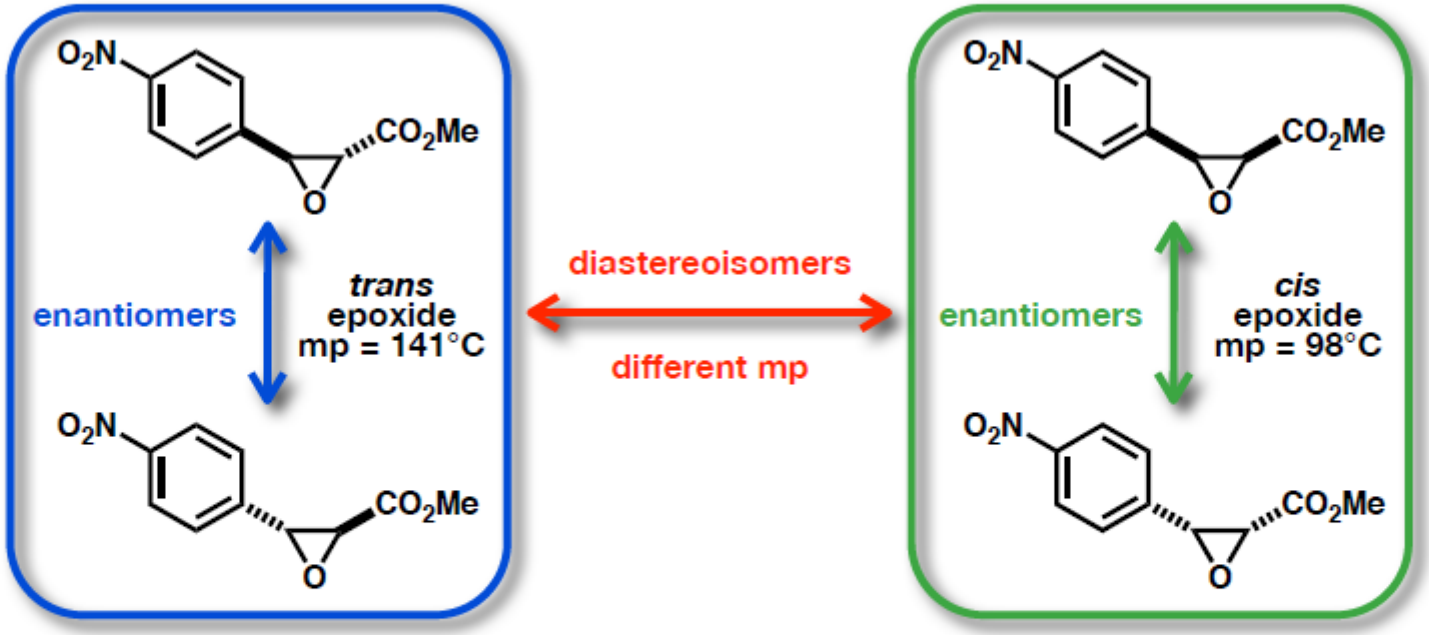
Αυτές οι ενώσεις λέγονται διαστερεοισομερή και για ν στερεογονικά στοιχεία σε ένα μόριο υπάρχουν 2^{ν} διαστερεοϊσομερή

Ανά δύο, τα διαστερεοϊσομερή που σχετίζονται με ένα μόριο έχουν μια επιπλέον συγγένεια: είναι εναντιομερή δηλαδή σχέση αντικειμένου / κατοπτρικού ειδώλου



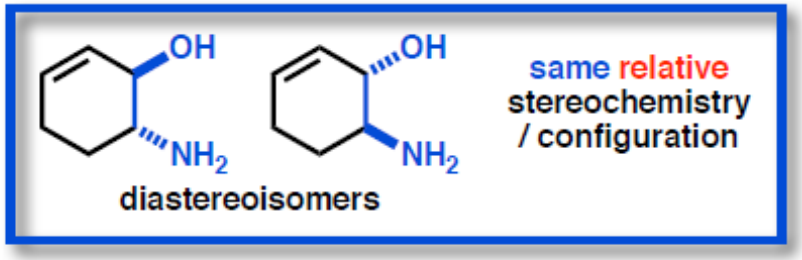
Ιδιότητες Διαστεροϊσομερών

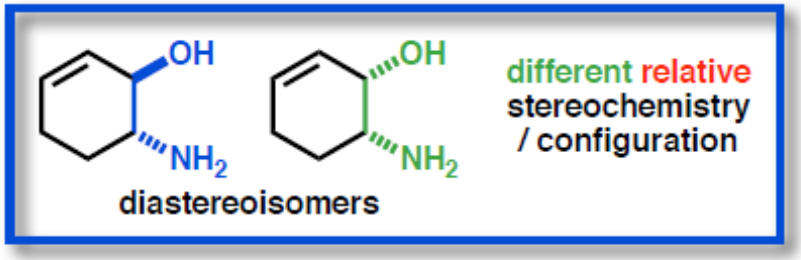
- Two enantiomers have **identical** physical properties in an achiral environment
- Two **diastereoisomers** have **different** physical properties



- Different physical properties, such as crystallinity or polarity allow diastereoisomers to be separated

Σχετική και Απόλυτη Στερεοχημεία Διαστεροϊσομερών

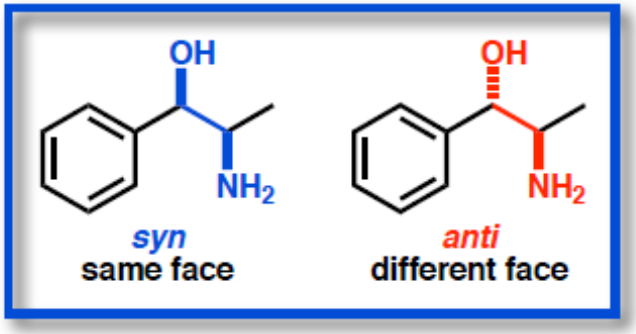




- Diastereoisomers can have the **same relative** stereochemistry
- The stereoisomers above differ only by their **absolute** stereochemistry
- Or they can have **different relative** stereochemistry

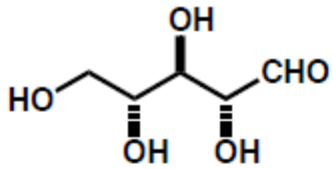
- **Relative stereochemistry** - defines configuration with respect to any other stereogenic element within the molecule but does NOT differentiate between enantiomers

- In simple systems the two different relative stereochemistries are defined as below

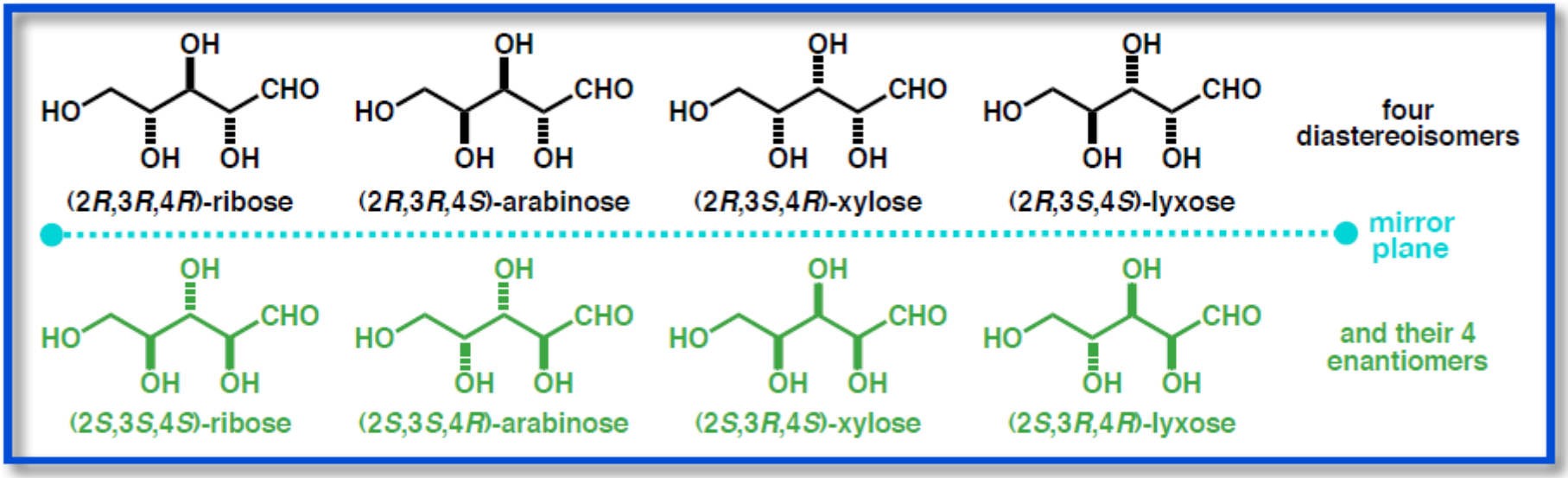


- Occasionally you will see the terms *erthyro* & *threo* - depending on the convention used, these can mean two either relative stereochemistry so I will not use them!

Παράδειγμα πολλαπλών Διαστεροϊσομερών

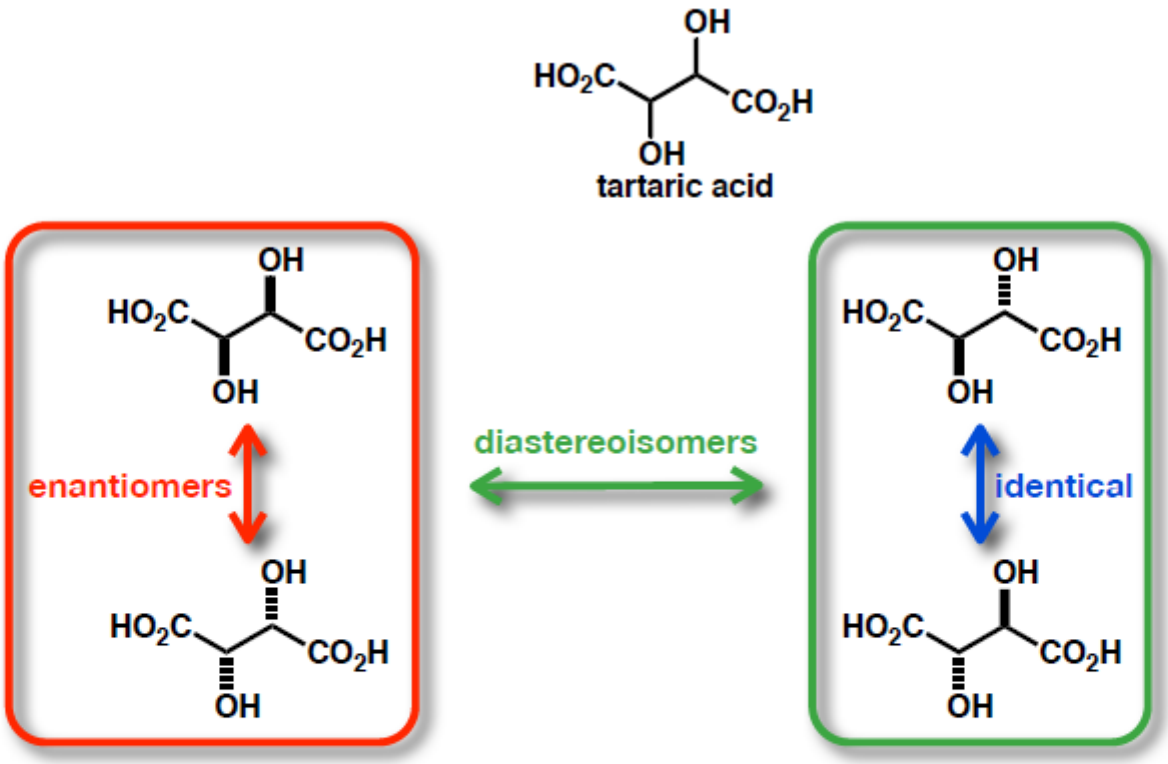


(2*R*,3*R*,4*R*)-2,3,4,5-tetrahydroxypentanal
ribose



- If a molecule has 3 stereogenic centres then it has potentially **8 stereoisomers** (4 diastereoisomers & 4 enantiomers)
- If a molecule has ***n*** stereogenic centres then it has potentially **2^n stereoisomers**
- Problem is, the molecule will never have more than 2^n stereoisomers but it might have less...

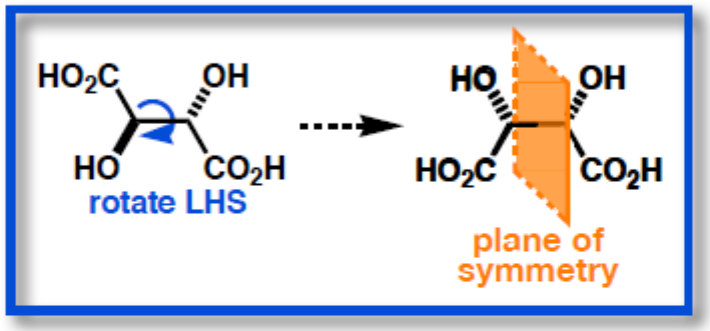
Μέσο-ενώσεις



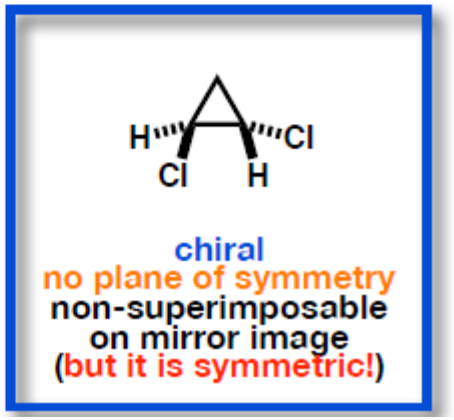
- Tartaric acid has 2 stereogenic centres. But does it have 4 diastereoisomers?
- 2 diastereoisomers with different relative stereochemistry
- 2 mirror images with different relative stereochemistry
- 1 is an **enantiomer**
- The other is **identical** / same compound
- Simple rotation shows that the two mirror images are superimposable

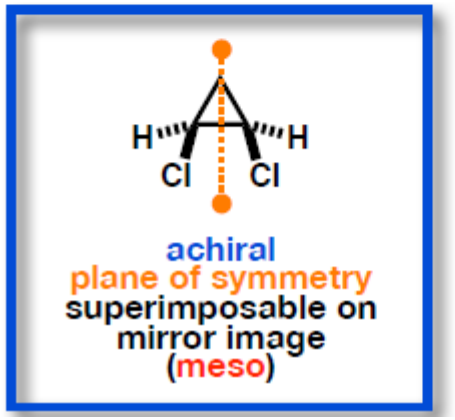
Μέσο-ενώσεις

- **Meso compounds** - an achiral member of a set of diastereoisomers that also includes at least one chiral member
- Simplistically - a molecule that contains at least one stereogenic centre **but** has a **plane of symmetry** and is thus **achiral**
- Meso compounds have a plane of symmetry with (*R*) configuration on one side and (*S*) on the other

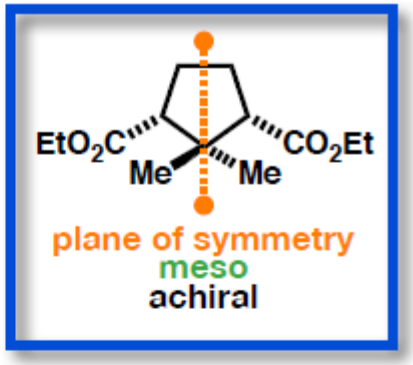


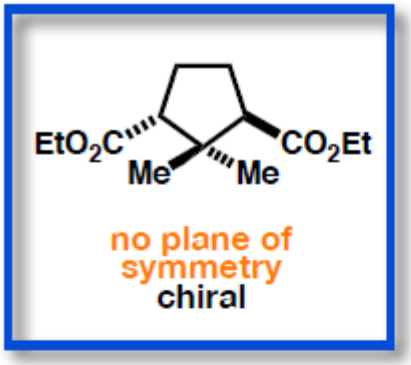
- Another example...



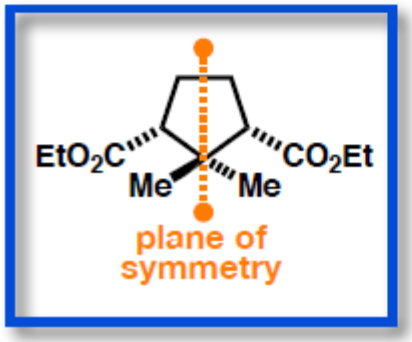


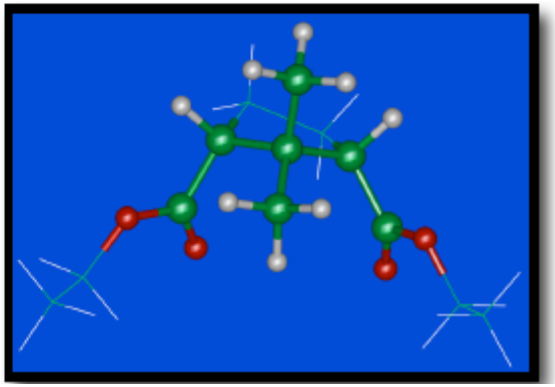
Μέσο-ενώσεις

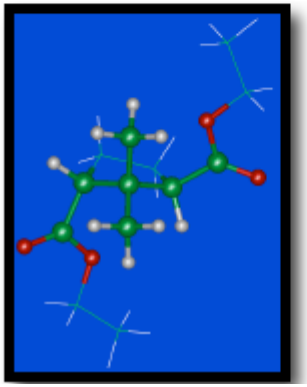


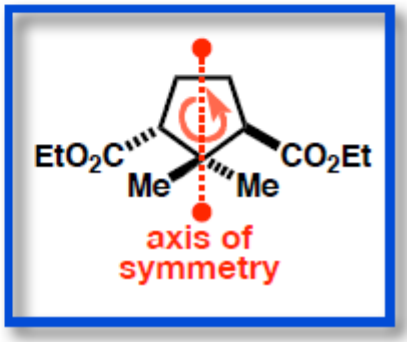


- One compound displays two CH_3 peaks in ^1H nmr; the other just one peak. Which one is which?
- The meso compound shows two peaks for the *cis* and *anti* CH_3 (wrt to CO_2Et)
  This compound is **achiral**
- The chiral ester shows only one peak because it is symmetrical
  It has a **C_2 axis** of symmetry
  This molecule is **chiral** but **symmetrical**

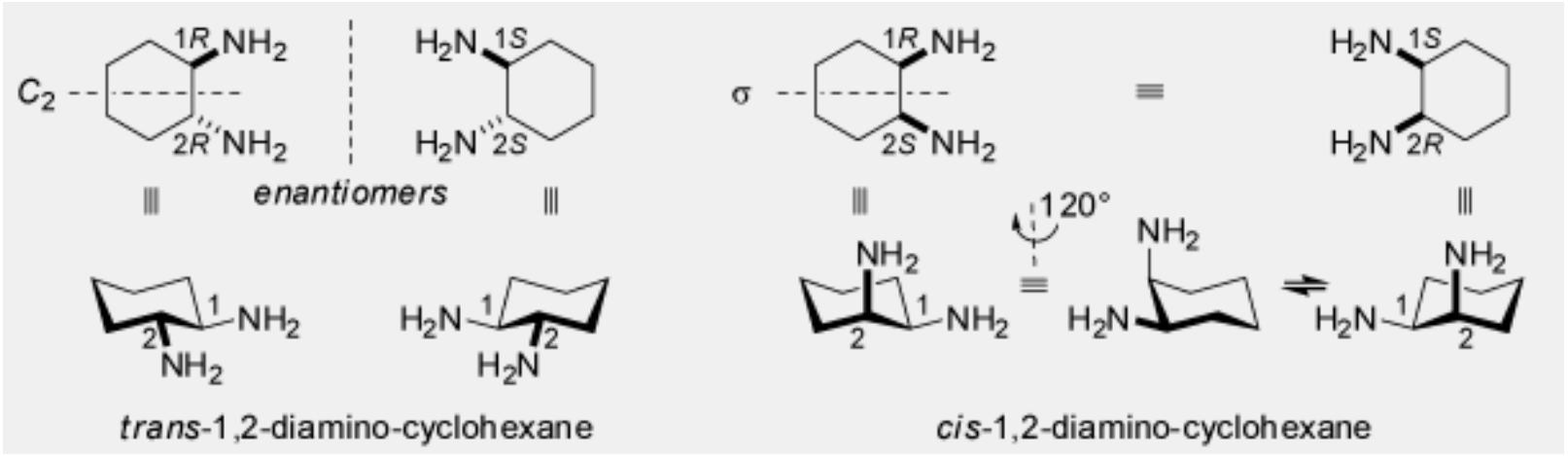


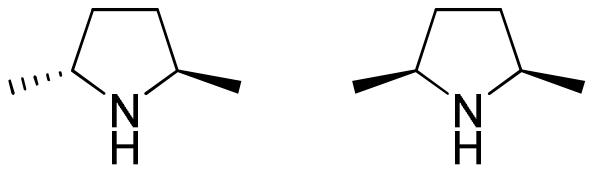


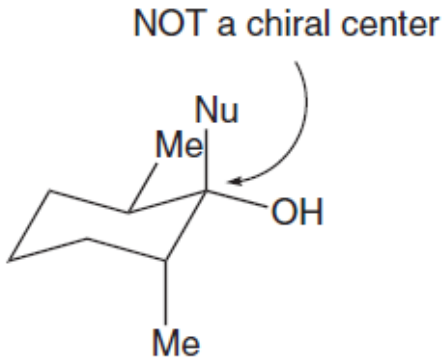




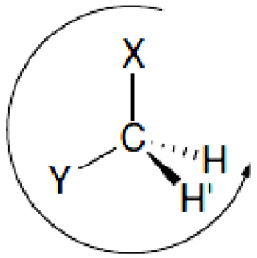
Μέσο-ενώσεις



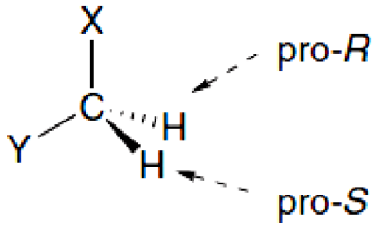


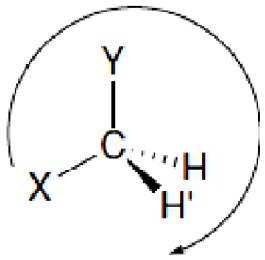


Εναντιο/διαστερεο-τοπικοι υποκαταστάτες



S





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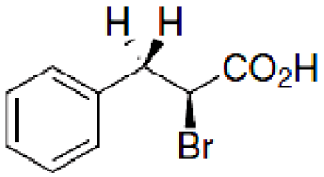
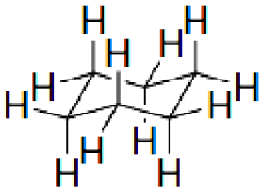
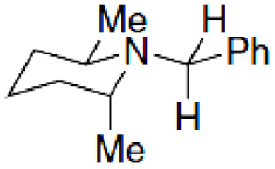


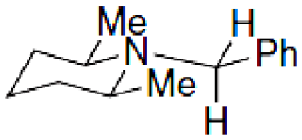
Hydrogens diastereotopic



All hydrogens equivalent because of rapid ring interconversion



Hydrogens diastereotopic



Hydrogens equivalent

Enantiomeric excess and enatiomeric ratio

Enantiomeric excess (% ee) is defined as the excess of one enantiomer over the other, and this definition makes this measurement unambiguous.

$$\%\text{ee} = \frac{|\%\text{R} - \%\text{S}|}{\%\text{R} + \%\text{S}} \times 100 = 100 - 2 \times (\%\text{S})(\text{for R})$$

The enantiomeric excess is not directly related to, for example, kinetics of the reaction that produces the chiral compound. Already Horeau had suggested that enantiomeric purity P_E should be expressed in terms of the fraction of the more abundant enantiomer to the sum of both enantiomers [44]:

$$P_E = \frac{R}{R + S}$$

This definition, or the equivalent *enantiomer ratio* (er = R:S), are more directly related to the kinetics, and therefore more useful in certain cases [46]. It is worth remembering that both expressions are useful, and one can easily interconvert ee and er. The definition of enantiomer ratio is equivalent to the ratio of reaction rates:

$$er = \frac{R}{S} = \frac{k_R}{k_S} = -e^{\frac{\Delta\Delta G^{\neq}}{RT}}$$

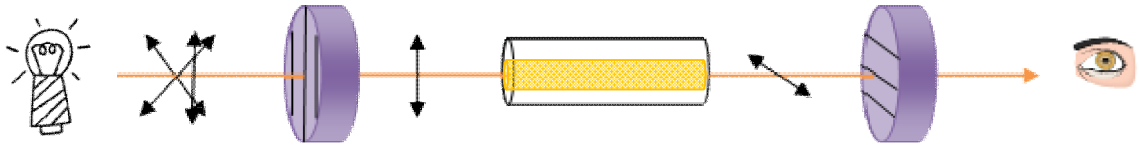
Μέτρηση οπτικής καθαρότητας

- **Είναι απαραίτητο να γνωρίζουμε την οπτική καθαρότητα του προϊόντος και έτσι να αξιολογούμε την αποτελεσματικότητα της στρατηγικής ασύμμετρης σύνθεσης που έχουμε επιλέξει**

- **Πολωσιμετρία**
- **Ανάλυση με χειρόμορφες στήλες HPLC ή GC**
- **Συμπλοκοποίηση με Χειρόμορφα αντιδραστήρια μετατόπισης NMR (shift reagents)**
- **Κυκλικός Διχρωϊσμός (Circular Dichroism)**
- **Κρυσταλλογραφία με ακτίνες Χ**
- **Μετατροπή του προϊόντος σε διαστερεοισομερικά παράγωγα και χρήση NMR, HPLC, GC, X-Ray.**

Πολωσιμετρία

- Optical activity was discovered by E.L. Malus (1808)
- Chiral molecules rotate the plane of polarization of polarized light



$$[\alpha]_\lambda = \frac{\alpha}{l \times c}$$

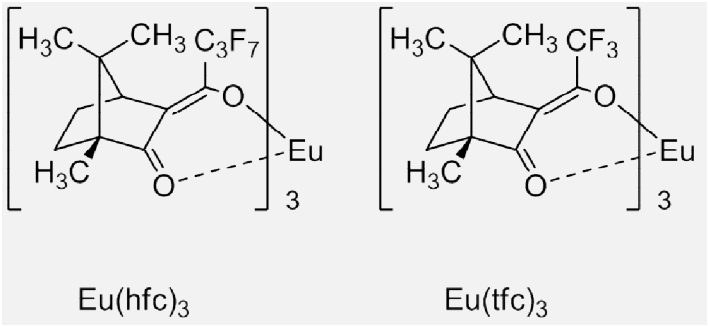
$$\%o.p. = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

- How does it work?
  - Monochromatic light is polarized by a Nicol prism (polarizer)
  - The plane-polarized light passes through a polarimetry cell in which the plane of the light will be rotated if the cells contains a chiral compound
  - The analyzer at the end of the setup rotates the plane of the light back to its original orientation

- Disadvantages
  - Very sensititive to impurities, solvent and temperature.
  - Not linear with concentration of sample

Αντιδραστήρια μετατόπισης NMR (shift reagents)

- Chiral NMR shift reagents are compounds that contain lanthanide ions that form complexes with chelating molecules i.e., chiral camphor derivatives like in $Eu(hfc)_3$ or $Eu(tfc)_3$

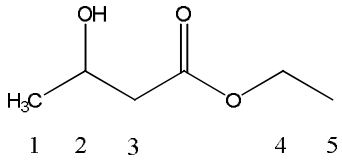


$Eu(hfc)_3$ $Eu(tfc)_3$

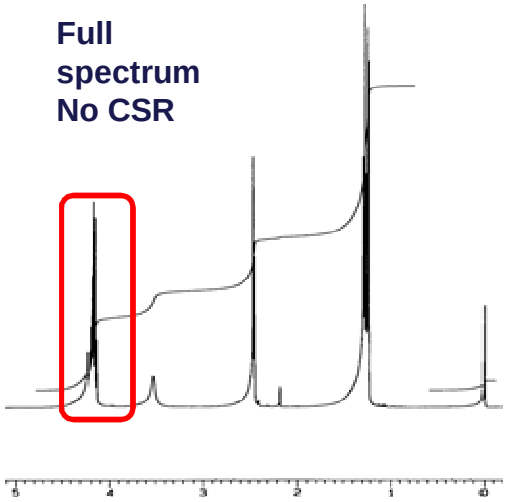
The strength of the effect of the chiral shift reagent depends on

- The nature of the NMR shift reagent (metal and ligand)
- The concentration of the NMR shift reagent
- The nature of the polar group (OH, NH_2, CO_2H) of the molecule binding to the metal
- The proximity of the hydrogen atom to the metal ion
- The solvent because it determines how strong the molecule is coordinated to the metal
- The temperature

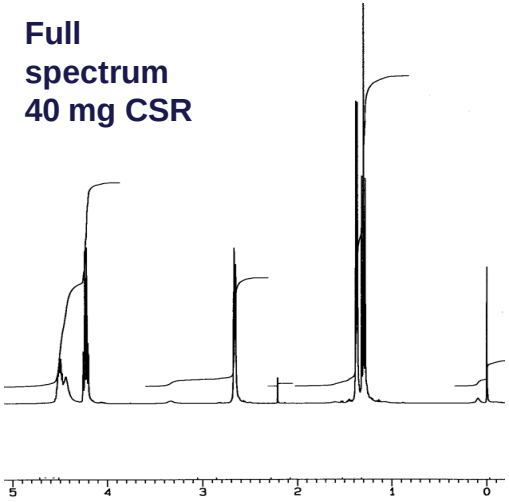
Most chiral shift reagents are very expensive (> $100/g)
Complexes are paramagnetic and therefore line broadening is observed (resolution issues)
Accuracy is moderate 2-5%



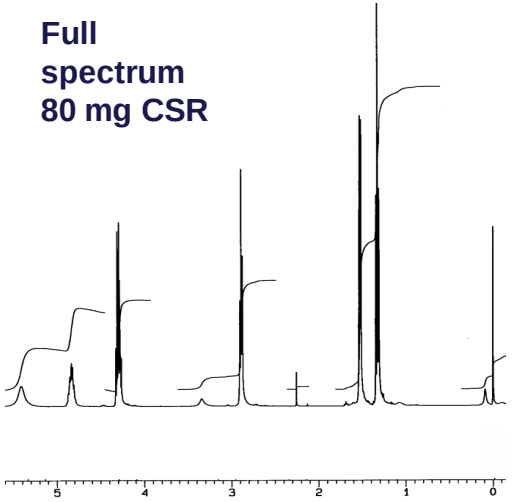
Full spectrum No CSR



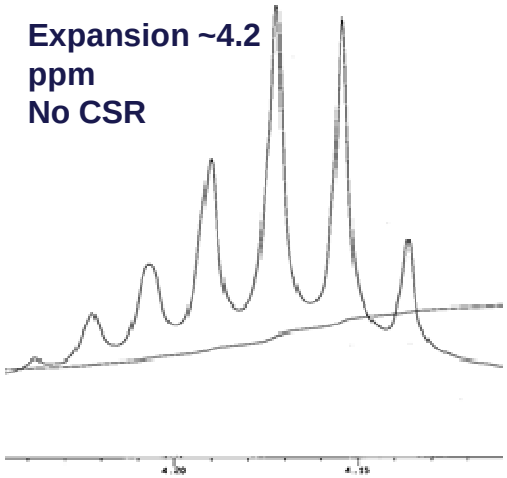
Full spectrum 40 mg CSR



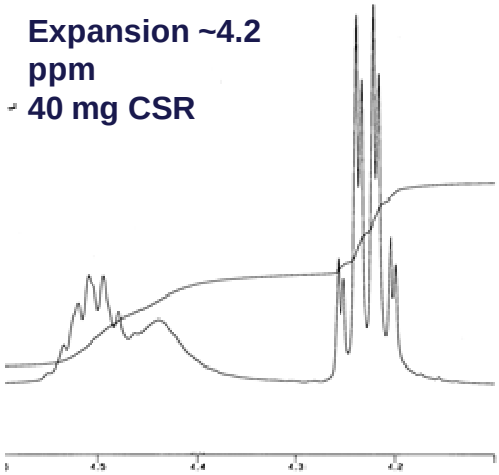
Full spectrum 80 mg CSR



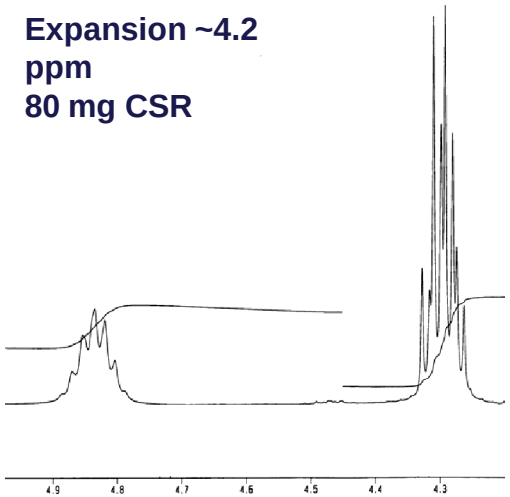
Expansion ~4.2 ppm No CSR



Expansion ~4.2 ppm 40 mg CSR

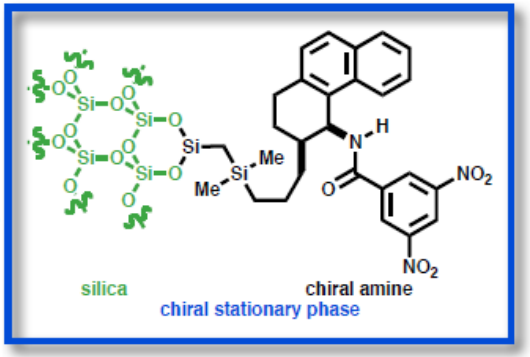


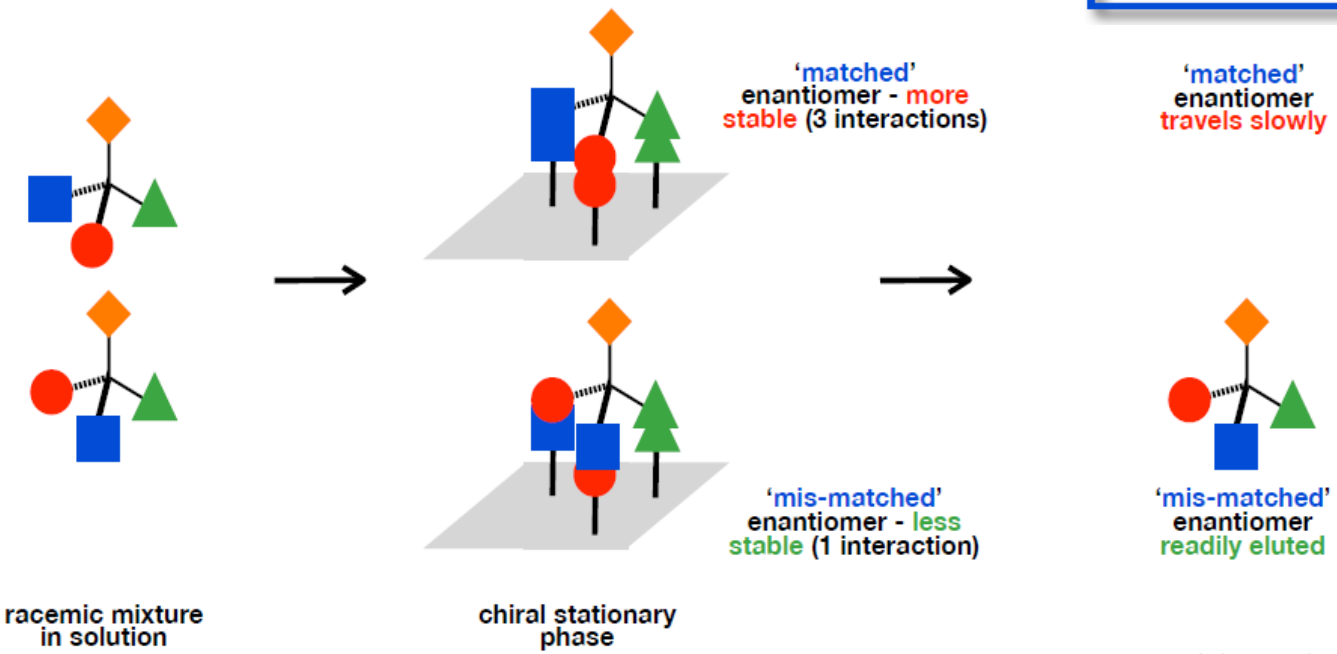
Expansion ~4.2 ppm 80 mg CSR



Αρχή διαχωρισμού με χειρόμορφες στήλες HPLC or GC

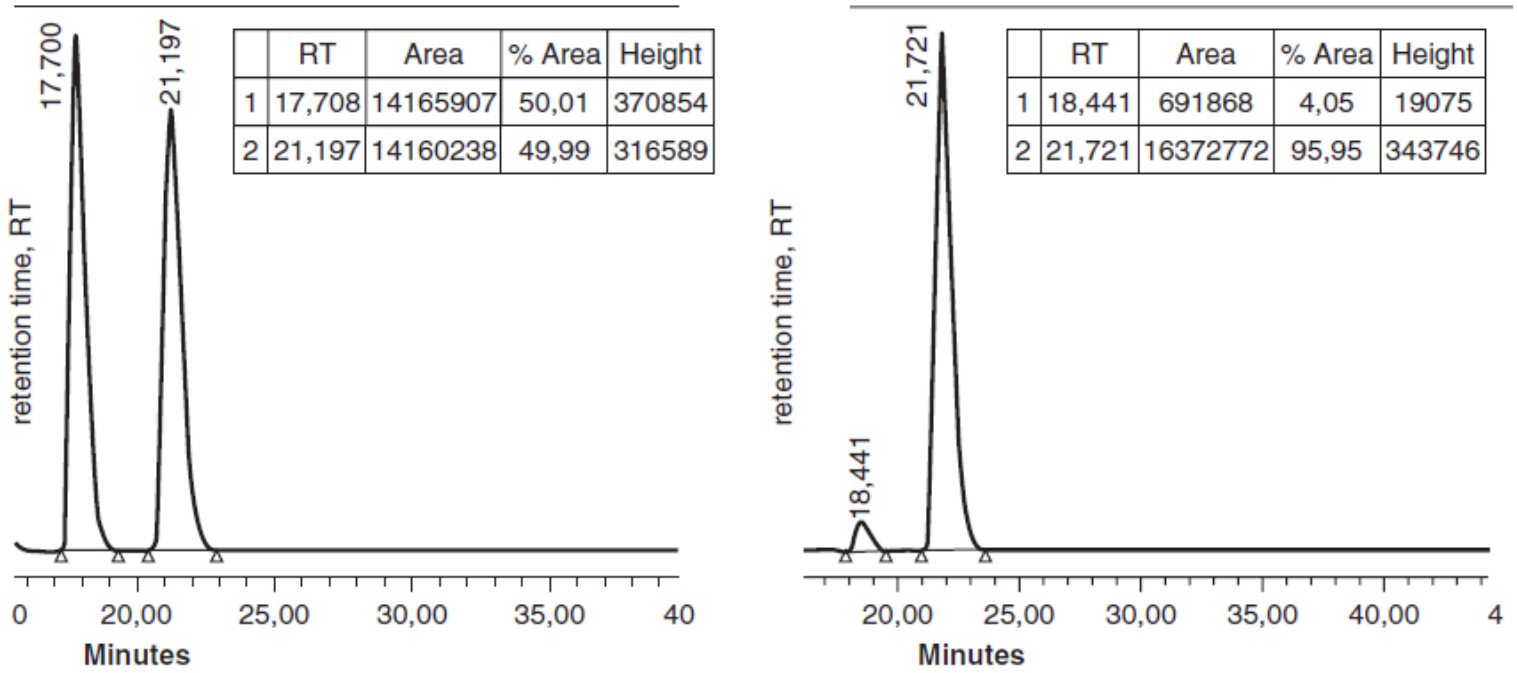
- **Resolution** - the separation of enantiomers from either a racemic mixture or enantiomerically enriched mixture
- **Chiral chromatography** - Normally HPLC or GC
- A racemic solution is passed over a chiral stationary phase
- Compound has rapid and reversible diastereotopic interaction with stationary phase
- Hopefully, each complex has a different stability allowing separation





- Measurements of **ee** by HPLC or GC are quick and accurate (±0.05%)
- Chiral stationary phase may only work for limited types of compounds
- Columns are expensive (>£1000)
- Need **both enantiomers** to set-up an accurate method

Παράδειγμα προσδιορισμού ee με χειρόμορφη στήλη HPLC or GC



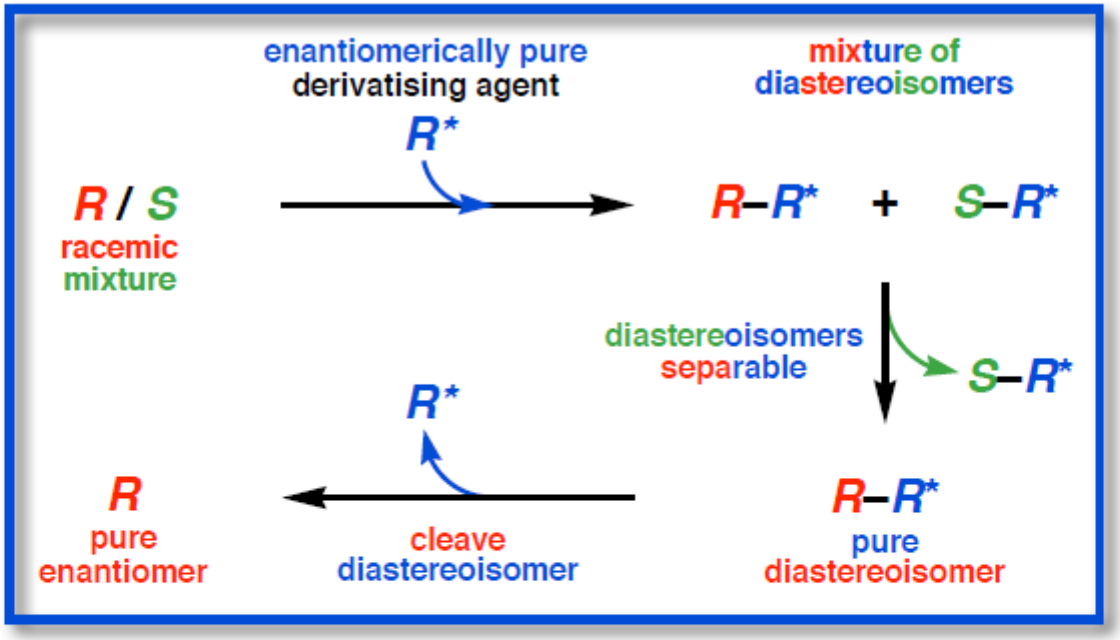
	RT	Area	% Area	Height
1	17,708	14165907	50,01	370854
2	21,197	14160238	49,99	316589

	RT	Area	% Area	Height
1	18,441	691868	4,05	19075
2	21,721	16372772	95,95	343746

Figure 2.20 *Chromatograms obtained from compound of Figure 2.18: (a) racemic mixture on achiral medium and (b) enantioenriched sample of the same (er = 96:4, or 92% ee)*

Developing a chiral HPLC (GC) method may not be straight forward or even successful
Optimisation requires screening of numerous solvent systems, temperatures, flow rates and different types of chiral columns!

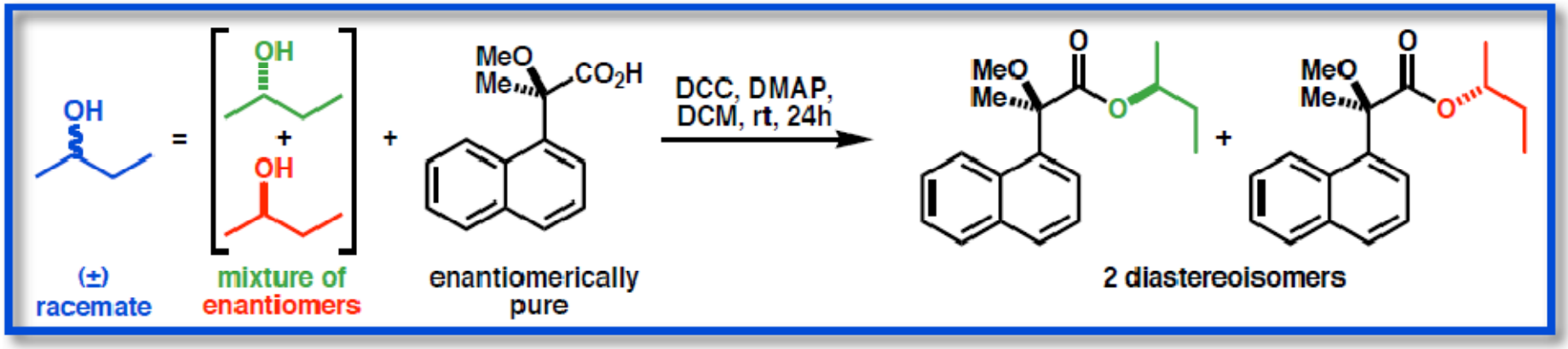
Παραγωγοποίηση σε διαστεροισομερή



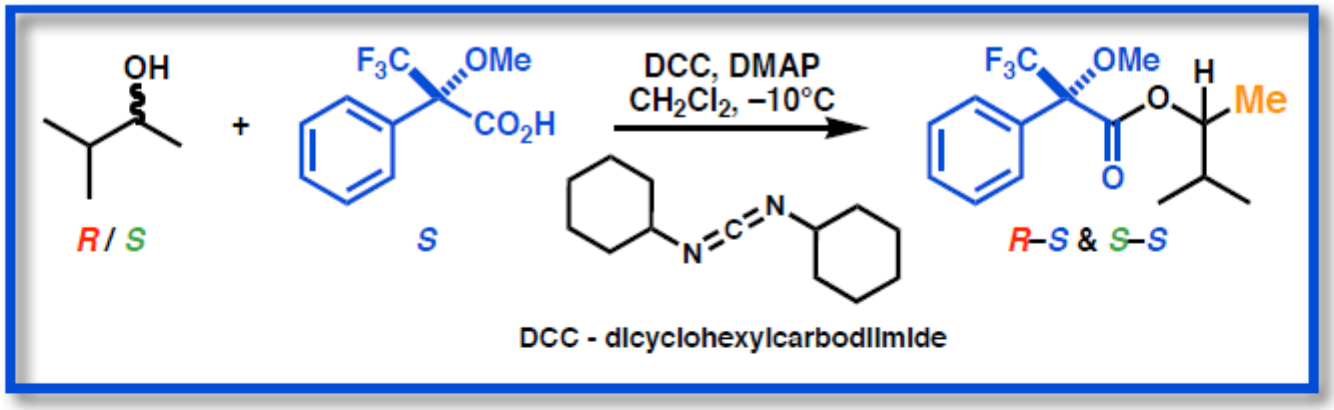
- **Remember a good chiral derivatising agent should:**
- Be enantiomerically pure (or it is pointless)
- Coupling reaction of both enantiomers must reach 100% (if you are measuring ee)
- Coupling conditions should not racemise stereogenic centre
- Enantiomers must contain point of attachment
- Above list probably influenced depending whether you are measuring %ee or preparatively separating enantiomers

Παραγωγοποίηση σε διαστεροισομερή

- A racemic mixture of **enantiomers** can be converted to a mixture of **diastereoisomers** by covalently attaching a second, enantiomerically pure unit
- The advantage of this over the previous methods is there is normally larger signal separation in nmr
- There is no reversibility
- Diastereoisomers can often be separated by normal, achiral chromatography



Παραγωγοποίηση αλκοολών και αμινών με Mosher's acid



- Popular derivatising agent for alcohols and amines is α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or Mosher's acid
- Difference in nmr signals between diastereoisomers (above): ^{1}H nmr Δδ = 0.08 (Me)
  ^{19}F nmr Δδ = 0.17 (CF_3)
- Typical difference in chemical shifts in ^{1}H nmr 0.15 ppm
- ^{19}F nmr gives one signal for each diastereoisomer
- No α-hydrogen so configurationally stable
- Diastereoisomers can frequently be separated

- In many cases use of both enantiomers of MTPA can be used to determine the absolute configuration of a stereocentre (73JACS512, 73JOC2143 & 91JACS4092)

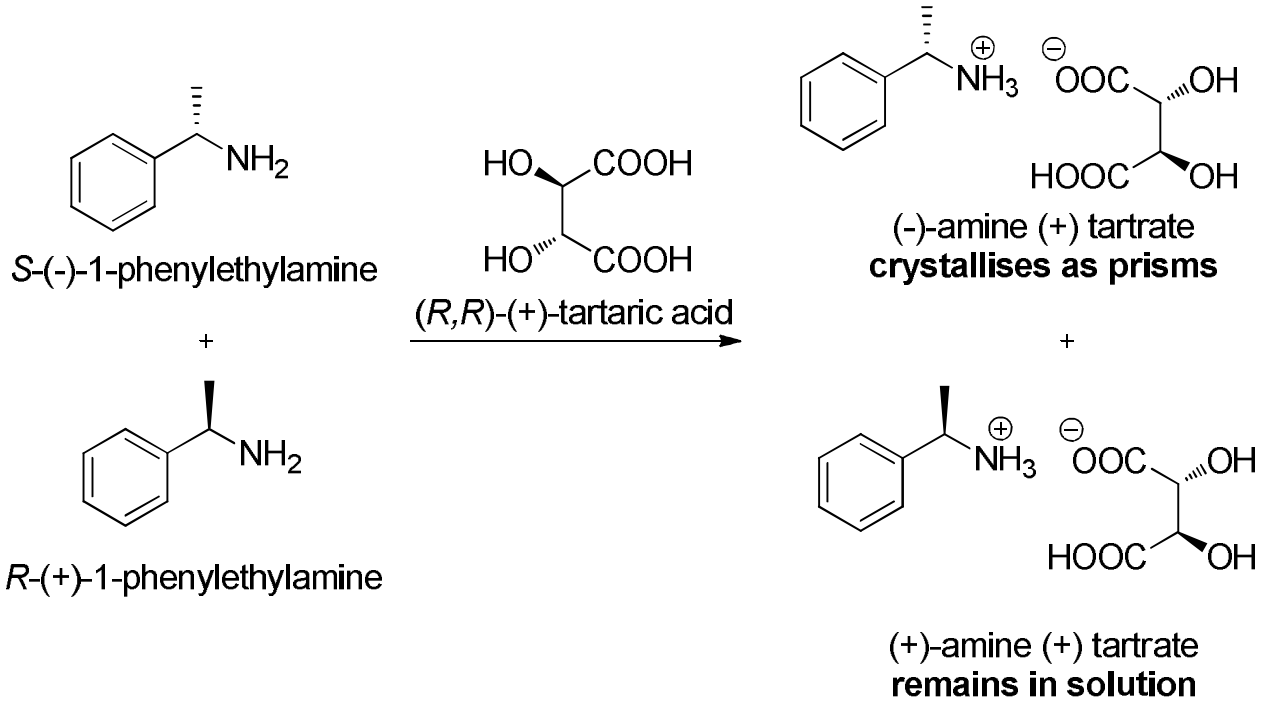
Στρατηγικές για ασύμμετρη σύνθεση

Στοιχειομετρικές μέθοδοι	**Χειρόμορφο υπόστρωμα** **Χειρόμορφο αντιδραστήριο** **Χειρόμορφο βοήθημα**
Ασύμμετρη Κατάλυση	**Χειρόμορφα σύμπλοκα μετάλλων** **Ασύμμετρη οργανοκατάλυση** **Ενζυμική κατάλυση**

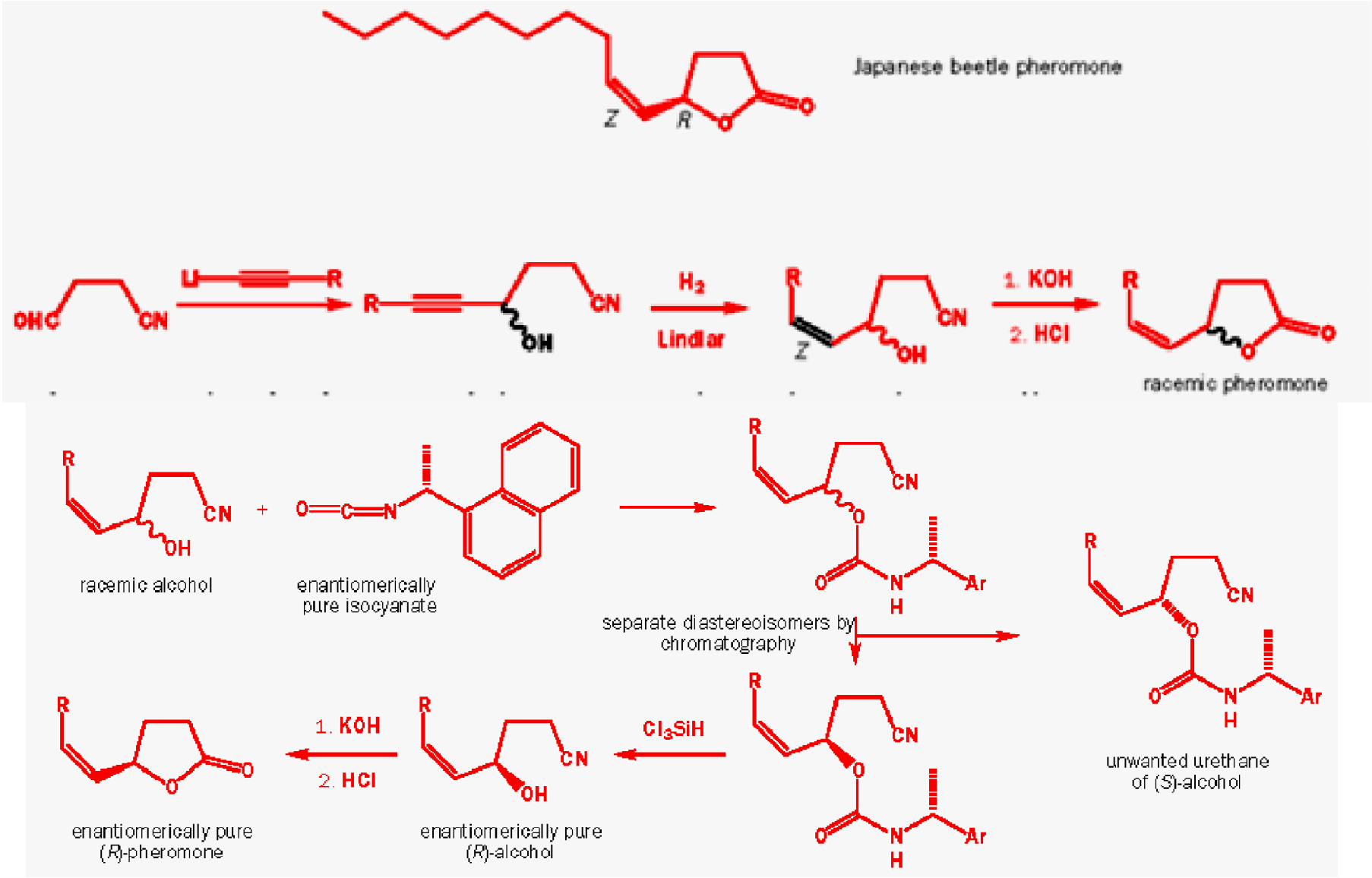
Διαχωρισμός	**Κλασσικός διαχωρισμός** **Κινητικός διαχωρισμός** **Δυναμικός κινητικός διαχωρισμός**

Απλός Διαχωρισμός ρακεμικών αλάτων

Αυτή η μέθοδος ενδείκνυται για οξέα ή βάσεις και βασίζεται στη διαφορετική διαλυτότητα που παρουσιάζουν διαστρεοισομερικά άλατα. Γενικά το ανεπιθύμητο εναντιομερές/ διαστ. άλας (50%) αποτελεί απόβλητο και συνεπώς αυτή η μέθοδος δεν είναι οικονομικά συμφέρουσα, εκτός και αν πρόκειται για απλό ή φθηνό προϊόν και το χειρόμορφο αντιδραστήριο διαχωρισμού μπορεί να ανακυκλωθεί. Το κύριο πλεονέκτημά της είναι ότι μπορεί να διερευνηθεί γρήγορα με εμπορικά διαθέσιμα αντιδραστήρια και να ληφθούν καθαρά δείγματα των εναντιομερών.

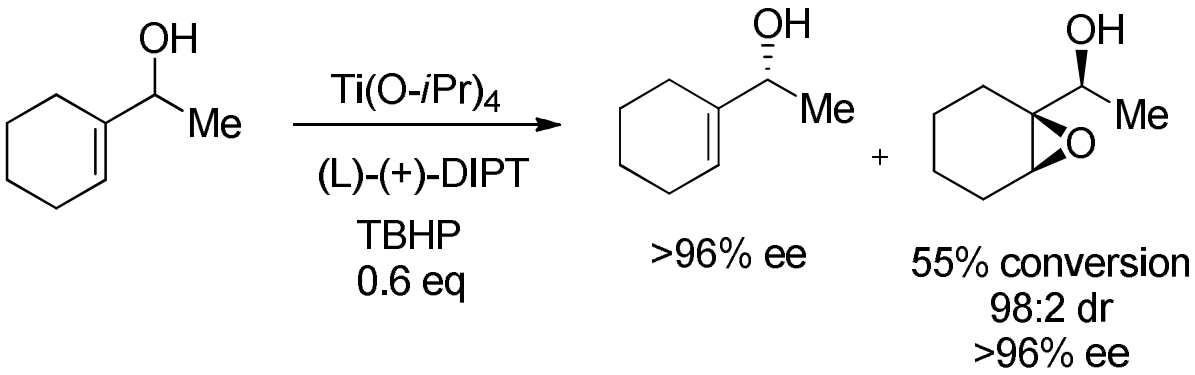


Απλός Διαχωρισμός Διαστεροισομερών Παραγώγων

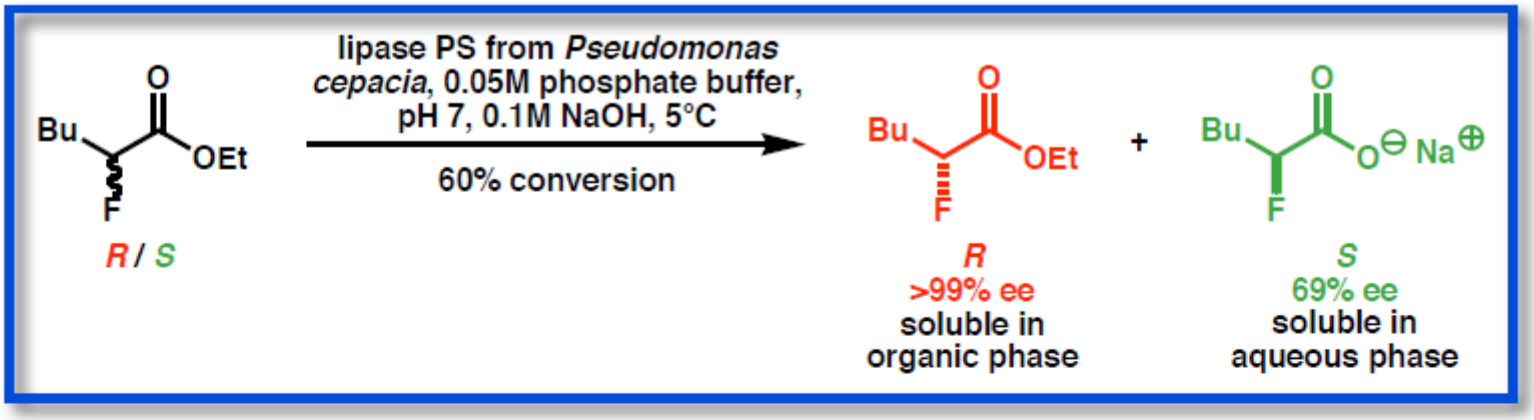


Κινητικός Διαχωρισμός Ρακεμικών Μειγμάτων

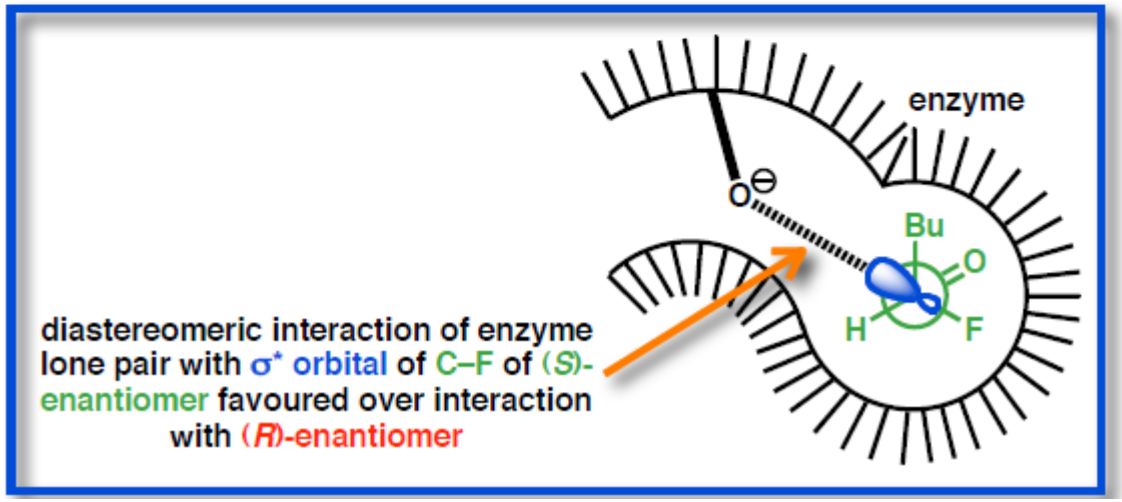
Βασίζεται στη διαφορετική ταχύτητα με την οποία αντιδρούν χειρόμορφα μόρια με επίσης χειρόμορφα μόρια. Έτσι όταν παρουσιαστεί ένα εναντιομερές ενός χειρόμορφου αντιδραστηρίου Α σε ένα ρακεμικό μειγμα αντιδρώντος Β, ένα εναντιομερές του Β θα αντιδράσει με το χειρόμορφο αντιδραστήριο Α αρκετά γρηγορότερα από το άλλο εναντιομερές του Β. Για καλύτερα αποτελέσματα συνήθως χρησιμοποιείται υποστοιχειομετρική ποσότητα του Α ώστε να αποφευχθεί η αντίδρασή του με το εναπομείνων εναντιομερές του Β. Λαμβάνονται δύο διαφορετικά χειρόμορφα προϊόντα: ένα νέο προϊόν από το μετασχηματισμό του ενός εναντιομερούς και το άλλο αρχικό εναντιομερές που δεν αντέδρασε και έμεινε ανέπαφο

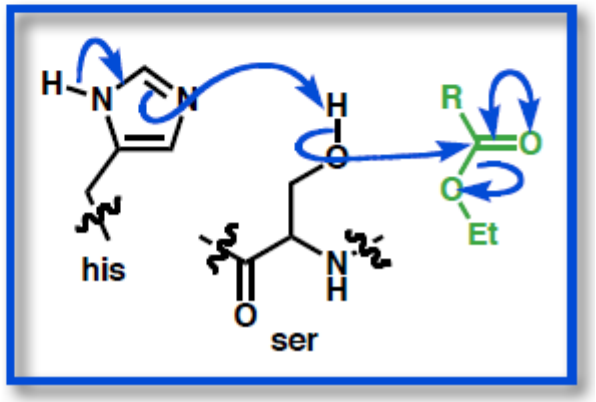


Κινητικός Διαχωρισμός Ρακεμικών Μειγμάτων μέσω Ενζύμων



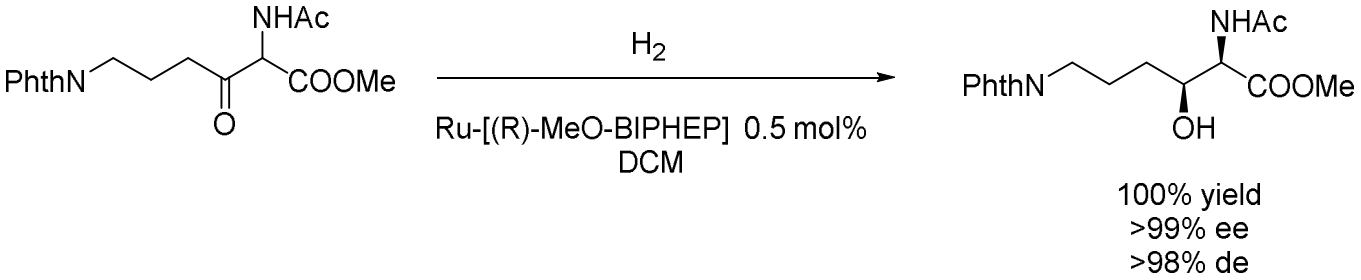
- **Enzymes** are very useful for the resolution of certain compounds
- Frequently they display very high selectivity
- There can be limitations due to solubility, normally only one enantiomer exists and can be too substrate specific
- Below is the rationale for the selectivity observed above...





Δυναμικός Κινητικός Διαχωρισμός

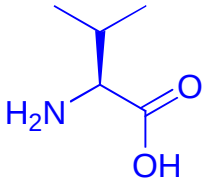
Όπως στον κινητικό διαχωρισμό αλλά με δυνατότητα ρακεμοποίησης του εναπομείναντος εναντιομερούς και περαιτέρω μετατροπή του στο τελικό προϊόν. Τελικά όλο το αρχικό ρακεμικό μείγμα των δύο εναντιομερών μετατρέπεται σε ένα χειρόμορφο προϊόν.

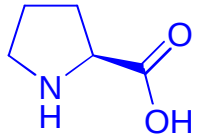


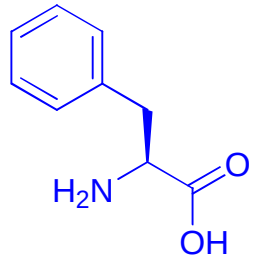
Στοιχειομετρικές μέθοδοι 1. Χειρόμορφο υπόστρωμα

Η φύση πραγματοποιεί ασύμμετρη σύνθεση παρασκευάζοντας απλά χειρόμορφα μόρια τα οποία τα εξελίσσει σε πολυπλοκότερα. Τα σημαντικότερα/απλούστερα χειρόμορφα φυσικά προϊόντα που η φύση χρησιμοποιεί ως πρώτες ύλες είναι τα αμινοξέα, οι υδατάνθρακες και τα τερπένια

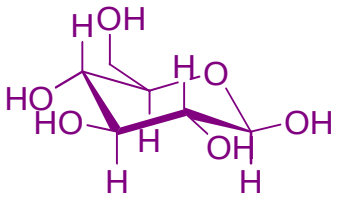
Αμινοξέα

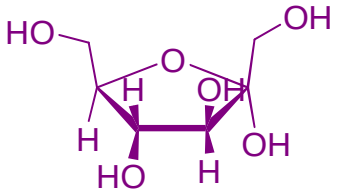


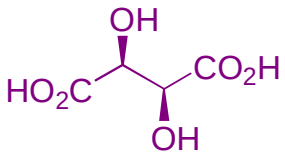




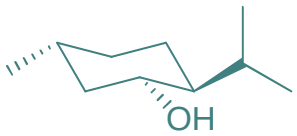
Υδατάνθρακες







Τερπένια



Στοιχειομετρικές μέθοδοι 1. Χειρόμορφο υπόστρωμα

Στο εργαστήριο, εφαρμόζοντας αντιθετική ανάλυση ή απλά παρατηρώντας το μόριο-στόχο, είναι πιθανό να σχετίσουμε κάποιο χειρόμορφο τμήμα του με τη δομή ενός απλού χειρόμορφου φυσικού προϊόντος και να το χρησιμοποιήσουμε – τροποποιήσουμε για τη σύνθεση του στόχου

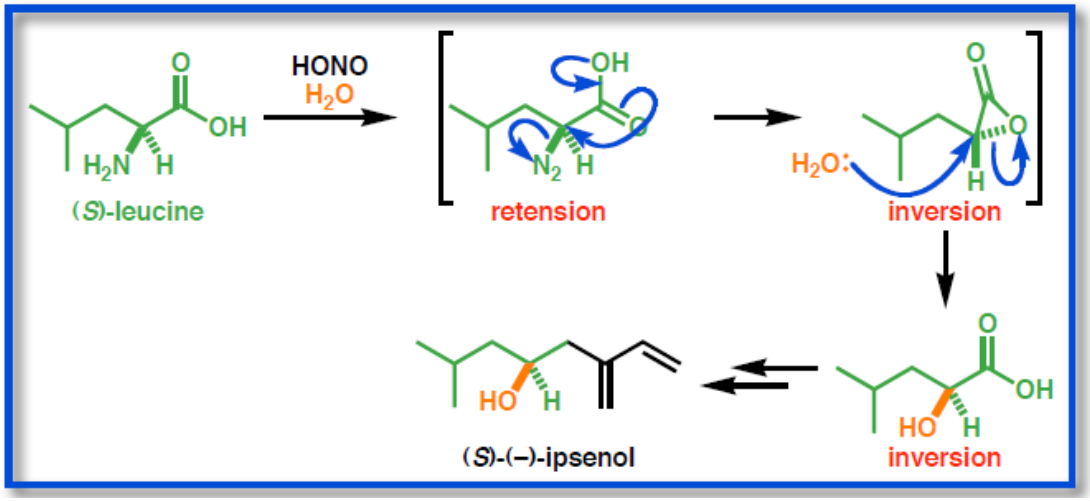
Αυτή η στρατηγική χρησιμοποιούταν παλαιότερα πριν την πρόοδο της ασύμμετρης σύνθεσης με καταλύτες και χειρόμορφα βοηθήματα

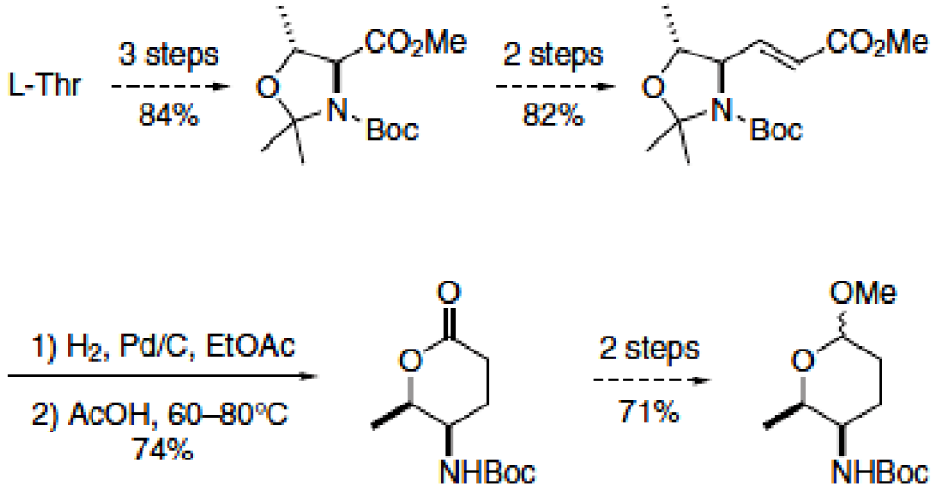
Ενδείκνυται όταν το χειρόμορφο τμήμα ενός μορίου αντιστοιχεί σε ένα φυσικό υπόστρωμα το οποίο είναι διαθέσιμο σε μεγάλες ποσότητες και είναι σχετικά φθηνό. Κάτι τέτοιο δεν ισχύει για τους οπτικούς αντίποδες φυσικών προϊόντων.

Αν το υπάρχων στερεογονικό κέντρο χρησιμοποιείται για να καθοδηγήσει το σχηματισμό ενός νέου, για μέγιστη εκλεκτικότητα απαιτείται εγγύτητα ή στερεοχημική επικοινωνία- μεταξύ των δύο κέντρων

Απαιτούνται λεπτοί και χρονοβόροι μετασχηματισμοί για να μετατραπεί ένα σχετικά απλό φυσικό υπόστρωμα σε ένα πολύπλοκο μόριο.

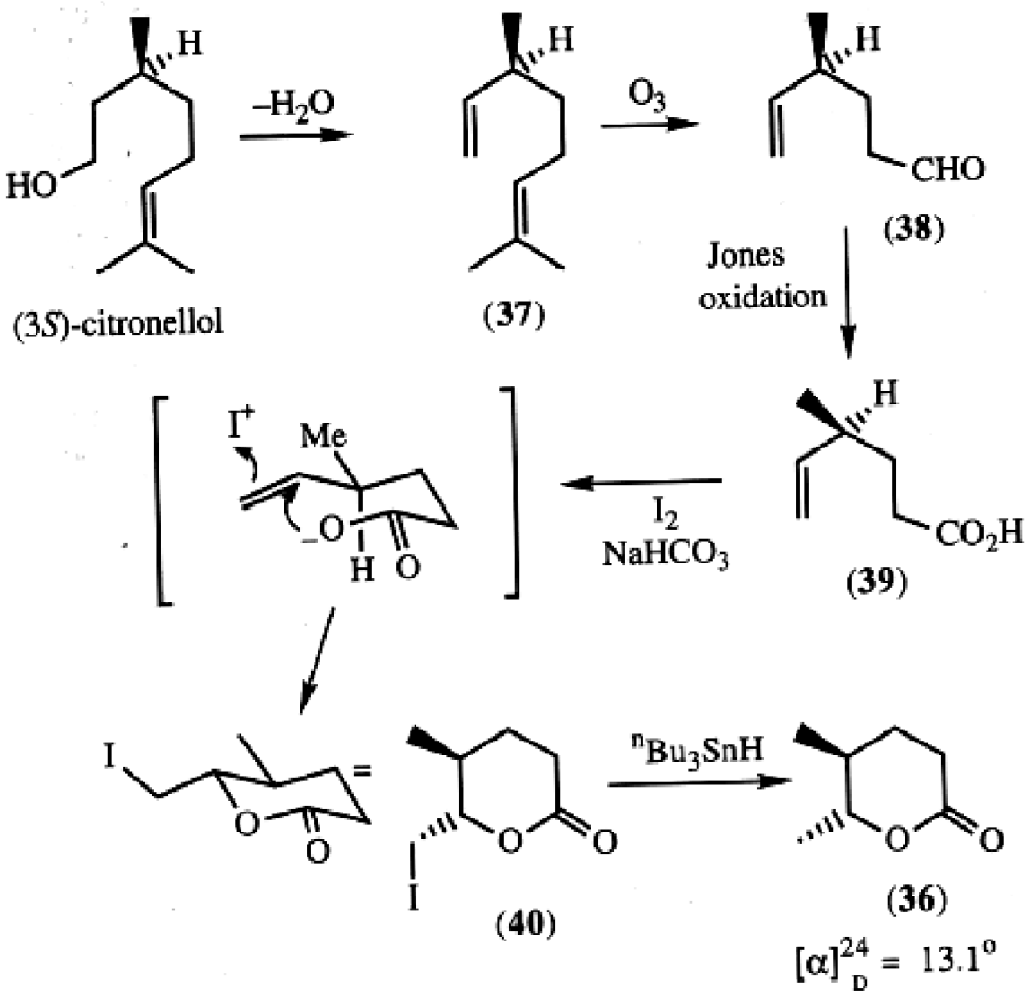
Χρήση αμινοξέος ως χειρόμορφο υπόστρωμα



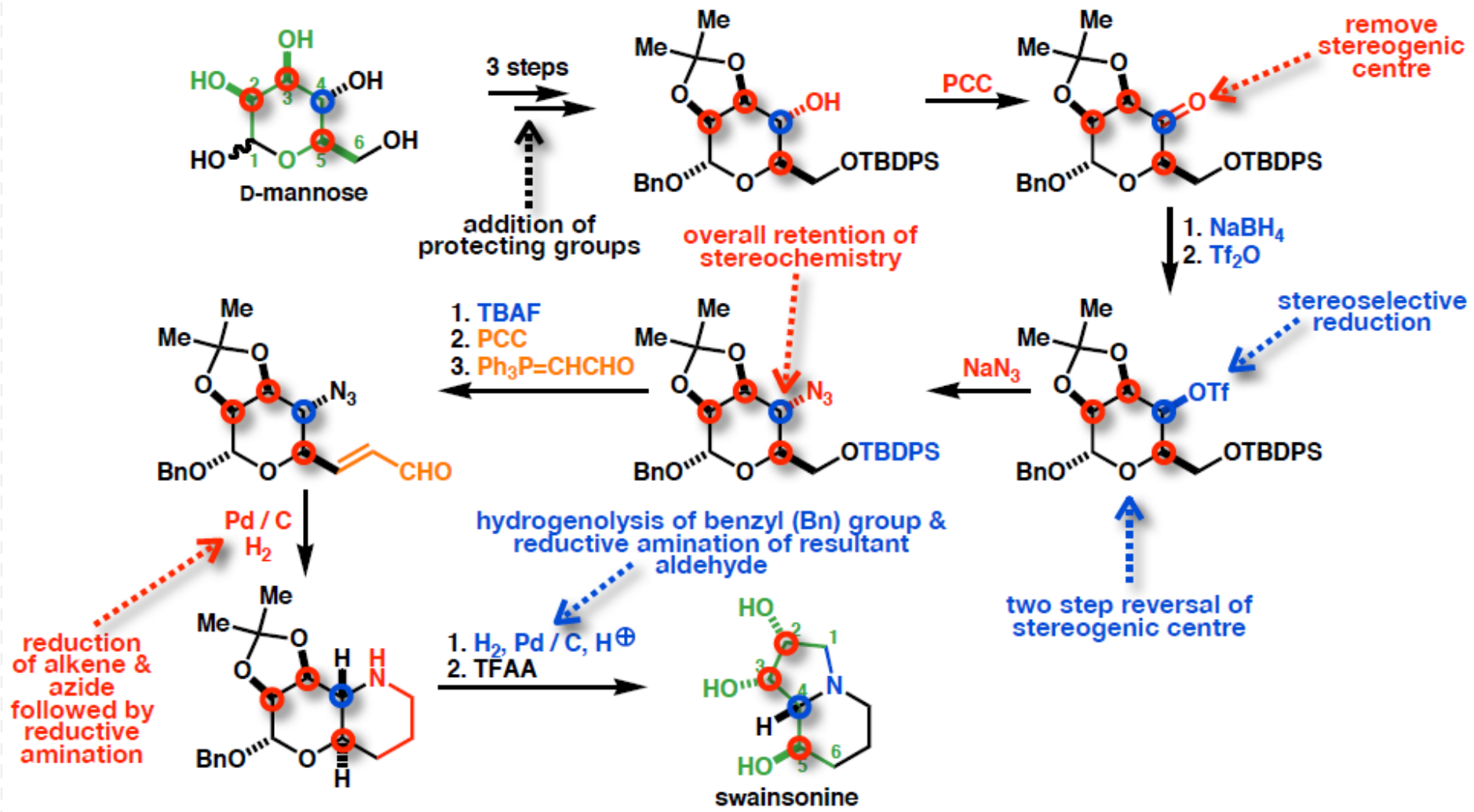


Scheme 4.3 *Synthesis of ossamine/epi-tolyposamine*

Χρήση τερπενίου ως χειρόμορφο υπόστρωμα

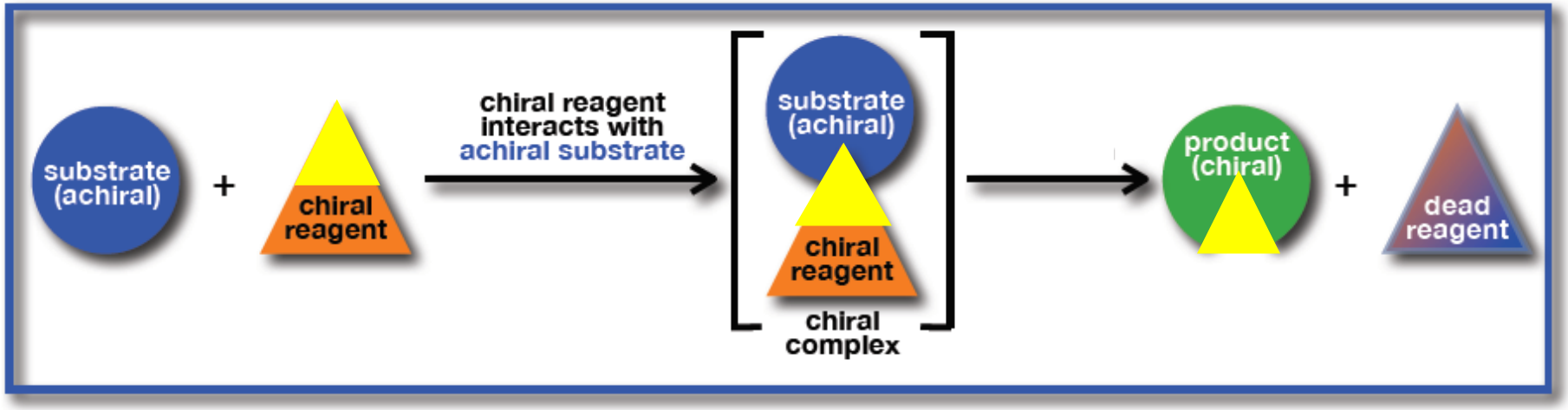


Χρήση υδατάνθρακα ως χειρόμορφο υπόστρωμα



- In this example three stereogenic centres are retained
- One stereogenic centre undergoes multiple inversion -- but overall it is retained

Στοιχειομετρικές μέθοδοι 2. Χειρόμορφο αντιδραστήριο



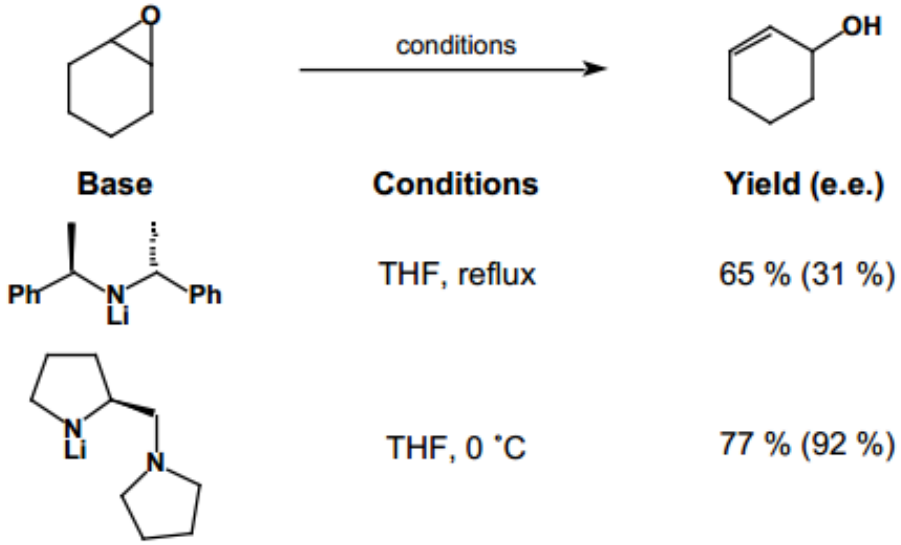
- **Chiral reagent** - stereochemistry initially resides on the reagent
- **Advantages** - No coupling / cleavage steps required
  Often override substrate control
  Can be far milder than chiral auxiliaries
- **Disadvantages** - Need a stoichiometric quantity (not atom economic)
  Frequently expensive
  Problematic work-ups

ΠΑΡΑΔΕΙΓΜΑΤΑ ΑΝΤΙΔΡΑΣΕΩΝ

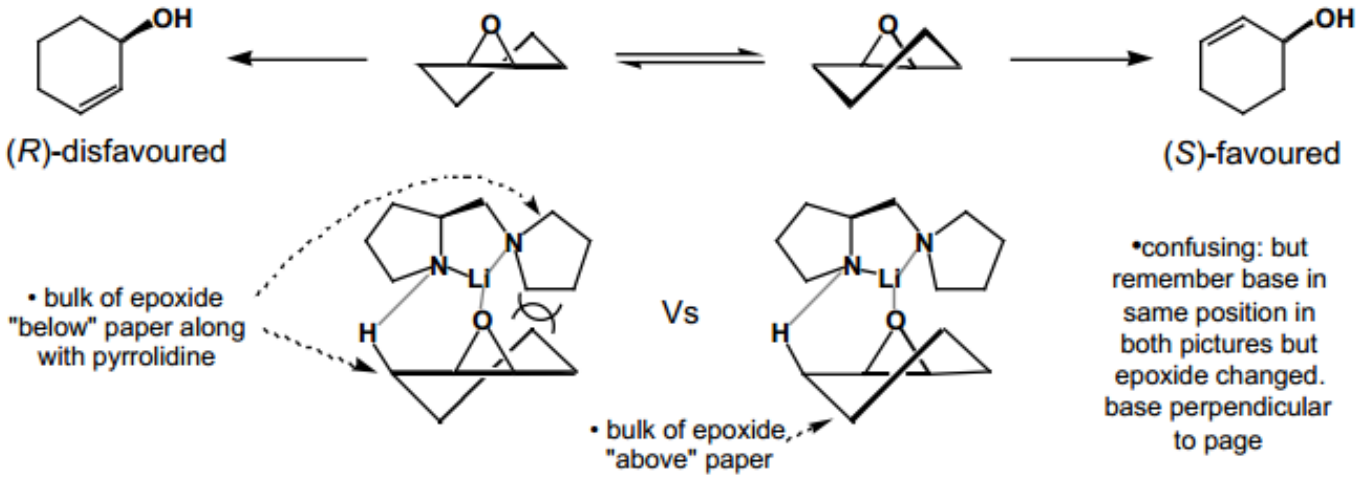
- **Αποπρωτονίωση – Αλκυλίωση**
- **Αναγωγή καρβονυλίου**
- **Προσθήκη σε καρβονύλιο**
- **Οξείδωση**

Χειρόμορφα αντιδραστήρια 1. Εκλεκτική Αποπρωτονίωση

Χειρόμορφες βάσεις

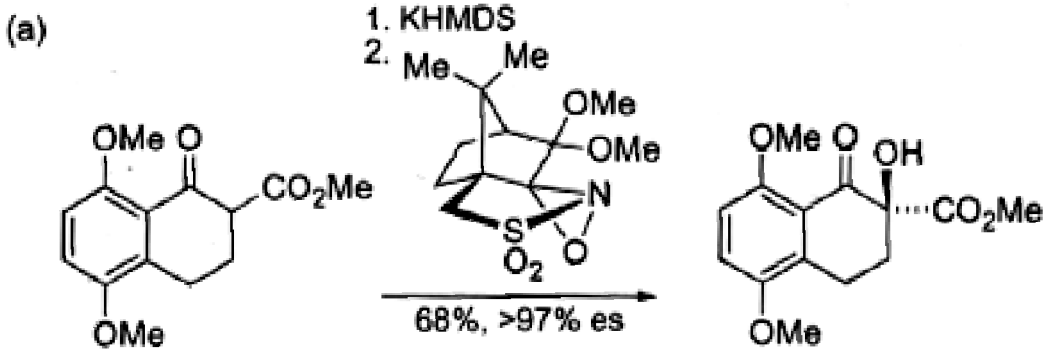


Proposed mechanism

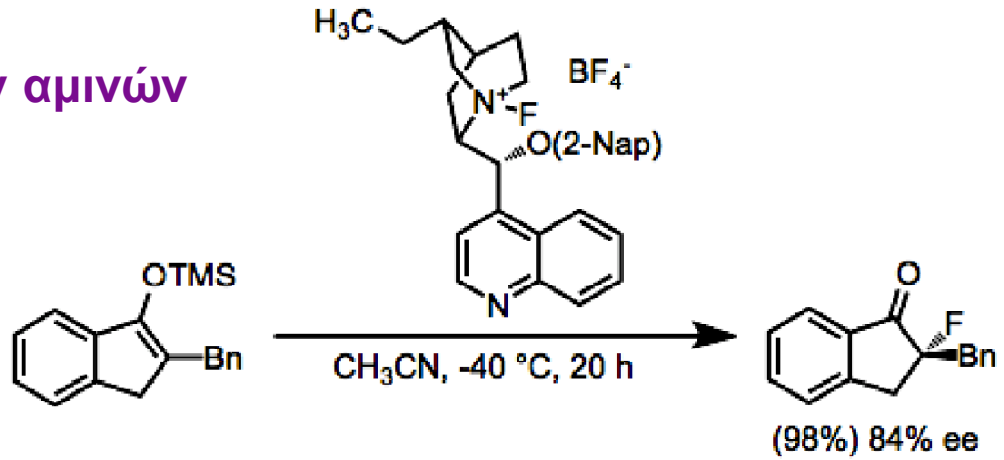


Χειρόμορφα αντιδραστήρια 2. α-Υποκατάσταση

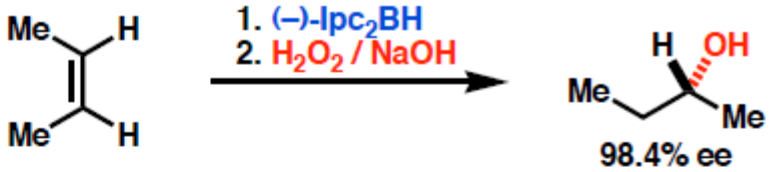
Οξαζιριδίνες από χειρόμορφες ιμίνες

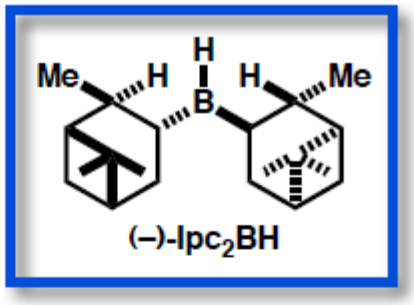


N-F Άλατα χειρόμορφων αμινών

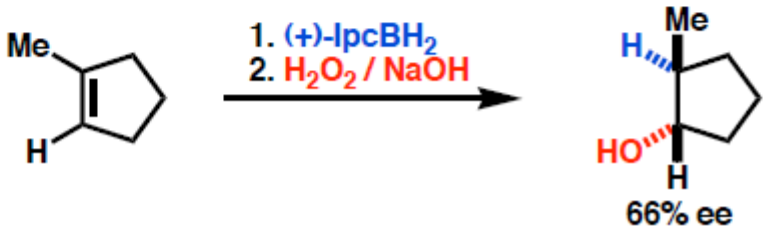


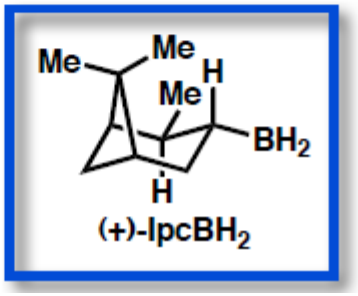
Χειρόμορφα αντιδραστήρια 3. Υδροβορίωση



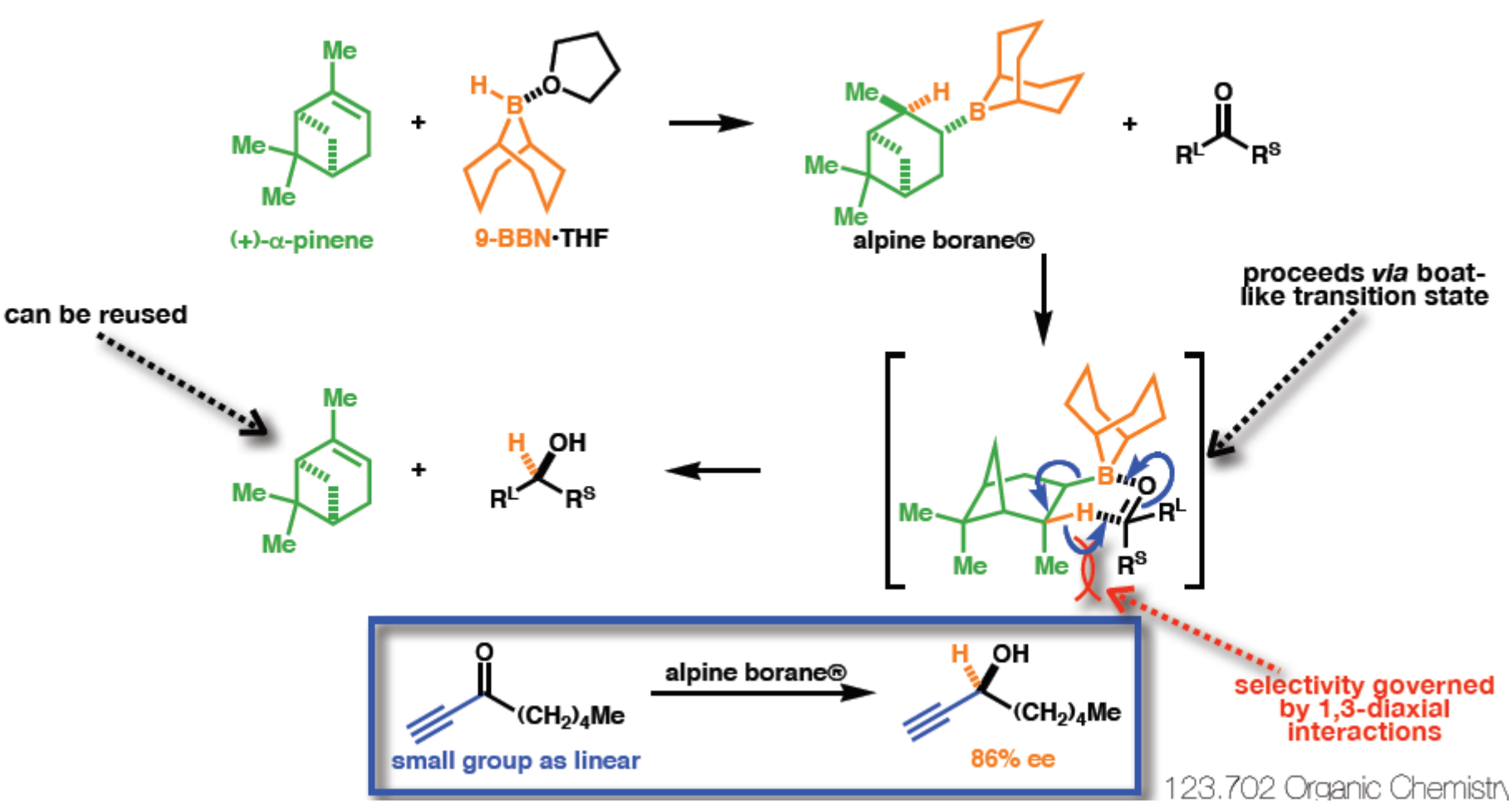


- The two compounds formed previously, mono- & diisopinocampheylborane are common reagents for the stereoselective hydroboration of alkenes
- **Ipc_2BH** is very effective for ***cis***-alkenes but less effective for *trans*
- **$IpcBH_2$** gives higher enantiomeric excess with *trans* and trisubstituted alkenes





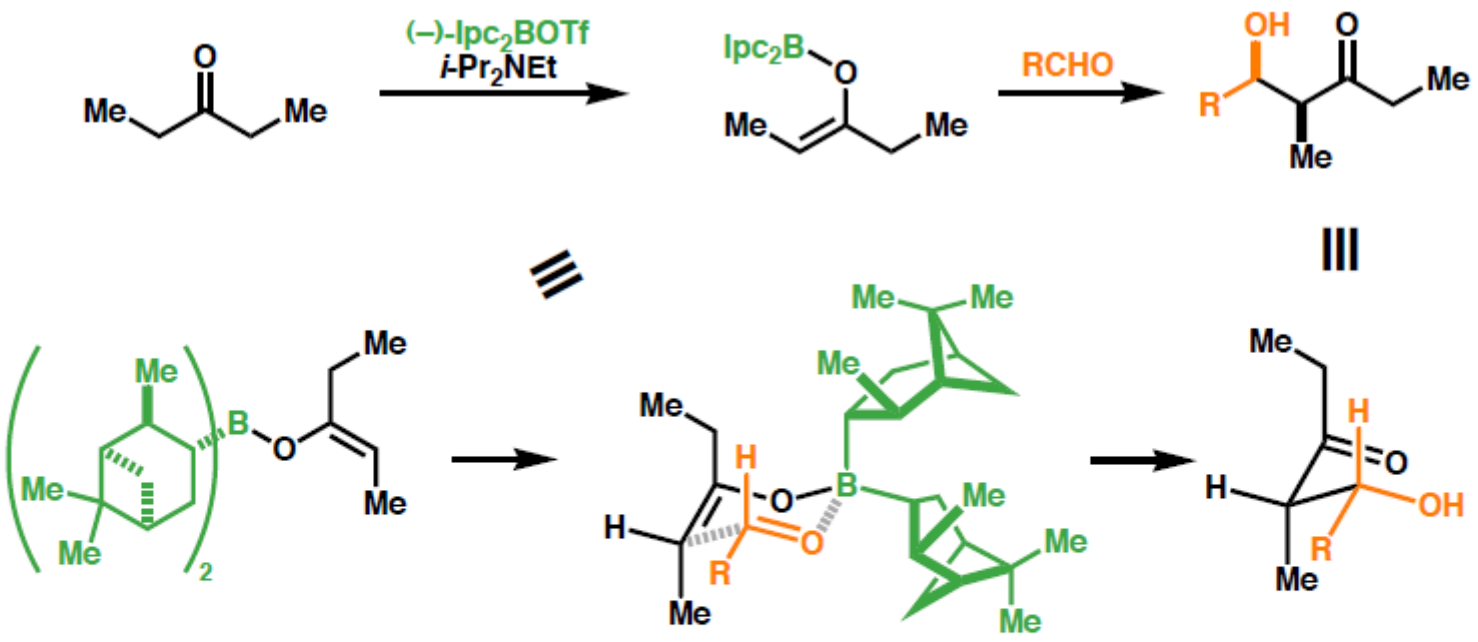
Χειρόμορφα αντιδραστήρια 4α. Αναγωγή καρβονυλίου



Χειρόμορφα αντιδραστήρια 4β. Αναγωγή καρβονυλίου

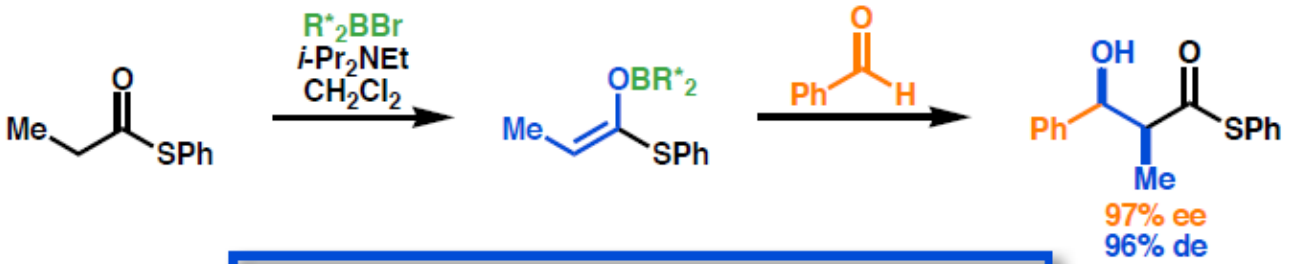
- (+)-Ipc_2BCl is a more reactive, Lewis acidic version of Alpine-borane
- Might want to revise the Mitsunobu reaction (step 2)
- M. Srebnik, P.V. Ramachandran & H.C. Brown, *J. Org. Chem.*, **1988**, *53*, 2916

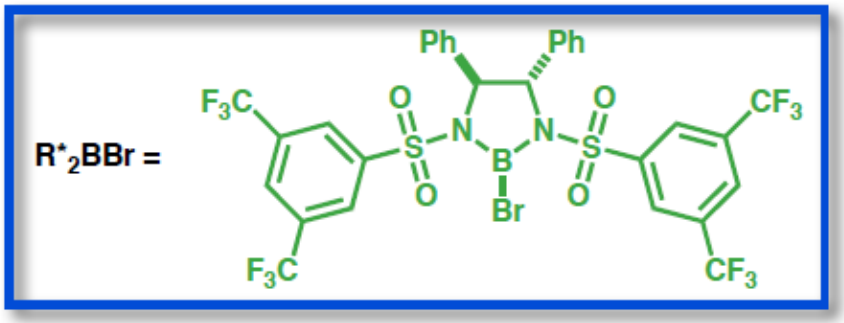
Χειρόμορφα αντιδραστήρια 5α. Aldol reaction



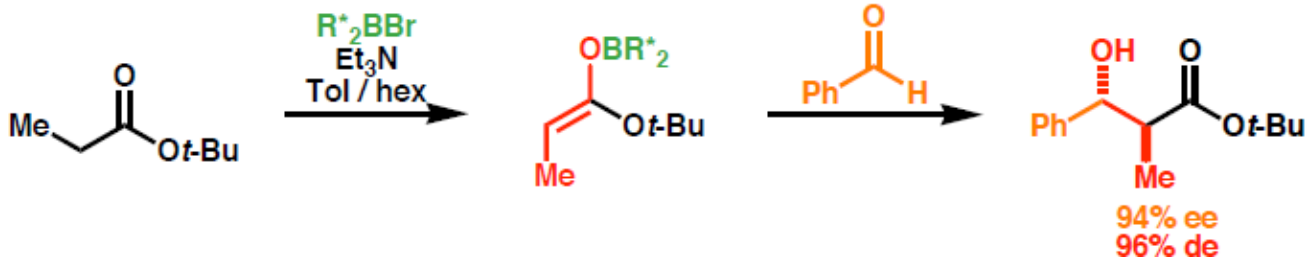
- Hopefully it is becoming clear that the use of **chiral reagents** is more efficient
- In this reaction, the standard pinene derivative is being utilised
- The transition state is analogous to that of Brown allylation
- Interaction between the enolate and the methyl group of the Ipc moiety is minimised

Χειρόμορφα αντιδραστήρια 5β. Aldol reaction

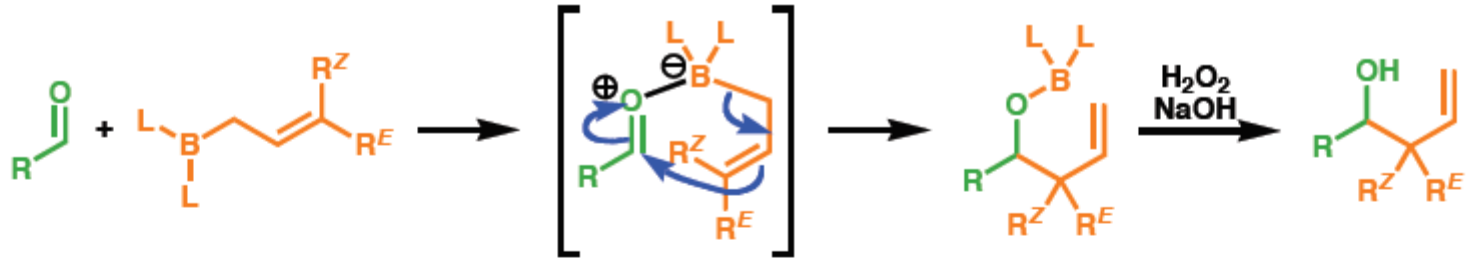




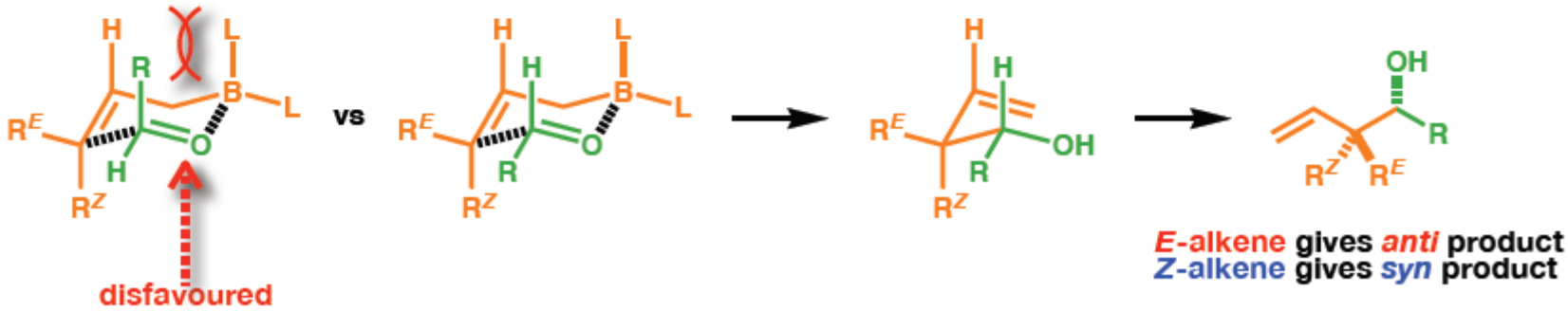
- Once again, the **geometry** of the enolate is important - it controls **relative** stereochemistry
- Use of the **thio-ester** results in the ***cis*-enolate** and thus the ***syn* aldol**
- Alternatively, use of the **ester** & a change of solvent gives the ***trans*-enolate** & ***anti*** product



Χειρόμορφα αντιδραστήρια 6α. Προσθήκη σε καρβονύλιο

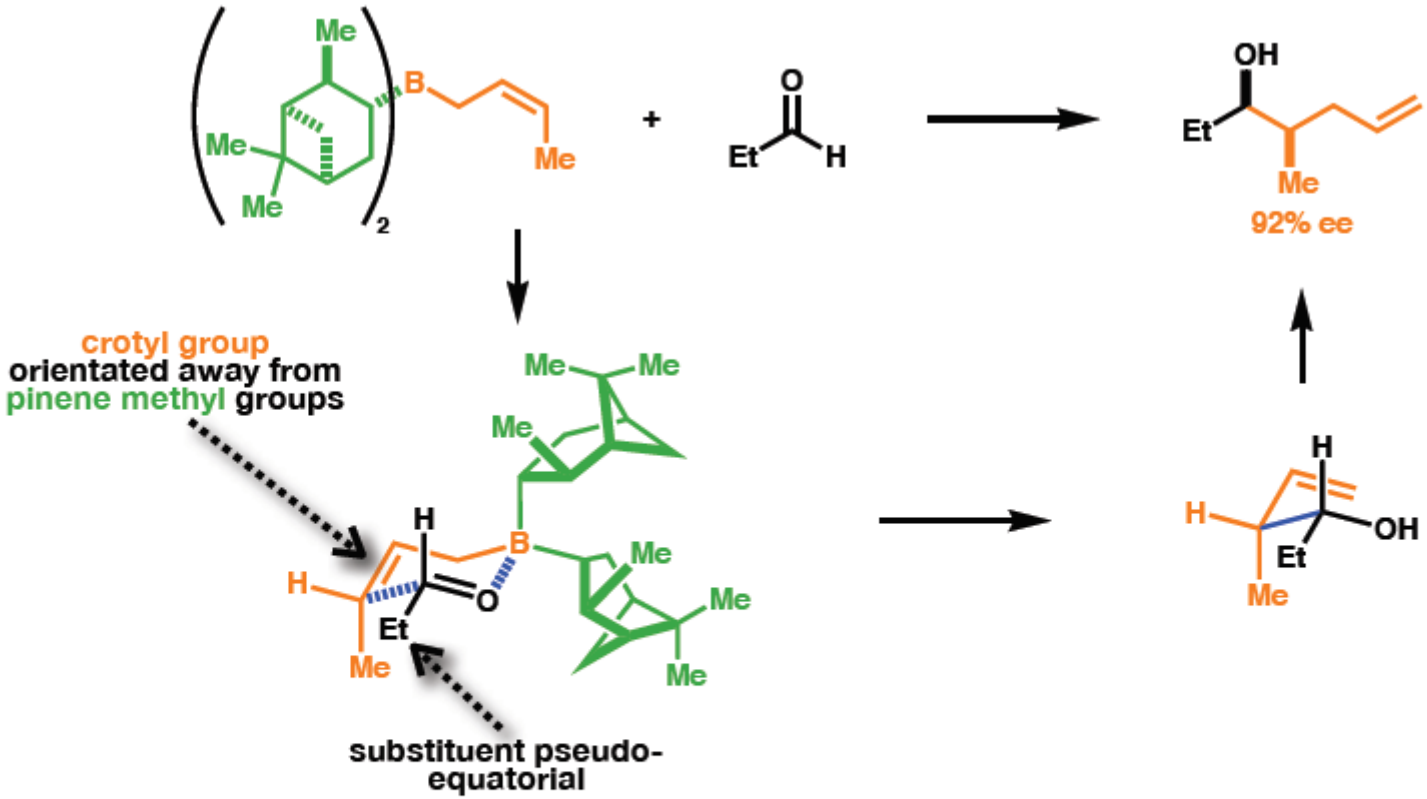


- Allyl boron reagents have been used extensively in the synthesis of homoallylic alcohols
- Reaction always proceeds *via* coordination of Lewis basic carbonyl and Lewis acidic boron
- This activates carbonyl as it is more **electrophilic** and weakens B–C bond, making the reagent more **nucleophilic**
- Funnily enough, reaction proceeds by a **6-membered transition state**



- Aldehyde will place substituent in pseudo-equatorial position (**1,3-diaxail strain**)
- Therefore **alkene geometry** controls the **relative stereochemistry** (like aldol rct)

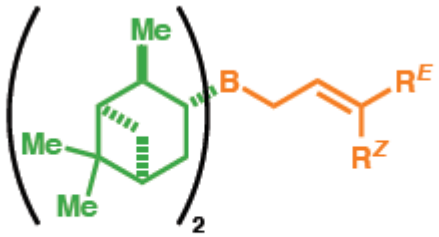
Χειρόμορφα αντιδραστήρια 6β. Προσθήκη σε καρβονύλιο



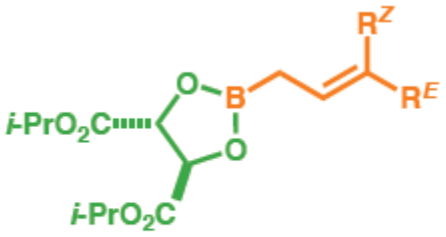
- Reagent is synthesized from pinene in two steps
- Gives excellent selectivity but can be hard to handle (make prior to reaction)

- Remember pinene controls absolute configuration
  Geometry of alkene controls relative stereochemistry

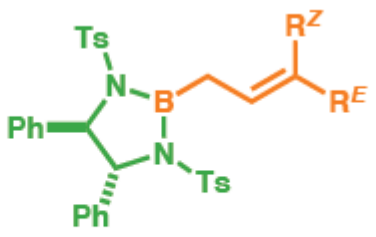
Χειρόμορφα αντιδραστήρια 6γ. Προσθήκη σε καρβονύλιο



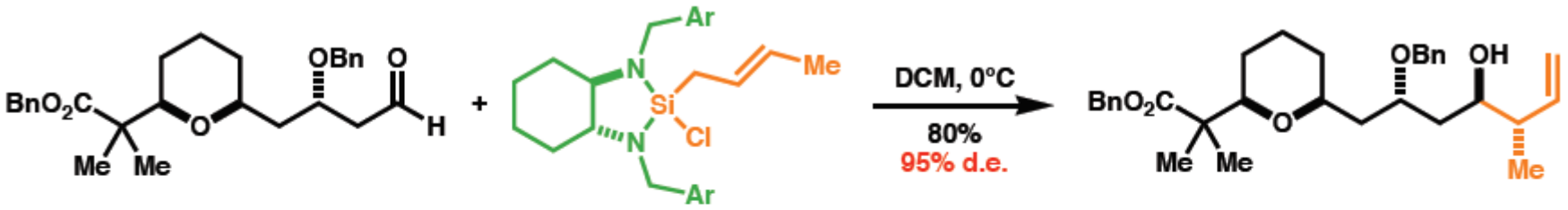
attacks on *si* face of RCHO

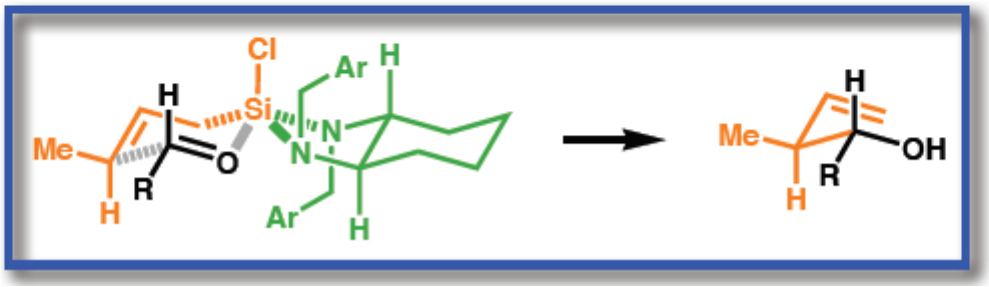


attacks on *si* face of RCHO
tartaric acid derivative

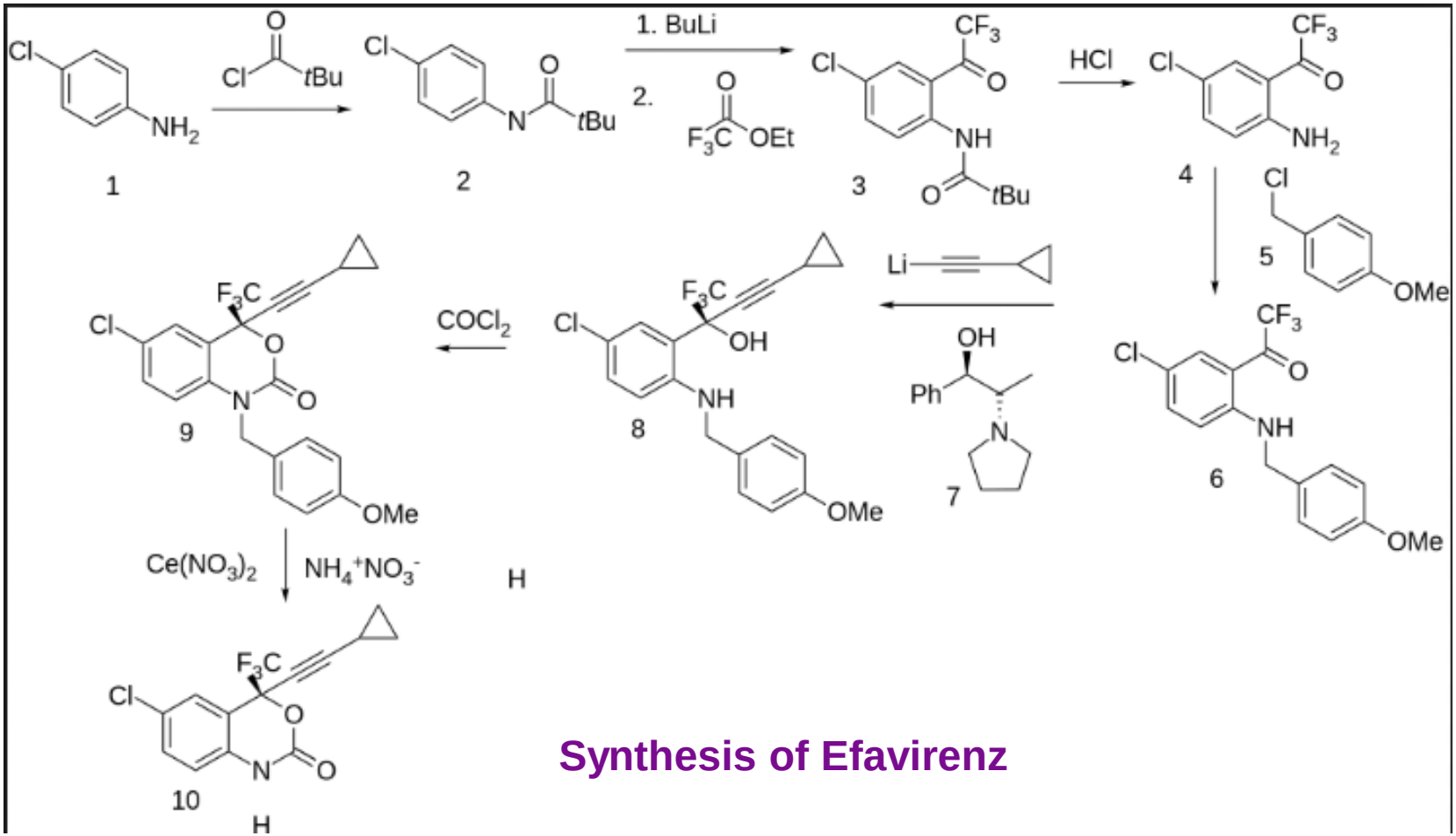


attacks on *re* face of RCHO



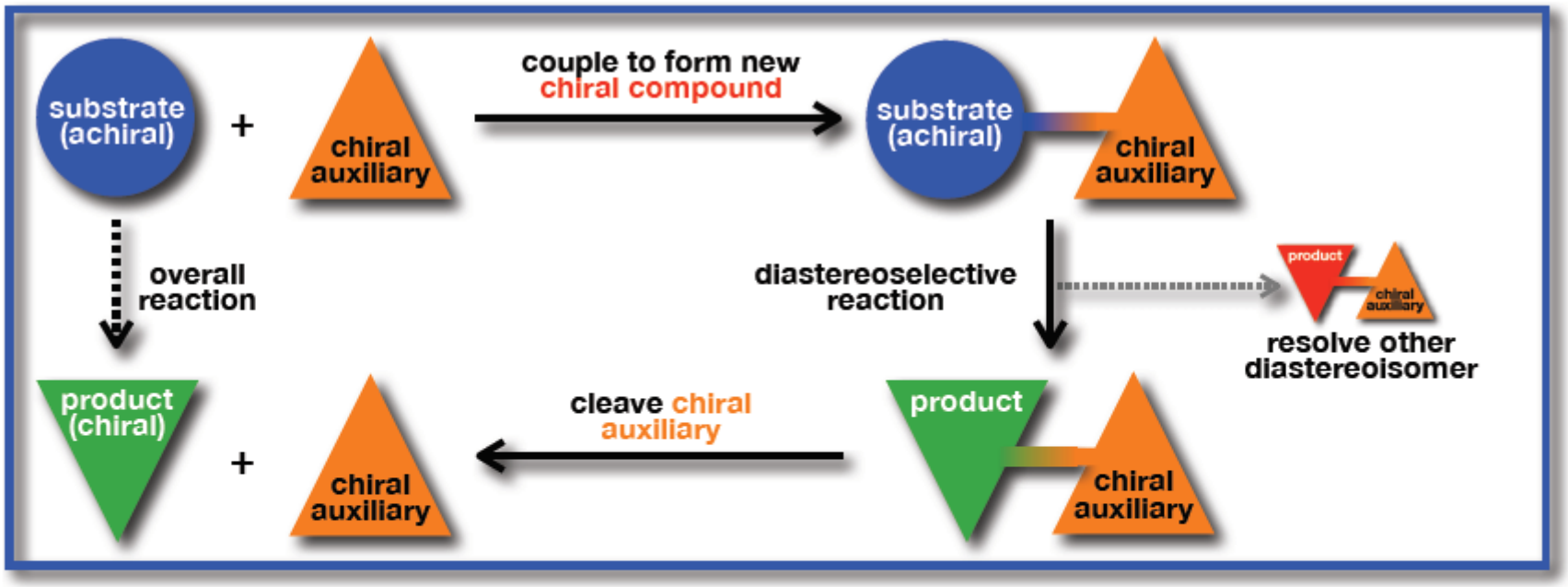


Χειρόμορφα αντιδραστήρια 6δ. Προσθήκη σε καρβονύλιο



Synthesis of Efavirenz

Στοιχειομετρικές μέθοδοι 2. Χειρόμορφο βοήθημα



- **Chiral auxiliary** - allows enantioselective synthesis *via* diastereoselective reaction
- Add chiral unit to substrate to control stereoselective reaction
- Can act as a built in resolving agent (if reaction not diastereoselective)
- **Problems** - need point of attachment
  adds additional steps
  cleavage conditions must not damage product!

Στοιχειομετρικές μέθοδοι 2. Χειρόμορφο βοήθημα

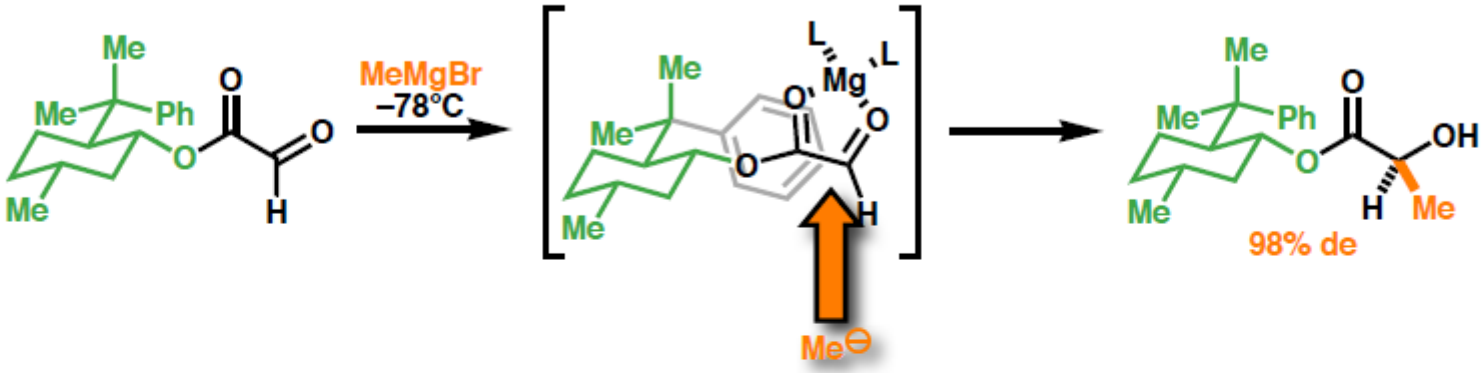
A good chiral auxiliary must be **1)** available in both enantiomeric forms, **2)** quick and easy to make, **3)** easy to put on, **4**) give good levels of asymmetric induction, **5)** easy to take off and **6)** recyclable.

Advantages:
Levels of diastereocontrol usually high.
Diastereomers can be separated by conventional methods (chromatography, crystallisation).
Auxiliary can be recycled.
Sense of asymmetric induction can be determined by X-ray crystalography.

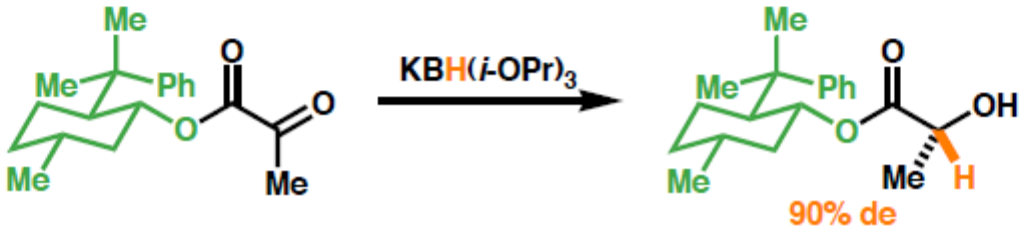
Disadvantages:
Both enantiomers of auxiliary not readily available.
Chiral auxiliaries need to be prepared.
Extra steps – instaltion and removal
Need stoichiometric amount of chirality

Εστέρες ως Χειρόμορφα βοηθήματα

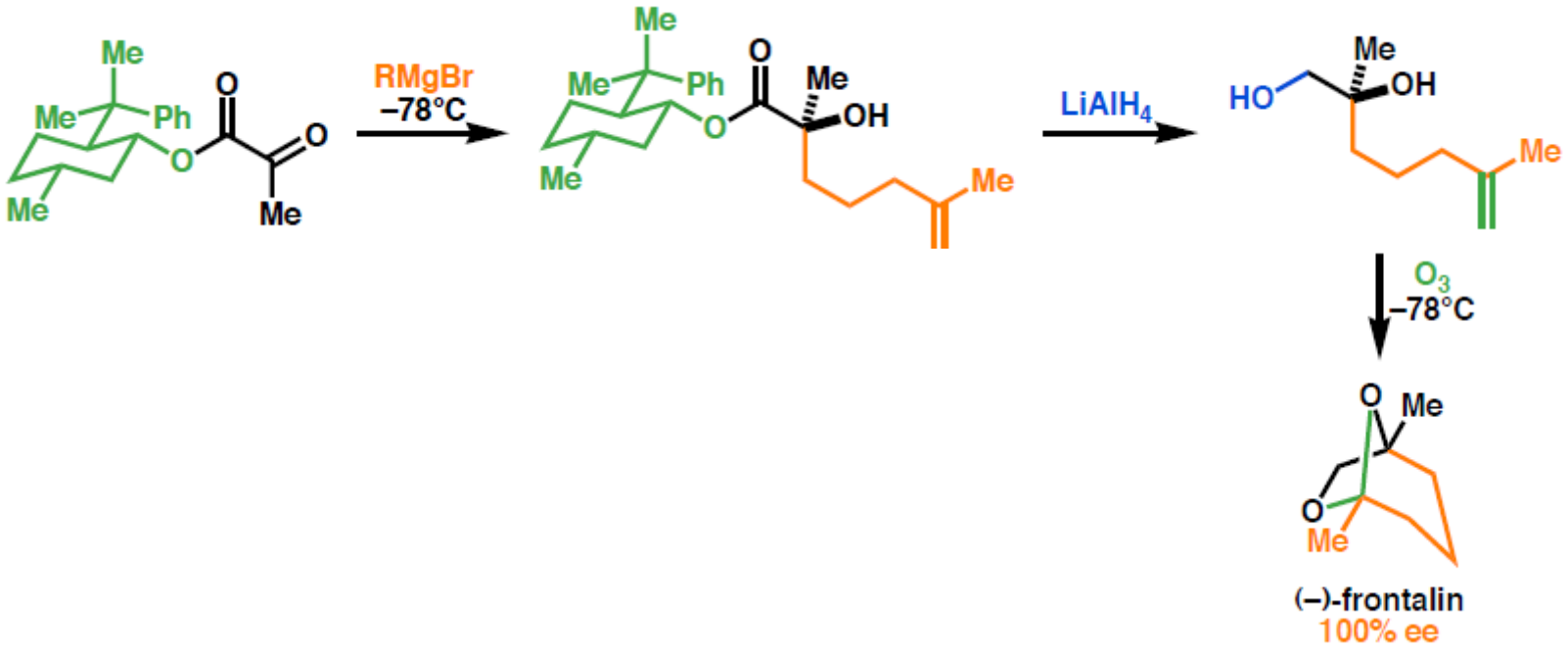
- If molecule does not contain a stereogenic centre then we can use a **chiral auxiliary**
- The chiral auxiliary can be removed at a later stage

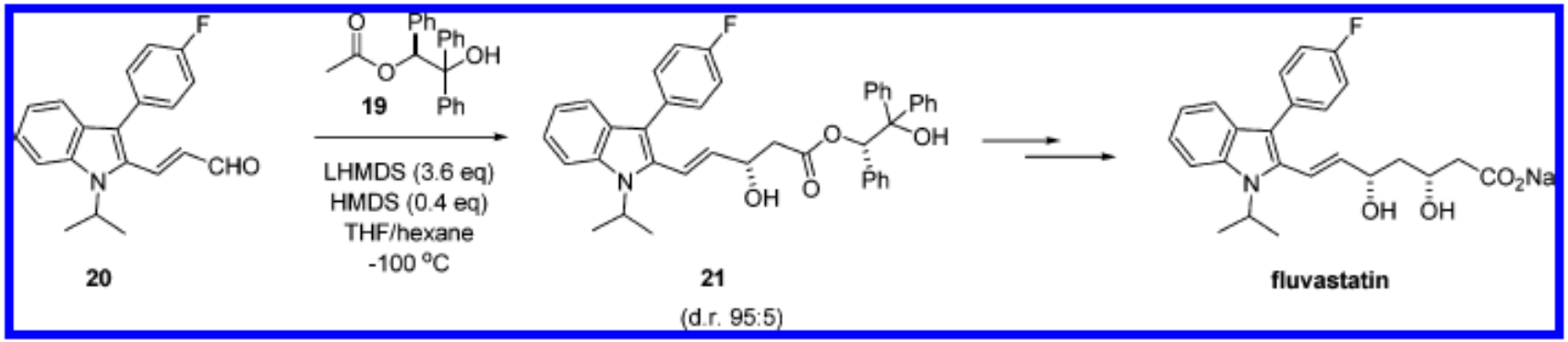


- Opposite diastereoisomer can be obtained from reduction of the ketone
- Note: there is lower diastereoselectivity in the second addition as the nucleophile, 'H^-' is smaller

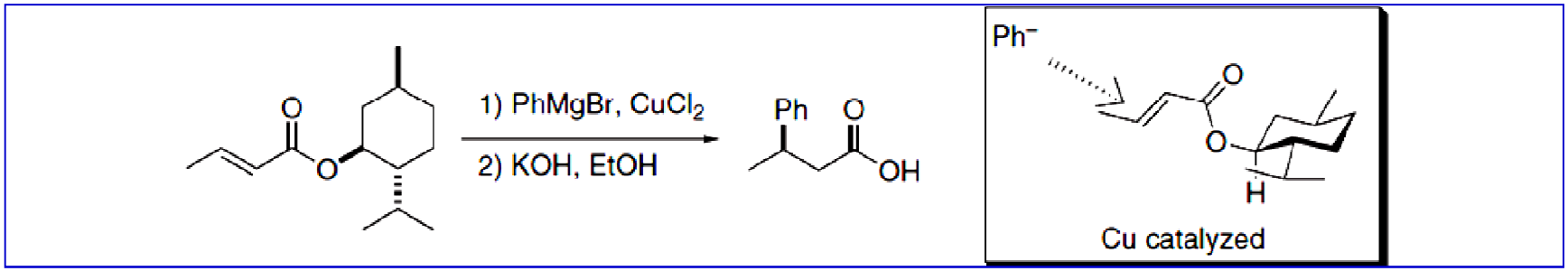


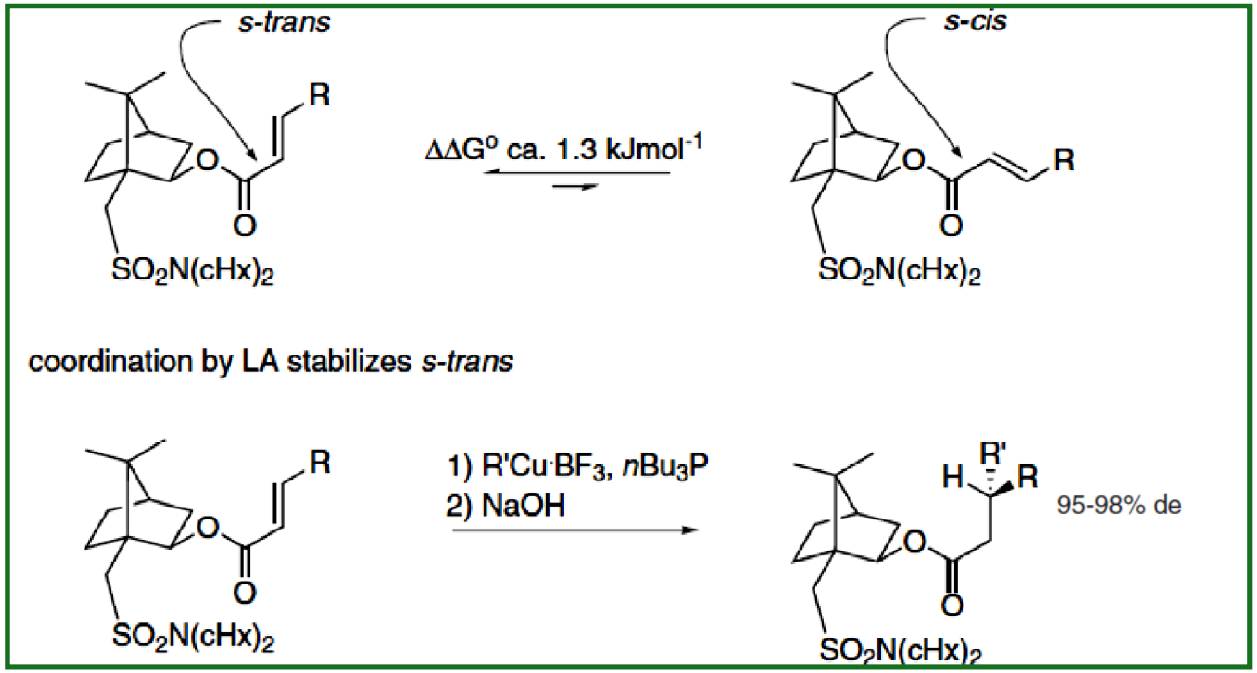
Χειρόμορφοι Εστέρες - αλδολική συμπύκνωση



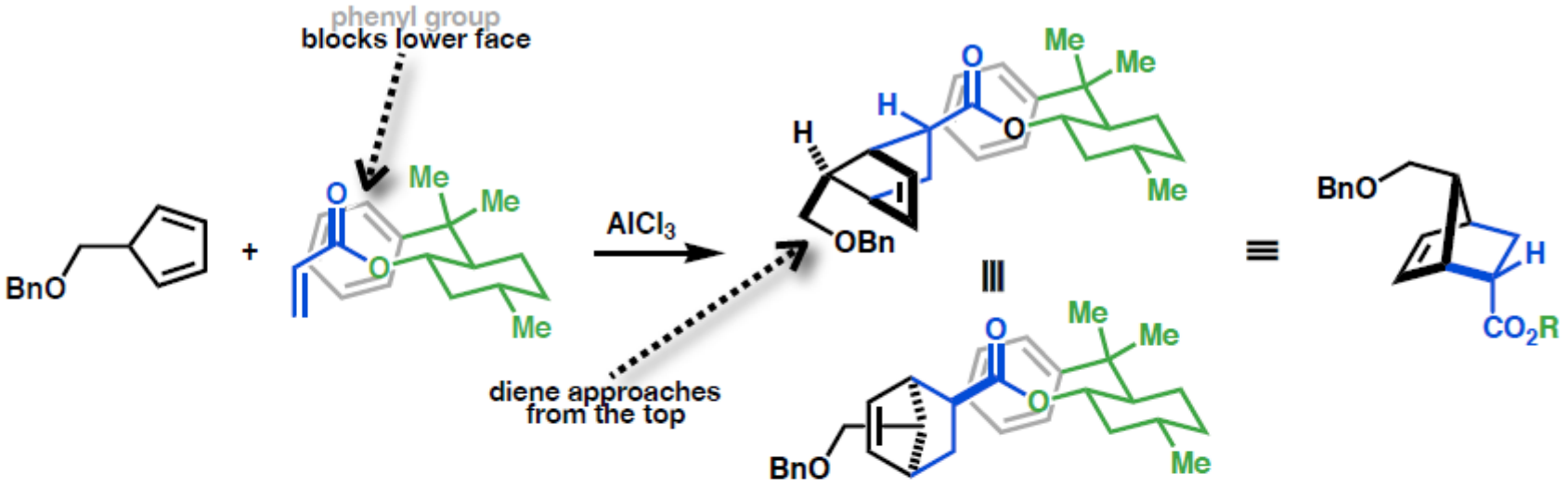


Χειρόμορφο βοήθημα για ασύμμετρη συζ. προσθήκη

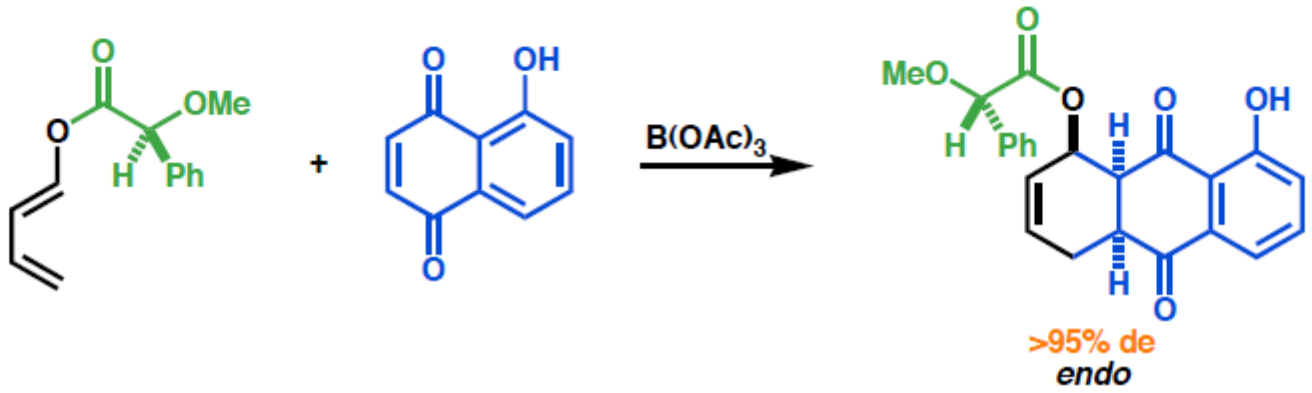




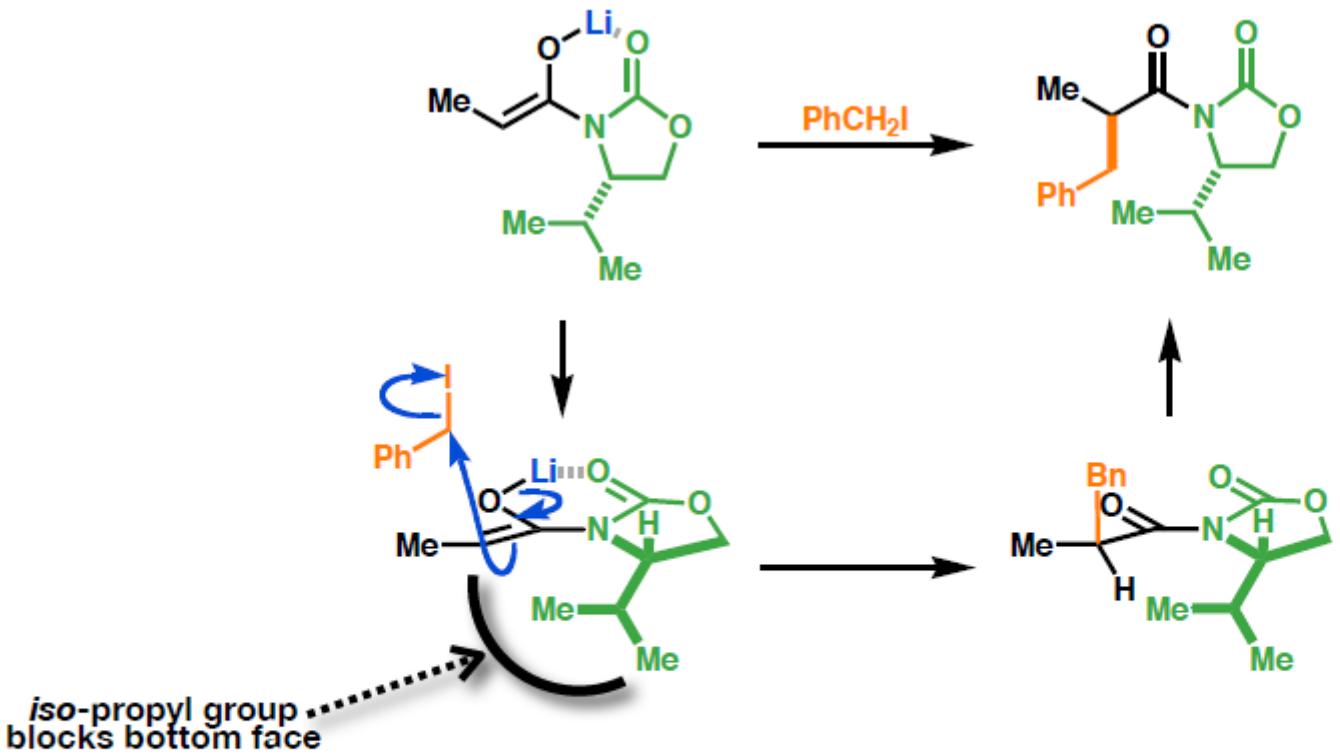
Χειρόμορφοι Εστέρες – Diels Alder



- It is possible to attach the **chiral auxiliary** to the **diene** as well

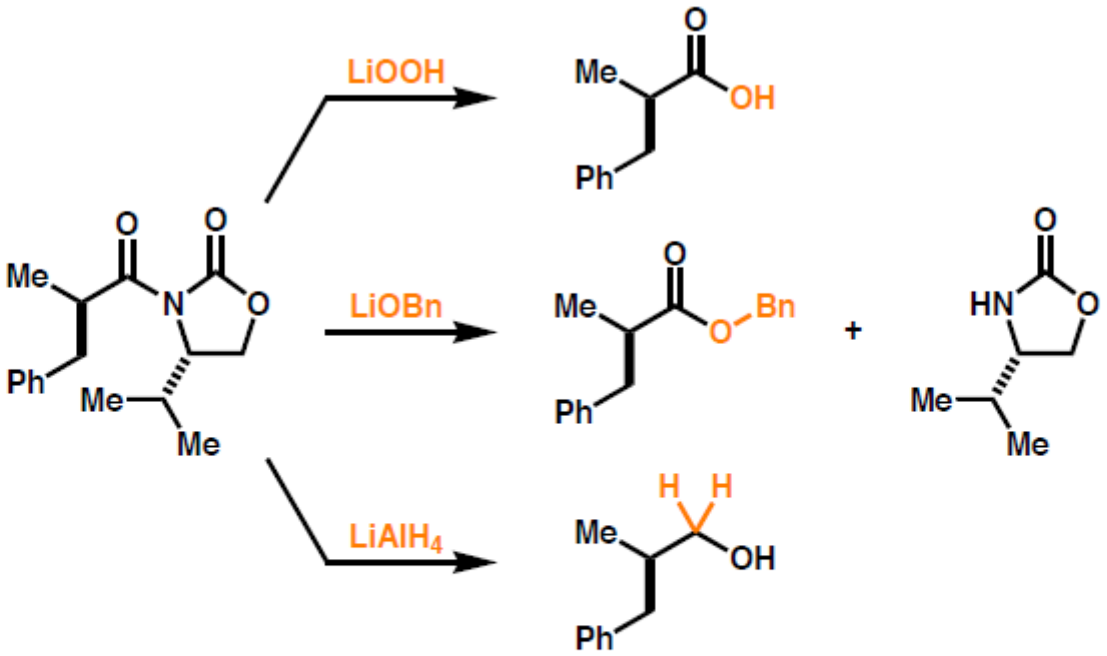


Evans' oxazolidinones



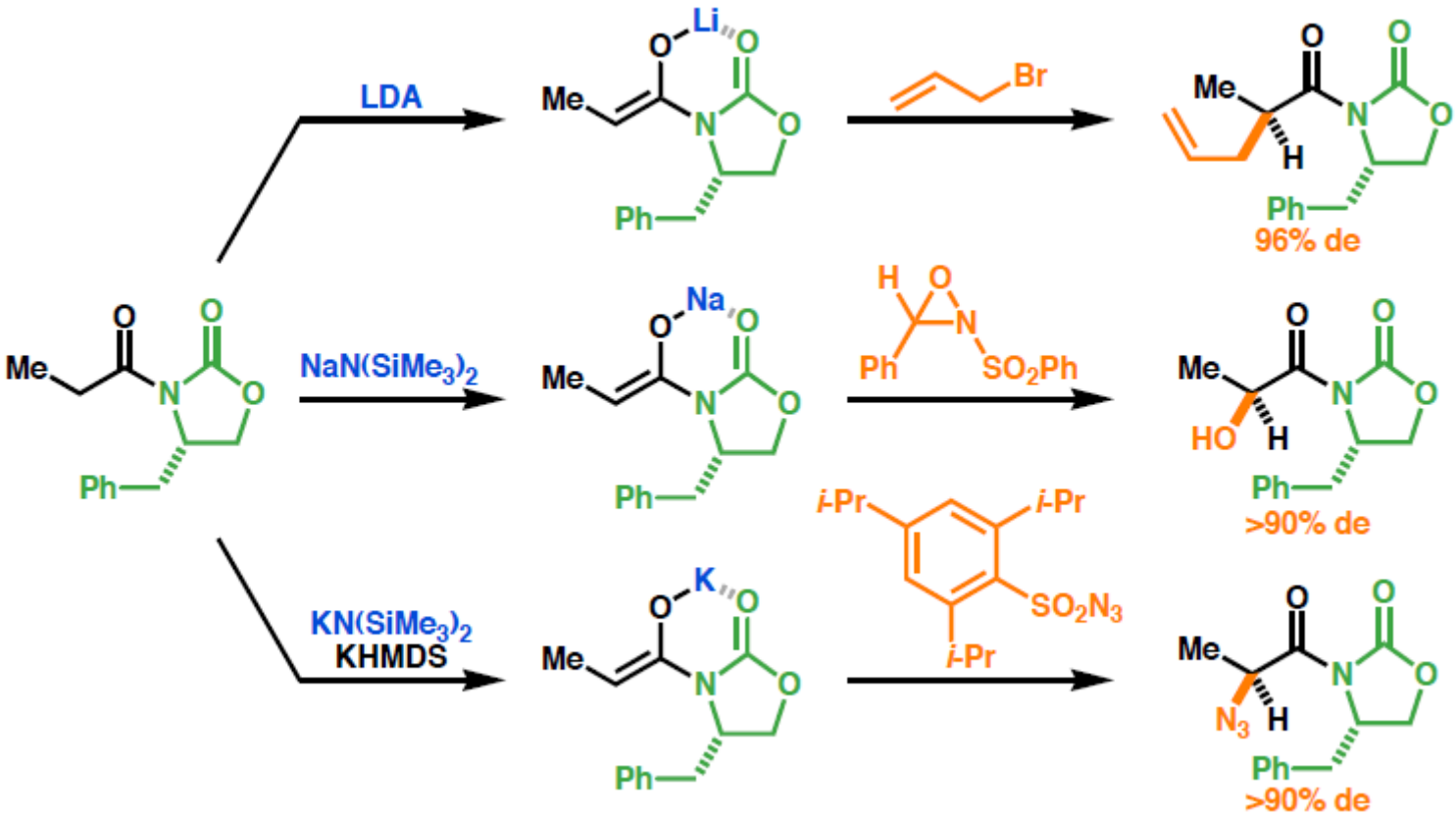
- Clearly (I hope) one face of the enolate is blocked
- Chelation results in a rigid structure that provides maximum steric hindrance
- The electrophile can only approach from one face

Evans' oxazolidinones - Removal

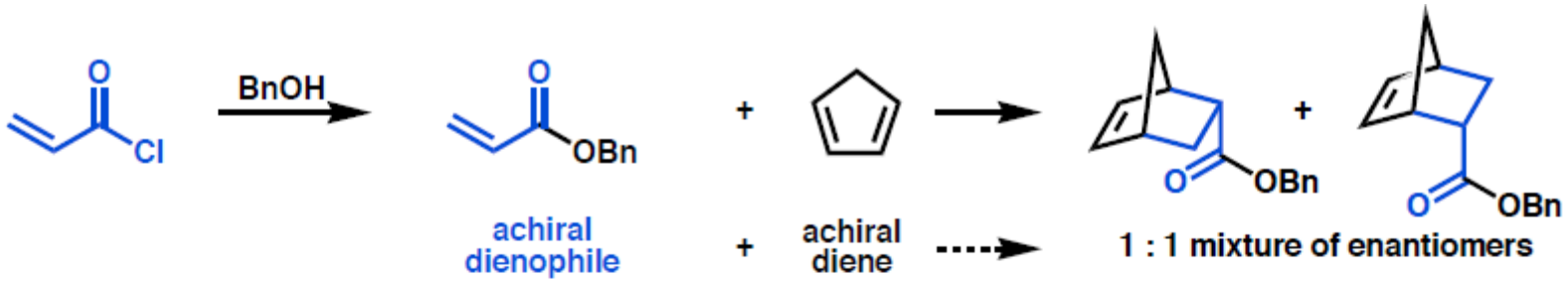


- For an auxiliary to be of any use in synthesis it must be readily removed
- Oxazolidinones are easily converted to carboxylic acids, esters and alcohols

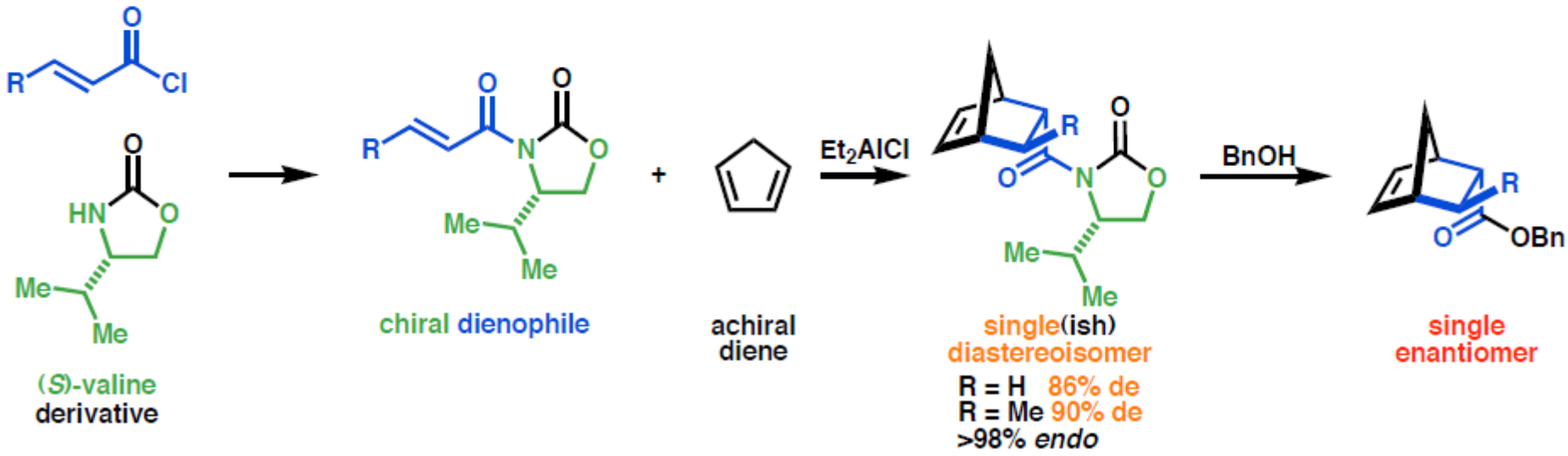
Evans' oxazolidinones α- substitution



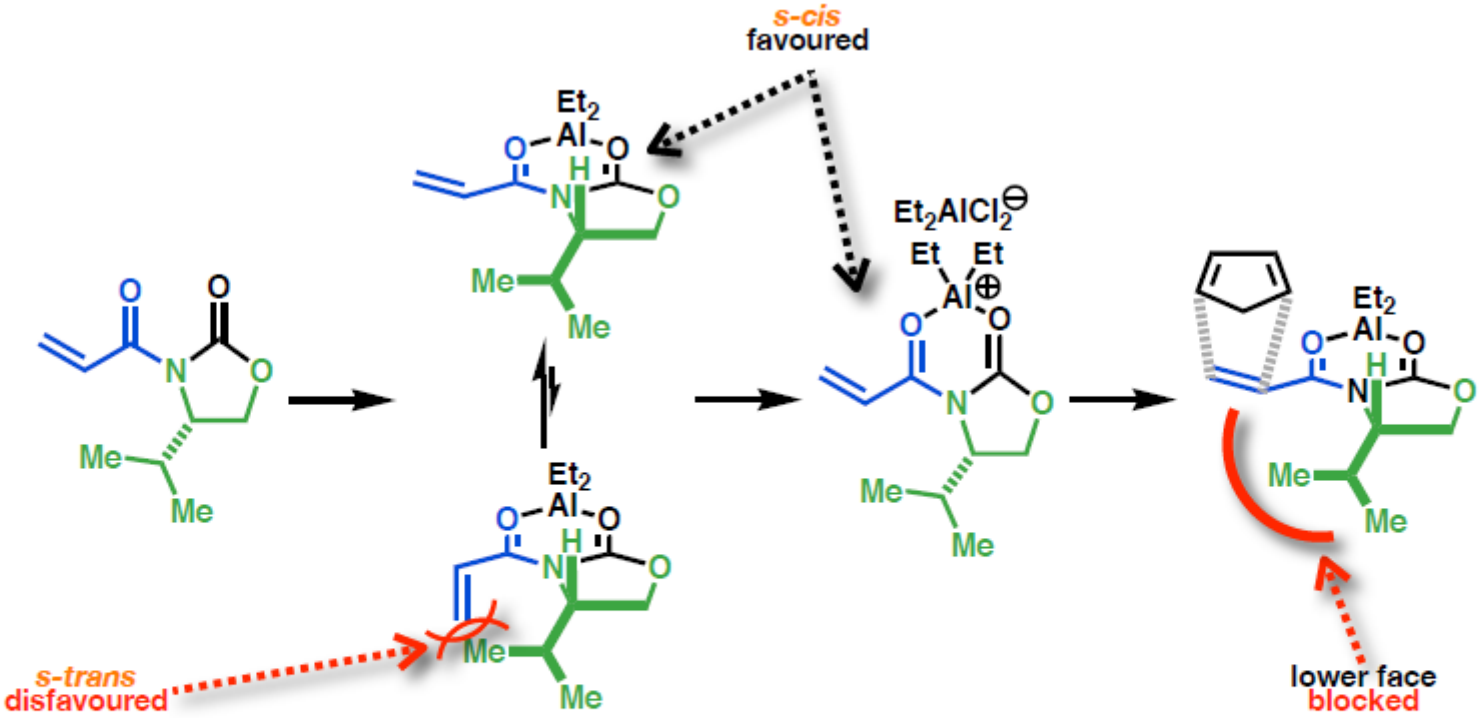
Evans' oxazolidinones - Diels Alder



- One diastereoisomer is formed - the ***endo*** product
- But mixture of **enantiomers**
- If we add a **chiral auxiliary** then there are two possible *endo* diastereoisomers
- But one predominates - thus we can prepare a **single enantiomer**

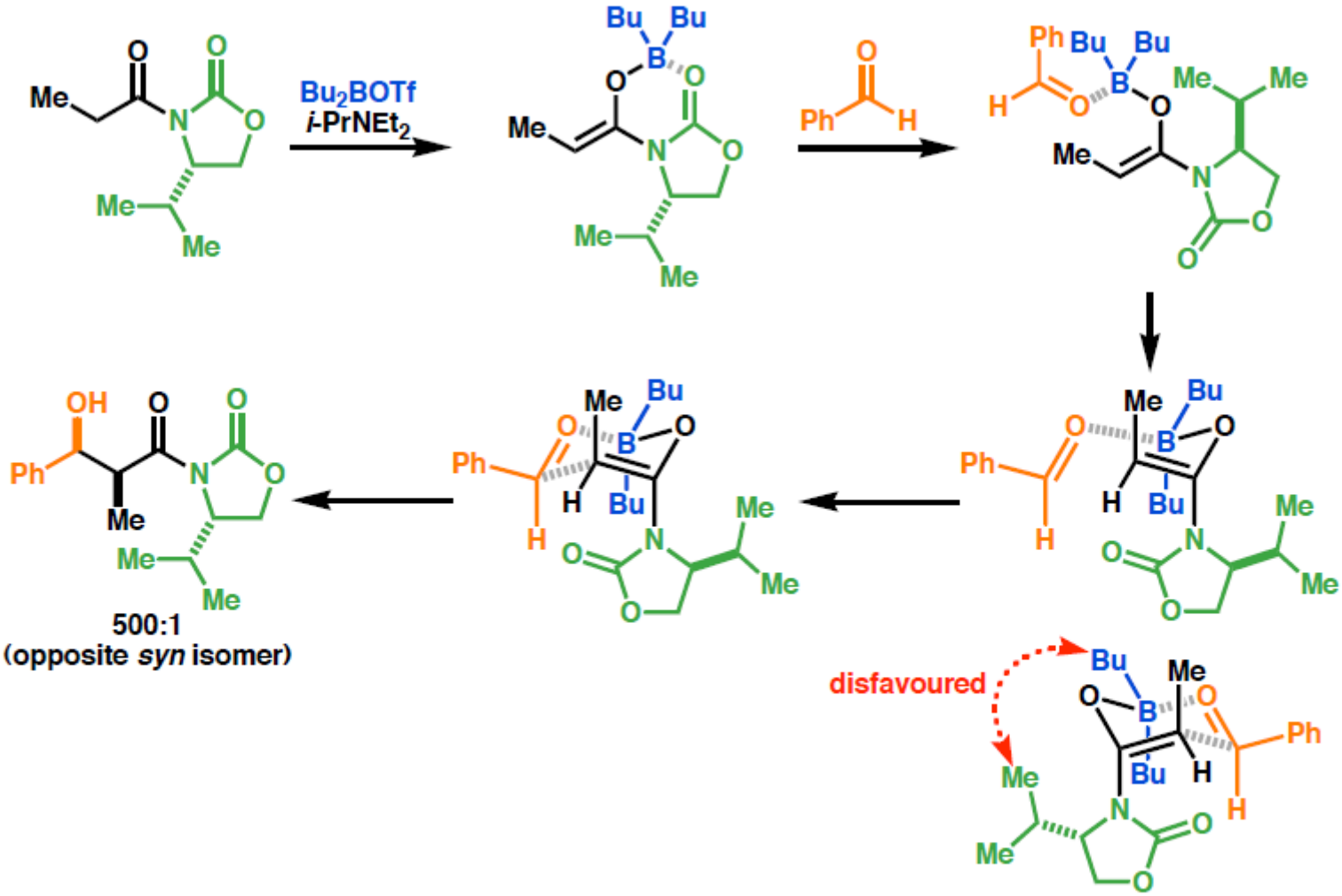


Evans' oxazolidinones - Diels Alder



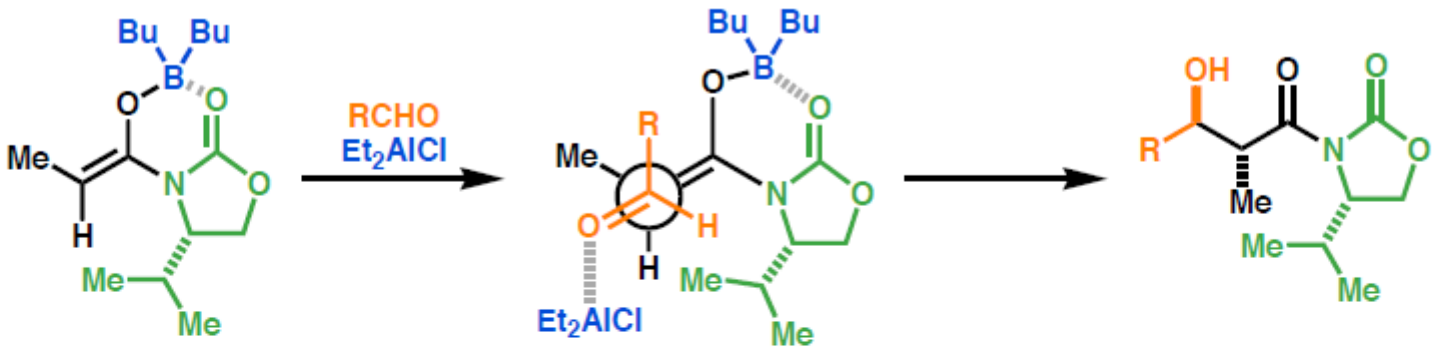
- Coordination to the **Lewis acid** activates **dienophile**
- The **rigid chelate** governs reactive conformation (*s-cis*) as *s-trans* disfavoured
- *iso*-Propyl group blocks bottom face
- Diene's approach maximises secondary orbital overlap and favours ***endo*** product

Evans' oxazolidinones for aldol reactions



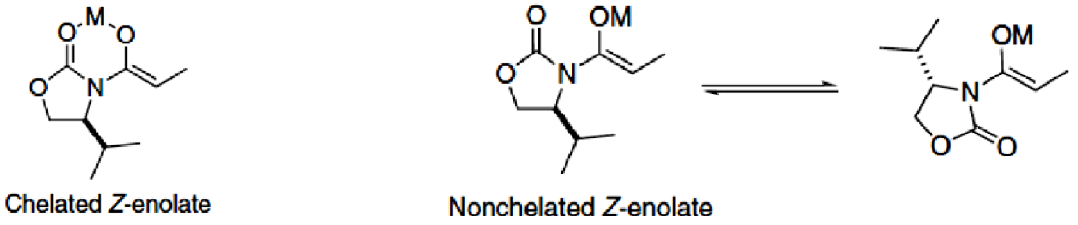
- Initially, boron-enolate formation gives the **chelate**
- This must be broken for the boron to chelate the aldehyde, a requirement of the aldol
- The auxiliary then rotates to minimise steric and electronic repulsions
- Aldehyde approaches from the opposite face to auxiliary

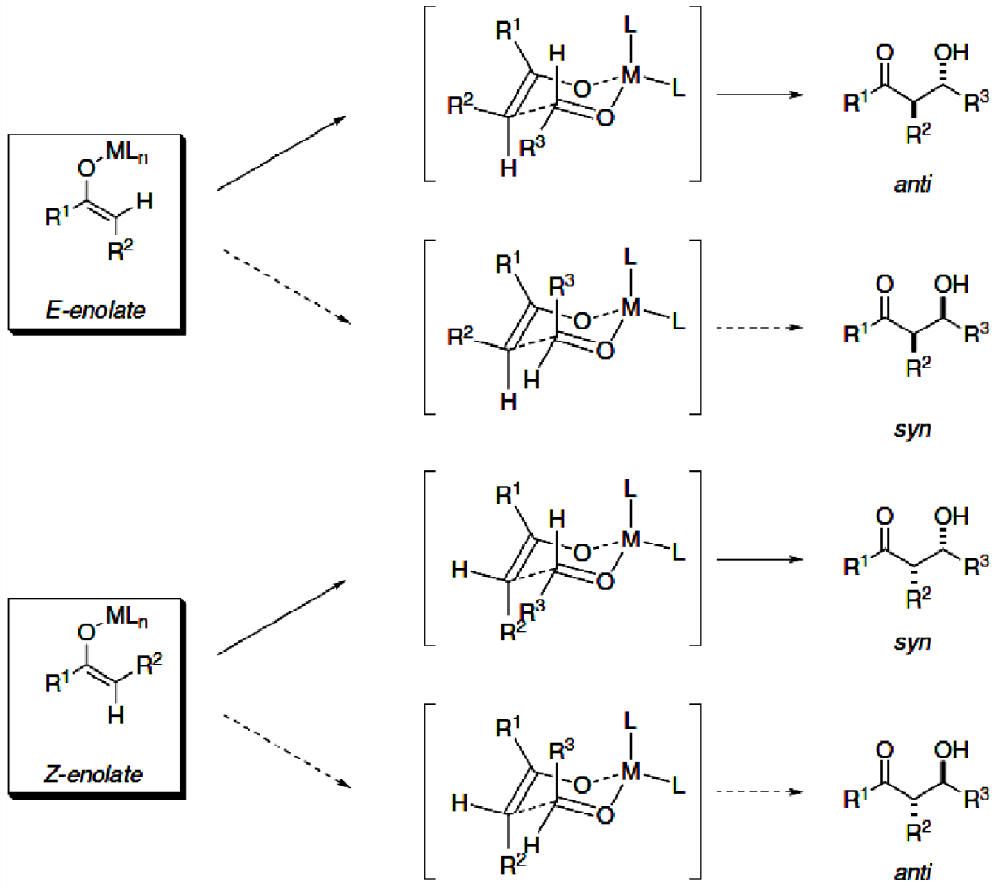
Evans' oxazolidinones reverse selectivity



- The reaction can be made to favour ***anti*** diastereoisomer by forcing it to proceed *via* an **'open' transition state**
- The **aluminium Lewis acid** preferentially coordinates to the aldehyde instead of the boron

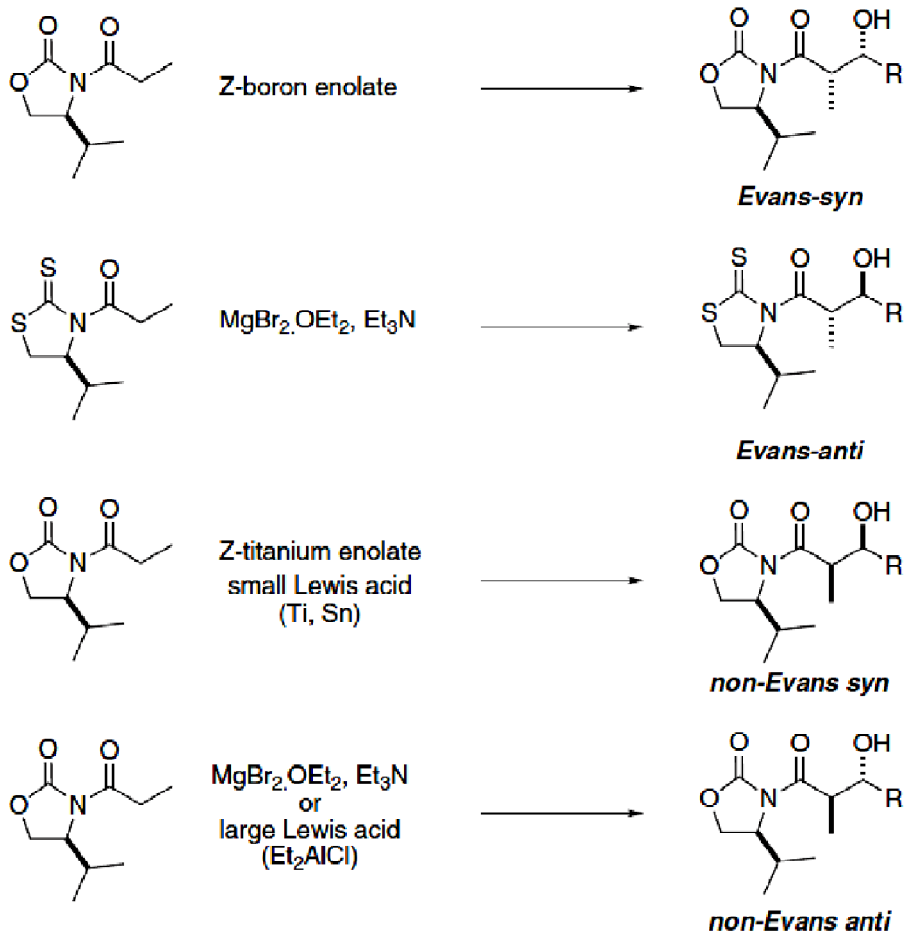
Evans' oxazolidinones for aldol reactions

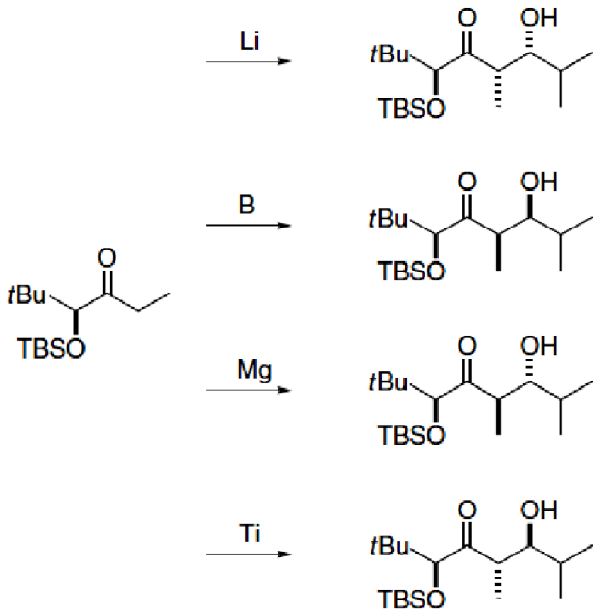




Scheme 3.41 *Zimmermann-Traxler transition states for type 1 aldol reactions*

Evans' oxazolidinones for aldol reactions

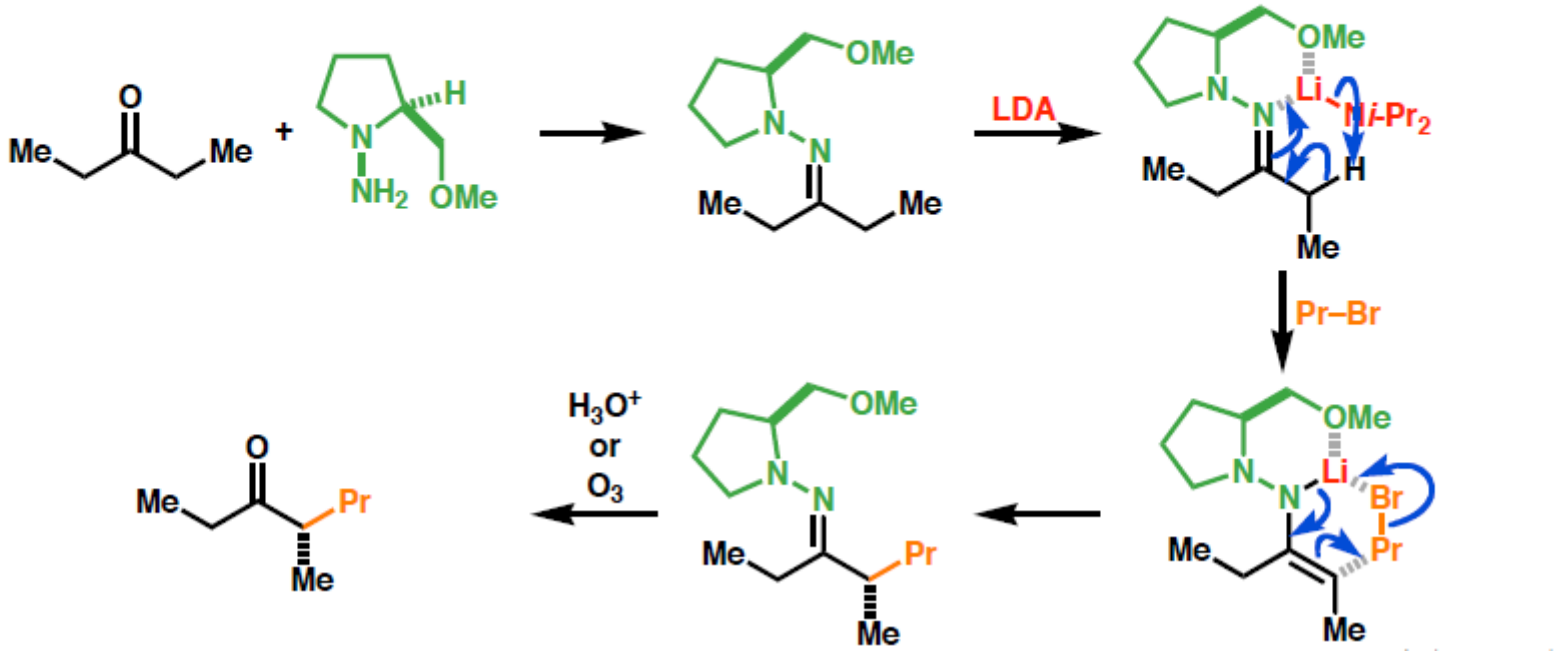




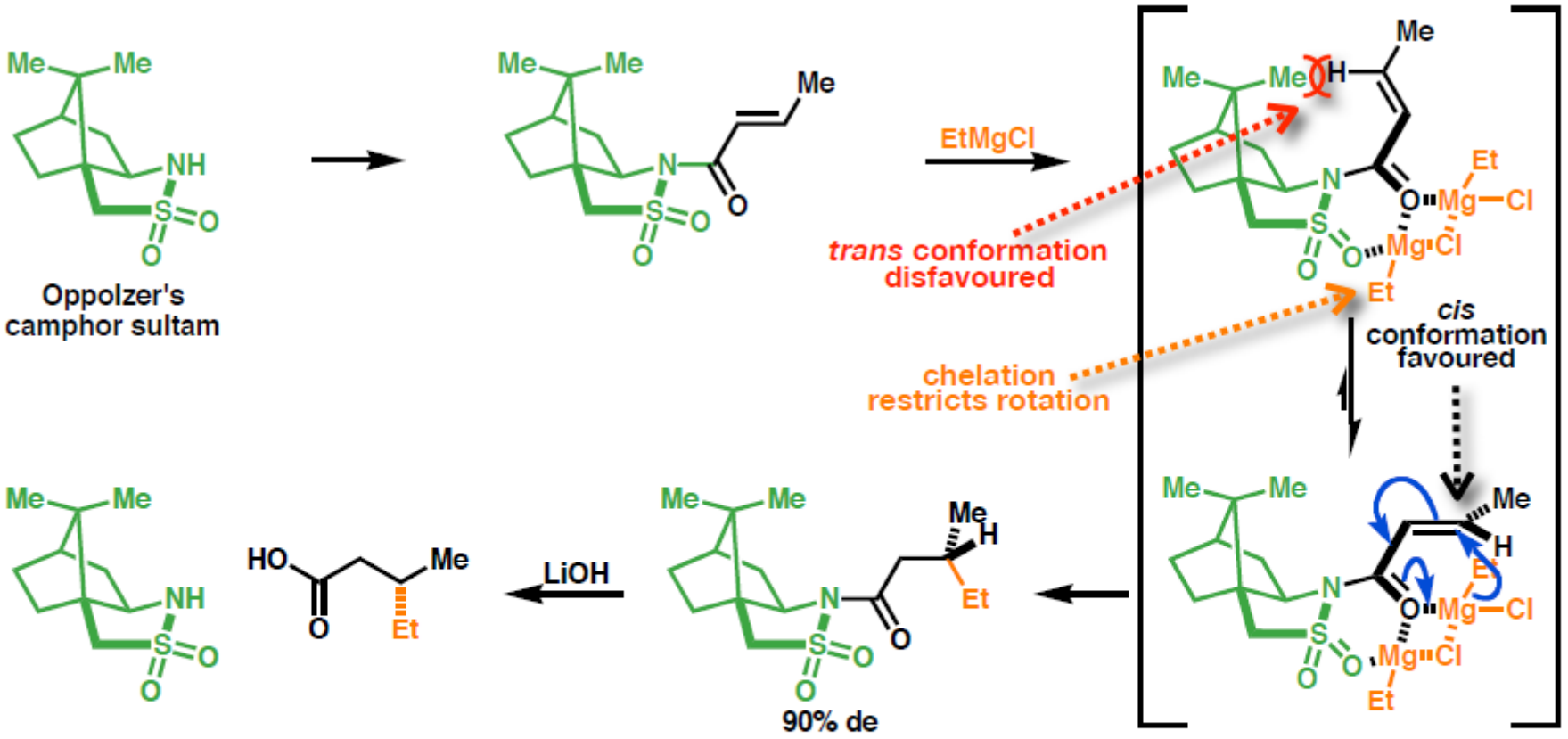
Scheme 3.47 Heathcock aldols

Ender's SAMP/RAMP

- A simple auxiliary for the reaction of the enolates of ketones & aldehydes is Ender's hydrazones, **SAMP** & **RAMP**
- A rigid enolate-like structure allows highly **diastereoselective** reactions
- Hydrolysis is not always possible & the auxiliary must be removed *via* **ozonolysis**

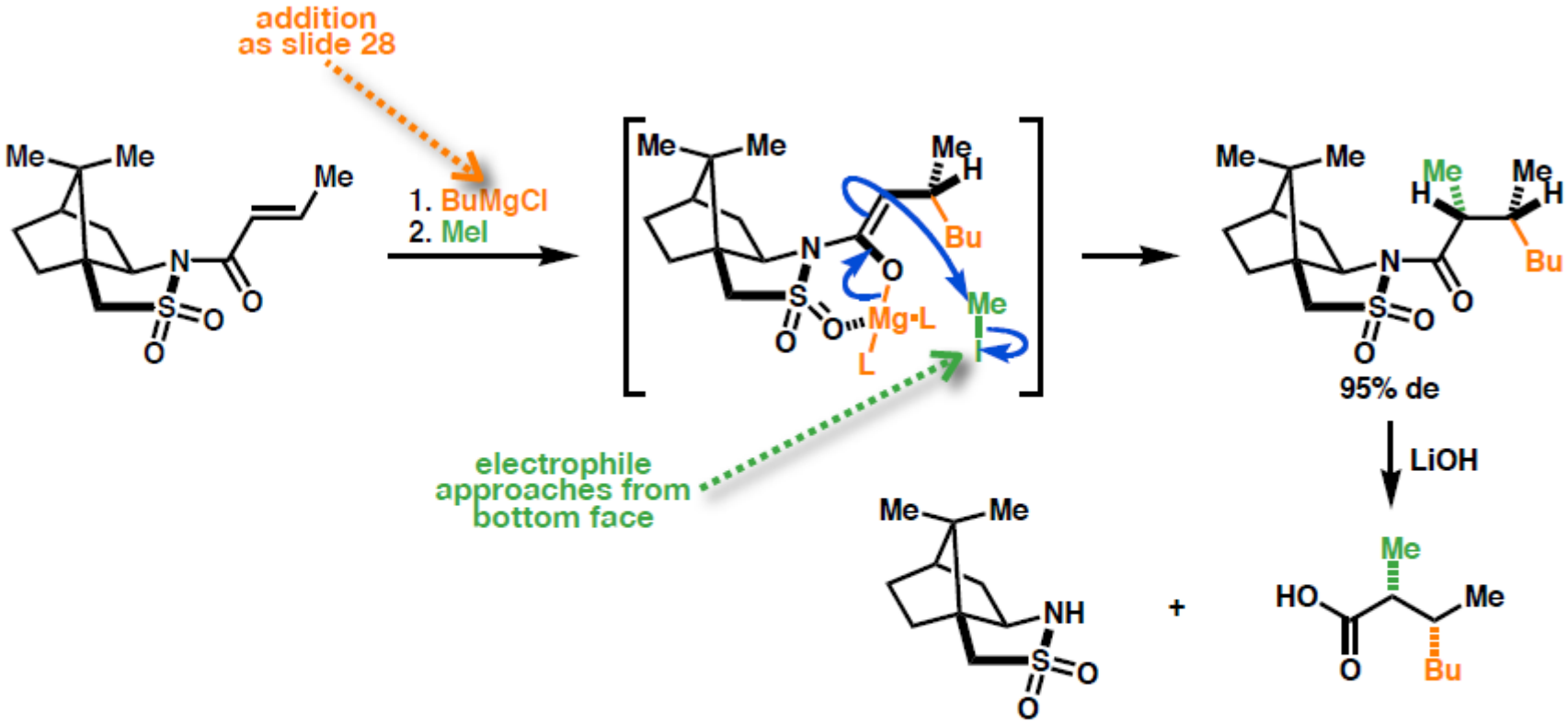


Oppolzer’s sultam



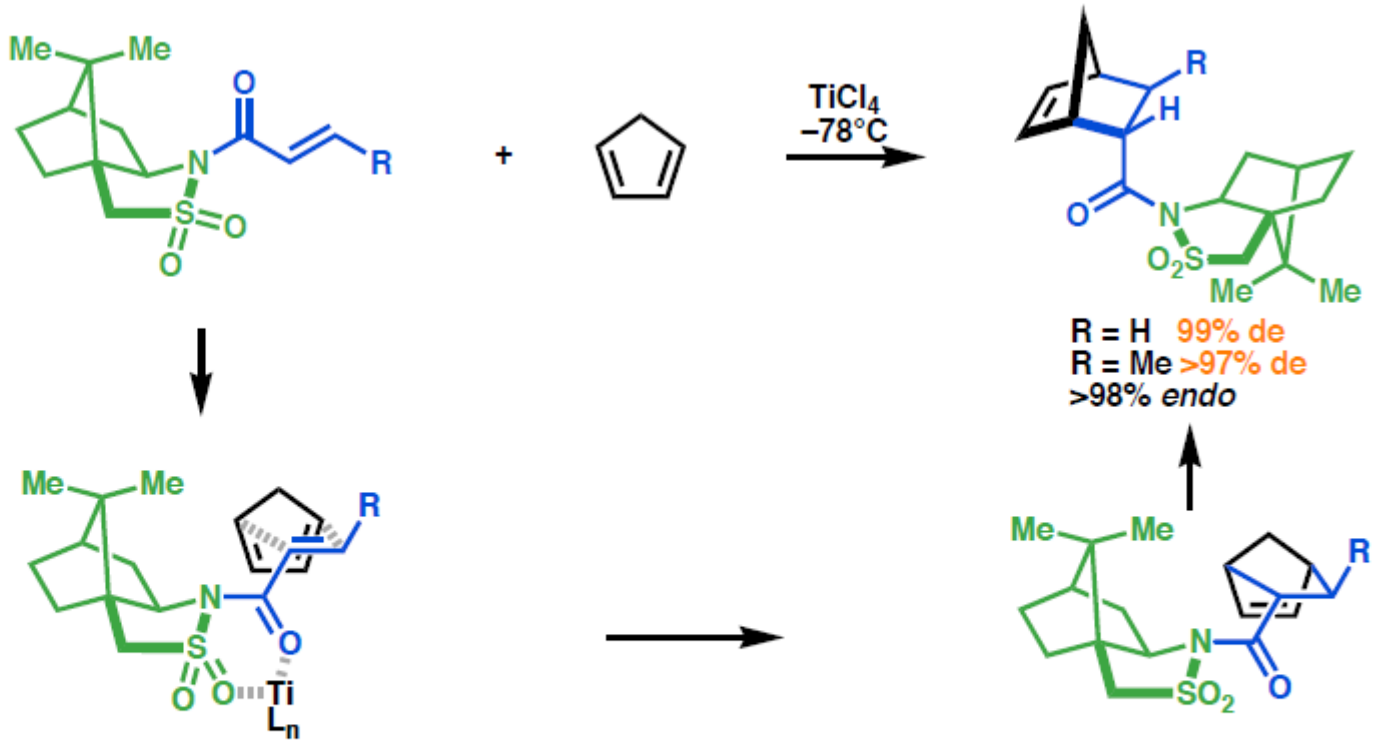
- Possible to use **chiral auxiliary** to control 1,4-nucleophilic addition
- Chelation of amide and sultam oxygens to Mg restricts rotation and favours *cis* conformation
- Addition occurs from most sterically accessible side
- **Chiral auxiliary** readily cleaved (& reused) to give **enantiomerically** pure compound *via* **diastereoselective** reaction

Oppolzer's sultam για ασύμμετρη συζ. προσθήκη



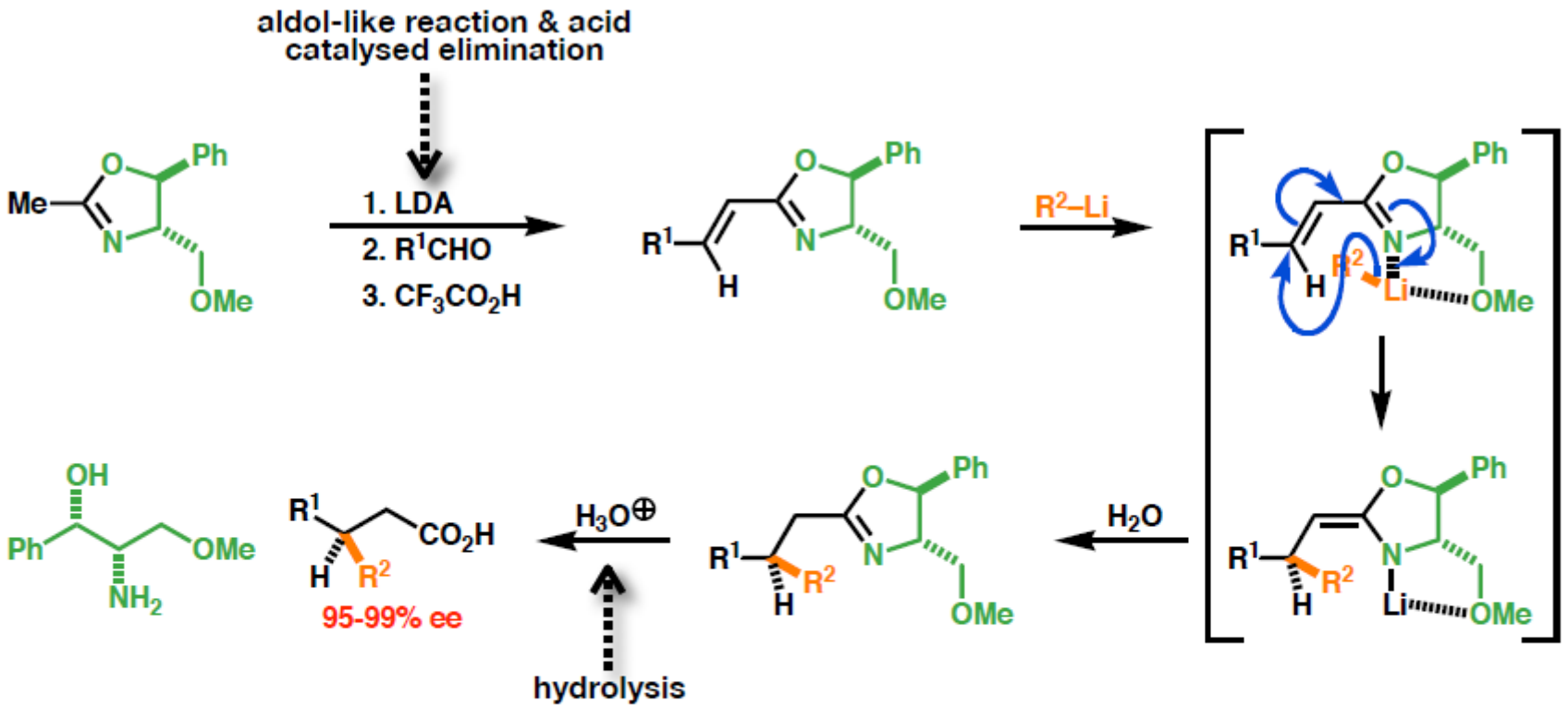
- It possible to utilise 1,4-addition to introduce **two** stereogenic centres
- The first addition (**BuMgBr**) occurs as before to generate an **enolate**
- The enolate can then be trapped by an appropriate electrophile
- Once again the sultam chiral auxiliary controls the face of addition (of **Me**)

Oppolzer’s sultam για ασύμμετρη Diels Alder



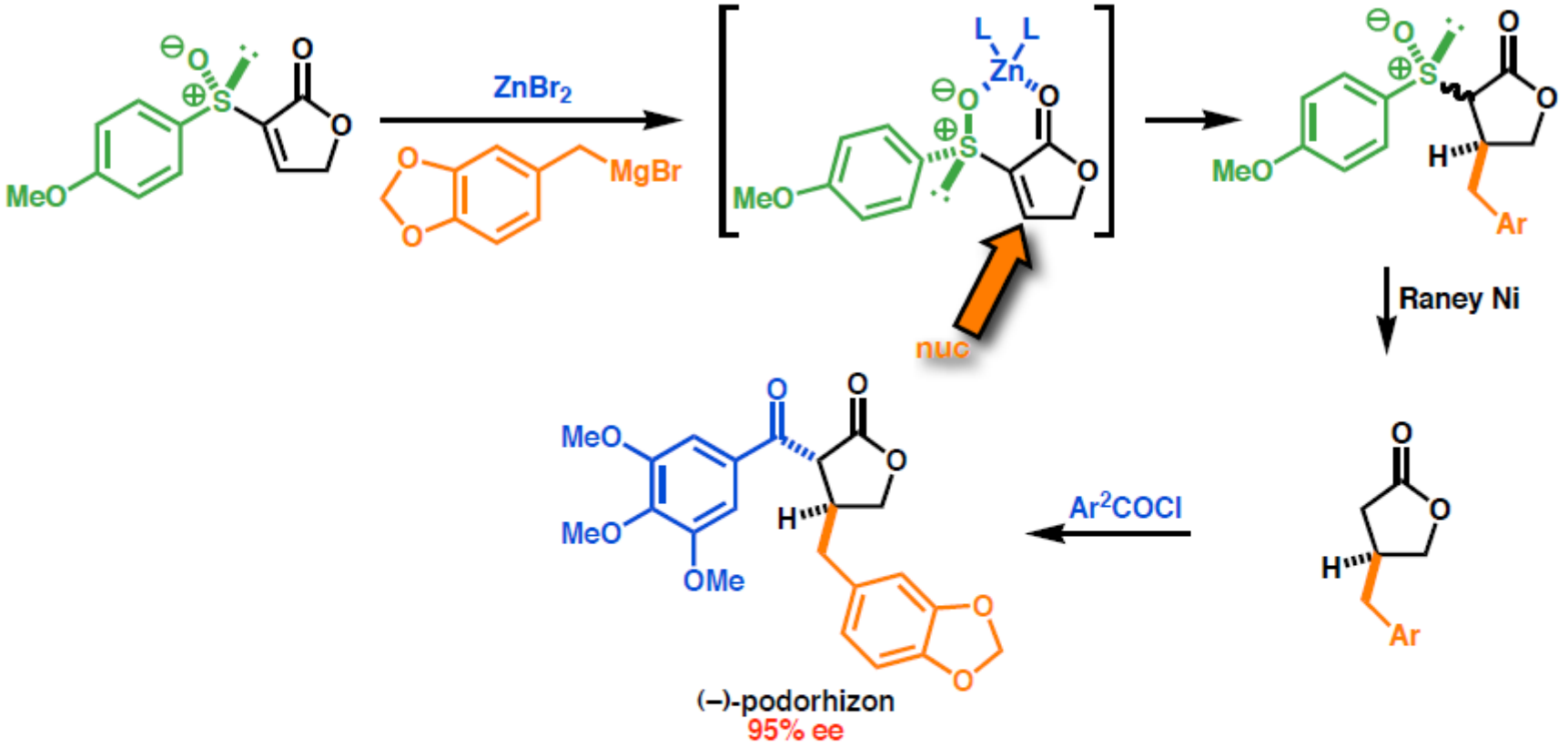
- A range of auxiliaries can be utilised
- Most give good diastereoselectivities

Chiral Oxazolines



- A second chiral auxiliary is the **oxazoline** (5-membered ring) of Meyers'
- It can be prepared from carboxylic acids (normally in 3 steps) or from condensation of the amino alcohol and a nitrile
- As can be seen excellent **enantiomeric excesses** can be achieved *via* a highly **diastereoselective** reaction

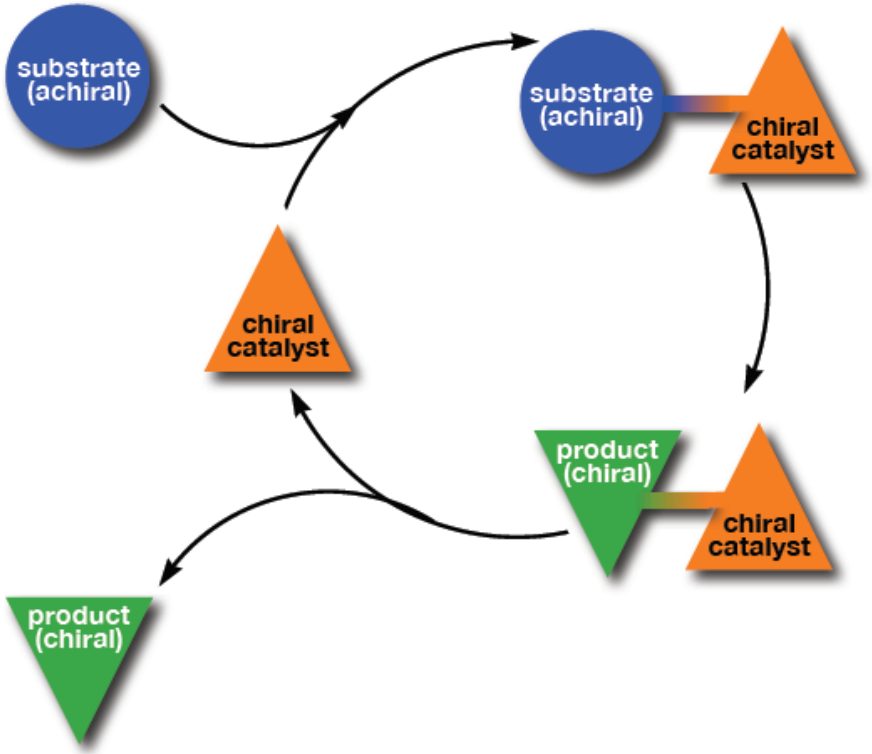
Chiral sulfoxides



- **Sulfoxide** is a good chiral auxiliary; not only does it introduce a stereocentre but it activates the alkene by addition of an extra electron-withdrawing group
- **Lewis acid** tethers groups together to give a rigid cyclic chelate
- **Nucleophile** attacks from opposite face to bulky aryl group
- Sulfoxide is readily removed under reductive conditions
- Simple substrate control of enolate chemistry instals **aryl** group on opposite face to **substituent**

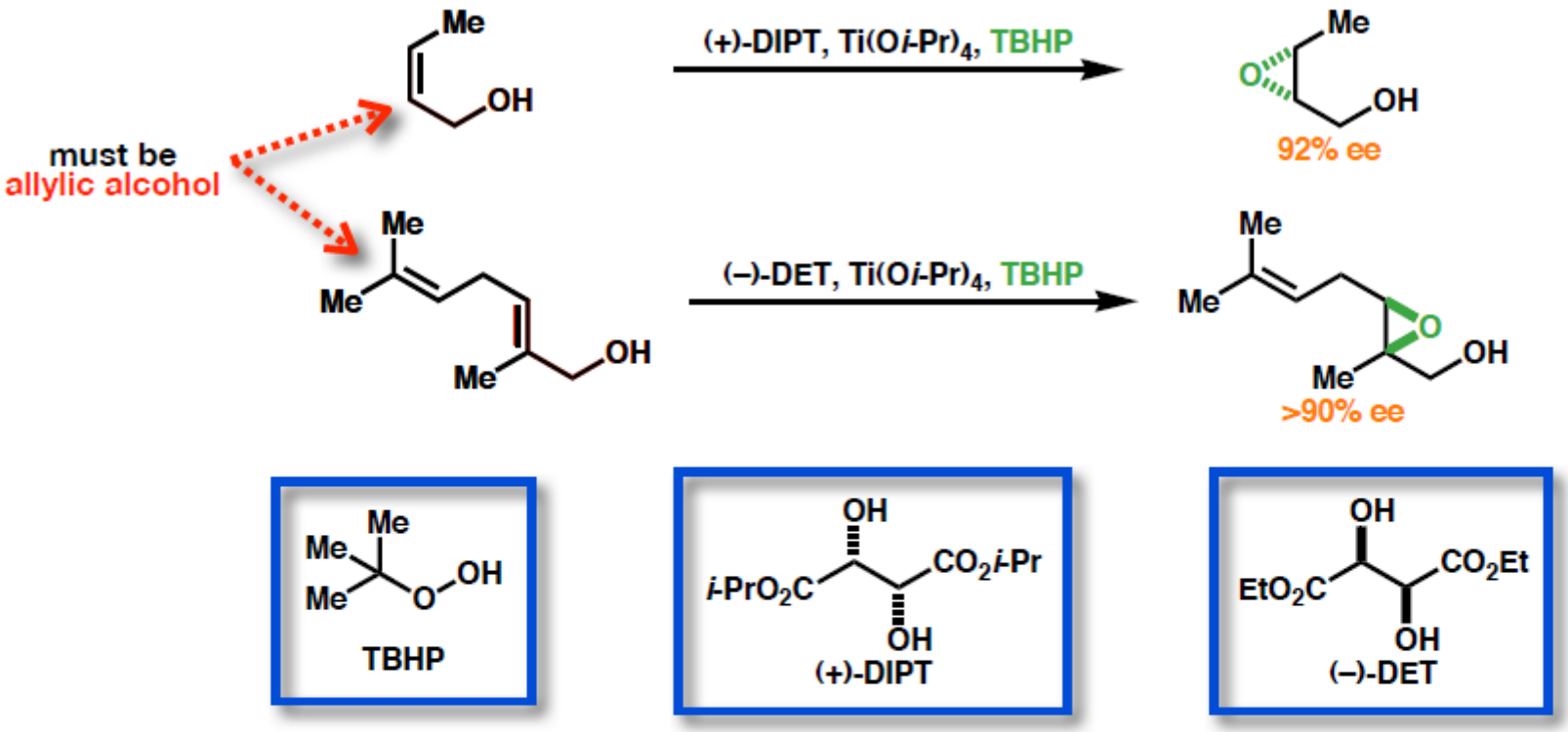
Καταλυτικές μέθοδοι ασύμμετρης σύνθεσης

Stereoselective synthesis: chiral catalysis



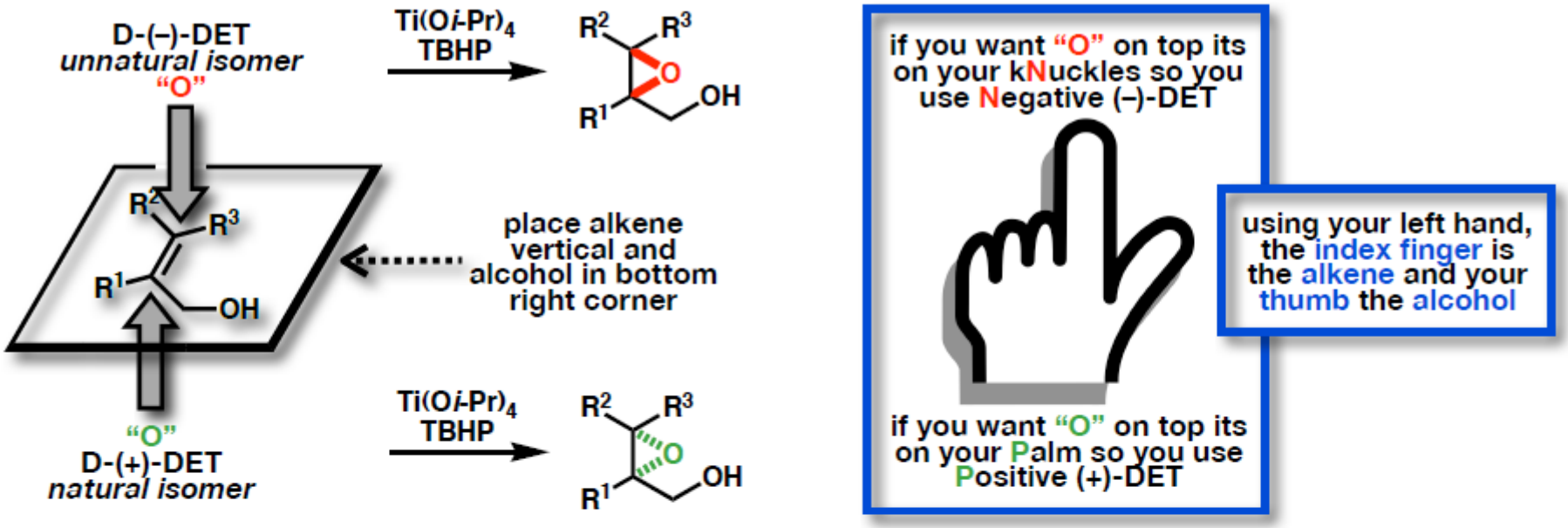
- **Chiral catalysis** - ideally a reagent that accelerates a reaction (without being destroyed) in a chiral environment thus permitting one chiral molecule to generate millions of new chiral molecules...

The Sharpless Asymmetric Epoxidation of Allylic Alcohols

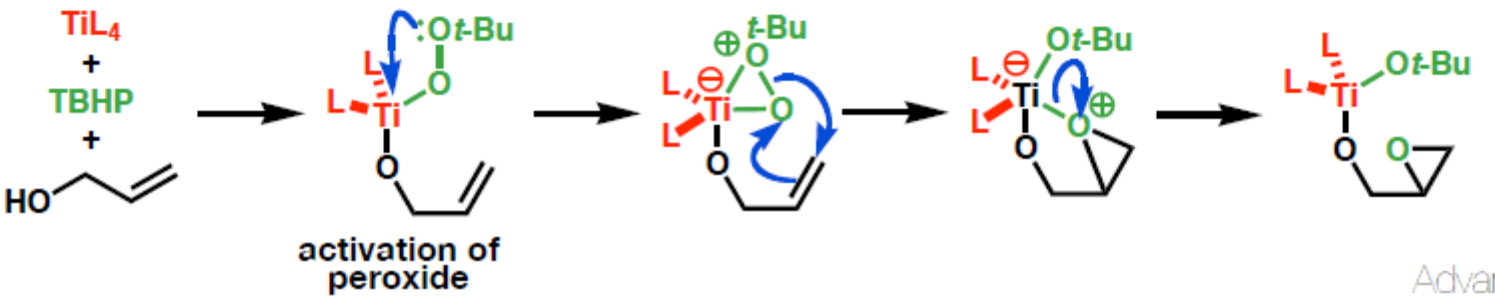


- Sharpless asymmetric epoxidation was the first general asymmetric catalyst
- There are a large number of practical considerations that we will not discuss
- Suffice to say it works for a wide range of compounds in a very predictable manner
- Compounds **must** be **allylic alcohols**
- Second example shows that this limitation allows highly selective reactions

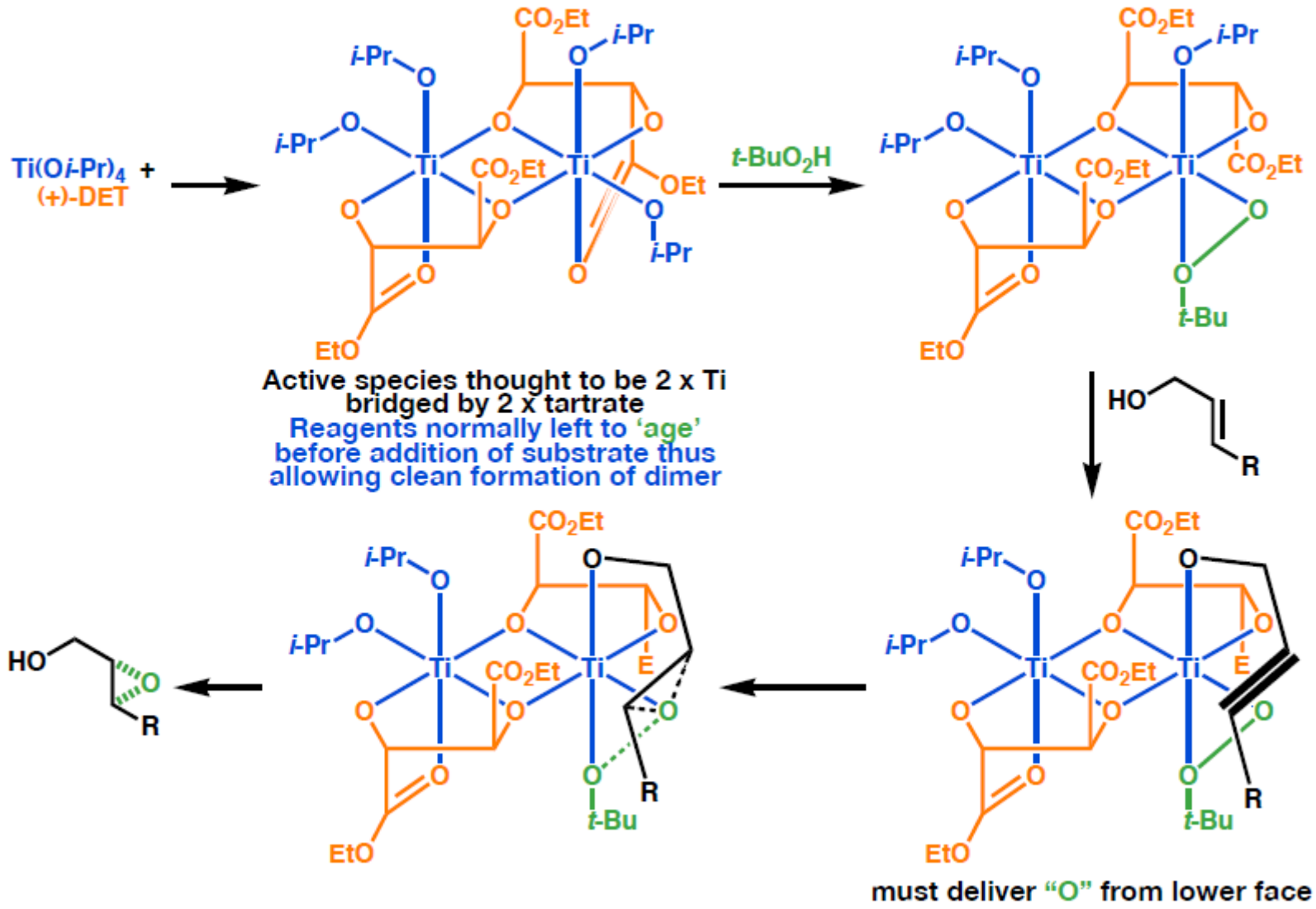
SAE: Predicting product stereochemistry



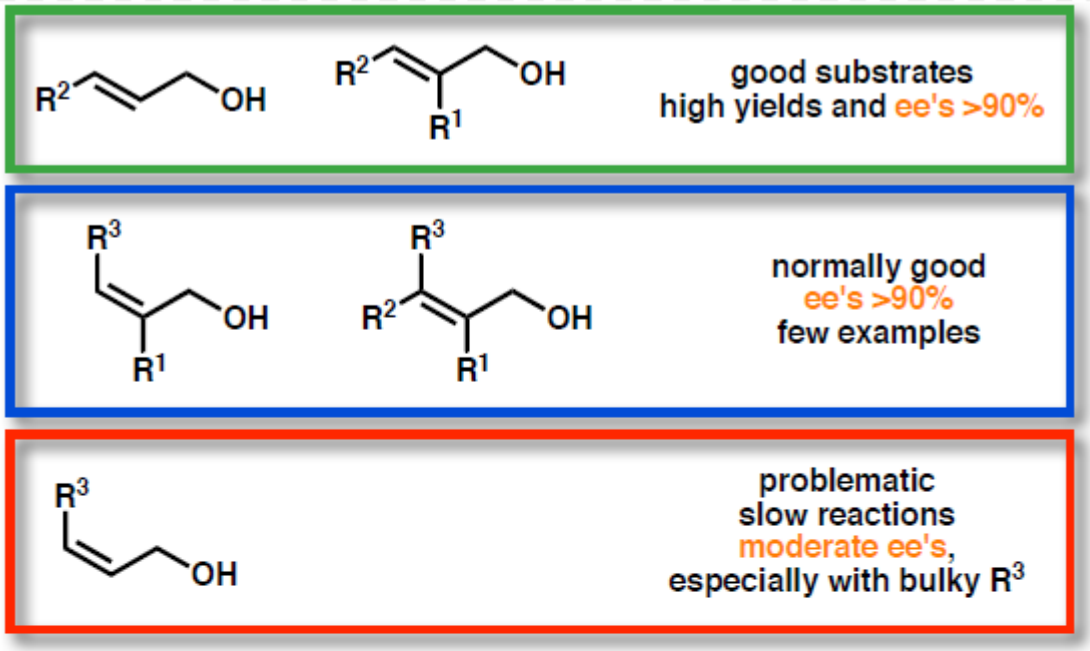
- SAE is highly predictable -- the mnemonic above is accurate for most allylic alcohols
- To understand where this comes from we must look at the mechanism
- A simplified version of the basic epoxidation is given below



SAE: Mchanism

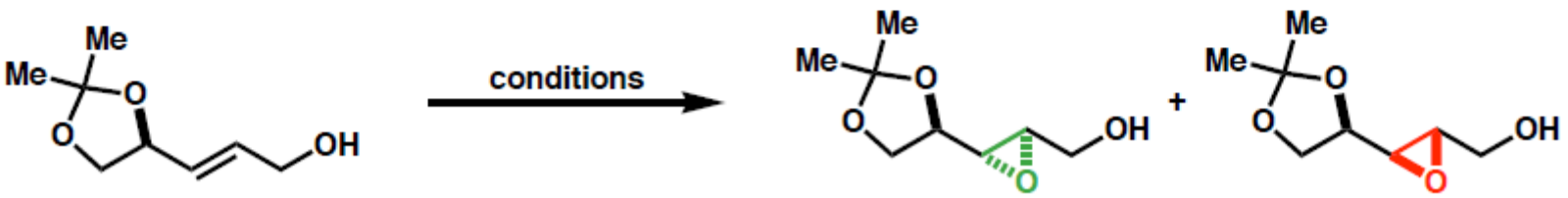


SAE: Substrate scope

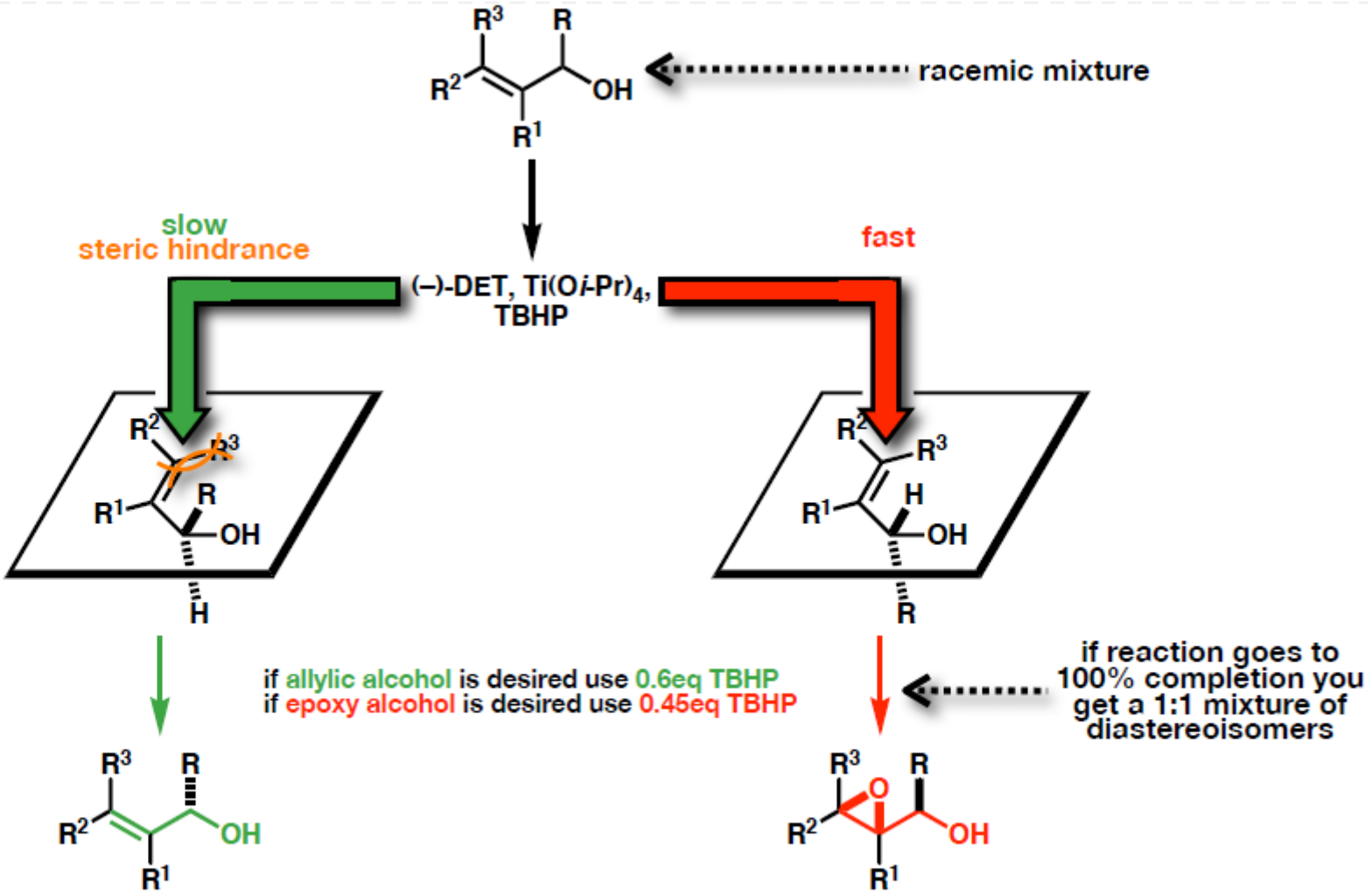


- SAE works for a wide range of allylic alcohols
- Only *cis* di-substituted alkenes appear to be problematic

- Example below shows that SAE can over-ride the inherent selectivity of a substrate
- Furthermore, it demonstrates the concept of ***matched*** & ***mismatched***
- When the catalyst & substrate reinforce each other spectacular (or *matched*) results are achieved

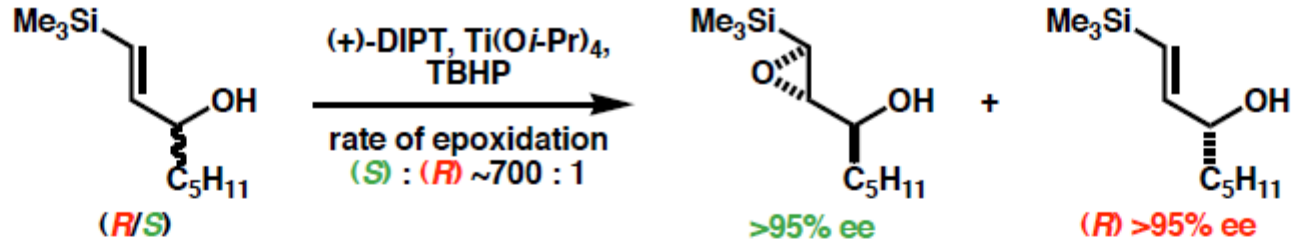


SAE: Application in Kinetic Resolution

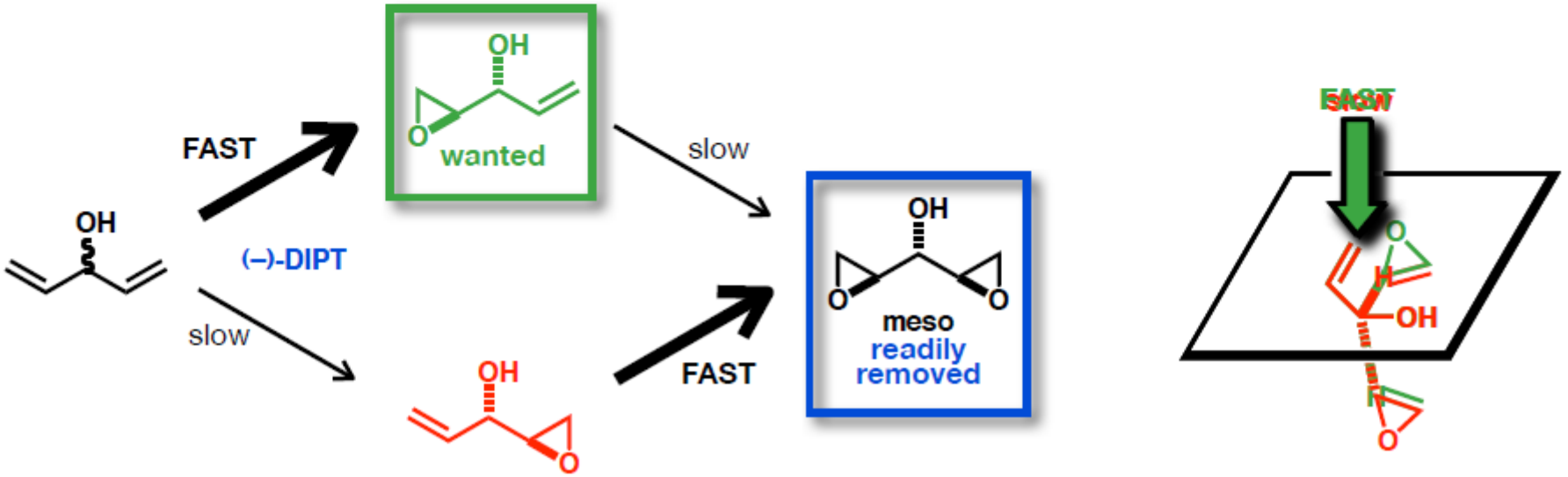


- Both enantiomers should be epoxidised from same face
- But **rate** of epoxidation is different
- If sufficient rate difference then stop the reaction at 50% conversion

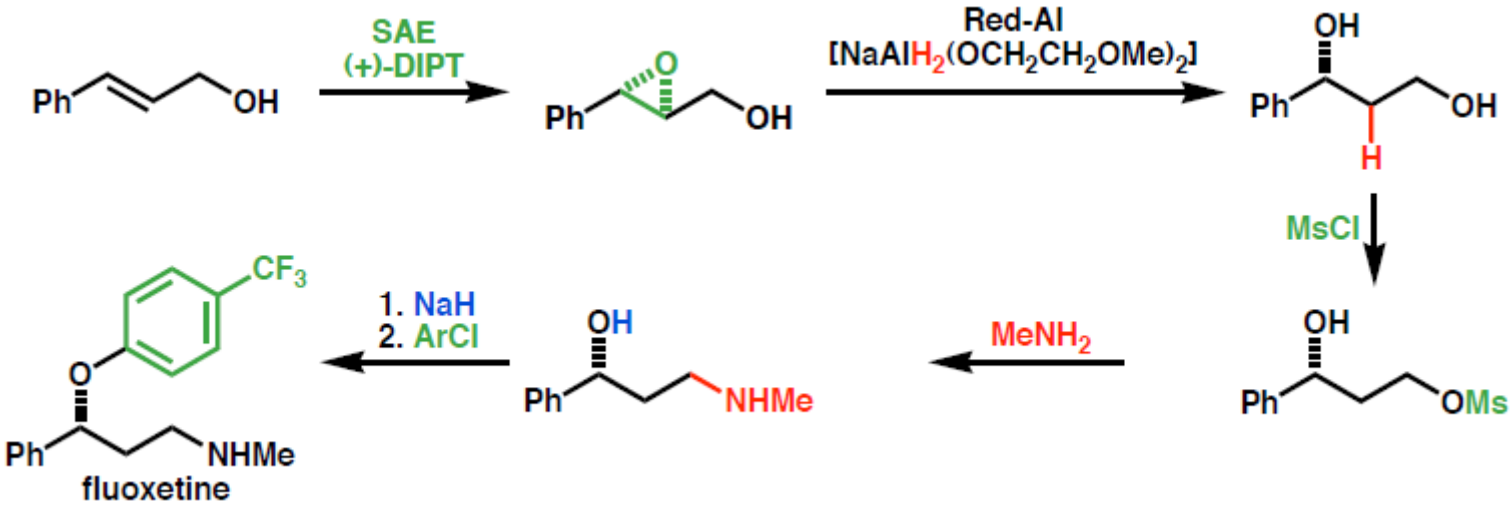
SAE: Application in Kinetic Resolution & Desymmetrisation

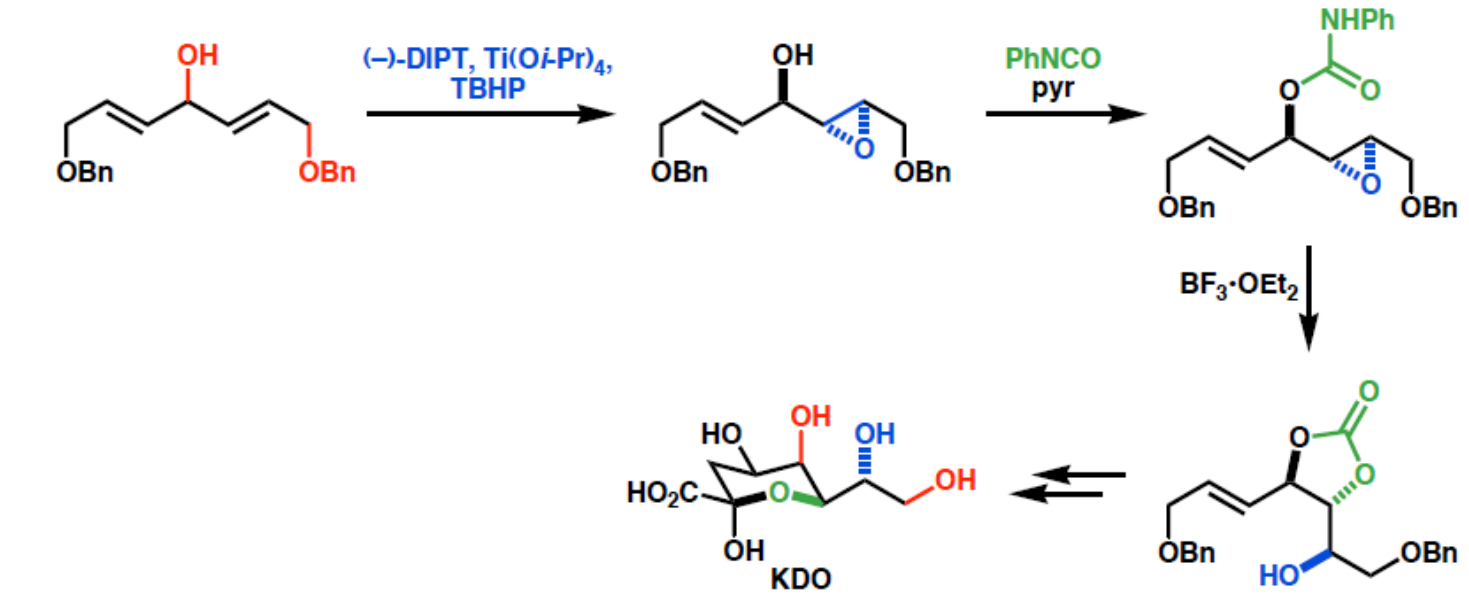


- Kinetic resolution normally works efficiently
- The problem with kinetic resolution is that is can only give a maximum yield of 50%
- **Desymmetrisation** of a ***meso*** compound allows 100% yield
- Effectively, the same as two kinetic resolutions, first desymmetrises compound second removes unwanted enantiomer
- ee of desired product increases with time (84% ee 3hrs → >97% 140hrs)



SAE: Applications in the Synthesis

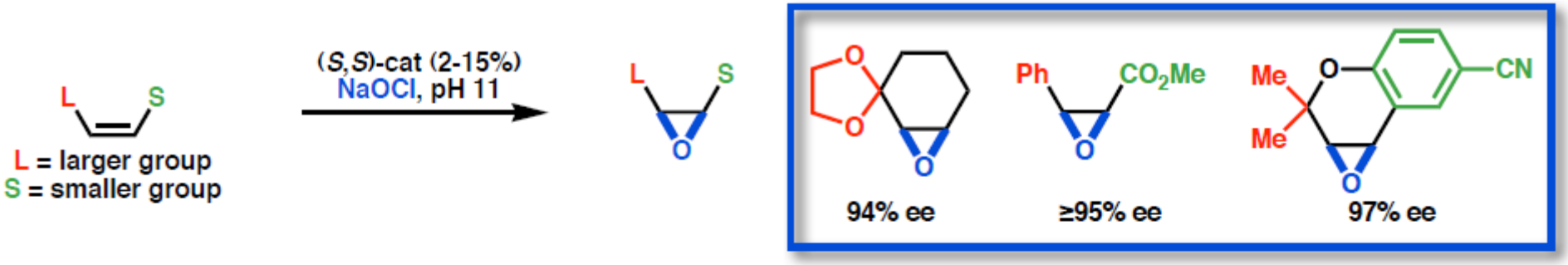


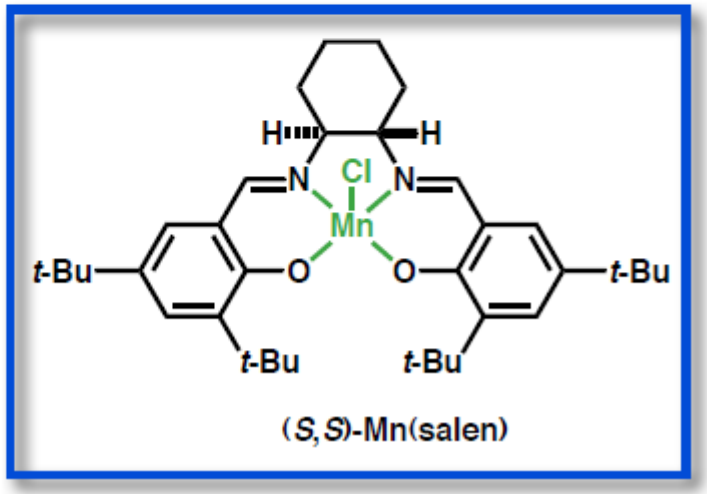


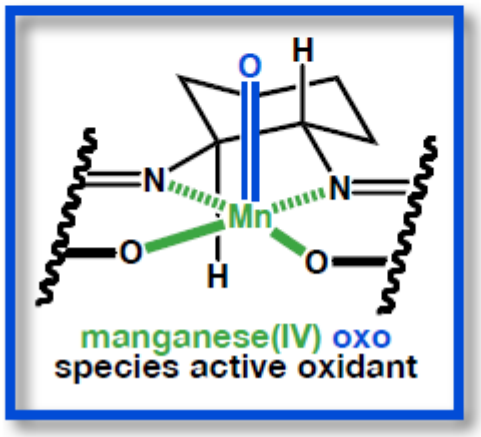
The Jacobsen-Katsuki epoxidation with salen complexes

Works best with cyclic di-substituted simple alkenes

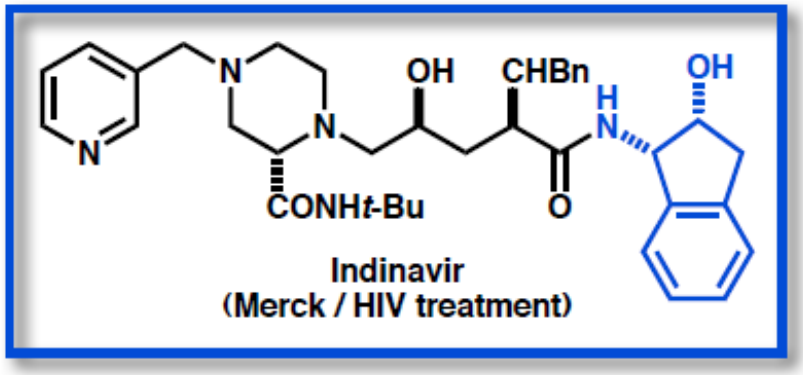
Mechanism proceeds via radicals

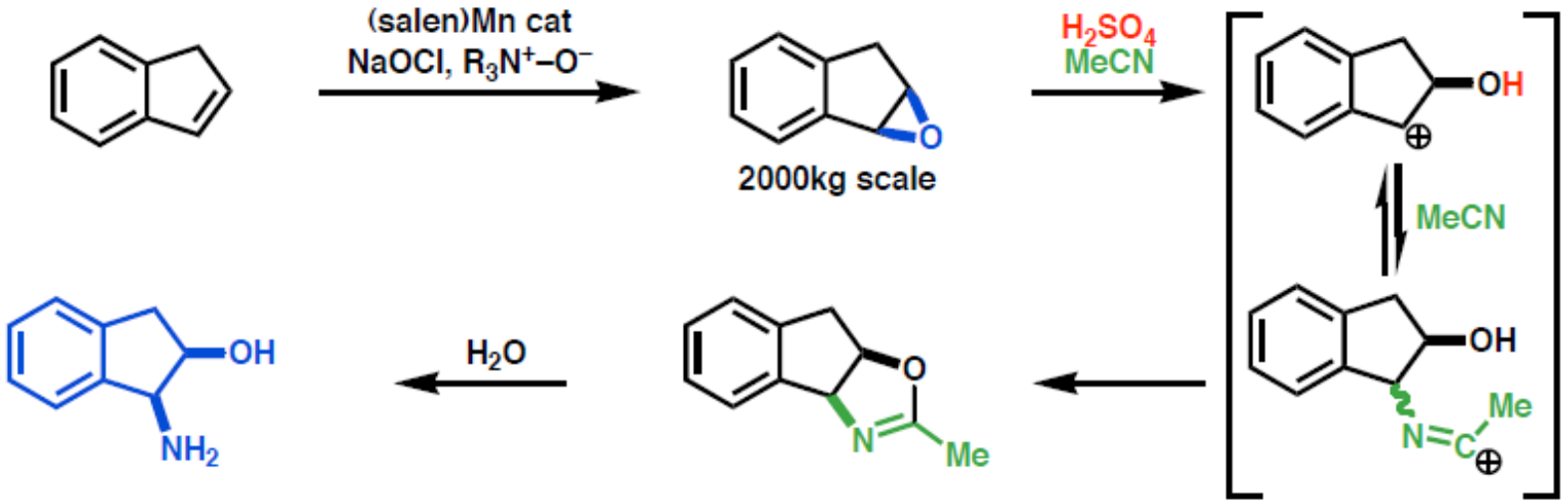






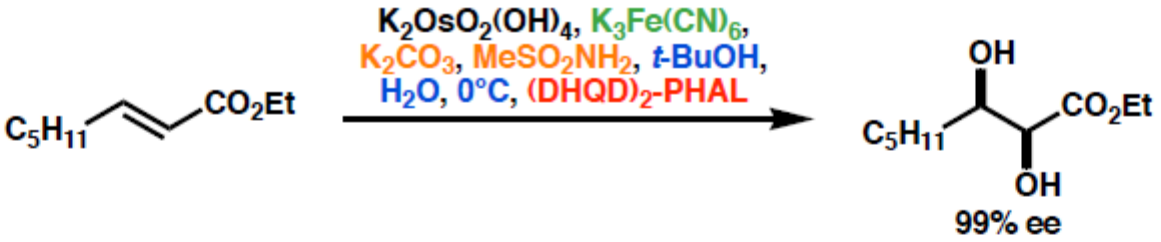
The Jacobsen-Katsuki epoxidation: Example in Synthesis



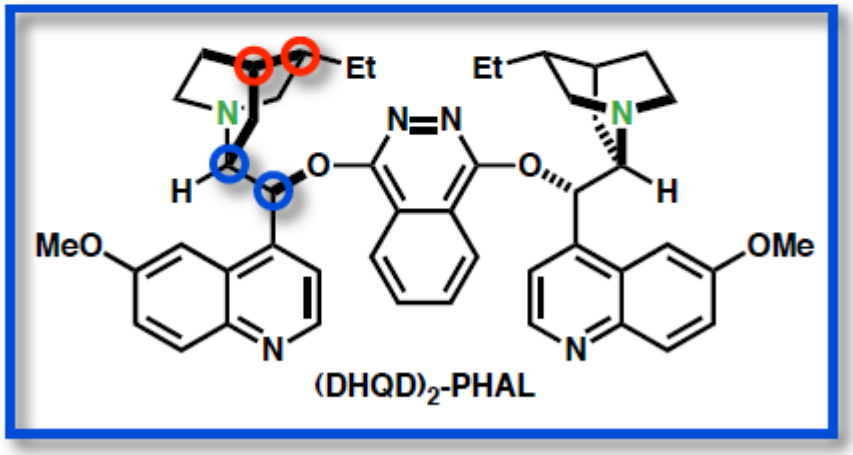


- This example demonstrates the industrial potential of such catalytic systems

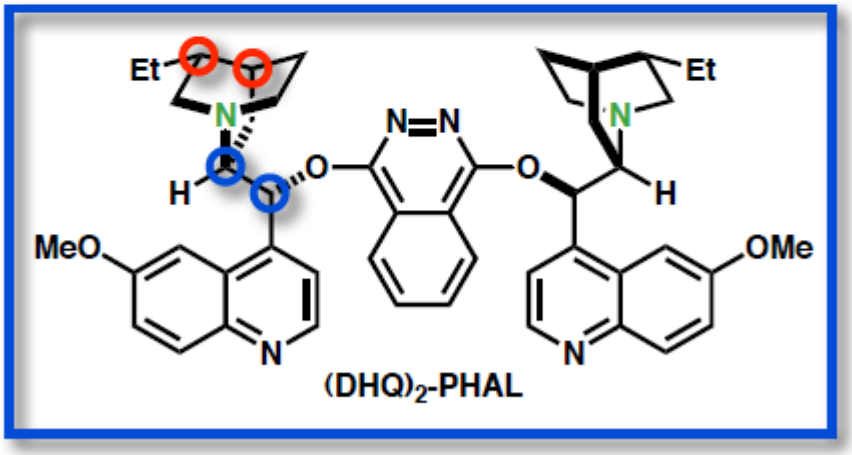
The Sharpless Asymmetric Dihydroxylation



- Looks complicated but isn't too bad...
- The active, catalytic, **oxidant** is **$K_2OsO_2(OH)_4$** - OsO_4 is too volatile & toxic
- **$K_3Fe(CN)_6$** is the **stoichiometric oxidant**
- **K_2CO_3** & **$MeSO_2NH_2$** accelerate the reaction
- Normally use a biphasic **solvent** system
- And the two **ligands** are...



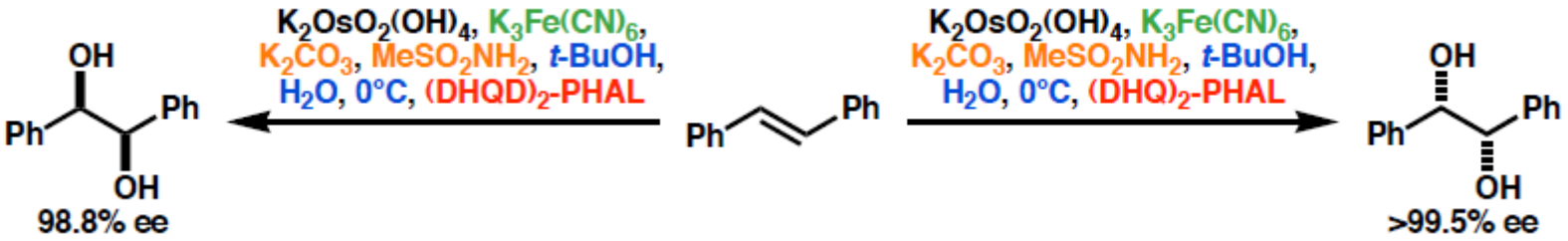
$(DHQD)_2$-PHAL

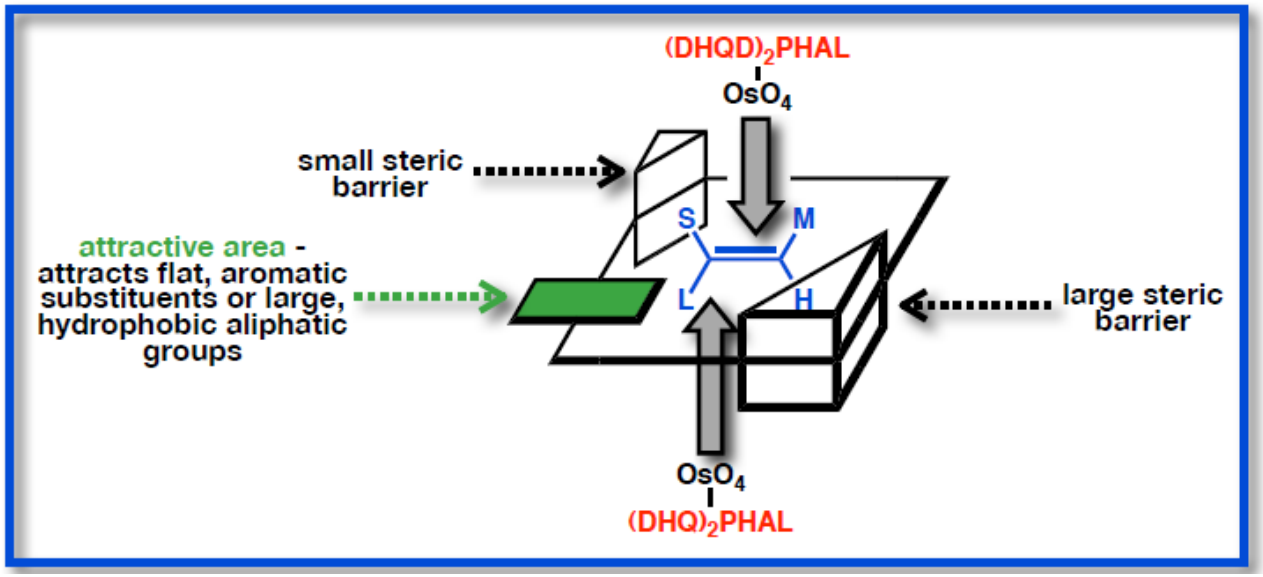


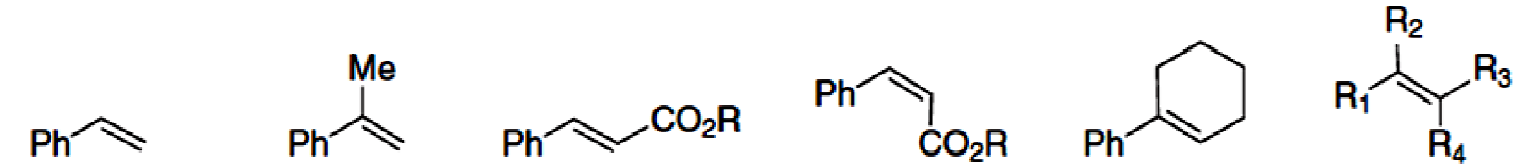
$(DHQ)_2$-PHAL

- Ligands are pseudo-enantiomers (only blue centres are inverted; red are not)
- They act if they were enantiomers (see slide 26)
- Coordinate to the metal *via* the green nitrogen

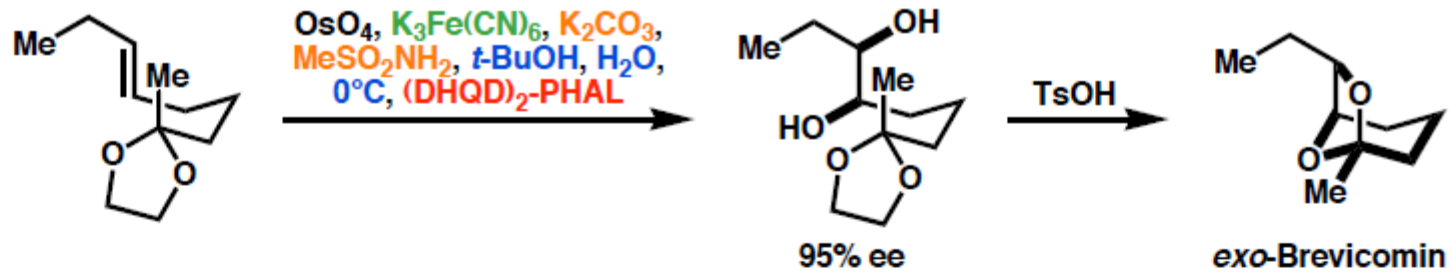
The Sharpless Asymmetric Dihydroxylation: Substrate scope





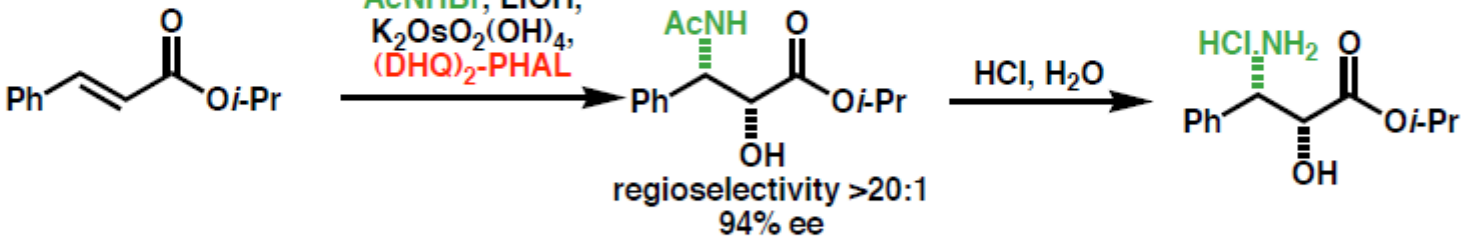


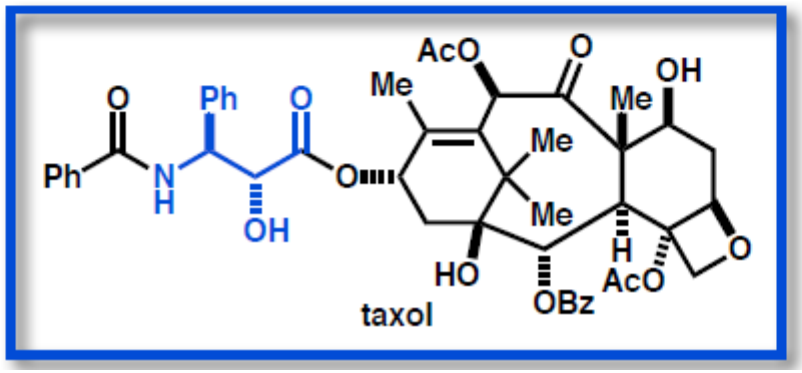
The Sharpless Asymmetric Aminohydroxylation



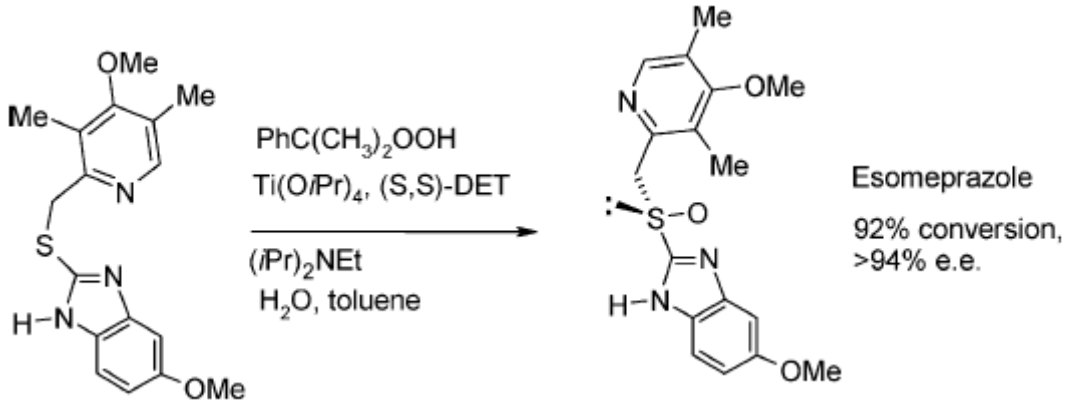
- The simple example above shows the power of the SAD reaction in synthesis

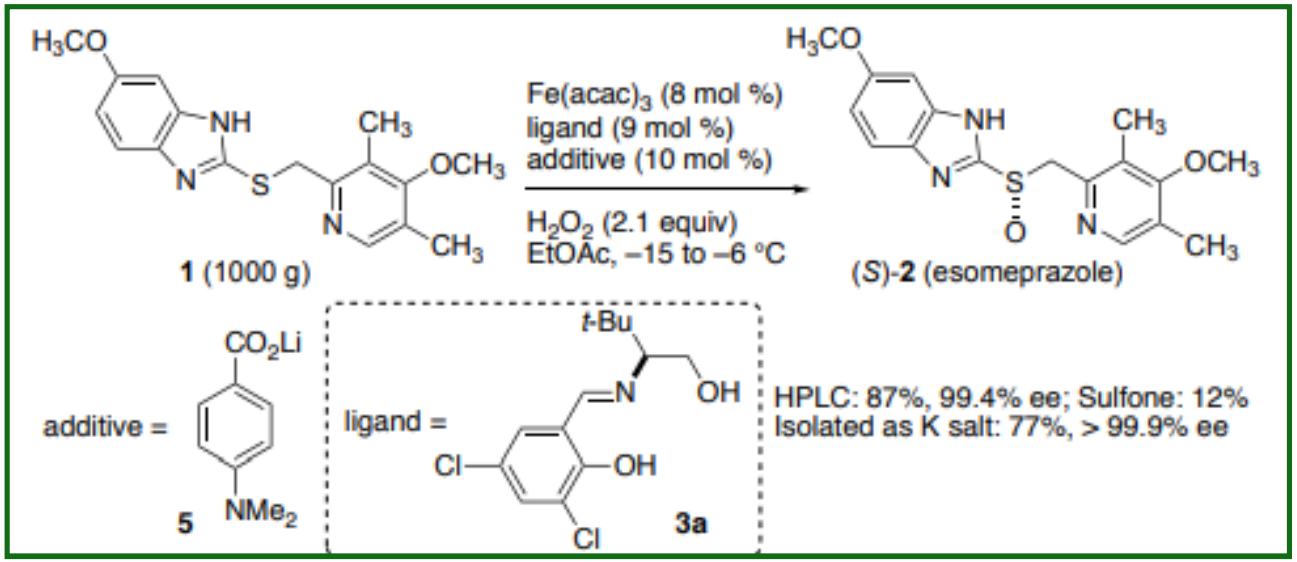
- A variant has now been developed that permits **aminohydrodroxylation**
- Used in the semi-synthesis of Taxol



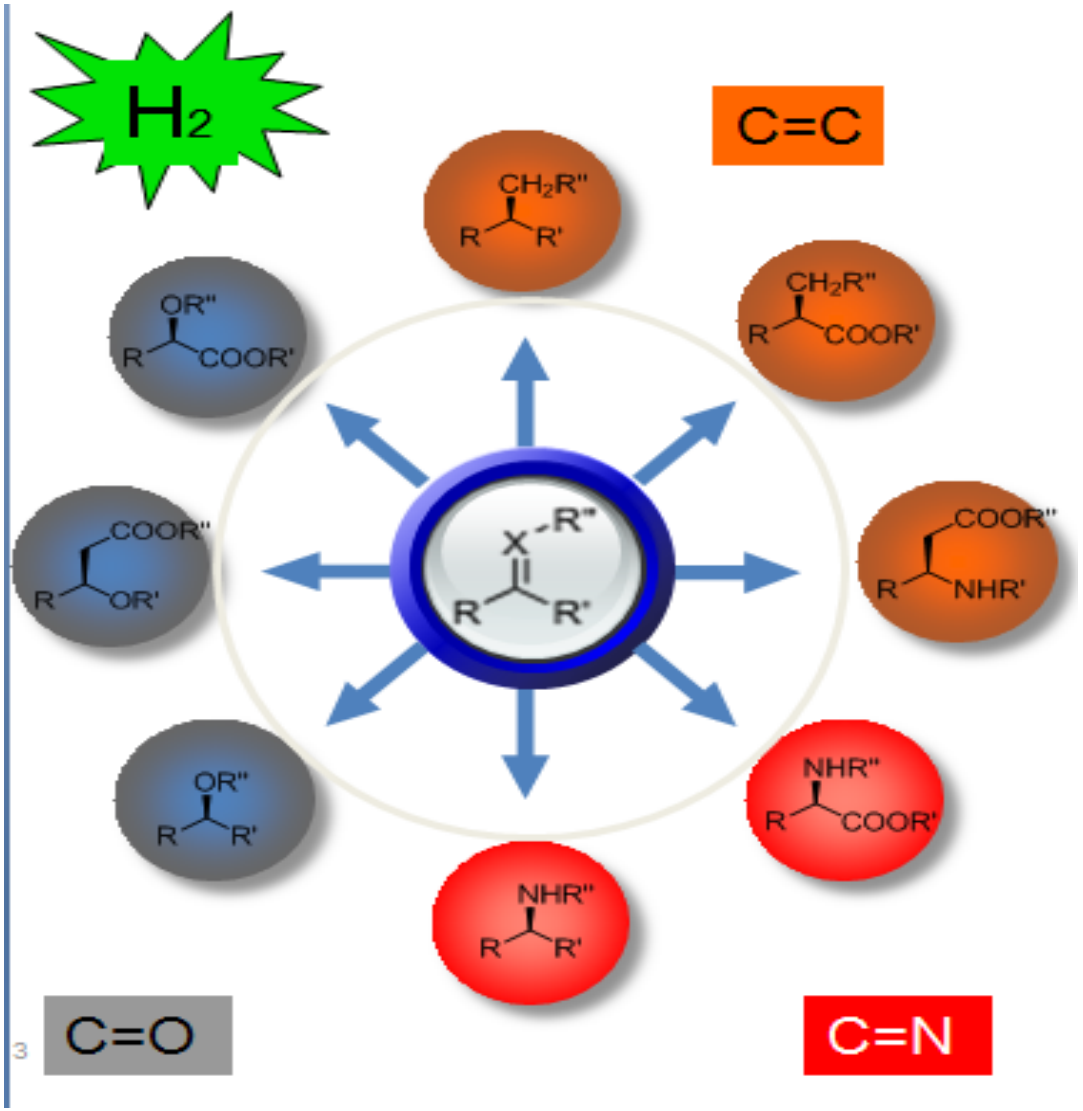


Asymmetric sulfoxidation

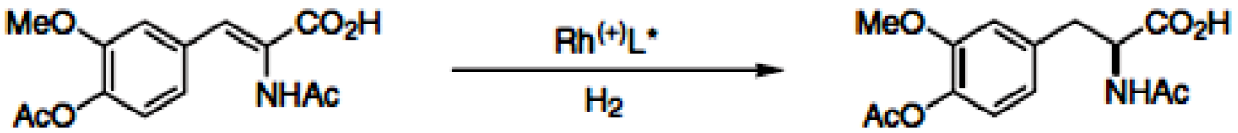




Asymmetric Hydrogenation



Asymmetric Hydrogenation

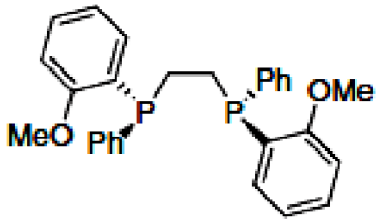


Kagan, 1972

DIOP

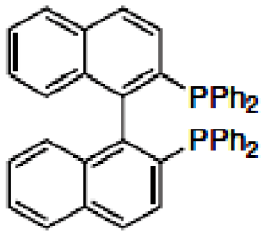
51% ee

DIPAMP-Rh
(Knowles, 1977)



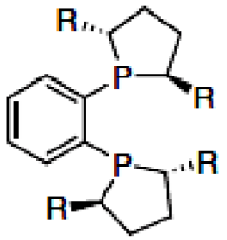
Enamides: ~95% ee
Enol derivatives: ~90% ee
Unsats: ~88% ee

BINAP-Ru or -Rh
(Noyori, 1980)



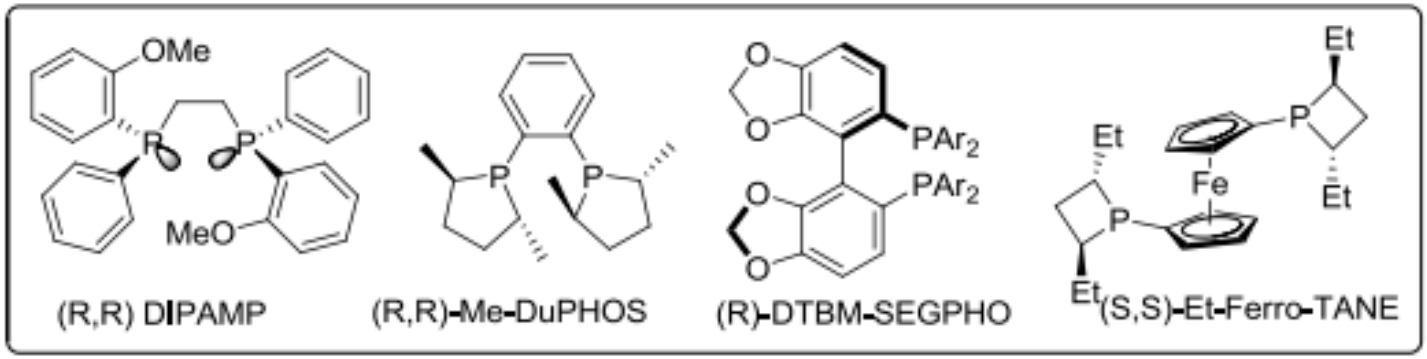
Enamides: ~98% ee
Enol derivatives: ~95% ee
Unsats: ~90% ee

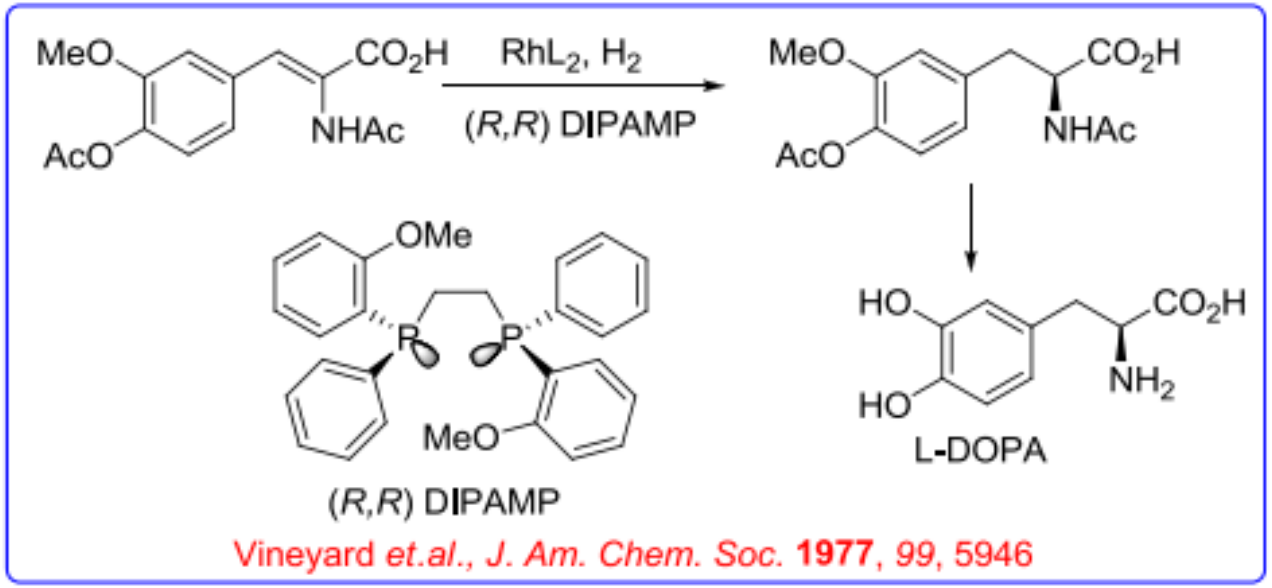
DuPHOS-Rh
(Burk, 1991)



Enamides: ~99% ee
Enol derivatives: ~95% ee
Unsats: ~98% ee

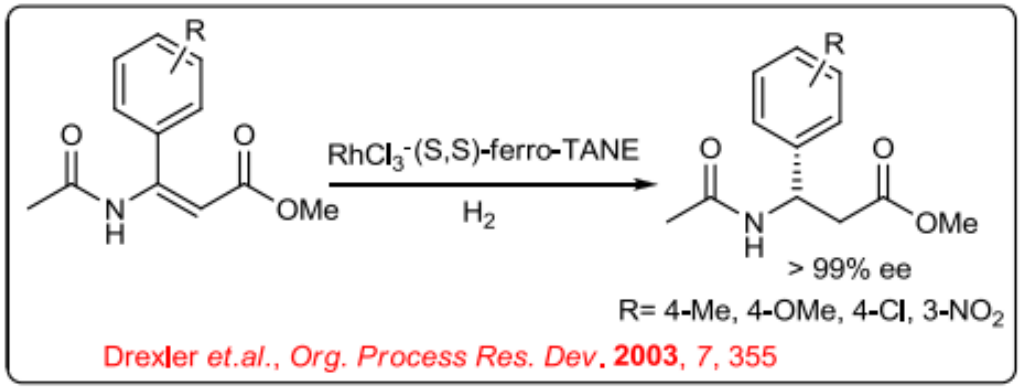
Asymmetric Hydrogenation of α,β-unsaturated α-aminoacids

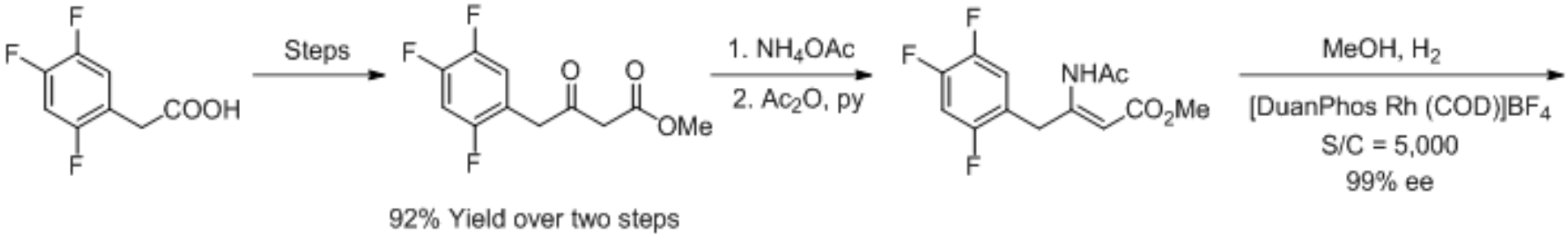


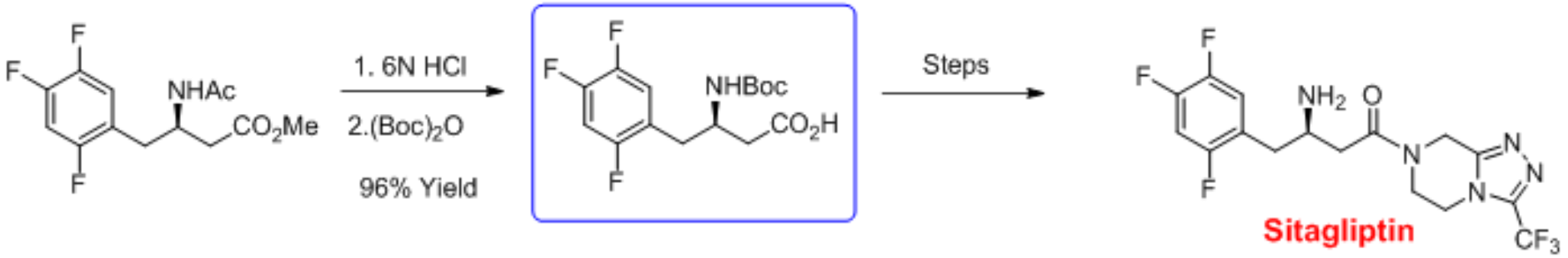


Vineyard *et.al.*, *J. Am. Chem. Soc.* **1977**, *99*, 5946

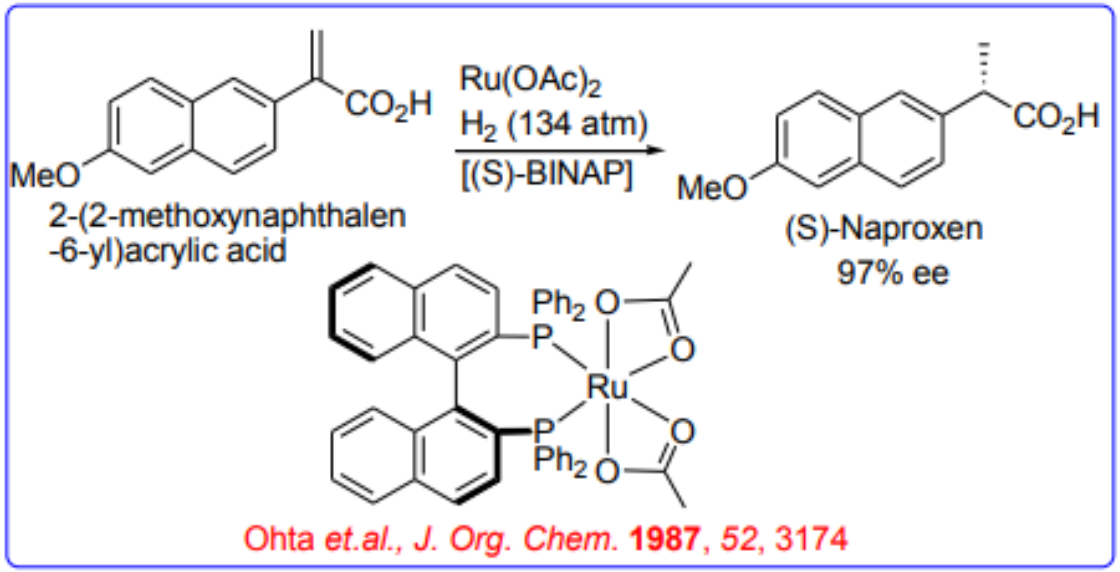
Asymmetric Hydrogenation of α,β-unsaturated β-aminoacids



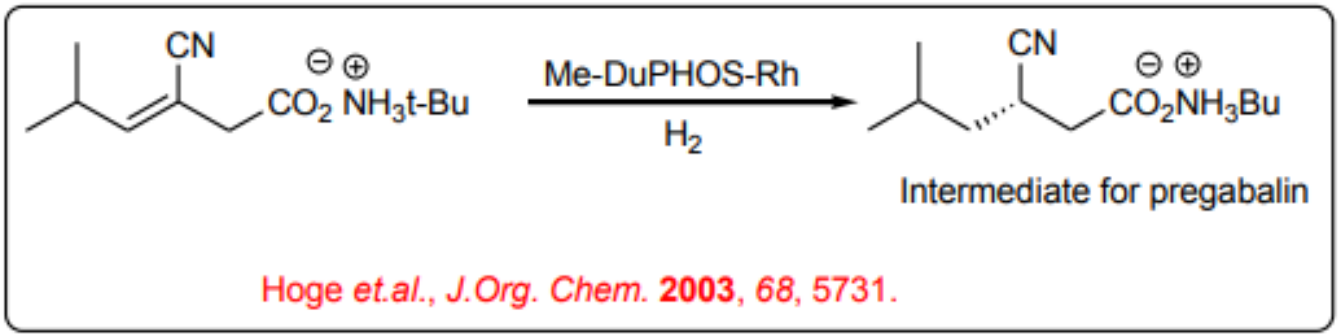




Asymmetric Hydrogenation of α,β-unsaturated acids/nitriles

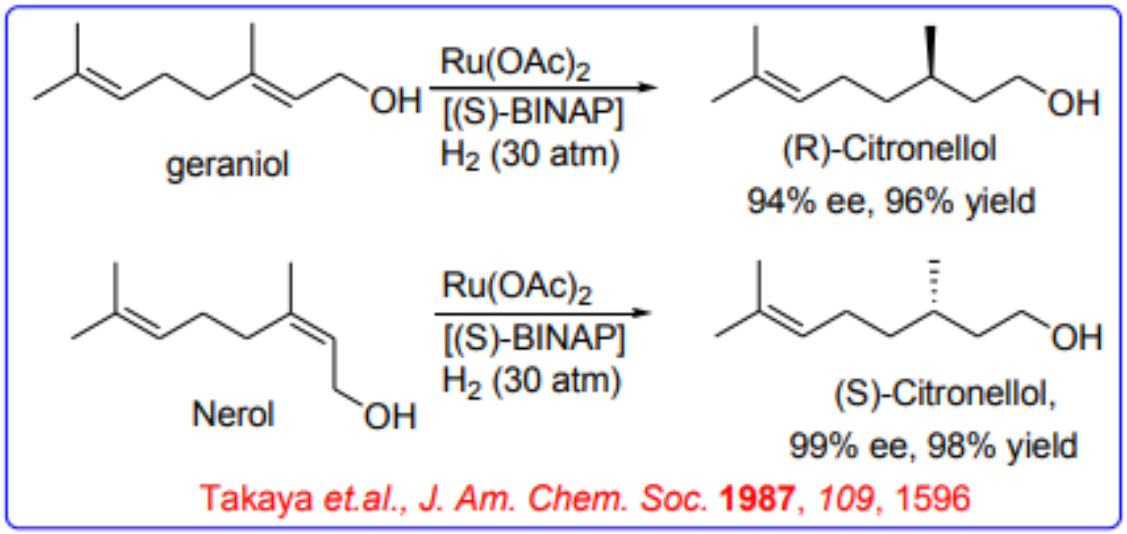


Ohta *et.al., J. Org. Chem.* **1987**, *52*, 3174

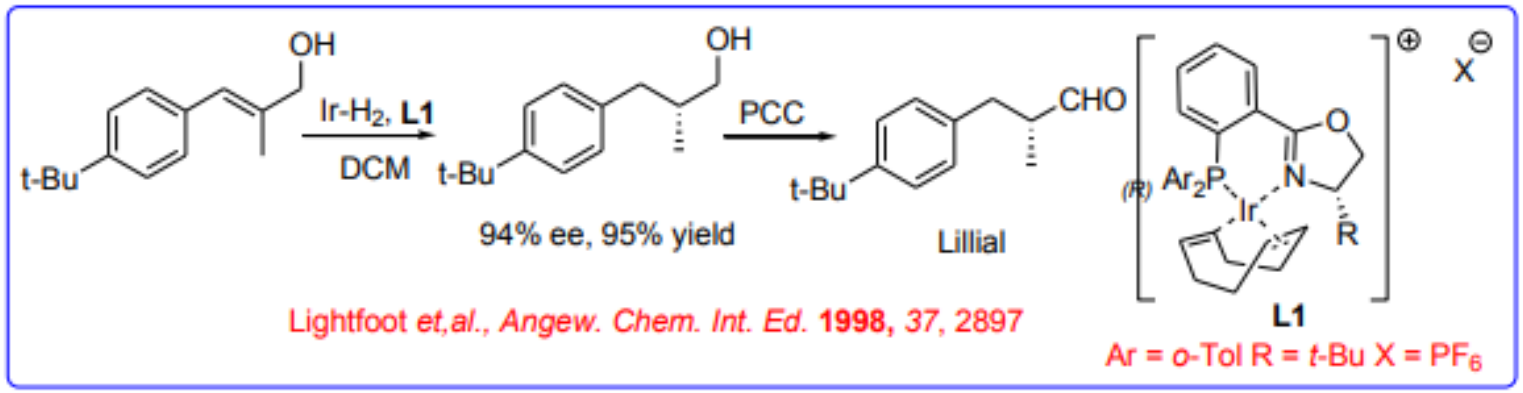


Hoge *et.al., J.Org. Chem.* **2003**, *68*, 5731.

Asymmetric Hydrogenation of allylic alcohols

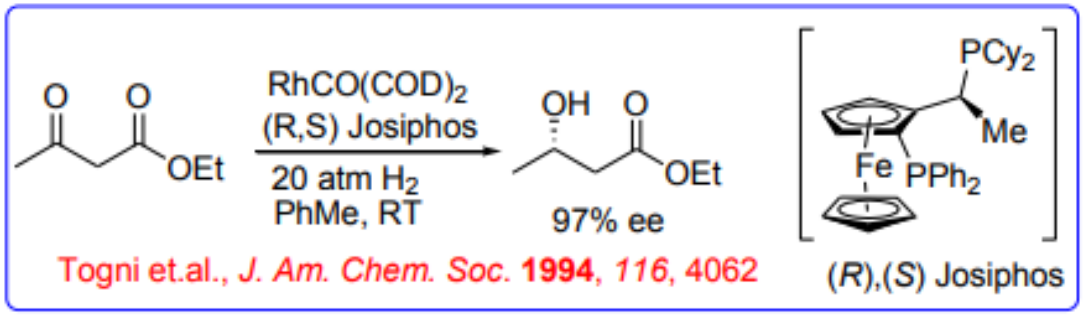


Scheme 6. Synthesis of *(S)* and *(R)*-Citronellol by Chiral Reduction of Geraniol and Nerol

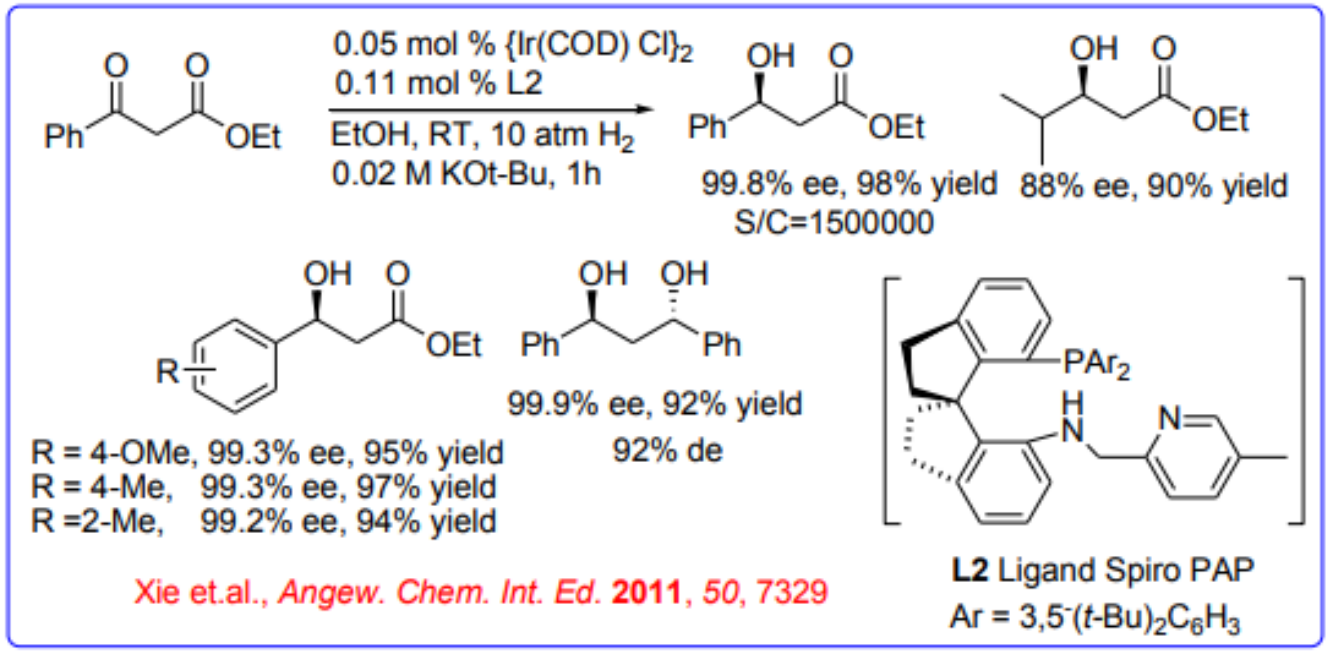


Scheme 7. Asymmetric Synthesis of Lillial.

Asymmetric Hydrogenation of α-ketoesters



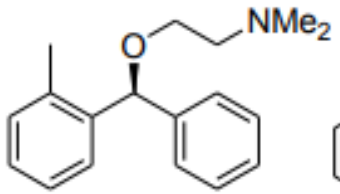
Togni et.al., *J. Am. Chem. Soc.* **1994**, *116*, 4062



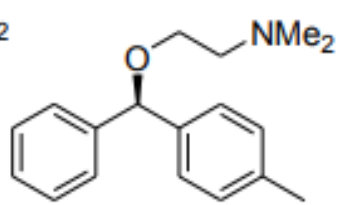
Xie et.al., *Angew. Chem. Int. Ed.* **2011**, *50*, 7329

Scheme 7. Enantioselective hydrogenation of β-ketoesters

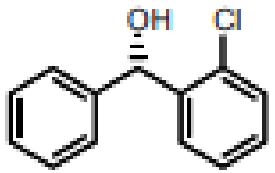
Asymmetric Hydrogenation of ketones

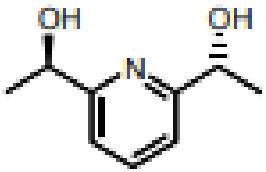


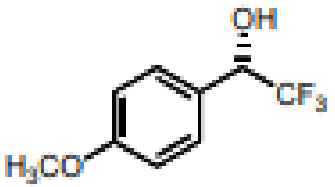
(S)-orphenadrine

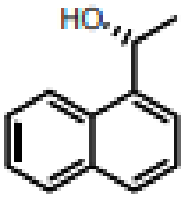


(R)-neobenodine

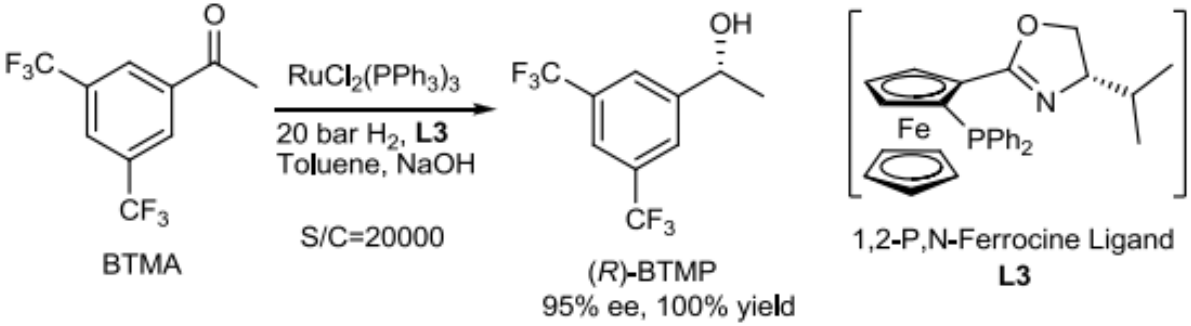






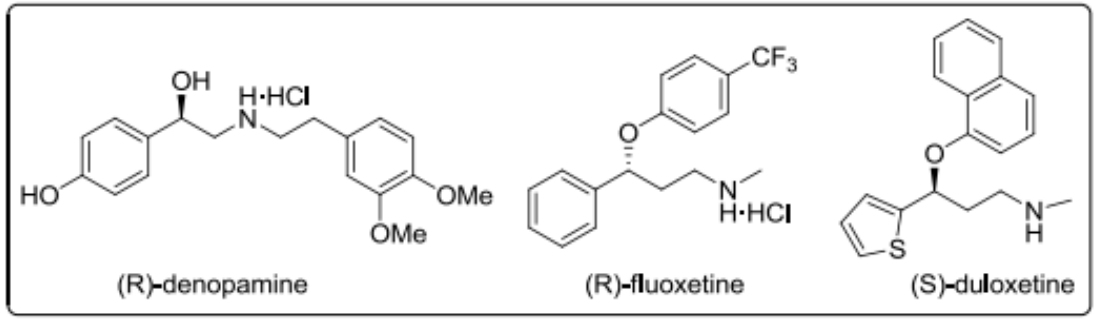


The enantioselective hydrogenation of 3,5-bistrifluoromethyl acetophenone (BTMA) can be carried out using a Ru/phosphine-oxazoline complex (Scheme 9). The reaction is compatible with 140-kg scale at 20 bar and 25 °C with S/C ratios of 20,000. The synthesis of the ligand is shown in Scheme 10.

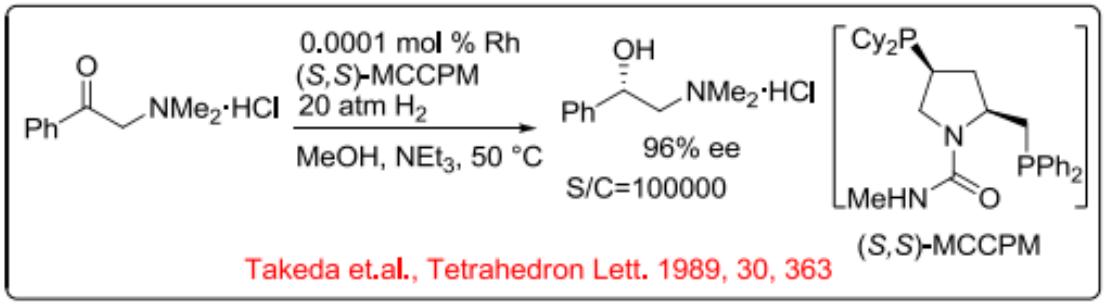


Naud *et.al.*, *Org. Pro. Res. & Dev.* **2007**, *11*, 519

Asymmetric Hydrogenation of amino ketones

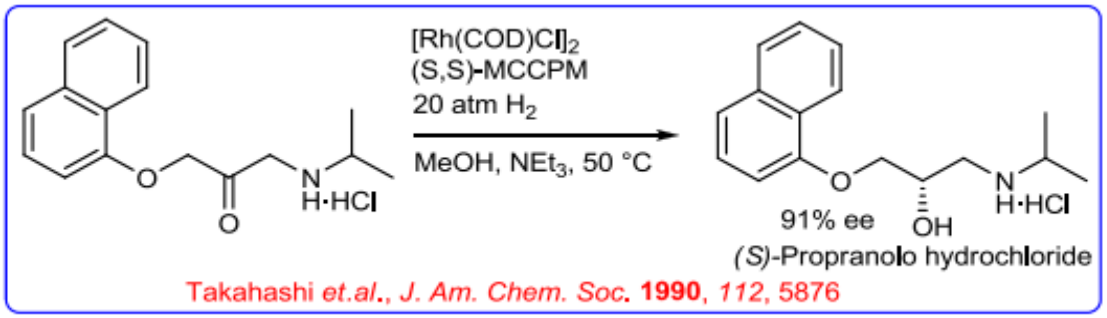


(R)-denopamine (R)-fluoxetine (S)-duloxetine



(S,S)-MCCPM

Takeda et.al., Tetrahedron Lett. 1989, 30, 363

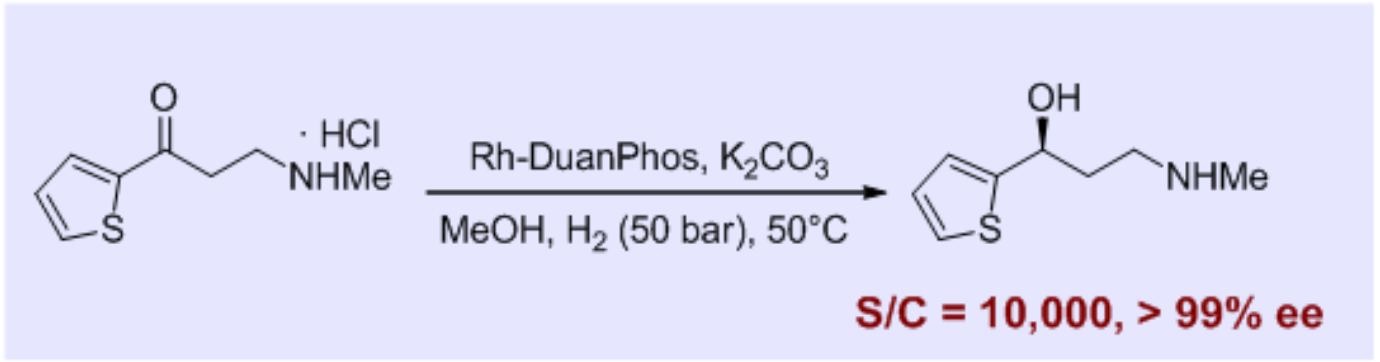


(S)-Propranolo hydrochloride

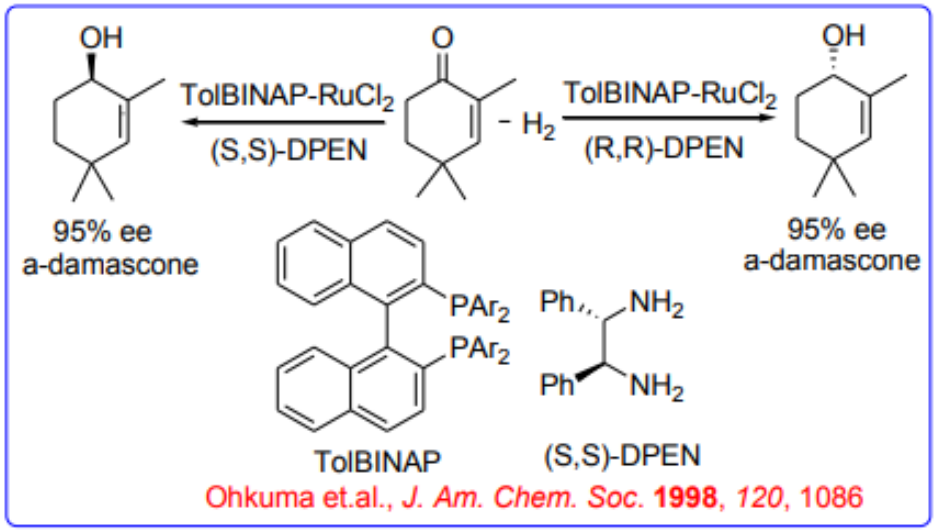
Takahashi *et.al.*, *J. Am. Chem. Soc.* **1990**, *112*, 5876

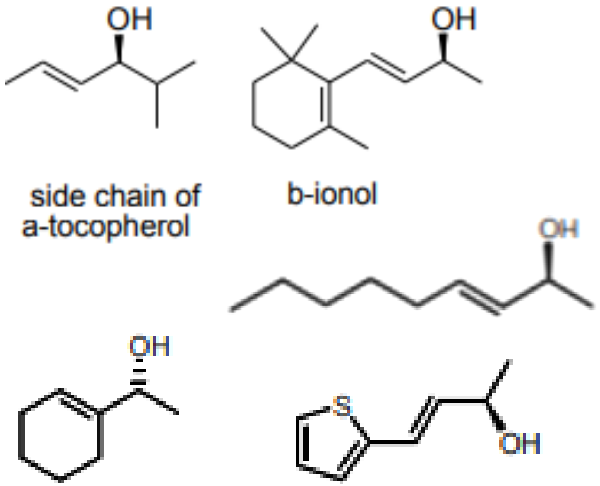
Scheme 11. Key step for the Direct Synthesis of *(S)*-Propranolol

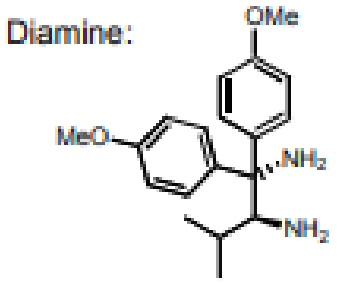
Synthesis of Duloxetine



Asymmetric Hydrogenation of α,β-unsaturated ketones

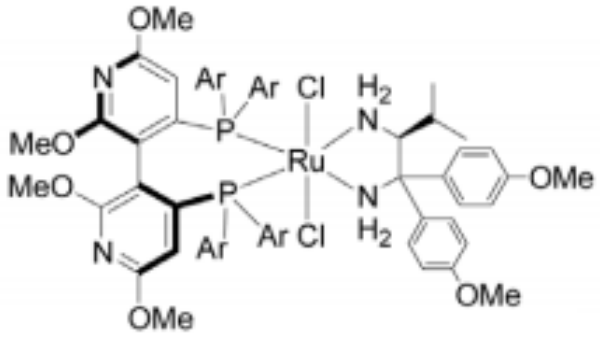






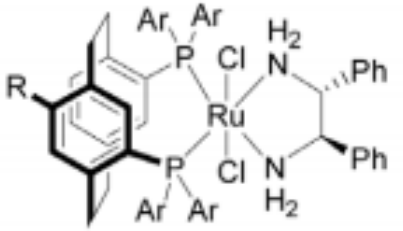
5

(*S*)-DAIPEN



7

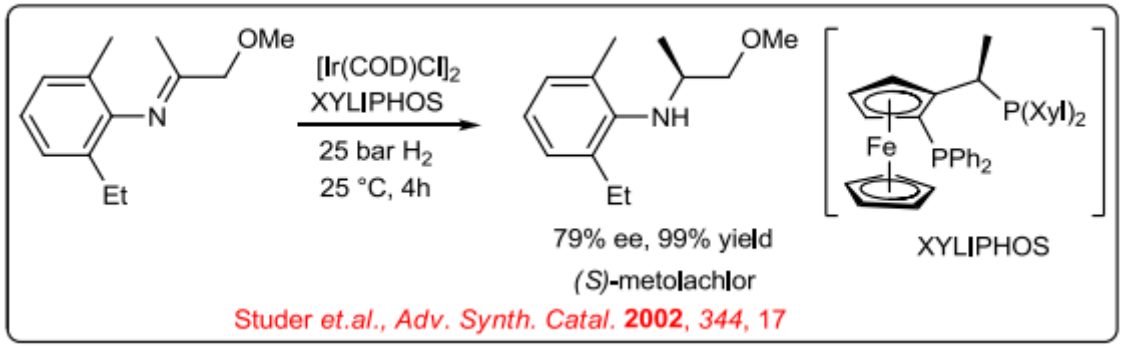
[(*S*)-PPhos $RuCl_2$ (*S*)-DAIPEN]



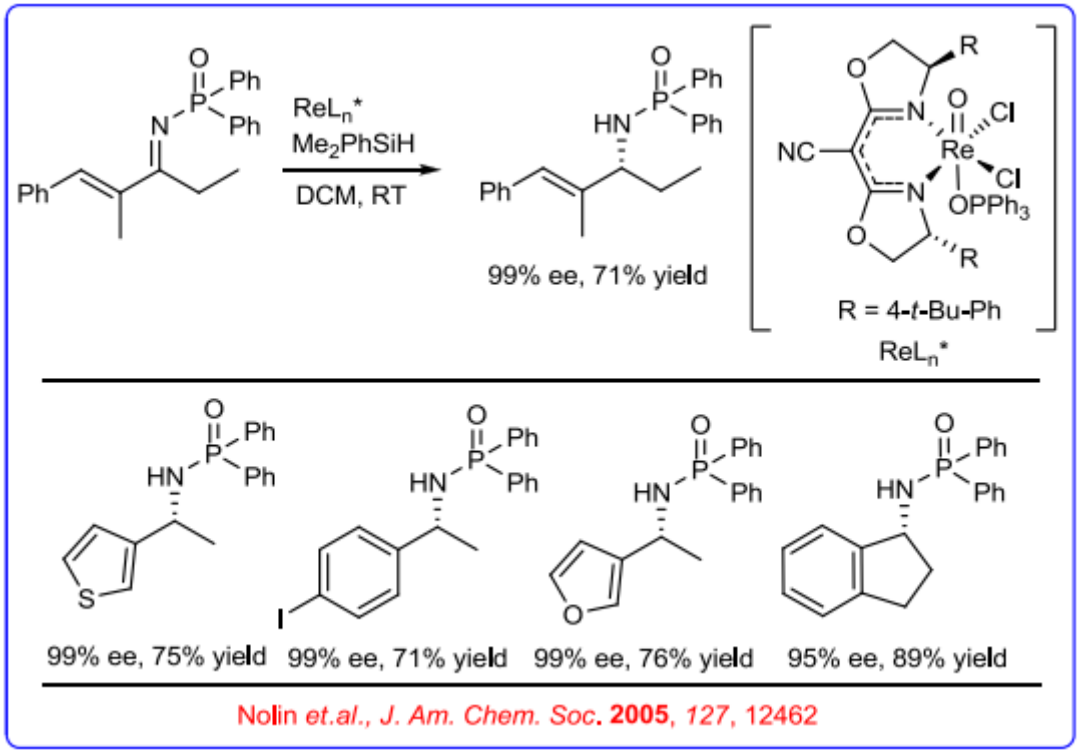
8

[(*S*)-ParaPhos $RuCl_2$ (*R*,*R*)-DPEN]

Asymmetric Hydrogenation of imines

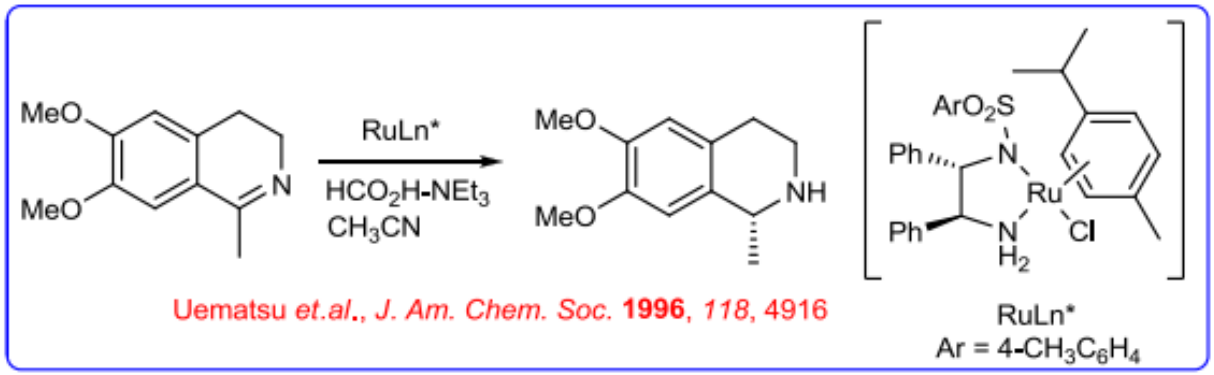


Studer *et.al., Adv. Synth. Catal.* **2002**, *344*, 17



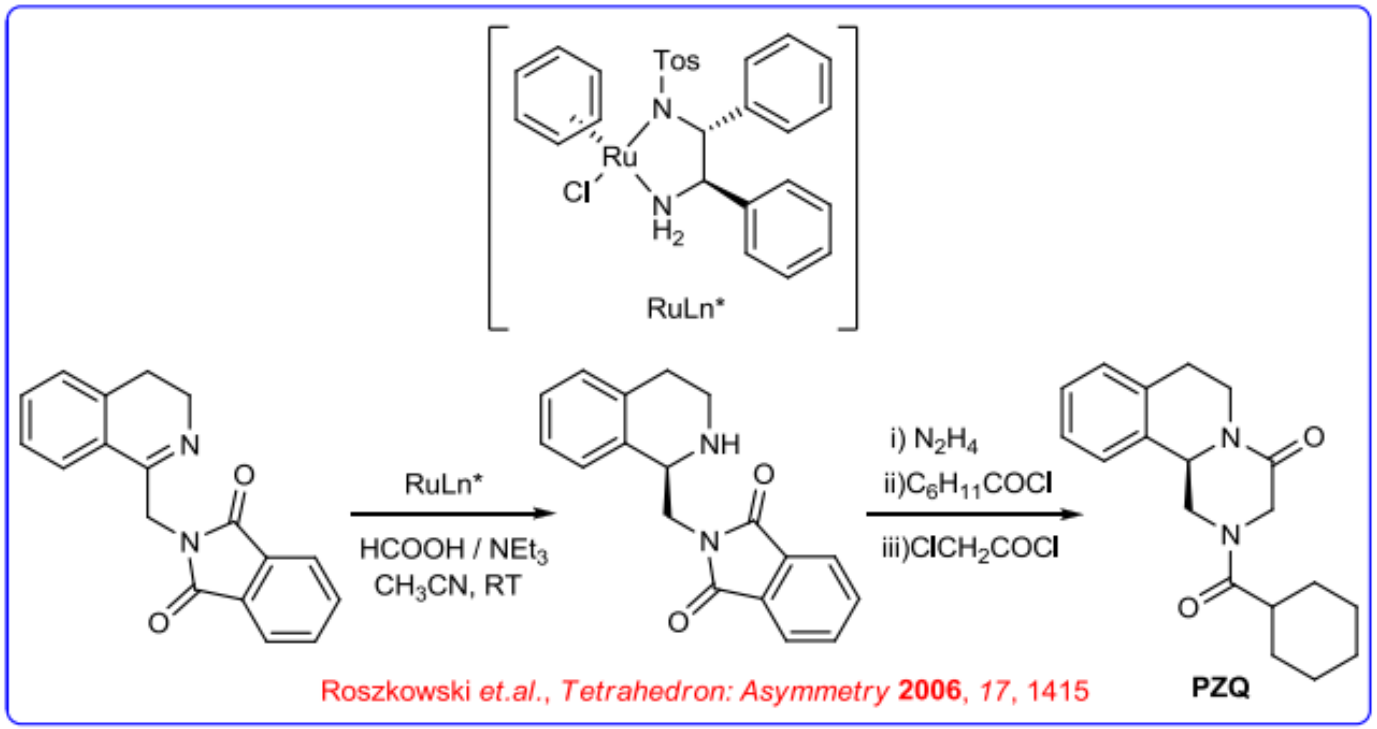
Nolin *et.al., J. Am. Chem. Soc.* **2005**, *127*, 12462

Transfer Asymmetric Hydrogenation of Imines



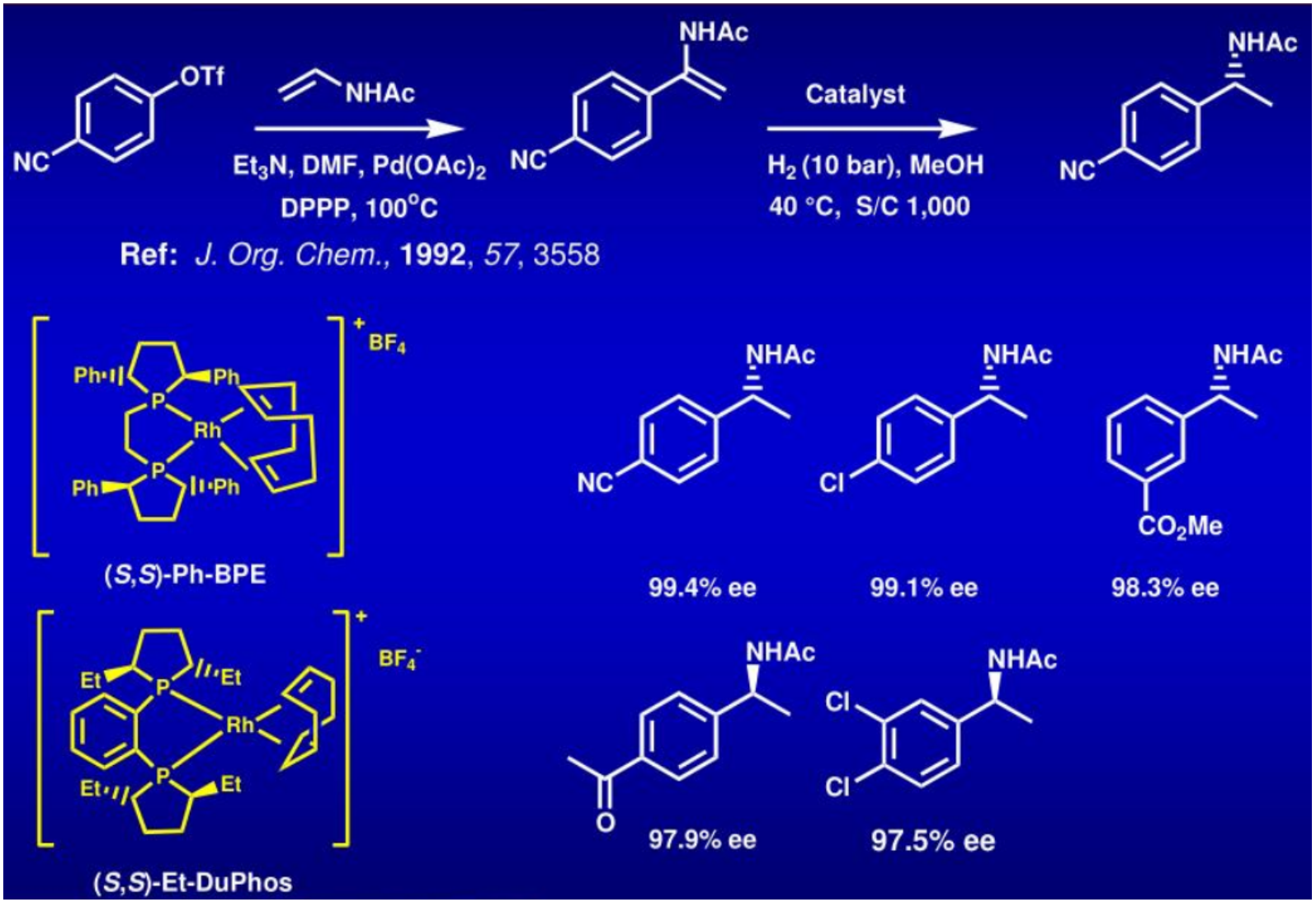
Uematsu *et.al.*, *J. Am. Chem. Soc.* **1996**, *118*, 4916

Scheme 6. Catalytic enantioselective conjugate reduction of imines

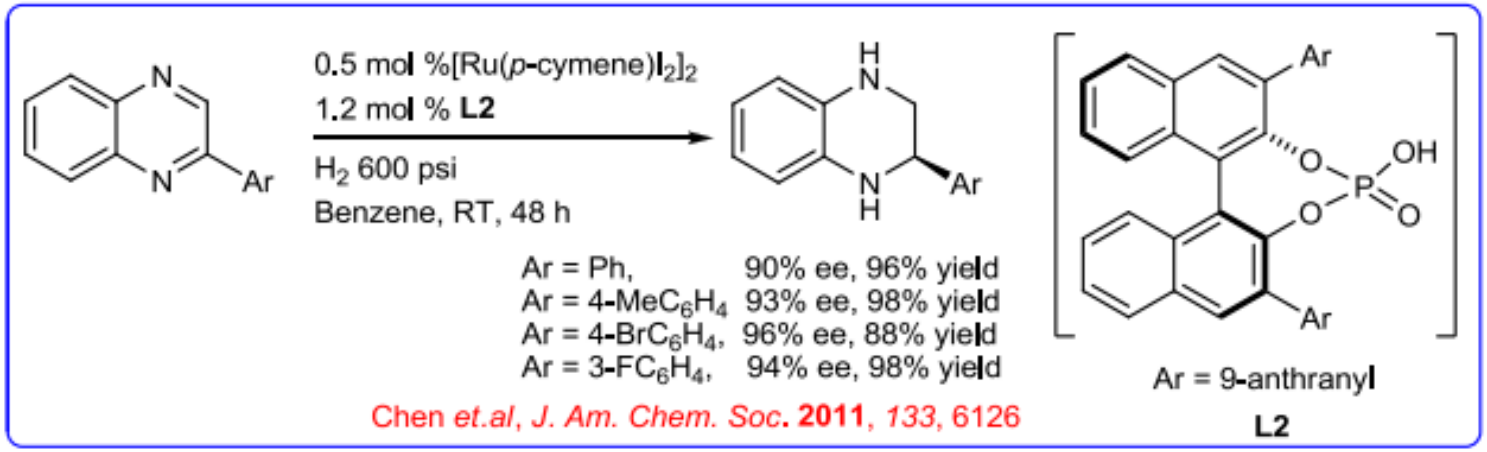


Roszkowski *et.al.*, *Tetrahedron: Asymmetry* **2006**, *17*, 1415

Asymmetric Hydrogenation of enamides

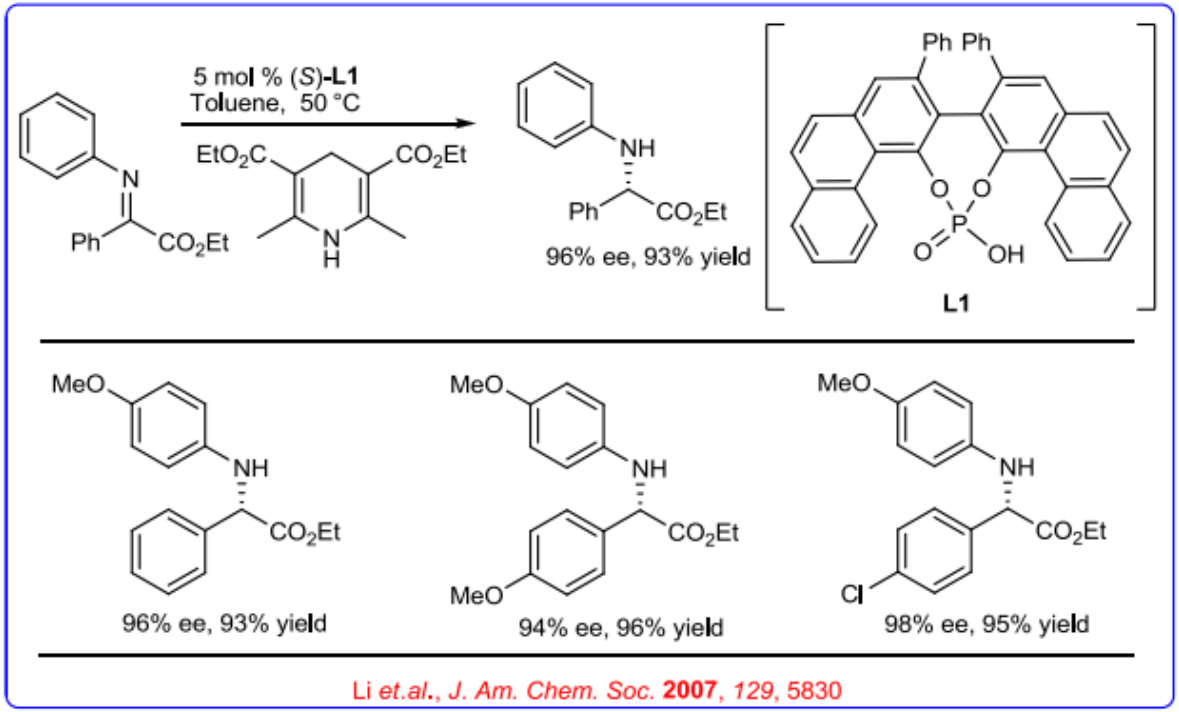


Hydrogenation of chiral Iminium salts

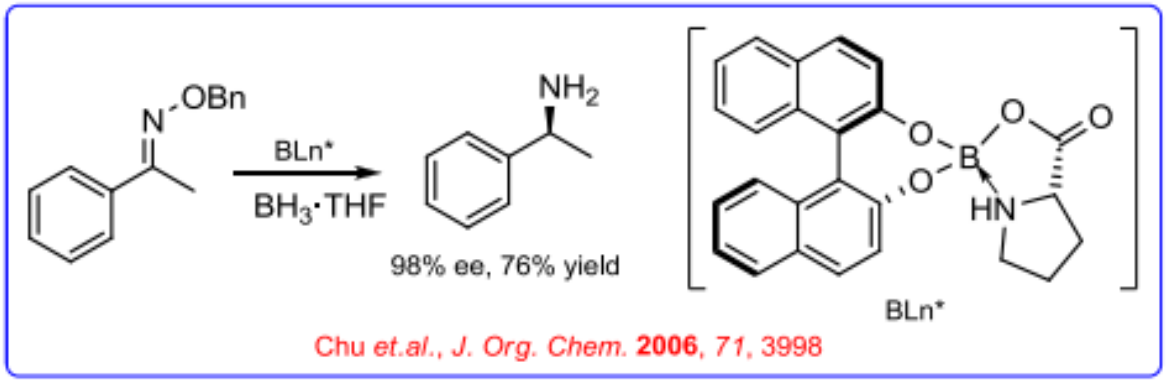


Scheme 5. Metal/Brønsted Acid Catalysis for Enantioselective Reduction of Quinoxalines

Chiral Lewis acid catalysis: Imine Reduction

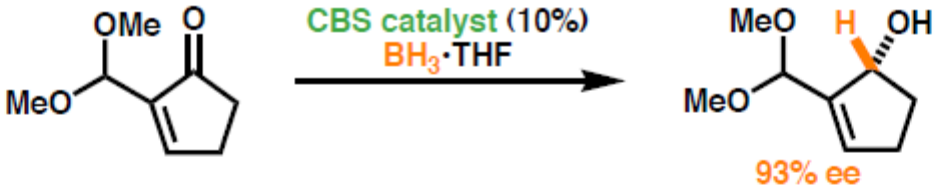


Li *et.al.*, *J. Am. Chem. Soc.* **2007**, *129*, 5830

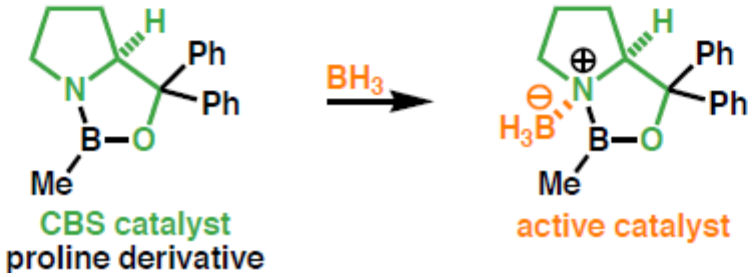


Chu *et.al.*, *J. Org. Chem.* **2006**, *71*, 3998

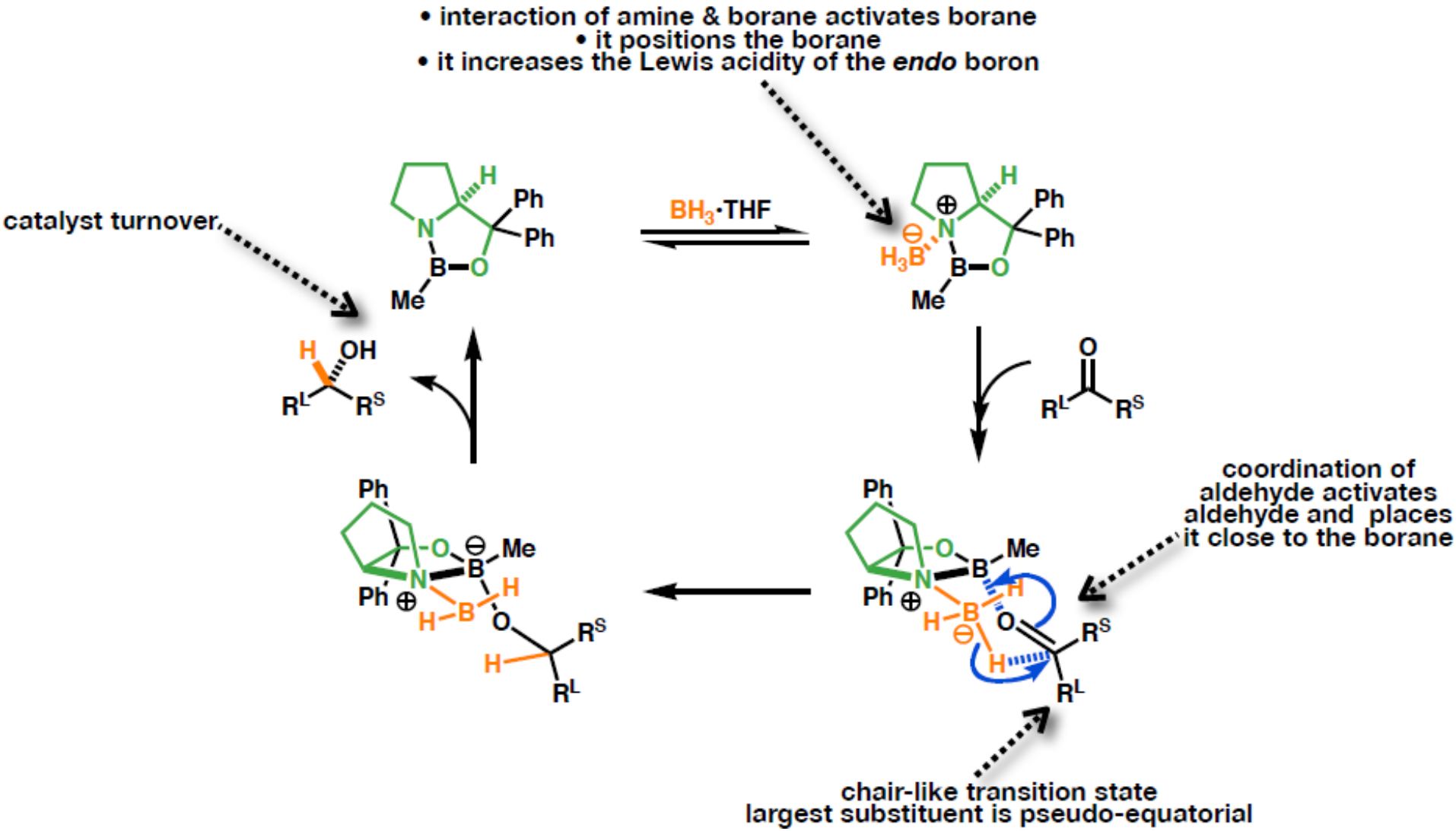
Chiral Lewis Acids Catalysis - Ketone reduction



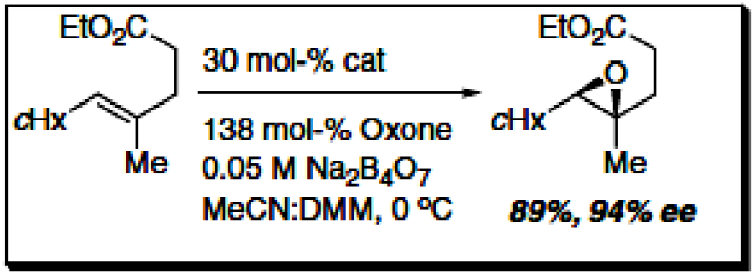
- An efficient catalyst for the reduction of ketones is **C**orey-**B**akshi-**S**hibata catalyst (CBS)
- This catalyst brings a ketone and borane together in a chiral environment
- The reagent is prepared from a **proline** derivative
- The reaction utilises ~10% heterocycle and a stoichiometric amount of borane and works most effectively if there is a big difference between each of the substituents on the ketone
- The mechanism is quite elegant...

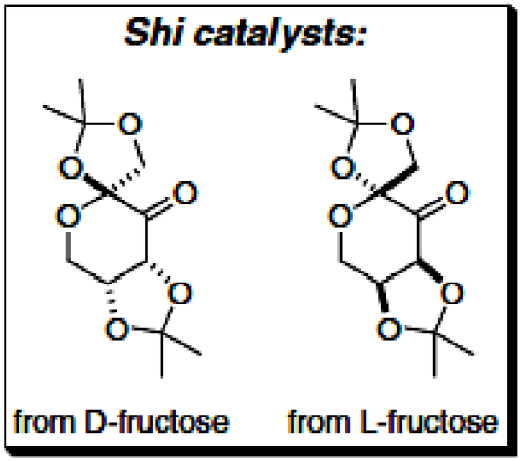


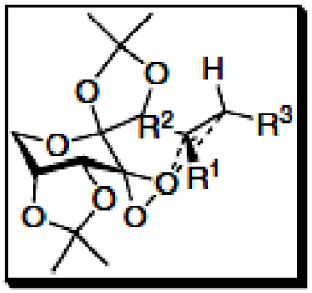
Mechanism of CBS reduction

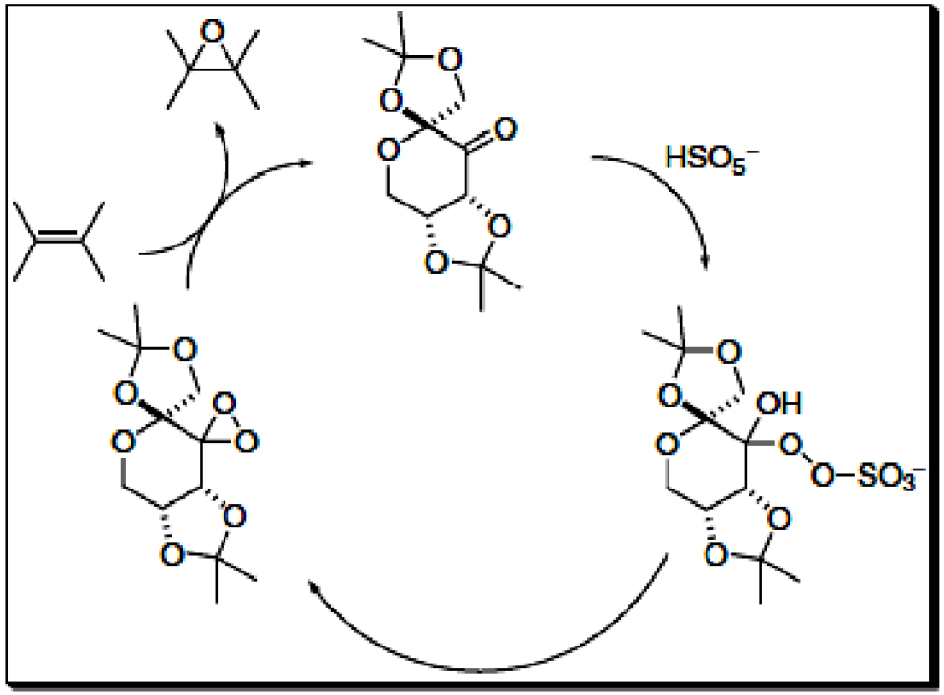


Organocatalytic epoxidation by chiral ketones/dioxiranes

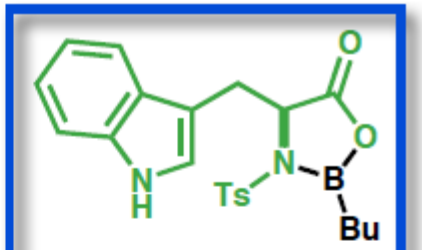




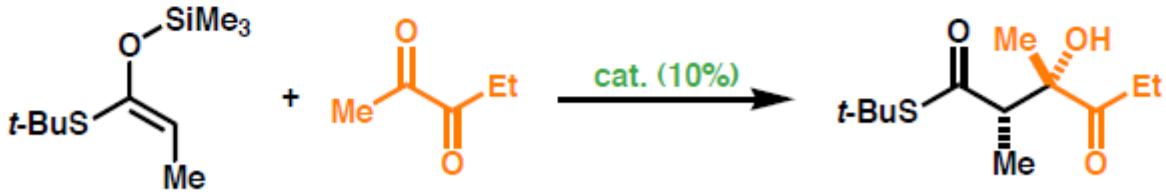


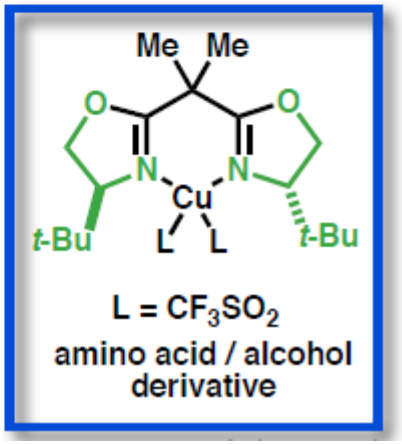


Chiral Lewis acid catalysis: Aldol reaction

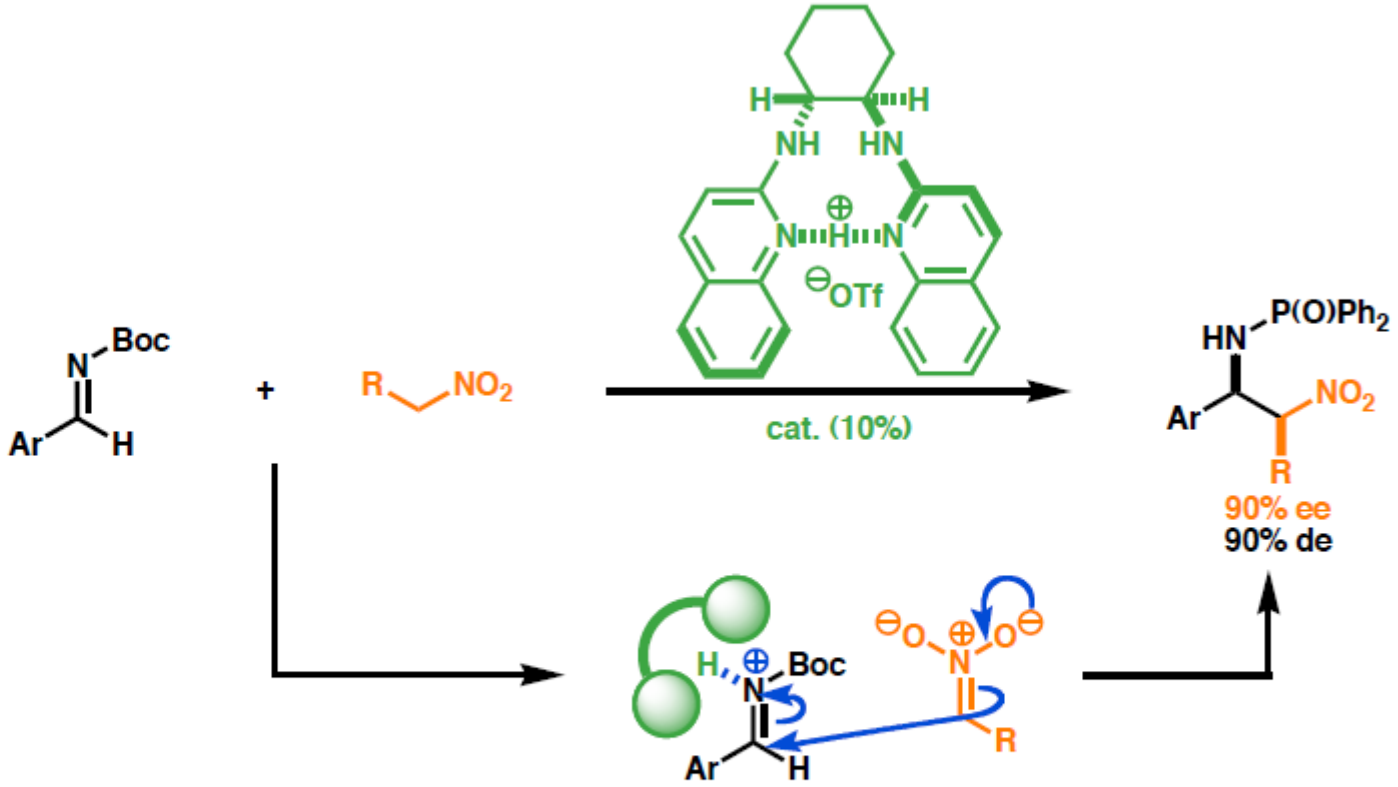


- The Mukaiyama aldol reaction is the reaction of **silyl enol ethers** with aldehydes
- The reaction can be catalysed by **chiral Lewis acids**
- The above example shows the use of a boron derivative of **tryptophan**
- The example below utilises a **bis(oxazoline)** ligand; these amino acid derived ligands are extremely versatile ligands for enantioselective synthesis (note they are symmetric but chiral)
- The regioselectivity probably results from attack at the **least hindered** carbonyl



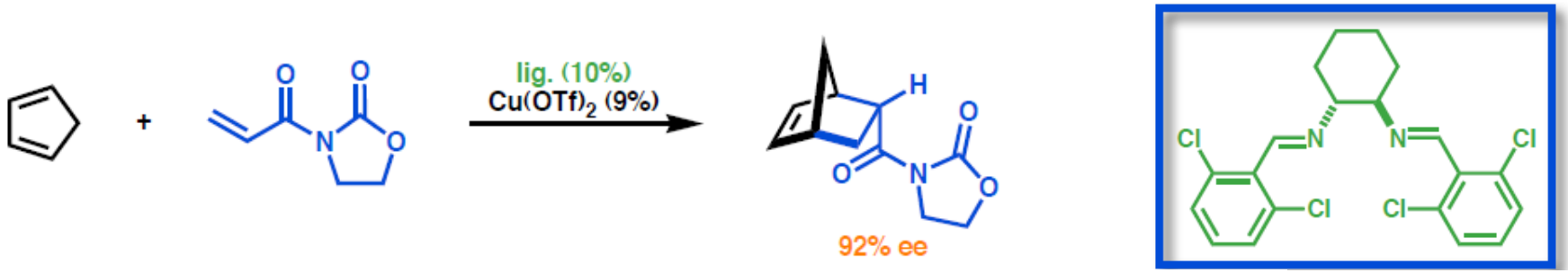


Chiral Lewis acid catalysis: Aza-Henry reaction



- Acts as a ‘chiral proton’
- Protonation of the imine forms a highly electrophilic species
- Aza-Henry reaction can then proceed to give the new amine

Chiral Lewis acid catalysis: Diels-Alder reaction



- The **oxazolidinone** substituent on the **dienophile** is important
- Good selectivities are only achieved when there are **two binding points** on the dienophile
- The two carbonyl groups allow a rigid chelate to be formed & maximise the commincation of chirality

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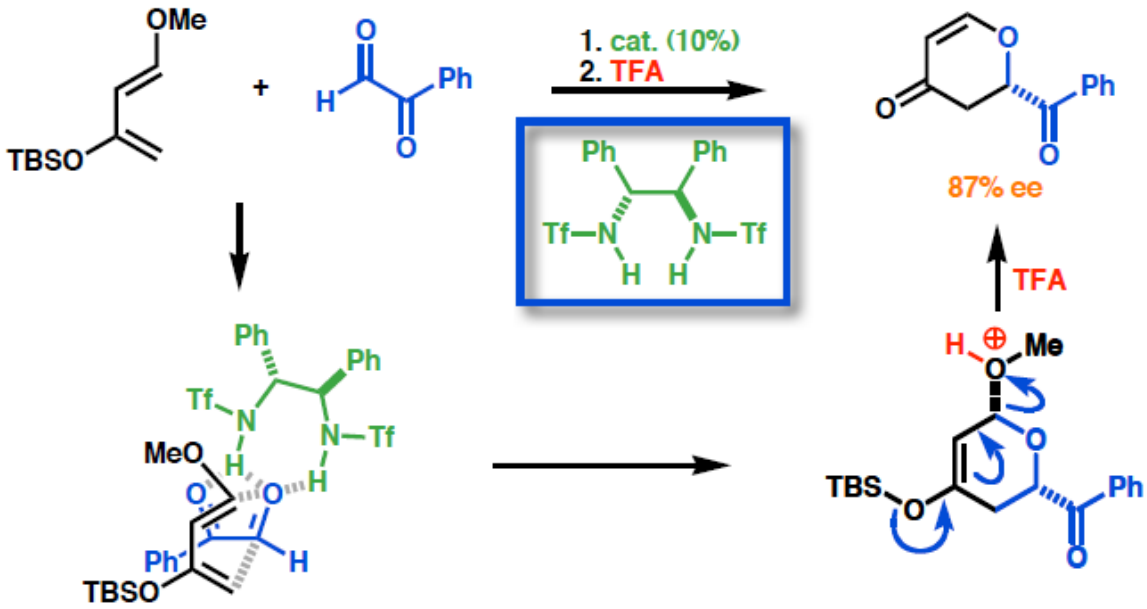


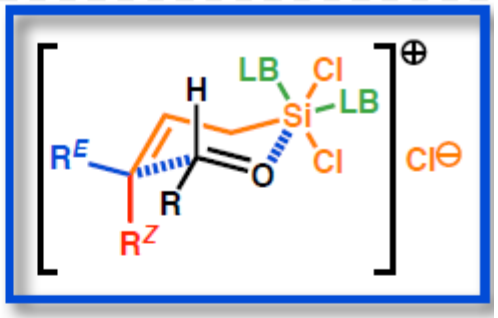
Example of hetero Diels-Alder

Aldehyde is the dienophile

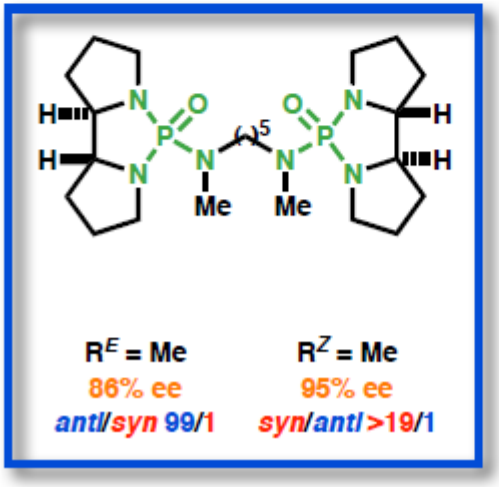
Must use very electron rich diene

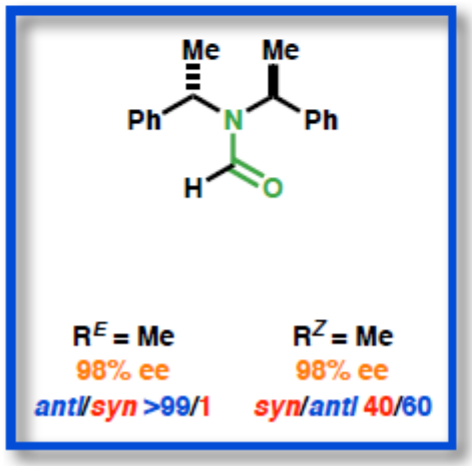
Polar N-H act as Lewis acid

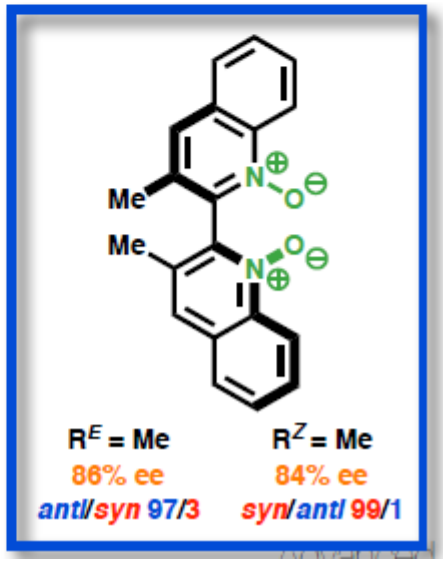
Chiral Lewis base catalysis: allylation of carbonyls



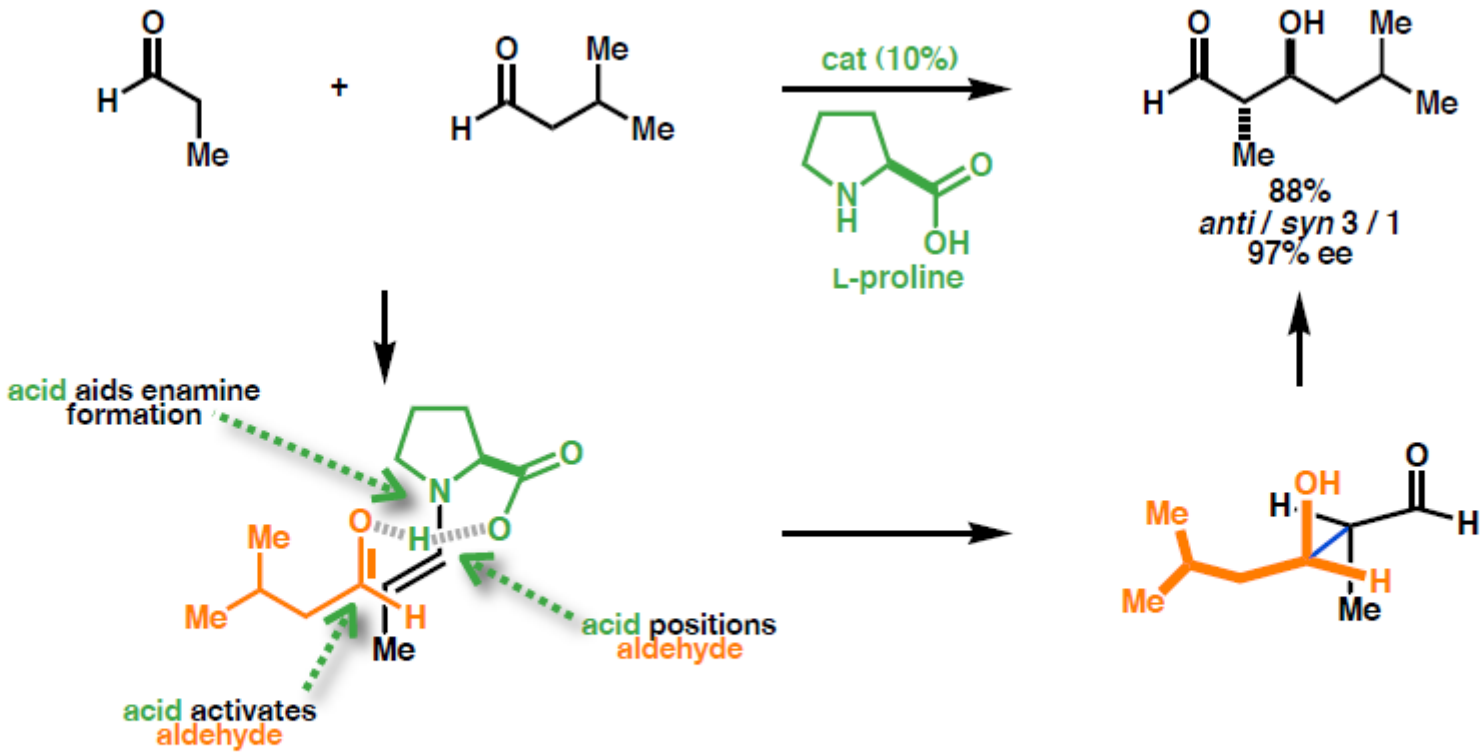
- An alternative strategy is the use of **Lewis bases** to activate the crotyl reagent
- Reaction proceeds *via* the activation of the **nucleophile** to generate a hypervalent silicon species
- This species coordinates with the aldehyde, thus **activating** the aldehyde and allowing the reaction to proceed by a highly ordered **closed transition state**
- As a result good **diastereoselectivities** are observed and the geometry of nucleophile controls the **relative** stereochemistry





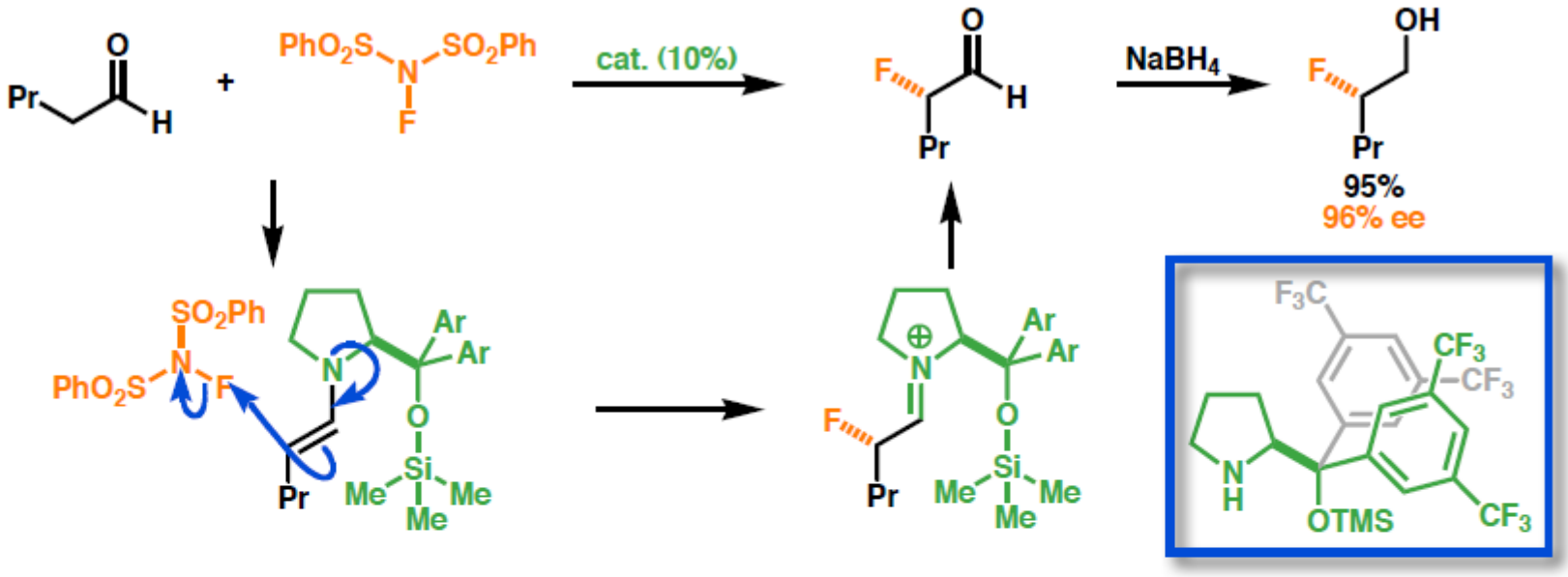


Chiral Enamine catalysis: Aldol reaction

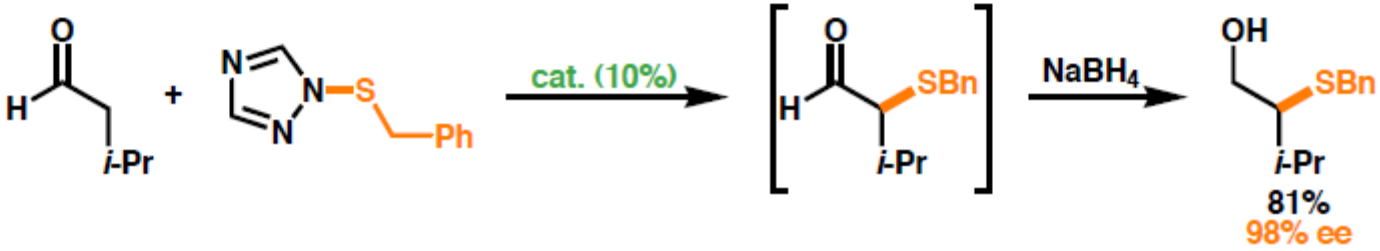


- Proline can catalyse the **direct aldol** reaction of simple aldehydes
- Other simple amino acids can also be used in this reaction
- In addition a number of derivatives have been prepared that show more 'practical' characteristics

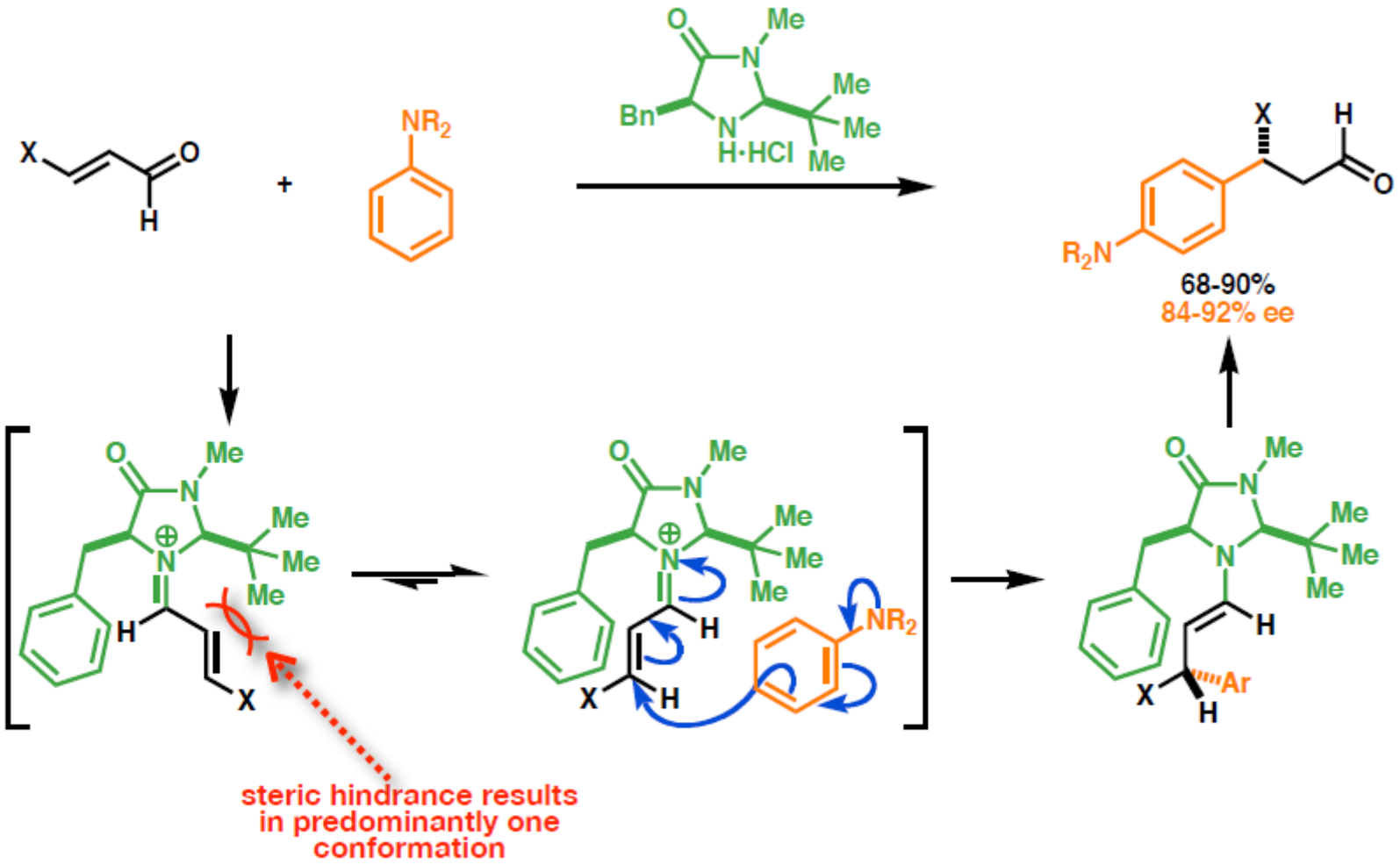
Chiral Enamine catalysis: α-functionalisation



- Secondary amines can be utilised as catalysts in enolate-like chemistry
- Initially an **enamine** is formed that then reacts in a **diastereoselective** manner
- Finally, *in situ* hydrolysis gives the product and regenerates the catalyst

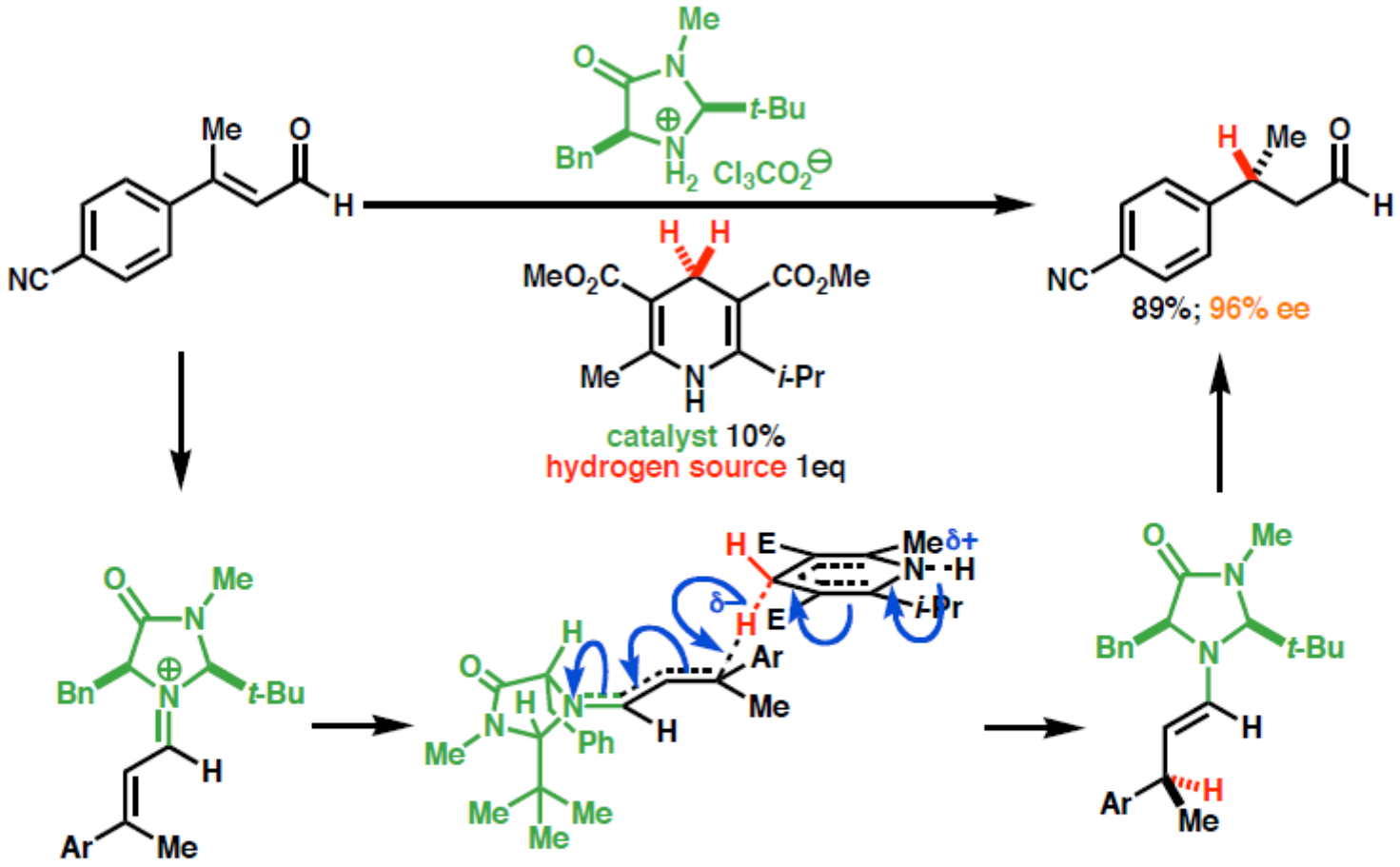


Chiral Enamine Catalysis: Conjugate addition to Enals



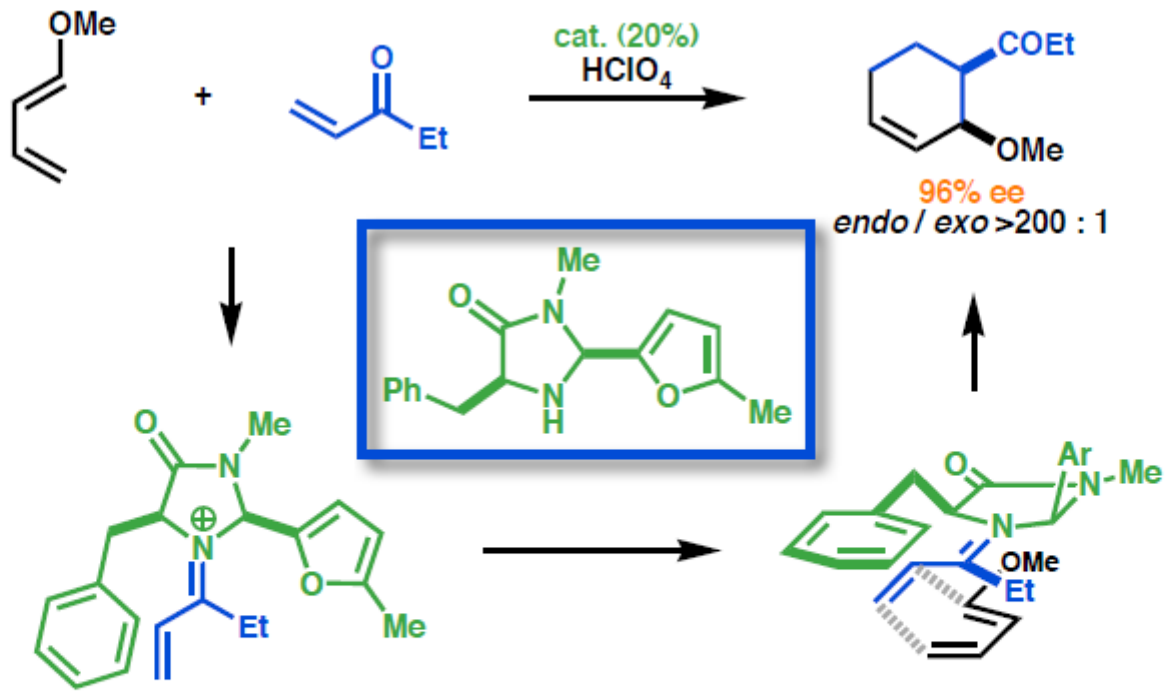
- A range of reactions can be achieved, including enantioselective Friedel-Crafts
- Catalyst ensures that the enone reacts *via* one conformation
- Must use electron rich aromatic substrates

Chiral Enamine Catalysis: Conjugate reduction of Enals



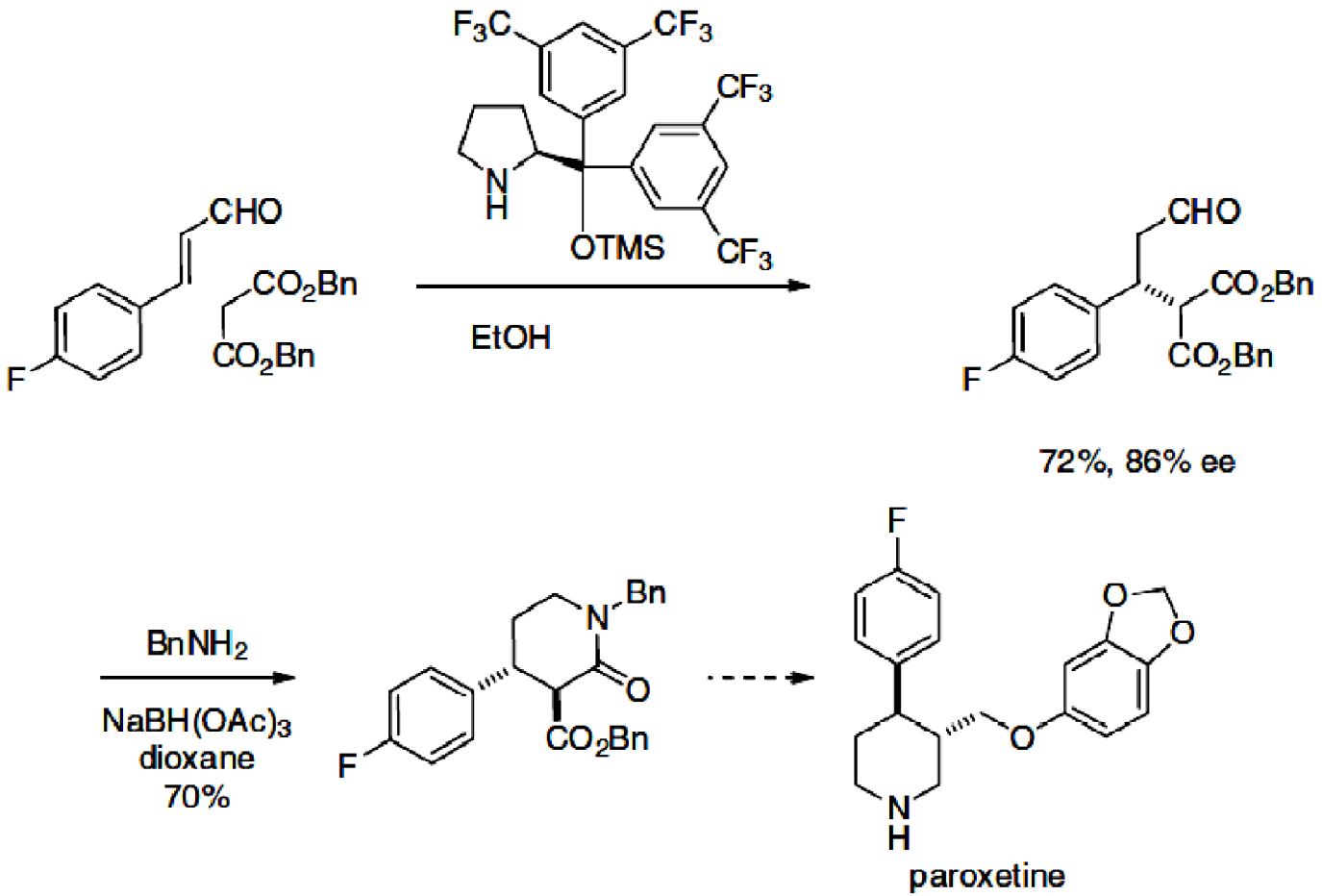
- A recent development is the use of small organic molecules to achieve hydrogenation
- Inspire by nature
- Based on the formation of a highly reactive **iminium ion** (this is the basis of many **organocatalytic** reactions)

Chiral Enamine Catalysis: Diels-Alder with Enals/Enones

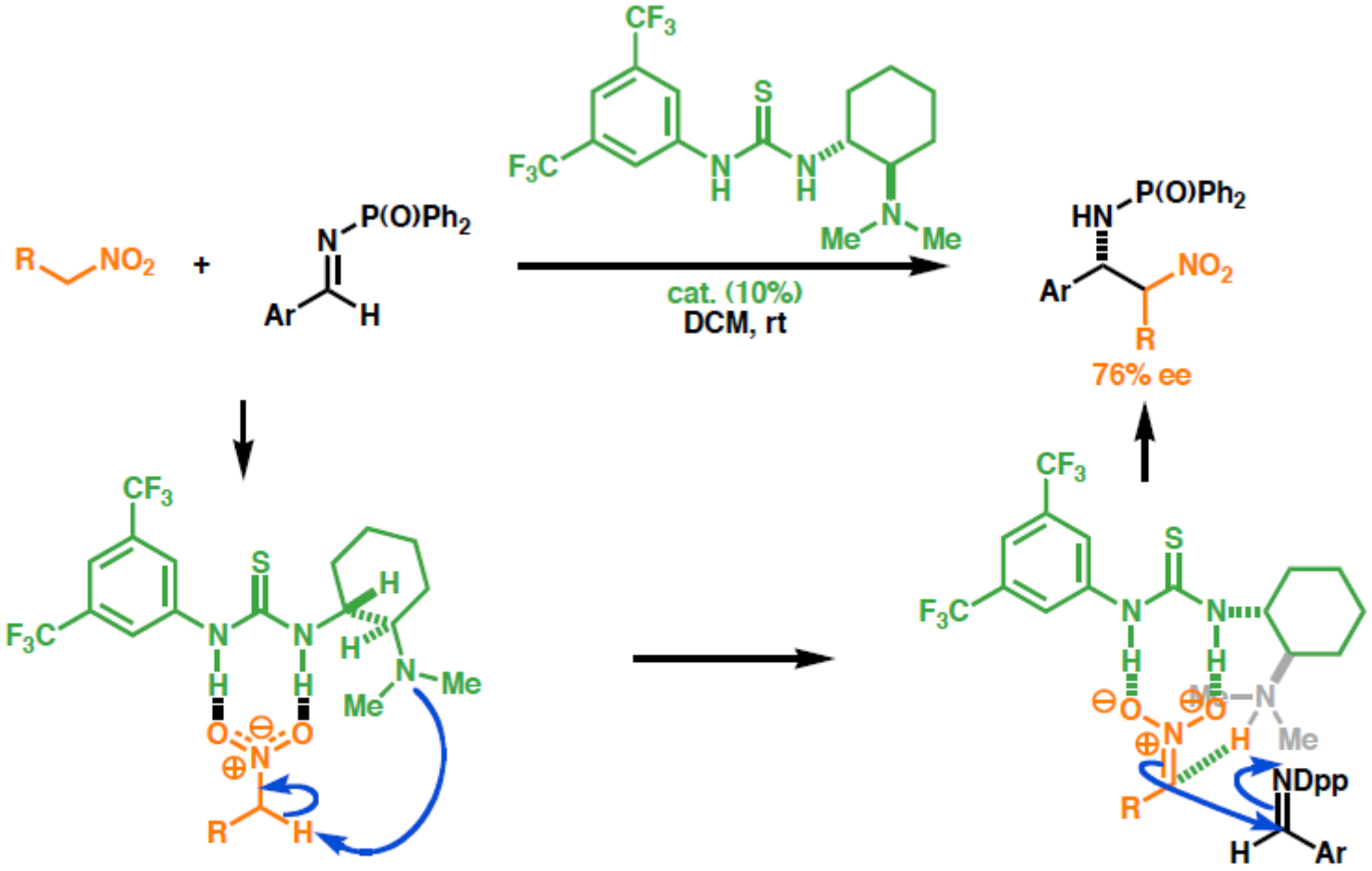


- Organic secondary amines can catalyse certain Diels-Alder reactions
- The reaction proceeds *via* the formation of an **iminium** species
- This charged species lowers the energy of the **LUMO** thus catalysing the reaction
- In addition one face of dienophile is blocked thus allowing the high selectivity

Chiral Enamine Catalysis: Examples in Synthesis

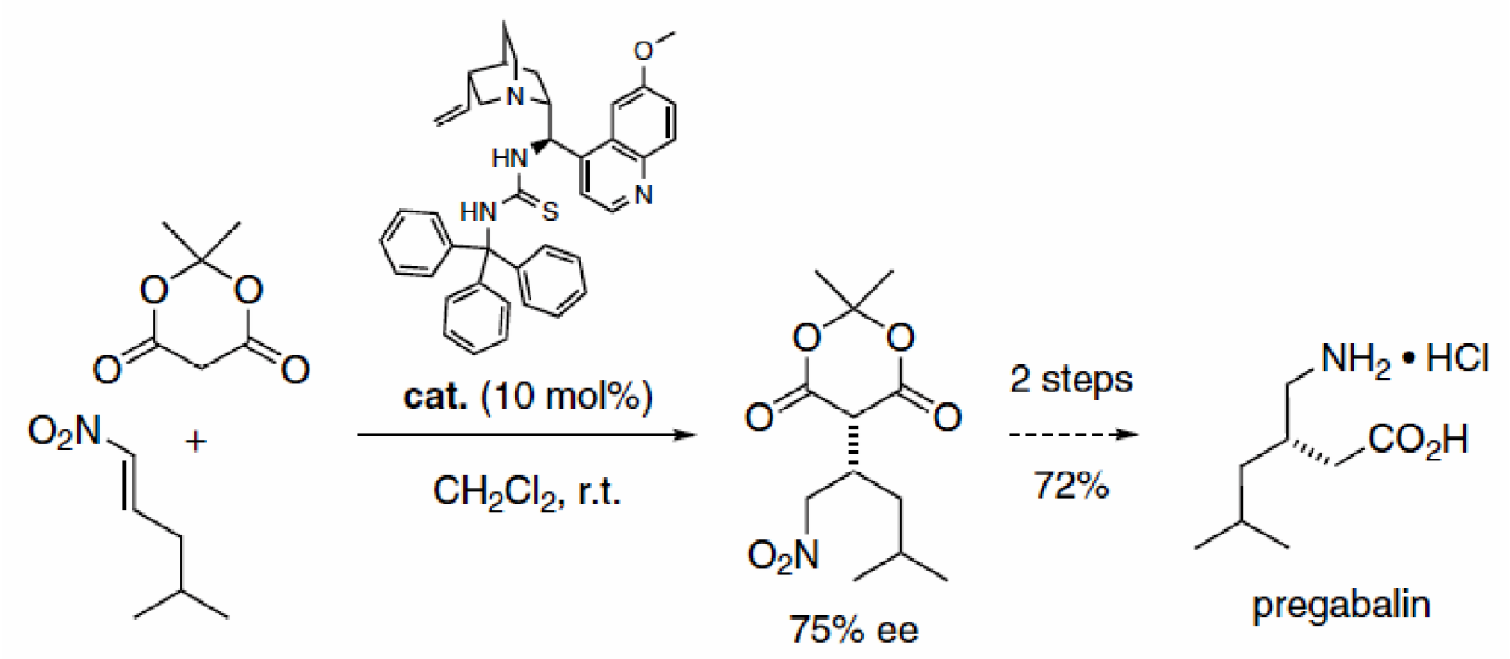


Bifunctional Urea Catalysis: Aza-Henry reaction

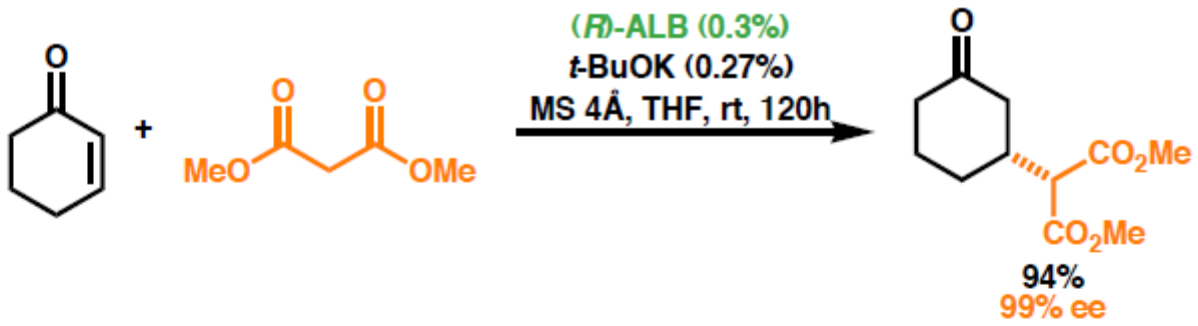


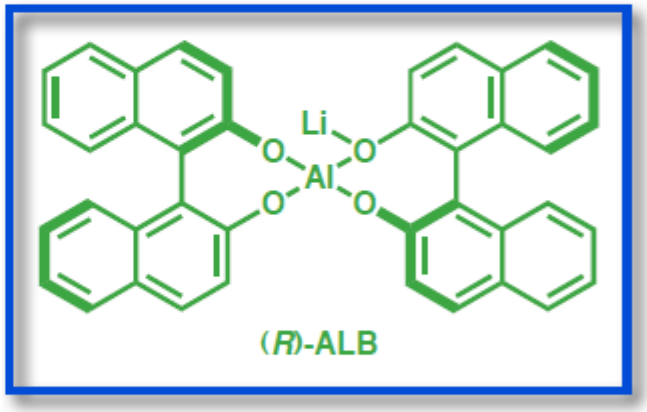
- Thio(urea) acts as a Lewis acid to activate & position the nitro substrate
- Pendent amine functionality deprotonates the nitro α-C–H and presumably an electrostatic interaction shields the bottom face of the nitro enolate

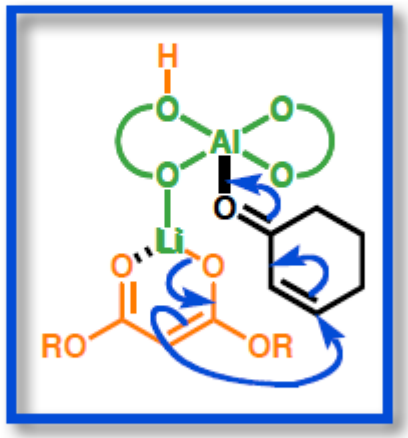
Bifunctional Urea Catalysis: Example in Synthesis



Bifunctional Metal Complex Catalysis: Conjugate addition

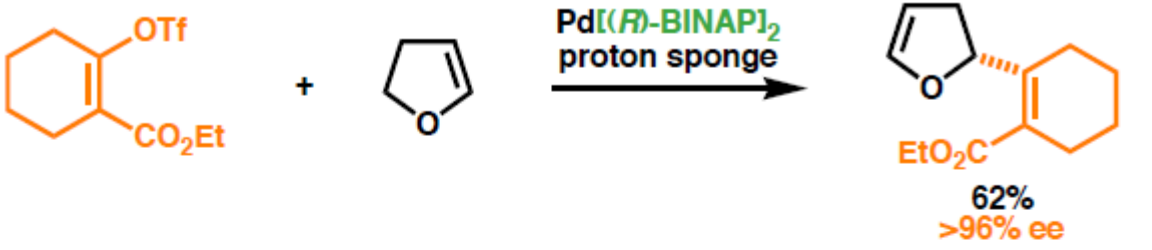


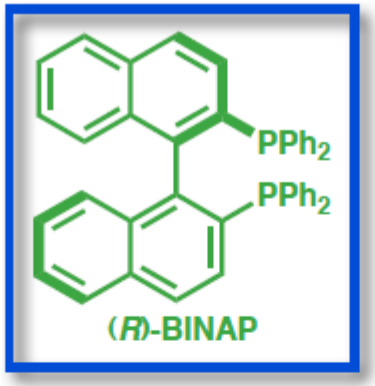


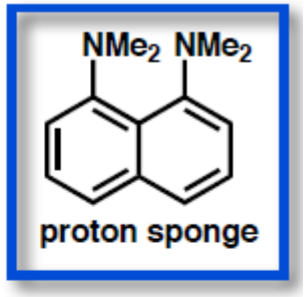


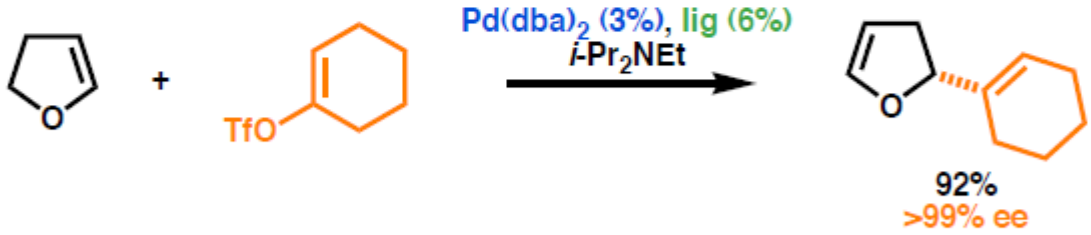
- Heterobimetallic catalyst of Shibasaki works remarkably well even at low catalyst loadings
- Aluminium acts as **Lewis acid** to activate enone
- **Lithium alkoxide** acts as Brønsted base to deprotonate malonate
- **Lithium alkoxide** also positions the enolate

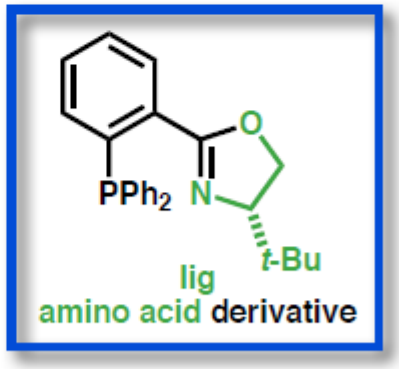
Asymmetric Heck reaction





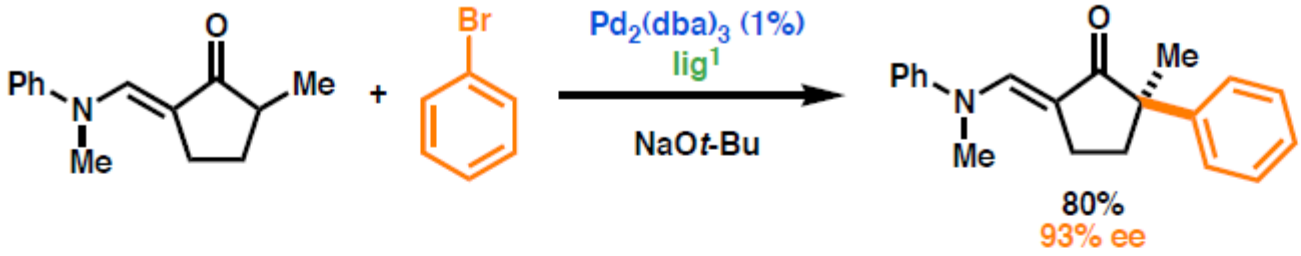


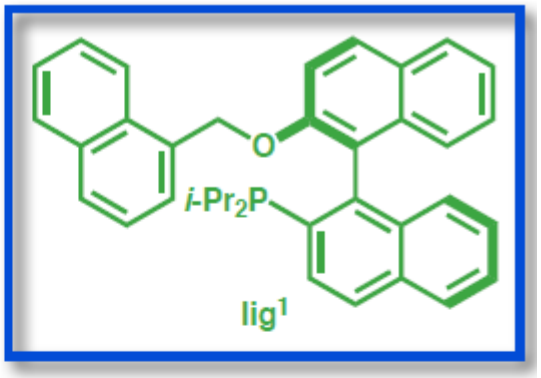




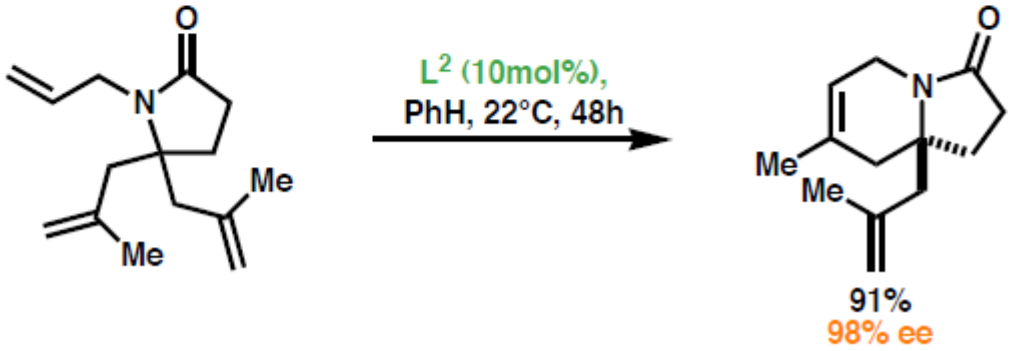
- With the use of chiral ligands the **Heck** reaction can be enantioselective
- Remember that we often see alkene migration

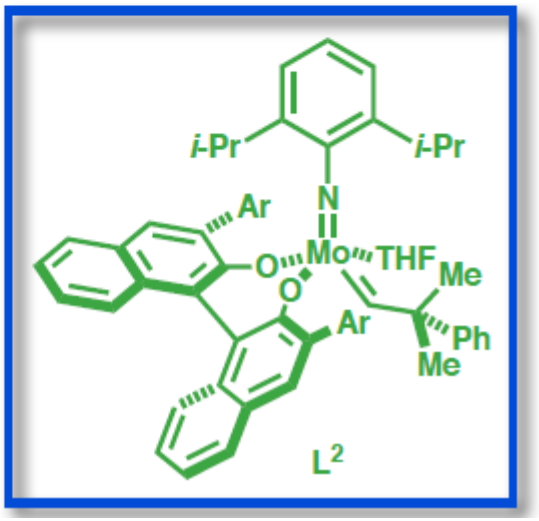
Asymmetric α-arylation of ketones and Metathesis reaction



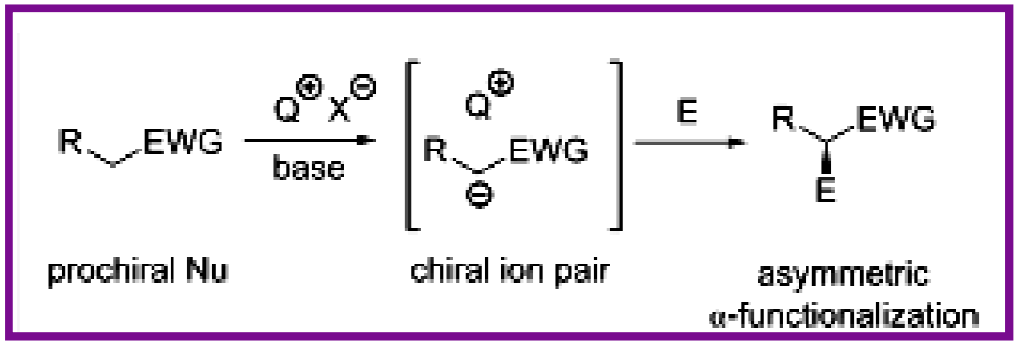


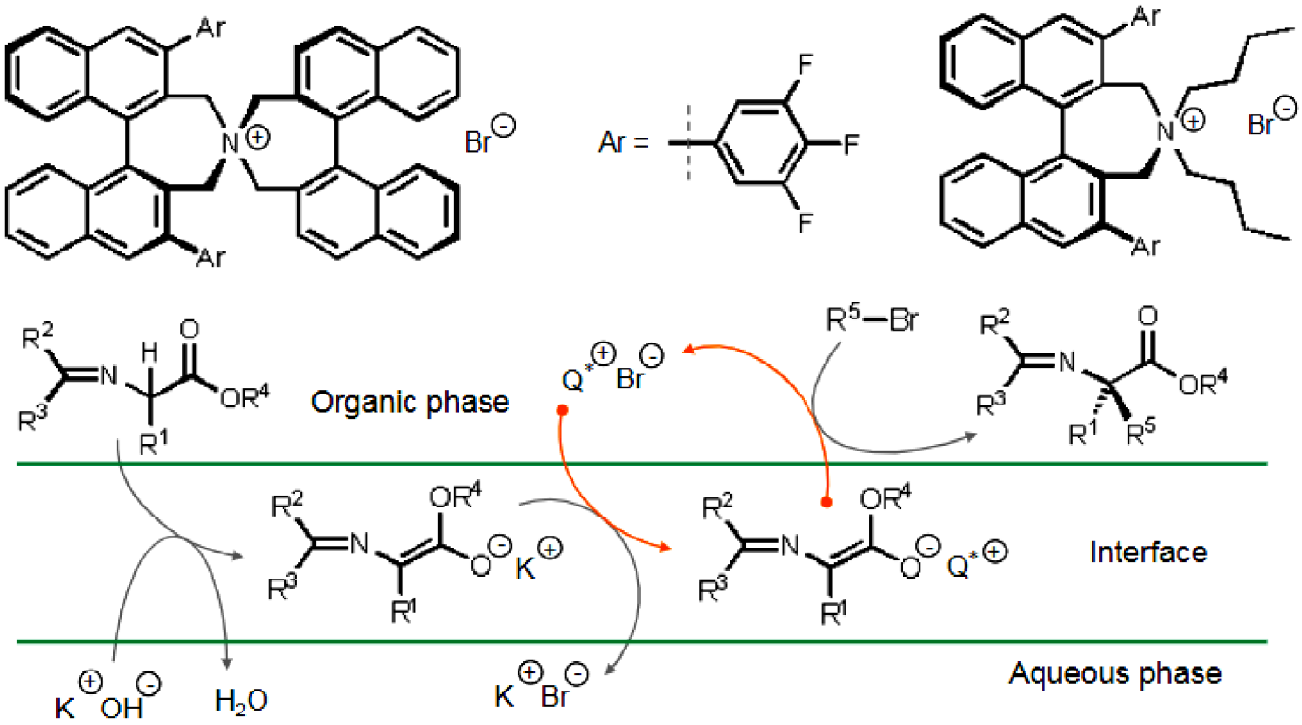
- **Pd(0)** chemitry has been utilised in the enantioselective **arylation** of enolates
- The reaction is related to much of Pd chemistry you have covered
- Below is an example of a **chiral** variant of the **Schrock metathesis** catalyst
- The reaction involves **desymmetrisation** by selective reaction if one disubstituted alkene



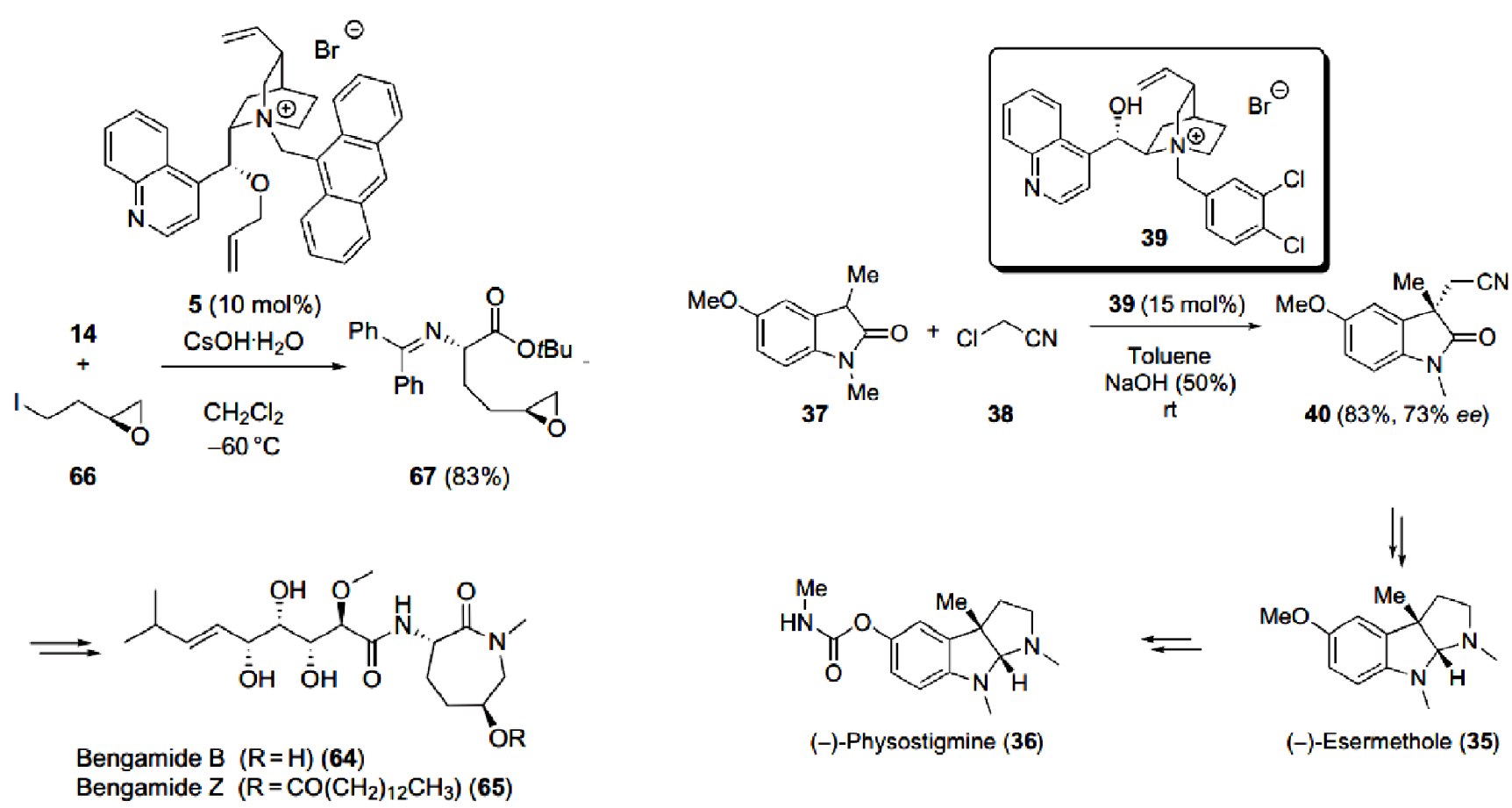


Chiral Phase Transfer Catalysis

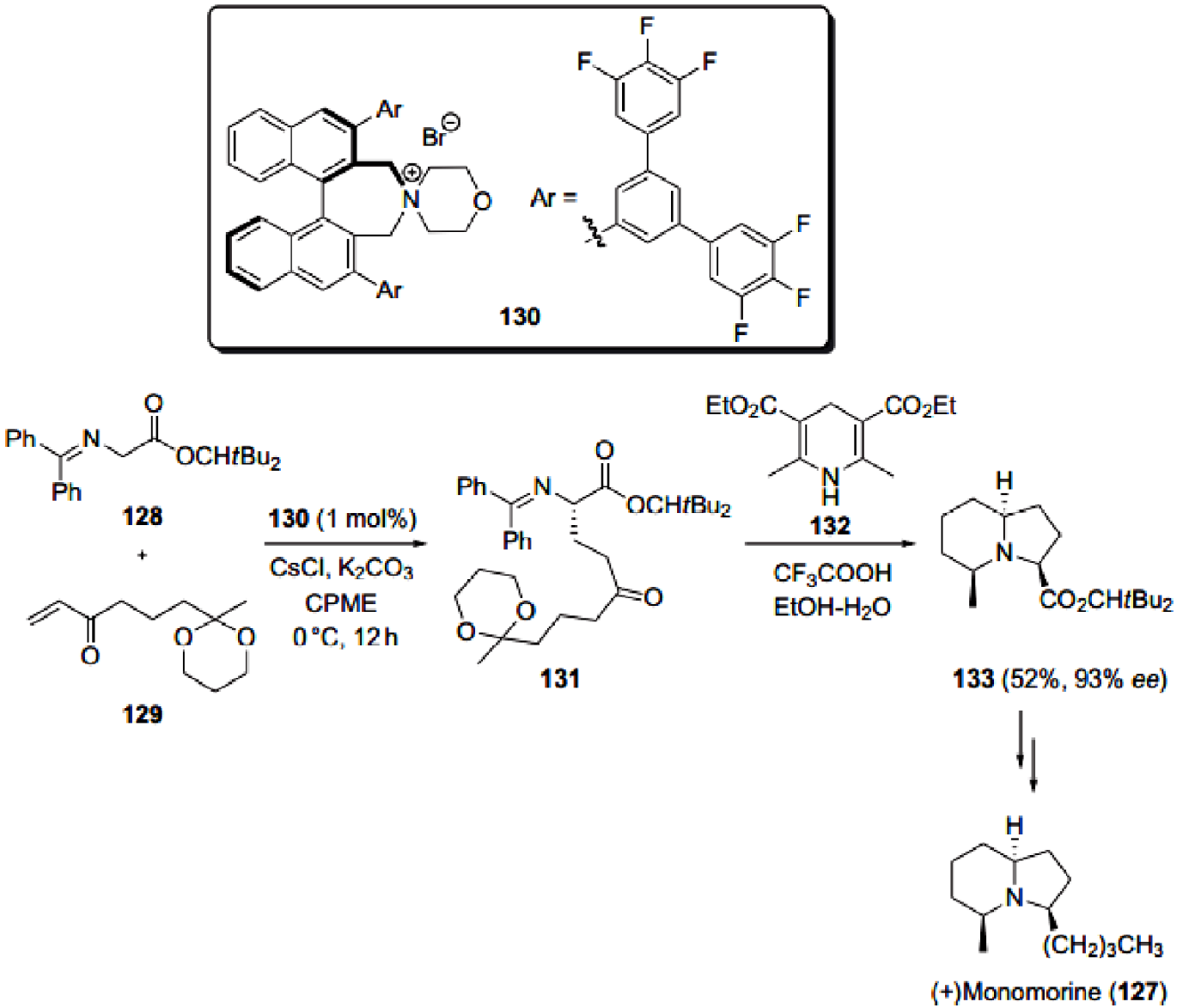




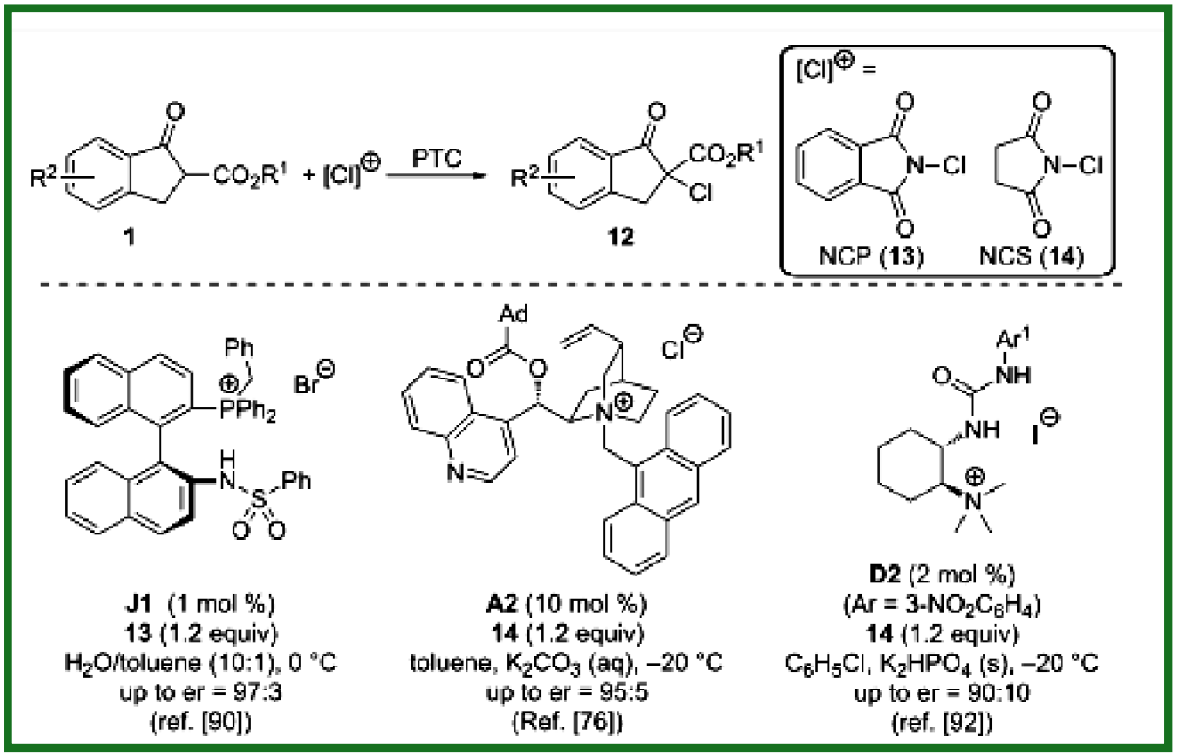
Chiral Phase Transfer Catalysis a-alkylation

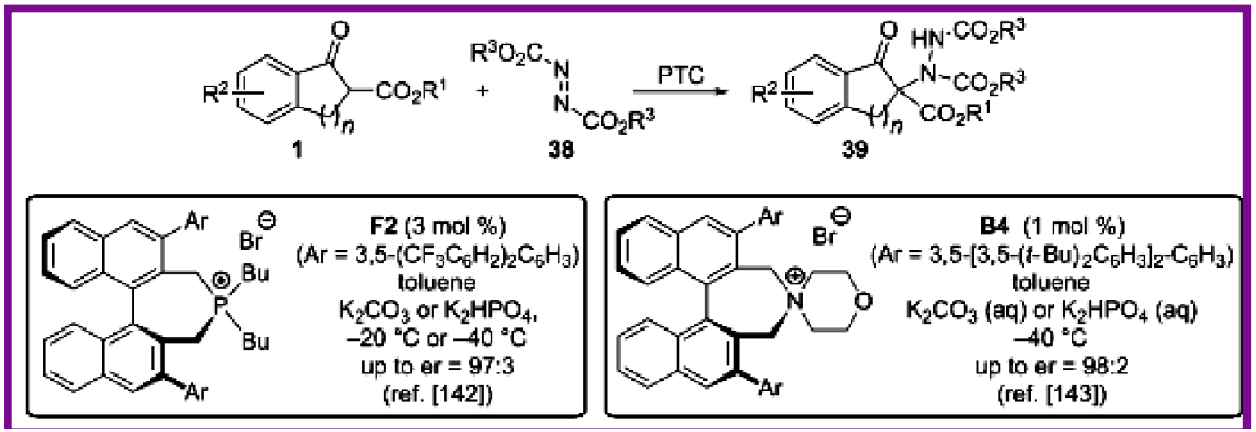


Chiral Phase Transfer Catalysis – Conjugate addition

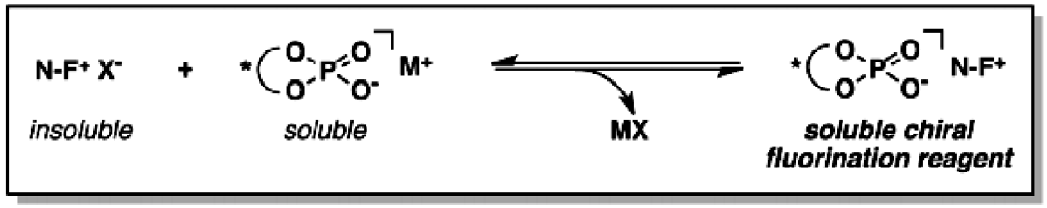


Chiral Phase Transfer Catalysis a-heterofunctionalisation

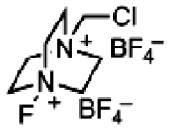




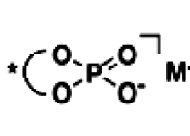
Chiral Phase Transfer Catalysis a-heterofunctionalisation



N-F⁺ X⁻ =



1, Selectfluor



M⁺ =

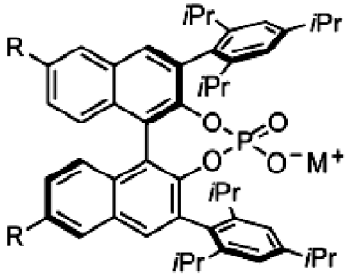
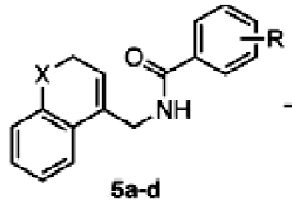


Fig. 1. Catalytic formation of a chiral fluorination reagent via chiral anion–mediated phase transfer in nonpolar solvents.

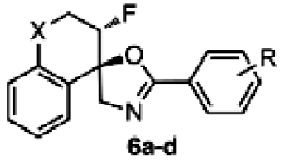
2a, R = C_8H_{17}, M^+ = Na^+
2b, R = C_8H_{17}, M^+ = H^+
2c, R = H, M^+ = H^+

A

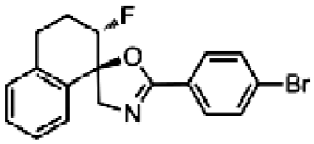


5a-d

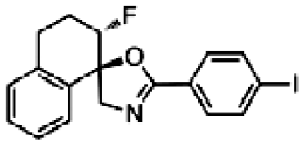
10 mol % **2b**
1.5 equiv. Selectfluor
1.25 equiv. Na_2CO_3
1:1 C_6H_5F/hexanes, 23 °C, 24 h



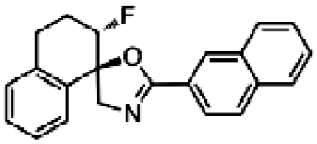
6a-d



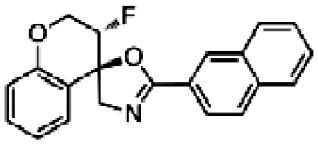
6a
87% yield (>20:1 dr)
93% ee



6b
71% yield (>20:1 dr)
93% ee



6c
80% yield (>20:1 dr)
96% ee



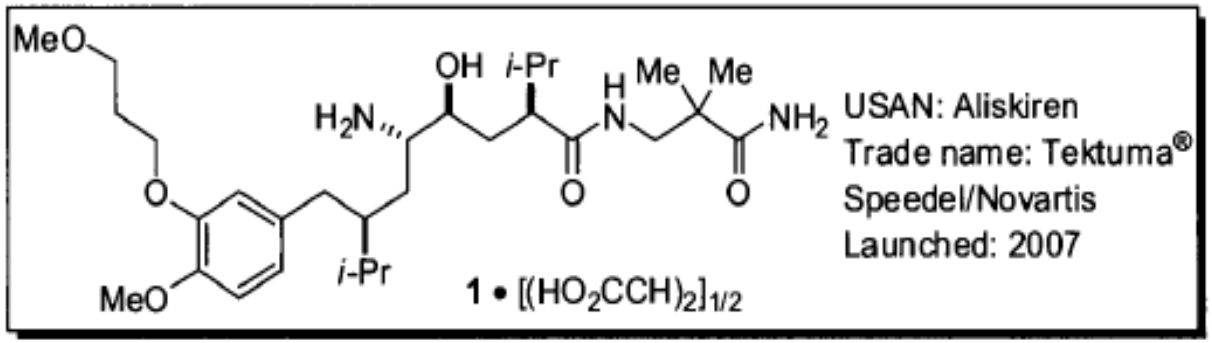
6d
70% yield (>20:1 dr)
92% ee

Summary of Asymmetric Synthesis Methods

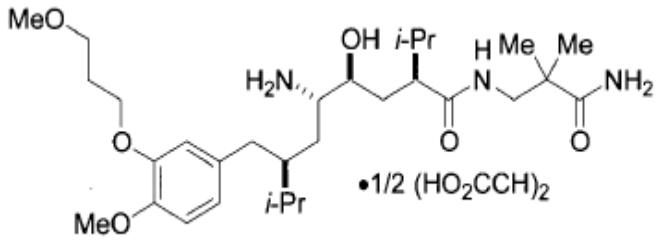
Method	Advantages	Disadvantages	Examples
resolution	both enantiomers available	maximum 50% yield	synthesis of (–)-propranolol
chiral pool	100% ee guaranteed	often only 1 enantiomer available	synthesis of (*R*)-sulcatol
chiral auxiliary	often excellent ee's; built in resolving agent	extra steps to introduce and remove auxiliary	oxazolidinones
chiral reagent	often excellent ee's; stereoselectivity can be independent of substrate control	only a few reagents are successful and often only for a few substrates	alpine-borane®, Brown allylation reagents
chiral catalyst	economical; only small amounts of recyclable material used	only a few reactions are really successful; frequently a lack of substrate generality	asymmetric hydrogenation; Sharpless epoxidation

- Hopefully this course has shown that the area of stereoselective synthesis (or more particularly, methodology for stereoselective synthesis) is a vast & fascinating topic
- There are many reactions we have not covered (there is already far too much material in the course)

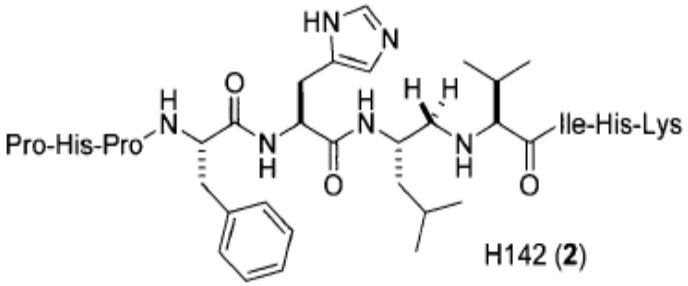
Η ανάπτυξη της ασύμμετρης σύνθεσης του Aliskiren (Tekturna)



The Renin-Angiotensin System (RAS)



aliskiren (**1**)



Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-✂-Val-Ile...

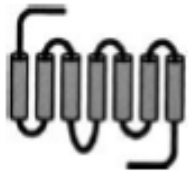
Angiotensinogen ***renin***

↓

Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-✂-His-Leu

Angiotensin I ***ACE***

↓

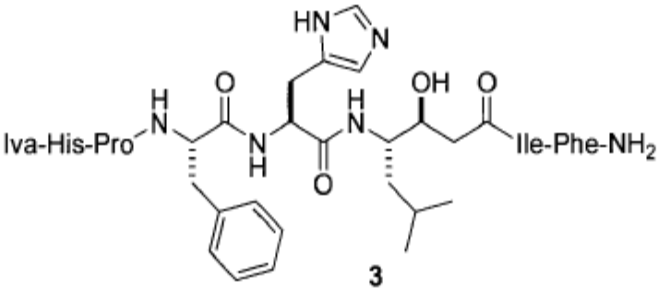
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe + 

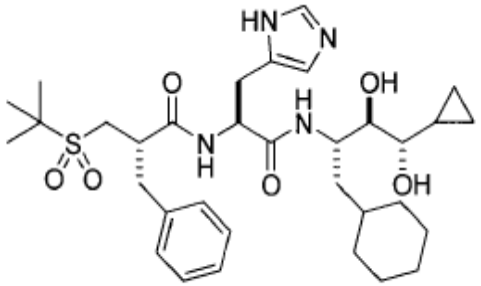
Angiotensin II

AT_1 receptor

↓

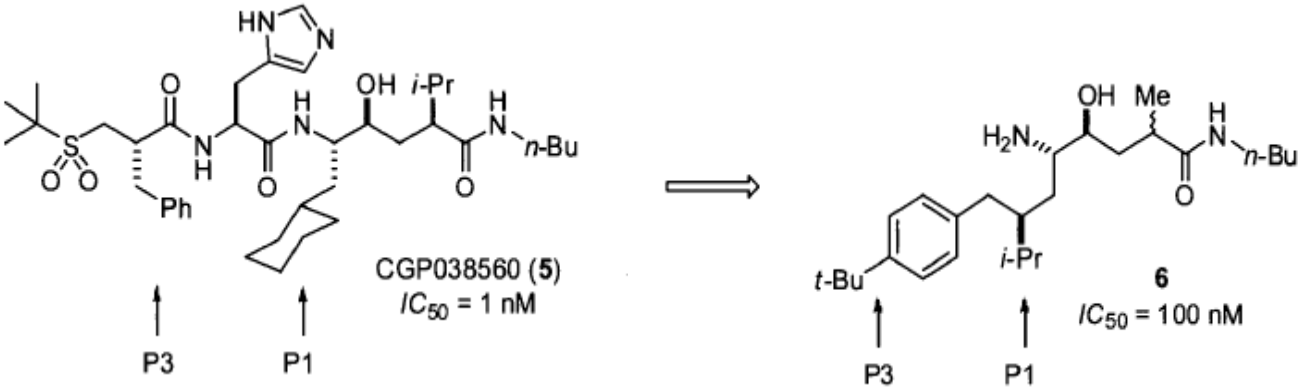
vasoconstriction, aldosterone release, sodium resorption





remikiren (**4**)

Structure-Activity Relationships (SARs)



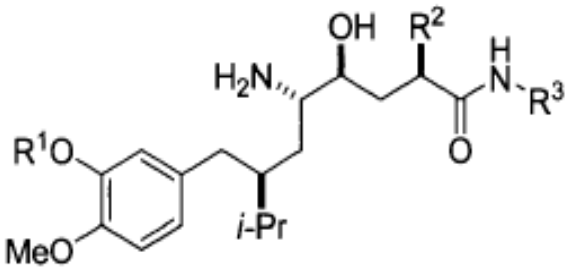
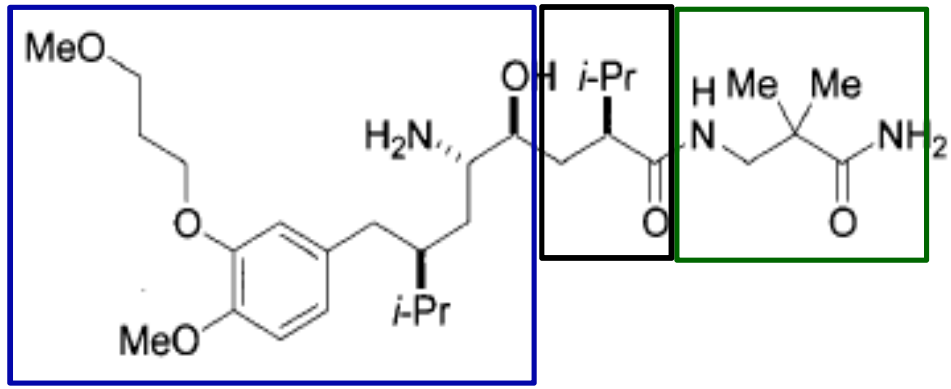


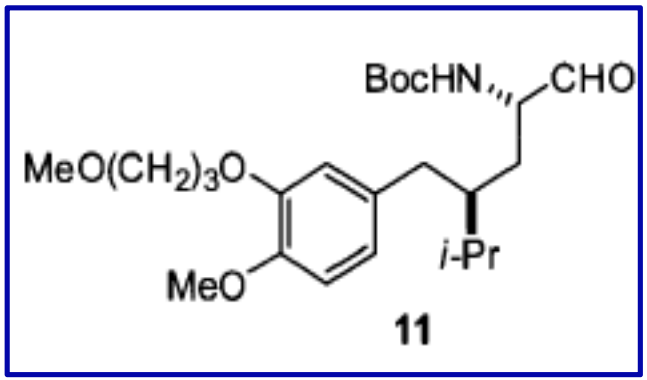
Table 2. Structure–Activity Relationships and the Discovery of Aliskiren

Cpd	R^1	R^2	R^3	Purified Renin IC_{50} (nM)	Plasma Renin IC_{50} (nM)	Peak ΔMAP (mm Hg)[a]	ΔMAP duration (h)[b]
7	$-(CH_2)_3OMe$	Me	*n*-Bu	1	1	–9	**8**
8	$-(CH_2)_4Me$	Me	*n*-Bu	4	70	NR	NR
9	$-(CH_2)_3OMe$	Me	$-(CH_2)_2CONH_2$	7	17	NR	NR
10	$-(CH_2)_3OMe$	*i*-Pr	$-(CH_2)_2CONH_2$	1	3	NR	NR
1	$-(CH_2)_3OMe$	*i*-Pr	$-CH_2C(Me)_2CONH_2$	0.6	0.6	–30	>24

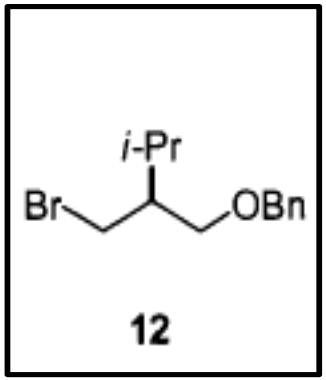
a, Maximum change in mean arterial pressure (MAP) from baseline upon 3 mg/kg oral dose in telemetered, sodium-depleted marmosets. *b*, Time until MAP levels returned to baseline. NR = not reported.

Retrosynthetic analysis of Discovery Route

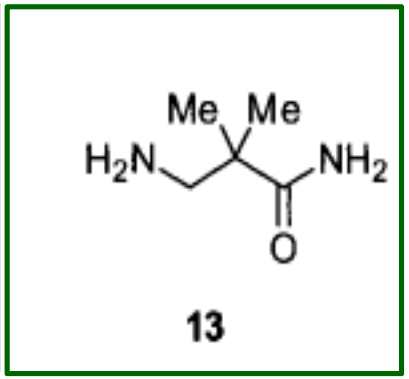




11

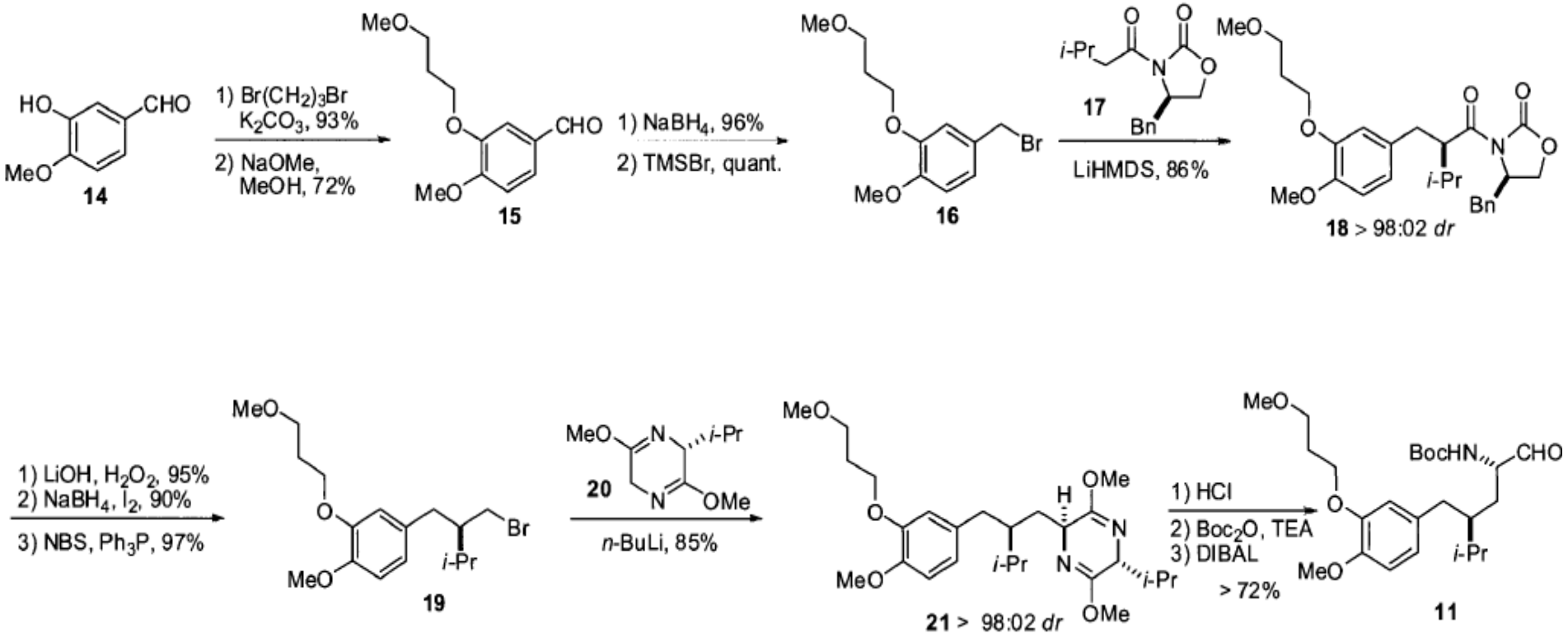


12

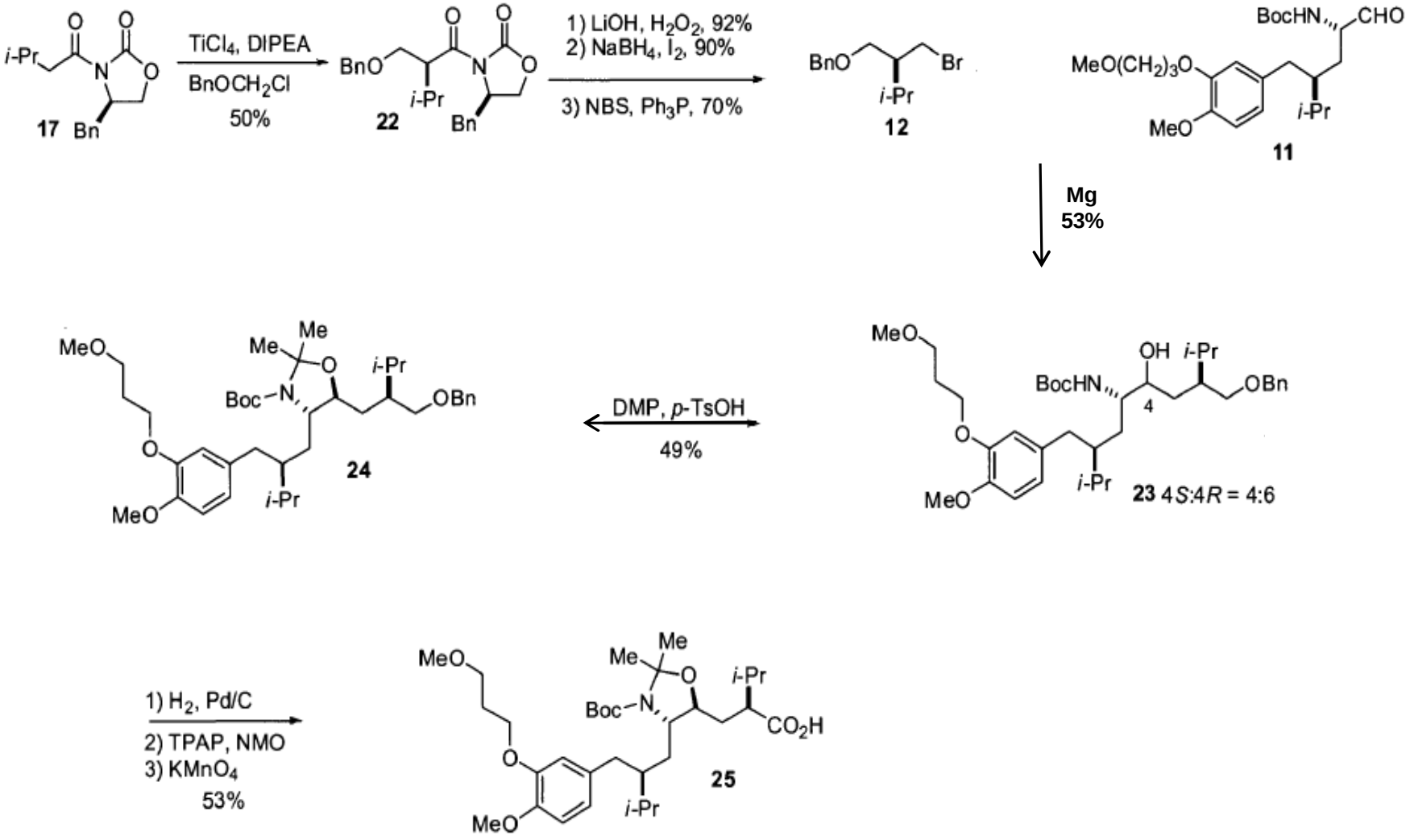


13

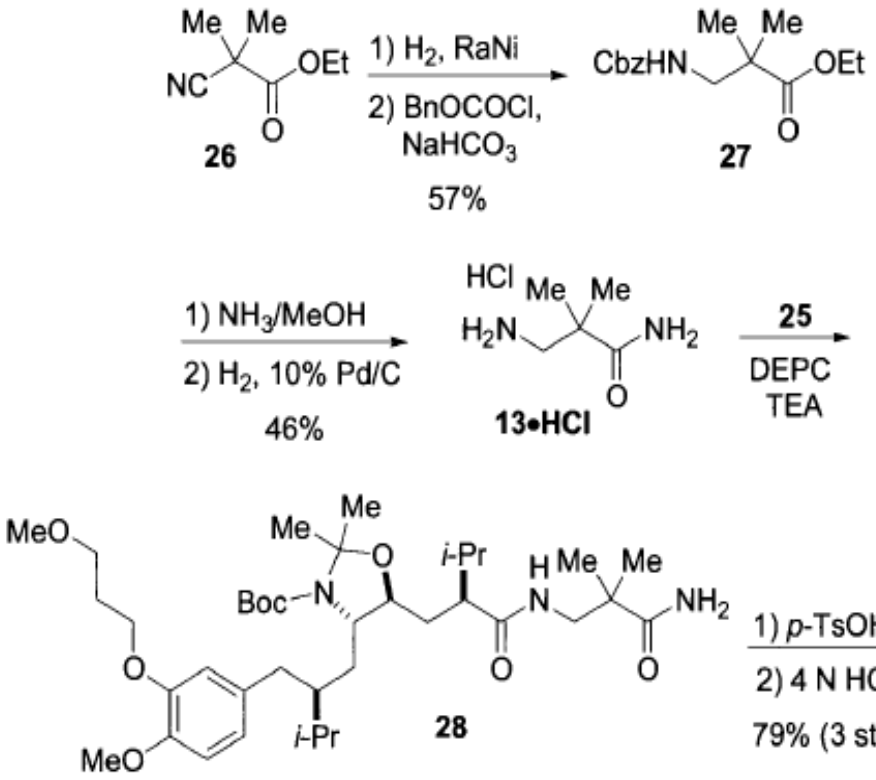
Synthesis of aldehyde fragment 11



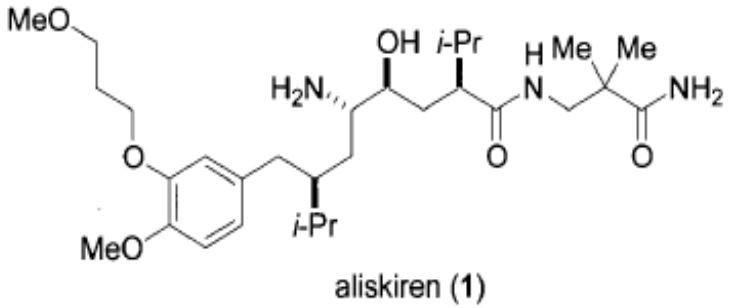
Synthesis of fragment 12 and coupling with fragment 11



Synthesis of fragment 13 and completion of synthesis

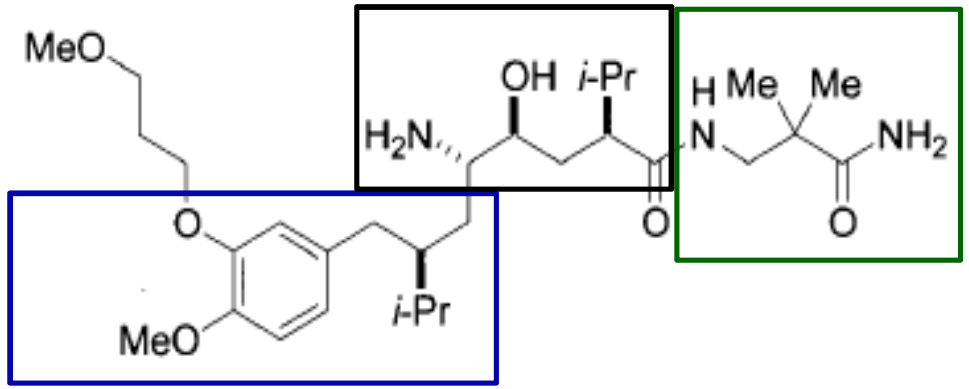


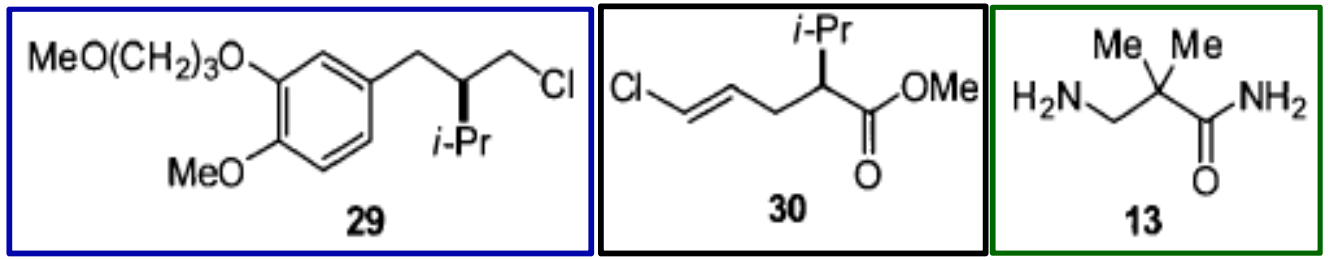
Discovery route:
20 steps and 3% yield overall



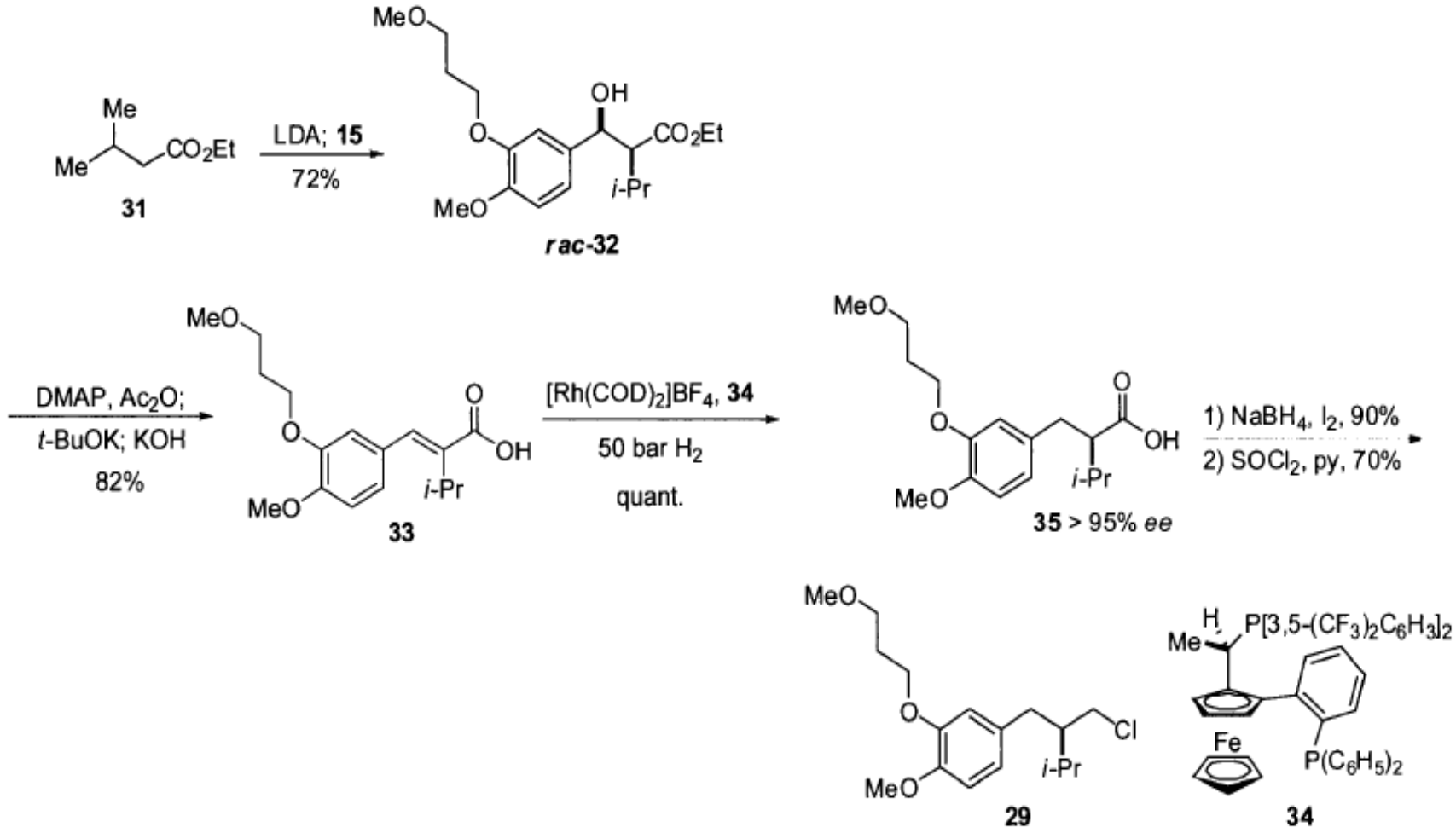
aliskiren (**1**)

Development towards the manufacturing route

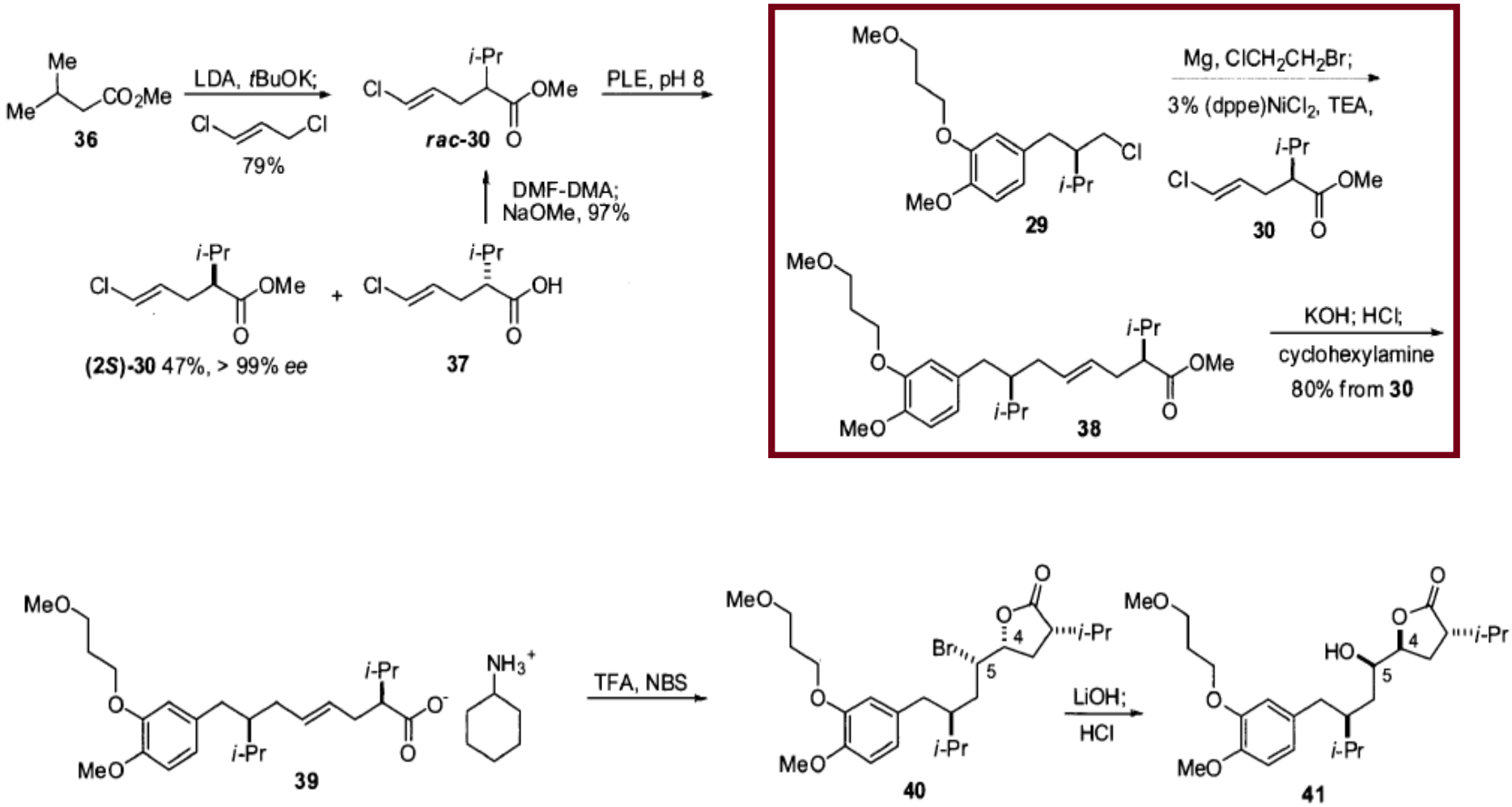




Synthesis of 29 with catalytic asymmetric hydrogenation



Synthesis of 30 and coupling with 29



Stereochemistry of bromolactonisation & End Game