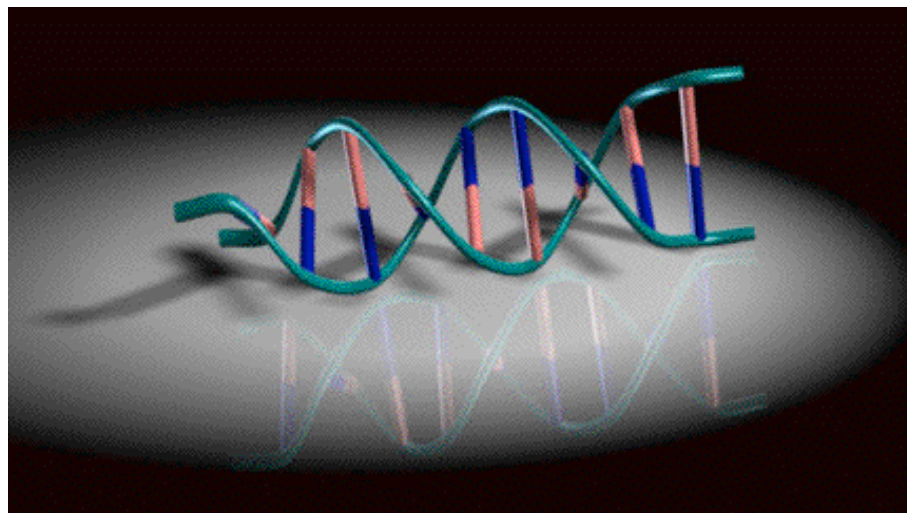


Conservation of Helical Asymmetry

Bryon Simmons
MacMillan Group Meeting
November 20, 2007

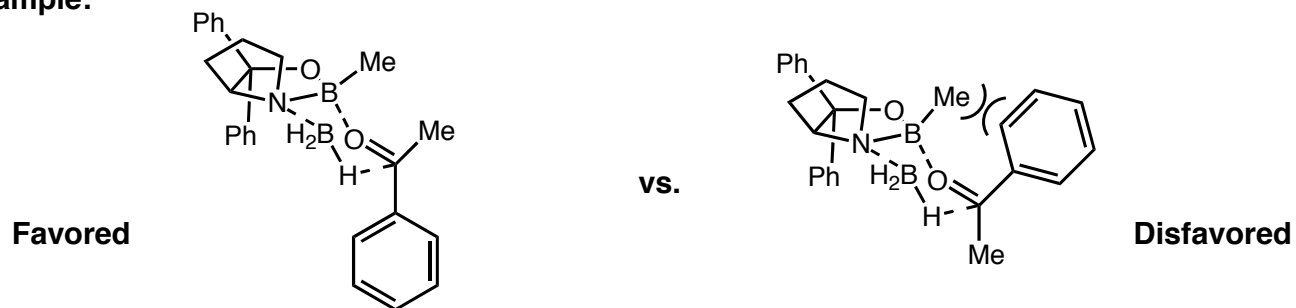


Wang, D. Z., *Tetrahedron*, **2005**, *61*, 7125
Wang, D. Z., *Tetrahedron*, **2005**, *61*, 7134
Wang, D. Z., *Mendeleev Comm.*, **2004**, *14*, 244
Wang, D. Z., *Chirality*, **2005**, *17*, 2005

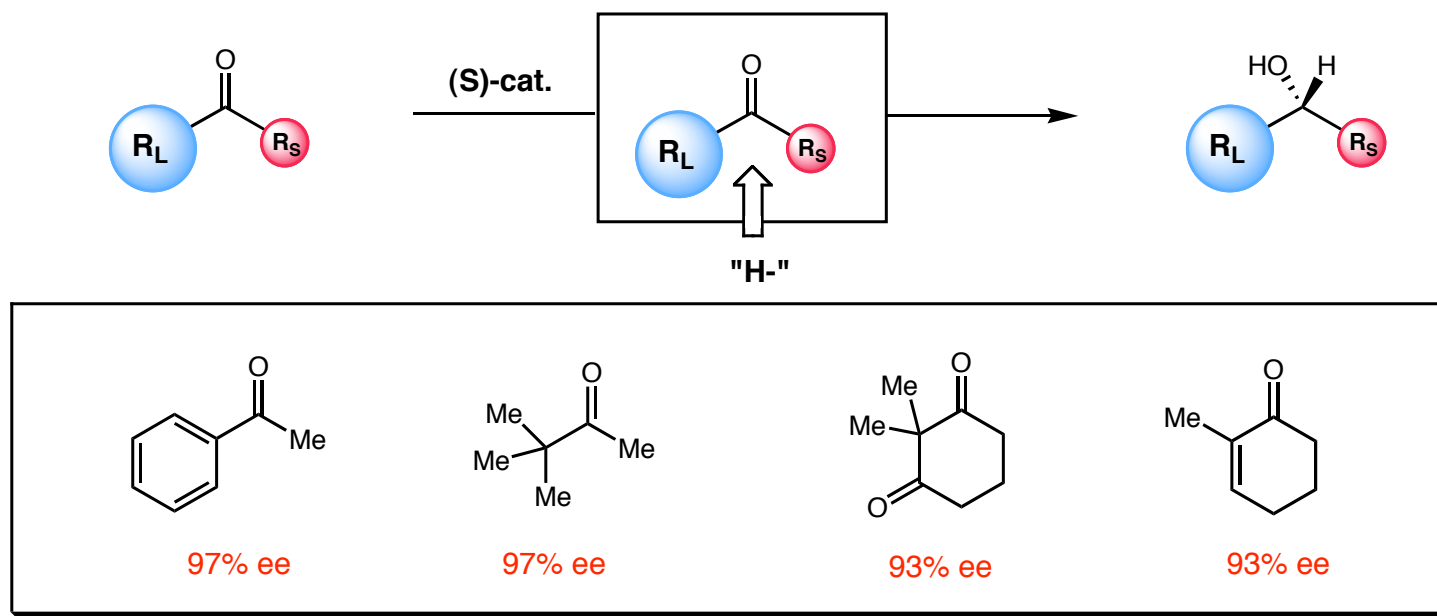
Traditional Rationale for Enantioselective Catalysis

- Enantioselection is usually thought to have a geometric origin, and therefore favorably develop through a transition state that has less steric hindrance. It is often analyzed by steric size-based considerations.

For example:

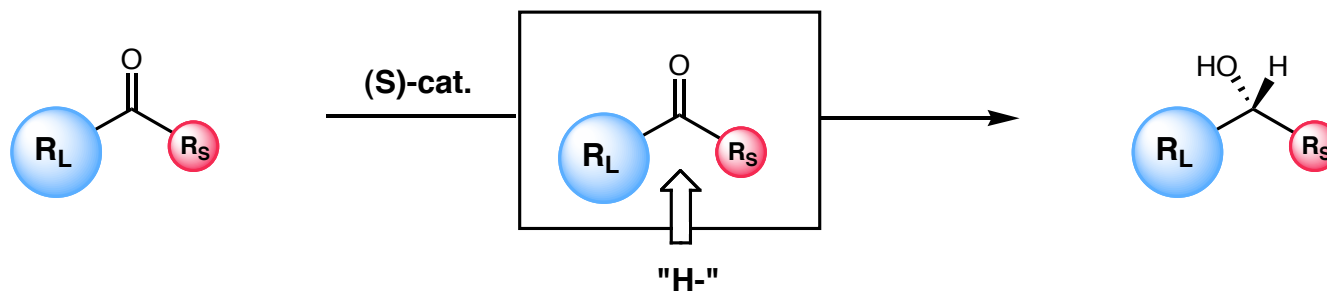


- Our models are usually generated after an empirical investigation of substrate scope.

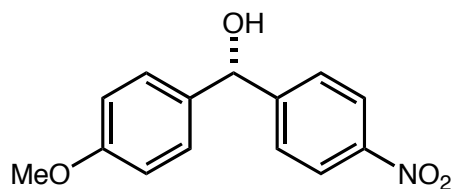


When the Steric Rationale Fails?

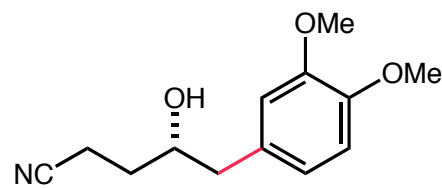
- However, experimental observations contradicting the prevalent steric theories abound in the literature. For example, these intriguing CBS reduction results don't seem to fit well within the steric model.



- In these cases R_L is essentially isosteric with R_S . Why is the selectivity so high?

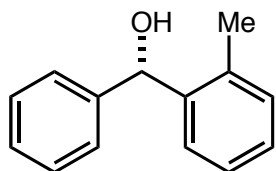


97% ee

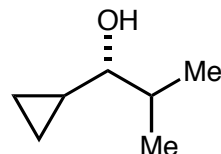


82% ee

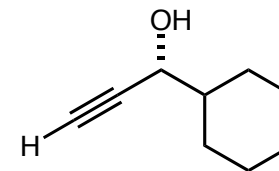
- Why would these examples give the opposite enantiomer than the model predicts?



95% ee



91% ee



98% ee

Corey, *ACIE*, 1998, 37, 1986

Molecular Chirality: Something Beyond Geometry?

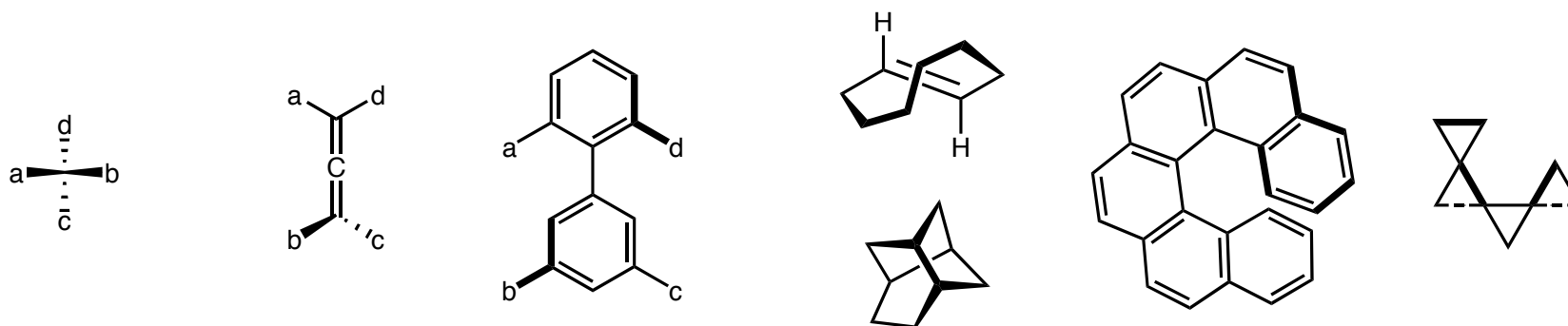
- Term "chirality" first coined in 1893, from Greek "cheir" (hand):

"I call any geometrical figure, or group of points, chiral, and say it has chirality if its image in a plane mirror ideally realized, cannot be brought to coincide with itself."

-Lord Kelvin



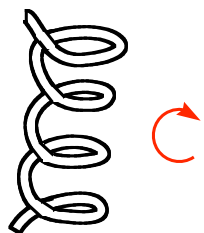
- Chirality was descriptor used by physicists to describe objects in the macro world even before the electron was discovered. Since then molecular chirality has been understood as a purely geometrical property.



- While it is true that chiralities in everyday objects and those in the molecular world share a geometrical link, it is intriguing to ask whether in the former there are also electronic implications. What is the common electronic structural character of these diverse molecular chiralities that makes them optically active?

Molecular Chirality: Something Beyond Geometry?

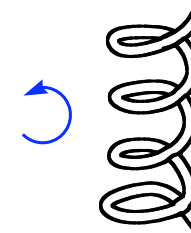
- It was first suggested by Fresnel in 1827 that a chiral microstructure, helical in nature is required for a substance to have different refractive indices for right and left-circular polarized light and thus exhibit optical activity.



left-hand helix

LHH

"...a **helix** system in which electrons are constrained to move on **helical** paths generally enters, explicitly or implicitly, into **all of the major theoretical models of optical activity**... A generally successful model of optical activity must require a connection between polarizability and bond structure."

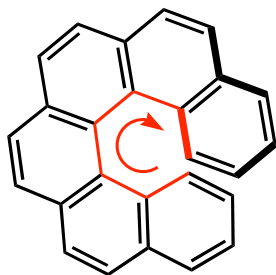


right-hand helix

RHH

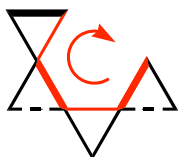
- J. H. Brewster [Top. Stereochemistry 1967, 2, 1]:

- Tinoco and Woody elegantly showed in 1964 that an electron constrained to move on a helix (the simplest chiral potential) does indeed lead to optical rotation and the sign is positive at long wavelengths.



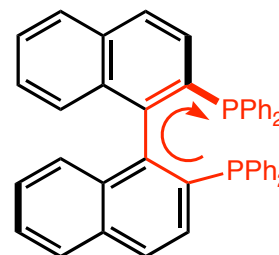
LHH

(C-C-C-C-C-C-C)



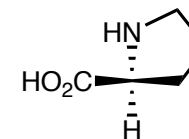
LHH

(C-C-C-C-C)



LHH

(P-C-C-C-C-P)

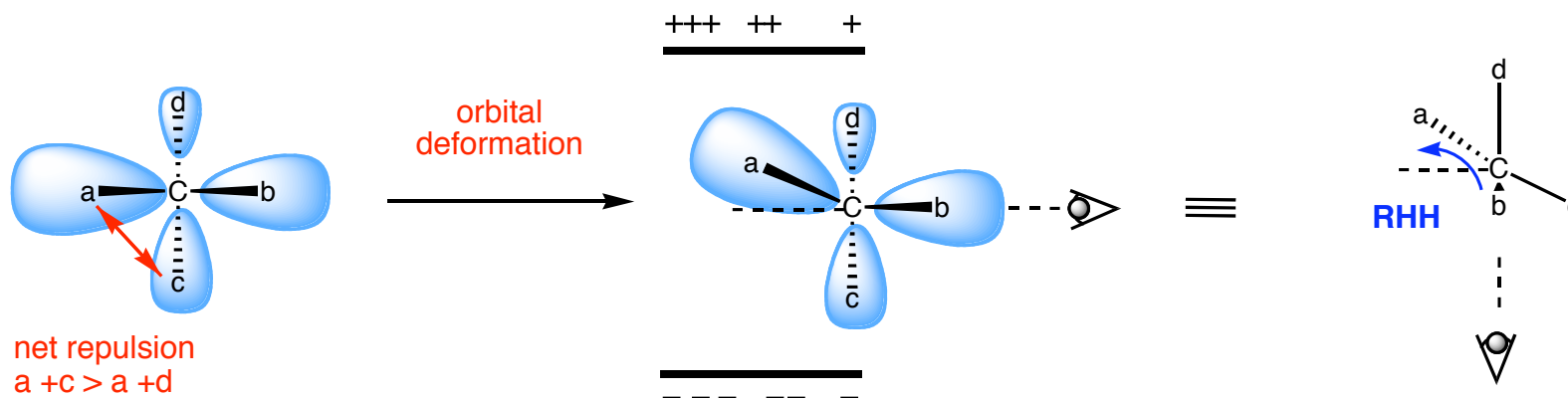


LHH

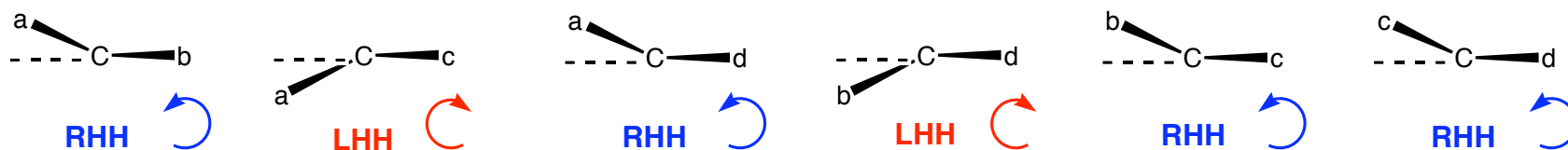
- Helical electronic topology exists in all chiral molecules. However despite the helix model's success, there seems to be a gap between theory and reality because helices in many simple molecules are hard to identify.

Assigning Helicity to Point-Chiral Molecules

- For a simple point-chiral molecule suppose that the polarizabilities of the substituents follow the trend $a > b > c > d$. The anisotropic fields of c and d should distort a -C- b from coplanarity into a microhelical structure.



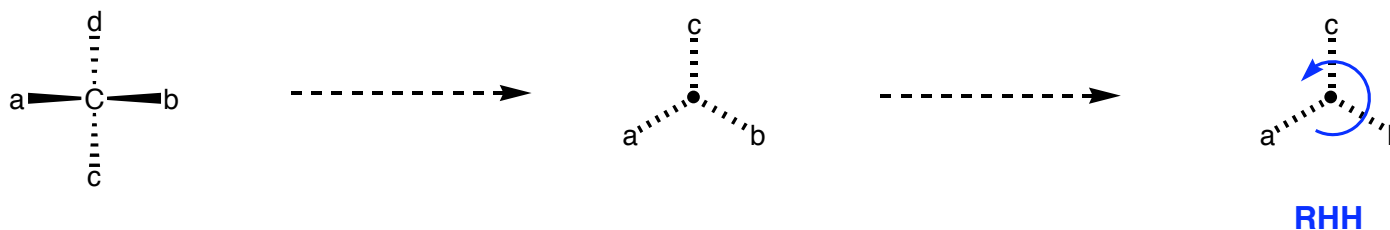
- If as in electronic theories of optical activity, the distortion increases with group polarizability, it is reasonable to expect the strength of repulsion represented by the double arrow to twist the a -C- b bond up. The bonds will thus be twisted into a right hand microhelix (**RHH**).



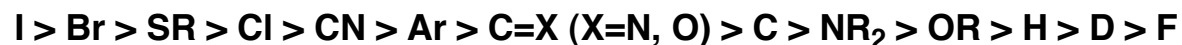
- Similar effects will twist the a -C- d , b -C- c , and c -C- d bond pairs into RHH's and the a -C- c and b -C- d bonds into LHH's. Since there are more RHH's than LHH's, the molecule has a net right handed helicity. If any two groups were identical the molecule's helicity and optical activity would disappear.

Assigning Helicity to Point-Chiral Molecules

- There is an easier way to determine helicity for simple molecules. Place least polarizable substituent coming out of plane. Travel from most to least polarizable substituent.



- Polarizability characterizes the sensitivity of a group's electron density to distort in an electronic field. It increases with higher electron density, lower nuclear attraction, larger electron shells, larger volume and smaller HOMO-LUMO gap.

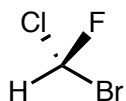


Brewster, *JACS*, **1959**, *81*, 7475

Miller, *JACS*, **1990**, *112*, 8533

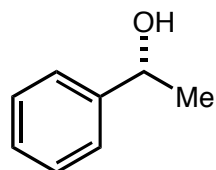
Assigning Helicity to Chiral Molecules

- Examples of helicity on point-chiral molecules:



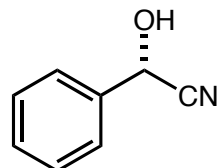
(+)-1 RHH

Br > Cl > H > F



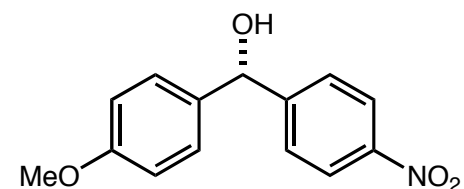
(+)-2 RHH

Ar > Me > OH > H



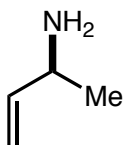
(-)-3 LHH

CN > Ar > OH > H



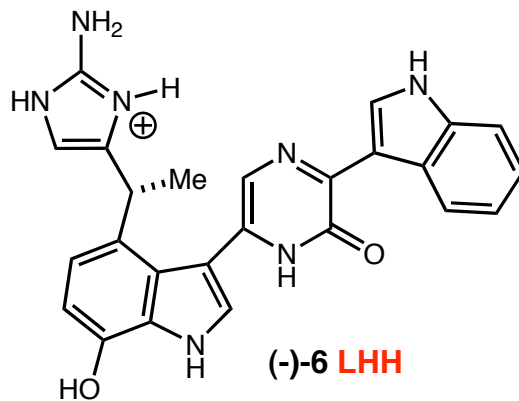
(+)-5 RHH

PhOMe > PhNO₂ > OH > H



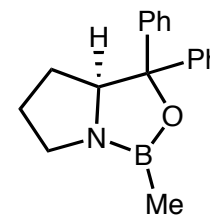
(-)-4 LHH

C=C > Me > NH > H



(-)-6 LHH

PhOH > Het > Me > H



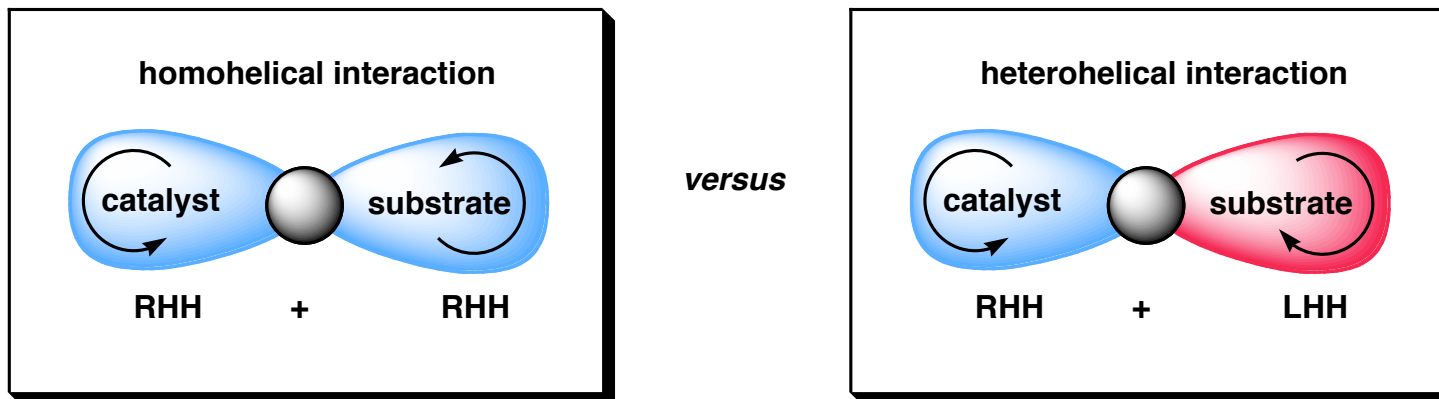
(+)-7 RHH

CH₂ > CR₃ > N > H

- For simple molecules with point chirality, the helicity also correctly predicts sign of optical rotation and stereochemistry base on polarizability sequence.

Are There Alternatives to Steric Rationale?

- David Z. Wang, of Columbia University, puts forth an electronic theory of chiral interactions or chiral version of standard HSAB theory that views all chiral molecules as **helices**.

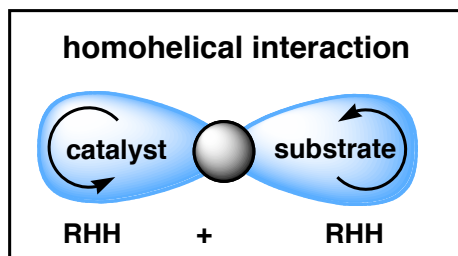


- Any two chiral molecules (eg. catalyst and substrate) will interact in such a way that their chirality/electronic helicity match resulting in a **homohelical interaction** or oppose each other giving rise to a **heterohelical interaction**.
- The homohelical interaction is calculated to be as high as **9.5 (kcal/mol)** lower in energy than the complimentary heterohelical interaction. This has its physical roots in the fact that the homohelical interaction expands the helicity of the system while the heterohelical interaction compresses the helix.
- The **conservation of electronic helicity** therefore has implication anytime two chiral molecules interact--for example asymmetric catalysis, kinetic resolution, chiral chromatography and even liquid crystals.

Wang, D. Z., *Tetrahedron*, **2005**, *61*, 7125
Wang, D. Z., *Tetrahedron*, **2005**, *61*, 7134
Wang, D. Z., *Mendeleev Comm.*, **2004**, *14*, 244
Wang, D. Z., *Chirality*, **2005**, *17*, 2005

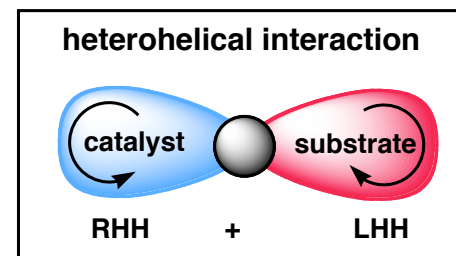
Electron-on-a-Helix Model

- In 1964 Tinoco and Woody showed that the states and eigenvalues of an electron constrained to move on a helix can be solved exactly. The model is simplest for a chiral molecule and has proven analytically effective when applied to a variety of real systems. The energy of an electron of mass m constrained on a k -turn helix of a radius a and pitch $2\pi b$ is:



$$E_n = \frac{h^2 n^2}{8mk^2(a^2 + b^2)}$$

where $n = 1, 2, 3 \dots$



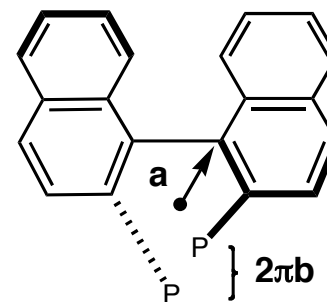
- A **homohelical interaction extends the helix**, it can be viewed as adding an additional turn k' radius a' and pitch $2\pi b'$ to the original helix. Contrast a diastereomeric **heterohelical interaction compresses** the helix and subtracts the same.

$$E_{homo} = \frac{h^2 n^2}{8m(k + k')^2([a + a']^2 + [b + b']^2)}$$

$$E_{hetero} = \frac{h^2 n^2}{8m(k - k')^2([a - a']^2 + [b - b']^2)}$$

- It follows that E_{homo} is always less than E_{hetero} .

$$\begin{aligned} \Delta\Delta G &= E_{homo} = 2E_{BINAP} \\ &= 2N_A h^2 \times 10^{-3} / 8nm_e k^2 (a^2 + b^2) \times 4.2 \times 10^{-20} \\ &= 43.7 / nk^2 (a^2 + b^2) \\ &= 9.5 \text{ (kcal/mol)} \end{aligned}$$

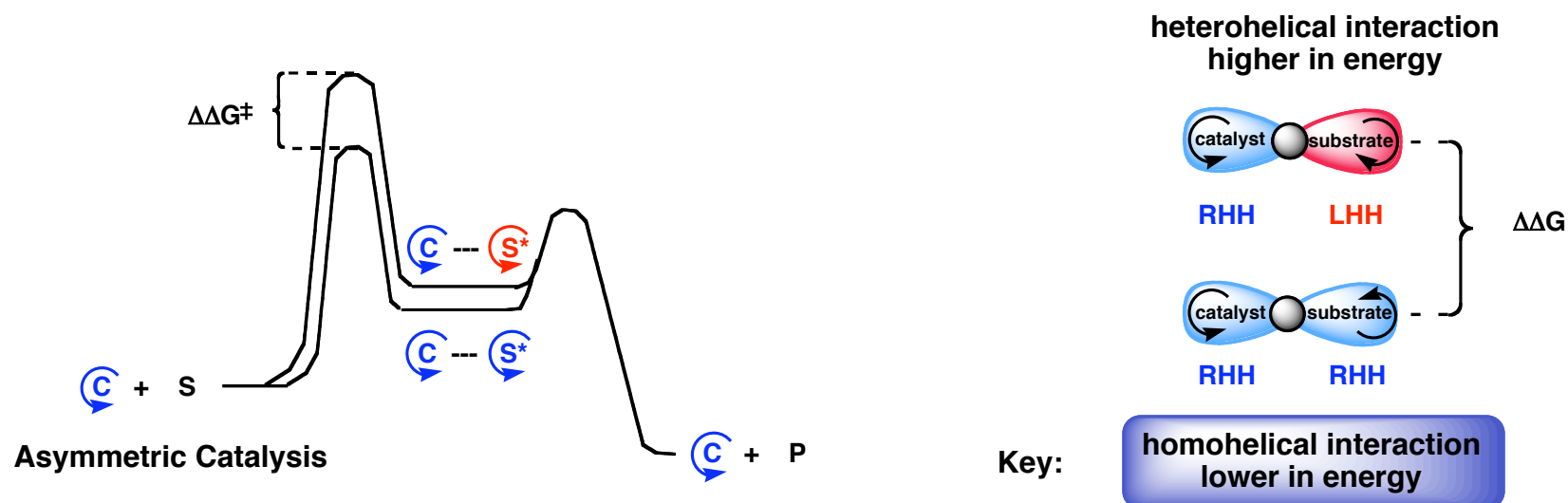


$$\begin{aligned} a &= 1.5 \text{ \AA} \\ b &= 0.24 \text{ \AA} \\ k &= 1 \\ n &= 2 \end{aligned}$$

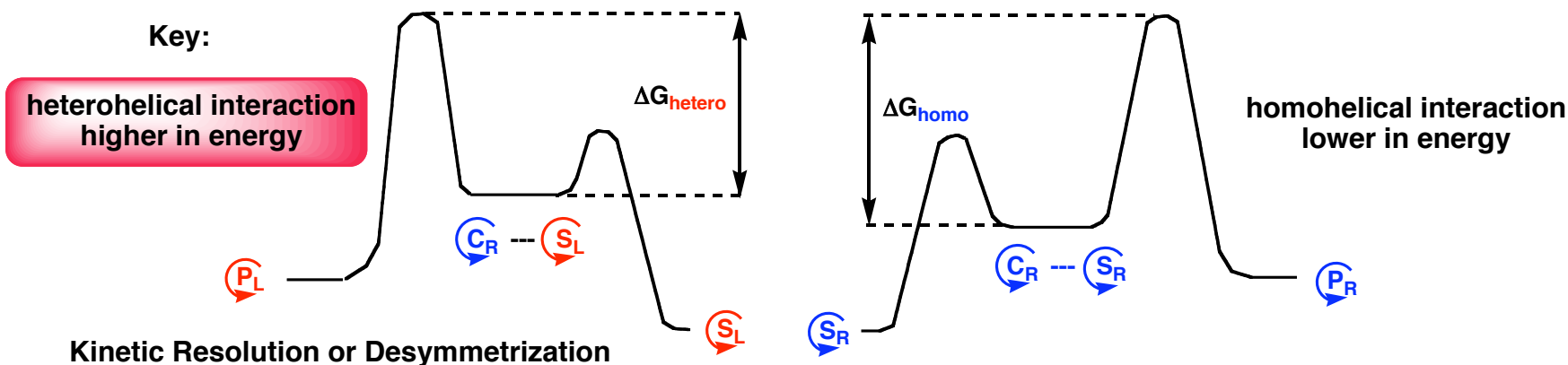
- $\Delta\Delta G^\ddagger = E_{homo} - E_{hetero}$. For BINAP + a perfectly helically matched substrate this could be as high as 9.5 kcal/mol.

Asymmetric Catalysis and Kinetic Resolution

- Initial coordination of pro-chiral substrate (**S**) to catalyst (**C**) induces helicity in substrate (**S***). Turnover then occurs and preference for one enantiomer of product (**P**) is observed.

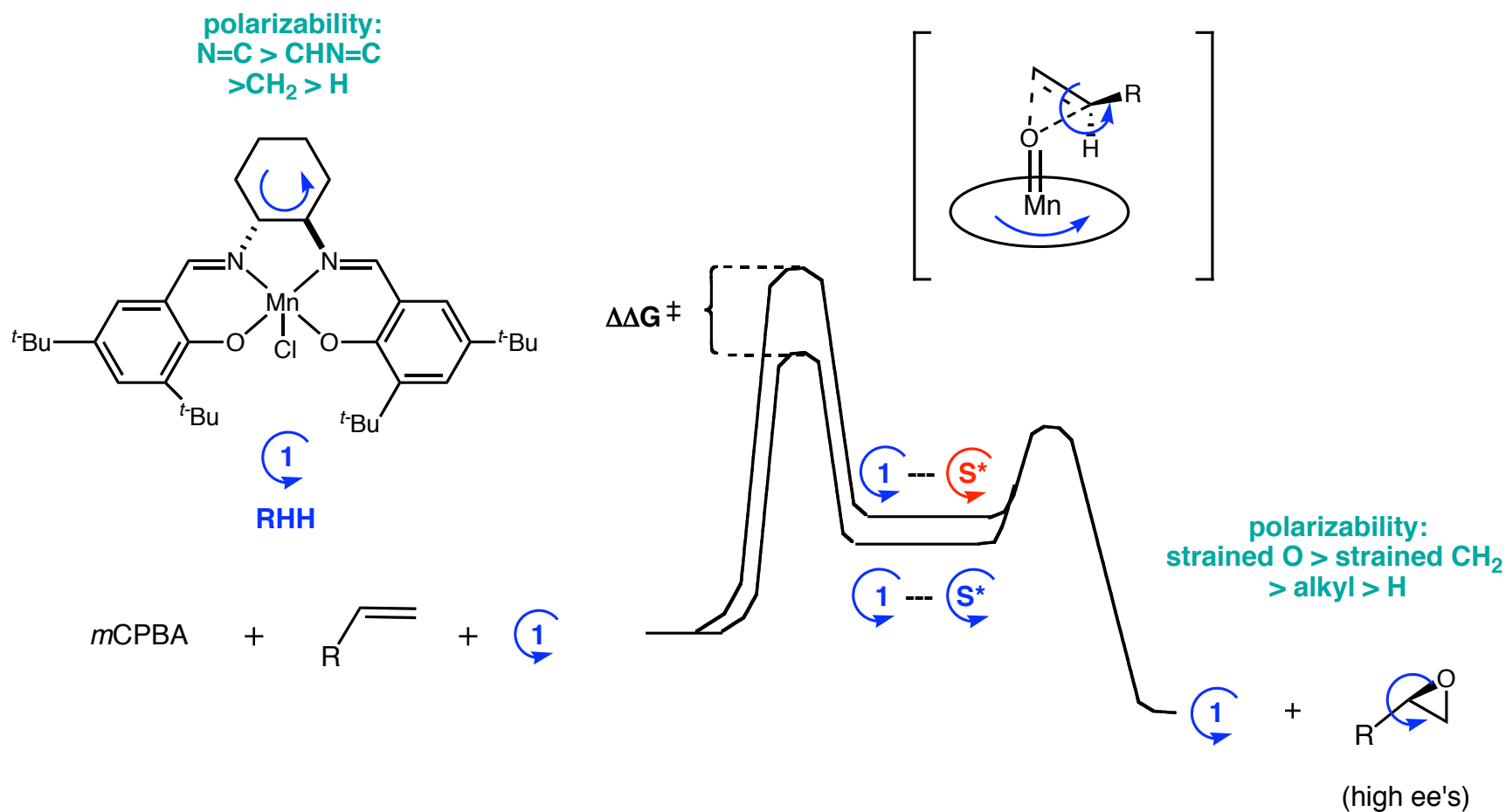


- Both enantiomers of substrate (**S_L** and **S_R**) bind to catalyst (**C_R**). The higher-energy heterohelical interaction leads to an increased rate for the heterohelical substrate-catalyst complex to form product (**P_L**) compared to the homohelical complex.



Jacobsen Epoxidation

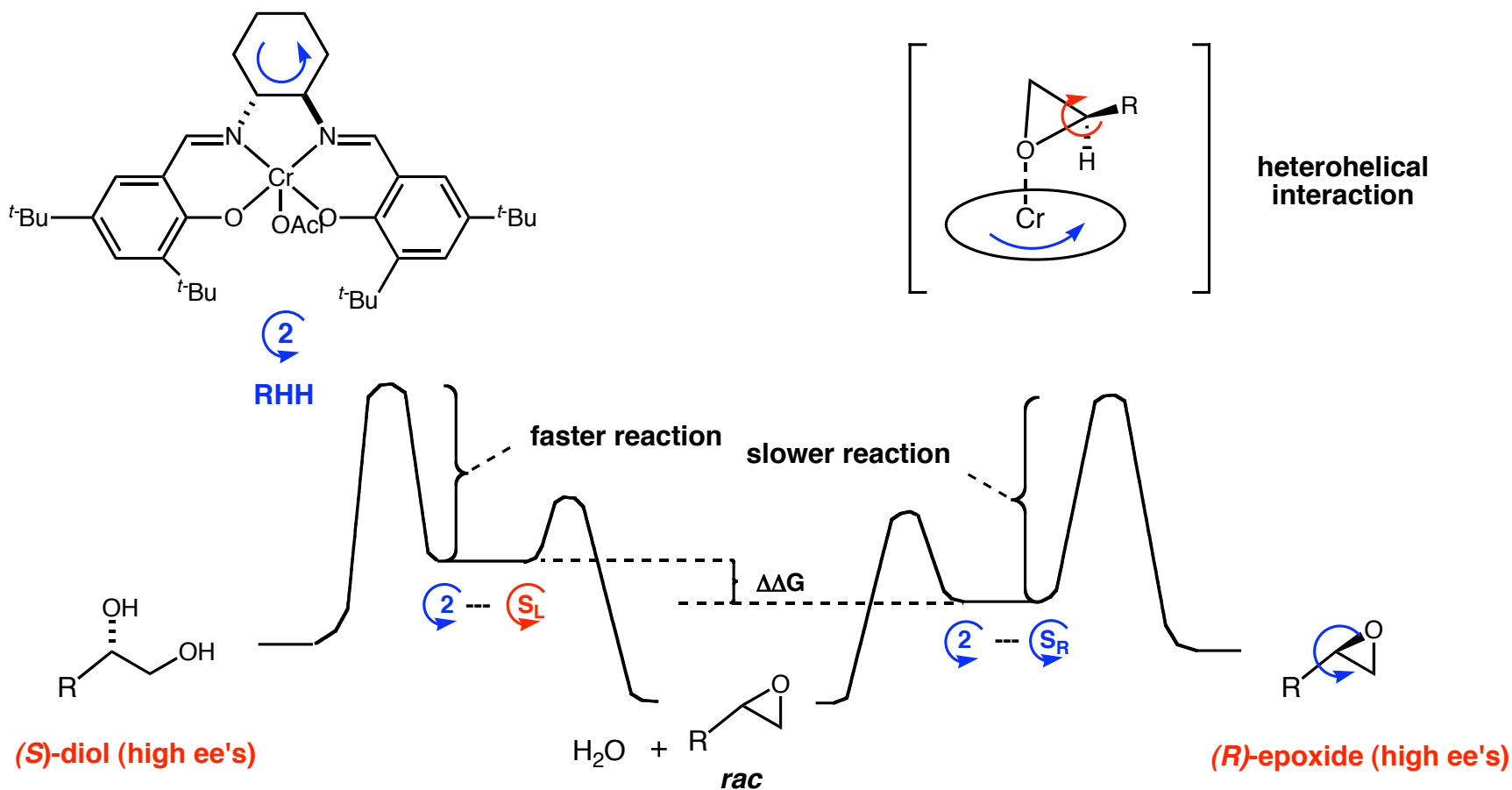
- The right-handed helical twisting in the Salen ring is homohelically transferred to the (*R*)-epoxide shown.



- The shown homohelical induction transition state is constructed on the basis of the mechanistic model proposed by Jacobsen.

Jacobsen Kinetic Resolution

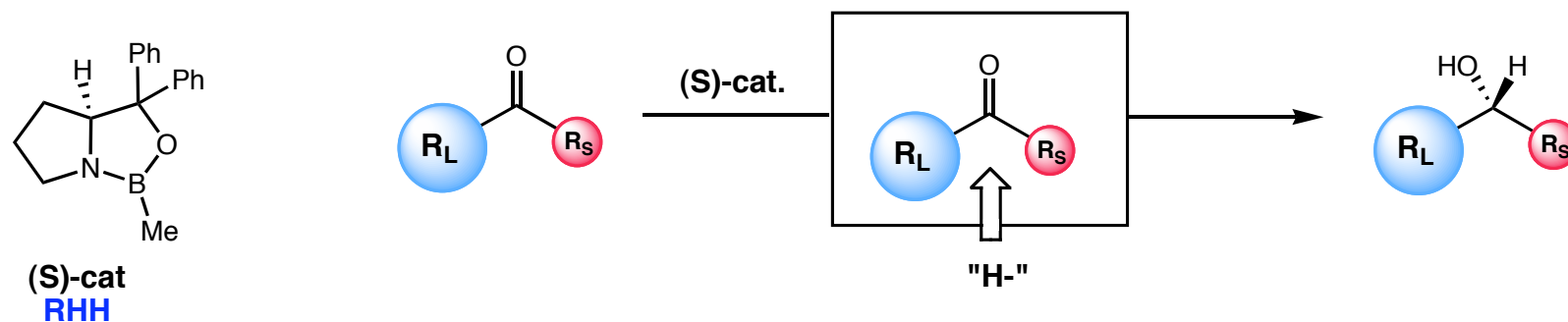
- Changing the metal from Mn to Cr and the axial ligand to OAc doesn't change the catalyst's helical handedness, but transforms the epoxidation catalyst into an efficient ring-opening catalyst.



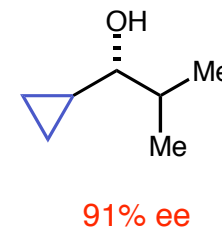
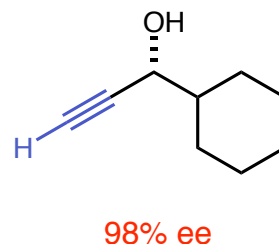
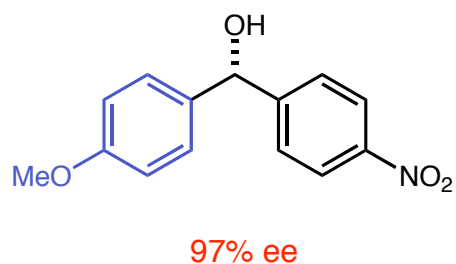
- The stereochemical interactions between the catalyst **2** and the epoxide should resemble the epoxidation transition state. It is indeed observed that the heterohelical (*S*)-epoxides undergo facile ring opening to afford enantioenriched 1,2 diols.

Homohelical Rationale for CBS Reduction

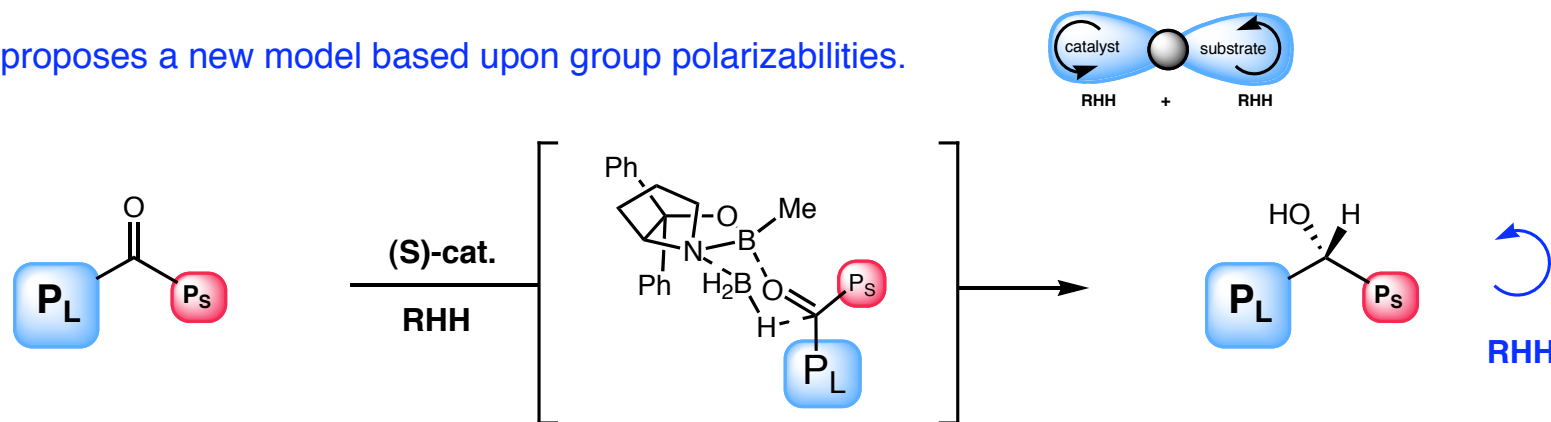
- Previous rationale based on sterics.



- How can steric arguments account for the following results? In each case the more polarizable group is highlighted in blue.

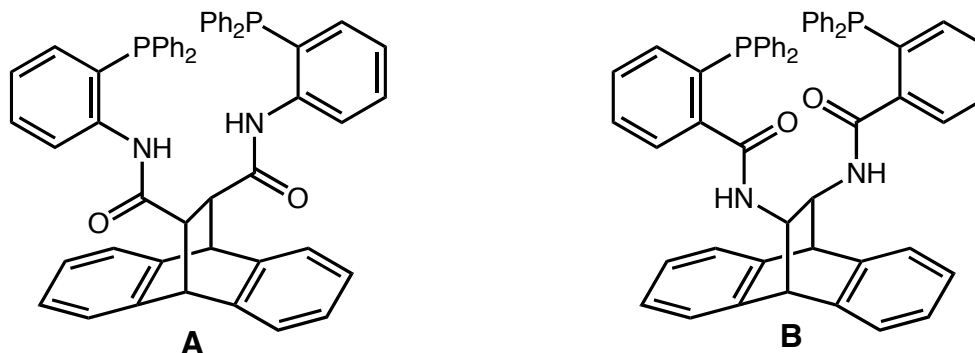


- Wang proposes a new model based upon group polarizabilities.

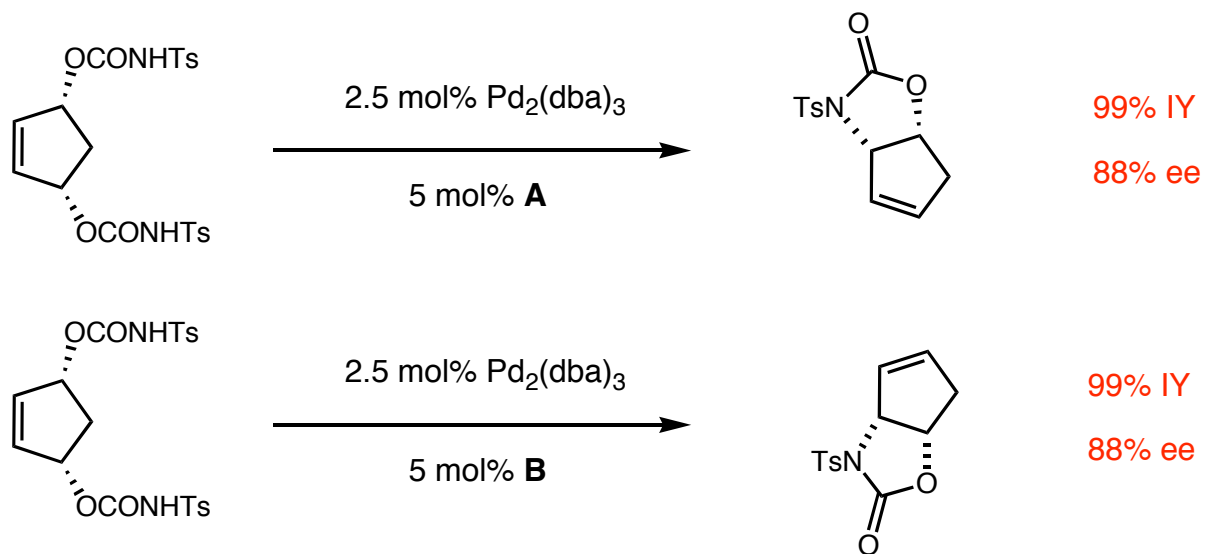


Asymmetric Desymmetrization of meso-Allylic Alcohols

- Ligands A and B should be isosteric:

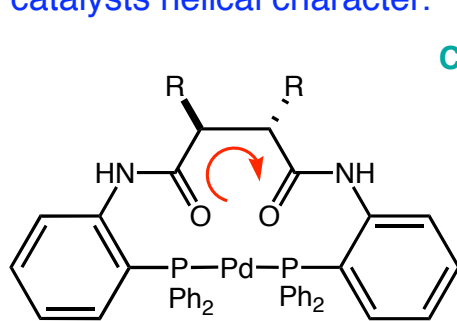


- However they afford products of the opposite enantiomeric series:

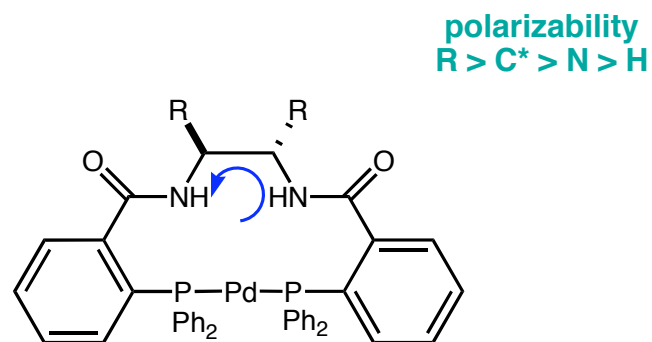


Asymmetric Desymmetrization of meso-Allylic Alcohols

- While the two catalysts have the same sense of chirality, inverting the amide function reverses the sense of the catalysts helical character.

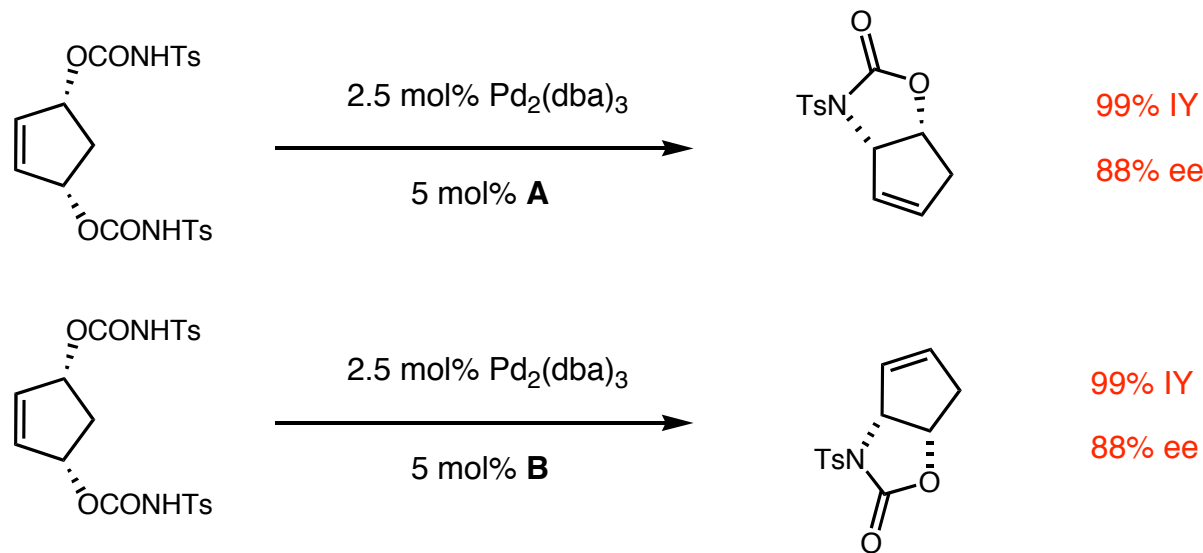


LHH



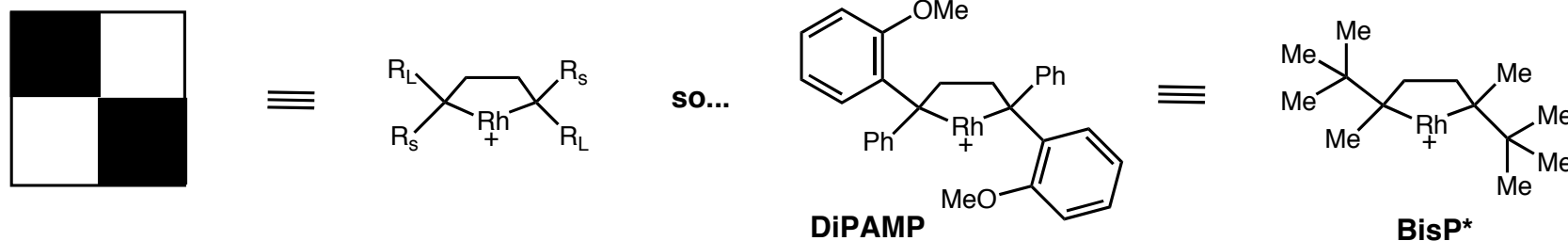
RHH

- The polarizability of the catalyst flips from $C=O > C$ to $N < C$. The helical nature of the catalyst then determines which enantiomer of product is formed.

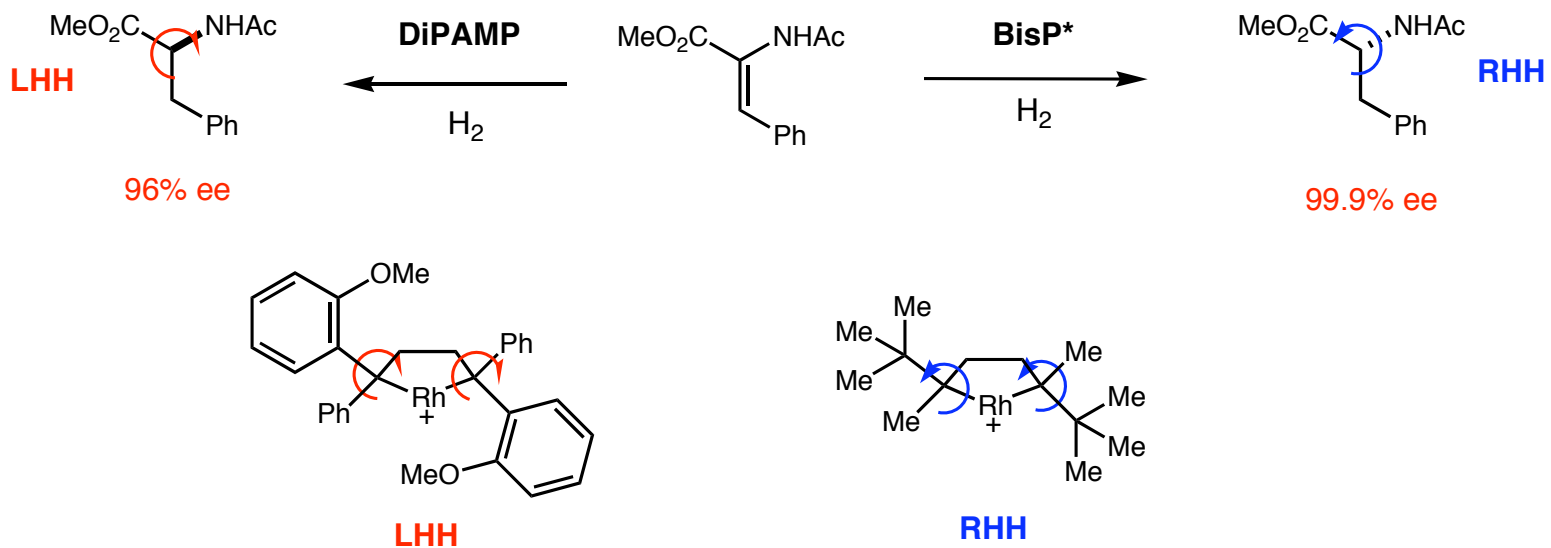


Asymmetric Rh Catalyzed Hydrogenations

- According to the quadrant rule, two chiral diphosphine catalysts with the same relative sterics should afford the same enantiomer of hydrogenation product.



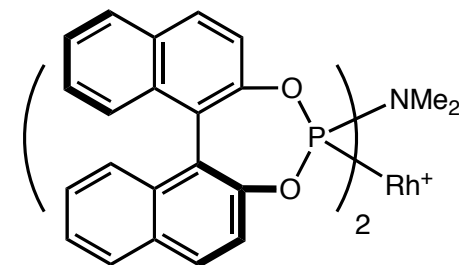
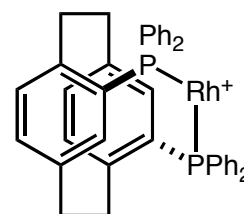
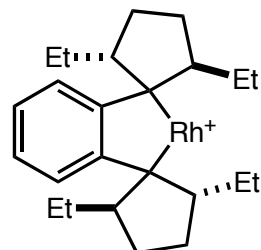
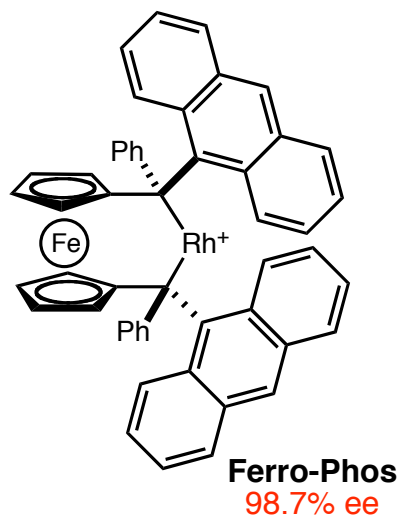
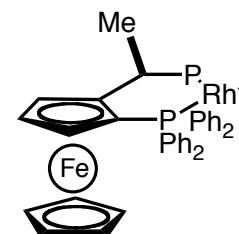
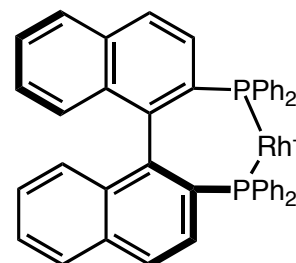
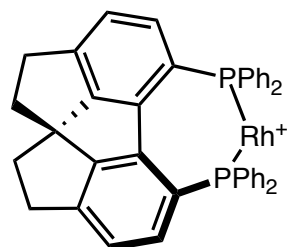
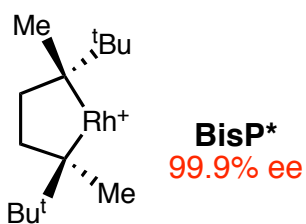
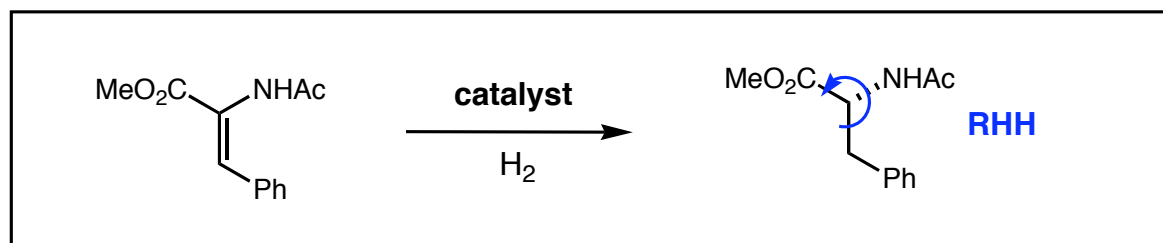
- However even though the two catalysts belong to the same quadrant class they give opposite absolute stereoinductions.



- Interestingly, TECH predicts the exact stereochemical outcomes for the two catalysts.

Asymmetric Rh Catalyzed Hydrogenations

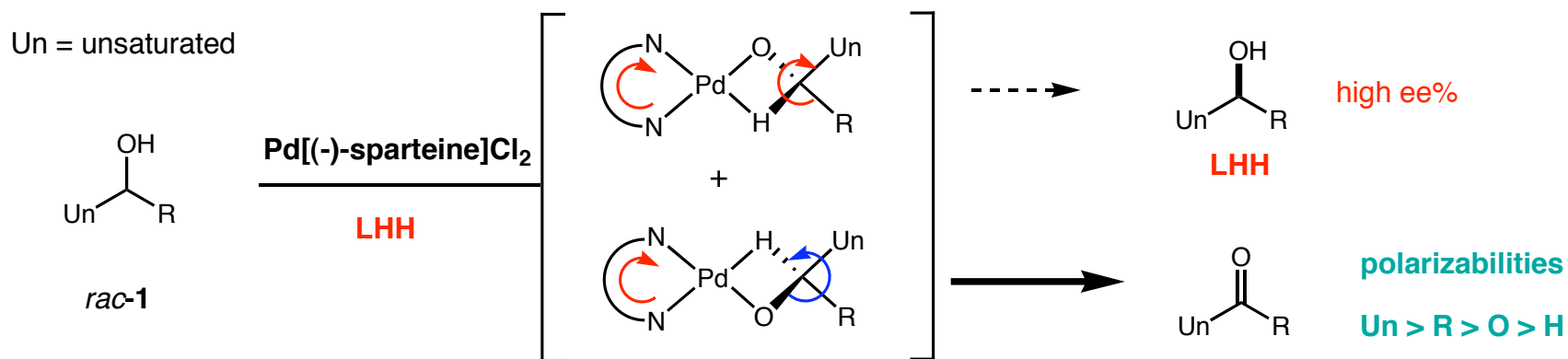
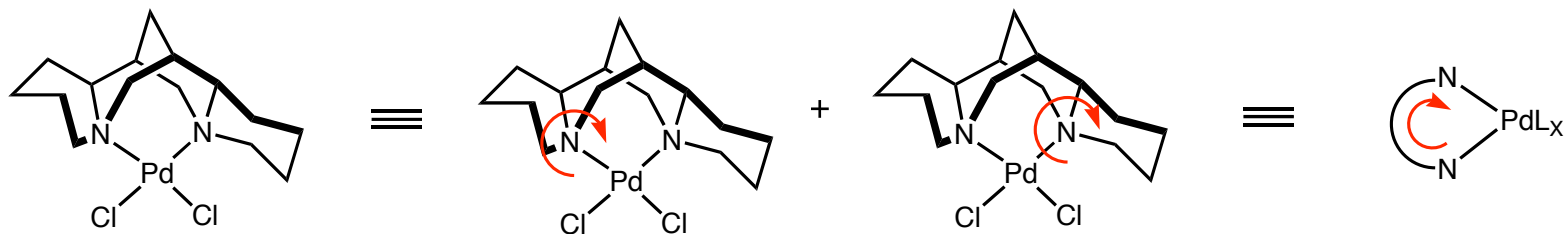
- In fact all these catalysts give rise to the same enantiomer of reduced product.



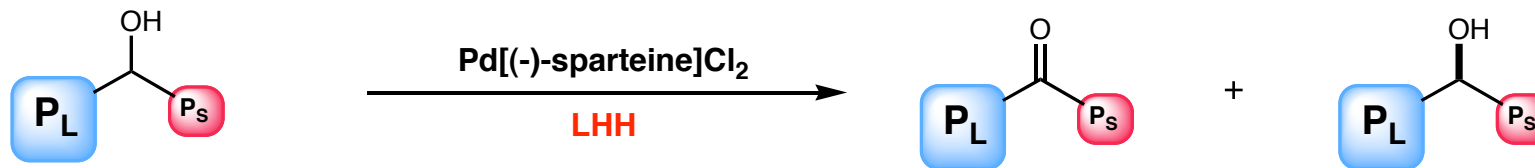
- If all these catalysts/"keys" can open the same "lock," what is it that they really have in common?

Stoltz Oxidative Kinetic Resolution

- Recent mechanistic work shows that intramolecular deprotonation in the Pd-bound alcohol generates a readily accessible site for the β -hydrogen. It is therefore expected that the Pd-O and Pd-H coordinations should couple the catalyst and substrate ring helices together.

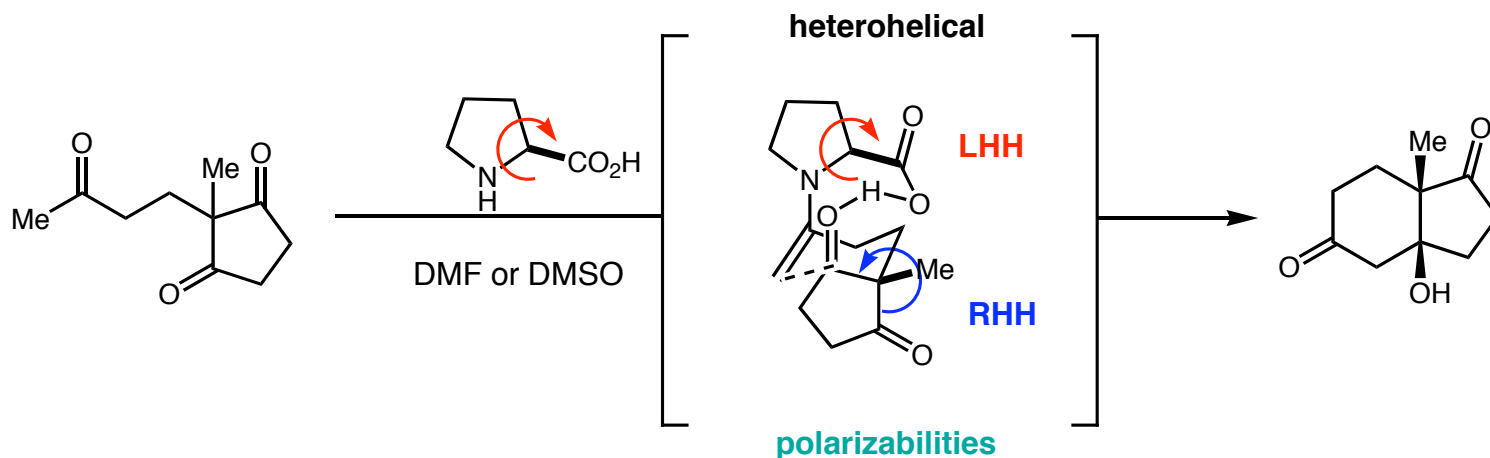


- Homohelical recognition control easily predicts the reaction outcome.



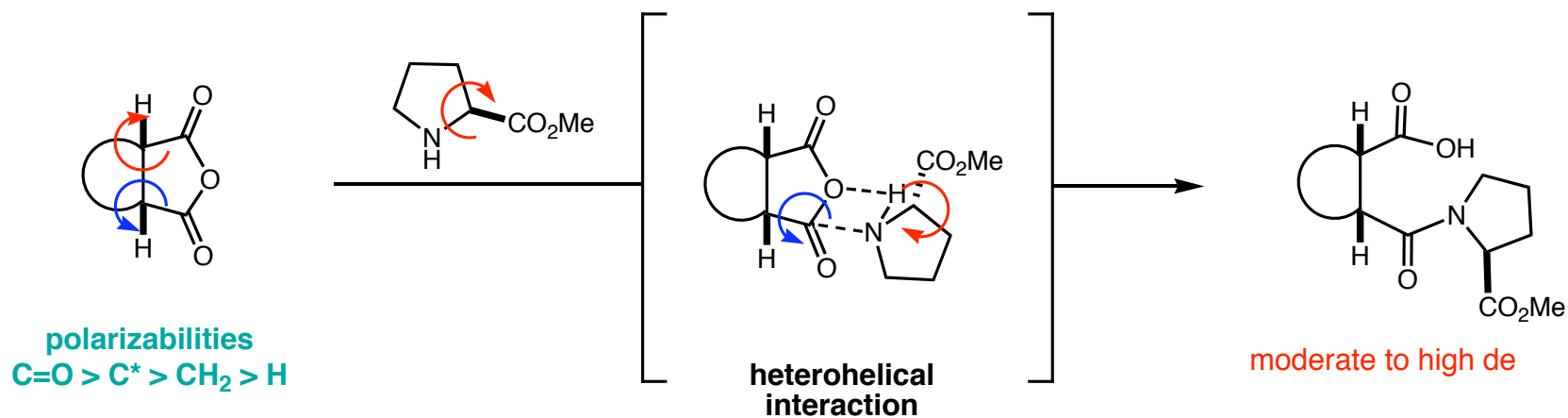
Proline Organocatalysis & Desymmetrization

- Some meso-ketones are catalytically desymmetrized by L-pro (right handed) in extremely high ee's. The stereochemical courses in them can again be deduced from the homohelical catalyst/substrate associations.



Hajos, *JOC*, 1974, 39, 1615

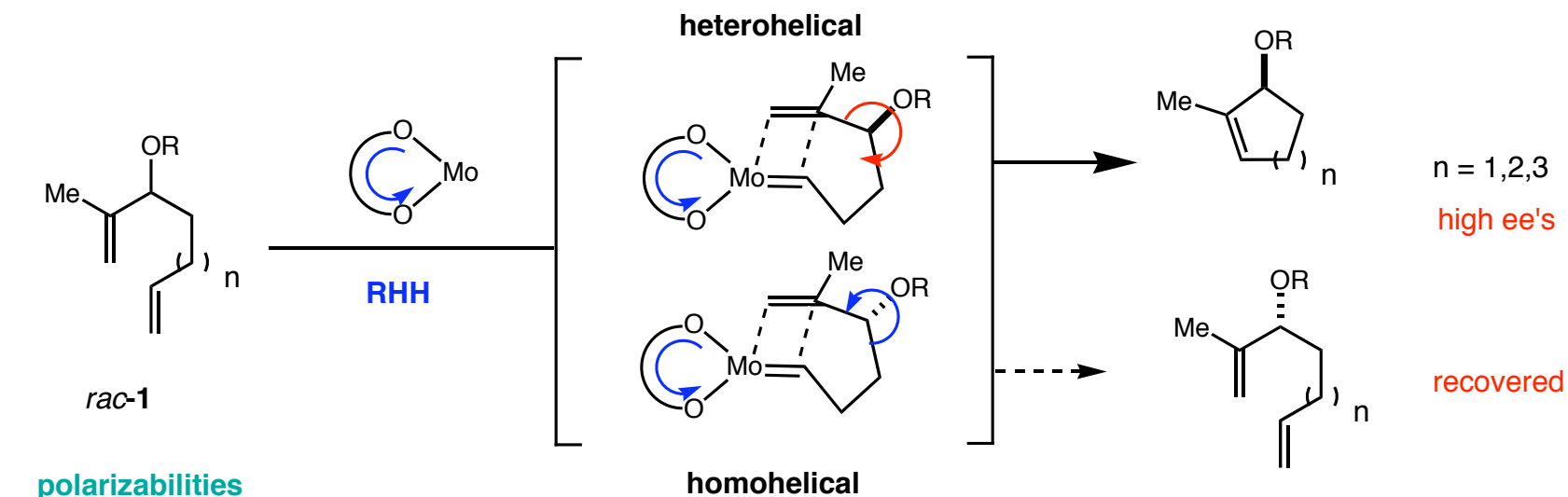
- Meso-anhydrides are desymmetrized using L-pro methyl ester.



Albers, *Synthesis*, 1996, 393

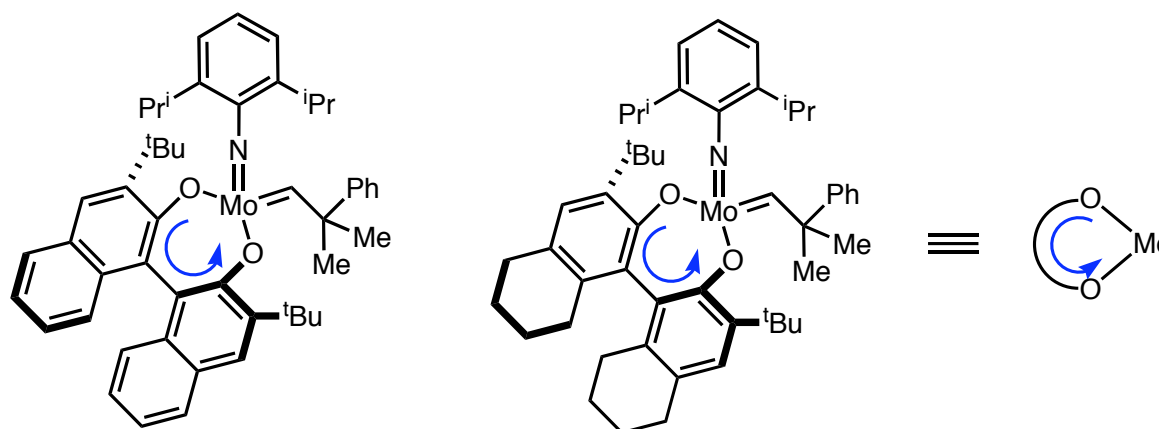
Kinetic Resolution: RCM

- Right handed catalyst interacts with both enantiomers of **1**. The heterohelical complex is higher in energy lowering the activation barrier to form cyclized product.



polarizabilities

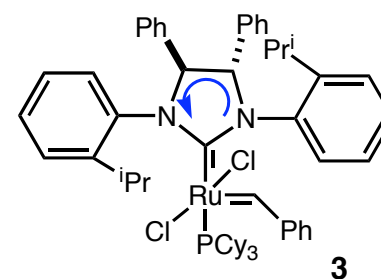
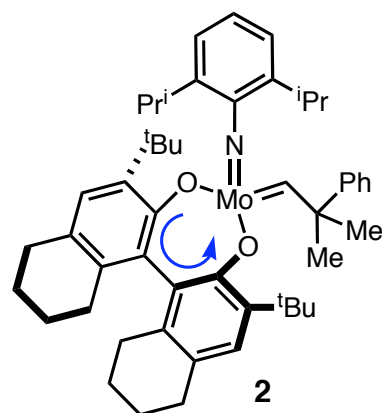
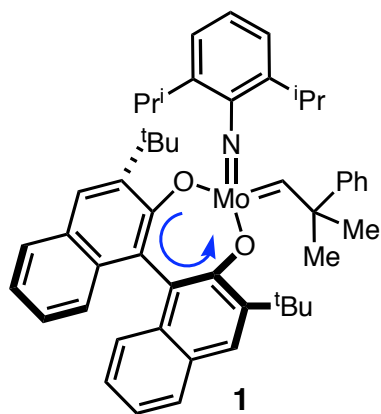
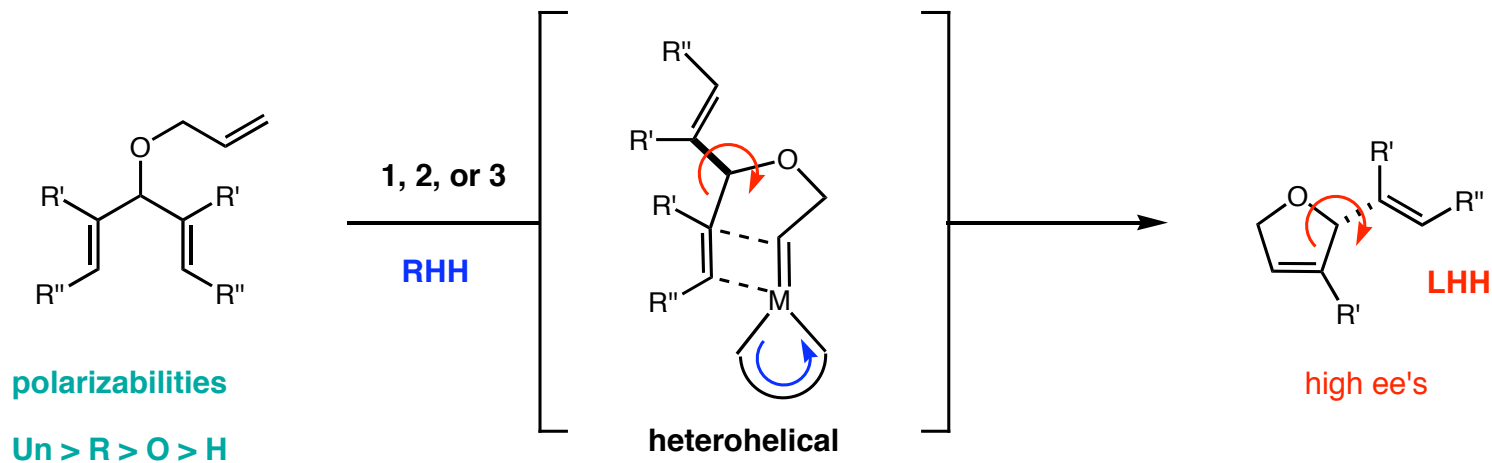
$Un > CH_2 > OR > H$



Hoveyda, Schrock *Chem. E. J.*, **2001**, 7, 945

Desymmetrization: RCM

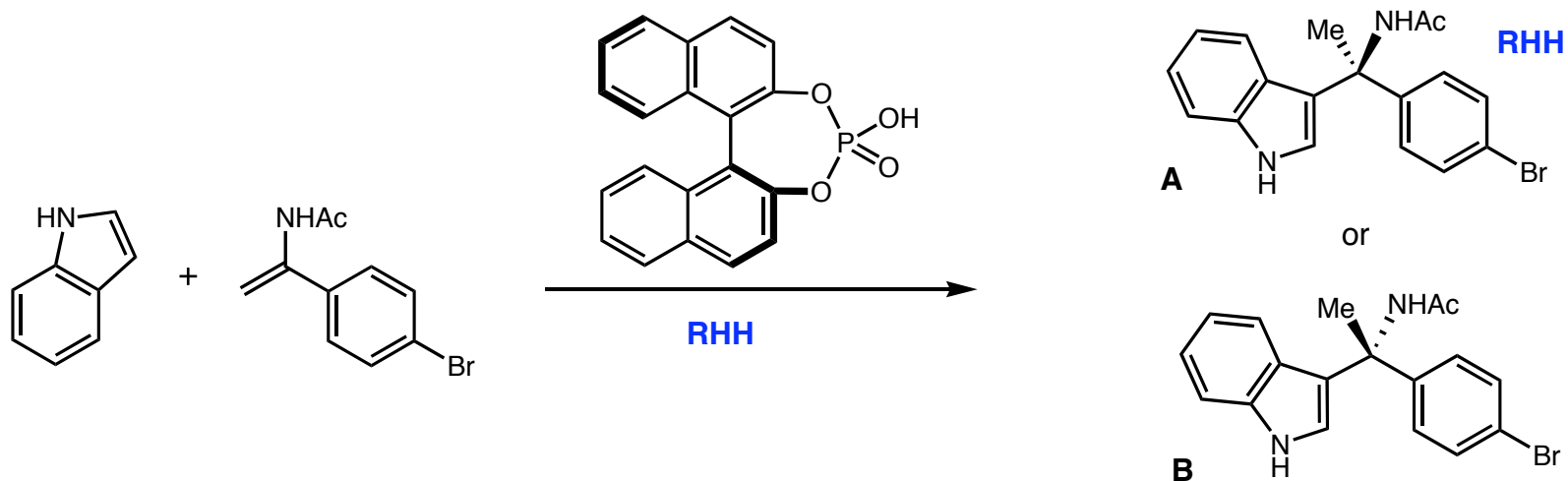
- Right handed catalyst interacts with the prochiral substrate. The heterohelical complex is higher in energy lowering the activation barrier to form cyclized product.



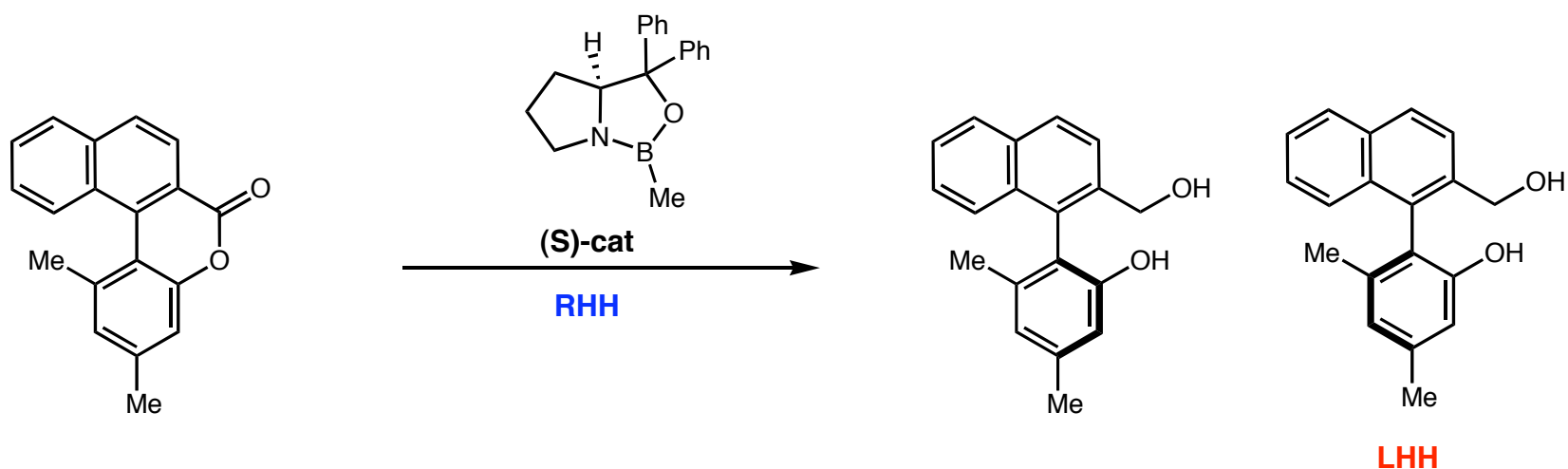
Hoveyda, Schrock *JACS*, **2003**, *125*, 12502
Grubbs *OL*, **2001**, *3*, 3225

Predictive Power of Helical Arguments

- Zhao et. al. reported this transformation recently (*ACIE*, 2007, 46, ASAP), using helical arguments which is the major enantiomer formed?



- Brinkman et. al. reported this transformation (*JOC*, 2000, 65, 2517), using helical arguments which is the major product formed?



Conclusions

- Chirality = Helicity. Relative orientation of polarizable groups in space gives rise to optical activity.
- Homohelical interactions are electronically favored and lower in energy.
- For a reaction to be highly enantioselective, the overall helicity as well as the helical characters of the catalyst and substrate must be matched (i.e. matched polarizabilities).
- Wang proposes the following: "to design a good catalyst... rather than focusing on the rigidity, bulkiness or C_2 -symmetry of the catalyst, one should focus more on the polarizability properties, thus the helical character of the substrate... with which the catalyst will interact."

