

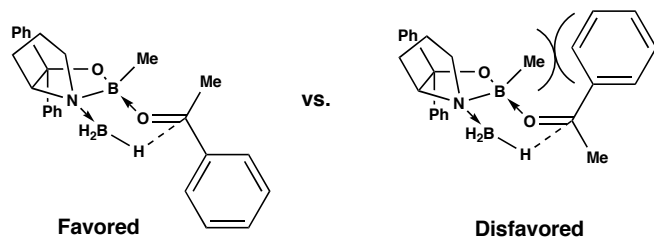
Conservation of Helical Asymmetry

Term "chirality" coined in 1893, derived 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, can not be brought to coincide with itself.
-Lord Kelvin

Molecular chirality often seen as solely a geometrical property, and thus enantioselection and asymmetric reaction design are rationalized using mostly steric-based arguments.

For example:



Are there alternatives?

Helical theory of chirality:

(Wand, D. Z. *Tetrahedron*, 2005, 61, 7125; 7134)

David Zhigang Wang, graduate student of professor Thomas J. Katz at Columbia, puts forth a novel *electronic* theory of chiral interactions (can also think of as a chiral version of standard HSAB theory), that views all chiral molecules as helices.

How can a chiral center have helicity?

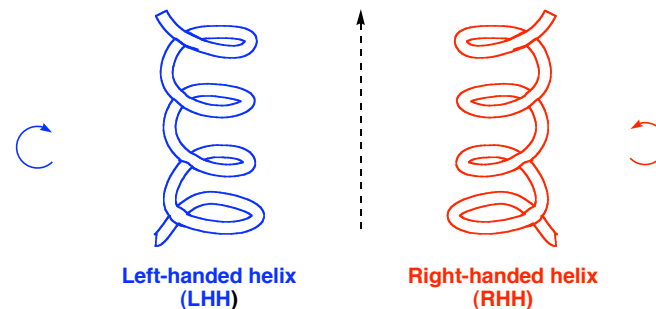
Since all bonds at a chiral center are dissimilar, unbalanced electronic interactions arise.

The magnitude of these interactions comes from the polarizability of the groups attached to the center.

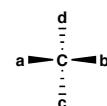
The end result is to deform the bonds into helices.

The sum of these helices gives a chiral molecule a net helicity that is either right- or left-handed.

chirality = helicity



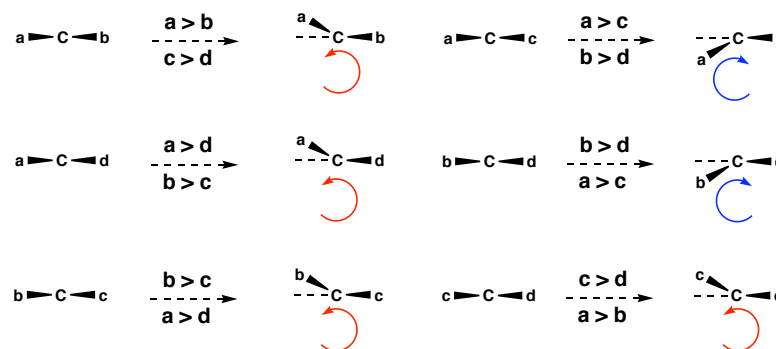
Determining a point chiral molecule's helicity- Yin method:



Take a simple 5-atom chiral molecule whose groups have the following polarizability: $a > b > c > d$

Because of this, any 2 bonds will be distorted dissimilarly, with larger distortions arising from more highly polarized groups.

Each of the six distortions creates a micro-helix.

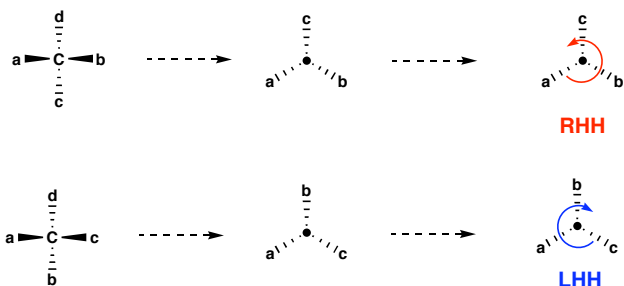


The sum of these micro-helices creates an overall helix or net helicity. Here there are 4 RHH and 2 LHH resulting in a net RHH.

Quick and Dirty Helicity Determination:

(works for simple cases)

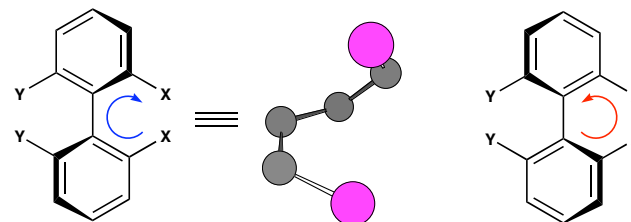
- Place least polarizable substituent coming out of plane
- Travel from most to least polarizable substituent



(point thumb at least, move fingers from most to least)

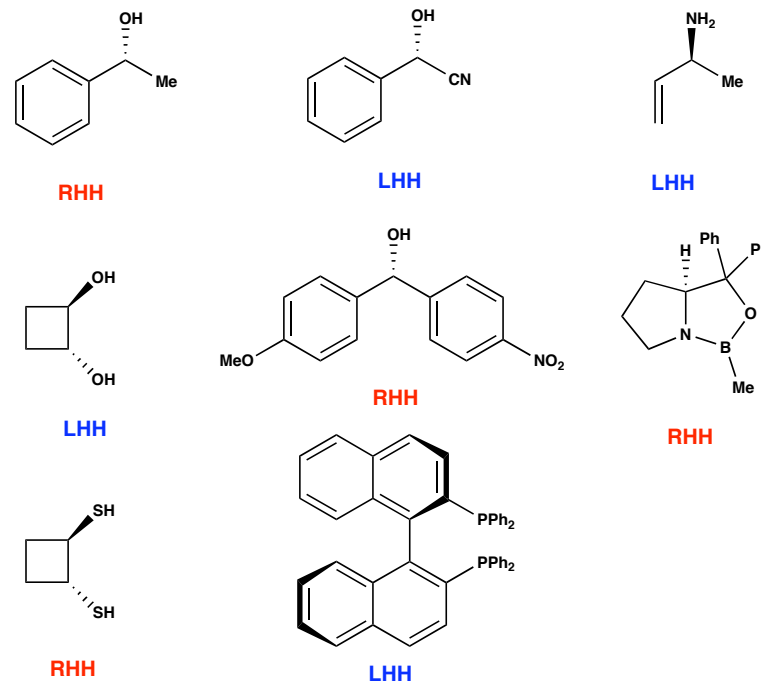
Polarizability rankings:

- $I > Br > SR > Cl > CN > Ar > C=X (X = N, O) > C > NR_2 > OR > H > D > F$
- transition metals (Rh, Ru, Pd, Ti, Os) > C, N
- higher order bonded > lower order bonded
 $C \equiv C > C = C > C - C$
- strained alkyls > unstrained alkyls
 $\triangle CH_2 > Me \quad \square CH_2 > \text{cyclopentane } CH_2 > \text{isopropyl } C$
- for *simple** alkyls, $CH_3 > CH_2 > CH > C$
 (* non-heteroatom containing alkyls)
- for aromatics, electron rich > electron poor
 $PhOMe > PhR > Ph > PhNO_2$
 $Ph > Pyridine > thiazole > oxazole$
- epoxide O > C
- $R_3P > C$

For axially chiral biaryls with polarizability $X > Y$:

(trace helix made by X-C-C-C-X)

Examples:



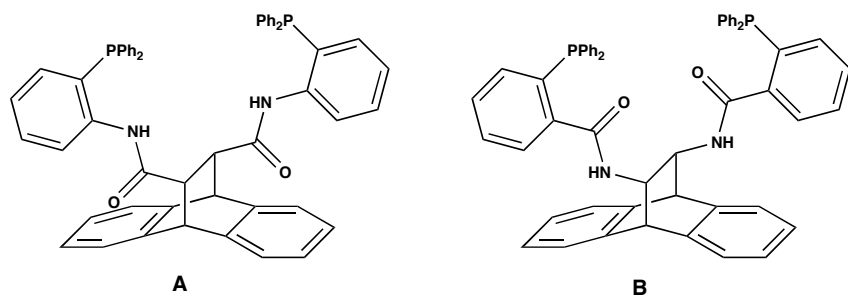
Conservation of Helical Asymmetry

Principle of homohelicity- homohelical interactions are *always* lower in energy than heterohelical interactions.

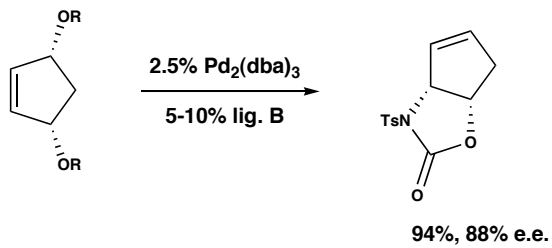
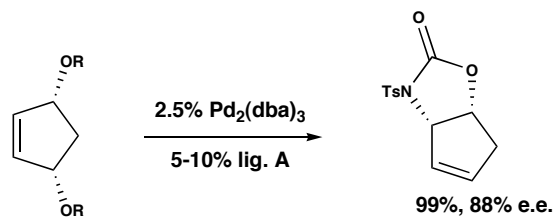
Some instances where simple steric arguments fail-

Trost desymmetrization of *meso*-allylic alcohols:

Ligands A and B should be isosteric:

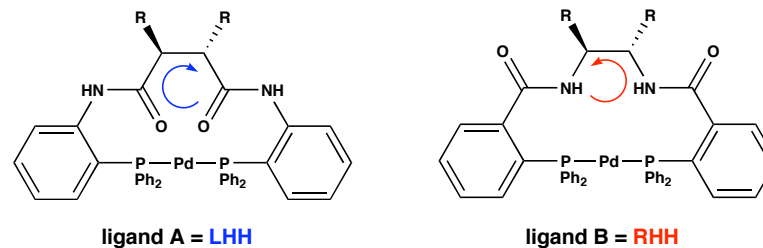


However,



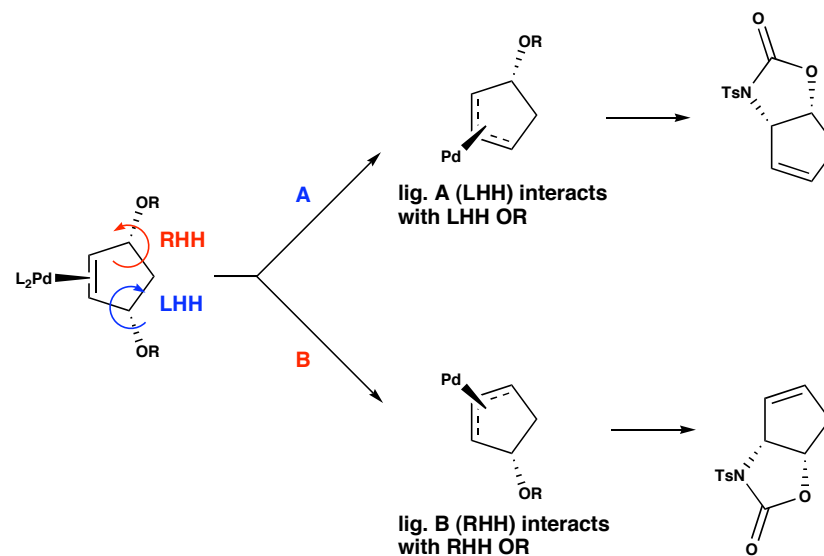
R = CONHTs

Helical argument:



Due to polarizability rankings, A and B are not isohelical!

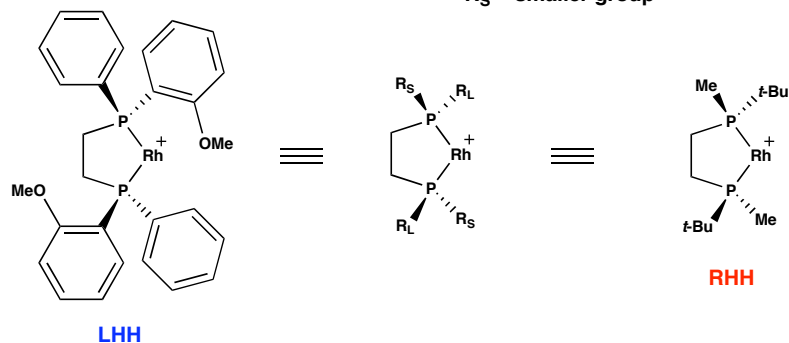
Furthermore, helicity accounts for absolute sense of stereoreinduction:



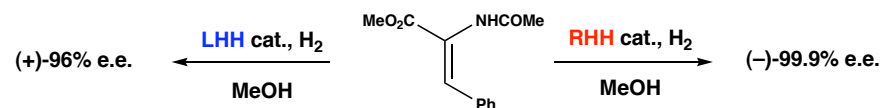
Conservation of Helical Asymmetry

Asymmetric Rh hydrogenations:

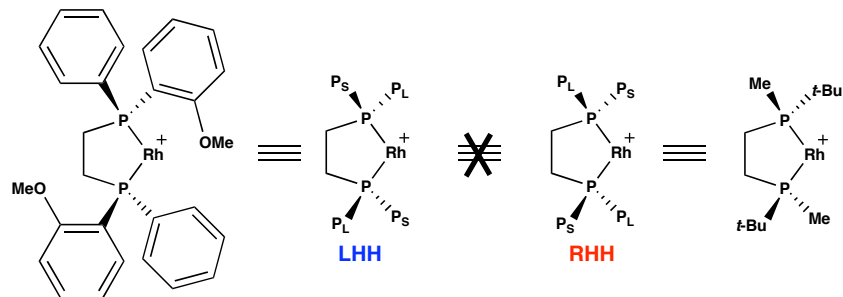
P_L = group of larger polarizability
 P_S = group of smaller polarizability
 R_L = larger group
 R_S = smaller group



Two catalysts should have same relative sterics, however they give opposite absolute stere inductions:

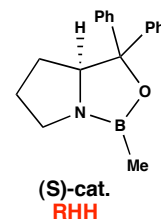


Helicity argument: polarizability rankings- $\text{Me} > t\text{-Bu}$, $\text{PhOMe} > \text{Ph}$, thus two catalysts have opposite helicities:

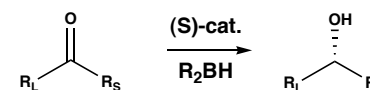


Thus, Wang theory *predicts* opposite enantiomers for the two catalysts.

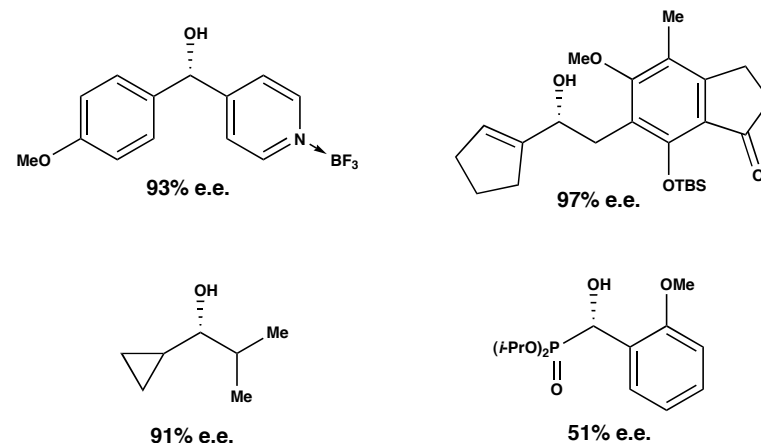
CBS reductions:



Previous rationale based on sterics:

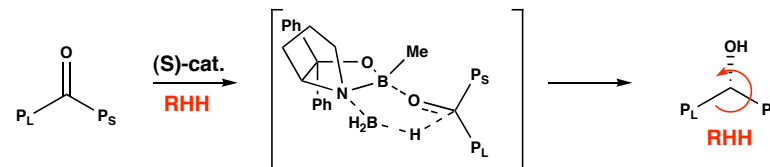


How can steric arguments account for the following results with the (S)-cat.?



All products are RHH, matching (S)-CBS helicity.

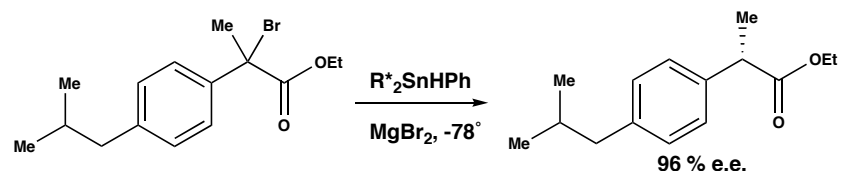
Possible new model for CBS reductions:



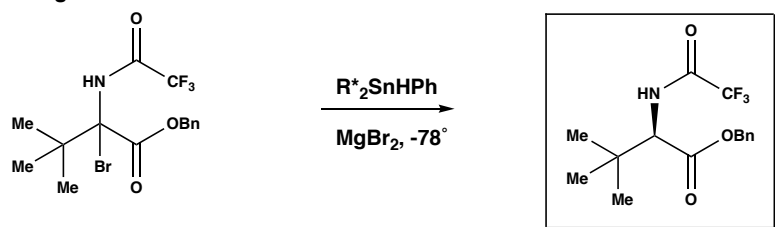
Conservation of Helical Asymmetry

Asymmetric radical reductions:

Chemists at Chirogen have discovered the following highly enantioselective free radical reaction (*C&EN*, July 14, 2003, 34-35):

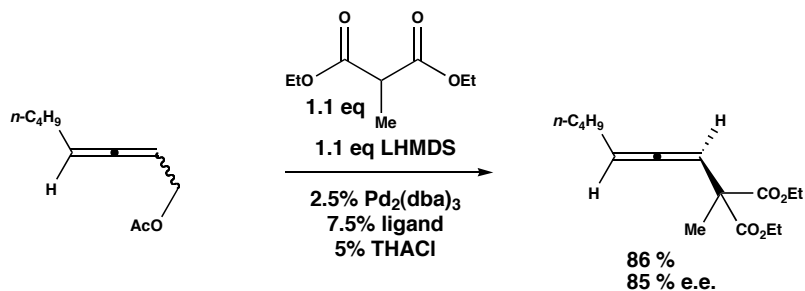
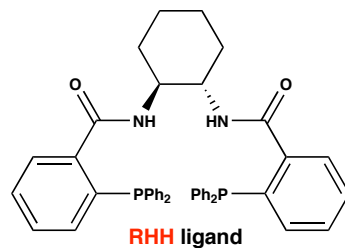
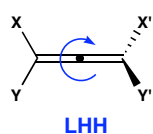
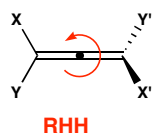


Based on these results and the polarizability rankings, predict the product of the following reaction:



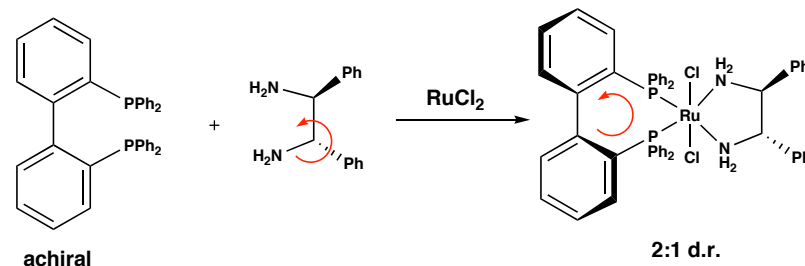
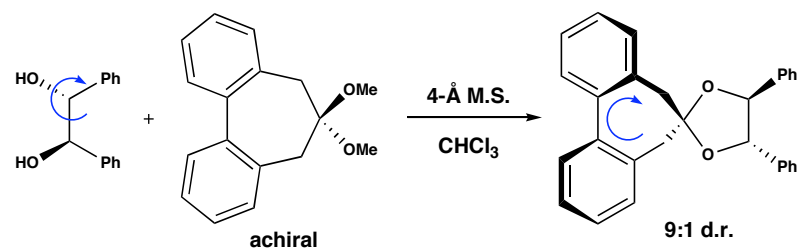
Trost DYKAT of allenes (*JACS ASAP*):

For allenes with $X > X'$ and $Y > Y'$:

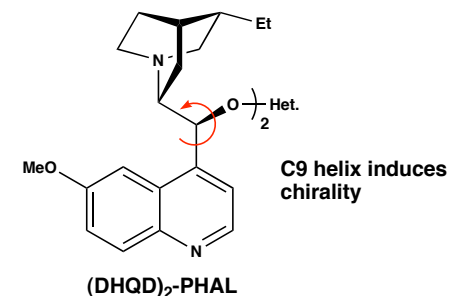
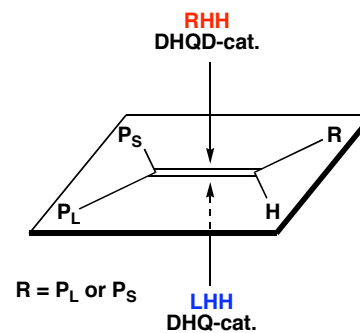


(6 other examples follow prediction as well)

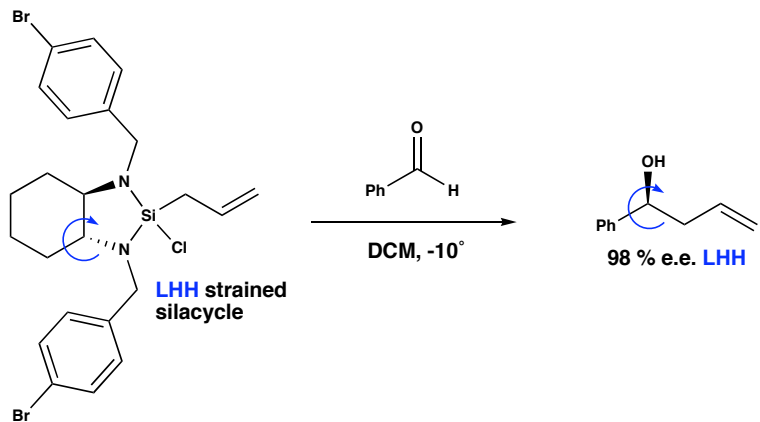
Homohelical point-to-axial chirality transfer:



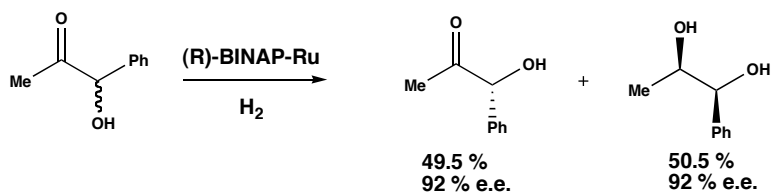
Wang's proposed model for Sharpless AD:



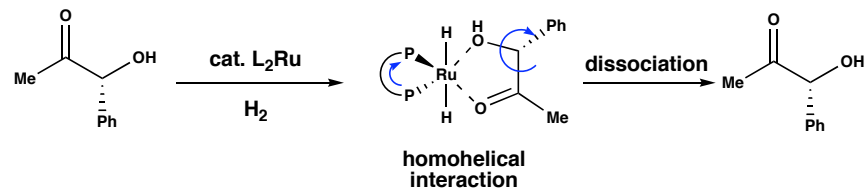
Conservation of Helical Asymmetry

Leighton allylation (Leighton, *ACIEE*, 2003, 42, 946):

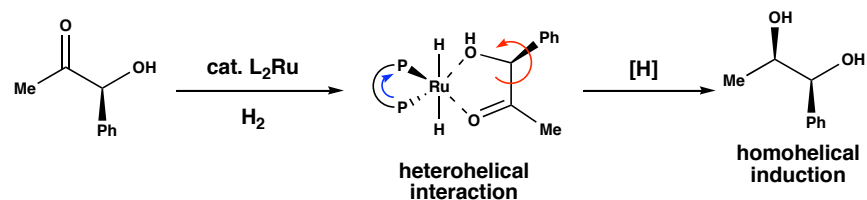
Helicity in kinetic resolution:



One enantiomer reacts at a faster rate with chiral catalyst resulting in product and starting material being recovered in high enantiomeric excess.

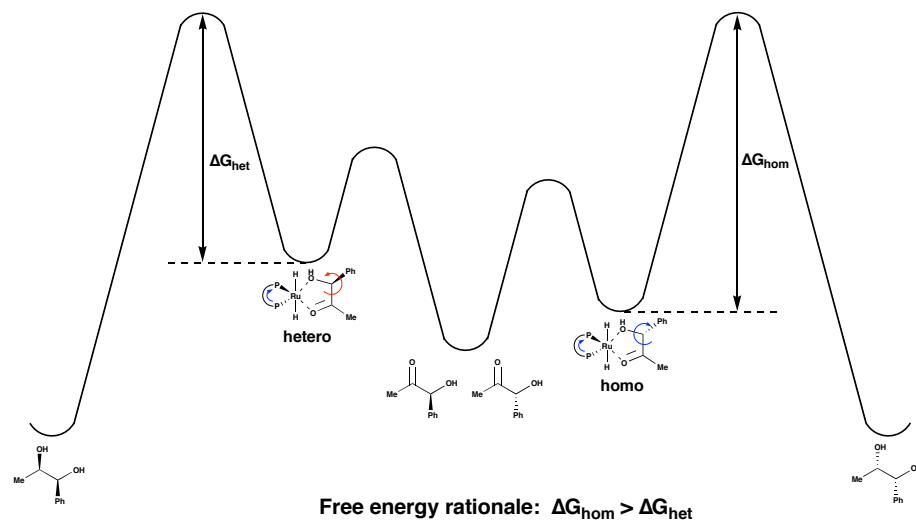


Homohelical adduct is lower in energy, hence less reactive leading to unreacted material.



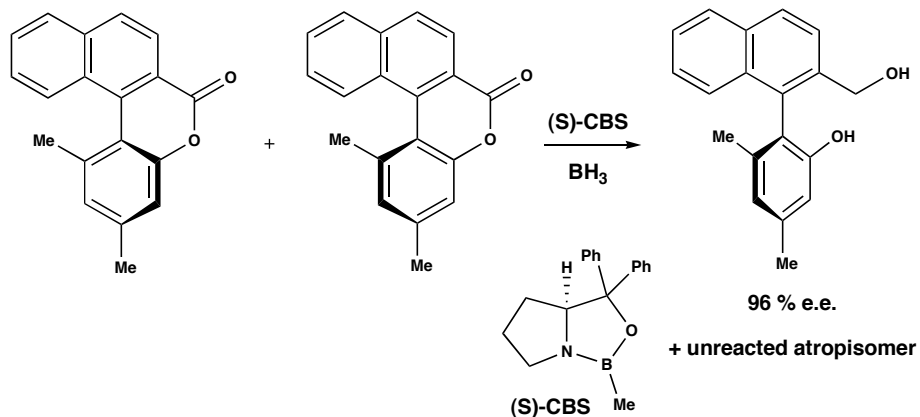
Heterohelical adduct is higher in energy, hence more reactive leading to reduction.

Free energy diagram:



Free energy rationale: $\Delta G_{hom} > \Delta G_{het}$

With this knowledge, rationalize the following result:
(G. Bringmann, *JOC*, 2000, 65, 2517)



Reaction design based on helicity?

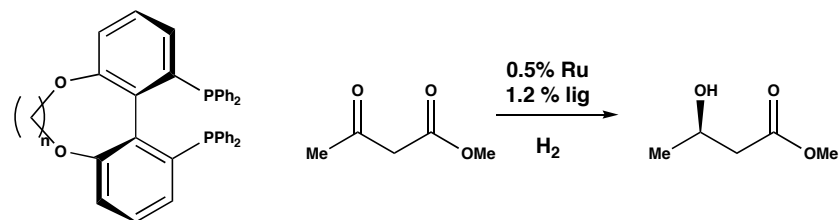
Recall that homohelical interactions are always favored.

For a reaction to be highly enantioselective, the overall helicity as well as the helical characters of the interacting species (i.e. catalyst and substrate) must be matched.

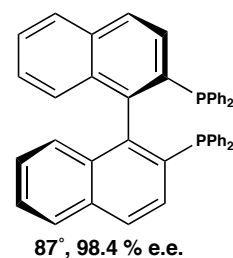
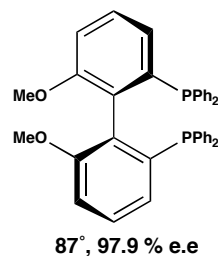
In practical term this comes down to polarizability matching.

Wang proposes the following: "to design a good catalyst . . . , rather than focusing on the rigidity, bulkiness or C₂-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."

Helicity fine-tuning:



n	1	2	3	4	5	6
□	60°	74°	77°	88°	94°	106°
% e.e.	90.9	90.8	97.7	99.1	97.1	96.5



What is next for this theory?

"Simple steric-based stereochemical rationals formulated AFTER one knows the experimental results are not appealing to me anymore (they abound in literature really; They are typically more arts than sciences!). I firmly believe, as expressed in that thesis chapter, there MUST be a more general scenario that is beyond steric effects."

—David Zhigang Wang (personal communication)