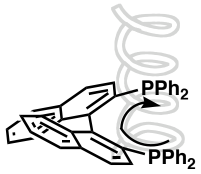
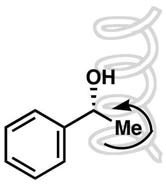
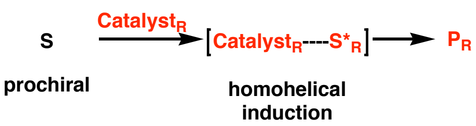




Helical Asymmetry

Electronic Effects in Enantioselective Reactions

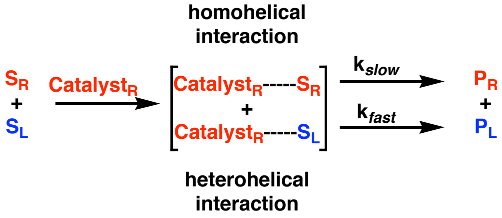


Asymmetric Catalysis

$$S \xrightarrow{\text{Catalyst}_R} [\text{Catalyst}_R\text{----}S^*_R] \longrightarrow P_R$$

prochiral

homohelical induction



Kinetic Resolution

homohelical interaction

$$\begin{matrix} S_R \\ + \\ S_L \end{matrix} \xrightarrow{\text{Catalyst}_R} \left[\begin{matrix} \text{Catalyst}_R\text{-----}S_R \\ + \\ \text{Catalyst}_R\text{-----}S_L \end{matrix}\right] \begin{matrix} \xrightarrow{k_{slow}} \\ \\ \xrightarrow{k_{fast}} \end{matrix} \begin{matrix} P_R \\ + \\ P_L \end{matrix}$$

heterohelical interaction

David Ebner
Literature Presentation
March 29, 2004
8 pm, 147 Noyes

Outline

I. Intro to Helicity

A. Polarizability
B. Assignment of Helicity
C. Optical Rotation

II. Helicity in Reactions

A. Asymmetric Catalysis
B. Kinetic Resolution
C. Tandem Processes

?

David Z. Wang

III. Helicity Matching

References:

D. Z. Wang, CPS: orgchem/0403001. URL: http://preprint.chemweb.com/orgchem/0403001.
D. Z. Wang, CPS: orgchem/0403002. URL: http://preprint.chemweb.com/orgchem/0403002.

These references, as well as supplementary information and a personal communication from D. Z. Wang answering some issues can be found on the group server. (Group Items –> Things from Brian –> David Wang Helical Asymmetry)

What is Helicity?

Helicity is the property of having a screw-type or spiral pattern.

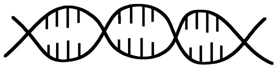
In molecules, there are two types of helices:

A **geometric helix** exists when atoms in a molecule are arranged into a spiral pattern, such as in a DNA molecule. These helices may be smaller than a full helix turn, as in BINAP.
A **physical helix** exists when electrons (bonds) in a molecule twist in a particular direction. This twisting leads to electrons moving in a helical path.

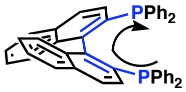
Helicity is a common concept in physics and biochemistry. In organic chemistry, however, its use has been limited to theories of optical rotation, in attempts to relate the stereochemistry of molecules to the clockwise or counter-clockwise rotation of light. Enantiomers will have opposite helicity.

Theories of optical rotation have tried to identify helical structures in chiral molecules by recognizing that net rotation is due to the chiral molecules having different refractive indices for left- and right-polarized light. Since refractive indices are directly related to polarizability, physical helices are determined using polarizability differences.

Some Geometric Helices:



DNA



***(R)*-BINAP**

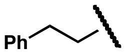
Polarizability

Polarizability characterizes the sensitivity of a group's electron density to distort in an electric field.

Though unknown for many functionalities, polarizability usually follows general trends, increasing with:
–Larger numbers of electron shells within a group (**I** > Br > Cl > F)
–Lower nuclear charge within a period (C > N > O > F)
–Lower HOMO-LUMO gap (more conjugation)
–Less substituted alkyl carbons ($CH_3 > CH_2R > CHR_2 > CR_3$)
–More strained bonds (cyclopropyl CH_2 > linear CH_2)
–Higher electron density ($B^- > C$)

Some polarizabilities have been quantified based on Brewster's refractive indices list:
I > Br > SH > Cl > CN > Ph > C=O > $CH_3 > NH_2$ > OH > H > D > F

Further relationships can be gathered, for example:
–Transition metals > any organic group
–Alkyne > Alkene > Alkane
–P in R_3P > C
–Ph > C=O, C=N, Cyclopropyl
–$\mathbf{C}H_2NR_2$, $\mathbf{C}H(OR)_2 > CH_3$
–Ketone > Ester

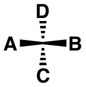
Note that the most important contributor to the polarizability of a group is the atom that is directly attached to the rest of the molecule.
Thus, the polarizability of  would be best represented as a CH_2.

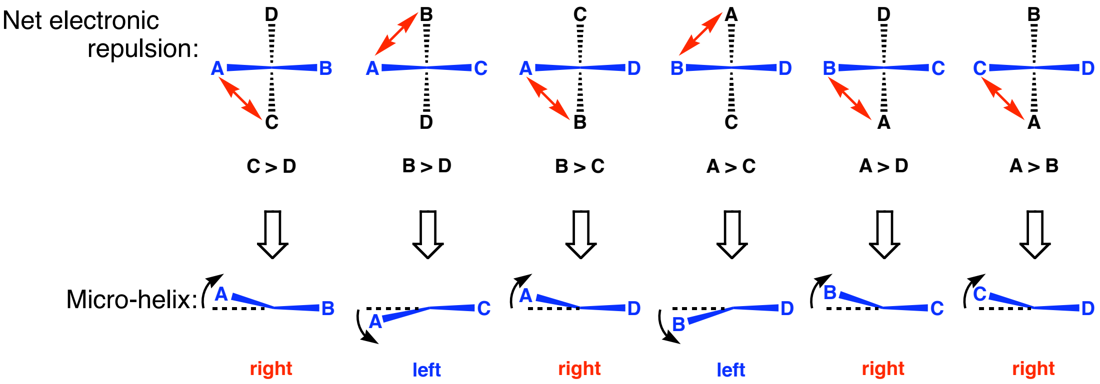
Brewster, *J. Am. Chem. Soc.* **1959**, *81*, 7475
Miller, *J. Am. Chem. Soc.* **1990**, *112*, 8533

Assigning Helicity in Molecules

Helicity is either right- or left-handed (clockwise or counterclockwise, respectively).
Determining helicity depends on the type of chirality within the molecule.

Point Chiral Molecules:

For point chiral molecule  , let the polarizabilities of the substituents be A > B > C > D.



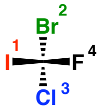
More right-handed than left-handed micro-helices results in a net right-handed molecule

While this procedure is general, there is an easier way...

Helicity in Point-Chiral Molecules

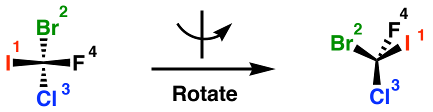
The physical helicity in point-chiral molecules can be assigned using polarizability.
This method is similar to that for determining *R* or *S* configuration.

1. Assign polarizability ranking to all four groups attached to chiral center. For example:

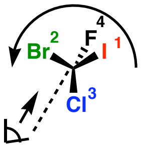


(Polarizability: I > Br > Cl > F)

2. Rotate molecule so that atom with lowest polarizability is facing away.



3. Trace a path around the molecule from highest to lowest polarizability.
   If the path traced is clockwise, the molecule has right-handed helicity.
   If the path traced is counter-clockwise, the molecule has left-handed helicity.

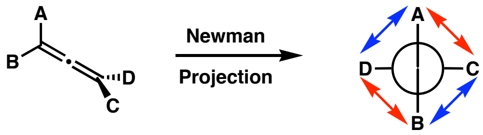


Counter-clockwise = left-handed molecule

Axial Helicity

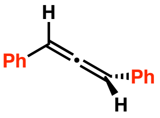
For axial helicity, there are four main micro-helices to investigate. Two will be right-handed, and two will be left-handed. Thus, look for the dominant micro-helix (the two most polarizable groups).

In allenes, look at the Newman projection:

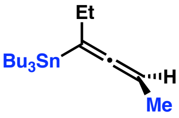


Right-Handed: A-C or B-D interaction dominates
Left-Handed: A-D or B-C interaction dominates

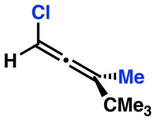
The helicity even predicts the sign of optical rotation! Thus,



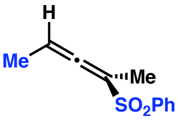
(+), right



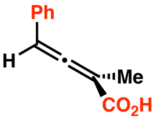
(–), left



(–), left



(–), left

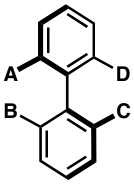


(+), right

Previously, *Lowe's Rule* was used to determine rotation. This rule states that if an allene is viewed in its Newman projection as above with the most polarizable substituent on top, then if the more polarizable substituent along the horizontal axis is to the right, the allene is dextrorotary (right-handed). We will see more about helicity and optical rotation soon...

Biaryl Helicity

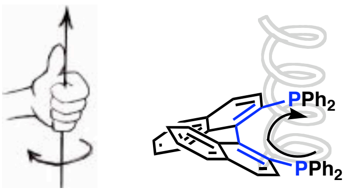
Atropisomeric biaryls can also be assigned.



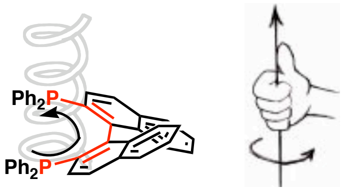
If A-B or C-D is the dominant interaction, the molecule is right-handed.
If A-C or B-D is the dominant interaction, the molecule is left-handed.

Note that for atropisomeric biaryl systems, the micro-helices (and thus the overall helicity) are both geometric and physical. Thus, an easier method may be to view the geometric helix turns:

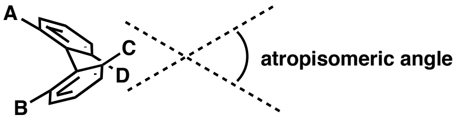
Left-Handed



Right-Handed

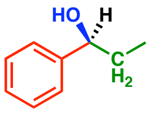


Dramatic variations in the net helicity are possible due to the atropisomeric dihedral angle, so definite assignments for optical rotation can be difficult.

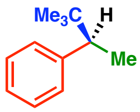


Optical Rotation and Helicity

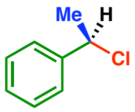
We saw before that for allenes, helicities predict the same sign of optical rotation as Lowe's Rule. For simple molecules with point-chirality, the helicity also correctly predicts stereochemistry (Polarizability sequence for each molecule is red > green > blue > black):



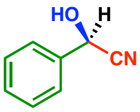
(*S*)-(–)-left



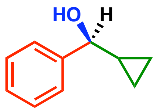
(*R*)-(–)-left



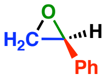
(*R*)-(+)-right



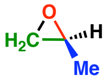
(*R*)-(+)-right



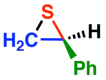
(*S*)-(–)-left



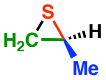
(*S*)-(–)-left



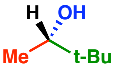
(*S*)-(–)-left



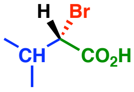
(*S*)-(+)-right



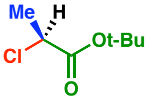
(*S*)-(–)-left



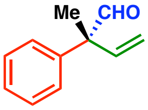
(*S*)-(+)-right



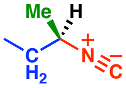
(*S*)-(–)-left



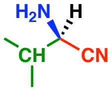
(*S*)-(–)-left



(*R*)-(+)-right



(*R*)-(–)-left



(*R*)-(+)-right

Important Note: This method is based on the physical helices' contribution to optical rotation. It works well when the geometrical contribution is minimal, as in small and conformationally flexible molecules with no geometrical helices. Also, inter- and intramolecular associations must be small.

Helicity in Chiral Interactions

Any two chiral molecules will either have the same helicity (**homohelical** interaction) or different helicity (**heterohelical** interaction).

$$\begin{matrix} S_R & C_R \\ C_L & S_L \end{matrix} \longrightarrow \begin{matrix} C_R\text{-----}S_R \\ C_L\text{-----}S_L \end{matrix} \quad \textbf{OR} \quad \begin{matrix} C_R\text{-----}S_L \\ C_L\text{-----}S_R \end{matrix}$$

For many types of interactions, including asymmetric reactions and kinetic resolutions, steric arguments (geometric helices) have commonly been used to explain the specific interactions that occur. Electronics (physical helices) are important too, though!

In fact, example after example demonstrates that **electronic homohelical interactions are favored and correctly predict the interactions that occur!** This preference is presumably due to an energetic stabilization from homohelical interactions, both in induction and recognition interactions.

Homohelical induction: One molecule with a particular helicity causes a prochiral molecule to have the same helicity.

$$\begin{matrix} \textbf{S} \\ \textbf{prochiral} \end{matrix} \; \overset{C}{\rightrightarrows} \; \begin{matrix} C\text{-----}S^* \;\; \textbf{homohelical interaction: favored} \\ C\text{-----}S^* \;\; \textbf{heterohelical interaction: disfavored} \end{matrix}$$

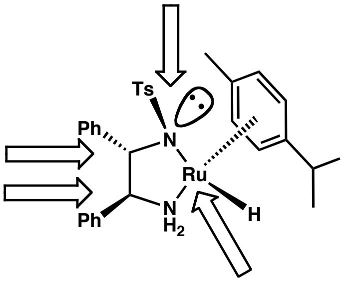
Homohelical recognition: One molecule with a particular helicity interacts more favorably with another molecule of the same helicity than one with opposite helicity.

$$\begin{matrix} S_R \longrightarrow C\text{-----}S^* \;\; \textbf{homohelical interaction: more stable (less reactive)} \\ + \quad C \\ S_L \longrightarrow C\text{-----}S^* \;\; \textbf{heterohelical interaction: less stable (more reactive)} \end{matrix}$$

Helices in Reactions: Simplifications

While the overall helicity is useful for assigning a sign of optical rotation to a molecule, in reactions, this picture can be simplified.

The closer a stereocenter is to the site of reaction, the greater influence its helicity will have on the outcome of the reaction.



This left-handed induced stereocenter may play some role in the reaction

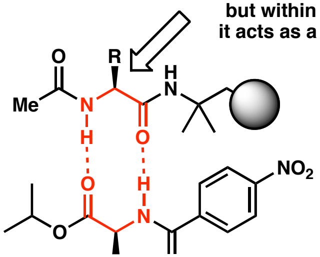
These right-handed stereocenters only indirectly affect the reaction

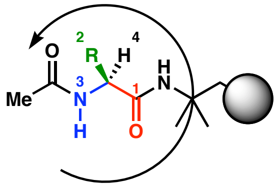
This left-handed stereocenter at Ru is closest to the reactive site. Thus, it will have the greatest influence.

More Simplifications for Reactions

Furthermore, chiral chelating ligands will create rings. The actual helicity of the ligand by itself is not as important as the helicity of the ring helix in the reactive complex. The ring atoms are closer to the action than the pendant groups.

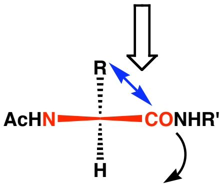
Technically, this center is left-handed, but within the ring (shown in red) it acts as a right-handed ring helix.





C=O > R > N > H
Therefore, the arrow goes counter-clockwise.
Thus, left-handed.

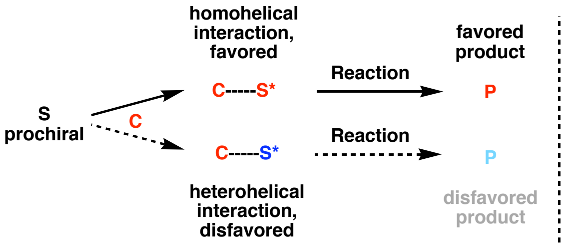
C=O > N and R > H
This interaction is the most important in deforming the bonding orbitals, and creates the dominant micro-helix, leading to a right-handed ring helix twist.

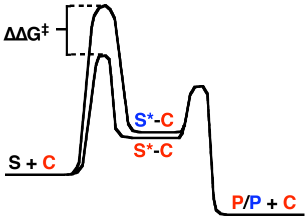


Asymmetric Catalysis and Kinetic Resolution

Asymmetric Catalysis

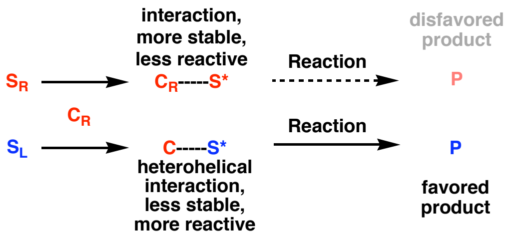
Initial coordination of pro-chiral substrate (S) to catalyst (C) induces helicity in substrate (S*).
Greater stability of homohelical interaction does not prevent transformation from occuring.
Preference for one enantiomer of product (P) is observed.

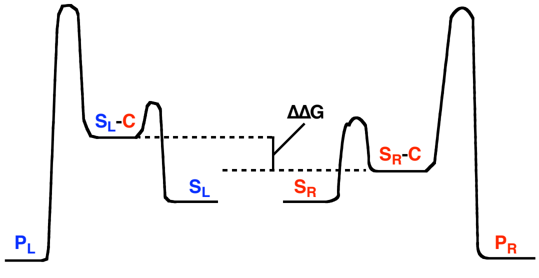




Kinetic Resolution

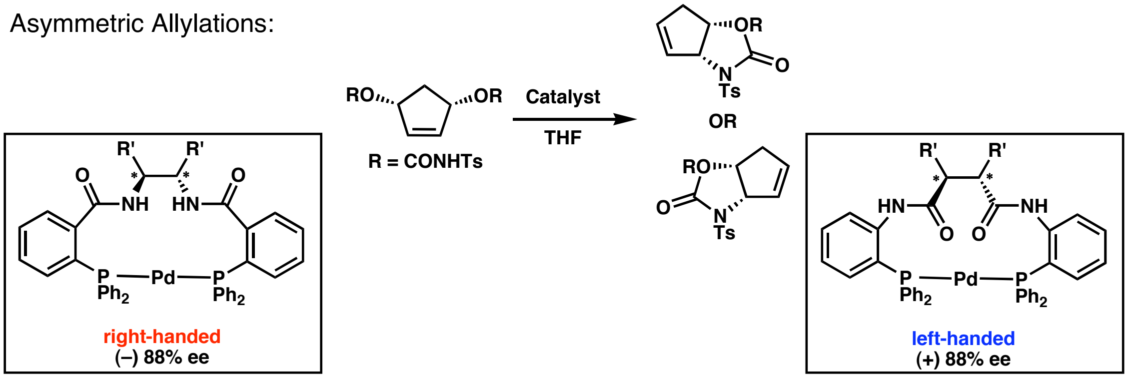
Both enantiomers of substrate (S_R and S_L) bind to catalyst (C_R). The stabilizing interaction leads to a decreased rate for the homohelical substrate-catalyst complex compared to the heterohelical complex.





Puzzling Results Explained

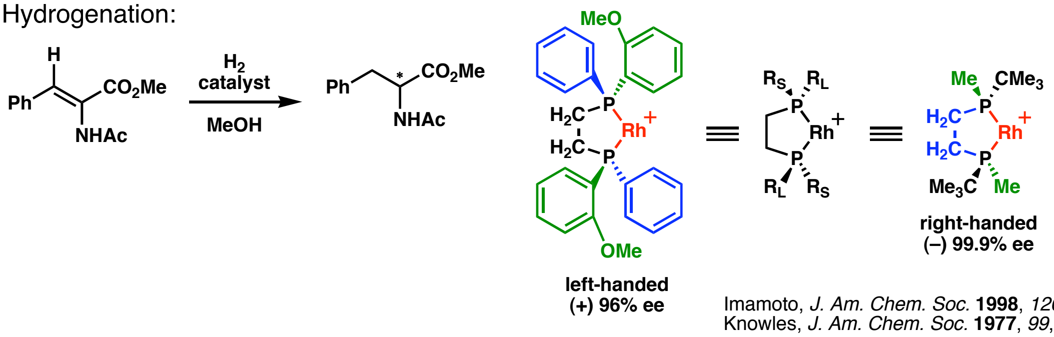
Asymmetric Allylations:



R' = *trans*-9,10-dihydro-9,10-ethanoanthracene

Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 2386

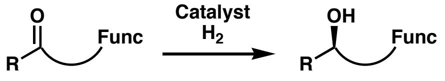
Hydrogenation:



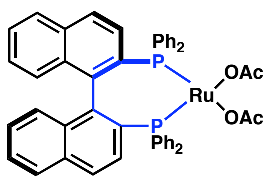
Imamoto, *J. Am. Chem. Soc.* **1998**, *120*, 1635
Knowles, *J. Am. Chem. Soc.* **1977**, *99*, 5946

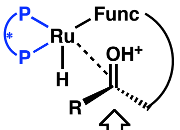
Ketone Reductions: Ru

Functionalized Ketone Hydrogenation



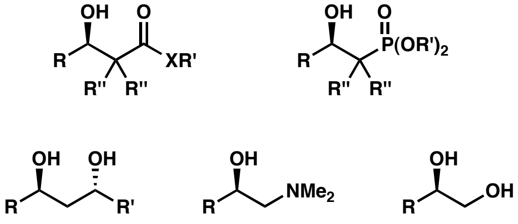
Left-handed Ru catalyst:



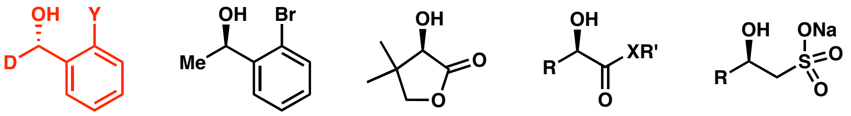


left-handed ligand ring helix

homohelical **left-handed** substrate helix



In other cases, polarizability of R > OH^+. Since OH^+ > D, other enantiomer is observed!

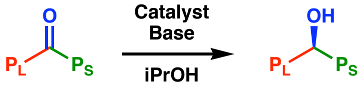


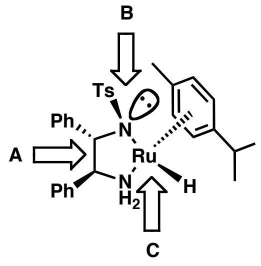
R, R', R'' = alkyl, aryl X = NH, NR', O, S Y = OMe, Br

Noyori, *Angew. Chem. Int. Ed.* **2001**, *40*, 40

Ketone Reductions: More Ru

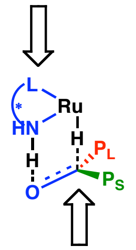
Transfer Hydrogenation of Unfunctionalized Ketones





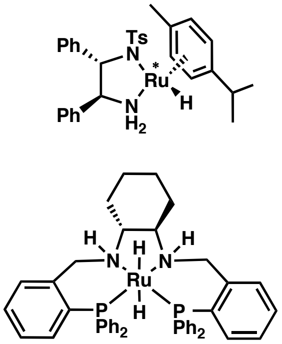
Both backbone stereocenters are **right-handed** (A), but they enforce a **left-handed** nitrogen center (B), which causes the Ru to arrange in a **left-handed** octahedral structure (C)!

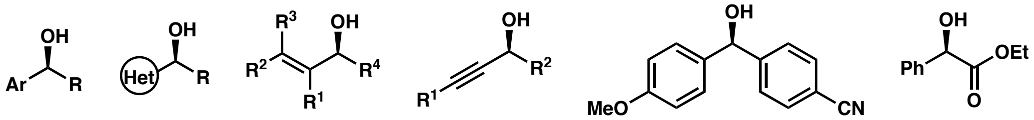
left-handed ligand helix



homohelical **left-handed** substrate helix

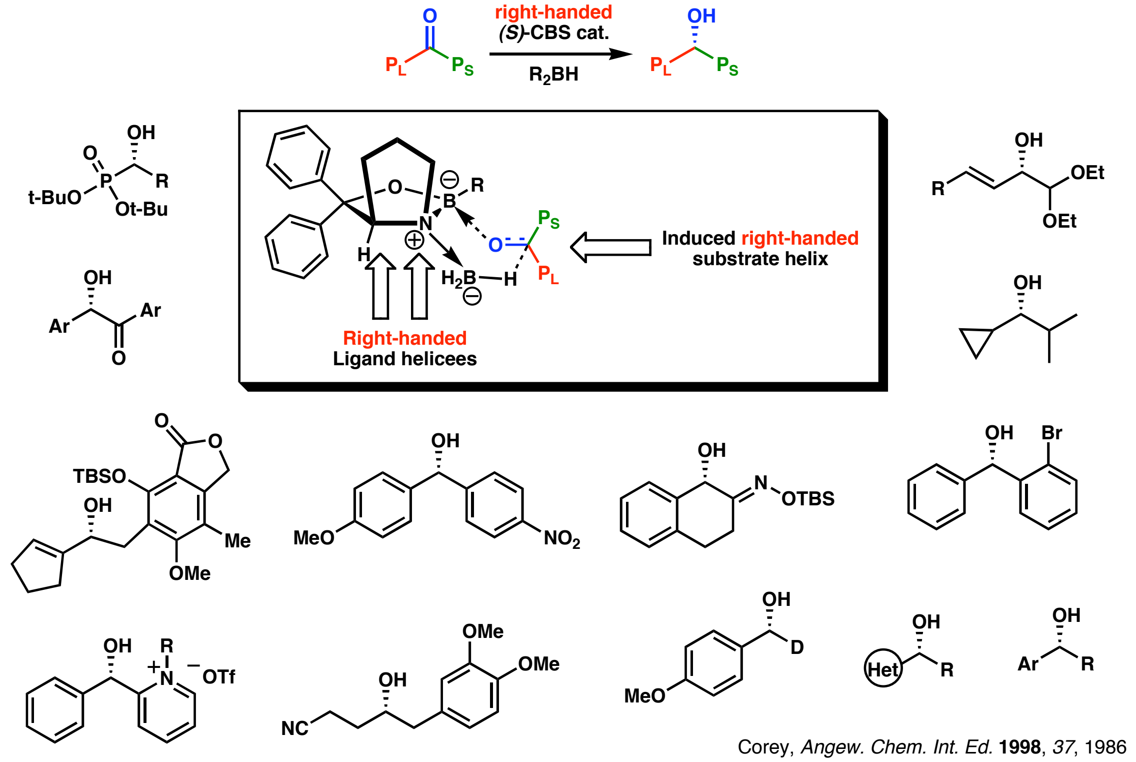
Left-handed Ru catalysts:





Noyori, *Acc. Chem. Res.* **1997**, *30*, 97
Noyori, *J. Org. Chem.* **2001**, *66*, 7931

Ketone Reductions: CBS

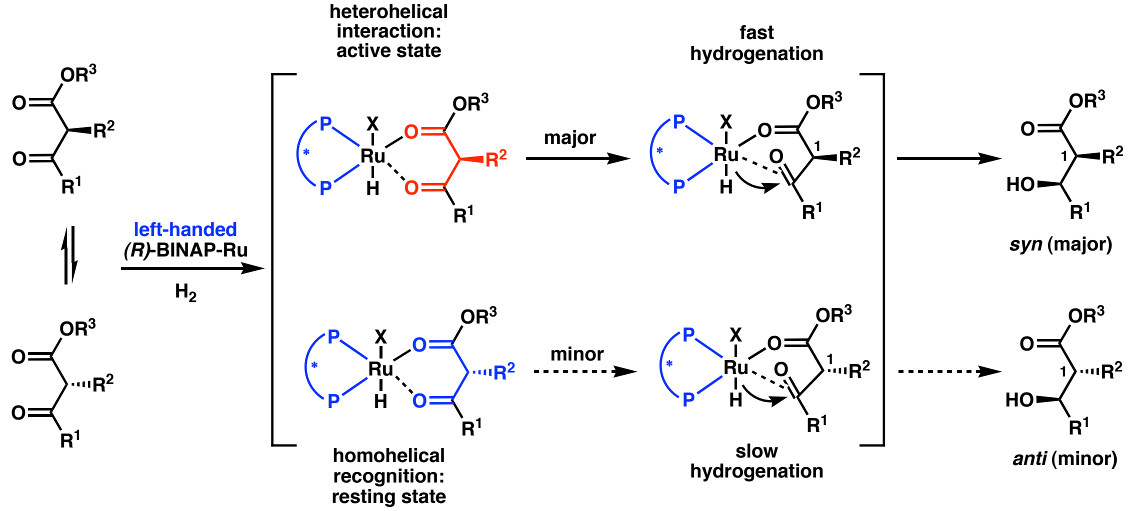


Corey, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986

Kinetic Resolution: Hydrogenation

Dynamic kinetic resolution of ß-ketoesters

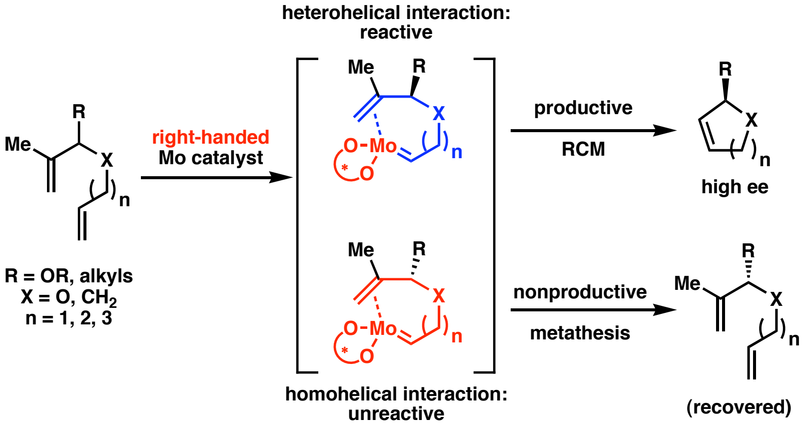
Both ketoesters, which are in equilibrium in the reaction, bind to the catalyst. Binding of the left-handed ketoester leads to a homohelical interaction - too stable for hydrogenation. Right-handed ketoester binding leads to a heterohelical interaction, which promotes hydrogenation through destabilization of the intermediate. Note that the reduction leads to a left-handed helix at the alcohol center. Also, reduction of the ketone reverses the helicity at carbon 1, leading to a left-handed helix there too!

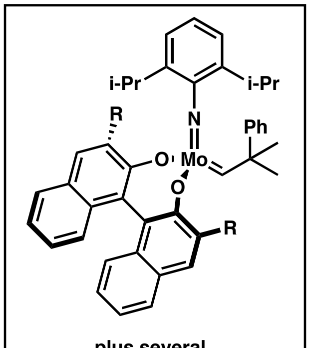


Noyori, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36

Kinetic Resolution: RCM

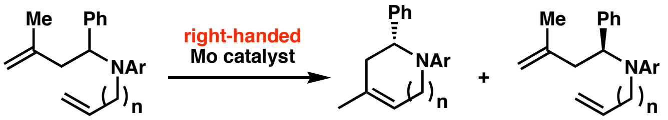
Asymmetric Ring Closing Metathesis Based Kinetic Resolution

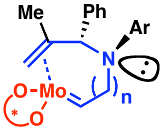




plus several similar catalysts

But,

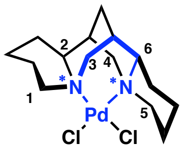




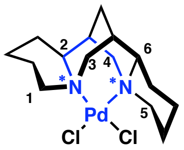
Induced helicity of amine closer to Mo than carbon stereocenter. Also, lone pair is highly polarizable, creating greater ring twist than original stereocenter.

Hoveyda, Schrock, *Chem. Eur. J.* **2001**, *7*, 945
Hoveyda, Schrock, *J. Am. Chem. Soc.* **2002**, *124*, 6991

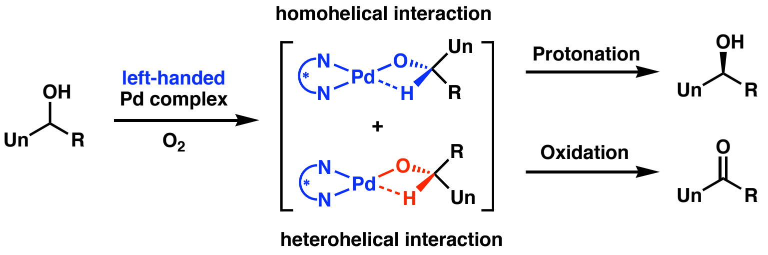
Oxidative Kinetic Resolution of Alcohols



ring A: left-handed
$C^1 > C^2$ and Pd >> C^3
Thus, the left nitrogen is left-handed.
The right nitrogen does not contribute to helicity in this ring since $C^4 \approx C^5$.



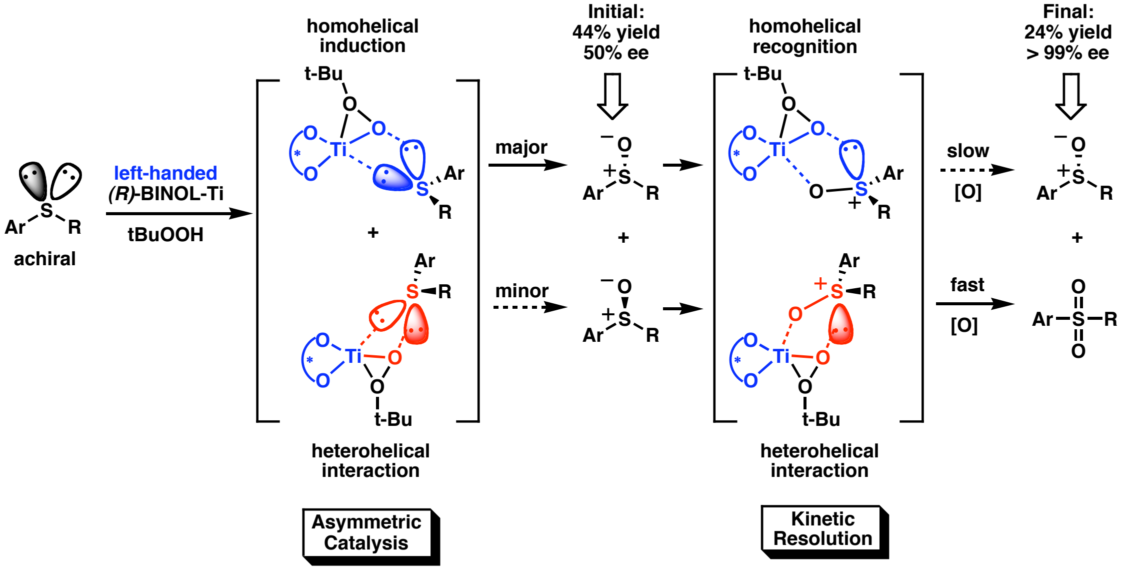
ring B: left-handed
$C^5 > C^6$ and Pd >> C^4
Thus, the right nitrogen is left-handed.
The left nitrogen does not contribute to helicity in this ring since $C^1 \approx C^3$.



Polarizabilities
Un > R, O > H

Tandem Processes: Asymmetric Catalysis and Kinetic Resolution

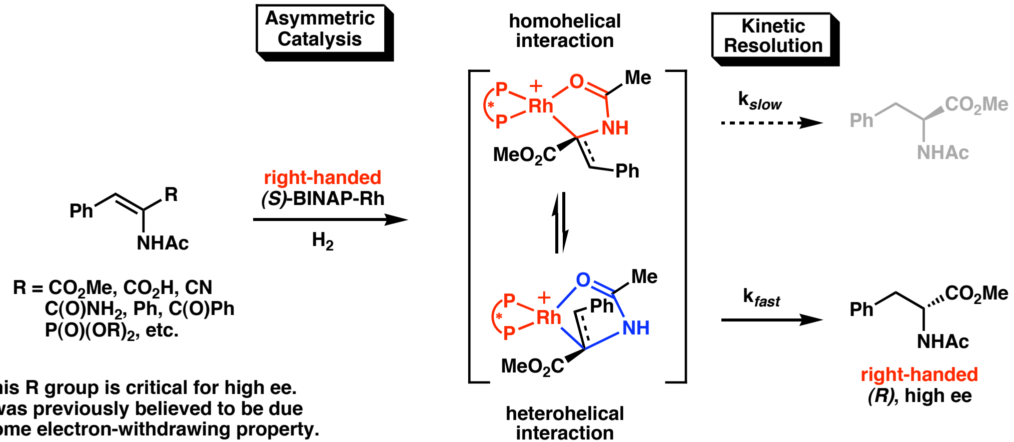
Enantioselective Sulfide Oxidation for Synthesis of Sulfoxides



Uemura, *J. Org. Chem.* **1993**, *58*, 4529

Another Tandem Process

Hydrogenation of Enamides - Tandem Asymmetric Catalysis and Dynamic Kinetic Resolution!



R = CO_2Me, CO_2H, CN
$C(O)NH_2$, Ph, C(O)Ph
$P(O)(OR)_2$, etc.

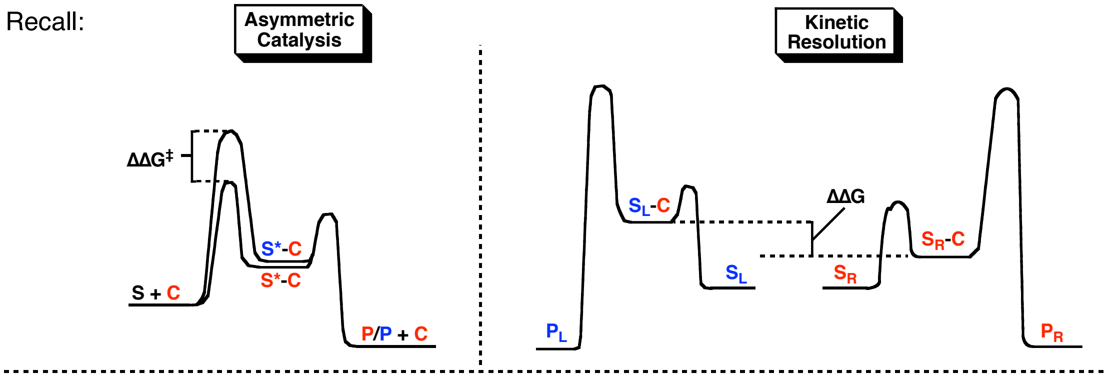
This R group is critical for high ee.
It was previously believed to be due
to some electron-withdrawing property.
Helicity makes it very clear: polarizability!

The initial coordination appears to be highly selective for homohelical induction. However, this is the much slower reacting complex to reach the product. Eventually, all of the enamide is channeled through the heterohelical complex to reach the product with high ee.

Halpern, *Pure Appl. Chem.* **1983**, *55*, 99
Koenig, in *Asymmetric Synthesis,* **1985,** Vol. 5, Ch. 3.

Helical Character Matching

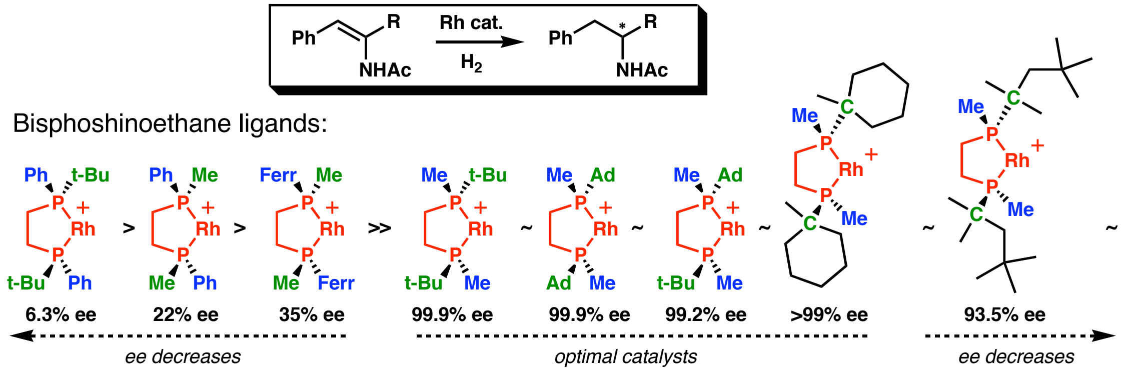
Recall:



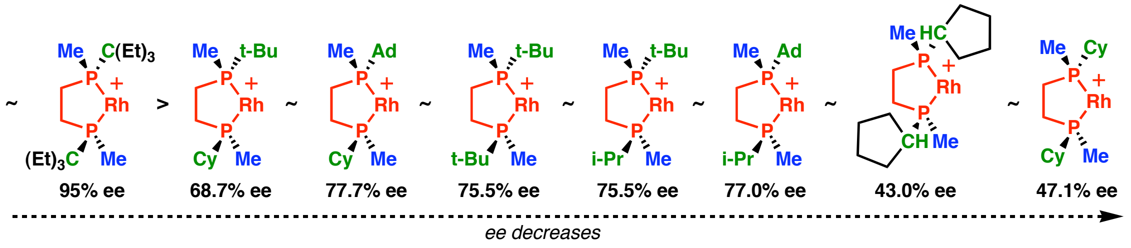
For the most selective reaction, ΔΔG must be maximized. This occurs when the helicities of S* (S_R) and C are equal. Similar to hard-soft acid-base theory (which is also based on polarizabilities), optimal interaction will occur when S* and C have the same helicity character, as well as the same handedness. Thus, by modifying the catalyst helicity (or substrate helicity), a rational method for optimizing selectivity in asymmetric reactions is realized.

Return to Enamide Hydrogenations

Extensive study of bisphosphine ligands in the Rh-catalyzed hydrogenation of enamides provides opportunity to see helicity matching in action!

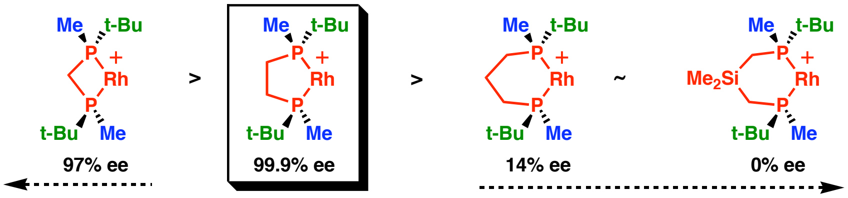


Bisphoshinoethane ligands:



Return to Enamide Hydrogenations 2

Helix Ring Size Affects Helicity!



97% ee

99.9% ee

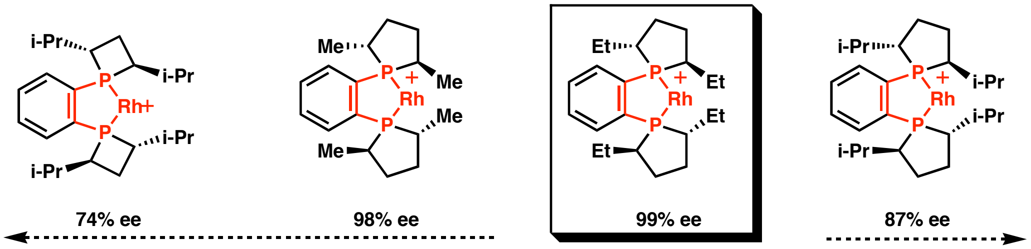
14% ee

0% ee

ee decreases

optimal catalyst

ee decreases



74% ee

98% ee

99% ee

87% ee

ee decreases

optimal catalyst

ee decreases

Similar effects can be seen for a variety of other ligand variations, as well as substrate variations: