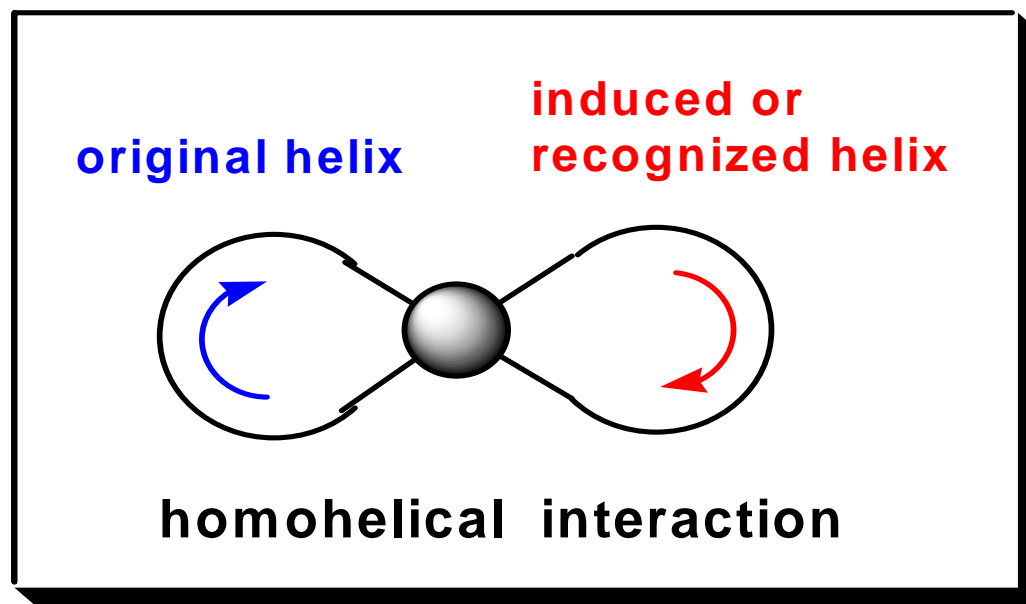


Conservation of Helical Asymmetry: A New Electronic Helix Theory for Molecular Chirality and Its Application in Rational Design of Enantioselective Catalysis

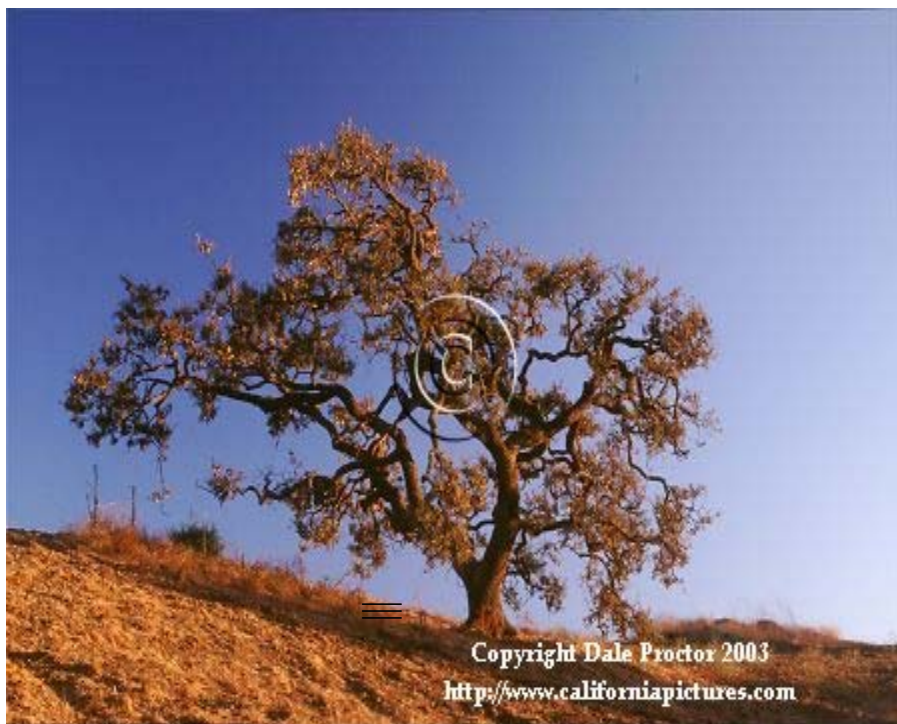


David Zhigang Wang 王智刚

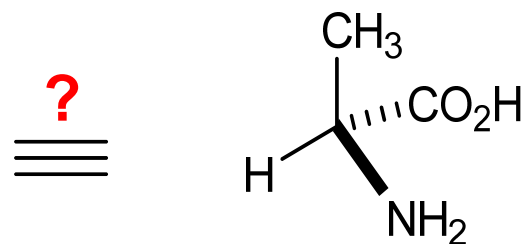
Shenzhen Graduate School, Peking University

北京大学 深圳研究生院

A Disturbing Message on Molecular Chirality



Chirality at Macro-scale World

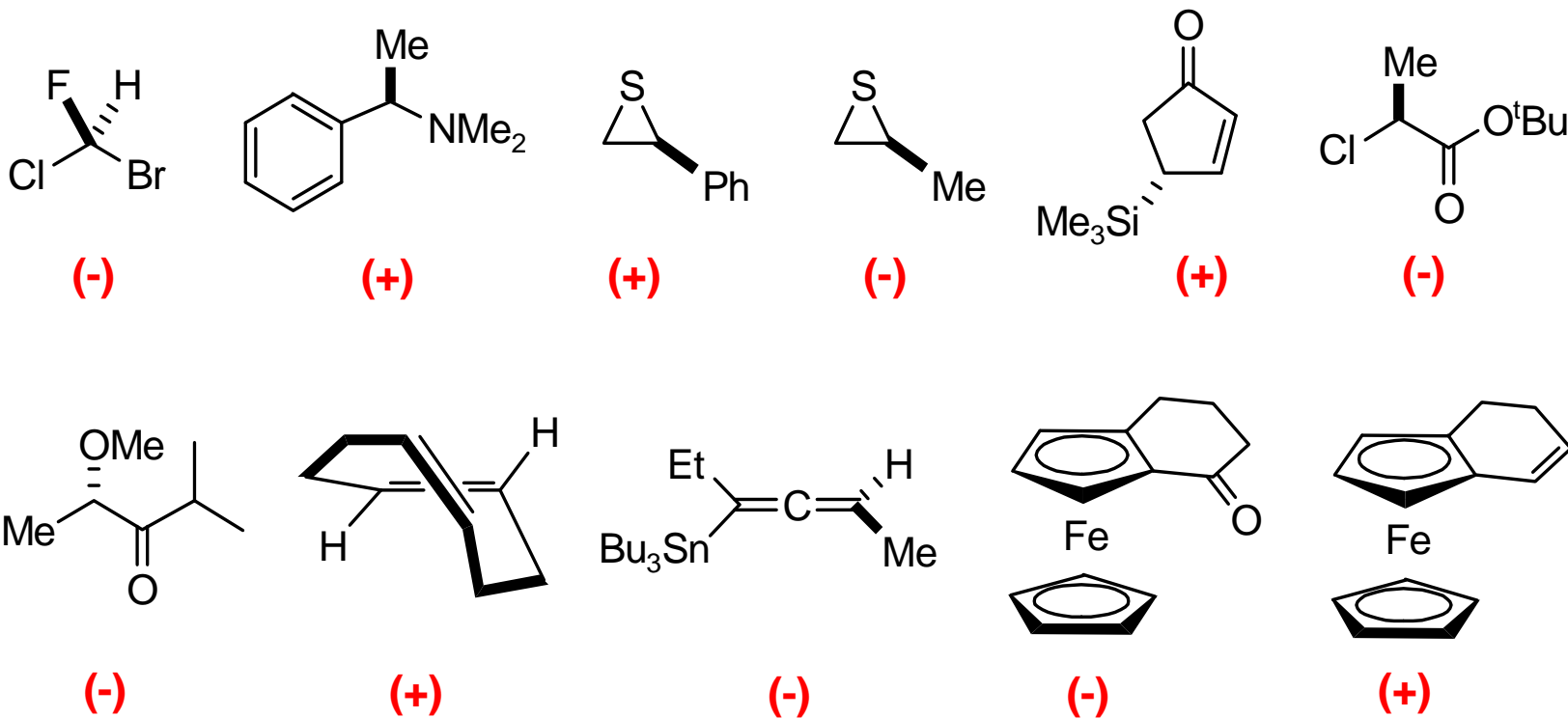


Chirality at Molecular World

The way we view chirality at macro-scale world is practically the same as that we understand molecular chirality, *i.e., they are both thought to be simply steric !*

Note: The concept of chirality was first coined by Lord Kelvin in 1893, 4 years *before* the discovery of the electron by J. Thomson in 1897

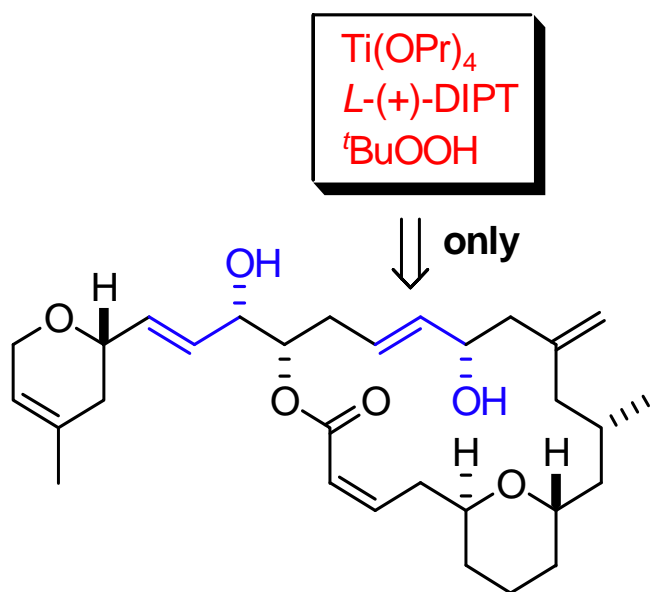
Absolute Configuration-Rotation Correlation



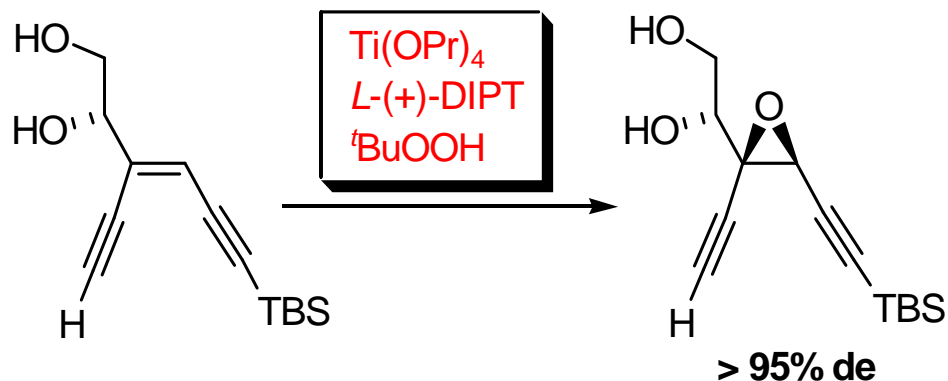
Can we predict a small molecule's absolute configuration readily on the basis of its optical rotation sign, or *vice versa*?

Abnormal Stereoselectivity

Asymmetric Epoxidation



Angew. Chem. Int. Ed. **2006**, 45, 190.



*Stereochemistry anomalous
to the Shapless mnemonic !*

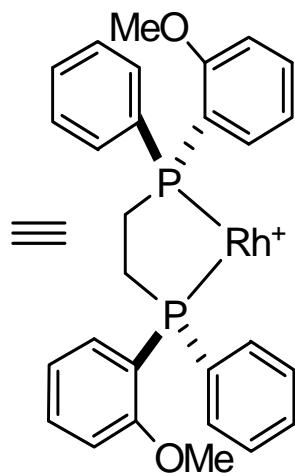
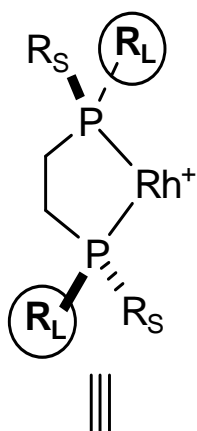
J. Am. Chem. Soc. **1996**, 118, 10006.

Can we predict these critical stereochemical courses
beforehand, so synthesis can be more rationally planned?

Surprising Stereochemical Reversal

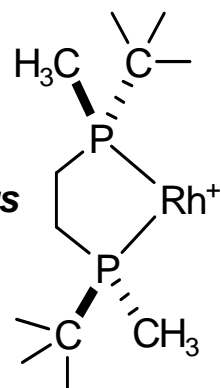
Asymmetric Hydrogenation

Quadrant
Diagram

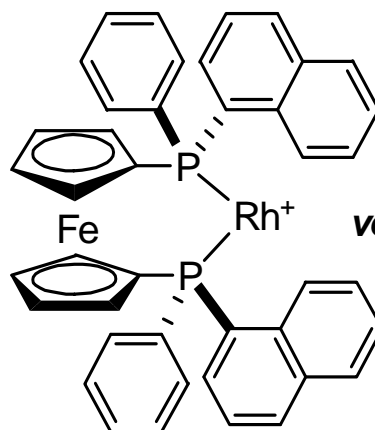


a: 96% ee (+)

versus

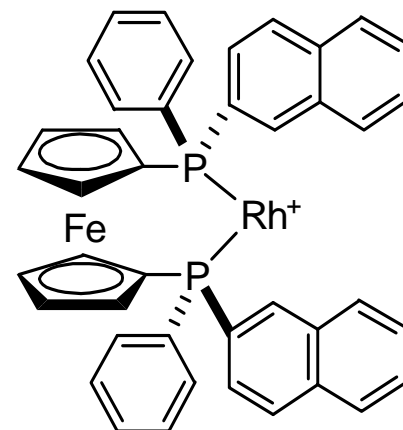


b: 99.9% ee (-)



c: 97.3% ee

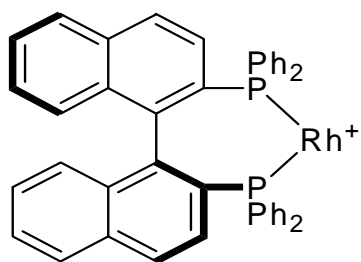
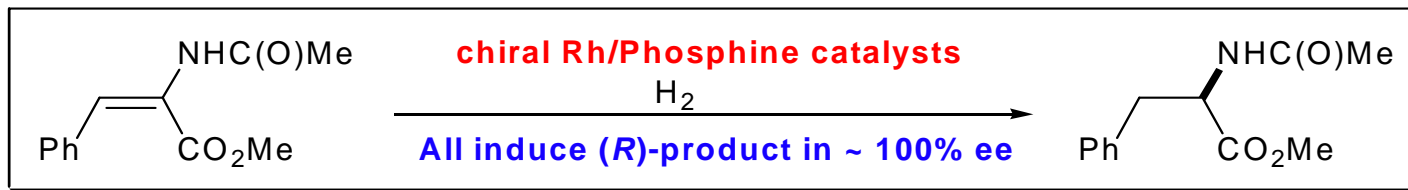
versus



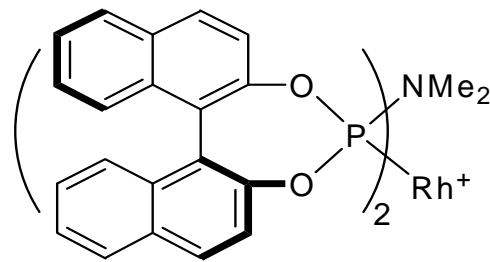
d: 7.6% ee

Why these sterically similar catalysts behave so differently in asymmetric hydrogenation of the same substrate?

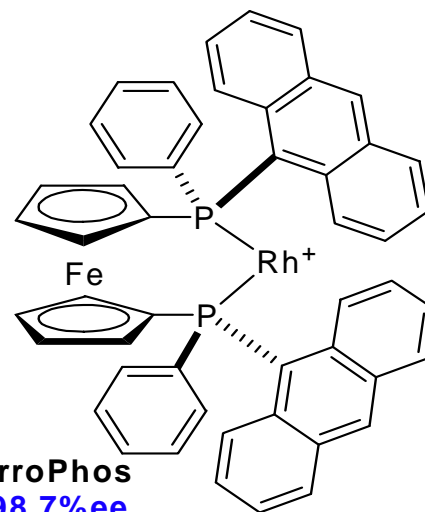
The *Lock-and-Key* Wisdom !?



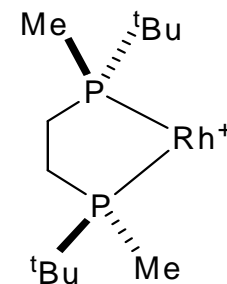
BINAP
100%ee



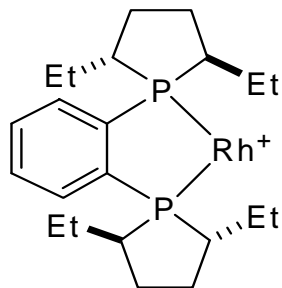
MonoPhos
98.7%ee



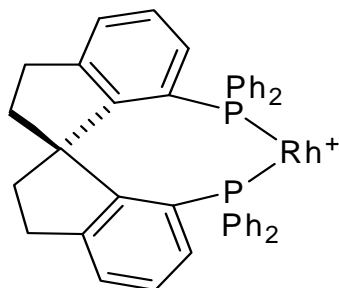
FerroPhos
98.7%ee



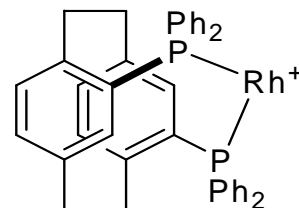
BisP*
99.9%ee



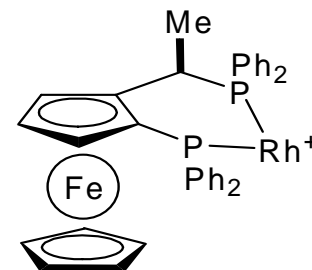
DuPhos
99%ee



Spiro-Phos
99%ee



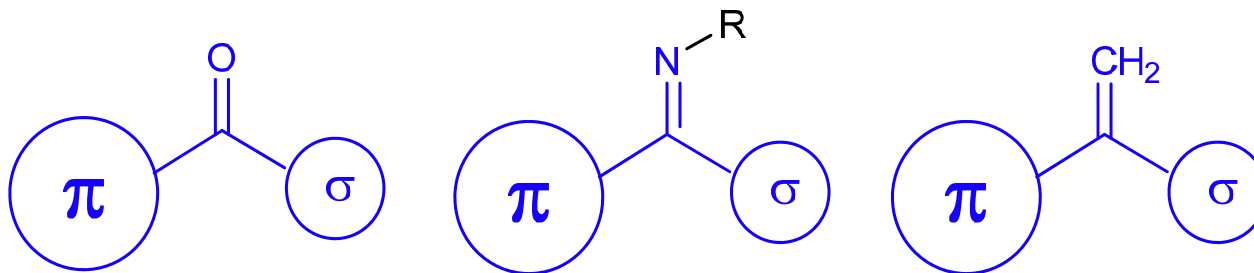
PhanePhos
98%ee



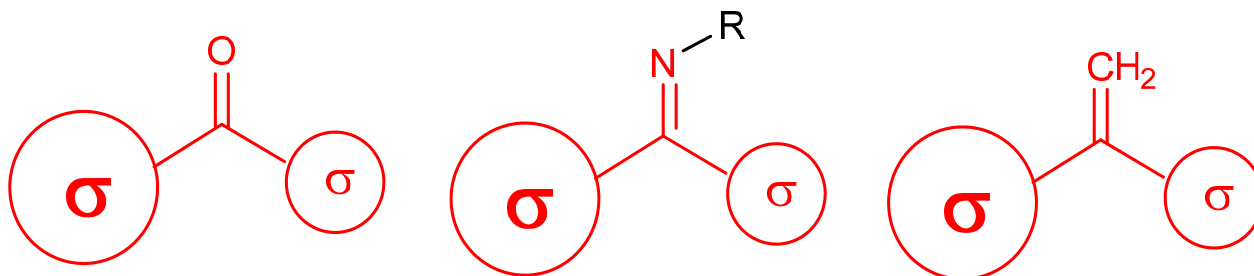
Josi-Phos
99%ee

All these “keys” can open the same “lock”,
so what do they really have in common?

Substrates in Asymmetric Catalysis



Good Substrates: Generally High ee%



Bad Substrates: Generally Low ee%

π -group: aromatic, hetero-aromatic, alkenyl, alkynyl, frocenylyl, carbonyl, etc

σ -group: simple alkyl

The beneficial role of pi-group on enantioselection does not seem to be steric in nature, what is its electronic implication?

The *State-of-the-Art* of Asymmetric Synthesis

Highly Empirical !

The discovery and development of chiral catalysts typically relies on screening rather than rational design.

Implication:

Something critical is missing in our fundamental understanding of molecular chirality !

A General Electronic Scenario That Goes Beyond Conventional Steric Wisdom

For a Highlight:

***Chem & Eng News*, 2003, September 29 issue, 34-35.**

For a full account of the theory:

Wang, *Tetrahedron*, 2005, 61, 7125-7133, & Supporting Material.

Wang, *Tetrahedron*, 2005, 61, 7134-7143.

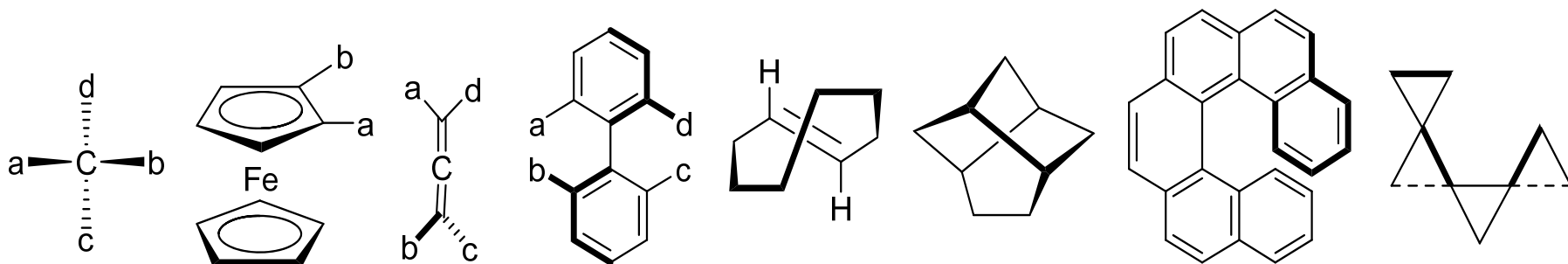
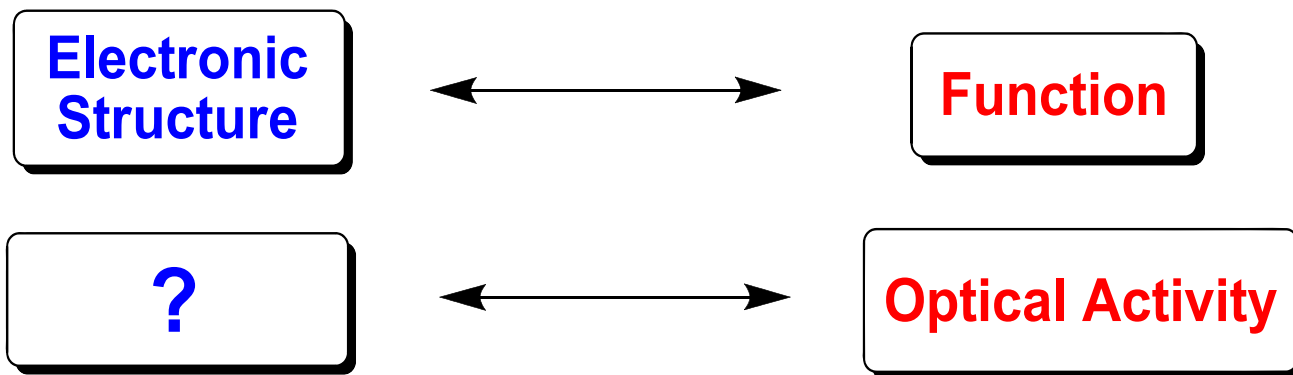
For a theoretical treatment:

Wang, *Chirality*, 2005, 17, 177-182.

For a brief overview:

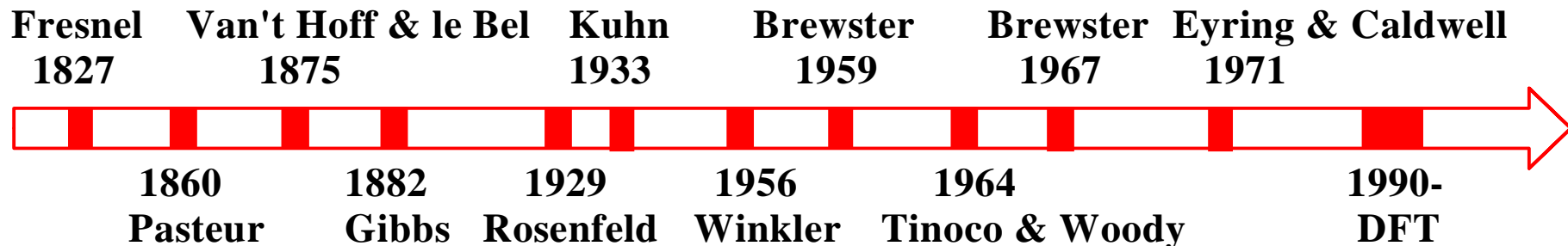
Wang, *Mendeleev Communications*, 2004, 6, 244-247.

A Question Suggested By the First Principle



What is the **common electronic basis** for their optically activity ?

Understanding Molecular Chirality: The Timeline



As pointed out by Brewster [*Top. Stereochem*, 1967, 2, 1]:

“... . 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 electronic polarizability and bond structure”.

Question: Do helical electronic structures exist in real molecules?

Correlation
with Theory

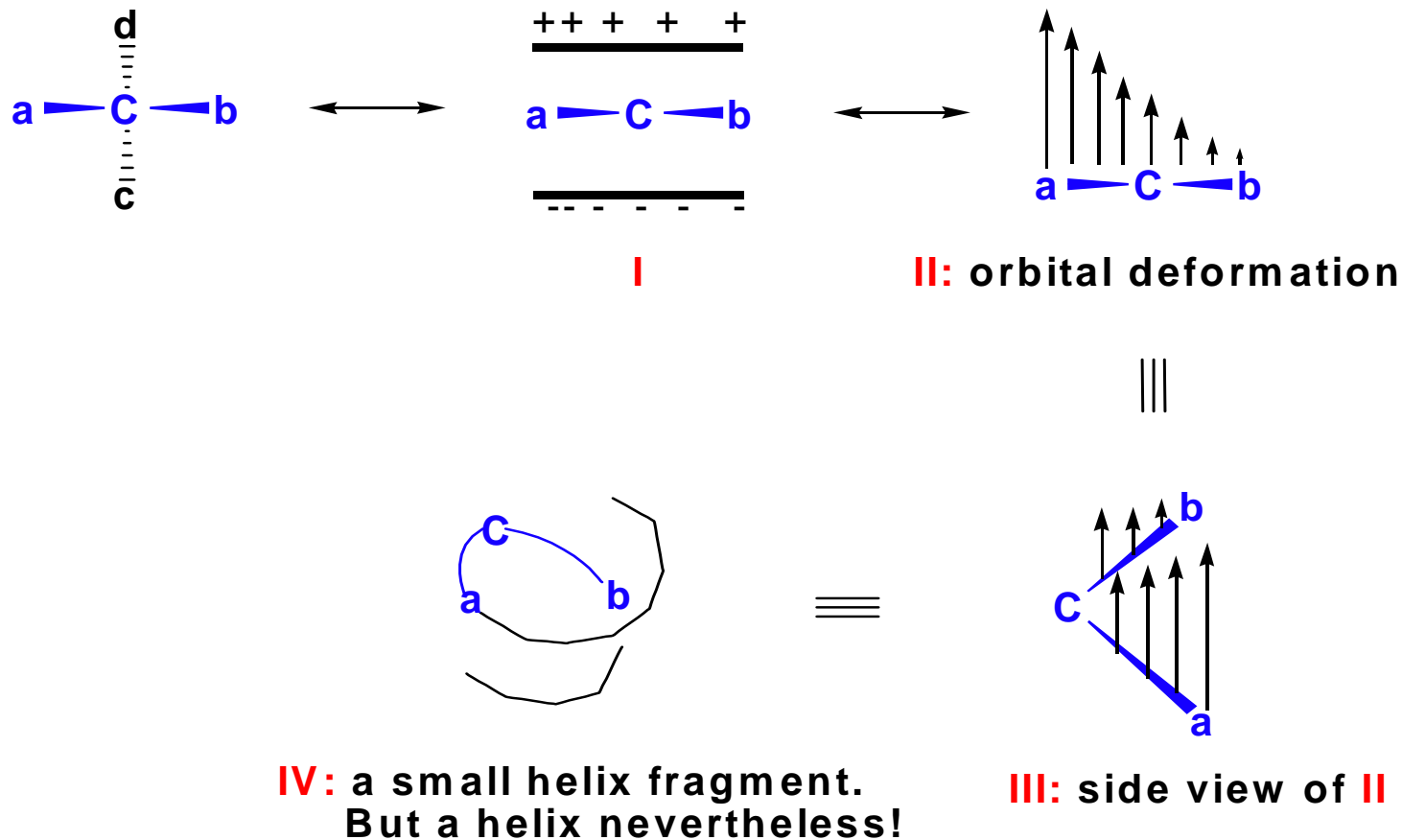


Helical Electronic Structures



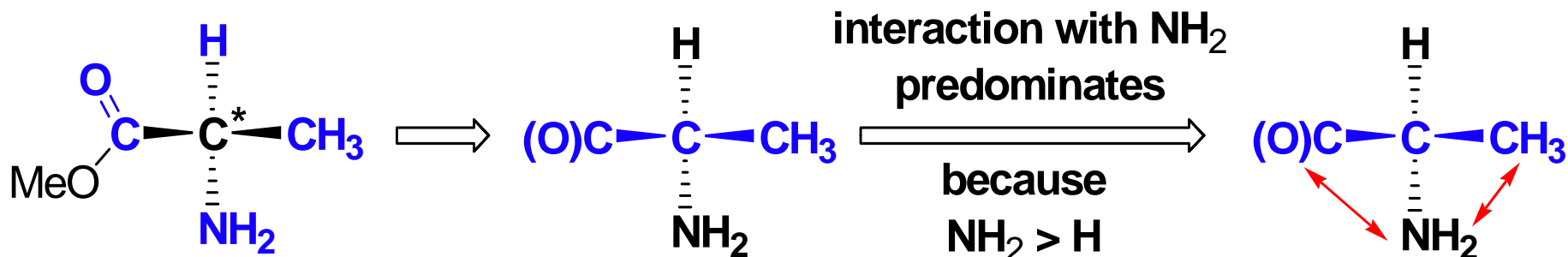
Understanding
Chiral Interaction

Covalent Bond Helical Deformation in Asymmetric Electronic Environment



- * Group electronic interaction can be measured by its **Polarizability**
- * Unbalanced group electronic interactions in C^*abcd deform a pair of covalent bond into a micro-helical structure

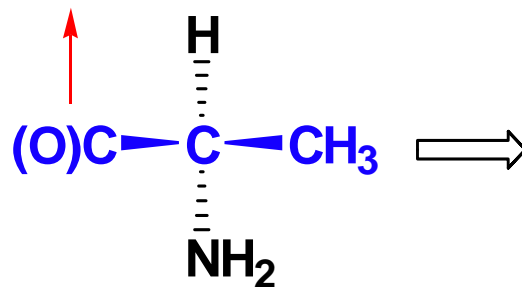
Twist of a Pair of Covalent Bonds into a Helix



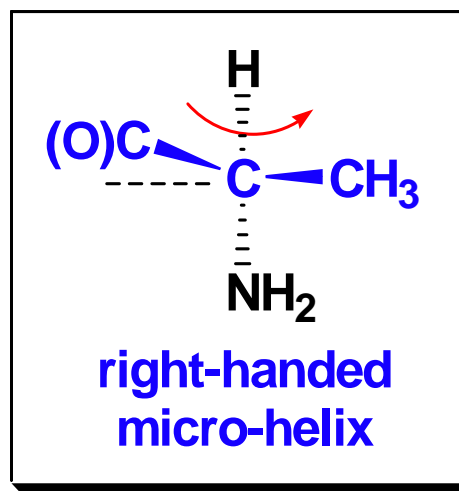
Local Polarizability:
 $\text{C}=\text{O} > \text{CH}_3 > \text{NH}_2 > \text{H}$

interaction with $\text{C}=\text{O}$
predominates

because
 $\text{C}=\text{O} > \text{CH}_3$

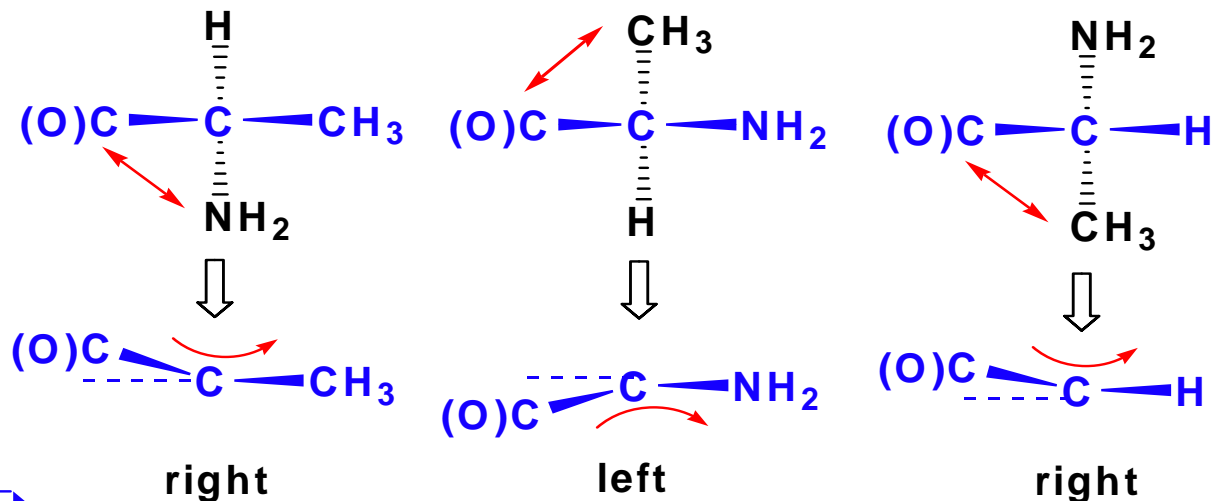


The net result should
be to twist $(\text{O})\text{C}-\text{C}^*$ bond
up more than CH_3-C^* bond

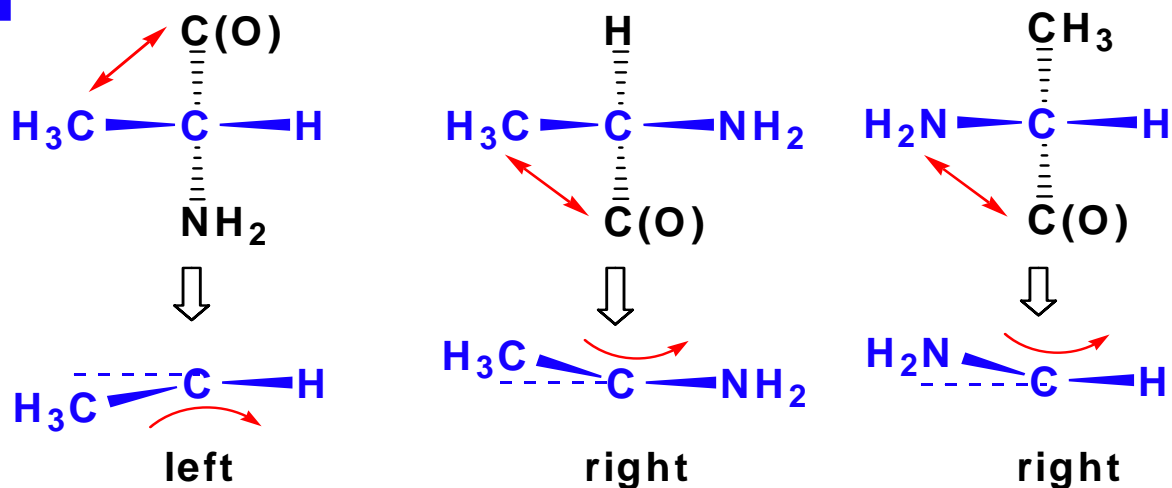


counter-
clockwise:
right-handed

There Are Totally 6 Helices Around a Chiral Center

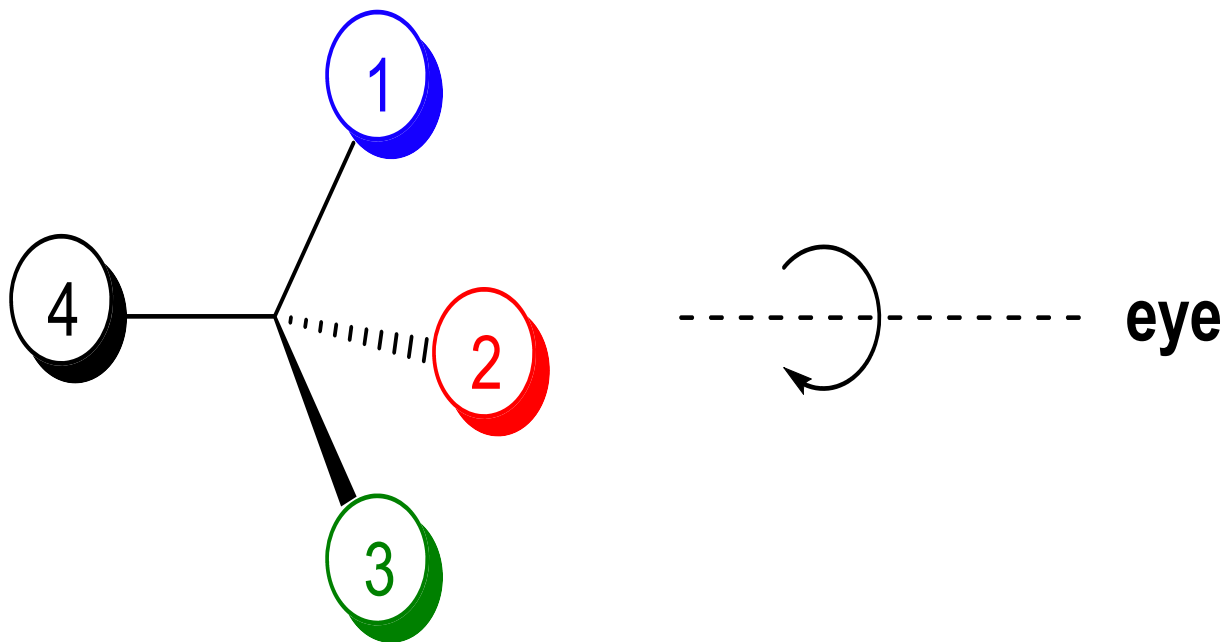


$$C_4^2 = 6$$



This molecule has a net right-handed helicity and is dextrorotatory. It can also be shown that the net helicity, thus optical activity, diminishes if any two groups are the same.

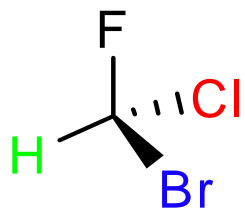
Local Polarizability: $1 > 2 > 3 > 4$



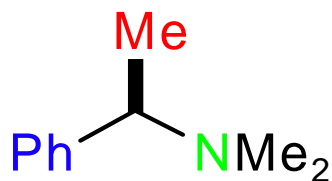
The Molecule Must Show (+)-Rotation Sign at Long Wavelengths

A Simple Method for Assigning Molecular Absolute Stereochemistry from Its Optical Rotation Signs

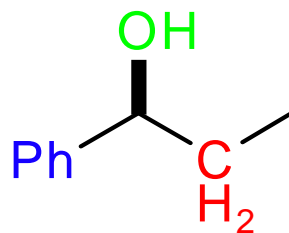
Local Group Polarizabilities: **Blue** > **Red** > **Green** > H)



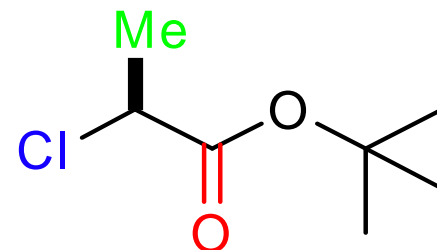
(S)-(+)



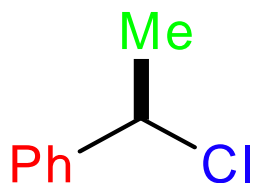
(R)-(+)



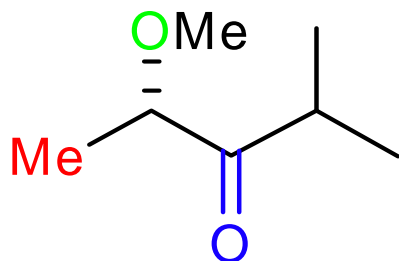
(S)-(-)



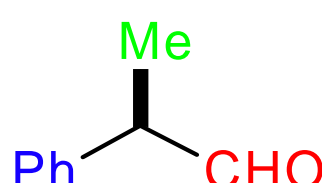
(S)-(-)



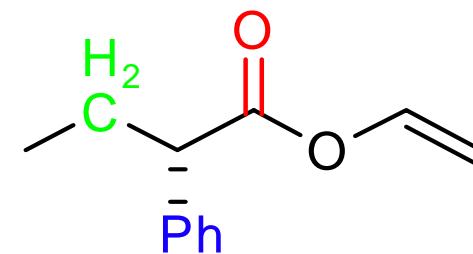
(R)-(+)



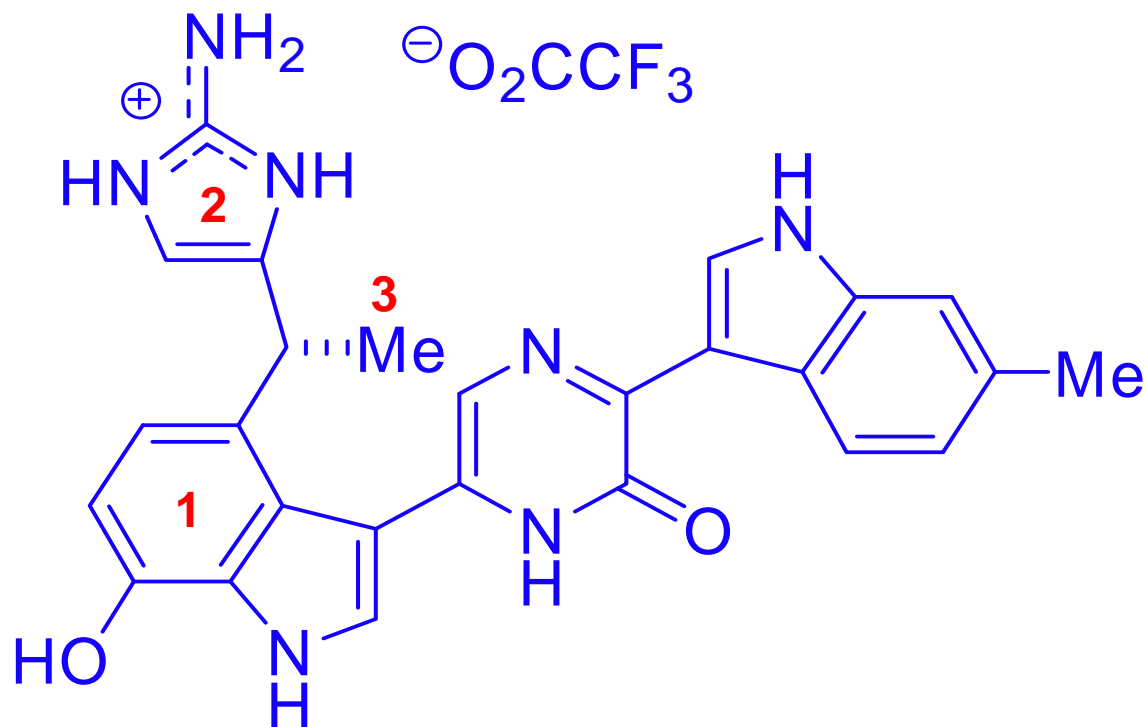
(S)-(-)



(R)-(-)



(S)-(+)



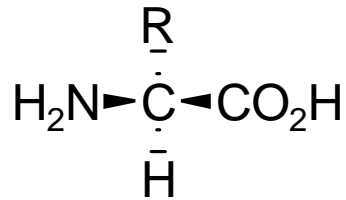
Dragamacidine D

The natural *Dragamacidine D* shows (-)-rotation, so it must have (*R*)-absolute configuration!

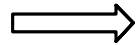
Private communication with the Stoltz group at Caltech

Right-handed Helicity in Life's Building Blocks

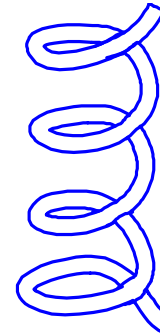
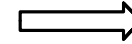
**Polarizabilities: any $R > H$; and $CO_2H > NH_2$
Nature varies R group, but not H.**



L-amino acids



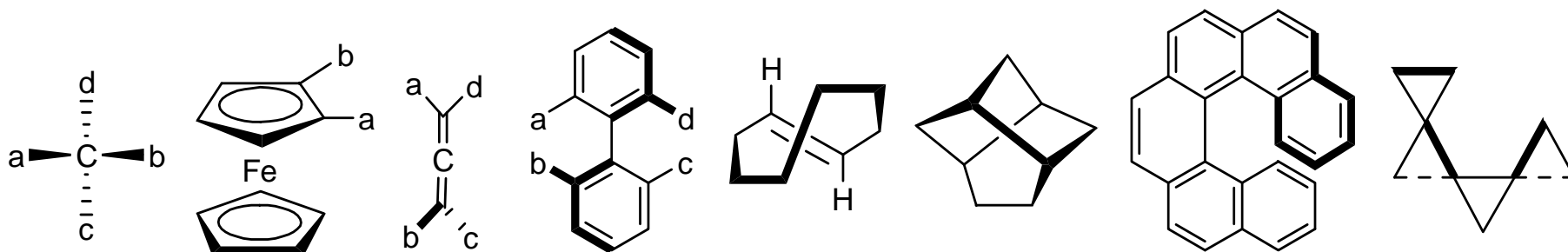
right-handed



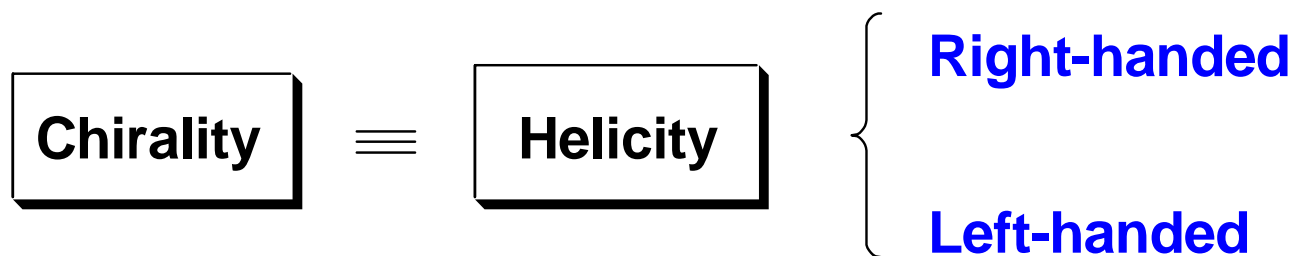
**right-handed
polypeptides**

All L-amino acids feature right-handed helicity in the $H_2N-C^*-CO_2H$ moiety !

Generalization of Diverse Molecular Chiralities



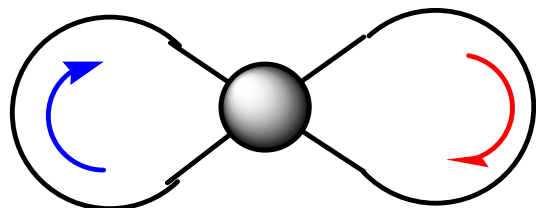
All types of chiralities feature helical electronic structures.



These helical electronic characteristics of molecular chirality differ distinctly from their steric properties, and they play critical role in stereochemical interactions.

Chiral Interactions: Only Two Possibilities

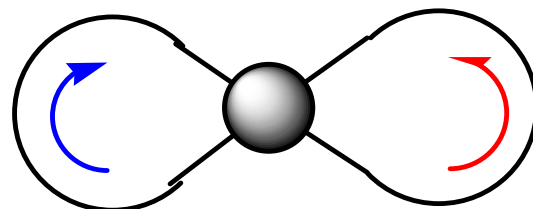
original helix induced or
 recognized helix



Homohelical Interaction

versus

original helix induced or
 recognized helix

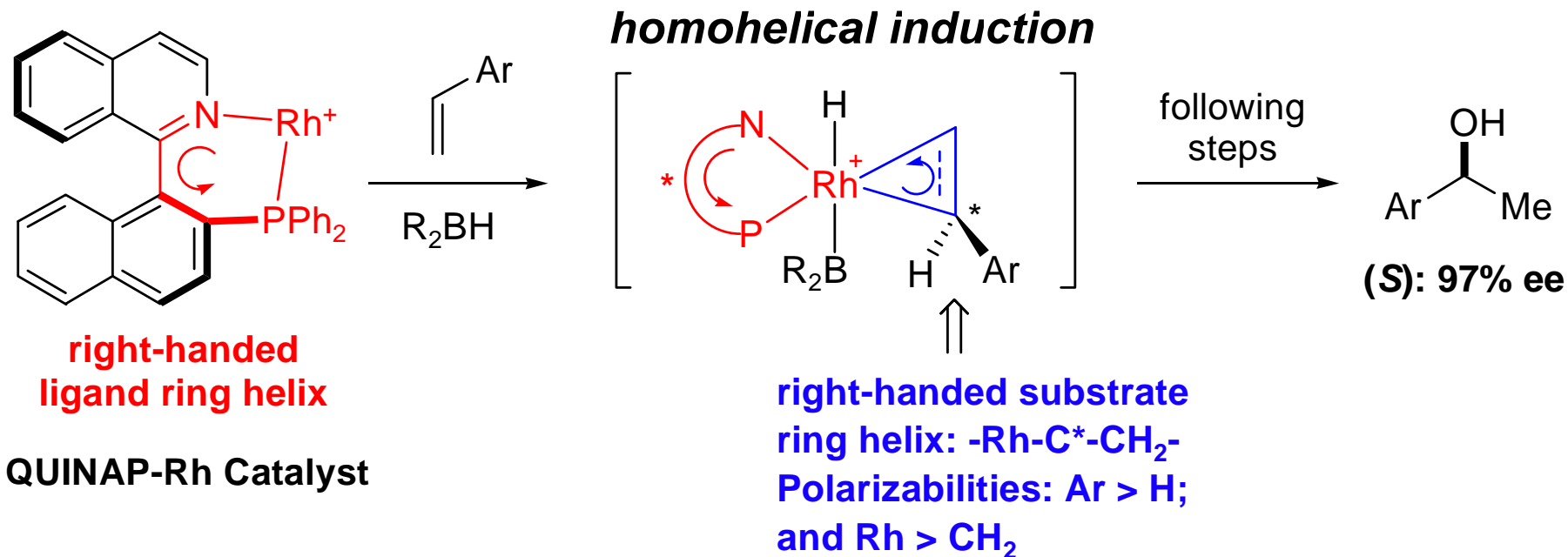


Heterohelical Interaction

It was proved that, in agreement with experiments, the homohelical interaction is always *electronically* energetically favored, that is, **electronic helicity is conserved in a chiral interaction process.**

How Can Enantioselection Arise Electronically? A Homohelical Induction Analysis

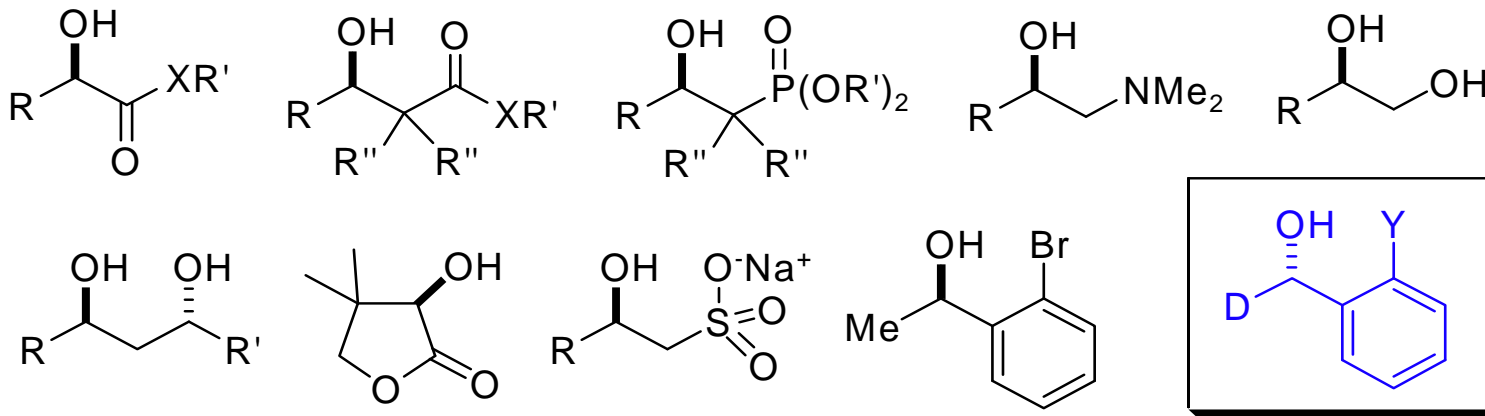
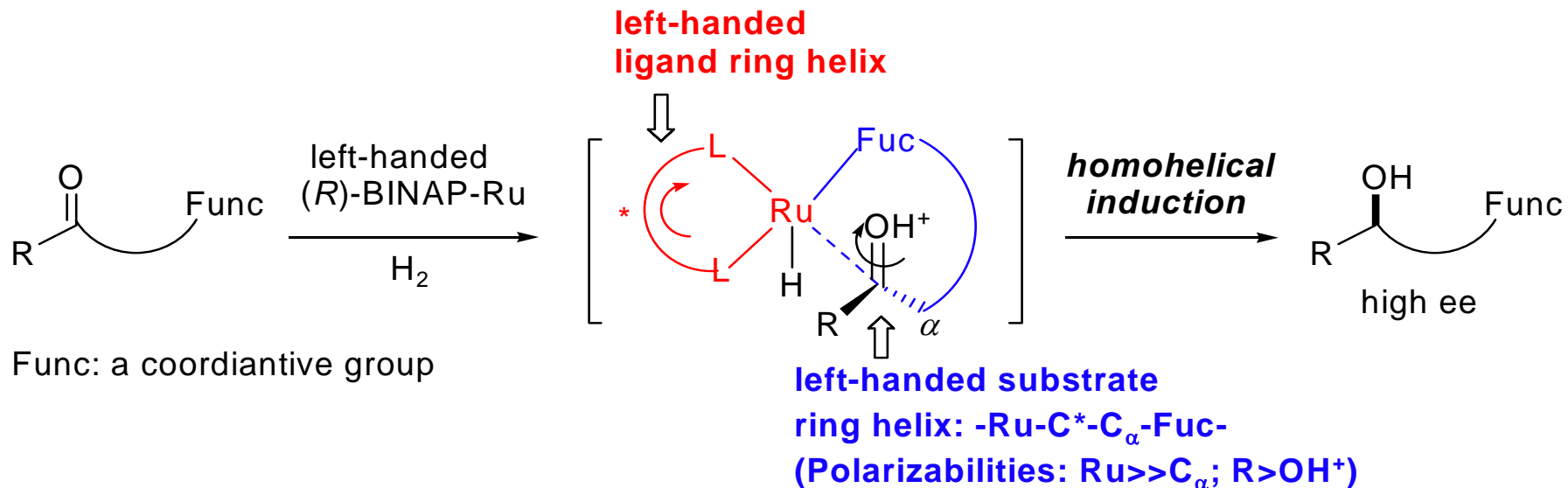
Asymmetric Hydroboration of Vinyl Arenes



Principle: The Conservation of Helical Asymmetry

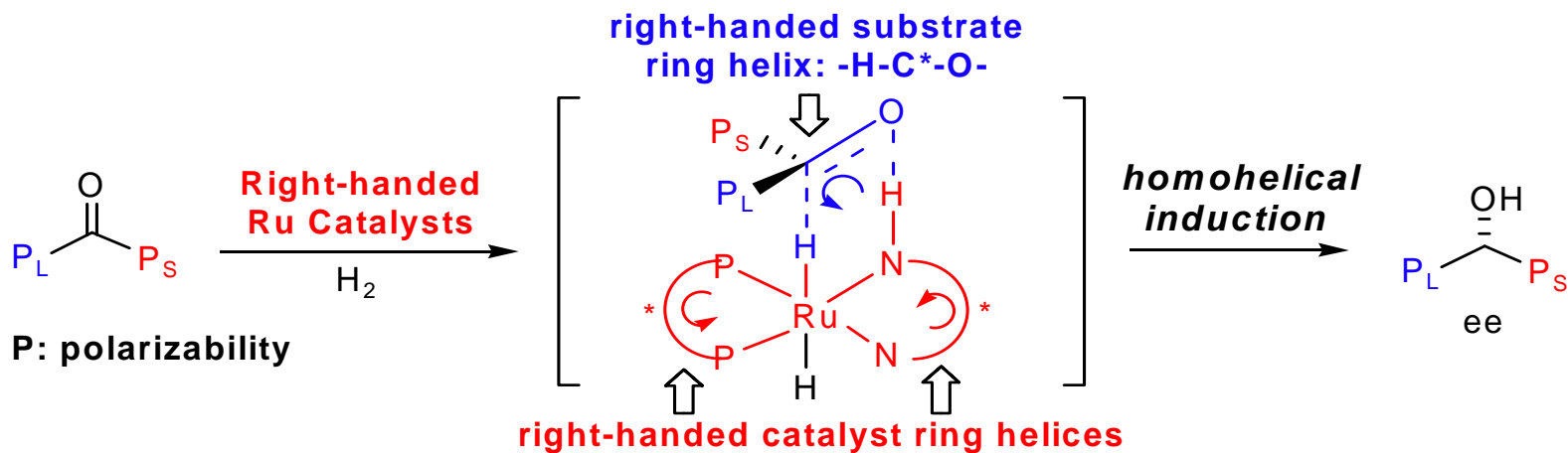
A chiral catalyst will electronically prefer forming the chiral product that allows it to preserve its helicity in the ee-determining step.

Asymmetric Hydrogenation of Functionalized Ketones

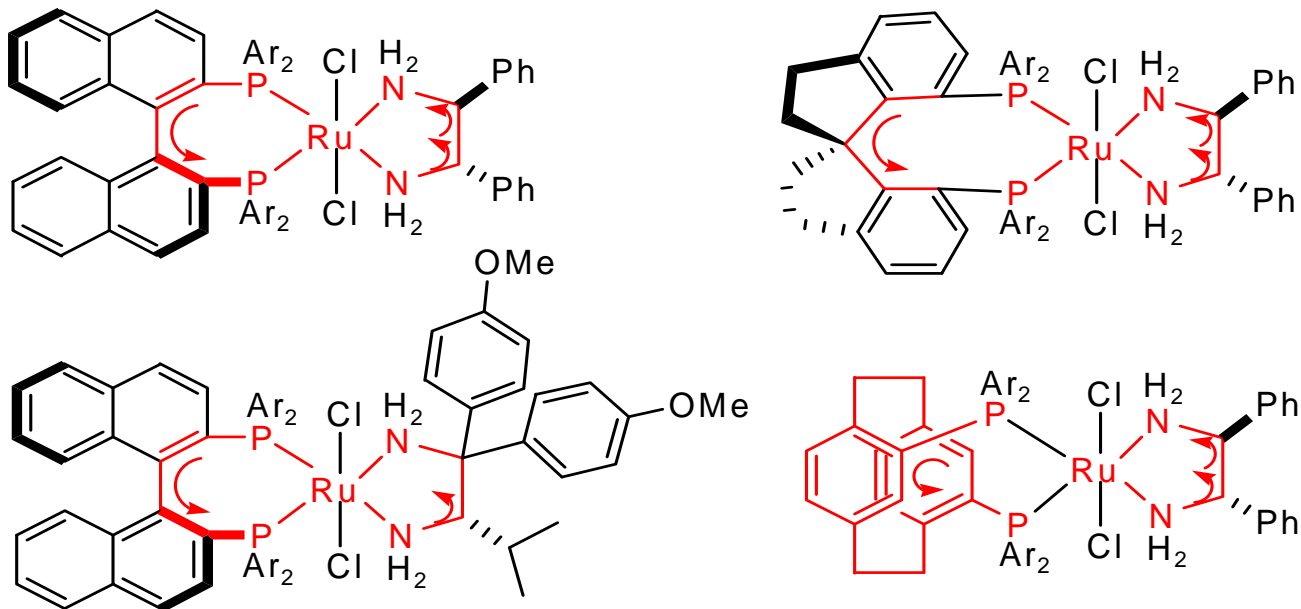


**D is less polarizable than OH⁺,
 so facial selection is reversed !**

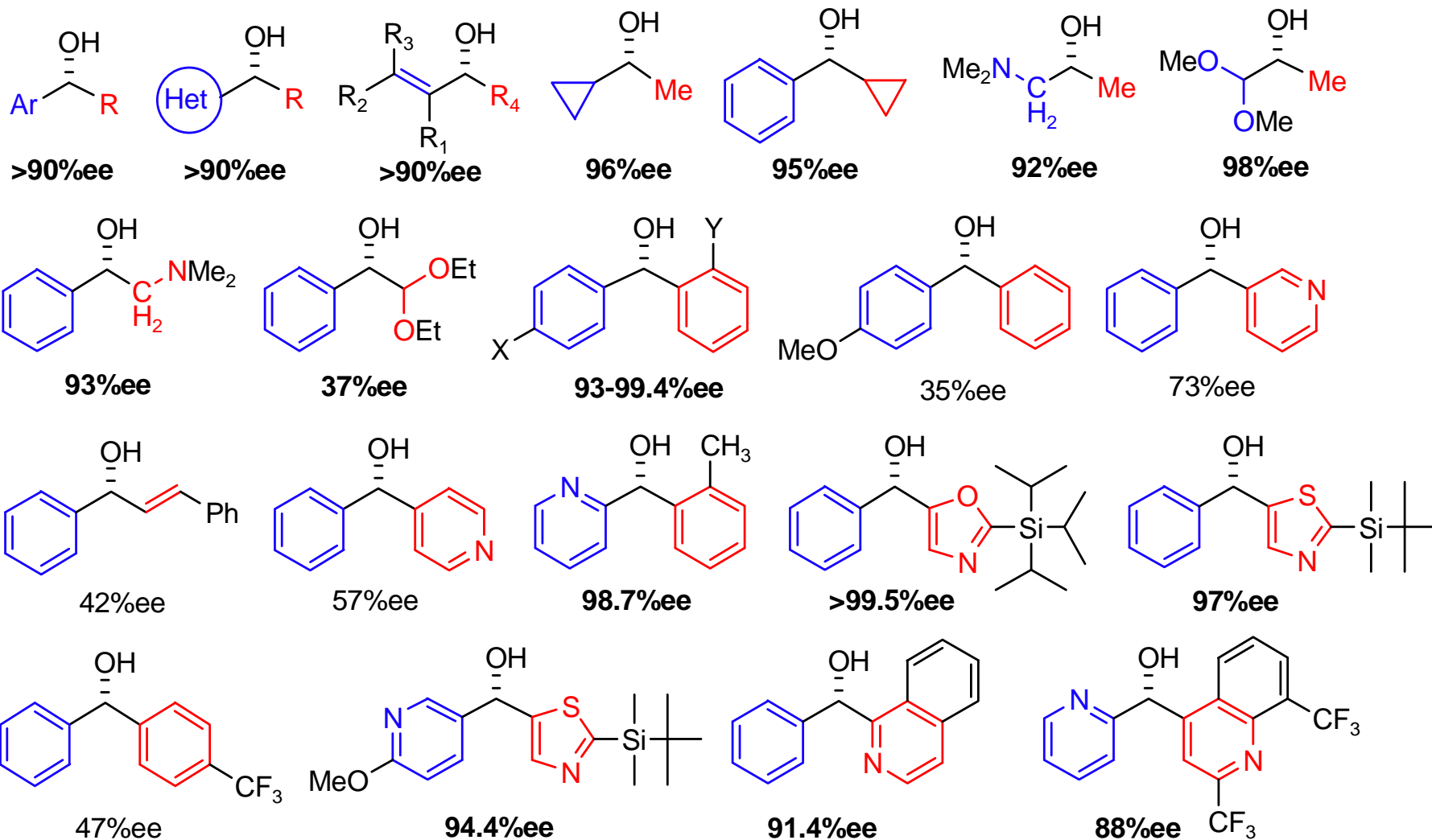
Asymmetric Hydrogenation of Unfunctionalized Ketones



Right-handed Ru Catalysts



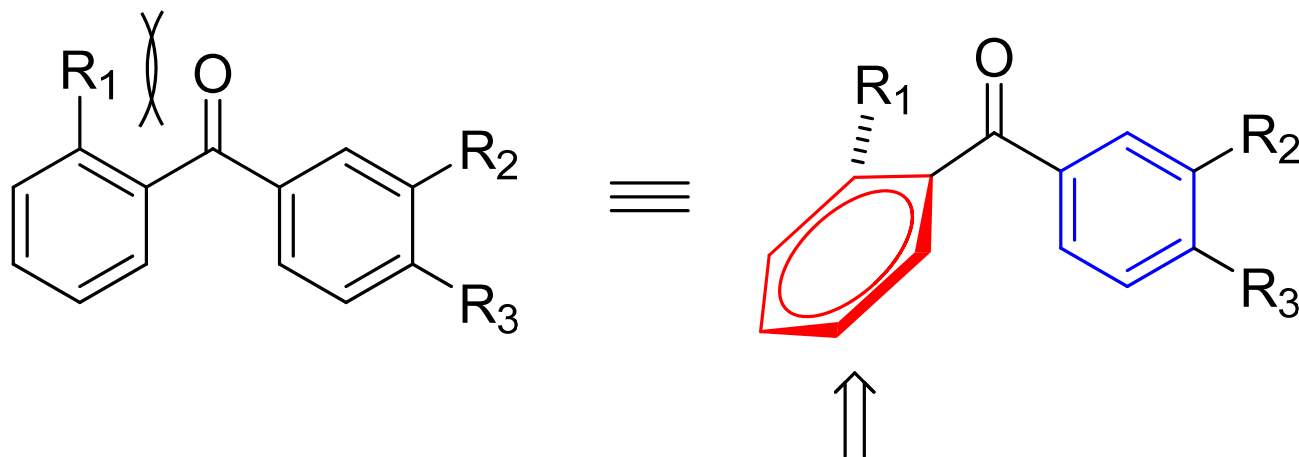
Substrates Survey: Polarizability Matters, Not Size



The larger the polarizability difference, the higher the ee

What Is So Special About *Ortho*-Bisaryl Ketones ?

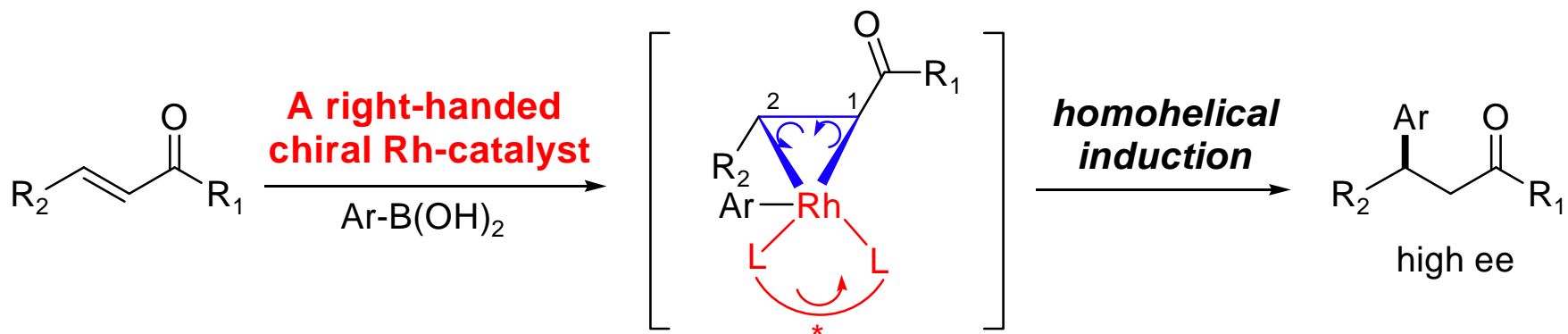
**R₁-Oxygen Lone Pairs
Electronic Repulsions**



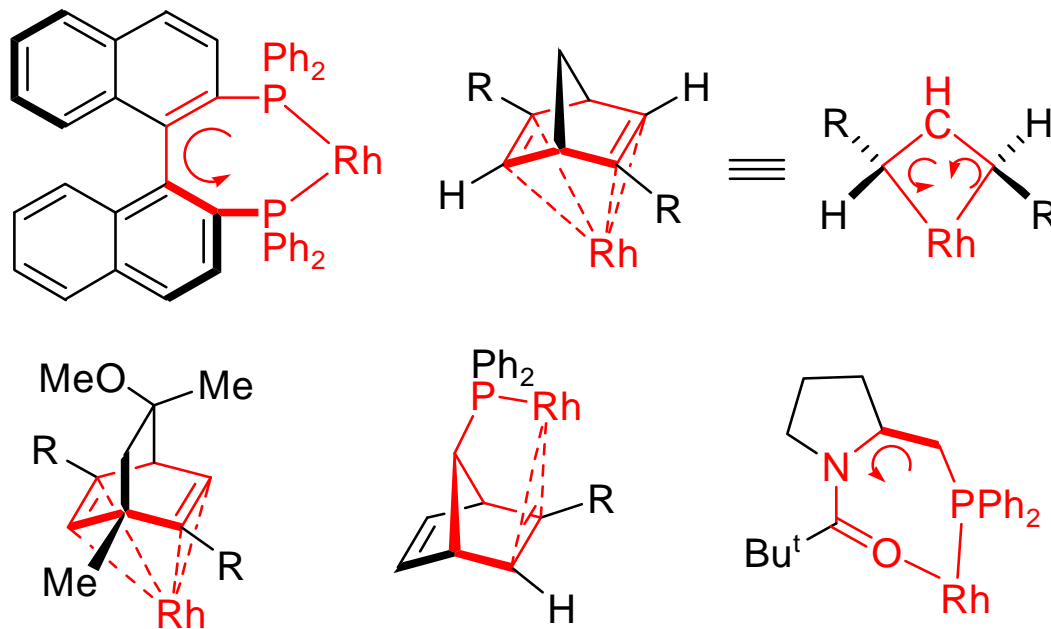
**Rotation Reduces The Phenyl Ring π
Electronic Polarizability That It Can Otherwise
Impose On Reaction Transition State**

Thus regardless of what R_1 , R_2 or R_3 group is, *the phenyl ring in red is always significantly lower in electronic polarizability than the phenyl ring in blue*, making them outstanding substrates in asymmetric catalysis.

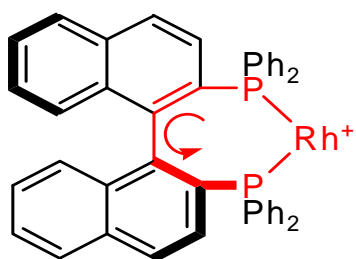
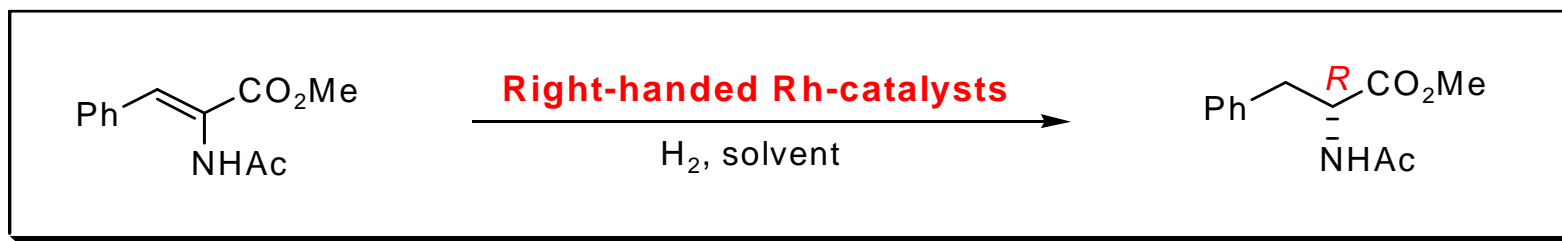
Asymmetric Conjugate Addition



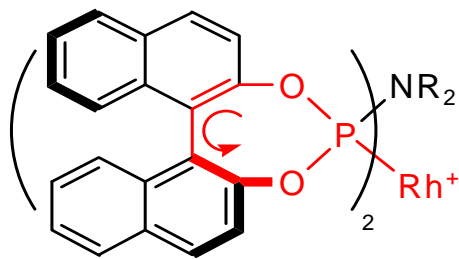
Right-handed Rh-catalysts



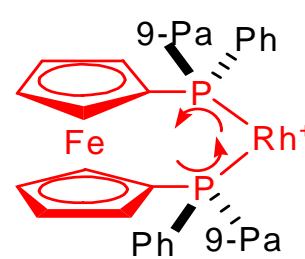
Chiral Induction: Profound Helical Electronic Control



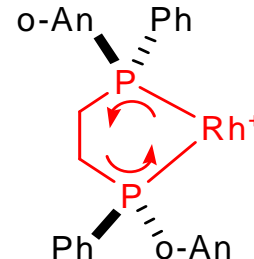
1: BINAP



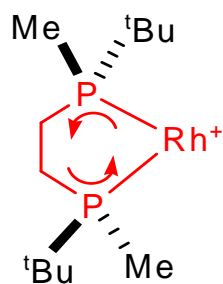
2: MonoPhos



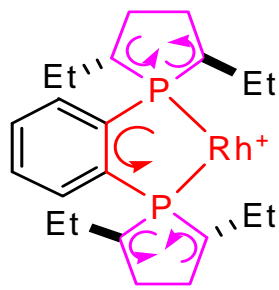
3: FerroPhos



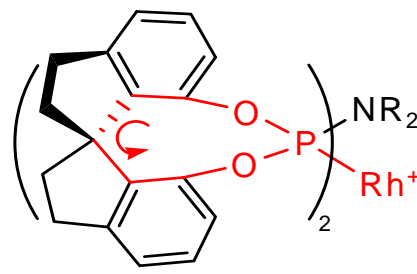
4: DIPAMP



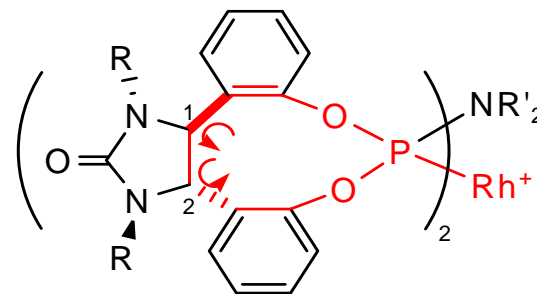
5: BisP*



6: DuPhos



7: SpiroPhos



8: DpenPhos

The catalyst rings (in red) all feature right-handed helicity, therefore they all induce (R)-product in high enantioselections.

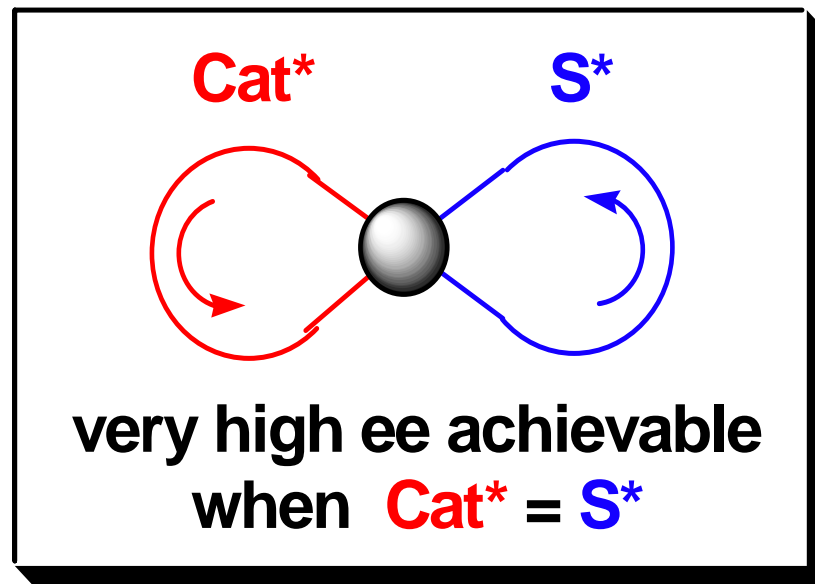
How Chiral Should A Catalyst Be To Induce Perfect Enantioselection for a Given Substrate?

Catalyst-substrate Helical Character Matching for Highly Enantioselective Asymmetric Catalysis:

Cat*: catalyst helix character

S*: substrate helix character

 interaction means

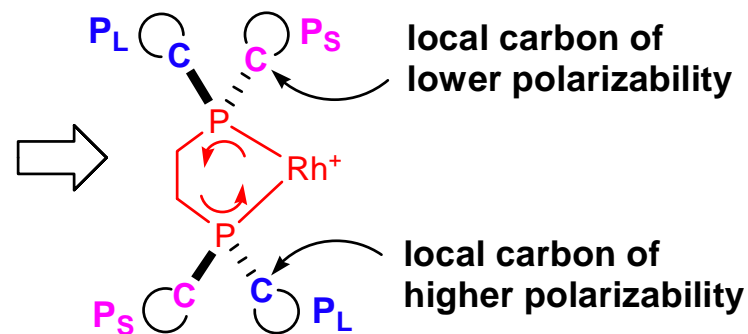


Answer: When they are matched in helical characters (energies) !

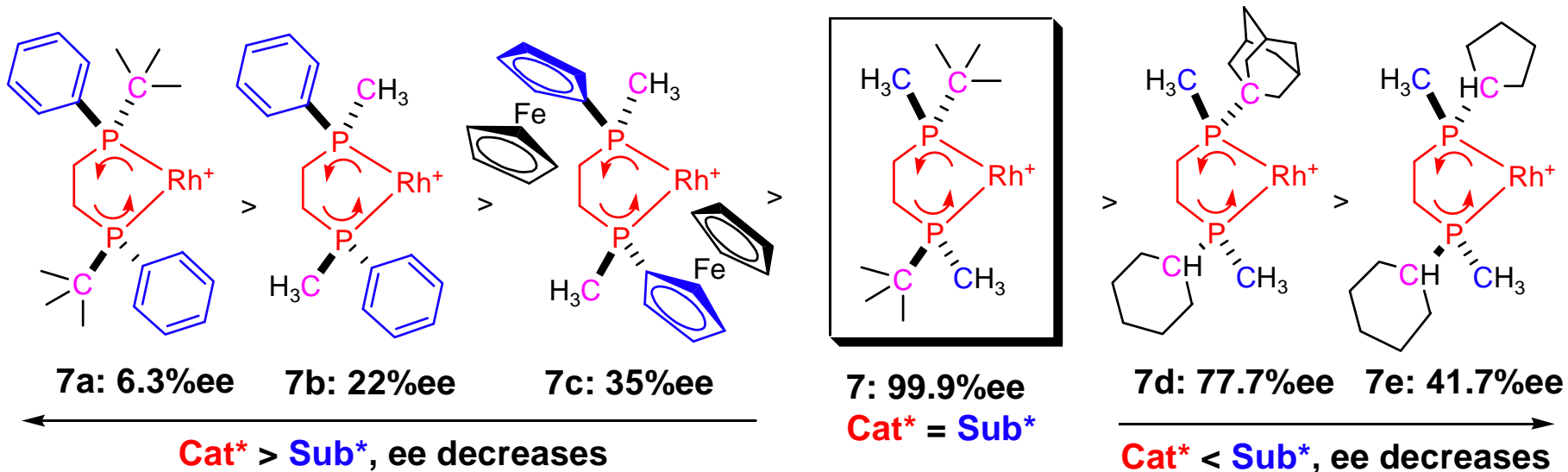
The result highlights the importance of polarizability (energy) matching in chiral space for high enantioselection, and the work in essence is a chiral version of the classical hard and soft acid-base theory.

Catalyst-substrate Helical Character Matching Determines Enantioselection

Catalysts are ranked by their corresponding ring helix character which decreases as their P_L -versus- P_S polarizability difference decreases



Catalyst ring helix character decreases



Cat^* : catalyst ring helix (in red) character
 Sub^* : substrate ring helix (not shown) character

The Theory is General and Predictive !

Hydrogenation

- * Hydrogenation of functionalized and unfunctionalized ketones
- * Hydrogenation of functionalized and unfunctionalized alkenes

Hydroboration

Transfer hydrogenation

Epoxidation

- * Sharpless AE
- * Ketone-catalyzed processes, Salen systems

Dihydroxylation (Sharpless AD)

Ring closing metathesis

Heck reaction

Conjugate addition

Alkylation

Acylation

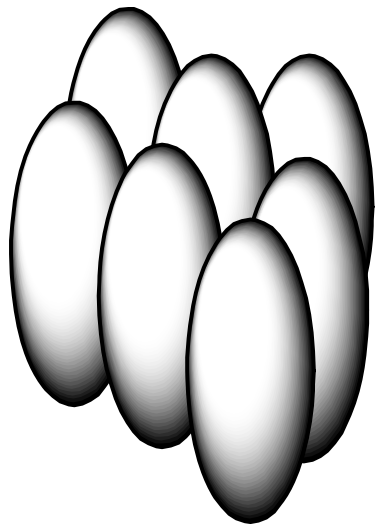
Sulfides/sulfoxides oxidation

Ring opening of lactones and anhydrides

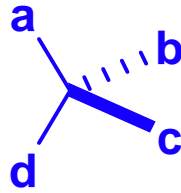
Proline organocatalysis

Applications Into Liquid Crystals

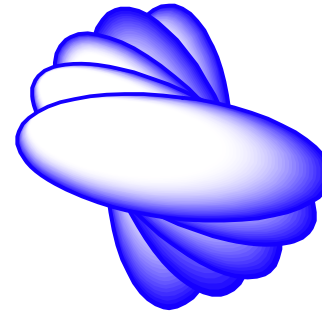
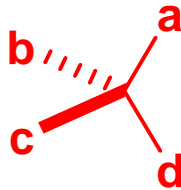
Homohelical Induction



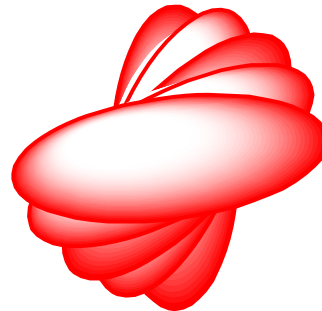
Nematic
Liquid Crystal



Enantiomeric



right-handed
helix



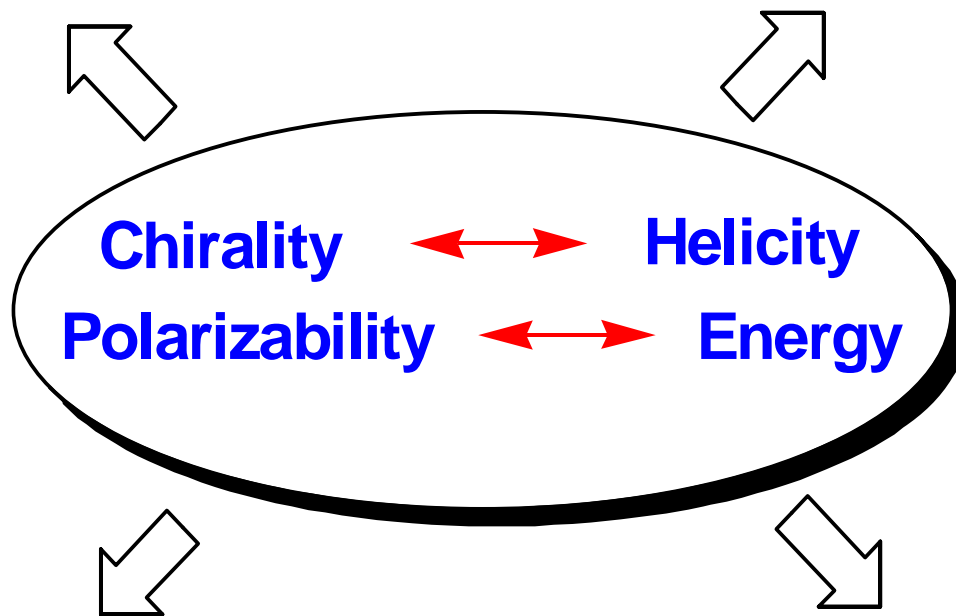
left-handed
helix

The induction of macro-structural helix by a chiral dopant follows faithfully a homohelical induction mechanism.

A Unified Roadmap to the World of Chirality

The Principle of Maximum Hardness
in Chemical Reactions: Electron-pushing
in Bond Breaking and Forming Events

Structure-function Correlation
in Optical Activity: The Quantum
Mechanical Helix Theory of Chirality



The Hard and Soft Acid-base
Theory in Chemical Reactions

Homohelical Electronic Interactions:
The Conservation of Helical Asymmetry
in Chiral induction and Recognition

This helix theory in essence is a chiral version of HSAB.

Summary

1. Chirality = Helicity, *they are just the same thing.*
2. Homohelical interactions are *electronically* favored.
3. These interactions are most favored when the interacting helices are *energetically equal* to each other.

The work should aid rational design of chiral systems.

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