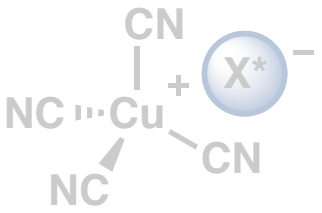
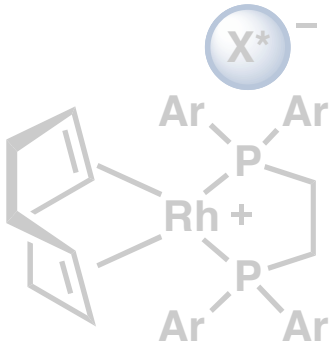
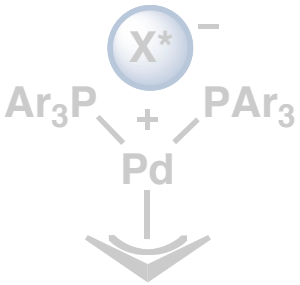
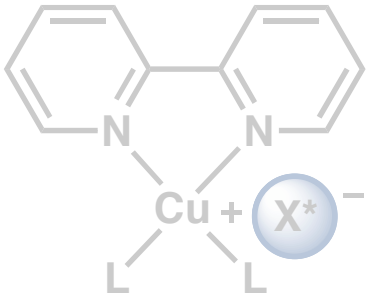


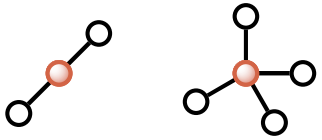




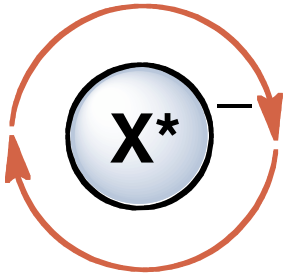


Chiral Counterions in Asymmetric Transition Metal-Catalyzed Reactions

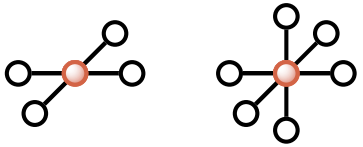
Stoltz / Reisman Group Meeting

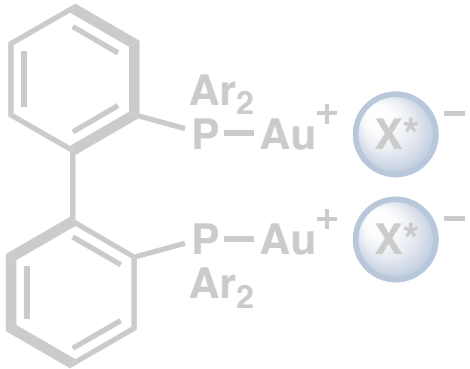


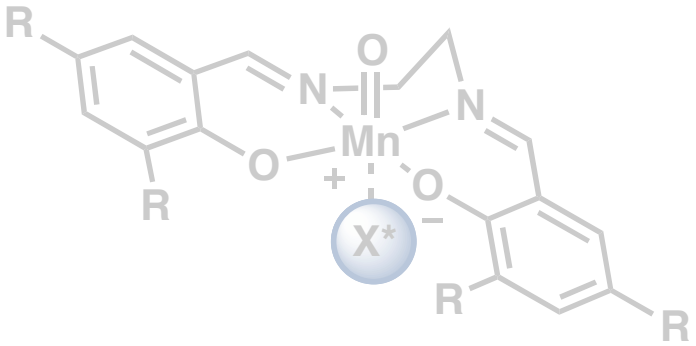
Allen Hong
Stoltz Group

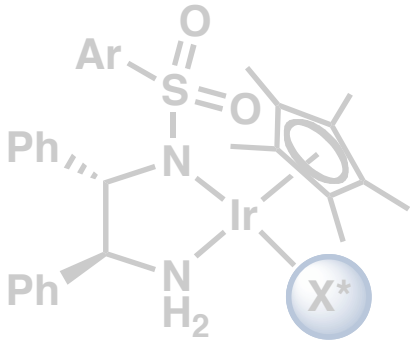


March 21, 2011
147 Noyes
8:00 pm





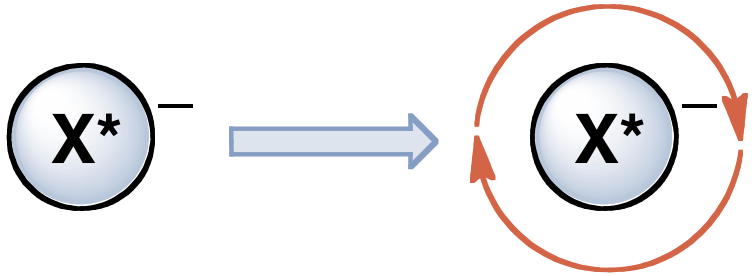




Chiral Counterions in Asymmetric Transition Metal-Catalyzed Reactions

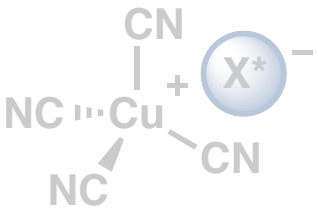
chiral cations and anions have a long history in chemistry...

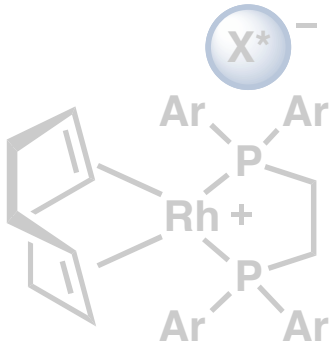
- *classical resolution*
- *phase-transfer catalysis*

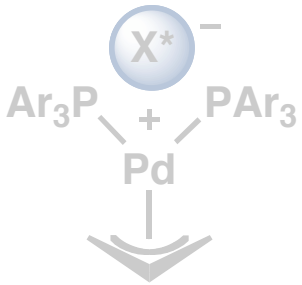


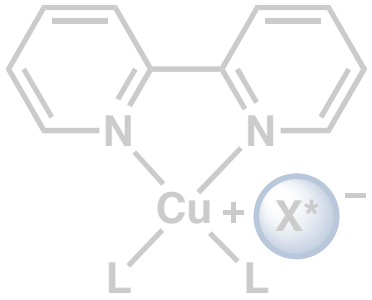
... but successful application of chiral anions to asymmetric catalysis is relatively recent

- *organocatalysis*
- *transition metal catalysis*





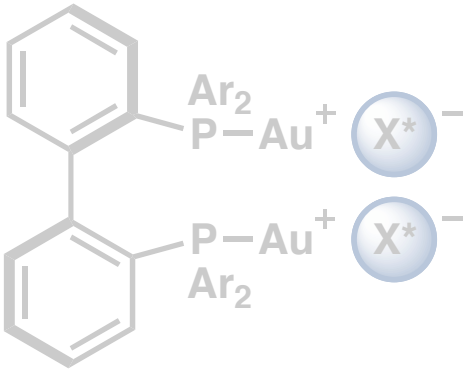


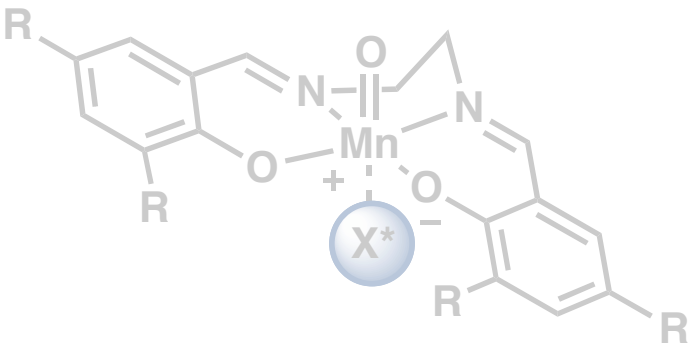


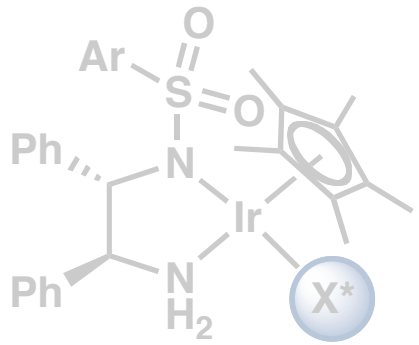
- ***Background and Concepts***
  Brief History and Asymmetric Ion Pairing Considerations

- ***Enantioselective Transition Metal Catalyzed Reactions***
  Asymmetric Induction by Chiral Counterions

- ***Cooperative Catalysis***
  Chiral Brønsted Acids and Chiral Counterions

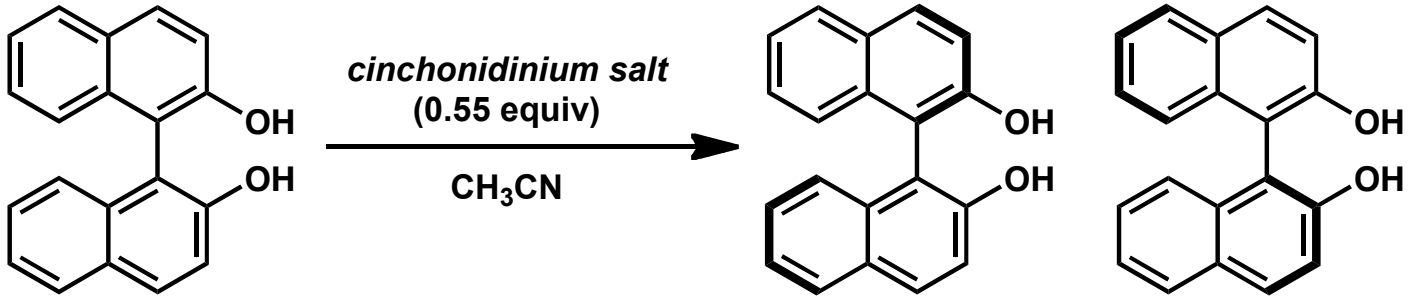






Classical Resolution and Chiral Auxiliaries

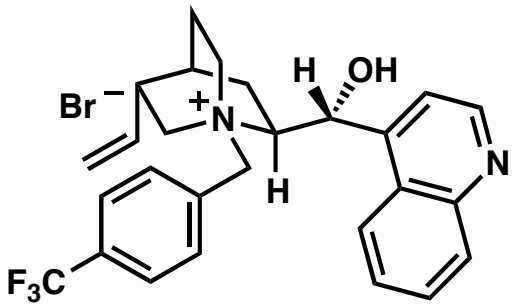
Chiral Ammonium Salt Resolution of rac-BINOL



rac

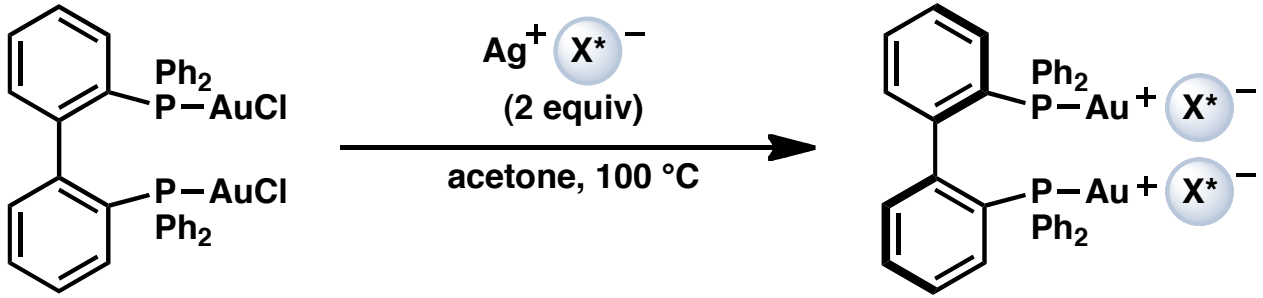
89-93% recovery
99.0% ee

85-88% recovery
99.8% ee



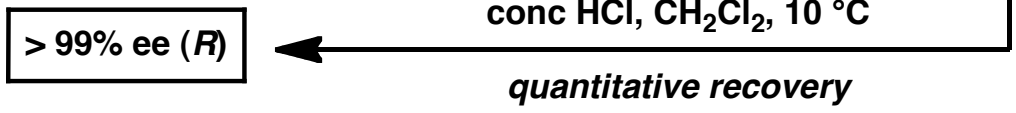
cinchonidium salt

Diastereoconvergent Ion Pairing and Recovery of Enantioenriched Metal Complexes



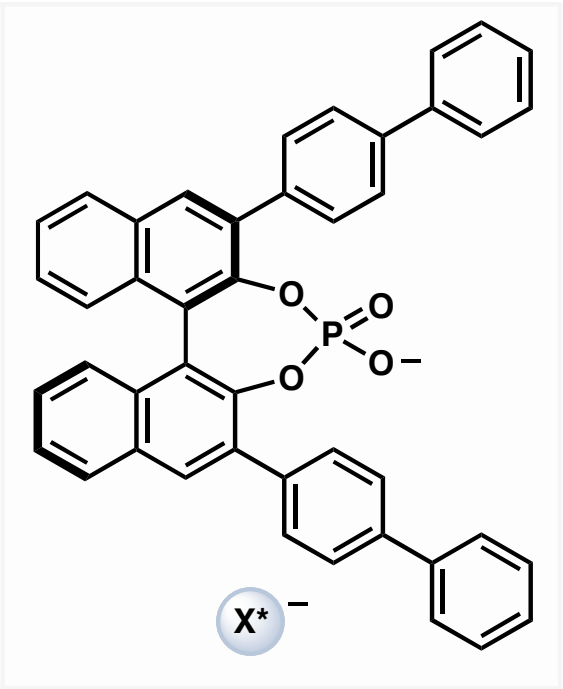
rac

100 : 0 dr



quantitative recovery

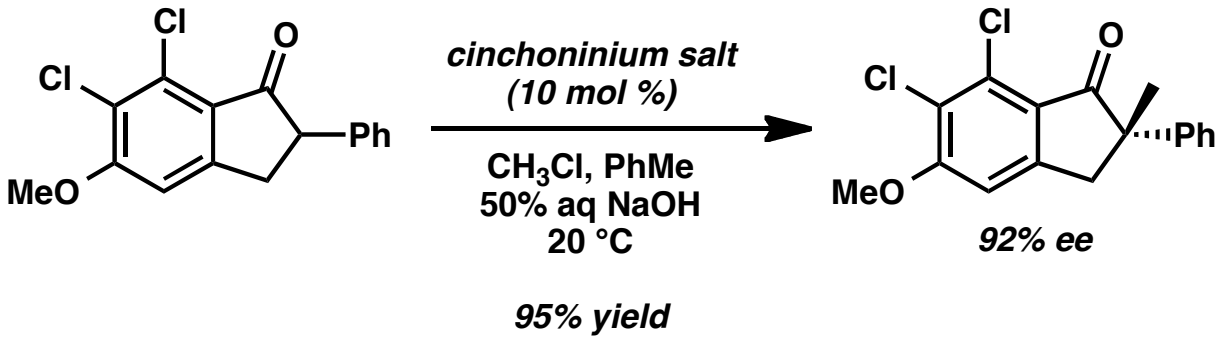
isomerization activation energy
$\Delta G^{\ddagger}$ = 26.2 kcal•mol^{-1} (in DCE)

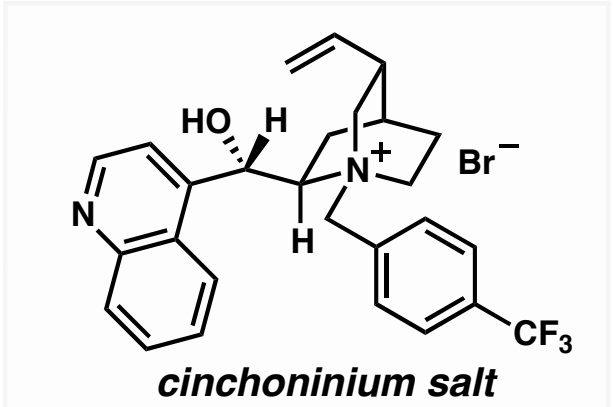


Reider, *Org. Synth.* **2004**, *10*, 93–95.
Mikami, *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.

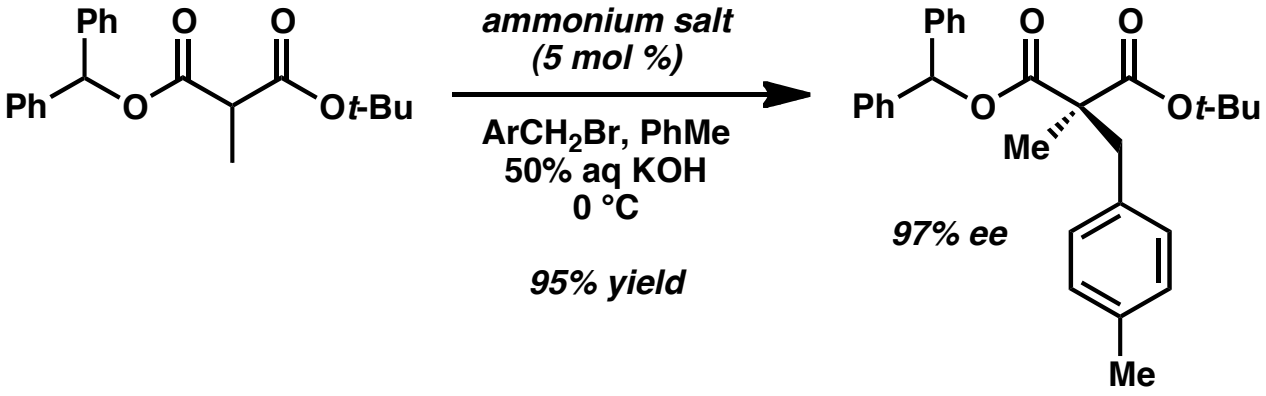
Chiral Cations in Phase Transfer Catalysis

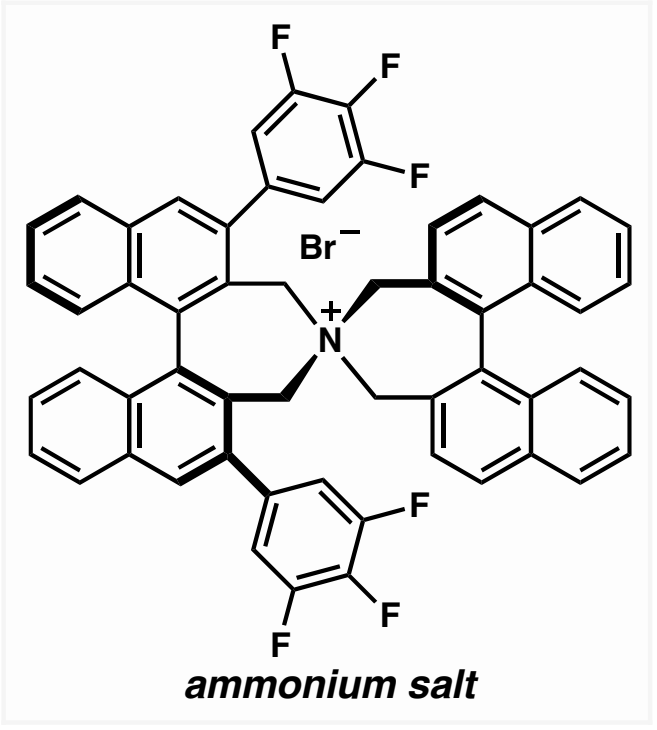
Asymmetric Enolate Alkylation





Asymmetric Malonate Diester Benzylation

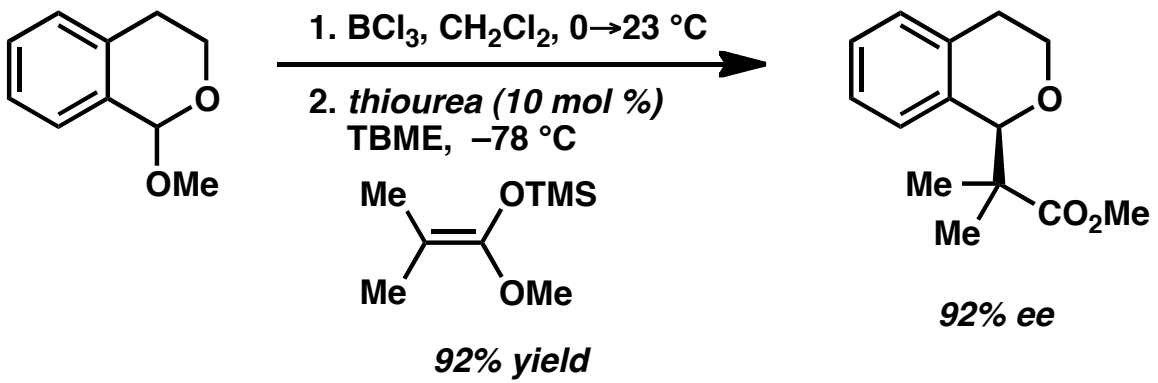


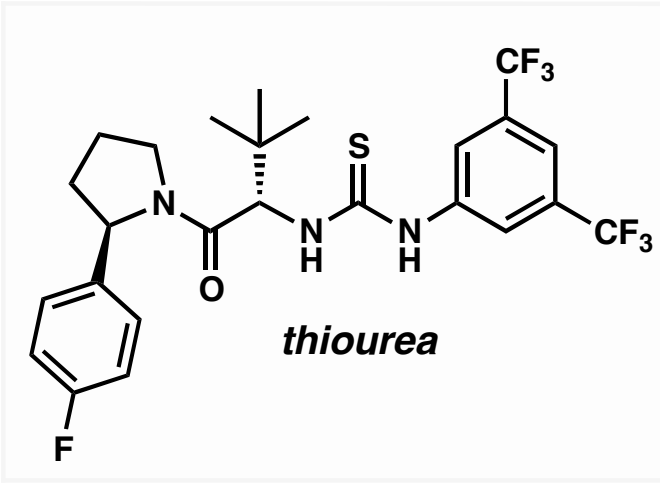


Dolling, *J. Am. Chem. Soc.* **1984**, *106*, 446–447.
Park, *J. Am. Chem. Soc.* **2011**, *ASAP*, doi: ja110349a

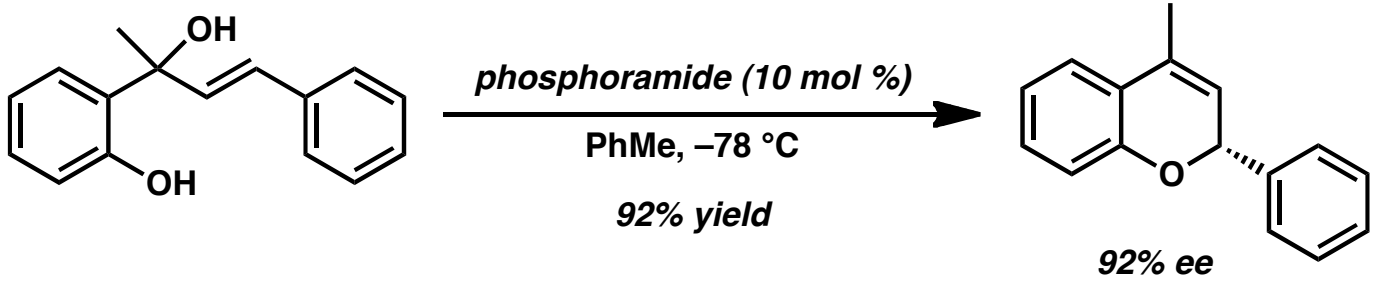
Chiral Anionic Complexes / Anions in Organocatalysis

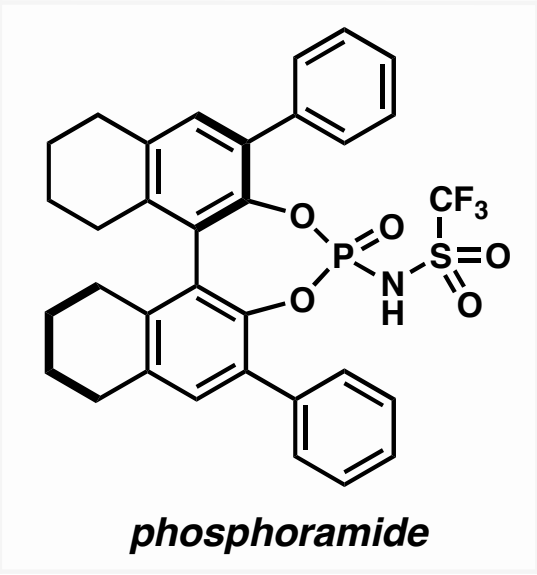
H-Bond Donor / Anion-Binding Catalysis





Brønsted Acid Catalysis

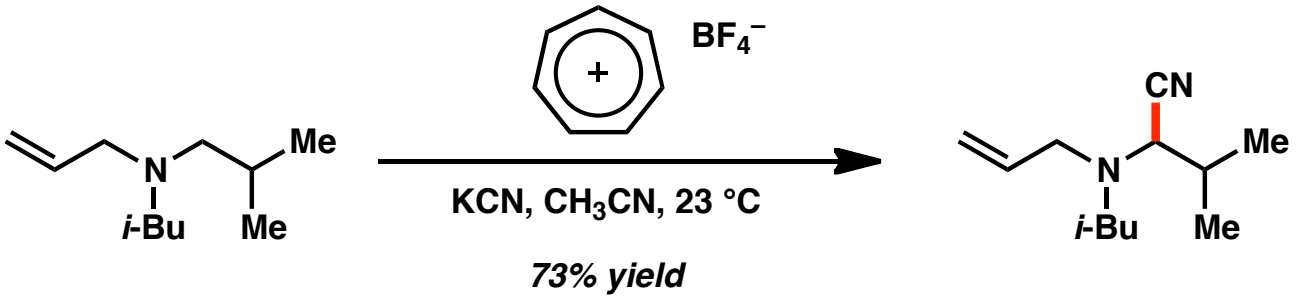


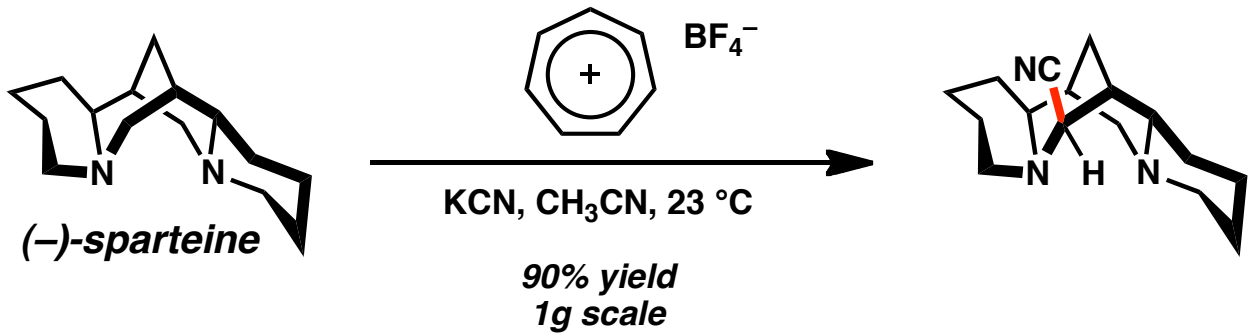


Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.
Rueping, *J. Am. Chem. Soc.* **2011**, *ASAP*, doi: ja110213t

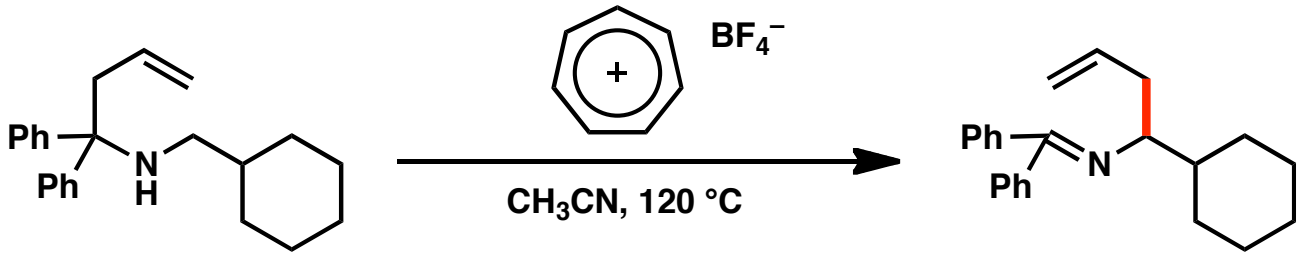
Aromatic Ion Pair Mediated Transformations

α-Cyanation of Amines

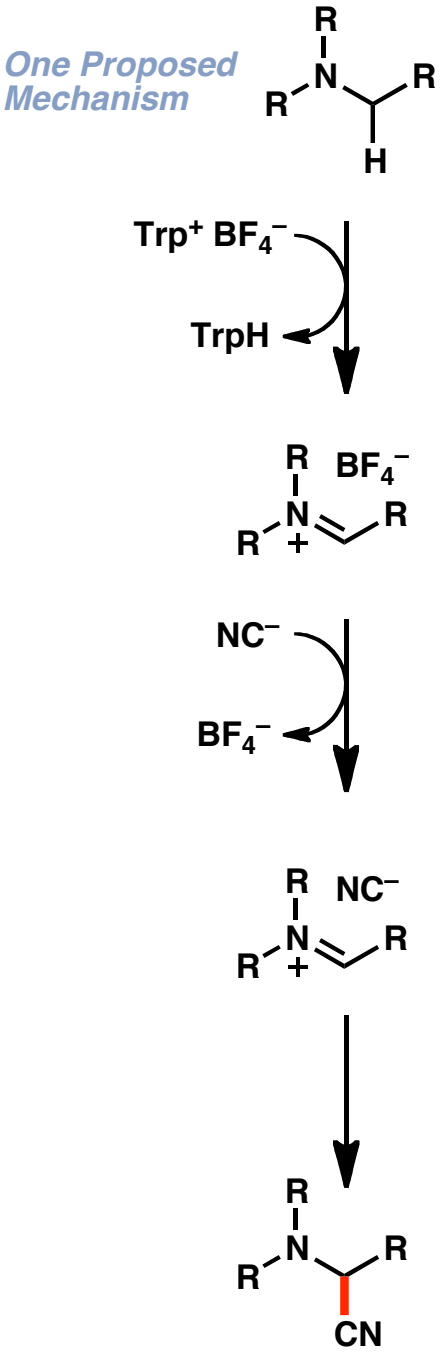




Oxidative Aza-Cope Rearrangement



One Proposed Mechanism



Lambert, *J. Am. Chem. Soc.* **2011**, *133,* 1260–1262.

Chiral Counterions in Asymmetric Transition Metal-Catalyzed Reactions

chiral cations and anions have a long history in chemistry...

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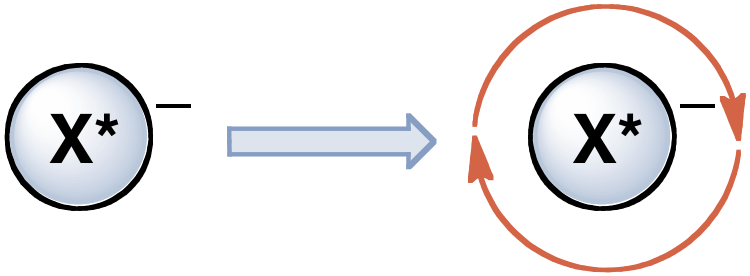


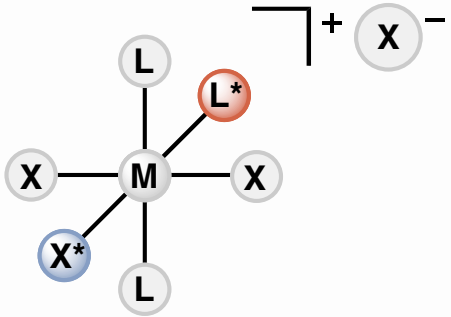
... but successful application of chiral anions to asymmetric catalysis is relatively recent

- *organocatalysis*
- *transition metal catalysis*

Approaches to Developing Catalytic Asymmetric Reactions

Conventional Approach:

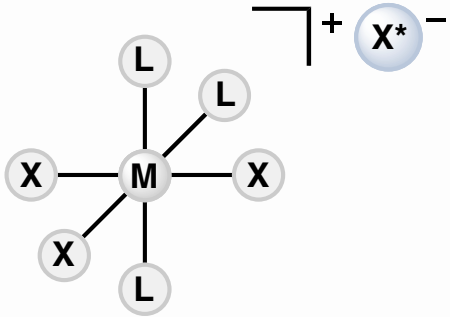
- *Chiral X-Type, L-Type Ligands bound to M*
- *Achiral Noncoordinating Counterion*



steric information within coordination sphere

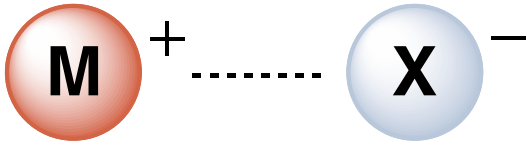
Alternative Approach:

- *Achiral X-Type, L-Type Ligands bound to M*
- *Chiral Noncoordinating Counterion*



steric information outside coordination sphere

Coulomb's Law and Ion Pairing in Solution



$$E = \frac{q_1 q_2}{4\pi\varepsilon\varepsilon_0 r}$$

q_1 = charge of M^+

q_2 = charge of X^-

r = distance between M^+ and X^-

ε = dielectric constant

ε_0 = vacuum permittivity constant

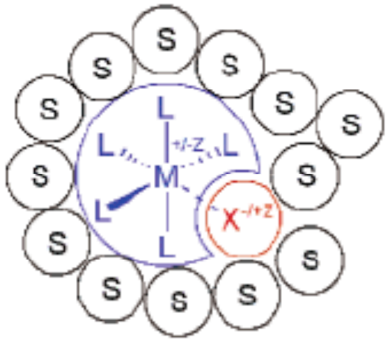
ion pair: a cation-anion pair that are close enough in space such that the energy associated with their electrostatic attraction is larger than the thermal energy available to separate them

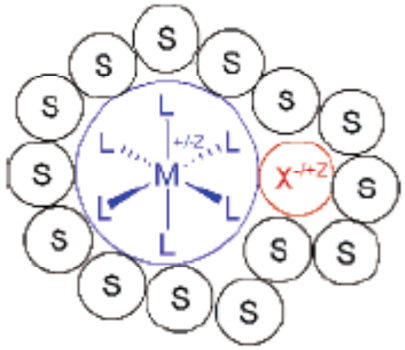
factors affecting ion pairing in solution ⇒

- solvent
- size and shape of ions
- temperature

Anslyn and Dougherty, *Modern Physical Organic Chemistry*, University Science Books: Sausalito, California, 2006.

Inner Sphere Ion Pairs and Outer Sphere Ion Pairs





Inner Sphere Ion Pair (ISIP)
(X-Type Ligands)

within M coordination sphere

dative or non-dative bonds to M

orbital interactions with M

steric effects

electronic effects

...

Outer Sphere Ion Pair (OSIP)
(Noncoordinating Anions)

outside M coordination sphere

no dative or non-dative bonds to M

no orbital interactions with M

steric effects

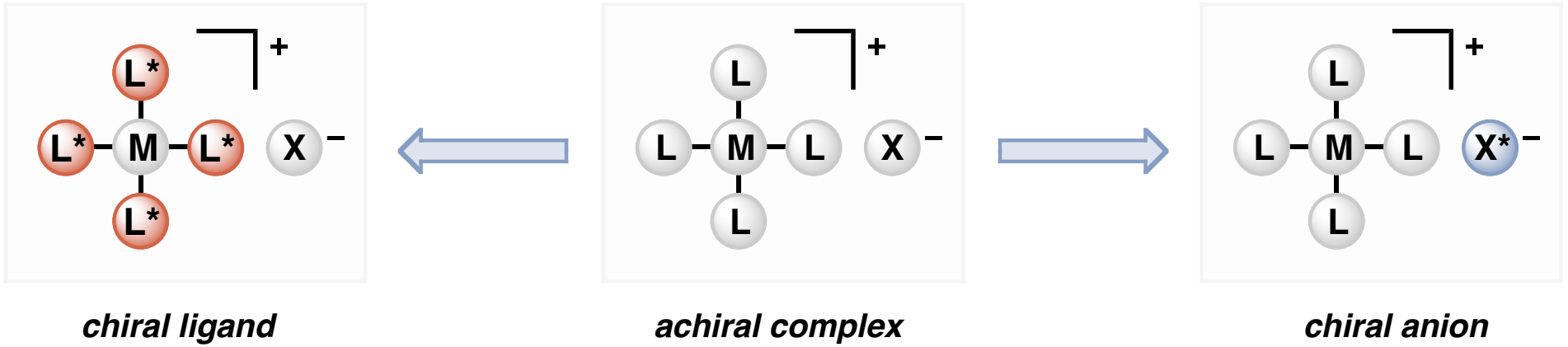
no electronic effects

sometimes difficult to distinguish!

some anions can be both in the same catalyst system!

Macchioni, *Chem. Rev.* **2005,** *105,* 2039-2073.

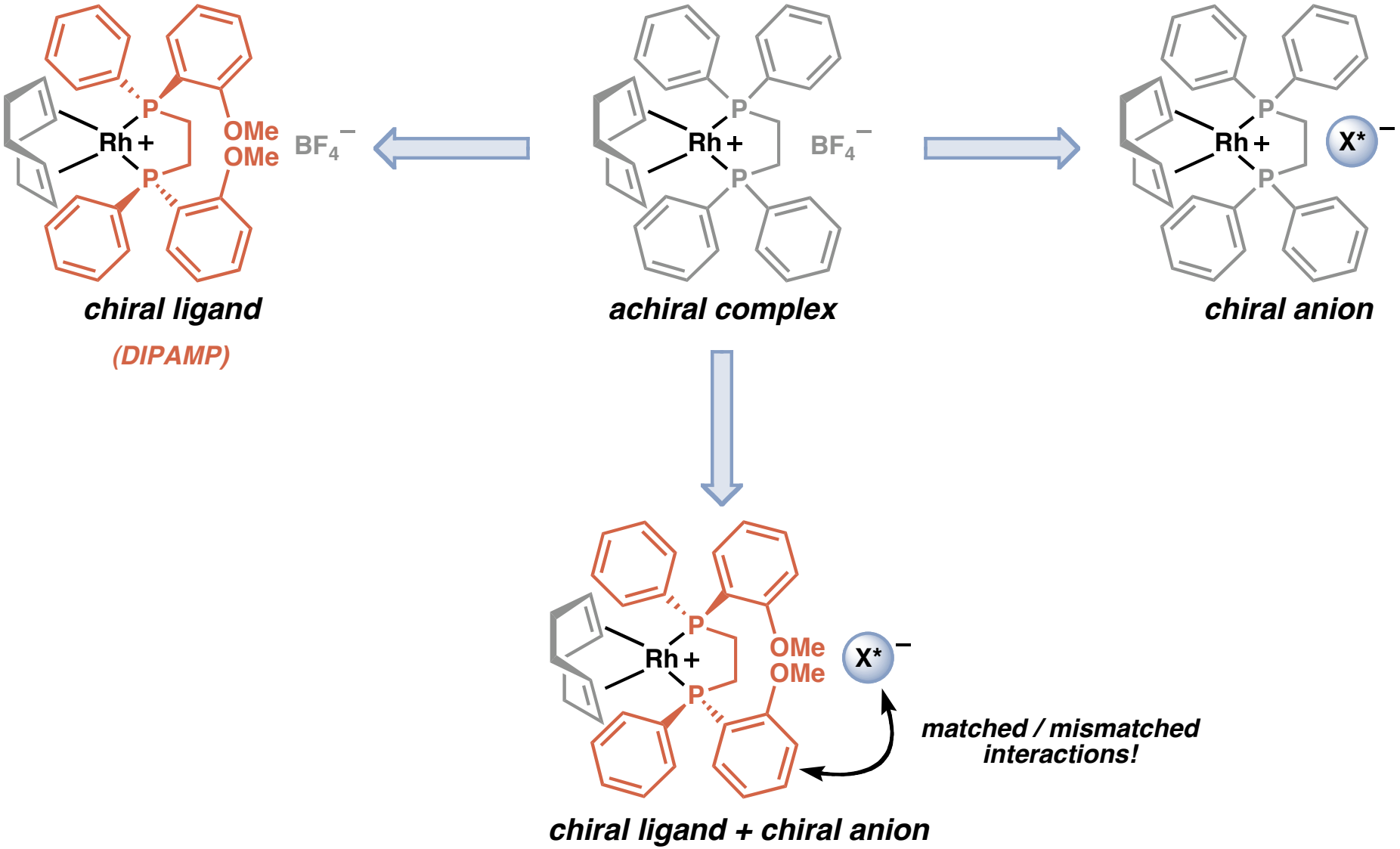
Chiral Ligands and Chiral Counterions



chiral ligand ***achiral complex*** ***chiral anion***

chiral ligand + chiral anion

Chiral Ligands and Chiral Counterions



chiral ligand

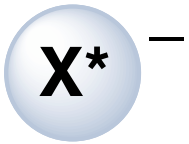
(DIPAMP)

achiral complex

chiral anion

chiral ligand + chiral anion

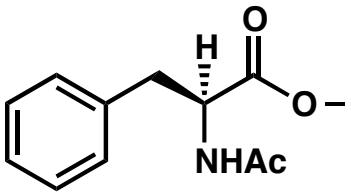
Chiral Counterions for Transition Metals



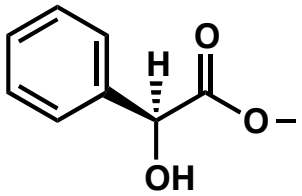
coordinating → ***noncoordinating***

Common Achiral Anions

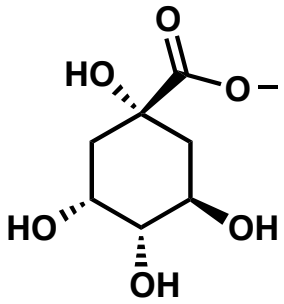
Cl^- Br^- I^-	AcO^- TfO^-	BF_4^-	PF_6^- SbF_6^-
no chiral analogs	***chiral pool carboxylates and sulfonates***	***tetrahedral center***	***octahedral center***



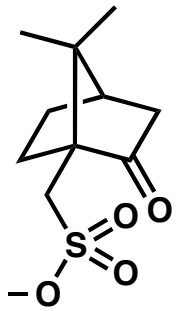
amino acids



mandelic acid



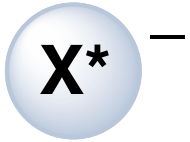
quinic acid

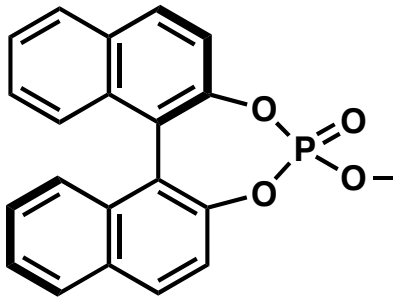


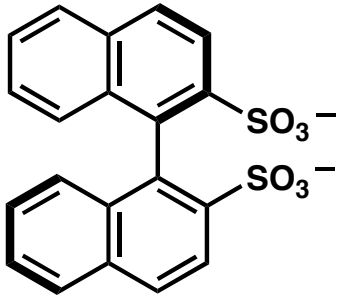
camphorsulfonic acid

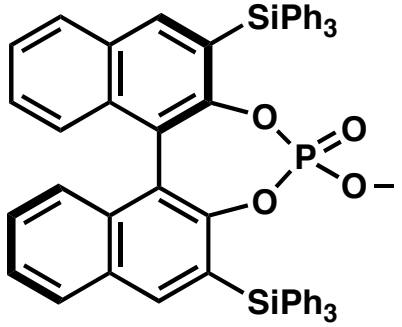
Lacour, *Chem. Commun.* **2009**, 7073–7089.
Lacour, *Chem. Soc. Rev.* **2003**, *32,* 373–382.

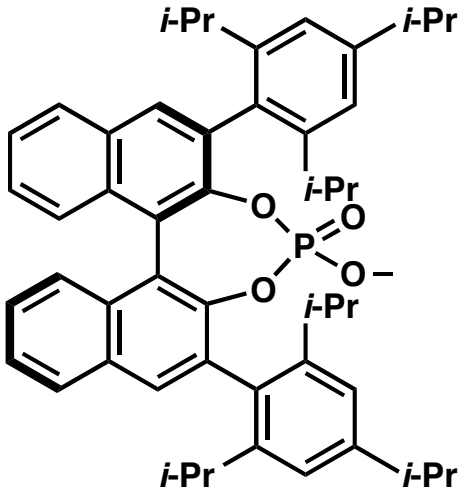
Chiral Counterions for Transition Metals

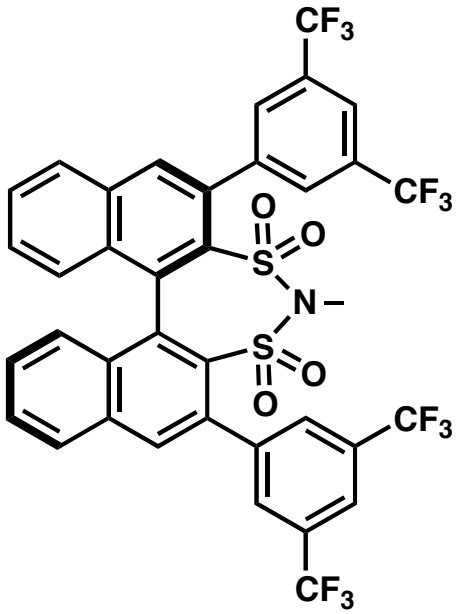


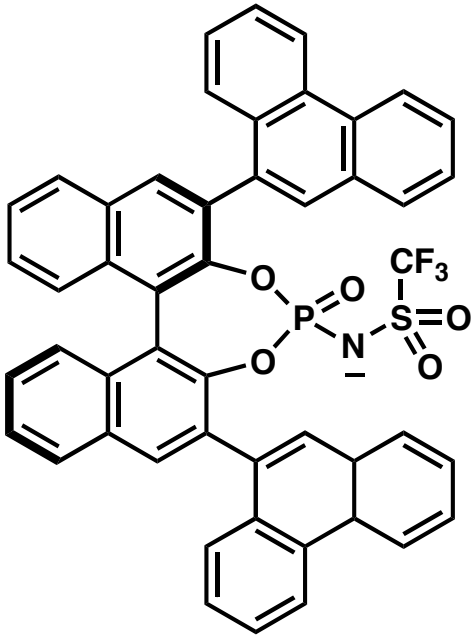












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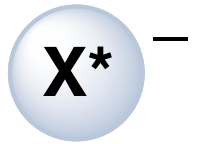
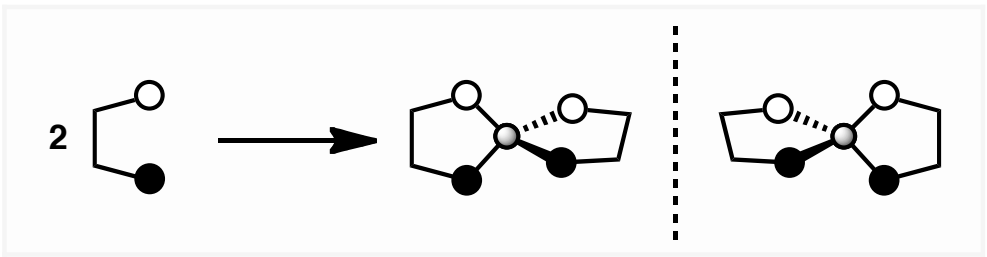
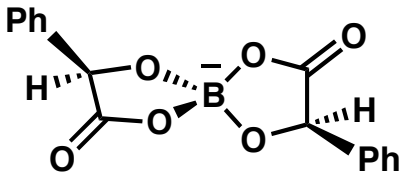
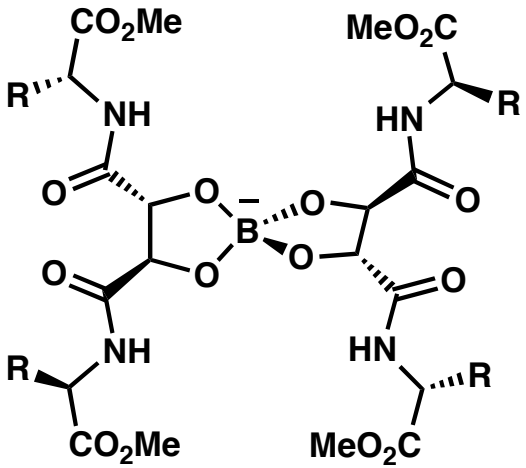
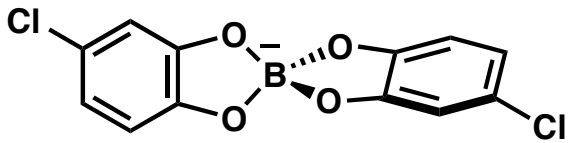
Chiral Counterions for Transition Metals

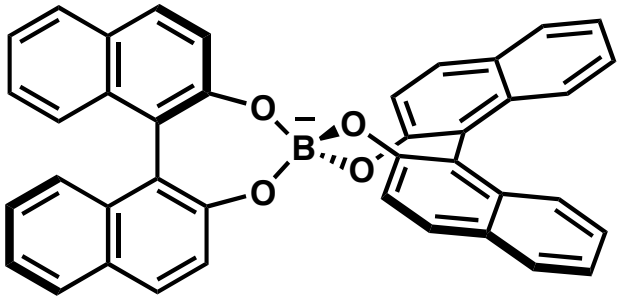


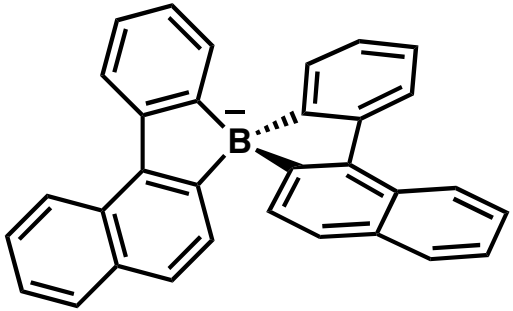


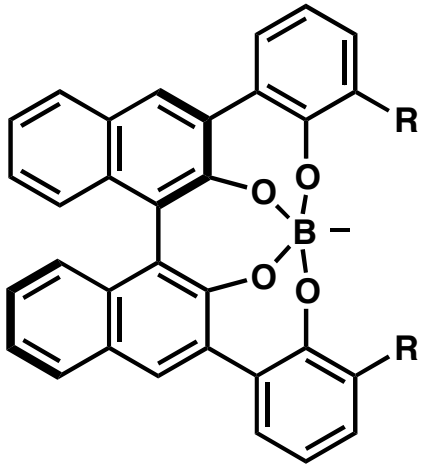












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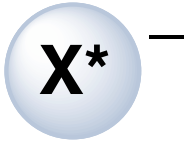
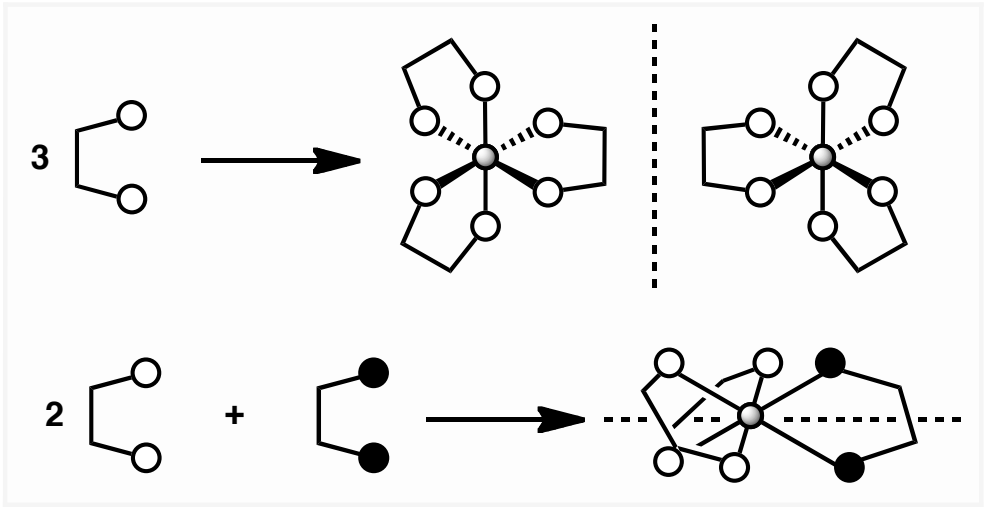
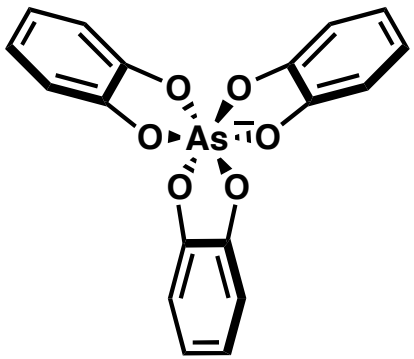
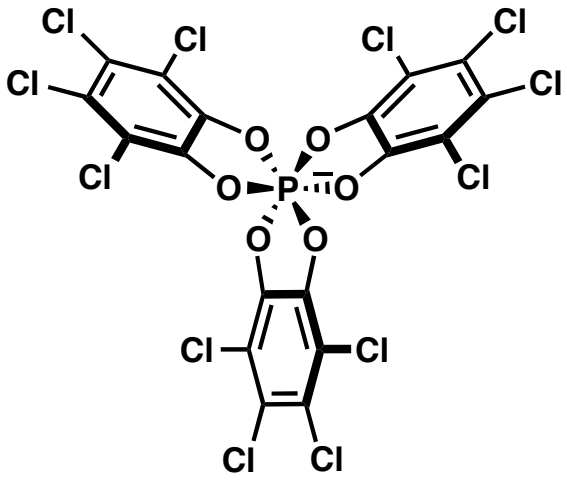
Chiral Counterions for Transition Metals

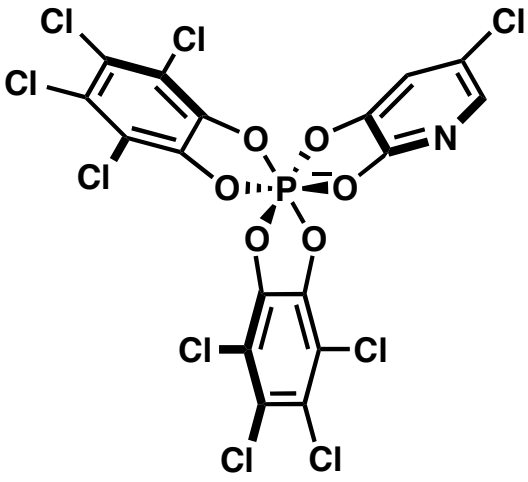








TRISPHAT



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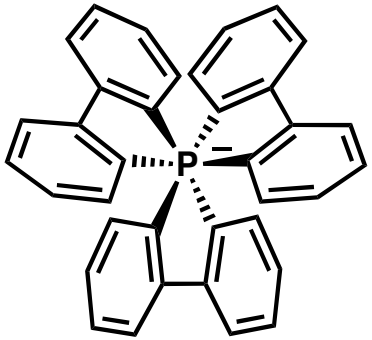

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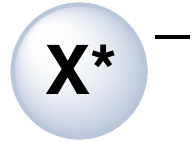
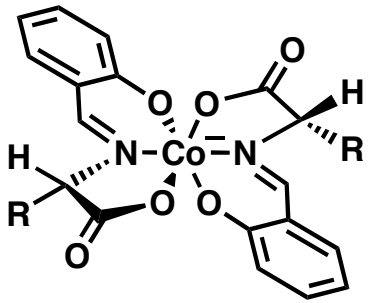
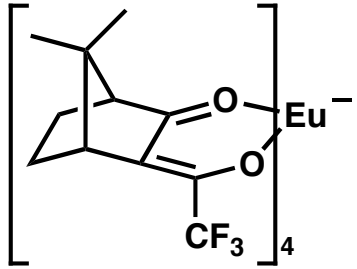
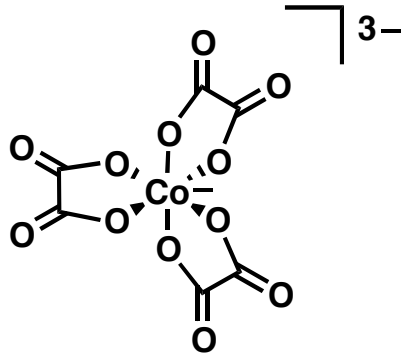
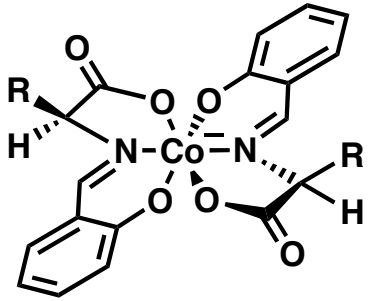
Chiral Counterions for Transition Metals

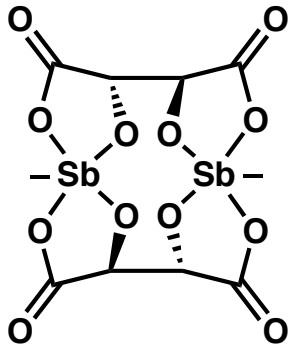


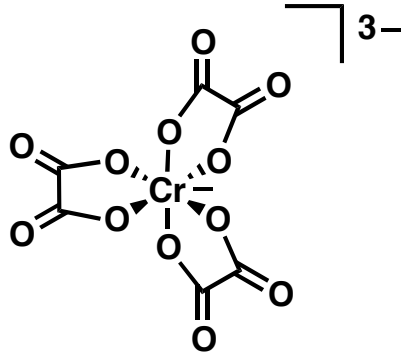












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The Pfeiffer Effect and Asymmetric Ion Pairing

Pfeiffer Effect: The perturbation of a racemic mixture composed of equilibrating enantiomers by the addition of an external chiral species

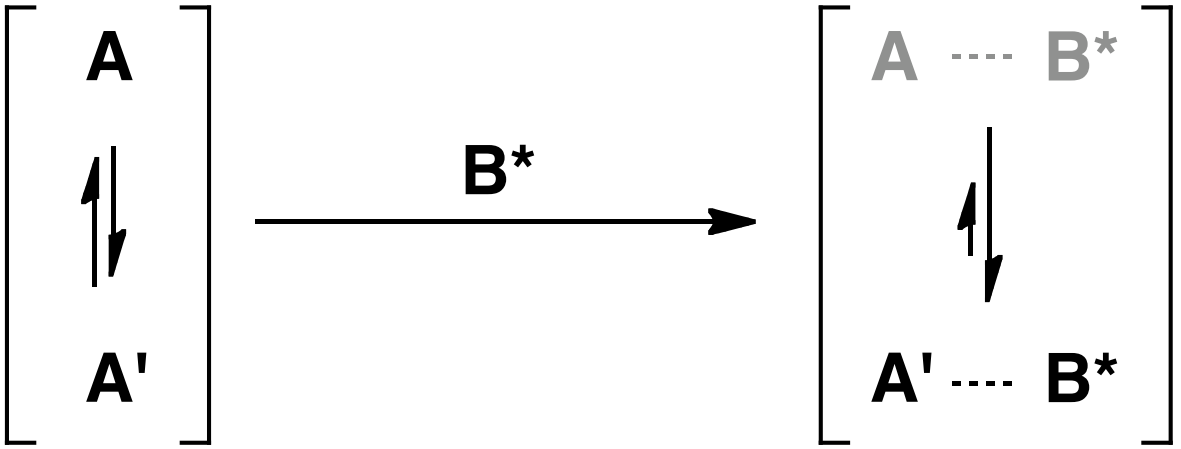
If A and A' are enantiomers...

$$\mathbf{A = \sigma(A')}$$

and both interact with an external chiral species B*

A ---- B*

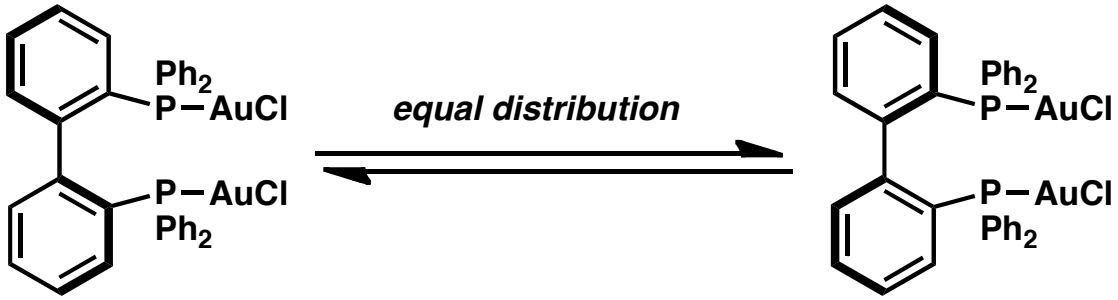
A' ---- B*



equal ratio in forms A and A'

unequal ratio of forms A and A'

Biasing of Enantiomorphic Conformations of BIPHEP Ligands



Pfeiffer, *Chem. Ber.* **1931**, *64*, 2667–2671.

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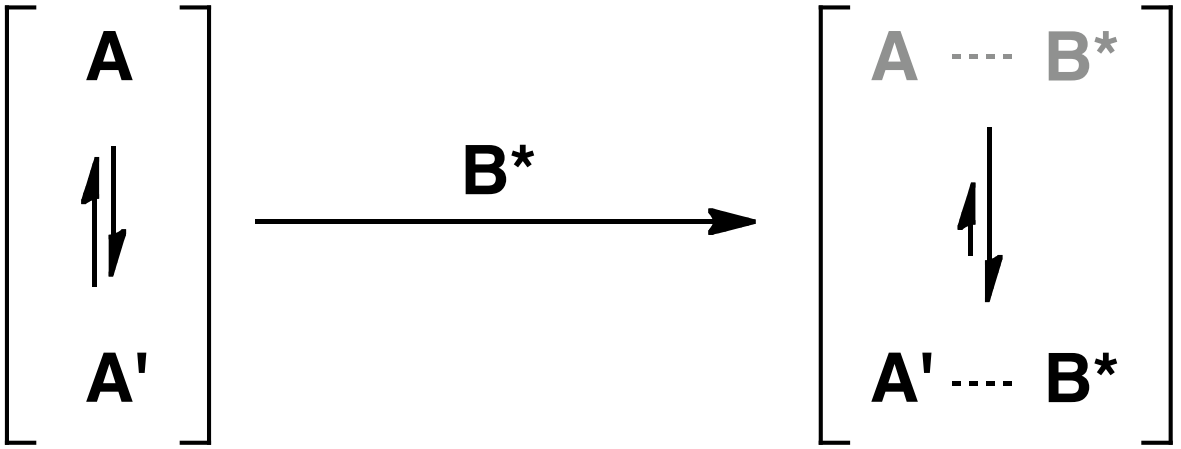

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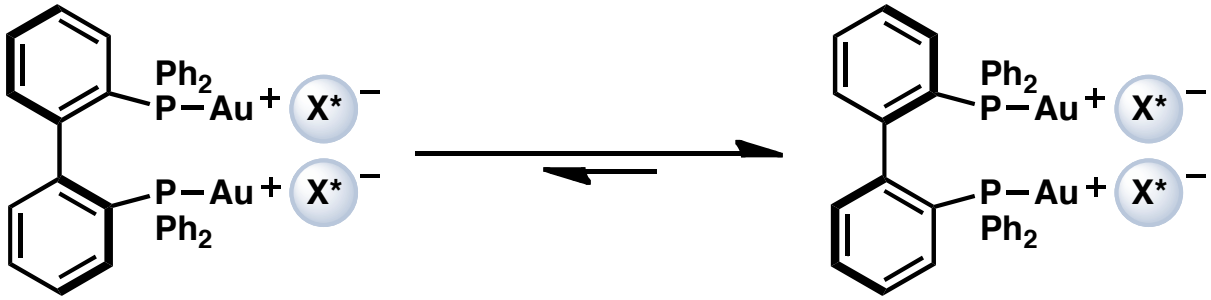
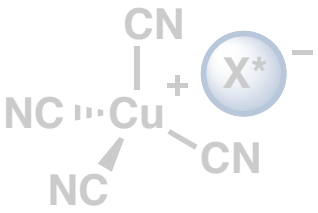
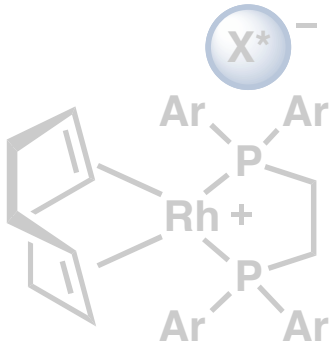


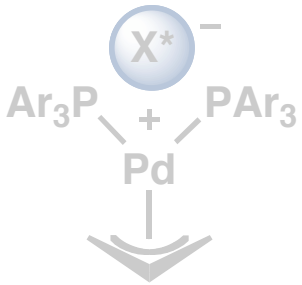
not observed

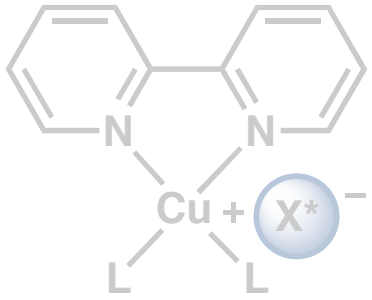
single diastereomer

Pfeiffer, *Chem. Ber.* **1931**, *64*, 2667–2671.





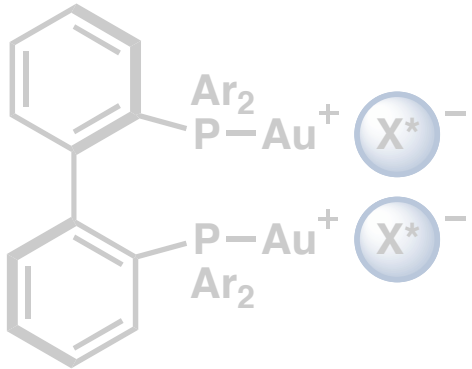


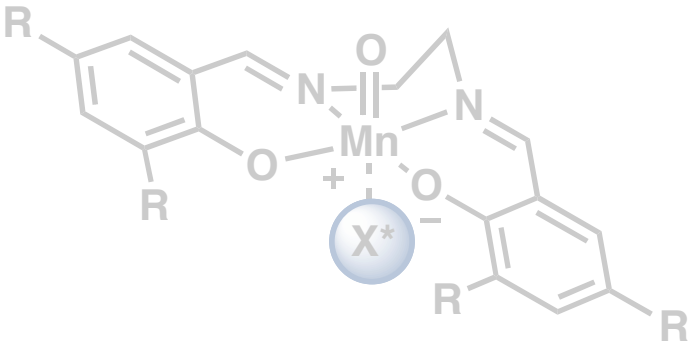


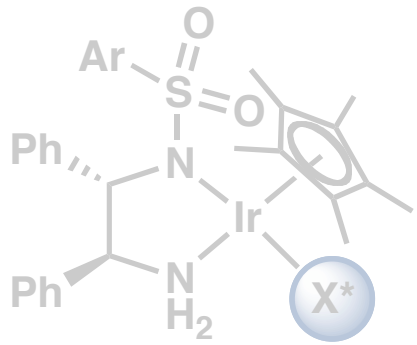
- ***Background and Concepts***
  Brief History and Asymmetric Ion Pairing Considerations

- ***Enantioselective Transition Metal Catalyzed Reactions***
  Asymmetric Induction by Chiral Counterions

- ***Cooperative Catalysis***
  Chiral Brønsted Acids and Chiral Counterions

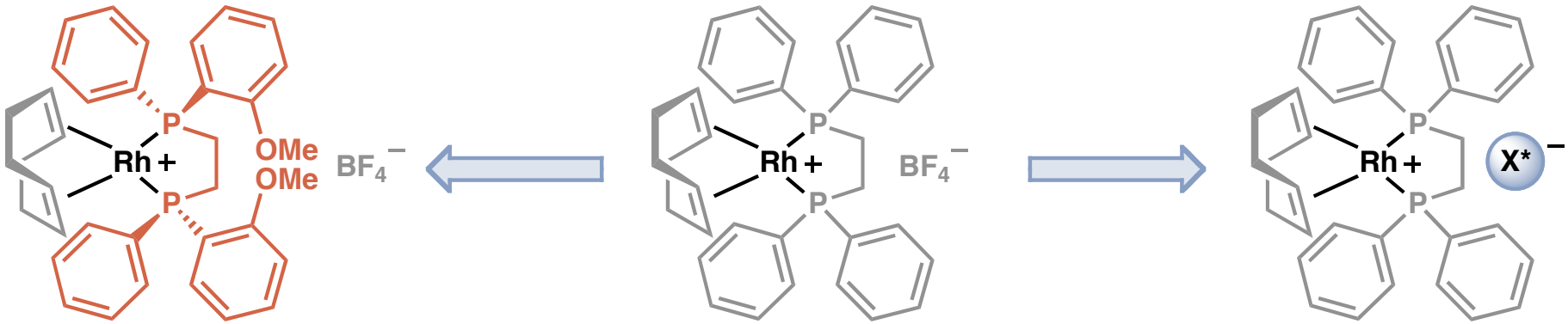






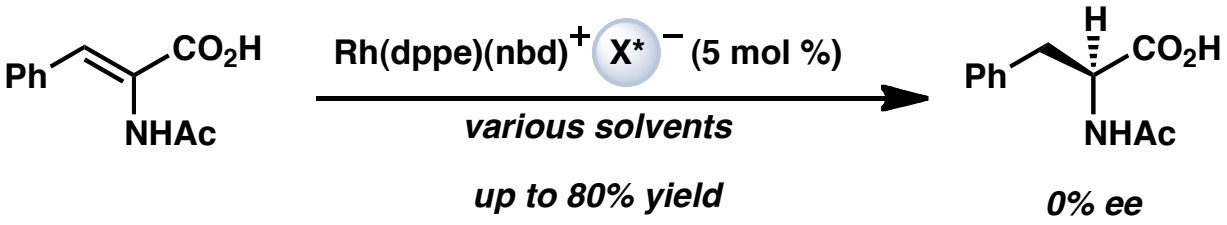
Rh-Catalyzed Olefin Hydrogenation

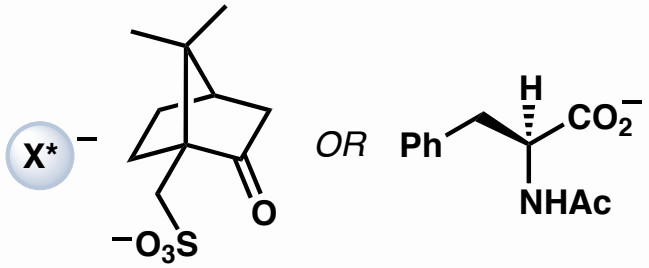
Reaction Design

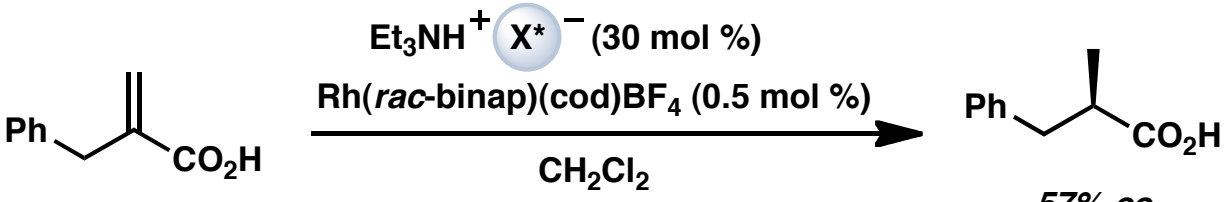


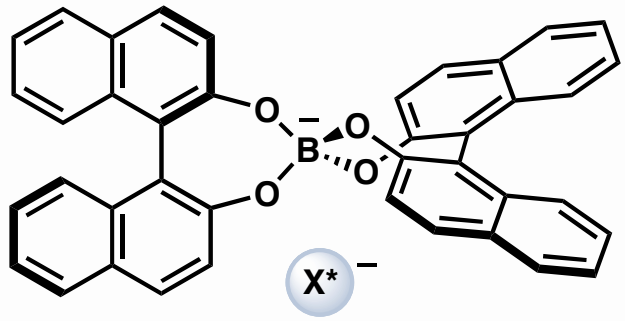
chiral ligand ***achiral complex*** ***chiral anion***

Olefin Hydrogenation





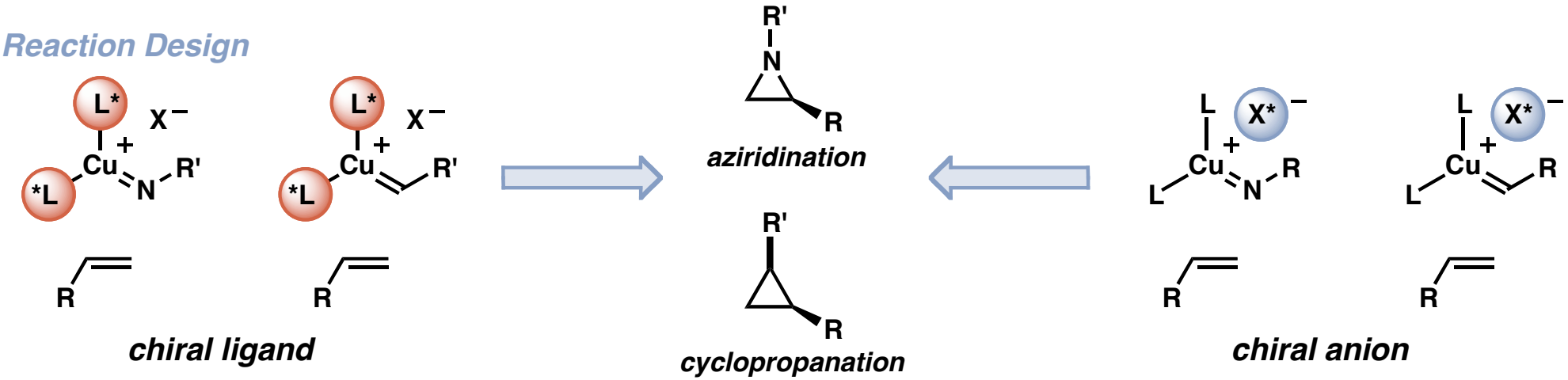




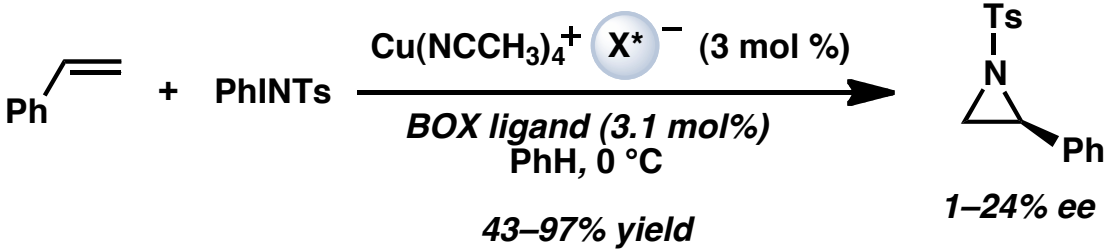
Dorta, Milstein, *J. Organomet. Chem.* **2004**, *689*, 751–758.
Leitner, *ChemCatChem* **2010**, *2*, 55–57.

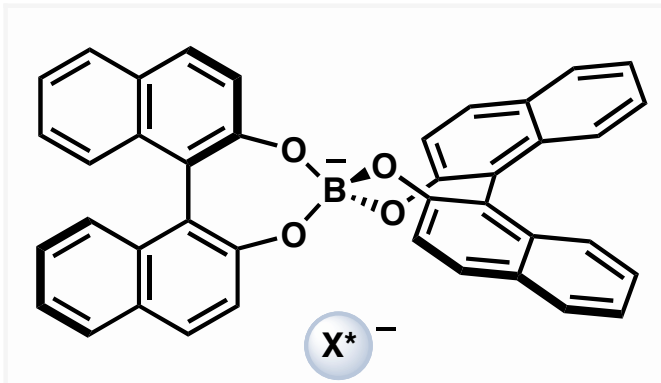
Cu-Catalyzed Aziridination and Cyclopropanantion

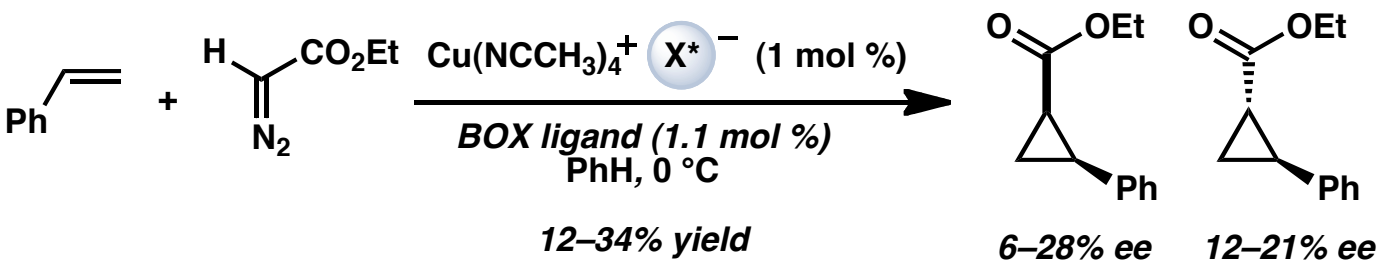
Reaction Design

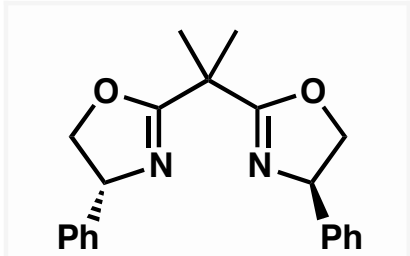


Cu(I)-Catalyzed Aziridination and Cyclopropanation





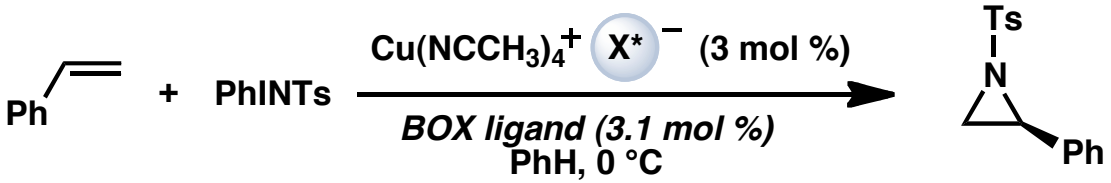




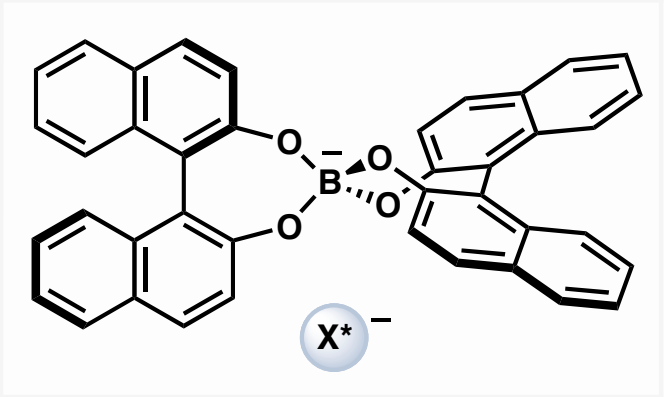
Arndtsen, *Org. Lett.* **2000,** *2,* 4165–4168.

Cu-Catalyzed Aziridination and Cyclopropanantion

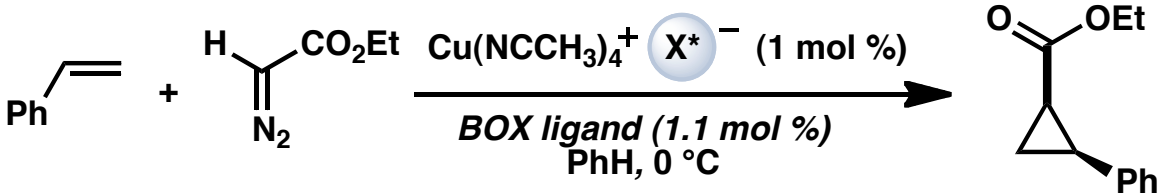
Ligand-Anion Steric Matched/Mismatched Effects



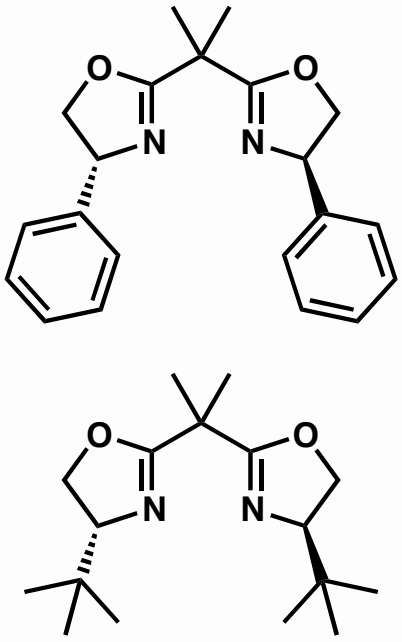
	(*R*)-PhBOX + (*S*)-X* −	*22% ee (S)*
chiral ligand has dominant effect	(*R*)-PhBOX + (*R*)-X* −	*24% ee (S)*
	(*S*)-*t*-BuBOX + (*S*)-X* −	*13% ee (R)*
	(*S*)-*t*-BuBOX + (*R*)-X* −	*12% ee (R)*



Matched/Mismatched and Temperature Effects



chiral anion shows more of an effect	(*R*)–PhBOX + (*S*)-X* −	0 °C	*6% ee (R)*
	(*R*)–PhBOX + (*R*)-X* −	0 °C	*28% ee (S)*
... but ion pairing lost at higher temp	(*S*)–PhBOX + (*S*)-X* −	25 °C	*6% ee (R)*
	(*S*)–PhBOX + (*R*)-X* −	25 °C	*8% ee (R)*

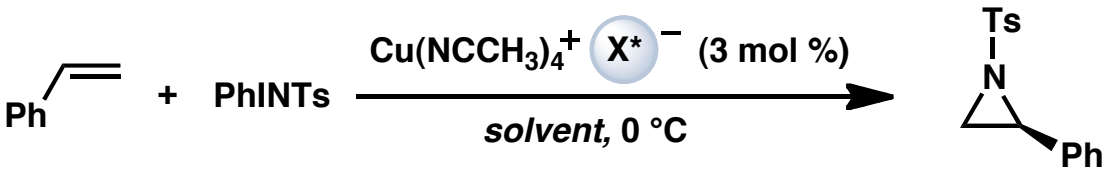


BOX ligands

Arndtsen, *Org. Lett.* **2000,** *2,* 4165–4168.

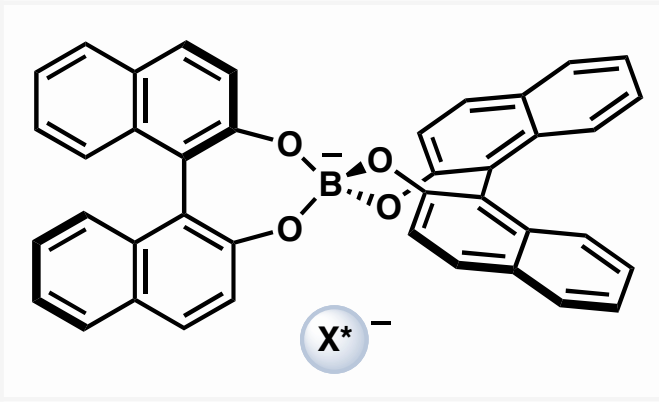
Cu-Catalyzed Aziridination and Cyclopropanantion

Solvent Effects

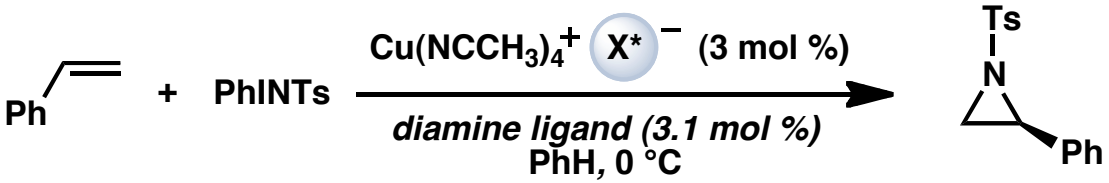


more polar solvents disrupt ion pairing

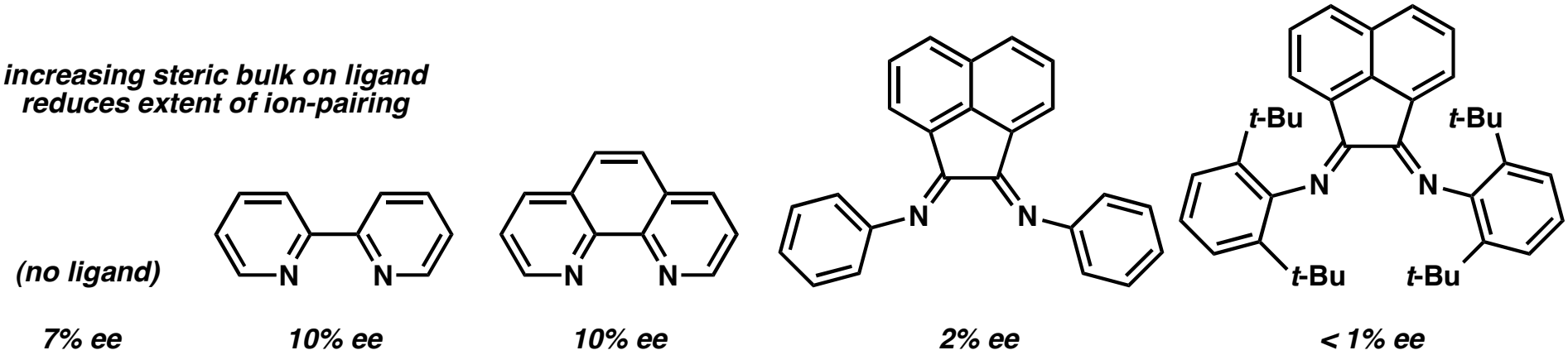
PhH	*7% ee*
CH_2Cl_2	*4% ee*
CH_3CN	*< 1% ee*



Ligand Substitution Effects



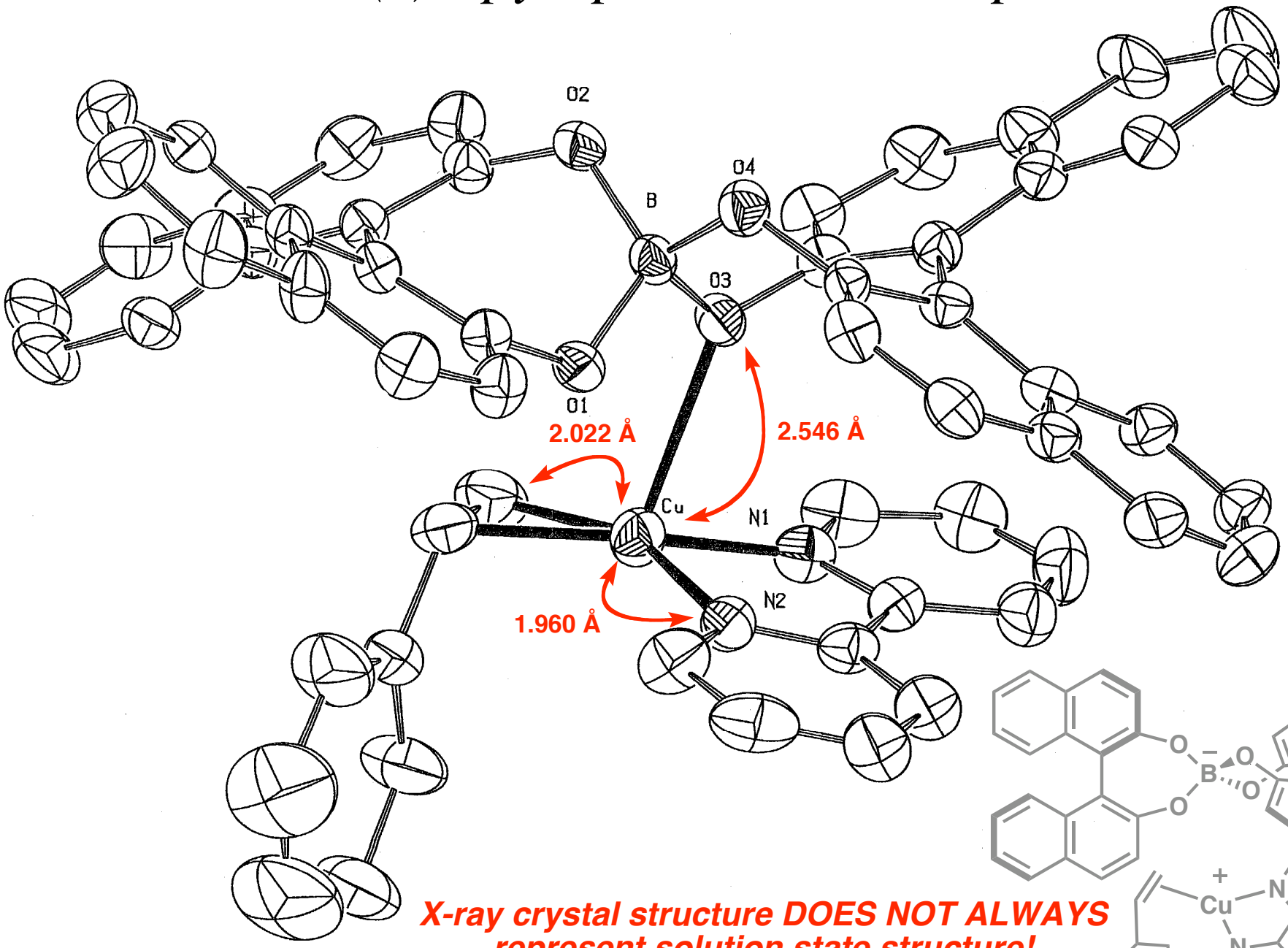
increasing steric bulk on ligand reduces extent of ion-pairing



7% ee	*10% ee*	*10% ee*	*2% ee*	*< 1% ee*

Arndtsen, *Org. Lett.* **2000,** *2,* 4165–4168.

Cu(I)-bpy-Spiroborate Complex

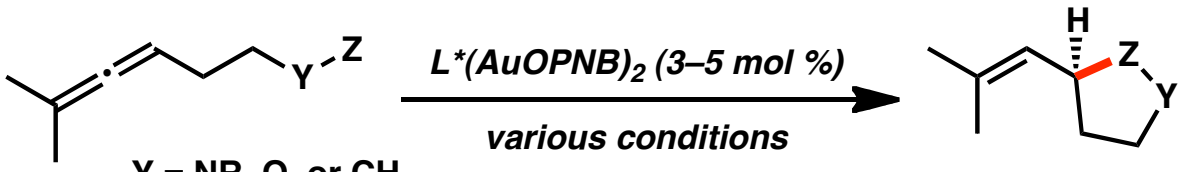


X-ray crystal structure DOES NOT ALWAYS represent solution state structure!

Arndtsen, *Org. Lett.* **2000**, *2*, 4165–4168.

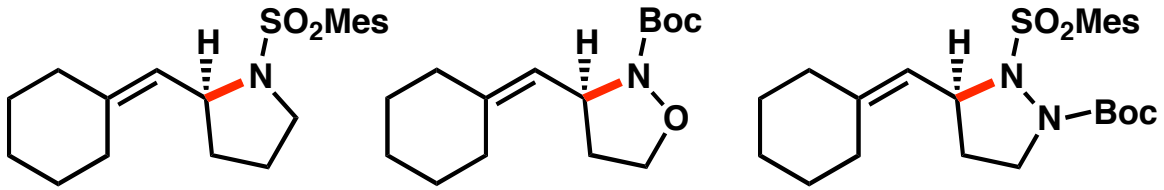
Au-Catalyzed Allene Heterocyclizations

Early Observations from Hydroaminations / Hydroalkoxylations

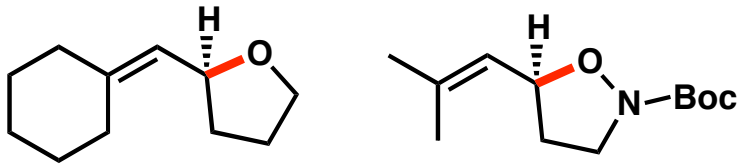


Y = NR, O, or CH_2
Z = NHR, OH

hydroaminations
70–99% ee

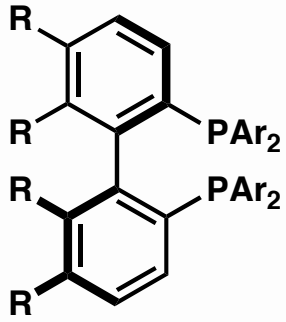


hydroalkoxylations
0–8% ee



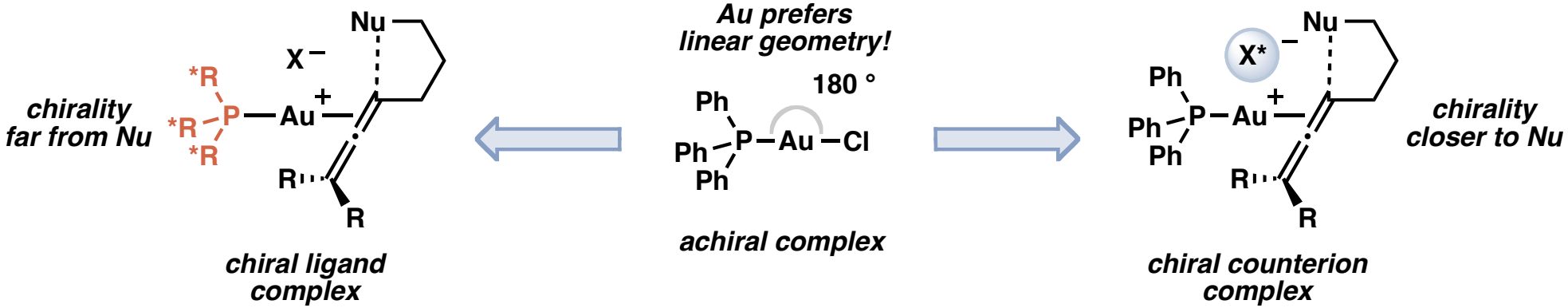
L* = atropisomeric bis-phosphines

BINAP, SEGPHOS
ClMeOBIPHEP



OPNB = *p*-$NO_2C_6H_4CO_2^-$

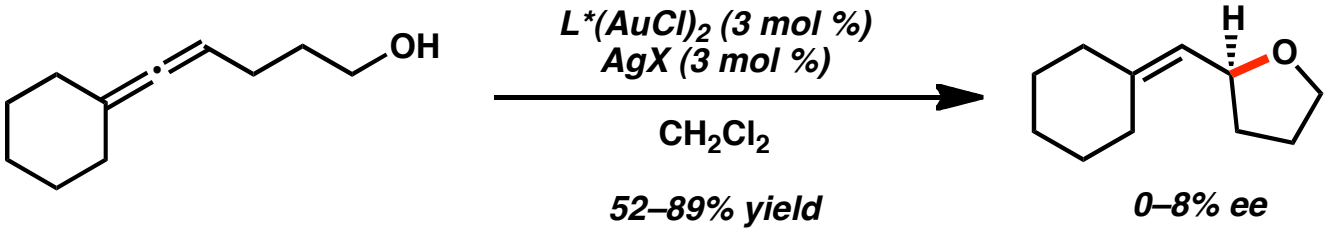
Reaction Design



Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452–2353.
Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601.

Au-Catalyzed Allene Heterocyclizations

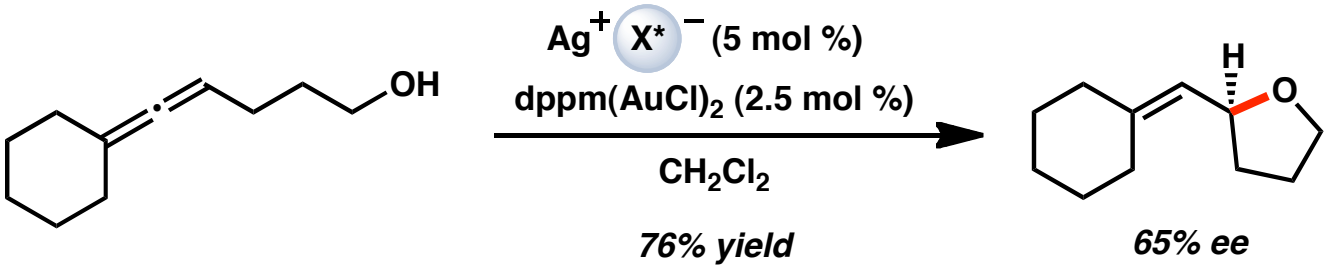
Comparing Hydroalkoxylation Reactions with Different Counterions

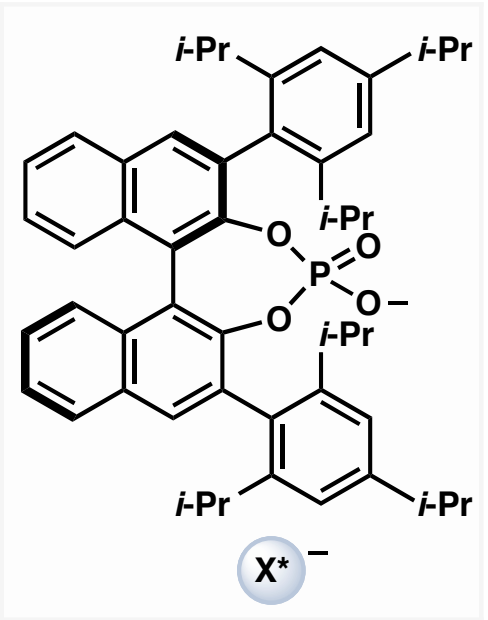


*L** = atropisomeric bis-phosphines

BINAP, SEGPHOS

X = BF_4^- or $PNBO^-$





increasing ε ↓

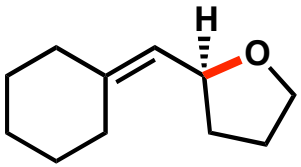
solvent	ε	yield (%)	ee (%)
PhH	2	90	97
THF	8	83	76
CH_2Cl_2	9	76	65
acetone	21	71	37
CH_3NO_2	36	60	18

polar solvents disrupt ion pairing

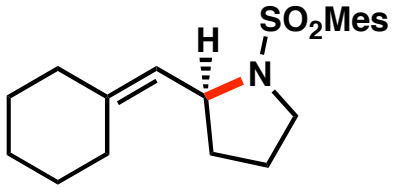
Toste, *Nature* **2007**, *317*, 496–499.

Au-Catalyzed Allene Heterocyclizations

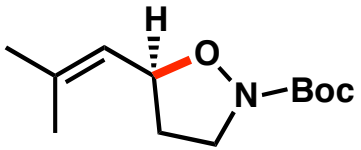
Extension Chiral Anion Conditions to other Heterocyclizations



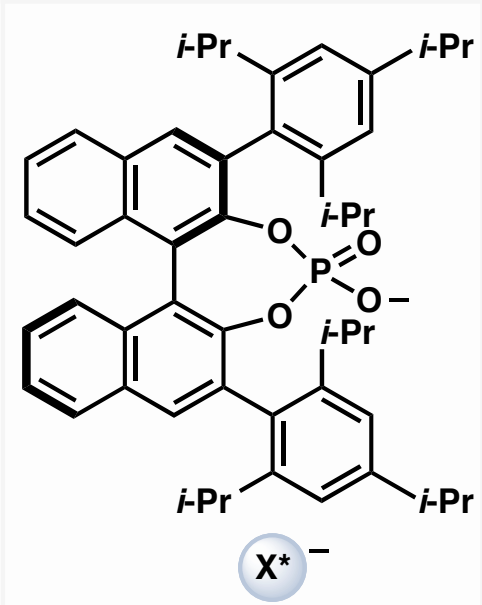
90% yield
97% ee



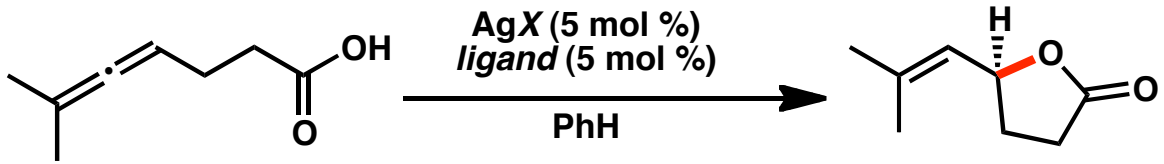
97% yield
97% ee



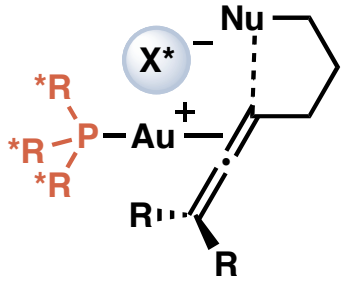
98% yield
98% ee



Synergistic Ligand-Counterion Effects



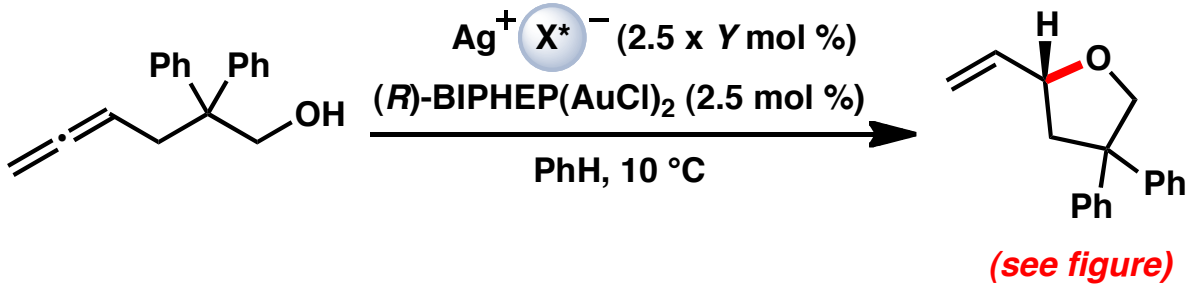
ligand	X	yield (%)	ee (%)
(*R*)-BINAP	*p*-$NO_2C_6H_3CO_2^-$	80	38
dppm	X*$^-$	89	12
(*R*)-BINAP	X*$^-$	91	3
(*S*)-BINAP	X*$^-$	88	82



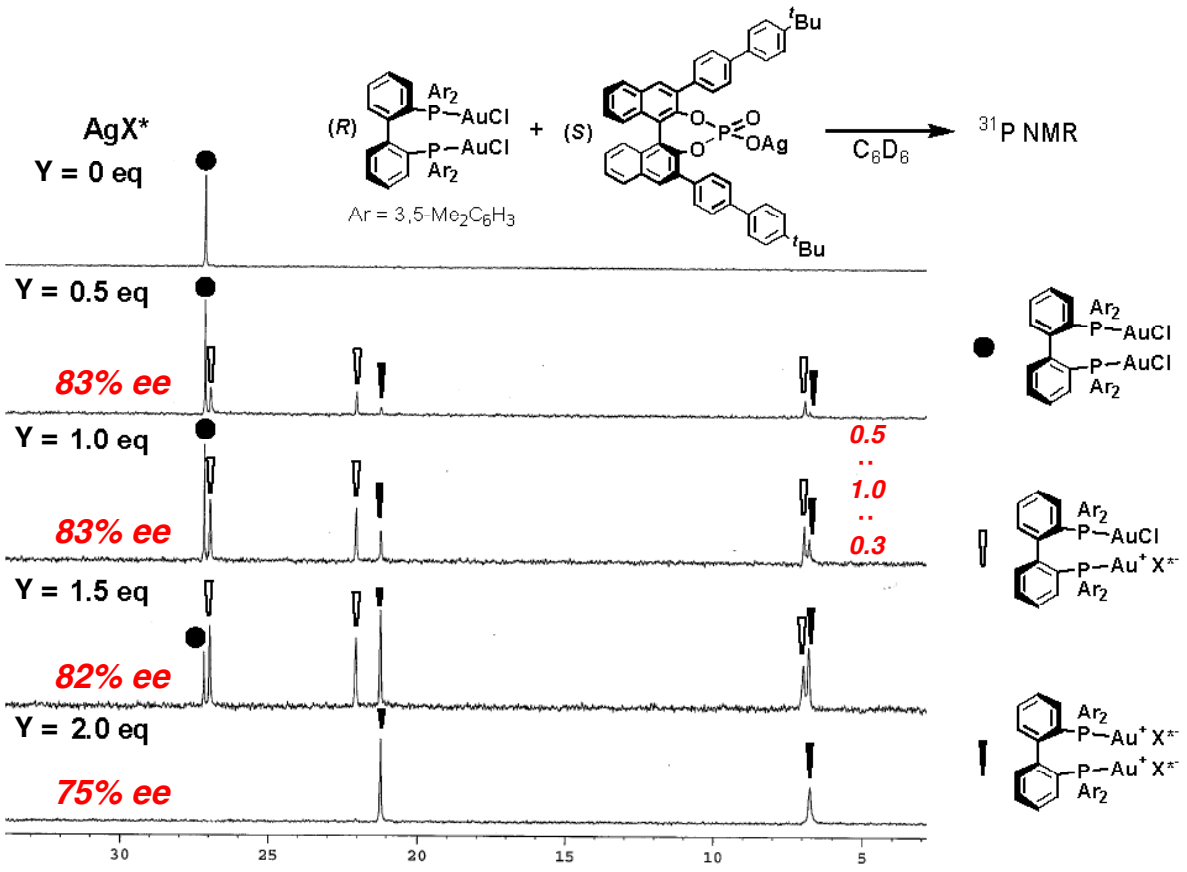
highest ee with matched chiral ligand and chiral anion

Toste, *Nature* **2007**, *317*, 496–499.
Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 598–601.

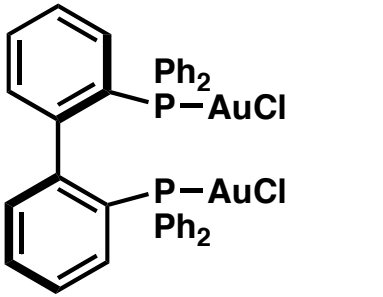
Titration of Dinuclear Au Complexes with AgX Salts*

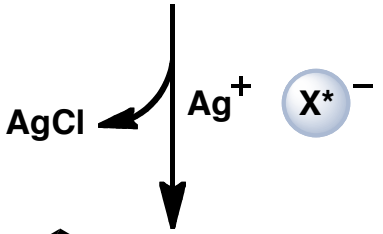


(see figure)

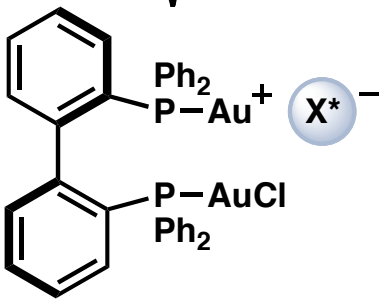


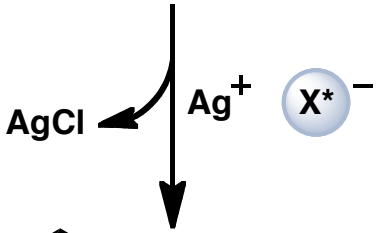
inert



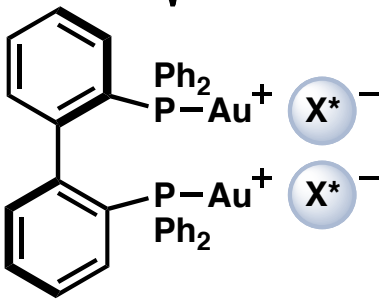


higher activity
higher selectivity



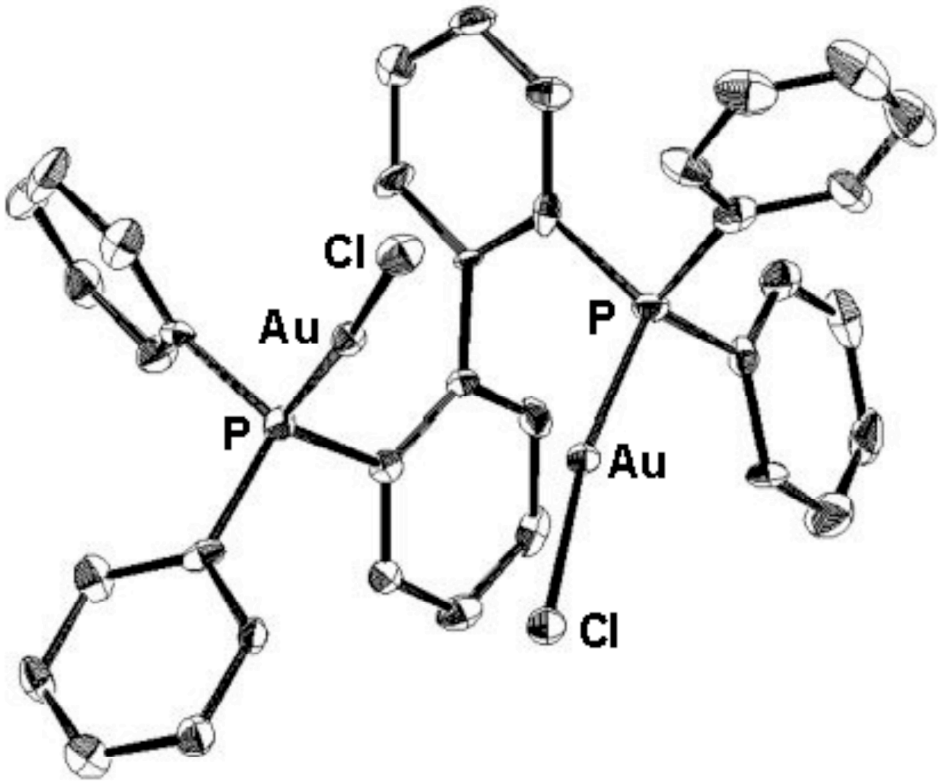


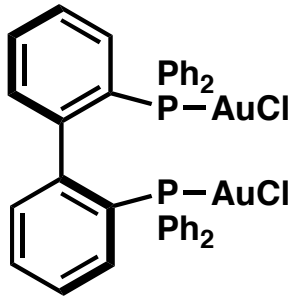
lower activity
lower selectivity



Aikawa, Mikami, *Adv. Synth. Catal.* **2010**, *352*, 3131–3135.

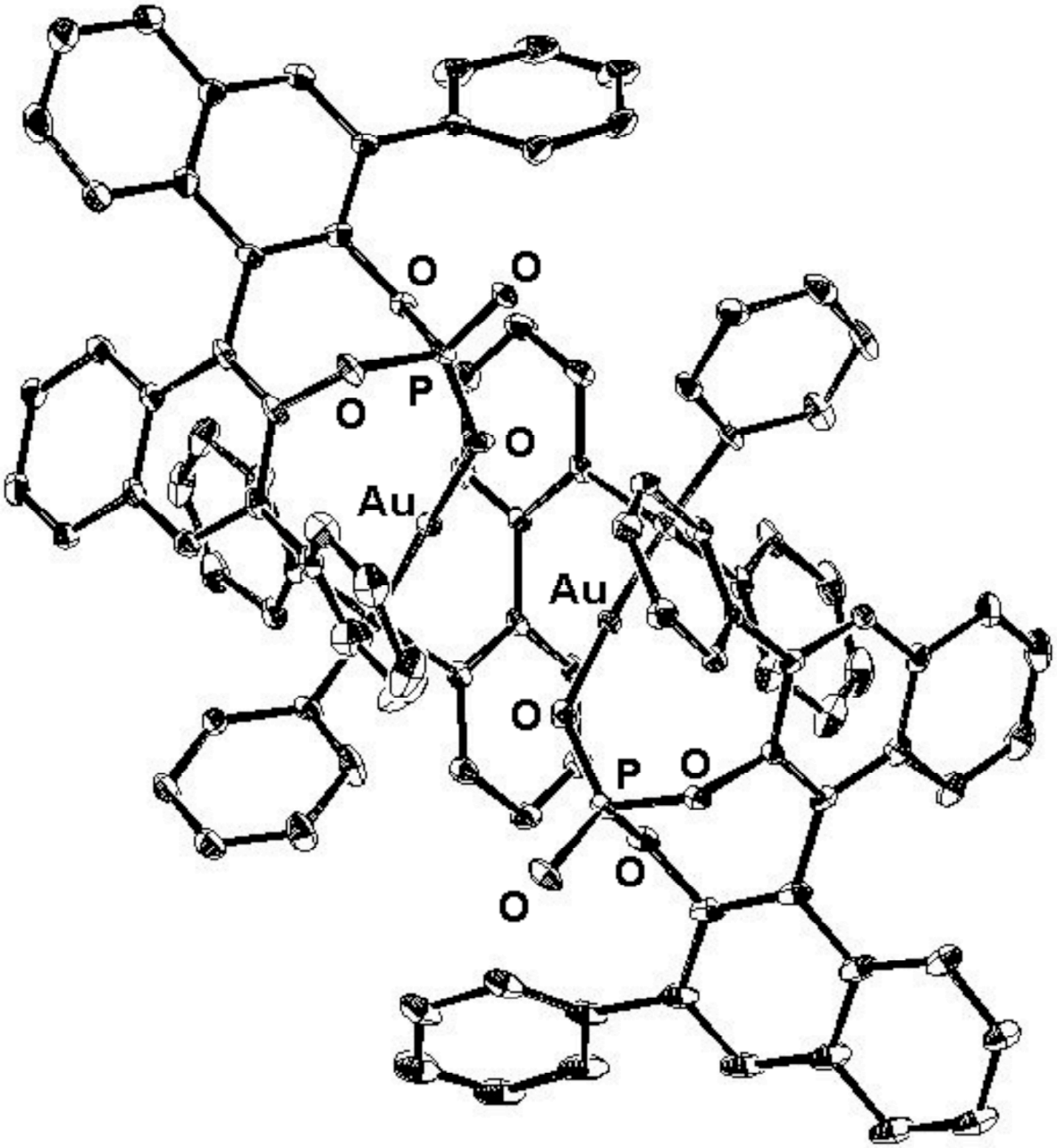
X-Ray Crystal Structure of BIPHEP(AuCl)$_2$

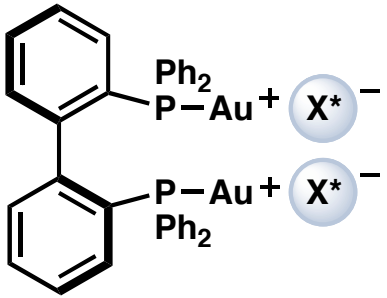


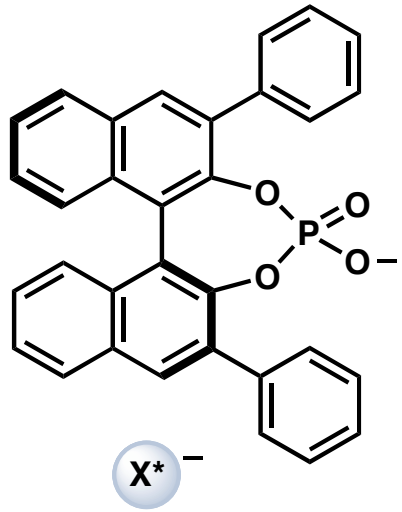


Mikami, *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.

X-Ray Crystal Structure of BIPHEP(AuX)$_2$*



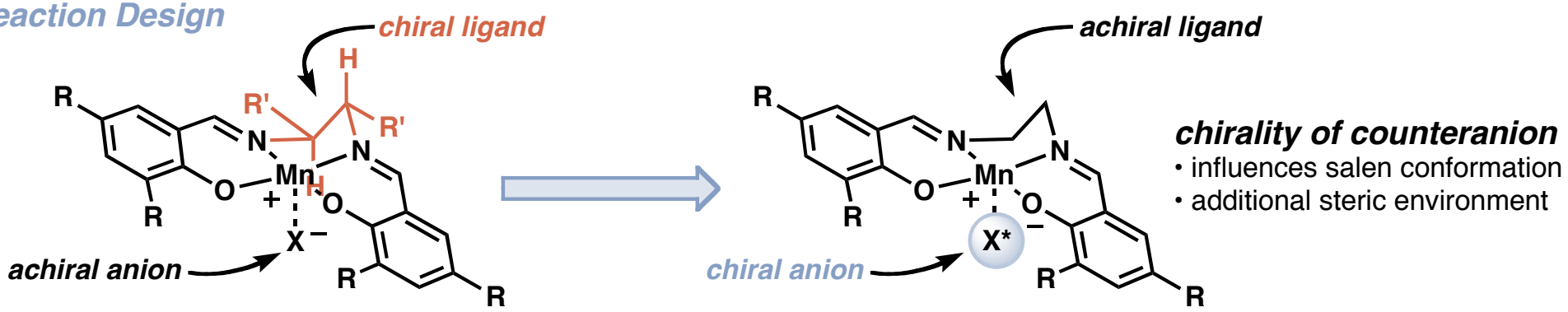




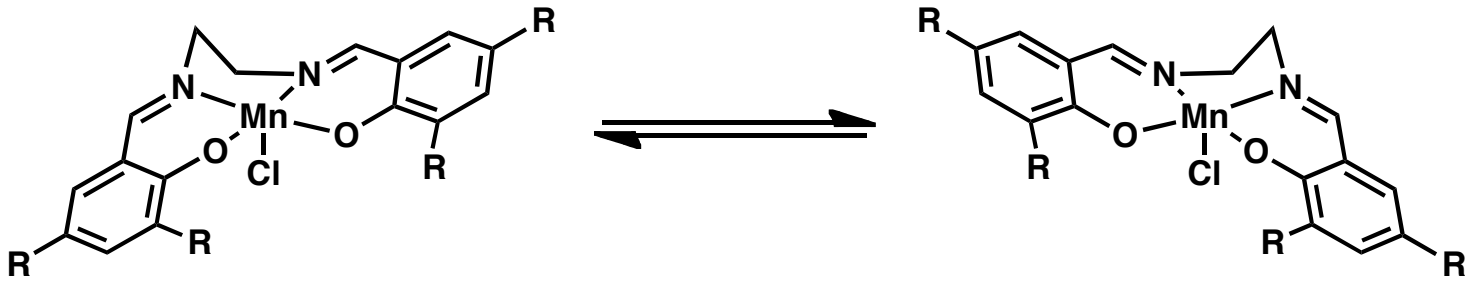
Mikami, *Angew. Chem. Int. Ed.* **2009**, *48*, 6073–6077.

Mn-Catalyzed Olefin Epoxidation

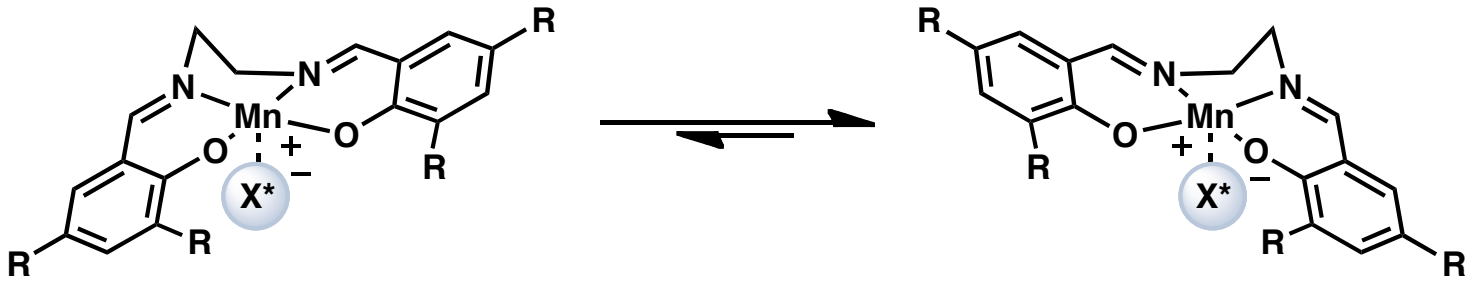
Reaction Design



[Mn-salen]Cl complex has two enantiomorphic conformations



Addition of chiral anion can bias conformational equilibrium

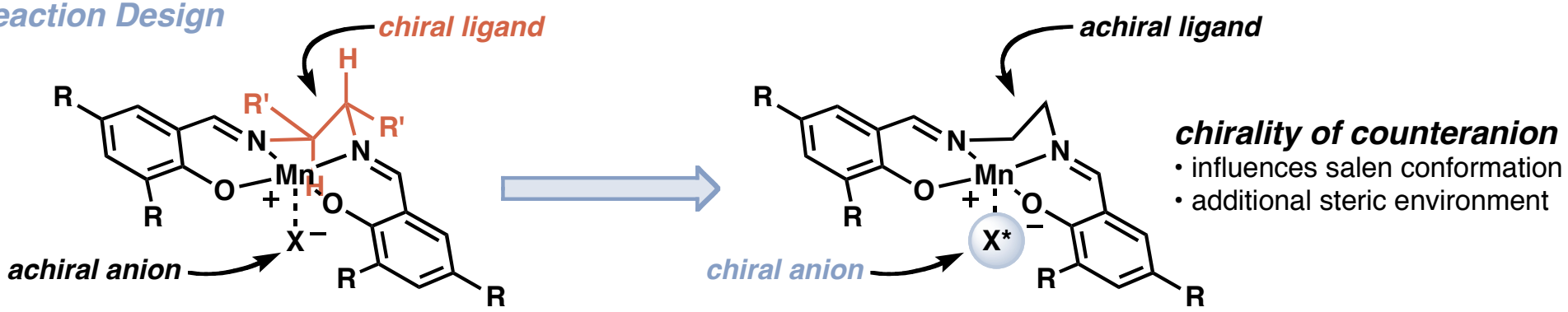


Pfeiffer effect

List, *Angew. Chem. Int. Ed.* **2010**, *49*, 628–631.

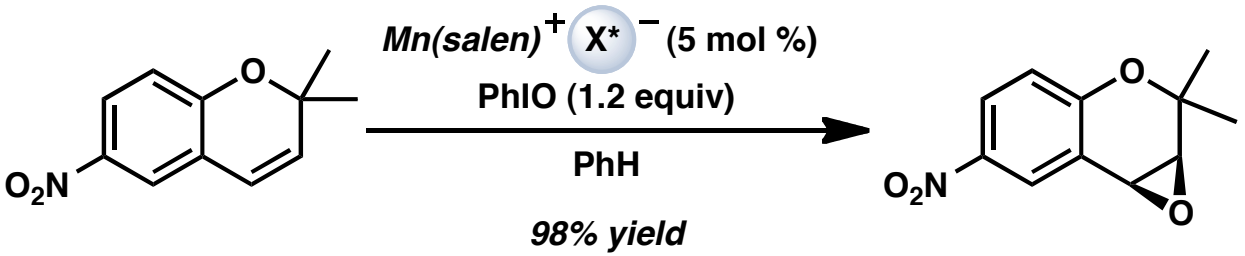
Mn-Catalyzed Olefin Epoxidation

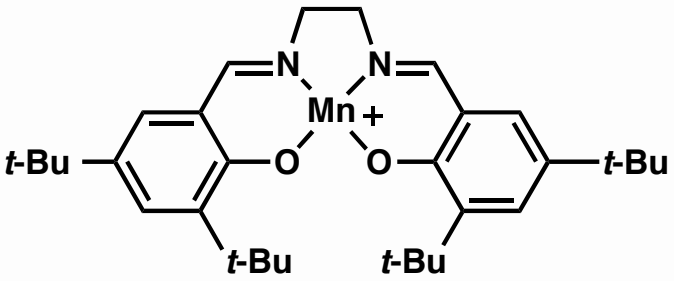
Reaction Design



chirality of counteranion
- influences salen conformation
- additional steric environment

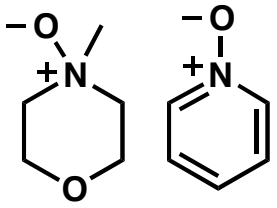
Asymmetric Olefin Epoxidation



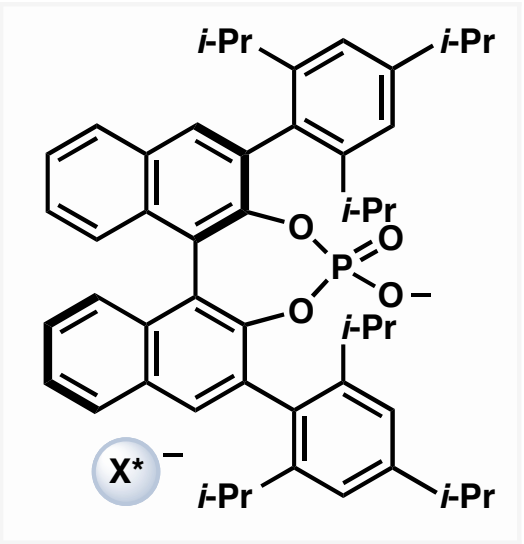


substrate scope
- very similar to Jacobsen chiral diamine system
- slightly higher yields for e⁻ deficient olefins and styrene

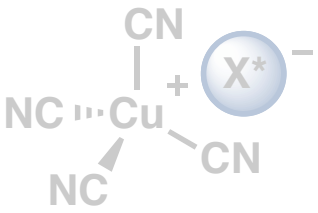
reactivity
- neutral donors not required for activity, dramatically reduce ee
- displace chiral anion and relieves postulated "frustrated" ion pair

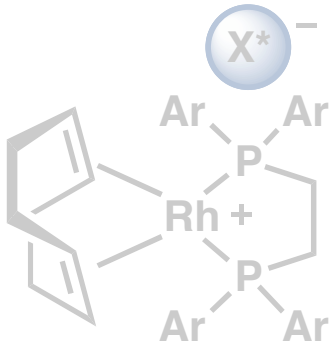


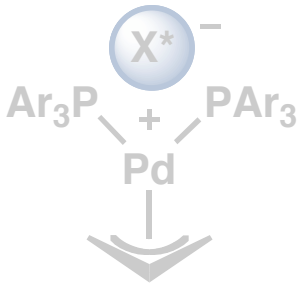
neutral donors

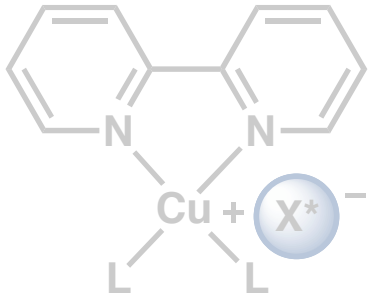


List, *Angew. Chem. Int. Ed.* **2010**, *49*, 628–631.





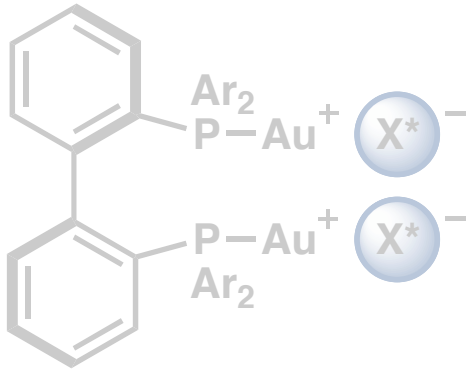


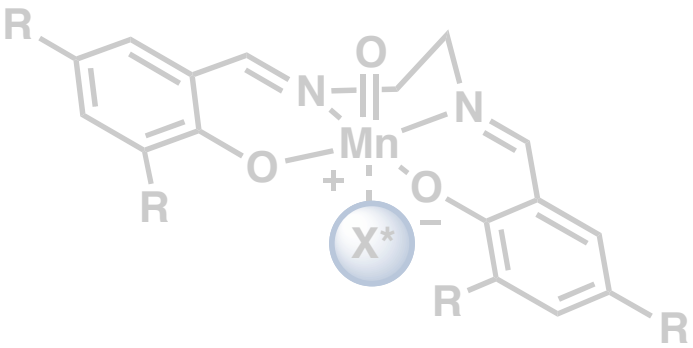


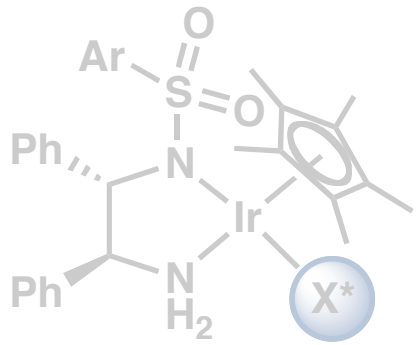
- ***Background and Concepts***
  Brief History and Asymmetric Ion Pairing Considerations

- ***Enantioselective Transition Metal Catalyzed Reactions***
  Asymmetric Induction by Chiral Counterions

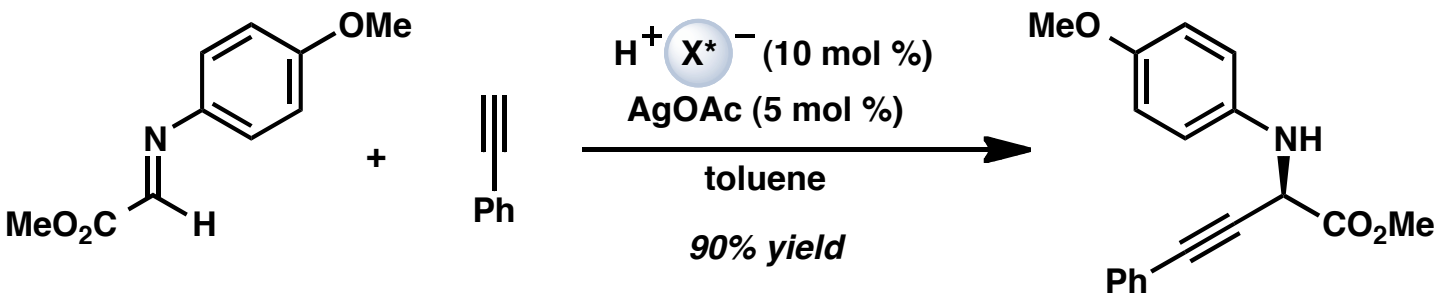
- ***Cooperative Catalysis***
  Chiral Brønsted Acids and Chiral Counterions







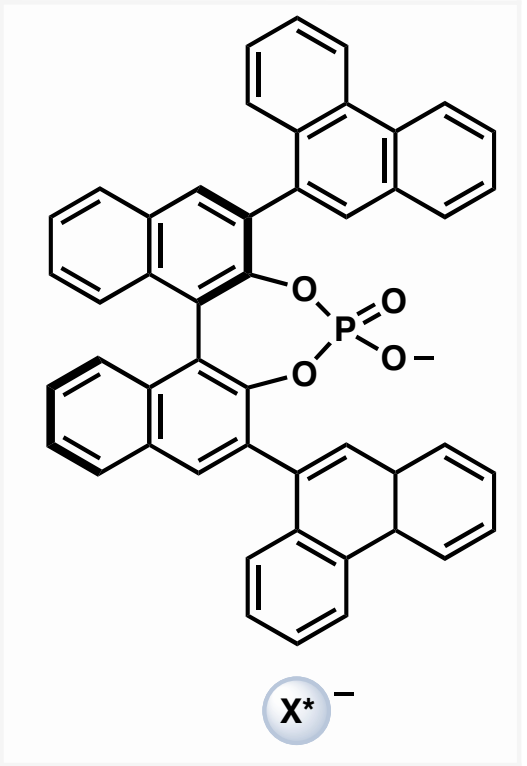
Ag- and Brønsted Acid Catalyzed Propargylation



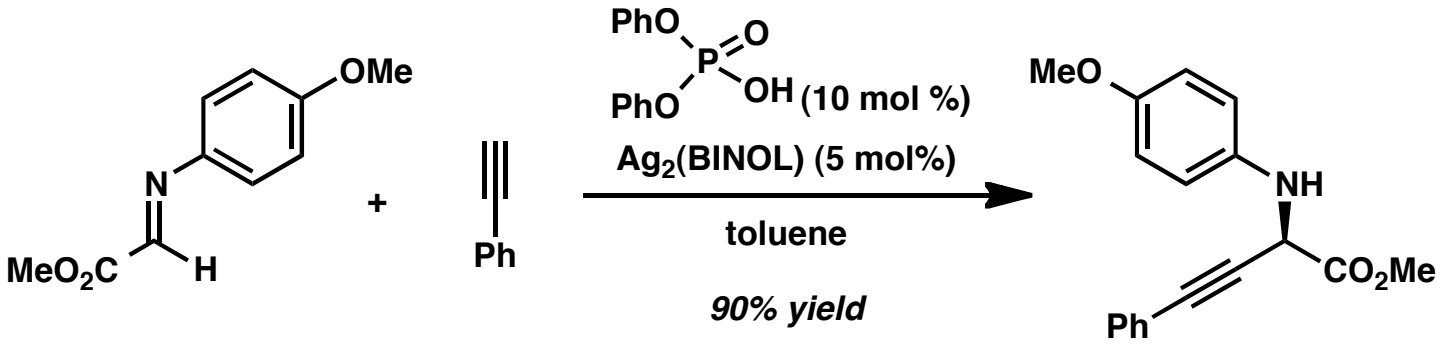
solvent	ε	ee (%)
PhH	2	72
toluene	2.38	82
p-xylene	—	68
$(n\text{-BuO})_2$	—	45
$CHCl_3$	4.81	6
CH_2Cl_2	9.1	52

increasing ε

irregular trend between ee and solvent polarity



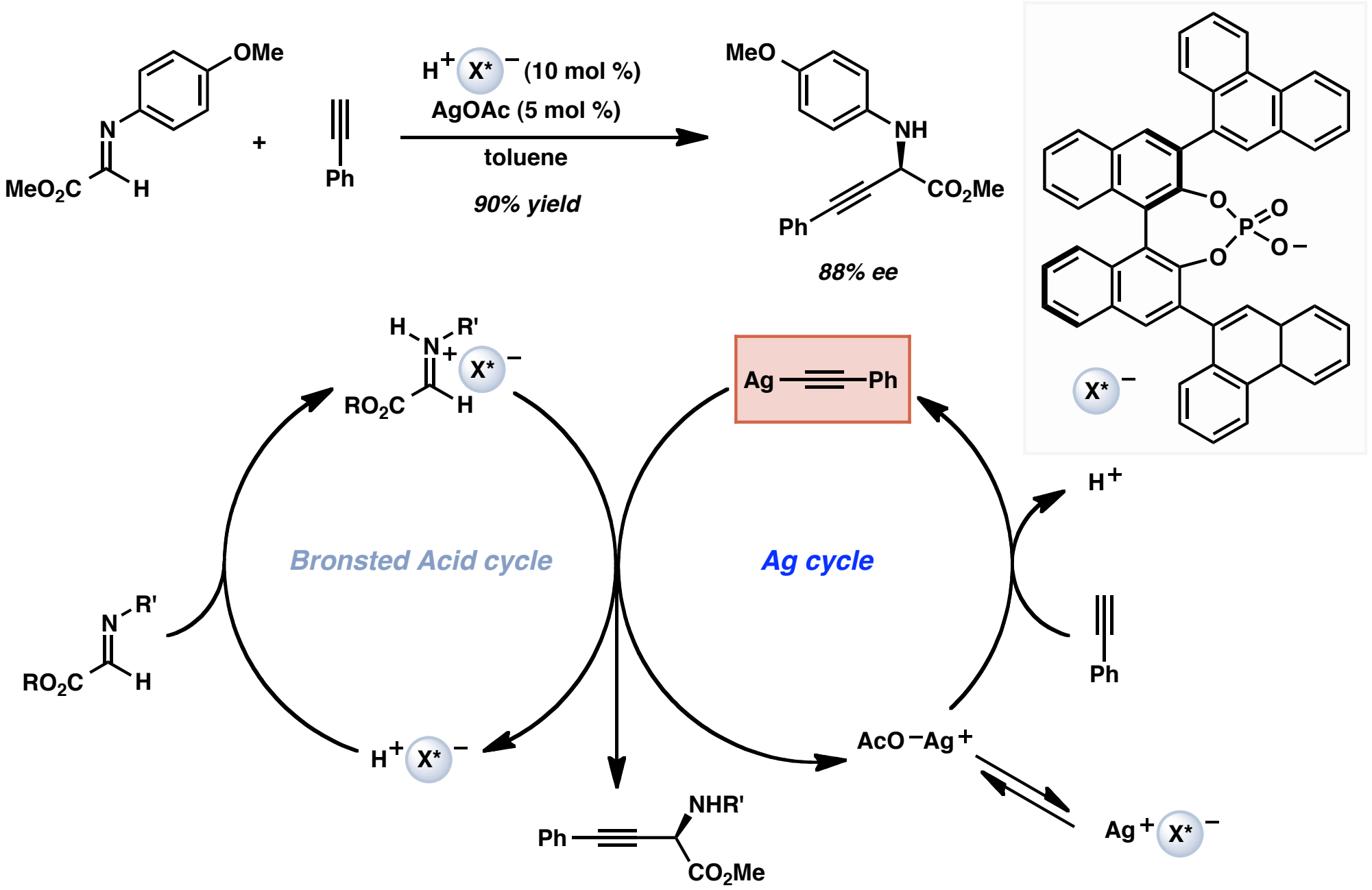
A Control Experiment in Footnotes



chiral silver complex may not be involved!

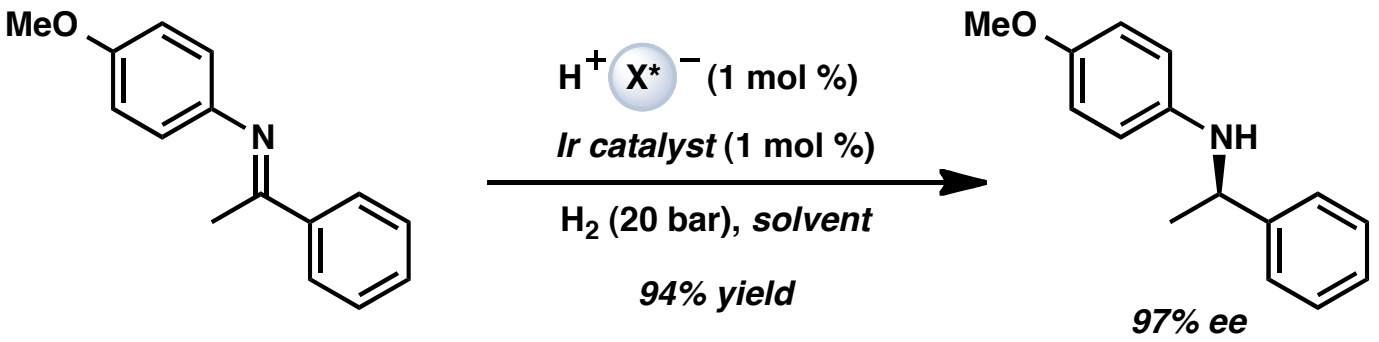
Rueping, *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906.

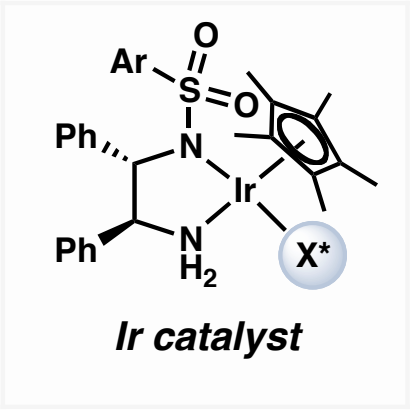
Ag- and Brønsted Acid Catalyzed Propargylation



Rueping, *Angew. Chem. Int. Ed.* **2007**, *46*, 6903–6906.

Ir- and Brønsted Acid Catalyzed Imine Hydrogenation





Temperature Effect

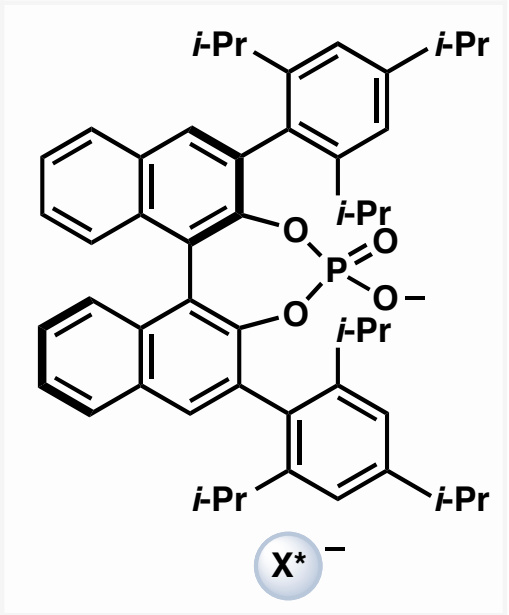
20 °C	97% ee
10 °C	99% ee

Solvent Effect

$PhCH_3$	97% ee
THF	92% ee
CH_3CN	10% ee

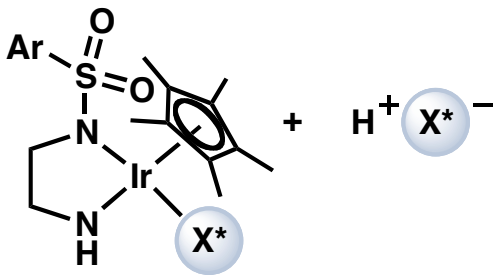
Match/Mismatch Effect

(*S,S*)-*Ir catalyst* + X* −	3% ee
(*R,R*)-*Ir catalyst* + X* −	92% ee

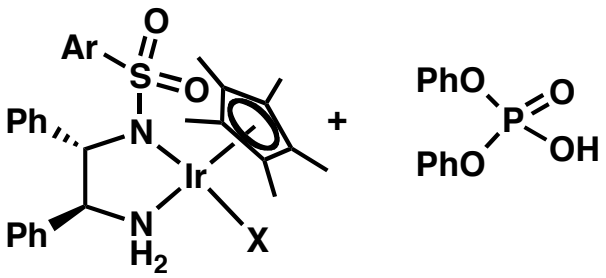


Additional Experiments?

- achiral diamine Ir-catalyst + *chiral acid?*



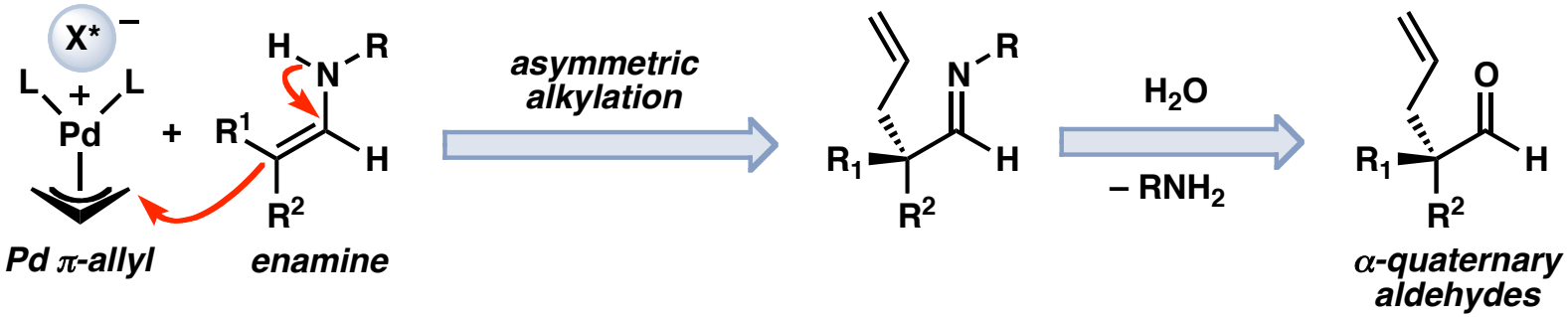
- *chiral diamine Ir-catalyst* + achiral acid?



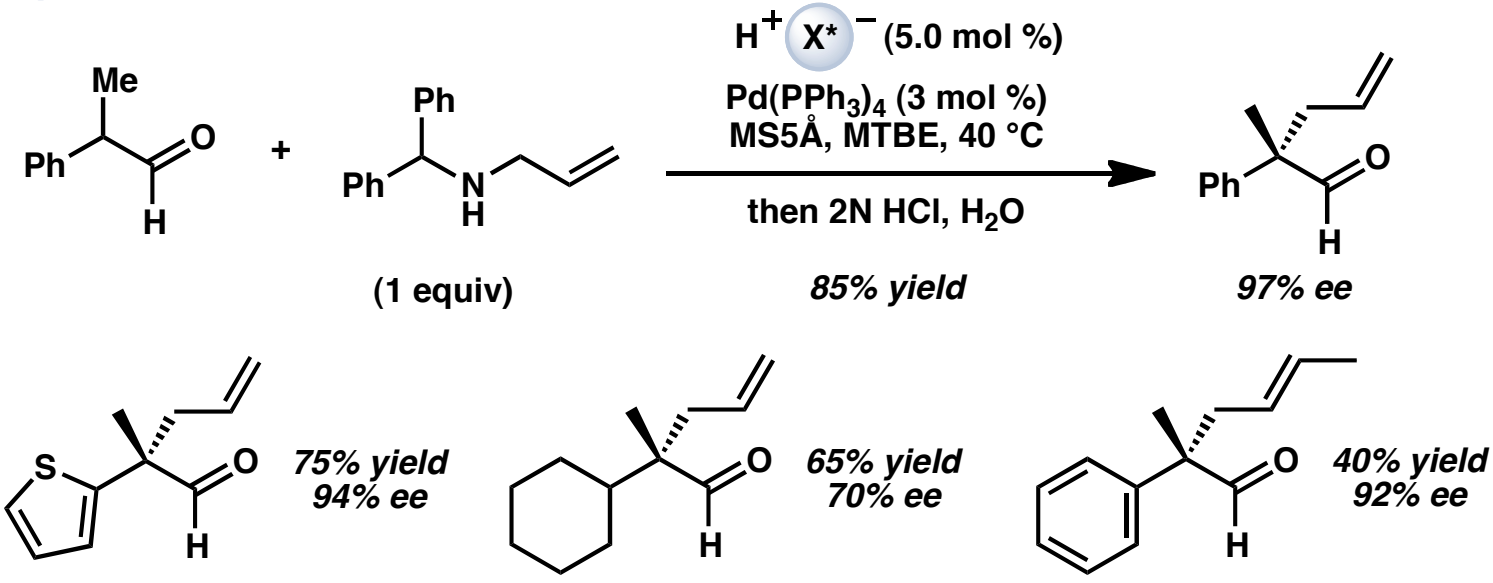
Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 14450–14451.

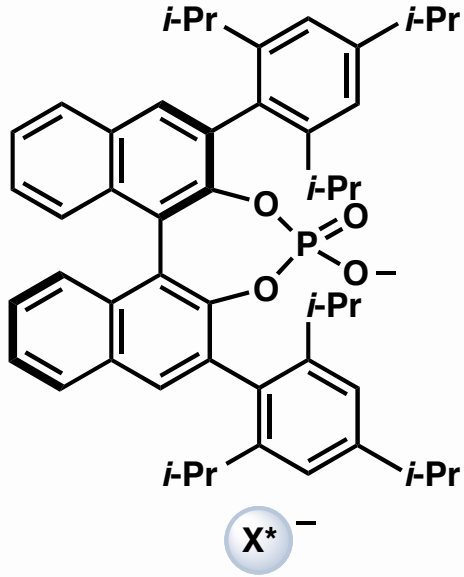
Pd- and Brønsted Acid Catalyzed Aldehyde Allylation

Reaction Design:



Optimized Reaction Conditions



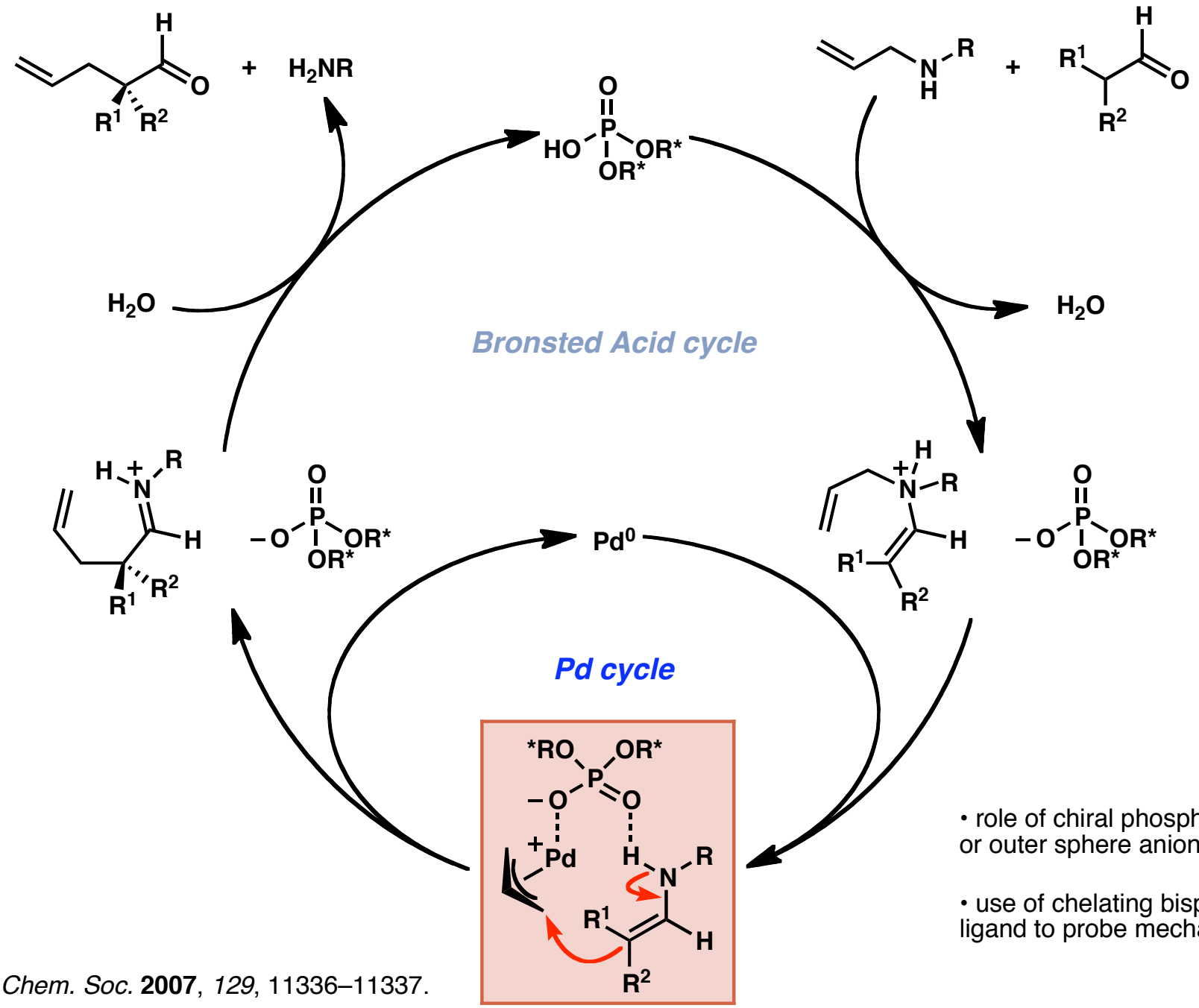


Additional Experiments?

- reactions in other solvents not reported
- comparison of different temperatures for single substrate

List, *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337.

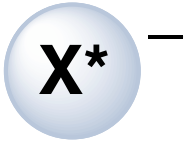
Pd- and Brønsted Acid Catalyzed Aldehyde Allylation



- role of chiral phosphate as inner or outer sphere anion unclear
- use of chelating bisphosphine ligand to probe mechanism

List, *J. Am. Chem. Soc.* **2007**, *129*, 11336–11337.

Designing Reactions with Chiral Counterions



Some Special Considerations for Designing Asymmetric Transition Metal Catalyzed Reactions Using a Chiral Counterion Approach:

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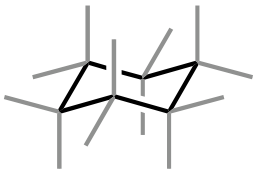
***Solvent effects*:** more polar solvents will increase the distance between the ion pair and affect enantioselectivity

T

***Temperature*:** lower temperatures can promote more effective ion-pairing in solution.

***Stereochemistry*:** if chiral ligands or racemic chiral ligands are used, matched/mismatched sterics should be considered.

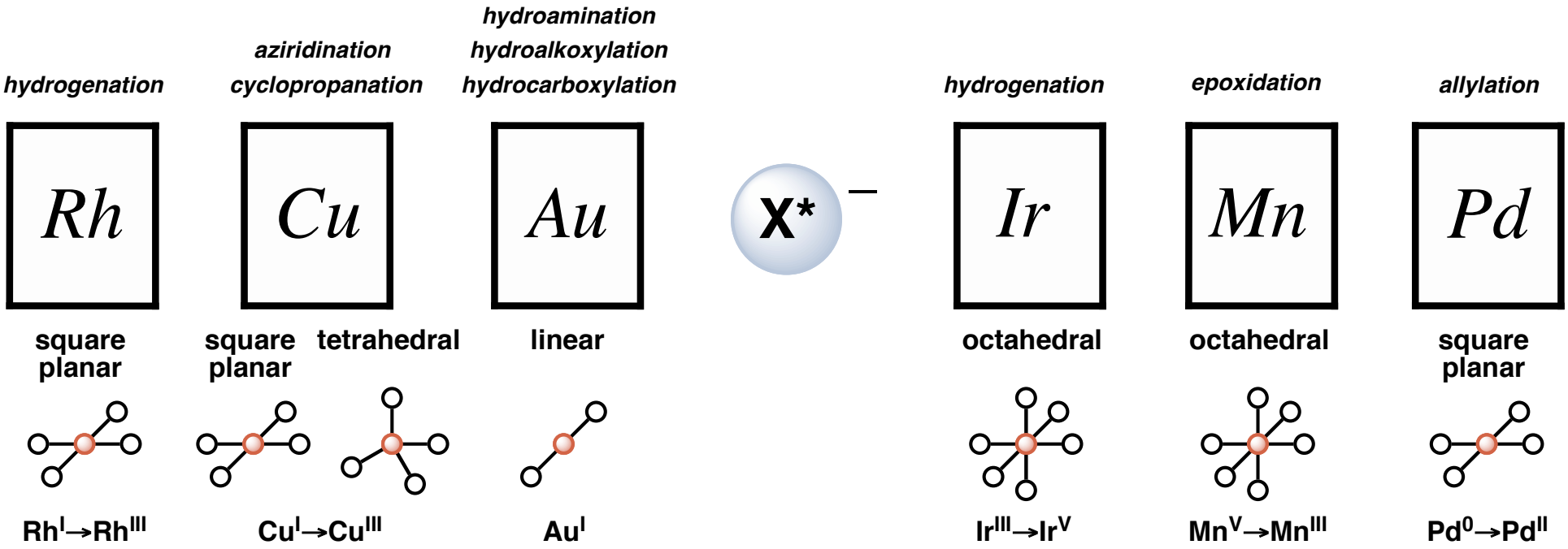


***Conformational Equilibria*:** Ligands with enantiomorphic conformations can be influenced by anion binding (Pfeiffer effect)

$\left[M^{+} \right]^{\ddagger}$

***Transition State*:** Bond-forming transition state of the reaction should have cationic character at metal center to enable ion pairing.

Chiral Counterions Summary



- *Alternative source of chiral information when chiral ligand approach proves challenging*
- *Reaction development requires consideration of key criteria (TS, solvent, stereochem, ...)*
- *Capable of forming ion pairs with cationic metals with diverse coordination geometries*
- *Amenable to different types of transition metal catalyzed reactions*
- *Participate in reactions with changes in metal oxidation state*
- *Can be combined with other modes of asymmetric induction (chiral ligands, Brønsted acids, ...)*
- *Chiral noncoordinating anions in asymmetric catalysis not fully explored... Much is still unknown*

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Dr. Scott Virgil

Stoltz Group
Reisman Group