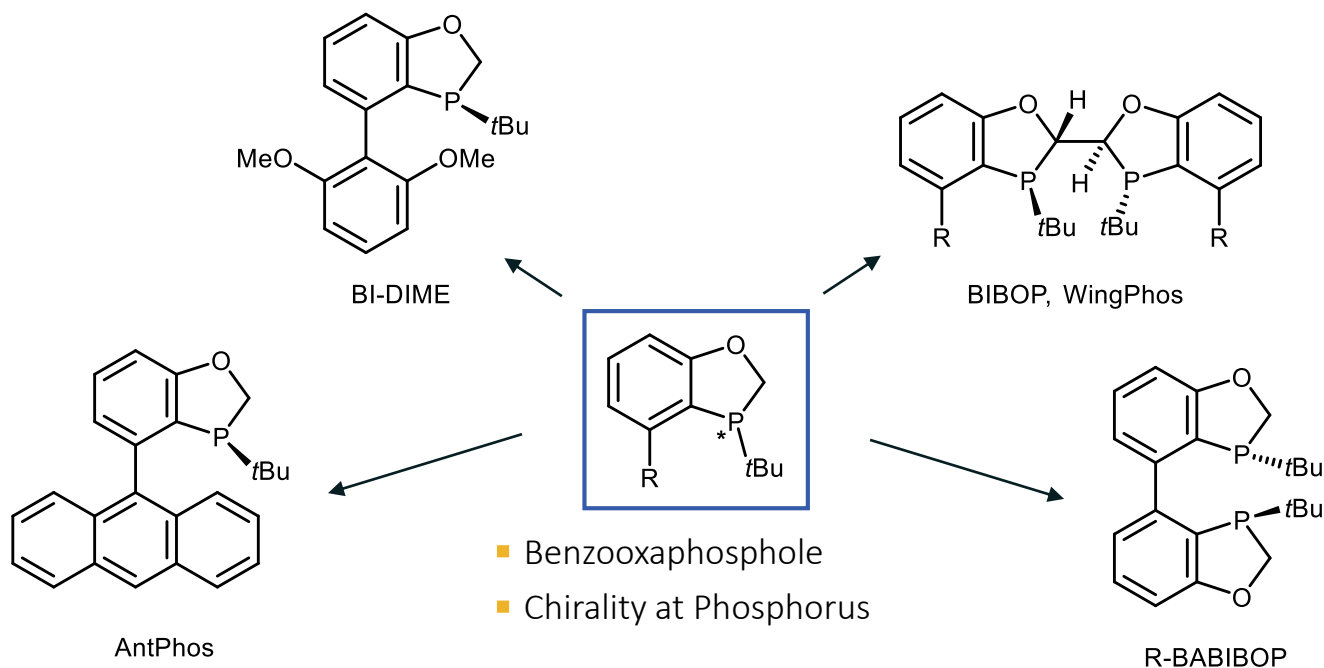


P-Chiral Ligands for Applications in Asymmetric Catalysis



Ian Powers, Ph.D.

Strem Chemicals Technical Presentation

May 2020

Strem Chemicals, Inc.

Expertise in Manufacturing High Quality Chemicals



Strem Chemicals, Inc.

Corporate Headquarters
Newburyport, MA USA

European Headquarters
Strasbourg, France

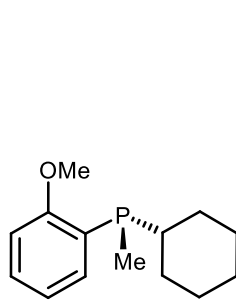


- Established in 1964
- More than 55 years of experience in manufacturing and handling high quality inorganics and organometallics
- 5,000+ specialty chemicals available
- Laboratory Chemicals for R&D
- cGMP Products Manufactured in Kilo-lab Suites
- High Pressure Materials
- Custom Synthesis Projects
- Customers include:
 - Academic, industrial and government R&D laboratories
 - Commercial scale businesses in the pharmaceutical, microelectronics, chemical & petrochemical industries

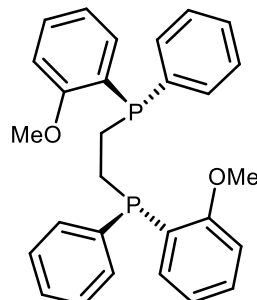


History of P-Chiral Phosphines

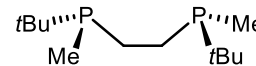
- Development
- Design Challenges



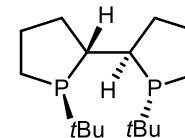
(S)-CAMP



(S,S)-DIPAMP



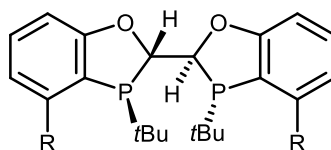
(S,S)-BisP*



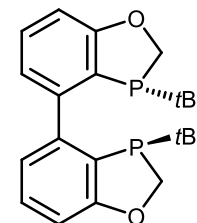
(S,S,R,R)-TangPhos

Diphosphine Ligands

- Development
- Applications in catalysis



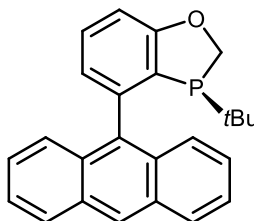
BIBOP, WingPhos



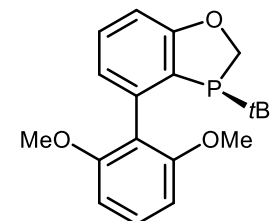
R-BABIBOP

Monophosphine Ligands

- Development
- Applications in catalysis



AntPhos



BI-DIME

Conclusions and Outlook

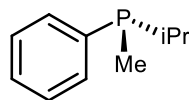
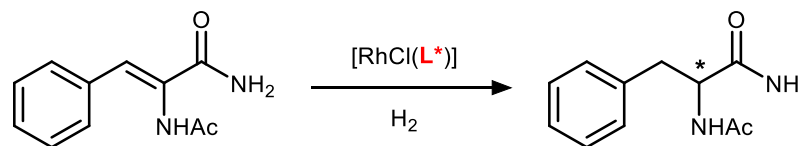
- Summary and Resources

1970s: William Knowles *et al*



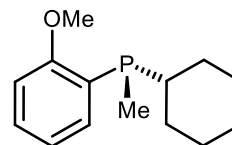
P-Chiral Phosphine

- Chiral information located directly on P atom



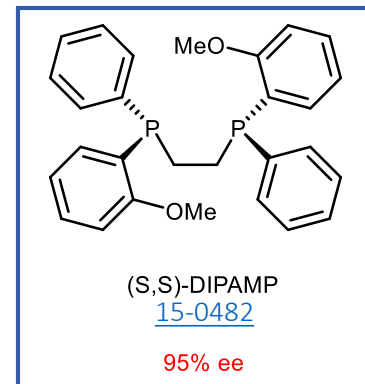
(S)-methylpropylphenyl phosphine

28% ee



(S)-CAMP

80% ee

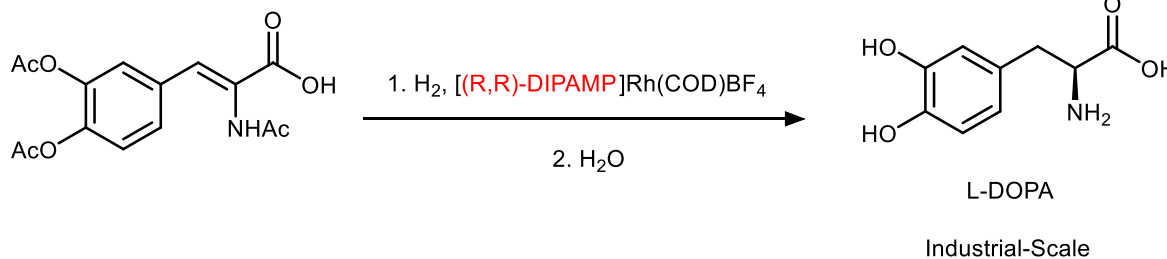


(S,S)-DIPAMP

[15-0482](#)

95% ee

- "Chiral Wilkinson's Catalyst"
- Only modest selectivity for hydrogenation of substituted styrene derivatives

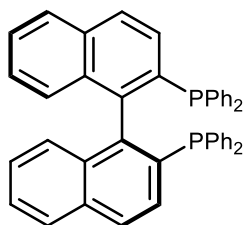


L-DOPA

Industrial-Scale

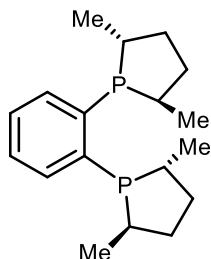
- Synthesis of the antidepressant L-DOPA
- First P-chiral ligand used in a commercial synthesis.

1980s and early 1990s:



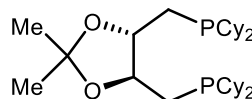
(S)-BINAP

■ Noyori *et al*



(S,S)-Me-DuPhos

■ Burk *et al*



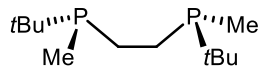
(S,S)-Cy-DIOP

■ Achiwa *et al*

- P-Chiral Phosphines difficult to synthesize and isolate
- Field of asymmetric catalysis dominated by phosphines with remote chirality

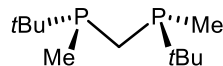
Late 1990s, early 2000s:

- Resolution with (-)-Sparteine:
Only one enantiomer accessible

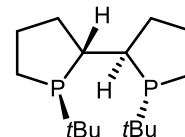


(S,S)-BisP*

■ Tsuneo Imamoto *et al*



(S,S)-MiniPhos



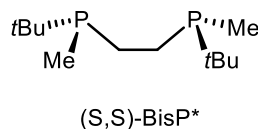
(S,S,R,R)-TangPhos

■ Xumu Zhang and Wenjun Tang

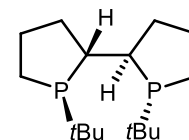
- Rigid backbone leads to increased selectivity

Challenges with prior ligands:

- Air sensitive
- Liquids or oils at RT
- Difficult to handle

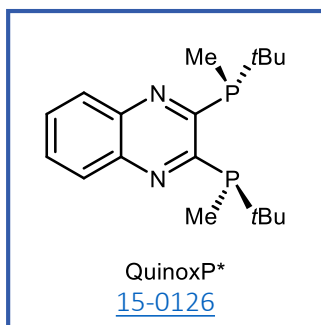


- Low rigidity
- Racemization at higher temps
- Difficult to obtain both isomers

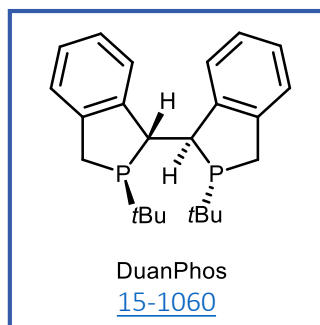


(S,S,R,R)-TangPhos

2005:



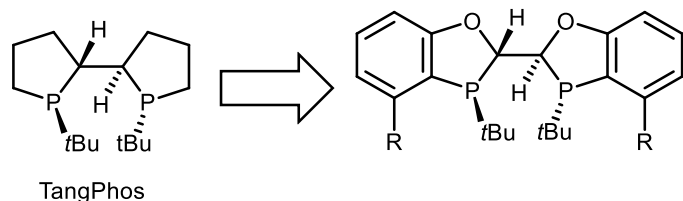
■ Imamoto *et al*



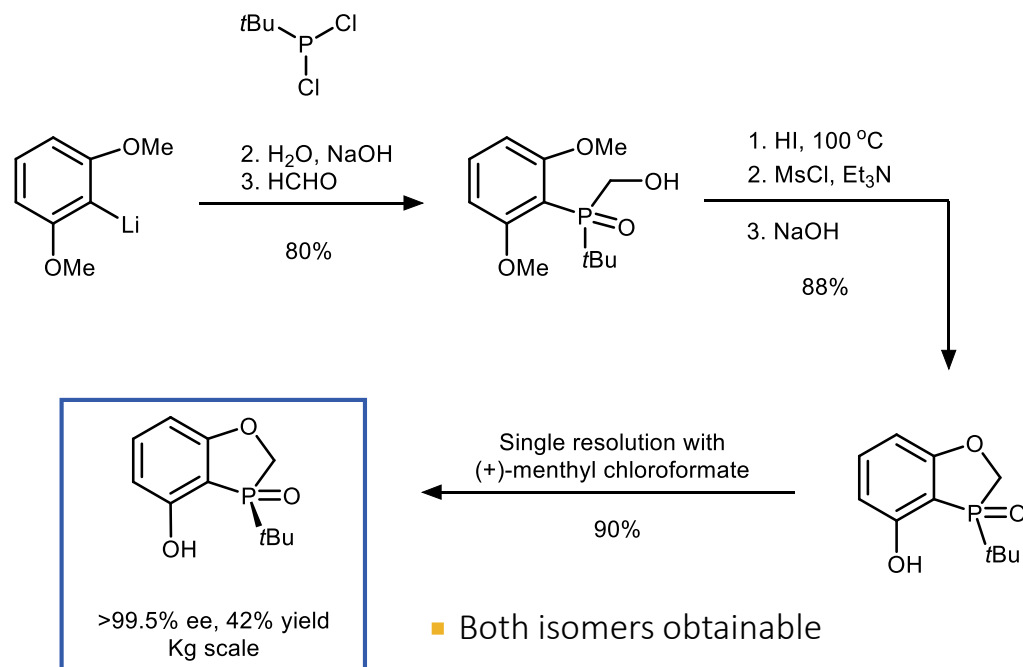
■ Xumu Zhang and Duan Liu

- Air stable
- Solid at RT
- Resolution with (+) or (-) DBT:
Both enantiomers accessible

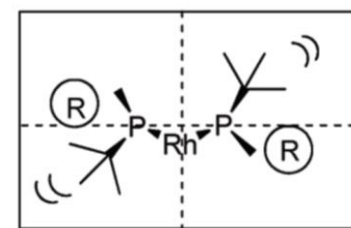
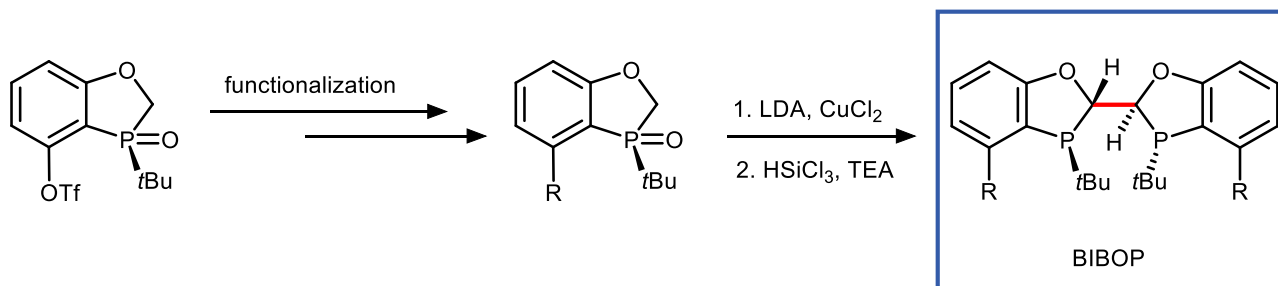
Wenjun Tang *et al*, Boehringer Ingelheim



- Can an air-stable, modular P-chiral phosphine be developed?
- Benzooxaphosphole Core generates a wide variety of potential structures

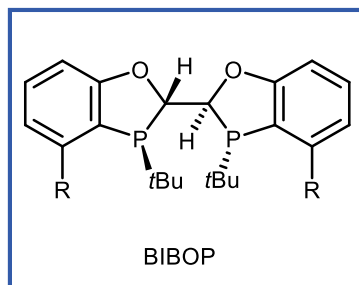


- Both isomers obtainable



- Rigid, tunable BIBOP ligand framework
- Air-stable

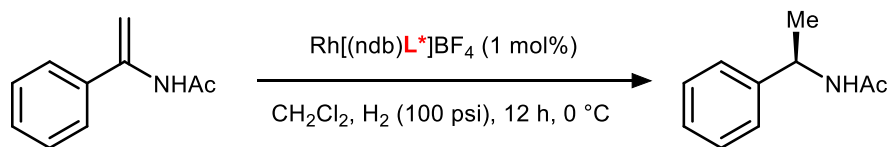
- C₂ Symmetry



- Ligand variation demonstrates the importance of tunability
- Parent BIBOP and MeO-BIBOP give consistently high % ee

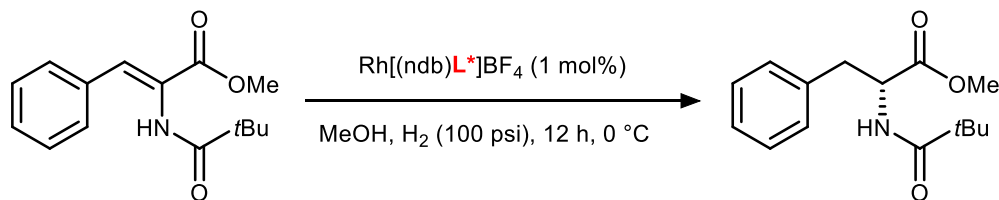
■ R = H (**L1**), OMe (**L2**), Me (**L3**), Ph (**L4**)

Asymmetric hydrogenation of α -arylenamides

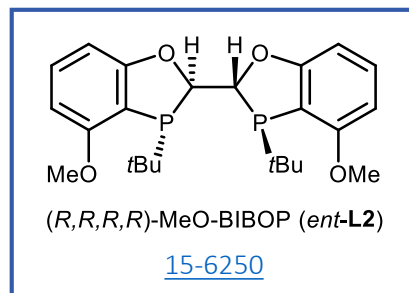


- **L1**, R = H: 99% ee
- **L2**, R = OMe: 92% ee
- **L3**, R = Ph: 49% ee
- **L4**, R = Me: 4% ee

Asymmetric hydrogenation of α -(acylamino)acrylic acids

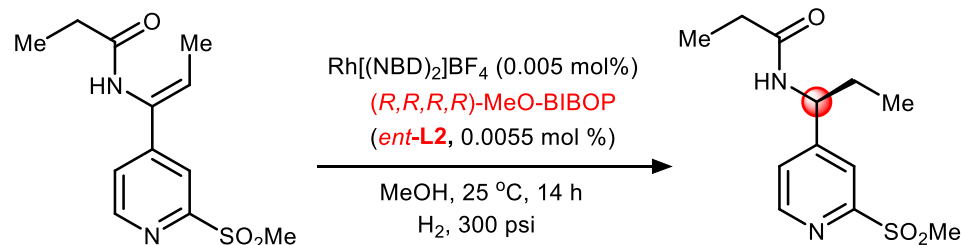


- **L1**, R = H: 99% ee
- **L2**, R = OMe: 93% ee
- **L3**, R = Ph: 20% ee
- **L4**, R = Me: 94% ee



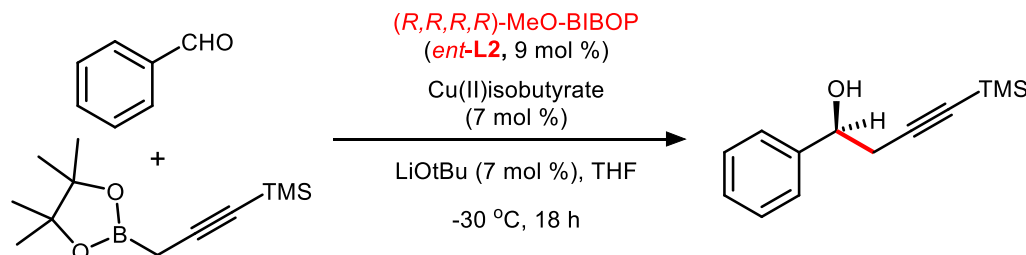
- Most electron-rich BIBOP ligand

- Hydrogenation at low catalyst loading



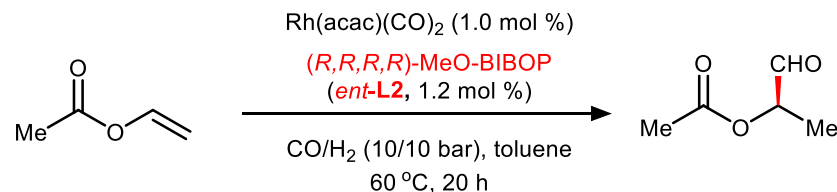
- 99% Yield
97% ee

- Propargylation

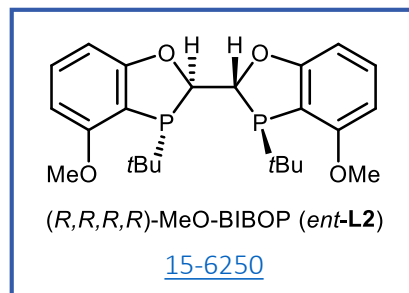


- 99% Yield
97% ee

- Hydroformylation

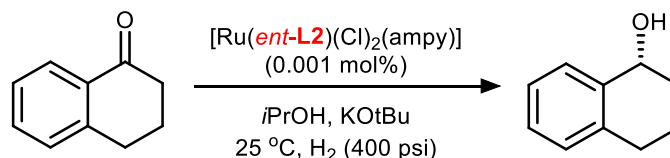


- >99% Conversion
285:1 branched:linear
90% ee

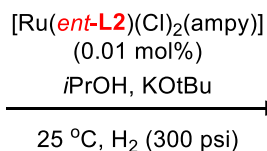
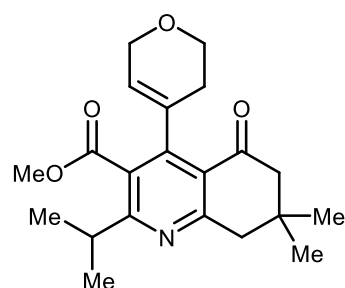


- Most electron-rich BIBOP ligand

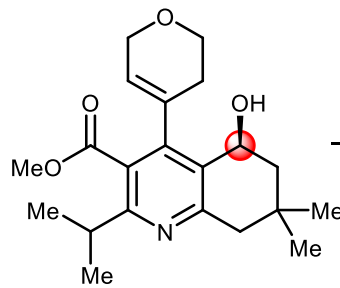
- Hydrogenation at low catalyst loading



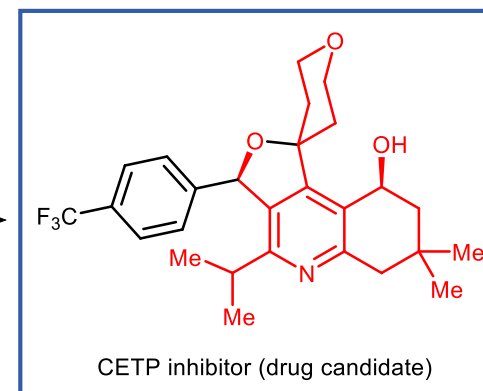
- 98% Yield
92% ee

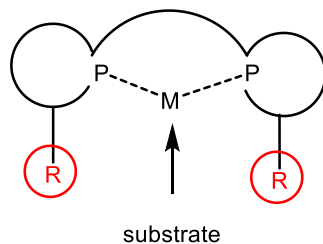
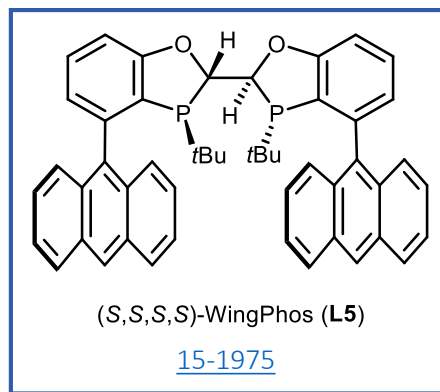


TON > 10,000
kilogram-scale

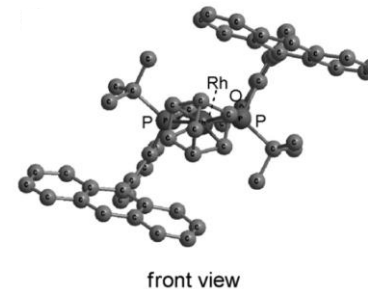
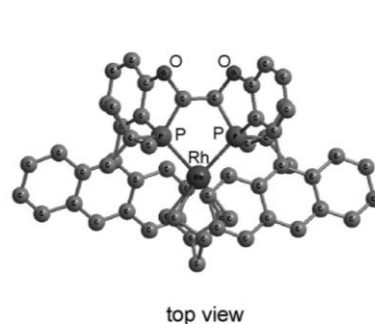


>98% ee, 98% yield



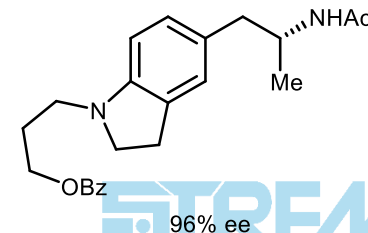
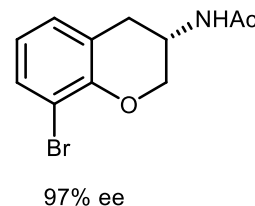
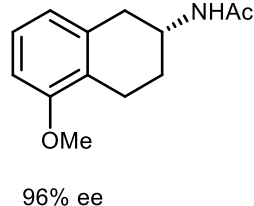
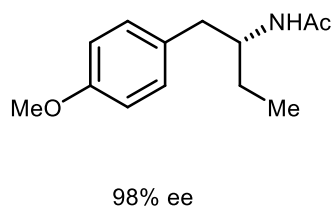
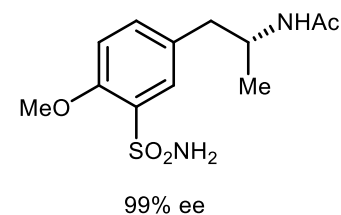
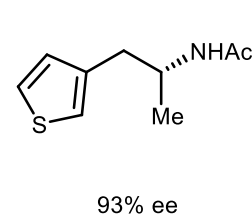
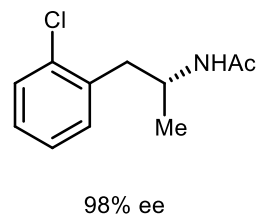
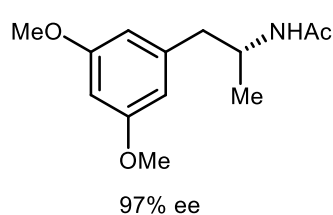
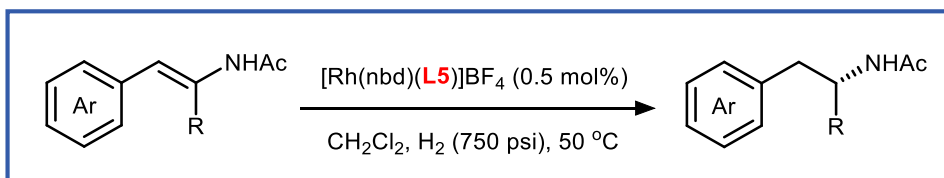


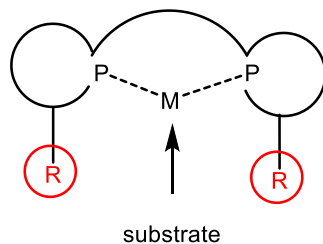
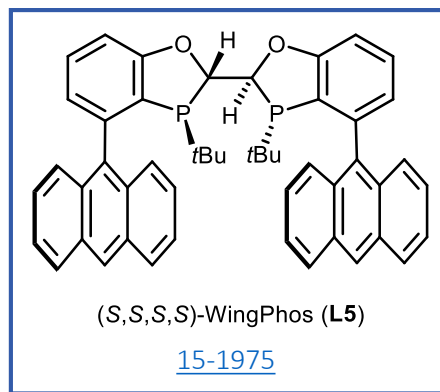
■ Deep chiral pocket



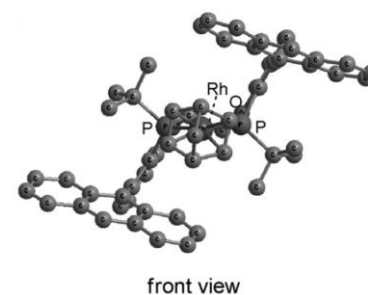
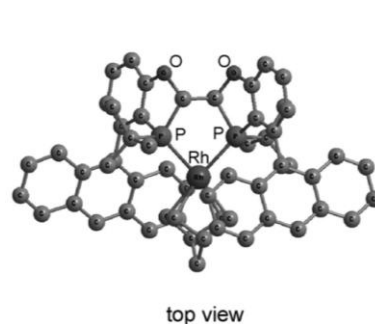
■ *t*-Bu groups control anthracene orientation

■ Asymmetric hydrogenation of β -arylenamides



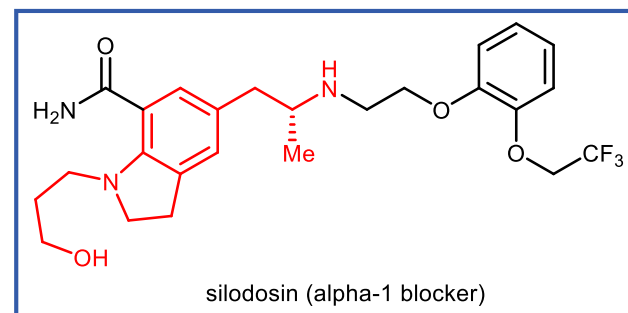
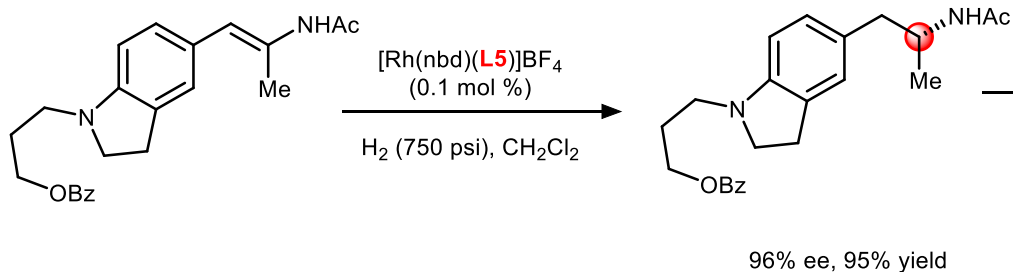
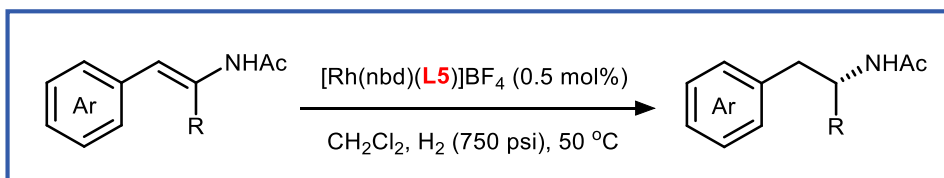


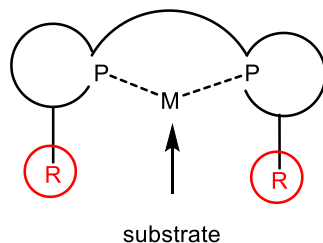
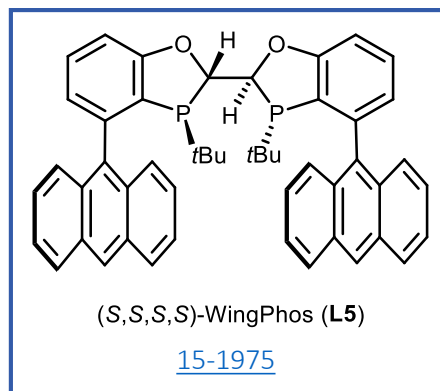
■ Deep chiral pocket



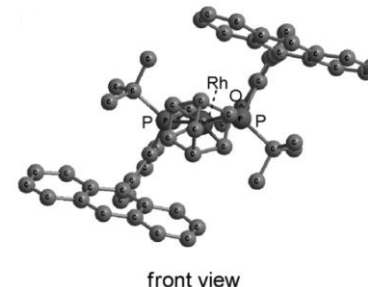
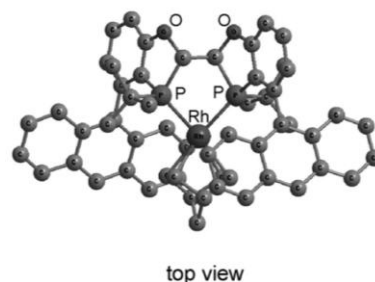
■ *t*-Bu groups control anthracene orientation

■ Asymmetric hydrogenation of β -arylenamides



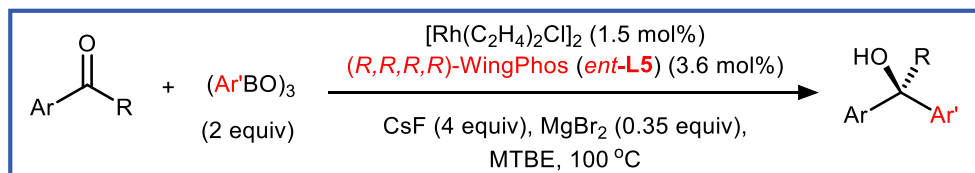


■ Deep chiral pocket

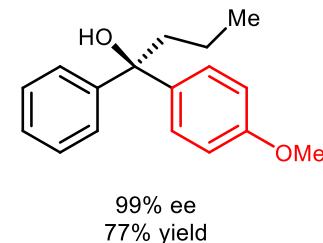
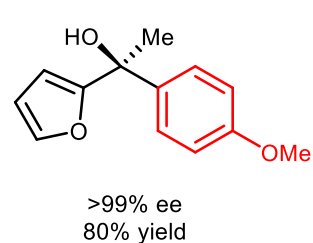
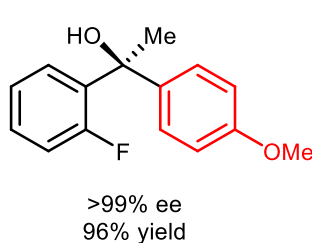


■ *t*-Bu groups control anthracene orientation

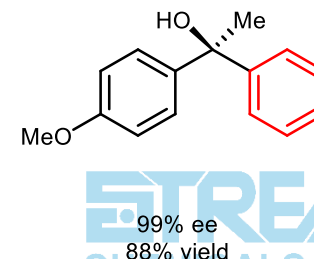
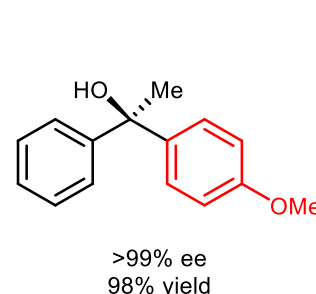
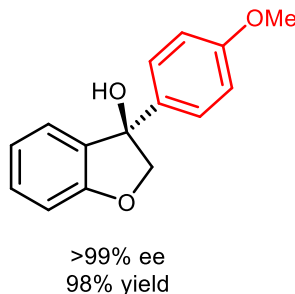
■ Tertiary alcohol synthesis via addition of arylboroxines to aryl ketones

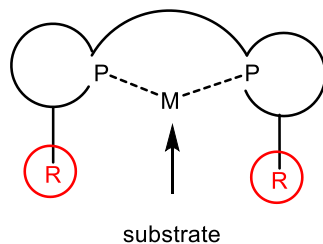
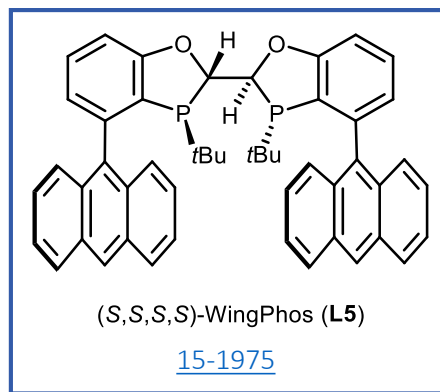


■ Substrate aryl interactions with ligand anthracyl groups may contribute to selectivity

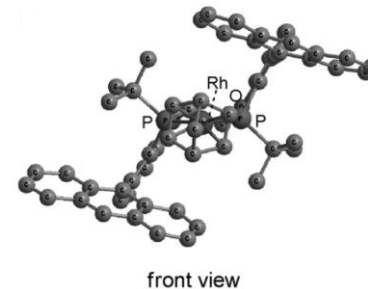
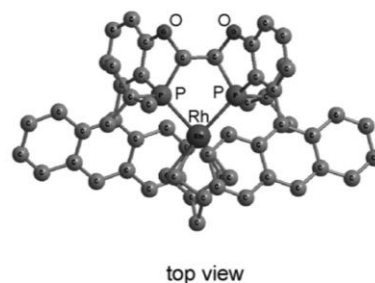


■ No ligand racemization at 100 °C



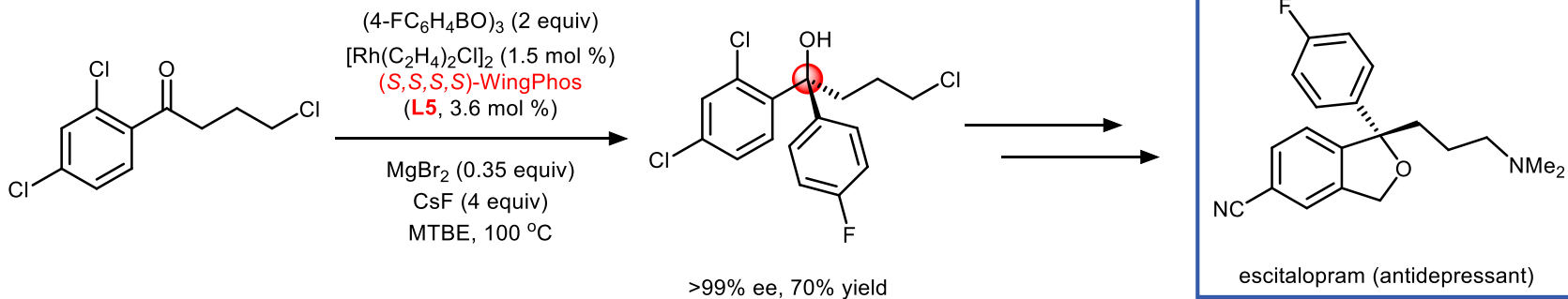
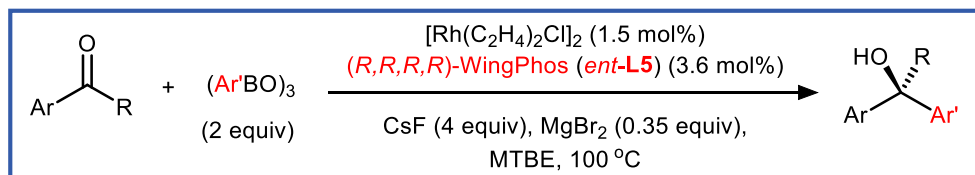


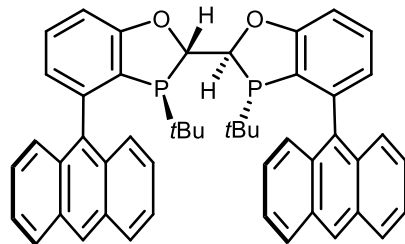
■ Deep chiral pocket



■ *t*-Bu groups control anthracene orientation

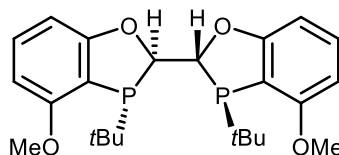
- Tertiary alcohol synthesis via addition of arylboroxines to aryl ketones





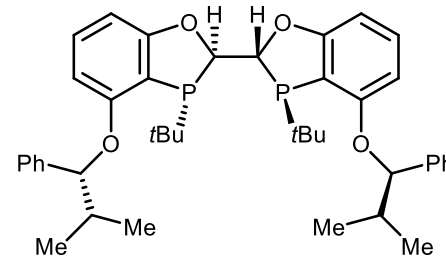
(S,S,S,S)-WingPhos (**L5**)

[15-1975](#)



(R,R,R,R)-MeO-BIBOP (*ent*-**L2**)

[15-6250](#)



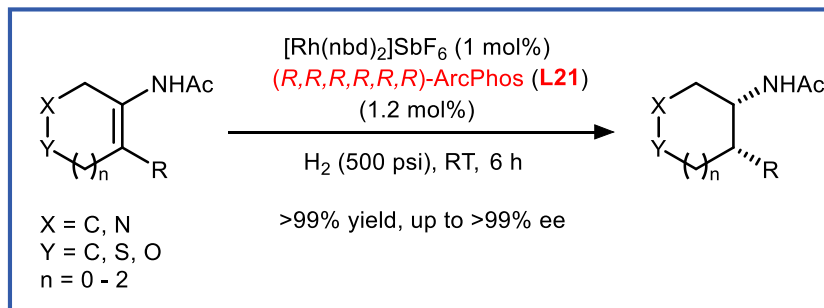
(R,R,R,R,R,R)-ArcPhos (**L21**)

[Please inquire](#)

- Deep chiral pockets

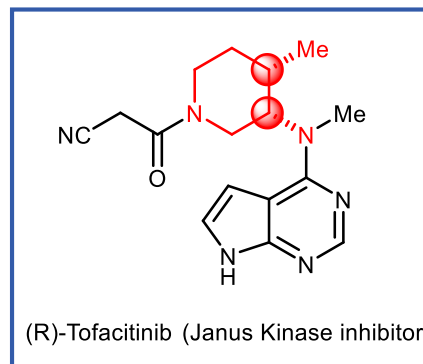
- Electron rich

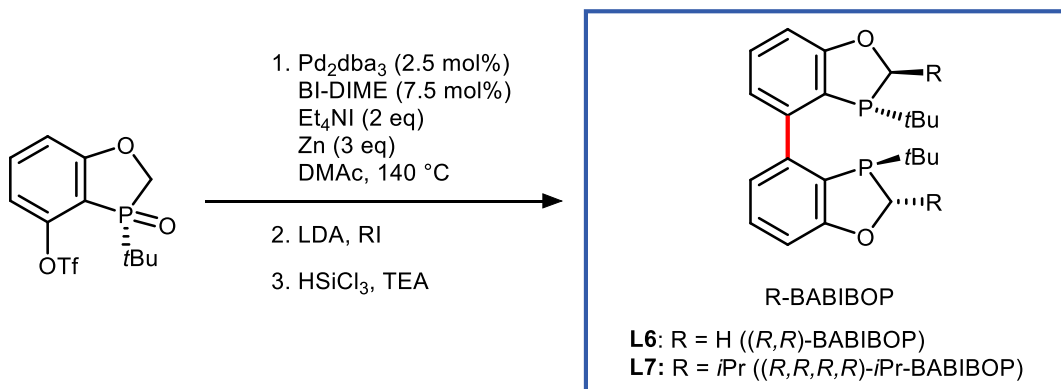
- Electron rich with deep chiral pockets



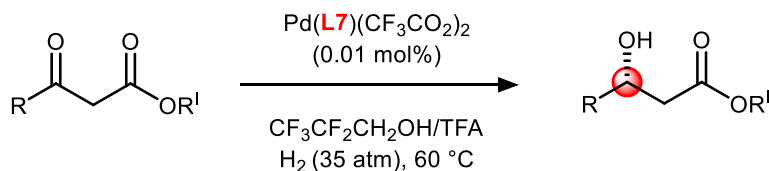
- Rhodium-catalyzed hydrogenation of aliphatic cyclic tetrasubstituted enamides
- With MeO-BIBOP: up to 70% ee
- With WingPhos: up to 20% ee

- First enantioselective synthesis of (R)-Tofacitinib

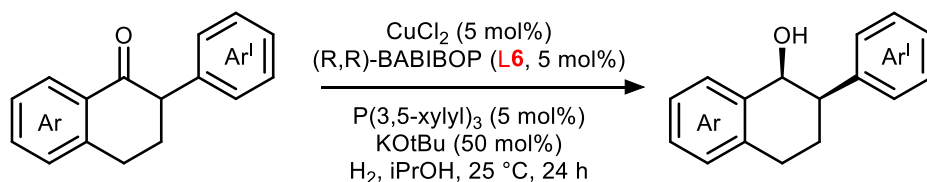




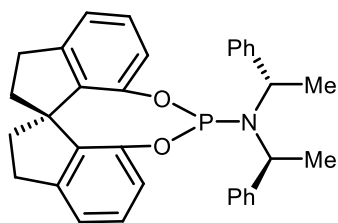
- Coupled via ArOTf
- Binding mode similar to BINAP
- Tunability through methylene and aryl R groups



- R = alkyl, aryl
- Up to 99% ee, 99% yield
- Highest reported selectivity for Pd-catalyzed hydrogenation

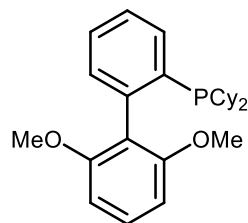


- Cu-catalyzed hydrogenation of ketones via dynamic kinetic resolution
- Up to 96% ee, 95% yield >99:1 d.r.
- With BIBOP: 54% ee



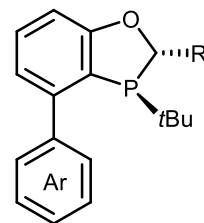
monophosphoramidite

^{31}P NMR δ = 124.9 ppm



S-Phos (Buchwald)

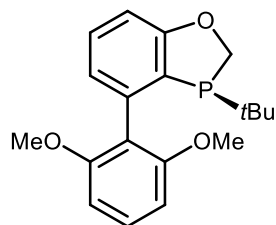
^{31}P NMR δ = -8.6 ppm



P-chiral biaryl
monophosphorus ligand

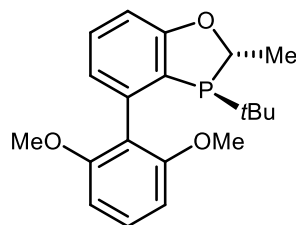
^{31}P NMR δ = -7.9 ppm (**L8**)

- Air-stable rigid framework
- Electron rich phosphorus compared to phosphoramidites
- Highly tunable structure



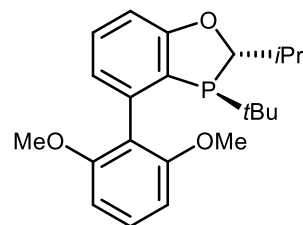
(S)-BI-DIME (**L8**)

[15-6210](#)



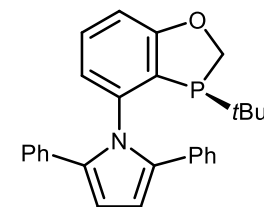
(S,S)-Me-BI-DIME (**L9**)

[15-6220](#)



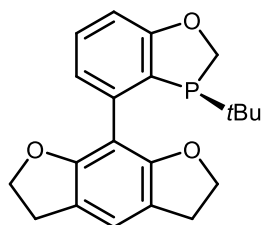
(S,S)-iPr-BI-DIME (**L10**)

[15-6230](#)



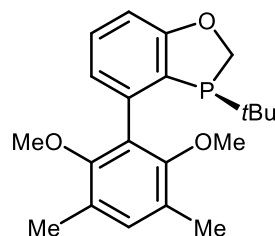
L11

[15-6320](#)



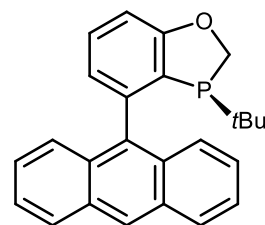
L12

[15-6295](#)



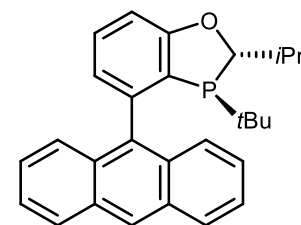
L13

[15-6840](#)



(S)-AntPhos (**L14**)

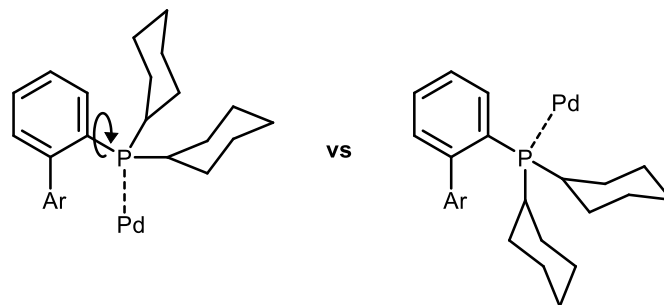
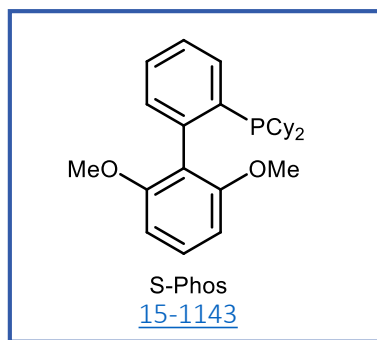
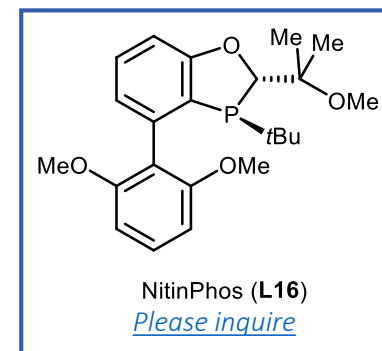
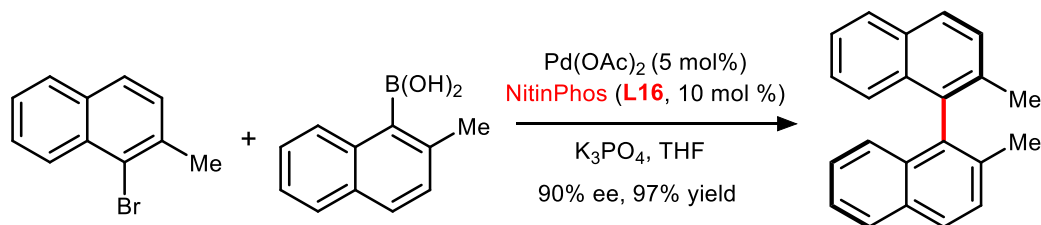
[15-1967](#)



(S)-iPr-AntPhos (**L15**)

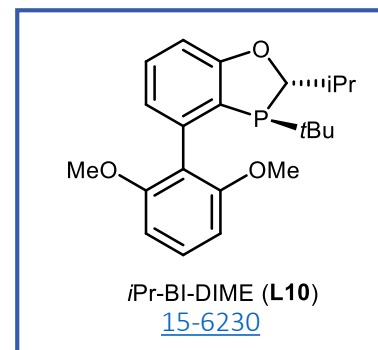
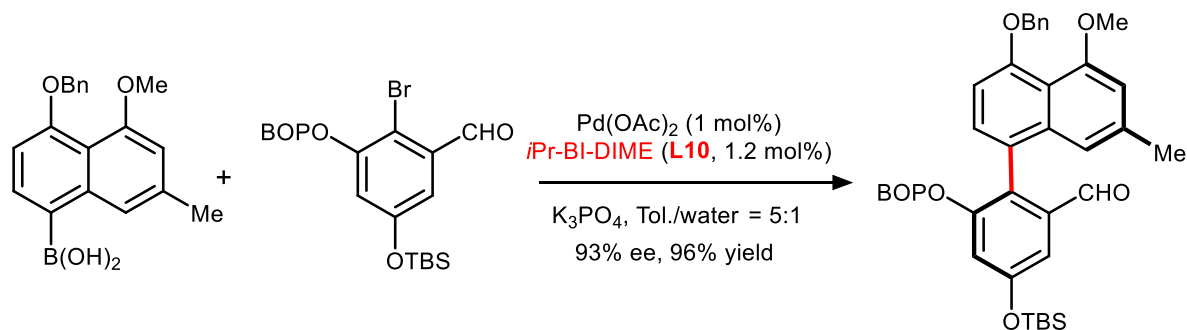
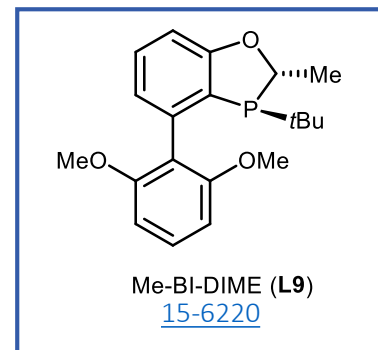
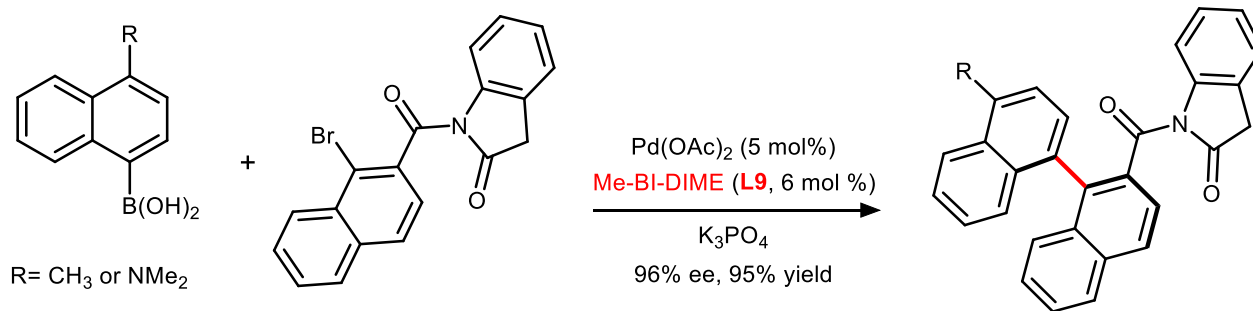
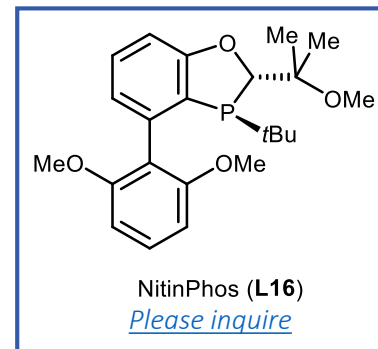
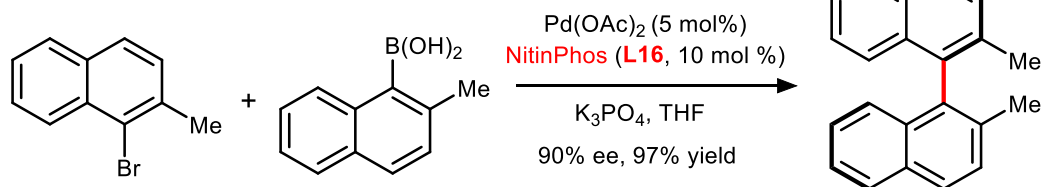
[15-6820](#)

- Sterically hindered conformer facilitates transmetallation and reductive elimination for highly substituted substrates

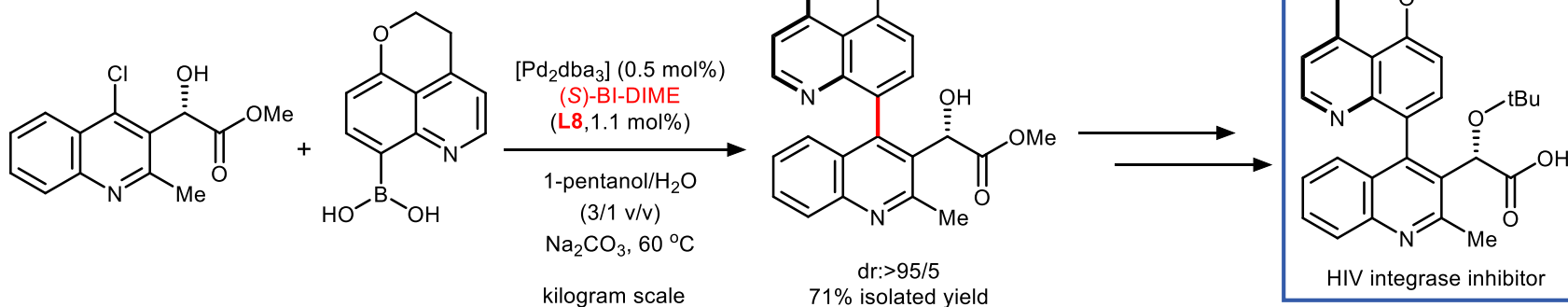
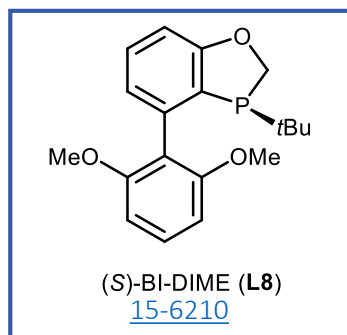
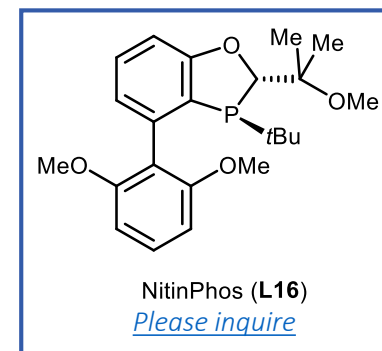
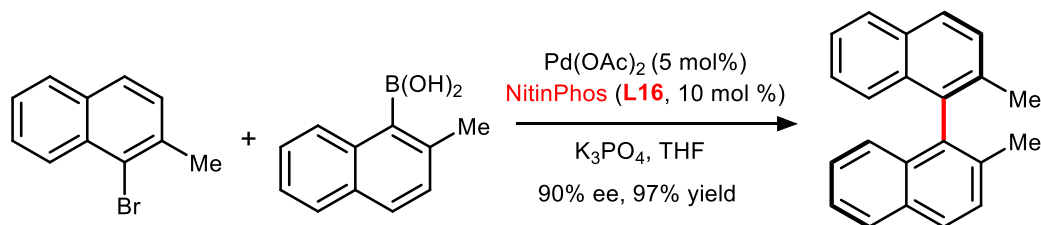


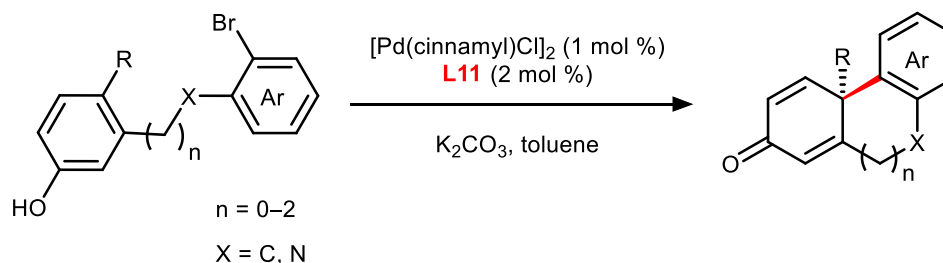
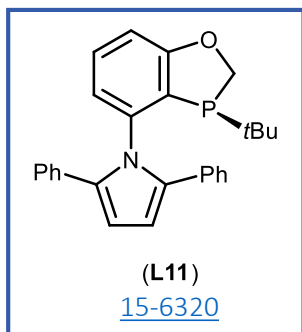
- Multiple conformers of S-Phos can make reductive elimination of hindered complexes challenging

- Sterically hindered conformer facilitates transmetallation and reductive elimination for highly substituted substrates



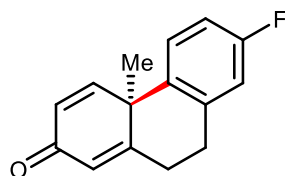
- Sterically hindered conformer facilitates transmetallation and reductive elimination for highly substituted substrates



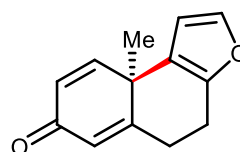


- Kinetically favored RE product

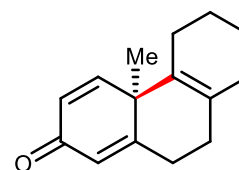
- Both **L11** and AntPhos are effective ligands



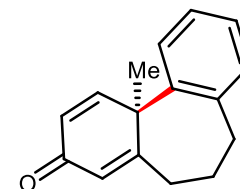
86% yield, 91% ee



60% yield, 99% ee
from vinyl triflate



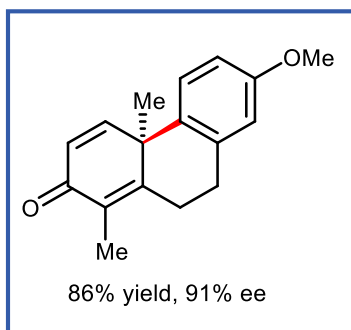
99% yield, 99% ee



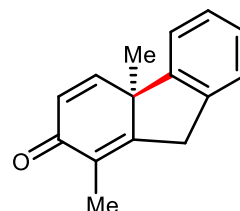
35% yield, 96% ee

- Common motif in steroids and terpenes

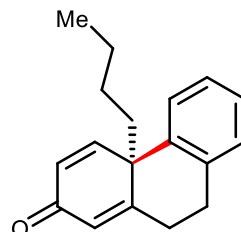
- Kaurene intermediate (4 steps)



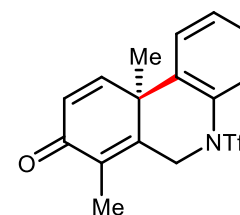
86% yield, 91% ee



95% yield, 83% ee

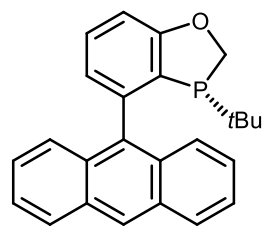


96% yield, 91% ee

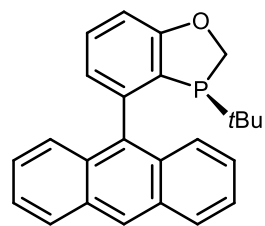
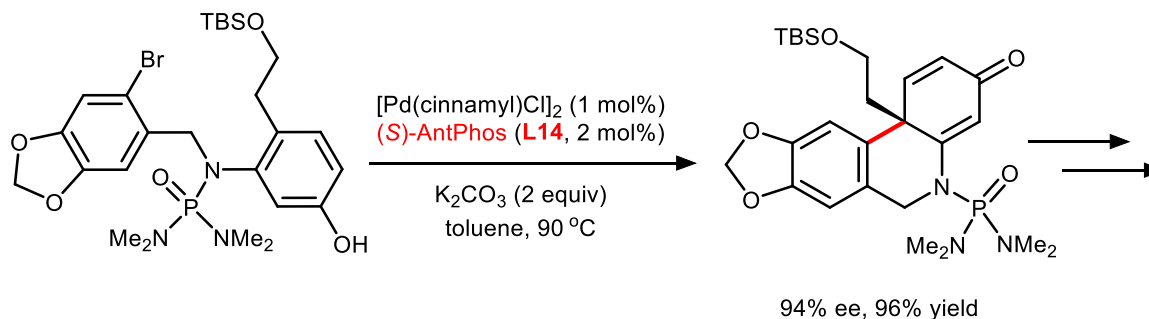
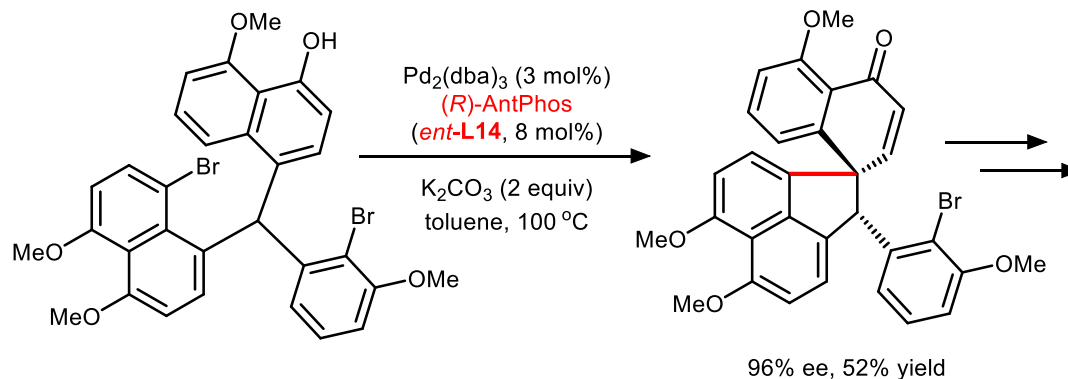


65% yield, 97% ee

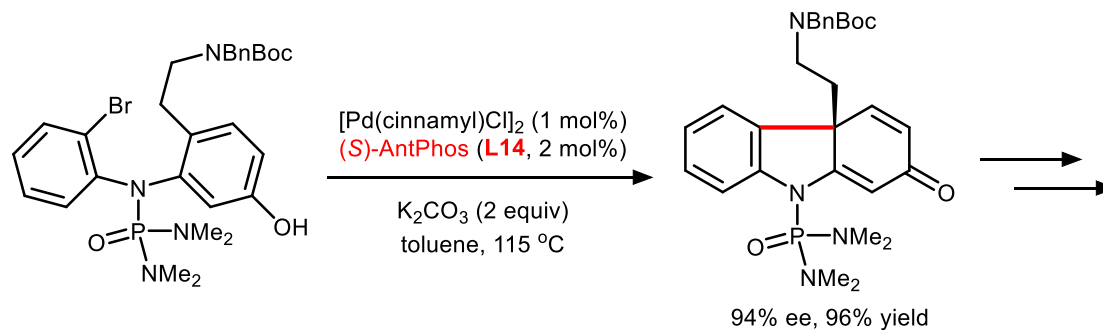
- Previously 14 steps via asymmetric Heck reaction

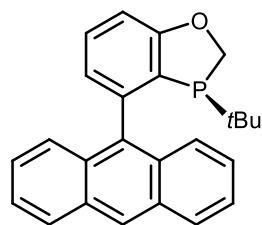


(*R*)-AntPhos (*ent*-**L14**)
15-1963

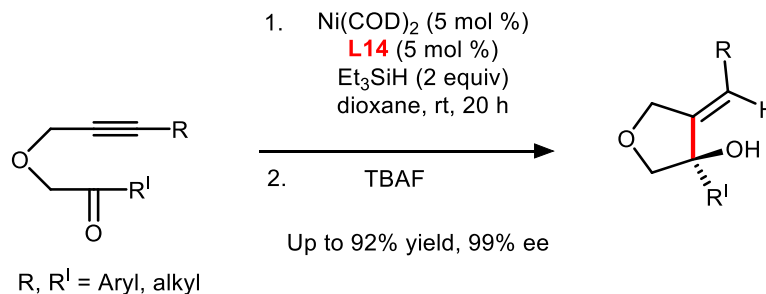


(*S*)-AntPhos (**L14**)
15-1967

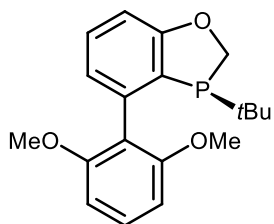




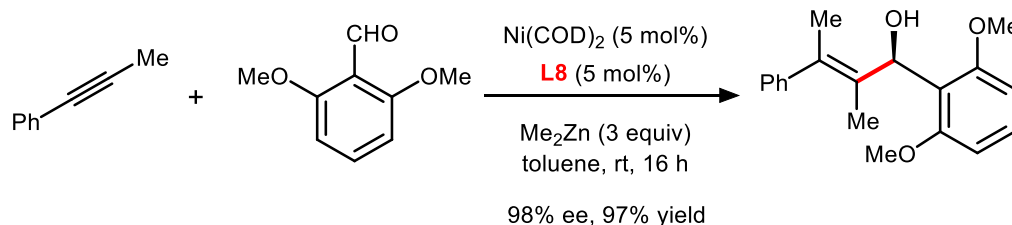
(S)-AntPhos (**L14**)
[15-1967](#)



- aldehyde/ketone coupling
- Yield with S-Phos: 98% (racemic)
- Monophosphines well-suited to Ni's smaller radius

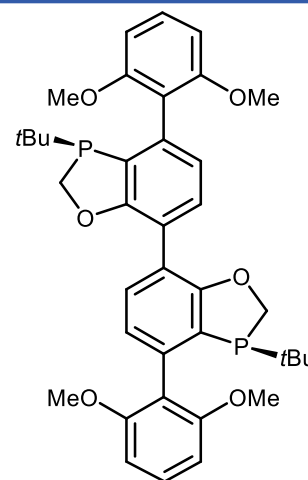
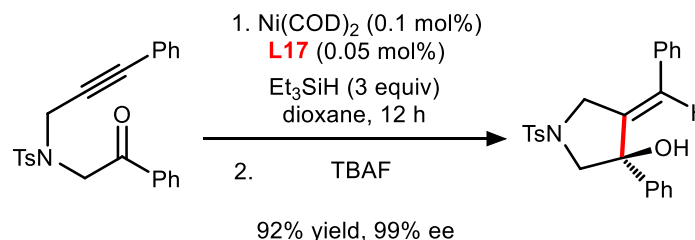


(S)-BI-DIME (**L8**)
[15-6210](#)

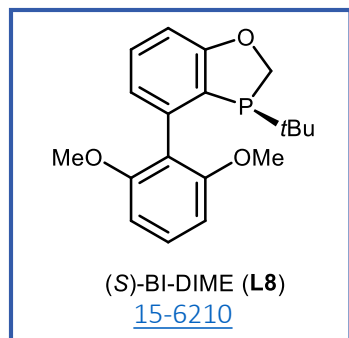


- High loading relative to Rh, Ir, etc

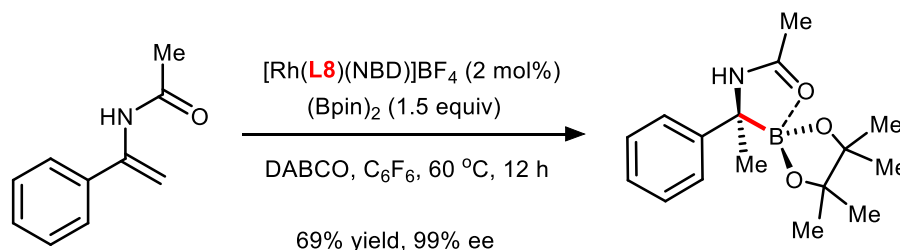
- Ligand dimer reduces entropy
- Increased stability towards C–H activation and ring opening
- 50-fold decrease in loading



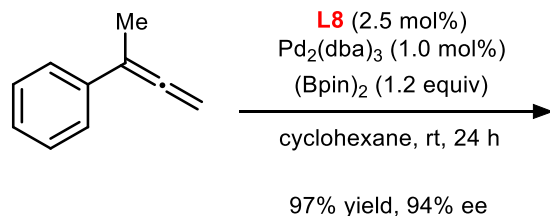
L17: (S,S)-DI-BIDIME]
[Please inquire](#)



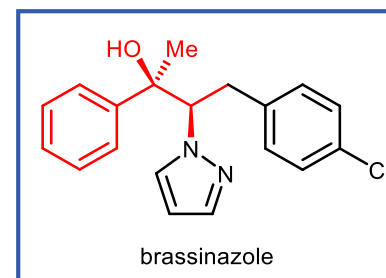
- Asymmetric hydroboration
- High Markovnikov selectivities
- Access to chiral α -amino tertiary boronic esters
- Compatible with a variety of aryl groups

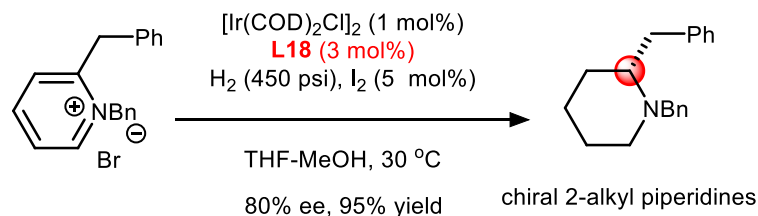
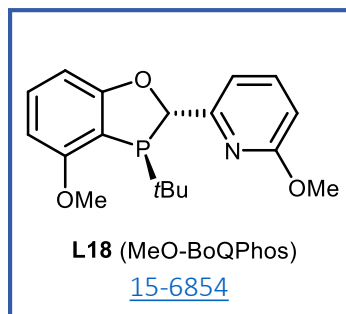


- Diboration of allenes

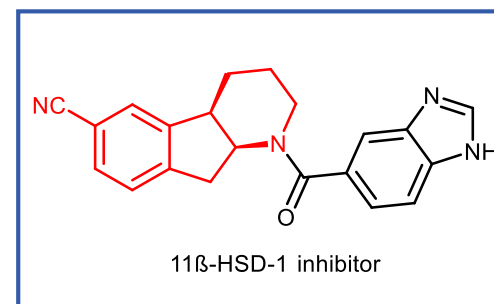
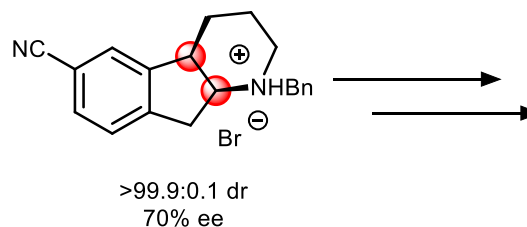
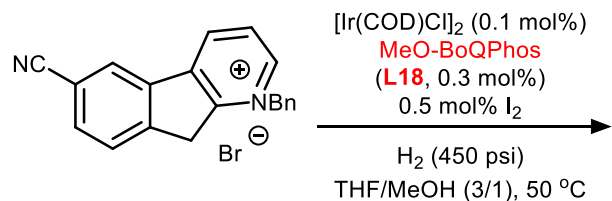


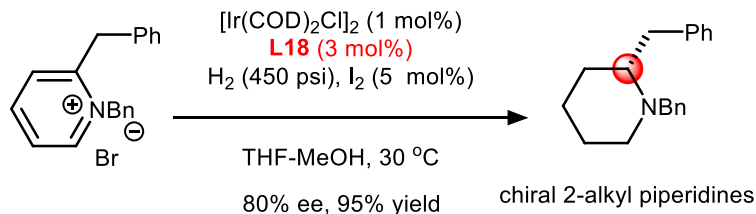
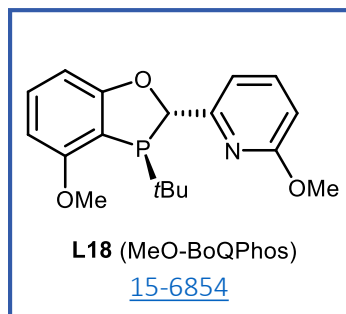
- First enantioselective synthesis of brassinazole



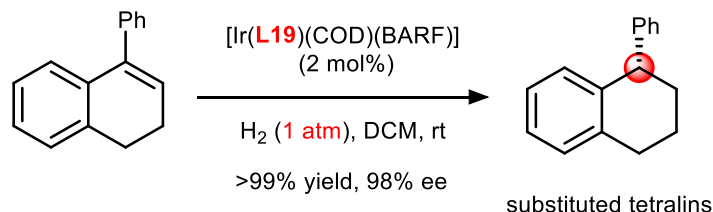
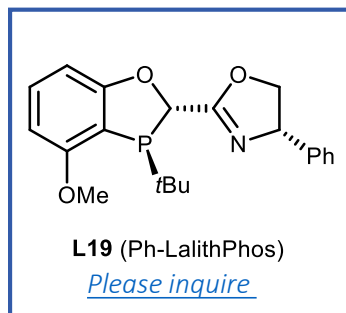


- Monophosphines with secondary interactions
- Asymmetric hydrogenation of pyridinium salts

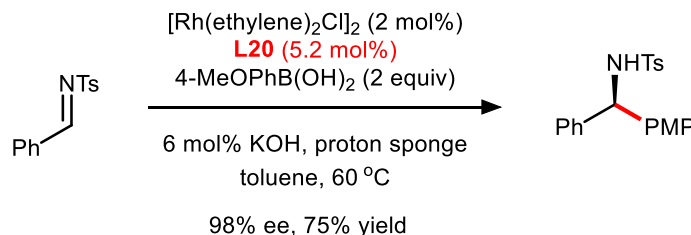
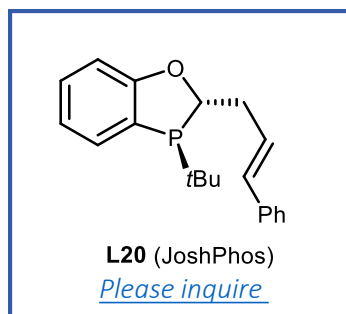




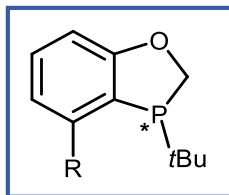
- Monophosphines with secondary interactions
- Asymmetric hydrogenation of pyridinium salts



- Asymmetric hydrogenation of dialins at low pressure
- Substrates with few directing groups



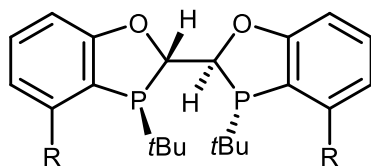
- Addition of boronic acids to imine electrophiles
- P, π -hybrid ligands



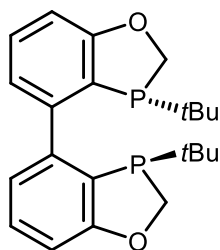
- Benzooxaphosphole



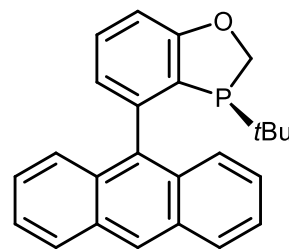
- Air stable, rigid P-chiral ligand framework
- High levels of enantioinduction
- Highly tunable, wide variety of ligands
- Broad synthetic applications in asymmetric catalysis



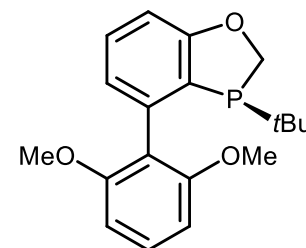
BIBOP, WingPhos



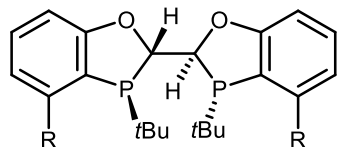
R-BABIBOP



AntPhos

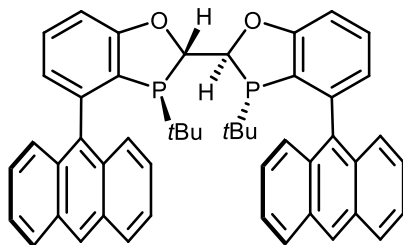


BI-DIME



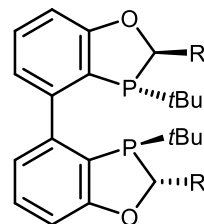
BIBOP (L1-4)

L1, R = H: [15-6270](#); [15-6275](#) (ent)
 L2, R = OMe: [15-6255](#); [15-6250](#) (ent)
 L3, R = Me: ([Please inquire](#))
 L4, R = Ph: [15-6265](#); [15-6260](#) (ent)



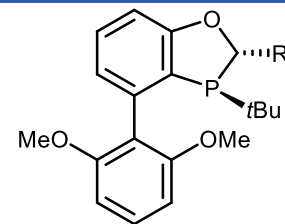
(S,S,S,S)-WingPhos (L5)

L5: [15-1975](#); [15-1970](#) (ent)



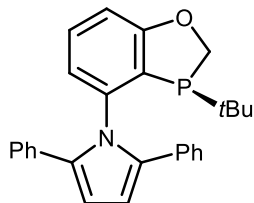
R-BABIBOP

L6, R = H: [15-6415](#); [15-6410](#) (ent)
 L7, R = iPr: [15-6445](#); [15-6430](#) (ent)



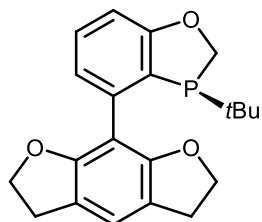
(S)-BI-DIME (L8)

L8, R = H: [15-6210](#); [15-6211](#) (ent)
 L9, R = Me: [15-6220](#); [15-6225](#) (ent)
 L10, R = iPr: [15-6230](#); [15-6235](#) (ent)



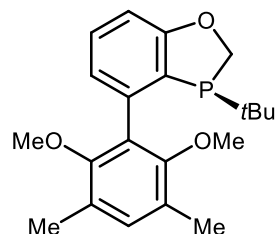
L11

L5: [15-6320](#); [15-6315](#) (ent)



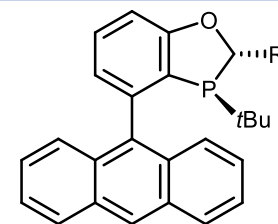
L12

L12: [15-6295](#); [15-6290](#) (ent)



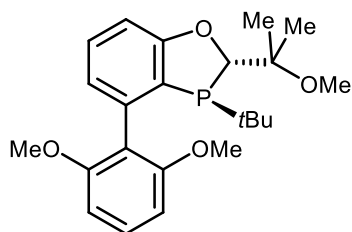
L13

L13: [15-6840](#); [15-6834](#) (ent)



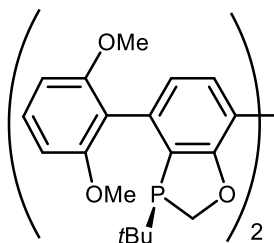
(S)-AntPhos (L14)

L14, R = H: [15-1967](#); [15-1963](#) (ent)
 L15, R = iPr: [15-6820](#); [15-6818](#) (ent)



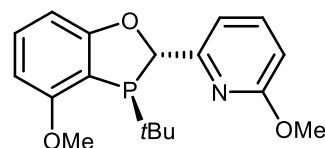
NitinPhos (L16)

L16: [Please inquire](#)



L17: (S,S)-DI-BIDIME]

L17: [Please inquire](#)



L18 (MeO-BoQPhos)

L18: [15-6854](#); [15-6860](#) (ent)
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