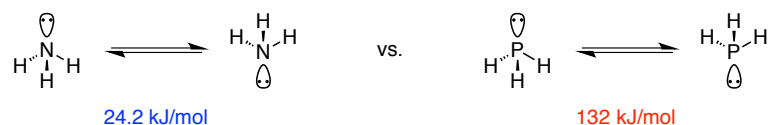


# P-Stereogenic Compounds

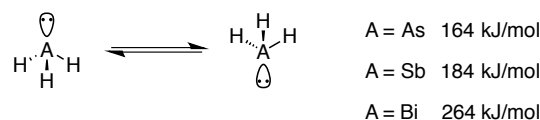
Brandon Rosen

29 March 2014

## Configurational Stability of P-Chiral Molecules

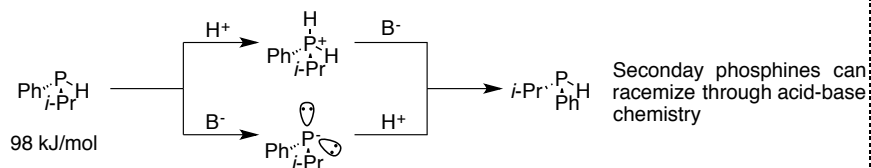
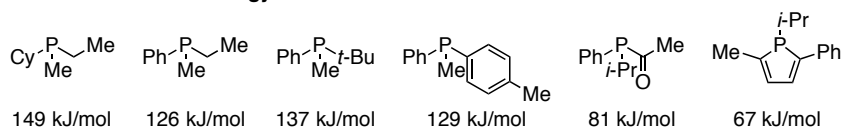


### Inversion Energy Barriers

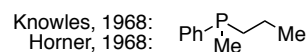
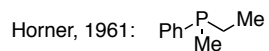
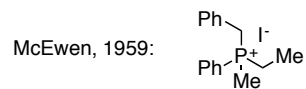
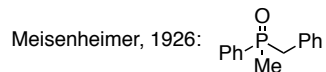
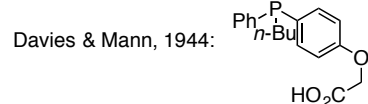
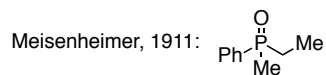


Schwerdtfeger, JACS **1992**, *96*, 6807

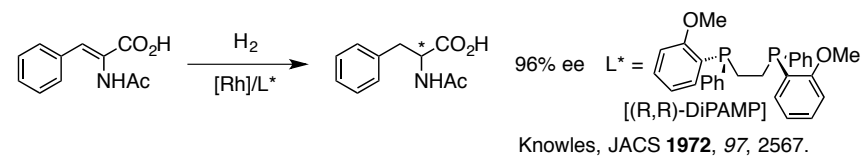
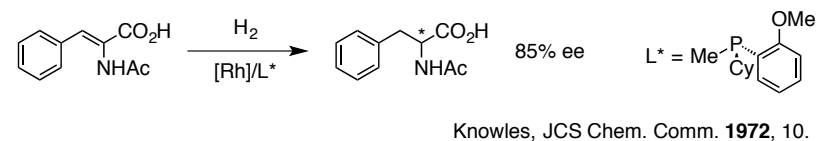
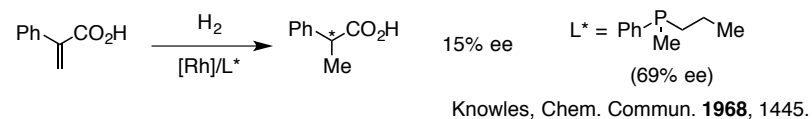
### Additional Inversion Energy Barriers



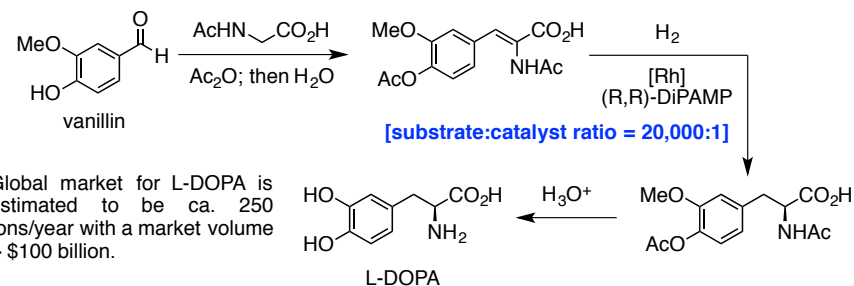
## Early Investigations into P-Chiral Molecules



## Asymmetric Hydrogenation



## Monsanto Synthesis of L-DOPA



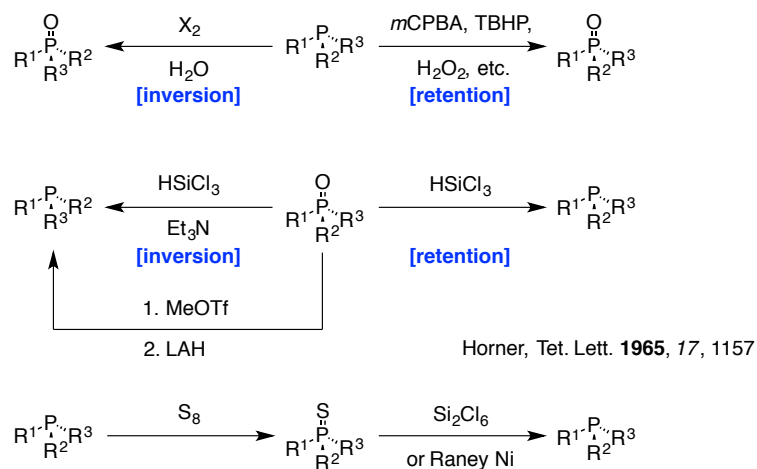
In 2001, William S. Knowles was awarded the Nobel Prize in Chemistry for his "work on chirally catalysed hydrogenation reactions".



"The inventive process is not clearly understood, but one factor that seems to be important is to have a heavy infusion of naivety."

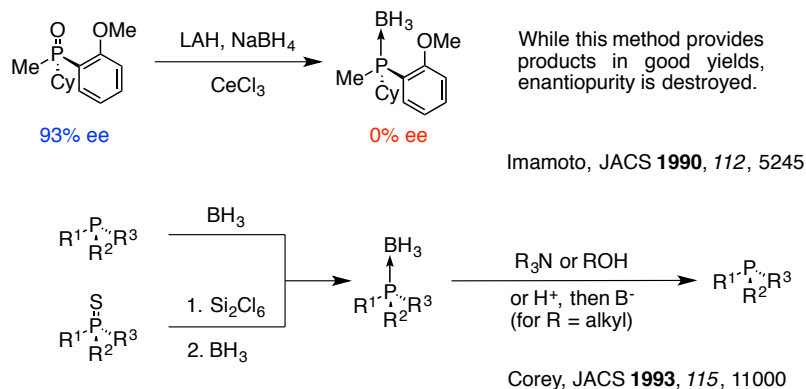
## Interconversions Between P-Chiral Molecules

## Phosphine Oxides and Phosphine Sulfides



## Phosphine Boranes

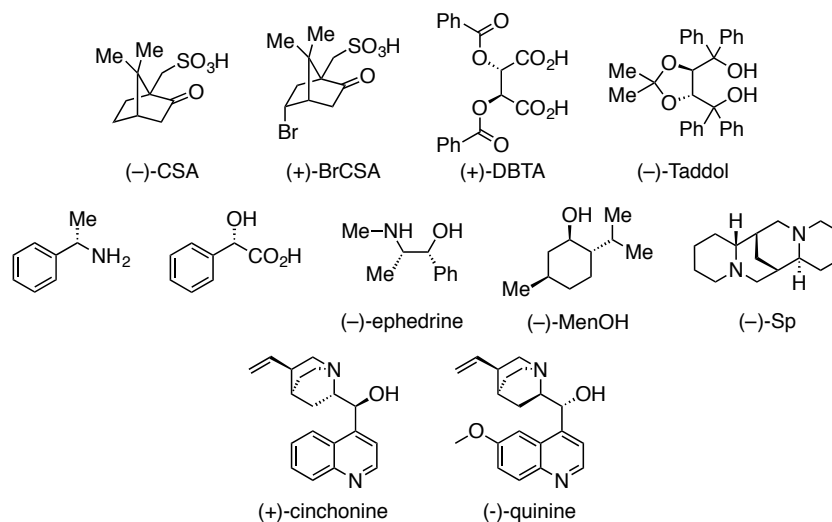
Phosphine-borane complexes are very stable and allow functionalization at phosphorus or an attached methyl group, as well as stabilizing alkyl phosphines.



Many phosphine-borane complexes can be used directly as ligands in organometallic reactions. See Jugé, JOMC, **2001**, 624, 333.

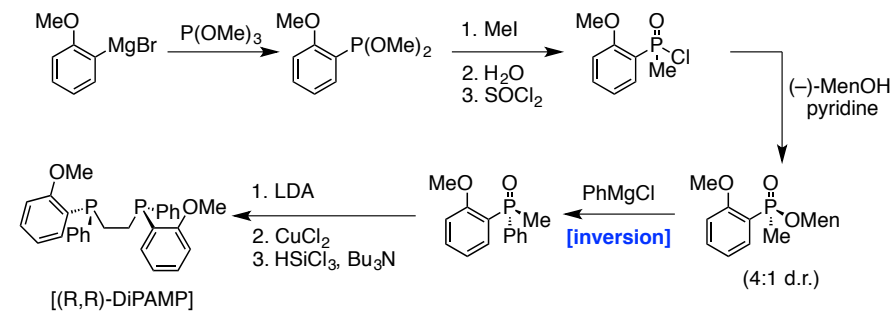
## Resolution of Racemic/Diastereomeric Mixtures

## Chiral Auxiliaries for Resolution of Phosphine Oxides/Phosphonium Salts

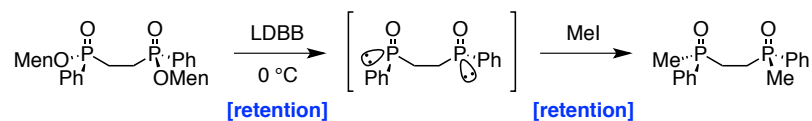


## Resolution of Menthylphosphinates

The use of menthyl phosphinates as a method for the synthesis of optically active phosphines was first reported in 1967: Mislow JACS **1967**, 89, 4784 and JACS **1968**, 90, 4842.



## Resolution of Menthylphosphinates

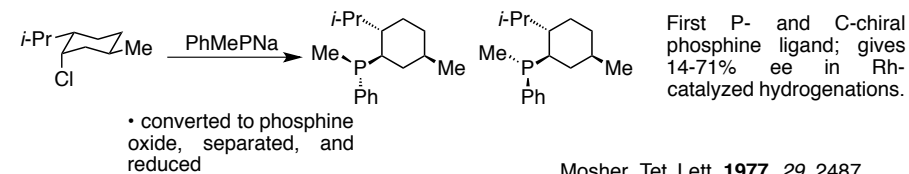
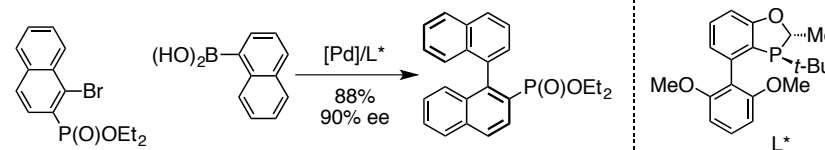
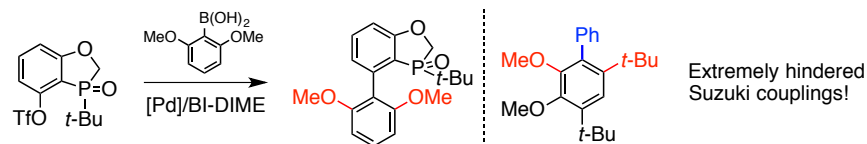
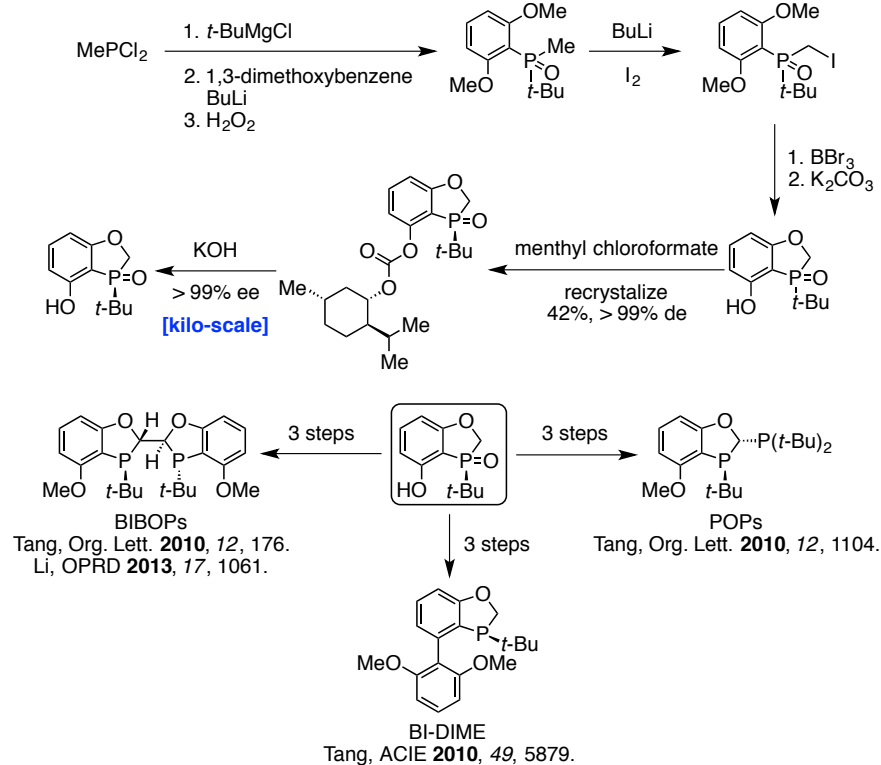
Imamoto, Tet. Lett. **1991**, 32, 3375

## Resolution of Menthylphosphinite Borane Complexes

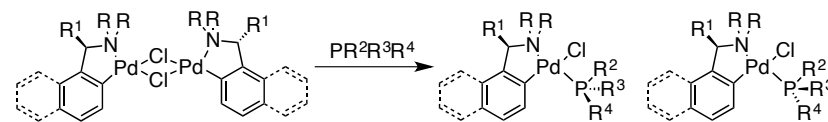
Menthylphosphinite borane complexes react analogously to menthylphosphinates. While Grignard reagents are typically employed for functionalization of menthylphosphinates, organolithiums are preferred for menthylphosphinite boranes.

For reduction of the menthyl group, LiNap or Li/NH<sub>3</sub> is preferred.

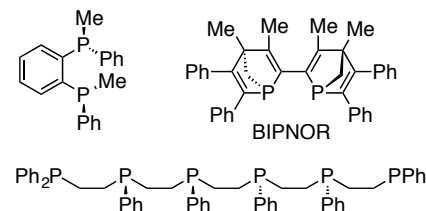
## Other Methods Based on Menthol Derivatives

Mosher, Tet. Lett. **1977**, 29, 2487.

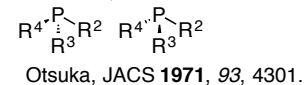
## Resolution with Cyclometallated Pd Complexes



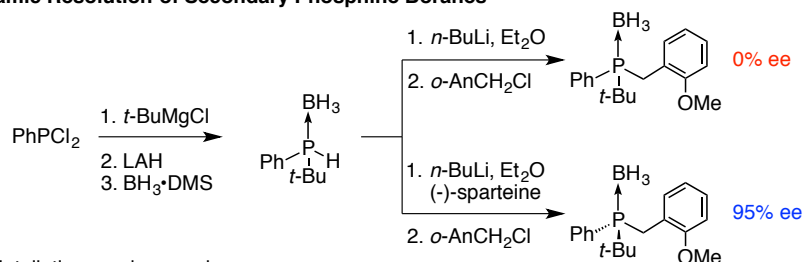
Examples of P-stereogenic phosphines resolved in this manner:



1. separate  
2. dppe

Otsuka, JACS **1971**, 93, 4301.

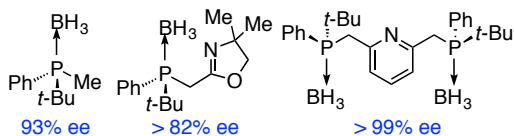
## Dynamic Resolution of Secondary Phosphine Boranes



• Metallation and quench occur rapidly at  $-78^\circ\text{C}$ , but equilibration at room temp is required; equilibration at  $0^\circ\text{C}$  results in product with 35% ee

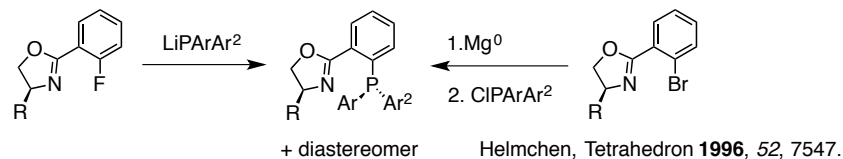
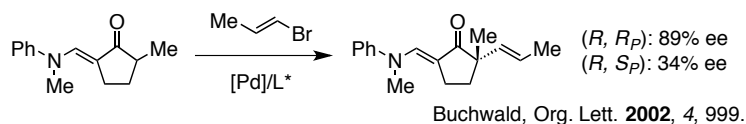
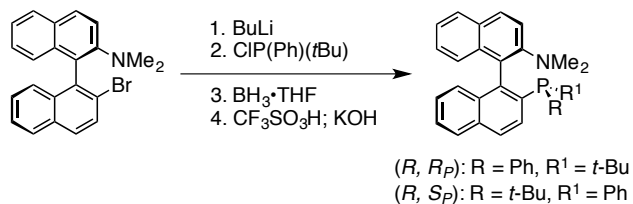
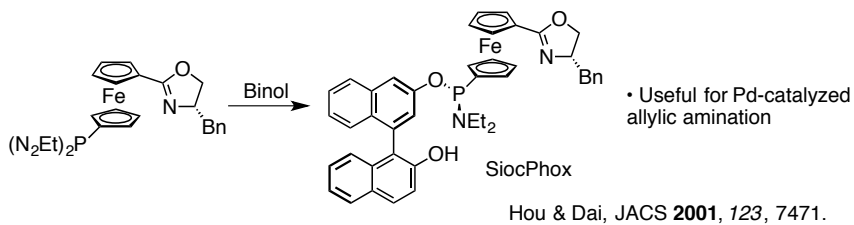
• Use of THF results in completely unselective quench

• Generally limited to  $\text{P}(\text{BH}_3)(\text{Ph})(t\text{-Bu})$



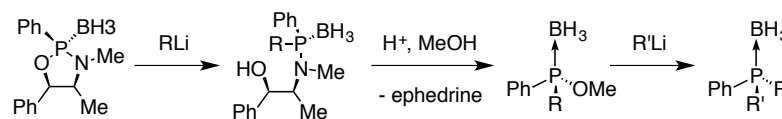
Livinghouse, JACS **1997**, 120, 5116.

## Other Chiral Backbones



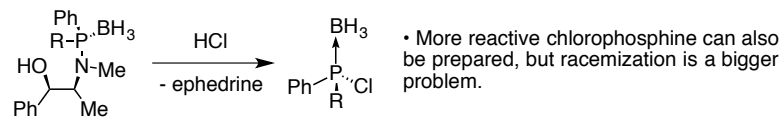
## P-Stereogenic Compounds Derived From Heterocycles

## Jugé's Method



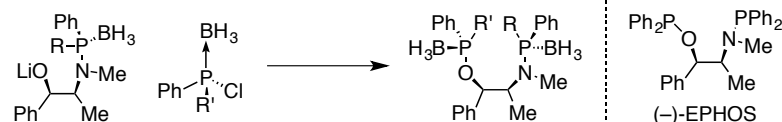
• Modular nature of this route allows synthesis of enantiomers with ease

Jugé, Tet. Lett. **1970**, 31, 6357.



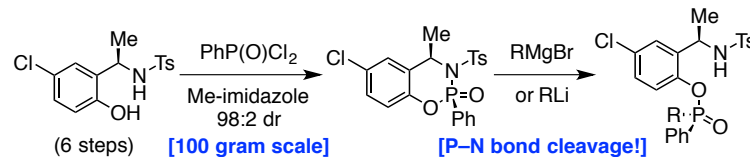
Jugé, Tetrahedron: Asym. **2000**, 11, 3939.

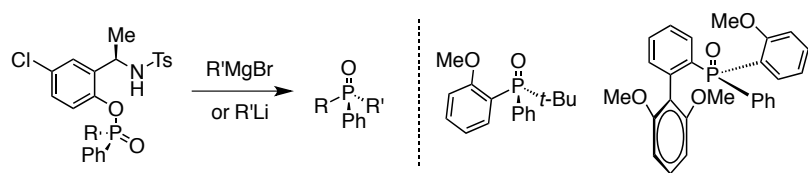
## Preparation of P-Stereogenic AMPP Ligands:



Jugé, Tetrahedron: Asym. **1999**, 10, 4729.

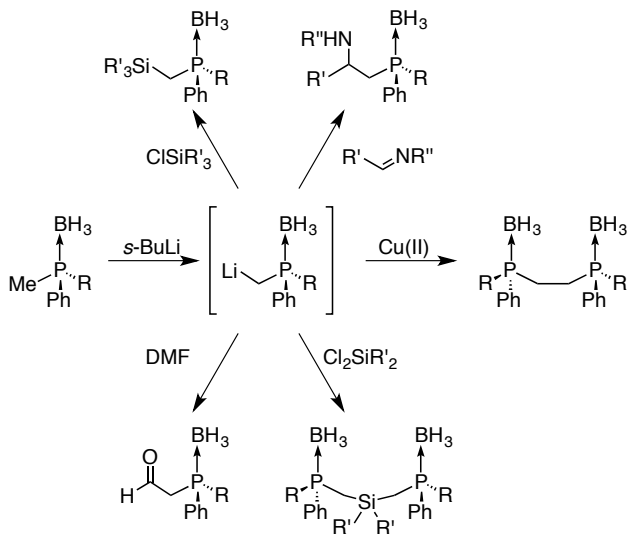
## Boehringer Ingelheim Modification



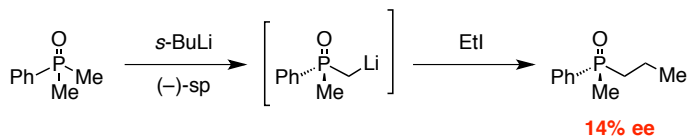
Han, JACS **2013**, *135*, 2474.

• Phosphines prepared using Jugé's method and its variations are generally limited to Ph-substituted phosphines; trialkylphosphines are inaccessible.

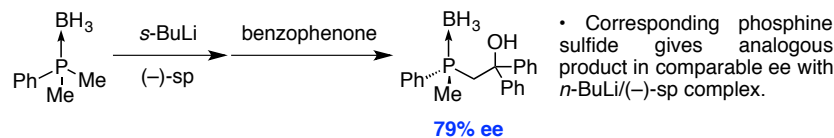
## Functionalization of Phosphines Prepared Using Jugé's Method



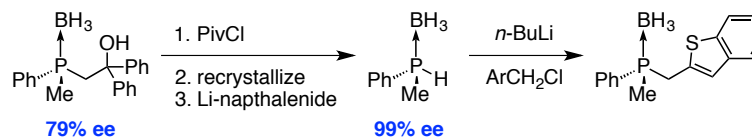
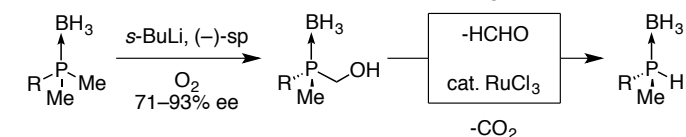
## P-Stereogenic Compounds By Enantioselective Deprotonation

Raston & White, J. Chem. Soc. Dalton Trans. **1989**, 105.

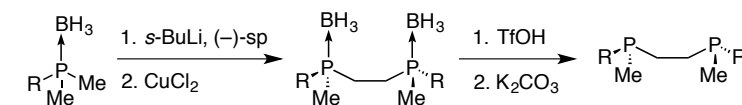
## Deprotonation of Dimethylphosphine Derivatives



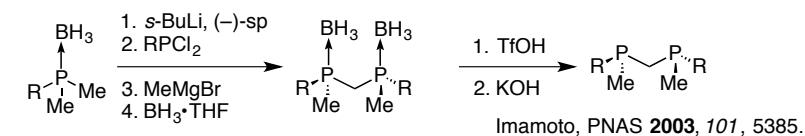
• Corresponding phosphine sulfide gives analogous product in comparable ee with *n*-BuLi/(-)-sp complex.

Evans, JACS **1995**, *117*, 9075.Livinghouse, JOC **2001**, *66*, 1514.Imamoto, JOC **2000**, *65*, 4185.

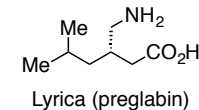
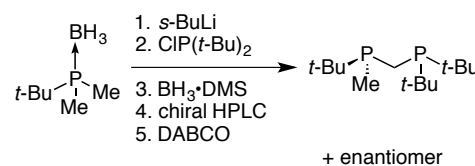
**BisP\* ligands:** R = *t*-Bu, Et<sub>3</sub>C, 1-adamantyl, cyclopentyl, cyclohexyl, 1-methylcyclohexyl.



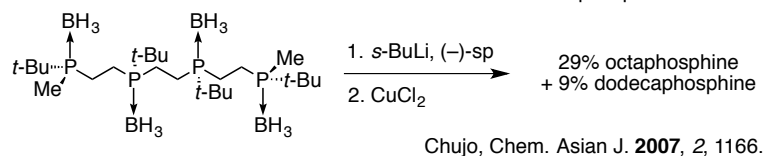
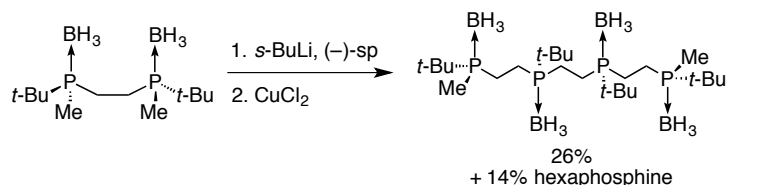
**MiniPHOS ligands:** R = *t*-Bu, *i*-Pr, cyclohexyl, Ph.

Imamoto, PNAS **2003**, *101*, 5385.

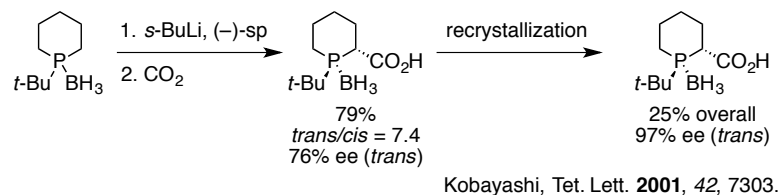
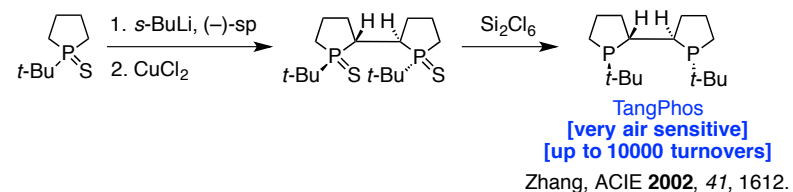
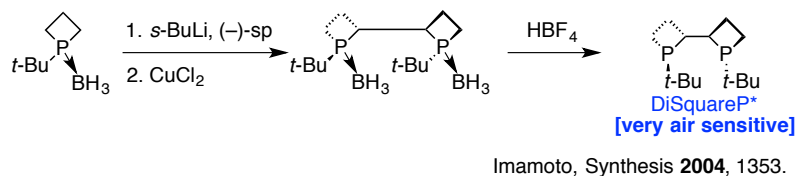
## Trichickenfootphos

Hoge, JACS **2004**, *126*, 5966.

## Optically Active Oligophosphines or: Just Because We Can



## Deprotonation of Cyclic Phosphine Derivatives



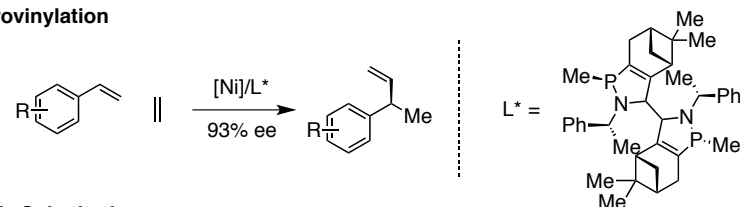
"This is an interesting result because up to now the six-membered phosphinane ring has been rarely present in ligands for enantioselective catalysis, especially compared to the very common five-membered phospholane counterpart. Therefore, further developments in this area should be seen in the near future."

"Although the desymmetrisation of tert-butyl dimethylphosphine borane and the analogous sulfide has been widely used, the application of the same chemistry to other substrates, especially cyclic phosphines, is still relatively undeveloped and further advances are likely to appear."

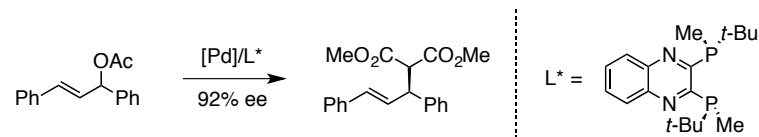
"Because this method relies almost entirely on (-)-sparteine, the use of other (+)-sparteine variants or other chirality inducers merits exploration."

## Miscellaneous Reactions Employing P-Stereogenic Ligands

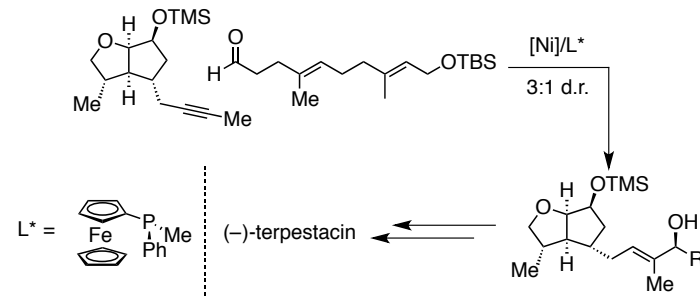
## Hydrovinylation



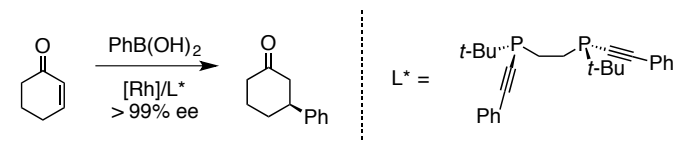
## Allylic Substitution



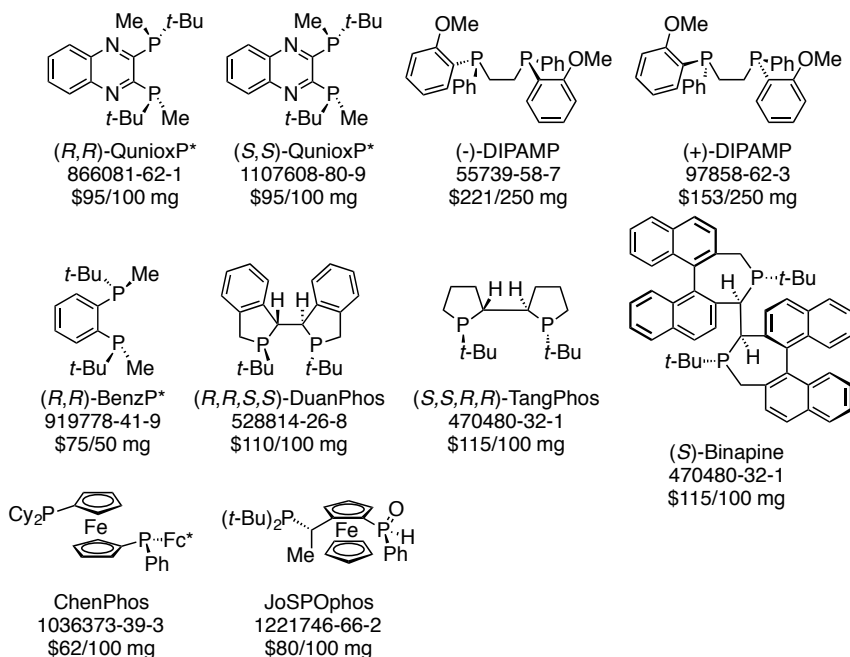
## Reductive Alkyne-Aldehyde Coupling



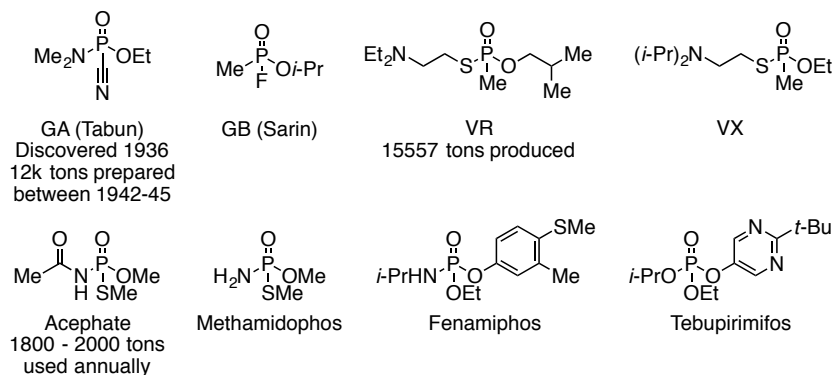
## Rh-Catalyzed Conjugate Additions



## Some Commercially Available P-Stereogenic Ligands



## Some (Very Dangerous) P-Stereogenic Compounds



## Some Medicinally Relevant P-Stereogenic Compounds

