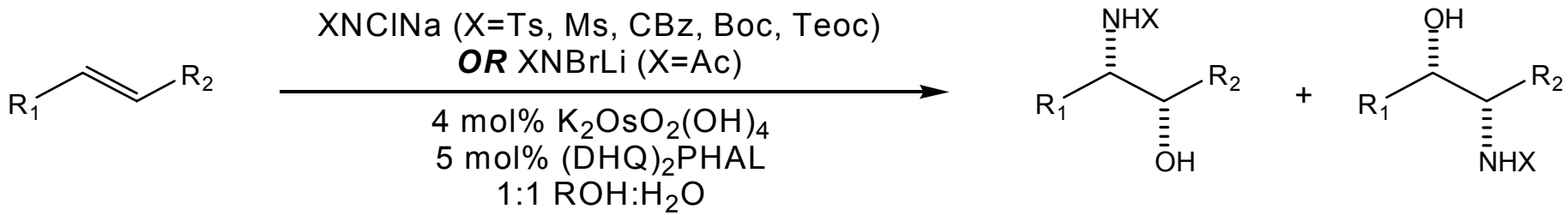
Asymmetric Aminohydroxylation of Alkenes



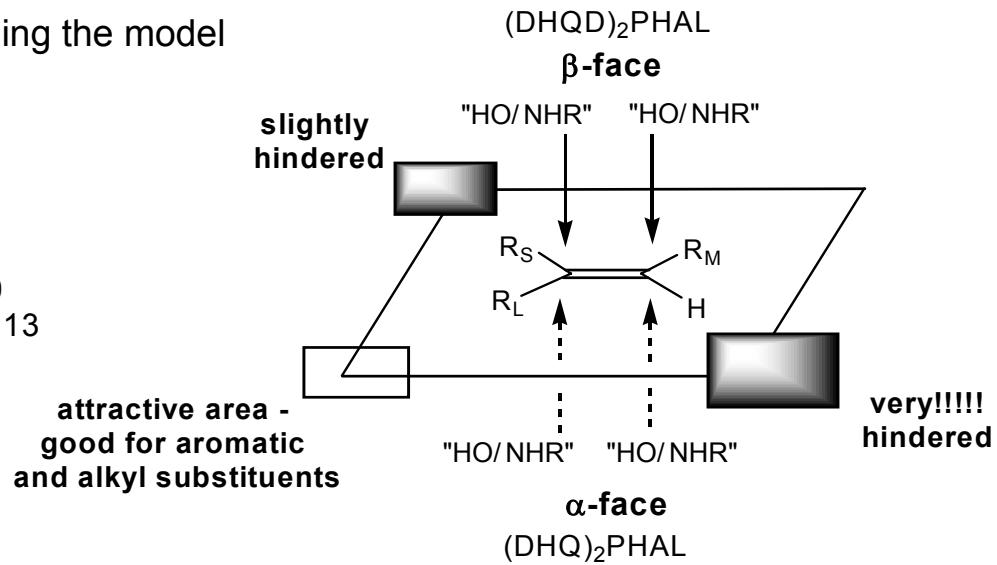
• originally developed with chloramine T (Na^+ClNTs^-), as for a racemic protocol developed by Sharpless in the 1980s 1980s

• found that the reaction works better with smaller N-substituents, (eg $MeSO_2$-), and even better still with salts of N-halocarbamates (NC(O)OR; ease of deprotection!) or N-haloamides

• regiocontrol is a problem, particularly with electronically unbiased alkene substituents

• in most respects the reaction is similar to the AD, including the model for asymmetric induction
(note that, for a given olefin, the HO/NHR are delivered to the same face in both regioisomeric products)

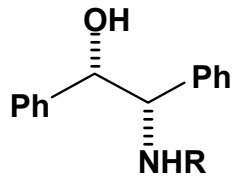
chloramine-T: *Angew.* ., **1996**, *35*, 451
chloramine-M: *Angew. Chem., Int. Ed. Engl.*, **1996**, *35,* 2810
halocarbamates: *Angew. Chem., Int. Ed. Engl.*, **1996**, *35*, 2813
haloamides: *Org. Lett.*, **2000**, *2*, 2221



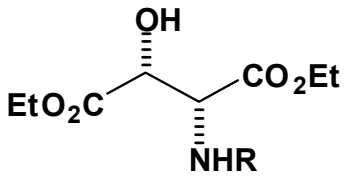
Scope of the asymmetric aminohydroxylation

(all reactions shown carried out with $(DHQ)_2$-PHAL; figure shown is *ee*)

Symmetrical trans-alkenes:

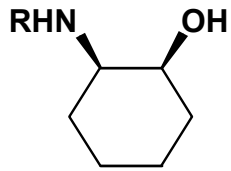


R = Ts	62
R = Ms	75
R = Cbz	91
R = Ac	94



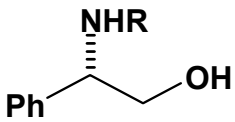
R = Ts	77
R = Ms	95
R = Cbz	84
R = Ac	- -

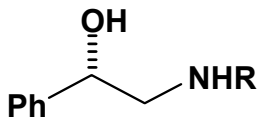
Symmetrical cis-alkenes:



R = Ts	45
R = Ms	66
R = Cbz	63
R = Ac	- -

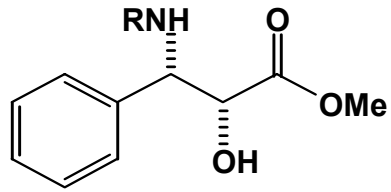
Styrenes:

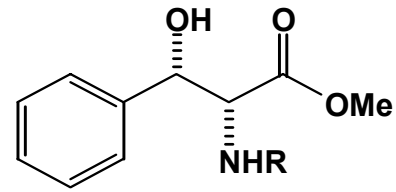




R = Ts	50	2 : 1
R = Ms	- -	- -
R = Cbz	93	1 : 1
R = Ac	88	1 : 6

Cinnamates (electronically distinguished):





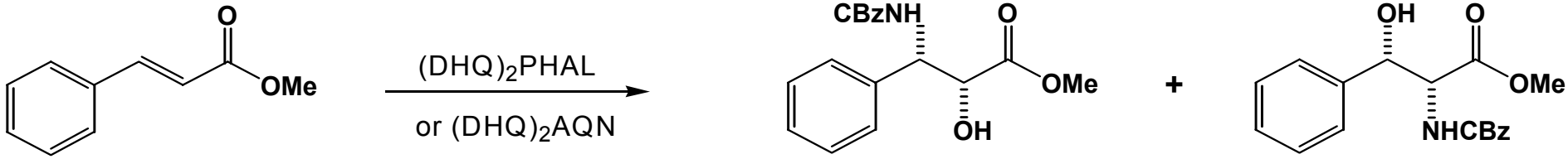
regiochemistry

R = Ts	81	5 : 1
R = Ms	95	9 : 1
R = Cbz	94	10 : 1
R = Ac*	99	20 : 1

* - ^{i}Pr ester

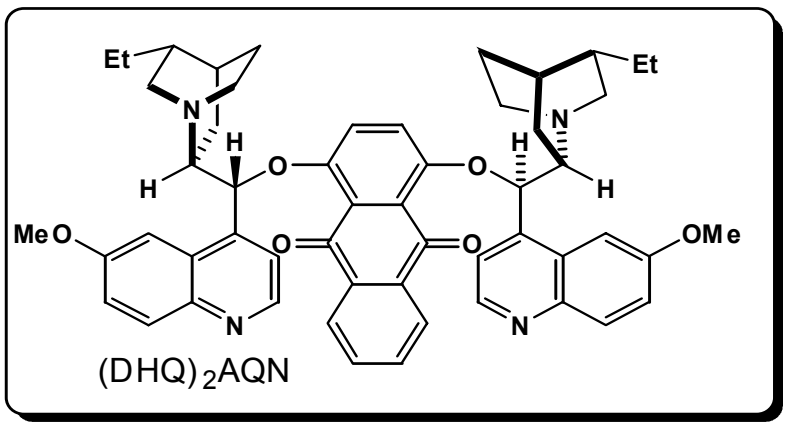
•

Regiochemical control by adjustment of aromatic linking group



$(DHQ)_2PHAL$	(94% *ee*)	>10 : 1
$(DHQ)_2AQN$		21 : 79 (95% *ee*)

$(DHQ)_2PHAL$	(93% *ee*)	ca. 1 : 1
$(DHQ)_2AQN$		1 : 13 (88% *ee*)



Tetrahedron Lett., **1998**, *39*, 2507;
Angew. Chem., Int. Ed. Engl., **1997**, *36*, 1483

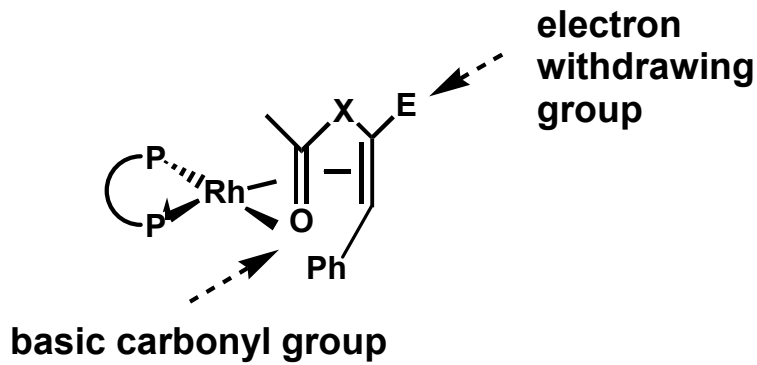
Asymmetric Hydrogenation of Alkenes

- H_2 is cheap and reduction is atom efficient! Can generate two asymmetric centres simultaneously

- Homogeneous catalysts based on Rh (I) or Ru (II) with chiral phosphine ligands

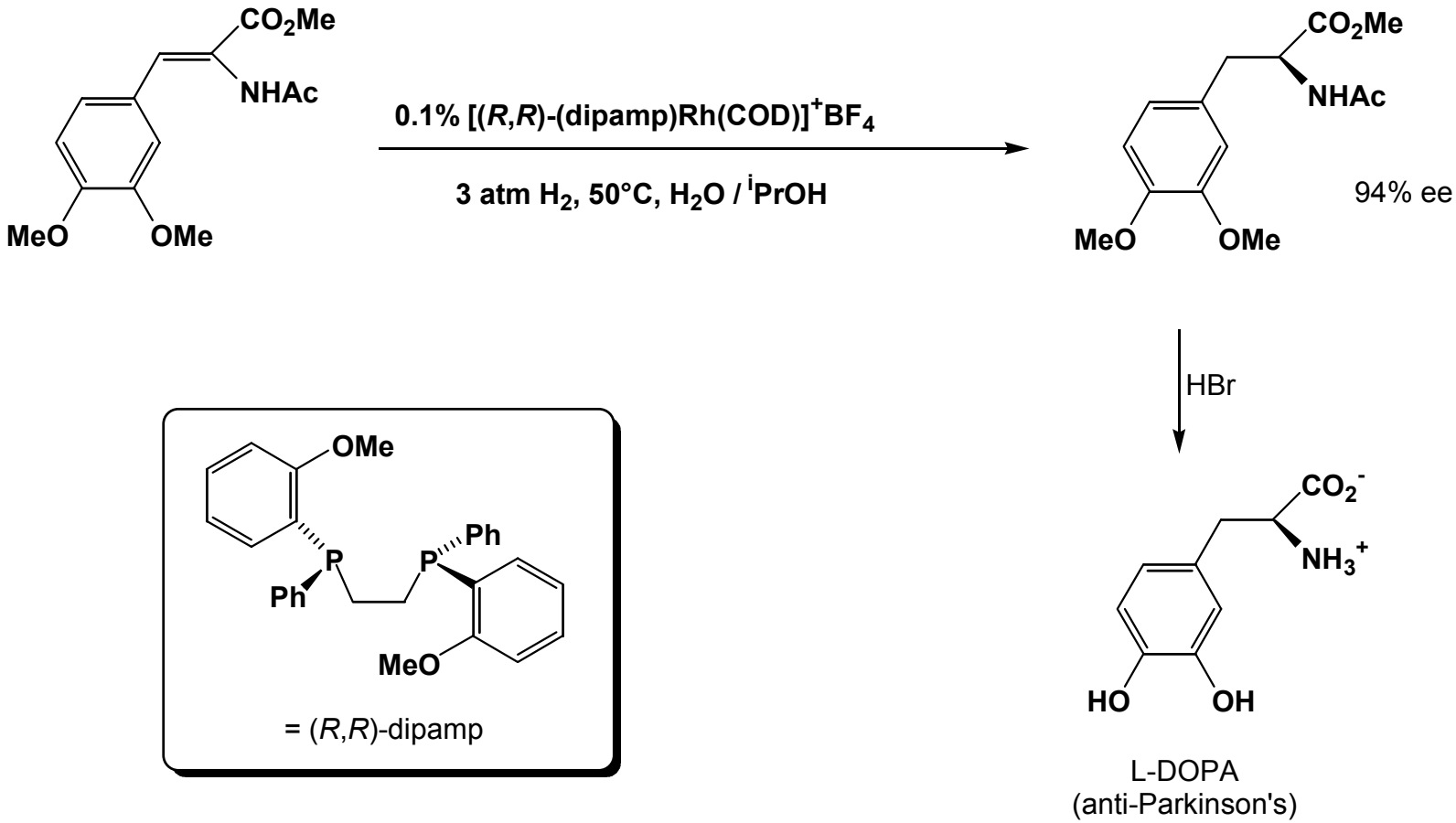
For Rh catalysts, general substrate structure:

e.g. Aminoacrylates (X=NH, E=CO_2R)



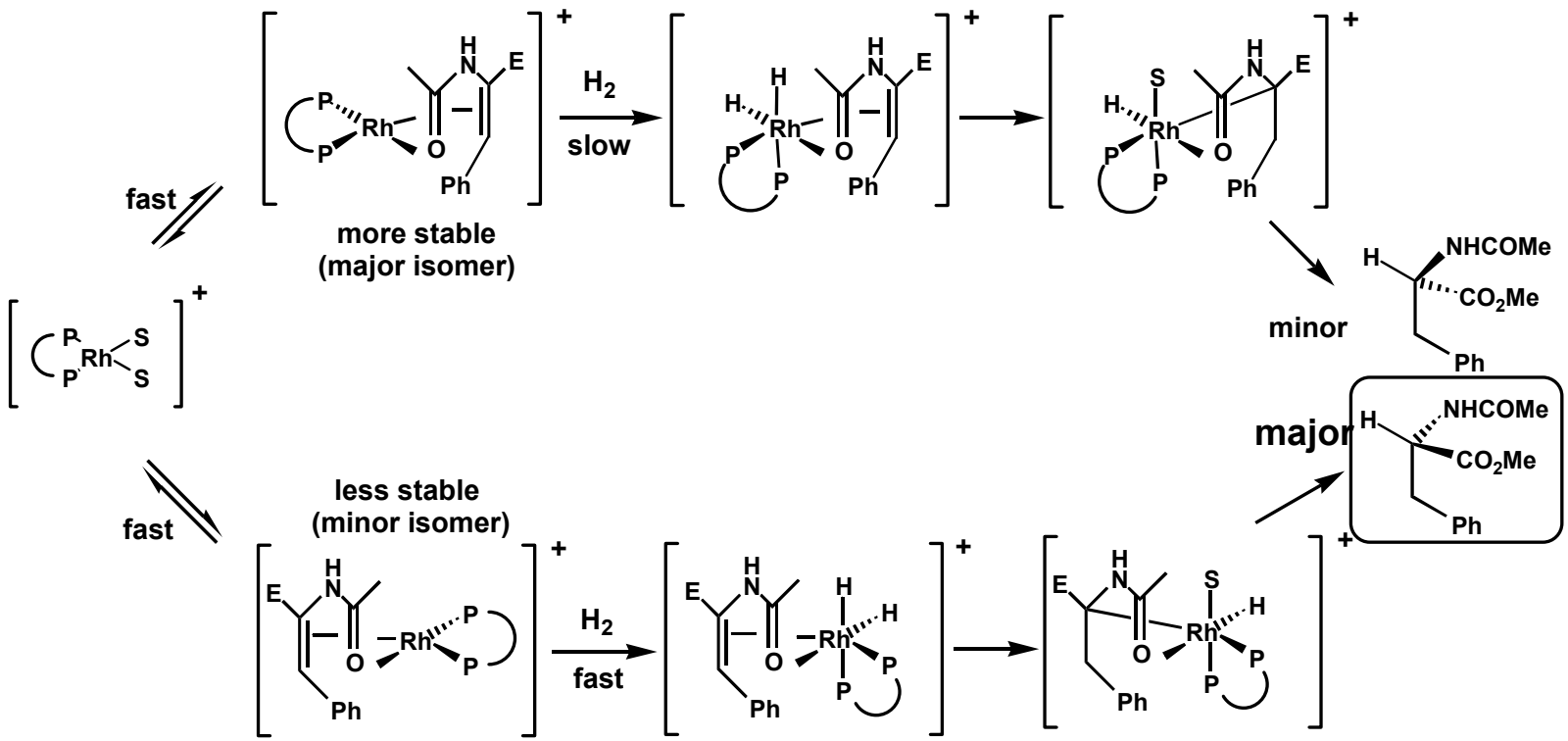
Also (usually Ru catalysts):
- Enamides
- Acrylic acids
- Allylic alcohols

Asymmetric Homogeneous Hydrogenation with Chiral Diphosphines: Monsanto synthesis of L-DOPA



- W.S. Knowles – share of 2001 Nobel Prize.
  Review of Monsanto work on L-DOPA synthesis: *J. Chem. Ed.*, **1986,** *63***,** 222
- First large-scale application of asymmetric hydrogenation, but the ligand lacks generality.

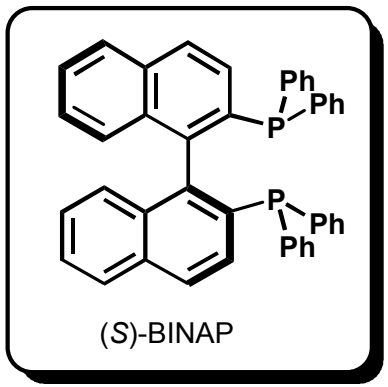
Mechanism of hydrogenation with Rh(I)dipamp



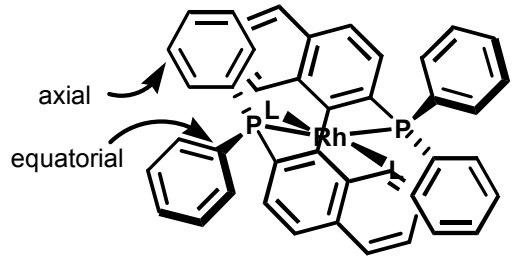
But…recent work suggests that this does not operate in all cases (*e.g.* electron-rich phosphines)…
See commentary in *Angew. Chem. Int. Ed.* 2001, *40*, 4611.

Rh(I)-BINAP Complexes

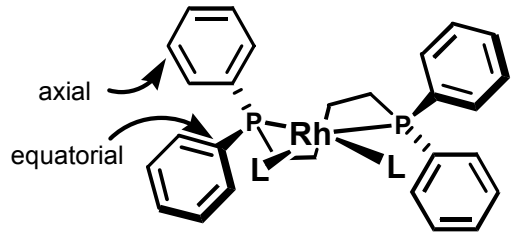
- **Axially chiral binaphthyl diphosphine ligands offer improved ee's and wider substrate tolerance in aminoacrylate reduction.**



(*S*)-BINAP

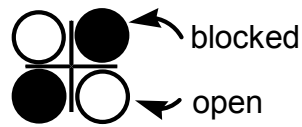


Simplified by removing backbone:



equatorially disposed phenyl groups block coordination in that 'quadrant'

Chiral enviromnment has 4 quadrants, two "blocked" and two "open":

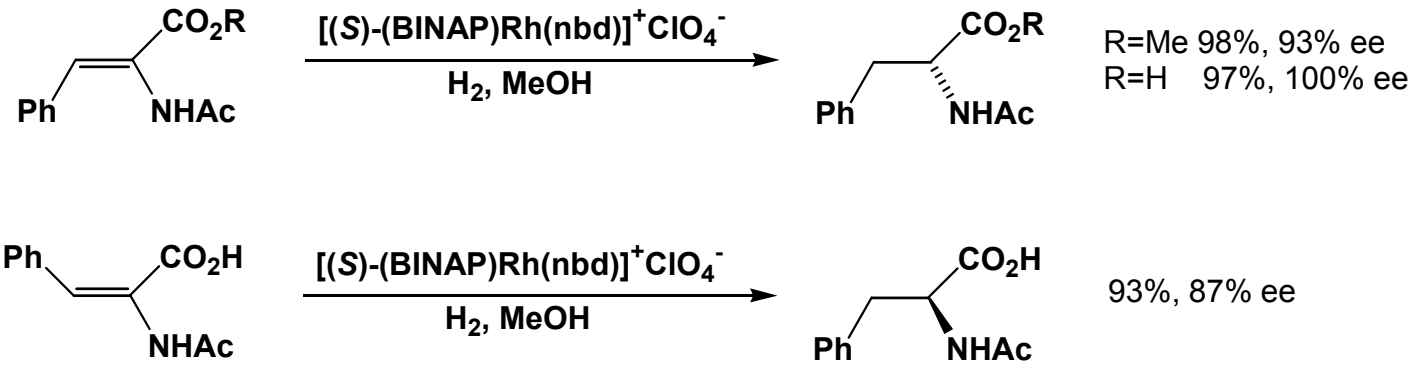


For alternative pictures, see Figure 8 in: Noyori, *J. Am. Chem. Soc.* **2002**, *124*, 6649

Rh(I)-BINAP-catalysed hydrogenation of aminoacrylates

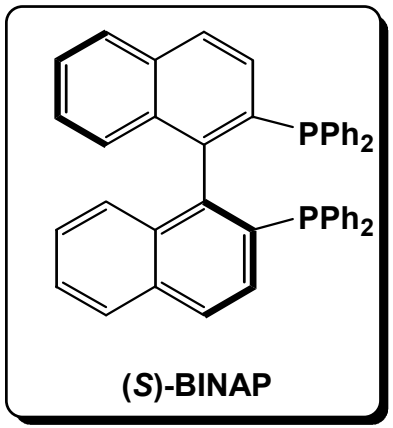
Noyori, *J. Am. Chem. Soc*. **1980**, *102*, 7932.

Note that for a given ligand enantiomer, the sense of asymmetric induction is determined by acrylate geometry (hence need geometrically pure starting materials):



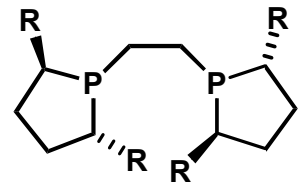
One drawback is that chirality transfer from chiral backbone to coordinating PPh_2 groups is not always efficient.

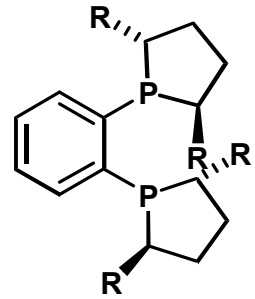
Also, no bis(diarylphosphine) ligand gives >99% ee for a range of acylaminoacrylates



Rhodium (I)-diphosphole complexes: electron rich, sterically demanding ligand systems

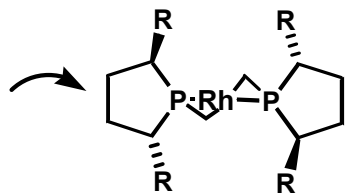
Review: Burk, *Acc. Chem. Res*. **2000**, *33*, 363

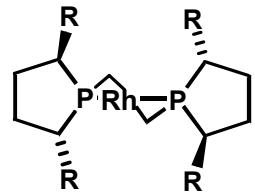
(*R*,*R*)-BPE 

R = Me, Et, Pr 

(*R,R*)-DuPHOS

- electron rich alkylphosphines allow increased back-bonding to alkene substrates - more tightly held
- flexible backbone in BPE leads to two ligand environments, one less selective than the other:

R groups held away from coordination sites 



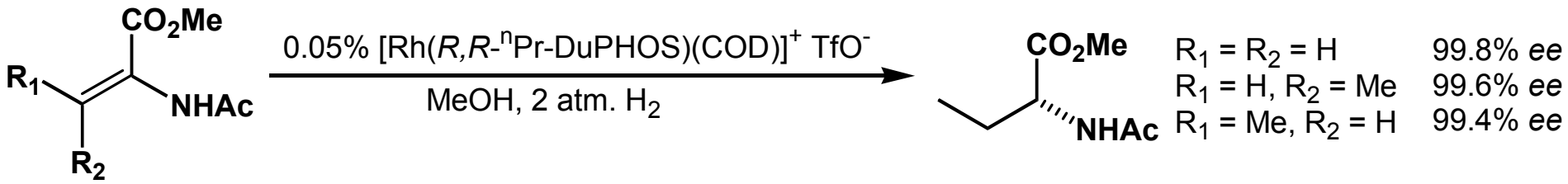
R groups held towards coordination sites

...so rigid DuPHOS generally better (although BPE can still be useful with VERY hindered substrates)

M. J. Burk, *J. Am. Chem. Soc*., **1993**, *115*, 10125

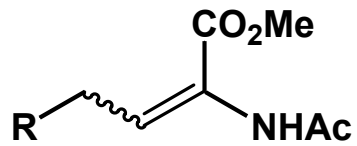
DuPHOS and BPE are outstanding ligands for Rh catalysed hydrogenation of aminoacrylates

- unlike BINAP, the sense of enantioselectivity is independent of acrylamide geometry - mixtures can be used!



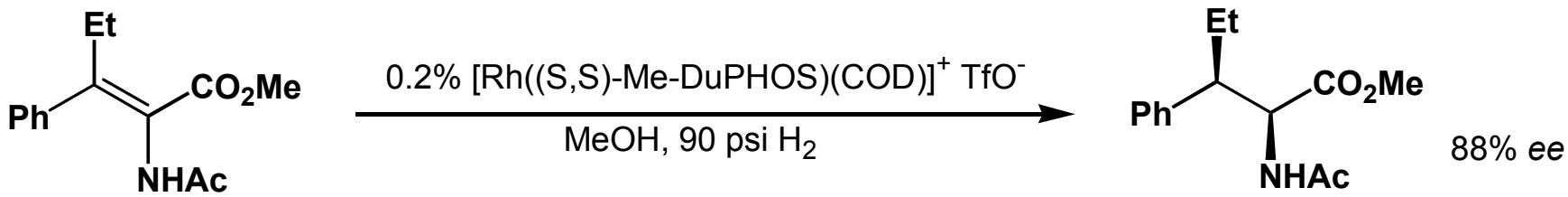
- also works for N-Cbz aminoacrylates - direct access to usefully protected amino acids

- very substrate tolerant - the following all give >99% *ee* with Et-DuPHOS



R = H, Me, Et, i-Pr, Ph, 1-naph, 2-naph, 2-thiophenyl, ferrocenyl, 4-(X)-Ph, 3-(X)-Ph, 3,5-di(X)-Ph (X = F, Br, OMe, CF_3)

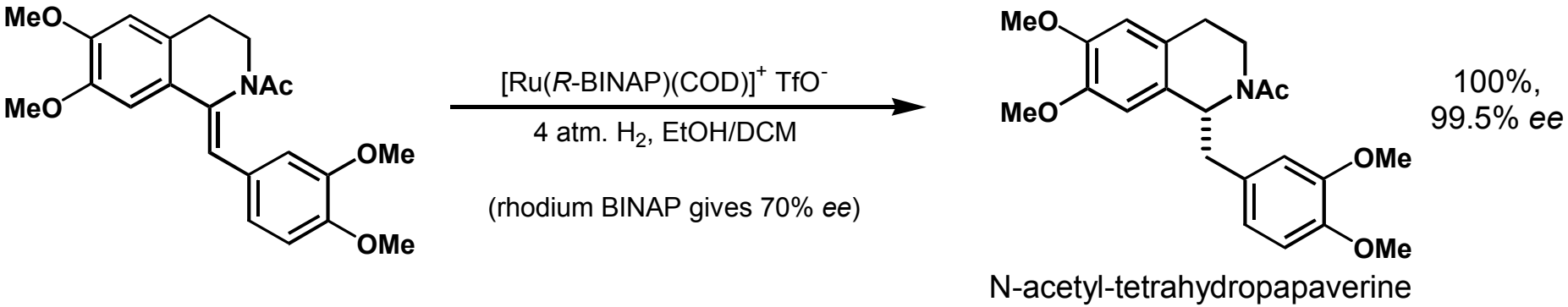
- even works for tetrasubstituted aminoacrylates - other ligands give <70% *ee* and are slow



M. J. Burk, *J. Am. Chem. Soc.*, **1993**, *115*, 10125; *J. Am. Chem. Soc.*, **1995**, *117*, 9375

Asymmetric reduction of enamides

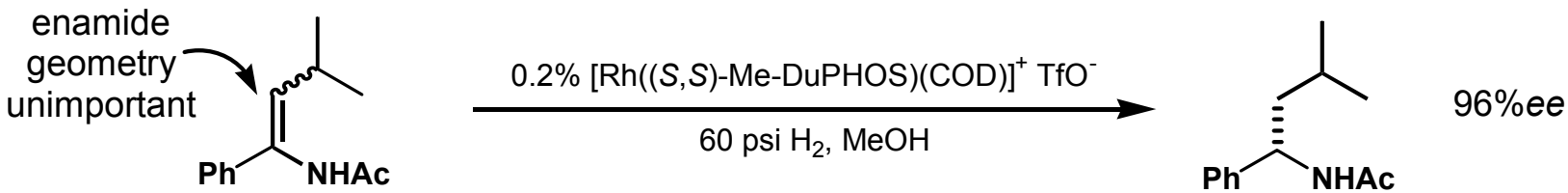
ruthenium BINAP mediated reduction of cyclic enamides



N-acetyl-tetrahydropapaverine

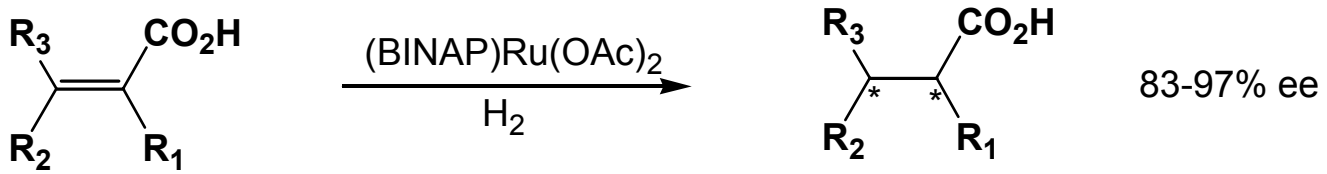
Noyori, Takaya, *J. Am. Chem. Soc.*, **1986**, *108*, 7117

rhodium DuPHOS mediated reduction of acyclic enamides



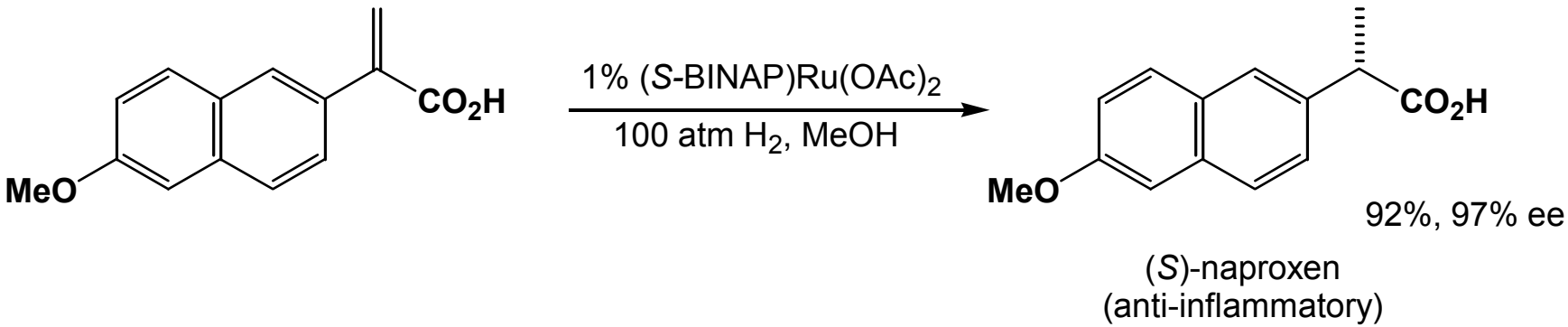
Burk, *J. Am. Chem. Soc.*, **1996**, *118*, 5142

Ru-diphosphine catalysed reduction of acrylic acids



83-97% ee

e.g.



92%, 97% ee

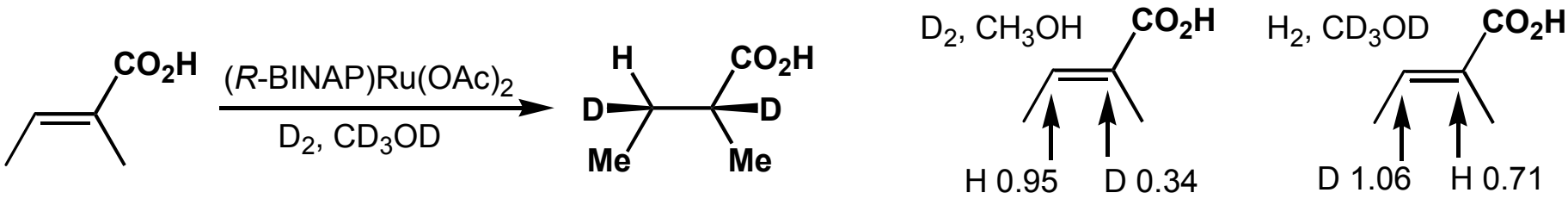
(*S*)-naproxen
(anti-inflammatory)

Noyori, Takaya, *Inorg. Chem*.**, 1988,** *27***,** 566**;** *J. Org. Chem*. **1987,** *52***,** 3174**.**

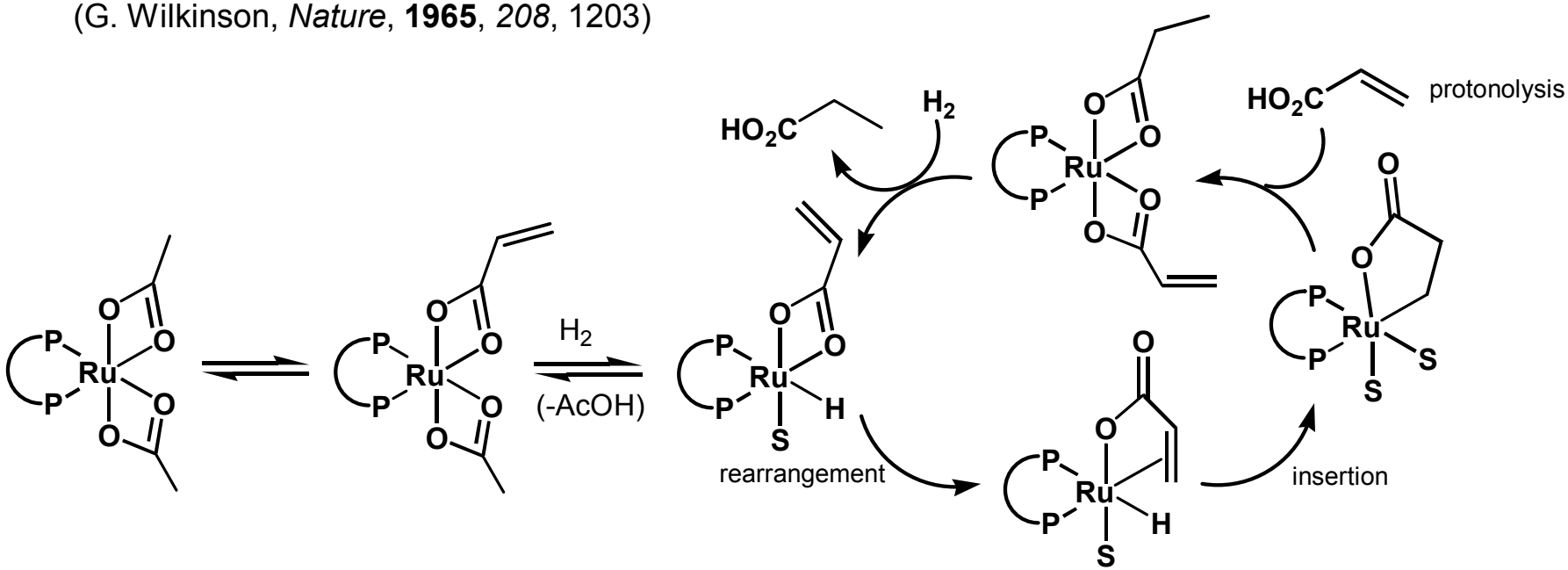
• Corresponding methyl esters are inert to this catalyst
For use of Rh-DuPHOS catalysts in acrylate reduction, see: Burk. *J. Org. Chem*., **1999**, *64*, 3290.

Mechanism of hydrogenation with Ru BINAP complexes is different from Rh

- Like the rhodium counterpart, the hydrogenation is stereospecifically *syn*; but unlike the rhodium reaction, the α-hydrogen is incorporated from the gas source, the β-hydrogen from protonolysis by solvent



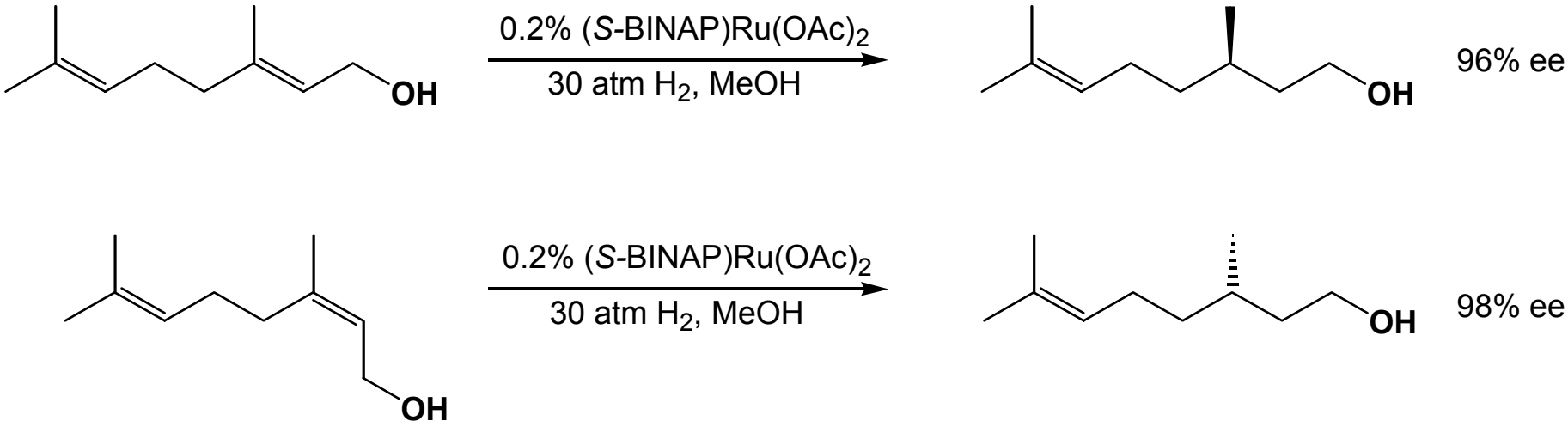
- Ruthenium (II) prefers to form monohydrides, whereas rhodium (I) prefers to form dihydrides (G. Wilkinson, *Nature*, **1965**, *208*, 1203)



H. Takaya, R. Noyori, *Tetrahedron Lett.*, **1990**, *31*, 7189, *J. Am. Chem. Soc.* **2002**, *124*, 6649

Ru-BINAP catalysed reduction of allylic alcohols

- **Sense of induction depends on alkene geometry:**



Noyori, Takaya, *J. Am. Chem. Soc.*., **1987**, *109*, 1596; *J. Org. Chem*. **1988**, *53*, 708.