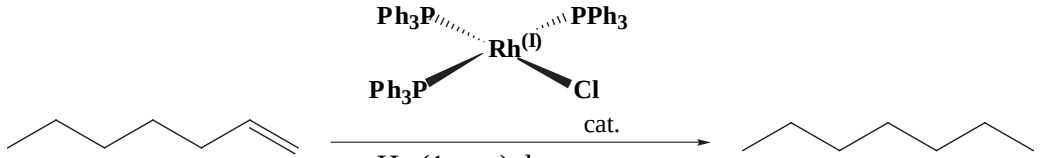
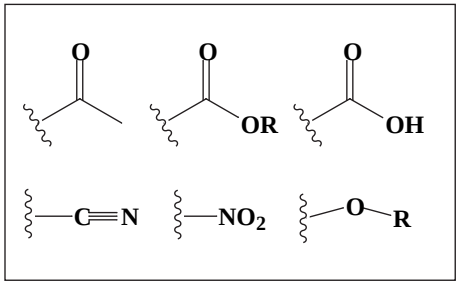
Wilkinson's Catalyst

Wilkinson's original report:

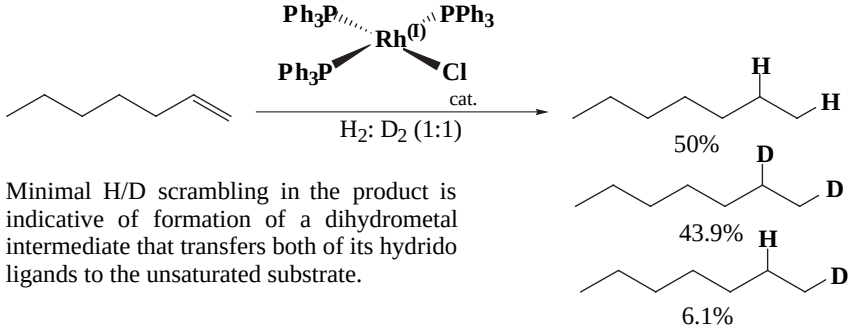


Investigations into the reactivity of $(PPh_3)RhCl$ uncovered its high activity as a homogeneous hydrogenation catalyst. This was the first homogeneous catalyst that compared in rates with heterogeneous counterparts.

Functionality tolerated

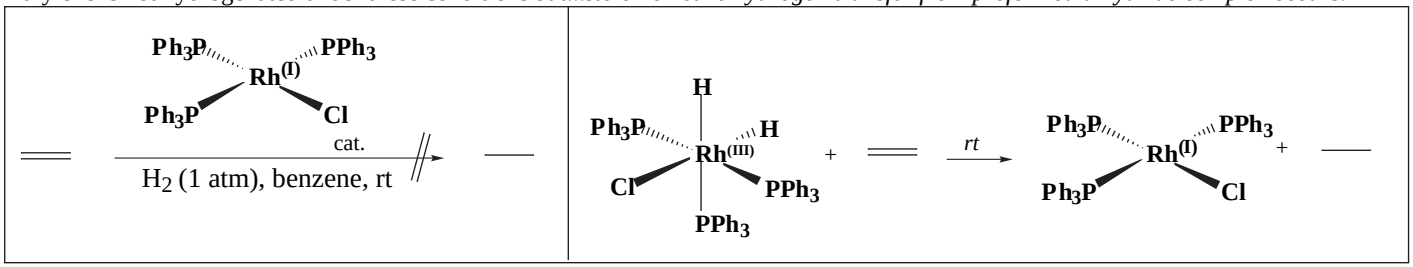


Compatibility with carbonyl groups indicates that the metal hydride intermediate is primarily covalent in character (lacks hydridic properties characteristic of strongly ionic M-H). See Structure & Bonding pg. 28.



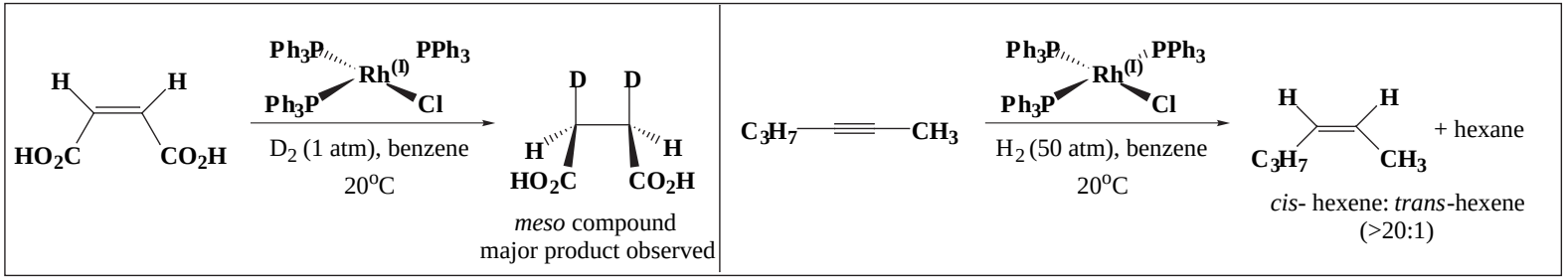
Minimal H/D scrambling in the product is indicative of formation of a dihydrometal intermediate that transfers both of its hydrido ligands to the unsaturated substrate.

Ethylene is not hydrogenated under these conditions *but...stoichiometric hydrogen transfer from preformed dihydride complex occurs.*



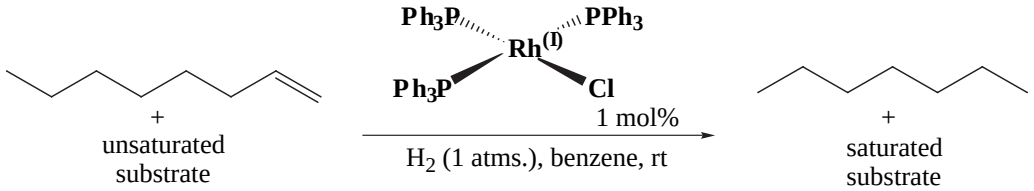
Data indicates that formation of an ethylene/ $Rh(Cl)(PPh_3)_3$ complex inhibits hydrogen activation by the complex. This implies that dihydride formation precedes olefin complexation in the catalytic cycle.

The stereochemical outcome of this experiment indicates that the mechanism involves stereospecific *cis* hydrometallation of the unsaturated substrate followed by stereospecific reductive elimination from the resulting alkenyl (or alkyl) hydrido species.

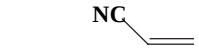
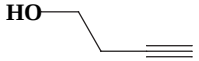
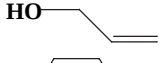
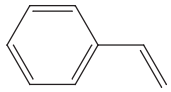
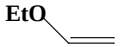
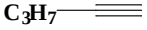
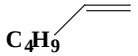
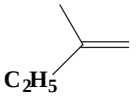
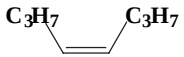
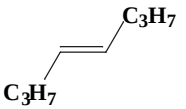


Wilkinson *J. Chem. Soc. (A)* **1966**, 1711.

Wilkinson: substrate selectivity



competition figure = rate of hydrogenation of unsaturated substrate / rate of hydrogenation of 1-octene

unsaturated substrate	*competition figure*
	14.7
	9.1
	3.4
	2.6
	1.8
 , also 1-heptyne, 1-octyne	1.7
 also, 1-decene, 1-dodecene	**1.0**
cyclohexene	0.92
1,3-cyclooctadiene	0.75
	0.71
	0.69
	0.54
	0.17

Unsaturated substrates containing functionality are hydrogenated more rapidly than their unfunctionalized counterparts. The effect is suggested to result from polar functional group assisted olefin coordination to the catalyst.

Terminal alkynes are hydrogenated more rapidly than terminal alkenes. This selectivity may be enhanced by use of acidic alcohol co-solvents (e.g. in benzene/ 2,2,2-trifluoroethanol, 1-hexyne: 1-octene (12:1).

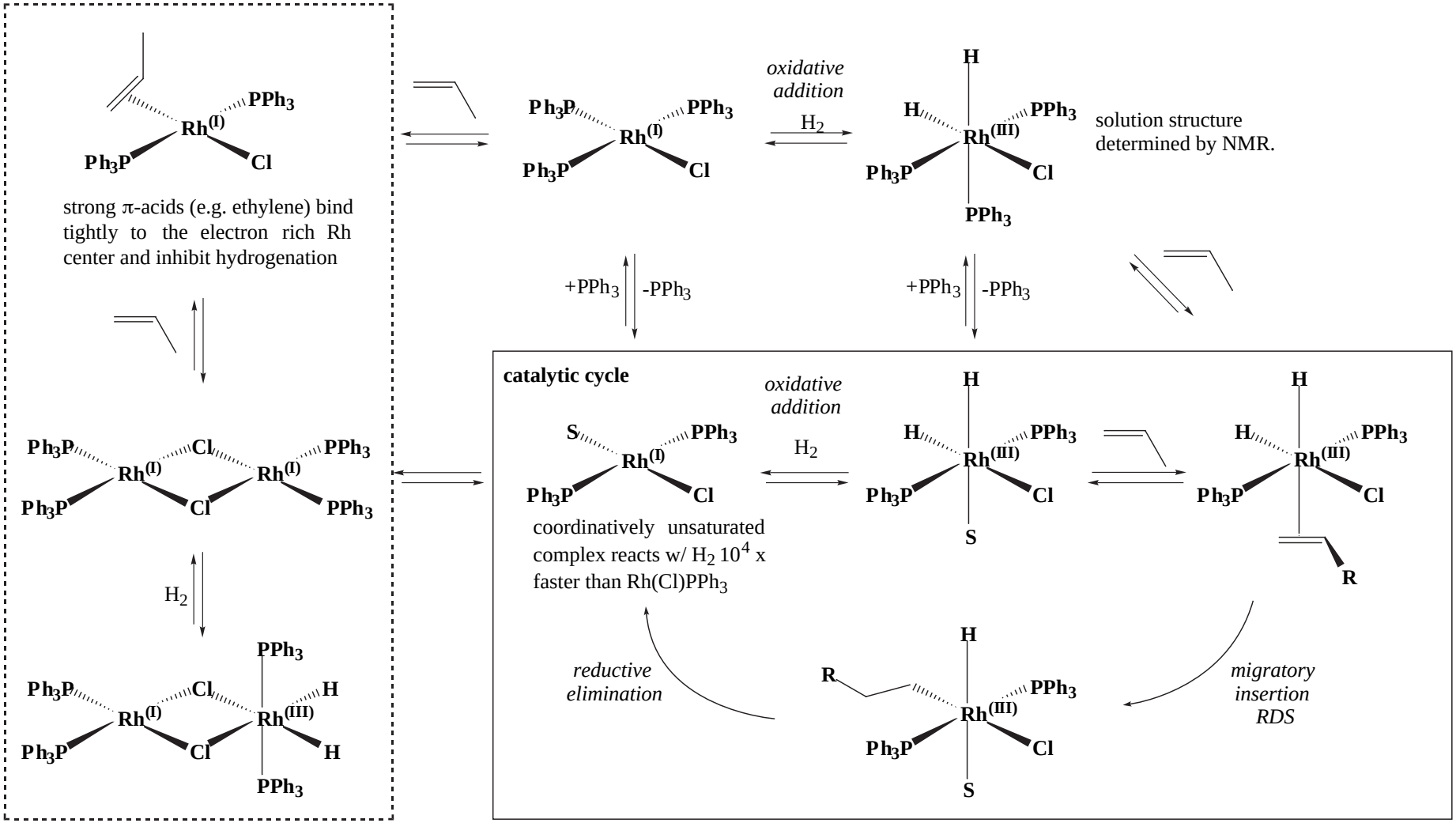
Terminal alkenes between C6-C12 are hydrogenated at the same rate. The same is observed for terminal alkynes. An increase in carbon chain length does not appear to affect olefin/catalyst interaction.

Conjugated dienes are reduced slower than isolated alkenes.

Internal and branched alkenes (alkynes) are hydrogenated slower than terminal alkenes (alkynes). These differences are rationalized in terms of steric effects on olefin interaction with the catalyst and have been used to effect selective alkene hydrogenations in polyene compounds.

Candlin *Faraday Discuss. Chem. Soc.* **1968** (46) 60.

Wilkinson hydrogenation: classic dihydride mechanism

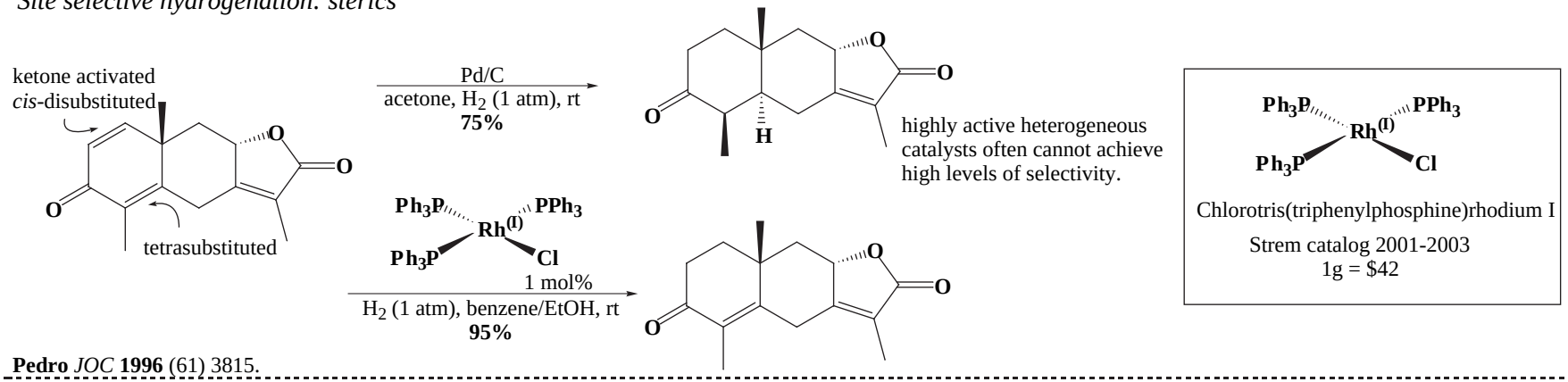


Intermediates observed by NMR or as isolated solids in the reaction system. Formation of these "side-products" results in a reduction in the rate of hydrogenation.

Halpern *Chem. Comm.* **1973** 629.
Halpern *J. Mol. Catal.* **1976** (2) 65.
Halpern *Inorg. Chim. Acta.* **1981** (50) 11.

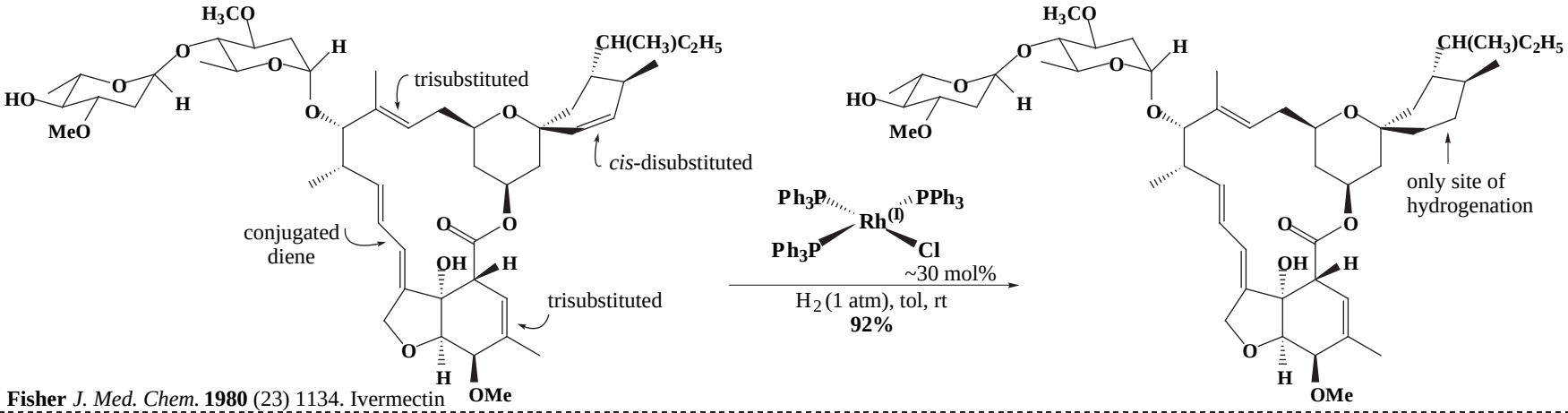
Wilkinson: site selectivity

Site selective hydrogenation: sterics



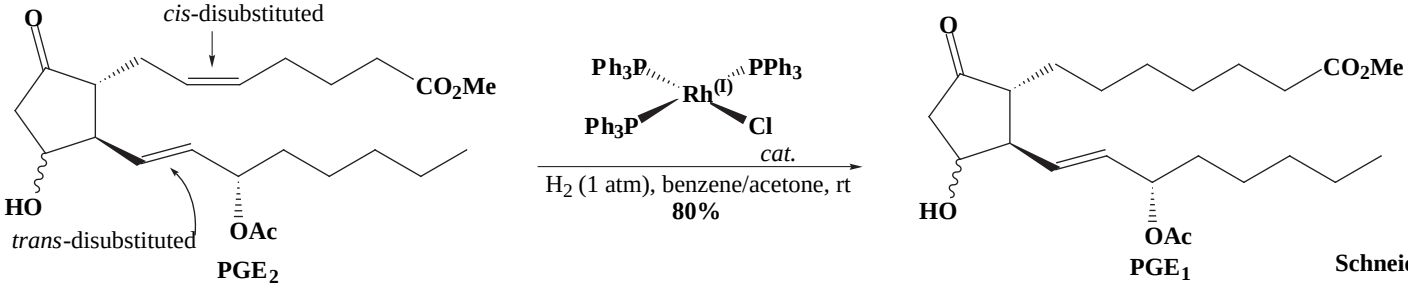
Pedro *JOC* **1996** (61) 3815.

Site selective hydrogenation: sterics and electronics



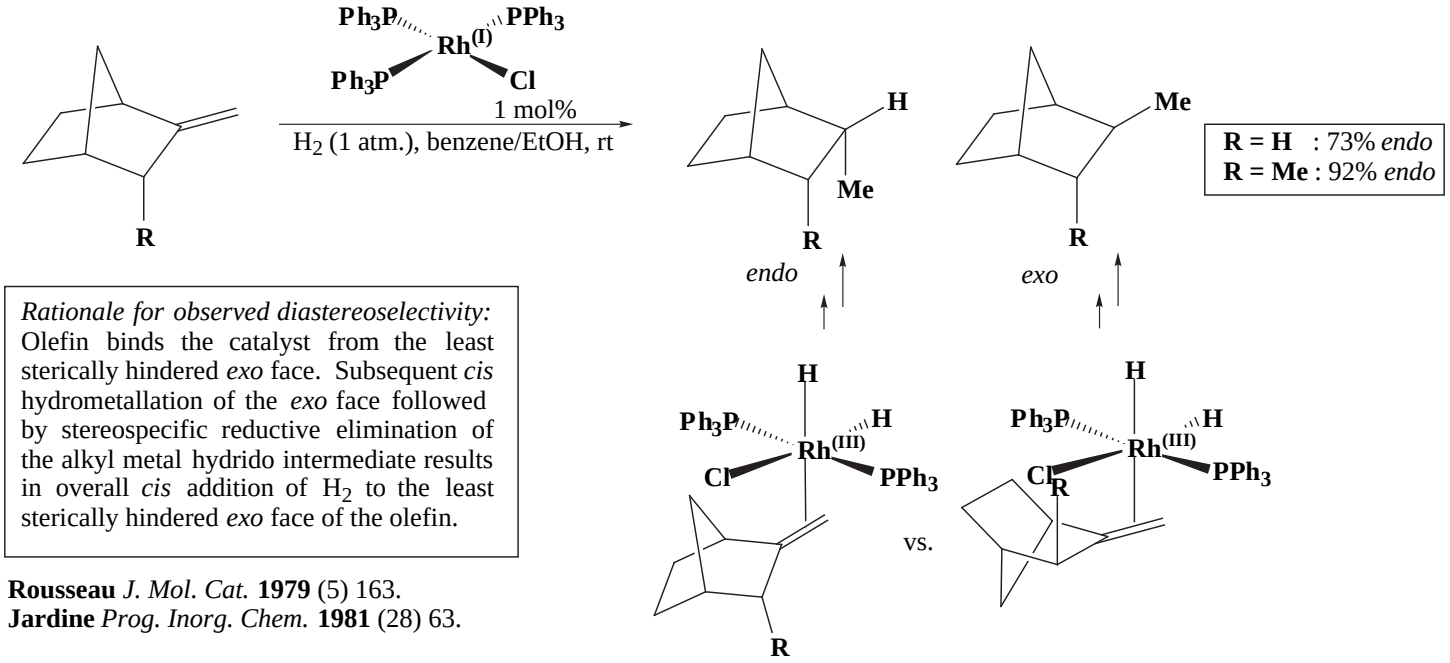
Fisher *J. Med. Chem.* **1980** (23) 1134. Ivermectin

cis vs. *trans*-disubstituted olefins:



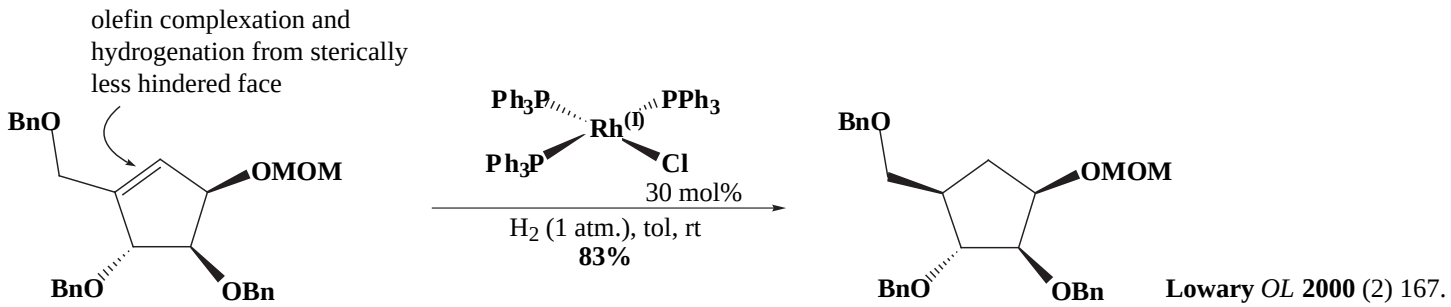
Schneider *JOC* **1973** (38) 951.

Wilkinson: diastereoselectivity



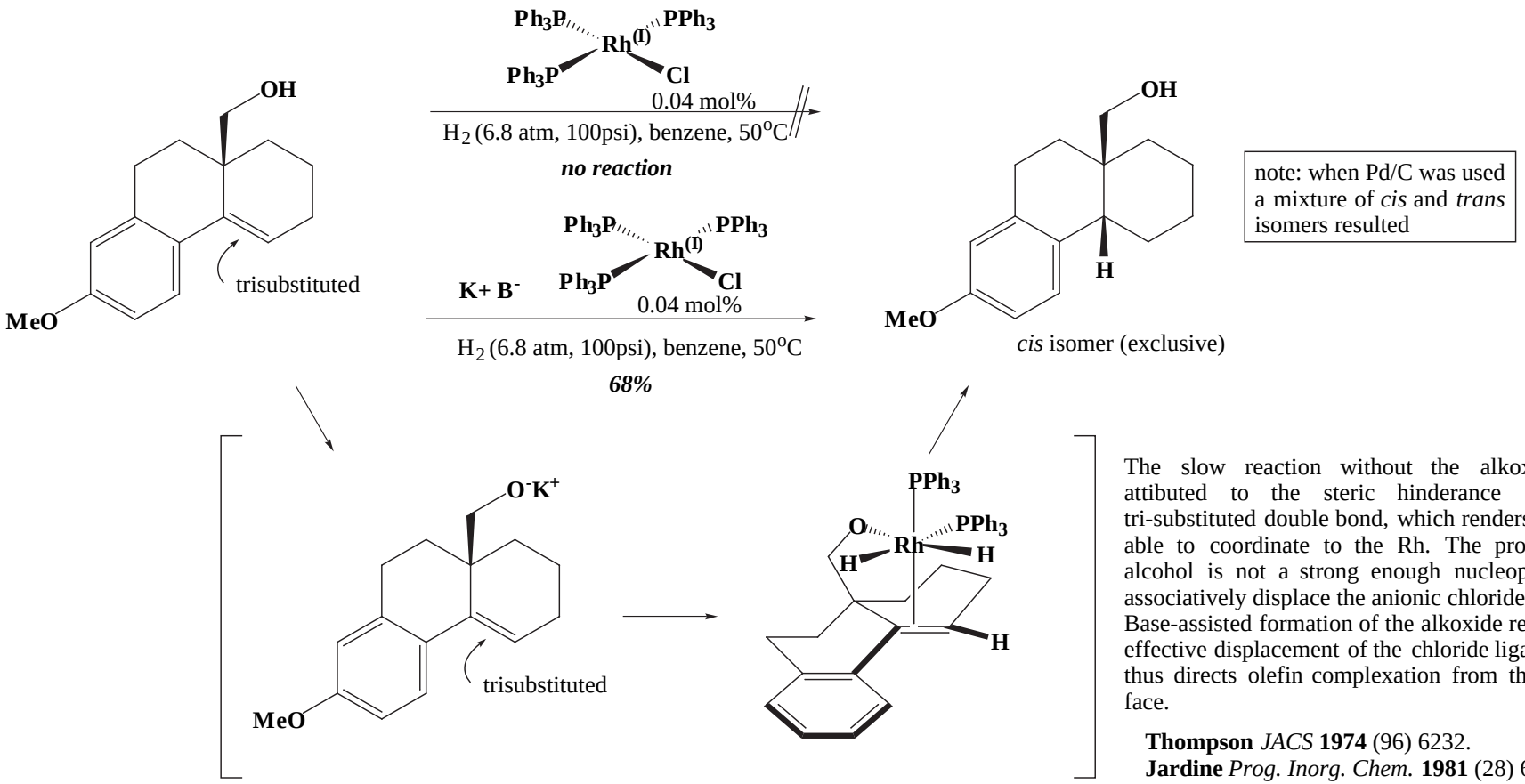
Rationale for observed diastereoselectivity: Olefin binds the catalyst from the least sterically hindered *exo* face. Subsequent *cis* hydrometallation of the *exo* face followed by stereospecific reductive elimination of the alkyl metal hydrido intermediate results in overall *cis* addition of H_2 to the least sterically hindered *exo* face of the olefin.

Rousseau *J. Mol. Cat.* **1979** (5) 163.
Jardine *Prog. Inorg. Chem.* **1981** (28) 63.



Lowary *OL* **2000** (2) 167.

Wilkinson: directing group effects

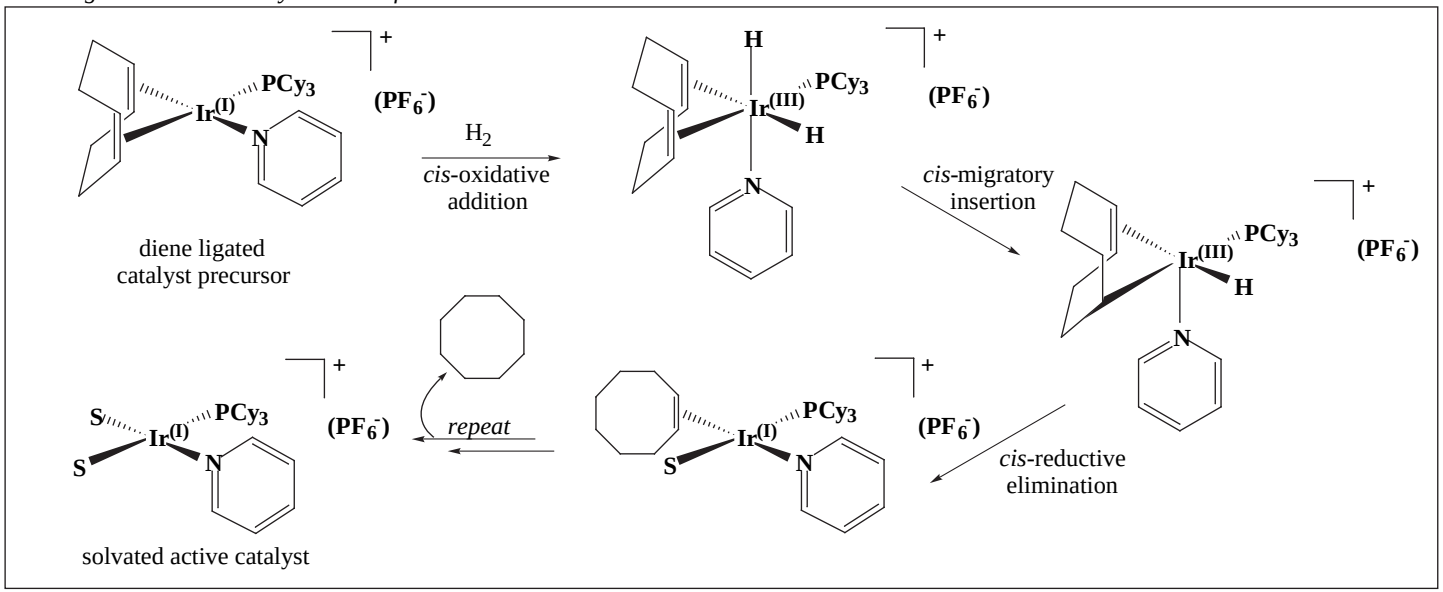


The slow reaction without the alkoxide is attibuted to the steric hinderance of the tri-substituted double bond, which renders it less able to coordinate to the Rh. The protonated alcohol is not a strong enough nucleophile to associatively displace the anionic chloride ligand. Base-assisted formation of the alkoxide results in effective displacement of the chloride ligand and thus directs olefin complexation from the same face.

Thompson *JACS* **1974** (96) 6232.
Jardine *Prog. Inorg. Chem.* **1981** (28) 63.

Schrock- Osborn /Crabtree: Cationic catalysts

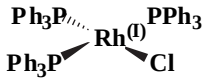
Diene ligated cationic catalysts mode of activation:



Crabtree *Acc Chem Res* **1979** (12) 331.

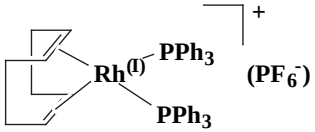
Turnover Frequency (TOF)

Wilkinson's catalyst



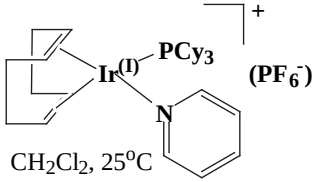
benzene/EtOH, 25°C

Schrock-Osborn catalyst



CH_2Cl_2, 25°C

Crabtree's catalyst



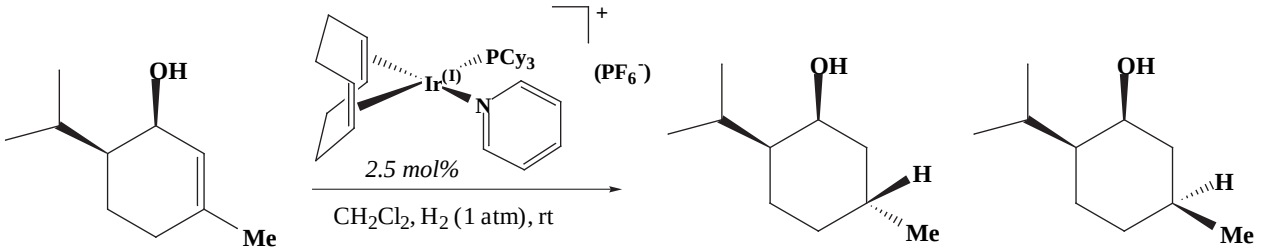
CH_2Cl_2, 25°C

650	700	13	----
4000	10	----	----
6400	4500	3800	4000

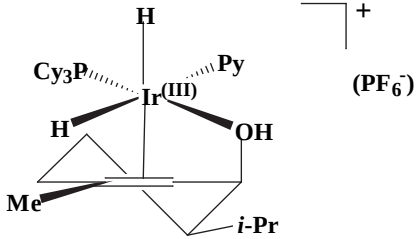
TOF = mol reduced substrate/mol catalyst/h

"Coordinatively" unsaturated cationic hydrogenation catalysts are the most active homogeneous hydrogenation catalysts developed thus far. Use of weakly coordinating solvents provides the olefin substrate with relatively free access to the metal's reactive site. These cationic catalysts are also remarkably selective....

Cationic catalysts: substrate-directed hydrogenations

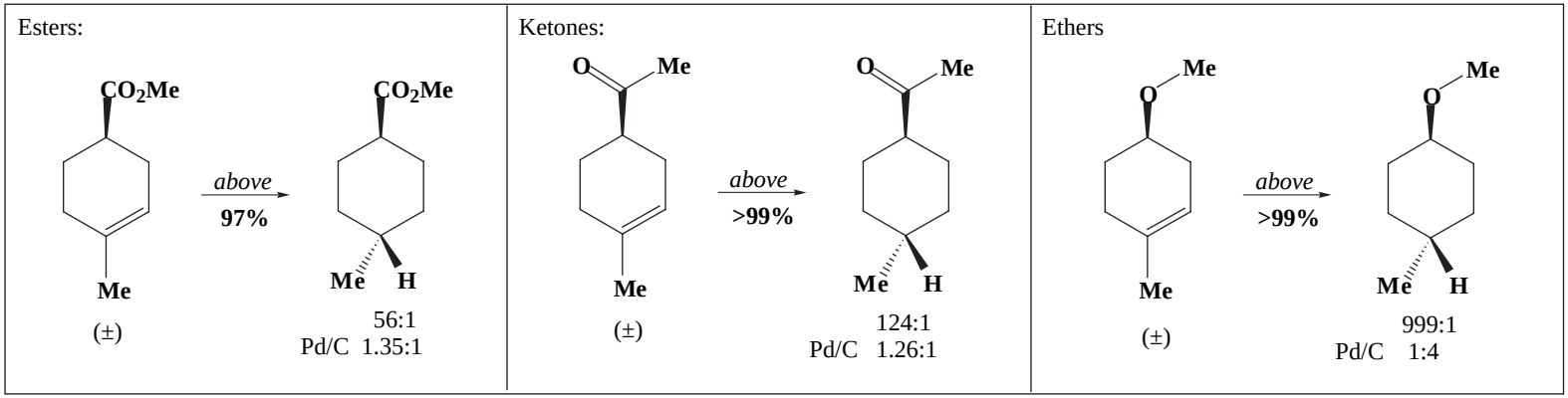


The availability of a second "open" coordination site on the catalyst now makes it possible to bind a ligating group on the substrate in addition to the olefin. This "two-point" binding has important implications on the selectivity of product formation. The ability of a late metal complex to effectively bind hard functionality (hydroxyls, ketones, etc...) is attributed to the lewis acidic properties imparted on the complex by the overall positive charge.

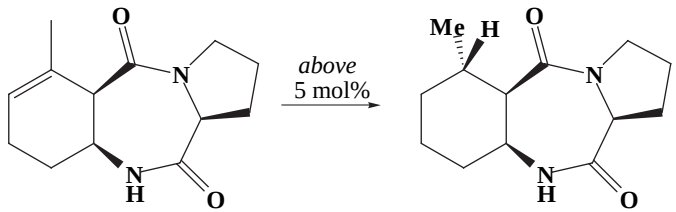


Crabtree *JOC* **1986** (51) 2655.

Other functionalities with lewis basic sites also direct:

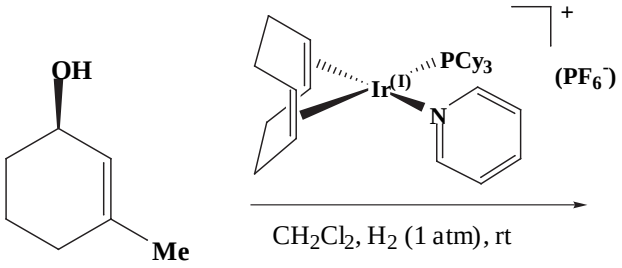


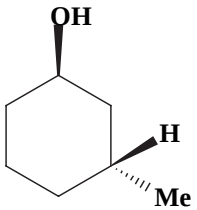
Amides:



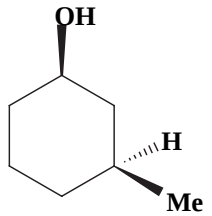
For a comprehensive review of cyclic and acyclic substrate-directed hydrogenations see: **Hoveyda, Evans, and Fu** *Chem. Rev.* **1993** (93) 1307 and D.A. Evans; Chem 206 notes.

High catalyst loadings: diminished yields and selectivities





A



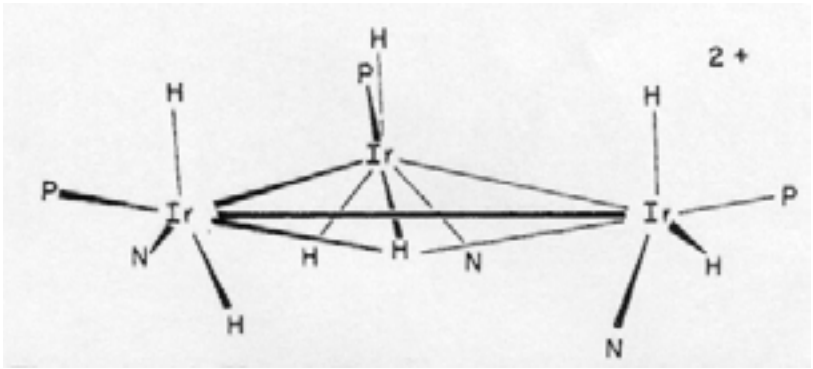
B

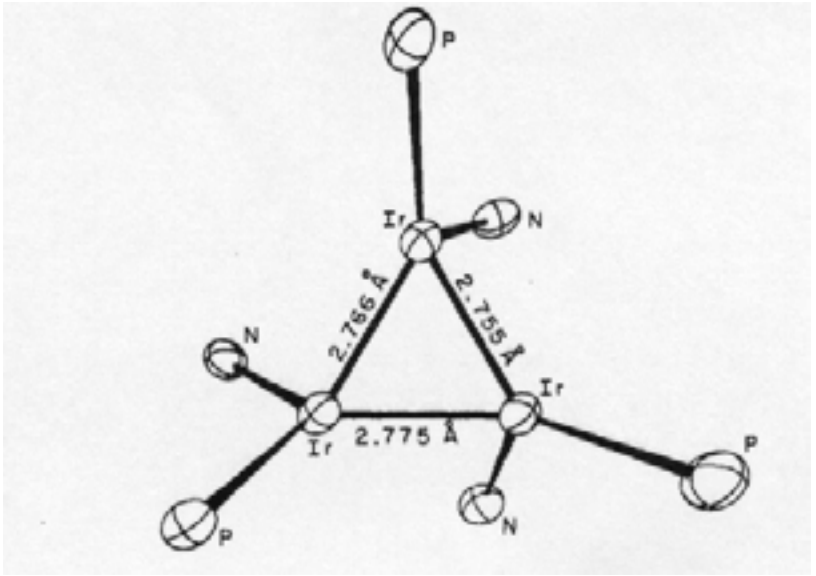
A decrease in selectivity is observed at higher catalyst loadings. It is possible that higher catalyst loadings promote the formation of dimeric (Crabtree suggested M-H-M) species that no longer have the "open" coordination site necessary for providing effective directing effects in olefin hydrogenation. No experimental data exists thus far to support this hypothesis.

	yield	selectivity (ratio A:B)
2.5 mol%	99%	139:1
20 mol%	48%	74:1

Stork *JACS* **1983** (105) 1072.
Crabtree *JOC* **1986** (51) 2655.

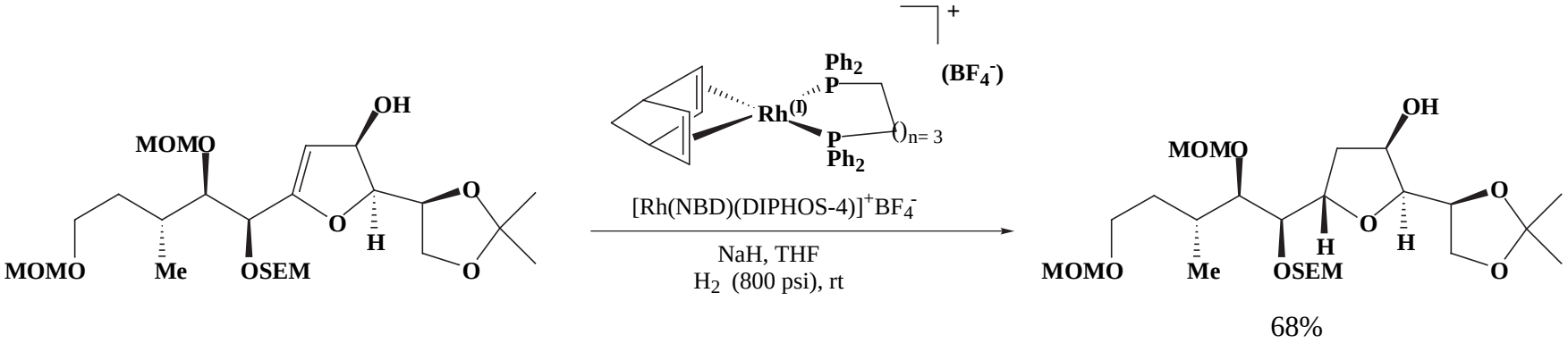
Dimished yields are observed with higher catalyst loadings. This can be rationalized on the basis that higher catalyst loadings promote the irreversible trimerization of the coordinatively unsaturated catalysts to yield inactive triiridium hydride bridged complexes. Such complexes have been isolated by Crabtree from reaction mixtures of more sterically hindered olefins that did not proceed to completion.





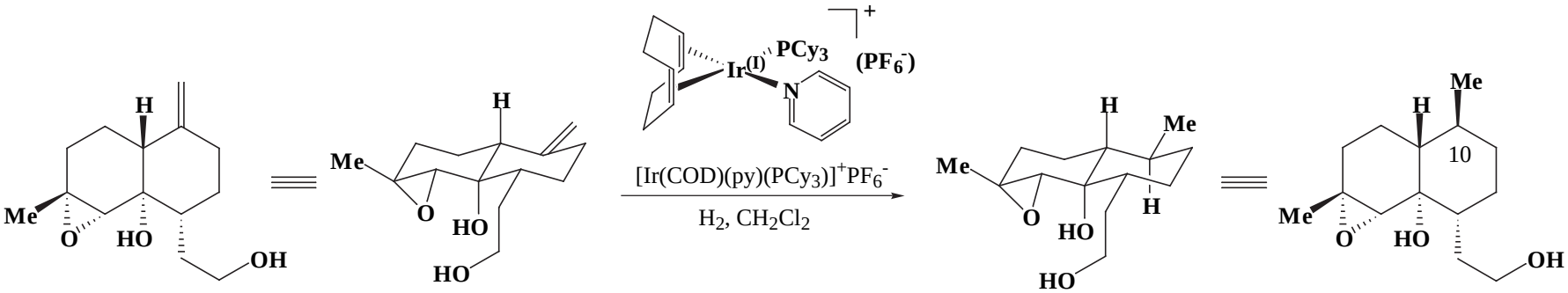
Crabtree *Acc. Chem. Res.* **1979** (12) 331.

Synthetic applications of directed hydrogenations



68%

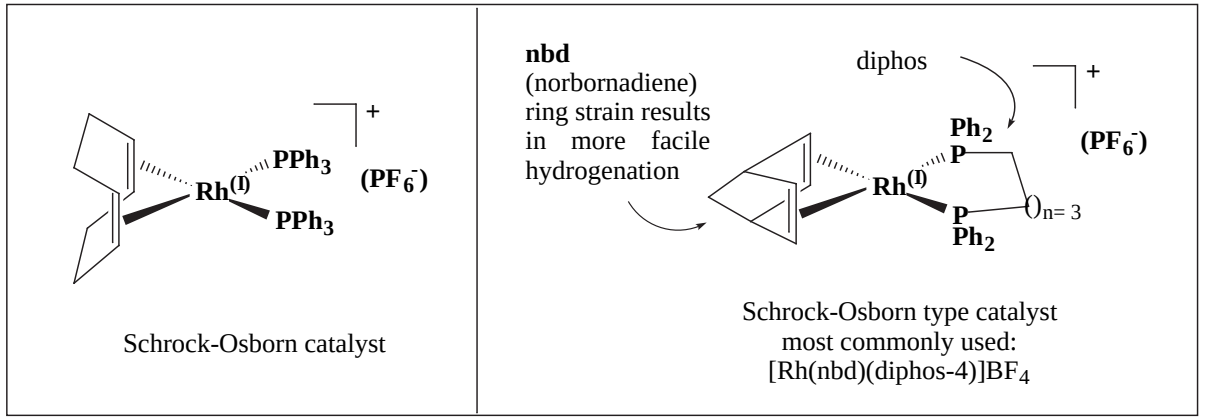
Paquette *OL* **2002** (4) 937.



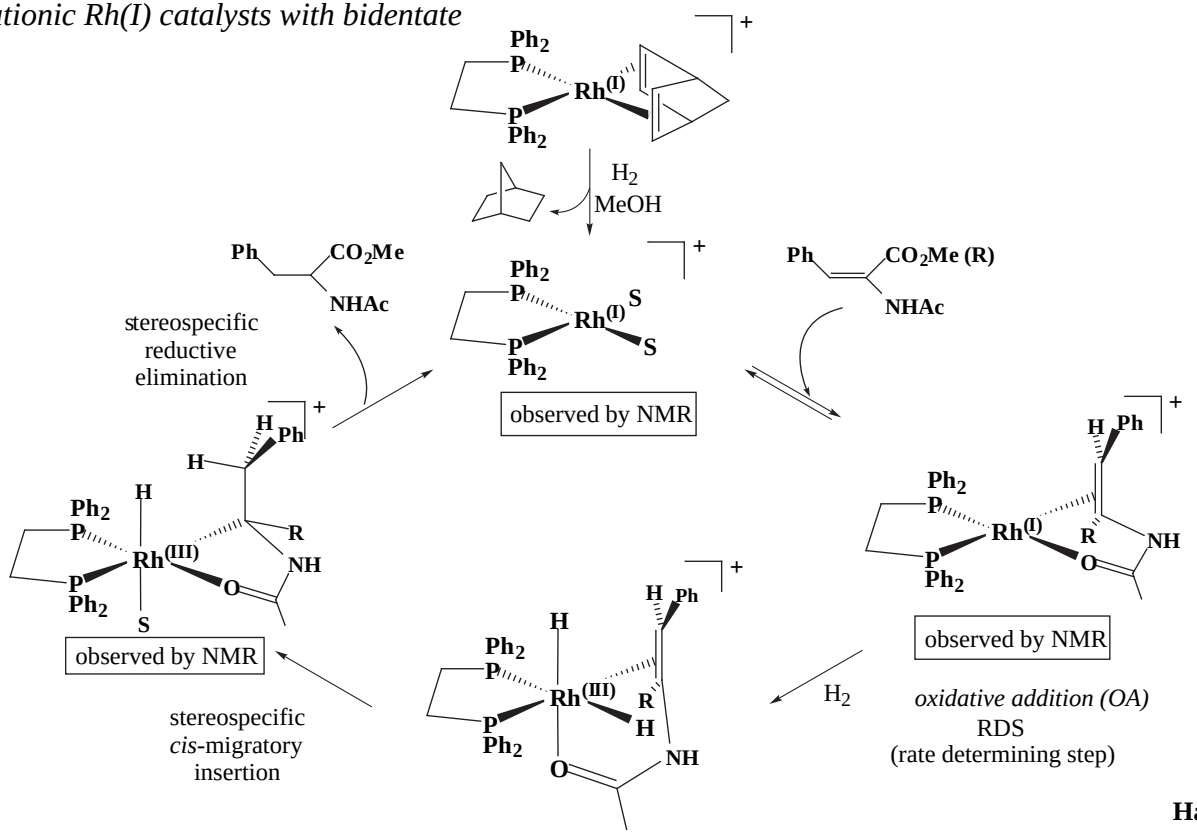
99% Yield,
d.r. 11:1 at C10

Barriault *OL* **2001** (3) 1925.

Mechanism of hydrogenation: bidentate cationic complexes



Halpern's mechanism for cationic Rh(I) catalysts with bidentate phosphine ligands:

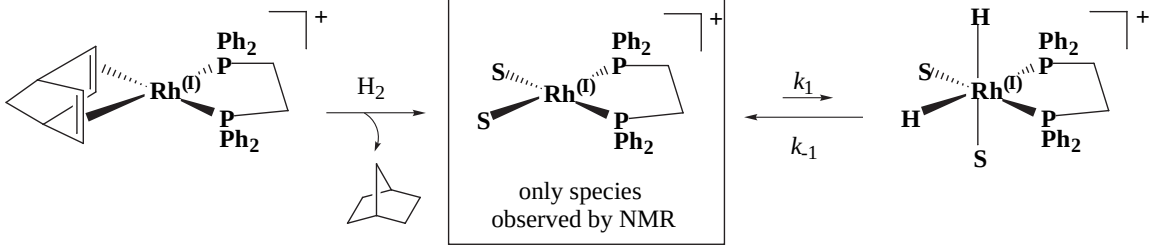


Halpern *Science* **1982** (217) 401.

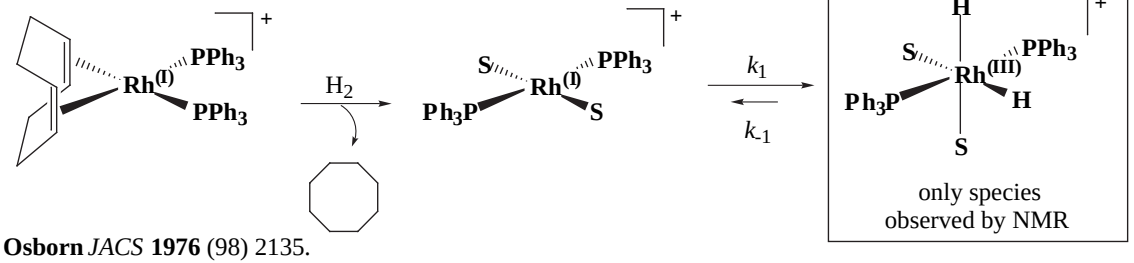
Mechanism of monodentate cationic complexes

Halpern notes that the hydrogenation mechanism for *bidentate* ligated cationic complexes where olefin substrate coordination precedes oxidative addition of H_2 may not be operating for cationic catalysts with *monodentate ligands.* Schrock-Osborn invoke involvement of the dihydride complex (below) in the principle hydrogenation pathway for their catalyst. Halpern notes some significant differences in the reactivities towards H_2 of the catalysts w/ bidentate and monodentate phosphine ligands.

In the absence of olefin substrate, no further uptake of H_2 can be detected. The only species observed by NMR is the cationic, 4-coordinate solvated species.



Treatment of the monodentate catalyst with H_2 resulted in detection of the Rh(III)-dihydride complex.

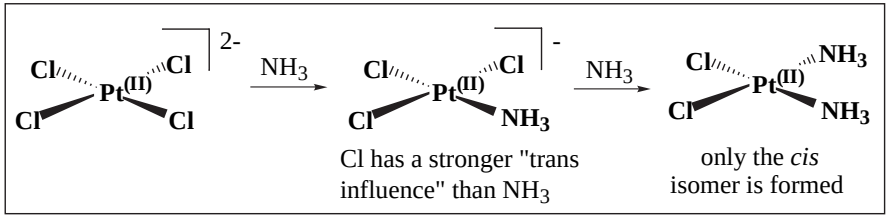


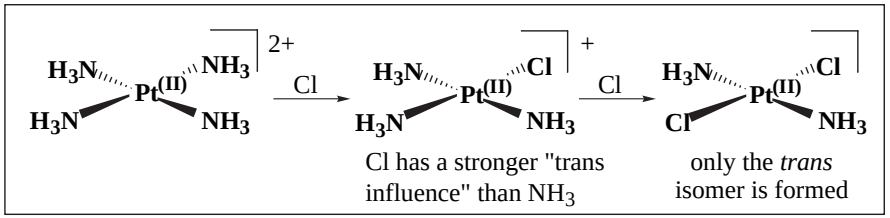
Halpern *JACS* **1977** (99) 8055. **Schrock & Osborn** *JACS* **1976** (98) 2135.

The Trans Effect:

To explain the difference in reactivities towards H_2 of the catalysts, Halpern invokes the ***trans effect***. The *trans* effect is defined as the labilization of ligands *trans* to certain other ligands. The *trans* effect often arises when a ligand shares an orbital with another ligand of strong σ-bonding character. Because phosphine forms a strong σ bond with Rh, trans Rh-H bonds formed will be weak because the orbital is not as available for bonding to H. In the case of the bidentate complex, *cis* addition of H_2 requires that one hydride share an orbital with a phosphine. Since both hydride and phosphine are strong σ-bonding ligands, the dihydride adduct, once formed, is highly unstable and thus rapidly reverts back *via* reductive elimination to the solvated 4-coordinate species. In the case of the monodentate phosphine complex, a H_2 adduct can form where neither H ligand is *trans* to a phosphine.

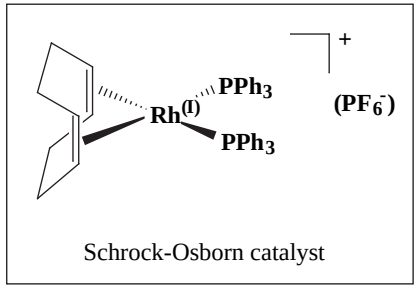
Classic example of the trans effect: synthesis of "cis-platinum" a chemotherapeutic agent



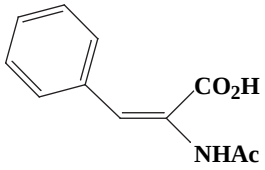


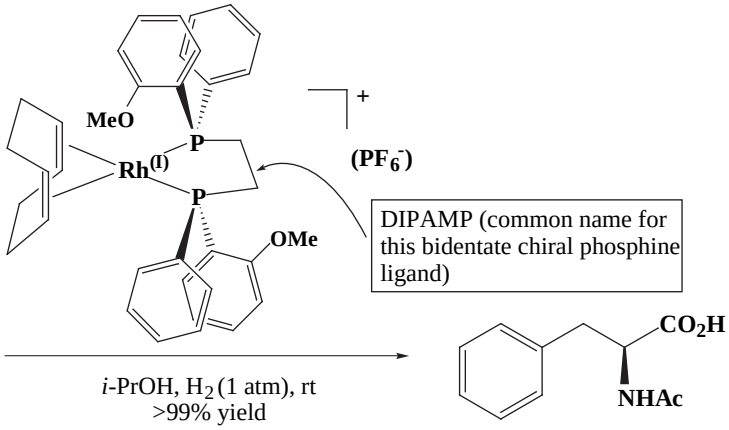
Asymmetric Hydrogenation

A bidentate, C_2 symmetric version of the cationic Schrock-Osborn catalyst affords extraordinarily high levels of enantioselectivity in the hydrogenation of achiral enamides. This was the first demonstration that a chiral transition metal complex could effectively transfer chirality to a non-chiral substrate with selectivities that rival those observed in enzymes. Recall that this led to the 1st commericalized asymmetric process using a chiral transition metal complex: Monsanto Process for the industrial production of *L*-DOPA (see Structure and Bonding, pg. 4)



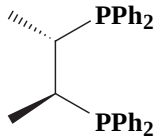
Schrock-Osborn catalyst



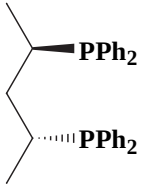


Knowles *JACS* **1975** (97) 2567. ***93% ee***

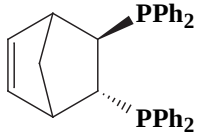
A variety of bidentate chiral phosphines have since been synthesized and used to effect the hydrogenation of aromatic enamides (important substrates for the efficient generation of amino acids):



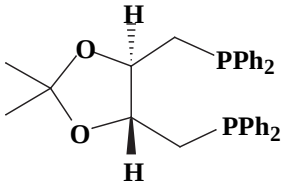
Chiraphos (99% ee)



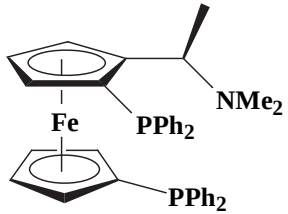
SKEWPHOS (92% ee)



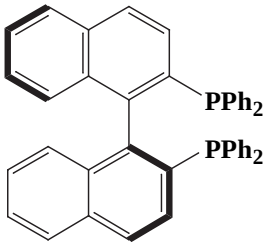
NORPHOS (95% ee)



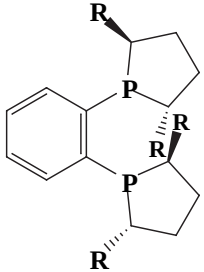
DIOP (85% ee)



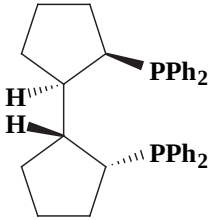
BPPFA (93% ee)



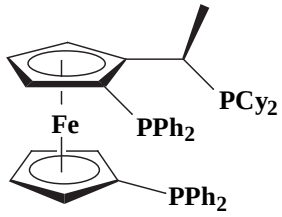
BINAP (100% ee)



DuPHOS (99% ee)



BICP (97% ee)



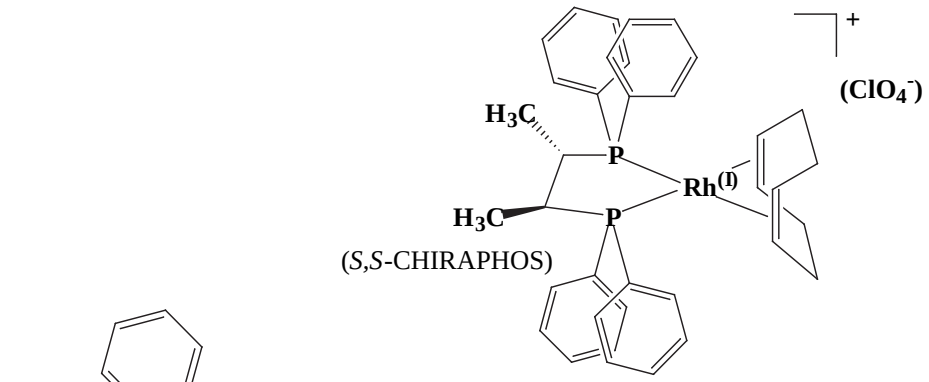
JOSIPHOS (96% ee)

We'll see these ligands again effecting asymmetry in a wide assortment of mechanistically unrelated metal catalyzed reactions with prochiral substrates. "Privileged ligand class": ligands that communicate asymmetry effectively with a transition state localized at the metal center, irrespective of the nature of the transition state.

E.N. Jacobsen;
personal communication

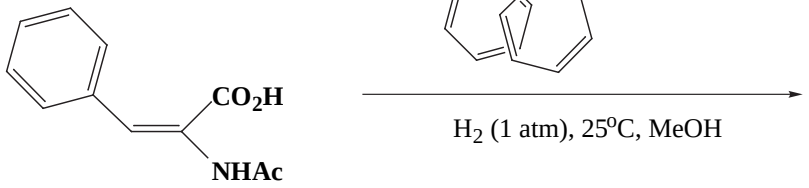
E. N. Jacobsen. Chem 153 notes. Spring 2001.
For review on DuPhos: **Burk** *Acc. Chem. Res.* **2000** (33) 363.

Origin of Asymmetric Induction

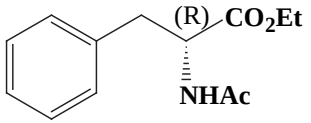


(*S,S*-CHIRAPHOS)

It was concluded from kinetic measurements that the minor diastereomer was 580 fold more reactive towards H_2 oxidative addition (recall the RDS at rt). This factor offsets its lower concentration in solution and results in a 60:1 product ratio in favor of the R enantiomer.

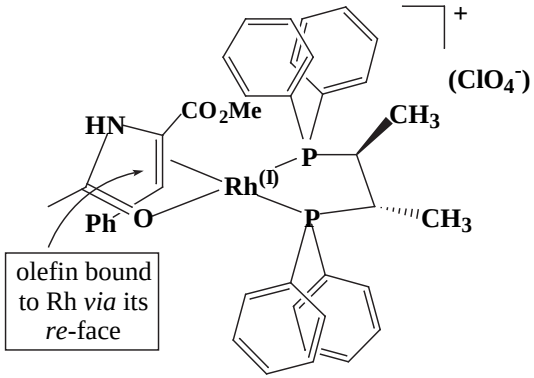


H_2 (1 atm), 25°C, MeOH



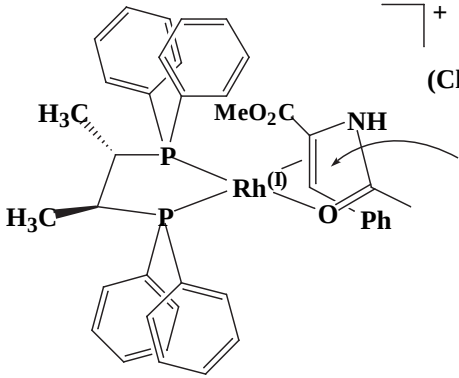
***N*-acetyl-(*R*)-phenylalanine**
>95% ee

stereospecific H migratory insertion / stereospecific H/C reductive elimination both to the olefin face bound to Rh



olefin bound to Rh *via* its *re*-face

major diastereomer formed in solution (identified by NMR and x-ray crystallography)

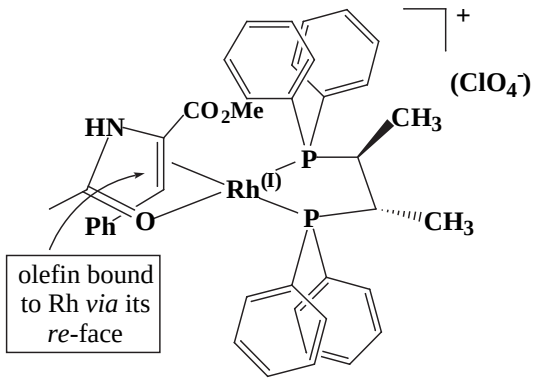


olefin bound to Rh *via* its *si*-face

minor diastereomer formed none detected by NMR (must be less than 5% present in solution)

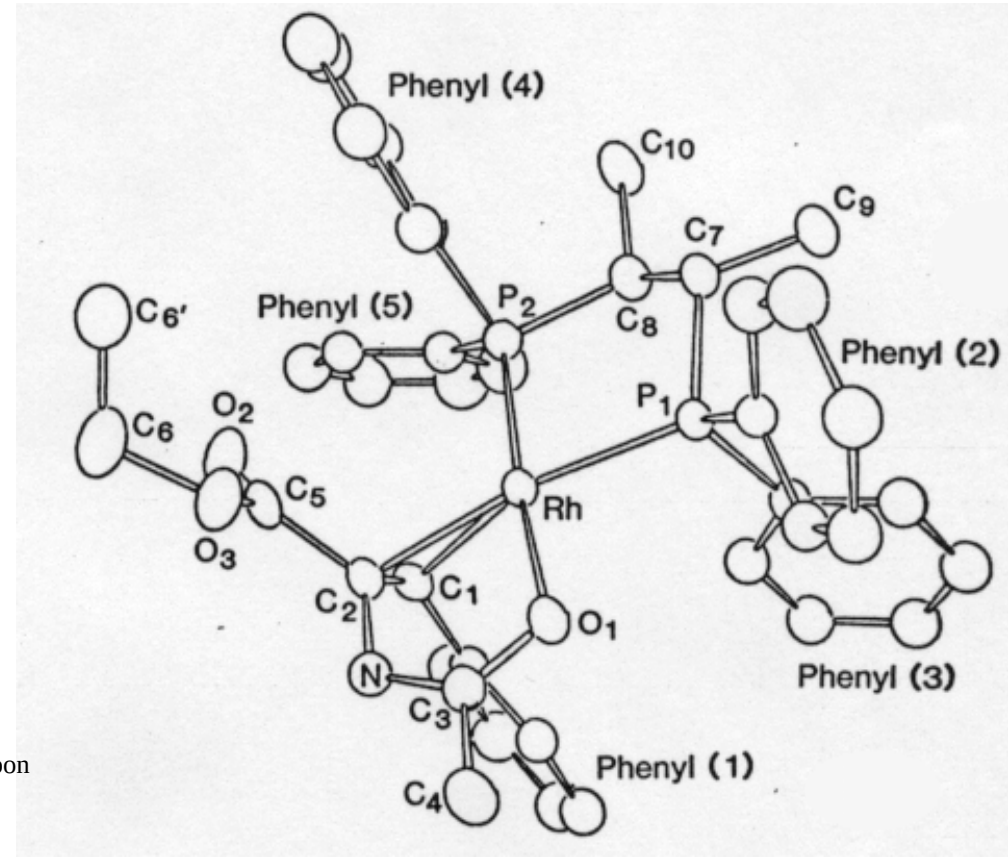
Halpern *Science* **1982** (217) 401.

Crystal structure of major diastereomer

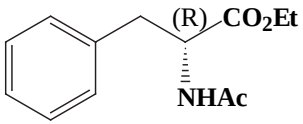


olefin bound to Rh *via* its *re*-face

major diastereomer formed in solution (identified by NMR and x-ray crystallography)

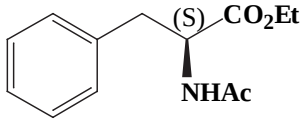


Major enantiomer observed upon exposing crystal to H_2:



***N*-acetyl-(*R*)-phenylalanine**
>95% ee

Minor enantiomer observed upon exposing crystal to H_2.

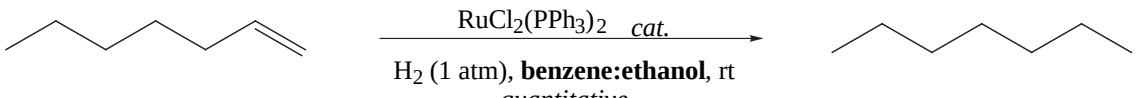


Halpern *Science* **1982** (217) 401.

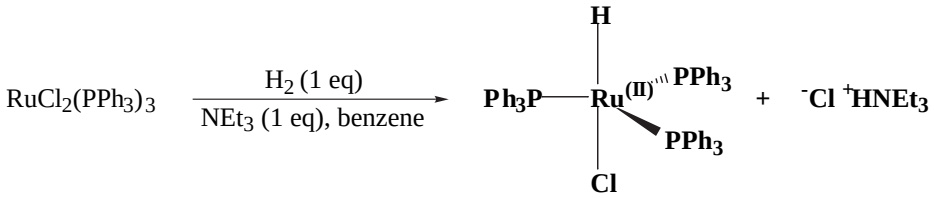
Monohydride catalysts: $RuClH(PPh_3)_3$

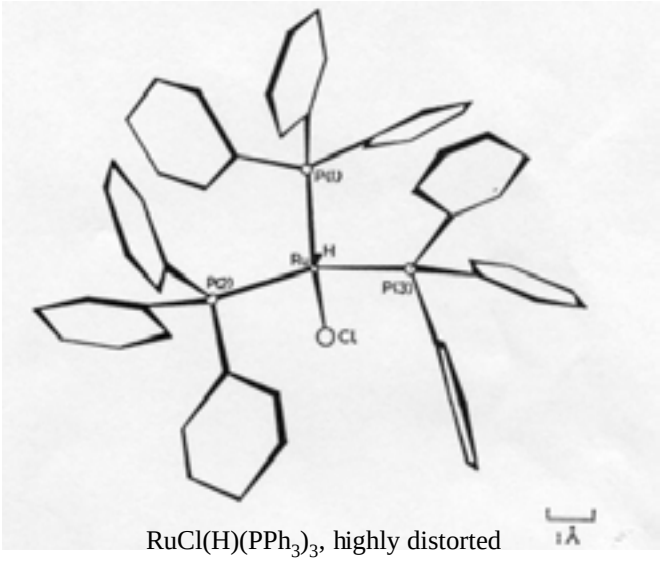
Wilkinson's original report:

"In contrast to the rhodium system, ethanol plays an intimate part in the hydrogenation mechanism; in the absence of such a co-solvent, hydrogenation is exceedingly slow." **Wilkinson** *Nature* **1965** (208) 1203.



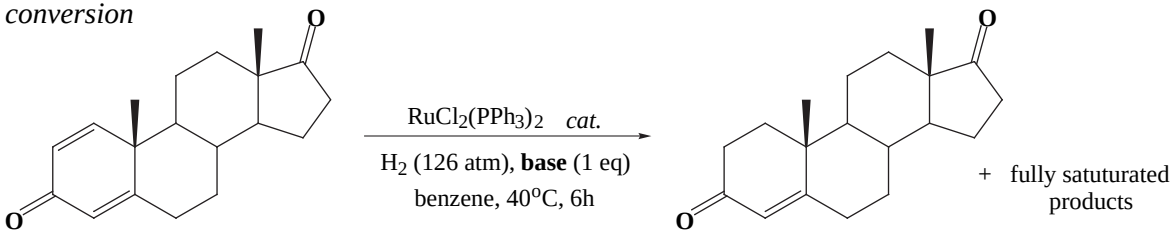
The active species was identified as the monohydride, thought to form *via* heterolytic cleavage of H_2, with ethanol acting as a base. The monohydride can also be prepared in 100% benzene if an equivalent of NEt_3 is added. One mole of H_2 is absorbed with respect to Ru and amine hydrochloride is quantitatively formed. **Wilkinson** *J. Chem. Soc. (A)* **1968** 3143.





$RuCl(H)(PPh_3)_3$, highly distorted trigonal bipyramidal. **Skapski** *Chem. Comm.* **1968** 1230.

Effect of base on conversion

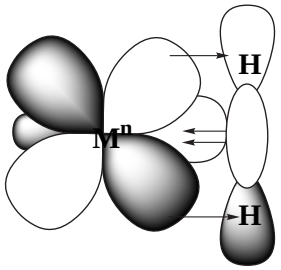


Base	% Conversion
NEt_3	95.4
Et_2NH	95.4
$BuNH_2$	86.5
aniline	88.1
Ca_2CO_3	95.2
Na_2CO_3	73.0
none	76.0

Tsuneda *Bull. Chem. Soc. Jpn.* **1973** (46) 279.

Mechanism of H_2 Activation

Base promoted heterolytic cleavage:



σ-complex

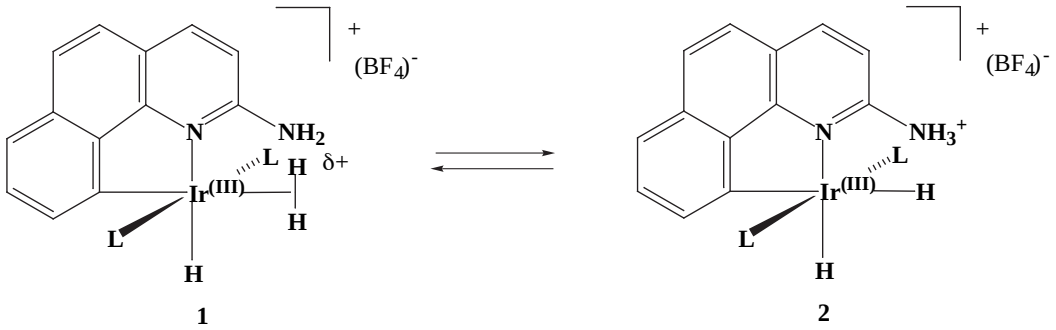
σ-donation>>
π-backbonding
heterolytic cleavage

M^n—H + BH^+

note: there is no oxidation state change at the metal

generally observed for electrophilic metals that are in their highest stable oxidation state within the context of their ligand framework.

Example:

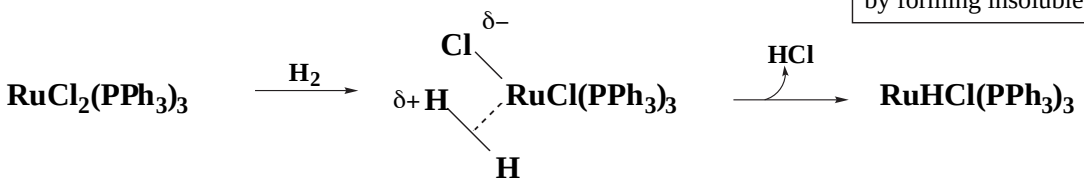


Complexation of dihydrogen to the electrophilic, cationic Ir(III) center is predominantly σ-donating in nature. Donation of electron density from the H-H σ-bond to an empty Ir orbital leaves the H-H with a partial positive charge. The pendent NH_2 group is thought to act as an internal base effecting heterolytic cleavage of the acidified dihydrogen σ-complex *via* deprotonation.When L = PPh_3, the equilibrium lies far to the right and only the dihydride **2** is observed. When more basic alkyl phosphines are used (L= PBu_3) the equilibrium lies to the left with the H_2 complex **1** being observed exclusively by NMR. It was hypothesized that moving to a more basic phosphine increases the electron density at the metal center. This makes the metal a less effective σ-acceptor and attenuates its ability to effectively acidify the dihydrogen complex.

Crabtree *Chem. Commun.* **1999** 297.

σ-bond metathesis: the base is effectively one of the ligands on the metal

external amine base may still drive the rxn forward by forming insoluble amine hydrochloride salts



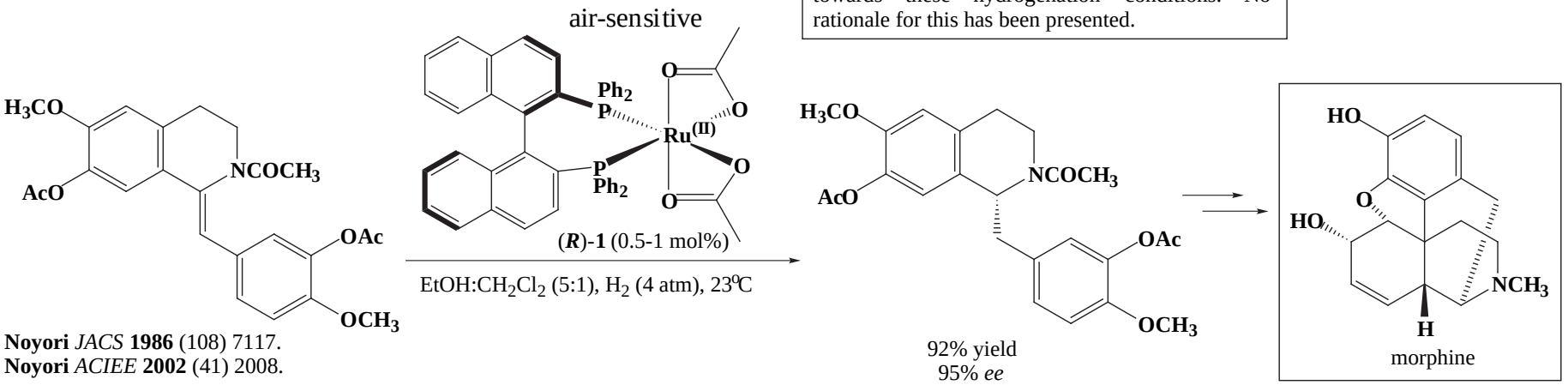
σ-bond metathesis

Crabtree *The Organometallic Chemistry of the Transition Metals: 3rd Edition*; Wiley: New York; 2001.

BINAP-Ru complexes: Noyori increases the substrate scope for asymmetric hydrogenations

The first report: asymmetric hydrogenation of (Z)-enamides

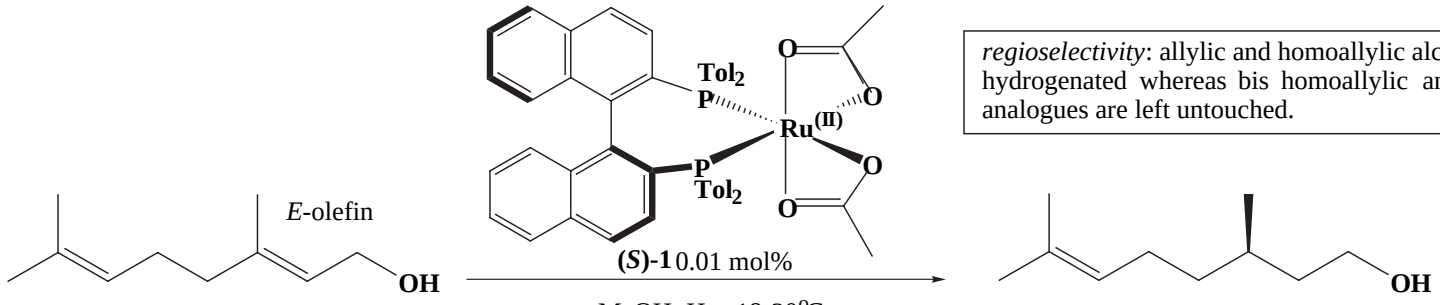
Interestingly, *E*-enamides are completely unreactive towards these hydrogenation conditions. No rationale for this has been presented.



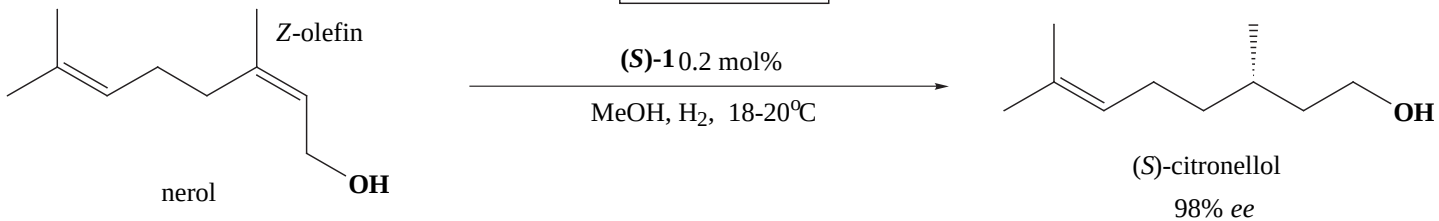
Noyori *JACS* **1986** (108) 7117.
Noyori *ACIEE* **2002** (41) 2008.

Asymmetric hydrogenation of allylic and homoallylic alcohols:

regioselectivity: allylic and homoallylic alcohols are hydrogenated whereas bis homoallylic and higher analogues are left untouched.



97 to >99% yields

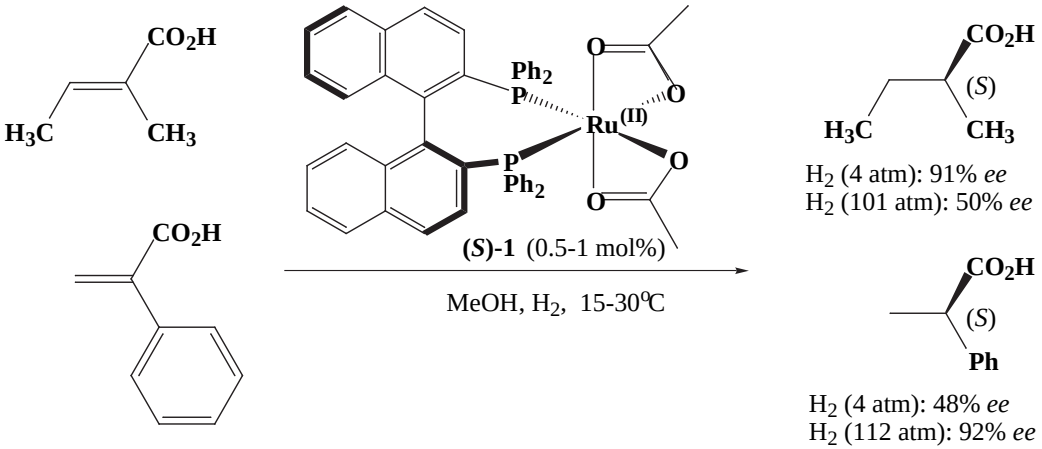


allylic olefin geometry may dictate the stereochemical outcome of the hydrogenation. Practical consequence: to obtain high ee's must start with stereochemically pure olefins.

Noyori *JACS* **1987** (109) 1596.

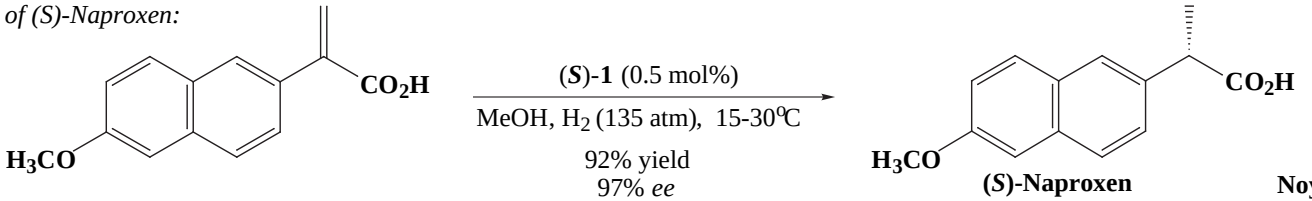
BINAP-Ru complexes: Noyori increases the substrate scope for asymmetric hydrogenations

The first demonstration of high asymmetric induction in the hydrogenation of substrates lacking an acylamino group: asymmetric hydrogenation of α,β-unsaturated carboxylic acids



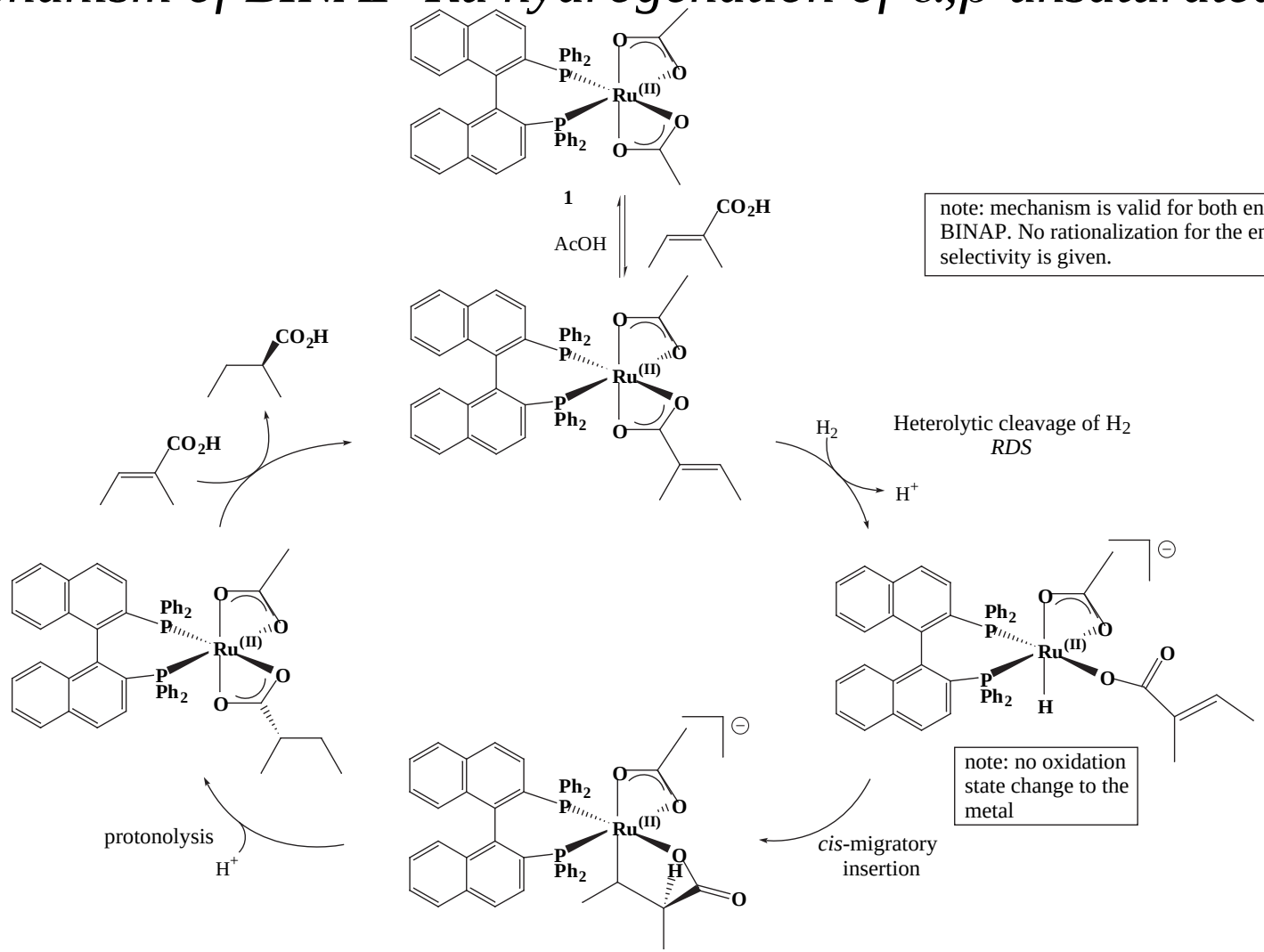
The degree of asymmetric induction is significantly affected by the H_2 pressure in a substrate specific manner. The implication of this is that a range of H_2 pressures must be screened to achieve optimal asymmetric induction on a substrate by substrate basis. No trend was observed and no rationale for the emperical observation was given.

Asymmetric Synthesis of (S)-Naproxen:

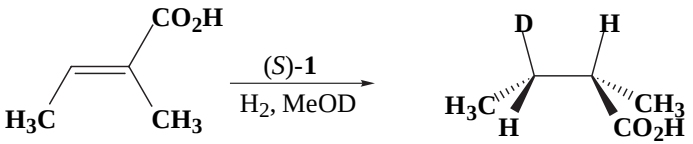


Noyori *JOC* **1987** (52) 3174.

Mechanism of BINAP-Ru hydrogenation of α,β-unsaturated acids



Reactions in MeOD



Experiment indicates that the hydrogen α to the acid comes from H_2 whereas the β-hydrogen comes from MeOH. Regio- and stereospecific deuterium incorporation indicates that *cis*-migratory insertion of the Ru-H is stereospecific as is cleavage of the Ru-C bond *via* protonolysis. The lack of D incorporation into the α position indicates that the rate of H/D exchange between the Ru-H and solvent is slow.

Halpern *JACS* **1991** (113) 589.

Question of the Week

$Ru(CH_3CO_2)_2$-[(*S*)-BINAP] catalyzes the hydrogenation of α-(acylamino)acrylic esters to give the (*S*) saturated product in >90% ee's. Propose a mechanism that accounts for the observed mixture of hydrogenation products when the reaction is run in MeOD. Note: your mechanism need not rationalize the absolute stereochemistry obtained.