MAX-PLANCK-INSTITUT
FÜR KOLLOID- UND
GRENZFLÄCHENFORSCHUNG

HOMOGENEOUS HYDROGENATION

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Biomolecular Systems

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8.1 INTRODUCTION — HOMOGENEOUS HYDROGENATION

Heterogeneous hydrogenation

Pt, Pd… solid or supported (e.g. Pd/C)

Easy separation and reuse

Homogeneous hydrogenation[1]

Unique stereoselectivity

Beyond alkenes

[1]M. Calvin *Trans. Faraday Soc.*, **1938**, 34, 1181. DOI: 10.1039/TF9383401181

8.1 INTRODUCTION — HOMOGENEOUS HYDROGENATION

- 1965 Wilkinson
- Industrially common in its asymmetric form (e.g. drug synthesis)
- Asymmetric (Nobel 2001, Noyori + Knowles)

8.1 INTRODUCTION — HOMOGENEOUS HYDROGENATION

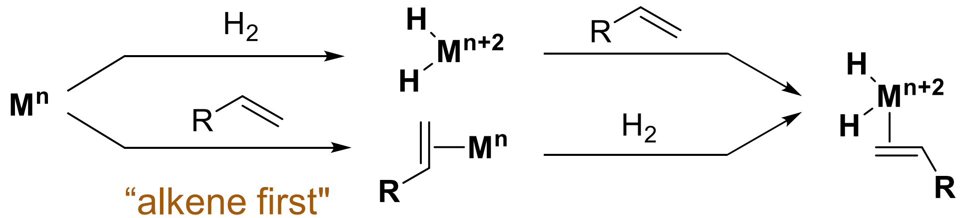
Homogeneous catalytic hydrogenation

Classical hydrogenation | **Transfer hydrogenation**

General Mechanisms

hydride

“hydrogen first"



“alkene first"

alkene

8.2.1 WILKINSON’S CATALYST - SYNTHESIS

$[RhCl(PPh_3)_3]$

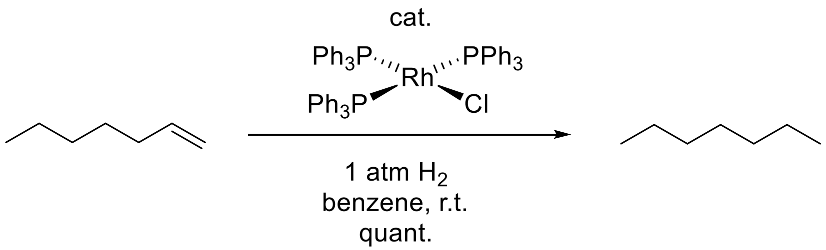
$$[RhCl_3(H_2O)_3] + PPh_3 \xrightarrow{EtOH} [RhCl(PPh_3)_3] + Ph_3PCl_2 \xrightarrow{H_2O} PPh_3O + HCl$$

drawback: limited phospine diversity

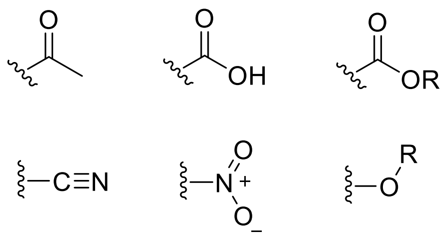
$$[Rh(cod)_2Cl]_2 \xrightarrow[n \leq 3]{nL} L_nRhCl \qquad L = PPh_3, R'R_2P$$

drawback: less direct

8.2.2 WILKINSON'S CATALYST - REACTIVITY

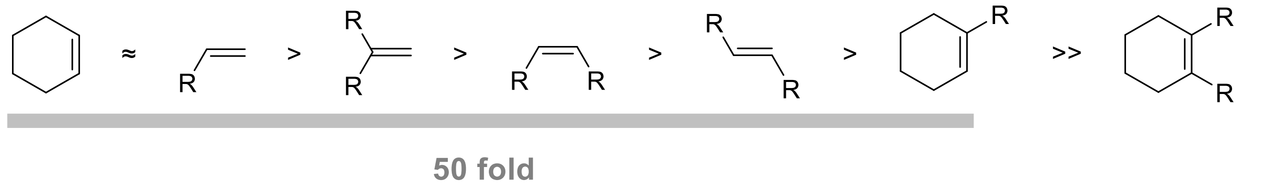


tolerated functional groups:

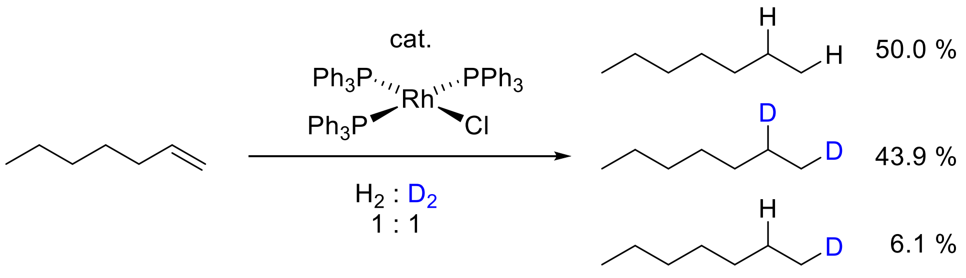


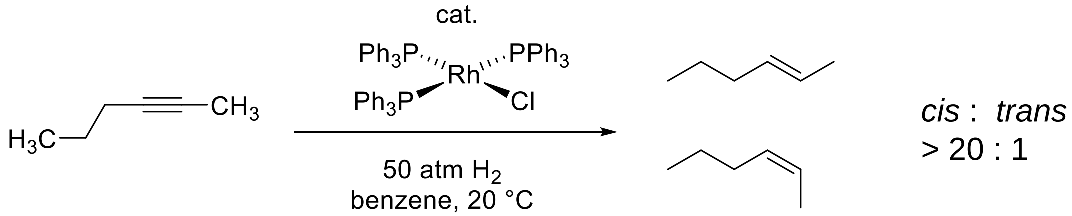
Wilkinson, *J. Chem. Soc. (A)* **1966**, 1711. DOI: 10.1039/J19660001711

8.2.2 WILKINSON'S CATALYST - REACTIVITY



- cis selective
- ambient temperature, pressure
- in benzene with alcoholic co-solvents
- no H_2/D_2 scrambling

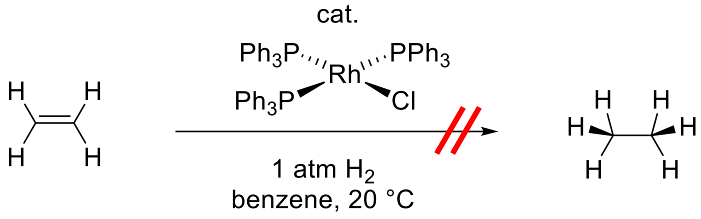


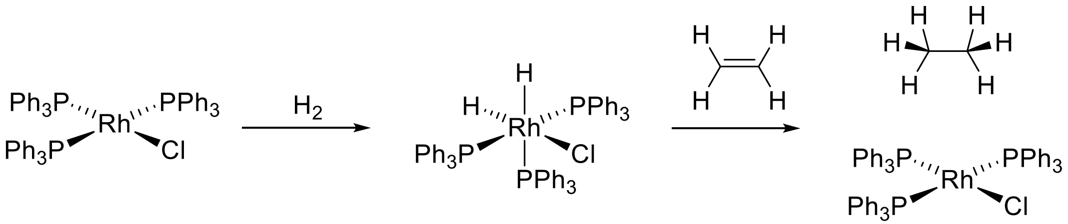


Wilkinson, *J. Chem. Soc. (A)* **1966**, 1711. DOI: 10.1039/J19660001711

8.2.2 WILKINSON’S CATALYST - REACTIVITY

ethylene is not hydrogenated (likely forms a stable complex with Rh)

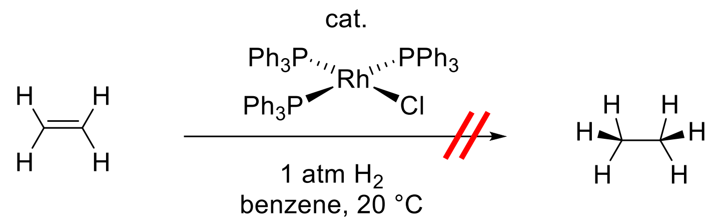




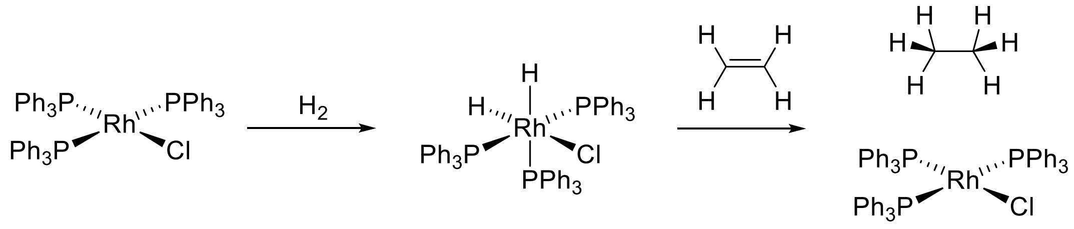
but it reacts stoichimetrically with preformed dihydride complex

HYDROGENATION: WILKINSON'S CATALYST

ethylene is not hydrogenated

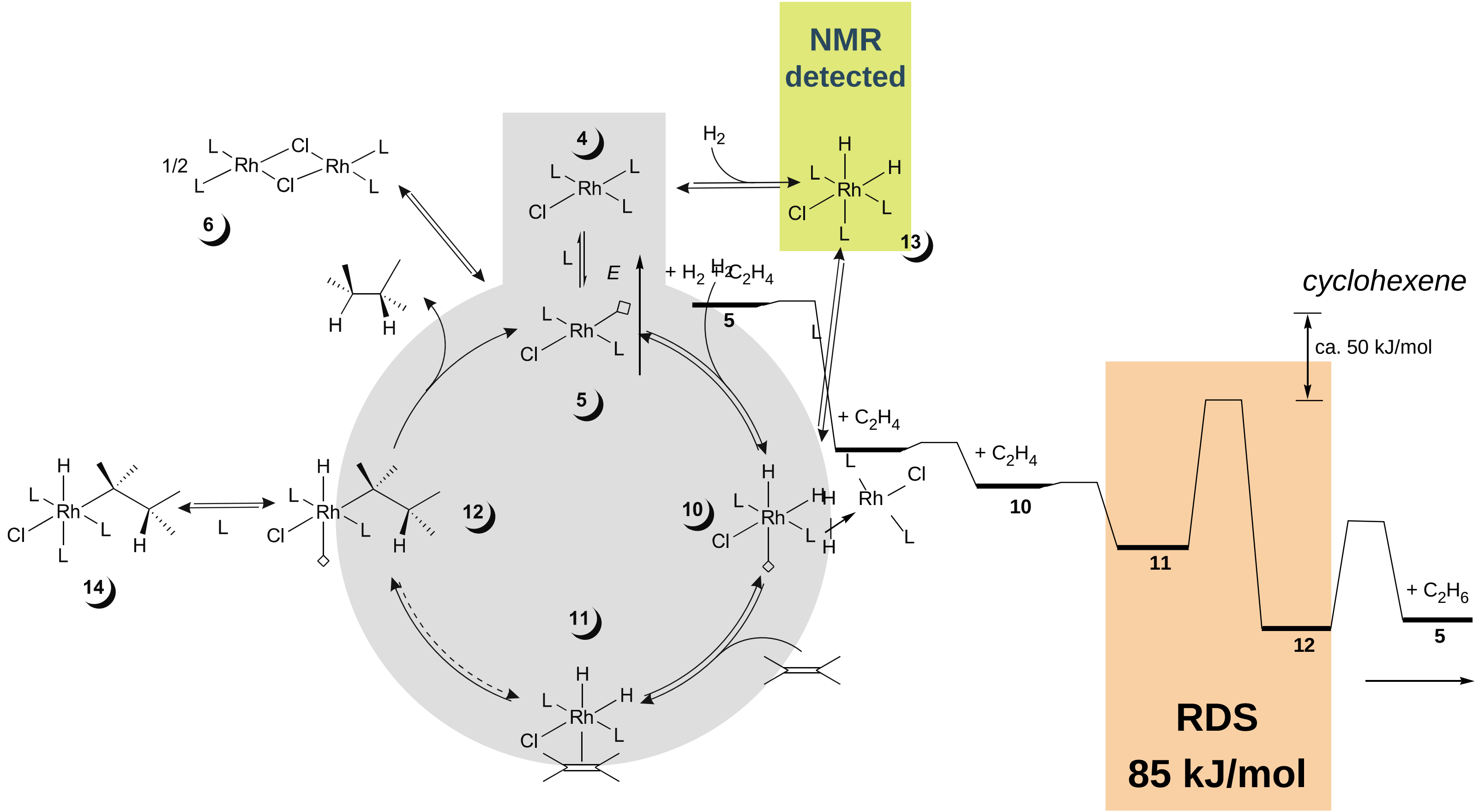


but...

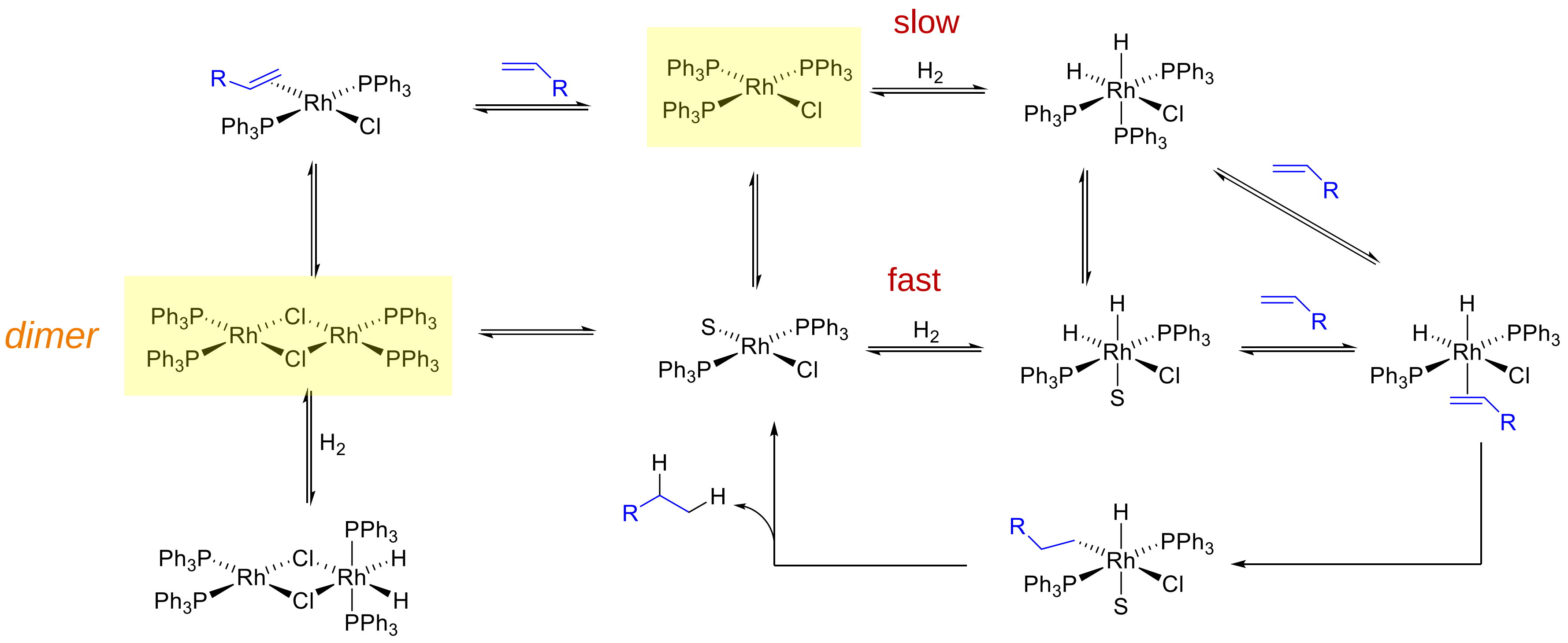


ethylene reacts stoichimetrically
with preformed dihydride complex

8.2.3 WILKINSON'S CATALYST – MECHANISM



8.2.3 WILKINSON'S CATALYST – MECHANISM

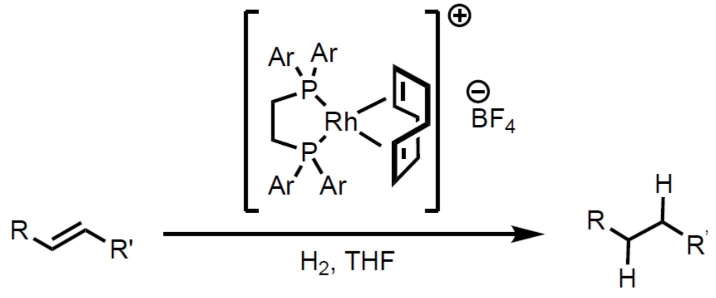


Halpern *Inorg. Chim. Acta* **1981**, *50*, 11. DOI: bndbhq

8.3 SCHROCK – OSBORN, POD #1

Cationic Rh complex (1969-1976)

The Schrock–Osborn catalyst shown below is highly active for the hydrogenation of olefins. **Propose the active (on-cycle) catalyst in the transformation.**



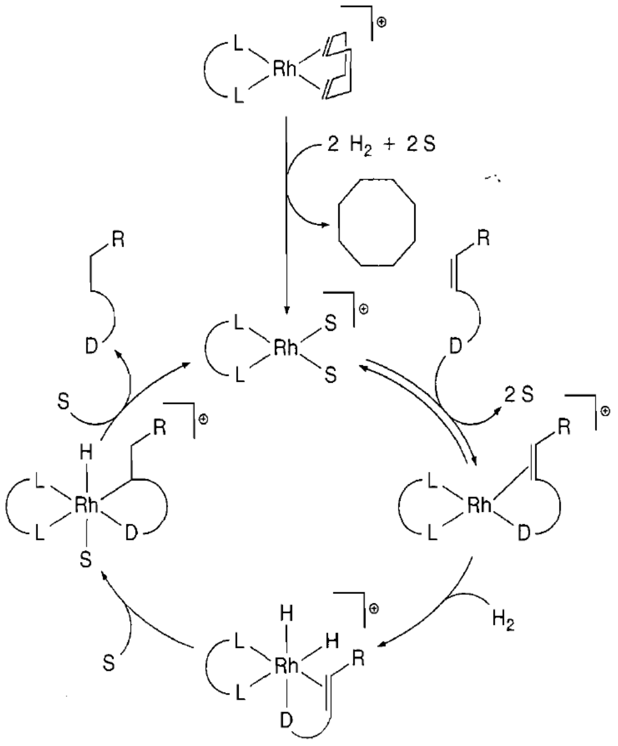
8.3.1 SCHROCK – OSBORN

Reactivity:

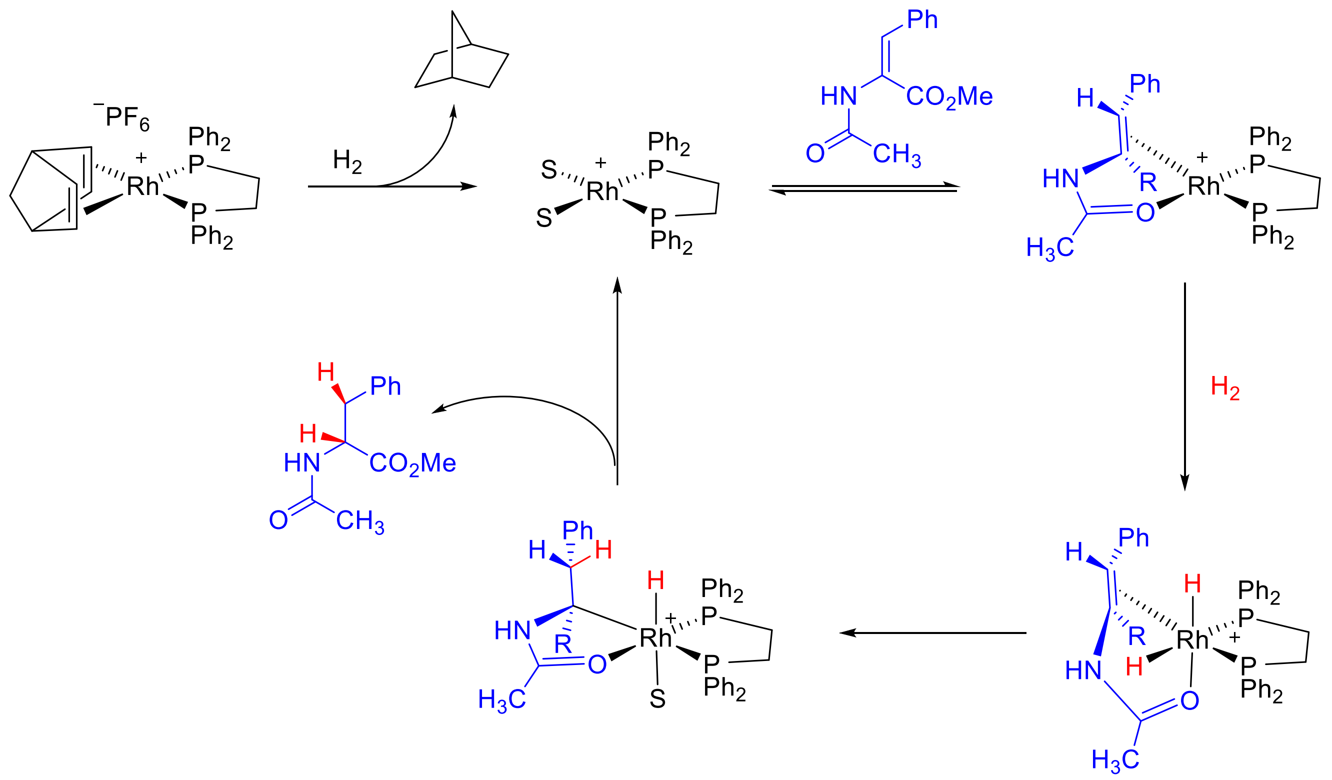
- Bidentate phosphines more reactive than monodentate
- Cationic Rh
- Intermediate $[RhL_2S_2]^+$ is acidic and can react with bases, H^+ needed

Mechanism

- Olefin first



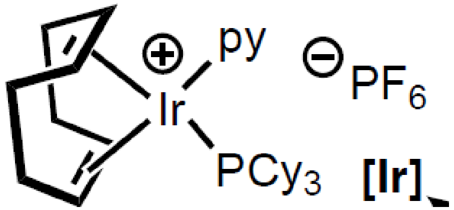
8.3.2 SCHROCK – OSBORN – MECHANISM

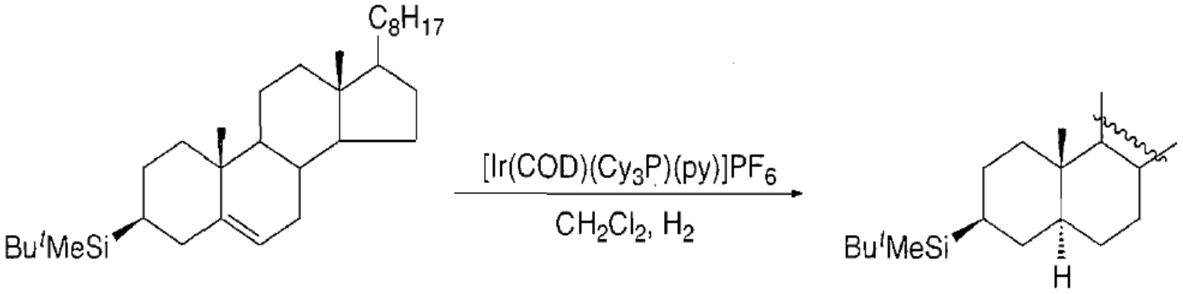


Halpern *Science* **1982**, *217*, 401. DOI: 10.1126/science.217.4558.401

8.4.1 CRABTREE'S CATALYST

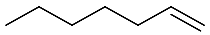
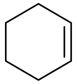
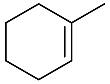
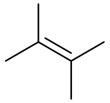
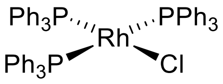
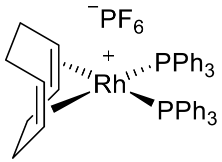
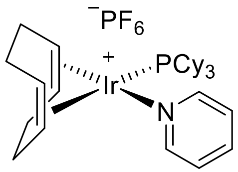
- 1977
- Non-coordinating solvents (CH_2Cl_2 vs. ROH Wilkinson)
- Most active hydrogenation catalyst known
- Active vs. hindered olefins





Crabtree, *Account Chem Res* **1979** 12, 9, 331. DOI: 10.1021/ar50141a005

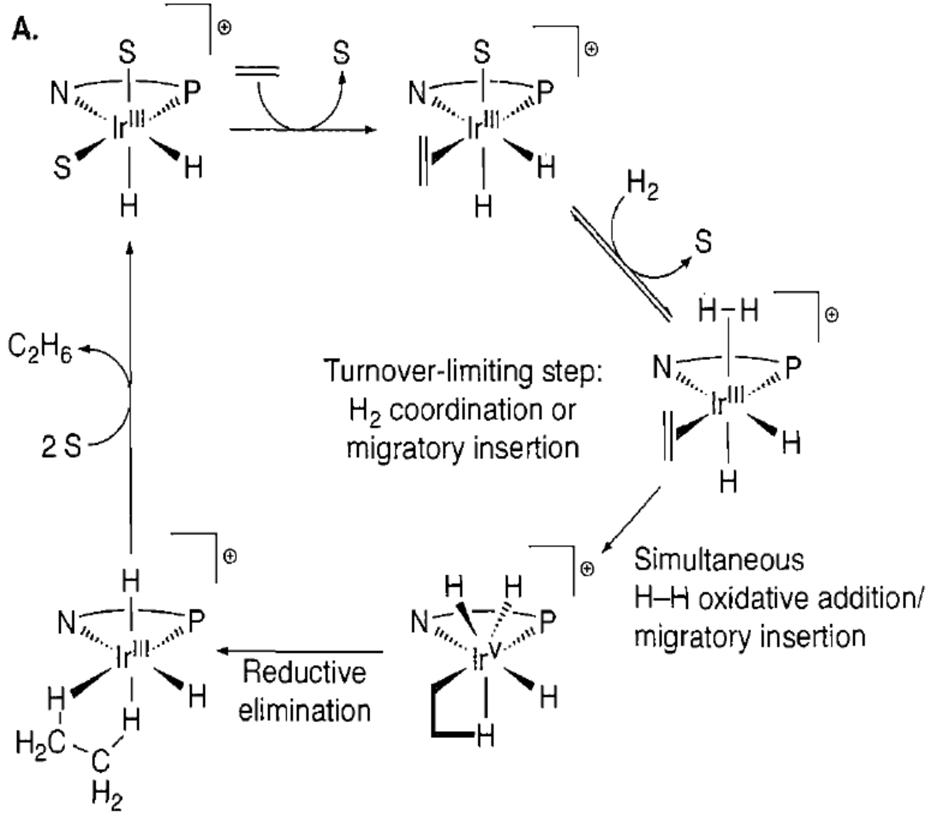
8.4.1 CRABTREE’S CATALYST – REACTIVITY

					
Wilkinson‘s catalyst		650	700	13	-
Schrock-Osborn catalyst		4000	10	-	-
Crabtree‘s catalyst		6400	4500	3800	4000

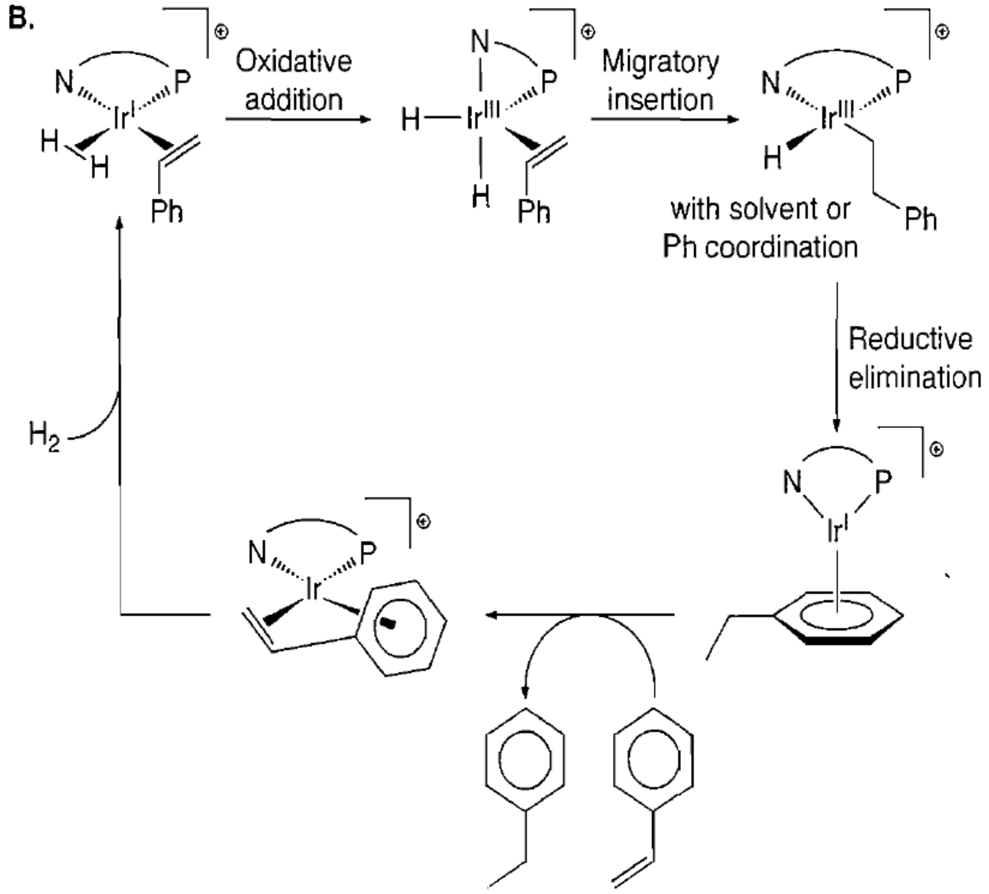
TOF / h^{-1}

Crabtree *Acc. Chem. Res.* **1979**, *12*, 331

8.4.1 CRABTREE'S CATALYST – MECHANISTIC DEBATE



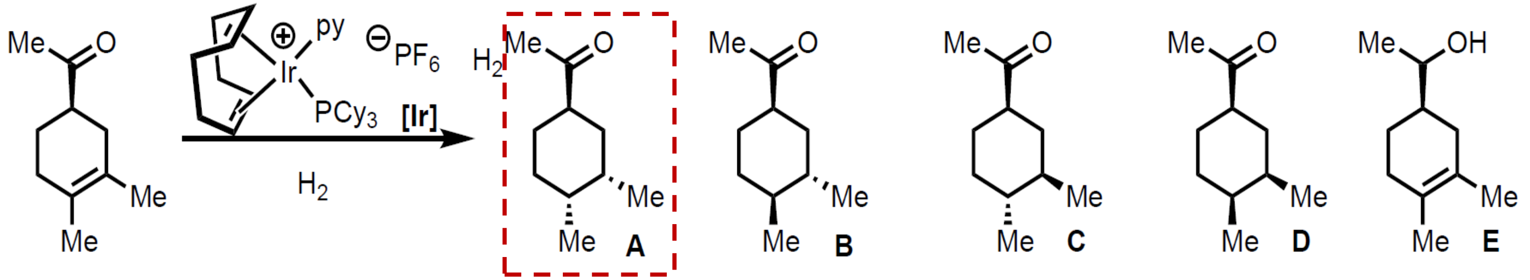
vs.



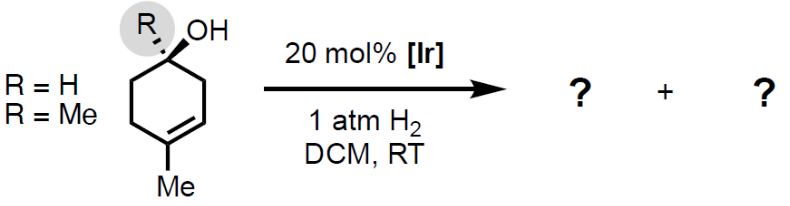
POD #2

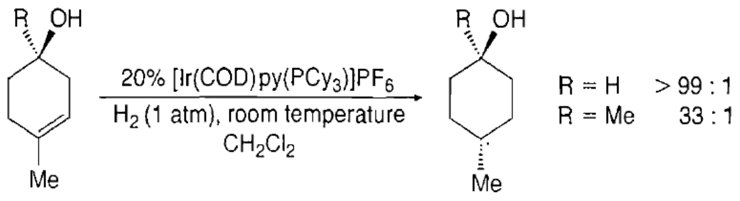
Consider the following iridium-catalyzed hydrogenation reactions.

a) Predict the major product and propose an intermediate to rationalize your choice.



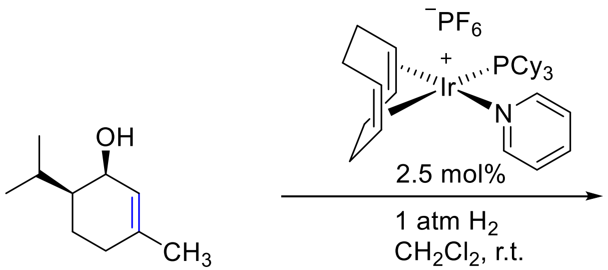
a) For each starting material, draw the two possible products, predict the major product, and discuss how the product distribution will change (moving from R = H to R = Me).

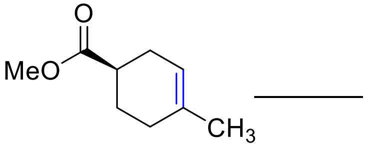


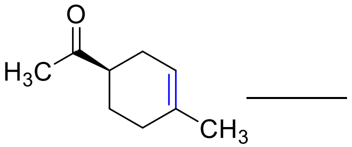


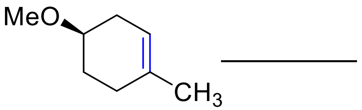
ACIE **1987** 26, 190. DOI: 10.1002/anie.198701901
JACS **1983** 105, 1072. DOI: 10.1021/ja00342a080

8.4.2 CRABTREE'S CATALYST – DIRECTED HYDROGENATION



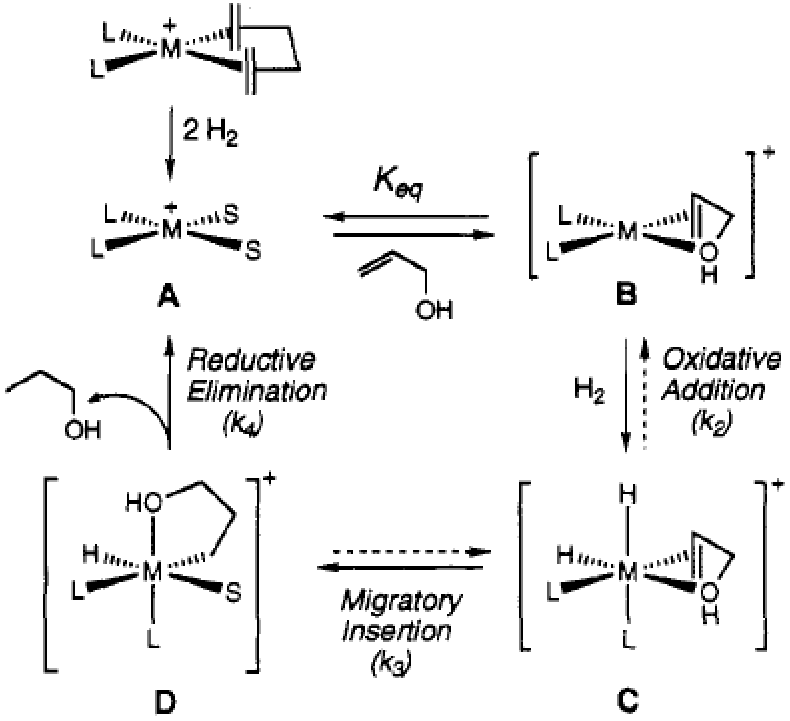


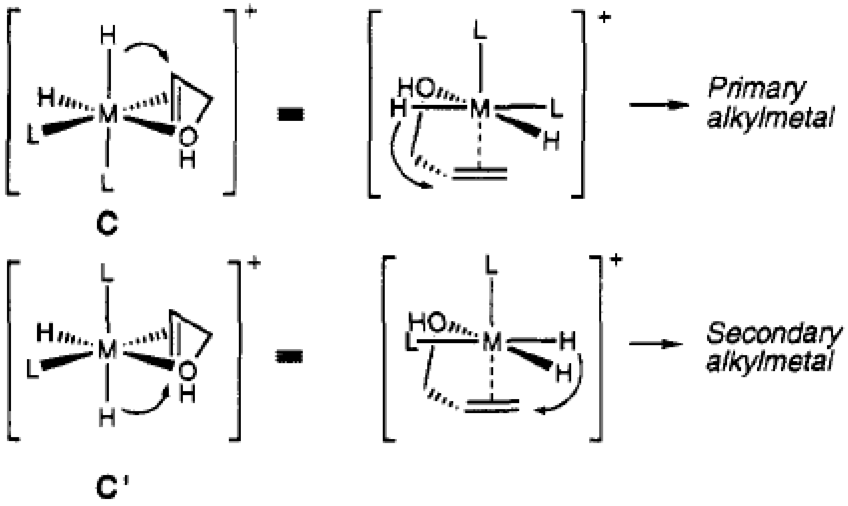




Crabtree *JOC* **1986**, *51*, 2655

8.4.2 CRABTREE'S CATALYST – DIRECTED HYDROGENATION

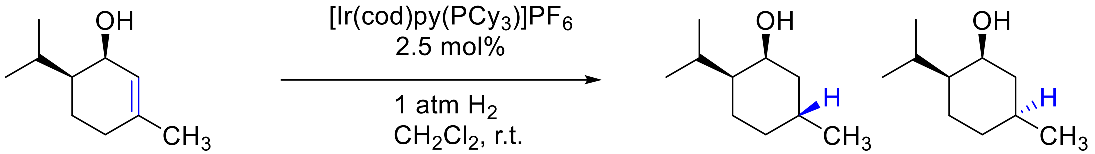




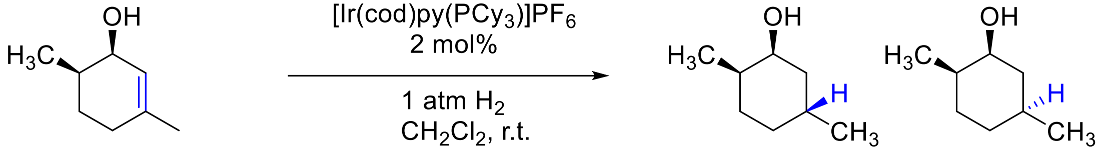
Evans *Chem Rev* **1993** 93, 4, 1307. DOI: 10.1021/cr00020a002

8.4.2 CRABTREE’S CATALYST – DIRECTED HYDROGENATION

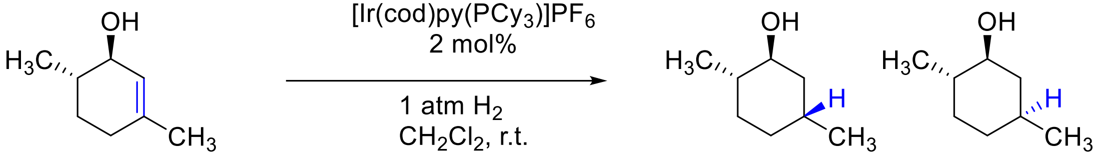
Allylic alcohols
substituent proximal to DG -> low impact



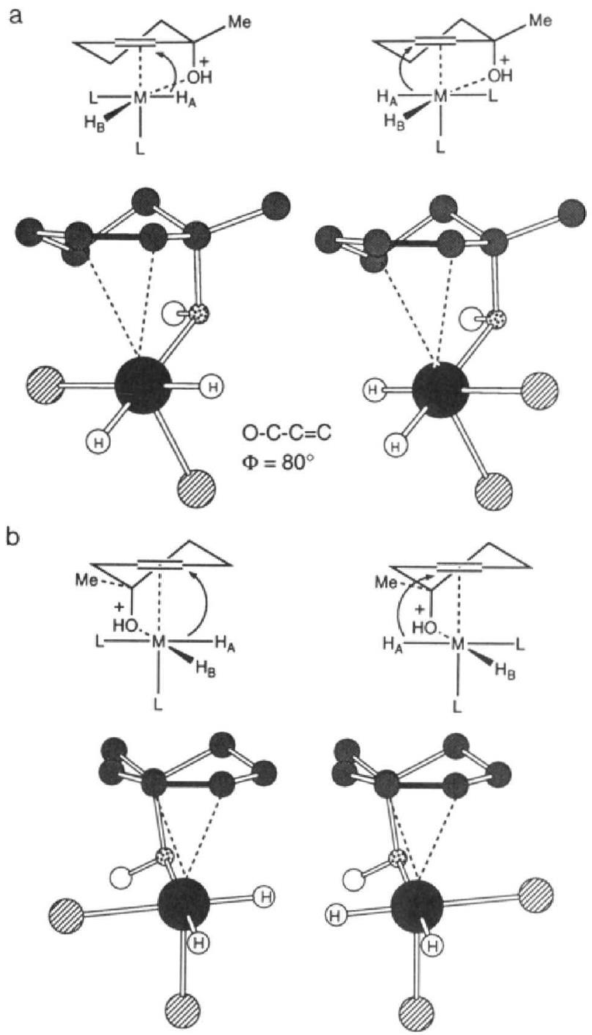
64 : 1
cf. Pd/C, EtOH: 1 : 5



65 : 1



36 : 1

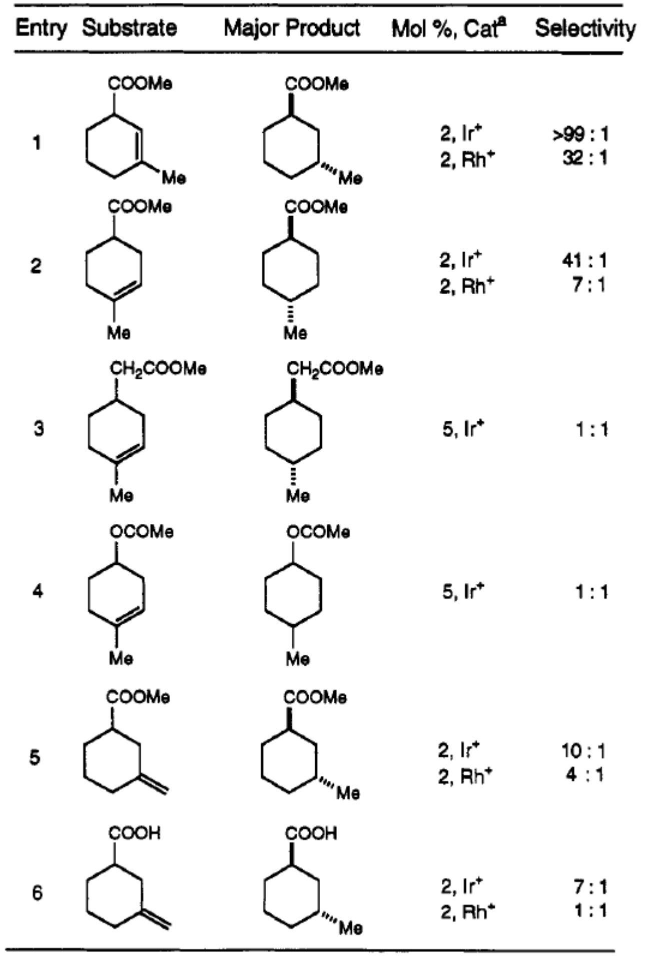


Cyclic allylic alcohols

Cyclic homoallylic alcohols

Evans *Chem Rev* **1993** 93, 4, 1307. DOI: 10.1021/cr00020a002

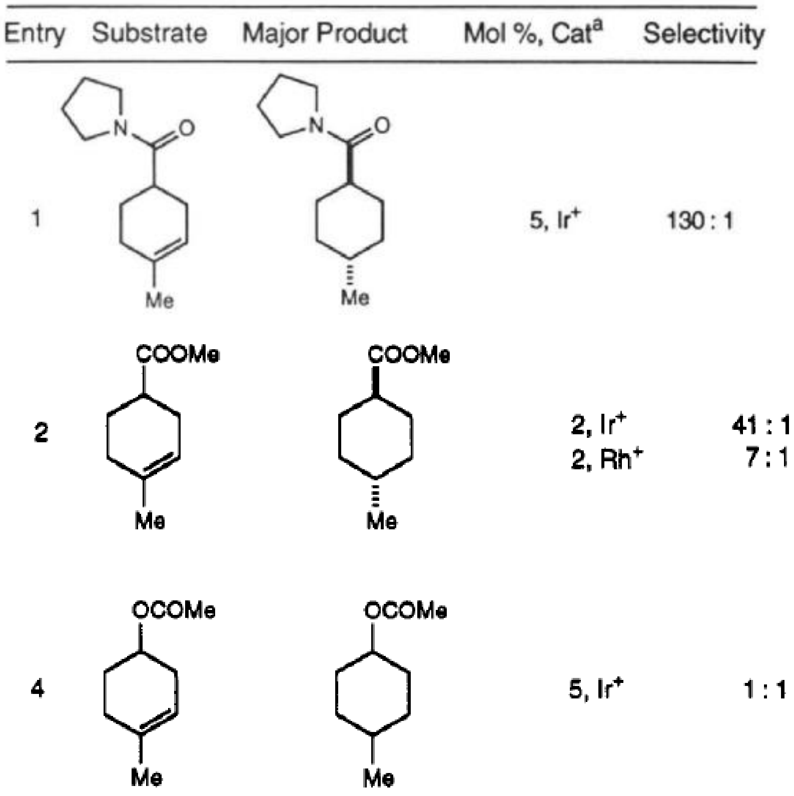
8.4.2 CRABTREE'S CATALYST – DIRECTED HYDROGENATION



Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1	COOMe, Me	COOMe, Me	2, Ir+ 2, Rh+	>99 : 1 32 : 1
2	COOMe, Me	COOMe, Me	2, Ir+ 2, Rh+	41 : 1 7 : 1
3	CH_2COOMe, Me	CH_2COOMe, Me	5, Ir+	1 : 1
4	OCOMe, Me	OCOMe, Me	5, Ir+	1 : 1
5	COOMe	COOMe, Me	2, Ir+ 2, Rh+	10 : 1 4 : 1
6	COOH	COOH, Me	2, Ir+ 2, Rh+	7 : 1 1 : 1

[a] Catalysts: $[Rh(nbd)(diphos\text{-}4)]BF_4(Rh^+)$; $[Ir(cod)py(PCY_3)]PF_6(Ir^+)$. Reactions were run at 15 psi H_2.

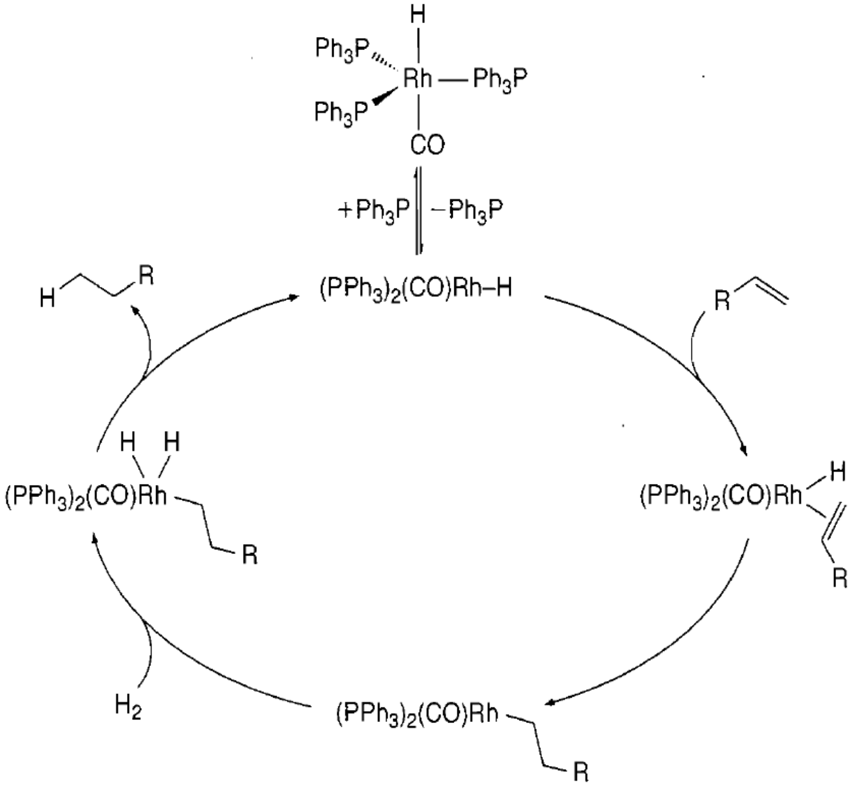
Evans *Chem Rev* **1993** 93, 4, 1307. DOI: 10.1021/cr00020a002



Entry	Substrate	Major Product	Mol %, Cat[a]	Selectivity
1	N, O, Me	N, O, Me	5, Ir+	130 : 1
2	COOMe, Me	COOMe, Me	2, Ir+ 2, Rh+	41 : 1 7 : 1
4	OCOMe, Me	OCOMe, Me	5, Ir+	1 : 1

- Amide better DG than esters

8.5.1 MONOHYDRIDE INTERMEDIATES – TERMINAL OLEFINS



slow

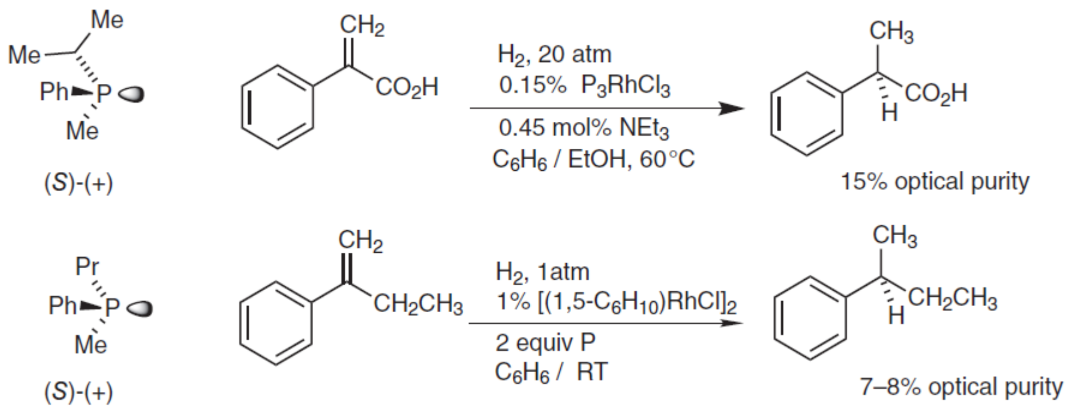
Origin of regioselectivity:

- Monohydride mechanism
  (H_2 OA is slow, and 1,2migratory insertion reversible, with terminal alkyl-Rh favored due to sterics)
- CO ligand makes Rh more electrophilic
  (thus agostic interactions -> more β-elimination -> isomerization as result of 1,2-migratory insertion + β-elimination)

8.6.1 ASYMMETRIC HOMOGENEOUS HYDROGENATION

Knowles

Horner



*“**ATKINSON** Did you consider the possibility of using a bi-phosphine, optically active?*

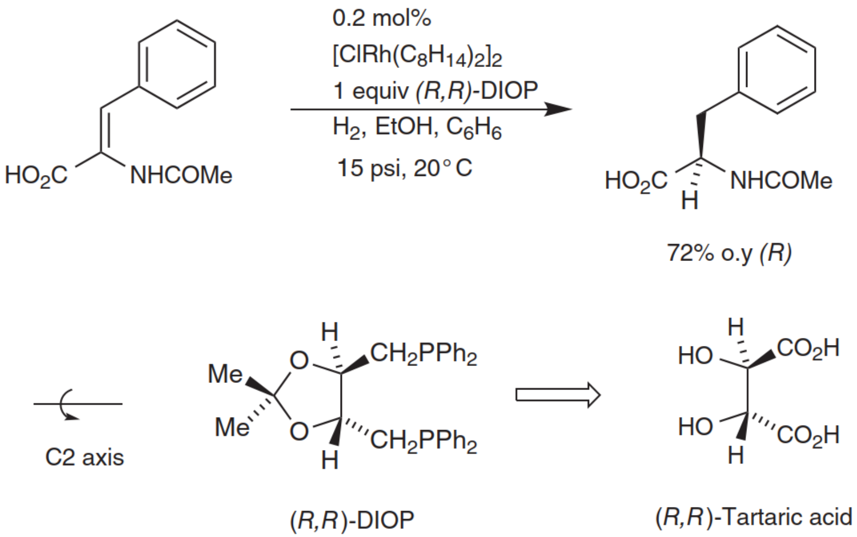
***KNOWLES** We’ve considered that very strongly. The main problem is that of synthetically making it”*

at a 1970 conference

[As reported in: *Asymmetric Hydrogenation and Transfer Hydrogenation*, Wiley, 2021, p. 13]

Knowles, *Chem. Commun.*, **1968,** 22, 1445. DOI: 10.1039/C19680001445
Horner, *ACIE*, **1968**, 7, 942. DOI: 10.1002/anie.196809422

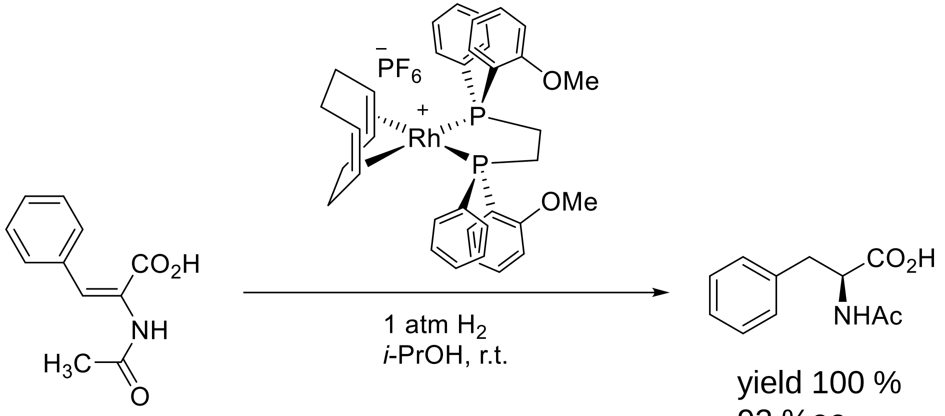
8.6.2 DIOP: FIRST CHIRAL BIPHOSPHINE



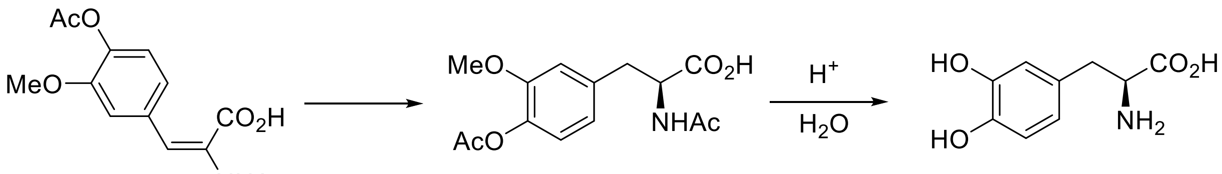
Dang and Kagan, *Chem. Commun.*, **1971**, 481. DOI: 10.1039/C29710000481

8.6.6 ASYMMETRIC HYDROGENATION: KNOWLES

Nobel Prize 2001 (w/ Noyori)



yield 100 %
93 %*ee*

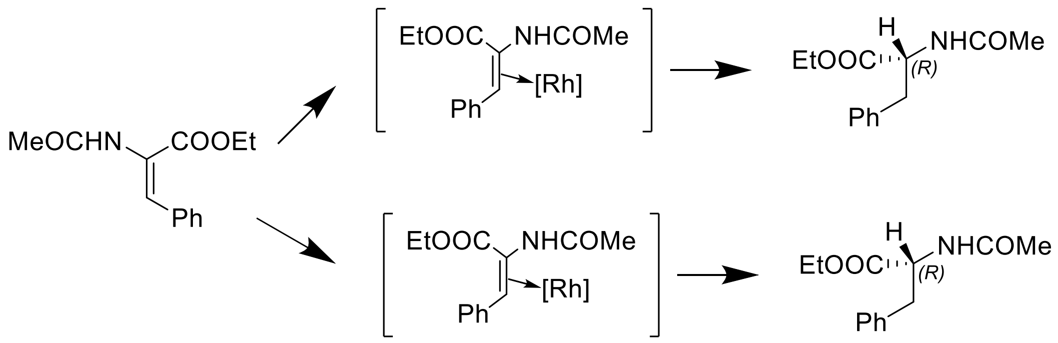


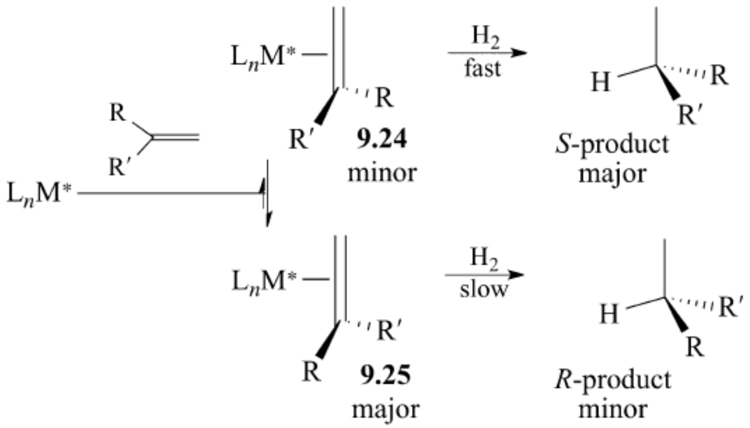
L-DOPA

yield 100 %
95 %*ee*

Knowles *JACS* **1975** 97, 2567. DOI: 10.1021/ja00842a058
mechanism: Halpern *Science* **1982,** 217, 401. DOI: 10.1126/science.217.4558.401

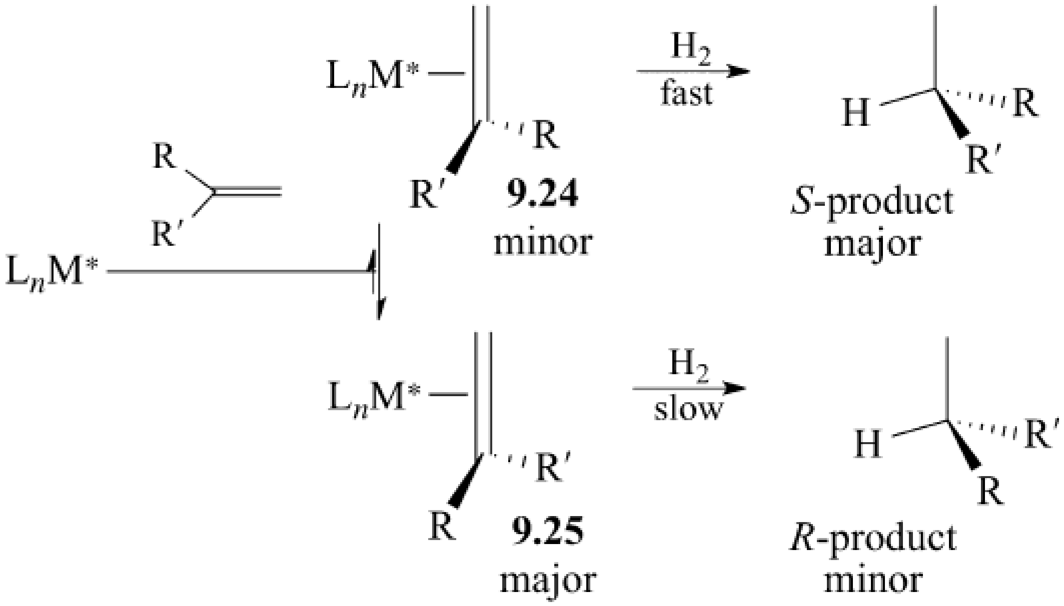
8.6.6 ASYMMETRIC HYDROGENATION: KNOWLES



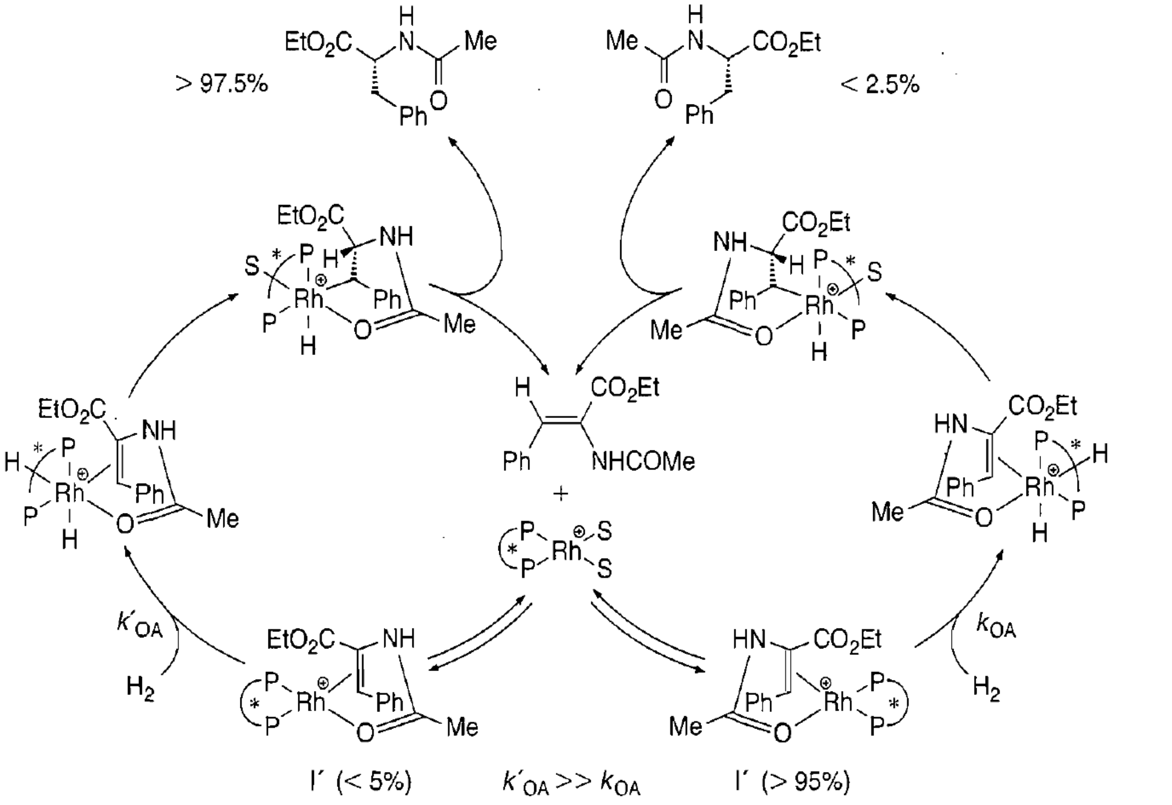


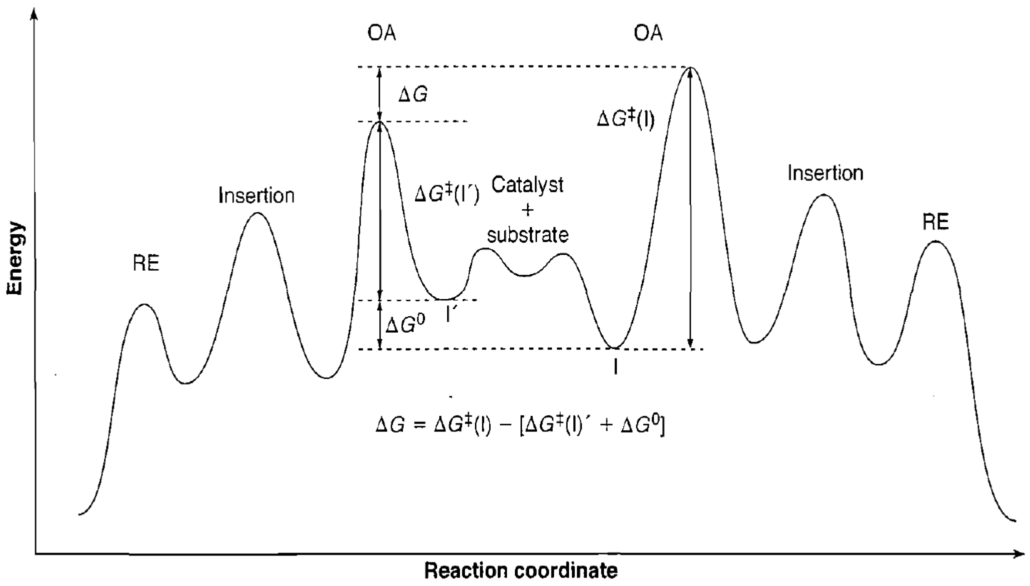
Knowles *JACS* **1975** 97, 2567. DOI: 10.1021/ja00842a058
mechanism: Halpern *Science* **1982,** 217, 401. DOI: 10.1126/science.217.4558.401

8.6.6 ASYMMETRIC HYDROGENATION: KNOWLES



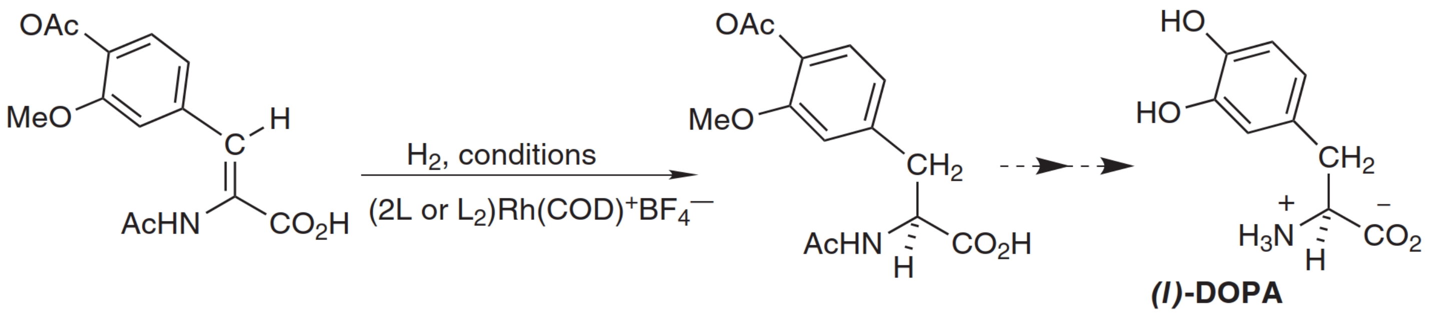
8.6.6 ASYMMETRIC HYDROGENATION: KNOWLES





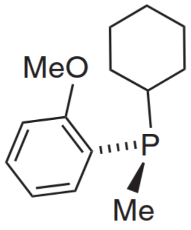
Halpern *Science* **1982,** 217, 401. DOI: 10.1126/science.217.4558.401

8.6.3 APPLICATION IN L-DOPA SYNTHESIS

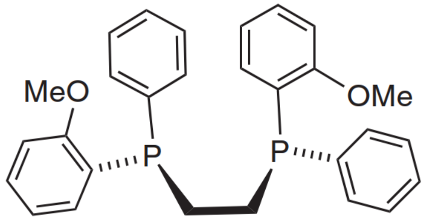


Monodentate
CAMP

Cyclohexyl o-**a**nisyl
methyl**p**hosphine



I *(R)*-CAMP
H_2, 10 psi.,0.03% cat., 50 °C,
i-PrOH, **88% o.p.**



L_2, *(R,R)*-DIPAMP
H_2, 60 psi.,0.05% cat., 4 h.
88% *i*-PrOH, **94% o.p.**

Bidentate
DIPAMP
(dimerized PAMP)

Phenyl o-**a**nylsyl
methyl**p**hospine

Dang and Kagan, *Chem. Commun.*, **1971**, 481. DOI: 10.1039/C29710000481