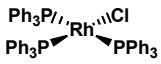
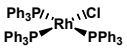
Categories and Dichotomies:

Heterogeneous or Homogeneous	Heterolytic or Homolytic H_2 Activation
Neutral or Cationic	Racemic or Enantioselective
Directed or Non-directed	Syn or Trans Addition

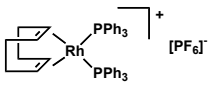
Homogeneous Hydrogenation



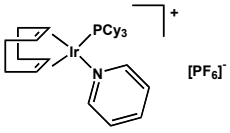
Advantages:	Disadvantages:
Mild conditions	Purification
Improved selectivity	$$$$
Directed Hydrogenation	Often less reactive than heterogeneous
Enantioselective Hydrogenation	
Mechanistically accessible	



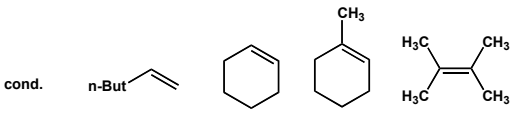
Wilkinson's Catalyst
1st eg of homogeneous cat with activity similar to heterogeneous
J. Chem. Soc. (A) 1966, 1711



Schrock-Osborn Cat
Cationic version of Wilkinson's
JACS, 1976, 2134, 2143, 4450



Crabtree's catalyst
Acc. Chem. Res. 1979, 331

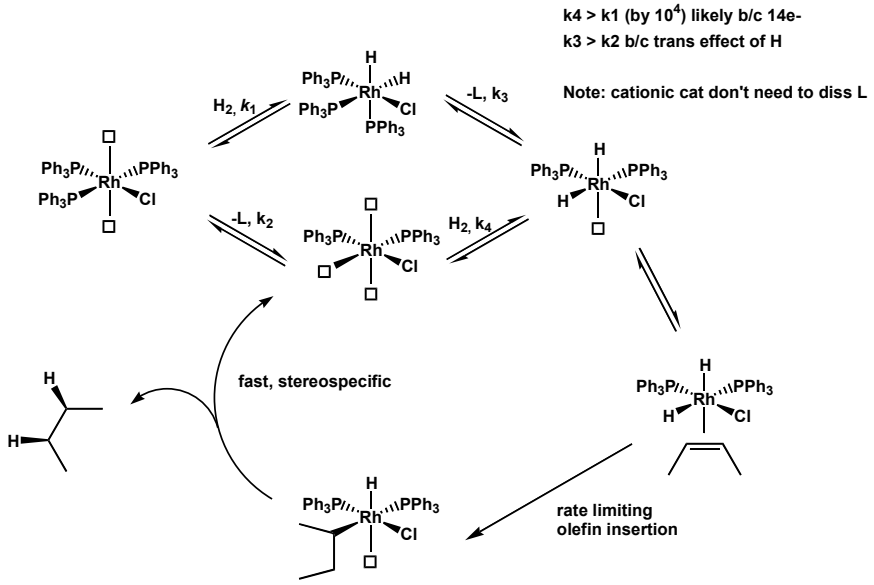


	TOF			
rt, Benz/EtOH	650	700	13	--
rt, CH_2Cl_2	4000	10	--	--
0°C, CH_2Cl_2	6400	4500	3800	4000

-cationic cat more active than neutral
-Ir only cat. for tri- and tetra-substituted olefins

Ready; Catalysis Hydrogenation

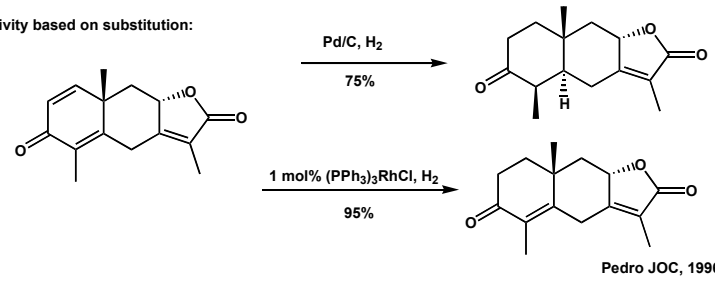
Mechanism of Hydrogenation with Wilkinson's Cat



Ready; Catalysis Hydrogenation

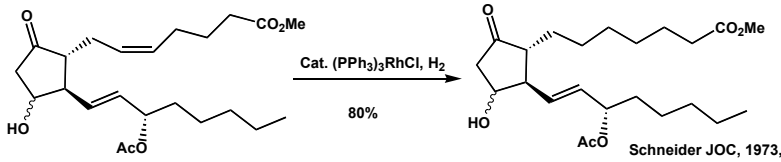
Reactions with Wilkinson's Catalyst

selectivity based on substitution:



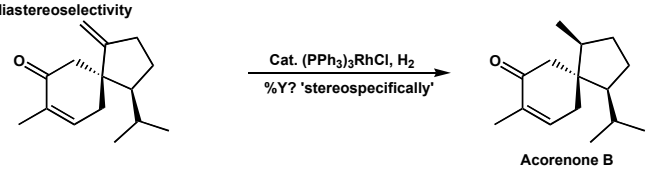
Pedro JOC, 1996, 3815

selectivity based based on geometry:



Schneider JOC, 1973, 951

diastereoselectivity

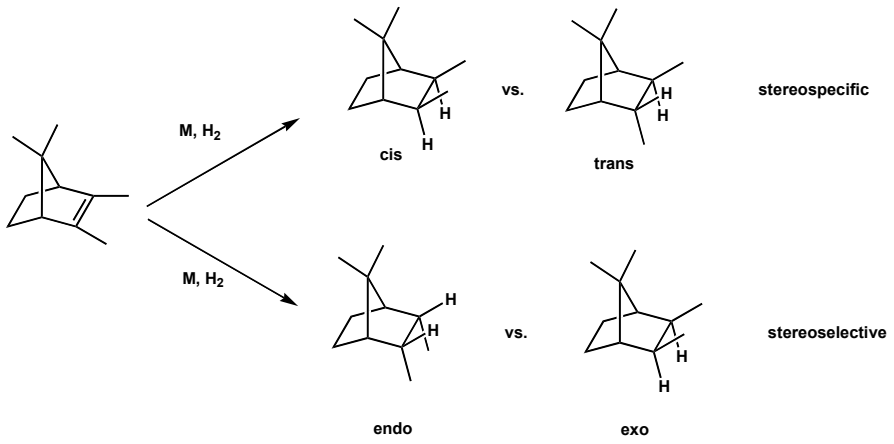


Semmelhack JACS, 1980, 5924

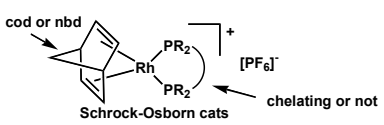
Acorenone B

Stereospecific: Stereochemical outcome dictated by mechanism
Stereoselective: Stereochemical outcome dictated by relative rates

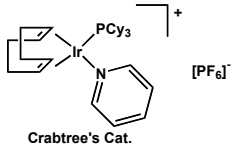
really good stereoselectivity does not get promoted to stereospecificity



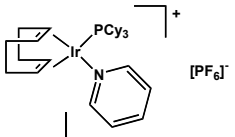
Cationic Catalysts:
-very reactive
-can be directed



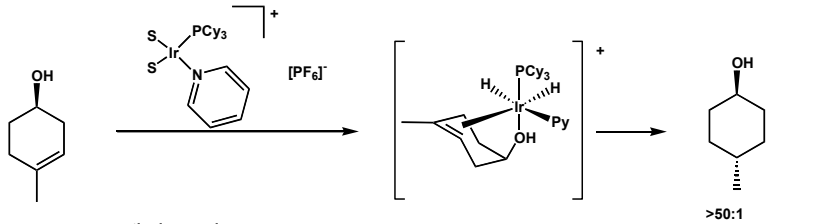
Schrock-Osborn cats



Crabtree's Cat.



-c-oct

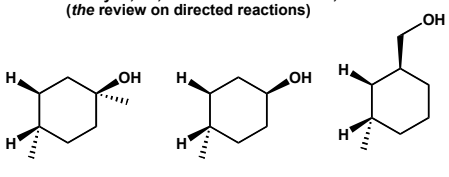


cationic complexes:
-open coordination site for chelating group
-positive charge = lewis acidic

>50:1
Evans, TL, 1984, 4637

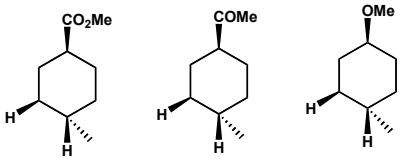
Directed Reductions: examples

Hoveyda, Fu, Evans Chem Rev. 1993, 1307
(*the* review on directed reactions)



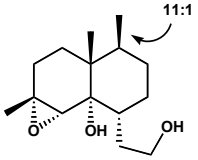
tertiary >100:1 | secondary 33:1 | primary 6:1

Stork, JACS 1983, 1072



Ir^+ / Pd/C: 56:1 / 1.4:1 | >100:1 / 1.3:1 | >100:1 / 1.4:1

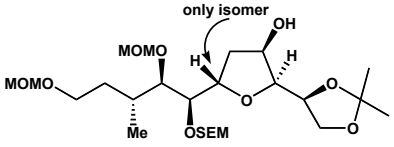
in synthesis:



Cond: $[Ir(COD)(Py)(PCy_3)]PF_6$

99%

Barriault, OL, 2001, 1925



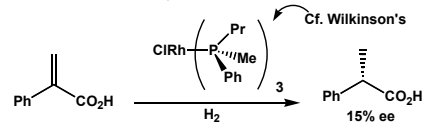
Cond: NaH, $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$, 800 psi H_2

68%

Paquette, OL, 2002, 937

Asymmetric Hydrogenation

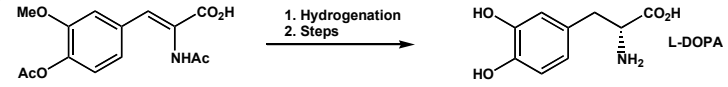
an experiment that changed the world:

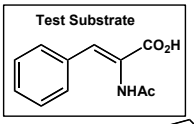


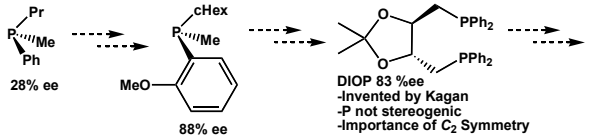
The inventive process is not clearly understood, but one factor that seems to be important is to have a heavy infusion of naivety. That is why, so frequently, it is not the experts that do the inventing, but they are the ones who, once the lead is established, come in and exploit the area
Knowles, Nobel Lecture (ACIEE, 2002, 1998)

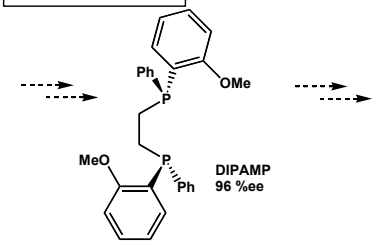
-Phosphines configurationally stable under rxn conditions
-can communicate asymmetry to substrate
-1st eg of asymmetric hydrogenation

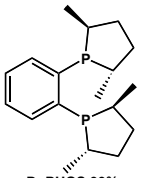
Target Rxn:

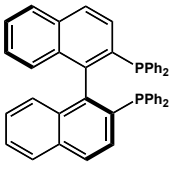




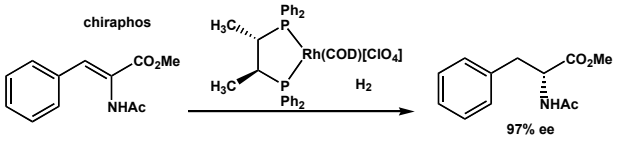


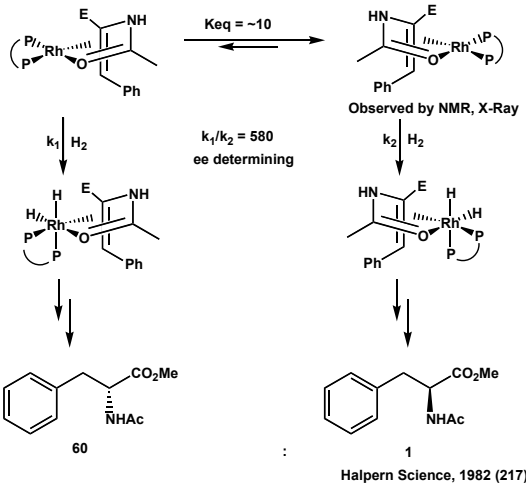






Ready; Catalysis Hydrogenation





Curtin-Hammett:
Equilibrium between two reactive intermediates on separate reactions paths.

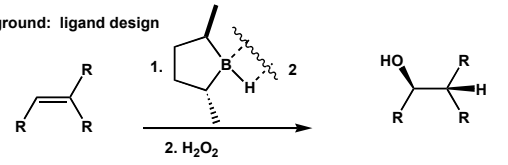
ee-determining: 1st irreversible step that involves enantioselection

Halpern Science, 1982 (217) 401

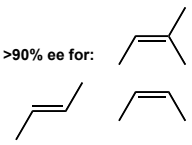
Ready; Catalysis Hydrogenation

General Enantioselective Synthesis of Amino Acids

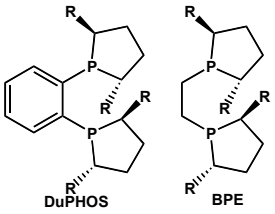
Background: ligand design



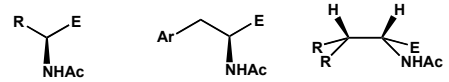
>90% ee for:



-a "simple and asthetically pleasing" chiral borane
-synthesized in 7 steps (resolution)
-Masamune, Jacs, 1985, 4549



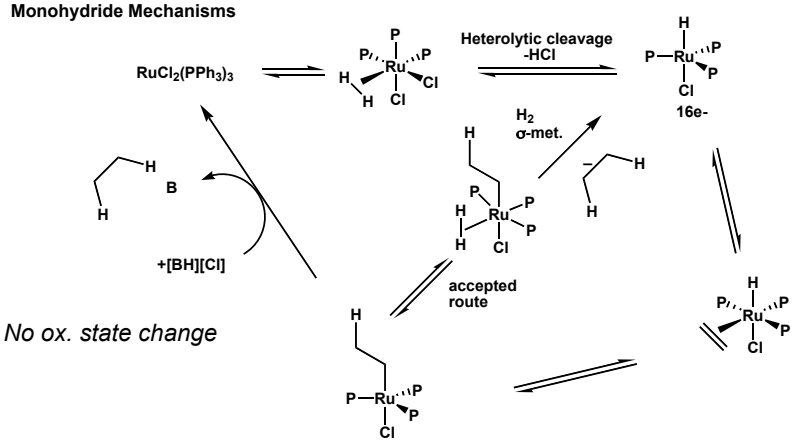
-e rich
-steric tuning possible
-stereogenic centers close to Rh
-comercially available (strem)
-Burk, JACS, 1993, 10125

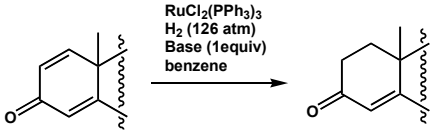


Like NMR experiments, comming up with a catchy name seems to be as important as the actual utility

One of the most general asymmetric cat rxns

Monohydride Mechanisms

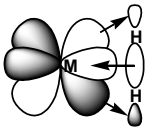




base	conv.
NEt3	95
Aniline	88
Na2CO3	73
None	76

Tsuneda, Bull Chem Soc, Jpn, 1973 (46) 279

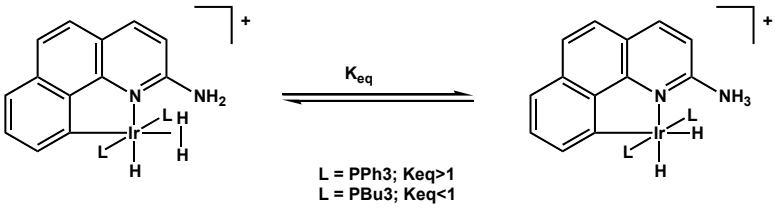
Heterolytic activation: Mechanistic Considerations



$\sigma_{HH->M} > \pi_{M->HH}$ → $M^n—H + H^+$ no ox state change

$\pi_{M->HH} > \sigma_{HH->M}$ → $M^{(n+2)}(H)_2$ +2 ox. state change

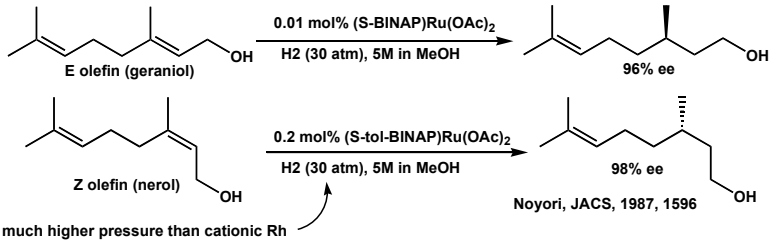
-σ-coordination acidifies H
-common for high ox state metals
-heterolytic more favored for e- poor M
-effect of other ligands:

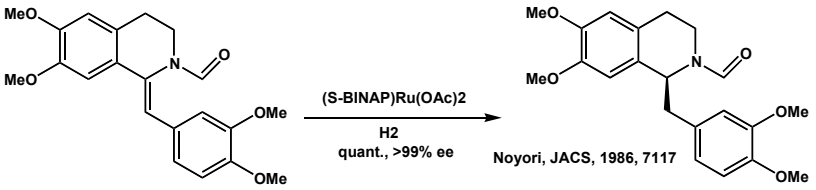


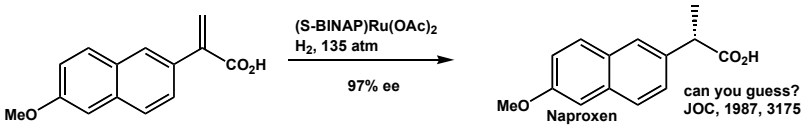
crabtree, chem com. 1999, 297

Ready; Catalysis Hydrogenation

(BINAP)Ru(II) complexes: Great catalysts for directed asymmetric reduction:

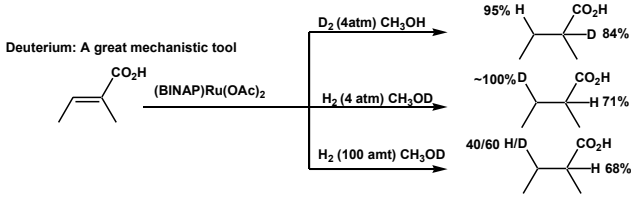


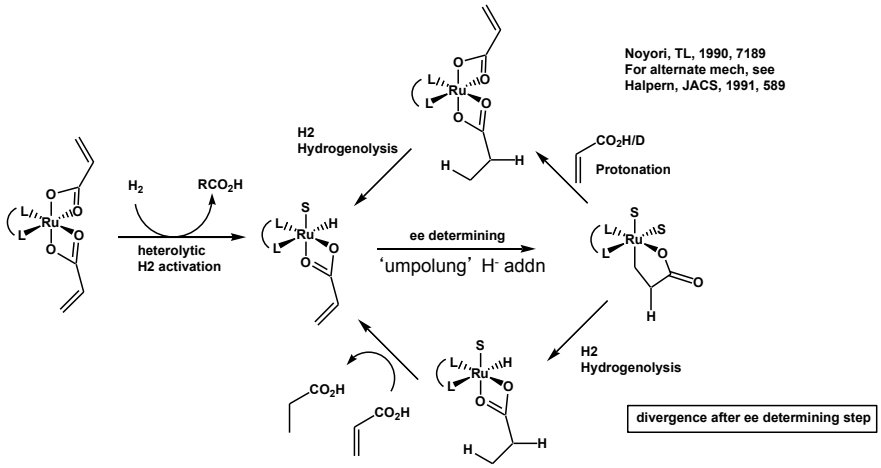




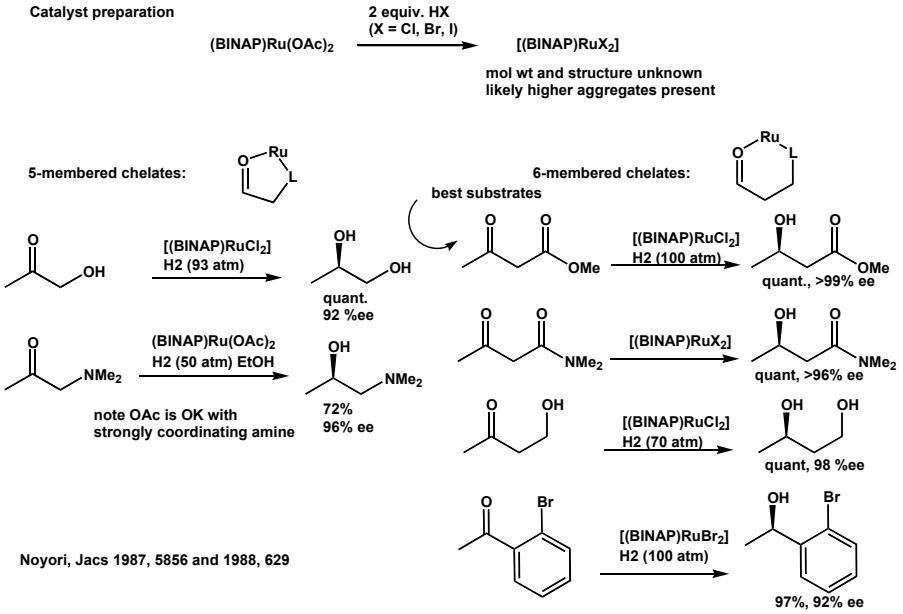
Ready; Catalysis Hydrogenation

Deuterium: A great mechanistic tool





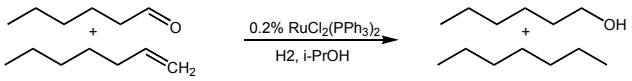
Substrate-Directed asymmetric Ketone Hydrogenations (aka 'Noyori hydrogenations')



Noyori, Jacs 1987, 5856 and 1988, 629

Non-Directed Asymmetric Ketone Hydrogenations (aka 'Noyori hydrogenations')

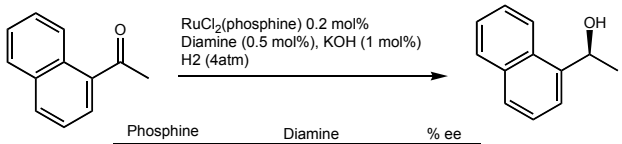
challege: how to reduce carbonyl in presence of olefin?
answer: Additive change reactivity (generally true in catalysis; very hard to predict! Review: ACIEE, 1999, 1570)

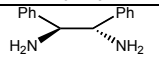
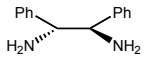
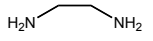
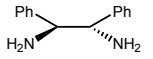


additive	relative rate: aldehyde	relative rate: olefin
none	1	250
KOH (1%), $H_2N(CH_2)_2NH_2$ (0.5%)	1500	1

Noyori, Jacs 1995, 10417

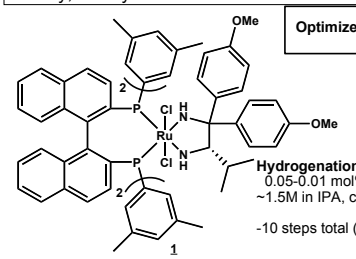
Enantioselective version:



Phosphine	Diamine	% ee
S-Binap		97
"		14
"		57
PPh_3		75

Noyori, JACS, 1995, 2675

Ready; Catalysis Hydrogenation

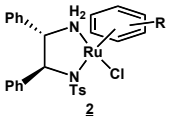


Optimized systems for non-directed hydrogenation:

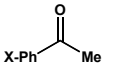
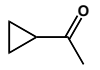
Hydrogenation conditions with 1
0.05-0.01 mol% Ru
~1.5M in IPA, cat K2CO3, 8-10 atm H2

-10 steps total (4 for P, 4 for N) to make cat

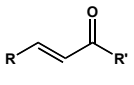
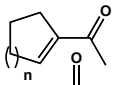
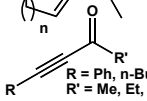
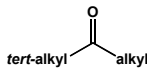
Transfer Hydrogenation conditions with 2
0.5-0.1 mol% Ru, 2M 5:2 HCO2H:Et3N
or
0.5-0.1 mol% Ru, 2.5-0.5 mol% KOH, 0.1M IPA



2

Substrate		1	% ee (% y)* 2-IPA	2-HCO2H
	X = H	99	97	98
	3-Cl		98	97
	4-Cl	99	93	95
	3-OMe		96	98
	4-OMe	99	72(53)	97
		99		
4-Br,I,NO2,NH2				
	n = 1		91 (45)	99
	n = 2		97 (65)	99
		95		

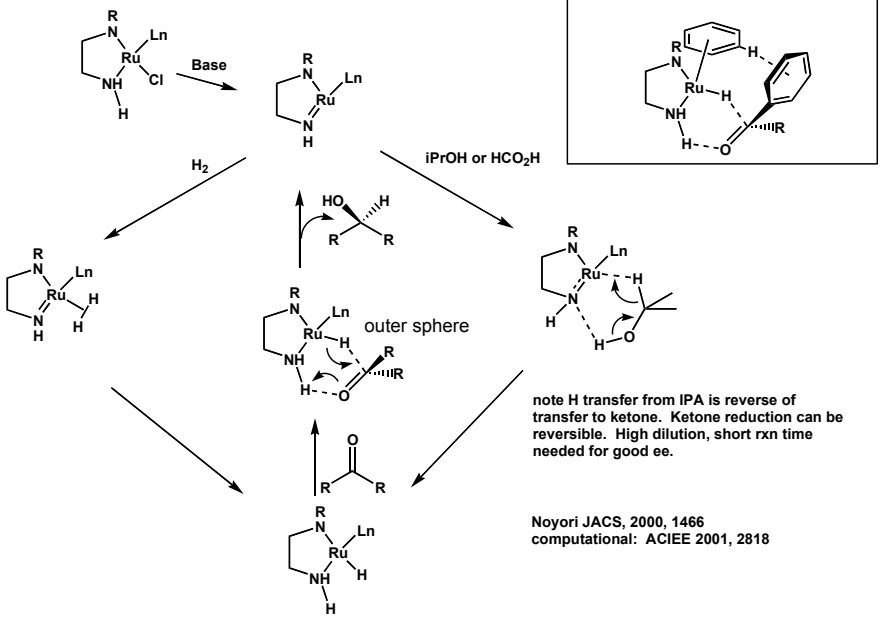
* all %y >90 unless noted

Substrate		1	% ee (% y)* 2-IPA	2-HCO2H
	R = Ph R' = Me	96		
	R = Ph R' = iPr	86		
	R = pent R' = Me	97		
	n = 1-3	99		
	R = Ph, n-Bu TMS R' = Me, Et, iPr, tBu, cHex		97-99	
	*tert*-alkyl alkyl/vinyl/aryl	90-97		

Noyori, JACS
1996, 2521
1997, 8738
1998, 13529
2005, 8288

Ready; Catalysis Hydrogenation

Mechanism of Ru(diamine) hydrogenations



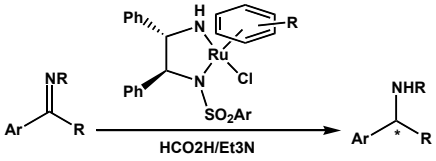
Stereochemical model: CH -> π donatation

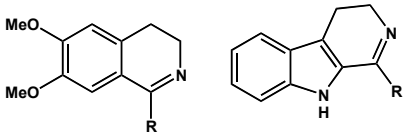
note H transfer from IPA is reverse of transfer to ketone. Ketone reduction can be reversible. High dilution, short rxn time needed for good ee.

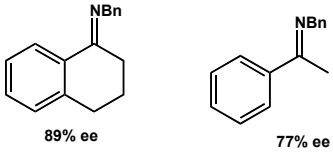
Noyori JACS, 2000, 1466
computational: ACIEE 2001, 2818

Ready; Catalysis | Hydrogenation

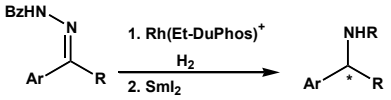
Immine Hydrogenation: Same story, less effective

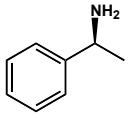




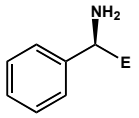


Noyori, JACS, 1996, 4916





88-95 %ee

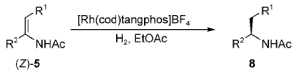


91% ee

Burk, JACS, 1992, 6266
Tet, 1994, 4399

Asymmetric hydrogenation of imines (enamines).
Group on N: a variable and a burden

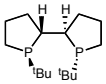
Table 3: Asymmetric hydrogenation of (*Z*)-**5** with the Rh/tangphos catalytic system.[a]



(*Z*)-**5** → **8**

Entry	Substrate	R^1	R^2	Product	*ee* [%][b]	Config.[c]
1	(*Z*)-**5a**	Ph	Me	**8a**	99.3	*S*
2	(*Z*)-**5b**	*o*-$MeOC_6H_4$	Me	**8b**	99.0	*S*
3	(*Z*)-**5c**	*p*-$MeOC_6H_4$	Me	**8c**	96.6	*S*
4	(*Z*)-**5d**	*m*-$MeOC_6H_4$	Me	**8d**	99.1	*S*
5	(*Z*)-**5e**	*m*-MeC_6H_4	Me	**8e**	99.1	*S*
6	(*Z*)-**5f**	*p*-MeC_6H_4	Me	**8f**	98.8	*S*
7	(*Z*)-**5g**	*o*-ClC_6H_4	Me	**8g**	>99.9	*S*
8	(*Z*)-**5h**	1-napthyl-C_6H_4	Me	**8h**	99.1	*S*
9	(*Z*)-**5i**	Ph	Ph	**8i**	98.3	*S*
10[d]	(*Z*)-**5a**	Ph	Me	**8a**	98.7	*S*

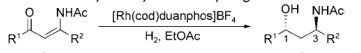
[a] Unless mentioned otherwise, all reactions were carried out with a substrate/catalyst ratio of 100:1 in EtOAc at room temperature under 30 bar hydrogen pressure for 20 h. In all cases, 100% conversion was observed. [b] Determined by chiral GC methods. [c] The absolute configuration was assigned by comparison of the observed optical rotation with reported data. [d] Substrate/catalyst = 1000:1.



TangPhos

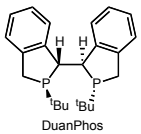
Zhang, ACIE, 2009, 800

Table 3: Rhodium-catalyzed asymmetric hydrogenation of **2a–2n**.[a]



2 → **3**

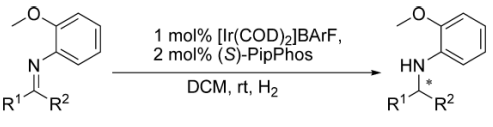
Entry	**2**	R^1	R^2	P_{H_2} [bar]	**3**	Yield[b] [%]	*ee*[c] [%]	d.r.[d] (*syn*/*anti*)
1	**2a**	C_6H_5	Me	20	**3a**[c]	100	99	5:95
2	**2b**	*p*-MeC_6H_4	Me	100	**3b**	97	97	7:93
3	**2c**	*p*-$MeOC_6H_4$	Me	100	**3c**	95	95	8:92
4	**2d**	*p*-FC_6H_4	Me	20	**3d**	100	97	4:96
5	**2e**	*p*-ClC_6H_4	Me	20	**3e**	100	99	4:96
6	**2f**	*p*-BrC_6H_4	Me	100	**3f**	95	98	6:94
7	**2g**	*p*-$tBuC_6H_4$	Me	100	**3g**	96	97	8:92
8	**2h**	*p*-CyC_6H_4	Me	100	**3h**	93	97	8:92
9	**2i**	*m*-MeC_6H_4	Me	20	**3i**	100	99	4:96
10	**2j**	*o*-MeC_6H_4	Me	20	**3j**	100	94	14:86
11	**2k**	thiophen-2-yl	Me	20	**3k**	100	99	5:95
12	**2l**	2-naphthyl	Me	20	**3l**	100	97	<1:99
13	**2m**	C_6H_5	Et	20	**3m**	100	96	5:95
14	**2n**	Me	Me	20	**3n**	100	96	<1:99



DuanPhos

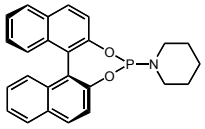
Zhang, ACIE, 2009, 6052

Table 3. Asymmetric Hydrogenation of *N*-2-MeO-phenyl Imines[a]



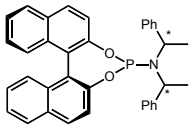
3a, **7a**-**16a** → **3b**, **7b**-**16b**

entry	imine	R^1	R^2	P (bar)	time[b] (h)	ee[c] (%)
1	**3a**	Ph	Me	5	10	97
2	**7a**	2-naphthyl	Me	1	11	99
3	**7a**	2-naphthyl	Me	5	6	97
4	**8a**	4-Me-Ph	Me	5	10	98
5	**9a**	4-Cl-Ph	Me	5	3	97
6	**10a**	4-CF_3-Ph	Me	5	6	97
7	**11a**	4-F-Ph	Me	5	6	97
8	**12a**	3-Me-Ph	Me	5	30	93
9	**13a**	3-NO_2-Ph	Me	5	0.2	61
10	**14a**	Ph	Et	5	19	94[d]
11	**15a**	Ph	Pr	5	20	97[d]
12	**16a**	*n*-butyl	Me	5	10	16[d]



PipPhos

compare to:

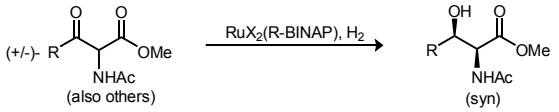


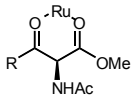
PipPhos

Minnard, Feringa, de Vries, JACS, 2009, 8358

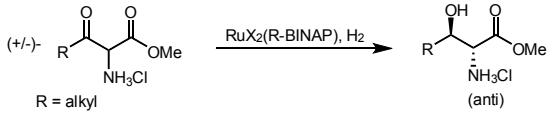
Ready; Catalysis — Hydrogenation

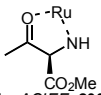
Dynamic Kinetic Resolution



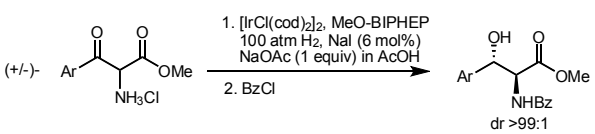


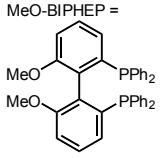
Noyori, *JACS*, **1989,** 9134; **1993,** 144; **1995,** 2931





Hamada, *ACIEE*, **2004,** 882



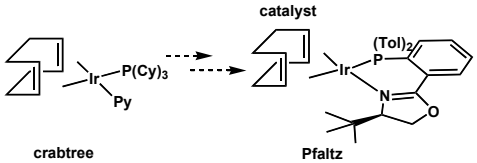


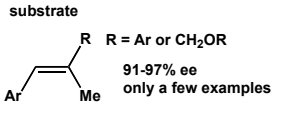
Hamada, *JACS*, **2005,** 5784

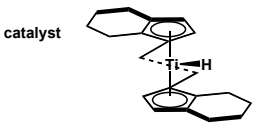
'...suggests that the Ir-catalyzed hydrogenation may proceed with a different mechanism from that of the Ru-catalyzed hydrogenation.'

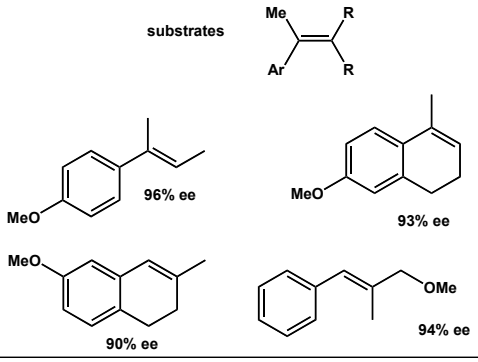
Ready; Catalysis Hydrogenation

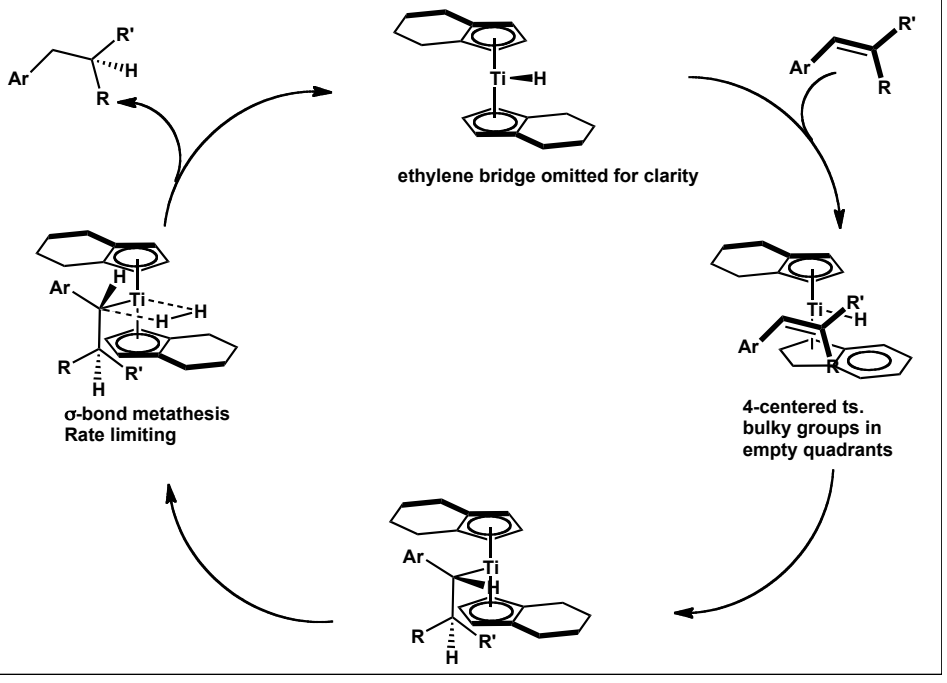
Simple olefins: Largely unsolved substrate class



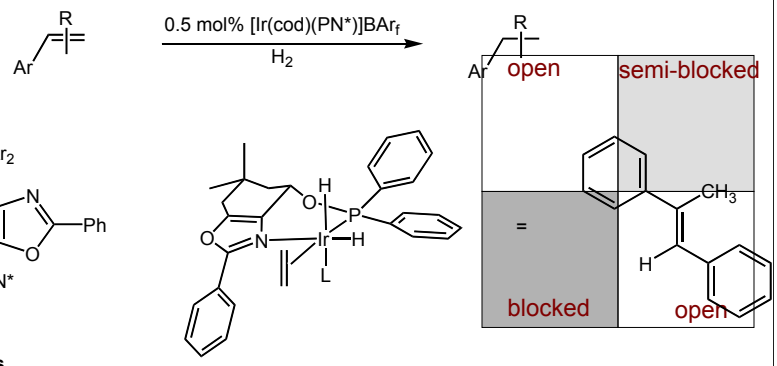




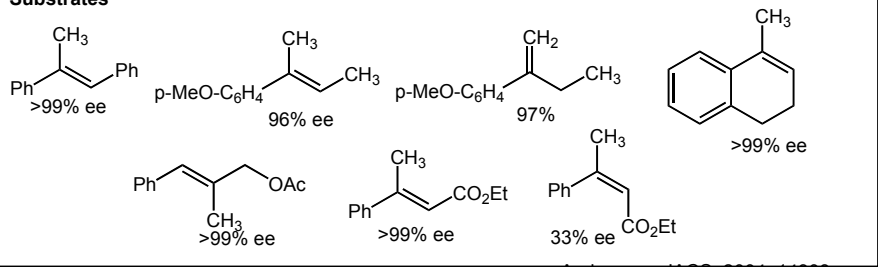




Ready; Catalysis Hydrogenation

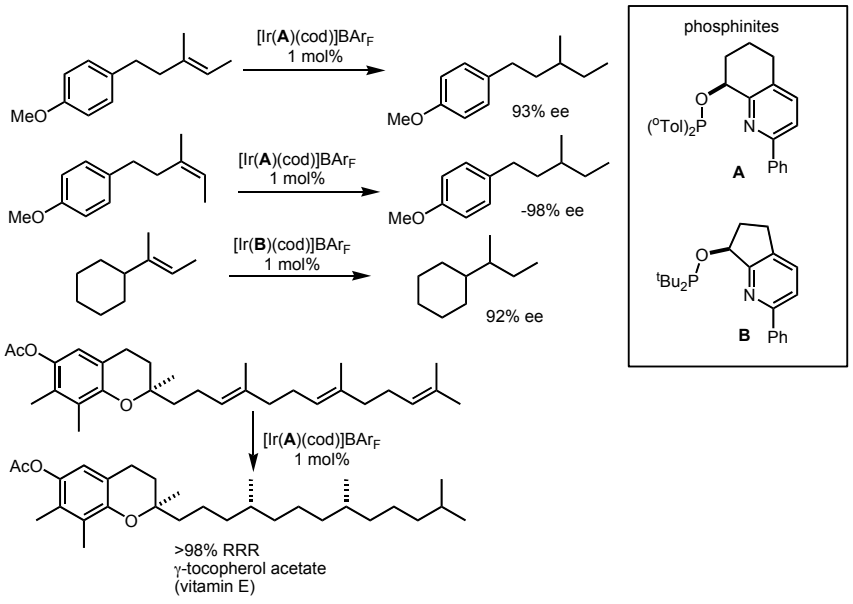


Substrates



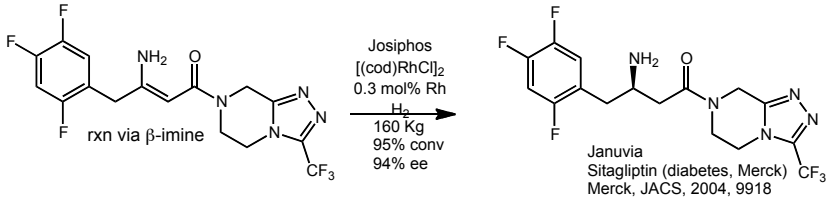
Ready; Catalysis Hydrogenation

Asymmetric hydrogenation of truly unfunctionalized olefins: Pfaltz, *Science*, *311*, **2006,** 644

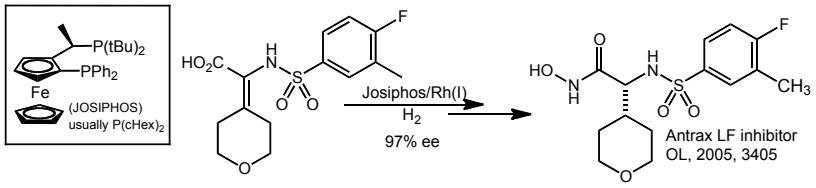


Ready; Catalysis Hydrogenation

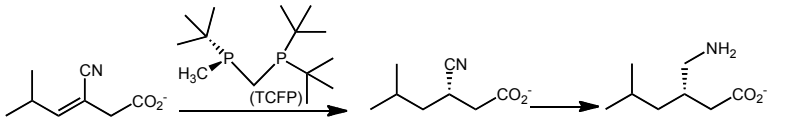
Some recent industrial applications of asymmetric hydrogenation:



Januvia
Sitagliptin (diabetes, Merck)
Merck, JACS, 2004, 9918



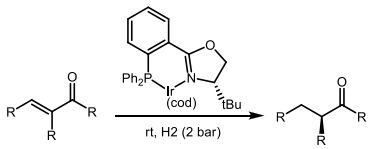
Antrax LF inhibitor
OL, 2005, 3405



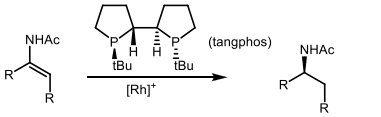
TCFP = trichickenfootphos

pregabalin (Lyrica)
Anxiety, epilepsy and pain
Pfizer, JACS, 2004, 5966

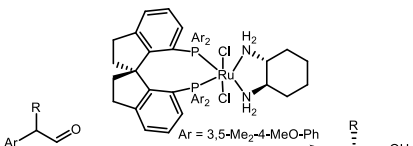
Recent examples of asymmetric hydrogenation



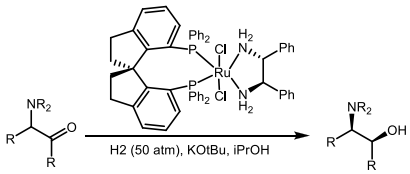
Bolm, ACIE, 2008, 8920



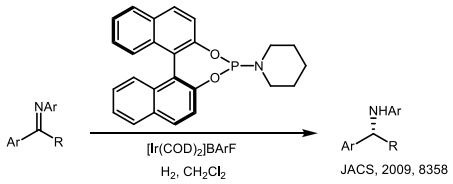
Zhang, ACIE, 2009, 800



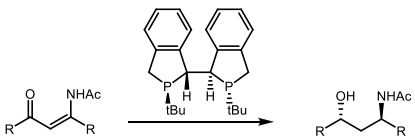
Zhou, JACS, 2007, 1868



Zhou, JACS, 2009, 4222



JACS, 2009, 8358



ACIE, 2009, 6052