

SBM 2014-5

Hydrogenation - 2 Lectures

John Brown

L1 Hydrogenation of Alkenes

The main elements involved as catalysts in homogeneous hydrogenation are shown

PERIODIC TABLE OF THE ELEMENTS

<http://www.ktf-split.hr/periodni/en/>

RELATIVE ATOMIC MASS (1)

GROUP IUPAC

GROUP CAS

ATOMIC NUMBER

SYMBOL

ELEMENT NAME

■ Metal ■ Semimetal ■ Nonmetal
1 Alkali metal 16 Chalcogens element
2 Alkaline earth metal 17 Halogens element
3-10 Transition metals 18 Noble gas
■ Lanthanide
■ Actinide

STANDARD STATE (25 °C; 101 kPa)

Ne - gas Fe - solid
Ga - liquid Tc - synthetic

PERIOD	1 IA		2 IIA		3-10										11 IB		12 IIB		13 IIIA		14 IVA		15 VA		16 VIA		17 VIIA		18 VIIIA											
1	1 1.0079 H HYDROGEN		2 9.0122 He HELIUM																						2 4.0026 He HELIUM															
2	3 6.941 Li LITHIUM		4 9.0122 Be BERYLLIUM																						5 10.811 B BORON			6 12.011 C CARBON	7 14.007 N NITROGEN	8 15.999 O OXYGEN	9 18.998 F FLUORINE	10 20.180 Ne NEON								
3	11 22.990 Na SODIUM		12 24.305 Mg MAGNESIUM																						13 10.811 Al ALUMINIUM	14 28.086 Si SILICON	15 30.974 P PHOSPHORUS	16 32.065 S SULPHUR	17 35.453 Cl CHLORINE	18 39.948 Ar ARGON										
4	19 39.098 K POTASSIUM		20 40.078 Ca CALCIUM																						21 44.956 Sc SCANDIUM	22 47.867 Ti TITANIUM	23 50.942 V VANADIUM	24 51.996 Cr CHROMIUM	25 54.938 Mn MANGANESE	26 55.845 Fe IRON	27 58.933 Co COBALT	28 58.693 Ni NICKEL	29 63.546 Cu COPPER	30 65.39 Zn ZINC	31 69.723 Ga GALLIUM	32 72.64 Ge GERMANIUM	33 74.922 As ARSENIC	34 78.96 Se SELENIUM	35 79.904 Br BROMINE	36 83.80 Kr KRYPTON
5	37 85.468 Rb RUBIDIUM		38 87.62 Sr STRONTIUM																						39 88.906 Y YTTRIUM	40 91.224 Zr ZIRCONIUM	41 92.906 Nb NIOBIUM	42 95.94 Mo MOLYBDENUM	43 (98) Tc TECHNETIUM	44 101.07 Ru RUTHENIUM	45 102.91 Rh RHODIUM	46 106.42 Pd PALLADIUM	47 107.87 Ag SILVER	48 112.41 Cd CADMIUM	49 114.82 In INDIUM	50 118.71 Sn TIN	51 121.76 Sb ANTIMONY	52 127.60 Te TELLURIUM	53 126.90 I IODINE	54 131.29 Xe XENON
6	55 132.91 Cs CAESIUM		56 137.33 Ba BARIUM																						57-71 La-Lu Lanthanide	72 178.49 Hf HAFNIUM	73 180.95 Ta TANTALUM	74 183.84 W TUNGSTEN	75 186.21 Re RHENIUM	76 190.23 Os OSMIUM	77 192.22 Ir IRIDIUM	78 195.08 Pt PLATINUM	79 196.97 Au GOLD	80 200.59 Hg MERCURY	81 204.38 Tl THALLIUM	82 207.2 Pb LEAD	83 208.98 Bi BISMUTH	84 (209) Po POLONIUM	85 (210) At ASTATINE	86 (222) Rn RADON
7	87 (223) Fr FRANCIUM		88 (226) Ra RADIUM																						89-103 Ac-Lr Actinide	104 (261) Rf RUTHERFORDIUM	105 (262) Db DUBNIUM	106 (266) Sg SEABORGIUM	107 (263) Bh BOHRIUM	108 (277) Hs HASSIUM	109 (268) Mt MEITNERIUM	110 (281) Uun UNUNNIUM	111 (272) Uuu UNUNUNIUM	112 (285) Uub UNUNBIUM	114 (289) Uuq UNUNQUADIUM					

(1) Pure Appl. Chem., 73, No. 4, 667-683 (2001)
Relative atomic mass is shown with five significant figures. For elements having no stable nuclides, the value enclosed in brackets indicates the mass number of the longest-lived isotope of the element.

However three such elements (Th, Pa, and U) do have a characteristic terrestrial isotopic composition, and for these an atomic weight is tabulated.

Editor: Aditya Vardhan (adivar@netlinx.com)

LANTHANIDE

57 138.91 La LANTHANUM	58 140.12 Ce CERIUM	59 140.91 Pr PRASEODYMIUM	60 144.24 Nd NEODYMIUM	61 (145) Pm PROMETHIUM	62 150.36 Sm SAMARIUM	63 151.96 Eu EUROPIUM	64 157.25 Gd GADOLINIUM	65 158.93 Tb TERBIUM	66 162.50 Dy DYSPROSIUM	67 164.93 Ho HOLMIUM	68 167.26 Er ERBIUM	69 168.93 Tm THULIUM	70 173.04 Yb YTTERBIUM	71 174.97 Lu LUTETIUM
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ACTINIDE

89 (227) Ac ACTINIUM	90 232.04 Th THORIUM	91 231.04 Pa PROTACTINIUM	92 238.03 U URANIUM	93 (237) Np NEPTUNIUM	94 (244) Pu PLUTONIUM	95 (243) Am AMERICIUM	96 (247) Cm CURIUM	97 (247) Bk BERKELIUM	98 (251) Cf CALIFORNIUM	99 (252) Es EINSTEINIUM	100 (257) Fm FERMIUM	101 (258) Md MENDELEVIUM	102 (259) No NOBELIUM	103 (262) Lr LAWRENCIUM
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General characteristics of OM catalysis

44	101.07	45	102.91	46	106.42
Ru		Rh		Pd	
RUTHENIUM		RHOIDIUM		PALLADIUM	
76	190.23	77	192.22	78	195.08
Os		Ir		Pt	
OSMIUM		IRIDIUM		PLATINUM	
108 (277)		109 (268)		110 (281)	
Hs		Mt		Uun	
HASSIUM		MEITNERIUM		UNUNILUM	

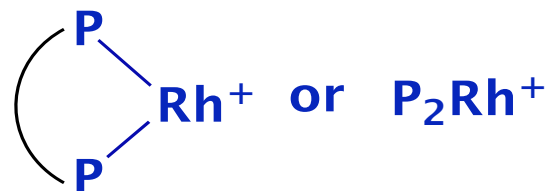
Reactive intermediates are *coordinatively unsaturated*, with 12, 14 or 16 electron valence shells

Coordination numbers are commonly 2 – 6, with square planar (4) and trigonal bipyramid or square-based pyramid (5) common

The key metals have variable oxidation states with (I – III) or (0 – II – IV) frequent; most (not all!) reactions involve diamagnetic states

The Key Metals in Asymmetric Hydrogenation

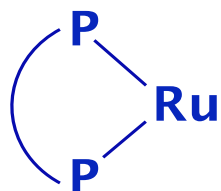
Rhodium



huge range
of ligands

need strong donor groups
(eg enamide)

Ruthenium

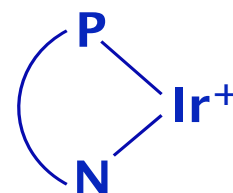


BINAP and
close relatives

wide range of reactants with
varying donor groups

alkenes or ketones

Iridium



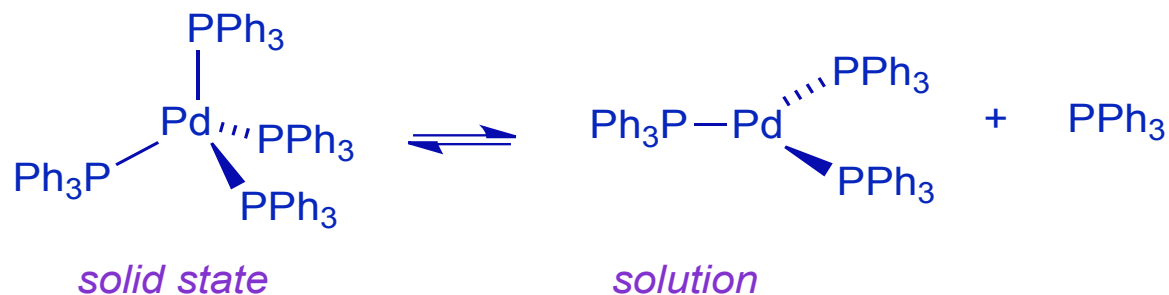
related ligands
6-ring chelate

alkenes without
secondary donor group

The basic reactions in OM catalysis are simple

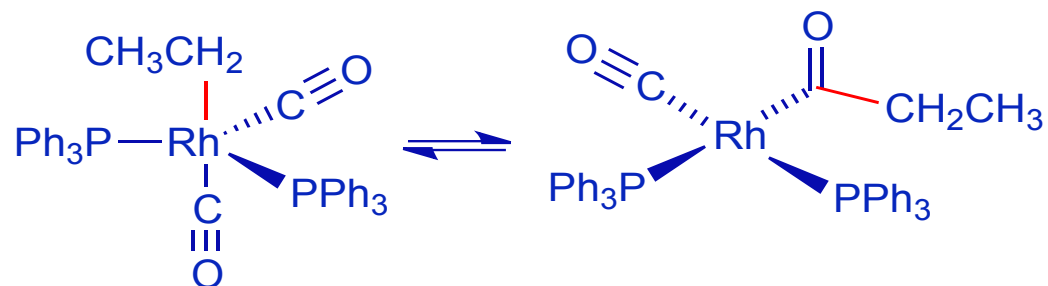
Ligand association and dissociation: $M + L \rightleftharpoons ML$

Example:



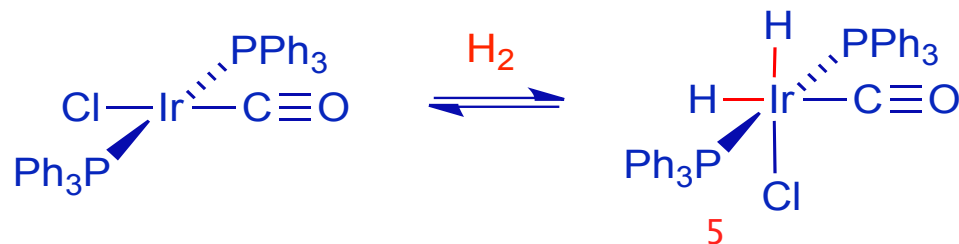
cis-Ligand Migration

Example:

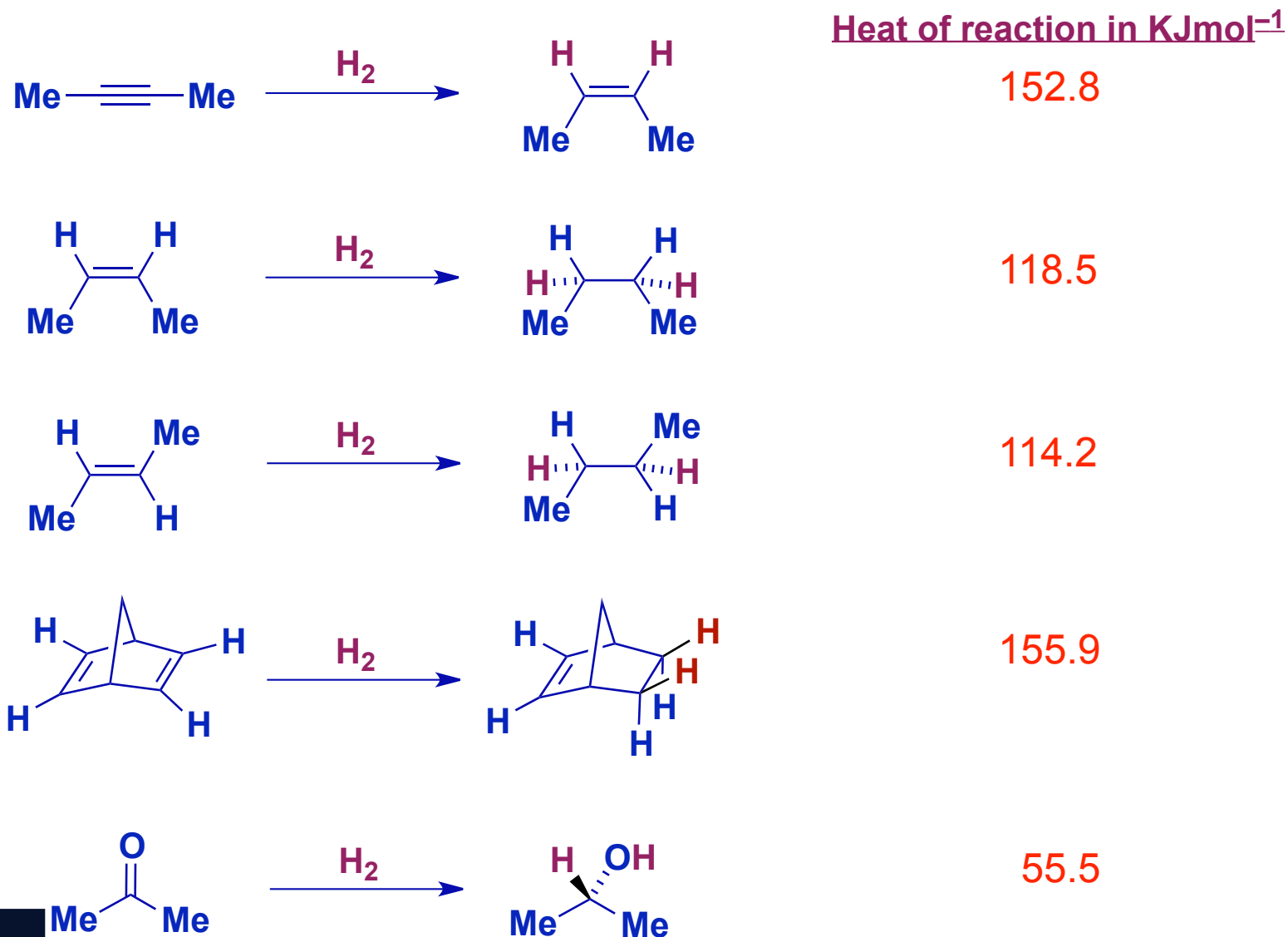


Oxidative addition /
reductive elimination

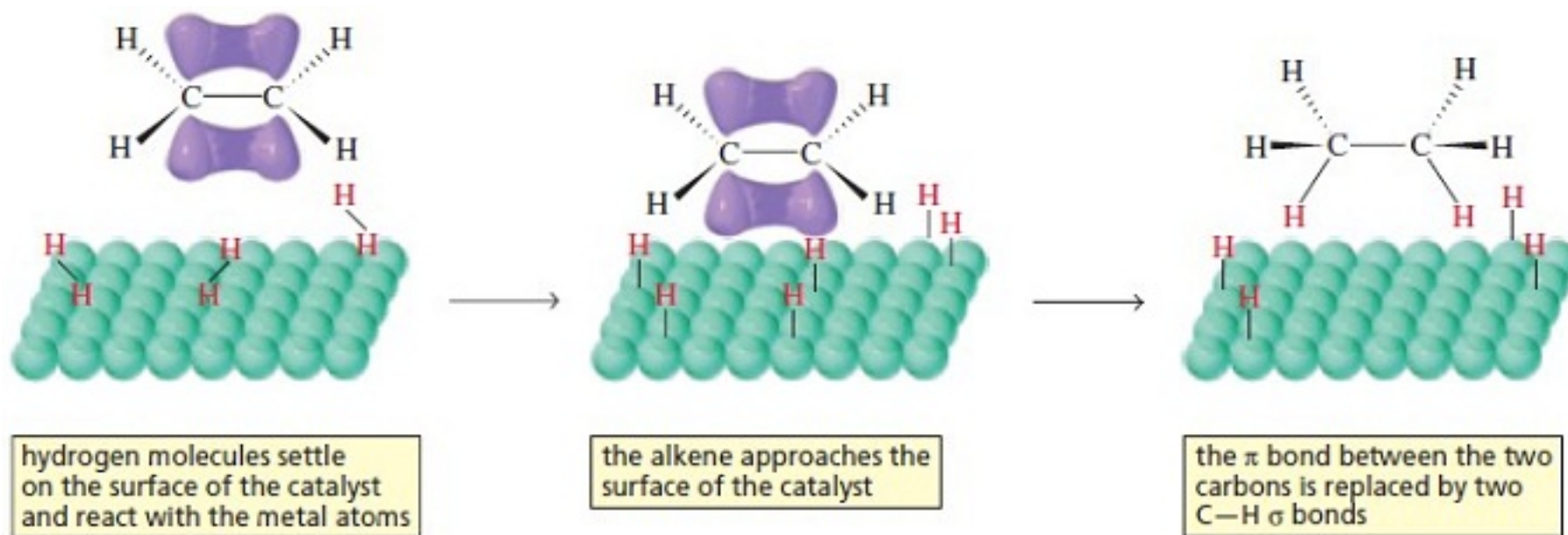
Example:



Hydrogenation of alkenes and alkynes is favoured energetically

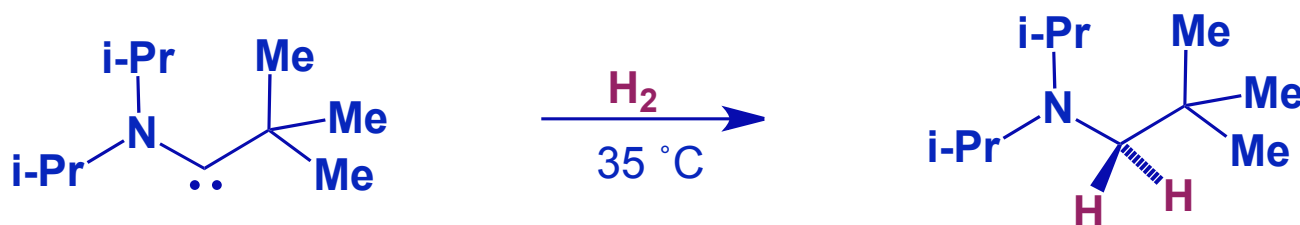


Metal surfaces (especially of platinum metals) activate hydrogen and are good hydrogenation catalysts

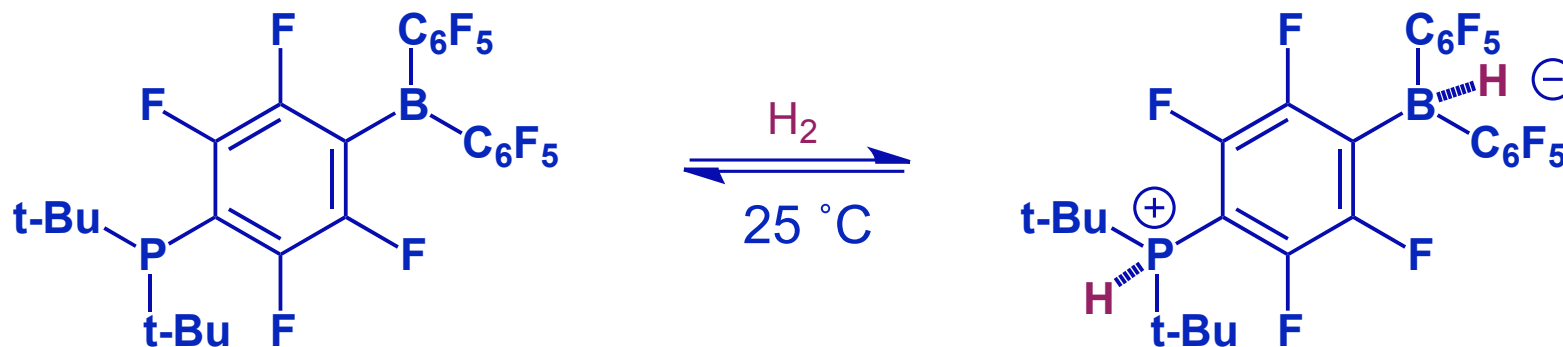


Activation of hydrogen without metals is very rare but examples do exist

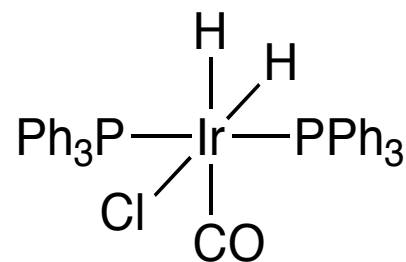
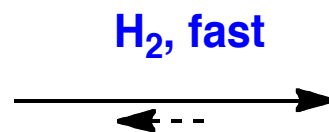
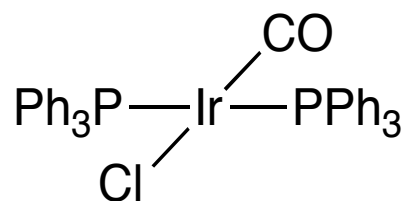
Make the reaction very exothermic through a high energy starting material – a bulky carbene:



Frustrated Lewis Pairs (acid and base – one accepts H⁺, the other H⁻)



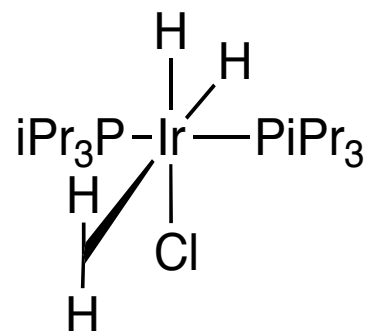
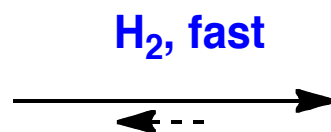
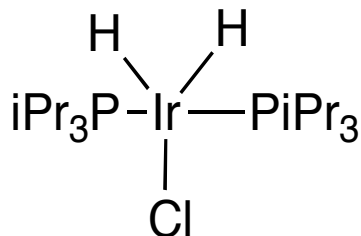
Dihydride and dihydrogen complexes of known structure – this shows us how dihydrogen can bond to a transition metal.



Two M-H
sigma bonds

Vaska's compound 16 e

Dihydride 18 e

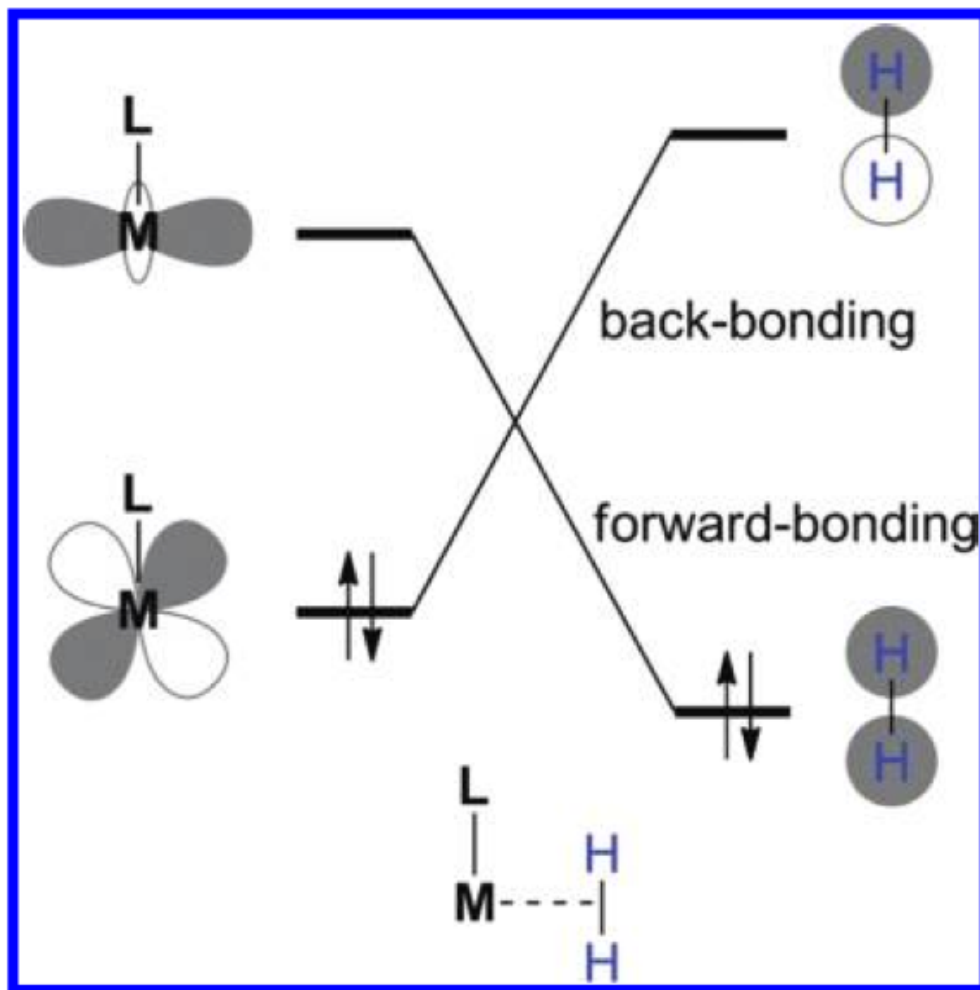


One H₂ acts as
a 2-electron donor

16 e

Dihydrogen complex 18 e

The eta-2 dihydride is a probable intermediate in the activation of H₂ by a metal complex



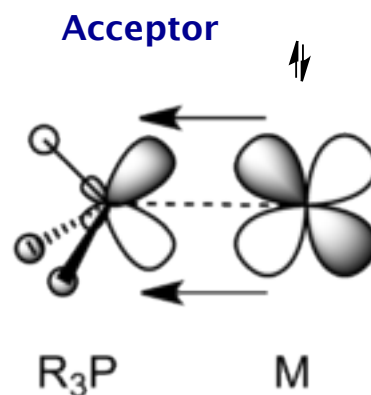
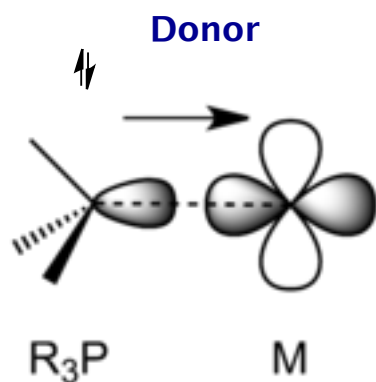
H₂ antibonding orbital acts as acceptor.

After coordination the H-H bond is longer and weaker

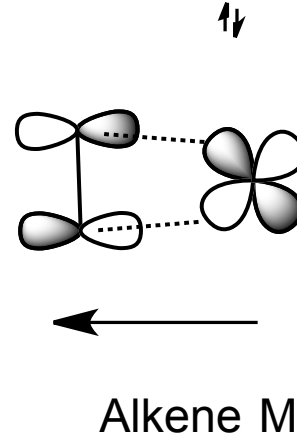
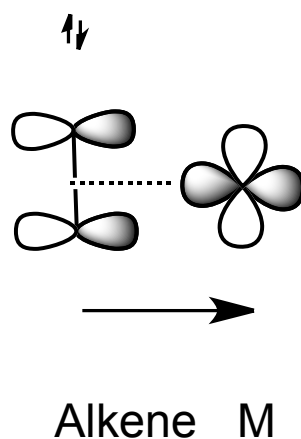
H₂ bonding orbital acts as donor.

Phosphines and alkenes (also alkynes) are bound to the metal through donor and acceptor orbital interactions

In the course of the reaction, aided by phosphorus ligands, the metal must be bound to both hydrogen and the alkene:



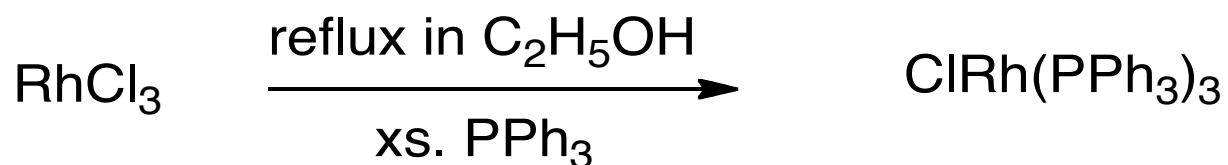
Tertiary phosphines



Alkenes

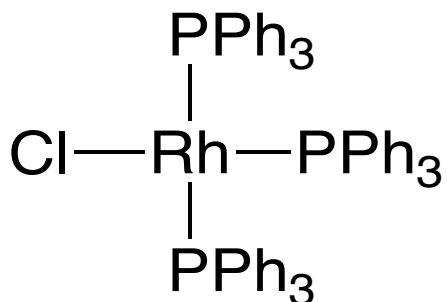
Chatto Dewar Duncanson Model

Wilkinson's catalyst (1966)– the first practical homogeneous hydrogenation catalyst



Usually as a trihydrate

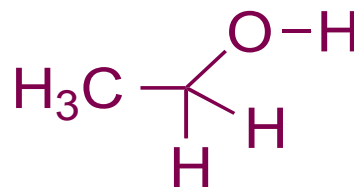
NB Change in Rh oxidation state



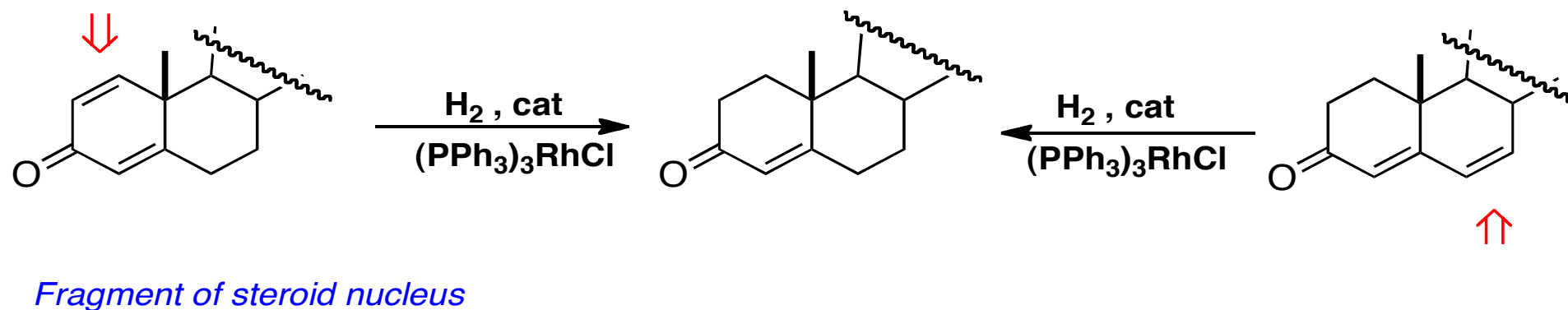
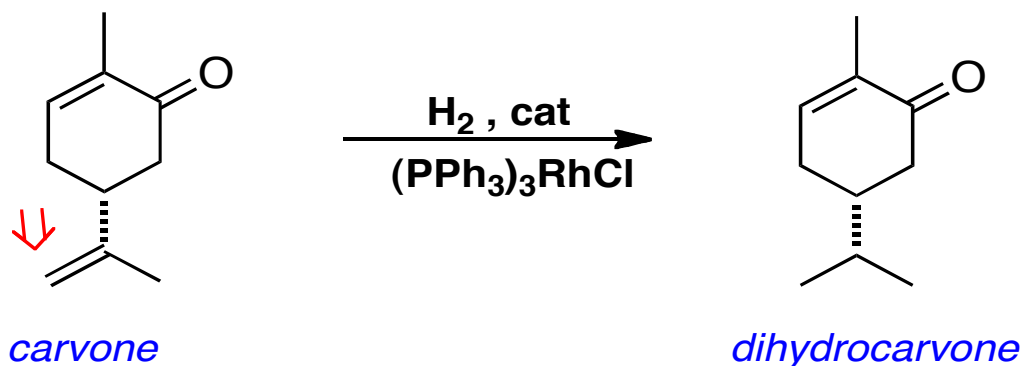
idealised square-planar structure

16e -coordinatively unsaturated

How does Rh(III) become Rh(I) in this procedure; there must be a reducing agent?? How could ethanol participate?



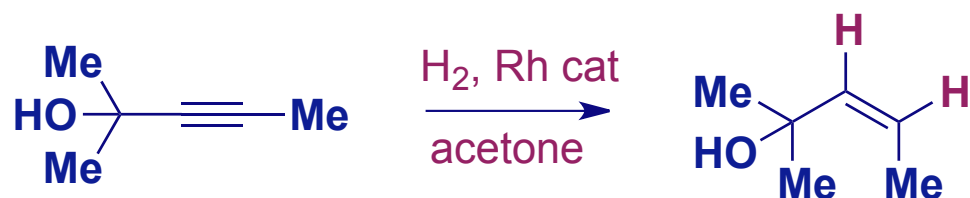
Homogeneous hydrogenation with Wilkinson's catalyst is selective for less substituted double bonds – chemoselectivity



What would happen with a heterogeneous catalyst like Pd/C?

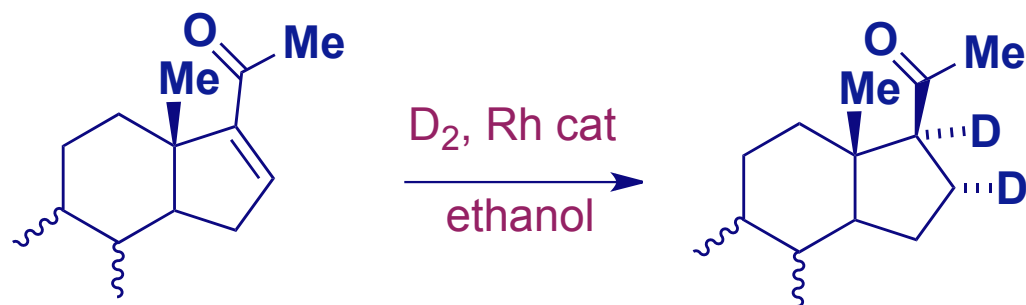
Examples of simple rhodium homogeneous hydrogenations – control of stereochemistry

Alkynes give cis-alkenes:

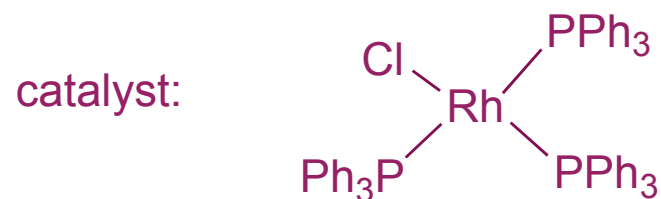


Norbornadiene is removed in the first hydrogenation cycle

Alkenes are reduced by cis- addition of dihydrogen



part of a steroid



D₂ adds like H₂, to the lower face of the molecule

Requirements for successful homogeneous hydrogenation

The catalyst must be coordinatively unsaturated, and undergo rapid addition and elimination reactions.

The hydrogen affinity must be strong enough to complex H_2 , but not too strongly that the dihydride is too stabilized.

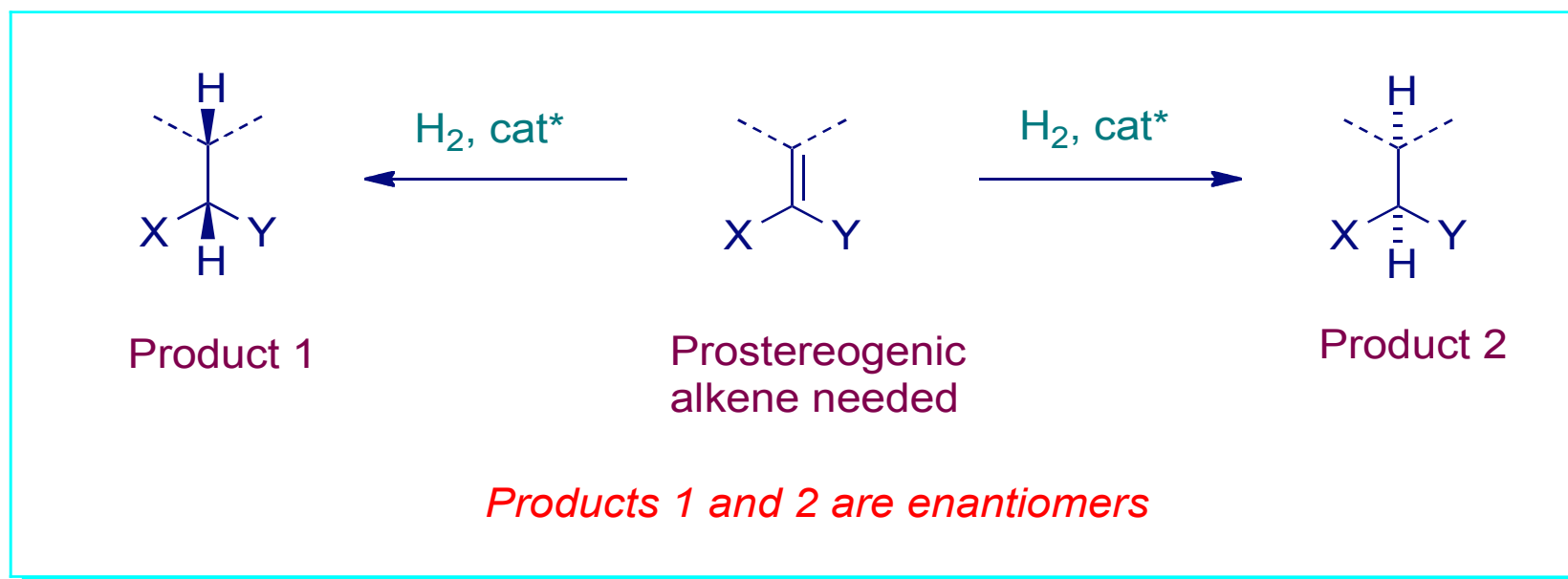
The substrate – alkene, alkyne or carbonyl compound – must be able to bind to the transition metal centre adjacent to bound hydrogen.

Intermediates in the catalytic reaction, and especially the alkylhydride, must break down rapidly.

Rapid ligand addition and dissociation is helpful.

Origins of and requirements for asymmetric hydrogenation of alkenes

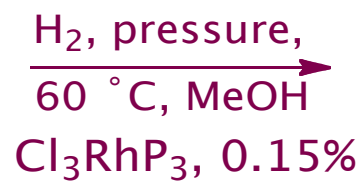
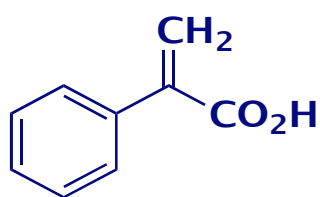
(Rhodium) Asymmetric Hydrogenation was the first successful example of high enantioselectivity using a purely chemical catalyst:



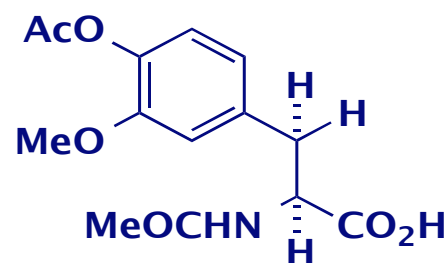
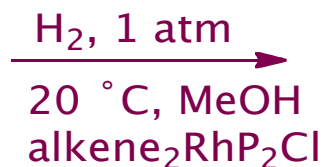
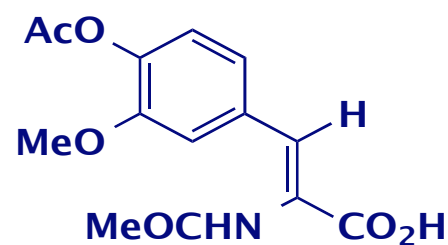
Success depends on asymmetry in the product that arises from asymmetry in the ligand of cat^* . The atom substituted by H, X and Y is a stereogenic centre; products 1 and 2 are **enantiomers**.

The initial observation (above) and the first successful development (below) in asymmetric hydrogenation

Reactions

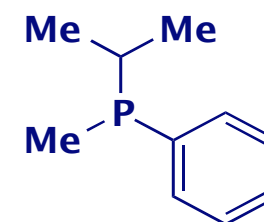


"15% optical purity"

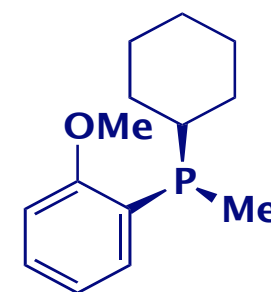


88% (S)-enantiomer

Ligands

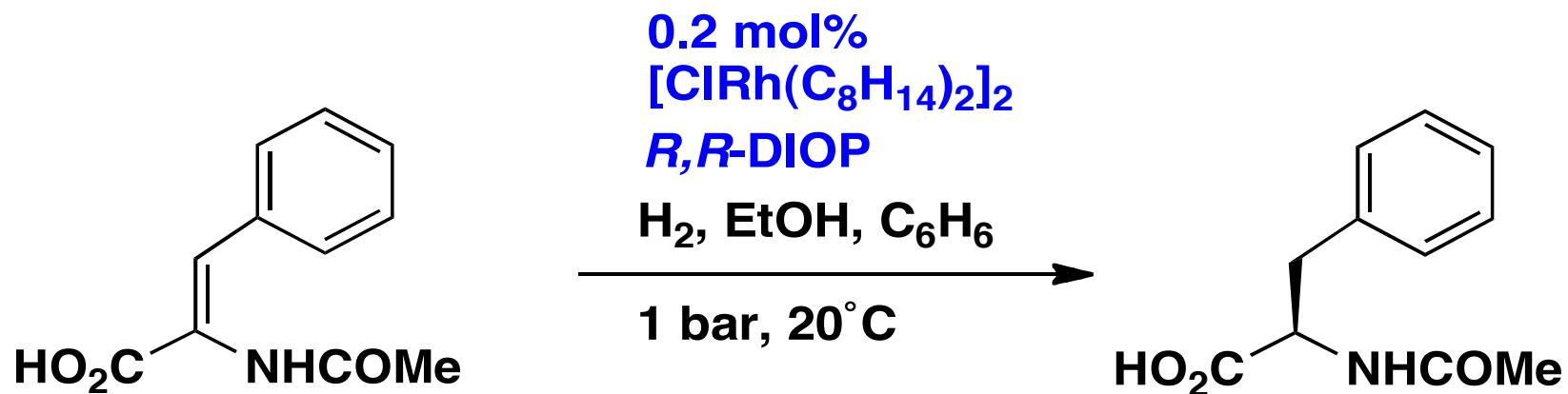


"69% optical purity"

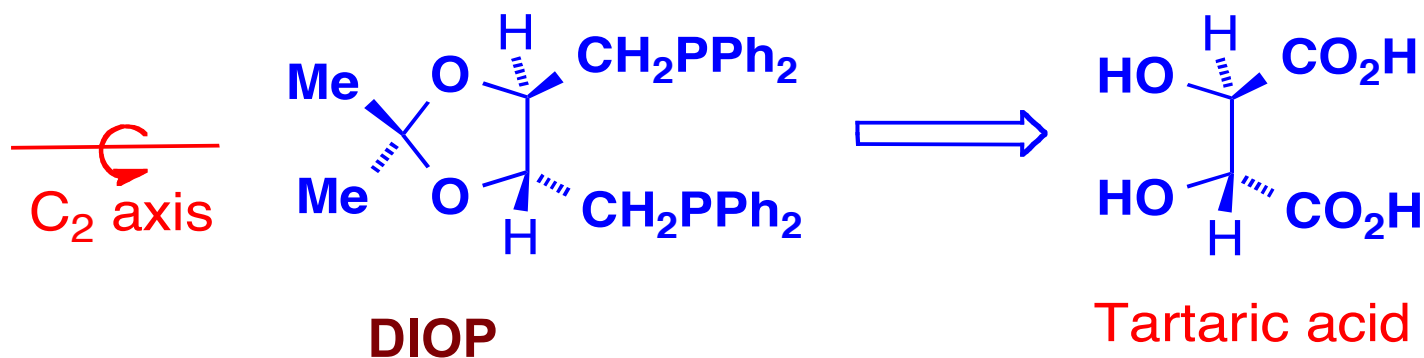


≥ 95% optical purity

Kagan's DIOP catalyst for the synthesis of N-acetylphenylalanine – first use of **chelating** diphosphine



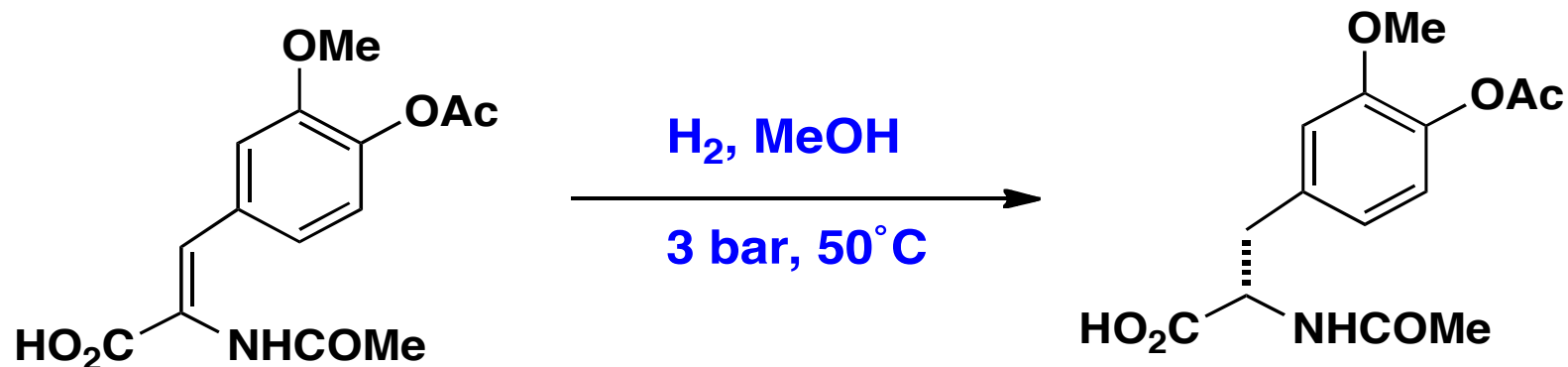
72% e.e. (R)



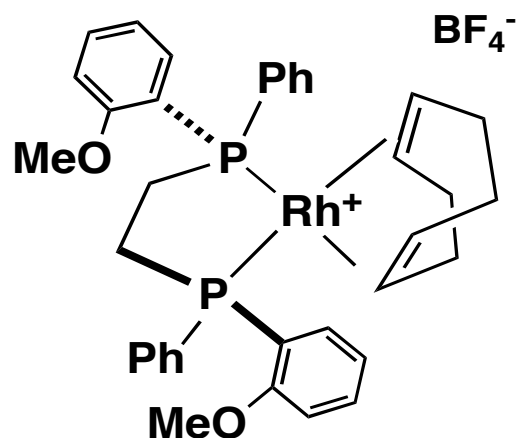
DIOP

Tartaric acid

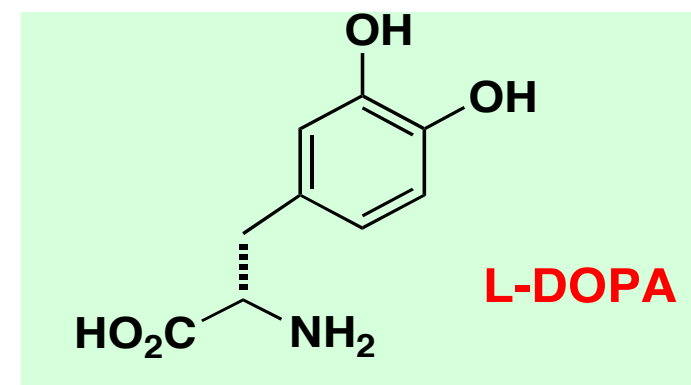
The Monsanto process for the synthesis of dehydroamino acids (WS Knowles) post 1975 (NB catalyst precursor)



96% e.e; 100% e.e. after
recrystallisation / MeOH



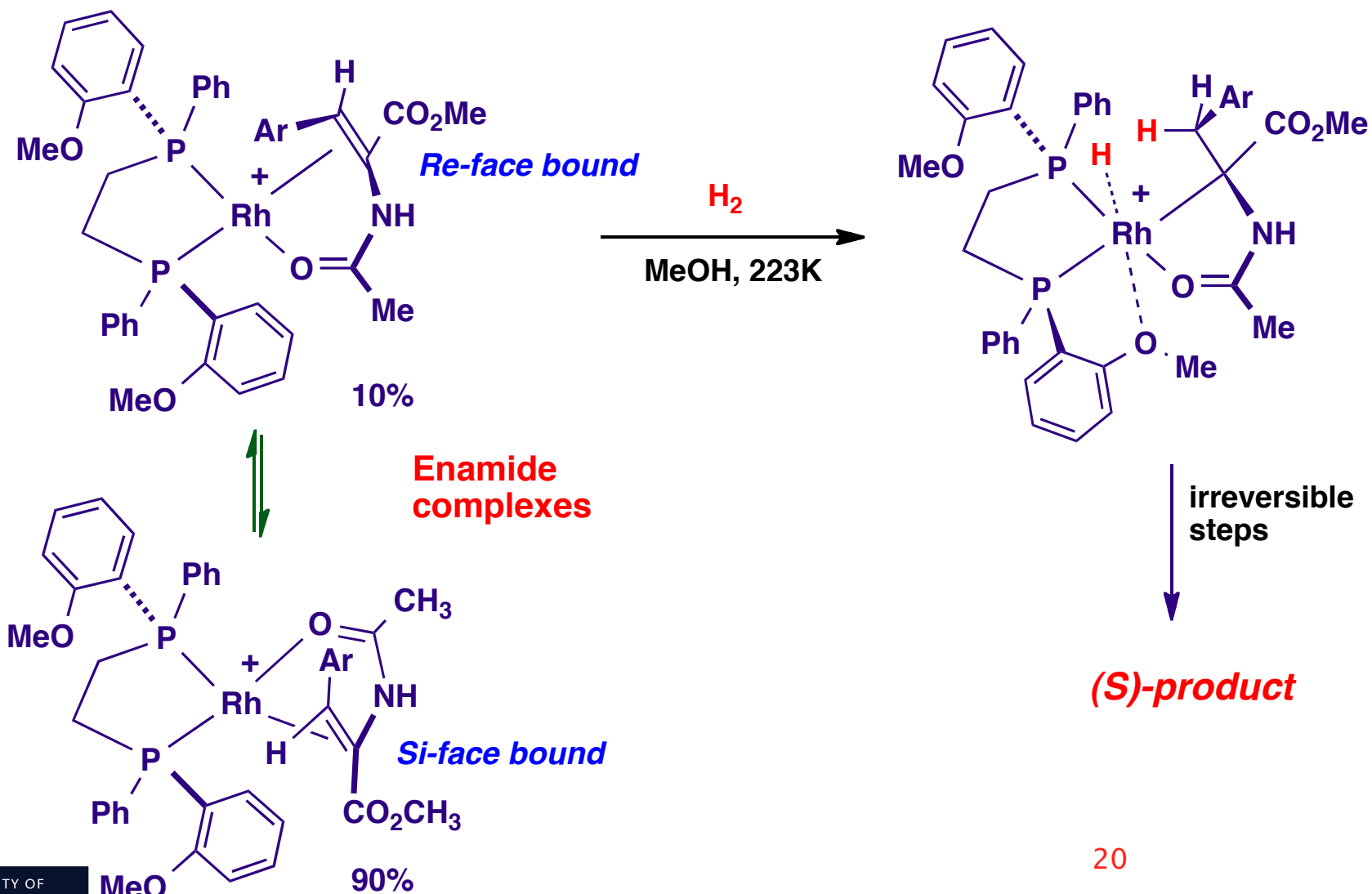
catalyst/ substrate
1/ >10000



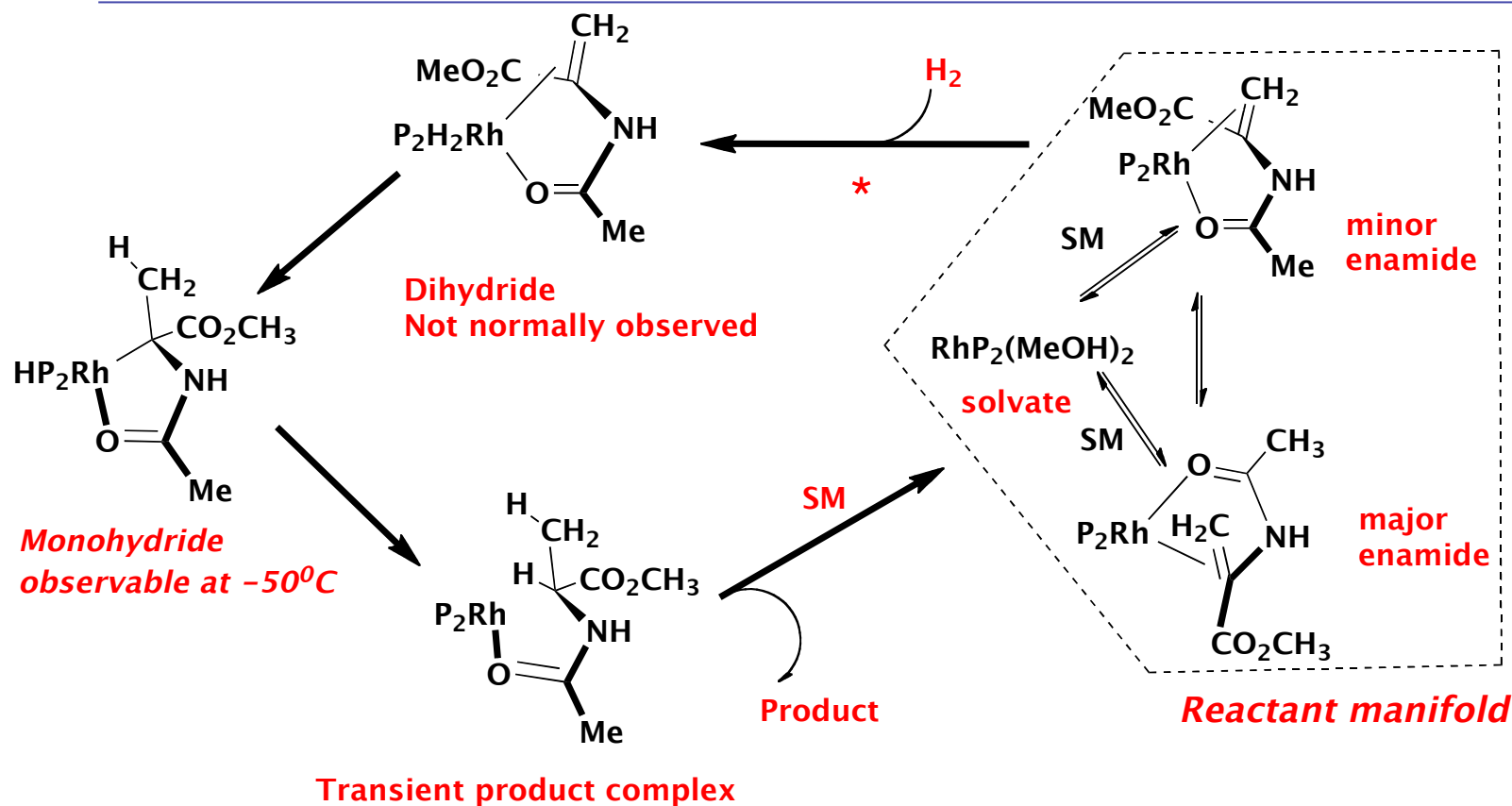
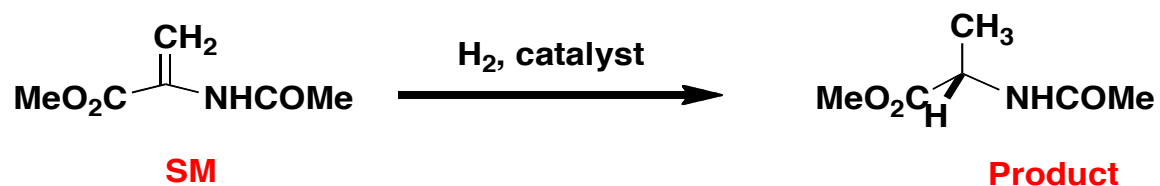
Chelating ligand

Medical use of L-DOPA?

The ^{31}P NMR species observable in the presence of H_2 - only at low temperature

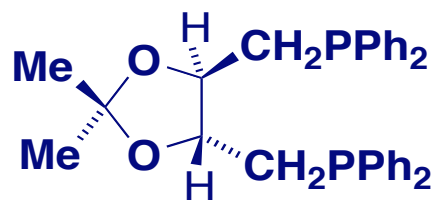


Rhodium asymmetric hydrogenation has been a rich source of reactive intermediates; all cations here:



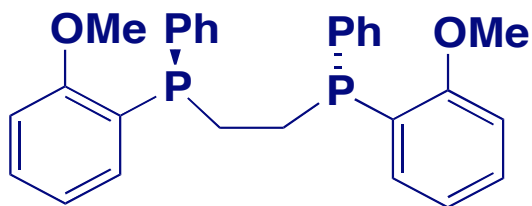
Computational chemistry indicates a further intermediate between the minor enamide and the monohydride at *. Suggest what this might be.

Ligand summary. Types of chelate ligand, all with twofold symmetry axes (C_2)



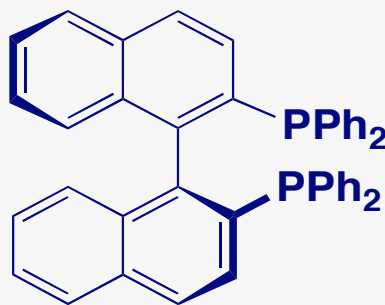
***(R,R)*-DIOP**

First chelating chiral biphosphine; backbone chirality



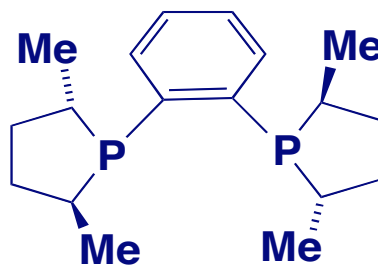
***(R,R)*-DIPAMP**

Monsanto ligand for L-DOPA synthesis; P-chirality



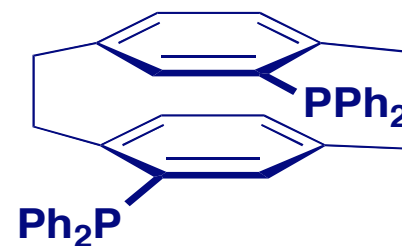
***(S)*-BINAP**

Best known of all chiral ligands; axial chirality



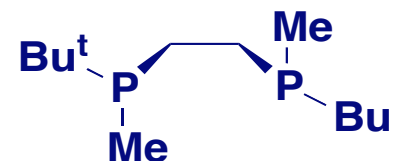
***(S,S)*-DUPHOS**

Very effective use of alpha-phospholane substituents



***(S,S)*-PHANEPHOS**

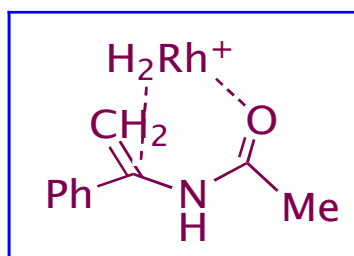
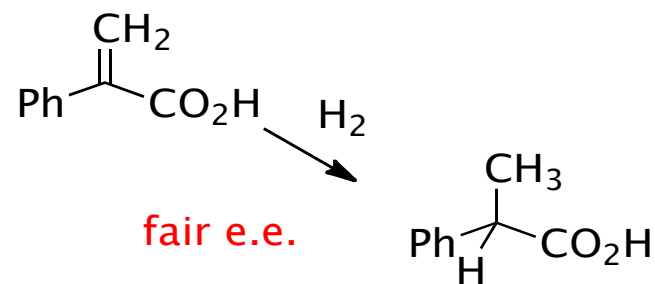
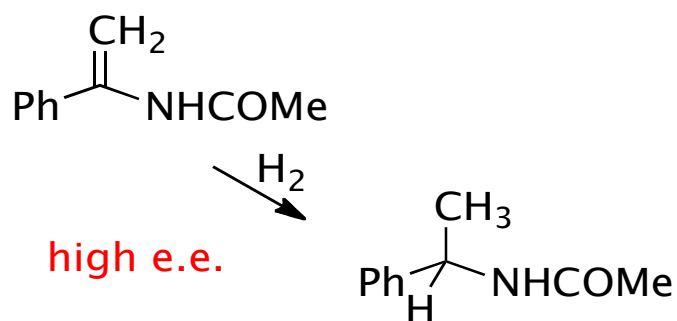
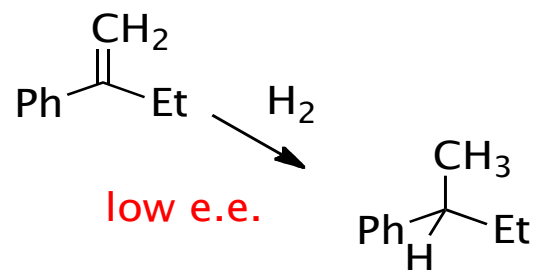
Example of planar chirality



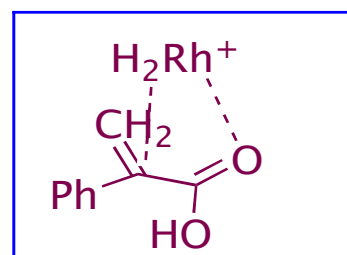
(R,R)*-BisPP

Simple concept; high enantioselectivity

Successful asymmetric hydrogenation with rhodium complexes = polar functional group that can also bind to the metal to form a chelate



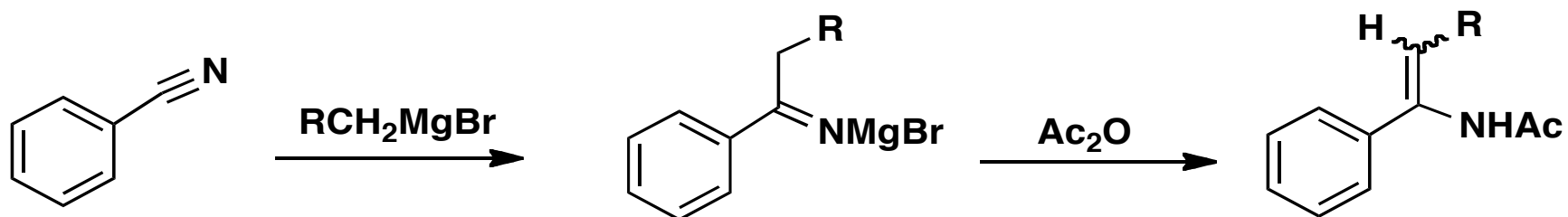
Strong binding



Less strong binding

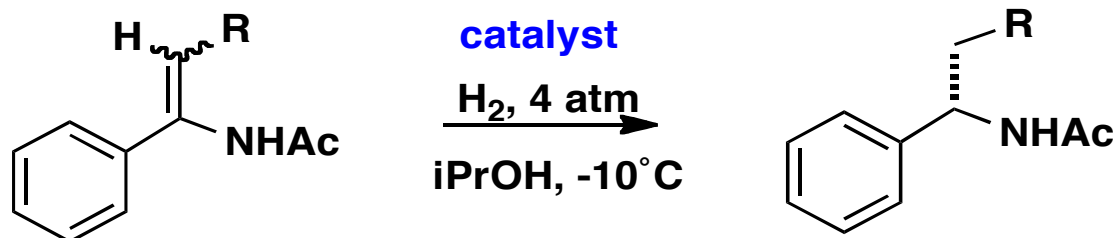
Hydrogenation of simple enamides with a rhodium catalyst and DUPHOS-type ligand

Synthesis



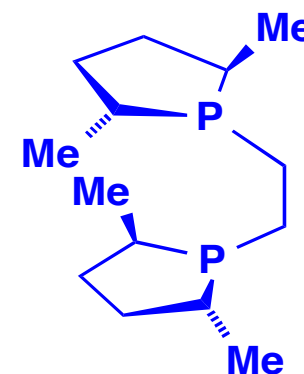
enamide

Hydrogenation



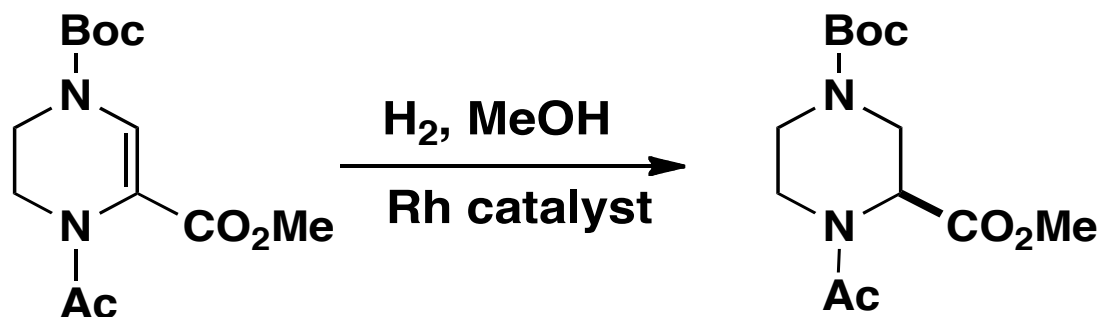
E and Z mixture

95- 97% e.e

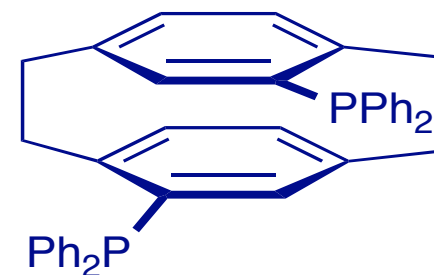


as Rh ligand

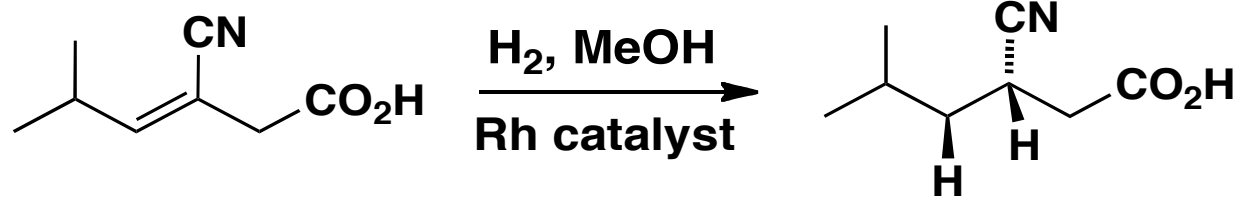
Examples of drug precursors synthesised by asymmetric hydrogenation. Need to vary ligand to optimise results



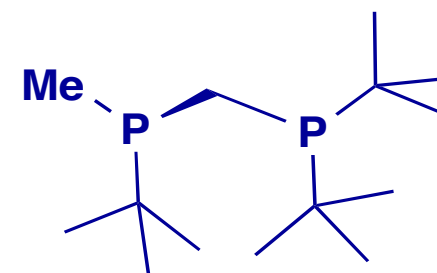
86% e.e.



Phanephos

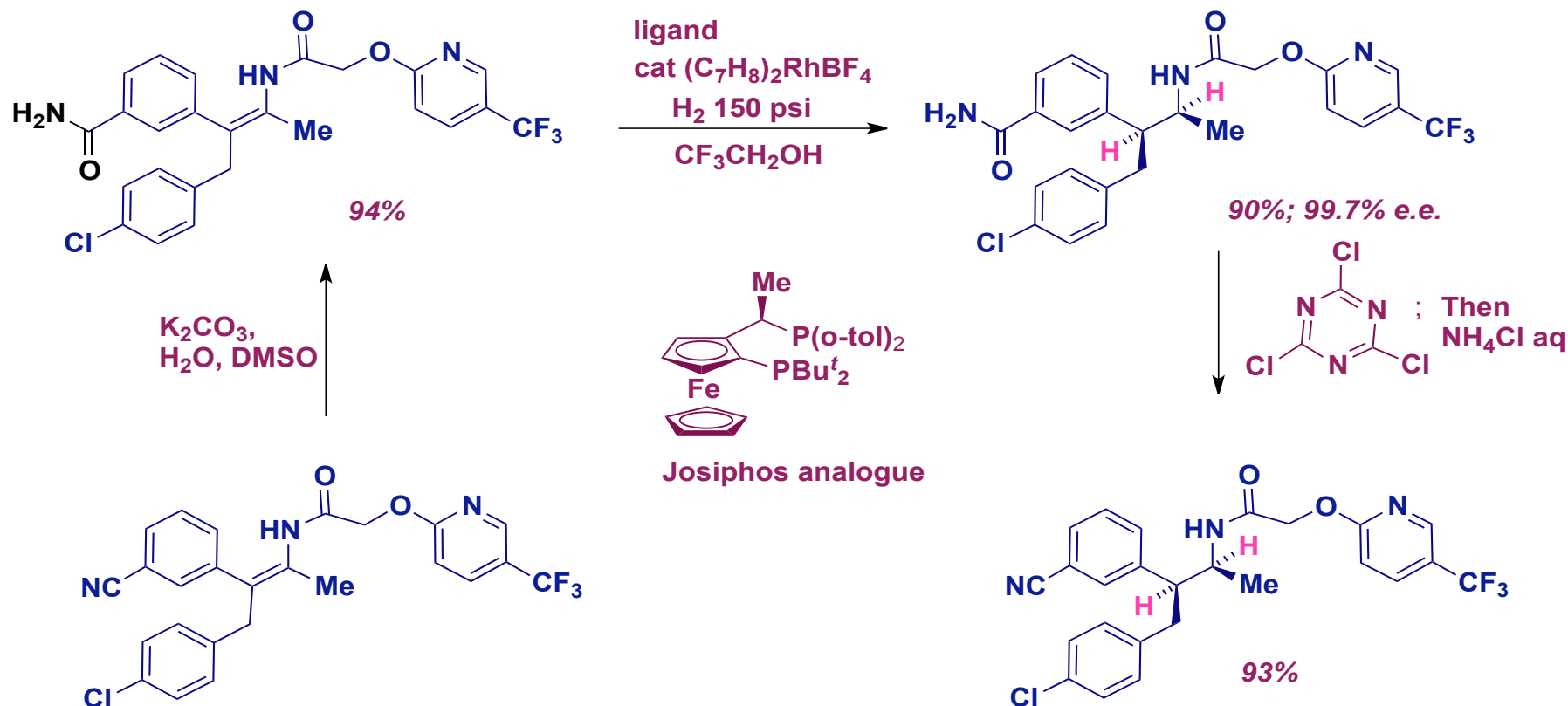


98% e.e.



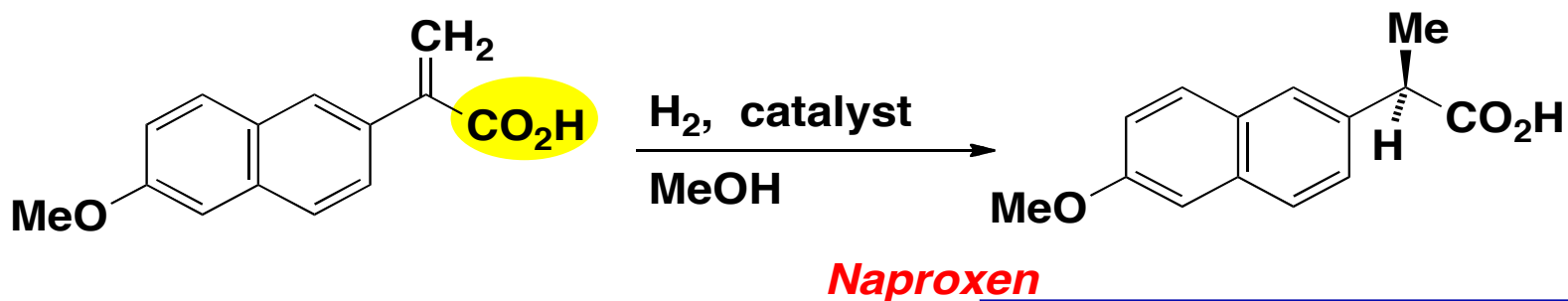
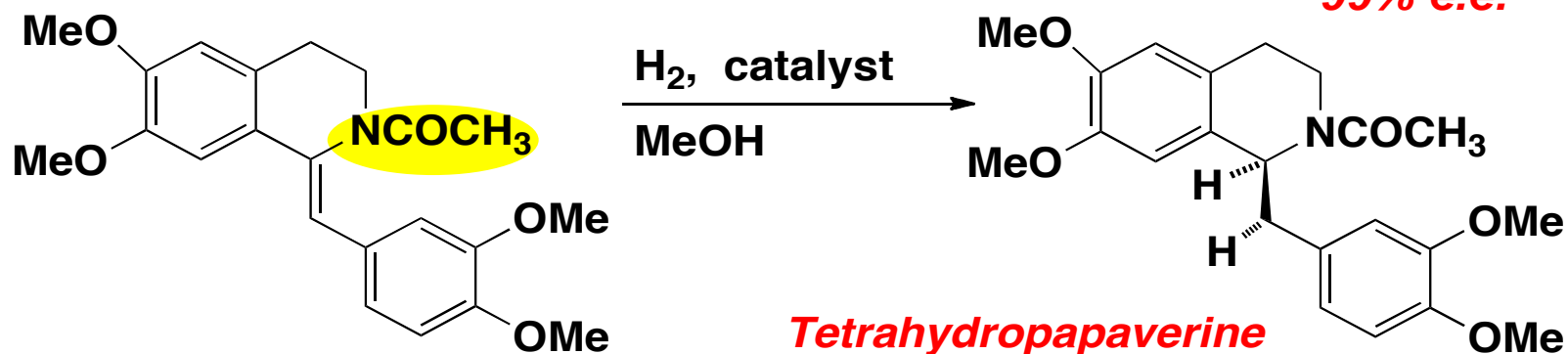
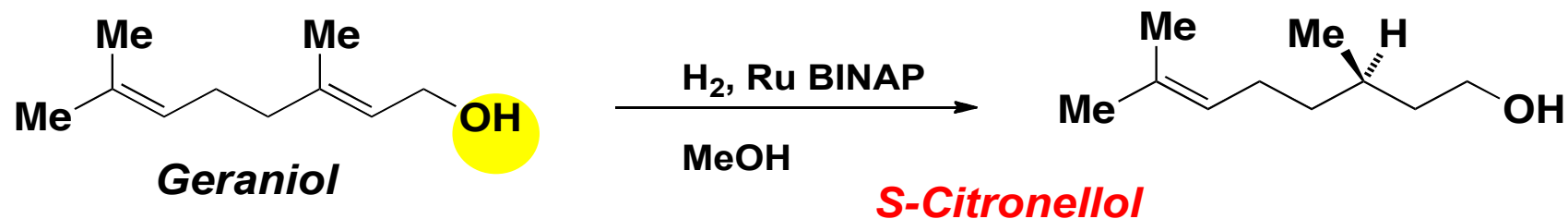
Trichickenfootphos

Asymmetric hydrogenation as the key step in the synthesis of anti-obesity drug Taranabant

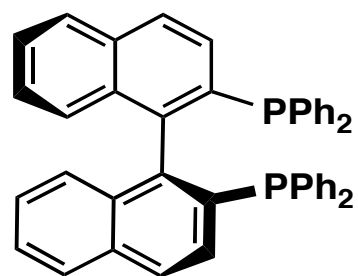


Debra J. Wallace,^{*,†} Kevin R. Campos,^{*,†} C. Scott Shultz,^{*,†} Artis Klapars,[†] Daniel Zewge,[†] Brian R. Crump,[‡] Brian D. Phenix,[‡] J. Christopher McWilliams,[†] Shane Krska,[†] Yongkui Sun,[†] Cheng-yi Chen,[†] and Felix Spindler[§]
 Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, U.S.A., Department of Chemical Process DeVelopment and Commercialization, Merck Research Laboratories, Rahway, New Jersey 07065, U.S.A., and SoNias AG, P.O. Box 4002, Basel, Switzerland; Organic Process Research & Development **2009**, 13, 84–90

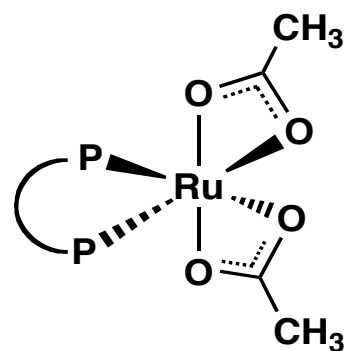
Ru(BINAP) catalysed hydrogenations have a wider scope than Rh-catalysed hydrogenations



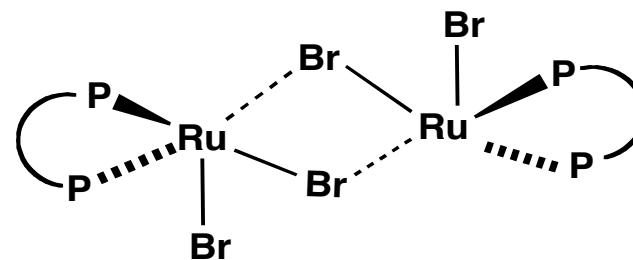
BINAP is the key to successful ruthenium hydrogenations



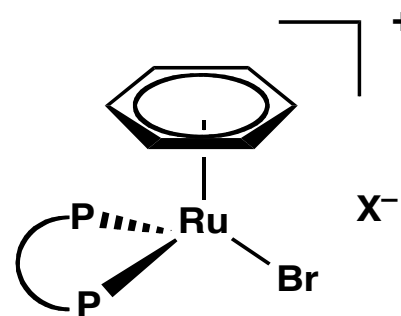
Some of the many Ru(II)
catalyst precursors



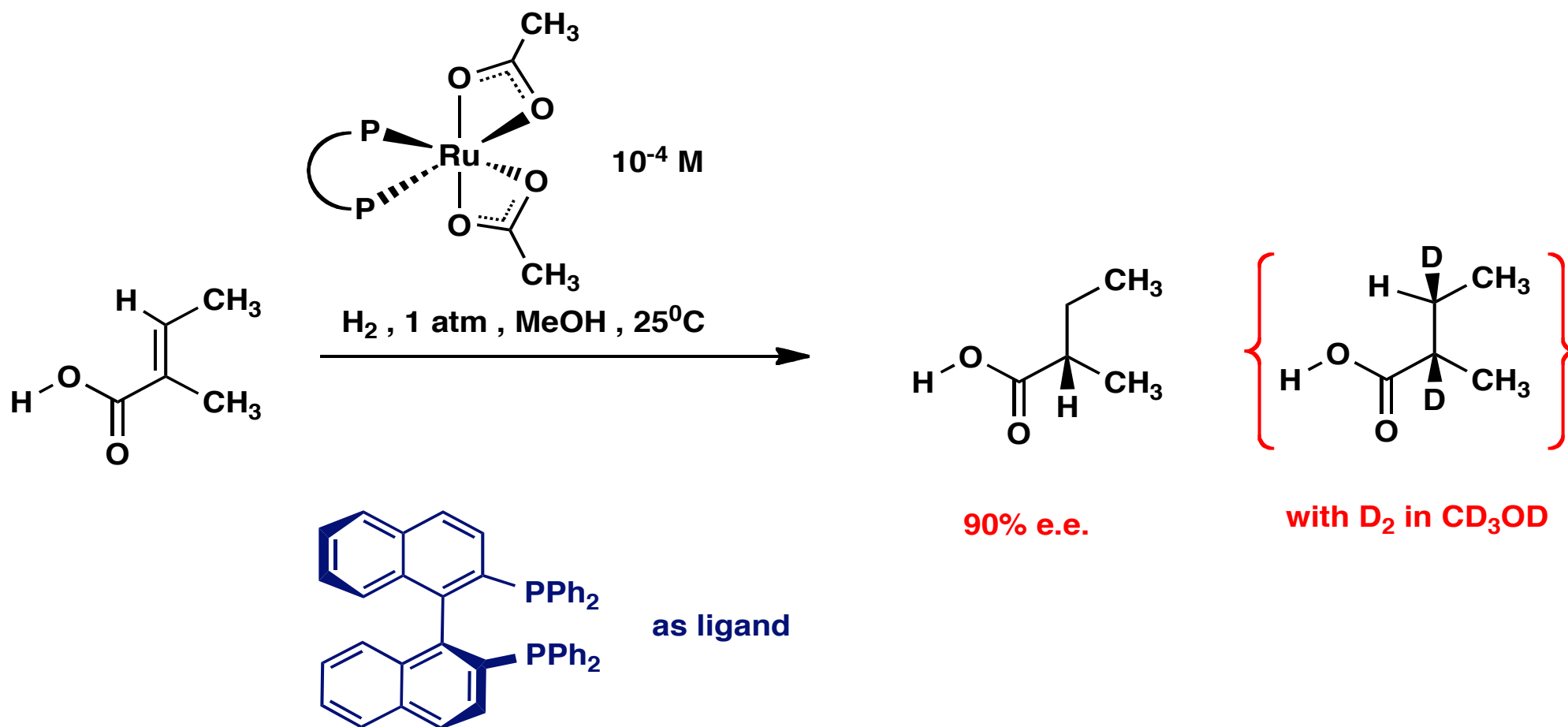
Better for
alkenes



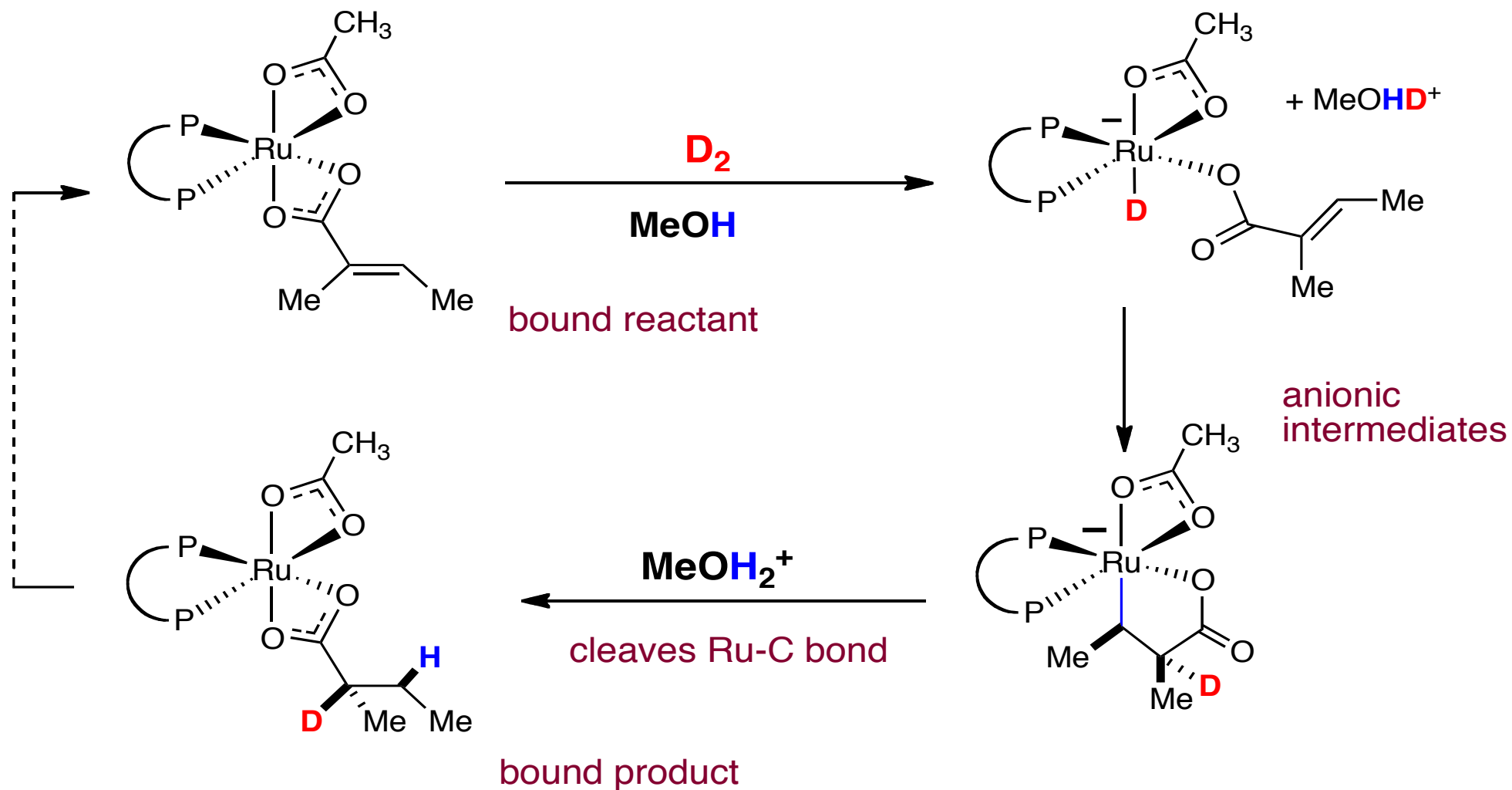
Better for
heteroatomic
double bonds



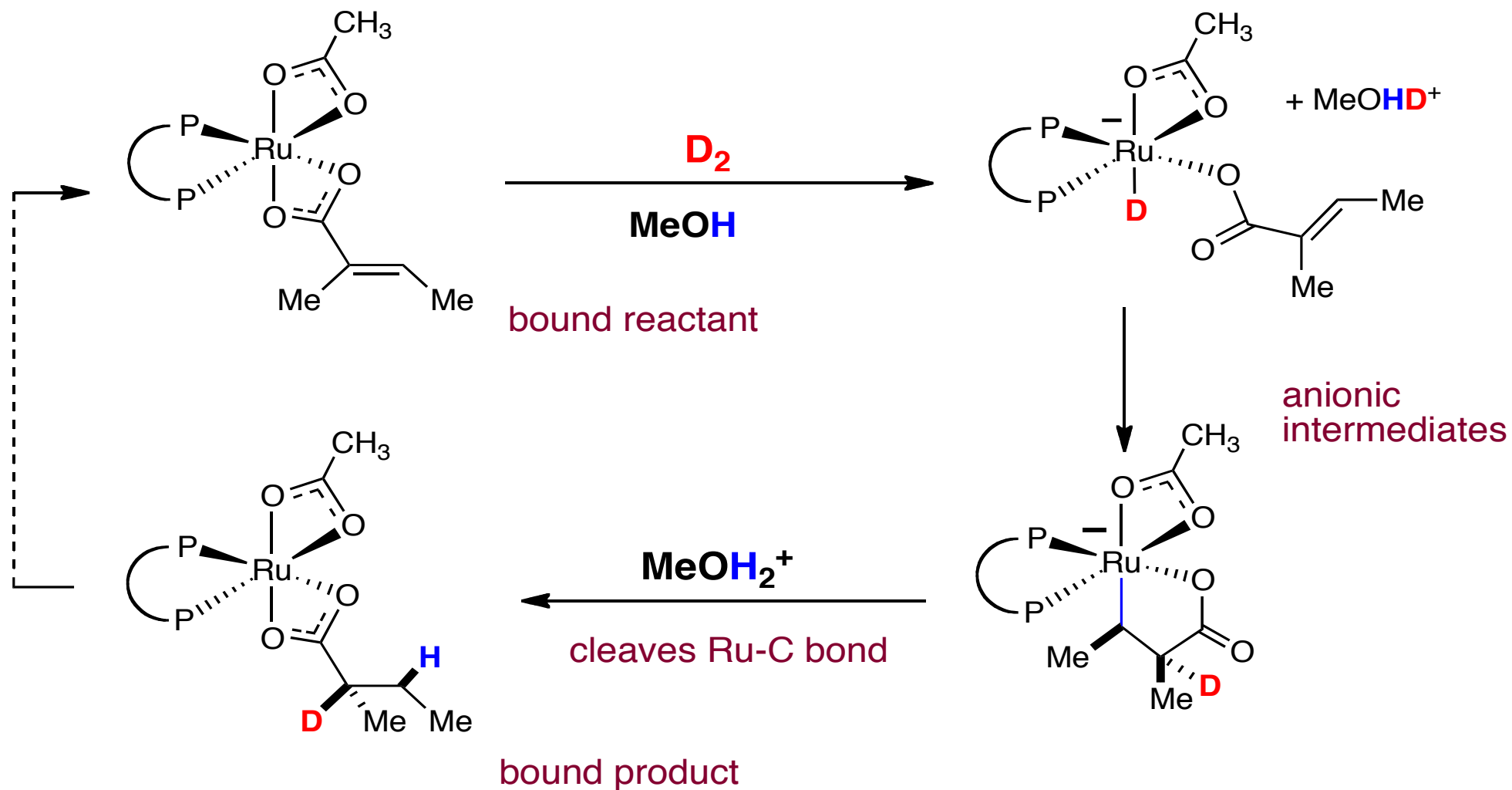
Ruthenium catalysed hydrogenation of unsaturated carboxylic acids is effective- **mechanism 1**



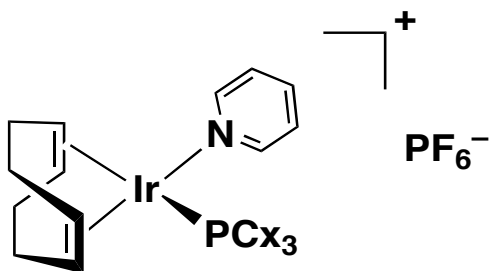
The two hydrogens are delivered distinctly – the first from H₂, the second from solvent



The two hydrogens are delivered distinctly – the first from H₂, the second from solvent

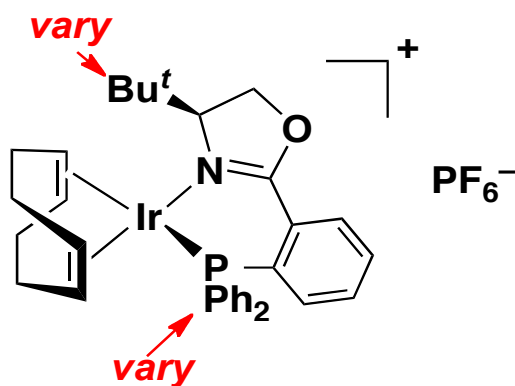


Basics of Iridium asymmetric hydrogenation; P-N catalysts, chelate forming



Crabtree's original catalyst 1977-1980. Fast hydrogenation even of tetrasubstituted alkenes *in non-protic solvents*.

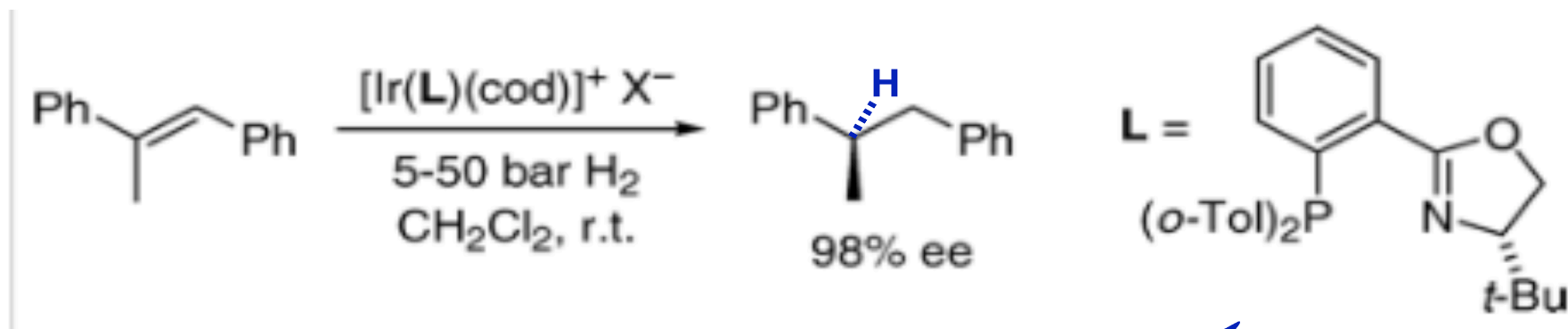
Never used commercially; limited turnover before deactivation



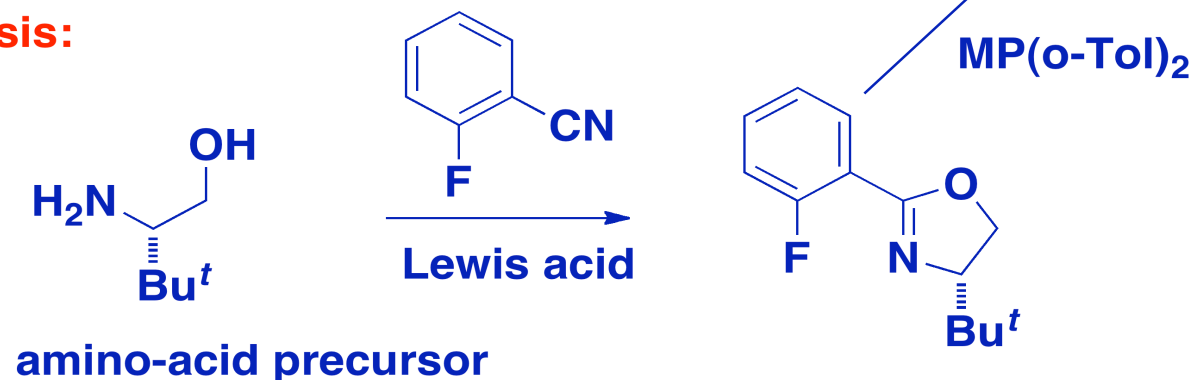
Pfaltz introduced a family of chelate PHOX-based analogues for asymmetric hydrogenation. Similar limitations; high pressures needed for satisfactory e.e.s

High sensitivity to water; annulled by switching to the hydrophobic BARf counter-ion.

Iridium asymmetric hydrogenation follows naturally from the Crabtree catalyst (>20 years later)

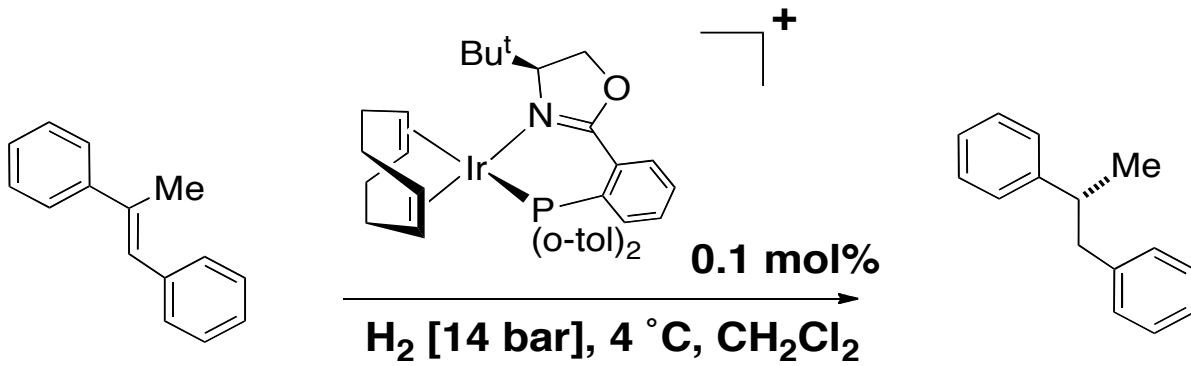
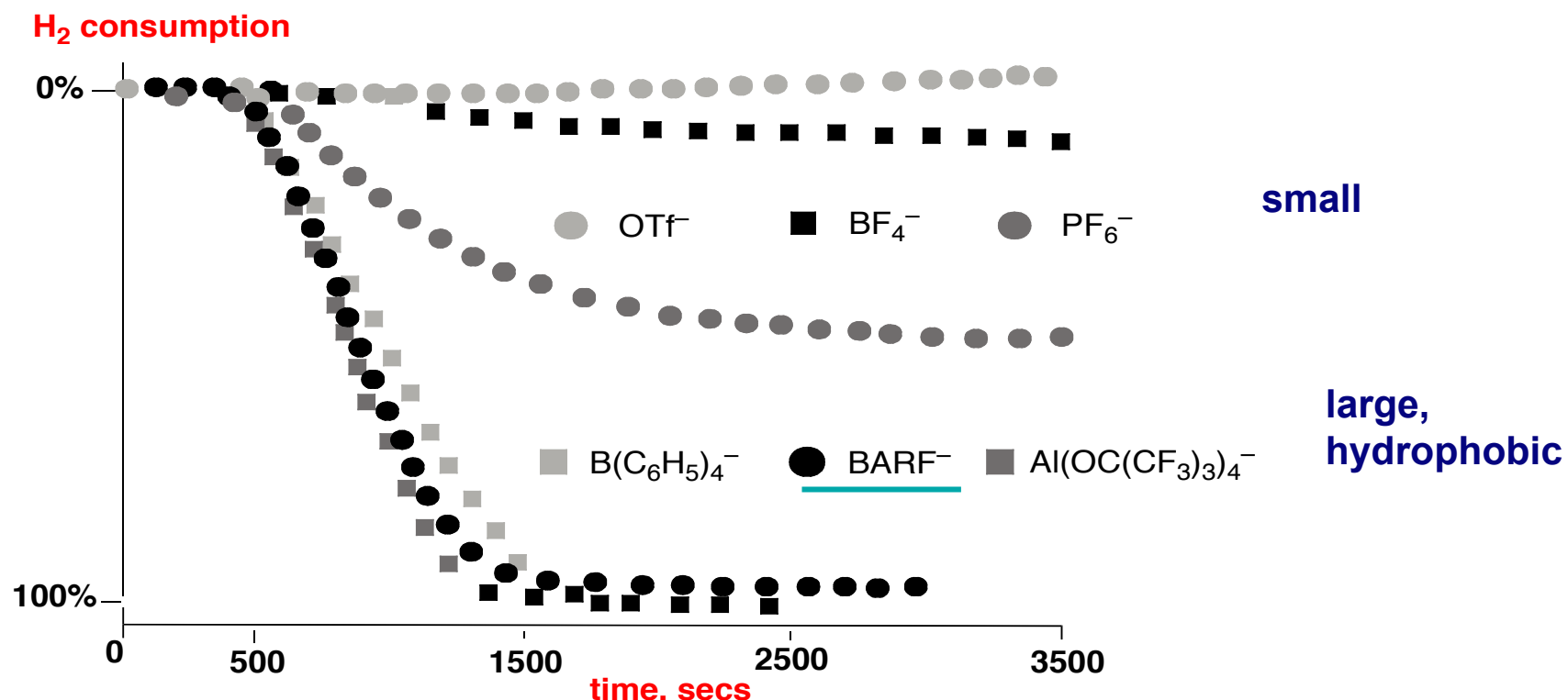


Ligand synthesis:



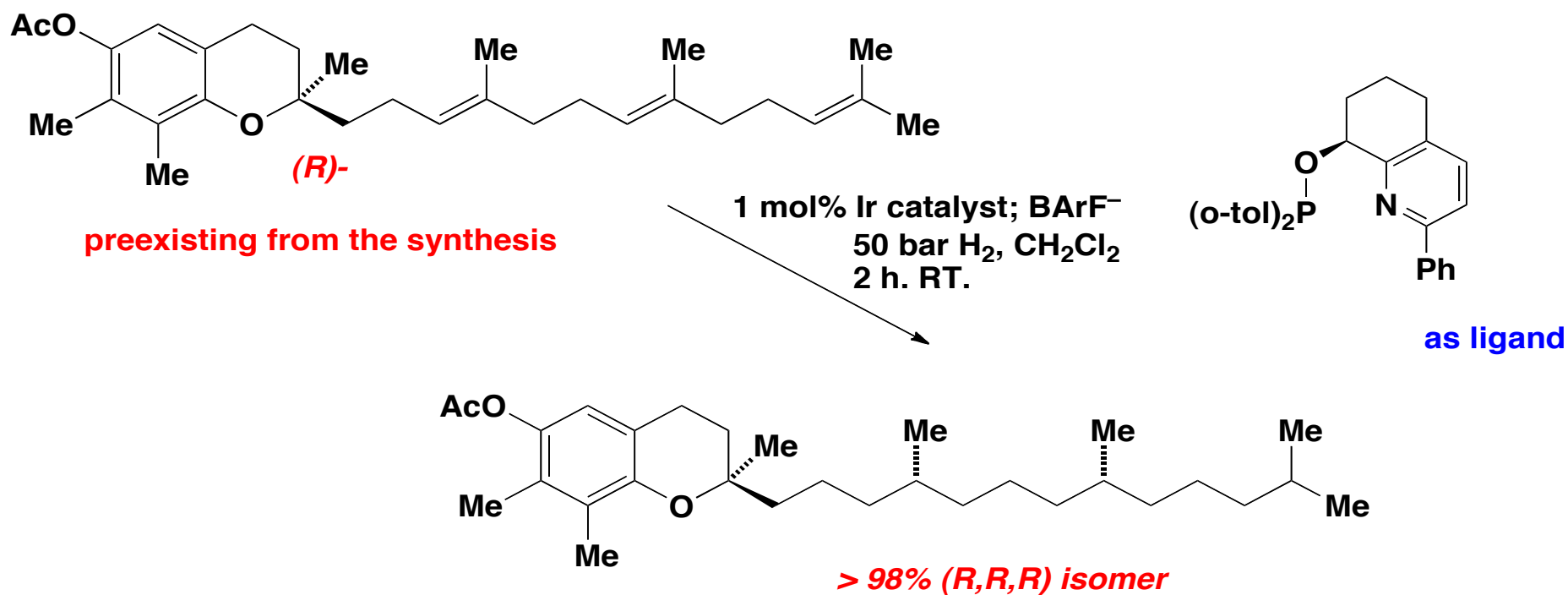
NB – no chelating groups in the substrate

The counter-ion is critical, and the solution must be anhydrous as well

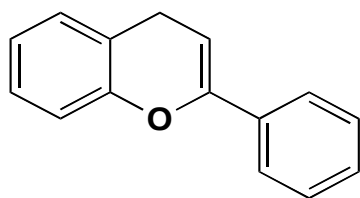


What's BARF?
(look up
"non-coordinating
anion" in Wiki)

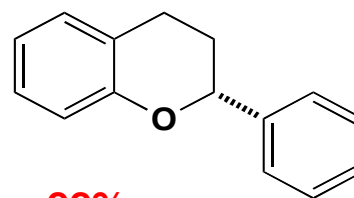
A hydrogenation-based enantioselective synthesis of Vitamin E. Two crucial stereocentres introduced without directing groups



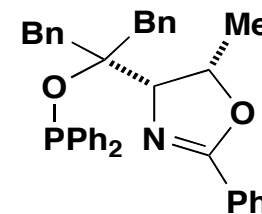
Some examples of asymmetric hydrogenation with Ir catalysts - di, tri- and even tetrasubstituted alkenes



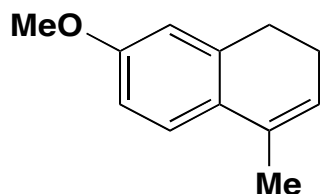
1 mol% Ir catalyst
50 bar H₂, CH₂Cl₂
2 h. RT.



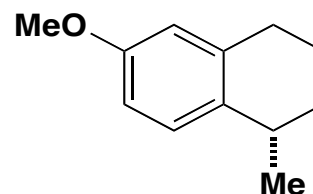
99% e.e.



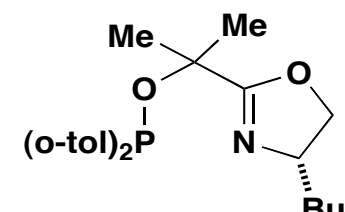
ligand



1 mol% Ir catalyst
50 bar H₂, CH₂Cl₂
2 h. RT.

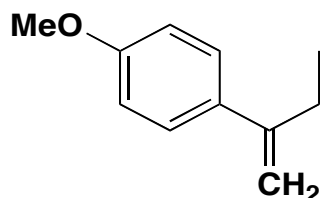


99% e.e.

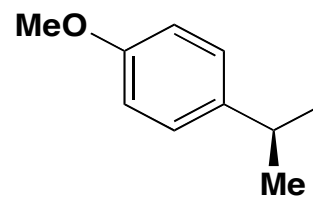


ligand

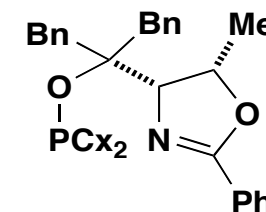
Compare:



1 mol% Ir catalyst
1 bar H₂, CH₂Cl₂
2 h. RT.



94% e.e.



ligand

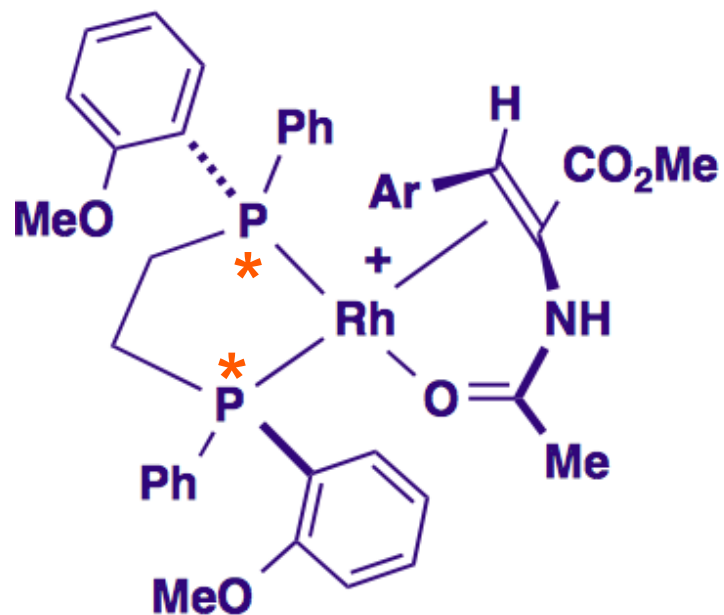
Synthetic range of asymmetric hydrogenation

Rhodium – valuable for enamides, dehydroamino acids – huge variety of ligands available; practical applications involve optimization of catalyst as well as reaction conditions. Phosphoramidites as mono-P ligands

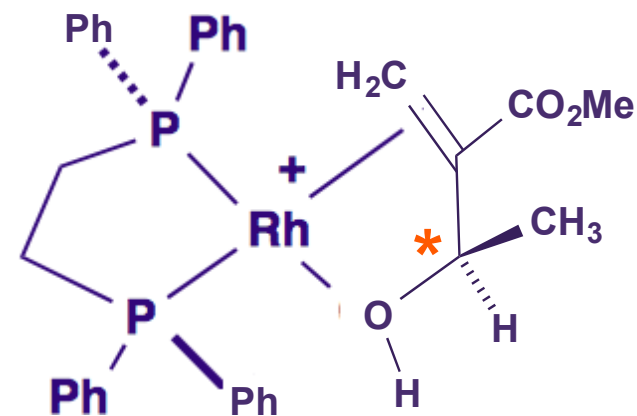
Ruthenium – much wider variety of functional groups efficient in metal binding, so more versatile. Catalysis with BINAP or related ligands designed on the same principle.

Iridium – works for cases where the alkene lacks binding groups. Most successful ligands form PN chelates.

What happens if we move the stereogenic centre from the ligand to the substrate?



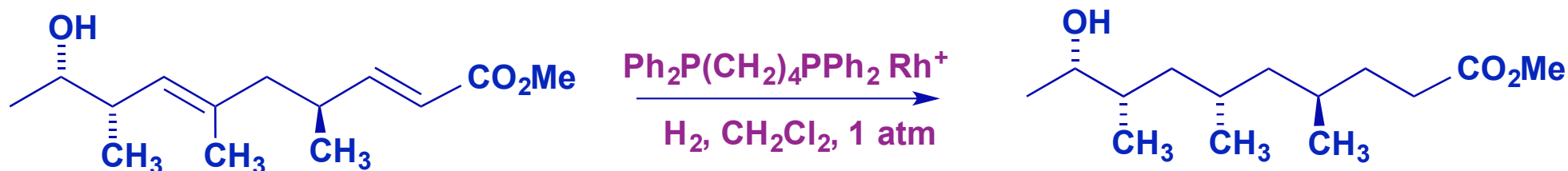
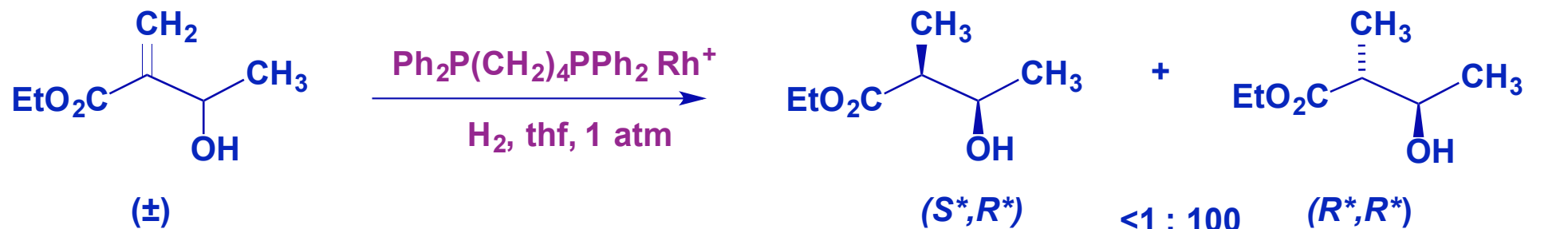
Asymmetric hydrogenation



Directed hydrogenation

* Stereogenic centre

Directed hydrogenations – alcohol as directing group (could be C=O of ester, amide, etc.)

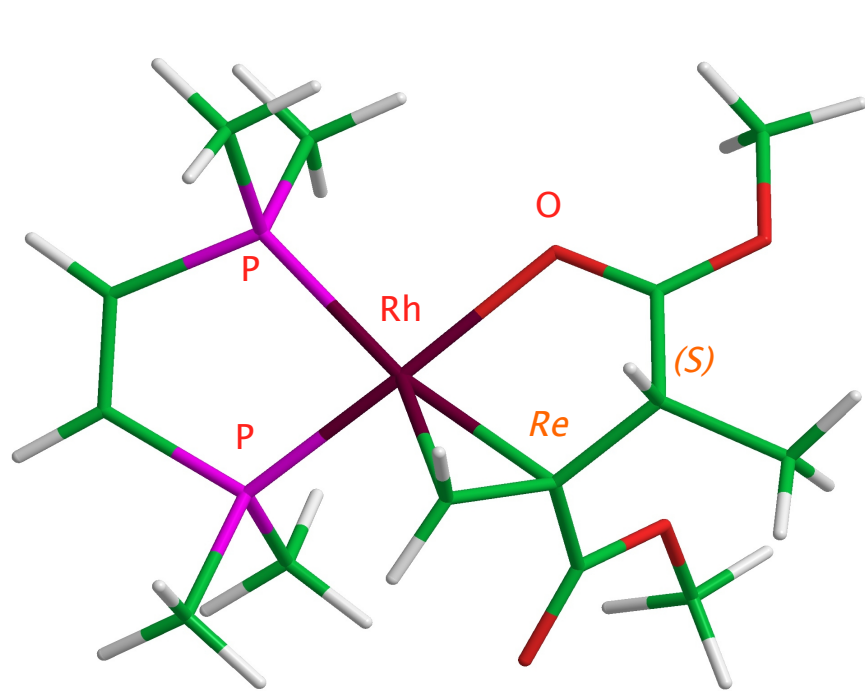


route to fragment C1 - C10 of ionomycin

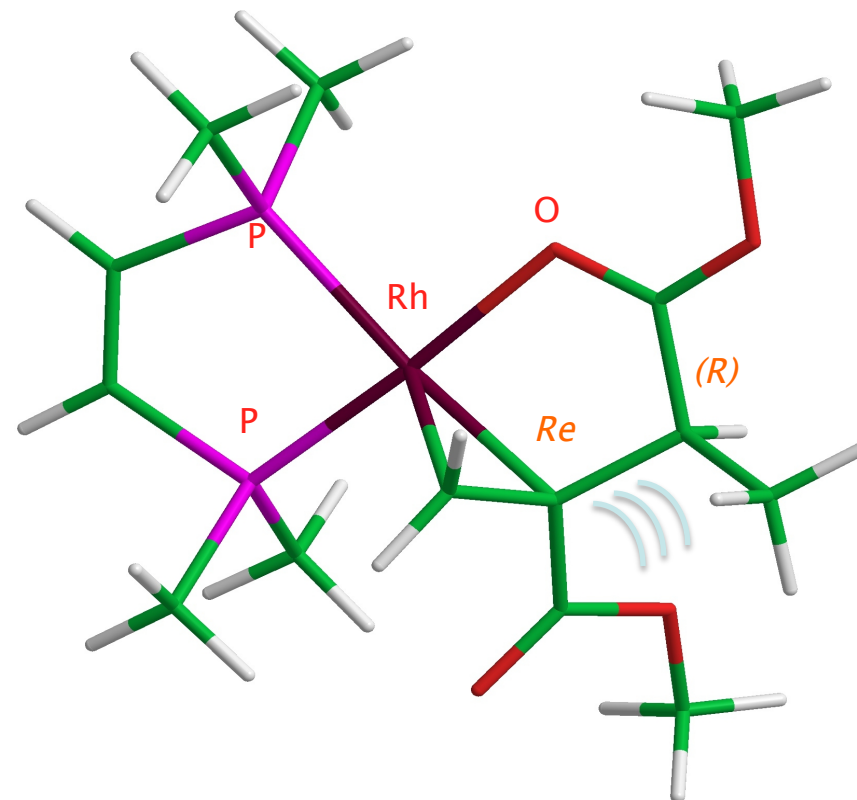
94% diastereoselectivity

see: Hoveyda, Evans, Fu *Chem. Rev.* 1993, 93, 1307; Brown, *Angew. Chem. Int. Ed.*, 1987, 26, 190.

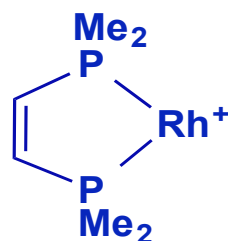
Analysis of ground state binding with model ligand reveals selectivity that matches the results of hydrogenation



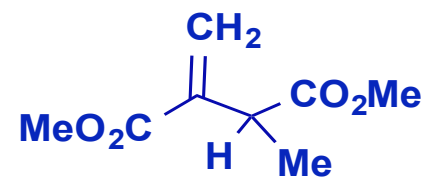
Preferred by 3 kcal mol⁻¹



DFT: ω B97xD / 6-31G(d,p) [Rh (SDD)] SCRF - MeOH



binding



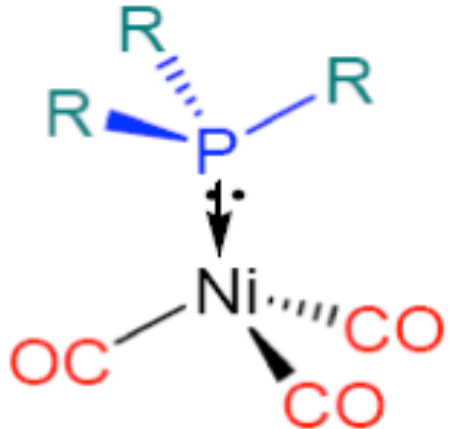
Appendix– Properties of phosphine ligands

Following 3 slides show variations at phosphorus

a) Different phosphines possess different electronic effects

Increasing donor ability

L in L–Ni(CO) ₃ :	ν_{CO}
PBu ^t ₃	2056.1
PMe ₃	2064.1
PPh ₃	2068.9
P(OMe) ₃	2079.5
P(OPh) ₃	2085.0
PF ₃	2110.8



Note different names: PR₃ – phosphine; P(OR)₃ - phosphite

We can measure IR stretching frequencies: The more electron-withdrawing the ligand, the more back-donation from the metal to P. This affects the CO

bond:



ν higher



ν lower

b) The bulk of a phosphine ligand can be expressed through its cone angle

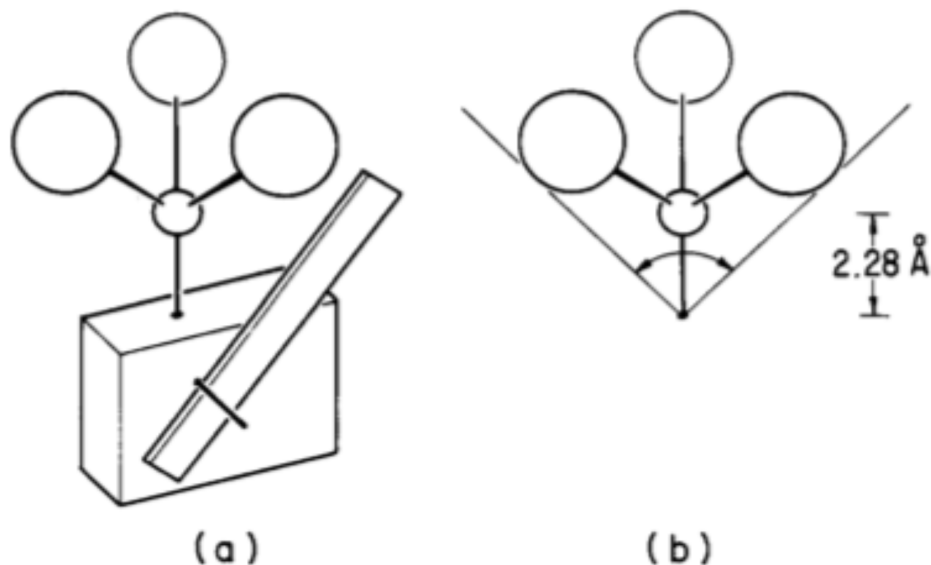


Figure 4. (a) Ligand angle measuring device; (b) the cone angle, from ref 2.

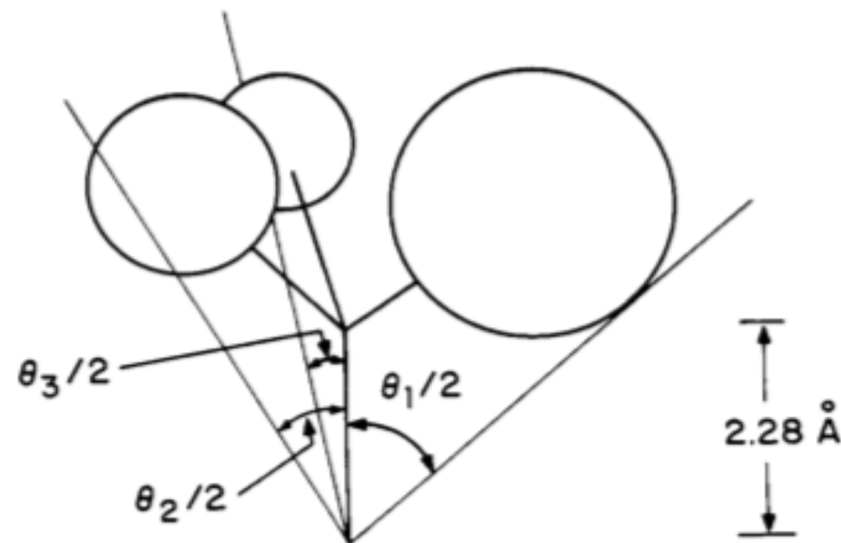
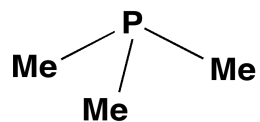


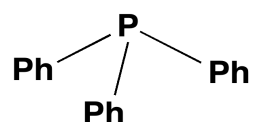
Figure 6. Method of measuring cone angles for unsymmetrical ligands.

$$\theta = (2/3) \sum_{i=1}^3 \theta_i/2$$

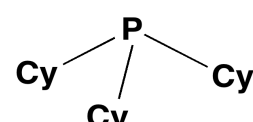


Cone angle

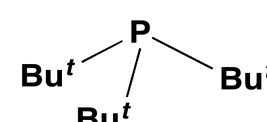
120°



145°

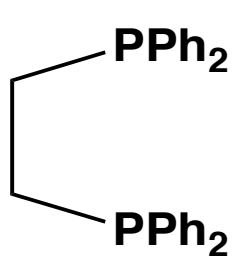


170°

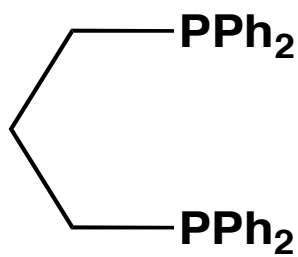


182°

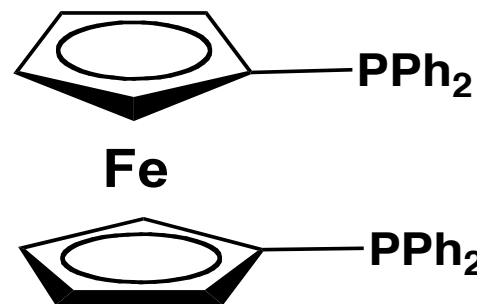
c) Bite angles P–M–P provide an important parameter for the comparison of different chelate ligands



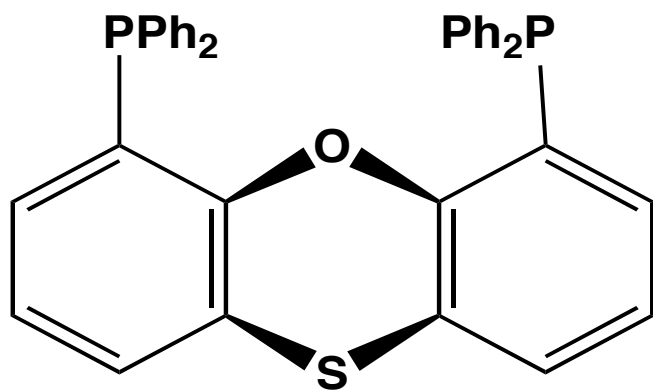
85°



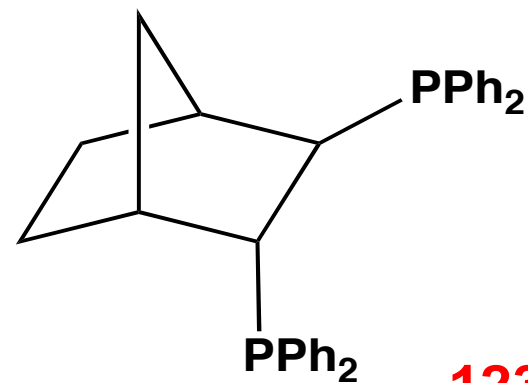
91°



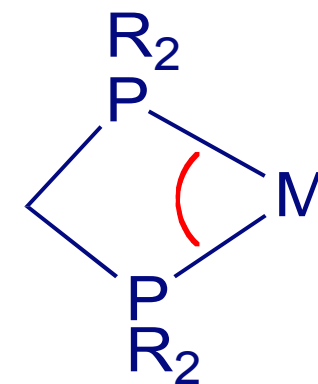
97°



112°

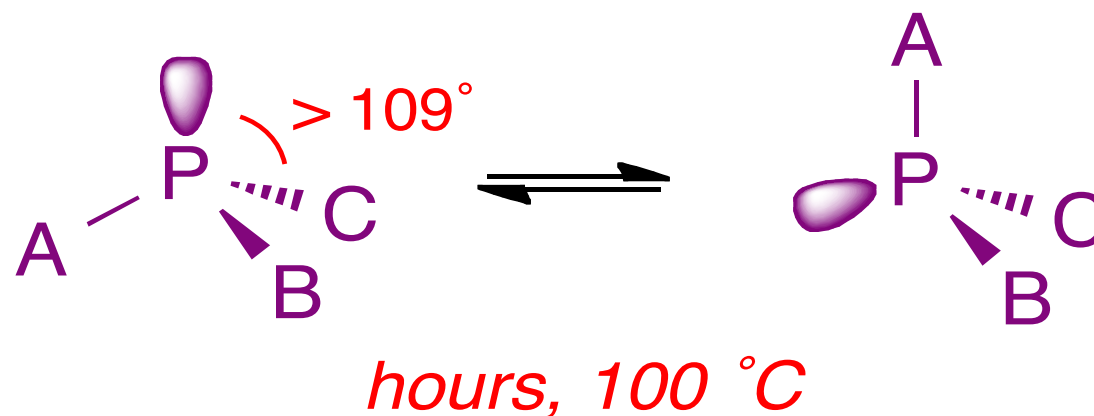
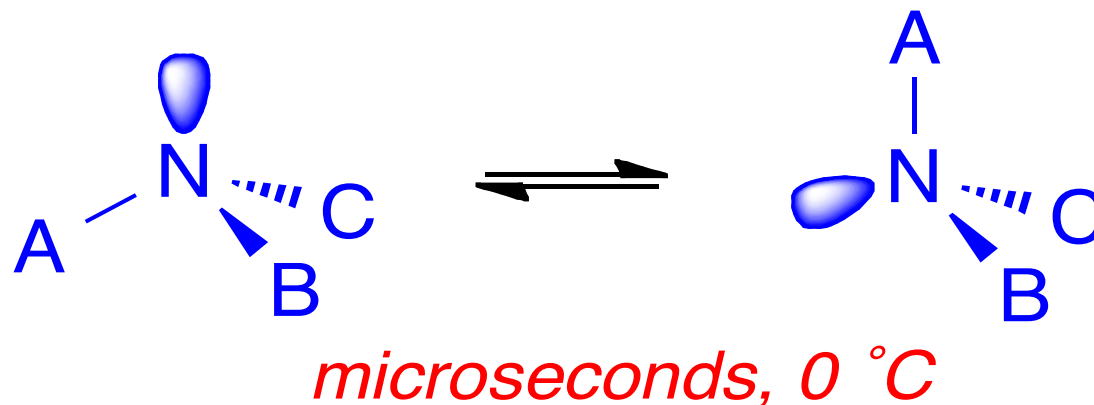


123°



Bite angle

Trivalent phosphorus is stereochemically far more stable than trivalent nitrogen; allows P-stereogenic ligands



What causes this remarkable difference?

SBM 2014 Lecture 2

John Brown

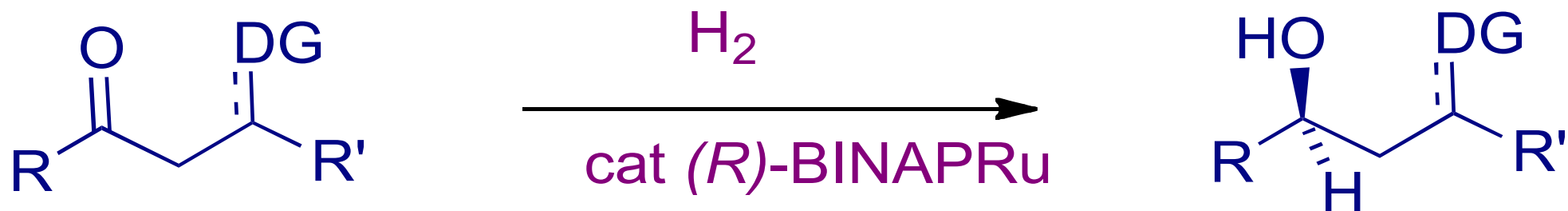
Hydrogenation of Ketones and Imines

Transfer Hydrogenation

Dehydrogenation and Dehydrogenative
Coupling

Interception of Reactive Intermediates

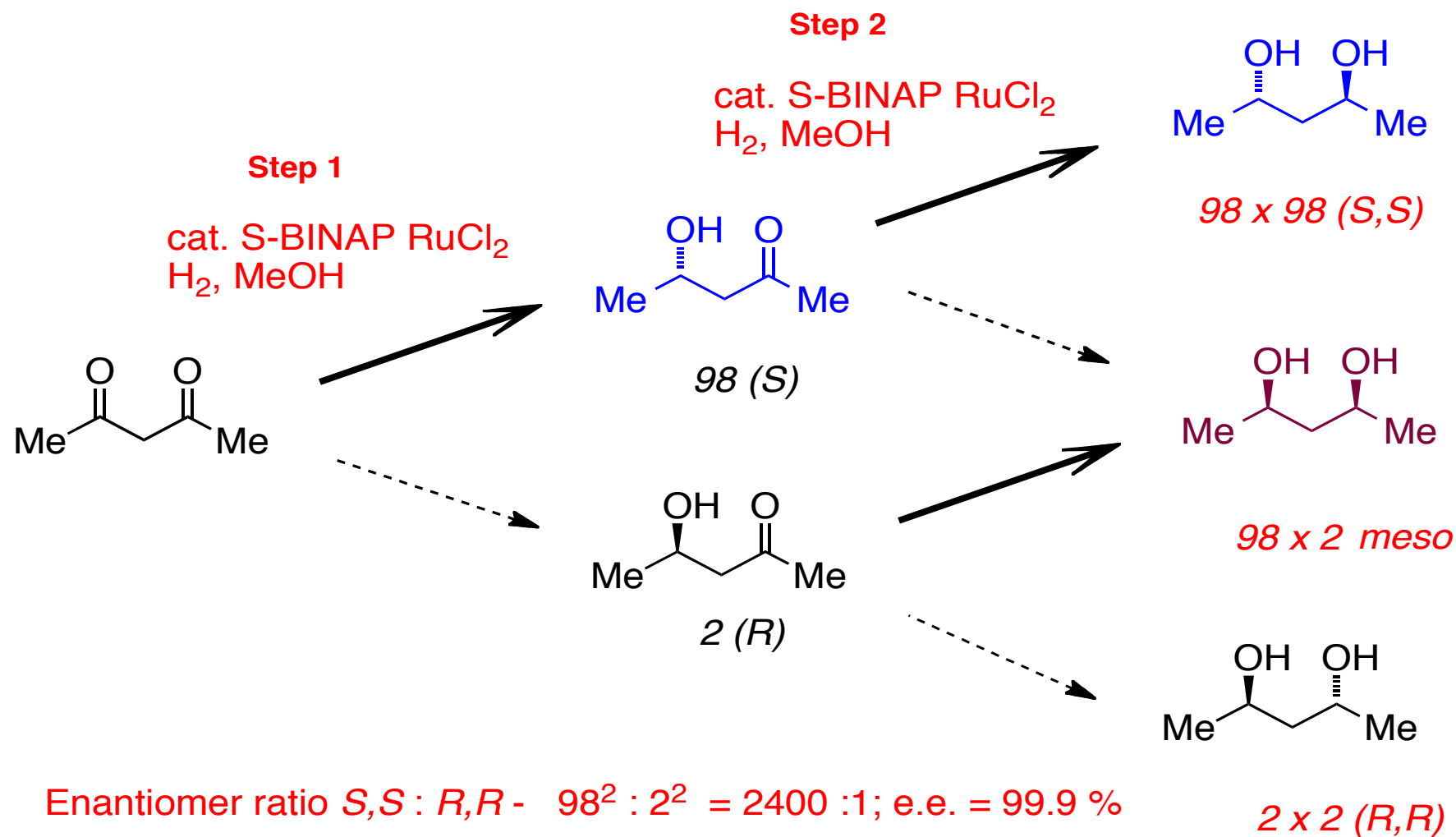
Increased versatility for Ru catalysis – many ketones are hydrogenated in high enantiomer excess



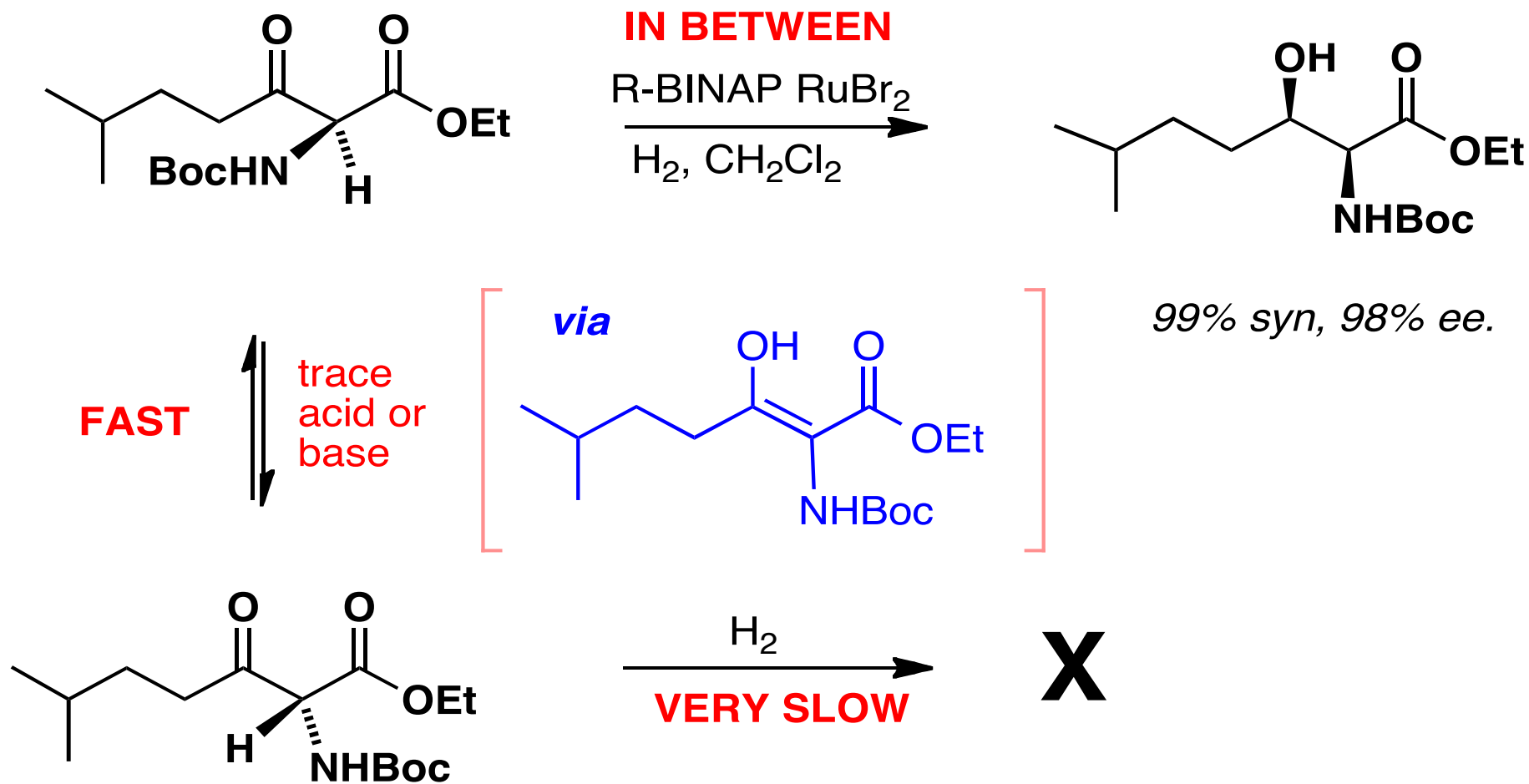
DG is a directing group (lone pair bond to Ru catalyst)

Ru hydrogenation of **ketones** provides an example of **double asymmetric induction**

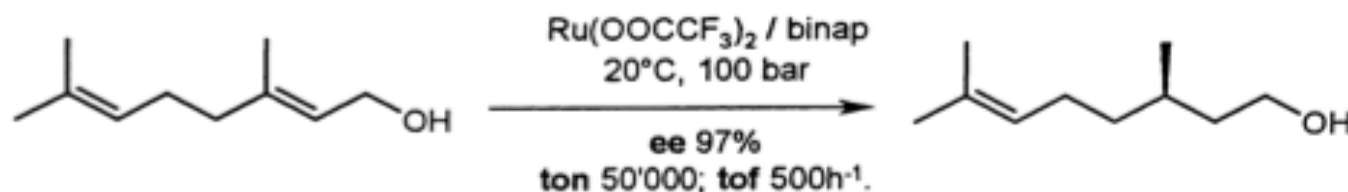
e.e. of final product is enormous



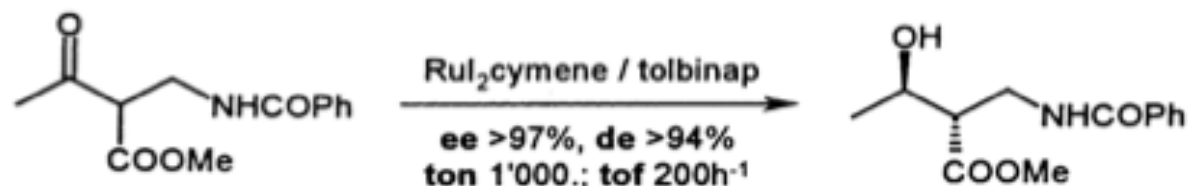
High diastereoselectivity and fast keto-enol tautomerisation lead to **Dynamic Kinetic Resolution** from a racemic reactant.



Ruthenium has provided asymmetric catalysts for both ketone and alkene reduction



Takasago [41–43]: citronellol and intermediate for Vitamin E; scale 300 t per year
Success factors: Ru precursor, anion, catalyst filtration possible, high chemoselectivity



Takasago [41,42,49]: intermediate for carbapenem (antibiotic); 50–120 t per year
Success factors: dynamic kinetic resolution, ligand fine tuning

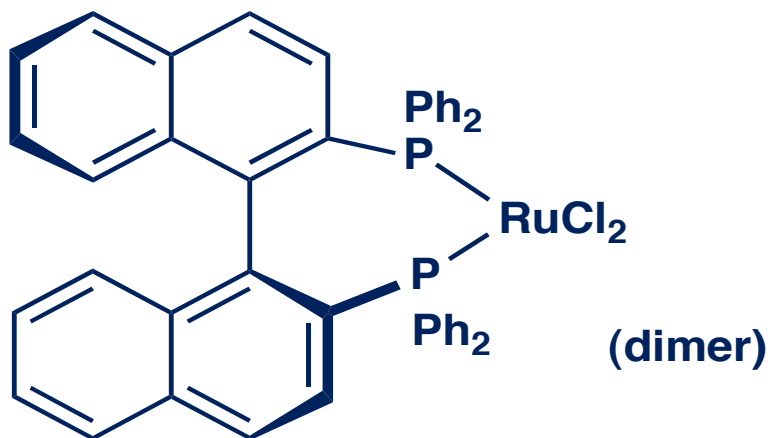
Enantioselective catalysis in fine chemicals production

H.U. Blaser*, F. Spindler, M. Studer

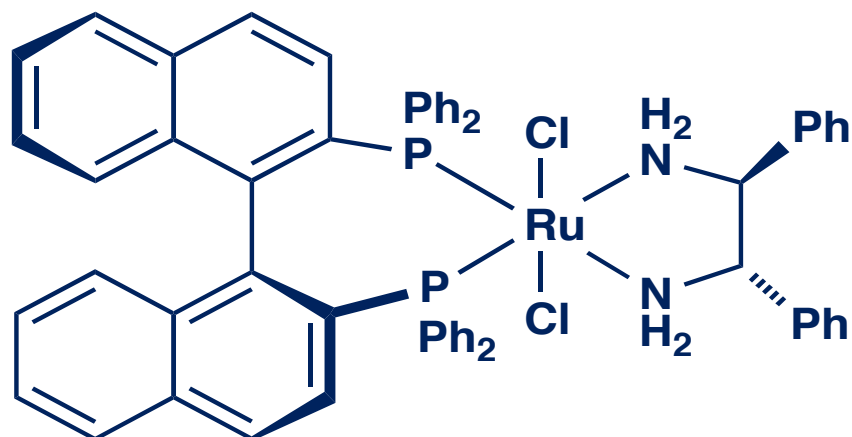
Solvias AG, Postfach, CH-4002 Basel, Switzerland

Applied Catalysis A: General 221 (2001) 119–143

P_2N_2Ru complexes; a further breakthrough in Ru catalysis of hydrogenation



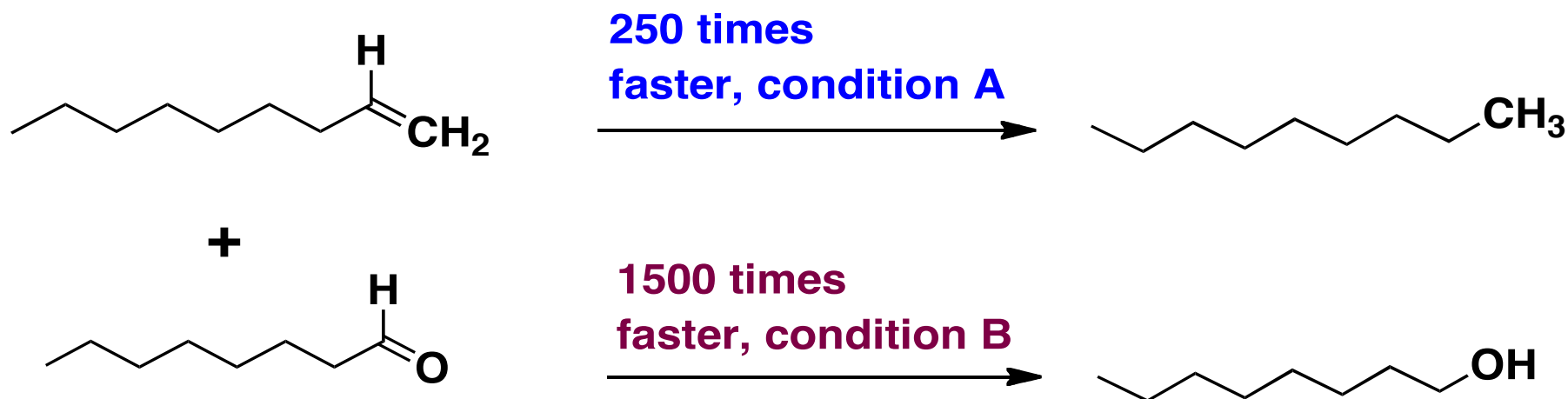
1st generation catalyst



2nd generation catalyst

Completely different mechanism

In the presence of base, metal hydrides are formed that change the reaction pathway

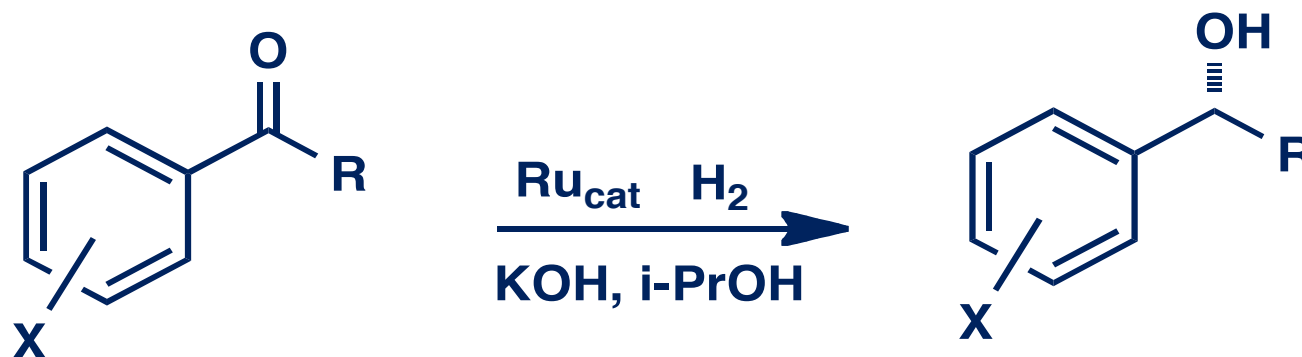


Allow competition for catalyst and reagent

- A** Cl₂Ru(PPh₃)₃, H₂, i-PrOH, toluene
B as A, add KOH, H₂N(CH₂)₂NH₂.

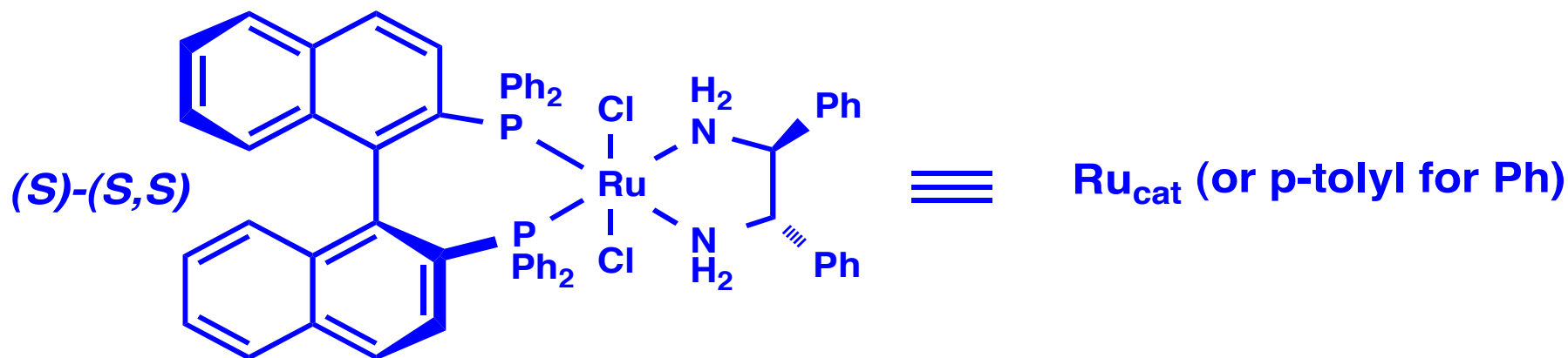
In B; Ru-H is formed from Ru-Cl by the base; how?

The method is useful for asymmetric reductions in the absence of a directing group

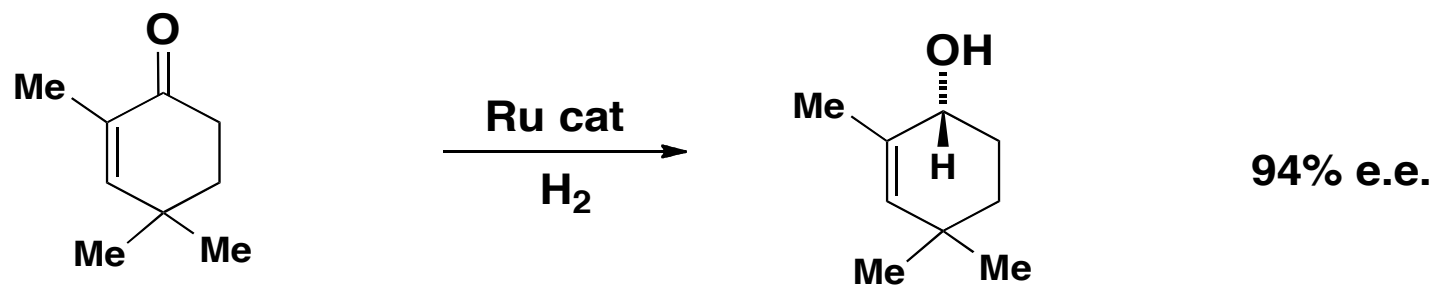
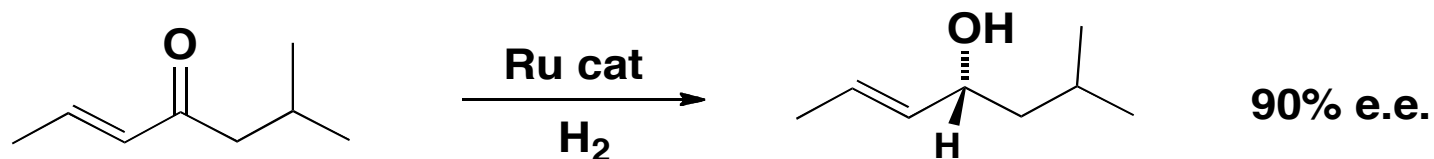
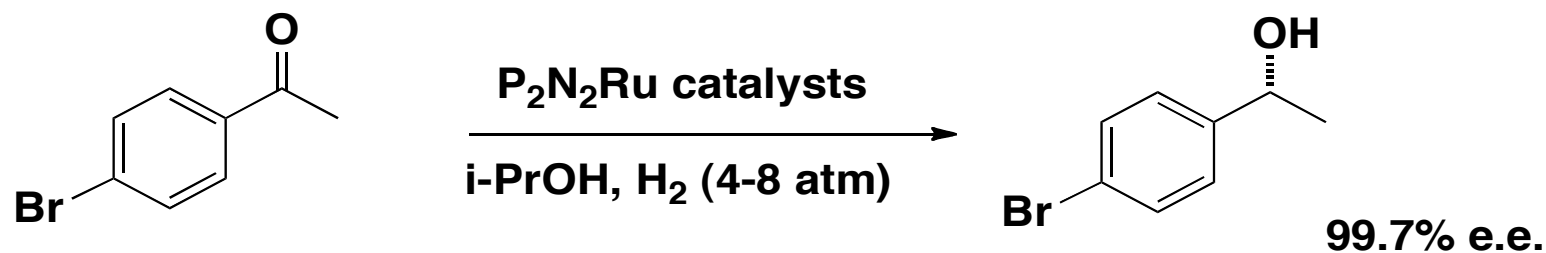


R = Me, i-Pr, t-Bu
X = Me, t-Bu, OMe, Cl, C(O)Me

(R)-isomer
> 90% e.e.



Getting close to a universal method for selective reduction of ketones

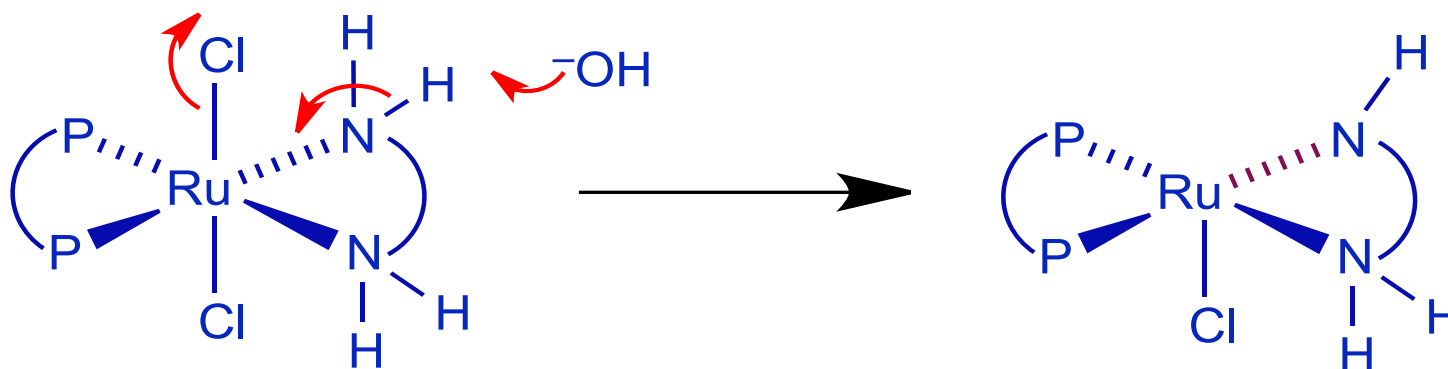


C=C Double bonds are unaffected; simple ketones are reduced by the same catalysts

Hydrogenation with P_2N_2Ru complexes. How it works 1. Consider the essentials.

The catalyst is introduced as a Rh(II) dichloride with both ligands in place. A strong base is needed in order to activate this pre-catalytic state.

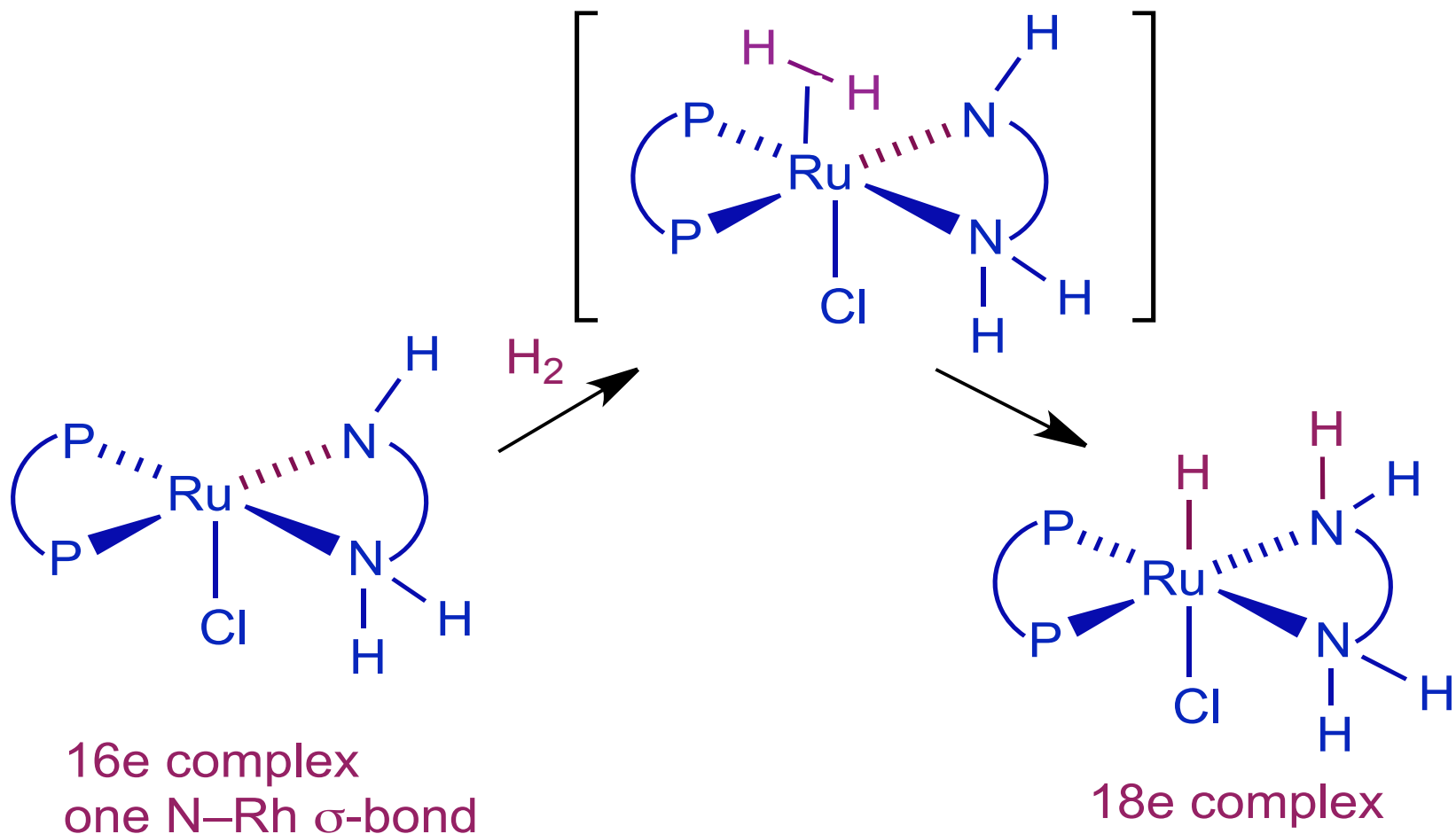
The key reaction involves HCl elimination by the base, then H_2 addition - basic equation:



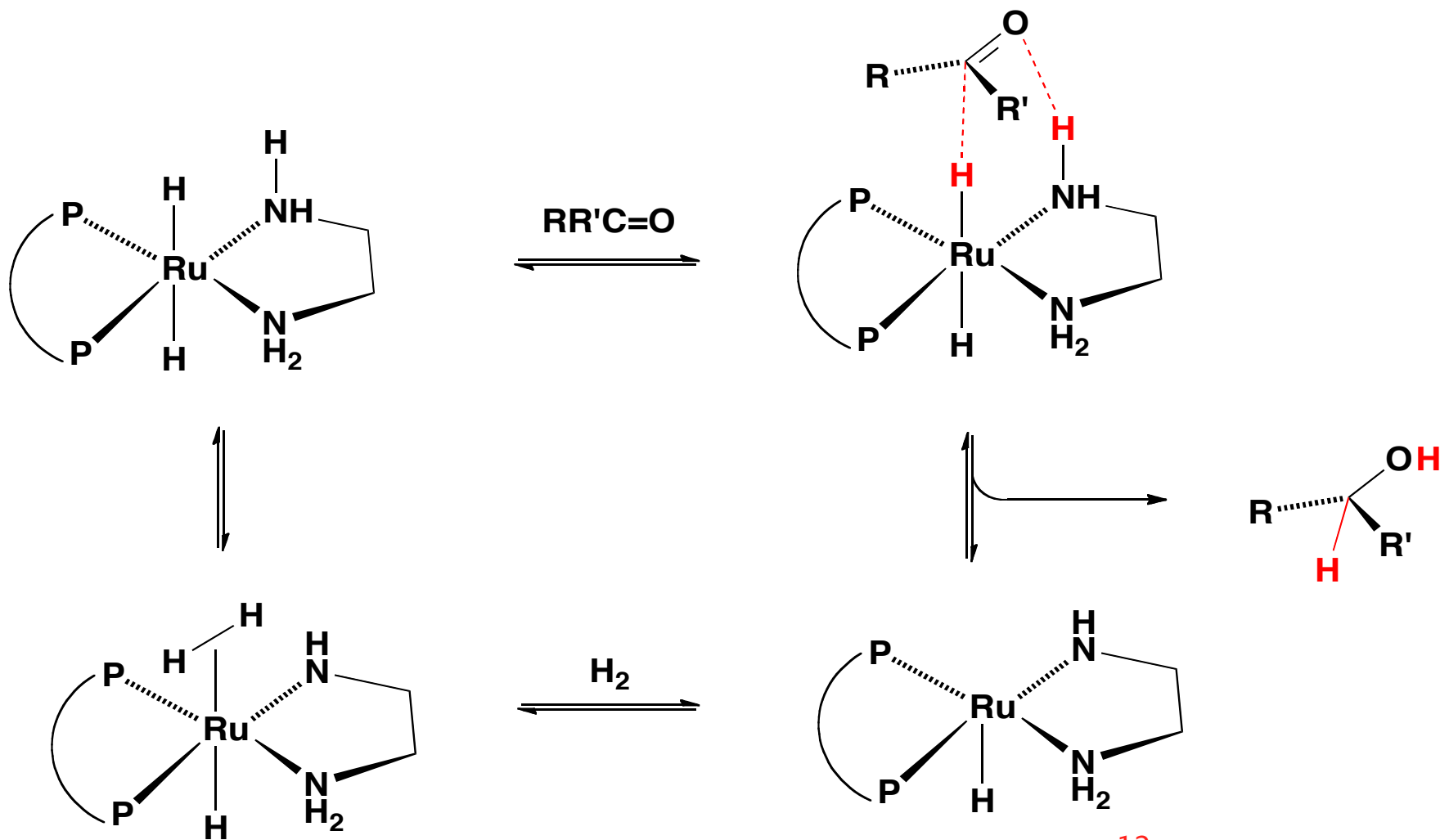
18e complex -
all PN 2e donors

16e complex
one N-Rh σ -bond
10

How it works 2. The precatalyst needs to be reduced first to replace Cl^- by H^- to make the active catalyst. The process can be repeated to make a Ru dihydride

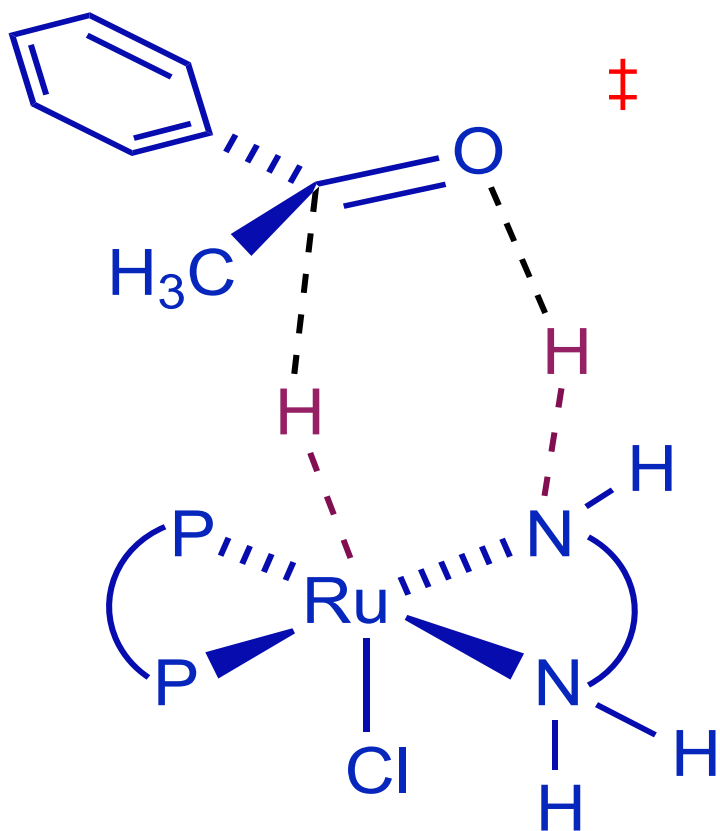


How it works 3. Once the catalyst has formed a very simple mechanism ensues; the ketone is never bound to Ru

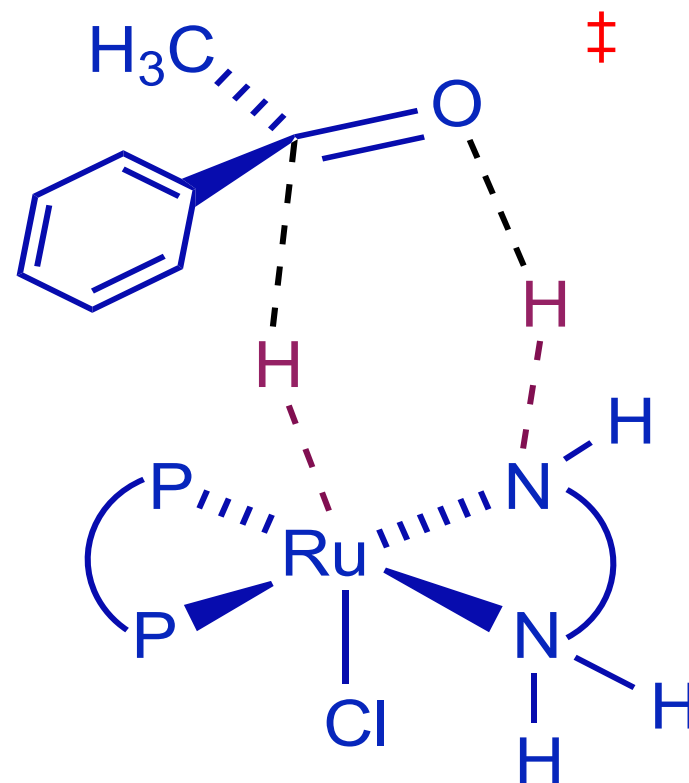


12

How it works 4. With a single enantiomer catalyst the configuration of the product is determined by stereoselection in the H₂ transfer step



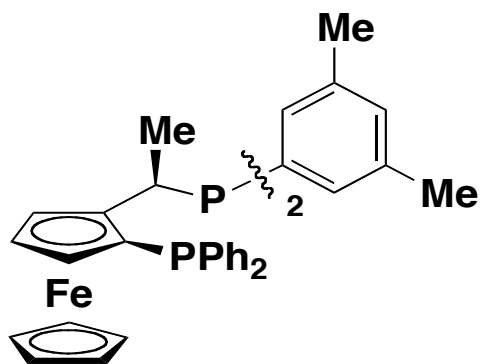
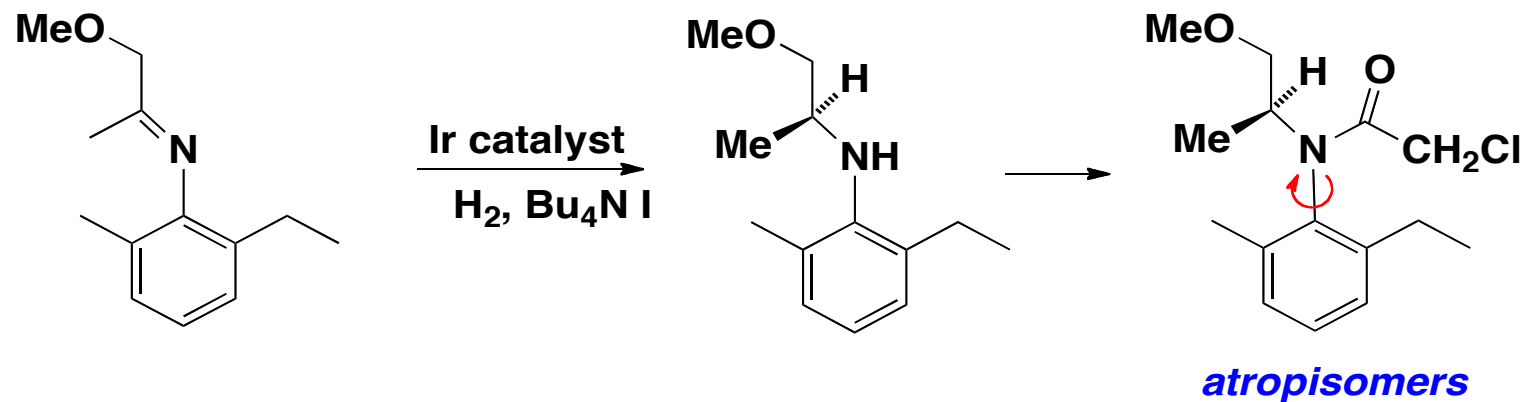
re-face



si-face

13

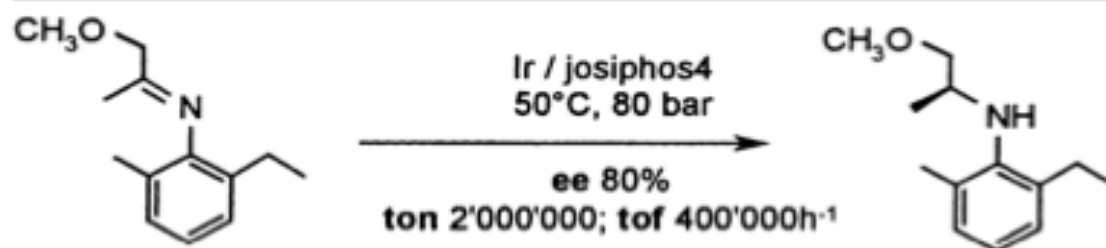
Iridium catalysts are also effective for the reduction of imines (NB PP catalysts)



ligand - has both central and planar chirality

Classic example is the synthesis of the herbicide metolachlor produced on a **multi-ton scale**

Iridium catalysis has provided the most substantial scale-up in asymmetric hydrogenation Metolachlor; herbicide



Ciba-Geigy/Syngenta (Solvias) [44,47]: intermediate for (S)-metolachlor herbicide (Dual Magnum[®]), >10000 t per year
Success factors: Ir catalyst, ligand type and ligand tuning, iodide/acid addition
Critical issues: impurities

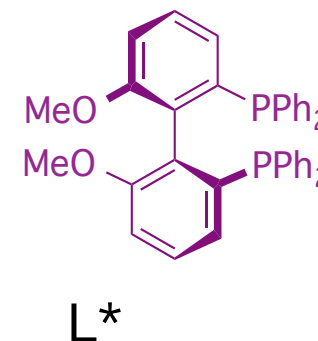
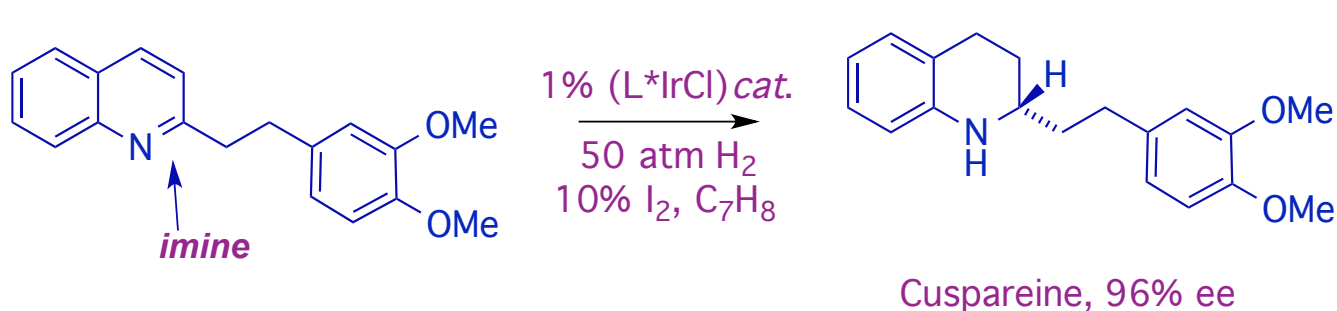
Enantioselective catalysis in fine chemicals production

H.U. Blaser*, F. Spindler, M. Studer

Solvias AG, Postfach, CH-4002 Basel, Switzerland

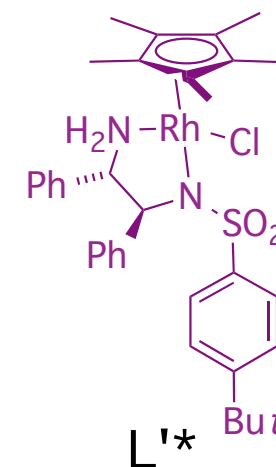
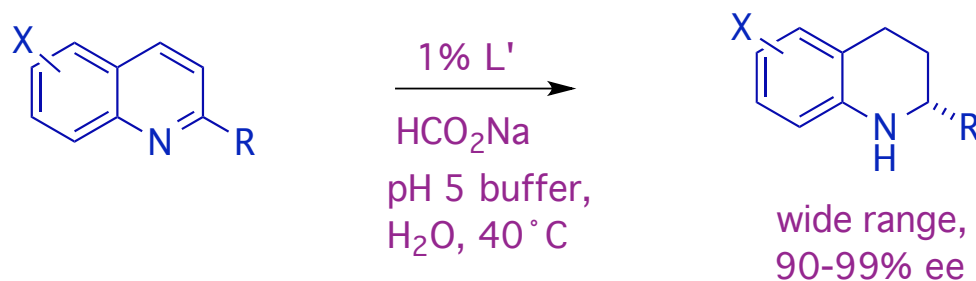
Applied Catalysis A: General 221 (2001) 119–143

Many heterocyclic systems are responsive to asymmetric hydrogenation



Generally high pressure of H_2 is needed, and I_2 promotes the reaction

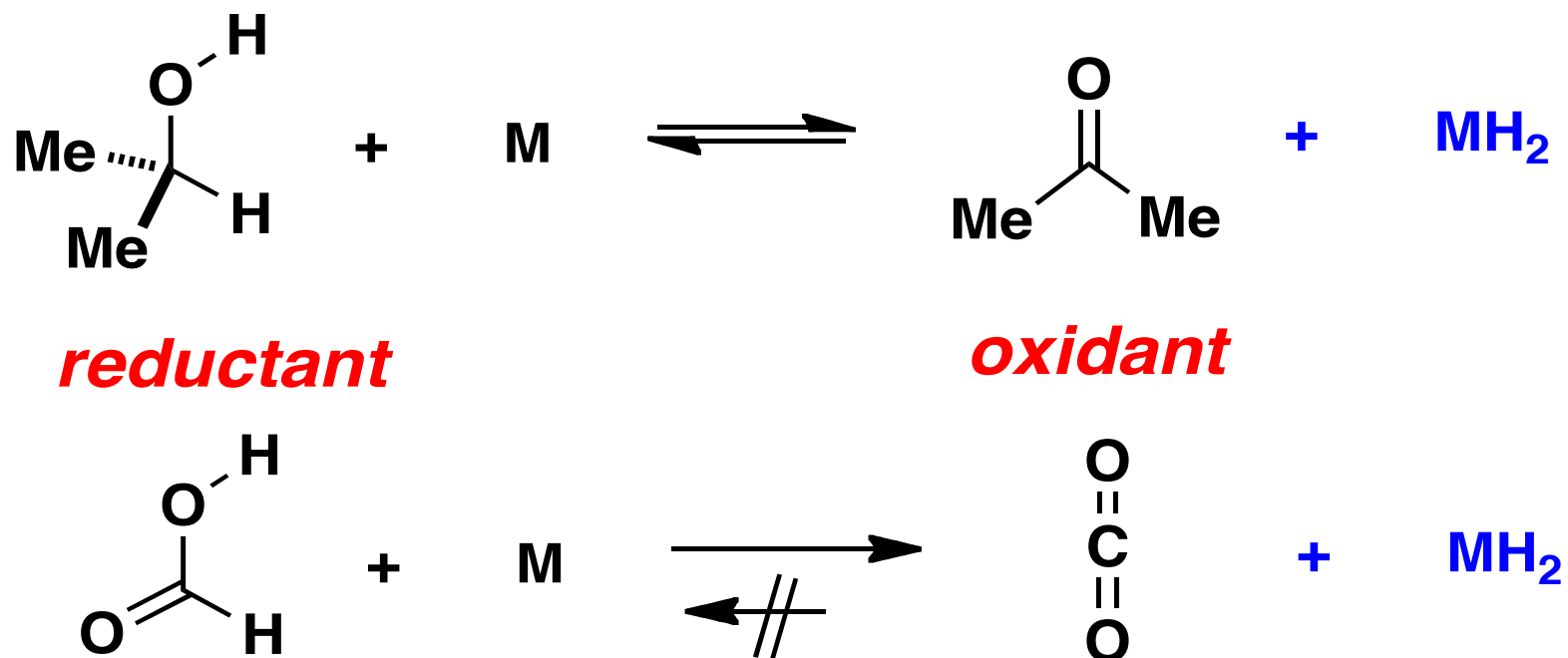
Y-G Zhou et al., *J.Am.Chem.Soc.*, 2003, 105, 10536



Transfer hydrogenation provides a neat solution under ambient conditions; the reactant is activated by N-protonation

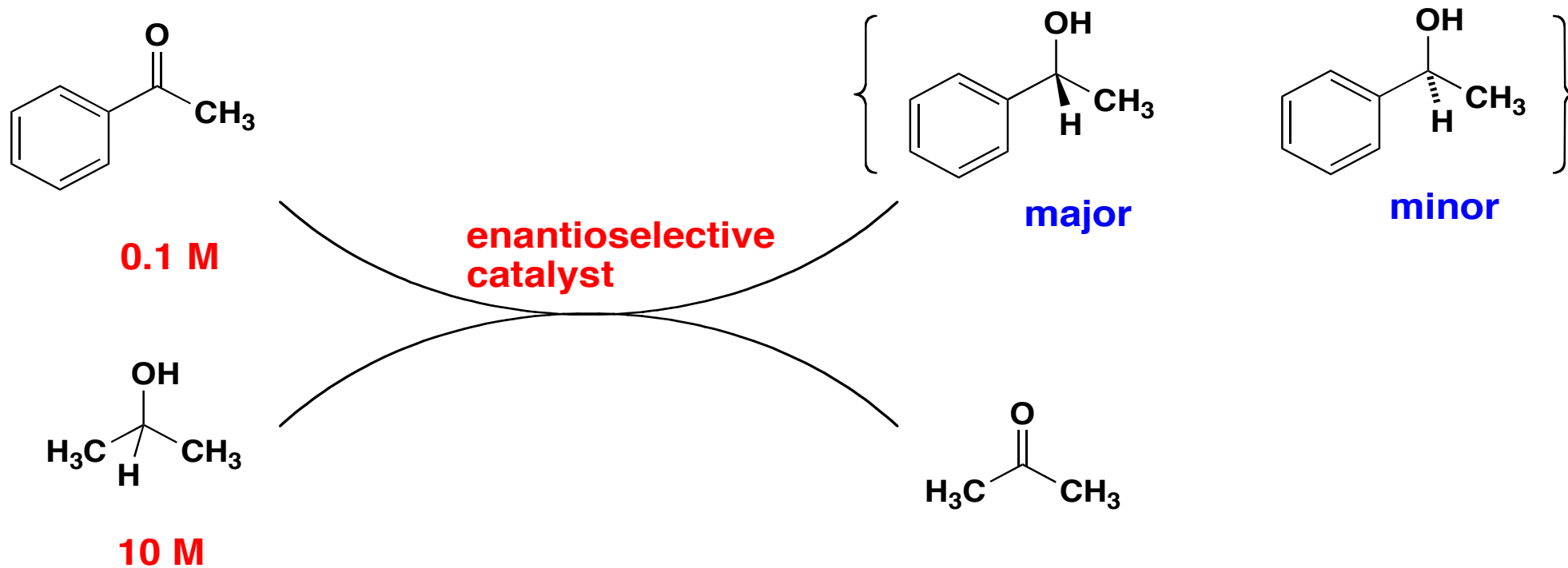
J. Xiao et. al. *Angew. Chem.* 2009, 48, 6524

Basic principles of a metal-catalysed transfer hydrogenation



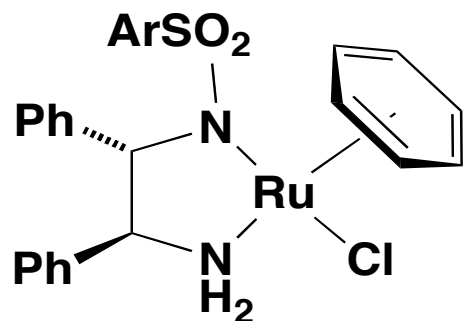
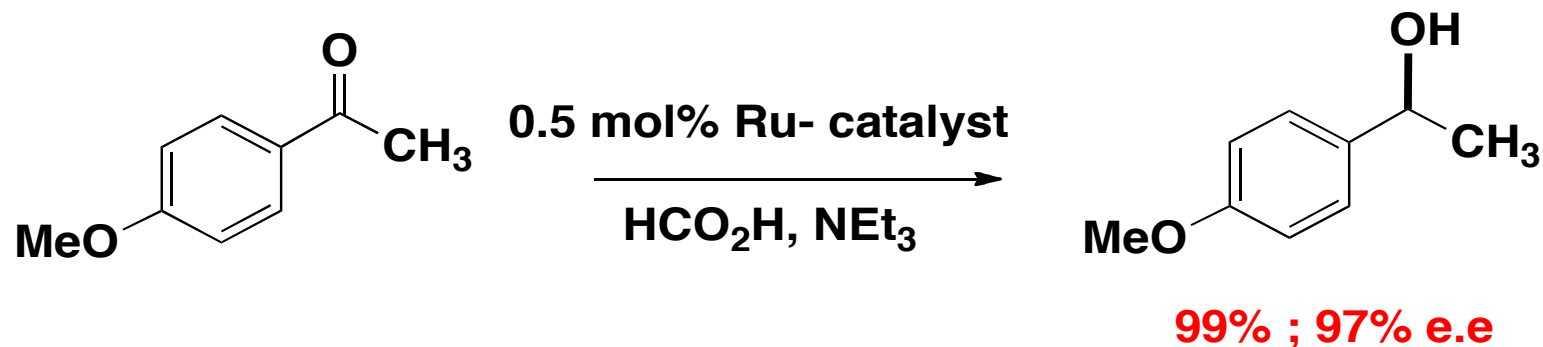
Transfer hydrogenation from isopropanol or formic acid

Consider the formal catalytic cycle using i-PrOH as the reducing agent; a displaced equilibrium

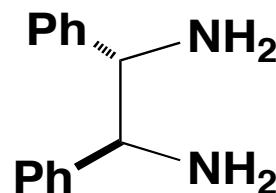


Equilibrium is driven by mass action

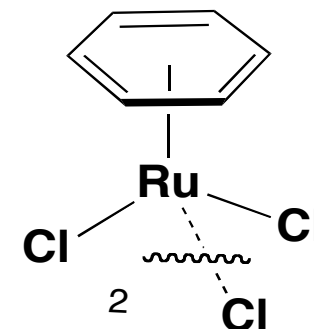
Noyori and Ikariya found an effective and enantioselective Ru-catalyst family
(also other arenes)



*Ruthenium catalyst
derived from:*



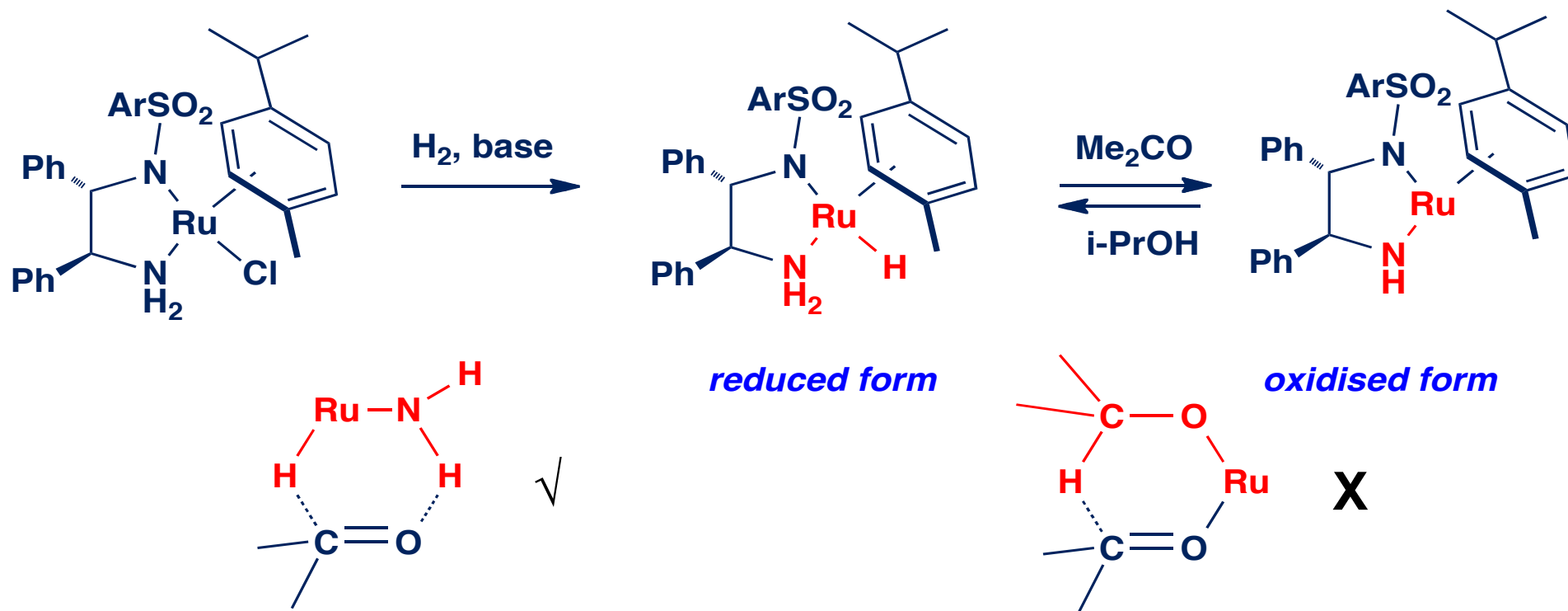
and



Previous work had been largely Ir complex based and less effective;

A base is involved!

The reaction mechanism could be “classical” or a concerted hydrogen transfer. No evidence for a Ru-alkoxide has ever been found

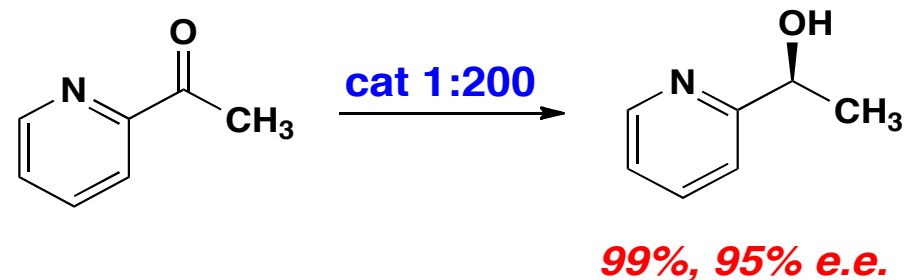
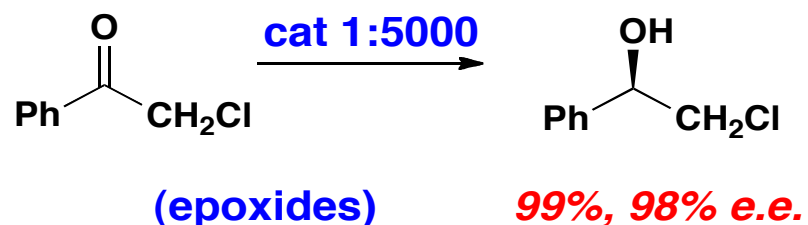
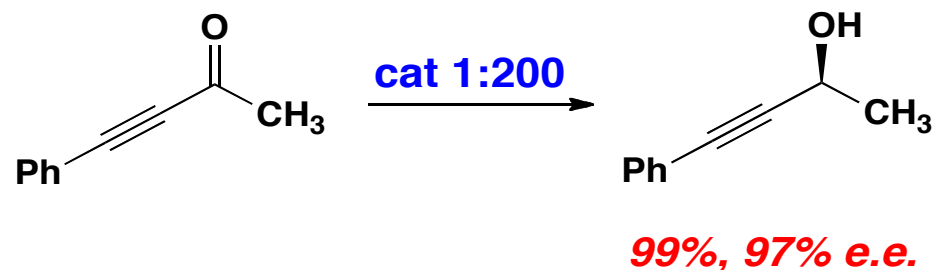
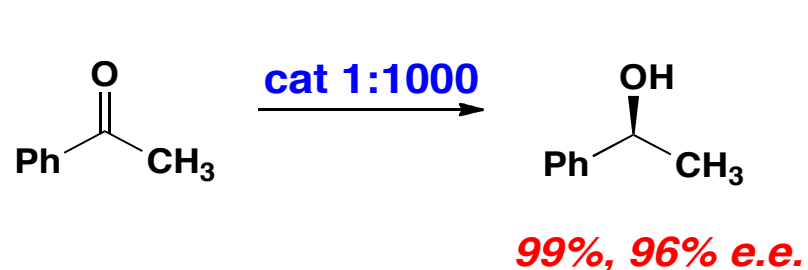


reduction mechanism ?

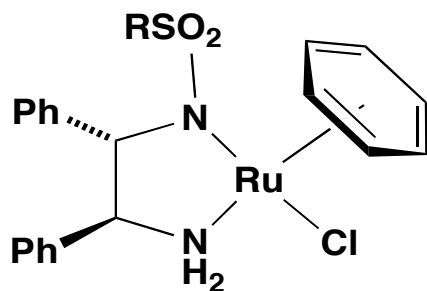
conventional Meerwein-Ponndorf-Verley through Ru alkoxide

Compare P_2N_2Ru catalysts + H_2 . any differences?

The range of transfer hydrogenation can be demonstrated from the selection below

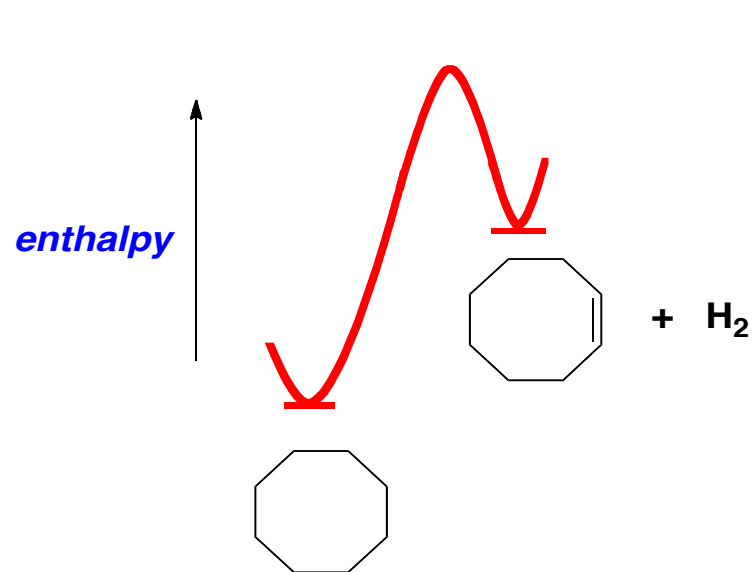


Reducing agent may be $i\text{-PrOH}$ or $\text{NEt}_3/\text{HCO}_2\text{H}$ azeotrope

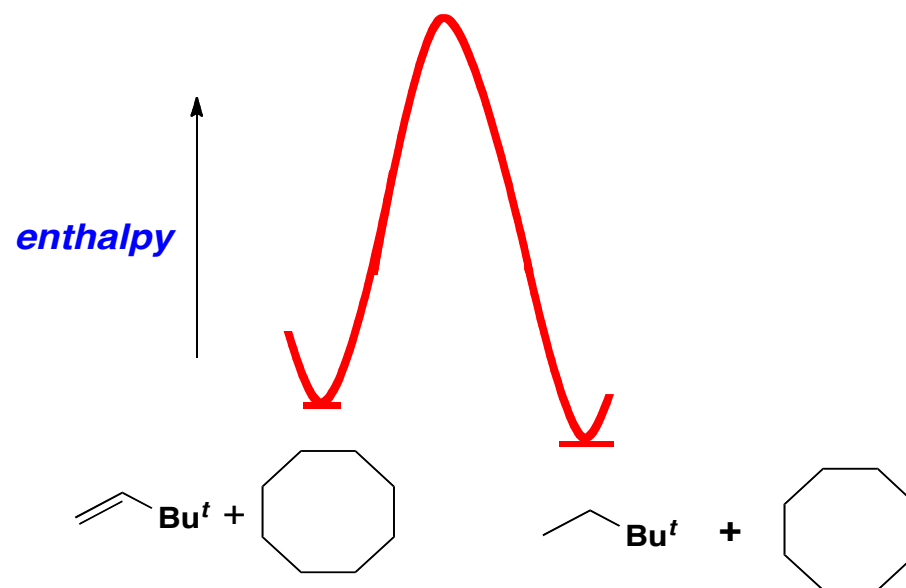


vary R, arene

Dehydrogenation. Reverse of hydrogenation is possible (in principle) but we must include an energy sink



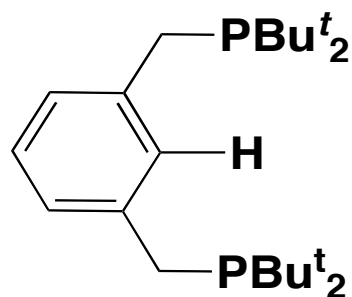
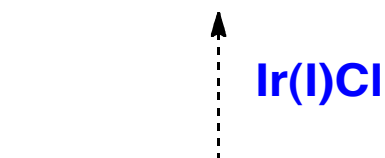
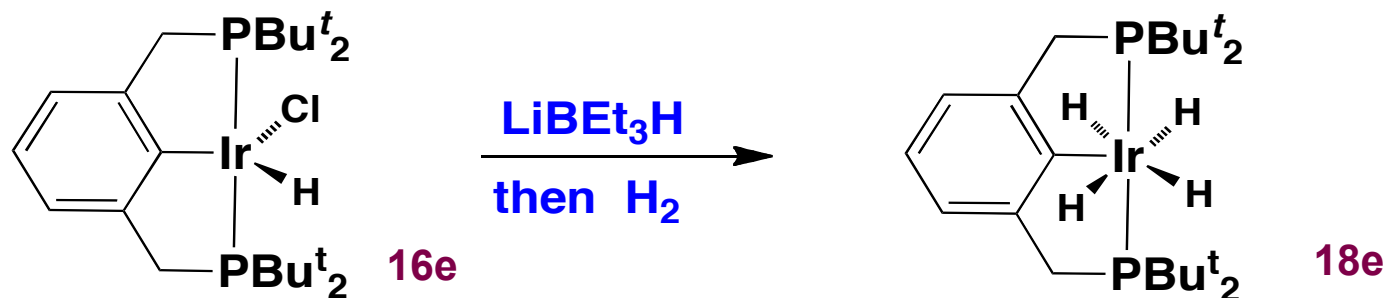
The dehydrogenation of an alkene is highly endothermic $\Delta H_0 = \text{ca. } 120 \text{ KJmol}^{-1}$



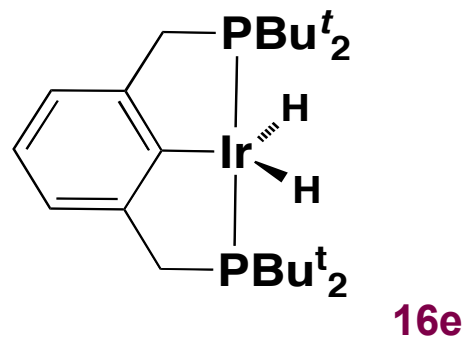
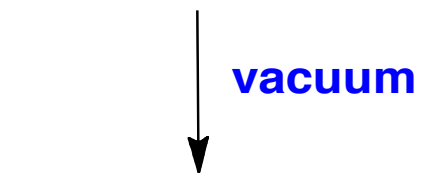
An acceptor alkene can make the reaction mildly exothermic

Cyclooctane is more strained than cyclohexane - why is this?

Pincer iridium complexes have provided the most successful application of catalytic dehydrogenation



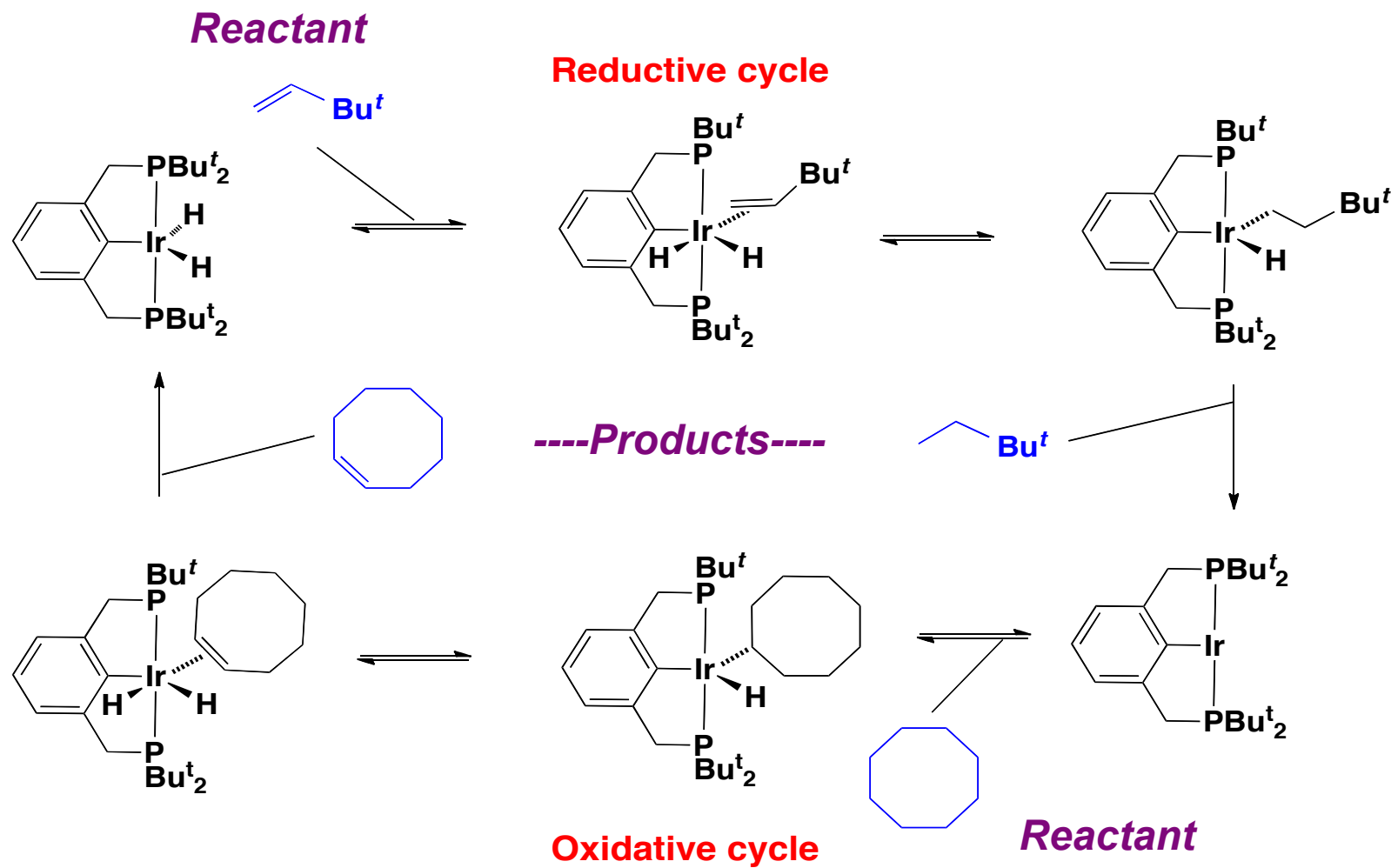
**pincer ligand;
electron-rich**



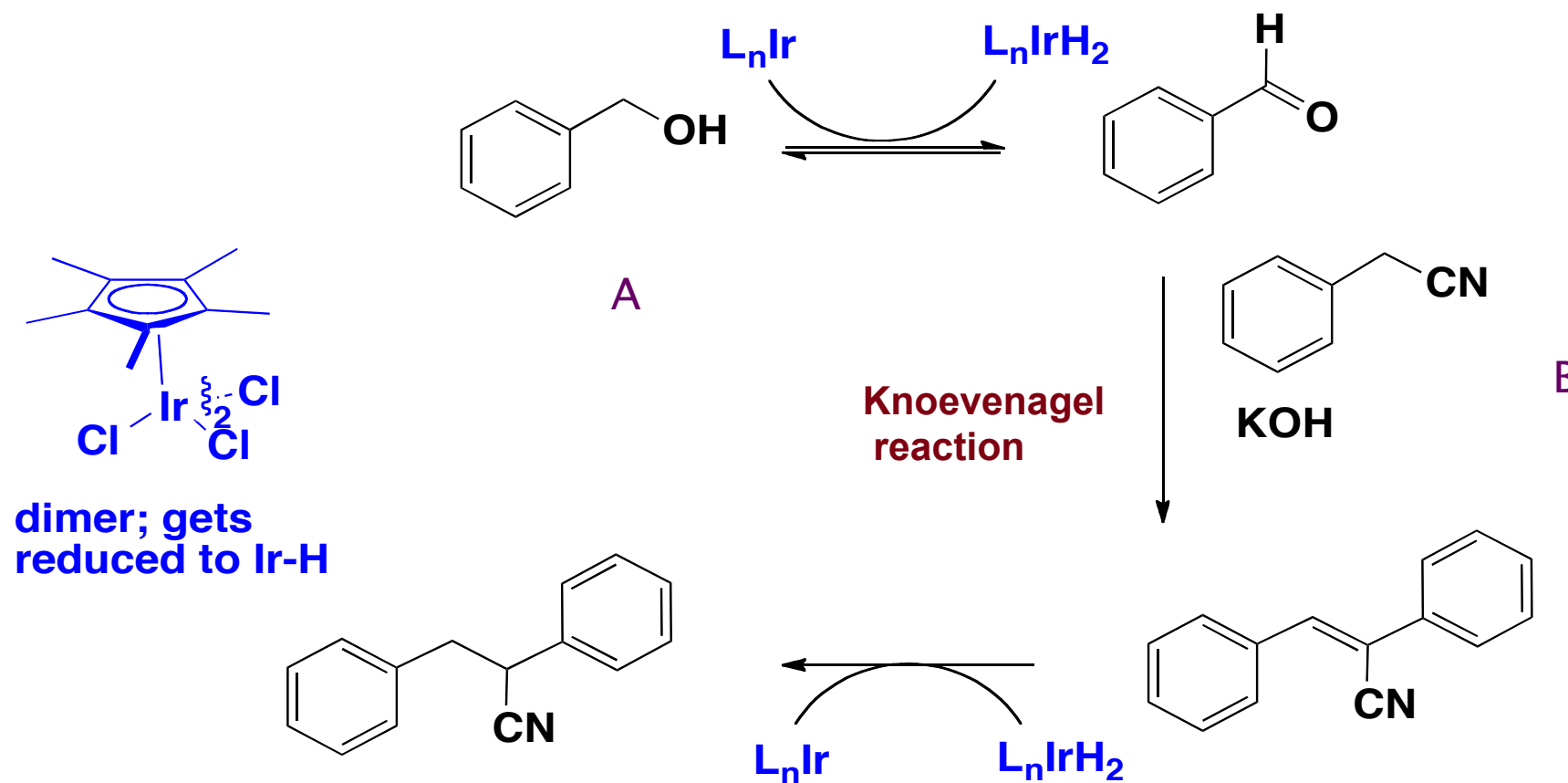
**Need to transfer H_2 to
added alkene to
generate the active
catalyst.**

**catalyst for
dehydrogenation**

Even in this case the reaction requires high temperatures and turnovers are limited (ca. 200)



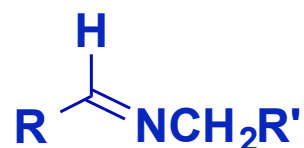
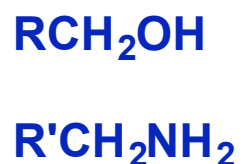
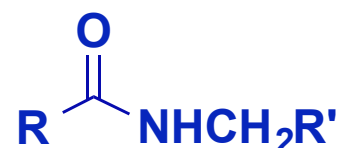
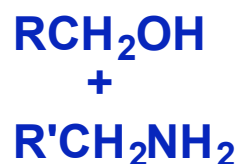
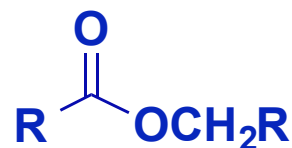
The concept of “borrowing hydrogen” uses the same catalyst for both the oxidation and reduction steps. Knoevenagel step is not catalysed



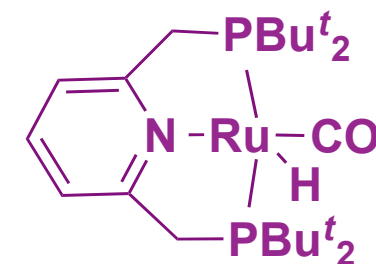
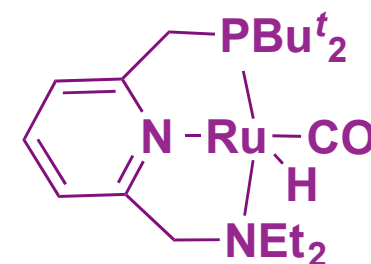
**Conditions: 110 °C, 2 mol% Ir catalyst, 15 mol% KOH, 15 h. A and B
(or 10 minutes μ wave, 110 °C)**

An interesting series of dehydrogenative couplings were discovered by Milstein and co-workers from 2007 onwards

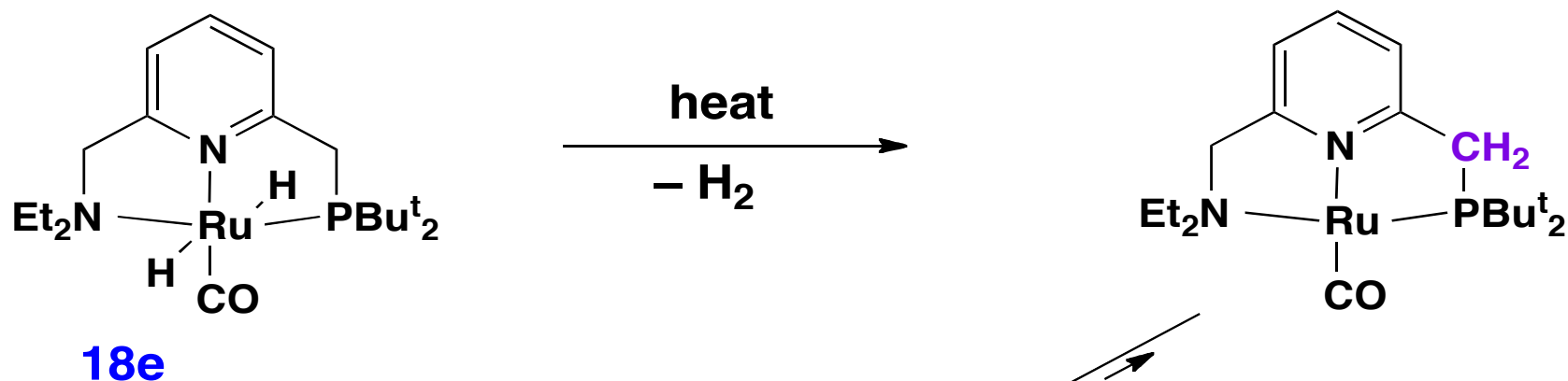
NB Use of Pincer ligands



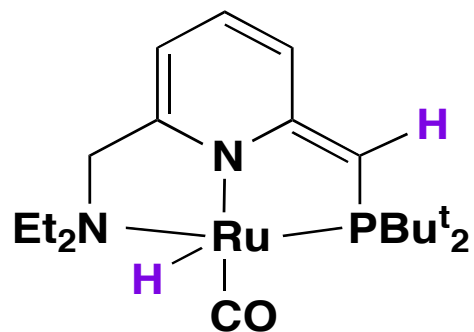
Catalyst



A pincer Ru complex with a labile C-H is activated to loss of hydrogen

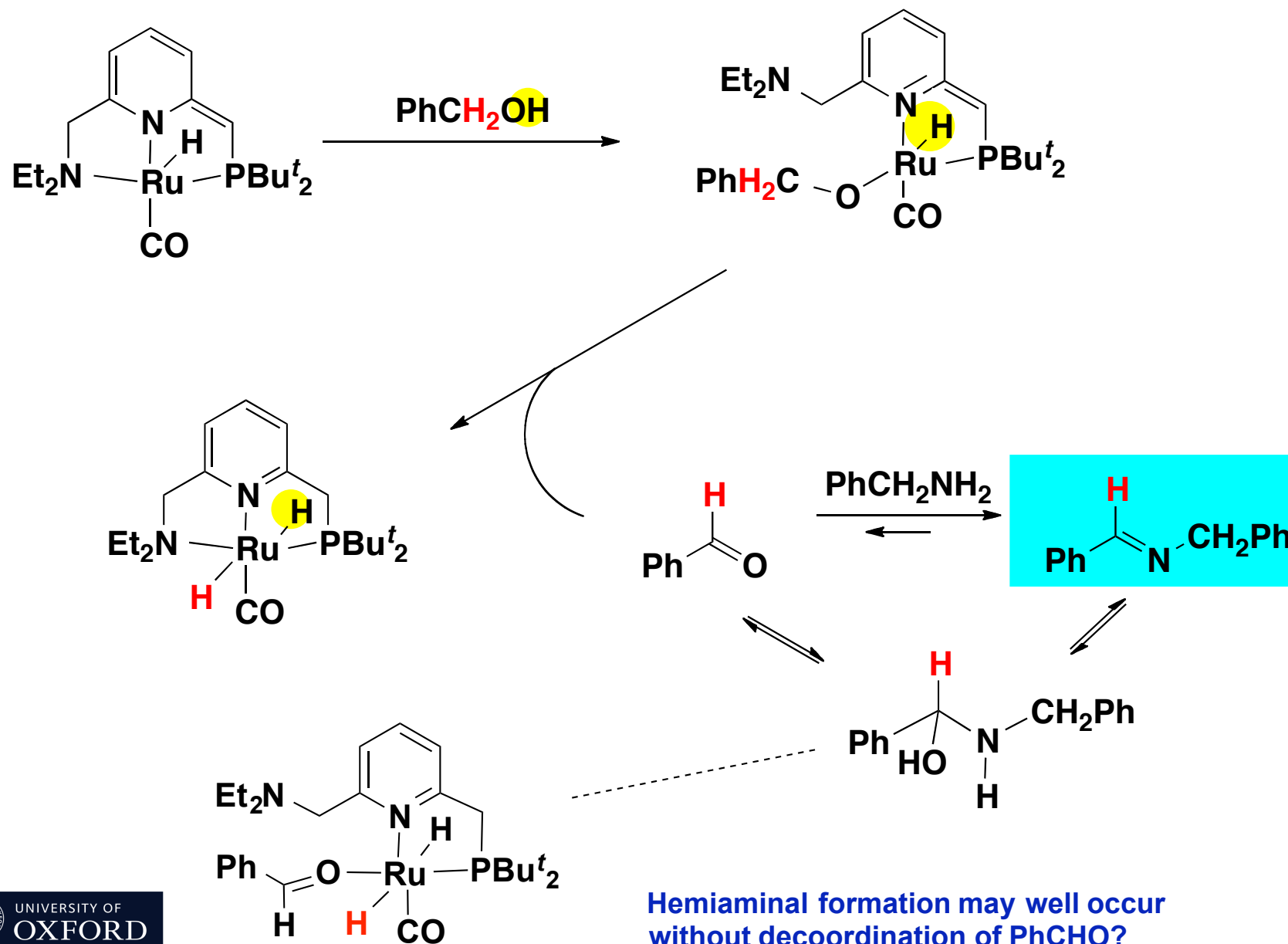


Complex is stabilised by borrowing hydrogen from the side-chain

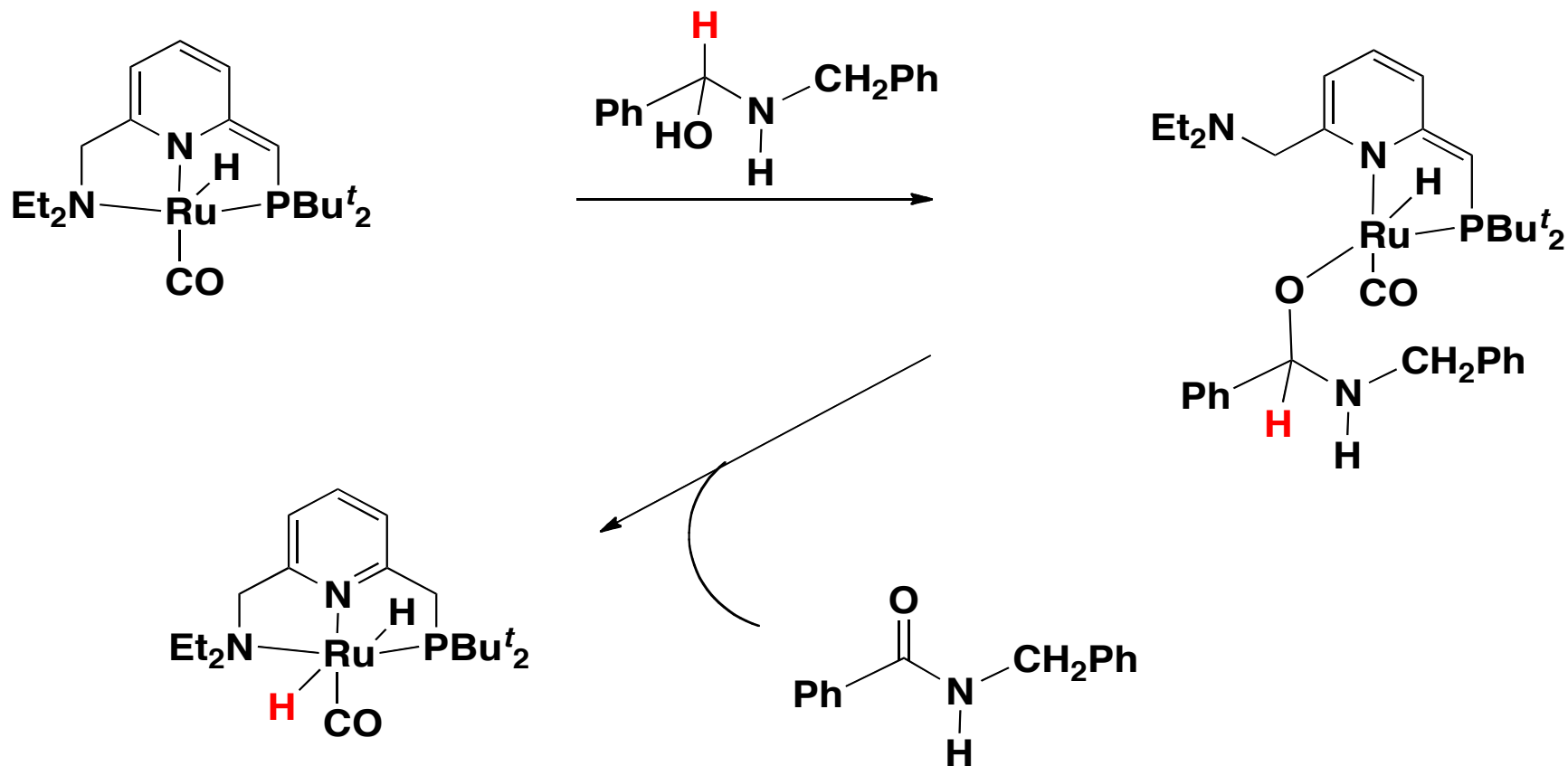


Why is the original dehydrogenation product stabilised by H-transfer?

The N-Ru bond is also labile leading to easy ligand displacements; **primary alcohol and amine** to imine by a β -elimination route (Step 1)



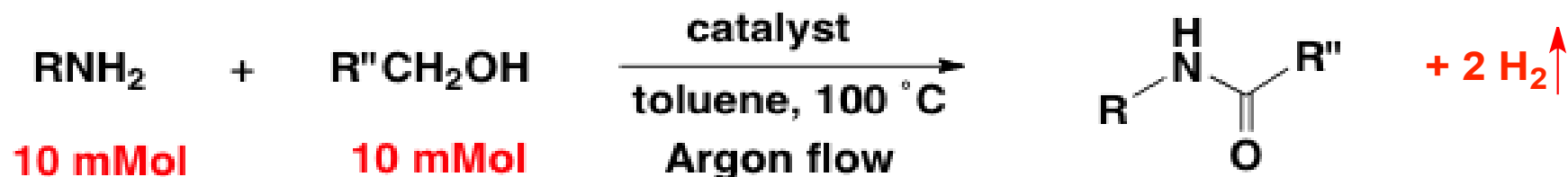
Step 2. Another oxidative step converts the hemiaminal into an amide; cycle is completed by H₂ loss



How many different molecules of catalyst are involved in the overall cycle?

Amide - formed catalytically from alcohol and amine

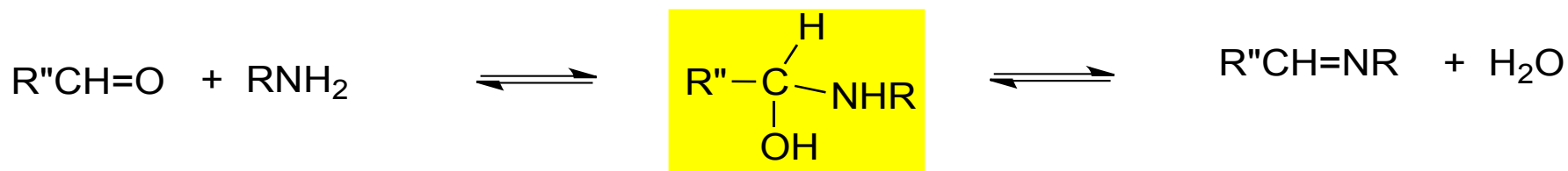
Here's a summary of the sequence of reactions



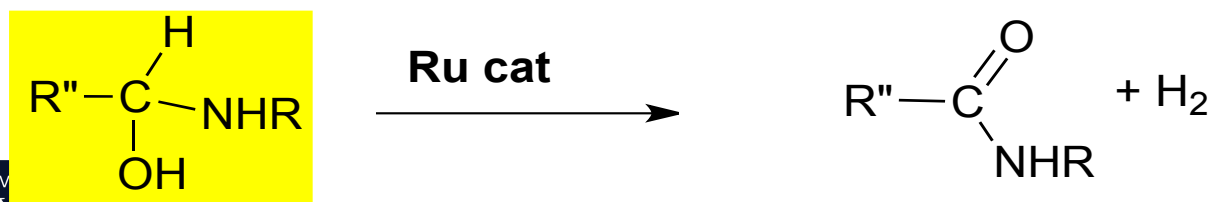
1. First activate the primary alcohol (-H₂):



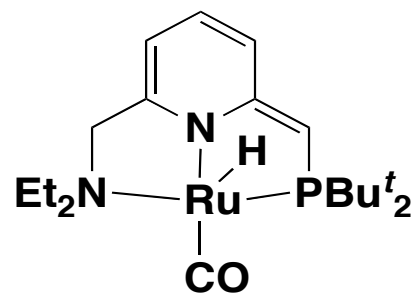
2. Then activate the hemiaminal equilibrium (without dissociation of RCHO):



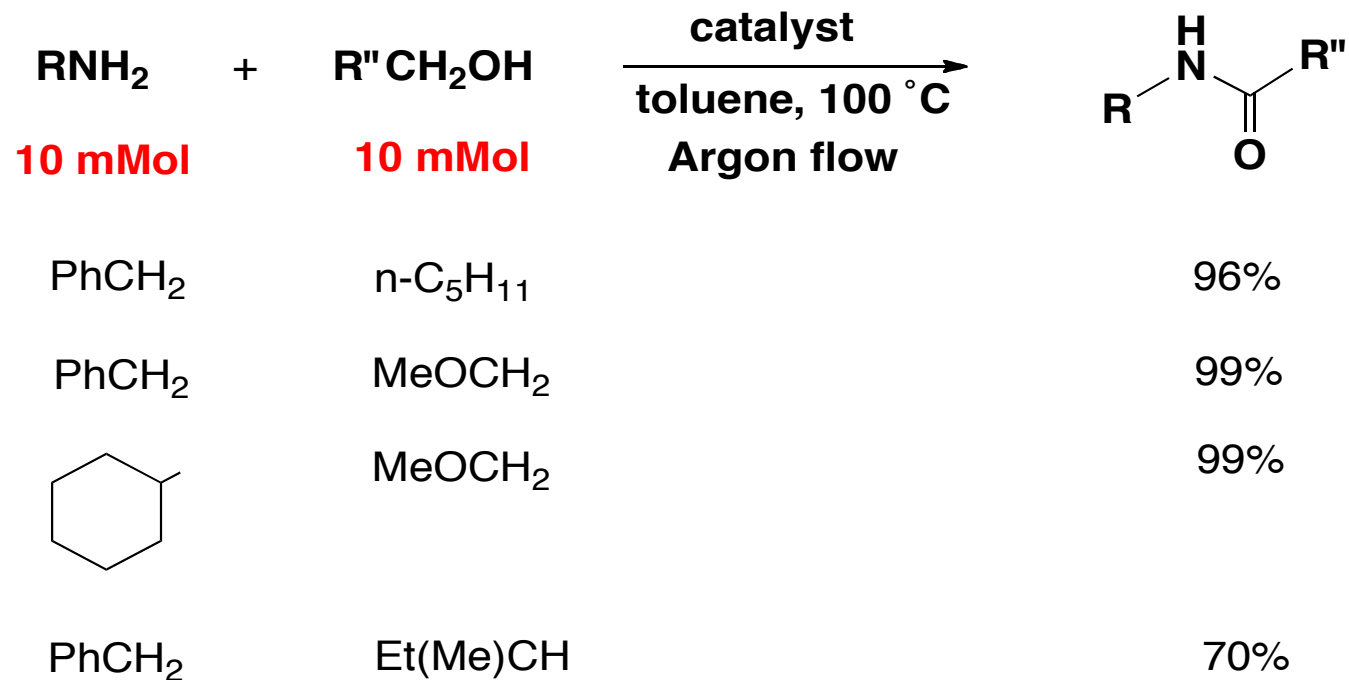
3. Finally dehydrogenate the hemiaminal to give the amide product:



Overall catalytic reaction and conditions

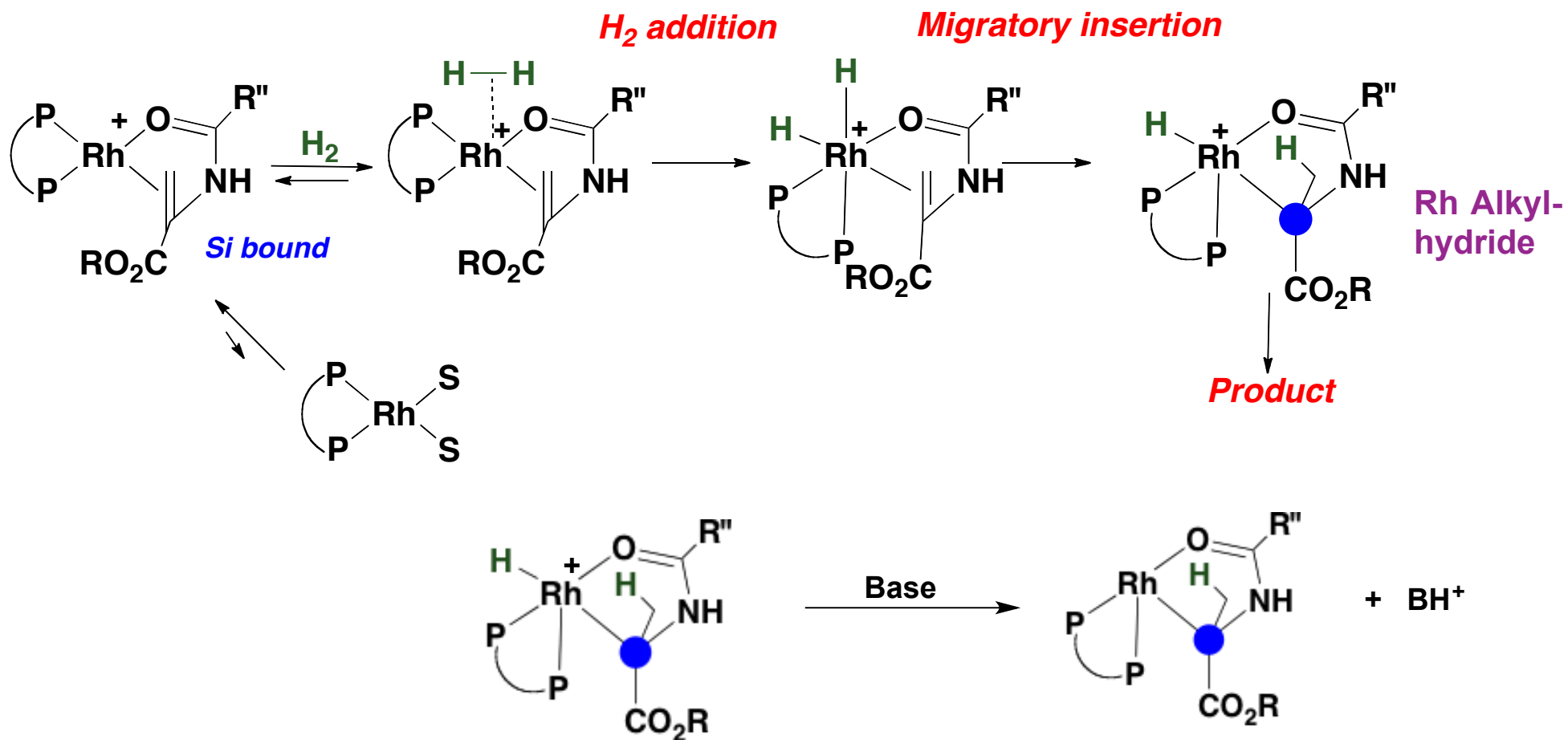


catalyst 0.01 mMol



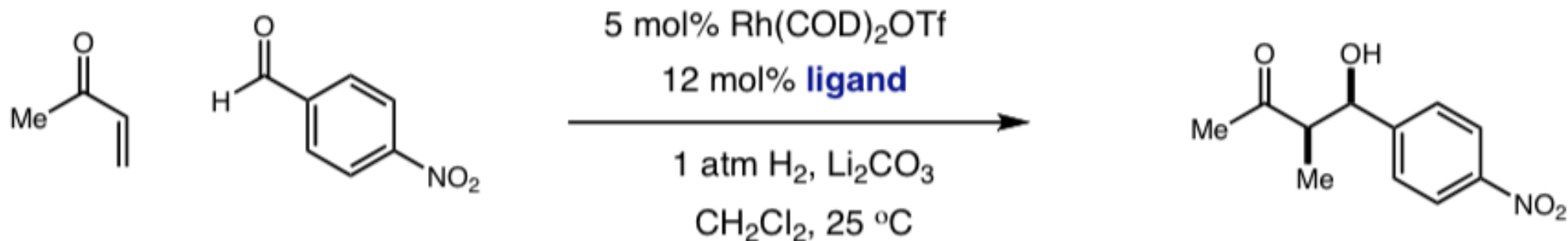
(secondary alcohol → ketone, lower yield)

Consider the individual steps in a hydrogenation reaction

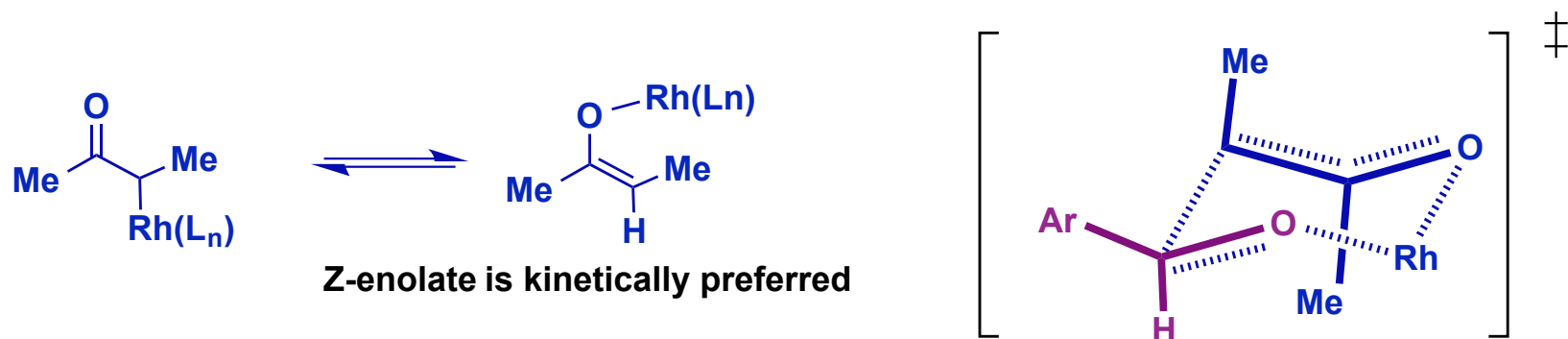


Is it possible to intercept the ensuing Rh-alkyl species?

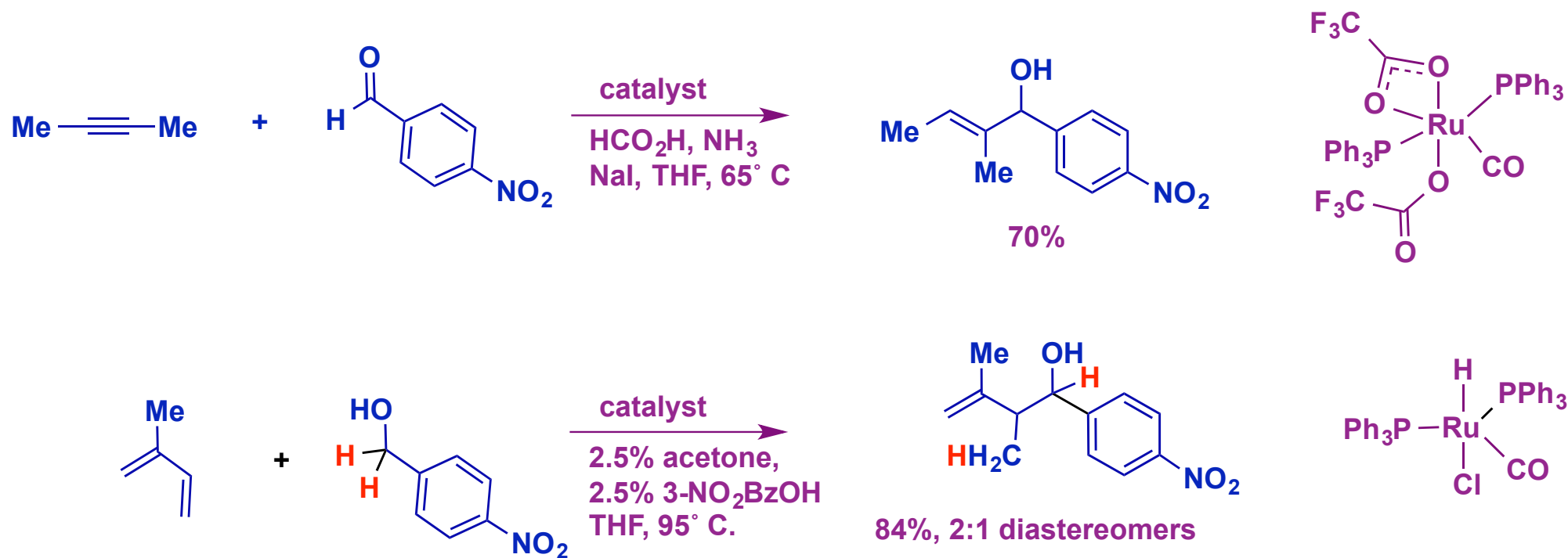
Intercepting the intermediate in hydrogenation (Krische)



Best ligand is tri(2-furyl)phosphine; 74% yield, 95% rac syn-diastereomer



Intercepting the intermediate in transfer hydrogenation (Krische)



M. J. Krische et al., *Chem. Comm.* 2009, 7278; *Angew. Chem. Int. Ed.*, 2009, 48, 34 (reviews)

Two important concepts for catalytic reactions in synthesis

Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. In an ideal chemical process **all atoms of the reactants appear in the product.**

Redox economy is defined as the **minimization** of the number of non-strategic (those that do not set stereochemistry or are not skeleton-building) or corrective **oxidation and reduction steps** in synthesis.

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