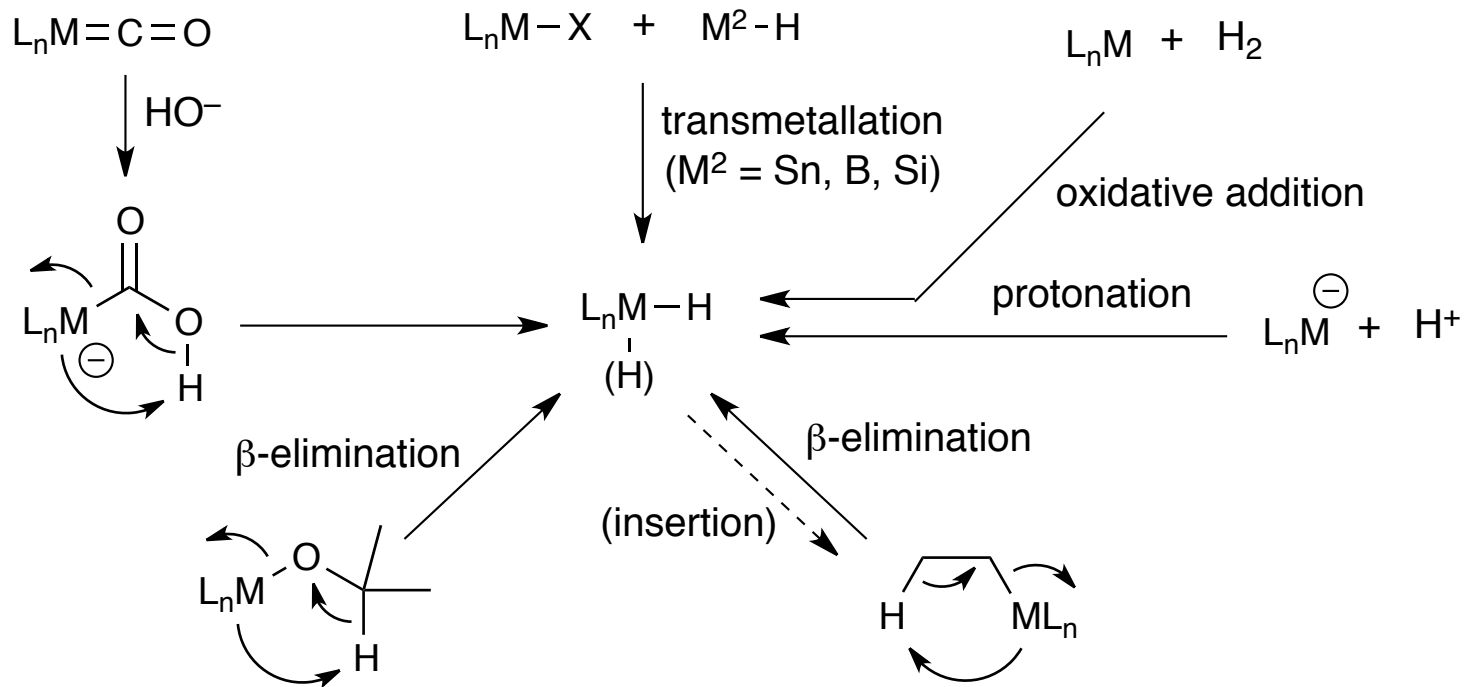


Metal Hydrides

Transition metal hydrides are important intermediates and show up in many different processes, such as hydrogenation, hydroformylation, and hydrometallation. Because of their facile generation (see below) they can often be a bit of a nuisance. Their reactivity can vary from hydride donors to strong protic acids.

Many different routes to metal hydrides:

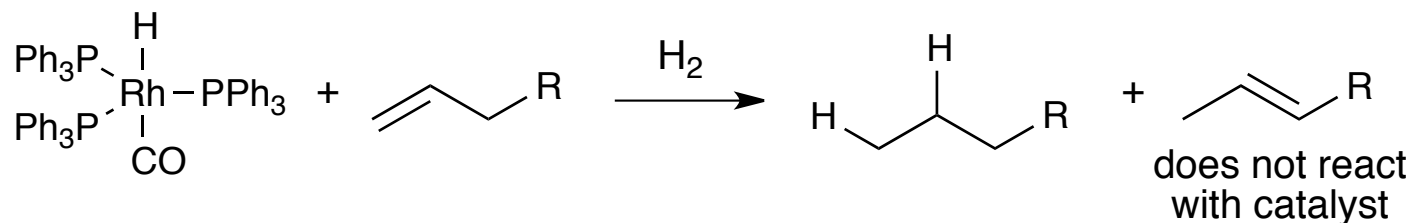


Common Homogeneous Hydrogenation Catalysts

Homogeneous hydrogenation are usually carried out with catalysts based on Rh, Ru, and Ir. These complexes are more sensitive than heterogeneous catalysts (Pd/C), but are more selective. Also the presence of ligands around the metal allows for asymmetric hydrogenation.

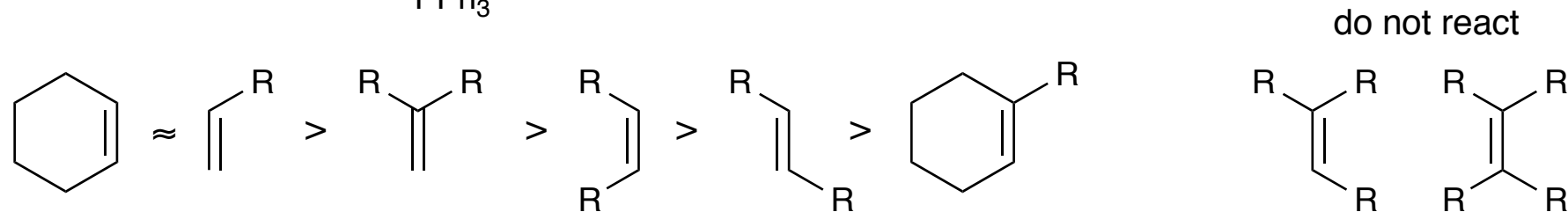
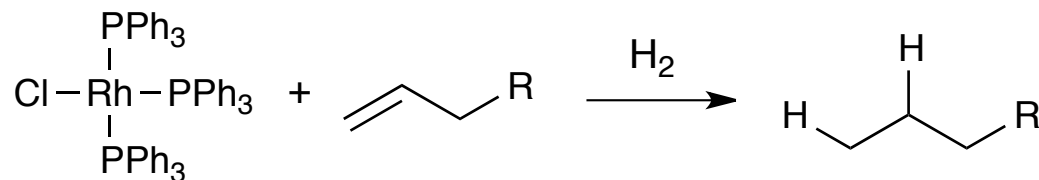
Two classes of hydrogenation catalysts—monohydride and dihydride. Each have different mechanisms and different selectivities.

$\text{Rh}(\text{H})(\text{PPh}_3)_3(\text{CO})$: monohydride catalyst, specific for terminal alkenes, double bond isomerization competes, little used



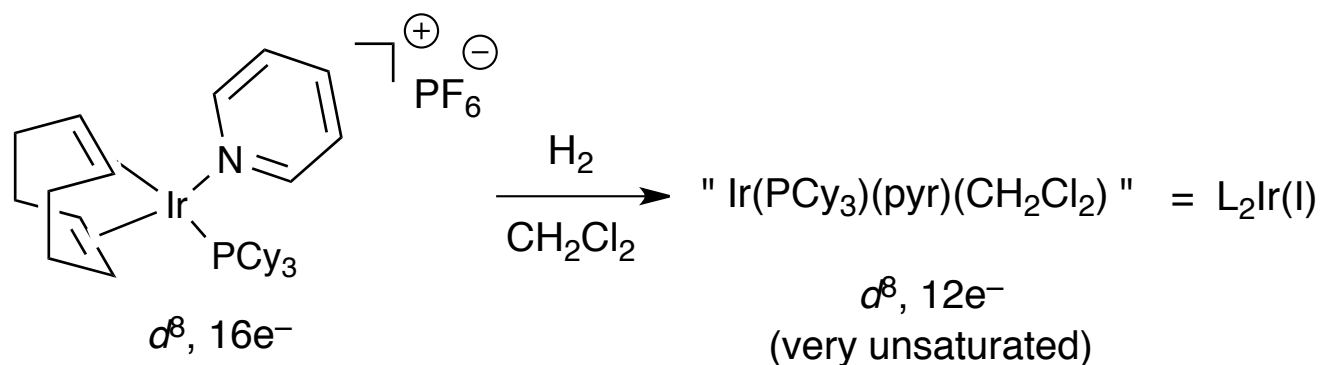
The monohydride pathway is also important with Ru(II) asymmetric hydrogenations

$\text{RhCl}(\text{PPh}_3)_3$ —Wilkinson's catalyst: dihydride catalyst, predictable olefin selectivities, no isomerization with neutral conditions


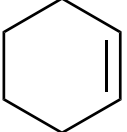
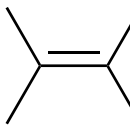


Common Homogeneous Hydrogenation Catalysts

$\text{Ir}(\text{cod})(\text{PCy}_3)(\text{Pyr})\text{PF}_6$ —Crabtree's catalyst: at least 100 times more active than Wilkinson's catalyst, typically used with nonpolar, noncoordinating solvents (CH_2Cl_2), dihydride mechanism

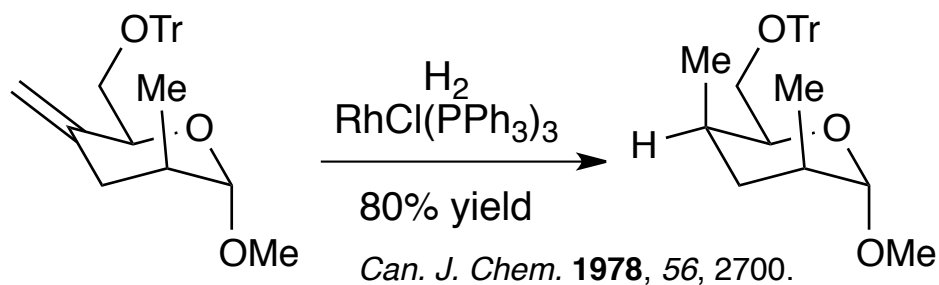
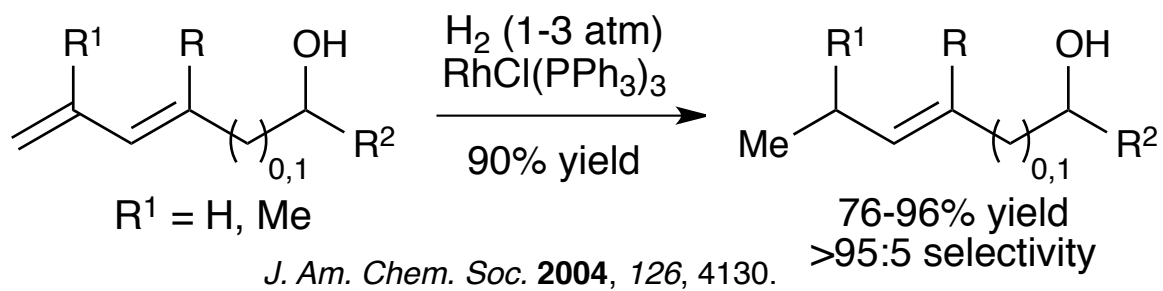
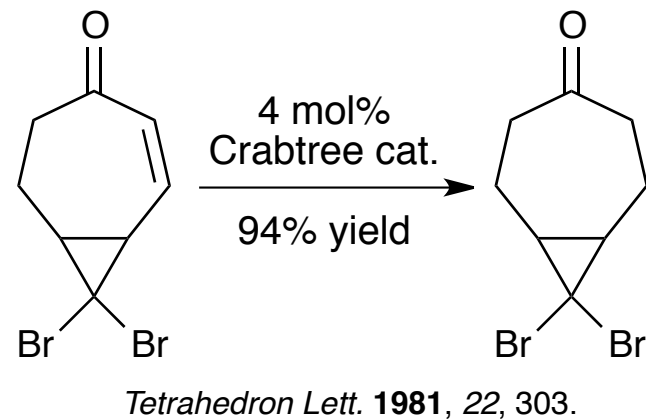
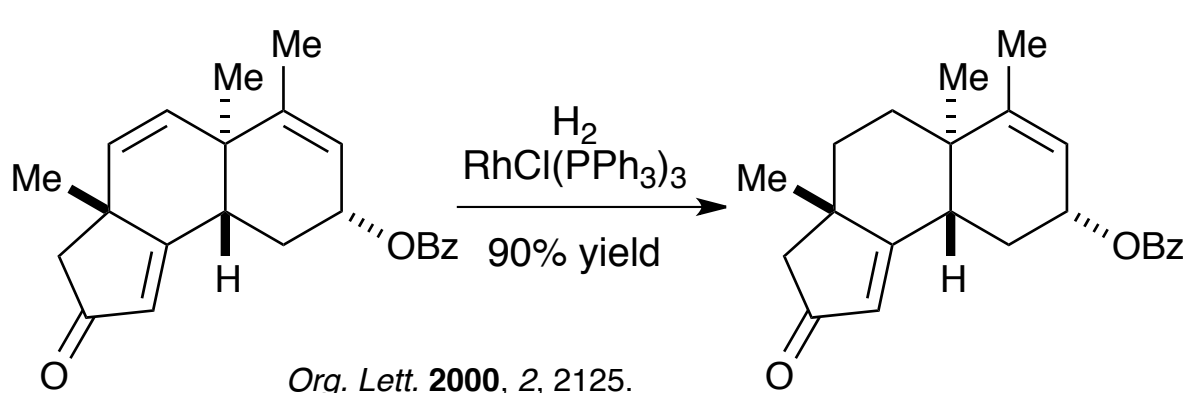


In the presence of H_2 , the cod ligand suffers hydrogenation, while the solvent may be loosely associated with the metal, it can be replaced by just about any olefin, including tri- and tetrasubstituted.

			
Crabtree's cat.	6400	4500	4000
Wilkinson's cat.	650	700	0
	<i>turnover frequency (h^{-1})</i>		

Cationic Rh catalysts are used as well and have a similar mechanism

Homogeneous Hydrogenation Examples

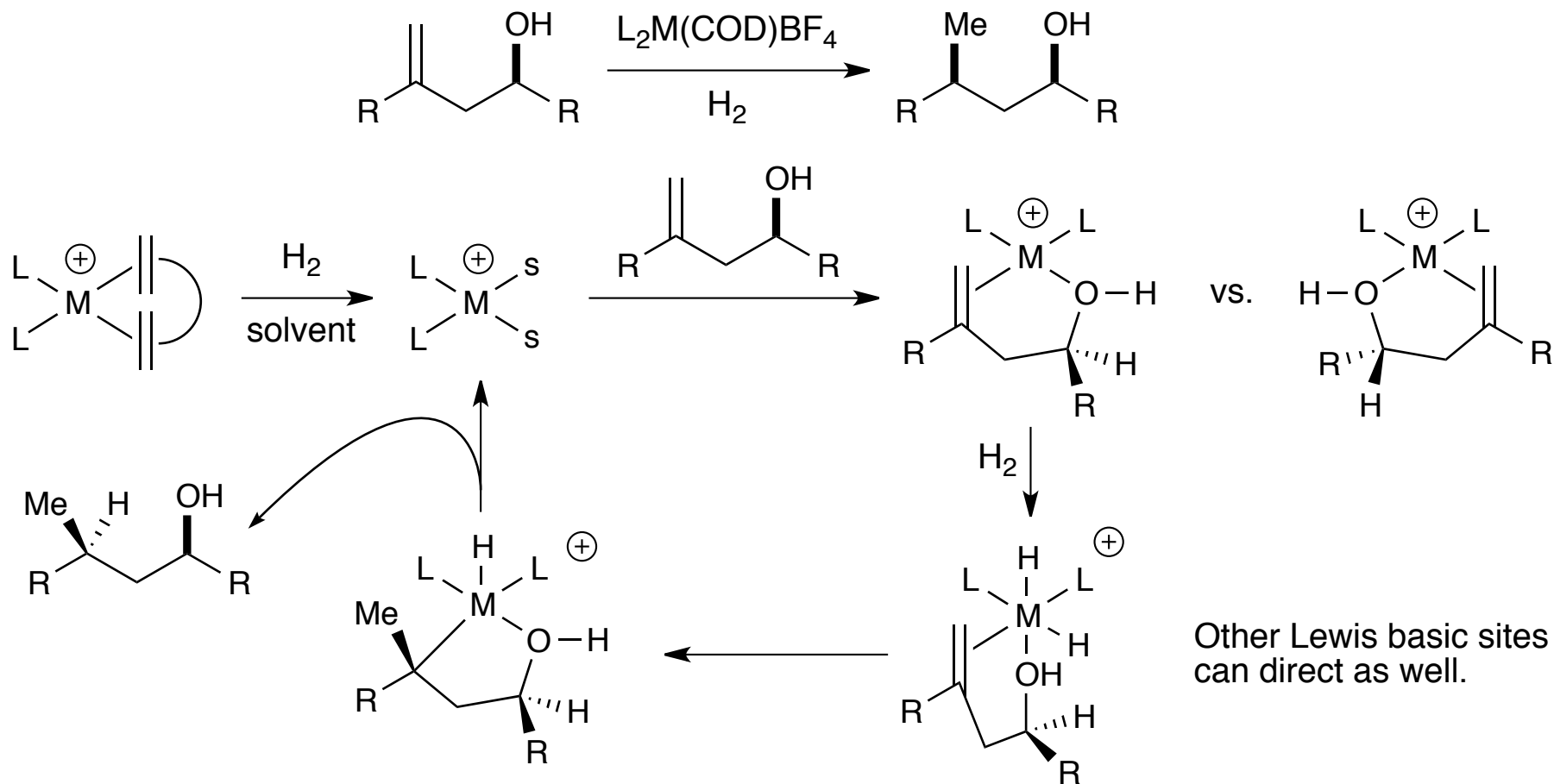


Directed Hydrogenations

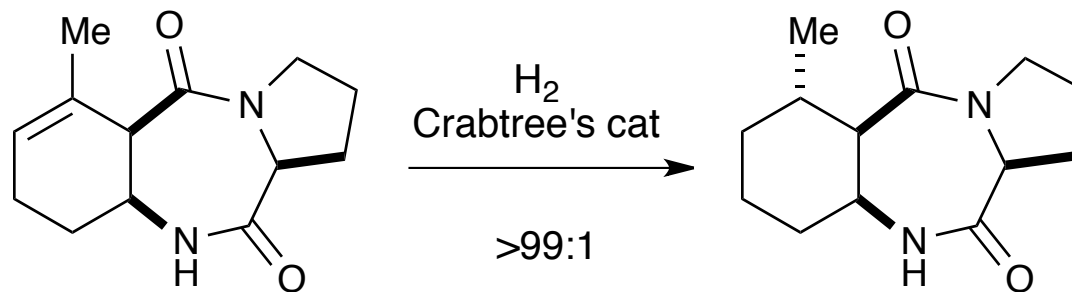
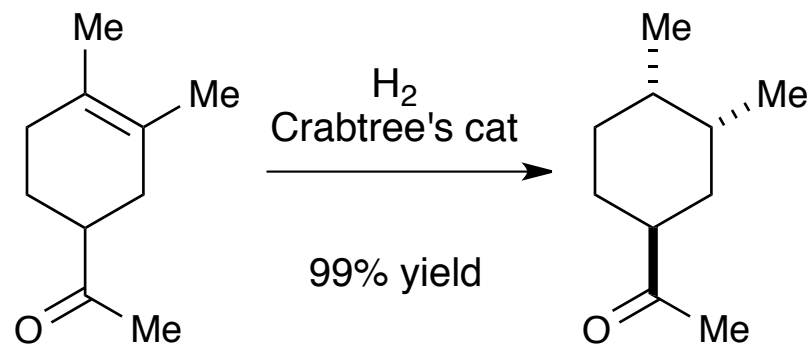
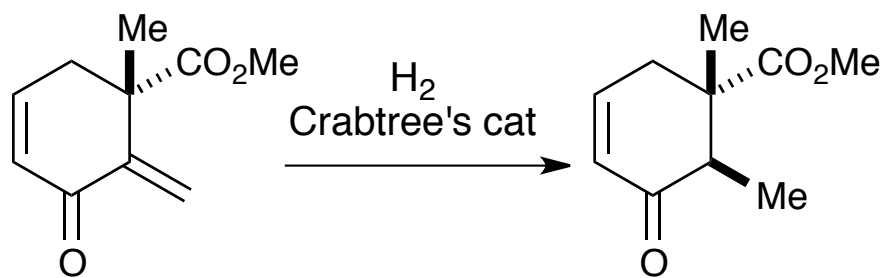
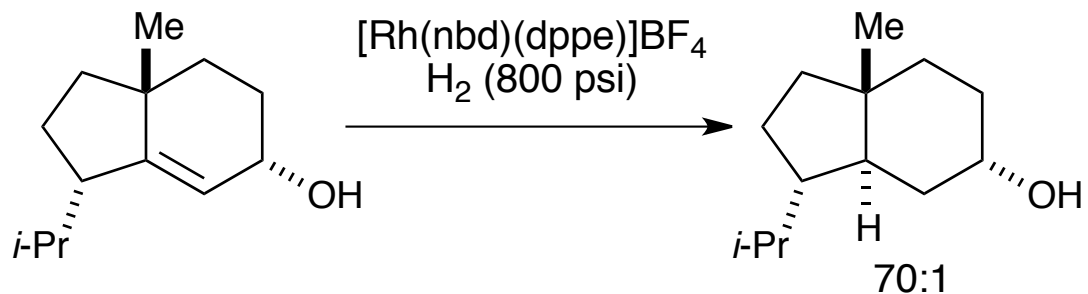
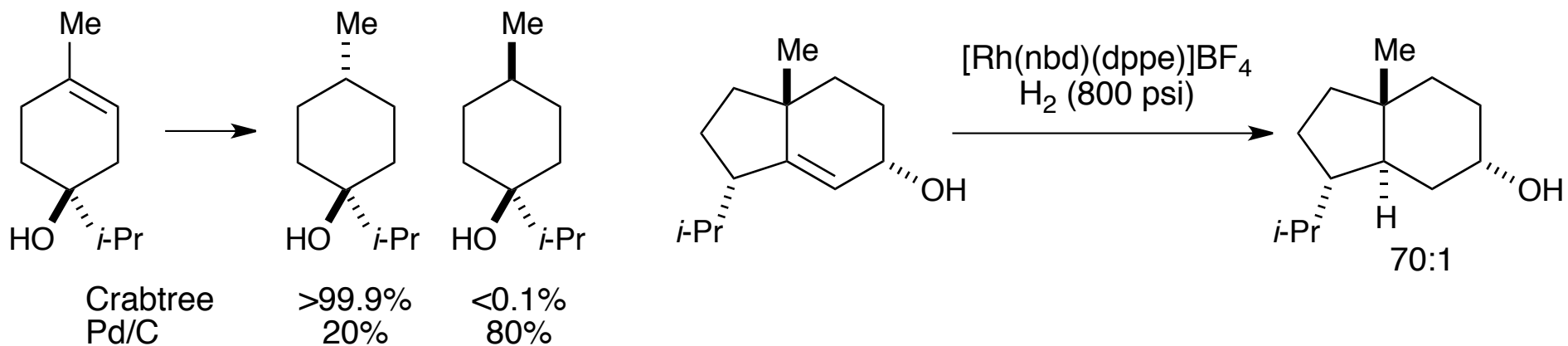
Lewis basic groups (typically alcohols) in the allylic or homoallylic position can be used to direct the delivery of the hydrogenation from the same side, often with high diastereoselectivity. Cationic catalysts are usually employed.

Utility is in setting new stereocenters diastereoselectively

Typical catalysts: $[\text{Ir}(\text{COD})\text{pyr}(\text{PCy}_3)]\text{PF}_6$
 $[\text{Rh}(\text{nbd})(\text{dppe})]\text{BF}_4$
 $[\text{Ir}(\text{COD})(\text{dppb})]\text{BF}_4$



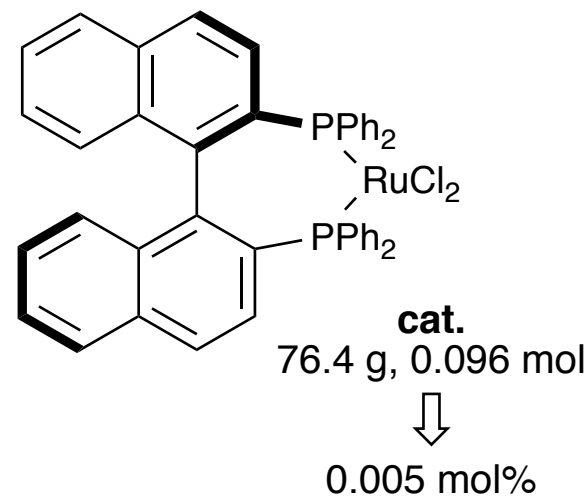
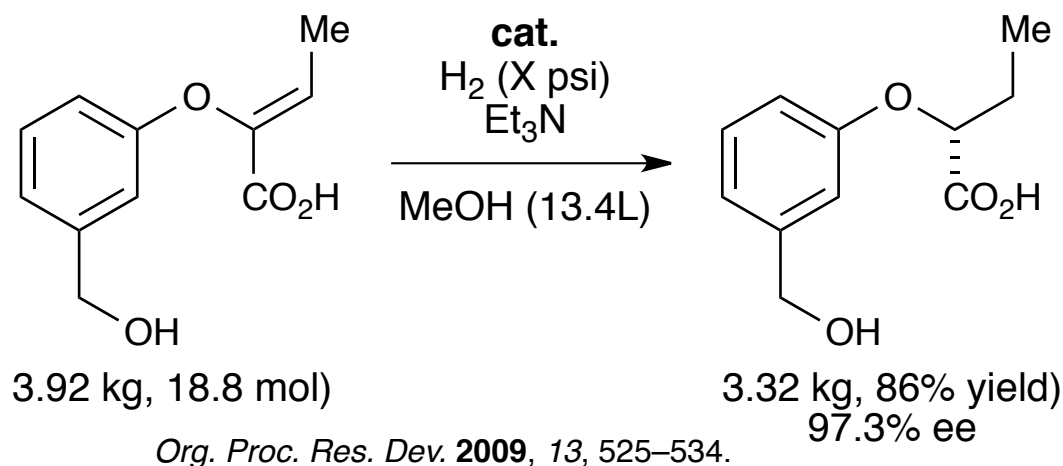
Directed Hydrogenation Examples



Asymmetric Hydrogenations

Asymmetric hydrogenation has matured into an incredibly important technique for bench chemists as well as industrial chemists. Very clean reactions, essentially no background reaction to introduce racemic material, often very low catalyst loading can be used with modern ligands.

Editorial: If a process chemist can make a chiral center by hydrogenation that will likely become the preferred route.

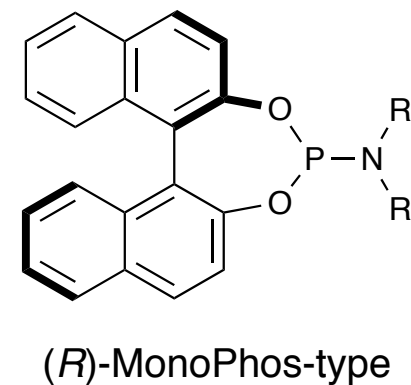
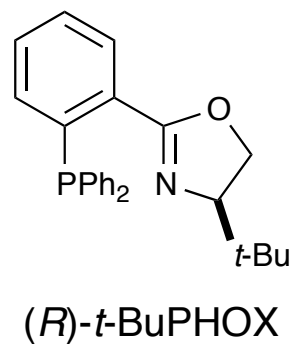
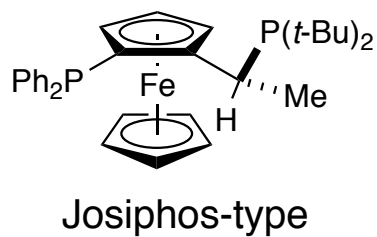
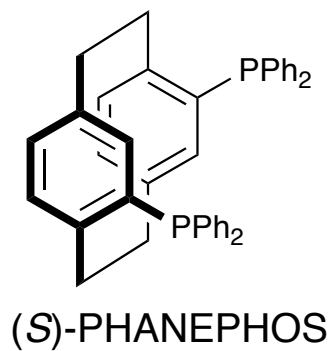
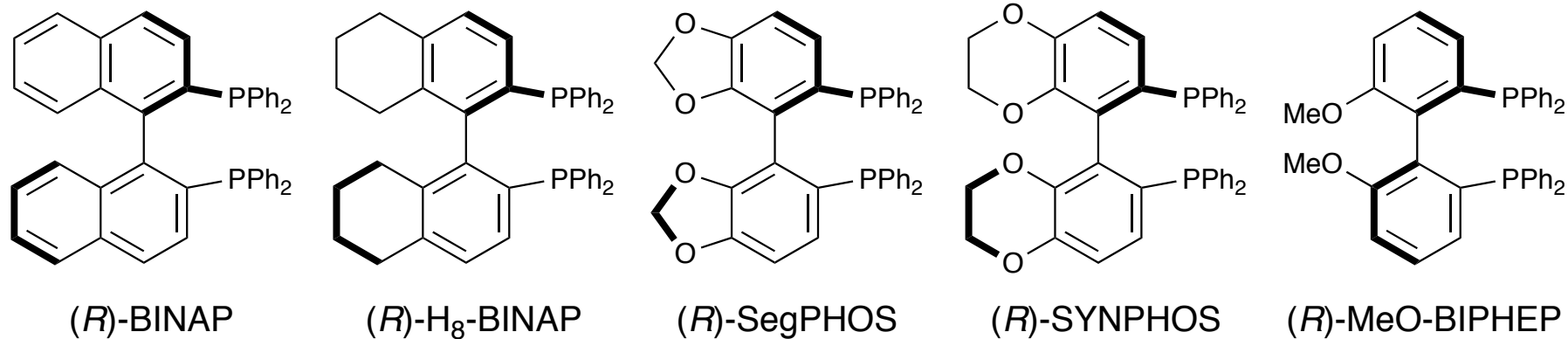
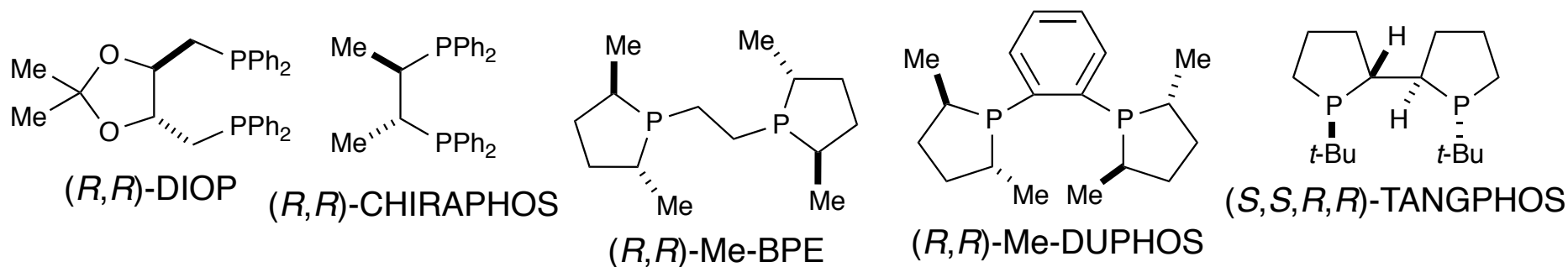


2001 Nobel Prize in Chemistry: 1/4 William S. Knowles, 1/4 Ryoji Noyori both for asymmetric hydrogenation technology

Where does current innovation take us? Many substrate types can be considered to be "solved problems", though others are still challenging. Many times this problem is "nothing more" than screening ligands.

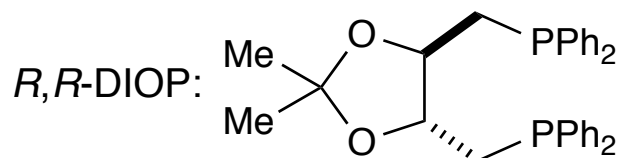
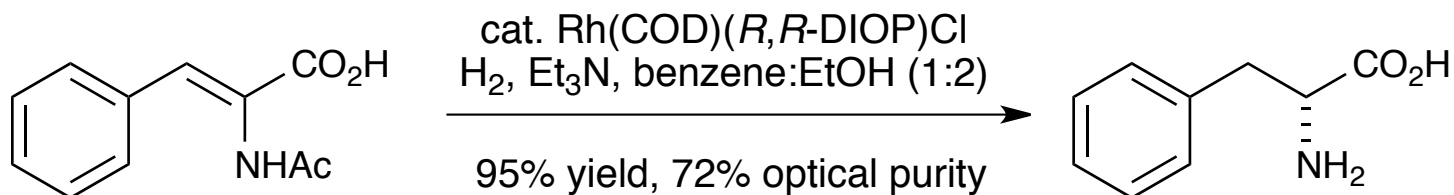
Asymmetric Hydrogenations-Ligand Survey

Some of the more commonly used phosphine ligands:

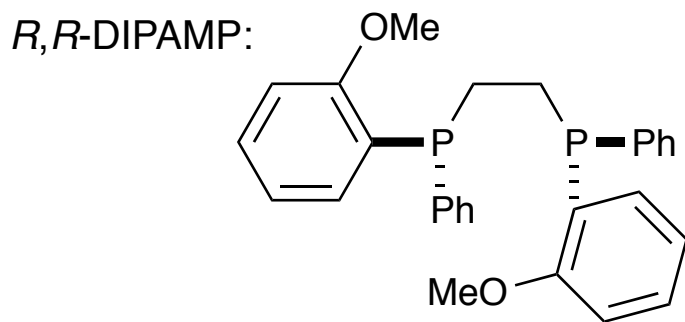
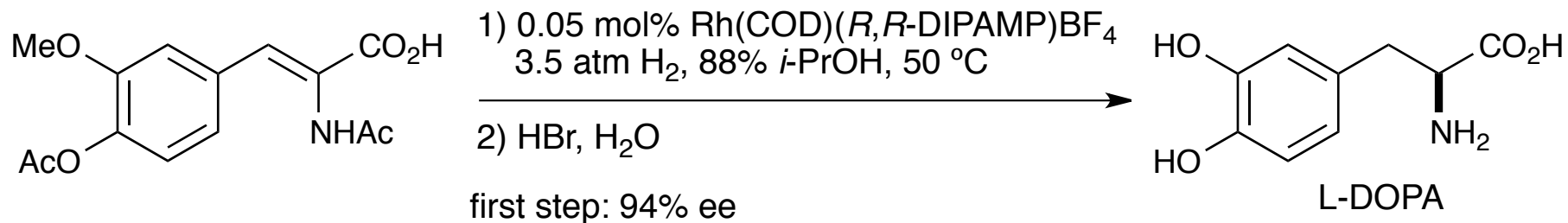


Asymmetric Hydrogenations—The First Highly Selective Results

The first highly selective hydrogenation results:



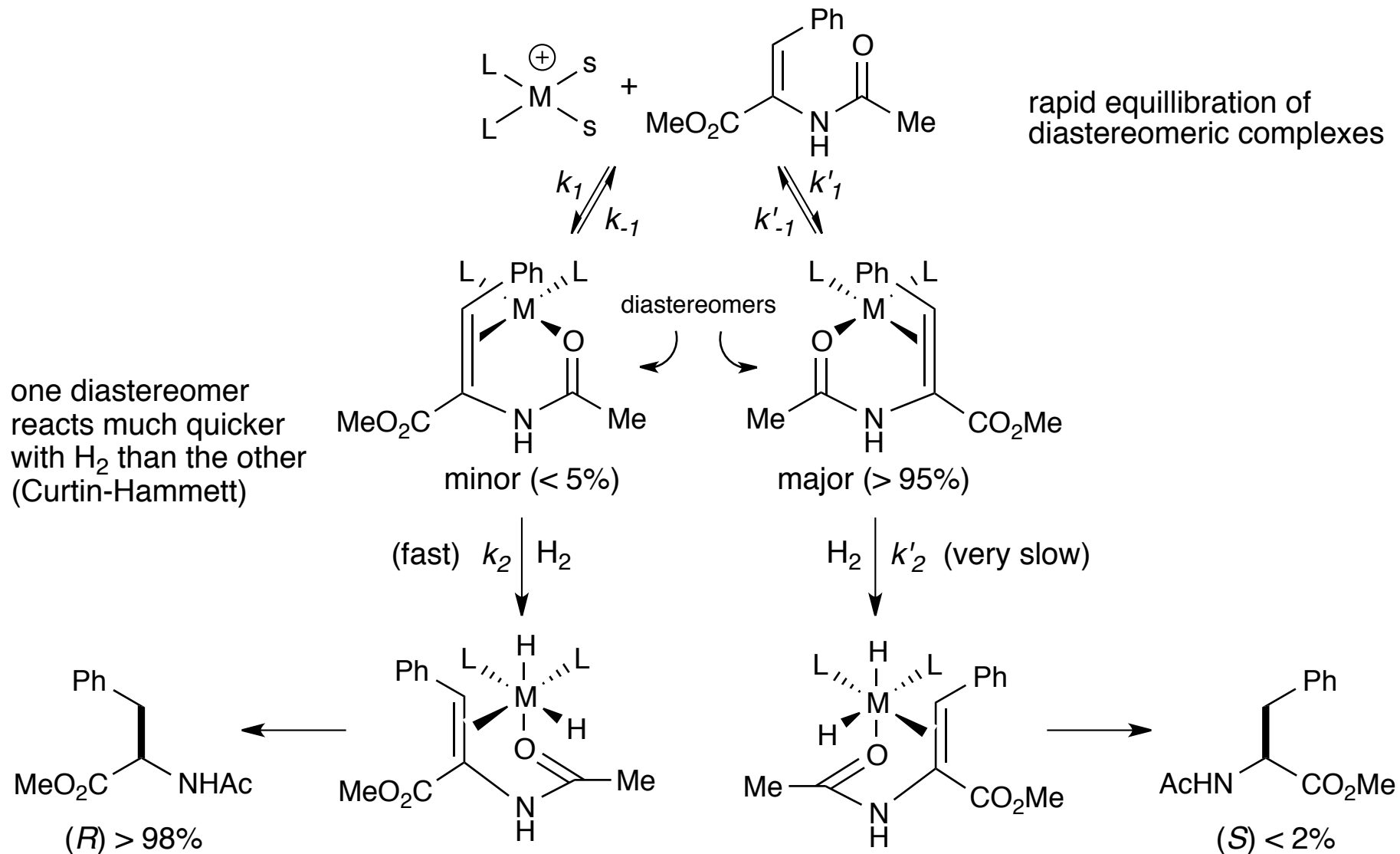
Kagan: *J. Chem. Soc., Chem. Commun.* **1971**, 481



Knowles (Monsanto): *J. Am. Chem. Soc.* **1975**, *97*, 2567
J. Am. Chem. Soc. **1977**, *99*, 5946

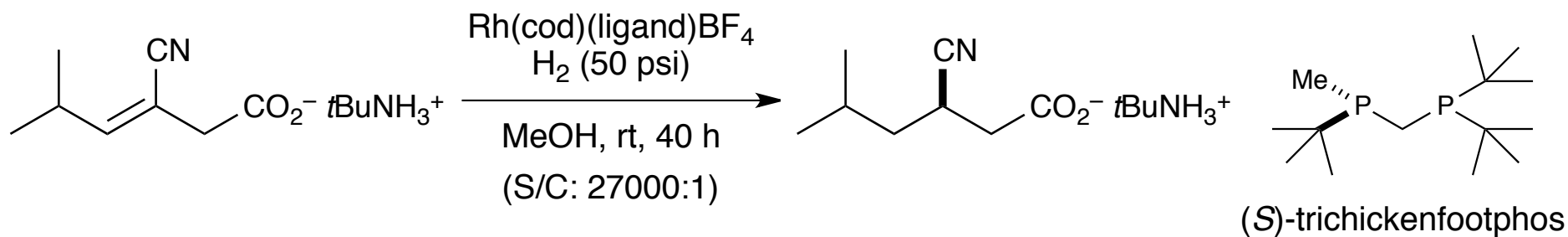
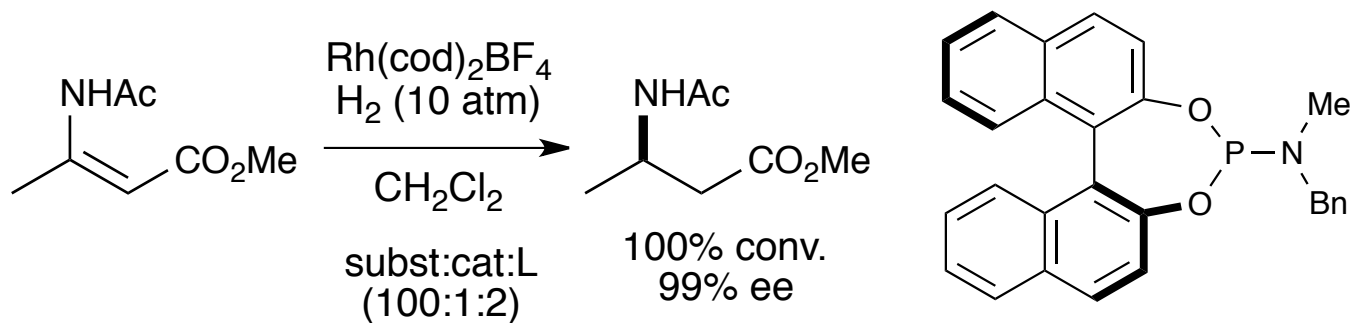
Asymmetric Hydrogenations—The First Highly Selective Results

Mechanism of acetamidopropenoates is best studied and illustrates the issues associated with selectivity. All other mechanisms we have discussed still hold. The chiral ligand means diastereomeric complexes can be formed, each with their own set of rate constants



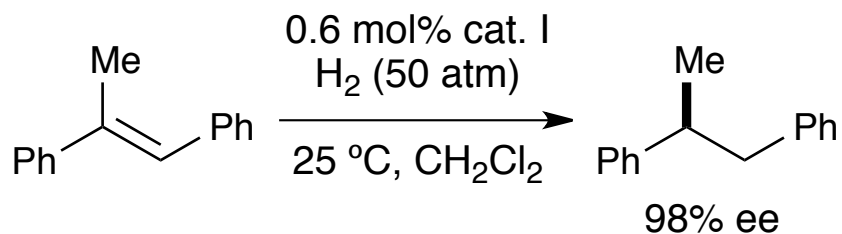
Asymmetric Hydrogenations-Some examples

Too many examples to make a representative list - best to search for similar system. Many cases need functional group to bind to metal

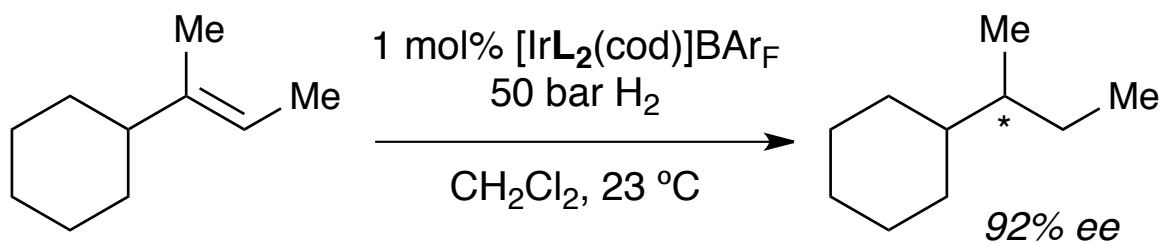
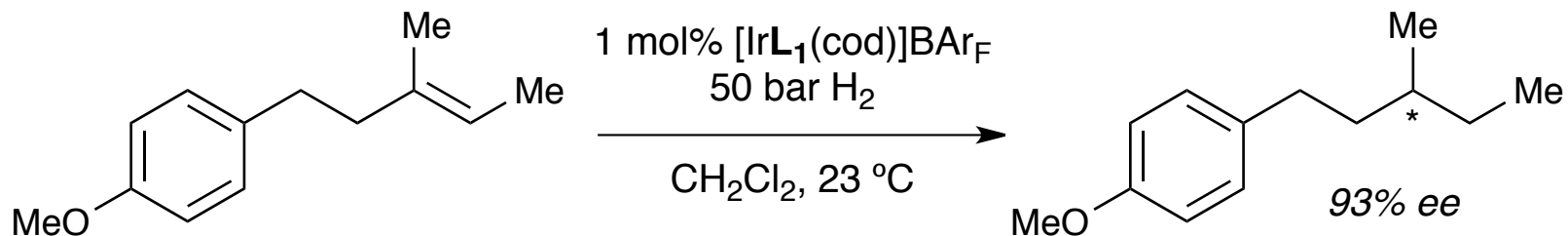
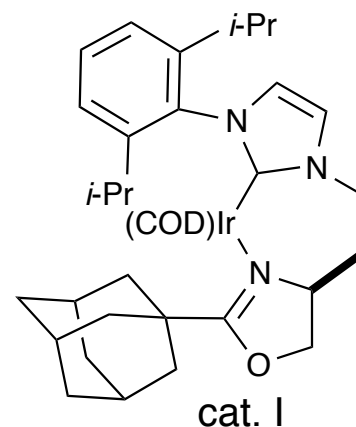


Asymmetric Hydrogenations-Some examples

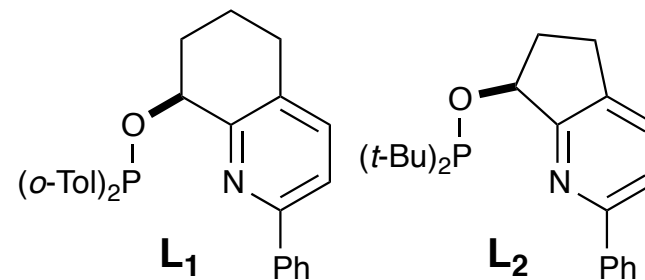
Iridium is becoming important for isolated olefins



J. Am. Chem. Soc. **2003**, 125, 113.

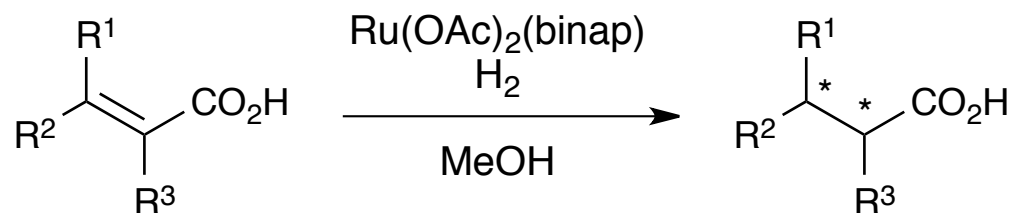


Science **2006**, 311, 642.

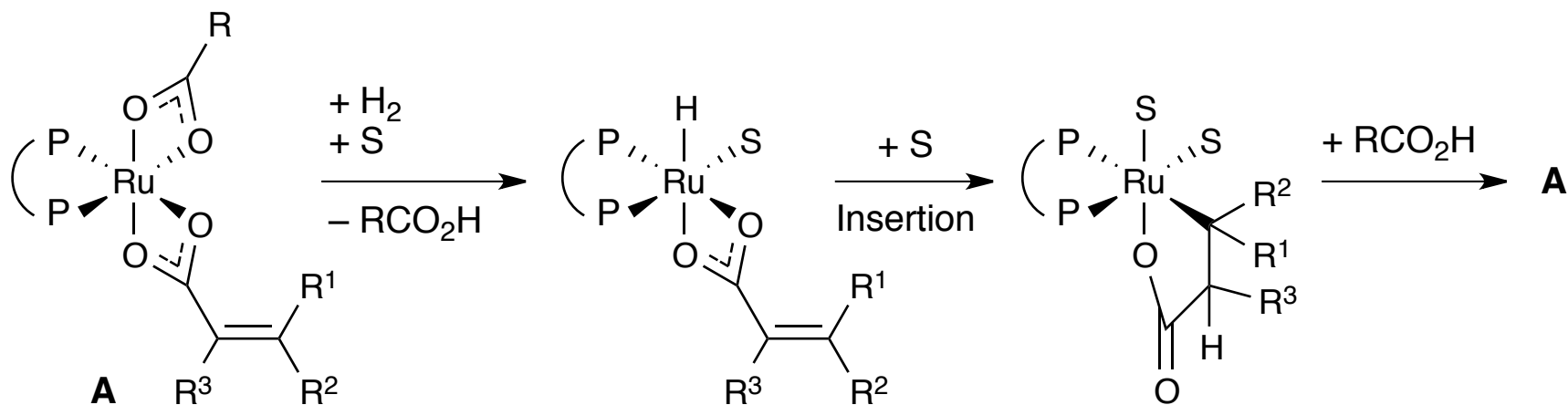


Ru-Catalyzed Asymmetric Hydrogenations

Ruthenium catalysts are also quite useful, but proceed through a different mechanism. Useful for unsaturated acids, but other coordinating groups work as well. Thought to proceed through a "monohydride mechanism"



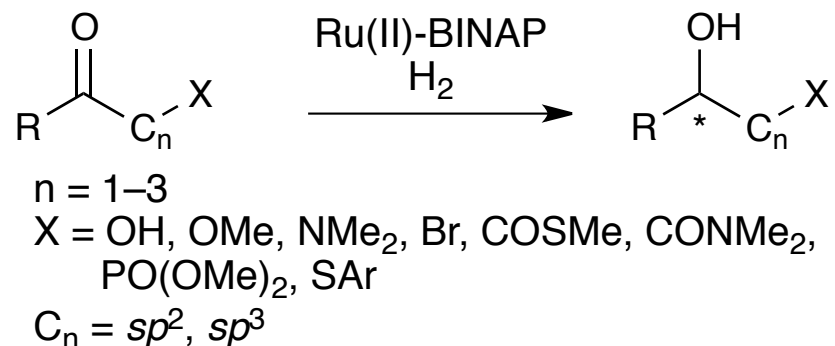
Mechanism of olefin hydrogenation by $\text{L}_n\text{Ru(OAc)}_2$



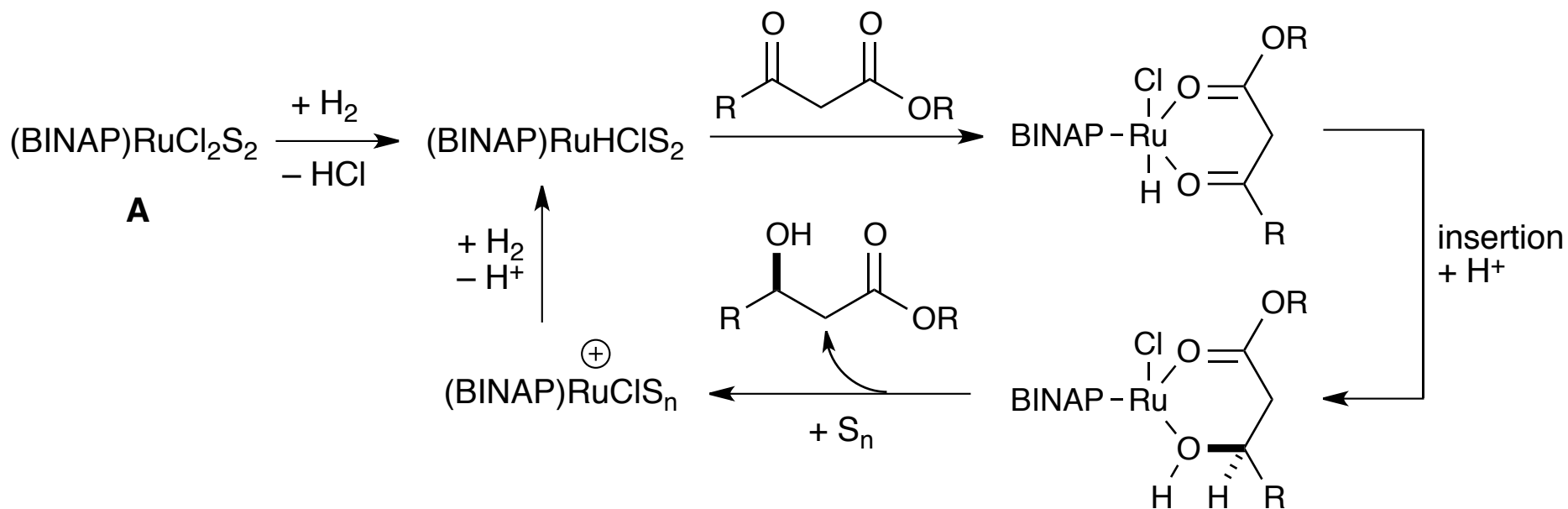
Ruthenium remains in +2 oxidation state throughout the mechanism.

Noyori Asymmetric Hydrogenation

Most hydrogenation catalysts are selective for olefins over other potentially reduceable functional groups (ketones, aldehydes, esters, etc.). But halogen- or methallyl-containing Ru(+2) catalysts can reduce ketones, as long as there is a heteroatom in the α -, β -, or γ -position.

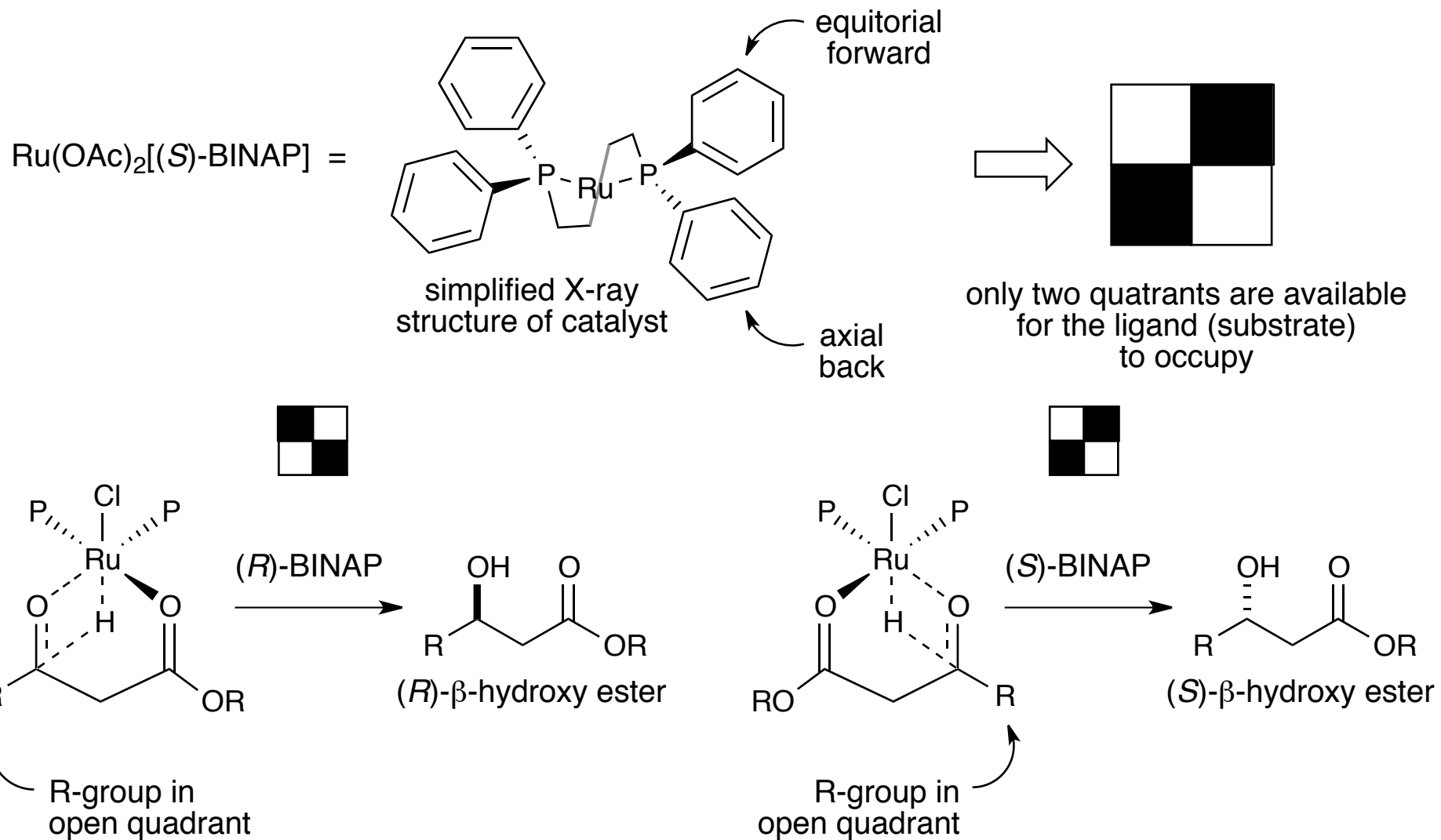


reduction of β -ketoesters is illustrative of overall mechanism



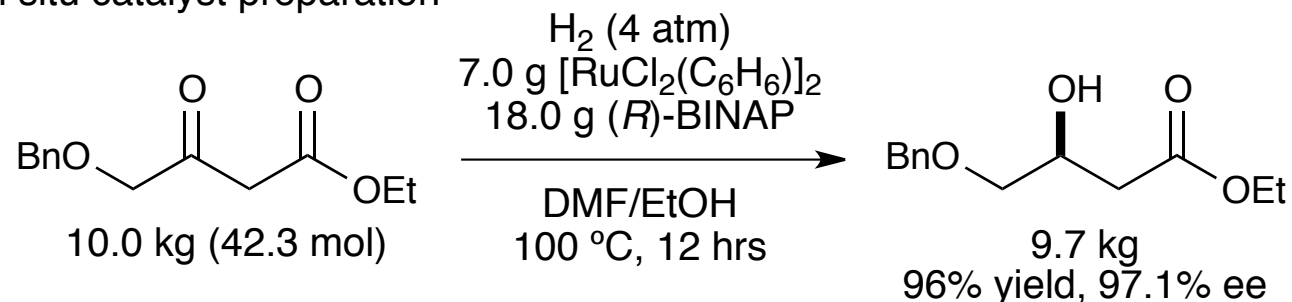
Noyori Asymmetric Hydrogenation

The stereoselectivity can be rationalized by a "quadrant" model. This is a fairly general model that can be used in many metal-catalyzed reactions.

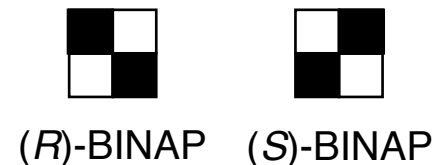


Noyori Asymmetric Hydrogenation-Examples

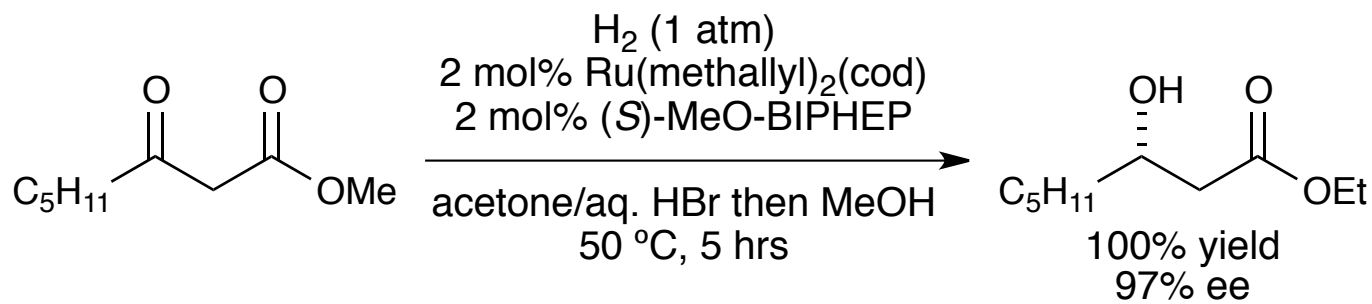
in situ catalyst preparation



Synthesis **1995**, 1014

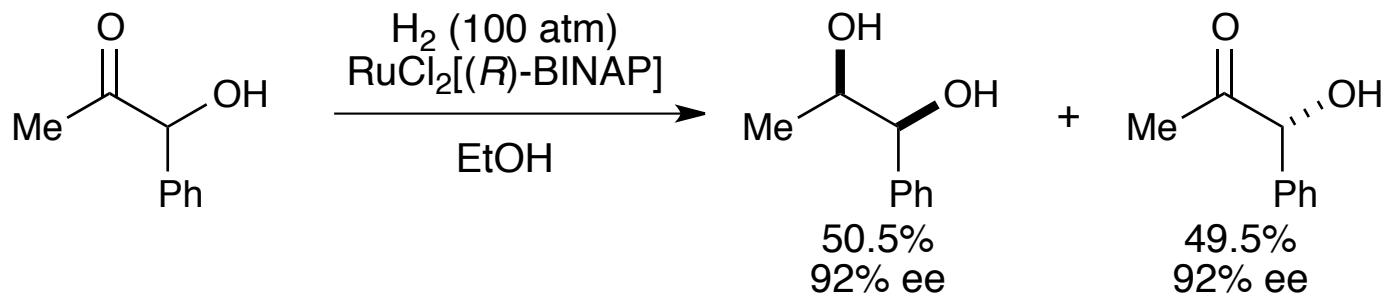


methallyl precursor allows for use of 1 atm H₂



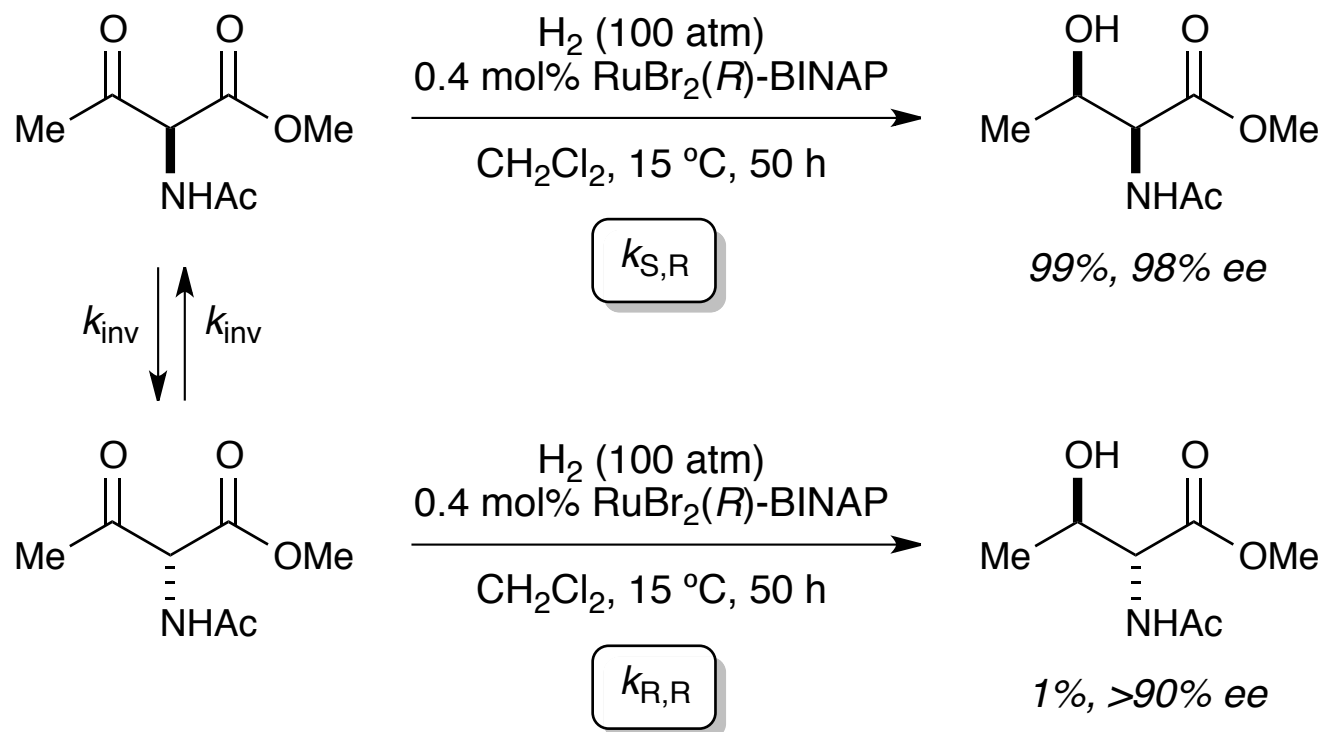
Tetrahedron Lett. **1995**, 36, 4801

other binding groups possible as well. In this case a kinetic resolution.



Noyori Dynamic Kinetic Asymmetric Hydrogenation

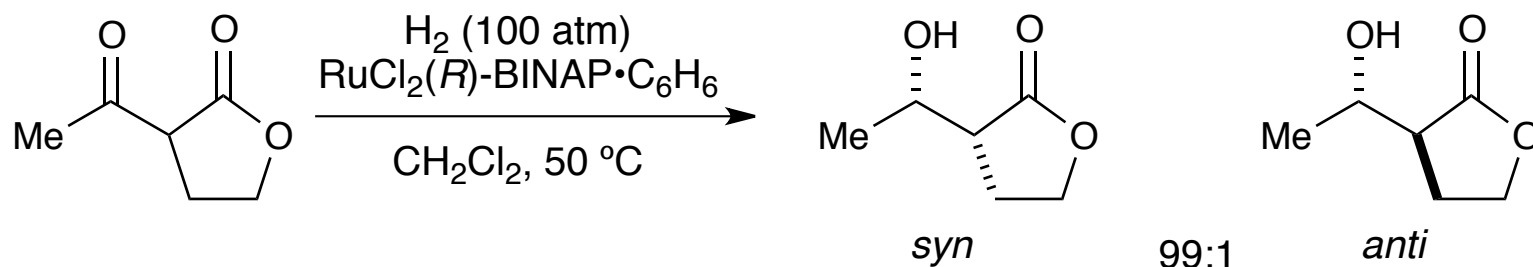
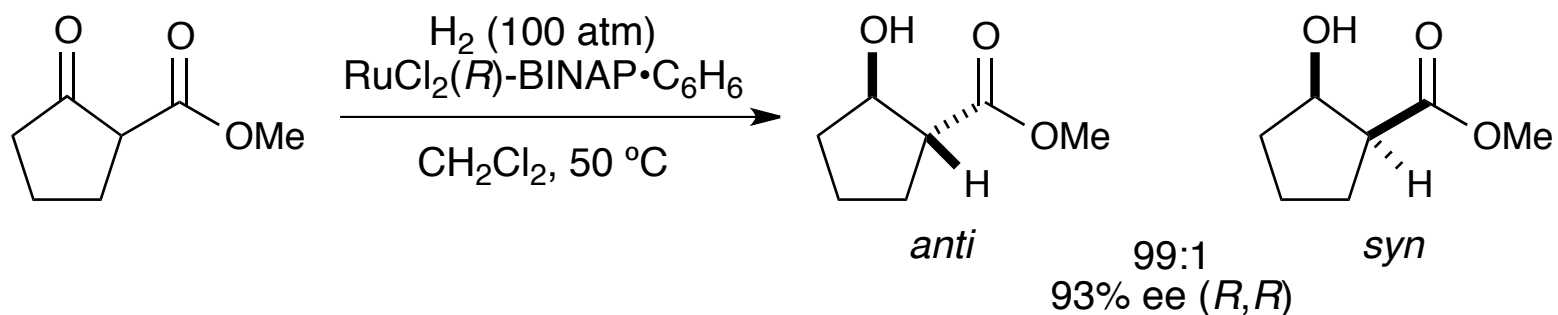
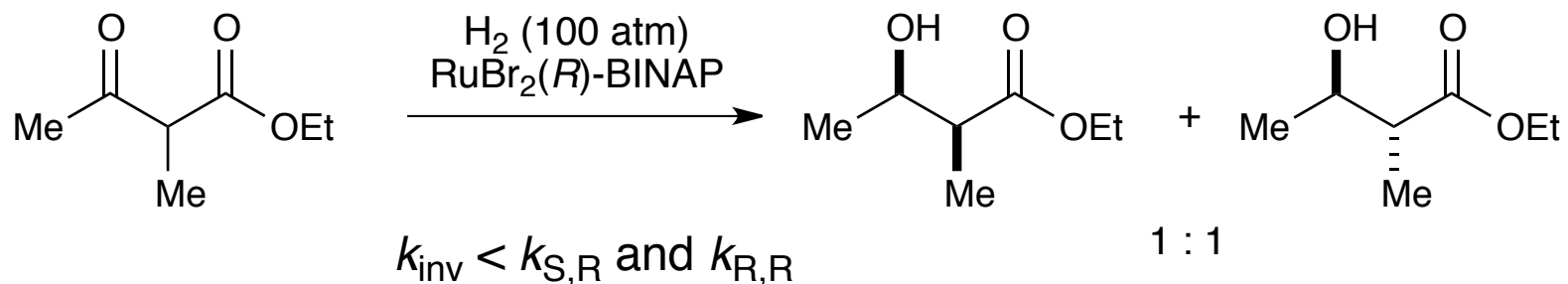
Racemic β -ketoesters – If the initial stereocenter present in the starting material can undergo rapid epimerization under the reaction conditions, a single diastereomer will be formed and with high ee.



$$k_{inv} > k_{S,R} \text{ and } k_{R,R}$$

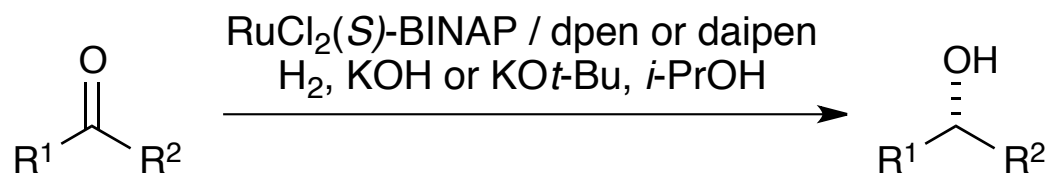
The stereoisomer of the alcohol is dependent on the ligand, but the configuration of the α -position is substrate dependent.

Noyori Dynamic Kinetic Asymmetric Hydrogenation

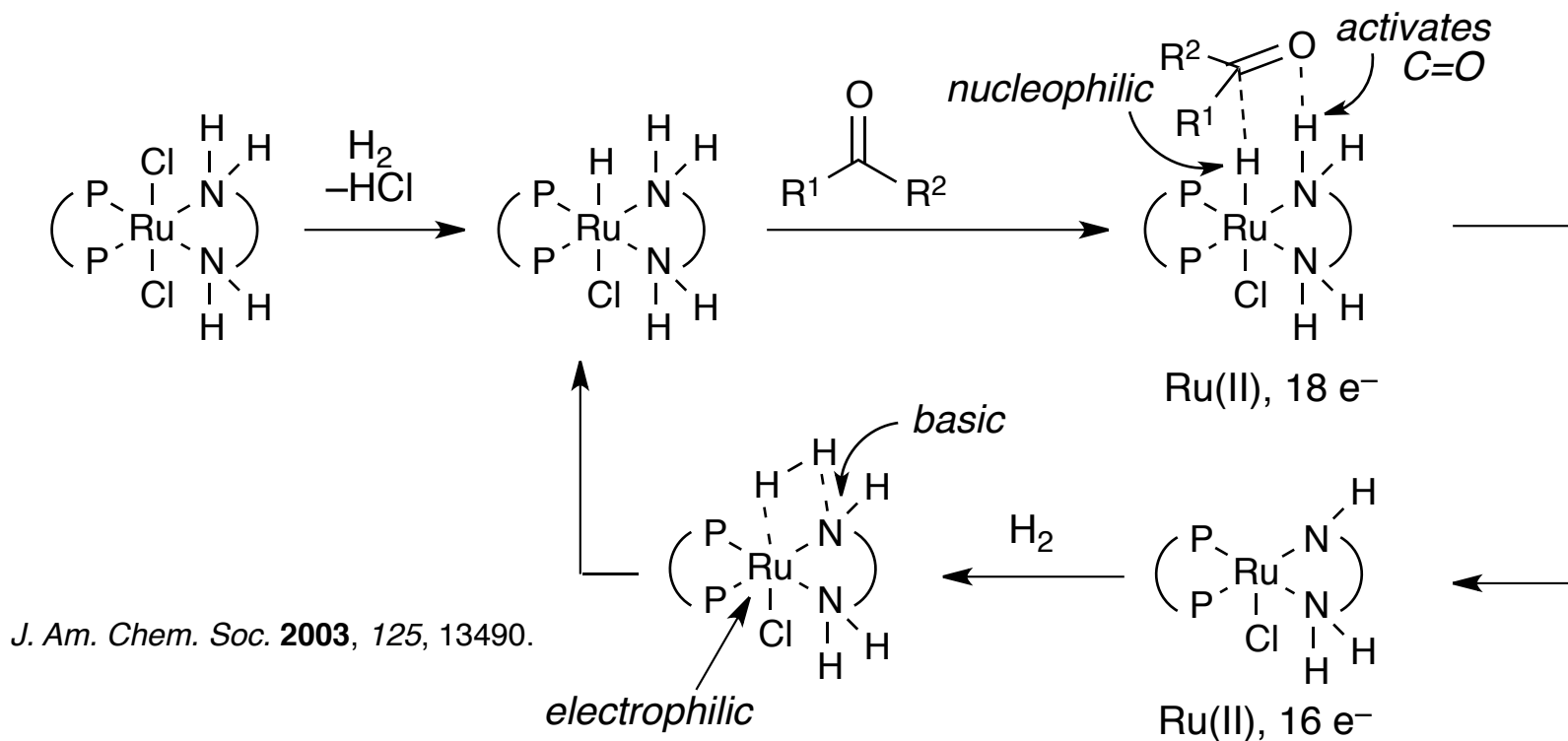
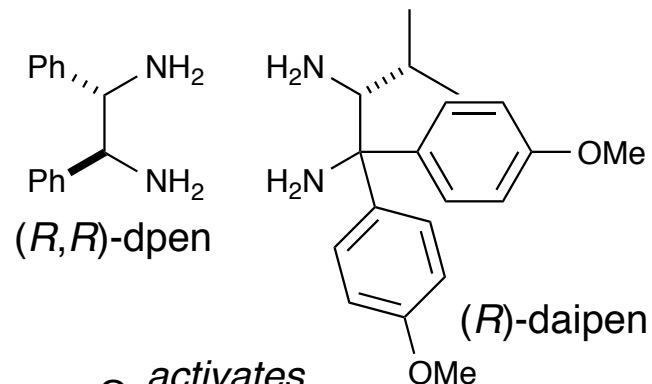


Hydrogenation of "Unfunctionalized" Ketones

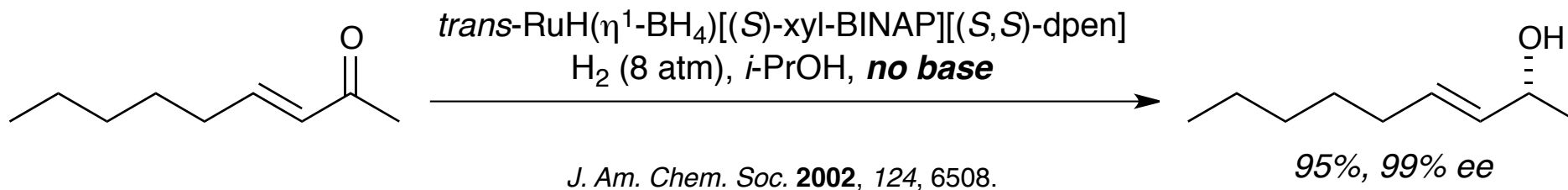
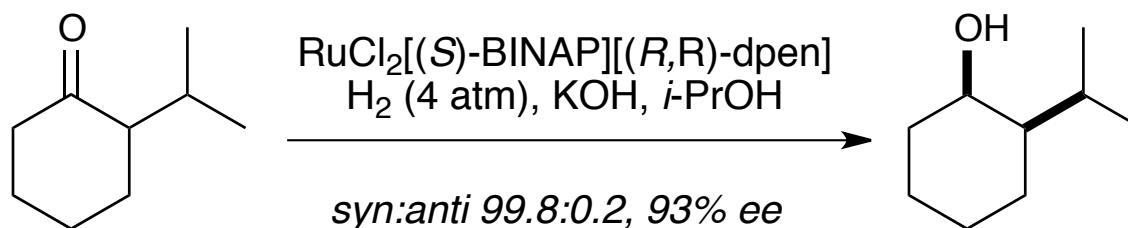
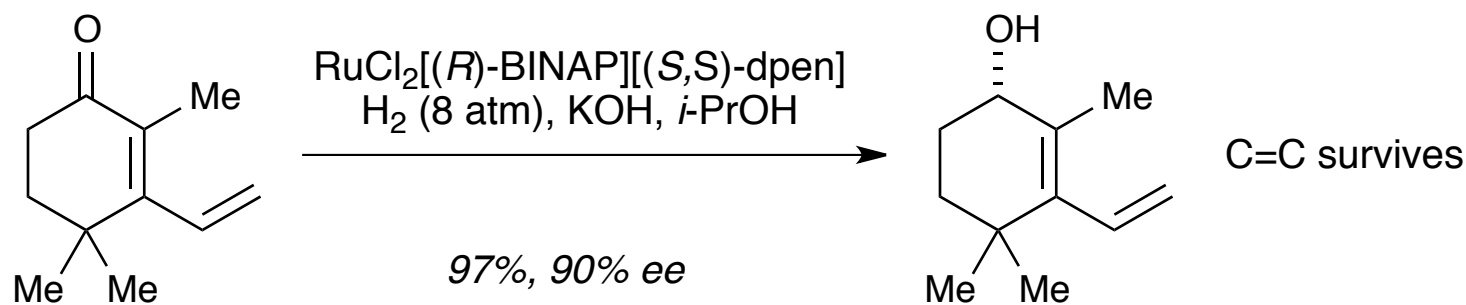
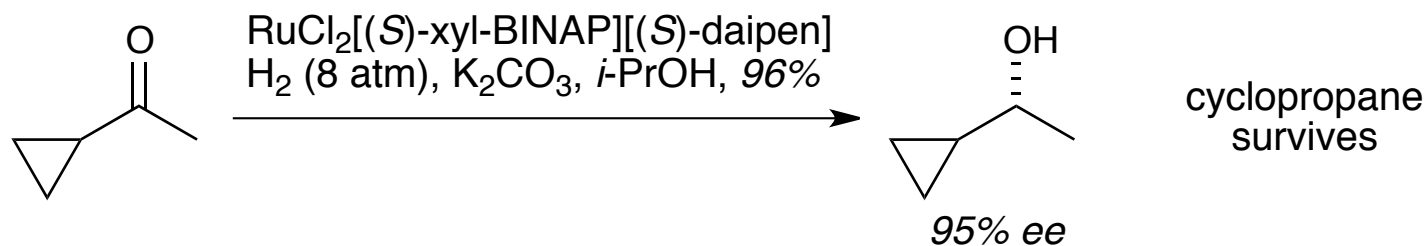
By combining a chiral diamine ligand with a chiral phosphine, the asymmetric hydrogenation of "unfunctionalized" (ketones without a second binding group) ketones can be achieved.



J. Am. Chem. Soc. **1998**, *120*, 13529.



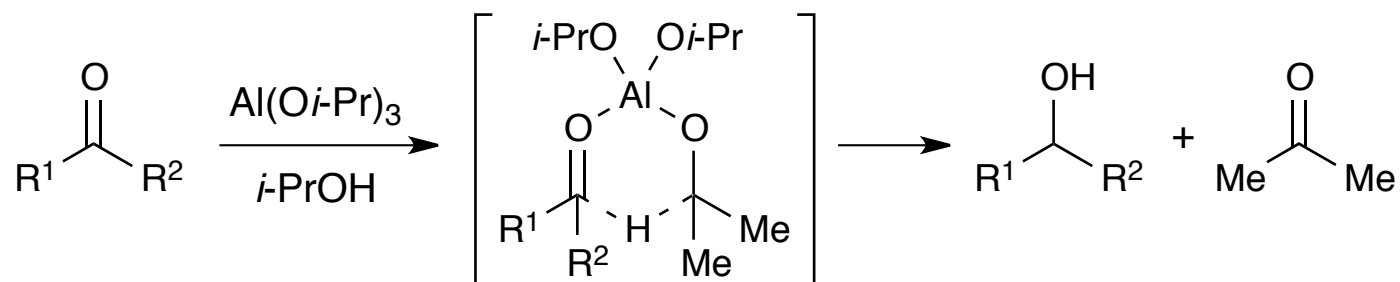
Hydrogenation of "Unfunctionalized" Ketones



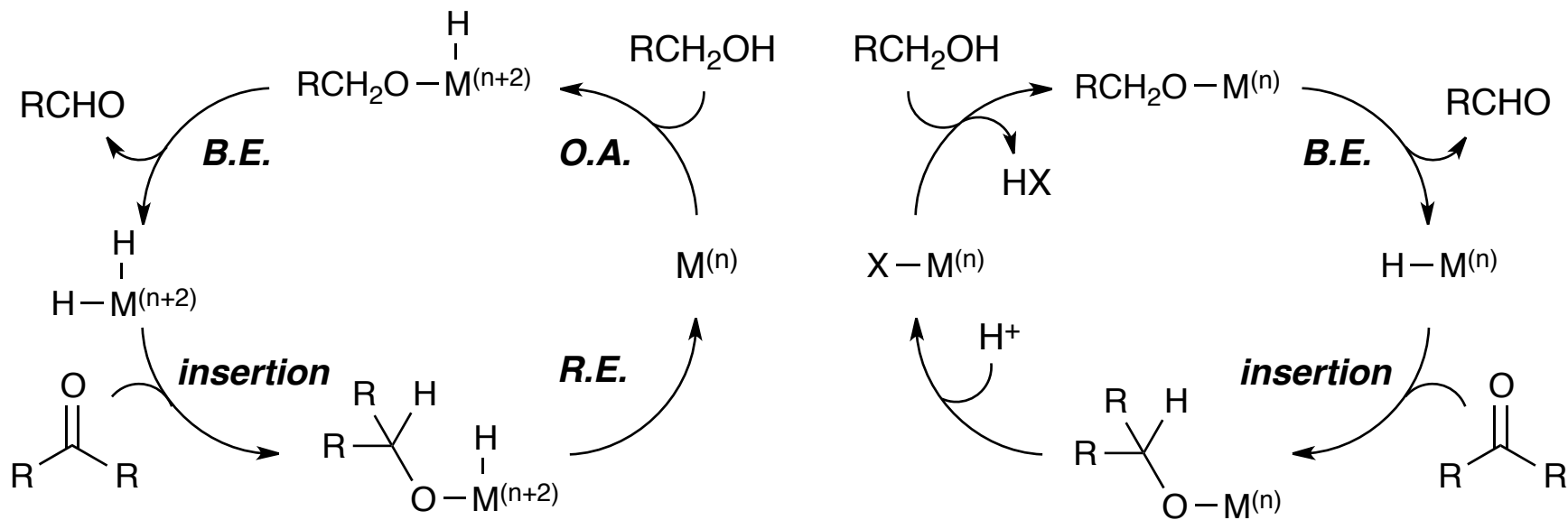
Asymmetric Transfer Hydrogenation

In all previous examples, H₂ served as the terminal reductant. The elements of H₂ can come from other sources as well (isopropanol and formic acid).

Meerwein-Ponndorf-Verley Reduction

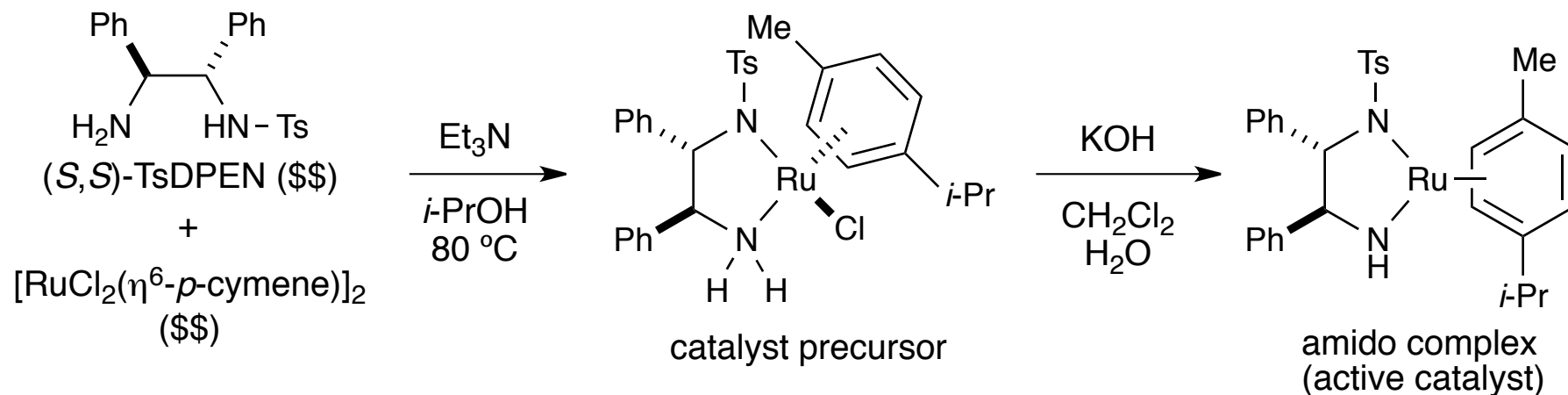


Metal-catalyzed transfer hydrogenation – Two mechanisms are possible

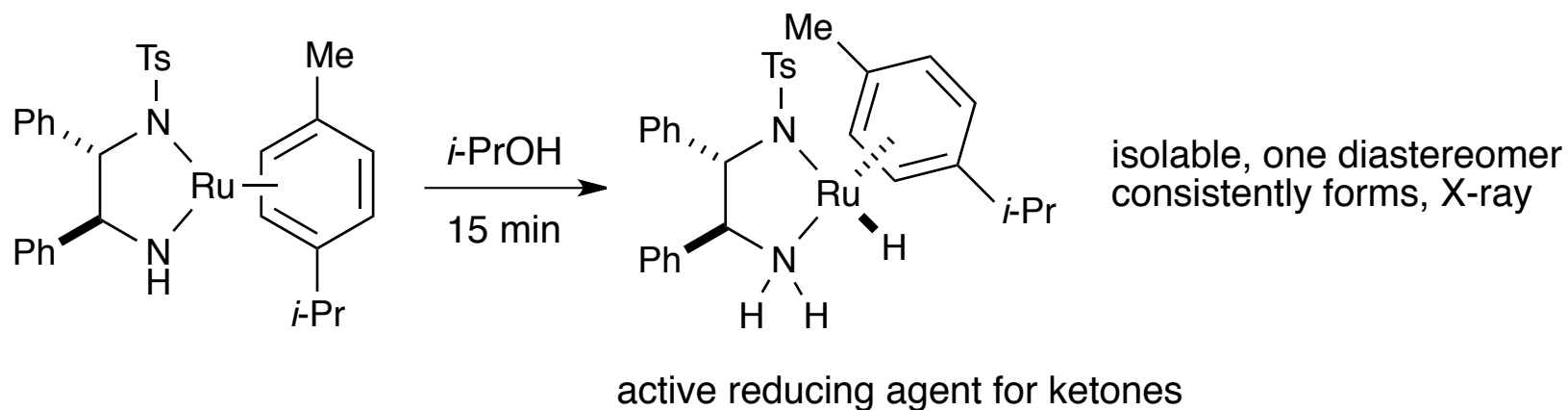


Asymmetric Transfer Hydrogenation

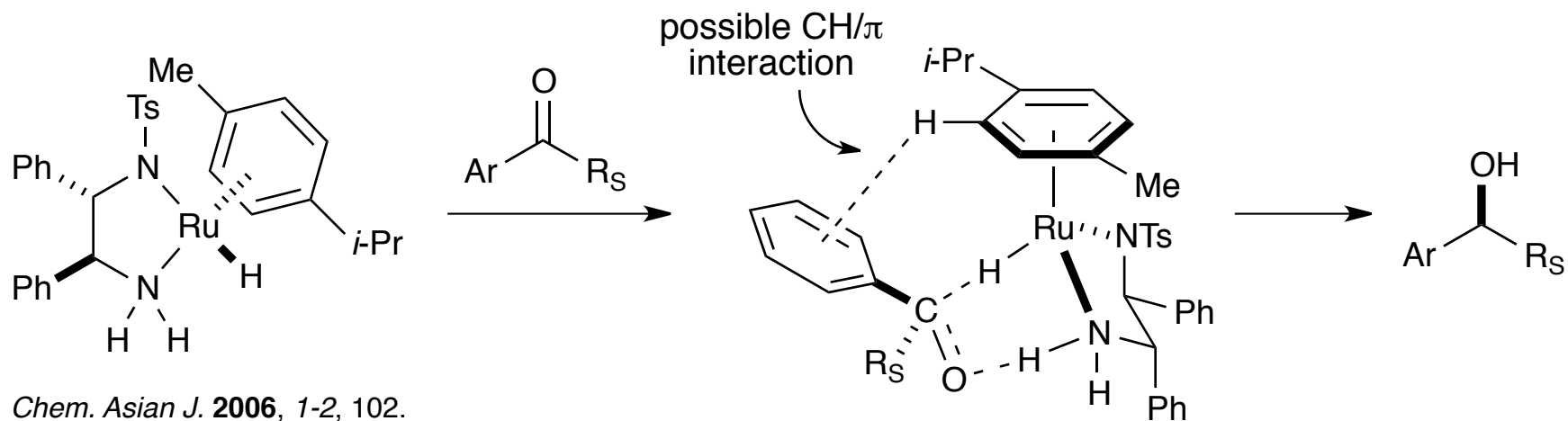
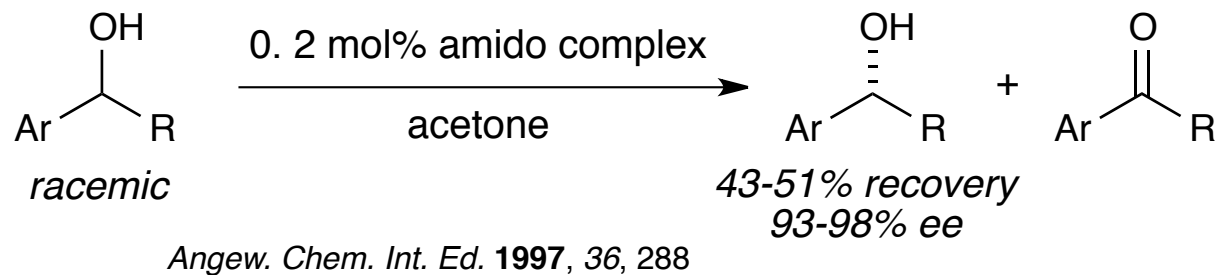
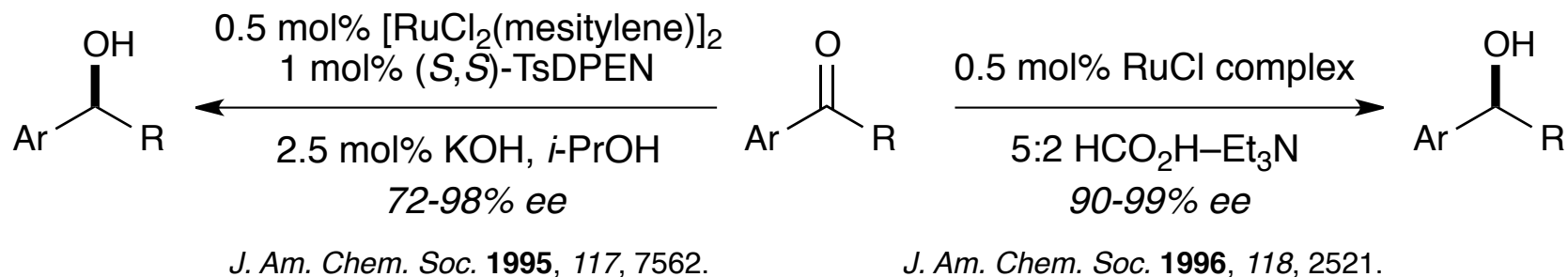
Noyori CATHY catalysts – Catalytic Asymmetric Transfer Hydrogenation



both complexes easy to prepare and are reasonably stable

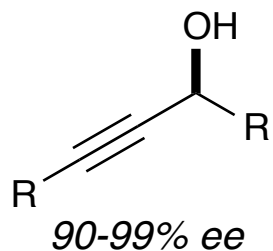


Asymmetric Transfer Hydrogenation

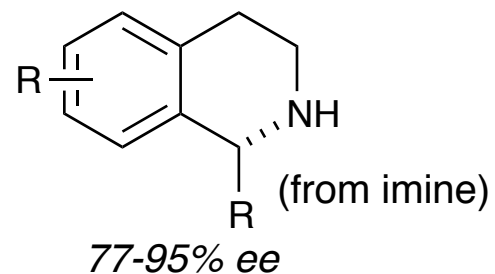


Asymmetric Transfer Hydrogenation

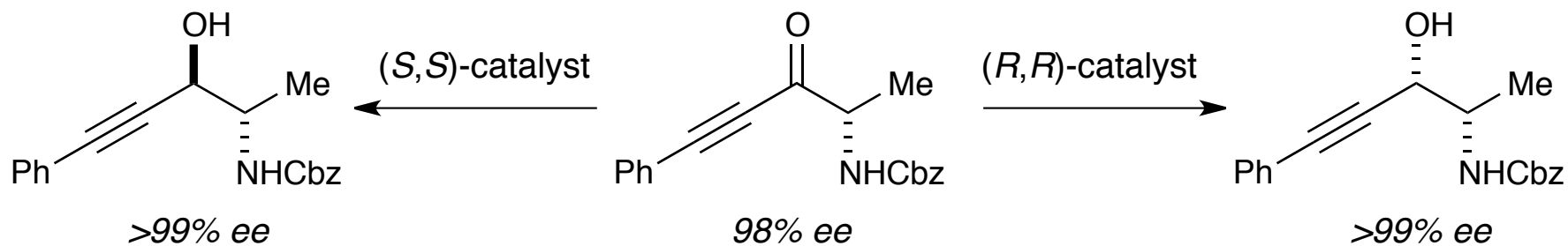
some other reductions



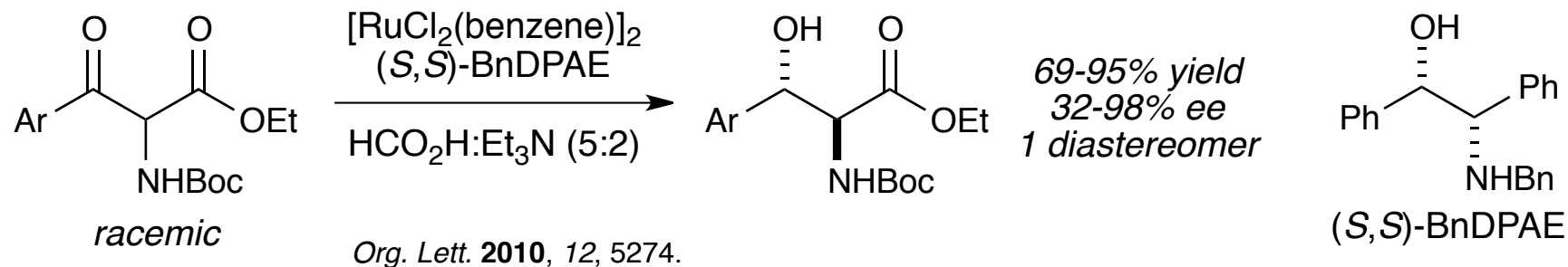
J. Am. Chem. Soc. **1997**, *119*, 8738.



J. Am. Chem. Soc. **1996**, *118*, 4916.



J. Am. Chem. Soc. **1997**, *119*, 8738.

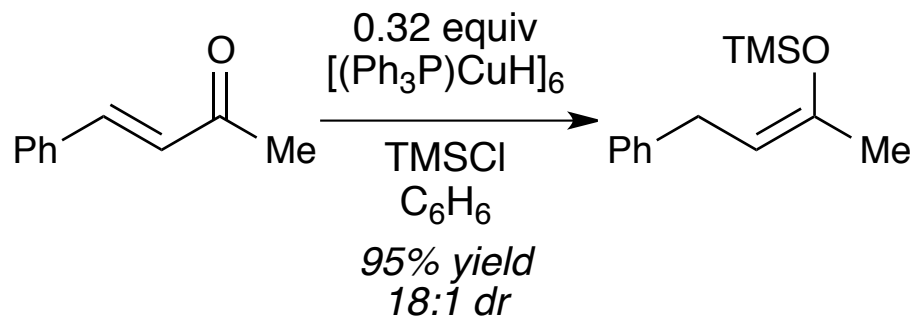
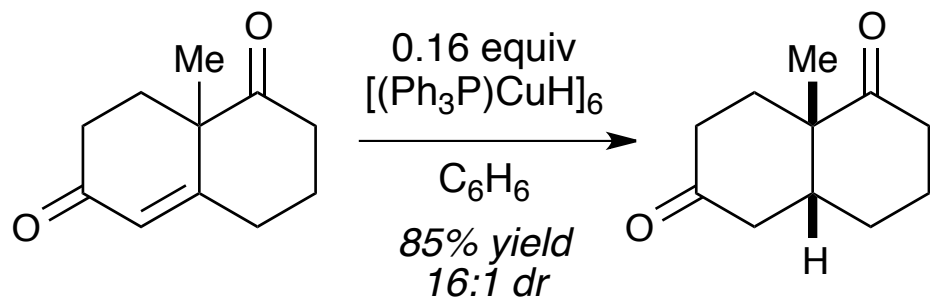
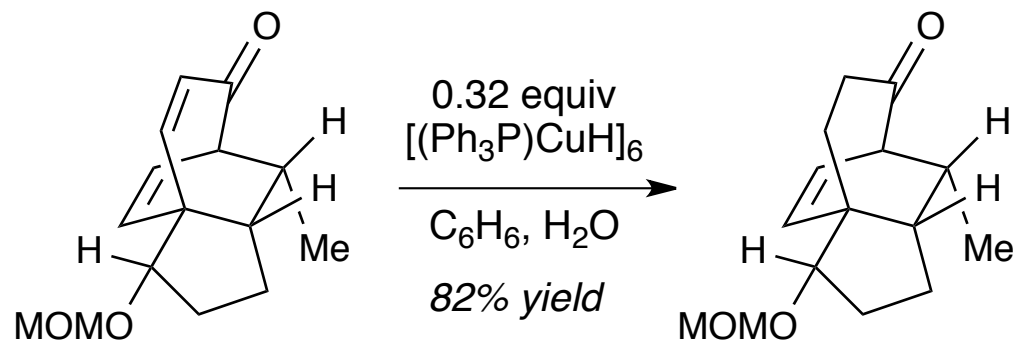


Org. Lett. **2010**, *12*, 5274.

Enone Reductions With Copper Hydrides

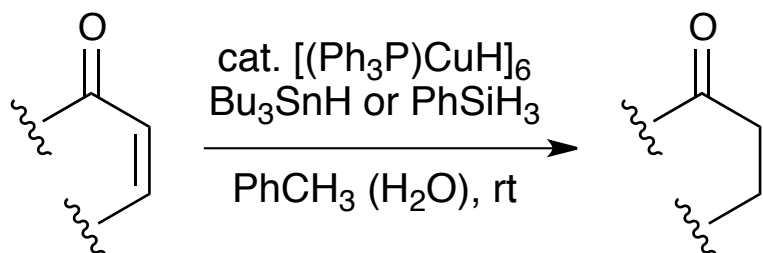
Much like the selective reaction of alkyl cuprates with enones, copper hydrides will reduce enones through a 1,4-addition pathway.

Stryker's reagent – $[(\text{Ph}_3\text{P})\text{CuH}]_6$: reduces double bond of conjugated ketones, aldehydes, esters, nitriles, and nitro compounds. stoichiometric reagent. *E*-enones reduced faster than *Z*-enones.

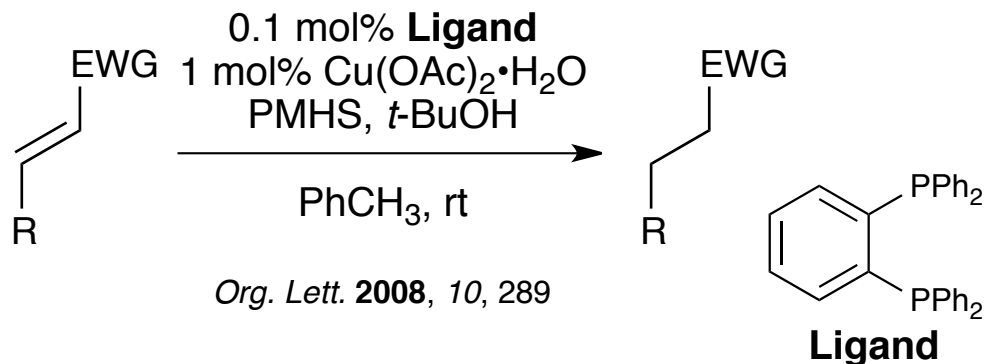


Enone Reductions With Copper Hydrides

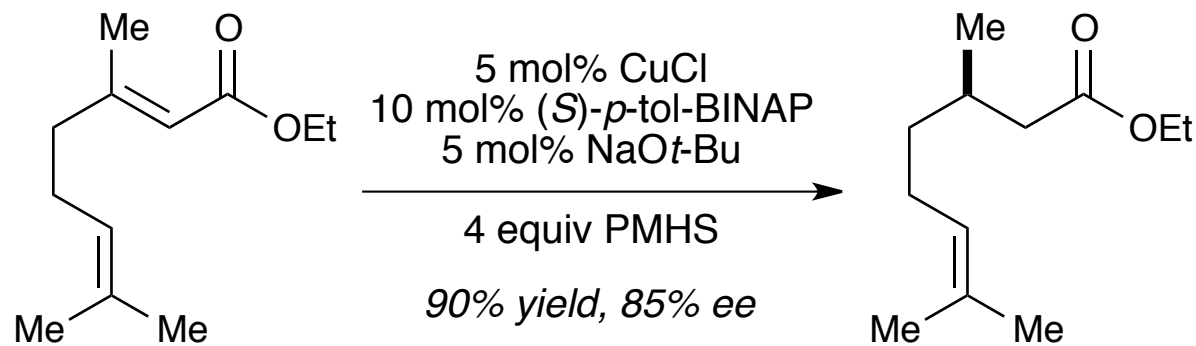
Catalytic methods have also been developed to address the atom economy of the process and to introduce asymmetry.



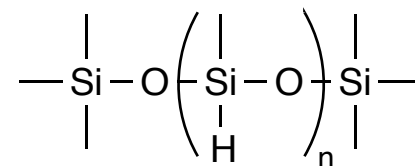
Tetrahedron Lett. **1998**, 39, 4627.



Org. Lett. **2008**, 10, 289



J. Am. Chem. Soc. **1999**, 121, 9473.



PMHS = polymethylhydrosiloxane

has been extended to other substrates