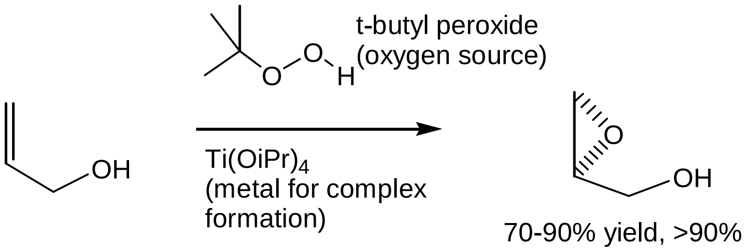
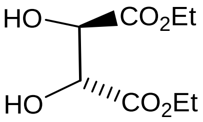
CH3E4 notes: Asymmetric Catalysis, Prof Martin Wills

You are aware of the importance of chirality. This section will focus on asymmetric catalysis, i.e. the use of a catalyst to create new enantiomerically pure molecules. This can be achieved in several ways:

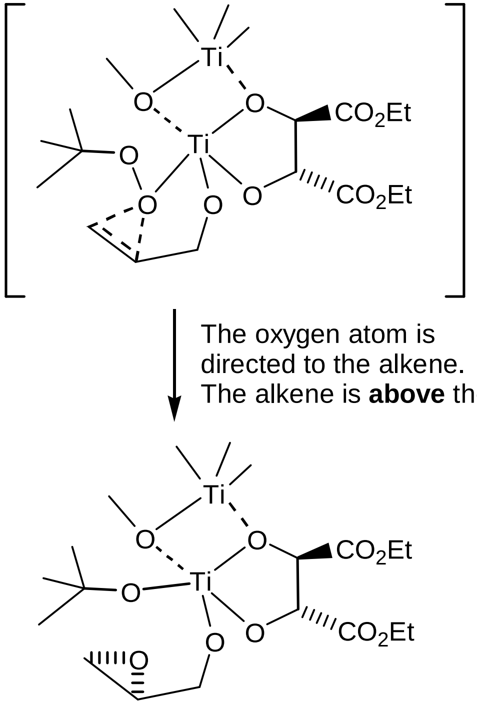
1) A metal may template the Reaction, e.g. Sharpless Epoxidation of allylic alcohols:



70-90% yield, >90% e.e.



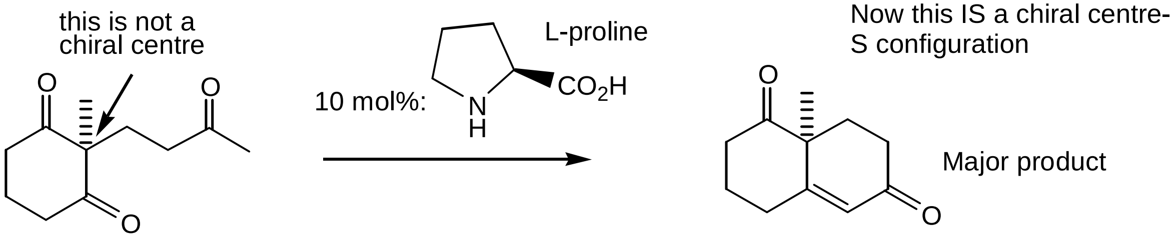
(+)-diethyl tartrate (source of chirality)



The oxygen atom is directed to the alkene.
The alkene is **above** the peroxide.

2) A covalent intermediate may be formed:

Proline catalyses the asymmetric cyclisation of a diketone (known as the Robinson annelation reaction).



this is not a chiral centre

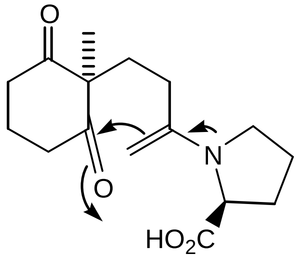
10 mol%:

L-proline

Now this IS a chiral centre- S configuration

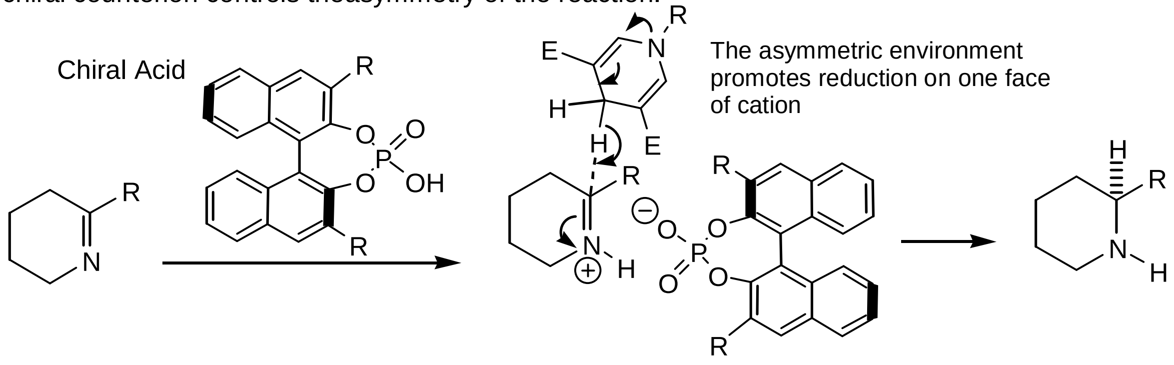
Major product

Mechanism is via:



3) The reaction may take place within an asymmetric environment controlled by an external source:

The chiral counterion controls theasymmetry of the reaction.



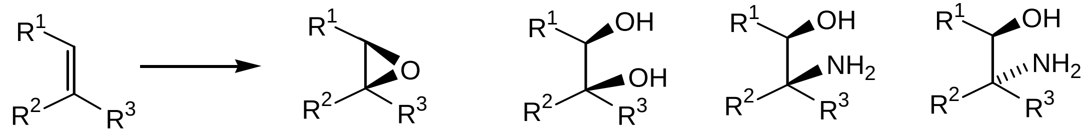
Chiral Acid

The asymmetric environment promotes reduction on one face of cation

The key features of these approaches will be described and examples from the literature will be described.

Oxidation reactions of alkenes:

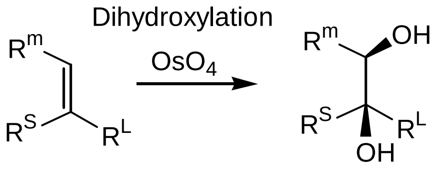
This represents a good way to create chiral centres.



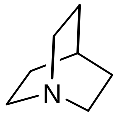
epoxidation Dihydroxylation aminohydroxylation

Historical: The Sharpless epoxidation was one of the first examples of asymmetric catalysis (see earlier slide). The Sharpless dihydroxylation reaction employs ligand-acceleration to turn the known dihydroxyation reaction into an asymmetric version.

This process depends on the use of an amine to accelerate a reaction:

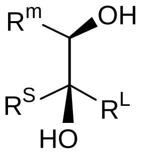


use of the amine below speeds the reaction up:

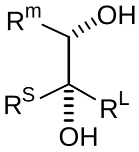


R^L=large group, R^M=medium group, R^S=small group.

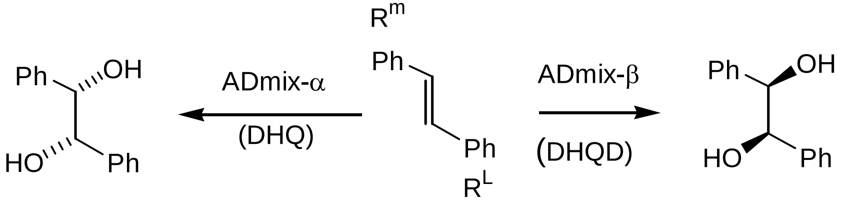
DHQD gives:



DHQ gives:



How to remember::

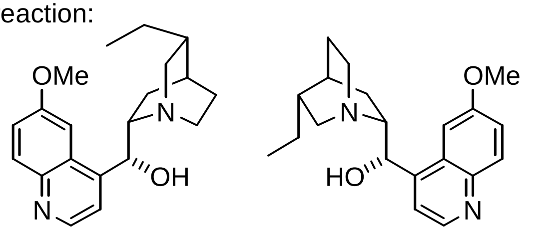


2 x 'OH' added to lower face.

in this orientation

2 x 'OH' added to upper face.

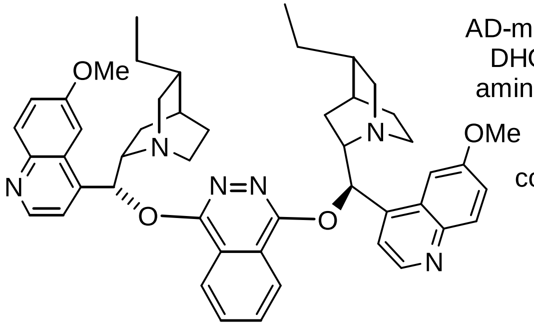
Sharpless et al realised that enantiomerically-enriched amines could change this to an asymmetric reaction:



Dihydroquinine (DHQ) Dihydroquinidine (DHQD)

'psuedo enantiomers'

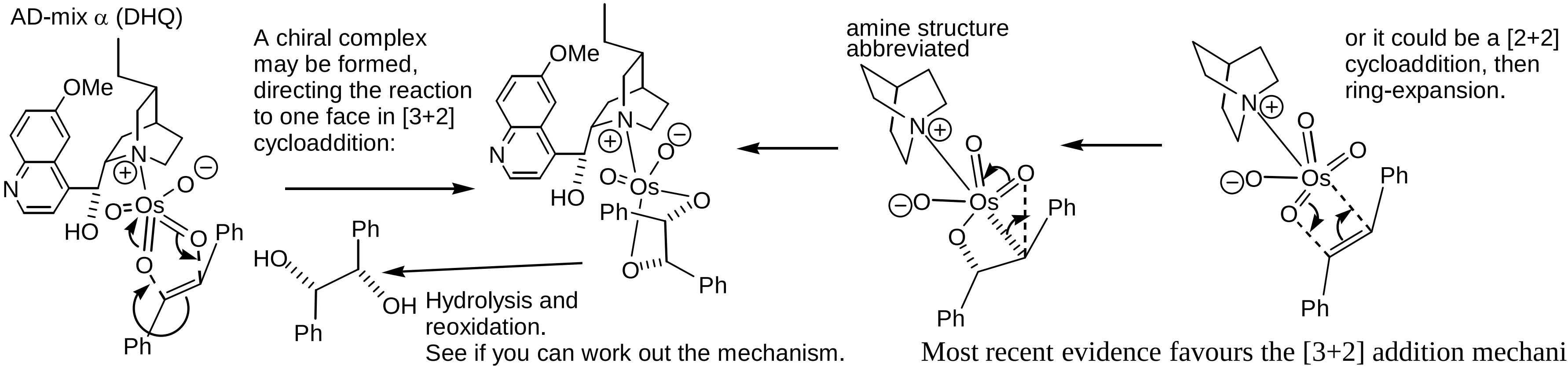
ADmix-α contains a dimer of quinine '$(DHQ)_2$PHAL'
ADmix-β contains a dimer of quinidine '$(DHQD)_2$PHAL)'
(also a small amount of osmium salt + stoichiometric $K_3Fe(CN)_6$



AD-mix α contains DHQ (note both amine groups are of the same absolute configuration):

Oxidation reactions of alkenes:

The mechanism may be one of a number of possibilities:



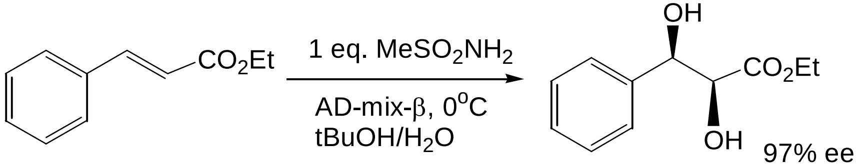
A chiral complex may be formed, directing the reaction to one face in [3+2] cycloaddition:

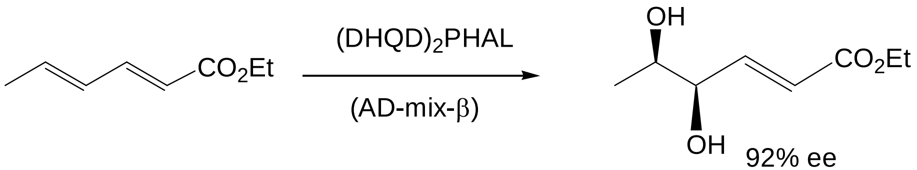
amine structure abbreviated

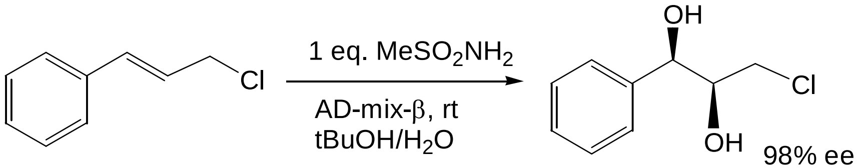
or it could be a [2+2] cycloaddition, then ring-expansion.

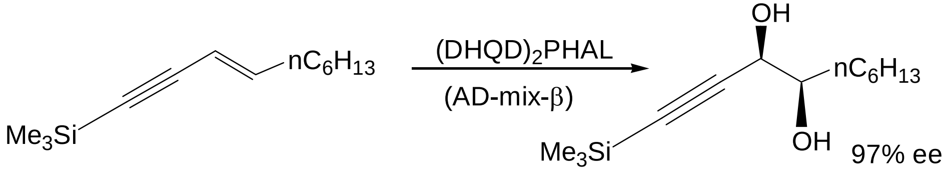
Hydrolysis and reoxidation.
See if you can work out the mechanism.

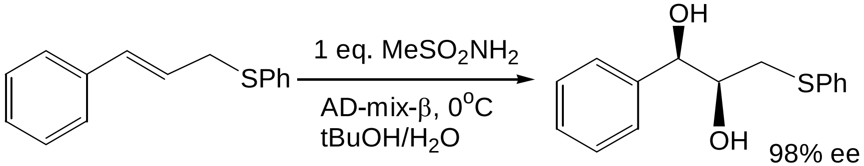
Most recent evidence favours the [3+2] addition mechanism:
K. B. Sharpless et al, *J. Am. Chem. Soc.* **1997**, 119, 9907.

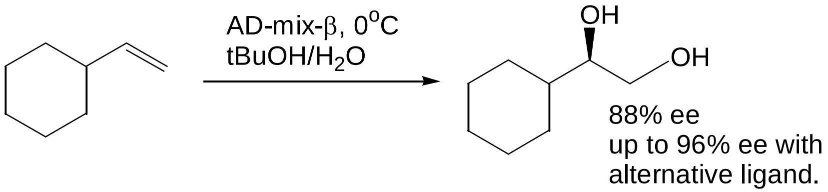


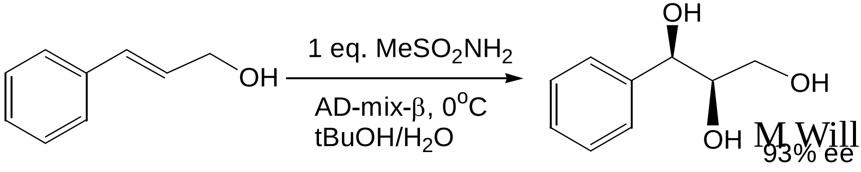


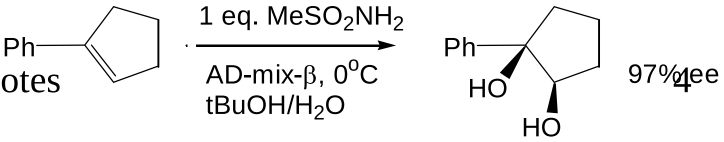




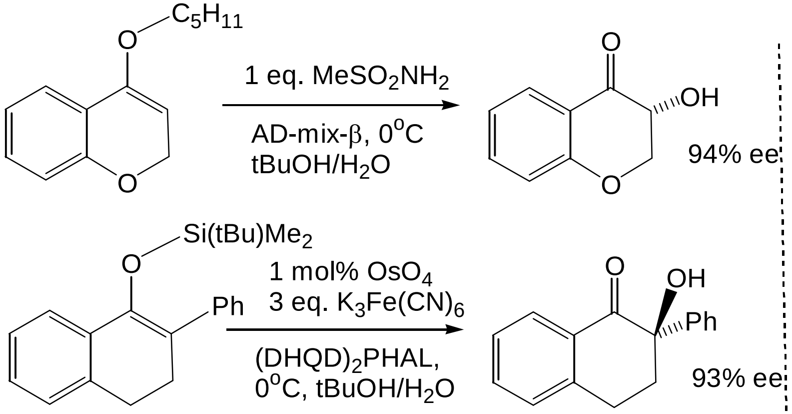




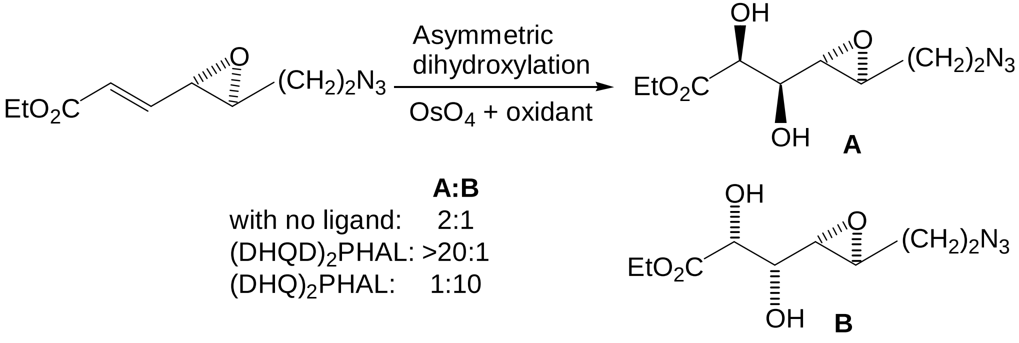




Oxidation reactions of alkenes:

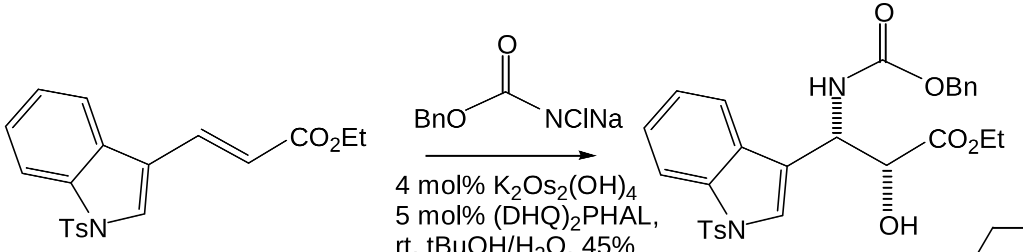


Diastereoselective reactions:



	A:B
with no ligand:	2:1
$(DHQD)_2$PHAL:	>20:1
$(DHQ)_2$PHAL:	1:10

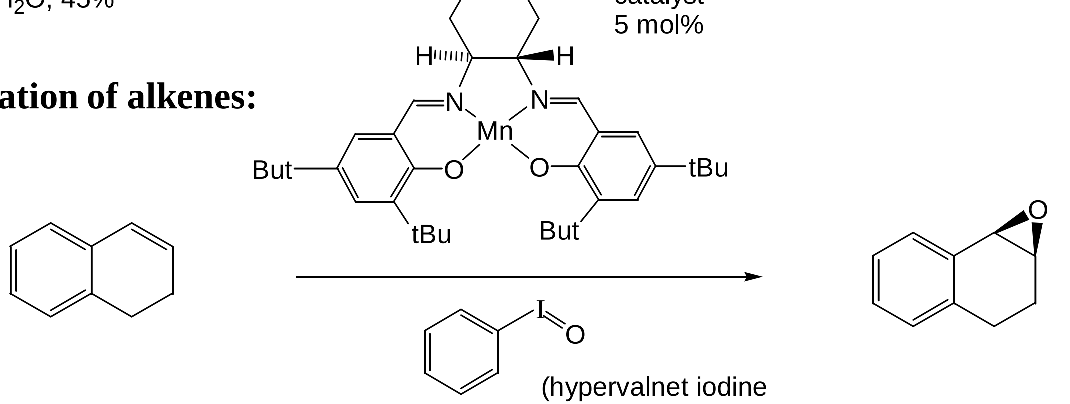
Sharpless aminodihydroxylation is a closely-related process



>15:1 regioselectivity,
93% ee

Jacobsen epoxidation of alkenes:

The iodine reagent transfers its oxygen atom to Mn, then the Mn tranfers in to the alkene in a second step. The chirality of the catalyst controls the absolute configuration. Advantage? You are not limited to allylic alcohols

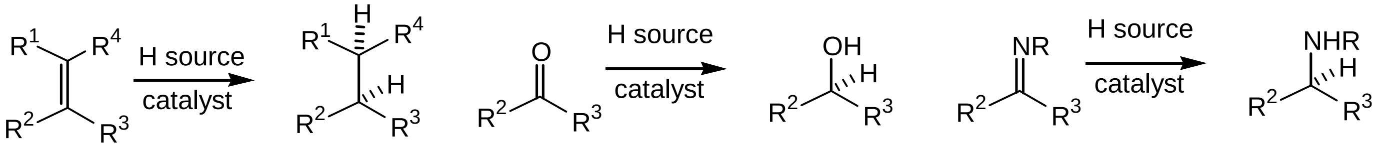


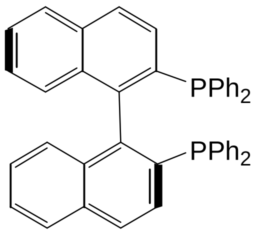
(hypervalnet iodine reagent)
Source of oxygen.

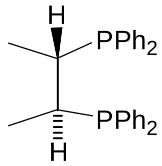
Reduction reactions of Double bonds (C=C, C=N, C=O):

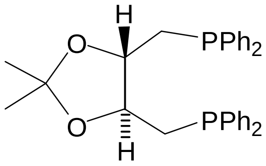
This is a major area of asymmetric catalysis
- atom efficient, low waste, low energy.

H source might be H_2 gas, hydride, or
an organic molecle (transfer hydrogenation)

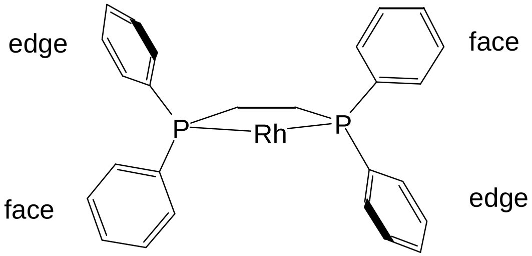



S-BINAP
(often used
with Ru(II))

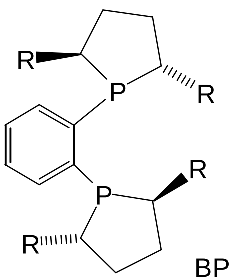

Chiraphos/Rh(I)


DIOP/Rh(I)

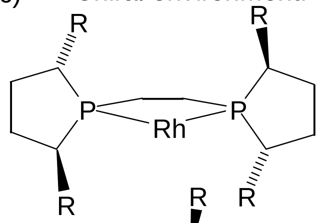
Rh/Diphosphine complex- ligands
create a chiral environment at the metal



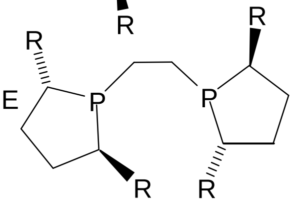
DuPHOS (R=Me, Et etc)



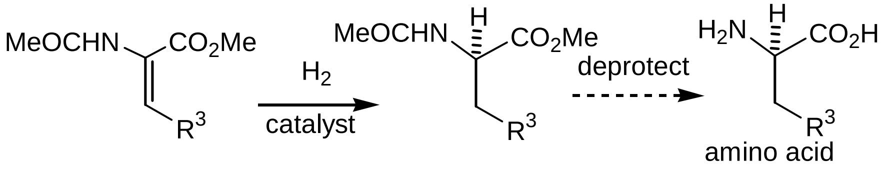
Chiral environment:

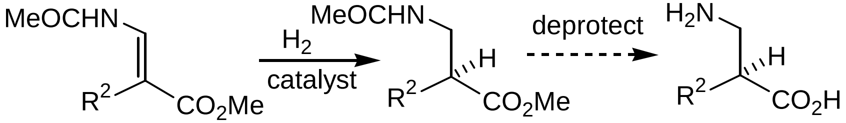


BPE

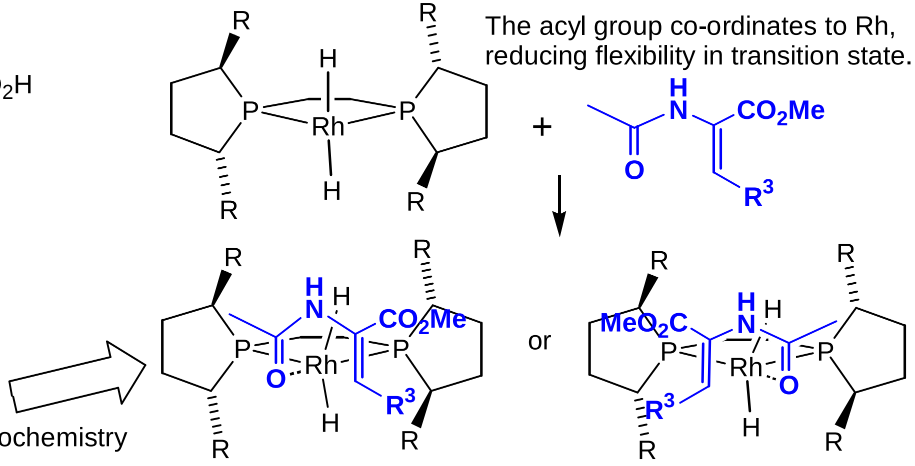


Examples of generalised applications (specific examples to follow).





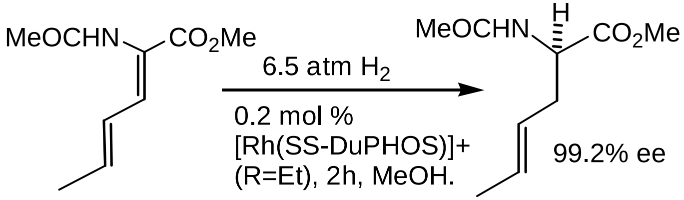
The acyl group co-ordinates to Rh,
reducing flexibility in transition state.



Two diastereoisomers may be formed, energy difference influences stereochemistry

Reduction reactions of C=C Double bonds using Rh(I) complexes– representative examples:

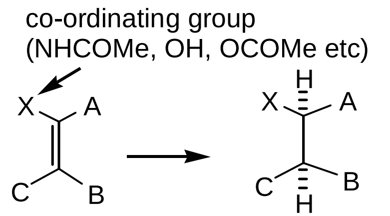
Examples of specific examples to follow:



6.5 atm H_2

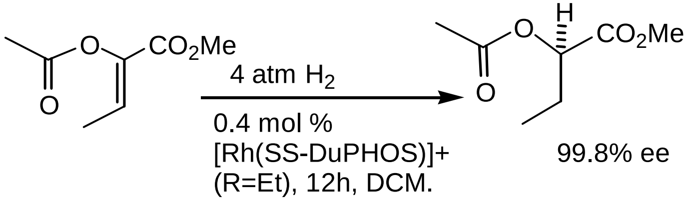
0.2 mol %
[Rh(SS-DuPHOS)]+
(R=Et), 2h, MeOH.

99.2% ee



co-ordinating group
(NHCOMe, OH, OCOMe etc)

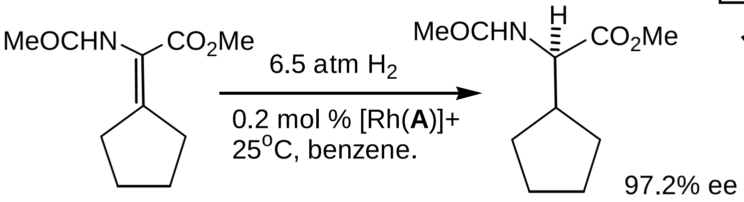
Addiition of hydrogen is relative
to the co-ordinating group



4 atm H_2

0.4 mol %
[Rh(SS-DuPHOS)]+
(R=Et), 12h, DCM.

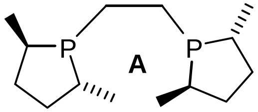
99.8% ee



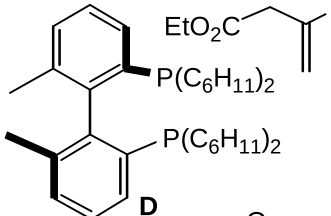
6.5 atm H_2

0.2 mol % [Rh(**A**)]+
25°C, benzene.

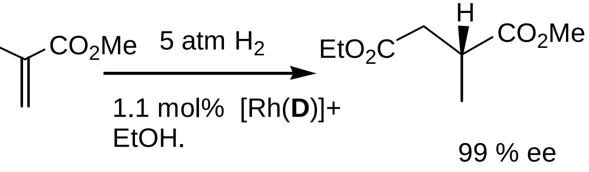
97.2% ee



A



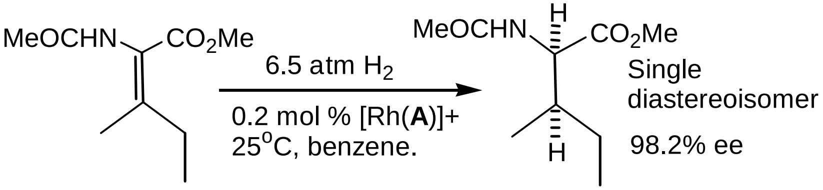
D



5 atm H_2

1.1 mol% [Rh(**D**)]+
EtOH.

99 % ee

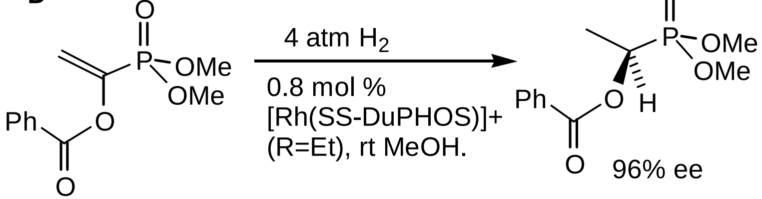


6.5 atm H_2

0.2 mol % [Rh(**A**)]+
25°C, benzene.

Single
diastereoisomer

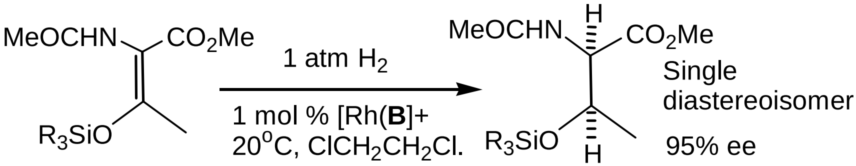
98.2% ee



4 atm H_2

0.8 mol %
[Rh(SS-DuPHOS)]+
(R=Et), rt MeOH.

96% ee

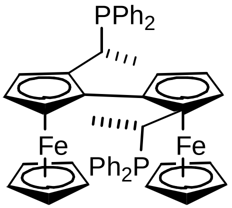


1 atm H_2

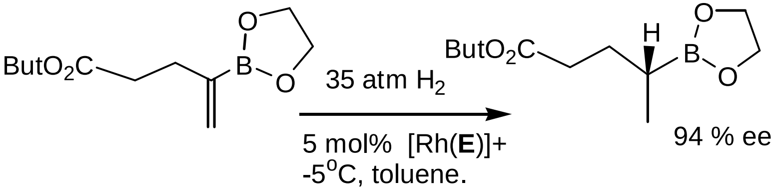
1 mol % [Rh(**B**]+
20°C, $ClCH_2CH_2Cl$.

Single
diastereoisomer

95% ee



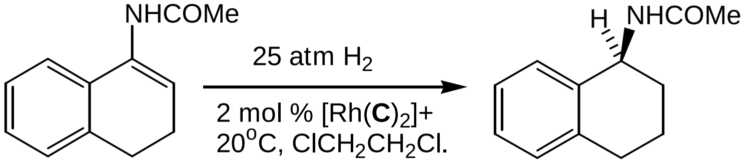
B



35 atm H_2

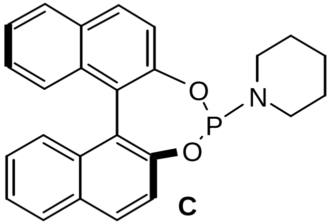
5 mol% [Rh(**E**)]+
-5°C, toluene.

94 % ee

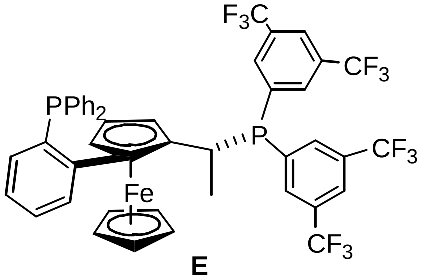


25 atm H_2

2 mol % $[Rh(\mathbf{C})_2]$+
20°C, $ClCH_2CH_2Cl$.



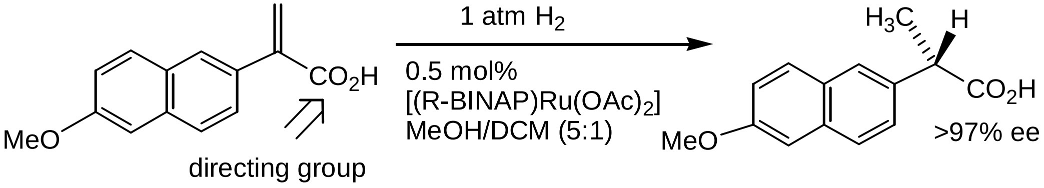
C

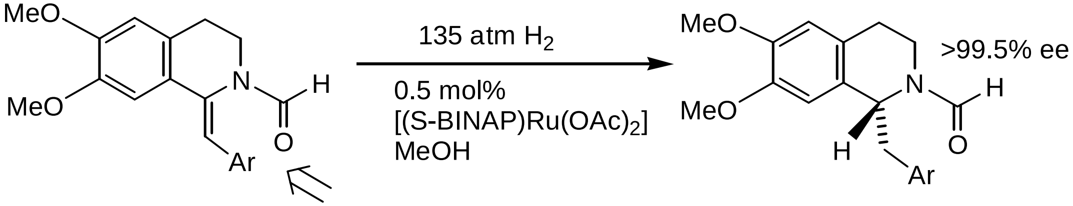


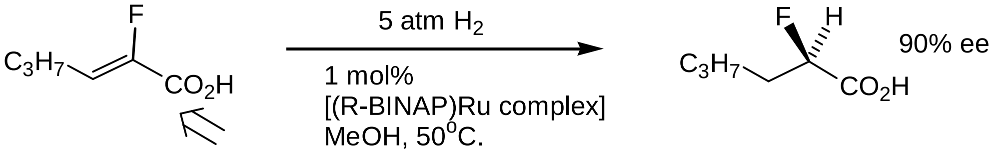
E

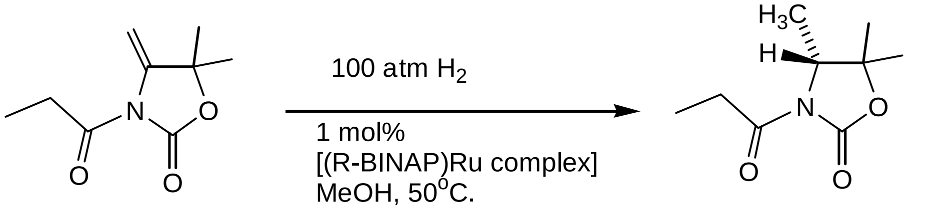
Reduction reactions of Double bonds using catalysts derived from Ru(II) (C=C):

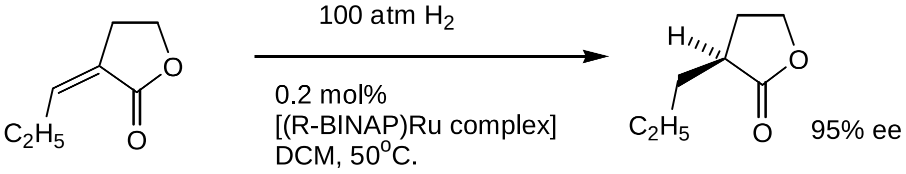
Directing groups on the substrate help to improve rates and enantioselectivity:
(BINAP or similar biaryl ligands are generally favoured)



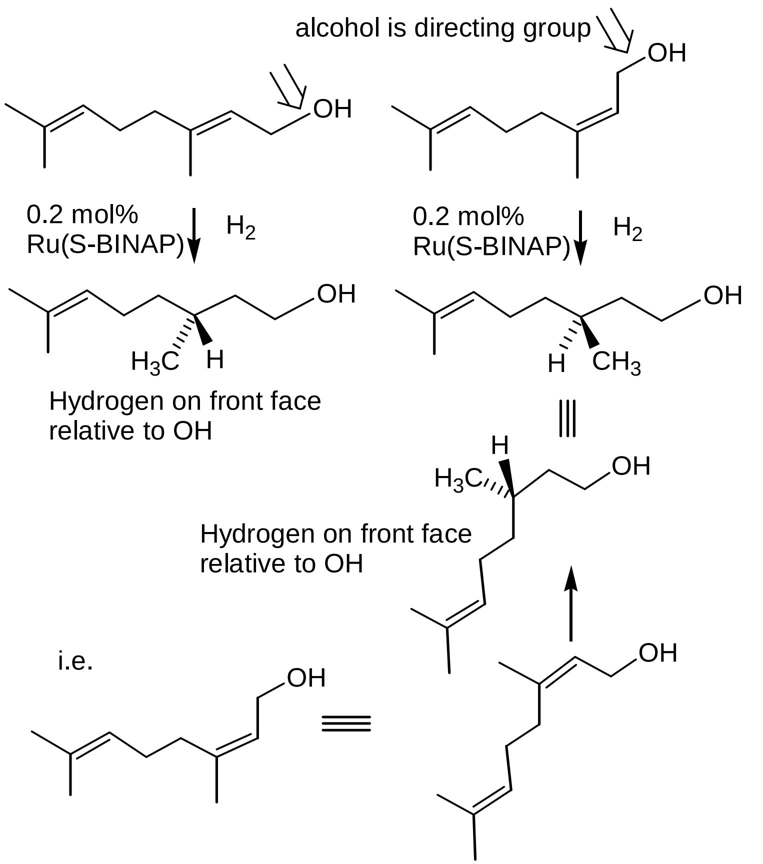








Allyliic alcohols provide a good example of how the directing group works.

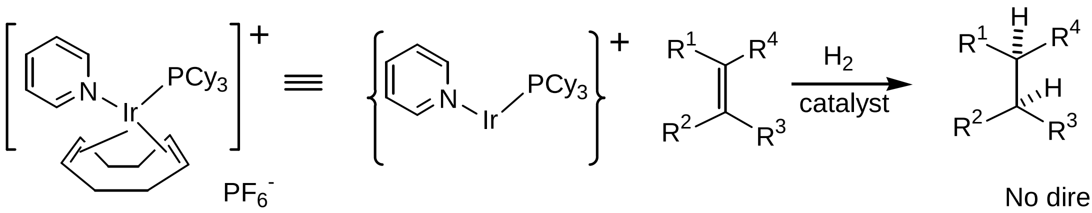


Hydrogen on front face relative to OH

Hydrogen on front face relative to OH

Reduction reactions of isolated C=C double bonds can be achieved with variants of Crabtree's catalyst:

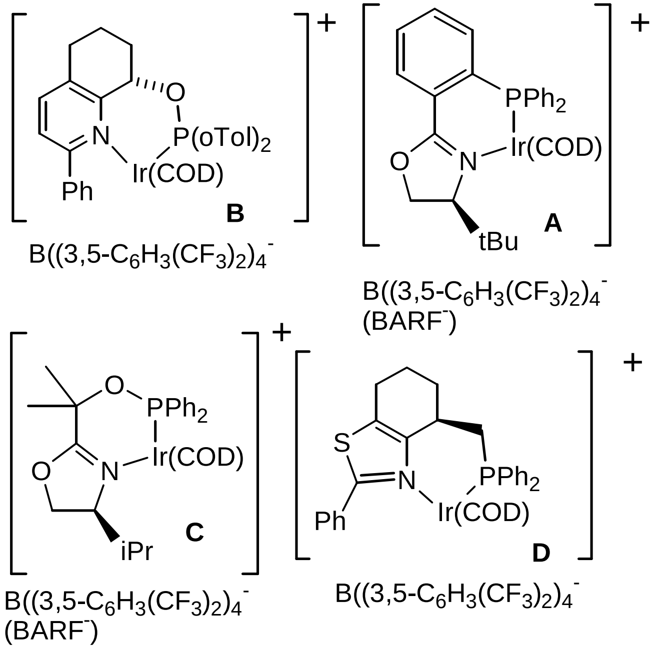
Crabtree's catalyst works well on isolated (i.e. no nearby co-ordinating group) C=C, bonds:

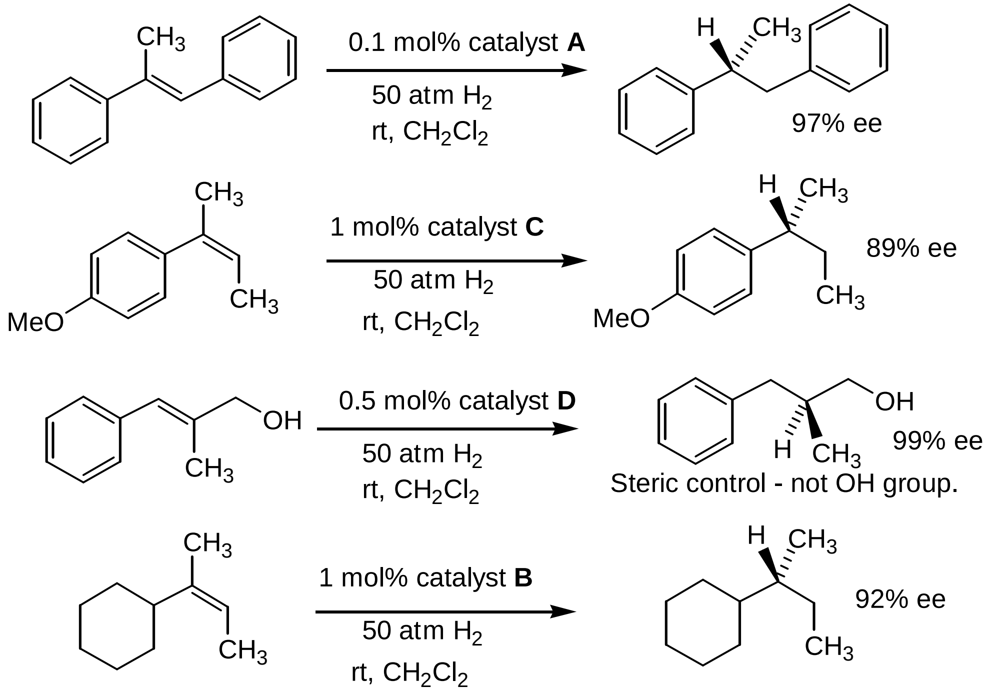


The catalyst is prepared with a cycloactadiene (COD) ligand but this is hydrogenated at the start of the catalytic cycle. The 'parent' Crabtree catalyst is, of course, non-chiral.

No directing group required

Asymmetric versions of the Crabtree catalyst (prepared as COD complexes, but with the COD left off for clarity):

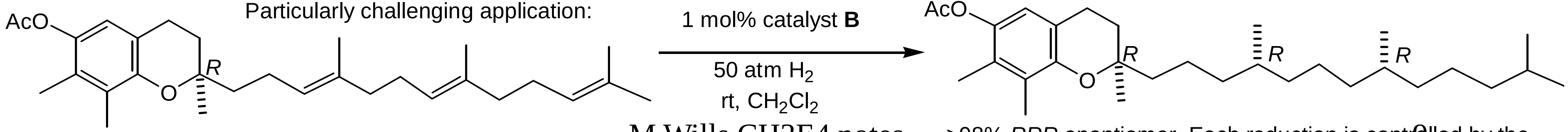




Steric control - not OH group.

Particularly challenging application:

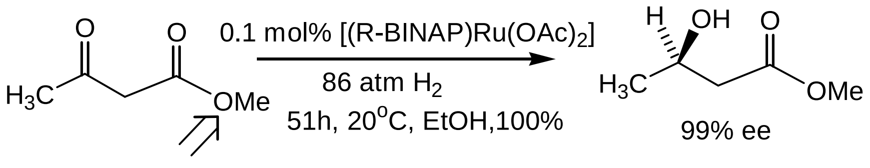
Vitamin E precursor

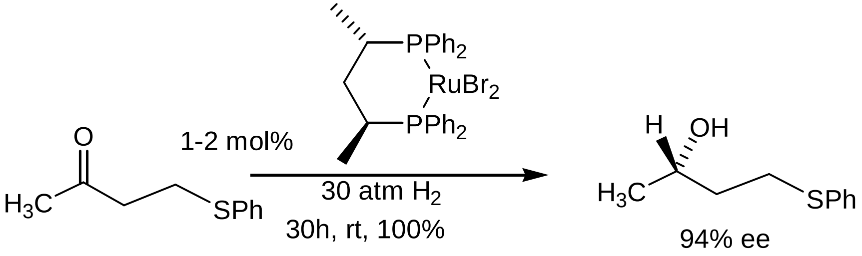


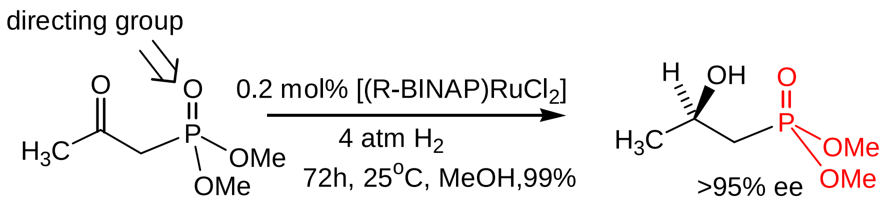
>98% *RRR* enantiomer. Each reduction is controlled by the catalyst i.e. it is not diastereocontrol.

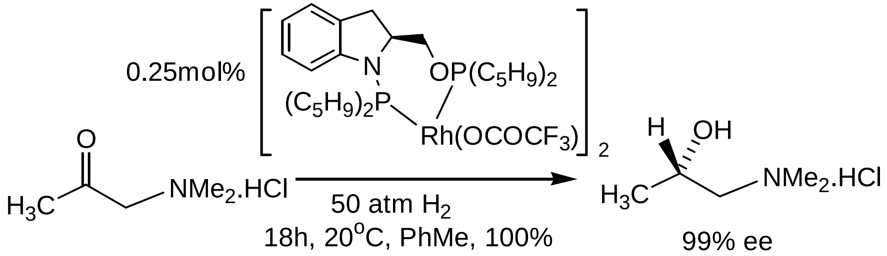
Reduction reactions of C=O Double bonds using organometallic complexes:

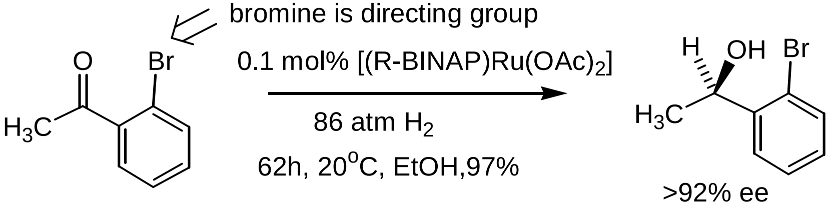
The same principle regarding directing groups also applies to C=O reduction, Ru and Rh are most commonly used:

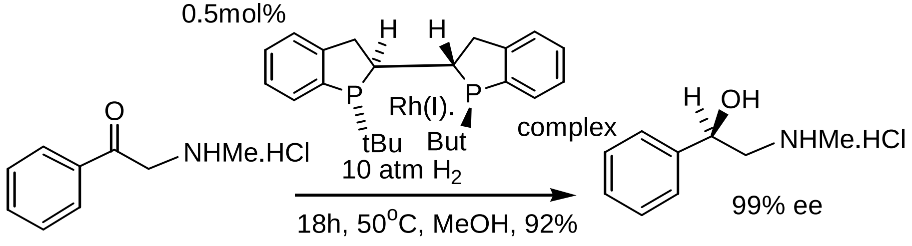








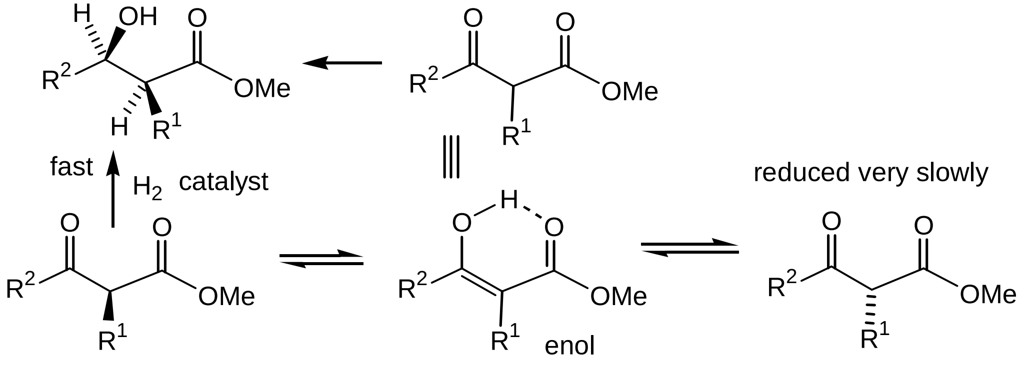


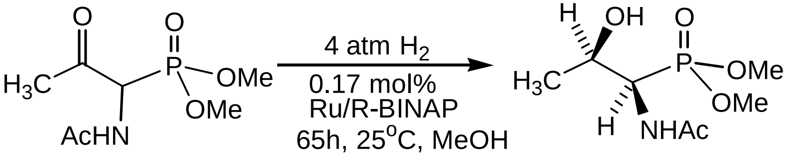


Reduction reactions of C=O Double bonds using organometallic complexes:

Dynamic kinetic resolution can result in formation of two chiral centres:

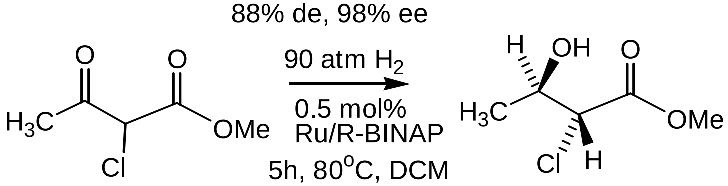
Principle: The substrate is rapidly racemising and one enantiomer is selectively reduced:



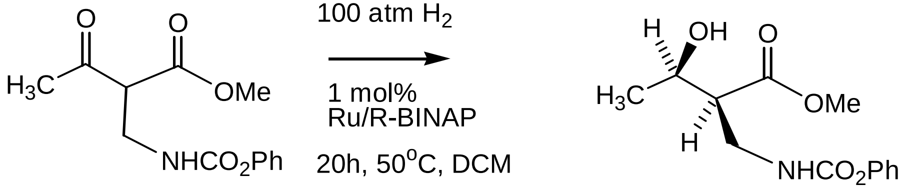


94% de
>98% ee

e.g.

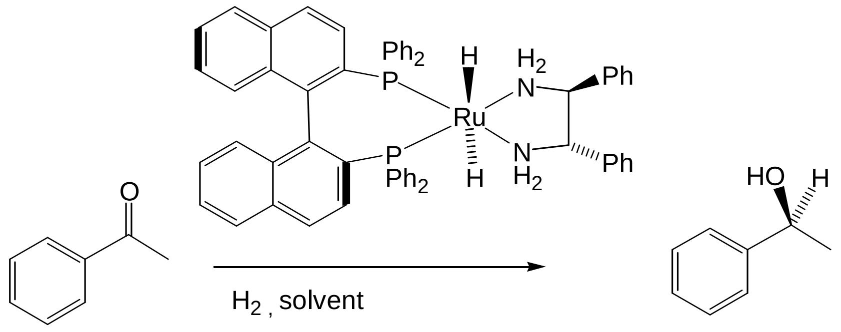


98% de
99% ee



88% de
98% ee

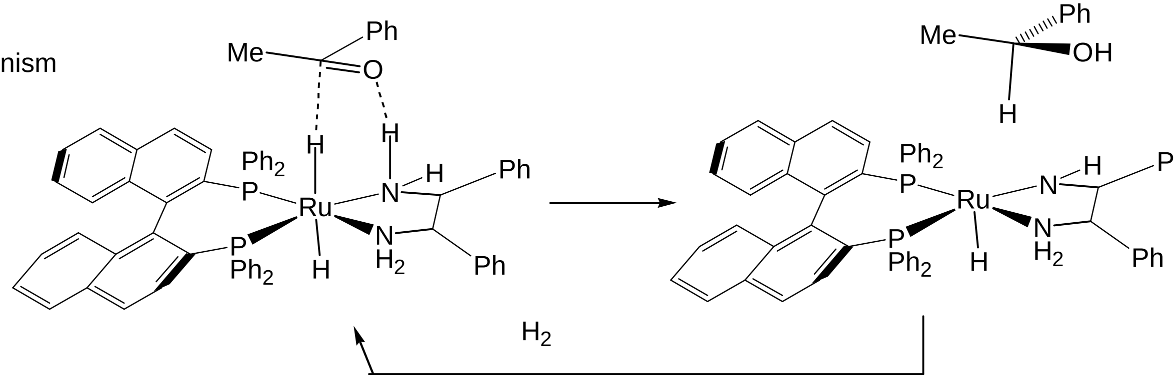
Ketone reduction by pressure hydrogenation (I.e. hydrogen gas) can be achieved using a modified catalyst containing a diamine, which changes the mechanism.

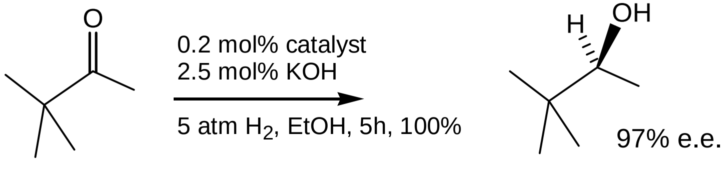


H_2 , solvent

Very high e.e.
from very low
catalyst loadings

Mechanism

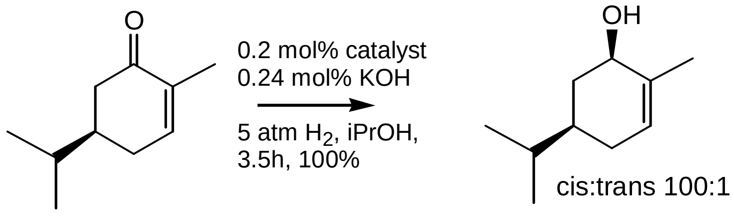




0.2 mol% catalyst
2.5 mol% KOH

5 atm H_2, EtOH, 5h, 100%

97% e.e.

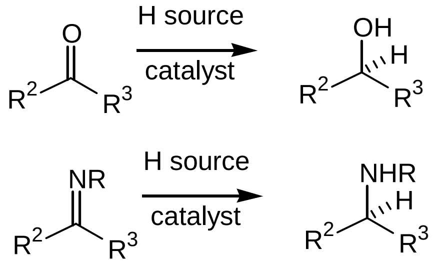


0.2 mol% catalyst
0.24 mol% KOH

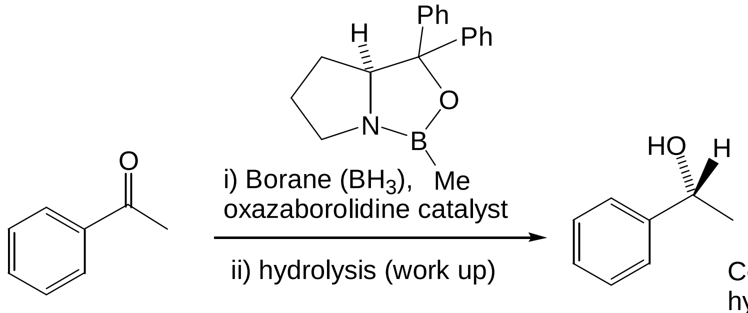
5 atm H_2, iPrOH,
3.5h, 100%

cis:trans 100:1

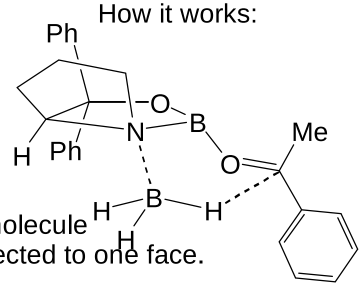
The use of hydride type reagents:



Oxazaborolidines require a relatively high catalyst loading of 10%, But are effective in several applications.



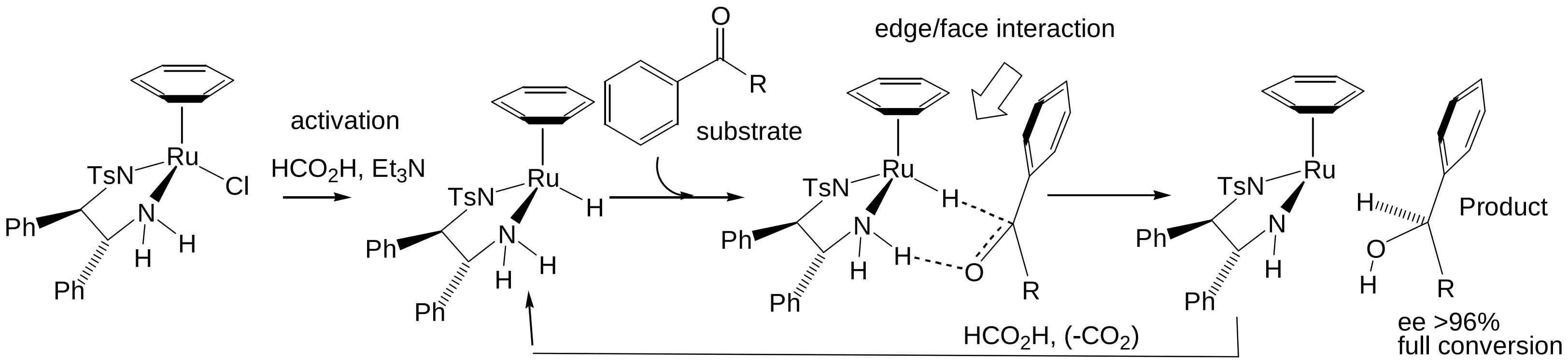
How it works:



Concave molecule hydride directed to one face.

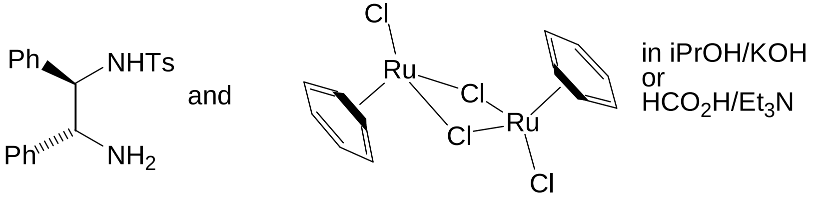
More contemporary focus is on asymmetric transfer hydrogenation and on organocatalysis.

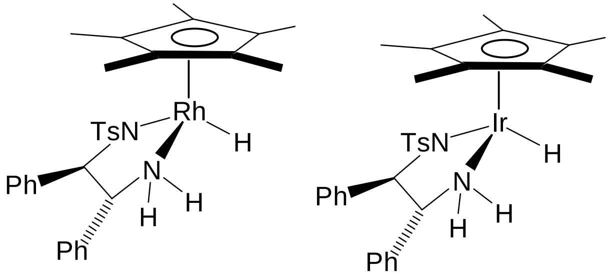
Transfer hydrogenation – Ru catalysts.



ee >96%
full conversion

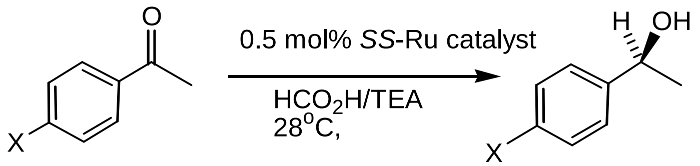
Catalyst prepared by combining:





Rhodium and iridium complexes are isoeletronic with Cp' on metal in place of arene.

Examples of reductions using transfer hydrogenation with metal complexes: add C=O and C=N reductions.

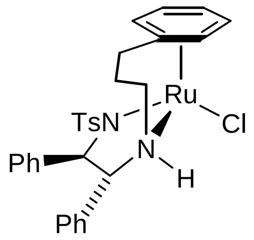


0.5 mol% *SS*-Ru catalyst

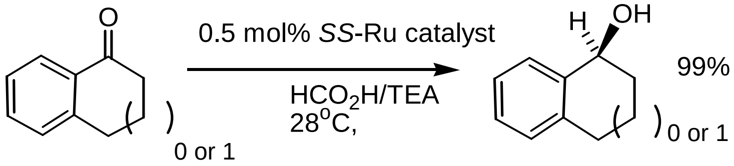
HCO$_2$H/TEA
28^{o}C,

X=H, 98% ee
X=Cl, 95% ee
X=OMe 96% ee

A wide range of substituents can be tolerated, except for ortho-groups, which result in reduced selectivities.



Improved catalyst with a link between amine and arene ring.
Following reactions are with this catalyst.

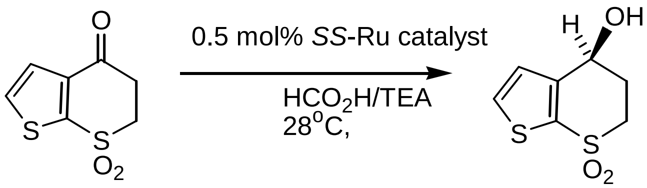


0.5 mol% *SS*-Ru catalyst

HCO$_2$H/TEA
28^{o}C,

99% ee

(i.e. fused five or six-membered ring)

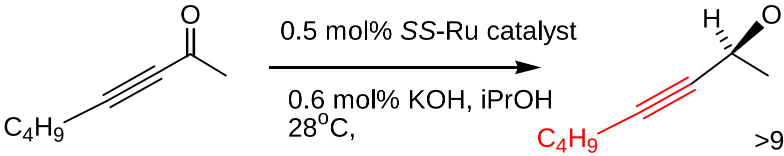


0.5 mol% *SS*-Ru catalyst

HCO$_2$H/TEA
28^{o}C,

98% ee

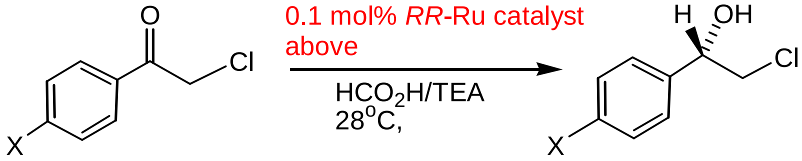
Precursor to jknown drug



0.5 mol% *SS*-Ru catalyst

0.6 mol% KOH, iPrOH
28^{o}C,

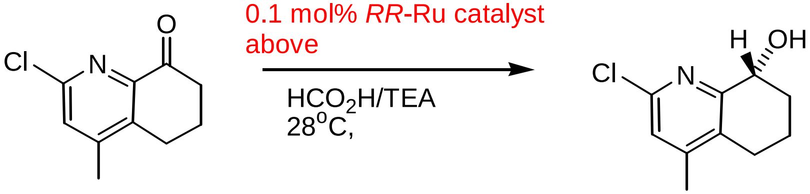
>99% ee



0.1 mol% *RR*-Ru catalyst above

HCO$_2$H/TEA
28^{o}C,

X=H, Cl, OMe
typically 96% ee

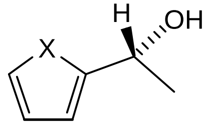


0.1 mol% *RR*-Ru catalyst above

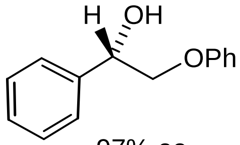
HCO$_2$H/TEA
28^{o}C,

up to 97% ee

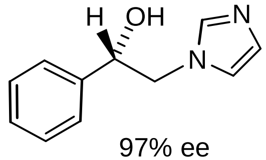
Other reduction products:



98% ee X=O
97% ee X=S

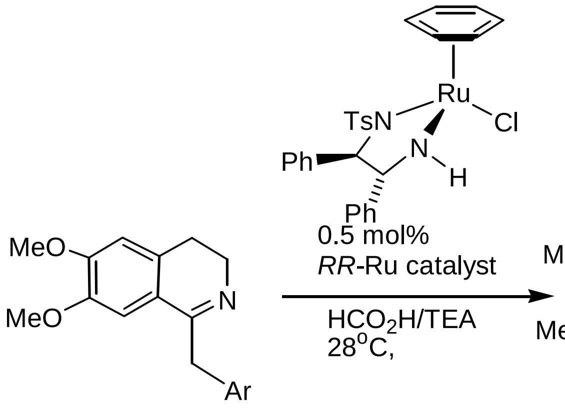


97% ee



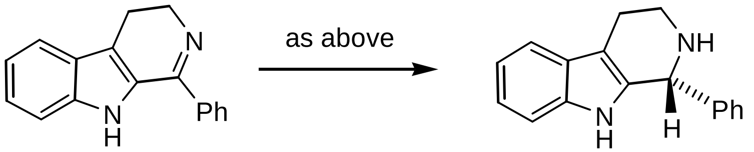
97% ee

Some imines can also be reduced by asymmetric transfer hydrogenation:



0.5 mol%
RR-Ru catalyst

HCO_2H/TEA
28^{o}C,

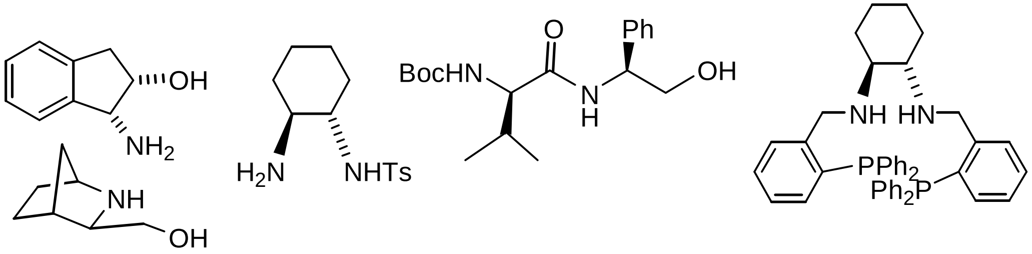


as above

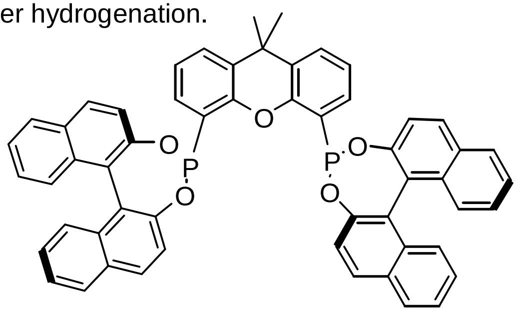
Typically >96% ee

Typically >98% ee

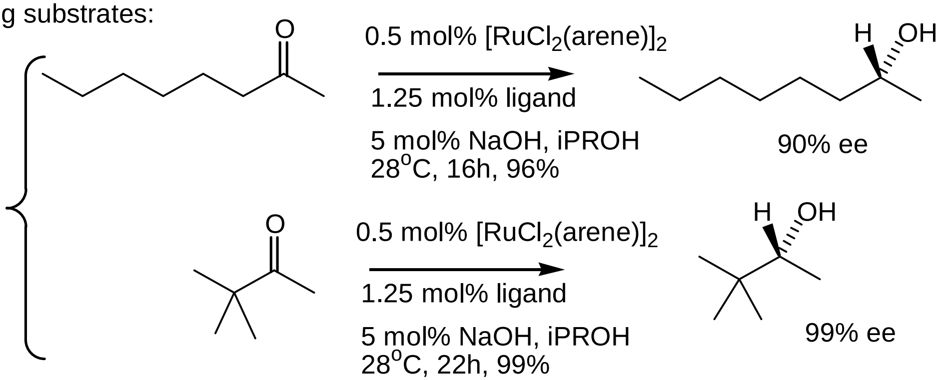
Other ligands can be used with ruthenium(II)
in asymmetric catalysis (and also with Rh and Ir), e.g.



Excellent ligand for
transfer hydrogenation.



Challenging substrates:



0.5 mol% [RuCl$_2$(arene)]$_2$

1.25 mol% ligand

5 mol% NaOH, iPROH
28^{o}C, 16h, 96%

90% ee

0.5 mol% [RuCl$_2$(arene)]$_2$

1.25 mol% ligand

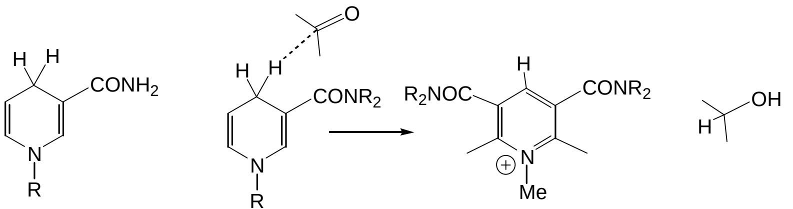
5 mol% NaOH, iPROH
28^{o}C, 22h, 99%

99% ee

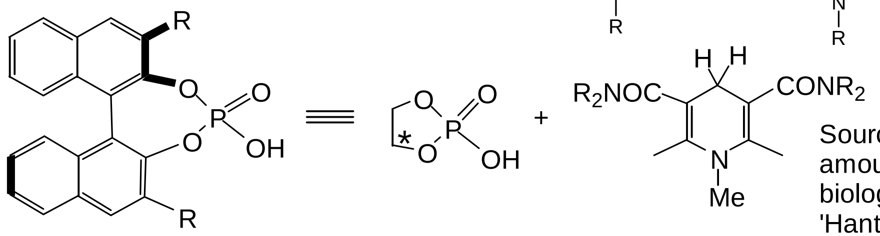
Asymmetric transfer hydrogenation by organocatalysis:

Use combination of a chiral acid with a hydride source:

Inspired by Nature's NADH;
a coenzyme which transfers hydride



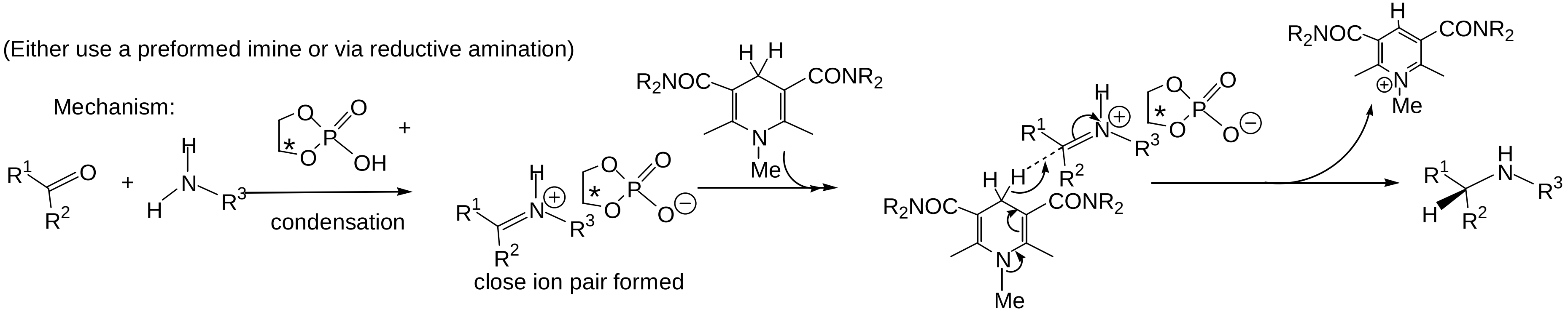
Homochiral acid (directs reaction)
R=aryl ring, trialkylsilyl etc., usually a bulky group. Catalytic amount needed.



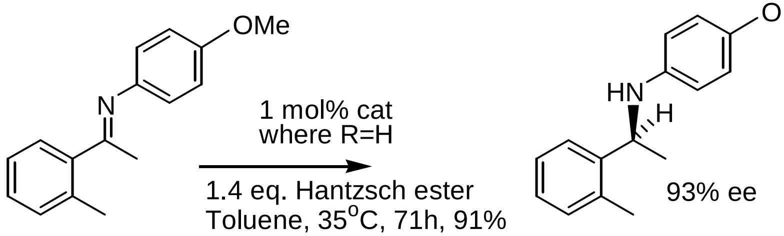
Source of hydride - stoichiometric amount needed. Similar to NADH used in biological transformations. Known as 'Hantzsch ester'.

(Either use a preformed imine or via reductive amination)

Mechanism:

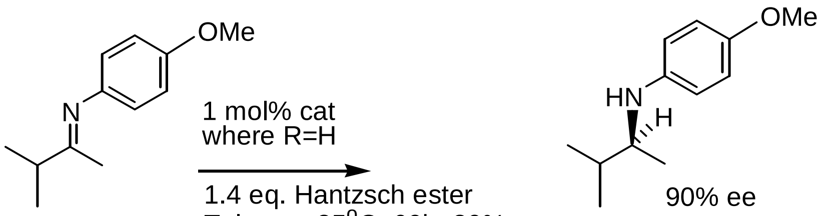


Some examples of reductions:



1 mol% cat
where R=H

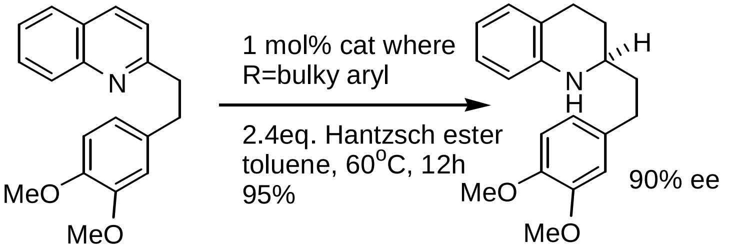
1.4 eq. Hantzsch ester
Toluene, 35^{o}C, 71h, 91%



1 mol% cat
where R=H

1.4 eq. Hantzsch ester
Toluene, 35^{o}C, 60h, 80%

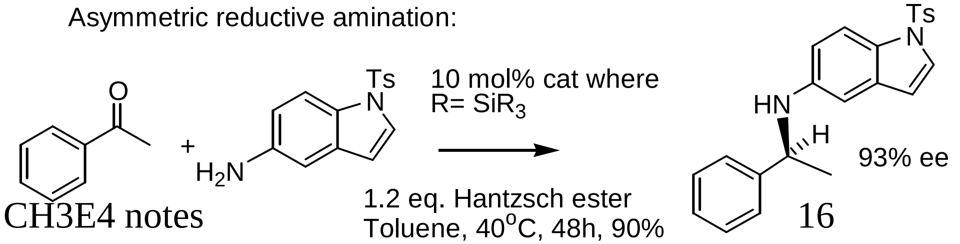
fully heteroaromatic rings can be reduced:



1 mol% cat where
R=bulky aryl

2.4eq. Hantzsch ester
toluene, 60^{o}C, 12h
95%

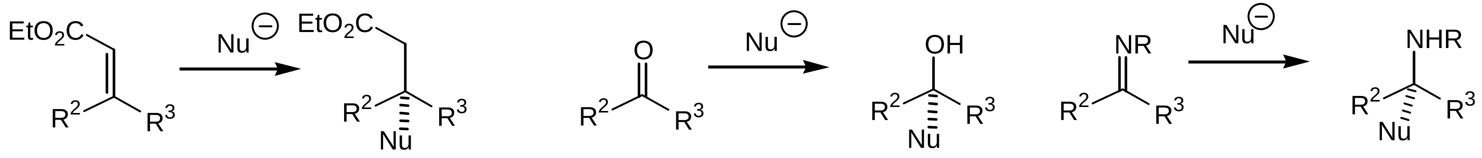
Asymmetric reductive amination:

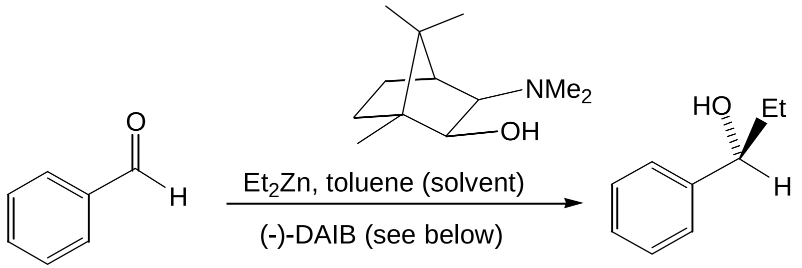


10 mol% cat where
R= SiR_3

1.2 eq. Hantzsch ester
Toluene, 40^{o}C, 48h, 90%
+ molecular seives

Formation of chiral centres by nucleophilic additions to unsaturated bonds.





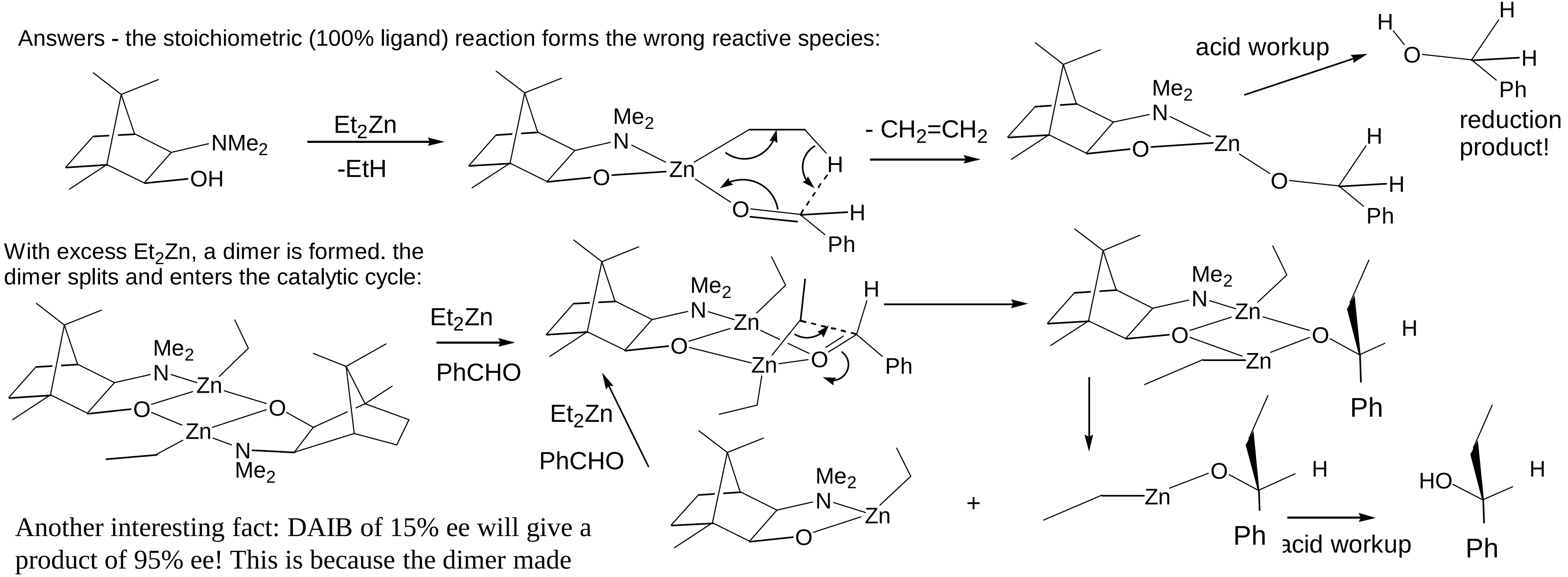
Results:

mol% DAIB used (relative to Et_2Zn	Yield	E.e.
0 (i.e. none)	0%	-
2 (0.02 eq.)	97%	98
100 (1.0 eq.)	0%	-

How come a little bit of amino alcohol catalyses the reaction, but a lot of it doesn't?

Answers - the stoichiometric (100% ligand) reaction forms the wrong reactive species:

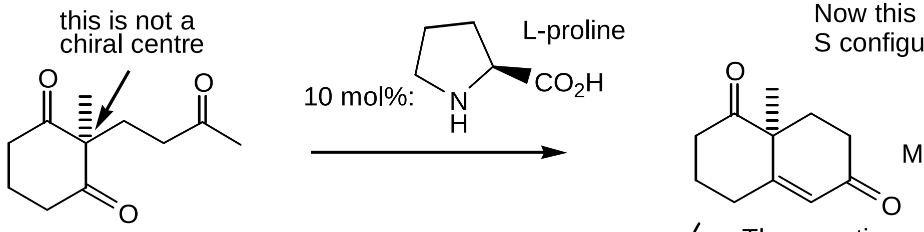
With excess Et_2Zn, a dimer is formed. the dimer splits and enters the catalytic cycle:



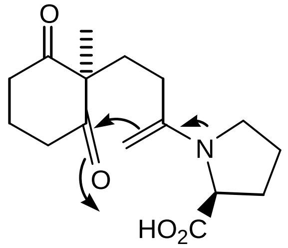
Another interesting fact: DAIB of 15% ee will give a product of 95% ee! This is because the dimer made from one of each enantiomer is more stable, and does not split up to enter the catalytic cycle.

More applications of organocatalysis

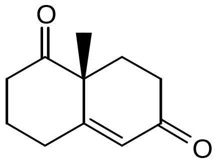
Some time ago, it was found that proline catalyses the asymmetric cyclisation of a diketone (known as the Robinson annelation reaction).



Mechanism is via:

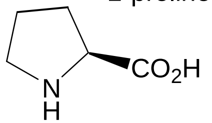


(The enantiomeric compound is:

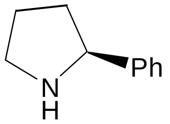

)

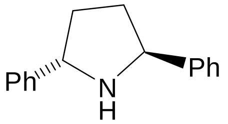
Examples of common organocatalysts:

L-proline

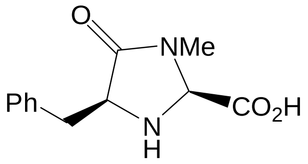


or pyrrolidines:



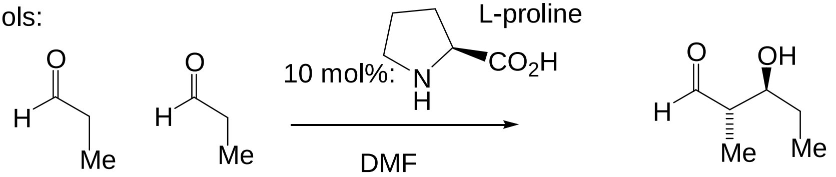


or other N-heterocycles:



This is now the basis for many other reactions e.g.:

Aldols:

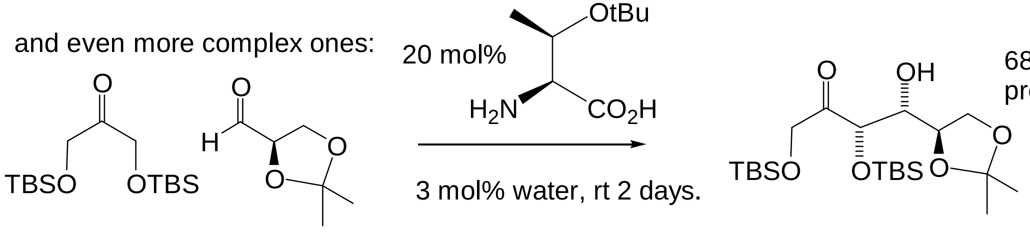


90% yield

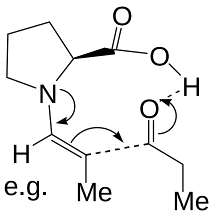
4:1 *anti:syn*

anti product e.e.: 99%

and even more complex ones:



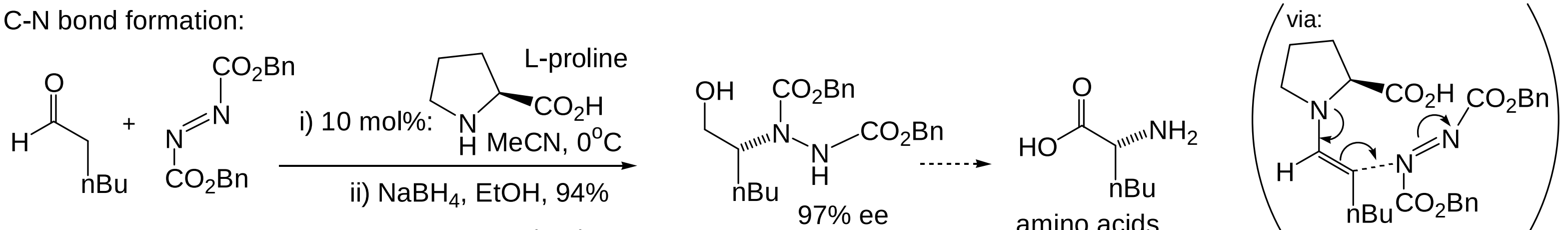
68%, major product: D-fructose precursor

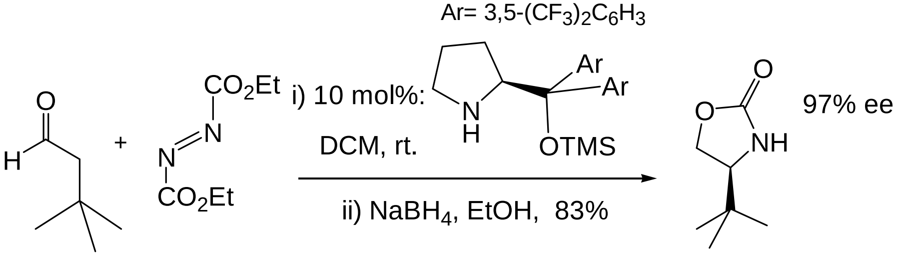


These reactions take place via formation of an enamine which then reacts with the other reagent e.g.

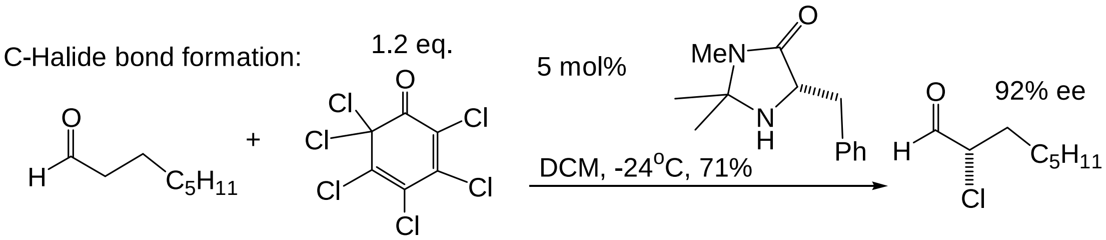
More applications of organocatalysis which proceed via formation of an enamine – bonds to C atoms:

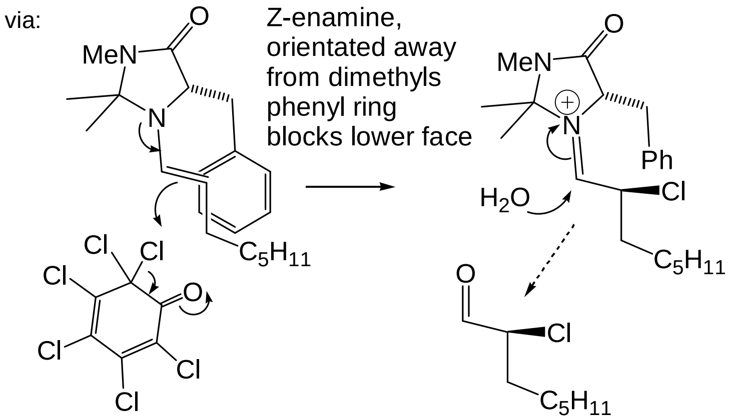
C-N bond formation:

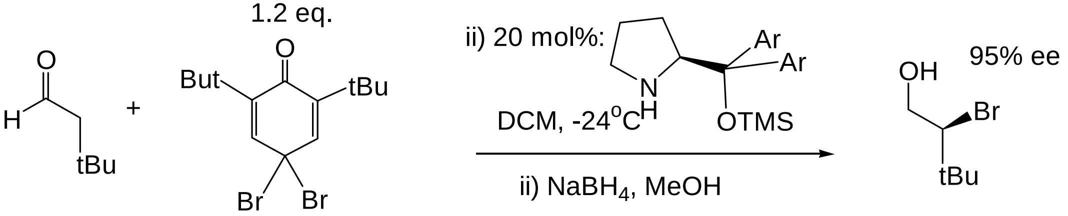




C-Halide bond formation:



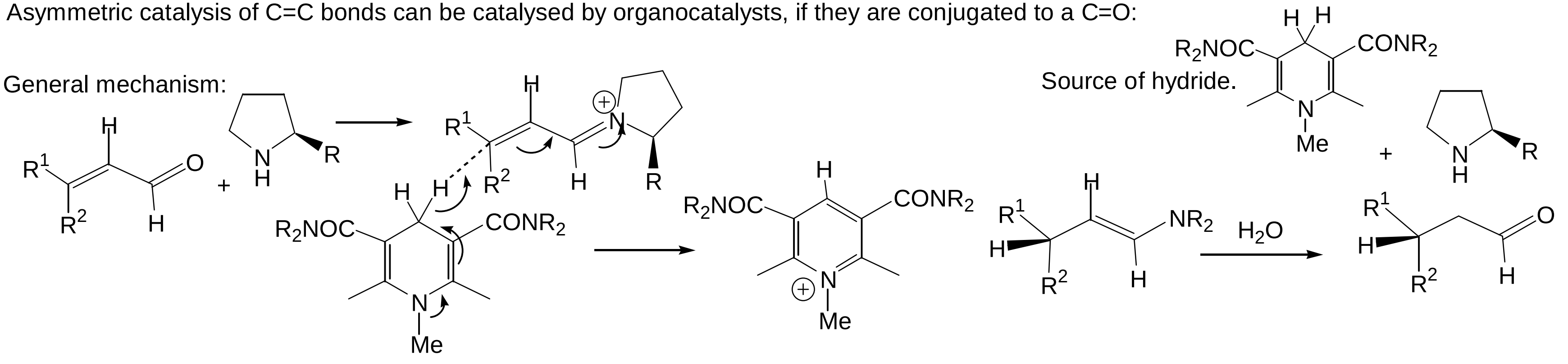




C=C reduction by organocatalysis:

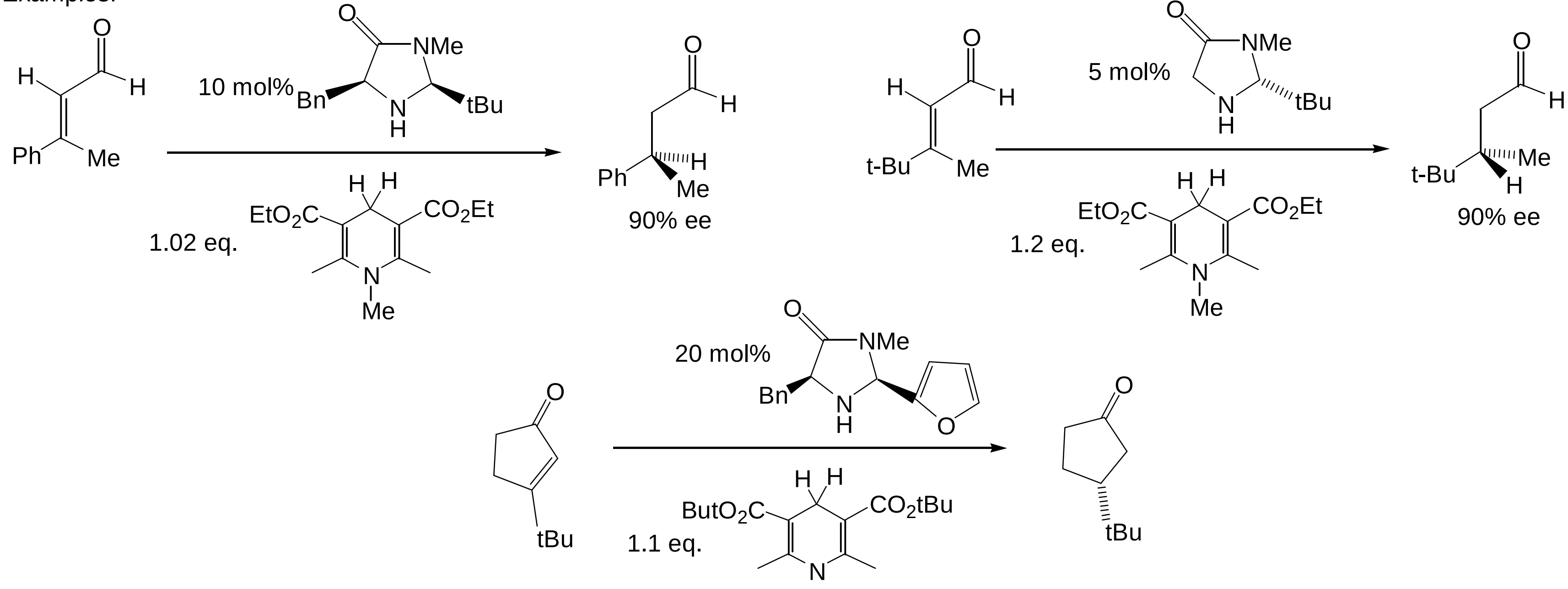
Asymmetric catalysis of C=C bonds can be catalysed by organocatalysts, if they are conjugated to a C=O:

General mechanism:



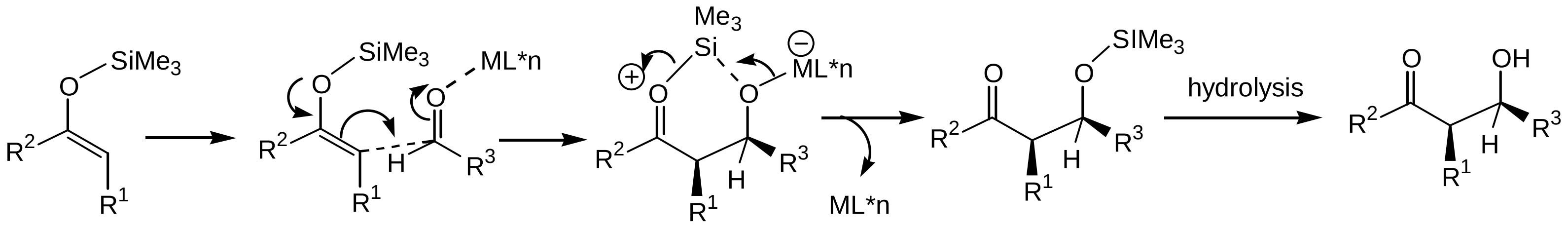
Source of hydride.

Examples:



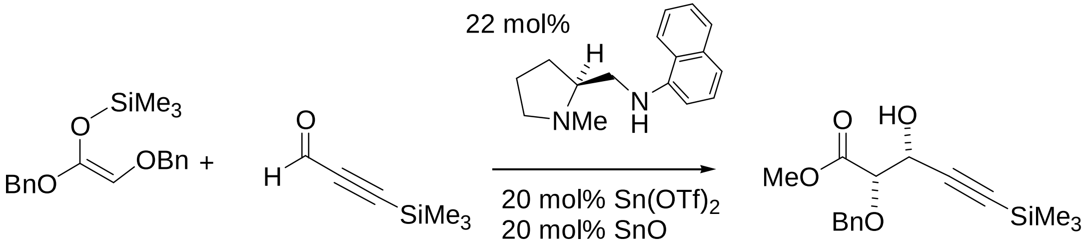
Additions to C=O – aldol reactions are a very important class of synthetic reaction.

Catalytic asymmetric aldol reactions can be directed by a chiral Lewis acid (ML*n), which initially binds to the electrophilic component the silyl enol ether is required as nucleophile (known as the 'Mukaiyama aldol' reaction:



Silyl enol ether

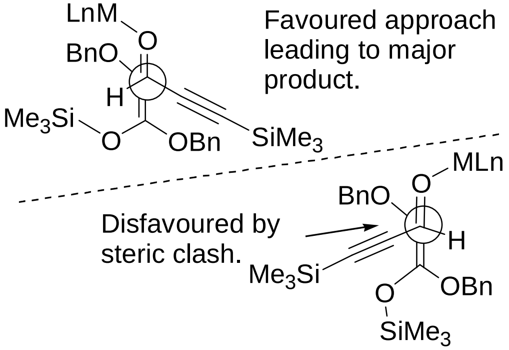
Open transitions states operate in this case, rather than chair-like cyclic ones:



22 mol%

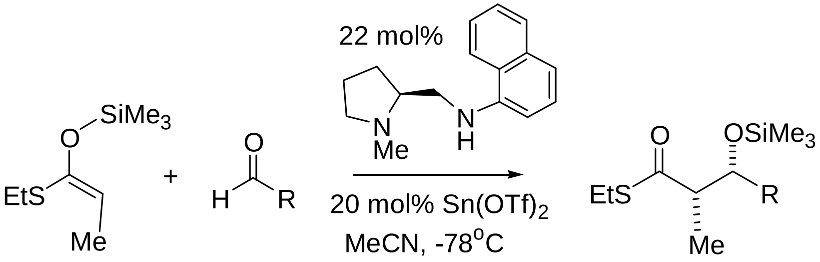
20 mol% $Sn(OTf)_2$
20 mol% SnO
MeCN, -78^{o}C

97:3 syn:anti, 91% ee.



Favoured approach leading to major product.

Disfavoured by steric clash.



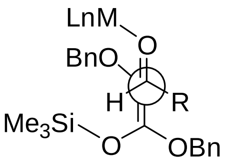
22 mol%

20 mol% $Sn(OTf)_2$
MeCN, -78^{o}C

R=Ph, 93:7 syn:anti, 90% ee (syn)

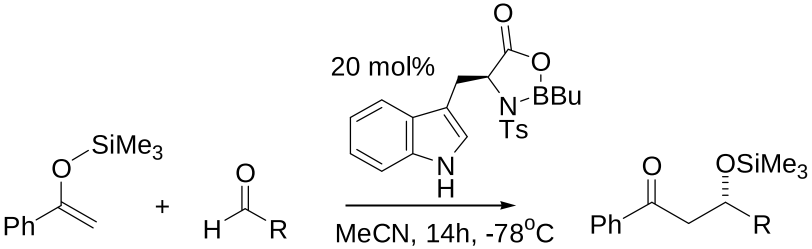
R=nC_7H_{15}, 100:0 syn:anti >98% ee

Open transitions states operates again in this case and ligand determines overall face selectivity:



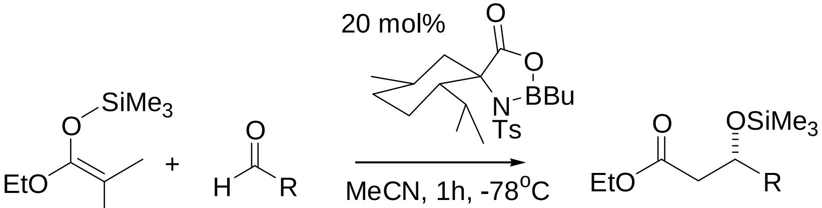
Favoured approach leading to major product.

Other examples of metal/ligand-catalysed asymmetric aldol reactions:

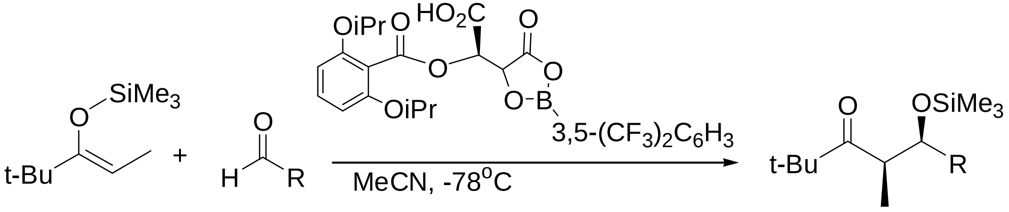


R=Ph, 89% ee
R=nC_6H_{13}, 93% ee

No relative stereocontrol in this case, just absolute- by the catalyst.

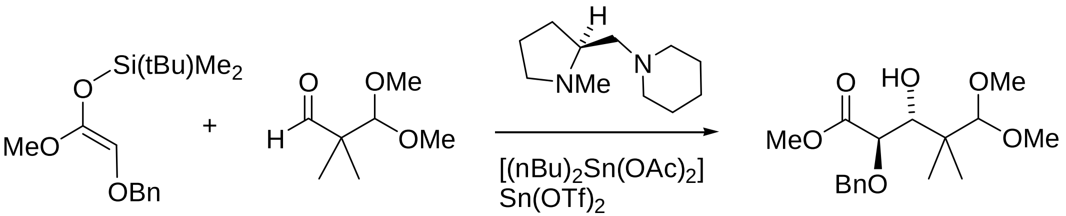


91-99% ee



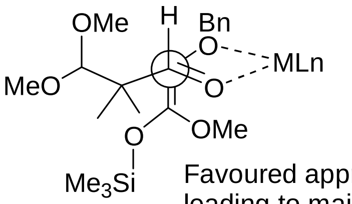
93:7 syn:anti, 94% ee

Although in some cases, the relative stereochemistry can be changed by a different combination of reagents:



major product, 87% ee.

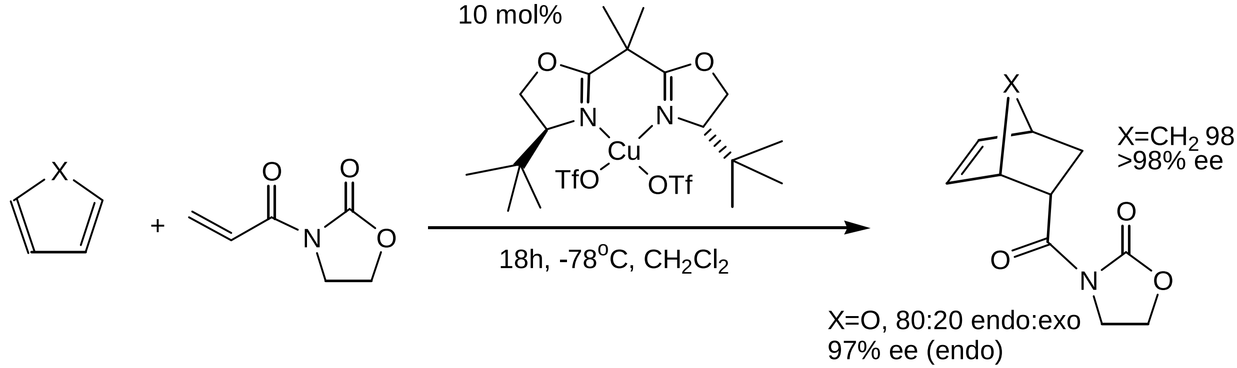
Mukaiyama, *Chem. Eur. J.* 1999, **5**, 121-161



Favoured approach leading to major product.

Cycloaddition reactions can be catalysed by Lewis acid/chiral ligands:

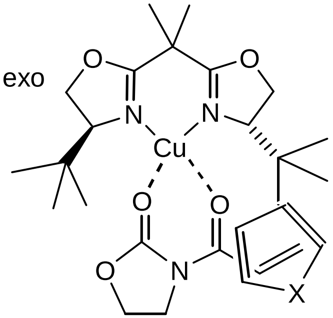
The ligand and metal choice can have a dramatic effect:

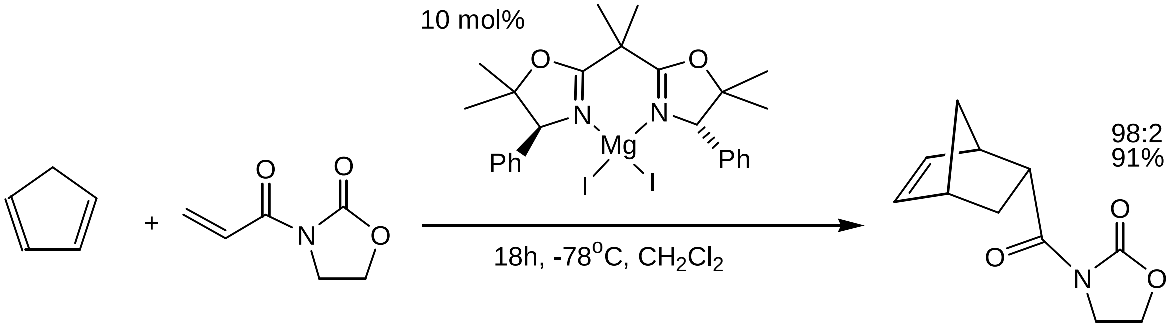


$X=CH_2$ 98:2 endo:exo
>98% ee

X=O, 80:20 endo:exo
97% ee (endo)

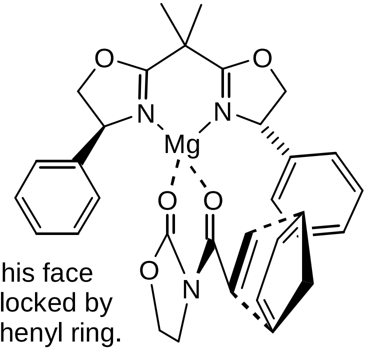
Cu complex thought to be square planar
tBu blocks lower face, Cp adds from other side



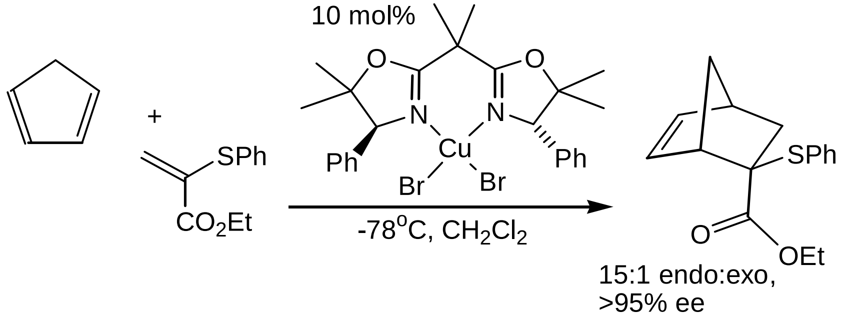


98:2 endo:exo
91% ee

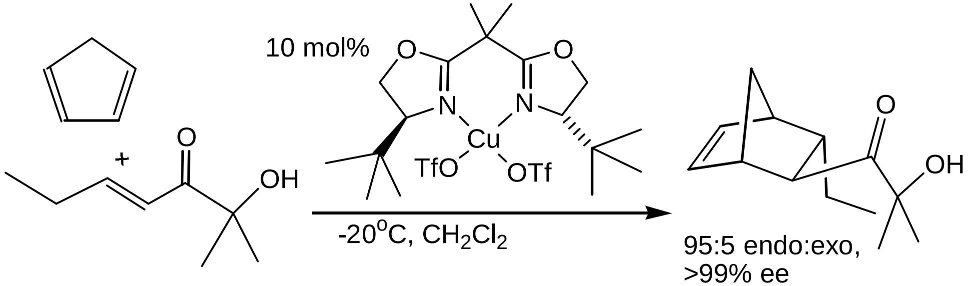
Mg complex thought to be tetrahedral,
Ph blocks lower face, Cp adds from other side



This face
blocked by
phenyl ring.



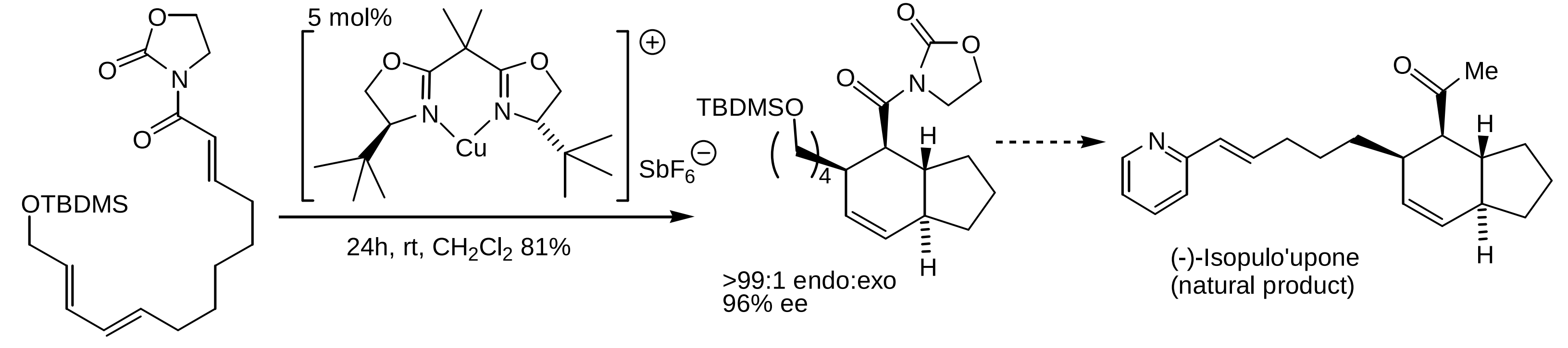
15:1 endo:exo,
>95% ee



95:5 endo:exo,
>99% ee

There are many other similar catalysts for Lewis-acid catalysed Diels-Alder reactions.

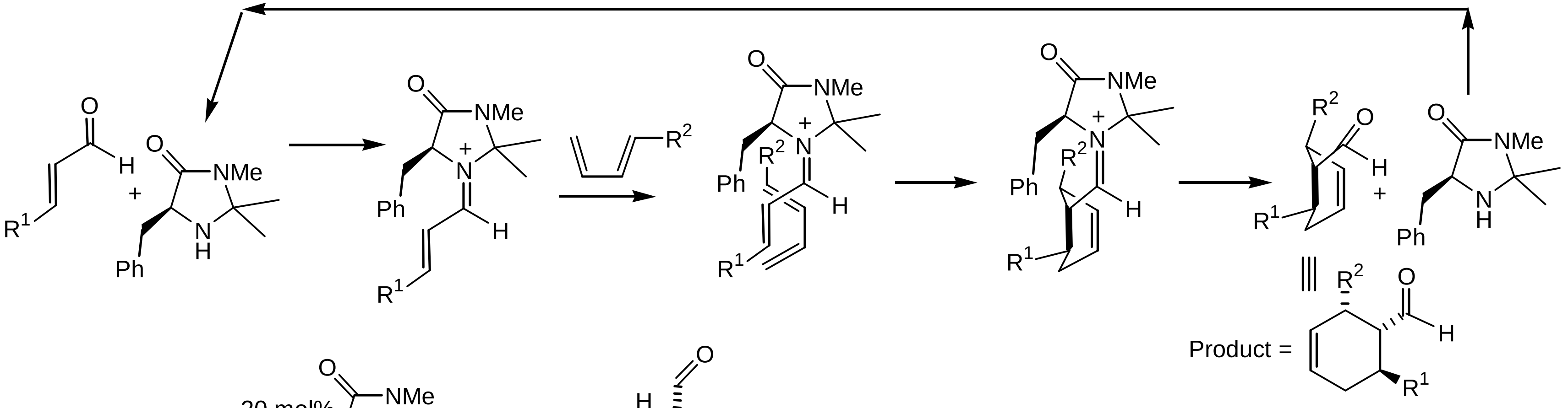
Intramolecular versions also work:

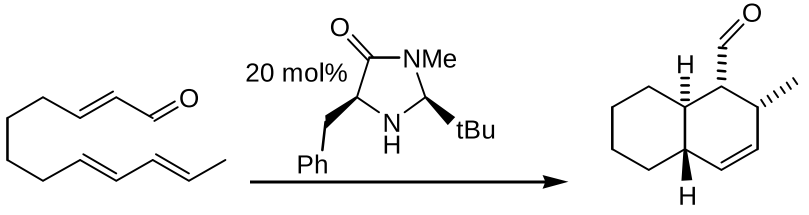


>99:1 endo:exo
96% ee

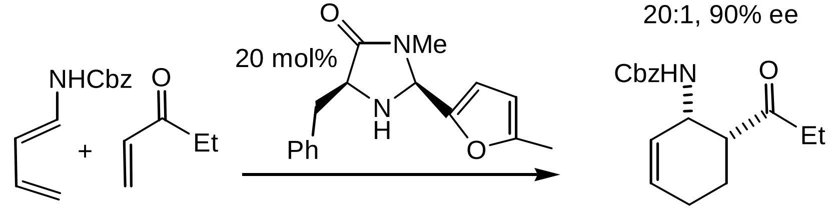
(-)-Isopulo'upone
(natural product)

Organocatalysts can be applied to Diels-Alder reactions, by forming a cationic intermediate:

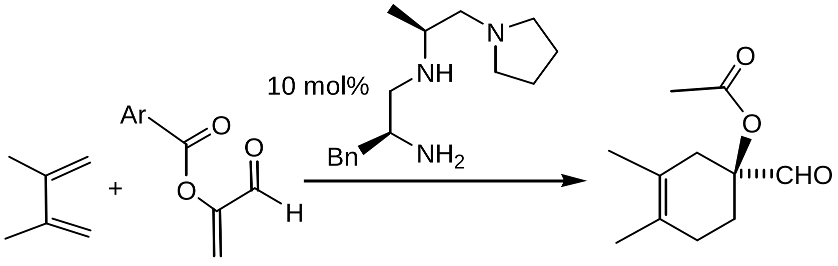




20:1, 90% ee

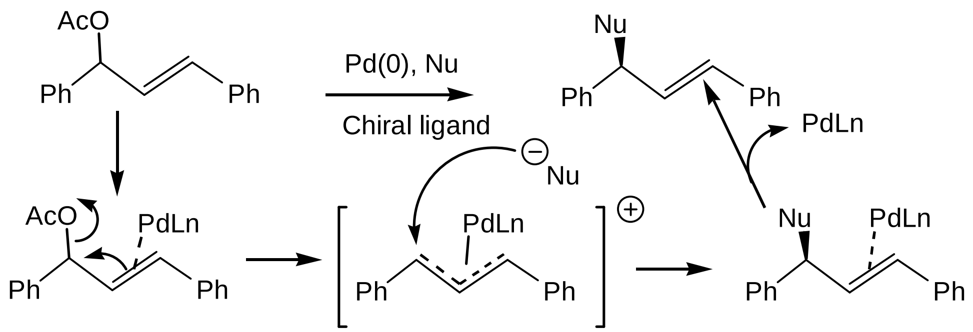


>100:1, 98% ee



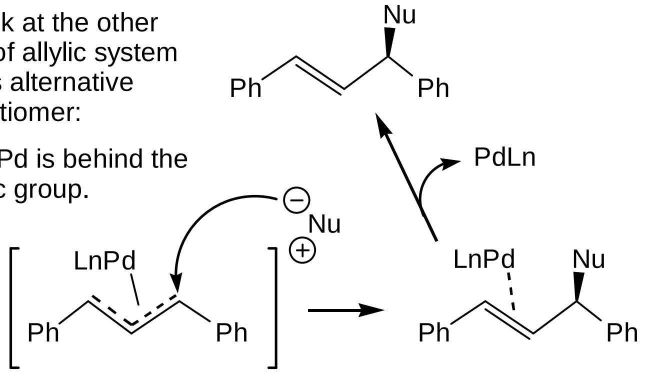
92% ee

Allylic substitution reactions are powerful methods for forming C-C bonds:

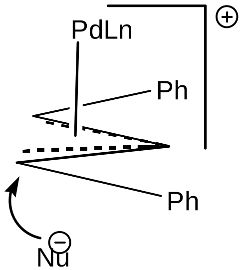


Attack at the other end of allylic system gives alternative enantiomer:

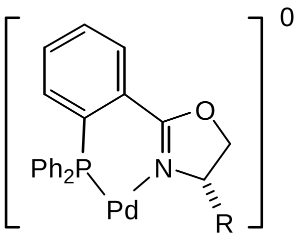
The Pd is behind the allylic group.

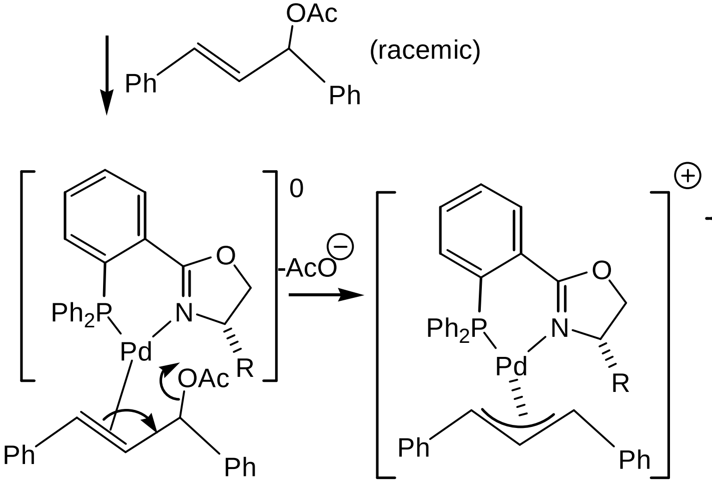


Nucleophile adds trans to PdLn group

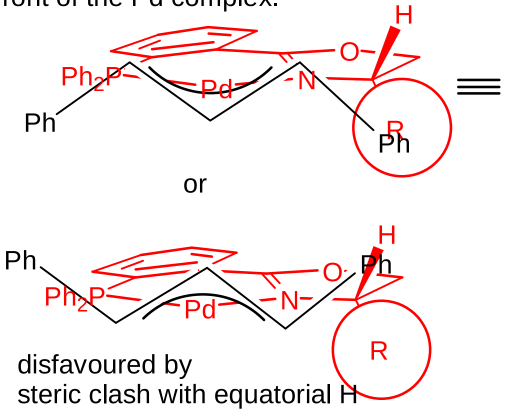


Example ligand:

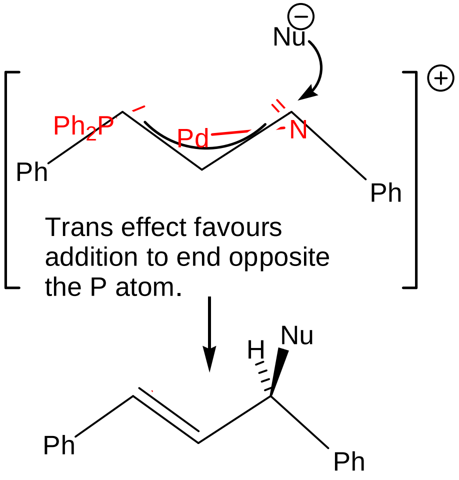




Favoured conformation: the allyl group is in front of the Pd complex.



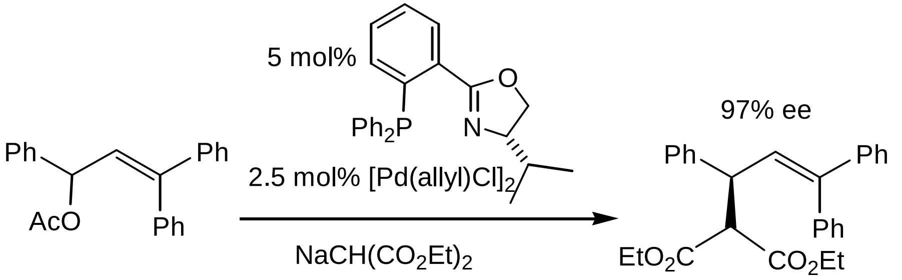
disfavoured by steric clash with equatorial H or slower to react.



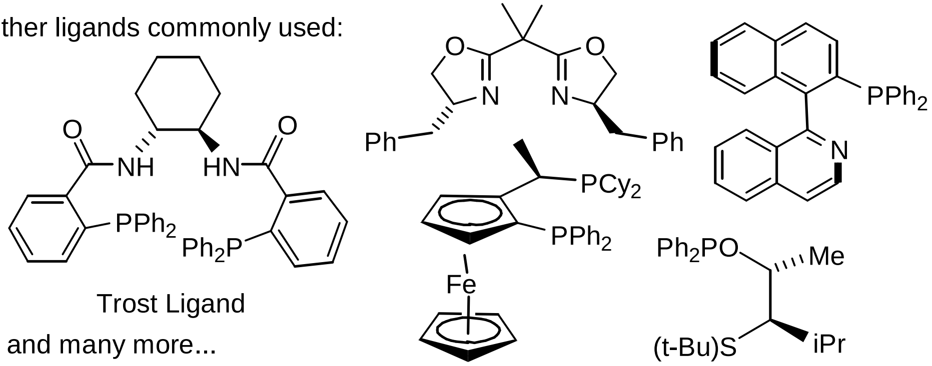
Trans effect favours addition to end opposite the P atom.

(enantiomerically enriched) and catalyst is released to re-enter cycle.

Allylic substitution reactions – examples of ligands and reactions:



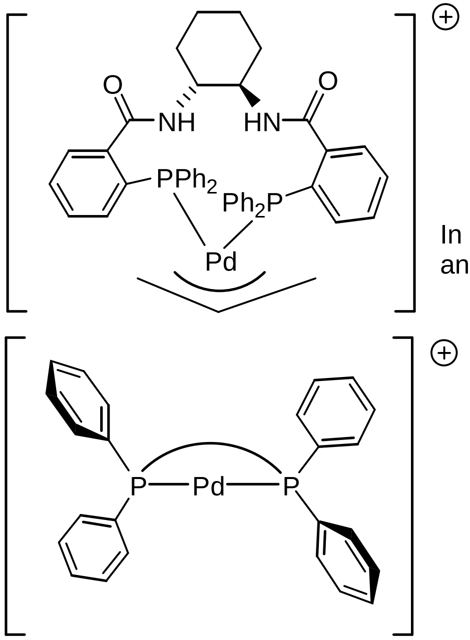
Other ligands commonly used:

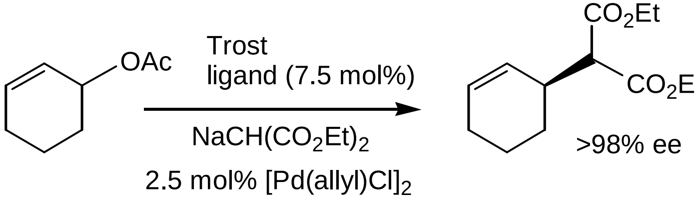


Trost Ligand

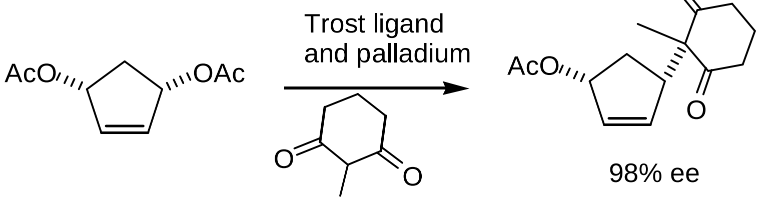
and many more...

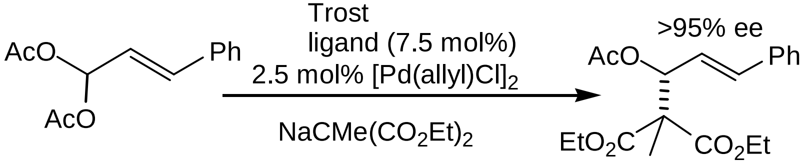
Trost ligand creates a chiral environment through the phenyl rings on the phosphines.

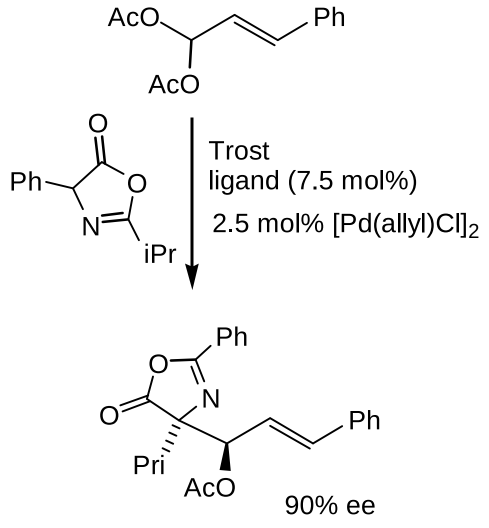




In this example (below) the catalyst displaces one OAc selectively, and also controls the regio and stereochemistry of the reaction.

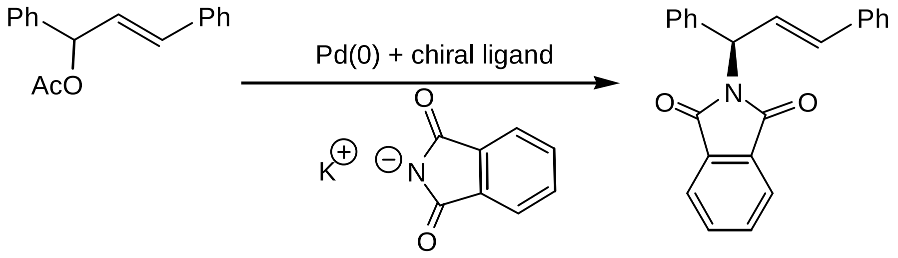


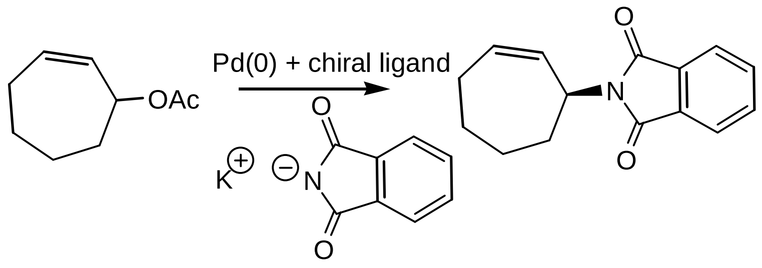


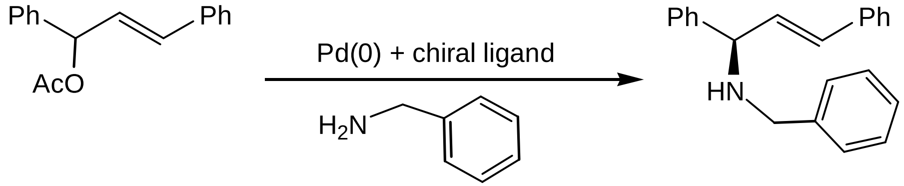


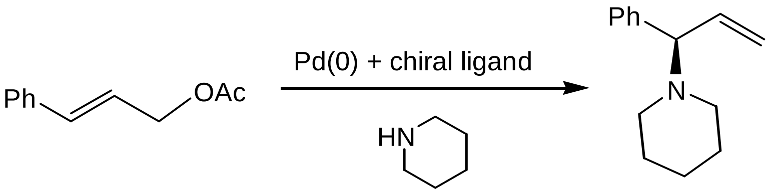
Allylic substitution reactions – examples of ligands and reactions:

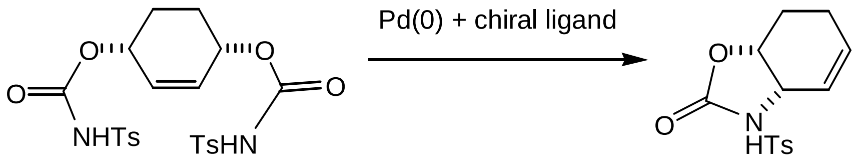
Other transformations which can be achieved by allylic substitution - soft nucleophiles generally favoured, otherwise the only limits are your own imagination...

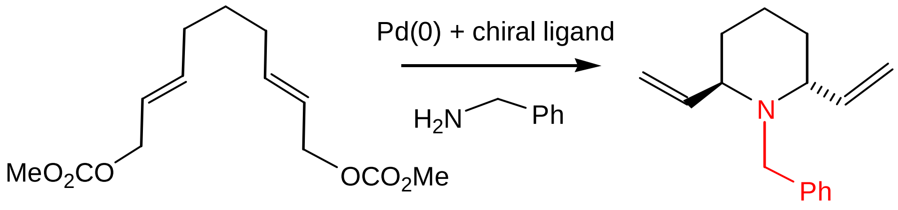






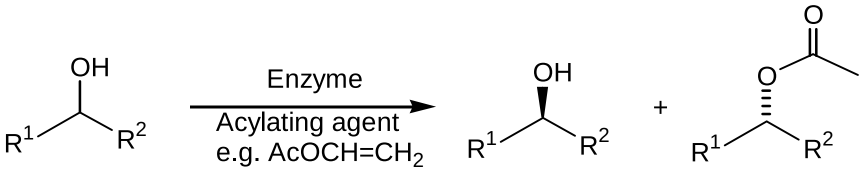






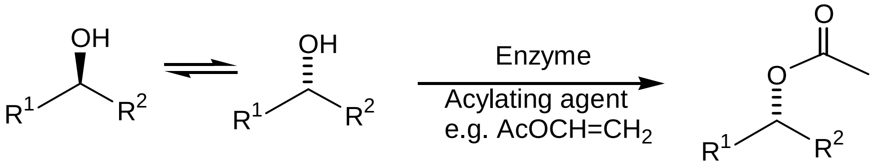
Uses of enzymes in asymmetric synthesis

this can
Invert an alcohol overall.



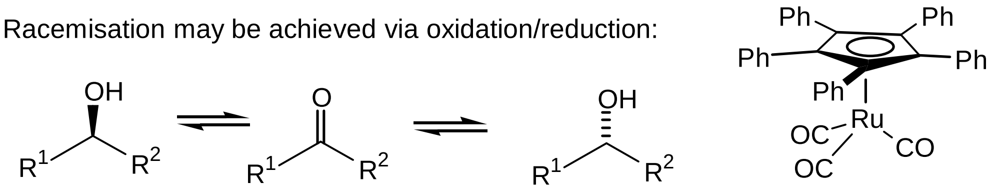
one enantiomer formed selectively 50% max yield.

Dynamic kinetic resolution can produce 100% yield.

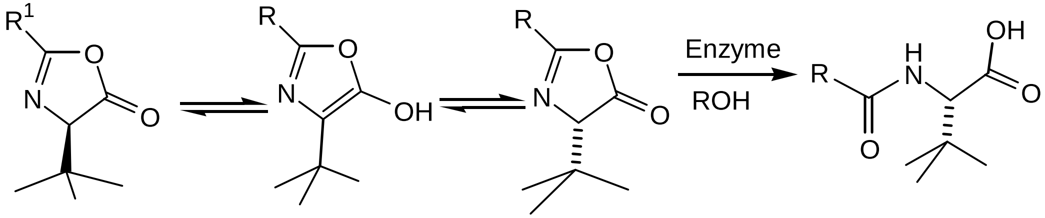


one enantiomer formed selectively 100% max yield.

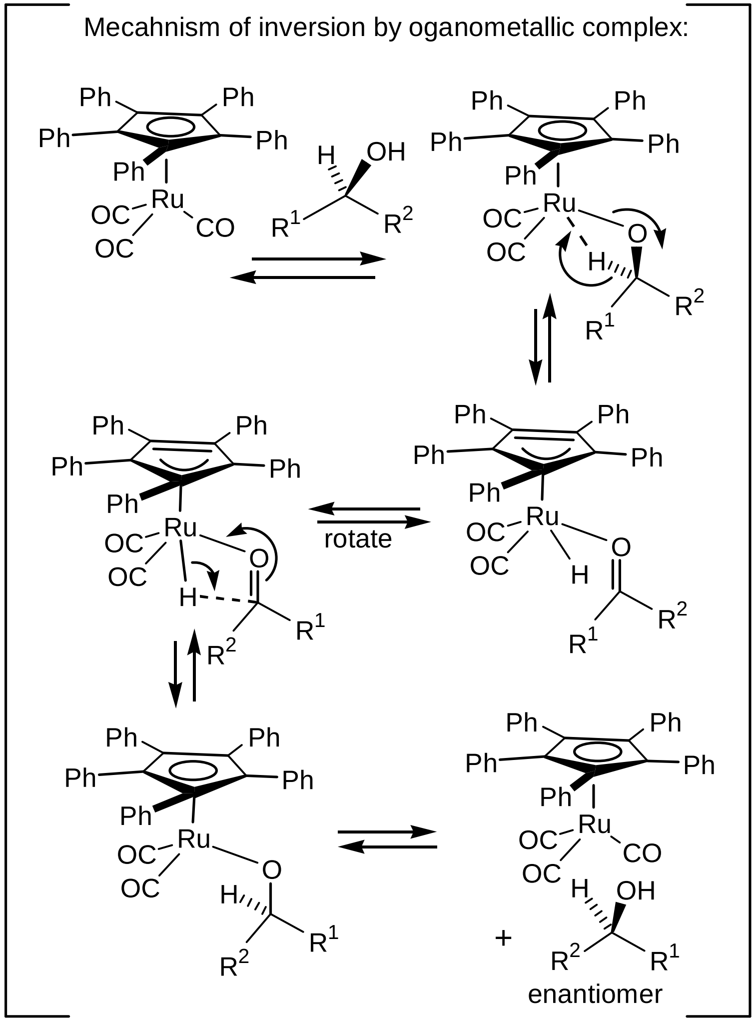
Racemisation may be achieved via oxidation/reduction:



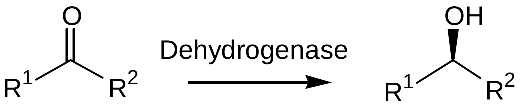
Selective ring opening of a heterocycle:



Mecahnism of inversion by oganometallic complex:

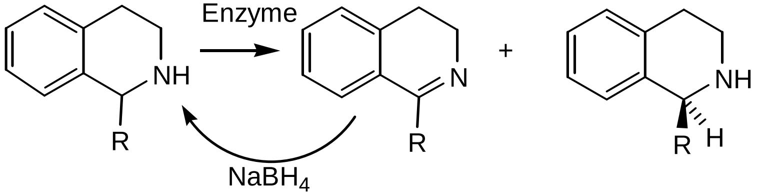


Uses of dehydrogenase enzymes in synthesis.

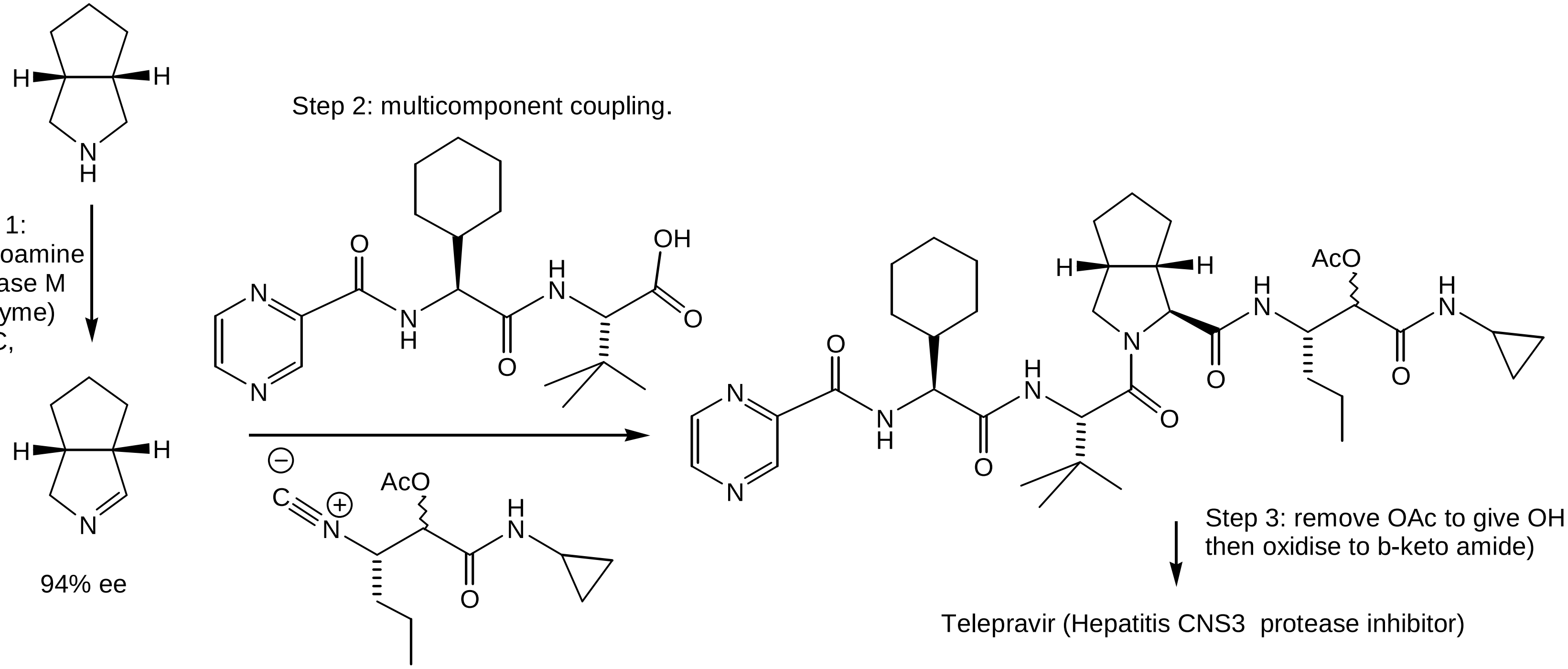


Enzymes can be 'evolved towards particular substrates - Reetz etc.

Amine 'deracemisation' using an enzyme.



Over several cycles, all in situ, almost complete conversion to product is achieved.



step 1: monoamine oxidase M (enzyme) 37^{o}C,

94% ee

Step 2: multicomponent coupling.

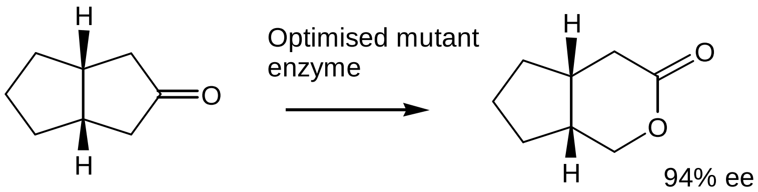
Step 3: remove OAc to give OH, then oxidise to b-keto amide)

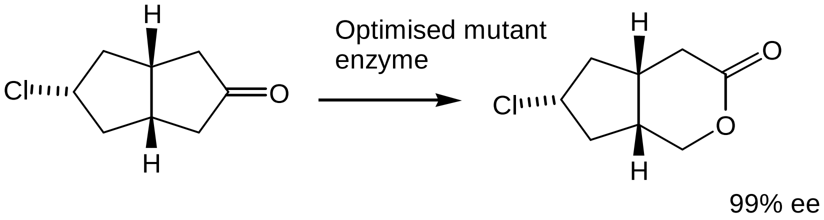
Telepravir (Hepatitis CNS3 protease inhibitor)

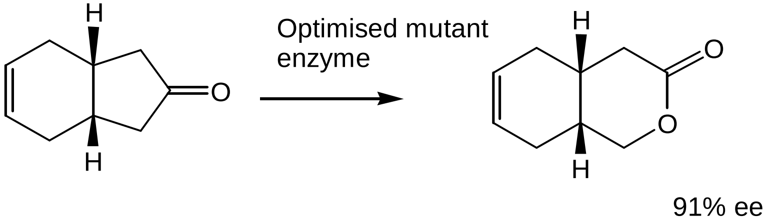
Enzyme catalysis: amine oxidation.
Chem. Commun. **2010**, 7918-7920.

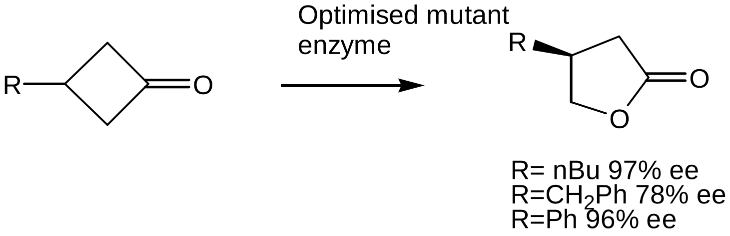
Review on directed evolution by Reetz: M. T. Reetz, *Angew. Chem. Int. Ed.* **2011**, 50, 138-174.

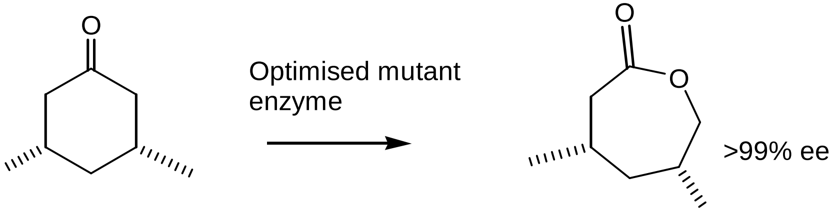
By undertaking cycles of directed evolution, highly selective enzymes can be prepared, as shown by the example of desymmetrisation (Baeyer-Villiger reaction) shown below:

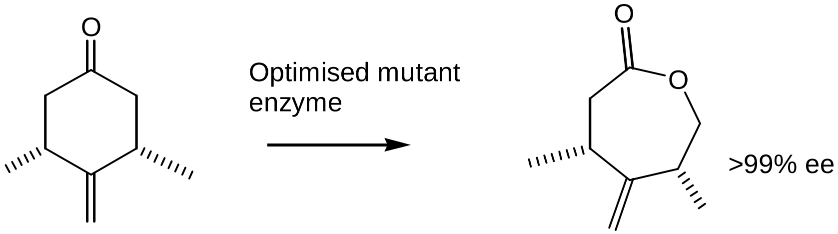


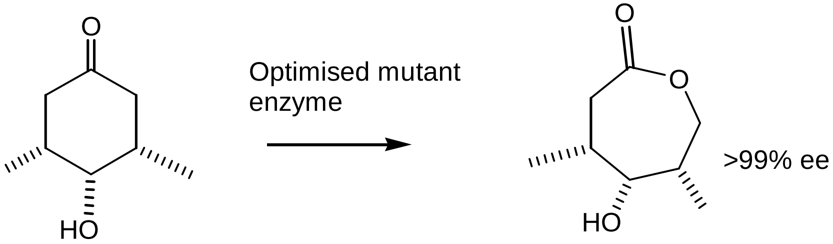


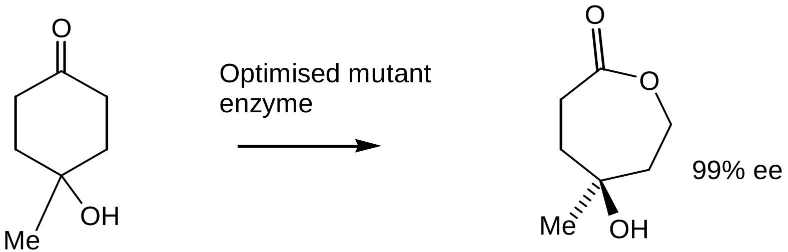






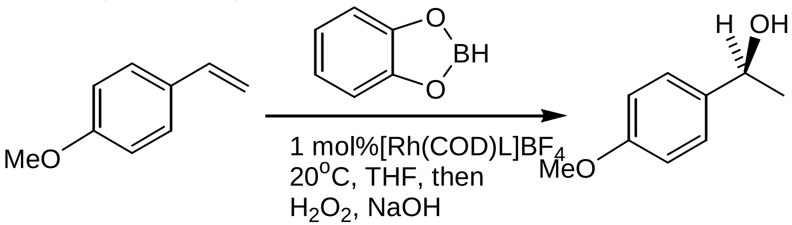


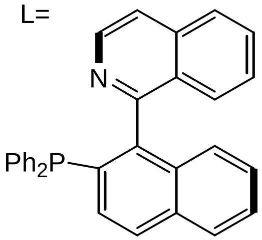




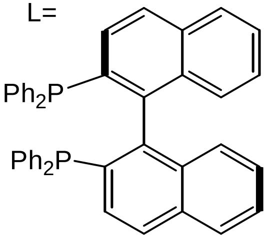
Other asymmetric reactions – for interest,

Asymmetric hydroboration:



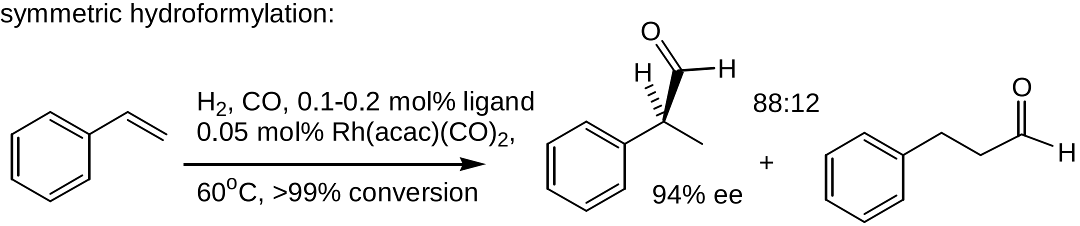


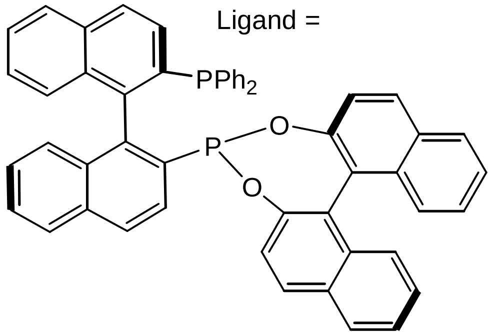
Product formed in 88% ee.



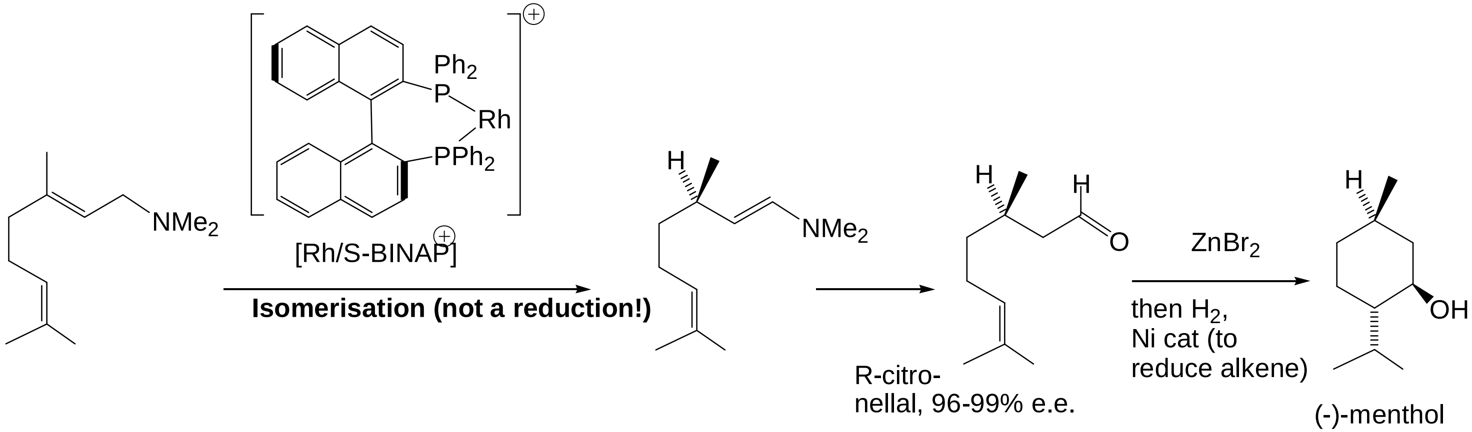
Product formed in 96% ee.

Asymmetric hydroformylation:





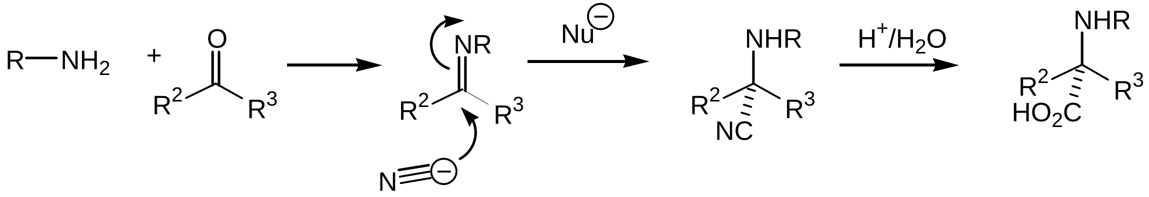
Asymmetric catalysis – Isomerisation.



(-)-menthol

There are many other reactions which have been converted into asymmetric processes…

Catalytic Strecker synthesis:



Other reactions:

Hydrosilylation

Hydroacylation

Hydrocyanation

Epoxidation using iminium salts

Asymmetric allylation

Hetero Diels-Alders

1,3-dipolar cycloadditions.

[2+2] cycloadditions

Cyclopropanation

Cross coupling reactions

Conjugate addition reactions

Etc. etc.