Lecture XXXIII: Enantioselective Catalysis

04-22-2020

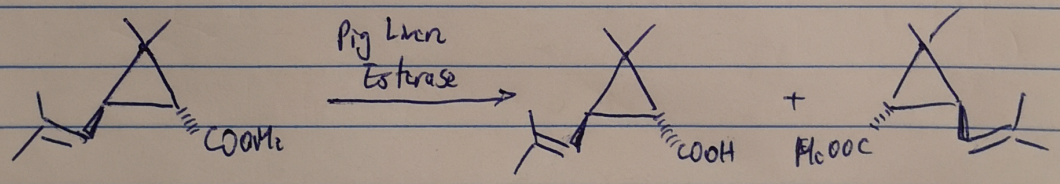
$$A \xrightarrow[\text{low loading}]{\text{chiral catalyst}} B^* \quad \text{single enantiomer}$$

$$(R)\text{-}A + (S)\text{-}A \xrightarrow[\text{catalyst}]{\text{or}} (R)\text{-}A + B^* \quad \text{chiral resolution}$$

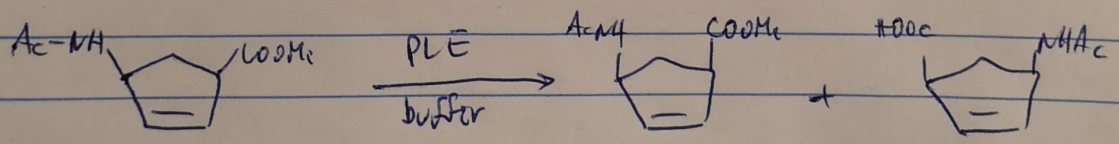
Three main classes of catalysts:

- enzymes
- TM catalysts
- organocatalysts

Enzymes can be used either on their own or in whole cell experiments, where an actual microorganism is used:

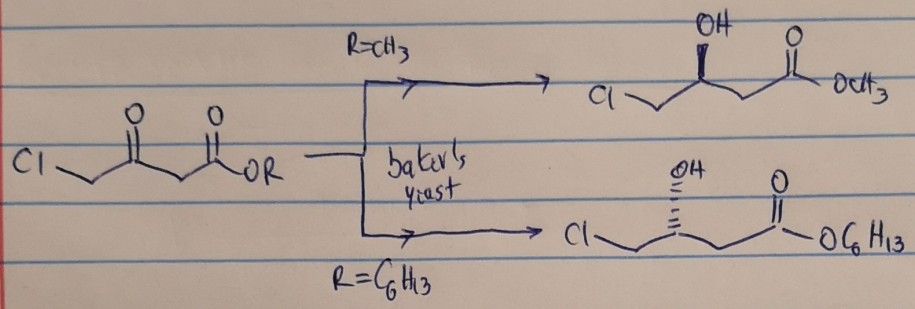


racemic — 46% ee — 40% ee



87% ee — 97% ee

Some examples of using whole organisms will often involve baker's yeast:

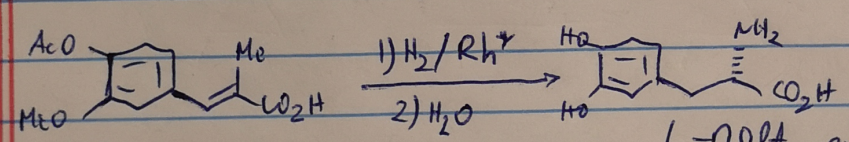


Enzyme pros:	Enzyme cons:
-not limited to natural substrates	-some rxns inaccesible
-mild conditions	-often do not work in org. solvents
-high specificity	-fragile

Transition metal-based asymmitric catalysts

This is now a vast area, with hundreds of catalysts capable of targeting virtually any reaction. First reactions studied were asymmitric hydrogenation and oxidation of prochiral alkenes.

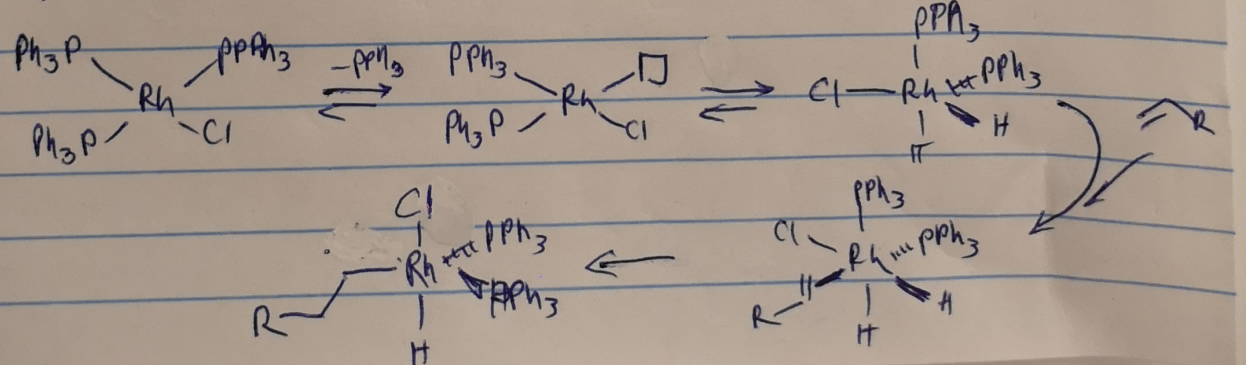
William Knowles (Monsanto):



JACS 1975, 97, 1975

L-DOPA, anti-Parkinson's disease drug

This reaction used asymmitric hydrogenation based on the Wilkinson's catalyst:



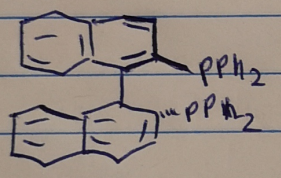
Replacement of two PPh_3 ligands with a chiral, C_2-symmetric chelating bisphosphine created a chiral environment around the metal, allowing enantioselective reduction. This was also the first industrial application of asymmetric synthesis.

There were previous examples:

1956, Pd catalyst deposited on silk (Nature, 1956, 178, 323)

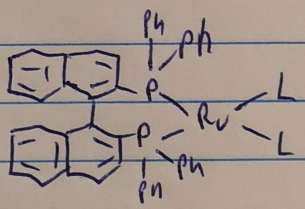
1968, first homogeneous examples

Noyori expanded this work to hydrogenation of polar substrates: aldehydes, ketones, and imines. He also used a C_2-symmetric bisphosphine:



BINAP

BINAP-Ru complex

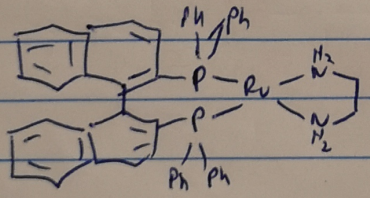


only alkenes

$L = Cl^{\ominus}, CO_2^{\ominus}$

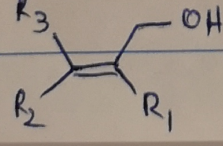
Functionalized C=O bonds

BINAP-Ru(diamine) complex

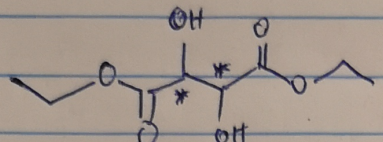


→ works on simple ketones/aldehydes

Noyori and Knowles shared 1/2 of the Nobel Prize in Chemistry in 2001. The other half went to Barry Sharpless, for asymmetric epoxidations of alkenes. Initially, this worked only on allylic alcohols.



His work used a complex between tartarates and Ti.

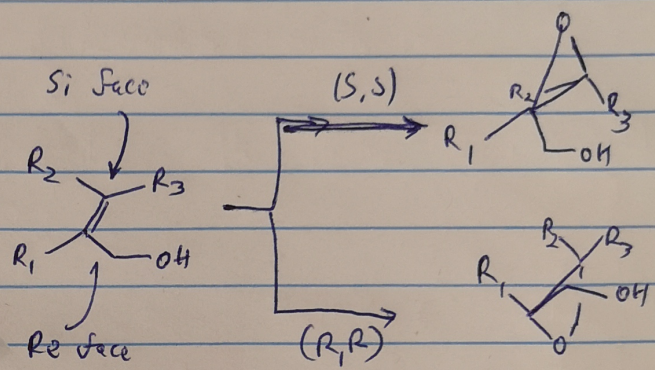


diethyl tartarate

can be S,S or R,R
(or meso, but that's not chiral)

S,S is (−)
R,R is (+)

t-BuOOH	$Ti(O\text{-}i\text{-}Pr)_4$ catalyst
oxidant	(5–10 mol%)

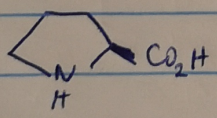


This reaction creates chiral epoxides which are very versatile synthetic intermediates—the reason behind its popularity.

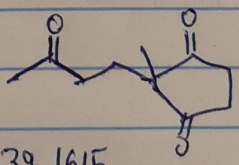
The transition-metal catalyzed enantioselective reactions are now a huge field, with dozens of books and reviews written on them.

Chiral Organocatalysts

This is a rapidly expanding area today. First chiral organocatalyst was simply proline:

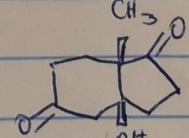


naturally occuring AA
cheap, the only 2° amine
rigid structure



JOC, 1974, 39, 1615
ACIE, 1971, 10, 496

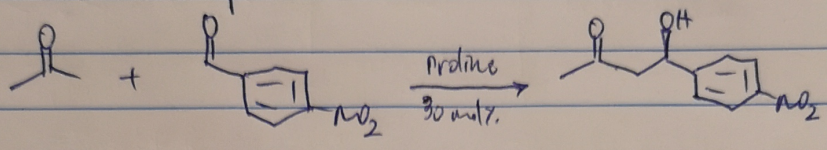
proline (3%)



93% ee

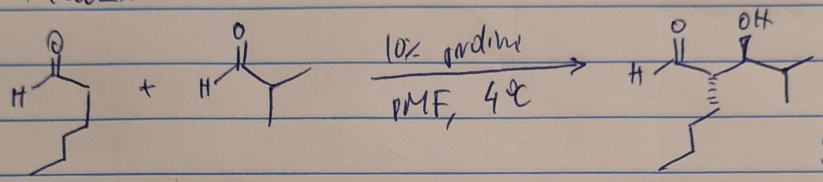
Hajos–Parrish–Eder–Sauer–Wiechert reaction

Barbas (2000). accomplished an intermolecular version: JACS, 2000, 122, 2395



68%
78% ee

MacMillan (2002):



80%
98% ee

JACS 2002, 124, 6798

Mechanism: