Uni Rostock, Gastvorlesung Asymmetrische Katalyse, 7.-8. Dez. 2007

Übersicht über das industrielle Potential von enantioselektiven katalytischen Reaktionen

Hans-Ulrich Blaser, SOLVIAS AG, Basel Switzerland

Amazing where you can go

Übersichtsartikel

H.U. Blaser, B. Pugin, F. Spindler

"Progress in enantioselective catalysis assessed from an industrial point of view"

J. Mol. Catal. A: Chemical 231 (2005) 1

Criteria for an Industrial Catalyst (Hydrogenation)

solvias

Enantiomeric excess, ee

>99% (pharma); >80% (agro or if further enrichment easy)

Catalyst productivity, ton ⇒ catalyst cost

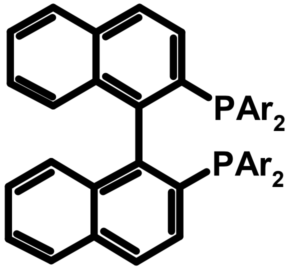
>1000 (small scale, high value); >50‘000 (large scale, low price)

Catalyst activity, tof ⇒ production capacity

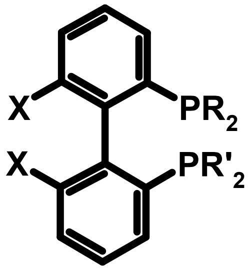
>500/h (small scale); >10‘000/h (large scale)

Commercial Ligands

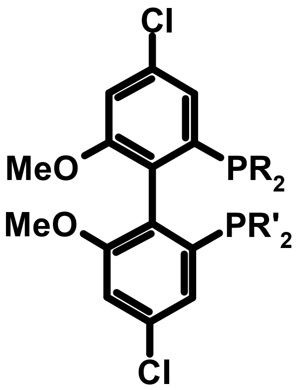
Biaryldiphosphines (BIAR)



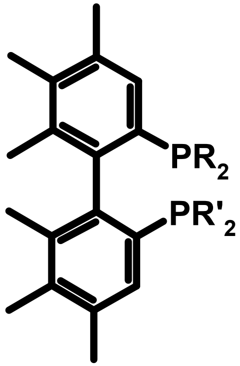
BINAP
(various suppliers)



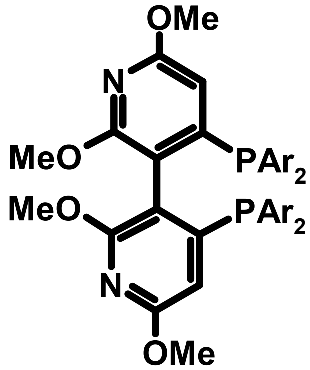
BIPHEP
(Roche)



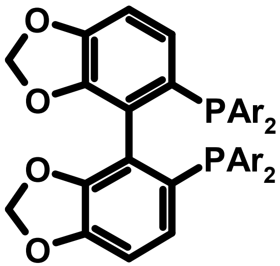
Cl-MeOBIPHEP
(Bayer)



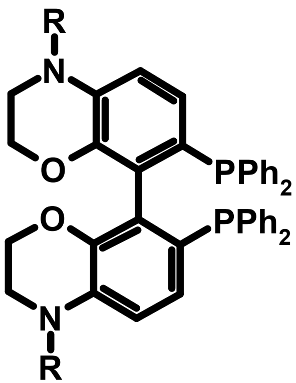
HEXAPHEMP
(Dow Chirotech)



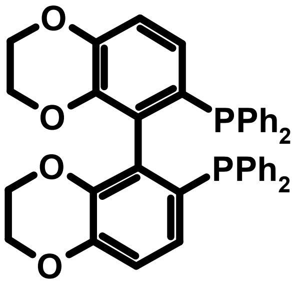
P-PHOS
(Johnson Matthey)



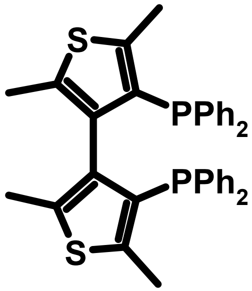
SEGPHOS
(Takasago



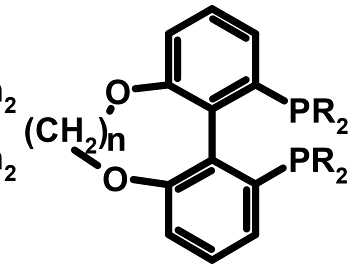
SOLPHOS
(Solvias)



SYNPHOS[a)]
(Synkem)



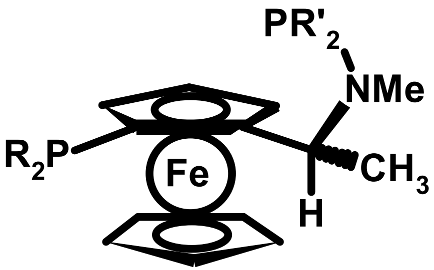
TMBTP
(Chemi



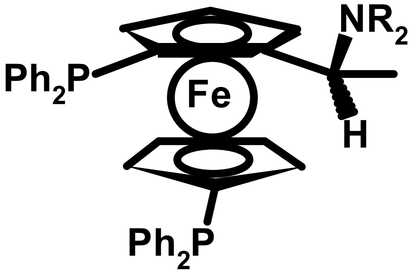
TUNEPHOS
(Chiral Quest)

Commercial Ligands

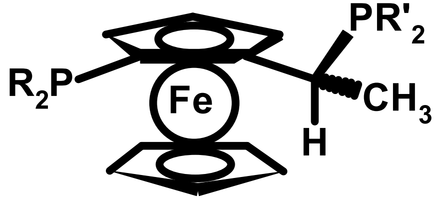
Ferrocenyldiphosphines (FERRO)



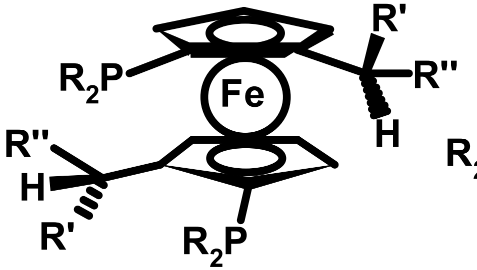
BOPHOZ
(Johnson Matthey)



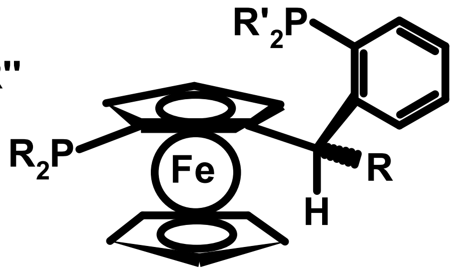
BPPFA



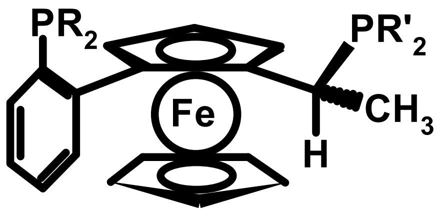
JOSIPHOS
(Solvias)



MANDYPHOS
(Umicore/Solvias)

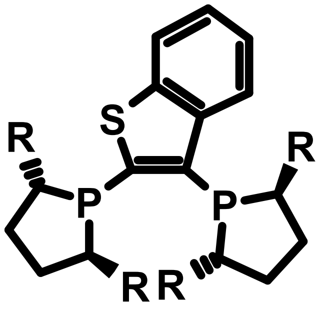


TANIAPHOS
(Umicore/Solvias)

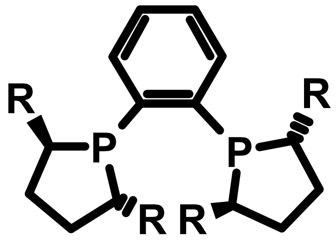


WALPHOS
(Solvias)

Commercial Ligands
Pospholane Ligands (CYCL)

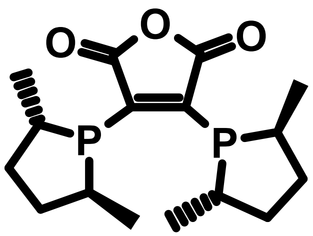


BUTIPHANE
(Solvias)

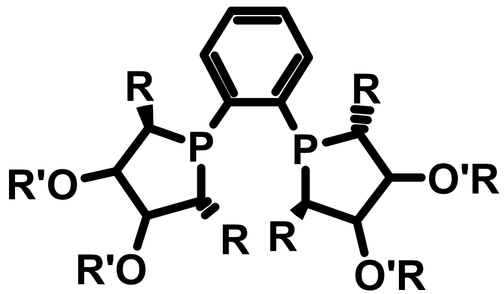


DUPHOS
(Dow Chirotech)

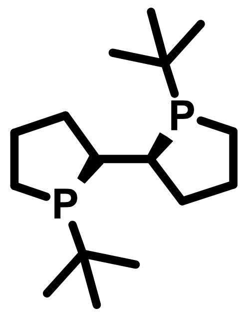
FERROTANE
(Dow Chirotech)



MALPHOS
(Degussa)



ROPHOS
(Solvias)

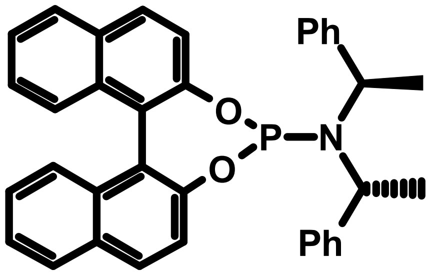


TANGPHOS
(Chiral Quest)

Commercial Ligands

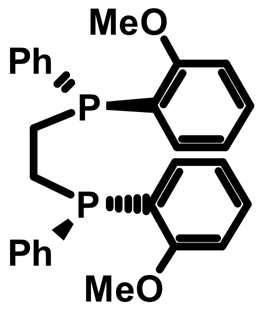
Miscellaneous

(MONO)

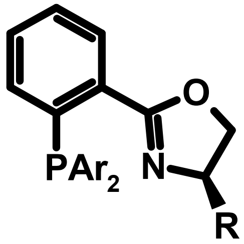


MONOPHOS
(DSM)

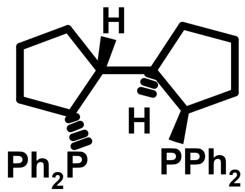
(PCHIRAL)



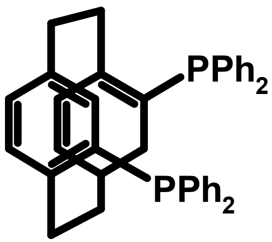
DIPAMP



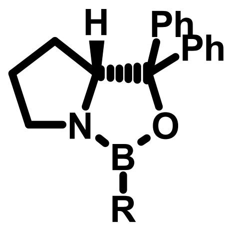
P^OXAZ
(Solvias))



BICP
(DSM)



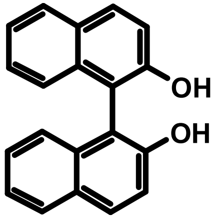
PHANEPHOS
(Johnson Matthey
Dow Chirotech)



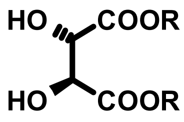
OXABOR

Commercial Ligands

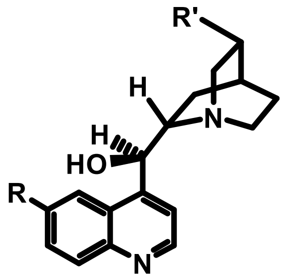
Miscellaneous



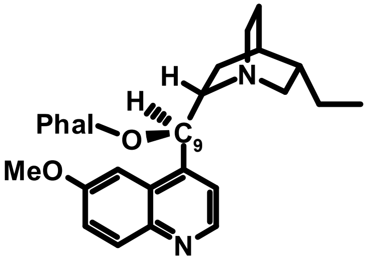
BINOL
(various



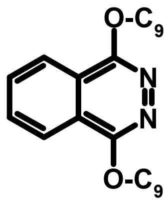
R = Et DET
R = i-Pr DIPT
R = H tartaric acid



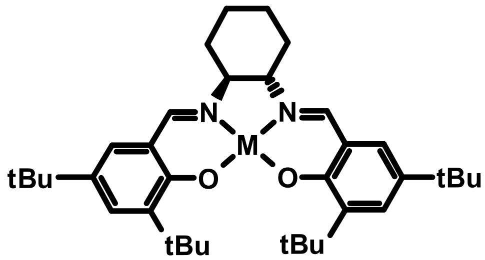
R = H R' = Vin cinchonidine (CN)
R = H R' = Et hydrocinchonidine (HCN)
R = OMe R' = Vin quinine (QN)



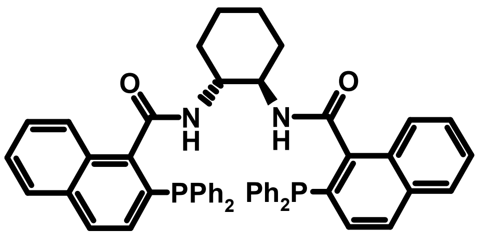
$(DHQD)_2$PHAL
(Rhodia Chirex)



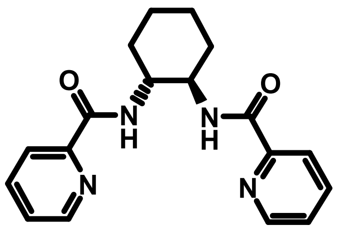
PHAL



SALEN
(Rhodia Chirex)



Trost ligands
(Dow Chirotech)



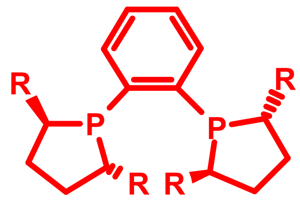
Hydrogenation of Olefins

solvias

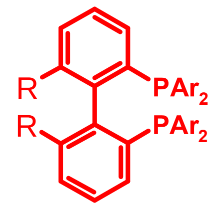
Substrates	ee (%)	TON[a)]	TOF (h^{-1})	Preferred catalyst types
Enamides, enol acetates, itaconates	90-99	1'000-50'000	200-5'000	Rh/PCYCL, Rh/FERRO, Rh/MONO, Rh/PCHIRAL, Ru/BIAR, Rh/VARIOUS
Allylic alcohols	80-95	10'000-50'000	1'000-5'000	Ru/BIAR
α,β-Unsaturated acids	85-95	2'000-20'000	500-3'000	Ru/BIAR, (Rh/PCYCL, Rh/FERRO)
Tetrasubstituted C=C	85-95	500-2'000	200-500	Ru/BIAR, Ru/PCYCL, Rh/FERRO, Rh/PCHIRAL
C=C without privileged function	80-95	20-100	2-5	Ir/P^OXAZ (Ru/BIAR, Rh/PCYCL)

Hydrogenation of Olefins

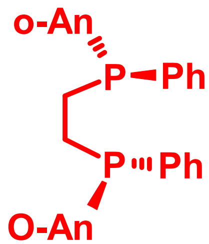
Enamides., Enolacetate, Itaconate



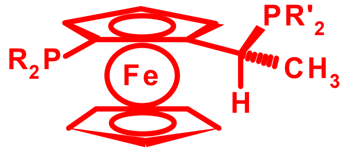
duphos
Dupont/Dow



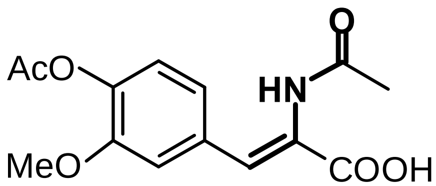
biphep
Roche/Solvias



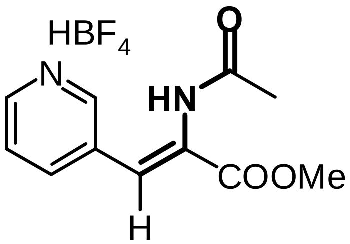
dipamp



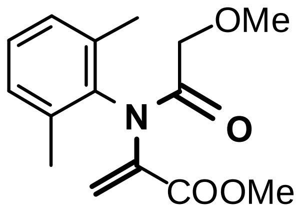
josiphos
Solvias



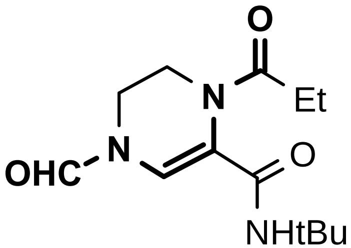
Rh/DIPAMP; ee 95%
TON 20'000; TOF 1000/h
small scale production
Monsanto [6c]



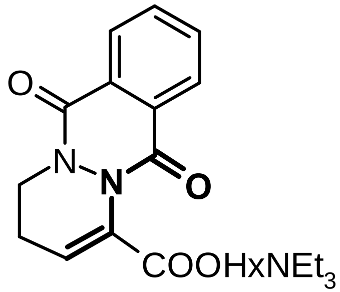
Rh/DUPHOS; ee 98%
TON 20'000; TOF n.a.
pilot process, >200 kg
Dow/ChiroTech [26]



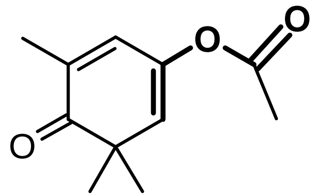
Rh/DUPHOS; ee 96%
TON 50'000; TOF 5'200/h
pilot process, kg scale
Ciba-Geigy/Solvias [27]



Rh/JOSIPHOS; ee 97%
TON 1'000; TOF 450/h
pilot process, >200 kg
Lonza [28]

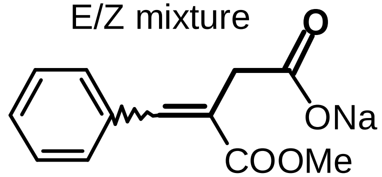


Ru/BIPHEP; ee >99%
TON 20'000; TOF 830/h
pilot process, >10 kg
Roche [11d,29a]



Rh/DUPHOS; ee 98%
TON 20'000; TOF 5'000/h
pilot process, multi kg
Roche [29a]

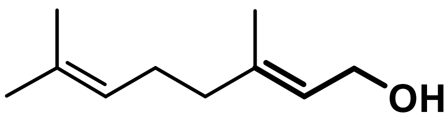
E/Z mixture



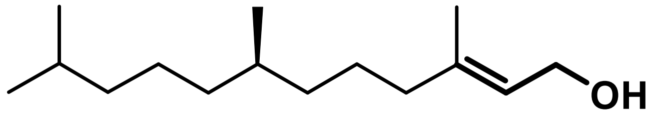
Rh/DUPHOS; ee 97%
TON 1'000; TOF n.a.
pilot process, >kg scale
ChiroTech [31]

Hydrogenation of Olefins

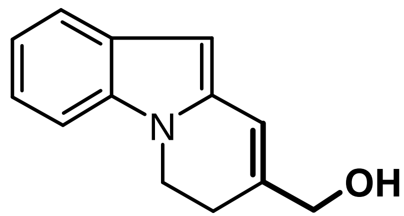
C=C-CH_2OH, C=CCOOH



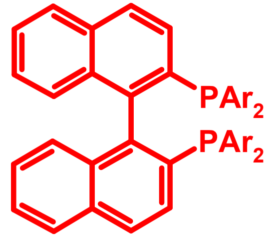
Ru/BINAP; ee 97%
TON 50'000; TOF 500/h
production process 300 t/y
Takasago [32]



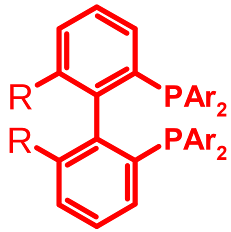
Ru/BIPHEP; de >98%
TON 100'000; TOF 10'000/h
pilot process, kg scale
Roche [11d]



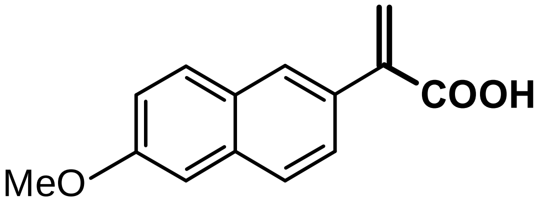
Ru/BIPHEP; ee 98%
TON 5'000; TOF 200/h
bench scale
Roche [33]



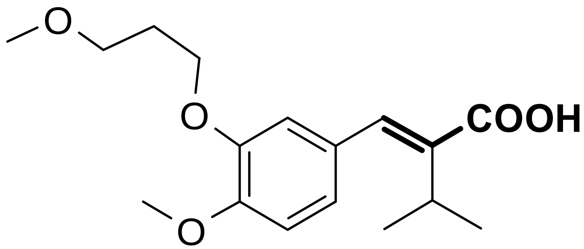
binap



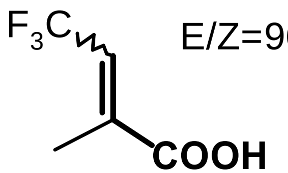
biphep
Roche/Solvias



Ru/BINAP; ee 97%
TON 3'000; TOF 300/h
bench scale
Takasago [32]

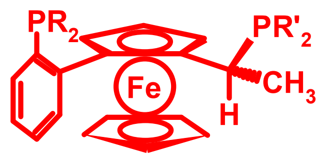


Rh/WALPHOS; ee 95%
TON 5000, TOF ca .800/h
pilot scale
Novartis/Solvias [24]



E/Z=96/4

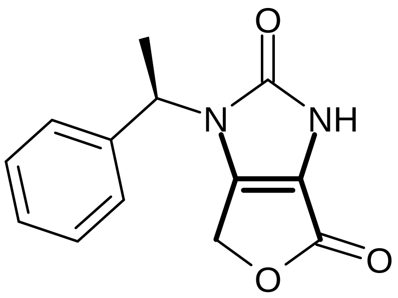
Ru/TMBTP; ee 92%
TON 20'000; TOF 6'600/h
pilot process, >100 kg
Chemi [34a]



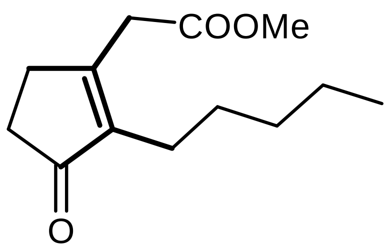
walphos
Solvias

Hydrogenation of Olefins

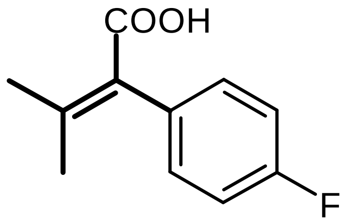
Miscellaneous



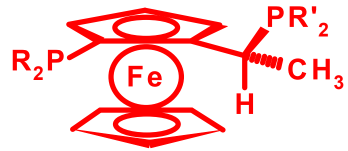
Rh/JOSIPHOS; de 99%
TON 2'000; TOF n.a.
medium scale production
Lonza [35]



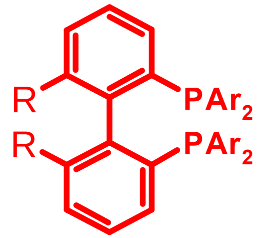
Ru/JOSIPHOS or DUPHOS; ee 90%
TON 2'000; TOF 200/h
medium scale production
Firmenich [36]



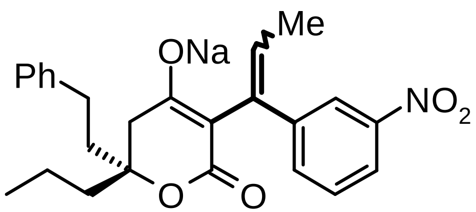
Ru/BIPHEP; ee 94%
TON 1'000; TOF ca. 400/h
pilot process, >10 kg
Roche [11d]



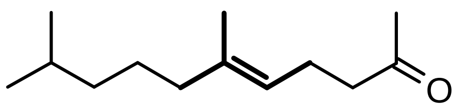
josiphos



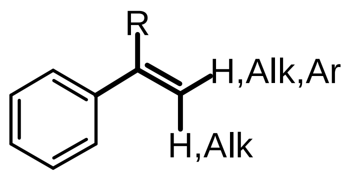
biphep



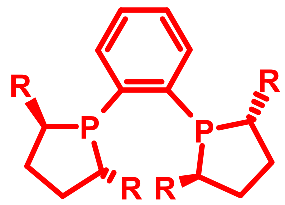
Rh/DUPHOS; de 93%
TON 1'000; TOF n.a.
small scale production
Dow Chirotech [26]



Ru/BIPHEP; ee 94%
TON 1'000; TOF 45/h
bench scale
Roche [11d]



Ir/P^OXAZ; ee up to 99%
TON 200-1000; TOF 100-500/h
laboratory procedure
Pfaltz / Solvias [37]



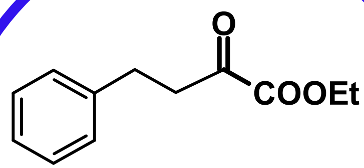
duphos

Hydrogenation of Ketones

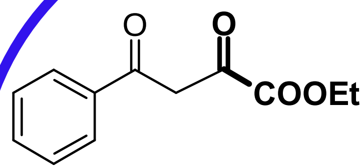
Substrate / Reducing agent	ee (%)	TON[a)]	TOF (h^{-1})	Preferred catalyst types
RCOCHRCOOR / H_2	90-98	5'000-50'000	2'000-10'000	Ru/BIAR, Ru/FERRO, Ni/TARTRATE
RCOCOOR / H_2	90-95	1'000-5'000	100-500	Rh/AMPP, Ru/BIAR, Pt/CINCHONA
RCOCHRX / H_2 X = NHR, OR	90-95	1'000-5'000	100-500	Ru/BIAR, Rh/FERRO, Rh/AMPP, Pt/CINCHONA
ArCOR / H_2	90-95	5'000-20'000	500-10'000	Ru/BIAR-diamine
ArCOR / *i*-PrOH or HCOOH/NEt_3	85-95	1'000-5'000	100-500	Ru, Rh, or Ir / O^N, N^N, P^N
Various ketones / BH_3	85-95	20-50	5-10	OXABOR

Hydrogenation of Ketones

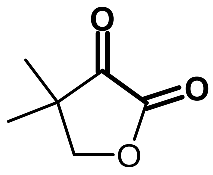
α- or β-functionalized ketones



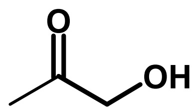
$Pt\text{-}Al_2O_3$/HCd; ee 82-94%
TON 4'000; TOF1'000/h
small scale production
Ciba-Geigy/Solvias [39]



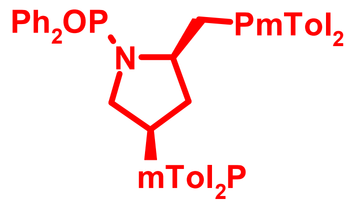
$Pt\text{-}Al_2O_3$/HCd; ee 70-87%
TON n.a.; TOF n.a.
small scale production
Ciba SC/Solvias [40]



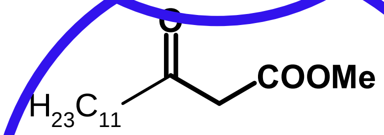
Rh/PPM; ee 91%
TON 200'000; TOF 15'000/h
pilot process, >100 kg
Roche [11d]



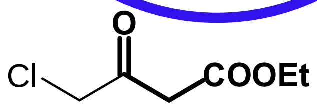
Ru/BINAP; ee 94%
TON 2'000.; TOF 300/h
medium scale production
Takasago [32]



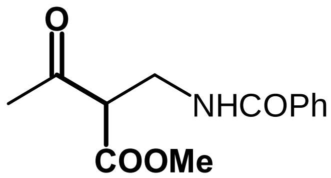
ppm



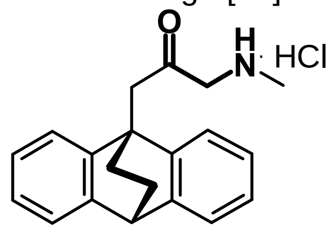
RaNi/tartrate/NaBr; ee 91%
TON 160 (16 recycl); TOF 2/h
pilot process, >100 kg
Roche [41]



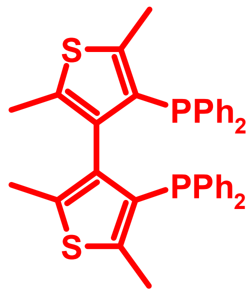
Ru/TMBTP; ee 97%
TON 20'000; TOF 15'000/h
pilot process, >100 kg
Chemi [34a]



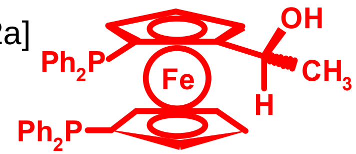
Ru/BINAP; ee >97%, de >94%
TON 1'000.; TOF 200/h
large scale production
Takasago [32]



Rh/BPPFOH; ee 97%
TON 2'000; TOF 125/h
pilot process, >10 kg
Ciba-Geigy/Solvias [42a]



tmbtp
Chemi

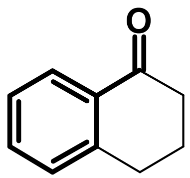


bppfoh

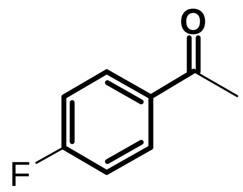
Heterogeneous catalysts

Reduction of Ketones

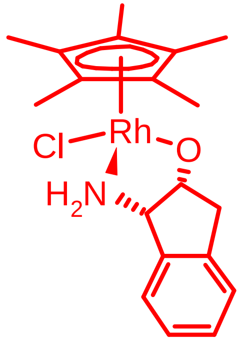
Aryl ketones



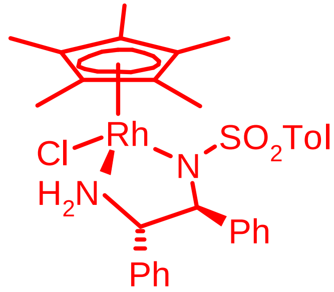
CAT A; i-PrOH/i-PrONa
ee 97%, TOF 500-2500/h
pilot process, 200 l scale
Avecia [6d]



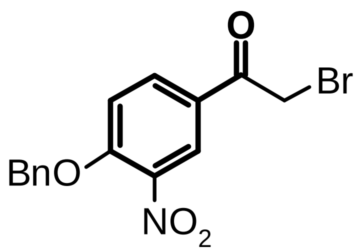
CAT B; HCOOH/NEt_3
ee 98%, TOF 75/h
pilot process, 50 l scale
Avecia [6d]



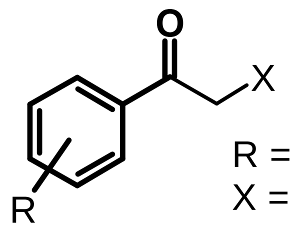
CAT A



CAT B

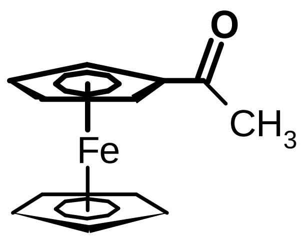


OXABOR/BH_3.Me_2S
ee 94%; TON 17, TOF n.a.
pilot process, multi kg
Sepracor [44]

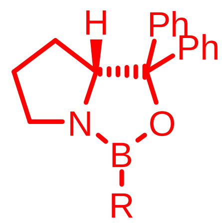


R = Cl
X = Cl, Br

OXABOR/BH_3.Me_2S
ee 99%; TON 20-30; TOF n.a
small scale production
PPG-Sipsy [45]



OXABOR/BH_3.Me_2S
ee 92%; TON 20; TOF ca. 5/h
pilot process, 50 kg
Lonza [46]



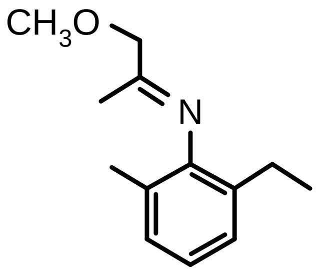
OXABOR

Hydrogenation of Imines

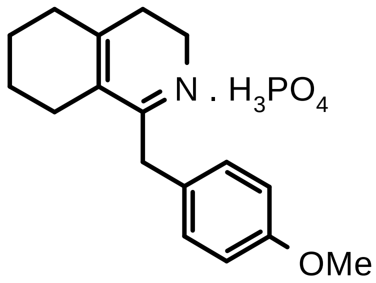
solvias

Reaction	ee (%)	TON	TOF (h-1)	Preferred catalyst types
N-Aryl imines	80-90	500-10'000	50-100	Ir/FERRO, Rh/BDPP, Ir/P^OXAZ, Ru/P^P/N^N
Alkyl imines	80-90	50-500	5-50	Rh/BDPP, (Ir/P^OXAZ)
Cyclic imines	90-98	50-1'000	1-50	Ti/EBTHI, Ir/FERRO, Ir/BIAR
Various C=N-X	80-95	100-500	5-100	Rh/PCYCL, Ru/BIAR, Rh/FERRO

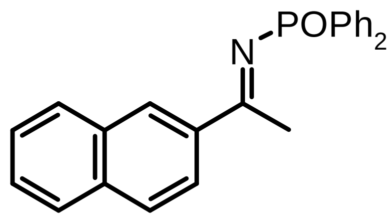
Hydrogenation of Imines



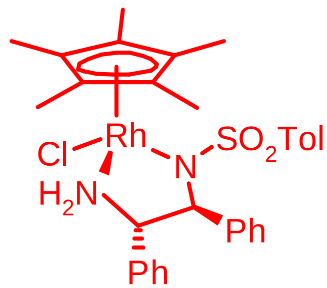
Ir/JOSIPHOS; ee 80%
TON 2'000'000; TOF >400'000/h
very large scale production
Ciba-Geigy/Syngenta/Solvias [51]



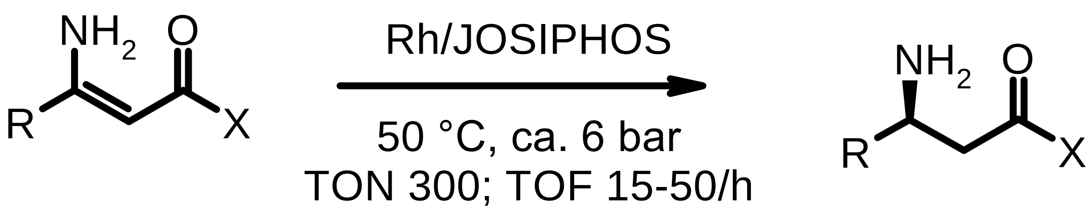
Ir/JOSIPHOS; ee 90%
TON 1'500; TOF n.a.
pilot process, >100 kg
Lonza (Solvias) [35]



CAT B[a)]; HCOOH/NEt_3
ee 99%, TON >200; TOF 1000/h
pilot process
Avecia [6d]



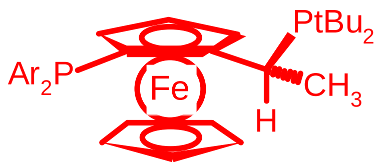
CAT B



R = Ar, Bn
X = OMe, NHPh

ee 82-97%

Merck; production process



JOSIPHOS
Ar = Ph,

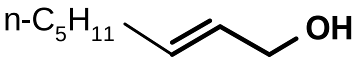
Oxidations

solvias

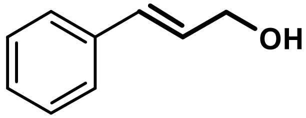
Reaction	ee (%)	TON	TOF (h^{-1})	Preferred catalyst types
Epoxidation of allylic alcohols	85-95	10-40	up to 20	Ti/TART
Epoxidation of C=C	80-95	50-2000	50-200	Mn/SALEN
Dihydroxylation of C=C	85-95	100-500	50-100	Os/CINCH
Aminohydroxylation of C=C	85-95	20-100	5-20	Os/CINCH
Sulfide oxidation	80-95	2-20	1-5	Ti/TART

Oxidations

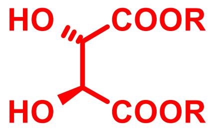
Ti/DIPT; ee 88-90%
TON >40; TOF <1h
medium scale production
Arco/PPG-Sipsy [4c]



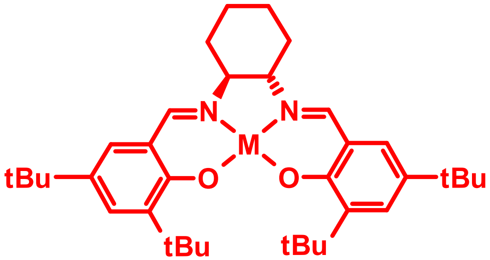
Ti/DET; ee >98%
TON 8; TOF n.a.
pilot process, >10 kg
Upjohn [55]



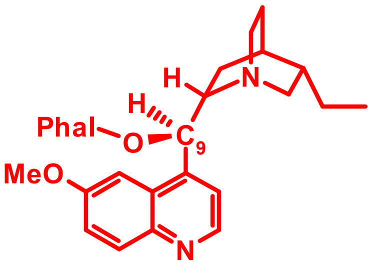
Ti/DIPT; ee 96%
TON 20; TOF ca.1
bench scale
HöchstMarionRoussel [30b]



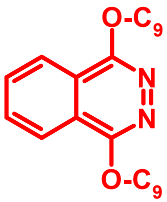
R = Et DET
R = i-Pr DIPT
R = H tartaric acid



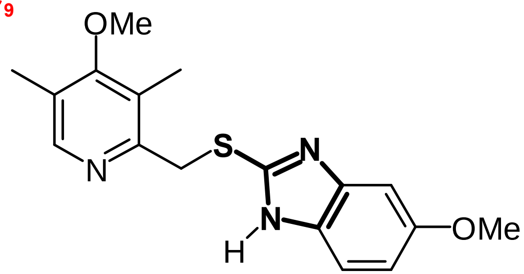
SALEN
(Rhodia Chirex)

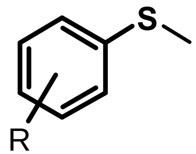


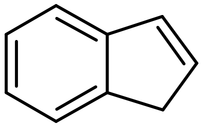
(DHQD)$_2$PHAL
(Rhodia Chirex)



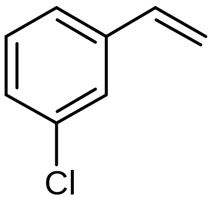
PHAL







epoxidation
Mn/SALEN; ee 88%
TON >250; TOF ca. 250
small scale process
Rhodia Chirex [42b]



dihydroxylation
Os/(DHQD)2PHAL; ee 95%
ton ca. 500; tof 50-100
pilot process, >10 kg
Rhodia Chirex [56]

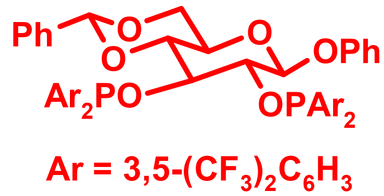
Ti/TART, ee 92-93%
TON 3-4; TOF 3-4
medium scale production
AstraZeneca [6e,63]

Ti/TART; ee 98%
TON n.a.; TOF n.a.
pilot process, <100 kg
Lonza [28]

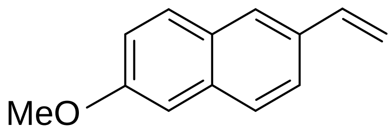
Addition Reactions to C=C

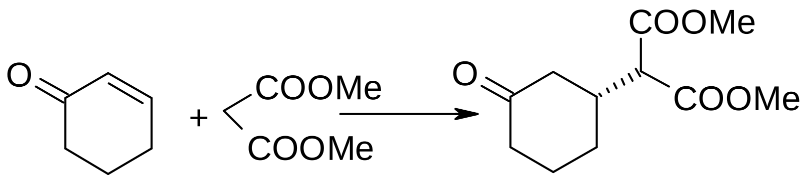
Reaction	ee (%)	TON	TOF (h^{-1})	Preferred catalyst types
Hydrocarbonylation	85-95	100-1000	300-500	Rh/BIAR, Pd/BINO, various
Hydrosilylation	85-95	200-1'000	20-100	Pd/MOP
Hydroboration	85-95	50-100	5-200	Rh/QUINAP, Rh/FERRO
Michael addition	85-95	50-200	5-100	var/BINO, Cu/PAMID
Cyclopropanation	85-95	50-1'000	20-100	Cu/OXAZ, Rh/CARB[c)]
Diels-Alder reaction	85-95	10-100	1-10	Cu/OXAZ, M/O^O, M/N^O, M/N^N

Addition Reactions to C=C



glup

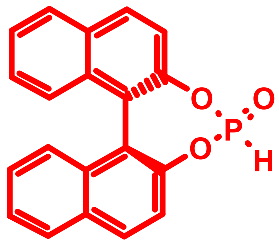




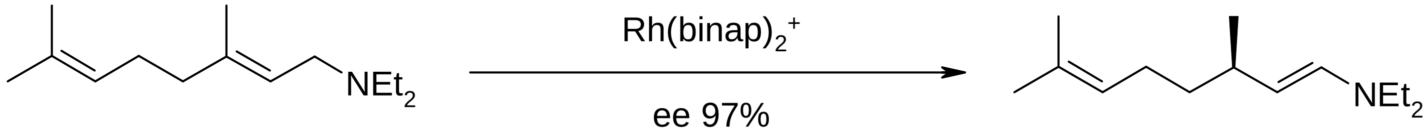
hydrocyanation
Ni/GLUP; ee 90%
TON 5'000; TOF ~200/h
bench scale
DuPont [12k]

hydrocarboxylation
Pd/BINAPO; ee 91%
TON <20; TOF <1/h
laboratory experiment
Alper [37]

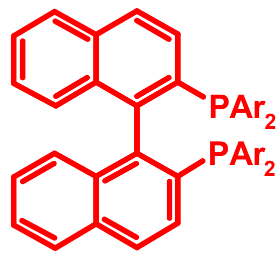
Michael addition
AlLi-BINOL; ee 99%
ton 330; tof 33/h
bench scale, kg
Shibasaki [38]



binapo



ee 97%
TON 400'000 (recycled); TOF 440/h
production process, >1000 t/y
Takasago [52]

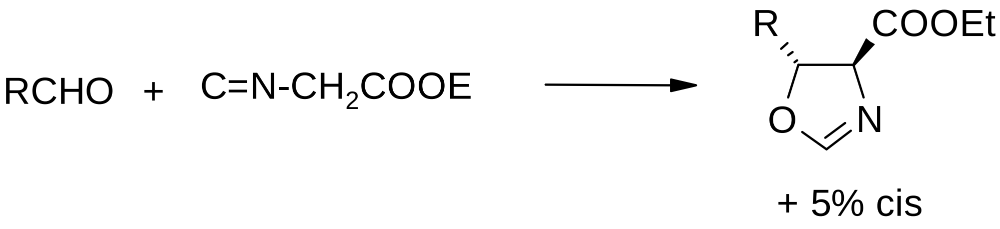


binap

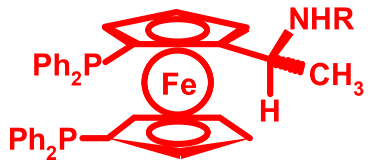
Addition Reactions to C=O

Reaction	ee (%)	TON	TOF (h^{-1})	Preferred catalyst types
Aldol reaction	90-95	5-20	1-10	Ln/BINOL, Ag/BIAR, Cu/OXAZ
Ene reaction	90-95	5-20	1-10	Ti/BINOL
Addition of MR to RCHO	90-95	5-100	1-20	M/N^O, M/O^O, M/N^N
Hetero Diels-Alder	85-95	10-50	2-10	Cu/OXAZ, M/O^O, M/N^O, M/N^N
Addition of CN^- to C=O	90-95	10-100	low	Ti/BINOL, M/N^N, M/SALEN

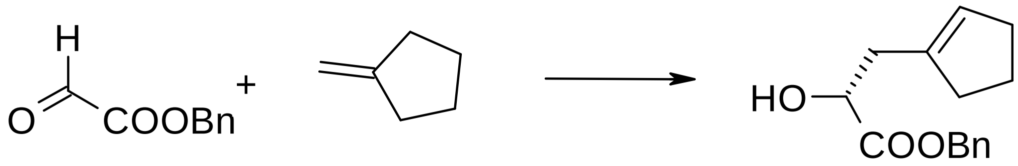
Addition Reactions to C=O, C=N



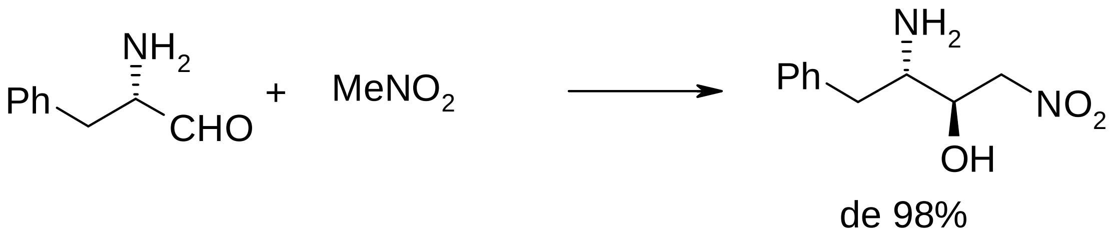
gold aldol; Au/BPPFA
ee 85-90%; TON 100; TOF 5
bench scale, kg scale
Ciba-Geigy [72]



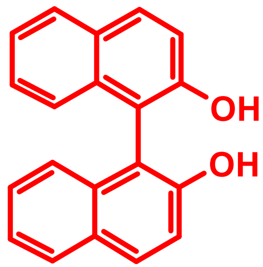
bppfa



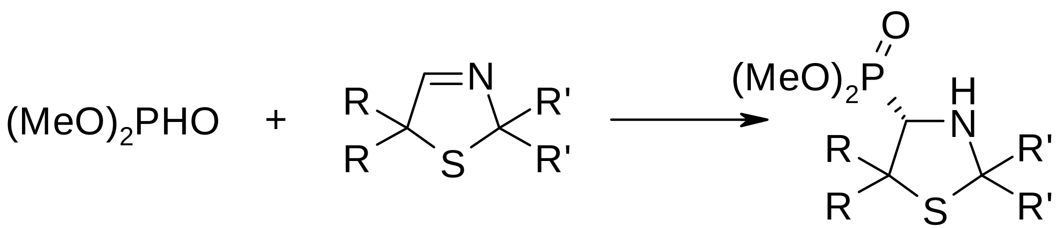
ene reaction, Ti/BINOL
ee 98%, TON 70; TOF 3/h
pilot process, multi 100 kg
Roche [11d]



nitro aldol; LaLi/BINOL complex
ee 96%; TON 30; TOF <1/h
small scale process
Kaneka [73]



BINOL
(various



R, R' = Me, Et, $(CH_2)_3$

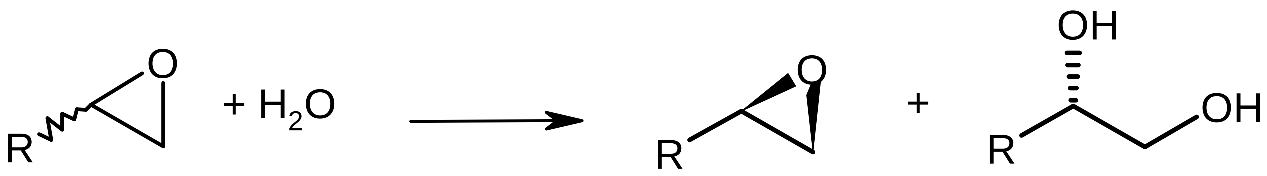
YbK/BINOL; ee 92-96%
TON 20; TOF <1/h
small scale production
Hokko Chemical Co. [76]

Miscellaneous Reactions

Reaction	ee (%)	TON[a)]	TOF (h^{-1})	Preferred catalyst types
Allylic substitution	85-95	50-1'000	20-100	Pd, Mo/Trost lig, Pd/P^OXAZ, Pd/OXAZ, various
Cross coupling	80-90	500-200	2-20	Ni/P^N
Heck reaction	80-95	10-100	1-10	Pd/BIAR, Pd/P^OXAZ
Metathesis	90-95	20-100	10-100	Ru/carbene, Mo/O^O
Kinetic resolution of epoxides	98-99	500-1000	20-40	Co or Cr/SALEN

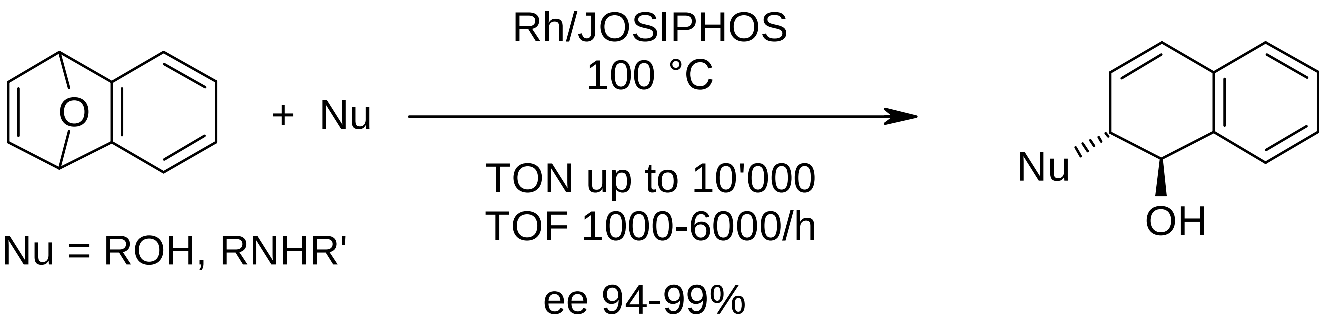
Miscellaneous Reactions

solvias



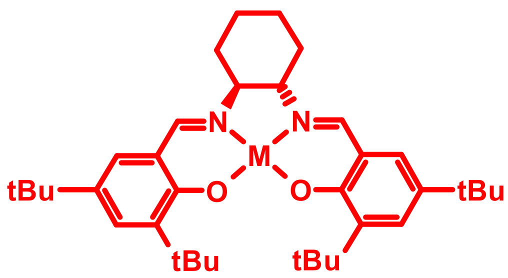
R = Me, Et, CH_2Cl

HKR, R = CH_2Cl
Co/SALEN; ee >99%
TON ca. 250; TOF ca. 30/h
medium scale process
Rhodia ChiRex [106c]

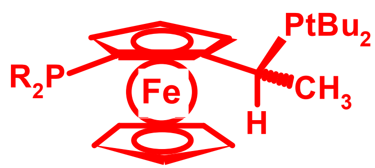


Nu = ROH, RNHR'

Bench scale (multi kg)
Solvias



SALEN
(Rhodia Chirex)



JOSIPHOS

Summary Assessment

solvias

Existing applications, broad scope	• Hydrogenation of enamides and itaconates • Hydrogenation of β-functionalized C=O
Existing applications, medium scope	• Hydrogenation of C=C-COOR and C=C-CH-OH • Hydrogenation of α-functionalized and aryl C=O • Hydrogenation of C=N-Ar

Summary Assessment

Existing applications, narrow scope, niche applications	• Hydrogenation / reduction of other C=C and C=O • Hydrogenation of and addition to various C=N • Dihydroxylation and epoxidation of C=C • Oxidation of aryl sulfides • Epoxide opening (kinetic resolution) • Isomerization, cyclopropanation, hydrocyanation of C=C

Summary Assessment

solvias

Broad substrate scope, good chance for selected application	• (Hetero) Diels Alder • Michael additions, allylic alkylation • Aldol and ene reactions • Various addition reactions to C=O and C=N
Narrow substrate scope, niche applications only	• Aminohydroxylation of C=C • Hydrocarbonylation, hydroboration, hydrosilylation of C=C • Cross coupling, metathesis and Heck reactions