

JOHNSON MATTHEY

Phosphorous Ligands in Homogenous Catalysis

Chemsource Symposium 14th June 2006

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Objectives

Brief overview of industrial homogeneous asymmetric catalysis (....a little biased towards hydrogenation....)

and

discussion of some practical problems and opportunities for industrial applications

From the viewpoint of a catalyst and technology company:
Johnson Matthey Catalysts, Catalysis and Chiral Technologies



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The growing market for enantioselective catalysis

The request for **single isomer products** is driven by:

- Superior performance of single isomers
- Regulatory requirements

Fine chemicals, pharmaceutical intermediates, agrochemicals, vitamins, flavour and fragrances:

- Small scale / high value products
- Multi-step synthesis, usually in batch equipment
- Time to market critical (for pharmaceuticals)



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Synthesis of enantiopure molecules

Separation of enantiomers

classical resolution (crystallisation of diastereoisomers)

chromatographic technology (simulated moving bed)

Synthesis from chiral pool

Enantioselective synthesis

chiral auxiliaries

biocatalysis

asymmetric catalysis



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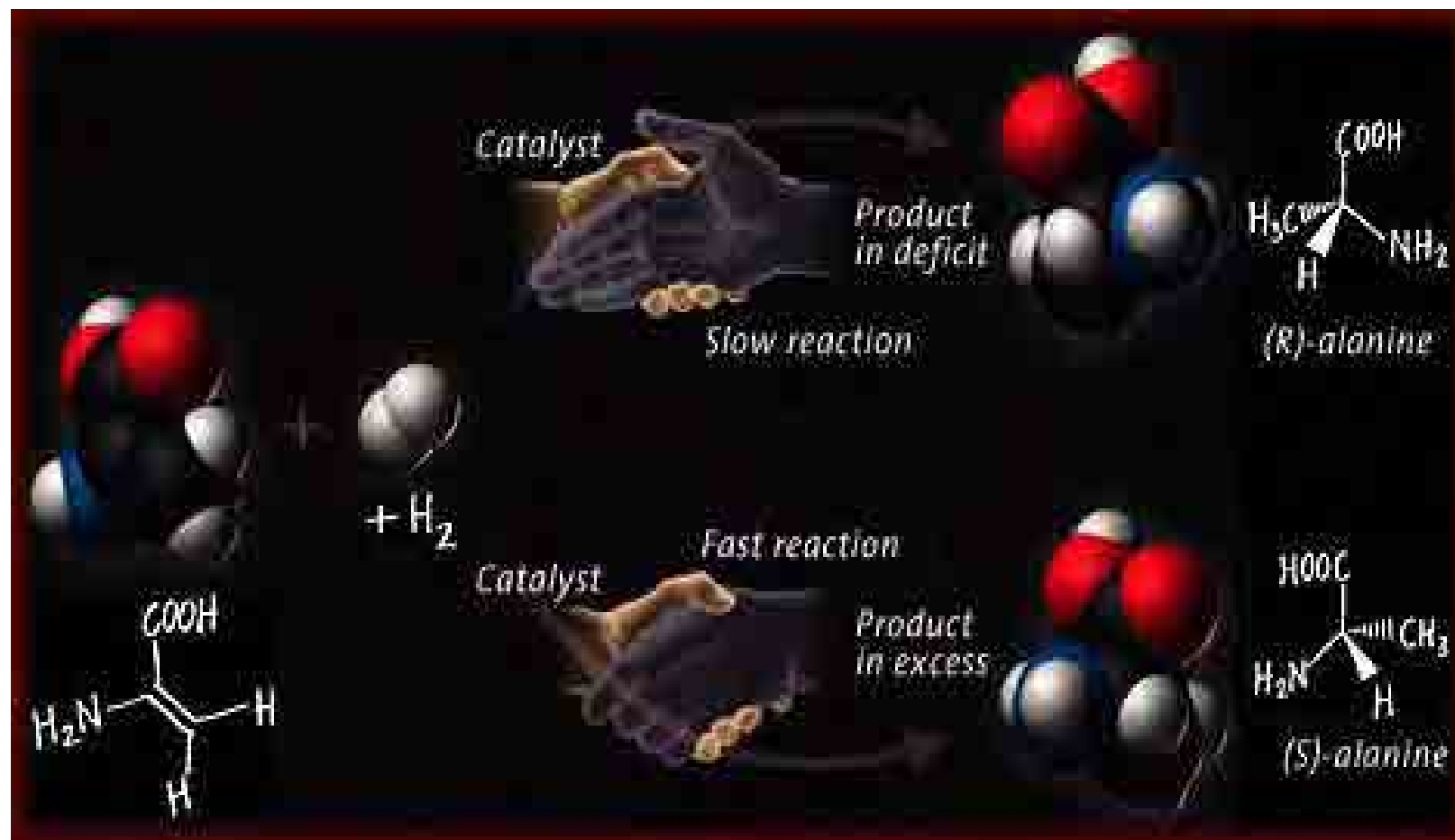
Advantages of asymmetric catalysis

- No loss of one enantiomer (as for separation/classic resolution)
- No loss of chiral auxiliary (as for enantioselective synthesis)
- Easier, cleaner, more efficient industrial processes (volume efficiency / catalyst separation / possible catalyst recycling)



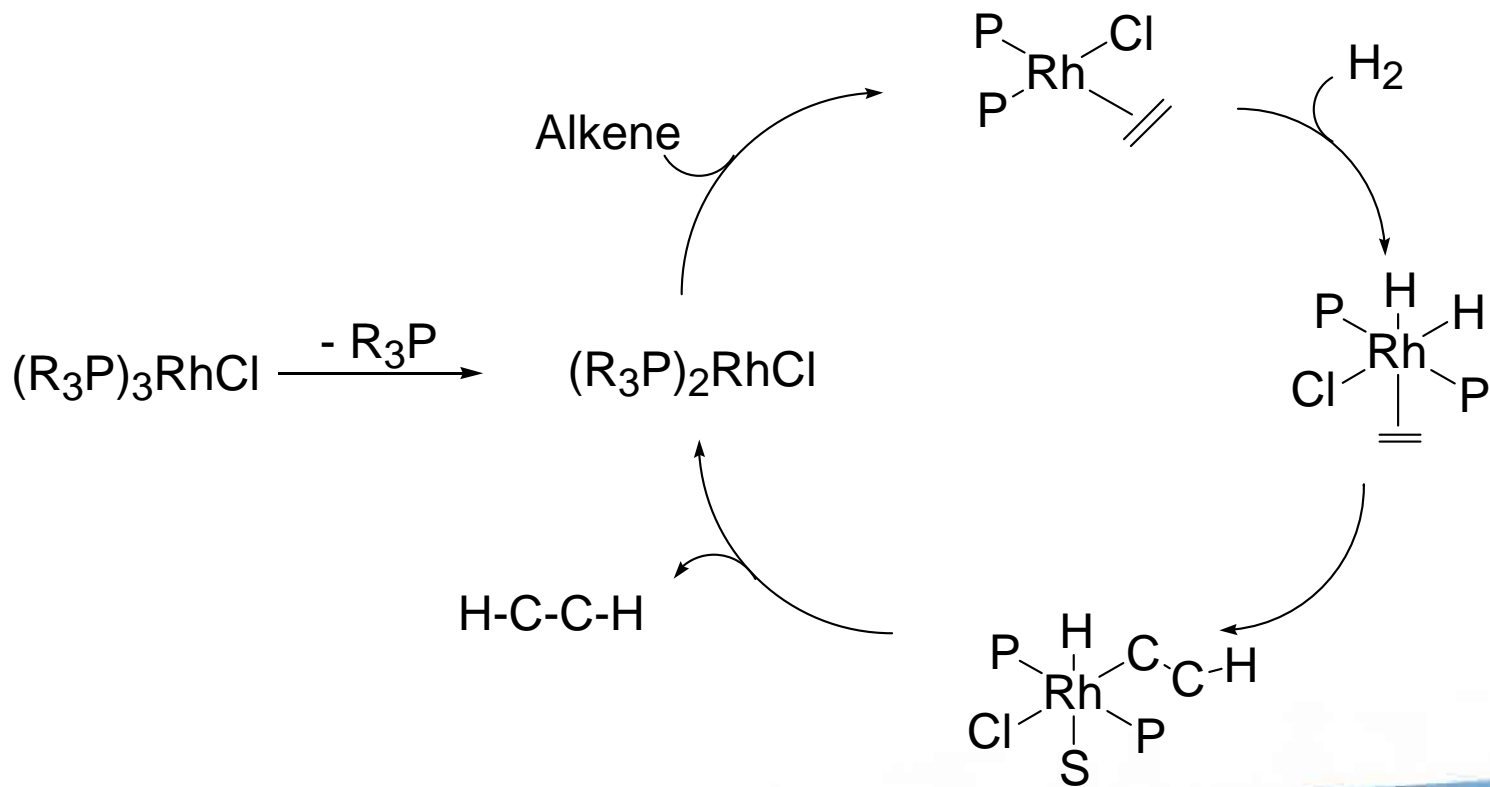
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Asymmetric Hydrogenation



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Hydrogenation of alkenes - Wilkinson's Catalyst

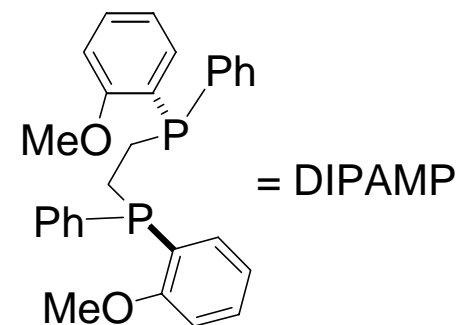
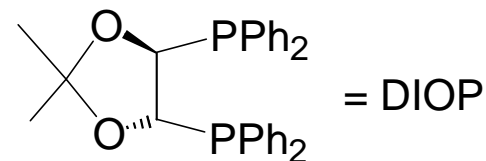
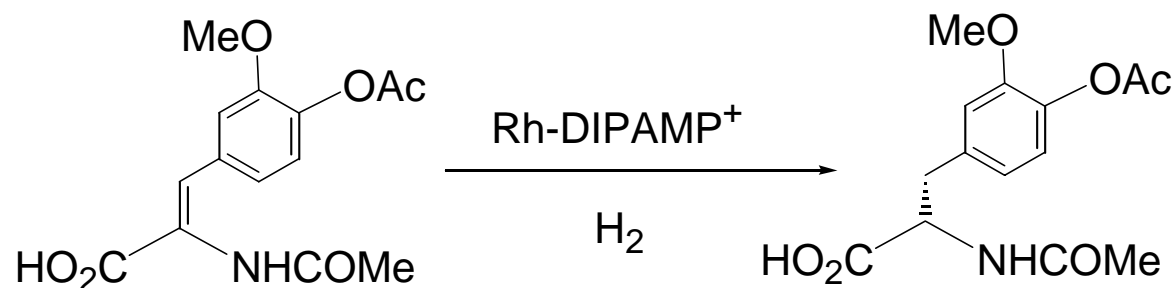


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Monsanto: synthesis of L-DOPA

Knowles and Horner reported in 1968 the first homogeneously catalysed asymmetric hydrogenation of olefines with Rh-chiral monophosphines

Kagan devised in 1971 the bidentate ligand DIOP



Knowles group at Monsanto developed the asymmetric hydrogenation of the intermediate for L-Dopa, 95% ee, TON 20,000, TOF 1,000, scale 1 t / y

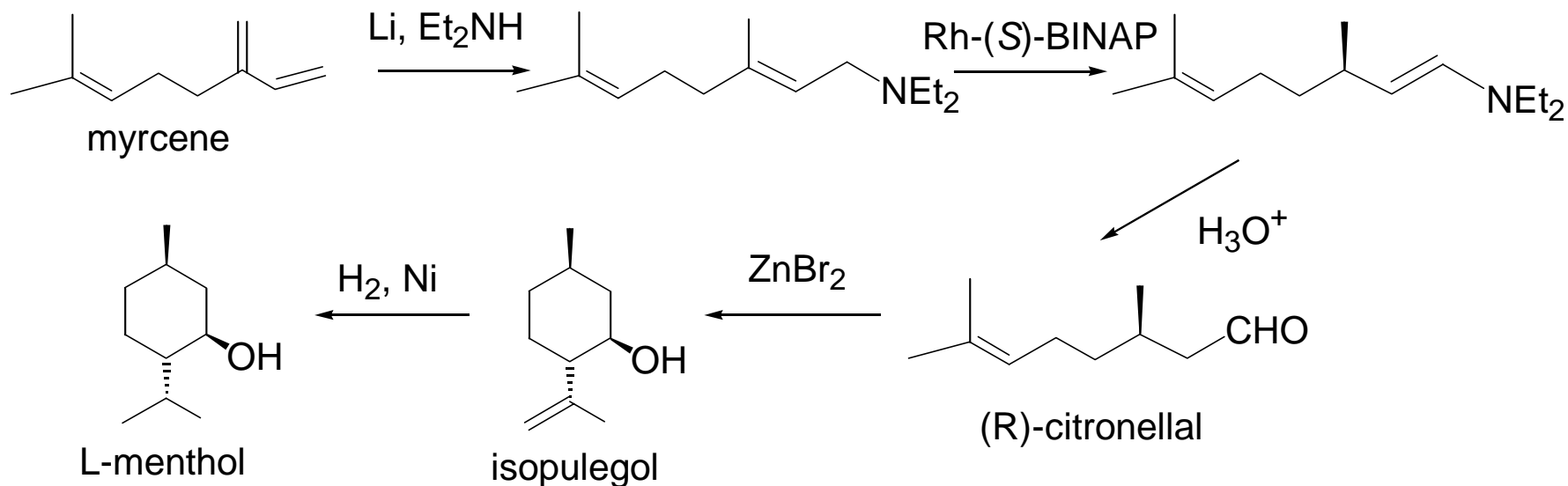


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Takasago: synthesis of *L*-Menthol

In 1980 Noyori introduced BINAP as ligand for asymmetric hydrogenation

Asymmetric isomerisation of allyl amine catalysed by BINAP-Rh developed for Takasago.



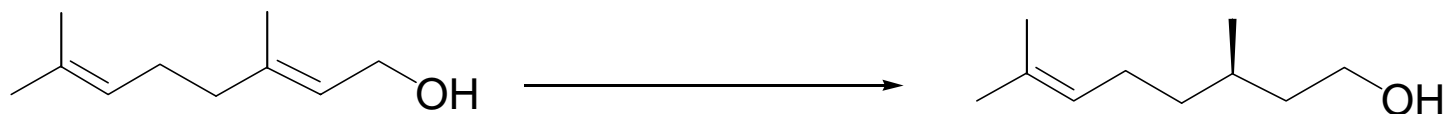
Intermediate for *L*-menthol produced in > 1000 t per year (TON: 400,000, TOF 440, 97% ee).



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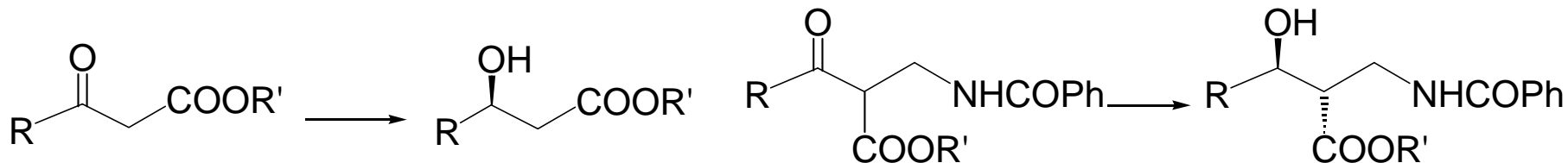
BINAP in asymmetric hydrogenation

BINAP-Ru-carboxylate complexes reduce unsaturated acids and allylic alcohols



Takasago, intermediate for Vitamin E (Ru-BINAP, 300t/y, TON 50,000, 97% ee),

BINAP-Ru-halide complexes reduce ketoesters



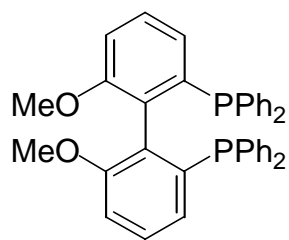
Takasago, NCS Technologies
(up to TON 20,000, 98% ee, multi 100 Kg)

Takasago (dynamic kinetic resolution
100t/y, 97% ee, 94%de)

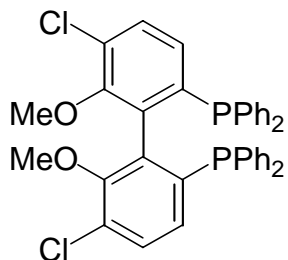


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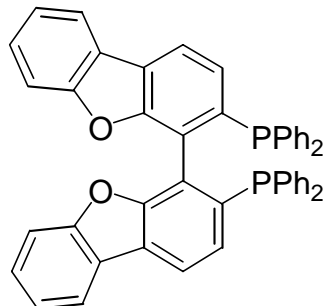
BINAP-type ligands are indispensable tools for asymmetric catalysis



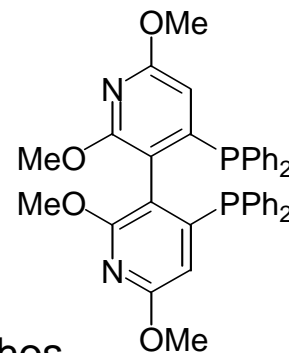
MeO-BIPHEP
(Roche)



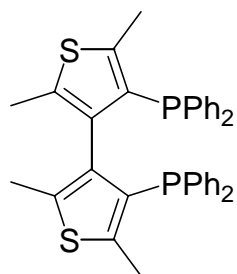
Cl-MeO-BIPHEP
(Bayer)



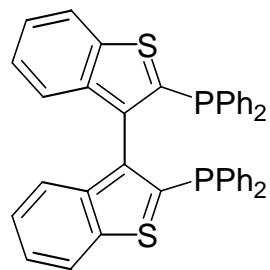
Bibfup (Bayer)



P-Phos
(Chan / Johnson Matthey)

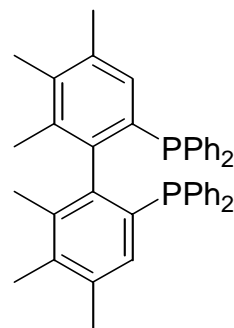


TMBTP
(Sannicolo / Chemi)

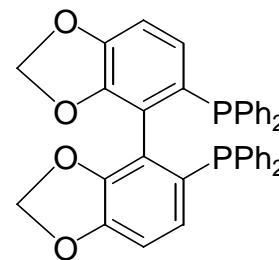


BITIANAP

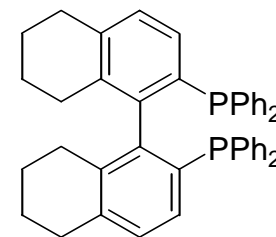
(Sannicolo / Chemi)



Hexaphemp
(Chirotech / Dow)



Seguphos
(Takasago)



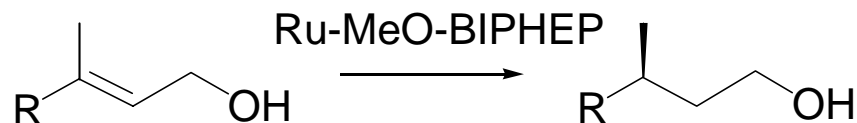
H₈-BINAP



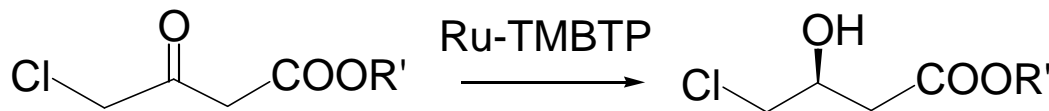
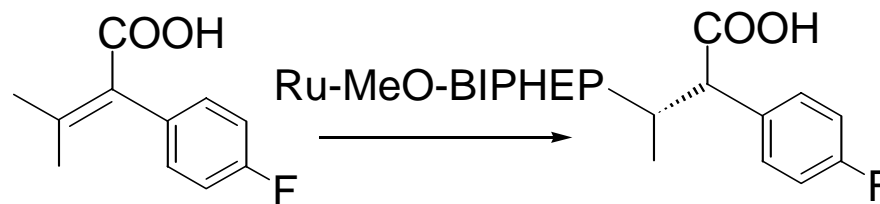
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Some applications of BINAP analogues

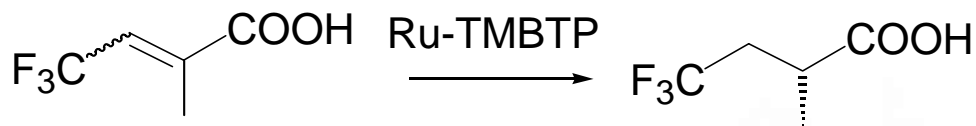
Roche: TON 10-
100,000, TOF -10,000,
> 98% ee



Roche: TON 1,000, TOF
400, 94% ee, multi 10 Kg



Chemi: intermediate for carnitine,
TON 20,000, TOF 15,000, 97% ee



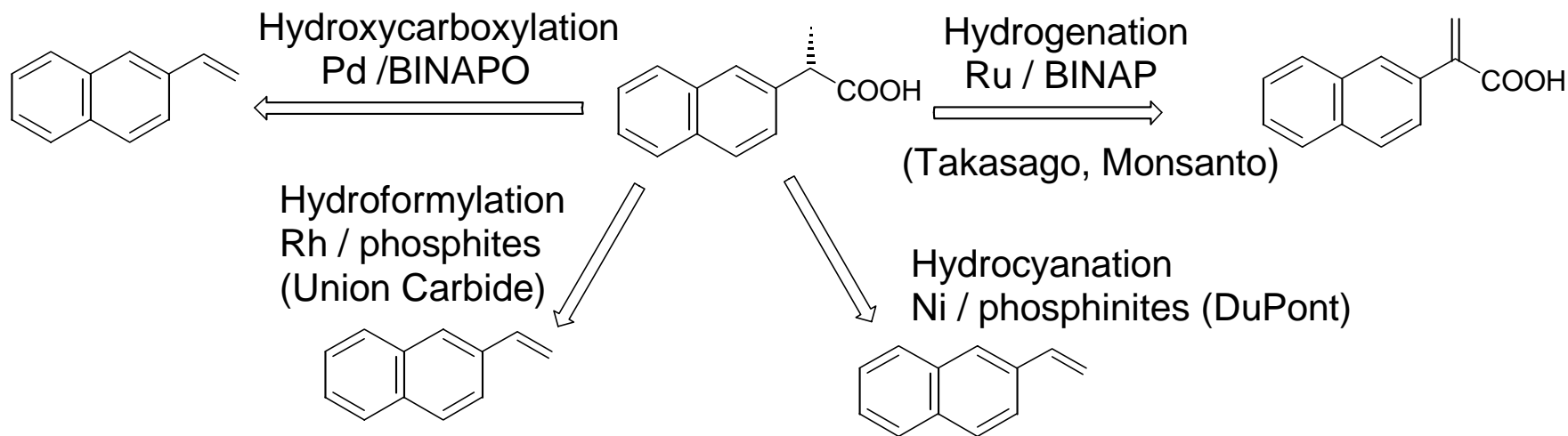
Chemi: TON 20,000, TOF
6,600, 92% ee, multi 100
Kg



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...Not only success stories....

Catalytic synthesis of (S)-Naproxen



No catalytic approach could compete with the original resolution strategy:

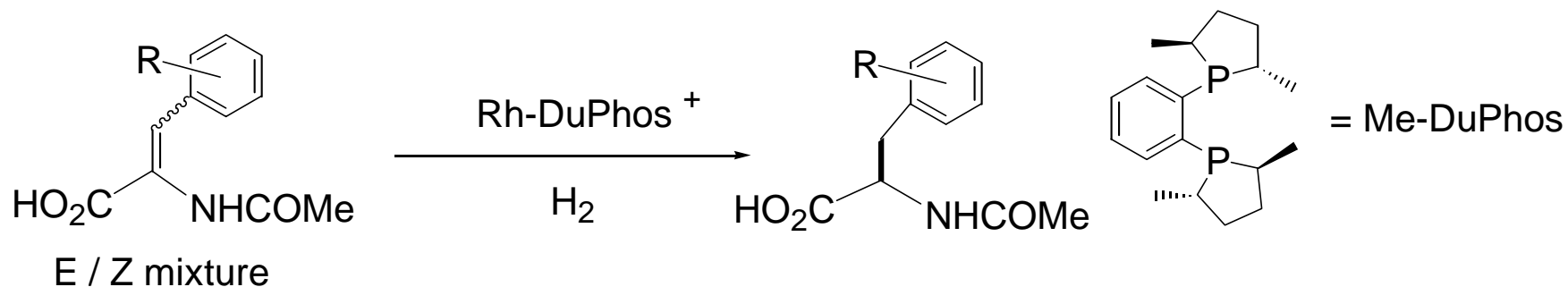
- optimised resolution with recycling of unwanted enantiomer (Syntex)
- starting materials for catalytic reactions are expensive
- some catalytic transformations are not yet efficient enough and further enantioenrichment is required



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Synthesis of aminoacids *via* asymmetric hydrogenation

In 1990 the problem of the hydrogenation of E/Z mixtures was solved by the introduction of bidentate phospholanes (DuPhos, BPE) by M. Burk at DuPont

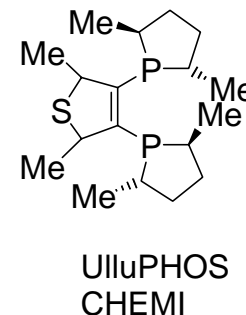
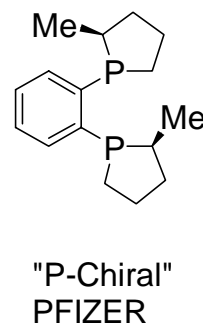
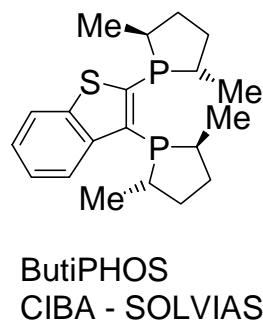
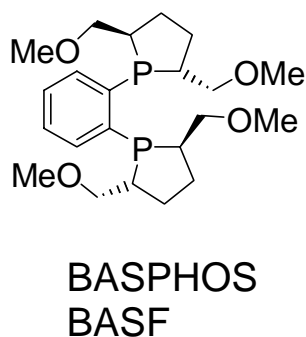
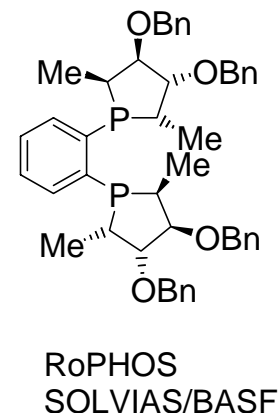
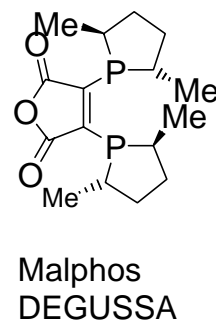
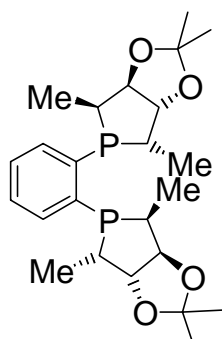
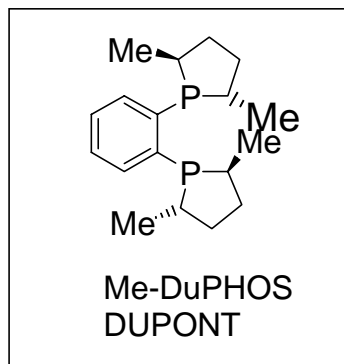


Chirotech: various dehydroaminoacids hydrogenated in multi 10 Kg batches, TON > 1,000, >98 % ee, often in combination with biocatalytic deacetylation

M. Burk *Acc. Chem. Res.* **2000**, 362


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..... More phospholane ligands ...

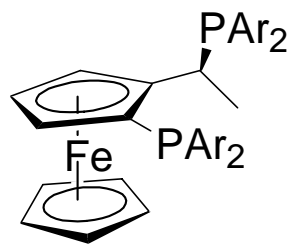


These ligands are functionally equivalent to DuPHOS and fall outside the scope of DuPont patents

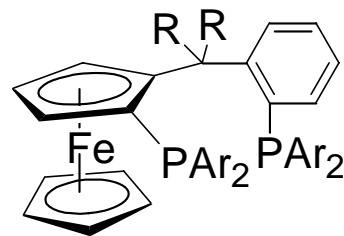


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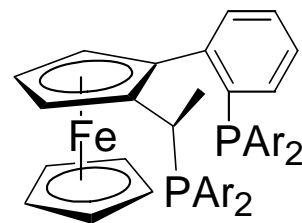
Ligands based on the ferrocene backbone



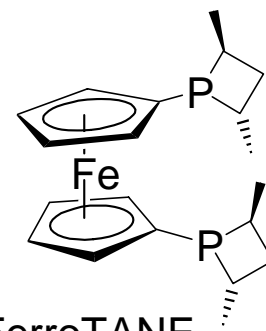
Josiphos
(Ciba/Solvias)



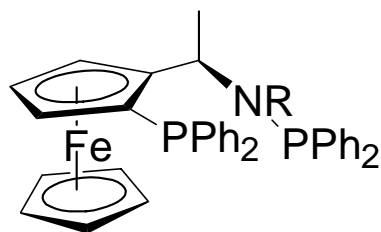
TaniaPhos
(Solvias)



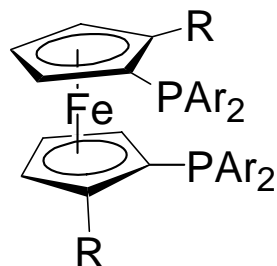
MandyPhos
(Solvias)



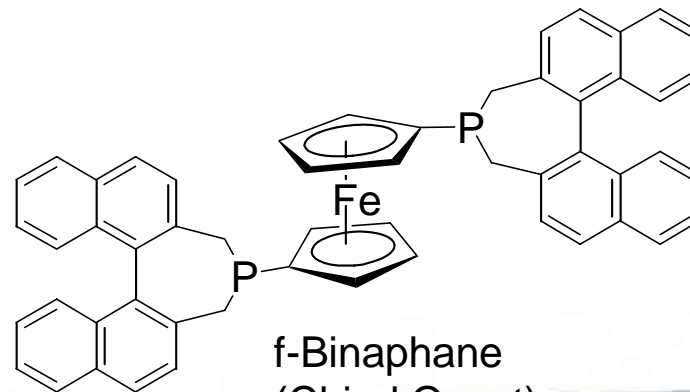
FerroTANE
(Chirotech)



BoPhoz
(Eastman)



R = CONR₂ JAFAPhos
(Aventis/Johnson Matthey)

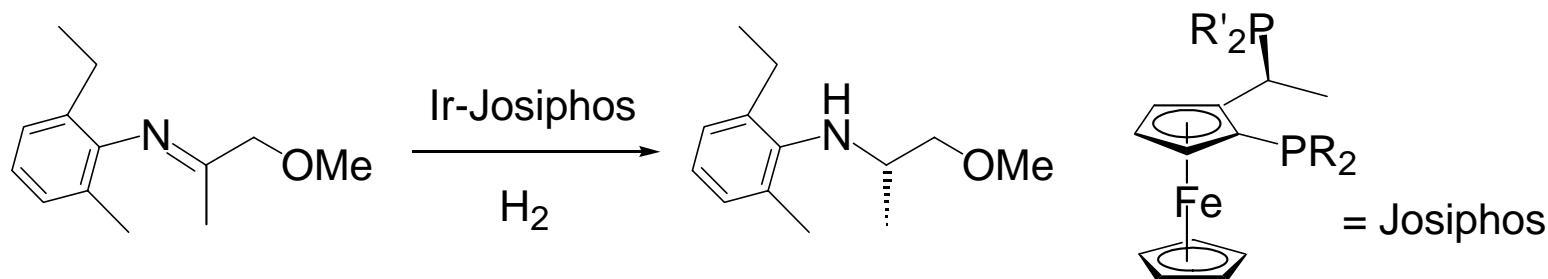


f-Binaphane
(Chiral Quest)



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Ciba/Syngenta/Solvias: synthesis of (S)-Metolachlor



Intermediate for an herbicide, >100,000 t/y, 80% ee, TON 2,000,000, TOF 400,000

Critical factors:

moderate enantioselectivity requirement

Identification of appropriate additives

development of a family of ligands

commitment to >10 years research

The history of Metolachlor chiral switch:

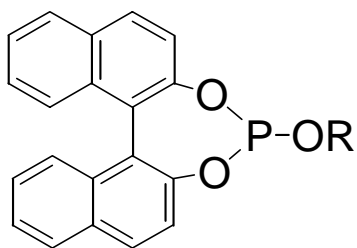
H.U. Blaser *Adv.Synth.Catal.* **2002**, 17



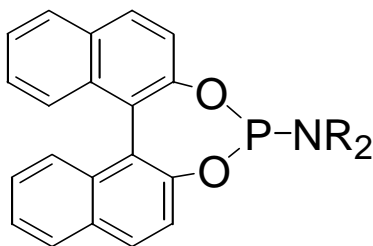
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Ligands for asymmetric hydrogenation: new trends

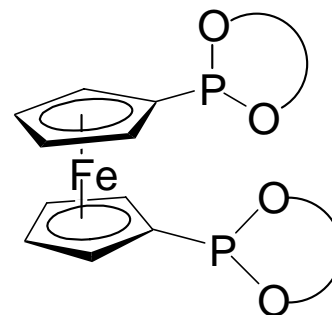
- Monodentate ligands are being “rediscovered”
- Phosphites, phosphonites, phosphoramidates are used
- as cheap alternative ligands



Monophosphites
(Reetz, Bayer)



MonoPhos
(Feringa, DSM)



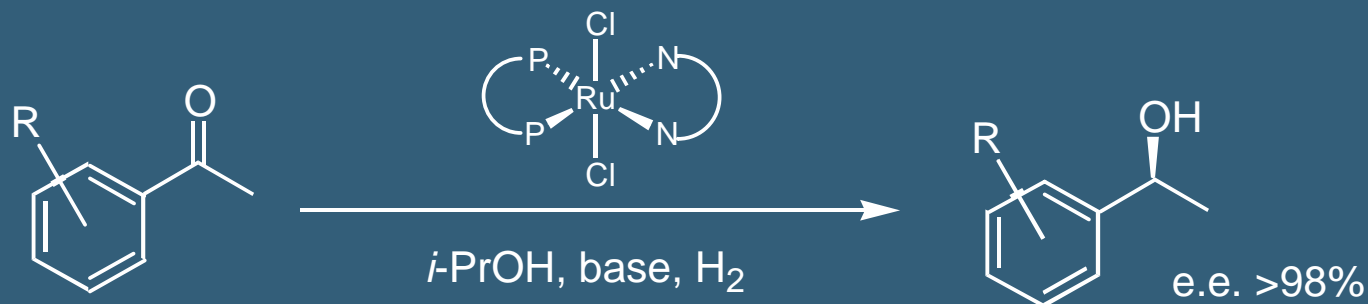
Phosphonites (Reetz)

Will the reduced cost of the ligand
compensate for the reduced activity?



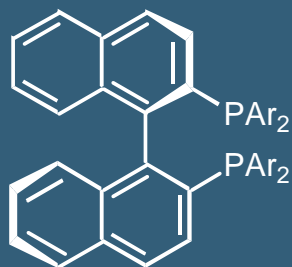
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Ketone Hydrogenation Technology



Original work by Noyori (1995):

Phosphine:

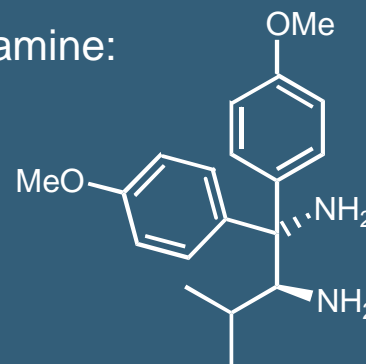


Ar = Ph
(*R*)-BINAP

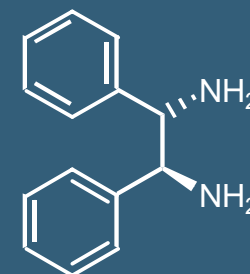
Ar = *p*-CH₃-C₆H₄
(*R*)-Tol-BINAP

Ar = 3,5-(CH₃)₂-C₆H₃
(*R*)-Xyl-BINAP

Diamine:



(*S*)-DAIPEN



(*S,S*)-DPEN

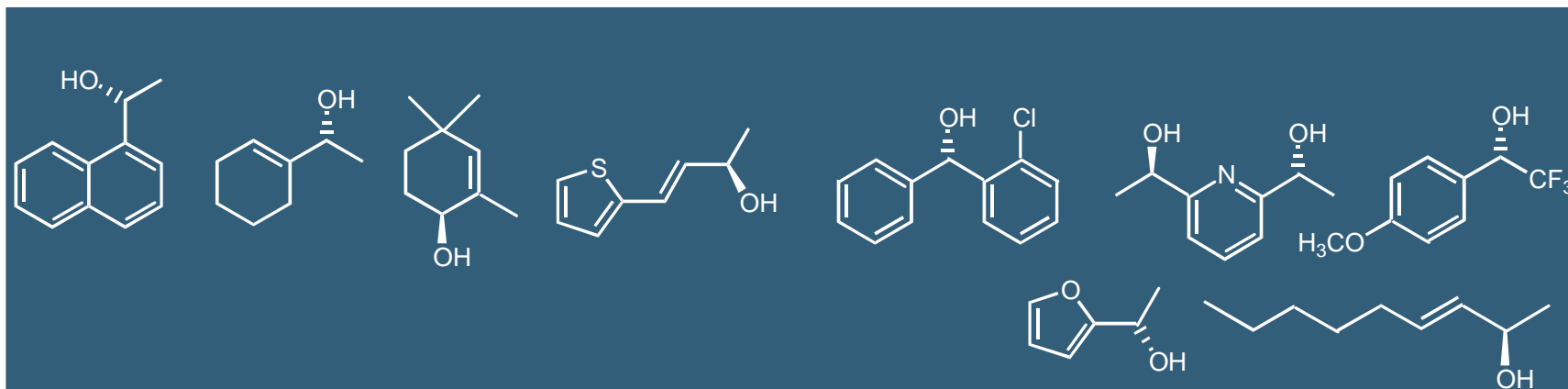
Noyori, Nobel lecture, *Angew.Chem.Int.Ed.* **2002**, 2008

Noyori *et al.* *Angew.Chem.Int.Ed.* **2001**, 40



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Scope and Potential of Ketone Hydrogenation Technology



The reaction has excellent industrial applicability:

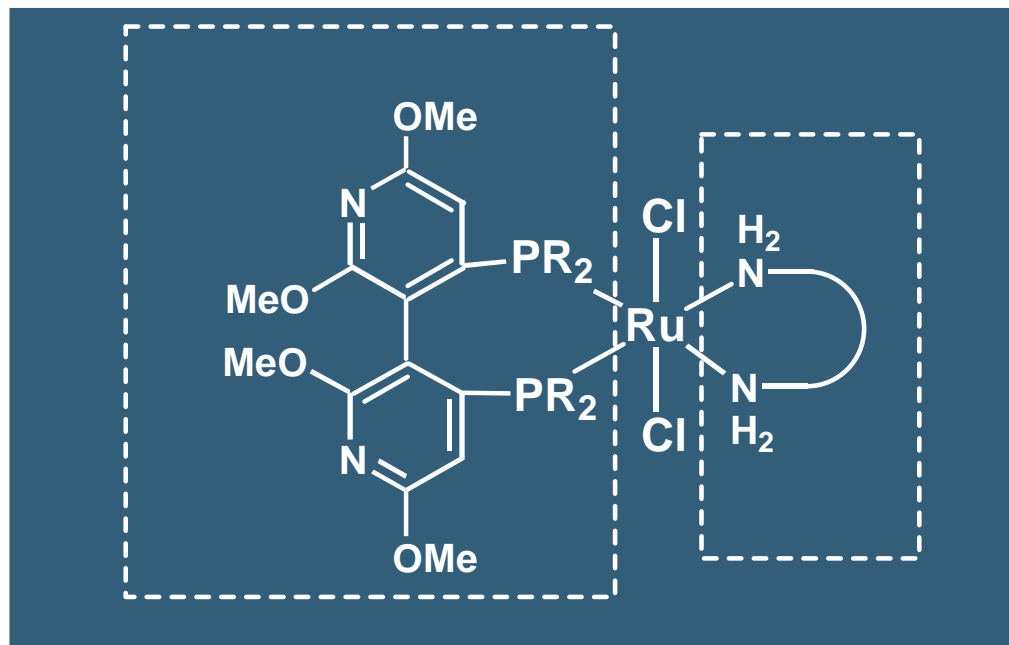
- High selectivity (>98% ee), activity (TON up to 100,000) and broad scope
- It can be applied to existing processes without changes in the synthetic strategy



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New Ligands for Ketone Hydrogenation

Main focus for the development of new catalysts has been, so far, the phosphine ligand.



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New Ligands for Ketone Hydrogenation – Part I

Phanephos-Ru-DPEN is more active than BINAP complexes and activated more quickly TON up to 100,000 and TOF up to 60 sec^{-1}

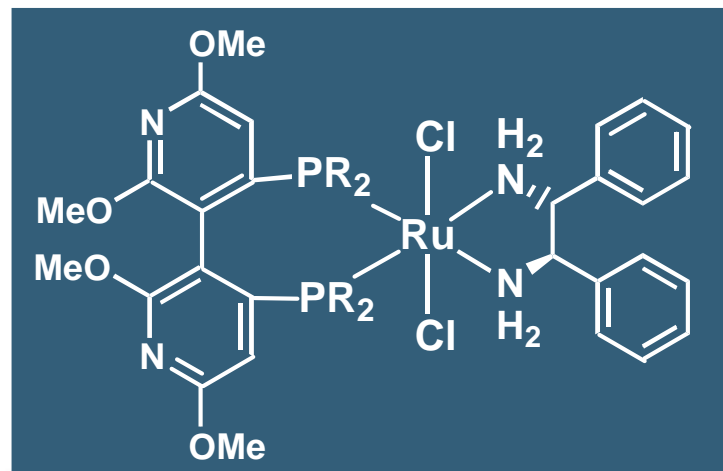
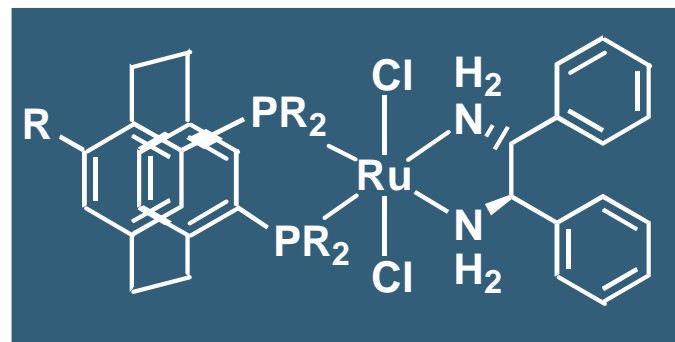
Phanephos: M. Burk *et al* *Org. Lett.* **2000**, 4173

Paraphos: JM CCT *Org. Lett.* **2004**, 1927

Xyl-P-Phos and P-Phos-Ru-DPEN are competitive with BINAP complexes and do not require expensive diamines. TON up to 100,000

A. Chan *et al* *J.Org.Chem.* **2002**, 7908

A. Chan *et al* *Eur.J.Chem.* **2003**, 2963

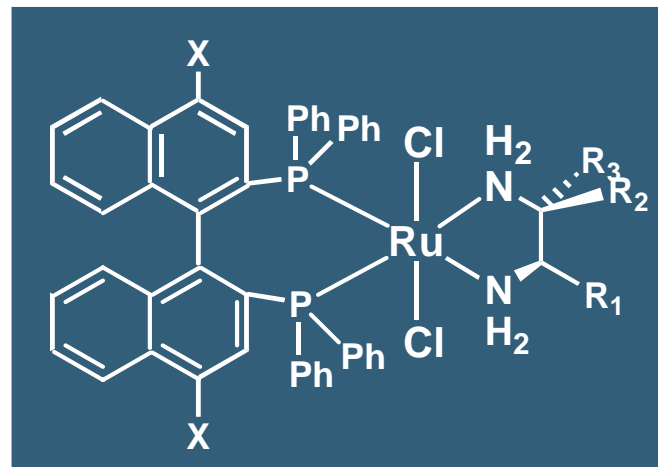


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New Ligands for Ketone Hydrogenation – Part II

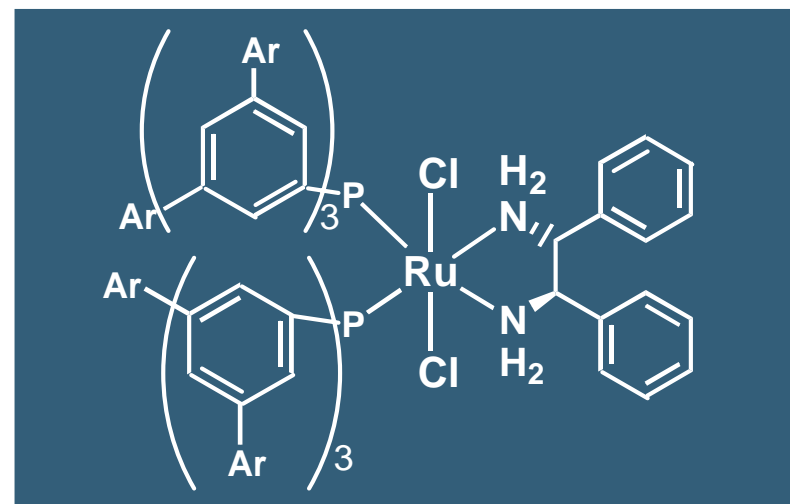
4,4'-Disubstituted BINAP provide a suitable chiral pocket even without Xyl substituents. TON of up to 1,000,000

W. Lin *et al.*, *Org. Lett.* **2004**, 2937



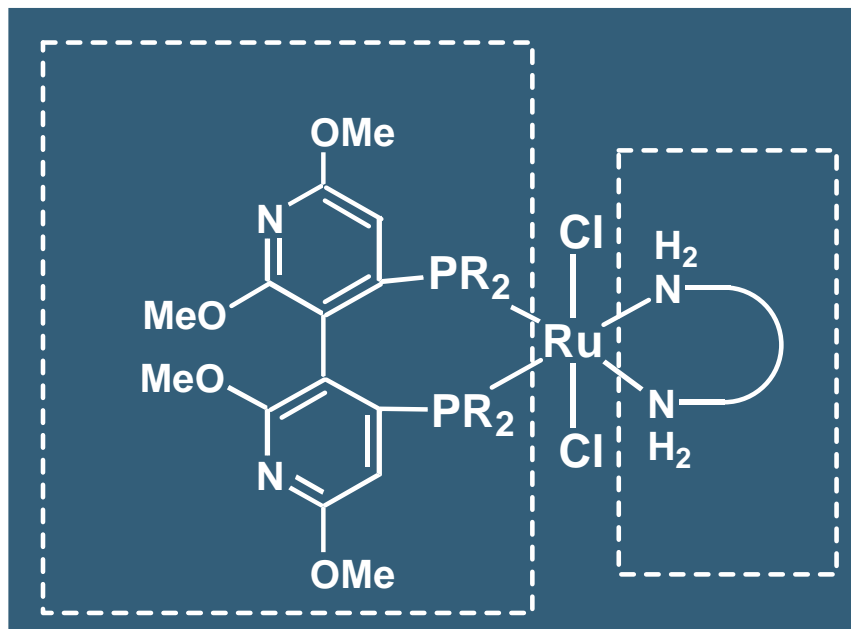
Bulky aromatic monophosphine ligands give activity and selectivity comparable with the best bidentate ligands

Ding *et al.*, *Adv.Synth.Catal.* **2005**, 1193



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New Diamine Ligands for Ketone Hydrogenation



Diamines different from 1,2 diamines will change the orientation of the N-H group and will open the opportunity to further catalyst tuning

Ketone hydrogenation mechanism studied by Noyori *et al.*, *J.Am.Chem.Soc.* **2003**, 13490

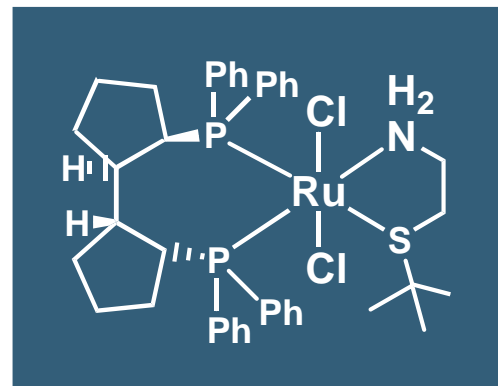


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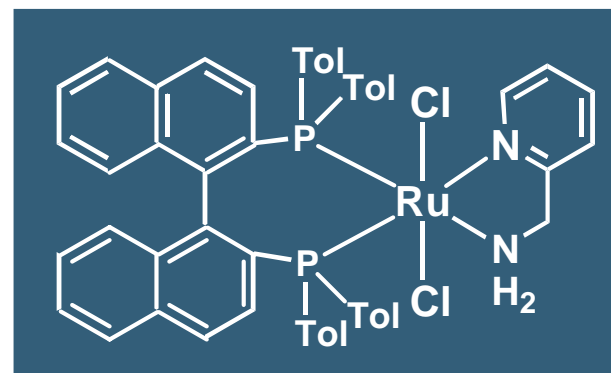
New Focus on the Amine Ligand

Aminothioethers combined with BICP
give high selectivity in n-BuOH, TON up to
1000

D. Ager, D. Genov
Angew.Chem.Int.Ed. **2004**, 2816



The use of aminomethylpyridine makes
possible the reduction of aliphatic t-Butyl
ketones in EtOH, TON up to 100,000

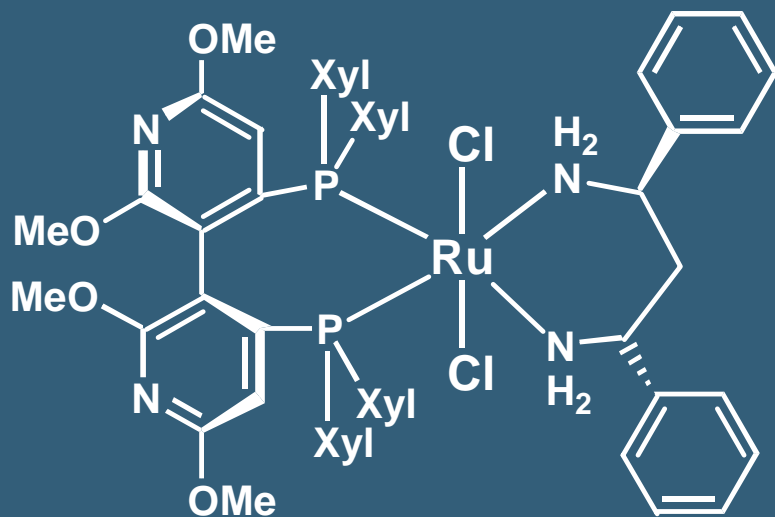


R. Noyori *et al* *J.Am.Chem.Soc.* **2005**, 8288

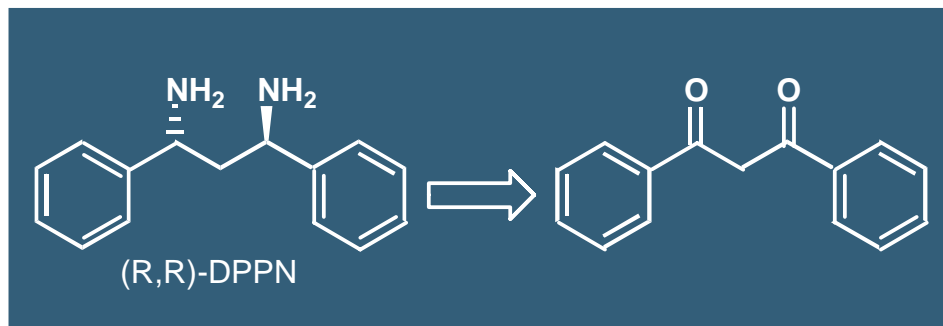


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1,3 –Diamines: [Xyl-P-Phos RuCl₂ DPPN]



[(S)-Xyl-P-Phos RuCl₂ (R,R)-DPPN]

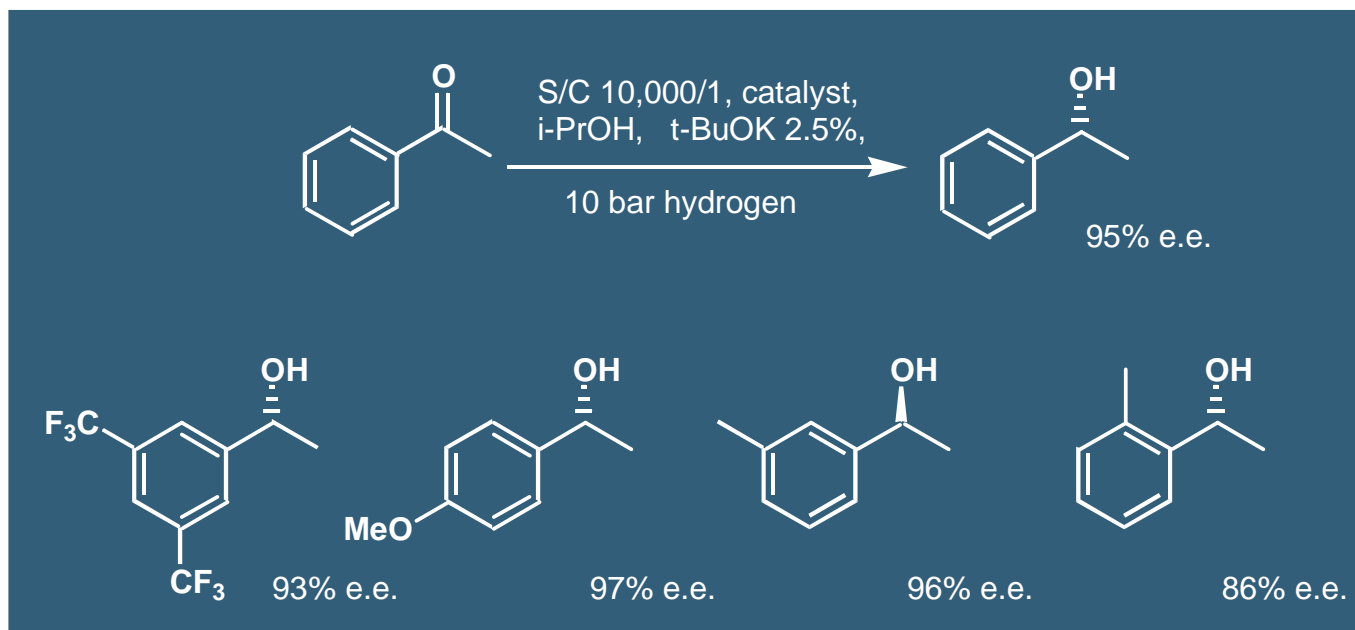


G. Grasa, A. Zanotti, W. Hems, *Journal of Organometallic Chemistry*, in print.



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1,3 –Diamines: [Xyl-P-Phos RuCl₂ DPPN]



The properties of the DPPN are broadly similar to the analogous DPEN catalysts.

Xyl-Phos gives better selectivity than P-Phos.

Strong matching/mismatching effect.



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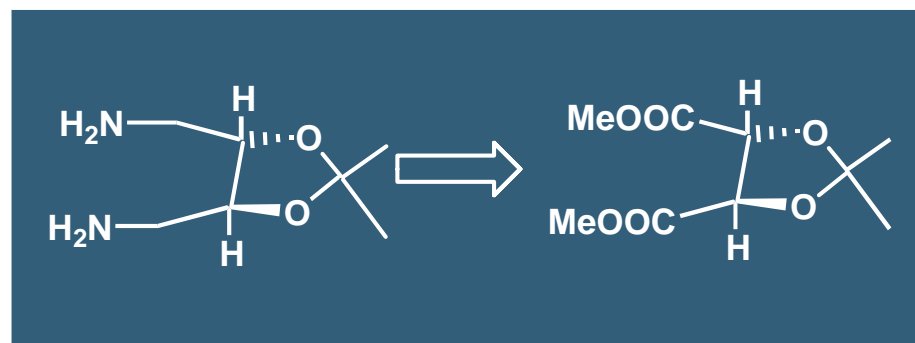
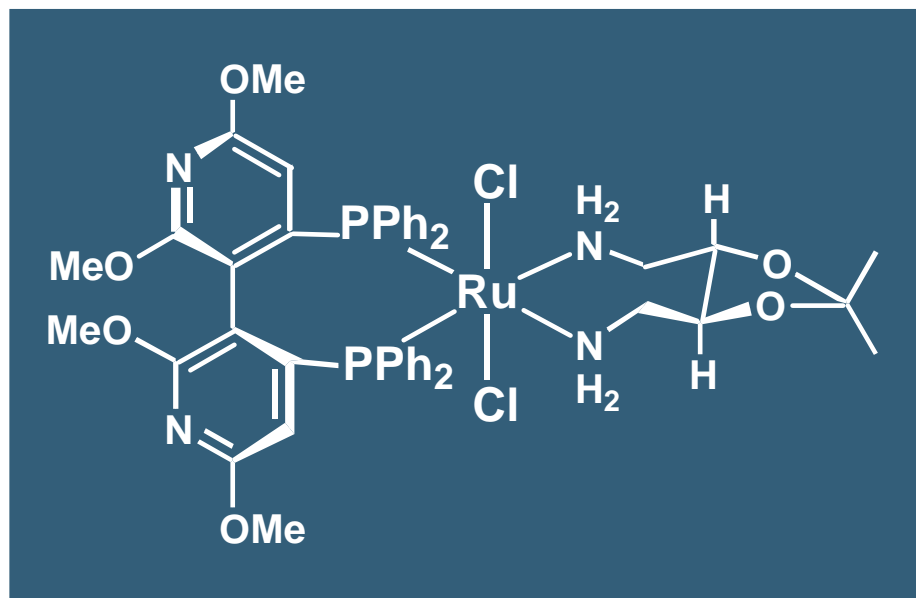
1,3 –Diamines: [Xyl-P-Phos RuCl₂ DPPN]

- Rates and enantioselectivity make the DPPN catalyst a useful addition to ketone hydrogenation technology but no significant advantages are obtained over the DPEN ligand



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1,4-Diamines: [P-Phos RuCl₂ (DAMTar)]

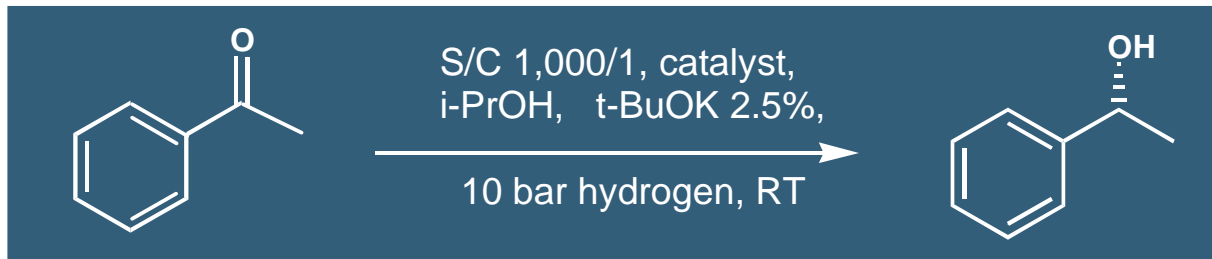


G.Grasa, A. Zanotti, J. Medlock,
W. Hems, *Org. Lett.*, **2005**, 1449



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Hydrogenation of Acetophenone



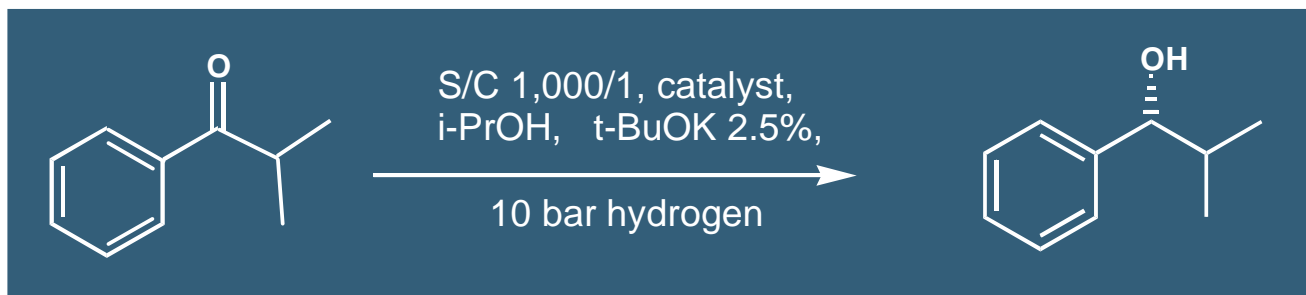
| | |
|--------------------------------------|---------------|
| (R)-P-Phos / (R,R) 1,4-diamine : | 75 % e.e. (R) |
| (S)-P-Phos / (R,R) 1,4-diamine : | 81% e.e. (S) |
| (R)-Xyl-P-Phos / (R,R) 1,4 diamine : | 55% e.e. (S) |
| (S)-Xyl-P-Phos / (R,R) 1,4 diamine : | 51% e.e. (R) |

- P-Phos better than Xyl-P-Phos
- Limited matching/mismatching of phosphine/diamine ligands
- Moderate results obtained on acetophenone but higher selectivity with 2-MeO-acetophenone (93%ee)



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Catalysts

Hydrogenation of Iso-Butyrophenone



(S)-P-Phos / (R,R) 1,4-diamine : 97 % e.e. (S)

(S)-P-Phos / (S,S) 1,4-diamine : 95% e.e. (S)

Catalyst with
racemic diamine !

(S)-P-Phos / (rac) 1,4 diamine : 96% e.e. (S)

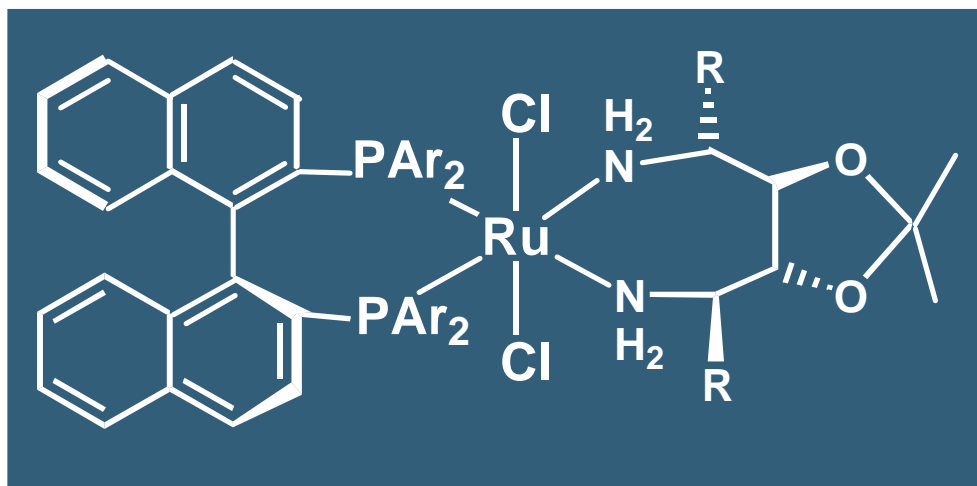
Changing the ring size imparts new properties to the catalyst:

- Enhanced stereocontrol by the phosphine ligand
- Rate acceleration vs. DPEN catalyst



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Catalysts

1,4-Diamines: [BINAP RuCl₂ IPHAN]



Hydrogenation of tetralone
with BINAP / 1,4-diamines

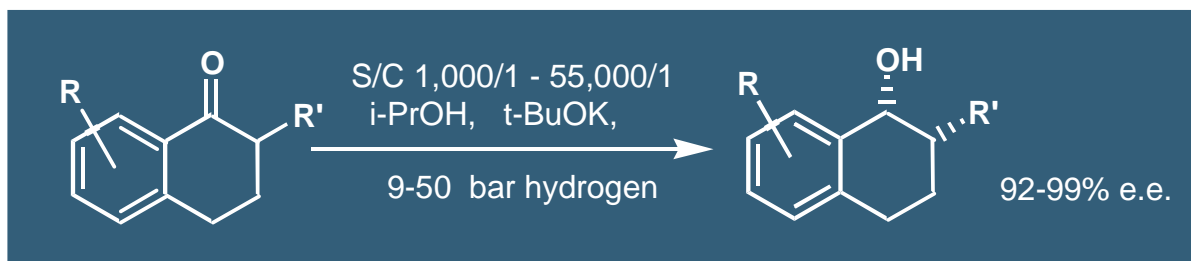
Dynamic kinetic resolution
is possible

R. Noyori *et al.* *Org. Lett.*, **2004**, 2681



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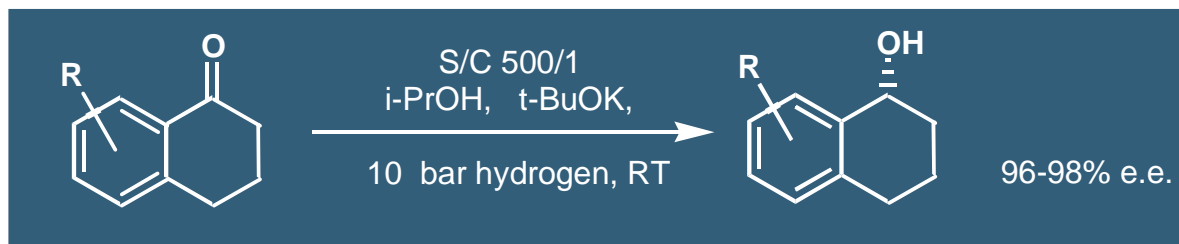
Hydrogenation of Cyclic Ketones



(*S*)-Xyl-BINAP RuCl₂ (*R*)-IPHAN: tetralone and 7-substituted tetralones

(*S*)-Tol-BINAP RuCl₂ (*R*)-IPHAN: 4,5 and 6-substituted tetralones

Dynamic kinetic resolution is possible



(*S*)-Xyl-P-Phos RuCl₂ (*R*)-DAMTar: tetralone and 6-MeO-tetralone



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Catalysts

(P-Phos) and (BINAP) RuCl₂ (1,4-Diamines)

- 1,4-diamine ligands are complementary to 1,2-diamine ligands
- The catalysts bearing 1,4-diamines are practically useful and expand the range of substrates for asymmetric hydrogenation.
- The different ring sizes in the Ru-diamines impart different properties to the catalyst



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Where next?

- Process and development
- Understanding of the factors that govern the reactivity of the catalyst
- Creativity in testing new combination of ligands

The goals:

- Application on scale of the existing asymmetric hydrogenations
- Application to new substrates and transformations



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