DSM

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The Combinatorial Approach to Asymmetric Hydrogenation.

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DSM Pharma Chemicals

and

University of Groningen

IASOC 2004, Ischia

Unlimited. DSM

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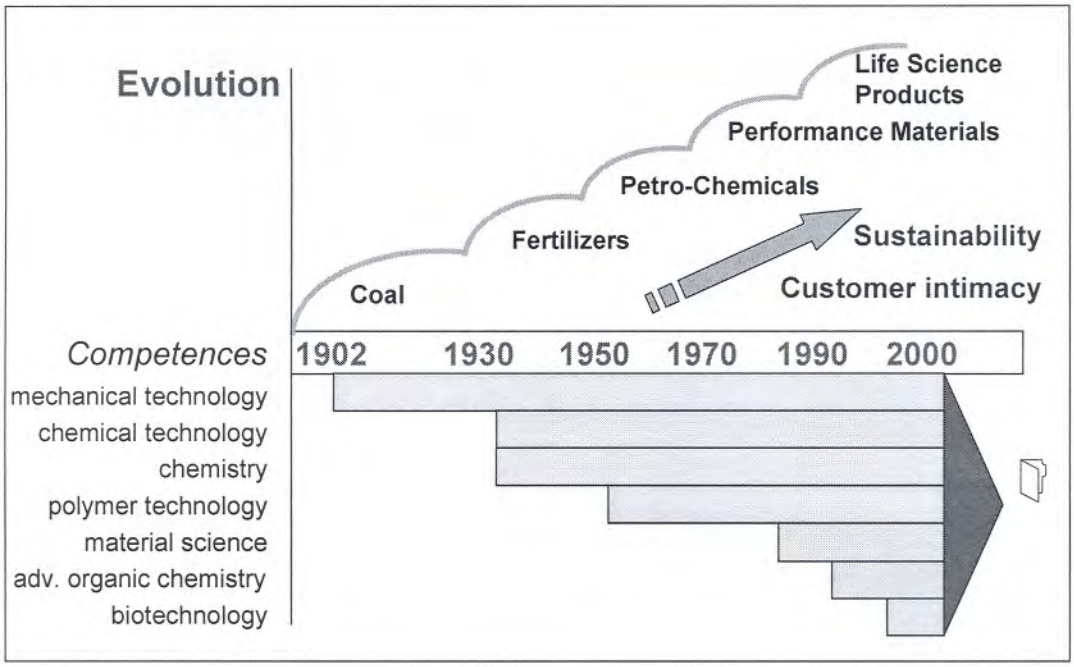
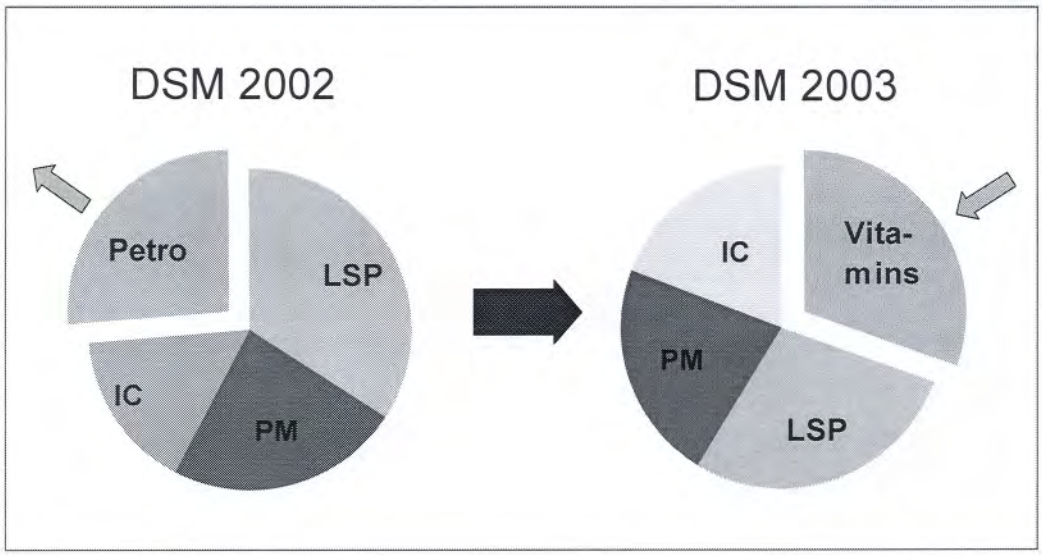
DSM. A century of change



Strategic impact Petrochem & Roche deals



Total sales ~ € 7 bn
Specialties from ~ 50% to > 80%

Homogeneous Catalysis for Fine Chemicals

Important technologies

- Asymmetric hydrogenation (olefins, ketones, imines, enamides)
- Asymmetric transfer hydrogenation (ketones)
- Asymmetric epoxidation
- Aromatic substitution
    - Heck
    - Suzuki/Negishi
    - Sonogashira
    - Amination
    - Cyanation
- CO chemistry (hydroformylation, carbonylation, amidocarbonylation)
- Isomerisation and racemisation
- Oxidation
    - benzylic and allylic oxidation
    - alcohols to aldehydes or acids
    - olefins to epoxides

Asymmetric Hydrogenation

- Nobel prize winning chemistry
- Several hundred ligands known
- Many thousands examples on lab-scale

Till about 5 years ago the use of this technology for the production of fine chemicals was scarce.

Why?

Reviews

H.U. Blaser, F. Spindler and M. Studer, *Appl. Catal.: A General*, **2001**, *221*, 119.

J.G. de Vries in *Encyclopedia of Catalysis,* I. Horvath, ed. **2003**, Vol 3, p *295.*

Obstacles that need to be overcome

1. Time to market constraints in pharmaceuticals production leads to very short development time
2. Competing technologies
3. Cost
   - Cost of metal (Rh or Ru)
   - Cost of ligand
   - Activity of the catalyst.
   - Stability of the catalyst
   - Recovery or recyclability
4. Availability of catalysts on short notice
5. Patents and high cost of licensing
6. Reliability, real or perceived

Combinatorial / HTE approach to asymmetric hydrogenation

Goal: Find catalytic solution for customer requests within 3 weeks

Requirements:

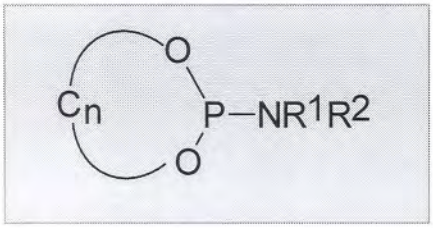
- *Hardware*
  - Endeavor (8 high pressure reactors)
  - Two proprietary reactors for high pressure (96 and 28 vessels)
- *HTE Analysis*
  - GC
  - HPLC (including chiral HPLC)
  - Flow-NMR
- *Libraries of ligands*

Review: *J.G. de Vries and A.H.M. de Vries, Eur. J. Org. Chem.,* ***2003,*** *799-811.*

Review Ligand libraries: *C. Gennari, U. Piarulli, Chem. Rev.* ***2003****, 103, 3071.*

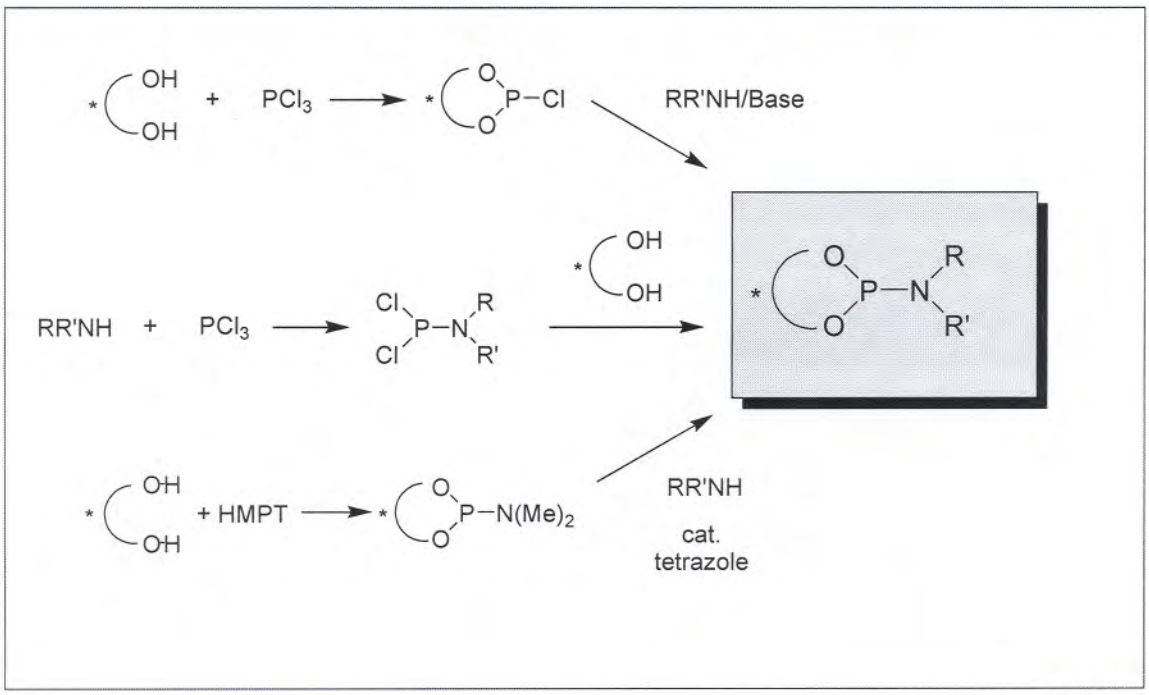
Libraries of ligands

- Libraries of phosphine ligands are not easy to prepare.
- Phosphoramidites on the contrary are easily prepared in 2 steps:

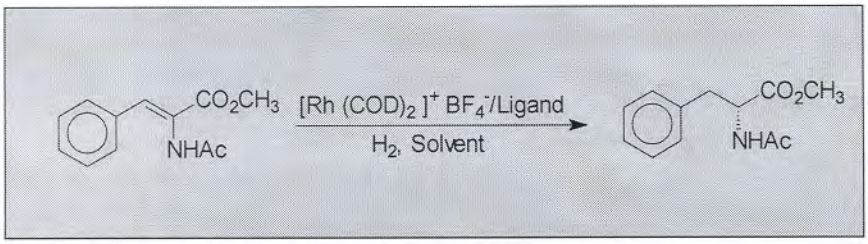


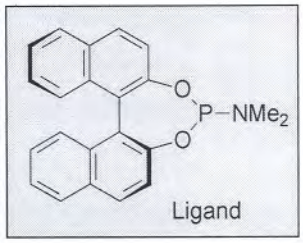
- Diversity from both diol and amine part.
- Chirality from BINOL or TADDOL skeleton or chiral amine.
- Very successful in copper catalysed asymmetric 1,4 addition of Et_2Zn to cyclic enones (B. Feringa et al, RUG)
- Not known for asymmetric hydrogenation!

Easy synthesis of phosphoramidites



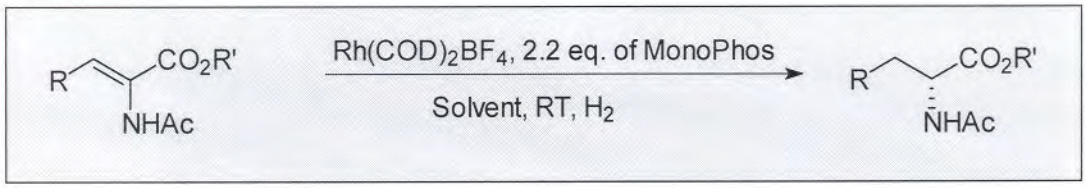
Strong solvent effect but highly enantioselective!





Entry	Solvent	Temp	e.e.
1.	CH_3OH	RT	70%
2.	CH_2Cl_2	RT	95%
3.	CH_2Cl_2	5°C	97%
4.	THF	RT	93%
5.	Acetone	RT	92%
6.	$PrOCH_2CH_2OH$	RT	77%

Asymmetric hydrogenations with MonoPhos™

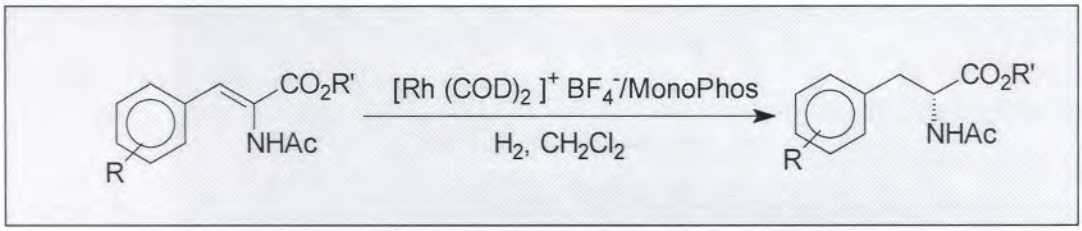


Entry	R	R'	Solvent	e.e. (RT)	e.e (0°C)
1.	Ph	Me	CH_2Cl_2	95%	97%
2.	Ph	H	EtOAc	97%	
3.	H	Me	EtOAc		>99%
4.	H	H	EtOAc	>99%	

M. van den Berg, A.J. Minnaard, E.P. Schudde, J. van Esch, A.H.M. de Vries, J.G. de Vries and B.L. Feringa, *J.Am.Chem.Soc.*, **2000**, *122*, 11539.

WO 02/04466

Substituted phenylalanines



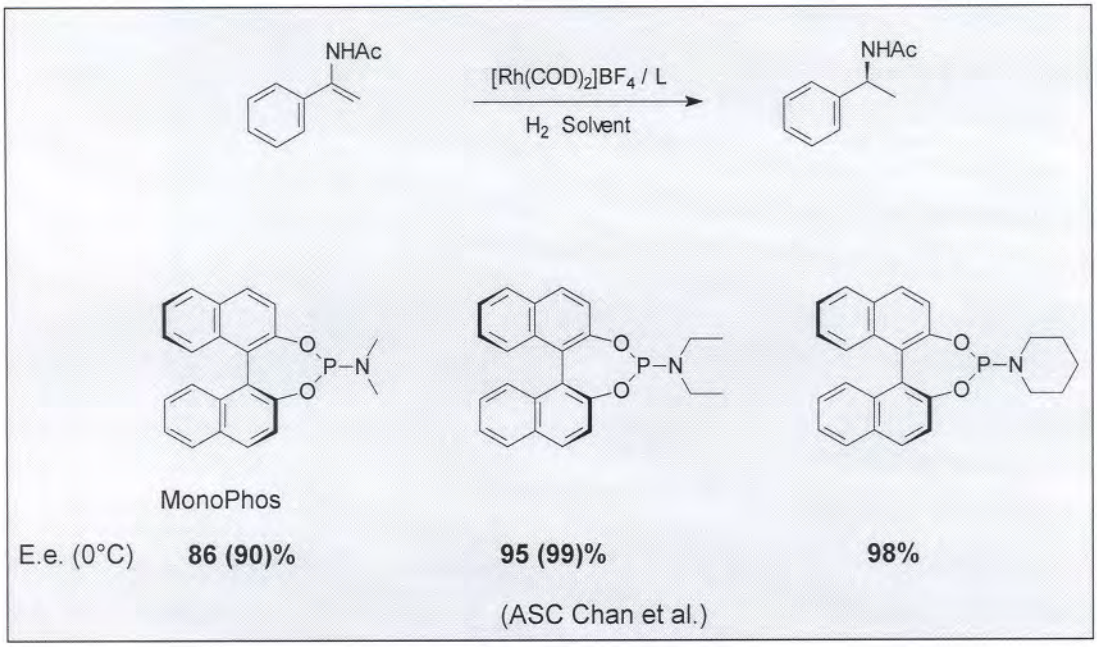
	R	R	Solvent	e.e. (RT)	e.e. (0 °C)
1.	H	Me	CH_2Cl_2	95%	97%
2.	3-MeO	H	CH_2Cl_2	97%	
3.	4- Ph	Me	CH_2Cl_2	95%	
4.	4-OAc, 3-OMe	Me	EtOAc	94%	98%
5.	4-Ac	Me	CH_2Cl_2	99%	

M. van den Berg *et al.*, *Adv. Synth. Catal.* **2003**, *345*, 308-322.

Advantages of MonoPhos™ hydrogenations

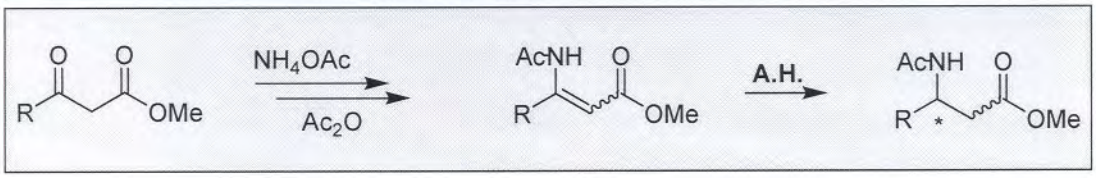
- MonoPhos can be prepared in a single step from commercially available BINOL (Compare with DUPHOS: 6 steps).
- MonoPhos is an order of magnitude cheaper than currently available bisphosphines.
- The hydrogenation rate can be increased by increasing the H_2 pressure *without loss in enantioselectivity*!
- At S/C ratio of 2000 full conversion in 2 h at 10 bar.
- Method of choice for asymmetric olefin hydrogenation.
- Large library of ligands available.

Subtle ligand effects in enamide hydrogenation



H. Bernsmann *et al.*, submitted to JOC

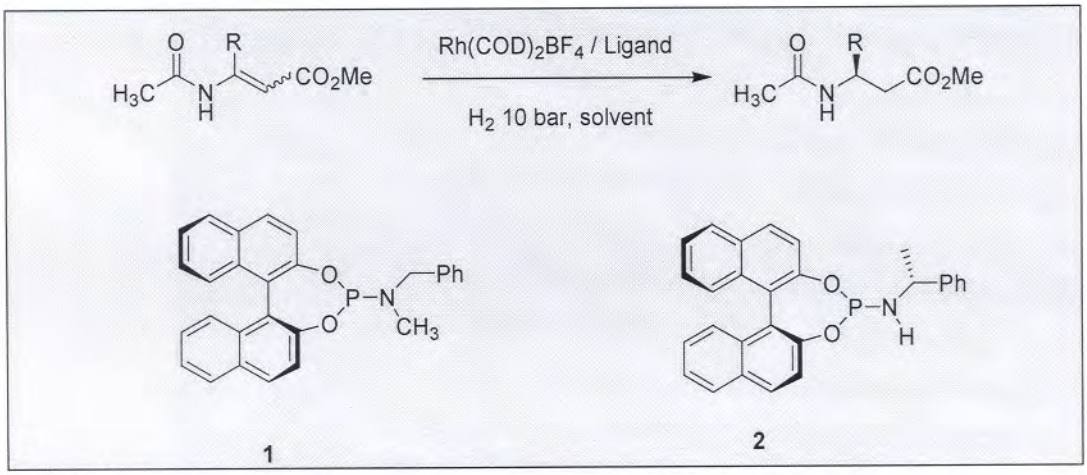
β-Amino Acids by Asymmetric Hydrogenation



- Synthesis of precursors: *Z/E* mixtures with predominantly Z
- Asymmetric hydrogenation of *E* is facile.
- Asymmetric hydrogenation of *Z* is difficult. For R = aryl so far only a few successful catalyst systems known: Ru-BINAPO, Tangphos (X. Zhang *et al.*)
- Two strategies can be developed:
  - find good ligand for Z
  - synthesis of only E

  (See: D. Heller *et al. Angew. Chem. Int. Ed.* **2003**, *42*, 913)

Beta-amino acids



Substrate	Ligand	Solvent	e.e.
E- R = CH_3	***MonoPhos***	CH_2Cl_2	95%
E- R = CH_3	**1**	CH_2Cl_2	99%
Z- R = CH_3	**2**	*i*PrOH	95%
Z- R = Ph	**2**	*i*PrOH	92%

D. Peña et al,
J. Am. Chem. Soc.,
2002, *124*, 14552-3.

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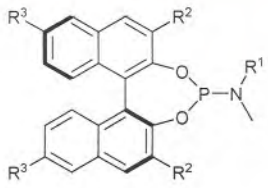
Cocktails anyone?

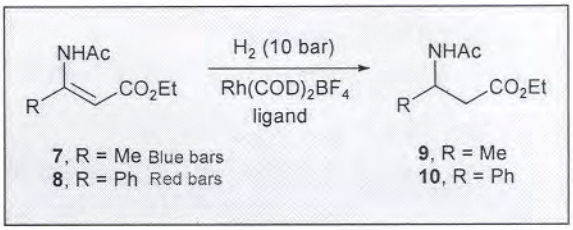
- What happens if you mix ligands?

RhL^1L^1 ⇌ RhL^1L^2 ⇌ RhL^2L^2

Combinatorial Catalysis with Mixtures of Monodentate Ligands

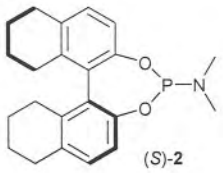


(*S*)-**1**, R^1 = Me, R^2 = R^3 = H
(*S*)-**3**, R^1 = R^2 = Me, R^3 = H
(*S*)-**4**, R^1 = Me, R^2 = H, R^3 = Br
(*S*)-**5**, R^1 = Bn, R^2 = R^3 = H

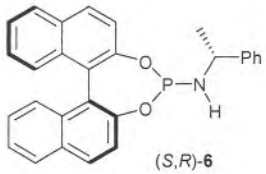


7, R = Me Blue bars
8, R = Ph Red bars

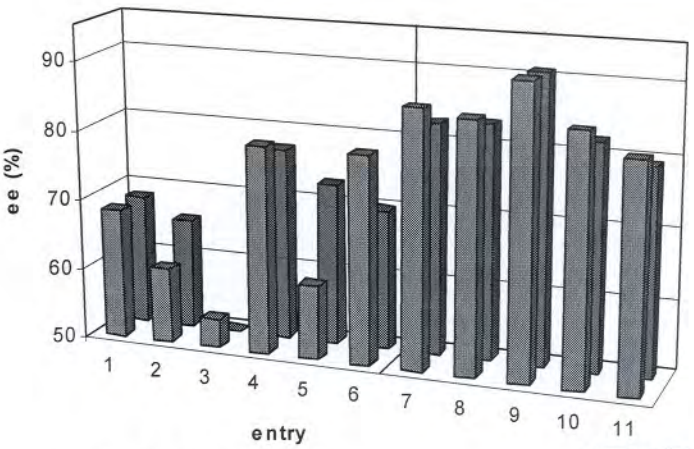
9, R = Me
10, R = Ph



(*S*)-**2**



(*S,R*)-**6**

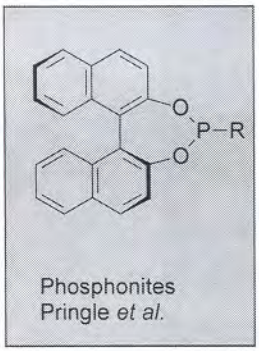


7 = 6 +1; 8 = 6 + 2; etc.

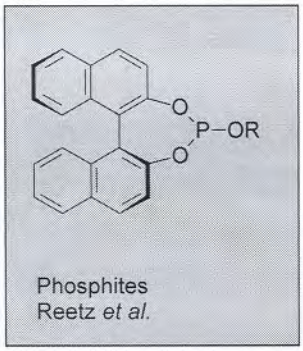
Combinatorial catalysis.....

- ...works! (D. Peña *et al. Org. Biomol. Chem.*, **2003**, *1*, 1087.).
- From NMR: Almost exclusive formation of mixed complex in case of e.e. enhancement.
- Most tested combinations gave lower enantioselectivity than the homo-catalysts.
- Significantly increases the scope of asymmetric hydrogenation.
- Also shown to work with monodentate phosphites. (M.Reetz *et al. Angew. Chem. Int. Ed.* **2003,** *42,* 790.)

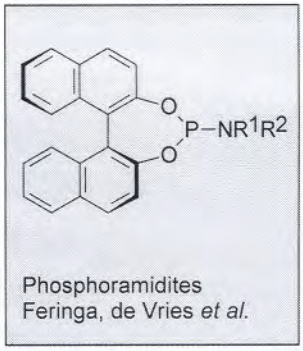
New low-cost monodentate ligand families



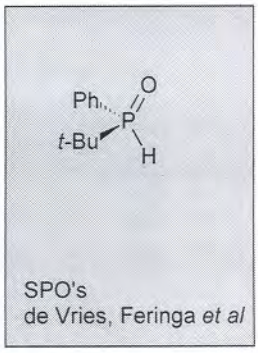
Phosphonites
Pringle *et al.*



Phosphites
Reetz *et al.*



Phosphoramidites
Feringa, de Vries *et al.*

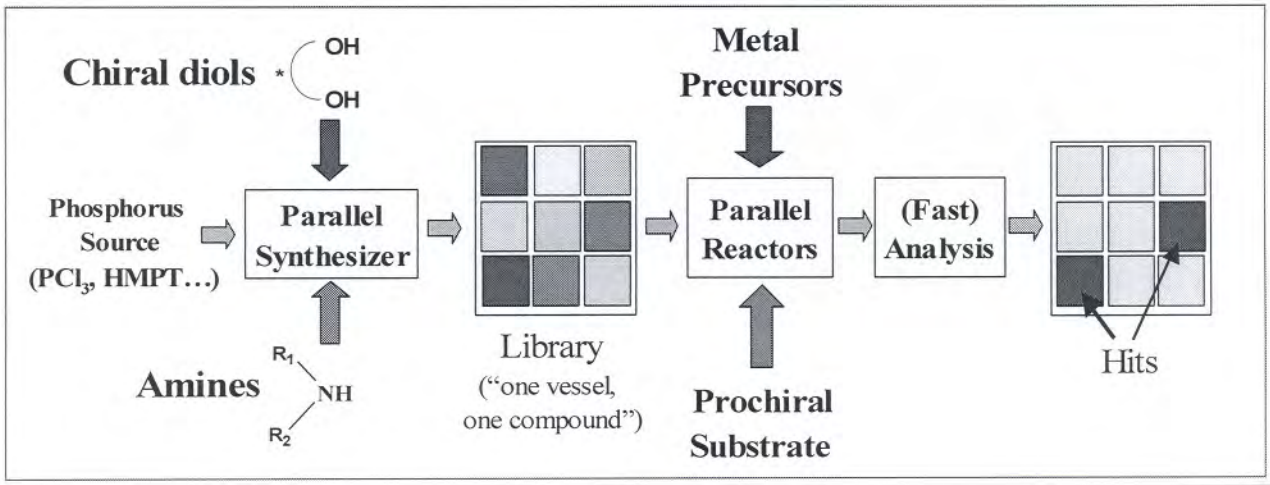


SPO's
de Vries, Feringa *et al*

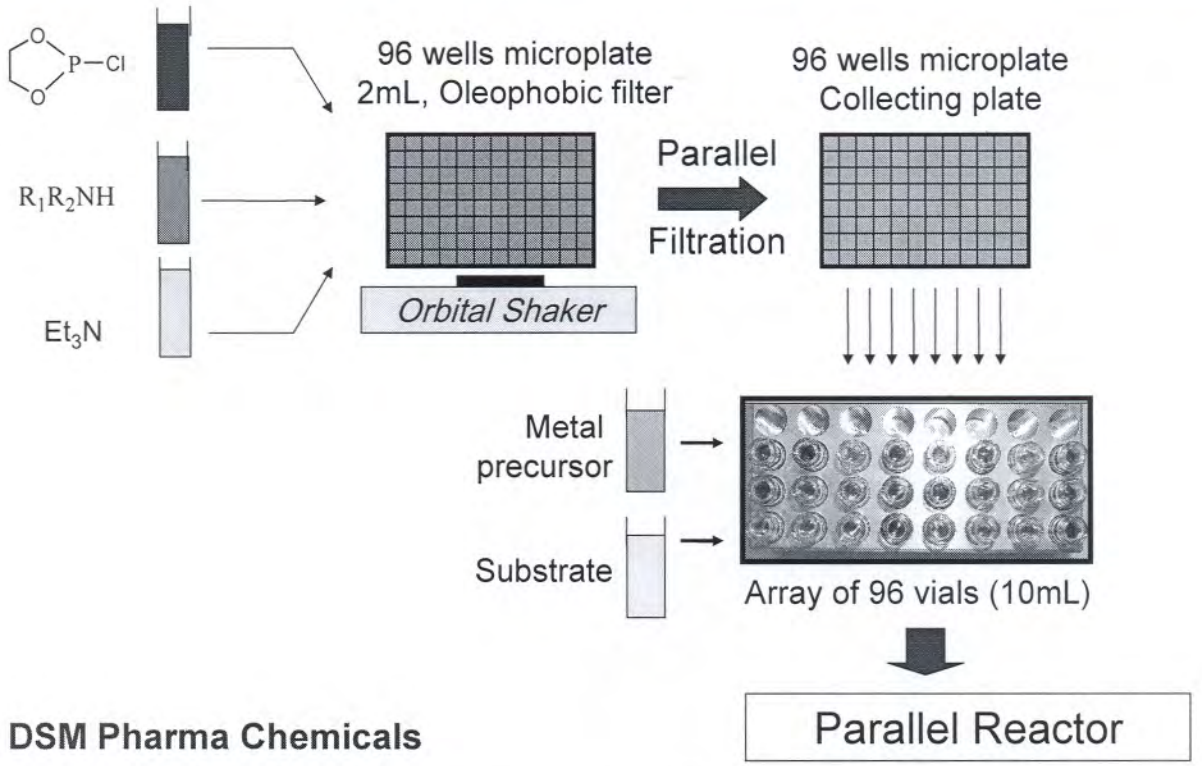
- They can all be synthesized in 1-2 steps
- Other applications besides hydrogenation: Asymmetric Heck, hydroarylation, hydrosilylation, allylic substitution.

The combinatorial approach to ligand finding

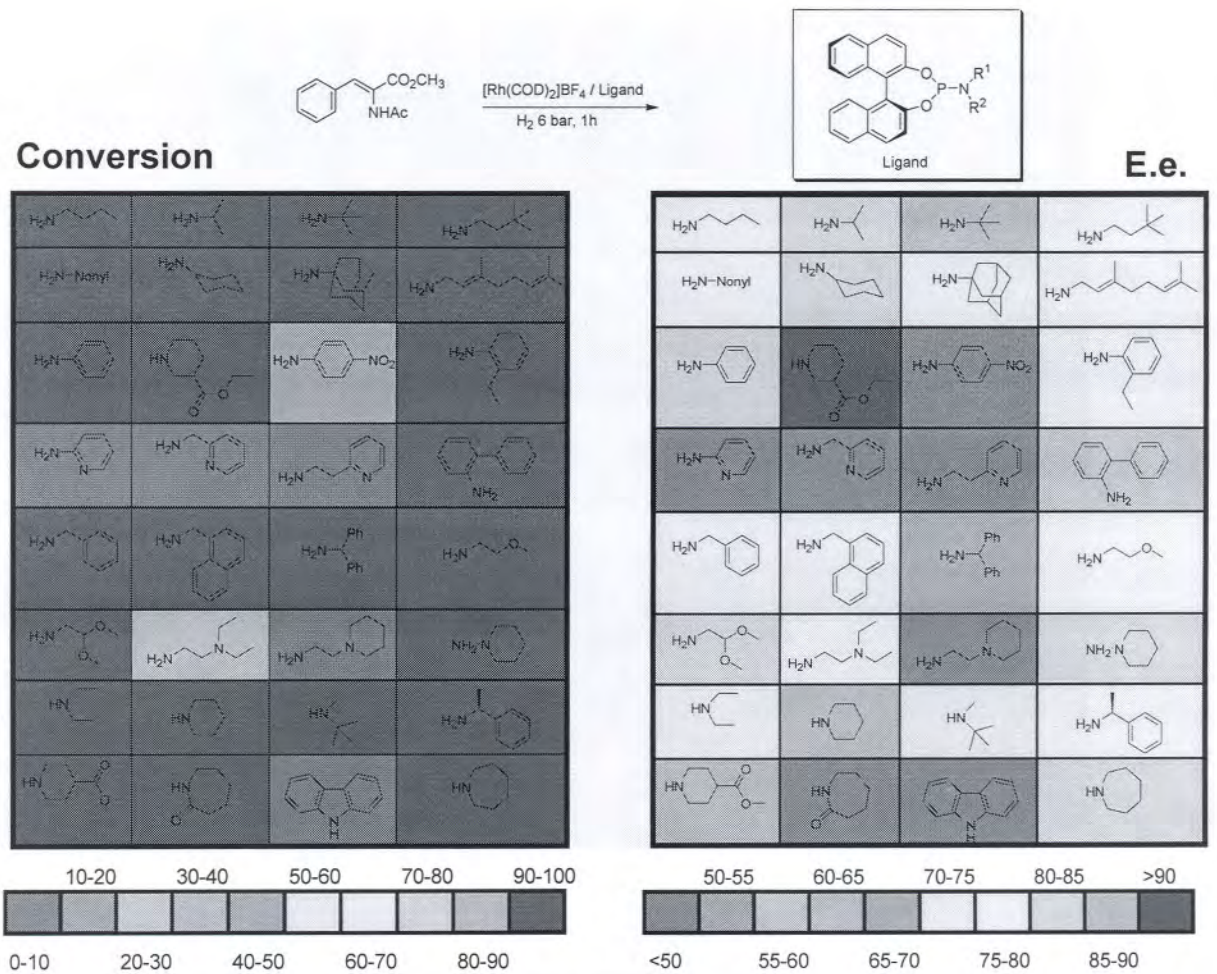
- So far ligand libraries have been made manually. Each ligand synthesised and purified separately.
- Can we make ligands in a robot?
- What about purification?

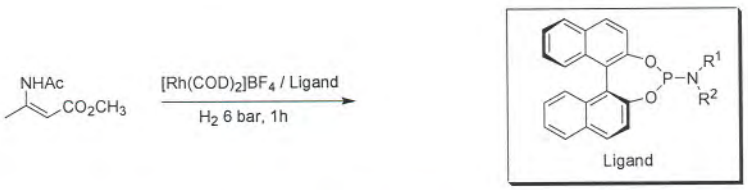


96 New ligands in 1 day, tested the next day



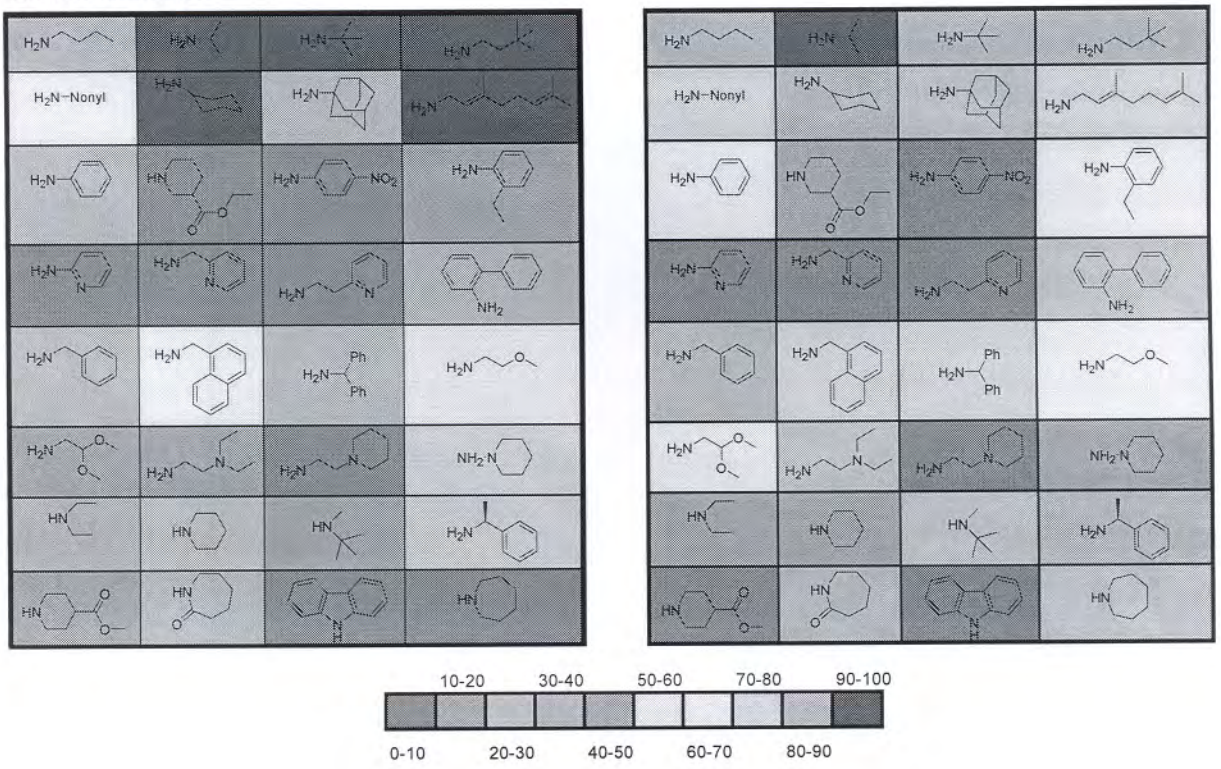
DSM Pharma Chemicals





Conversion

E.e.



Comparison

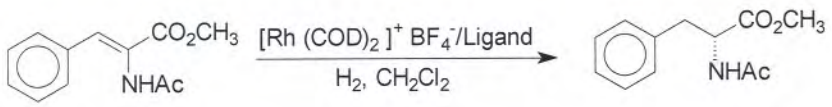
Ligand	Purified ligands		Library ligands	
	Conv. (%)	Ee (%)	Conv (%)	Ee (%)
NEt_2	8	46	11	41
Piperidine	11	55	7	43
NH–α–MeBenz	96	94	51	88
NHiPr	100	95	95	92

Instant Libraries!

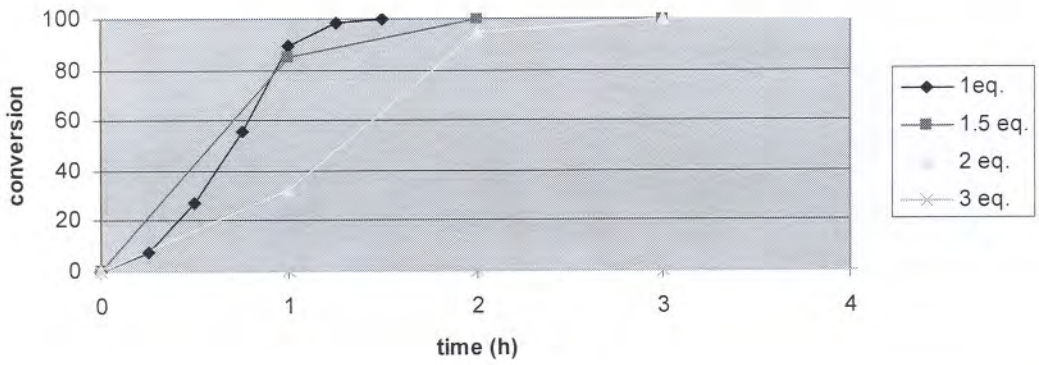
- This HTE approach enables a very fast synthesis of a wide range of phosphoramidites and their screening in asymmetric olefin hydrogenation of
- Also less easy accessible N-H ligands can be tested.
- E.e's are slightly lower than for the conventional reaction. However, the order is representative.
- Can also be applied to other monodentate ligand fanilies
- Can also be applied in other catalytic chemistry (C-C bond formation)

L. Lefort, J.A.F. Boogers, A.H.M. de Vries and J.G. de Vries, *Org Lett,* ***2004***

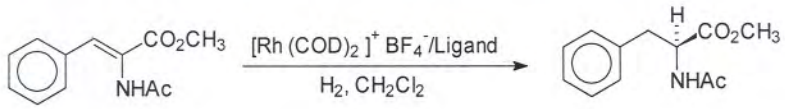
Effect of Ligand/Rh ratio



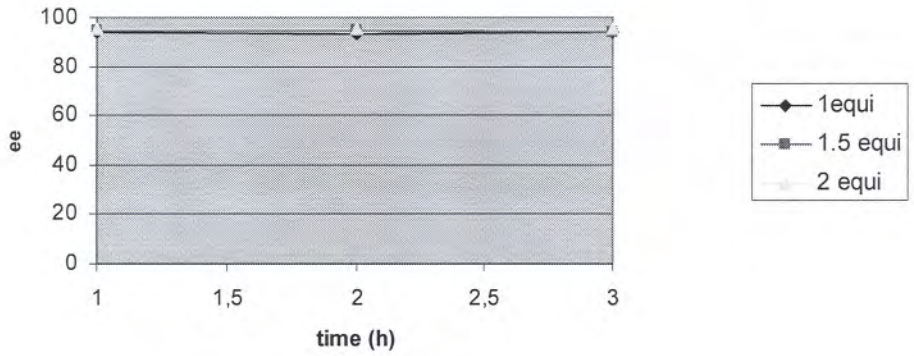
Rate dependence on Monophos/Rh ratio



Effect of Ligand/Rh ratio

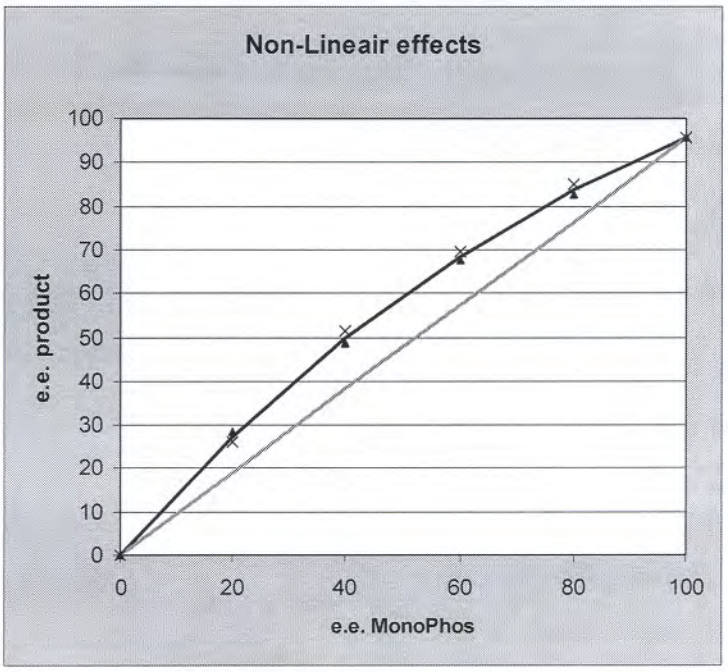


E.e dependence on MonoPhos/Rh ratio

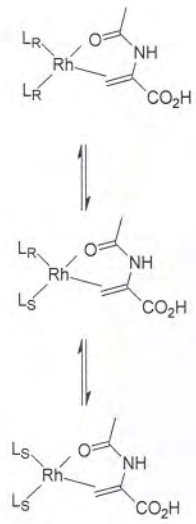


How many ligands on rhodium

- Asymmetric Amplification!
- More than 1 ligand on rhodium?



Possible equilibria in solution



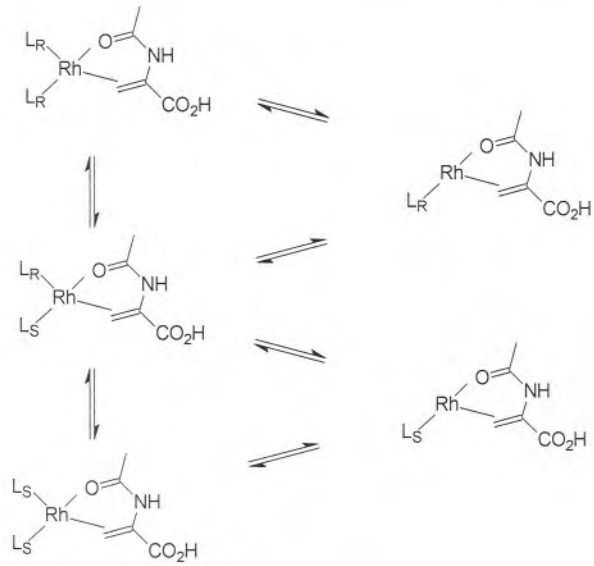
If the "racemic" catalyst is slower than the enantiopure catalysts the e.e. will be higher than expected; positive asymmetric amplification.

If the "racemic" catalyst is faster than the enantiopure catalysts: e.e. will be lower than expected; negative asymmetric amplification.

This experiment proves the existence of RhL_2,

But.....

Possible equilibria in solution



• ..it does not rule out the existence of catalytically active RhL.

•NMR, MS and kinetic studies needed.

Electrospray MS

Experiment with 5 mol% Rh followed over time with ES-MS (cationic mode):

After 30 min: RhL_2(nbd), RhL_2(Substrate), RhL_3, RhL_3(Substrate)

After 60 min: RhL_2(nbd), RhL_2(Substrate), RhL_3, RhL_4

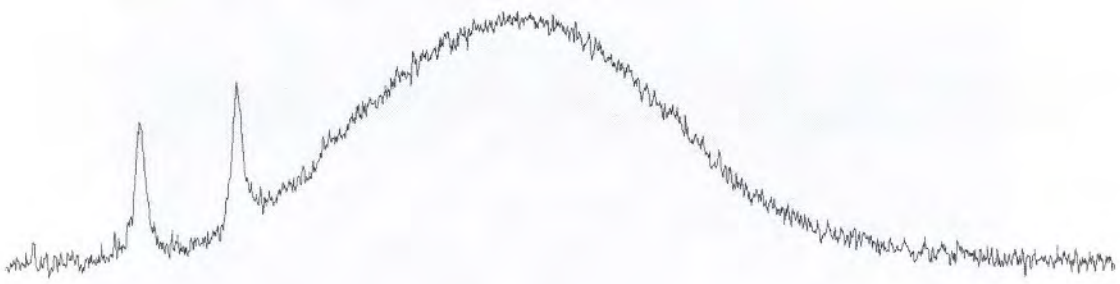
After 120 min: RhL_2(Substrate), RhL_3, RhL_4

Conclusions:

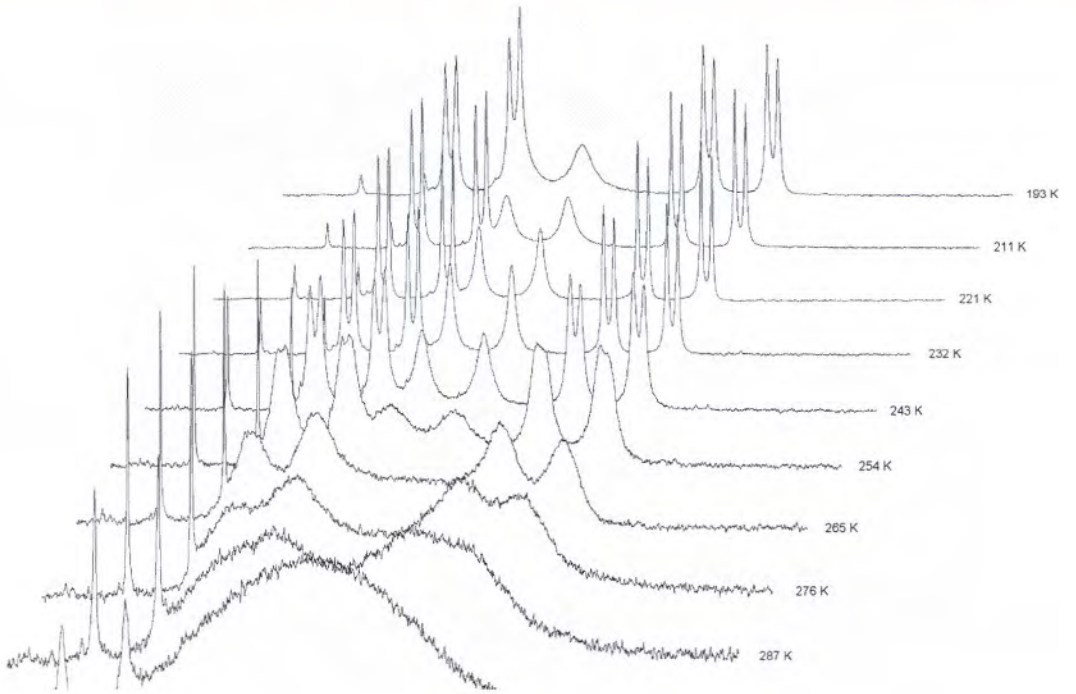
- **No RhL derived complexes found**
- **RhL_3 and RhL_4 cannot lead to products**
- **From results with mixtures of ligands: Only RhL_2 (not RhL) is an active catalyst!**
- **A large part of the rhodium is tied up in inproductive complexes.**

^{31}P NMR

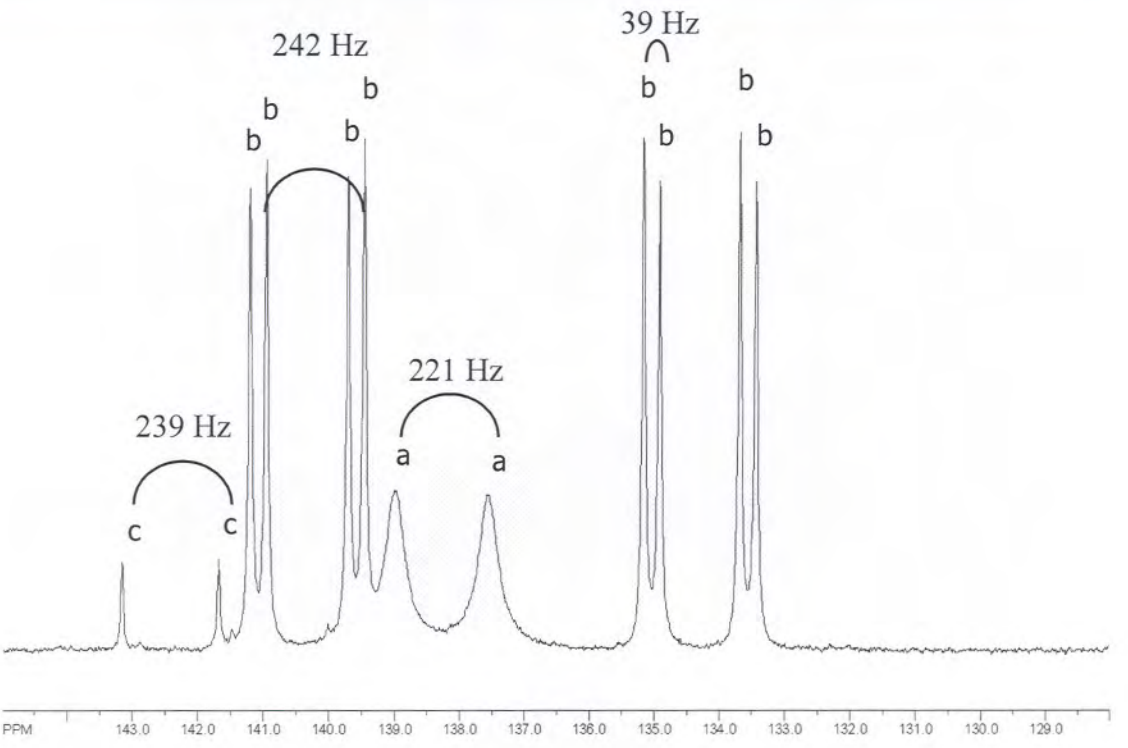
Complex made from $Rh(COD)_2BF_4$ + 2 MonoPhos; slowly added



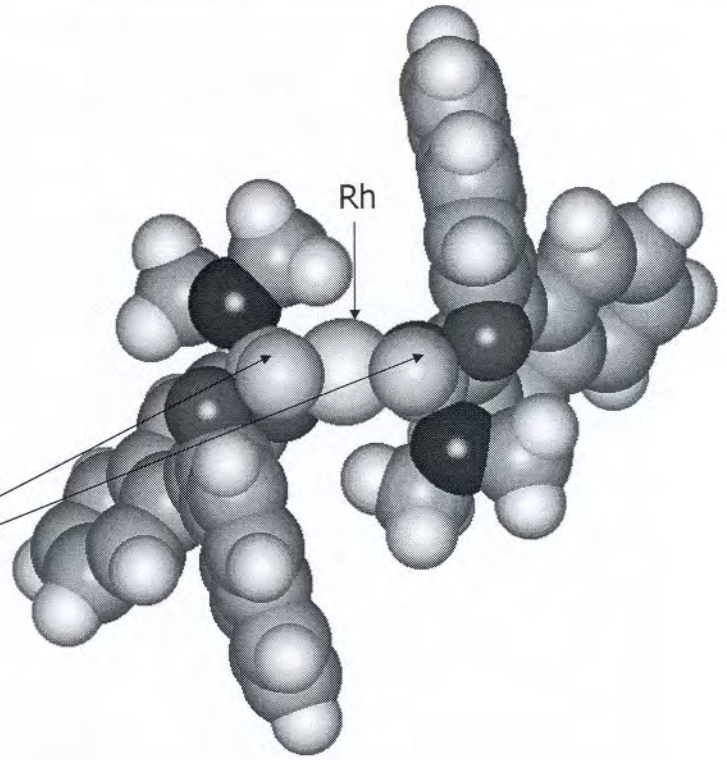
$Rh(MonoPhos)_2(COD)BF_4$
^{31}P NMR in CD_2Cl_2 at various temperatures



^{31}P NMR $Rh(MonoPhos)_2(COD)BF_4$ in CD_2Cl_2 at 211K

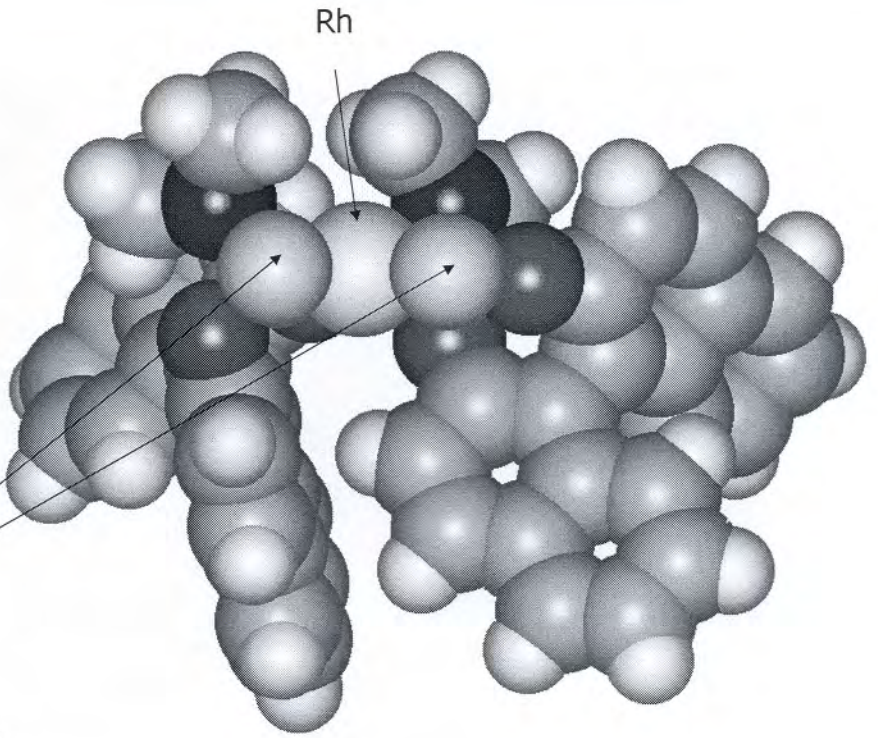


complex 'a' of $Rh(MonoPhos)_2(COD)BF_4$ is presumed to have the following structure



Coordination sites of the cyclooctadiene, COD omitted for clarity

complex 'b' of $Rh(MonoPhos)_2(COD)BF_4$ is presumed to have the following structure



Coordination sites of the cyclooctadiene, COD omitted for clarity

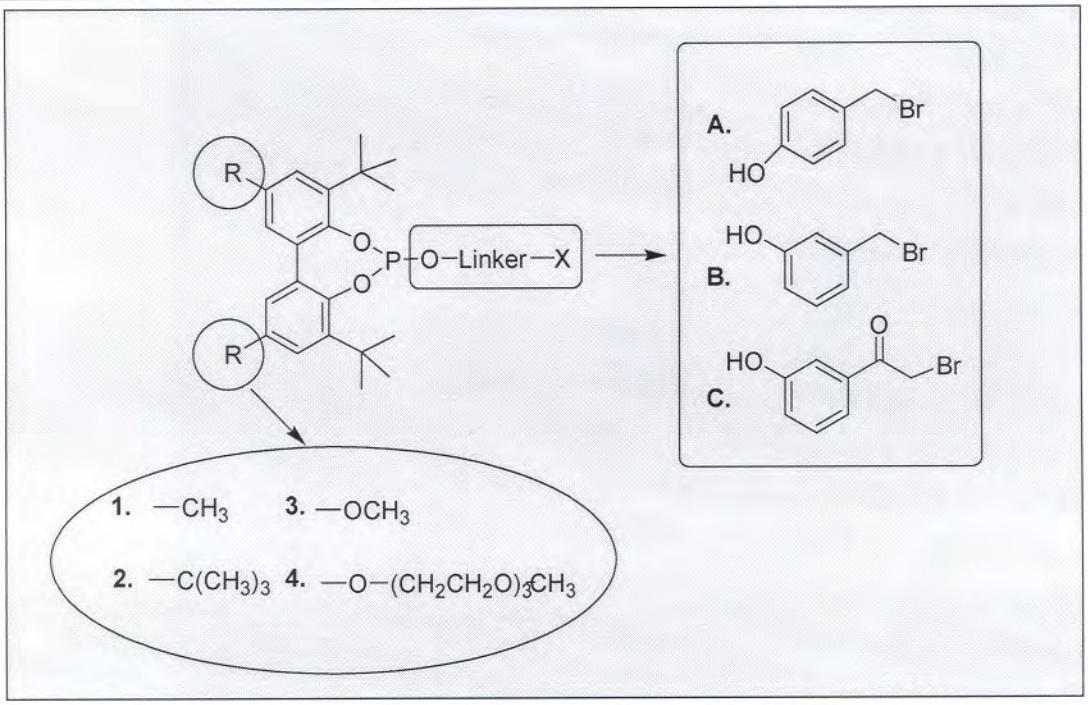
Chiral catalysis: Enzymes *vs* transition metals

- Transition metal catalysed reactions very good for:
  - Hydrogenation
  - C-C bond formation
  - Oxidation
- Enzymes are very good in:
  - Hydrolytic reactions
  - Chiral induction
  - Enormous diversity readily available in large numbers!
- Can we wed the best properties of both?
- Prior art: Whitesides and Ward (biotin linked catalysed bound to Avidin)

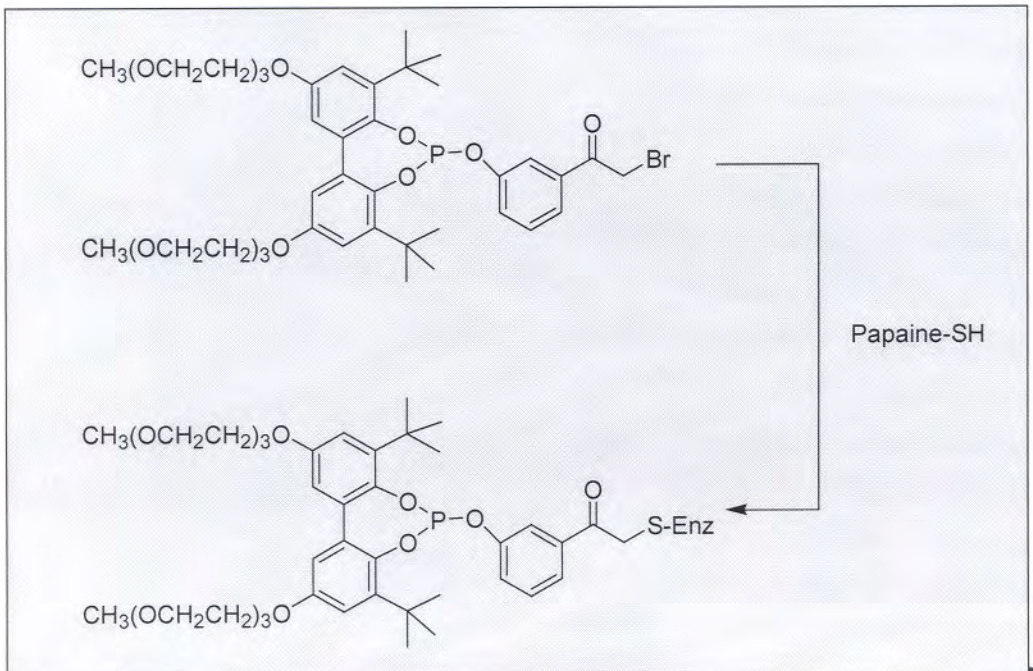
Artificial co-factors

- Combine homogeneous catalysts that are good in hydrogenation and hydroformylation with an enzyme!
- Enzyme-Ligand-Metal
- Unfavourable weight ratio demands highly active catalyst
- Catalyst needs to be stable in aqueous environment
- Attachment at single position in enzyme for reproducibility.
- Start: Papain plus rhodium/phosphite complexes
- **Enzyme-S-linker-O-P(OR)$_2$Rh-(COD)BF$_4$**

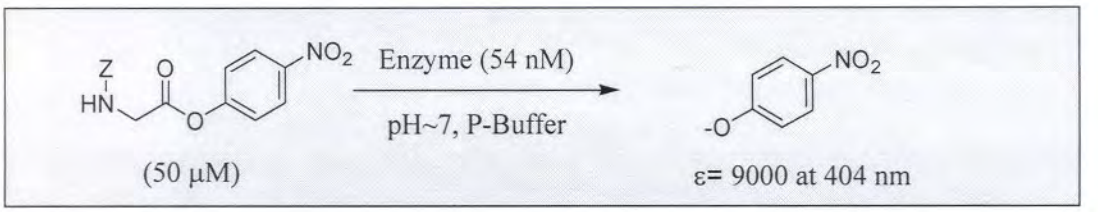
Ligand system

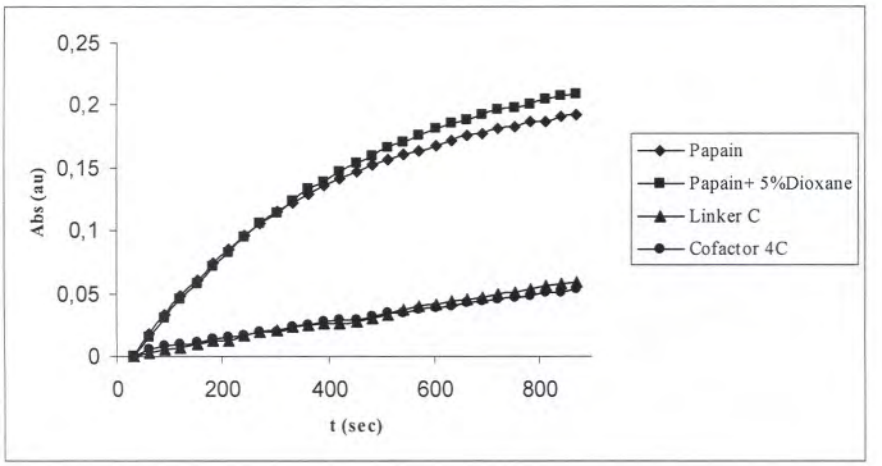


Selective binding of ligand to enzyme on Cys-SH



Binding of ligand to papain is monitored by activity assay

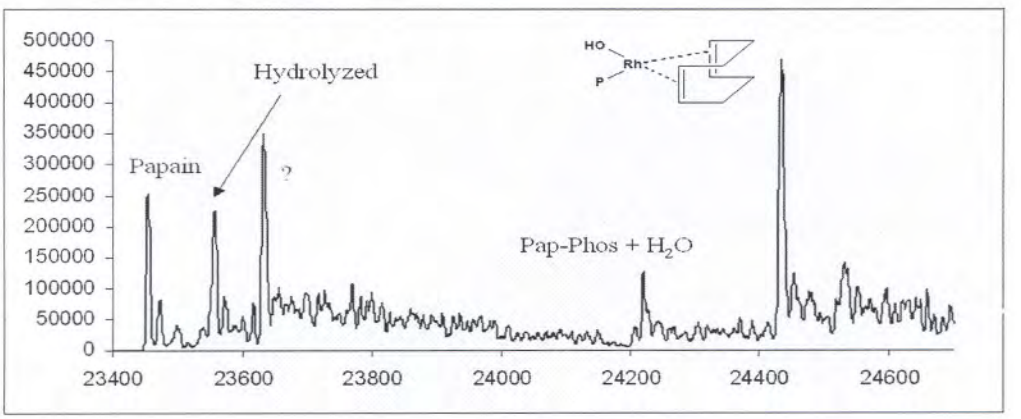




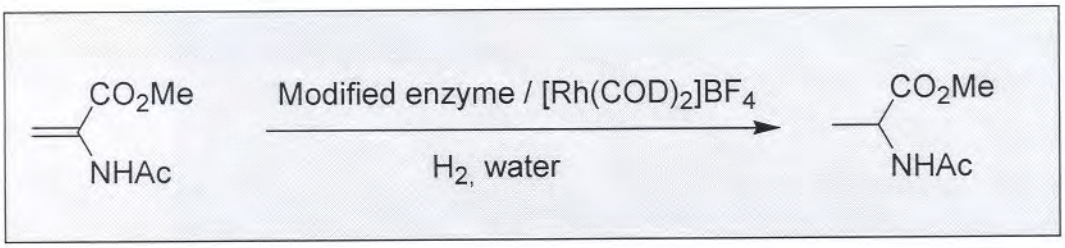
Mass Spectroscopy

After treatment of the ligated enzyme with $[Rh(COD)_2]BF_4$ and purification only a single Rh is bound to the enzyme!

ESI-MS



Modified enzyme is a good hydrogenation catalyst!



- Product N-Ac-Ala-OH is racemic
- Native papain reacted with Rh-precursor and purified in the same manner shows no reactivity.
- Next step: other enzymes and substrates.

Lavinia Panella, unpublished results

Conclusions

- Monodentate phosphoramidites are excellent ligands for enantioselective olefin hydrogenation.
- Monophos is at least an order of magnitude cheaper than existing bisphosphine ligands.
- A library of 96 phosphoramidite ligands can be made in a single day and screened in catalysis the next day.
- Monophos™ and other phosphoramidites are available in research quantities via STREM
- Combination of transition metal catalysts with enzymes is a promising new field.

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