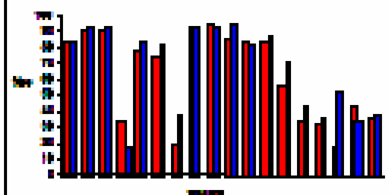
Process Aspects of Asymmetric Hydrogenation
SCI Process Development Symposium
5th-7th December 2007



Screen | Catalyst Selection | Catalyst Production | Manufacture

Dr Ian C. Lennon

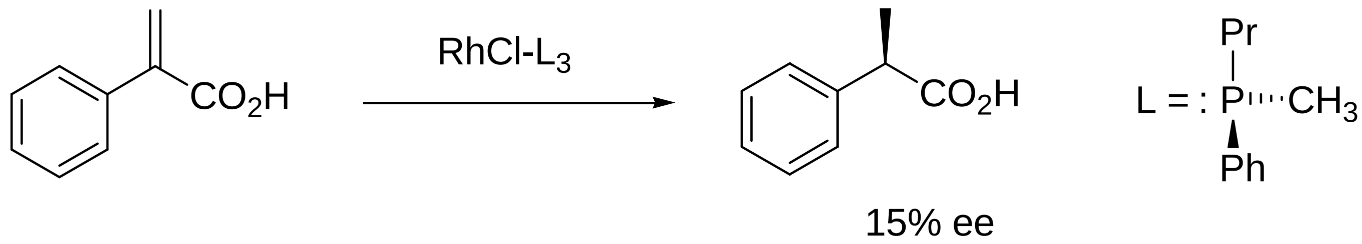
Dowpharma, Cambridge, UK

Outline of Presentation

"Some" Process Aspects of Asymmetric Hydrogenation

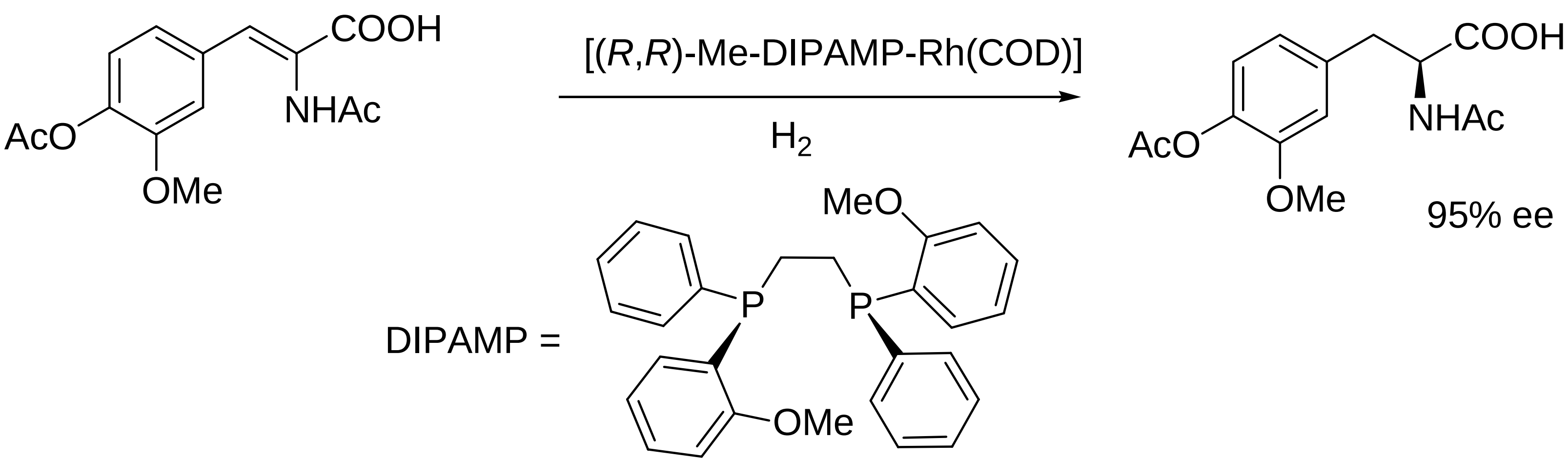
- Introduction and overview
- Process requirements
- Catalyst Screening
- Precatalyst Manufacture
- Substrate Synthesis
- Scale-up Issues

Early Applications of Asymmetric Hydrogenation



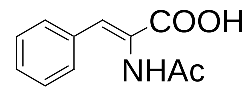
W.S. Knowles and M. J. Sabacky *Chem. Commun.*, **1968**, 1445
L. Horner et al. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942

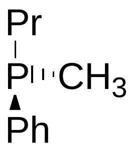
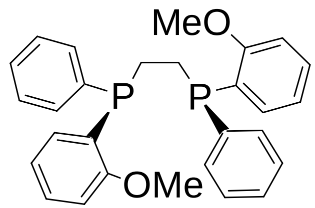
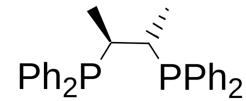
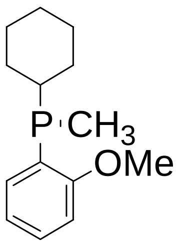
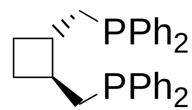
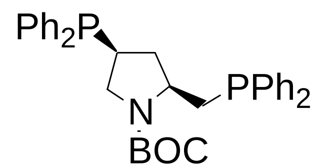
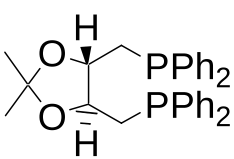
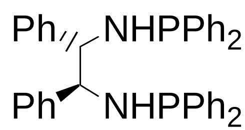
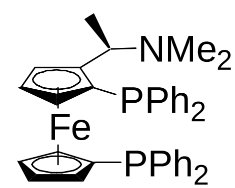
Monsanto L-DOPA process



W.S. Knowles *Angew. Chem., Int. Ed.* **2002**, *41*, 1998

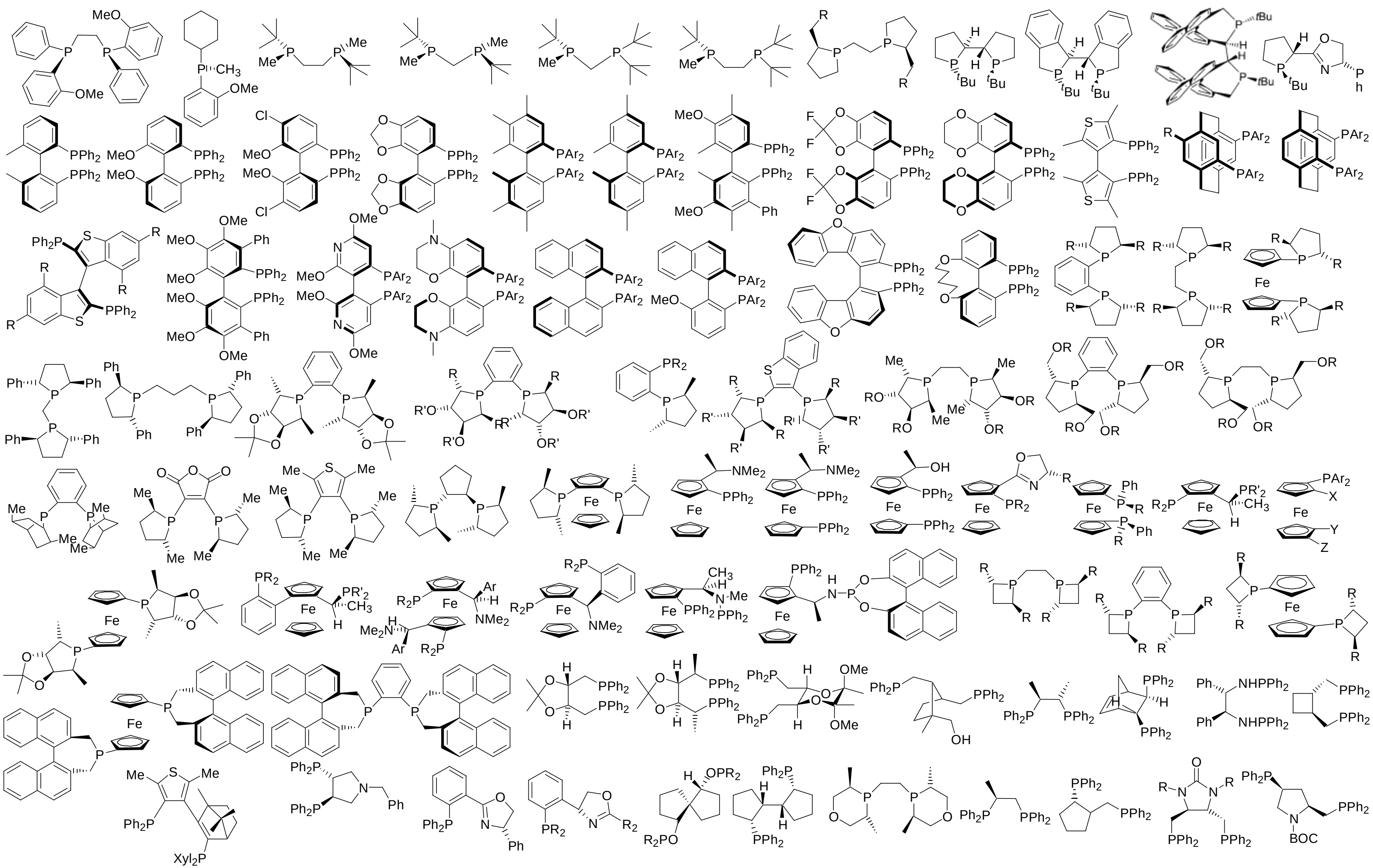
Some of the First Applied Phosphine Ligands



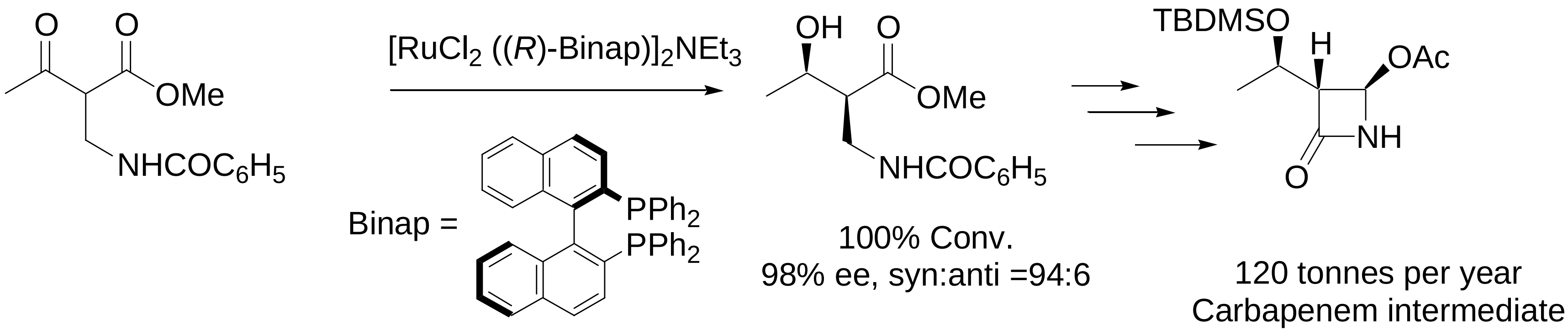
Ligand	% ee	Ligand	% ee	Ligand	% ee
	28%	 DIPAMP - 1974	95%	 CHIRAPHOS - 1977	95%
 CAMP - 1970	88%	 Rhone-Poulenc - 1974	87%	 BPPM -1976	91%
 DIOP - 1971	83%	 PNNP - 1974	94%	 BPPFA - 1980	93%

W.S. Knowles *Acc. Chem. Res.* **1983**, *16*, 106

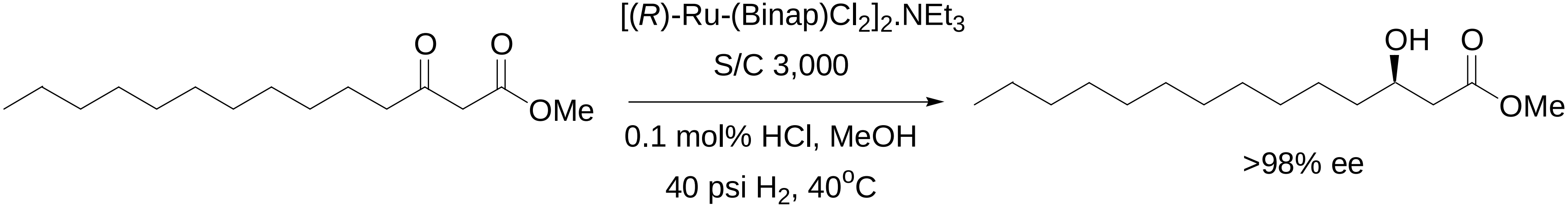
Some of the 3,000 Known Phosphine Ligands



Noyori's Binap Complexes

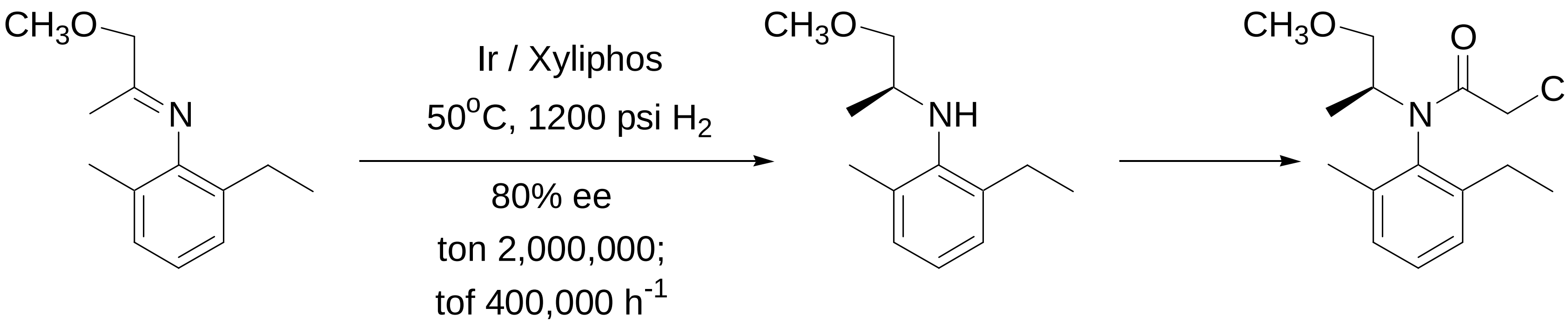


Asymmetric Catalysis in Organic Synthesis, R. Noyori
John Wiley & Sons, **1994**

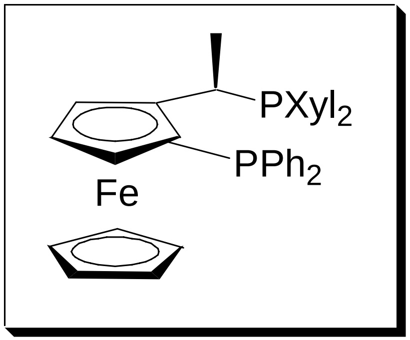


S. A. King et al *J. Org. Chem.* **1992**, *57*, 6689

Largest Scale Industrial Asymmetric Hydrogenation



Metolachlor

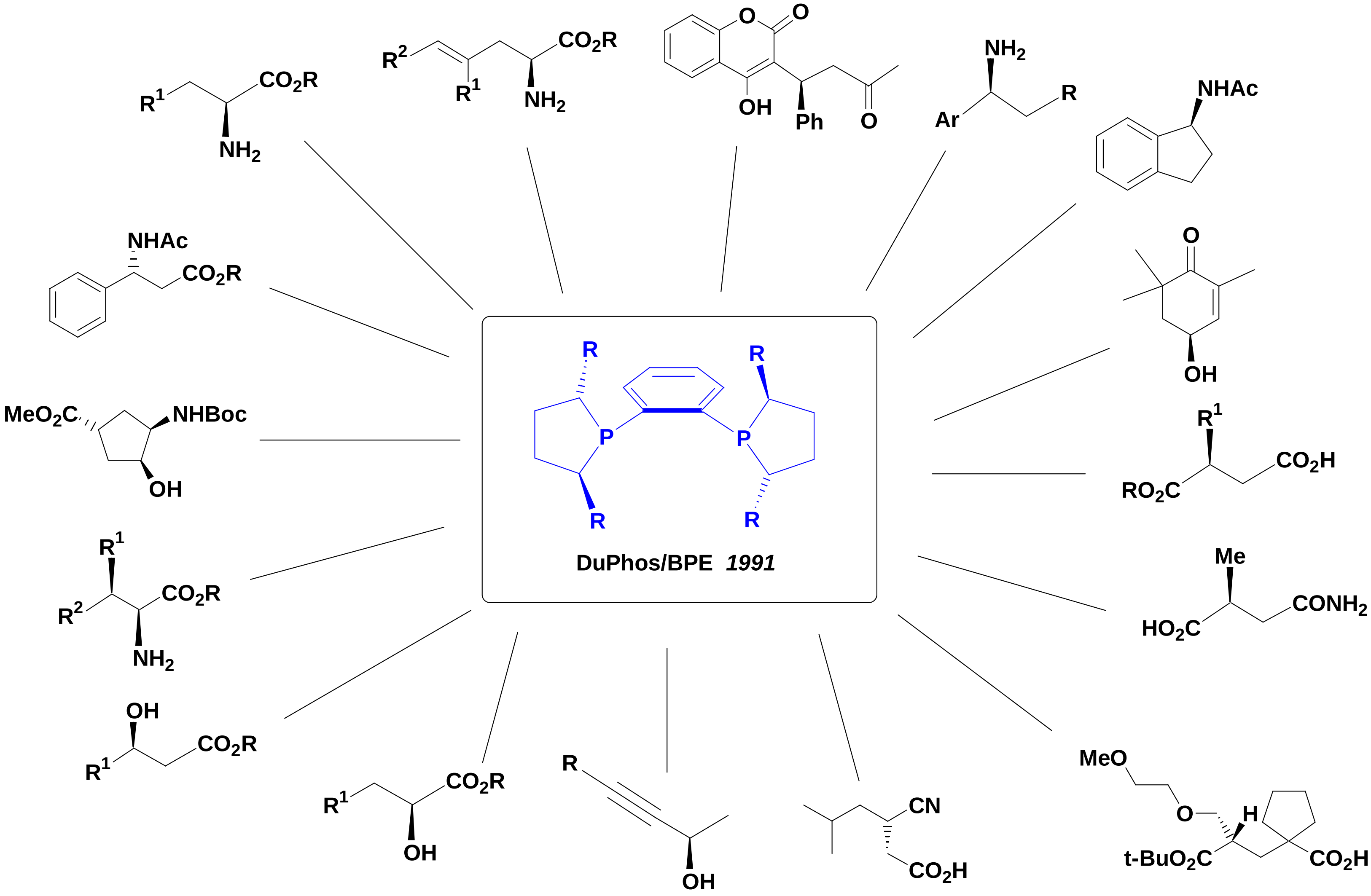
Xyliphos = 

>20,000 tonnes per year

1982 - Laboratory work
1993 - JosiPhos first reported
1996 - First Production batch

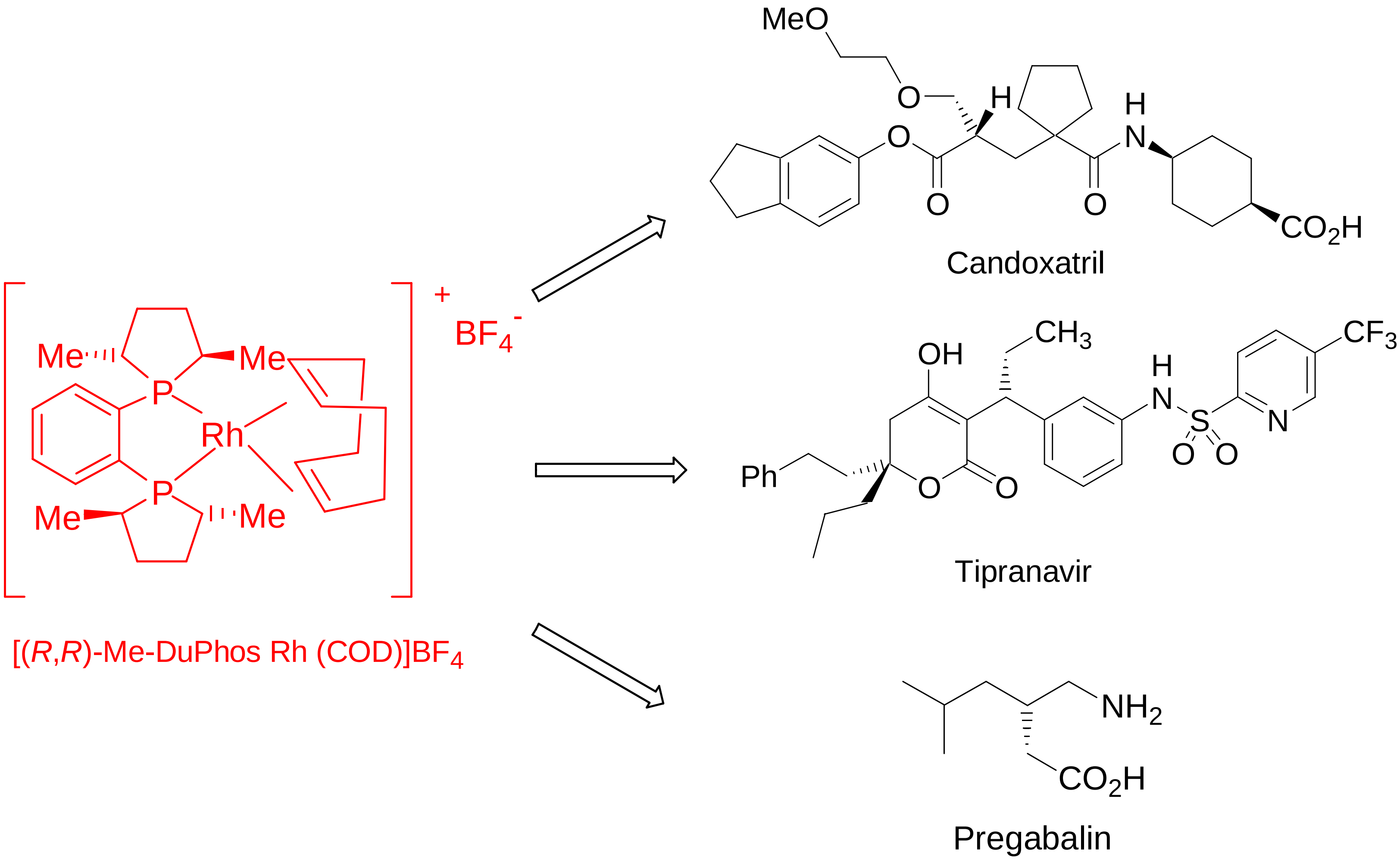
Hans-Ulrich Blaser *Adv. Synth. Catal*. **2002**, *344*, 17

Scope of the DuPhos / BPE Hydrogenation



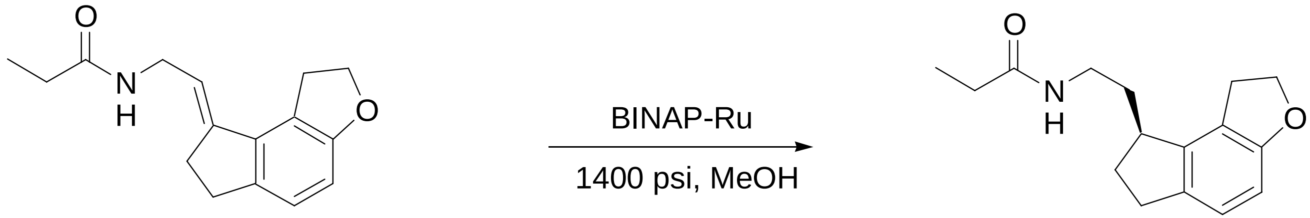
M. J. Burk *Acc. Chem. Res.* 2000, *33*, 363

Applications of Rh-Me-DuPhos Catalyst

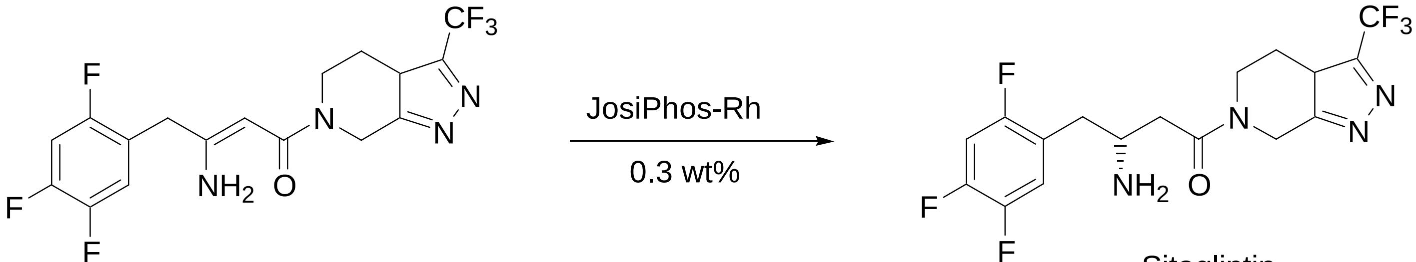


Reviews: *Synthesis* **2003**,1639; *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 855

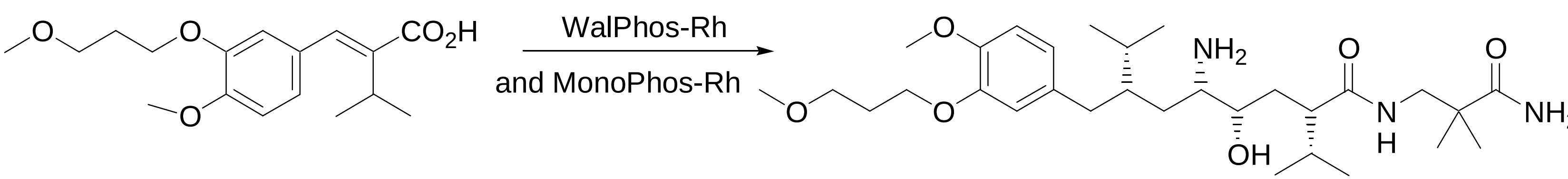
FDA Approved Drugs and Asymmetric Hydrogenation



Rozerem
Takeda, Launched-2005, insomnia



Sitagliptin
Merck, Launched-2006, diabetes



Aliskiren
Novartis, Launched 2007, hypertension

Process Requirements

- Choice of Catalyst Complex – screening
- Availability of the Chosen Catalyst (Security of Supply)
- Synthesis, Purity and *Selection of Substrate*
- Substrate to Catalyst Ratio (Activity of the catalyst)
- Enantiomeric Excess
- Choice of Solvent
- Concentration, Temperature, Pressure
- Removal of spent catalyst from the product
- Reactor Configuration, e.g. Agitation

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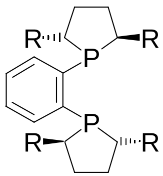
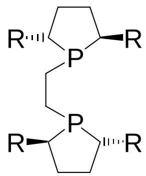
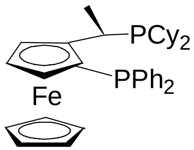
Screening for Asymmetric Hydrogenation



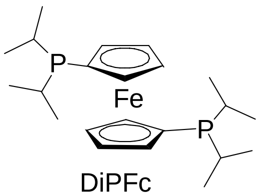
DuPHOS



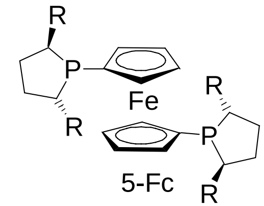
BPE



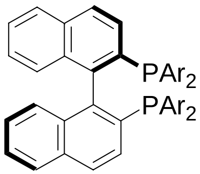
(*R*)-(*S*)-JOSIPHOS



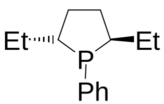
DiPFc



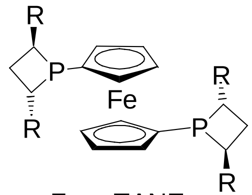
5-Fc



Ar = Ph (*R*)-BINAP
Ar = 4MeC_6H_4 (*R*)-TolBINAP

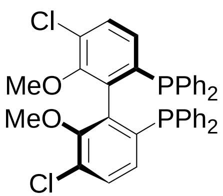


(*R*)-EtPhenylLANE

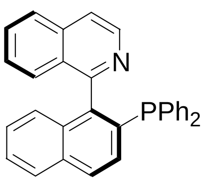


FerroTANE

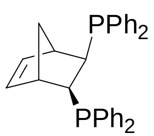
> "Since achieving 95 % e.e. only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective"
>
> **W.S. Knowles, 1983**



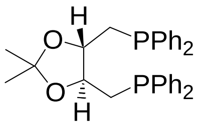
(*R*)-Cl-MeO-BIPHEP



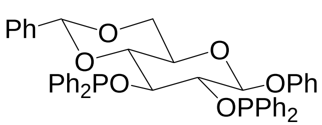
(*R*)-QUINAP



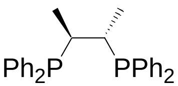
(2*R*,3*R*)-NORPHOS



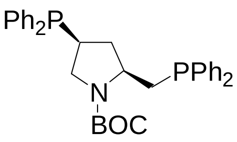
(*S*,*S*)-DIOP



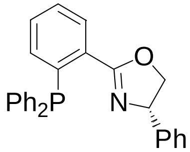
CARBOPHOS



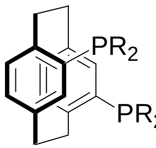
(*S*,*S*)-CHIRAPHOS



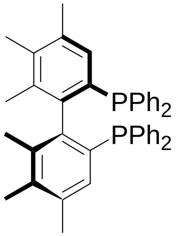
BPPM



(*R*)-Phosphinooxazoline



(*R*)-PhanePhos

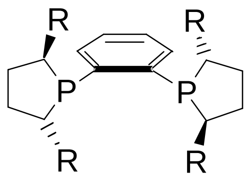


(*R*)-HexaPHEMP

Ligand collection for asymmetric hydrogenation screening

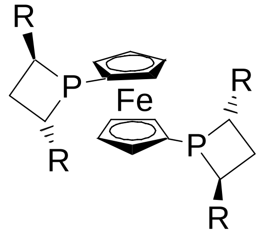
Dowpharma Asymmetric Hydrogenation Screening

- More than 400 rhodium, ruthenium and iridium catalysts are available
- Proprietary ligands based on four major classes:



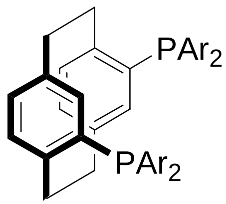
Phospholanes
(DuPhos, BPE, 5-Fc)

(exclusive licence from DuPont)



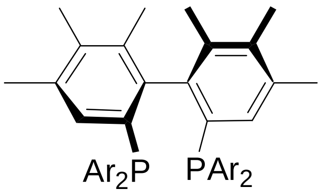
Phosphetanes
(FerroTANE)

(ChiroTech patent)



Paracyclophane ligands
(PhanePHOS)

(Licence from Merck)



Biaryl phosphines
(HexaPHEMP)

(ChiroTech patent)

Production of
unnatural aminoacids

(rhodium catalysis combined
with biocatalysis)

Production of
peptidomimetics

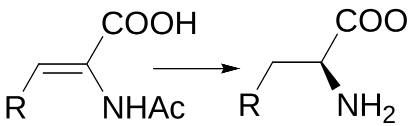
(rhodium catalysis)

Production of
chiral alcohols

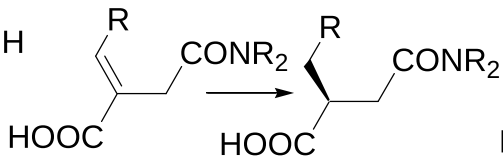
(ruthenium catalysis /
JST technology)

Production of chiral
β-hydroxyesters and diols

(ruthenium catalysis)



>99% e.e.



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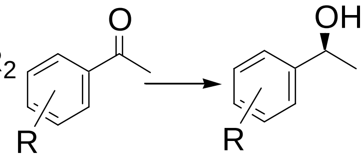

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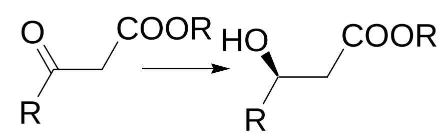
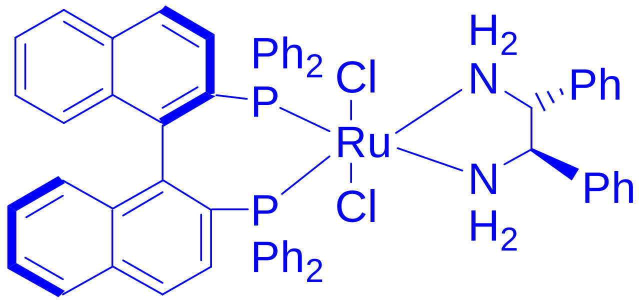
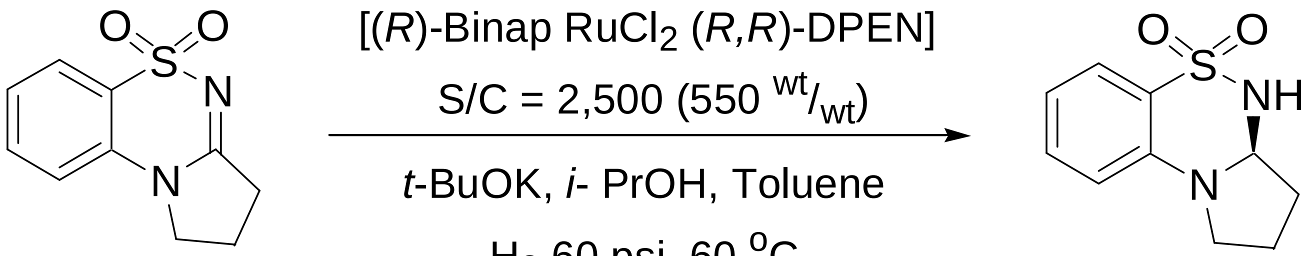


>98% e.e.

Thiadiazine Hydrogenation - Unbiased Catalyst Screening



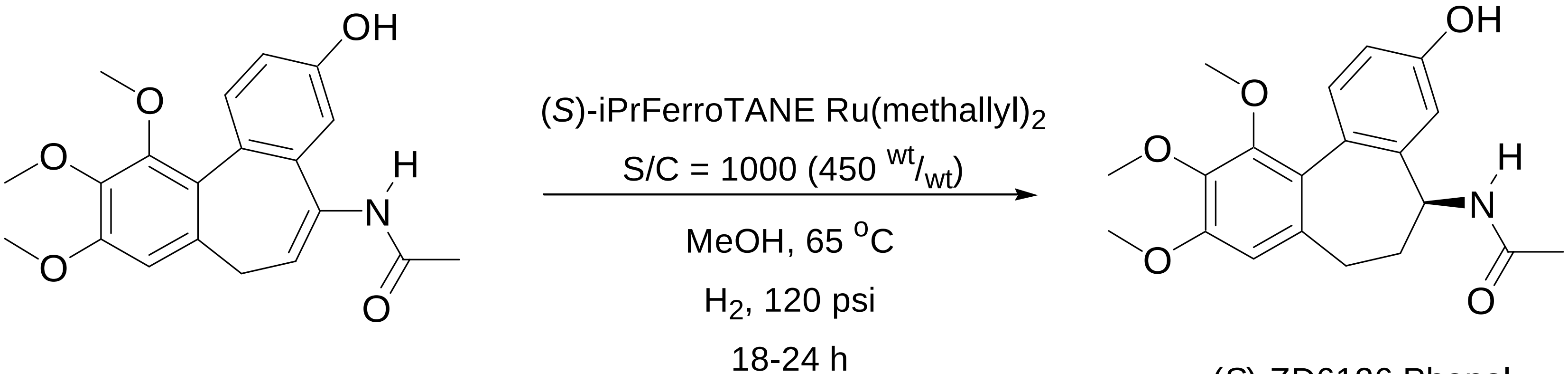


97% Yield, 87% ee

- Substrate inert to all other asymmetric hydrogenation reactions
- Best system identified was not proprietary to Dowpharma
- An equivalent of base required for full conversion.
- Product crystallises to >99% ee

Dowpharma/Oril Joint Publication: *Tetrahedron Asymmetry* 2003, *14*, 3431

Asymmetric Hydrogenation Screen for ZD-6126 Enamide



ZD6126 Enamide

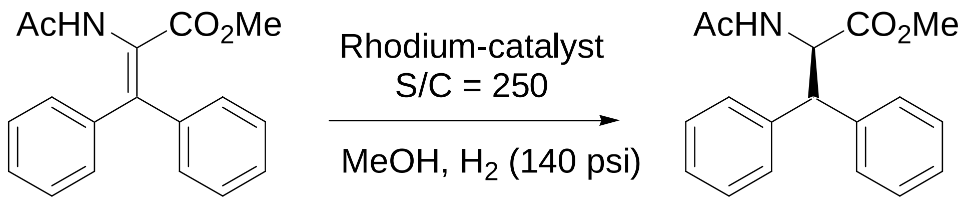
(*S*)-ZD6126 Phenol

Catalyst	S/C	ee
(*R*)-^{i}Pr-DuPhos-Rh	100	53%
(*S*)-^{t}Bu-FerroTANE-Rh	1000	91%
(*R*)-(*S*)-JosiPHOS-Rh	100	56%
(*R*)-Me-DuPhos-Ru	100	73%
(*S*)-^{i}Pr-FerroTANE-Ru	1000	90%

- Project carried out with AstraZeneca, Macclesfield.
- Over 100 Rh, Ru and Ir catalysts screened.
- Suitable Rh and Ru catalysts were identified, based on the FerroTANE ligand

Joint Publication *Tetrahedron Lett*. 2007, *48*, 4623-4626

Catalyst Screen for Diphenylalanine



Precatalyst	$t_{1/2}$	Temp	ee
[(*R*,*R*)-Me-BPE Rh COD]BF_4	1 h 25 m	60 °C	70%
[(*R*,*R*)-PhanePhos Rh COD]BF_4	2.5 m	60 °C	88%
[(*R*,*R*)-Me-BPE Rh COD]BF_4	3 h 9 m	50 °C	76%
[(*R*,*R*)-PhanePhos Rh COD]BF_4	3 m	50 °C	88%
[(*R*,*R*)-Me-FerroTANE Rh COD]BF_4	13 m	50 °C	72%
[(*R*,*R*)-Me-5-Fc Rh COD]BF_4	2 m	50 °C	75%
[(*R*,*R*)-Ph-BPE Rh COD]BF_4	3 h 23 m	50 °C	94%
[(*R*,*R*)-Bis P* Rh COD]BF_4	5 h 17 m	50 °C	51%
[(*R*,*R*)-Et-DuPhos Rh COD]BF_4	nd	50 °C	53%

- PhanePhos provides the most active catalyst system
- Diphenylalanine derivatives have been manufactured on a ton scale

See Dowpharma Patent Application WO 2006/127273

Process Requirements

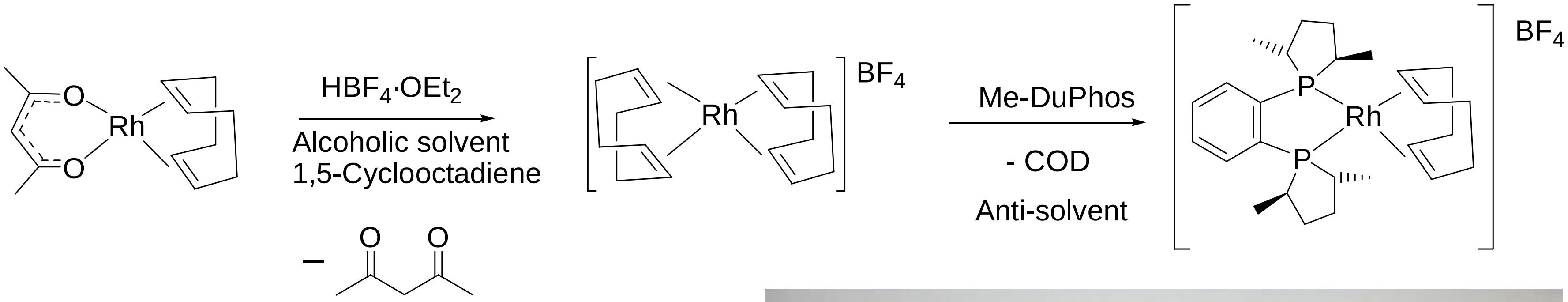
- Choice of Catalyst Complex – screening
- **Availability of the Chosen Catalyst (Security of Supply)**
- Synthesis, Purity and Selection of Substrate
- Substrate to Catalyst Ratio (Activity of the catalyst)
- Enantiomeric Excess
- Choice of Solvent
- Concentration, Temperature, Pressure
- Removal of spent catalyst from the product
- Reactor Configuration, e.g. Agitation

Commercial Scale Precatalyst Manufacture

- Dowpharma has >12 years of asymmetric hydrogenation experience
- >10 precatalysts made on a Kg+ scale
- [Me-DuPhos Rh(COD)]BF_4 available on a multi-10's kg scale
- Rh-PhanePhos precatalyst produced on a multi-kilogram scale
- Many metric tons of chiral products are manufactured using our asymmetric hydrogenation technology

Catalyst Scale-Up – Batch Variation

[Me-DuPhos Rh (COD)]BF_4 – A Historical Perspective

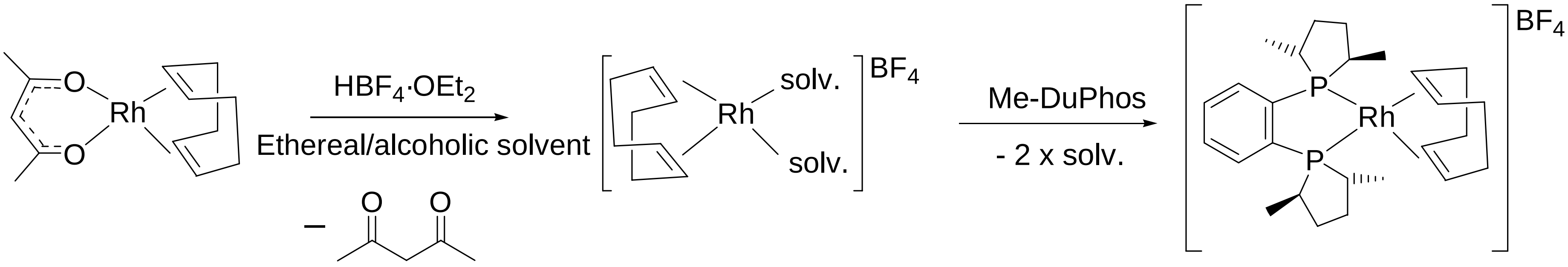


- Insoluble intermediate
- Low recovery
- Low volume efficiency
- Unpredictable product form

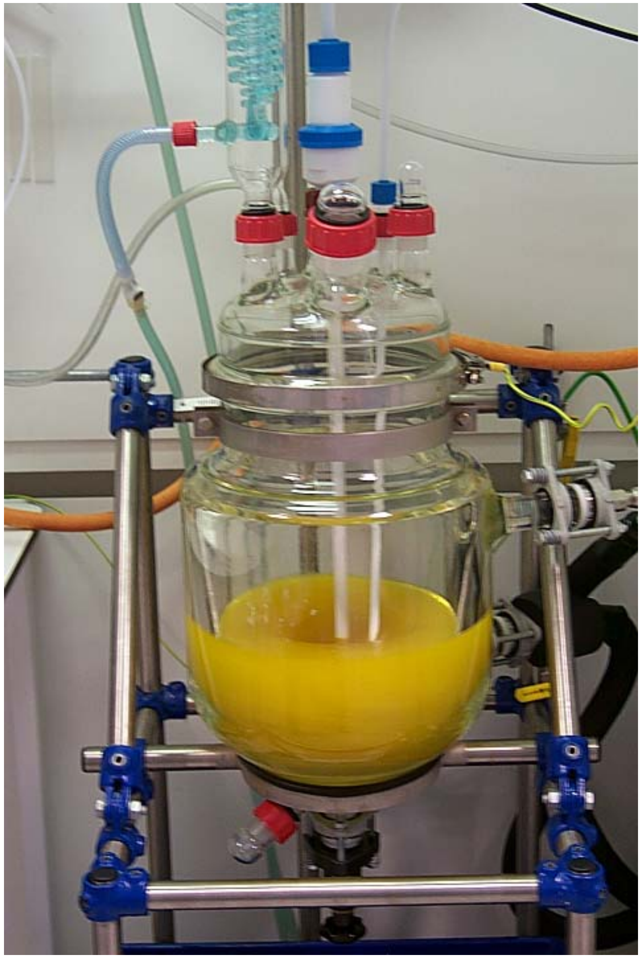
Catalyst Scale-Up

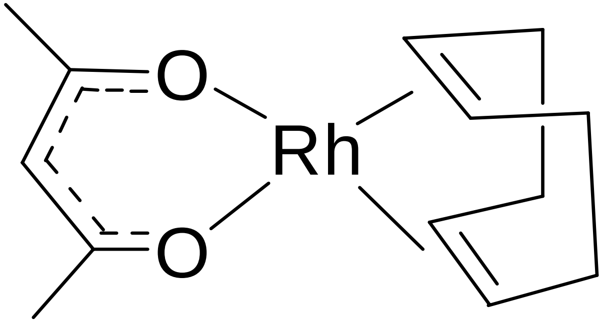
- Soluble SM & reactive intermediate
- High volume efficiency
- ~2.5kg from 20L vessel
- Uniform granular product form
- T_{react} reduced from 78ºC to 55ºC
- Product isolated at RT
- Productivity increased ~100% / volume
- Recovery increased from 75 to 96%

New route



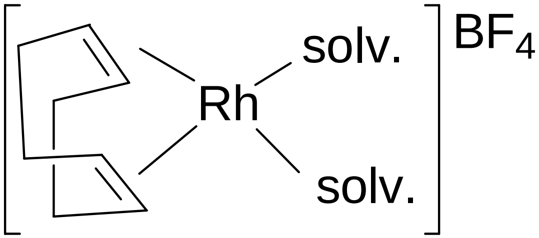
Catalyst Scale-Up: Test-Rig Reactions





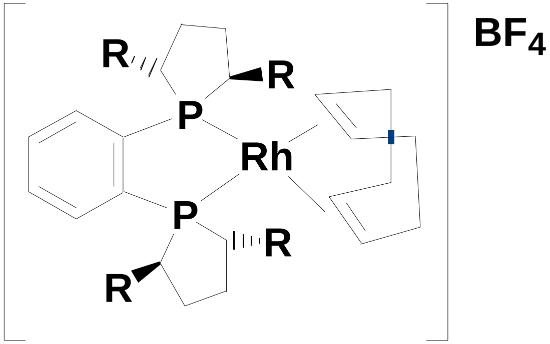
1. [Rh(COD)acac] in ethereal solvents

Catalyst Scale-Up: Test-Rig Reactions



1. [Rh(COD)acac] in ethereal solvents
2. Add acid in alcoholic solvent

Catalyst Scale-Up: Test-Rig Reactions

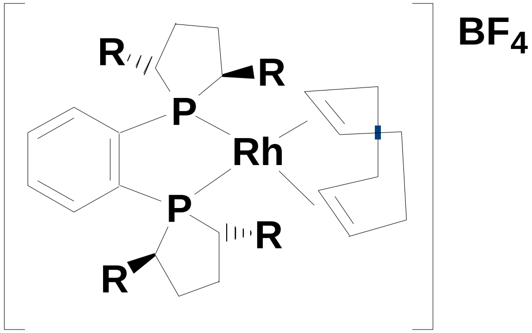


1. [Rh(COD)acac] in ethereal solvents

2. Add acid in alcoholic solvent

3. Add ligand in ethereal solvent

Catalyst Scale-Up: Isolated Catalyst

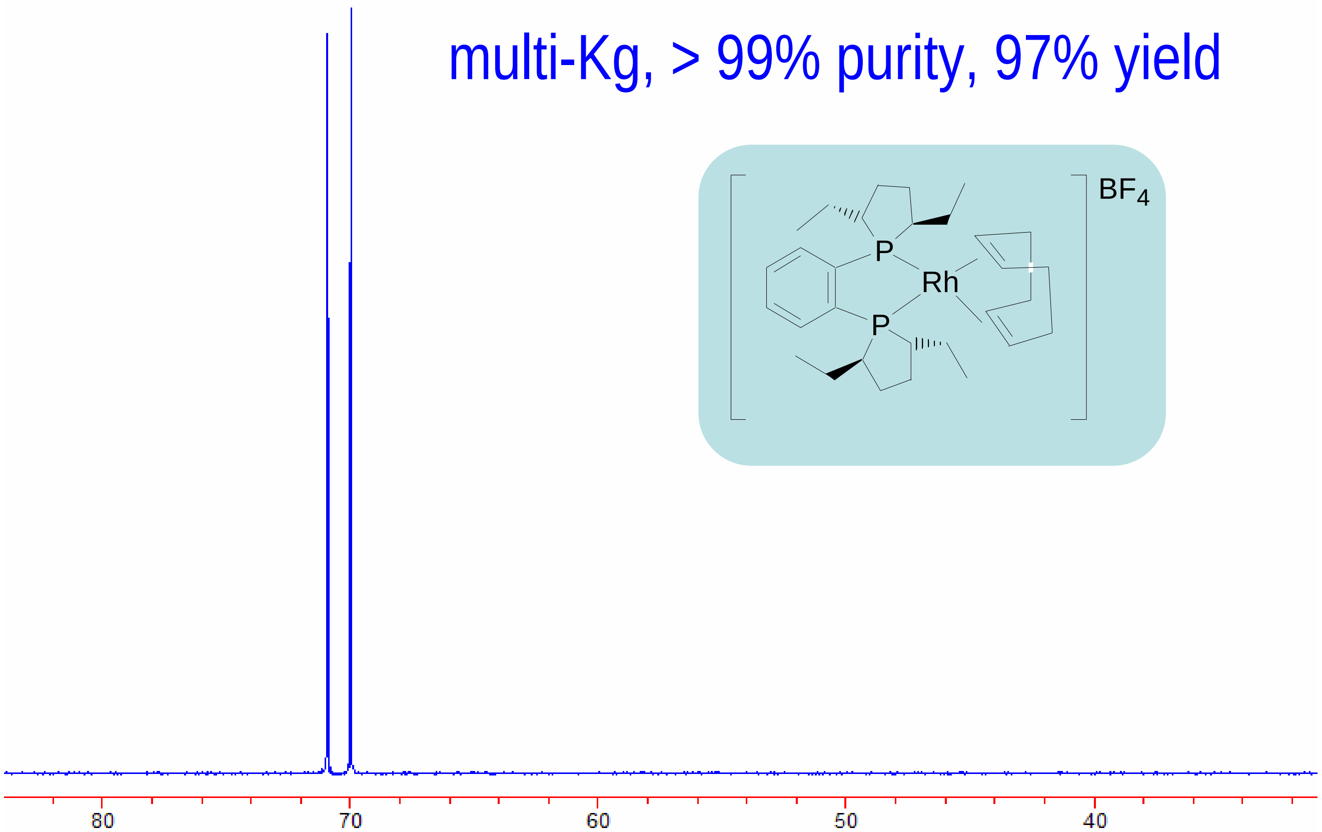


1. [Rh(COD)acac] in ethereal solvents
2. Add acid in alcoholic solvent
3. Add ligand in ethereal solvent
4. Isolate robust material in high yield
5. Optional recrystallisation

Catalyst Scale-Up: Extending the Scope

^{31}P-NMR – Isolated material at 25 ^{o}C

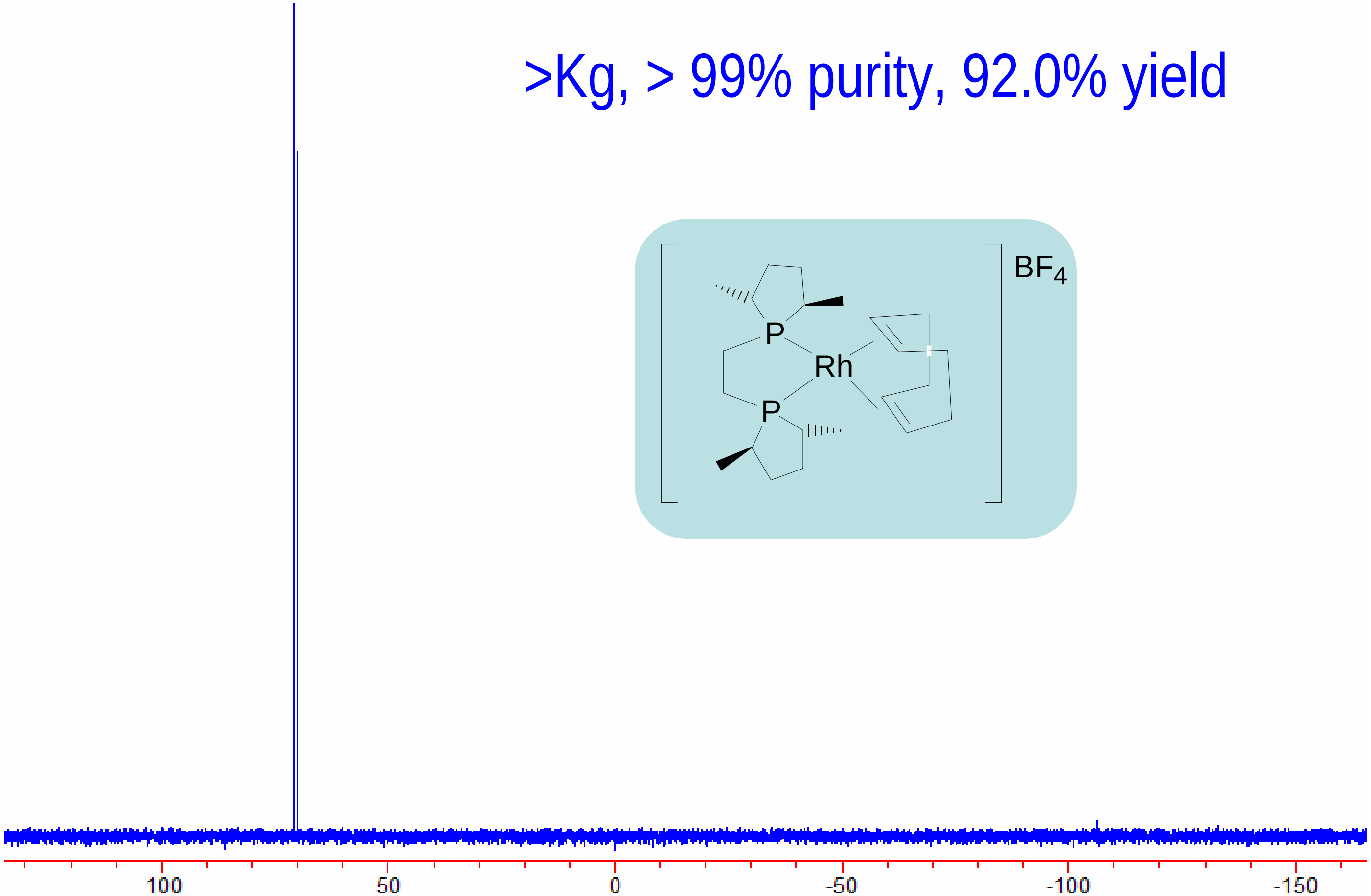
multi-Kg, > 99% purity, 97% yield



Catalyst Scale-Up: Extending the Scope

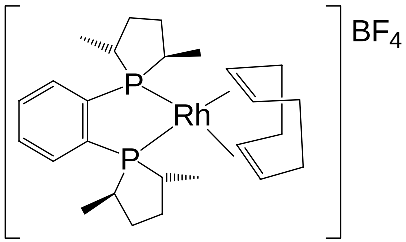
Isolated material

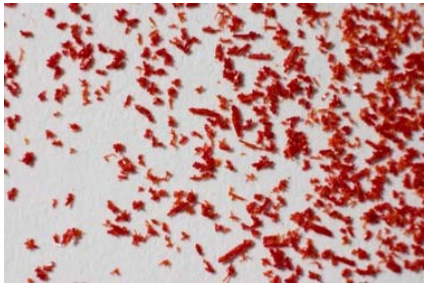
>Kg, > 99% purity, 92.0% yield

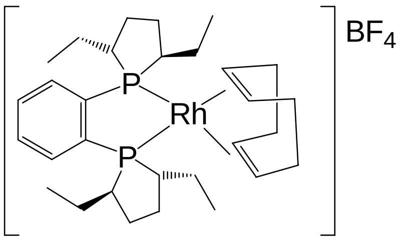


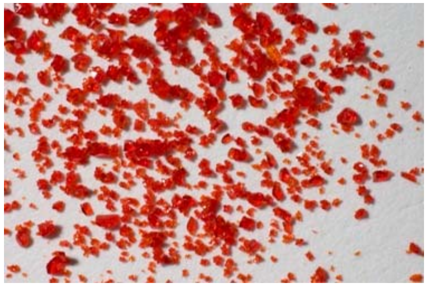
Catalyst Scale-Up: Extending the Scope

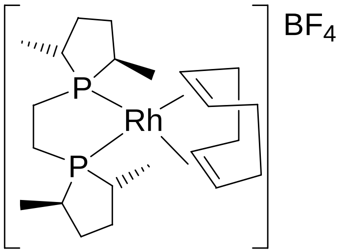
Isolated Catalysts – Product form comparisons

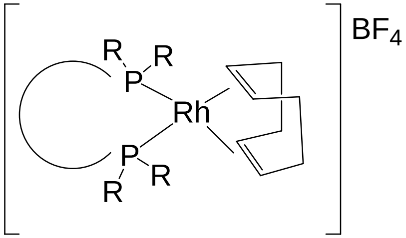




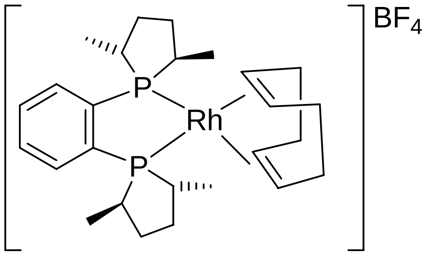




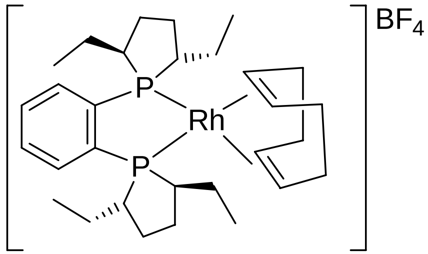




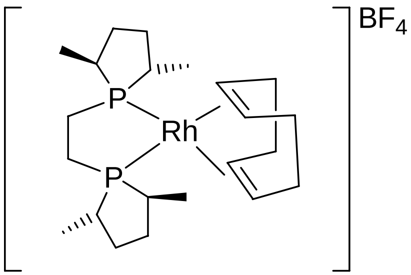
Catalyst Scale-Up: Extending the Scope



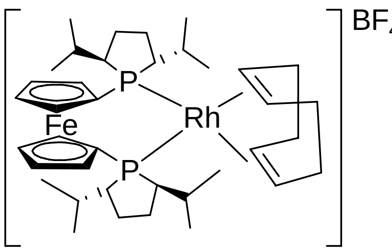
95%



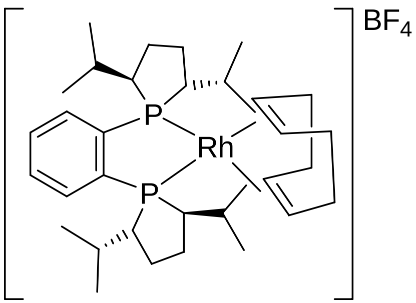
97%



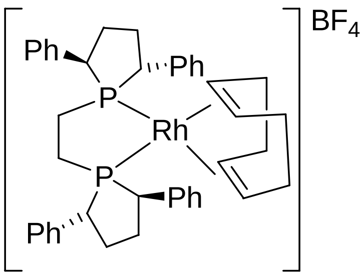
96.4%



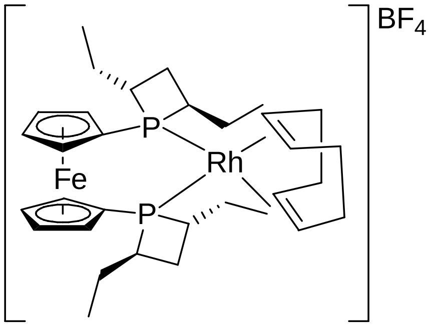
97%



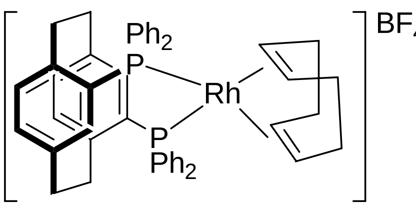
94%



97.5%



91%



95%

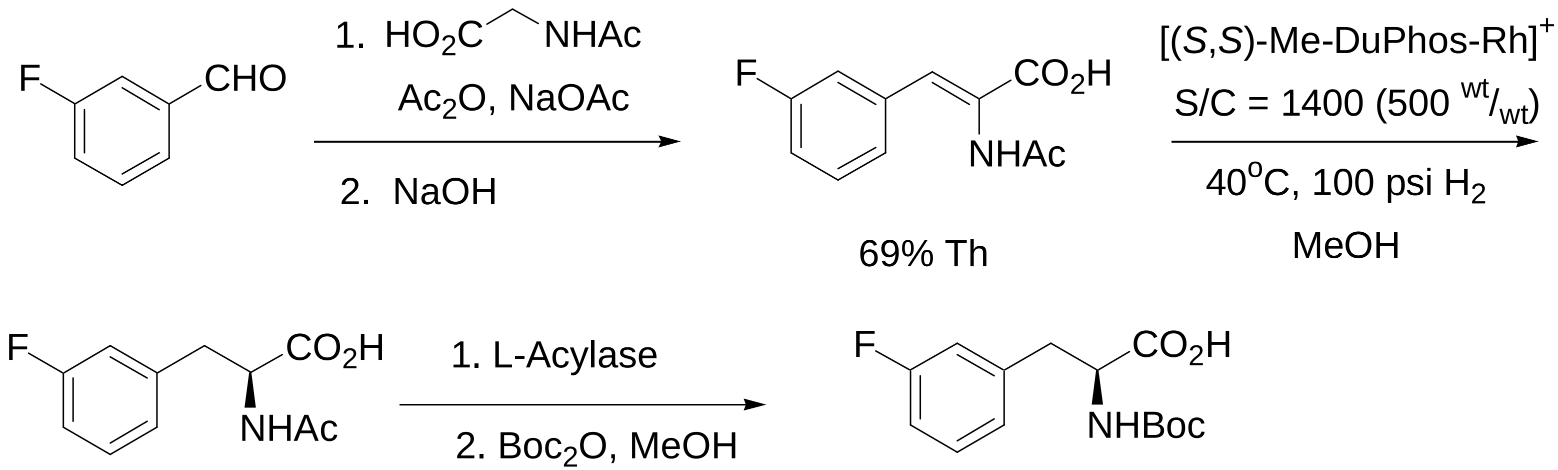
WO 2005032712

- Widely applicable to typical phosphine ligands
- 10 proprietary systems operated at Kg scale
- Largely compatible with analogous iridium complexes

Process Requirements

- Choice of Catalyst Complex – screening
- Availability of the Chosen Catalyst (Security of Supply)
- **Synthesis, Purity and Selection of Substrate**
- Substrate to Catalyst Ratio (Activity of the catalyst)
- Enantiomeric Excess
- Choice of Solvent
- Concentration, Temperature, Pressure
- Removal of spent catalyst from the product
- Reactor Configuration, e.g. Agitation

Substrate Synthesis: Manufacture of α-Amino Acids



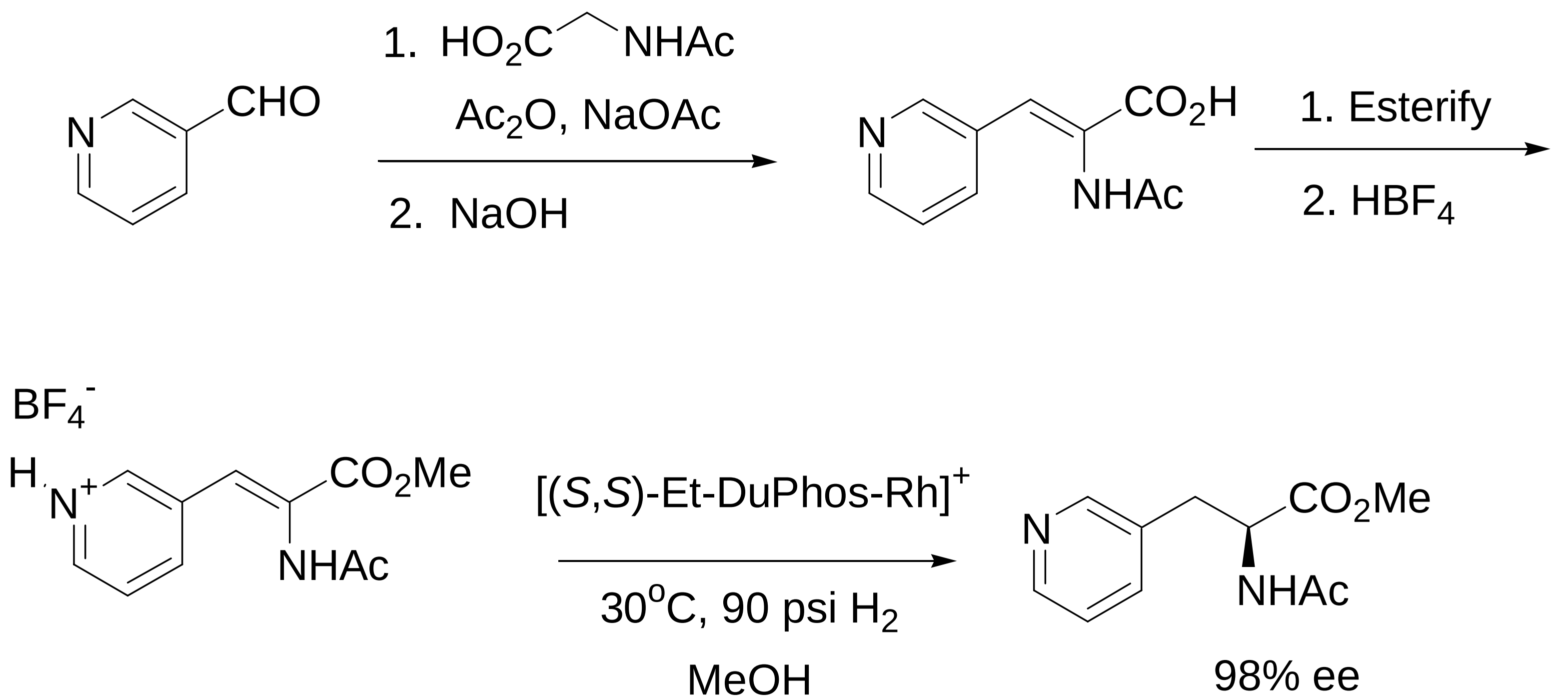
69% Th over three steps
>99% ee, >98% purity

Key Issues

- Use of Erlenmeyer reaction is preferable to Horner-Emmons chemistry, which can give low level of phosphorus impurities that poison catalysis
- Erlenmeyer route is scaleable and cost effective
- Conditions for the DuPhos Hydrogenation are mild and scaleable
- Many 100's kg of product have been made using this route

Asymmetric Catalysis on Industrial Scale Eds Blaser and Schmidt. Page 269.

Substrate Synthesis: Manufacture of α-Amino Acids

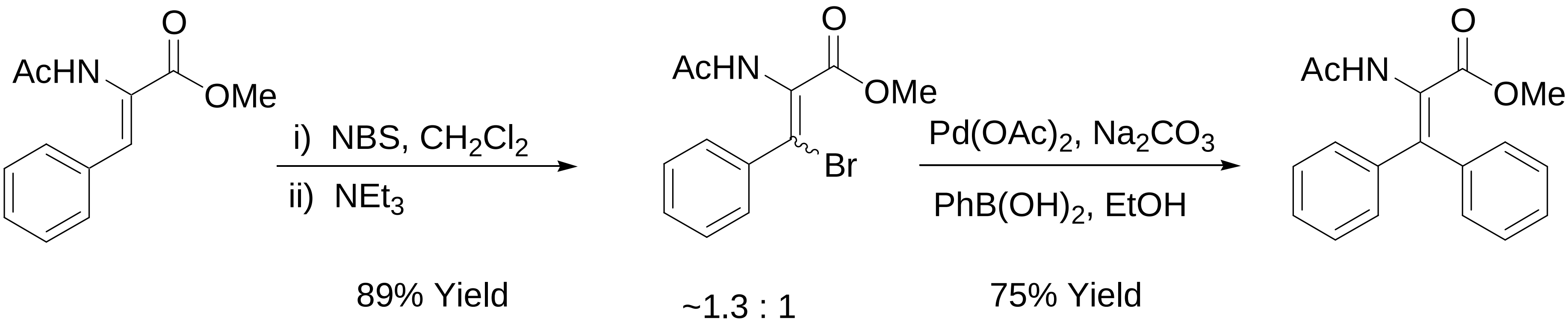


Key Issues

- ❖ Competitive binding to the pyridyl group made the catalysis inefficient
- ❖ The optimum substrate was the methyl ester-HBF_4 salt
- ❖ >200 Kg produced

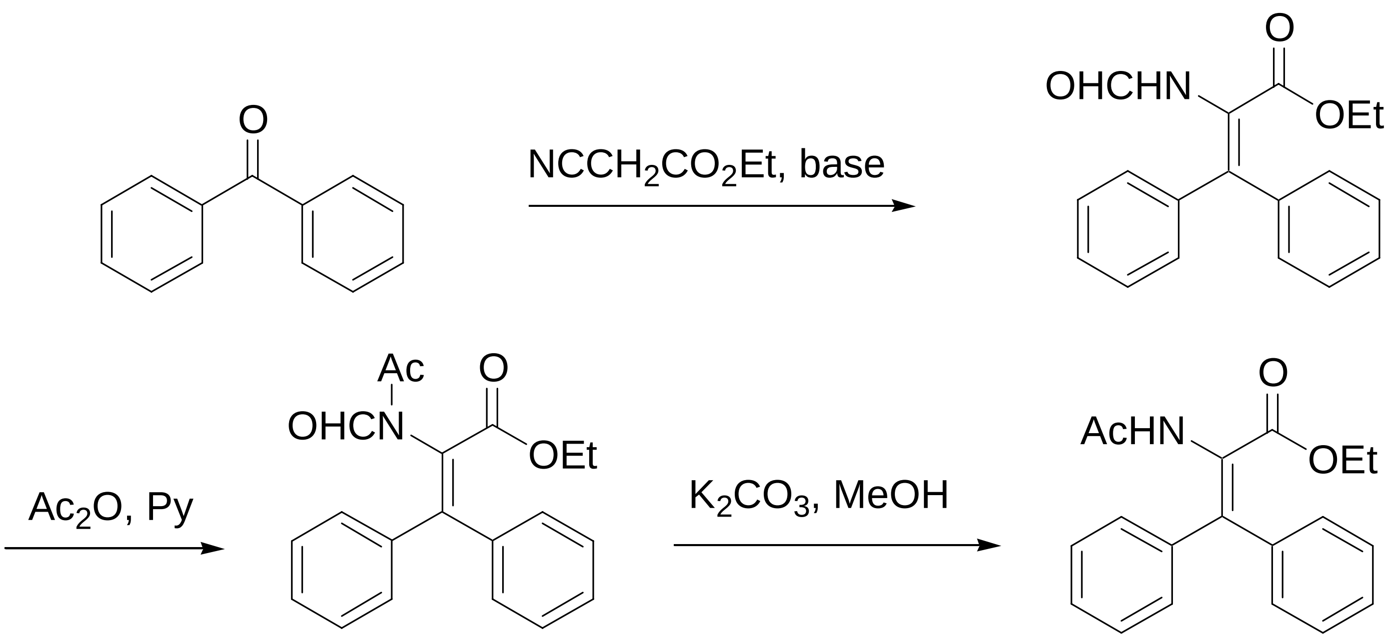
Asymmetric Catalysis on Industrial Scale Eds Blaser and Schmidt. Page 269.

Diphenylalanine – Substrate Synthesis



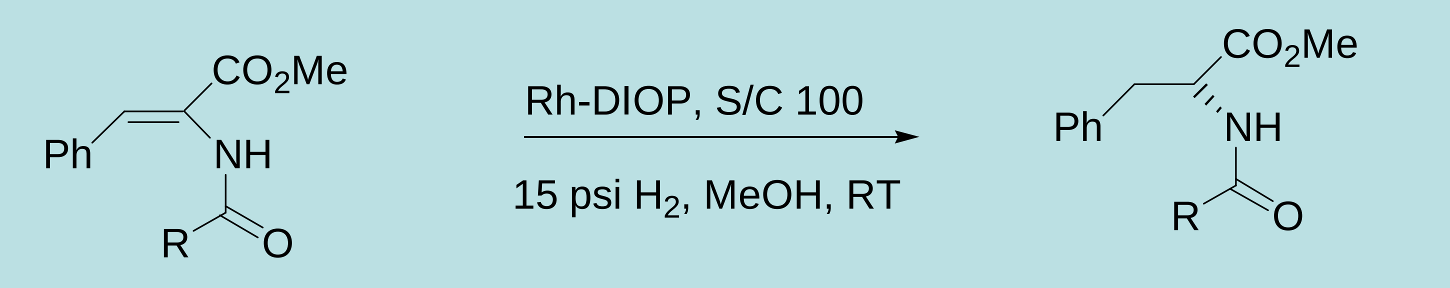
- Substrate synthesized according to Burk et al. *Tetrahedron Lett*. **1997**, *38*,1309, using the Suzuki conditions of Deng et al. *Synthesis* **2003**, 337
- Commercially available dehydroamino acid and boronic acid
- Both steps good yield
- Alternative substrate synthesis devised

Diphenylalanine- Alternative Substrate Synthesis



- Synthesis of the *N*-Formyl intermediate followed procedures reported in *Bioorg. Med. Chem. Lett*. **1992**, *2*, 1085
- Commercially available ketone and isocyanide
- *N*-protecting group exchange required, *N*-formyl is a poor hydrogenation substrate

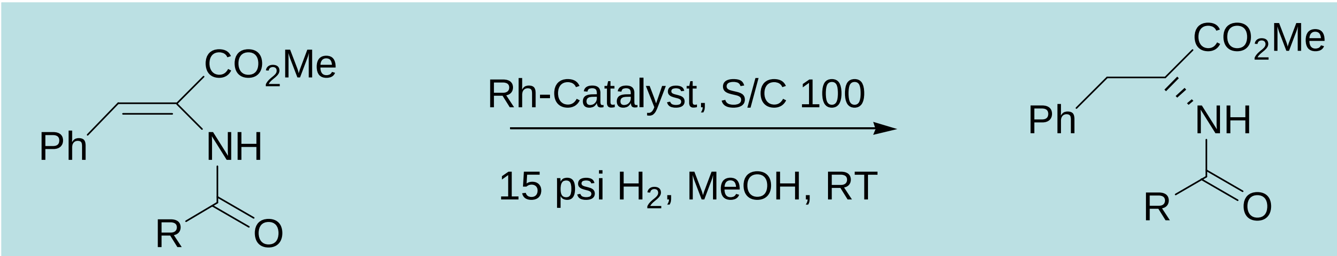
Substrate Selection: Directing Groups

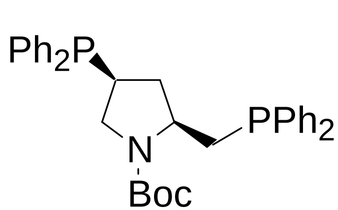


Group	t/2	Conversion	ee
R = H	-	40	60%
R = CH_3	15 min	100	83%
R = Ph	16 min	100	68%
R = OBn	50 min	100	33%
R = O^tBu	60 min	100	9%
R = CF_3	-	58	16%

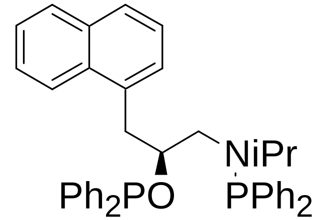
Tetrahedron 1979, *35*, 2381; *Tetrahedron: Asymm*. 1993, *4*, 2047

Substrate Selection: Directing Groups





BPPM

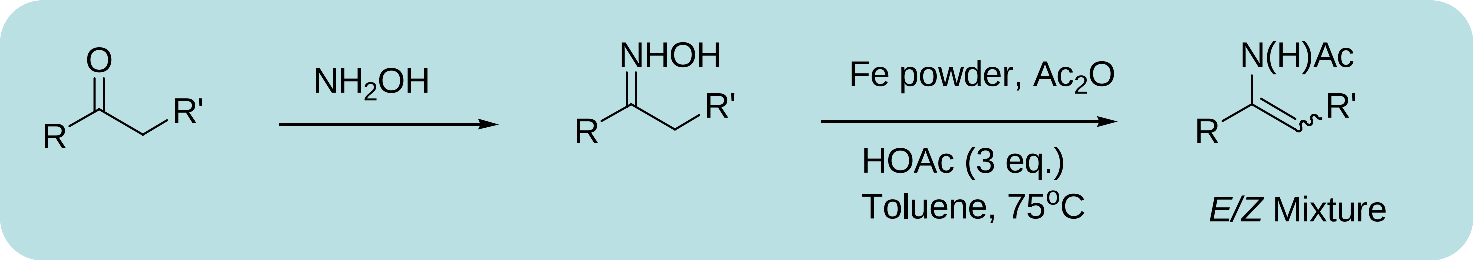


Propraphos

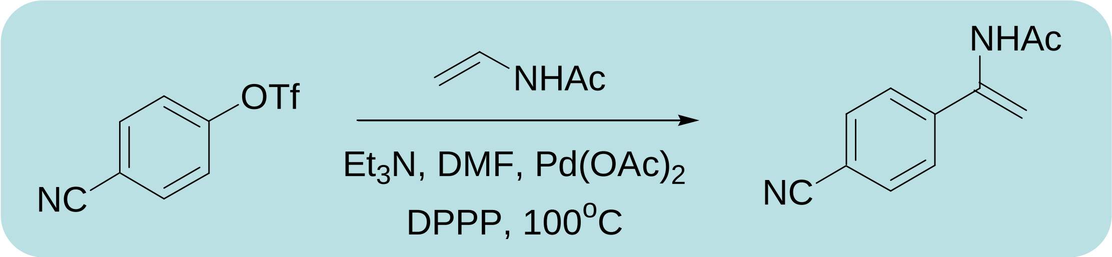
Group	t/2	ee	t/2	ee
R = CH_3	16 min	93%	16 min	86%
R = Ph	15 min	80%	10 min	90%
R = OtBu	80 min	82%	50 min	93%
R = OBn	60 min	87%	120 min	88%

Tetrahedron: Asymm. 1993, *4*, 2047

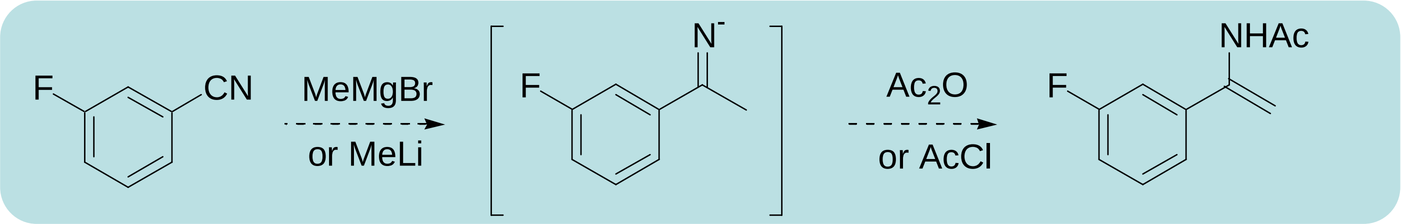
Syntheses of Enamide Substrates



Chirotech Paper: Burk et al. *J. Org. Chem*. **1998**, *63*, 6084

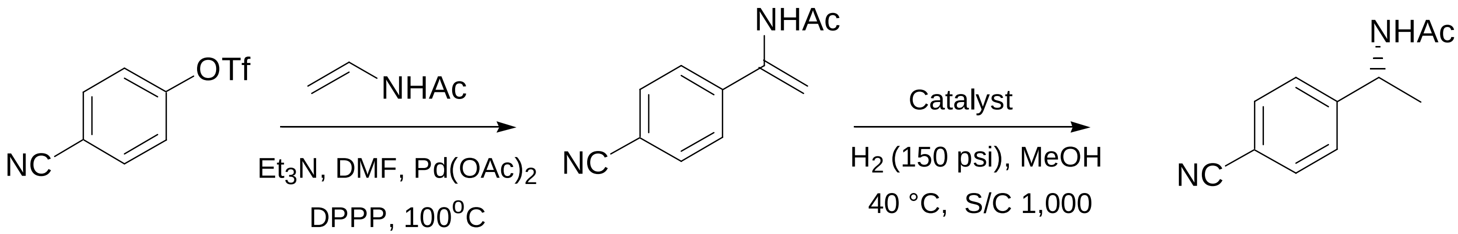


Dowpharma Paper: Meek et al. *Tetrahedron Lett.* **2004,** *45,* 9277

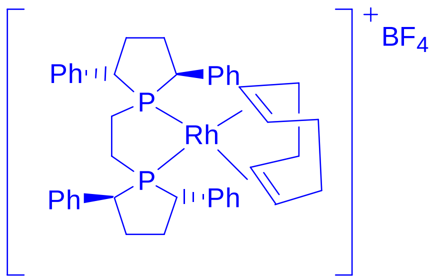


Burk et al. *J. Am. Chem. Soc*. **1996**, *118*, 5142 (supporting info.)

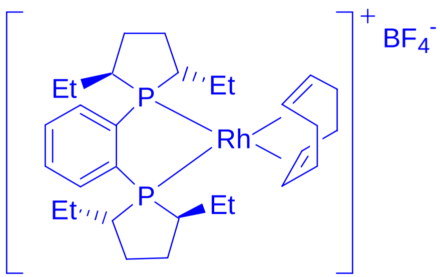
Enamide Substrate Synthesis – Heck Coupling



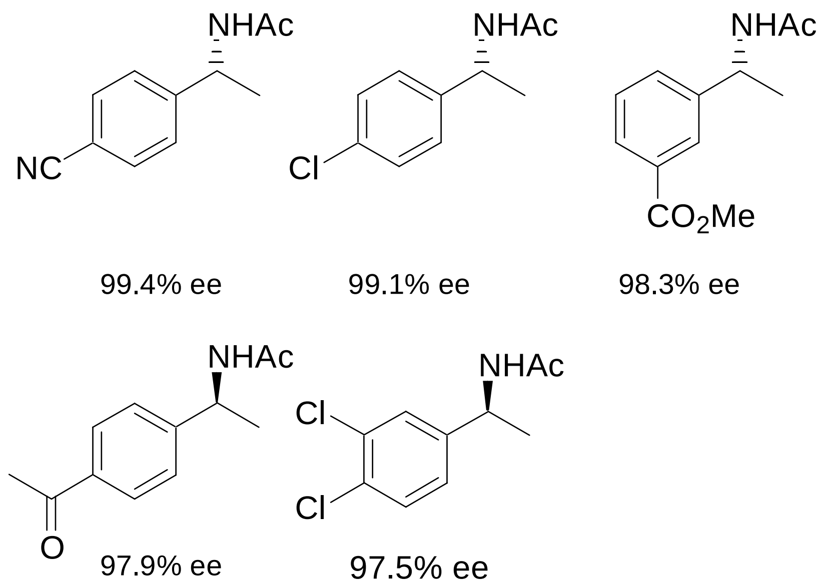
Ref: *J. Org. Chem.*, 1992, *57*, 3558



(*S*,*S*)-Ph-BPE

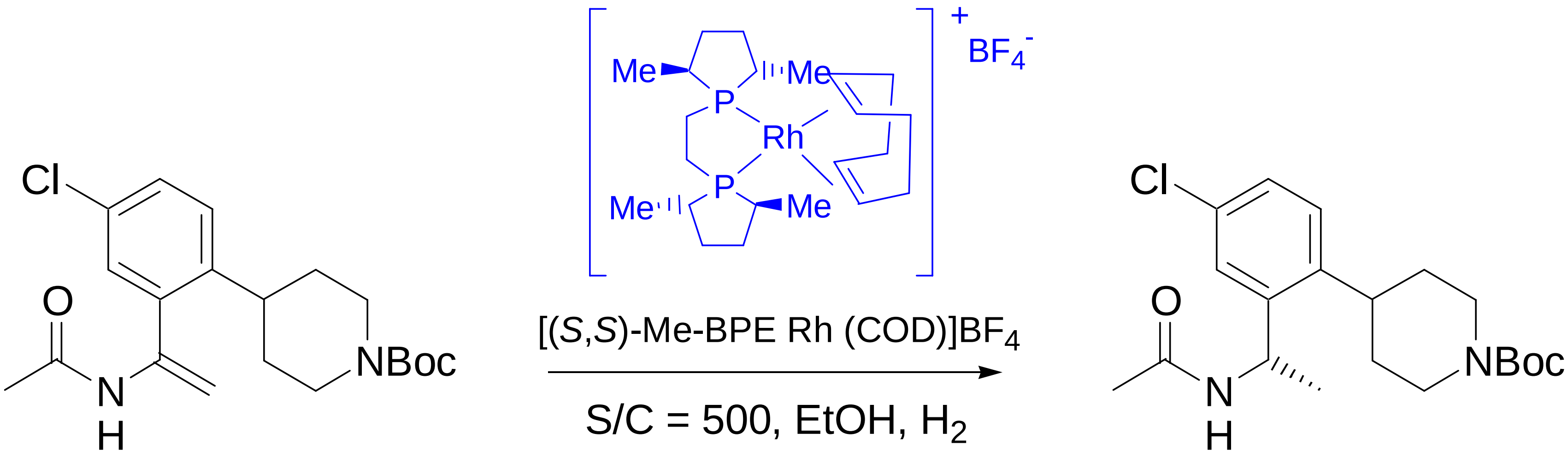


(*S*,*S*)-Et-DuPhos



Dowpharma Paper: *Tetrahedron Lett.* **2004,** *45,* 9277

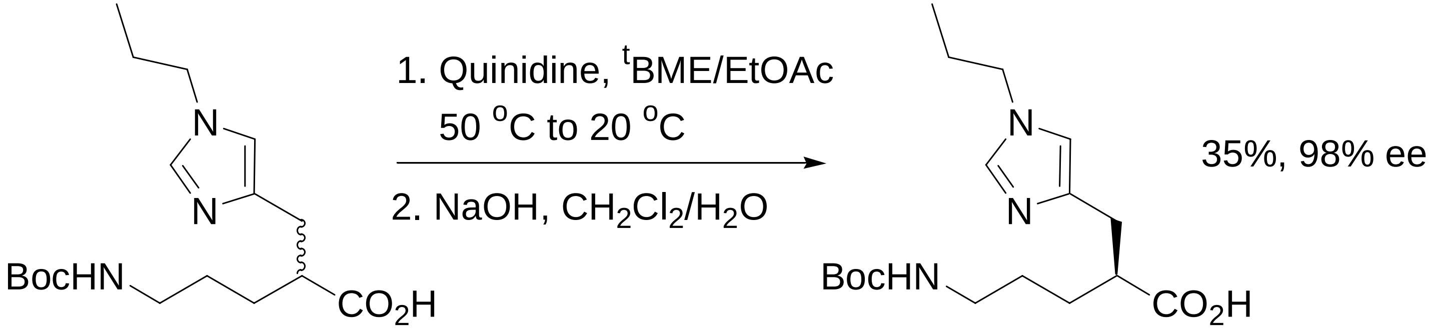
Merck Enamide Hydrogenation



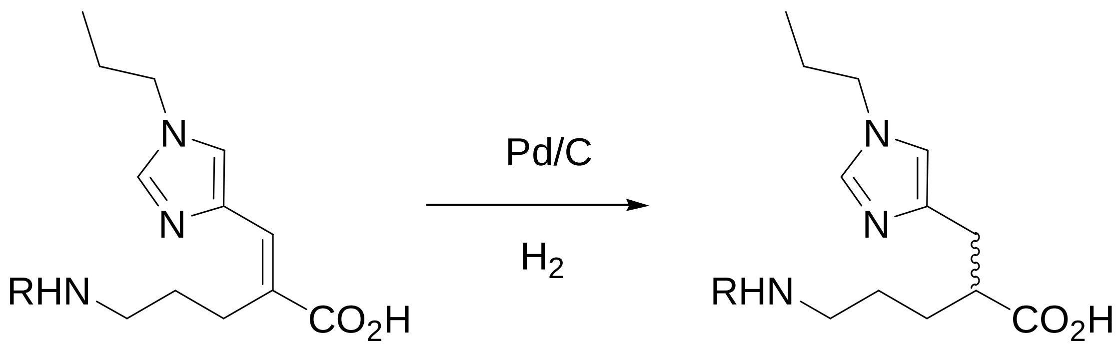
88% ee, 100% assay yield

- Substrate synthesised using the Benzonitrile method
- Purification of the substrate was found to be important to obtain a robust process
- Numerous ligands screened, best results with BPE, Binaphane and DuPhos
- BPE gave the best catalyst loadings (See WO 2006/057904)
- Me-BPE-Rh catalysts are relatively low molecular weight, S/C 500 = 345 $^{wt}/_{wt}$
- Precatalyst supplied by Dowpharma

Process Issue - Choice of Technology



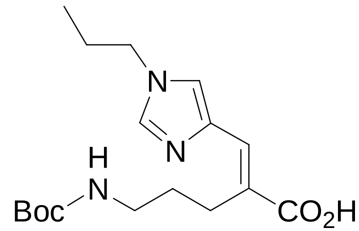
- Diastereoisomeric salt resolution gave the product in good e.e.
- The nature of a resolution, the yield is low, but a quick solution
- Need a higher yielding route to meet manufacturing requirements



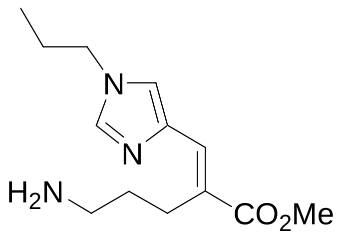
- Route to racemic imidazole is *via* Pd/C reduction

Pfizer & Dowpharma Paper: *Org. Lett.*, 2005, 7, 1931

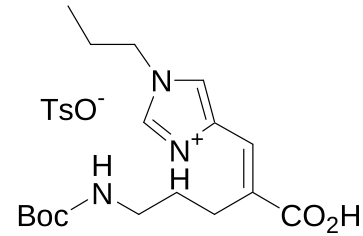
Process Issue – Selecting the Right Substrate



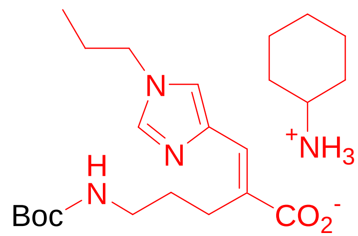
20% conv. 40% e.e.
[(*R*,*R*)-*i*-Pr-FerroTANE Ru (methallyl)$_2$]



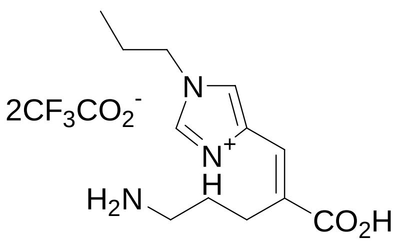
60% conv. 14% e.e.
[(*R*)-Binap RuCl$_2$]



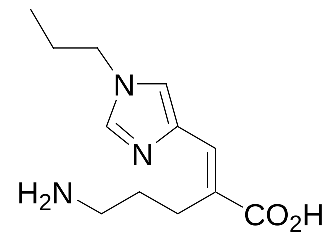
95% conv. 77% e.e.
[(*R*)-Tol-Binap Ru (C_6H_6)Cl]Cl
(loss of Boc group)



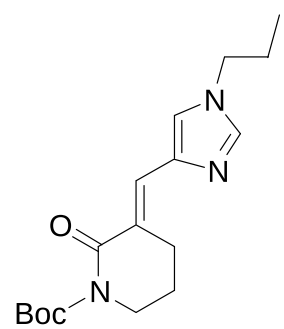
100% conv. 26% e.e.
[(*R*,*R*)-*i*-Pr-DuPhos Ru ($OCOCF_3$)$_2$]



100% conv. 83% e.e.
[(*R*,*R*)-*i*-Pr-DuPhos Ru ($OCOCF_3$)$_2$]



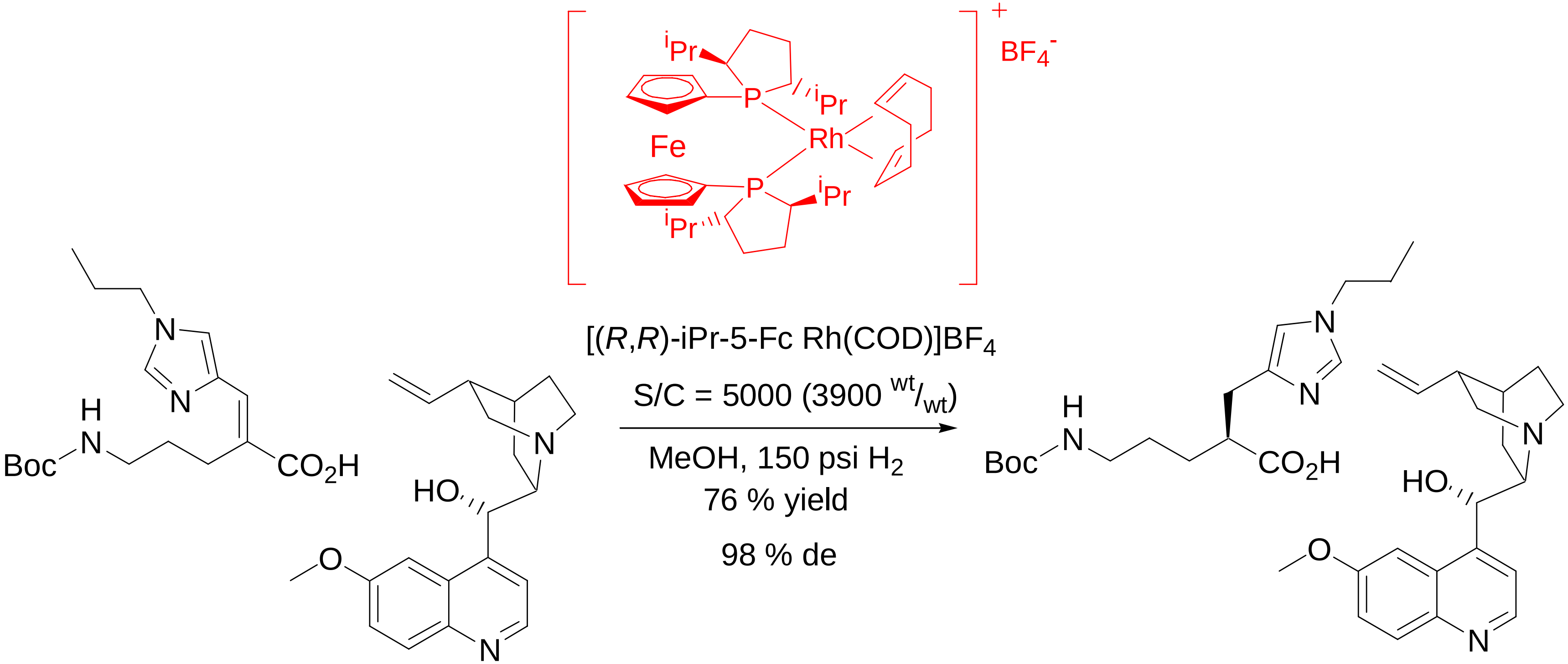
100% conv. 56% e.e.
[(*S*,*S*)-*i*-Pr-FerroTANE Ru (methallyl)$_2$]



93% conv. No assay available
[(*R*,*R*)-*i*-Pr-BPE Ru (methallyl)$_2$]

Pfizer & Dowpharma Paper: *Org. Lett.*, 2005, *7*, 1931

Optimised Process for a δ-Amino Acid



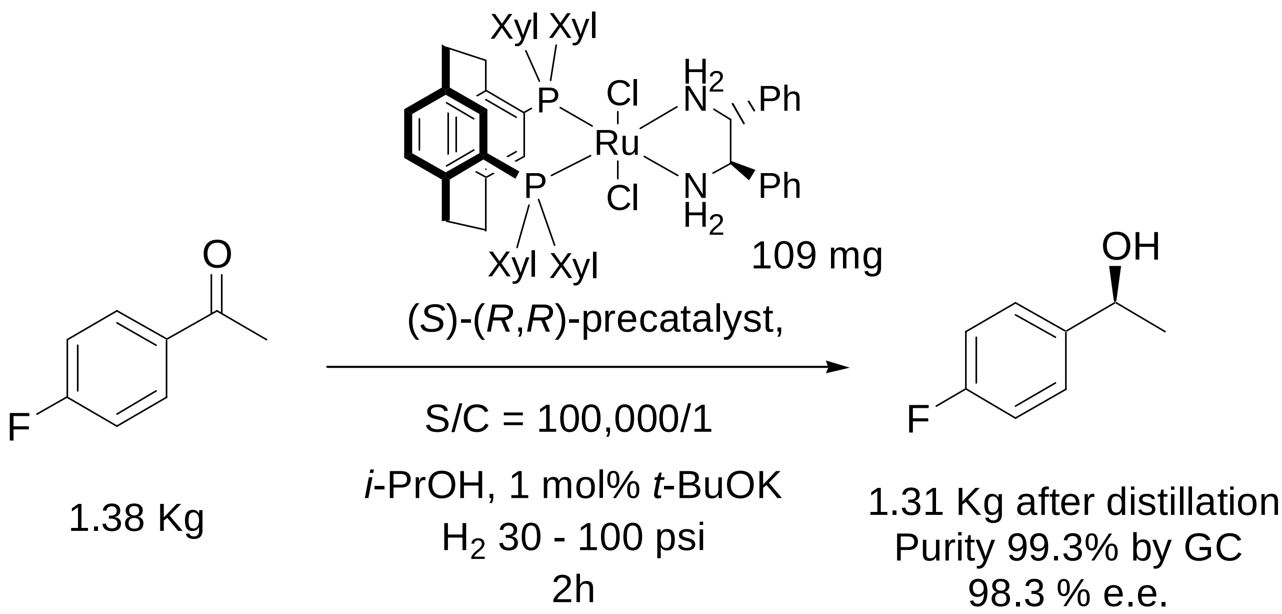
- After an extensive screen of 8 substrates and >100 catalysts we found that the quinidine salt could be hydrogenated in good de.
- We chose the most <u>active</u> and not the most selective catalyst for this process
- Compared with the classical resolution we were able to double the yield of product. Pfizer made >20 Kg by this route.

Pfizer & Dowpharma Paper: *Org. Lett.*, 2005, *7*, 1931

Process Requirements

- Choice of Catalyst Complex – screening
- Availability of the Chosen Catalyst (Security of Supply)
- Synthesis, Purity and Selection of Substrate
- **Substrate to Catalyst Ratio and Purity of Substrate**
- Enantiomeric Excess
- Choice of Solvent
- Concentration, Temperature, Pressure
- Removal of spent catalyst from the product
- Reactor Configuration, e.g. Agitation

Substrate Purity for Ketone Hydrogenation

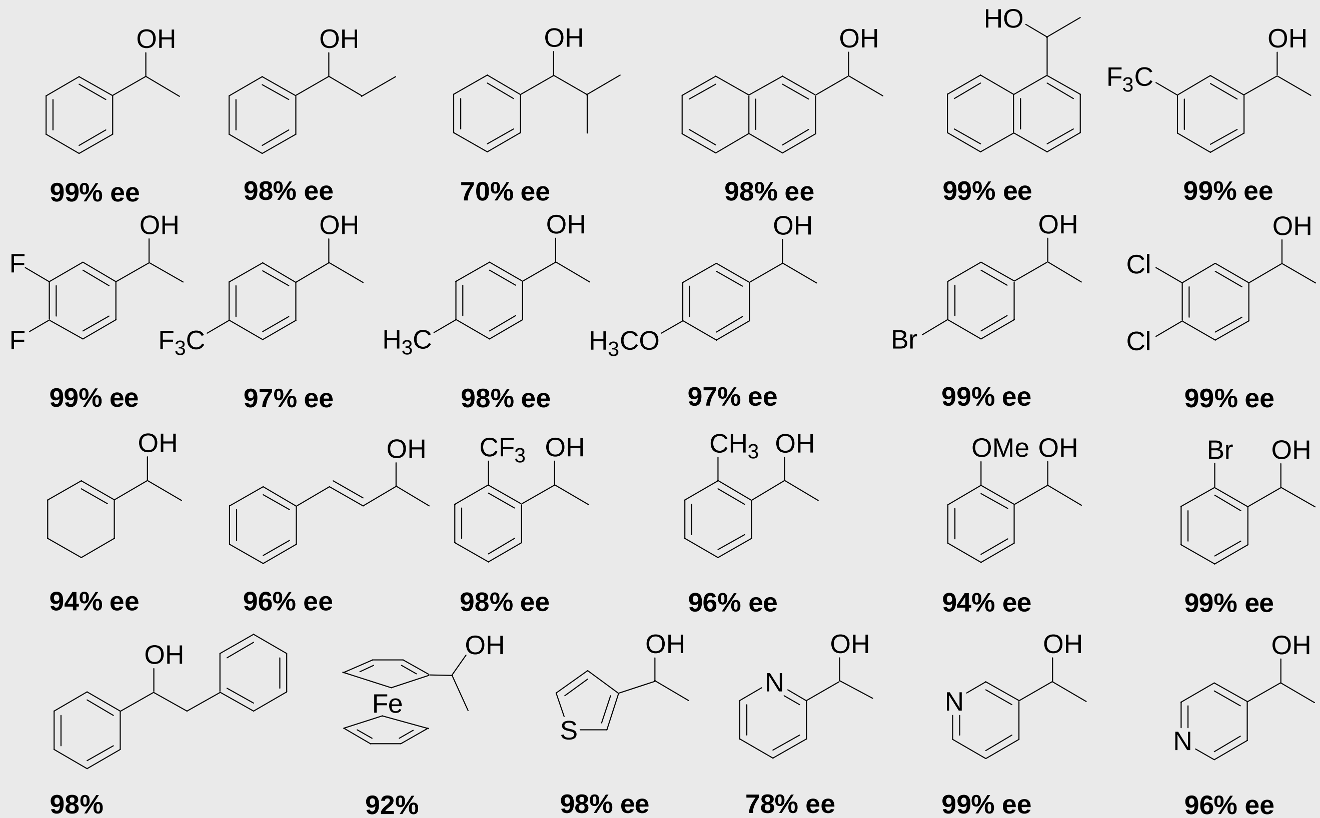


- PhanePhos-based ligand best
- Substrate distilled before use. No reaction with commercial substrate
- S/C 100,000 : 1 achieved (13,000/1 $^{wt}/_{wt}$)
- Several other examples at 100s kg scale

Org. Lett. **2000**, *2*, 4173 and *Org. Process Res. Dev.* **2003**, *7*, 89

Chiral Alcohols: Asymmetric Hydrogenation

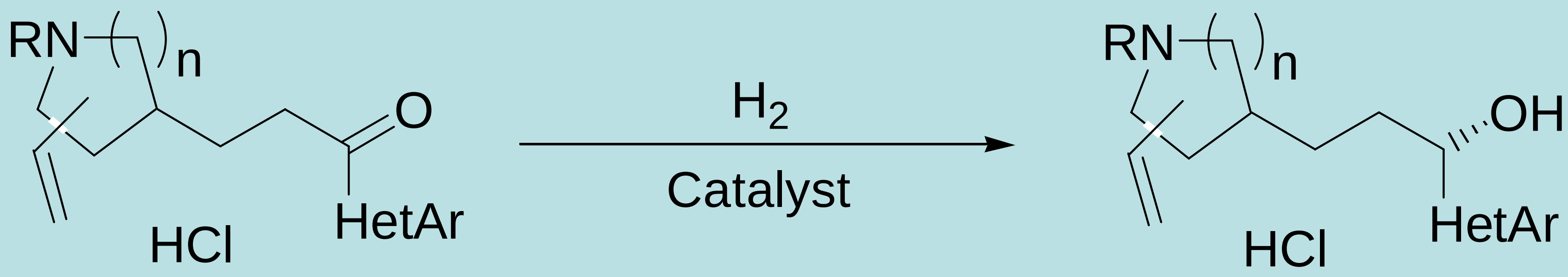
❖ Single enantiomer alcohols made using ketone hydrogenation



Dowpharma[SM]

Dowpharma Papers: *Org. Lett.* 2000, *2*, 4173 and *Org. Process Res. Dev.* 2003, *7*, 89

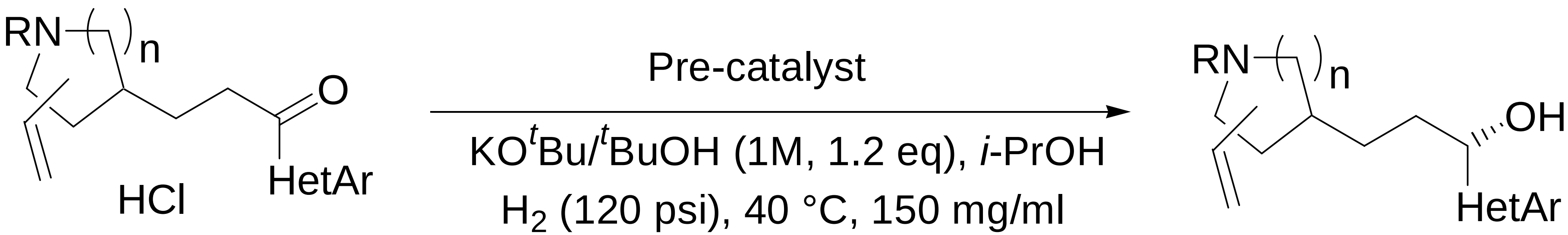
Large Scale Asymmetric Ketone Hydrogenation



Aims

- >95% de
- >95% chemical purity
- >80% overall yield
- Minimal reduction of the olefin

Catalyst Screen and Loading



Pre-catalyst	*S/C*	*Time[a] (min)*	*Conv. (%)*	*Over-reduction (%)*	*de (%)*
[(*R*)-HexaPHEMP $RuCl_2$ (*R*,*R*)-DPEN]	10,000	60	100	1.3	96
[(*R*)-HexaPHEMP $RuCl_2$ (*R*,*R*)-DPEN]	50,000	270	95	1.2	96
[(*S*)-PhanePhos $RuCl_2$ (*R*,*R*)-DPEN]	10,000	250	100	1.0	92

- HexaPHEMP provided the best de and least olefin reduction
- Starting material contains 0.9% olefin-reduced material

Manufacturing Campaigns – Mirfield, UK

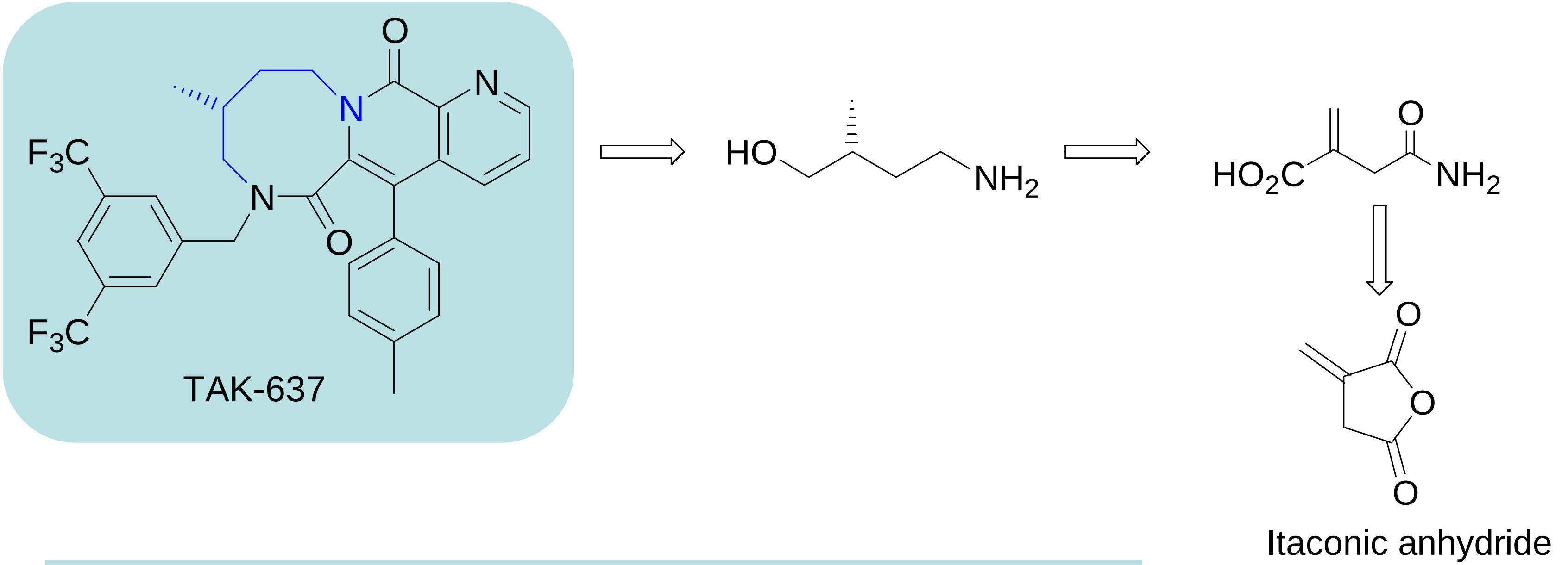
- S/C 10000-11000, 5 mol% KO^{t}Bu/^{t}BuOH (1M)
- Pre-catalyst added as a solid
- >97% de produced in all batches
- Four campaigns making >500 Kg product
- Rapid implementation of the process from the laboratory to the plant

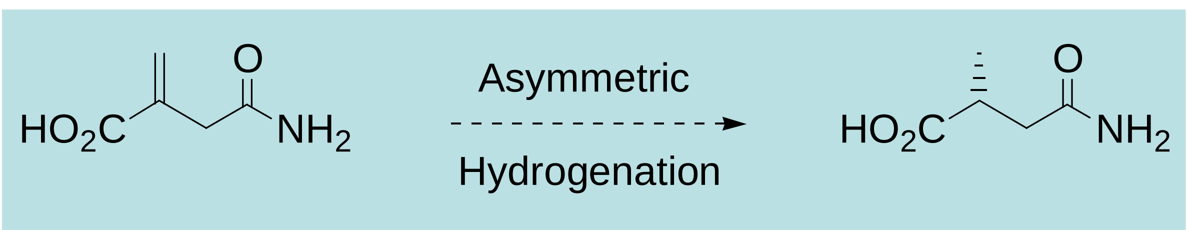
Process Requirements

- Choice of Catalyst Complex – screening
- Availability of the Chosen Catalyst (Security of Supply)
- Synthesis, Purity and Selection of Substrate
- Substrate to Catalyst Ratio and Purity of Substrate
- Enantiomeric Excess
- **Choice of Solvent**
- **Concentration, Temperature, Pressure**
- **Removal of spent catalyst from the product**

Reactor Configuration, e.g. Agitation

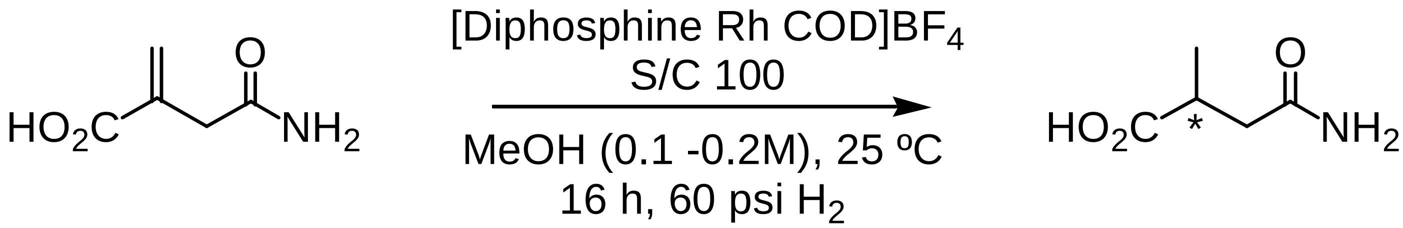
Case Study: Methylenesuccinamic acid Hydrogenation

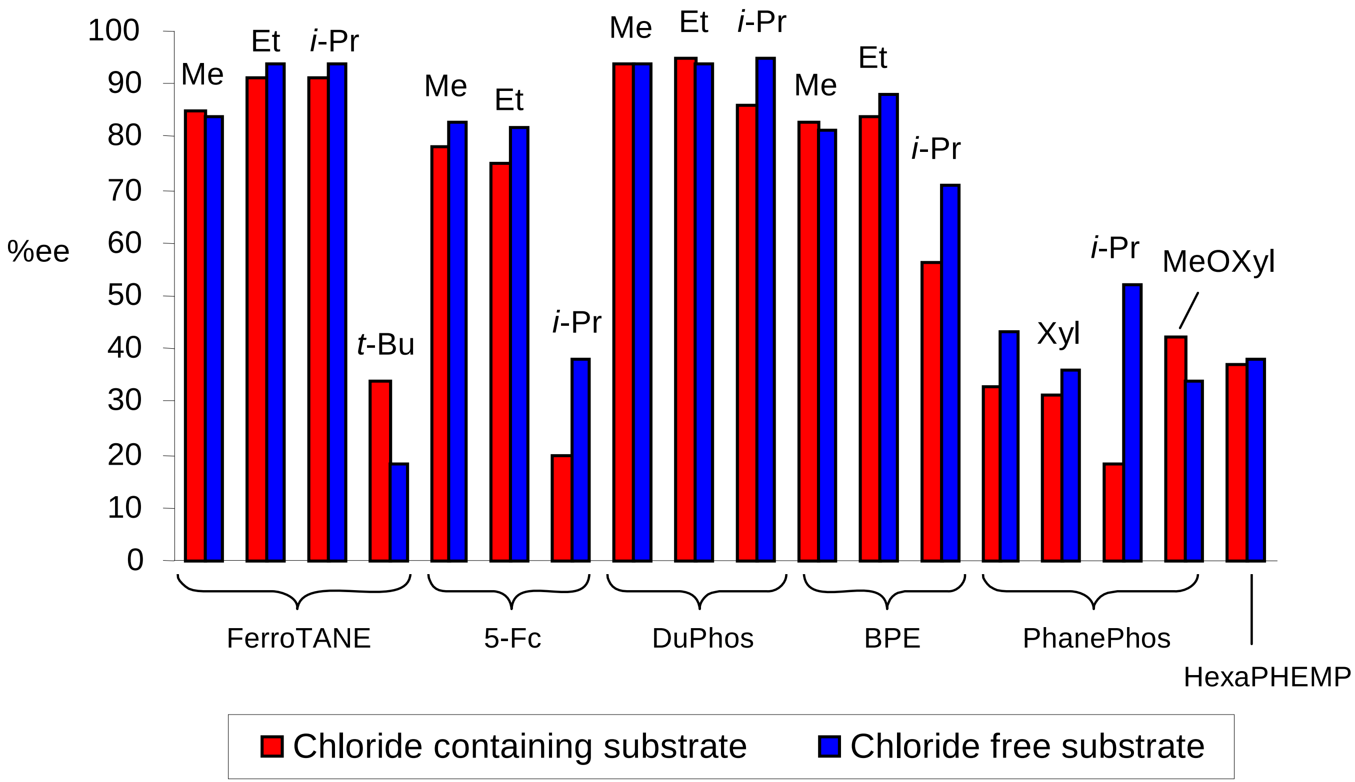


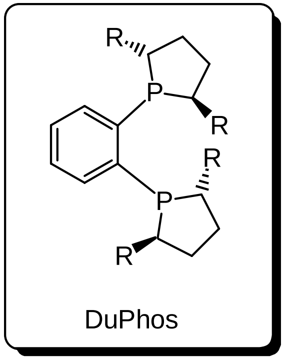


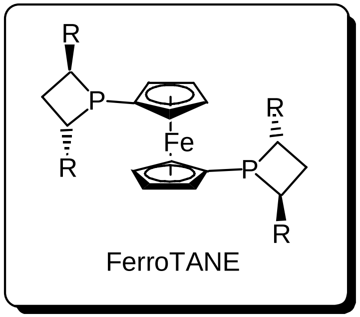
- Substrate readily made from Itaconate anhydride by reaction with NH_4OH
- Reaction was quenched with HCl according to literature preparation

Screen of Rh Precatalysts

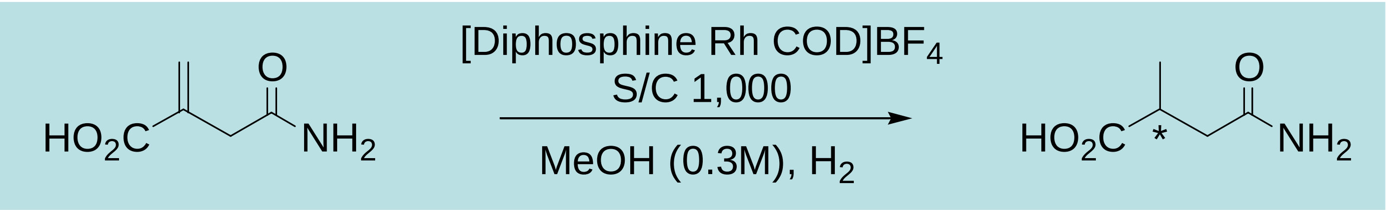








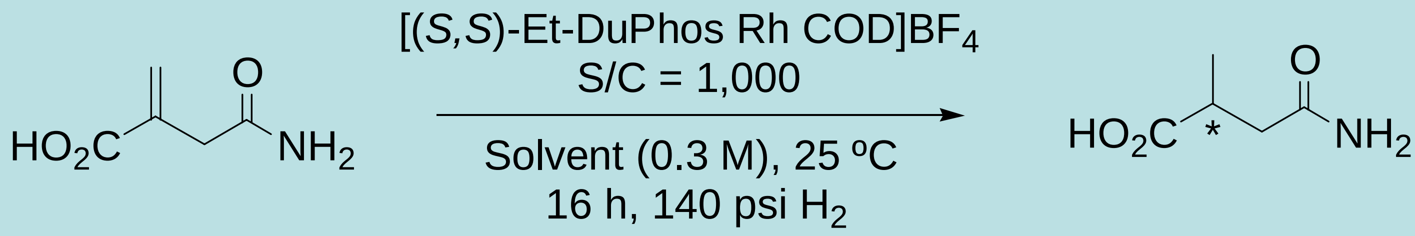
Temperature & Pressure



Precatalyst	*Temp (ºC)*	*H_2 Pressure (psi)*	*TOF (h^{-1})*	*Conv. (%)*	*ee (%)*
[(*S*,*S*)-Et-DuPhos Rh COD]BF_4	0	60	18	33	93 (*R*)
"	20	60	250	> 98	94 (*R*)
"	45	60	430	> 98	96 (*R*)
"	20	140	500	> 98	97 (*R*)
"	45	140	667	> 98	95 (*R*)
[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	20	60	500	> 98	87 (*R*)
"	20	140	1333	> 98	72 (*R*)
"	45	140	3000	> 98	86 (*R*)

- Enantioselectivity is retained at higher temperatures and pressures for Et-DuPhos-Rh catalyst

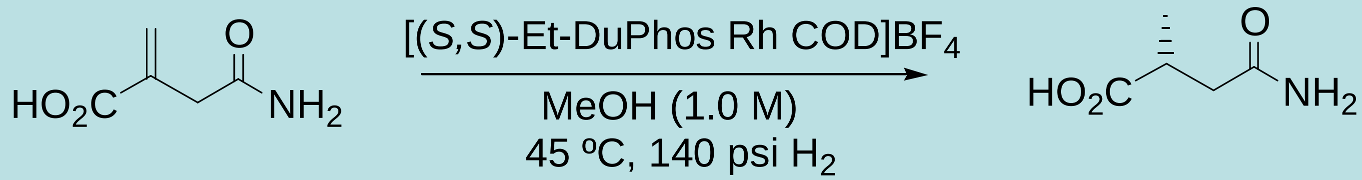
Solvent Screen



Solvent	*Conv. (%)*	*ee (%)*	*Solvent*	*Conv. (%)*
MeOH	> 98	97 (*R*)	EtOAc	21
EtOH	37	84 (*R*)	CH_2Cl_2	2
i-PrOH	87	97 (*R*)	Acetone	9
CF_3CH_2OH	5	-	Toluene	0
THF	24	17 (*S*)	α,α,αTrifluorotoluene	0

- Alcoholic solvents are generally the best for asymmetric hydrogenation
- Methanol is probably the most commonly used solvent
- This is very much substrate and type of hydrogenation dependant
- For example [Diphosphine $RuCl_2$ Diamine] hydrogenations require ^{i}PrOH

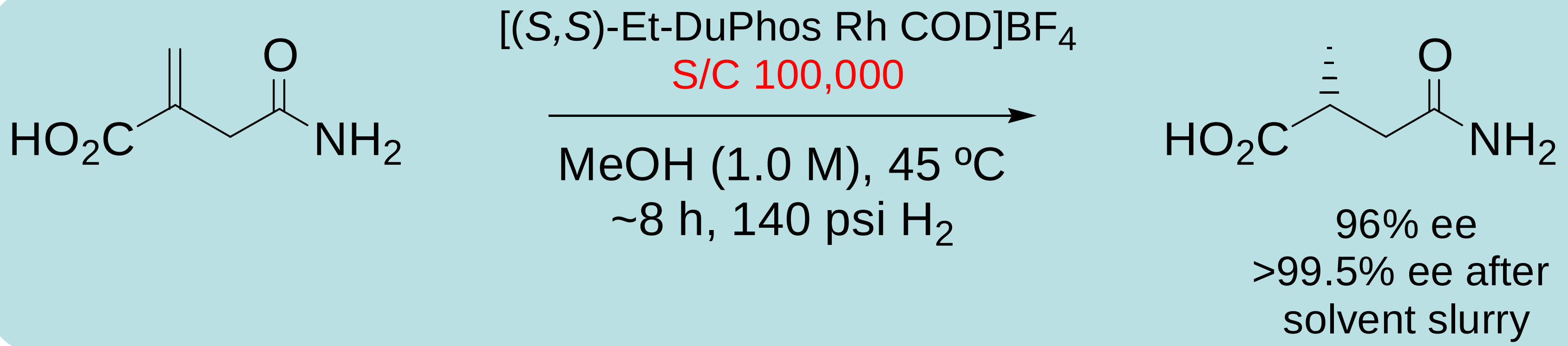
Effect of Chloride Ions



S/C	*Substrate Input*	*TOF (h^{-1})*	*Time*	*Conv. (%)*	*ee (%)*
1,000	15 g	513	1 h 57 min	> 98	97 (*R*)
1,000	15 g	15000	4 min	> 98	96 (*R*)
1,000	15 g	1935	31 min	> 98	97 (*S*)
5,000	15 g	12500	24 min	> 98	97 (*R*)
10,000	15 g	13043	46 min	> 98	96 (*R*)
20,000	15 g	11765	1 h 42 min	> 98	97 (*R*)
50,000	40 g	12397	4 h 2 min	> 98	97 (*R*)
100,000	40 g	13423	7 h 27 min	> 98	96 (*R*)

- Removal of chloride increases rate by factor of 30
- This effect was reproduced by preparing the precatalyst from $[RhCl(COD)]_2$ & 2 eq. of (*R*,*R*)-Et-DuPhos

Asymmetric Hydrogenation of Methylenesuccinamic acid



- Chloride impurity identified that limited S/C to 1000:1
- Synthesis of substrate from itaconic anhydride was modified
- Complete conversion with 96 % e.e. at S/C 100,000:1 ($^{w}/_{w}$ ~21,400)
- Upgraded to 99.5 % e.e. with a single reslurry (MeOH)
- Rh content reduces from 9.0 ± 0.4 ppm to 0.88 ± 0.05 ppm

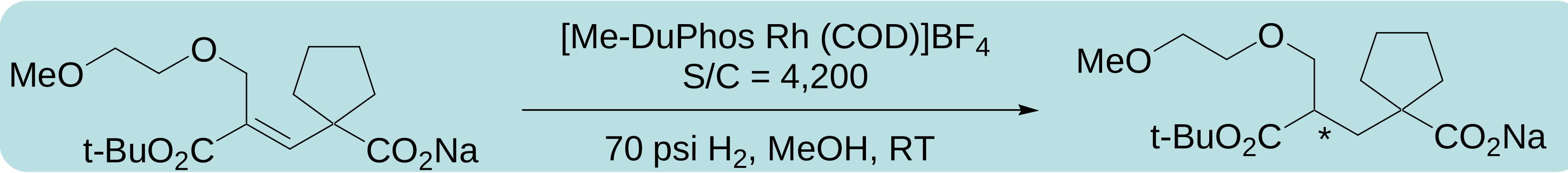
  (36 ± 1 ppm to 9.8 ± 0.4 ppm for S/C 20,000)

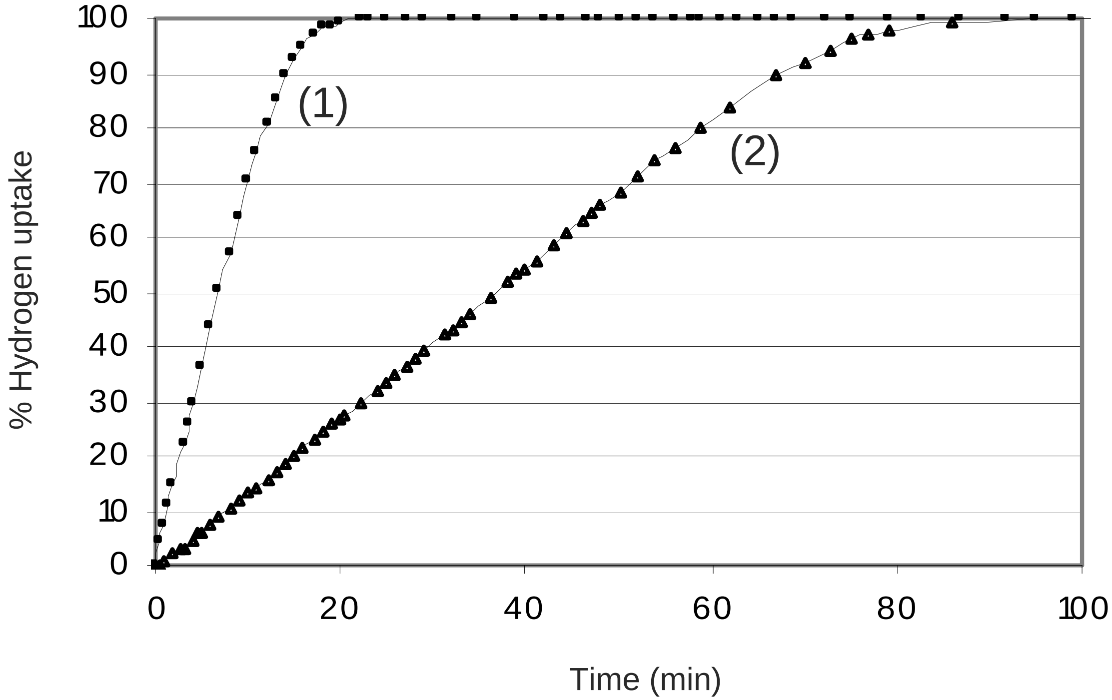
Dowpharma paper: *Org. Process Res. Dev.* **2003**, *7*, 407

Process Requirements

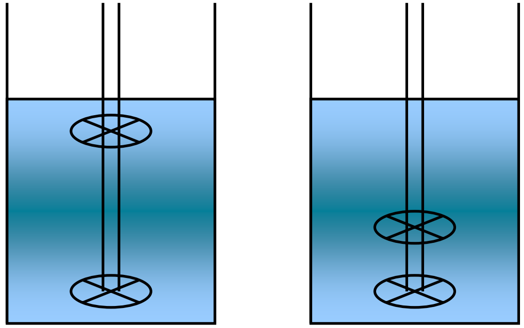
- Choice of Catalyst Complex – screening
- Availability of the Chosen Catalyst (Security of Supply)
- Synthesis, Purity and Selection of Substrate
- Substrate to Catalyst Ratio and Purity of Substrate
- Enantiomeric Excess
- Choice of Solvent
- Concentration, Temperature, Pressure
- Removal of spent catalyst from the product
- **Reactor Configuration, e.g. Agitation**

Process Issue – Reactor Configuration





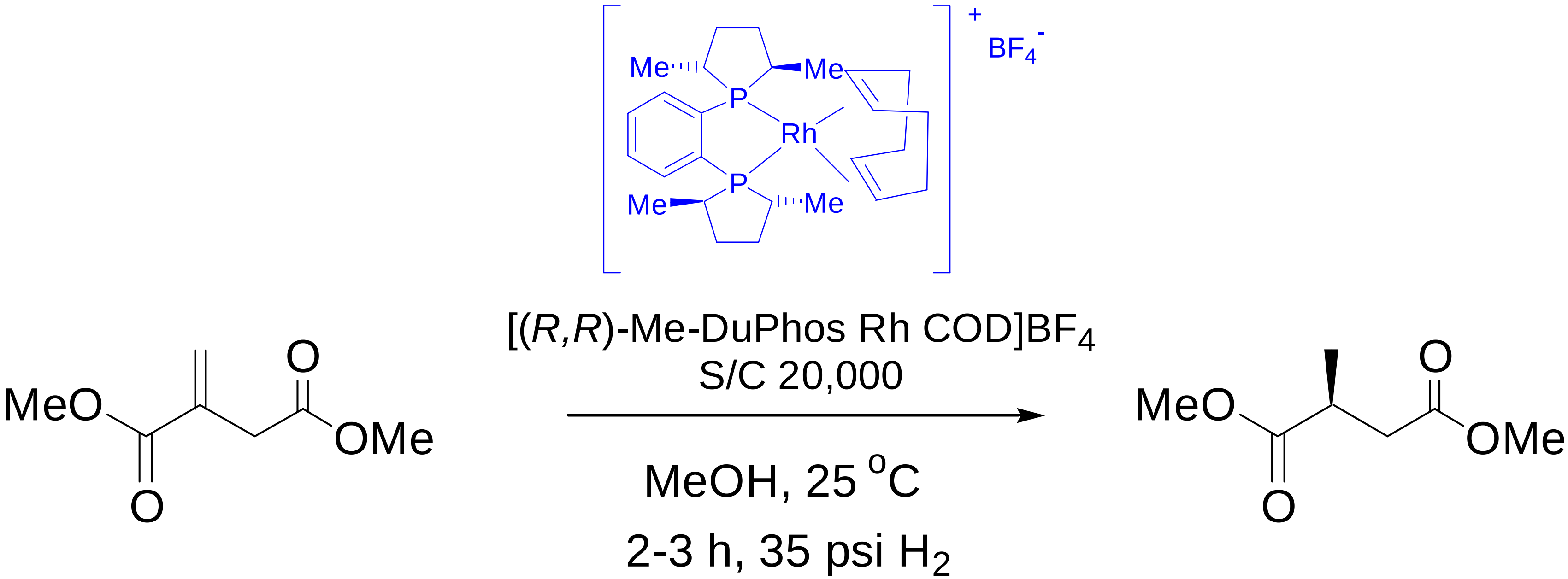
Reactor stirring efficiency:



(1) (2)

- Hydrogen availability is a critical process parameter
- Non-optimal stirring and hydrogen absorption can lead to slow/failed reactions

Large Scale Asymmetric Hydrogenation of DMI



- Ton-scale manufacture (Molar S/C 20,000 = 5,200 wt/wt)
- Consistent >97 ee obtained over multiple runs
- Reaction time typically 2-3 hours
- Commercial Manufacture carried out in Midland, Michigan

Conclusions

- There has been an increasing number of asymmetric hydrogenation processes carried out on a manufacturing scale over the last 4 decades
- Asymmetric hydrogenation technology is now routinely used for the manufacture of pharmaceutical intermediates
- With a greater number of catalyst systems available and a better understanding of the process issues surrounding asymmetric hydrogenation technology, there are increased applications for this technology – e.g. Tipranavir, Rozerem, Sitagliptin and Aliskiren
- Dowpharma technology is available for customers to use in their own, preferred third party suppliers or Dowpharma facilities
- Security of supply of the catalyst is of paramount importance

Acknowledgments

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