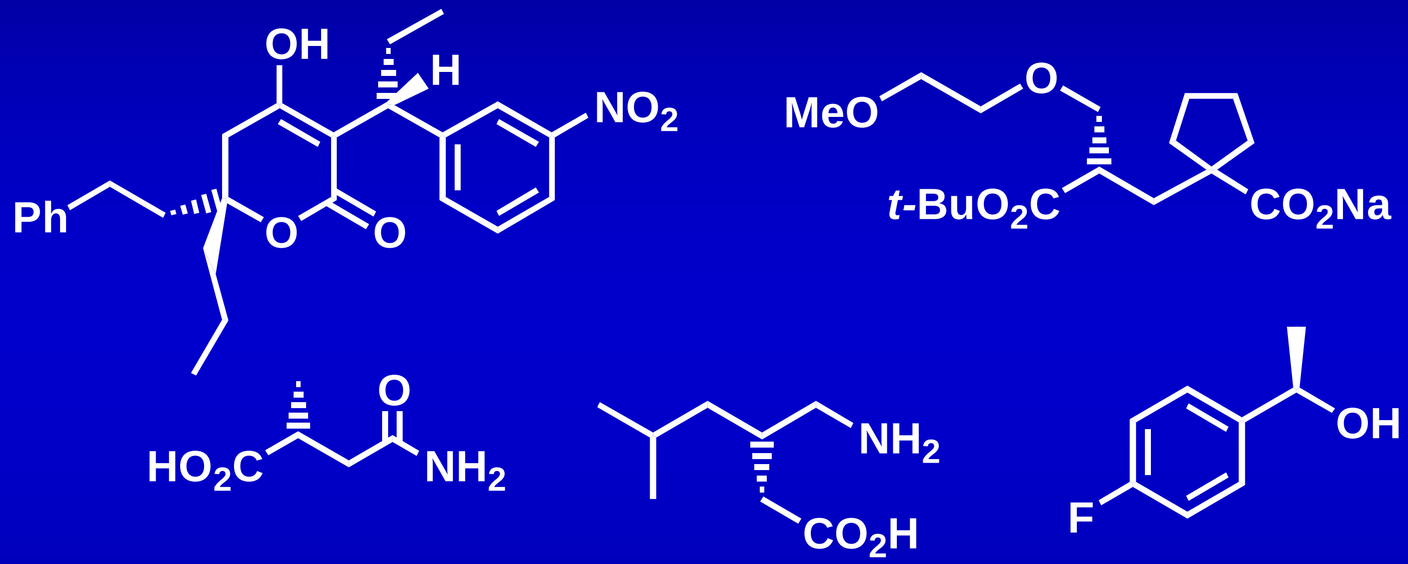
Process Requirements for the Development of Asymmetric Hydrogenation Reactions: From the Bench to Kilogram Scale



Ian C. Lennon
Dow**pharma**, Cambridge, UK

Dow**pharma**

Outline of Talk

Process Requirements for the Development of Asymmetric Hydrogenation Reactions: From the Bench to Kilogram Scale

– Known Asymmetric Hydrogenation Processes

– Process Requirements

– Screening Methodology for 2-Methylenesuccinamic Acid

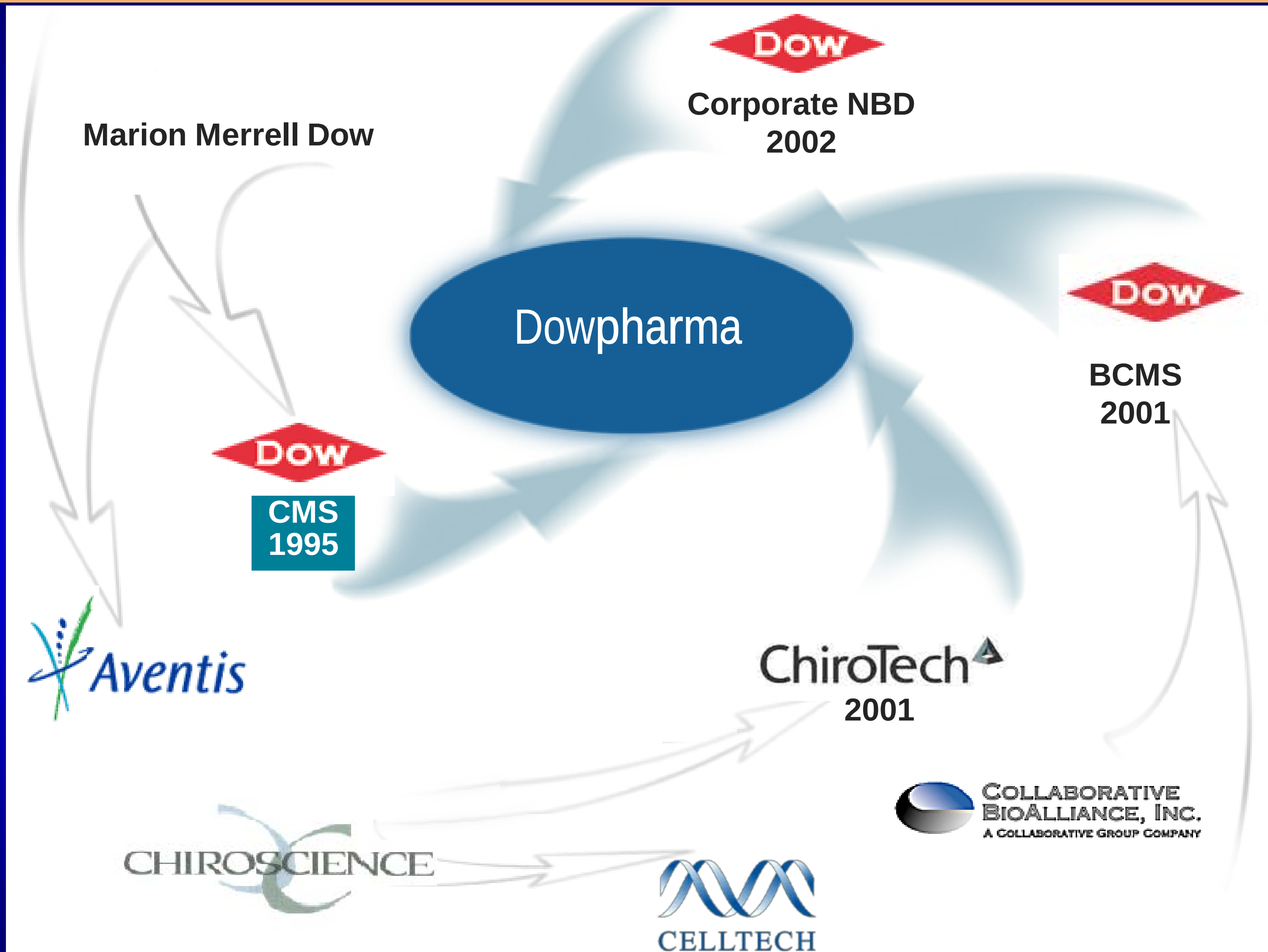
– Optimisation Studies for 2-Methylenesuccinamic Acid

– Case Studies (Candoxatril, Pregabalin, 4-F-Acetophenone)

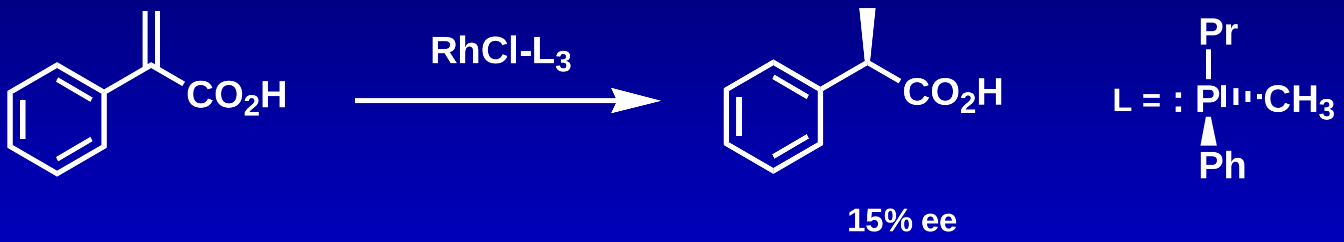
– Imine Hydrogenation (Thiadiazine)

– Conclusions

Dowpharma Formation

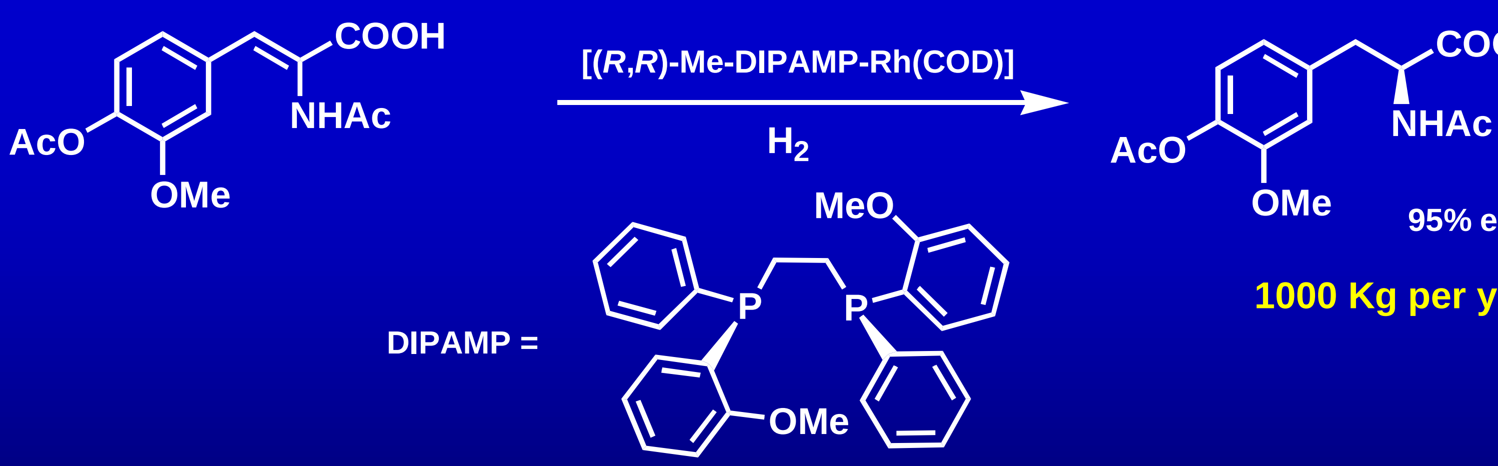


Early Applications of Asymmetric Hydrogenation



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

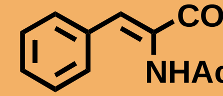
Monsanto L-DOPA process



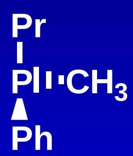
1000 Kg per year

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

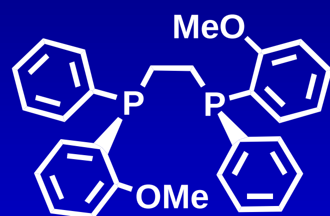
Some of the First Applied Phosphine Ligands



Ligand % ee Ligand % ee Ligand % ee

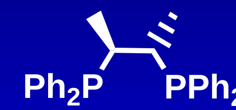


28%



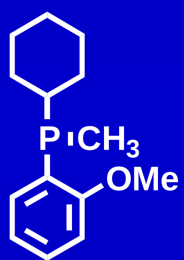
95%

DIPAMP - 1974



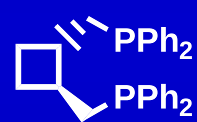
95%

CHIRAPHOS - 1977



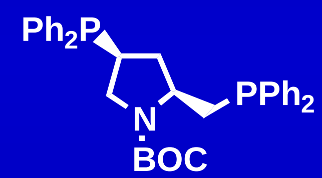
88%

CAMP - 1970



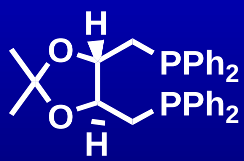
87%

Rhone-Poulenc - 1974



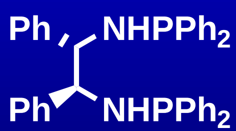
91%

BPPM -1976



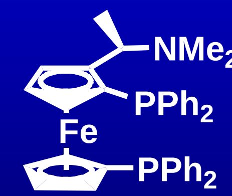
83%

DIOP - 1971



94%

PNNP - 1974



93%

BPPFA - 1980

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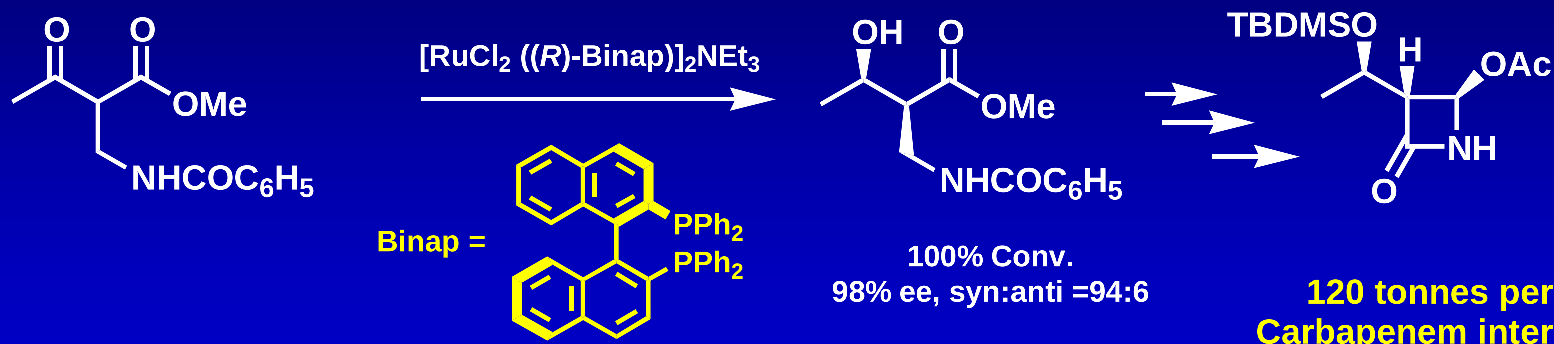
W.S. Knowles *Acc. Chem. Res.* 1983, *16*, 106

Noyori's Binap Complexes



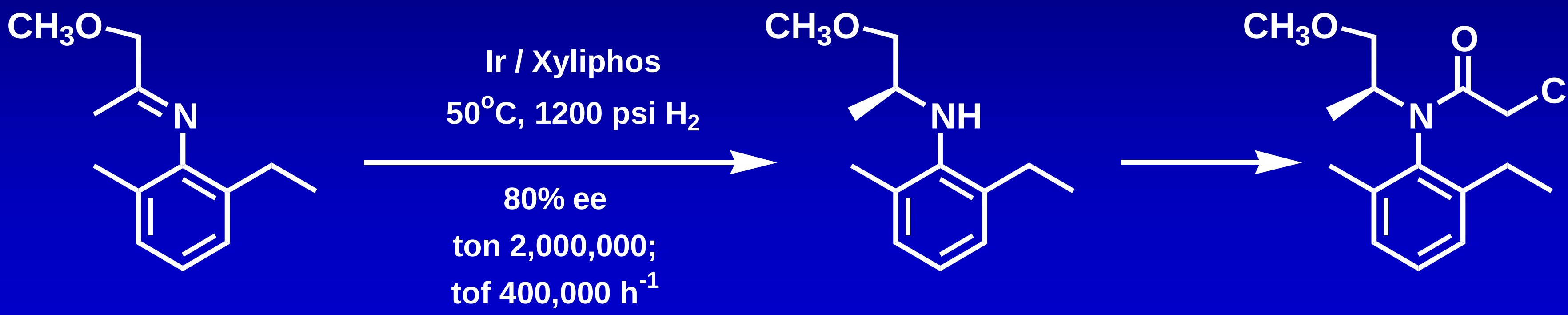
120 tonnes per year
Carbapenem intermediate

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

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

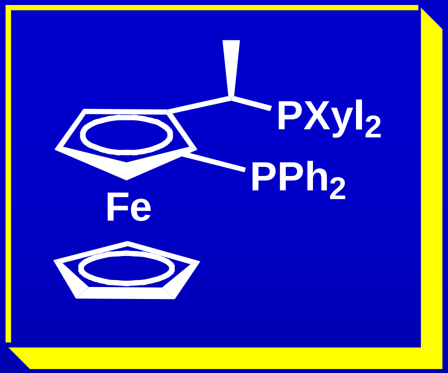
Largest Scale Industrial Asymmetric Hydrogenation

DOW



Metolachor

Xyliphos =

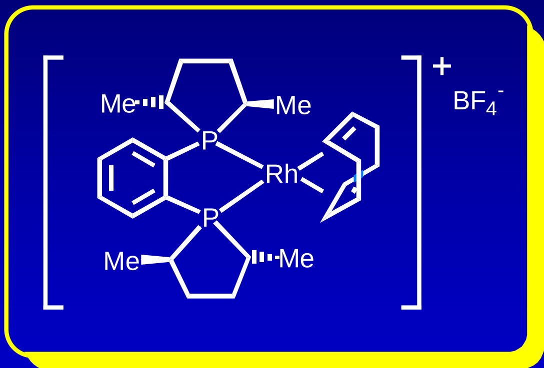


>10,000 tonnes per year

1982 - Laboratory work
1996 - First Production batch

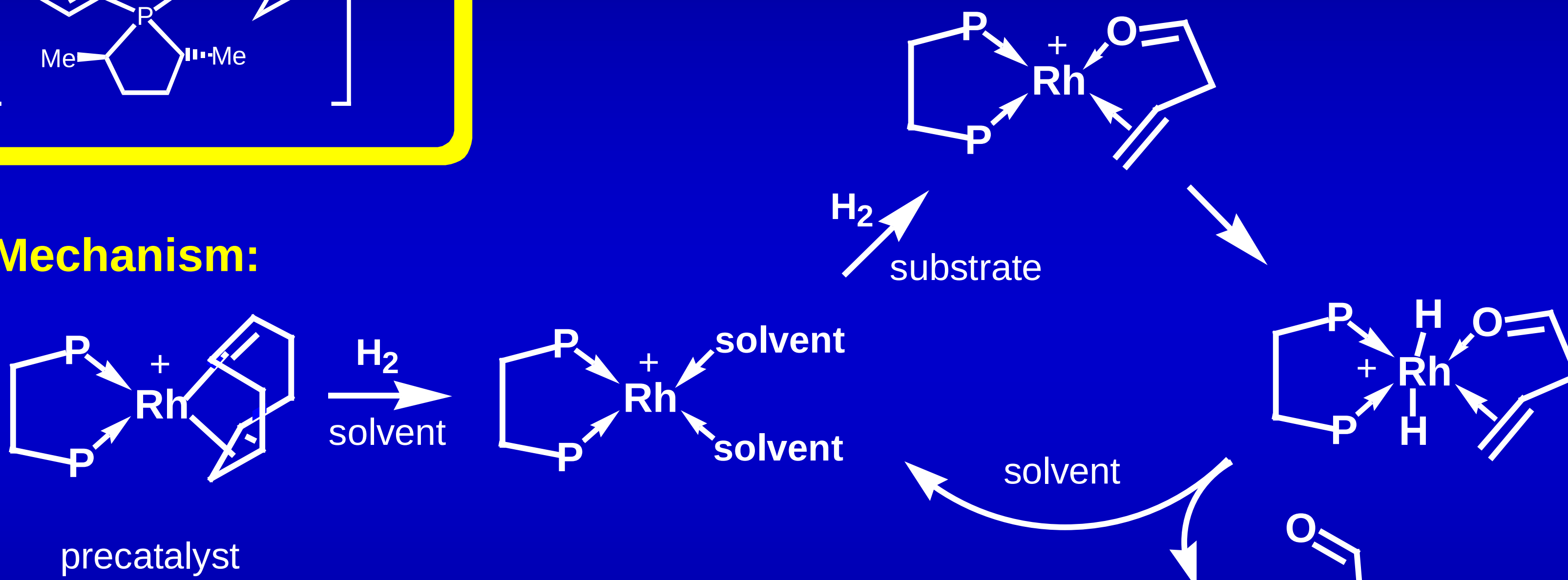
Hans-Ulrich Blaser *Adv. Synth. Catal.* 2002, *344*, 17

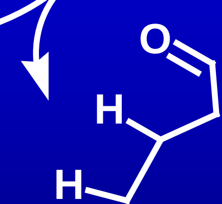
Rh-DuPhos Asymmetric Hydrogenation



DuPhos licensed from DuPont since 1995: license now assigned to Dow

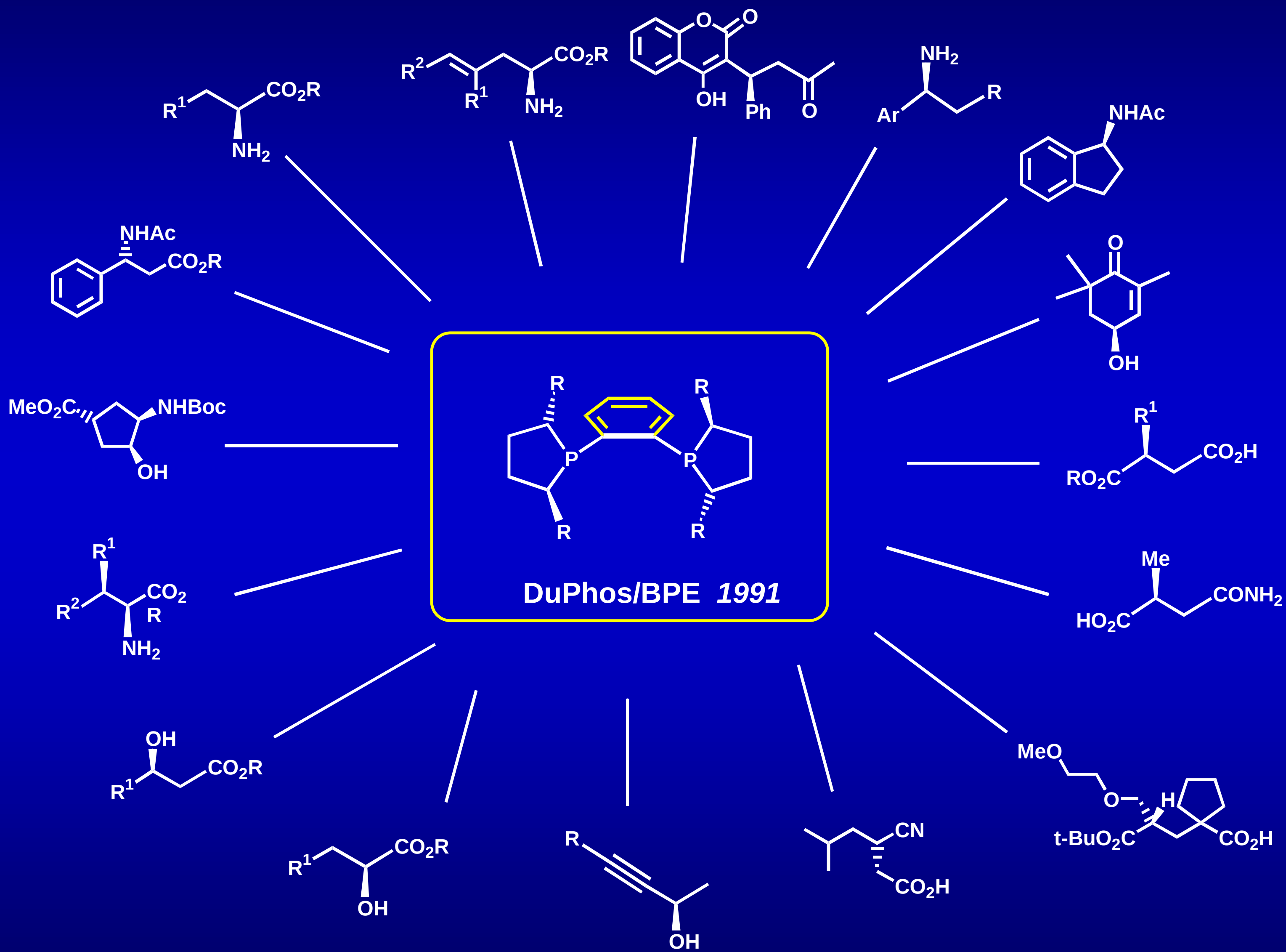
Mechanism:





- **The substrate binds to the metal**
- **The substrate carbonyl group controls the orientation of hydrogenation**

Scope of the DuPhos / BPE Hydrogenation



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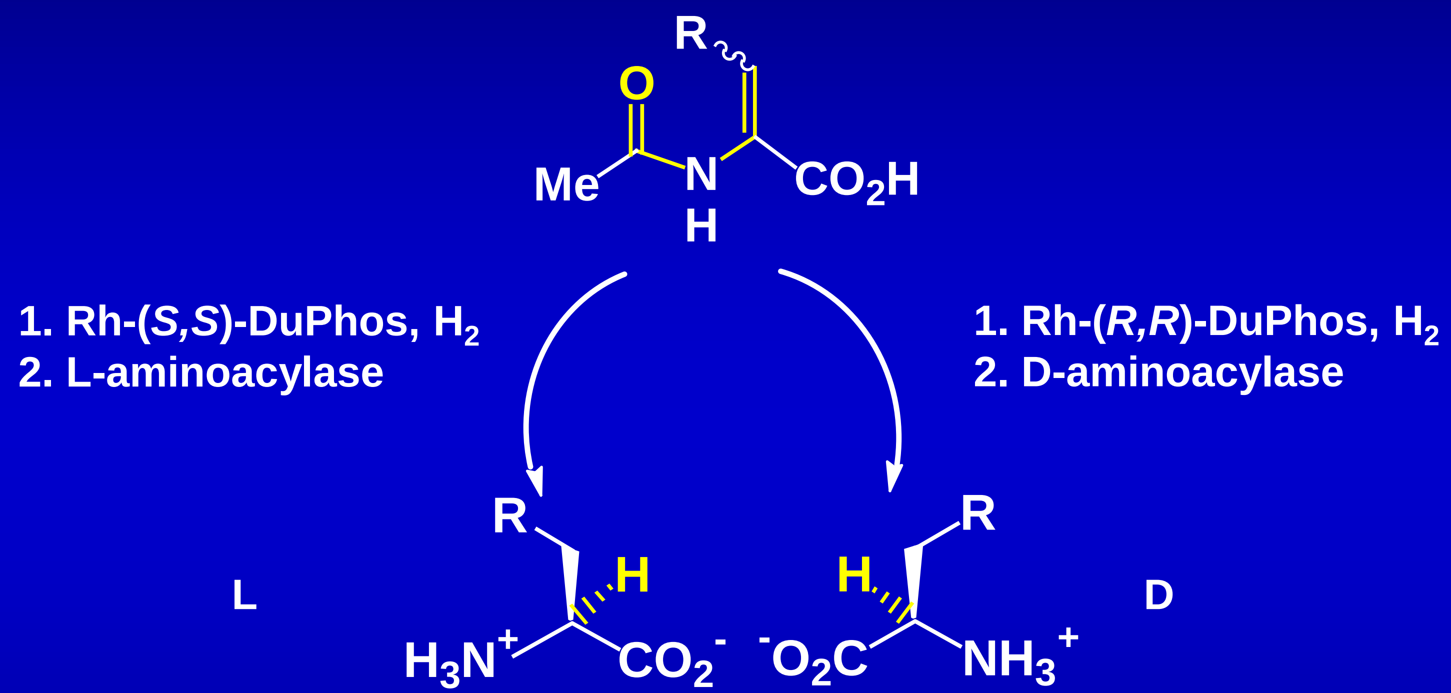
M. J. Burk *Acc. Chem. Res.* **2000**, *33*, 363

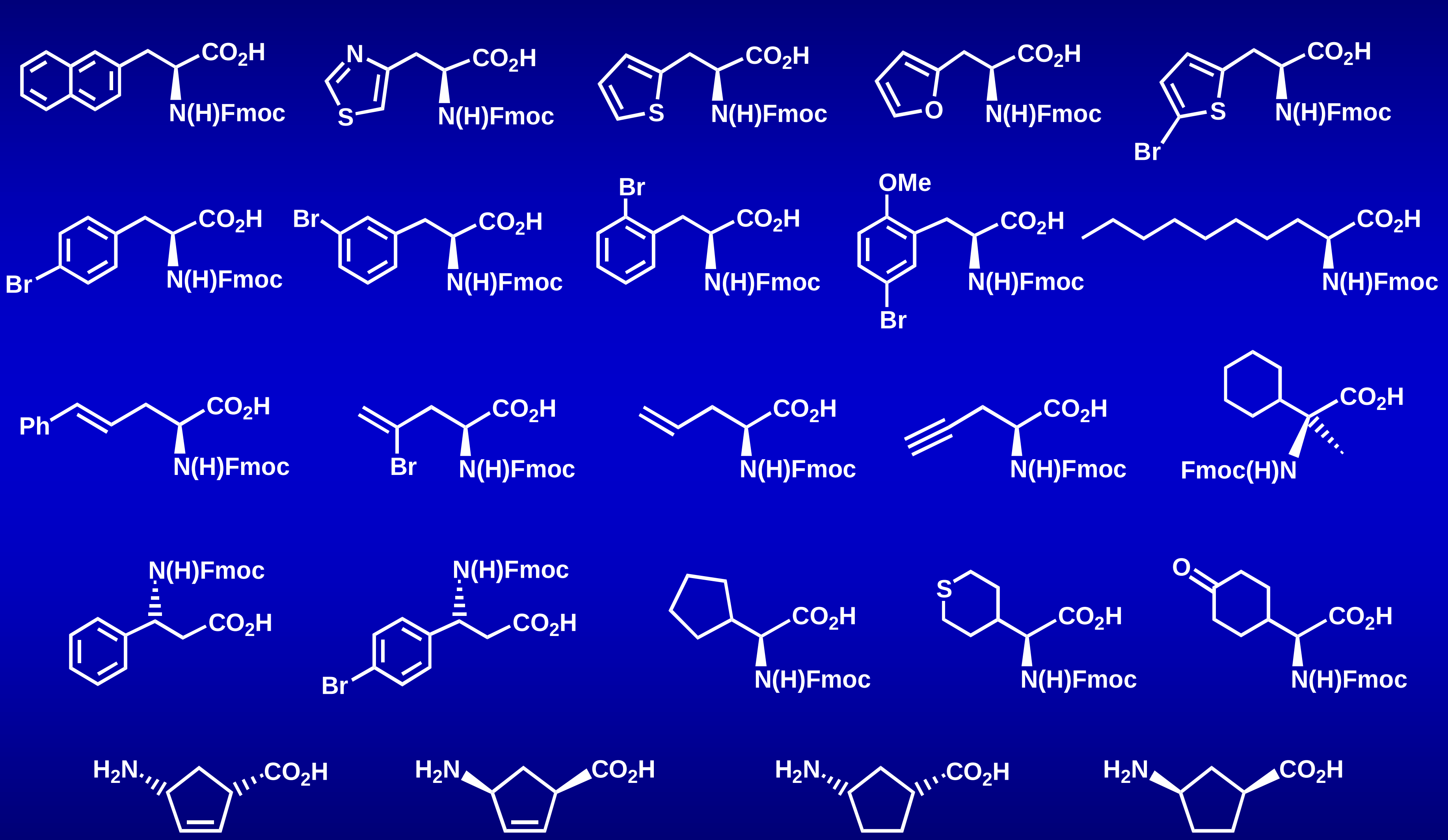
Asymmetric Hydrogenation & Biocatalysis combined



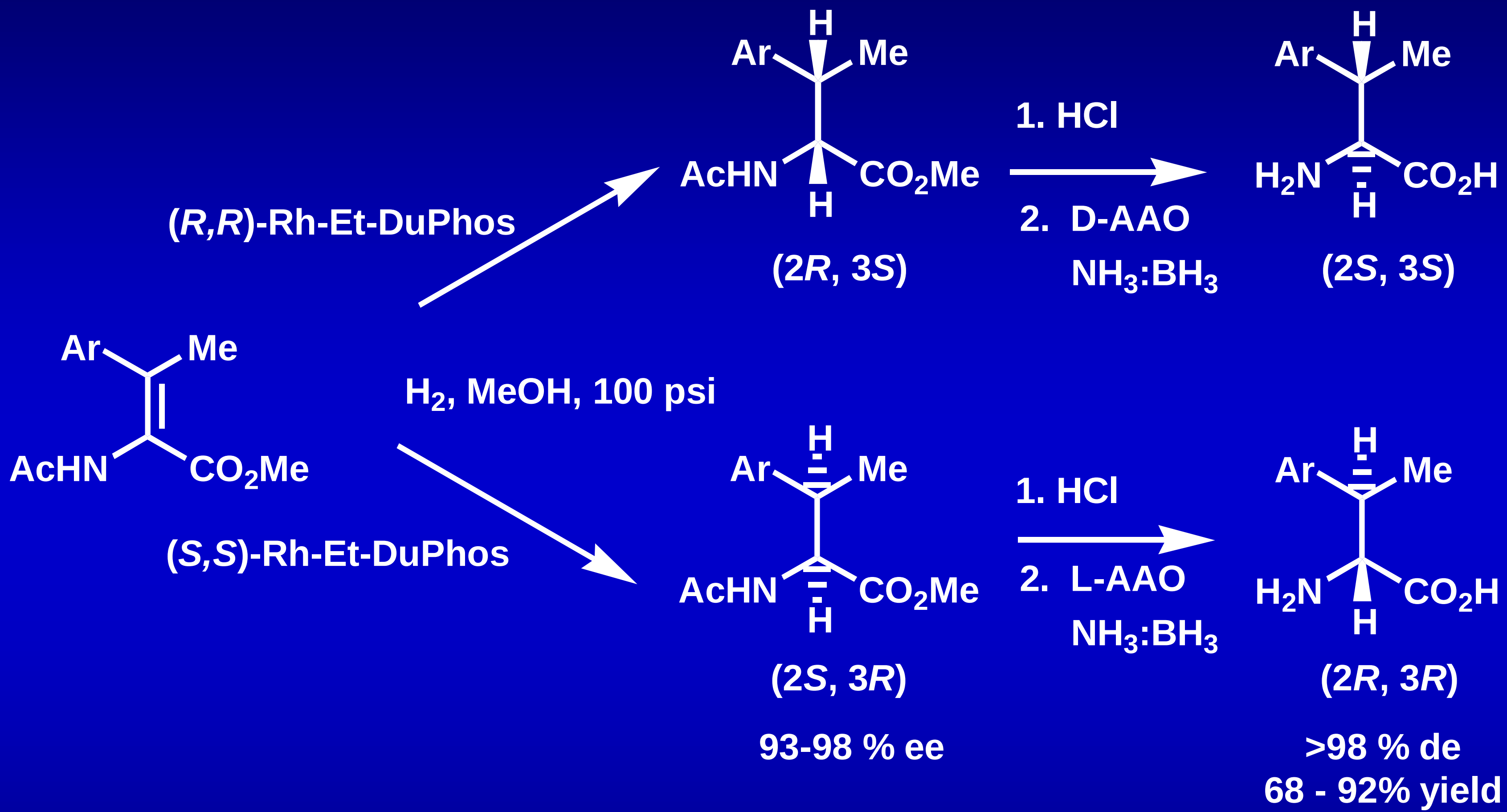
Combination of technologies provides an efficient process
100's kg of several amino acids made this way

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

Amino Acids Prepared Using Chemo/Biocatalysis



β-Branched α-Amino Acids



- **Combination of asymmetric hydrogenation and amino acid oxidase provides access to all four diastereoisomers of β-branched α-amino acids**

Dowpharma

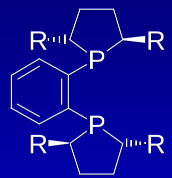
In Collaboration with Nick Turner

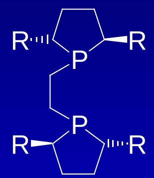
***J. Am. Chem. Soc.* 2004, *126*, 4098**

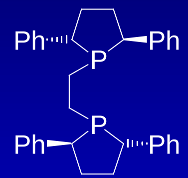
Process Requirements

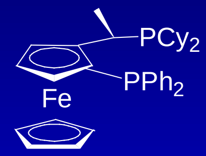
- Choice of Catalyst Complex
- Synthesis and Purity of Substrate
- Solvent
- Temperature
- Pressure
- Concentration
- Enantiomeric Excess
- Substrate to Catalyst Ratio (Activity of the catalyst)
- Removal of spent catalyst from the product
- Availability of the Chosen Catalyst (Security of Supply)

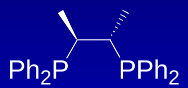
Screening for Asymmetric Hydrogenation

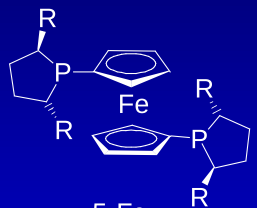

DuPhos

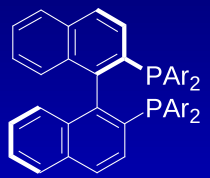

BPE

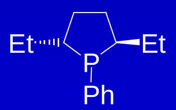

Ph-BPE

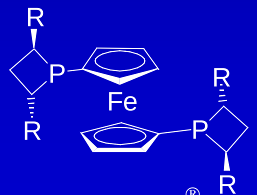

(*R*)-(*S*)-JOSIPHOS


(*S*,*S*)-CHIRAPHOS


5-Fc


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

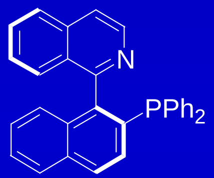

(*R*)-EtPhenylLANE

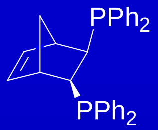

FerroTANE®

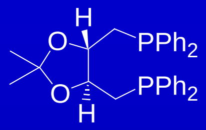
"Since achieving 95 % e.e. only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict the type of ligand structures will be effective"

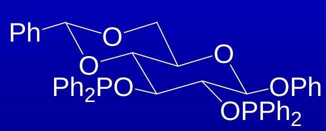
W.S. Knowles, 1983

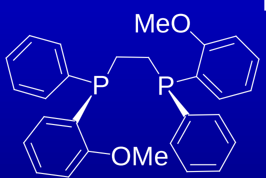

(*R*)-Cl-MeO-BIPHEP

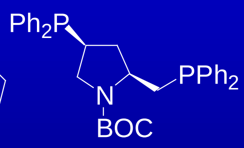

(*R*)-QUINAP

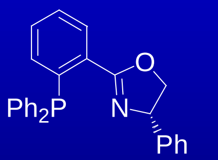

(2*R*,3*R*)-NORPHOS

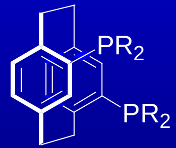

(*S*,*S*)-DIOP

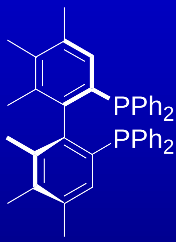

CARBOPHOS


(*R*,*R*)-DIPAMP


BPPM


(*R*)-Phosphinooxazoline


(*R*)-PhanePhos

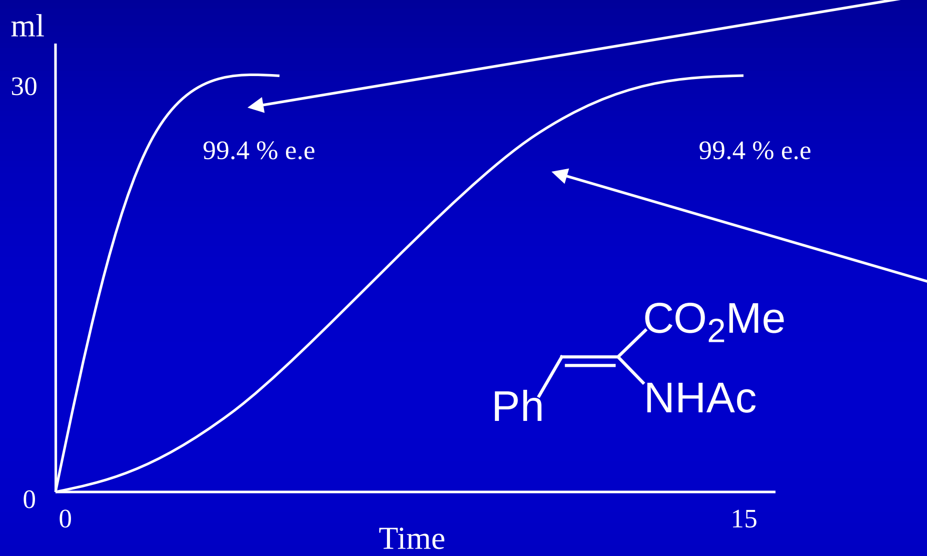

(*R*)-HexaPHEMP

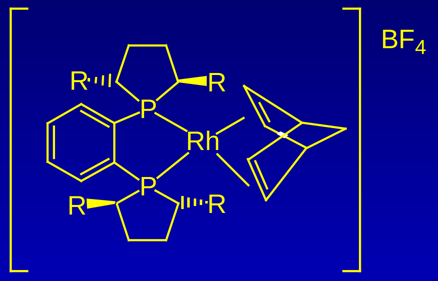

(*R*)-Xyl-TetraPHEMP

Ligand collection for asymmetric hydrogenation screening

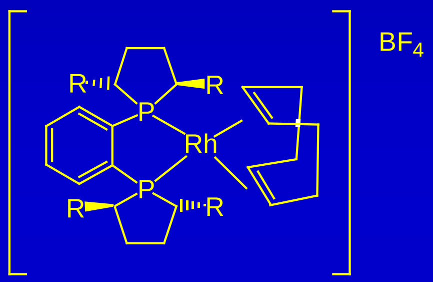
COD Versus NBD Precatalysts

Heller’s Findings





NBD-Precatalyst



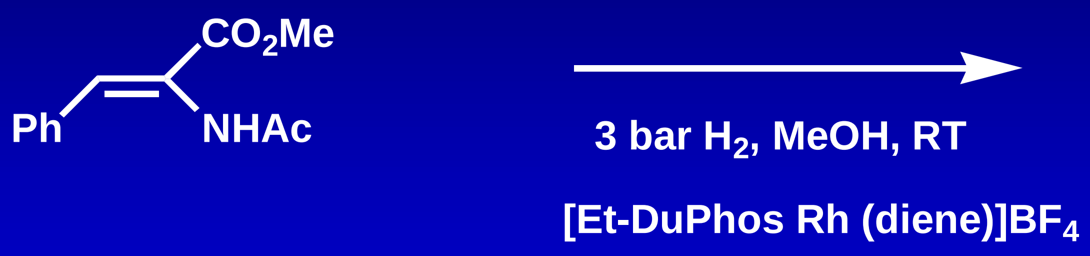
COD-Precatalyst

> “….the use of NBD precatalyst in the asymmetric hydrogenation has significant advantages over the application of the usually sold and applied COD complexes”

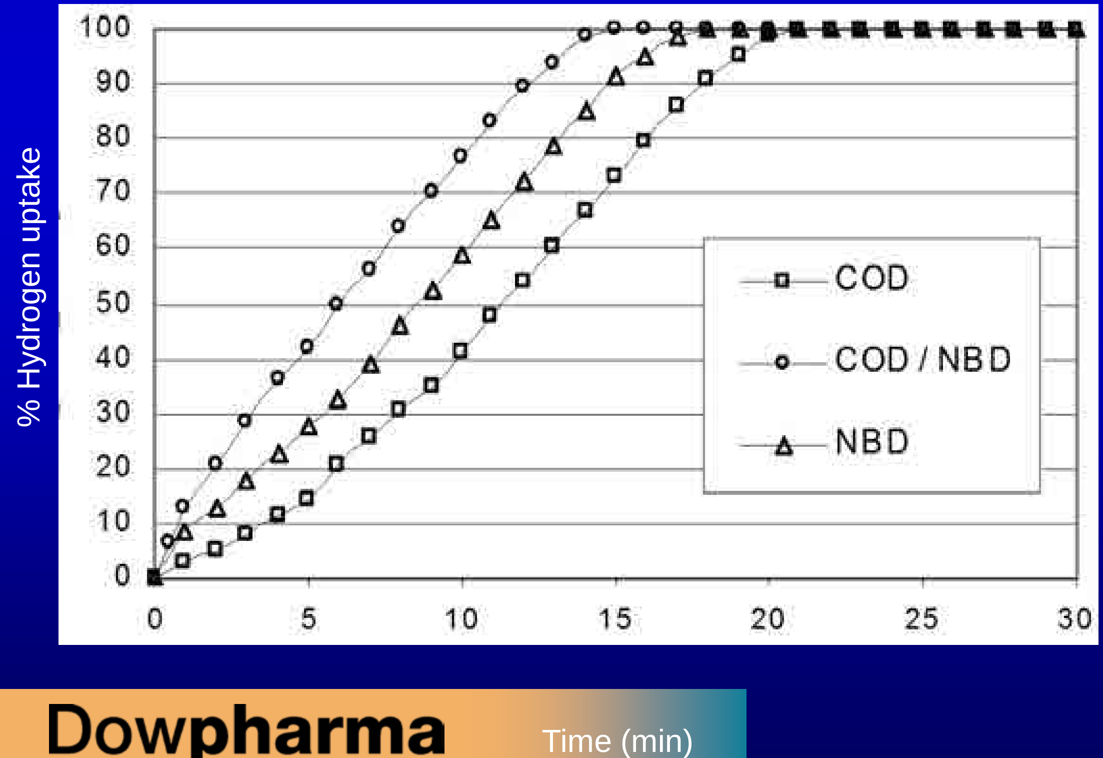
> “…..the frequently used COD complexes do not imply optimal activity in the catalysis, at least for five-membered chelates, and cannot therefore be regarded very economically”

Borner & Heller, *Tetrahedron Lett*., **2001**, *42*, 223
challenges economy of use of COD precatalyst - but at S/C 100:1.

Methyl acetamidocinnamate



>99 % e.e

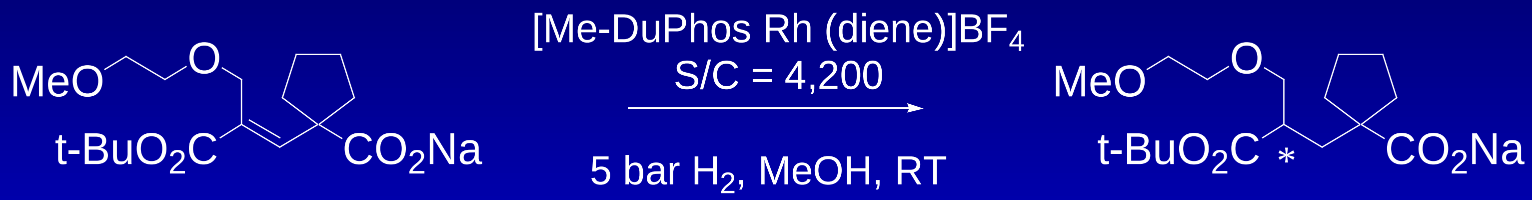


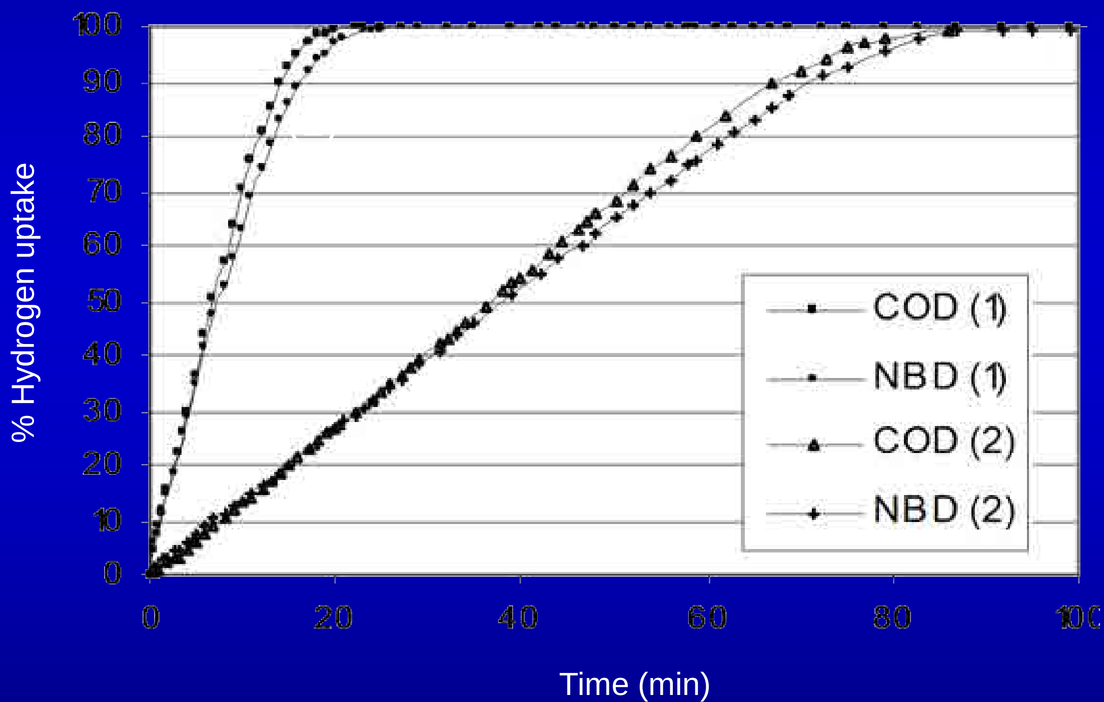
Competition reactions:

***(R,R)*- COD + *(S,S)*- NBD**

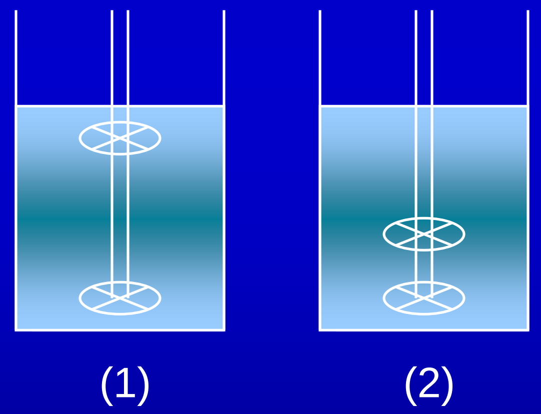
- **At S/C = 2,000 e.e. = 23%**
- **At S/C = 5,000 e.e. = 7%**

Candoxatril Precursor





Reactor stirring efficiency:



Hydrogen availability more important than COD vs NBD

ChiroTech publication: *Tetrahedron Letters*, **2001**, *42*, 7481

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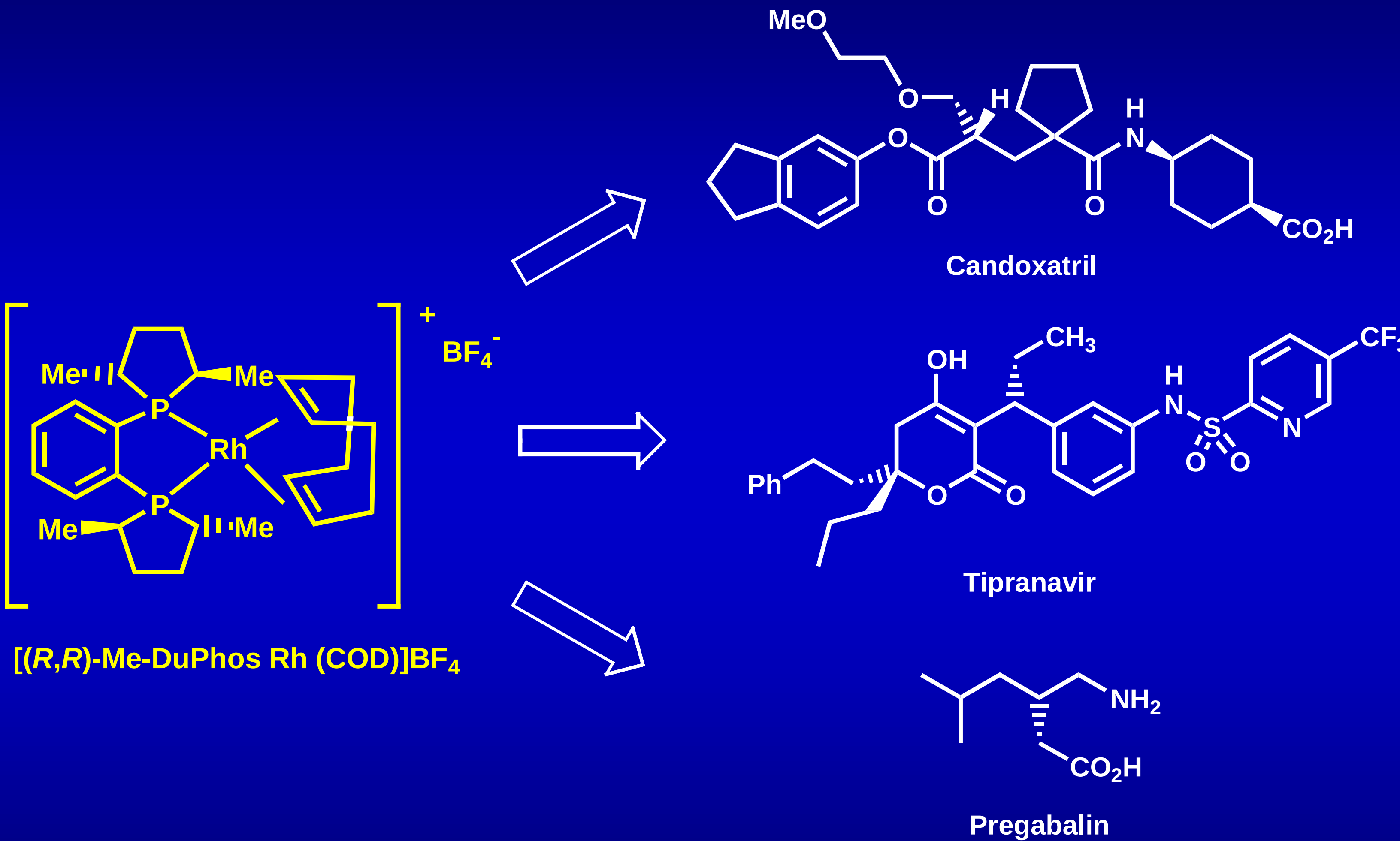
Applications of Rh-Me-DuPhos Catalyst



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Reviews: *Synthesis* **2003**,1639

Curr. Opin. Drug Discovery Dev. **2003**, *6*, 855

[(Me-DuPhos)Rh(COD)]BF_4 Manufacture

- Multiple Kilogram quantities produced
- Using a scaleable process

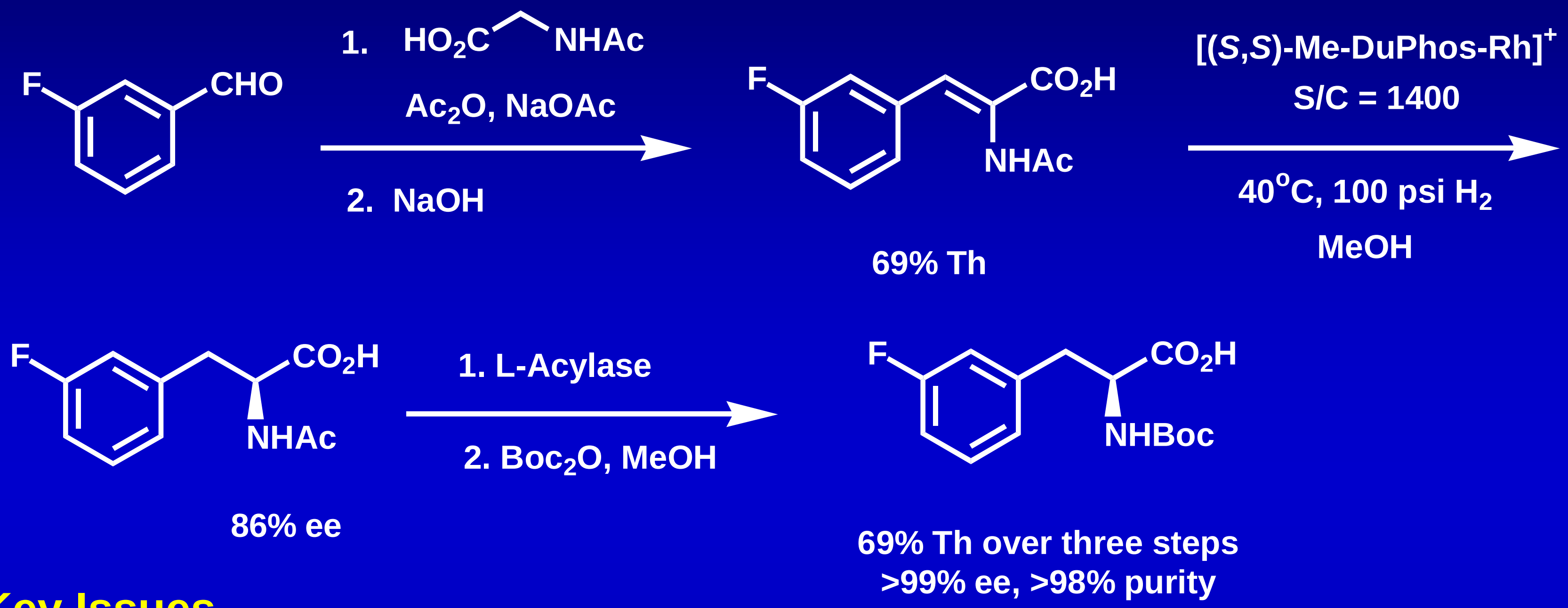
Dowpharma

Security of Supply

- Dowpharma manufactures a number of catalyst systems on a multi-kilogram, kilogram and multi-100 g scale
- Dowpharma offer manufacturing operational excellence, based on a history rooted in the manufacture of pharmaceuticals
- We have developed secure and robust supply chains for important intermediates
- All catalysts are manufactured to a precise specification and are subject to a use test prior to dispatch
- Dowpharma has the ability to manufacture catalysts at a variety of sites in Europe and North America. In addition, we have the capability to increase capacity as required
- We offer tailored commercial terms for licensing and supply agreements
- Dowpharma has a well defined intellectual property position on all catalyst systems

See: *Chimica oggi,* December **2003**, 63-67

Substrate Synthesis: Manufacture of α-Amino Acids

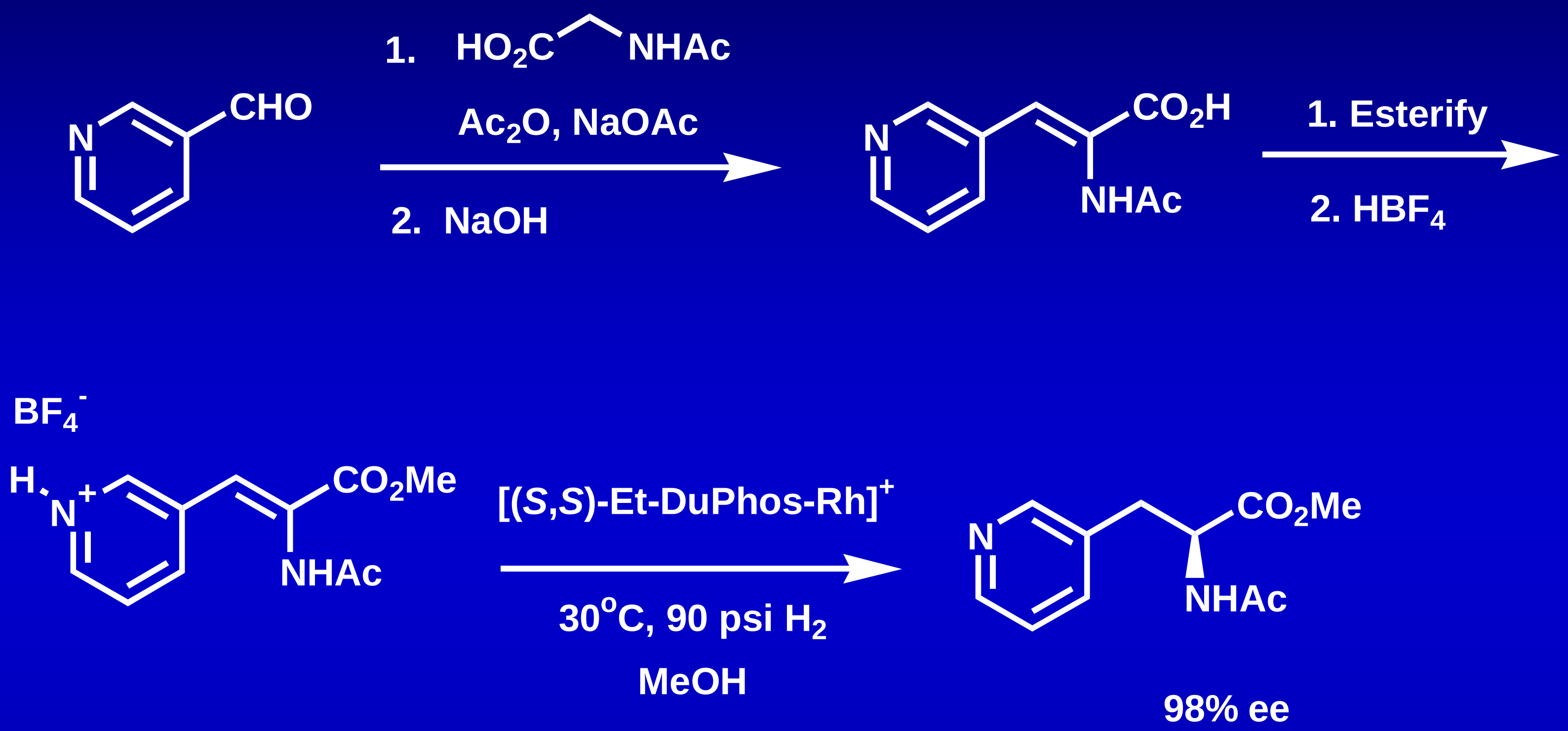


Key Issues

- 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.

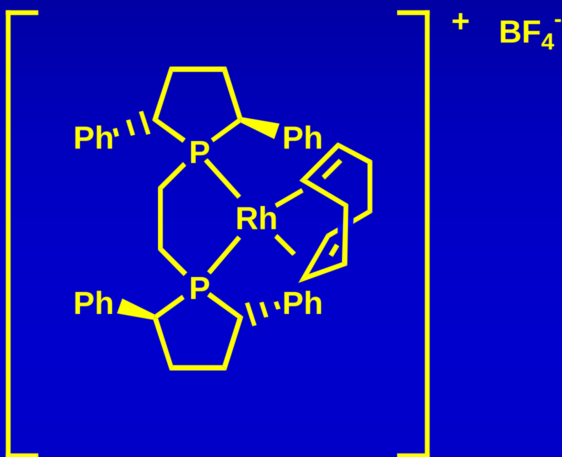
Substrate Synthesis: Manufacture of α-Amino Acids

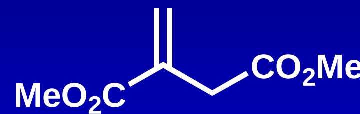


Key Issues

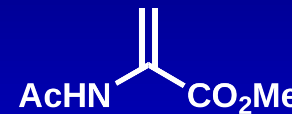
- Competitive binding to the pyridyl group made the catalysis inefficient
- The optimum substrate was the methyl ester-HBF_4 salt
- >200 Kg produced

Activity of Catalysts: Ph-BPE



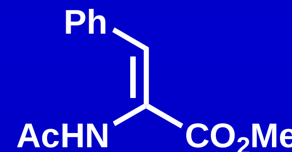


S/C 100 000
100% conv.
99% e.e.

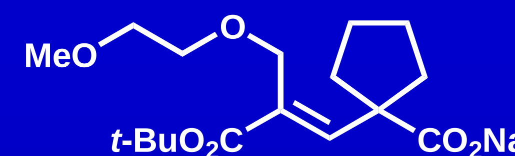


S/C 5000
100% conv.
97% e.e.

S/C 5000
100% conv.
99% e.e.



S/C 5000
100% conv.
99% e.e.



S/C 1000
100% conv.
98% e.e.

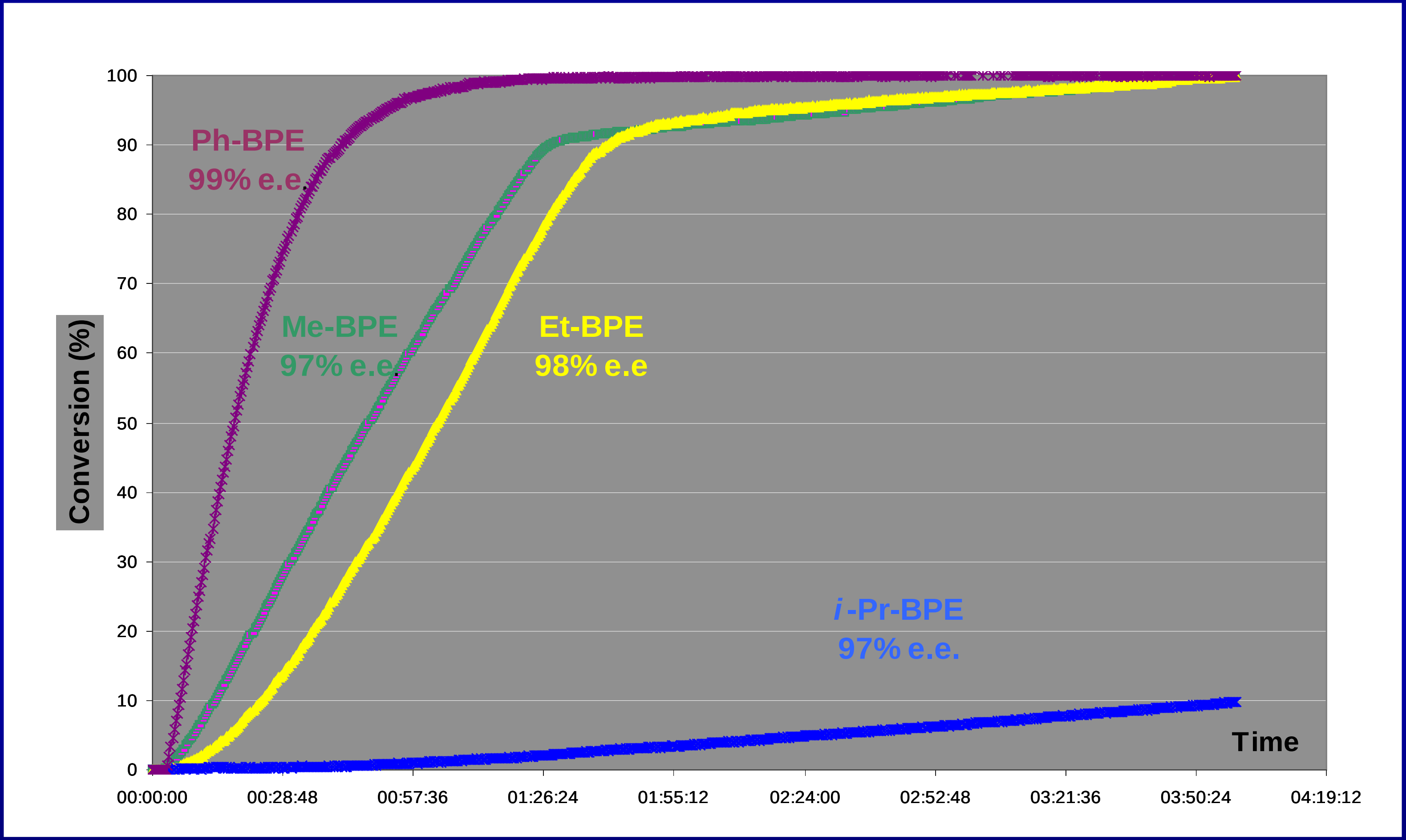
- **Enhanced selectivity and activity over alkyl BPE ligands**

Dowpharma Paper: *Org. Lett.* 2003, *5*, 1273

Fast Reaction Rates with Ph-BPE Ligand

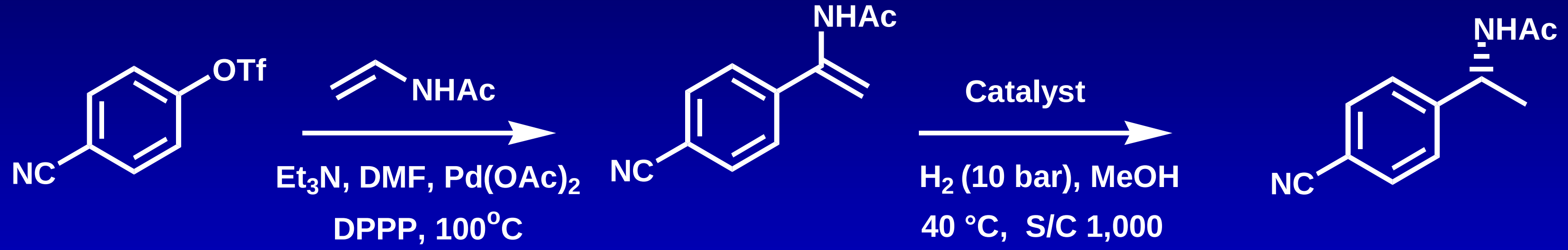
DOW

Rates of asymmetric hydrogenation of methyl acetamidocinnamate

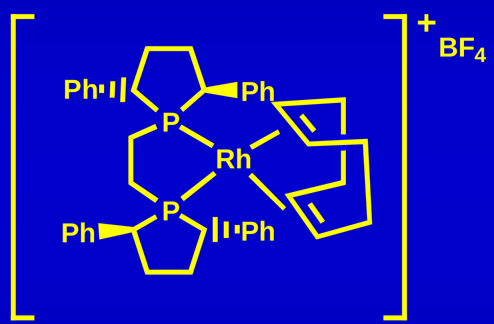


Optimizing the catalysis: Argonaut Endeavor

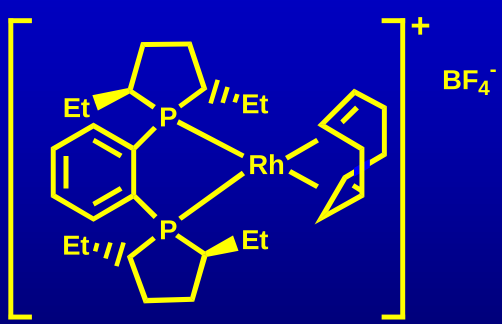
A New Approach to Acyl Enamides



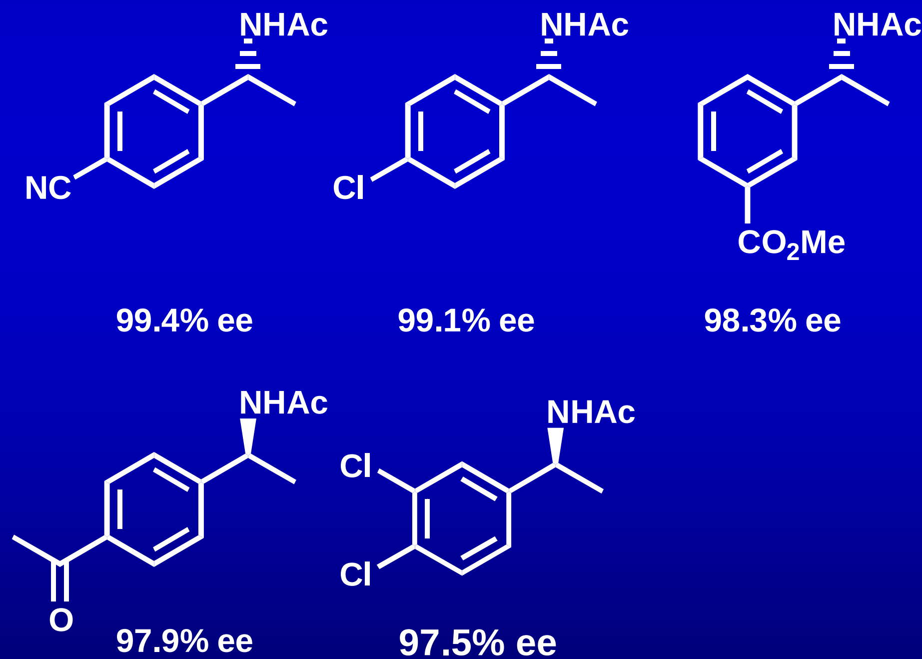
Ref: *J. Org. Chem.*, **1992**, *57*, 3558



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

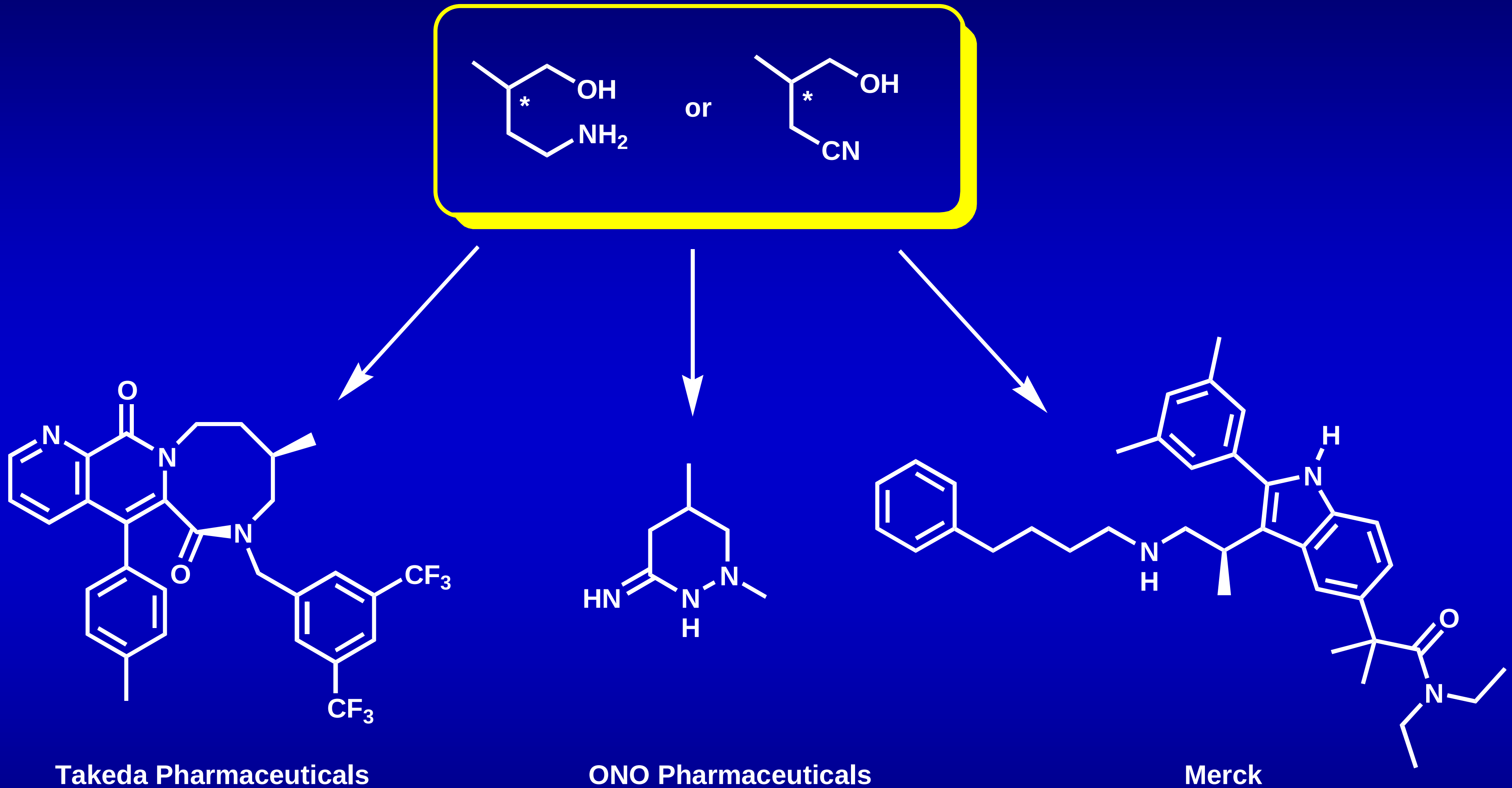


(*S*,*S*)-Et-DuPhos



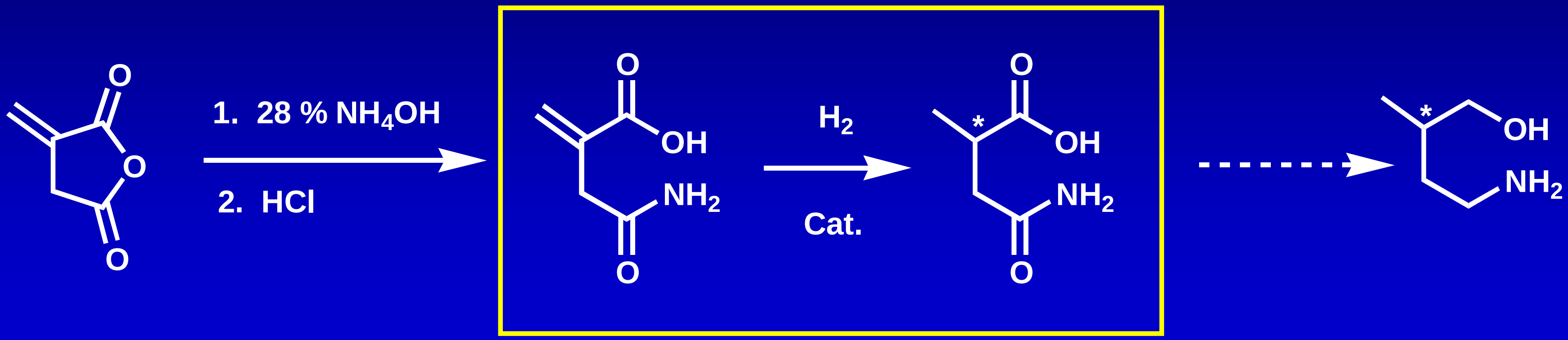
Dowpharma

4-Amino-2-methyl butanol and 4-hydroxy-3-methyl-butyronitrile



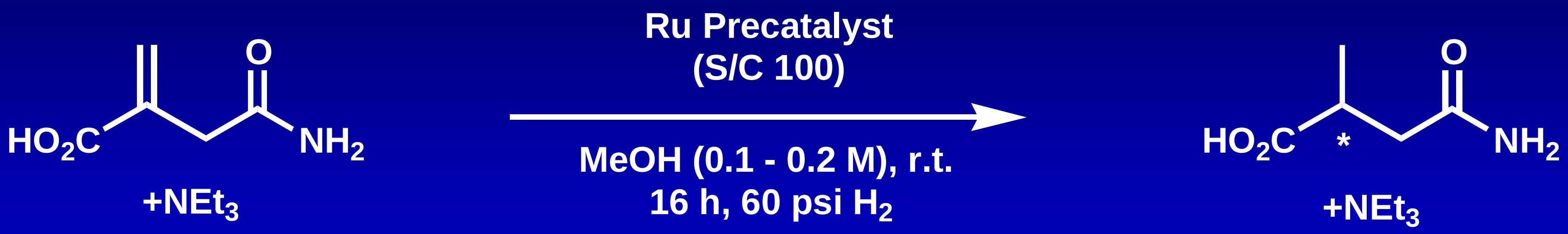
- **Chiral building blocks for several biologically active compounds**

Substrate Synthesis: Methylenesuccinamic acid



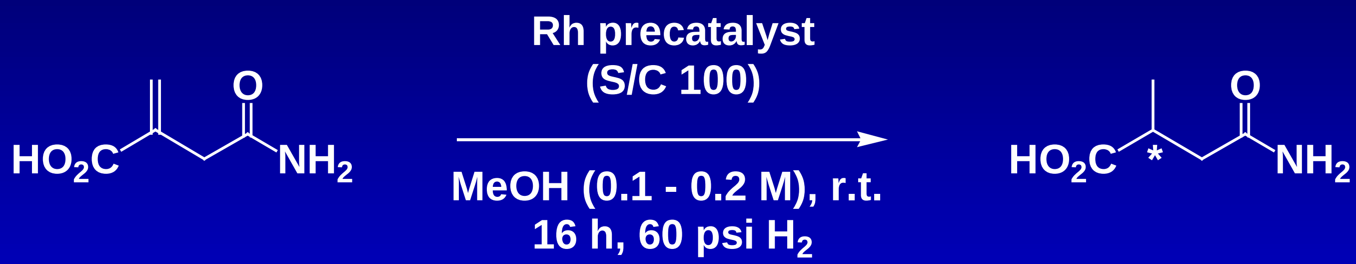
- Substrate synthesis from readily available materials
- Scaleable process
- Substrate contains ~ 1 mol % of a chloride containing impurity

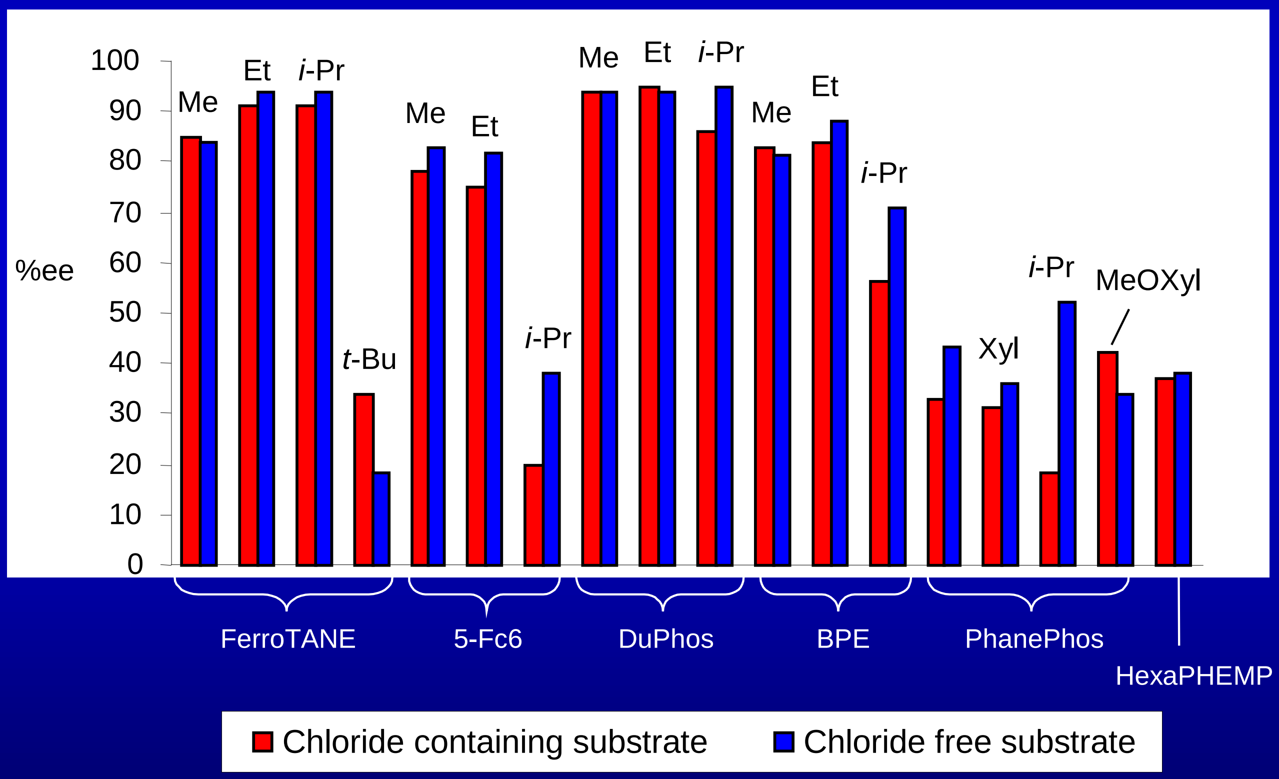
Asymmetric Hydrogenation of Methylenesuccinamic acid

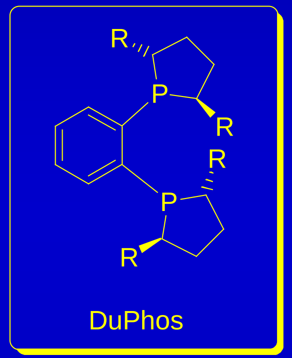


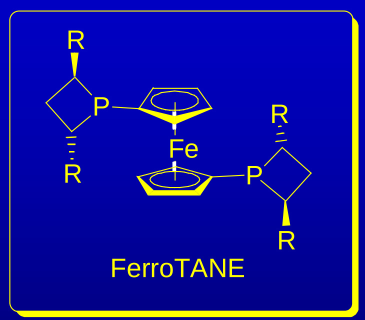
Entry	*Precatalyst*	*Conv. (%)*	*e.e. (%)*
1	[(*S*)-HexaPHEMP Ru Cl_2]$_2$ NEt_3	> 98	18 (*S*)
2	[(*S*)-HexaPHEMP Ru $(CF_3CO_2)_2$]	> 98	40 (*R*)
3	[(*R*)-BINAP Ru $(CF_3CO_2)_2$]	> 98	56 (*S*)
4	[(*R*,*R*)-Me-DuPhos Ru $(CF_3CO_2)_2$]	< 5	-
5	[(*R*,*R*)-*i*-Pr-DuPhos Ru $(CF_3CO_2)_2$]	> 98	1 (*S*)
6	[(*R*,*R*)-*i*-Pr-BPE Ru $(C_4H_7)_2$]	> 98	2 (*S*)
7	[(*R*,*R*)-Me-FerroTANE Ru $(C_4H_7)_2$]	~ 10	-
8	[(*S*,*S*)-*i*-Pr-FerroTANE Ru $(C_4H_7)_2$]	> 98	41 (*S*)
9	[(*R*,*R*)-Me-FerroLANE Ru $(C_4H_7)_2$]	> 98	11 (*S*)
10	[(*R*,*R*)-Et-FerroLANE Ru $(CF_3CO_2)_2$]	> 98	3 (*S*)
11	[(*R*)-(*S*)-JOSIPHOS Ru $(CF_3CO_2)_2$]	> 98	1 (*S*)

Asymmetric Hydrogenation of Methylenesuccinamic acid









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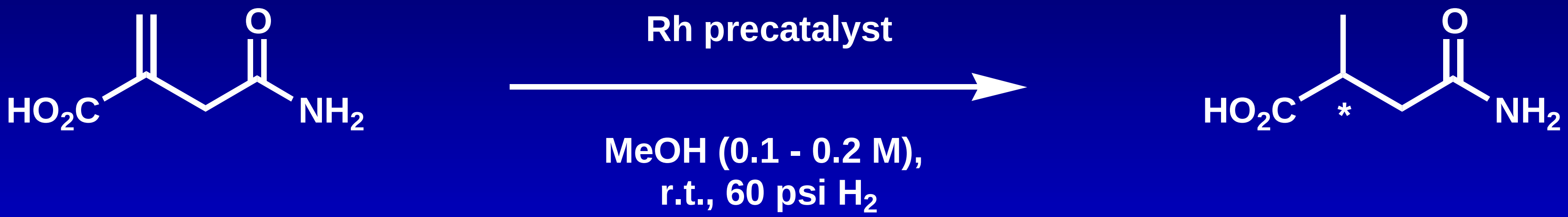
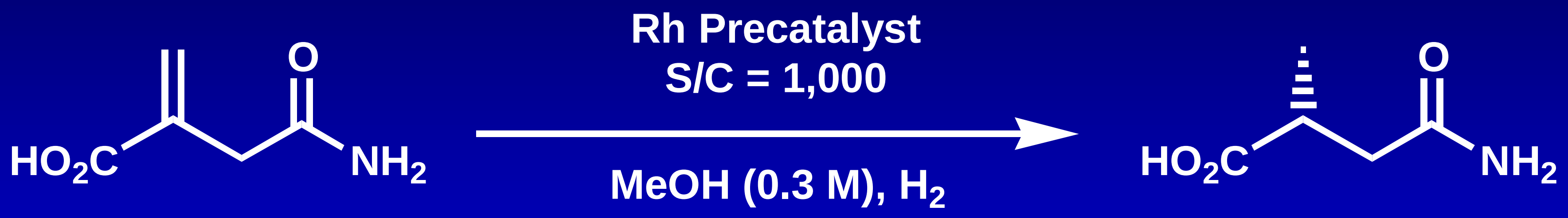
Substrate to Catalyst Ratio (S/C)



Entry	*Precatalyst*	*S/C*	*Conv. (%)*	*ee (%)*
1	[(*R*,*R*)-Me-DuPhos Rh COD]BF_4	100	> 98	94 (*S*)
2	[(*R*,*R*)-Me-DuPhos Rh COD]BF_4	1,000	> 98	87 (*S*)
3	[(*S*,*S*)-Et-DuPhos Rh COD]BF_4	100	> 98	95 (*R*)
4	[(*S*,*S*)-Et-DuPhos Rh COD]BF_4	1,000	> 98	94 (*R*)
5	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	100	> 98	93 (*R*)
6	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	1,000	> 98	87 (*R*)
7	[(*S*,*S*)-i-Pr-FerroTANE Rh COD]BF_4	100	> 98	91 (*S*)
8	[(*S*,*S*)-i-Pr-FerroTANE Rh COD]BF_4	1,000	> 98	83 (*S*)

- **Performance of Et-DuPhos holds at higher S/C**

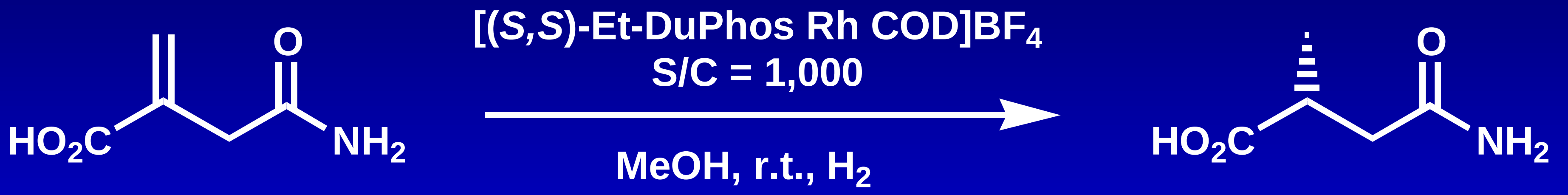
Temperature and Pressure



Entry	*Precatalyst*	*Temp (ºC)*	*H_2 Pressure (psi)*	*Time (min)*	*Conv. (%)*	*ee (%)*
1	[(*S*,*S*)-Et-DuPhos Rh COD]BF_4	0	60	>18 h	33	93 (*R*)
2	"	20	60	240	> 98	94 (*R*)
3	"	45	60	140	> 98	96 (*R*)
4	"	20	140	120	> 98	97 (*R*)
5	"	45	140	90	> 98	95 (*R*)
6	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	20	60	120	> 98	87 (*R*)
7	"	20	140	45	> 98	72 (*R*)
8	"	45	140	20	> 98	86 (*R*)

- **Enantioselectivity is retained at higher temperatures and pressures**

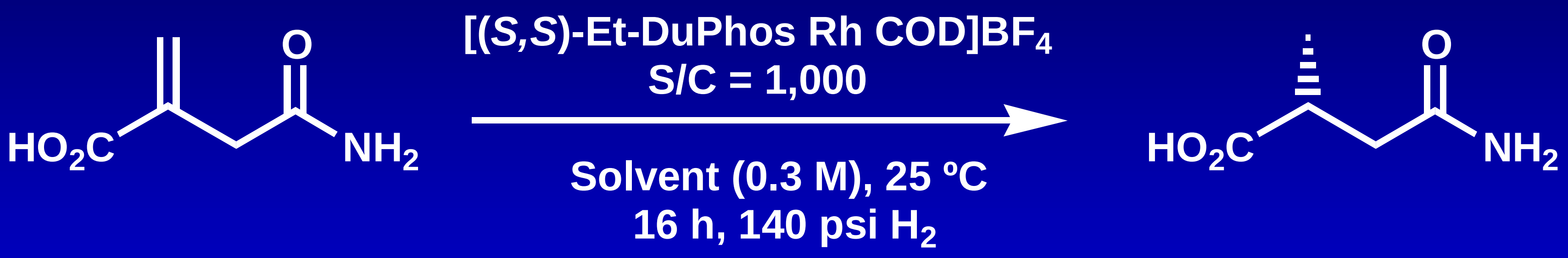
Concentration and Effect of NEt_3



Entry	*H_2 Pressure (psi)*	*Conc. (M)*	*Time (h)*	*Additive*	*Conv. (%)*	*ee (%)*
1	60	0.3	4	-	> 98	94 (*R*)
2	60	0.3	2.5	NEt_3	> 98	74 (*R*)
3	60	1.0	<10	-	> 98	94 (*R*)
4	60	1.0	5	NEt_3	> 98	69 (*R*)
5	140	0.3	2	-	> 98	97 (*R*)
6	140	0.3	2	NEt_3	> 98	72 (*R*)
7	140	1.0	<8	-	> 98	97 (*R*)
8	140	1.0	5	NEt_3	> 98	68 (*R*)

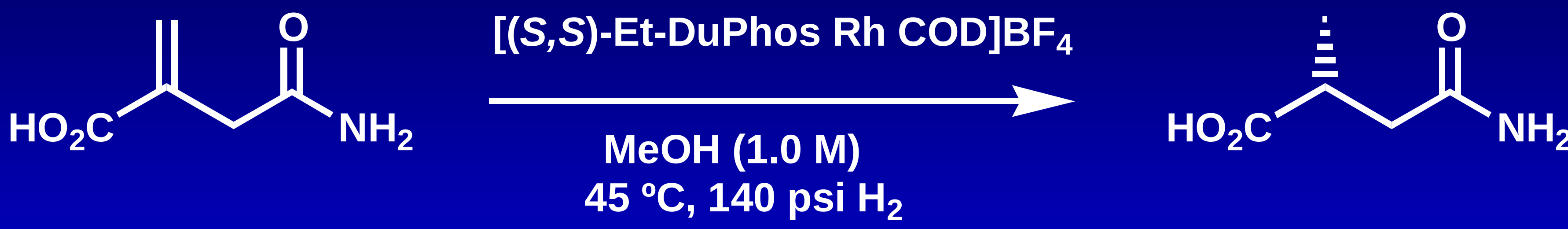
- **NEt_3 increases the reaction rate, but reduces enantioselectivity**

Solvent Screen



Entry	*Solvent*	*Conv. (%)*	*ee (%)*
1	MeOH	> 98	97 (*R*)
2	EtOH	37	84 (*R*)
3	*i*-PrOH	87	97 (*R*)
4	CF_3CH_2OH	5	-
5	THF	24	17 (*S*)
6	EtOAc	21	-
7	CH_2Cl_2	2	-
8	Acetone	9	-
9	Toluene	0	-
10	α,α,α-Trifluorotoluene	0	-

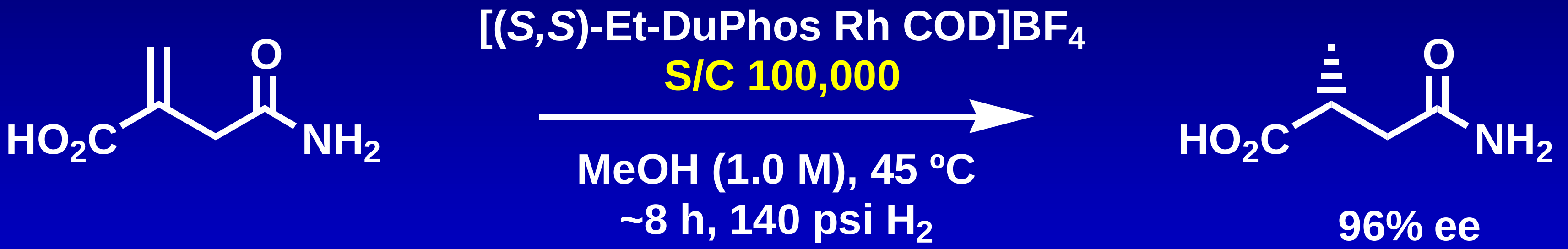
Effect of Chloride Contaminant



Entry	*S/C*	*Substrate Input*	*Time*	*Conv. (%)*	*ee (%)*
1	1,000	15 g	1 h 57 min	> 98	97 (*R*)
2	1,000	15 g	4 min	> 98	96 (*R*)
3	5,000	15 g	24 min	> 98	97 (*R*)
4	10,000	15 g	46 min	> 98	96 (*R*)
5	20,000	15 g	1 h 42 min	> 98	97 (*R*)
6	50,000	40 g	4 h 2 min	> 98	97 (*R*)
7	100,000	40 g	7 h 27 min	> 98	96 (*R*)

- **Removal of Cl^- increases rate by a factor of 30**

Asymmetric Hydrogenation of Methylenesuccinamic acid

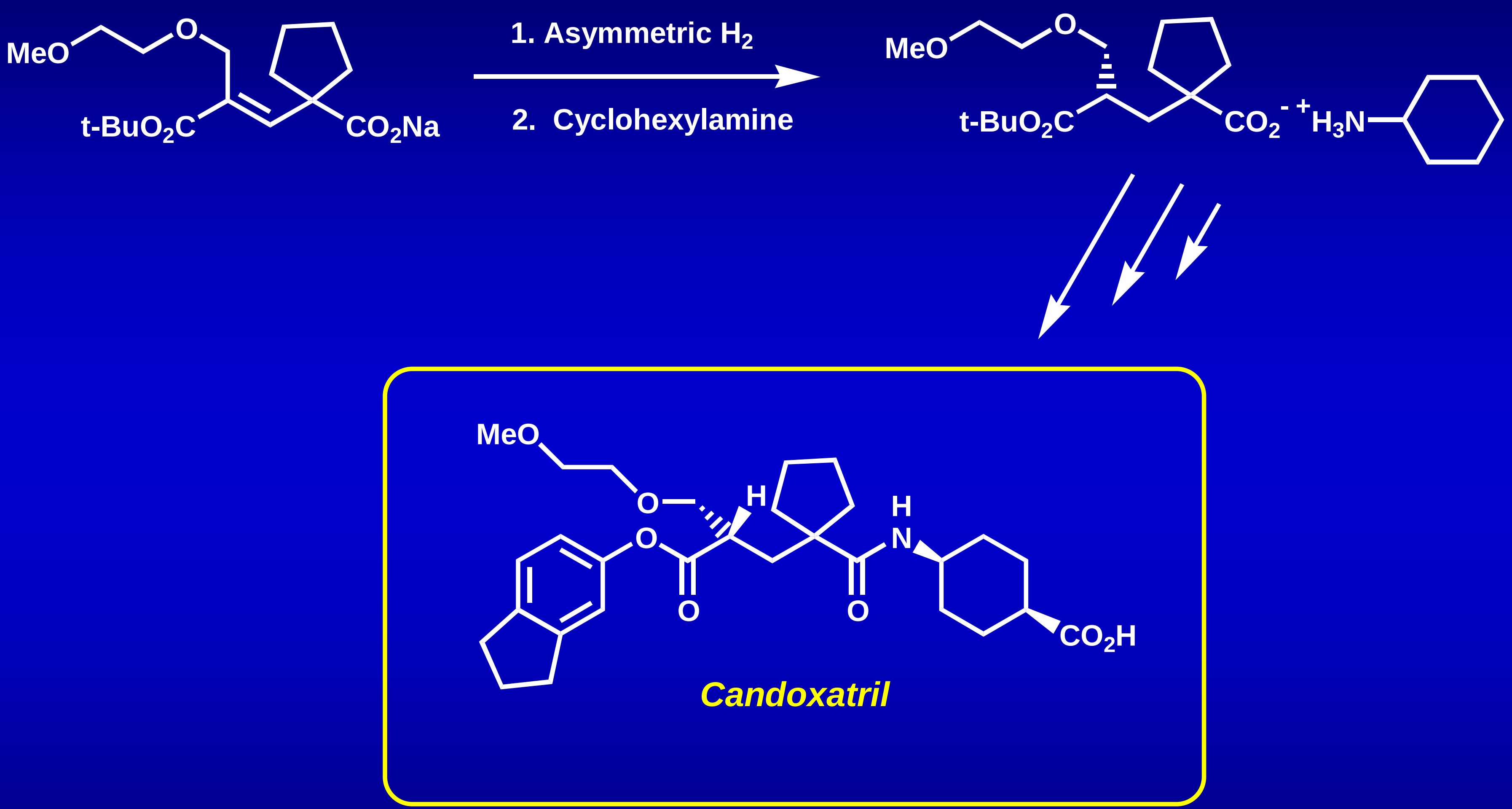


96% ee
>99.5% ee after
crystal digestion

- Complete conversion with 96 % e.e. at S/C 100,000:1 (w/w ~21,400)
- Chloride impurity identified that limited S/C to 1000:1
- 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)

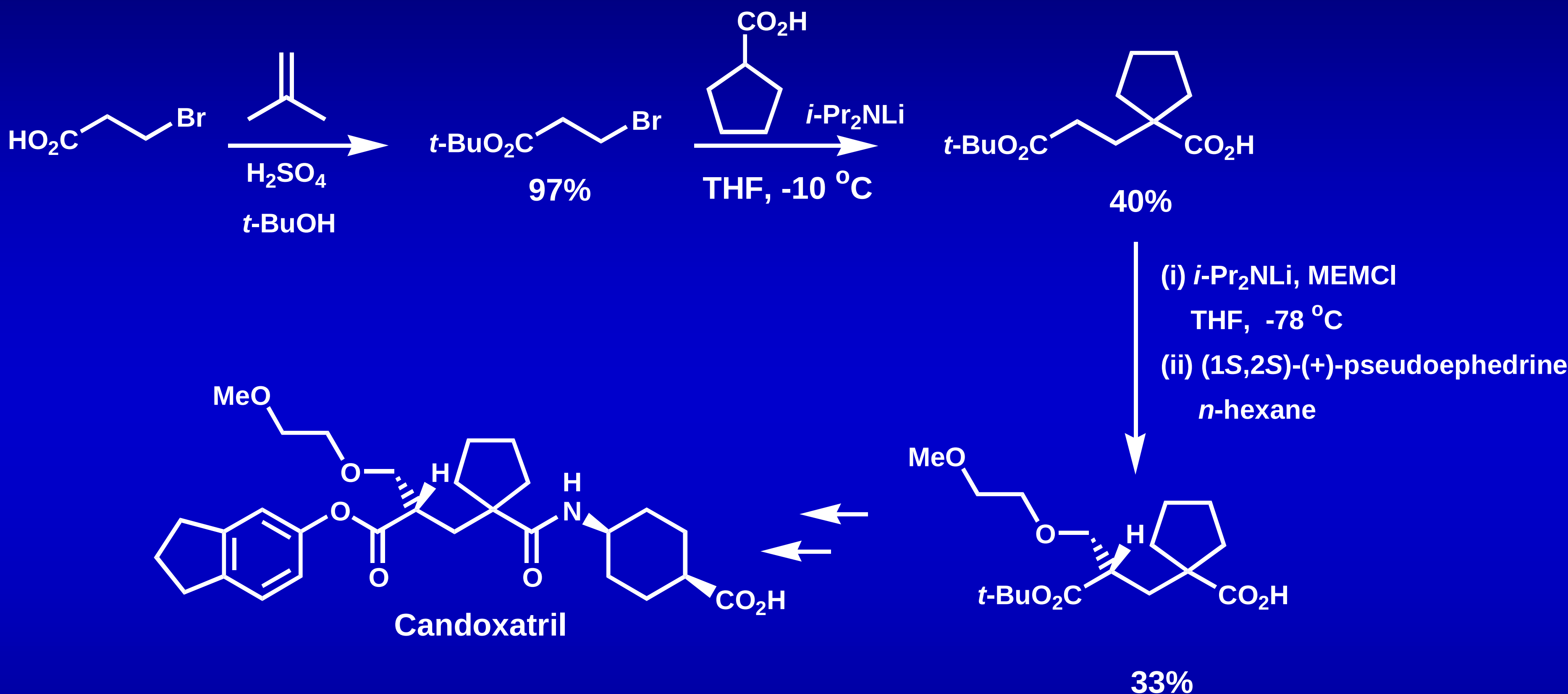
Dowpharma paper: *Org. Process Res. Dev.* 2003, 7, 407.

Pfizer's Candoxatril for Congestive Heart Failure



Substrate Synthesis: *Tetrahedron Letts*. **1999,** *40*, 2187

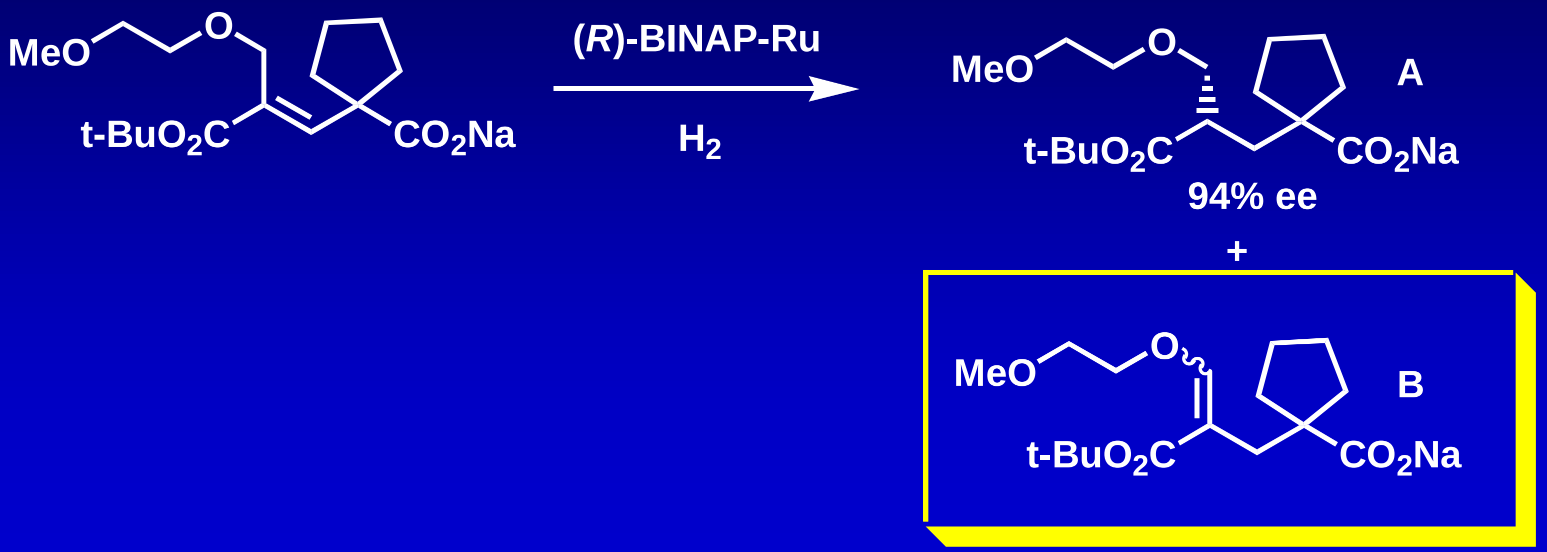
Pfizer's Candoxatril: Original Route



13% overall yield from 3-bromopropionic acid

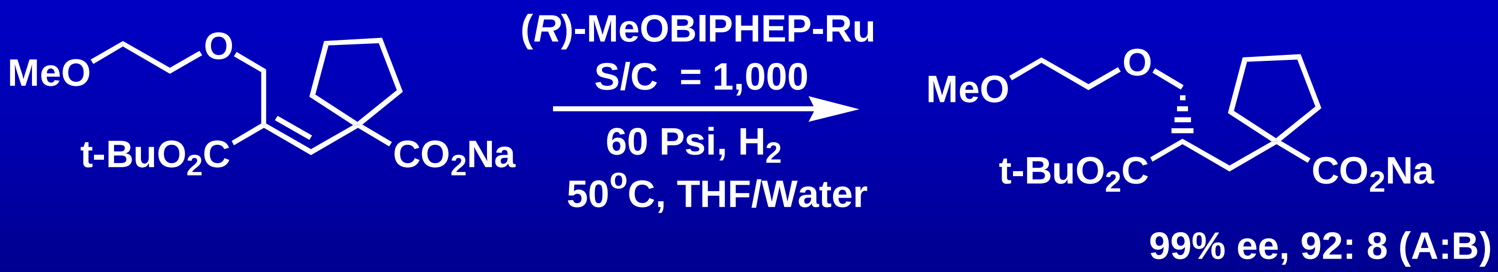
Pfizer Patent: EP 0342850

New Asymmetric Hydrogenation Route



25% Isomerised substrate - Inert to H_2 conditions

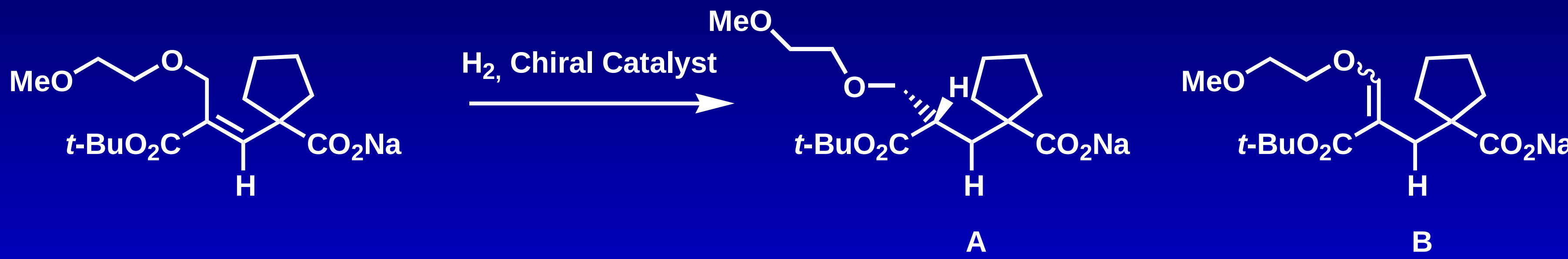
SIPSY Conditions



M. Bulliard *et al.* *Org. Process Res. Dev.* **2001**, *5*, 438

Dowpharma

Screen for Asymmetric Hydrogenation Catalyst



Catalyst System	Conf.	ee[%]	A:B
[((+)-DIOPRh(COD)]Cl	*R*	24	100:0
[((*R*)-PROPHOS)Rh(COD)]Cl	*S*	8	100:0
[((*S*,*S*)-BPPM)Rh(COD)]Cl	*S*	22	100:0
[((*S*)-BINAP)Rh(COD)]Cl	*S*	78	100:0
[((*R*)-BINAP)Rh(COD)ClO_4	*R*	80	100:0
[((*S*)-BINAP)$_2$RuHCl]	*R*	82	92:8
[(*R*)-BINAP](*p*-cymene)RuCl]Cl	*S*	94	75:25
[((*S*,*S*)-Me-BPE)Rh(COD)]BF_4	*R*	80	100:0
[((*S*,*S*)-Et-BPE)Rh(COD)]BF_4	*R*	97	100:0
[((*R*,*R*)-*i*-Pr-BPE)Rh(COD)]BF_4	*R*	92	100:0
[((*R*,*R*)-Me-DuPHOS)Rh(COD)]BF_4	*S*	>99	100:0
[((*S*,*S*)-Et-DuPHOS)Rh(COD)]BF_4	*R*	99	100:0

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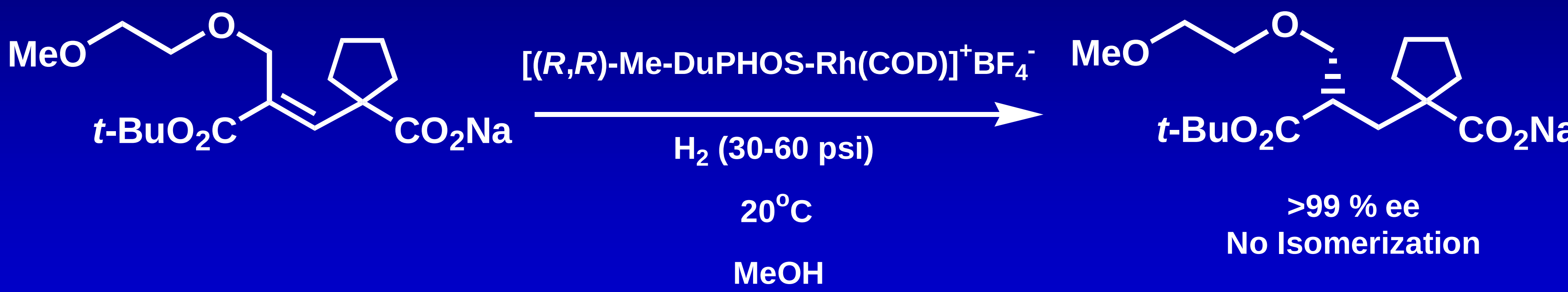
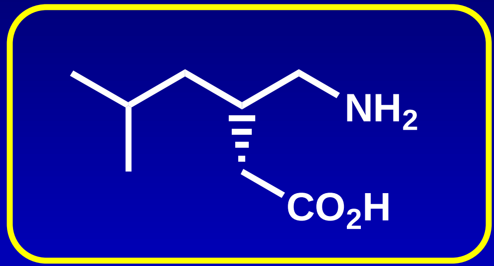
Candoxatril: Me-DuPHOS-Rh-Catalysed Process



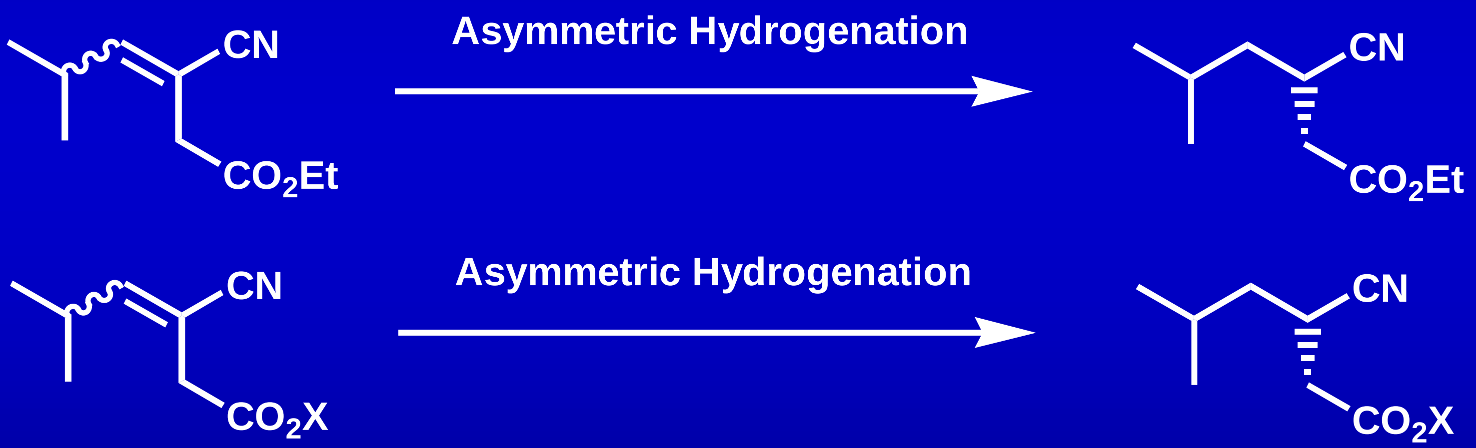
- Cationic (*R*,*R*)-Me-DuPHOS-Rh Found to be Superior
- S/C Ratio = 3500/1 (5000/1 readily obtainable)
- Reaction Time = 3 h
- Conversion = 100% (No Isomerization)
- Isolated Crude Yield = 97%
- Demonstrated on 12 kg Scale in Pfizer Pilot Plant

Joint Publication: *J. Org. Chem*. **1999**, *64*, 3290

Asymmetric Hydrogenation Route to Pregabalin

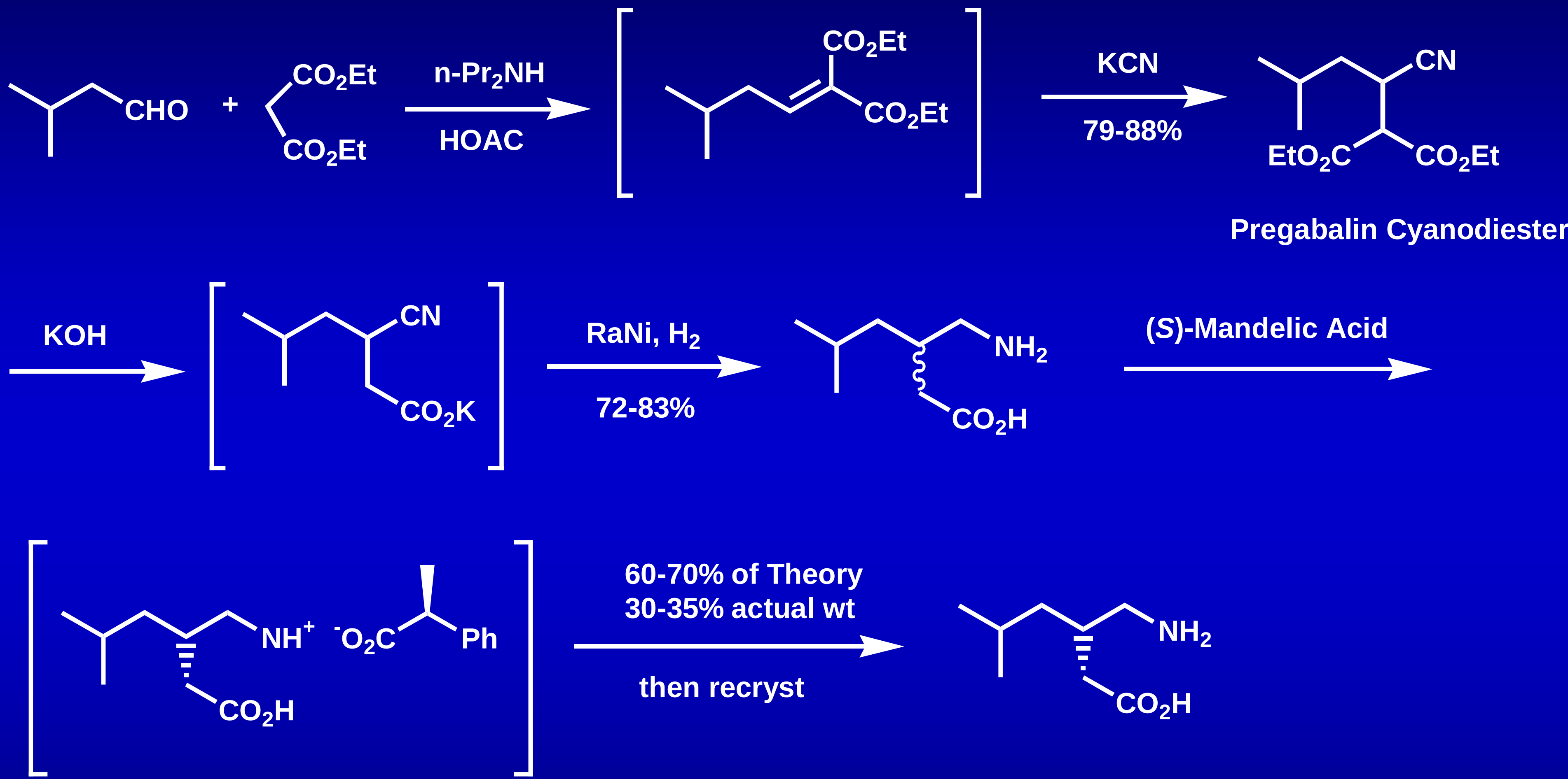


Pregabalin



Pregabalin is a potent anticonvulsant in late stage clinical trials
A resolution route, that uses (*S*)-mandelic acid, has been reported (Org. Process Res. Dev. 1997, 1, 26).

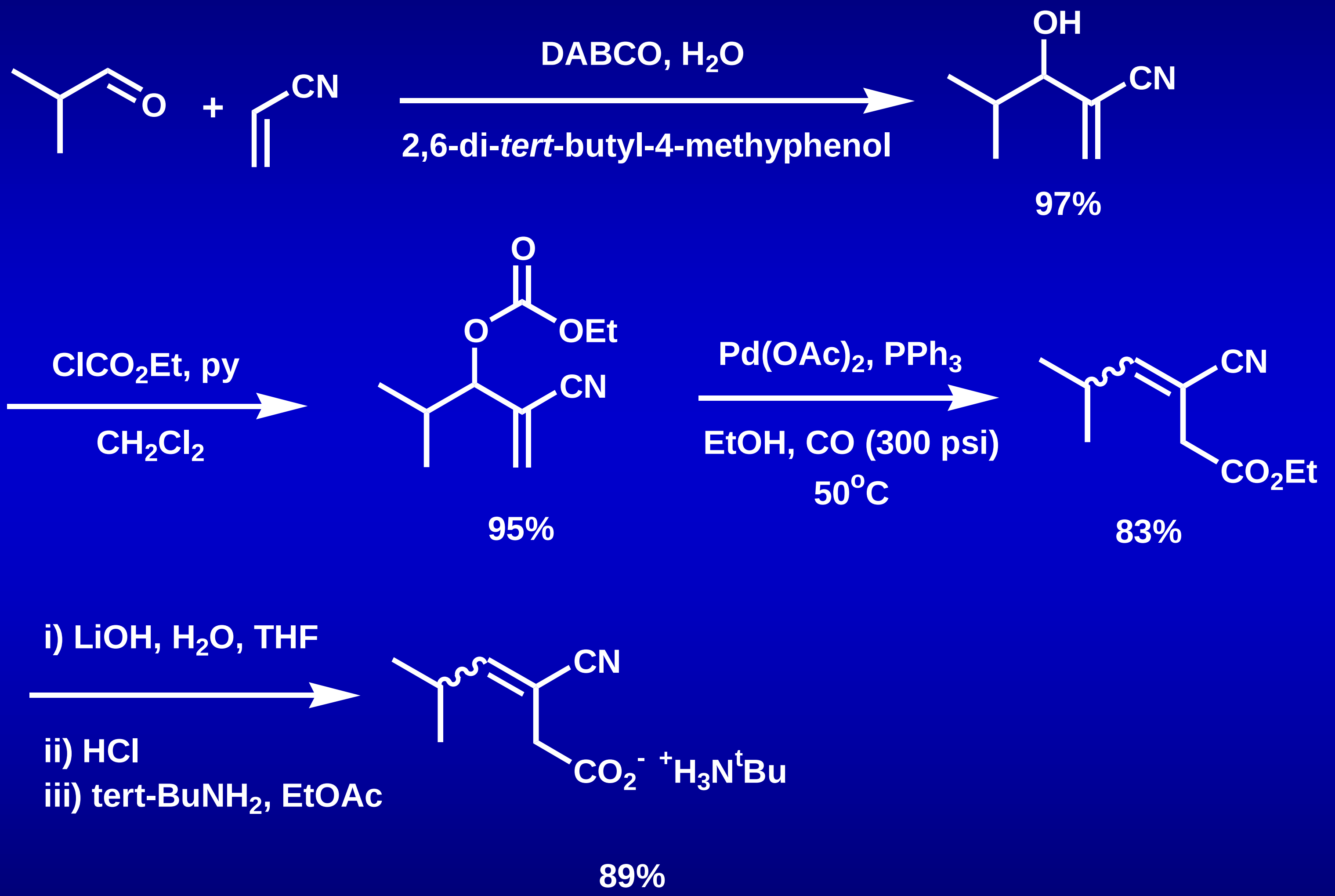
Classical Resolution Route to Pregabalin



- 15 MT made for clinical trials
- Overall yield of 25% at best
- 4 isolated solids, 2 for resolution

(Org. Process Res. Dev. 1997, 1, 26).

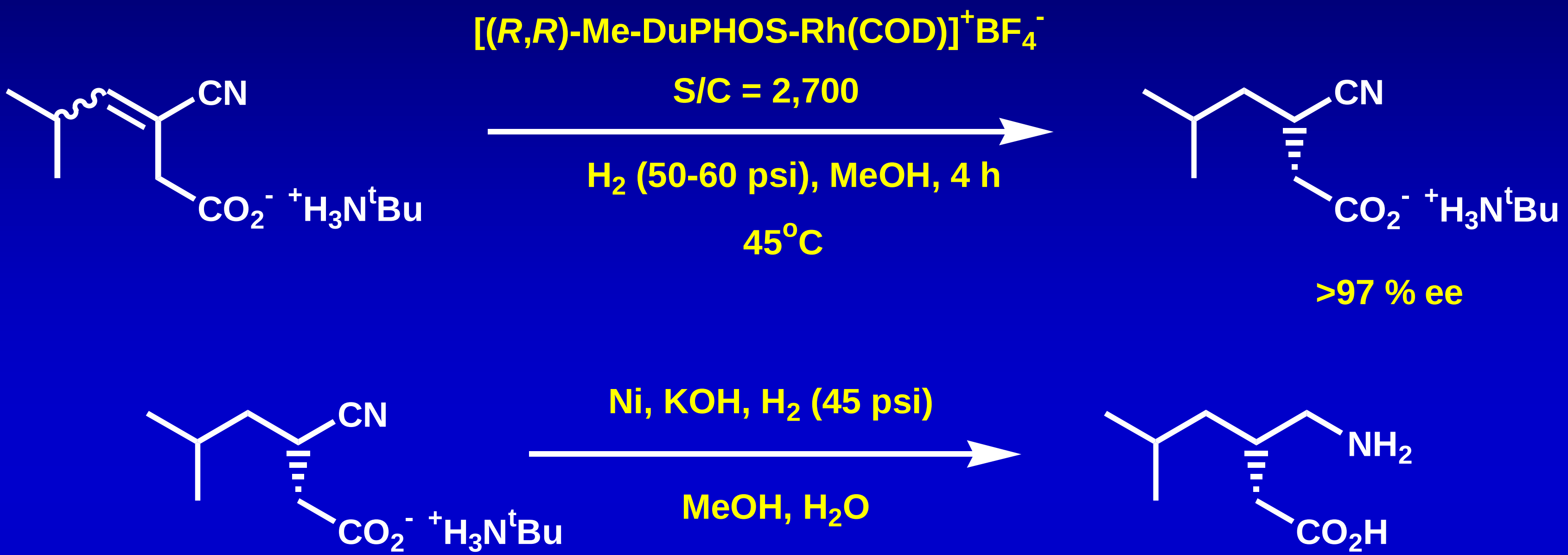
Pregabalin – Substrate Synthesis



Dowpharma

J. Org. Chem. **2003**, *68*, 5731

Successful Hydrogenation: Pregabalin



>97 % ee

>97 % ee

73% yield, 99.7 % ee

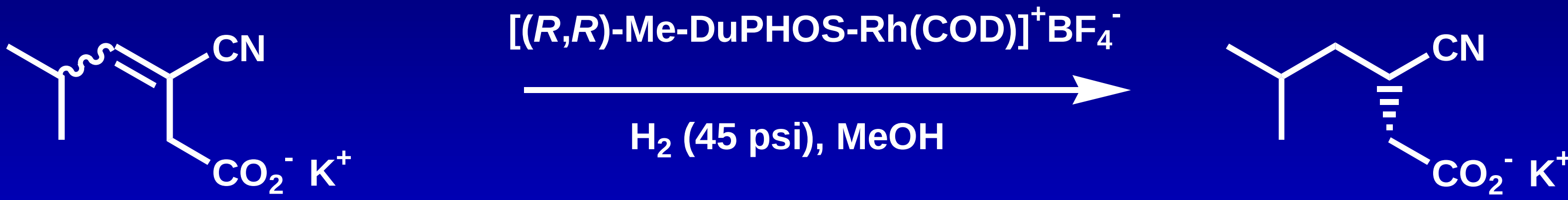
Pregabalin

- Reduction in cost of goods and waste over resolution route
- Improvement in throughput (Bill Kissel MPPCC, 2001)
- Resolution route 25% yield, hydrogenation 50% overall yield
- Collaborative Project Carried out with Pfizer, Holland, Michigan

Dowpharma

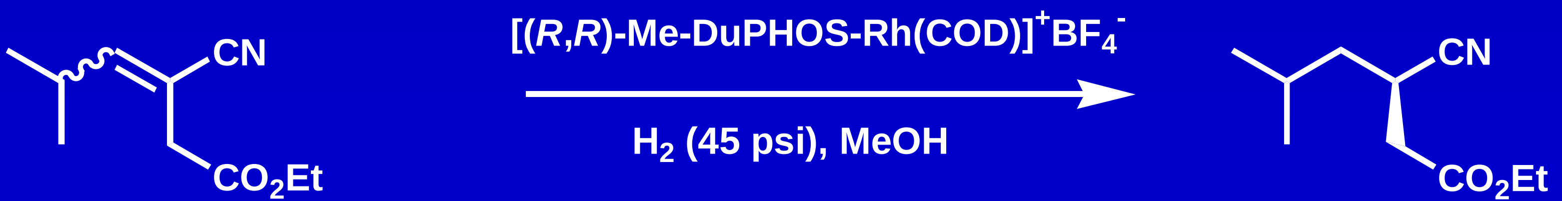
Joint Paper *J. Org. Chem.* **2003**, *68*, 5731

Alternative Substrates: Pregabalin



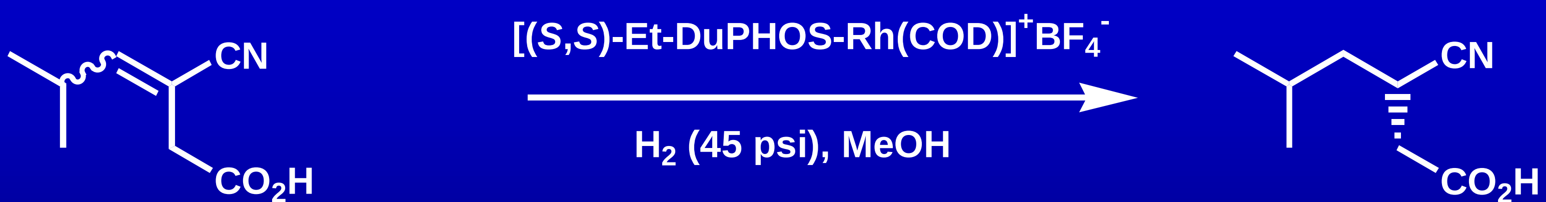
97.5 % ee

S/C = 3,200/1
2.5 hours



23 % ee

S/C = 1,000/1
3 hours



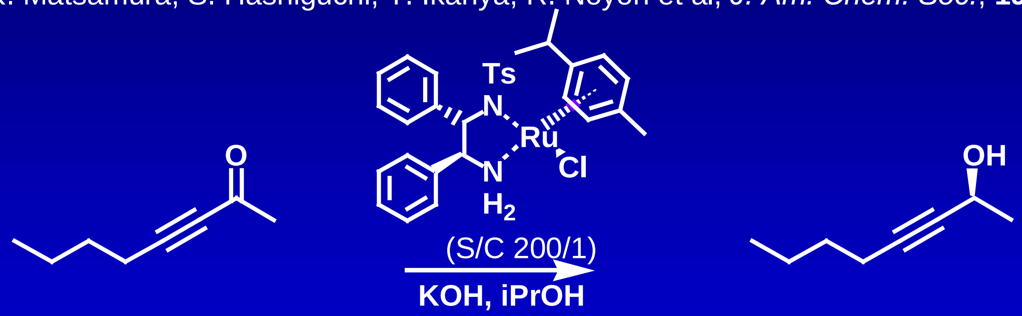
56% ee

S/C = 100/1
100 hours

Noyori / Ikariya Hydrogenation Technology

K. Matsamura, S. Hashiguchi, T. Ikariya, R. Noyori et al, *J. Am. Chem. Soc.*, **1997**, *119*, 8738

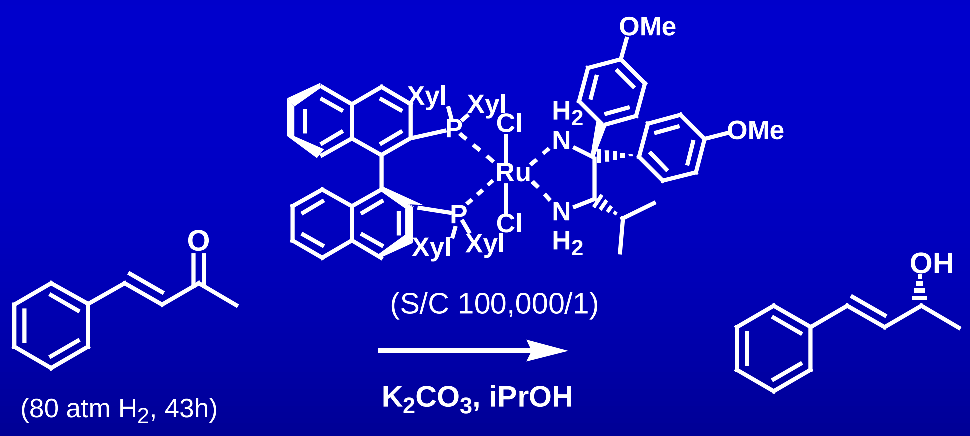
TRANSFER HYDROGENATION



98% ee, 70% yield

T. Ohkuma, ... T. Ikariya, R. Noyori et al, *J. Am. Chem. Soc.*, **1998**, *120*, 13529

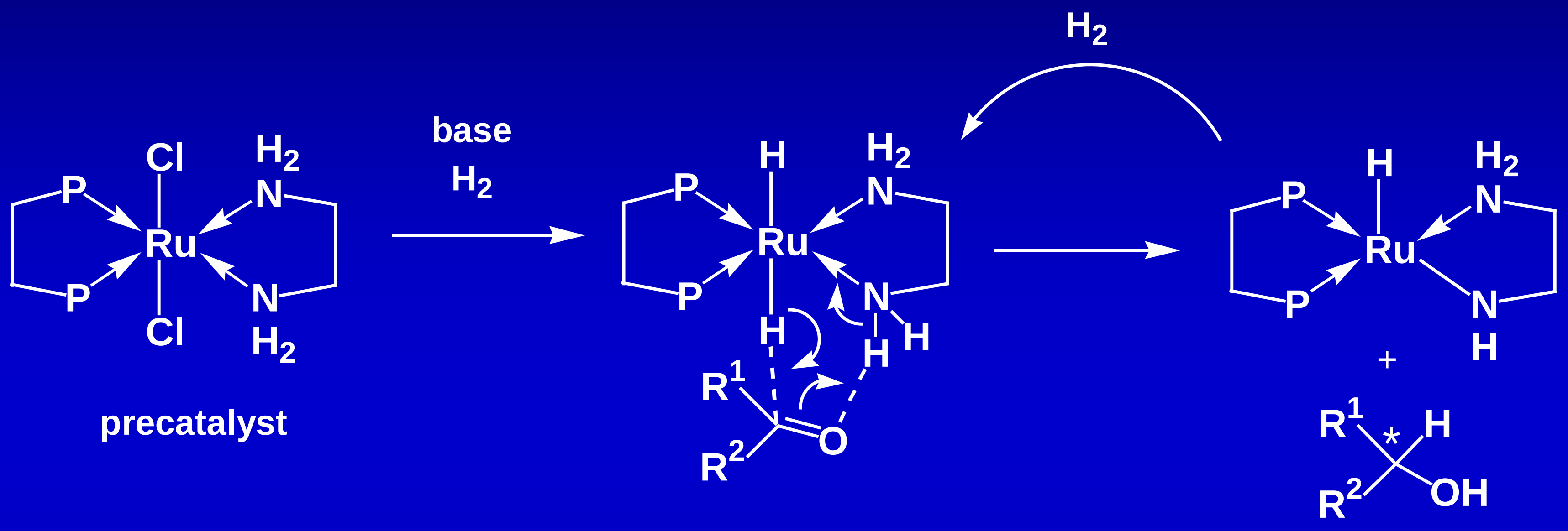
PRESSURE HYDROGENATION



97% ee, 100% yield

- **Licensed obtained in Dec 2000 from the Japan Science and Technology Corporation**

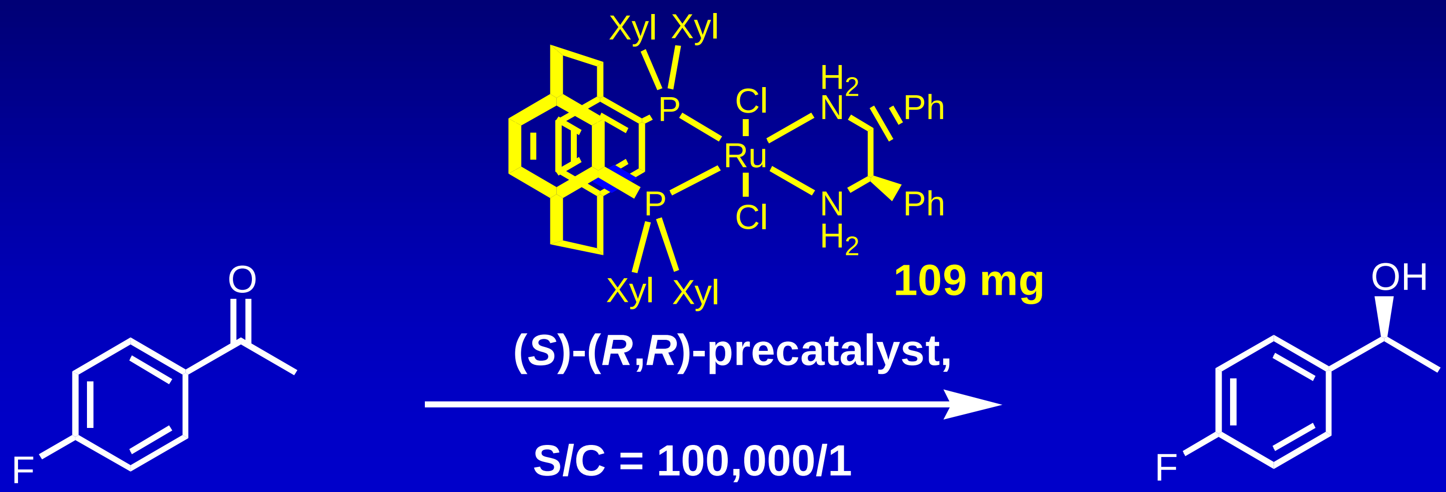
Mechanism of Noyori Hydrogenation



- The substrate does not bind to the metal
- Chiral environment created by both diphosphine and diamine

R. Noyori et al. *J. Am. Chem. Soc.* **2003**, *125*, 6510

Kilogram Scale Reactions



109 mg

(*S*)-(*R*,*R*)-precatalyst,

S/C = 100,000/1

***i*-PrOH, 1 mol% *t*-BuOK**
H_2 30 - 100 psi
2h

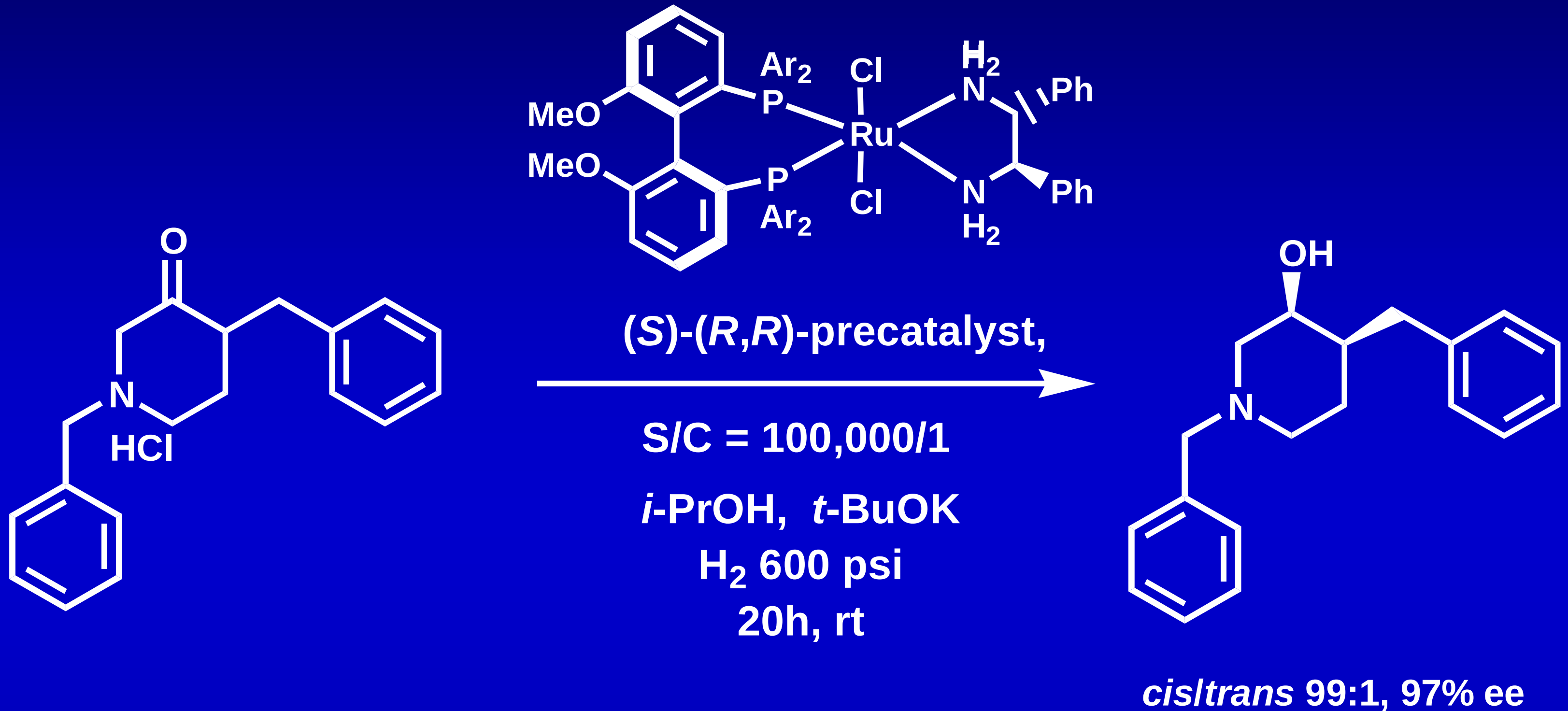
1.38 Kg

1.31 Kg after distillation
Purity 99.3% by GC
98.3 % e.e.

- PhanePhos-based ligand best
- Substrate distilled before use
- S/C 100,000 : 1 achieved
- Catalyst removed by short path distillation
- Another example at 100s kgs scale

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

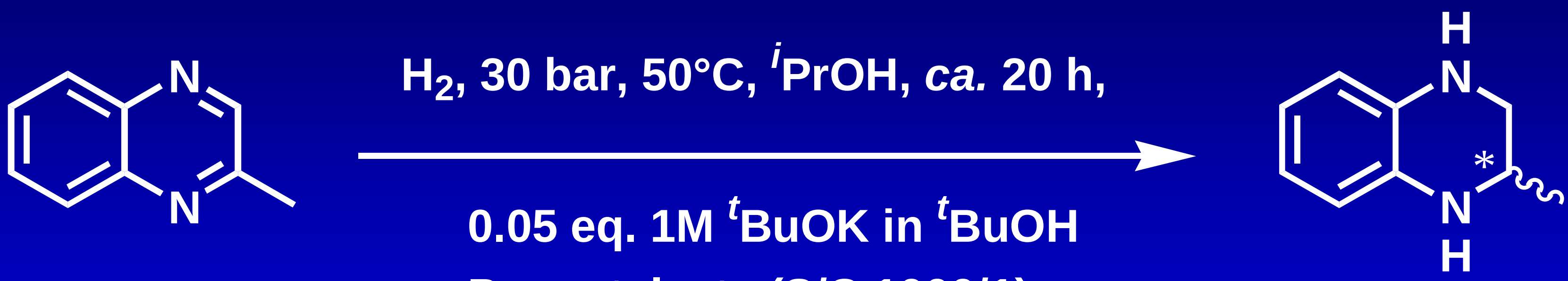
Dynamic Ketone Hydrogenation



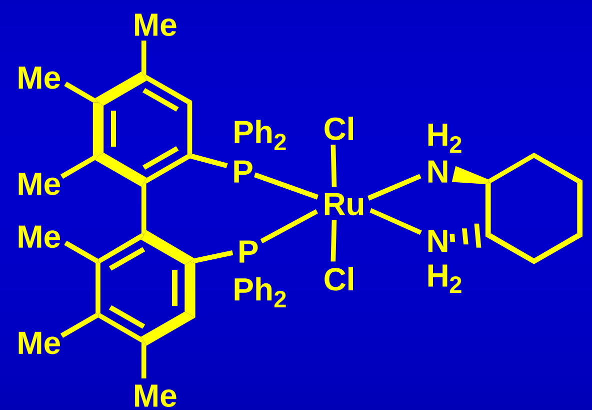
- Catalyst loading of 200,000 demonstrated
- Xyl-MeOBIPHEP gave 79% ee at S/C 1,000,000
- 9 Kg of product produced
- Overall yield of route using asymmetric hydrogenation was 53%.
- Discovery synthesis 3.5% overall yield

Roche, *Org. Process Res. Dev.* 2003, *7*, 418

Asymmetric Hydrogenation of 2-Methylquinoxaline



Pre-catalysts (S/C 1000/1):

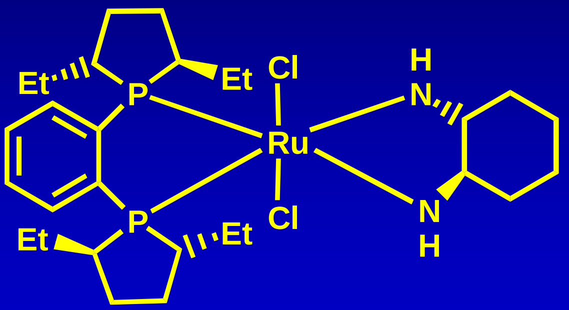


[(*S*)-HexaPHEMP.$RuCl_2$.(*S*,*S*)-DACH]: 69% ee, >99% Conv.

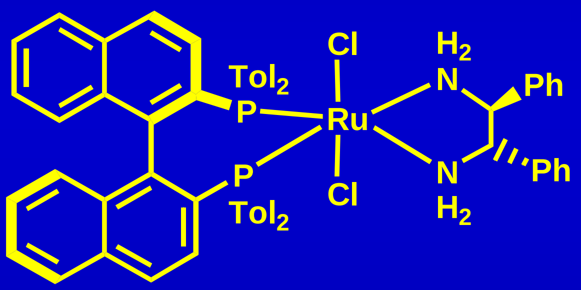
[(*S*)-BINAP.$RuCl_2$.(*S*,*S*)-DACH]: 61% ee, >99% Conv.

Patent: US 652868 and *Adv. Synth. Catal*., 2003, *345*, 195-201.

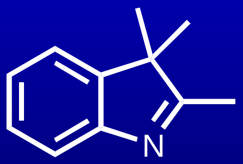
Reduction of Imines

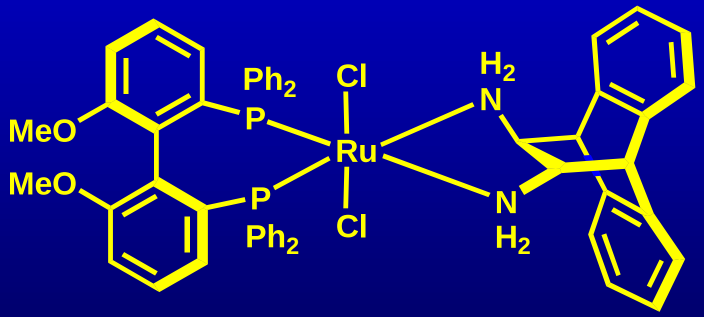


94% ee



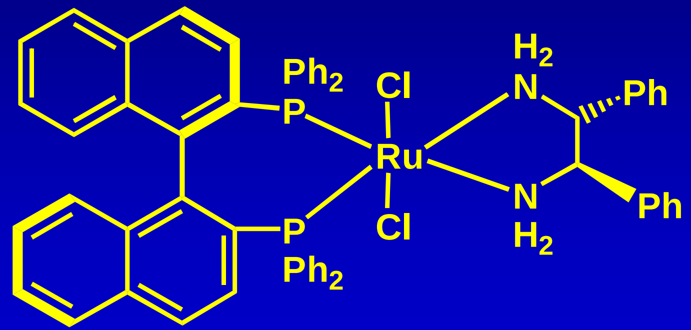
62% ee





88% ee

Customer Example - Thiadiazine



[(*R*)-BINAP $RuCl_2$ (*R,R*)-DPEN]

S/C = 2,500

→

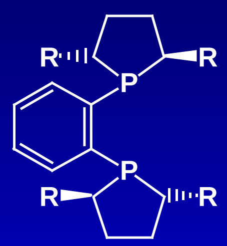
t-BuOK, *i*- PrOH, Toluene

H_2 60 psi, 60 ^{o}C

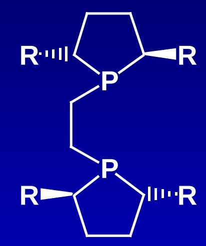
97% Yield, 87% ee

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

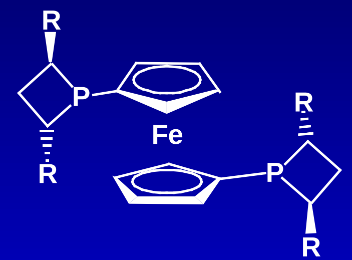
Ligands and Catalysts Available from Strem



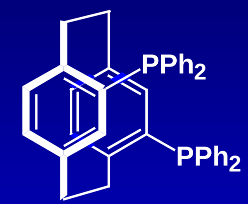
DuPhos



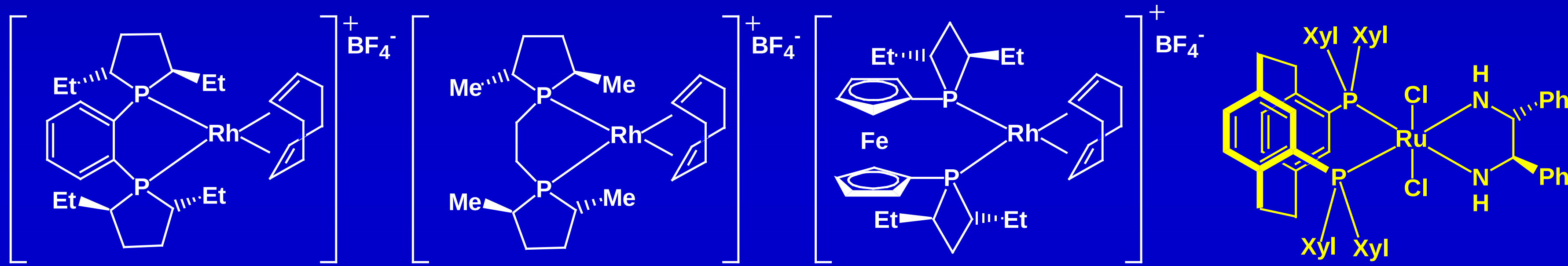
BPE

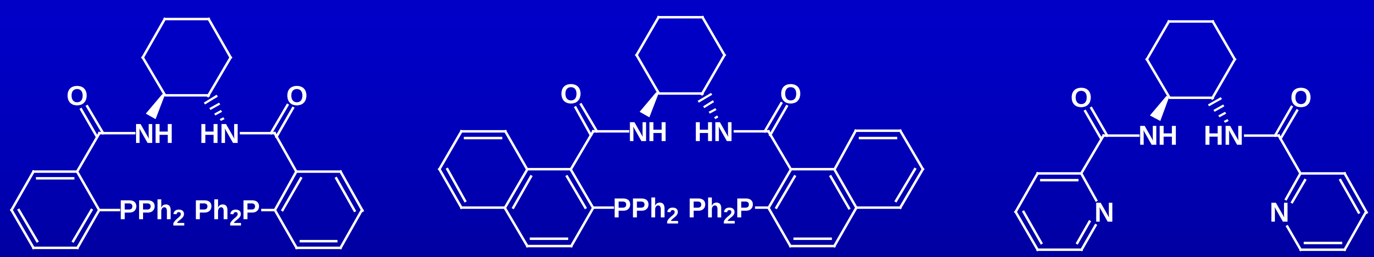


FerroTANE[TM]



PhanePhos





Trost Ligands

Many Dowpharma ligand and catalyst systems are available from the Strem Chemical Catalogue for Research use only.

Conclusions

Dow

- A number of asymmetric hydrogenation processes have been carried out on a manufacturing scale over the last 30 years
- Despite these successes, the technology is still not 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, we are starting to see increased applications for this technology
- In this talk we have reviewed several case studies of successful applications of asymmetric hydrogenation
- With a good understanding of catalyst selection, substrate purity, solvent, temperature and pressure variables, it is relatively straightforward to develop a successful process
- Security of supply of the catalyst is of paramount importance

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Thank You !