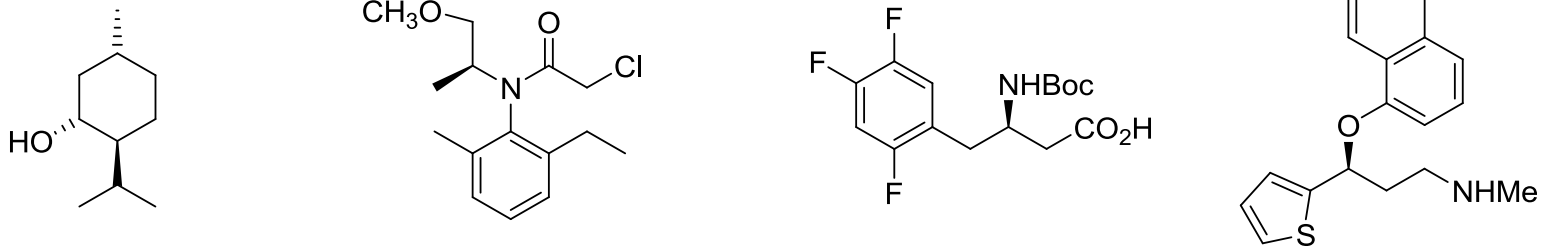
Asymmetric Hydrogenation: A Sustainable Technology for Pharmaceutical Manufacture

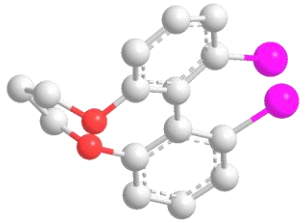
Presentation for the RSC Symposium 2016: Survival in the Speciality Chemicals Industry
1st June 2016



Dr Ian C. Lennon
Senior Vice President, Global Business Development
Chiral Quest Corp., Cambridge, UK
ilennon@chiralquest.com

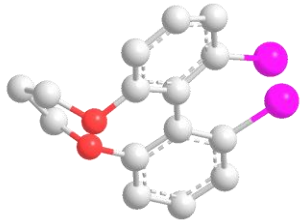
CHIRAL QUEST

Outline of the Presentation



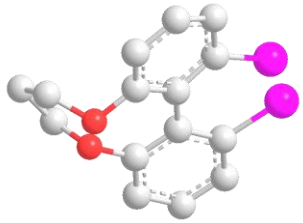
- Short Introduction to Chiral Quest
- Asymmetric Hydrogenation Background
- Asymmetric Hydrogenation: A Sustainable Technology?
- Chiral Quest's Examples of Asymmetric Hydrogenation
  - Manufacture of Phenylalanines
  - Manufacture of Chiral Alcohols
  - Applications to Generic Pharmaceuticals
- Conclusions

Background of Chiral Quest



- 2000: Founded by Professor Xumu Zhang
- 2003: Chiral Quest's NJ R&D Lab (near Princeton) established
- 2005: Scale-up facilities, Chiral Quest Jiashan (near Shanghai)
- 2008: Chiral Quest Receives Series B Financing of $13 m
- 2009: New Chiral Quest pilot plant opened May 2009 in Suzhou, Biobay
- 2012: Purchase of Jiang Xi Long Life Biopharmaceuticals Co. Ltd
- 2013: New R&D Laboratories in Suzhou opened and Series C Financing completed - $23 Million
- 2013: Chiral Quest files a US DMF for Duloxetine and Sitagliptin Ints.
- 2014: New workshops complete and the current plant capacity is >310 KL.
- 2014: REACH registration for (*S*)-MMAA completed
- 2015: Chinese Drug Manufacture Permit obtained

Management Team



Dr James Wu, CEO

PhD Organic Chemist, SIOC. 10 years with GSK in Senior Management roles, 7 years with other Chinese companies (GM and CTO). Founder of Jiang Xi Long Life

Dr. Ian Lennon, Senior Vice President, Global Business Development

More than 27 years pharmaceutical industry experience, in process chemistry and business development, with Merck, Parke Davis, Chirotech, DowPharma and Dr Reddy's

Dr. Wenge Li, Vice President, Research & Development

Wenge has been with Chiral Quest since 2002 and has extensive experience in the application and development of asymmetric hydrogenation

Dr. Wenjun Tang, Senior Consultant

Research professor at SIOC, specialized in catalysis, synthesis and processes, 6 years pharmaceutical industry experience with Boehringer Ingelheim in process chemistry.

Commercial Manufacturing Facility

- Jiang Xi Long Life, located in Jiangxi Province, P.R. China.
- Wholly owned by Chiral Quest and has 208 employees

Commercial Manufacturing Facility

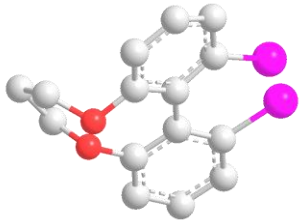
- Jiang Xi Long Life, located in Jiangxi Province, P.R. China.
- Wholly owned by Chiral Quest and has 208 employees

New Chiral Quest Manufacturing Facility

- Jiang Xi Long Life, located in Jiangxi Province, P.R. China
- >170 reaction Vessels (>310,000 L volume capacity)
- New workshop will open in March 2016 with 40 more vessels
- High pressure vessels (1 x 100 L, 2 x 500 L, 4 x 1000 L, 2 x 2000 L), up to 100 atm
- Temperature range from -80°C to 300°C
  (10 vessels for -80°C, 50-2,000 L)
- 4 distillation column towers (to 0.1mmHg)
- Licenses for Toxic chemicals including:-
  NaCN, Cl_2, $POCl_3$, Cl-SO_3H,
  $ClCOOC_2H_5$ and CH_3SO_2Cl

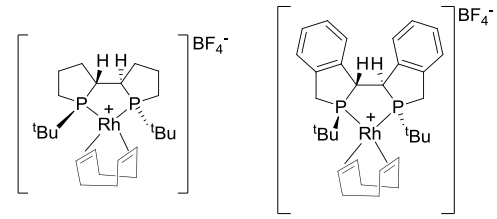
- Long Life has Chinese High Tech Certification
- In 2015 Chinese Drug Manufacture Permit granted, by the CFDA
- This was a hardware and software audit that determined that the plant is capable of cGMP manufacture

Expertise in Asymmetric Hydrogenation



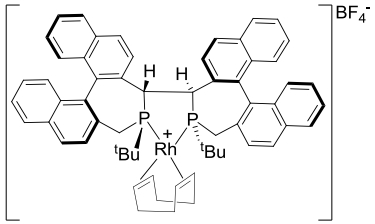
11 Hydrogenation reactors with high pressure capability (100 L to 2000 L)

- 2 x 2,300 L, 1 x 1,300L , 3 x 1000 L, 2 x 500 L and 1 x100 L stainless steel hydrogenation reactors (maximum rating 100 atm)
- 1 x 1000 L and 1 x 100 L glass lined hydrogenation reactor (10 atm)
- Our own proprietary catalysts

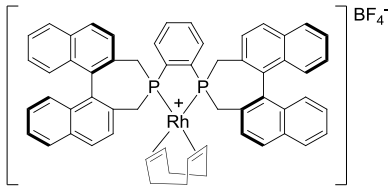


Rh-TangPhos Complex

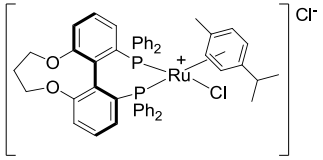
Rh-DuanPhos Complex



Rh-Binapine Complex



Rh-Binaphane Complex



Ru-C_3-TunePhos Complex

CHIRAL QUEST

Chiral Quest Suzhou – Headquarters

Headquarters

- Chiral Quest has its HQ on the Suzhou Industrial Park
- The new R&D center and HQ houses 31 employees and was opened in July 2013

- R&D, Administration, Finance, HR, QA/QC and business development functions are located at the new Suzhou HQ
- Chiral Quest employs 3 PhD, 5 MS and 6 BS level chemists and 5 analysts
- Chiral Quest has a total of 240 employees

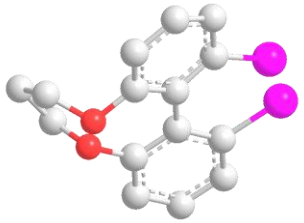
Chiral Quest Suzhou – R&D Centre

Research & Development

- All R&D is carried out in the new Suzhou R&D Centre
- Modern and well equipped chemical Laboratories for >40 chemists

- Glove boxes for handling air-sensitive compounds
- Analytical equipment, including HPLC's, GC's and LCMS

Catalytic Asymmetric Hydrogenation



Avoids wasteful production of 50% of the wrong isomer

The most powerful Chemocatalysis method

Over **70%** of commercial asymmetric catalytic processes involve asymmetric hydrogenation

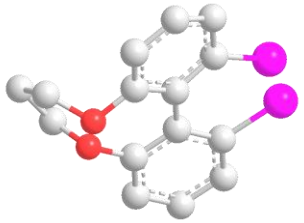
Asymmetric hydrogenation can be applied to make over **50% of all chiral moieties** in pharma products

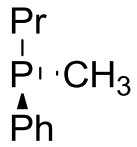
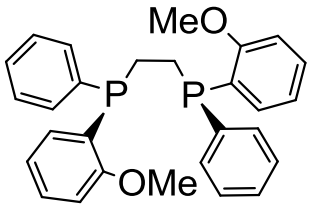
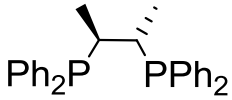
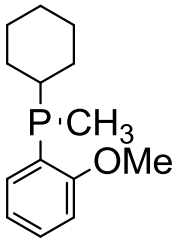
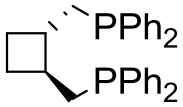
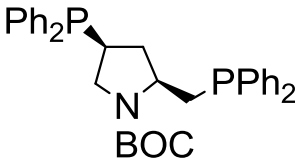
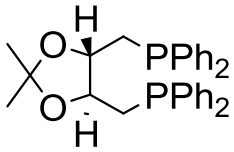
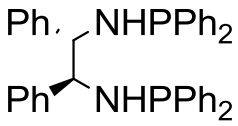
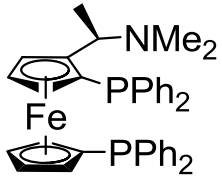
Nobel Prize in Chemistry 2001

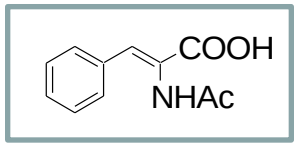
Reactions Under Pressure!

Reproduced with the kind permission of Chimica Oggi/Chemistry Today

Some of the First Applied Phosphine Ligands



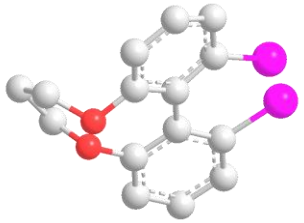
Ligand	% ee	Ligand	% ee	Ligand	% ee
	28%		95%		95%
1968		DIPAMP - 1974		CHIRAPHOS - 1977	
	88%		87%		91%
CAMP - 1970		Rhone-Poulenc - 1974		BPPM -1976	
	83%		94%		93%
DIOP - 1971		PNNP - 1974		BPPFA - 1980	

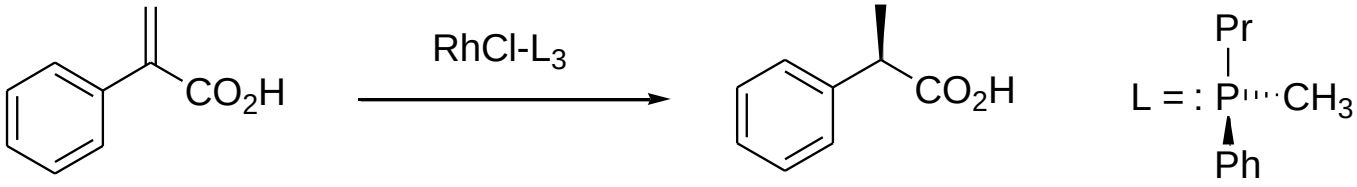


W.S. Knowles *Acc. Chem. Res.* **1983**, *16*, 106

CHIRAL QUEST

Early Applications of Asymmetric Hydrogenation

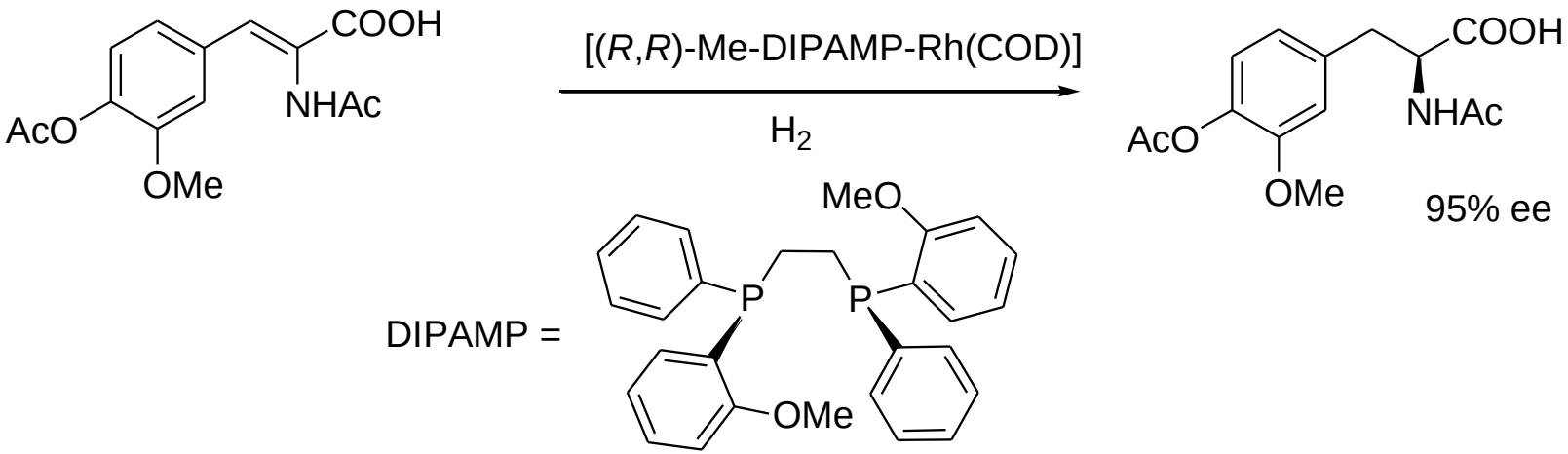




15% ee

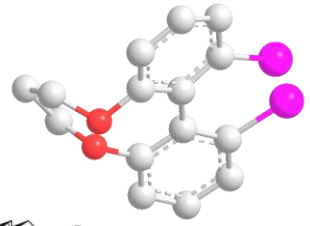
W.S. Knowles and M. J. Sabacky *Chem. Commun.*, **1968**, 1445
L. Horner et al. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942

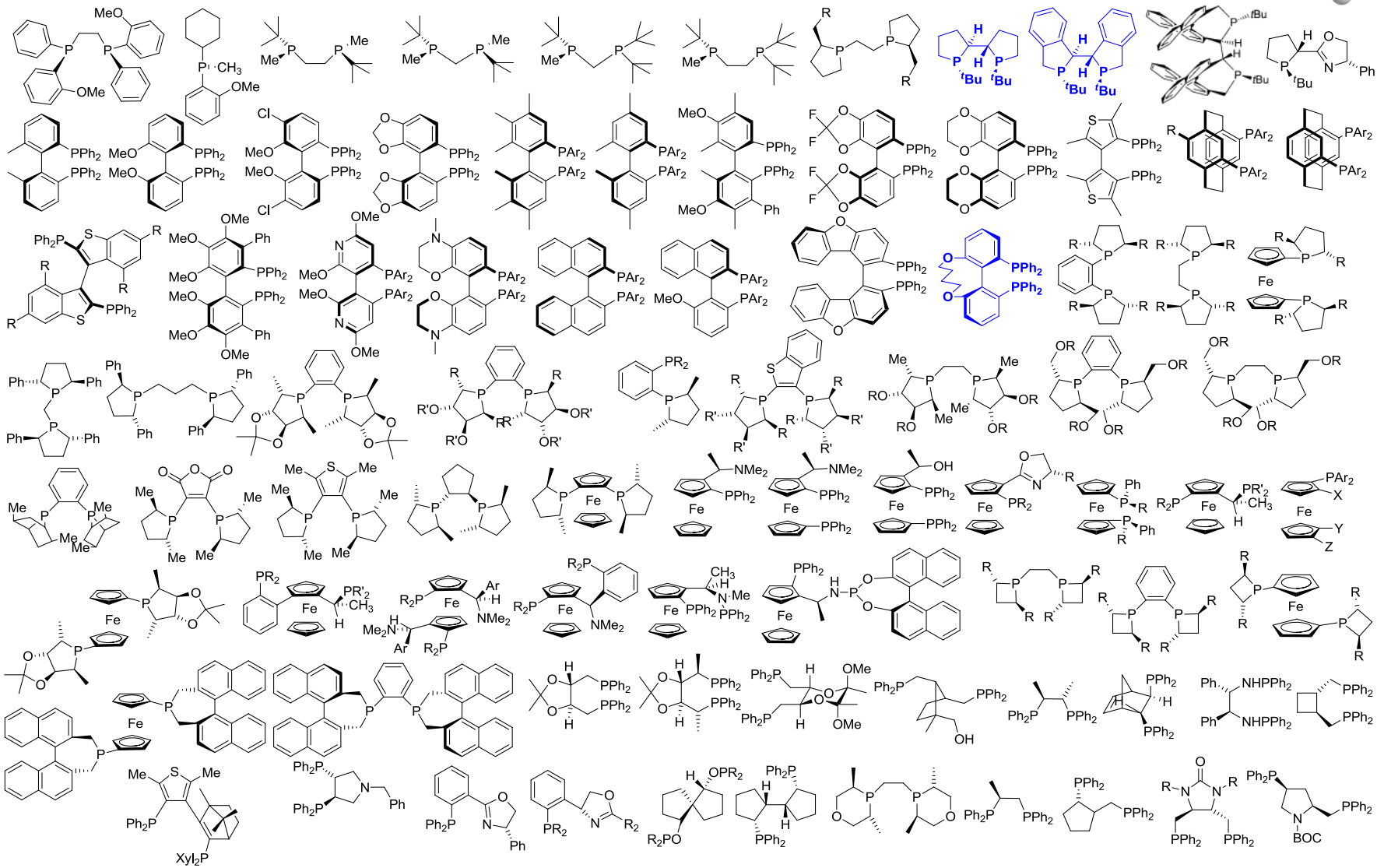
Monsanto L-DOPA process



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

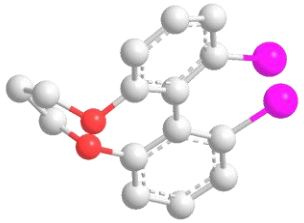
Some of the 3,000 Known Phosphine Ligands

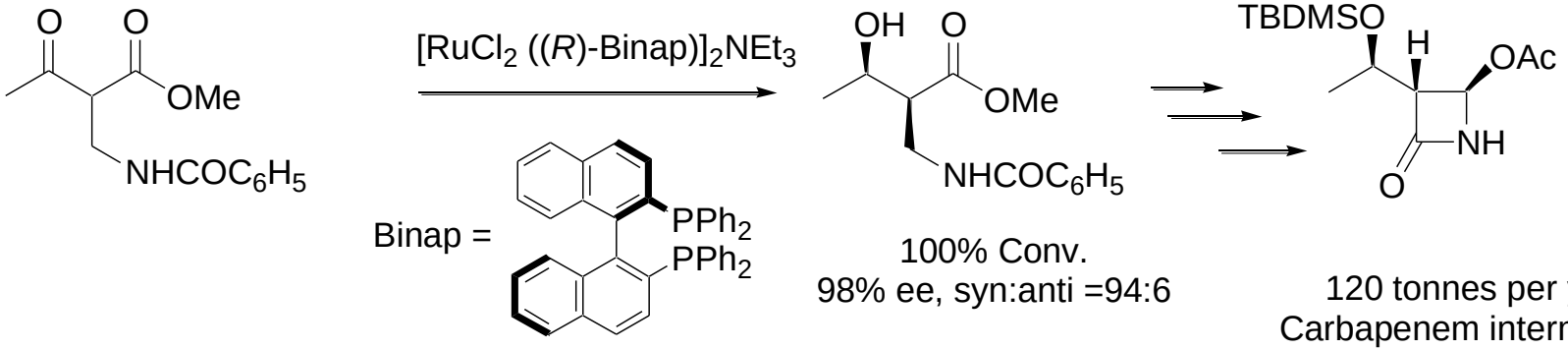




CHIRAL QUEST

Noyori's Binap Complexes

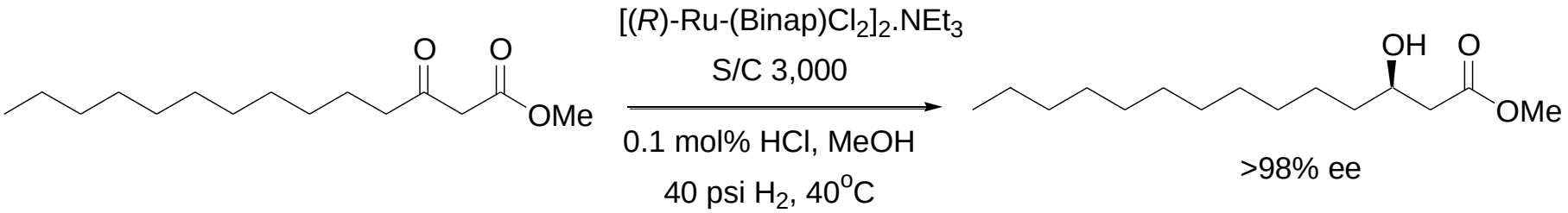




100% Conv.
98% ee, syn:anti =94:6

120 tonnes per year
Carbapenem intermediate

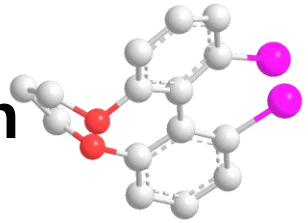
Asymmetric Catalysis in Organic Synthesis, R. Noyori
John Wiley & Sons, **1994**

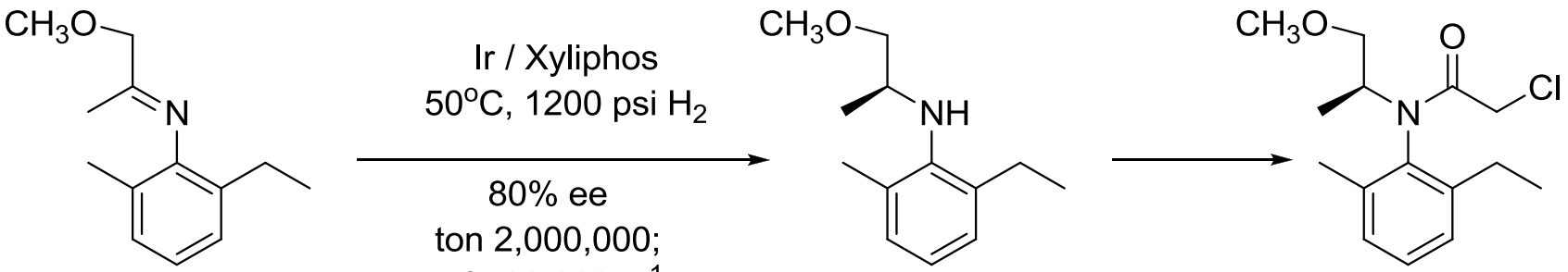


>98% ee

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

Largest Scale Industrial Asymmetric Hydrogenation

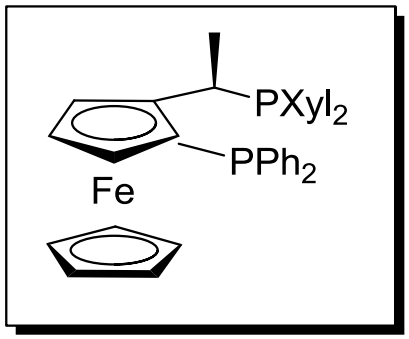




Metolachlor

>20,000 tonnes per year

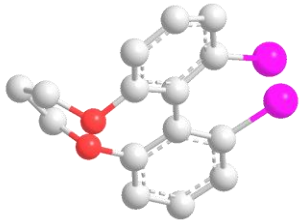
Xyliphos =

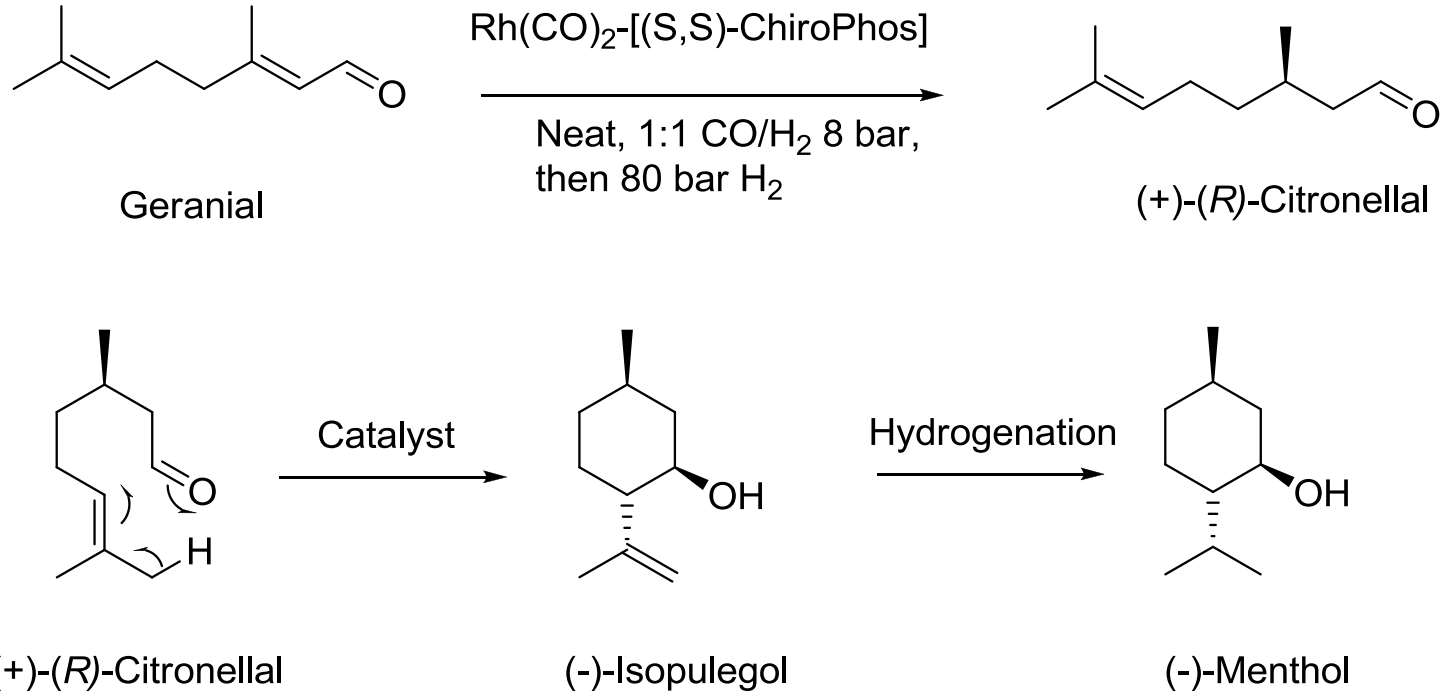


1982 - Laboratory work
1993 - JosiPhos first reported
1996 - First Production batch

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

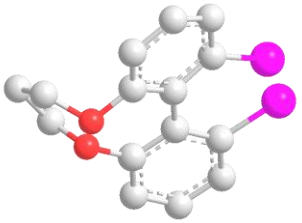
BASF Menthol Process

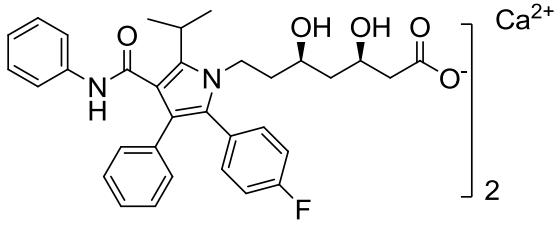




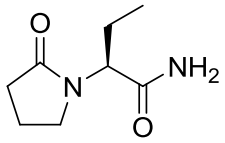
- Worldwide consumption of Menthol is 20,000 MT
- Takasago and Symrise manufacture 5,000 MT
- Rest comes from natural sources
- BASF capacity for Menthol is 3 – 5,000 MT, sells for $19/kg
- BASF back integrated into Geranial

Application of Asymmetric Hydrogenation to Drugs

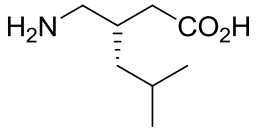




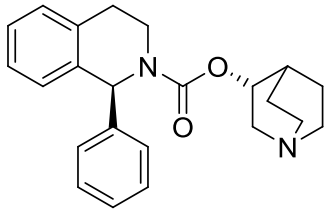
Atorvastatin
Pfizer, 1997, Hyperlipidemia



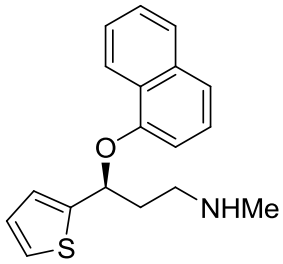
Levetiracetam
UCB, 2000, Epilepsy
Rh-DuPhos



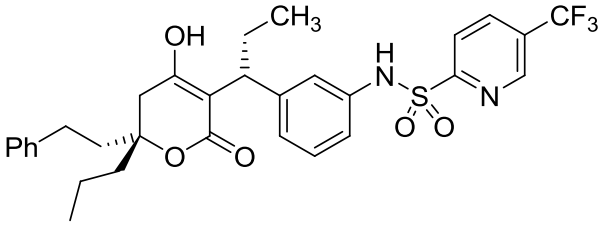
Pregabalin
Pfizer, 2004, Neuropathic pain
[(*R*,*R*)-Me-DuPhos Rh]



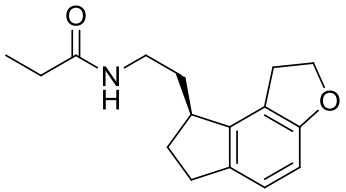
Solifenacin
Astellas, 2004, Overactive bladder



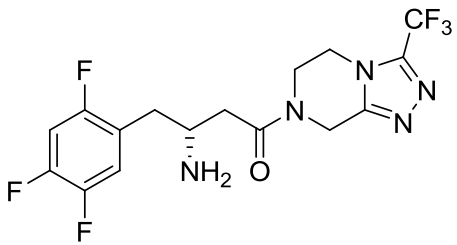
(*S*)-Duloxetine
Lilly, 2004, Depression



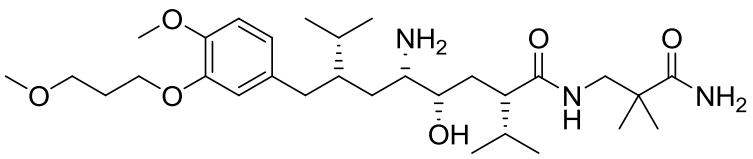
Tipranavir
BI, 2005, HIV
[(*R*,*R*)-Me-DuPhos Rh]



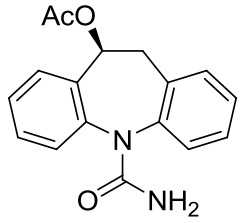
Rozerem
Takeda, 2005, insomnia
BINAP-Ru



Sitagliptin
Merck, 2006, Diabetes
^{t}Bu-JosiPhos-Rh

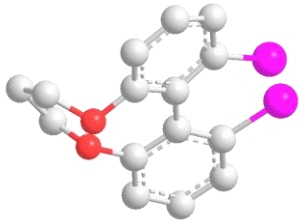


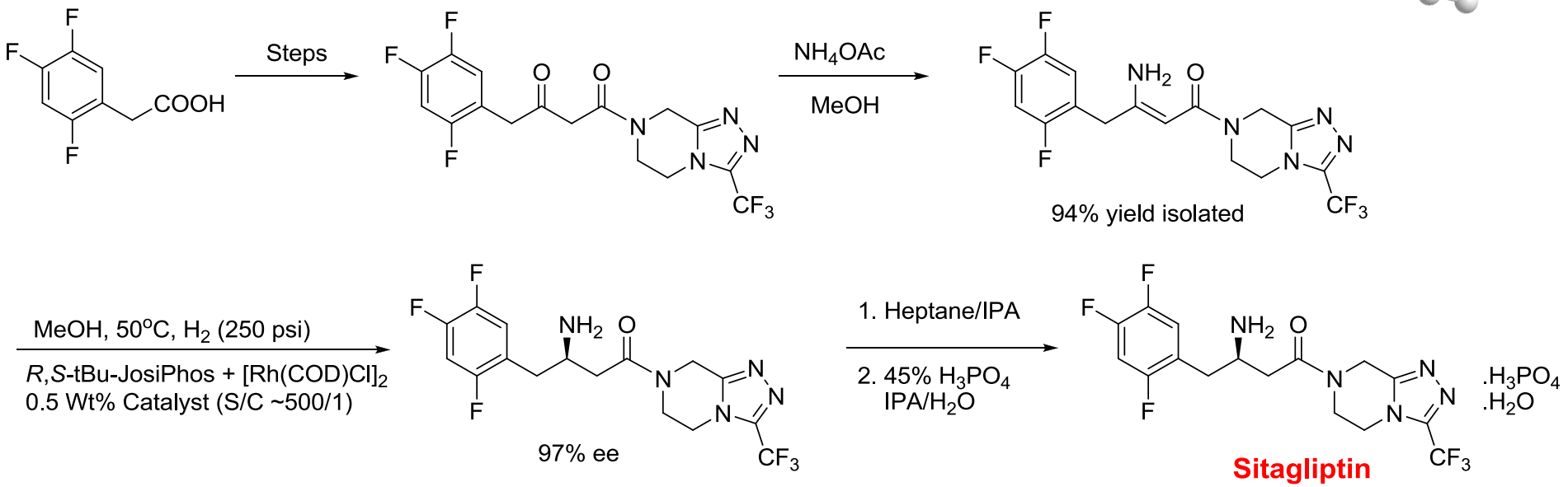
Aliskiren
Novartis, 2007, Hypertension
MonoPhos-Rh, WalPhos-Rh



Eslicarbazepine acetate,
Eisai, 2009, Epilepsy
RuCl(*S*,*S*-TsDPEN(*p*-Cymene)]

Merck's Hydrogenation Route to Sitagliptin



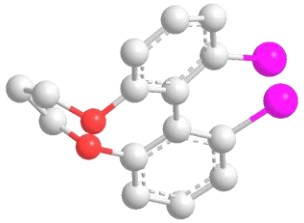


Sitagliptin

Diabetes type 2
2012 Sales $5.98 Billion,
Patent Expiry 2022

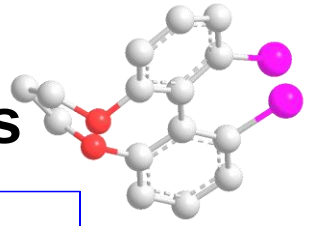
- Hydrogenation is of an advanced imine intermediate, but catalyst loading high.
- Rh is recovered onto Ecosorb and sent for refining – 94% recovery
- First ever final stage asymmetric hydrogenation process for a API
- Probably the largest Scale Asymmetric Hydrogenation for an API -100-200 MT/year
- 2006 Presidential Green Chemistry Award!

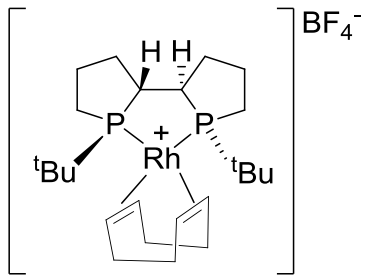
Asymmetric Hydrogenation: A Sustainable Technology?



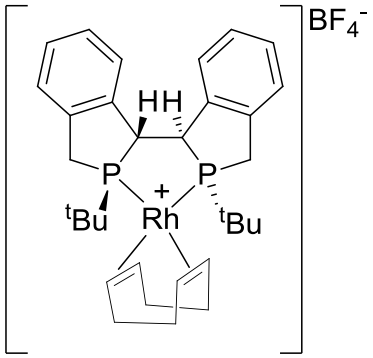
- Can achieve very good catalyst loadings (S/C >120,000/1)
- Single solvent, substrate, hydrogen and catalyst
- Provides pure product, single solvent and catalyst – Easy Work-up
- Metal is not destroyed and can be recovered!
- 30,000 kg of rhodium consumed worldwide in 2012
- 24,300 kg (81%) went into Catalytic Converters ($^1/_3$ recovered)
- 964 kg of rhodium was used in the glass industry
- 2,520 kg in the chemical industry (not Pharmaceuticals!)
- Pharmaceuticals comes behind Dentistry, Jewellery and electronics in Rh usage
- This technology meets many of the Principles of Green Chemistry

Chiral Quest Asymmetric Hydrogenation Catalysts

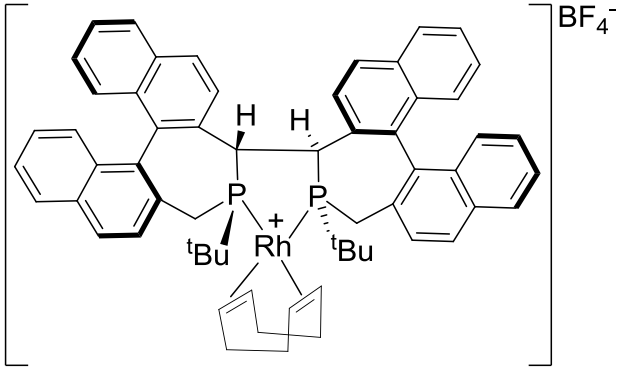




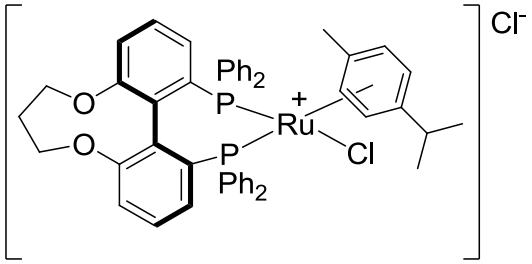
Rh-TangPhos Complex



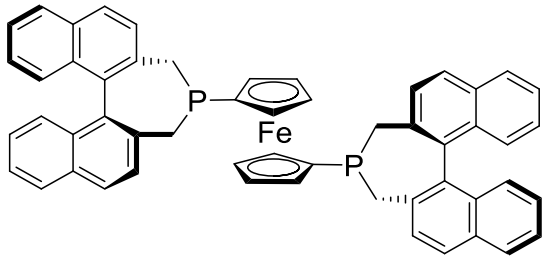
Rh-DuanPhos Complex



Rh-Binapine Complex



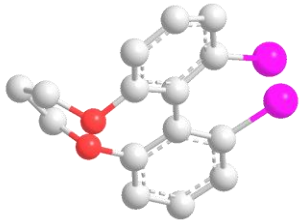
Ru-C_3-TunePhos Complex



(*S,S*)-f-Binaphane Ligand

- Catalysts made on a Kg scale for our manufacturing requirements
- >30 kg of DuanPhos made to support manufacturing

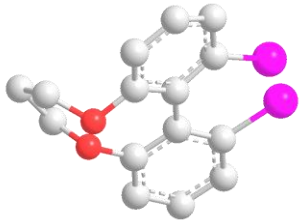
RSM's Made Using Asymmetric Hydrogenation

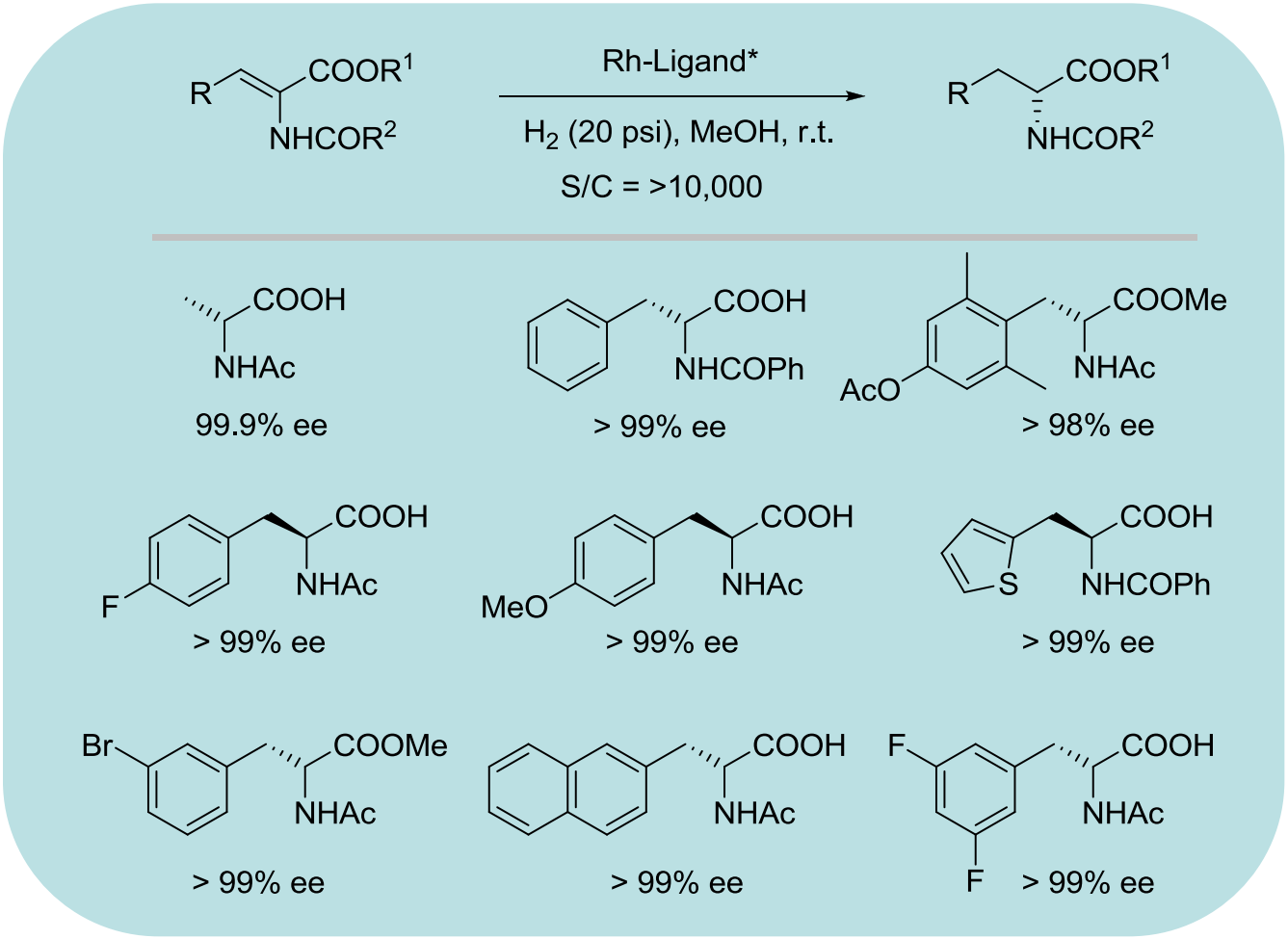


Clinical Phase	Approx. Volume
FDA Approved	>5 MT
FDA Approved	>4 MT
FDA Approved – 3 products	100-200 kg
Pre-Registration	>10 MT
PIII – 2 products	1 to >3 MT
PII – 2 products	100 – 200 kg
PI – 3 products	50 – 100 kg
Pre-Clinical – 3 products	1-10 kg

- Chiral Quest applies Asymmetric Hydrogenation Technology for 16-20 products
- Many of these are now on MT scale
- We can manufacture 130-150 MT of products per year

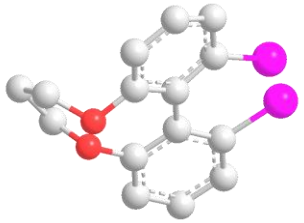
Manufacture of α-Amino Acids

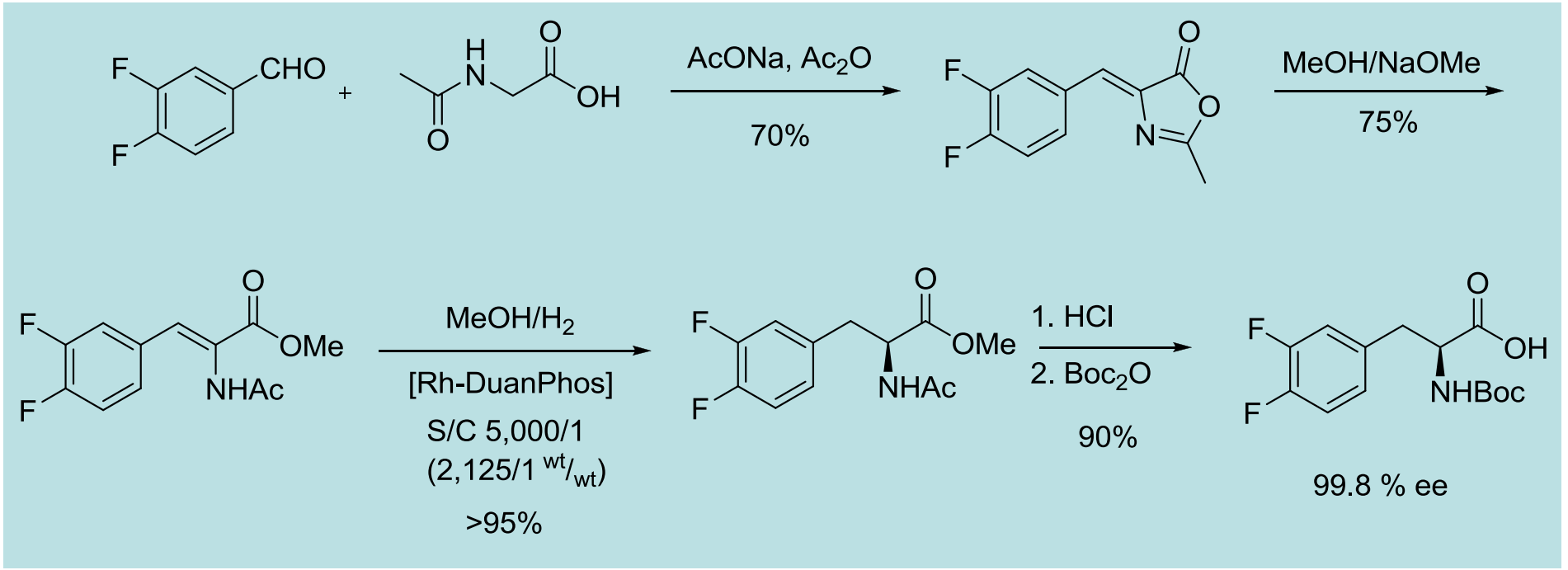




- Same Rh-DuanPhos catalyst can produce many Phenylalanine products

Manufacture of (*S*)-*N*-Boc-3,4-Difluorophenylalanine



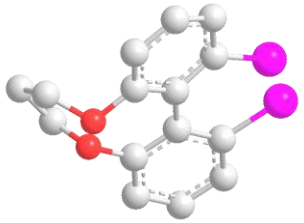


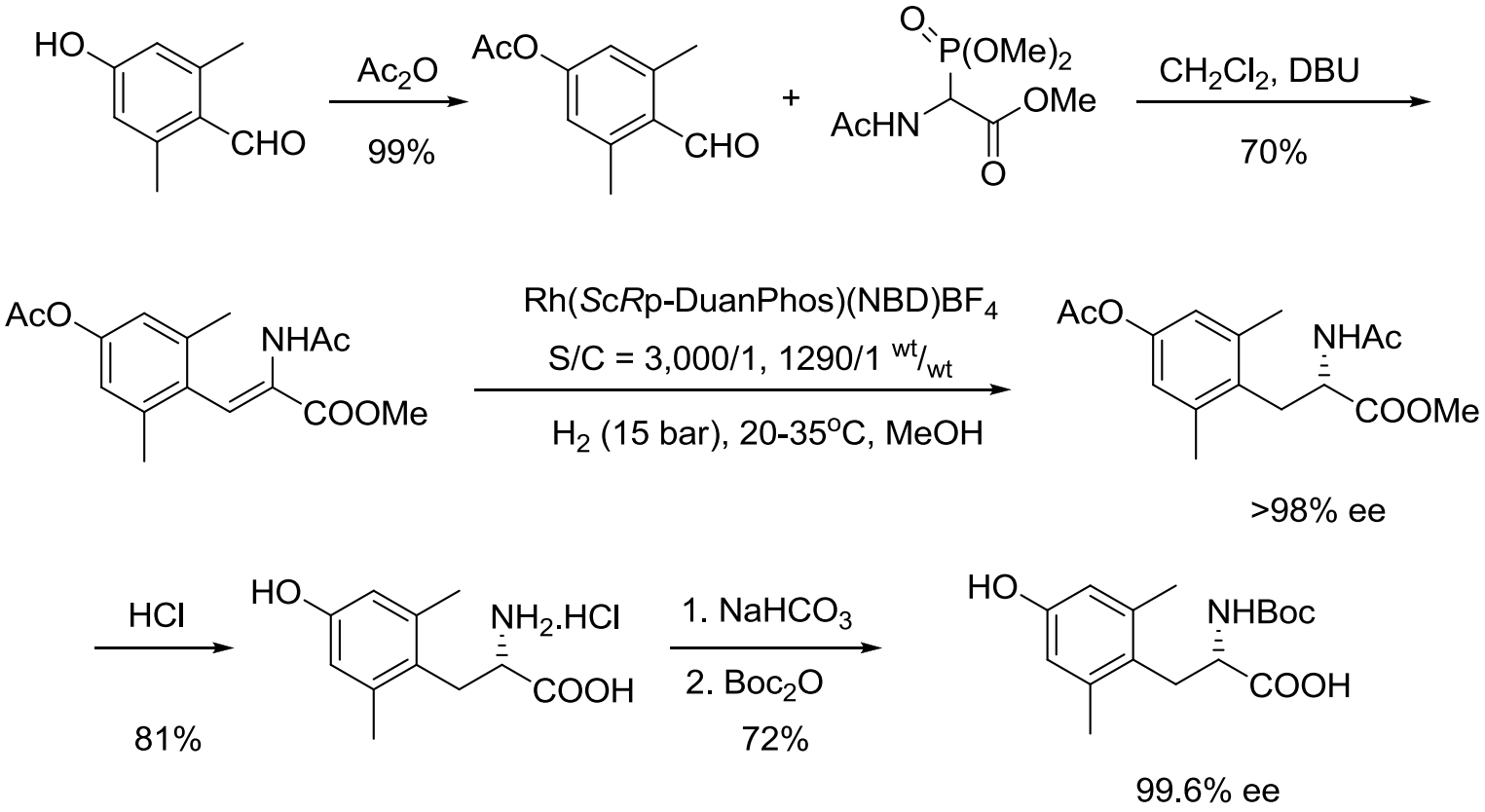
- Vantia therapeutics made a request for 15 kg of (*S*)-*N*-Boc-3,4-Difluorophenylalanine
- The product was made, shipped and received by the customer in under 10 weeks from receipt of a purchase order
- Conditions for the Rh-DuanPhos hydrogenation are mild and scaleable.

CHIRAL QUEST

Vantia therapeutics

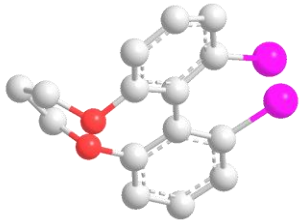
Route to *N*-Boc-(*S*)-2,6-Dimethyltyrosine

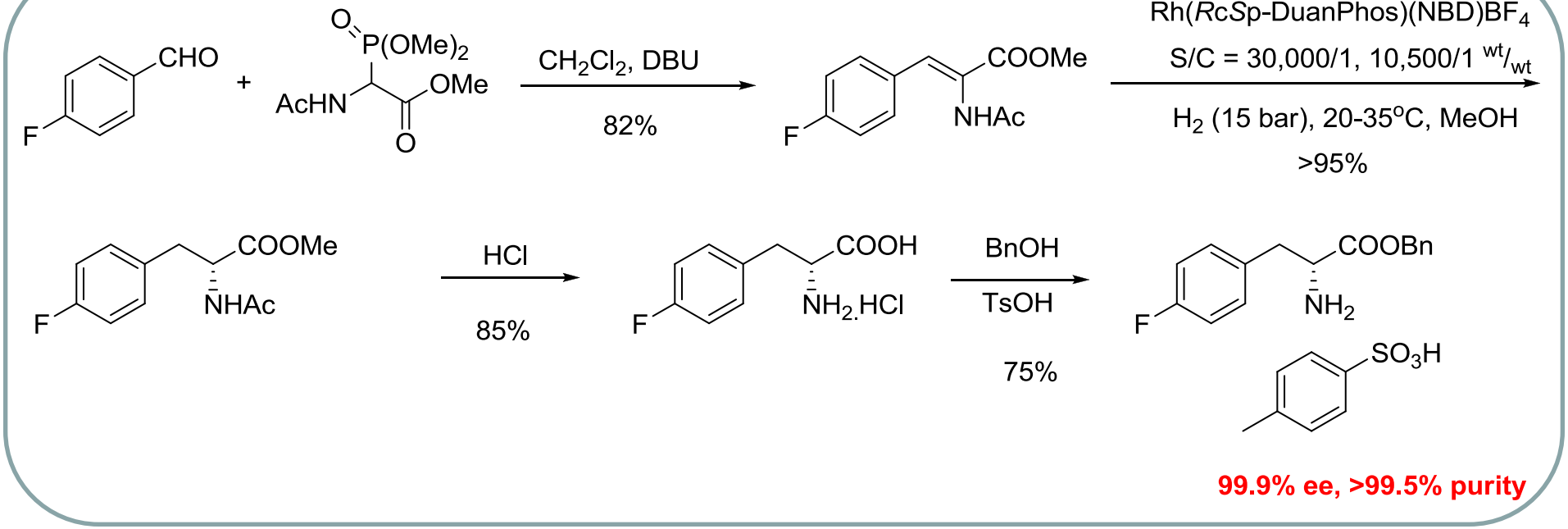




- The Erlenmeyer route does not work for the sterically hindered aldehyde
- The Horner-Emmons reagent is routinely manufactured on a MT scale
- This reagent is now routinely used for α-amino acid manufacture

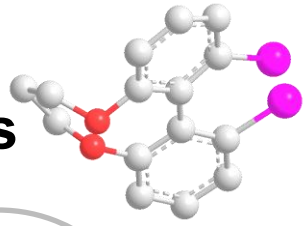
4-Fluoro-D-phenylalanine Benzyl ester Ts Salt

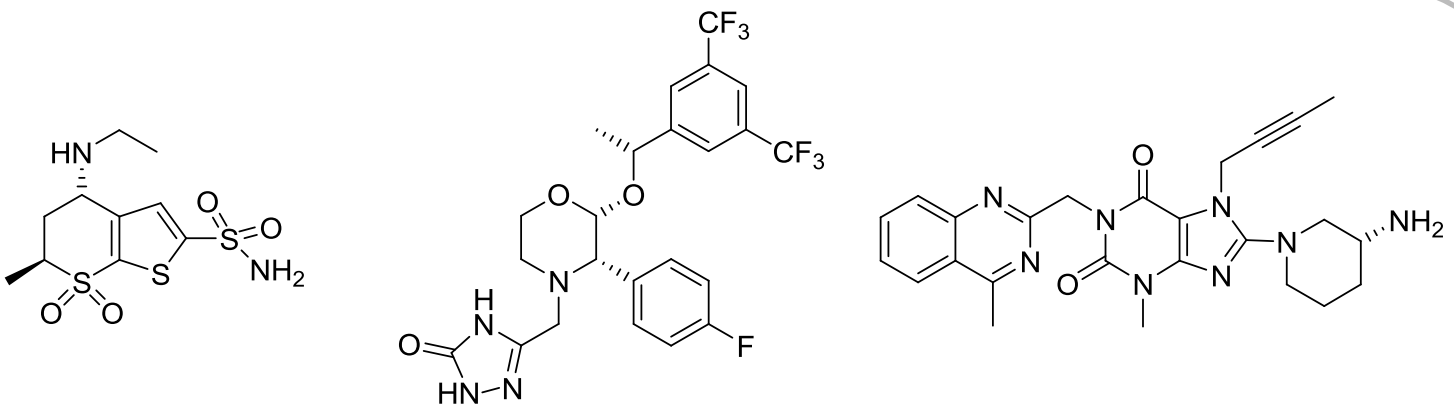




- Chiral Quest has manufactured 5 and 50 kg lots of this product for CML Europe
- High enantiomeric excess (99.9%) and purity (99.5%) was achieved.

Chiral Quest Advantaged Chiral API's and Intermediates



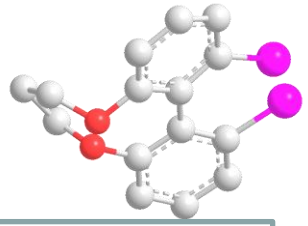


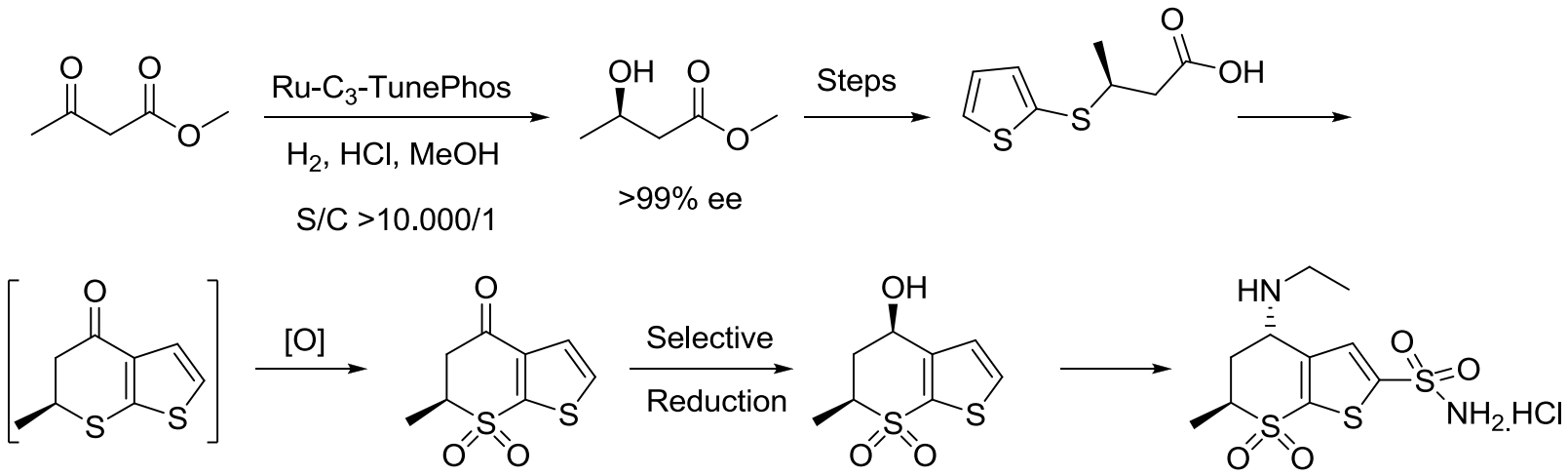
Dorzolamide | Aprepitant | Linagliptin

Duloxetine | Sitagliptin | Rasagiline

- Examples of Active Pharmaceutical Ingredients that can be manufactured using Chiral Quest Technology

Synthesis of a Dorzolamide Intermediate





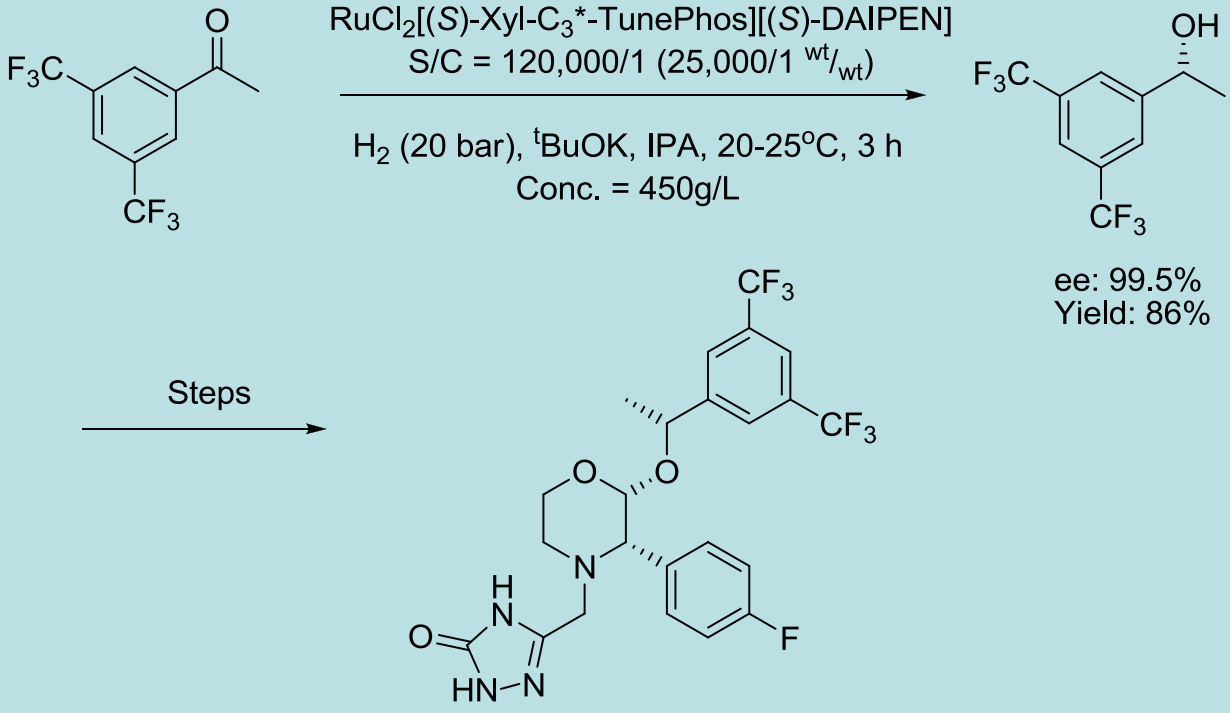
Dorzolamide

Glaucoma

2012 sales, **$642 Million,** Patent Expiry 2008

- Asymmetric hydrogenation of methyl acetoacetate requires a Hastelloy reactor
- Chiral Quest has a 1,000 L Hastelloy hydrogenation vessel
- >5MT of this intermediate has been manufactured

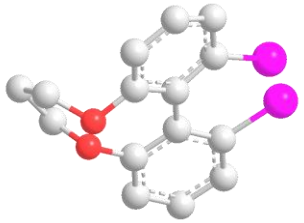
Intermediate for Aprepitant

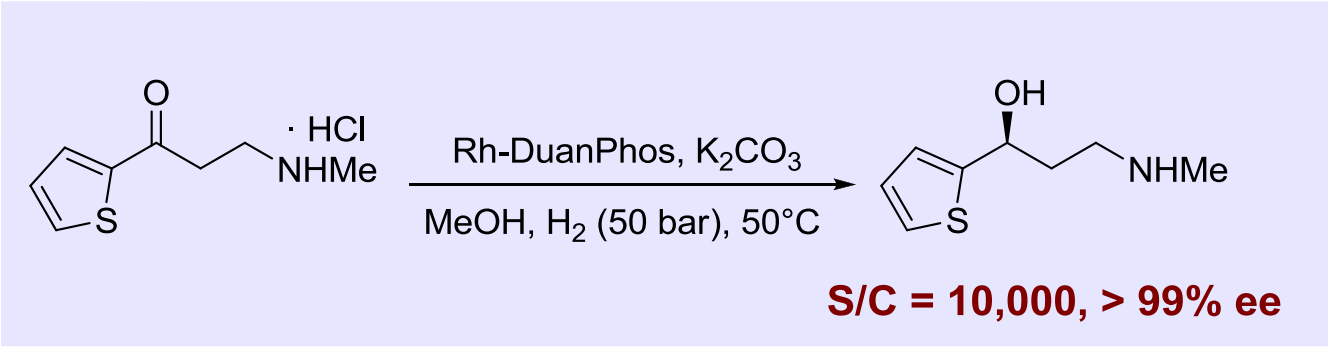


Chemotherapy-induced nausea/vomiting
2012 sales, **$309 Million,** Patent Expiry 2013

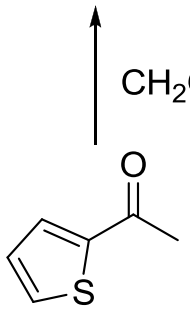
- In excess of 10 MT of the chiral alcohol for Aprepitant has been manufactured
- Chiral Quest obtained a license for the ketone hydrogenation technology from the Japan Science & Technology Agency in December 2009

Chiral Quest's Approach to the Key Intermediate of Duloxetine

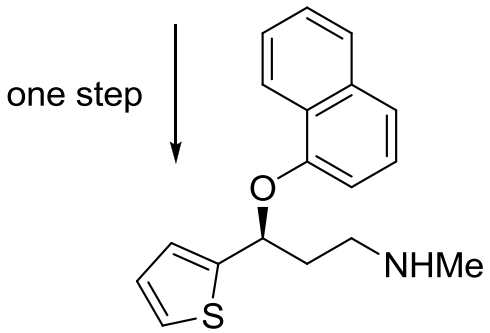




S/C = 10,000, > 99% ee



starting material



(*S*)-Duloxetine (Cymbalta™)

Antidepressants, Reuptake Inhibitors
2012 sales, **$5.3 Billion**

- Process transferred to Jiang Xi Long Life and is in routine production.
- >30,000 kg of MMAA has been manufactured , >99% ee, >99% purity

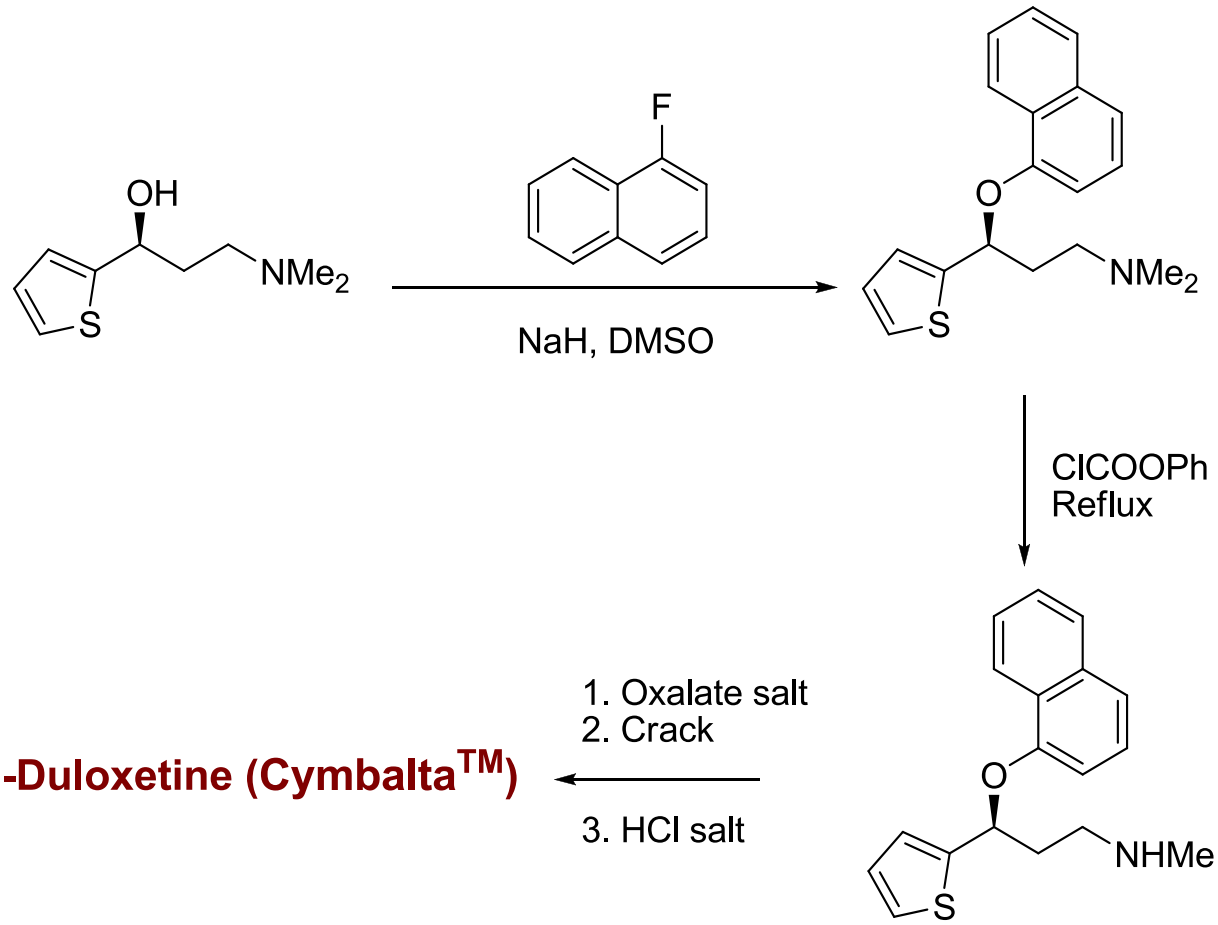
Chiral Quest has filed a US DMF for the MMAA process – Ref. Number 26862

REACH Registration completed – Registration No. 01-2120053179-54-0000

CHIRAL QUEST

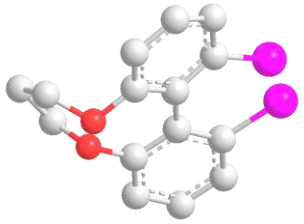
Lonza

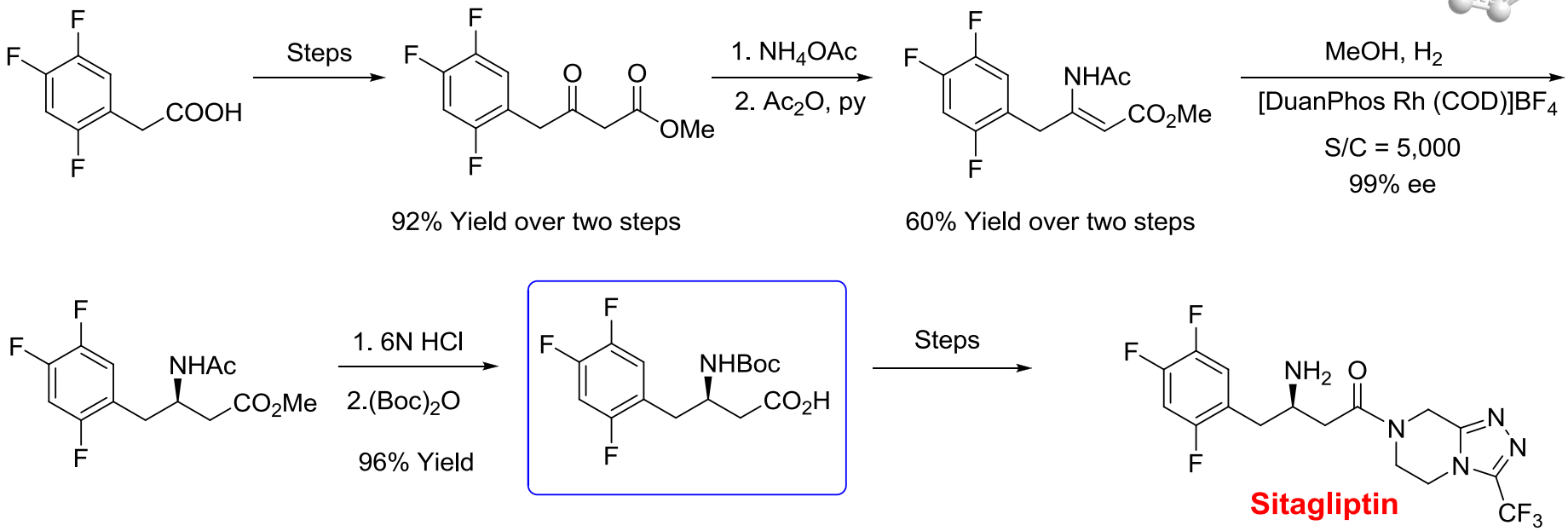
Traditional Routes to Duloxetine



- DMAA is made by resolution
- Methyl Chloride is the by-product of demethylation!
- An extra purification process by an oxalate salt is required

Chiral Quest's Route to Sitagliptin Intermediate

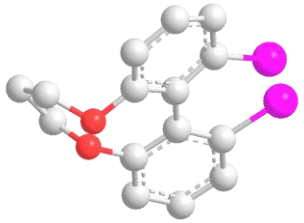




Diabetes type 2
2012 Sales $5.98 Billion,
Patent Expiry 2022

- Highly efficient asymmetric hydrogenation process, S/C = 5,000 (2,360/1 $^{wt}/_{wt}$)
- Three manufacturing campaigns completed >25,000 kg made.
- Granted US and Chinese patents, US 8,278,486 B2 and CN102271504B. Pending in Europe and India.
- **Chiral Quest has filed a US DMF for the Sitagliptin process – Ref. Number 27115**

Summary



- Many products are made annually using Asymmetric Hydrogenation
- The process is highly efficient, providing high enantiomer excess, high purity and producing very little waste.
- If volumes are high enough, then continuous flow plants can be built
- Unfortunately, this is rarely the case in Pharmaceuticals
- Chiral Quest offers the manufacture of a range of products on a commercial scale, such as Chiral Alcohols, α- and β-Amino acids using this technology

CHIRAL QUEST

A Recognized Leader in Chiral and Process Chemistry

Ian Lennon

ilennon@chiralquest.com

Please Visit Chiral Quest at Stand H10

June 2016