

# Sophisticated Molecules for the Pharmaceutical Industry

**Zach**<sup></sup>  
**Zambon Chemicals**

# Pharma: Business Results

TOTAL  
PHARMA  
REVENUES

682

mio€

+2,7%  
VS 2017

NET  
INCOME

59

mio€

EBITDA

112

mio€

## BUSINESS PHARMA

Cough and Cold  
Women's Health  
Pain  
Gastro  
Parkinson's disease  
Severe Respiratory Diseases  
Other

45%

16%

9%

10%

5%

5%

10%



# Pharma: Business Results

Offices in **20 countries**  
across South America,  
Europe and Asia.

Present in **87 countries**  
around the world



## SALES BY GEOGRAPHICAL AREA

Italy **21%**

North and  
South America **11%**

Europe **45%**

Eastern Europe **6%**

Asia **17%**

## PHARMA PEOPLE

Production **628**

Sales & Marketing **1363**

G&A **179**

R&D / Medical Affairs **287**

TOTAL **2.457**

# Industrial Business Operations

## Cadempino

**76** million units manufactured  
third parties and generics  
manufacturers of carbapenems

## Vicenza

**65** million units manufactured  
**230 ckt** demonstrate the site's  
extraordinary complexity

## Sao Paulo

**4** million units  
produces

## Haikou

**20** million units  
manufactured

## Virtual Plant

**12** million units  
manufactured  
units sold (including **Xedago®**  
for 600K boxes)

**138** million in  
global sales  
including **Xedago®** and **Flutmucl®**  
antidote

**4 MANUFACTURING PLANTS: VICENZA (ITALY),  
CADEMPINO (SWITZERLAND), HAIKOU (CHINA) AND  
SÃO PAULO (BRAZIL) SUPPLY PRODUCTS AND  
SERVICES TO 87 COUNTRIES WORLDWIDE**

**IN 2018 INVESTMENTS FOR APPROXIMATELY  
18 MILLION EUROS FOR NEW FACILITIES AND  
UPGRADE OF PROCESSES AND TECHNOLOGIES**

**HIGHER AND GROWING SYNERGY AMONG  
THE DIFFERENT GROUP PLANTS**

# Zambon Group

## TOTAL REVENUES (moe)

\*DISCONTINUED OPERATIONS



## GLOBAL SALES

Region	2018
NORTH AND SOUTH AMERICA	11%
EUROPE	47%
ITALY	20%
EASTERN EUROPE	6%
ASIA PACIFIC AND OTHERS	16%



32%

HIGH-SCHOOL GRADUATES

WOMEN

50%

57%

UNIVERSITY GRADUATES

389  
G&A

1.370  
MARKETING

2.729  
OF WHOM 771 IN ITALY

769  
PRODUCTION

201  
R&D  
MEDICAL  
MARKETING





# Zach System

# Zach

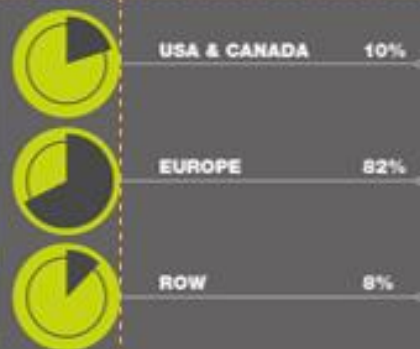
## A SOLID DEVELOPMENT PLAN FOR CHEMICAL BUSINESS

Zach is the chemical division of the Zambon Group and it focuses on producing Active Pharmaceutical Ingredients (APIs) and advanced intermediates for the pharmaceutical industry.

### % REVENUES BY SEGMENT



### % BY GEOGRAPHIC AREA



### SALES REVENUES



### ZACH PEOPLE

PRODUCTION	78%
SALES & MARKETING	2%
G&A	10%
R&D	10%



# Zach: IN FEW WORDS

- FDA inspected manufacturing site
- A strong track records with different Authorities
- **177** people
- R&D team on site – **18** people
- A Kilolab plant
- A GMP pilot plant
- A broad range of technologies
- Spray-drying of APIs & Low Endotoxin Excipients
- A flexible manufacturing facility
- **OEL  $\geq$  1 $\mu$ g/m<sup>3</sup>** (max. OEB 4)



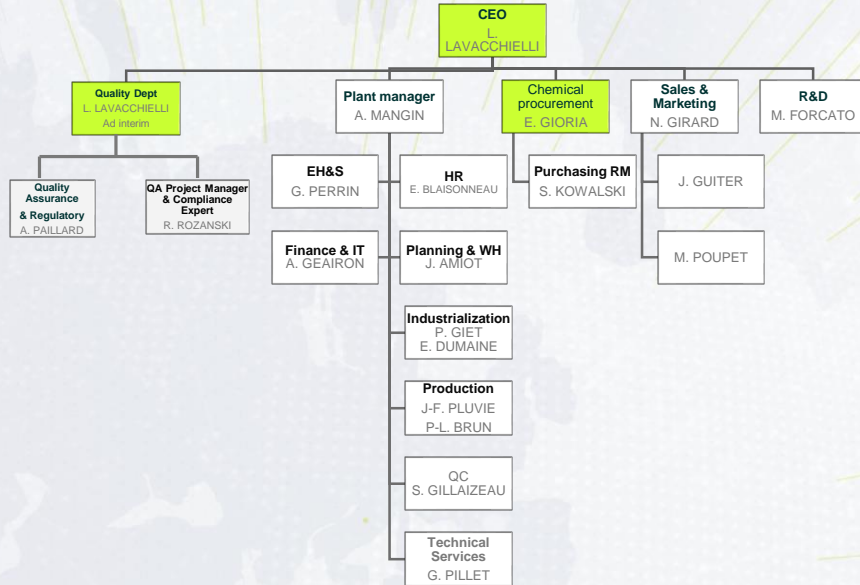


# Zach: IN FEW WORDS

- REVENUES (2018): **33 MM€**
- HEADCOUNT (2018): **177** people
- CAPEX (2017): **5 MM€**
  - Filter-dryer of 4m<sup>2</sup> in Hastelloy in a new extension building
  - Pin-Mill
  - New HPAPI Lab
  - A Lasentech probe
- CAPEX (2018): **2,7 MM€**
  - Warehouse  
(Temperature Monitoring, bar code stock management)
  - R&D Lab revamping
  - Operational investments



# Zach: ORGANIZATION



## 4 SHIFTS FOR PRODUCTION

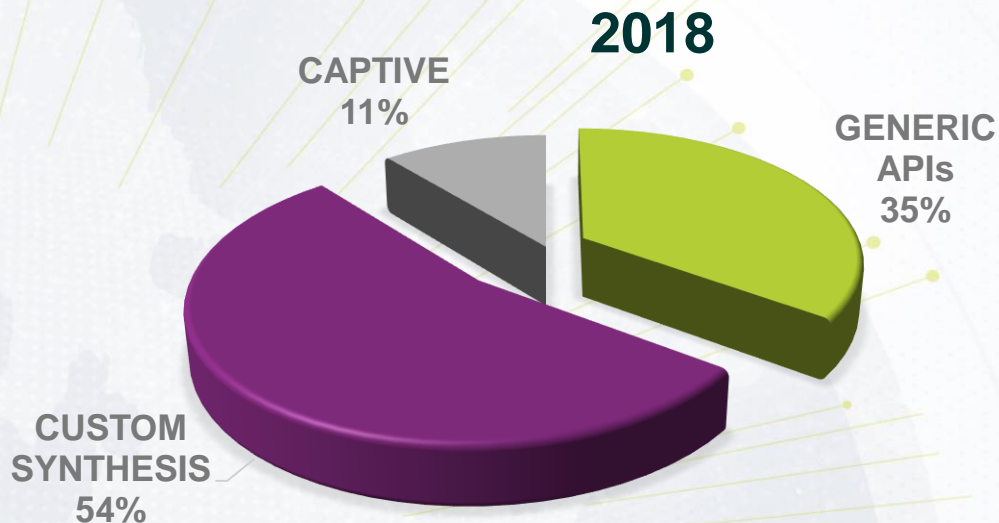
24 hours/day, 6 days/week

can be expanded to shifts to adapt on the demand

## 177 EMPLOYEES

- Production 68
- Warehouse/scheduling 11
- Technical service 22
- Analytical Department 31
- QA/RA 8
- EHS 4
- R&D 18
- Administration 15

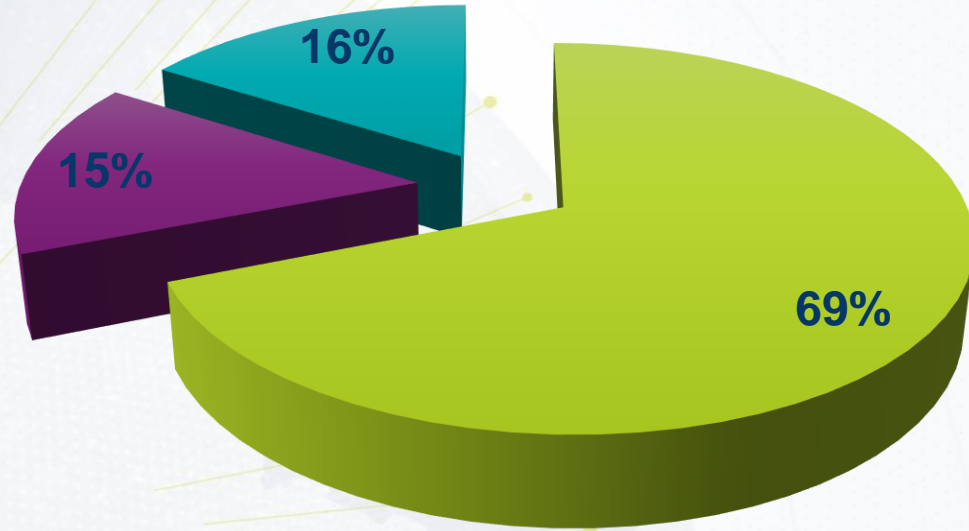
# Our 3 Legs Business Model



**Plan is to grow the custom manufacturing activity together with the captive business**

# Pedigree of Our Products

- **19 APIs**
  - 14 commercial stage
  - 5 under development
- **6-9 Intermediates**
  - RSM or GMP stages
- **8 EXCIPIENTS**  
Mainly for injectable use



■ APIs ■ RSM ■ EXCIPIENTS



# QA: HIGH QUALITY STANDARDS

## FDA

- Last Inspection in 10/2018
- 1 Form 483 (2 observations)

## ANSM

- Local Authorities
- 2017

## PMDA


- Japanese Authorities
- 2006+ Regular Paper Inspection

## KOREAN FDA

- 2003 & 2011

## CUSTOMER AUDITS

10 to 15 Audit per Year



**KILOLAB  
PILOT PLANT  
PRODUCTION CAPACITY  
FINISHING UNIT**

# Our Kilolab Plant

- **cGMP KILOLAB** to support early-phase clinical studies
- **2 REACTION UNITS** equipped with:
  - 15L Glass lined reactor working at  $-90^{\circ}\text{C}$  to  $160^{\circ}\text{C}$
  - 30L Glass lined reactor working at  $-40^{\circ}\text{C}$  to  $160^{\circ}\text{C}$
  - 1 GL filter-dryer of 0,07 m<sup>2</sup>





# Our Pilot Plant

- 11 reactors with a total capacity of **5100 L**
- 5 glass lined reactors (100 to 600 L)
- 6 stainless steel reactors (50 to 1,000 L)
- **CRYOGENIC** unit stainless steel (70L)
- Temperature range (from  $-80^{\circ}\text{C}$  to  $+150^{\circ}\text{C}$ )
- **2 HYDROGENATION** reactors (400 L & 1000 L, 5 bar)
- 3 filter dryers (0.2 to 0.7 m<sup>2</sup>), 2 in clean rooms
- **Wiped film evaporator**





# Production Capacity

Capacities	Glass-lined - Coated	SS	Notes
<b>Reactors</b>			
1000 to 2000 L	1	3	1 cryogenic (-90°C)
2000 to 3000 L	4	2	
3000 to 4000 L	3	4	3 autoclaves (up to 12 bar)
4000 to 6000 L	0	1	
6000 to 8000 L	4	0	
8000 to 10000 L	1	1	
<b>Isolation Equipments</b>			
Filter-dryer 2500		1	
Filter-dryer 3000		4	
Filter-dryer 4000		1	ISO 8
Centrifuge 1100	1		ISO 8
Centrifuge 1300	1		
Press-filter		2	
Wiped Film Evaporator		1	

# Finishing Unit

- Clean rooms dedicated to drying, particle size reduction and packaging of API's
- ISO 8 clean rooms & ISO7 laminar flow
- On site production of purified and Low Pyrogen water
- **11 Dryers:**
  - Filter dryers
  - GL tumble dryer
  - S.S. pan dryer
- **2 Blenders**
- **3 Hammer Mills (1 blanketed with N2)**  
**1 Pin Mill / 1 Micronizer**
- **2 Spray Dryers - Ultrafiltration & Nanofiltration Units**
- **1 Freeze Dryer (bulk)**





**R&D**

# R&D Team

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# R&D Team

## 18 EMPLOYEES

10 Process Chemistry (PC)

3 Project man. (PM)

2 Process Safety (PS)

6 Analytical Development (AD)

## 10 projects/year

**R&D  
MNGR**

**Assistant  
0.5 FTE**

	R&D	PC	PS	AD
HC	18	10	2	6
FTE	17.5	10	2	5.5
EDU	4 PhD	4		
	1 Msc			1
	13 Bac+2	6	2	5

**PC/PM  
3FTE**

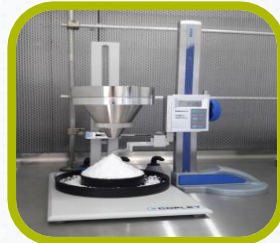
**PC/PM  
2 FTE**

**PC  
2 FTE**

**PC  
2 FTE**

**PS  
2FTE**

**AD  
5,5 FTE**





## **R&D Capabilities:**

- **PROCESS CHEMISTRY LABS**
- **PROCESS SAFETY LAB**
- **ANALYTICAL LABS**

# Facilities, Capabilities, Utilities

## PROCESS CHEMISTRY

- **Process chemistry labs**  
(100 ml – 10 lt glass reactors)
- **Ozonolysis lab**  
(batch and continuous flow)
- **Hydrogenation lab**  
(screening and preparations)
- **Kilo-lab**  
(15/30 lt glass reactors; - 80°- 160°C)
- **HP API Lab**  
(OEB5, OEL > 0.1  $\mu\text{g}/\text{m}^3$ )





# Facilities, Capabilities, Utilities

## PURIFICATION / SEPARATION

- ❑ **WFE**  
(Wiped Film Evaporation)
- ❑ Automated **flash chromatography**  
(Biotage Isolera®)



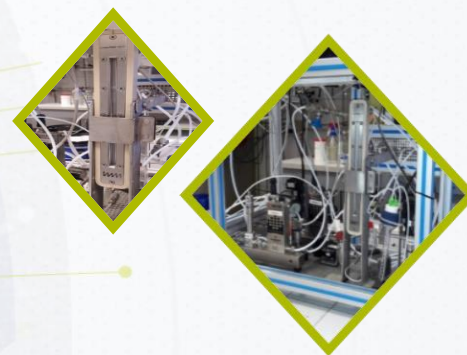
## HYDROGENATION

- ❑ 3 working cells, low/high P 100-2000 ml reactors
- ❑ 1 cell parallel screening system (**Argonaut Endeavor**)



## OZONOLYSIS

- ❑ Ozonizers:
  - **Ozonia CFS1** (O<sub>2</sub> feed, 12% O<sub>3</sub>)
  - **Ozonia CFS3** (air feed, up to 5% O<sub>3</sub>)
- ❑ **IMM®FFMR**  
(Lab scale: 10 g/hr, MLab: 100 g/hr)





# Facilities, Capabilities, Utilities

## PROCESS SAFETY LAB

- Mid-High temp **RC1** (MT)
- Low temp **RC1** (HEL)
- **DSC** (TA instruments)
- **TGA** (TA instruments)
- HEL Phitec II **ARC**



# Facilities, Capabilities, Utilities

## ROUTINE ANALYSIS

- 8 HPLC
  - (HPLC: UV/CAD/RID)
  - (UPLC: UV/CAD/ELSD)
- 3 GC (HP)
- 1 HS-GC
- Titration, KF systems



## PAT

- FTIR probe (lab/pilot/industrial applications)
- RAMAN probes (lab batch, MR and ATEX)
- FBRM probe (ATEX)



## STRUCTURAL CHARACTERIZATION

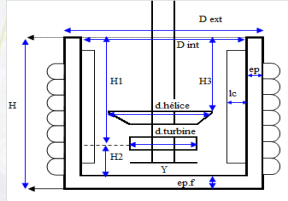
- 1 HPLC-MS (ESI-APCI/Ion Trap)
- 1 GC-MS (EI-CI/quadrupole)
- 1 Bruker 400 MHz NMR spectrometer



# Solid state engineering and characterization

## PARTICLE ENGINEERING

- Customized glass reactors (scale-down of industrial reactors)

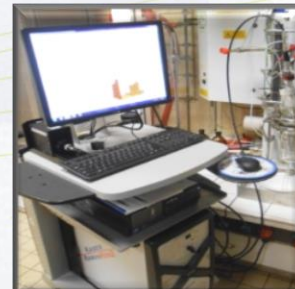


- GFD® Lab-scale filter-dryer and centrifuge
- ATEX FBRM® probe (Mettler Toledo)
- Spray-dryer Buchi B-290 A (aq./org. slns)



## POWDER CHARACTERIZATION

- RAMAN probe for powders
- DSC (TA instruments)
- Access to XRPD, SS-NMR, SEM (Angers, Rouen)
- Malvern/Sympatec for PSD (Zach Avrillé QC)
- Powder flowability measurement (Copley):
  - Flodex
  - Shear cell
  - Static angle of repose





# Facilities, Capabilities, Utilities

**NOT ACCEPTED**

**CONFINEMENT**

**Ordinary lab PPE**

**Zach SOP PQHSE1001**



## HP API LAB

- HPAPI LAB1: 2 working hoods, 1 washing hood
- HPAPI LAB2: 1 flexible working hood designed to host spray-dryer
- Separate airlock entry for users and materials
- Trained personnel
- Tyvek suite
- Specific samples handling and labeling
- Cleaning and decontamination SOPs
- Waste handling
- Performance down to **OEL = 0.1 µg/m³ (OEB5)**

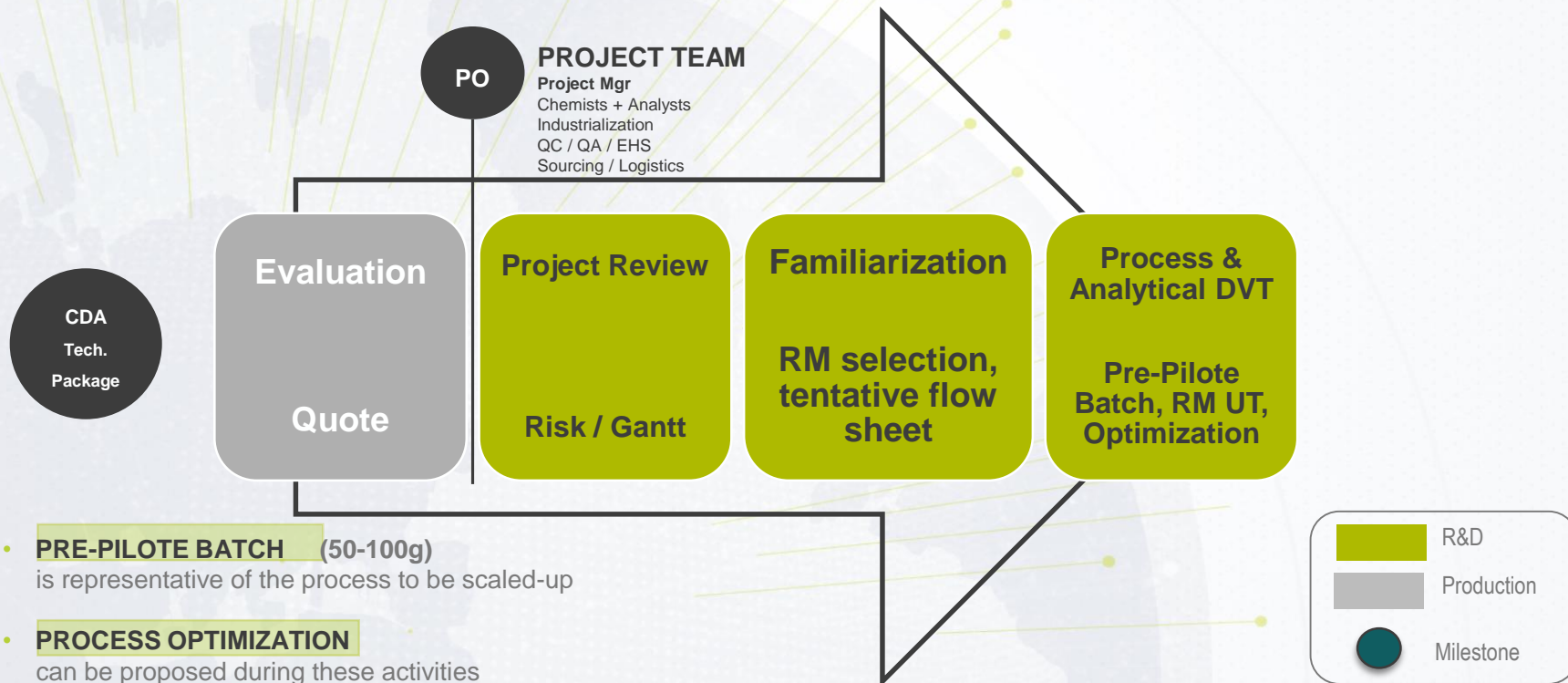




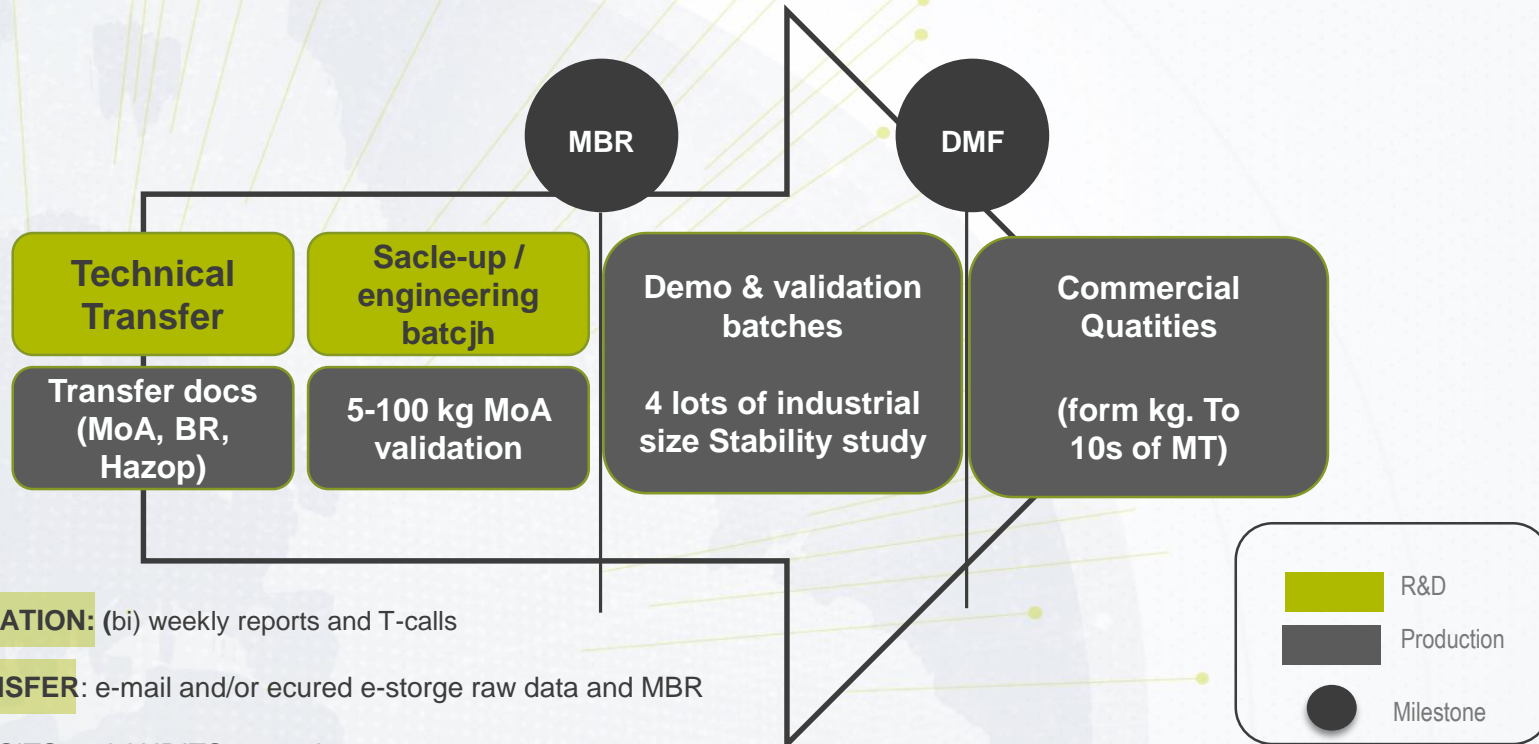


# Project Management

# Project management 1/2



# Project management 2/2





## Zach:

- KNOW-HOW
- CORE TECHNOLOGIES



# Core Chemistry and Technologies 1/2

			BATCH SIZE	QTY/Y
<b>C=C, C=O, C-O REDUCTION</b>	<b>Catalytic H<sub>2</sub></b>	Pd/C, Pt/C, PtO <sub>2</sub> , Ir/C	100s kg	10s MT
	<b>Asymmetric H<sub>2</sub></b>	RhL*, RuL*	10s kg	10s kg
	<b>Hydride reduction</b>	LAH (powdr, sln), DIBAL (sln), TtBuO-LAH (sln), NaBH <sub>4</sub>	10s-100s kg	1-100 MT
	<b>C=O reduction</b>	BH <sub>3</sub> /THF	100s kg	1s MT
	<b>CBS reduction</b>	(R)-DPP+BH <sub>3</sub> /THF	10s kg	1s MT
	<b>C-O cleavage</b>	TES, TIBAL (pure, sln)	100s kg	1s MT
<b>OXYDATION</b>	<b>Ozonolysis</b>	Batch SS 50/1500 lt, cryo	100s kg	1s MT
	<b>Asymmetric oxdn</b>	Sharpless, -15°C	100s kg	1s MT
	<b>Periodate, Permanganate</b>	NaIO <sub>4</sub> , 75°C; KMnO <sub>4</sub> , 25°C	10s kg	100s kg
<b>METALATION, ALKYLATION, C-C</b>	<b>Lithiations</b>	RLi, LDA, Li in NH <sub>3(l)</sub>	100s kg	Up to 100 MT
	<b>DMS, DES alkylation</b>	r.t., heat	1 MT	Up to 100 MT
	<b>Eschweiler-Clarke</b>	HCOOH/HCHO	1 MT	Up to 100 MT
	<b>Cyanation</b>	KCN, NaCN	100s kg	10s MT
	<b>Grignard</b>	Mg/ether, AlkMgCl/ether; VinylMgCl, -80°C	100s kg	1-5 MT
	<b>Pd-cat coupling</b>	Heck, Suzuki	100s kg	1 MT

# Core Chemistry and Technologies 2/2

			BATCH SIZE	QTY/Y
PRODUCT CLASS	Steroids (8 APIs/reg. interm.)	OEL $\geq 1\mu\text{g}/\text{m}^3$	100s kg	1-10 MT
	Excipients (8 specialties)	$\beta$ , $\gamma$ -CD based specialties	100s kg	10s MT
PURIFICATION TECHNIQUES	Distillation	Rectification column, 11 theoretical plates, 170°C	100s kg	10s MT
	WFE	Pilot: 1-10 kg/hr; <5 mbar; industrial: 5-50 kg/hr; 1 mbar	100s kg	10s MT
	Crystallization/Resolution		100s kg	100s kg
	Ultrafiltration	Cut off $\approx 1000$ Da	100s kg	10s MT
	Nanofiltration	Cut off $\approx 300$ Da	100s kg	<10MT
	Electrodialysis		10s kg	100s kg
SS ENGINEERING, PHYSICAL TREATMENT, DRYING	Spherical agglomeration	Particle downsizing technology	10s kg	100s kg
	Milling, Micronization	Hammermill, pinmill, jet mill	10s kg	10s MT
	Spray-drying	PSD1 (aq/org sln), PSD2 (aq sln)...(PSD4: aq/org sln)	1-500 kg	10s MT
	Freeze-drying	Bulk: 50 m <sup>2</sup>	100s kg	1s MT

# Spray-Dryer (PSD1)

- ❑ A new Spray dryer for **SOLVENT SOLUTIONS**:
  - Drying gas (N2) rate 100 kg/h
  - Inlet temperature  $\leq 250$  °C
  - Spray: bi-fluid nozzle
  - ATEX design
  
- ❑ **CAPACITY IN OPERATION**:
  - Flow of SD product : 1 – 3 kg/h
  - Annual capacity : > **2 000 kg**
  
- ❑ **ENVIRONMENT** : handling of products **OEL  $\geq 1\mu\text{g}/\text{m}^3$**
  
- ❑ **FEEDING**:
  - Disposable containment to load solid active RM
  - Fed with **low pyrogen water production unit**
  
- ❑ **FINISHING CONDITIONS**:
  - State of the art containment for packaging
  - **ISO 8** room
  - Possible option : sieving



# Spray-Dryer (PSD2)



- Drying gas (air) rate: 360 kg/h
- Inlet temperature  $\leq 250$  °C
- Spray: High Pressure nozzle / bi fluid nozzle
- Sanitary design (+ steam decontamination)

## □ **CAPACITY IN OPERATION:**

- FLOW of SD product: 7 to 10 kg/h
- Annual capacity :**20MT**

## □ **ENVIRONMENT** handling of products **OEL $\geq 1$ $\mu\text{g}/\text{m}^3$**

## □ **FEEDING**

- Disposable containment to load solid active RM
- Fed with **low pyrogen water** produced on-site

## □ **FINISHING CONDITIONS**

- State of the art containment for packaging
- ISO 7 laminar flow
- Possible option : sieving



# Hydride Reduction

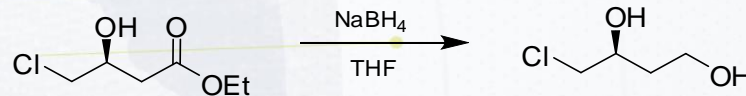
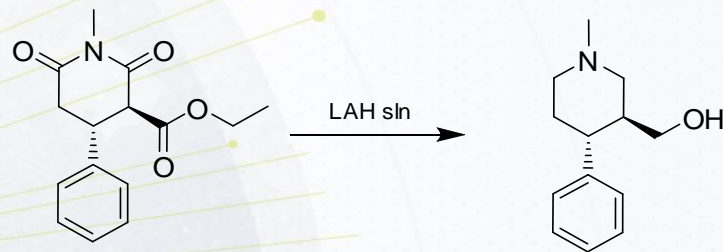
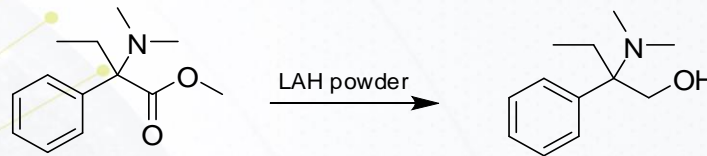
- 30 YEARS EXPERIENCE**

on tens of tons scale

- Handling of both powder and in solution

LAH on several tens of tons scale

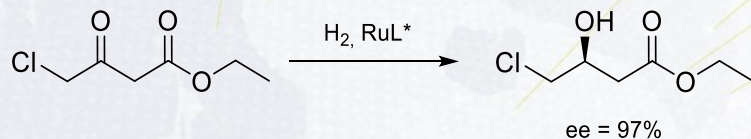
Ester to primary alcohol transformation:



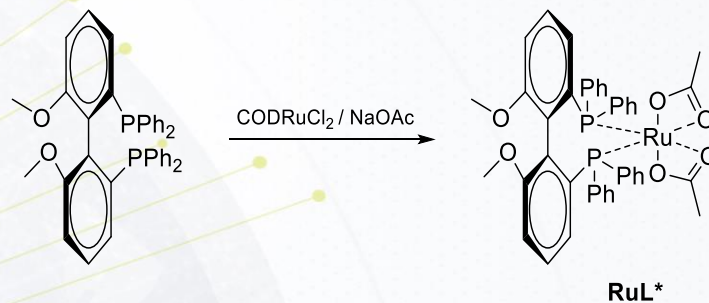
# Catalytic asymmetric hydrogenation

## Hydrogenation of C=O and C=C bonds

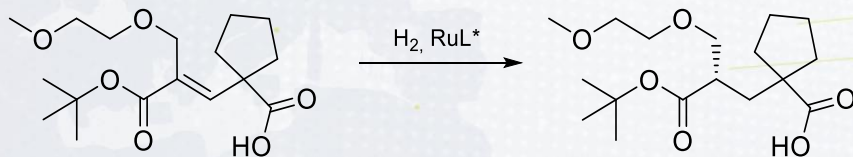
### Case study 1:



### Process for catalyst preparation

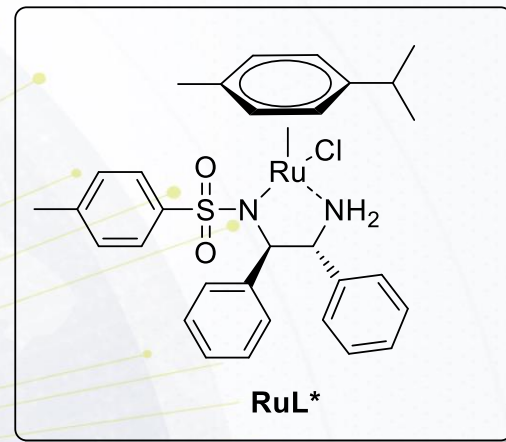
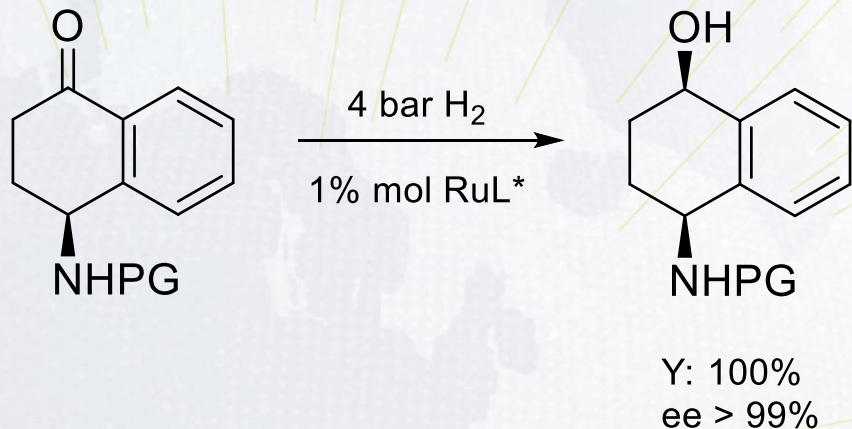


### Case study 2: Synthesis of Candoxatril, OPRD 2001, 5, 438



# Catalytic Asymmetric Hydrogenation

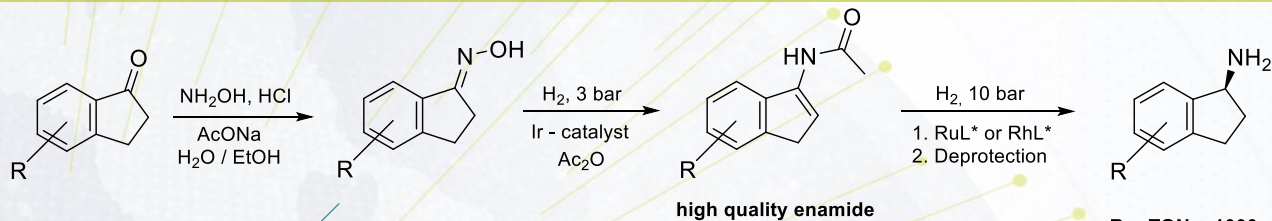
**Asymmetric C=O hydrogenation:**



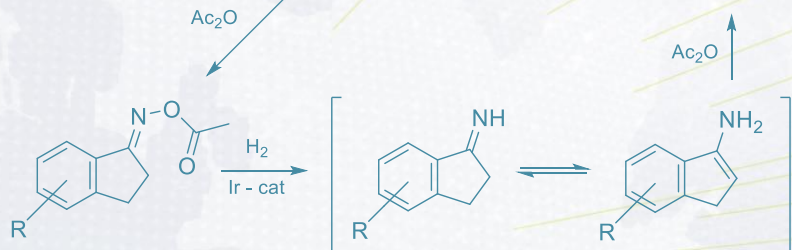
**Chiral Ru catalyst commercially available  
2 × 40 kg pilot batches**

# Proprietary technology to chiral amines

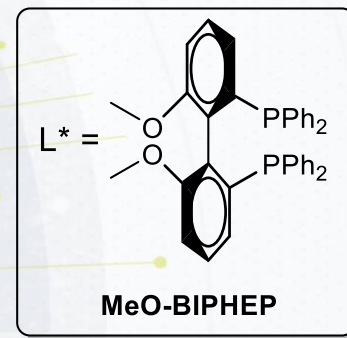
Powerful catalytic technology to convert a ketone into the corresponding enamide, via the oxime, based on catalytic asymmetric hydrogenation



Ru: TON = 1000  
Rh: TON = 10000



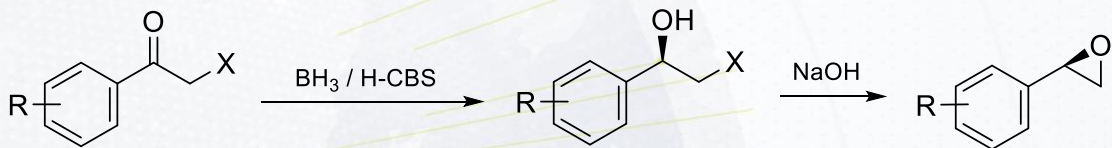
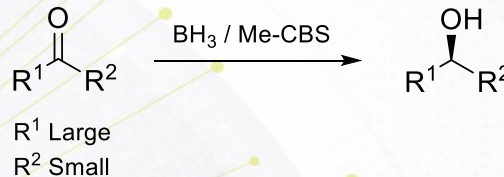
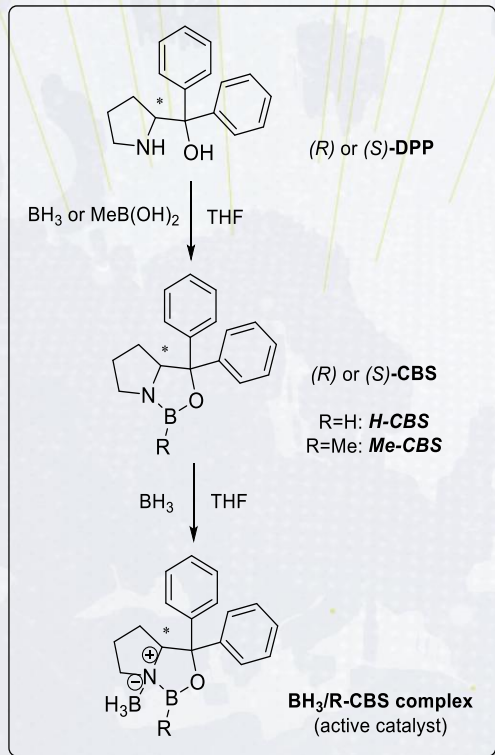
**Patent granted in 2009 (EP 1,720,823)**  
**Several pilot campaigns up to 250 kg**





# CBS asymmetric C=O reduction

Well-known technology for the asymmetric reduction of ketones



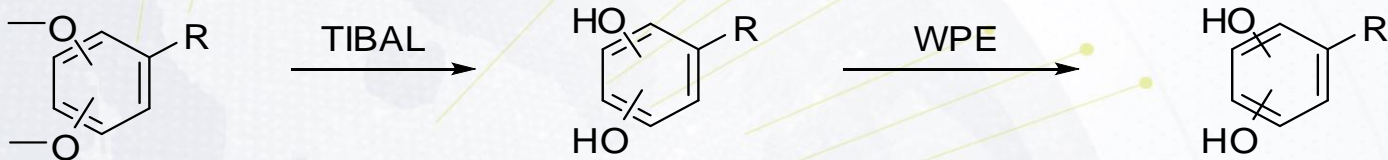
X = Br, Cl  
R = Halogen, Alkoxy, etc.

(both enantiomers)

- *R*- and/or *S*-Diphenyl prolinol (*R/S*-DPP) manufactured in-house
- Proprietary process for Me-CBS and for in-situ  $\text{BH}_3$  complex generation (US 7,586,015)

# TIBAL-promoted demethylation

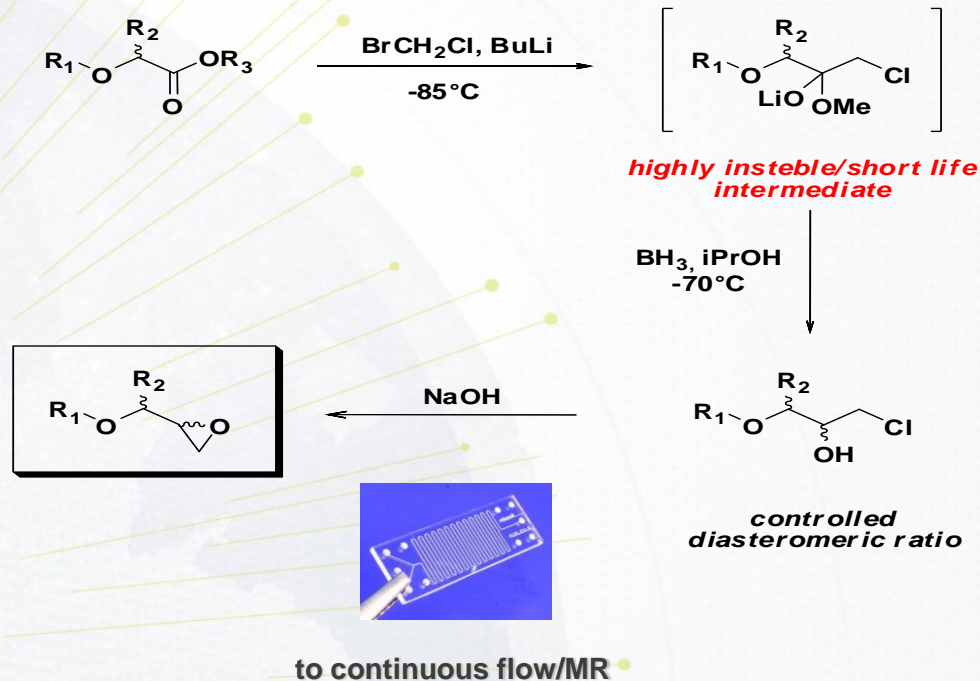
Cost cutting new process  
using pure TIBAL



**TIBAL: TriisoButyl Aluminium Hydride**  
**Industrial quantities (1 MT of TIBAL per batch)**

# Cryogenic Lithiation (ALKLI/BH<sub>3</sub> REDUCTION)

- Patented chemistry
- industrial manufactures on MT scale performed (1500L cryogenic reactor)
- continuous flow process in micro-reactors at lab scale (under development)

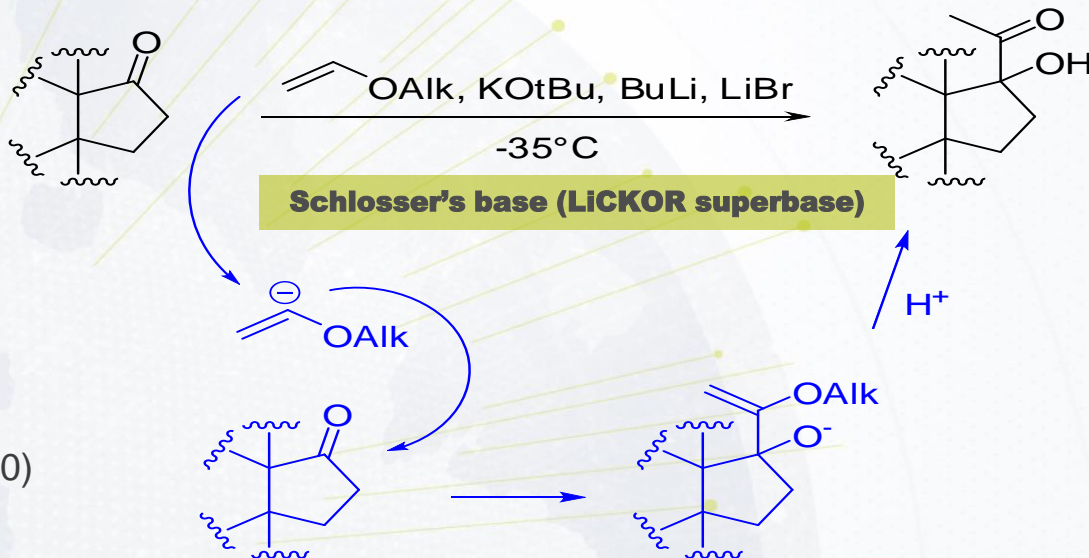


# Cryogenic Lithiation (Schlosser base)

## Synthesis of an API (under development)

- Schlosser superbases technology  
(*n*-BuLi + *t*-BuOK)

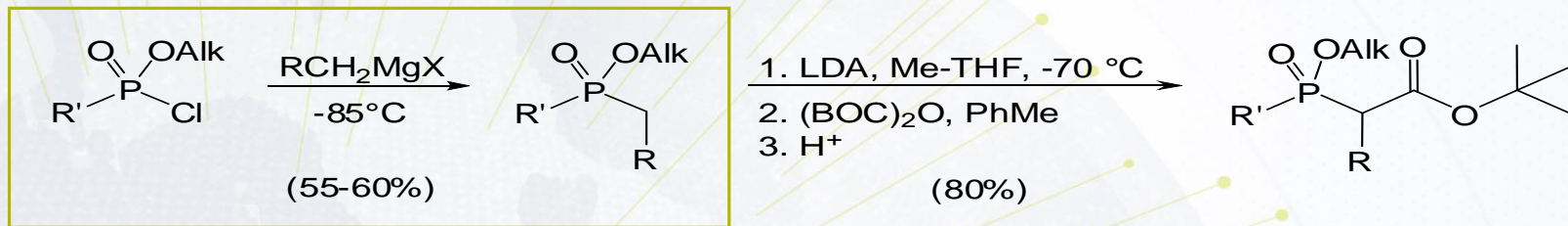
- Validated process for the manufacture of a **steroidal API**  
(about 300 kg, batch size : 70)





# Grignard + cryogenic lithiation (LDA)

## Synthesis of a RSM



**Yield x 2** wrt to entry process upon use of cryogenic conditions

- Telescoping Grignard alkylation and LDA-promoted carbonylation
- Handling of  $(\text{BOC})_2\text{O}$  as a concentrated toluene solution
- Batch size 5 – 25 kg

# Ozonolysis – BATCH + CONTINUOUS FLOW IN FFMR

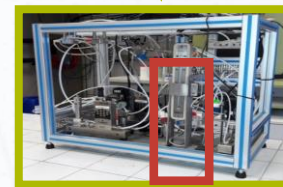
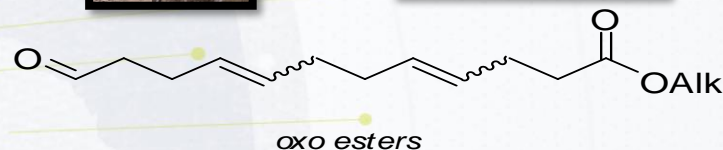
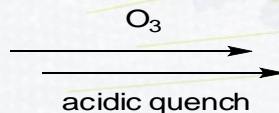
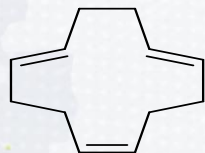
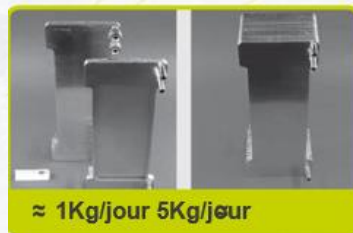
## ❑ OZONOLYSIS TODAY IN BATCH:

- 50L SS reactor (**Pilot**)
- 1500L SS reactor (**Industrial**)

## ❑ FF-Microreactors (PP)

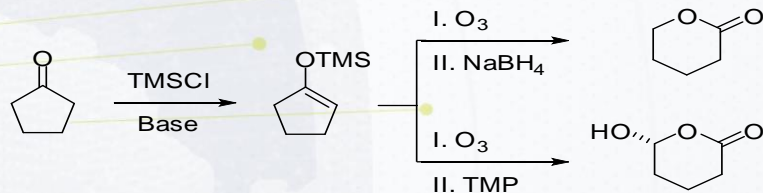
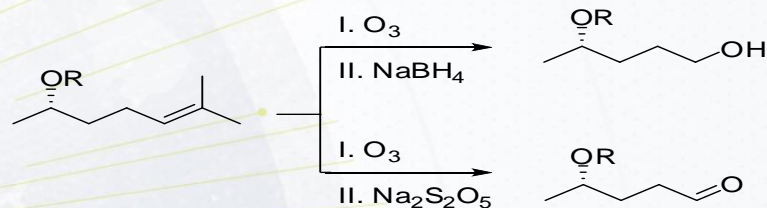
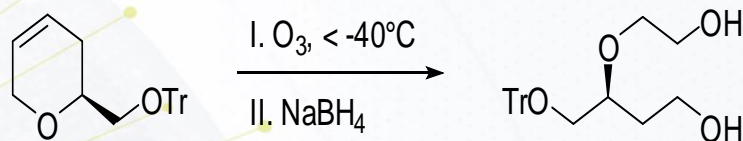
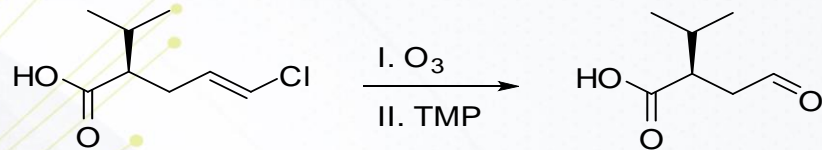
- ↓ Single product train
- ↑ Safety
- ↑ Higher Temperatures
- ↑ Productivity
- ↑ Chemoselectivity

## ❑ Case study



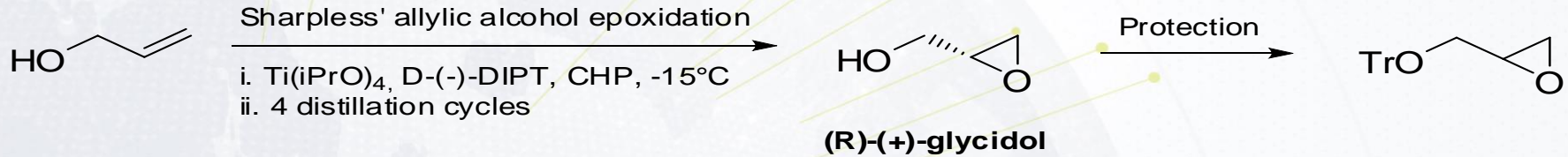
# Ozonolysis - EXAMPLES

- **LOW TEMPERATURE PROCESS**  
applicable to hundred of kg scale
- Tunable end product by choice of reductive quench:
  - ozonide to alcohol ( $\text{NaBH}_4$ )
  - ozonide to aldehyde ( $\text{H}_2$  Metal/C,  $(\text{MeO})_3\text{P}$ ,  $\text{Na}_2\text{S}_2\text{O}_5$ )
- **>10 years EXPERIENCE** in development of safe scalable in-batch processes
- **2015:** implementation of continuous ozonolysis in FFMR



# Sharpless asymmetric epoxydation

## Application of the Sharpless' asymmetric epoxydation protocol to (R)-(+)-glycidol synthesis

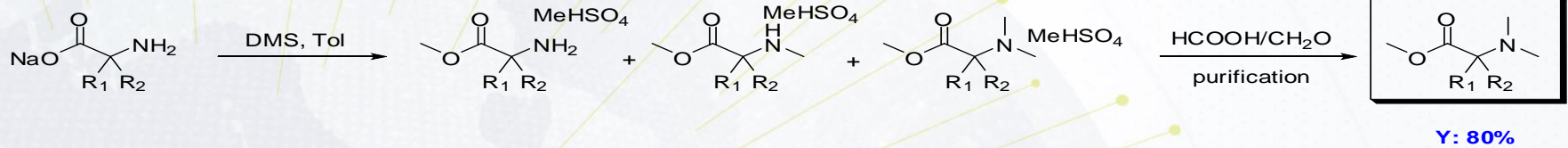


**Industrial manufacture on multi-tons scale**  
**Management of safety risks due to polymerization**  
**Complex purification through distillation**

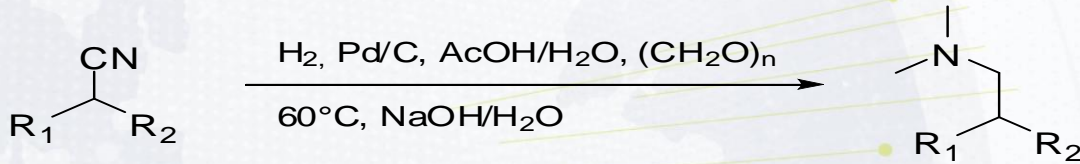


# DMS, Eschweiler-Clarke methylation

## Synthesis of a commercial API through a dimethylated C $\alpha$ -tetrasubstituted AA



## Synthesis of a custom API:

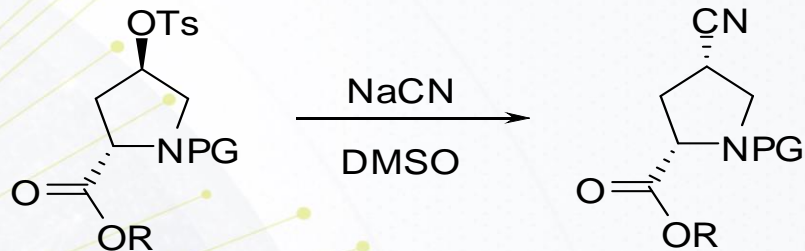


**Manufacture of several tens of Tons per year**

# Cyanation

- ACETONCYANHYDRINE/NAH PROCESS**

replaced by direct NaCN cyanation



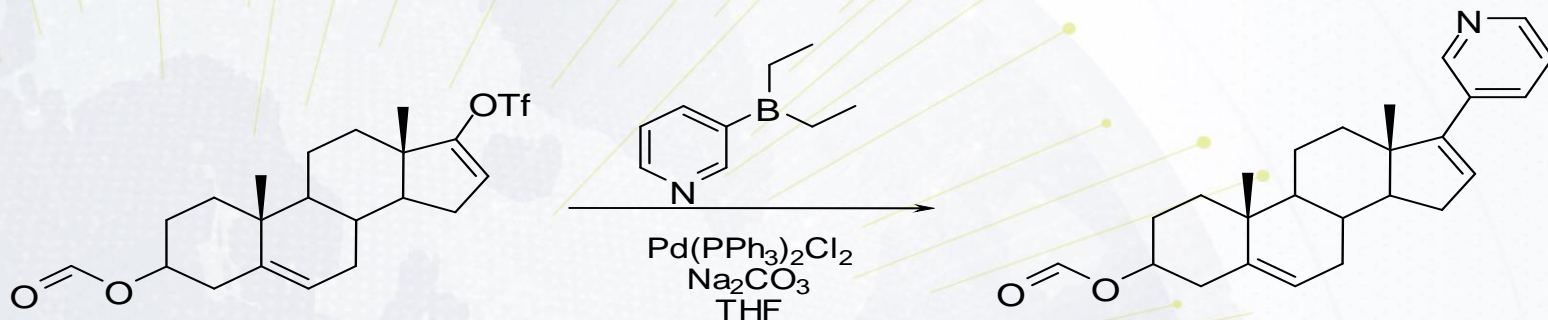
- LAH REDUCTION**

followed by KCN cyanation



# Suzuki coupling

**Synthesis of a GMP intermediate  
for a generic API**



**PAT through FTIR probe**  
**Validated generic API (5 synthetic steps)**  
**Batch size: 120 kg, ≈ 1 MT manufactured**

# PAT at industrial scale

## FITR

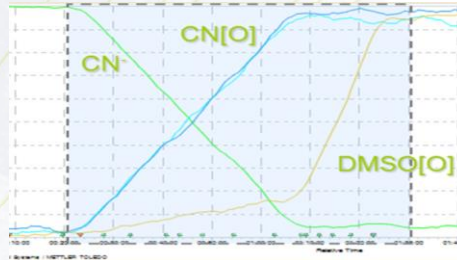
EoR IPC for the formation of a poorly stable intermediate – traditional IPC sampling replaced by FTIR PAT



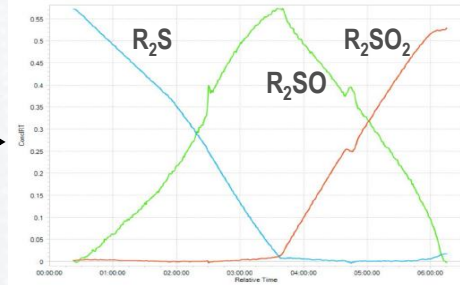
## RAMAN

CN<sup>-</sup> streams  
(DMSO/H<sub>2</sub>O)

NaClO



R<sub>2</sub>S  
Aq. H<sub>2</sub>O<sub>2</sub>



## FBRM

Real-time monitoring crystal growth/ripening in crystallization processes

