ROADMAP TO SCALE-UP SUCCESS: FROM BENCH TO MARKET

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medichem

EUROPEAN COMPANY LEADING IN GENERIC APIs & FDFs

With over 40 years of experience. A solid global client base and unparalleled FDA inspection record. Also, leading chlorhexidine manufacturer since 1985. Stable and profitable family-owned organization with 440 employees.

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Combino Pharm

96.000 m² OF MANUFACTURING SITES...

SPAIN CELRÀ

APIs and Chlorhexidine
(25.000 m²)

MALTA HAL FAR

APIs (8.800 m²) and oral finished dosage forms (6.600 m²)

CHINA ANHUI

Intermediates and Chlorhexidine
(55.300 m²)

FDA inspected since 1985 - No "Form 483" records in Celrà and Malta APIs plants
FDA inspection in our FDF Malta plant expected in 2017
Full respect for the environment at all our sites (ISO certified)

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Combino Pharm

INNOVATION FOCUSED

With large part of our resources (over 25%) devoted to R&D working in an extensive pipeline. Ready to grow in the FDF area after reorganizing and refocusing the business (historically more API minded).
Strategy based in looking into unique products with higher added value.

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Combino Pharm

MANUFACTURING CAPABILITIES & TECHNIQUES

API CAPACITY

SPAIN

Glass lined
60 m^3, 20 reactors
Stainless steel
70 m^3, 20 reactors
Tank farm
600 m^3

MALTA

Glass lined
60 m^3, 20 reactors
Stainless steel
70 m^3, 20 reactors
Tank farm
600 m^3

CHINA

Glass lined
76 m^3, 54 reactors
(155 m^3, 72 reactors
from 2016)
Tank farm
160 m^3

FDF CAPACITY

MALTA

Tablets
200,000,000 per year
Capsules
85,000,000 per year
Packaging
10,000,000 blister/year

EQUIPMENT

COMMON

Reactors
Centrifuges
Filter-dryers
Paddle-dryers
Pin mills
Conical mills
Micronizers

SPECIAL UNITS

Corning® Continuous Flow G4
Hydrogenator Biazzi® to 10 bars
Preparative HPLC i200mm
Micronizer from i50 to i300mm
Temp -80° C to +200° C

HPAPI CAPACITY

MALTA

Class 4: OEL down to 40 ng/m^3
Reactors: 2 x 15 lt
Nutsche Filter, Dryer, Mill and Micronizer

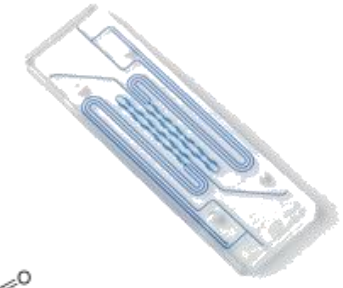
FLOWIDIZING PHARMA

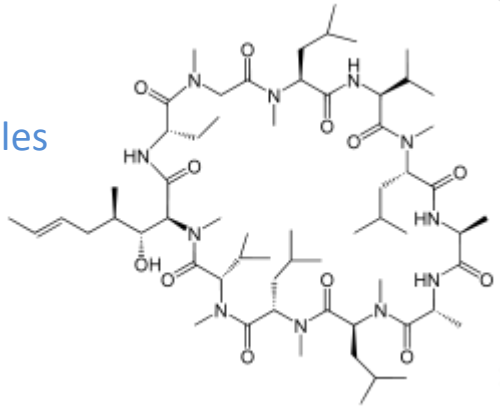
Pharmaceutical companies relies on multipurpose batch reactors

Same reactor for activation, coupling, neutralization, extraction, distillation **…**

However there is a growing interest on…

- Synthetize highly functionalized and chiral molecules
- Process intensification and cost reduction
- Achieve safer and greener processes
- Enable new technologies for a faster screening/optimization or even new reactivity





FLOWIDIZING PHARMA

uni-que medichem team products

…and flow chemistry has numerous advantages towards this end…

- Very efficient heat and mass transfer
- Easier impurities control (degradation/consecutive reactions)
- Scale-up effects minimized
- Faster process optimization
- Inline monitoring allows real time performance control

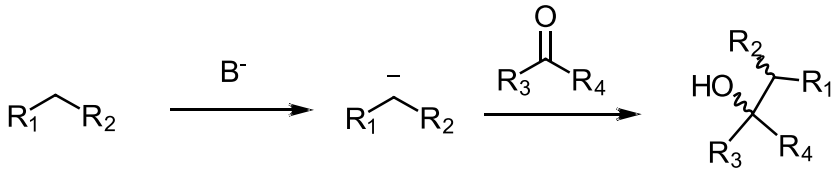
… opening the scope to…

- Highly energetic reactions (thermal safety issues)
- Reactions difficult to scale-up
- Reactions with hazardous/unstable intermediates

Identification of right candidates

- **Organometallic reaction**

  Fast and highly exothermic, cryogenic, unstable intermediates



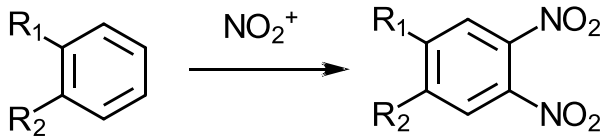
✓ Heat transfer

✓ Mixing

✓ Extreme reaction conditions

- **Nitration reaction**

  Hazardous reagents involved and risk of explosion

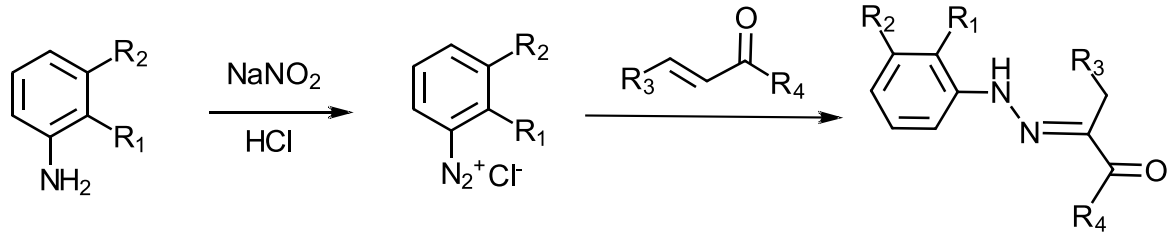


✓ Mixing

✓ Safety

- **Diazotization reaction**

  Precipitation of the N_2^+ salt and shock-sensitivity



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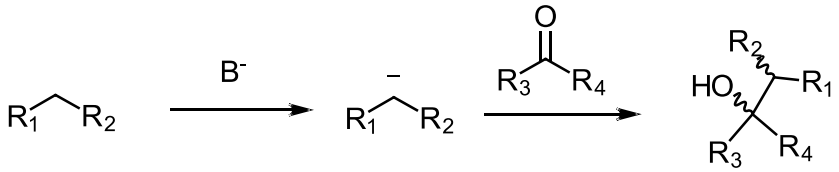

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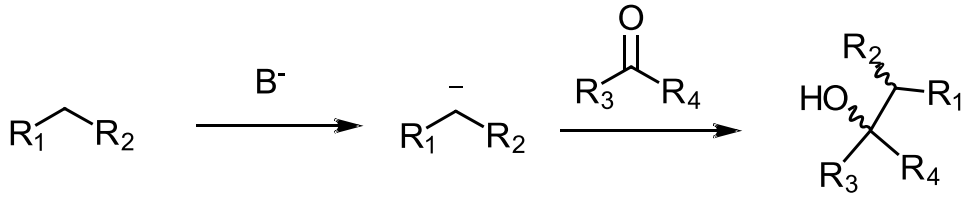
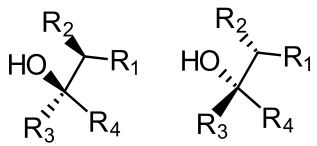
ORGANOMETALLIC reaction

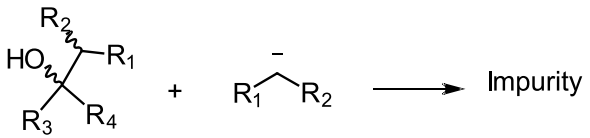


Batch reaction

- *Cryogenic reaction (-70 ºC)*
- *Poor yield (31%)*
- *Unstable intermediate*
- *Moisture and oxygen sensitive*
- *Impurities*



Diastereomeric pair

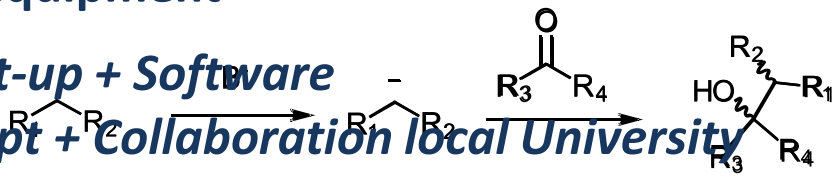


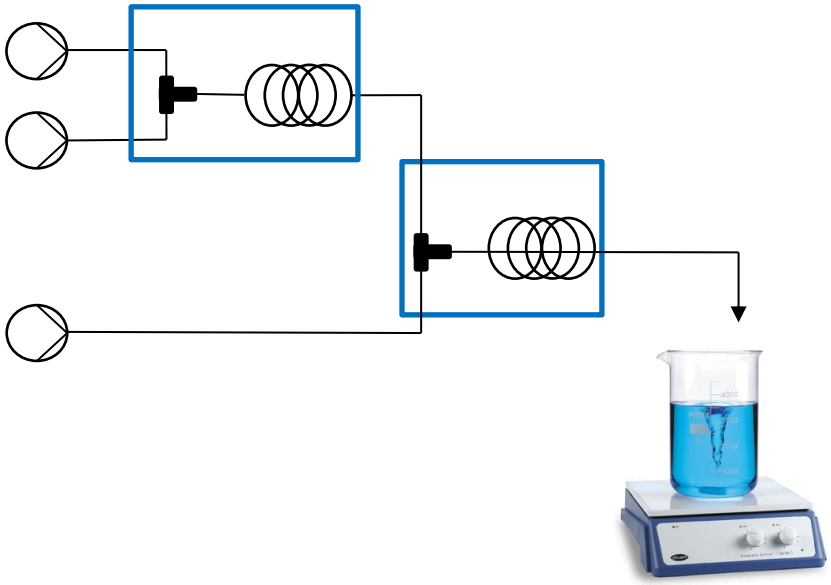
Consecutive reaction

ORGANOMETALLIC reaction

- **HOME-MADE lab equipment**

Home-made set-up + Software Engineering Dept + Collaboration local University



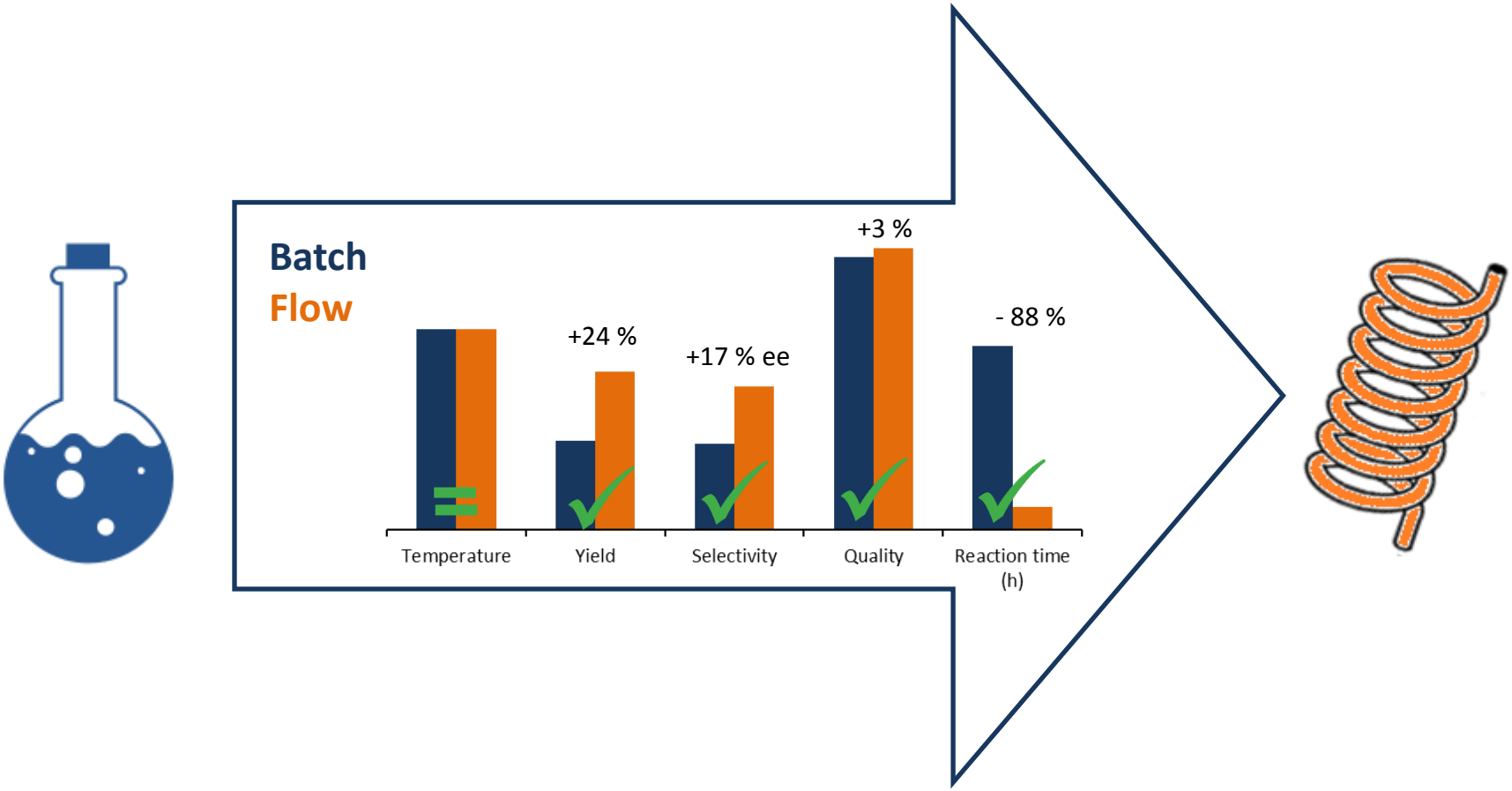


Schematic flow set-up

Picture of the lab set-up

ORGANOMETALLIC reaction

Comparison between batch and flow



ORGANOMETALLIC reaction

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But how to scale up a home-made flow system?

- Flow industrial equipment not available in-house
- To maintain heat exchange performance similar to lab scale was critical for successful scale-up
- We contacted CORNING, company with experience in the scale-up of flow processes
- 1 week feasibility studies at Medichem site

  G1 Corning reactor

  Scale-up factor of 3

Glass reactors: visual monitoring of reaction (color)

Scale-up with Corning Technology (Kilo-lab scale)

Technology transfer for scale-up

1/8” tubing

Corning Technology

Heart-shape profile (better mixing)
Jacketed reactors (better heat transfer)
Feed precooling

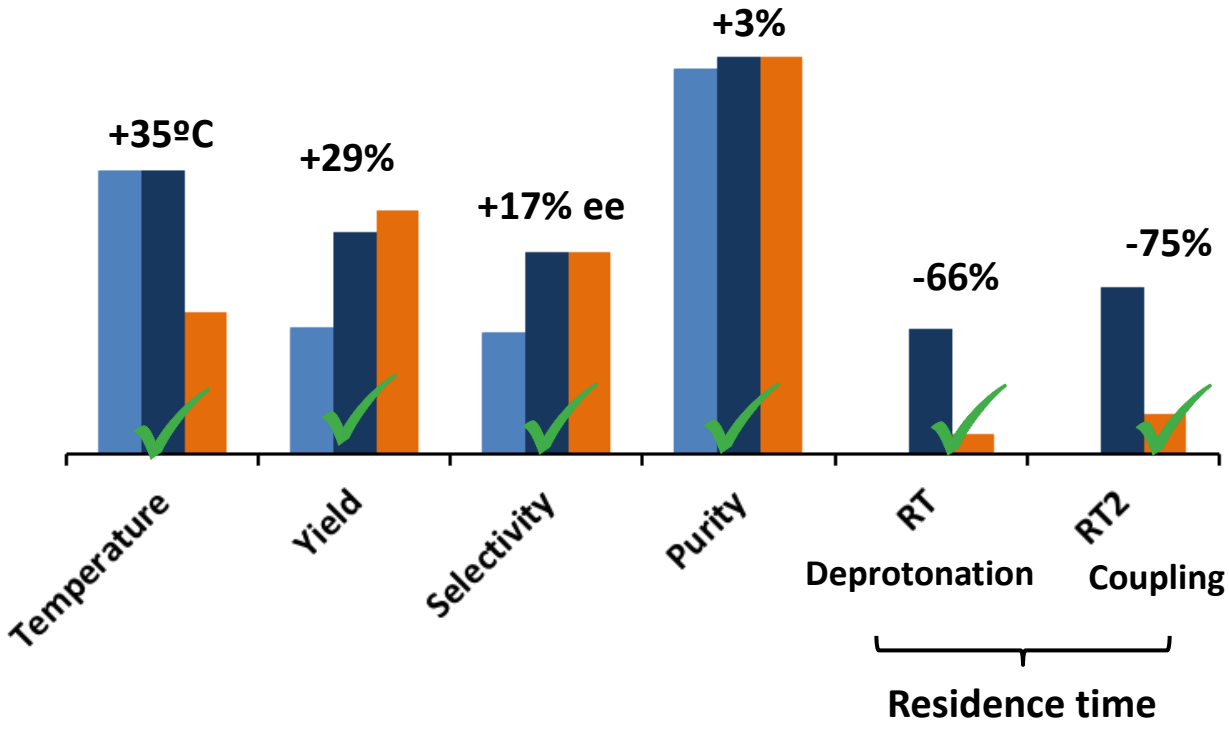
ORGANOMETALLIC reaction

Scale-up with Corning Technology (Kilo-lab scale)

Batch

Home-made system

Corning G1 Advanced-flow reactor



ORGANOMETALLIC reaction

- **Target: production of 3 pilot batches of intermediate**
- **Industrial equipment**

  G4 Corning reactor → Scale-up *factor of 30*

  3 automated dosing lines Atex Compliant (0-20 bar)

  Huber 620W (7,5 kW at - 40ºC)

ORGANOMETALLIC reaction

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  G4 Corning reactor → Scale-up *factor of 30*

  3 automated dosing lines Atex Compliant (0-20 bar)

  Huber 620W (7,5 kW at - 40ºC)

***Similar yield / impurity profile* as feasibility trials**

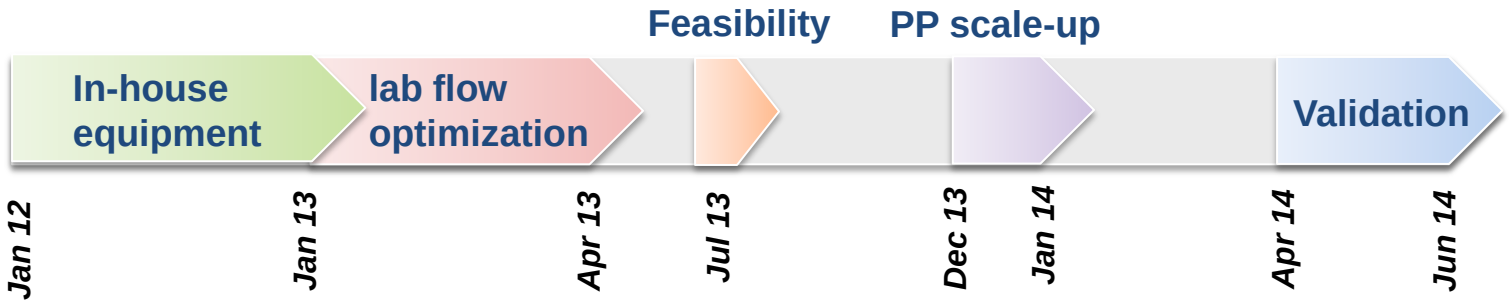
COGS reduction by 30-40 % vs sourced intermediate

Reduction of amount of raw materials and solvents

Return on investment: 1 year !

ORGANOMETALLIC reaction

Timeline of the project



Main goal accomplished: In-house intermediate → desired availability and quality

Main challenge faced: Pressure build-up each 2-3 h

Processing time 16 h with 5 min cleaning every 2 h

FLOWIDIZING PHARMA

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Identification of right candidates

- Organometallic reaction

  Fast and highly exothermic

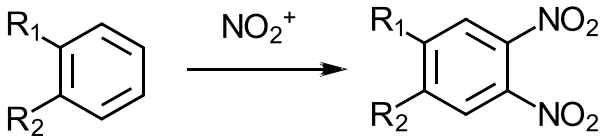
Heat transfer

Mixing

Extreme reaction conditions

- **Nitration reaction**

  Hazardous reagents involved and risk of explosion



Mixing

Safety

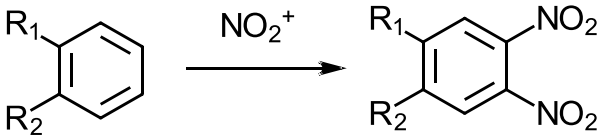
- Diazotization reaction

  Precipitation of the N_2^+ salt and shock-sensitivity

Safety

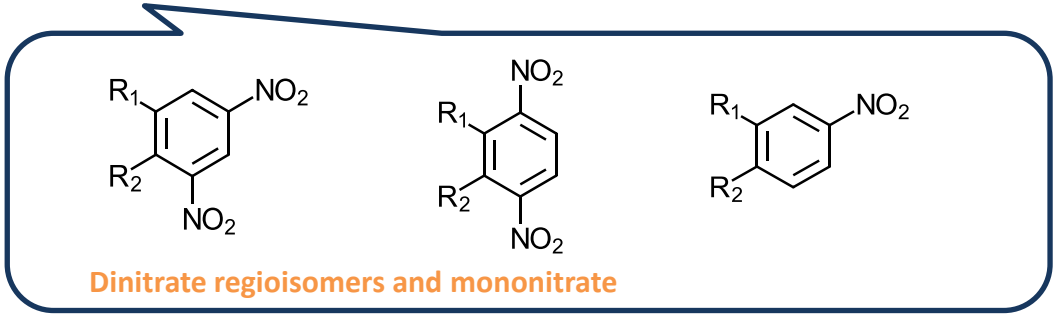
NITRATION reaction

Hazardous reagents involved and risk of explosion



Batch reaction

- *Time: Slow addition under controlled temperature + 16h reaction*
- *70 % yield*
- *Expensive catalyst*
- *Limited batch size (0.5 kg)*
- *Impurities*



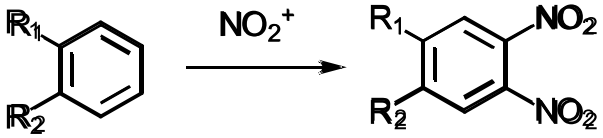
Dinitrate regioisomers and mononitrate

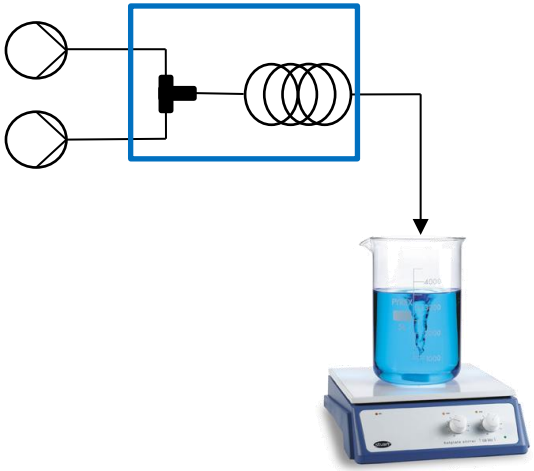
NITRATION reaction

- **HOME-MADE lab equipment**

Metal-free double piston pumps

PTFE pipes and glass vessels





Schematic flow set-up

Picture of the lab set-up

NITRATION reaction

- **HOME-MADE lab equipment**

  Metal-free double piston pumps
  PTFE pipes and glass vessels

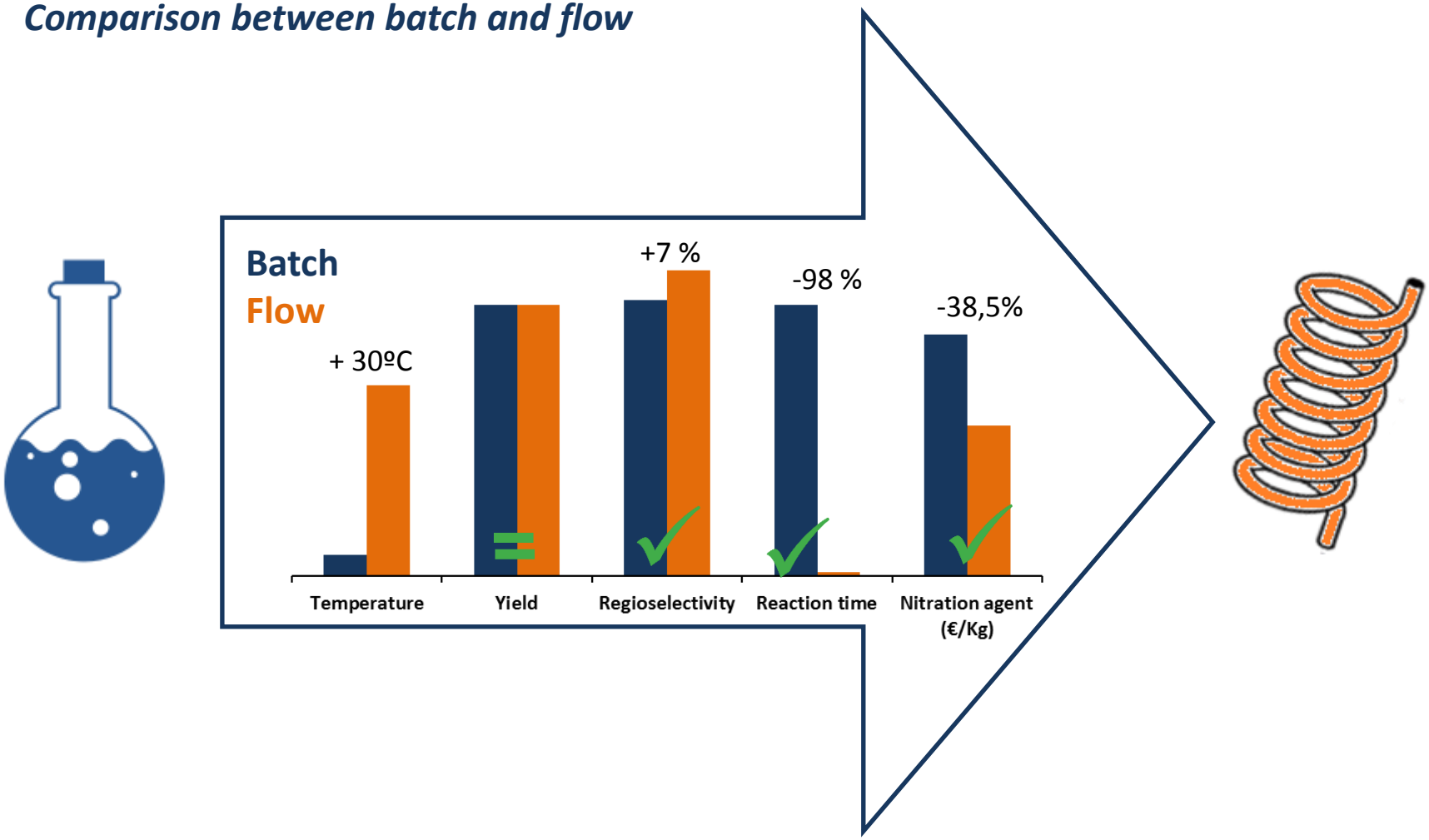
Simple pipe did not work due to poor mass transfer ✗

↓

Glass-beads packed bed was used to improve mixing ✓

NITRATION reaction

Comparison between batch and flow



NITRATION reaction

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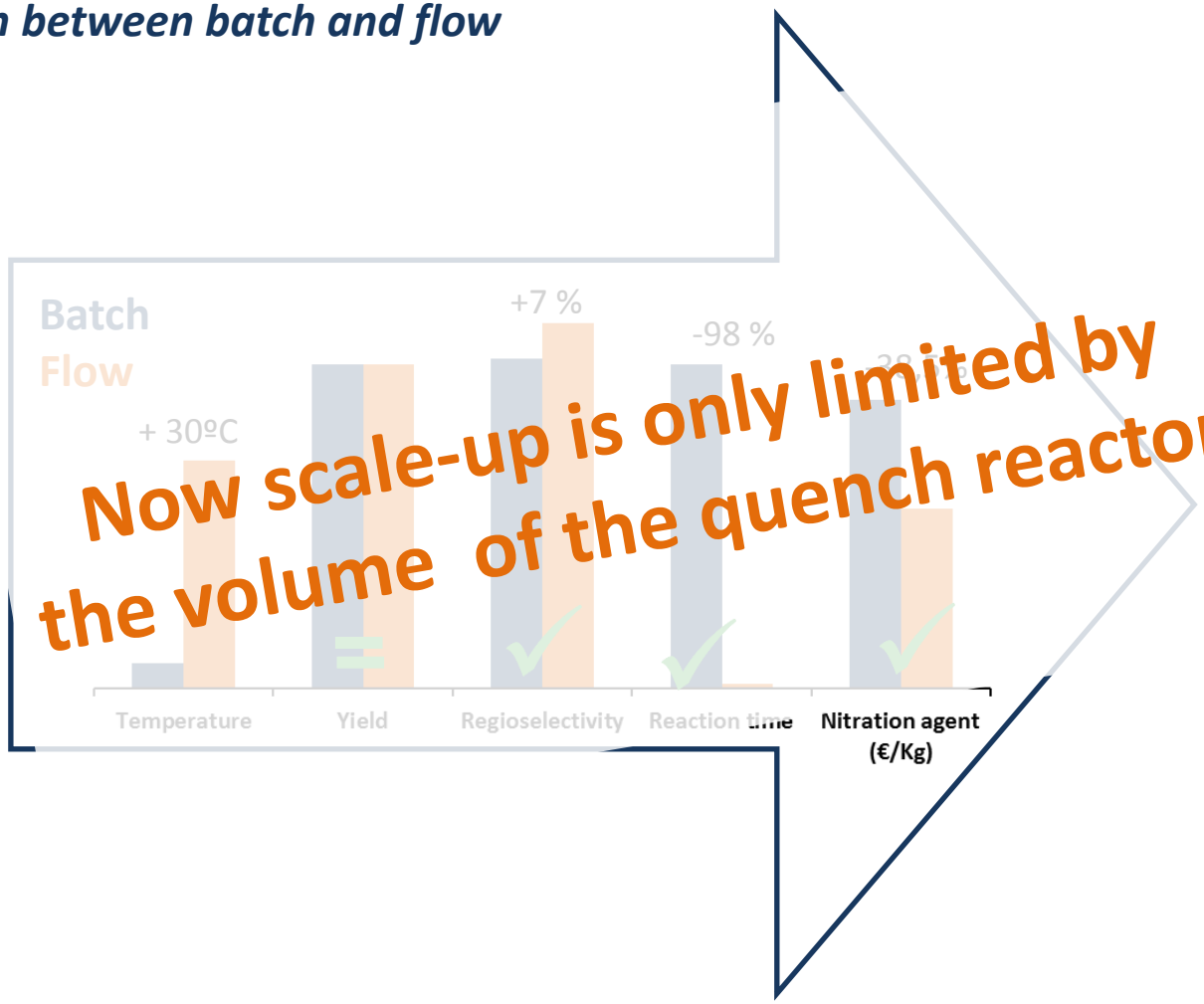


Now scale-up is only limited by the volume of the quench reactor!

NITRATION reaction

Scale-up: *Renting equipment at kilo-lab scale (x8) for paramters fine tunning was needed to guarantee seamless scale-up to production*

Kilo-lab G1 reactor

x 240

SiC reactor

x 8

Glass-beads packed bed pipe

NITRATION reaction

- **Target: production of 3 pilot batches of intermediate**
- **Industrial equipment**

  Medichem SiC industrial reactor → Scale-up *factor of 30 from kilo-lab*

  2 automated dosing lines Atex Compliant (0-20 bar)

  Huber 620W

***Similar yield / impurity profile* as feasibility trials**

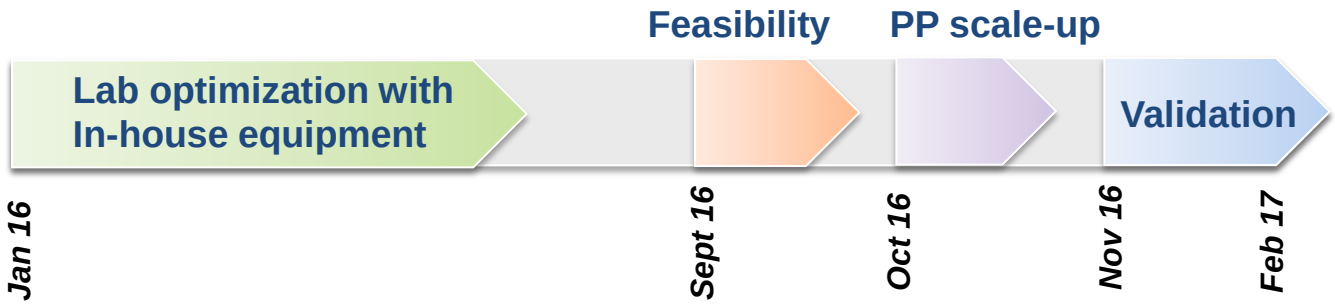
COGS reduction by 23 % compared to batch

Easier work-up due to a change of solvent for the nitration

Safety increased! Max. volume of reaction mixture < 1 L

NITRATION reaction

Timeline of the project



Main goal accomplished: In-house intermediate → desired availability and quality
Flow step to be included in the DMF of two internal APIs

Flow optimization can be very fast! From lab to first validation batch in less than one year

FLOWIDIZING PHARMA

team unique products medichem

Identification of right candidates

- Organometallic reaction

  Fast and highly exothermic

✓ Heat transfer

✓ Mixing

✓ Extreme reaction conditions

- Nitration reaction

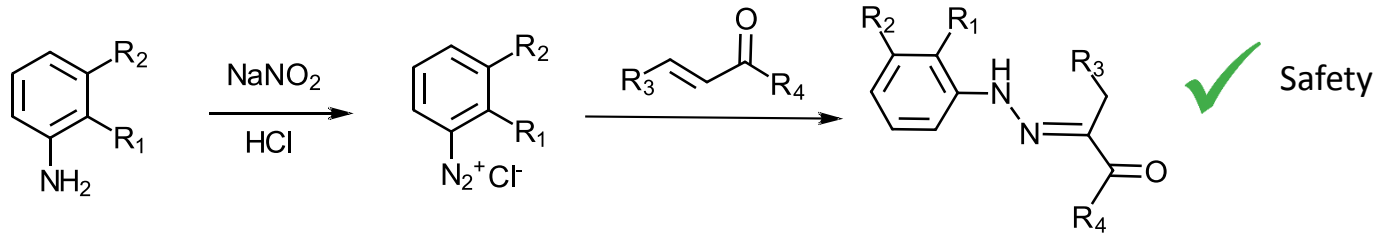
  Hazardous reagents involved and risk of explosion

✓ Mixing

✓ Safety

- **Diazotization reaction**

  Precipitation of the N_2^+ salt and shock-sensitivity

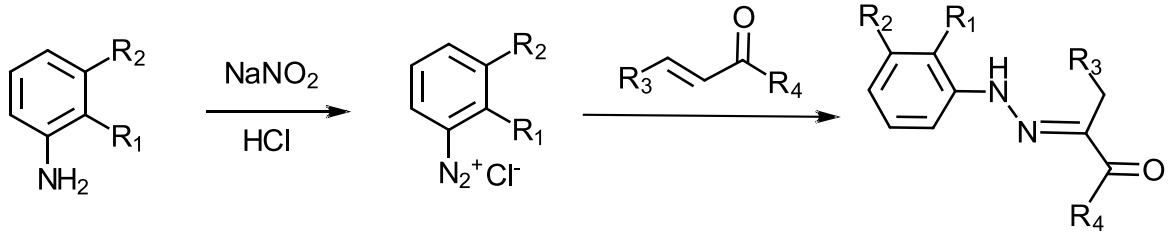


✓ Safety

DIAZOTIZATION reaction

- **Diazotization reaction**

Precipitation of the N_2^+ salt and shock-sensitivity



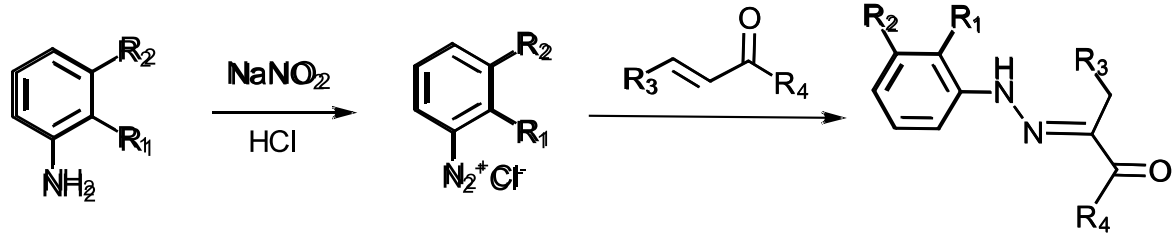
Batch reaction

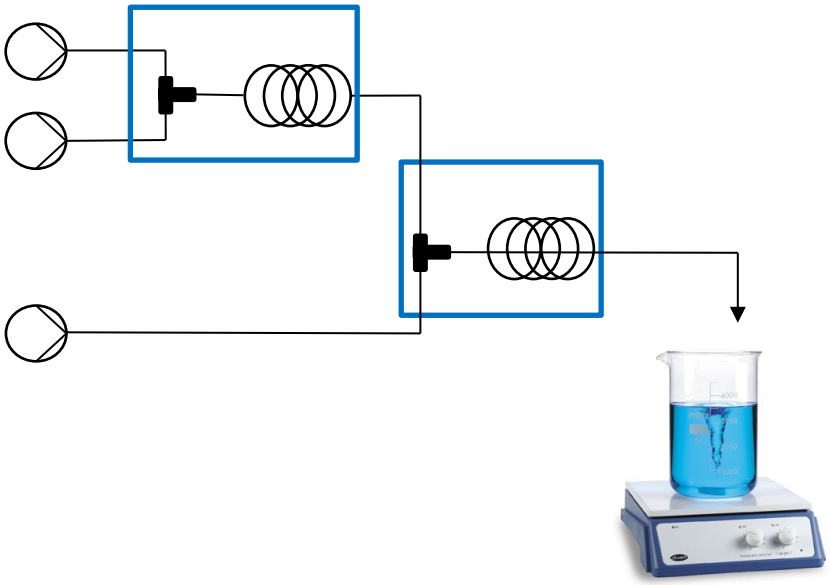
- ***Strict temperature control during the reaction (N_2^+ decomposition)***
- ***56 % yield***
- ***Limited batch size (0.5 kg) due to the possibility of shock-friction sensitivity (precipitation of N_2^+Cl salt)***

DIAZOTIZATION reaction

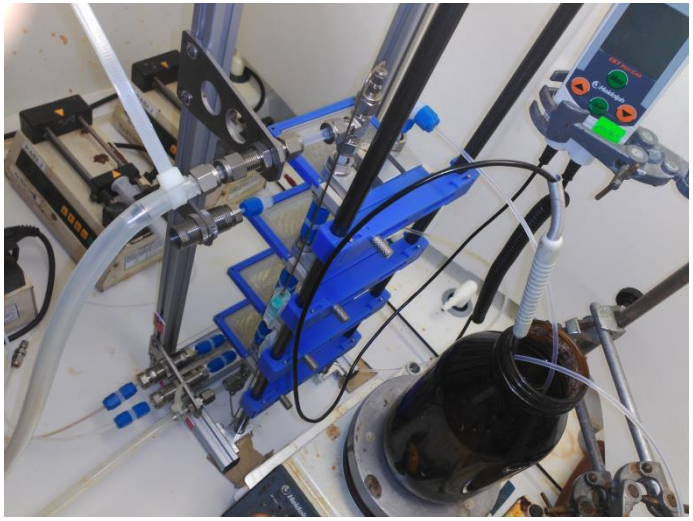
- **Diazotization reaction**

Precipitation of the N_2^+ salt and shock-sensitivity





Schematic flow set-up

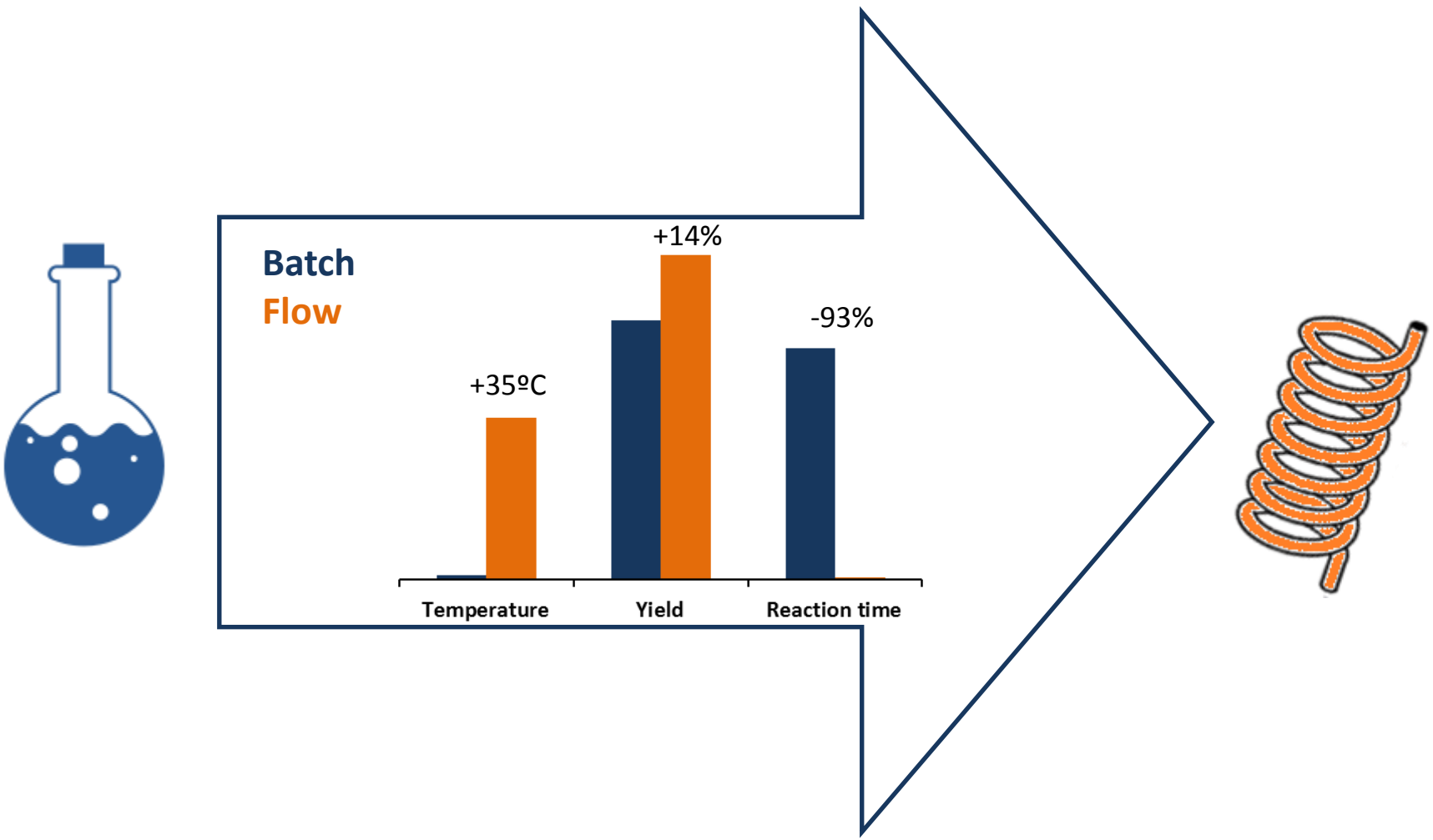


Picture of the lab set-up

DIAZOTIZATION reaction

medichem team uni-que products

Comparison between batch and flow



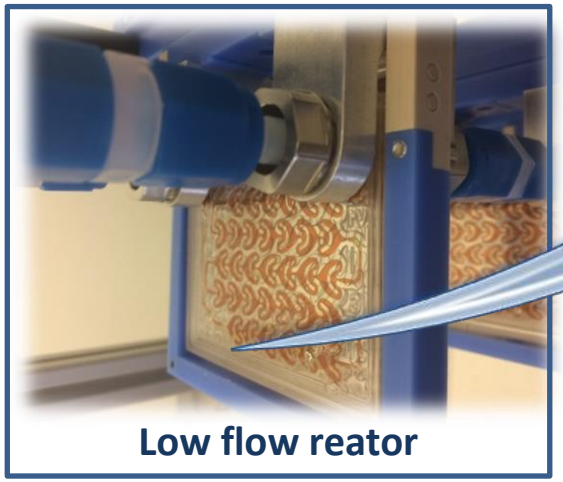
NITRATION reaction

***Direct* scale-up**

Direct scale-up expected!

Feasibility and optimization performed at lab scale with seamless scale-up expected up to production scale.

x 500

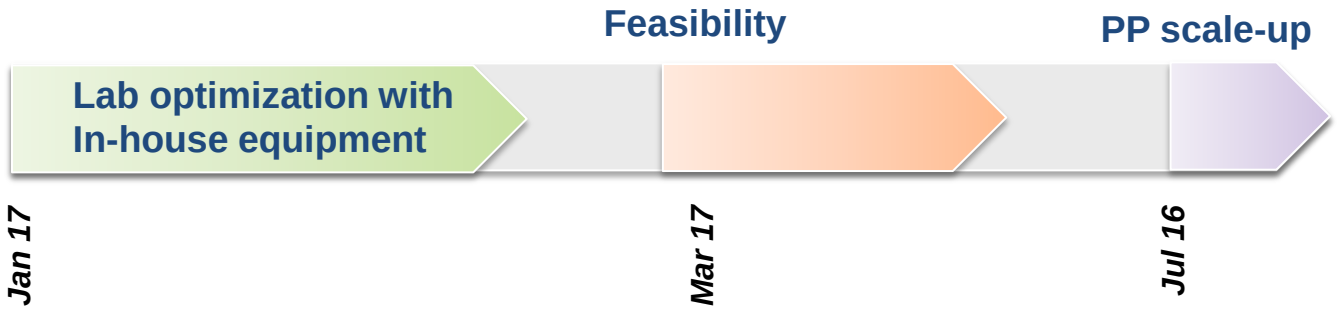


Low flow reator

SiC reactor

DIAZOTIZATION reaction

Timeline of the project



Main goal accomplished: First synthesis of an API (final step) in flow

- Better control of impurities
- Safer scale-up
- Possibility to work under oversaturated conditions during short RT

Scale-up planned for the next summer!

CONCLUDING remarks

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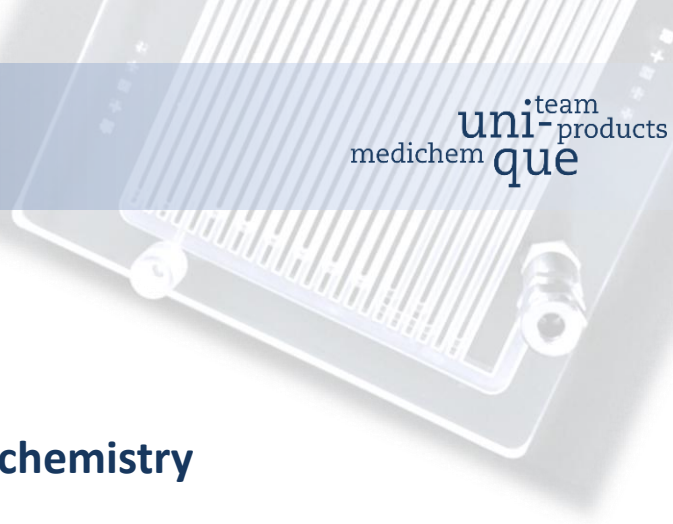
medichem que

OUR STRATEGY TO DETECT FLOW CANDIDATES

- **Flow is now took into consideration for ALL existing/incoming projects when it supposes a competitive advantage.**

  - ✓ Fast kinetics (i.e. cryogenic)
  - ✓ Mass transfer limitation
  - ✓ Very exothermic/endothermic reactions
  - ✓ Hazardous/unstable intermediates
  - ✓ Limitation of the solvent temperature
  - ✓ Critical uniformity of the residence time (scale-up effect)

CONCLUDING remarks



FROM BENCH TO MARKET

- We are able to develop, scale-up and validate flow chemistry processes under GMPs.
- Flow technology is considered indistinctly for intermediates and API
- We have a multipurpose industrial flow system installed in a GMP and FDA inspected API manufacturing plant.
- Flow equipment is portable and installable in any of our plants.

THANKS TO...
ALL THE MEDICHEM TEAM

medichem

…. AND TO ALL OF YOU FOR YOUR KIND ATTENTION!!

ChemSpec Europe 2017, May 31th , Munich, Germany

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