

# *Sustainability and Green Chemistry at Evotec*





# Drug Discovery Chemistry community

Rich pool of talent at all levels

## Drug Discovery Chemistry Leadership Team

- Wealth of drug discovery experience and insight applied to all projects and collaborations

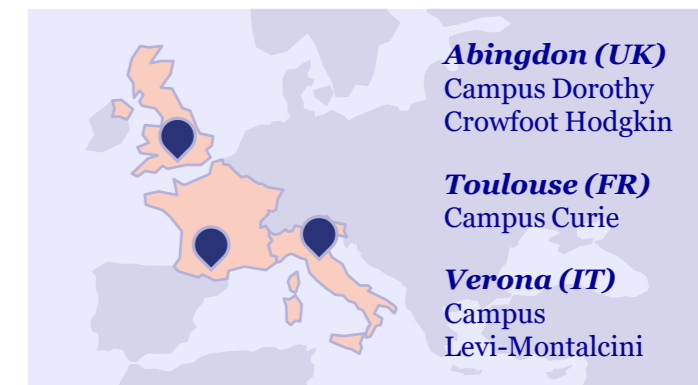
## Project Leaders

- Experienced cohort of project leaders (typically 10-15 years' experience)
- Single point of contact with Evotec partners
- Talented scientists with a proven track record of delivery (quality chemical assets including, clinical candidates, publications, patents, keynote presentations etc.)

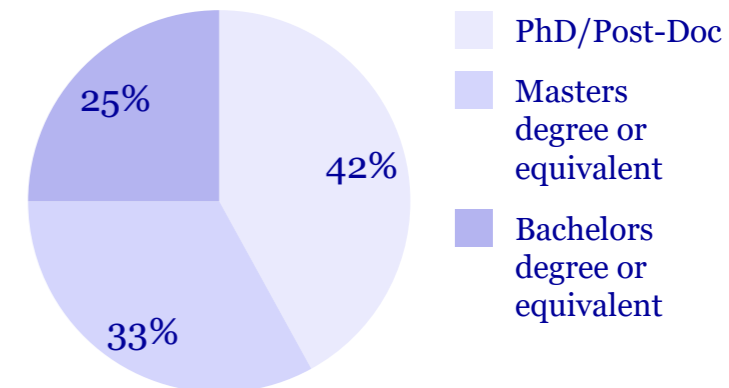
## Chemistry Resource

- Global capacity of 450 chemists encompassing medicinal, analytical and computational chemistry
- High quality design and synthetic capabilities (~325 lab chemists; 40% female: 60% male)
- High proportion (>42% lab-based and ~50% overall) of PhDs
- Cutting-edge groups in AI/ML generative and computational design and cheminformatics

## Integrated Drug Discovery sites



## Diploma level of lab chemists





# Evotec's "Molecular Design and Make" philosophy

Design and synthesis of tomorrow's medicines in Drug Discovery Chemistry

## Gap Analysis

How do compound properties differ from the target profile? How can this be improved?

## Define the Pharmacophore

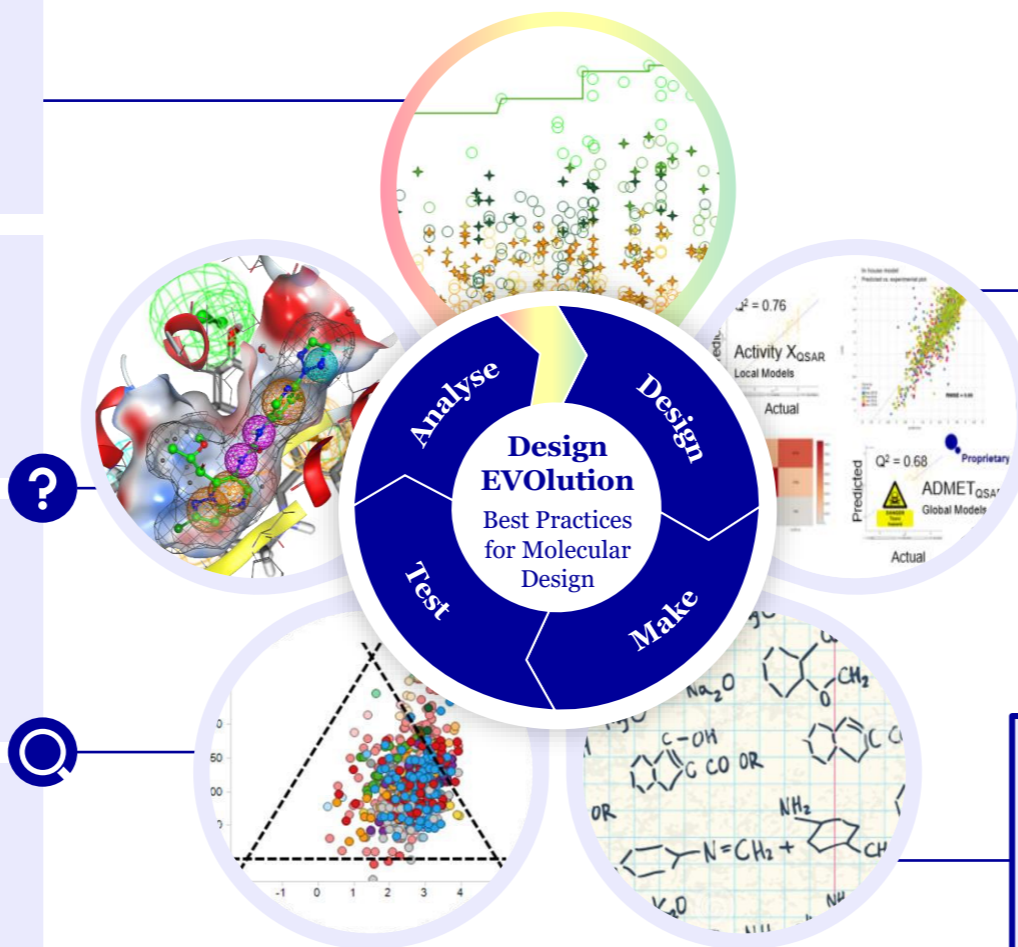
Which molecular features are driving compound potency?

## Molecular conformation

Understand impact on biological & property profile

## Focus on properties

Align with desirable property space. Make the right compounds first time.



## Design Efficiency

Rapid iterative design. Matched pairs. Maximum information from fewest compounds.



## In Silico Methods

DMPK models. Local ML models. Prediction-driven, generative design and active learning (AI/ML/DL).















## Make-Synthesis

Right first time. Good chemical route planning & execution. Minimise needs for re-synthesis. Apply best technologies. Integrate green chemistry principles.



# Enabling technologies at Evotec – 11 fields of expertise

Supported by cutting-edge equipments associated with expert chemists

Technologies	Description	Status
 <b>Green &amp; Alternative Chemistries</b>	Raise awareness – Propose alternatives – Lead sustainable initiatives	Active
 <b>Micellar Chemistry</b>	<i>Use micellar properties as a new paradigm for sustainable chemistry</i>	Active
<b>Mechanochemistry</b>	<i>Use mechanical forces as a new paradigm for sustainable chemistry</i>	<i>Under investigation</i>
 <b>FlowChem</b>	Increase productivity and efficiency with better control of H&S risks and organic waste reduction	Active
 <b>Biocatalysis</b>	Set up enzymatic processes as relevant alternatives to classical organic chemistry	Active
 <b>Resins</b>	Test and promote resins to simplify all stages of chemical syntheses (>30 resins available in house)	Active
 <b>Parallel</b>	Offer various tools and equipment for library preparation	Active
 <b>HTE &amp; Automated Chemistry</b>	Propose chemical reaction screening – Develop direct-to-biology approach	Active
 <b>Capsules</b>	Homemade screening kits for HTE – Caps for library preparation – Hazardous chemical encapsulation	Active
 <b>Gas</b>	Offer safe conditions to use high pressure gases among H <sub>2</sub> , O <sub>2</sub> , O <sub>3</sub> , CO, CO <sub>2</sub> , SO <sub>2</sub> , HCl, NH <sub>3</sub> and N <sub>2</sub>	Active
 <b>LSF</b>	Allow direct site-specific diversification of advanced scaffolds	Active
 <b>PhotoChem</b>	Harness light and redox potentials for synthetic applications	Active
 <b>ElectroChem</b>	Harness electricity and redox potentials for synthetic applications	Active



# Green & sustainable chemistry – Context

Global awareness of the problem – How to increase productivity without worsening our environmental footprint ?

More and more “mainstream” solvents are banned or are proposed to be banned by the relevant authorities, due to their harmful effects on human health and/or the environment ...

## REACH<sup>1</sup>

### N,N-dimethylformamide restricted from December 2023

The European Commission has published a regulation restricting **N,N-dimethylformamide (DMF)** – an aprotic solvent used in many industrial applications in the EU. This decision follows the proposal of the Italian authorities and the opinion of ECHA’s scientific committees.



... and the pharmaceutical R&D sector are becoming more and more aware of their global impact and the necessity to act

## Waste<sup>3</sup>

Labs produce a lot of waste. It's estimated that every year the plastic waste alone from laboratories could cover an area 23x the size of Manhattan ankle deep. Although much of this waste is hazardous, a lot of it isn't. In fact, anything that can be thrown in the trash has the potential to have a different end of life.

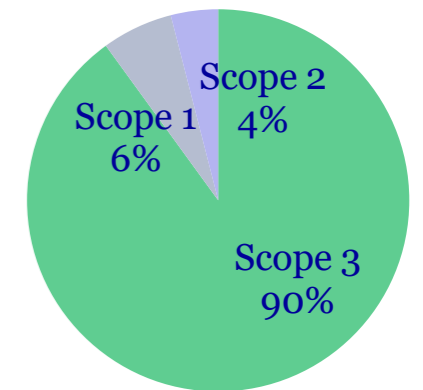
Scope 1 : direct greenhouse gas emission (e.g. offices, trucks)

Scope 2 : Greenhouse gas emission from electricity usage

Scope 3 : Indirect greenhouse emission (e.g, waste, supply chain, travel...)

-> **Scope 3 amounts for 90 % of life science industry footprint**

### Life science industry



<sup>1</sup> [https://echa.europa.eu/da/view-article/-/journal\\_content/title/9109026-58](https://echa.europa.eu/da/view-article/-/journal_content/title/9109026-58)

<sup>2</sup> <https://www.sgs.com/en/news/2024/05/safeguards-7724-us-epa-expands-methylene-chloride-restrictions-to-most-uses>

<sup>3</sup> <https://www.mygreenlab.org/waste.html>

<sup>4</sup> <https://www.mightybytes.com/blog/scope-3-emissions-in-your-digital-supply-chain/>

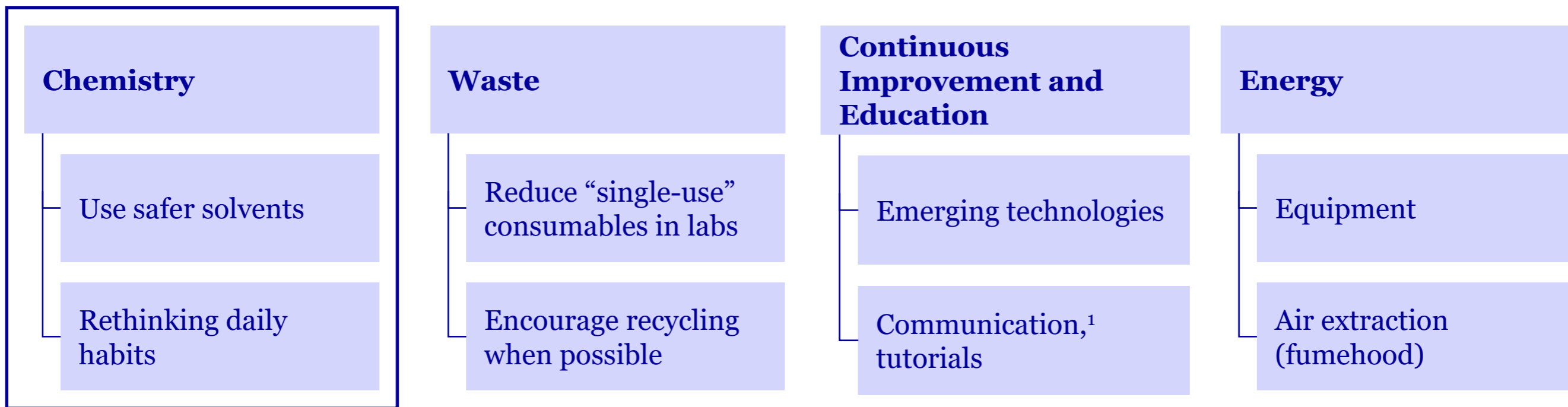
<sup>5</sup> <https://www.camelot-mc.com/blog/how-blockchain-can-help-to-manage-co%E2%82%82-data-across-the-value-chain/>



# Green & sustainable chemistry @ Evotec

A global strategy and a continuous improvement initiative

- **Green chemistry implemented while maintaining our level of excellence in drug discovery** (this presentation)
  - Improvement of our chemical processes and working habits with a sustainable vision
  - Expertise in alternative chemistry
- **Sustainability as part of the global initiative: 4 pillars identified to reduce our environmental impact**
  - Our chemists committed to adopt more responsible practices





# How does it translate to our everyday work in the lab?

Constant improvement of our chemical processes

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- Objectives: design processes that reduce or eliminate the use or generation of hazardous substances.
  - Green chemistry applies across the life cycle of a chemical product (from design to disposal).
- 

## Reaction

- Solvent Replacement
- Catalyst loading
- Reagent stoichiometry

## Work-up

- Solvent choice
- Adjust
- Avoid

## Purification

- Solvent choice
- Reverse-phase
- Recrystallization / Trituration



# Rethinking our processes to favour sustainability

Promote the use of safer & greener solvent

At Evotec we are committed to reduce the environmental impact of our activities, by adopting the green chemistry principles. A lot of alternative solvents can be used as replacement of hazardous solvents

		DCM H351 <sup>2</sup>	THF H351 <sup>2</sup>	Dioxane H351 <sup>2</sup>	Et <sub>2</sub> O	Toluene H361d <sup>2</sup>	DMSO	DMF H360D <sup>2</sup>	NMP
ACN									
2-propanol									
2Me-THF									
CPME									
MTPH									
Cyrene									
DMI									
GVL									
TMO									
DMC, DEC									
Eucalyptol									
NBP									

## Broad applications

- Pd-catalyzed reactions
  - ✓ Suzuki, Buchwald, Sonogashira ...
  - X-coupling
  - ✓ C-H arylation
- S<sub>N</sub>Ar
- Amide coupling
- Reductive amination
- Reduction/Oxidation
- Lithiation
- Alkylation
- Protection/Deprotection
- Radical reactions





# CMR solvent replacement – A lot of alternatives (i)

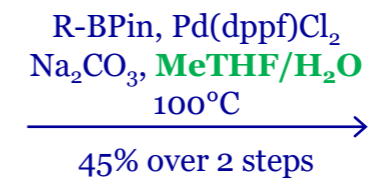
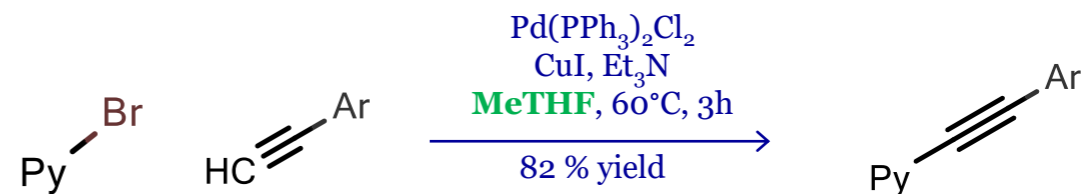
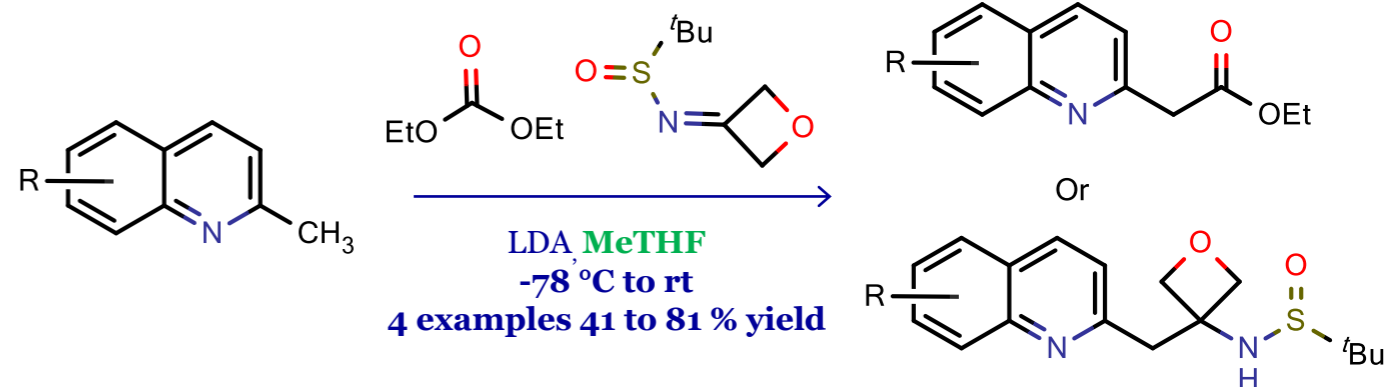
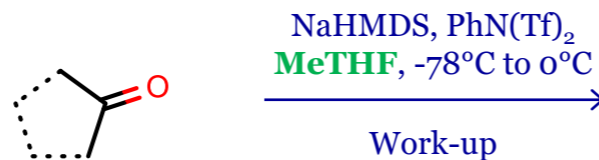
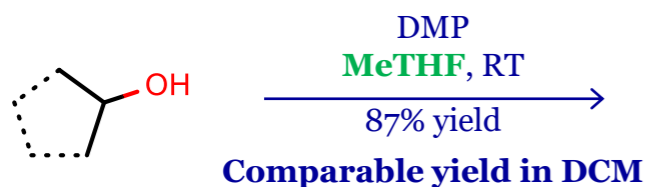
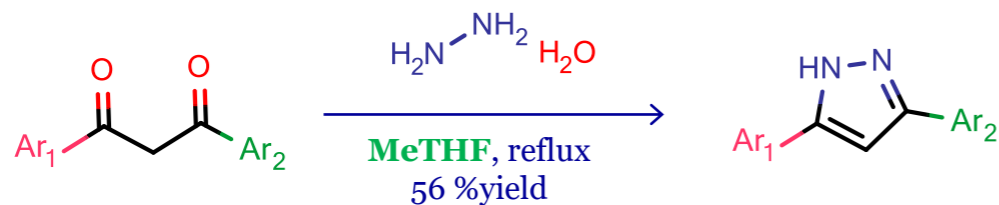
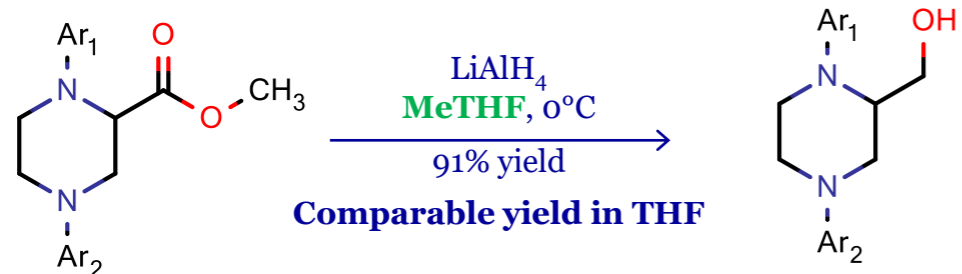
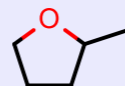
Miscellaneous & selected internal examples

Reaction

Work-up

Purification

THF/DCM/Dioxane/Toluene → Me-THF





# CMR solvent replacement – A lot of alternatives (iii)

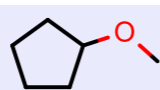
Miscellaneous & selected internal examples

Reaction

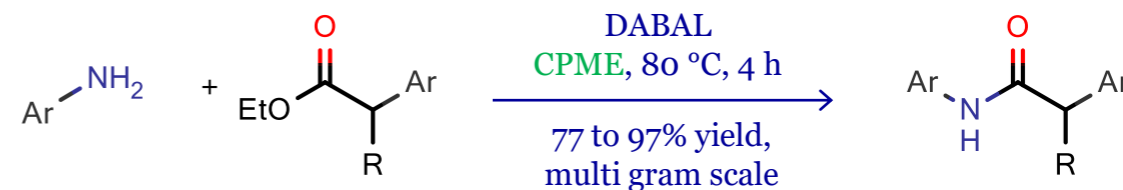
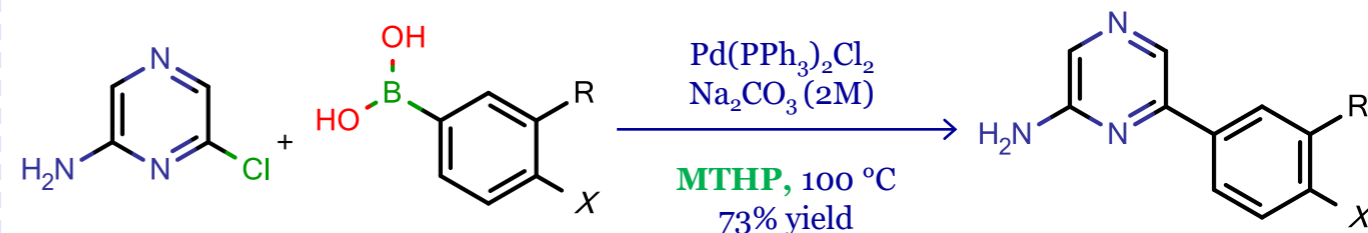
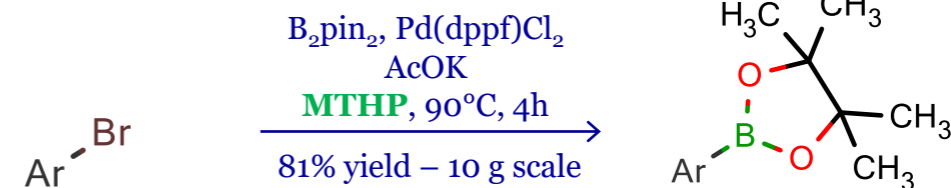
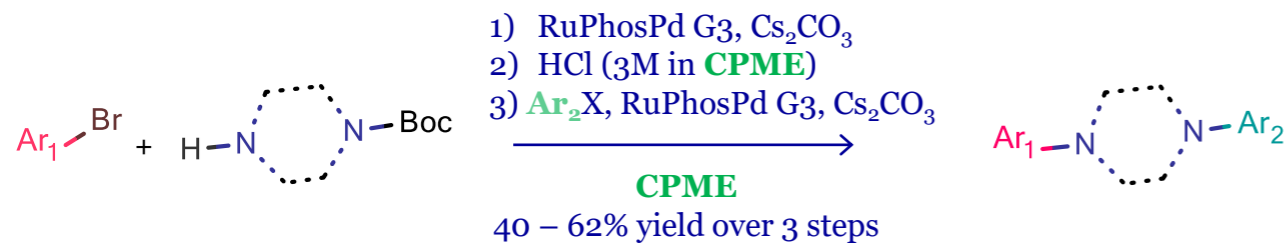
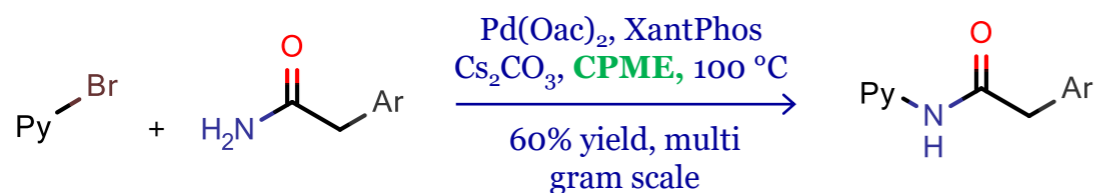
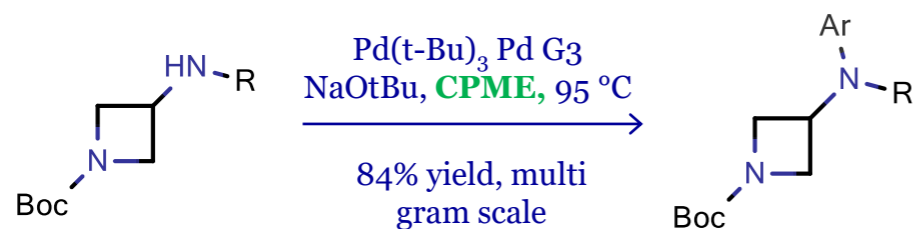
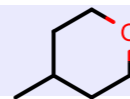
Work-up

Purification

THF/DCM/Dioxane/Toluene → CPME



MTHP





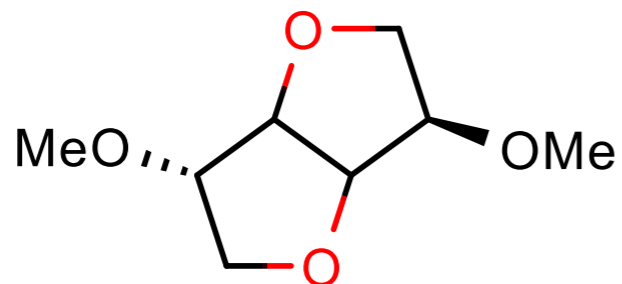
# Dimethyl isosorbide as a solvent worth being known

A promising solvent for DMF, DMSO & NMP replacement

Reaction

Work-up

Purification



- Dimethyl isosorbide (DMI)
- MW: 174.19 g/mol
- BP: 235°C
- MP: -70°C

## Benefits

- Water soluble (easily removed during work-up)
- Dipolarity/polarizability similar to DMF, DMAc (close properties)
- Compatible with strong bases (*e.g.* NaH) and strong acids
- Low toxicity (used in cosmetic and formulation)
- Derived from renewable feedstocks (cellulose, sorbitol)

## Applications

- Pd-catalyzed cross coupling reactions
- Alkylation
- Amide coupling

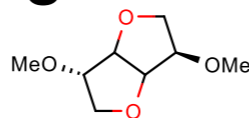
## Tips

- For liquid-liquid extraction: use of ethers (isopropylether, MTBE) recommended
- Residual DMI easily removed through reverse phase: DMI behaves as DMSO (early elution)



# DMI as a promising solvent for DMF replacement

Some internal examples

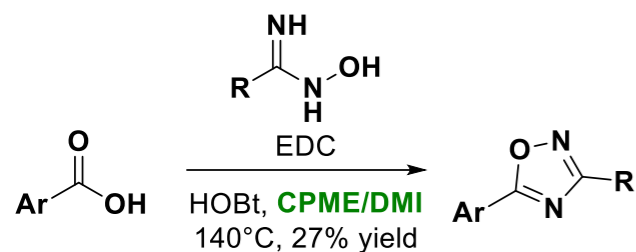


Reaction

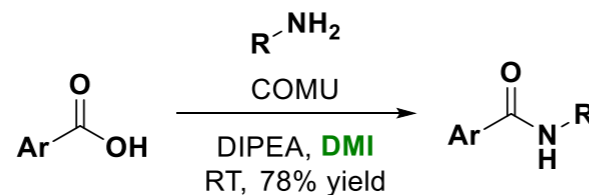
Work-up

Purification

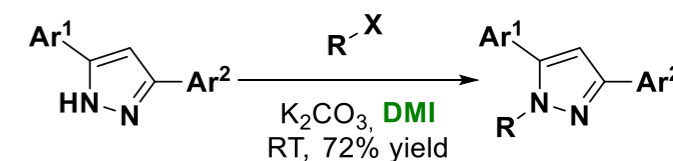
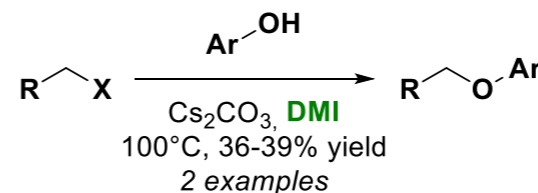
## Amide coupling/heterocycle formation



Similar yield obtained with DMF

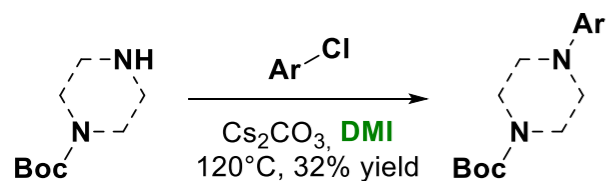


## Alkylation

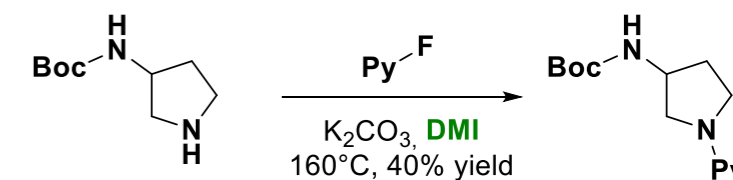
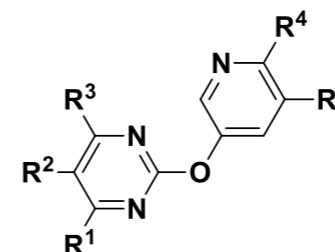
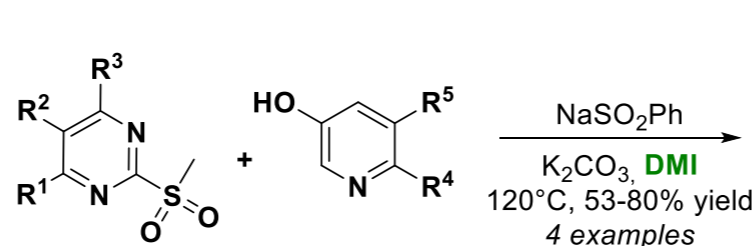


Product collected by precipitation after water addition (same as in DMF)

## Nucleophilic aromatic substitution (S<sub>N</sub>Ar)



Improved yield compared to DMF from 22 to 32%



Similar yield obtained with DMF, faster conversion



# CMR solvent replacement – A lot of alternatives (ii)

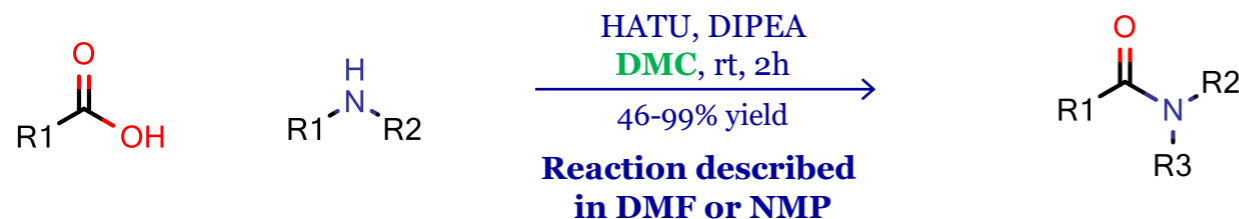
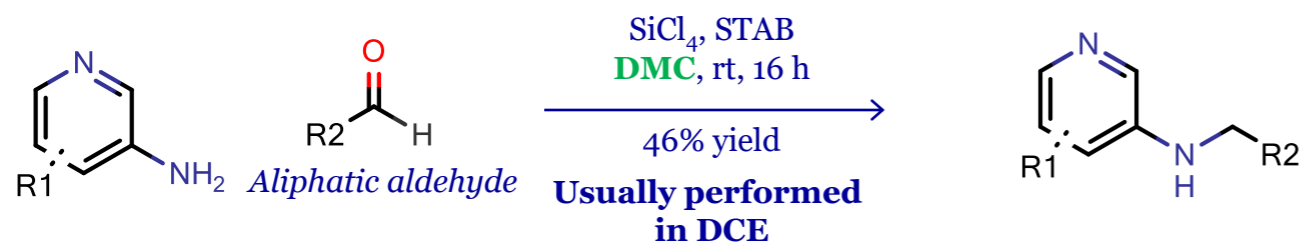
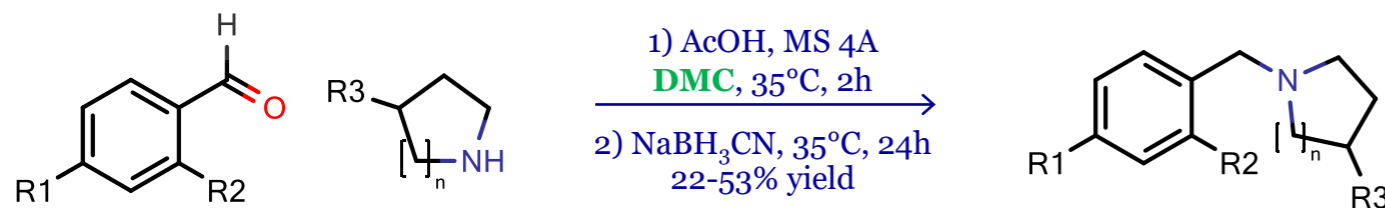
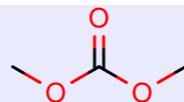
Miscellaneous & selected internal examples

Reaction

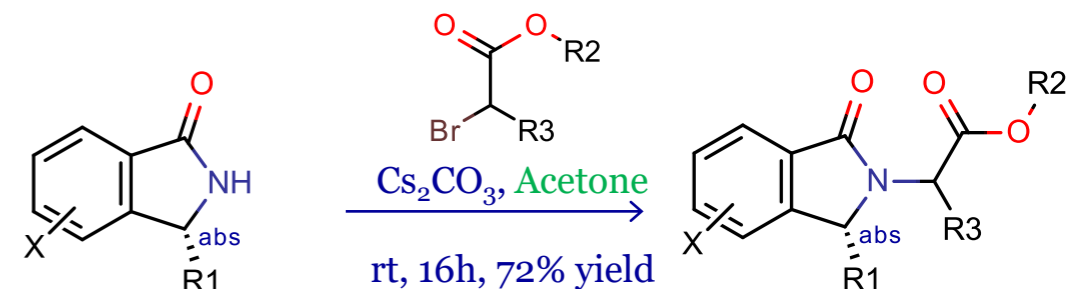
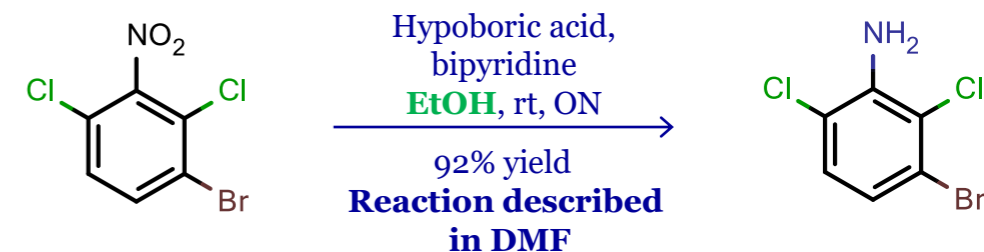
Work-up

Purification

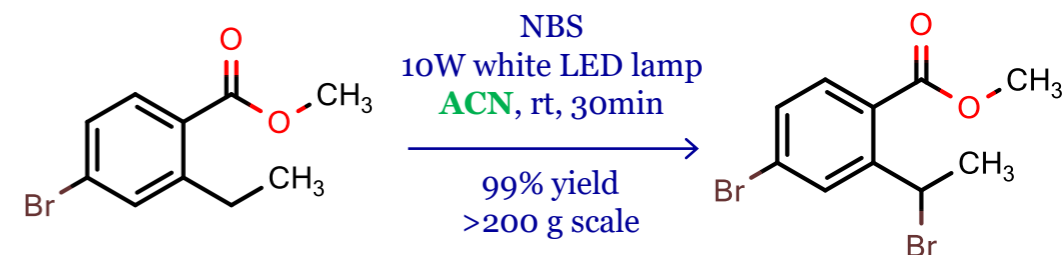
DCE/Toluene/DMF/NMP → DMC (dimethyl carbonate)



DMF → EtOH, acetone



DCE/CCl<sub>4</sub> → ACN





# Changing our working habits

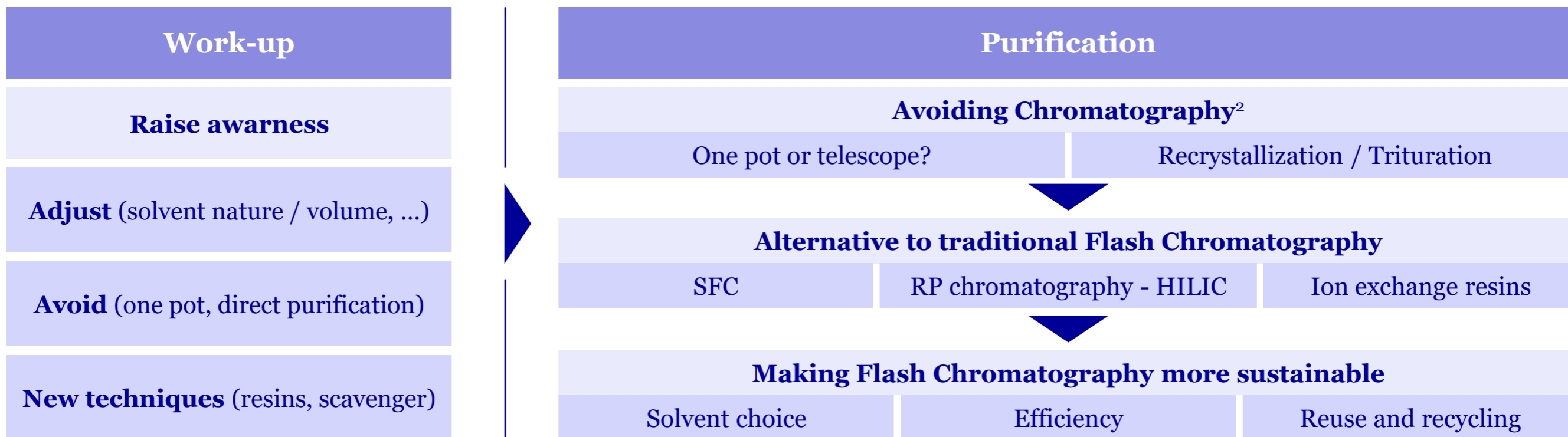
Suggest alternatives and foster lab habits change

Reaction

Work-up

Purification

- In discovery chemistry, our main source of solvent usages occurs during **work-up** and **column chromatography** steps
- This means that we must target these two steps as priority to have a meaningful impact
- Decision tree<sup>1</sup>





# FastWoRX as an excellent alternative for work-up

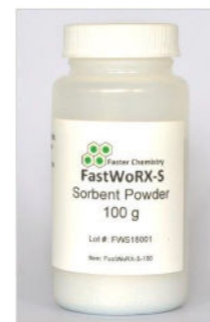
Reduce the amount of solvent used

Reaction

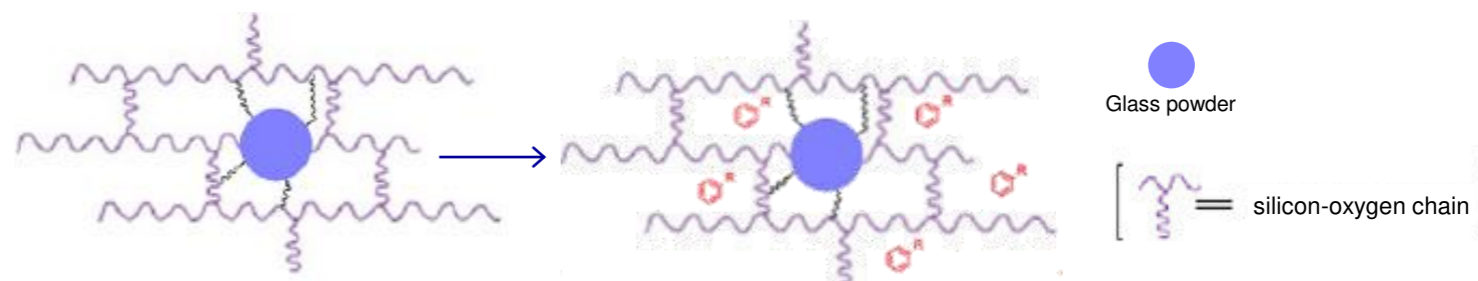
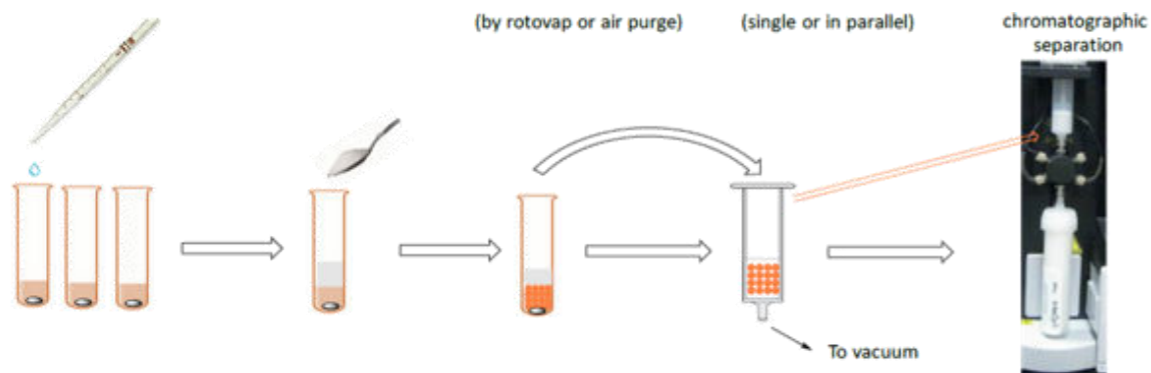
Work-up

Purification

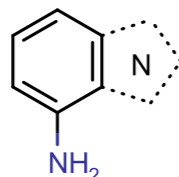
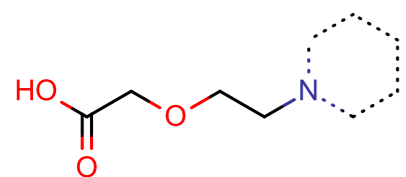
- Replace the liquid-liquid extraction phase (~90% less solvent used)
- Simplified work-ups (no emulsions) and may avoid purification
- Time efficient
- Application from mg to g scale  
(6 to 10 g of FastWoRX per g of organic product)



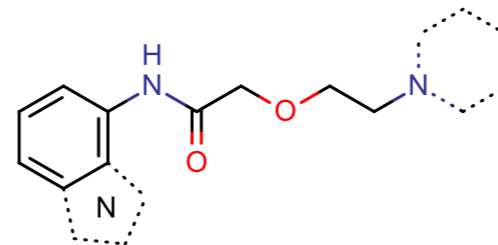
- Available at Sigma Aldrich: ~**80€/100g**
- Can be used with DMF/DMSO/DMI or other
- Compatible with water soluble solvents
- Can be **washed and recycled**



## Application



HATU, DIPEA  
DMI, RT, 1h  
Water quench  
Then FastWoRX  
82% yield



- ✓ Reaction carried out on 1 g scale (8 g of FastWoRX used)
- ✓ No purification needed, only the EP was retained (removal of SM and reagent)
- ✓ Elution with EtOAc



# Column chromatography vs LLE (acido-basic)

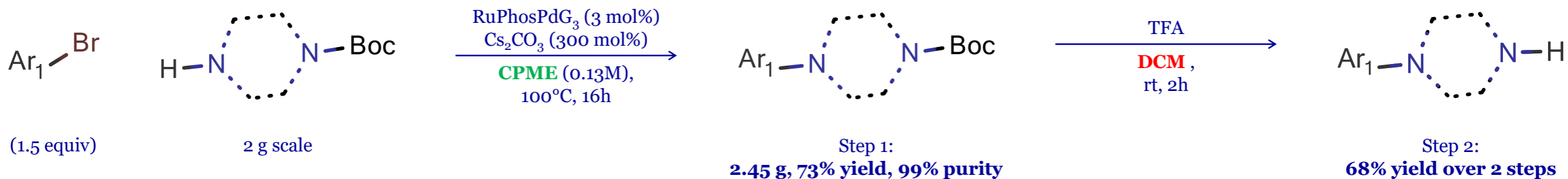
Reaction sequence

Reaction

Work-up

Purification

## First approach : intermediate purification



## Work-up/Purification

### First step

- 1) Quench with  $\text{NH}_4\text{Cl}$
- 2) Extraction with EtOAc
- 3) Phase separation then concentration
- 4) Column chromatography (heptane/AcOEt)

### Second step

Concentration in vacuo





# Column chromatography vs LLE (acido-basic)

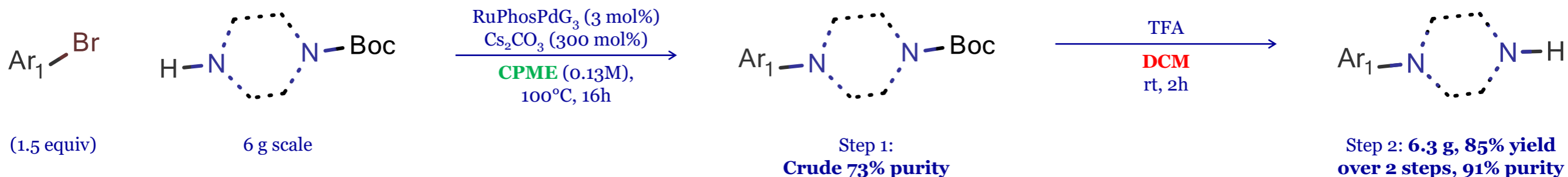
Reaction sequence

Reaction

Work-up

Purification

## Second approach – Isolation/ « purification » by liquid-liquid extraction (LLE)



## Work-up/Purification

### First step

- 1) Quench with NH<sub>4</sub>Cl
- 2) Phase separation then concentration

### Second step

- 1) Reaction mixture concentrated
- 2) Crude dissolved in EtOAc and H<sub>2</sub>O, conc. HCl added until pH 2)  
– **Product transferred to aqueous phase**
- 3) Organic phase discarded (contains impurities only)
- 4) Acidic aqueous layer treated with solid K<sub>2</sub>CO<sub>3</sub> until pH 9
- 5) Product back extracted with EtOAc

- Smart work-up enables rapid product isolation and avoids column usage (>15 L of eluent saved)
- Further improvement : use of HCl (3M in CPME) for boc deprotection step : Product collected by filtration



# Alternative to flash chromatography

## HILIC columns

Reaction

Work-up

Purification

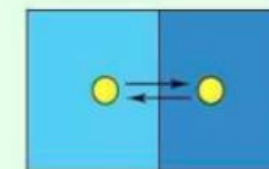
**HILIC chromatography is a suitable technique for the purification of very polar intermediates**

### Principle

- Stationary phase : unbonded silica, amino or anionic bonded phases, etc.
- Mobile phase typically ACN (weak solvent) and water (strong) : typically, 95 to 50% ACN
- Combination of partition chromatography and electrostatic/H-bond interactions
- The more polar an analyte is, the more retained it is

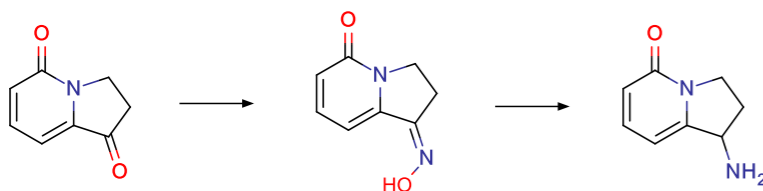
### Partition Chromatography

Separation is based on solute partitioning between two liquid phases. (relative solubility)

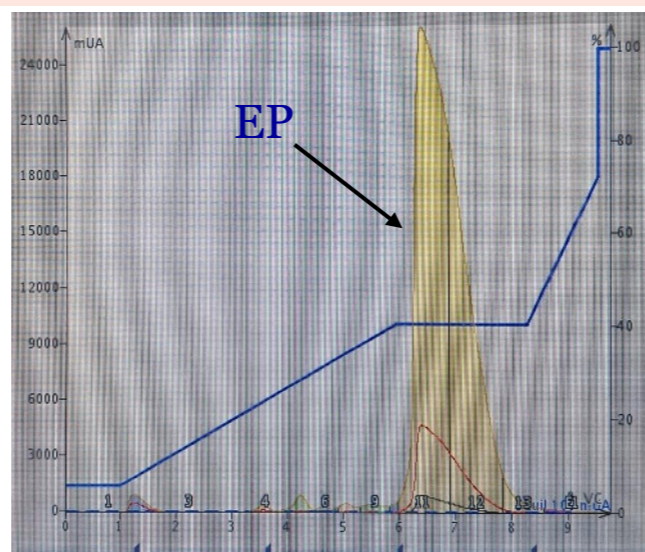


### Example

#### Reaction sequence



- Reaction run on 800 mg scale of sm
- Product very polar and soluble in water



- Liquid loading in 95% acetonitrile + AcOH/water
- Elution with acetonitrile + 0.5% acetic acid (solvent A, weak) and water + 0.5% acetic acid (solvent B, strong)
- Purification on 40g Si column
- Compound isolated as acetic acid salt and then de-salted by SCX catch-release
- Columns can be reused several times



# DCM/MeOH efficiently replaced during flash chromatography (i)

EtOAc/EtOH (3:1) in heptane now commonly used in our labs

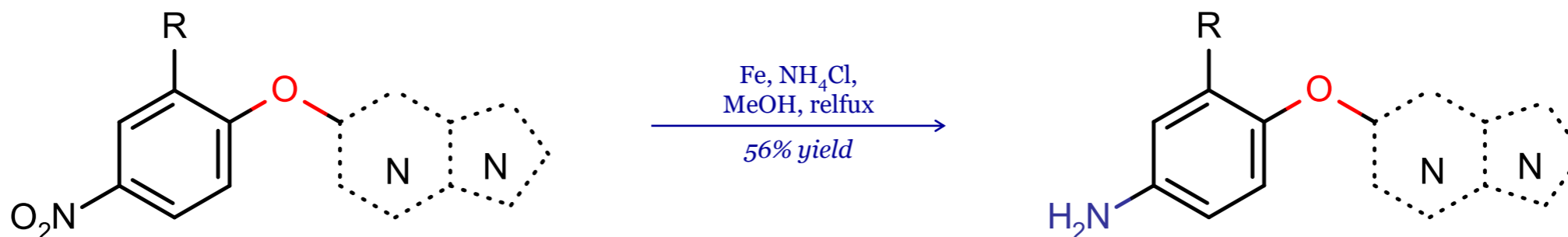
Reaction

Work-up

Purification

- DCM poses significant health and environmental problems. Necessity to find alternatives, in particular for chromatography

## Case study



## Purification

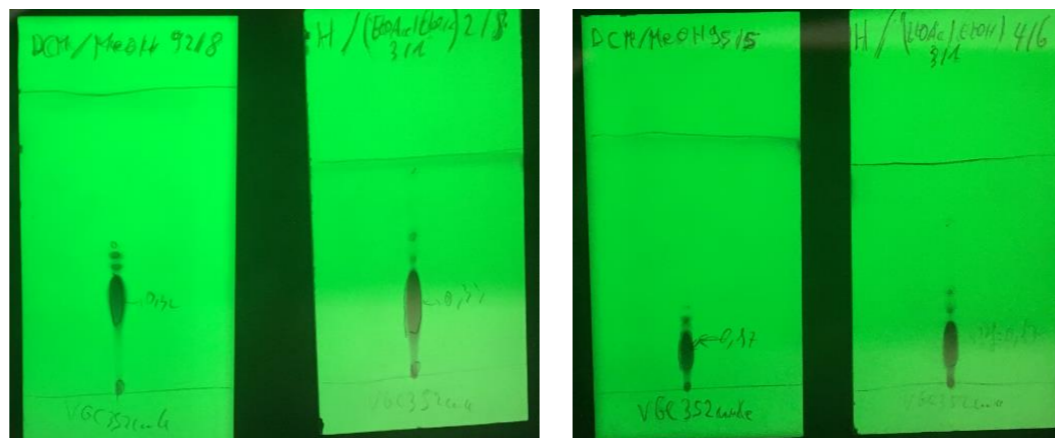
### Batch 1:

0-6% MeOH in DCM:

Good LCMS profile, minor impurities observed by <sup>1</sup>H NMR

### Batch 2:

10-60% (EtOAc/EtOH 3:1) in heptane: similar LCMS profile, <sup>1</sup>H NMR purity improved

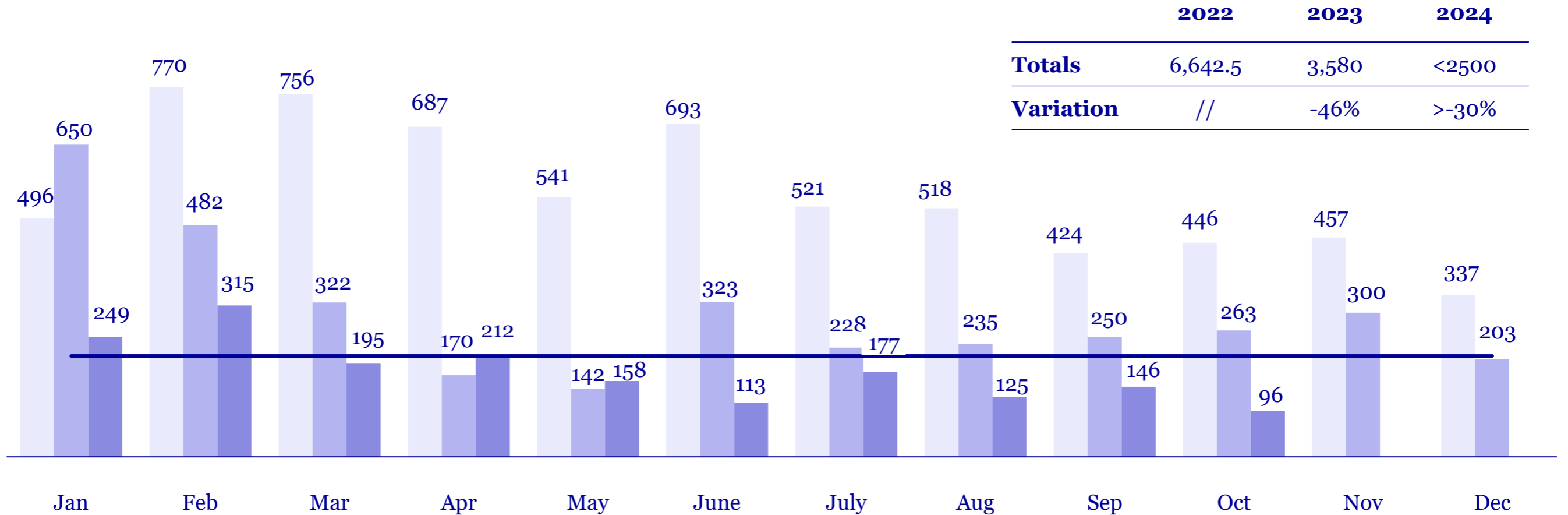


- Similar TLC profile
- Better separation with EtOAc:EtOH (3:1) in heptane solvent system – less coelution



# Concrete impact of our efforts!

DCM consumption over the past months/years at Toulouse Evotec site



**2024 objective:** <2500 l per year corresponding to <210 l/month – **On track** (1800 L Jan-Oct period)

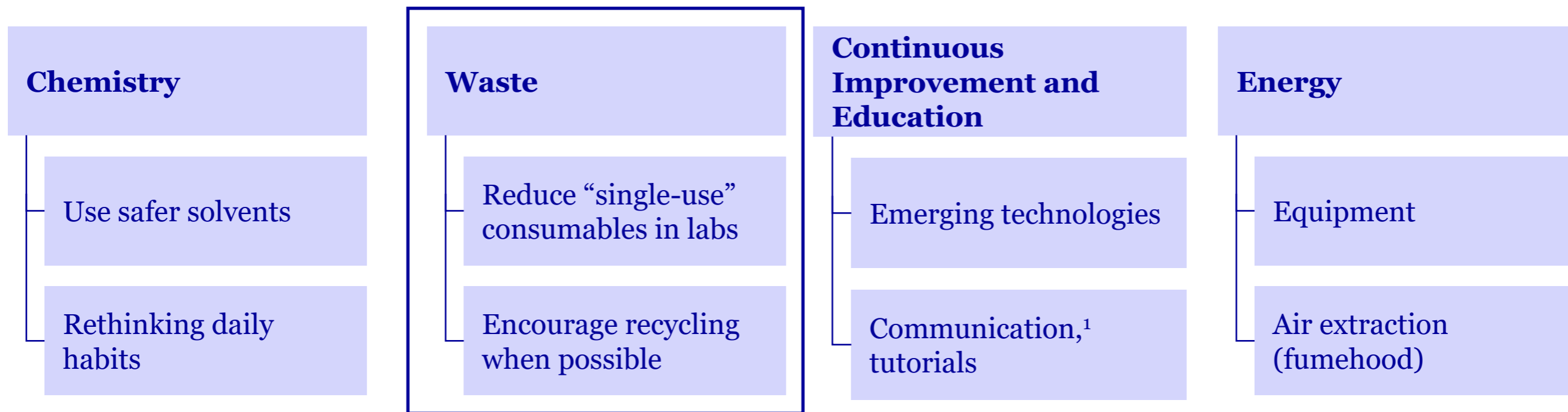
■ 2022   
 ■ 2023   
 ■ 2024   
 — Objective 2024 (210 litres/month)



# Green & sustainable chemistry @ Evotec

A global strategy and a continuous improvement initiative

- **Green chemistry implemented while maintaining our level of excellence in drug discovery** (this presentation)
  - Improvement of our chemical processes and working habits with a sustainable vision
  - Expertise in alternative chemistry
- **Sustainability as part of the global initiative: 4 pillars identified to reduce our environmental impact**
  - Our chemists committed to adopt more responsible practices

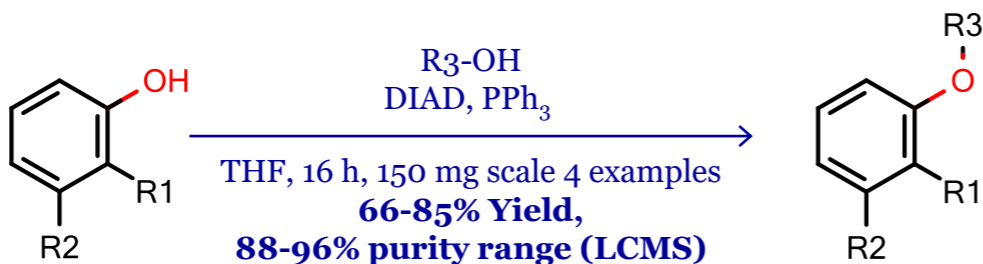




# Making flash chromatography more sustainable

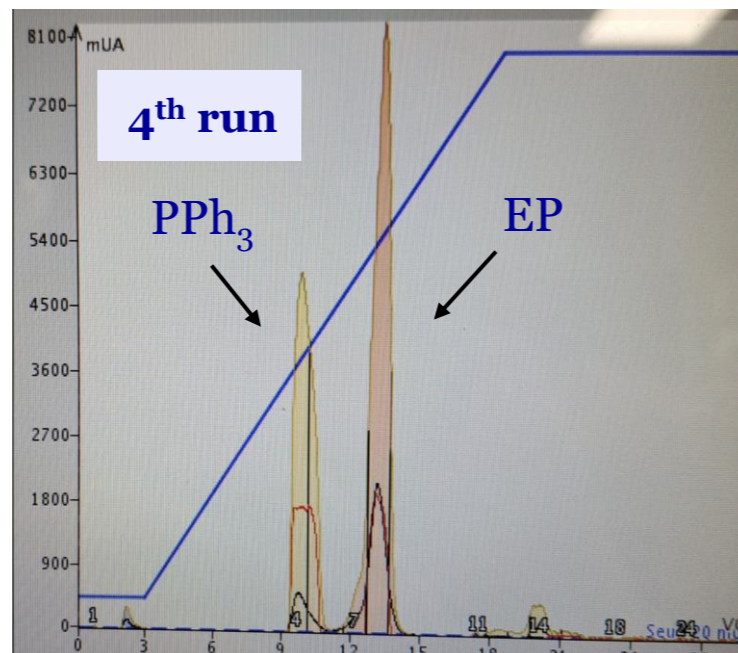
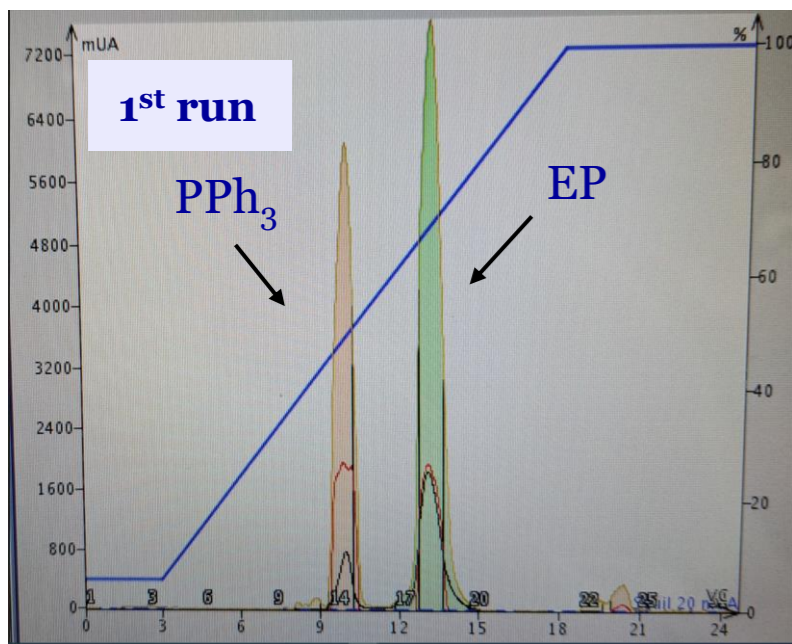
## Column reuse

### Case study : Library synthesis



- Mitsunobu reaction (convenient for library synthesis)
- Up to 4 intermediates purified using the same column (12 g, interchim 30 μM)
- Conditions : Dryload, gradient : 5-100 % (EtOAc/EtOH 3:1, 2% NH<sub>4</sub>OH) in heptane

## Purification

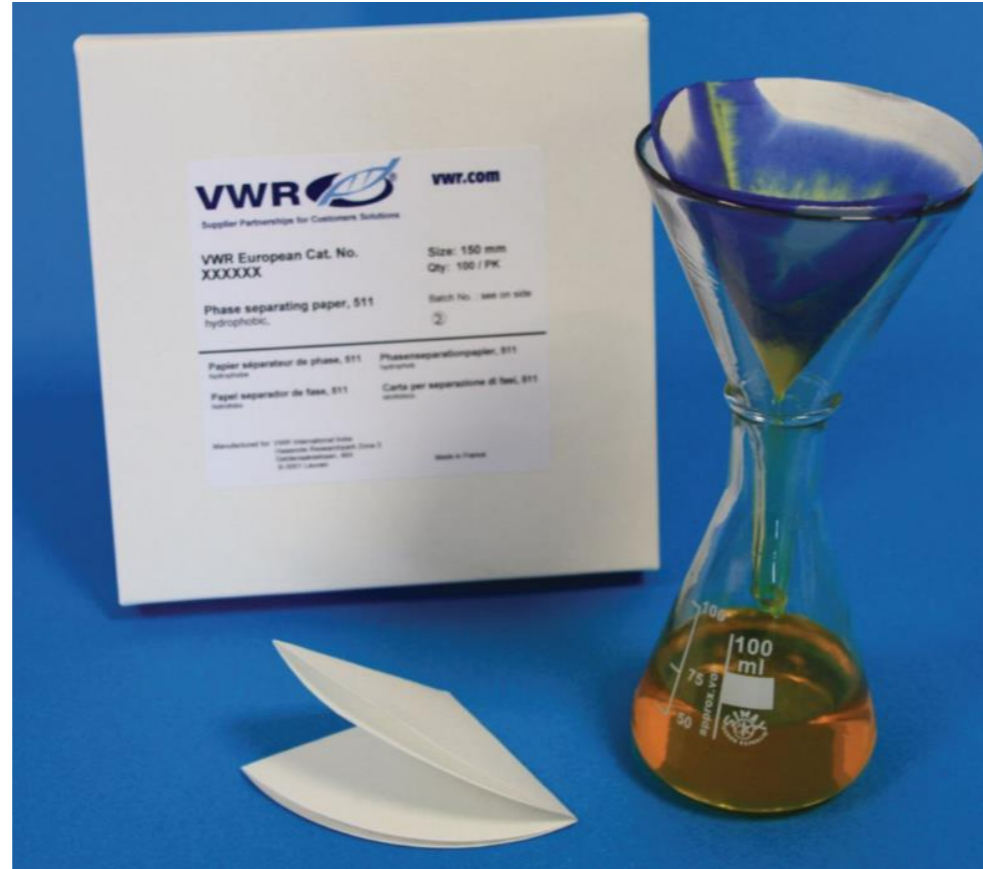
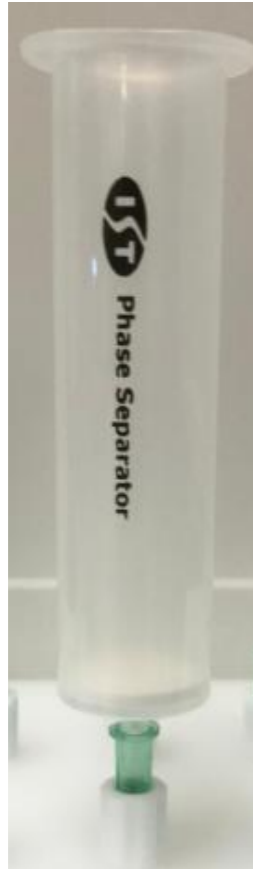


- No cross-contamination and no major loss of resolution observed
- Column washed with 100% MeOH (2 CV), then EtOAc/EtOH 3:1 (2 CV), and heptane (1 CV), between each run (1CV = 17 mL)
- Possible improvement : reduction in CV number (15 CV would have been enough instead of 24 in those examples)
- Wash method improved with the use of EtOH instead of MeOH



# Replace, or reuse plastic consumables as much as possible

2 examples



- Remove phase separator from our stock room
- Replace with hydrophobic or sulfate salt



- Reuse dry load system

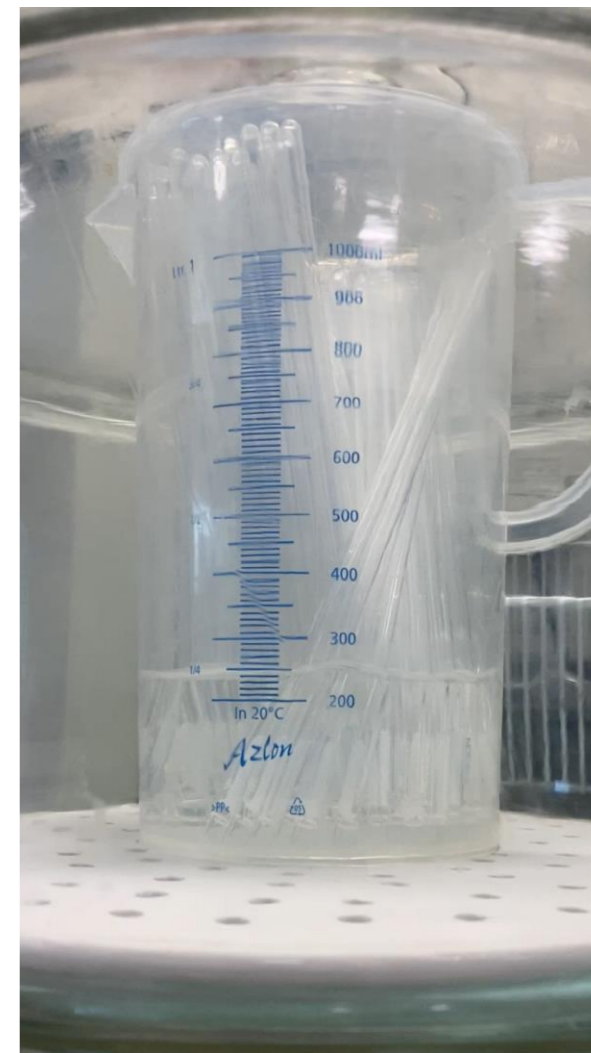
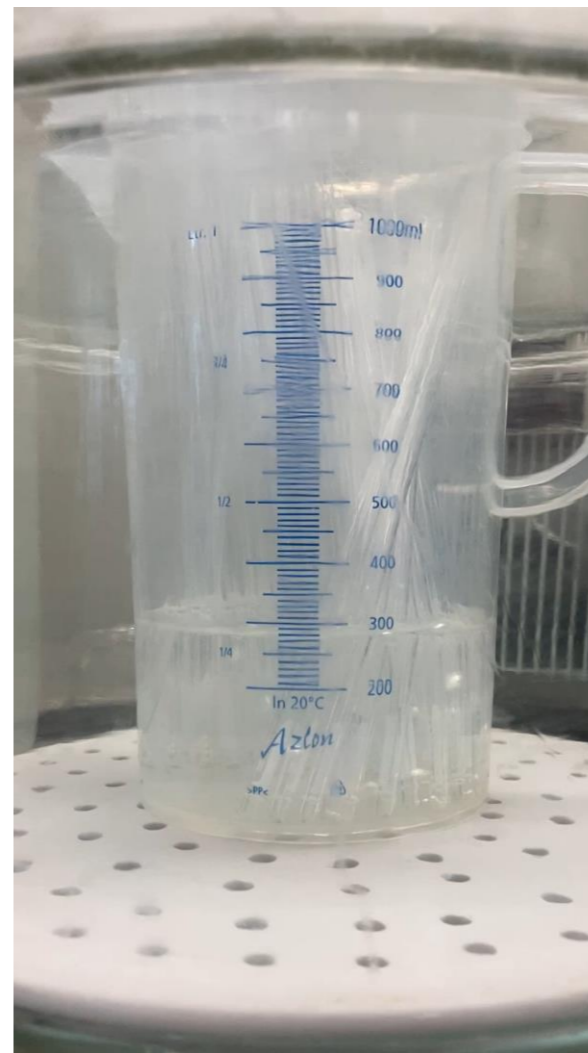
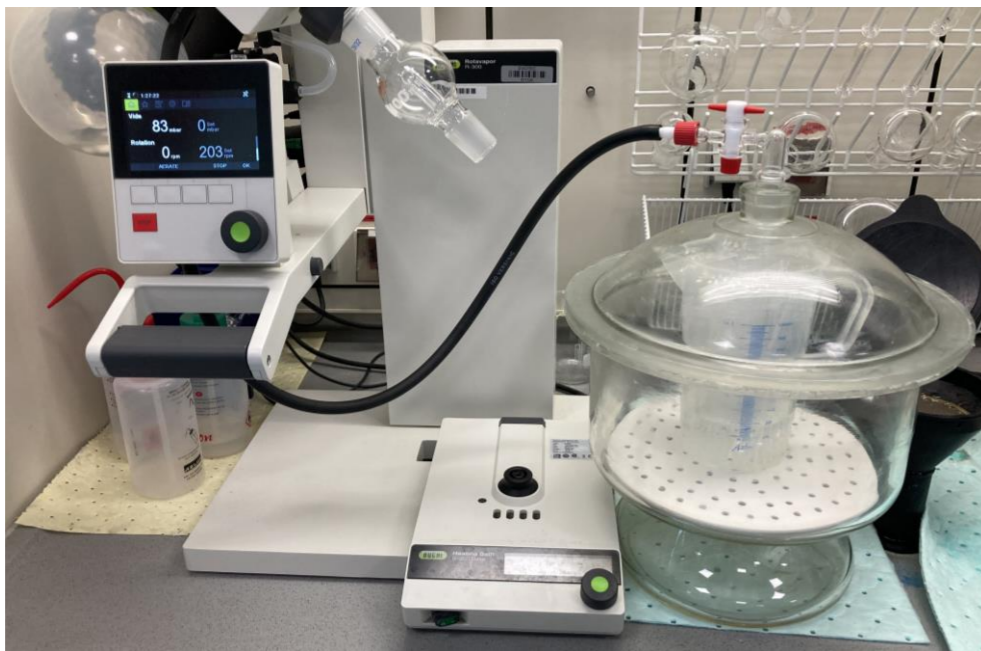


# Reducing glass waste

NMR tubes cleaning process - newly in place

## Vacuum desiccator as a simple, robust, and inexpensive NMR tubes cleaner<sup>1</sup>

- Simple, robust, and inexpensive way for cleaning several NMR tubes
- Up to 300 NMR tubes cleaned simultaneously with a minimum amount of solvent



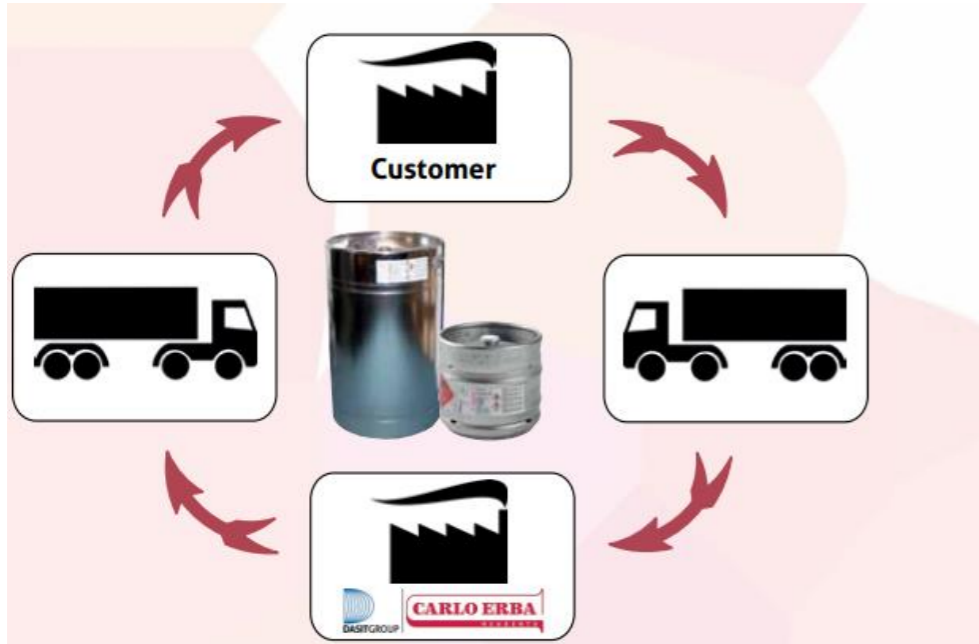




## Reducing glass waste (2)

Shuttle service - Used for our column chromatography solvents

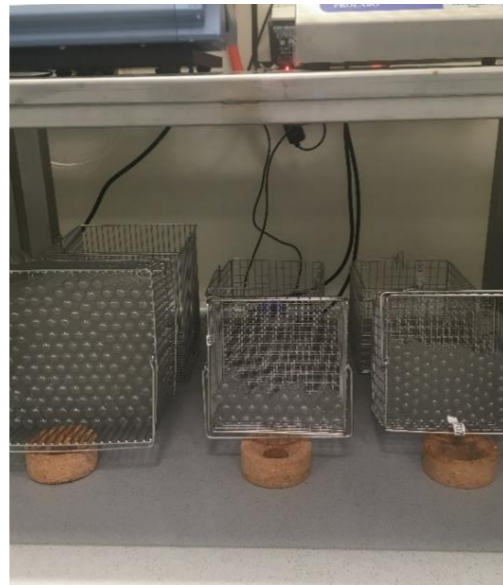
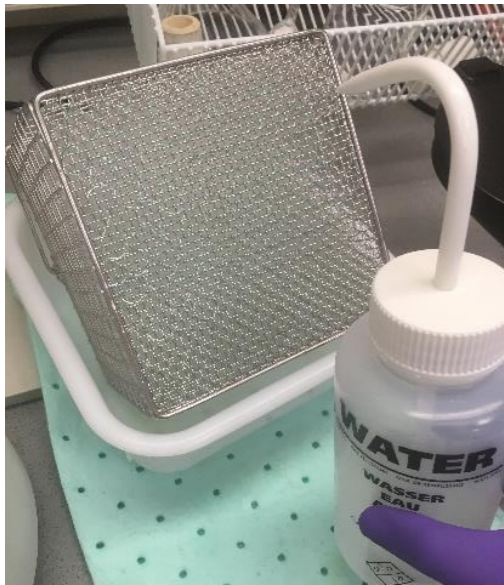
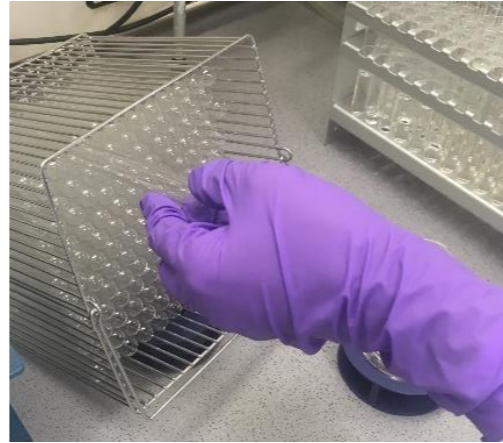
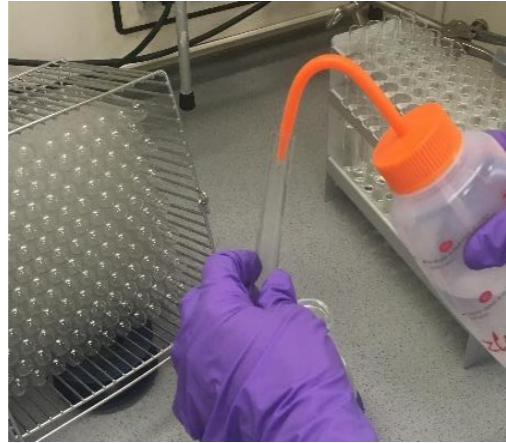
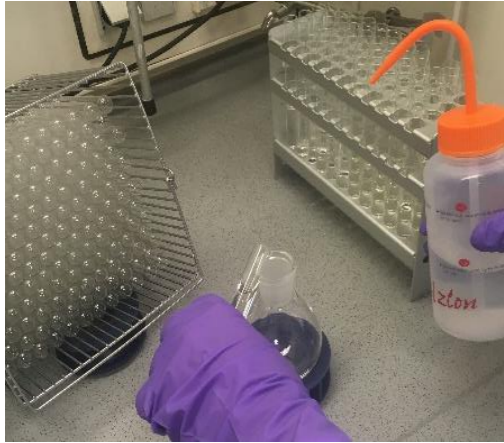
- **Partnership with Carlo Erba®**
- **Replacement of non-recyclable glass bottle with returnable stainless-steel canisters**
  - Currently used for heptane and AcOEt/EtOH (3:1) will be extended to 3 other solvents: EtOAc, ACN & acetone
  - Safer than glass bottle
  - Cheaper and more sustainable than glass bottle





# Recycling column chromatography tubes

Tutorial to favor habits change





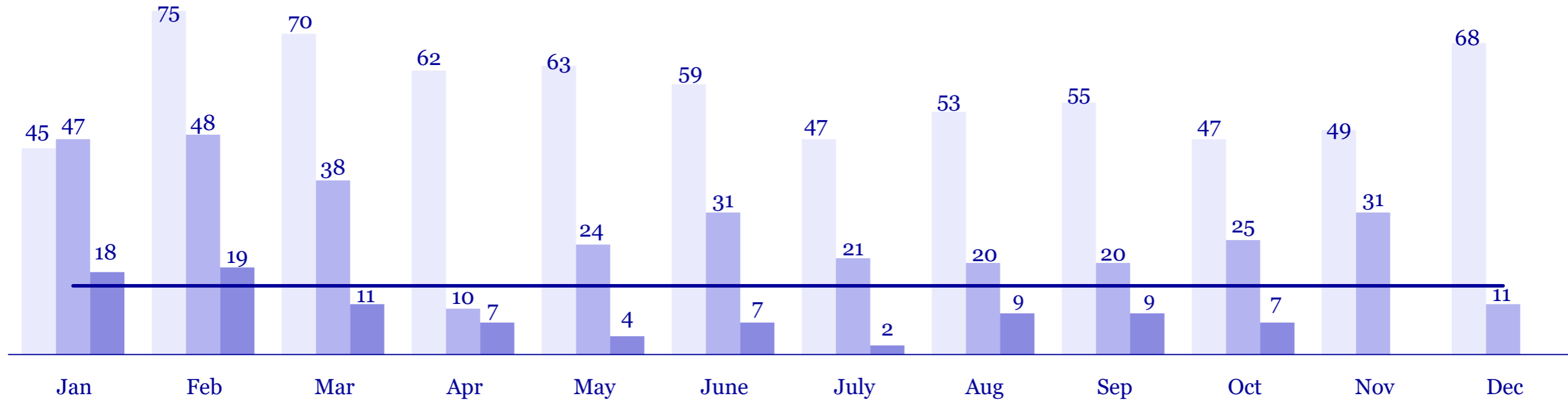
# Reducing glass waste (3)

Reuse column tubes

**Significant reduction** of tubes consumption observed throughout the years

Annual consumption of tubes (Toulouse, in box)

	2022	2023	2024
<b>Totals</b>	663	315	<150
<b>Variation</b>	//	-52%	>-52%



**2024 objective:** <150 boxes a year corresponding to <15 box/month – **on track** (93 boxes ordered – Jan-Oct)

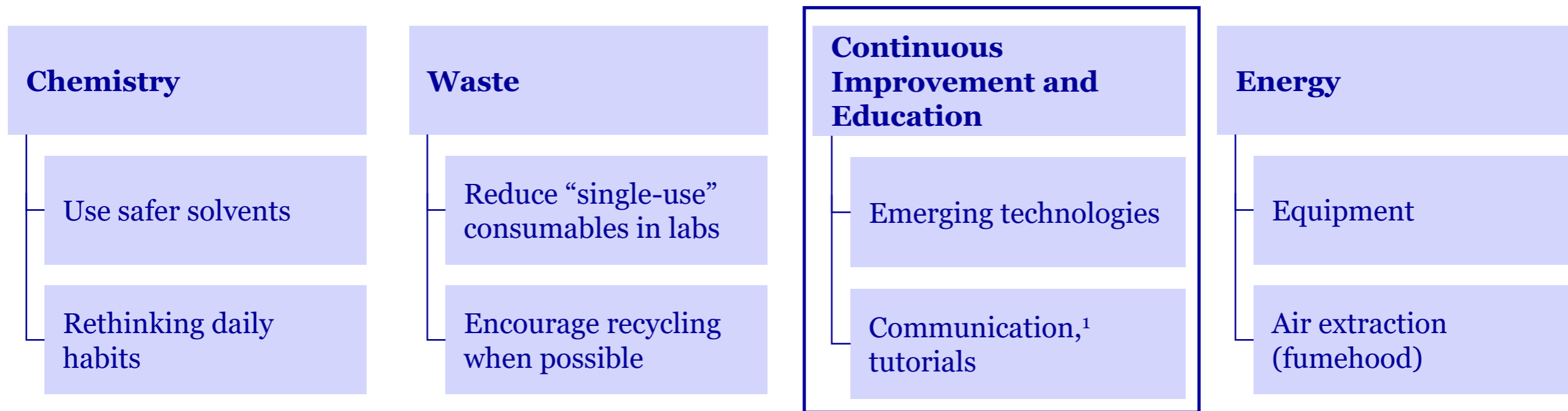
■ 2022   ■ 2023   ■ 2024   — Objective 2023 (250 litres/month)



# Green & sustainable chemistry @ Evotec

A global strategy and a continuous improvement initiative

- **Green chemistry implemented while maintaining our level of excellence in drug discovery** (this presentation)
  - Improvement of our chemical processes and working habits with a sustainable vision
  - Expertise in alternative chemistry
- **Sustainability as part of the global initiative: 4 pillars identified to reduce our environmental impact**
  - Our chemists committed to adopt more responsible practices





# Emerging technologies

## Biocatalysis

### Initial synthesis



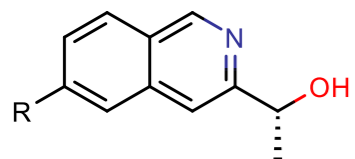
### Key features

- Racemic mixture
- Chiral separation of both enantiomer revealed that only the (S) stereochemistry is biologically active
- The separation led to loss of material, need to develop an asymmetric synthesis

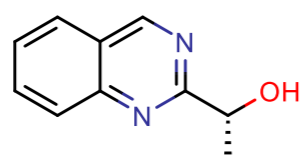
### Noyori reduction



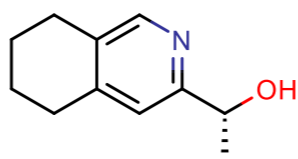
### Enzymatic reduction



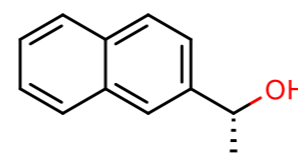
R = Cl, F, Br, Me...  
>90% yield, >99% ee



>90% yield, >99% ee



>90% yield, >99% ee



>90% yield, >99% ee

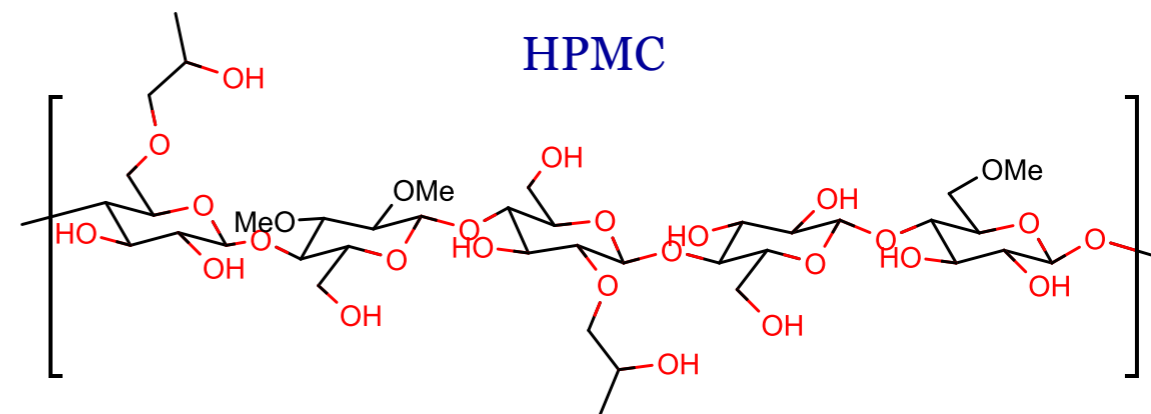
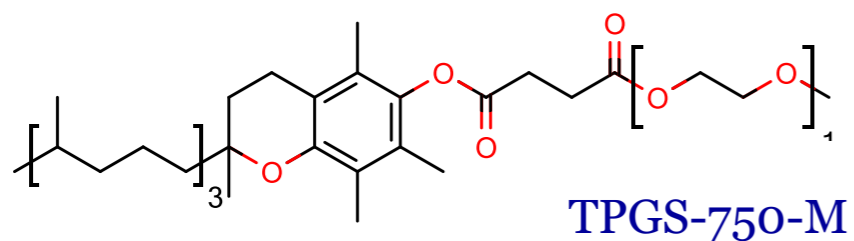
- Robust methodology, large variety of substrates
- High yield and ee
- > 50 examples successfully synthesized
- Scaled-up to 2 g



# Emerging technologies

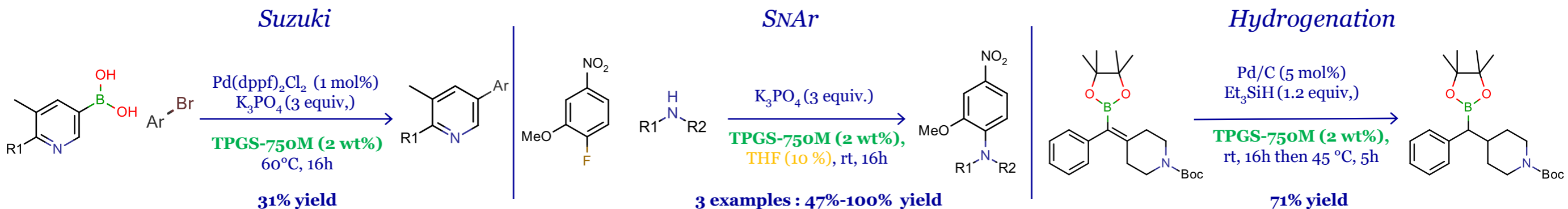
## Micellar chemistry

**Concept : perform conventional chemistry in water, using environmentally benign surfactants**



**Known applications : cross-coupling reactions,  $S_NAr$ , amide coupling...<sup>1</sup>**

### Internal examples



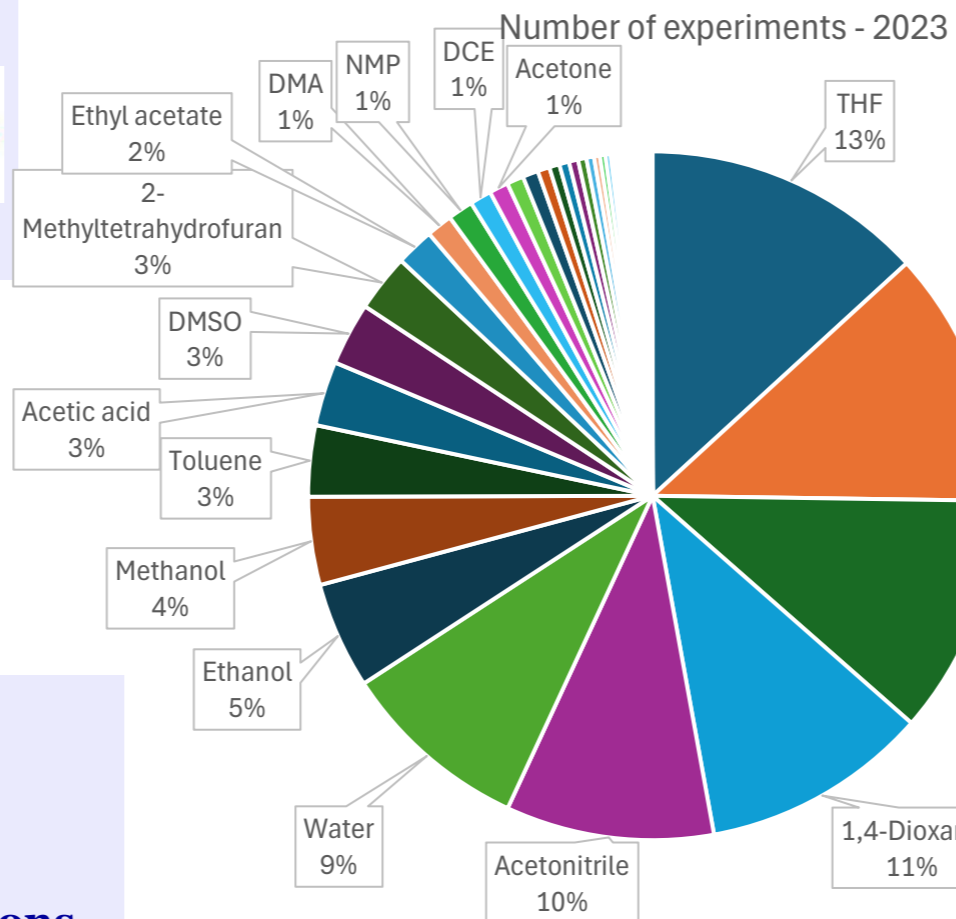


# Continuous improvement

## CMR-free month challenge

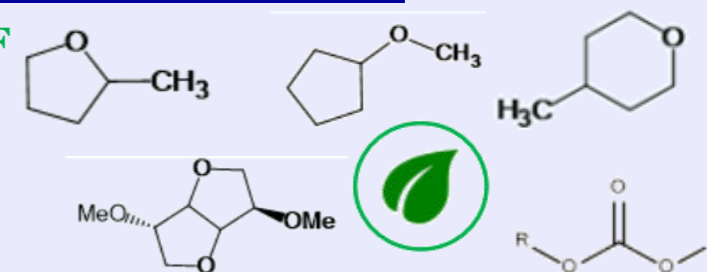
### 4 targeted solvents :

- THF
- DCM
- DMF
- DIOXANE



### 5 replacement solvents :

- MeTHF
- MTHP
- CPME
- DMC
- DMI



### 4 reaction types :

- Cross-coupling reactions,
- Amide couplings,
- Alkylations/Reductive aminations
- SNAr

### 4 recommendations:

- Cross-coupling reactions :  
✓ **Dioxane** -> **MeTHF, CPME, MeTHF**
- Amide couplings :  
✓ **DMF** -> **DMC, DMI**
- Alkylations/Reductive aminations  
✓ **DMF, DCM** -> **DMC, CPME**
- SNAr  
✓ **DMF** -> **DMI**



# Continuous improvement

## CMR-free month challenge - Guidance



Reaction Type	Conditions	Recommended Solvents
<b>Alkylation</b>	Strong bases	MeCN, CPME, MeTHF
	Weak bases	MeCN, CPME, MeTHF, Acetone
<b>Amide Formation</b>	Coupling agents	DMC, DMI, MeCN, EtOAc, MeTHF, CPME
	From ester (DABAL, AlMe <sub>3</sub> )	CPME
<b>Reductive Amination</b>	NaBH(OAc) <sub>3</sub>	EtOAc, DMC
	Ti(OiPr) <sub>4</sub> or Ti(OEt) <sub>4</sub>	MTHP, CPME
<b>SNAr</b>	Strong bases	DMI, MeCN
	Weak bases/acidic	iPrOH, MeCN, DMI
<b>Pd/Cu Cross Couplings</b>	Suzuki, Buchwald, Sonogashira...	MeTHF, CPME, MTHP, MeCN, iPrOH, tBuOH
<b>Protections</b>	Boc <sub>2</sub> O, CBzCl, MOMCl, TBSCl...	CPME, MeTHF, MeCN
<b>Deprotections</b>	Acidic (HCl)	CPME, iPrOH
	Basic (Weak base)	MeCN, MeTHF, CPME
<b>Oxidations</b>	mCPBA, Dess-Martin	MeTHF
<b>Reductions</b>	LiAlH <sub>4</sub> /DIBAL	MeTHF, CPME
	NaBH <sub>4</sub>	EtOH

DCM, DMF, Dioxane, and THF are some of the most frequently used reaction solvents.

They all carry the “**Serious Health Hazard**” GHS pictogram



All of the solvents in this table are more sustainable, and more importantly for you, safer alternatives.





# The “Green and Alternative Chemistry” working group

Thanks to all my colleagues and the global chemistry community

## Green chemistry group – Toulouse

Chloé Keignart, Sylvain Veau, Sandy Pèrié, Jerome Toum, Nicolas Molinier, Kim Spielmann, Sylvain Picon, Julien Malassis



### Enzymatic chemistry

- Marion Trillaud
- Virginie Suchaud
- Claire Blanger
- Jane Totobenazara

### Micellar chemistry

- Perrine Remaud
- Guillaume Lafitte
- Sylvain Veau
- Maxime Follain





# ***Back-up slides***



# Decrease catalyst loading with no conversion impact

Pd equivalent

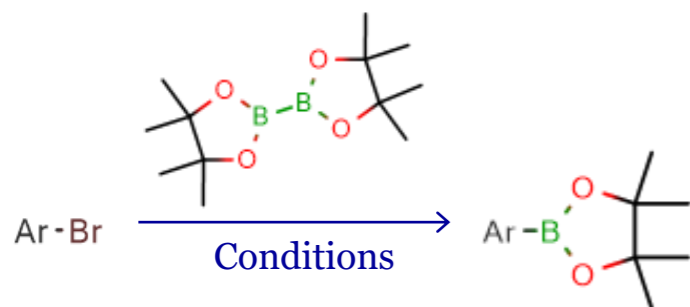
Reaction

Work-up

Purification

- Conditions for Pd-catalysed coupling reactions (Suzuki, Buchwald, Sonogashira, ...): a 10% catalyst loading is usually selected by default. This loading is usually kept on larger scale (1 to 10 g) which requires a significant quantity of catalyst
- However, most reactions do not require such loading
- Recommendations: for the optimisation work (20 to 100 mg), opt for a 5 mol % loading instead of 10 mol %, and reduce this quantity as much as possible on larger scale (to 1-3 mol %)
- More environmentally aware approach (Pd is part of endangered element)<sup>1</sup> and reduces the residual Pd content in final batch

## Case study: Miyaura borylation



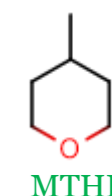
### Initial conditions

- ArBr (1 equiv.),
- B<sub>2</sub>Pin<sub>2</sub> (1.3 equiv.)
- Pd(dppf)Cl<sub>2</sub> (10 mol%)
- AcOK (3 equiv.)
- 1,4-dioxane 0.17 M
- 80 °C, 16 h, **83 % yield**
- **400 mg catalyst/1 g ArBr**

### Optimised conditions<sup>1</sup>

- ArBr (1 equiv.),
- B<sub>2</sub>Pin<sub>2</sub> (1.3 equiv.)
- Pd(dppf)Cl<sub>2</sub> (2 mol%)
- AcOK (3 equiv.)
- MTHP 0.28 M
- 90 °C, 4 h, **81 % yield**
- **80 mg catalyst /1g ArBr**

- ✓ Reaction carried out on 12 g scale
- ✓ MTHP non miscible with H<sub>2</sub>O
  - w.u made easier
  - solvent could be recycled
- ✓ Catalyst loading reduced by 5-fold
  - Purification made easier



12 g scale: 900 mg of catalyst used, instead of 4.6 g. Sigma: 329 Euros for 5 g of Pd(dppf)Cl<sub>2</sub>



# DCM/MeOH efficiently replaced during flash chromatography (ii)

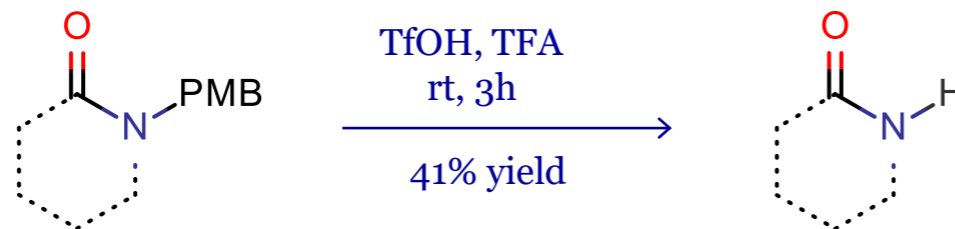
EtOAc/EtOH (3:1) in MTBE highly efficient for very polar compounds

Reaction

Work-up

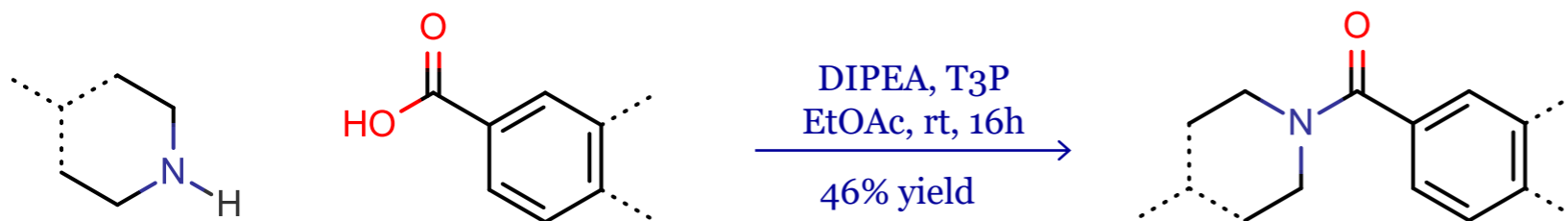
Purification

## Case study 2



## Purification

- Normal phase column chromatography: (EtOAc/EtOH 3:1) in MTBE from 0% to 15% gave similar yield and product purity than MeOH in DCM



MTBE/(EtOAc/  
EtOH mix) 9:1



Heptane/(EtOAc/  
EtOH mix) 1:1

## Purification

- Normal phase column chromatography: (EtOAc/EtOH 3:1) in MTBE from 0% to 30%



# CMR solvent replacement – A lot of alternatives (iv)

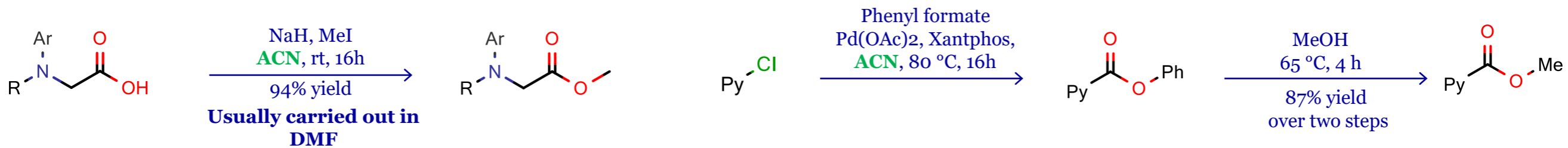
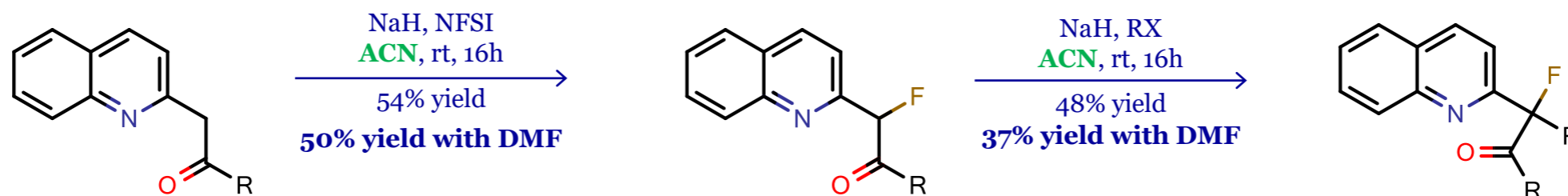
Miscellaneous & selected internal examples

Reaction

Work-up

Purification

DMF/NMP/Dioxane → ACN



Explosion hazards when combining DMF and NaH : see <https://pubs.acs.org/doi/10.1021/acs.oprd.9b00276>



# Partnership with Rosachem®

Platform for chemicals exchange

- **Rosachem®: platform that offers to collect chemicals and equipments no longer needed by company or university, to "donate" them to other organisations (subscription system)**
- **Revalue our unused and store reagents**
- **Decrease Evotec carbon footprint**
  - Avoid destruction
  - Favor circular economy

1	Container Barcode	Seau	CAS Number	Molecule Name	Risk Code
15	1073990	B	31301-51-6	2-chloro-5-fluoropyridine	H226, H301, H302, H310, H315, H318, H330, H335, P261, P280,
16	1075069	A	161491-24-3	1-tert-butyl 3-methyl 4-oxopiperidine-1,3-dicarboxylate	H303, H313, H333
17	1076550	A	1118-68-9	2-(dimethylamino)acetic acid	H302, P264, P270, P330, R10, R48/20/21/22, Xn
18	1077025	C	7087-68-5		
19	1078204	B	10344-42-0	4-bromo-3,6-dichloropyridazine	H302, H315, H319, H335
20	1078575	B	54675-23-9	6-bromo-4-hydroxy-1,2-dihydroquinolin-2-one	H302, H315, H319, H332, H335
21	1079609	B	91-22-5	QUINOLINE	H301, H312, H315, H319, H350, H400, H410,
22	1079919	B	96-48-0	gamma-Butyrolactone	N/A
23	1090737	A	54010-75-2	zinc bis(trifluoromethanesulfonate)	H314
24	1091831	A	446-52-6	2-fluorobenzaldehyde	H226, H302, H315, H319, H335, P210, P241, P261, P405, R10, X
25	1093303	B	109384-19-2	tert-butyl 4-hydroxypiperidine-1-carboxylate	H315, H319, H335,
26	1095881	B	3034-53-5	2-Bromothiazole	H315, H319, H335, P261, P280, P321, P405, R10, R48/20/21/22,
27	1096176	A	540-72-7	sodium thiocyanate	H302, H312, H319, H331, H332, H412, P261, P273, P280, P311,
28	1096216	A	23062-17-1	2-methyl-1,3-oxazole-4-carboxylic acid	H319,
29	1096217	A	81477-91-0	benzyl N-(diphenylmethylidene)glycinate	H303, H313, H333
30	1096543	A	1367674-43-8	1-methyl-6-oxopiperidine-2-carboxylic acid	N/A
31	1096545	A	72002-30-3	(2R)-6-oxopiperidine-2-carboxylic acid	H302, H315, H319, H335
32	1097129	A	454712-26-6	tert-butyl 3-(methylamino)pyrrolidine-1-carboxylate	H301, H400, P273, N, T
33	1097337	A	63725-51-9	6-chloro-1H-pyrazolo[3,4-b]pyridine	H302, H315, H319, H335
34	1097381	A	1059626-05-9	(4-fluorobenzyl)hydrazine hydrochloride (1:1)	H302
35	1097394	A	75513-35-8	3-(1,3-dioxo-3,4-dihydroisquinolin-2(1H)-yl)propanoic acid	N/A
36	1097815	A	144-49-0		
37	1097859	A	7340-90-1	5-tert-butyl-2-methylbenzenethiol	H226, H304, H315, H317, H319, H336, H373, H400, H410, P210,
38	1097915	A	606488-94-2	3-hydroxycyclohexane-1-carboxylic acid	N/A

*331 compounds diverted from destruction, so far (>15 kg)*



Innovante



Ecologique



Economique



Collaborative



# Abbreviations – CMR classification

A lot of commonly used solvents associated with CMR hazards ...

<b>Hazard statements</b>	<b>Category 1A or 1B</b>	<b>Category 2</b>	<b>Effects on or via lactation</b>
Carcinogenic	H350: May cause cancer	H351: Suspected of causing cancer	
Mutagenic	H340: May cause genetic defects	H341: Suspected of causing genetic defects	
Reprotoxic	H360: May damage fertility or the unborn child	H361: Suspected of damaging fertility or the unborn child	H362: May cause harm to breast-fed children

## **CMR solvents list (associated risk phrases)**

- Category 1
  - **DCE:** H350
  - **Toluene:** H361d Suspected of damaging the unborn child.
  - **DMF:** H360d
  - **DMA:** H360d May damage the unborn child
  - **NMP:** H360
- Category 2
  - **DCM:** H351
  - **THF:** H351
  - **Dioxane:** H351
  - **CHCl<sub>3</sub>:** H351





## Other

### Polystyrene boxes and gel packs collection

#### Polystyrene boxes

##### Collection points implemented in all departments

- Boxes having the appropriate size/dimensions (2 sizes accepted) will be directly reused for shipments, by the distribution team.
- The rest will be separately collected by Knauf, to recycle them as insulating panels.

#### Gel packs



##### Collection points also implemented

- Solid gel packs collected and reused by the distribution team
- Soft gel packs are also collected. We are currently working with Toulouse metropole to divert this item from incineration





## Other

### Other initiatives

#### Solvent and detergents bottles reused for liquid waste

- A significant amount 10L bottles are purchased each year to place our liquid waste (3000 bottles)
- In parallel, we also empty a lot of 10 L bottles waste, that we through away as such (300 bottles).
- Collection point has been implemented for this bottles, which are not reused
- Work to extend this to other items



#### Disposable coffee cups

- **70000** disposable coffee cups used on site each year
- August 2024 : coffee is now free only if you bring your own cup
- A drastic reduction in the disposable coffee cup usage has already been observed





# Promote a sustainability culture within the scientific community

## Sharing our knowledge

Evotec  
76,084 followers  
1yr · 🌐

Evotec was very happy to present green & sustainable chemistry during the poster session of JCO2022 congress in Palaiseau France! What a nice place to discuss our science. Great event, with fantastic lectures! If you missed ...see more

Poster:  
**Green Chemistry at Evotec**

Presented at JCO2022 Congress

DOWNLOAD

👍 140    3 reposts

👍 Like    💬 Comment    🔄 Repost    ➦ Send

**Sustainability and Green Chemistry at Evotec**

14 November 2022  
Resource Type: Blog, Medicinal Chemistry, Posters

- **Shared information** via LinkedIn posts and on Evotec website
- Providing the chemists community with **scientific productions** – enrich & share Evotec science pool (e.g. solvent guide, tips, ...)
- **Attending conferences** – Poster session & communication
- **Sharing** our results and observations with the scientific community

I am participating in the 2024  
**FREEZER CHALLENGE**

JOIN ME

www.freezerchallenge.org

freezer challenge

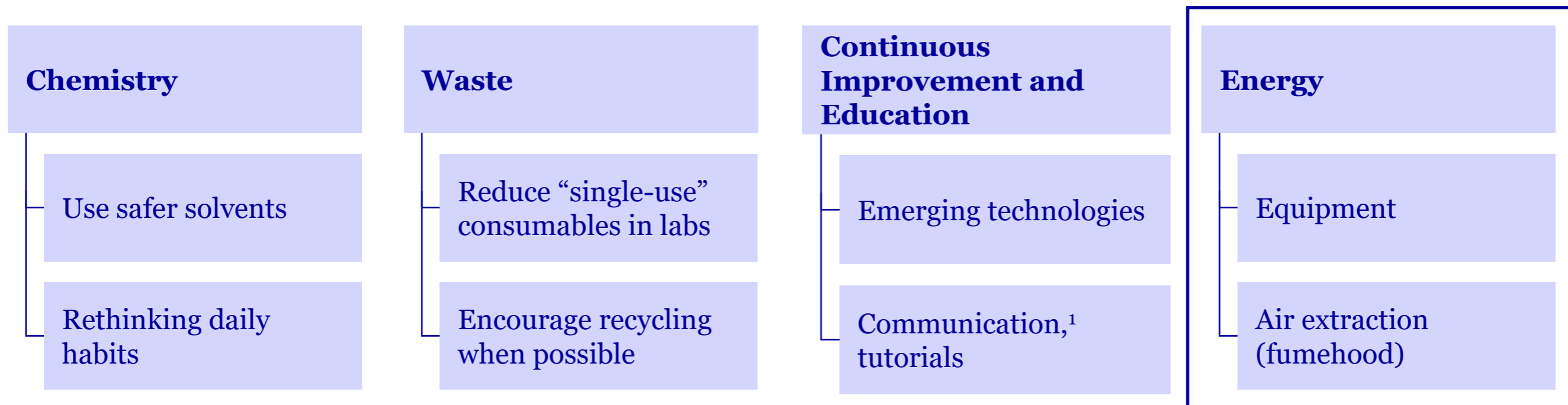




# Green & sustainable chemistry @ Evotec

A global strategy and a continuous improvement initiative

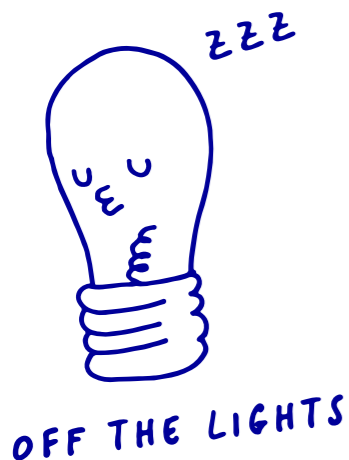
- **Green chemistry implemented while maintaining our level of excellence in drug discovery** (this presentation)
  - Improvement of our chemical processes and working habits with a sustainable vision
  - Expertise in alternative chemistry
- **Sustainability as part of the global initiative: 4 pillars identified to reduce our environmental impact**
  - Our chemists committed to adopt more responsible practices





# Energy saving

Small habits change, big difference



*Turn off the fume hood lights when not in use*



*Switch on the equipment only when in use*



*Share the equipment wherever possible*

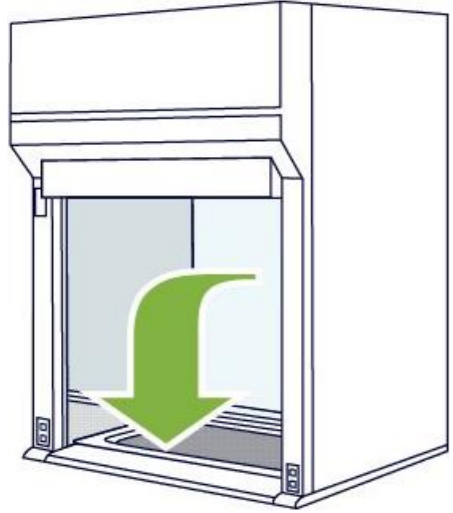


- **Small water baths can consume as much energy as a dishwasher every hour**
- **Regularly defrost freezers (once a year) – 65.5 kWh/day saved for chemistry department only**
- **Reduce paper printing, turn-off every unused machines**
- **Regularly clean the e-mail box, use sharepoint for attach document**



# Energy saving

## Air extraction



*Shut the sash!*  
*Light control system*



*Green light:*  
*Optimized extraction capacity*  
*Minimum energy*



*Orange light:*  
*Not ideal, although*  
*Ok to work*



*Red light:*  
*Unsafe*

- **A single fumehood left open can consume as much energy as 3.5 households**
- **Evotec Toulouse: traffic light system has been implemented in every lab -energy saving + safety improvement**



# Sustainable & green chemistry = savings + safety

## Main achievements

- **Shuttle service** (5 solvents identified, to be started by the end of this year)
  - Cheaper, safer and more sustainable (less waste)
  - **>22 k€/year** of savings for only 2 solvents!



- **Order rationalization** (collaboration with Fatiha Ouldaa and Léa Bézes)
  - Normal phase FCC from Interchim® **40 k€/year** of savings
  - Extension to reverse phase FCC and dry load ongoing
    - Anticipated savings for RP FCC: **44 k€/year**
    - Anticipated savings for dry load: **35 k€/year** (for single use) ; **50 k€/year** (if re-used 20 times)

- **Plastic consumables** (phase separators removed from the stock room)
  - Alternative: Hydrophobic papers & Na<sub>2</sub>SO<sub>4</sub>
  - **>10 k€/year** of savings



- **Bin ordering reduction**
  - A thousand less buckets (23 and 10L) ordered in 2023 compared to 2022 (3686 vs 4760)
  - **23% reduction- 5,7 k€ of savings** – Mainly attributed to our global effort in consumable use reduction



# Improving the chemist's toolbox

Enabling technologies to assist progression of partnered projects and iR&D<sup>1</sup> activities

