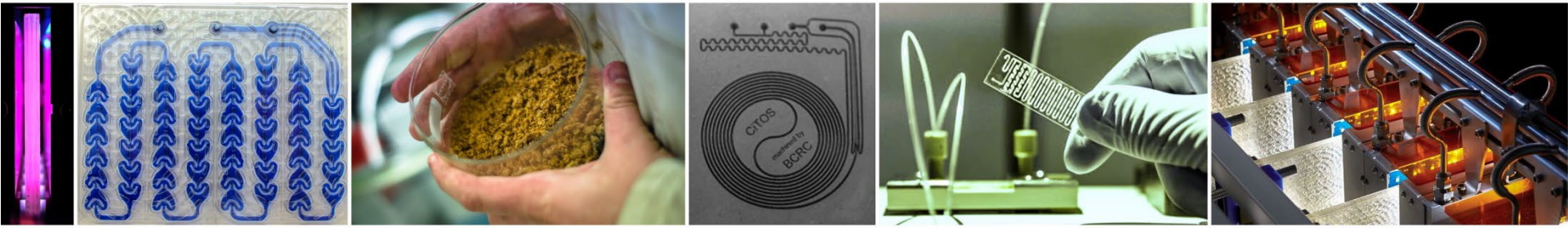

On the synergy between *in silico* approaches and flow

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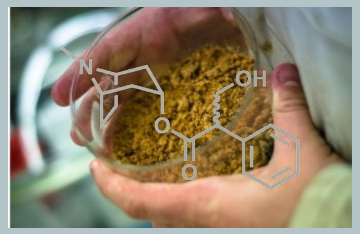
Flow Chemistry Europe 2024 Malaga

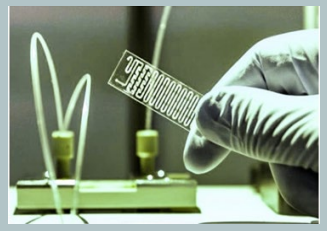
Research areas



ORGANIC CHEMISTRY

Improving chemical synthesis on R&D and production scales

Connecting fundamentals of reactivity and technology



PROCESS TECHNOLOGY

COMPUTATIONAL CHEMISTRY

Interplay of flow tech & quantum chemistry

FLOW

Multiple synergies are possible

1 | Mechanisms and selectivities

Multiple synergies are possible

1 | Mechanisms and selectivities & **2 | Guiding corrective actions**

Multiple synergies are possible

1 | Mechanisms and selectivities & 2 | Guiding corrective actions

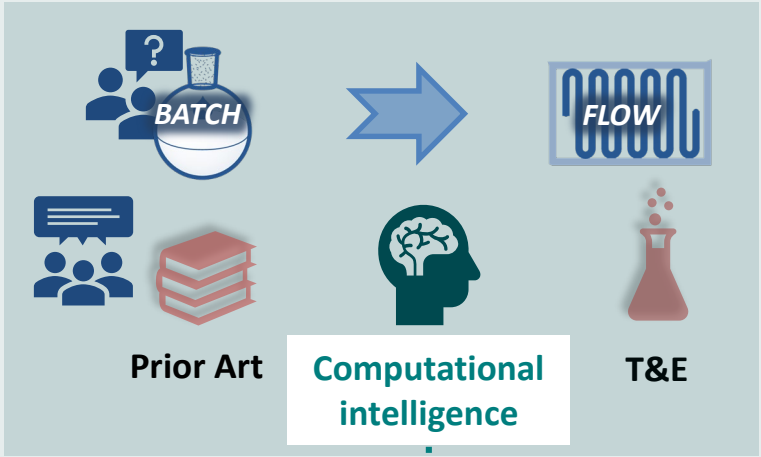
3 | High activity/toxicity compounds

Multiple synergies are possible

1 | Mechanisms and selectivities & 2 | Guiding corrective actions

3 | High activity/toxicity compounds

4 | Predicting feasibility



Timeframe?

DFT

$$k = \frac{\kappa k_B T}{h} e^{\left(\frac{-\Delta G^{\ddagger}}{RT}\right)}$$

Eyring

T/P compatibility

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{-\Delta H_{vap}}{R} * \left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

Is my reaction suitable for flow ?

If 95% conv.:

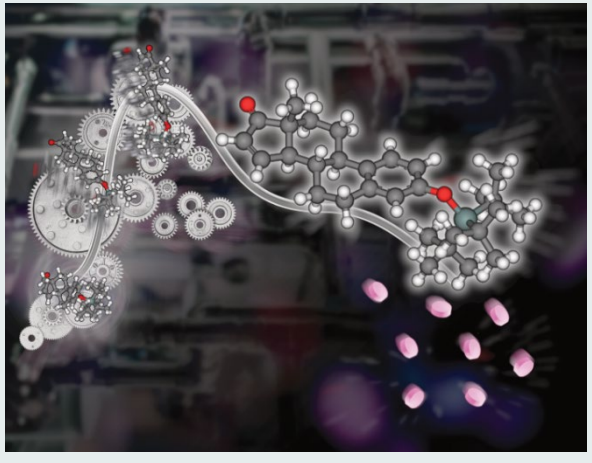
$\Delta G^{\ddagger}$(kcal mol^{-1})	5	10	15	20	25	30
1^{rst}, 0.1 M, 25 °C	<1 sec	<1 sec	<1 sec	2 min	6 days	73 years
1^{rst}, 0.5 M, 25 °C	<1 sec	<1 sec	<1 sec	2 min	6 days	73 years
1^{rst}, 0.1 M, 100 °C	<1 sec	<1 sec	<1 sec	<1 sec	1 min 30 s	20 hours
2nd, 0.1 M, 25 °C	<1 sec	<1 sec	2 sec	117 min	376 days	4766 years
2nd, 0.5 M, 25 °C	<1 sec	<1 sec	<1 sec	23 min	75 days	953 years
2nd, 0.1 M, 100 °C	<1 sec	<1 sec	<1 sec	6 sec	1 h 30	53 days

Predicting feasibility in flow

A priori computational intelligence

Minimizing chemical exposure, reducing waste and guiding flow experiments

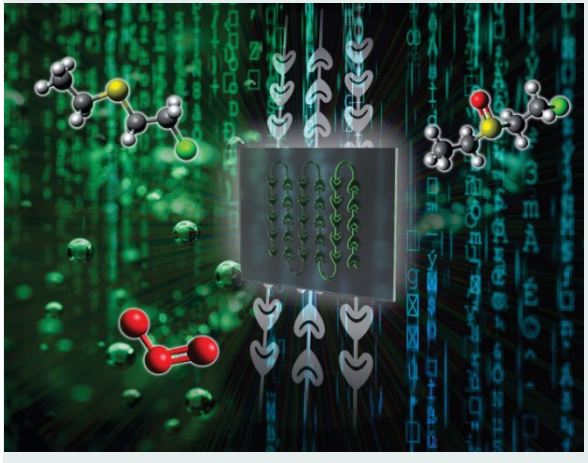
Estetrol (E_4) API
Thermolysis



Goals

- Lower production costs
- Increase productivity
- Minimize contacts with hormonal compounds

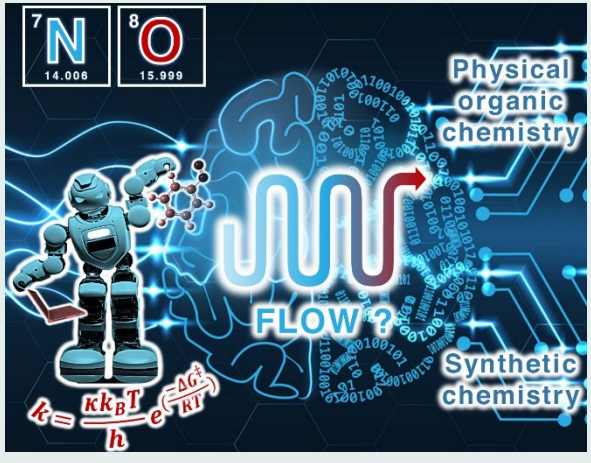
CWA neutralization
Ozonolysis



Goals

- Find the best simulant
- Assess suitability
- Avoid overoxidation

Discovery
Electrophilic aminations



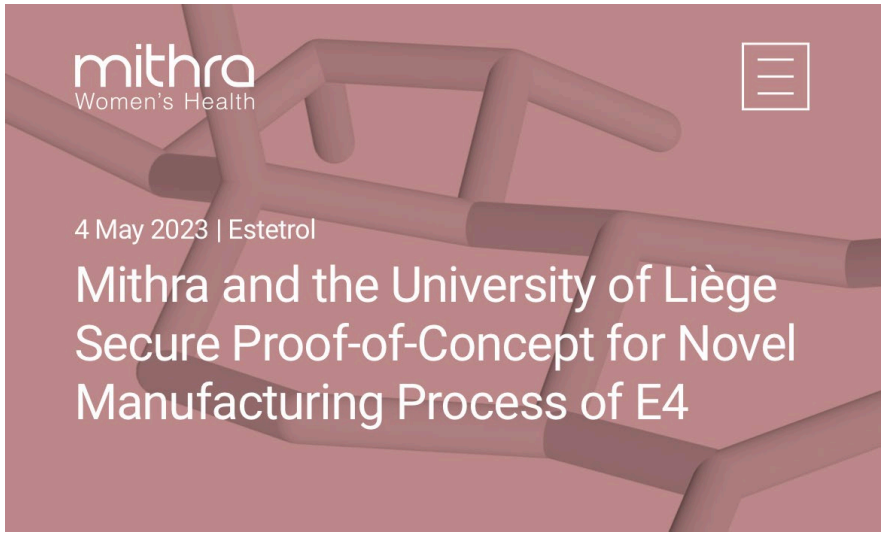
Goals

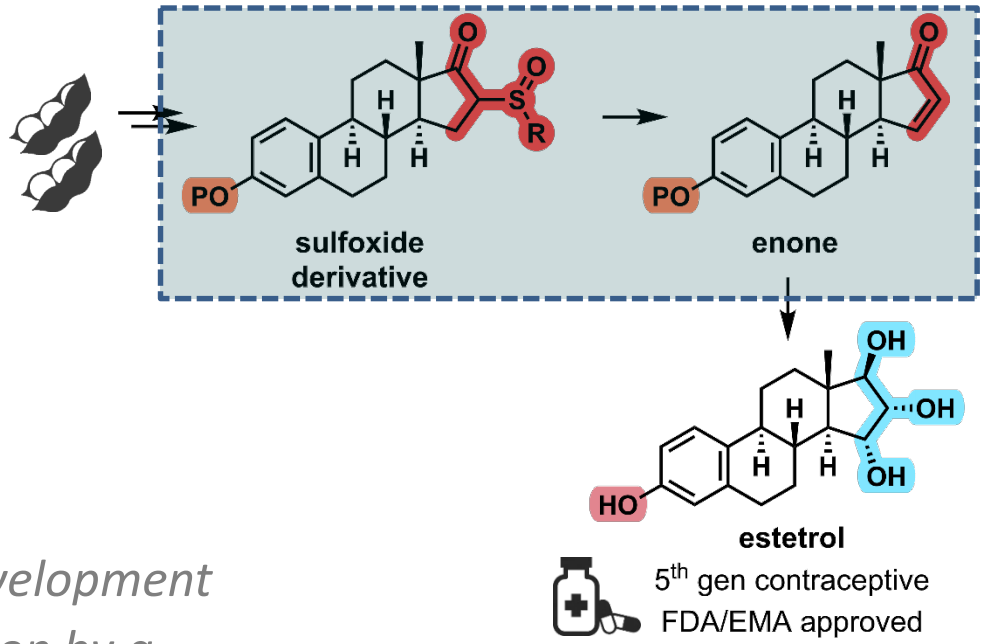
- Fast prediction
- Suitable for libraries
- General approach?

Predicting feasibility in flow

Thermolysis of a steroid sulfoxide derivative

Accelerate batch-to-flow transposition toward intensification





"Mithra and CiTOS will continue their development work, with initial commercial production by a CDMO using the enhanced manufacturing process expected in 2026/27"

React Chem Eng, 2023, 8, 1565

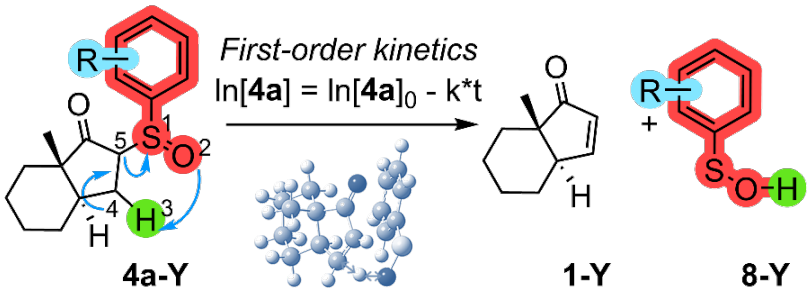
Predicting feasibility in flow

Thermolysis of a steroid sulfoxide derivative

Accelerate batch-to-flow transposition toward intensification

- Computational routine

TS analysis and activation barrier calculation



a priori kinetic data and feasibility under flow conditions

Timeframe?

$$k = \frac{\kappa k_B T}{h} e^{\left(\frac{-\Delta G^{\ddagger}}{RT}\right)}$$

	T (°C)	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$t_{99\%conv.}$ (min)
1	25	28.0	379527620
2	100	27.7	16526
3	150	27.6	145
4	200	27.4	3
5	250	27.3	0.2

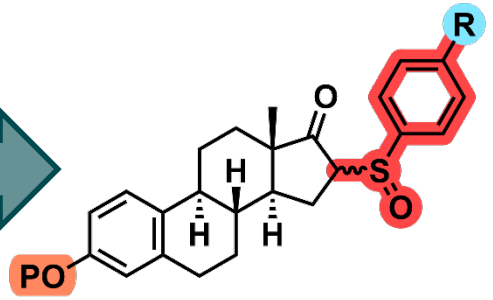
T/P compatibility w/ reactor setup

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{-\Delta H_{vap}}{R} * \left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$

B3LYP-GD3BJ/6-31+G*//M08HX/6-311++G** (SMD = toluene, 413 K)

React Chem Eng, 2023, 8, 1565

S(re)ARs



sulf-4a (R = H), **3 min** $$

sulf-4b (benzothiazole), **11 min** $

sulf-4c (R = Me), **15 min** $$$$

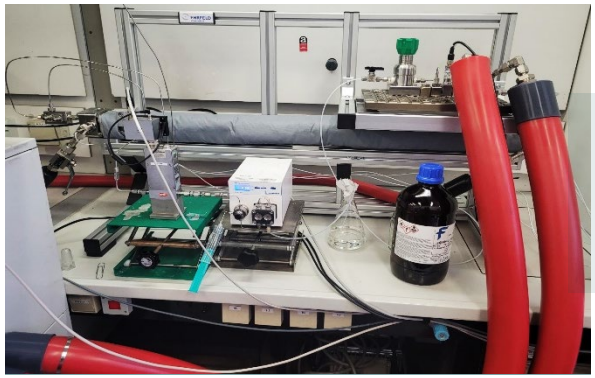
TOP 3
among 22 potential candidates

Predicting feasibility in flow

Thermolysis of a steroid sulfoxide derivative

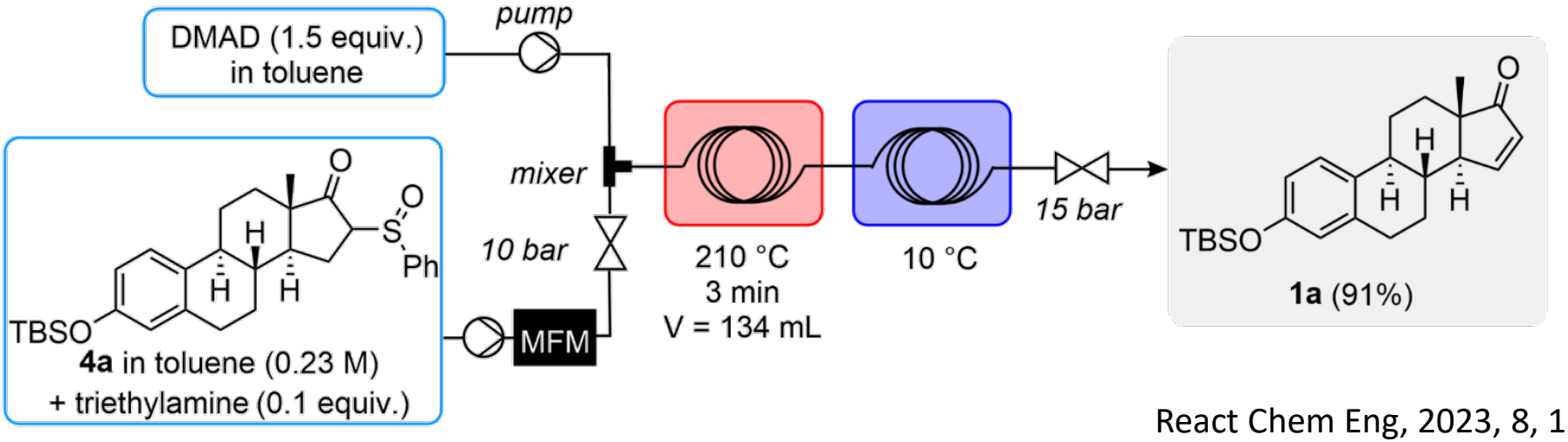
Accelerate batch-to-flow transposition toward intensification

- Translation into an intensified flow process at pilot scale



210 °C and 3 min
STY: 1.13 kg L^{-1} h^{-1}

1.1 mt per year
several million doses
*(15 mg **E_4**)*



React Chem Eng, 2023, 8, 1565

Predicting feasibility in flow

Neutralization of chemical warfare agents with ozone

Selectivity and feasibility under flow conditions

- Can we achieve fast and selective reactions for mobile neutralization setups?

Chemical neutralization

highly toxic sulfur vesicants

HD

[O]

less toxic sulfoxides

HDO

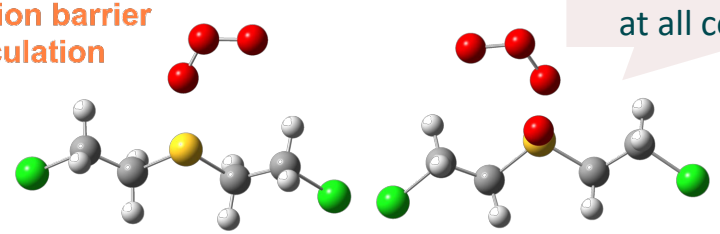
[O]

highly toxic sulfones

$CEVSO_2$

Overoxidation – avoid at all costs!

TS analysis and activation barrier calculation



$TS_{ox.1}$
$\Delta G^{\ddagger}$ = 3.2 kcal mol^{-1}

$TS_{ox.2}$
$\Delta G^{\ddagger}$ = 9.2 kcal mol^{-1}

Overoxidation – avoid at all costs!

Fast reactions (<1 s)

a priori kinetic data and feasibility under flow conditions

HD

military clearance
OPCW ban

simulant:

CEES

CEPS

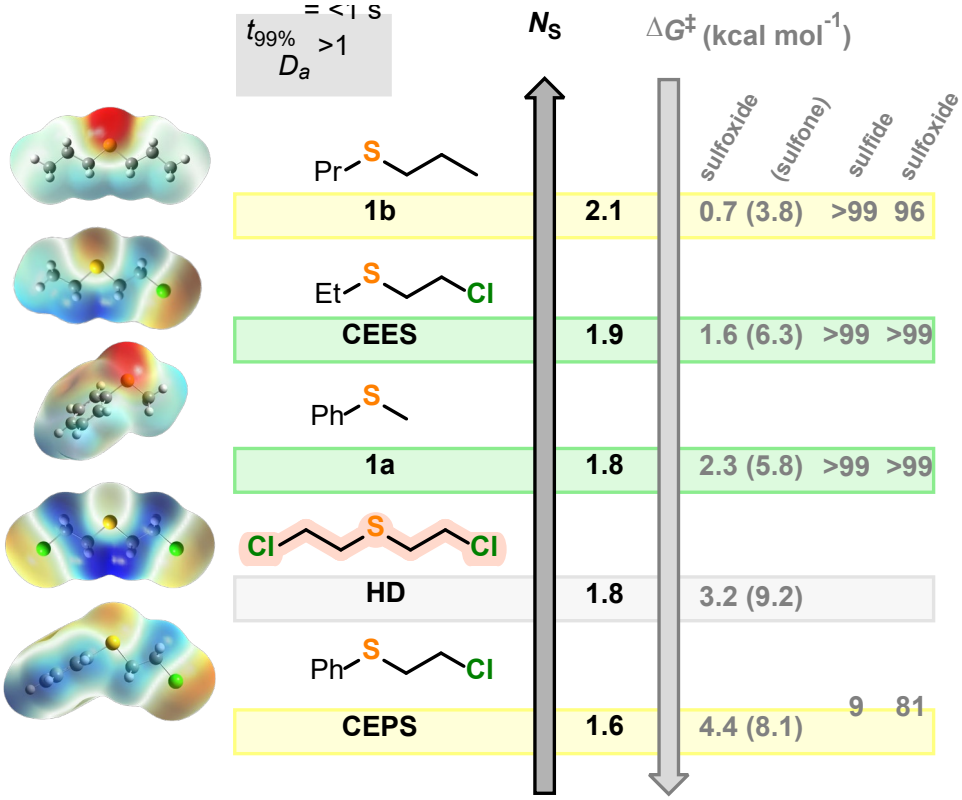
Green Chem 2020, 22, 4105; Green Chem 2021, 23, 2336; Green Chem 2024, 26, 1281

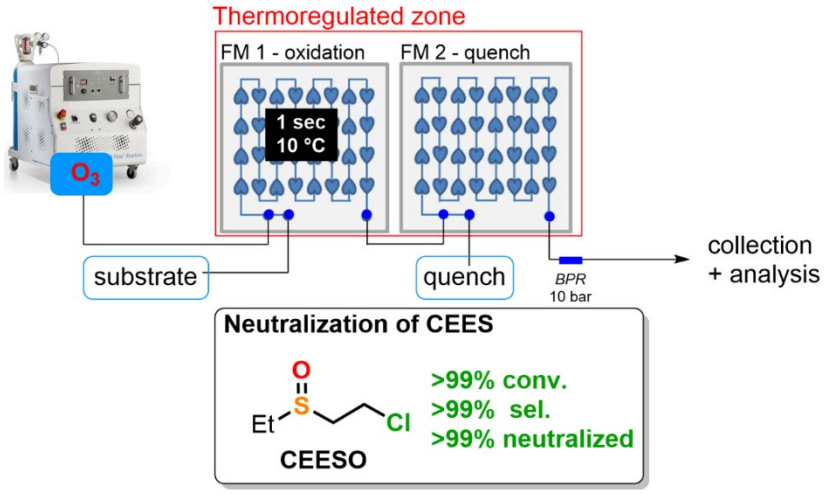
Predicting feasibility in flow

Neutralization of chemical warfare agents with ozone

Selectivity and feasibility under flow conditions

- Transposition in flow with suitable simulants





- No additives/catalysts
- Simple and scalable setup
- Feeds only on O_2
- Commercial ozone generator

Green Chem 2020, 22, 4105; Green Chem 2021, 23, 2336; Green Chem 2024, 26, 1281

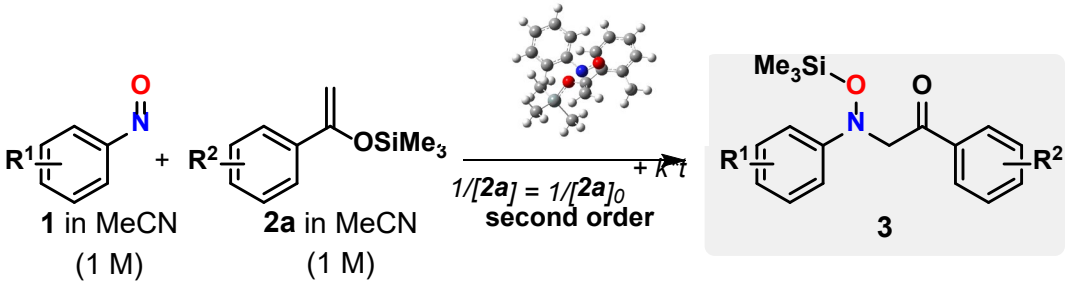
Predicting feasibility in flow

Electrophilic aminations toward librairies of aminoketones

Toward non-generic, tailored conditions

- Can we speed up the prediction process?

TS analysis and activation barrier calculation



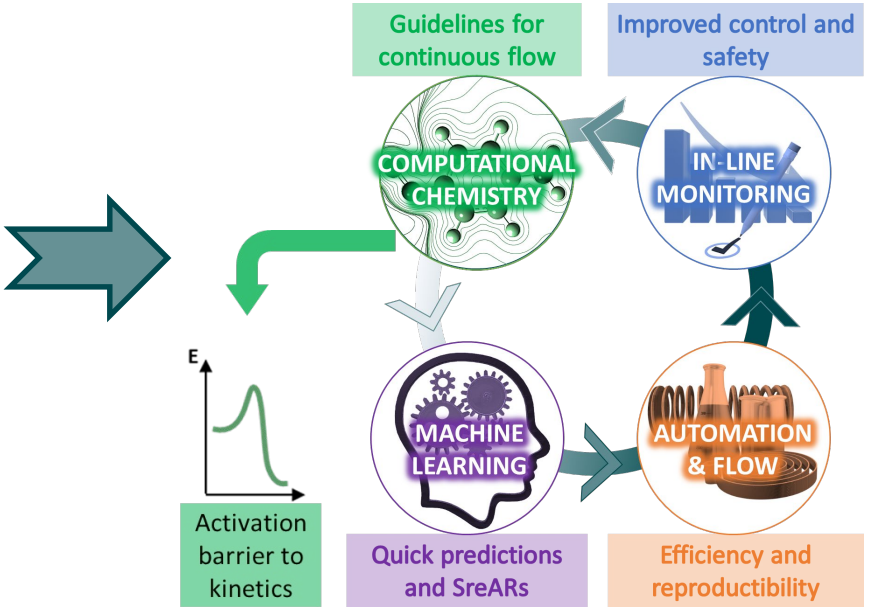
a priori kinetic data and feasibility under flow conditions

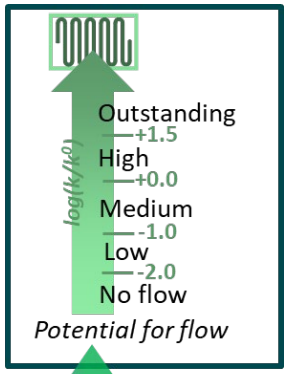
Timeframe?

$$k = \frac{\kappa k_B T}{h} e^{\left(\frac{-\Delta G^{\ddagger}}{RT}\right)}$$

Entry	T (°C)	$t_{90\%conv.}$ at 0.5 M (min)
1	25	589
2	50	168
3	100	22
4	150	4

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{-\Delta H_{vap}}{R} * \left(\frac{1}{T_2} - \frac{1}{T_1}\right)$$





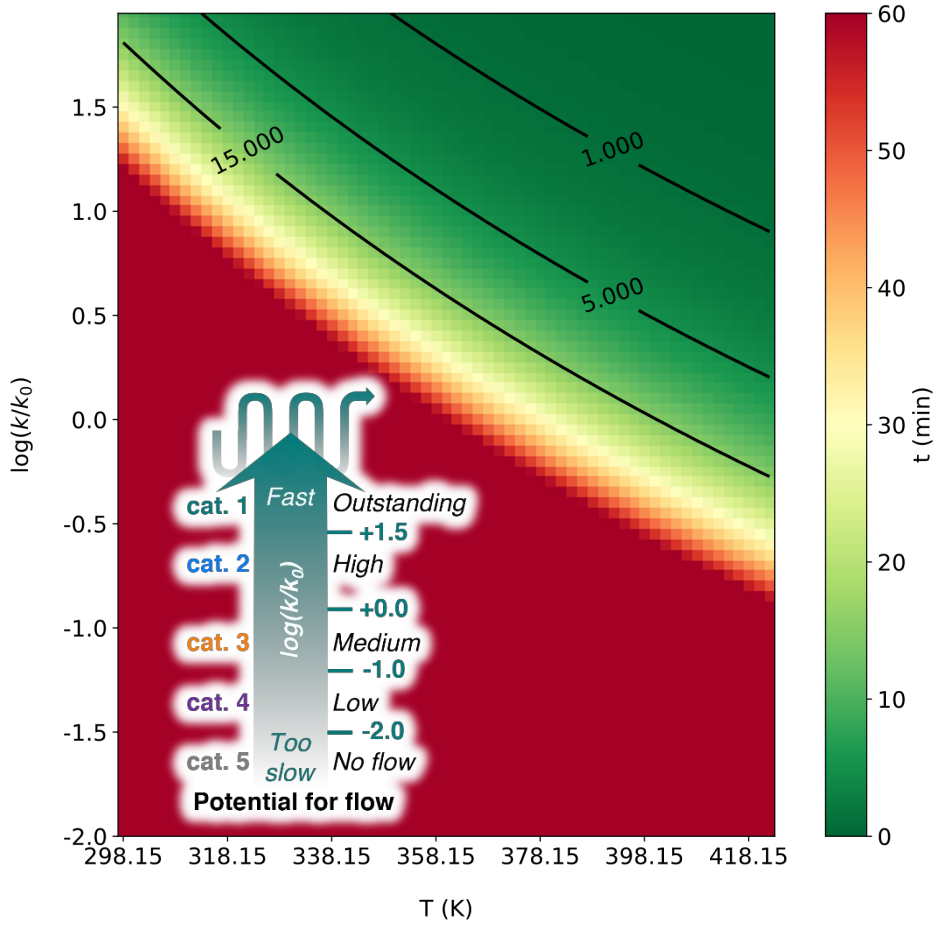
TO FLOW OR NOT TO FLOW?

Angew Chem Int Ed, 2024, 63, e202311526 *MAE: 0.3 kcal mol^{-1}*

Predicting feasibility in flow

Electrophilic aminations toward librairies of aminoketones

Toward non-generic, tailored conditions



Category 1 = *outstanding* (**log(*k*/*k*$_0$)**>1.5): no thermal activation for completion within 15 min or short residence times (<1 min) if thermal activation

Category 2 = *high* (1.5>**log(*k*/*k*$_0$)**>0.0): thermal activation and residence times of 1-5 min at 150 °C depending on concentration and target conversion

Category 3 = *medium* (0.0>**log(*k*/*k*$_0$)**>-1.0): thermal activation and longer residence times (5-15 min at 150 °C) to achieve high conversions

Category 4 = *low* (-1.0>**log(*k*/*k*$_0$)**>-2.0): extremely high temperatures (>150 °C) or lower conversions in a flow system within 15 min

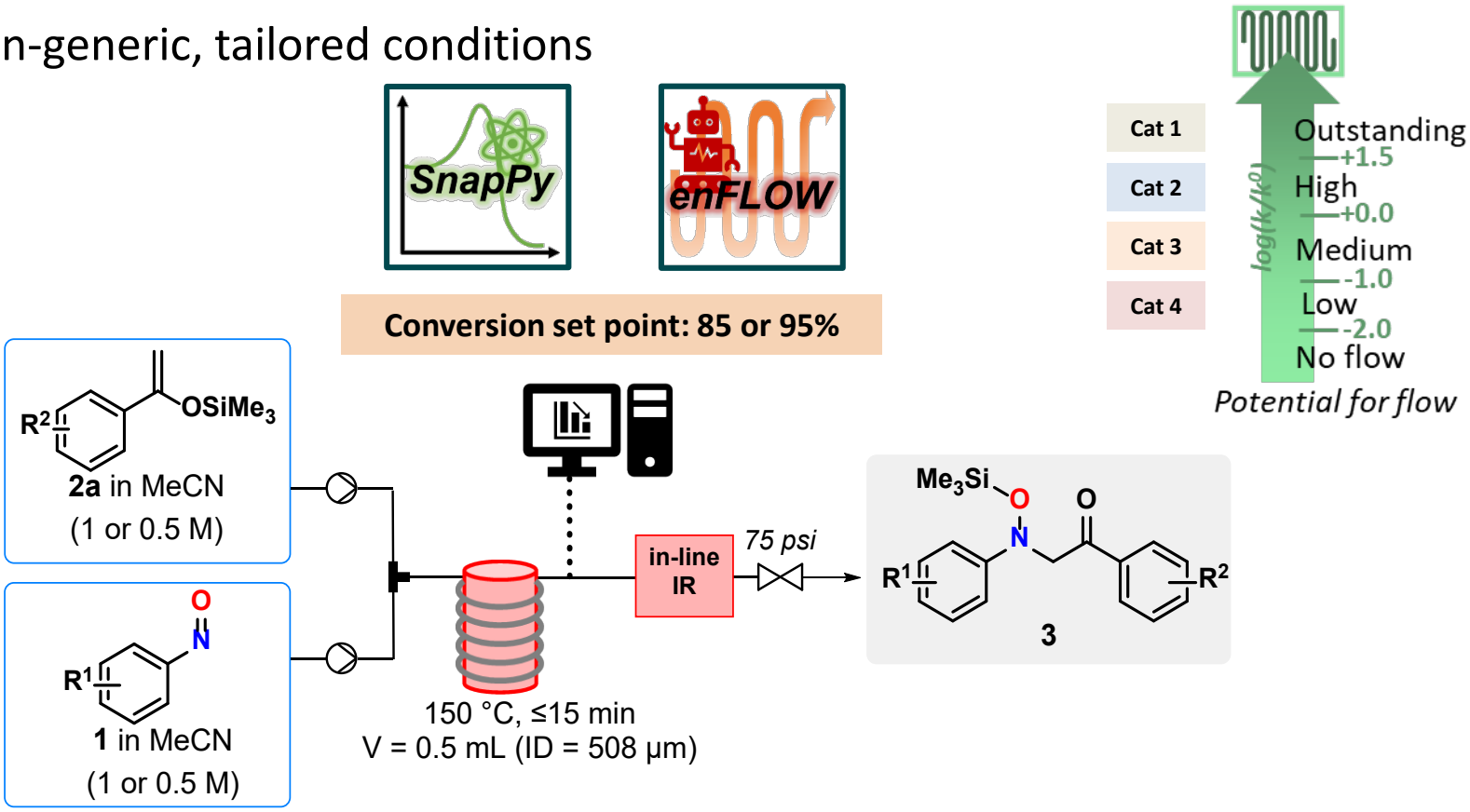
Category 5 = *NOGO* (**log(*k*/*k*$_0$)**<-2.0): too slow to be performed in flow even with high temperatures

Angew Chem Int Ed, 2024, 63, e202311526

Predicting feasibility in flow

Electrophilic aminations toward librairies of aminoketones

Toward non-generic, tailored conditions



1 set of experimental conditions
(non generic) per substrate

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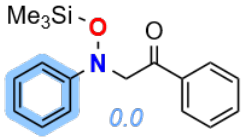
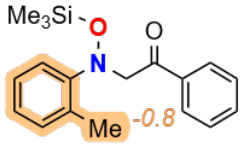
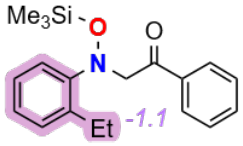
Predicting feasibility in flow



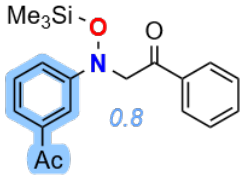
3a (0.5 M, 4 min)
[90%], 93%, (89%)



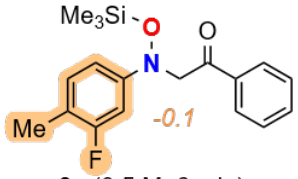
3b (0.5 M, 15 min)
[90%], 82%, (71%)



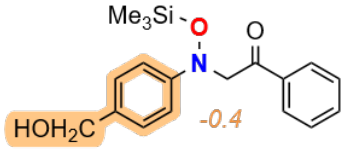
3c (0.5 M, 15 min)
3 equiv. **2b**
[85%], 83%, (70%)



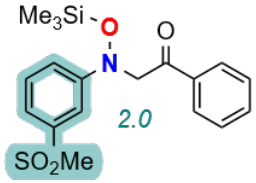
3d (0.25 M, 1 min)
[90%], 92%, (90%)



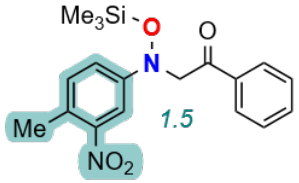
3e (0.5 M, 6 min)
[95%], 98%, (96%)



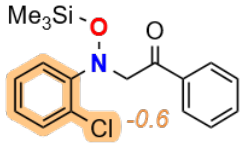
3f (0.25 M, 15 min)
[95%], 96%, (86%)



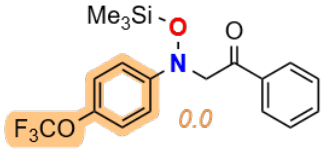
3g (0.25 M, 10 sec)
[90%], 90%, (89%)



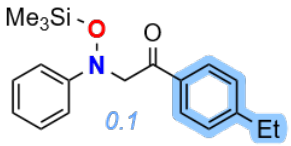
3h (0.25 M, 15 sec)
[95%], 94%, (90%)



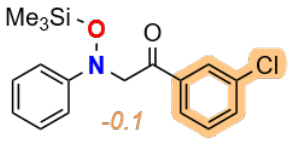
3i (0.5 M, 13 min)
[95%], 95%, (60%)



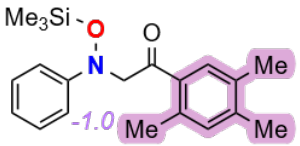
3j (0.25 M, 8 min)
[95%], 93%, (91%)



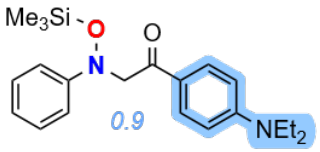
3k (0.5 M, 4 min)
[90%], 90%, (79%)



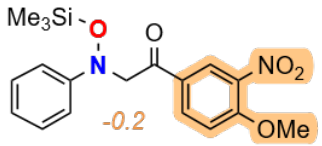
3l (0.5 M, 5 min)
[90%], 91%, (61%)



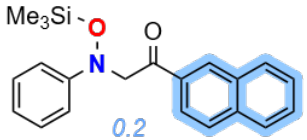
3m (0.5 M, 15 min)
[85%], 93%, (23%)



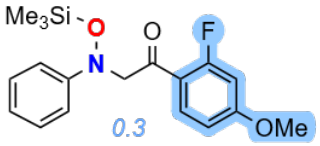
3n (0.5 M, 1 min)
[95%], 92%, (89%)



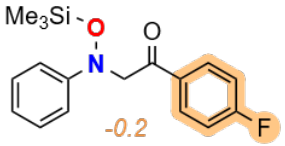
3o (0.5 M, 5 min)
[90%], 93%, (86%)



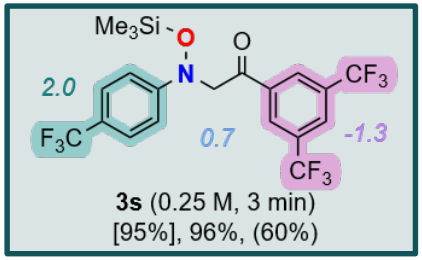
3p (0.5 M, 2 min)
[90%], 91%, (89%)



3q (0.5 M, 2 min)
[90%], 89%, (65%)



3r (0.5 M, 6 min)
[90%], 96%, (42%)



3s (0.25 M, 3 min)
[95%], 96%, (60%)

[conv.$^{th.}$], conv.$^{exp.}$, (yield) – cat. 1, cat. 2, cat. 3, cat. 4

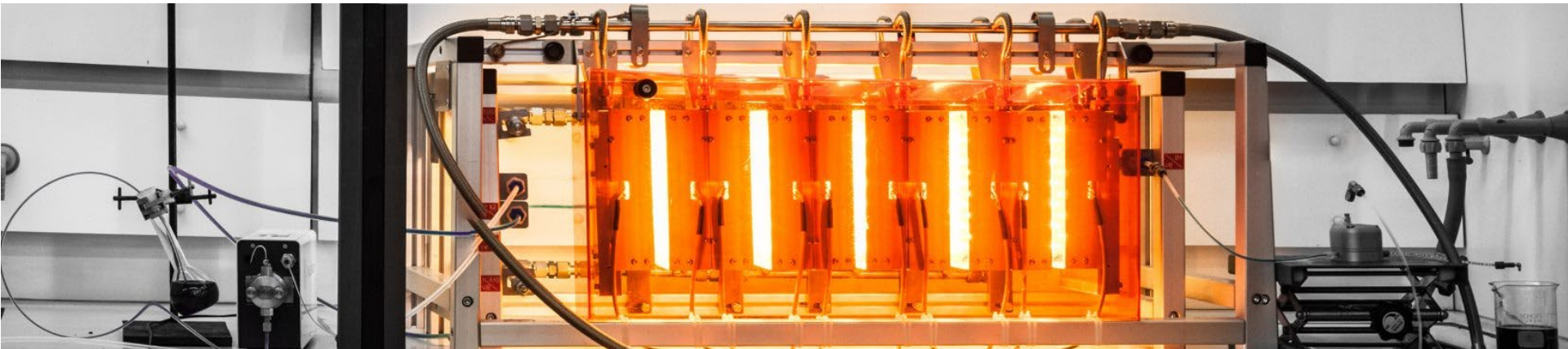
Angew Chem Int Ed, 2024, 63, e202311526

Conclusion

On the synergy between *in silico* approaches and flow

A multifaceted synergy

- Safer process conditions
- Rationalizing mechanisms and foreseeing corrective actions
- Predicting feasibility under flow conditions
- Accelerating the transposition toward flow with *a priori* intelligence
- Hybrid experimental/*in silico* models



Technology platform

FloW4all platform

Since 2023 – integrates the **Corning Qualified Laboratory**

flow4all@uliege.be

Flow tech resource center in Wallonia

Applied (industrial) aspects of manufacturing valued-added chemicals

CORNING
Advanced-Flow™ Reactors

Corning® Advanced-Flow™ Reactors
QUALIFIED LAB

The future flows through Corning® Advanced-Flow™ Reactors

Our strengths

Unique expertise & equipment
Lab to pilot
Scalable processes
(including un-/less conventional)
Multistep complex flow processes

Our services

consulting, flow process development, training, demos

Dr. D. Silva
Scientific Manager

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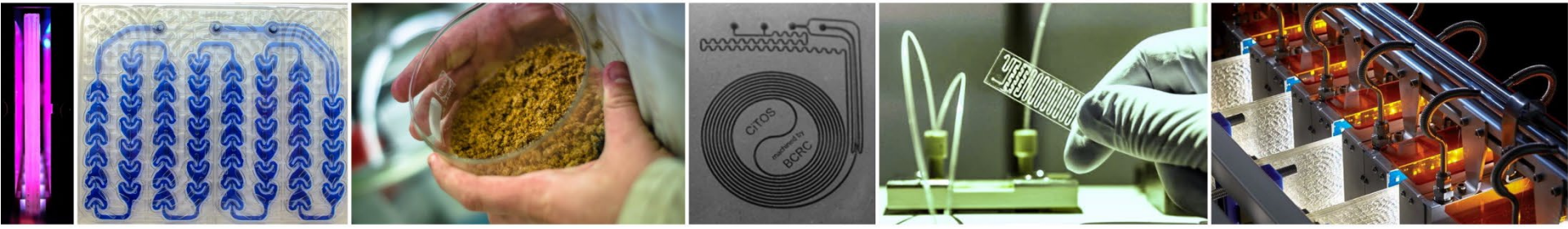
OPM Oncodesign Precision Medicine · GSK · FINCHIMICA TRUST IN AGROSCIENCE · WEYLCHEM



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