Synthèse organique en réacteurs miniaturisés à flux continu: faire mieux avec moins

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Mardis de la Chimie Durable - SCF

March 9th 2021

SCF

CNRS

INSA — Institut National des Sciences Appliquées Rouen Normandie

Université de Rouen Normandie

Normandie Université

Batch vs. Microflow

Fast reactions — *Slow reactions*

limited by mass and heat transfer | kinetic regime

Macrobatch reactor

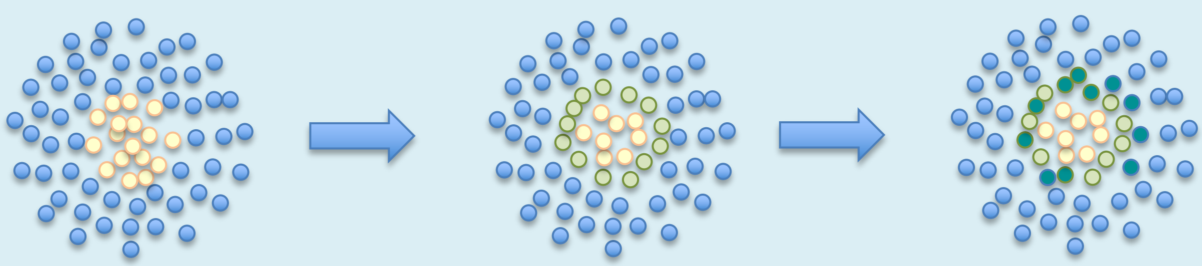
millisecond, second → minute, hour

P. Rys, *Acc. Chem. Res.* 1976, 345

A + B → P1 + P2

$k_1 \gg k_2$ → High selectivity for P1

$$\begin{cases} A + B \xrightarrow{k_1} P1 \\ A + P1 \xrightarrow{k_2} P2 \end{cases}$$



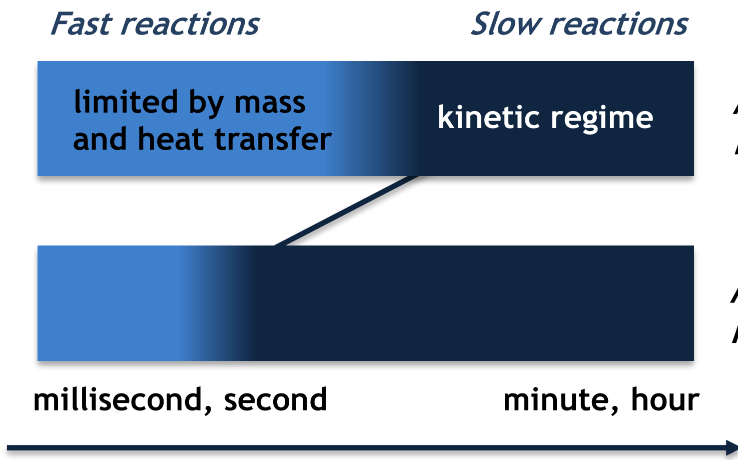
$r_{mixing} < r_{reaction}$

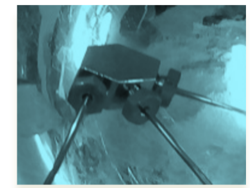
↓

unselective reaction

Batch vs. Microflow

Jun-ichi Yoshida
(1953-2019)



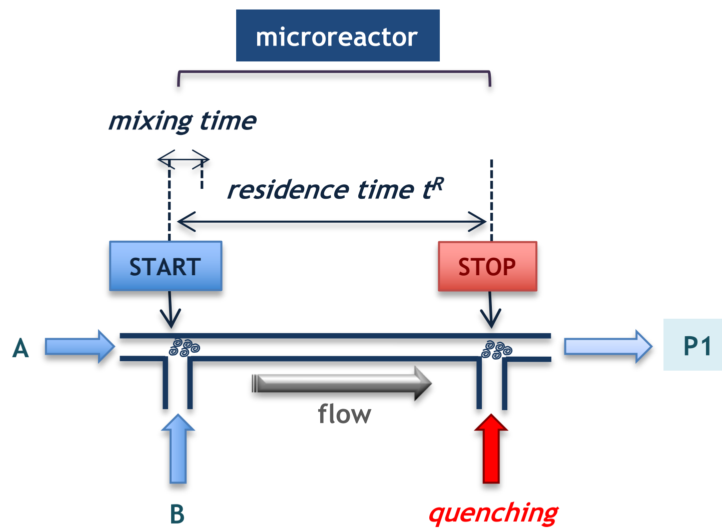


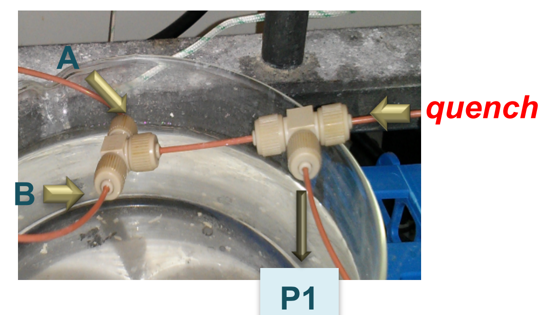
J.-i. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* 2011, 331

Fast mixing

Temperature control

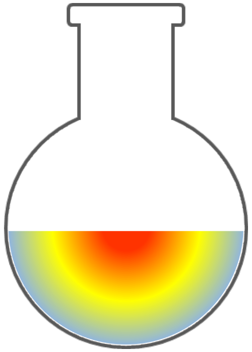
Very precise reaction time
Flash chemistry

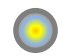




M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chemical Reviews*, 2017, 11796

Batch vs. Microflow





downsizing consequences

ID = 1.5 cm (10 mL)
S/V ratio = 3.6 cm^{-1} when half-filled

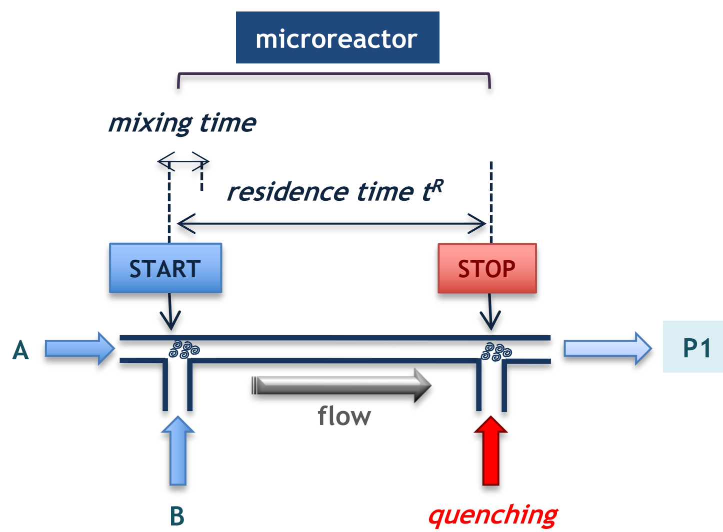
ID = 0.1 cm
S/V ratio = 40 cm^{-1}

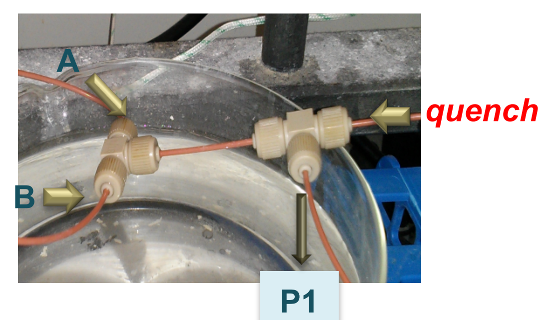
ID = 0.025 cm
S/V ratio = 160 cm^{-1}

Fast mixing

Temperature control

Very precise reaction time
Flash chemistry





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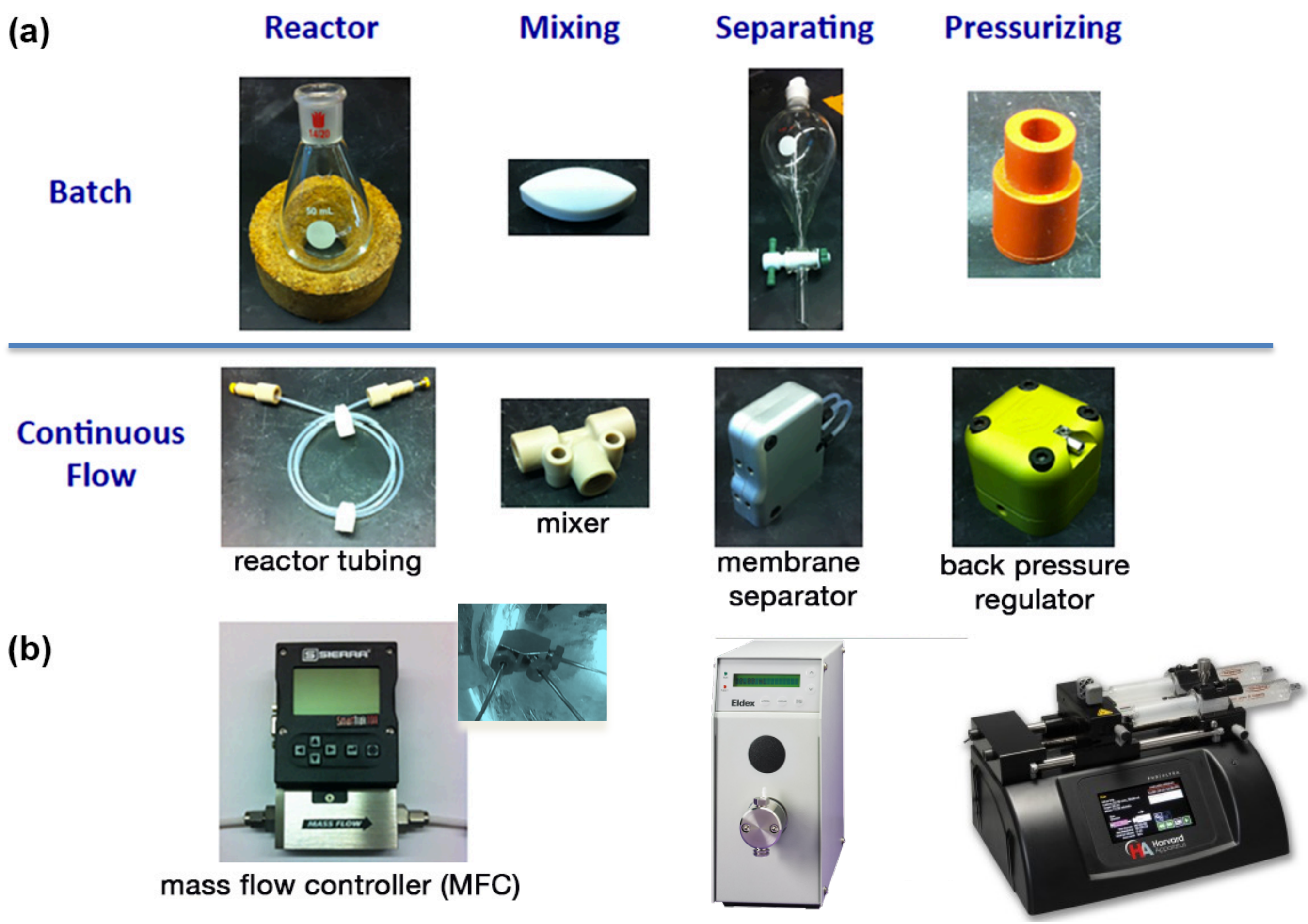
All-in-one devices

Equipment



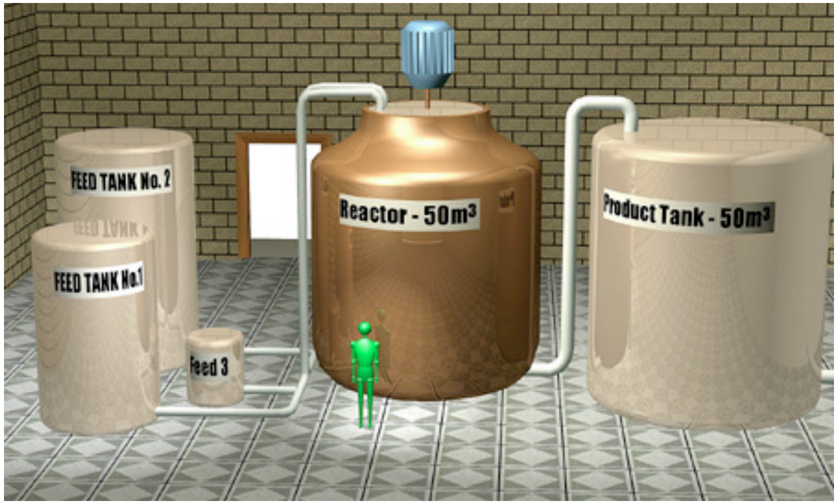
J. A. M. Lummiss, P. D. Morse, R. L. Beingessner, T. F. Jamison, *Chem. Rec.* 2017, 667

Continuous flow for process intensification

Laboratory
(50 mg - 10 g)

scale up

Transposition issues



Factory
(kgs - tons)

- material
- physical phenomena (stirring, heating)
- hazard (toxicity, explosivity)
- new synthetic path

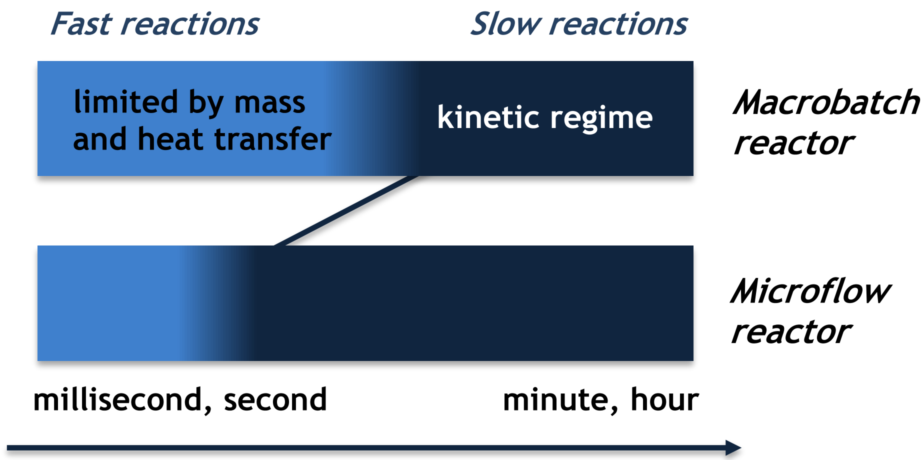
Flow

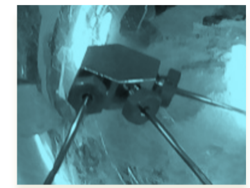
amount produced depends on flow rate and time → space-time yield = amount of product obtained per hour for one liter of reactor volume (g/L/h)

M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chemical Reviews*, 2017, 11796

Microflow to overcome competitive consecutive reactions

Jun-ichi Yoshida
(1953-2019)





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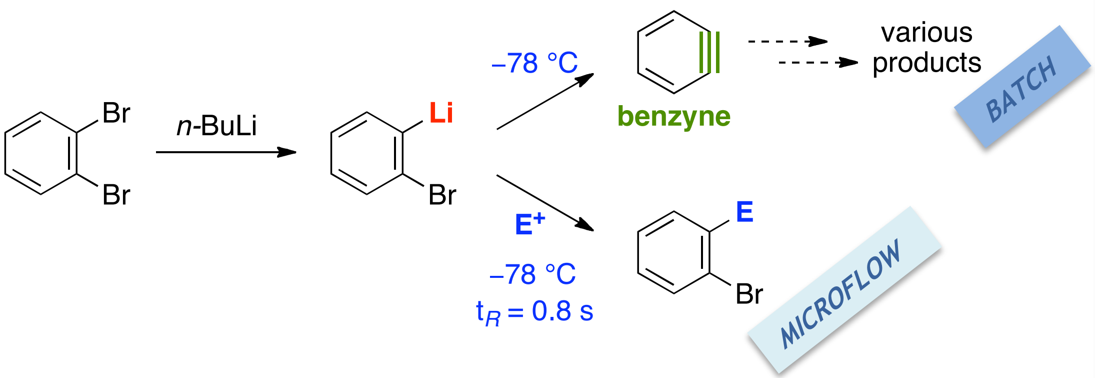
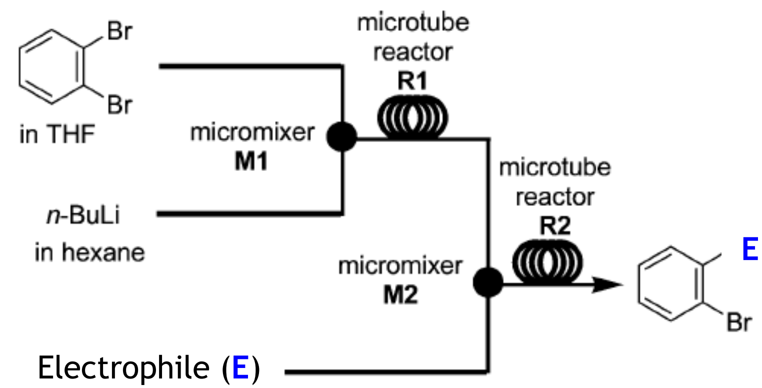
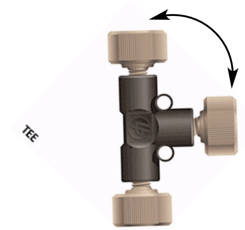


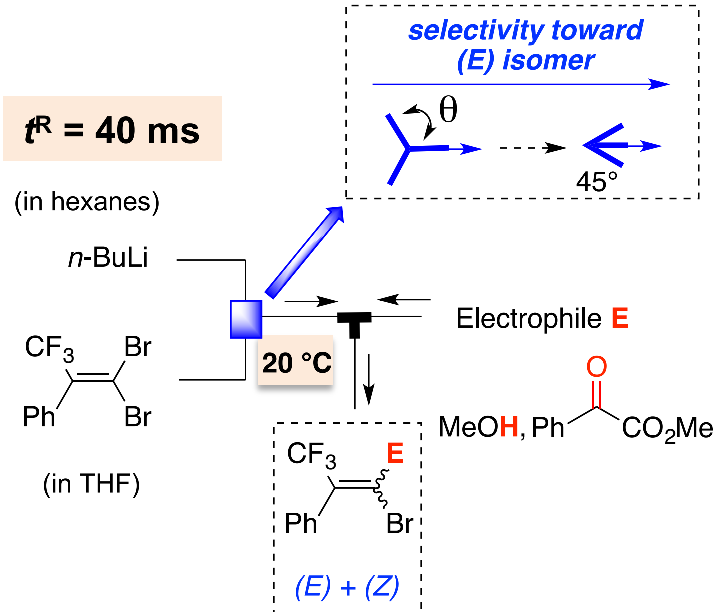


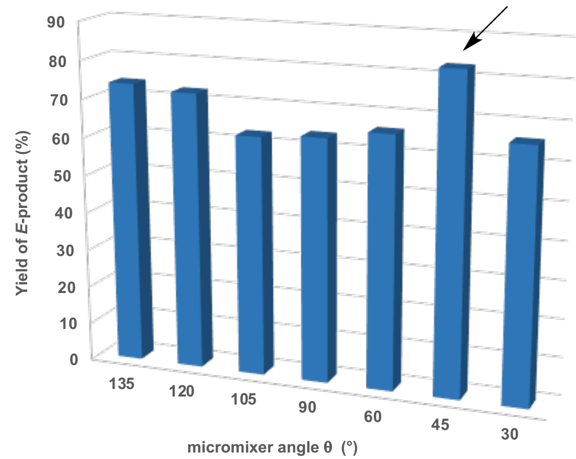
J.-i. Yoshida et al., *J. Am. Chem. Soc.* 2007, 3046

Selective Br-Li exchange / micromixer shape

angle influences mixing

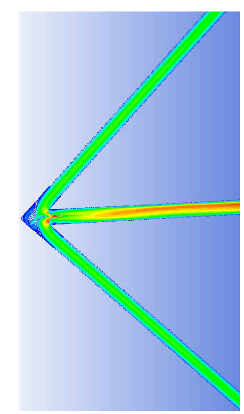






B. Picard, K. Pérez, T. Lebleu, D. Vuluga, F. Burel, D. C. Harrowven, I. Chataigner, J. Maddaluno, J. Legros *J. Flow Chem.* 2020, 139

K. Pérez, B. Picard, I. Chataigner, J. Maddaluno, A. Nagaki, J.-I. Yoshida, D. Vuluga, F. Burel, R. Hreinz, L. Falk, J.-M. Commenge, J. Legros, *OPR&D* 2020, 787



45°angle favors mixing of THF and hexane phases

Productivity = 6.7 g/h

Space-time yield = 81 kg/L/h

Collab J.M. Commenge, L. Falk, R. Hreinz (LRGP-Nancy)

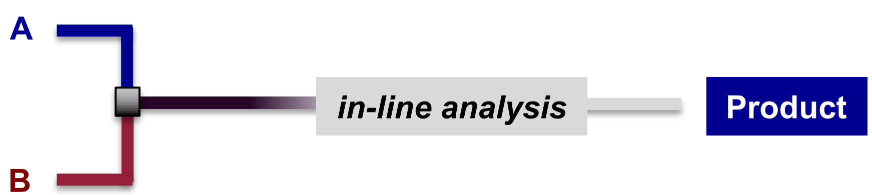
On-board devices / In-line analysis

advantages

- ✓ Temperature control (heat transfer)
- ✓ Mixing (mass transfer)
- ✓ Reproducibility
- ✓ Optimization
- ✓ Inherent scalability

but also

- ✓ « On-board » systems
- ✓ In-line analysis



IR spectrometer

S. V. Ley, I. R. Baxendale. *Org. Process Res. Dev.* 2010, 393
P. Knochel, S. V. Ley, *Org. Process Res. Dev.* 2012, 1102

NMR spectrometer

J. Bart, *J. Am. Chem. Soc.* 2009, 5014
E. Danieli, B. Blümich, V. P. Ananikov, *Chem. Rev.* 2014, 5641
P. Giraudeau, F.-X. Felpin, *React. Chem. Eng.* 2018, 399

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t^R = volume/flow rate (Q)

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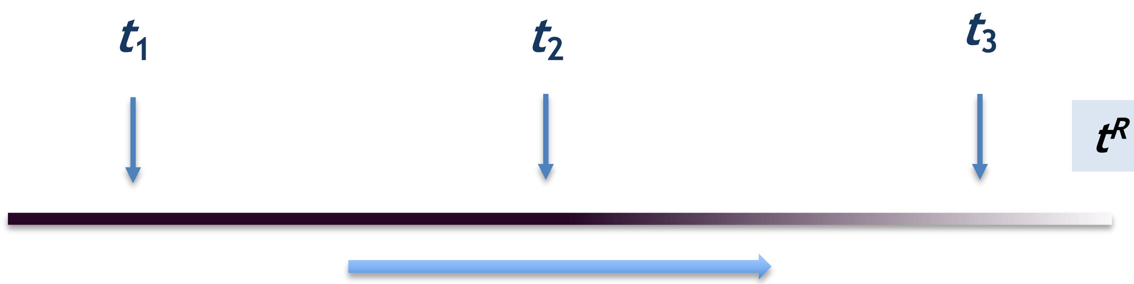

t^R = volume/flow rate (Q)

On-board devices / In-line analysis

advantages

- ✓ Temperature control (heat transfer)
- ✓ Mixing (mass transfer)
- ✓ Reproducibility
- ✓ Optimization
- ✓ Inherent scalability

but also

- ✓ « On-board » systems
- ✓ In-line analysis

t_n

t^R = volume/flow rate (Q)

t decreases when Q increases (and vice versa)

On-board devices / In-line analysis

advantages

- ✓ Temperature control (heat transfer)
- ✓ Mixing (mass transfer)
- ✓ Reproducibility
- ✓ Optimization
- ✓ Inherent scalability

but also

- ✓ « On-board » systems
- ✓ In-line analysis

Application to the on-field and sustainable Neutralisation of chemical warfare agents (CWA)

IR spectrometer

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P. Knochel, S. V. Ley, *Org. Process Res. Dev.* 2012, 1102

NMR spectrometer

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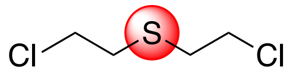
E. Danieli, B. Blümich, V. P. Ananikov, *Chem. Rev.* 2014, 5641
P. Giraudeau, F.-X. Felpin, *React. Chem. Eng.* 2018, 399

Chemical warfare agents (CWA)

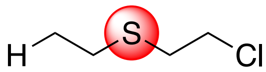
OPCW

https://www.opcw.org/

Blistering agents

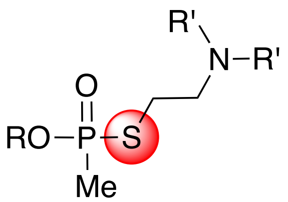


yperite (HD)



CEES

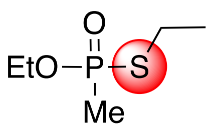
Nerve agents



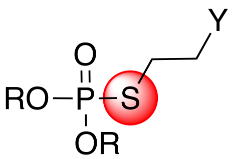
VX R = Et, R' = *i*-Pr

R-VX (VR) R = *i*-Bu, R' = Et

C-VX R = *n*-Bu, R' = Et

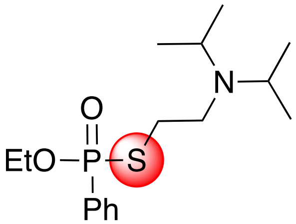


LG-61



Demeton-S R = Et, Y = SEt

Tetriso R = *i*-Pr, Y = N(*i*-Pr)$_2$

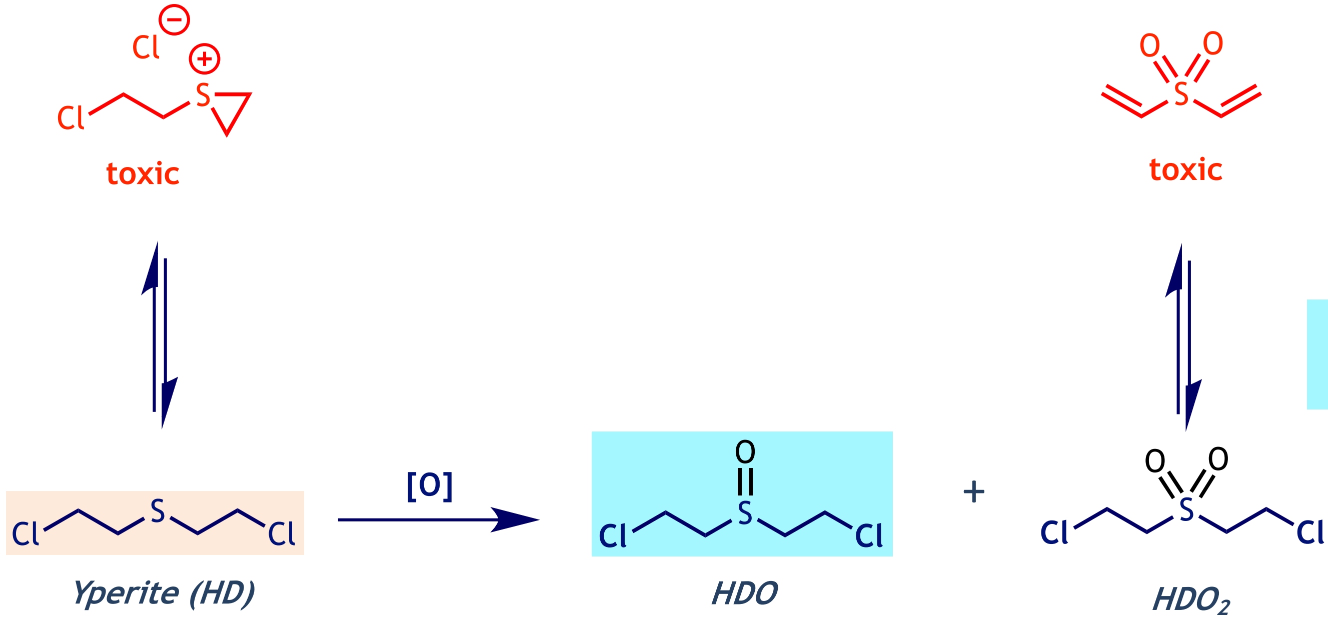


PhX

B. Picard, I. Chataigner, J. Maddaluno, J. Legros, *Org. Biomol. Chem.* 2019, 6528

P.-Y. Renard, H. Schwebel, P. Vayron, L. Josien, A. Valleix and C. Mioskowski, *Chem. - Eur. J.*, 2002, 2910

Neutralisation of « mustard gas » yperite



100% selectivity for sulfoxide required

innocuous

neutralisation by pulverisation of Decon Green

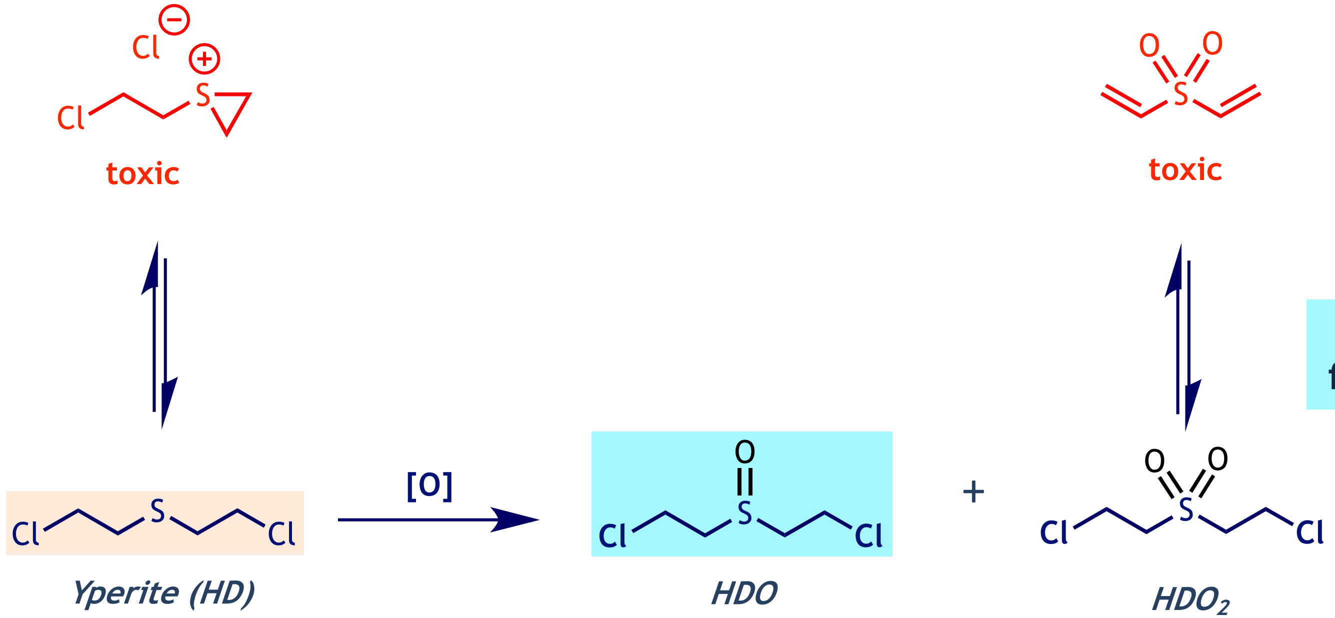
Potential threat of « mustard gas

moved and destroyed in a secured remote place

- Simple
- Efficient/scalable
- Movable
- Sustainable
- In-line monitoring

B. Picard, I. Chataigner, J. Maddaluno, J. Legros, *Org. Biomol. Chem.* 2019, 6528
Y. J. Jang, K. Kim, O. G. Tsay, D. A. Atwood, D. G. Churchill, *Chem. Rev.* 2015, *115*, PR1

Neutralisation of « mustard gas » yperite



100% selectivity for sulfoxide required

Potential threat of « mustard gas »

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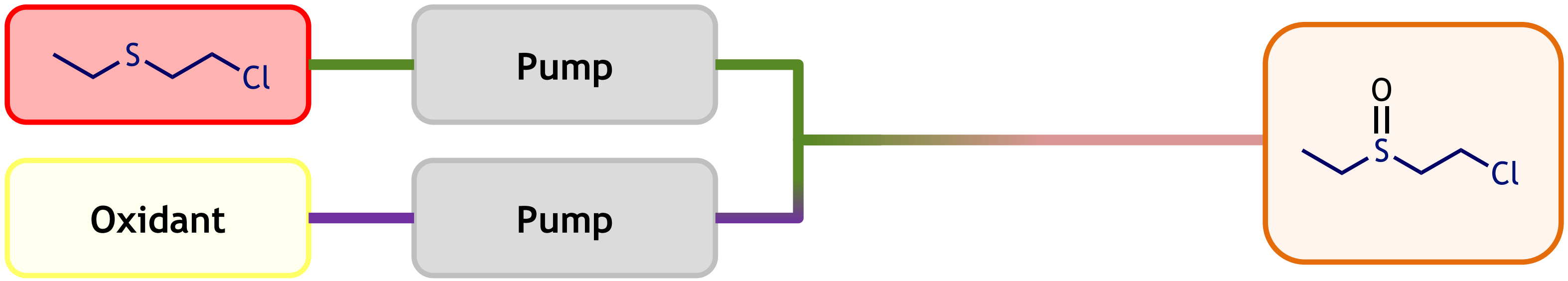
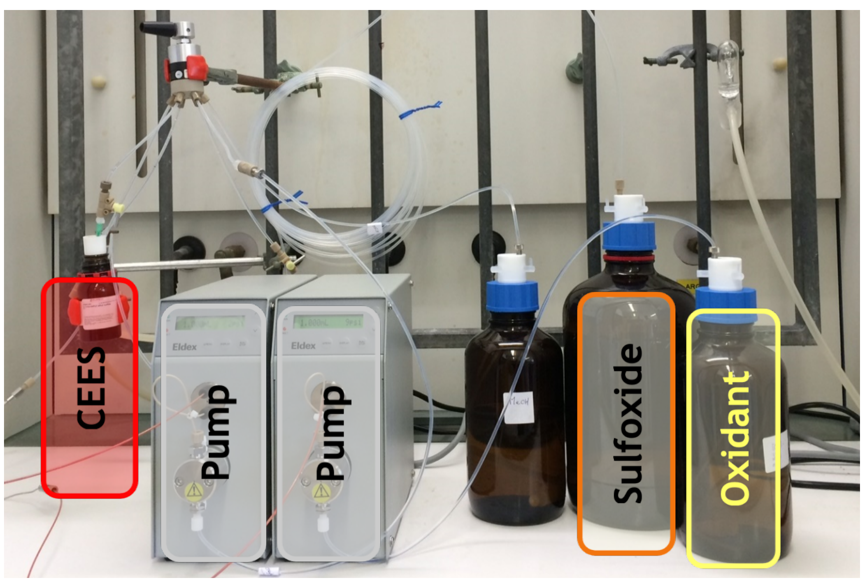
flow device ?

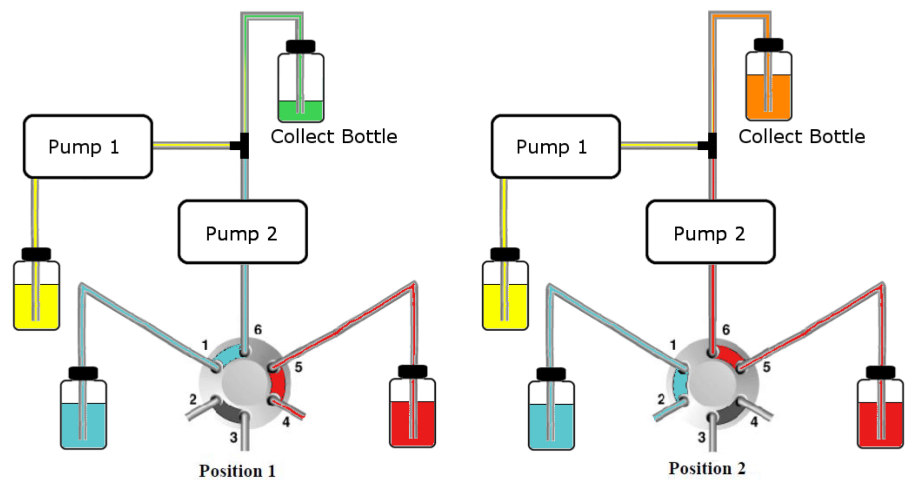
Flow neutralisation of mustard gas simulants with H_2O_2 / MSA in MeOH

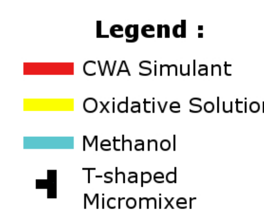


H_2O_2 / CH_3SO_3H

in alcohol







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Angew. Chem. Int. Ed. 2017, 7568

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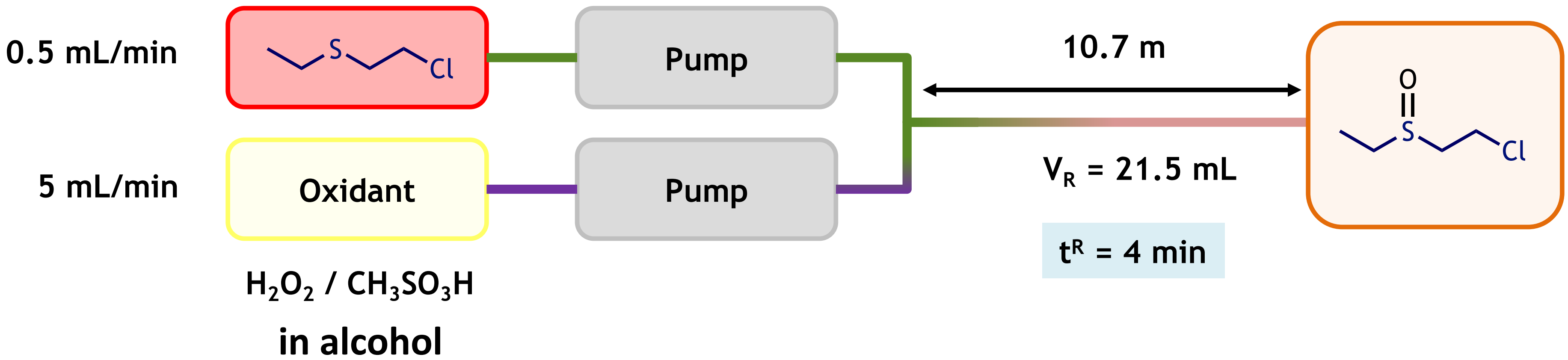

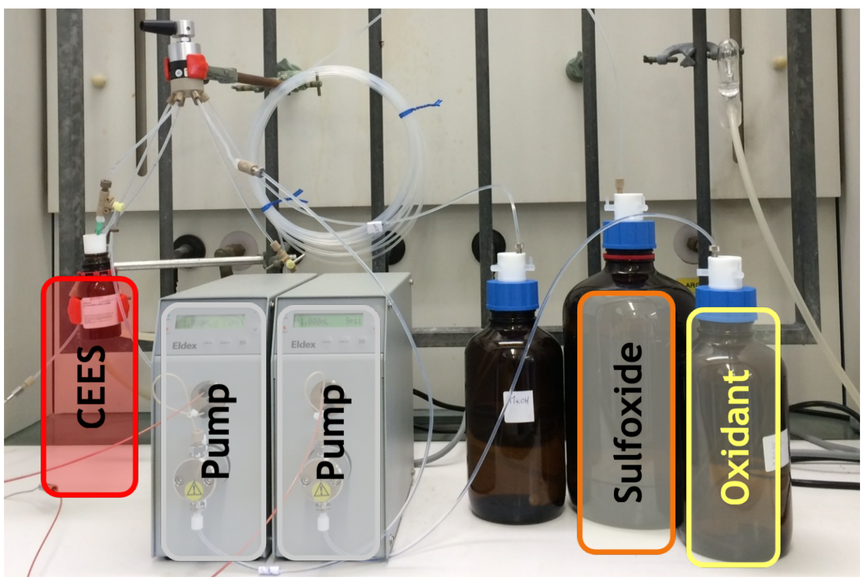

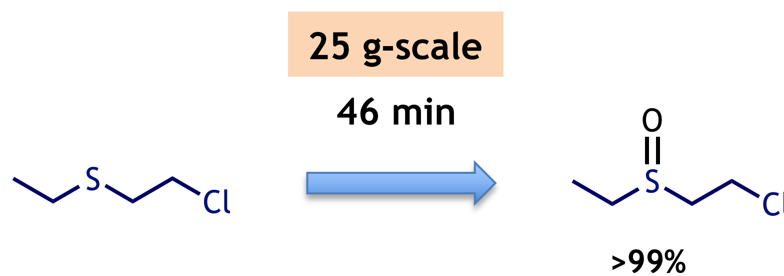

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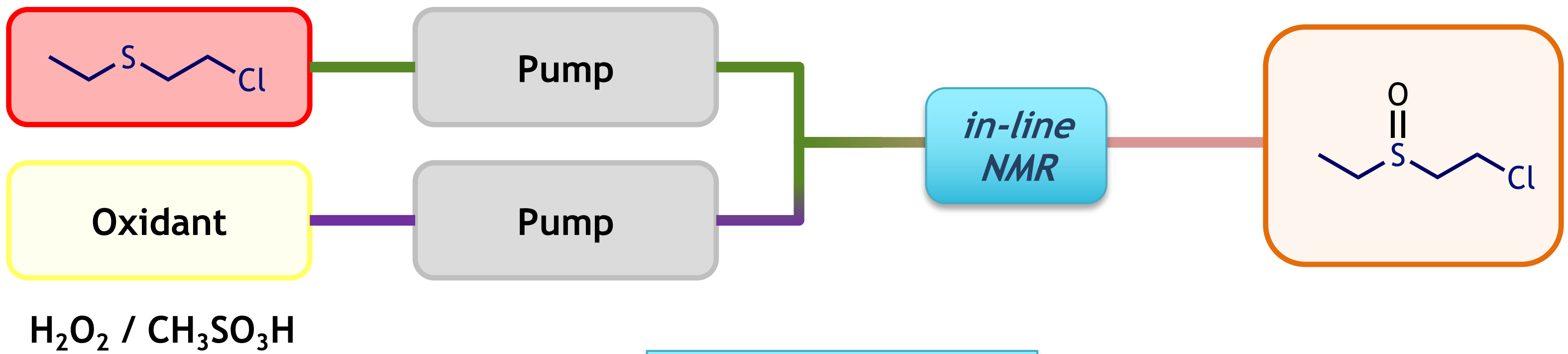
in-line NMR monitoring → ***Collab. P. Giraudeau/F.X. Felpin (CEISAM, Univ Nantes)***



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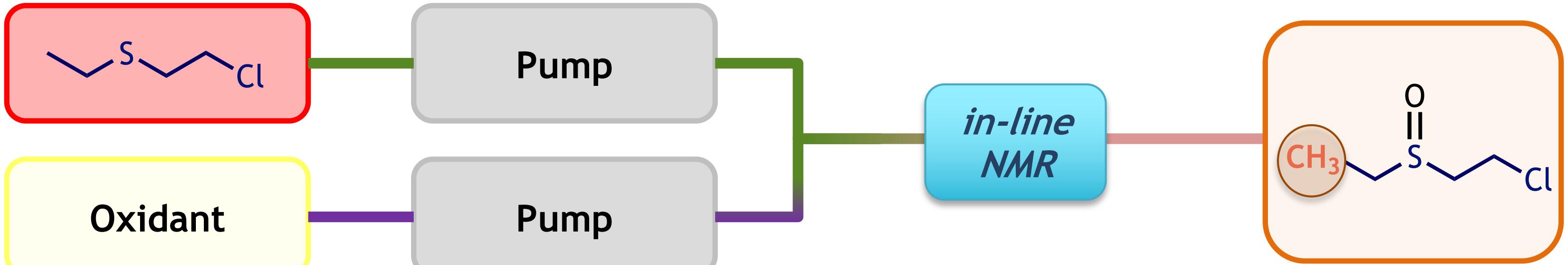
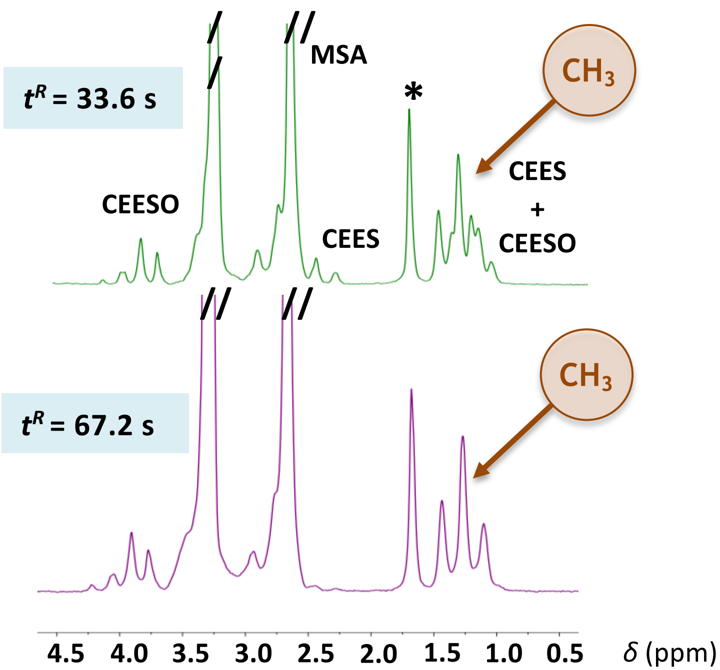
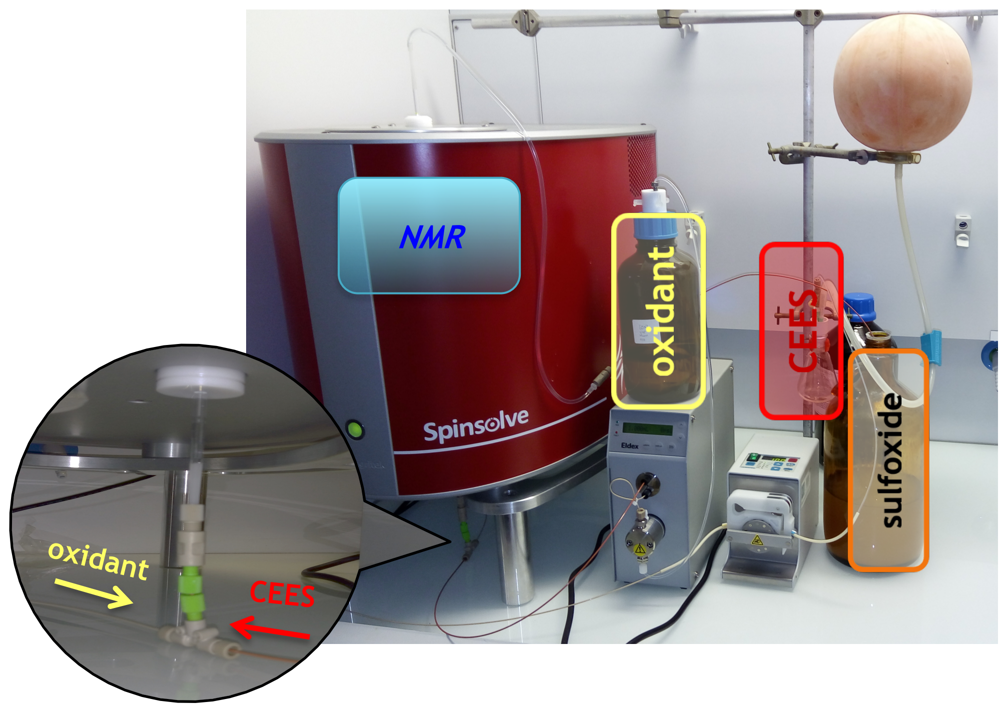


H_2O_2 / CH_3SO_3H





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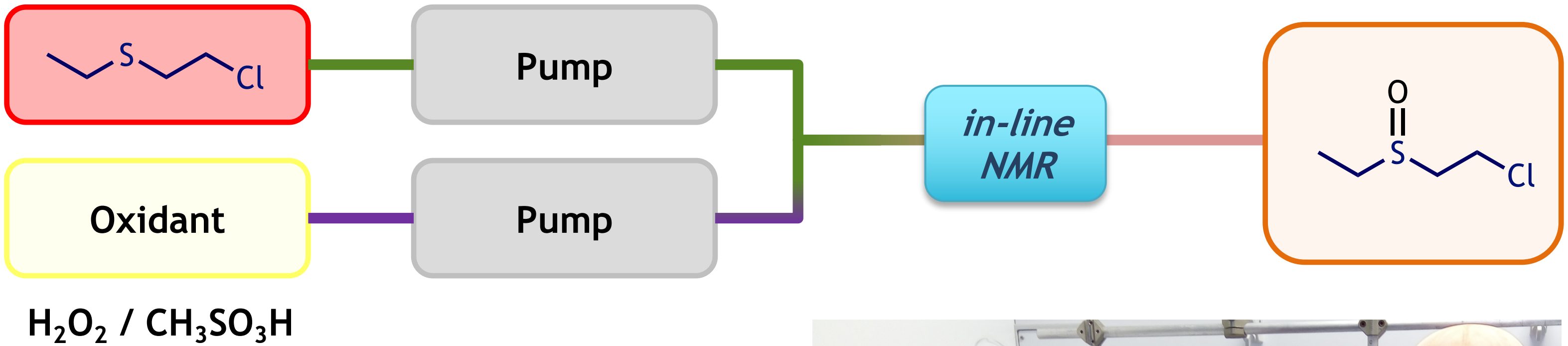

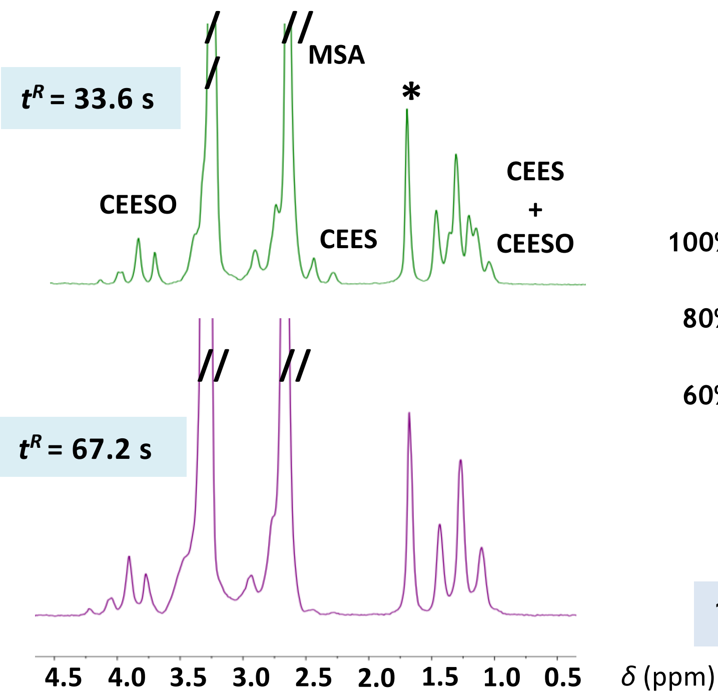

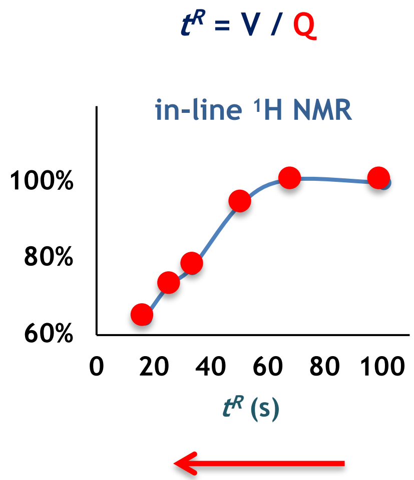

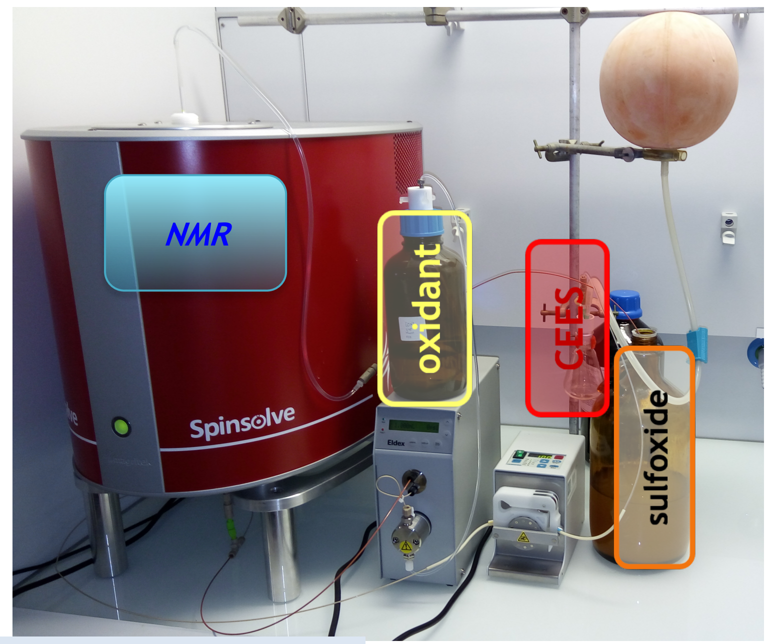

^{1}H NMR monitoring by flow rate increase

B. Picard, B. Gouilleux, T. Lebleu, J. Maddaluno, I. Chataigner, M. Penhoat, F.-X. Felpin, P. Giraudeau, J. Legros
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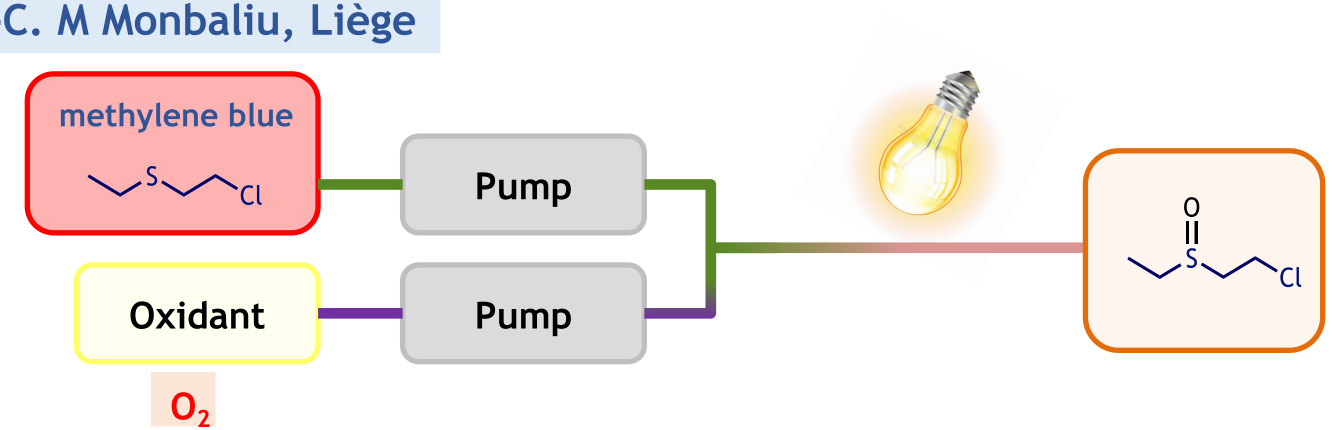
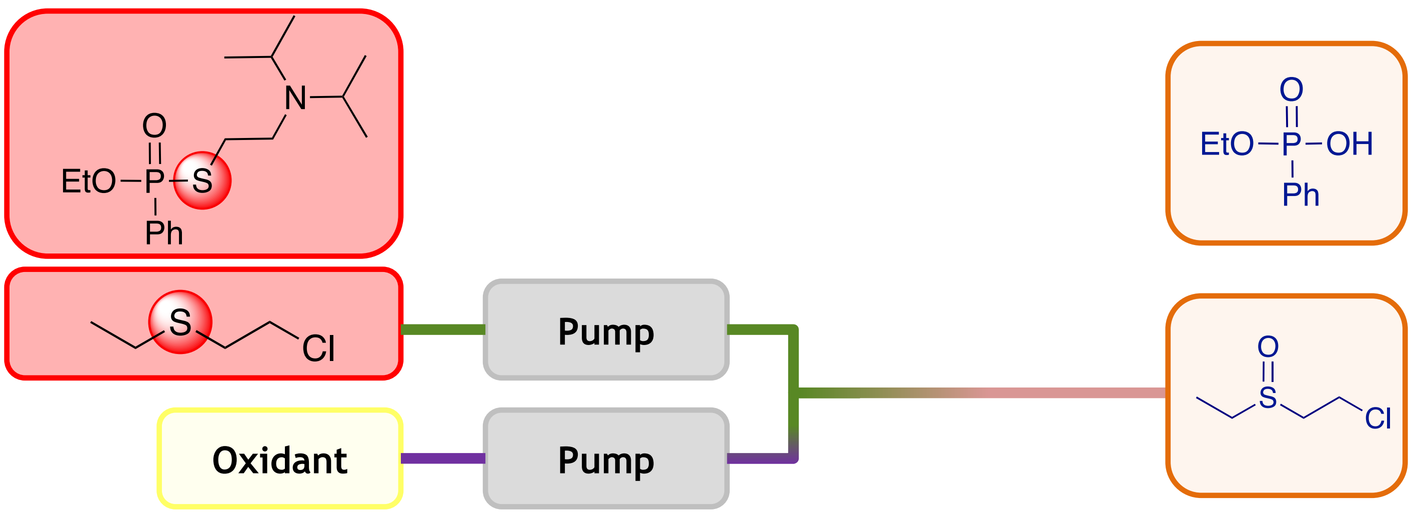
Oxidative flow neutralisation of CWA simulants

J.-C. M Monbaliu, Liège



J.-C. M. Monbaliu et al., *Green Chem.*, 2020, 4105



A. Delaune, S. Mansour, J. Legros et al., *Manuscrit en révision*

Other projects related to sustainable chemistry in flow

Flow polymerisation of biobased monomers

With K. Pérez, F. Burel, D. Vuluga (PBS, INSA Rouen)

Thermodynamic and kinetic studies for the flow valorisation of fructose

ANR PRCI « MUST » (PI: S. Leveneur, LSPC, INSA Rouen)

PhD student: A. Cordier

Conclusion

Miniaturized reactors in continuous flow →

- ✓ fast thermalisation and mass transfer
- ✓ fine reaction time control
- ✓ scalability

⇨ **Friendlier reaction conditions and higher selectivity for fast reactions**

- ✓ Organolithium chemistry
- ✓ Neutralisation of mustard gas and VX simulants

Acknowledgements

COBRA - Rouen

Dr. Jacques MADDALUNO

Prof. Isabelle CHATAIGNER

Antonin DELAUNE
PhD student (2020-)

Baptiste PICARD
PhD student (2015-2018)

Sergui MANSOUR
PDRA (2018-)

Katia PEREZ
PhD student (2019-)

Prof. Pierre-Yves RENARD

Dr. Ludovic JEAN

CEISAM - Nantes

Prof. Patrick GIRAUDEAU

Prof. François-Xavier FELPIN

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S. Descroix, J. Legros, J.-B. Salmon

dans *Etonnante chimie*

(Ed : F. Teyssandier, O. Parisel)

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