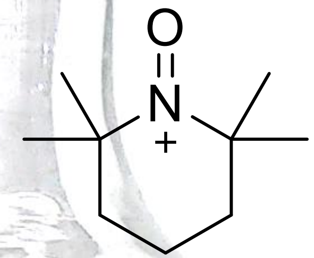
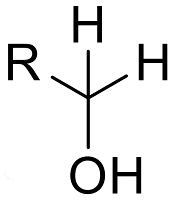
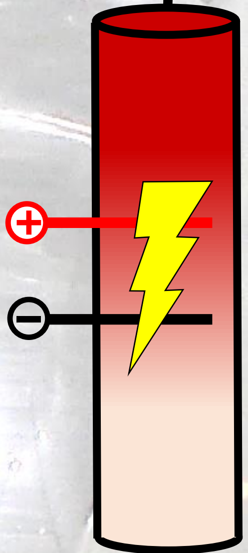
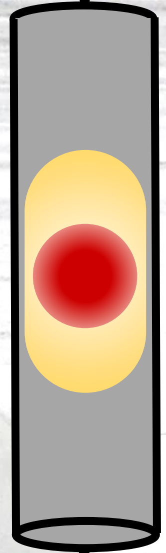




Continuous anodic oxidation of TEMPO as a mediator for selective synthesis of aldehydes from primary alcohols



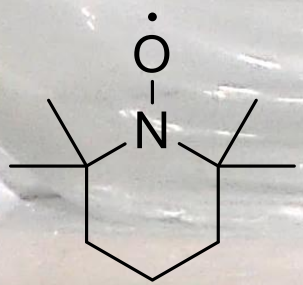


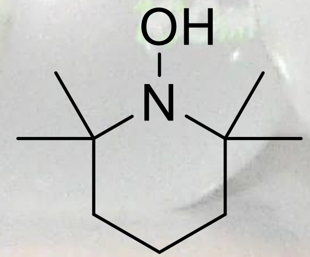
Christoph Deckers[1], Martin Linden[1], Julian Heinrich[1], Holger Löwe[1,2*]

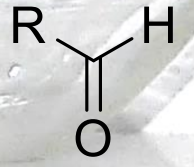
[1] Johannes Gutenberg-University Mainz, Duesbergweg 10-14, D-55128 Mainz, Germany

[2] Fraunhofer ICT-IMM, Carl-Zeiss-Str. 18-20, 55129 Mainz, Germany

* *loewe@uni-mainz.de*







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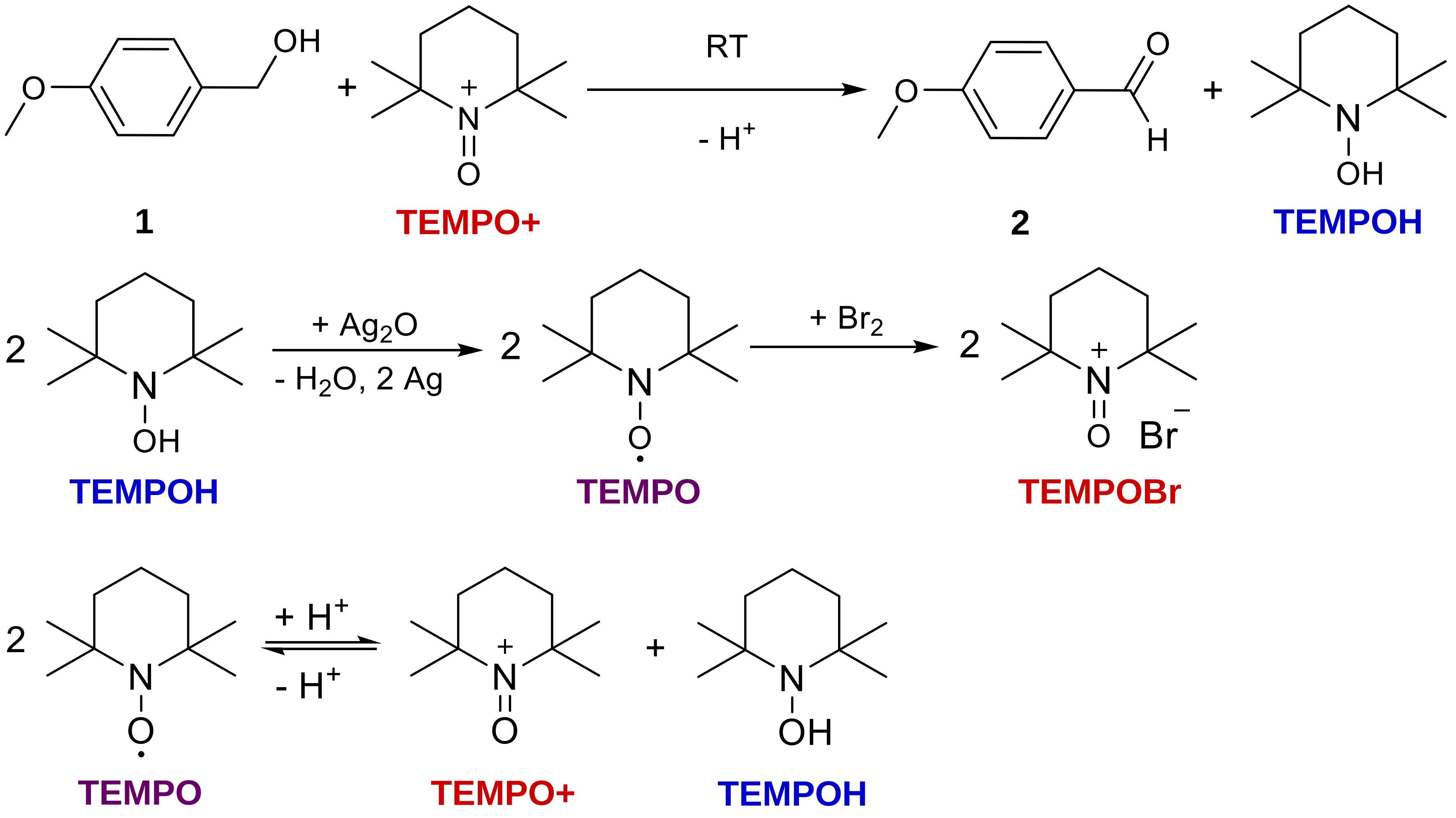
Outline

- Anelli Oxidation
- One-Phase Approach
  - Mixing and Residence Time
- Multi-Phase Approach
  - Mixed Double Emulsions
- Electrooxidation
  - Voltammetry Experiments → Batch Process → Continuous Process
- Outlook

Anelli Oxidation



V.A. Golubev,
E.G. Rozantsev,
M.B. Neimann, *Izv.Akad.Nauk SSSR*, **1965**, *11*, 1927-1936.

P.L. Anelli, C. Biffi,
F. Montanari, S. Quici,
J.Org.Chem., **1987**, *52*, 2559-2562.

M. Zhao, J. Li, E. Mano,
et al., *J.Org.Chem.*, **1999**, *64*, 2564-2566.

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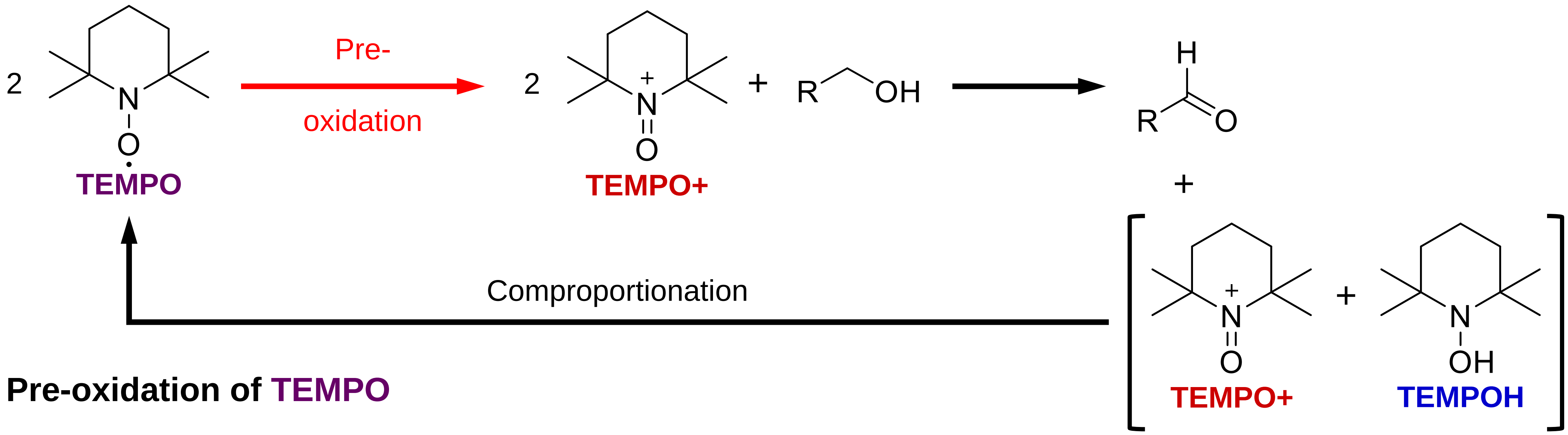
Anelli Oxidation

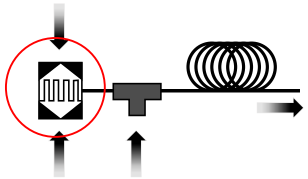
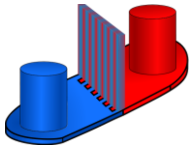
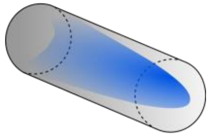
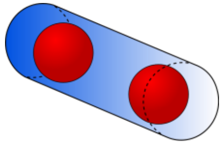


Pre-oxidation of TEMPO

- NaOCl in situ causes *side products*
- Br_2 in organic solvents (*requires separation*)
- electrochemical oxidation in water (*several alcohols insoluble, solvent changes, phase separation*)

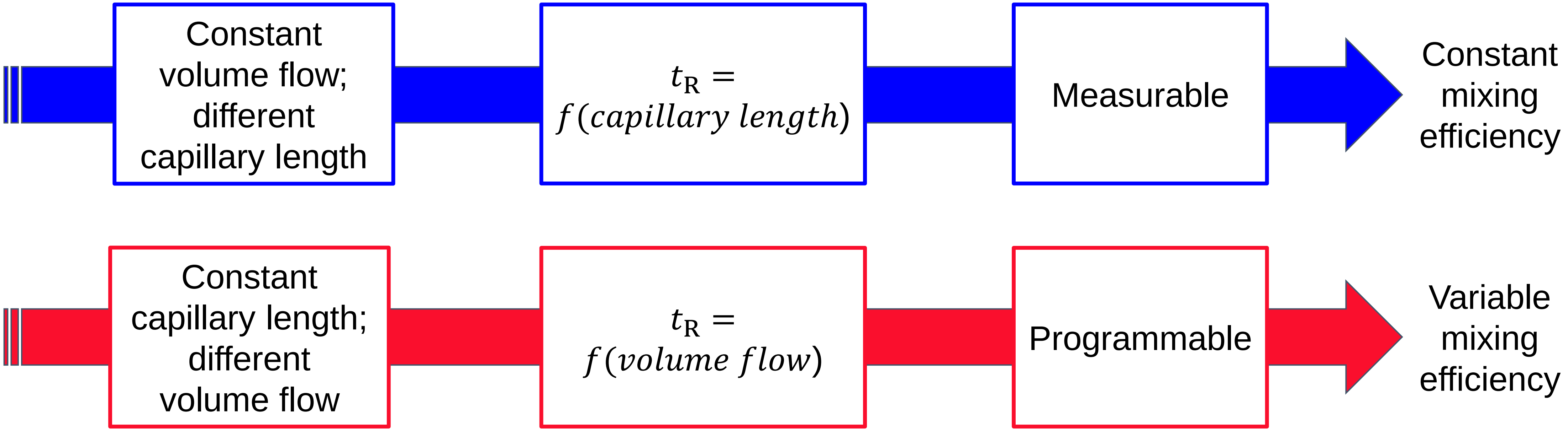
multiphase flow with excess of TEMPO+

One-Phase Approach

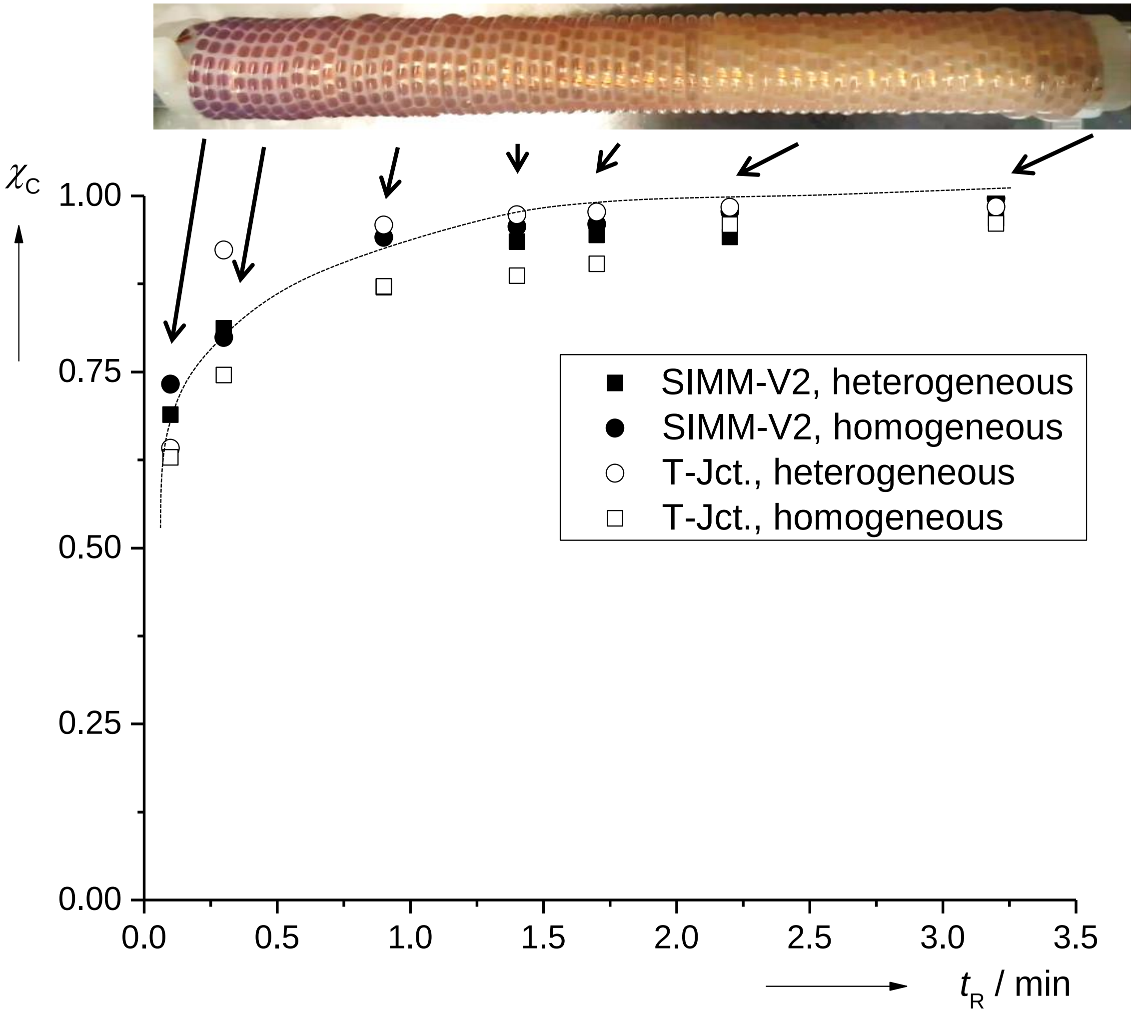
Mixer  Segment	 T-Piece	 SIMM-V2
 Continuous flow	Small window for efficient mixing; broad residence time distribution	Mixing controlled; broad residence time distribution
 Segmented flow	Residence time controlled	Mixing and residence time controlled

One-Phase Approach

$$\text{Residence time } t_R = \frac{\text{Channel length}}{\text{Volume flow}}$$



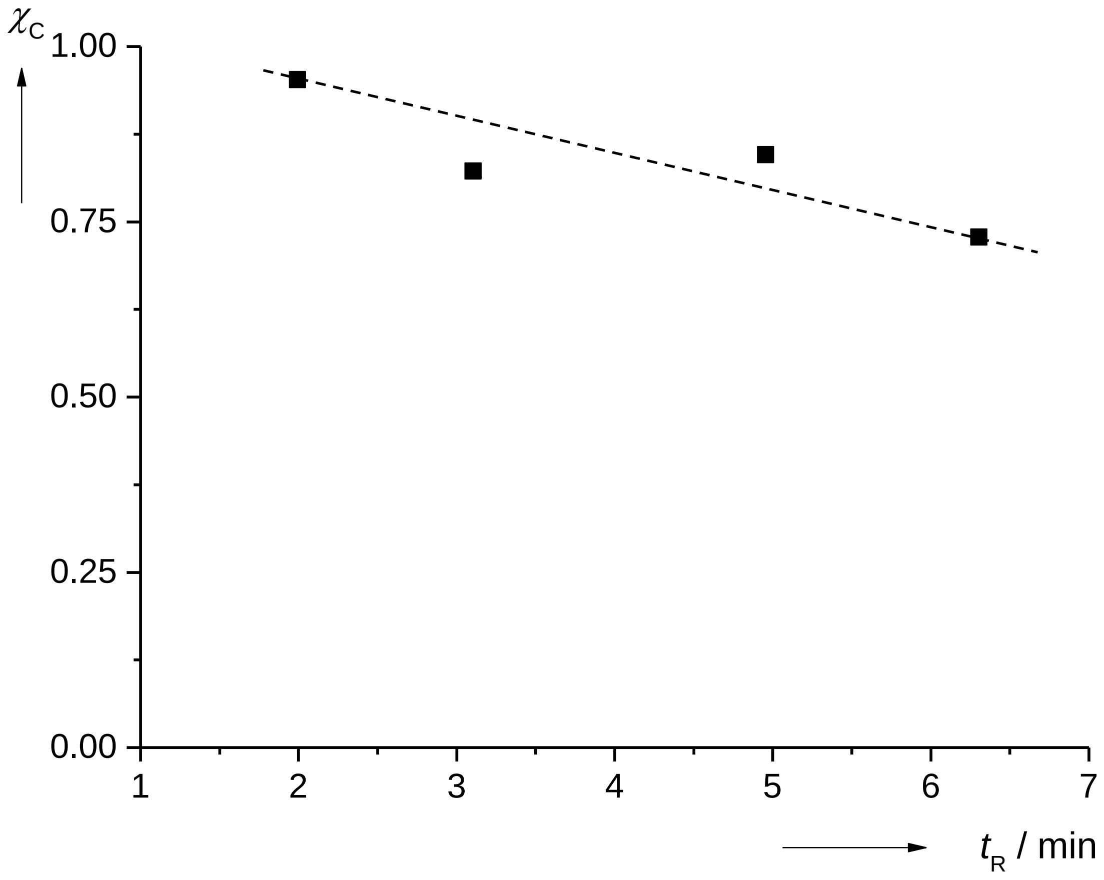
One-Phase Approach



Residence time dependency:

- Fixed flow rates
- Observation by GC and by eye (bleaching)
- Full conversion after approx. 3.5 min
- No significant differences between mixer types and flow patterns
  - Kinetic limit reached

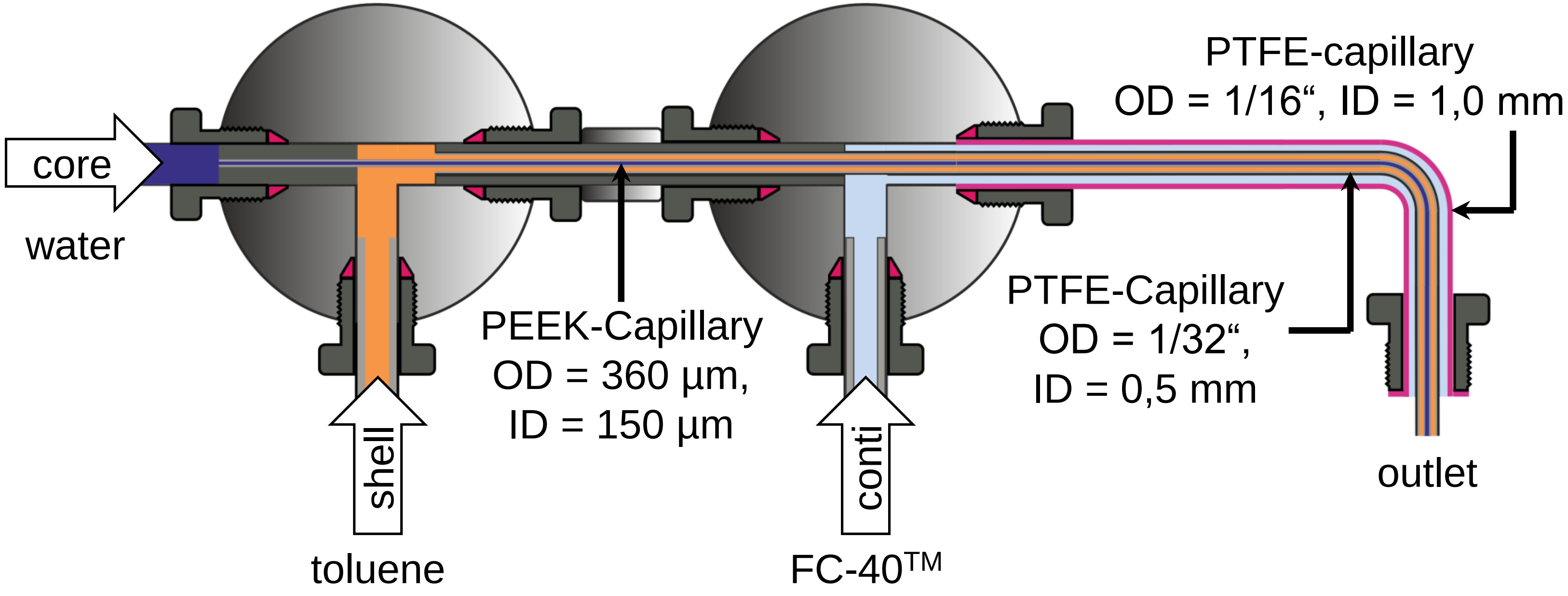
One-Phase Approach

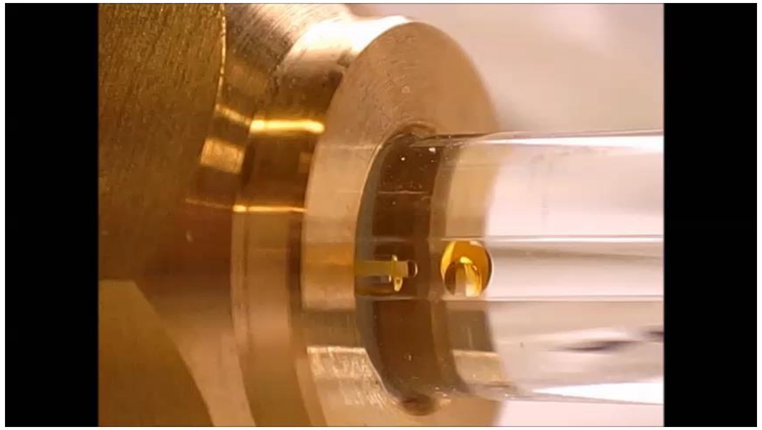


Flow rate/mixing dependency:

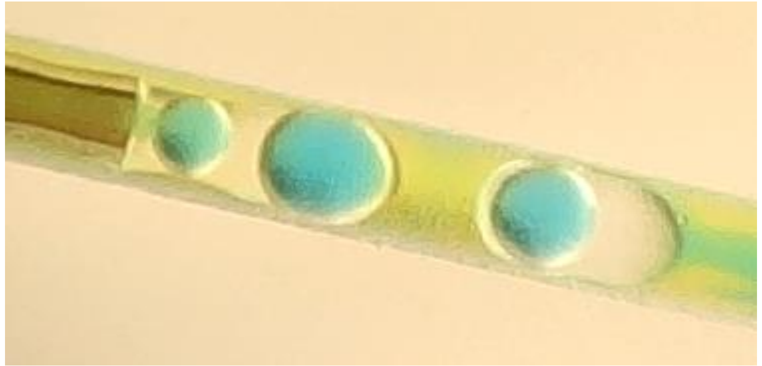
- Fixed reactor volume
- Conversion decreases with increasing residence time
  - Decreasing flow rate/mixing efficiency
- Increased reaction time unable to compensate loss in mixing efficiency

Multi-Phase Approach





Video: Link



Coaxial double emulsion generator

- 2 T-junctions to insert core and shell capillary into main channel
- Coplanar outlet of inner capillaries
- Core droplet is infused into shell droplet while latter is generated

V. Misuk, A. Mai, Y. Zhao, J. Heinrich, D. Rauber, K. Giannopoulos, H. Löwe, *J. Flow Chem.*, **2015**, *5*(*2*), 101–109.

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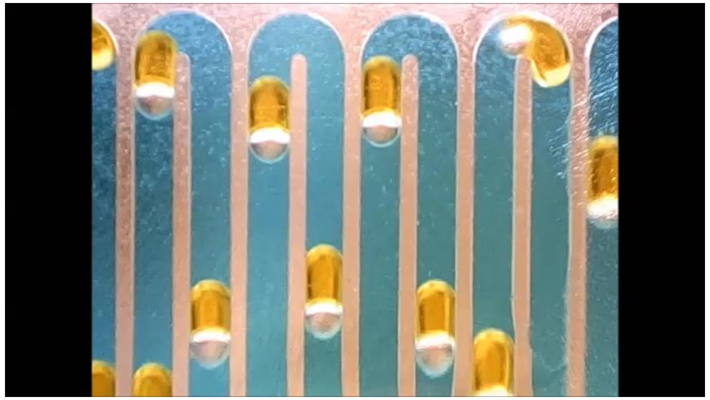
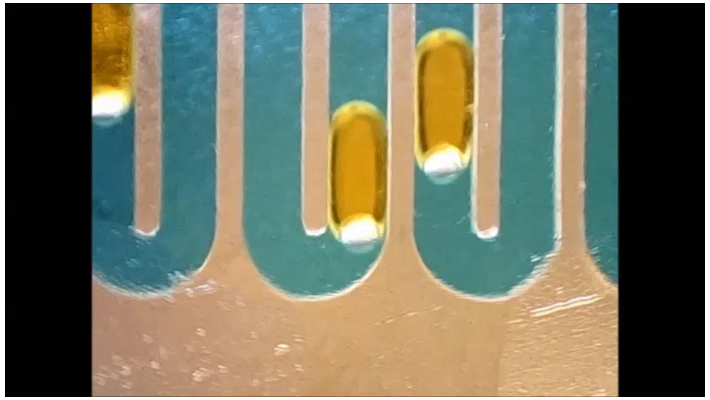
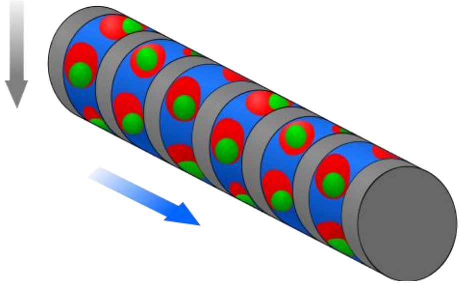
Multi-Phase Approach



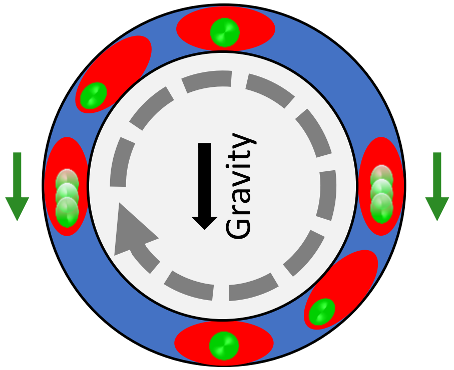
Video: Link



Video: Link



Reversal point



Reversal point

Passive mixing:

- Gravity induced
- Capillary coiled on cylinder
- Double emulsion, core droplet pulled downwards by gravity
  - Crosses shell droplet twice every winding

V. Misuk, A. Mai, Y. Zhao, J. Heinrich, D. Rauber, K. Giannopoulos, H. Löwe, *J. Flow Chem.*, **2015**, *5*(*2*), 101–109.

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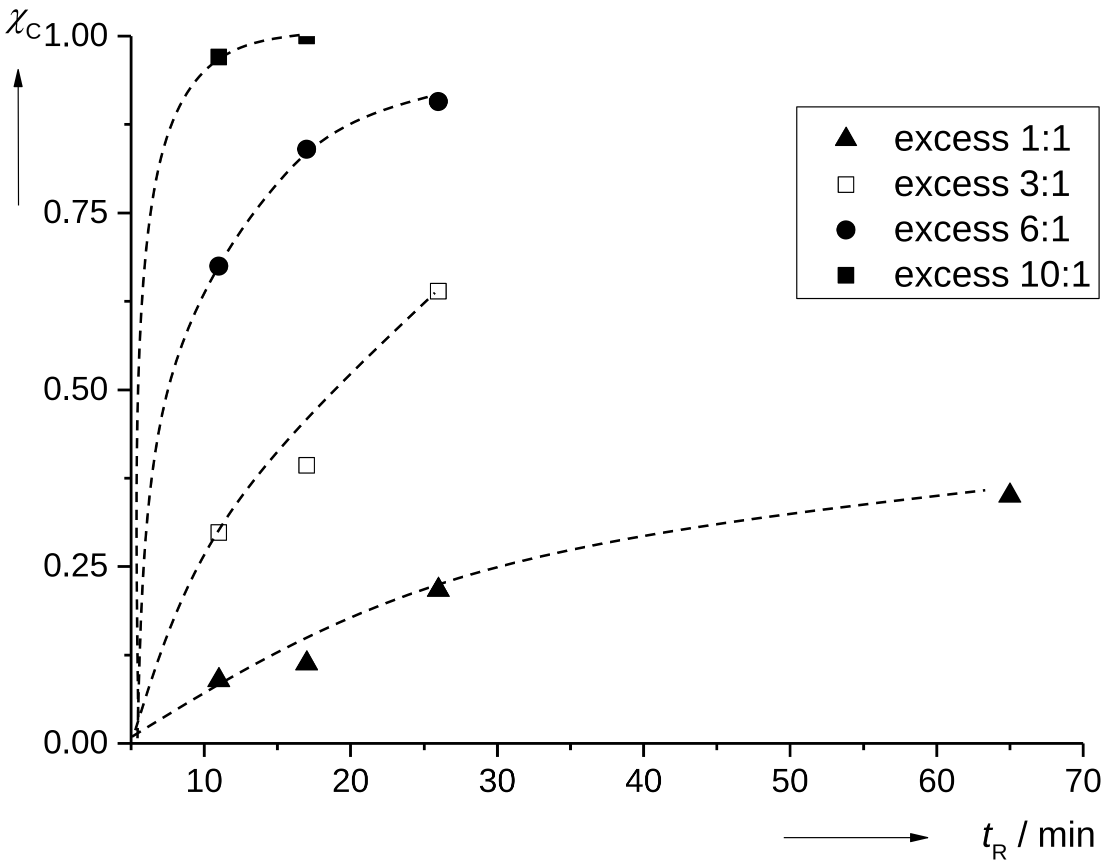
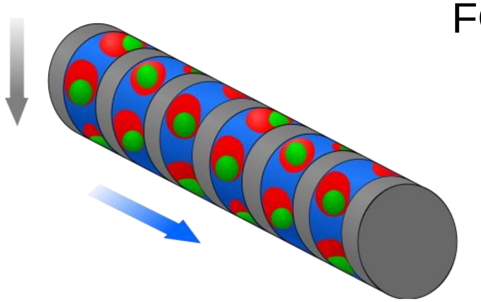
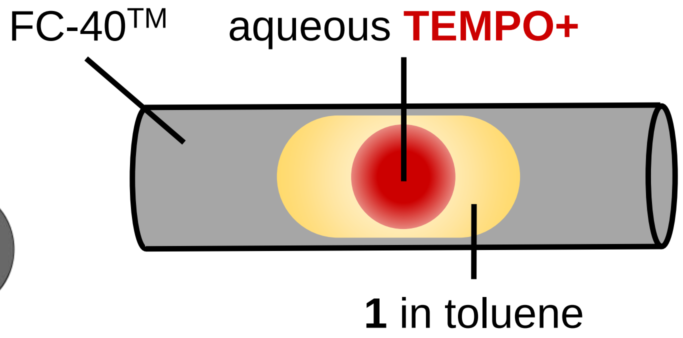
Multi-Phase Approach



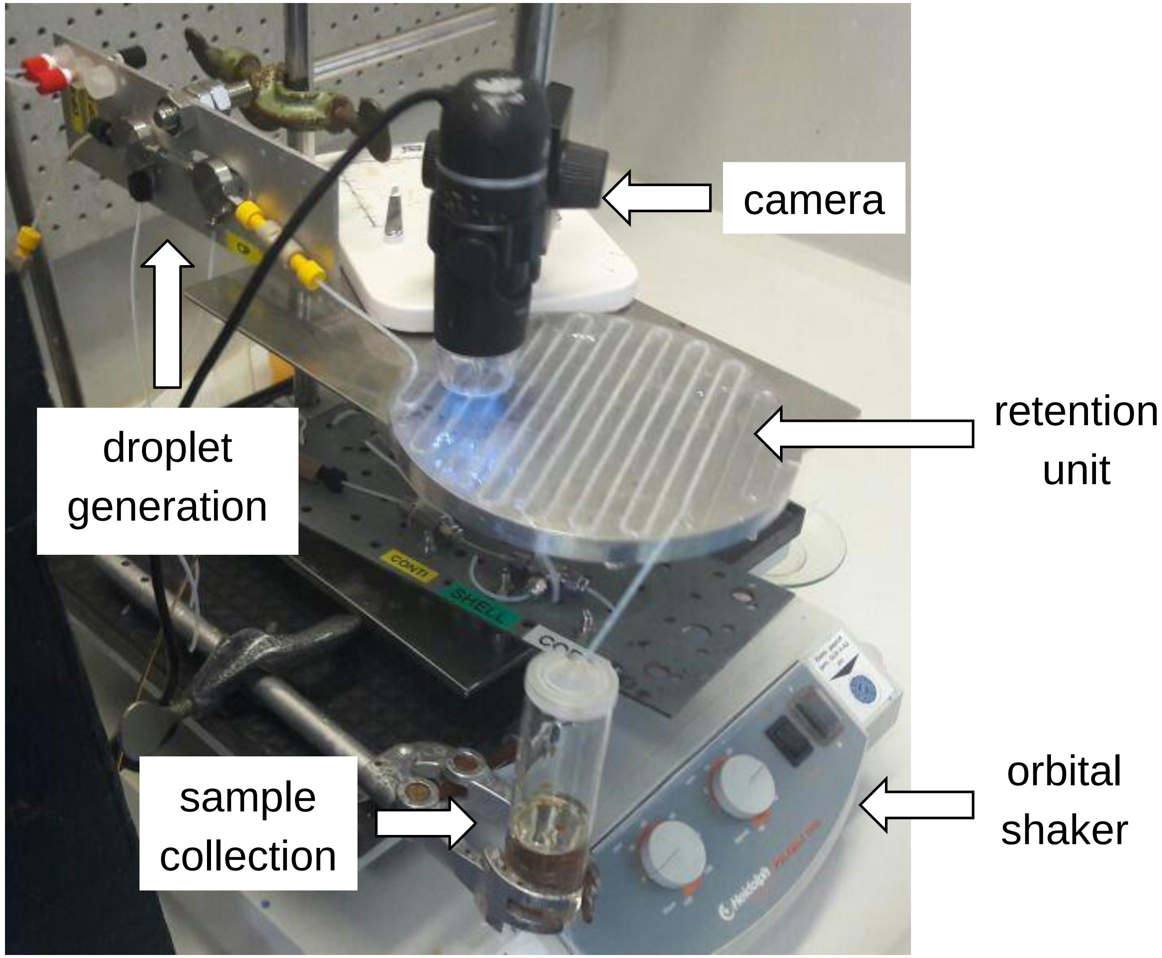


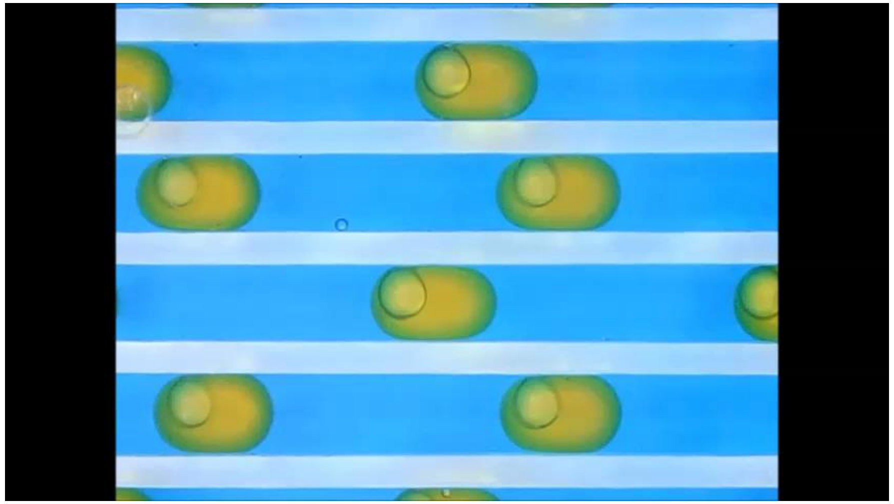


Gravity induced mixing:

- Oxidant and alcohol in different phases
  - Interface reaction
  - Extended reaction time necessary
- 9-fold excess of **TEMPO+** reduces reaction time to 17 min
- Easy recycling of remaining **TEMPO+**

Multi-Phase Approach





Video: [Link]

Active mixing:

- Retention unit mounted on orbital shaker
- Double emulsion, jiggling of core droplet
  - Stirring of shell phase with adjustable frequency

V. Misuk, A. Mai, Y. Zhao, J. Heinrich, D. Rauber, K. Giannopoulos, H. Löwe, *J. Flow Chem.*, **2015**, *5*(*2*), 101–109.

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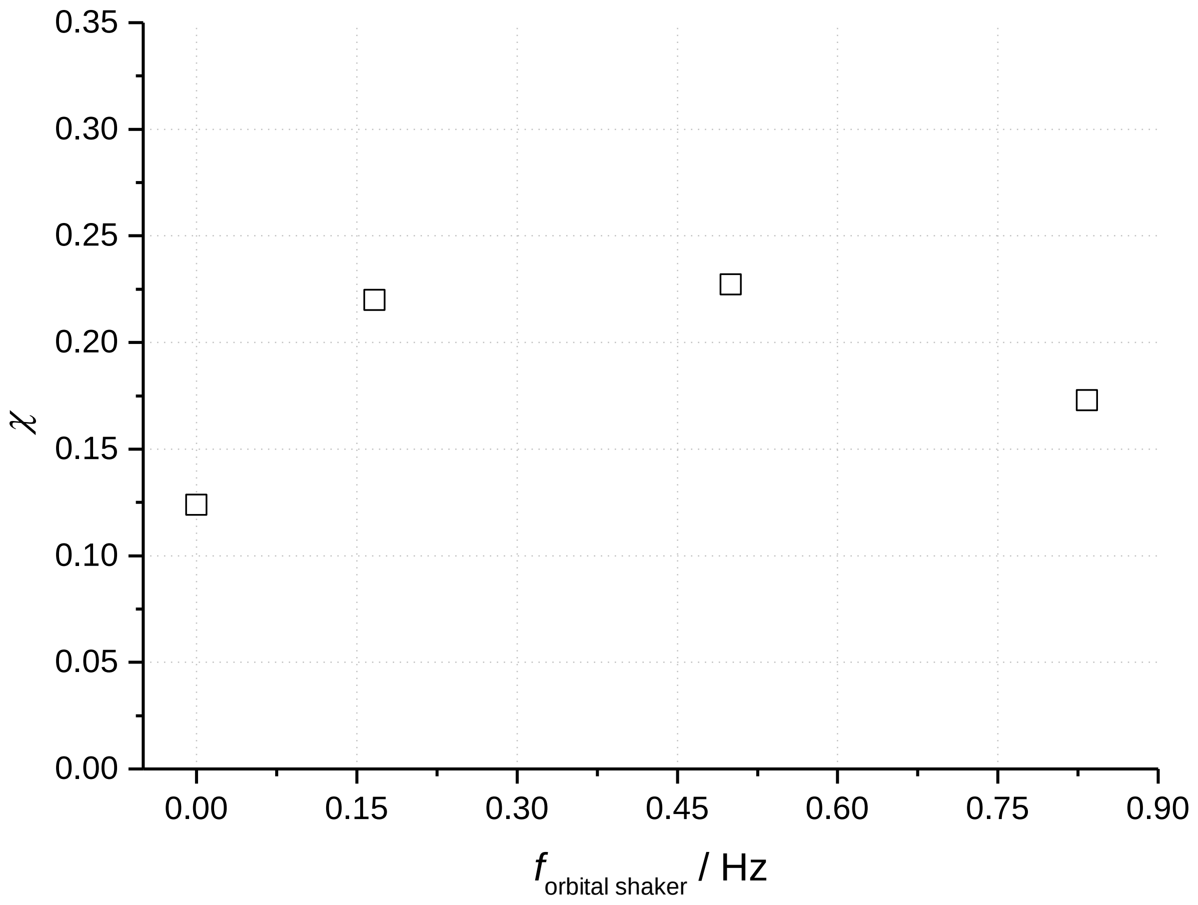
Multi-Phase Approach

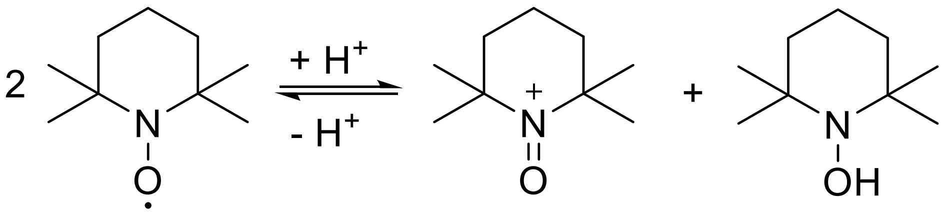


Stirred double emulsion:

- 1.7 eq of **TEMPO+** used
- Conversion 12% in 3 min without mixing
- Increase to approx. 22% conversion between 0.2 Hz and 0.5 Hz
- Maximum expected around 0.35 Hz

- Further Investigation necessary

Electrooxidation



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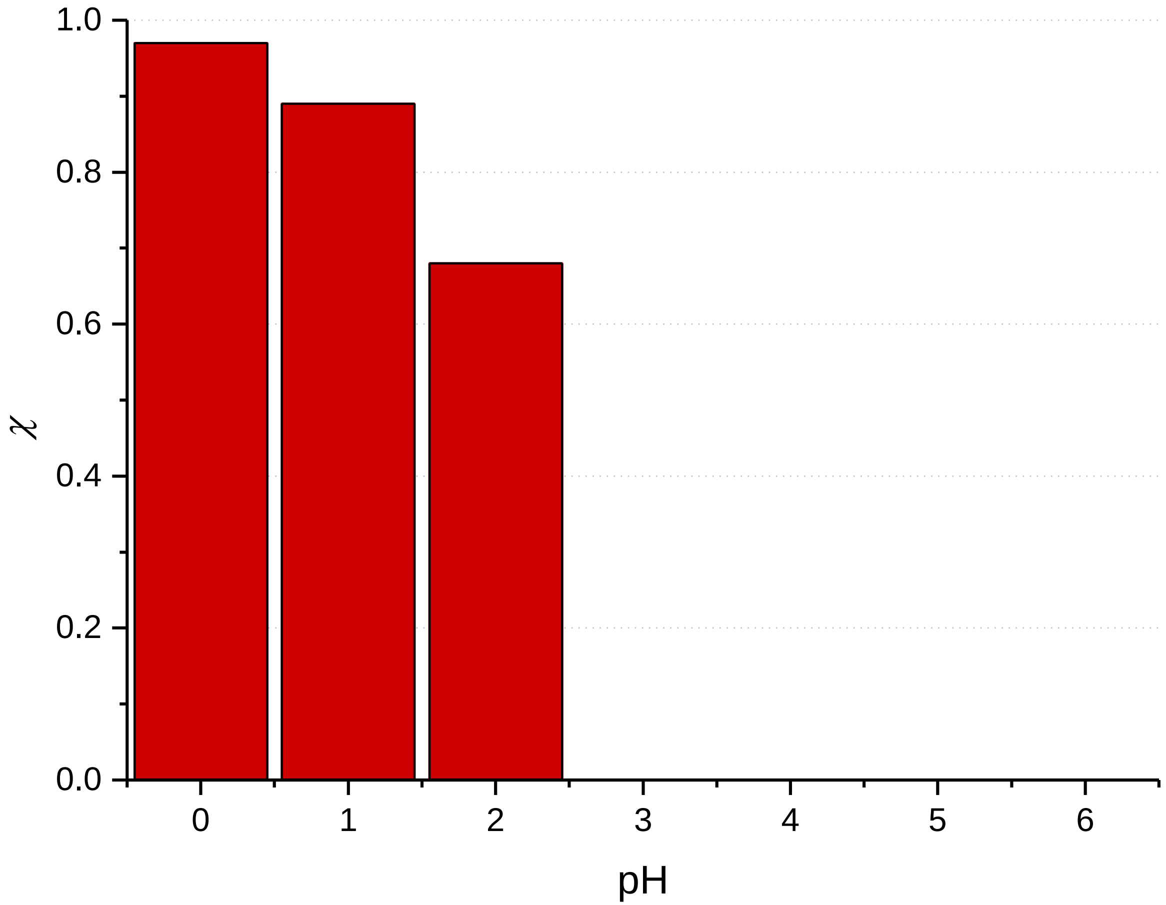
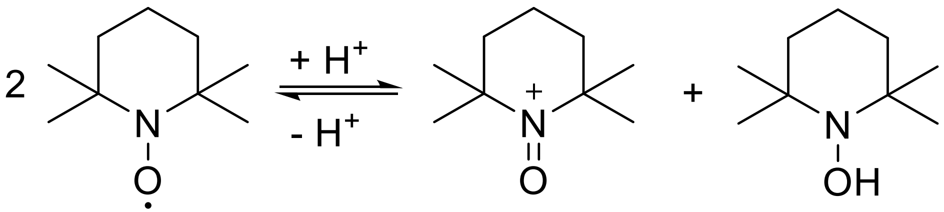


Disproportionation of TEMPO:

- Full conversion to **TEMPO+** and **TEMPOH** at pH = 0
- At pH = 2 **TEMPO+** yield is 68%
  - Proportion of 33% of **TEMPO+**, **TEMPO** and **TEMPOH** each
- pH ≥ 3 suppresses disproportionation

Electrooxidation



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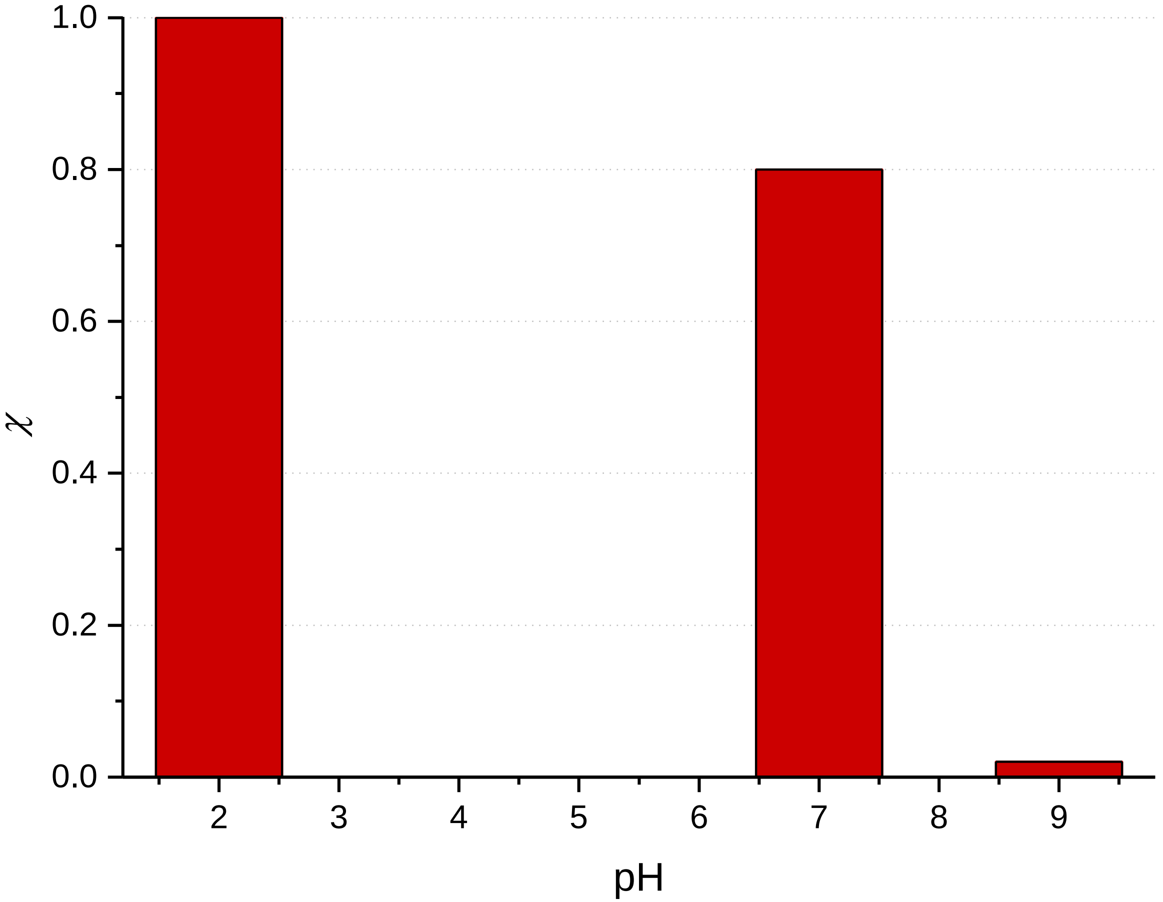
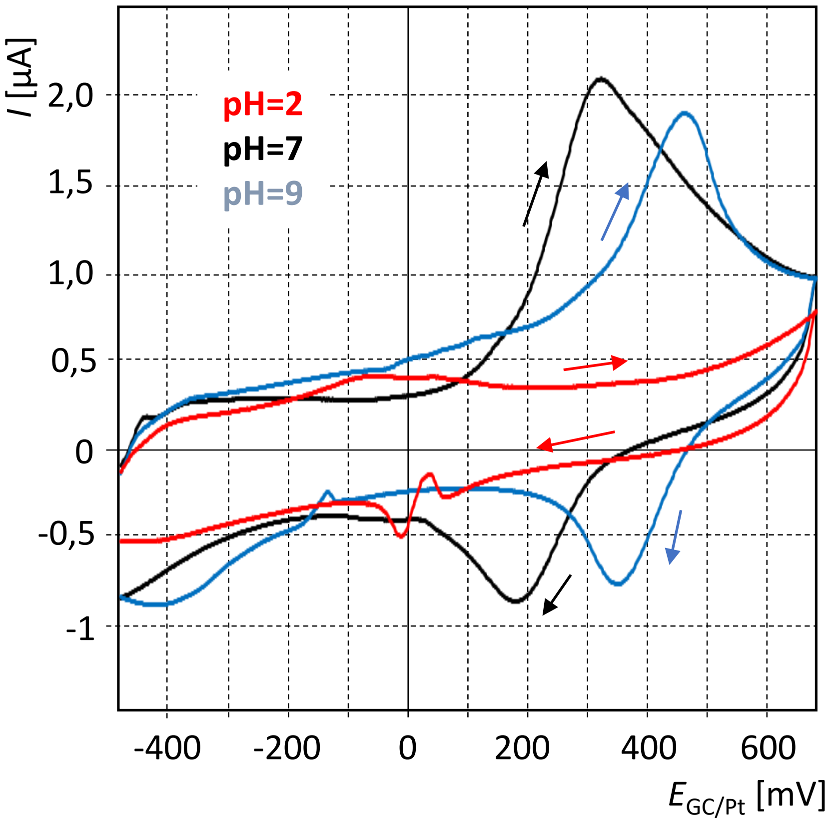


Comproportionation of TEMPO+ and TEMPOH:

- **TEMPOH** formed in situ by adding **1** to **TEMPO+**
- Almost total comproportionation at pH = 9
- 80% **TEMPO+** left in neutral media
- No comproportionation at pH = 2

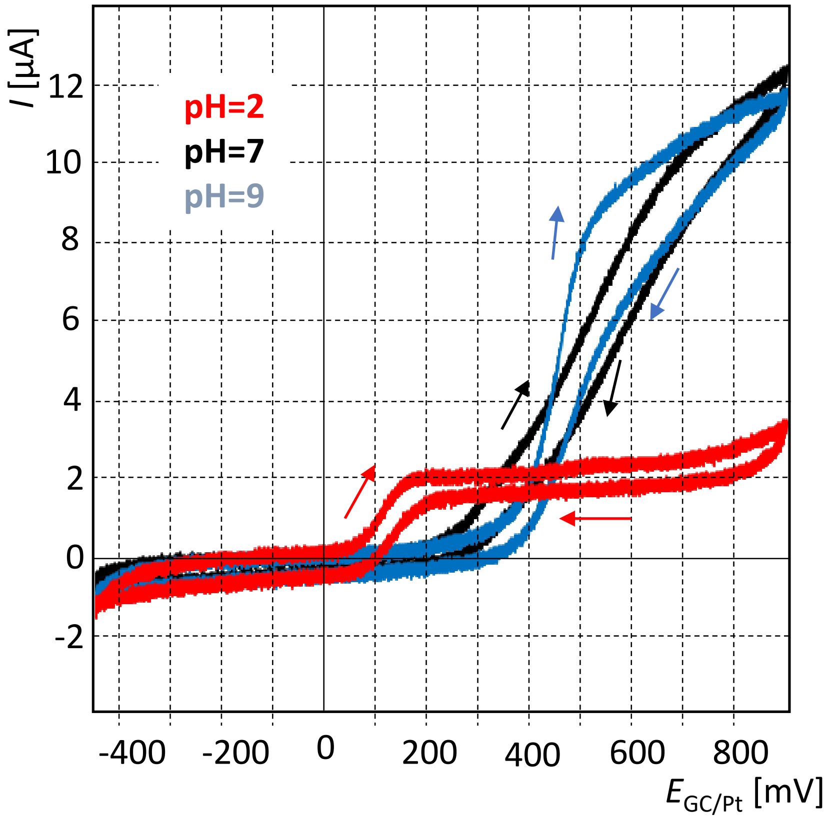
Alcohol oxidation with stochiometric amounts of TEMPO+ requires pH < 2

Electrooxidation

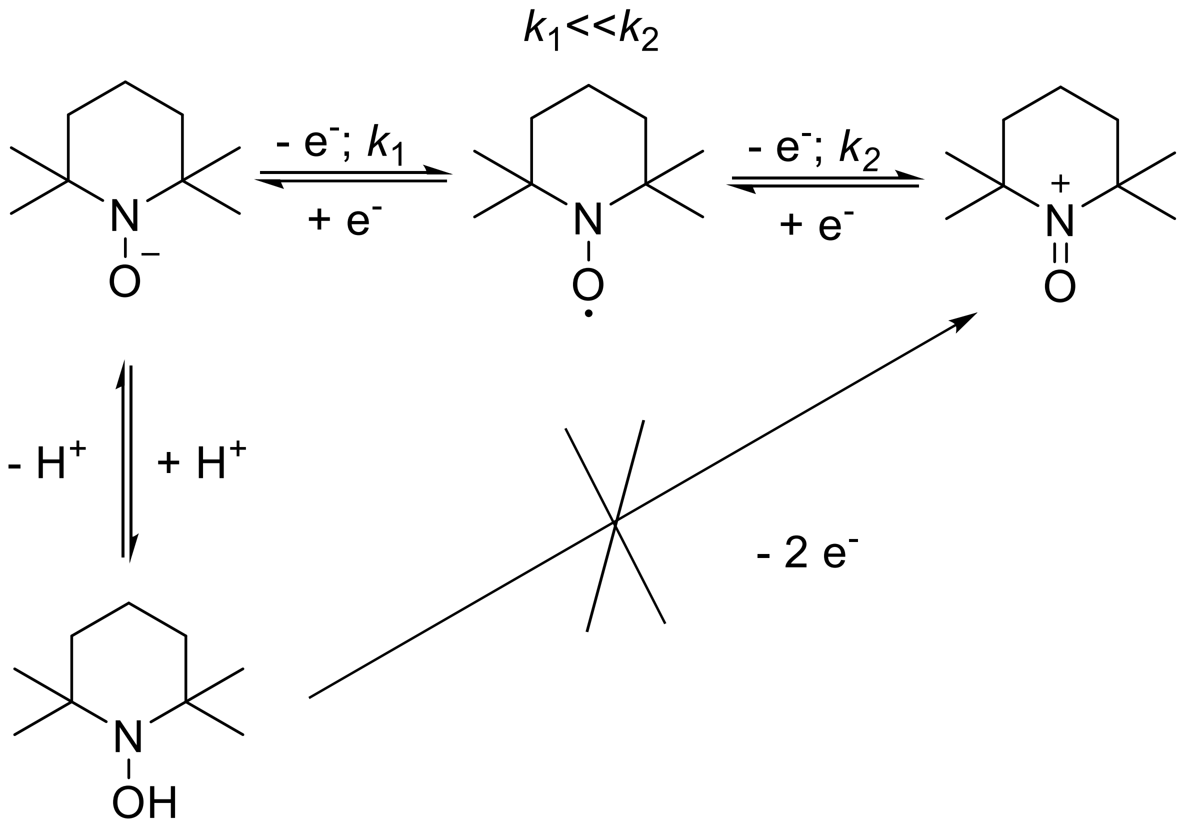


CV and RDE measurements of TEMPOH:

- No conversion to TEMPO+ observed in acidic medium (pH = 2)
- Neutral or alkaline medium required
- Intermediary TEMPO not observed
  - Proved by additional CV/RDE measurements of TEMPO



Electrooxidation

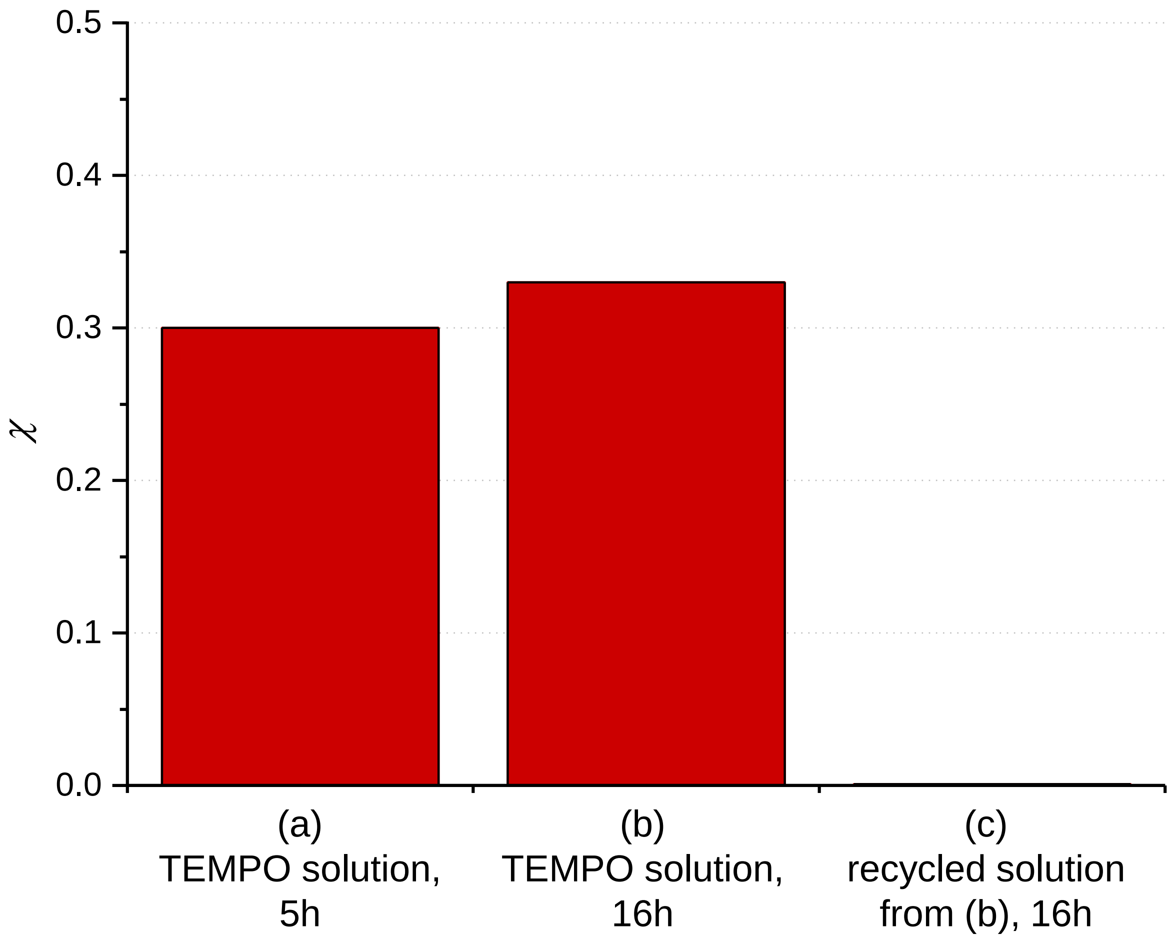


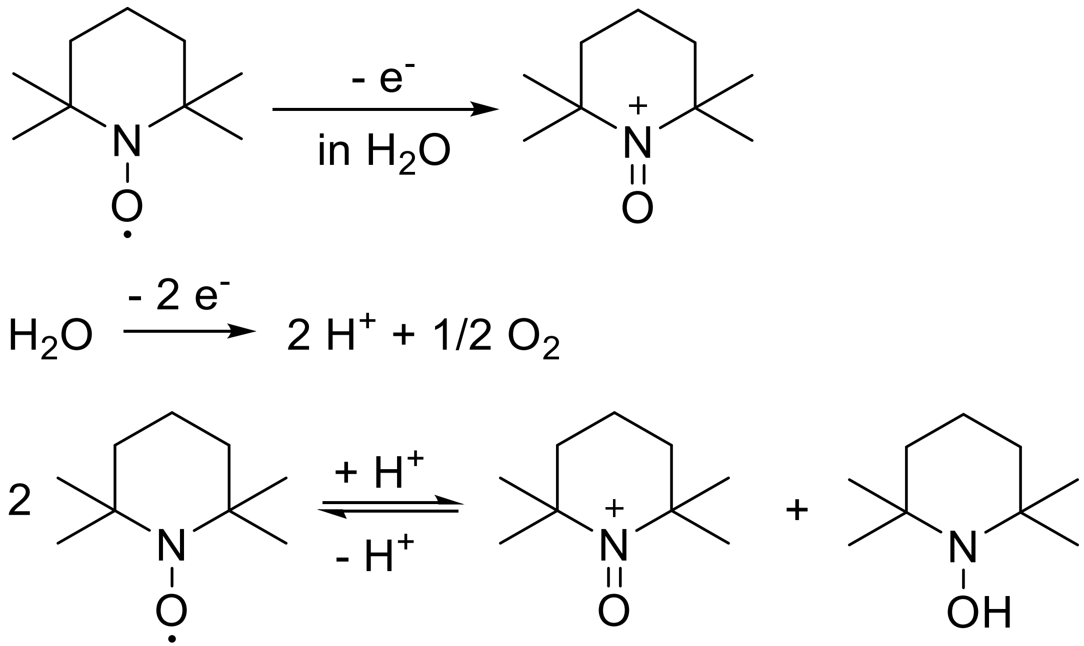
Oxidation path:

- Easy oxidation **TEMPO** → **TEMPO+**
- No direct oxidation **TEMPOH** → **TEMPO+**
- Only in alkaline media
  - Preceding deprotonation to **TEMPO-**
  - **TEMPO-** → **TEMPO** → **TEMPO+**
  - **TEMPO-** → **TEMPO** much slower than **TEMPO** → **TEMPO+**

A. M. Janiszewska, M. Grzeszczuk, *Electroanalysis*, **2004**, *16 (20)*, 1673-1681.

Electrooxidation





Batch electrolysis:

- Maximum yield 33%
- Decomposition of water acidifies anolyte
    - Disproportionation of **TEMPO**

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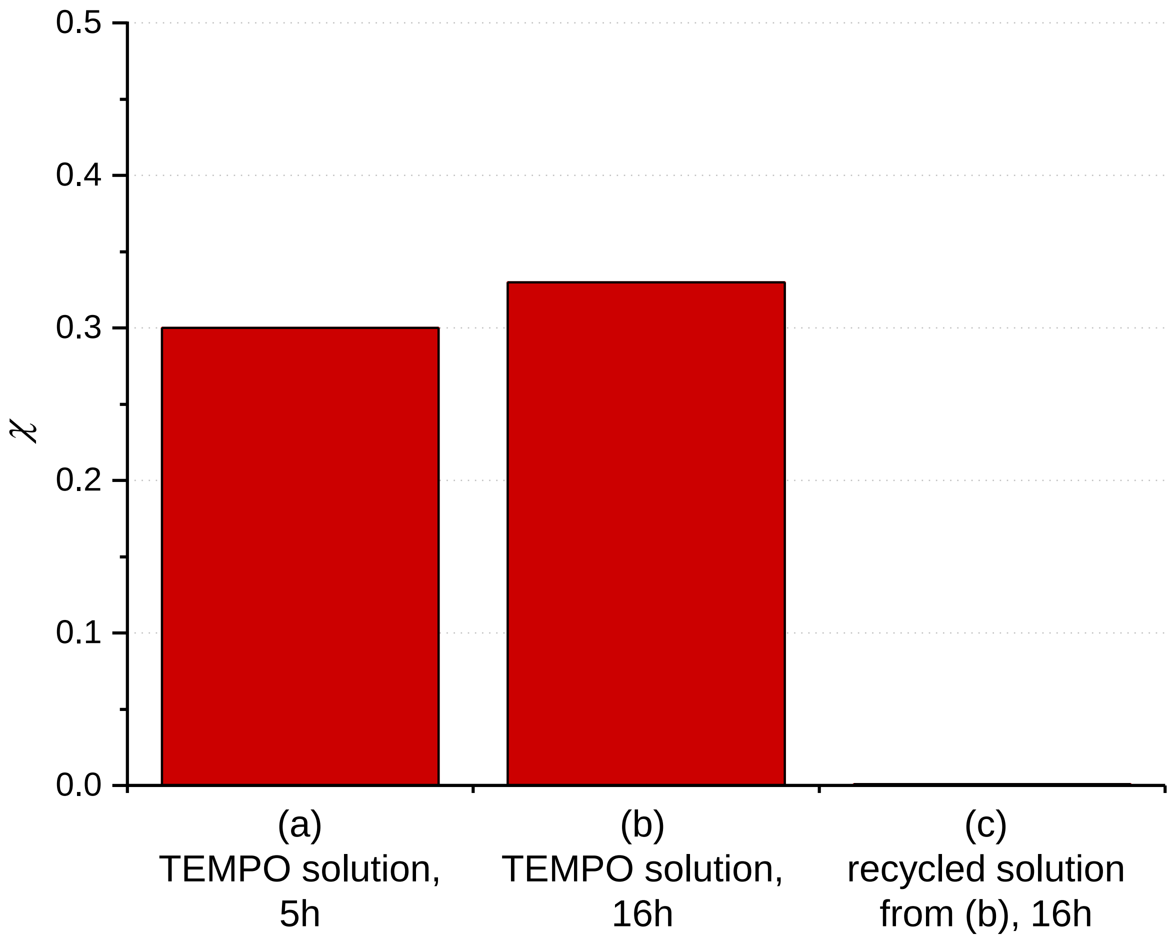
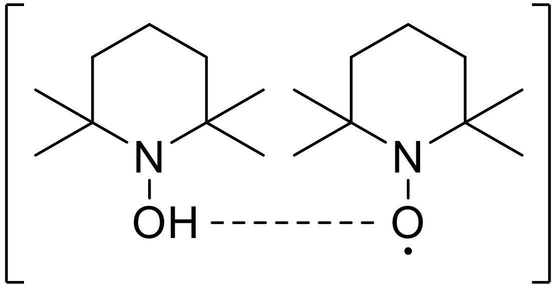
Electrooxidation





A. M. Janiszewska, M. Grzeszczuk, *Electroanalysis*, **2004**, *16 (20)*, 1673-1681.

Batch electrolysis:

- Maximum yield 33%
- Decomposition of water acidifies anolyte
  - Disproportionation of **TEMPO**
- **TEMPOH** associates with **TEMPO**
  - Oxidation is prevented

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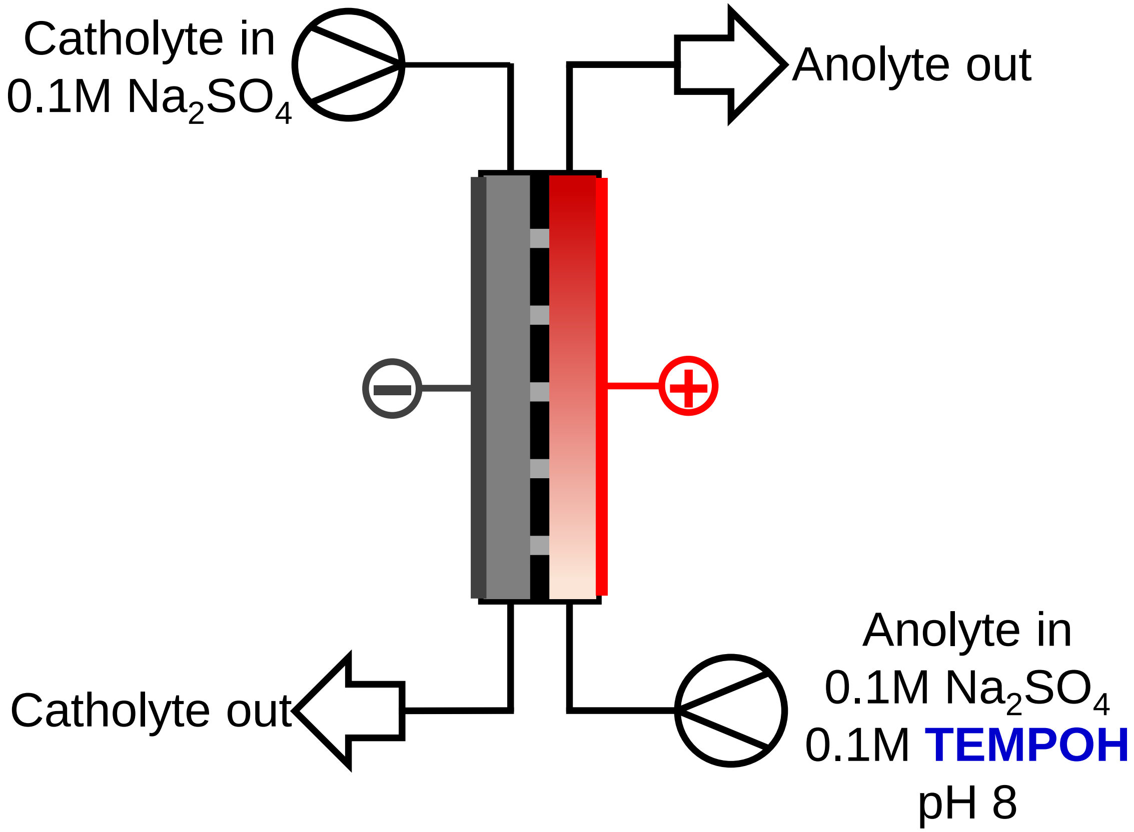
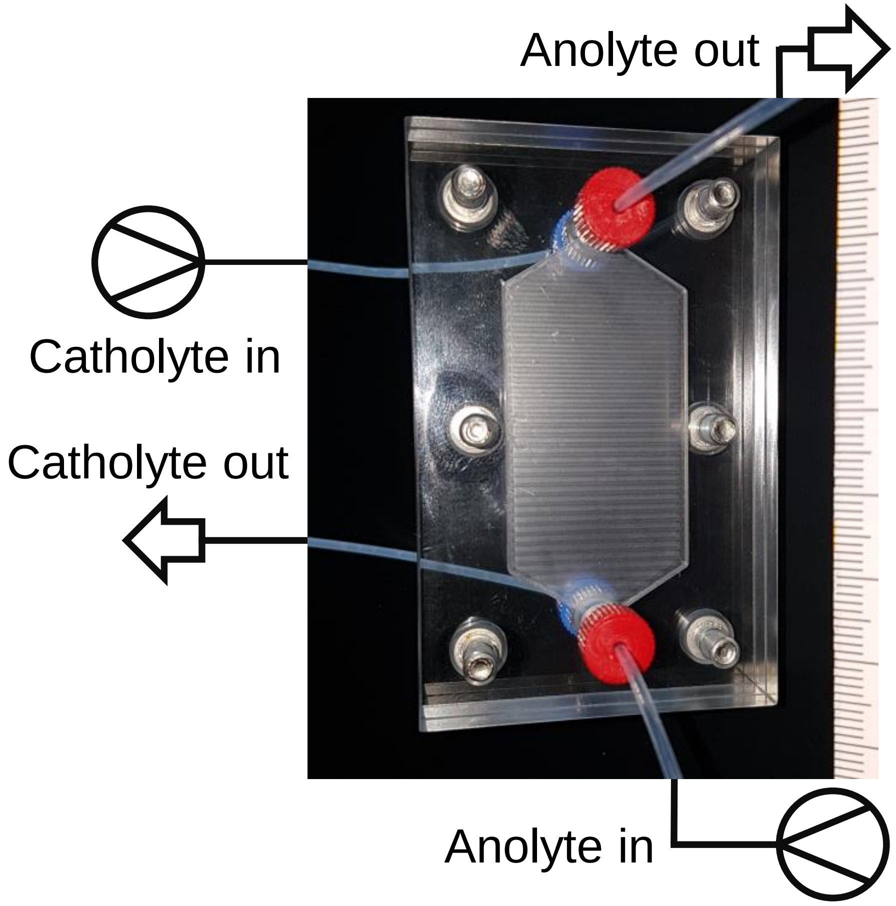
Electrooxidation





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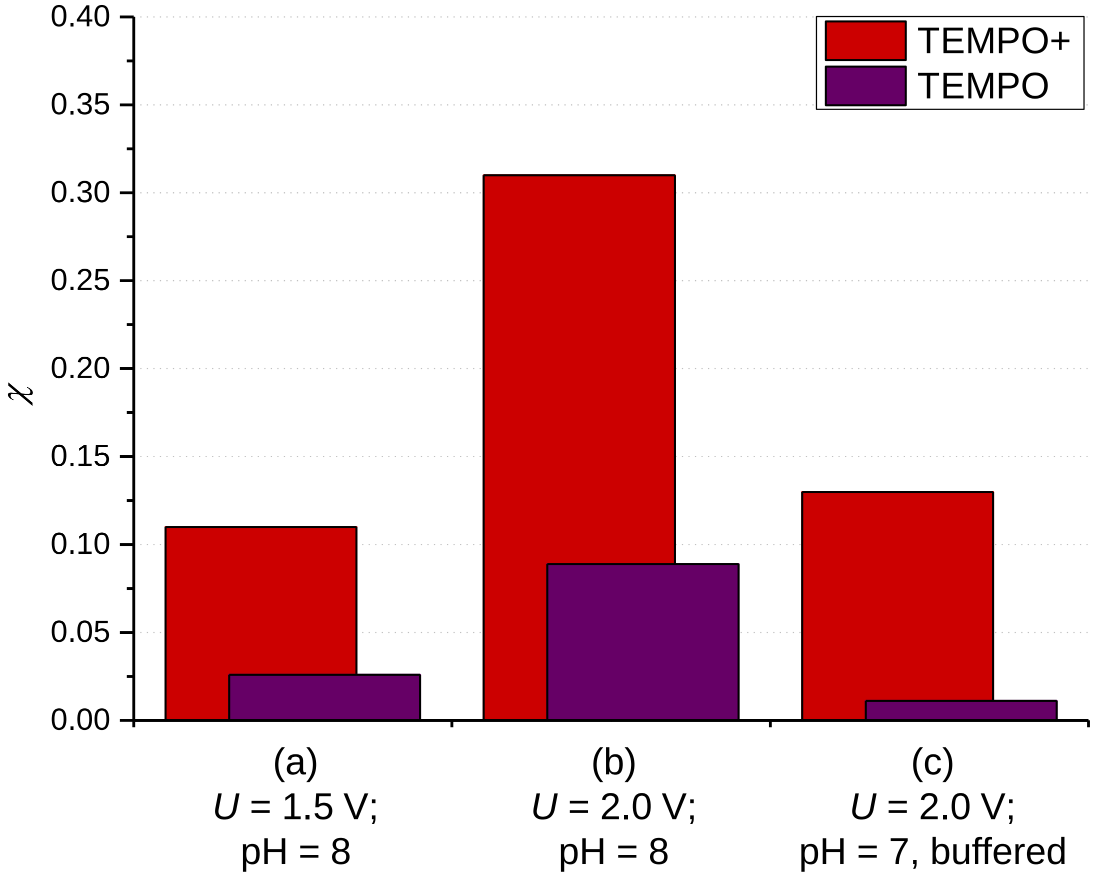
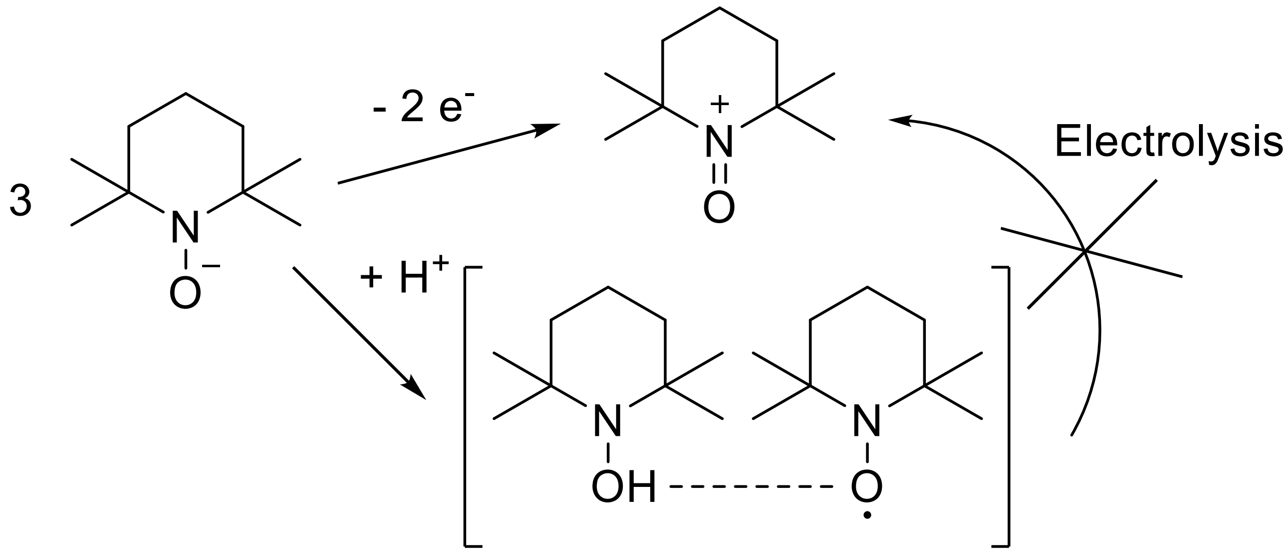
Electrooxidation





Continuous electrolysis:

- Decomposition of water → acidification
- Maximum yield 33%
- Buffering at pH = 7 prevents dimerization, lowers oxidation yield due to protonation of **TEMPO-**

Automated reaction monitoring and control with microcontrollers on the way to the "Internet of Lab"
Automated reaction monitoring and control with microcontrollers on the way to the "Internet of Lab"

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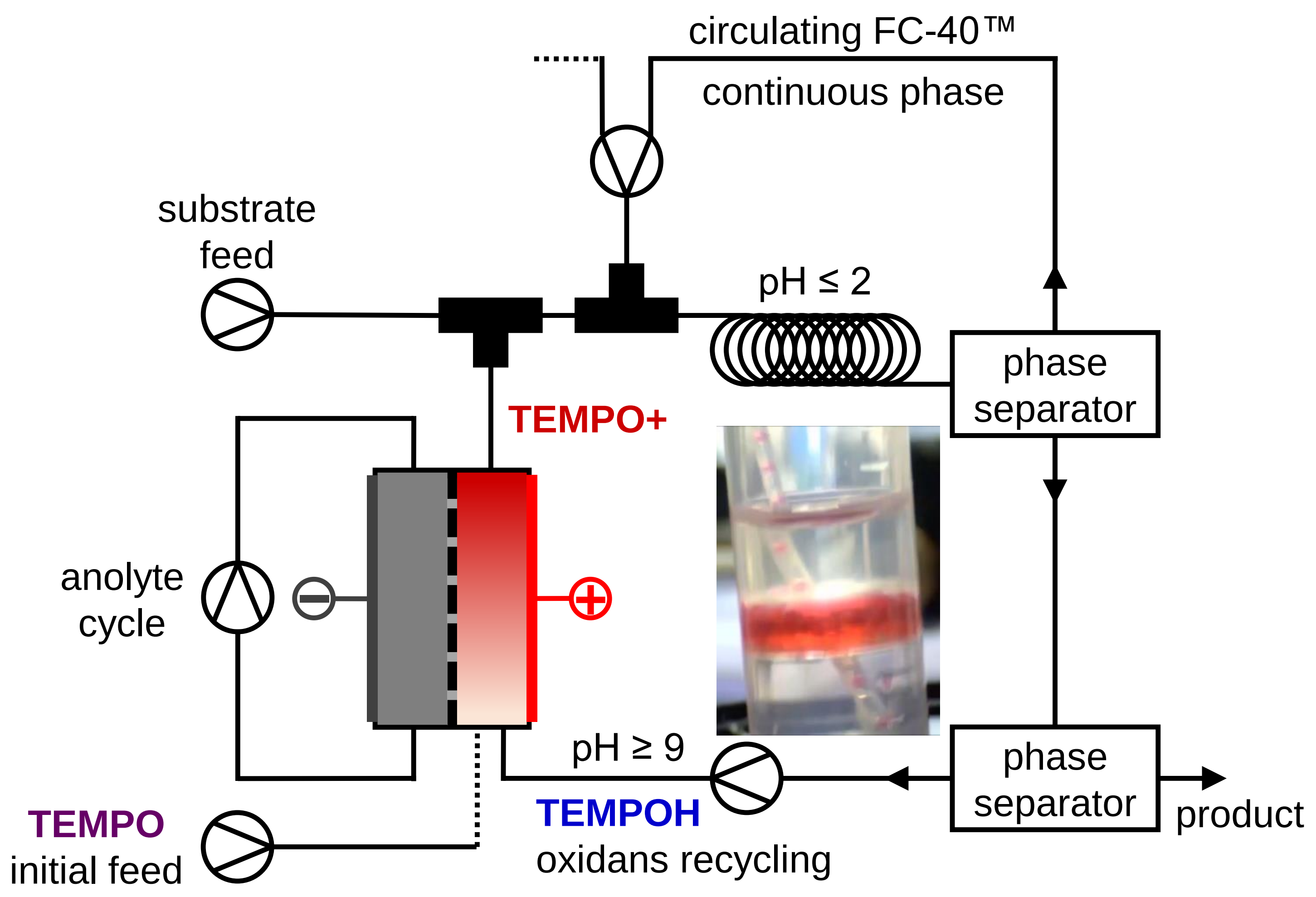
Outlook



Electrochemical microstructured reactor:

- Divided cell (Nafion™ membrane)
- Ti meshed metal baffle, platinized
- Galvanostatic mode

Challanges:

- pH change required
- Flow rate adjustment
- Continuous phase separation
- Recirculation of mediator

Objective: Fully automated process

J. Heinrich, *Automated reaction monitoring and control with microcontrollers on the way to the "Internet of Lab"*, Ph.D. Thesis, University Mainz, **2018**.

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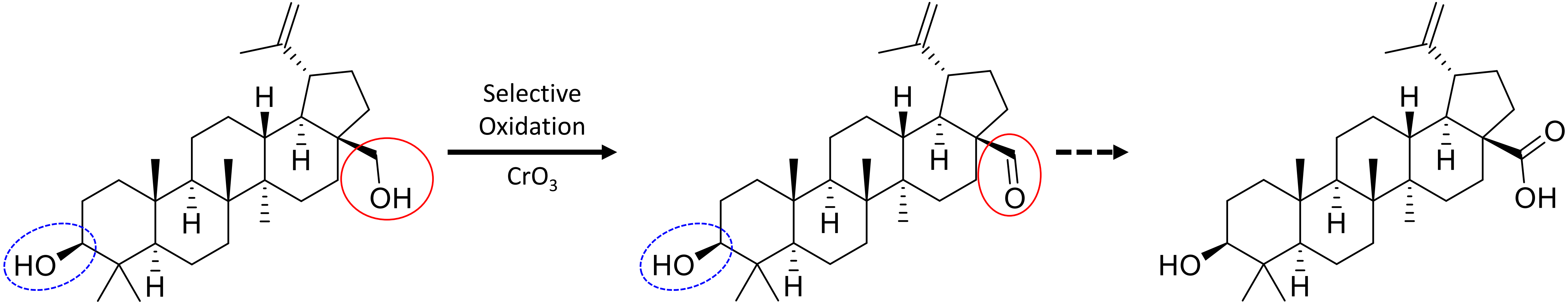
Outlook



Betulin
(3*β*)-Lup-20(29)-en-3,28-diol

Betulin aldehyde

Betulinic acid
and derivates

Betula
pendule

Fraxinus
americana

Sorbus
americana

API synthesis from natural/renewable resources

- Antitumor and –inflammatory properties
- Treatment of leukemia, malaria etc.

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Conclusions

- One-phase process requires much shorter reaction time than multi-phase reaction
- Multi-phase approach simplifies oxidans recycling significantly
  - Allows usage of huge excess of oxidans
  - Allows mixing in segmented flow
- Disproportionation equilibrium of **TEMPO** requires pH < 2 for optimal oxidation conditions
- Alkaline medium required for reoxidation of **TEMPOH**
- Water decomposition and association of **TEMPOH** and **TEMPO** major problems in batch and continuous oxidation, maximum yield of **TEMPO+** 33%
- Fully integrated continuous process requires pH changes and continuous phase separation
- Applications in API synthesis, focus on betulin and derivates

Thank You!

Prof. Dr. Holger Löwe

Christoph Deckers

Dr. Julian Heinrich