Novel Process Windows as Gate Opener towards Green Chemistry

NEXTLAB 2014
Rueil-Malmaison (France)
2-4 April 2014

Elnaz Shahbazali
e.shahbazali@tue.nl

Eindhoven University of Technology
Department of Chemical Engineering and Chemistry
Micro Flow Chemistry and Process Technology
The microreactor instrumentation has widened engineering windows

Question is: can it widen chemical windows? Novel Process Windows
CHEMICAL AND PHOTOCHEMICAL ACTIVATION WITH INCREASING COMPLEXITY

- **Standard high-p,T**: Ruﬁnamide
  - two reactants (neat or 1)
  - Photo-reac
  - Direct adipic acid

- **Advanced high-p,T**: Mizaroki-Heck
  - base
  - Heterog
  - Reactant
  - Trifluoromethylation

- **Multiphase cat.**
  - Reactant rearrang.
  - Catalyst
HUISGEN CYCLOADDITION – TEMPERATURE INFLUENCE IN FLOW

\[
\begin{align*}
\text{F} & \quad \text{N}_3 \\
\text{F} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{OMe} & \quad \text{O} \\
\end{align*}
\]

\(2 + 3 \rightarrow 4\)

catalyst-free, neat or NMP, 135°C

83%, 200°C, 10 min

PRESSURE IMPACT FOR 1,3 DIPOLAR CYCLOADDITIONS

TU Darmstadt 2000 bar
Home-built 400 bar
Labrix 25 bar


HUISGEN CYCLOADDITION
– PRESSURE INFLUENCE IN FLOW


400 bar, 0.25 M, 30 min
HUISGEN CYCLOADDITION
– PRESSURE INFLUENCE IN AUTOCLAVE-BATCH

\[
\begin{align*}
\text{F} & \quad \text{N}_3 \\
\text{F} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{N} = \text{N} \\
\text{F} & \quad \text{O} \\
\end{align*}
\]

High-p

\[
\begin{align*}
\text{NMP, 24 hrs} & \quad 90 \, ^\circ\text{C} \\
\end{align*}
\]

24h

\begin{align*}
\text{Yield (\%)} & \quad \text{Pressure, (bar)} \\
\end{align*}

\[
\begin{align*}
\text{1,4} & \quad \text{1,5} \\
\end{align*}
\]

HUISGEN CYCLOADDITION – TEMPERATURE INFLUENCE IN FLOW

1st step-optimized conditions, as:
• Non-cat batch: 1440 min (24 h), 0.25 M
• Non-cat flow: 30 min, 1.0 M
• Cat flow: 5 min, 0.25 M

Windows with yield >70%

Supported Liquid-Phase Catalysis (SLPC) to Mizoroki-Heck alkenylation

Realized proof of concept with an initial study\(^1\), but

- Conversion and yield were limited to 21%
- Therefore: system not yet tested for extended time on stream
- Therefore: Pd leaching not investigated

Performance after multi-parameter optimization

- 94% yield/conversion (26 min, 230°C)

On-stream catalyst retention

- Catalyst stable for extended time on stream, after initial stabilization period
- No Pd detected in product
Claisen Rearrangement in Flow

- Thermal Rearrangement [1]/Sigmatropic rearrangement

- Photo Rearrangement/Radical mechanism

Different isomers: ortho and para allyl phenyl ether

Widen chemical library, X: H, CH₃, OCH₃, …CN, NO₂, …, by S_N flow coupling

Mechanistic study and flow chemistry ➔ Follow desired transition pathway to desired product

PHOTOCATALYTIC TRIFLUOROMETHYLATION OF HETEROARENES

\[ \text{CF}_3\text{I or RCF}_2\text{I, Ru(bpy)}_3\text{Cl}_2 \]

Blue LED, TMEDA, MeCN

\[ \text{Continuous microflow} \]

**Photo-cat cycle**

Dr. T. Noel, Assist. prof.

METAL-FREE PHOTOCATALYTIC TRIFLUOROMETHYLATION OF HETEROARENES

Photo-cat cycle

Continuous microflow

CF₃I or RCF₂I, Eosin Y
White LED, TMEDA, MeCN

Substrate Perfluoroalkyl Halide Product Yield[b]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Perfluoroalkyl Halide</th>
<th>Product</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(CF₂)₃I</td>
<td>CF₃(CF₂)₃I</td>
<td>(CF₂)₅CF₃</td>
<td>99%[b]</td>
</tr>
<tr>
<td>Me(CF₂)₃I</td>
<td>CF₃(CF₂)₃I</td>
<td>(CF₂)₅CF₃</td>
<td>86%</td>
</tr>
<tr>
<td>Me(CF₂)₃I</td>
<td>CF₃(CF₂)₃I</td>
<td>(CF₂)₅CF₃</td>
<td>88%</td>
</tr>
<tr>
<td>Me(CF₂)₃I</td>
<td>(CF₂)₂CFI</td>
<td>(CF₂)₅CF₃</td>
<td>84%</td>
</tr>
<tr>
<td>Me(CF₂)₃I</td>
<td>(CF₂)₂CFI</td>
<td>(CF₂)₅CF₃</td>
<td>80%</td>
</tr>
<tr>
<td>Me(CF₂)₃I</td>
<td>EtCOOCF₂Br</td>
<td>(CF₂)₅CF₃</td>
<td>30%</td>
</tr>
</tbody>
</table>

Eosin Y 2.04 Euro/g Rose Bengal 4.76 Euro/g

INTERPLAY BETWEEN CHEMICAL AND PHOTOCHEMICAL ACTIVATION

Eosin Y → Eosin Y* → SET → Eosin Y⁻ → RF⁻ → RF⁻ → TMEDA → SET → TMEDA⁺⁺ → RF⁺⁺ → C → -H⁺ → D

Visible light
CONVENTIONAL PRODUCTION PROCESS FOR ADIPIC ACID

Step 1

Process operates at only 3-6% conversion to ensure higher selectivity to K/A oil, requiring a huge recycle

Production of large amounts of undesired N$_2$O

Step 2
Reaction:

The schematic diagram for the low pressure reaction device:

- Syringe pump
- Packed bed reactor
- Micromixer
- Hydrogen peroxide and sodium tungstate

Cyclohexene and phase transfer catalyst

Process simplification

DIRECT ROUTE AND SETUP

\[
\text{Cyclohexene} + 4\text{H}_2\text{O}_2 \xrightarrow{\text{Na}_2\text{WO}_4} \text{Cyclohexanecarboxylic acid} + 4\text{H}_2\text{O}
\]

- Oxidation
- Hydrolysis
- Oxidation

Packed bed reactor

Syringe pump

Micromixer

Hydrogen peroxide and sodium tungstate

Product

\[
\text{Adipic acid}
\]
Oxidising agent, solvent, Co-catalyst, PT catalyst,

\[ n(H_2O_2): n(\text{cyclohexene}): n(\text{Na}_2\text{WO}_4): n(\text{PTC}) = 440:100:6:6 \]

50\% H_2O_2, c(H^+) = 1.27\text{mol/l}

n(H₂O₂): n(cyclohexene): n(Na₂WO₄): n(PTC)=440:100:6:6, 50% H₂O₂,
c(H₂SO₄)=0.22 mol/l

63% yield by reactor splitting
Small hot spots - safe operation in micro packed bed reactors
n(H₂O₂): n(cyclohexene): n(Na₂WO₄): n(PTC)=440:100:6:6, 50% H₂O₂, c(H₂SO₄)=0.22 mol/l, three reactors (5cm-5cm-10cm)

Temperature steps 70-100-110 °C resulted in 66% yield of adipic acid.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactor</th>
<th>Residence time [min]</th>
<th>STY [kg/(l•h)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Batch reactor [1]</td>
<td>480</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>1-stage packed bed reactor [2]</td>
<td>20</td>
<td>0.57</td>
</tr>
<tr>
<td>3</td>
<td>2-stage packed bed reactor</td>
<td>20</td>
<td>0.72</td>
</tr>
<tr>
<td>4</td>
<td>3-stage packed bed reactor</td>
<td>20</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Reaction conditions: \( n(\text{H}_2\text{O}_2): n(\text{cyclohexene}): n(\text{Na}_2\text{WO}_4): n(\text{PTC})=440:100:6:6 \), 50\% \( \text{H}_2\text{O}_2 \), \( c(\text{H}_2\text{SO}_4)=0.22\text{mol/l} \)

SFP Group: Micro Flow Chemistry and Process Technology

Dr. T. Noel, Assistant prof.

Dr. Q. Wang, Assistant prof.

G. Kolb, Part-time prof.

N. Straathof, PhD

E. Shahbazzali, PhD

M. Shang, PhD

S. Sundaram, PhD

I. Dencic, PhD

I. Vural, PhD

S. Stouten, PhD

H. Gemoets, Master/PhD

B. Spasova, PhD at IMM/TUD

J. Tibhe, PhD

A. Anastasopolou, PhD

B. Patil, PhD

L. Borukhova, PhD

J. Smit, Editorial Assistant

A. Hemert, Secretariat