### Bulk chemicals (2009 figures)

The traditional stronghold of aerobic oxidation catalysis

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Mton/year</th>
<th>Air</th>
<th>O₂</th>
<th>HNO₃</th>
<th>Cl₂</th>
<th>ROOH</th>
<th>H₂O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terephthalic acid</td>
<td>44</td>
<td>•</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>19</td>
<td>•</td>
<td></td>
<td></td>
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<tr>
<td>Ethene oxide</td>
<td>18</td>
<td></td>
<td>•</td>
<td></td>
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</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>18</td>
<td>•</td>
<td>•</td>
<td></td>
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<td></td>
<td>•</td>
</tr>
<tr>
<td>Propene oxide</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>•</td>
<td>•</td>
<td>•</td>
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<tr>
<td>Cyclohexanone</td>
<td>6</td>
<td>•</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vinyl acetate</td>
<td>6</td>
<td>•</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acrylonitrile</td>
<td>6</td>
<td>•</td>
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<td></td>
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</tr>
<tr>
<td>Styrene (ex Propene oxide/Styrene)</td>
<td>5</td>
<td>•</td>
<td>•</td>
<td></td>
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<td></td>
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<tr>
<td>Phenol/Acetone</td>
<td>5</td>
<td>•</td>
<td></td>
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<tr>
<td>Phthalic anhydride</td>
<td>5</td>
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</tr>
<tr>
<td>Acrylic acid</td>
<td>5</td>
<td>•</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTBE (ex Propene oxide/tButyl alcohol)</td>
<td>4</td>
<td>•</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipic acid</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>•</td>
</tr>
<tr>
<td>Maleic anhydride</td>
<td>2</td>
<td>•</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hydrogen cyanide</td>
<td>2</td>
<td>•</td>
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</tr>
</tbody>
</table>
The renaissance of aerobic oxidation catalysis

From bulk to fine

# Publications related to catalytic oxidation with oxygen in journals on organic synthesis (SciFinder 31 July 2015)
Cost & waste reduction: $O_2$ for Pd catalyzed C-H activation

Cross-dehydrogenative arene-arene coupling

\[
\text{X} \text{B(OH)}_2 + \text{X} \text{PhY} \xrightarrow{\text{salts}} \text{X} \text{Ph-Ph-Y}
\]

Suzuki cross coupling

\[
\text{X} \text{PhH} + \text{X} \text{PhY} \xrightarrow{\text{salts}} \text{X} \text{Ph-Ph-Y}
\]

Direct arylation

\[
\text{X} \text{PhH} + \text{HPhY} \xrightarrow{[O]} \text{X} \text{Ph-Ph-Y}
\]

Cross-dehydrogenative coupling
DSM example on aerobic Pd catalyzed biaryl synthesis

Key green chemistry research areas—a perspective from pharmaceutical manufacturers

David A. J. Chilton, Russell Hebb and Tony Y. M. Zhang

Recent advances in metal-catalysed cross-coupling reactions have greatly facilitated the versatility of incorporating aryls for medicinal chemistry. However, most of these reactions rely on the availability of aryl bromides or iodides. Direct activation of aryl hydrogen (converting Ar–H into Ar–Ar) will be of great potential.
Cost & waste reduction: \( \text{O}_2 \) for Cu catalyzed dehydrogenation

Cross dehydrogenative N-N coupling

\[
\begin{align*}
\text{R'} \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{NH}_2
\end{array}
\quad \begin{array}{c}
\text{NR}_2 \\
\text{NR}_2
\end{array}
\quad \text{CuBr (5 mol%)} \\
\text{phen (5 mol%)} \\
\text{air}
\end{align*}
\]

including:

Triazolo-pyridines, pyrazines, pyridazines, and pyrimidines from guanidyl-N-heterocycles

Roche pharma: *J. Org. Chem.* 2015, 80, 1249
Aerobic Cu catalysis revolutionizes heterocycle synthesis

Another revolution: (aerobic) carbocatalysis

Graphene:
\( C \)

Graphene oxide:
\( C_xO_yH_z \)

Graphitic carbon nitride:
\( C_3N_4 \)

B-doped graphene:
\( C_xB_y \)

N-doped graphene:
\( C_xN_yH_z \)
Carbocatalysis: multi-purpose applications

Selected examples of unusual or useful reactions, survival of oxidation-sensitive groups, and/or demonstrated superiority over other tested oxidation methods.
More organocatalysis: aerobic alcohol oxidations

From heterogeneous carbocatalysts to homogeneous nitroxyls

TEMPO

AZADO

R = X = H: AZADO
R = Me, X = H: 1-Me-AZADO
R = H, X = F: 5-F-AZADO

norAZADO

ABNO

X = H₂: ABNO
X = O: ketoABNO

Kg availability from Nissan

P.L. Anelli (TEMPO)
Y. Iwabuchi (AZADOs; ABNOs)

2 Steps from acetonedicarboxylic acid

Iwabuchi review: Chem. Pharm. Bull. 2013, 61, 1197
Preparation and properties of ketoABNO

- Redox potential in MeCN vs ferrocene: 416 mV (cf AZADO: 188 mV; TEMPO: 239 mV) ⇒ suitable organocatalyst for electron-deficient alcohols
- α-Carbonyl methylene groups may reduce organocatalyst stability under basic bleach conditions, but ketoABNO found to be effective under (non-basic) aerobic conditions

Improved prep and aerobic oxidns: B. Karimi, ChemSusChem 2014, 7, 2735
Transition metal-like catalyst turnovers

Under "Anelli bleach" conditions for unactivated alcohols

Nitroxyls as organocatalysts for aerobic alcohol oxidations

Dominated by two protocols

nitroxylic orgcat
Cu cat + ligand
base add
aprotic polar solv

\( \text{OH} \quad \rightarrow \quad \text{O}_2 \quad \rightarrow \quad \text{CO} \)

\( \text{H} \)

nitroxylic orgcat
\( \text{NO}_x \) cocat
acidic solv/add
Transition metal-like catalyst turnovers

Under "aerobic Cu" conditions for activated alcohols

0.05 mol% ketoABNO
Cul 7.5 mol%
bpy/NMI 7.5/10.5 mol%

O₂ from air (1 or 40 bar)
MeCN; 25°C

90% Conversion in 20 min at 40 bar air; unactivated secondary alcohols:
several hrs at 0.1 mol%/RT/1 bar air (Cu cat decomposition at 40 bar!)

"FOX" (flow oxidation) project goals

- Set-up of a safe, continuous flow system for catalytic aerobic oxidations, also based on pure oxygen besides air
- Implementation of online analysis (FT-IR)
- Kick-off transformation: oxidation of primary and secondary alcohols to industrially relevant aldehydes and ketones

Recent publications by S.S. Stahl on flow protocols for aerobic Cu/nitroxyl catalyzed alcohol oxidations:
*Org. Process Res. Dev.* **2013**, **17**, 1247 (elevated P&T using 9% O$_2$/N$_2$ in a stainless steel or PTFE tube reactor)
Remarkably broad scope of aerobic Cu/nitroxyl cat systems

Tolerates sterically bulk around alcohol

Primary or secondary alcohol

CuOTf/MeO_bpy/NMI/ABNO
metal + orgcat
hybrid system

1 bar air or O₂
MeCN solv
RT or 70°C, 1-3 h

Aldehyde or ketone

Tolerates coordinating heteroatoms

Two relevant alcohol oxidations

Benzylic but bulky

Deactivated and bulky

Epoxone

10-30 mol%  

Oxone or H$_2$O$_2$/MeCN

Necessitates low cat costs!
In house pilot plant experience on 220 lbs Epoxol oxidation

Potentially cheap lab alcohol ox methods failed on scale-up!

- Bleach instead of periodate caused product and catalyst degradation
- TEMPO + bleach (Anelli) not active (too hindered alcohol)
- Stoichiometric chromate not feasible on large scale
- NaIO₄ offered acceptable cost because DSM was a periodate producer at the time

Implementation of online FT-IR analysis

Benzyl alcohol (704 cm\(^{-1}\)) \(\rightarrow\) benzaldehyde (1704 cm\(^{-1}\))

Switch from \(N_2\) to \(O_2\)
Design of the Taylor flow reactor

Pumping & mixing gases

G/L mixing: Taylor flow

Dilution with N₂

Pumping & mixing liquids

Reactor

FT-IR

Glass vessel
Benzyl alcohol oxidation under Taylor flow conditions

Dependence on oxygen pressure

0.25 M BnOH; 25°C; O₂/sub = 1; 2/2/2/5 CuOTf/bpy/TEMPO/NMI

Rate increases with oxygen pressure

⇒ Turnover-limiting oxidation of Cu(I) by O₂
Taylor flow: slow rate with near-stoichiometric $O_2/sub = 0.5$

$RCH_2OH + 0.5 O_2 \rightarrow RCH(O) + H_2O$

Pumping & mixing gases

G/L mixing: Taylor flow

Dilution with $N_2$

Cooler

New reactor set up: single phase reactor

G slugs much smaller than L slugs $\Rightarrow$ G/L mixing insufficient

Good Taylor flow $\Rightarrow$ efficient G/L mixing

$O_2/sub = 2$

$O_2/sub = 1$
Design of the single phase reactor

Pumping & mixing gases

P = 34 bar G/solvent pre-mixing

Cooler

Dilution with \( N_2 \)

Pumping & mixing liquids

3D printed zig-zag reactor

FT-IR

Glass vessel

P = 34 bar G/solvent pre-mixing
3D printed zig-zag reactor

How it looks like: inside and outside

Zig-zag assures turbulent (non-laminar) flow despite the commercially relevant millimeter diameter scale of the tube
3D printing by Selective Laser Melting: principle

SLM produces homogenous metal objects directly from 3D CAD data by selectively melting fine layers of metal powder with a laser beam.
3D printing by Selective Laser Melting: practice

Developed by ILT Fraunhofer Aachen (1995)
Benzyl alcohol oxidation under various flow regimes

Taylor vs. single phase conditions

Rate increases by using single phase conditions
✓ O₂/sub can be lowered to 0.55 (10% excess)

0.25 M BnOH; 25°C; 5/5/5/10 mol% CuOTf/bpy/TEMPO/NMI
Oxidation of fenchyl alcohol as a model for Epoxol

Catalyst optimization: "more is better" except for NMI

0.25 M Fenchyl alcohol; 60 min@70°C/1 bar O₂ (balloon); 0.1 mol% ketoABNO

✓ Optimum at 5 mol% NMI irrespective of NMI/Cu ratio
Mechanism of Cu/nitrooxyl aerobic alcohol oxidation

Oxidation of Epoxol under Taylor flow conditions

Molar $O_2$/Epoxol ratio and oxygen pressure: "more is better"…?

![Graphs showing yield vs. time for different oxygen pressures and molar ratios.](image)

0.2 M Epoxol; 25°C; 5/5/1/10 mol% CuOTf/bpy/ketoABNO/NMI

- Rate hardly increases with molar $O_2$/alcohol ratio and $P(O_2)$
  - Turnover-limiting cleavage of the C–H bond

(Cf turnover-limiting oxidation of Cu(I) by $O_2$ for BnOH)
Oxidation of Epoxol under single phase conditions

Conversion does not continuously increase with temperature

0.2 M Epoxol; 33 bar $O_2$; $O_2$/sub = 1; 7.5/7.5/0.25/10 mol% CuOTf/bpy/ketoABNO/NMI

✓ Full conversion with 0.25 mol% ketoABNO within 17 min at 100°C
Copper(I) source: triflate or iodide...?

<table>
<thead>
<tr>
<th><strong>CuOTf</strong></th>
<th><strong>Cul</strong> <em>(S.S. Stahl, Org. Process Res. Dev. a.s.a.p.)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires bpy and NMI (besides nitroxyl)</td>
<td>Requires only NMI (besides nitroxyl)</td>
</tr>
<tr>
<td>Fluoride source in waste water may be problematic in some countries</td>
<td>Acceptable halide for waste water</td>
</tr>
<tr>
<td>No corrosion problems encountered when using stainless steel reactor</td>
<td>Corrosive $\Rightarrow$ PTFE reactor required (less P&amp;T robust and less heat conductive)</td>
</tr>
<tr>
<td>Too expensive as such, but expected to be readily available as MeCN solution from (ultrasonic) Cu + HOTf reaction</td>
<td>Readily commercially available</td>
</tr>
</tbody>
</table>

\[
\text{Cu} + 2 \text{HOTf} \xrightarrow{\text{ultrasound}} \text{MeCN} \quad \text{Cu(OTf)}_2 + \text{H}_2
\]

\[
\text{Cu} + \text{Cu(OTf)}_2 \xrightarrow{\text{MeCN}} 2 \text{CuOTf} \quad \text{SUM}
\]

\[
2 \text{Cu} + 2 \text{HOTf} \xrightarrow{\text{(as MeCN solution)}} 2 \text{CuOTf} + \text{H}_2
\]
Summary

- Catalytic aerobic oxidation is finally escaping from its bulk chemical stronghold and makes its way into fine chemicals/pharma manufacture.
- This trend is driven by the significant reductions of (raw materials) cost, waste and number of steps enabled by new developments in aerobic oxidation catalysis.
- Example: aerobic Epoxol → Epoxone opens the door to broader large-scale application of this versatile asymmetric epoxidation organocatalyst.
- Scalable, safe, and efficient aerobic processing is enabled by continuous flow reactors, in particular zig-zag reactors for single phase conditions.
- 3D printing has enabled cost-efficient manufacture of flow reactors with full freedom of design: create the ideal asset for demanding chemistry.
- Smooth integration in existing hardware, wide diversity of applications:
  - Cryogenic organometallic chemistry
  - High temperature (‘in the melt’)
  - Catalytic (aerobic) oxidations
  - Catalytic hydrogenation
  - Nitrations
  - Cyclopropanations (‘Ethyl diazoacetate’)
  - Polymerizations
  - Azide Chemistry

Process R&D services via DSM InnoSyn®
Interested? Contact: andre.vries-de@dsm.com
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