Sustainable manufacturing at CABB

Chlorination and sulfonation – surprisingly sustainable

Dr. Jörg Schrickel
New Business Development, CABB AG
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Sustainable manufacturing

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Conclusion

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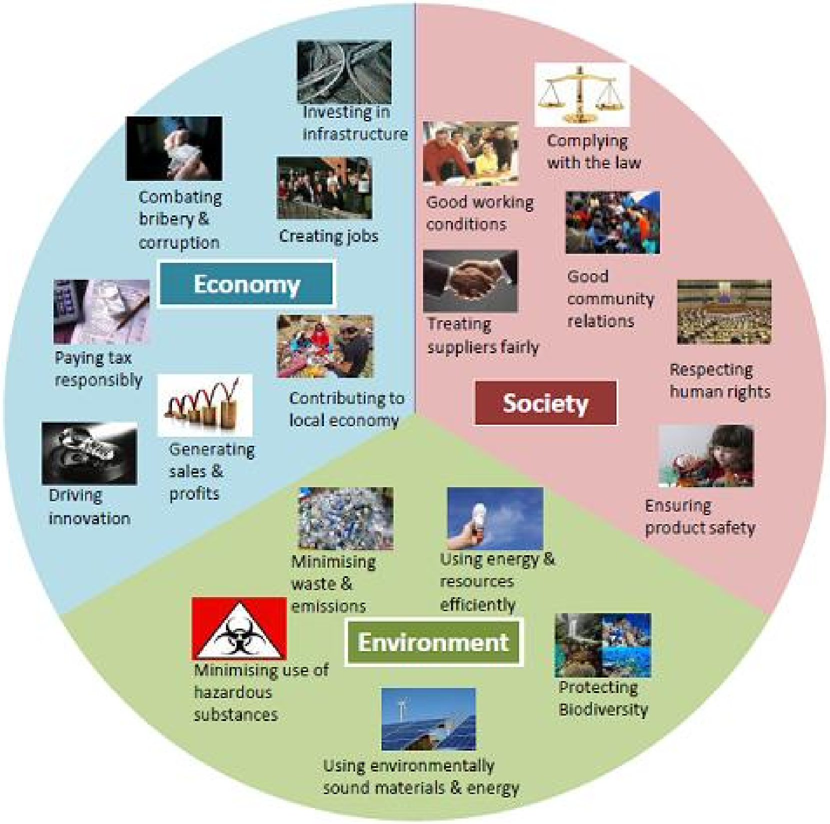
Sustainability

Economy, Ecology, Society

- Efficient, safe and environmentally benign chemical products and processes
- Protecting and enhancing human health and the environment
- Reducing the environmental impact of processes and products, minimising waste
- Extending the quality of life; competitive, knowledge-based, enterprise-led economy



Source: OECD

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12 Principles of Green Chemistry

Prevention of waste: It is better to prevent waste than to treat or clean up waste.

Atom Economy: Design of synthesis to maximize the incorporation of all materials used in the process into the final product.

Less Hazardous Chemical Syntheses: Design of synthesis to use and generate substances that possess little or no toxicity to human health and the environment. Wherever practicable.

Designing Safer Chemicals: Design of chemical products to effect their desired function while minimizing their toxicity.

Safer Solvents and Auxiliaries: Use of auxiliaries (solvents, separation agents, etc.) should be made unnecessary wherever possible.

Design for Energy Efficiency: Minimization of energy requirements of chemical processes.

Use of Renewable Feedstocks: Use of renewable raw materials or feedstocks whenever technically and economically practicable.

Reduce Derivatives: Minimisation of unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) to prevent use of additional reagents and generation of waste.

Catalysis: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

Design for Degradation: Design of chemical products to break down into innocuous degradation products and do not persist in the environment.

Real-time analysis for Pollution Prevention: Development of analytical methodologies to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

Inherently Safer Chemistry for Accident Prevention: Use of substances in a chemical process to minimize the potential for chemical accidents, including releases, explosions, and fires.

(by the ACS Green Chemistry Institute)

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Metrics

Process Mass Intensity (PMI)

$$\text{PMI} = \frac{\text{total mass of incoming materials in a process (incl. solvents and water) [kg]}}{\text{total amount of product [kg]}}$$

Environmental factor

$$\text{E-factor} = \frac{\text{total mass of waste [kg]}}{\text{total amount of product [kg]}}$$

Atom efficiency

$$\text{Atom efficiency} = \frac{\text{mass of atoms in desired product}}{\text{mass of atoms in reactants}} \times 100\%$$

Industry sector	Product tonnage	E-factor
Oil refining	10^6 - 10^8	~ 0.1
Bulk chemicals	10^4 - 10^6	1 – 5
Fine chemicals	10^2 – 10^4	5 – 50
Pharmaceuticals	10^1 - 10^2	25 – 100+

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CABB at a glance

- Integrated, global provider of fine chemicals and custom manufacturing solutions
- Focus on selected building blocks based on distinctive technologies in chlorination, sulfonation and other key chemistries
- Balanced mix of products and services with leading positions across various markets
- Two business units: Custom Manufacturing and Acetyls
  - Global market leader in Monochloroacetic Acid and its derivatives (salts, esters, acid chlorides)
  - Strong player in Custom Manufacturing, especially for the agrochemical industry

- Young company with a century of history
- 1’000+ employees
- > 430 Mio € sales
- 6 production sites

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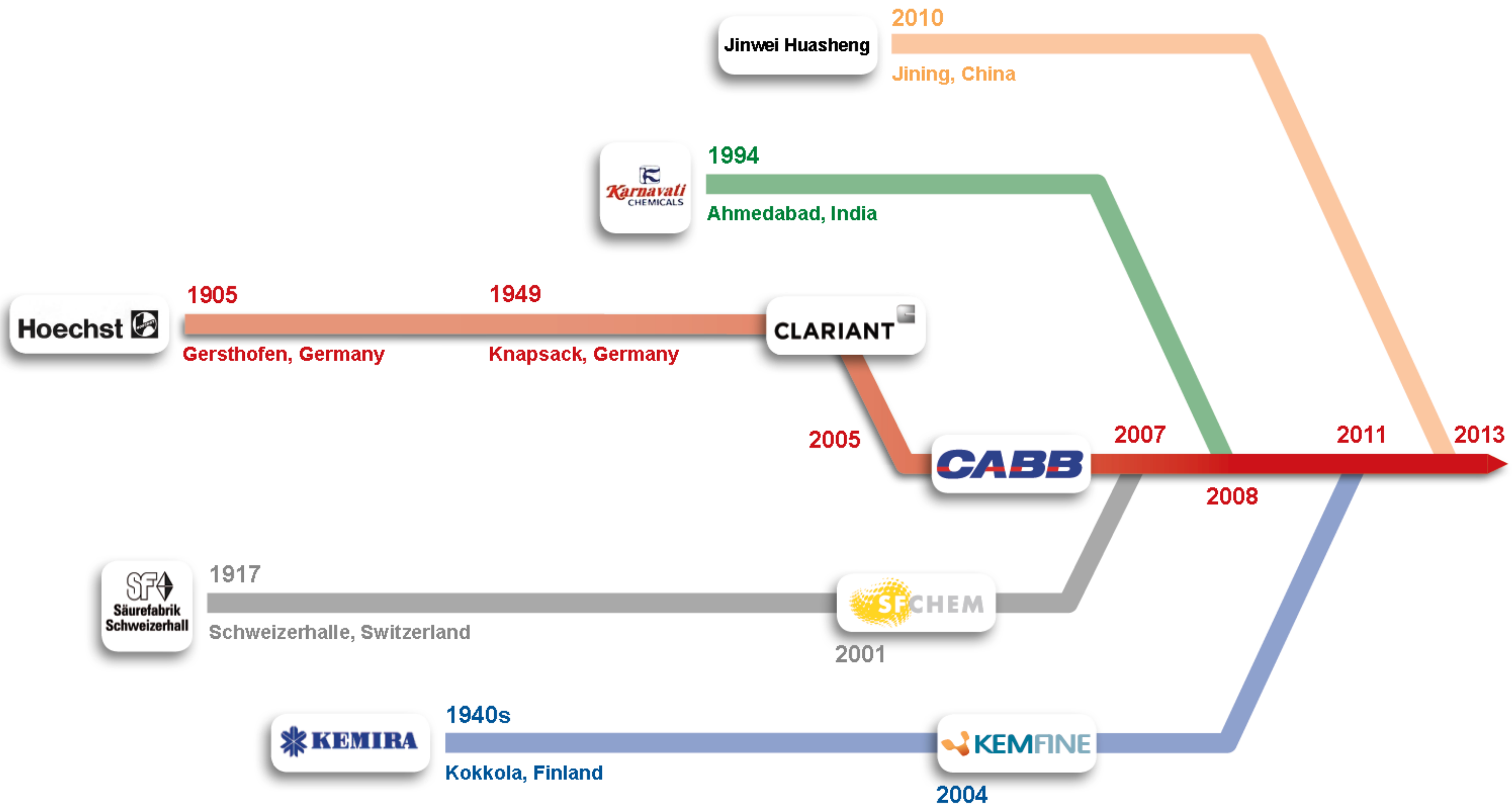
More than a century of chemistry



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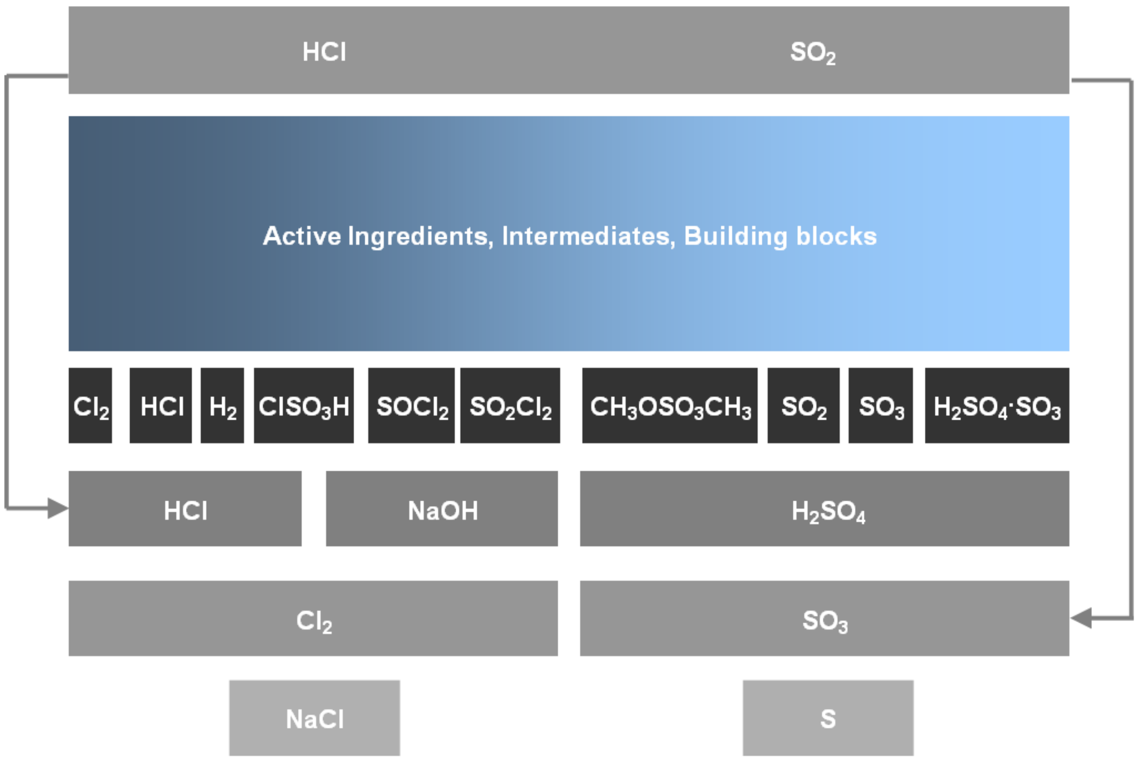
CABB‘s Verbund and recycling system



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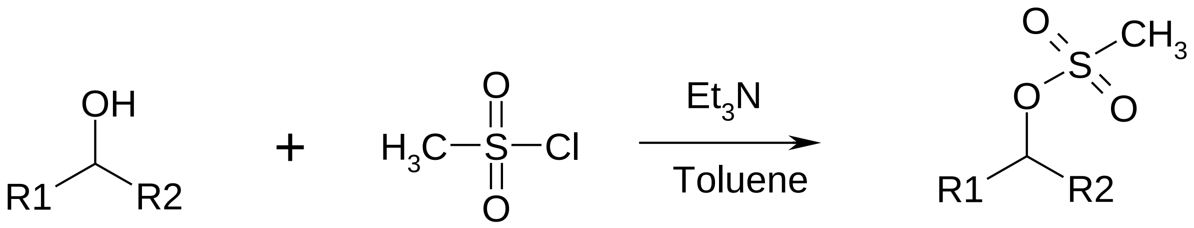
Case study: Mesylation reaction: batch to continuous



- Reaction of a secondary alcohol with methanesulfonyl chloride in the presence of a tertiary amine in toluene (which is completely recycled)
- Mesylation reaction was originally designed as a batch process
- Reaction was changed into a continuous process
- Same equipment was used
- Further work-up was not modified

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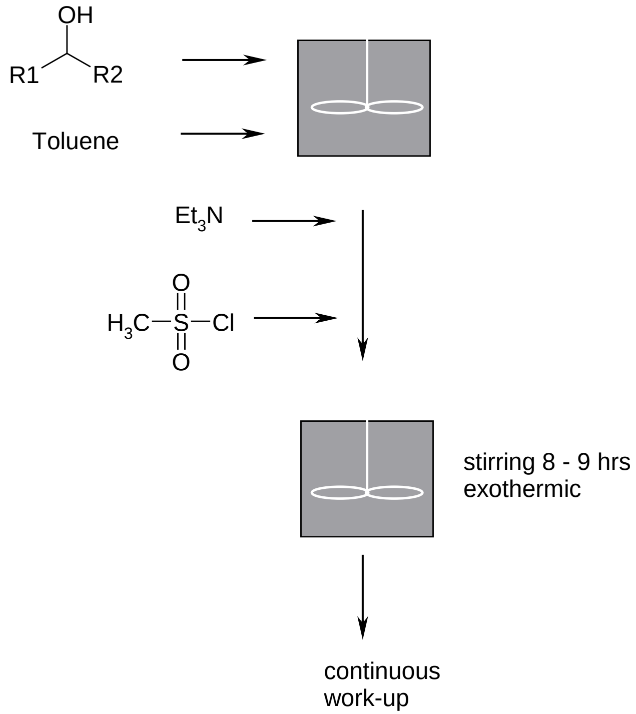
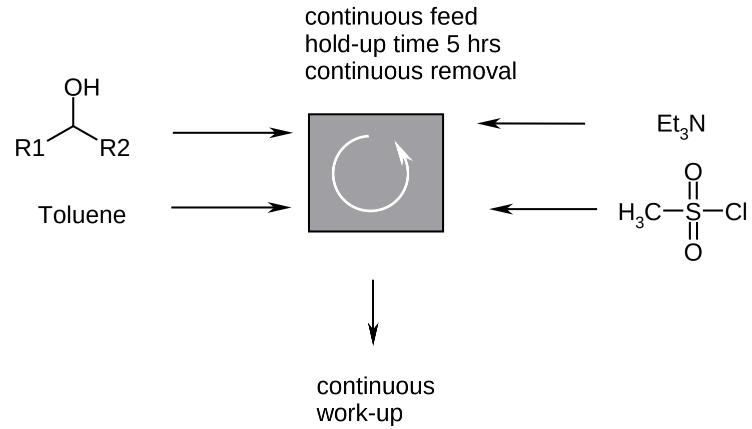
Mesylation reaction: batch to continuous

Original batch reaction



CABB continuous reaction



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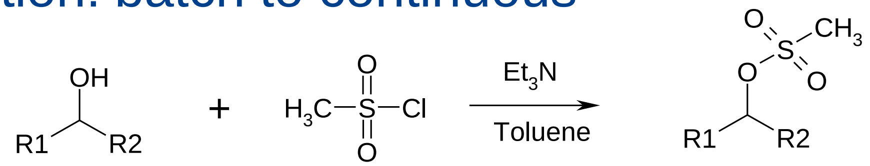
Mesylation reaction: batch to continuous



	batch	continuous
Output	**83%**	**100%**
Electricity	**116%**	**100%**
Steam	**106%**	**100%**
Cooling water	**145%**	**100%**
PMI	**10.8**	**7.4**
E-factor	**8.1**	**5.4**

Results:

- Less energy through constant reactor temperature
- Less waste and cooling water
- 20% increase of output per day
- Reduction of amount of toluene
- Batch process: E-factor is 50% higher; PMI is 46% higher than continuous

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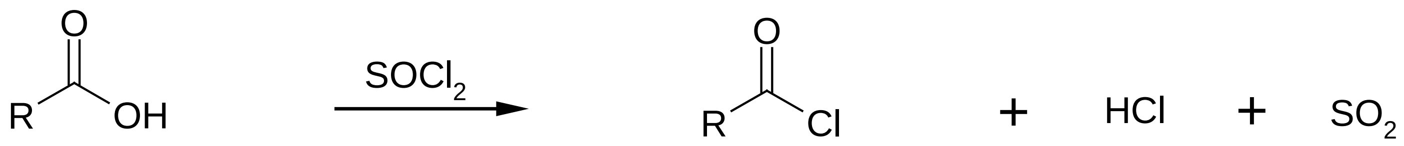
Case study: Chlorination reaction



- Acid chloride formation
- Reaction of a carboxylic acid with thionyl chloride, frequently applied reaction
- Thionyl chloride is an inexpensive, transportable, easy-to-handle and commonly used chlorination reagent
- HCl and SO_2 are generated as off-gases
- Comparison: scrubber vs CABB‘s Verbund and recycling system

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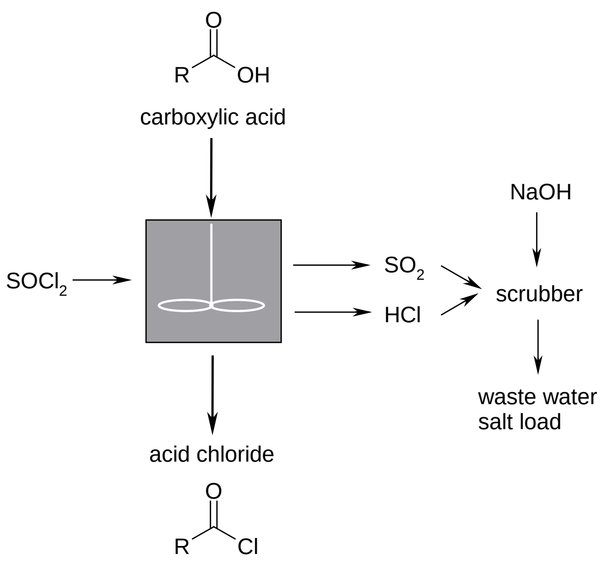
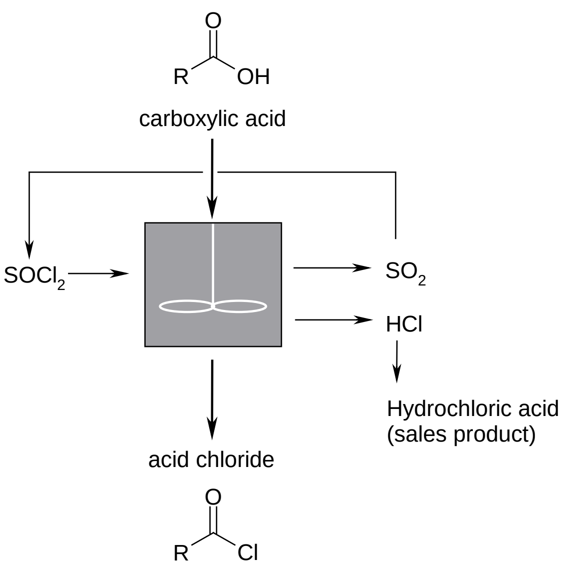
Chlorination reaction: scrubber vs recycling system

Conventional chlorination with scrubber



Chlorination at CABB's Verbund system



- SO_2 and HCl are generated as off-gases
- For better comparison both reactions are carried out as batch process
- Removal of off-gases:
  - conventional scrubber (neutralisation with caustic soda → waste water)
  - CABB‘s recycling system (SO_2 is recycled into SO_3, HCl is converted into hydrochloric acid)

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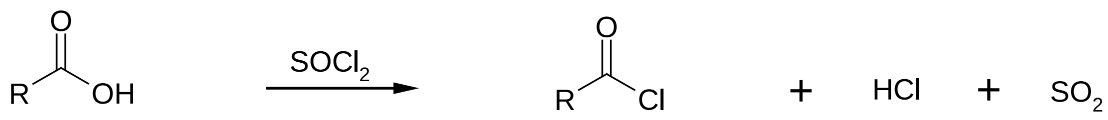
Chlorination reaction: scrubber vs recycling system



	scrubber	Verbund
Electricity	**142 %**	**100%**
Steam	**111 %**	**100%**
Caustic soda	**3.7 kg per kg product**	**0 kg**
Waste water	**4.7 kg per kg product**	**0 kg**
PMI	**6.3**	**2.1**
E-factor	**4.7**	**0.04**

Scrubber:

- Large volumes of caustic soda required for scrubber process
- Scrubber generates large amounts of waste water containing salts

Verbund and recycling system:

- Requires less energy
- Reagent is completely used or recycled
- HCl is converted into hydrochloric acid; SO_2 is completely recycled into SO_3

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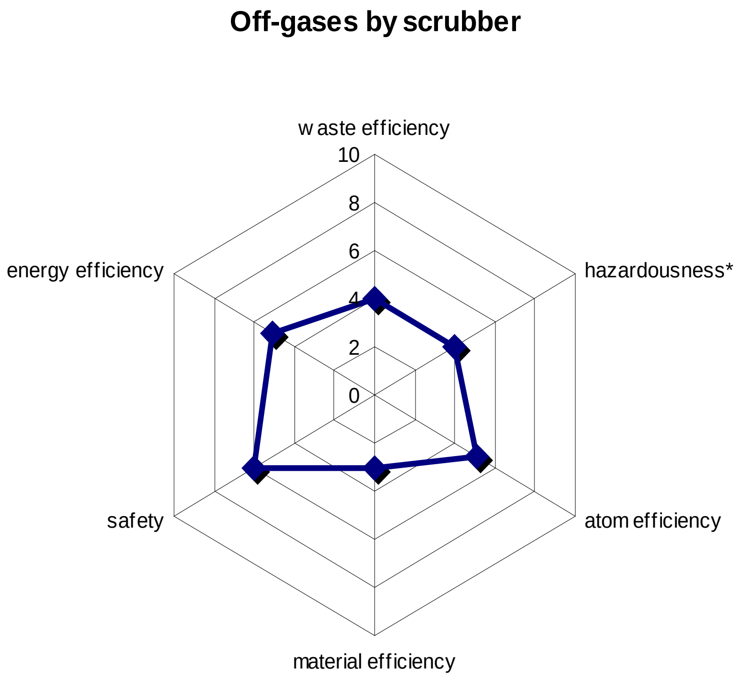
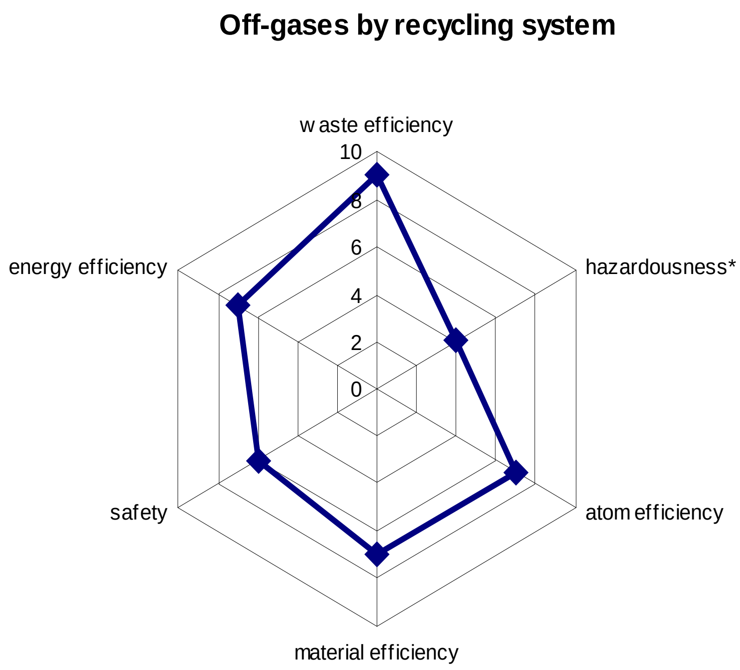
Chlorination reaction: scrubber vs recycling system





*hazardousness: not hazardous = 10

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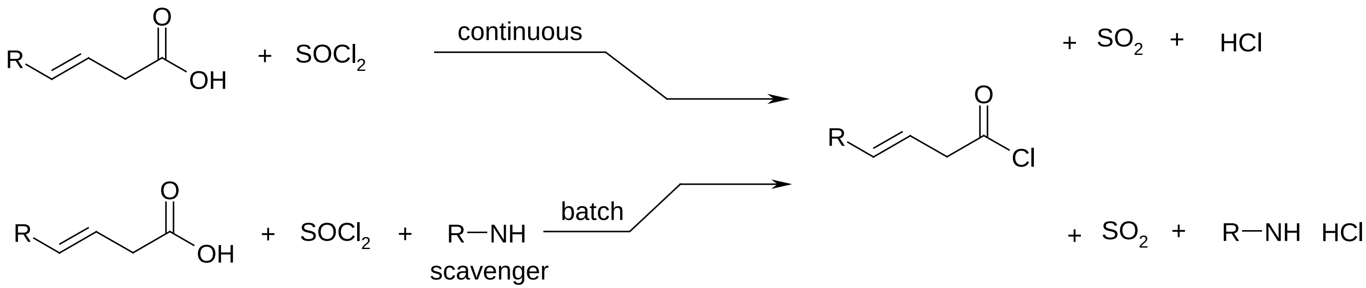
Continuous chlorination: quality and side-products



Acid sensitive substrates need scavenger in batch processes

- Less good PMI and E-factor

Continuous processes can be carried out without scavengers:

- Better sustainability
- Better quality of the product
- Constant reaction conditions lead to higher quality
- Less energy requirement

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Case study: Amide formation

Investigation of 128 drug candidates regarding amide formation[1]

65% of steps include an amide formation

- 44% are based on acid chloride formation, generated by thionyl chloride reaction and removal of HCl and SO_2 by scrubber
- 36% are based on coupling reagents like N-ethyl N-(3-dimethylaminopropyl)carbodiimide (IRRITANT!) catalysed by HOBt, 1-propylphosphonic acid cyclic anhydride or N,N'-carbonyldiimidazole
- 20% others

[1] Green Chem. 2007, 9, 411-420

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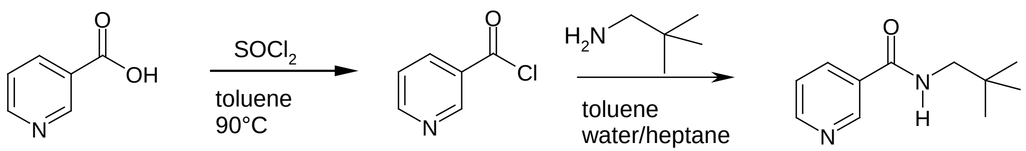
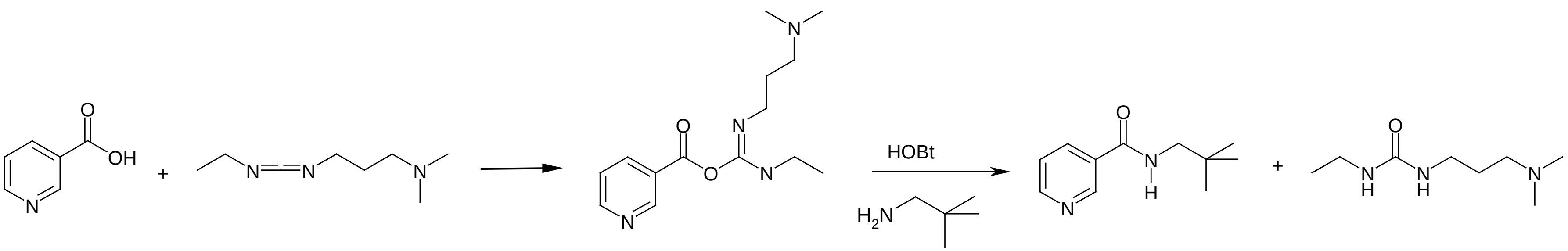
Amide formation: hazardous vs less hazardous





- Hazard: acid chloride formation and subsequent amidation
- Non-hazard: Reaction of carboxylic acid with EDC, then HOBt and subsequently amidation
- Hazard: more straightforward, less waste but hazard
- Non-hazard: derivatisation, large molecules, more waste, no hazards

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Amide formation: hazardous vs less hazardous

	Less hazardous	Hazardous
Electricity	75%	100%
Steam	71%	100%
Atom efficiency	45%	53%
PMI	12.2	4.3
E-factor	11.3	2.2

Less hazardous:

- Less atom efficient process
- Less material efficient and more waste generating
- More energy efficient

Hazardous:

- Higher atom efficiency
- More material efficient process, 5 times less waste
- Higher energy demand

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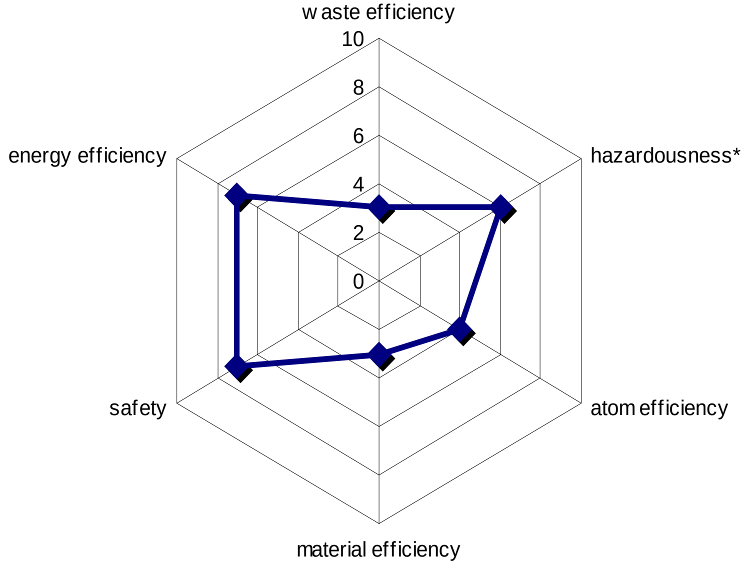
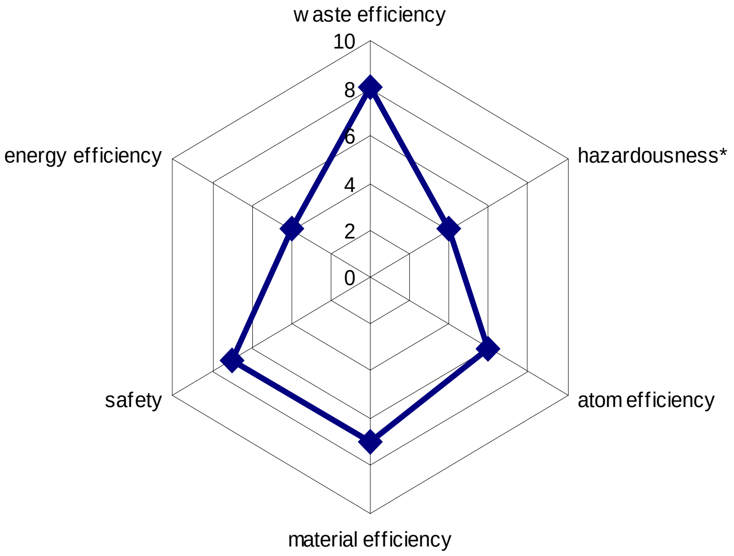
Amide formation: hazardous vs less hazardous

Amide formation with EDC



Amide formation with TC



*hazardousness: not hazardous = 10

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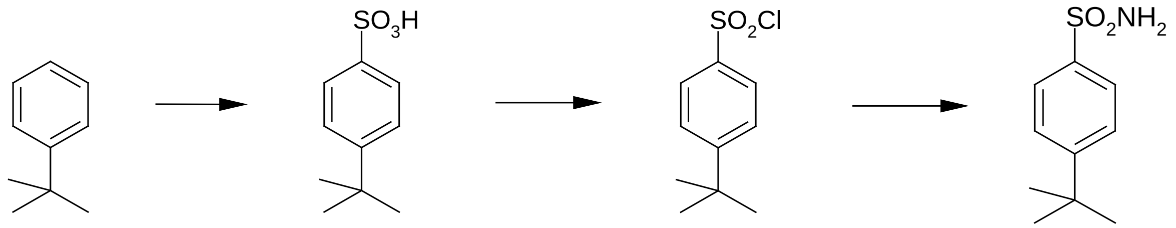
Case study: Sulfonamide reaction



Sulfonation and amidation:

- Widely used reaction in pharma and agro applications
- Important class of chemical products
- Use of hazards not to avoid

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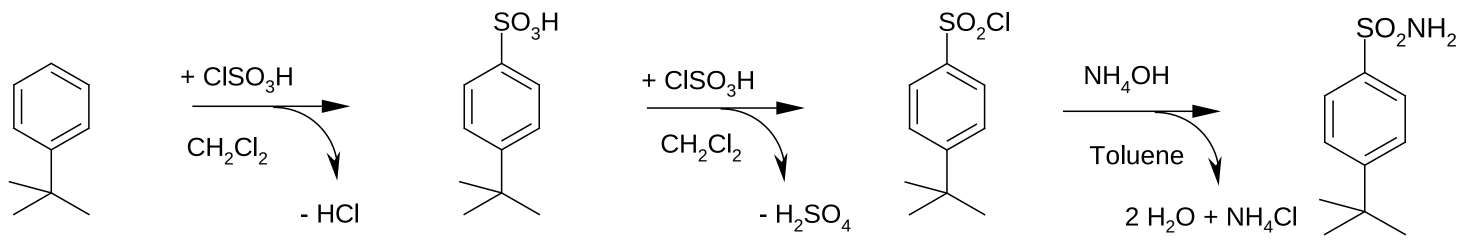
Sulfonamide reaction: conventional



Original process:

- Reaction of aromatic compound with chlorosulfonic acid in dichloromethane at -5°C
- Subsequent reaction of intermediately formed sulfonic acid with CSA to yield sulfonyl chloride
- Reaction of sulfonyl chloride with acqueous ammonia solution to yield sulfonamide

- HCl and H_2SO_4 are removed as acqueous waste
- Dichloromethane and toluene are completely recycled

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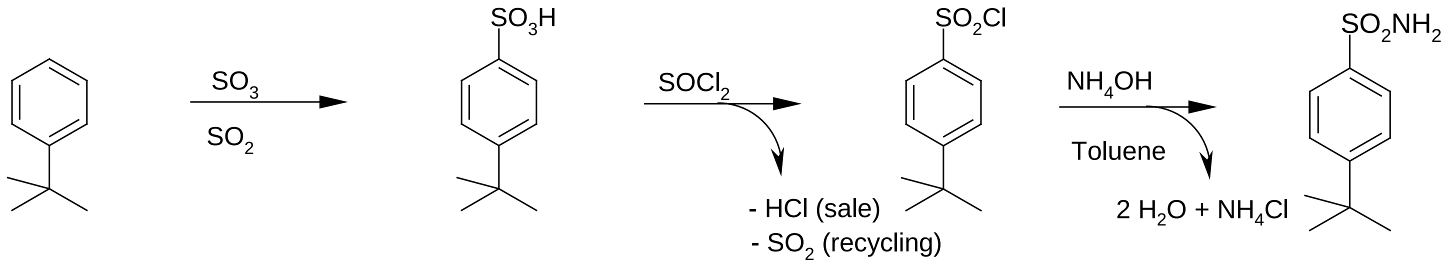
Sulfonamide reaction: improved



CABB‘s improved process

- Reaction of aromatic compound with SO_3 in liquid SO_2 at -20°C
- Reaction of sulfonic acid with thionyl chloride
- Reaction mixture is heated to 25°C which leads to evaporation of SO_2
- Reaction of sulfonyl chloride with acqueous ammonia solution in toluene
- SO_2 evaporates and is completely recycled
- HCl is converted into hydrochloric acid sales product
- One pot synthesis

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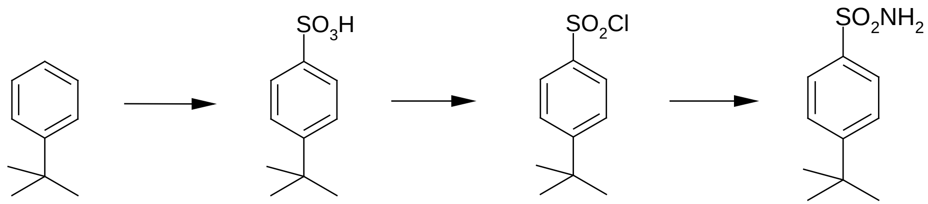
Sulfonation and amidation



	$CH_3Cl/CSA/CSA$	$SO_2/SO_3/SOCl_2$
Electricity	**118%**	**100%**
Steam	**118%**	**100%**
Waste water	**13 kg per kg product**	**5.9 kg per kg product**
PMI	**20.2**	**10.4**
E-factor	**19.0**	**6.7**
Atom efficiency	**44%**	**51%**

Results:

- No chlorinated nor other solvent necessary
- Sulfur dioxide comes out of the pipeline and is evaporated into the Verbund system
- Different sulfonation technology: advantage of direct sulfonation with liquid sulfur trioxide
- Most efficient use of reagents (no loss of one molecule CSA as sulfuric and hydrochloric acid)

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Conclusion

- There is an additional parameter in chemical manufacturing: sustainability
- Continuous processes support sustainability
- Safe processes support sustainability
- Waste prevention/reduction supports sustainability

Dr. Jörg Schrickel

Manager New Business Development

joerg.schrickel@cabb-chemicals.com

www.cabb-chemicals.com