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Lonza

Process for the preparation of γ -butyrolactones

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Outline

- Introduction
 - Lonza LSIR
 - Goal – ABL
 - Current processes for ABL
 - Idea
- Results
 - Synthesis
 - Down stream process
 - Alternative concepts
- Summary, conclusions, outlook



LONZA

Introduction



Lonza Overview

- Life sciences driven company
- Headquartered in Basel (Switzerland)
- Sales of CHF 2.87 billion in 2007

- Global operations:
 - 26 production and R&D facilities
 - Employs over 7,700 people

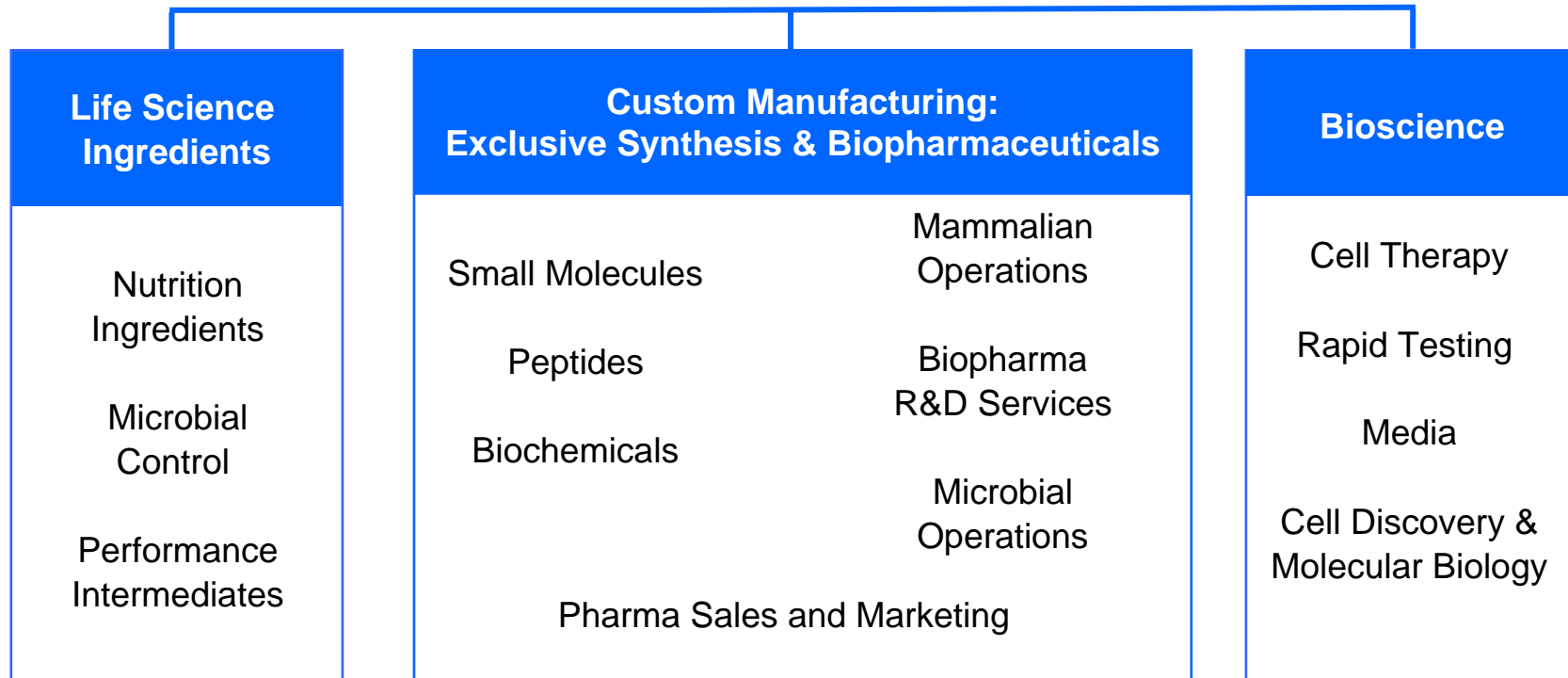
- Global leader in custom manufacturing:
 - Active pharmaceutical ingredients both chemical and biological
 - Cell Therapy

- Leading positions in product market niches:
 - Endotoxin detection
 - Cell-based research products
 - Nutrition Ingredients
 - Microbial Control products
 - Performance Intermediates



Lonza's Life-Science Platform

Lonza

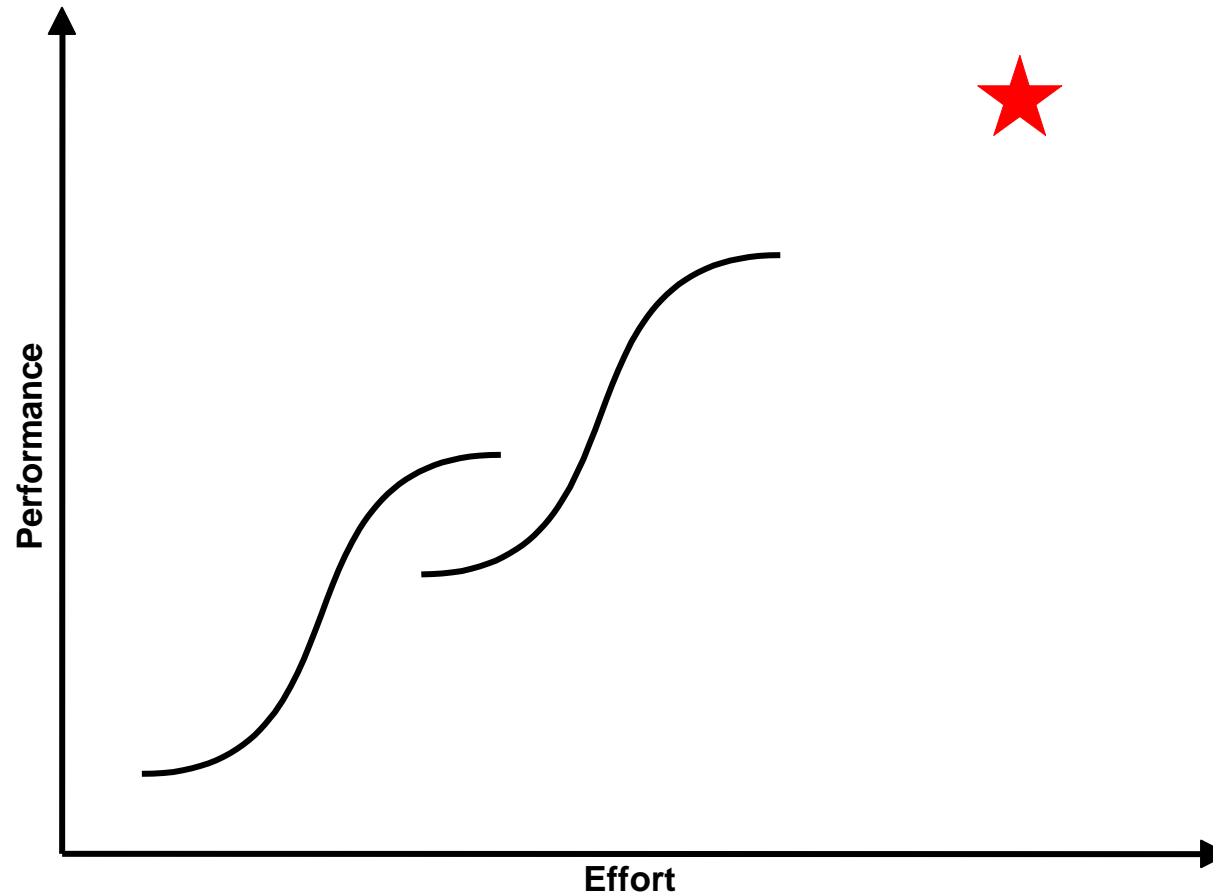


LSIR

- **Lonza Life Science Ingredients Research & Development**
- Process development for
 - Catalogue and exclusive products (ISO)
 - Dedicated and multi-purpose plants (batch and conti)
- Design of new plants

- Unit operations approach
- Multi-disciplinary teams (Chemistry, Engineering, Analytics, Production, SHE)
- Process fit into existing plants
- Direct scale-up from Lab (1 – 10 L) to plant (2 – 10 m³)

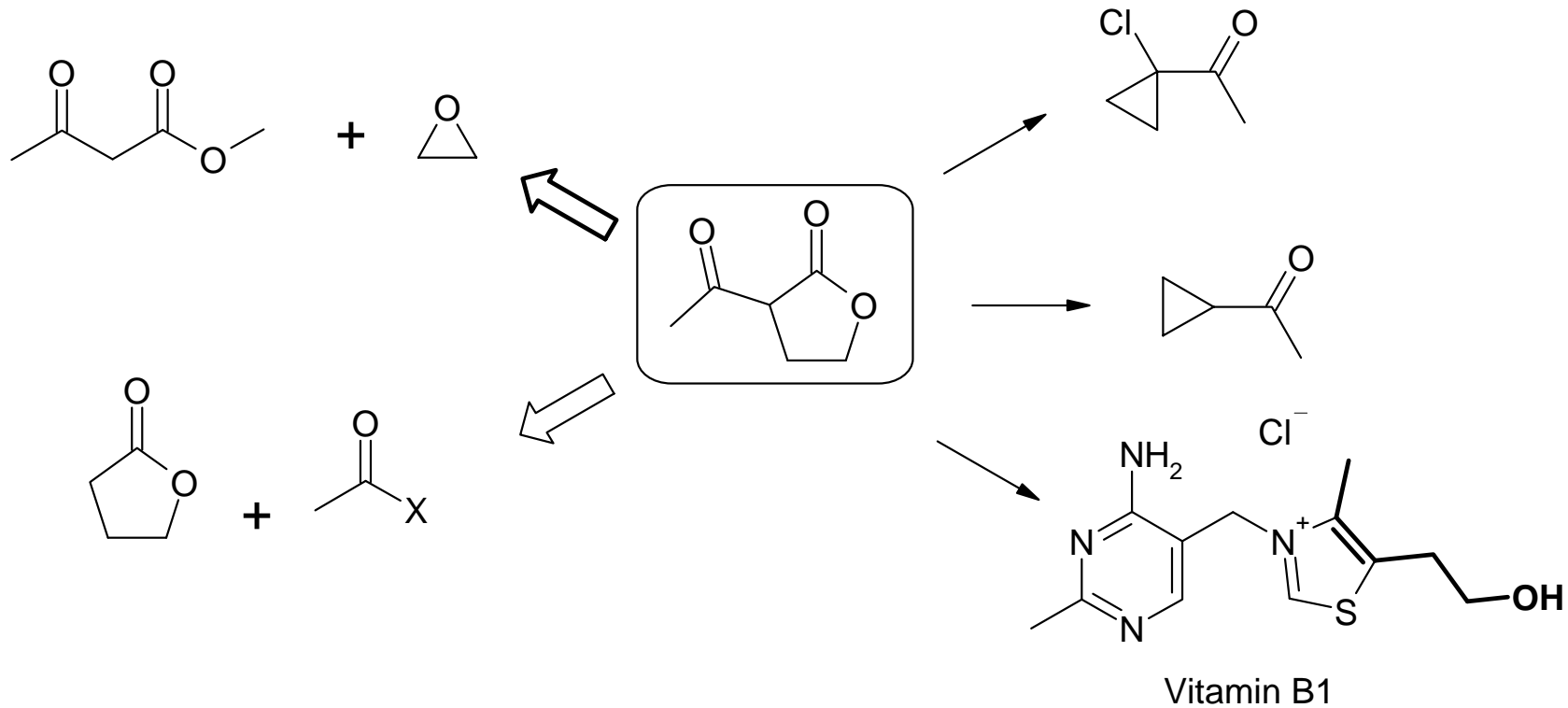
Innovation



- incremental improvements → step change
- ★ ideal process – what would it be like?

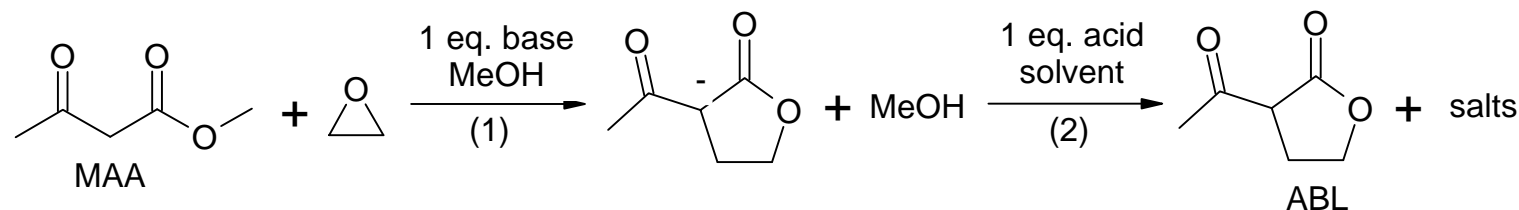


Goal – γ -Acetylbutyrolactone (ABL)



- ABL is a liquid intermediate for agro products and vitamin B1
- Goal: a process for ABL from diketene-derived methyl acetoacetate (MAA)

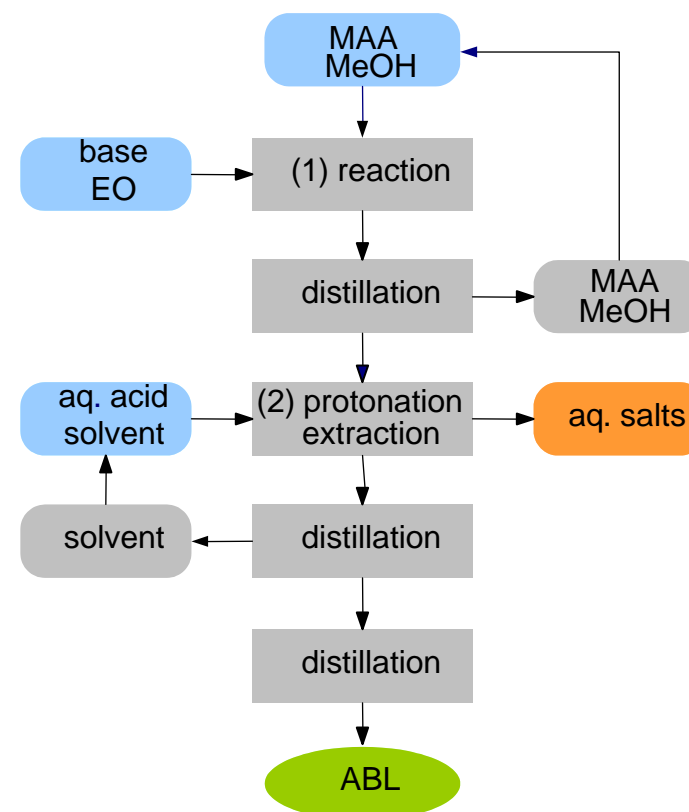
Current processes for ABL from MAA



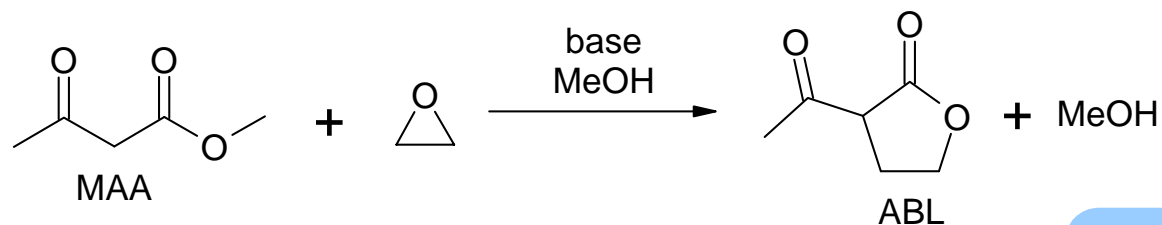
- (1) 33% NaOMe¹ or 10% NaOH²
- (2) AcOH¹ or aq. H₂SO₄², toluene

- 75 - 78% yield (75% conv., 81% sel.)
- Lots of salts and waste water
- Low throughput
- High cost
- alternative w/u concepts³
 - H₂O/scCO₂
 - Electrodialysis

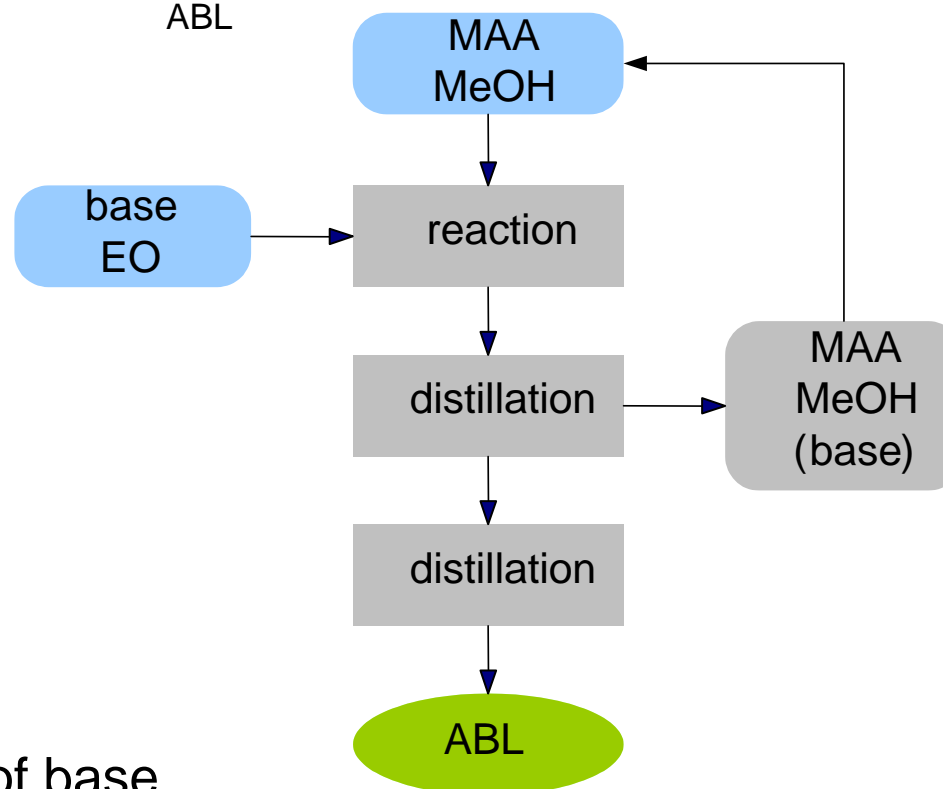
1) Lonza process. 2) Daicel process. 3) Degussa.



Desired process – idea



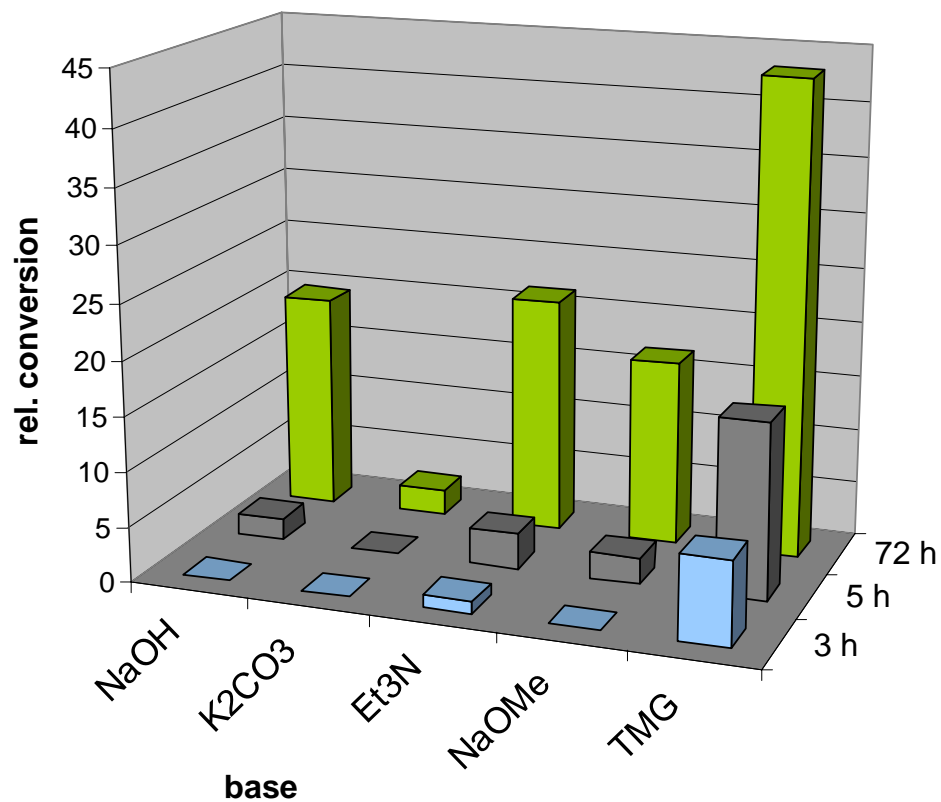
- Catalytic or recycled base
- Remove base by distillation
- No aq. work-up
- No acidification
- Less waste water/salts
- Fewer unit operations
- Lower costs
- Try it with catalytic amounts of base



Results – Synthesis



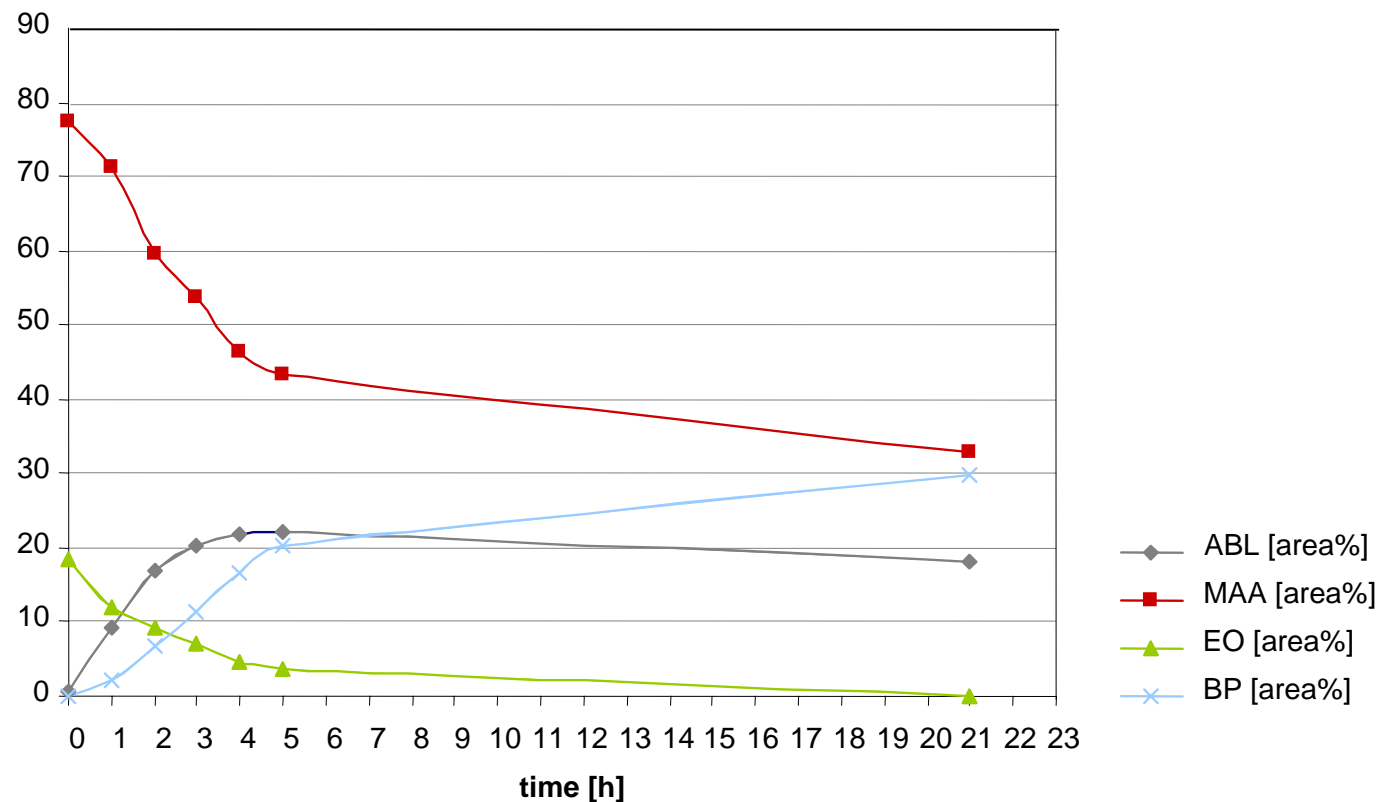
Screening with 0.2 eq. of base at 25°C¹



➤ **ABL can be made with a cat. amount of base!**

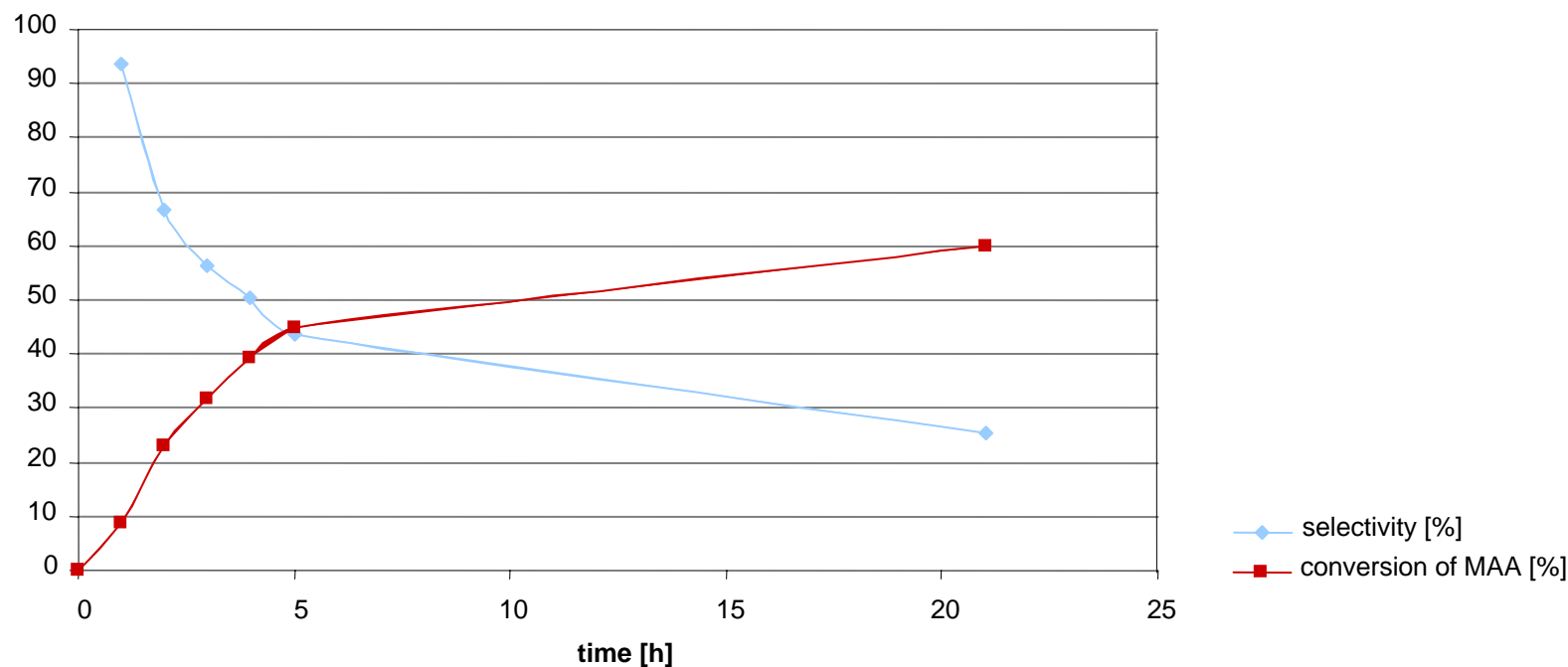
- 1) Conditions: 1 eq. of EO, 11 eq. of MeOH
 rel. conv. = $\frac{ABL(a\%)}{ABL(a\%) + MAA(a\%)}$

Kinetics with 0.2 eq. of Et₃N at 60°C (I)¹



1) Conditions: 1 eq. of EO, 11 eq. of MeOH, 5 – 60°C

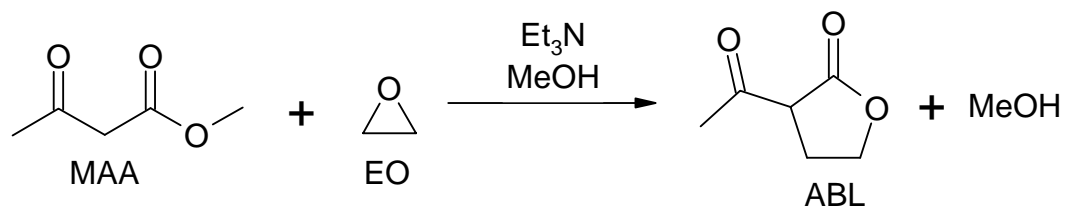
Kinetics with 0.2 eq. of Et₃N at 60°C (II)



- Incomplete conversion of MAA (kink)
- Rapidly decreasing selectivity
- Is it really catalytic in base?



Further studies with Et₃N¹

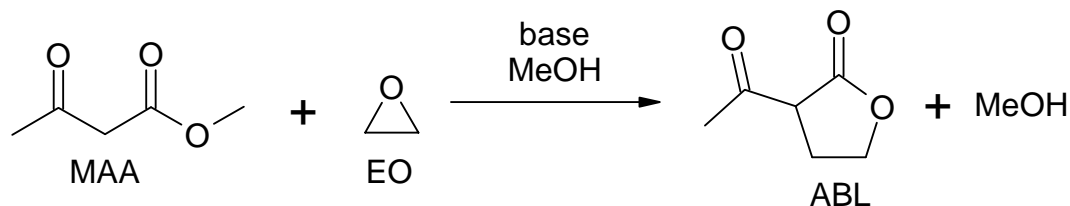


	EO	Et ₃ N	time	MAA conv.	ABL sel.
	[eq]	[eq.]	[h]	[%]	[%]
1	1.0	0.2	2	22.8	66.7
2	1.0	1.0	3	34.7	64.8
3	1.4	1.0	2	50.8	72.9
4	2.0	1.0	5	67.7	75.0

- 1 eq. of Et₃N required
- > 1 eq. of EO required

1) Conditions: 11.2 eq. of MeOH, 5 – 60°C

Further studies with trialkyl amine bases¹



	EO	Base		time	MAA conv.	ABL sel.
	[eq]		[eq.]	[h]	[%]	[%]
5	1.0	Me ₃ N	1.0	2	7.0	87.5
6	2.0	Me ₃ N	1.0	2	48.7	79.7
7	1.0	Dec ₂ MeN	1.0	1	21.9	67.9
8	2.0	Dec ₂ MeN	1.0	2	62.9	71.7

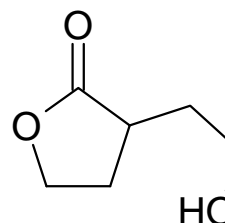
- 1 eq. of base required
- 2 eq. of EO required

1) Conditions: 11.2 eq. of MeOH, 5 – 60°C

Further studies with strong amine bases¹

	EO	Base		time	MAA conv.	ABL sel.
	[eq]		[eq.]	[h]	[%]	[%]
9	1.0	TMG	0.2	5	36.8	48.8
10	1.0	TMG	1.0	1	44.7	76.8
11	2.1	TMG	0.2	25	98.0	NA
12	1.0	DBU	1.0	3	59.3	82.2

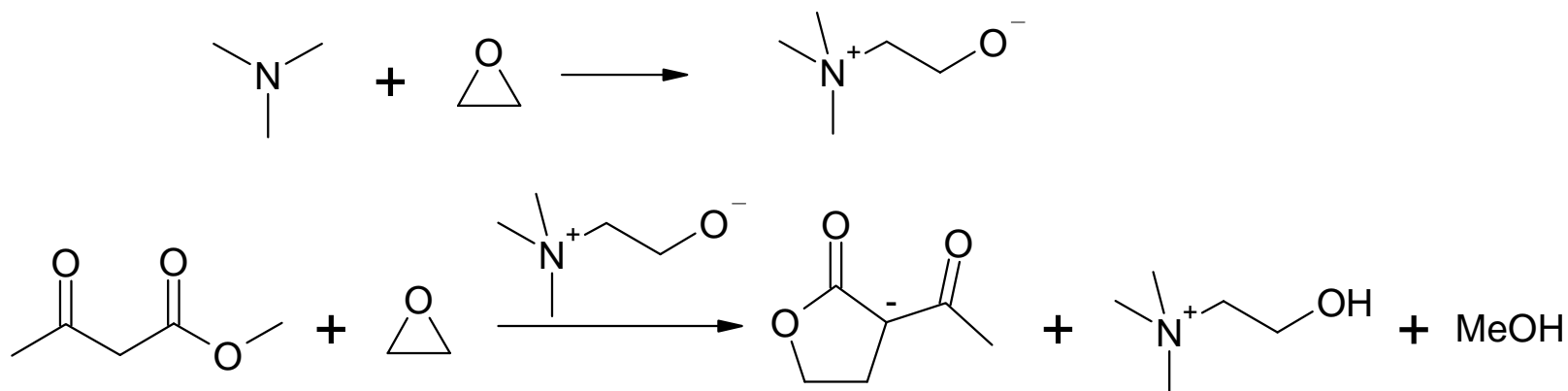
- 1 eq. of base required
- 1 eq. of EO sufficient!
- Entry 11: different product, hydroxyethyl-GBL (> 65% sel.)



1) Conditions: 11.2 eq. of MeOH, 5 – 60°C

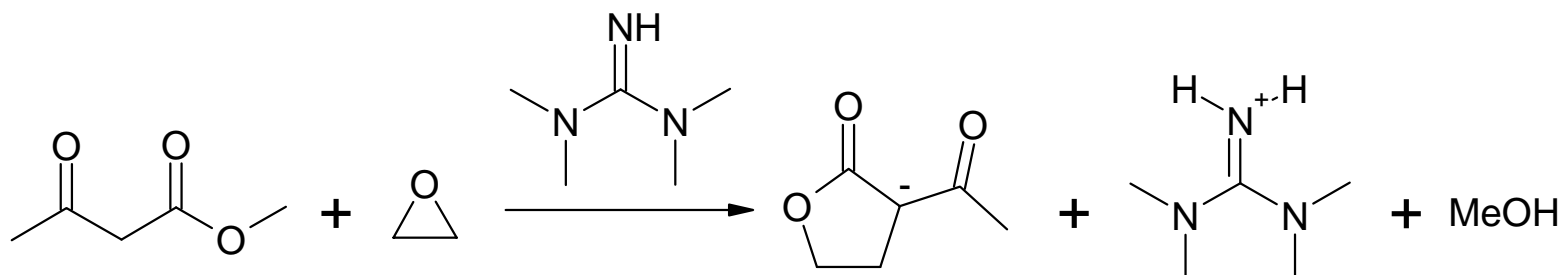
Reaction mechanism – Me₃N

- ¹H-NMR reveals the formation of choline
- This is the active base in the system
 - ABL is formed as a salt
 - 1 eq. of amine is required
 - 1 eq. of EO is consumed by the amine

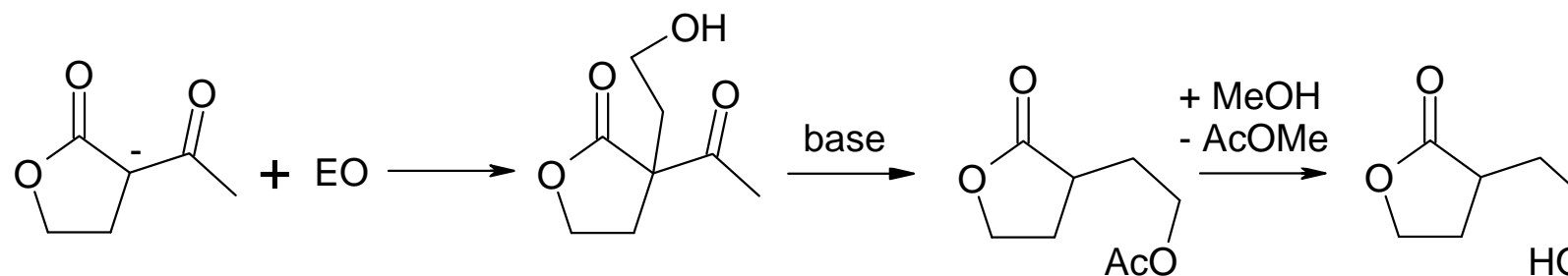


Reaction mechanism – TMG, DBU

- The amine itself is the base
- ABL is formed as a salt
 - 1 eq. of base is required



- By-product formation by reaction of ABL⁻ with EO

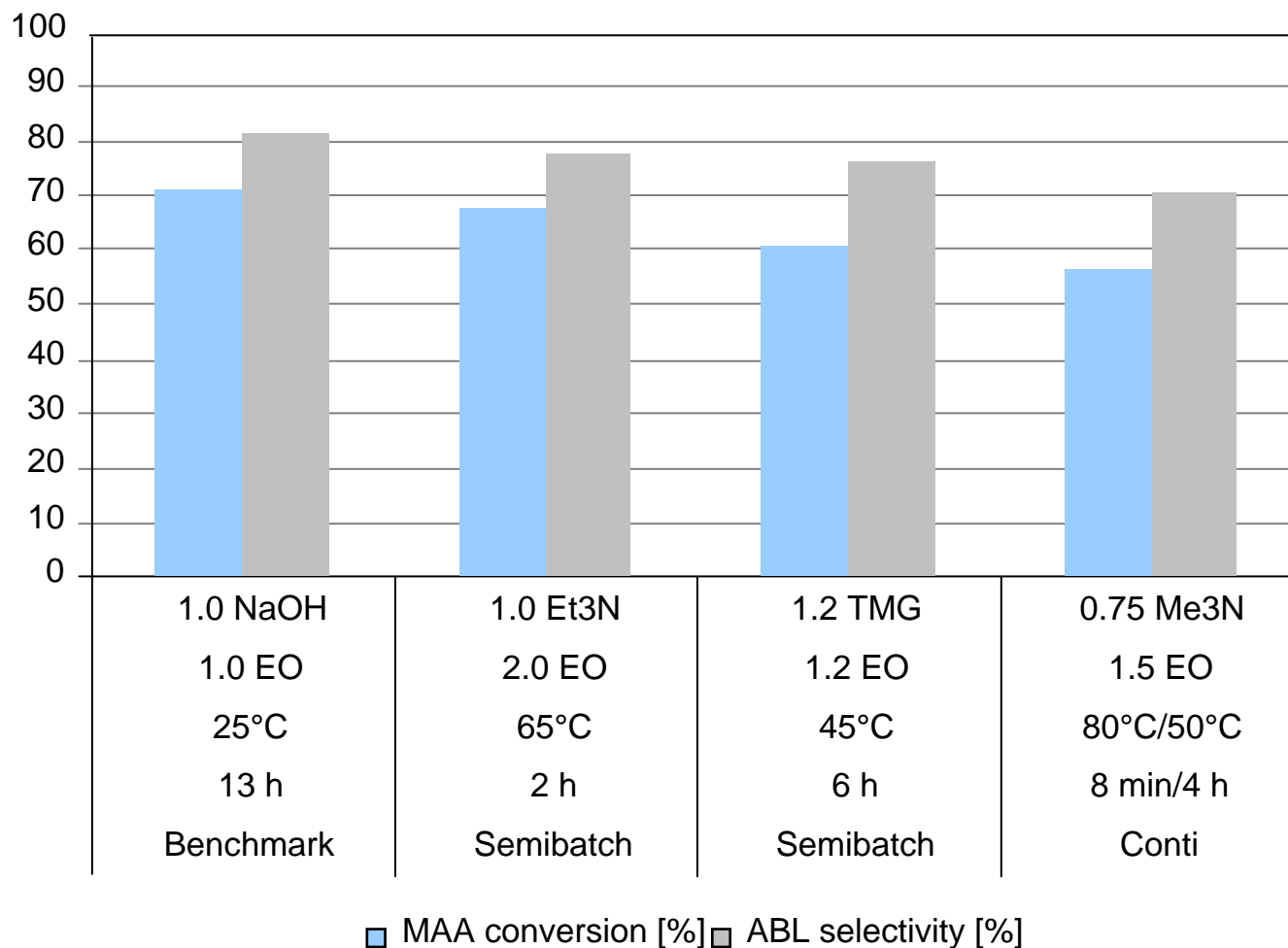


Optimisation

- Various process modes were examined
 - Batch
 - Semi-batch
 - CSTR
 - Conti (micro reactor)

- Optimisation by statistical DOE
 - Et₃N semi batch (RSM CC0530)
 - TMG semi batch (screening FF0408 with cp)
 - Me₃N two-stage conti (screening)

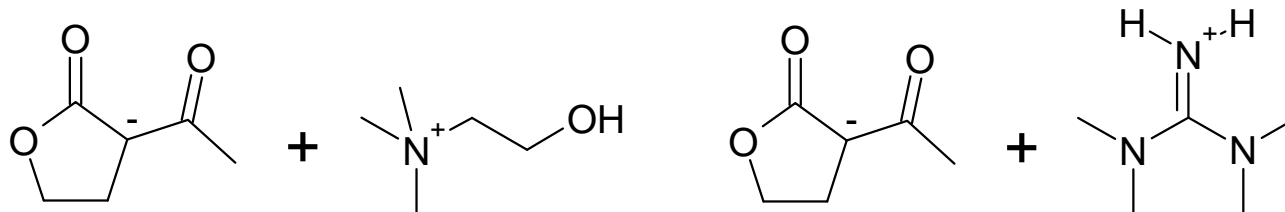
Optimisation – best results



Results – Down Stream Process

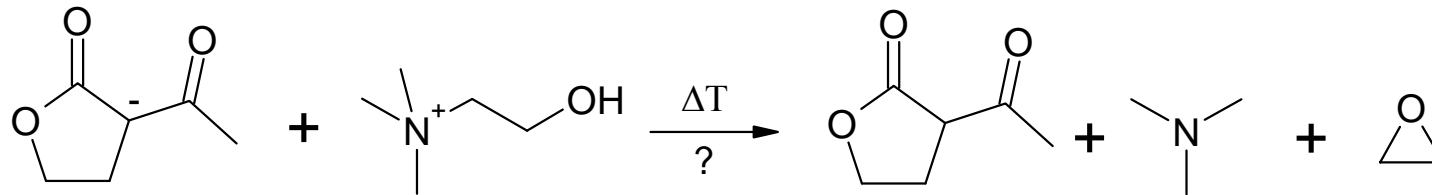
Goal, challenge

- The reaction mixture contains ABL, unreacted MAA, base, and MeOH
- Goal: isolate ABL, MAA, and base
- ABL and MAA are thermally not very stable
- ABL is formed as a choline or TMG salt



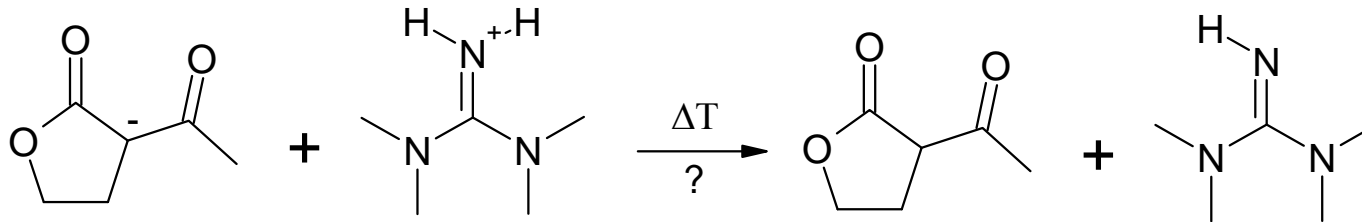
- Can we still isolate it by distillation?
- Comment: choline can be broken down thermally to Me₃N, EO, glycols (applied in another process)

Me₃N process



- Concentration of the reaction mixture (- MeOH) worked well
- Further batch or thin film distillation lead to
 - cleavage of choline, but Me₃N and EO could not be isolated
 - decomposition of ABL and of MAA
- Distillation of ABL from the Me₃N reaction mixture is not feasible

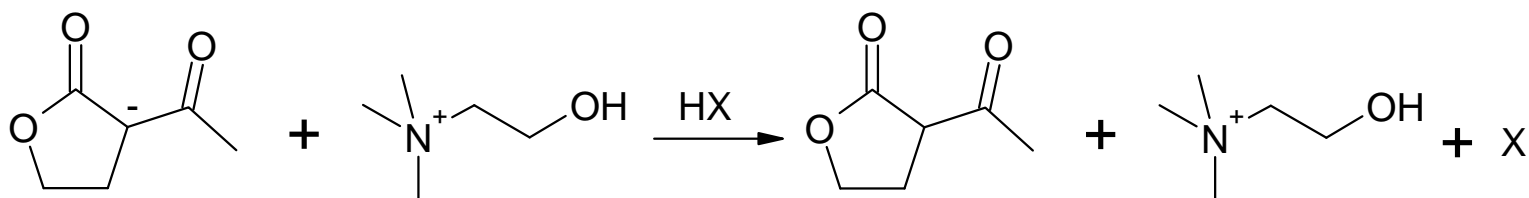
TMG process



- Concentration of the reaction mixture (- MeOH) worked well
- Further thin film distillation lead to
 - decomposition of TMG
 - decomposition of ABL and of MAA
- Distillation of ABL from the TMG reaction mixture is not feasible

Extraction of ABL (Me₃N process)

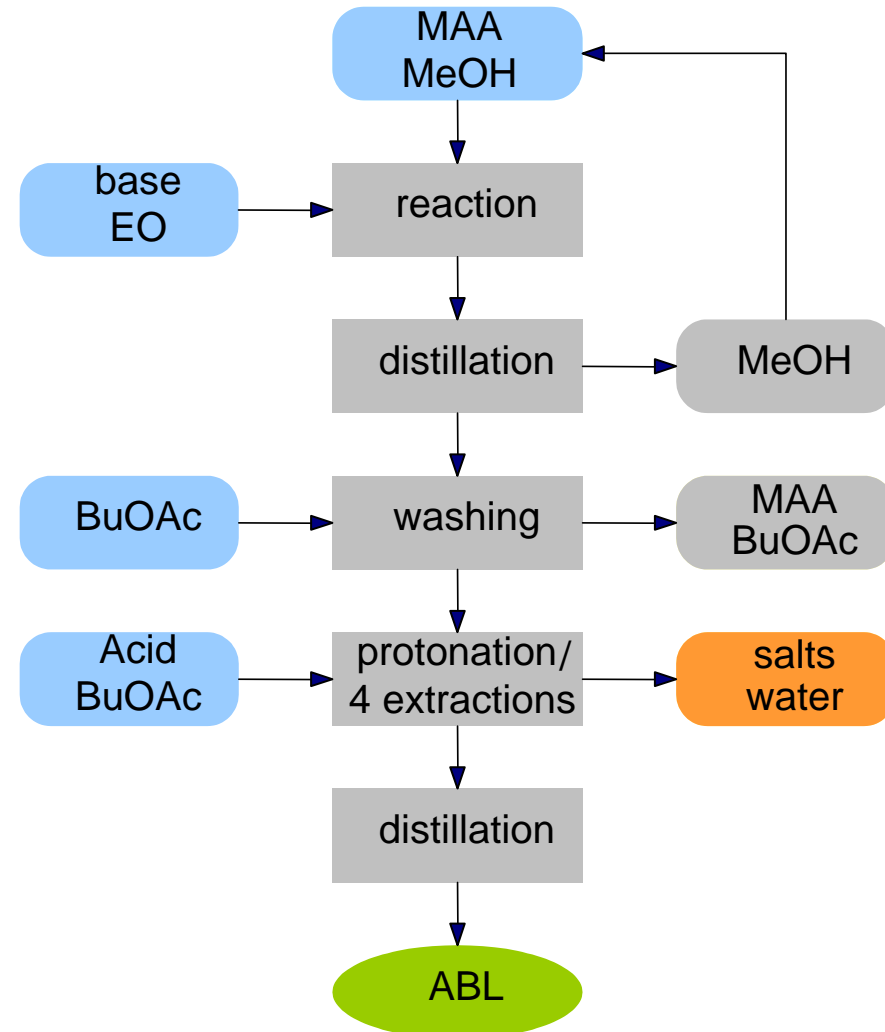
- MeOH removed by distillation
- Solvent screen for extraction of the residue
 - Extraction of ABL and MAA is possible only after acidification



- BuOAc is the best extraction solvent for ABL
(distribution coefficient BuOAc/H₂O = 1.9)
- A process for the isolation of ABL relying on extraction was developed

Extraction process

- Pure ABL isolated
- 60% yield of the workup
- Too many UO
- Too complex
- Too much waste
- Too expensive



Alternative synthetic processes

- Phase transfer catalysis
 - only traces of ABL
- ABL directly from diketene
 - only traces of ABL
- Solid bases¹

	Base		time	T	MAA conv.	ABL sel.
		[eq.]	[h]	[°C]	[%]	[%]
13	K ₂ CO ₃	1.0	3.5	40	48.6	72.2
14	K ₂ CO ₃	0.1	7	40	18.9	45.9
15	BaO	0.3	5.5	25 - 60	37.6	68.5

- Isolation of ABL cumbersome

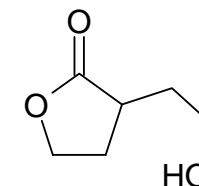
1) Conditions: 1.0 eq. of EO, 11.2 eq. of MeOH

Summary, Conclusions, Outlook



Summary, Conclusions

- We developed a novel process for ABL from MAA using organic amine bases
- The conversion and selectivity are comparable to the benchmark
- The DSP and isolation of ABL are still challenging
- An organocatalytic process for hydroxyethyl-GBL was discovered
- It proved very beneficial to examine the
 - kinetics, ▶
 - reaction mechanism,
 - and thermodynamics of the process
- It was fruitful to think of something new rather than to start with current processes ▶



Outlook

- In another process development project we wanted to
 - avoid the use of an organic solvent
 - reduce the excess of a reagent
 - increase the yield
 - increase the throughput
 - reduce the no. of unit operations

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- In another process development project we wanted to
 - ✓ avoid the use of an organic solvent
 - ✓ reduce the excess of a reagent
 - ✓ increase the yield
 - ✓ increase the throughput
 - ✓ reduce the no. of unit operations

- Kinetic and mechanistic studies led to a better understanding of the chemistry and allowed us to implement all of these improvements!

Acknowledgements

- Dr. Andreas Heyl Project Manager
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- Peter Tschudin Lab technician
- Rinaldo Escher Lab technician

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End