Model Reactions for Library Synthesis Using X-Cube Flash

ThalesNano Flow Chemistry Seminar and User Group Meeting

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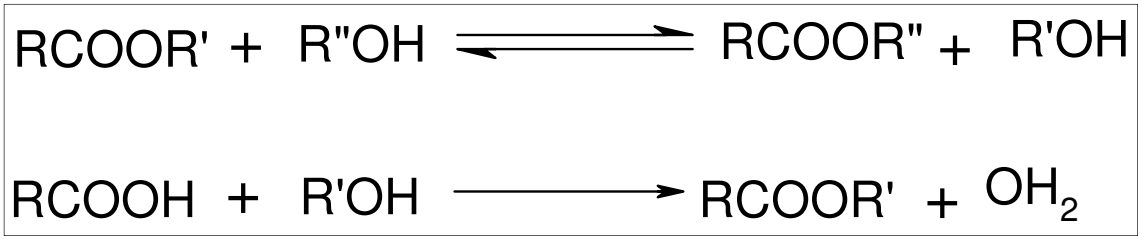
Hit Recognition Using X-Cube Flash?

- Need for novel technologies to enable fast track and cost effective hit identification
- Limitations of HTS and VS
- Importance of fragment-based lead discovery
- Library design
  - One bead - one compound or…
  - Diversity orientated synthesis → **Make dynamic combinatorial libraries with X-Cube Flash**
    - Fast
    - Cheap: low quantity from the starting materials
    - Green
  - Coupled with screening and reequilibrating

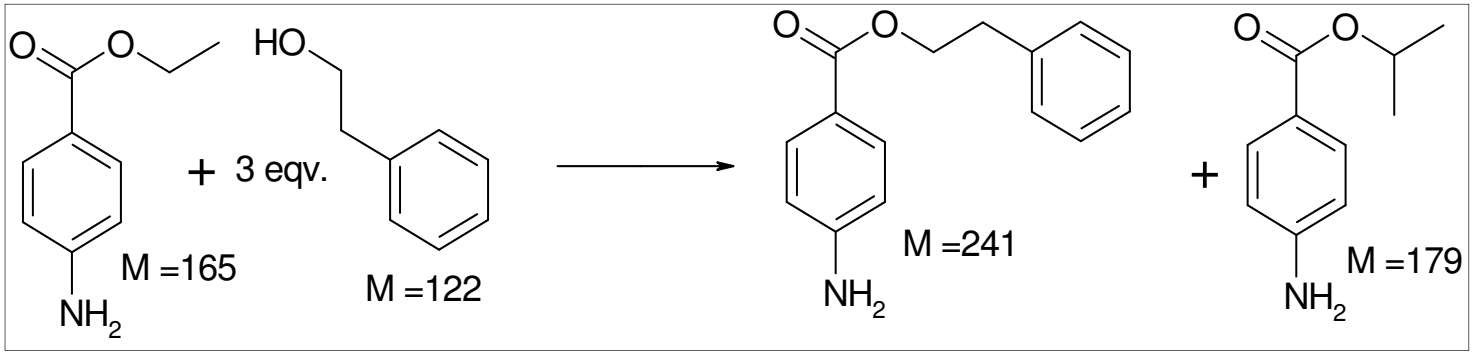
Esterification and Transesterification

- **Many possibility for the activation (transesterification)[1]**
  - **Acid catalyst**
    - H_2SO_4, H_3PO_4, HCl etc.
  - **Base catalyst**
    - KO^tBu, NH_3, DBU etc.
  - **Lewis-acid and metal-alkoxide catalyst**
  - **Titanium-alkoxide catalysts ($Ti(OiPr)_4$)**



1 Junzo Otera; Chem. Rev. 1993, 93, 1449-1470

Transesterification- XCF or MW



Green backround → Microwave

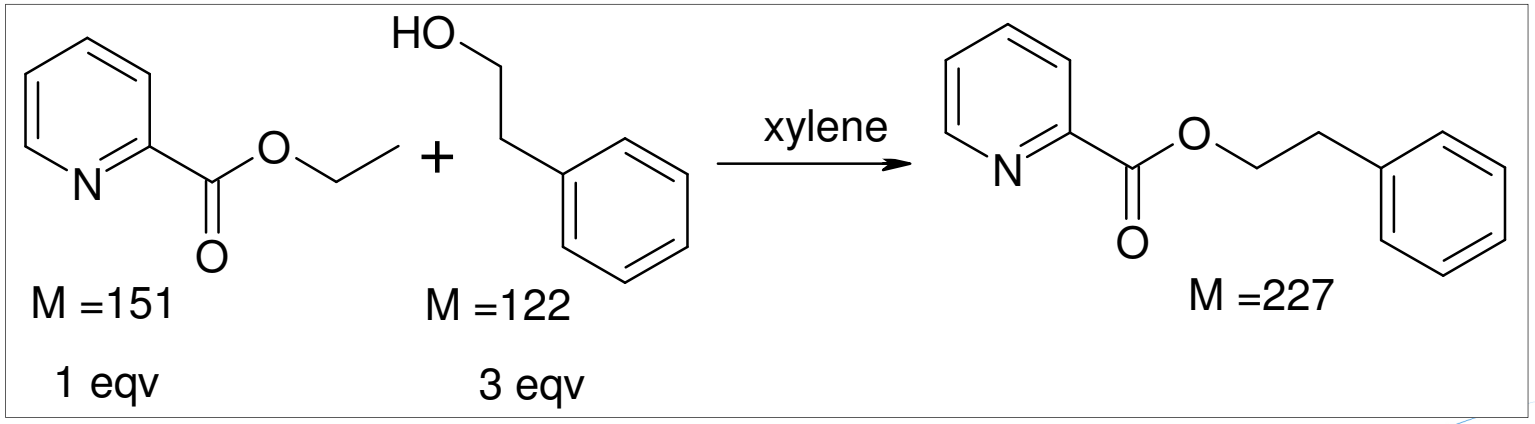
Red backround → X-Cube Flash

XCF / MW	Solvent	Catalyst	*T* / °C	*p* / bar	*t* / min	*Product / %	*iPr-ester / %	*Starting materials / %
SG-79	xylene	-	190		55	0	-	100
SG-80	xylene	30 mol% $Ti(OiPr)_4$	170		35	77	4	19
SG-75	xylene	-	150	80	16	0	-	100
SG-75/2	xylene	-	170	80	16	1	-	99
SG-77	xylene	60 mol% $Ti(OiPr)_4$	170	80	16	38	15	34

*All percentage data is based on LC-MS

Transesterification

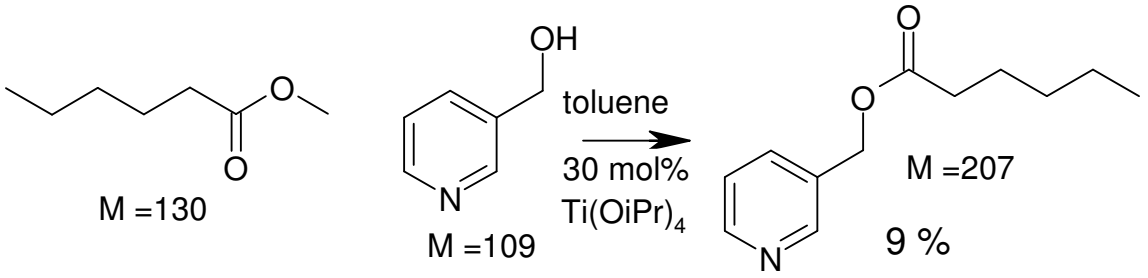
- SG-84
  - XCF 90 bar, 180 C, 20 min
  - 30 % expected compound
- SG-85
  - XCF 90 bar, 180 C, 20 min
  - 20 mol% $Ti(OiPr)_4$ catalyst
  - 45 % expected compound



Transesterification

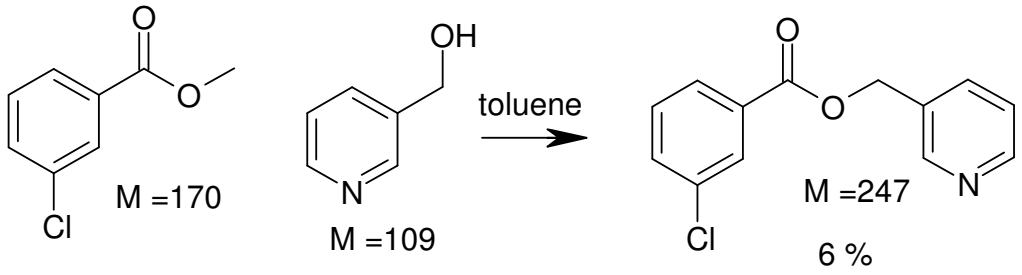
SG-123

- XCF 90 bar, 170 C, 16 min



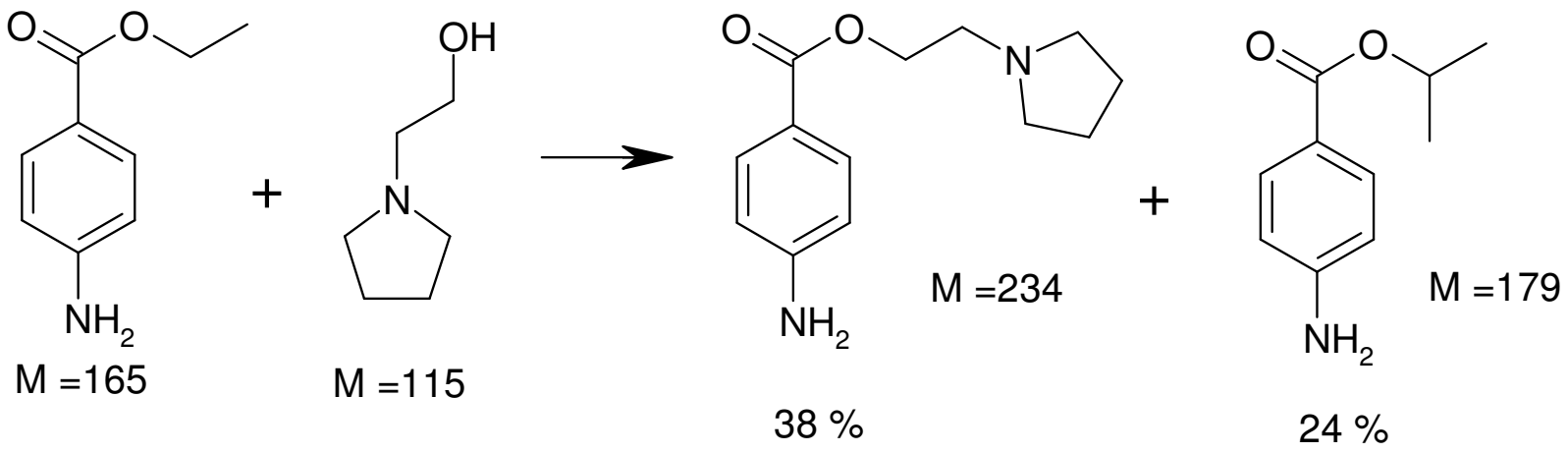
SG-125

- Precipitation affected by $Ti(OiPr)_4$
- 2 drop cc. H_2SO_4
- XCF 90 bar, 170 C, 16 min



Transesterification

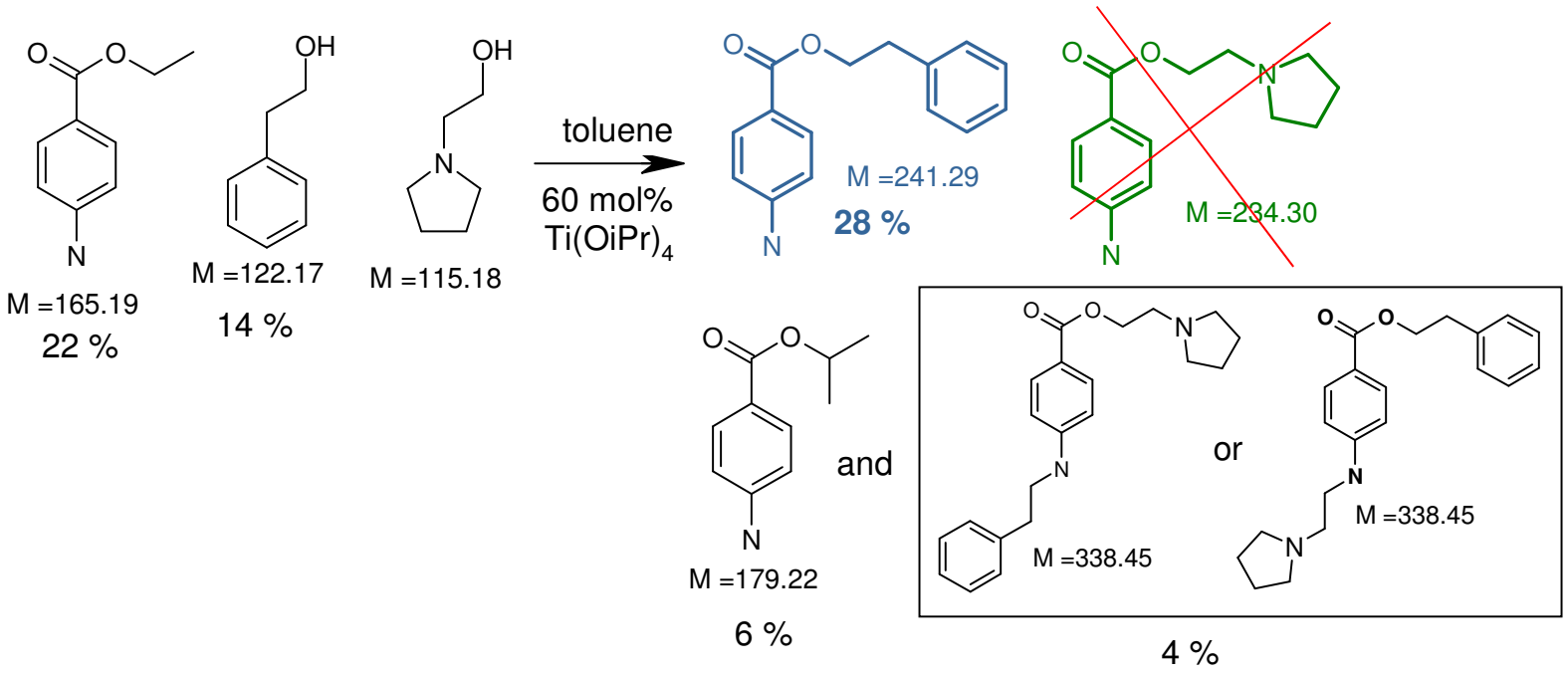
- SG-111
  - XCF 170 C, 150 bar, 16 min
  - 60 mol% $Ti(OiPr)_4$
  - 3 eqv. alcohol



Transesterification - Library Synthesis I.

Library synthesis I. – SG-112

- XCF 170 C, 150 bar, 16 min
- Each alcohol was 3 equivalent

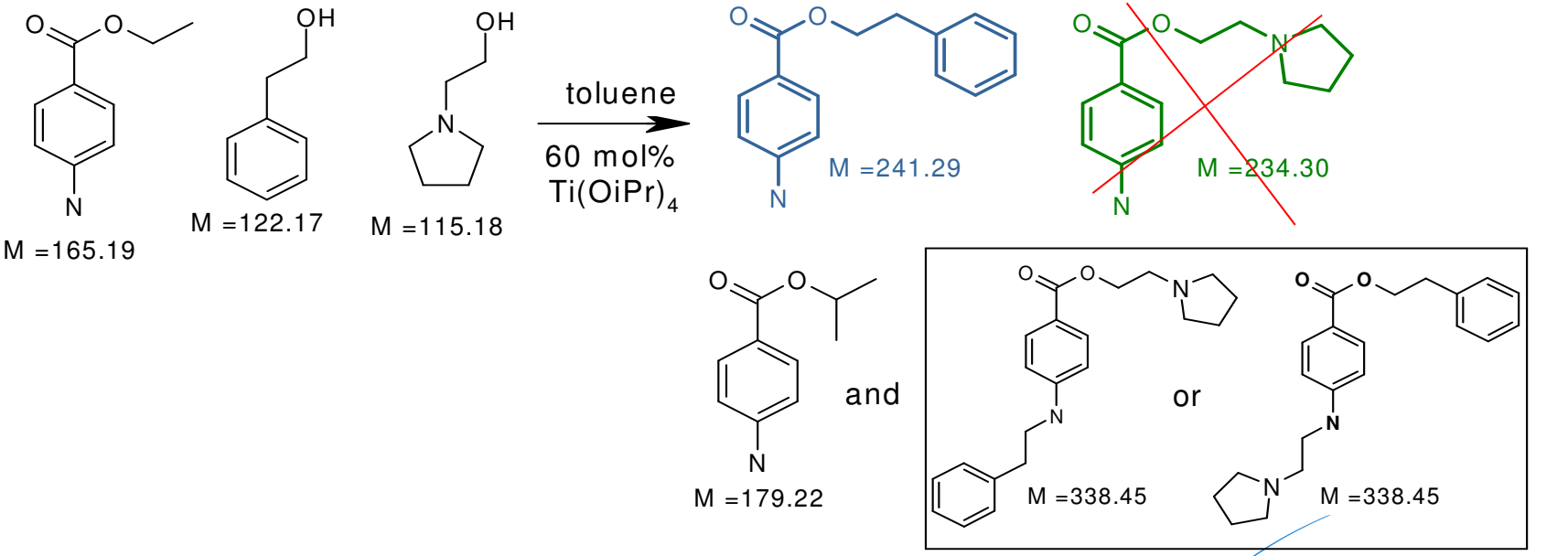


Transesterification - Library Synthesis II.

Library synthesis II. – SG-116

- 1 equivalent from the starting materials
- Conditions: toluene, 60 mol% $Ti(OiPr)_4$, 80 bar, 16 min residence time
- Blockage problems ☹

T / C	241 / %	234 / %	179 / %	338 / %	165 / %	122 / %
150	4	0	4	≈ 1	63	9
170	15	0	26	≈ 1	38	9
190	21	0	27	≈ 1	32	9
210	12	0	3	≈ 1	55	12



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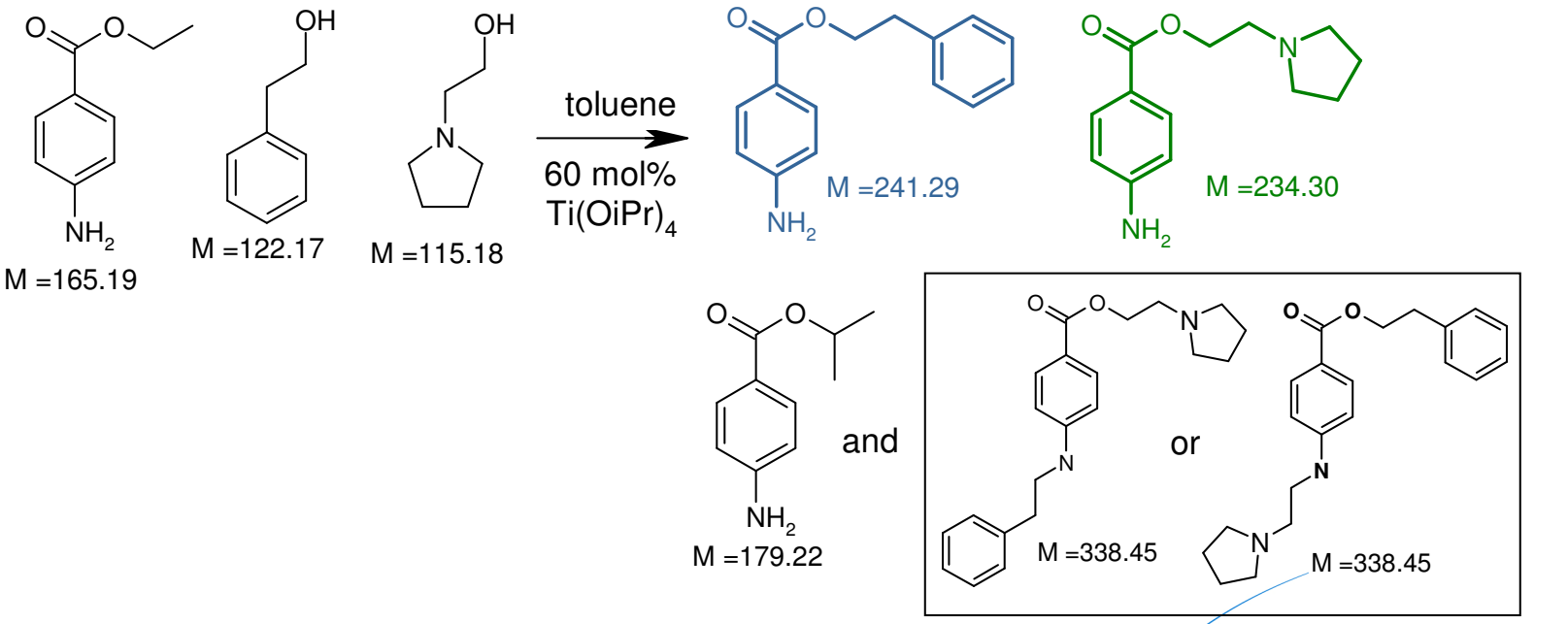
Transesterification - Library Synthesis III.

- **Library synthesis III. – SG-117**
  - 0.5 equivalent from the alcohols
  - Conditions: toluene, 60 mol% $Ti(OiPr)_4$, 90 bar, 16 min

T / C	241 / %	234 / %	179 / %	338 / %	165 / %	122 / %
170	11	3	23	0	57	
190	20	5	19	0	44	



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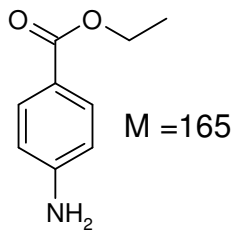
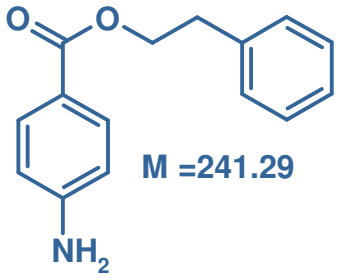
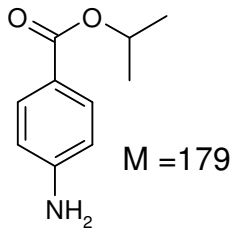
Transesterification - Library synthesis IV.

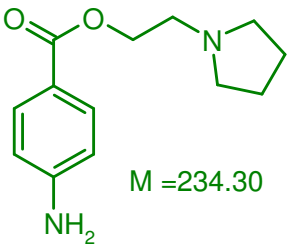
Summarization table

- Conditions: toluene, 60 mol% catalyst, 16 min



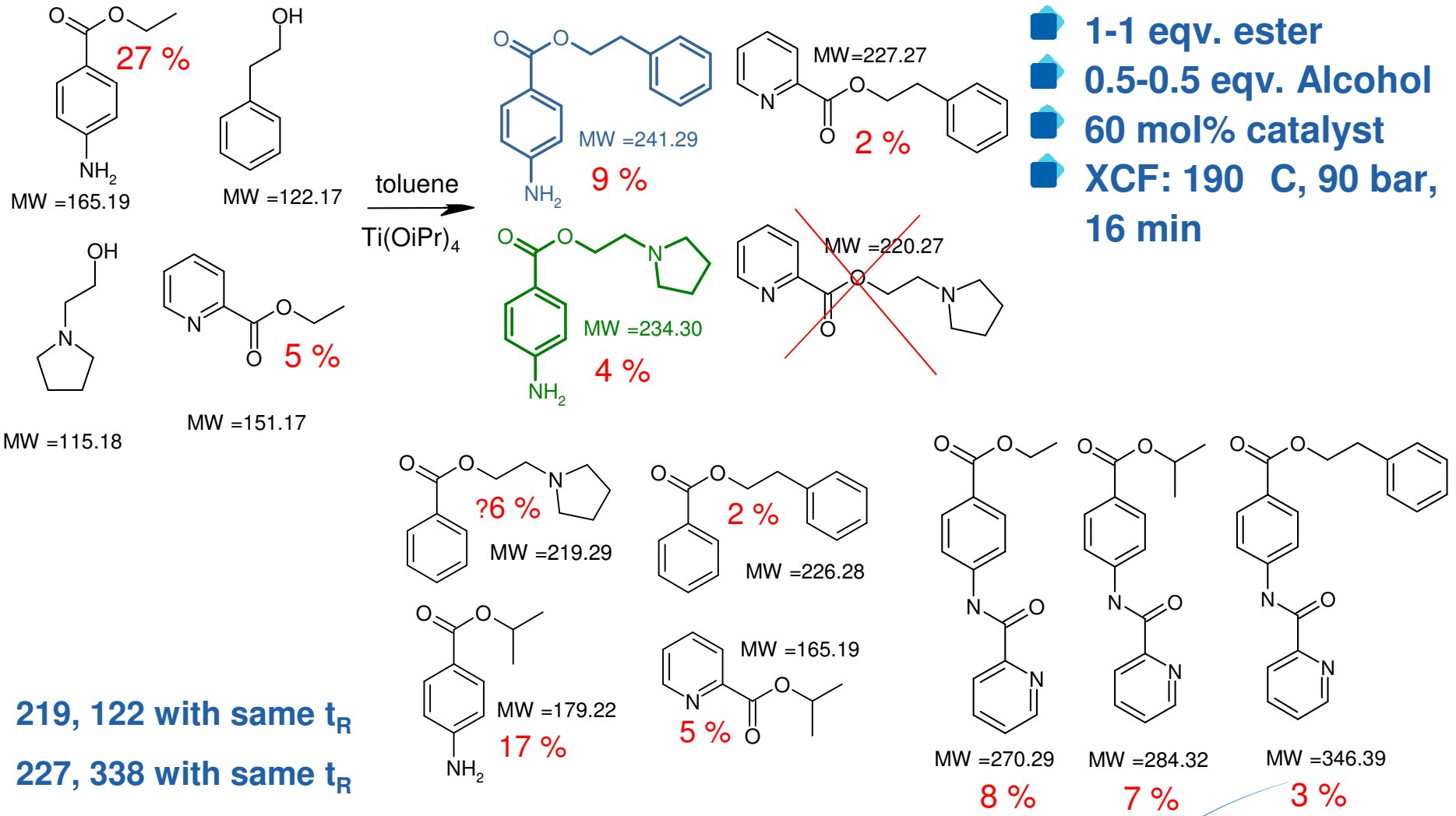






XCF	Alcohol / eqv.	*T* / °C	*p* / bar	241 / %	234 / %	179 / %	338 / %	165 / %	122 / %
SG-112	3	170	150	28	0	6	4	22	14
SG-116-1	1	150	80	4	0	4	≈ 1	63	9
SG-116-2	1	170	80	15	0	26	≈ 1	38	9
SG-116-3	1	190	80	21	0	27	≈ 1	32	9
SG-116-4	1	210	80	12	0	3	≈ 1	55	12
SG-117-1	0,5	170	90	11	3	23	0	57	
SG-117-2	0,5	190	90	20	5	19	0	44	

Transesterification - Library Synthesis V. SG-118

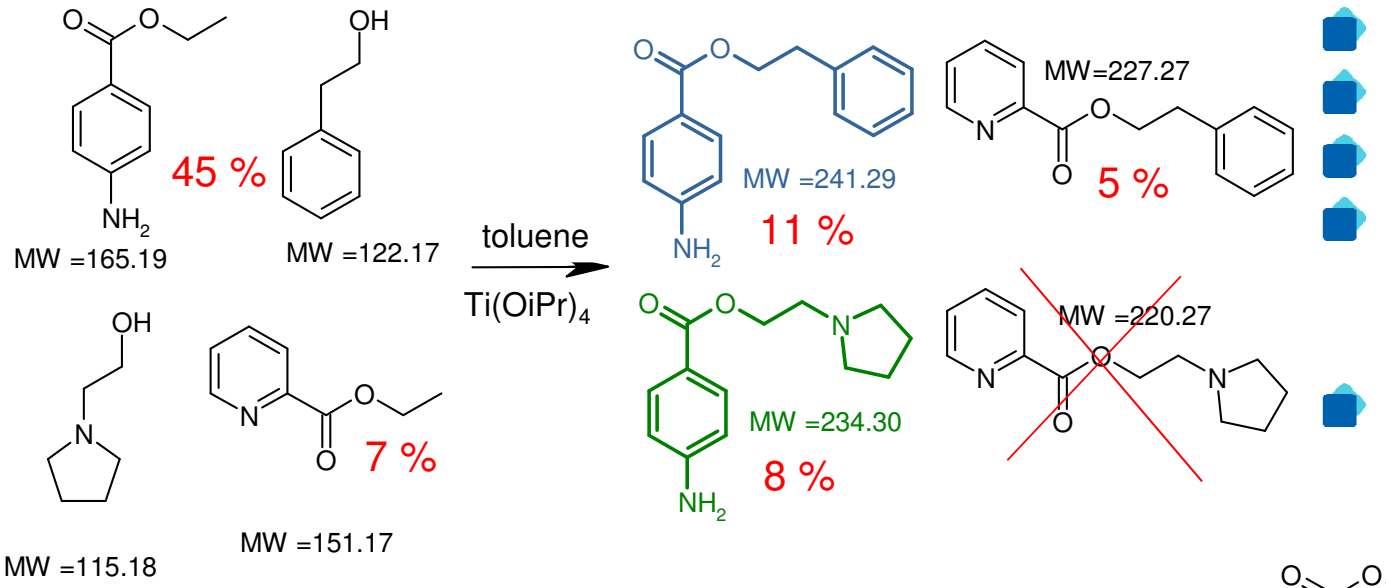


- 1-1 eqv. ester
- 0.5-0.5 eqv. Alcohol
- 60 mol% catalyst
- XCF: 190 C, 90 bar, 16 min

219, 122 with same t_R

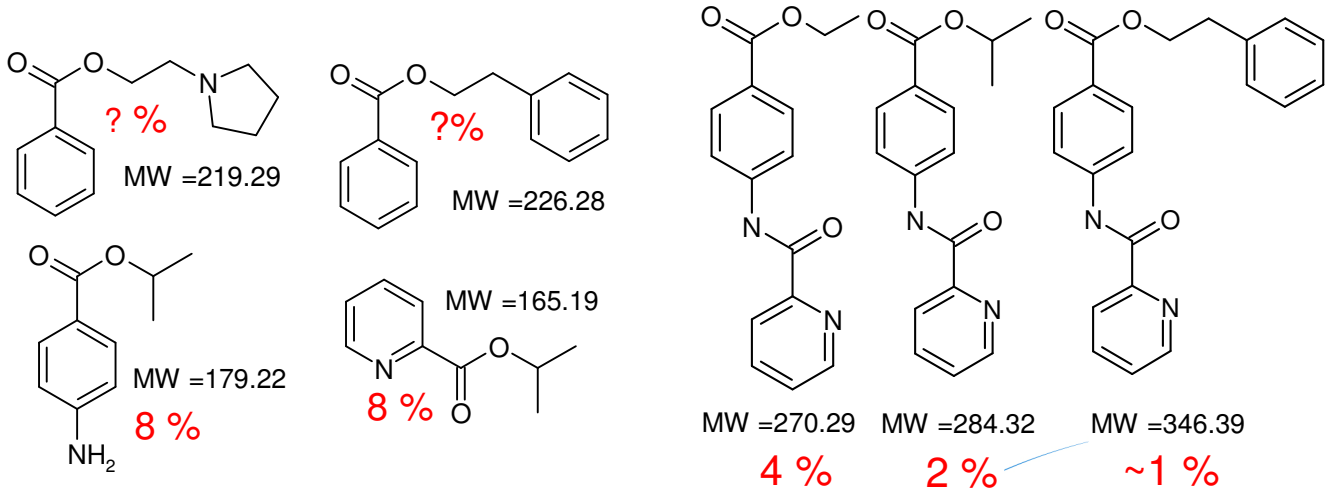
227, 338 with same t_R

Transesterification - Library Synthesis V. SG-120



- 1-1 eqv. ester
- 1-1 eqv. alcohol
- 60 mol% catalyst
- XCF: 90 bar, 16 min
  - 170 C → ☹
  - 190 C → ☺
- Blockage problems ☹

122, 165(s) with same t_R



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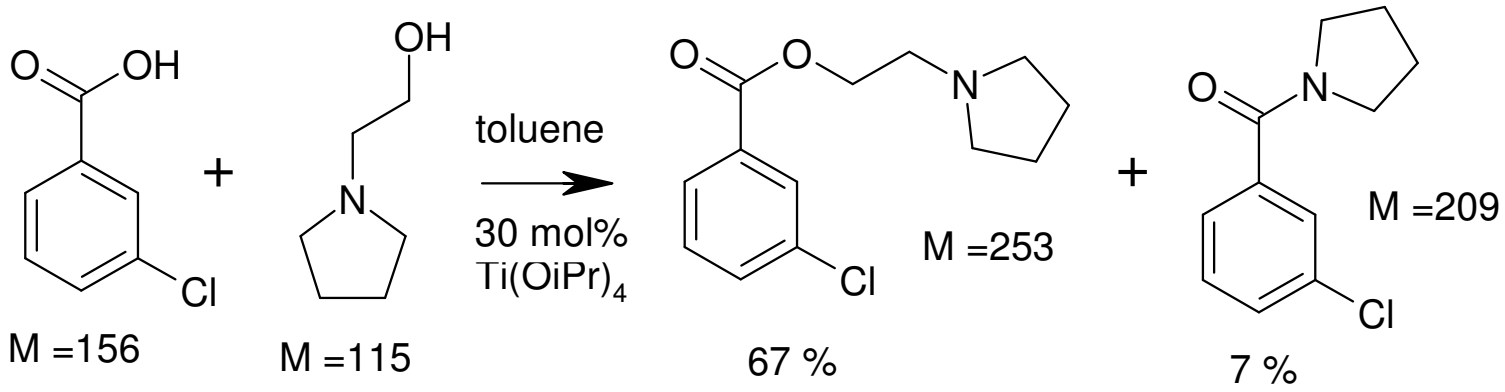
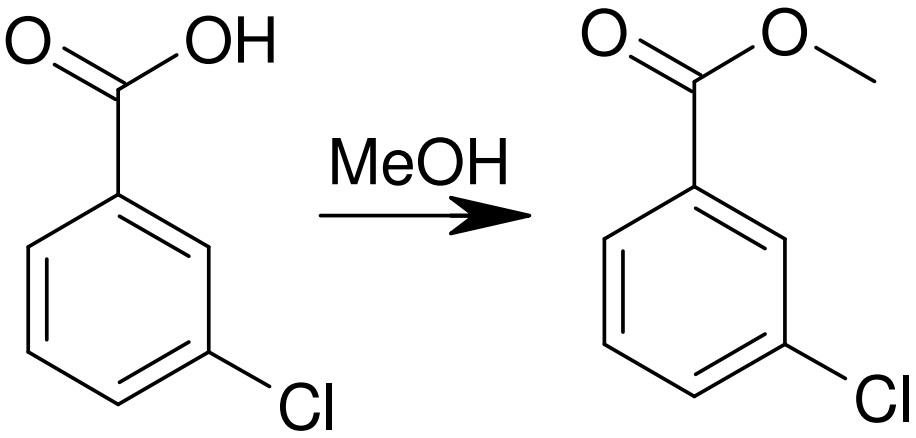
Esterification

- X-Cube Flash 190 C, 90 bar, 16 min
  - 3 equivalent alcohol

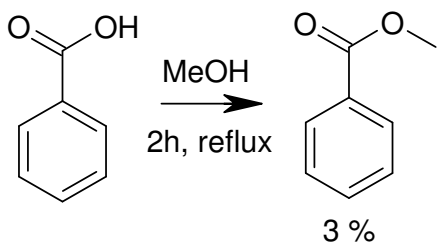


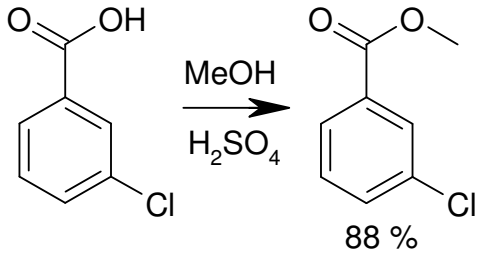
Esterification under supercritical conditions

- **245 C, 150 bar, 16 min**
  - Purity > 99 %
  - High yield (>95 %)
- **350 C, 150 bar, 16 min**
  - Degradation



- **Benzoic acid + MeOH → 3 % ester[1]**
- **m-chloro-benzoic acid + MeOH in the presence of H_2SO_4 in ultrasonicator bath → 88 % ester after 5 hour[2]**

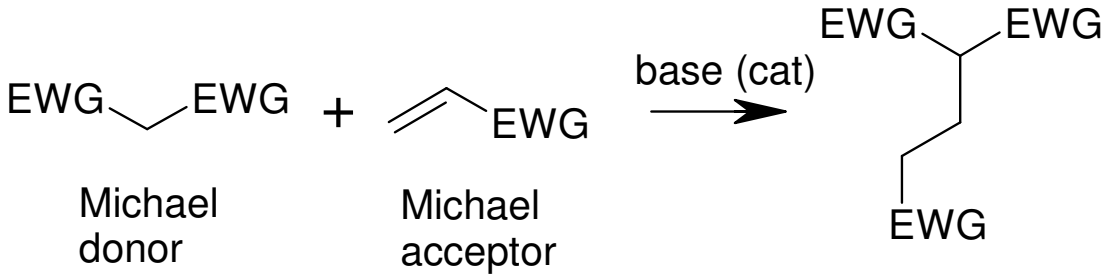


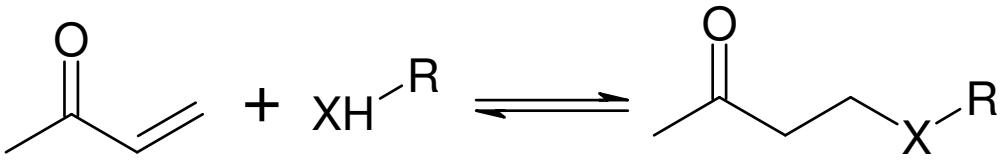


- 1 Kumar, Chattopadhyay; Tetrahedron Letters, Vol. 28, pp 3713-3714, *1987*
- 2 Maikap et al.; Synthetic Communications, 20(15), 2267-2271, *1990*

Michael-addition

- Useful method for the mild formation of C-C, C-S, C-N, C-O bond
- Thermodinamically controlled
- Reversible

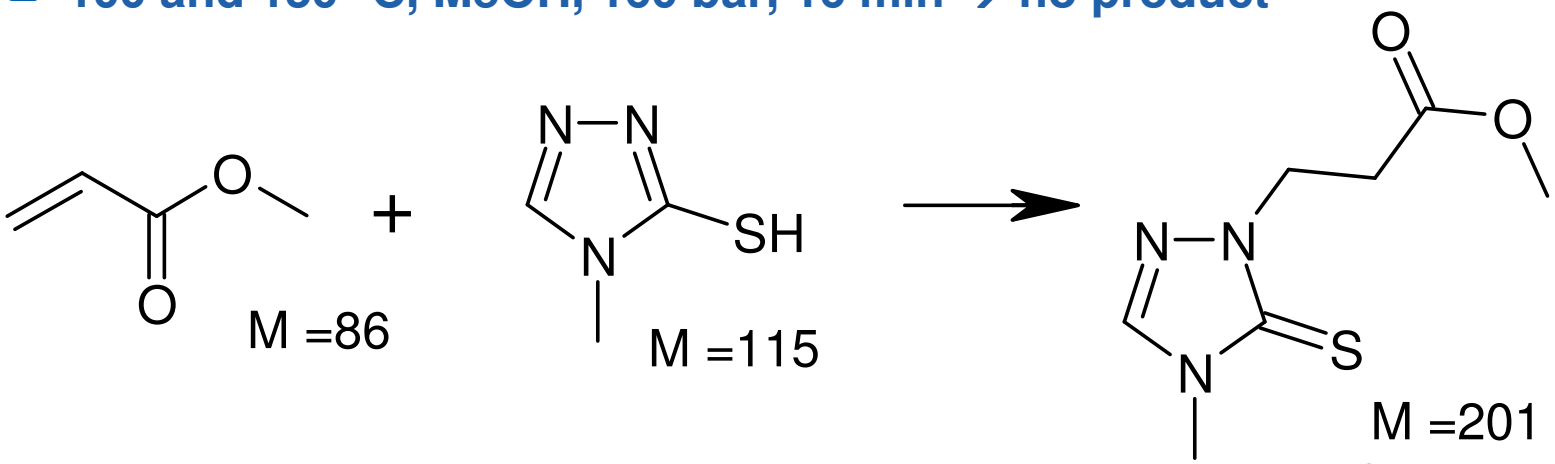




X = S, O, NH

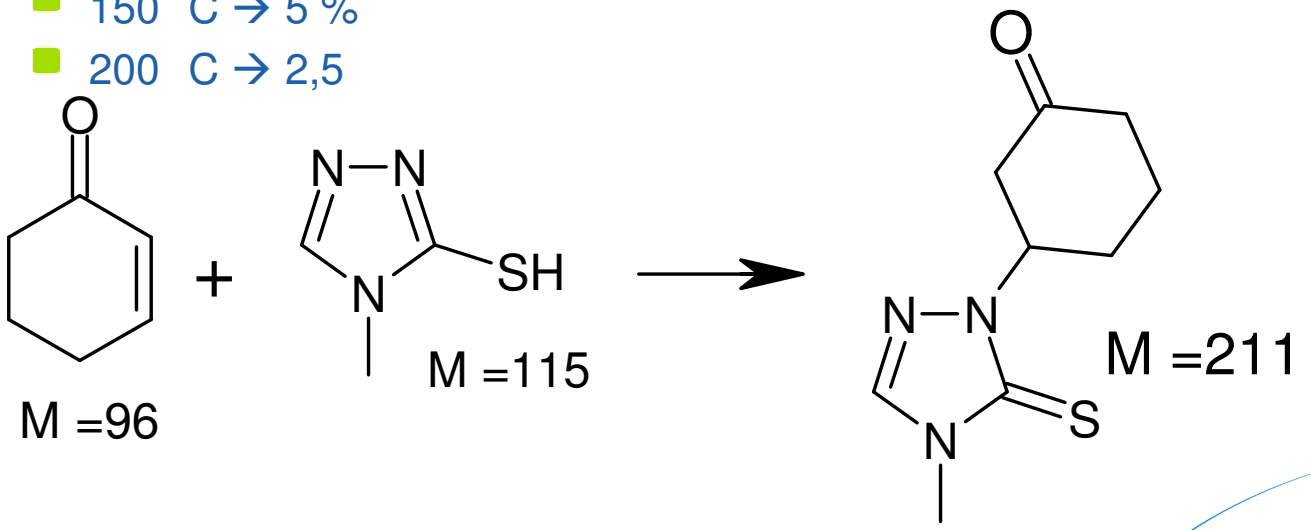
Michael-addition I.

- **Batch**
  - **Conditions: MeOH, 20 mol% NaOH, 40 C, 20-48 h**
  - **Polymerisation of methyl-acrylate**
  - **Mainly aza-Michael (Batch)**
    - 3 isomer could arise (based on LC-MS)
    - Only the main component was isolated
- **XCF**
  - **100 and 150 C, MeOH, 160 bar, 16 min → no product**

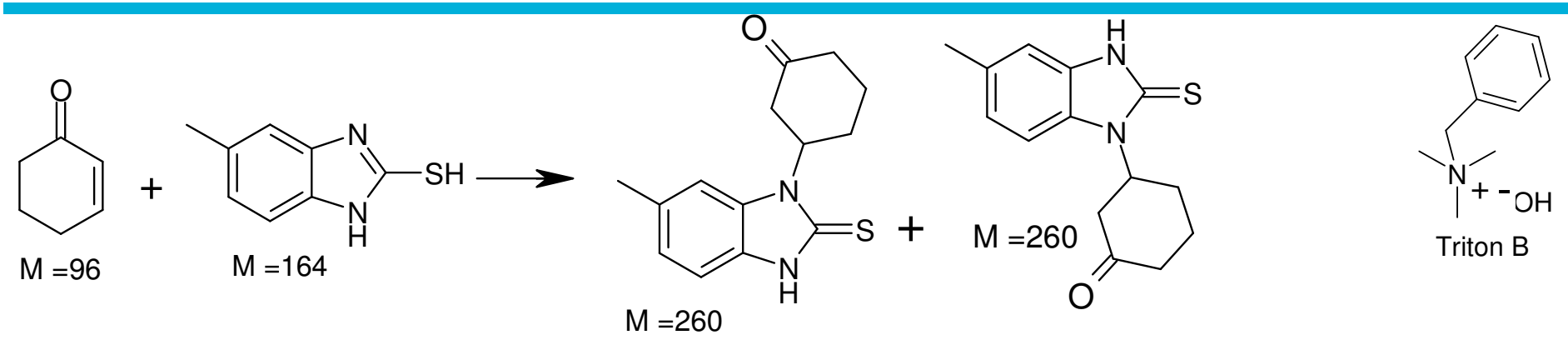


Michael-addition II.

- Batch
  - Conditions: EtOH, 20 mol% NaOH, 20 – 48 h
  - After 22 h 60 % from 211
- XCF
  - Conditions: 160 bar, 16 min, without catalyst!
    - 60 C → 30,5 %
    - 100 C → 43,4 %
    - 150 C → 5 %
    - 200 C → 2,5

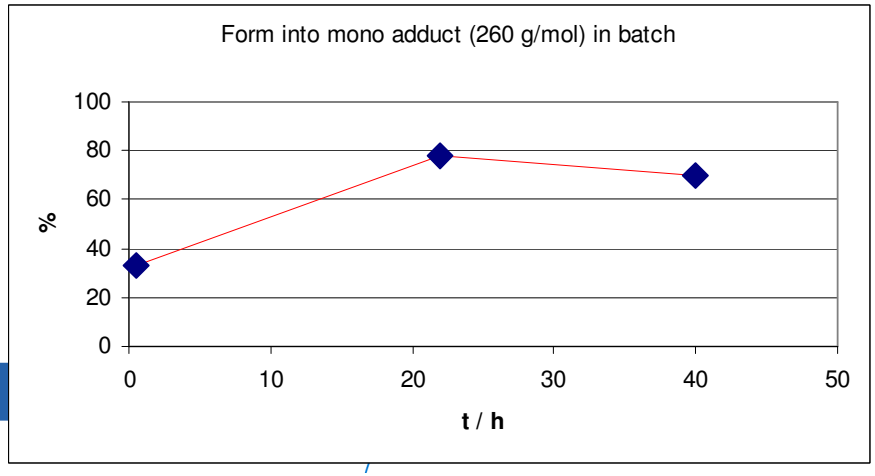


Michael-addition III.



XCF / Batch	Catalyst	*T* / C	*t* / min	260 / %	356 / %
Batch	20 mol% NaOH	RT	40 h	70	<1
XCF	-	100	32	1,3	-
XCF	-	150	32	0,3	-
XCF	10 mol% Triton B	100	16	10	-
XCF	10 mol% Triton B	150	16	0	-
XCF	100 mol% Triton B	100	16	5* **	-
XCF	20 mol% Triton B	100	16	11*	-
XCF	20 mol% Triton B	160	16	0**	-
XCF	40 mol% Triton B	100	16	13**	-
XCF	40 mol% Triton B	160	16	0**	-

- General conditions:
  - Batch: 1 bar, EtOH
  - XCF: 160 bar, MeOH
- * after 3 hour circulation ≈0
- ** benzylation of 164



Summing up and recommendations

- **Esterification, transesterification suitable for library synthesis**
  - **Limitations**
    - Homogenous solution
    - Sometimes separation from the solution after the loop
    - Detection (difficulties if too many products)
- **Michael-addition**
  - **No problem with solubility (yet)**
  - **Necessary to optimize the conditions**
  - **Water as solvent?**

- **Recommendations for X-Cube Flash**
  - **Use high pressure**
  - **Do not use flow rate under 0.5 ml/min**
  - **Use diluted solutions**
  - **Always wash the loop with excess of the solvent**

Many thanks for your attention