Enantioselective Synthesis of Vinylglycine Derivatives Using Continuous-Flow Thermolysis

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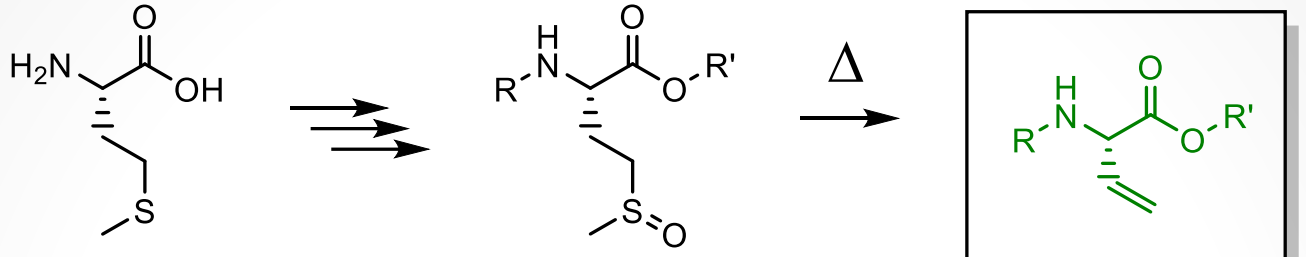
1. Introduction

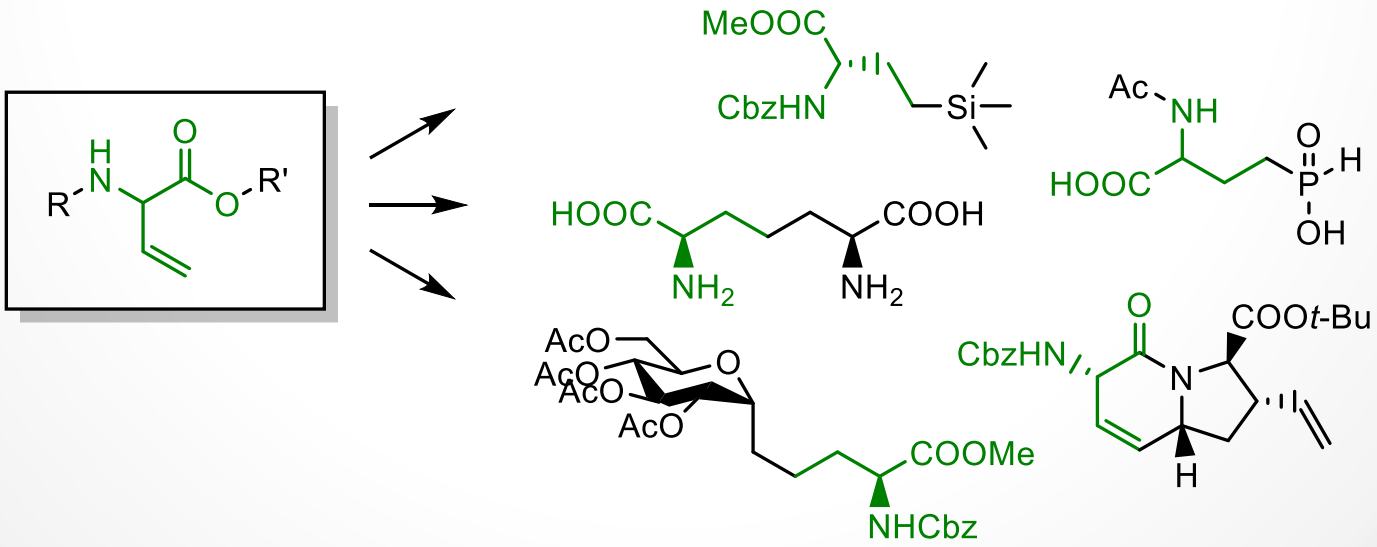
- Most straightforward synthesis:



0.28 USD/g

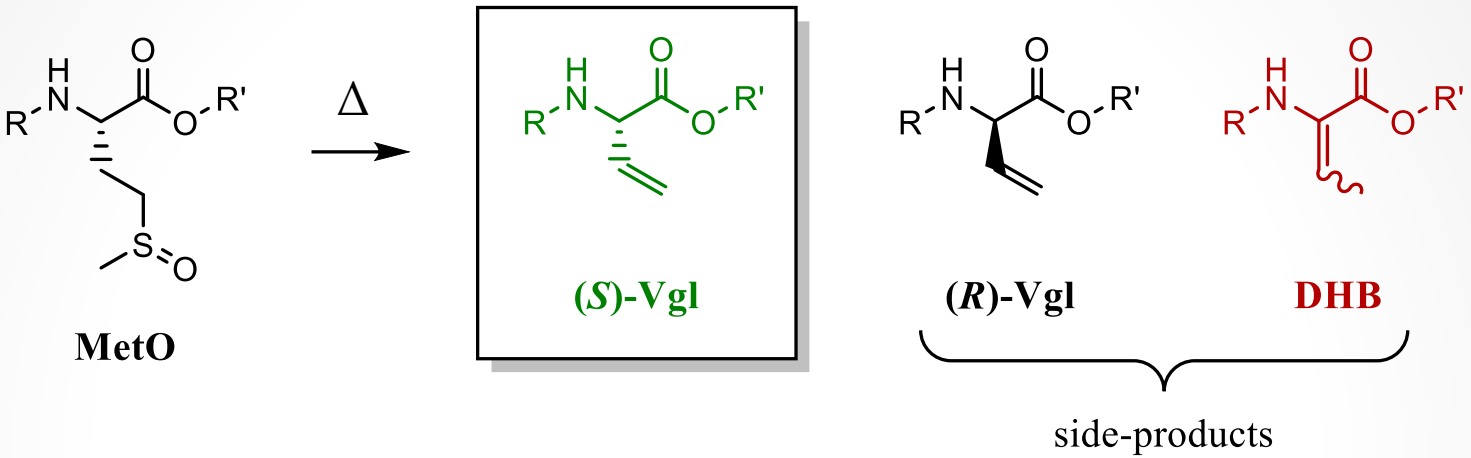
190 USD/g

- Vgl is an interesting building block



2. Background

- Thermolysis step and side-products:



- Previously described methods:

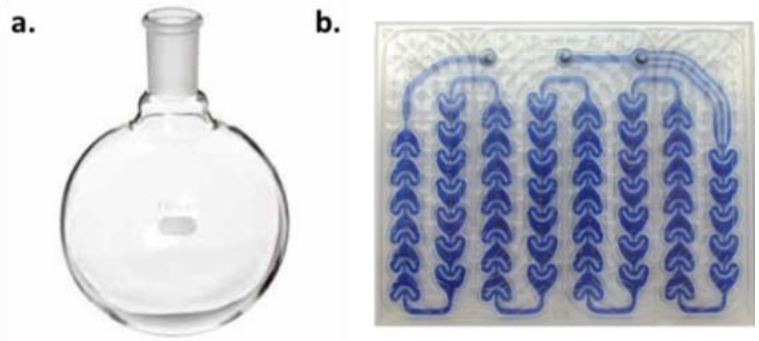
Conventional reflux:
- ☺ Universal glassware
- ☹ Long reaction time at high T
- ☹ T limited by solvent
- ☹ Unusual solvents
- ☹ High quantities of DHB
- ☹ Low ee

Kugelrohr apparatus:
- ☺ High ee
- ☺ Low amount of DHB
- ☺ No solvent
- ☹ Low yields
- ☹ Poor reproducibility (difficult to control vacuum and T)
- ☹ Not scalable

3. Finding a solution

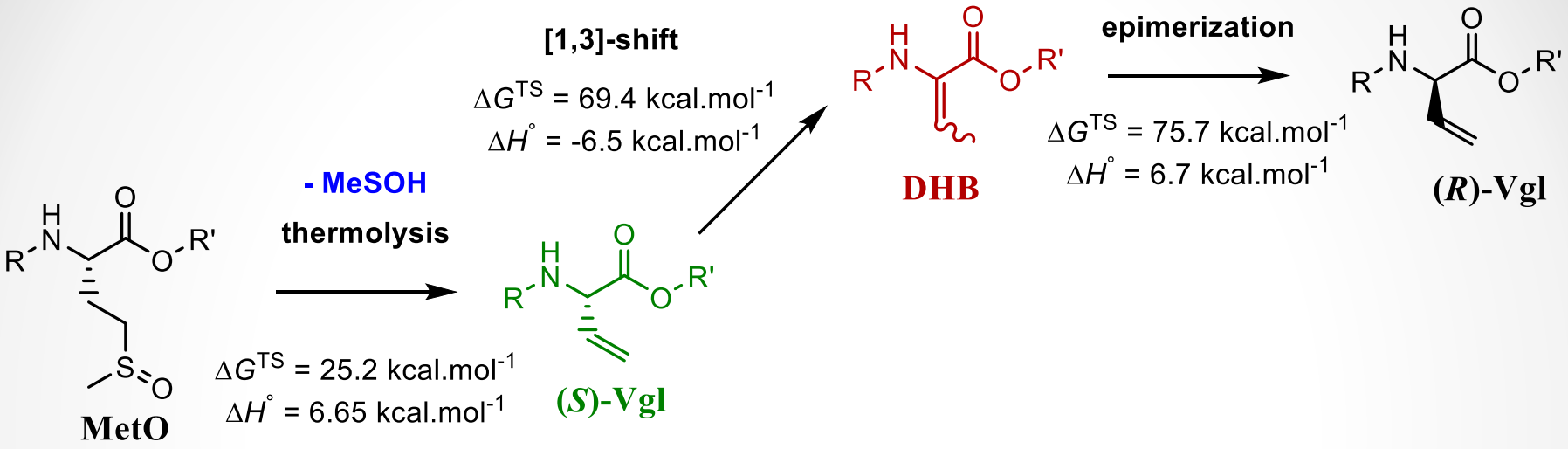
- Flow chemistry (CHIM9265-1 👍)
  - ☺ Pressure control
  - ☺ Temperature not limited by the solvent
  - ☺ Usual solvents
  - ☺ Accurate control of residence time & reaction conditions
  - ☺ As soon as Vgl is formed, it is no longer exposed to high T
  - ☺ Larger scale accessible through numbering-up

  ➡ Promote formation of **Vgl** (kinetic product) over **DHB** (thermodynamic product).



- Side product formation (DHB + racemization)
  - ➡ Rationalization by computational studies

4. Computational studies



computational studies were performed at the B3LYP/6-31+G* level of theory

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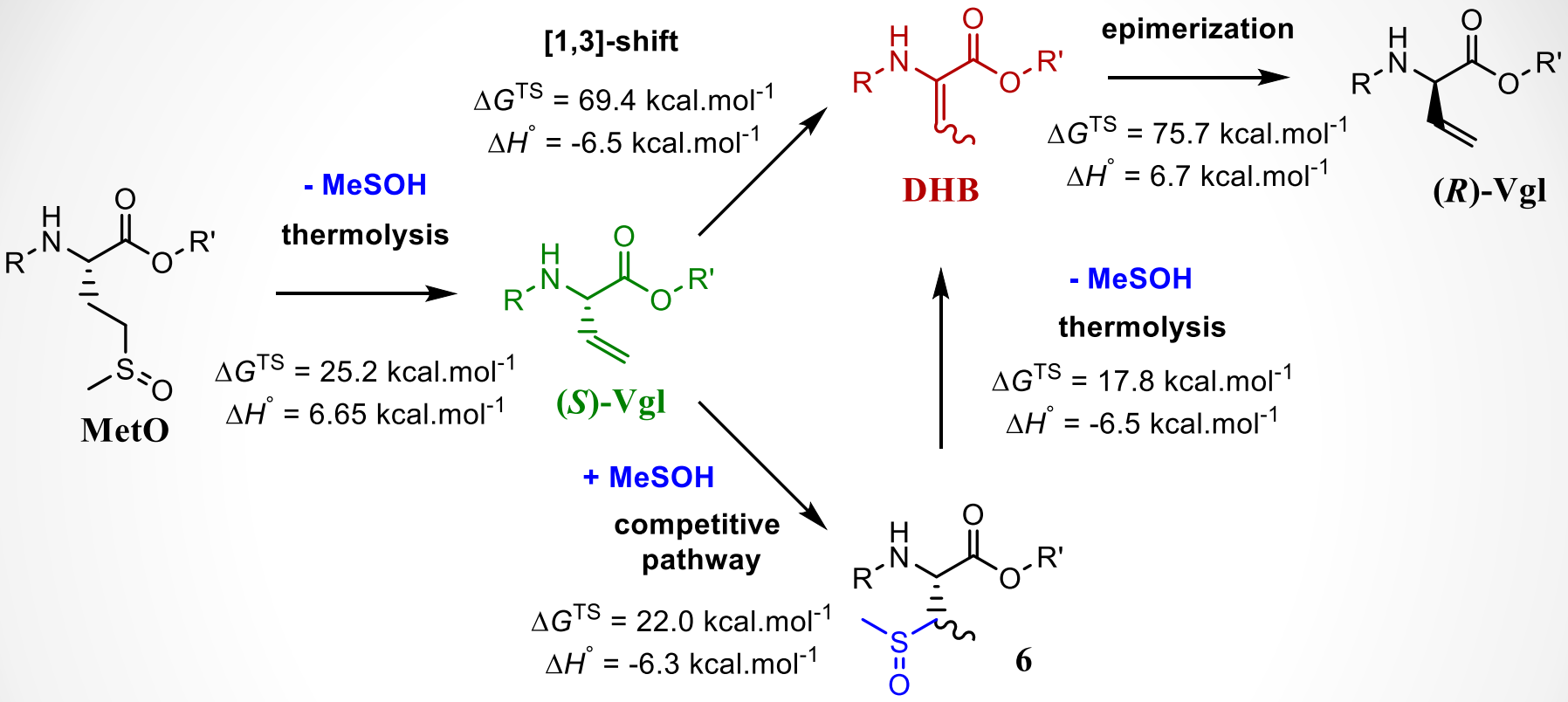

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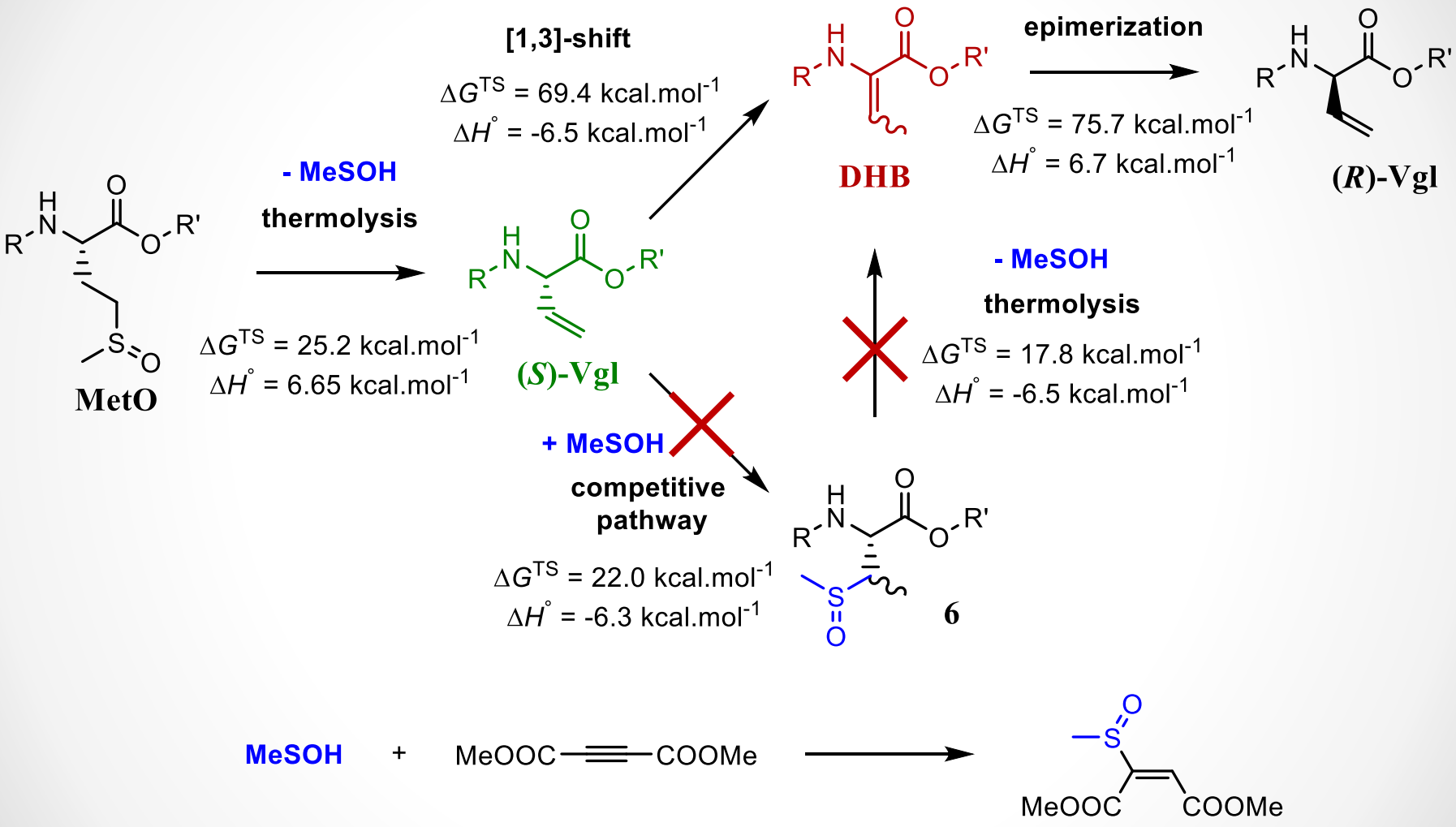

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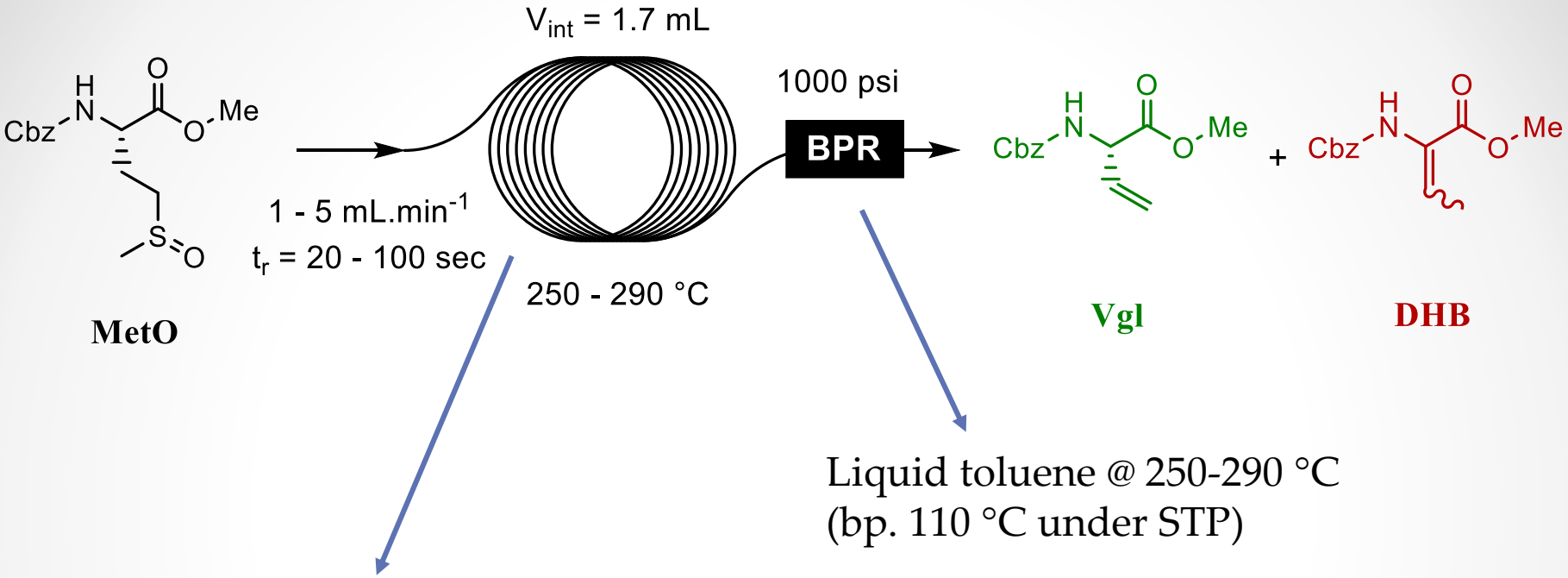
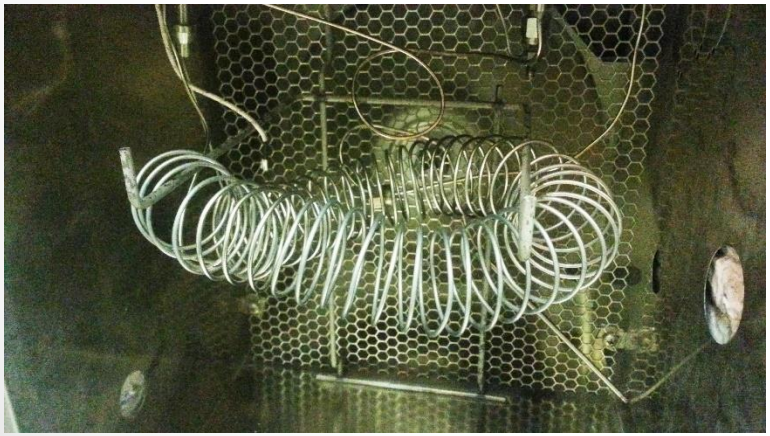
5. Mesofluidic device

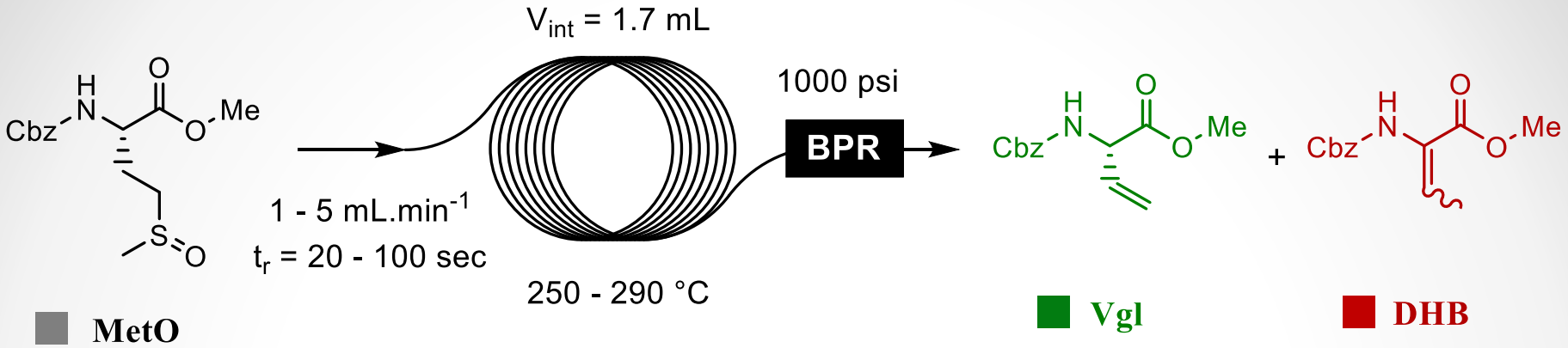


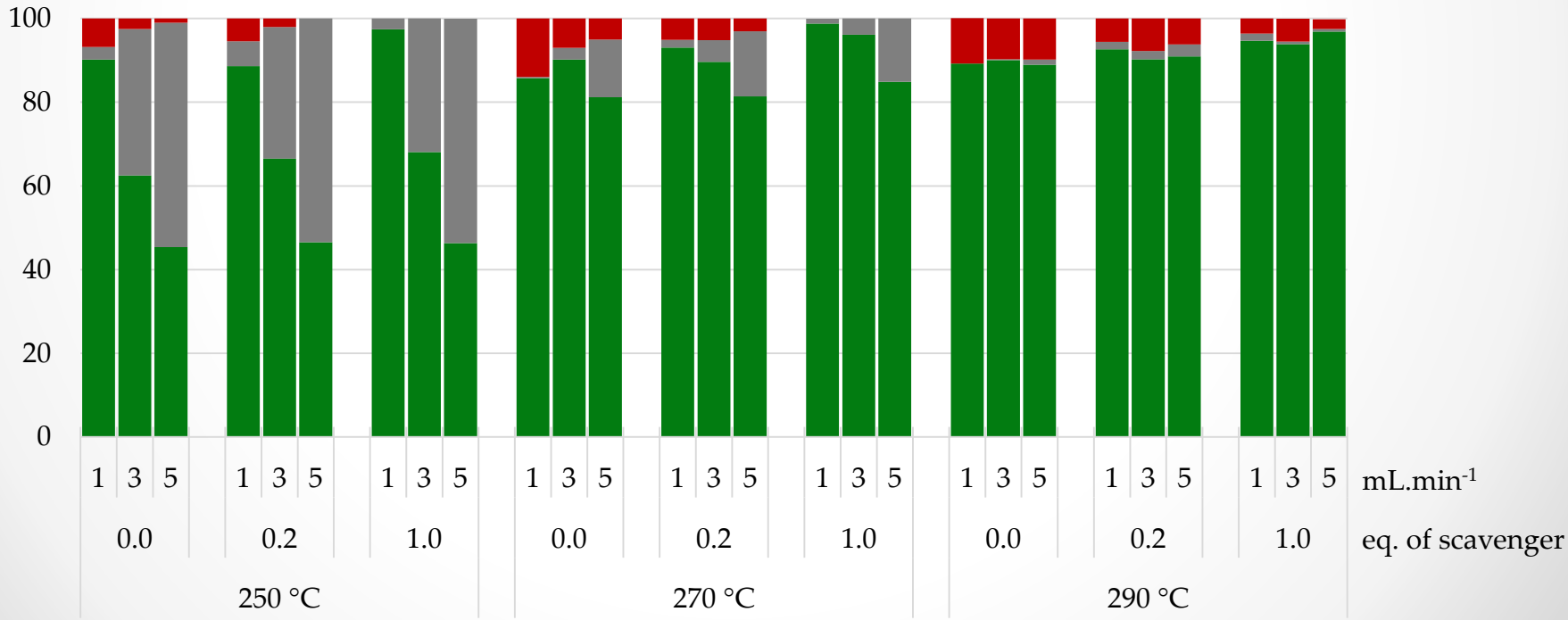
Liquid toluene @ 250-290 °C
(bp. 110 °C under STP)



Stainless steal
L = 6 m
$Ø_{ext}$ = 1/16”
$Ø_{int}$ = 500 µm
for optimal heat exchange

5. Experimental results





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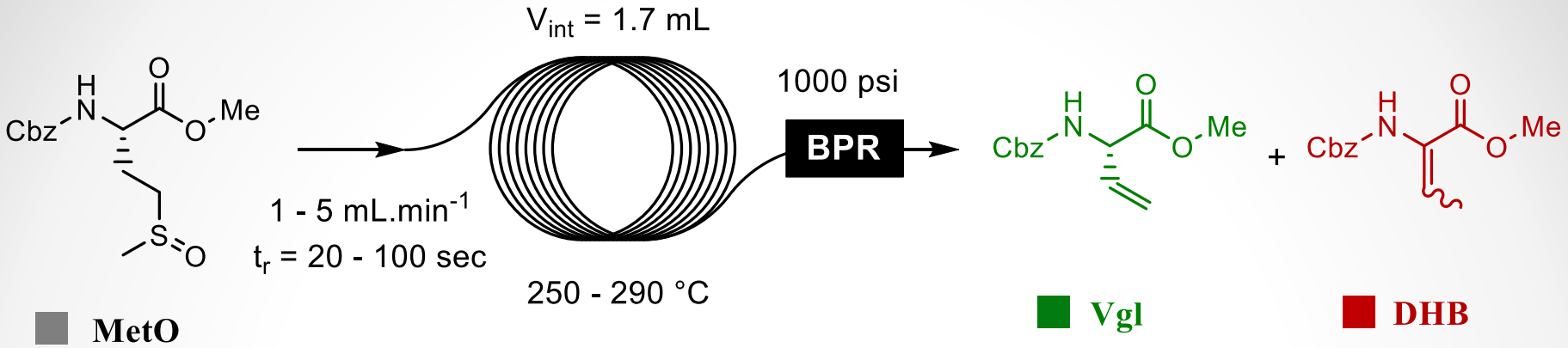

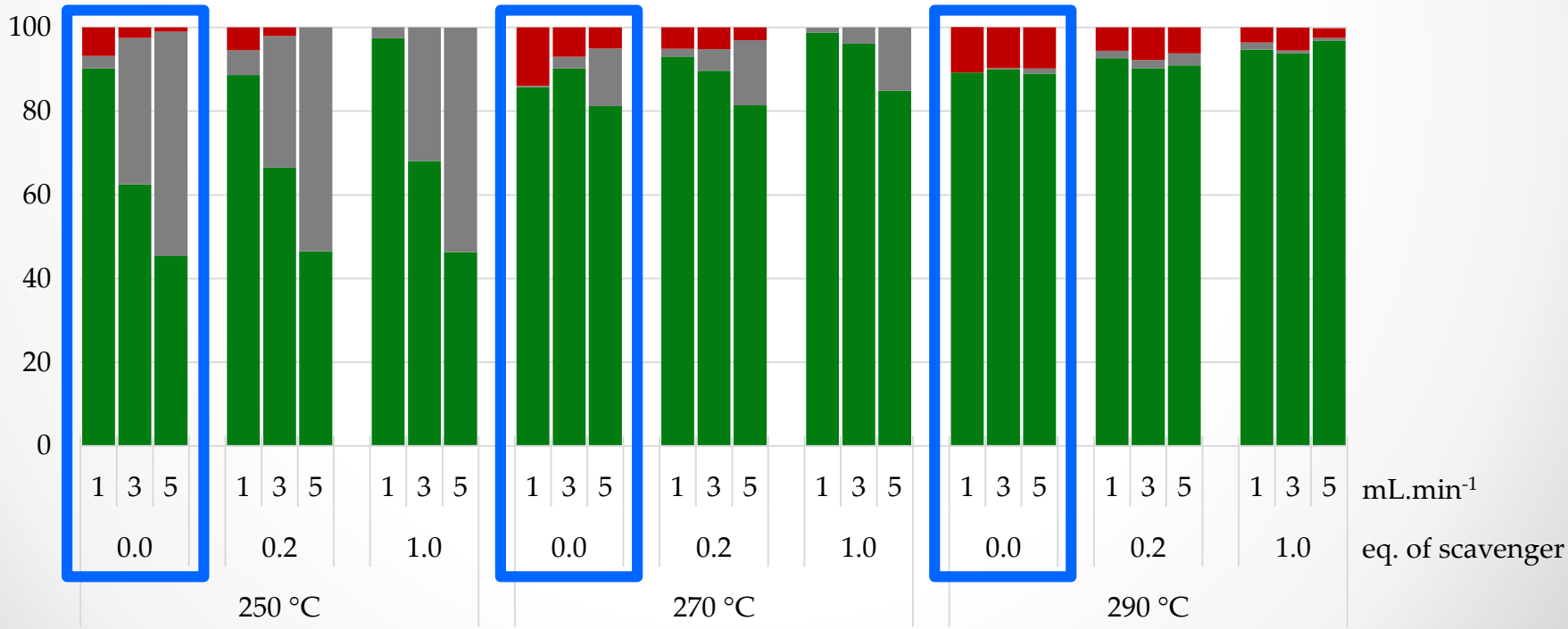

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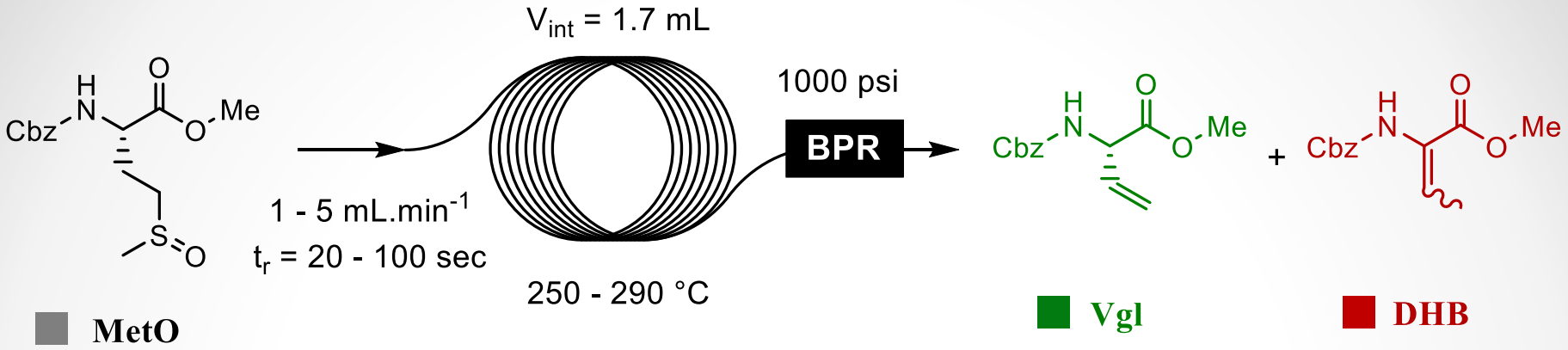

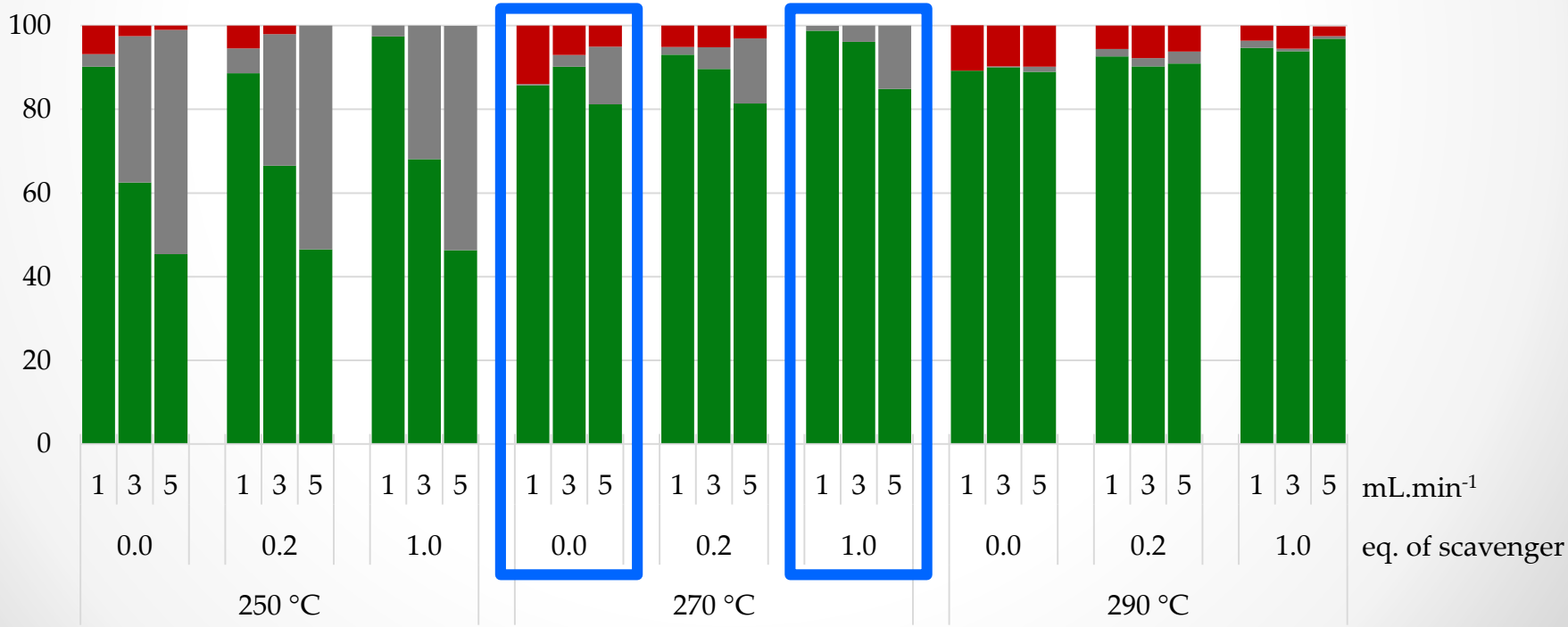

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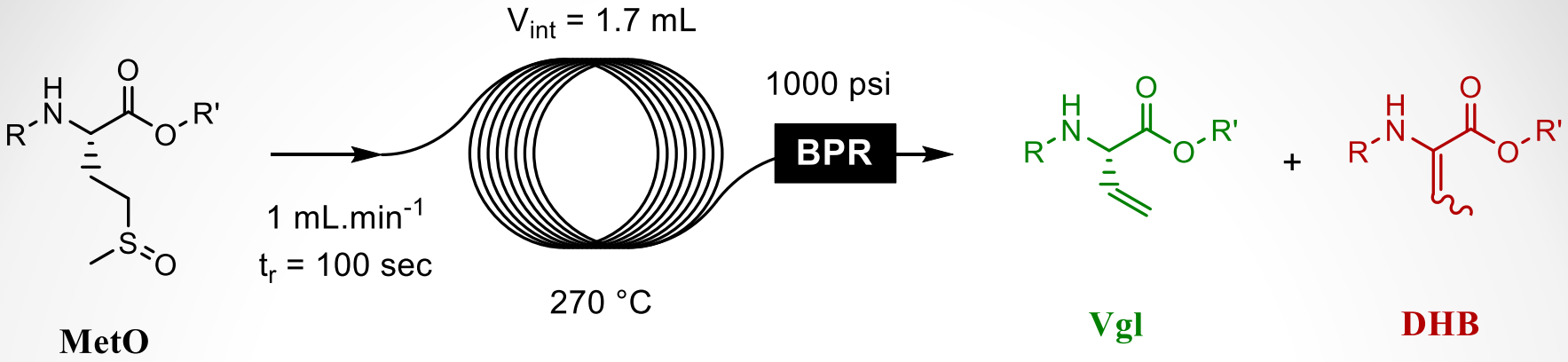

	MetO (%)	**Vgl** (%)	**DHB** (%)
CBzNH-MetO-OMe	1.2	98.8	0
BocNH-MetO-OMe	/	/	/
FmocNH-MetO-OMe	1.6	98.4	0
NBOCNH-MetO-OMe	2.4	97.6	0
CbzNH-MetO-OBn	1.5	98.5	0
BocNH-MetO-OBn	/	/	/
FmocNH-MetO-OBn	2.1	97.9	0
NBOCNH-MetO-OBn	3.3	96.7	0

6. Conclusion

- We designed and build a mesofluidic device capable of producing **11.5 g.day^{-1}** (190 USD/g) of CbzNH-Vgl-OMe with **high yields (~99%)** and **ee (>95%)**.

- Best conditions also work for a **variety of protecting groups**.

- Contrary to batch methods, production can be **continuously monitored** and tune if necessary.

- Great **reproducibility**

- Production could be raised simply by **numbering up**.

Thanks for your attention