Petasis Olefination in a Continuous Flow Microwave Reactor: *exo*-Glycals from Sugar-Lactones

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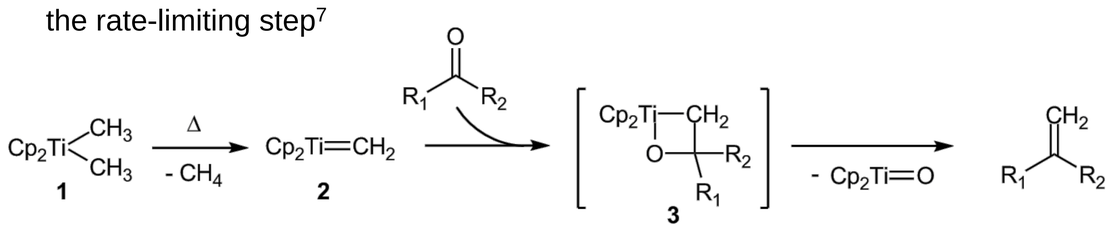
Introduction

Owing to their distinct nucleophilic reactivity, enol ethers and, in particular, *exo*-glycals are considered interesting synthons for further conversion, as for example to spiroketals[1] or *C*-glycosides[2]. Commonly applied olefination reactions, e.g. Wittig-, Horner-, Julia- or Peterson-olefination[3], require basic reaction conditions not applicable to the conversion of carboxylic esters to enol ethers. The Tebbe olefination[4] is useful for the synthesis of enol ethers from esters. However, the required reagent is very sensitive to moisture. In contrast, the Petasis olefination[5] of esters not only provides non-basic conditions, the reagent dimethyltitanocene **1** dissolved in toluene/THF also is stable towards moisture and air. It can be stored at + 4 °C over a longer period without decomposition[6]. Upon heating the molecule eliminates methane and forms the active titan carbenoide species **2**, which can react with the carbonyl compound in a cycloaddition reaction to form the more or less stable titanacycle **3**. After cycloreversion the olefinated product is released.

Reaction under batch conditions

- Substrate and reagent are dissolved in toluene/THF and heated in the dark under inert atmosphere at 65-80 °C for several hours
- Methane-elimination to form the reactive species starts at about 65 °C and is the rate-limiting step[7]



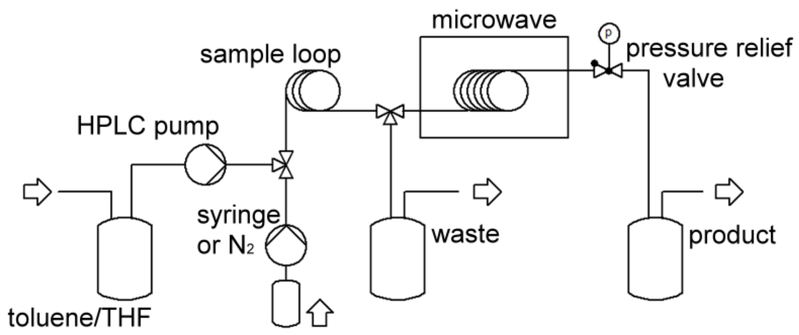
Increase of the temperature should strongly enhance the reaction rate limited by the boiling point of THF of 66 °C under atmospheric pressure.

Continuous flow microwave reactor under pressure (8 bar)

→ Optimization of crucial parameters with small amount of chemicals possible

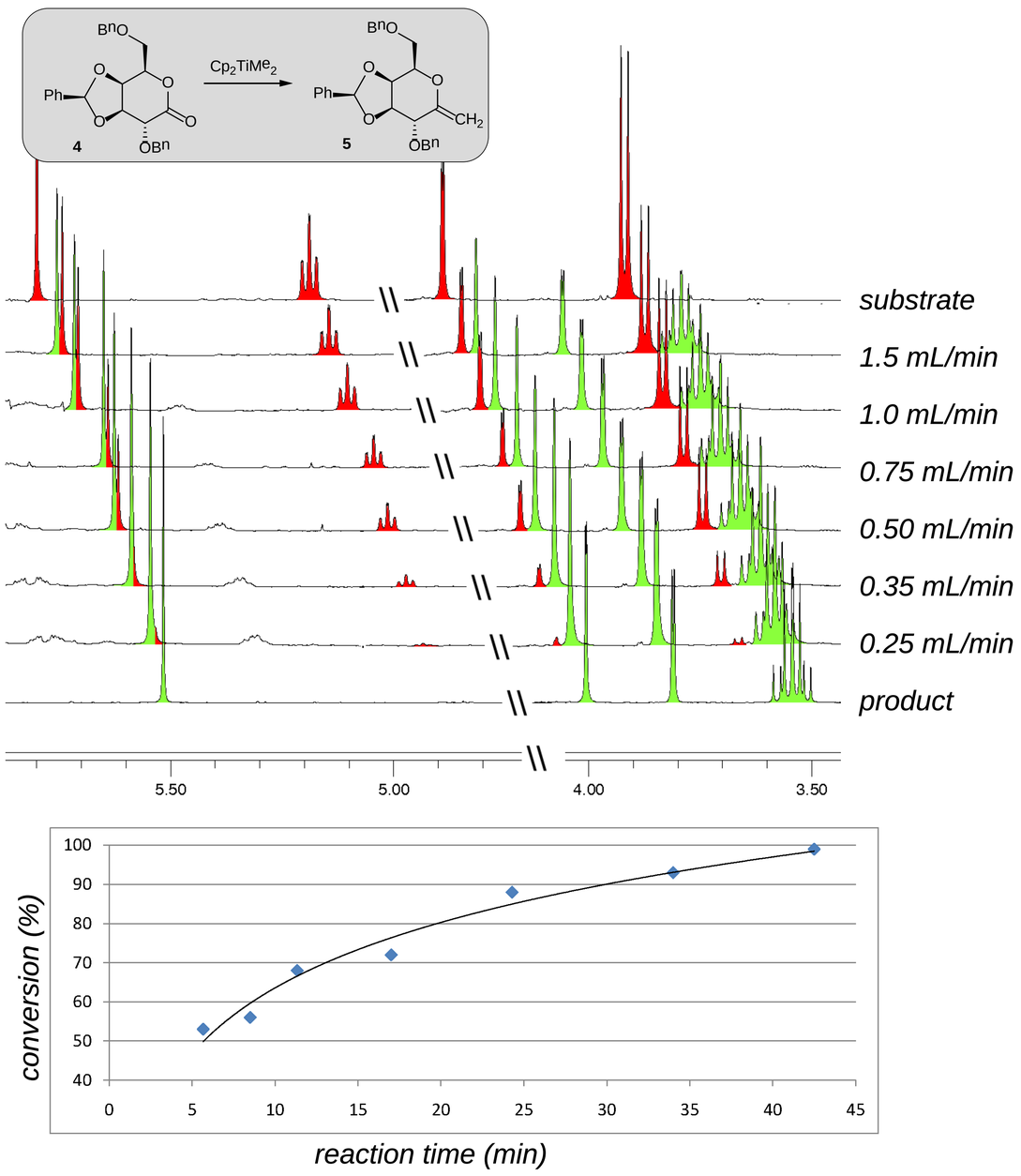
Continuous flow setup

- HPLC pump for delivering solvents and reactants
- Sample loop: capillaries (PTFE, 3.2 mm OD, 1.6 mm ID), total volume 6 mL
- Flow reactor (total volume 8.5 mL)
- Microwave oven for heating the reaction mixture
- Pressure relief valve to ensure the appropriate pressure



Reaction under continuous flow conditions

- The olefination reaction can monitored by NMR after each run as illustrated for the galactose-derived sugar-lactone **4**



Preparative application

- Glucose-derived building block **6** reacts remarkably faster under similar conditions
  → complete conversion already reached after 5.67 min (at 1.5 mL/min)
- The formation of **2** by α-elimination must be completed very fast in both cases
- Contrary to the assumptions under batch conditions, the rate determining step must be the bimolecular reaction of **2** with the substrate
- Higher concentrations = faster reaction
  → remarkably accelerated conversion by increasing the Petasis reagent concentration from 0.18 M to 0.46 M
- Lowering the reaction time in the best cases down to only 2.8 min

		Continuous Flow		**Microwave Batch**	
		Yield	Time	Yield	Time
D-galactose	(8 steps) → **4** → **5**	71 %	5.7 min	70 %	30 min
D-glucose	(6 steps) → **6** → **7**	65 %	5.7 min	67 %	30 min
D-galactose	(6 steps) → **8** → **9**	52 %	5.7 min	50 %	30 min
D-galactose	(8 steps) → **10** → **11**	70 %	5.7 min	70 %	30 min
D-galactose	(7 steps) → **12** → **13**	50 %	5.7 min	51 %	30 min
L-fucose	(6 steps) → **14** → **15**	74 %	8.5 min	74 %	30 min
		Thermal batch:		74 %	720 min[8]

- Preparative application of the continuous flow reaction even on gram-scale
- Scale-up by simply increasing the operation time of the reactor
- No changes regarding conversion or yield

Summary

The olefination of complex sugar-derived lactones to *exo*-glycals was achieved under continuous flow conditions. This procedure allowed an optimization of the conversion by regulation of the residence time and the concentration on milligram-scale, before the ready scale-up of the reaction to a gram-scale production. It can be concluded from these results, that micro reactors are also efficient in preparative microwave-assisted conversions of other sensitive carbonyl substrates under continuous flow conditions.

References

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