Flow Chemistry in Multi-step Fine Chemical Synthesis

Main reference: *OPRD.* **2016**, *20*, 2-15.

Flow chemistry in general (single- and multi-step systems)

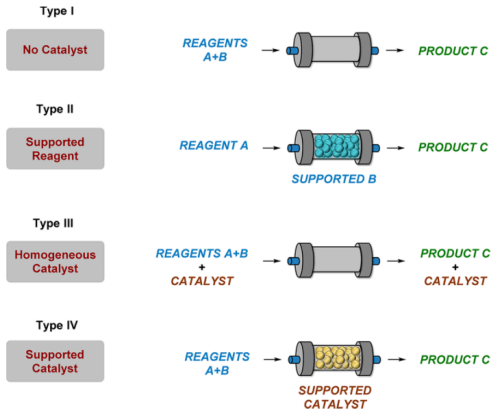
Advantage

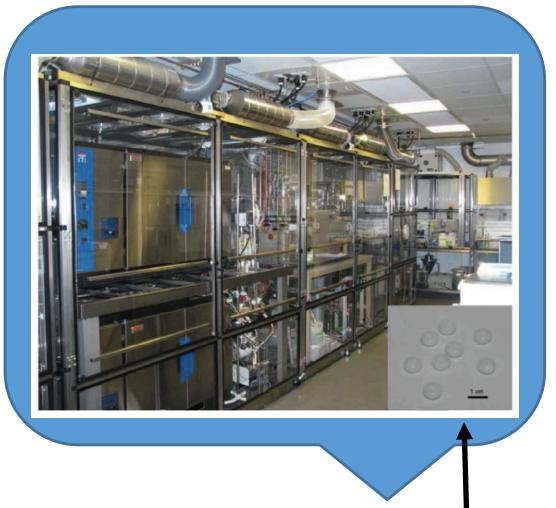
- Automated process
- Improved safety in handling hazardous chemicals
- Usually provide higher efficiency than batch system (time, quantity, etc.)
- Easily combined with other enabling technologies such as mw irradiation, phtochemistry, microreactor technology, etc.

…..and many many more.

Challenge

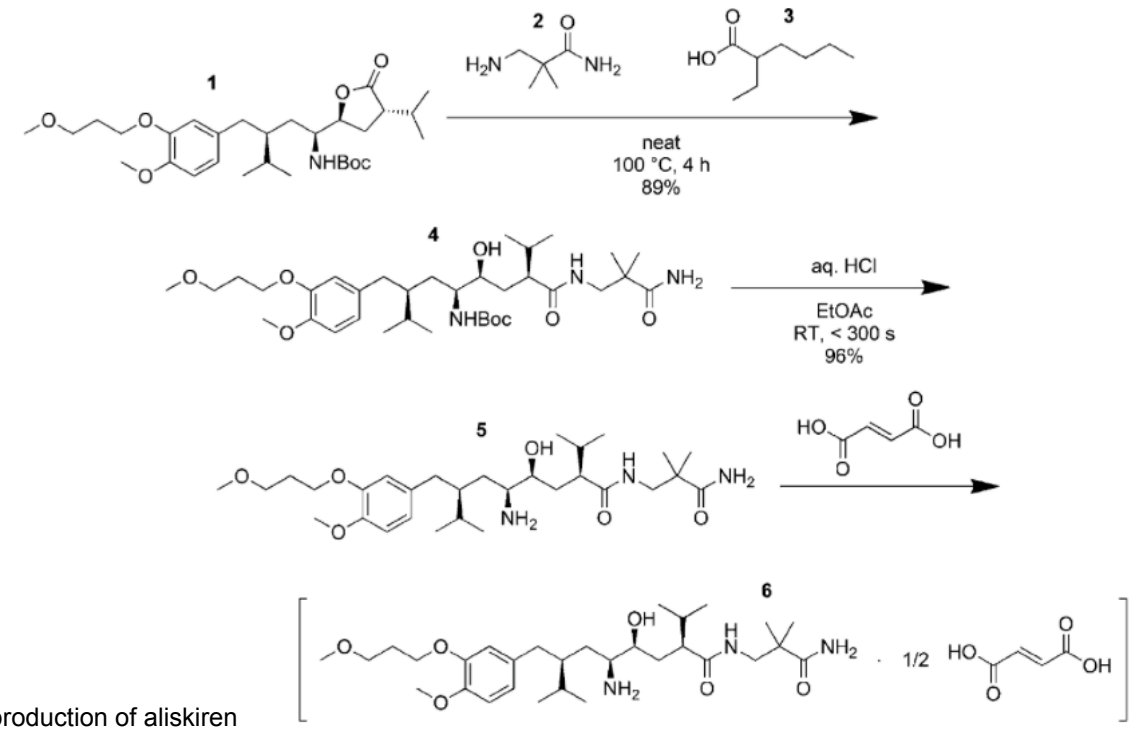
- insoluble solid formation (clogging)
- incompatibility of reaction conditions (additional non-chemical steps such as solvent exchange necessary)
- accummulation of impurities





Examples of multi-step continuous flow systems in the synthesis of NPs and APIs

aliskiren hemifumarate: Novartis-MIT, *ACIE.* **2013**, *52*, 12359, *OPRD.* **2014**, *18*, 402.



- 100 g/h production of aliskiren
- Batch system: 300 h processing time, 21 unit operations
  flow system: 48 h processing time, 13 unit operations

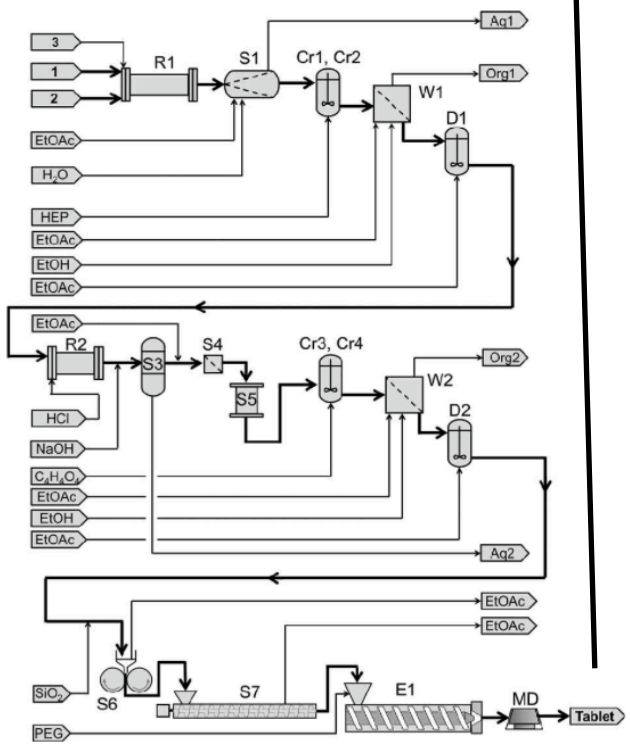


Figure 1. Process flow diagram including the major unit operations. R reactor, S separation, Cr crystallization, W filter/wash, D dilution tank, E extruder, MD mold. A detailed diagram is provided in the Supporting Information (Figure S1).

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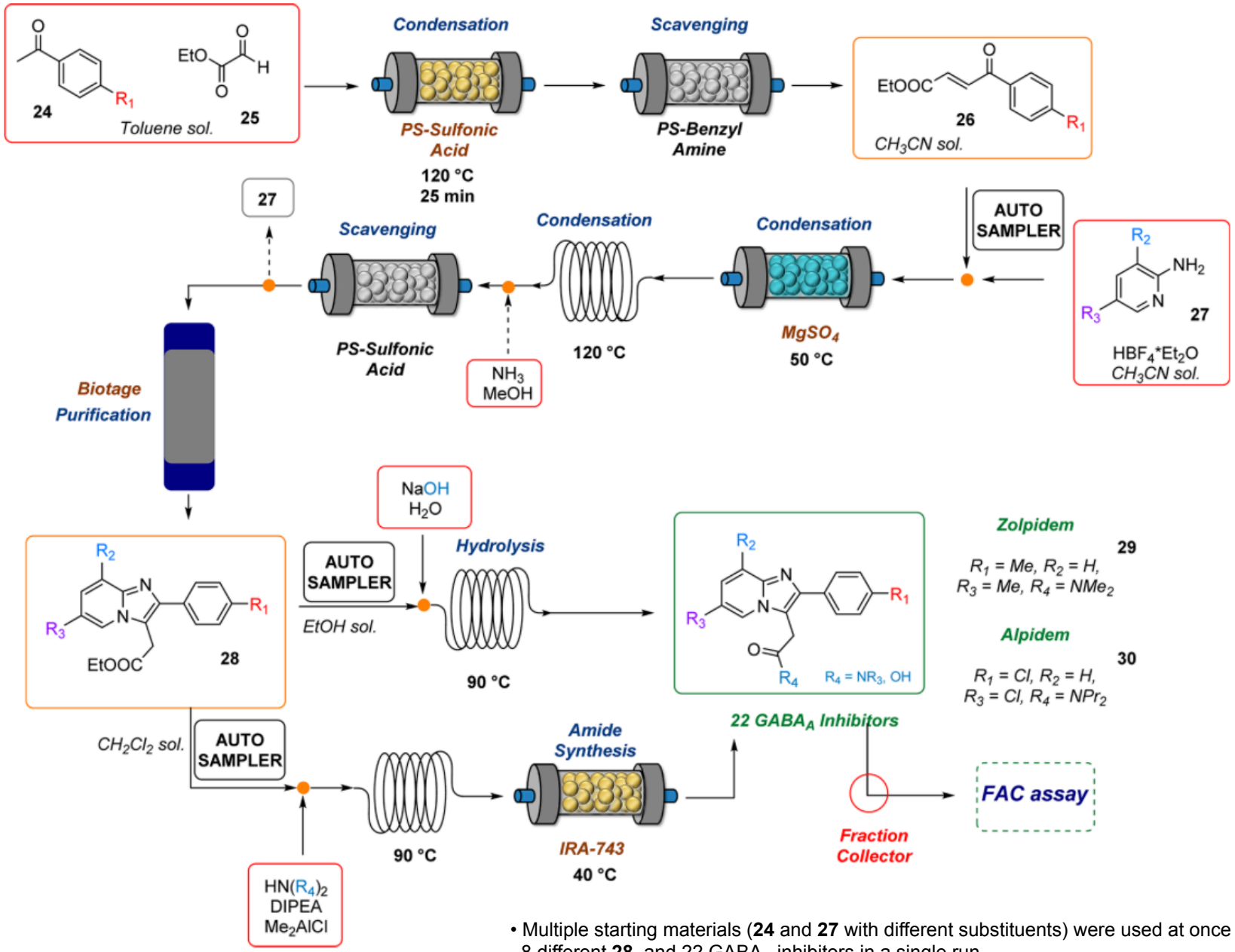
imidazopyridines (GABA$_A$ inhibitors): Ley, *CS*, **2013**, *4*, 764.



- Multiple starting materials (**24** and **27** with different substituents) were used at once to synthesize 8 different **28**, and 22 GABA$_A$ inhibitors in a single run.
- Directly connected to FAC (frontal affinity chromatography) assay as an inline screening device.

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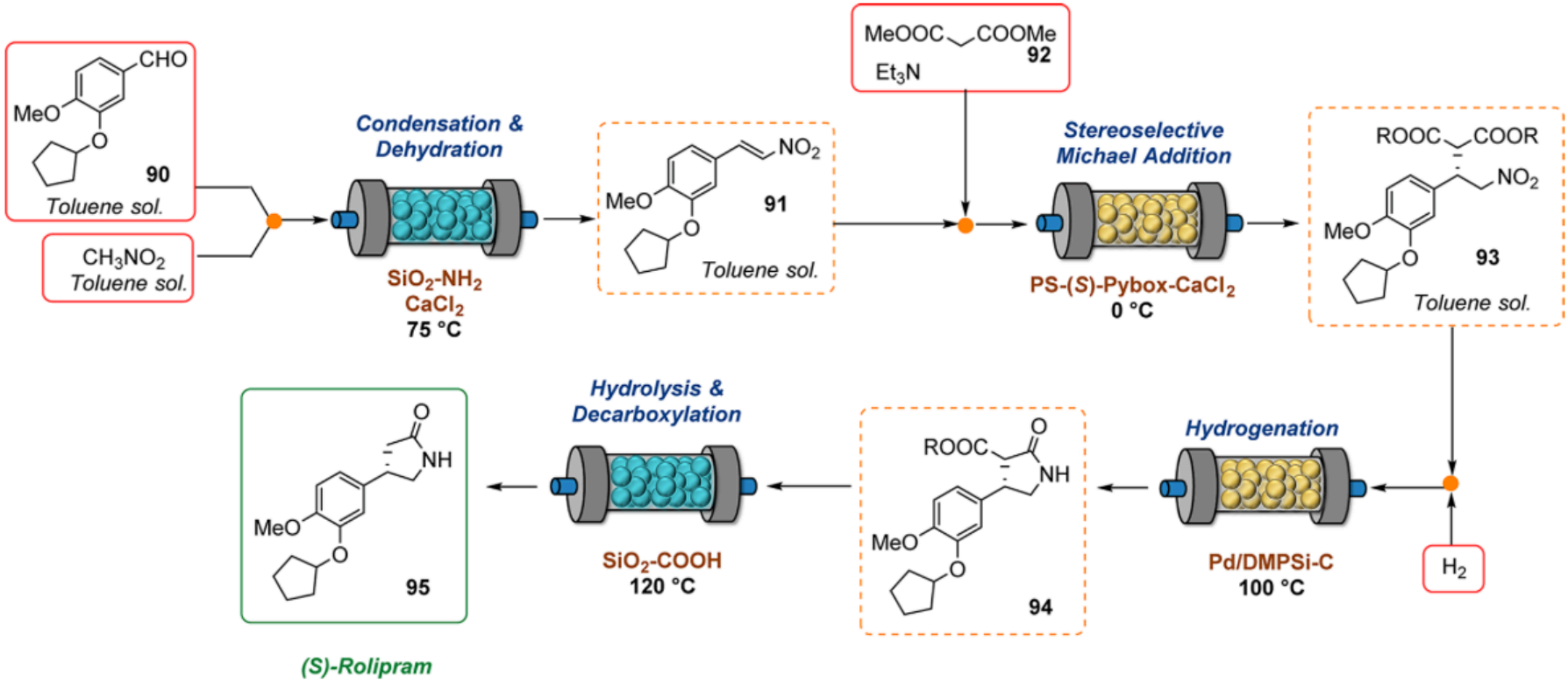
***(S)*-Rolipram**: Kobayashi, *Nature*, **2015**, *520*, 329.



- Type IV reactor used for asymmetric Michael addition, avoiding catalyst separation
- Overall yield 50% from aldehyde SM.
- Flow output: 1g/day, stable for at least one week.