

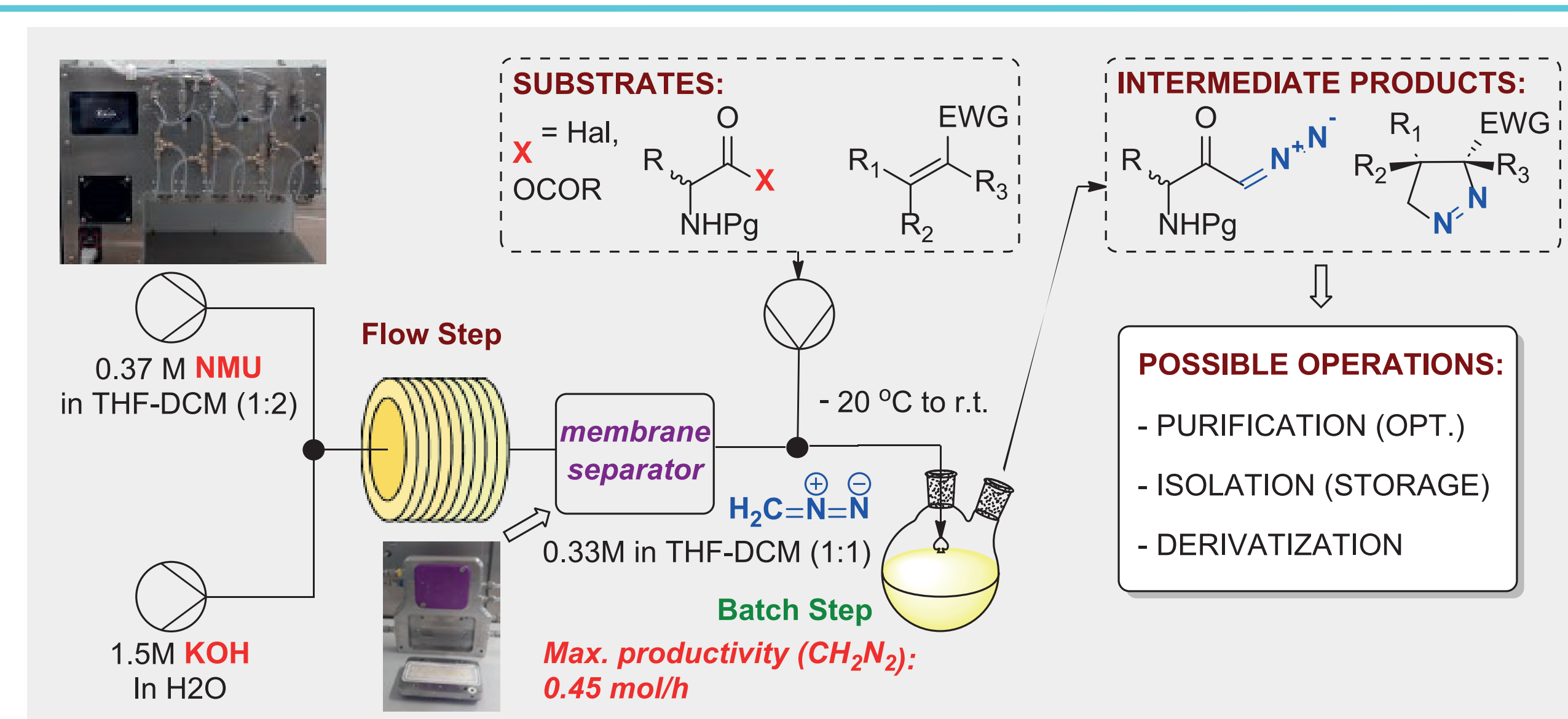
Safe, Multigram Flow Generation of Diazomethane for Organic Synthesis

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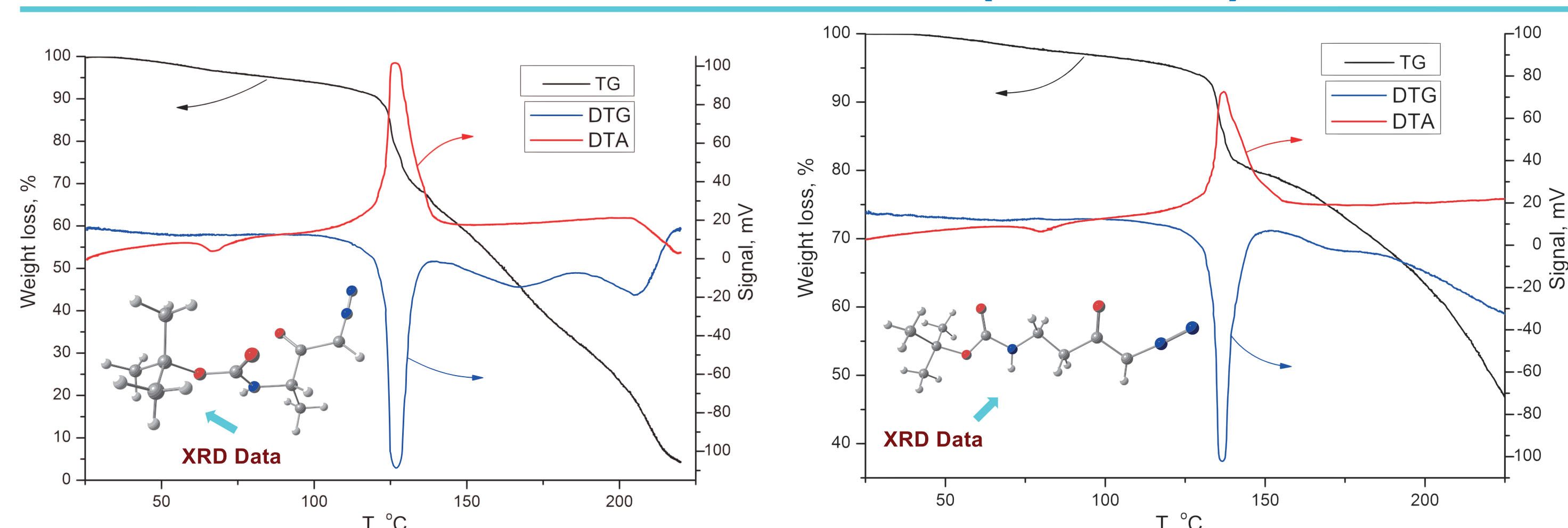
Background of the project

Dry Diazomethane in Flow: Safety, Large Scale, Wide Diversity of Products

- A flow system for generating diazomethane enables the synthesis of MedChem building blocks and intermediates with productivity up to 0.45 mol/h, **scalable to hundreds of grams per operation**.
- Diazoketones**, synthesized using this system, are **valuable, bench-stable reagents¹** on their own, and can be used for **synthesis of 2,4-thiazoles² and pyrazoles**, as well as other cyclization reactions.
- The use of flow photoreactor enables the synthesis of **β -amino acids³, azetidinones, piperidinones, and cyclopropenes**, with the **preservation of chirality** of the starting acids for diazoketones and their derivatives.



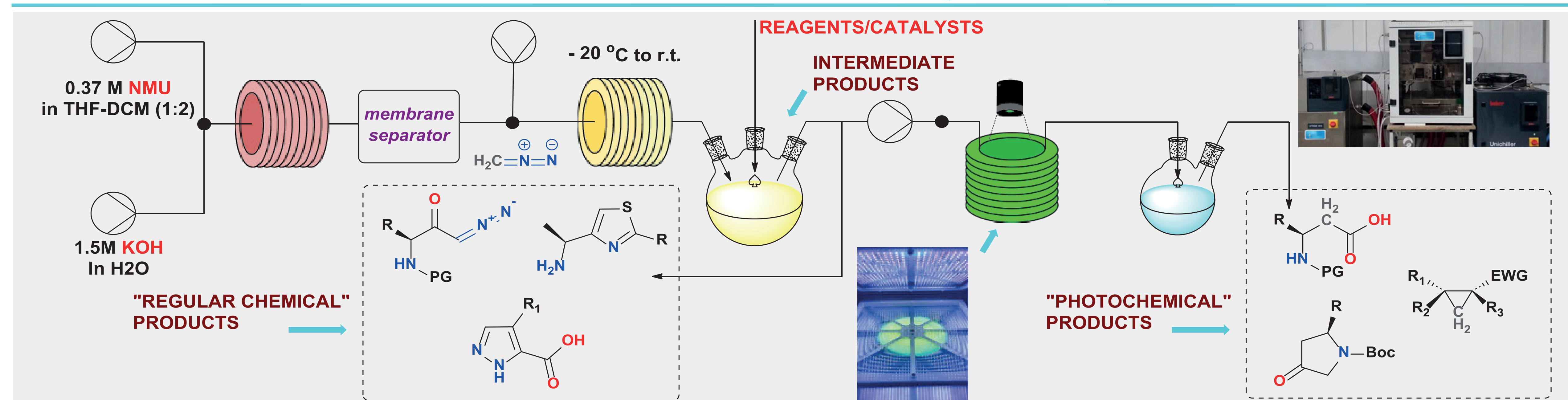
Amino Acid-Derived Diazoketones (AADDKs) Thermal Stability Summary: Safe, Bench Stable



- AADDKs** remain stable after a year at room temperature, showing promise as **bench-stable synthetic equivalents for halogenoketones**.
- TGA** of diazoketones show their decomposition between 110-142 °C, exothermically, indicating **medium thermal risk and reaction hazard indices**.

T(1 st process), °C	137	142
T(2 nd process), °C	160	167
E _A (1 st process), kJ/mol	220	115
T, °C range for EA	140-153	142-160

Flow-Generated Diazomethane in Reaction Cascade: Setup and Scope of the Products



Synthetic results

121 Examples						
AADDKs	89% yield	76% yield	82% yield	85% yield	78% yield	73% yield
64 Examples						
2,4-Thiazoles	90% yield	83% yield, 99/99 ee	84% yield, 99/99 ee	92% yield, 99/99 ee	95% yield	96% yield, 99/99 ee
6 Examples						
1H-pyrazole-5-carboxylic acids	59% yield	86% yield	71% yield	68% yield	48% yield	79% yield
14 Examples						
Cyclopropanes	86% yield	81% yield	86% yield	87% yield	84% yield	78% yield
121 Examples						
Homologated AAs	Boc: 78% yield, 100/100 ee; Fmoc: 65% yield, 99/99 ee	88% yield, 100/100 ee; 76% yield, 99/99 ee	77% yield, 99/99 ee; 69% yield, 99/99 ee	77% yield, 99/99 ee; 70% yield, 99/99 ee	80% yield, 99/99 ee; 77% yield, 99/99 ee	84% yield, 100/100 ee; 80% yield, 100/100 ee

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References

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