

Flow (hetero)aromatic Li-organic generation via H/Li and Br/Li exchange: scope and limitations



Oleksandr Andrushko, Yurii Dmytriv, Vitalina Levchenko, Alexander Pashenko, Serhiy Ryabukhin, Dmytro Volochnyuk

Automated organolithium generation and reactions in flow

Nowadays, rapid advancements are occurring in industrial organolithium processes using flow reactors, but these face significant challenges, e.g., the precipitation of LiBr and its complexes in Br/Li exchange reactions. Our next-generation in-house reactor overcomes this limitation by enabling both hydrocarbon and bromide-based lithium exchanges, thereby facilitating more sustainable development of these important chemical reactions through continuous manufacturing pipelines.

Our integrated lithiation approach:

- Constant development since 2018

Eur. J. Org. Chem., 2019: 3636-3648,
DOI:10.1002/ejoc.201900450

- Successful industrial implementation for the API synthesis

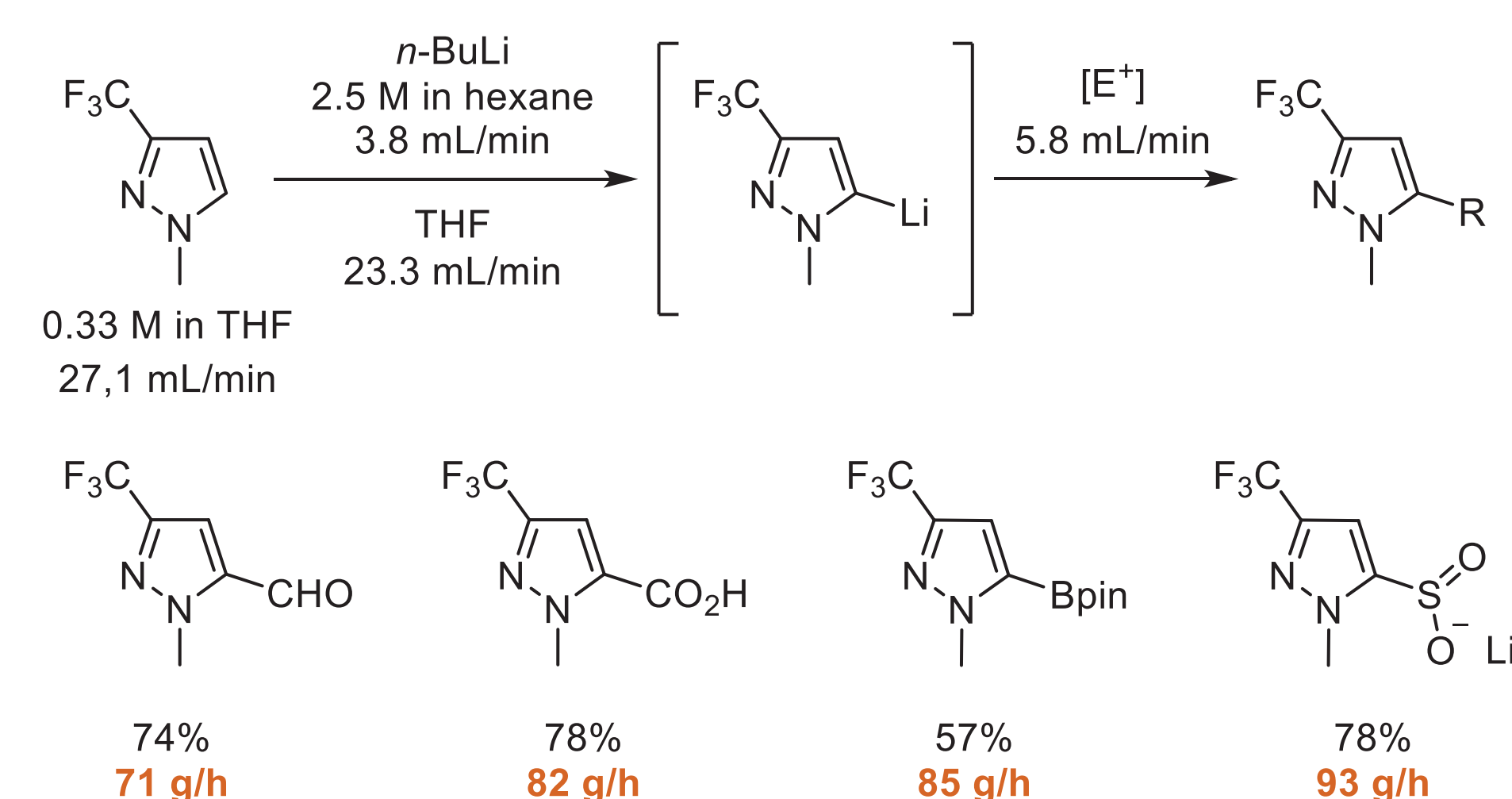
Org. Process Res. Dev. 2020 24 (11), 2619-2632,
DOI:10.1021/acs.oprd.0c00300

Highlight in Synfacts 2021; 17(02): 0141

DOI: 10.1055/s-0040-1719359

- High flow setup automatization with integrated approach from substrate to product
- Wide scope of substrates for both H/Li and Br/Li

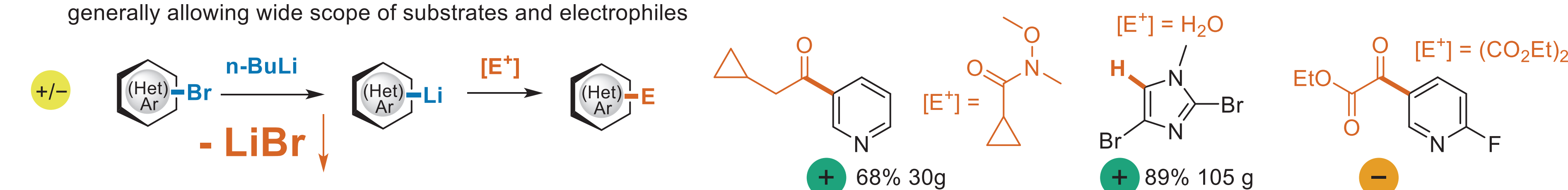
Industrial API synthesis



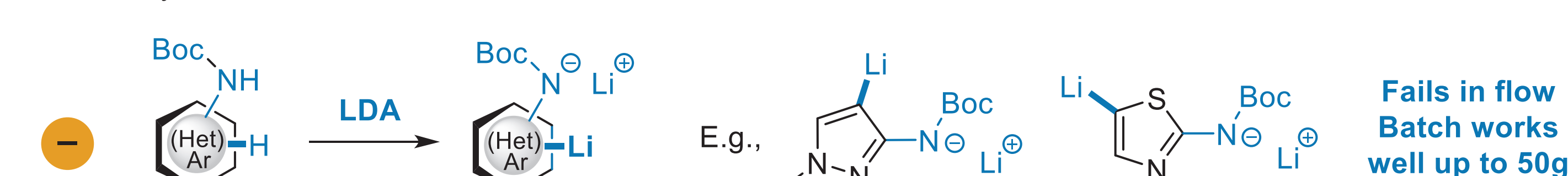
Scope and limitations of lithiation reactions in flow conditions

After testing >1000 substrates :

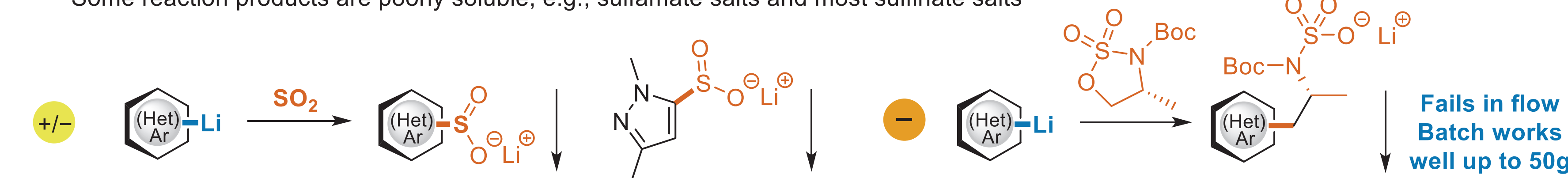
The lithiation can often lead to salt precipitation at low temperatures (-78°C) or worse selectivity at high temperatures ($\geq -50^\circ\text{C}$), while generally allowing wide scope of substrates and electrophiles



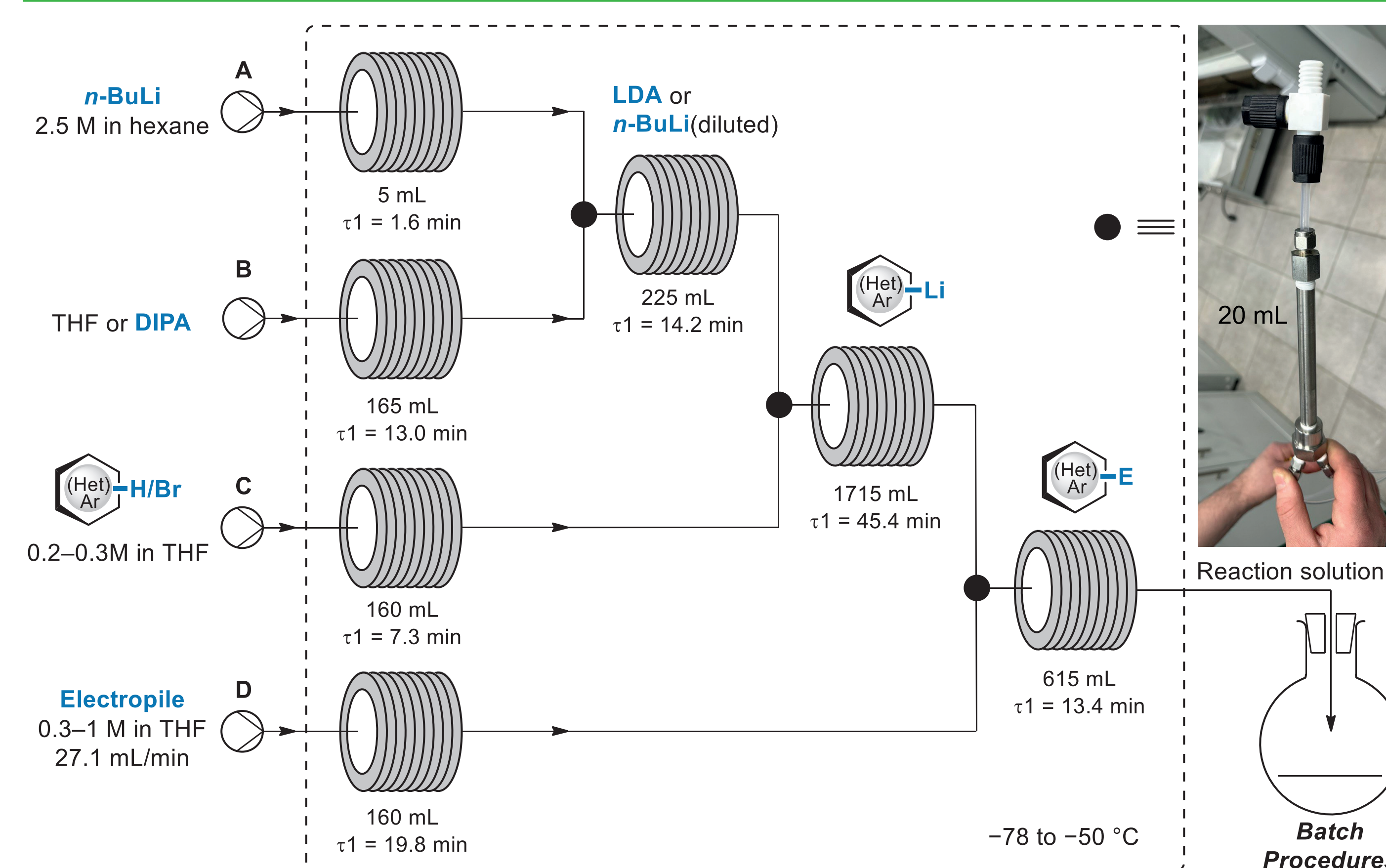
Poorly soluble dilithium salts can form with LDA



Some reaction products are poorly soluble, e.g., sulfamate salts and most sulfonate salts

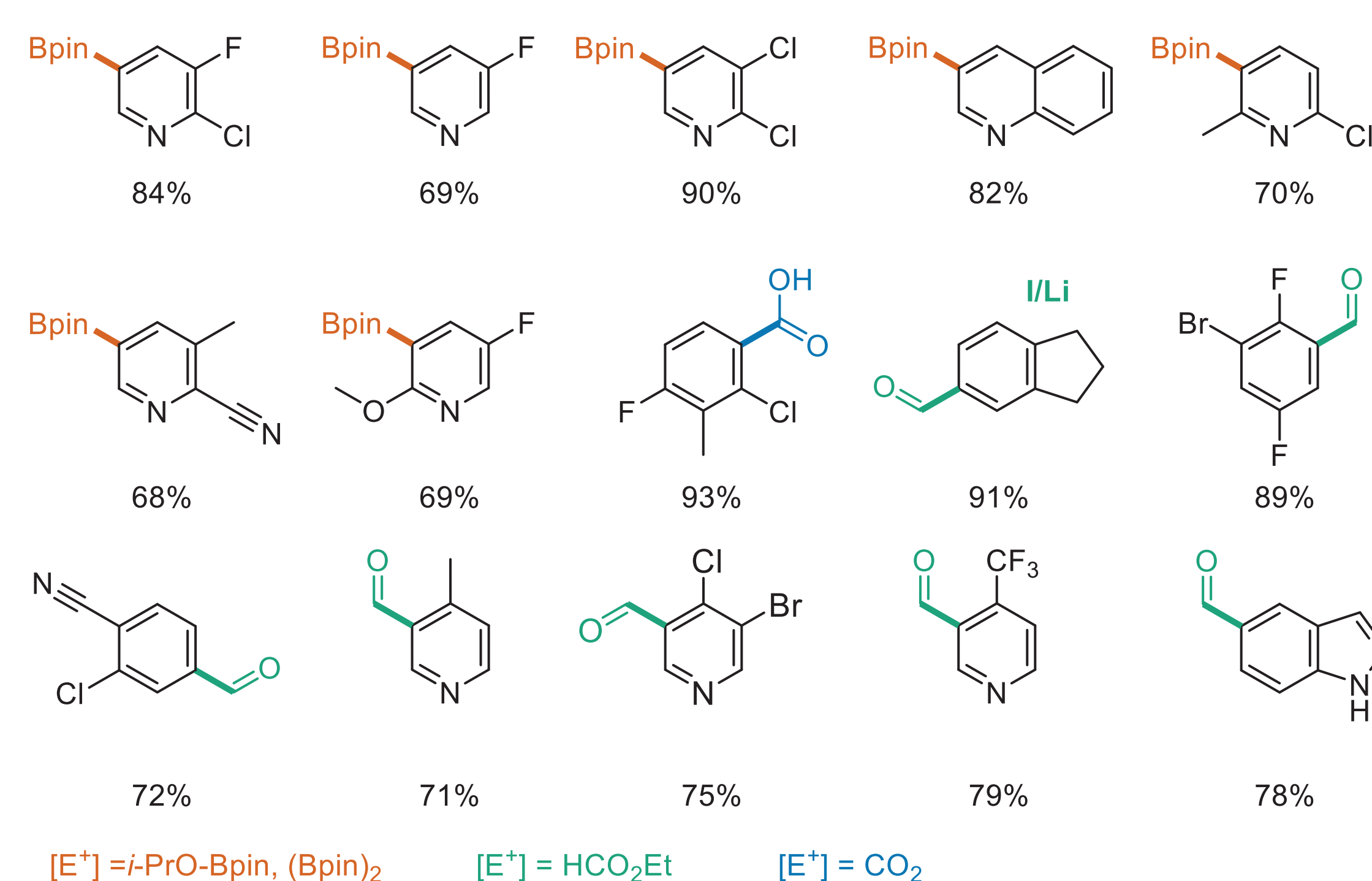


Fourth gen flow setup

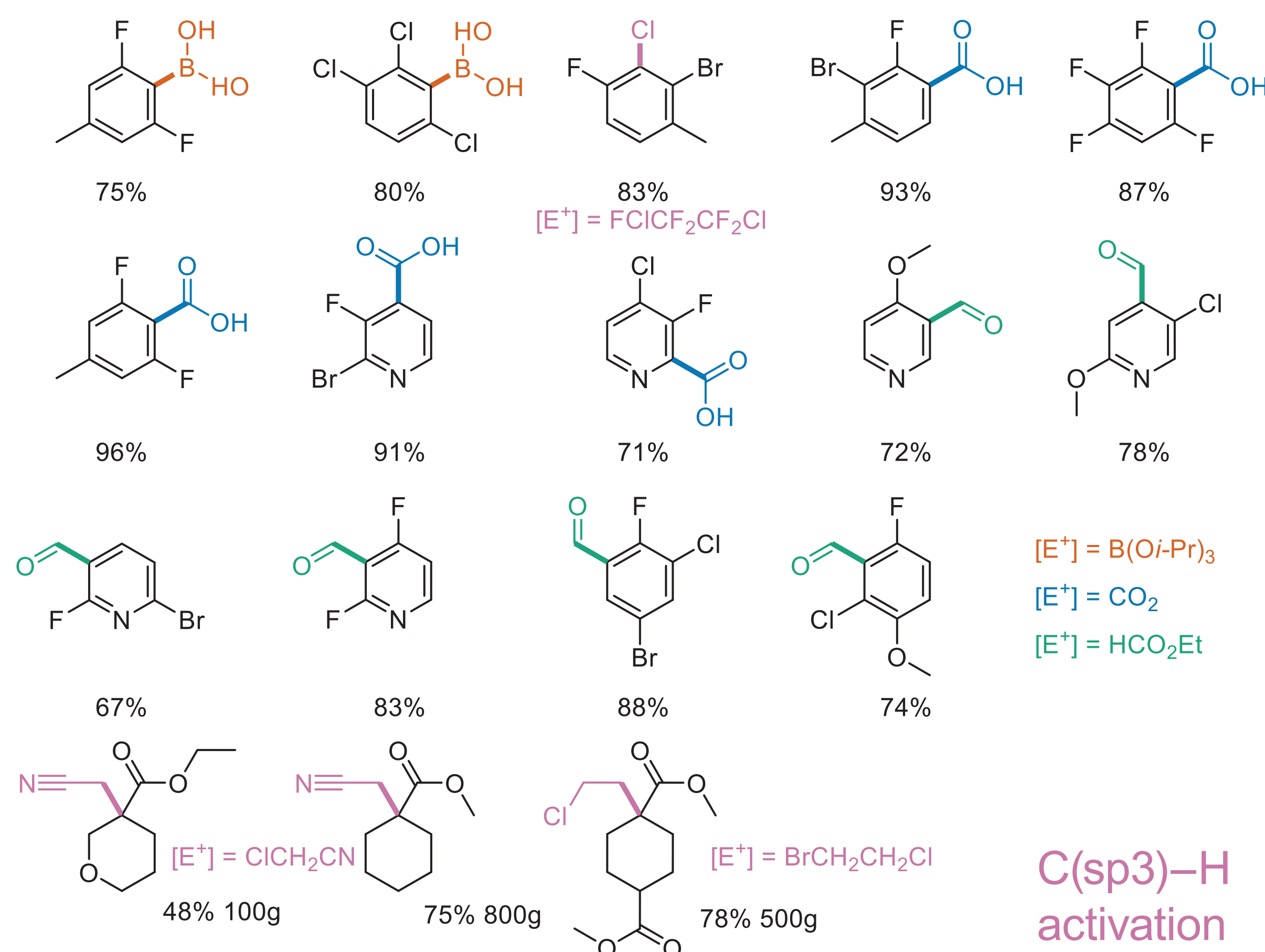


Examples

Br/Li exchange with n-BuLi



H/Li exchange with LDA



All examples are on over 100 g preparative scale

Contact

Serhiy V. Ryabukhin, Prof. Dr. Sci., s.v.ryabukhin@gmail.com
Dmytro M. Volochnyuk, Prof. Dr. Sci., d.volochnyuk@gmail.com