# In-flow organolithium/magnesium/zinc compounds vs batch classical approaches

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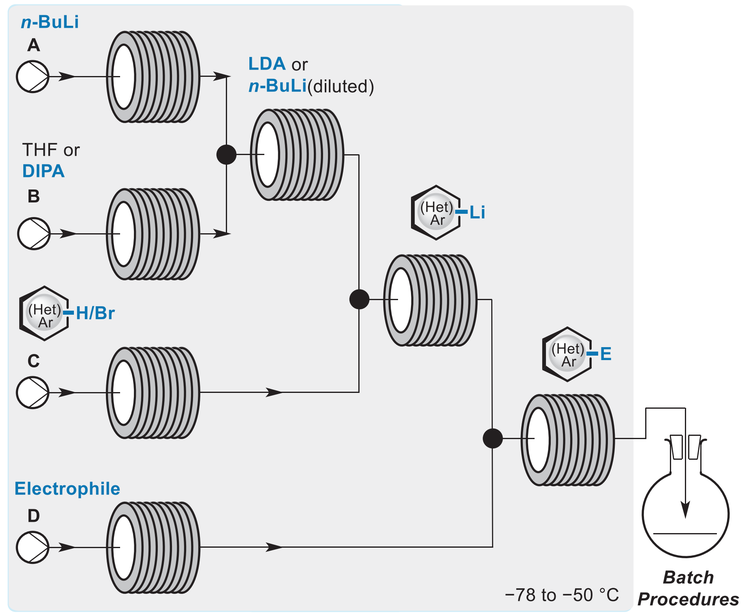
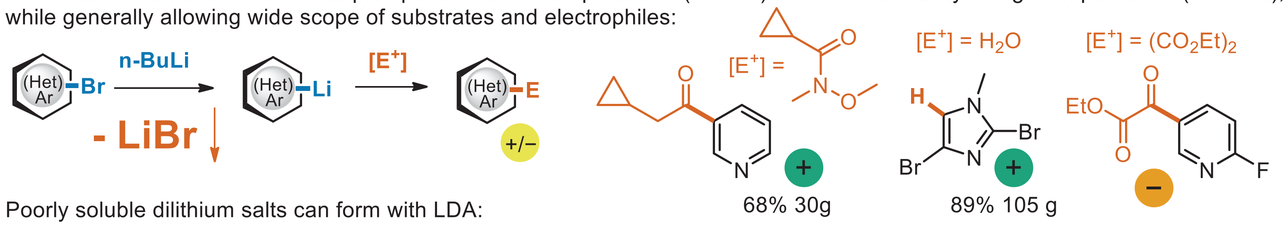
## Gen. 4 lithiation flow reactor



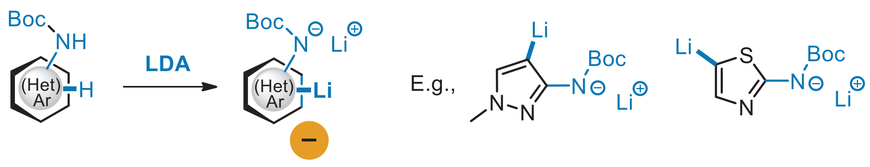

## Scope and limitations of lithiation reactions in flow conditions

### After testing >1000 substrates

The lithiation can often lead to salt precipitation at low temperatures (−78 °C) or worse selectivity at high temperatures (≥−50 °C), while generally allowing wide scope of substrates and electrophiles:

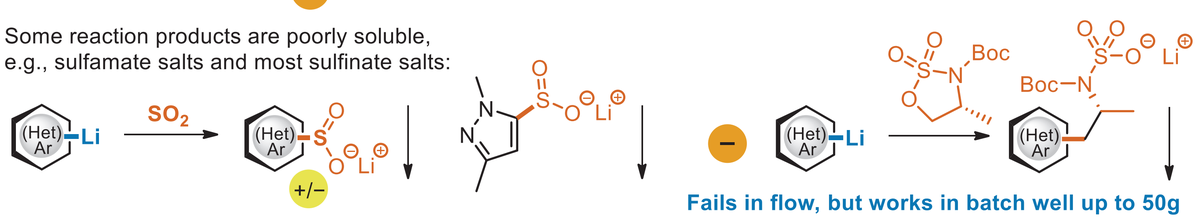



Poorly soluble dilithium salts can form with LDA:



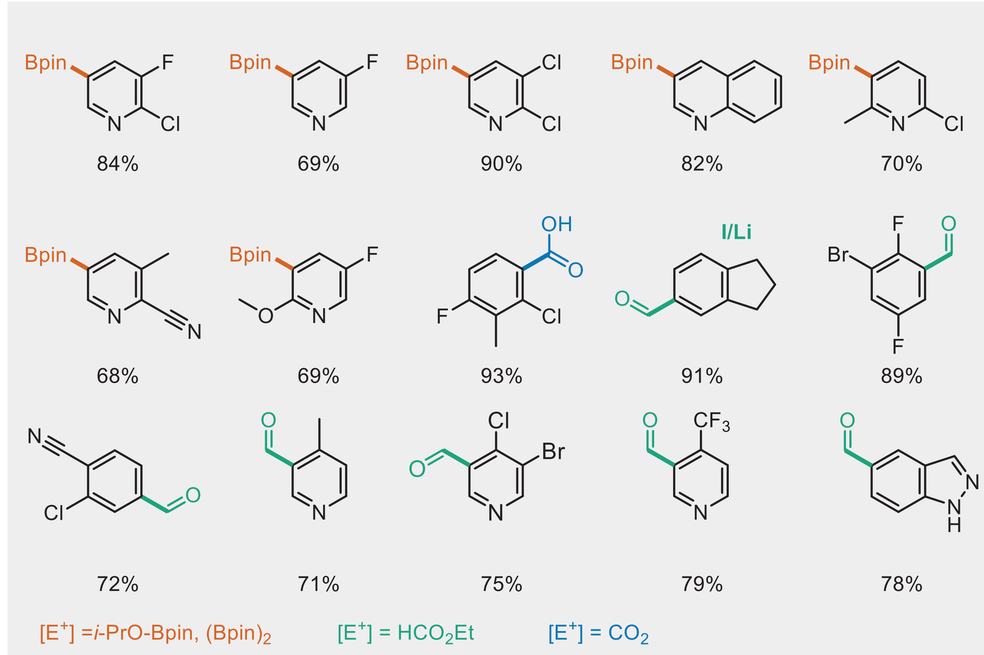

**Fails in flow**
**Batch works well up to 50g**

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

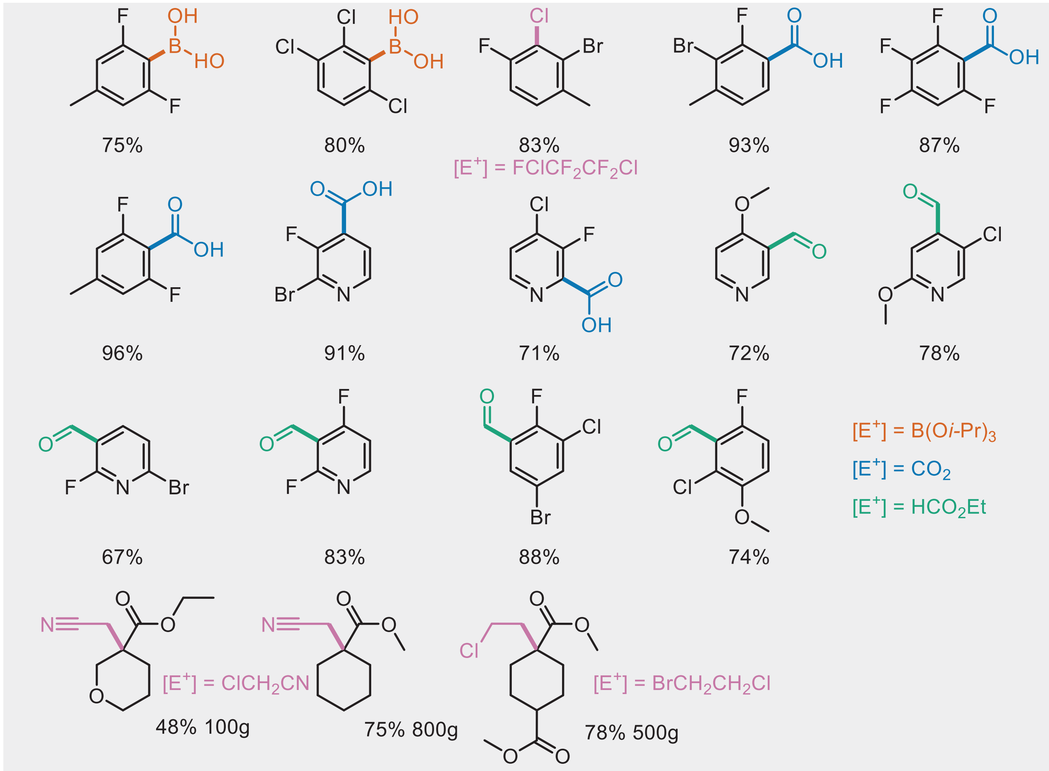



**Fails in flow, but works in batch well up to 50g**

## Examples: Br/Li exchange with n-BuLi



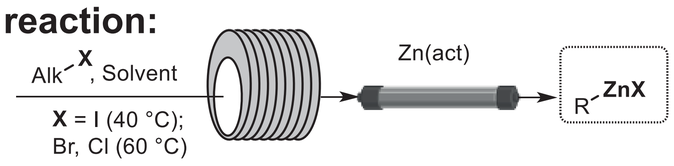

## H/Li exchange with LDA



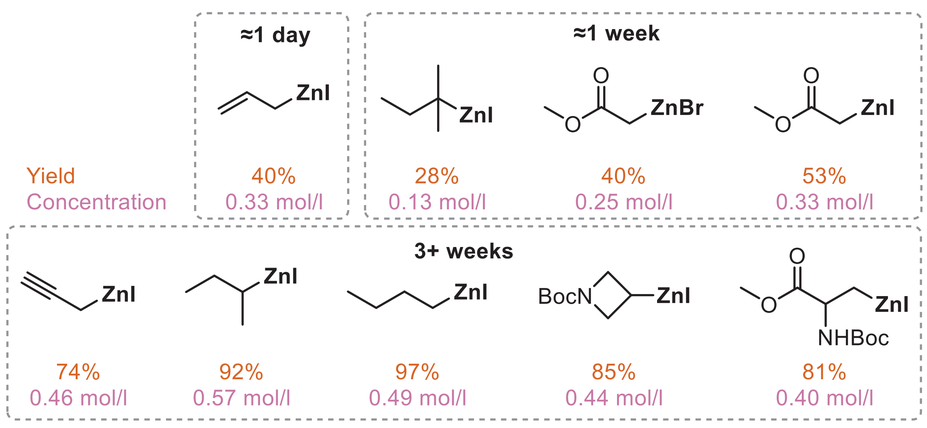

## Zn-organic species generation and their stability

Our flow system using zinc-packed columns can generate up to 8 different organozinc species on demand for immediate use or for storage if further stabilized with lithium salts.

**General reaction:**

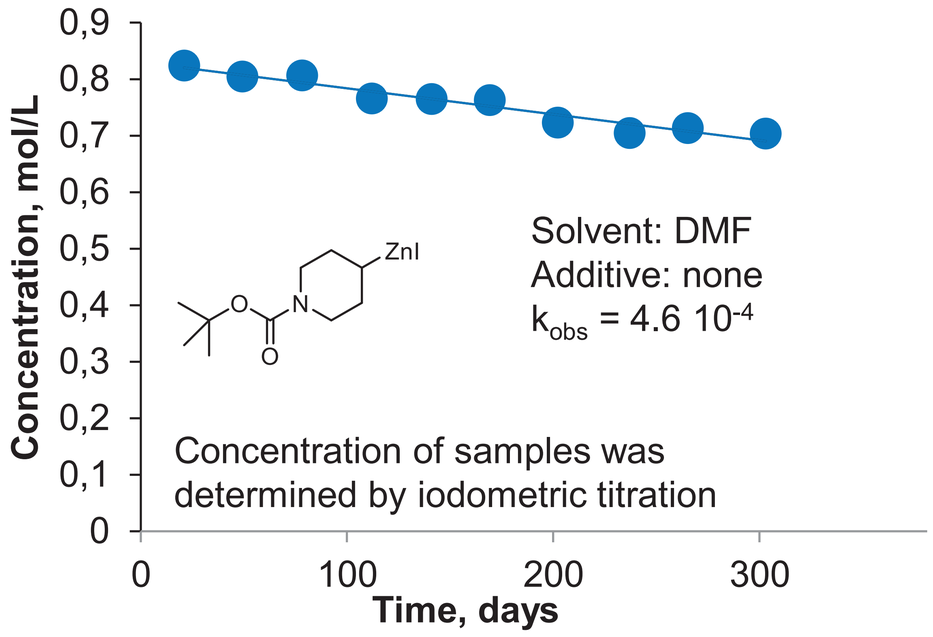


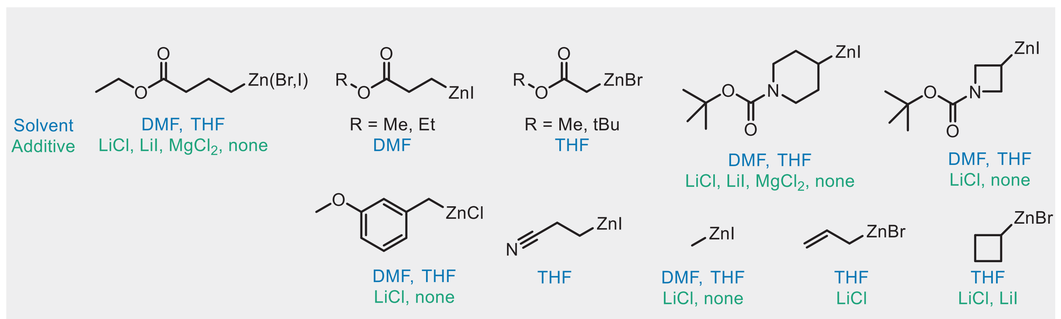

Yields and the bench stability in THF without additives:




- A variety of samples and conditions tested comprising: solvent (THF or DMF) and metal salt additives (LiCl, LiI, MgCl2)
- Difference between DMF and THF solvents is not statistically significant.
- LiCl has a significant stabilizing effect, reducing degradation rates ($p < 0.05$)
- The decomposition constants vary in the range from $1.15\ 10^{-4}$ mol $L^{-1}$ $d^{-1}$ to $12.41 \cdot 10^{-4}$ mol $L^{-1}$ $d^{-1}$
- Stabilized organozinc species can be stored from 6 to 12 months.

Influence of solvent and additives on organozinc stability

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## References

1. *Eur. J. Org. Chem.*, **2019**: 3636-3648, DOI:10.1002/ejoc.201900450
2. *Org. Process Res. Dev.* **2020** *24* (11), 2619-2632, DOI:10.1021/acs.oprd.0c00300