

# In-flow Generation of Diverse Zn-organics for the MedChem Libraries via Parallel Synthesis



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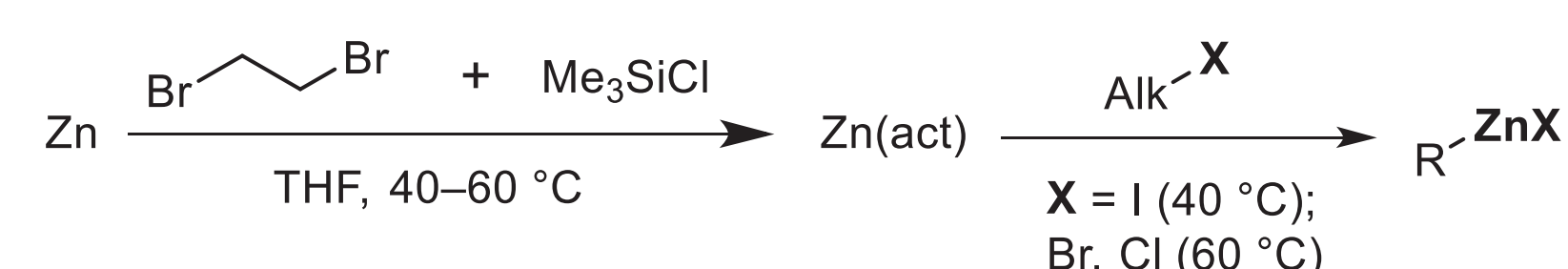
## Automated organolithium generation and reactions in flow

Flow technology is an integral part of modern drug discovery, offering enhanced safety and easy scale-up. However, not all reactions can be successfully adapted to flow processes because of their inherent constraints, particularly the poor solubility of intermediates or final products. Sensitive reagents like organozinc species and reactions involving Zn with poorly soluble intermediates require specialized handling that isn't always feasible or effective in standard flow systems.

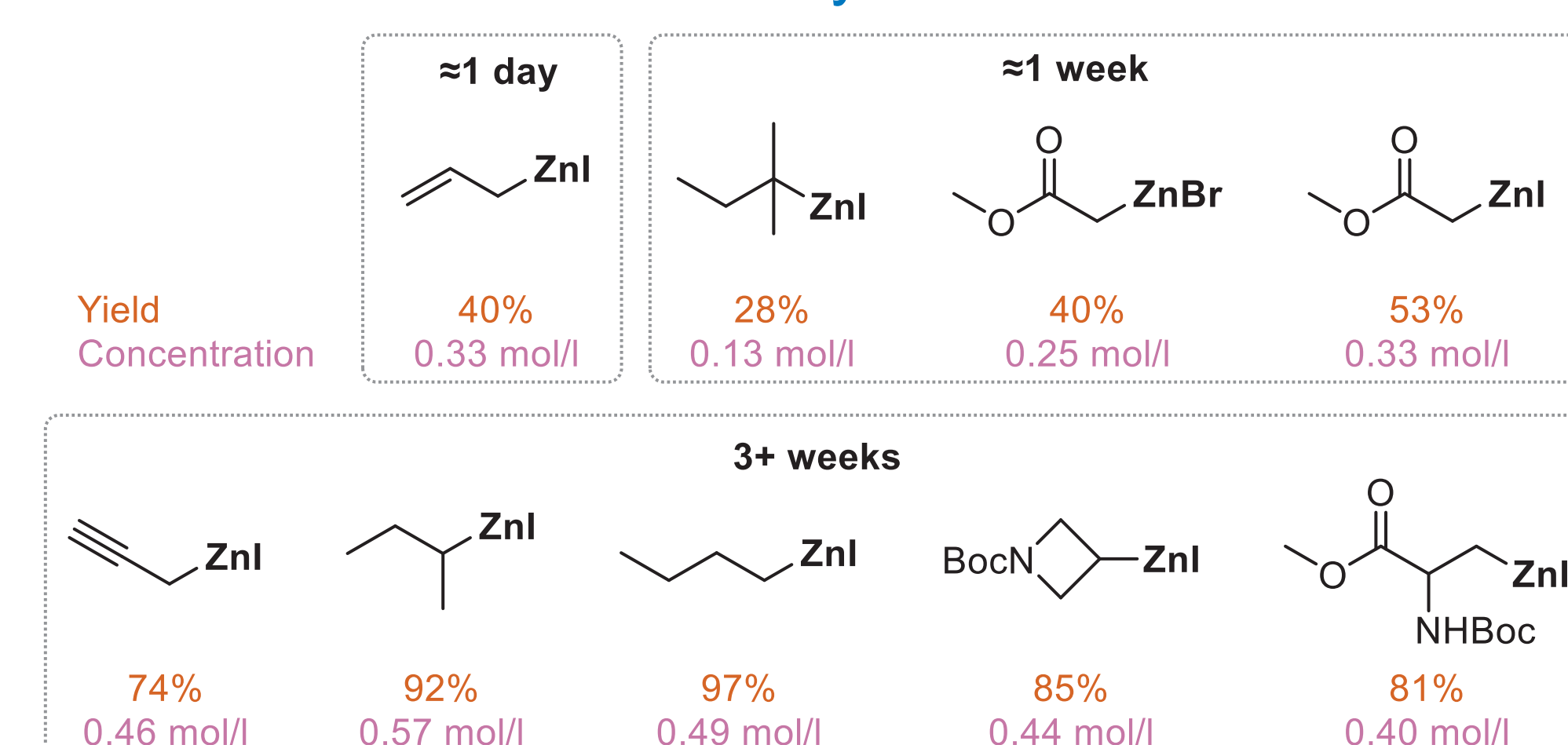
Our flow system using zinc-packed columns can generate up to 8 different organozinc species on demand for immediate use or for storage if further stabilized with lithium salts.

## Zn-organic species generation and their stability

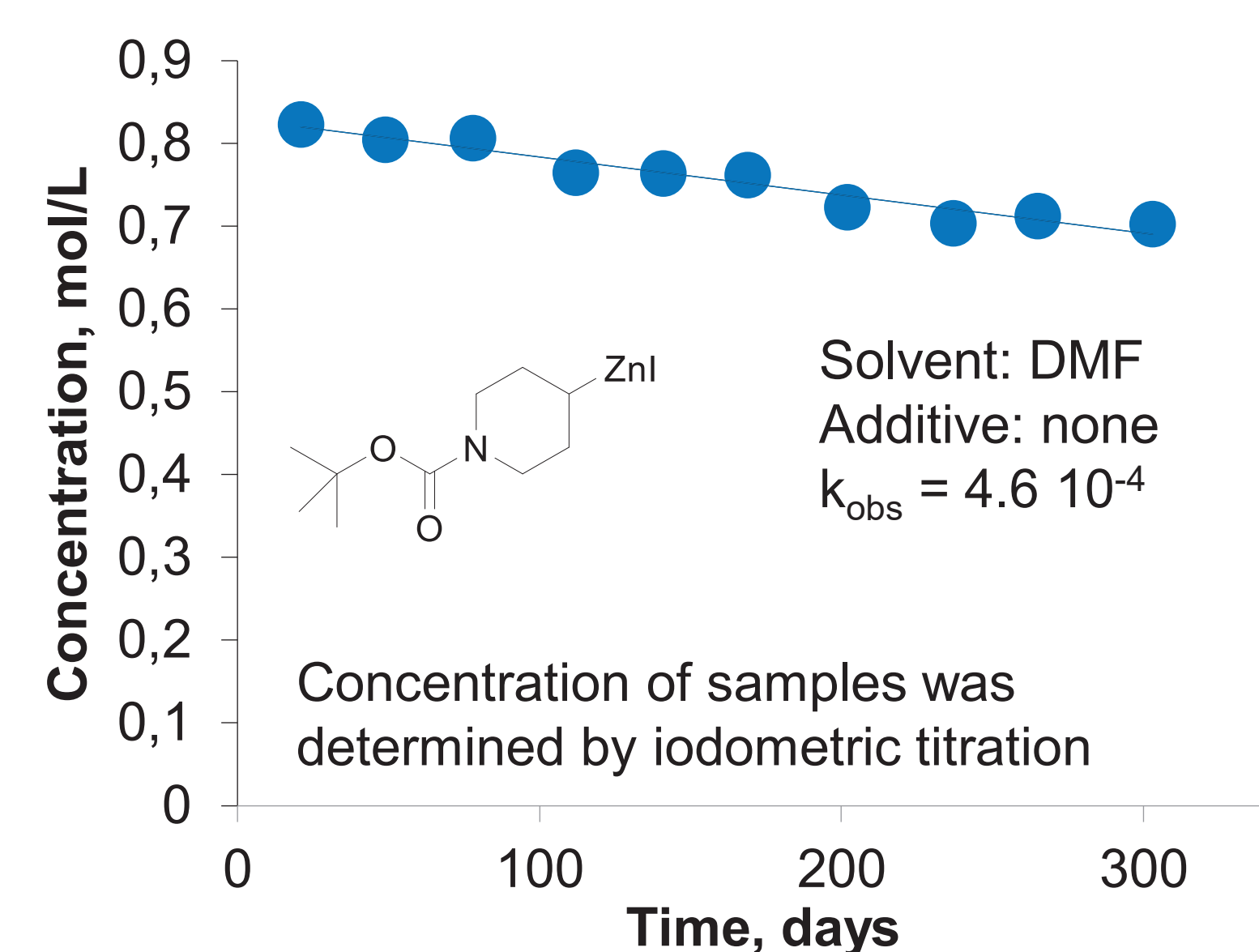
General reaction:



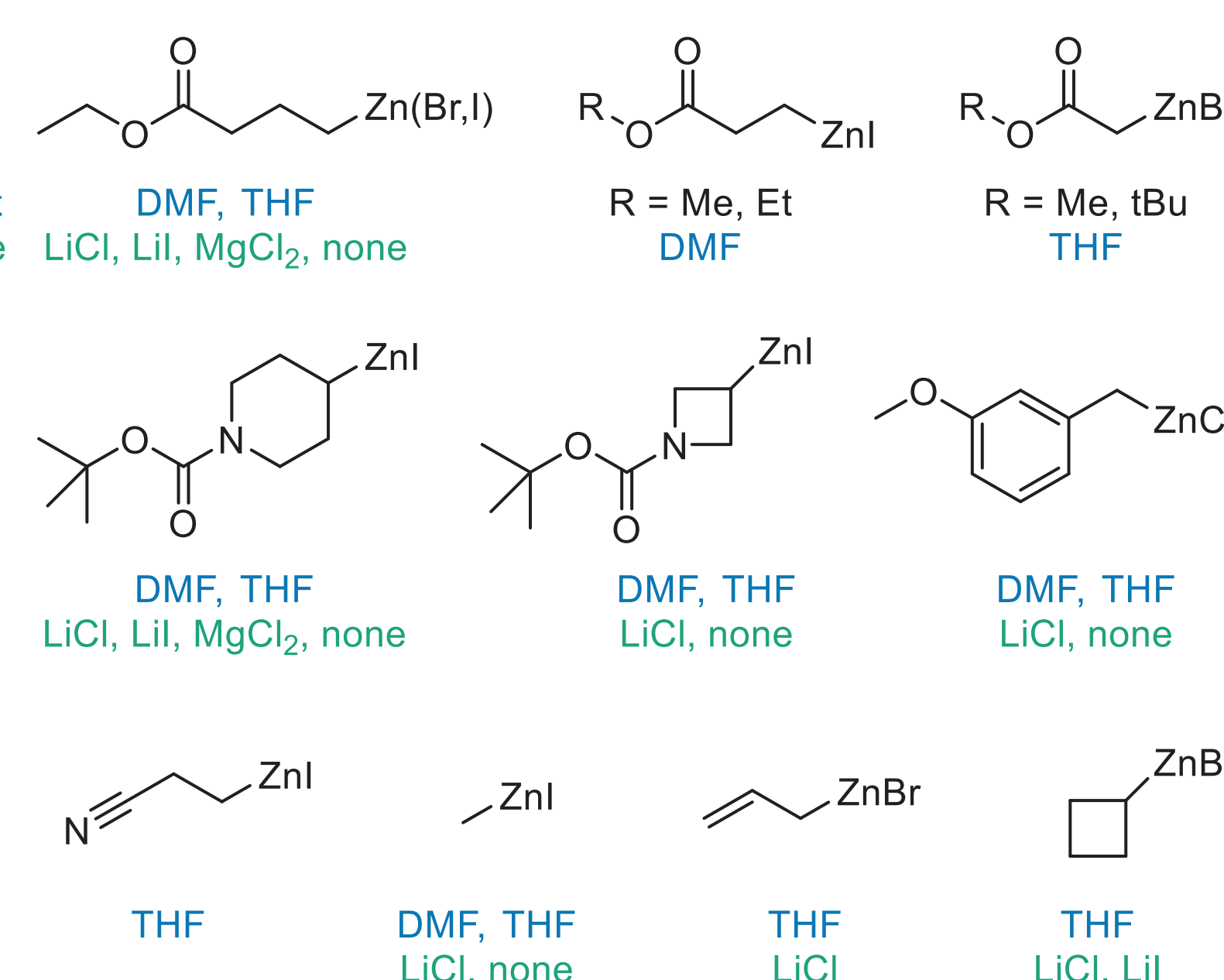
Yields and the bench stability in THF without additives:



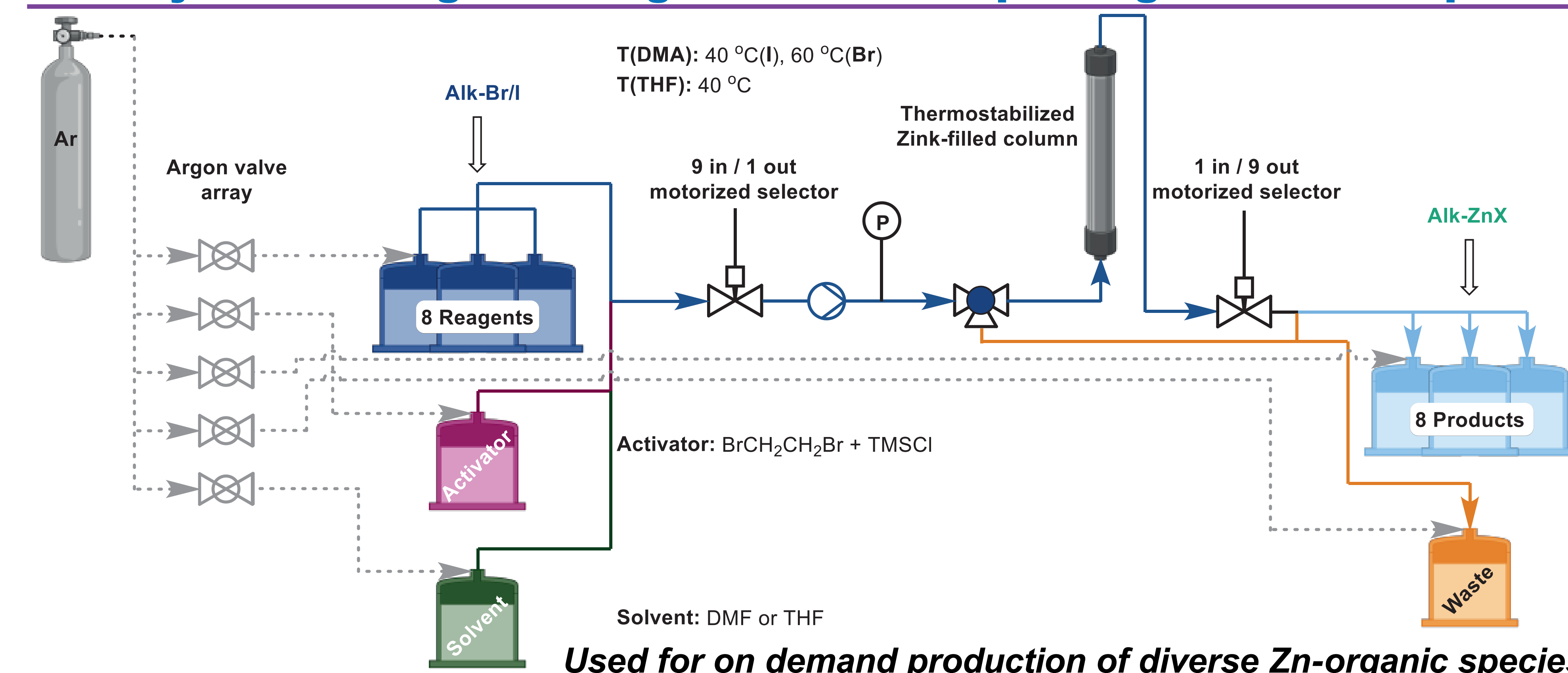
Influence of solvent and additives on organozinc stability



- A variety of samples and conditions tested comprising: solvent (THF or DMF) and metal salt additives (LiCl, LiI, MgCl<sub>2</sub>)
- 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  $1.15 \cdot 10^{-4} \text{ mol L}^{-1} \text{ d}^{-1}$  to  $12,41 \cdot 10^{-4} \text{ mol L}^{-1} \text{ d}^{-1}$
- Stabilized organozinc species can be stored from 6 to 12 months.



## Flow system for organozinc generation for up to eight different species



## Parallel synthesis approach to Negishi cross-coupling of RZnX with HetAr bromides

Reaction scheme: Het-Br + ZnX (1.2 or 2.4 eq.) in DMF or THF with LiCl (1.2 or 0 eq) and catalyst (Pd-PEPPSI-IPent or Pd(dppf)Cl<sub>2</sub>) yields Het-Ar.

Het-Br	UV intensity ratio (product/1,3,5-trimethoxybenzene standard)					
	0.009	0.090	0.071	n.d.	0.174	0.166
	0.007	0.027	0.102	0.054	0.182	0.011
	0.019	0.142	0.254	0.118	0.291	n.d.
	0.058	0.637	1.290	0.515	0.955	0.023
	n.d.	0.512	0.501	0.197	1.268	0.065
	n.d.	n.d.	n.d.	0.163	n.d.	0.839
	n.d.	n.d.	n.d.	n.d.	n.d.	0.150
	n.d.	n.d.	n.d.	0.032	n.d.	0.000
Solvent	THF	DMF	THF-Rieke	THF/LiCl	DMF/LiCl	DMF
Catalyst	Pd-PEPPSI-IPent			Pd(dppf)Cl <sub>2</sub>		

In general, use of DMF as a solvent and LiCl as an additive leads to higher yields of cross-coupling products

## Contact

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