# Organozinc Compounds in N,N-Dimethylformamide: Stability Towards Degradation And Reactivity in Negishi Cross-Coupling Reactions



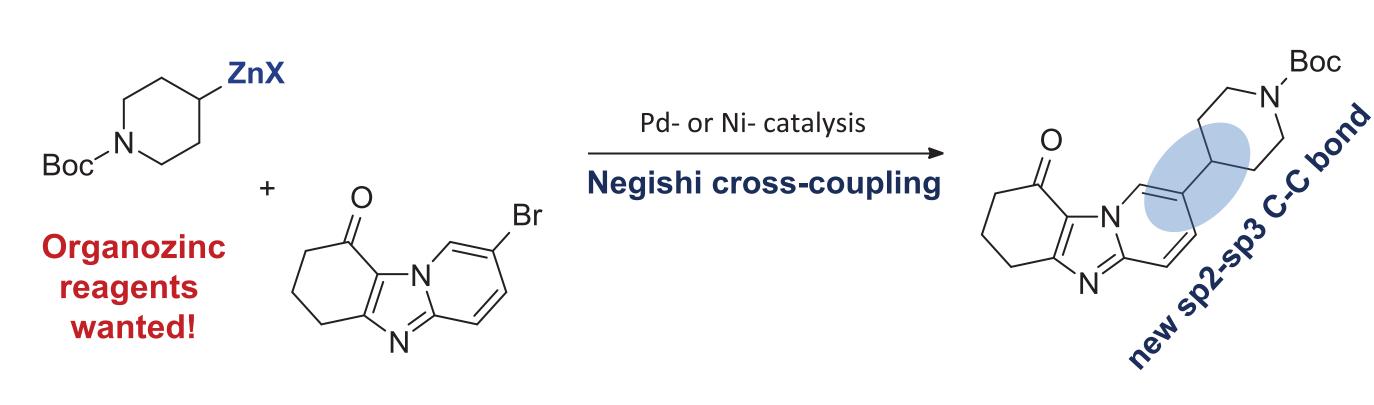




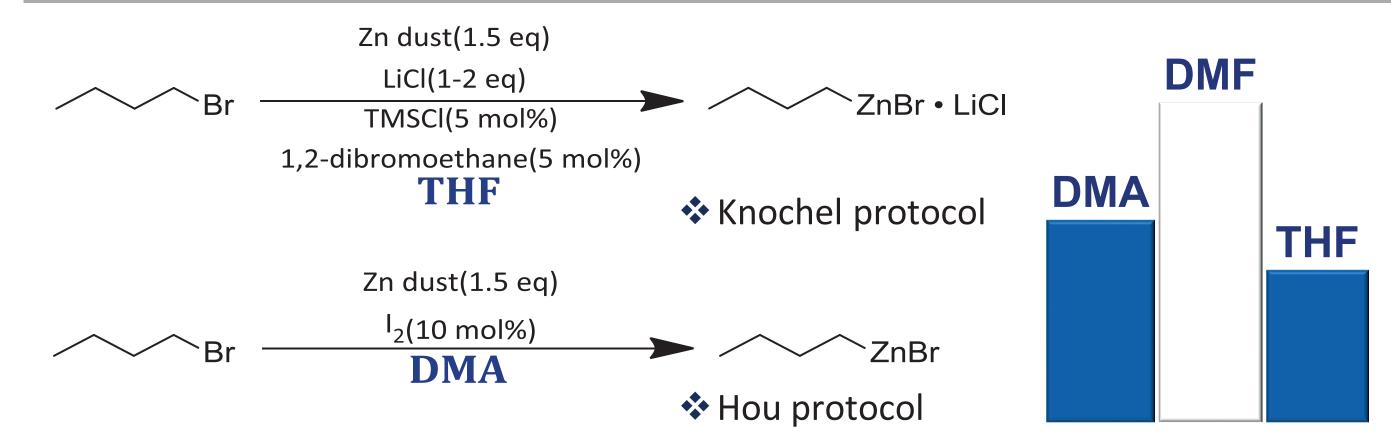


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### **Background & Overview of the Project**



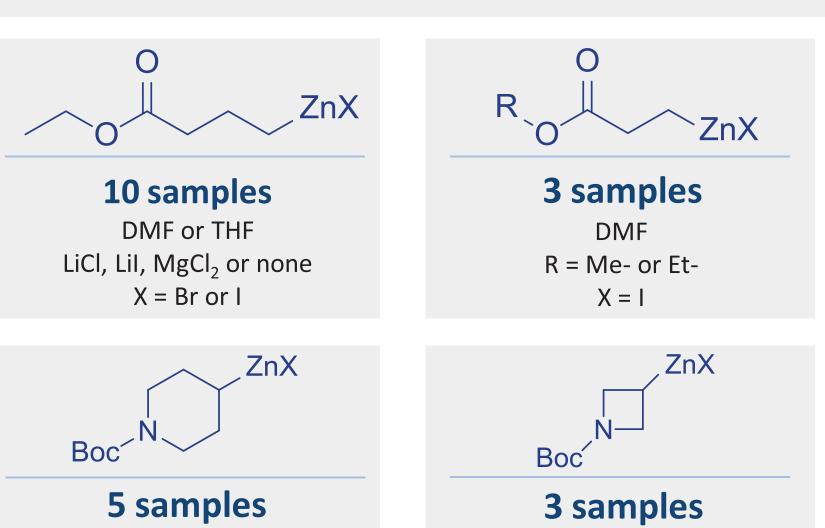
- Negishi cross-coupling reaction is an efficient tool for creating new sp2-sp3 carbon-carbon bonds in the synthesis of MedChem libraries
- Lack of commercially available stock solutions of organozinc compounds hinders the implementation of Negishi cross-coupling in HTE screening

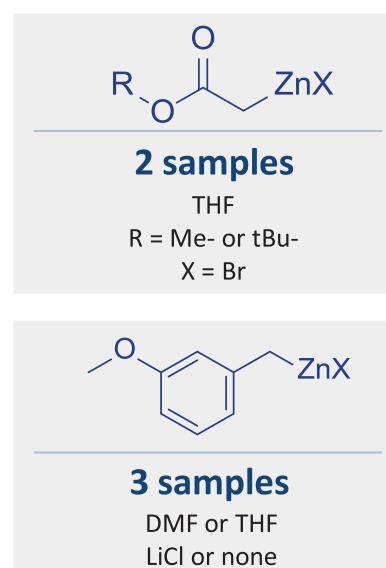


- High solubility of polar organic compounds in DMF
- Polar solvents are known to accelerate the rate of Negishi reaction
- DMF is often neglected as a solvent for the storage and use of organometallic compounds

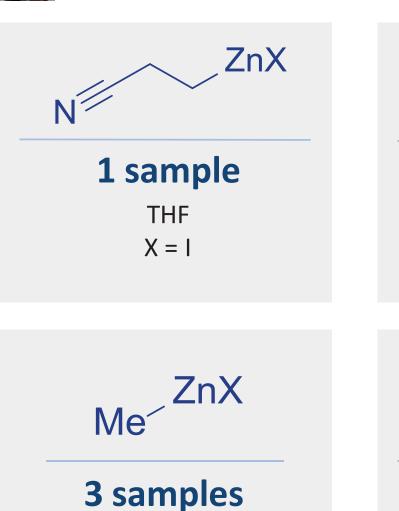
# THIS WORK Zn dust(1.5 eq) LiCl, LiBr, Lil (1-2 eq) or no additive TMSCI (5 mol%) 1,2-dibromoethane (5 mol%) DMF

- Stable stock solutions of organozinc compounds in DMF were prepared up to 4 mol scale
- Samples of various organozinc compounds in THF and DMF were prepared to check their stability over time





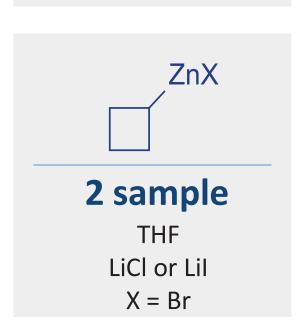
X = CI



DMF or THF

LiCl or none

X = I

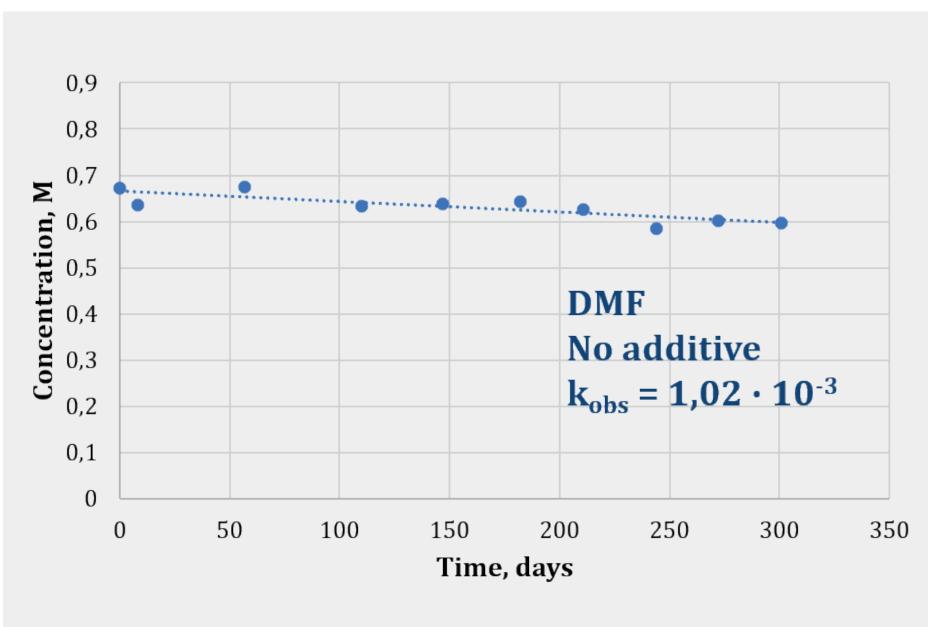


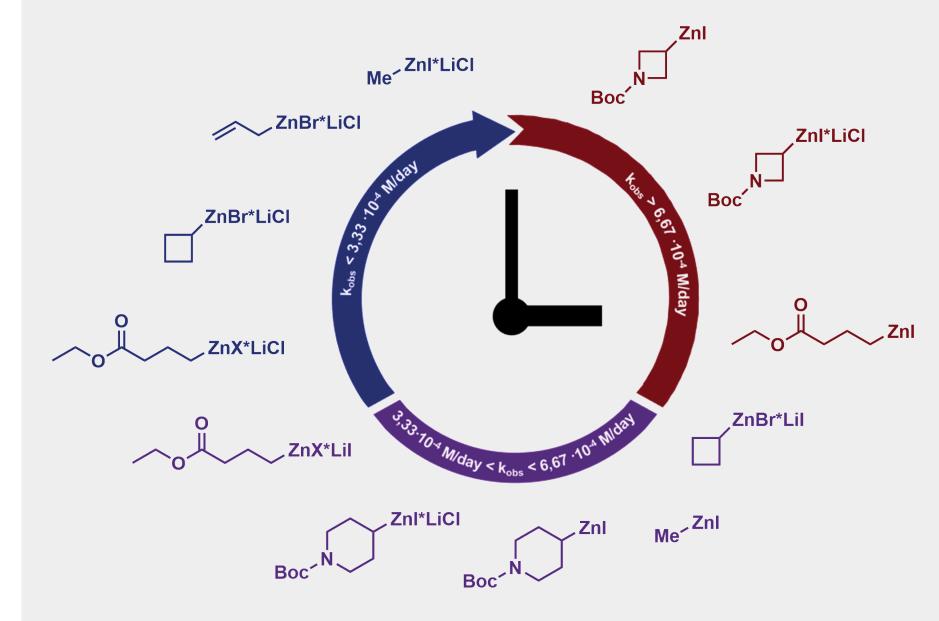
1 sample

LiCl

X = Br

## Stability of organozinc compounds towards decomposition



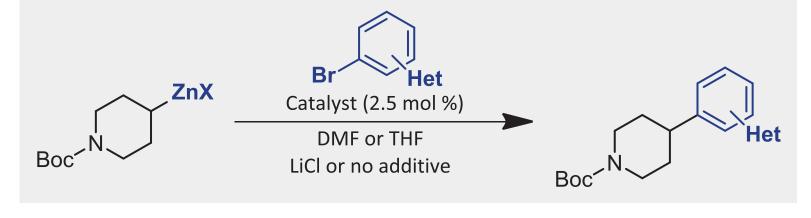






- The concentration of organozinc reagent samples was measured by iodometry for a period of up to 10 months
- The concentration of organozinc reagents decreased linearly with kobs varying from 1.2·10-3 to 12.4·10-3 day-1
- All samples of organozinc compounds can be efficiently used for a period from 6 to 12 months as a reagent for a Negishi cross-coupling
- The choice between DMF and THF as a solvent does not have a significant impact on the stability of organozinc reagents towards decomposition

# Reactivity of organozinc compounds in Negishi cross-coupling reaction



- Samples of N-Boc piperidine zinc halide, varied in solvent (DMF or THF) and additive (with or without LiCI) used, were tested in cross-coupling reaction with heteroaryl halides
- Solutions of organozinc compounds in DMF in the presence of LiCl generally show higher reactivity in the Negishi cross-coupling reaction

	THF Pd-PEPPSI-IPent No additive	DMF Pd-PEPPSI-IPent No additive	THF Pd-PEPPSI-IPent LiCl	DMF Pd-PEPPSI-IPent LiCl	DMF Pd(dppf)Cl <sub>2</sub> No additive
N Br	61%	75%	61%	82%	85%
Br	60%	61%	62%	80%	53%
Br Cl-NH+	86%	91%	91%	100%	79%
Br	15%	94%	66%	100%	3%
Br	21%	2%	14%	0%	80%
Br	25%	0%	17%	5%	17%
Br	13%	0%	21%	12%	27%

### Contact

DMF or THF

LiCl, Lil, MgCl<sub>2</sub> or none

DMF or THF

LiCl or none

X = I