Functionalization of N-Heterocycles using Li, Mg and Zn Organometallics

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Transition metal catalyzed cross-couplings and aminations are important tools for the pharmaceutical and agrochemical industries, especially heterocyclic organozinc and –magnesium reagents have proven their utility for these applications. Herein, we will first describe the most important methods for preparing polyfunctional organozinc and organomagnesium reagents and describe their use for performing cobalt-catalyzed cross-couplings and aminations.

- Preparation of Zn, Mg organometallics

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\begin{align*}
\text{Ar-X} & \xrightarrow{\text{Mg, LiCl, ZnCl}_2} \text{Ar}_2\text{ZnCl} \\
\text{Ar-H} & \xrightarrow{\text{TMPZnCl}} \text{ArZnX}
\end{align*}
\]

- Diastereoselective cross-couplings

\[
\begin{align*}
\text{R}^1 & \xrightarrow{\text{CoCl}_2(\text{L})\text{C}, \text{cat. ligand}} \text{THF, 0°C} \xrightarrow{\text{54-85% yield, dr up to 99:1}} \text{R}^2
\end{align*}
\]

- New electrophilic aminations

1) CN (5.0 equiv) MeOH, 55°C, 12 h
2) mCPBA (1.1 equiv) DCM, -78°C to 25°C, 12 h
3) BzCl, NEt$_3$, DMAP DCM, 25°C, 30 min

\[
\begin{align*}
\text{anabasine} & \xrightarrow{1) \text{CN (5.0 equiv) MeOH, 55°C, 12 h}} \text{O} \xrightarrow{2) \text{mCPBA (1.1 equiv) DCM, -78°C to 25°C, 12 h}} \text{O} \xrightarrow{3) \text{BzCl, NEt}_3, \text{DMP DCM, 25°C, 30 min}} \text{O}
\end{align*}
\]

- C-H Activations of N-arylazoles

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\begin{align*}
\text{N} & \xrightarrow{\text{TMPMgBu(1.0 equiv)}} \text{N} \xrightarrow{\text{ZnCl}_2(1.2 \text{ equiv})} \text{N}
\end{align*}
\]

References: