Copper-Catalyzed Cross-Coupling of Nonactivated Secondary Alkyl Halides and Tosylates with Secondary Alkyl Grignard Reagents

Cu-Catalyzed Coupling of Secondary Alkyl Electrophiles and Alkyl Grignards

**Significance:** A novel method for the cross-coupling of nonactivated secondary alkyl halides and pseudo halides with secondary Grignard reagents with a copper catalyst is described. The addition of TMEDA and LiOMe was found to be crucial for the success of the reaction. A broad range of functional groups including esters, amides and aryl halides, is tolerated under the reaction conditions.

**Comment:** Interestingly, the reaction proceeds according to a classical SN2 mechanism with inversion of configuration. Therefore, easily accessible chiral secondary alcohols can be converted into chiral tosylates and alkylated with a copper-catalyst with either primary or secondary alkyl Grignard reagents to furnish the products in high enantiomeric excess.

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\begin{align*}
\text{Alk}^1 \text{X} + \text{Alk}^3 \text{MgBr} & \rightarrow \text{CuI (10 mol%)} \\
& \text{TMEDA (20 mol%)} \\
& \text{LiOMe (1 equiv)} \\
& 0 \degree C, 24 \text{ h} \\
\text{Alk}^1 \text{Alk}^2 \text{Alk}^3 & \rightarrow \text{Alk}^1 \text{Alk}^2 (2 \text{ equiv}) \\
\text{X = OTs, Cl, Br, I} \\
\text{Alk}^1 & = \text{various substituted alkyl groups} \\
\text{Alk}^2 & = \text{linear and branched aliphatic chains} \\
\text{Alk}^3/4 & = \text{cyclic and linear aliphatics}
\end{align*}
\]

**Selected examples:**

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\begin{align*}
\text{Cy} & \quad 81\% \text{ yield} \\
\text{X = OTs} & \\
\text{Cy} & \quad 74\% \text{ yield} \\
\text{Br} & \quad 64\% \text{ yield} \\
\text{X = Br} & \\
\text{Cy} & \quad 89\% \text{ yield} \\
\text{Br} & \quad 70\% \text{ yield} \\
\text{X = OTs} & \\
\text{Cy} & \quad 67\% \text{ yield} \\
\text{OTs} & \quad 98\% \text{ ee} \\
\text{X = OTs} & \\
\text{Cy} & \quad 99\% \text{ ee} \\
\text{OTs} & \quad 99\% \text{ ee} \\
\text{X = OTs} &
\end{align*}
\]