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.

Selected examples:

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\begin{align*}
&\text{Cy} & \text{81% yield} & X = \text{OTs} \\
&\text{BuOOC} & \text{74% yield} & X = \text{Br} \\
&\text{Hex} & \text{64% yield} & X = \text{Br}
\end{align*}
\]

\[
\begin{align*}
&\text{Cy} & \text{99% ee} & X = \text{OTs} \\
&\text{Br} & \text{67% yield} & X = \text{OTs}
\end{align*}
\]