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 $S_N^2$ 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{Cu(I)} (10 \text{ mol\%}) \\
& \text{TMEDA} (20 \text{ mol\%}) \\
& \text{LiOMe (1 equiv)} \\
& 0 \degree C, 24 \text{ h} \\
\end{align*}
\]

\[
\begin{align*}
\text{Alk}^1 \text{Alk}^2 & \rightarrow \text{Alk}^3 \text{Alk}^4 \\
\text{X} = \text{OTs, Cl, Br, I} \\
\text{Alk}^1 = \text{various substituted alkyl groups} \\
\text{Alk}^2 = \text{linear and branched aliphatic chains} \\
\text{Alk}^3/4 = \text{cyclic and linear aliphatics} \\
\end{align*}
\]

Selected examples:

- **81% yield**  
  $X = \text{OTs}$

- **74% yield**  
  $X = \text{Br}$

- **64% yield**  
  $X = \text{Br}$

- **89% yield**  
  $X = \text{Br}$

- **70% yield**  
  99% ee  
  $X = \text{OTs}$

- **67% yield**  
  98% ee  
  $X = \text{OTs}$