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

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Cu-Catalyzed Coupling of Secondary Alkyl Electrophiles and Alkyl Grignards

X = OTs, Cl, Br, I

Alk¹ = various substituted alkyl groups

Alk² = linear and branched aliphatic chains

Alk^{3/4} = cyclic and linear aliphatics

Selected examples:

81% yield
X = OTs

74% yield
X = Br

64% yield
X = Br

89% yield
X = Br

70% yield
99% ee
X = OTs

67% yield
98% ee
X = OTs

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_N2 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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