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A REMARKABLE CATALYTIC EFFECT OF Cu(II) SPECIES FOR CONJUGATE ADDITION OF GRIGNARD REAGENTS TO α,β-UNSATURATED ESTERS

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Abstract: In the presence of Me_3Si-Cl, Cu(II) are not reduced by Grignard reagents but exhibit remarkable catalytic activity for their conjugate addition to α,β-unsaturated esters.

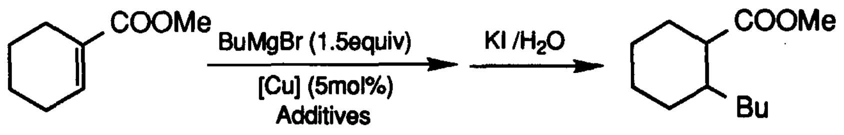
Since Kharasch's finding,1) Cu(I) salts have been often employed as efficient catalysts for conjugate addition of Grignard reagents,2) but efficacy of Cu(II) species has never been recognized in the field of organocopper chemistry. For a long period, it has been believed Cu(II) salts are not appropriate to effect the conjugate addition or to prepare organocopper reagents because they are readily reduced with Grignard reagents or alkyllithium to Cu(I) or Cu(0).3) By introducing a chlorosilane as an accelerator, conjugate addition reaction have recently been developed extensively either by using a Cu(I) catalyzed reaction of Grignard reagents4) or a stoichiometric amount of dialkylcuprates.5)

In contrary to the progress on conjugate addition to enones, there have been found only limited examples for conjugate addition to enoates, e.g by using RCu-$BF_3$6) or a combination of mixed cuprate with Me_3Si-acetylide and Me_3Si-Cl.7) During studies on TMS-Cl accelerated conjugate addition, we have found that Cu(II) salts facilitate such addition of Grignard reagents to enoates. Under appropriate reaction conditions, Cu(II) salts have been proven not to be reduced with Grignard reagents, but act as efficient catalysts. Thus, in the presence of a catalytic amount (ca.1-5 mol%) of Cu(II), conjugate addition of Grignard reagents took place rapidly to afford the addition products in excellent yields. After completion of the reaction, content of Cu(II) was analyzed by treating the aqueous solution with KI and the liberated iodine was titrated with a standard solution of $Na_2S_2O_3$.8) The results are shown in Table 1.

As shown in these results, Me_3Si-Cl or Me_3Si-Cl/HMPA prevents the reduction of Cu(II) species which act as efficient catalysts.

In addition to the results in Table 1, use of Cu(II) has greatly improved the conjugate addition reaction of several Grignard reagents. Introduction of methyl group to enoates usually suffers from much difficulty.9) Most of methylcopper reagents have exhibited little tendency for the conjugate addition, and even on using MeCu-BF_3 complex, a large excess amount (ca.10 equiv) of the reagent was required to perform this transformation in synthetically acceptable yield.10) In contrary, reactions in the presence of certain Cu(II) has allowed us to introduce methyl group almost quantitatively by using 1.5 equiv of the Grignard reagent (see Table 2). Among Cu(II) species briefly examined, salicylaldehyde N-*i*-propylimine complex (Cu[N-^{i}Pr-Sal]$_2$) has exhibited a most efficient catalytic activity. Such transformation could not be effected so well with a Cu(I) catalyst even on using a chlorosilane.

Table 1. Conjugate Addition and Analysis of Cu(II) after the Reaction

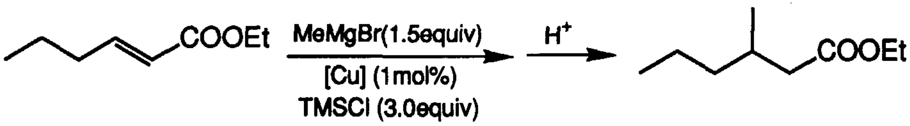


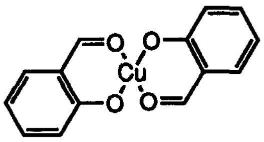
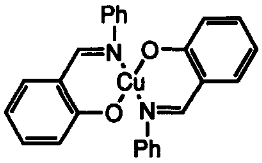
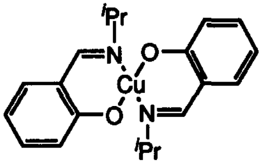
[Cu]	Additives(equiv)	Temp.(°C)	Yield(%)[b]	Cu(II)(%)
CuBr	TMSCl(3),HMPA(3)	-46	99	0
$CuBr_2$	————	-46~-23	2	9
$CuBr_2$	HMPA(3)	-46~-23	0	0
$CuBr_2$	TMSCl(3)	-46~-23	78	88
$CuBr_2$	TMSCl(3),HMPA(3)	-46	99	99

a) The reaction was performed in a 4:1 mixture of Et_2O and THF for 1 h.

b) Yield of the conjugate addition product.

Table 2. Conjugate Addition of Methyl Grignard Reagent[a)]



[Cu]	CuI	CuBr$_2$	 Cu(Sal)$_2$	 Cu(N-Ph·Sal)$_2$	 Cu(N-^{i}Pr·Sal)$_2$
Yield,%	trace	trace	44	33	99

a) The reaction was performed in a 1:5 mixture of Et$_2$O and THF at -46 °C for 1 h.

The following procedures are representative.

Conjugate Addition Reaction of Methylmagnesium Bromide to Ethyl 2-Hexenoate: To i-propylsalicylaldimine copper (II) complex (3.9 mg, 0.01 mmol) in THF (2.5 ml) were added Me_3SiCl (0.326 g, 3.0 mmol), ethyl 2-hexenoate (0.142 g, 1.0 mmol), and then methylmagnesium bromide (0.42 ml of a 3.57M ether solution, 1.50 mmol) at -45 °C. After it was stirred for 1hr at that temperature, HCl (ca. 3 ml of 3N solution) was added and the aqueous layer was extracted with ether. The organic layer was washed with sat. aq $NaHCO_3$ solution, dried over anhyd $MgSO_4$. Removal of the solvent afforded ethyl 3-methylhexanoate quantitatively which was >99% pure based on GLC and ^1H NMR: (200MHz, CDCl3) δ 0.90 (m, 6H), 1.30 (m, 7H), 2.0 (m, 1H), 2.10 (dd, J = 8.0 and 16.0 Hz, 1H), 2.32 (dd, J = 8.0 and 16.0 Hz, 1H), 4.14 (q, J = 8.0 Hz, 2H).

At present, the real role of Cu(II) species in these conjugate addition reactions has not yet been clear, but reaction mechanism might be different from the reaction catalyzed by Cu(I). At any event, the results described here may open a new entry to organocopper(II) species as promising reagents for 1,4-addition reactions.

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