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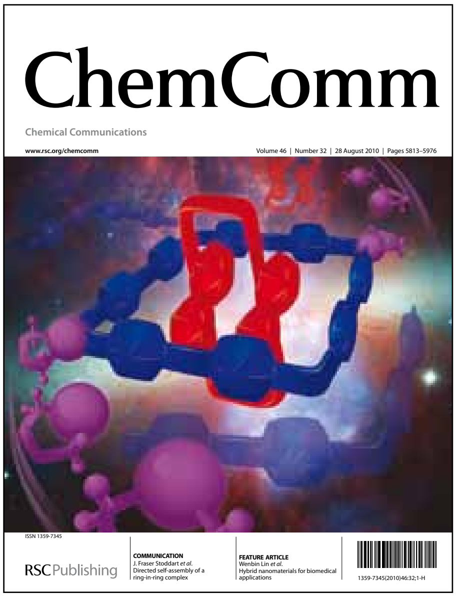

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ARTICLE TYPE

Copper Nanoparticle-Catalyzed Cross-Coupling of Alkyl Halides with Grignard Reagents

Ju Hyun Kim and Young Keun Chung*

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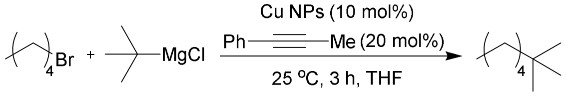
DOI: 10.1039/b000000x

Cross-coupling reaction between alkyl bromides and chlorides and various Grignard reagents was carried out in the presence of commercially available copper or copper oxide nanoparticles as a catalyst and an alkyne additive. The catalytic system shows the high activity, broad scope, and good functional group tolerance.

Transition metal-catalyzed cross-coupling reactions between two different partners, e.g., an organometallic reagent and an electrophile, have been developed as an arsenal for the formation of carbon–carbon bonds in organic synthesis.[1] Thus, a variety of electrophilic coupling partners, aryl, vinyl, and alkynyl halides, and pseudo-halides, can be readily coupled. However, the coupling of non-activated alkyl halides, especially having tertiary alkyl carbon, remain difficult due to steric hindrance, chance to β-hydride elimination, and isomerization of alkylmetals.[2]
Since the pioneering work in 1972 by Kumada[2] and Corriu,[3] there has been rapid development in the use of transition-metal catalysts for a variety of alkyl-alkyl bond formation reactions using Grignard reagents.[4] In particular, copper- and nickel-based catalytic systems are unparalleled as catalysts.[5-12] Very recently, the cobalt-catalyzed cross-coupling of alkyl halides with secondary and tertiary alkyl Grignard reagents and the copolymer-incarcerated nickel nanoparticle (NP)-catalyzed Kumada reactions were reported.[13,14]
We observed that the chemistry of metal NPs matches the characteristics of the homogeneous metal complexes in many cases.[15] However, reports on the transition metal NP-catalyzed cross-coupling reactions of alkyl halides with Grignard reagents are quite rare.[14] Inspired by previous reports[9-11,17] on the copper-catalyzed cross-coupling reactions, we decided to explore the use of Cu NPs in the cross-coupling reaction of electrophiles with Grignard reagents and found that Cu NPs in the presence of an additive were quite effective catalysts in the cross-coupling reaction of alkyl bromides and chlorides with primary-, secondary-, tertiary-alkyl, or phenyl Grignard reagents under mild conditions. The Cu NPs used in this study are commercially available and reused five times without any loss of activity. The catalytic system doesn't need any pretreatment before use. Moreover, broad substrate scopes such as functionalized alkyl chloride are acceptable and high functional group tolerance could be realized our catalytic system. Thus, we have developed a more convenient methodology with respect to environmental and economic considerations in this study. Herein we communicate our preliminary results.



Scheme 1 Cross-coupling of 1-bromooctane with *t*-BuMgCl

Using 1-bromooctane as a model compound, we optimized the reaction with *t*-BuMgCl (Scheme 1). Without a catalyst, no coupling product was formed. In the presence of Cu NPs, which is commercially available, and an alkyne additive, the cross-coupling reactions went to completion. The reaction was highly dependent upon the size of the catalyst and the presence of the additive. We examined three different sizes (5-7 nm, 25-40 nm, and 40-60 nm) of copper NPs and four different alkynes as an additive (see the Supporting Information). The reaction time was highly dependent upon the alkyl halide. For example, the reaction of 5-bromo-1-pentanol with *t*-BuMgCl went to completion within 10 min. For the convenience of experimental manipulation, the cross-coupling reactions were carried out under the following reaction conditions: 1.0 mmol of a substrate, 10 mol% of Cu NPs,[18] 20 mol% of 1-phenylpropyne, 1 mL of THF, 25 °C, and 3 h of a reaction time. Interestingly, a catalytic reaction underwent in the presence of copper(II) oxide NPs. However, the reactivity of copper(II) oxide NPs was slight lower than that of copper NPs (see the SI). The scope of this catalytic system was explored under the optimized reaction conditions (Table 1). While the present work focuses on the coupling of secondary and tertiary alkyl Grignard reagents, the same method could be used to couple primary alkyl or phenyl Grignard reagents in high yields. All the Grignard reagents except phenyl magnesium chloride gave good to excellent yields under the optimized reaction conditions. In the reactions with PhMgCl (entries 4, 9, and 13), the high yields were obtained in the presence of 20 mol% of Cu NP at 80 °C for 12 h. Although MeMgCl seemed to be ineffective in the presence of a cobalt catalyst,[13] the use of it afforded a good yield (70%) with a 6% recovery of the reactant with our catalytic system (entry 5). For the reactions of 2-bromoethylbenzene and 2-bromoethyl-1,3-dioxane with alkyl Grignard reagents (entries 6-8 and 10), the cross- coupling reactions went to completion without an additive. Ester and acetal functional groups were tolerated (entries 10-13 and 14, respectively). A substrate containing an alcohol group was coupled in high yields when 2.5 eqivalents of a Grignard

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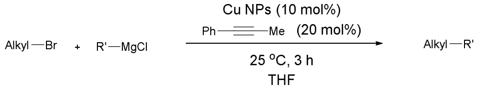
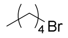
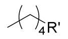
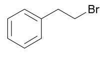
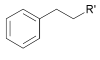
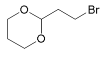
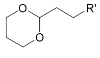
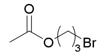
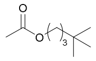
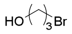
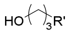
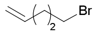
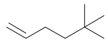
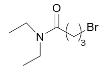
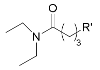
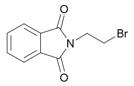
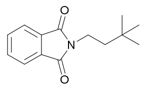
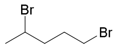
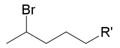
reagent was used (77-85%) (entries 15-17). An olefinic and an amide groups are also tolerated (entries 18 and 19-20). Interestingly, a phthalimide group, which is known to be incompatible with the homogeneous copper catalyst,[11] was tolerated by the Cu NP catalytic system (entry 21).

Table 1 Cu NP-catalyzed cross-coupling reactions of alkyl bromides with various Grignard reagents



Entry	Reactant	Product (R')		Yield (%)[a]
1-5			**1a** (*t*-Bu)	85
			2a (Cy)	96
			3a (*n*-Bu)	98
			4a (Ph)	91[b]
			5a (Me)	70
6-9			**6a** (*t*-Bu)	99
			7a (Cy)	95
			8a (*n*-Bu)	93
			9a (Ph)	99[b]
10-13			**10a** (*t*-Bu)	83[c]
			11a (Cy)	72[c]
			12a (*n*-Bu)	74[c]
			13a (Ph)	75[b,c]
14			**14a**	70[c]
15-17			**15a** (*t*-Bu)	78[c]
			16a (Cy)	85[c]
			17a (*n*-Bu)	77[c]
18			**18a**	82
19-20			**19a** (*t*-Bu)	75[c]
			20a (Cy)	70[c]
21			**21a**	61[c]
22			**22a** (*n*-Bu)	91

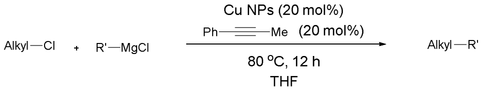
[a] Determined by GC analysis using 1,3,5-trimethylbenzene as an internal standard. [b] Reaction condition : 1 mmol of substrate, 20 mol% of catalyst, 80 °C, 12 h. [c] Isolated yields. Cy = cyclohexyl.

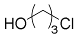
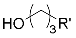
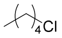
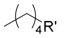
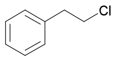
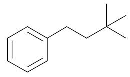
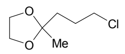
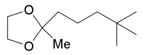
When 1,4-dibromopentane was used as a substrate, the primary alkylbromo moiety reacts with the *n*-butyl Grignard reagent to give 2-bromononane in high yield (entry 22). This observation may provide the synthetic utility of the site-selective cross-coupling reaction.

The reusability of the catalyst was also tested in the reaction of (2-bromoethyl) benzene with *t*-BuMgCl (see the SI). After the reaction was complete, the catalyst was separated from the reaction mixture by centrifugation, washed with diethyl ether and dichloromethane and dried *in vaccuo*. The recovered catalyst was reused in the next runs under the same reaction conditions. The results indicate that there is no appreciable difference in the yields of the product even after a fifth run. However, the yield of the sixth cycle decreased to 90%. The Cu NPs would be reused five times without deactivation, giving a final TON of 49. The elemental analysis (by ICP-AES) of the reaction mixture after completion of the reaction showed that 1.4 % of copper species was leached.[19] The decrease observed in the sixth run may be partly related to the decrease of the catalytic activity, presumably due to the air oxidation of the catalyst or the formation of MgO films on the copper particles or both.[18] Kobayashi et al.[14] also observed significant loss of activity of their copolymer-incarcerated Ni NP catalysts due to the deposition of magnesium salts on the NPs. The reusability of the catalyst strongly suggests a heterogeneous mechanism. However, we cannot ignore the possibility of a homogeneous reaction.

We next investigated the scope of the Cu NP-catalyzed cross-coupling reactions of alkyl chlorides with alkyl Grignard reagents. Several groups have studied the copper-catalyzed cross coupling of alkyl chlorides with alkyl Grignard reagents. Very different observations were reported depending on the catalytic system used. In the presence of CuCl as a catalyst, alkyl chlorides could not be coupled.[11] However, Kambe et al. reported the cross coupling of simple alkyl chlorides such as *n*-octyl chloride, 1-bromo-6-chlorohexane, and 6-chloro-1-hexene as substrates in the presence of $CuCl_2$ and 1-phenylpropyne.[9] Moreover, in the presence of $CoCl_2$ or Ni-pincer complex as a catalyst, the cross-coupling of alkyl chlorides were inefficient.[13,16] Thus, we examined our catalytic system with alkyl chlorides and optimized the reaction conditions (see the SI).

Table 2 Cu NP-catalyzed cross-coupling reactions of alkyl chlorides with alkyl Grignard reagent



Entry	Reactant	Product (R')		Yield (%)[a]
1-3			**1b**(*t*-Bu)	84
			2b(Cy)	92
			3b(*n*-Bu)	76
4-5			**4b**(*t*-Bu)	87[b]
			5b(Cy)	88[b]
6			**6b**	96[b]
7			**7b**	68

[a] Isolated yields, [b] Determined by GC analysis. Cy = cyclohexyl.

With the optimized reaction conditions in hand, we examined the scope of the reaction (Table 2). Among primary alkyl chlorides used in this study, alcohol and acetal derivatives (entries 1-3 and 7), *n*-octyl chloride (entries 4 and 5), and (2-chloroethyl) benzene (entry 6) were proved to be good substrates in the reaction with primary, secondary, or tertiary alkyl Grignard reagent. When a cross coupling reaction with PhMgCl was carried out under the same reaction conditions, the expected product was not obtained. Instead, biphenyl was obtained as a major product.

In the reaction of (2-bromoethyl) benzene, the addition of an alkyne additive was not required. However, in other cases, the addition of an alkyne additive was necessary. The role of the alkyne additive in the present catalytic reaction has not yet been clarified. Kambe et al.[9,20] suggested that the coordination of alkynes to the copper prevents the decomposition of thermally unstable alkylcopper intermediates. Two decades ago, a time-resolved study of gas-phase reactions of copper atoms with dimethylacetylene (DMA) had undertaken by Mitchell et al.[21] According to their report, CuL and CuL_2 (L = DMA) complexes were formed by Cu + L reactions and were characterized as π-

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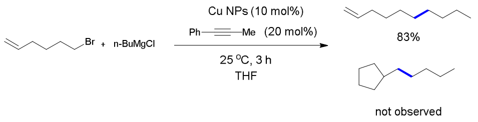
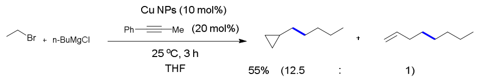
complexes.[21,22] Thus it seems that the role of the alkyne additive is to stabilize reactive alkylcopper intermediates, as Kambe et al. suggested.[9]

In order to gain some insight into the reaction mechanism, 6-bromo-1-hexene and (bromomethyl)cyclopropane and were reacted with *n*-BuMgCl. In the reaction of 6-bromo-1-hexene with *n*-BuMgCl (Eq. 1), 1-decene was formed, but no cyclized product was observed. However, in the case of (bromomethyl)cyclopropane (Eq. 2), pentylcyclopropane and 1-octene were obtained in a ratio of 12.5:1 with a total 55 % yield. These observations indicate that the coupling reaction occur mainly via an S_N2 mechanism.[9,11] In addition, the Cu NP-catalyzed cross-couplings undergo a minor radical pathway. It has been reported[23] that the rearrangement products were observed in the reaction of activated haloalkanes with alkenes in the presence of copper metal.



(1)



(2)

Although the exact mechanism for the reduction is not clear, we think that it is similar to that of other homogeneous copper-catalyzed reactions (see the SI).[9,24]

In conclusion, we have developed a Cu NP-based cross-coupling method that is remarkably simple and general. The Cu NPs used in this study are commercially available and the catalytic system doesn't need any pretreatment or preformed supports and ligands. The catalytic system is quite effective for the cross-coupling of primary alkyl bromides or chlorides with alkyl or aryl Grignard reagents. In view of the broad scope of the substrates, functional group tolerance, high reaction efficiencies, high product yields, and reusability, the Cu NP-catalyzed cross-coupling reaction can be expected to find wide synthetic applications. We are currently exploring the use of other additives for the Cu NP-catalysis to further widen the reaction scope of the cross-couplings and to expand the use of Cu NPs as catalysts in other related cross-coupling reactions. We are also studying what the active species is in the Cu NPs-catalyzed cross-coupling reaction.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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