Cross-Coupling Reactions

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Copper-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Primary-Alkyl Halides: Remarkable Effect of 1-Phenylpropyne**

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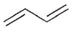
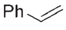
The copper-catalyzed cross-coupling of alkyl halides or sulfonates with Grignard reagents has become one of the most straightforward methods for constructing methylene chains.[1,2] A serious drawback of this reaction is its non-applicability toward alkyl chlorides, which are promising alkylating reagents because of their wide availability and low cost relative to their iodo and bromo analogues.[3,4] This lack of reactivity is probably due to the strong C−Cl bond relative to the C−I and C−Br bonds. We have recently reported that Cu catalyzes the cross-coupling reaction of non-activated alkyl fluorides with Grignard reagents in the presence of 1,3-butadiene additives under mild conditions;[5] however, the corresponding alkyl chlorides gave only poor yields of the cross-coupling products.[6] We describe herein the first example of a Cu-catalyzed cross-coupling reaction of alkyl chlorides with Grignard reagents in the presence of 1-phenylpropyne as an additive [Eq. (1)].

$$\text{Alkyl−Cl} \quad + \quad \text{R−MgX} \quad \xrightarrow[\text{THF}]{\text{cat. Cu} \atop \text{cat. Ph}-\!\!\equiv\!\!-\text{Me}} \quad \text{Alkyl−R} \qquad (1)$$

When *n*-nonyl chloride (1 mmol) was allowed to react with *n*BuMgCl (1.5 mmol) in the presence of catalytic amounts of $CuCl_2$ (0.02 mmol) and 1-phenylpropyne (0.1 mmol) in THF under reflux for 6 h, the cross-coupling product, tridecane, was obtained in greater than 98 % yield along with a trace amount of a reduction product, nonane (<1 %; Table 1, entry 1). This reaction proceeds at room temperature, but more slowly (Table 1, entry 2).[7] The use of a CuCl catalyst also afforded tridecane in high yields (Table 1, entry 3). In the absence of 1-phenylpropyne, tridecane was obtained in only 3 % yield, and 95 % of *n*-nonyl chloride was recovered (Table 1, entry 4). 1,3-Butadiene and styrene are far less effective as the ligand (Table 1, entries 5 and 6). We then examined other alkynes in the reaction. The yield of tridecane decreased as the length of the alkyl chain was increased (Table 1, entries 1, 7, and 8). Torane, phenyl acetylene, and 4-octyne gave moderate to poor yields of the coupling product (Table 1, entries 9–11). The presence of an *o*-methyl group on the aryl substituent resulted in a decreased product yield; however, a *p*-methyl group did not affect the reaction. These results suggest that the present cross-coupling reaction is sensitive to the steric hindrance around the C−C triple bond of the alkynes.

Table 1: Cross-coupling reaction of *n*Non−Cl with *n*Bu−MgCl.[a]

Entry	Additive	Product yield [%][b]		
		tridecane	nonane	nonenes
1	Ph−≡−Me	> 98	< 1	0
2[c]	Ph−≡−Me	91	1	0
3[d]	Ph−≡−Me	93	1	< 1
4	none	3	2	0
5		16	26	4
6		4	10	2
7	Ph−≡−Et	66	20	9
8	Ph−≡−*n*Non	13	12	1
9	Ph−≡−Ph	19	10	3
10	Ph−≡−H	44	5	0
11	*n*Pr−≡−*n*Pr	5	10	1
12	*o*-tol−≡−Me	12	18	1
13	*p*-tol−≡−Me	95	< 1	0

[a] *n*Non−Cl (1 mmol), $CuCl_2$ (0.02 mmol), additive (0.1 mmol), and *n*Bu−MgCl (1.5 mmol), THF (1.5 mL), reflux, 6 h; tol = tolyl. [b] GC yield based on *n*Non−Cl used. [c] Reaction was carried out at 25 °C for 48 h. [d] CuCl was used as the catalyst.

We have recently reported an example of a Ni-catalyzed cross-coupling reaction of a primary-alkyl chloride with *n*BuMgCl in the presence of 1,3-butadiene at 25 °C for 20 h which afforded dodecane in 96 % yield.[4a] However, this reaction cannot be applied to *sec*-butyl, *tert*-butyl, and phenyl Grignard reagents as shown in Equation (2). On the other hand, the Cu-catalyzed cross-coupling reaction proceeds efficiently with these alkyl and phenyl Grignard reagents. It should be noted that alkyl fluorides and mesylates (OMs)[8] can also undergo the present cross-coupling reaction to give rise to the corresponding products in almost quantitative yields [Eq. (3)].

We next examined independent reactions of alkyl electrophiles (alkyl-X; X = F, Cl, Br, OMs, OTs; OTs = tosylate) with *n*BuMgCl in the presence of catalytic amounts of $CuCl_2$ and 1-phenylpropyne in THF at 25 °C for 15 minutes to determine the reactivity of these electrophiles in the reaction. The corresponding coupling product was obtained in high

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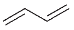
$$\underset{1\ \text{mmol}}{n\text{Oct–Cl}} + \underset{1.5\ \text{mmol}}{\text{R–MgX}} \xrightarrow[\text{THF}]{} n\text{Oct–R} \qquad (2)$$

R	3% $NiCl_2$ 50%  THF, 25 °C, 20 h	2% $CuCl_2$ 10% $\text{Ph–}\equiv\text{–Me}$ THF, reflux, 6 h
*n*Bu	96%	>98%
*s*Bu	1%	95%
*t*Bu	0%	>98%
Ph	4%	82%

$$\underset{1\ \text{mmol}}{n\text{Non–X}} + \underset{1.5\ \text{mmol}}{\text{R–MgCl}} \xrightarrow[\text{THF, reflux, 6 h}]{2\%\ CuCl_2,\ 10\%\ \text{Ph–}\equiv\text{–Me}} n\text{Non–R} \qquad (3)$$

R	X = F	X = OMs
*n*Bu	>98%	>98%
*s*Bu	>98%	96%
*t*Bu	>98%	>98%
Ph	>98%	>98%

yield from *n*-nonyl bromide and in moderate yields from *n*-heptyl tosylate and *n*-heptyl mesylate. In contrast, *n*-nonyl chloride and fluoride gave only small amounts of products [Eq. (4)]. These results indicate the reactivities of the alkyl electrophiles in the present cross-coupling reaction increase in the order: chloride < fluoride < mesylate < tosylate < bromide.

$$\underset{1\ \text{mmol}}{\text{Alkyl-X}} + \underset{1.5\ \text{mmol}}{n\text{Bu-MgCl}} \xrightarrow[\text{THF, 25 °C, 15 min}]{2\%\ CuCl_2,\ 10\%\ \text{Ph–}\equiv\text{–Me}} \text{Alkyl-}n\text{Bu} \qquad (4)$$

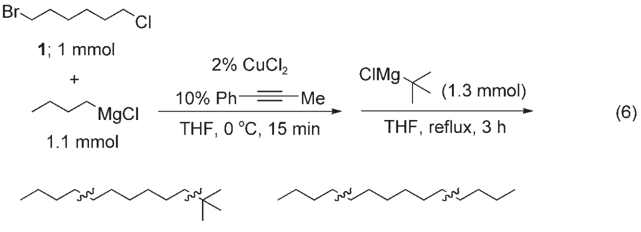
Alkyl-X	Yield
*n*Non-F	9%
*n*Non-Cl	1%
*n*Non-Br	>99%
*n*Hep-OMs	64%
*n*Hep-OTs	74%

To examine these abnormal reactivities of the alkyl halides (alkyl-X; X = F, Cl, Br) in this catalytic system we also carried out the following competitive experiments: A solution of *n*BuMgCl, $CuCl_2$, and 1-phenylpropyne in THF was added to a mixture of equimolar amounts of *n*-octyl fluoride, *n*-nonyl chloride, and *n*-decyl bromide [Eq. (5)]. After stirring the reaction for 30 minutes in THF under reflux, GC analysis of the resulting mixture indicated the selective formation of tetradecane in 98 % yield along with a 2 % yield of dodecane [Eq. (5)]. A similar reaction using only alkyl fluorides and chlorides resulted in the formation of dodecane and tridecane in 95 % and 5 % yields, respectively. These results indicate the reactivity of the alkyl halides to be in the order chloride < fluoride < bromide. Theoretical calculation of the strengths of the Me–X and X–MgCl bonds indicates that the reactions of the alkyl fluorides are not disfavored energetically relative to those of alkyl chlorides and alkyl bromides because of the formation of a strong F–Mg bond.[9] It is proposed that an interaction between Li and X plays an important role in the fission of the C–X bond for the related reaction of alkyl-X with R_2CuLi.[10]

$$\underset{1\ \text{mmol}}{n\text{Bu-MgCl}} + \underset{5\ \text{mmol}}{n\text{Oct-F}} + \underset{5\ \text{mmol}}{n\text{Non-Cl}} + \underset{(5\ \text{mmol})}{n\text{Dec-Br}} \xrightarrow[\text{THF, reflux, 30 min}]{2\%\ CuCl_2,\ 10\%\ \text{Ph–}\equiv\text{–Me}} \qquad (5)$$

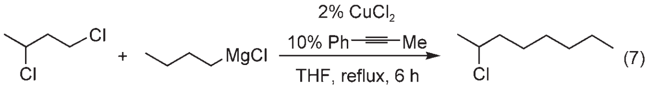
	*n*Bu-*n*Oct	+	*n*Bu-*n*Non	+	*n*Bu-*n*Dec
with *n*Dec-Br	2%		0%		98%
without *n*Dec-Br	95%		5%		–

These remarkable differences in reactivity, especially between the alkyl chlorides and bromides, prompted us to perform site-selective sequential cross-coupling reactions using dihaloalkanes. Reaction of 1-bromo-6-chlorohexane (**1**) with *n*BuMgCl (1.1 equiv) in the presence of catalytic amounts of $CuCl_2$ and 1-phenylpropyne at 0 °C for 15 minutes followed by addition of *t*BuMgCl (1.3 equiv) afforded a nearly quantitative yield of 2,2-dimethyldodecane (**2**) along with less than 1 % of tetradecane (**3**) [Eq. (6)].



2; >98%   **3**; <1%

Although the reaction of 2-octyl bromide with *n*BuMgCl under identical conditions as used in entry 1 of Table 1 afforded the corresponding cross-coupling product in 40 % yield, no reaction took place with 2-octyl chloride. This reactivity allows the successful synthesis of 2-octyl chloride (**4**) in high yield by using 1,3-dichlorobutane [Eq. (7)].



4; 89%

To examine the effect of 1-phenylpropyne in the present reaction system we then carried out the reaction of *n*-nonyl chloride with *n*BuMgCl in THF under reflux in the presence of 2 mol % of $CuCl_2$ and different amounts of 1-phenylpropyne. A graph of the time course of the formation of tridecane against the amount of additive is shown in Figure 1. Interestingly, as the amount of additive was increased, the reaction rate at the early stage decreased (see below). When only 2 mol % of the additive was employed the catalyst rapidly lost its activity and the reaction stopped.

It has been proposed that direct reaction of *sec*-alkyl iodides with lithium diorganocuprates may proceed by a

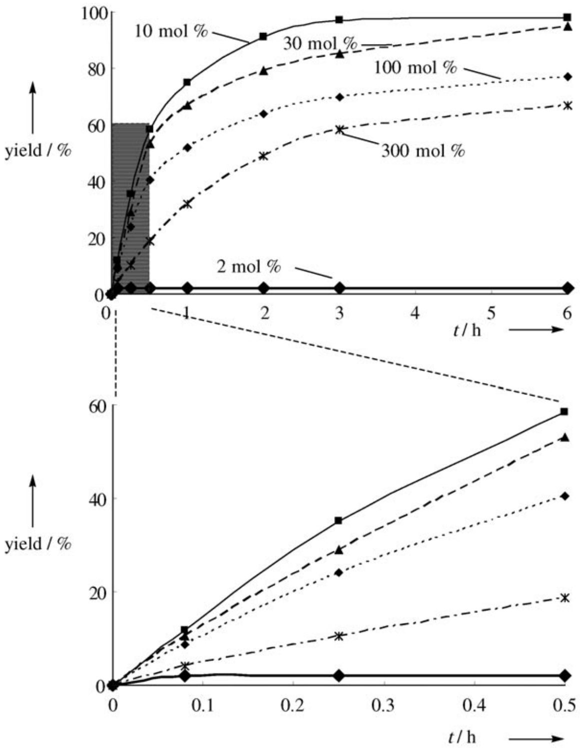
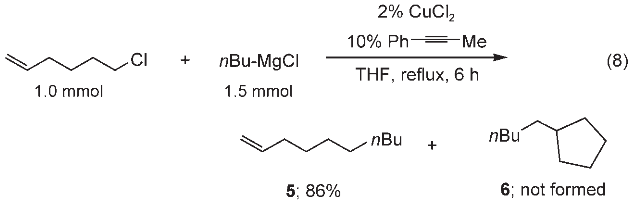
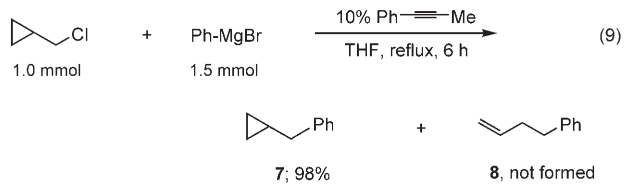


Figure 1. Time course of the Cu-catalyzed cross-coupling reaction using different amounts of 1-phenylpropyne in THF under reflux.

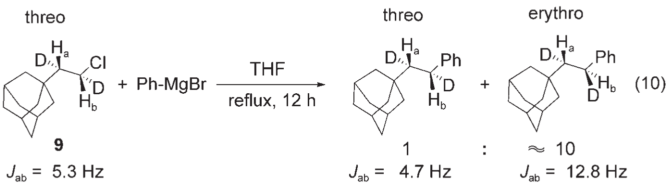
radical pathway.[11] We then carried out the cross-coupling reaction with 6-chloro-1-hexene [Eq. (8)]. Alkene **5** was



obtained in 86 % yield as the sole coupling product, without formation of cyclic compound **6**, which may arise from intramolecular cyclization of a 5-hexenyl radical.[12] We also carried out the coupling reaction of (chloromethyl)cyclopropane with PhMgBr. Benzylcyclopropane (**7**) was obtained in 98 % yield as the sole coupling product without formation of 4-phenyl-1-butene (**8**), which may arise from ring-opening of the cyclopropylmethyl radical [Eq. (9)].[13] These results would rule out a radical mechanism.

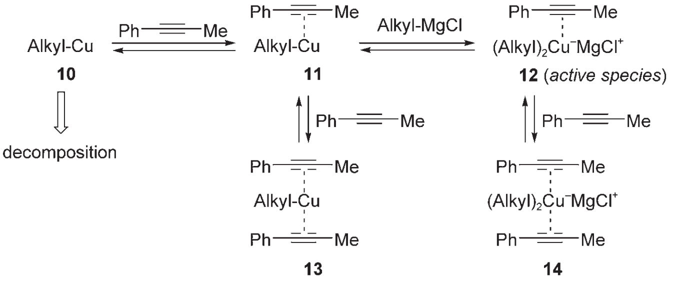


To gain insight into the stereochemistry of the present coupling reaction[14] we treated diastereometrically pure α,β-[D$_2$]-β-adamantylethyl chloride (**9**) with PhMgBr [Eq. (10)].



^{1}H NMR analysis of the products indicated that the cross-coupling reaction occurs primarily with inversion of configuration, with approximately 10:1 selectivity. This result suggests that the present cross-coupling reaction for primary-alkyl chlorides proceeds principally by an S$_N$2 mechanism.

Although the role of 1-phenylpropyne in the present catalytic reaction has not yet been clarified, it is possible that the coordination of alkynes to the copper(I) ion prevents decomposition of thermally unstable alkylcopper(I) intermediates **10**,[15,16] which may exist in equilibrium with other complexes **11**–**14** in the reaction media (Scheme 1). The coordination of alkynes to **10** then forms an alkyne–alkylcopper(I) complex **11**.[17] Complexation of **11** with the Grignard reagent forms an ate complex **12**, which would be a key species in the present cross-coupling reaction and react with the alkyl halides.[18] Increasing the concentration of the alkynes shifts the equilibrium toward the formation of bis(alkyne)copper(I) complexes (**13** and/or **14**),[19] which might be the resting states of the catalyst, thus resulting in a lowering of the rate of the coupling process.



Scheme 1. A plausible reaction pathway.

In conclusion, we have shown that the Cu-catalyzed alkyl–alkyl cross-coupling reaction between alkyl chlorides and Grignard reagents proceeds efficiently in the presence of 1-phenylpropyne as an additive, and is applicable to alkyl fluorides, mesylates, and tosylates.

Experimental Section

2 (CAS registry number 49598-54-1): A solution of *n*-butylmagnesium chloride (0.87 M, 1.25 mL, 1.1 mmol) in THF was added to a mixture of 1-bromo-6-chlorohexane (197 mg, 1.0 mmol) and catalytic amounts of CuCl$_2$ (2.9 mg, 0.02 mmol) and 1-phenypropyne

(11.8 mg, 0.1 mmol) at 0 °C under nitrogen. After stirring the mixture for 15 min at 0 °C, a solution of *tert*-butylmagnesium chloride (0.9 M, 1.45 mL, 1.3 mmol) in THF was added. After stirring the reaction mixture for 3 h at 68 °C, 1 M aqueous HCl was added. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the product was extracted with diethyl ether (10 mL). The organic layer was dried over $MgSO_4$, and evaporated to give a yellow crude product (98 %, GC yield). Purification by HPLC with $CHCl_3$ as the eluent afforded 180 mg (91 %) of **2**. IR (neat): 2926, 2855, 1468, 1392, 1364, 1250, 1014, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$–1.14 (m, 18 H), 0.88 (t, $J = 6.0$ Hz, 3 H), 0.86 ppm (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 44.4$, 32.1, 30.8, 30.4, 29.91, 29.87, 29.8, 29.6, 29.5, 24.7, 22.9, 14.3 ppm; MS (EI) m/z (relative intensity, %): 198 ($[M]^+$, 1), 183 (6), 140 (6), 85 (9), 71 (12), 57 (100), 56 (53), 43 (10), 41 (13); HRMS calcd for $C_{14}H_{30}$: 198.2347; found: 198.2357; elemental analysis calcd for $C_{14}H_{30}$: C 84.76, H 15.24; found: C 84.47, H 15.02.

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