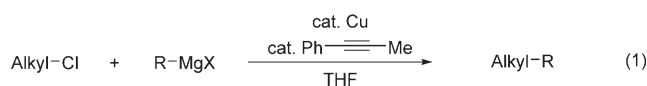


Copper-Catalyzed Cross-Coupling Reaction of Grignard Reagents with Primary-Alkyl Halides: Remarkable Effect of 1-Phenylpropyne**

Jun Terao,* Hirohisa Todo, Shameem Ara Begum, Hitoshi Kuniyasu, and Nobuaki Kambe*

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)].



When *n*-nonyl chloride (1 mmol) was allowed to react with *n*BuMgCl (1.5 mmol) in the presence of catalytic amounts of CuCl₂ (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

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

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

[a] *n*Non–Cl (1 mmol), CuCl₂ (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.

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.

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 CuCl₂ 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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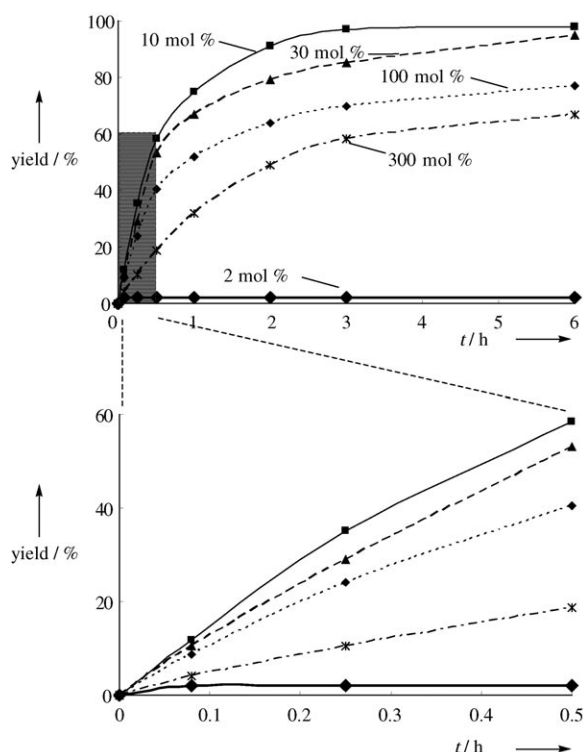
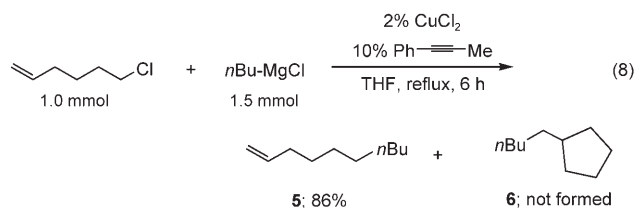
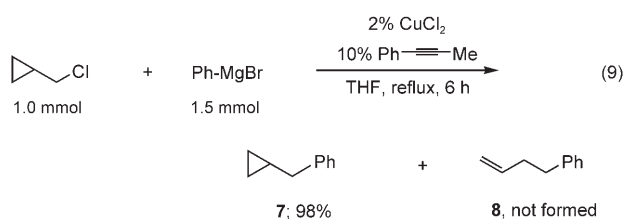


Figure 1. Time course of the Cu-catalyzed cross-coupling reaction using different amounts of 1-phenylpropyne in THF under reflux.

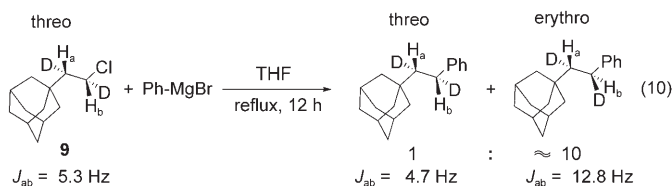
radical pathway.^[11] We then carried out the cross-coupling reaction with 6-chloro-1-hexene [Eq. (8)]. Alkene **5** was



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.

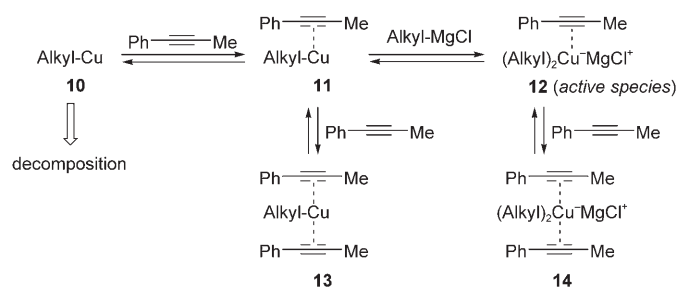


To gain insight into the stereochemistry of the present coupling reaction^[14] we treated diastereomerically pure α,β -[D₂]- β -adamantylethyl chloride (**9**) with PhMgBr [Eq. (10)].



¹H 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_N2 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



Scheme 1. A plausible reaction pathway.

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.

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 CuCl₂ (2.9 mg, 0.02 mmol) and 1-phenylpropyne

(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 NH₄Cl (10 mL) was added, and the product was extracted with diethyl ether (10 mL). The organic layer was dried over MgSO₄, and evaporated to give a yellow crude product (98%, GC yield). Purification by HPLC with CHCl₃ as the eluent afforded 180 mg (91%) of **2**. IR (neat): 2926, 2855, 1468, 1392, 1364, 1250, 1014, 722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.26–1.14 (m, 18H), 0.88 (t, *J* = 6.0 Hz, 3H), 0.86 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 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 C₁₄H₃₀: 198.2347; found: 198.2357; elemental analysis calcd for C₁₄H₃₀: C 84.76, H 15.24; found: C 84.47, H 15.02.

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