

Copper-Catalyzed Cross-Coupling of Alkyl and Aryl Grignard Reagents with Alkynyl Halides**

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Alkyl–alkynyl cross-coupling can be achieved through one of two pathways. The first one consists in alkylating a metal acetylide with a primary alkyl iodide or bromide. Sodium, potassium, or lithium acetylides have been extensively used, but the reaction suffers from some limitations.^[1] As an example, the substitution reaction does not tolerate the presence of reactive functional groups such as esters or nitriles.^[1a] On the other hand, β -branched primary, secondary, or tertiary alkyl halides mainly undergo an elimination reaction and do not lead to the substitution product, or in only poor yields.^[1a] The coupling of tertiary alkyl halides with alkynylalanes was reported.^[2] However, the method is not general, and only one of the three alkynyl groups is transferred.

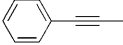
The alkyl–alkynyl cross-coupling can also be performed according to a second pathway, which involves reacting an alkylmetal with an alkynyl halide. The first attempts were carried out by reacting iodo- or bromoalkynes with Grignard reagents in the presence of cobalt salts,^[3] or organocopper derivatives.^[4] However, poor to moderate yields are generally obtained. Later, a few trialkylaluminum reagents were coupled successfully with alkynyl bromides under nickel catalysis,^[5] however only one alkyl group was transferred in moderate to good yields. An interesting general method was described by Yeh and Knochel in 1989,^[6] in which functionalized organocuprate reagents, $\text{Alk}_{\text{Fg}}\text{-Cu(CN)ZnI}$ (Fg = functional group), react with simple bromo- or iodoalkynes to afford functionalized alkynes in good yields. However, the reaction conditions (12–16 h at -65°C), and the use of a stoichiometric amount of copper are not very convenient for large-scale preparations.

The aryl–alkynyl coupling is generally performed by using the well-known Sonogashira reaction between aromatic halides and terminal alkynes in the presence of both copper and palladium salts.^[7] In contrast, the coupling of an arylmetal with an alkynyl halide has been almost ignored until now. In 1972, Oliver and Walton^[8] studied the reaction of arylcopper reagents with iodo-trimethylsilylacetylene, but the reaction has not been extended to other substrates.

In fact, it should be noted that as a rule, no general procedure is currently available to couple aryl or alkyl Grignard reagents with alkynyl halides. Herein we report the first efficient copper-catalyzed alkynylation of alkyl and aryl Grignard reagents.

Weedon and co-workers^[4] reported that the copper-catalyzed coupling of alkyl Grignard reagents with alkynyl halides only gives poor yields of the substitution product. As mentioned by Normant and co-workers,^[9] the halogen/magnesium exchange generally takes place predominantly. Recently, in the light of our experience in copper-catalyzed cross-coupling reactions with Grignard reagents,^[10] we decided to reinvestigate this reaction and we discovered that, in fact, satisfactory yields can be obtained by slowly introducing the Grignard reagent to the reaction mixture. As an example, in the presence of 3 mol % CuCl_2 in THF at 0°C , the addition of $n\text{BuMgCl}$ (12 mmol) to heptynyl bromide (10 mmol) over a 45 minute period gave 73 % of 5-undecyne (Table 1, entry 1). To improve this result, we have tested the

Table 1: Influence of various ligands on the copper-catalyzed cross-coupling of $n\text{BuMgCl}$ with heptynyl bromide.^[a]

$n\text{BuMgCl} + \text{Br}-\text{C}\equiv\text{C}-n\text{Pent} \xrightarrow[\text{THF, } 0^\circ\text{C}]{\substack{3 \text{ mol \% CuCl}_2 \\ 10 \text{ mol \% ligand}}} n\text{Bu}-\text{C}\equiv\text{C}-n\text{Pent}$		
Entry	Ligand	Yield [%] ^[b]
1	no ligand	73
2		79
3	dppe	< 5
4	PPh_3	84
5	TMEDA ^[c]	87
6	Me_2S	87
7	$\text{OP}(\text{OEt})_3$	90
8	NMP	91
9	NMP (4 mol %)	91

[a] The reactions were performed on a 10 mmol scale. $n\text{BuMgCl}$ (12 mmol) was added by using a syringe pump over a 45 minute period. [b] Yield determined by GC (pentadecane as internal standard). [c] TMEDA = N,N,N',N' -tetramethylethylenediamine.

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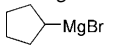
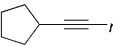
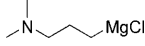
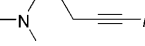
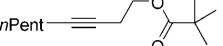
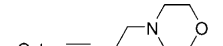


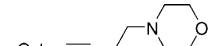



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influence of various ligands on the course of the reaction (Table 1). 1-Phenylpropyne, successfully used as a ligand by Kambe and co-workers for the copper-catalyzed coupling between alkyl Grignard reagents and alkyl chlorides,^[11] has only a moderate effect on the reaction (Table 1, entry 2). Surprisingly, the addition of 10 mol % dppe (diphenylphosphinoethane) has a clear detrimental effect whereas the addition of triphenylphosphine is beneficial (Table 1,

entries 3 and 4). As a rule, excellent yields are obtained with σ -donor ligands (10 mol %) like TMEDA (Table 1, entry 5), dimethylsulfide (Table 1, entry 6), triethylphosphate (Table 1, entry 7), or *N*-methylpyrrolidinone (NMP; Table 1, entry 8). Notably, an excellent yield of the coupling product (91 %) was obtained by using only 4 mol % NMP and 3 mol % CuCl_2 (Table 1, entry 9).

As illustrated in Table 2, various aliphatic internal alkynes were prepared in good to excellent yields by using this procedure. Satisfactory results were obtained with primary

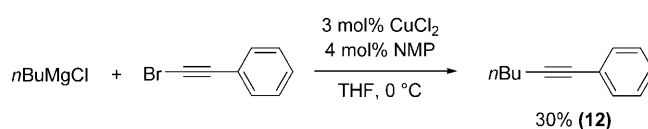
Table 2: Copper-catalyzed cross-coupling of alkyl Grignard reagents with alkynyl bromides.^[a]

AlkMgX + Br—C≡C—Alk'		3 mol % CuCl_2 4 mol % NMP THF, 0 °C	Alk—C≡C—Alk'		
Entry	AlkMgX	Product	Yield [%] ^[b]		
1	<i>n</i> BuMgCl	<i>n</i> Bu—C≡C— <i>n</i> Pent	1	91 ^[c]	
2	<i>n</i> OctMgCl	<i>n</i> Oct—C≡C— <i>n</i> Pent	2	89	
3	<i>s</i> BuMgCl	<i>s</i> Bu—C≡C— <i>n</i> Pent	3	90	
4		 — <i>n</i> Pent	4	78	
5	<i>t</i> BuMgCl	<i>t</i> Bu—C≡C— <i>n</i> Pent	5	92	
6		 — <i>n</i> Pent	6	94	
7	<i>n</i> BuMgCl	<i>n</i> Bu—C≡C—SiMe ₃	7	65	
8	<i>n</i> PentMgCl	<i>n</i> Pent—C≡C— 	8	88	
9	<i>n</i> OctMgCl	<i>n</i> Oct—C≡C— 	9	92	
10		 — 	10	89	
11		 — 	11	81	

[a] The reactions were performed on a 10 mmol scale. AlkMgCl (12 mmol) was added by using a syringe pump over a 45 minute period. [b] Yield of isolated product. [c] From *n*PentC≡Cl, the reaction gave a mixture of *n*PentC≡CH (55 %) and *n*PentC≡C—C≡C*n*Pent (35 %).

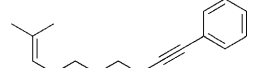
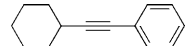
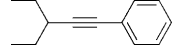
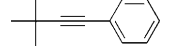
alkyl (Table 2, entries 1, 2, and 7–9), as well as with acyclic or cyclic secondary alkyl Grignard reagents (Table 2, entries 3 and 4). Interestingly, tertiary alkyl Grignard reagents can also be used successfully; as an example, 2,2-dimethyl-3-nonyne was obtained in 92 % yield from *tert*-butylmagnesium chloride (Table 2, entry 5). Notably, the reaction is very chemoselective, and various functionalized Grignard reagents or functionalized alkynyl halides have been employed successfully (Table 2, entries 6–11). The procedure allows a rapid and simple access to various functionalized alkynes in high yields. The reaction failed with alkynyl bromides derived from arylacetylenes since the Br/Mg exchange is mainly observed (Scheme 1).

Fortunately, we discovered that the substitution product can be prepared successfully by using the corresponding alkynyl chlorides (Table 3); in this case the use of NMP was not necessary.^[12] In this way, good yields of 1-alkyl-2-phenylacetylenes were obtained from *n*-alkyl Grignard reagents



Scheme 1. Copper-catalyzed cross-coupling of *n*BuMgCl with 1-bromo-2-phenylacetylene.

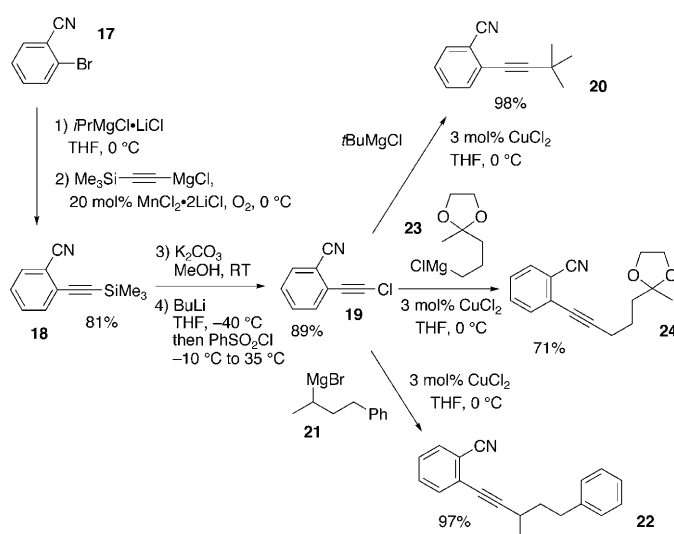
Table 3: Copper-catalyzed cross-coupling of alkyl Grignard reagents with 1-chloro-2-phenylacetylene.^[a]

AlkMgX + Cl—C≡C—Ph		3 mol % CuCl_2 THF, 0 °C	Alk—C≡C—Ph		
Entry	Product	Yield [%] ^[b]			
1	<i>n</i> Bu—C≡C—Ph	12	78		
2		13	77		
3		14	92		
4		15	93		
5		16	91		

[a] The reactions were performed on a 10 mmol scale. AlkMgCl (12 mmol) was added by using a syringe pump over a 15 minute period. [b] Yield of isolated product.

(Table 3, entries 1 and 2). Yields are still more impressive with secondary cyclic or acyclic, as well as with tertiary alkyl Grignard reagents (Table 3, entries 3–5).

This procedure was used to prepare various functionalized arylacetylenes from 2-bromobenzonitrile **17** (Scheme 2). The arylacetylene derivative **18** was prepared from **17** in two steps. After a classical Br/Mg exchange reaction,^[13] the resulting 2-cyanophenylmagnesium halide was coupled with trimethylsilyl-ethynylmagnesium chloride by action of oxygen in the



Scheme 2. Copper-catalyzed cross-coupling of alkyl Grignard reagents with chloroarylacetylene **19**.

presence of MnCl_2 according to a procedure recently reported.^[14] Compound **18** was obtained in 81 % yield, and subsequent desilylation^[15] delivered 2-cyanophenylacetylene, which was isolated and then chlorinated^[16] to give **19** in 89 % yield. Chloroalkyne **19** was then coupled in the presence of copper chloride with *tert*-butylmagnesium chloride or with the secondary alkyl Grignard reagent **21** to give respectively the arylacetylenes **20** and **22** in excellent yields. On the other hand, the use of the functionalized Grignard reagent **23** led to the highly functionalized arylacetylene **24** in 71 % yield.

Encouraged by these results, we have tried to extend the reaction to the arylation of alkynyl bromides. Indeed, arylacetylenes derivatives are attractive, since they have numerous applications as optical materials or organic conductors.^[17] Our first attempts were effective and aryl Grignard reagents bearing electron-withdrawing (Table 4, entry 1) or electron-donating groups (Table 4, entry 2), as well as various functionalized alkynyl bromides (Table 4, entries 3–9) have been coupled in satisfactory yields.

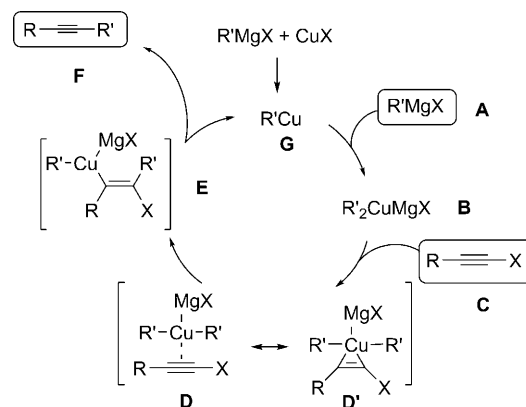
The Br/Mg exchange is not observed, except in the case of the reaction of methyl 3-bromopropiolate with 4-anisylmagnesium bromide which only gave 48 % yield of the cross-coupling product, since 4-bromoanisole is formed as a side product in 50 % yield (Table 4, entry 7). In this case, the use of electron-deficient (Table 4, entry 8) or hindered (Table 4, entry 9) aryl Grignard reagents precludes the Br/Mg exchange reaction, and the expected methyl 3-arylpropiolates were isolated in good yields.

Table 4: Copper-catalyzed cross-coupling of aryl Grignard reagents with alkynyl bromides.^[a]

$\text{ArMgBr} + \text{Br}-\text{C}\equiv\text{C}-\text{Alk} \xrightarrow[\text{THF, 0}^\circ\text{C}]{3 \text{ mol\% CuCl}_2, 10 \text{ mol\% NMP}} \text{Ar}-\text{C}\equiv\text{C}-\text{Alk}$				
Entry	ArMgBr	Product		Yield [%] ^[b]
1			25	84
2			26	78
3			27	52
4			28	58
5			29	73
6			30	72
7			31	48
8			32	85
9			33	83

[a] The reactions were performed on a 10 mmol scale. ArMgBr (12 mmol) was added by using a syringe pump over a 48 minute period. [b] Yield of isolated product.

To explain our results, a reasonable mechanism is proposed in Scheme 3. The catalytic cycle starts by the formation of the cuprate **B** from the Grignard reagent **A**. The



Scheme 3. Putative mechanism of the copper-catalyzed cross-coupling between $\text{R}'\text{MgX}$ and alkynyl halides.

haloalkyne **C** then reacts with **B** to give the vinylcopper reagent **E** via the complex **D/D'** (carbocupration). Formally, **E** results from a reductive elimination from the metal-lacetylenecyclopropene **D'**. The unstable vinylcopper **E** quickly undergoes a β -halogen elimination to afford the substitution product **F** and the organocopper **G**, which then reacts with **A** to regenerate the cuprate **B**.

This mechanism is consistent with our observations and with the results described in the literature. It is known that organocopper RCu readily reacts with alkoxyacetylene $\text{R}'\text{C}\equiv\text{COR''}$ to give a vinyl copper species in which the R group is connected to the carbon center bearing the oxygen atom.^[18] From chloroalkyne $\text{R}'\text{C}\equiv\text{CCl}$, the carbocupration also occurs, but the vinylcopper bearing a copper and a chlorine atom in the β -position is very unstable and only the elimination product $\text{R}'\text{C}\equiv\text{CR}$ is obtained, albeit in moderate yield.^[18] It is reported that the carbocupration of compounds such as $\text{RC}\equiv\text{CZ}$ ($\text{Z} = \text{OEt}, \text{Cl}$) must be performed in THF,^[18] whereas the same reaction with simple terminal alkynes $\text{RC}\equiv\text{CH}$ takes place in diethyl ether.^[19] In the case of $\text{RC}\equiv\text{CZ}$, the triple bond is more π acceptor than in the case of a simple terminal alkyne because of the presence of the electron-withdrawing substituent Z. Therefore, the role of THF, a better σ -donor ligand than diethyl ether, would be to favor the complexation of the copper(I) species to the triple bond by increasing the electronic density of the copper atom. According to the results described in the literature, the carbocupration is not a very rapid reaction.^[19d,20] Therefore, the addition to the triple bond is very likely the slow step in the catalytic cycle proposed in Scheme 3. Therefore, the improvement in the yield observed in the presence of NMP, a good σ -donor ligand, could result from the strengthening of the interaction between the copper atom and the triple bond (**D'** rather than **D**), which favors the carbocupration process. A similar effect was observed with various other σ -donor ligands such as TMEDA or triethyl phosphate (Table 1, entries 5 and 7). In the light of these considerations, the slow addition of the

Grignard reagent is required to avoid the presence of a large excess of Grignard reagent which directly reacts with the halogenoalkyne **C** through a metal–halogen exchange reaction.^[9] Of course, the presence of NMP also disfavors this side reaction since it accelerates the copper-catalyzed reaction.

In conclusion, we disclosed herein a very simple and efficient method for the preparation of a vast array of simple or functionalized internal alkynes. It is the first general procedure to couple aryl as well as secondary or tertiary alkyl Grignard reagents with alkynyl halides. This high yielding procedure is very attractive for large-scale preparations since it is performed under mild reaction conditions by using Grignard reagents, which are the most common commercially available organometallic reagents.

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