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Iron–Copper Cooperative Catalysis in the Reactions of Alkyl Grignard Reagents: Exchange Reaction with Alkenes and Carbometalation of Alkynes

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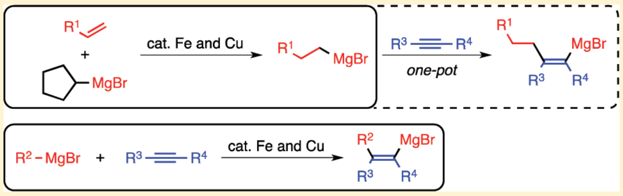
Supporting Information



ABSTRACT: Iron–copper cooperative catalysis is shown to be effective for an alkene–Grignard exchange reaction and alkylmagnesiation of alkynes. The Grignard exchange between terminal alkenes ($RCH{=}CH_2$) and cyclopentylmagnesium bromide was catalyzed by $FeCl_3$ (2.5 mol %) and CuBr (5 mol %) in combination with PBu_3 (10 mol %) to give RCH_2CH_2MgBr in high yields. 1-Alkyl Grignard reagents add to alkynes in the presence of a catalyst system consisting of $Fe(acac)_3$, CuBr, PBu_3, and *N,N,N′,N′*-tetramethylethylenediamine to give *β*-alkylvinyl Grignard reagents. The exchange reaction and carbometalation take place on iron, whereas copper assists with the exchange of organic groups between organoiron and organomagnesium species through transmetalation with these species. Sequential reactions consisting of the alkene–Grignard exchange and the alkylmagnesiation of alkynes were successfully conducted by adding an alkyne to a mixture of the first reaction. Isomerization of Grignard reagents from 2-alkyl to 1-alkyl catalyzed by Fe–Cu also is applicable as the first 1-alkyl Grignard formation step.

■ INTRODUCTION

Alkyl Grignard reagents are in a remarkable position among organometallic compounds in organic synthesis because of their high availability and ease of handling.[1] When an alkyl halide is available, we can obtain the corresponding alkyl Grignard reagent simply by mixing the alkyl halide with magnesium metal (direct method). However, the desired alkyl halides are not always readily available, and it is difficult to apply the direct method to the synthesis of alkyl Grignard reagents having C–X (X = halogen) or O–H bonds, which are not compatible with the Grignard formation step. Thus, there is still room for development of other synthetic methods. Primary alkyl Grignard reagents are known to be produced by isomerization of secondary alkyl Grignard reagents, which are otherwise structurally stable,[2] under the influence of transition-metal catalysis by Ti(IV)[3] or Ni(II)[4] through a *β*-hydride elimination–hydrometalation sequence.[5] As a mechanistically related reaction, the exchange between alkyl Grignard reagents and alkenes gives primary alkyl Grignard reagents derived from alkenes.[6] Although both the isomerization and exchange reactions are attractive alternatives to the direct method, their efficiencies were not sufficient in the reported examples.[3,4,6]

Carbometalation of alkynes is one of the most convenient methods for constructing alkene-based frameworks.[7] Among these, many examples of the addition of alkyl Grignard reagents to alkynes have been presented, probably because of the high availability of the starting alkyl Grignard reagents and the high utility of the resulting *β*-alkylvinyl Grignard reagents. However, high yields of alkylmagnesiation have been attained only for alkynes having a specific group such as a heteroatom[8,9] or a silyl[10] group, except for intramolecular reactions.[11] Although Jousseaume and co-workers reported that the nickel-catalyzed methylmagnesiation of alkynes having no heteroatoms proceeds in yields of up to 65%, alkyl Grignard reagents having *β*-hydrogen atoms add to alkynes in only ≤22% yields.[12–14]

Two catalysts sometimes work cooperatively to promote a reaction that does not take place with either of the catalysts alone.[15] Two of the most famous examples of cooperative catalysis are the Wacker oxidation[16] and the Sonogashira–Hagihara coupling,[17] each of which represents a major type of cooperative catalysis.[18] In the former type, the first catalyst contacts essentially with all of the substrates and transforms them into the desired products, whereas the second catalyst restores the first catalyst back to the original state. In the Wacker oxidation, a palladium(II) complex transforms ethylene and water into acetaldehyde and is transformed into a palladium(0) complex, which is oxidized back to the palladium(II) complex by a copper(II) catalyst with the aid of oxygen as a terminal oxidant. There have been many reports on this type of cooperative catalysis, in particular on oxidation reactions. In the latter type, the first and second catalysts contact with substrates A and B, respectively, to give two distinct intermediates, which are combined into one species leading to the product. The Sonogashira–Hagihara coupling employs palladium(0) and copper(I) catalysts that react with an organic halide (R–X) and a terminal alkyne (R′–C≡C–H), respectively. Transmetala-

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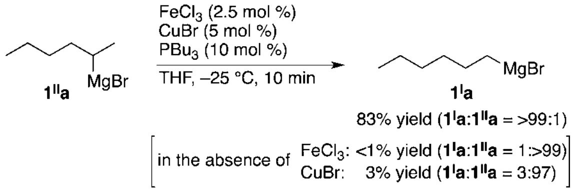
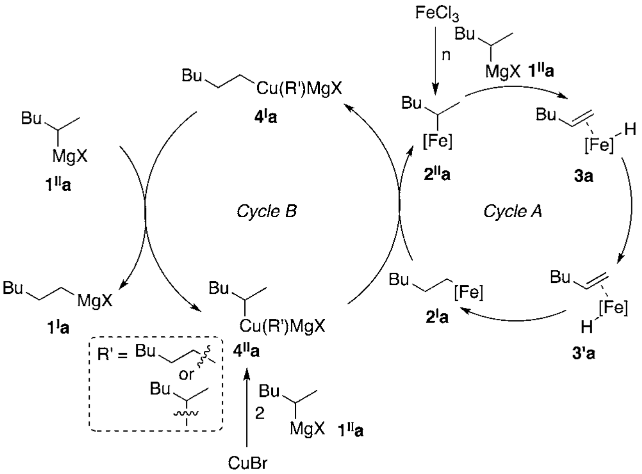
tion between the resulting R−Pd^{II}−X and R′−C≡C−Cu^{I} species gives R−Pd^{II}−C≡C−R′, which undergoes reductive elimination to give the coupling product R−C≡C−R′ and regenerate the palladium(0) and copper(I) catalysts. Cooperative catalysis of this type should offer ample opportunities not only for improvement of the known transformation but also for the development of new reactions that are not possible with any single catalyst.

We have reported that Fe−Cu cooperative catalysis is effective for arylmagnesiation of dialkylacetylenes having no heteroatoms.[19] In this cooperative catalysis, which is classified into the group of the Sonogashira−Hagihara coupling, iron is engaged in addition to alkynes, and copper takes charge of exchange of organic groups between iron and magnesium by transmetalation. The Fe−Cu cooperative catalysis has also been applied to the isomerization of alkyl Grignard reagents from 2-alkyl to 1-alkyl.[20] For example, 2-hexylmagnesium bromide ($\mathbf{1^{II}a}$) was fully isomerized to the 1-hexyl derivative ($\mathbf{1^{I}a}$) in 83% yield by reaction at −25 °C for 10 min in tetrahydrofuran (THF) in the presence of $FeCl_3$ (2.5 mol %), CuBr (5 mol %), and PBu_3 (10 mol %) (Scheme 1). In contrast, the reaction in the absence of $FeCl_3$ or CuBr gave only <1 or 3% yield of $\mathbf{1^{I}a}$. The driving force for this reaction must be the high thermodynamic stability of primary alkyl Grignard reagents in comparison with secondary derivatives. Several examinations, including D-labeling experiments and stoichiometric reactions using $FeCl_3$ or CuBr, showed that the roles of iron and copper are essentially the same as in the arylmagnesiation of alkynes (Scheme 2). Thus, the reaction of $FeCl_3$ with $\mathbf{1^{II}a}$ gives 2-hexyliron ($\mathbf{2^{II}a}$), which undergoes β-hydride elimination to give hydride complex **3a** coordinated with 1-hexene. After rotation of the alkene on the iron, hydroferration converts **3′a** into 1-hexyliron ($\mathbf{2^{I}a}$), which undergoes transmetalation with 2-alkylcuprate $\mathbf{4^{II}a}$ generated from CuBr and $\mathbf{1^{II}a}$, giving 1-alkylcuprate $\mathbf{4^{I}a}$ and regenerating $\mathbf{2^{II}a}$. Further transmetalation of $\mathbf{4^{I}a}$ with $\mathbf{1^{II}a}$ gives isomerized 1-alkyl Grignard reagent $\mathbf{1^{I}a}$ and regenerates $\mathbf{4^{II}a}$.

Scheme 1



Scheme 2

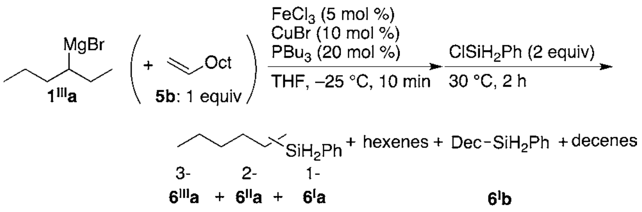


Here we report that iron−copper cooperative catalysis is effective for the alkene−Grignard exchange reaction and alkylmagnesiation of alkynes. Terminal alkenes are transformed into the corresponding 1-alkyl Grignard reagents in high to moderate yields through the use of cyclopentylmagnesium bromide as an exchanging alkyl Grignard reagent.[21] Alkylmetalation of alkynes, including those having no heteroatoms, proceeded with alkyl Grignard reagents having β-hydrogen atoms. Furthermore, under iron−copper cooperative catalysis, it is possible to perform the alkene−Grignard exchange and the alkylmagnesiation sequentially just by adding an alkyne to the mixture of the first reaction, where the isomerization of 2-alkyl Grignard reagents also can be used for the first 1-alkyl Grignard formation step.

RESULTS AND DISCUSSION

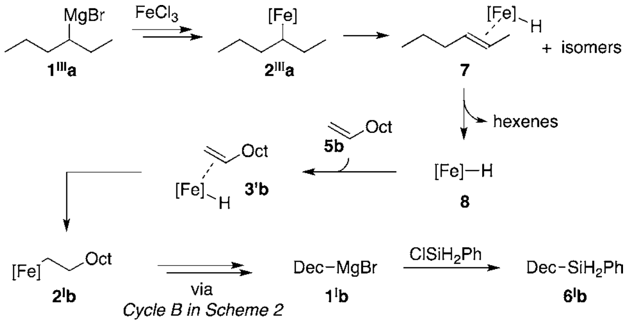
Exchange Reaction between Alkyl Grignard Reagents and Alkenes. Under the conditions that were effective for isomerization of 2-hexylmagnesium bromide ($\mathbf{1^{II}a}$) to the 1-hexyl derivative $\mathbf{1^{I}a}$, 3-hexyl Grignard reagent $\mathbf{1^{III}a}$ did not undergo efficient isomerization to $\mathbf{1^{I}a}$ even in the presence of twice the amount of the Fe−Cu catalyst. Thus, treatment of $\mathbf{1^{III}a}$ (1 equiv) with $FeCl_3$ (5 mol %), CuBr (10 mol %), and PBu_3 (20 mol %) in THF at −25 °C for 10 min followed by the reaction of the resulting alkyl Grignard reagents with $ClSiH_2Ph$ (2 equiv) at 30 °C for 2 h gave 3-hexyl(phenyl)silane ($\mathbf{6^{III}a}$) and 1-hexylsilane $\mathbf{6^{I}a}$ in yields of 61 and 10%, respectively (Scheme 3). A considerable amount of hexenes (18% yield), mainly consisting of internal ones, were produced, probably through dissociation of the sterically demanding internal alkenes from complexes **7** generated from $\mathbf{2^{III}a}$ (Scheme 4).

Scheme 3



	$\mathbf{6^{III}a}$	$\mathbf{6^{II}a}$	$\mathbf{6^{I}a}$	hexenes	$\mathbf{6^{I}b}$	decenes
GC yield (%)	61	<1	10	18	—	—
(with **5b**	5	<1	15	44	60	31)

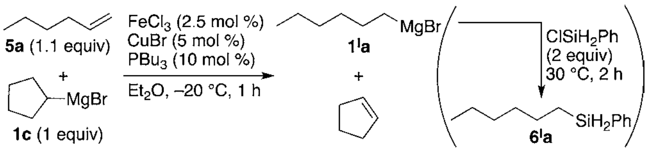
Scheme 4



The low catalytic activity likely can be ascribed to the instability of free iron–hydride complex **8**. To prevent decomposition of **8**, the reaction of **1$^{\text{III}}$a** in the presence of 1-decene (**5b**) (1 equiv) was conducted, and it gave a 60% yield of 1-decylsilane **6$^{\text{I}}$b**, where most of the MgBr moiety was transferred from the C_6 to the C_{10} component (Scheme 3).[6,22] As shown in Scheme 4, the added terminal alkene probably prevents decomposition of free iron–hydride complex **8** by forming complex **3′b**, which is converted into **2$^{\text{I}}$b** through hydroferration and then to Grignard reagent **1$^{\text{I}}$b** via cycle B in Scheme 2.[23]

The reaction of 3-hexylmagnesium bromide (**1$^{\text{III}}$a**) with 1-decene (**5b**) to give a 60% yield of 1-decyl Grignard reagent **1$^{\text{I}}$b** shows the potential of the iron–copper system as a catalyst for the alkene–Grignard exchange reaction. Thus, we looked for more efficient exchanging alkyl Grignard reagents (R–MgBr) than **1$^{\text{III}}$a** in the exchange reaction of 1-hexene (**5a**). Of several alkyl Grignard reagents examined, cyclopentylmagnesium bromide (**1c**) was the most effective, affording a high yield of 1-hexylmagnesium bromide (**1$^{\text{I}}$a**) upon reaction at −20 °C for 1 h (Scheme 5), which was carried out under the conditions used for the isomerization of Grignard reagents.[20] Here again, the cooperative catalysis was apparent. No exchange took place with the copper catalyst alone, and only a 44% yield of **6$^{\text{I}}$a** was produced with the iron catalyst alone. Table 1 summarizes the efficiency of alkyl Grignard reagents in the exchange reaction with **5a**. Cyclohexylmagnesium bromide (**1d**) was much less effective, as 71% of the Grignard reagent remained unreacted (entry 2). The large difference lies most likely in the conformation of the intermediate alkyliron complex. Cyclopentyliron complexes readily take conformations in which one of the hydrogen atoms is located at the syn-periplanar position with respect to the iron, facilitating *β*-hydride elimination, while such conformations are not available with cyclohexyliron complexes. 3-Pentylmagnesium bromide (**1e**) gave the second best result of the four alkyl Grignard reagents examined. Because primary alkyl Grignard reagents and 1-alkenes are in an equilibrium under the Fe–Cu catalyst system, 1-propylmagnesium bromide (**1$^{\text{I}}$f**) was not a Grignard reagent of choice for the present exchange reaction (entry 4).

Scheme 5

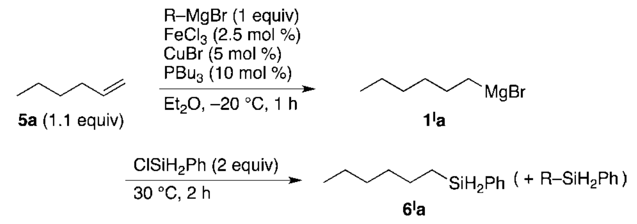


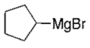
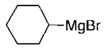
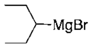
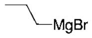
91% GC yield (80% isolated yield) of **6$^{\text{I}}$a** based on **1c**

[in the absence of FeCl$_3$: <1% GC yield
CuBr: 44% GC yield]

The Fe–Cu-catalyzed exchange reaction using cyclopentylmagnesium bromide (**1c**) to give 1-alkyl Grignard reagent **1$^{\text{I}}$** was applicable to various terminal alkenes (Table 2). Trapping of the reaction mixture by ClSiH$_2$Ph showed that MgBr is attached exclusively to the nonsubstituted carbon atom of the alkene. All of the alkenes used in Table 2 are more readily accessible than the corresponding 1-alkyl halides, which are required for the preparation of the same Grignard reagents by the direct method. Diene **5k** underwent a selective exchange reaction at the monosubstituted alkene moiety (entry 5). A dimagnesioalkane, which was converted to **6$^{\text{I}}$l**, was obtained from diene **5l** having double bonds at both terminals (entry 6).

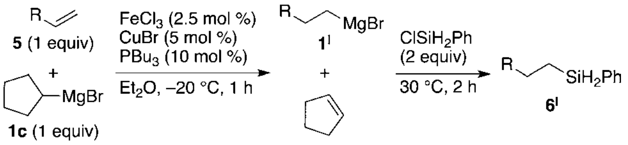
Table 1. Exchange Reaction between an Alkyl Grignard Reagent and 1-Hexene[a]

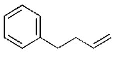
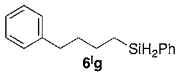
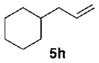
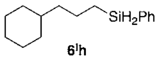
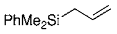
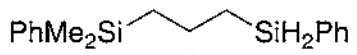
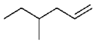
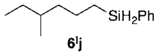
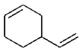
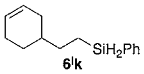
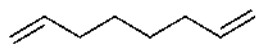
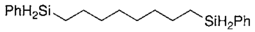


entry	R–MgBr	yield (%)[b] 6$^{\text{I}}$a	R–SiH$_2$Ph
1	 **1c**	91 (80)[c]	2
2	 **1d**	7	71
3	 **1e**	66	11 (+ 15)[d]
4	 **1$^{\text{I}}$f**	36	50

[a] The reaction was carried out in Et$_2$O (1.6 mL) at −20 °C for 1 h under a nitrogen atmosphere using 1-hexene (**5a**) (0.44 mmol), an alkylmagnesium bromide (R–MgBr) (0.40 mmol), and PBu$_3$ (0.040 mmol) in the presence of FeCl$_3$ (0.010 mmol) and CuBr (0.020 mmol), which was followed by treatment with ClSiH$_2$Ph (0.80 mmol) at 30 °C for 2 h. [b] Determined by GC based on R–MgBr. [c] The yield after isolation is given in parentheses. [d] The yield of 1-pentyl(phenyl)silane is shown in parentheses.

Table 2. Exchange Reaction between Cyclopentylmagnesium Bromide and Terminal Alkenes[a]

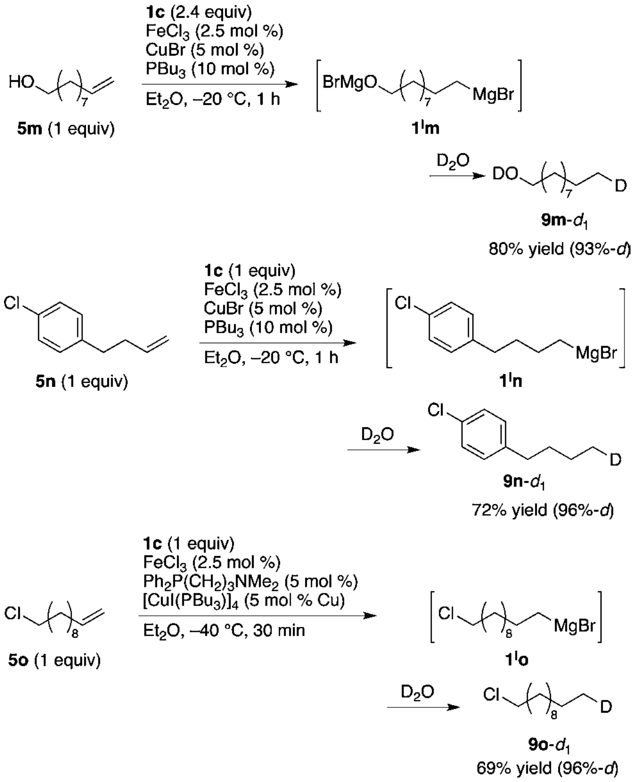


entry	5	time (h)	yield (%)[b]	product
1	 **5g**	1	72	 **6$^{\text{I}}$g**
2	 **5h**	2	68	 **6$^{\text{I}}$h**
3	 **5i**	6	60[c]	 **6$^{\text{I}}$i**
4	 **5j**	2	72	 **6$^{\text{I}}$j**
5	 **5k**	6	51	 **6$^{\text{I}}$k**
6	 **5l**	6	61	 **6$^{\text{I}}$l**

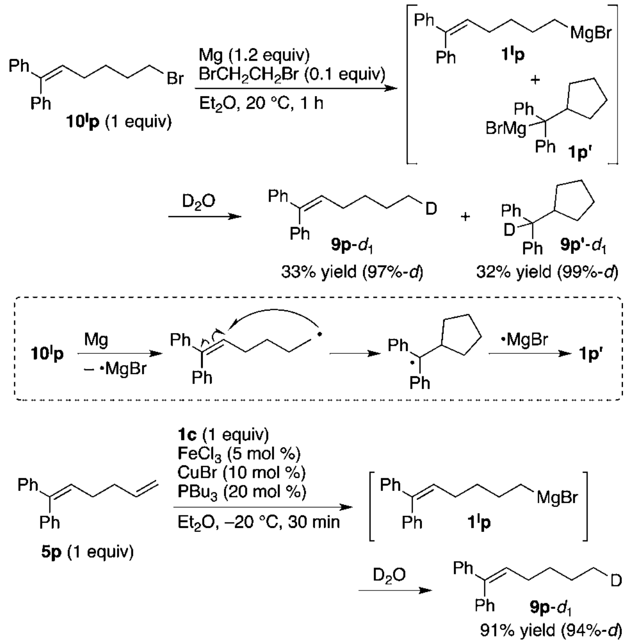
[a] The reaction was carried out in Et$_2$O (1.6 mL) at −20 °C under a nitrogen atmosphere using terminal alkene **5** (0.40 mmol) and cyclopentylmagnesium bromide (**1c**) (0.40 mmol) in the presence of FeCl$_3$ (0.010 mmol), CuBr (0.020 mmol), and PBu$_3$ (0.040 mmol), which was followed by treatment with ClSiH$_2$Ph (0.80 mmol) at 30 °C for 2 h. [b] Yields of the isolated products. [c] 2-(Phenylsilyl)-1-(phenyldimethylsilyl)propane also was produced in 3% yield.

The exchange reaction was applied to the synthesis of alkyl Grignard reagents having functional groups that are not compatible with the direct Grignard synthesis from a halide and magnesium metal (Scheme 6). Hydroxyalkene **5m** underwent the exchange reaction to give alkyl Grignard reagent **1$^{\text{I}}$m** with an alcolate moiety at the expense of an extra

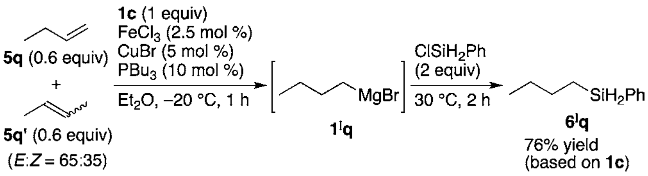
Scheme 6



Scheme 7



Scheme 8



equivalent of **1c**. The reaction was applicable to the preparation of alkyl Grignard reagent **1**^{I}**n**, which has a chloroarene moiety and is difficult to synthesize from the corresponding dihalo compound through selective transformation of the haloalkane moiety over the haloarene. In the reaction of chloroalkene **5o** under the standard conditions at −20 °C, competitive HCl elimination at the chloroalkane moiety lowered the yield of 11-chloroundecylmagnesium bromide (**1**^{I}**o**). The reaction at a lower temperature (−40 °C) using a catalyst consisting of $FeCl_3$, *N*,*N*-dimethyl[3-(diphenylphosphino)propyl]amine, and $[CuI(PBu_3)]_4$ gave an improved yield of chloroalkyl Grignard reagent **1**^{I}**o**.

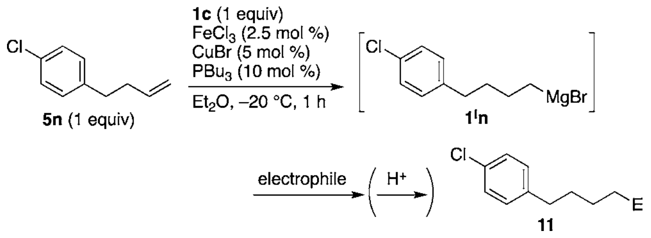
Grignard formation from alkyl halides and Mg is sometimes hampered by side reactions induced by alkyl radical intermediates. The reaction of 6-bromo-1,1-diphenyl-1-hexene (**10**^{I}**p**) with Mg gave a 1:1 mixture of linear and cyclic alkyl Grignard reagents **1**^{I}**p** and **1p**′, respectively, the structures of which were confirmed by quenching the reaction mixture with D_2O (Scheme 7).[24] The formation of **1p**′ is thought to occur when the 6,6-diphenyl-5-hexenyl radical generated by transfer of a single electron from Mg to haloalkene **10**^{I}**p** cyclizes before receiving one more electron from Mg. In contrast, the exchange reaction between 1,1-diphenyl-1,5-hexadiene (**5p**) and **1c** gave only linear Grignard reagent **1**^{I}**p** in a high yield.

Subjecting an isomeric mixture of 1-butene and (*Z*)- and (*E*)-2-butene to the Fe−Cu cooperative catalysis gave isomerically pure 1-butyl Grignard reagent **1**^{I}**q**, the structure of which was confirmed after transformation to 1-butylsilane **6**^{I}**q** (Scheme 8).

In addition to $ClSiH_2Ph$ and D_2O, carbon and heteroatom electrophiles react with alkyl Grignard reagents obtained by exchange reactions with alkenes. Thus, a reaction mixture of 4-(4-chlorophenyl)-1-butene (**5n**) and **1c** under the iron−copper catalysis was treated with carbon dioxide at −20 °C for 30 min to give 5-phenylpentanoic acid in 75% yield after acidic workup (Table 3, entry 1). Benzaldehyde also reacted as a carbon electrophile, giving the benzylic alcohol (entry 2). The reaction with iodine gave the 1-alkyl iodide, corresponding to anti-Markovnikov hydrohalogenation of a terminal alkene (entry 3).

Alkylmagnesiation of Alkynes. The reaction conditions that were effective for the arylmagnesiation of alkynes,[19] which was carried out in THF at 60 °C, did not work efficiently in the present alkylmagnesiation. Thus, the reaction of butylmagnesium bromide (**1**^{I}**q**) (2 equiv) with 1-phenyl-1-hexyne (**12a**) (1 equiv) in THF in the presence of $Fe(acac)_3$ (5 mol %), CuBr (10 mol %), and PBu_3 (40 mol %) at 60 °C for 3 h followed by methanolysis gave only a 20% yield of 2-butyl-1-phenyl-1-hexene (**14qa**) with 65% conversion of **12a** (Table 4, entry 1). Changing the solvent from THF to Et_2O drastically improved the yield and the reaction rate, giving **14qa** in 78% yield at −20 °C (entry 2).[25] A large amount of a yellowish-brown precipitate was observed in the reaction in THF at −20 °C, and the yield of **14qa** was only 2% after 3 h (entry 3). Although reduction of the amount (20 mol %) of PBu_3 severely lowered the yield, a combination of PBu_3 (20 mol %) with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (20 mol %) improved the yield to 87% (entries 4 and 5). The use of TMEDA in the absence of PBu_3 was totally ineffective (entry 6). A small amount (2%) of **14qa** was observed in a quenched sample of the reaction after 1 min in the presence of the iron catalyst alone, though it disappeared after 3 h (entries 7 and 8). In contrast, **14qa** was not observed at all with the copper catalyst alone in either a short or long reaction period, with alkyne **12a** mostly remaining unreacted (entries 9 and 10). These results clearly show that

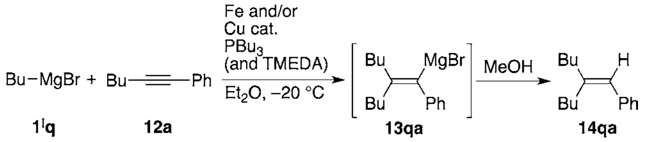
Table 3. Reaction of an Exchange Product with Electrophiles[a]



entry	electrophile (equiv)	conditions	E	yield (%)[b]
1	CO_2(g) (excess)	−20 °C, 30 min	CO_2H	75
2	PhCHO (1)	−20 °C, 10 min	CH(OH)Ph	73
3	I_2 (2)	−78 °C, 15 min	I	81

[a] Grignard reagent **1**$^{\rm I}$**n** obtained as a reaction mixture was treated with an electrophile. [b] Yields of the isolated products.

Table 4. Butylmagnesiation of 1-Phenyl-1-hexyne Followed by Methanolysis[a]



	amount (mol %)					
entry	$Fe(acac)_3$	CuBr	additive (mol %)	time	conv. of **12a** (%)[b]	yield of **14qa** (%)[b]
1[c,d]	5	10	PBu_3 (40)	3 h	65	20
2	5	10	PBu_3 (40)	3 h	>99	78
3[c]	5	10	PBu_3 (40)	3 h	15	2
4	5	10	PBu_3 (20)	3 h	53	34
5	5	10	PBu_3 (20), TMEDA (20)	3 h	>99	87 (86)[e]
6	5	10	TMEDA (40)	3 h	14	<1
7	5	0	PBu_3 (20), TMEDA (20)	1 min	8	2
8	5	0	PBu_3 (20), TMEDA (20)	3 h	18	<1
9	0	10	PBu_3 (20), TMEDA (20)	1 min	<1	<1
10	0	10	PBu_3 (20), TMEDA (20)	3 h	1	<1

[a] The reaction was carried out at −20 °C in Et_2O (1.8 mL) under a nitrogen atmosphere using butylmagnesium bromide (**1**$^{\rm I}$**q**) (0.80 mmol) and 1-phenyl-1-hexyne (**12a**) (0.40 mmol) in the presence of $Fe(acac)_3$ (0.020 mmol) and/or CuBr (0.040 mmol). [b] Determined by GC. [c] THF was used as the solvent instead of Et_2O. [d] Reaction temperature = 60 °C. [e] The yield after isolation is given in parentheses.

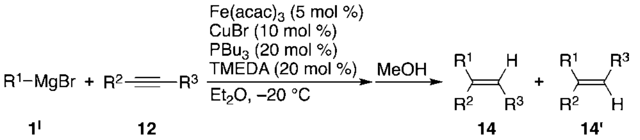
the cooperative catalysis is essential for the alkylmagnesiation to take place.

The scope of the alkylmagnesiation of alkynes is shown in Table 5. The yields were high for the reaction of aryl alkynes having an electron-donating or -withdrawing substituent on the aryl group (entries 1−4). An aryl chloride moiety was compatible with the alkylmagnesiation (entry 5). The introduction of a bulky alkyl group at the ortho position of the aryl group on the alkyne retarded the reaction, but acceptable yields of the adduct were obtained (entries 6 and 7). A heteroarylacetylene and an ynoate reacted with **1**$^{\rm I}$**q** in high yields (entries 8 and 9). Dialkylacetylenes were unreactive under these conditions. The reaction of **1**$^{\rm I}$**q** with 1-phenyl-1-butyne (**12k**) gave a mixture of stereoisomers (**14qk**:**14′qk** = 45:55), showing that the present alkylmagnesiation unfortunately does not proceed stereoselectively (entry 10). When the reaction was quenched after a reaction time of 1 min, a nearly equimolar isomeric mixture (**14qk**:**14′qk** = 49:51, 6% yield) was produced. The isomerization possibly takes place at the stage of intermediate alkenyliron and/or -copper complexes. As the alkyl group on the alkyne became bulkier, the yield of adduct decreased (entries 11 and 12), but even the reaction of an isopropylacetylene gave a 59% yield of the addition product. Other alkyl Grignard reagents, including one having a methoxy group, underwent the addition (entries 13−16). The reaction using butylmagnesium chloride and dibutylmagnesium also gave the alkylmagnesiation products (entries 17 and 18).

The generation of alkenyl Grignard reagents by the alkylmagnesiation was confirmed by the production of deuterated alkene **14qa**-d_1 in a high deuteration ratio (98% D) upon deuteriolysis of the reaction mixture of **1**$^{\rm I}$**q** and **12a** (Scheme 9). The alkylmagnesiation products are applicable to carbon−carbon bond-forming reactions. For example, allylic alcohol **15** was obtained in high yield by the reaction of **13qa** with benzaldehyde.

The result that both the iron and copper catalysts are needed to promote the alkylmagnesiation of alkynes, as in the case with the arylmagnesiation, prompted us to consider a mechanism of cooperative catalysis similar to that proposed for the arylmagnesiation.[19] To confirm that the iron complex is responsible for the alkylmetalation, we conducted stoichiometric reactions using an iron or copper complex, as shown in Scheme 10. Treatment of equimolar amounts of $Fe(acac)_3$ and 1-phenyl-1-hexyne (**12a**) with neopentylmagnesium bromide (**1**$^{\rm I}$**r**) (10 equiv) in the presence of PBu_3 (4 equiv) and TMEDA (4 equiv) at 20 °C for 2 h gave a 62% yield of **14ra**. In contrast, **14ra** was not produced at all in the same treatment with CuBr instead of $Fe(acac)_3$. These results in addition to

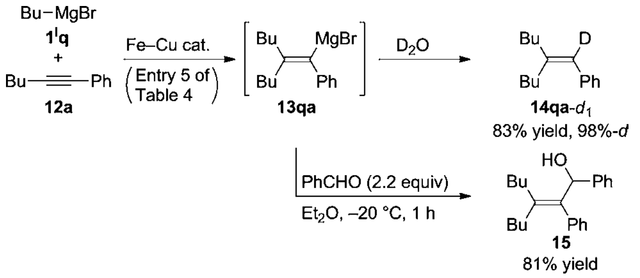
Table 5. Alkylmagnesiation of Alkynes Followed by Methanolysis[a]



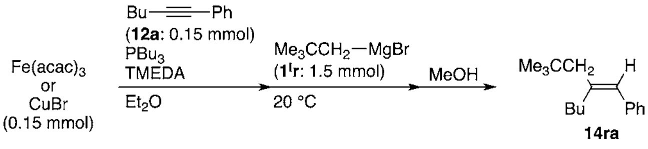
entry	R^1	R^2	R^3	time (h)	yield (%)[b]	**14**:**14′**[c]
1	Bu ($\mathbf{1^Iq}$)	Bu	4-MeOC_6H_4 (**12b**)	3	80	—
2	Bu ($\mathbf{1^Iq}$)	Bu	3-MeOC_6H_4 (**12c**)	3	85	—
3	Bu ($\mathbf{1^Iq}$)	Bu	$4\text{-(CF}_3)C_6H_4$ (**12d**)	3	86	—
4	Bu ($\mathbf{1^Iq}$)	Bu	$3\text{-(CF}_3)C_6H_4$ (**12e**)	3	93	—
5	Bu ($\mathbf{1^Iq}$)	Bu	4-ClC_6H_4 (**12f**)	3	77	—
6	Bu ($\mathbf{1^Iq}$)	Bu	2-MeC_6H_4 (**12g**)	3	93	—
7	Bu ($\mathbf{1^Iq}$)	Bu	2-(*i*-Pr)C_6H_4 (**12h**)	18	71	—
8	Bu ($\mathbf{1^Iq}$)	Bu	2-thienyl (**12i**)	3	79	—
9[d]	Bu ($\mathbf{1^Iq}$)	Bu	CO_2Et (**12j**)	0.2	84	—
10	Bu ($\mathbf{1^Iq}$)	Et	Ph (**12k**)	3	87	45:55
11	Bu ($\mathbf{1^Iq}$)	*i*-Bu	Ph (**12l**)	21	76	39:61
12	Bu ($\mathbf{1^Iq}$)	*i*-Pr	Ph (**12m**)	21	59	64:36
13	Hex ($\mathbf{1^Ia}$)	Bu	Ph (**12a**)	3	85	53:47[f]
14	*i*-Bu ($\mathbf{1^Iq'}$)	Bu	Ph (**12a**)	9	88	79:21
15	Me_3CCH_2 ($\mathbf{1^Ir}$)	Bu	Ph (**12a**)	3	61	97:3
16[e]	$MeO(CH_2)_4$ ($\mathbf{1^Is}$)	Hex	Ph (**12n**)	4	57	54:46[f]
17	Bu (BuMgCl)	Bu	Ph (**12a**)	3	89[g]	—
18	Bu (Bu_2Mg)	Bu	Ph (**12a**)	3	88[g]	—

[a] The reaction was carried out at −20 °C in Et_2O (1.8 mL) under a nitrogen atmosphere using alkylmagnesium bromide $\mathbf{1^I}$ (0.80 mmol) and alkyne **12** (0.40 mmol) in the presence of $Fe(acac)_3$ (0.020 mmol), CuBr (0.040 mmol), PBu_3 (0.080 mmol), and TMEDA (0.080 mmol). [b] Yields of the isolated products based on **12**. [c] Determined by GC and/or ^1H NMR spectroscopy. [d] Reaction temperature = −78 °C. [e] $MeO(CH_2)_4MgCl$ was used. [f] The configuration was not determined. [g] Determined by GC.

Scheme 9

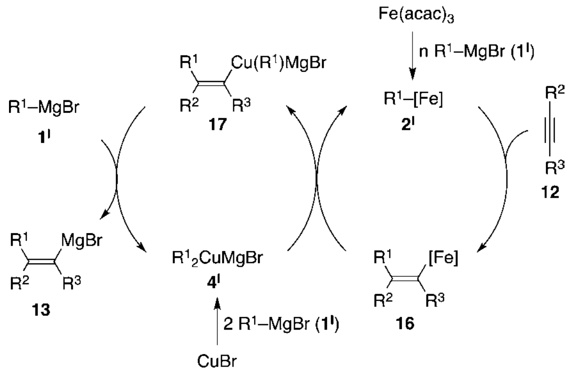


Scheme 10



complex	PBu_3	TMEDA	time	conv. of **12a**	yield	*E*:*Z*
$Fe(acac)_3$	0.60 mmol	0.60 mmol	2 h	>99%	62%	79:21
CuBr	0.30 mmol	0.30 mmol	24 h	<5%	<1%	—

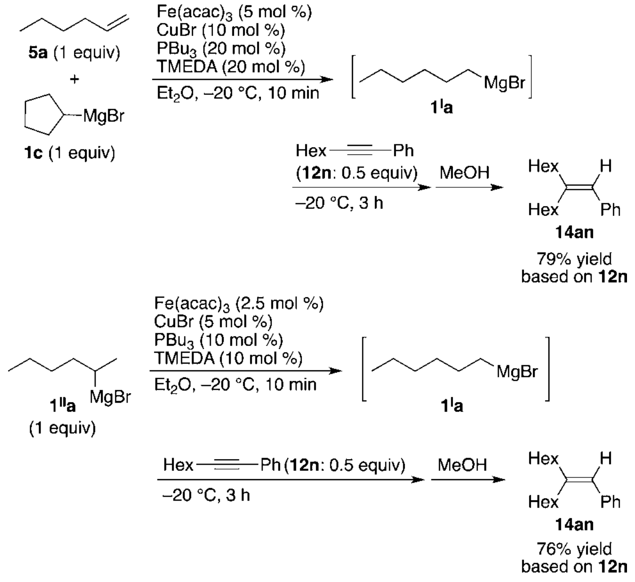
Scheme 11



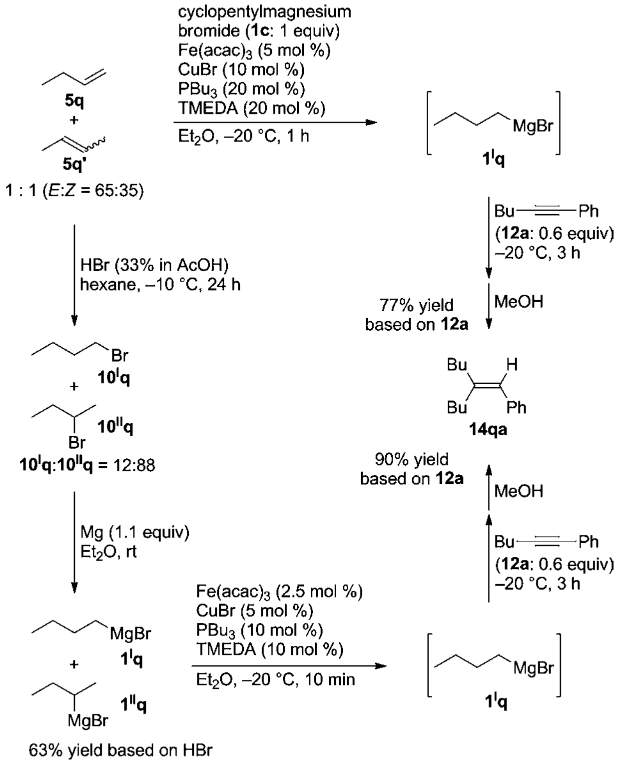
other observations prompted us to draw a plausible catalytic cycle (Scheme 11) wherein addition of alkyl groups to alkynes takes place on iron and transmetalation of cuprates promotes the exchange of organic groups between iron and magnesium. Thus, the low-valent alkyliron species $\mathbf{2^I}$ generated from $Fe(acac)_3$ upon reaction with excess alkyl Grignard reagent $\mathbf{1^I}$ adds to alkyne **12** to give alkenyliron **16**, which cannot undergo transmetalatation directly with $\mathbf{1^I}$. Thus, the iron complex alone cannot catalyze the alkylmagnesiation. If one supposes that **16** is unstable under the reaction conditions, the result that the yield of **14qa** generated by methanolysis of **16** is 2% or <1% in a short or long reaction period, respectively (Table 4, entries 7 and 8), can be rationally understood. In the presence of the copper cocatalyst, dialkylcuprate $\mathbf{4^I}$ generated from CuBr and $\mathbf{1^I}$ undergoes transmetalation with **16** to give alkenylcuprate **17** and regenerate alkyliron species $\mathbf{2^I}$. Finally, transmetalation of cuprate **17** with $\mathbf{1^I}$ gives alkylmagnesiation product **13** and regenerates dialkylcuprate $\mathbf{4^I}$.

Two Successive Reactions Both Catalyzed Cooperatively by Iron and Copper Complexes. We have shown that iron−copper cooperative catalysis is effective for both the alkene−Grignard exchange reaction to give 1-alkyl Grignard reagents and the alkylmagnesiation of alkynes to give alkenyl Grignard reagents. Thus, successive reactions of the alkene−Grignard exchange and the alkylmagnesiation of alkynes with the resulting 1-alkyl Grignard reagent would be expected to occur upon addition of the alkyne to a reaction mixture of the first reaction. This was realized by use of the catalyst system optimized for the alkylmagnesiation, which proceeds efficiently in the presence of PBu_3 and TMEDA. Thus, treatment of 1-hexene (**5a**) with cyclopentylmagnesium bromide (**1c**) in the presence of $Fe(acac)_3$ (5 mol %), CuBr (5 mol %), PBu_3 (20 mol %), and TMEDA (20 mol %) in Et_2O at −20 °C for 10 min was followed by addition of 1-phenyl-1-octyne (**12n**) (0.5 equiv), and quenching with methanol after 3 h gave 2-hexyl-1-phenyl-1-octene (**14an**) in 79% yield based on **12n** (Scheme 12). The addition product **14an** was also obtained from 2-hexylmagnesium bromide ($\mathbf{1^{II}a}$) and **12n** through isomerization followed by the alkylmagnesiation. As shown in Scheme 13, the exchange reaction with cyclopentyl Grignard reagent **1c** converted an isomeric mixture of butenes in a single step into isomerically pure 1-butyl Grignard reagent $\mathbf{1^{I}q}$, which added to alkyne **12a** to give the addition product **14qa**. An isomeric mixture of butylmagnesium bromides ($\mathbf{1^{I}q}$ and $\mathbf{1^{II}q}$) prepared from an isomeric mixture of butenes through hydrobromination followed by reaction with magnesium was treated with the iron−copper catalyst to give isomerically pure $\mathbf{1^{I}q}$, which underwent alkylmagnesiation of **12a** without the addition of an extra catalyst.

Scheme 12



Scheme 13



■ CONCLUSION

We have disclosed that iron−copper cooperative catalysis is effective for the exchange reaction between terminal alkenes and cyclopentylmagnesium bromide and for alkylmagnesiation of alkynes. Various terminal alkenes were transformed to 1-alkyl Grignard reagents, including those having a haloarene or haloalkane moiety and thus otherwise being not so readily accessible. The alkylmagnesiation was applied to various phenylalkynes having an electron-donating or -withdrawing substituent on the benzene ring. Studies of the reaction mechanism, including reactions using a stoichiometric amount of an iron or copper complex, revealed the roles of the iron and copper catalysts. In these reactions, transformation of the organic group takes place on iron through *β*-hydride elimination/hydroferration or alkylferration, whereas copper transfers the resulting organic group from iron to magnesium and brings the alkyl group of the starting Grignard reagent to iron.

The products of the exchange reaction are 1-alkyl Grignard reagents, which are exactly the substrates of the alkylmagnesiation. Thus, these two types of reactions were successively conducted in one pot by adding an alkyne after the first reaction. This was successful because the first reaction does not form any byproducts that would inhibit the second reaction and the catalyst system survives after the first reaction. This presents a rare example of a one-pot reaction consisting of two cooperatively catalyzed reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The transfer ratio of the MgBr moiety from the C6 to the C10 component was much less when 1-hexylmagnesium bromide (**1**$^{\mathrm{I}}$**a**) was used instead of **1**$^{\mathrm{III}}$**a**. Thus, the reaction of **1**$^{\mathrm{I}}$**a** in the presence of 1-decene (**5b**) under the same conditions as in Scheme 3 gave **6**$^{\mathrm{I}}$**a** (70% yield), hexenes (11% yield), **6**$^{\mathrm{I}}$**b** (7% yield), and decenes (92% yield).

(23) The addition of 1-decene after premixing all of the other components for 30 min did not affect the yields of **6**$^{\mathrm{III}}$**a**, **6**$^{\mathrm{I}}$**a**, and hexenes (59, 7, and 23%, respectively), and most of the 1-decene (**5b**) remained unreacted (**5b**, 83%; **6**$^{\mathrm{I}}$**b**, 3%).

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