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Copper-Catalyzed Regioselective Hydroalkylation of 1,3-Dienes with Alkyl Fluorides and Grignard Reagents**

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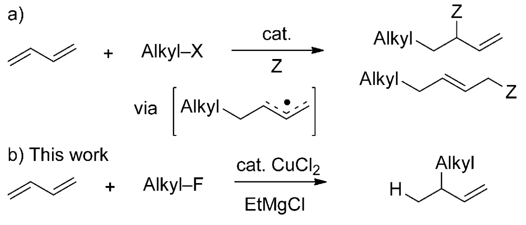
Abstract: *Copper complexes generated in situ from CuCl$_2$, alkyl Grignard reagents, and 1,3-dienes play important roles as catalytic active species for the 1,2-hydroalkylation of 1,3-dienes by alkyl fluorides through C–F bond cleavage. The alkyl group is introduced to an internal carbon atom of the 1,3-diene regioselectively, thus giving rise to the branched terminal alkene product.*

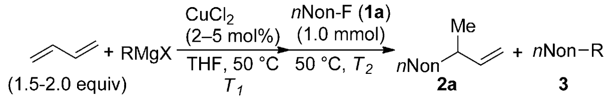
Although 1,3-butadiene is one of the most fundamental and important chemical feedstocks, and a number of transition-metal-catalyzed transformations of dienes to assemble various organic intermediates have been developed,[1–5] its alkylation to produce internal or terminal alkenes is rare. Among them, alkylation using readily available alkyl halides by addition of alkyl radicals toward 1,3-dienes is one of the most useful methods. However, the alkyl group from alkyl halides is introduced onto the terminal carbon atom of the 1,3-diene framework, due to the stability of thus formed allyl radicals (Scheme 1 a).[2] Therefore, alkylation of the internal carbon atom of the 1,3-dienes by simple alkyl halides has not been reported.[6] Herein, we report first general and regioselective copper-catalyzed 1,2-hydroalkylation of 1,3-dienes by alkyl fluorides as an electrophile, wherein an internal carbon atom of the 1,3-dienes is selectively alkylated to afford branched terminal alkenes (Scheme 1 b).



Scheme 1. Alkylation of 1,3-butadiene using alkyl halides.

Previously, we reported on cross-coupling reactions of alkyl fluorides with Grignard reagents using either Co, Ni, or Cu catalysts in the presence of unsaturated hydrocarbon ligands.[7–9] During the course of our studies on the cross-coupling of unactivated alkyl fluorides with alkyl Grignard reagents, we accidentally found that the addition order of the reagents, as well as the reaction conditions and the structures of reagents exerted a significant effect on the reaction course. For example, when *n*NonF (**1a**) was added to a mixture of 5 mol% of CuCl$_2$, 2 equivalents of *n*BuMgCl, and an excess amount of 1,3-butadiene in THF, and the mixture stirred at 50°C for 12 h, the expected cross-coupling product tridecane (**3**) was formed only in 17% yield and the terminal alkene **2a** was obtained as a single regioisomer in 72% yield (Table 1, entry 1). When CuCl$_2$ was treated with *n*BuMgCl and 1,3-butadiene at 50°C for 3 minutes prior to the addition of *n*NonF, **3** was formed in only 3% and the yield of **2a** was increased to 84% (entry 2). The cross-coupling was completely suppressed, thus giving rise to **2a** in 88% yield when the pretreatment time was prolonged to 10 minutes (entry 3). The amount of *n*BuMgCl can be reduced to 1.5 equivalents without loss in yield of **2** (entry 4). The use of EtMgCl gave

Table 1: Copper-catalyzed coupling reactions of alkyl fluorides, Grignard reagents, and 1,3-butadiene.[a]



Entry	RMgX (equiv)	T_1 [min]/T_2 [h]	Yield [%][b] **2a**	**3**
1	*n*BuMgCl (2.0)	0/12	72	17
2	*n*BuMgCl (2.0)	3/12	84	3
3	*n*BuMgCl (2.0)	10/12	88	n.d.
4[c]	*n*BuMgCl (1.5)	10/12	88	n.d.
5[c]	EtMgCl (1.5)	10/24	85	n.d.
6[c]	*s*BuMgCl (1.5)	10/24	n.d.	72
7[c]	*t*BuMgCl (2.5)	10/24	n.d.	78
8[c]	PhCH$_2$MgCl (1.5)	10/24	n.d.	23
9[c]	MeMgCl (1.5)	10/24	n.d.	n.d.
10[c]	PhMgCl (1.5)	10/24	n.d.	81

[a] RMgX (in THF, 1.5–2.5 mmol), 1,3-butadiene (1.5–2.0 mmol), and CuCl$_2$ (2–5 mol%) were stirred at 50°C for T_1, then *n*Non-F (1.0 mmol) was added and the reaction mixture stirred for T_2. [b] Yield was determined by GC. [c] *n*Oct-F (**1b**) was used instead of **1a**. n.d. = not detected, THF = tetrahydrofuran.

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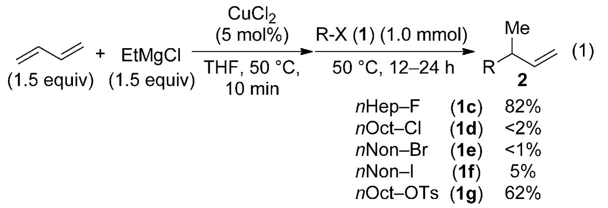
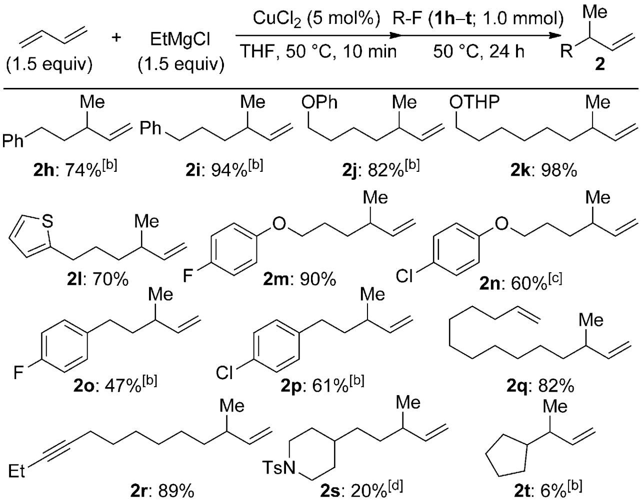
comparable yield of the hydroalkylated product **2** (entry 5). In contrast, when secondary and tertiary alkyl Grignard reagents were used, the cross-coupling reaction took place exclusively (entries 6 and 7).[10] This selectivity is probably a result of the greater stability of alkylcopper species having branched alkyl groups, and thus facilitates the catalysis of the direct cross-coupling. Grignard reagents having no β-hydrogen atom did not afford the desired product, thus suggesting Grignard reagents act as a hydride source (entries 8–10).

Although primary alkyl fluorides coupled with 1,3-butadiene to form alkylated terminal olefins in good yields, neither of the corresponding alkyl chlorides, bromides, or iodides gave either hydroalkylation or cross-coupling products [Eq. (1); Ts = 4-toluenesulfonyl], that is, the alkyl chloride (**1d**), bromide (**1e**), and iodide (**1f**) were completely consumed to give complex mixtures, including the corresponding alkanes by reduction, alkenes by elimination, and homocoupling products from alkyl halides.[10] The reaction of an alkyl tosylate similarly gave a hydroalkylation product in 62 % yield.



A variety of primary alkyl fluorides gave the corresponding terminal alkene **2** in good to excellent yields as single regioisomers (Table 2) and this reaction is tolerant of aryl ethers, THP ethers, and thiophene functionalities. Under the present reaction conditions, selective coupling at sp^3-hybridized carbon atoms was achieved even when alkyl fluorides carrying sp^2-carbon–halogen (F, Cl) bonds were employed (**1m–p**). An isolated terminal alkene (**1q**) and internal alkyne (**1r**) were well tolerated and the reaction took place exclusively at a carbon atom of the conjugated diene moieties. A secondary alkyl fluoride (**1t**), however, resulted in an unsatisfactory result.

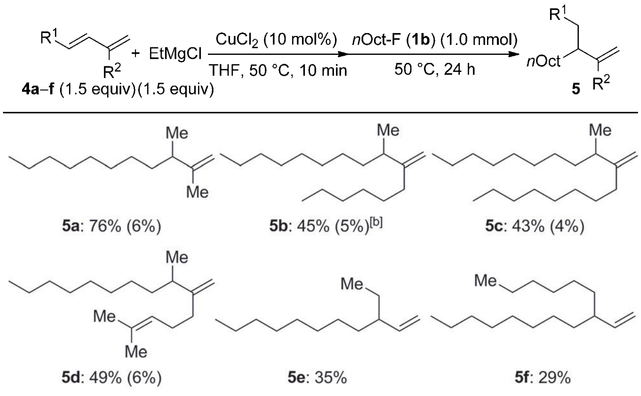
Table 2: Copper-catalyzed reductive alkylation of 1,3-butadiene with alkyl fluorides.[a]



[a] EtMgCl (in THF, 1.5 mmol), 1,3-butadiene (1.5 mmol), and $CuCl_2$ (5 mol %) were stirred at 50 °C for 10 min, then alkyl fluoride (1.0 mmol) was added and reaction mixture stirred for stirred for 24 h. [b] Yield was determined by GC. [c] 27 % of **1n** was recovered. [d] 31 % of **1s** was recovered. THP = tetrahydropyran.

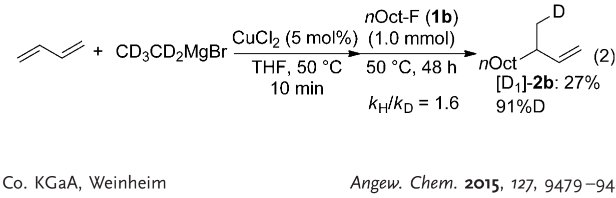
We next investigated the scope of substituted 1,3-dienes **4** (Table 3). Isoprene (**4a**) coupled with *n*OctF (**1b**) to afford the disubstituted terminal alkene **5a** in 56 % yield, where the less congested internal carbon atom of isoprene was selectively alkylated and accompanied by 6 % of a regioisomer formed by alkylation at internal carbon atom of the relatively congested C–C double bond. The yield was improved to 76 % by the use of 10 mol % of the copper catalyst. Longer alkyl chains slightly decreased the yields (**5b**,**c**). Myrcene (**4d**) reacted regioselectively at the least congested C–C double bond to give **5d**. When 1,3-pentadiene (**4e**) and nona-1,3-diene (**4f**) were used, hydroalkylation selectively proceeded at the internal double bond to give **5e** and **5f**, respectively, in moderate yields.[10,11]

Table 3: Copper-catalyzed reductive alkylation of 1,3-dienes with *n*Oct-F.[a]



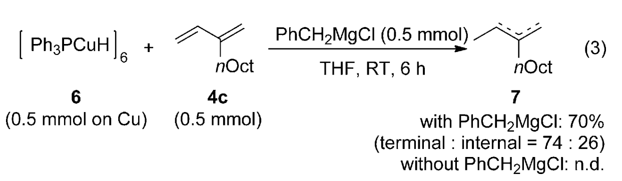
[a] A mixture of EtMgCl (in THF, 1.5 mmol), 1,3-diene (1.5 mmol), and $CuCl_2$ (10 mol %) was stirred at 50 °C for 10 min, then *n*OctF (1.0 mmol) was added and the reaction mixture stirred for 24 h. Yield of minor regioisomer given within parentheses. [b] Reaction time was 60 h.

To gain insight into the role of the Grignard reagents in the present reaction, we performed labeling experiments. When the reaction mixture was quenched by D_2O, no deuterated product was obtained. In contrast, when CD_3CD_2MgBr was used instead of EtMgCl, [D$_1$]-**2b** was obtained in 27 % yield with 91 % deuterium content at the terminal carbon atom [Eq. (2)]. These results clearly indicate that a hydrogen atom (deuterium in this case) of the Grignard reagent is transferred to the product, probably by hydro-

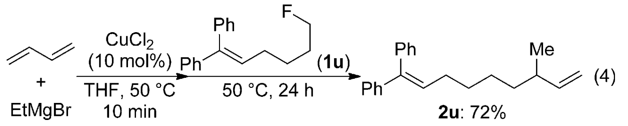


cupration of the diene with the copper hydride species generated by β-hydrogen elimination of alkyl copper intermediates.[12,13] A labeling experiment using CD_3CD_2MgBr indicated that the KIE of this reaction is 1.6.[14,15]

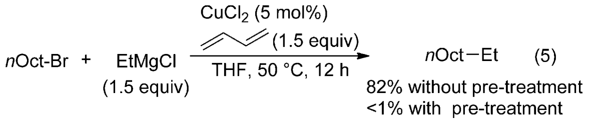
To shed light on the active species of the hydrocupration, we conducted stoichiometric reaction with the copper hydride complex **6** [Eq. (3)].[16,17] Although no hydrocupration of **6** with the neutral conjugated dienes proceeded at room temperature, the addition of 1 equivalent of a Grignard reagent did accelerate the reaction, dramatically, to give reduced olefins in 70 % overall yield after aqueous work up. These results may suggest that the active species of hydrocupration are ate complexes having a Cu−H moiety.[18]



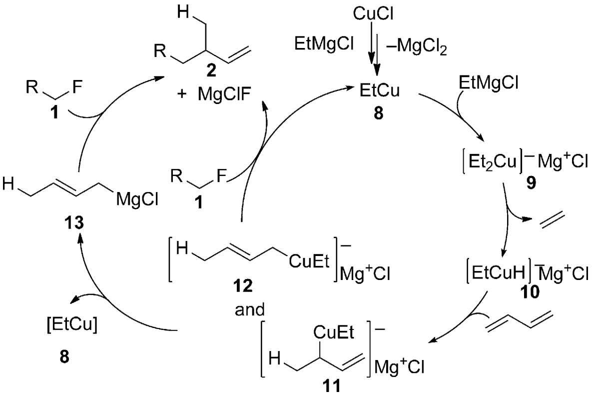
When the alkyl fluoride **1u** was used, the corresponding product **2u** was obtained in 72 % yield and any cyclized products, that can be formed by radical cyclization, were not observed [Eq. (4)].[19] This result may rule out a possibility of alkyl radical intermediates which might be possibly generated in situ from alkyl fluorides.



As we reported previously, copper catalyzes the cross-coupling of alkyl fluorides with alkyl Grignard reagents in the presence of 1,3-butadiene at 25 °C.[7a] This outcome is different to that of the current results, that is, cross-coupling versus reductive alkylation, and arises from pre-treatment of a copper salt with a Grignard reagent in the presence of 1,3-dienes (Table 1, entries 1–3). When EtMgCl was added to $CuCl_2$ in THF including 1,3-butadiene, a yellow solution, which is effective for cross-coupling reaction, is formed quickly. This solution gradually turns to a dark-reddish brown suspension on stirring at 50 °C and reductive alkylation begins to proceed. This observation implies the generation of a new active copper species. We then examined the reaction of *n*OctBr, which is more reactive than alkyl fluorides, in these solutions to probe the activities of the coppper species. When we mixed $CuCl_2$ (5 mol %), EtMgCl in THF, 1,3-butadiene, and *n*OctBr in this order at −78 °C and the obtained yellow solution was stirred at 50 °C, *n*OctBr coupled with EtMgCl in 82 % yield as reported previously.[7a] In contrast, when *n*OctBr was added to a THF solution after 10 minutes of stirring at 50 °C, no coupling product was obtained, thus indicating that an active catalytic species for cross-coupling transmuted completely to the other species [Eq. (5)].[10]



A plausible reaction pathway for this catalytic hydroalkylation is shown in Scheme 2. Catalytically active copper hydride ate complexes (**10**), probably generated by β-hydrogen elimination of the diethyl cuprate **9**, add to 1,3-butadiene to form the allyl cuprates **11** and/or **12**,[20] although the detailed structure of the copper species generated by pre-treatment is not clear yet. Then the resulting allyl cuprates, or the corresponding allylic Grignard reagent **13** derived from the allyl cuprates,[21] react with alkyl fluorides in an S_N2-type mechanism[7] at the γ-carbon atom of the allyl cuprates or allylic Grignard reagents, selectively,[22] to give the 1,2-addition product and regenerate the ethyl copper complex **8**.



Scheme 2. Plausible reaction pathways.

We then performed kinetic studies using isoprene (**4a**), *n*Oct-F (**1b**), EtMgCl, and $CuCl_2$,[10] and found that the reaction obeyed zero-order kinetics with respect to **1b** and **4a**, thus indicating that C−F bond cleavage is relatively fast in the current reaction despite the large bond dissociation energy of C−F bonds.[8] In contrast, the reaction obeyed first-order kinetics with respect to $CuCl_2$ and EtMgCl. These kinetic studies and the observed KIE may suggest the rate-limiting step to be diethyl cuprate formation from ethyl copper and EtMgCl or the subsequent β-H elimination.

In conclusion, we have developed the hydroalkylation of 1,3-butadiene using unactivated alkyl fluorides as electrophiles. The present reaction provides a new method for the synthesis of alkylated terminal alkenes through C−C bond formation between an internal carbon atom of 1,3-diene and an sp^3-carbon fragment. The current copper catalysis has several features, including hydrocupration of neutral conjugated diene, selective hydroalkylation of 1,3-dienes over alkenes and alkynes, catalytic cleavage of C−F bond, and selective C−C bond formation at the relatively congested internal carbon center of dienes. Alkyl fluorides are inert toward various reagents because of the strong C−F bonds. This feature will allow us to create a new synthetic route by the combination of the present reaction with other synthetic transformations. Mechanistic studies implied that the reaction proceeds through hydrocupration of dienes with ate complexes having Cu–H bonds and subsequent C–C bond formation with C–F bond cleavage as a relatively fast step. The ionic reaction mechanism for the C–C bond-forming step allows alkylation of the internal carbon atom of the 1,3-dienes, and is in sharp contrast to the previously reported alkylation of 1,3-dienes involving alkyl radicals as intermediates.

Keywords: alkylation · chemoselectivity · copper · magnesium · synthetic methods

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[17] We have revealed that the addition of triphenylphosphine has an insignificant effect on the present reaction (see the Supporting Information).

[18] The species is inert toward alkynes, as well as styrenes, and is in sharp contrast to hitherto known Cu-H species: See Ref. [12].

[19] The rate constant of the cyclization is known to be $k = 4.0 \times 10^7\,s^{-1}$ at 25 °C. See: M. Newcomb, S.-Y. Choi, J. H. Horner, *J. Org. Chem.* **1999**, *64*, 1225.

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[21] Although the crotyl Grignard reagent reacted with an alkyl fluoride in the absence of a copper catalyst to yield **2** in 94% accompanied by 5% of regioisomer under the same reaction conditions, a control experiment suggests that the transmetalation of crotyl copper with EtMgCl is either sluggish or did not take place (see the Supporting Information). Accordingly, we extrapolate that the present reaction proceeds through a coupling reaction of allyl copper intermediates with alkyl fluorides at this stage.

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