Cu-catalyzed regioselective carbomagnesiation of dienes and enynes with *sec*- and *tert*-alkyl Grignard reagents†

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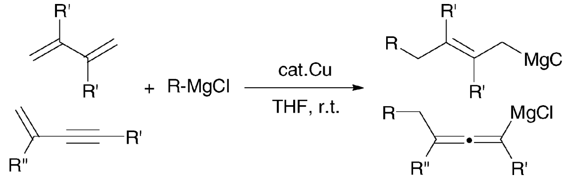
The carbomagnesiation of dienes and enynes with *sec*- and *tert*-alkyl Grignard reagents has been achieved by using copper salts as catalysts.

The addition of Grignard reagents across carbon–carbon multiple bonds (carbomagnesiation) is a principal and important reaction in organic syntheses for the generation of Grignard reagents with the complicated structure of carbon skeletons.[1] It is known that methyl, aryl, allyl, and primary-alkyl Grignard reagents efficiently undergo carbomagnesiation and form diverse unsaturated hydrocarbons such as alkenes, alkynes, and dienes in the absence or presence of transition metal catalysts (Zr,[2] Ti,[3] Mn,[4] Fe,[5] Ni,[6] Cu).[7] However, branched alkyl Grignard reagents such as *sec*- and *tert*-alkyl Grignard reagents are generally poor substrates for such transformations,[8] particularly for non-activated unsaturated hydrocarbons having no heteroatom moieties.[9,10] Recently, we have realized the Cu-catalyzed alkyl–alkyl cross-coupling reaction of alkyl fluorides with Grignard reagents in the presence of 1,3-butadiene as an additive.[11] During the course of this study, we have found that copper catalyzes the regioselective carbomagnesiation of unfunctionalized dienes and enynes using branched alkyl Grignard reagents (Scheme 1).

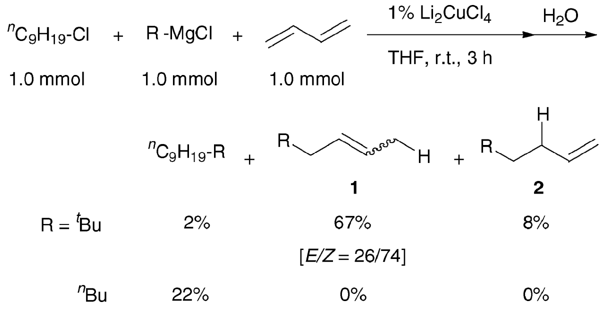


Scheme 1

The treatment of *n*-nonyl chloride (1.0 mmol) with *tert*-butylmagnesium chloride (1.0 mmol, 0.8 M THF solution) in the presence of Li_2CuCl_4 (0.01 mmol) and 1,3-butadiene (1.0 mmol) at 25 °C for 3 h followed by the typical aqueous work-up yielded 2% of the expected cross-coupling product. However, this reaction yielded 6,6-dimethyl-2-heptene (**1**) and 6,6-dimethyl-1-heptene (**2**) as the major products, probably *via* the addition of Grignard reagents to 1,3-butadiene followed by hydrolysis. On the other hand, the use of *n*-butylmagnesium chloride instead of *tert*-butylmagnesium chloride provided a 22% yield of the corresponding cross-coupling product, tridecane, without the formation of an additional product (Scheme 2).

We then added Bu_3SiCl to quench the reaction of 1,3-butadiene with *tert*-butylmagnesium chloride and found that the carbosilylation product of 1,3-butadiene was regio- and stereoselectively obtained (Table 1, entry 2). When 2-cyclohexenone was used as the electrophile instead of Bu_3SiCl under identical conditions, allylic alcohol was obtained as a single regioisomer (entry 4). These results imply that the allylic Grignard reagent **3**[13] is formed in the present reaction. Methyl substituted 1,3-butadiene also yielded the corresponding carbomagnesiation product, which was trapped with PhCOCl or CO_2, to give single regioisomers with 69% and 85% yields, respectively (entries 5 and 6). In the present reaction, silylation occurred at the terminal carbon of the allylmagnesium intermediate to yield a 1,4-adduct, probably due to the steric hindrance of the silyl group. On the other hand, benzoyl chlorides reacted with allylic Grignard reagents by a six-membered cyclic process to form 1,2-adducts.[14] The present reaction also proceeds efficiently when secondary alkyl Grignard reagents are used (entry 7).

We then compared the reaction rates of three alkyl Grignard reagents (RMgCl; R = ^{n}Bu, ^{s}Bu, ^{t}Bu). The reactions, which were performed using RMgCl, 1,3-butadiene and Bu_3SiCl for 0.5 h at 25 °C, followed by quenching with H_2O, produced **5** and **10** with 56% and 8% yields, respectively (entries 3 and 8). On the other hand, ^{n}BuMgCl di not react at all. These results



Scheme 2

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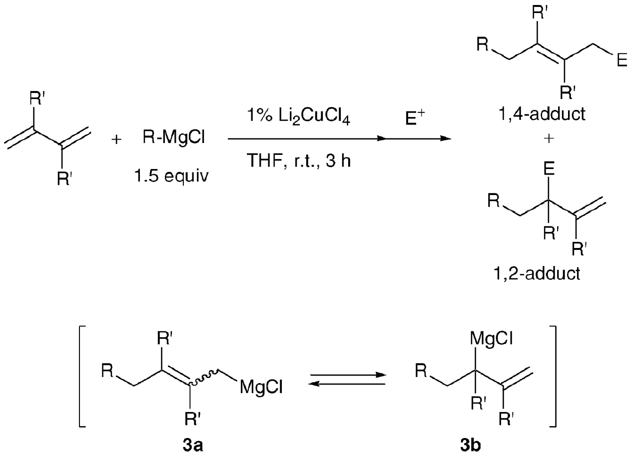
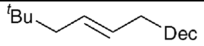
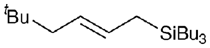
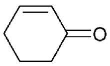
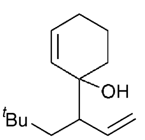
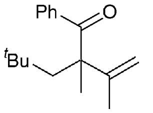
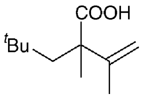
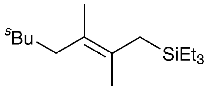
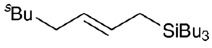
† Electronic supplementary information (ESI) available: Typical experimental procedures and analytical data of products. See DOI: 10.1039/b716678h

Table 1 Carbomagnesiation of dienes with *sec*- and *tert*-alkyl Grignard reagents[a]

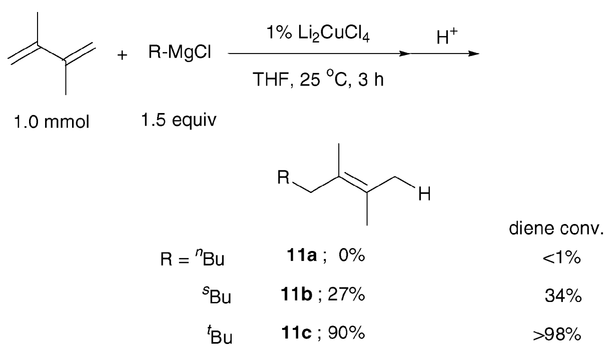


Entry	R	R′	E^+	Product	Yield[b]
1	^{t}Bu	H	DecBr		**4**; 82% [$E : Z$ = 70 : 30]
2	^{t}Bu	H	Bu_3SiCl		**5**; 73% [$E : Z$ = 100 : 0]
3					56% [$E : Z$ = 100 : 0][d]
4	^{t}Bu	H			**6**; 69%
5	^{t}Bu	Me	PhCOCl		**7**; 69%
6	^{t}Bu	Me	CO_2, H^+		**8**; 85%
7[c]	^{t}Bu	Me	Et_3SiCl		**9**; 78% [$E : Z$ = 100 : 0]
8	^{s}Bu	H	Bu_3SiCl		**10**; 8% [$E : Z$ = 100 : 0][d]
9					64%; [$E : Z$ = 100 : 0][e]

[a] The reaction was carried out in THF (1.6 ml) at room temperature for 3 h using a diene (1.0 mmol) and RMgCl (1.5 mmol) in the presence of Li_2CuCl_4 (0.01 mmol). [b] Isolated yield based on the dienes. [c] 6 h. [d] 0.5 h, GC yield based on the dienes. [e] 3 h, GC yield based on the dienes.

indicate that the reactivity of RMgCl was observed to be in the order ^{n}BuMgCl ≪ ^{s}BuMgCl < ^{t}BuMgCl, which may also imply that the alkyl groups are transferred as a radical species.

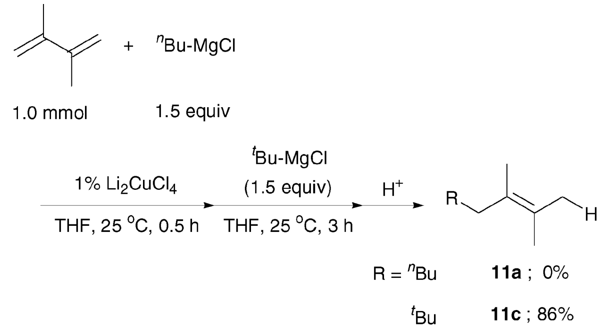
We performed the reaction of 2,3-dimethyl-1,3-butadiene with RMgCl (R = ^{n}Bu, ^{s}Bu, ^{t}Bu) at 25 °C for 3 h in order to examine the material balance of this reaction (Scheme 3). When ^{n}BuMgCl was used, the reaction never proceeded and 2,3-dimethyl-1,3-butadiene was recovered perfectly. After the reaction of 2,3-dimethyl-1,3-butadiene with ^{n}BuMgCl for 0.5 h at 25 °C, ^{t}BuMgCl was added to the reaction mixture for 3 h at 25 °C, as shown in Scheme 4. Interestingly, **11c** was obtained with an 86% yield, without forming any additional products incorporating the primary-alkyl group. These results indicate that the primary-alkyl Grignard reagent does not undergo an addition to butadiene without affecting the reaction and that the copper does not lose its catalytic activity even in the case of ^{n}BuMgCl.



Scheme 3

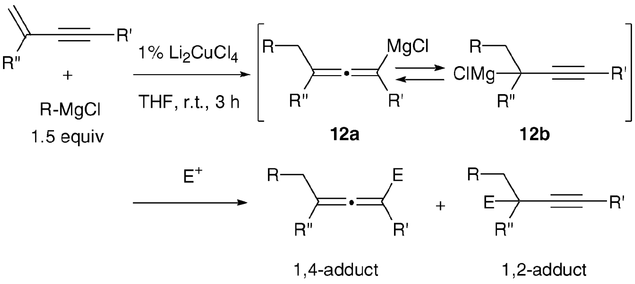
We also found that enynes efficiently underwent the present carbomagnesiation. For example, a reaction of 4-phenyl-1-butene-3-yne (1.0 mmol) with *tert*-butylmagnesium chloride (1.5 mmol) at 25 °C for 3 h produced allenyl and/or propargyl Grignard reagents **12**,[15] which were trapped with Et_3SiCl to form the carbosilylation product **14** in a 95% yield (Table 2, entry 1). Entry 2 shows an example of large-scale preparation (10 mmol of **13**) under identical conditions, where 2.8 g (93%) of **14** was obtained in a pure form by using silica gel column chromatography. This reaction also proceeded efficiently when *sec*-alkyl Grignard reagents were used (entries 3 and 4). As for the scope of the enynes, alkyl or silyl substituted enynes also gave good product yields (entries 5–8). Trisubstituted allenes were obtained by quenching the reaction mixture with allyl bromide (entry 4 and 5). Interestingly, when silyl substituted enynes were employed and the reactions were quenched with chlorosilanes, propargyl silanes (**20**, **22**) were obtained as the sole products (entries 6 and 7). Furthermore, when the reaction of 2-methyl-1-hexene-3-yne with Et_3SiCl was performed under identical conditions, tetrasubstituted allene (**24**) was obtained with a good yield (entry 8).

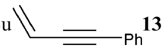
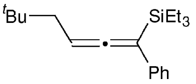
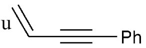
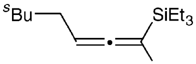
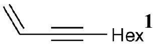
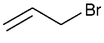
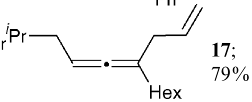
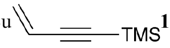
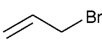
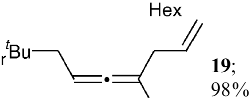
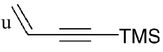
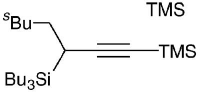
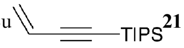
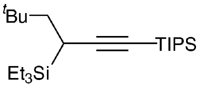
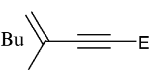
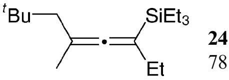
Although the detailed mechanism of this coupling reaction has not yet been clarified, a plausible reaction pathway is depicted in Scheme 5 for the case of 1,3-butadiene. *In situ* generated *sec*- and *tert*-alkyl copper(I) reagents **25** add to 1,3-butadiene to form allylic copper reagents **26**, which undergo transmetallation with Grignard reagents giving rise to allylic Grignard reagents **27** along with the regeneration of alkyl-



Scheme 4

Table 2 Carbomagnesiation of enynes with *sec*- and *tert*-alkyl Grignard reagents[a]

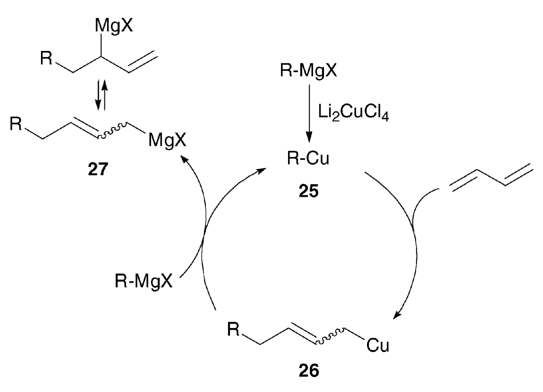


Entry	R	Enynes	Electrophile	Product	Yield[b]
1	^{t}Bu	 **13**	Et$_3$SiCl		**14**; 95%
2					93%[c]
3	^{s}Bu		Et$_3$SiCl		**15**; 79%
4	^{i}Pr	 **16**			**17**; 79%
5	^{t}Bu	 **18**			**19**; 98%
6	^{s}Bu		Bu$_3$SiCl		**20**; 86%
7	^{t}Bu	 **21**	Et$_3$SiCl		**22**; 68%
8	^{t}Bu	 **23**	Et$_3$SiCl		**24**; 78%

[a] The reaction was carried out in THF (1.6 ml) at 25 °C for 3 h using an enyne (1.0 mmol) and RMgCl (1.5 mmol) in the presence of Li$_2$CuCl$_4$ (0.01 mmol). [b] Isolated yield based on the dienes. [c] Reaction performed at a scale of 10 mmol.

copper **25**.[17] The first step has been reported.[18] The reaction of enynes would proceed similarly *via* the formation of allenyl and/or propargyl intermediates (**12**) instead of allylic ones.

In conclusion, a new method for the regioselective carbomagnesiation of dienes and enynes with *sec*- and *tert*-alkyl Grignard reagents by using a copper catalyst has been developed. Allyl, allenyl or propargyl Grignard reagents generated by the present method could be trapped with a variety of electrophiles such as alkyl and allyl bromides, chlorosilanes, enones, benzoyl chlorides, and carbon dioxide. The radical characteristics of carbocupration enable the introduction of secondary and tertiary alkyl groups to diene or enyne units.



Scheme 5

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