Silver-catalyzed carbomagnesiation of terminal aryl and silyl alkynes and enynes in the presence of 1,2-dibromoethane†

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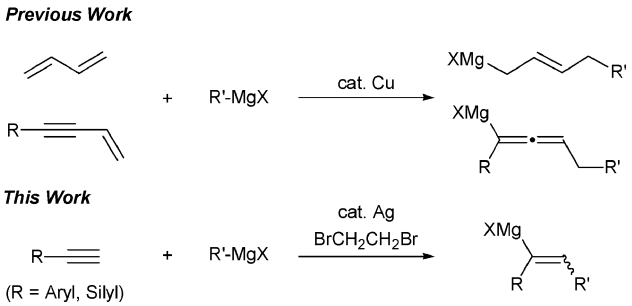
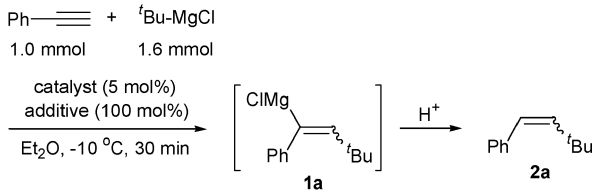
Regioselective carbomagnesiation of terminal alkynes and enynes with alkyl Grignard reagents has been achieved by the combined use of a silver catalyst and 1,2-dibromoethane.

Transition-metal catalyzed carbomagnesiation of carbon–carbon multiple bonds is a useful and attractive method for the preparation of Grignard reagents with concomitant construction of the desired carbon skeletons *via* new carbon–carbon bond formation.[1] To date, addition of aryl,[2] vinyl,[3] allyl,[4] and primary-alkyl[5] magnesium compounds toward carbon–carbon unsaturated bonds has been accomplished by the aid of various transition-metal catalysts. However, the use of secondary and tertiary-alkyl Grignard reagents had so far been limited, mostly to the reaction of activated alkynes or the ones having a heteroatom directing group,[6] until our discovery that Cu catalyzes carbomagnesiation of unfunctionalized dienes and enynes with secondary and tertiary alkyl Grignard reagents to give rise to conjugated allyl or allenyl Grignard reagents (Scheme 1).[7] If the similar addition to alkynes proceeds, vinyl Grignard reagents can be formed. However, the Cu-catalyzed system was not effective towards this transformation. Here, we disclose silver catalyzed regioselective carbomagnesiation of terminal alkynes with alkyl Grignard reagents in the presence of 1,2-dibromoethane. This reaction can also be applied to enynes.



Scheme 1

Table 1 Silver-catalyzed carbomagnesiation of phenylacetylene with ^{t}Bu–MgCl[a]



Entry	Catalyst	Additive	Yield (%)[b]	$E:Z$
1	AgOTs	None	28	1 : 99
2	AgOTs + PPh_3	None	59	2 : 98
3	AgOTs + $P(p\text{-}C_6H_4Cl)_3$	None	58	3 : 97
4	AgOTs	$BrCH_2CH_2Br$	76	2 : 98
5	AgOTs + PPh_3	$BrCH_2CH_2Br$	79	6 : 94
6	AgOTs + $P(p\text{-}C_6H_4Cl)_3$	$BrCH_2CH_2Br$	86	4 : 96
7	(IMes)AgCl	$BrCH_2CH_2Br$	98 (88)	2 : 98
8[c]	(IMes)AgCl	$BrCH_2CH_2Br$	88	1 : 99
9	(IMes)AgCl	$ClCH_2CH_2Cl$	34	1 : 99
10	(IMes)AgCl	ICH_2CH_2I	17	8 : 92

[a] Conditions: Ag catalyst (0.05 mmol), phenylacetylene (1.0 mmol), additive (100 mol%), ^{t}Bu–MgCl (1.6 mmol), −10 °C, 30 min. [b] GC yield. Isolated yield is in parentheses. [c] 50 mol% additive was used.

When the reaction of phenylacetylene (1.0 mmol) with ^{t}Bu–MgCl (1.6 mmol) was conducted in the presence of AgOTs (0.05 mmol) in Et_2O at −10 °C for 30 min and the reaction was quenched by aqueous HCl, the hydroalkylation product **2a** was obtained in 28% yield ($E:Z = 1:99$) (Table 1, Entry 1). Addition of PPh_3 or $P(p\text{-}C_6H_4Cl)_3$ increased the yield of **2a** and gave the by-product ^{t}Bu–^{t}Bu in 4% yield (Entries 2 and 3). The latter may be formed by reductive coupling of *tert*-alkyl silver complex intermediates.[8] This process reduces Ag(I) to Ag(0) and may terminate the catalytic cycle. Hayashi and Nagano reported that 1,2-dibromoethane acts as a reoxidizing reagent of Ag(0) complex to Ag(I) in the silver catalyzed homo-coupling reaction of alkyl Grignard reagents.[9] We re-examined the reaction in the presence of 1,2-dibromoethane (100 mol%) under the same conditions as Entry 1–3 and found that the yields of **2a** were significantly improved as shown in Entries 4–6. The use of (IMes)AgCl (IMes = 1,3-dimesitylimidazol-2-ylidene)[10] as a catalyst afforded **2a** in 98% GC yield (Entry 7). The product was obtained in pure form in 88% yield by silica gel column chromatography. When the amount of 1,2-dibromoethane was reduced to 50 mol%, the yield of **2a** decreased to 88% yield (Entry 8). 1,2-Dichloroethane and 1,2-diiodoethane were less efficient than 1,2-dibromoethane, and formed **2a** in 34% and 17% yields, respectively (Entries 9 and 10).

Results of the present silver catalyzed carbomagnesiation using other substrates are shown in Table 2. The present carbomagnesiation was applicable to *p*-, *m*- and *o*-methyl substituted phenylacetylene under the conditions of the (IMes)AgCl–$Br(CH_2)_2Br$ catalytic system (condition A) (Table 2, Entries 1–3). Methoxy and trifluoromethyl groups

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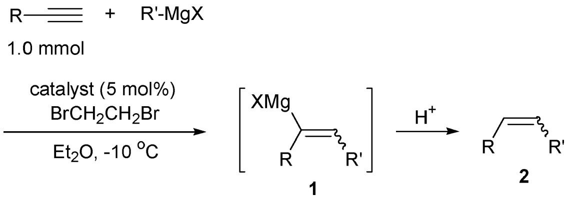
Table 2 Silver-catalyzed carbomagnesiation of terminal alkynes



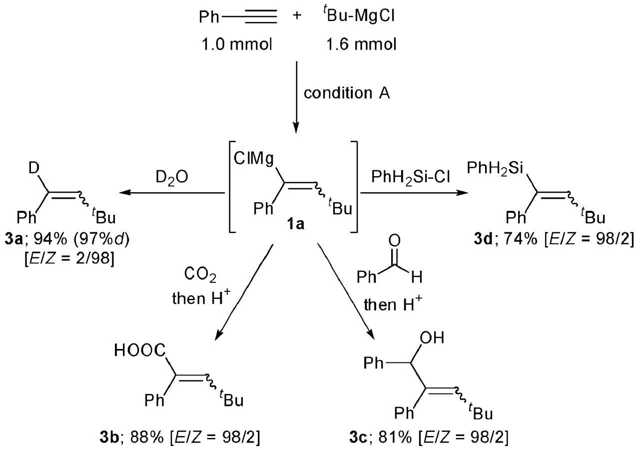
Entry	R	R'–MgX	Condition[a]	Product	Yield (%)[b]	*E* : *Z*
1	4-MeC_6H_4	^{t}Bu–MgCl	A	**2b**	88 (80)	2 : 98
2	3-MeC_6H_4	^{t}Bu–MgCl	A	**2c**	90 (83)	2 : 98
3	2-MeC_6H_4	^{t}Bu–MgCl	A	**2d**	91 (81)	7 : 93
4	4-$MeOC_6H_4$	^{t}Bu–MgCl	A	**2e**	(70)	2 : 98
5	4-$CF_3C_6H_4$	^{t}Bu–MgCl	A	**2f**	(81)	1 : 99
6	3-Thienyl	^{t}Bu–MgCl	A	**2g**	(65)	3 : 97
7	Ph	^{s}Bu–MgCl	A	**2h**	59 (43)	12 : 88
8	Ph	^{s}Bu–MgCl	B	**2h**	81 (68)	14 : 86
9	Ph	^{c}Hex–MgCl	B	**2i**	83 (71)	20 : 80
10	Ph	^{n}Bu–MgCl	A	**2j**	64 (49)	42 : 58
11	Ph	^{n}Bu–MgCl	C	**2j**	73 (58)	43 : 57
12	Ph	^{n}Oct–MgBr	C	**2k**	89 (73)	42 : 58
13	$PhMe_2Si$	^{t}Bu–MgCl	C	**2l**	(66)	8 : 92

[a] Condition A: (IMes)AgCl (5 mol%), phenylacetylene (1.0 mmol), 1,2-dibromoethane (100 mol%), R'–MgX (1.6 mmol), −10 °C, 30 min; B: AgOTs (5 mol%), P(*p*-$C_6H_4Cl)_3$ (5 mol%), phenylacetylene (1.0 mmol), 1,2-dibromoethane (200 mol%), R'–MgX (1.6 mmol), −10 °C, 30 min; C: (IMes)AgCl (5 mol%), phenylacetylene (1.0 mmol), 1,2-dibromoethane (200 mol%), R'–MgX (2.0 mmol), −10 °C, 3 h. [b] GC yield. Isolated yield is in parentheses.

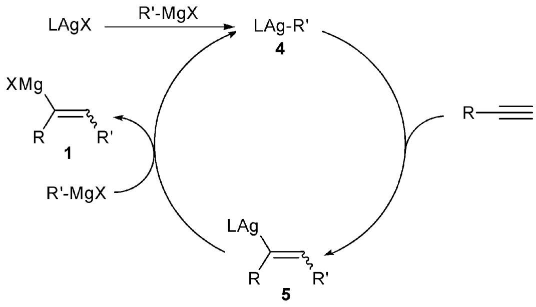
on the aryl ring did not significantly affect the yield of the products (Entries 4–5). Thienyl alkyne also underwent carbomagnesiation giving rise to the corresponding alkene in 65% isolated yield (Entry 6). ^{s}Bu–MgCl also added to phenylacetylene to give **2h** in 59% yield under the same conditions (Entry 7). Combined use of AgOTs (5 mol%) and P(*p*-$C_6H_4Cl)_3$ (5 mol%) was more suitable for *sec*-butylmagnesiation than (IMes)AgCl and gave **2h** in 81% yield (Entry 8, condition B). Under identical conditions, ^{c}Hex–MgCl also smoothly underwent carbomagnesiation to afford **2i** in 83% yield (Entry 9). Primary-alkyl Grignard reagents also gave hydroalkylated product **2j** and **2k** in moderate to good yields when the reaction was conducted for 3 h in the presence of a large amount of 1,2-dibromoethane (Entries 10–12, condition C). No reaction took place with methyl, benzyl or phenyl Grignard reagents. As for the alkynes, dimethylphenylsilyl alkyne gave **2l** in 66% isolated yield (entry 13). Aliphatic alkynes and internal alkynes, however, did not undergo carbomagnesiation under the conditions examined.

Vinyl Grignard reagents formed by the present carbomagnesiation can be trapped with various electrophiles (Scheme 2). For example, quenching of **1a** with D_2O gave deuterated product **3a** in 94% yield (97% *d*). Electrophilic trapping of **1a** with CO_2, benzaldehyde, and chlorophenylsilane afforded **3b**, **3c**, and **3d** in 88%, 81%, and 74% yields, respectively.

A plausible reaction mechanism is outlined in Scheme 3. The reaction of silver complex with alkyl Grignard reagent forms an alkyl silver complex **4**.[11] Then, **4** reacts with a terminal alkyne to afford vinyl silver complex **5** which undergoes transmetallation with alkyl Grignard reagents to give vinyl Grignard reagents **1** and regenerate **4**.



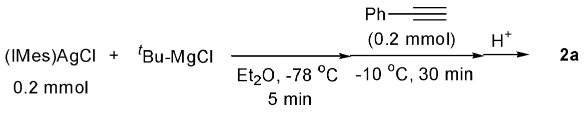
Scheme 2



Scheme 3

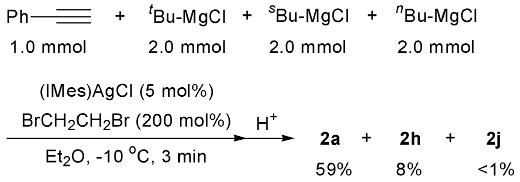
It has been known that alkyl silver ate complexes are formed from silver(I) complexes and alkyl lithium or Grignard reagents.[11] To confirm whether silver ate complexes rather than neutral complexes are active species toward terminal acetylenes in the present reaction, we carried out the reactions using stoichiometric amounts of (IMes)AgCl, ^{t}Bu–MgCl, and phenylacetylene. As shown in Scheme 4, desired product **2a** was obtained in 40% yield. The use of 2.0 equiv. of ^{t}Bu–MgCl, which may generate alkyl silver ate complexes, gave a similar result. These results may indicate that alkyl silver ate complexes do not play an important role in the present reaction.

To examine the reactivities of the alkyl Grignard reagents in this catalytic system, we performed the following competitive experiments: an Et_2O solution of (IMes)AgCl, phenylacetylene, and 1,2-dibromoethane was added to a mixture of equimolar amounts of ^{t}Bu–MgCl, ^{s}Bu–MgCl, and ^{n}Bu–MgCl. Quenching the reaction with H_2O afforded hydroalkylation products **2a**, **2h** and **2j** in 59%, 8%, and <1% yields, respectively (Scheme 5). Preferred formation of the products having a highly branched butyl group may suggest that the addition of alkyl silver complexes toward phenylacetylene proceeds *via* a radical mechanism.



^{t}Bu-MgCl	GC yield (%) **2a**
0.2 mmol	40 [*E*/*Z* = 4/96]
0.4 mmol	41 [*E*/*Z* = 1/99]

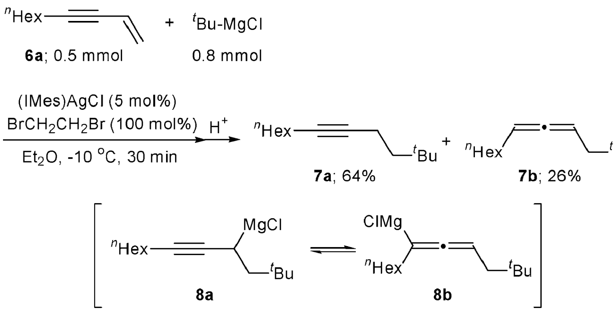
Scheme 4



Scheme 5

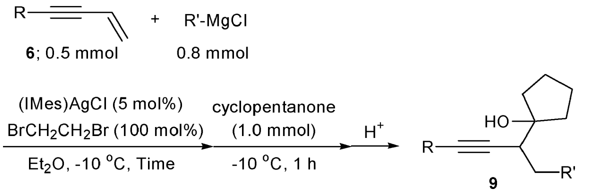
It is known that alkyl silver complexes add to enyne derivatives to give allenyl silver complexes.[11a,12] We then applied the present carbomagnesiation to enynes. The reaction of hexyl substituted enyne **6a** with ^{t}Bu–MgCl under condition A followed by hydrolysis gave a mixture of **7a** and **7b** in 64% and 26% yields, respectively (Scheme 6). This result indicates the formation of propargyl and/or allenyl Grignard reagents **8**.[13] When **8** was trapped with cyclopentanone, **9a** was obtained regioselectively in 85% yield as a single isomer (Table 3, Entry 1). The use of ^{s}Bu–MgCl also afforded the corresponding coupling product **9b** in 81% yield (Entry 2). On the other hand, carbomagnesiation using ^{n}Bu–MgCl failed to give **9c** (Entry 3). Phenyl and silyl substituted enyne **6b** and **6c** underwent carbomagnesiation and successive electrophilic trapping afforded coupling products **9d** and **9e** in good yields (Entries 4–5).

In conclusion, regioselective carbomagnesiation of terminal alkynes with various alkyl Grignard reagents was found to proceed using silver catalysts, such as (IMes)AgCl or AgOTs, in the presence of 1,2-dibromoethane as a reoxidizing reagent. Vinyl Grignard reagents generated by the present method were successfully trapped with various electrophiles. This catalytic system could also be applicable to the regioselective carbomagnesiation of enynes.



Scheme 6

Table 3 Silver-catalyzed carbomagnesiation of enynes



Entry	Enyne	Time	R′	Yield (%)
1	**6a** (R = ^{n}Hex)	30 min	^{t}Bu	**9a**; 85
2	**6a**	3 h	^{s}Bu	**9b**; 81
3	**6a**	3 h	^{n}Bu	**9c**; < 1
4	**6b** (R = Ph)	30 min	^{t}Bu	**9d**; 87
5	**6c** (R = TMS)	30 min	^{t}Bu	**9e**; 85

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