ORGANIC LETTERS

2011
Vol. 13, No. 17
4656–4659

Silver-Catalyzed Regioselective Carbomagnesiation of Alkynes with Alkyl Halides and Grignard Reagents

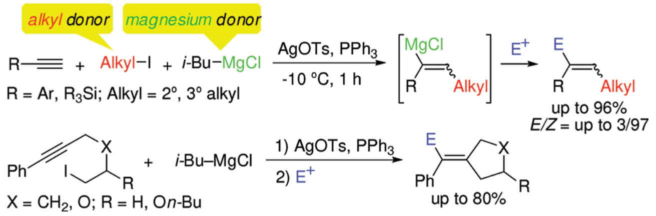
Nobuaki Kambe,[*,†] Yuusuke Moriwaki,[†] Yuuki Fujii,[†] Takanori Iwasaki,[†] and Jun Terao[‡]

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871 Japan, and Department of Energy, Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510 Japan

kambe@chem.eng.osaka-u.ac.jp

Received July 11, 2011

ABSTRACT



A silver-catalyzed carbomagnesiation of alkynes with alkyl halides and Grignard reagents afforded alkenyl Grignard reagents regioselectively, where the alkyl group of the alkyl halide, but not that of the Grignard reagent, was introduced into the alkyne. Application to δ-haloalkylacetylenes yielded cyclopentanes or a tetrahydrofuran containing an *exo*-methylene substituent via 5-*exo-dig* cyclization.

The addition of Grignard reagents to alkynes, i.e., carbomagnesiation, yields vinyl Grignard reagents **1** with the concomitant formation of a new C–C bond and a C–Mg bond (Scheme 1, route A).[1] Combinations of this reaction and subsequent trapping with electrophiles or metal-catalyzed coupling provide a useful and practical method for the synthesis of multisubstituted alkenes **2**. Although a variety of transition-metal catalysts, including Zr,[2] Cr,[3] Mn,[4] Fe,[5] Fe/Cu,[6] Ni,[7] Cu,[8] and Ag,[9] have been used in this carbomagnesiation, aryl, vinyl, methyl or allyl Grignard reagents have often been employed.[10] Primary alkyl Grignard reagents have, in some cases, been reported to work,[2,5a,7b,8c,8e–8i,9] but the reaction was inefficient[2,7b] and/or restricted to alkynes having a directing heteroatom group.[5a,8c,8e–8i] Reactions for the introduction of secondary[8c,g] or tertiary[7b,9] alkyl groups to alkynes are more limited, and sterically hindered alkyl Grignard reagents are less easily accessible. As a practical method for

---

[†] Osaka University.

[‡] Kyoto University.

(1) For reviews, see: (a) *Organomagnesium Methods in Organic Synthesis*; Wakefield, B. J., Ed.; Academic Press, Inc.: San Diego, 1995; pp 73–86. (b) Dzhemilev, U. M.; Ibragimov, A. G. *Russ. Chem. Rev.* **2005**, *74*, 807–823. (c) Itami, K.; Yoshida, J.-I. Carbomagnesiation Reactions. In *The Chemistry of Organomagnesium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2008; Chapter 14, pp 631–679.

(2) D'yakonov, V. A.; Makarov, A. A.; Dzhemilev, U. M. *Russ. J. Org. Chem.* **2009**, *45*, 1598–1609.

(3) Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1569–1571.

(4) (a) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076–6077. (b) Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1997**, *53*, 5061–5072. (c) Yorimitsu, H.; Tang, J.; Okada, K.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **1998**, 11–12. (d) Shinokubo, H.; Oshima, K. *Cat. Sur. Asia* **2003**, *7*, 39–46.

(5) (a) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050–15051. (b) Yamagami, T.; Shintani, R.; Shirakawa, E.; Hayashi, T. *Org. Lett.* **2007**, *9*, 1045–1048.

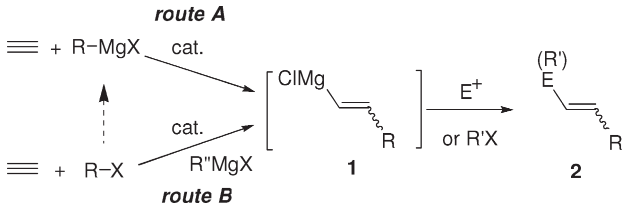
(6) Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164–17165.

(7) (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1972**, *44*, C1–C3. (b) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1978**, *162*, 209–222. (c) Snider, B. B.; Karras, M.; Conn, R. S. E. *J. Am. Chem. Soc.* **1978**, *100*, 4624–4626. (d) Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2007**, *36*, 1066–10067.

(8) (a) Xie, M.; Huang, X. *Synlett* **2003**, 477–480. (b) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671. (c) Chechik, H.; Marek, I. *Org. Lett.* **2003**, *5*, 5087–5089. (d) Xie, M.; Liu, L.; Wang, J.; Wang, S. *J. Organomet. Chem.* **2005**, *690*, 4058–4062. (e) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlet* **2005**, 2098–2100. (f) Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655–2660. (g) Fang, G.-H.; Yan, Z.-J.; Yang, J.; Deng, M.-Z. *Synthesis* **2006**, 1148–1154. (h) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2007**, 32–33. (i) Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373–379.

10.1021/ol2018664

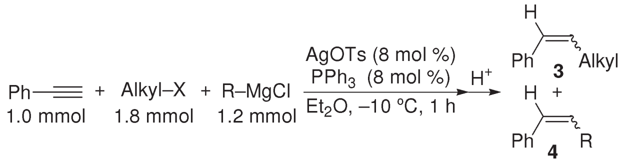
Scheme 1. Carbomagnesiation of Alkynes



overcoming these difficulties, we herein report a new catalytic system which enables the regioselective carbomagnesiation of alkynes with secondary and tertiary alkyl iodides and commercially available *i*-BuMgCl in the presence of a silver catalyst (Scheme 1, route B).[11,12] In this reaction, the alkyl group of an alkyl halide is transferred to an alkyne carbon to give the corresponding vinyl Grignard reagents **1**, and sterically hindered alkyl Grignard reagents (RMgX) do not have to be preformed.

We recently reported the silver-catalyzed regioselective carbomagnesiation of terminal alkynes with alkyl Grignard reagents by the combined use of a silver catalyst and 1,2-dibromoethane, which functions as a reoxidizing reagent.[9] These successful results prompted us to examine the use of other alkyl halides in this reaction, instead of 1,2-dibromoethane.[13] When phenylacetylene was reacted with *t*-Bu-MgCl in the presence of *n*-C$_5$H$_{11}$Br and a catalytic amount of AgOTs and PPh$_3$, the hydroalkylation product **4a** was obtained exclusively in 88% yield after workup, in which the *t*-Bu group of *t*-Bu-MgCl was introduced at the terminal carbon by direct addition (entry 1, Table 1). Interestingly, the reaction using *t*-C$_5$H$_{11}$Br and *t*-Bu-MgCl gave **3b** in 7% yield together with **4a** in 85% yield (entry 2). The yield of **3b** could be improved to 21% by employing Grignard reagents having a less branched alkyl group (entries 2−4). When a tertiary alkyl iodide, *t*-C$_5$H$_{11}$I, was employed instead of *t*-C$_5$H$_{11}$Br, the formation of **4c** was suppressed and **3b** was selectively produced in 91% yield (entry 5). The use of *i*-Bu-MgCl further improved the yield of **3b** to 96%.

Table 1. Carbomagnesiation of Alkynes with Alkyl Halides and Grignard Reagents



entry	alkyl-X	R	yield of *3*^{a} (%)	*E*/*Z*^{b}	yield of *4*^{a} (%)	*E*/*Z*^{b}
1	*n*-C$_5$H$_{11}$Br	*t*-Bu	**3a**: nd		**4a**: 88	3/97
2	*t*-C$_5$H$_{11}$Br	*t*-Bu	**3b**: 7	5/95	**4a**: 85	3/97
3	*t*-C$_5$H$_{11}$Br	*s*-Bu	**3b**: 11	8/92	**4b**: 65	17/83
4	*t*-C$_5$H$_{11}$Br	*n*-Bu	**3b**: 21	14/86	**4c**: 39	35/65
5	*t*-C$_5$H$_{11}$I	*n*-Bu	**3b**: 91	8/92	**4c**: nd	
6	*t*-C$_5$H$_{11}$I	*i*-Bu	**3b**: 96 (85)	18/82	**4d**: nd	

[a] GC yield. Isolated yield is in parentheses. [b] Determined by GC.

Using the optimized reaction conditions of entry 6 in Table 1, we investigated the use of various alkynes and alkyl iodides in the reaction (Table 2). Tertiary and secondary butyl iodides reacted readily with phenylacetylene, and their alkyl groups were transferred into the alkyne to afford **5a** and **5b** as the sole regioisomers in good to excellent yields with *E*/*Z* ratios approaching 1/4 and 3/7, respectively, although the reaction of *n*-Bu-I was less efficient and less selective (entries 1−3). 1-Adamantyl iodide and cyclohexyl iodide were also applicable (entries 4 and 5). In the latter case, the use of sterically bulky P(*o*-tol)$_3$ improved the stereoselectivity to $E/Z = 18/82$ (entry 6). Tolylacetylenes also reacted efficiently and both the yield and stereoselectivity increased in the order of *para*-, *meta*-, and *ortho*-substituted compounds (entries 7−9). *p*-Methoxyphenylacetylene gave a 1:1 mixture of stereoisomers, but the 4-CF$_3$ compound afforded the *Z*-isomer predominantly (entries 10 and 11). These results indicate that the stereoselectivity of the reaction is controlled, not only by steric effects but also by electronic effects. Although alkyl substituted alkynes such as 1-octyne (entry 12) or internal alkynes reacted sluggishly, silylacetylene reacted under the same reaction conditions (entry 13).

To demonstrate the synthetic utility of the reaction as a convenient and practical route to preparing trisubstituted alkenes, we investigated the reaction of the vinyl Grignard

---

(9) Fujii, Y.; Terao, J.; Kambe, N. *Chem. Commun.* **2009**, 1115–1117.

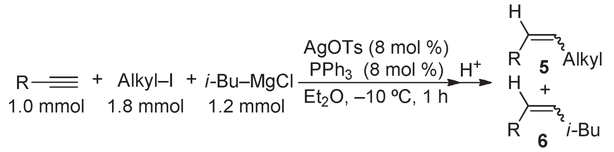
(10) Examples of the carbometalation of olefins and dienes using Ti: (a) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1975**, *97*, 6870–6871. (b) Terao, J.; Kato, Y.; Kambe, N. *Chem. Asian J.* **2008**, *3*, 1472–1478. Zr:(c) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43–51. (d) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079–5080. (e) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266–6268. (f) Lewis, D. P.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797–6800. (g) Bell, L.; Whitby, R. J.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron Lett.* **1996**, *37*, 7139–7142. (h) Fischer, R.; Walther, D.; Gebhardt, P.; Görls, H. *Organometallics* **2000**, *19*, 2532–2540. (i) Dzhemilev, U. M.; D'yakonov, V. A.; Khafizova, L. O.; Ibagimov, A. G. *Tetrahedron* **2004**, *60*, 1287–1290. Mn:(j) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2003**, *5*, 4623–4626. Fe:(k) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978–979. Ni:(l) Farády, L.; Bencze, L.; Markô, L. *J. Organomet. Chem.* **1969**, *17*, 107–116. Cu:(m) Simaan, S.; Masarwa, A.; Bertus, P.; Marech, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963–3965. (n) Todo, H.; Terao, J.; Watanabe, H.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2008**, 1332–1334. (o) Simaan, S.; Masarwa, A.; Zohar, E.; Stanger, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2009**, *15*, 8449–8464.

(11) We have reported that titanocene catalyzes regioselective alkylation of styrenes and 1,3-dienes with alkyl halides in the presence of *n*-Bu-MgCl: (a) Terao, J.; Saito, K.; Nii, S.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 11822–11823. (b) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291–5297. (c) Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2004**, *69*, 573–576.

(12) For alkenes, other groups reported on a Zr-catalyzed reaction. See for the intra- and intermolecular carbomagnesiation of alkenes using primary and secondary alkyl tosylates and Grignard reagents, see: (a) de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2001**, *3*, 2097–2100. (b) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395–398. For intramolecular vinylmagnesiation of alkenes with vinyl ether, see: (c) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6362–6365.

(13) Ag-catalyzed homocoupling of alkyl Grignrd reagents promoted by 1,2-dibromoethane has been reported; see: Nagano, T.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1152.

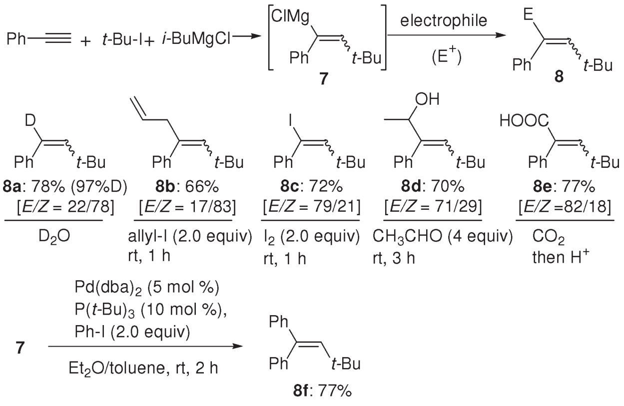
Table 2. Scope and Limitations of Alkynes and Alkyl Iodides



entry	R	alkyl	yield of **5**[a] (%)	E/Z[b]	yield of **6**[a] (%)	E/Z[b]
1	Ph	*t*-Bu	**5a**: 93(81)	22/78	nd	
2[c,d]	Ph	*s*-Bu	**5b**: 80 (67)	30/70	1	
3[c,d]	Ph	*n-Bu*	**5c**: 37	36/64	9	36/64
4[e]	Ph	1-Ad	**5d**: 61 (43)	32/68	4	31/69
5[c,d]	Ph	Cy	**5e**: 80	30/70	4	33/67
6[c,f]	Ph	Cy	**5e**: 58	18/82	2	22/78
7	4-MeC_6H_4	*t*-Bu	**5f**: 84 (76)	35/65	nd	
8	3-MeC_6H_4	*t*-Bu	**5g**: 90 (79)	26/74	nd	
9	2-MeC_6H_4	*t*-Bu	**5h**: 96 (85)	3/97	nd	
10	4-$MeOC_6H_4$	*t*-Bu	**5i**: 79 (73)	50/50	nd	
11	4-$CF_3C_6H_4$	*t*-Bu	**5j**: 68 (63)	11/89	nd	
12[g]	*n*-Hex	*t*-Bu	**5k**: nd		nd	
13[d,g]	$PhMe_2Si$	*t*-Bu	**5l**: 67 (52)	9/91	1	

[a] GC yield. Isolated yield is in parentheses. [b] Determined by GC analysis. [c] 3 h. [d] Slow addition of Grignard reagent; see the Supporting Infomation. [e] 4 h. [f] $P(o\text{-tol})_3$ was used instead of PPh_3. [g] 9 h.

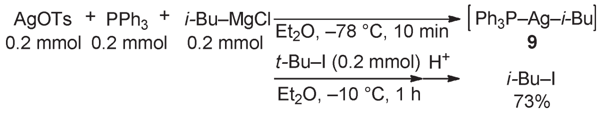
Scheme 2. Further Transformations of Vinyl Grignard Reagent **7**



reagent **7** prepared by the present procedure. The vinyl Grignard reagent **7** can be trapped with various electrophiles such as D_2O, allyl iodide, I_2, acetoaldehyde, and CO_2 to afford the corresponding trisubstituted alkenes **8a**–**e** (Scheme 2). Arylation has successfully been achieved by submitting the vinyl Grignard reagent **7** to a Pd-catalyzed cross-coupling reaction by the simple addition of a catalyst, PhI and a phosphine to the resulting solution in a one-pot operation, which results in the production of the trisubstituted alkyne **8f** in 77% yield as a sole regioisomer (Scheme 2).[14]

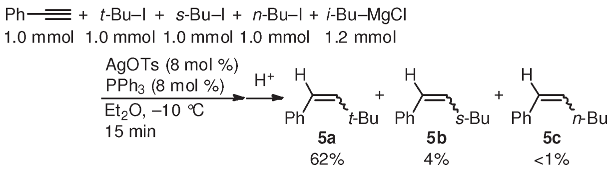
GC analysis of the resulting mixture in entry 1 of Table 2 indicated that 0.99 mmol of *i*-Bu-I was produced, along with 0.93 mmol of product **5a**. To probe the mechanism of this catalytic reaction, we carried out a stoichiometric reaction of **9**, generated by the reaction of equimolar amounts of AgOTs, PPh_3, and *i*-Bu-MgCl,[15f] with *t*-Bu-I at −10 °C for 1 h and confirmed that *i*-Bu-I was formed in 73% yield (Scheme 3). In the absence of AgOTs and PPh_3, the direct reaction of *t*-Bu-I with *i*-Bu-MgCl was inefficient, and the yield of *i*-Bu-I was only 11%, suggesting that **9** generated in situ undergoes exchange reaction with *t*-Bu-I to give *i*-Bu-I and Ph_3PAg-*t*-Bu (**10**).

Scheme 3. Stoichiometric Reaction of Complex **9** with *t*-BuI



To reveal the relative reactivity of alkyl halides, we performed a competitive experiment using equimolar amounts of *tert*-, *sec*-, and *n*-butyl iodides under the same conditions as entry 1 in Table 2 and obtained **5a**, **5b**, and **5c** in 62%, 4%, and < 1% yields, respectively (Scheme 4). This result suggests that the exchange reaction of **9** with an alkyl iodide and/or the addition of alkyl silver complexes **10** to terminal alkynes proceed via alkyl radical intermediates.

Scheme 4. Competitive Reaction of Alkyl Iodides



Taking these results into account, a plausible reaction pathway for this reaction is shown in Scheme 5. The catalytic cycle is triggered by the reaction of AgOTs with *i*-Bu-MgCl in the presence of PPh_3 to generate the isobutyl silver complex **9**.[15] Then, **9** reacts with the alkyl-I to give *i*-Bu-I and the alkyl silver complex **10**. The addition of **10** to the terminal alkyne, probably via homolitic cleavage of Ag–C bond of **10**,[15f] affords vinyl silver complex **11**,[15h] which then

---

(14) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (c) Yamamura, M.; Noritani, I.; Murahashi, S.-i. *J. Organomet. Chem.* **1975**, *91*, C39–C42.

(15) For the formation and reactions of alkyl silver complexes, see: (a) Gardner, J. H.; Borgstrom, P. *J. Am. Chem. Soc.* **1929**, *51*, 3375–3377. (b) Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 303–305. (c) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1483–1485. (d) Whitesides, G. M.; Panek, E. J.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 232–239. (e) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1120–1127. (f) Whitesides, G. M.; Bergbreiter, D. E.; Kendall, P. E. *J. Am. Chem. Soc.* **1974**, *96*, 2806–2813. (g) *Organometallic Mechanisms and Catalysis*; Kochi, J. K., Ed.; Academic Press: New York, 1978; pp 263, 374. (h) Westmijze, H.; Kleijm, H.; Vermeer, P. *J. Organomet. Chem.* **1979**, *172*, 377–383.

Scheme 5. Proposed Catalytic Cycle

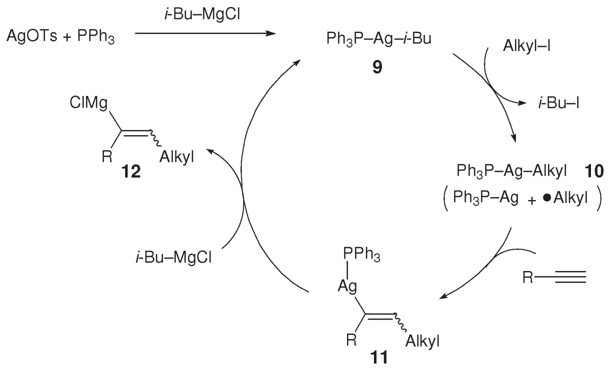
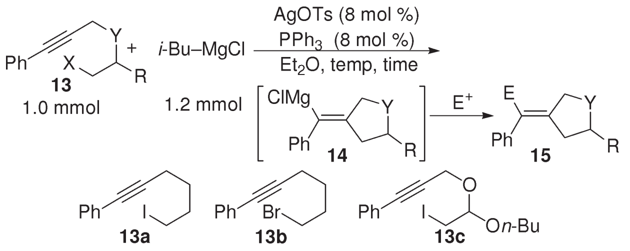


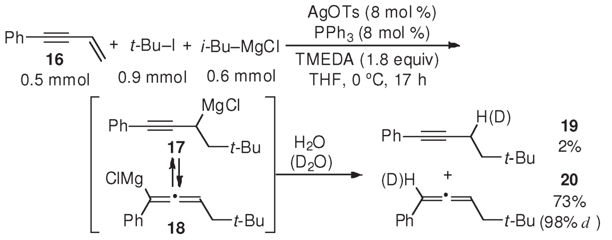
Table 3. Intramolecular Carbomagnesiation of Haloalkynes **13**



entry	**13** (X)	temp (°C)	time (h)	E$^+$	E	yield (%)[a]
1	**13a** (I)	−10	4	H$^+$	H	**15a**: 79
2	**13a** (I)	−10	4	CO$_2$ then H$^+$	COOH	**15b**: 75
3	**13b** (Br)	25	7	CO$_2$ then H$^+$	COOH	**15b**: 23
4[b]	**13c** (I)	25	3	D$^+$	D	**15c**: 80[c]

[a] Isolation yields. [b] THF and dichloroethane were used as solvents in the absence of PPh$_3$. [c] 96% d, E/Z = 42/58.

Scheme 6. Formation of an Allenyl Grignard Reagent from **16**



undergoes transmetalation with i-Bu-MgCl to give the vinyl Grignard reagent **12** and the regeneration of **9**.[16]

We then attempted to construct a ring by way of incorporating the 5-*exo-dig* cyclization process of 6-hexynyl radicals[17] into the present catalytic cycle. We employed 6-iodo-1-phenyl-1-hexyne (**13a**) as a substrate, and the reaction was conducted under the same optimized conditions as described above. The resulting Grignard reagent **14** was treated with NH$_4$Cl or CO$_2$ to give **15a** and **15b** as the sole cyclized products in 79% and 75% yield, respectively (Table 3, entries 1 and 2). The use of 6-bromo-1-phenyl-1-hexyne (**13b**) also gave the corresponding product **15b**, albeit in poor yield (23%, entry 3). This intramolecular reaction can be applied to the construction of heterocyclic rings, as exemplified by entry 4 in Table 3, in which an acetal **13c** was treated with i-Bu-MgCl in the presence of AgOTs to give a substituted THF **15c** in 80% yield (E/Z = 42/58, 96% d) after quenching with D$_2$O.

Finally, we attempted the carbomagnesiation of an enyne (Scheme 6) and found that the t-Bu group was introduced at the terminal carbon of the double bond to give an allenyl Grignard reagent **18**, which was efficiently trapped with D$_2$O to afford the trisubstituted allene **20** in 73% yield accompanied by a small amount of alkyne **19**.

In conclusion, we report herein on the silver-catalyzed regioselective carbomagnesiation of terminal alkynes using i-Bu-MgCl and alkyl iodides. In this reaction, the alkyl group of the alkyl iodide, and not that of the Grignard reagent, is introduced into the terminal alkyne carbon to give alkylated vinyl Grignard reagents. To the best of our knowledge, this is the first example of the three-component carbomagnesiation of alkynes in which an alkyl halide is used as a coupling component. The reaction proceeds via a radical mechanism and affords vinyl Grignard reagents efficiently when tertiary or secondary alkyl iodides are employed. The reaction provides a useful and convenient method for the synthesis of trisubstituted olefins by not only the simple trapping of the resulting vinyl Grignard reagents with electrophiles but also by further manipulation catalyzed by transition metals such as cross-coupling. The application of this reaction to δ-haloalkylalkynes led to the synthesis of five-membered (hetero) cycles bearing an *exo*-methylene substituent. Allenyl Grignard reagents can be prepared when enynes are employed.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (S) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Additional data, experimental details, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

[16] An alternative mechanism that alkyl radicals, generated by S$_H$2 reaction of alkyl iodides with i-Bu radical from **9**, directly attack alkynes without forming **10** may also be operating.

[17] Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941.