Regioselective allylgallation of terminal alkynes

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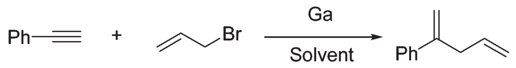
The reactions of terminal alkynes with allylgallium reagents generated *in situ* from gallium and allyl bromides gave the corresponding 1,4-dienes in good yield *via* Markovnikov addition in THF at 70 °C.

The carbometalation of C–C multiple bonds is a very important organic transformation.[1] In particular, the development of allylmetalation of simple unactivated alkynes toward the synthesis of 1,4-dienes is valuable in organic synthesis because of the utility of 1,4-dienes and the limited number of allylmetals available for this purpose.[2] To date various allylmetalations have been reported on the basis of nucleophilic character of allylmetals obtained from allyl halides and metals (Ta, Zr, Zn, Al, Ti, Si, and Sn).[2] Although organoindium reagents generated from the reaction of indium with allyl halides have been used extensively in carbonyl addition reactions,[3] additions to C–C multiple bonds and nitriles,[4] and cross-coupling reactions,[5] organogallium reagents have not been explored to a great extent in organic syntheses.[6] As part of the continuing effort to expand the synthetic utility of Group IIIa (In and Ga),[4g,7] we now report the efficient synthesis of 1,4-dienes *via* allylation of alkynes by organogallium reagents (Scheme 1).

We first investigated various experimental conditions in a model reaction using phenylacetylene and allyl bromide (Table 1). Although treatment of phenylacetylene with allyl bromide and gallium did not produce the desired compounds in THF at 25 °C (entry 1), refluxing the reaction mixture at 70 °C gave 2-phenyl-1,4-pentadiene, which is the Markovnikov addition product, in 82% yield (entry 2). No trace of the corresponding anti-Markovnikov addition product was detected by NMR spectroscopy in this reaction. The use of additives such as LiI, LiBr, and I_2 furnished 1,4-diene in 87%, 90%, and 85% yields, respectively, in THF at 70 °C (entries 6–8). Of the reaction conditions examined, the best results were obtained with 2.0 equiv. of gallium and 8.0 equiv. of allyl bromide in THF at 70 °C for 4 h, which provided 1,4-diene in 95% yield (entry 5).[8] THF was the best solvent among several reaction media (DMF, THF, $PhCH_3$, CH_3CN, THF–H_2O, and DMF–H_2O) that were evaluated.

To demonstrate the efficiency and scope of the present method, organogallium reagents generated *in situ* from gallium and allyl bromides were added to a variety of alkynes. The results are summarized in Table 2. Under the optimized conditions, 1-octyne and 3-phenyl-1-propyne reacted with allylgallium reagent to give 4-methylene-1-decene and 2-benzyl-1,4-pentadiene in 70% and 72% yields, respectively (entries 1 and 3). Treatment of 1-octyne with 3-bromo-2-methylpropene and gallium afforded the desired product in 62% yield (entry 2). In the course of the present study, we observed a very interesting and dramatic effect of a hydroxyl group, if it is suitably positioned relative to the triple bond, on the regioselectivity. Although allylation of 5-hexyn-1-ol provided 5-methylene-7-octen-1-ol in 51% yield (entry 4), 1-phenyl-2-propyn-1-ol gave 1-phenyl-1,2,5-hexatriene in 60% yield *via* anti-Markovnikov addition to the triple bond followed by elimination (entry 5). This implies that the change in selectivity for the formation of 1-phenyl-1,2,5-hexatriene *via* the anti-Markovnikov addition in the reaction of 1-phenyl-2-propyn-1-ol was caused by the coordination of the carbinol oxygen to an organogallium intermediate. Exposure of silylacetylene to 3-bromo-2-methylpropene and gallium produced 4-methyl-2-trimethylsilyl-1,4-pentadiene in 91% yield under the present conditions (entry 7). Both electron-rich (entries 10–13) and electron-deficient (entries 14 and 15) aromatic acetylenes are suitable substrates for allylgallation reactions and provide the corresponding 1,4-dienes in good to excellent yields. Treatment of 1,7-octadiyne with excess of allylgallium reagent gave rise to 4,9-di(methylene)-1,11-dodecadiene in 67% yield in THF for 18 h (entry 17). Under the optimum conditions, 1,7-octadiyne produced the desired product in 45% yield together with the double allylation product (entry 16). Internal alkynes failed to react with allylgallium reagents in contrast with terminal alkynes.

Table 1 Reaction optimization of allylgallation of phenylacetylene[a]



Entry	Ga (equiv.)	Solvent	Additive	Temp (°C)	Time (h)	Yield (%)[b]
1	1.0	THF		25	12	0
2	1.0	THF		70	5	82
3	1.0	DMF		70	12	0
4[c]	2.0	THF		70	12	67
5	2.0	THF		70	4	95(92)[d]
6[e]	1.0	THF	LiI	70	12	87
7[f]	1.0	THF	LiBr	70	6	90
8[g]	2.0	THF	I_2	70	5	85

[a] Reactions of Grignard type performed with 1.0 equiv. of phenylacetylene and 8.0 equiv. of allyl bromide in the presence of 2.0 equiv. of gallium (cut ingot-gallium into small pieces), unless otherwise noted. [b] GC yields were obtained on the basis of an internal standard (dodecane). [c] 3 equiv. of allyl bromide were used. [d] Isolated yield. [e] 3 equiv. of LiI were used. [f] 3 equiv. of LiBr were used. [g] 5 mol% of I_2 was used.

Scheme 1

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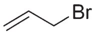
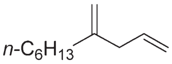
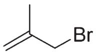
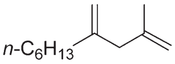
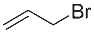
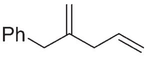
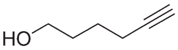
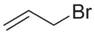
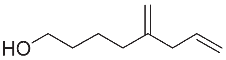
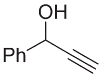
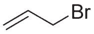
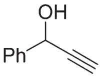
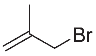
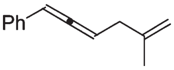
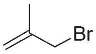
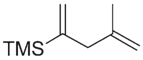
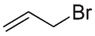
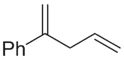
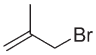
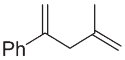
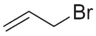
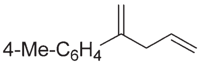
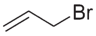
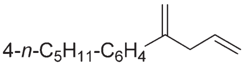
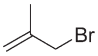
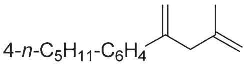
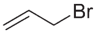
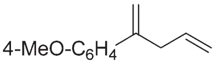
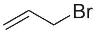
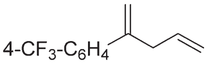
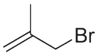
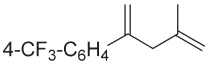
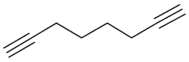
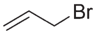
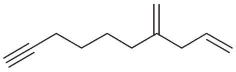
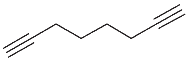
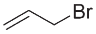
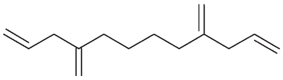
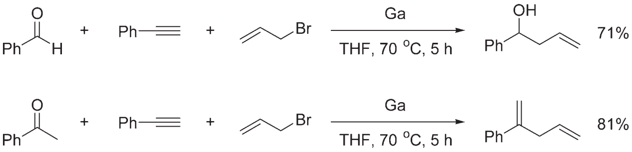
Table 2 Allylgallation of terminal alkynes with allyl bromide and gallium[a]

Entry	Alkyne	Allyl bromide	Time (h)	Product	Yield (%)[b]
1	$n\text{-C}_6\text{H}_{13}-\equiv$		8		70
2	$n\text{-C}_6\text{H}_{13}-\equiv$		10		62
3	$\text{PhCH}_2-\equiv$		6		72
4			8		51
5			5		60
6			8		53
7	$\text{TMS}-\equiv$		6		91[c]
8	$\text{Ph}-\equiv$		4		92
9	$\text{Ph}-\equiv$		4		80
10	$4\text{-Me-C}_6\text{H}_4-\equiv$		4		96
11	$4\text{-}n\text{-C}_5\text{H}_{11}\text{-C}_6\text{H}_4-\equiv$		6		95
12	$4\text{-}n\text{-C}_5\text{H}_{11}\text{-C}_6\text{H}_4-\equiv$		6		94
13	$4\text{-MeO-C}_6\text{H}_4-\equiv$		6		64
14	$4\text{-CF}_3\text{-C}_6\text{H}_4-\equiv$		4		60
15	$4\text{-CF}_3\text{-C}_6\text{H}_4-\equiv$		5		53
16			12		45(15)[d],(35)[e]
17			18		67[f]

[a] Reactions of Grignard type performed with terminal acetylene (1 mmol), allylic bromide (8.0 mmol), and Ga (2.0 mmol) in THF at 70 °C, unless otherwise noted. [b] Isolated yield. [c] GC yield was obtained on the basis of an internal standard (dodecane). [d] GC yield of starting material. [e] GC yield of 4,9-di(methylene)-1,11-dodecadiene. [f] Alkyne (1 mmol), allyl bromide (16 mmol), and Ga (4 mmol) were used.

Although subjecting allylgallium reagent to the mixture of 1 equiv. of benzaldehyde and 1 equiv. of phenylacetylene chemoselectively afforded 1-phenyl-3-butenol in 71% yield, competition reaction of acetophenone and phenylacetylene under the present conditions produced 2-phenyl-1,4-pentadiene in 81% yield (Scheme 2).



Scheme 2

In summary, we have demonstrated that allylation of alkynes by organogallium reagents produces 1,4-dienes in good yields. A variety of aliphatic and aromatic terminal acetylenes participate in this reaction. The present method complements existing synthetic methods as a result of advantageous features such as the ready availability of allyl bromide and operational simplicity. Further studies to explain the utility and mechanism of this reaction are under investigation.

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Notes and references

1 (*a*) J. F. Normant and A. Alexakis, *Synthesis*, 1981, 841; (*b*) E. Negishi, *Pure Appl. Chem.*, 1981, **53**, 2333; (*c*) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 38; (*d*) P. Knochel, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, **vol. 4**, p 865; (*e*) Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207; (*f*) P. Knochel, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Able, F. G. A. Stone, and G. Wilkinson, Pergamon Press, Oxford, 1995, **vol. 11**, p 159.

2 (*a*) G. A. Molander, *J. Org. Chem.*, 1983, **48**, 5409; (*b*) E. Negishi and J. A. Miller, *J. Am. Chem. Soc.*, 1983, **105**, 6761; (*c*) J. A. Miller and E. Negishi, *Tetrahedron Lett.*, 1984, **25**, 5863; (*d*) J. J. Eisch and M. P. Boleslawski, *J. Organomet. Chem.*, 1987, **334**, 1–2, C1; (*e*) T. Takahashi, M. Kotora, K. Kasai and N. Suzuki, *Tetrahedron Lett.*, 1994, **35**, 5685; (*f*) N. Chatani, N. Amishiro, T. Morii, T. Yamashita and S. Murai, *J. Org. Chem.*, 1995, **60**, 1834; (*g*) K. Takai, M. Yamada, H. Odaka, K. Utimoto, T. Fujii and I. Furukawa, *Chem. Lett.*, 1995, 315; (*h*) S. H. Yeon, J. S. Han, E. Hong, Y. Do and I. N. Jung, *J. Organomet. Chem.*, 1995, **499**, 159; (*i*) N. Asao, Y. Matsukawa and Y. Yamamoto, *Chem. Commun.*, 1996, 1513; (*j*) N. Asao, E. Yoshikawa and Y. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4874.

3 (*a*) C.-J. Li, *Chem. Rev.*, 1993, **93**, 2023; (*b*) P. Cintas, *Synlett*, 1995, 1087; (*c*) C.-J. Li, *Tetrahedron*, 1996, **52**, 5643; (*d*) C.-J. Li and T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997; (*e*) C.-J. Li and T.-H. Chan, *Tetrahedron*, 1999, **55**, 11149; (*f*) G. Babu and P. T. Perumal, *Aldrichimica Acta*, 2000, **33**, 16; (*g*) K. K. Chauhan and C. G. Frost, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3015; (*h*) A. N. Pae and Y. S. Cho, *Curr. Org. Chem.*, 2002, **6**, 715; (*i*) J. Podlech and T. C. Maier, *Synthesis*, 2003, 633.

4 (*a*) S. Araki, A. Imai, K. Shimizu, M. Yamada, A. Mori and Y. Butsugan, *J. Org. Chem.*, 1995, **60**, 1841; (*b*) S. Araki, H. Usui, M. Kato and Y. Butsugan, *J. Am. Chem. Soc.*, 1996, **118**, 4699; (*c*) B. C. Ranu and A. Majee, *Chem. Commun.*, 1997, 1225; (*d*) N. Fujiwara and Y. Yamamoto, *J. Org. Chem.*, 1997, **62**, 2318; (*e*) N. Fujiwara and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 4095; (*f*) E. Klaps and W. Schmid, *J. Org. Chem.*, 1999, **64**, 7537; (*g*) P. H. Lee, S. Kim, K. Lee, D. Seomoon, H. Kim, S. Lee, M. Kim, M. Han, K. Noh and T. Livinghouse, *Org. Lett.*, 2004, **6**, 4825.

5 (*a*) P. H. Lee, S.-Y. Sung and K. Lee, *Org. Lett.*, 2001, **3**, 3201; (*b*) K. Lee, J. Lee and P. H. Lee, *J. Org. Chem.*, 2002, **67**, 8265; (*c*) P. H. Lee, S.-Y. Sung, K. Lee and S. Chang, *Synlett*, 2002, 146; (*d*) K. Lee, D. Seomoon and P. H. Lee, *Angew. Chem. Int. Ed.*, 2002, **41**, 3901; (*e*) P. H. Lee, S. W. Lee and K. Lee, *Org. Lett.*, 2003, **5**, 1103; (*f*) P. H. Lee, S. W. Lee and D. Seomoon, *Org. Lett.*, 2003, **5**, 4963; (*g*) S. W. Lee, K. Lee, D. Seomoon, S. Kim, H. Kim, H. Kim, E. Shim, M. Lee, S. Lee, M. Kim and P. H. Lee, *J. Org. Chem.*, 2004, **69**, 4852; (*h*) P. H. Lee, D. Seomoon, K. Lee, S. Kim, H. Kim, H. Kim, E. Shim, M. Lee, S. Lee, M. Kim and M. Sridhar, *Adv. Synth. Catal.*, 2004, **346**, 1641; (*i*) P. H. Lee, E. Shim, K. Lee, D. Seomoon and S. Kim, *Bull. Korean Chem. Soc.*, 2005, **26**, 157; (*j*) P. H. Lee, D. Seomoon and K. Lee, *Org. Lett.*, 2005, **7**, 343.

6 (*a*) S. Araki, H. Ito and Y. Butsugan, *Appl. Organomet. Chem.*, 1988, **2**, 475; (*b*) M. Yamaguchi, T. Sotokawa and M. Hirama, *Chem. Commun.*, 1997, 743; (*c*) Y. Han, Z. Chi and Y.-Z. Huang, *Synth. Commun.*, 1999, **29**, 1287; (*d*) S.-I. Usugi, H. Yorimitsu and K. Oshima, *Tetrahedron Lett.*, 2001, **42**, 4535; (*e*) Z. Wang, S. Yuan and C.-J. Li, *Tetrahedron Lett.*, 2002, **43**, 5097; (*f*) T. Tsuji, S.-I. Usugi, H. Yorimitsu, H. Shinokubo, S. Matsubara and K. Oshima, *Chem. Lett.*, 2002, 2; (*g*) V. Nair, S. Ros, C. N. Jayan and B. S. Pillai, *Tetrahedron*, 2004, **60**, 1959; (*h*) M. Yamaguchi, in *Main Group Metals in Organic Synthesis*, ed. H. Yamamoto and K. Oshima, Wiley-VCH, Weinheim, 2004, vol. **1**, pp 307–322; (*i*) P. C. Andrew, A. C. Peatt and C. L. Raston, *Tetrahedron Lett.*, 2004, **45**, 243.

7 (*a*) P. H. Lee, K. Bang, K. Lee, C.-H. Lee and S. Chang, *Tetrahedron Lett.*, 2000, **41**, 7521; (*b*) P. H. Lee, H. Ahn, K. Lee, S.-Y. Sung and S. Kim, *Tetrahedron Lett.*, 2001, **42**, 37; (*c*) P. H. Lee, K. Bang, H. Ahn and K. Lee, *Bull. Korean Chem. Soc.*, 2001, **22**, 1385; (*d*) P. H. Lee, S. Seomoon and K. Lee, *Bull. Korean Chem. Soc.*, 2001, **22**, 1380; (*e*) P. H. Lee, K. Lee, S.-Y. Sung and S. Chang, *J. Org. Chem.*, 2001, **66**, 8646; (*f*) P. H. Lee, K. Lee and S. Chang, *Synth. Commun.*, 2001, **31**, 3189; (*g*) P. H. Lee, K. Bang, K. Lee, S.-Y. Sung and S. Chang, *Synth. Commun.*, 2001, **31**, 3781; (*h*) P. H. Lee, K. Lee and S. Kim, *Org. Lett.*, 2001, **3**, 3205; (*i*) K. Bang, K. Lee, Y. K. Park and P. H. Lee, *Bull. Korean Chem. Soc.*, 2002, **23**, 1272; (*j*) N. Iwasawa, T. Miura, K. Kiyota, H. Kusama, K. Lee and P. H. Lee, *Org. Lett.*, 2002, **4**, 4463; (*k*) P. H. Lee, D. Seomoon, K. Lee and Y. Heo, *J. Org. Chem.*, 2003, **68**, 2510; (*l*) T. Miura, K. Kiyota, H. Kusama, K. Lee, H. Kim, S. Kim, P. H. Lee and N. Iwasawa, *Org. Lett.*, 2003, **5**, 1725; (*m*) K. Lee, H. Kim, T. Miura, K. Kiyota, H. Kusama, S. Kim, N. Iwasawa and P. H. Lee, *J. Am. Chem. Soc.*, 2003, **125**, 9682; (*n*) P. H. Lee, D. Seomoon, S. Kim, K. Nagaiah, S. V. Damle and K. Lee, *Synthesis*, 2003, 2189; (*o*) S. V. Damle, D. Seomoon and P. H. Lee, *J. Org. Chem.*, 2003, **68**, 7085; (*p*) P. H. Lee, H. Kim, K. Lee, D. Seomoon, S. Kim, H. Kim, H. Kim, M. Lee, E. Shim, S. Lee, M. Kim, M. Han, K. Noh and M. Sridhar, *Bull. Korean Chem. Soc.*, 2004, **25**, 1687.

8 **Typical experimental procedure:** To a solution of gallium ingot (140 mg, 2.0 mmol, cut into small pieces) in THF (3 mL) was added allyl bromide (968 mg, 8.0 mmol) under a nitrogen atmosphere at room temperature. After the gallium ingot was dissolved for 30 min, phenylacetylene (120 mg, 1.0 mmol) was added to the reaction mixture. After being stirred at 70 °C for 4 h, the reaction mixture was quenched with 10% aqueous HCl solution. The aqueous layer was extracted with ether (3 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried with MgSO$_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using *n*-hexane to give 2-phenyl-1,4-pentadiene (92%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45-7.21 (m, 5H), 5.91 (ddt, J = 16.85, 10.09, 6.55 Hz, 1H), 5.39 (s, 1H), 5.14-5.05 (m, 3H), 3.25 (d, J = 5.64 Hz, 2H); ^{13}C NMR (100 MHz) δ 146.7, 141.3, 136.6, 128.6, 127.8, 126.4, 116.9, 113.6, 39.9.