

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 allylmatalation 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 allylmatalations 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 I₂ 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, PhCH₃, CH₃CN, THF–H₂O, and DMF–H₂O) 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



Scheme 1

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 I₂ was used.

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.

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

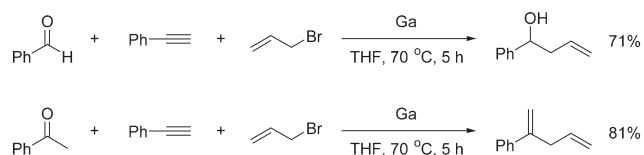
Entry	Alkyne	Allyl bromide	Time (h)	Product	Yield (%) ^b
1	$n\text{-C}_6\text{H}_{13}\text{-C}\equiv\text{C-H}$	$\text{CH}_2=\text{CH-CH}_2\text{Br}$	8	$n\text{-C}_6\text{H}_{13}\text{-C}(\text{CH}_3)=\text{CH-CH}_2\text{CH}=\text{CH}_2$	70
2	$n\text{-C}_6\text{H}_{13}\text{-C}\equiv\text{C-H}$	$(\text{CH}_3)_2\text{C}=\text{CH-CH}_2\text{Br}$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

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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- 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 MgSO₄, 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%). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz) δ 146.7, 141.3, 136.6, 128.6, 127.8, 126.4, 116.9, 113.6, 39.9.