

Dialkylaluminum Hydride-Promoted Cyclodimerization of Silylated 1,3-Enynes via Skeletal Rearrangement

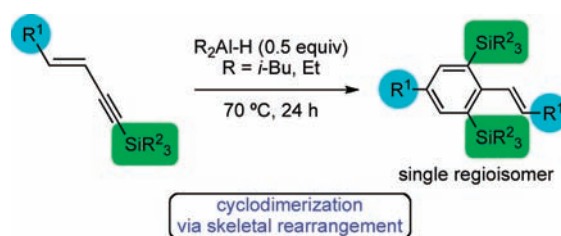
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Received September 26, 2011

ABSTRACT



The dialkylaluminum hydride-promoted reaction of 1-silylalk-3-en-1-yne gave symmetrical 1,2,3,5-tetrasubstituted benzenes as single regioisomers. The novel cyclodimerization via skeletal rearrangement can be rationalized by an unprecedented mechanism involving sequential hydroalumination, alkene isomerization, carboalumination, carbon–carbon bond cleavage, and retro-hydroalumination.

Regio-controlled synthesis of multisubstituted benzenes is one of the central fields in synthetic organic chemistry because polysubstituted arenes are ubiquitous units in functional molecular materials and biologically active compounds.^{1,2} Sequential substitution on existing benzene rings is a conventional way of dealing with this subject. However, this strategy is often accompanied by the problems of incomplete regio-selectivity, difficulty in direct introduction of desired substituents, and low efficiency of the linear multistep approach. For the last few decades, much attention has been focused on transition metal-catalyzed cycloaddition of two or more components, which enables a convergent, efficient approach to multisubstituted benzenes. So far [2 + 2 + 2] cycloaddition of two or three kinds of alkynes has been studied intensively.³ Highly selective construction of multisubstituted benzenes by this method appears in

recent reports, although the scope is still rather limited.⁴ 1,3-Enynes and 1,3-dicarbonyl compounds as well as alkynes serve as the components for benzene ring construction.^{5–7} Yamamoto, Gevorgyan, and co-workers have demonstrated that Pd-catalyzed cyclodimerization of 1,3-enynes and cycloaddition of 1,3-enynes to alkynes form

(1) For example, see the following book: Perepichka, D. F.; Perepichka, I. F.; Meng, H.; Wudl, F. *Organic Light-Emitting Materials and Devices*; Taylor & Francis: Boca Raton, FL, 2007.

(2) Scott, A. I.; Devon, T. K. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1972.

(3) (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 1129. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

(4) (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. (b) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712. (c) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625. (d) Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, *8*, 1439. (e) Hara, H.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2537.

(5) Pd-catalyzed cyclodimerization of 1,3-enynes: (a) Saito, S.; Salter, M. S.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970. (b) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347.

(6) Pd-catalyzed cycloaddition of 1,3-enynes to alkynes: (a) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313. (b) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391. (c) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. (d) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265. (e) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5818.

(7) Regioselective synthesis of multisubstituted benzenes from alkynes and 1,3-dicarbonyl compounds with Re or Mn catalysts: (a) Kuninobu, Y.; Nishi, M.; Yudha, S.; Takai, K. *Org. Lett.* **2008**, *10*, 3009. (b) Kuninobu, Y.; Takata, H.; Kawata, A.; Takai, K. *Org. Lett.* **2008**, *10*, 3133. (c) Yoshikai, N.; Zhang, S.-L.; Yamagata, K.; Tsuji, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 4099.

Table 1. Optimization of Reaction Conditions^a

entry	R in R ₂ AlH (equiv)	temp (°C)	time (h)	isolated yield (%)		
				2a	3a (EE:EZ) ^b	1a
1	<i>i</i> -Bu (1.0)	70	24	43	25 (70:30)	0
2 ^c	<i>i</i> -Bu (1.0)	70	24	9	54 (72:28)	0
3	<i>i</i> -Bu (1.0)	30	48	32	32 (47:53)	0
4 ^d	<i>i</i> -Bu (1.0)	110	24	11	— ^e	0
5	<i>i</i> -Bu (3.0)	70	24	0	— ^e	0
6	<i>i</i> -Bu (0.2)	70	70	42	— ^e	19
7	<i>i</i> -Bu (0.5)	70	24	46	17 (70:30)	0
8 ^f	<i>i</i> -Bu (0.5)	70	24	50	12 (70:30)	0
9 ^g	<i>i</i> -Bu (0.5)	70	24	55	11 (60:40)	0
10 ^h	<i>i</i> -Bu (0.5)	70	24	53	19 (62:38)	0
11 ⁱ	<i>i</i> -Bu (0.5)	70	24	60	13 (67:33)	0
12 ^h	Et (0.5)	70	24	67	12 (62:38)	0
13 ^h	Et (0.5)	70	24	62	15 (60:40)	0
14 ⁱ	Et (0.5)	70	24	62	— ^e	0

^aUnless otherwise noted, the reaction was carried out with **1a** (0.5 mmol) and R₂AlH in hexane (1.0 mL). ^bDetermined by ¹H NMR analysis. ^cWith 10 mL of hexane. ^dToluene (1.0 mL) was used instead of hexane. ^eNot isolated due to a complex mixture of products. ^fWith 0.5 mL of hexane. ^gWith 0.25 mL of hexane. ^hHeptane (0.25 mL in entries 10 and 13; 0.5 mL in entry 12) was used instead of hexane. ⁱWithout solvent.

multisubstituted benzenes with high regioselectivity. In this context, we herein report that dialkylaluminum hydrides (DIBAL-H and Et₂AlH) promote cyclodimerization of silylated 1,3-enynes to unprecedented tetrasubstituted benzenes with complete regio-control. This work provides a rare example of regio-controlled synthesis of multisubstituted benzenes using aluminum reagents.⁸

In the course of our study on synthetic use of vinylsilanes,⁹ we attempted the partial reduction of (*E*)-1-(trimethylsilyl)dec-3-en-1-yne (**1a**) with DIBAL-H to synthesize 1-silyl-1,3-diene **3a** (entry 1 in Table 1). However, **3a** was obtained in only a low yield. Surprisingly the reaction afforded tetrasubstituted benzene **2a**, an unprecedented dimer of **1a**, as the major product. No reaction occurred in the absence of DIBAL-H. Our attention was therefore focused on this novel cyclodimerization via skeletal rearrangement.

Optimization of the reaction conditions was initially conducted to improve the yield of **2a**. Under the conditions shown in entry 1 of Table 1, several solvents were used instead of hexane. Other less polar solvents (benzene,

toluene, xylene, and 1,2-dichloroethane) allowed the cyclodimerization to **2a** in less than 20% yields. Polar solvents such as THF and Et₂O prevented the cyclodimerization completely. The results brought by variation of other conditions are summarized in Table 1. Dilution with a 10-fold amount of hexane was not effective and increased the formation of **3a** (entry 2). The cyclodimerization proceeded even at 30 °C although the yield of **2a** dropped to 32% (entry 3). The reaction at 110 °C resulted in a complex mixture of products (entry 4). An excess amount of DIBAL-H suppressed the dimerization to **2a** (entry 5). Longer reaction with 0.2 equiv of DIBAL-H gave **2a** in a reasonable yield (entry 6). Use of 0.5 equiv of DIBAL-H improved the yield of **2a** to 46% (entry 7). The reactions using a decreased amount of solvent or under solvent-free conditions were also effective in the cyclodimerization (entries 8–11). Use of heptane as a slightly less volatile solvent gave a similar result (entry 10). Diethylaluminum hydride (Et₂AlH), a sterically less hindered aluminum hydride, was also used instead of DIBAL-H (entries 11–13). As a result, the Et₂AlH-promoted reaction in heptane achieved the best result (entry 12).

We next examined the cyclodimerization of 1,3-enynes **1** bearing a different silyl group (Table 2). The DIBAL-H-promoted reactions of enynes **1b** (*Si* = SiMe₂Ph), **1c** (*Si* = SiMe₂Bn), and **1d** (*Si* = SiMePh₂) gave the corresponding tetrasubstituted benzenes in 47–53% isolated yields (entries 1, 3, and 4). Use of Et₂AlH slightly improved the yield of **2b** (entry 2). Enyne **1e**, bearing a more sterically demanding silyl group (*Si* = SiPh₃), did not undergo the cyclodimerization, and diene **3e** and oligomeric compounds were formed (entry 5). Thus, the introduction of a TMS group was found to be more effective in the benzene ring formation than that of other silyl groups.

Table 2. Effects of Silyl Groups^a

entry	<i>Si</i>	enyne	product	yield (%)
1	PhMe ₂ Si	1b	2b	47
2 ^b	PhMe ₂ Si	1b	2b	51
3	BnMe ₂ Si	1c	2c	53
4	Ph ₂ MeSi	1d	2d	48
5	Ph ₃ Si	1e	2e	0 ^c

^aThe reaction was carried out with **1** (0.5 mmol) and DIBAL-H (0.25 mmol) at 70 °C for 24 h without solvent. ^bThe reaction was carried out with **1** (0.5 mmol) and Et₂AlH (0.25 mmol) in heptane (0.5 mL) at 70 °C for 24 h. ^cDiene **3e** was obtained in 31% yield along with oligomeric compounds.

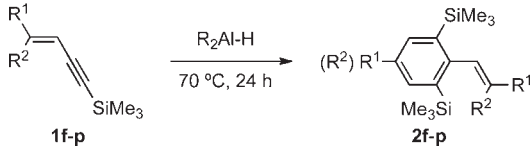
To elucidate the scope and limitations of the present cyclodimerization, the reaction of some 1,3-enynes bearing a TMS group was carried out with DIBAL-H and Et₂AlH (Table 3). 4-Cyclohexyl-1-(trimethylsilyl)but-3-en-1-yne (**1f**) was converted into the corresponding tetrasubstituted

(8) (a) Wilke, G.; Müller, H. *Justus Liebigs Ann. Chem.* **1960**, 629, 222. (b) Eisch, J. J.; Kaska, W. C. *J. Am. Chem. Soc.* **1966**, 88, 2213.

(9) Miura, K.; Inoue, G.; Sasagawa, H.; Kinoshita, H.; Ichikawa, J.; Hosomi, A. *Org. Lett.* **2009**, 11, 5066.

benzene in relatively good yields (entry 1). The cyclodimerization of **1g** and its *Z*-isomer **1h** proceeded with retention of the alkene geometry (entries 2 and 3). The *Z*-geometry slightly decelerated the cyclodimerization. Arylated enynes **1i–1** and **1n** also underwent the cyclodimerization to give stilbene derivatives in moderate yields (entries 4–7 and 9).¹⁰ In contrast, enyne **1m** was hardly dimerized to **2m** (entry 8). The unsuccessful result is likely due to the steric factor arising from the ortho substitution. No reaction occurred with 1,3-enyne **1o**, and **1o** was recovered quantitatively (entry 10). The ether functionality would make DIBAL-H inactive by coordination to inhibit any reaction. The reactions of **1p** (entry 11), **1q**, and **1r** resulted in complex mixtures of unidentified products. Thus the substituent at the terminal sp²-carbon of 1,3-enynes is necessary for benzene ring formation, while the substituent at the internal sp²-carbon prevents it.¹¹ The structure of **2f** was clearly determined by X-ray structure analysis.¹²

Table 3. Scope and Limitations of Cyclodimerization^a



entry	enyne 1		isolated yield (%)			
	R ¹	R ²	2	R = <i>i</i> -Bu ^b	R = Et ^c	
1	Cy	H	1f	2f	60	63
2	H	Me	1g	2g	35	51
3	Me	H	1h	2h	56	66
4	Ph	H	1i	2i	44	55
5	4-F-C ₆ H ₄	H	1j	2j	40	59
6	4-Cl-C ₆ H ₄	H	1k	2k	43	50
7	4-Me-C ₆ H ₄	H	1l	2l	48	51
8	2-Me-C ₆ H ₄	H	1m	2m	trace	
9	4-Ph-C ₆ H ₄	H	1n	2n	37	44
10	4-MeO-C ₆ H ₄	H	1o	2o	0	
11	H	H	1p	2p	CM ^d	

^a All reactions were carried out with **1** (0.5 mmol) and R₂Al-H (0.25 mmol) at 70 °C for 24 h. ^b The reactions were carried out without solvent (entries 1–3, and 11) or in heptane (0.125 mL in entries 4–10). ^c The reactions were carried out in heptane (0.5 mL in entries 1–3; 0.25 mL in entries 4–7, and 9). ^d CM: a complex mixture of products.



A plausible mechanism for the R₂AlH-promoted cyclodimerization of silylated 1,3-enynes is shown in Scheme 1.

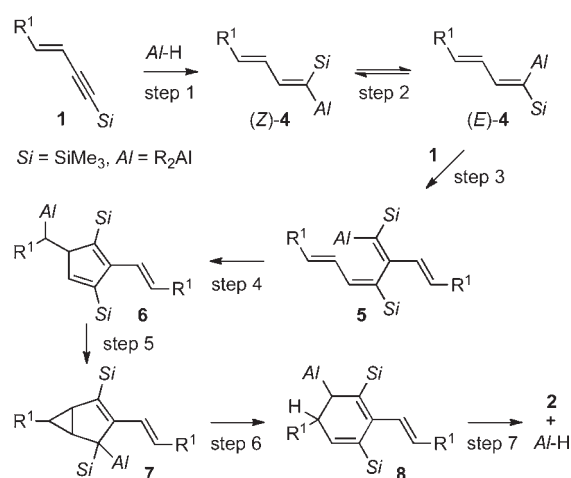
(10) The DIBAL-H-promoted reactions of **1i** and **1j** without solvent gave **2i** and **2j** in 40% and 33% yields, respectively.

(11) A silyl group is crucial for this transformation. Although the reaction of (*E*)-1,4-diphenylbut-1-en-3-yne was also carried out, no desired product was formed. (1*E*, 3*E*)-1,4-Diphenylbut-1,3-diene and its 1*Z*-isomer were obtained in 11% total yield (64:36).

(12) See the Supporting Information.

First, hydroalumination of the alkynylsilane part of **1** takes place with high regioselectivity (step 1).¹³ The resultant dienylaluminum (*Z*)-**4** is isomerized to (*E*)-**4** (step 2).¹⁴ Intermolecular carboalumination of **1** with (*E*)-**4** forms tetraenylaluminum **5** (step 3), which is cyclized to cyclopentadiene **6** by intramolecular carboalumination (step 4).¹⁵ Further carboalumination converts **6** into bicyclic intermediate **7** (step 5). The ring-opening reaction (C–C bond cleavage) of cyclopropylcarbanyl aluminum **7** yields cyclohexadienylaluminum **8** (step 6).¹⁶ Then the retro-hydroalumination of **8** provides **2** with release of R₂AlH (step 7).^{17,18} The improved results with Et₂AlH is attributable to the sterically less congested character of the Et₂Al groups, which allows easy access of C–C unsaturated bonds to the reactive sites (Al–H and Al–C bonds) of Et₂AlH and Et₂Al-based intermediates. The reduced bulkiness would also promote the isomerization of (*Z*)-**4** because it minimizes the steric interaction between *Z*-configured dialkylaluminum and alkenyl groups in (*E*)-**4**.

Scheme 1. Plausible Mechanism



The reaction of enyne **1s**, bearing a triethylsilyl group, afforded tetraene **9** and cyclopentadiene **10** with **2s** and **3s** (Scheme 2). Since the conversion of **1s** into **9** can be

(13) Eisch, J. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 8, Chapter 3.11, p 733.

(14) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520.

(15) For intermolecular carboalumination with alkynes, see: (a) Wilke, G.; Müller, H. *Justus Liebig's Ann. Chem.* **1960**, *629*, 222. (b) Eisch, J. J.; Kaska, W. C. *J. Am. Chem. Soc.* **1966**, *88*, 2213. (c) Zweifel, G.; Snow, J. T.; Whitney, C. C. *J. Am. Chem. Soc.* **1968**, *90*, 7139. (d) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, *3*, 841.

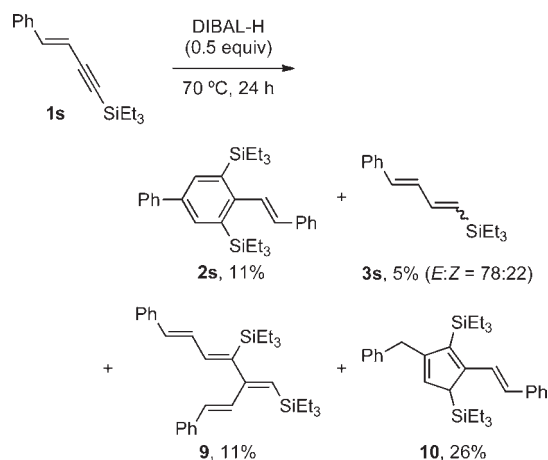
(16) For rearrangement of (cyclopropylcarbanyl)metals, see: (1) Maercker, A.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1742. (2) Pannell, K. H.; Kapoor, R. N.; Wells, M.; Giasolli, T.; Parkanyi, L. *Organometallics* **1987**, *6*, 663. (3) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. J. *Am. Chem. Soc.* **1992**, *114*, 10091.

(17) For retro-hydroalumination to regenerate DIBAL-H, see: Ziegler, H.; Martin, H.; Krupp, F. *Justus Liebig's Ann. Chem.* **1960**, *629*, 14.

(18) Wilson and Chum reported the DIBAL-H-catalyzed cyclization of α,ω -dienes. The proposed mechanism involves hydroalumination of one C–C double bond, intramolecular carboalumination of another C–C double bond, and retro-hydroalumination with regeneration of DIBAL-H. Chum, P. W.; Wilson, S. E. *Tetrahedron Lett.* **1976**, *16*, 1257.

explained by intermolecular carboalumination of **1s** with dienylaluminum (*Z*)-**4s** ($Si = SiEt_3$, $R^1 = Ph$), it partly justifies the validity of the proposed intermolecular carboalumination from (*E*)-**4** to tetraenylaluminum **5** (step 3 in Scheme 1). The formation of **10** is indicative of the presence of intermediate **6s** ($Si = SiEt_3$, $R^1 = Ph$). The path from **6s** to **10** can be rationalized by hydrolysis of the C–Al bond followed by alkene migration. In the reaction of **1s**, the bulky triethylsilyl group probably inhibits intramolecular carboalumination of **6s** (step 5 in Scheme 1) to cause the formation of **10**.

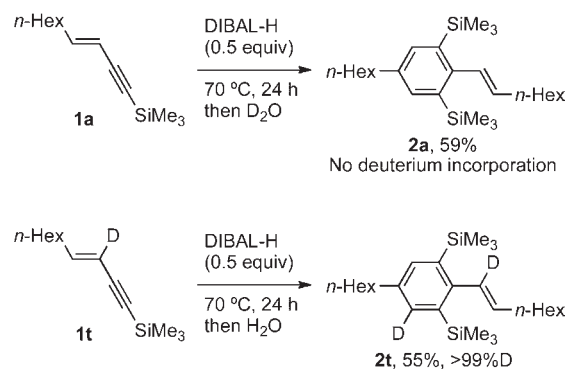
Scheme 2. Cyclodimerization of Enyne **1s**



To ascertain the last retro-hydroalumination step (step 7 in Scheme 1), the reaction mixture from **1a** was quenched with D_2O (Scheme 3). 1H NMR analysis of the product **2a** revealed that no D-incorporation occurred. Additionally the cyclodimerization of D-labeled 1,3-enyne **1t** afforded **2t** without erosion of D-content. These results clearly rule out the possibility of hydrolysis of **8** followed by aerobic aromatization to **2**. The retro-hydroalumination step

(19) For recent studies on synthetic use of alkenylaluminums, see: (a) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736. (b) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 4778 and references therein.

Scheme 3. Deuterium-Labeling Experiments



implies that a catalytic amount of R_2AlH can promote the cyclodimerization of **1**. In practice, however, the catalytic use is not feasible for the cyclodimerization of **1** because of many side reactions caused by R_2AlH .

In summary, we have found a R_2AlH -promoted cyclodimerization of silylated 1,3-enynes taking place via skeletal rearrangement. This novel reaction proceeds with complete regioselectivity to provide rapid access to unprecedented tetrasubstituted benzenes without using transition metal catalysis. This work has revealed that alkenylaluminum reagents have a high potential for regioselective construction of multisubstituted benzenes.¹⁹ Several experimental results suggest an intriguing mechanism for the cyclodimerization. At present, the R_2AlH -promoted cross-coupling between two different 1,3-enynes is under investigation in this laboratory.

Acknowledgment. We thank senior assistant professor Mikio Yasutake (Saitama University) for X-ray crystal analysis and Mr. Takao Sugiyama (Saitama University) for HRMS analysis.

Supporting Information Available. Detailed experimental procedures and characterization data for all new compounds. X-ray crystallographic data for **2f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.