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Hydroalumination-Triggered Cyclization of Silylated 1,3-Dien-5-ynes to Polysubstituted Benzenes

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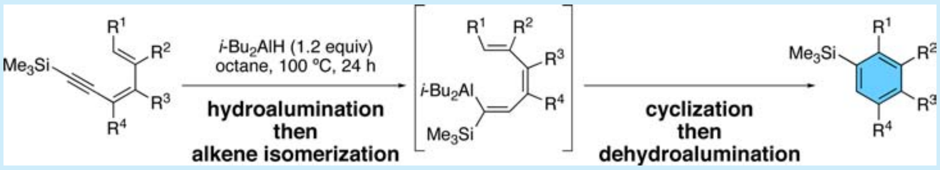
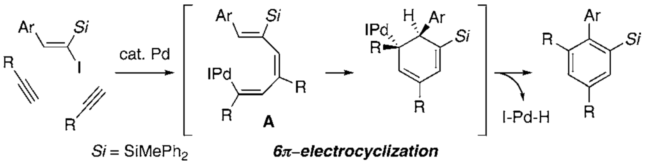
S *Supporting Information*



ABSTRACT: Regiocontrolled synthesis of polysubstituted benzenes from silylated 1,3-dien-5-ynes has been achieved by using diisobutylaluminum hydride (DIBAL-H). Hydroalumination of the alkyne moiety with DIBAL-H triggers the aromatic cyclization, which usually proceeds without rearrangement and loss of the existing substituents. The related unusual cyclizations to different types of polysubstituted benzenes are also described.

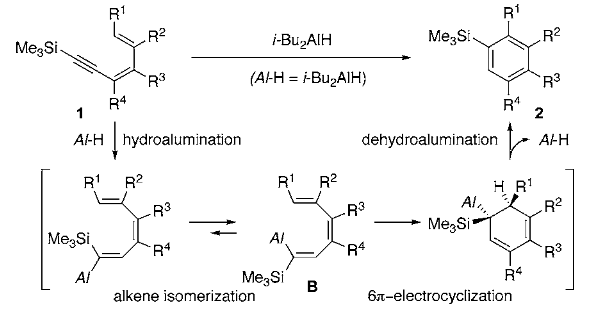
Polysubstituted benzene motifs appear ubiquitously in various compounds from biologically active molecules to functional molecular materials. Hence, much effort has been devoted to synthetic methods for constructing polysubstituted benzenes.[1,2] During our campaign to develop effective access to polysubstitued benzenes,[3,4] we found that the Pd-catalyzed intermolecular reaction of β-iodo-β-silylstyrenes with terminal alkynes affords 1,2,3,5-tetrasubstituted benzenes efficiently under mild reaction conditions.[4] The [2 + 2 + 2] cycloaddition has been proposed to proceed through 6π-electrocyclization of trienylpalladium intermediate **A** (Scheme 1).[5] Based on the reaction mechanism, we envisioned that other metalated trienes would also provide polysubstituted benzenes by a similar reaction sequence involving disrotatory 6π-electrocyclization and dehydrometalation. To ensure the feasibility, we attempted the cyclization of trienylaluminums prepared from 1,3-dien-5-ynes and diisobutylaluminum hydride (DIBAL-H).[6] We report herein that the hydroalumination-triggered reaction of silylated 1,3-dien-5-ynes is valuable for regioselective synthesis of polysubstituted benzenes.

Scheme 1. Benzene Construction via 6π-Electrocyclization of Trienylpalladium Intermediate



Hydroalumination of 1-silyl-1-alkynes with DIBAL-H takes place in a *syn*-addition mode to give (*Z*)-1-alumino-1-silyl-1-alkenes with high regioselectivity. In the absence of coordinative solvents containing a heteroatom, the initially formed *syn*-adducts easily undergo geometrical isomerization leading to the thermodynamically favored (*E*)-isomers.[7] This information promoted us to utilize the silicon-directed hydroalumination-isomerization sequence for the preparation of trienylaluminums having the same configuration as trienylpalladium intermediate **A**. As shown in Scheme 2, we built up a working hypothesis to develop a new benzene-forming reaction. It consists of four steps: regioselective hydroalumination of a silylated 1,3-dien-5-yne **1**, geometrical isomerization of the initial adduct to the corresponding trienylaluminum intermediate **B**, disrotatory 6π-electrocyclization of **B**,[6] and aromatization of the resultant 5-aluminocyclohexa-1,3-diene with elimination of DIBAL-H.

Scheme 2. Working Hypothesis for DIBAL-H-Promoted Aromatic Cyclization



To explore our scenario, we commenced the optimization of reaction conditions using silylated 1,3-dien-5-yne **1a** (Table 1).[8] Treatment of **1a** with an equimolecular amount of DIBAL-H at ambient temperature provided the desired tetrasubstituted

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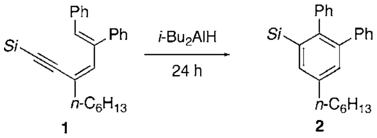
Table 1. Optimization of Reaction Conditions[a]



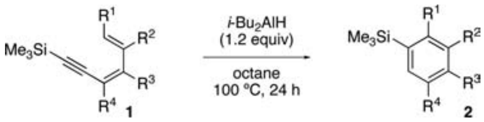
entry	Si	1	DIBAL-H (equiv)	temp (°C)	solvent	2, yield[b] (%)
1	Me_3Si	**1a**	1.0	rt	hexane	**2a**, 34[c]
2	Me_3Si	**1a**	1.0	50	hexane	**2a**, 71[c]
3	Me_3Si	**1a**	1.0	50	THF	**2a**, 0
4	Me_3Si	**1a**	1.0	100	octane	**2a**, 74[c](69)[b]
5	Me_3Si	**1a**	1.0	150	decane	**2a**, 67[c]
6	Me_3Si	**1a**	0	100	octane	**2a**, 0
7	Me_3Si	**1a**	0.2	100	octane	**2a**, trace
8	Me_3Si	**1a**	0.5	100	octane	**2a**, 53
9[d]	Me_3Si	**1a**	0.5	100	octane	**2a**, 49
10	Me_3Si	**1a**	1.2	100	octane	**2a**, 78
11	Me_3Si	**1a**	1.5	100	octane	**2a**, 31[c]
12[e]	Me_3Si	**1a**	1.2	100	octane	**2a**, 72
13	Me_3Si	**1a**	1.2	100	toluene	**2a**, 65
14	Ph_2MeSi	**1b**	1.2	100	octane	**2b**, 53
15	$i\text{-}Pr_3Si$	**1c**	1.2	100	octane	**2c**, 0
16	H	**1d**	1.2	100	octane	**2d**, 0

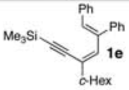
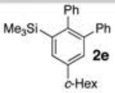
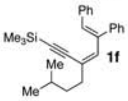
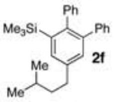
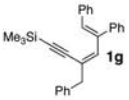
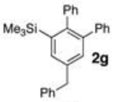
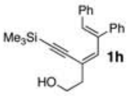
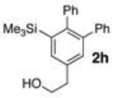
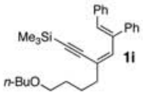
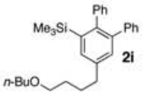
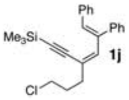
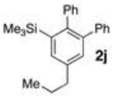
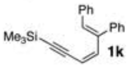
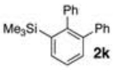
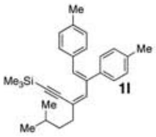
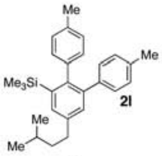
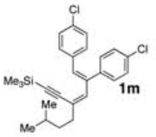
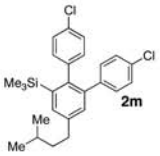
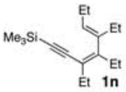
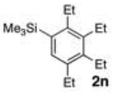
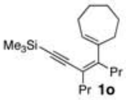
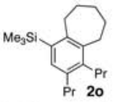
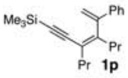
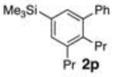
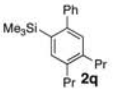
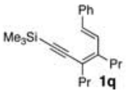
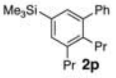
[a] Unless otherwise noted, all reactions were carried out with **1** (0.30 mmol) and DIBAL-H in solvent (0.30 mL) for 24 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis using dibenzyl ether as an internal standard. [d] Me_2AlH was used instead of DIBAL-H. [e] The reaction time was 12 h.

benzene **2a** in only 34% yield even though **1a** was consumed completely (entry 1). The reaction at 50 °C formed **2a** in 71% yield (entry 2). In contrast, **1a** was recovered intact when THF was used as solvent (entry 3). A further elevation in reaction temperature improved the yield to 74% (entry 4). However, the yield of **2a** decreased slightly at 150 °C (entry 5). In the absence of DIBAL-H, dienyne **1a** was recovered intact (entry 6). This control experiment makes it clear that the present reaction is not just a thermal electrocyclization of 1,3-dien-5-ynes.[9] A reduced amount of DIBAL-H (0.2 equiv) hardly promoted the cyclization (entry 7). Use of 0.5 equiv of DIBAL-H or Me_2AlH resulted in a moderate yield of **2a** (entries 8 and 9). These results are indicative of no catalytic activity of these aluminum hydrides. The reaction with 1.2 equiv of DIBAL-H gave the best result (entry 10), while a further increase in amount of DIBAL-H caused complex side reactions (entry 11). Shortening of the reaction time brought a drop in yield (entry 12). Toluene was not effective as solvent in promoting the present cyclization (entry 13). Modification of the silyl group of **1a** strongly affected the DIBAL-H-promoted cyclization. As shown in the reaction of **1b** (*Si* = Ph_2MeSi), introduction of a bulky silyl group retarded the cyclization (entry 14). With **1c**, bearing a more hindered silyl group (*Si* = $i\text{-}Pr_3Si$), no desired product was detected with full recovery of **1c** (entry 15). Additionally, the reaction of the nonsilylated substrate **1d** resulted in a complex mixture of unidentified products (entry 16).

With the optimized conditions in hand, we tested substrate scope and limitations with various silylated 1,3-dien-5-ynes (Table 2).[8] First, we investigated the variation of reaction efficiency by altering the substituent R^4. Dienyne **1e**, bearing a cyclohexyl group as R^4, was converted into **2e** in 59% yield. The structure of **2e** was clearly confirmed by X-ray structure analysis

Table 2. Scope and Limitations[a]



entry	1,3-dien-5-yne 1	product 2	yield (%)[b]
1			59
2			85
3			92
4			40[c,d]
5			35[c]
6			16
7			0
8			93
9			85
10			89
11			64
12		 	65 **2p**:**2q** 1.0:1.4
13			5

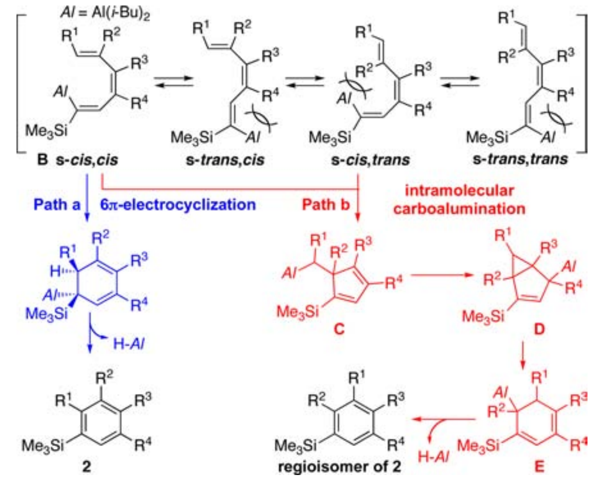
[a] Unless otherwise noted, all reactions were carried out with **1** (0.30 mmol) and DIBAL-H (0.36 mmol) in octane (0.30 mL) at 100 °C for 24 h. [b] Isolated yield. [c] 2.5 equiv of DIBAL-H was used. [d] The yield was estimated by ^1H NMR analysis using dibenzyl ether as an internal standard.

(entry 1). Introduction of isopentyl and benzyl groups as R^4 succeeded in efficient cyclization to tetrasubstituted benzenes **2f** and **2g** (entries 2 and 3). In contrast, 1,3-dien-5-ynes **1h** and **1i**, bearing an oxygen-functionalized alkyl group, were cyclized sluggishly even with 2.5 equiv of DIBAL-H (entries 4 and 5). A complex mixture of unidentified products was formed in each case. When alkyl chloride **1j** (R^4 = (CH$_2$)$_3$Cl) was treated with DIBAL-H, dechlorinated product **2j** was obtained in only 16% isolated yield (entry 6). The sp^3-carbon−chlorine bond was not tolerant of the reaction conditions. Since the reaction of dienyne **1k** (R^4 = H) with DIBAL-H gave no desired product (entry 7), the substituent R^4 (R^4 $\neq$ H) is essential for the aromatic cyclization. Dienynes **1l** and **1m**, analogues of **1f** by slight modification in R^1 and R^2, were efficiently cyclized to the corresponding tetrasubstituted benzenes (entries 8 and 9). It is noteworthy that the sp^2-carbon−chlorine bond of **1m** was compatible with the present cyclization.

We next turned our attention to the cyclization of 1,3-dien-5-ynes having a different pattern of substitution. 1,2,3,4-Tetrasubstituted dienyne **1n** was smoothly converted into pentasubstituted benzene **2n** in high yield (entry 10). Benzocycloheptane **2o** was obtained from **1o** in moderate yield (entry 11). Intriguingly, the cyclization of dienyne **1p** (R^1 = H) afforded 1,2,3,5-tetrasubstituted benzene **2p** and its 1,2,4,5-tetrasubstituted regioisomer **2q** in moderate combined yield (entry 12).[10] Upon treatment with DIBAL-H, dienyne **1q** (R^2 = H) did not turn into the expected product **2q**. Instead, the rearranged product **2p** was formed in a rather low yield (entry 13). This result indicates that the substituent R^2 (R^2 $\neq$ H) is crucial for an efficient cyclization.

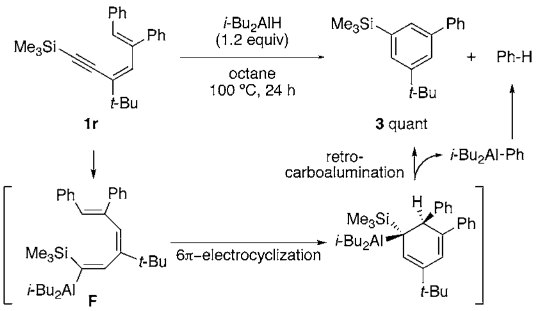
As shown in Scheme 2, a plausible mechanism for the DIBAL-H-promoted aromatization involves the 6π-electrocyclization of trienylaluminum intermediate **B** followed by dehydroalumination. There are four possible planar conformations of the 6π-electron system **B**, the s-*cis,cis* conformer of which is accessible to the postulated 6π-electrocyclization (Scheme 3, path a).[11] The presence of the substituents R^2 and R^4 makes other conformers unstable by steric repulsion between the aluminum moiety and R^2 or R^4, and brings about conformational fixation of **B** to the s-*cis,cis* conformation. This is a probable reason for the positive effects of these substituents on the present cyclization. Although the aromatization step by dehydroalumination gives a sense of anticipation that DIBAL-H can work catalytically, in actual, DIBAL-H was found to have no catalytic activity (Table 1). This discrepancy may be due to thermal decomposition and side reactions of organoaluminum species under these conditions. The rearranged cyclization of **1p** and **1q** can be explained by path b, which consists of intramolecular carboalumination of the s-*cis,cis*- or s-*cis,trans*-conformer of **B**, further carboalumination of the cyclized intermediate **C**, ring-opening of cyclopropylcarbinylaluminum **D**, and dehydroalumination of cyclohexadienylaluminum **E**. A similar reaction sequence has been proposed in our pervious report on the dialkylaluminum hydride-promoted cyclodimerization of silylated 1,3-enynes.[3] The switch from path a to path b is attributable to easy approach of the aluminum moiety to the C1−C2 double bond in the absence of the substituent R^1 or R^2. The rearranged cyclization suggests a possibility that the aromatic cyclization of other substrates bearing the same substituents as R^1 and R^2 proceeds via path b. This path seems inconsistent with the fact that the substrates bearing both substituents R^1 and R^2 are reactive toward the aromatic cyclization because steric effects caused by these substituents would retard the carboalumination steps. In addition, the results shown in entries 12 and 13 of Table 2 indicate that the presence of R^1 (R^1 $\neq$ H) gives an ill effect on the rearranged cyclization. At this stage, however, it is not clear which path is mainly operative.[12]

Scheme 3. Effects of Substituents and Plausible Mechanism



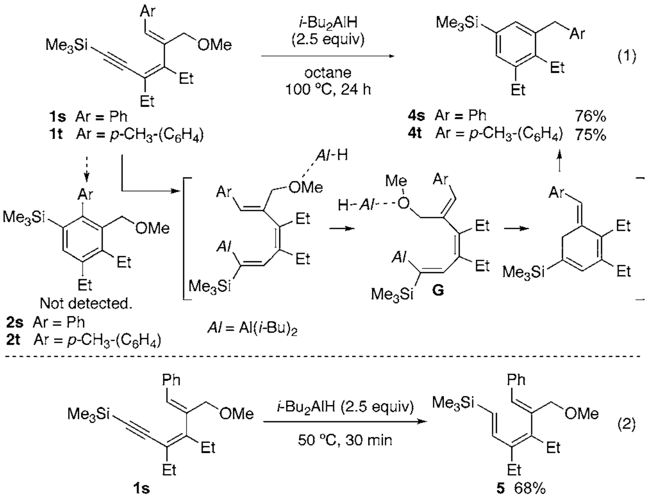
To our surprise, the DIBAL-H-promoted reaction of dienyne **1r**, bearing a *tert*-butyl group as R^4, gave 1,3,5-trisubstituted benzene **3** in quantitative yield with the loss of the 1-phenyl group (Scheme 4). The structure of **3** was confirmed by comparing the NMR data for the desilylated form of **3** with the reported data for 3-*tert*-butylbiphenyl.[13] To trace the eliminated phenyl group, the reaction of **1r** was conducted in a sealed tube at 100 °C for 24 h, and the reaction mixture was checked by GC before and after quenching with methanol. This experiment revealed that benzene was formed in 59% yield before quenching and that the yield increased to 68% after quenching. Additionally, treatment of the reaction mixture with iodine afforded iodobenzene in 4% yield. On the basis of these observations, it is likely that the reaction path forming **3** involves disrotatory 6π-electrocyclization of the initially formed trienylaluminum intermediate **F** without geometrical isomerization and the elimination of a phenylaluminum speices (i-Bu$_2$AlPh), that is, a retro-carboalumination.[14] The major part of i-Bu$_2$AlPh would suffer from thermal decomposition leading to benzene during the reaction.

Scheme 4. Dephenylative Aromatization



Dienynes **1s** and **1t**, bearing a methoxymethyl group, also underwent an unexpected cyclization instead of the usual cyclization to **2**. Treatment of **1s** and **1t** with 2.5 equiv of DIBAL-H provided benzyl-substituted benzenes **4s** and **4t**, respectively, in good yield (Scheme 5, eq 1).[15] A reduced amount

Scheme 5. Aromatization via Non-6π-electrocyclization



of DIBAL-H (1.2 equiv) did not promote the cyclization of **1s** at all, and an almost quantitative amount of **1s** was recovered. The reaction of **1s** with DIBAL-H (2.5 equiv) at 50 °C for 30 min gave triene **5** in 68% with 32% recovery of **1s** (Scheme 5, eq 2). When the reaction mixture was subjected to ^{1}H and ^{13}C NMR analyses before quenching with water, the NMR signals of protons and carbons α to the ethereal oxygen appeared in lower magnetic fields than those for **5**. These observations indicate that DIBAL-H is used not only for hydroalumination of the alkyne part but also for coordination to the ethereal oxygen. Considering the electrophilic activation of the allylic carbon bearing a methoxy group, the formation of **4** can be rationalized by intramolecular nucleophilic substitution of trienylaluminum[16] intermediate **G** and subsequent aromatization via 1,3-hydrogen shift.

In summary, we developed the regiocontrolled synthesis of polysubstituted benzenes from silylated 1,3-dien-5-ynes by using DIBAL-H. Although this method for benzene construction is rather limited in substrate scope, it enables the synthesis of unsymetrically polysubstituted benzenes hardly obtainable by the known methods. The introduction of a trimethylslilyl group on the benzene ring serves to broaden the range of accessible substituted benzenes on the basis of synthetic utility of arylsilanes. In addition, the present study revealed some interesting reactivities of organoalunimum reagents, which are valuable for further development of aluminum-mediated synthetic methods. Further study on the reaction mechanism is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and crystallographic data for **2e** (CCDC 983139) and **4s′** (CCDC 983140) (CIF). This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

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