Zirconium-Mediated Selective Synthesis of 1,2,4,5-Tetrasubstituted Benzenes from Two Silyl-Substituted Alkynes and One Internal Alkyne

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Selective synthesis of 1,2,4,5-tetrasubstituted benzenes was achieved via formation of 2,5-bis(trimethylsilyl)zirconacyclopentadienes from 2 equiv of TMS-substituted alkynes with Cp₂ZrBu₂ and Cu-mediated formation of 1,4-disilylbenzene by cycloaddition of zirconacyclopentadienes to disubstituted alkynes. Preparation of 1,2,3,4,9,10-hexasubstituted pentacene and 2,3,6,11-tetrasubstituted naphthacene derivatives were demonstrated by a homologation or coupling method using tetrasubstituted benzene.

It is well-known that benzene derivatives have been synthesized by cyclotrimerization of alkynes using transition-metal complexes.¹ One of the major problems of the reactions is the difficulty in regioselective intermolecular cyclotrimerization with unsymmetrical alkynes to give multisubstituted benzene derivatives. As shown in Scheme 1, when two terminal alkynes react with transition metals, the corresponding metalacycles are obtained as a mixture of three possible regioisomers.² The following cyclization with one internal alkyne affords a mixture of three benzene derivatives.

Previously, our group reported the zirconium-mediated cycloadditions of different alkynes to prepare highly sub-

stituted benzenes with excellent selectivity in high yields as shown in Scheme 2.³ These reactions can be applied for synthesis of hexa-, penta-, and 1,2,3,5-tetrasubstituted benzenes with excellent selectivity and high yields. But there are no reports for preparation of 1,2,4,5-tetrasubstituted benzene derivatives via coupling of two terminal alkynes and one internal alkyne with zirconocene.

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The reason is the poor regioselectivity in the zirconacycle formation with two terminal alkynes and intolerance of the low-valent zirconocene species for the acidic hydrogen of the terminal alkyne employed.



Our strategy for a synthesis of 1,2,4,5-tetrasubstituted benzene as a single product was shown in Scheme 3. For this purpose, silylalkynes seem to be suitable because of their characteristic properties. The reaction of Cp₂Zr(II) species with silylalkynes proceeds with excellent regioselectivity to afford the corresponding 2,5-disilyl-substituted zirconacy-clopentadienes as single products in high yields.⁴ Cycload-dition reaction of the 2,5-disilylzirconacyclopentadiene with an internal alkyne followed by removal of the introduced silyl groups can afford the desired tetrasubstituted benzene derivative.

Unexpectedly, the formation of a Dewar benzene derivative **3** was found in the cycloaddition reaction of 2,5-disilylsubstituted zirconacyclopentadiene **2** with dimethyl acetylenedicarboxylate (DMAD) in the presence of CuCl (Scheme 4). At the beginning, the above-mentioned strategy was examined with 1-trimethylsilyl-1-hexyne (**1d**, R = Bu) as a starting material. Silylalkyne **1d** was treated with Cp₂ZrBu₂ in THF to produce 2,5-disilyl-substituted zirconacyclopentadiene **2d**, which was cyclized with DMAD in the presence



of CuCl at room temperature. The NMR analysis of the reaction mixture revealed that the formation of the corresponding benzene 4d and Dewar benzene 3d in 18 and 45% yields, respectively. It is worth noting that Dewar benzene 3d was afforded as a major product regardless of its highly strained structure. The ¹³C NMR spectrum of **3d** in CDCl₃ showed a characteristic quaternary carbon signal appeared at 57.1 ppm, which was assignable to the bridgehead carbon of Dewar benzene. Fortunately, the Dewar benzene 3d was quantitatively converted to the benzene 4d after heating in toluene at 100 °C for 3 h.5 Totally, the desired benzene derivative 3d was obtained in 63% yield from silvlalkyne 1d. Finally, the silvl groups were removed cleanly by treatment with 2 equiv of TBAF in THF for 1 h, and the corresponding 1,2,4,5-tetrasubstituted benzene 5d was obtained in 90% yield.



The results of the reactions with various alkynes are summarized in Table 1. In most cases, the Dewar benzenes **3** were obtained as major products along with their benzene isomers **4**. On the other hand, in the reactions with decylor 2-thienyl-substituted silylalkynes, only the corresponding benzene isomers were formed (entries 8 and 10). The two benzene isomers **3** and **4** were easily separable by a silica gel chromatography except for entries 9, 11, and 12. To obtain the desired 1,2,4,5-tetrasubstituted benzene **5**, the

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separation of **3** and **4** is not necessary, since a simple heating of the mixture caused the facile conversion of Dewar benzene **3** into benzene **4** quantitatively. The following desilylation with TBAF produced the desired benzene **5** in a good total yield based on silylalkyne **1**.

Table 1. Formation of Dewar Benzenes 3 and Benzenes 4 and 1,2,4,5-Tetrasubstituted Benzenes $\mathbf{5}$

					yields ^{a} (%)		
entry	product	\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	3	4	5
1	a	Me	$\rm CO_2Me$	$\rm CO_2Me$	17	39	53
2	b	\mathbf{Et}	$\rm CO_2Me$	$\rm CO_2Me$	51	26	70
3	с	\mathbf{Pr}	$\rm CO_2Me$	$\rm CO_2Me$	42	21	59
4	d	Bu	$\rm CO_2Me$	$\rm CO_2Me$	45	18	57
5	е	C_5H_{11}	$\rm CO_2Me$	$\rm CO_2Me$	48	25	69
6	f	C_6H_{13}	$\rm CO_2Me$	$\rm CO_2Me$	34	30	58
7	g	C_8H_{17}	$\rm CO_2Me$	$\rm CO_2Me$	21	21	40
8	h	$\mathrm{C}_{10}\mathrm{H}_{21}$	$\rm CO_2Me$	$\rm CO_2Me$	0	29	27
9	i	Ph	$\rm CO_2 Et$	$\rm CO_2 Et$	28	56	76
10	j	2-thienyl	$\rm CO_2 Et$	$\rm CO_2 Et$	0	64	60
11	k	Me	Ph	$\rm CO_2 Et$	53	6	55
12	1	Me	Me	$\mathrm{CO}_2\mathrm{Et}$	53	8	58
^{<i>a</i>} Isolated yields based on silylalkynes.							

In the case of 2,5-bis(silylated) bicyclic zirconacyclopentadienes prepared from bis(silylated) diynes, the formation of Dewar benzene isomers was not observed. Only benzene derivatives were obtained in high yields as we reported.^{3a} Probably the steric effect of the side ring of the bicyclic zirconacycle inhibited the formation of Dewar benzene derivatives.

It was reported that the Dewar benzenes were formed as minor products in the copper-mediated cycloaddition of tetraalkyl-substituted zirconacyclopentadienes with arylpropiolates.^{6a} Zirconium(η^6 -benzene)(AlCl₄)₂-catalyzed cyclotrimerization of 2-butyne was also known for the formation of hexamethyl Dewar benzene.^{6b}



When dimethylphenylsilyl group was used for the reaction instead of trimethylsilyl group, a similar result was obtained as shown in Scheme 5.

Scheme 6 showed a possible mechanism for benzene and Dewar benzene formation. As we reported previously,^{3a} the reaction of zirconacyclopentadiene 2 with DMAD in the



presence of CuCl afforded the corresponding dicopper—hexatriene intermediate **6** via transmetalation from Zr to Cu followed by Michael addition to DMAD. After intramolecular Michael addition, the corresponding dicopper—cyclohexadiene intermediate **7** is formed. Copper metals in **7** move to allylic positions to give sterically stable form **8**. These two species are interconvertible by migration of copper metals. From **7**, benzene **4** is formed and from **8**, Dewar benzene **3** is formed.

As shown in Scheme 7, when the reaction of zirconacyclopentadiene 2d with DMAD and CuCl was carried out at -78 °C and quenched at the same temperature, linear triene 9 was formed in high yield. If the reaction mixture was warmed from -78 °C to room temperature, the corresponding benzene and Dewar benzene were obtained. This suggests that both benzene and Dewar benzene derivatives are formed via the same intermediate, linear triene 9.



Substituted naphthacenes and pentacenes have attracted much attention as soluble organic materials such as semiconductors.⁷ We have developed a homologation method,⁸ a double-homologation method,⁹ and a coupling method¹⁰ for the formation of substituted naphthacenes and pentacenes.

Preparation of 2,3,6,11-tetraalkylnaphthacenes was demonstrated by a coupling method using 1,2,4,5-tetrasubstituted benzenes as shown in Scheme 8. Reduction of 3,4,5,6-

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tetrasubstituted phthalates **4** with LiAlH₄, hydrolysis with 2 N H₂SO₄, and successive bromination of the resulting diol with PBr₃ gave cleanly dibromo-*o*-xylenes **10**. The NMR analysis of these steps showed that the protodesilylation occurred at the bromination step, probably due to HBr generated from the reaction of the alcohol with PBr₃ or contaminated in it. Alkynylation of **10** with 1-hexynyllithium afforded **12**. The Zr,Cu-mediated coupling of diyne **12** with 1,2-diiodobenzene afforded dihydronaphthacene derivatives **13**. Finally, dihydronaphthacenes **13** were aromatized with 1 equiv of DDQ at 100 °C in toluene. The desired naphthacenes **14** were obtained as a yellow solid in moderate yields.



Preparation of 1,2,3,4,9,10-hexasubstituted pentacene derivative **18f** from 1,2,4,5-tetrasubstituted benzene was also demonstrated by a homologation method as shown in Scheme 9. Reaction of dibromo-*o*-xylene prepared by the same way as **10c,d** from **4f** with trimethylsilylethyllithium or -magnesium halide did not lead to the formation of desired diyne **12f**. Therefore, dibromide was converted to diiodo-*o*-xylene **11f**. Diiodo-*o*-xylene **11f** cleanly reacted with trimethylsilylethynylmagnesium bromide in the presence of CuCl to give the desired diyne **12f**. The diyne **12f** was treated with Cp₂ZrBu₂ (Negishi reagent) followed by the reaction with DMAD in the presence of CuCl to afford dihydroanthracene derivative **15f**. The tricyclic skeleton of **15f** could be again extended to pentacyclic compound **17f** by the same combination of procedures as for **15f**. Similar desilylation occurred



in the homologation procedures as described before. The tetrahydropentacene **17f** reacted with the excess of DDQ (3 equiv) to give the Diels–Alder adduct. To recover the pentacene, the pentacene–DDQ adduct was treated with 50 equiv of γ -terpinene at 100 °C in toluene. The pentacene **18f** was isolated in a good yield as a blue solid by a column chromatography.¹⁰ The naphthacenes **14c,d** and pentacene **18f** are stable under nitrogen and have good solubility in a variety of organic solvents.

In summary, a synthetic method was developed for 1,2,4,5tetrasubstituted benzenes from silylalkynes and an internal alkyne with the Zr,Cu system. The sequence included the unexpected Dewar benzene formation in the reaction of 2,5disilyl-substituted zirconacyclopentadienes with DMAD in the presence of CuCl. Dewar benzenes were quantitatively converted to the corresponding benzenes by heating, and the removal of the silyl groups afforded the desired 1,2,4,5tetrasubstituted benzenes. These 1,2,4,5-tetrasubstituted benzenes were converted into soluble substituted pentacenes and naphthacenes by homologation and coupling method.

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Supporting Information Available: Experimental procedure, spectral data, and NMR charts for all new compounds. These materials are available free of charge via the Internet at http://pubs.acs.org.

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