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Formation of Seven-Membered Carbocycles via 7-*endo* Mode Cyclization of Lithioheptatrienes

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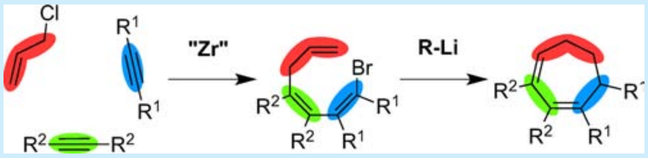
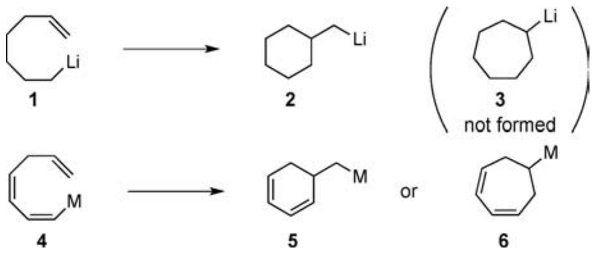
Supporting Information



ABSTRACT: The highly selective synthesis of triene derivatives was achieved by a zirconocene-mediated three-component coupling reaction, and the trienes were efficiently subjected to 7-*endo* mode cyclization. The reaction of unsymmetrical zirconacyclopentadienes prepared from two different alkynes with *N*-bromosuccinimide (NBS) followed by treatment with allyl halides in the presence of CuCl afforded the corresponding heptatrienes in good yields. When the trienes reacted with an organolithium reagent, 7-*endo* mode cyclization occurred smoothly to give the corresponding cycloheptadiene.

Intramolecular carbometalation to multiple C−C bonds is a fundamental tool for the construction of carbocyclic skeletons.[1,2] A number of metal-mediated or catalyzed carbocyclization reactions have been developed as synthetic methodologies. That said, some exceptions have been reported, where the intramolecular carbometalation reaction proceeds in *exo* fashion.[1] For example, when heptenylmetal **1** is cyclized, the 6-*exo* product **2** is obtained exclusively or predominantly (Scheme 1), and the 7-*endo* cyclization product **3** is not formed.

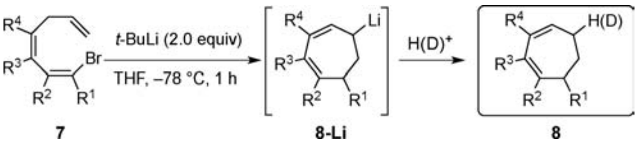
Scheme 1. Intramolecular Carbometalation



Our group previously reported zirconium-mediated eight-membered ring formation.[3] The key point of our strategy was the introduction of a conjugated diene moiety into the substrate to decrease the flexibility of the molecule; otherwise, no eight-membered ring product was obtained at all. We hypothesized that this methodology would also be applied to the regioselective intramolecular carbometalative cyclization of **4** to affording the 7-*endo* product **6**.

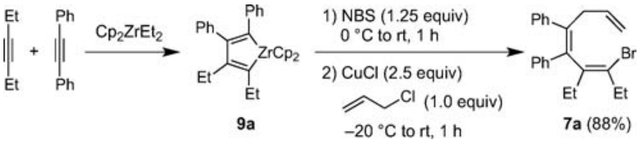
Herein, we report 7-*endo* carbolithiation[4−6] of 1-bromoheptatrienes **7**, which can be conveniently prepared from zirconacyclopentadienes. To a THF solution of bromotriene **7** was added 2 equiv of *t*-BuLi at −78 °C, and the mixture was stirred for 1 h. Acid treatment of the mixture gave the corresponding 7-*endo* cyclization product, cycloheptadiene **8** in high yield (Scheme 2).

Scheme 2. 7-*endo* Mode Cyclization of Bromoheptatrienes 7



We recently reported a selective coupling reaction of different alkynes to give linear oligoene derivatives.[7] This method prompted us to synthesize suitable substrates to examine the above-mentioned novel carbolithiation reaction. Scheme 3 shows the synthesis of the cyclization precursors.

Scheme 3. Synthesis of Bromoheptatriene 7a



Two different alkynes were selectively coupled on Zr using Cp_2ZrEt_2 to give the corresponding unsymmetrical zirconacyclopentadiene **9a**, as we reported previously.[8] Bromination of one Zr−C bond by addition of NBS[9] followed by the reaction with allyl chloride in the presence of CuCl furnished the corresponding bromoheptatriene **7a** in high yield after the usual workup.[3,10]

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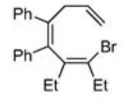
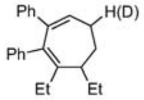
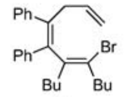
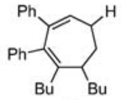
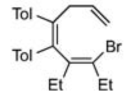
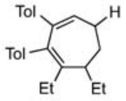
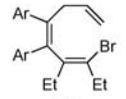
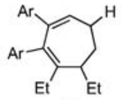
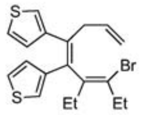
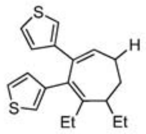
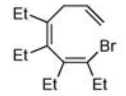
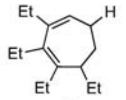
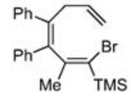
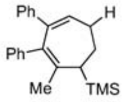
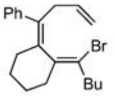
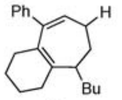
Table 1 summarizes the results of the synthesis of bromoheptatrienes 7 from various substrates and their 7-*endo* mode cyclization. When triene **7a** was treated with *t*-BuLi, the corresponding cycloheptadiene **8a** was obtained in high yield (Table 1, entry 1). The deuterated product **8a(D)** was obtained by treatment with D_2O instead of hydrolysis. This result showed the position of Li in the final product **8a-Li** before hydrolysis. Two butyl groups were introduced by using 5-decyne instead of 3-hexyne (Table 1, entry 2). The phenyl groups could be replaced with *p*-tolyl and *p*-fluorophenyl groups, which gave the corresponding seven-membered-ring products **8c** and **8d** (Table 1, entries 3 and 4). Heteroaromatic rings were also applicable (Table 1, entry 5). Non-arylated substrate **7f** cyclized effectively, but the product **8f** was obtained as a 4:1 mixture of double-bond positional isomers (Table 1, entry 6). Silyl-substituted cycloheptadiene **8g** was synthesized in 63% yield (Table 1, entry 7). Fused seven- and six-membered-ring carbocycle **8h** was synthesized by this method (Table 1, entry 8). The structure of cycloheptadiene **8a** was unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information).

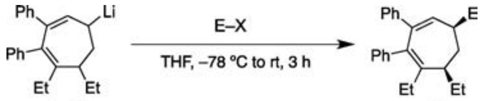
Table 1. 7-*endo* Carbolithiation Reaction Using Various Trienes

entry	7	yield (%)[a]	8	yield (%)[a]
1	 **7a**	88 (80)	 **8a**	73 (69)
2	 **7b**	85 (78)	 **8b**	72 (64)
3	 **7c**	80 (71)	 **8c**	58 (50)
4[b]	 **7d**	78 (65)	 **8d**	71 (63)
5[c]	 **7e**	73 (66)	 **8e**	53 (45)
6[d]	 **7f**	93 (76)	 **8f**	79 (65)
7	 **7g**	65 (57)	 **8g**	63 (56)
8	 **7h**	83 (70)	 **8h**	75 (68)

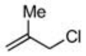
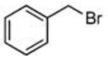
[a] NMR yields. Isolated yields are given in parentheses. [b] Ar = p-FC_6H_4. [c] The reaction was carried out at 50 °C. [d] Cycloheptadiene **7f** was obtained as a mixture with the minor isomer 1,2,3,4-tetraethylcyclohepta-1,4-diene in a 4:1 ratio.

When intermediate **8a-Li** was treated with electrophiles, the corresponding coupling products **10** were obtained in good yields (Table 2). Silylated cycloheptadiene **10a** was obtained by the simple addition of chlorotrimethylsilane. Cu-mediated allylation and alkylation reactions successively proceeded to give **10b** and **10c**, respectively. Benzylated product **10d** was verified by X-ray analysis, which showed the *cis* configuration between the introduced benzyl group and the ethyl group at the 7-position (see the Supporting Information).[11]

Table 2. Reaction of 8a-Li with Various Electrophiles



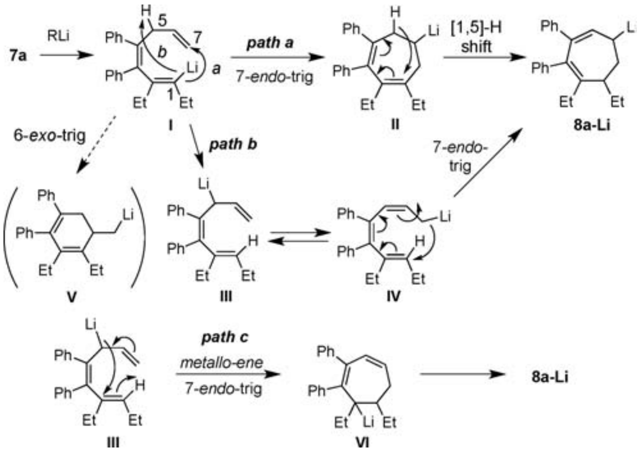
8a-Li **10**

entry	E–X	additive	10	yield (%)[a]
1	TMS–Cl	none	**10a**	71
2	Me–I	CuCl	**10b**	51
3		CuCl	**10c**	70
4		CuCl	**10d**	68

[a] NMR yields.

Here three reaction pathways are presented for this 7-*endo* carbolithiation reaction (Scheme 4). At the beginning of the reaction, Li/Br exchange proceeds to form alkenyllithium **I**. After that, addition of the Li–C bond on C1 to the C6–C7 double bond in 7-*endo*-trig mode affords lithiated carbocycle **II** (Scheme 4, path *a*). The subsequent sigmatropic [1,5]-hydrogen shift affords 7-*endo* product **8a-Li**. On the other hand, intermediate **I** can be converted into **III** via abstraction of the acidic proton on C5 (Scheme 4, path *b*). The allylic migration of lithium forms intermediate **IV**, and intramolecular carbolithiation in 7-*endo*-trig mode affords product **8a-Li**. The

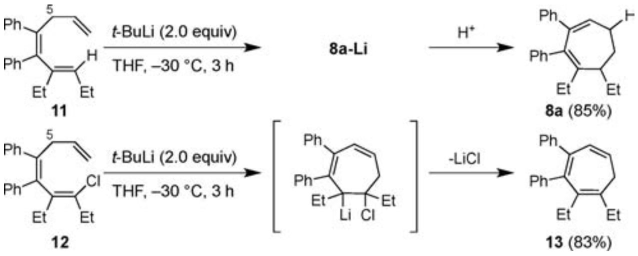
Scheme 4. Plausible Reaction Pathway



cyclization step might be considered as a symmetry-allowed eight-electron electrocyclic reaction. As the third pathway, cyclization of intermediate **III** by metallo-ene reaction to afford **VI** is also possible (Scheme 4, path *c*).[12]

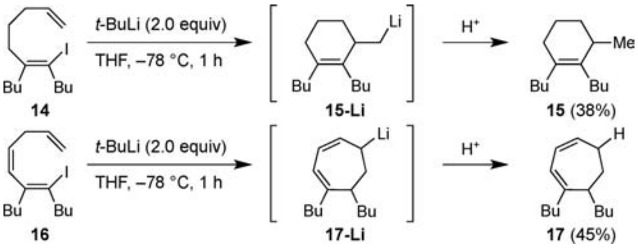
As shown in Scheme 5, when dehalogenated triene **11** was employed for the reaction, the same cycloheptadiene **8a** was obtained in 73% yield. Furthermore, chlorinated heptatriene **12** gave the corresponding cycloheptatriene **13** in high yield. With these trienes, lithiation would occur at C5 instead of C1. These results strongly indicate the existence of intermediate **III**.

Scheme 5. Reaction of Trienes 11 and 12 with *t*-BuLi



To show the importance of the conjugate diene moiety, cyclization reactions of compounds **14** and **16** were examined, as shown in Scheme 6. When iododiene **14** was subjected to the same cyclization conditions, cyclization proceeded in 6-*exo* mode to afford the corresponding cyclohexene **15**. The same reaction of iodotriene **16**, however, gave the seven-membered-ring product **17**. These results clearly showed the importance of the conjugated diene system for 7-*endo* mode cyclization.

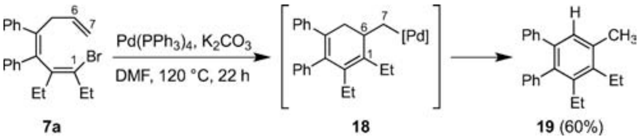
Scheme 6. Effect of the Conjugated Diene System on the Intramolecular Carbolithiation



Notably, the carbometalation of heptatrienes **7** gave not only 7-*endo* cyclization products but also 6-*exo* products when the metal was changed. The reaction of **7a** with a catalytic amount of $Pd(PPh_3)_4$ afforded the 6-*exo* cyclization product **19** in 60% yield, and no 7-*endo* product was observed (Scheme 7). The organopalladium generated by initial oxidative addition is coordinated to the C6−C7 double bond, and the subsequent insertion gives intermediate **18** predominaltly.

In conclusion, we have developed a highly selective 7-*endo* mode cyclization using heptatrienes **7**, which can be conveniently prepared by zirconium-mediated reactions. The regioselective carbolithiation giving **8** was achieved by the introduction of a conjugated diene moiety into the starting compound. On the other hand, treatment of **7** with a palladium catalyst gave 6-*exo* cyclization product **19**.

Scheme 7. 6-*exo* Mode Cyclization of 6a with a Pd Catalyst



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02956.

Detailed experimental procedures and compound characterization data (PDF)
Crystallographic data for **8a** (CIF)
Crystallographic data for **10d** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) Formation of the *anti* products would cause steric hindrance between the two substituents at C5 and C1. We assume that diastereoselective introduction of electrophiles was achieved by the steric effect.

(12) The conversion of intermediate **VI** into **8a-Li** seems to be very fast. As we mentioned in Scheme 2, quenching the reaction with D_2O gave **8a(D)** in which deuterium was introduced at C5 selectively. No C1-deuterated product was observed in the studies.