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Borylative Radical Cyclizations of Benzo[3,4]cyclodec-3-ene-1,5diynes and *N*-Heterocyclic Carbene–Boranes

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Abstract: Borylative radical cyclization of benzo[3,4]cyclodec-3-ene-1,5-diynes to provide 5-borylated 6,7,8,9tetrahydrobenzo[a]azulenes has been developed. The experimental results suggest that the reaction proceeds by a radical chain mechanism, and di-tert-butyl hyponitrite (TBHN) works as a good radical initiator to form boryl radicals from N-heterocyclic carbeneboranes (NHC-boranes). The present reaction is a rare model to illustrate addition of boryl radicals to alkynes.

The chemistry of boron-centered radicals has been recently an attractive and challenging subject in the main group chemistry because boron compounds have been historically used mainly for ionic and metal-catalyzed reactions. Interesting structures and reactivity of several boron-centered radicals have been identified thus far.^[1] However, the application of boron-centered radicals to synthetic methods has less explored compared with those of other radical species.^[2]

Borane complexes and borohydride compounds typically work as a hydride source. Since homolytic bond dissociation energies (BDEs) of B-H bonds are typically large,^[3] these do not apparently work as a hydrogen donor to radicals. However, welldesigned radical reactions with borohydride compounds have been reported.^[4] N-Heterocyclic carbene-boranes (NHCboranes) are good precursors of relatively stable boryl radicals because their B-H BDEs are lower than those of typical borane complexes.^[5] Therefore, they can work as replacements of typical radical mediators such as tributyltin hydride (Bu₃SnH) in Barton-McCombie reactions^[6], radical dehalogenation of organohalides^[7] and of malononitriles.^[8] decvanations Nevertheless, there are only a few examples of addition of NHCboryl radicals to carbon-carbon multiple bonds. NHC-boryl radicals are nucleophilic and induce polymerization of acrylates by the addition reaction.^[9] On the other hand, the addition of boron-centered radicals including NHC-boryl radicals to alkynes has been much less explored (Figure 1A). Lalevée and coworkers reported that addition of triethylamine-boryl radical (Et₃N-BH₂•) to cyclohexylacetylene was relatively fast in electron paramagnetic resonance (EPR) experiments.^[10]

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Recently, Ogawa and co-workers reported methods for diboronation of alkynes putatively involving addition of pinacolboryl radicals to alkynes.^[11]

Programmed cascade reactions initiated by intermolecular addition of various carbon- and heteroatom-centered radicals to triple bonds are useful methods to construct functionalized cyclic frameworks.^[12] With the intention to develop a new radical reaction involving addition of boryl radicals to alkynes followed by radical cyclization, we tried radical reactions of two model substrates, enyne 1a^[13] and alkynal 1b^[14], with 1,3dimethylimidazol-2-ylidene borane (2a). To promote formation of a boryl radical from 2a, we added di-tert-butyl hyponitrite (TBHN)^[15], which forms highly reactive tert-butoxy radical (tBuO•) with release of nitrogen gas under heating conditions.^[7b] However, cyclized products 3a and 3b were not detected in either case (Figure 1B). Since 5-exo-trig radical cyclization onto double bonds is generally fast,^[16] the absence of cyclized products suggests that addition of the NHC-boryl radical to a simple terminal alkyne is unfavorable.

(A) Radical addition to alkynes

$$X \cdot + = R \longrightarrow X_{--R} \longrightarrow$$
 further bond formation

X = Group 14–16 elements (C, Si, Sn, N, P, O, S, Se etc.) \implies many examples

 $X = Boron (B) \implies very limited examples$

(B) Attempt of the boryl radical addition-cyclization reaction



(C) Isolation of borylated carbocycle 5a from a heating mixture of diyne 4 and NHC-borane 2a



Figure 1. Background of this study.

During another preliminary study, we conducted Masamune-Bergman reactions^[17] of benzo[3,4]cyclodec-3-ene-1,5-diyne (4)^[18] with NHC-borane **2a** under heating conditions. In many experiments, we isolated small amounts of 5-borylated 6,7,8,9-tetrahydrobenzo[*a*]azulene **5a** (Figure 1C). The structure was supported by NMR spectroscopy, high resolution mass spectrometry and UV-vis spectroscopy. The ¹¹B NMR spectrum showed a triplet at -25.0 ppm in CDCl₃, indicating production of a *B*-monosubstituted NHC-borane compound.

Production of borylated carbocycle **5a** suggests that addition of a boryl radical to an alkyne occurred. Product **5a** could be

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COMMUNICATION

formed by a radical cascade reaction induced by intermolecular addition of NHC-boryl radical 6 formed by the reaction of 2a with p-benzyne, which is a biradical intermediate, to the alkyne of divne 4.^[19] This was supported by detection of 1,2,3,4tetrahydroanthracene.^[18] Alkenyl radical 7 formed by the addition reaction of NHC-boryl radical 6 could cyclize onto the other alkyne to form cyclopentyl radical 8, while 8 could abstract a hydrogen atom from NHC-borane 2a to give product 5a. Since the NHC-boryl radical 6 is generated again in the final step, the overall process is a chain reaction. Both stabilization of the resultant alkenyl radical 7 by the aromatic ring and the strain of alkynes might promote addition of the NHC-boryl radical to the alkynes in this reaction. For the cyclization step, there is a theoretical study of 5-endo-dig cyclization of 1,2diethynylbenzenes, and it suggested that 5-endo-dig cyclization after addition of radicals to the alkyne does not have a high barrier.^[20] The radical cyclization of divne 4 would be more favorable due to its strained structure.^[21]

In this communication, we describe borylative radical cyclization of benzo[3,4]cyclodec-3-ene-1,5-diynes with NHC-boranes to produce 5-borylated 6,7,8,9-tetrahydrobenzo[*a*]azulenes, which illustrates that boryl radical addition to alkynes has been realized.^[22,23]



Scheme 1. Proposed mechanism of the reaction of ${\bf 4}$ with boryl radical ${\bf 6}$ to produce ${\bf 5a}.$

We looked for a suitable radical initiator that would efficiently induce the radical chain reaction to 5-borylated 6,7,8,9tetrahydrobenzo[a]azulene 5a. Azobisisobutyronitrile and Et₃B/O₂, which are typical radical initiators, did not form 5a at 60 °C and room temperature.^[8,9] However, the use of a substoichiometric amount (0.2 equiv) of TBHN induced the reaction of divne 4 with NHC-borane 2a (5 equiv) in heating benzene (0.1 M) to provide cyclized product 5a in 22% yield (Table 1, Entry 1). A significant amount of the starting material was not consumed in this reaction. Elevating the temperature and increasing the amount of TBHN improved the results, but there was still recovery of the starting material (Entries 2, 5 and 6). There was no impact in the diluted conditions (0.02 M) (Entry 3), but the reaction in a high concentration (0.5 M) complicated the reaction with low recovery of the starting material (Entry 4). Replacing the solvent with benzotrifluoride at 100 °C slightly improved the conversion ratio of product 5a (Entry 7).[24] Increasing the amount of TBHN further improved yield of cyclized product 5a (Entries 8 and 9). However, the use of decreased amount of NHC-borane 2a (2 equiv) significantly diminished the yield of product 5a (Entry 10). On the other hand, a larger amount of 2a (10 equiv) slightly improved the result (Entry 11). In the present reaction, most of the unreacted NHCborane could be recovered by silica gel chromatography. Thus, we succeeded in obtaining 5-borylated 6.7.8.9tetrahydrobenzo[a]azulene 5a in acceptable yield by optimizing reaction conditions. The product based on Masamune-Bergman reaction, such as 1,2,3,4-tetrahydroanthracene, was hardly detected in these cases.

Table 1. Optimization of the reactions between 4 and 2a.^[a]



Entry	TBHN (equiv)	Solvent	Temp [°C]	Time [h]	5a [%] ^[b]	4 [%] ^[b]
1	0.2	PhH	60	4	22	60
2	0.2	PhH	80	2	35	33
3 ^[c]	0.2	PhH	80	0.5	30	40
4 ^[d]	0.2	PhH	80	1.5	33	8
5	0.3	PhH	80	0.5	39	18
6 ^[e]	0.2	PhH	100	0.5	40	22
7	0.2	$PhCF_3$	100	0.5	46	28
8	0.35	$PhCF_3$	100	0.5	55	19
9	0.4	$PhCF_3$	100	0.5	59	trace
10 ^[f]	0.4	$PhCF_3$	100	0.5	31	23
11 ^[g]	0.4	$PhCF_3$	100	0.5	65	0

[a] Conditions: 4 (0.15 mmol), 2a (0.75 mmol), TBHN (0.03-0.06 mmol) in solvent (1.5 mL) at 60-100 °C. [b] Yield of isolated compounds. [c] 7.5 mL (0.02 M) of solvent was used. [d] 0.3 mL (0.5 M) of solvent was used. [e] The reaction was performed in a sealed tube. [f] 2 equiv (0.3 mmol) of 2a was used. [g] 10 equiv (1.5 mmol) of 2a was used.

We next surveyed preparative reactions of several NHCboranes with divne 4 under the conditions of Entry 9 in Table 1 diyne The reaction of with (Figure 2). 4 1.3dimethylbenzimidazol-2-ylidene borane (2b) gave a complex mixture, and cyclized product 5b could not be isolated in a pure form. However, when 1,3,4,5-tetramethylimidazol-2-ylidene borane (2c) and 1,3-diisopropylimidazol-2-ylidene borane (2f) were reacted with diyne 4, the corresponding cyclized products 5c and 5f were obtained in 59% and 51% yield. 1,4-Dimethyl-1,2,4-triazolium-5-ylidene borane (**2d**) provided the corresponding cyclized product 5d in 40% yield, but the reaction

COMMUNICATION

with 4,5-dichloro-1,3-dimethylimidazol-2-ylidene borane (2e) was complex like the reaction with **5b**, and the corresponding cyclized product **5e** was isolated in 19% yield. Small amounts of side products tentatively identified as 1,2-hydroborated compounds of the alkyne were detected along with **5d** and **5e** (see the Supporting Information). The reaction with dippimidazolylidene borane **2g** (dipp is 2,6-diisopropylphenyl) did not produce cyclized compound **5g** at all probably due to a steric factor, and starting **4** was recovered in 77% yield. These results imply that the borylative radical reaction is sensitive to electronic and steric factors of NHCs.

Reactions of some divne analogues were next tested with NHC-borane 2a, and results are shown in Figure 2. Reactions of diynes having a 3,4-disubstituted arene provided 5-borylated 6,7,8,9-tetrahydrobenzo[a]azulene derivatives 9-12 in 36-57% yield under the standard conditions. Reactions of diynes having electron-donating groups such as methyl or methoxy groups provided cyclized products 11 and 12 but do not fully completed under standard conditions. The use of increased amounts of reagents (TBHN: 0.5 equiv, 2a: 10 equiv) increased consumption of the starting diynes. These results suggest that addition of the NHC-boryl radical to electron-rich alkynes is less favorable compared to the case of divne 4. This is consistent with nucleophilicity of NHC-boryl radicals.^[6b,9] These results also support that the rate-limiting step might be addition of the NHCboryl radical to the alkyne. Thus, these examples illustrated that the reaction provided an access to the novel borylated ringfused system.

The effect of ortho-substituted groups of diynes was tested using representative diynes 13, 16, and 19. The reaction of diyne 13 having an ortho-methyl group provided product 14 as a major product, indicating that the boryl radical reacted with a less hindered alkyne. A small amount of another isomer 15 was also isolated in this reaction. Two reactions using different amounts of reagents gave almost the same results, and the ratio of products 14 and 15 was approximately 80:20. The reaction of 16 having an ortho-methoxy group was more complex than that of 13, and cyclized product 17 (20% yield) and a complex mixture including many side products were isolated. The starting diyne 16 was fully consumed in this reaction. We next performed the reaction at a lower temperature (80 °C) with 10 equiv of 2a and 0.4 equiv of TBHN to suppress excessive side reactions. Product 17 was obtained in slightly improved yield, and main side products could be tentatively identified as 1,2hydroboration compounds of alkynes (ca. 18% yield) because some unidentified products disappeared in this case (see the Supporting Information). We could not find another cyclized isomer 18 from isolated products in this reaction. Analogue 19 having methoxy groups at two ortho-positions of alkynes did not give a cyclized product 20. In this reaction, no borylated side products were detected by ¹¹B NMR analysis of the reaction mixture, and significant amounts of the starting material did not seem to be consumed. Thus, ortho-substituent groups seemed to sterically affect the reaction.

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Reactions of diyne 4 with several NHC-boranes



Reactions of several symmetrical diyne analogues with NHC-borane 2a



Reactions of analogues having ortho-substituted groups with NHC-borane 2a



Figure 2. Results of TBHN-initiated radical reactions between several diynes and NHC-boranes. Reaction conditions: diyne (0.15 mmol), NHC-borane (0.75 mmol), TBHN (0.06 mmol) in PhCF₃ (1.5 mL) for 0.5 h at 100 °C. [a] Yield in parenthesis is based on a recovered starting material. [b] 10 equiv (1.5 mmol) of 2a and 0.5 equiv (0.075 mmol) of TBHN were used. [c] 10 equiv (1.5 mmol) of 2a and 0.4 equiv (0.06 mmol) of TBHN were used at 80 °C.

We briefly investigated the isotope effect in the radical reaction of diyne **4** using a mixture of NHC-borane **2a** and NHC-borane **2a**-*d* having deuterium atoms (90% D), of which the total H/D ratio was approximately equal (Scheme 2). Cyclized compound **5a**-*d* having deuterium atoms was detected in isolated products. The ratio of H to D on the cyclopentene moiety was estimated at 70:30 by ¹H NMR analysis. The observed value is not large but is consistent with typical Bu₃SnH-mediated radical reactions ($k_H/k_D = ca. 2.3$),^[25] indicating

COMMUNICATION

that the step of irreversible B-H bond cleavage determined the distribution of the product. $^{\mbox{[}^{26\mbox{]}}}$



Scheme 2. Isotope effect in the reaction of 4 with the NHC-borane.

We tried to transform the borylated compound 5a into other derivatives by Suzuki-Miyaura reaction. It is known that NHCarylboranes (NHC-BH₂Ar) can be transformed into the corresponding NHC-difluoro(aryl)boranes (NHC-BF₂Ar), which work as precursors of Suzuki-Miyaura reaction, with Selectfluor.^[27] However, treatment of **5a** with Selectfluor did not provide the corresponding difluoroborane derivative at all. In this reaction, a mixture of unidentified products having no boron component was isolated, suggesting that alkenes of 5a reacted with Selectfluor. Next, we tried to transform B-H bonds to B-CI bonds with N-chlorosuccinimide (NCS). Since NHC-BCl₂R could be isolated by silica gel chromatography, we tested a one-pot Suzuki-Miyaura reaction by forming a borate intermediate in situ under basic conditions. After treatment of 5a with NCS in CH₂Cl₂ and stirring for 15 min at 0 °C, 4-iodoanisole, 1.1'bis(diphenylphosphino)ferrocene]palladium(II) dichloride with dichloromethane [PdCl₂(dppf)•CH₂Cl₂], sodium carbonate, and THF were directly added to the reaction mixture, and the resultant mixture was heated for 2.5 hours. In this reaction, a desired coupling product 21 was not obtained at all, and a deboronated product 22 was exclusively obtained in 87% yield (Scheme 3, Eq. 1, Method A). This result indicated that olefins of 5a were intact by NCS. A deboronated product 22 was hardly detected in a mixture of 5a and NCS in CDCI₃ by ¹H NMR analysis. When water was subsequently added to this mixture, a deboronated product 22 was detected along with a compound tentatively identified as the corresponding boronic acid by ¹H NMR analysis.^[28] Obviously, deboronation occurred in the step of hydrolysis of NHC-BCl₂R. In the absence of water, sodium carbonate would exclusively cause deboronation to give 22. In light of these NMR experiments, Suzuki-Miyaura reaction was performed in THF and water (10:1), but a coupling compound 21 was not produced. When the temperature was elevated to 100 °C in toluene and water (10:1) in Suzuki-Miyaura reaction, a small amount of the desired product 21 was detected. Eventually, we obtained coupling product 21 in 51% yield by a one-pot strategy consisting of treatment of 5a with NCS, subsequent addition of THF/water (10:1) and stirring at room temperature for 1 hour, and Suzuki-Miyaura reaction at 100 °C in toluene (Scheme 3, Eq. 1, Method B). When 4-iodonitrobenzene was used as a coupling partner, the corresponding coupling product was isolated as a mixture 23 including two olefinic isomers (Scheme 3 Eq. 2). The minor isomer (C9 isomer) would be

produced from the major isomer (C10 isomer) under basic conditions. Prolonging the reaction time slightly increased the amount of the minor isomer (C9 isomer).

MeC



Scheme 3. Transformation of 5a by Suzuki-Miyaura reaction.

In conclusion, we developed cascade radical reactions of benzo[3,4]cyclodec-3-ene-1,5-diynes and N-heterocyclic carbene-boranes in the presence of di-tert-butyl hyponitrite to provide 5-borylated 6,7,8,9-tetrahydrobenzo[a]azulene derivatives. Examples of the synthesis of such carbocyclic systems are limited.^[29] The reaction was assumed to be a radical chain process involving intermolecular boryl radical addition to the alkyne followed by cyclization. It should be noted that this approach would be difficult due to release of free borane or large B-H BDEs if typical borane complexes or borohydrides are used. However, this study illustrated that boron-centered radicals are applicable to not only intermolecular radical addition to alkynes but also cascade reactions by properly designing the substrates and reaction conditions. We anticipate that this study will serve as a motif to develop various cascade reactions with boron-centered radicals in the future.

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Keywords: alkynes • boron • main group chemistry • radical reactions • strained molecules

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Addition of boryl radicals to alkynes occurs when a mixture of strained benzo[3,4]cyclodec-3-ene-1,5-diynes and *N*-heterocyclic carbene–boranes are exposed to radical conditions with di-*tert*-butyl hyponitrite. The addition reaction induces subsequent radical cyclization to provide 5-borylated 6,7,8,9-tetrahydrobenzo[a]azulenes. Further transformation of the borylated compound has been achieved by using a modified procedure for Suzuki-Miyaura reaction.

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Page No. – Page No.

Borylative Radical Cyclizations of Benzo[3,4]cyclodec-3-ene-1,5-diynes and *N*-Heterocyclic Carbene–Boranes