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Borylation

Metal-Free Temperature-Controlled Regiodivergent Borylative Cyclizations of Enynes: BCl_3-Promoted Skeletal Rearrangement

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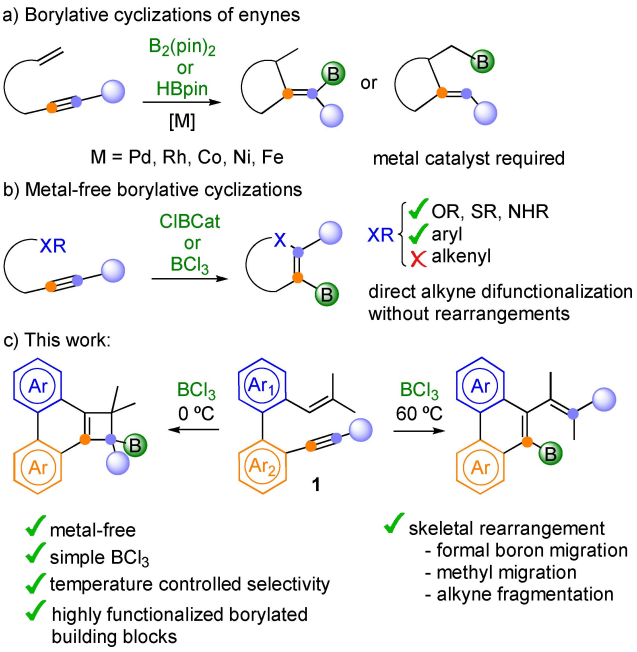
Abstract: Metal-free borylative cyclization of biphenyl-embedded 1,3,5-trien-7-ynes in the presence of simple and inexpensive BCl_3 provided synthetically useful borylated building blocks. The outcome of the process depends on the reaction temperature, with borylated phenanthrenes obtained at 60 °C and phenanthrene-fused borylated cyclobutanes formed at 0 °C. Based on DFT calculations, a mechanism for these novel transformations has been proposed, which involves an uncommon skeletal rearrangement, including migration of a methyl group and alkyne fragmentation, unprecedented in BCl_3-promoted cyclization reactions.

Organoboronic acids and their esters are highly valuable reagents which can be engaged in a variety of useful transformations.[1] Moreover, they are quite stable and therefore easy to handle, display low toxicity and show high functional group tolerance. These characteristics make them very attractive for organic synthesis and, consequently, the development of methods for the preparation of borylated building blocks is of great interest.[2] Typical procedures for the introduction of boron substituents in organic molecules, such as the addition of organolithium compounds to electrophilic boron reagents, or the palladium-catalyzed Miyaura borylation of halogenated derivatives, require prefunctionalized substrates.[2] More recently, metal-catalyzed C–H borylation strategies have avoided the need for prefunctionalized compounds,[3] but the number of building blocks available through this strategy is limited by the intrinsic regioselectivity of each substrate.[4] Therefore, the development of mild and efficient methodologies for the synthesis of borylated building blocks is still highly desirable.

Borylative cyclizations offer an appealing alternative to classical methods, as they provide a rapid increase in molecular complexity by the simultaneous formation of a cycle and a C–B bond under mild conditions.[5] In particular, enynes are highly useful starting materials in the preparation of cyclic building blocks containing either alkenyl or alkylboronates by means of borylative cyclizations using $B_2(pin)_2$ or HBpin as boron sources and different metal complexes as catalysts (Scheme 1a).[5a] Metal-free alternatives for the borylative cyclization of enynes are limited to a single report of $B(C_6F_5)_3$-promoted processes[6–8] that, despite being conceptually very interesting, do not provide synthetically useful building blocks.

Interestingly, the possibility of carrying out metal-free borylative cyclizations leading to valuable building blocks has been recently demonstrated (Scheme 1b). Thus, Blum has reported B-chlorocatecholborane (ClBcat)-promoted heterocyclizations[9] and Ingleson has proved that simple BCl_3 is able to promote not only heterocyclizations,[10] but also carbocyclizations in which an aromatic ring acts as internal nucleophile.[11,12]



Scheme 1. Borylative cyclizations.

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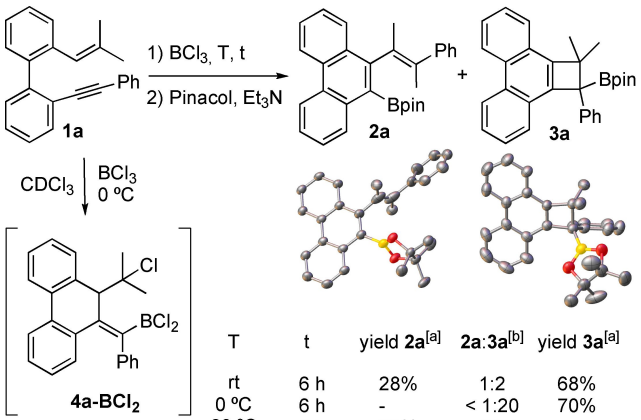
These processes are quite simple from a structural and mechanistic point of view. The role of the electrophilic boron source is limited to activating the alkyne, which becomes difunctionalized along the transformation, forming a C–B bond in one terminus and a C–X or C–C in the other, with the concomitant formation of a new ring (see Scheme 1b). To the best of our knowledge, further skeletal rearrangements have never been observed in these reactions. In this context, and in the course of our studies on gold-catalyzed cycloisomerizations of enynes,[13] we considered that biphenyl embedded trienynes **1** could be suitable precursors for the preparation of borylated polycyclic building blocks, through a selective borylative cyclization. Herein we report a temperature controlled BCl_3-promoted borocyclization of **1** affording selectively borylated cyclobutanes fused to a phenanthrene skeleton at 0 °C and borylated phenanthrenes when the transformation is carried out at 60 °C (Scheme 1c). Moreover, a novel mechanism was unraveled involving skeletal rearrangements including formal 1,2-boron migration, methyl migration and alkyne fragmentation.

At the outset, we selected 1,3,5-trien-7-yne **1a** as model substrate and BCl_3 as electrophilic boron reagent. Both reagents were mixed in a 1:1 ratio in 1,2-dichloroethane (DCE) at room temperature for 6 h. A treatment with pinacol/Et_3N was performed in order to form the corresponding stable pinacolate esters from the presumably unstable BCl_2-containing products, which would be formed in a borylative cyclization. Interestingly, under these conditions, full conversion to borylated products occurred, although a mixture of two compounds was obtained (Scheme 2). The major product was phenanthrene-fused borylated cyclobutane **3a**, coming from a formal [2+2] borylative cycloaddition, whereas borylated-phenanthrene **2a** was formed as a minor product. The structure of **2a** is



T	t	yield **2a**[a]	**2a**:**3a**[b]	yield **3a**[a]
rt	6 h	28%	1:2	68%
0 °C	6 h	-	< 1:20	70%
60 °C	6 h	76%	> 20:1	-
rt	24 h	66%	2:1	24%

Reactions conducted in 1,2-DCE (0.03M) using 0.2 mmol of **1a**, 1 equiv. of BCl_3, 1.1 equiv. of pinacol and 15 equiv. of NEt_3.
[a] Isolated yield.
[b] Determined by ^{1}H-NMR of the crude reaction mixture.

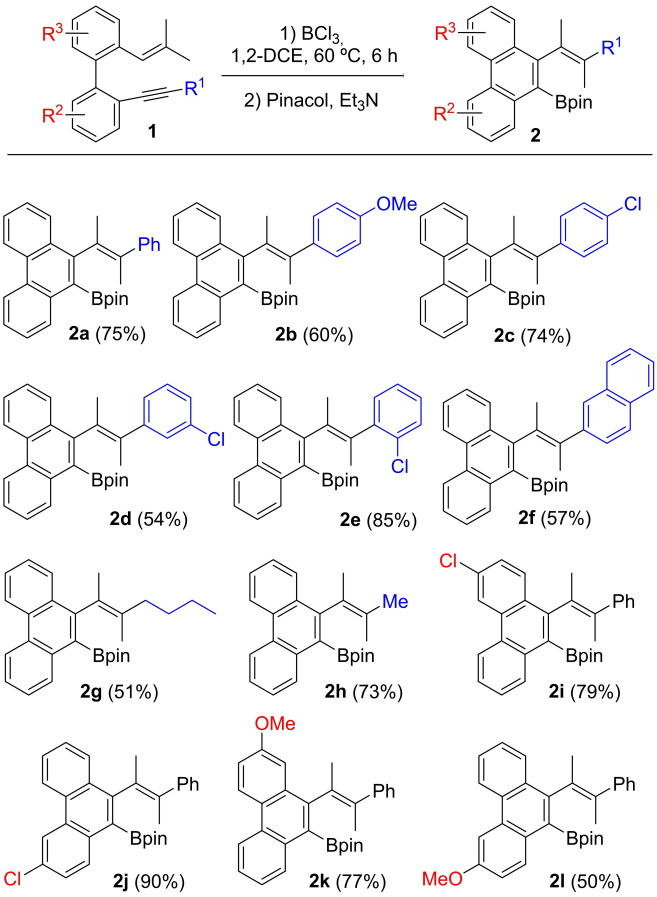
Scheme 2. Preliminary results.

particularly remarkable, as a significant skeletal rearrangement occurred, involving at least a methyl migration and apparently an alkyne cleavage. The structures of both **2a** and **3a** were confirmed by X-ray diffraction analysis.[14]

Given the interest of this result, we optimized the reaction conditions towards the selective synthesis of either **2a** or **3a** (see Supporting Information for details). The temperature turned out to be crucial for the selectivity of this transformation (Scheme 2). Thus, borylated cyclobutane **3a** was exclusively formed at 0 °C, whereas borylated phenanthrene **2a** was the only observed product at 60 °C. In both cases the corresponding products were isolated in good yields. The ratio of **2a** *vs* **3a** changed in favor of **2a** when the reaction time at room temperature was increased from 6 h to 24 h. These results suggest that the formation of **3a** occurs under kinetic control, while **2a** is thermodynamically favored. On the other hand, reaction of model substrate **1a** with BCl_3 at 0 °C in $CDCl_3$ showed the formation of **4a-BCl$_2$** as major product, pointing to this species as the one initially formed in the reaction media.[15] Thus, addition of pinacol/Et_3N would not only transform the BCl_2 moiety in the corresponding pinacol ester, but would also trigger a base-promoted ring closing finally leading to **3a**.[16,17]

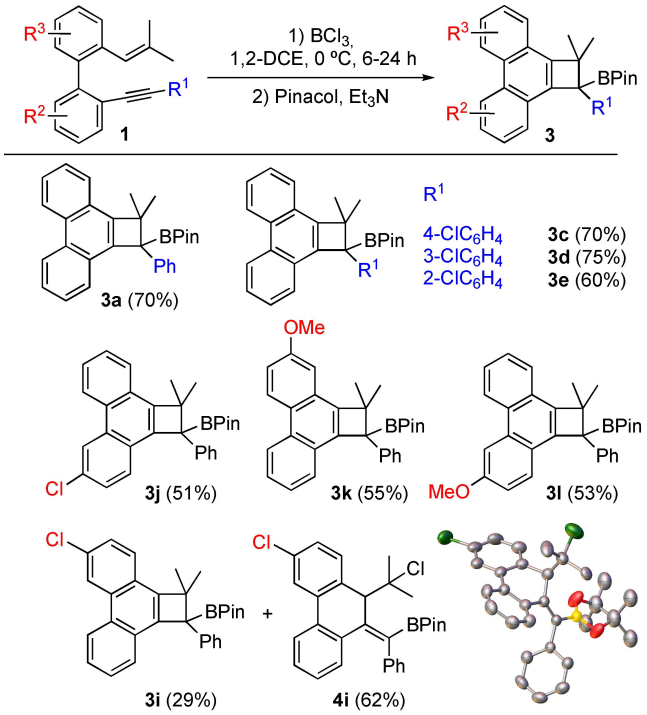
Under the optimal conditions for the selective synthesis of either **2a**, at 60 °C, or **3a**, at 0 °C, we explored the scope of each of these transformations. The borocyclization of enynes **1** at 60 °C provided a range of borylated phenanthrenes **2** with varied substitution both in the alkenyl substituent and in the external rings of the phenanthrene skeleton (Scheme 3). This method tolerates a wide range of substituents in the triple bond of the starting material (R^1), including electron-rich (**2b**) and electron-withdrawing aryl rings substituted in either *para* (**2c**), *meta* (**2d**) or *ortho* (**2e**) position, as well as a bicyclic aromatic naphthyl group (**2f**). Aliphatic substituents in this position also provide the corresponding borylated phenanthrenes (**2g**,**h**) in good yields. Moreover, both electron-withdrawing (**2i**,**j**) and electron-donating groups (**2k**,**l**) can be present in any of the rings of the original biphenyl, without significantly affecting the outcome of the borylative cyclization. 2D NMR experiments on compound **2i**, whose precursor has a chlorine atom in one of the rings of the biphenyl, confirmed the relative position of the substituents in the central ring of the phenanthrene with regard to the original rings of the biphenyl, showing that a significant skeletal rearrangement has taken place.

Next, we examined the scope of the synthesis of phenanthrene-fused borylated cyclobutanes **3** by borylative cyclization of enynes **1** at 0 °C (Scheme 4). In this regard, *o*-, *m*- and *p*-Cl substituted aromatic rings can be located at the terminus of the triple bond in the starting material, leading to the corresponding tetracyclic borylated derivatives in good yields (**3c**–**e**). Methoxy substituents in any of the biaryl rings are also tolerated (**3k**,**l**), as well as a chlorine substituent in the aryl ring bonded to the triple bond in the starting material (**3j**), with slightly lower yields. The presence of a chlorine atom in the other ring of the biaryl system gives rise to borylated dihydrophenanthrene **4i** as major product. Its structure was confirmed by X-ray



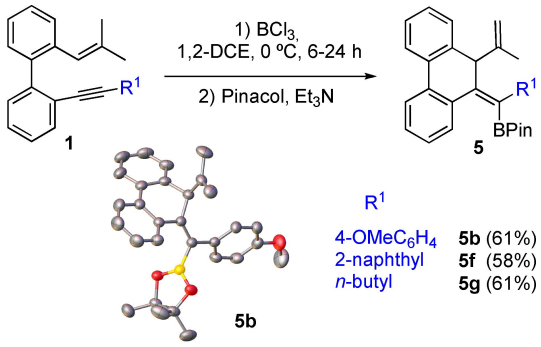
Reactions conducted in 1,2-DCE (0.06M) using 0.4 mmol of **1**, 1 equiv. of BCl_3, 1.1 equiv. of pinacol and 5 equiv. of NEt_3.

Scheme 3. Synthesis of borylated phenanthrenes.



Reactions conducted in 1,2-DCE (0.06M) using 0.4 mmol of **1**, 1 equiv. of BCl_3, 1.1 equiv. of pinacol and 5 equiv. of NEt_3.

Scheme 4. Synthesis of borylated cyclobutanes.



Reactions conducted in 1,2-DCE (0.06M) using 0.4 mmol of **1**, 1 equiv. of BCl_3, 1.1 equiv. of pinacol and 5 equiv. of NEt_3.

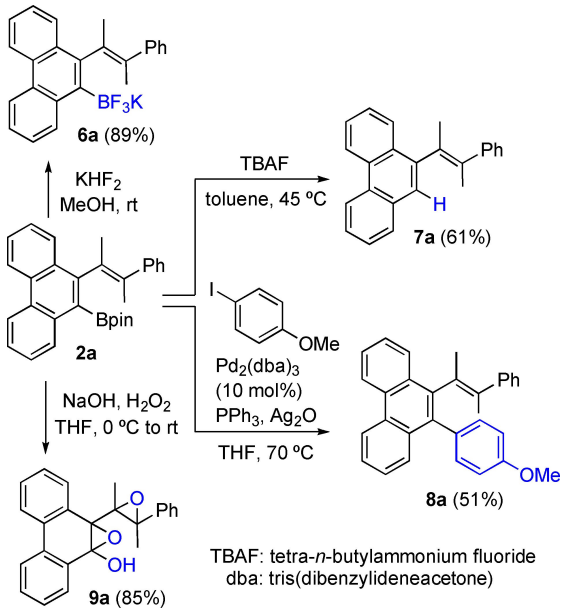
Scheme 5. Synthesis of dihydrophenathrenes **5**.

diffraction analysis.[14] Moreover, when the precursors **1b**,**f**,**g**—either with electron-rich aromatics or an alkyl group in the alkyne moiety—were reacted under the same conditions, cyclobutanes **3** were not formed upon addition of pinacol/Et_3N. Instead, the corresponding chlorinated derivatives **4** were the main species detected by ^1H NMR of the crude reaction mixture,[18] and related dihydrophenanthrenes **5** were isolated in good yields after column chromathography, as a consequence of HCl elimination during the purification step (Scheme 5).

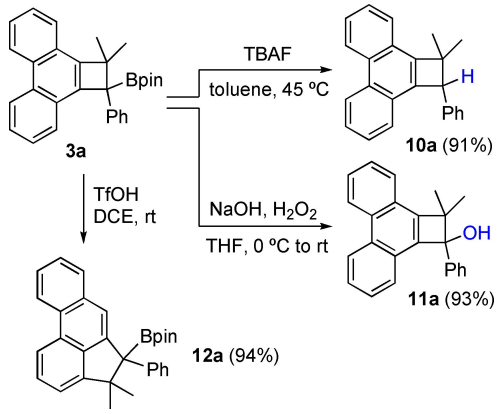
Finally, the synthetic utility of the borylated building blocks obtained with the reported methodology was assessed (Schemes 6 and 7). As shown in Scheme 6, **2a** is a suitable precursor of potassium trifluoroborate derivative **6a**. Moreover, protodeborylation to yield alkenylphenanthrene **7a** proceeded smoothly. Interestingly, the combination of borylative cyclization/protodeborylation provides a phenanthrene with a different substitution pattern to the one obtained from the same starting material under gold catalysis.[13a] Suzuki coupling with *p*-iodoanisole afforded 9,10-disubstituted phenanthrene **8a**, whereas oxidation of the C–B bond occurred with the simultaneous epoxidation of the alkenyl substituent and the central double bond of the phenanthrene system, leading to polyoxygenated compound **9a**.[19]

On the other hand (Scheme 7), borylated cyclobutane **3a** was easily protodeborylated to **10a** or oxidized to alcohol **11a**. Interestingly, treatment of **3a** with triflic acid (TfOH) provided tetracyclic compound **12a** in excellent yield, presumably through an acid-promoted cyclobutane ring opening followed by a Friedel–Crafts type cyclization.

A detailed computational analysis by DFT calculations was performed to gain insight into the reaction mechanism and rationalize the temperature-dependent synthetic regiodivergence toward cyclobutyl or phenanthryl derivatives. Figure 1 depicts the computed Gibbs energy profiles at both



Scheme 6. Derivatizations of borylated compound **2a**.



Scheme 7. Derivatizations of borylated compound **3a**.

0 and 60 °C, which are qualitatively similar until **III** (**4a-BCl_2** in Scheme 2) is formed. Thus, the profile at 0 °C is discussed as a model of the general behavior before reaching this step. The reaction starts from the complexation process between the enyne and BCl_3 (**I**). BCl_3 could coordinate to either C1 or C2 of the alkyne, but the transition state shown in Figure 1 (**$TS_{I\text{-}II}$**), leading to bonding at C1, is kinetically more favorable owing to its 1.4 kcal mol^{-1} lower energy barrier compared to the TS for coordination to C2.[16] In addition, the intermediate **II** is also more favorable than the one that would generate from C2 bonding, by about 0.9 kcal mol^{-1}. Next, **III** can be obtained via **$TS_{II\text{-}III}$** (2.1 kcal mol^{-1}), as a result of ring closing and chloride transfer from boron to carbon. This process is exothermic, with $\Delta G = -31.7$ kcal mol^{-1}. Finally, **III** would be deprotonated upon treatment with NEt_3, triggering a ring closing leading to **3a**, which explains why this product is the only one observed for most substrates upon treatment with NEt_3/pinacol. For some particular substituents this deprotonation would be disfavored, which explains the different outcome observed for **1b**,**f**,**g**.[16] Parallel DFT calculations carried out at 60 °C, show a similar energy profile to the one obtained at 0 °C until formation of **III**, with slightly higher energy values. Alternatively, **II** can evolve to cyclobutene-containing tetracycle **V**, which is slightly more stable than **III** at 60 °C, through a formal [2+2] cycloaddition and subsequent BCl_3 elimination.[20] Formation of **V** from **III**, via ring closing and loss of BCl_3, would also be possible. In any case, recoordination of BCl_3 to the cyclobutene moiety in **V** can occur, leading to **VI**, which is 2.5 kcal mol^{-1} more stable than **IV**. Transformation of **IV** in **VI** supposes a formal 1,2-boron migration, through the intermediacy of cyclobutene **V**. Next, **VII** can be obtained via chloride abstraction facilitated by BCl_3. Intermediate **VII** evolves through an endothermic 1,2-methyl migration ($\Delta G = +9.6$ kcal mol^{-1}). Finally, the formation of product **IX** can be explained through a concerted mechanism of proton loss and ring-opening in a highly thermodynamically favorable process implying aromatization of the central ring of the phenanthrene core. At 0 °C, coordination of BCl_3 to **V** to yield **VI** would not be feasible due to its high energy barrier, so **III** is the product obtained at this temperature, despite being thermodynamically less stable than **IX**.

In conclusion, the possibility of carrying out synthetically useful metal-free borylative enyne cyclizations has been demonstrated. Biphenyl embedded 1,3,5-trien-7-ynes react with BCl_3, in the absence of catalysts or additives, to generate novel polycyclic borylated building blocks. It is worth noting that the outcome of the process can be controlled adjusting the temperature of the reaction media, giving access to two different borylated skeletons, namely phenanthrenes **2** and cyclobutanes **3**, from the same starting materials **1**. Furthermore, the formation of compounds **2** proceeds, as endorsed by DFT studies, via an uncommon skeletal rearrangement unprecedented in BCl_3-promoted borylative cyclizations. This highly interesting fact opens the door to the design of innovative approaches for the synthesis of novel borylated compounds based on BCl_3-promoted cyclizations coupled with BCl_3 triggered rearrangements.

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Conflict of Interest

The authors declare no conflict of interest.

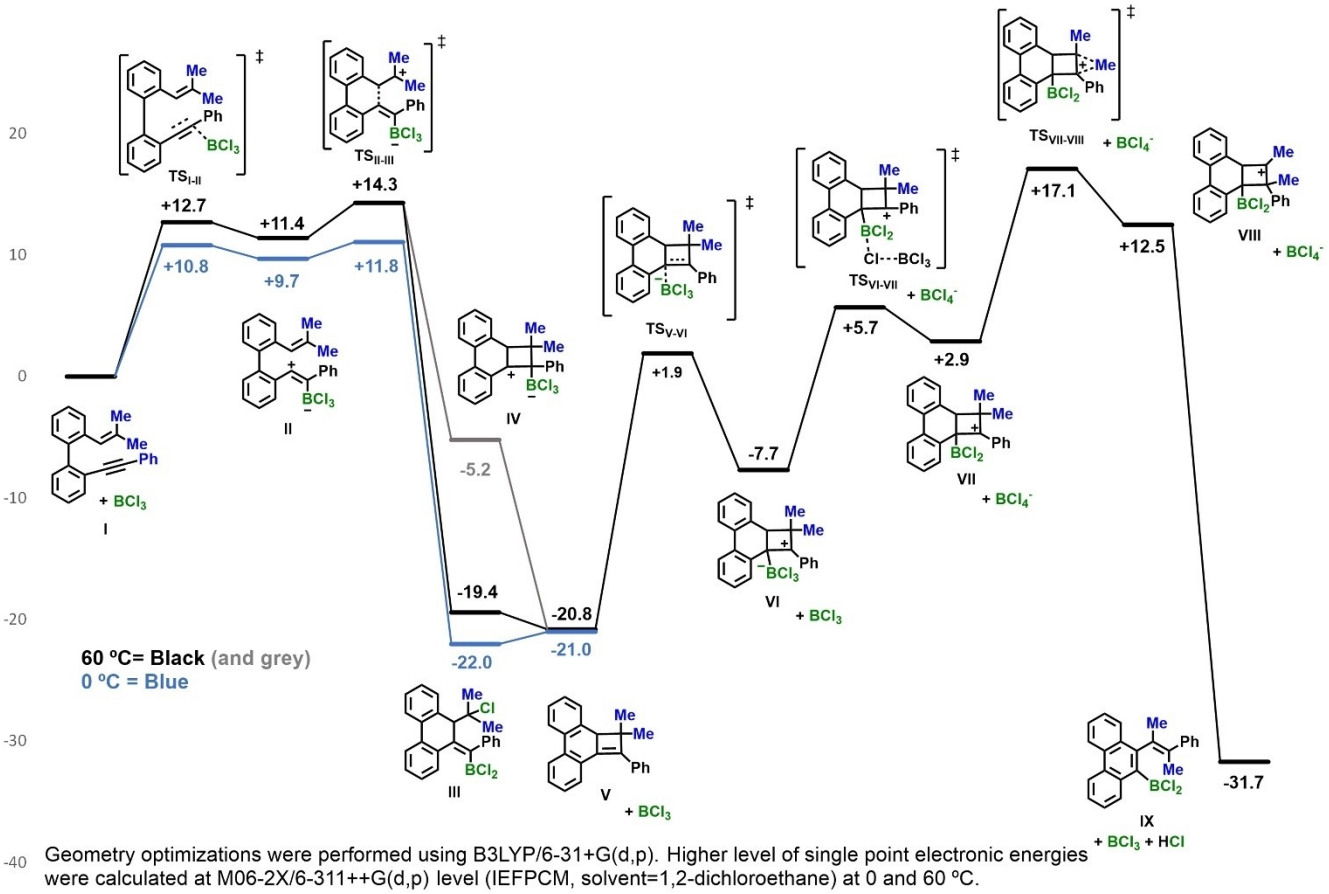

Figure 1. Computed Gibbs energy profile.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Boron · Cyclization · Enynes · Phenanthrenes · Rearrangement

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[14] Deposition Numbers 2098410 (for **2a**), 2098416 (for **3a**), 2098440 (for **4i**), 2098464 (for **5b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[15] The formation of **4** can be explained by a chlorine atom transfer from boron to carbon (see Figure 1). ^{11}B NMR of this compound shows a main signal at 56.0 ppm, consistent with the presence of C-BCl_2.

[16] For further information, see the Supporting Information.

[17] In addition, a reaction at 0 °C was performed and after 6 h an aliquot was treated with pinacol/Et_3N, confirming the exclusive formation of **3a**. Subsequent heating of the remaining mixture to 60 °C led to the formation of **2a** as single product, after the corresponding treatment with pinacol/Et_3N, showing that the species initially formed at 0 °C can be transformed into **2a**.

[18] Reaction of **1b** in chlorobenzene, a solvent more robust to halide loss than dichloroethane, also provided **4b** as major product in the crude reaction mixture, which precludes the possibility that the chlorine atom was coming from the solvent.

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[20] Cyclobutene-containing intermediates have been proposed for the reactions of substrates **1** under gold catalysis, and isolated for particular examples, see ref. [13a].

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