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The Aromatic Claisen Rearrangement of a 1,2-Azaborine

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Abstract

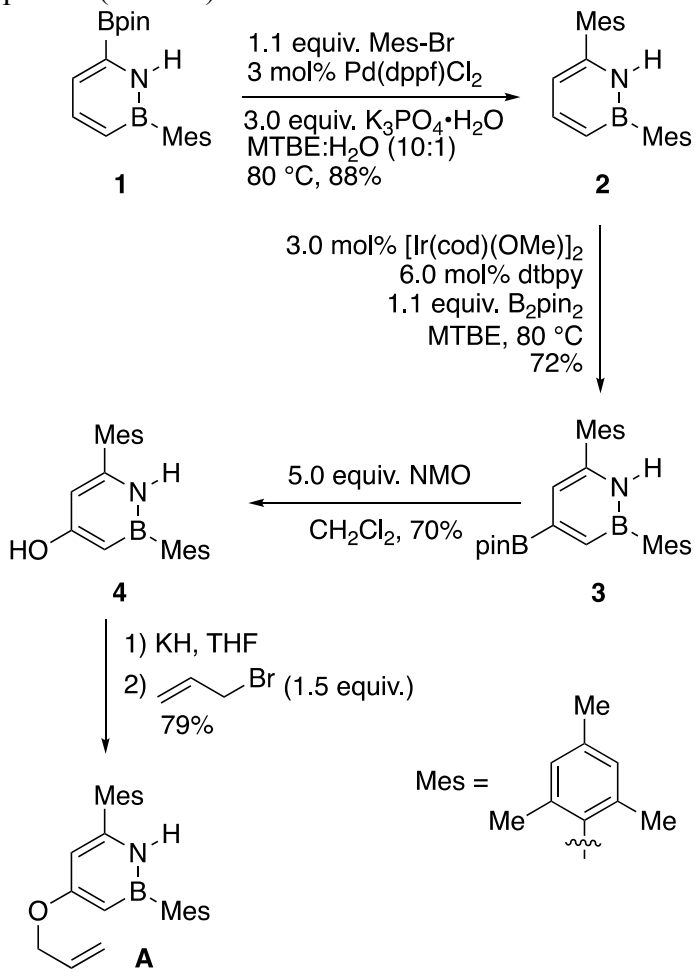
The first aromatic Claisen rearrangement of a 1,2-azaborine is described along with a quantitative kinetic comparison of the reaction of the azaborine with its direct all-carbon analogue. The azaborine **A** rearranged in a clean, regioselective fashion and reacted faster than the all-carbon substrate **B** at all temperatures from 140–180 °C. Activation free energies were extracted from observed first-order rate constants (**A**: $\Delta G_{298K}^{\ddagger}$ = 32.7 kcal/mol; **B**: $\Delta G_{298K}^{\ddagger}$ = 34.8 kcal/mol) corresponding to a twenty fold faster rate for **A** at observed reaction temperatures. DFT calculations show that the rearrangement proceeds via a concerted six-membered transition state and that the electronic structure of the $\pi_{BN/CC\text{-}ring}$ orbital is mostly responsible for the observed regioselectivity and relative reactivity.

By exchanging a CC unit for an isoelectronic and isostructural BN unit in an organic scaffold, it is possible to diversify electronic structure and chemical space without significantly altering the geometric footprint of a given scaffold. BN/CC isosterism[1] has shown potential in biomedical applications; for example, isosteric azaborines and benzenes can bind to biological targets in a similar structural way[2] but may convey different function as a result of hydrogen bonding[3] or other properties introduced by BN/CC isosterism.[4] Uncovering the basic properties and reactivity of *monocyclic* azaborines should therefore continue inform future applications. Our group as well as others have investigated the energetic,[5] magnetic,[6] structural,[7] and reactivity-related[8] consequences of BN/CC isosterism for the monocyclic 1,2-azaborine motif. In 2015 we found that the lower aromatic character of azaborines relative to benzenes facilitated a Diels-Alder reaction.[9] Thermal [4+2] cycloadditions of benzenes are rare,[10] presumably because their high resonance stabilization energy (RSE) creates unfavorable kinetic and thermodynamic conditions. It follows, then, that other pericyclic reactions that break aromaticity in their mechanisms should, in principle, be faster for an azaborine than for a direct, all-carbon analogue.

The aromatic Claisen rearrangement is one such pericyclic reaction that breaks aromaticity along its reaction coordinate.[11] Since Claisen's first report of the reaction in 1912,[12] many studies on its mechanism and scope have been reported, and the aromatic Claisen rearrangement has been executed in a number of complex molecule syntheses.[13,14] A kinetic study by White[15] in addition to that of Goering and Jacobson[16] showed that the reaction likely proceeds through a concerted mechanism. The rearrangement of heteroaryl allyl ethers has been reported,[17] but to our knowledge, there is only a single kinetic mechanistic study including heteroatoms in the aromatic moiety.[18] In this work, we describe the first aromatic Claisen rearrangement of an 1,2-azaborine-derived allyl ether, and we provide quantitative kinetics comparison of its rearrangement with the corresponding all-carbon analogue along with a computational mechanistic analysis.

We designed the substrates for our study with the following points in mind: 1) The boron atom on the BN substrate **A** should be protected from undesired reactivity using a mesityl group. 2) For the purpose of clean kinetic measurements, the all-carbon substrate **B** should be symmetric to avoid generation of isomers. Our synthetic strategy to 1,2-azaborine **A** involves

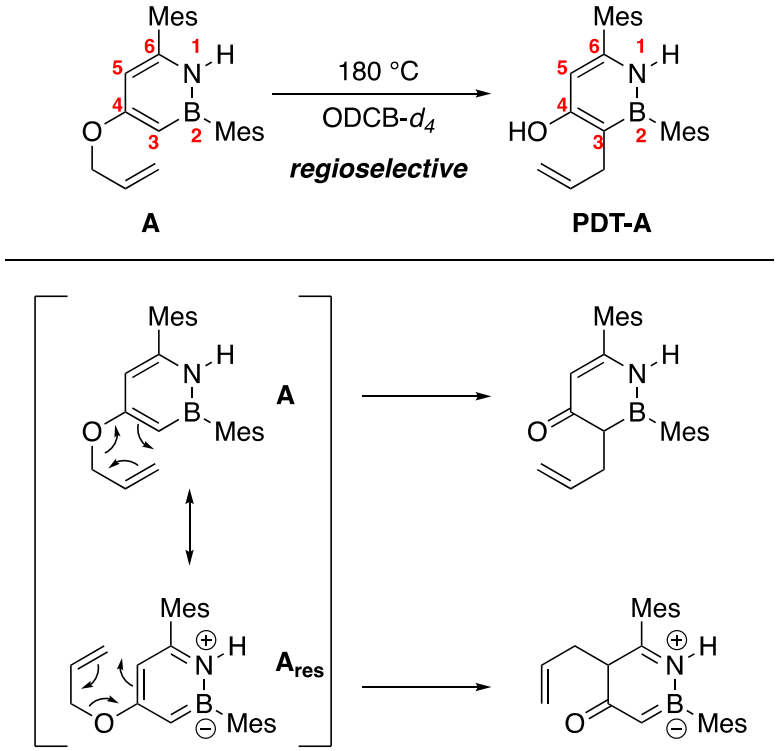
functionalization the BN-heterocyclic 1,2-azaborine core (Scheme 1).[8f] To this end, the known borylated 1,2-azaborine **1**[19] undergoes Suzuki-Miyaura coupling to give mesityl-substituted **2**. This compound is then borylated once more at the 4-position to yield **3**.[20] While the C-H borylation reaction to form **1** is quite facile and proceeds at room temperature, the second borylation to form **3** was more difficult and requires heating for an extended period of time. Oxidation of the newly installed C-Bpin group with *N*-methylmorpholine-*N*-oxide[20] yields phenolic compound **4**, which is then allylated after treatment with potassium hydride and allyl bromide to furnish the target compound **A**. We synthesized the direct, all-carbon analogue, *O*-allyl-(3,5-dimesityl)phenol **B** using a route involving the cross coupling of 3,5-dibromophenol, followed by the allylation of the phenol (see ESI).



Scheme 1. Synthesis of Azaborine **A**.

We observe full conversion of **A** regioselectively to **PDT-A** after heating **A** to 180 °C for 18 hours in ortho-dichlorobenzene-d_4 (ODCB-d_4) (Scheme 2, see ESI for HSQC data). While meta-substituted phenyl allyl ethers generally do not undergo the aromatic Claisen rearrangement regioselectively,[21] Moody has shown that heteroaromatic systems such as indoles and thiophenes can exhibit regioselectivity in this reaction.[22] Bond length alternation caused by heteroatoms in an aromatic ring implies that some bonds in the heteroarene are more olefinic in nature than others. The Claisen rearrangement should proceed through these more olefinic bonds on the arene rather than more σ-like bonds.[23] In the case for BN heterocycle **A**, the observed product may result from

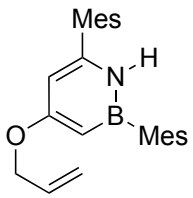
the reaction of the dominant resonance contributor more accurately described using the neutral valence bond structure **A** rather than the zwitterionic form $\mathbf{A}_{res}$ (Scheme 2). Our group has previously shown that the intra-ring C(3)–C(4) and C(5)–C(6) bonds are shorter than the C(4)–C(5) bond,[7] consistent with the observed rearrangement regioselectivity for **A**.

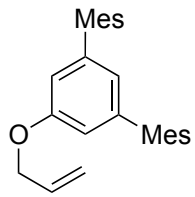


Scheme 2. Claisen rearrangement of **A** is regioselective for the 3-position.

We performed a kinetic comparison of the aromatic Claisen rearrangements of **A** and **B** using ^{1}H NMR (see ESI for details). Experiments were run in ODCB-d_4 in the temperature range of 140–180 °C. The first-order rate constants for the aromatic Claisen rearrangements of **A** and **B** are reported in Table 1 as the average of five runs at each temperature. The aromatic Claisen rearrangement of **A** is about twenty-fold faster than the analogous reaction of **B** at all temperatures investigated. Thus, it appears that BN/CC isosterism accelerates the aromatic Claisen rearrangement, consistent with our original hypothesis.

Table 1. Aromatic Claisen rearrangement first-order rate constants for **A** and **B** as measured by ^{1}H NMR and Eyring activation free energy extracted from analysis of the rate constants.





	A	**B**
T(˚C)	k x 10^{-6} (s^{-1})	
180	118 ± 12	6.5 ± 0.8
170	66 ± 5	3.6 ± 0.7
160	31 ± 5	1.6 ± 0.4
150	12 ± 3	0.50 ± 0.04
140	5.7 ± 0.3	0.30 ± 0.04
$\Delta G^{\ddagger}_{298K}$ (kcal/mol)	**+32.7 ± 0.5**	**+34.8 ± 0.6**

Using an Eyring plot (Figure 1), we determined that $\Delta G^{\ddagger}_{298K}$ ($\Delta G^{\ddagger}_{298K} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$, for T = 298K) for the rearrangement of **A** (+32.7 ± 0.5 kcal/mol) is smaller by 2.1 kcal/mol than the all-carbon compound **B** (+34.8 ± 0.6 kcal/mol). The experimentally determined activation enthalpy $\Delta H^{\ddagger}$ for the carbonaceous compound **B** (+29 kcal/mol) is apparently slightly larger than for BN heterocycle **A** (+28 kcal/mol). Additionally, the observed activation entropy $\Delta S^{\ddagger}$ for **B** (–18 e.u.) is apparently more negative than it is for **A** (–15 e.u.). These activation parameters[24] indicate an ordered transition state for both reactions, consistent with a concerted cyclic rearrangement process. The error range of the activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) is reported as the standard deviation from the calculated average of five independent runs for each reaction temperature. As can be seen from Figure 1, the experimentally determined $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for **A** and **B** are sufficiently similar so that any comparative interpretations are to be taken with extreme caution. On the other hand, the experimentally determined $\Delta G^{\ddagger}$ values are significantly distinct[25] for **A** and **B** (consistent with the clear observed slower reaction rates for **B** than **A**) to allow for these values to be used as a benchmark for a detailed computational mechanistic analysis.

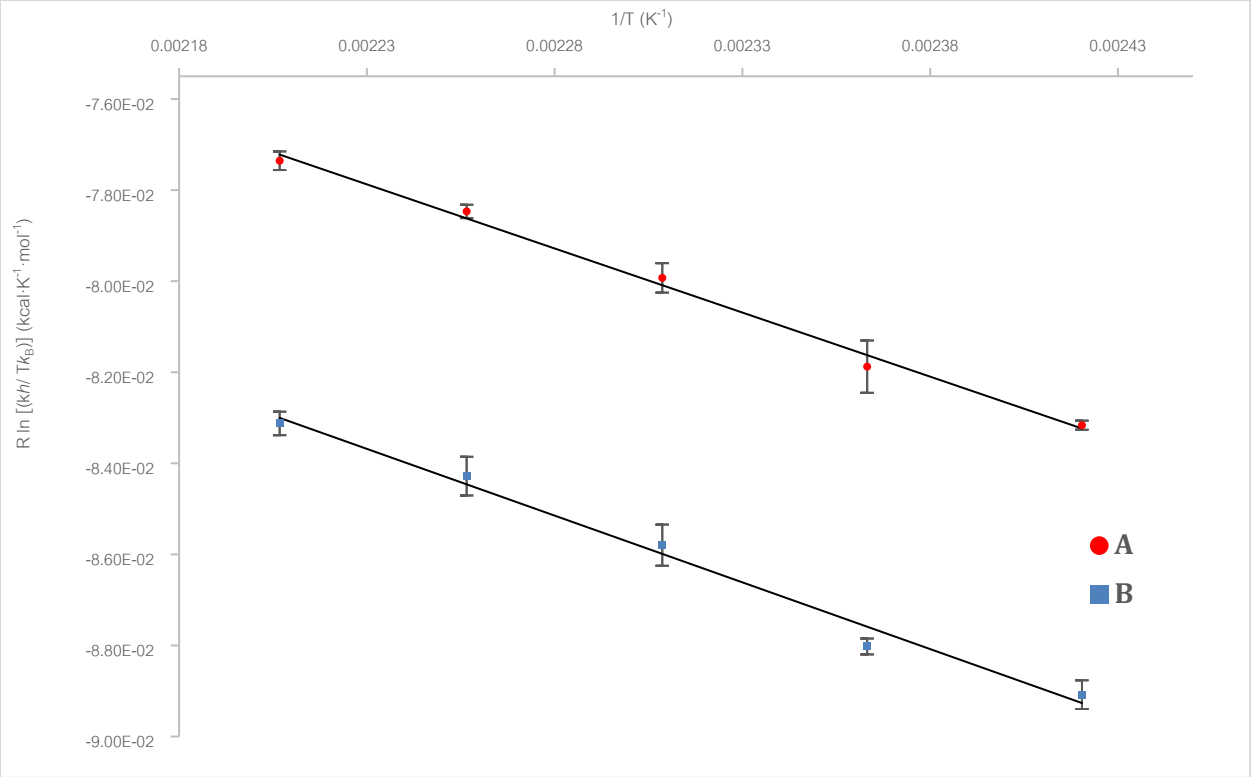


Figure 1: Eyring plots for **A** and **B**. Error bars are the standard deviation from the calculated average of five separate measurements.

We carried out DFT calculations[26] at SMD(o-DCB)-PBE0-D3(BJ)/6-31G** level of theory[27] in order to obtain better insights into the observed regiochemistry (C(3) vs. C(5)) of the aromatic Claisen rearrangment of the BN heterocycle **A** and to analyze the impact of BN/CC isosterism on the rate of the rearrangement (**A** vs. **B**). As can be seen from Figure 2, two rotamers (**A** and **A'**) were found on the potential energy surface (PES), with the double bond of the allyl group directed toward C3 or C5 atoms of the BN-heterocyclic ring, respectively. The energy difference between **A** and **A'** is 0.8 kcal/mol. In agreement with the experimental observations, DFT calculations reveal that the rearrangement to the C(3)-position from **A** is predicted to be 11.4 kcal/mol more favored than the rearrangement from **A** to the C(5)-position ($\Delta G^{\ddagger}_{DFTAC5}$ = 42.6 kcal/mol). The computed activation barrier for the rearrangement from **A** to **PDT-A** ($\Delta G^{\ddagger}_{DFTA}$ = 31.2 kcal/mol) matches well with the value determined from the Eyring analysis ($\Delta G^{\ddagger}_{expA}$ = +32.7 ± 0.5 kcal/mol). The reaction occurs in a quasi-synchronous concerted pathway via a 6-membered transition state. Analysis of the geometrical parameters reveals that the breaking C–O bond is elongated about 35.4 % for **TSA-C3** and 43.4 % for **TSA-C5**, compared to the C–O distance of the initial reactant **A**. On the other hand, the forming C–C bond is elongated by 39.9% for **TSA-C3** and 32.1% for **TSA-C5**, compared to the corresponding dearomatized keto-intermediates **IntA-C3** and **IntA-C5**, respectively. These bond distance variations indicate that **TSA-C3** is an earlier transition state than **TSA-C5**. The regioselectivity is governed both by orbital considerations and the thermodynamic stabilities of the dearomatized intermediates **IntA-C5** vs. **IntA-C3**. The two orbitals involved in this rearrangement are the HOMO (Figure 2), which is mainly localized on the π-system of the BN-ring, and the LUMO+5, which is the $\pi^*_{C=C}$ orbital of the O-allyl moiety. The HOMO of **A** shows a larger coefficient at C(3) position (~21 %) than the

C(5) (~12 %) position, consistent with the observed regioselectivity of the rearrangement. Additionally, the formation of **Int-C5** from **A** is endergonic by 18.5 kcal/mol in stark contrast to the formation of **Int-C3** which is exergonic by –2.8 kcal/mol. The difference in thermodynamic stabilities of **Int-C3** and **Int-C5** may be reflected in their corresponding transition states of formation according to the Hammonds postulate,[28] thus resulting in the observed C(3)-selective rearrangement.

We also computed the energy profile associated with the aromatic Claisen rearrangement for the carbonaceous compound **B (**Figure 2, black trace). Consistent with the experimental Eyring data, the activation barrier for the rearrangement of **B** ($\Delta G^{\ddagger}_{DFTB}$ = 34.0 kcal/mol) was computed to be 2.8 kcal/mol higher in energy than that for the BN analogue **A** ($\Delta G^{\ddagger}_{DFTA}$ = 31.2 kcal/mol). Similar to the unfavorable rearrangement to **PDT-A-C5**, the formation of the dearomatized intermediate **Int-B** from **B** is endergonic by 8.7 kcal/mol (vs. an exergonic reaction for **A**), which is consistent with a faster aromatic Claisen rearrangement for the BN derivative **A**. The computed geometrical features of the transition states indicate a relatively early transition state for the rearrangement of **A** ($\Delta(C–O_{break})$ = 35.4 % and $\Delta(C–C_{form})$ = 43.4 % compared to **A** and **IntA-C3**, respectively) and a relatively late transition state for **B** ($\Delta(C–O_{break})$ = 43.4 % and $\Delta(C–C_{form})$ = 36.2 % compared to **B** and **Int-B**, respectively).

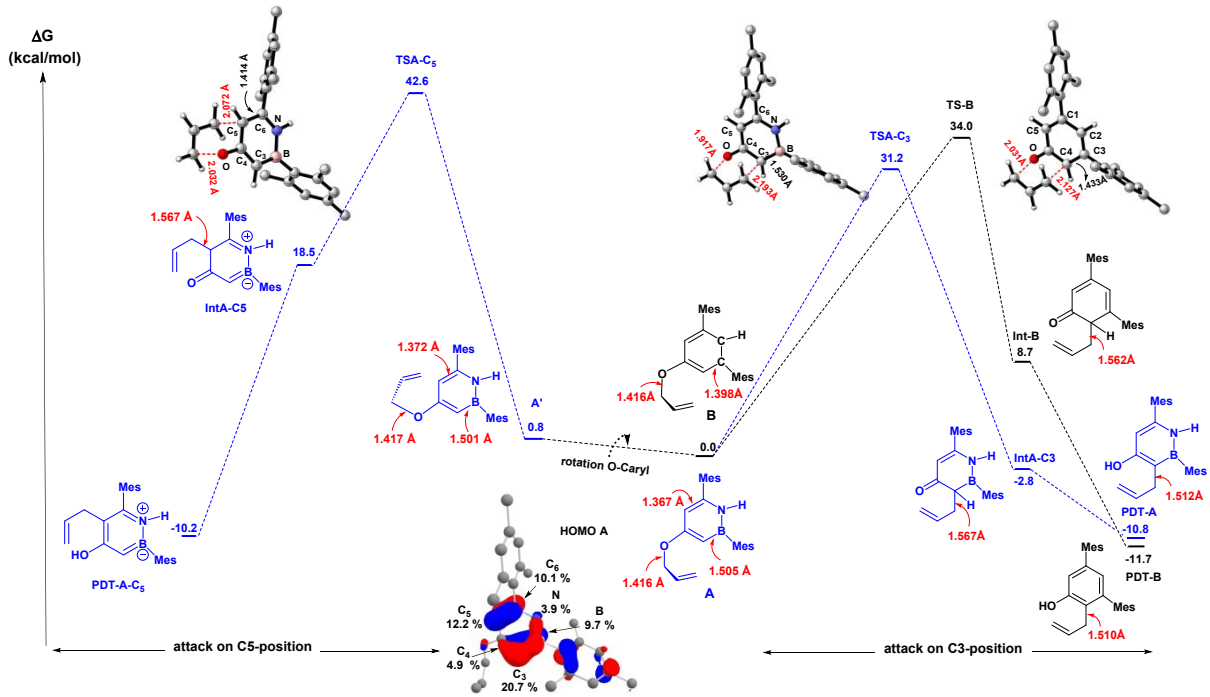


Figure 2. Calculated relative energy profiles for the aromatic Claisen rearrangement for **A** (C(3) and C(5) -positions, blue) and **B** (black) computed at SMD(o-DCB)-PBE0-D3(BJ)/6-31G** level of theory. Main distances in Å. Plot of the HOMO of **A** and main atomic orbital compositions in percents (%).

To isolate the electronic influences and remove steric bias on the reactivity of **A** and **B**,[29] we calculated the energy profiles for the unsubstituted compounds **A-H** and **B-H** (ESI, Figure S1, mesityl groups are replaced with H), and we found similar reactivity trends as with the mesityl substituted systems, i.e., the $\Delta G^{\ddagger}$ for **A-H** (31.6 kcal/mol) is smaller than the $\Delta G^{\ddagger}$ for **B-H** (34.9

kcal/mol). We analyzed the key molecular orbitals at play in the reactivity (i.e., $\pi_{BN/CC\text{-}ring}$ and $\pi^*_{C=C(O\text{-}allyl),}$ see ESI Figure S2) for **A**, **A-H**, **B**, **B-H**, and we found a good correlation (ESI, Figure S3) between the energy of the $\pi_{BN/CC\text{-}ring}$ orbital and the computed activation barriers. The higher the energy of the $\pi_{BN/CC\text{-}ring}$ orbital, the smaller is the computed activation free energy $\Delta G^{\ddagger}$ of the rearrangement, indicating that the reactivity difference between **A** and **B** is to a large extent governed by the electronic effects.

Finally, we explored the possibility of a radical pathway for the Claisen rearrangement by employing a radical scavenger, butylated hydroxytoluene (BHT), to trap potential radial intermediates. A stoichiometric amount BHT was added to the substrates **A** and **B**, and after heating the mixtures to 170 °C, we observe no BHT adduct formation.[30] Furthermore, the addition of the scavenger did not affect the rate of the reaction for either analogue **A** or **B** (See ESI for details). These observations are consistent with the proposed concerted six-membered cyclic rearrangement mechanism.

In summary, we described the first example of an aromatic Claisen rearrangement of an 1,2-azaborine. We show that the rearrangement of a C-4 substituted 1,2-azaborine-derived *O*-allyl ether **A** occurs regioselectively to form the C(3)-allyl-C(4)-hydroxy-1,2-azaborine product **PDT-A**. A kinetic analysis of the Claisen rearrangement of **A** in direct comparison with its carbonaceous analogue **B** reveals that the rearrangement for the BN heterocyclic motif is more facile across the examined temperature ranges between 140 °C and 180 °C, correlating with the observed aromaticity trends. Reaction activation free energy for **A** ($\Delta G_{298K}^{\ddagger}$ = 32.7 kcal/mol) and **B** ($\Delta G_{298K}^{\ddagger}$ = 34.8 kcal/mol) derived from first-order rate constants via Eyring analysis are consistent with those predicted by DFT calculations. Computational mechanistic analyses show that the rearrangement proceeds via a concerted six-membered transition state and that the electronic structure of the $\pi_{BN/CC\text{-}ring}$ orbital is mostly responsible for the observed regioselectivity and relative reactivity. In addition to fundamentally examining a classic reaction of arenes in the context of 1,2-azaborines, this work also provided a new synthetic tool box for the preparation of C(3),C(4)-disubstituted 1,2-azaborine derivatives.

Associated Content

Experimental procedures, compound characterization data, computational information (PDF).
Optimized cartesian coordinates (.XYZ)

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Notes
The authors declare no competing financial interest.

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