Ring Expansion of Cyclic Boronates *via* Oxyboration of Arynes

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Supporting Information Placeholder

ABSTRACT: The oxyboration of arynes has been achieved for the first time. A series of 2-aryl-1,3,2-dioxaborolane derivatives were reacted with aryne precursors in the presence of CsF to give the corresponding ring-expanded 7-membered borinic acid esters via selective boron–oxygen bond activation. Preliminary experimental mechanistic studies and density functional theory (DFT) calculations suggest that this unprecedented aryne oxyboration proceeds through the formation of boron ate complexes of arylboronates with CsF, followed by aryne insertion into the boron–oxygen bond.

Arynes are highly important class of synthetic intermediates that enable the 1,2-difunctionalization of aromatic rings.[1,2] These unique chemical species have found widespread use in the construction of functional polycyclic aromatics and structurally complicated bioactive compounds.[1,2] In the last decade, the borylative functionalization of arynes has been a particularly active research area, as this strategy allows the production of highly functionalized arylboron compounds that can serve as valuable reagents in organic synthesis (Figure 1A).[3–7] In 2010, Yoshida and coworkers reported the first borylation of arynes.[3a] They found that the copper(I)-catalyzed borylation of arynes using $B_2(pin)_2$ resulted in the formation of 1,2-diborylated arenes.[3a] Oestreich also developed a platinum(0)-catalyzed diboration of indolyne derivatives in 2015.[4] In 2013, Uchiyama reported the borylzincation of arynes with dialkylzinc and $B_2(pin)_2$.[5] Curran and Taniguchi later reported the hydroboration of arynes using *N*-heterocyclic carbene (NHC)-borane complexes.[6] Recently, Mizoguchi and Sakurai reported the carboboration of arynes with alkenylboronates via 1,2-metallate rearrangement.[7] Despite the very significant progress that has been made in aryne borylation chemistry, there are still no reports of aryne insertion into B–O bonds.[1–7] The development of such aryne oxyboration transformations poses a challenge because it requires the selective activation of B–O bonds, which have a relatively high bond dissociation energy (BDE) of 806 kJ/mol compared to other types of boron-based chemical bonds, such as B–B (297 kJ/mol), B–H (330 kJ/mol), and B–C (448 kJ/mol) bonds.[8] However, overcoming this challenge would open new avenues to functionalized arylboron compounds, which are difficult to prepare through other means.

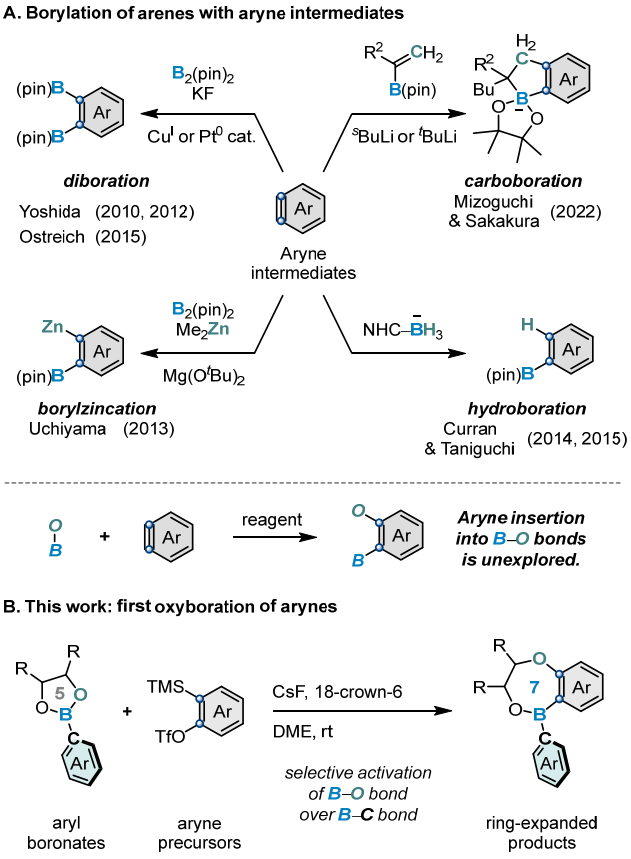
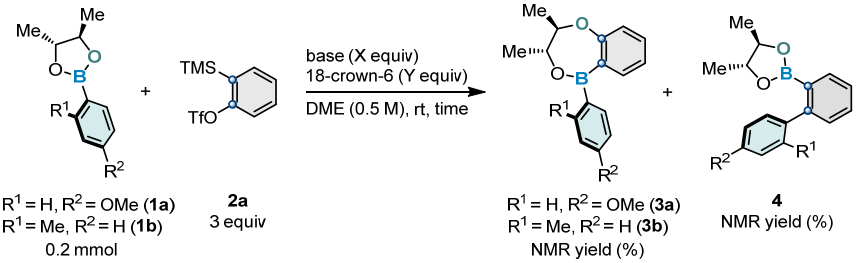


Figure 1. Borylative functionalization *via* aryne intermediates

Our group has an on-going interest in developing new borylation reactions to address significant challenges in synthetic chemistry.[9] In this work, we report the selective B–O bond activation of cyclic boronates, namely, 2-aryl-1,3,2-dioxaborolane derivatives, in the presence of arynes to give the ring-expanded 7-membered borinic acid cyclic esters (Figure 1B), which we discovered serendipitously in the course of our research into the functionalization of organoboron compounds. Notably, the B–O bond was selectively activated by the arynes, and B–C bond cleavage did not occur under the applied conditions (Figure 1B). Furthermore, we conducted experimental and theoretical investigations of the mechanism of this unprecedented oxyborylative ring expansion.

Table 1. Optimization Study for the Oxyboration of Arynes[a]



R^1 = H, R^2 = OMe (**1a**)
R^1 = Me, R^2 = H (**1b**)
0.2 mmol

2a
3 equiv

R^1 = H, R^2 = OMe (**3a**)
R^1 = Me, R^2 = H (**3b**)
NMR yield (%)

4
NMR yield (%)

entry	substrate	base	X (equiv)	Y (equiv)	time (h)	yield of **3** (%)[b]	yield of **4** (%)[b]
1	**1a**	CsF	3	3	1.5	41	<5
2	**1a**	KF	3	3	3	<5	<5
3	**1a**	RbF	3	3	3	43	<5
4	**1a**	RbF	3	3	1	41	<5
5	**1a**	CsF	6	6	1.5	48	<5
6	**1b**	CsF	3	3	1.5	70	<5
7	**1b**	CsF	3	0	1.5	29	<5

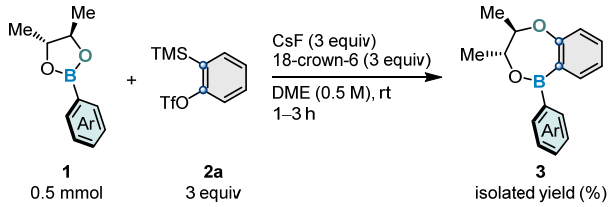
[a]Standard conditions: boronate **1** (0.2 mmol), aryne precursor **2a** (0.6 mmol), base, and 18-crown-6 in 1,2-dimethoxyethane (0.4 mL). [b]The yields of **3** and **4** were determined *via* NMR analysis using 1,2-dibromomethane as an internal standard.

To investigate this reactivity, we first optimized the reaction between 2-(4-methoxyphenyl)-4,5-dimethyl-1,3,2-dioxaborolane (**1a**) and aryne precursor **2a** in the presence of a fluoride base and 18-crown-6 (Table 1). When CsF was used as the base, the desired oxyboration product **3a** was obtained in moderate yield (entry 1, 41% yield). Notably, the carboboration product **4** was not detected. The reaction with KF resulted in no product formation (entry 2). The use of RbF as a base also afforded the desired product **3a**, but the yield remained moderate (entries 3 and 4, 43% and 41% yields, respectively). Increasing the amount of CsF and 18-crown-6 (6 equiv) improved the yield only slightly (entry 5, 48% yield). We surmised that the low yields under the conditions using an excess amount of CsF might be due to undesired side reactions or decomposition of product **3a** in situ that was promoted by fluoride anion. We thus decided to use 4,5-dimethyl-2-(*o*-tolyl)-1,3,2-dioxaborolane (**1b**) as the substrate (entry 6), and the desired ring-expanded product **3b** was obtained in good yield (entry 6, 70%). This result suggested that steric congestion around the boron center improves the stability of **3** toward undesired hydrolysis. Finally, we tested the reaction in the absence of 18-crown-6, which significantly decreased the yield of **3b** (entry 7, 29% yield).

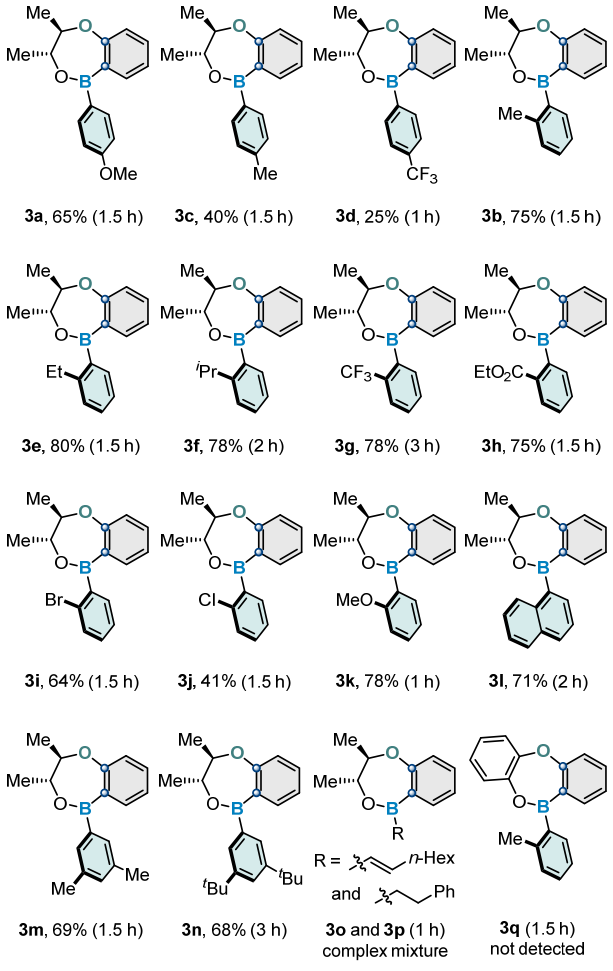
Having determined the optimal conditions, we next examined the substrate scope (Table 2). The ring-expanded 7-membered borinic acid esters could be isolated using flash silica gel column chromatography without significant decrease in the product yields. The reactions of substrates bearing *para*-substituents on the phenyl ring, such as methoxy (**1a**), methyl (**1c**), and trifluoromethyl (**1d**) groups afforded the corresponding oxyboration products (**3a**, **3c**, and **3d**) in low-to-moderate yields (65%, 40%, and 25% yield, respectively). The electron-withdrawing trifluoromethyl group of **1d** increased the Lewis acidity of the boron atom, leading to the undesired decomposition of **3d** during the reaction. Next, we investigated *ortho*-substituted arylboronates (**1b**, **1e**–**1k**). Because the *ortho*-substituents can improve the stability of the products under basic conditions, the desired products (**1b**, **1e**–**1k**) were obtained in good yields (41–80%). Notably, both sterically-hindered- and electron-deficient substrates were well tolerated. Furthermore, naphthalene-substituted substrate **1l** also underwent the oxyboration to give the desired product **3l** in good yield (71%). We found that the reactions with *meta*-substituted substrates (**1m** and **1n**) proceeded smoothly to give the ring-expanded products (**3m** and **3n**) in good yields. However, the use of alkenyl- and alkyl boronates (**1o** and **1p**) resulted in complex mixtures. We found that the reaction of boronic acid catechol esters (**1q**) did not provide the desired product **3q**.

Subsequently, we turned our attention to the effect of the boryl groups (Table 3). Various alkyl substituents on the boryl group were tolerated under the present conditions, and the corresponding products (**6a**–**6e**) were obtained in good-to-high yields (74–81%). The trans/cis stereochemistry of the substituents did not affect the reactivity (**6a**, 80% and **6c**, 79%). The reaction of a substrate bearing a cyclopentyl moiety (**5f**) proceeded to afford the corresponding boron-containing bicyclic compound (**6f**) in 73% yield. Ethylene glycol borate **5g** also underwent the borylative ring expansion to give the desired product **6g** in good yield (62%). Notably, the pinacol-containing boronate **5h** afforded the highly stable product **6h** in excellent yield (94%). We also attempted to use acyclic boronates in the oxyboration reaction; however, they did not afford the desired products (see the Supporting Information for details).

Table 2. Substrate Scope of Arylboronates[a]



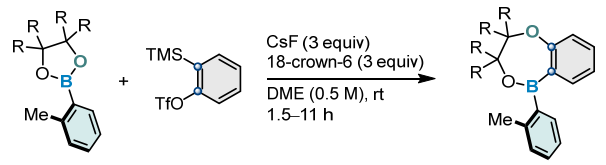
1 0.5 mmol + **2a** 3 equiv → **3** isolated yield (%)



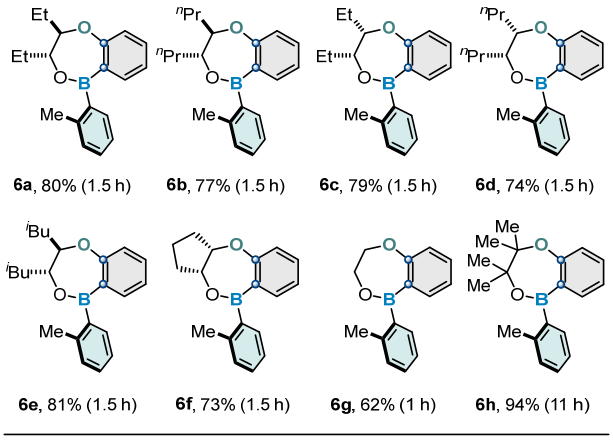
[a]See the Supporting Information for details of the reaction conditions.

Next, other aryne precursors with substitution at the benzene ring were tested (Table 4). An electron-deficient aryne precursor containing fluorine atoms (**2b**) afforded the corresponding oxyboration product **7a** in 55% yield. A good yield (68%) was also obtained when an electron-rich aryne precursor (**2c**) was employed as the substrate to give **7b**. The reaction of a sterically demanding aryne precursor (**2d**) proceeded smoothly under the optimized conditions to give the desired product **7c** in excellent yield (87%). We presume that the steric effect of the methyl substituents on the phenyl ring increased the stability of **7c** under the basic reaction conditions, resulting in the higher yield. Moreover, an unsymmetrical aryne precursor **2e** was applied for the oxyboration reaction of the boronate **1b**, and the regioselective oxyboration of **1b** was achieved to afford **7d** in 50% yield. The structure of **7d** was confirmed via single-crystal X-ray diffraction analysis (Figure 2).

Table 3. Effect of Boron Groups[a]

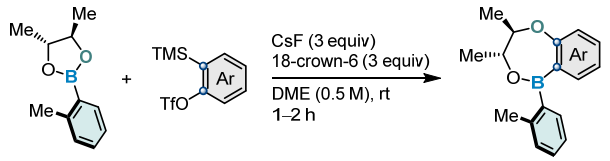


5 0.5 mmol + **2a** 3 equiv → **6** isolated yield (%)

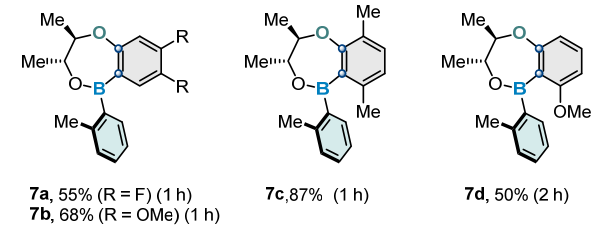


[a]See the Supporting Information for details of the reaction conditions.

Table 4. Reactions with Aryne Precursors with Substitution on the Benzene Ring[a]



1d 0.5 mmol + **2** 3 equiv → **7** isolated yield (%)



[a]See the Supporting Information for details of the reaction conditions.

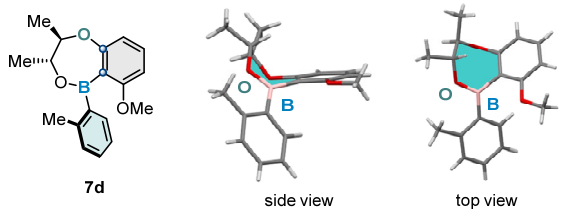
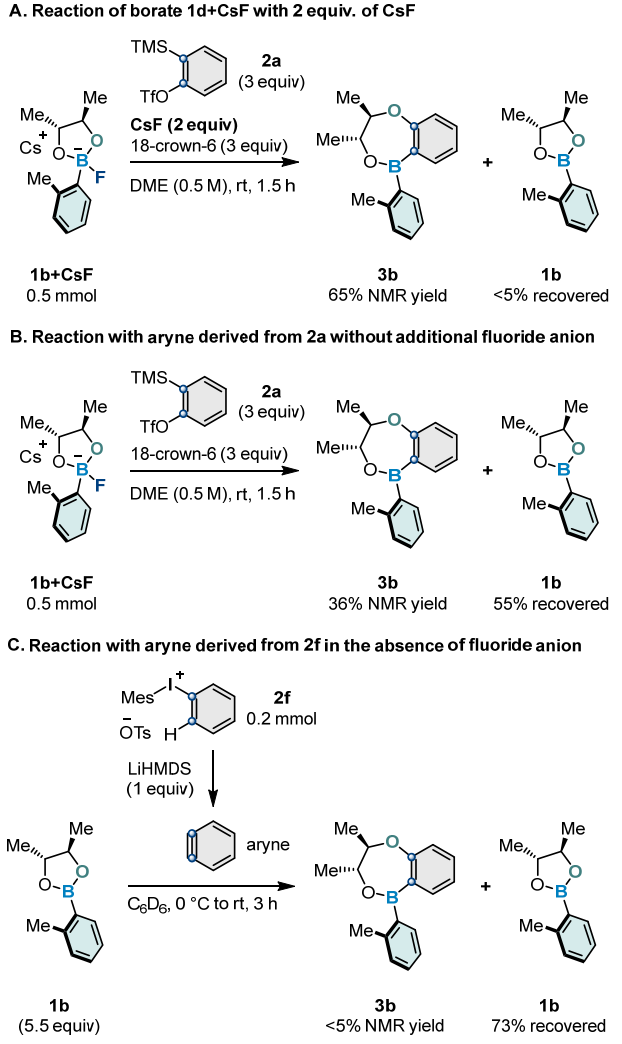


Figure 2. X-ray crystal structures of **7d**.

To obtain mechanistic insight into this transformation, we carried out several control experiments (Scheme 1). We prepared the fluorinated borate of **1b** (**1b+CsF**) and subjected it to oxyboration with CsF (2 equiv) and aryne precursor **2a** (Scheme 1A).[10] The desired product **3b** was obtained in 65% yield, which was comparable to the yield in the reaction using **1b** (Table 2, 75%). Also, we obtained the product **3b** in 46% yield when using alkoxylated borate of **1b** (**1b**+[K(O-*t*-Bu)]) under the same conditions as above (See the Supporting Information for details). Importantly, even in the absence of CsF, the reaction of **1b+CsF** afforded **3b**, albeit in lower yield (36% yield) (Scheme 1B). Importantly, we found that **3b** was not produced and **1b** was recovered (73%) when an aryne intermediate derived from the iodonium salt **2f** and lithium bis(trimethylsilyl)amide (LiHMDS) were used in the reaction (Scheme 1C).[11] ^{11}B NMR analysis of the reaction mixture showed that bulky LiHMDS did not coordinate the boron center of **1b**, and the corresponding boron ate complex did not form during the reaction (See the Supporting Information for details). These results suggested that the fluorinated borate was an active species in the aryne oxyboration, and that the borate can also serve as a fluoride anion source for the activation of the aryne precursor **2a**.

Scheme 1. Mechanistic Studies[a]



[a]See the Supporting Information for details of the reaction conditions.

Next, we conducted density functional theory (DFT) calculations to reveal the mechanistic details of the oxyboration involving borate species and arynes. The reaction pathways were systematically explored using the artificial force-induced reaction (AFIR) method,[12] which utilizes an artificial force to trigger possible reactions for the generation of a reaction network in an automatic manner. The resulting reaction network was analyzed, and all the pathways with accessible barriers were further optimized and summarized, as shown in Figure 3. In the figure, the pathways corresponding to the oxyboration of arynes (i.e., B–O bond cleavage) and the arylboration of arynes (i.e., B–C bond cleavage) are indicated by the colors blue and orange, respectively. In both cases, the first step is the binding of the O atom to the aryne, which subsequently generates an oxonium and a carbanion on the aryne. The formation of the oxonium greatly weakens the B–O bond and thus facilitates the nucleophilic attack of the carbanion on the B atom. As a result, the B–O cleavage pathway (via **TS-1B**) has a relatively low free energy barrier of only +19.6 kJ/mol, while the B–C cleavage pathway (via **TS-1A**) has a barrier of +118.7 kJ/mol. Our calculations thus suggest that the oxyboration is greatly preferred over the arylboration, in good agreement with our experimental observations. Importantly, further calculations using a non-fluorinated arylboronate highlighted the critical role that fluorine-substitution plays. For the non-fluorinated boron, the binding of the O atom to the benzyne is energetically unfavorable (ΔG = +75.3 kJ/mol). Moreover, the subsequent B–O bond cleavage was found to have a barrier of +85.9 kJ/mol, which was much higher than that for the fluorinated borate ($\Delta G^{\ddagger}$ = +19.6 kJ/mol), as no oxonium was formed and the B–O bond was not weakened. Additionally, the AFIR results suggested that the free aryne in the non-fluorinated case may cause other problems (e.g., C–H activations, **TS-3B**). The reason that oxonium formation does not occur in the case of non-fluorinated arylboronate is probably because the boron is only three-coordinate and thus remains highly electron-deficient (i.e., having only 6 electrons). The formation of oxonium in the vicinity of this highly electron-deficient B atom greatly destabilizes the system. Other reasons might include the participation of the lone pair of the oxygen in hyperconjugation with the vacant p orbital of the boron, making the nucleophilic attack on benzyne less favorable. These results strongly suggest the importance of including fluorides in the reaction system. The formation of the borate with CsF would increase the nucleophilicity of the oxygen on the boryl group, facilitating the nucleophilic attack of the oxygen on benzyne to form Int-1 (ΔG = –25.0 kJ/mol), which prevents the problematic formation of free benzyne. As a consequence of the weakened B–O bond, the subsequent ring expansion via B–O bond cleavage would proceed rapidly to form the 7-membered borinic acid cyclic ester.

In conclusion, we have developed the first example of the oxyboration of arynes to produce ring-expanded cyclic borinic acid esters. Experimental and computational studies suggested that this unprecedented borylative ring expansion proceeds via aryne insertion into the B–O bond of the in situ formed borate species. Further studies towards the development of aryne insertion into other boron–heteroatom bonds, other cyclic boronates, or acyclic boronates are currently in progress.

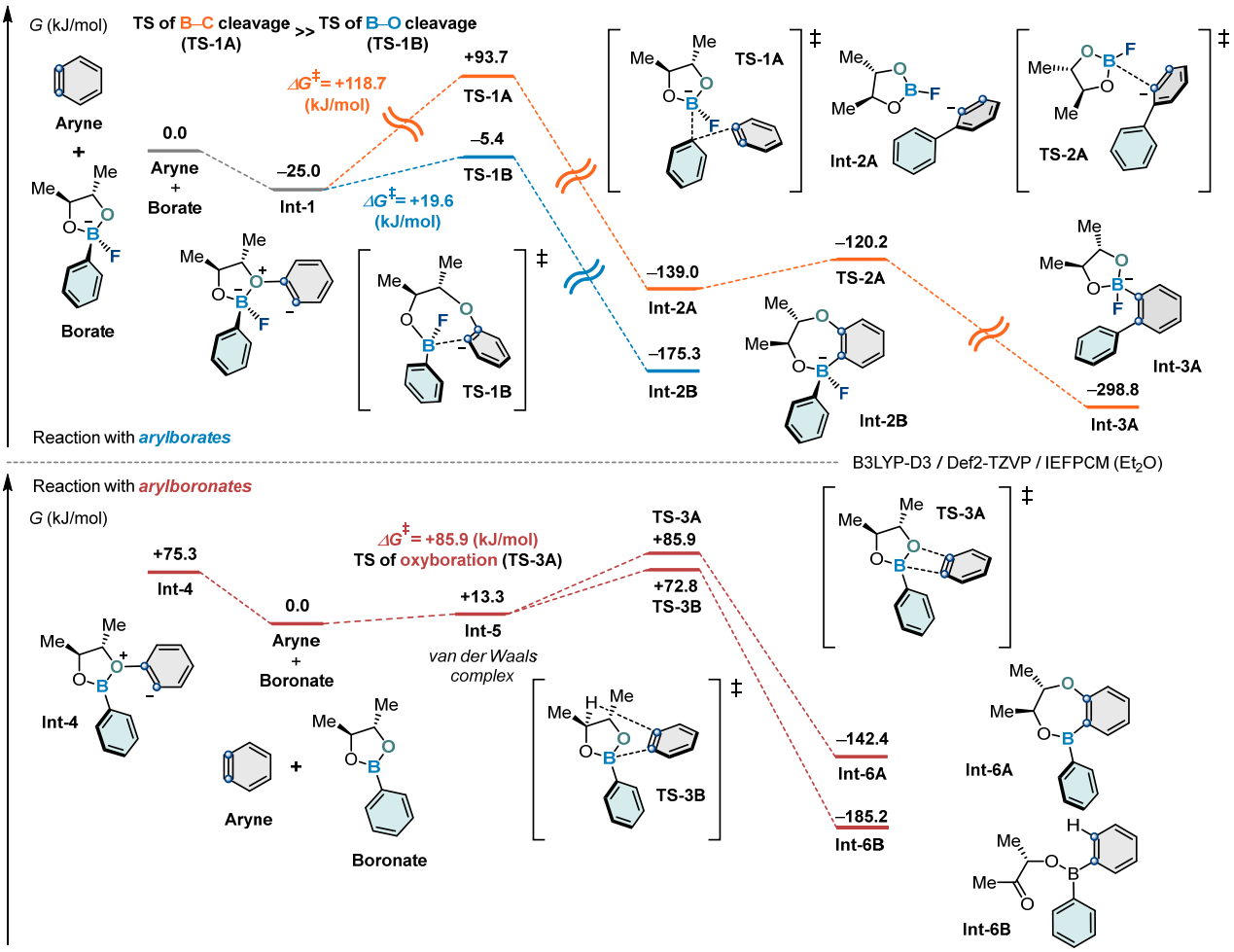


Figure 3. DFT calculations of the oxyboration/arylboration processes at B3LYP-D3/Def2-TZVP//B3LYP-D3/Def2-TZVP level of theory using IEF-PCM solvation model (solvent = Et_2O).

Supporting Information

Experimental procedures, compound characterization data, NMR spectra

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Notes

The authors declare no competing financial interests.

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