Palladium-catalyzed regioselective and stereo-invertive ring-opening borylation of 2-arylaziridines with bis(pinacolato)diboron: experimental and computational studies†

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A palladium catalyzed regioselective borylative ring opening reaction of 2-arylaziridines to give β-amino-β-arylethylborates was developed. The reaction reported herein represents the first example of ring-opening borylation of non-vinylc aziridines and direct borylative C(sp2)–N bond cleavage of neutral organic substrates. NMR studies and density functional theory (DFT) calculations suggested that the active intermediate for the reaction is a PdL2 complex \[L = \text{P}(t\text{-Bu})_2\text{Me}\]. The multi-component artificial force-induced reaction method (MC-AFIR) located the transition states for the regioselectivity-determining aziridine ring opening that proceeds in an S_N2 fashion, and explained the selectivity of the reaction. The full catalytic cycle consists of a selectivity-determining aziridine ring opening (oxidative addition), a proton transfer, phosphine ligand dissociation from the catalyst, boron–boron bond cleavage, and reductive elimination. Water is important to the drive the transmetalation step. The calculated overall mechanism and selectivity are consistent with the experimental results.

Over the past few years, numerous advances have been made in transition metal-catalyzed ring-opening cross coupling of aziridines, where aziridines can be utilized as a non-classical alkyl electrophilic partner [eqn (1)]. In 2012, Doyle reported the first Ni-catalyzed regioselective Negishi alkylation of 2-aryl-N-tosylaziridines that leads to branch-type products via the regioselective cleavage of a benzylic C–N bond. Since this report, several groups including us have developed Ni- and Pd-catalyzed regioselective ring-opening cross coupling reactions of aziridines to form C(sp^2)–C(sp^3) bonds, with the regioselectivity seemingly governed by the aziridine substrate rather than the catalyst [eqn (1)]. Despite the above-mentioned successes in C–C cross couplings, other catalytic ring-opening C–E (E ≠ C) bond forming reactions of aziridines based on a cross-coupling mechanism are also unexploited.

Our latest findings led us to seek new catalytic ring-opening C–E coupling systems of aziridines. Moreover, we became intrigued with the C–B coupling of aziridines to give β-amino-functionalized alkylboronates; alkylboronic acid

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†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data of new compounds, copies of NMR and HPLC charts, and calculation results. See DOI: 10.1039/c6sc01120a
derivatives serve not only as useful building blocks in organic synthesis, but are also biologically interesting motifs in medicinal chemistry.\textsuperscript{11} Only a few precedents in transition-metal-catalyzed borylative substitution of vinylaziridines \textit{via} C(sp\textsuperscript{3})–N bond cleavage have been reported. Szabó and Pineschi disclosed a Pd(n) pincer complex\textsuperscript{44} and a Ni(0)/BINAP\textsuperscript{13} system as catalysts for the borylative ring opening of vinylaziridines with diboron reagents via the cleavage of an allylic C–N bond to give \( \gamma \)-amino alkylboronic acid derivatives (formal \( \text{S}_{\text{N}}\text{2}' \)-type reaction),\textsuperscript{13} respectively [eqn (2)]. Nevertheless, to the best of our knowledge, the catalytic direct displacement of the C(sp\textsuperscript{3})–N bond of aziridines with a C(sp\textsuperscript{3})–B bond on the same carbon (formal \( \text{S}_{\text{N}}\text{2}- \text{type reaction} \) has never been described to date.

We herein report a regioselective ring-opening C–B cross-coupling reaction of 2-aryiaziridines that is realized using a Pd/P(\( \text{t-Bu} \))\textsubscript{2}Me/bpy catalytic system to give \( \gamma \)-amino alkylboronic acid derivatives (formal \( \text{S}_{\text{N}}\text{2}' \)-type reaction),\textsuperscript{13} respectively [eqn (3)]. It should be noted that the oxidative addition occurred at the C–N bond on the terminal carbon (the 3-position of the aziridine). The regiosomer of 3a was not detected in the crude \( ^{1} \text{H} \) NMR spectra, indicating that the regioslectivity in the ring-opening of 1a should be almost perfect. In fact, the regioselective oxidative addition dictated by the interactions between the substrate and the Pd(0) catalyst was supported by theoretical calculations (vide infra). The L : Pd ratio [L = P(\( \text{t-Bu} \))\textsubscript{2}Me] was found to have a significant impact on the product distribution (entries 2 and 3). As the L : Pd ratio was increased from 0.5 (entry 1) to 2 to 3, the yields of 3a decreased to 74% and 45%, respectively (entries 2 and 3). This irregular ratio of L : Pd implies that there might be a complex equilibrium of PdL\textsubscript{0} species generated \textit{in situ}, some of which are selectively active in the catalytic cycle. In fact, this speculation was partly supported with \( ^{31} \text{P} \) NMR experiments and theoretical calculations (vide infra). Addition of electron deficient unsaturated compounds, which can coordinate to metal complexes, is an effective strategy to suppress undesired \( \beta \)-hydride elimination or to accelerate reductive elimination, thereby often leading to better results in alkyl cross coupling reactions.\textsuperscript{21} Indeed, the effect of adding bpy was significantly effective for suppressing the formation of byproduct 6 as well as 5, which was presumably derived from the hydrolysis of 6 with H\textsubscript{2}O (entries 4–7). The effect of the ligands was also significant (entries 8–10). N-heterocyclic carbene (NHC) ligands, SIPr for instance,\textsuperscript{11A} promoted the consumption of 1a and produced undesired products 4 and 5 (entry 8). The results obtained from sterically demanding trialkyphosphine/Pd catalysts (entries 9 and 10) suggest a sluggish oxidative addition step, which is in good agreement with Wolfe's report.\textsuperscript{9} Furthermore, as mentioned in the introduction section, the ring opening borylation disclosed herein does not require the addition of any external base, which is usually used to activate the transmetalation step for the borylative substitution of alkyl halides. In connection with this, addition of water is crucial. Moreover, in the absence of H\textsubscript{2}O, no conversion of 1a was observed (entry 11), while at least 1 equiv. of H\textsubscript{2}O allowed the borylation (Table S11 in the ESI).
Theoretical calculations implied that H2O serves as a proton source (H+) as well as a source of internal base [Pd(OH)] to promote the four-membered transmetalation between B2(pin)2 and Pd (vide infra). To investigate the fate of the other B(pin) moiety of B2(pin)2 in the reaction, the 11B NMR spectrum of the crude product was acquired in benzene-d6. The only peak other than the remaining B2(pin)2 was detected at δ = 22.6 ppm as a slightly broad singlet. The comparison with the reported11B resonances of (pin)B-OCMe3 (10 mol%) and (pin)B-O-B(pin) (10 mol%) suggested that one of the B(pin) moieties of the starting diboron reagent was converted to (pin)B(OH) during the reaction.

Substrate scope and synthetic utility. After establishing the optimized conditions, we explored the substrate scope of the borylative substitution reaction (Table 2). In terms of 2-aryiaziridines, p-, m-, and o-tolyl-substituted aziridines 2b, 2c, and 2d smoothly underwent borylative ring opening in a regioselective manner to give the corresponding β-amido-β-tolylenboronates 3b, 3c, and 3d in good yields. Aziridine bearing a p-fluorophenyl substituent at the 2-position was efficiently borylated, giving the corresponding alkylboronate 3g. Notably, this ring opening borylation was applicable to the arylaziridines bearing a strong electron withdrawing group (NO2, OAc, and CO2Me), and kept these functionalities intact. This highlights an advantage of using neutral conditions.

Furthermore, the borylation was scalable, and 3a was prepared on a gram scale (2.89 g, 72% yield) from 10 mmol of 1a (pS17 of the ESI†). With respect to the limitation of substrate, 2-pyridyl- (1k) and 2-alkylaziridines (1l, 1m, and 1n) were not consumed under the reaction conditions. Furthermore, this reaction is very sensitive to the steric hindrance around the 3-positioned carbon, where oxidative addition to Pd(0) has occurred. For example, 2-methyl-2-phenylaziridine (1o) and trans-2-phenyl-3-methylaziridine (1p) were not consumed at all under the standard conditions. As for the scope of the N-functional groups of aziridines, p-MeOC6H4H2SO2 and p-BuSO2- substituted 2-phenylaziridines smoothly underwent borylation in a regioselective manner (at the 3-position) to produce the corresponding β-amino-β-phenylethylboronates 3r (65%) and 3s (52%), respectively. On the other hand, N-p-nosyl-2-phenylaziridine did not give borylated product (Table S12 in the ESI†).

Regarding the diboron reagents, the use of bis(neopentyl glycolato)diboron gave the corresponding aminoboronate product (3a′) in 39% yield, while the borylation using bis(hexylene

**Table 1 Evaluation of reaction parameters**

| Entry | Difference from the “standard conditions” | Yield (%) | Recovery of 1a (%) |
|-------|------------------------------------------|-----------|-------------------|
| 1     | None                                     | 81        | 13                |
| 2     | Cp(allyl)Pd (1 mol%/P(t-Bu)2Me (2 mol%) | 74        | 11                |
| 3     | Cp(allyl)Pd (1 mol%/P(t-Bu)2Me (3 mol%) | 45        | 10                |
| 4b    | Without bpy                              | 52        | 14                |
| 5b    |                                           | 0         | 10                |
| 6b    |                                           | Trace     | 3                 |
| 7b    |                                           | 64        | 8                 |

* Determined with GC or 1H NMR. b 1 mol% of Cp(allyl)Pd and 2 mol% of ligand were used. c 1 mol% of Cp(allyl)Pd and 0.5 mol% of ligand were used.
glycolato)diboron produced the corresponding borylated products in a low yield as an inseparable diastereomeric mixture, presumably due to the existence of two chiral centers on the benzylc and glycolate carbons (Table S13 in the ESI†).

Borylated product 3a was successfully transformed into β-amino-β-aryl-substituted allyltrifluoroborate 7 in excellent yield, which can serve as a versatile building block to synthesize β-amino-β-arylethanes through Pd-catalyzed cross coupling reactions [eqn (4)].

In order to understand the stereochemical outcome of the secondary stereogenic center of the borylated product and to demonstrate the utility of the alkylboronate, an enantiopure aziridine (R)-1a (99% ee from chiral HPLC analysis) was subjected to the standard reaction conditions (Scheme 1). HPLC analysis of the borylated product 3a revealed that the stereochemical information was completely retained (99% ee, S) through the reaction. This result excludes the possibility of the reaction pathway of oxidative addition/β-hydride elimination/re-insertion of [Pd-H] species leading to 3a, although it cannot perfectly exclude such a pathway. To demonstrate the synthetic utility of the enantiopure β-amino-alkylboronate (S)-3a, the asymmetric synthesis of 3-phenyl-1,2,3,4-tetrahydrosquinozine derivative was conducted (Scheme 1). The tetrahydrosquinozine skeleton is a ubiquitous motif in alkaloidal natural products and constitutes a biologically important aza-heterocycle. Enantiopure alkylboronate (S)-3a was subjected to the Pd-catalyzed Suzuki–Miyaura cross coupling with chlorobenzene to give the optically active 1,2-diphenylamine derivative (S)-8 in 69% yield, while keeping the enantiopurity intact (99% ee, chiral HPLC). The following Pictet–Spengler reaction successfully gave the enantiopure tetrahydrosquinozine product (S)-9 in excellent yield.

**Mechanistic aspect.** To obtain the stereochemical course in the oxidative addition step, a similar synthetic sequence using deuterated aziridine cis-1a-dδ to a substrate was conducted (Scheme 2). The stereochemistry on the terminal carbon (the 3-position) was completely inverted (for details, see the ESI†). This result agrees with the S2 nature of the oxidative addition process of aziridine toward Pd(0) complexes reported by our group and others. Moreover, this stereo-invertive process is supported with computational studies (vide infra).

To identify the Pd species generated by mixing P(r-Bu)2Me and Cp[allyl]Pd, we monitored the 31P{1H} NMR spectra of these mixtures in THF-d8 at 60 °C (Fig. 1). Upon addition of 2 equiv. of Cp(allyl)Pd to L (i.e., L : Pd = 0.5), the sharp resonance corresponding to free L at δ 15.3 ppm (Fig. 1a, lit. δ 12.5 ppm at room temperature in toluene-d8) completely disappeared and three new peaks appeared at δ 37.0 (sharp, strong), 44.7 (broad, weak), and 62.0 (broad, weak) ppm (Fig. 1b). According to the data reported by the Baird group, these peaks are assignable to a dinuclear Pd(0) complex [Pd2L2(μ-Cl)(μ-allyl)] (lit. δ 35.4 ppm at 65 °C in toluene-d8), a bispine phospine Pd(0) complex PdL2 (lit. δ 41.0 ppm at 65 °C in toluene-d8), and an [[(5-Cp)Pd(η1-allyl)L] species ([[(5-Cp)Pd(η1-PhC6H4L)] lit. δ 61.7 ppm at room temperature in toluene-d8], respectively, as illustrated in Fig. 1. After stirring the mixture at 60 °C for 1 h, the broadened weak peak at δ 62.0 ppm corresponding to [[(5-Cp)Pd(η1-allyl)L]...
disappeared, and the intensity of the peak at $\delta$ 44.7 ppm (PdL$_2$) increased as well (the integration ratio of [Pd$_2$L$_2$(μ-Cp)(μ-allyl)] : PdL$_2$ = 3 : 2, Fig. 1c). These peaks were not changed when bpy (10 equiv.) was added (Fig. S1b in the ESI†). This result would indicate that bpy does not coordinate to these Pd species, which was also supported by our computational results (vide infra). Moreover, upon addition of another equivalent of L (i.e., L : Pd = 1), the strongest sharp peak at $\delta$ 37.0 ppm (dinuclear Pd complex) disappeared, and a broad peak around $\delta$ 42.6 ppm appeared (Fig. 1d). Furthermore, addition of one more equivalent of L (L : Pd = 2) gave a significantly broadened peak ($\delta$ ~ 30 ppm, Fig. S1a in the ESI†), indicating significant exchange among several PdL$_n$ species. Our observations could indicate that PdL$_2$ undergoes rapid exchange with PdL$_n$ in THF–d$_8$ when the L : Pd ratio is greater than 0.5. Therefore, the same would be the case with the real reaction system.

Based on the NMR experiments, [Pd$_2$L$_2$(μ-Cp)(μ-allyl)] or PdL$_2$ would be the catalytically active Pd species (i.e., the starting point of the catalytic cycle). To determine which is the active species in the catalytic reaction, both complexes were generated separately as the sole components according to Baird’s conditions (i.e., 1 : 1 and 2 : 1 mixtures of L and Cp(allyl)Pd) were mixed in toluene–d$_8$ and stirred at 77 °C for 1 h, and the resulting Pd complexes were used as a catalyst in the borylation reaction in toluene (Schemes 3). As a result, when the dinuclear Pd(i) complex was found to be totally inert for the borylation reaction, the bisphosphine complex Pd(0)L$_2$ gave almost the same result as the real reaction system. Therefore, we conclude that Pd(0)L$_2$ would be the starting active species in the catalytic cycle, and this conclusion was strongly supported by theoretical methods (vide infra).

Computational part

Computational methods. Geometry optimizations were performed with the B3LYP-D3 31–36 functional as implemented in the Gaussian09 program. 37 The polarizable continuum model (PCM) was used as the implicit solvent model with a dielectric constant ($\varepsilon$) of 2.3714. 38 The SDD basis set and associated effective core potential were applied for Pd, 39,40 and 6–31G(d) basis sets were used for the other atoms (BS1). 41–44 All stationary points, local minima (LMs) or transition states (TSSs), were optimized without any constraint. Vibrational frequency calculations were performed to confirm the nature of the stationary points. Pseudo-IRC calculations were performed to confirm the connectivity between the TSSs and LMs. The final potential energies of the optimized structures were calculated as single-point energies on the optimized structures, where a SDD basis set was used for Pd, and cc-pVTZ basis sets were used for the other atoms (BS2). 45–47 In the results section, we report both the relative Gibbs free energy ($\Delta G$) at 298.15 K and 1 atm and the relative electronic energy with the zero point energy correction ($\Delta E$).

The aziridine ring opening step of the mechanism takes place via many different TSSs, and therefore a proper sampling is very important. An automatic exploration of all important reaction pathways was accomplished using the multi-component artificial force-induced reaction (MC-AFIR) method, as implemented in the global reaction route mapping (GRRM) strategy. 48–50 An artificial force parameter ($\gamma$) of 300 kJ mol$^{-1}$ was applied, and this is suitable for finding TSSs within 300 kJ mol$^{-1}$. The MC-AFIR calculations were terminated when no new AFIR LM was found for 10 consecutive AFIR paths (NFault = 10). In AFIR calculations, the energy and derivatives were obtained using the ONIOM(B3LYP-D3:PM6-D3) method. 51–57 Partitioning of the molecular system is shown in Fig. 2a. A model catalyst was used for MC-AFIR calculations (Fig. 2). SDD basis sets and the associated effective core potentials were used for palladium, and 3–21G basis sets (BS3) were applied for the high-level region of ONIOM calculations. 58–60 All AFIR paths were inspected and approximate TSSs were identified. Then, the real phosphate ligand was introduced to all approximate TSSs, and the TS structures were fully optimized (without artificial force) with B3LYP-D3/BS1 method. A Boltzmann distribution of the transition states was used to calculate the regioselectivity.
Energy decomposition analysis (EDA)\textsuperscript{61,62} was performed for the key TSs leading to the desired and undesired products. B3LYP-D3/BS2 level and PCM were used for the EDA. In this analysis, a TS structure was divided into A (catalyst) and B (substrate) (Fig. 3). INT\textsubscript{AB} is the interaction energy between A and B at their optimized TS structure. The deformation energy (DEF) is the energy of A and B at the optimized TS, relative to the optimized structures of isolated A and B (denoted as A\textsubscript{0} and B\textsubscript{0}). The energy difference (Δ\textsubscript{DEF}) between the optimized transition states, (A\textsubscript{B1}) and (A\textsubscript{B2}), is the sum of the internal energy difference (ΔINT\textsubscript{AB}) and the deformation energy difference (ΔDEF).

Thermodynamically stable complexes in solution. Our starting point was to explore thermodynamically stable complexes in solution. First, we checked the relative stability of PdL, PdL\textsubscript{2}, PdL\textsubscript{3}, and PdL\textsubscript{4} complexes [L = P(t-Bu)\textsubscript{2}Me]. Among them, the PdL\textsubscript{2} complex (I) is the most stable complex, and this is in agreement with our NMR studies. The PdL\textsubscript{3} and PdL complexes are 3.4 and 26.0 kcal mol\textsuperscript{-1} higher in energy, respectively. Despite several attempts, no PdL\textsubscript{4} complex was found, as one of the four ligands (L) always dissociated due to steric repulsion. We used PdL\textsubscript{2} (I) as a candidate to generate other possible complexes in solution. Moreover, the two vacant sites of the PdL\textsubscript{2} complex, A and B, can be filled by the potential ligands in solution, specifically H\textsubscript{2}O, solvent (denoted as Sol), and additive (denoted as bpy). Table 3 summarizes the possible complexes and energies relative to the PdL\textsubscript{2} complex (I).

 Starting from the PdL\textsubscript{2} complex (I), coordination of one H\textsubscript{2}O, L, and bpy on I gives rise to PdL\textsubscript{2}(H\textsubscript{2}O) (Iw, −0.5 kcal mol\textsuperscript{-1}), PdL\textsubscript{3} (3.4 kcal mol\textsuperscript{-1}), and PdL\textsubscript{2}(bpy) (4.0 kcal mol\textsuperscript{-1}) complexes, respectively. Among the three-coordinate complexes, Iw is the thermodynamically most stable complex, and is only 0.5 kcal mol\textsuperscript{-1} more stable than I. Therefore, both I and Iw can be formed in solution. In Iw, an H\textsubscript{2}O molecule coordinates to the metal with one of the two hydrogen atoms. It is important to note that the additive (bpy) can coordinate to the metal, and the resulting complex, PdL\textsubscript{2}(bpy), is, however, 4.5 kcal mol\textsuperscript{-1} higher than the most stable complex, Iw. All four-coordinate complexes found in the calculations, PdL\textsubscript{2}(bpy)(H\textsubscript{2}O) (2.8 kcal mol\textsuperscript{-1}), PdL\textsubscript{3}(H\textsubscript{2}O) (4.7 kcal mol\textsuperscript{-1}), and PdL\textsubscript{3}(H\textsubscript{2}O) (7.9 kcal mol\textsuperscript{-1}) are relatively higher in energy. Coordination of solvent (Sol) is not possible due to steric repulsion between the bulky groups of the solvent molecules (MTBE) and I. We concluded that the thermodynamically most stable complexes in solution are Iw and I. The general rules that lead to the formation of the thermodynamically stable complexes in solution are: (1) coordination of two ligands on PdL\textsubscript{2}, which gives rise to four-coordinate complexes, is not favorable; (2) in terms of making three-coordinate complexes, the binding preference of the third ligand follows the order H\textsubscript{2}O > L > bpy; (3) solvent MTBE would not coordinate to the PdL\textsubscript{2} complex due to steric repulsion; (4) coordination of the additive (bpy) is not favorable. According to Table 3, additive coordination on PdL\textsubscript{2} is not favorable as the subsequent complex PdL\textsubscript{2}(bpy) is 4.0 kcal mol\textsuperscript{-1} higher than PdL\textsubscript{2}, while the PdL\textsubscript{3}(bpy) complex is not stable. At the same time, it is important to note that aziridine binding on PdL\textsubscript{2} is relatively easier (vide infra), and the corresponding adduct is only 2.6 kcal mol\textsuperscript{-1} higher than PdL\textsubscript{2}. Therefore, the additive would not coordinate to the PdL\textsubscript{2} complex before the aziridine substrate binding. In our present mechanistic study, we do not consider the role of the additive in

Table 3 Possible complexes Pd(L)\textsubscript{2}(A)(B) [L = P(t-Bu)\textsubscript{2}Me, Sol = MTBE] and their relative Δ\textsubscript{G} (Δ\textsubscript{E} in parentheses) in kcal mol\textsuperscript{-1}.

| A | Empty | H\textsubscript{2}O | bpy | L | Sol |
|---|---|---|---|---|---|
| Empty | 0.0, (0.0) | −0.5, (−8.2) | 4.0, (−7.4) | 3.4, (−10.9) | X, (Sol) |
| H\textsubscript{2}O | − | 4.7, (−14.0) | 2.8, (−17.9) | 7.9, (−15.1) | X, (Sol) |
| bpy | − | − | X, (bpy) | X, (L) | X, (Sol) |
| L | − | − | − | X, (L) | X, (Sol) |
| Sol | − | − | − | − | X, (Sol) |

\textsuperscript{a} The symbol “X” indicates that the ligand in parentheses dissociates upon structure optimization.
the mechanism because the reaction works even in the absence of additive (Table 1, entry 4).

Aziridine ring-opening step. Our next task was the exploration of the aziridine ring-opening step. For this purpose, we used the most stable I and lw complexes as the active intermediates for the reaction, and 2-phenyl-N-tosyl-aziridine (I) was used as the substrate. Therefore, two independent MC-AFIR calculations, with and without an explicit water molecule, were performed as shown in Fig. 2c. The fully optimized TS structures, 73 TSs from lw and 33 TSs from I, were categorized into 15 groups: TSI-IIa through TSI-IIg from lw, and TSI-IIg through TSI-IIo from I, based on structural similarities (Fig. 4). The lowest energy TS of each group, their relative energies, and their existence probability are depicted in Table 4 (see Table S14 in the ESI† for a full description of all the TSs).

Among the calculated TSs (Table 4), TSI-t-lw (12.6 kcal mol\(^{-1}\)) which belongs to the TSI-IIg group is the lowest energy TS of this step. In this TS, the aziridine ring opening takes place at the less hindered carbon in an S\(\text{sp}^2\) fashion, leading to the desired product forming. The same product can be obtained through TSII-t-lw (12.9 kcal mol\(^{-1}\)), TSIII-t-lw (13.3 kcal mol\(^{-1}\)), TSIV-t-lw (13.4 kcal mol\(^{-1}\)), TSVI-t-lw (13.5 kcal mol\(^{-1}\)), TSII-t-l (13.6 kcal mol\(^{-1}\)), TSIII-t-l (13.7 kcal mol\(^{-1}\)), and TSIV-t-l (13.9 kcal mol\(^{-1}\)). On the other hand, at TSI-b-lw (13.2 kcal mol\(^{-1}\)) of the group TSI-IIb, aziridine ring opening occurs at the hindered carbon (the 2-position), and this is the lowest TS leading to the undesired product. Based on a Boltzmann distribution over the calculated TSs, the regioselectivity is calculated to be 89 : 11, which is qualitatively in agreement with the experimental results (99 : 1).

In the calculated TSs for TSI-IIb (31.5 kcal mol\(^{-1}\)), TSI-IIIb (30.9 kcal mol\(^{-1}\)), and TSI-IIb (24.7 kcal mol\(^{-1}\)), aziridine ring opening occurs at the less hindered carbon (Fig. 4). However, these TSs are relatively higher in energy due to the fact that the \(N\)-p-toluenesulfonyl and 2-phenyl substituents of the substrate are much closer to the bulky groups of lw or I. Similarly, TSs in the group of TSI-IIc (31.3 kcal mol\(^{-1}\)), TSI-IIc (31.9 kcal mol\(^{-1}\)), and TSI-IIc (28.1 kcal mol\(^{-1}\)) show high energy barriers, where aziridine ring opening occurs at the hindered carbon. TSs in the group of TSI-IIa (31.8 kcal mol\(^{-1}\)), TSI-IIa (31.8 kcal mol\(^{-1}\)), and TSI-IIa (28.1 kcal mol\(^{-1}\)) represent the aziridine ring opening through the carbon–carbon bond, which is, however, not possible due to very large reaction barriers. Furthermore, we checked the effect of \(\text{H}_2\text{O}\) molecules on aziridine ring opening. Starting from the lowest energy TS for this step (TSI-t-lw, 12.6 kcal mol\(^{-1}\)), up to four \(\text{H}_2\text{O}\) molecules were introduced, and the corresponding TSs were calculated. The calculated \(\Delta G\) of TSI-t-lw with one \(\text{H}_2\text{O}\) molecule (TSI-t-lw-w1, 16.1 kcal mol\(^{-1}\)), two \(\text{H}_2\text{O}\) molecules (TSI-t-lw-w2, 14.3 kcal mol\(^{-1}\)), three \(\text{H}_2\text{O}\) molecules (TSI-t-lw-w3, 15.6 kcal mol\(^{-1}\)), and four \(\text{H}_2\text{O}\) molecules (TSI-t-lw-w4, 16.4 kcal mol\(^{-1}\)) suggested that explicit \(\text{H}_2\text{O}\) molecules in the system would not stabilize the TSI-t-lw.

TSI-t-lw is a major contributor to the aziridine ring opening at the less hindered carbon, while TSI-b-lw is the lowest TS for aziridine ring opening at the hindered carbon (Fig. 5). The calculated Gibbs free energy difference between TSI-t-lw and TSI-b-lw is 0.6 kcal mol\(^{-1}\), while the potential energy difference is 3.2 kcal mol\(^{-1}\). When we do not consider the zero point energy corrections, the potential energy difference is 3.5 kcal mol\(^{-1}\), and we have used this value for the EDA. According to the EDA (Table 5), the origin of this difference comes from \(\Delta\text{INT}_{\text{E}}\) (3.9 kcal mol\(^{-1}\), indicating better interactions at TSI-t-lw. This is due to the fact that the aziridine substrate can approach closer to the metal in TSI-t-lw (Pd–C = 2.47 Å) (vs. Pd–C = 2.61 Å at TSI-b-lw) (Fig. 5) than in TSI-b-lw due to the lower steric repulsion.

The free energy profile for the early stages of the mechanism is shown in Fig. 6. The reaction starts from the thermodynamically most stable complex, lw. Therefore, we report energies relative to lw. Then, aziridine coordination on I leads to a complex II (2.6 kcal mol\(^{-1}\)), and the subsequent aziridine ring opening occurs through TSI-t-lw (TSII–III, 12.6 kcal mol\(^{-1}\)). Aziridine ring opening is also possible from lw (not shown in Fig. 6) with an overall barrier of 13.3 kcal mol\(^{-1}\) (TSIV-t-lw), which is, however, 0.7 kcal mol\(^{-1}\) higher than TSI-t-lw. Beyond TSI-t-lw, an intermediate, III (8.4 kcal mol\(^{-1}\)) is formed.

Proton transfer to anionic amine. The next step of the mechanism would be a proton transfer from \(\text{H}_2\text{O}\) molecules in solution to the anionic nitrogen atom in the water-coordinated intermediate III. This proton transfer process takes place smoothly from IIIw4 (0.3 kcal mol\(^{-1}\)), which is 8.1 kcal mol\(^{-1}\) more stable than III. Furthermore, three \(\text{H}_2\text{O}\) molecules make a hydrogen bonding network starting from the anionic amine that is connected to the metal through a water oxygen coordination. The TS for this proton transfer process is 12.0 kcal mol\(^{-1}\) (TSIII–IVw3). Proton transfer is also possible from the analogous intermediate with four \(\text{H}_2\text{O}\) molecules, IIIw5 (11.3 kcal mol\(^{-1}\)), and the subsequent transition state is, however, 1.3 kcal mol\(^{-1}\) higher than TSIII–IVw5 (not shown in Fig. 6). We were unable to locate TSs starting from the analogous

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**Fig. 4** Groups of transition states for the aziridine ring opening, starting from lw (TSI-IIa through TSI-IIg) and I (TSI-IIa through TSI-IIo), and energies of the lowest energy TS of each group relative to the PdL2(H2O) (lw) complex (Ar = p-tolyl; L = P(t-Bu)2Me). ΔG values are in plain text, and ΔE values are in italics.
Table 4  Low energy TSs for the aziridine ring opening starting from I and Iw

| TS       | Group/regioselectivity | △G   | △G (△E) | Existence probability (%) |
|----------|------------------------|------|---------|--------------------------|
| TS1-t-lw | K/terminal             | 0.0  | 12.6 (6.0) | 27.6                     |
| TS2-t-lw | K/terminal             | 0.3  | 12.9 (5.4) | 17.9                     |
| TS3-b-lw | L/benzyl               | 0.6  | 13.2 (9.2) | 10.0                     |
| TS4-t-l  | A/terminal             | 0.7  | 13.3 (5.9) | 9.6                      |
| TS5-t-lw | K/terminal             | 0.8  | 13.4 (6.9) | 7.1                      |
| TS6-t-l  | B/terminal             | 0.9  | 13.5 (7.7) | 6.1                      |
| TS7-t-l  | B/terminal             | 1.0  | 13.6 (7.7) | 4.8                      |
| TS8-t-l  | A/terminal             | 1.1  | 13.7 (6.8) | 4.6                      |
| TS9-t-lw | K/terminal             | 1.3  | 13.9 (7.6) | 2.9                      |
| TS10-t-lw| K/terminal             | 2.3  | 14.9 (7.6) | 0.6                      |
| TS11-b-l | D/benzyl               | 2.4  | 15.0 (7.6) | 0.5                      |
| TS12-t-lw| K/terminal             | 2.6  | 15.2 (–1.2) | 0.4                     |
| TS13-t-lw| K/terminal             | 2.6  | 15.2 (8.3) | 0.3                      |
| TS14-t-lw| K/terminal             | 2.7  | 15.3 (7.3) | 0.3                      |
| TS15-t-lw| K/terminal             | 3.3  | 15.9 (9.0) | 0.1                      |
| TS16-t-lw| K/terminal             | 3.5  | 16.1 (8.3) | 0.1                      |
| TS17-t-lw| K/terminal             | 3.6  | 16.2 (7.9) | 0.1                      |
| TS18-t-l  | B/terminal             | 3.7  | 16.3 (9.2) | 0.1                      |
| TS19-t-l  | A/terminal             | 3.7  | 16.3 (–0.8) | 0.1                     |

* △G and △E values are indicated in kcal mol⁻¹, relative to Iw. “t” and “b” indicate the terminal (3-position) and benzyl carbons (2-position), respectively.

intermediates with two H₂O molecules (IIIw₂, 1.1 kcal mol⁻¹) and one H₂O molecule (IIΙw₁, 2.3 kcal mol⁻¹), where the potential energy surface for the proton transfer processes was found to be repulsive (Fig. S2 and S3†). In IIIw₃, three water molecules form a complete head-to-tail chain between the anionic amines and Pd centres. As a result, the synchronous three proton transfer via TSIII–IVw₃ takes place and gives a protonated N, two H₂O molecules, and a hydroxyl group bound to the metal center. Based on our analysis, we conclude that three H₂O molecules are required for the proton transfer process, leading to an intermediate IVw₃ (2.0 kcal mol⁻¹). Once the proton is transferred, the chain of water molecules is no longer required, and the corresponding intermediate without H₂O, IV, is 2.7 kcal mol⁻¹ more stable than IVw₃.

B–B bond coordination and cleavage. Now, the B(pin)–B(pin) species binds to IV and the subsequent intermediate V (0.5 kcal mol⁻¹) is formed. Starting from V, inner-sphere B–B bond cleavage does not take place due to steric repulsion between the bulky alkyl groups in L and B(pin)–B(pin). One of the two phosphine ligands of the catalyst must dissociate, and the resulting intermediate, VI, is only 1.8 kcal mol⁻¹ higher than V. Then, B–B bond cleavage takes place in an inner sphere fashion with a barrier of 10.8 kcal mol⁻¹ (TsvI–VII), giving rise to VII (–2.1 kcal mol⁻¹). We have checked the possibility of ligand exchange between the (pin)B–OH and a stronger phosphine ligand L on intermediate VII, and the resulting complex, VIII, is 24.5 kcal mol⁻¹ more stable than VII.

cis-trans isomerization and reductive elimination. The energy profiles for the final stages of the reaction are shown in Fig. 7. In both the intermediates VII and VIII, B(pin) is trans to the alkyl group derived from the aziridine substrate, and therefore cis/trans isomerization must take place before the reductive elimination. The cis isomer VIIIc is 2.5 kcal mol⁻¹ more stable than the trans isomer VIII. This step may occur through ligand dissociation processes. Since we expect this isomerization to be a low energy process, we did not study this in depth. The subsequent reductive elimination from VIIIc occurs through a barrier of 0.1 kcal mol⁻¹ (TsvIIC–IX). In the resulting intermediate IX, the product (P) is still at the metal

![Fig. 5 Lowest energy TSs leading to the desired product (TS1-t-lw) and undesired product (TS3-b-lw). Bond lengths (red) are in Å and bond angles (green) are in degrees.](image)
coordination sphere, and \( \mathbf{P} \) can be removed easily to recover the active form of the catalyst, \( \text{PdL}_2 \) (I), for the next catalytic cycle. Similarly, the formation of the \( \text{cis} \) isomer of \( \text{VII} \), the less stable intermediate \( \text{VII}_0 \) (19.4 kcal mol\(^{-1}\)), and the subsequent reductive elimination can occur easily with a barrier of 5.7 kcal mol\(^{-1}\) (TS\( \text{VII}_0 \)–X). Then, a phosphine ligand (L) can coordinate to the resulting intermediate X, which ultimately yields the product, \( \mathbf{P} \).

**Side product formation**

Under the optimized reaction conditions, imine 6 is formed as a side product (Table 1). We have explored the mechanism for the side reaction as shown in Fig. S4 in the ESI.†

**Catalytic cycle**

Putting together the present results from the experimental and theoretical studies, the proposed catalytic cycle for the borylation is shown in Fig. 8 (black cycle). \( \text{Pd}(0)L_2 \) is generated through the sequential reduction of \( \text{Cp(allyl)Pd} \). Then, \( \text{Pd}(0)L_2 \) attacks the less hindered carbon of the aziridine in an \( \text{Sn}_2 \) fashion (a) to give a stereo-inverted oxidative adduct. A hydrogen bonded chain of \( \text{H}_2\text{O} \) molecules plays two roles in the following steps: (i) as a proton source to quench \( \text{TSN} \) (b) and (ii) as an internal base to form the \([\text{Pd(OH)}]\) species. This intermediate activates the \( \text{B–B} \) bond of \( \text{B}_2(\text{pin})_2 \) (c). The dissociation of a phosphine ligand (d) facilitates the transmetalation (e). The free phosphine ligand participates in the catalytic cycle again to form the (alkyl)\( \text{PdL}_2\text{B}(\text{pin}) \) complex (f). The \( \text{trans-cis} \) isomerization (g) followed by reductive elimination (h) leads to the \( \text{C–B} \) cross-coupled product and the completion of the catalytic cycle. A side reaction may occur after the oxidation addition (brown cycle): the oxidative adduct of aziridine undergoes hydrogen transfer (i) followed by reductive elimination (j) to produce an imine byproduct. Our computational study suggests that the aziridine ring-opening step for substrate 1a has barriers of 12.6 kcal mol\(^{-1}\) (terminal position) and
13.2 kcal mol\(^{-1}\) (benzylic position) (Table 4). For an alkyl aziridine, in particular 11, the aziridine ring-opening step showed barriers of 15.4 kcal mol\(^{-1}\) (2-position) and 16.3 kcal mol\(^{-1}\) (3-position). In the absence of the aryl group, the aziridine ring opening of 11 is 2.8 kcal mol\(^{-1}\) higher than 1, where the reaction is difficult with 11. This is qualitatively in agreement with our experimental results, where the reaction does not proceed with 11.

**Conclusions**

In conclusion, we have developed a Pd-catalyzed regioselective borylative ring opening reaction of 2-arylaziridines to give \(\beta\)-aminoalkylboronates that are otherwise difficult to synthesize using existing methodologies. Importantly, the regioselectivity of the ring opening is controlled by the interactions between the catalyst and the substrate. The \(\text{SN}_2\) nature of the oxidative addition of aziridine was verified using deuterated aziridine and computational studies. Furthermore, the borylative reaction is applicable under neutral conditions that allow for high functional compatibility. The mechanism of the full catalytic cycle was proposed using DFT and MC-AFIR methods. The aziridine ring opening is initiated by the active species PdL\(_2\). TSSs were systematically determined for the selectivity-determining aziridine ring opening step, and the calculations reasonably reproduced the experimental regioselectivity. The next step of the mechanism is a proton transfer that is facilitated by a H\(_2\)O hydrogen bond chain. The resulting Pd-hydroxo species activates the transmetalation step, where inner sphere boron–boron bond cleavage occurs, and leads to the final reductive elimination step. These experimental and theoretical findings open up an avenue to the further development of transition metal-catalyzed ring-opening C–E bond forming cross couplings of aziridines.

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