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Synthesis of Alkenylboronates from *N*-Tosylhydrazones through Palladium-Catalyzed Carbene Migratory Insertion

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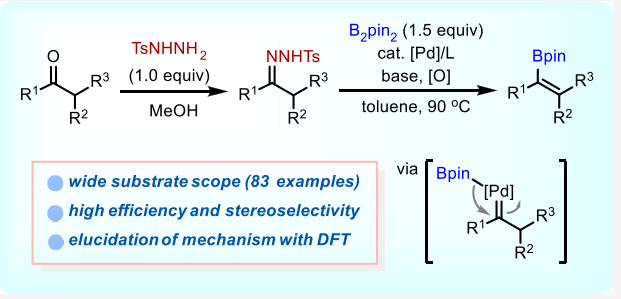
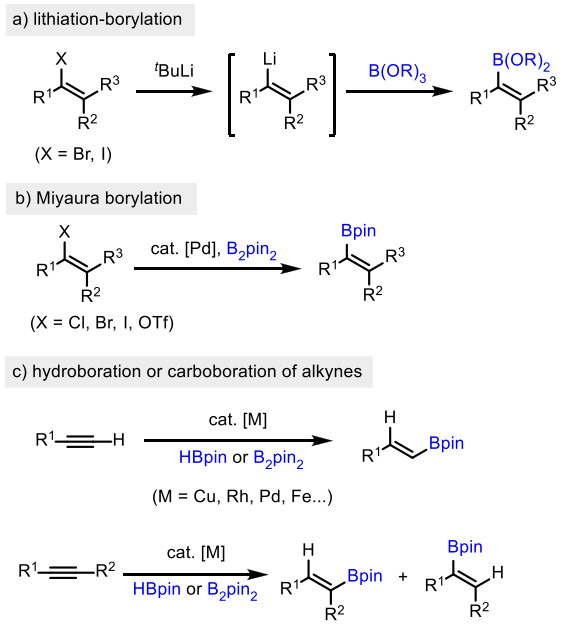
ABSTRACT: The palladium-catalyzed oxidative borylation reaction of *N*-tosylhydrazones has been developed. The reaction features mild conditions, broad substrate scope, and good functional group tolerance. It thus represents a highly efficient and practical method for the synthesis of di-, tri-, and tetrasubstituted alkenylboronates from readily available *N*-tosylhydrazones. One-pot Suzuki coupling and other transformations highlight the synthetic utility of the approach. DFT calculations have revealed that palladium-carbene formation and subsequent boryl migratory insertion are the key steps in the catalytic cycle. The high stereoselectivity observed in the formation of trisubstituted alkenylboronates has been explained by distortion-interaction analysis and NBO analysis.



INTRODUCTION

Organoboron compounds are valuable reagents due to their relative stability, low toxicity, and broad applications in organic synthesis, material sciences, and pharmaceuticals.[1] As one of the important classes of organoboron compounds, alkenylboronates are versatile building blocks for the synthesis of stereodefined alkenyl compounds through Suzuki−Miyaura cross-coupling,[2−4] Zweifel olefination,[5] Petasis reaction,[6] and other functional-group transformations.[7,8] In addition, alkenylboronates have also been applied to prepare alkylboronates through hydrofunctionalizations,[9−14] difunctionalizations,[15−18] conjunctive cross-couplings,[19−21] radical processes,[22,23] and cycloadditions.[24] Owing to the importance of alkenylboronates, the development of efficient methods for their preparation is of great significance. Several approaches have been established for the synthesis of alkenylboronates to date.[25] Some alkenylboronates can be prepared from the corresponding alkenyl halides or triflates through lithiation followed by treatment with trialkylborates (Scheme 1a)[26] or palladium-catalyzed Miyaura borylation (Scheme 1b).[27] However, most of the alkenyl halides or triflates are not commercially available and should be prepared under strongly acidic or basic conditions.[28−30] The hydroboration or carboboration of alkynes is another common method, which employ expensive and less abundant alkynes as the starting materials (Scheme 1c).[31,32] Whereas 1,2-disubstituted alkenylboronates can be readily accessed through anti-Markovnikov hydroboration of terminal alkynes,[33−38] only few examples have been reported for the synthesis of 1,1-disubstituted alkenylboronates with Markovnikov selectivity.[39,40] Moreover, hydroboration or carboboration of nonsymmetric internal alkynes toward tri- or tetrasubstituted alkenylboronates often

Scheme 1. Established Methods for the Synthesis of Alkenylboronates



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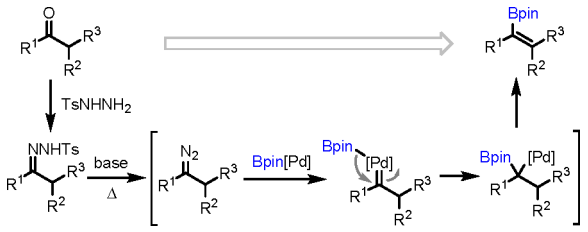
bears poor regioselectivities to deliver a mixture of regioisomers.[41−44] Other methods for the synthesis of alkenylboronates, including alkene cross-metathesis,[45,46] alkene dehydrogenative borylation,[47−50] and boron-Wittig reaction,[51−53] also have their limitations in substrate scope. Consequently, further development of highly efficient and selective reactions for the diverse synthesis of alkenylboronates is still in great demand.

Ketones are cheap and abundant building blocks in organic synthesis that show versatile reactivity.[54] Among them, the conversion of ketones into *N*-tosylhydrazones via simple condensation represents an important application. *N*-Tosylhydrazones are useful synthons that can undergo classic Shapiro reaction or Bamford−Steven reaction to prepare alkenes and diazo compounds.[55,56] Recently, *N*-tosylhydrazones have also been used as the coupling partners in transition-metal-catalyzed cross-coupling reactions.[57−60] In these reactions, diazo compounds are generated *in situ* and then react with organometallic species to form a metal carbene, followed by carbene migratory insertion and subsequent transformations. With suitable transition-metal catalysts and coupling partners, various coupling products can be generated. Our group and others have developed a series of cross-coupling reactions between *N*-tosylhydrazones and various carbon nucleophiles or electrophiles, which represent a type of powerful synthetic methods for C−C bond formations.[61−66] However, heteroatomic nucleophiles or electrophiles are still less explored for carbene-based cross-coupling to form C−X bonds.[67,68] As a continuation of our interest in carbene-based coupling reactions, we envisioned that diboron compounds may become carbene coupling partners under palladium catalysis, because boron−palladium species can be readily generated through transmetalation under mild conditions.[69] We expected that the boron−palladium species could participate in carbene migratory insertion followed by β-H elimination, which may provide a new approach for the synthesis of alkenylboronates (Scheme 2).[70] Herein, we reported our detailed study on the

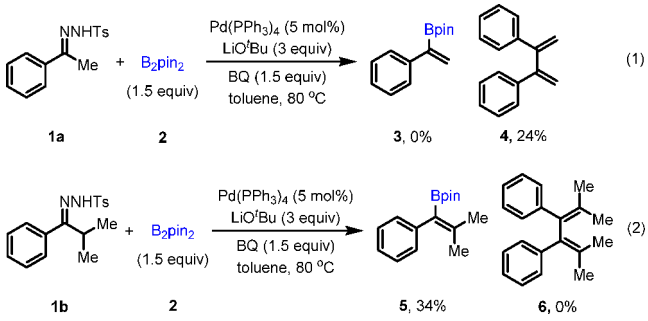
Scheme 2. Synthesis of Alkenylboronates from Ketones through Palladium-Catalyzed Carbene Migratory Insertion



palladium-catalyzed oxidative cross-coupling reaction between *N*-tosylhydrazones and diboron compounds. This reaction provides an efficient method for diverse synthesis of di-, tri-, and tetrasubstituted alkenylboronates from easily available ketones.[71−73] Computational studies substantiate the reaction pathway involving palladium carbene formation and migratory insertion of the boron group.

RESULTS AND DISCUSSION

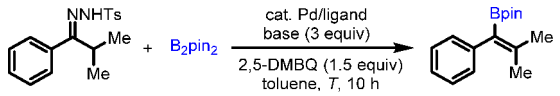
At the outset, we investigated this transformation by employing *N*-tosylhydrazone **1a** derived from acetophenone as the substrate and bis(pinacolato)diboron **2** as the borylation reagent. The reaction was carried out in toluene at 80 °C with $Pd(PPh_3)_4$ as the catalyst, LiO^tBu as the base, and *p*-benzoquinone (BQ) as the oxidant. However, we could not observe any desired alkenylboronate **3**. Carefully analyzing the reaction, we found that a considerable amount of product **4** was generated in this system, which might come from the oxidative dimerization of *N*-tosylhydrazone **1a** (eq 1). To



inhibit this side reaction, we used a sterically bulky *N*-tosylhydrazone **1b** as the substrate to attempt this reaction under the same conditions. Gratifyingly, the desired alkenylboronate **5** could be obtained in 34% yield and the oxidative dimerization was completely inhibited (eq 2).

Encouraged by this result, we further optimized the reaction conditions. A series of oxidants were first examined, and it was observed that 2,5-DMBQ could afford slightly improved yields for the reaction (Table 1, entries 1−3). Then the catalyst was screened. We found that $Pd(OAc)_2$ with PPh_3 as the ligand gave a better result (entry 4). Other solvents such as dioxane and MeCN were also tested, but only a trace amount of the product was observed (entries 5, 6). On elevating the

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	base	T (°C)	yield (%)[b]
1[c]	$Pd(PPh_3)_4$(5)	LiO^tBu	80	32
2[d]	$Pd(PPh_3)_4$(5)	LiO^tBu	80	41
3	$Pd(PPh_3)_4$(5)	LiO^tBu	80	42
4	$Pd(OAc)_2$(5)/PPh_3(10)	LiO^tBu	80	45
5[e]	$Pd(OAc)_2$(5)/PPh_3(10)	LiO^tBu	80	trace
6[f]	$Pd(OAc)_2$(5)/PPh_3(10)	LiO^tBu	80	trace
7	$Pd(OAc)_2$(5)/PPh_3(10)	LiO^tBu	90	60
8	$Pd(OAc)_2$(5)/PPh_3(10)	LiO^tBu	90	trace
9	$Pd(OAc)_2$(5)/PPh_3(10)	Cs_2CO_3	90	trace
10	$Pd(OAc)_2$(5)/PPh_3(10)	NaH	90	61
11[g]	$Pd(OAc)_2$(5)/PPh_3(10)	NaH	90	69
12[g]	$Pd(OAc)_2$(5)/P(*m*-tol)$_3$(10)	NaH	90	74
13[g]	$Pd(OAc)_2$(2.5)/P(*m*-tol)$_3$(5)	NaH	90	78

[a]If not otherwise noted, the reaction was carried out with **1b** (0.1 mmol), **2** (0.15 mmol), and 2,5-DMBQ (0.15 mmol) in 1.0 mL of toluene (0.1 M). [b]Isolated yields after silica gel column chromatography. [c]BQ is used as the oxidant instead of 2,5-DMBQ. [d]2,6-DMBQ is used as the oxidant instead of 2,5-DMBQ. [e]Dioxane was used as the solvent instead of toluene. [f]MeCN was used as the solvent instead of toluene. [g]2.0 mL of toluene (0.05 M) was used. BQ: 1,4-benzoquinone; 2,6-DMBQ: 2,6-dimethyl-1,4-benzoquinone; 2,5-DMBQ: 2,5-dimethyl-1,4-benzoquinone; P(*m*-tol)$_3$: tris(3-methylphenyl)phosphine.

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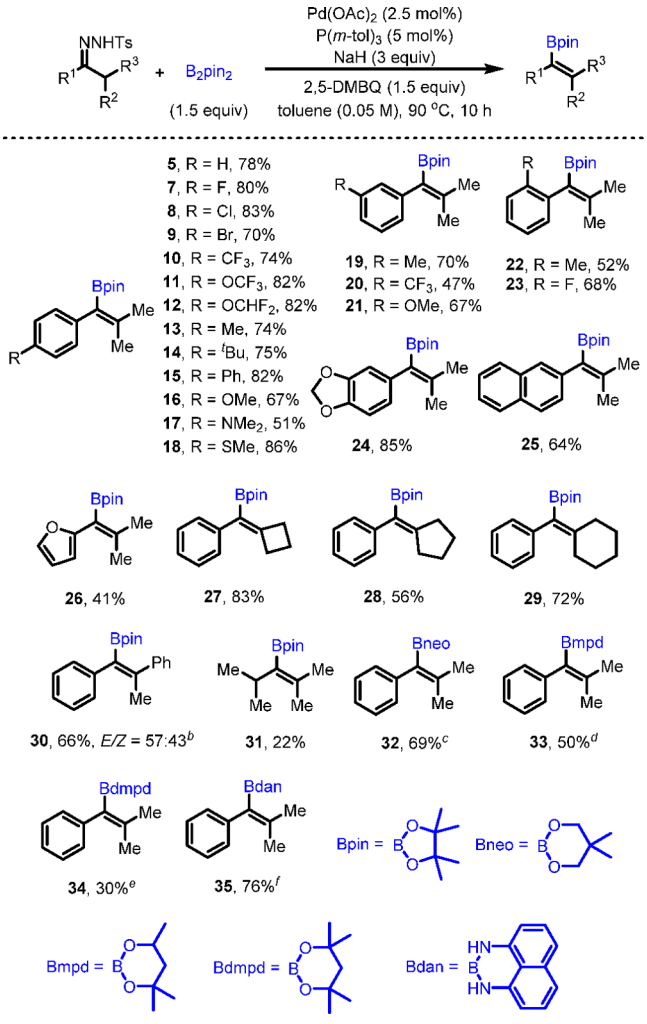
temperature to 90 °C, the yield could be improved to 60% (entry 7). Some other bases were also examined (entries 8–10). Despite that NaO^{t}Bu and K_2CO_3 showed deleterious effects on the reaction (entries 8, 9), we found that NaH could give a slightly improved yield (entry 10). It is noteworthy that lower concentration is beneficial for the reaction (entry 11). Further optimization of the ligand revealed that P(*m*-tol)$_3$ led to an increased yield of 74% (entry 12). Finally, by lowing the catalyst loading to 2.5 mol %, the desired product could be obtained in 78% yield (entry 13).

With the optimized conditions in hand, we then examined the substrate scope. First, we investigated *N*-tosylhydrazones bearing a secondary alkyl group adjacent to the hydrazone moiety, which could give tetrasubstituted alkenylboronates after β-H elimination (Scheme 3). Tetrasubstituted alkenylboronates are important synthetic precursors for the synthesis of tetrasubstituted alkenes, which are ubiquitous in bioactive molecules and pharmaceuticals.[74,75] However, the known methods for their synthesis are relatively rare.[41−44,76−80] Under the standard conditions, a variety of tetrasubstituted alkenylboronates could be prepared with good efficiency. For aromatic *N*-tosylhydrazones, the substrates bearing electron-withdrawing or weak electron-donating substituents at the *para*-position proceeded well, affording the corresponding products in good yields (**7**−**15**, **18**). For the substrates containing strong electron-donating groups like methoxy and dimethylamino, slightly diminished yields were obtained due to the inhibition of 1,2-H shift (**16**, **17**). The substituents at *meta*- or *ortho*-position does not significantly affect the reactivity (**19**−**23**). Notably, some sensitive functional groups in conventional synthetic methods, including aryl chloride and bromide, could be well tolerated (**8**, **9**). The reaction was also applicable to polycyclic or heterocyclic aromatic substrates (**24**−**26**).

Scheme 3. Substrate Scope for the Synthesis of Tetrasubstituted Alkenylboronates[a]



[a]Reaction conditions: *N*-tosylhydrazone (0.3 mmol), B_2pin_2 (0.45 mmol), $Pd(OAc)_2$ (2.5 mol %), P(*m*-tol)$_3$ (5 mol %), NaH (0.9 mmol), 2,5-DMBQ (0.45 mmol) in toluene (6 mL) at 90 °C for 10 h. All the yields refer to the isolated yields after silica gel column chromatography. [b]The *E*/*Z* ratio was determined by ^{1}H NMR of the isolated product. [c]B_2neo_2 instead of B_2pin_2. [d]B_2mpd_2 instead of B_2pin_2. [e]B_2dmpd_2 instead of B_2pin_2. [f]Bpin-Bdan instead of B_2pin_2.

In addition, exocyclic alkenylboronates could be prepared by employing the corresponding *N*-tosylhydrazones containing cyclobutyl, cyclopentyl, or cyclohexyl groups (**27**−**29**). A substrate with two different substituents at the α position ($R^2 \neq R^3$) was also suitable for the reaction, affording the product with *E*/*Z* isomers in good yield (**30**). The low stereoselectivity may come from the low diastereocontrol at the carbene migratory insertion step. The reaction also proceeded with aliphatic *N*-tosylhydrazone, albeit in low yield (**31**). We also evaluated some other commercially available diboron compounds, including B_2neo_2, B_2mpd_2, B_2dmpd_2, and Bpin-Bdan. All of these diboron reagents worked, affording the differently protected alkenylboronates in moderate to good yields (**32**−**35**).

Next, the reaction was extended to *N*-tosylhydrazones bearing a primary alkyl group adjacent to the hydrazone moiety for the synthesis of trisubstituted alkenylboronates (Scheme 4). Traditional approach for the synthesis of trisubstituted alkenylboronates usually relies on hydroboration of internal alkynes, which often give a mixture of regioisomers unless the substrates have large steric or electronic differentiation.[31,32] Moreover, *Z* products are often exclusively formed by the *syn*-addition mechanism. Based on our strategy, an assortment of trisubstituted alkenylboronates could be smoothly obtained from the corresponding *N*-tosylhydrazones with *E* isomers as the major products, which is a good complement to the previous approach. Substrates with diverse substitution patterns at α position (R^2) were competent for the reaction, affording the products in good yields and high *E*-selectivity (**36**−**43**). Both electron-rich and electron-deficient aryl *N*-tosylhydrazones underwent the oxidative borylation successfully (**44**−**56**). A variety of functional groups were compatible with the reaction conditions, including aryl chloride (**44**, **54**), bromide (**45**, **50**), boronate (**51**), ester (**52**), ether (**47**, **55**, **56**), amine (**48**), and silyl ether (**53**). Reactions of heteroaromatic or aliphatic substrates also occurred to give the corresponding products in relatively low yields (**57**−**59**).

Furthermore, some cyclic alkenylboronates, which cannot be prepared by alkyne hydroboration, could be readily synthesized from the corresponding cyclic *N*-tosylhydrazones by our strategy (Scheme 5). The reaction proceeded smoothly in all cases, affording the products in moderate to good yields (**60**−**69**).

Due to the importance as well as the limited methodology for the synthesis of 1,1-disubstituted alkenylboronates,[27,39,40]

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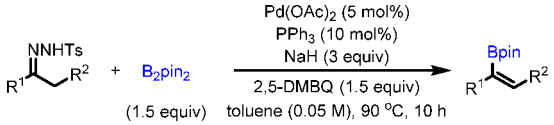
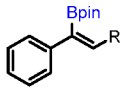
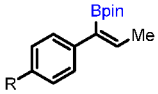
Scheme 4. Substrate Scope for the Synthesis of Trisubstituted Alkenylboronates[a]

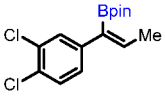




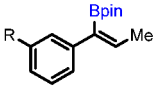
36, R = Me, 77%, *E*/*Z* = 91:9
37, R = Et, 77%, *E*/*Z* = 92:8
38, R = ^{n}Pr, 78%, *E*/*Z* = 92:8
39, R = ^{i}Pr, 60%, *E*/*Z* = 92:8
40, R = ^{n}Pent, 66%, *E*/*Z* = 92:8
41, R = ^{n}Dec, 56%, *E*/*Z* = 92:8
42, R = Bn, 71%, *E*/*Z* = 94:6
43, R = Ph, 57%, *E*/*Z* = 88:12[b]



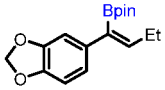
44, R = Cl, 65%, *E*/*Z* = 92:8
45, R = Br, 53%, *E*/*Z* = 91:9
46, R = CF_3, 52%, *E*/*Z* = 87:13
47, R = OMe, 76%, *E*/*Z* > 95:5
48, R = NMe_2, 61%, *E*/*Z* = 94:6



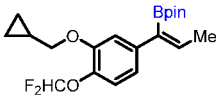
54, 58%, *E*/*Z* = 91:9



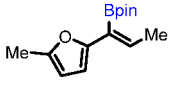
49, R = F, 66%, *E*/*Z* = 90:10
50, R = Br, 54%, *E*/*Z* = 90:10
51, R = Bpin, 65%, *E*/*Z* > 95:5
52, R = OPiv, 47%, *E*/*Z* > 95:5
53, R = OTBS, 75%, *E*/*Z* = 92:8



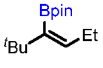
55, 78%, *E*/*Z* > 95:5



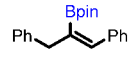
56, 83%, *E*/*Z* = 93:7



57, 29%, *E*/*Z* = 87:13



58, 22%, *E*/*Z* > 95:5



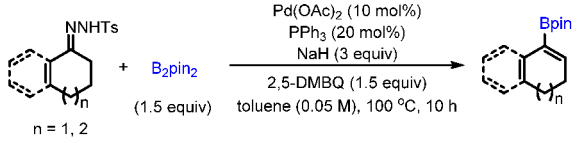
59, 35%, *E*/*Z* = 82:18

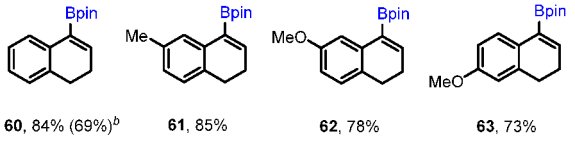
[a]Reaction conditions: *N*-tosylhydrazone (0.3 mmol), B_2pin_2 (0.45 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), NaH (0.9 mmol), 2,5-DMBQ (0.45 mmol) in toluene (6 mL) at 90 °C for 10 h. All the yields refer to the isolated yields after silica gel column chromatography. *E*/*Z* ratios were determined by ^{1}H NMR of isolated products. [b]The *E*/*Z* ratio was determined by GC-MS.

we further wished to expand the scope into methyl-substituted *N*-tosylhydrazones as the substrates. We first explored the reaction of **1a** with bis(pinacolato)diboron **2** again under the previously optimized reaction conditions (Table 2, entry 1), and the 1,1-disubstituted alkenylboronate **3** was isolated in 24% yield. On elevating the temperature to 100 °C, the yield was slightly improved (entry 2). Then, a series of BQ derivatives were examined (entries 3−6), indicating that the oxidant had a critical influence on this reaction. Despite that simple BQ could not promote this reaction (entry 3), BQs with bulky substituents are beneficial for the transformation (entries 4−6). The use of thymoquinone as the oxidant led to an increased yield (entry 5). With the more sterically bulky oxidant 2,3,5-trimethyl-1,4-benzoquinone (TMBQ), the yield could be further improved to 46% (entry 6). Finally, by changing the solvent to DCE, the reaction could afford the 1,1-disubstituted alkenylboronate **3** in 61% yield (entry 7).

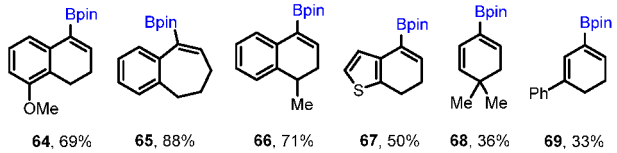
We then evaluated a series of methyl-substituted *N*-tosylhydrazones with different electronic and steric properties (Scheme 6). Substrates bearing electron-withdrawing or electron-donating substituents in the *para*-position of the

Scheme 5. Substrate Scope for the Synthesis of Cyclic Alkenylboronates[a]





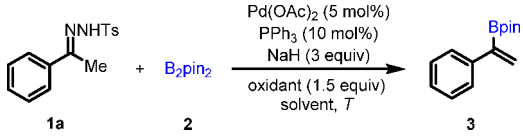
60, 84% (69%)[b]
61, 85%
62, 78%
63, 73%



64, 69%
65, 88%
66, 71%
67, 50%
68, 36%
69, 33%

[a]Reaction conditions: *N*-tosylhydrazone (0.3 mmol), B_2pin_2 (0.45 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), NaH (0.9 mmol), 2,5-DMBQ (0.45 mmol) in toluene (6 mL) at 100 °C for 10 h. All the yields refer to the isolated yields after silica gel column chromatography. [b]$Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %).

Table 2. Optimization of the Reaction Conditions for the Synthesis of 1,1-Disubstituted Alkenylboronates[a]



entry	oxidant	solvent	T(°C)	yield(%)[b]
1	2,5-DMBQ	toluene	90	24
2	2,5-DMBQ	toluene	100	31
3	BQ	toluene	100	0
4	2,6-DMBQ	toluene	100	31
5	thymoquinone	toluene	100	42
6	TMBQ	toluene	100	46
7	TMBQ	DCE	100	61

[a]The reaction was carried out with **1a** (0.1 mmol) and **2** (0.15 mmol) in 2.0 mL of solvent (0.05 M). [b]Isolated yields after silica gel column chromatography. Thymoquinone: 5-isopropyl-2-methyl-1,4-benzoquinone; TMBQ: 2,3,5-trimethyl-1,4-benzoquinone.

aromatic rings were all compatible and provided the desired products in moderate yields (**70**−**78**). *Meta*- and *ortho*-substituted as well as disubstituted aromatic *N*-tosylhydrazones were competent for this reaction, affording the corresponding products in moderate yields (**79**−**86**). The reaction also shows good tolerance for functional groups, such as halides (**70**, **71**, **80**, **83**), ester (**78**), ether (**73**, **81**, **84**, **85**), sulfide (**76**), and boronate (**77**). We also applied the reaction to the modification of complex molecules. Thus, the 1,1-disubstituted alkenylboronates derived from bioactive natural product estrone (**87**) and the fragrance tonalid (**88**) were successfully obtained through this methodology in moderate yields.

To demonstrate the practical applicability of this methodology, the standard reaction was carried out in gram scale (Scheme 7a). The alkenylboronate **5** (1.246 g) was successfully obtained with satisfactory yield under the standard reaction conditions. To simplify the reaction protocol, we also

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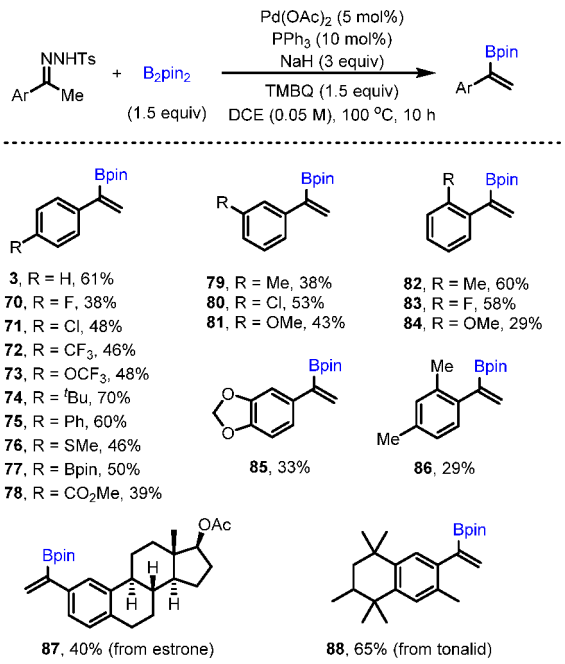
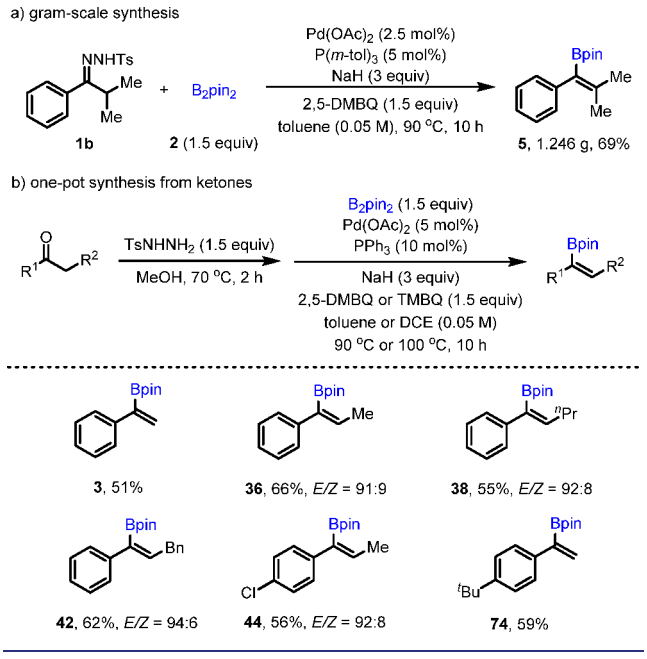
Scheme 6. Substrate Scope for the Synthesis of 1,1-Disubstituted Alkenylboronates[a]



[a]Reaction conditions: *N*-tosylhydrazone (0.3 mmol), B_2pin_2 (0.45 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), NaH (0.9 mmol), TMBQ (0.45 mmol) in DCE (6 mL) at 100 °C for 10 h. TMBQ: trimethylquinone. All yields refer to the isolated yields after silica gel column chromatography.

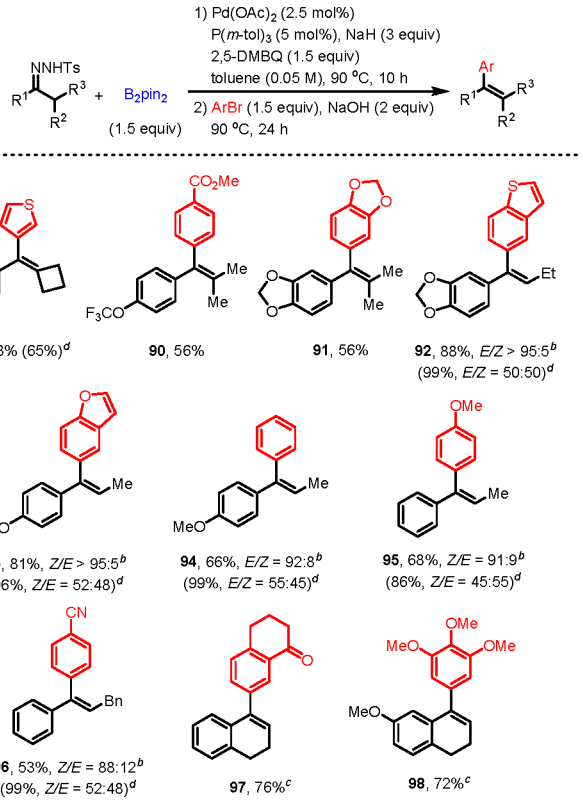
Scheme 7. Gram-Scale Synthesis and One-Pot Synthesis of Alkenylboronates from Ketones



performed the one-pot synthesis starting directly from the corresponding ketones (Scheme 7b). After the complete formation of *N*-tosylhydrazones followed by the removal of solvent, the oxidative borylation worked smoothly to afford alkenylboronate products (**3**, **36**, **38**, **42**, **44**, **74**) in moderate yields.

Furthermore, the synthetic utility of this protocol was investigated through a series of transformations of alkenylboronates. We first explored the one-pot oxidative borylation/Suzuki coupling reactions of *N*-tosylhydrazones, bis(pinacolato)diboron, and aryl bromides (Scheme 8). The

Scheme 8. One-Pot Oxidative Borylation/Suzuki Coupling Sequence[a]



[a]First step: reactions were performed with *N*-tosylhydrazone (0.3 mmol), B_2pin_2 (0.45 mmol), $Pd(OAc)_2$ (2.5 mol %), $P(m\text{-tol})_3$ (5 mol %), NaH (0.9 mmol), 2,5-DMBQ (0.45 mmol) in toluene (6 mL) at 90 °C for 10 h. Second step: ArBr (0.45 mmol), NaOH (2 M, 0.3 mL) were added, and reactions were stirred at 90 °C for 24 h. All yields refer to isolated yields after silica gel column chromatography. [b]First step: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %). *E*/*Z* ratios were determined by ^1H NMR of isolated products. [c]First step: $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), 100 °C. [d]Barluenga's coupling: *N*-tosylhydrazone (0.3 mmol), ArBr (0.3 mmol), Pd_2dba_3 (1 mol %), XPhos (2 mol %), LiO^tBu (0.66 mmol) in dioxane (1.8 mL) at 90 °C for 16 h.

reactions worked well by a single palladium catalyst, providing the polysubstituted alkenes in moderate to good yields without the requirement for isolation of the alkenylboronates (**89**–**98**). Notably, these sequential reactions could deliver trisubstituted alkenes with good stereoselectivities, which could not be achieved under Barluenga's coupling of *N*-tosylhydrazones with aryl bromides (**92**–**96**).[61] With appropriate combination of the substrates, stereodivergent synthesis of *Z* and *E* isomers could also be realized (**94**, **95**). A variety of functional groups, including heterocycle (**89**, **92**, **93**), ester (**90**), ether (**91**–**95**, **98**), nitrile (**96**), and ketone (**97**), were well tolerated.

In addition to the one-pot oxidative borylation/Suzuki coupling reactions, the synthetic usefulness of this borylation protocol has also been demonstrated by the further trans-

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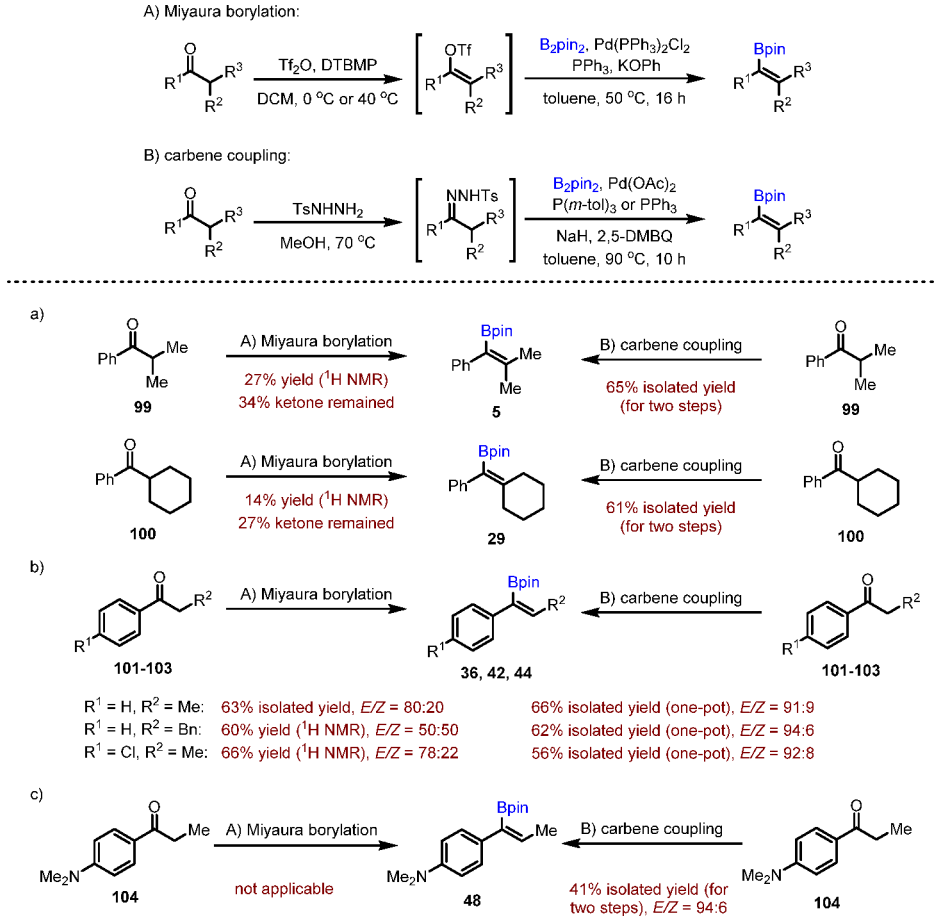
Scheme 9. Comparison between Miyaura Borylation and Carbene Coupling



formations of tetrasubstituted alkenylboronates (see Supporting Information for the details).

When considering the synthesis of alkenylboronates from ketones or aldehydes, the conventional approach would be Miyaura borylation.[27] Compared with the Miyaura borylation of ketones through alkenyltriflates, carbene coupling of *N*-tosylhydrazones shows advantages in some cases (Scheme 9). It is noteworthy that most of the alkenyltriflates derived from aromatic ketones are not stable, which can only be generated *in situ* for the Miyaura borylation. On the contrary, *N*-tosylhydrazones are a stable solid that can be readily isolated and purified through precipitation or column chromatography. For sterically bulky ketones such as **99** and **100**, the generation of tetrasubstituted alkenyltriflates was in low efficiency with a considerable amount of ketones remaining, so the subsequent Miyaura borylation delivered tetrasubstituted alkenylboronates **5** and **29** in low yields. Moreover, the alkenylboronate products could not be separated with the remaining ketones through column chromatography due to their similar polarity. In contrast, *N*-tosylhydrazones could be easily prepared from **99** and **100** to undergo carbene coupling, providing alkenylboronates **5** and **29** in good yields with high purity (Scheme 9a). The synthesis of trisubstituted alkenylboronates (**36**, **42**, **44**) from the corresponding ketones **101**−**103** through Miyaura borylation could be achieved in good yields. However, the stereoselectivities could not be well controlled, and the isolation of pure alkenyl boronates **42** and **44** was difficult because of the incomplete consumption of the ketone substrates. With carbene coupling processes, the trisubstituted alkenylboronates (**36**, **42**, **44**) could be produced through one-pot synthesis in both good yields and high *E*-selectivities (Scheme 9b). Finally, sensitive functional groups such as dimethylamino could not be tolerated in the triflation step for Miyaura borylation, while carbene coupling shows good compatibility of this functional group to afford the alkenylboronate product **48** in moderate yield (Scheme 9c).

■ COMPUTATIONAL STUDIES

On the basis of previous studies,[57−60,70] we proposed a plausible mechanism for this reaction (Scheme 10). The reaction starts with transmetalation between bis(pinacolato)-diboron and $Pd(OAc)_2$ to form the boron−palladium(II) species **B**. In contrast, *N*-tosylhydrazone generates the corresponding diazo compound in the presence of NaH as the base. Then, the boron−palladium species **B** decomposes the diazo compound to form palladium carbene species **C**, which undergoes boryl migratory insertion to generate intermediate **D**. Afterward, *cis* β-H elimination occurs to deliver the final product and generate the intermediate **E**. The intermediate **E** goes through reductive elimination to form Pd(0) species **F**, which is oxidized by the 2,5-DMBQ to generate Pd(II) species **A**. Finally, the transmetalation between Pd(II) species **A** and bis(pinacolato)diboron occurs to regenerate the active catalytic boron−palladium(II) species **B** for the next catalytic cycle II.

To gain more detailed insights into the reaction mechanism as well as the origin of the observed stereoselectivity, a density functional theory (DFT) study was carried out on the

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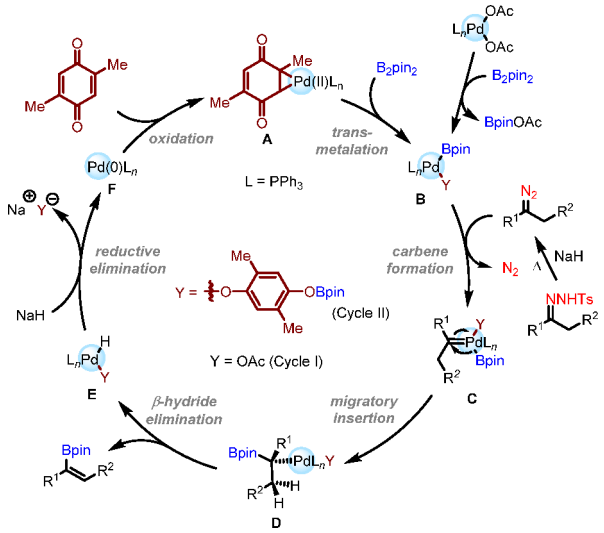
Scheme 10. Proposed Reaction Mechanism



oxidative borylation reaction catalyzed by palladium complex (as shown in Scheme 10) at the ωB97X-D/BSI level using the Gaussian 09 program.[81,82] BSI denotes that the effective core potential (ECP) of Pd with a double-ζ valence basis set (LANL2DZ) was used for the Pd center and the 6-31G (d,p) basis sets for all the other atoms.[83,84] The SMD polarizable continuum model using toluene as the solvent was employed in the calculation.[85] Free energies were calculated at 298.15 K. Thermal correction and entropy contribution to the Gibbs free energy were taken from the frequency calculations at the ωB97X-D/BSI level, in which the translational movement was evaluated using the method presented by Whitesides and co-workers.[86−90] The geometric structures are visualized using the VMD program.[91]

As shown in Scheme 10, the whole catalytic cycle could be divided into cycle I and cycle II, and the difference between cycle I and cycle II is the ligand Y of the active catalytic species that is OAc in cycle I while DMBQ-Bpin in cycle II. The calculated results indicate that cycle II by the boron−palladium(II) species **B1** (Y = DMBQ-Bpin) is energetically more favorable than cycle I by **A1** (Y = OAc). Therefore, in the following discussion, we only give the free energy profiles with **B1** as the active catalytic species. The free energy profiles of cycle II are shown in Figure 1, and those of cycle I are given in Figure S1A of the Supporting Information (SI). Both cycles I and II consist of six fundamental steps: the carbene formation step, the Bpin migratory insertion step, the β-hydride elimination step, the reductive elimination step, the oxidative addition step, and the transmetalation step.

We chose the formation of **5** from **1b** (Scheme 3 and Scheme 7a) as the model for computational study on the reaction pathway. As shown in Figure 1, the free energies of stationary points along the reaction pathway are relative to **B1**. First, the diazo compound **1b′** coordinates with **B1** to form intermediate **B2**, then **B2** decomposes by extrusion of N_2 gas to generate a Pd(II)-carbene species **B3** via transition state (TS) **TSB2−3** with an energy barrier of 9.25 kcal/mol (**B1** → **TSB2−3**). Similar to the palladium carbene species previously reported by our group,[92−94] complex **B3** is unstable and could easily undergo the Bpin migratory insertion via **TSB3−4** owning a low energy barrier of 0.09 kcal/mol, resulting in intermediate **B4**, which is exergonic by 23.62 kcal/mol.

Subsequently, β-hydride elimination step from **B4** to **B5** takes place through **TSB4−5** owing to a four-membered-ring structure, climbing an energy barrier of 0.41 kcal/mol to give π complex **B5**. Then the π complex **B5** dissociates into product **5** and intermediate **B6**. In the reductive elimination step from **B6** to **A7** via **TSB6−A7** having an energy barrier of 14.63 kcal/mol, the Pd(0) species **A7** is formed with the release of HOAc that could react with NaH to further enhance the thermodynamic driving force. Then the Pd(0) species is oxidized by 2,5-dimethyl-1,4-benzoquinone (2,5-DMBQ) to form the intermediate **A8**, which is exergonic by 22.58 kcal/mol. The B_2pin_2 substrate interacts with **A8** to form **A9** followed by a transmetalation process from **A9** to **B1**, which is a stepwise step. The Bpin moiety of **A9** undergoes Bpin transfer via **TSA9−10** to achieve **A10** with the formation of a B−O bond. The free energy barrier for the Bpin transfer is 13.00 kcal/mol from **A9** to **A10**. Afterward, the B−B σ-bond of B_2pin_2 part is cleaved via **TSA10−11** with an energy barrier of 12.60 kcal/mol, producing the intermediate **A11**. The formed

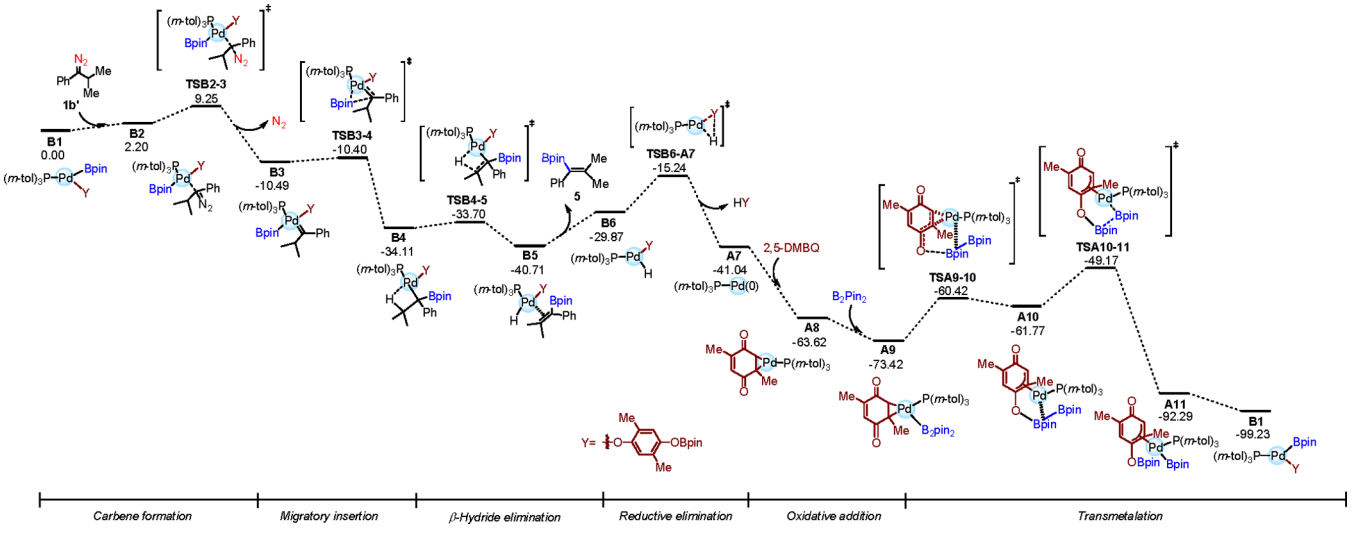


Figure 1. Free energy profiles of the oxidative borylation of *N*-tosylhydrazones catalyzed by catalytic species **B1** of cycle II. All energies are relative to **B1** (unit: kcal/mol).

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intermediate **A11** then isomerizes into more stable active catalytic species **B1** for the next catalytic cycle II. The calculated results indicate that the energy span of cycle I is 24.25 kcal/mol (**A9** → **TSA10−11**) for the transmetalation step.

Cycle I goes through the same fundamental steps as cycle II. Similarly, the calculated free energy barriers of the carbene formation step, the Bpin migratory insertion step, the *β*-hydride elimination step, the reductive elimination step, the oxidative addition step, and the transmetalation step of cycle I are 13.32, 5.68, 0.99, 13.82, 0.00, and 24.25 kcal/mol (Figure S1A), respectively, and those of cycle II are 9.25, 0.09, 0.41, 14.63, 0.00, and 24.25 kcal/mol, respectively. It is obvious that changing the OAc ligand to a DMBQ-Bpin ligand can reduce the energy barriers in the carbene formation step, Bpin migratory insertion step, and *β*-hydride elimination step, while slightly increase the energy barrier of the reductive elimination step (Figure 2). Depending on the barrier energy, the

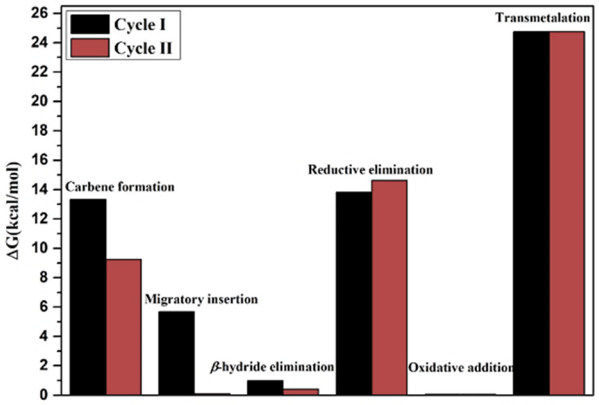

Figure 2. Comparison of the energy barriers of each fundamental steps in cycle I and cycle II.

transmetalation step is the rate-determining step in the whole cycle. In addition, the calculated results show that the energy barrier of the Bpin migratory insertion step in cycle II is only 0.09 kcal/mol, which indicates that the palladium carbene species **B3** could easily undergo migratory insertion and form a more stable complex **B4**. It is noteworthy that our previous computational studies in other palladium-catalyzed carbene coupling reactions all suggest facile migratory insertion of palladium carbene species.[92−94]

E isomers of trisubstituted alkenylboronates are the major products in this oxidative borylation reaction of *N*-tosylhydrazones catalyzed by a palladium complex (see Scheme 4). It is obvious that the selectivity-determining step is the *β*-hydride elimination step leading to *E*/*Z* isomers. In order to unveil the origin of the stereoselectivity of this reaction, we investigated the selectivity-determining step (*β*-hydride elimination step) for forming **36** shown in Scheme 4 as the model reaction. This model reaction used $Pd(OAc)_2$ with a PPh_3 ligand as the catalyst, and the corresponding catalytic species is boron−palladium(II) complex **C1**. In this part, all relative energies of the stationary points along the reaction pathways are relative to **C1**. The *β*-hydride elimination step is from **C4** to **C5**, which could form different stereoselective products. As shown in Figure 3, the energy barrier of the *β*-hydride elimination step is 1.76 kcal/mol along path *E*, leading to the *E* isomer via **TSC4−5E** having a four-membered-ring structure, giving *π*

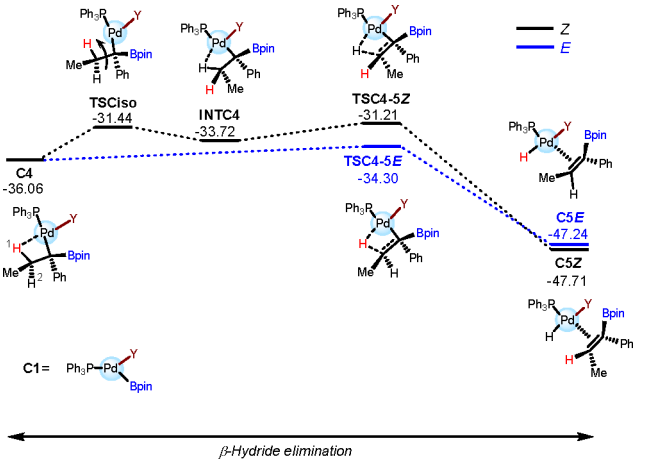

Figure 3. Free energy profiles for the *β*-hydride elimination step catalyzed by palladium. Path *E* and path *Z* indicate that the final product is an *E* isomer (in blue) and a *Z* isomer (in black), respectively. All energies are denoted in kcal/mol.

complex **C5E**. Alternatively, that is 4.85 kcal/mol (**C4** → **TSC4−5Z**) along path *Z* leading to the *Z* isomer via **TSC4−5Z**. To complete the *cis* *β*-hydride elimination (path Z), **C4** isomerizes into **INTC4**, in which H^2 interacts with the Pd center via an agostic interaction. The energy barrier of the isomerization is 4.62 kcal/mol. The calculated results indicate that the formation of the *Z* product is less favorable than that of *E*, explaining our observed stereoselectivity in the experiment.

The origin of stereoselectivity is related to electronic structures of stationary points along the *β*-hydride elimination step. To further unveil the nature of the stereoselectivity, the distortion-interaction analysis[95−97] has been carried out for **TSC4−5E** and **TSC4−5Z**. As shown in Figure 4A, in the energy decomposition analysis, the transition state was divided into two fragments. ΔE_{dist} (mono) and ΔE_{dist} (cat) are the distortion energies of the monomer moiety and remaining metal complex, respectively, and the interaction energy ΔE_{int} encompasses both destabilizing steric repulsions and stabilizing electrostatic and orbital interactions between these two fragments. DIA shows that the difference in total distortion energy between **TSC4−5E** and **TSC4−5Z** is small (16.83 vs 16.82 kcal/mol), and the lower energy of **TSC4−5E** compared with **TSC4−5Z** is mainly caused by the stronger interaction between the metal complex and monomer moiety (−36.89 vs −33.95 kcal/mol). The interaction between the organometallic complex and unsaturated hydrocarbons could be described by the Dewer−Chatt−Duncanson model.[98−100] The metal−ligand interaction could be considered to arise from the electron pair delocalization, in which a donation of olefin *π*-electrons into the metal and back-donation from the metal into the olefin *π** orbital occur. Meanwhile, the natural bond orbital (NBO) analysis shows the acceptor−donor interactions between the Pd−H bond and C1=C2 bond. In **TSC4−5E**, the second-order perturbative energy $E^{(2)}$ for the *π*(C1−C2) → *σ**(Pd−H1) interaction is 92.90 kcal/mol and the $E^{(2)}$ for *σ*(Pd−H1) → *π**(C1−C2) interaction is 67.14 kcal/mol, but in **TSC4−5Z**, the $E^{(2)}$ for the *π*(C1−C2) → *σ**(Pd−H2) interaction and *σ*(Pd−H2) → *π**(C1−C2) interaction is 83.66 and 66.31 kcal/mol, respectively. This indicates that the difference in energy between **TSC4−5E** and **TSC4−5Z** is due to the orbital interactions, which leads to the stereoselectivity.

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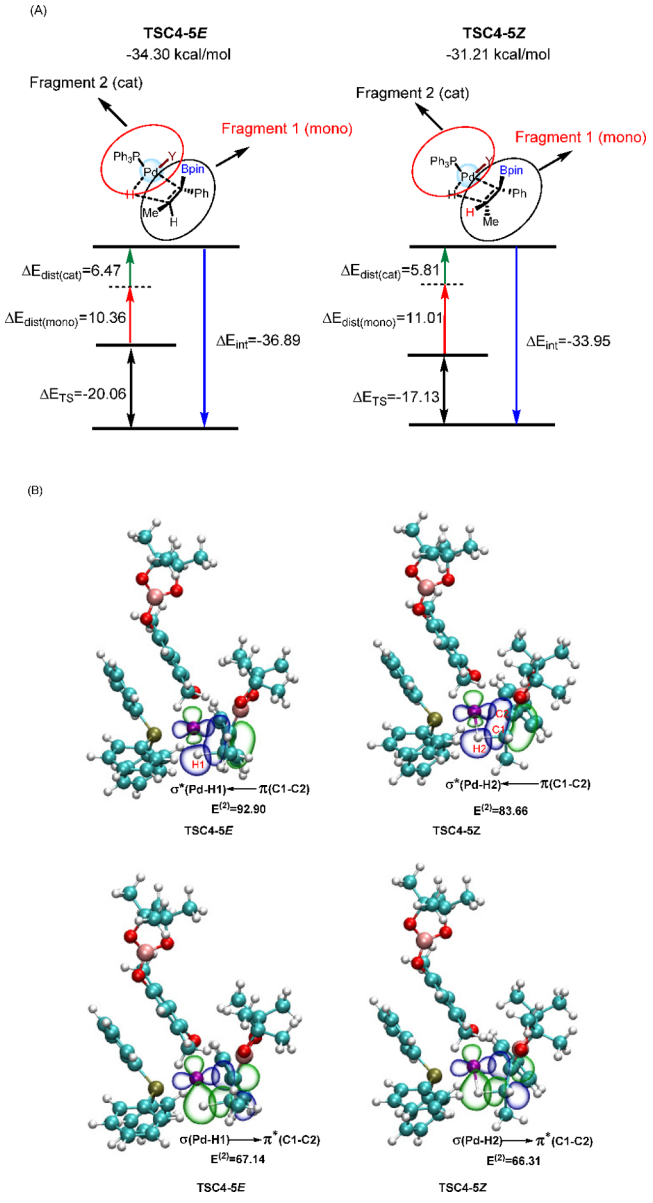

Figure 4. (A) Distortion-interaction analysis for **TSC4−5*E*** and **TSC4−5*Z***. (B) NBO view for the overlap of donor and acceptor orbitals in the **TSC4−5*E*** and **TSC4−5*Z***.

CONCLUSIONS

In summary, we have developed an efficient and selective method for the synthesis of alkenylboronates through palladium-catalyzed oxidative borylation of *N*-tosylhydrazones. The reaction shows good functional group tolerance, accessing a broad range of di-, tri-, and tetrasubstituted alkenylboronates in good yields. Various transformations of the products were explored, demonstrating the synthetic utility of the method. The one-pot oxidative borylation/Suzuki coupling processes provide a new approach for stereoselective synthesis of trisubstituted alkenes. DFT calculations support our proposed mechanism that involves palladium-carbene formation and subsequent boryl migratory insertion as the key steps. The origin of stereoselectivity is due to the orbital interactions between the Pd−H moiety and C1═C2 moiety in the β-hydride elimination step. This approach may bring new opportunities for the synthesis of complex molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c02331.

Experimental procedures and spectral data for all new compounds (PDF)

Detailed computational study and calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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