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Palladium-Catalyzed Cascade Heck Coupling and Allylboration of Iododiboron Compounds via Diboryl Radicals

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Abstract: Geminal bis(boronates) are versatile synthetic building blocks in organic chemistry. The fact that they predominantly serve as nucleophiles in the previous reports, however, has restrained their synthetic potential. Herein we disclose the ambiphilic reactivity of α-halogenated geminal bis(boronates), of which the first catalytic utilization was accomplished by merging a formal Heck cross-coupling with a highly diastereoselective allylboration of aldehydes or imines, providing a new avenue for rapid assembly of polyfunctionalized boron-containing compounds. We demonstrated that this cascade reaction is highly efficient and compatible with various functional groups, and a wide range of heterocycles. In contrast to a classical Pd(0/II) scenario, mechanistic experiments and DFT calculations have provided strong evidence for a catalytic cycle involving Pd(I)/diboryl carbon radical intermediates.

Introduction

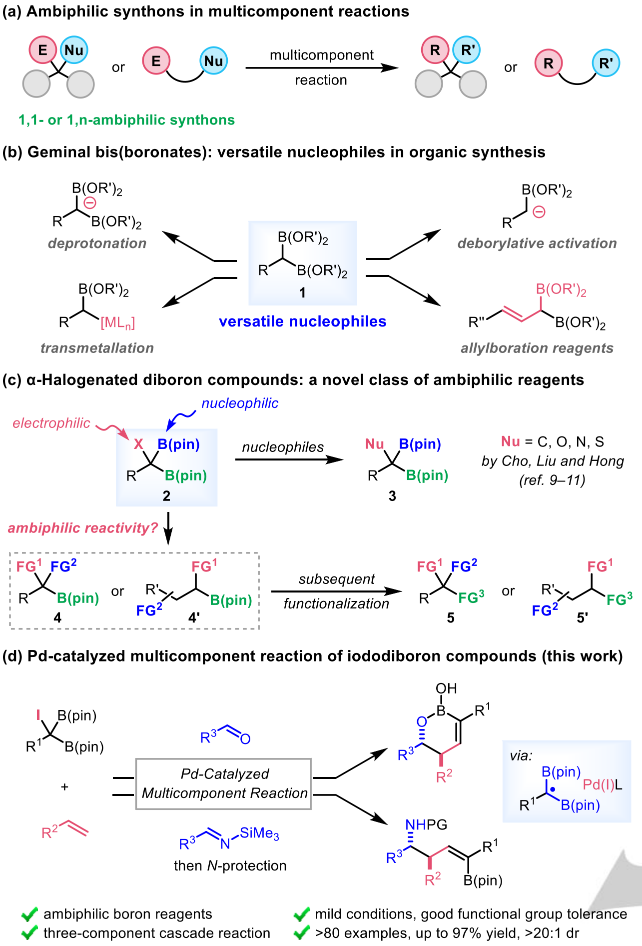
Ambiphilic synthons, a class of molecules possessing both electrophilic and nucleophilic sites, which can connect multiple substrates by sequential bond formation, are powerful building blocks for the expeditious construction of complex molecules.[1] This feature renders ambiphilic synthons particularly suitable for the development of multicomponent reactions (Scheme 1a),[2] and designing novel ambiphilic reagents hold significant potential to establish new synthetic methods with high efficiency.

Over the past decades, the growing importance of geminal bis(boronates) in organic synthesis has become evident.[3] They can serve as versatile reagents in a wide variety of transformations, mainly through four types of reactive intermediates (Scheme 1b).[4–7] Despite the notable advances, *gem*-diboron compounds have exclusively played the role of nucleophiles, which has limited their synthetic diversity. Inspired by the recent progress on the transformation of the ambiphilic α-halogenated mono-boronates,[8] we envisioned that introducing an electrophilic halogen substituent at the α-position (**1**→**2**) would invert the innate polarity of the carbon center, allowing the new motif to liberate new types of reactivity (Scheme 1c). Indeed, Cho,[9] Liu[10] and our group[11] independently developed substitution reactions of compounds **2** with a vast array of nucleophiles. Based on these work, we further reasoned that compounds **2** should be capable of reacting with two components, e.g., a nucleophile and an electrophile, in a single-step or cascade reaction to rapidly construct a polyfunctionalized boron-containing compound (**2**→**4** or **4'**),[12] which could be further diversified through subsequent functionalization[13] (**4**→**5**).

In this Article, we demonstrated the synthetic potential of iododiboron compounds as novel ambiphilic reagents by merging a palladium-catalyzed Heck cross-coupling with a highly diastereoselective allylboration of aldehydes or imines, providing a powerful platform for the convenient assembly of molecular complexity (Scheme 1d). This cascade reaction is highly efficient and compatible with various functional groups and a wide range of heterocycles. We also conducted mechanistic experiments and DFT calculations to provide evidence that supports a catalytic mechanism involving Pd(I)/diboryl radical intermediates.

Results and Discussion

Optimization of Cascade Heck Coupling/Allylboration Reaction of Iododiborons, Alkenes and Aldehydes. In our previous report,[11] α-halogenated geminal bis(boronates) can be prepared from the readily available 1,1-diborylalkanes. We chose iododiboron compound **6a** as the model substrate to start the investigation of its ambiphilic reactivity in the presence of a transition metal catalyst. In line with our design in Scheme 1c, we were delighted to discover a three-component reaction of **6a,** styrene, and benzaldehyde after extensive evaluation (Table 1; For the detailed screening results, see Table S1–S5 in the Supporting Information). With $Pd(OAc)_2$ as the precatalyst and Xantphos as the ligand, **8a** was isolated in 92% yield with >20:1 diastereoselectivity, and neither *syn*- nor *Z*-isomer was detected

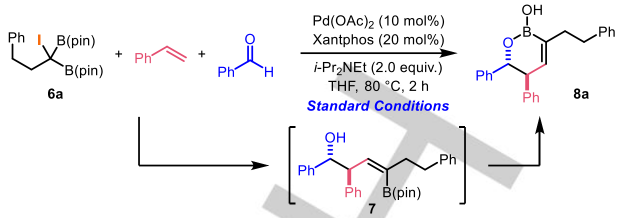


Scheme 1. Ambiphilic Utilization of α-Halogenated Geminal Bis(boronates).

under the standard conditions. Presumably, an internal allylic *gem*-diboron species was first generated via Heck-type cross-coupling[14–16] between **6a** and styrene. It subsequently underwent diastereoselective allylboration with benzaldehyde to afford compound **7**, an acyclic homoallylic alcohol bearing an (*E*)-vinylboronate moiety, which spontaneously cyclized to provide the final product **8a**.

The survey of various bidentate and monodentate ligands (Table S1) revealed that Xantphos was of particular significance, and any subtle modification of the ligand was devastating (Table 1, entries 2 and 3). No background reaction occurred in the absence of the ligand (entry 4). The investigation of the solvent (entry 5) showed that THF was the optimal choice. Next, the effect of different base additives was examined. Inorganic bases such as Cs_2CO_3 led to inferior results, mainly due to the decomposition of **6a** and the protodeboronation of the allylic *gem*-diboron intermediate (entry 6). The impact of replacing *i*-Pr_2NEt with less hindered tertiary or secondary amines was negligible (entry 7). However, the use of primary amine completely inhibited the reaction (entry 8). Lowering the temperature to 60 °C caused a decrease in the reaction rate (entry 9). Of note, identical yields were obtained when the reaction was carried out in the dark or under blue LED irradiation, but no product was obtained at ambient temperature even with irradiation, suggesting that a photochemical process was likely not involved in the reaction mechanism (entries 10–12). Lastly, the bromo- and chlorodiboron analogs were proved to be much less reactive (entries 13 and 14).

Table 1. Optimization of Cascade Heck Coupling/Allylboration Reaction of Iododiborons, Alkenes and Aldehydes.[a]



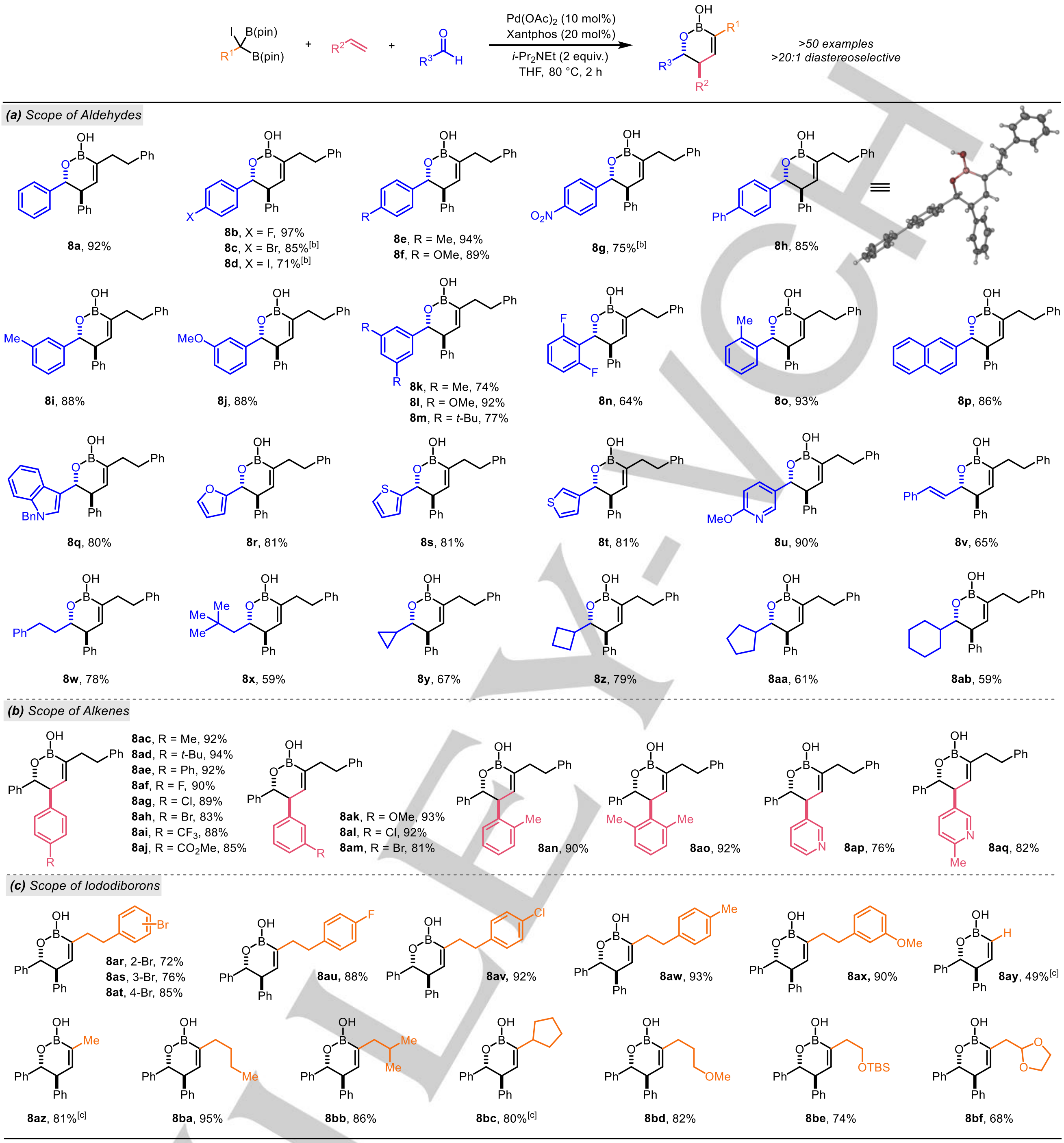
entry	variation from the standard conditions	isolated yield (%)
1	none	92
2	*N*-Xantphos as ligand	13
3	other ligands (see Table S1)	0
4	without ligand	0
5	other solvents (see Table S2)	<5–89
6	Cs_2CO_3 as base	62
7	Et_2NH as base	88
8	*n*-$BuNH_2$ as base	0
9	60 °C	36
10	in the dark	92
11	with irradiation[b]	92
12	at rt with irradition[b]	0
13	bromodiboron instead of iododiboron	9
14	chlorodiboron instead of iododiboron	0

[a] The standard conditions: iododiboron **6a** (0.12 mmol), styrene (0.2 mmol), benzaldehyde (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), Xantphos (0.02 mmol), *N*,*N*-diisopropylethylamine (0.2 mmol), THF (1 mL), 80 °C, 2 h. Isolated yields. [b] The reaction was performed in a photoreactor with blue LED irradiation (455–460 nm, 3 W).

Scope of Cascade Heck Coupling/Allylboration Reaction of Iododiborons, Alkenes and Aldehydes. With the optimized conditions in hand, the scope of aldehydes in the three-component cascade reaction was examined first (Table 2a). The cyclic structure, the relative configuration, and the *E*/*Z* configuration were confirmed by single crystal X-ray diffraction (**8h**).[17] It was found that benzaldehydes possessing different aryl substituents are all capable partners (**8a**–**o**). Both electron-donating and withdrawing groups at *ortho*-, *meta*- or *para*-position on the phenyl ring were compatible with the standard conditions, furnishing the desired products in good to excellent yields with >20:1 dr. We noticed that bromo, iodo, and nitro groups were particularly sensitive to the catalyst. This issue could be fixed by employing the aldehyde substrates after the Heck reaction was accomplished (**8c**, **8d** and **8g**). Notably, aldehydes bearing heteroaryl group, such as indole (**8q**), furan (**8r**), thiophene (**8s**, **8t**), and pyridine (**8u**), were also competent. Moreover, α, β-unsaturated aldehyde and aliphatic aldehydes were also qualified reaction partners, affording the desired products in moderate to good yield with excellent diastereoselectivity (**8v**–**ab**), which significantly broadened the scope of this cascade reaction.

Next, the generality of alkenes was evaluated (Table 2b). Various styrenes with *para*-substituent, including alkyl, phenyl, halogens, trifluoromethyl, and ester groups, reacted smoothly to

Table 2. Scope of Cascade Heck/Allylboration Reaction of Iododiborons, Alkenes and Aldehydes.[a]



[a] Standard conditions: iododiboron (0.12 mmol), alkene (0.2 mmol), aldehyde (0.1 mmol), Pd(OAc)$_2$ (0.01 mmol), Xantphos (0.02 mmol), *N*,*N*-diisopropylethylamine (0.2 mmol), THF (1 mL), 80 °C, 2 h. Isolated yields. [b] The Heck reaction was conducted under the standard conditions, then aldehyde (0.10 mmol), 80 °C, 2 h. [c] 2.0 equiv. iododiboron was employed.

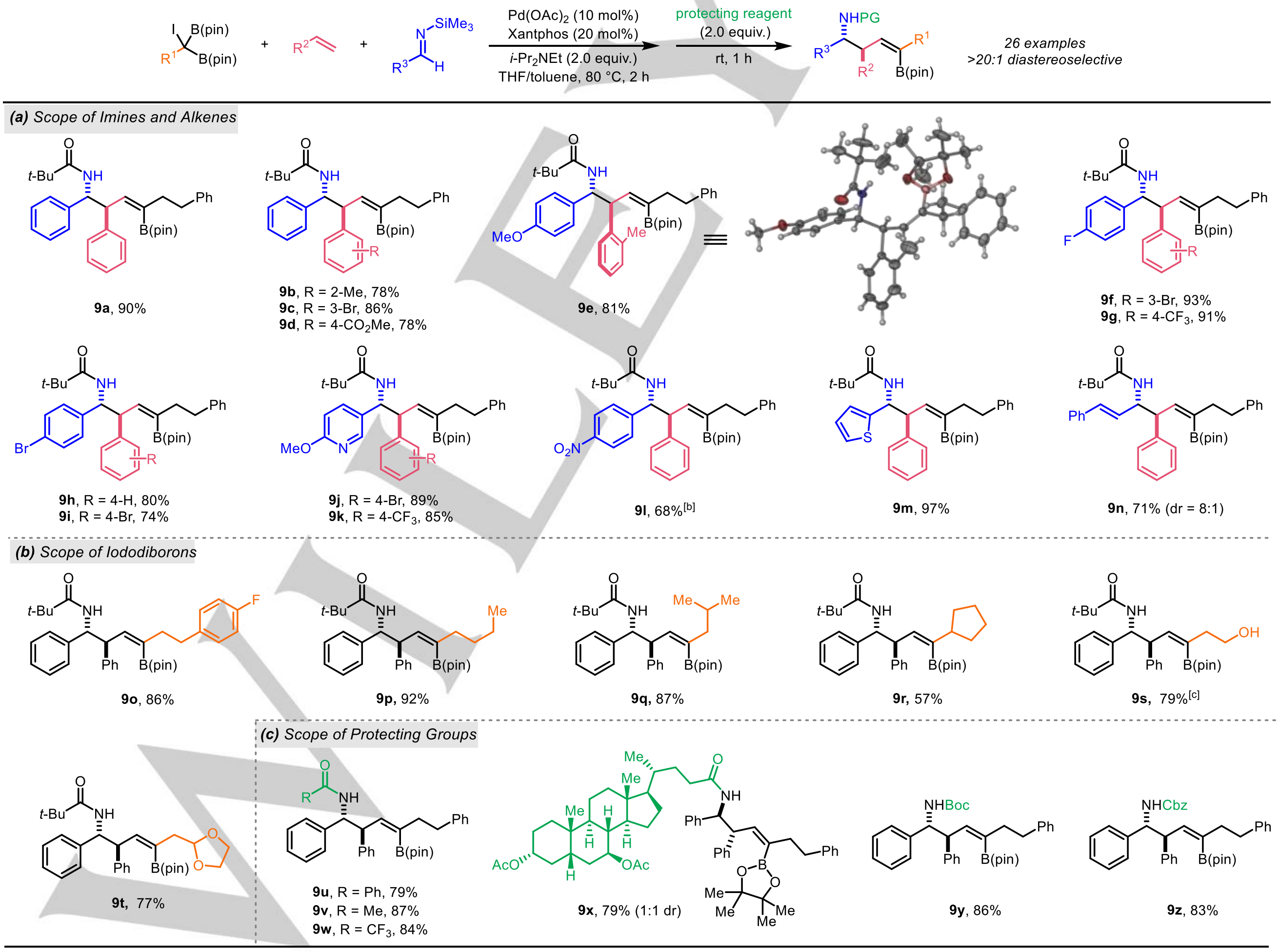
provide the corresponding products **8ac–aj** in good to excellent yields. Likewise, *meta*- and *ortho*-substituted styrenes could furnish the desired product efficiently (**8ak–ao**). It was noteworthy that in styrenes, the bromo group could be well accommodated (**8ah** and **8am**), which can serve as potential handles in subsequent cross-coupling transformations. *Ortho*-dimethyl substituted styrene also showed great reactivity, indicating that the steric hindrance on styrene has little impact on this transformation (**8ao**). Again, substrates with pyridine motifs, which often poison transition metal catalysts, were suitable components (**8ap** and **8aq**). Unfortunately, disubstituted styrenes were incompetent due to the steric hindrance, and without the formation of the stabilized benzyl radical, alkyl-substituted olefins were also inert under standard conditions. Alkenes bearing an electron-withdrawing group, however, could undergo a side reaction other than Heck cross-coupling, which is still under investigation.

Lastly, the scope of our reaction was further explored with substituted iododiborons (Table 2c). As expected, the installation of substituents like halogens and methoxy group on the phenyl ring did not interfere with the normal catalytic process (**8ar**–**ax**). Intriguingly, the less hindered substrates, such as unsubstituted or methyl-substituted iododiborons, were less effective, which could be partially amended by increasing the amount of the iododiborons to 2.0 equivalent (**8ay** and **8az**). Due to steric hindrance, a similar scenario was observed for the cyclopentyl-substituted starting material (**8bc**). Moreover, substrates bearing ether (**8bd**), silyl-protected alcohol (**8be**), and acetal (**8bf**) were all well tolerated in this transformation.

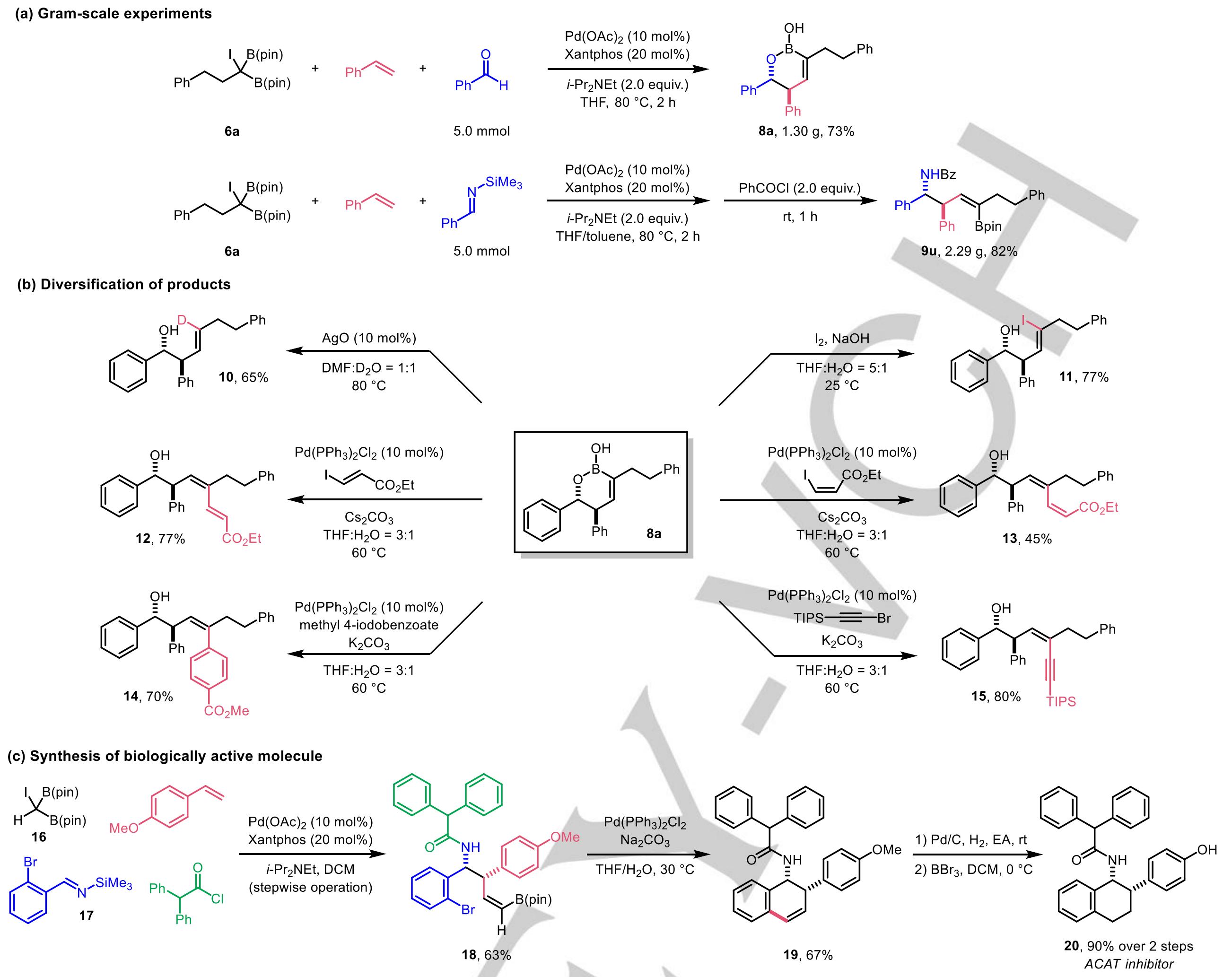
Scope of Cascade Heck Coupling/Allylboration Reaction of Iododiborons, Alkenes and Imines. Considering that imines are also promising substrates for allylation reactions,[18] we next sought to replace the aldehyde with an imine bearing a suitable protecting group. We envisioned that a similar cascade process would deliver products that possess both a vinyl boronate moiety and a homoallylic amino group, which is widespread in many biologically active compounds and can serve as an entity for the construction of myriad *N*-containing targets. Unfortunately, the initial screening of various imines with a regular protecting group, such as aryl, alkyl, acyl, sulfonyl, and phosphinoyl, failed to provide any sign of success. Gratifyingly, when a trimethylsilyl-protected aldimine, a rarely used substrate in allylboration,[19] was explored, a major product was observed in the crude NMR. This compound was subsequently protected by acylation using pivaloyl chloride to allow facile purification of the final product **9** by silica gel chromatography (see Table 3). The structure and configuration of the products were again confirmed by single crystal X-ray diffraction (**9e**).[17] Notably, although the B(pin) group was retained and a cyclic structure was not formed, 1,2-*anti*- and *E*-configuration were the same as those obtained in Table 2. We surmised that the fragile N–Si bond could be readily destructed under the reaction conditions, releasing the less hindered C=NH type imine *in situ* to participate in the allylboration.[19]

With suitable conditions in hand, the scope of this imine-involved cascade reaction was also investigated. Overall, the substrate scope and functional group tolerance were similar to the aldehyde version. As a concise demonstration, we compiled some selected examples in Table 3. In Part A, a combinational scope of imines and alkenes was exhibited. Typical functional groups, including halogens, ester, methoxy, trifluoromethyl, and nitro groups, as well as heterocycles, were all well tolerated in this transformation (**9a–m**), affording the corresponding products in up to 97% yield. α, β-Unsaturated imine (**9n**) was also competent with 8:1 diastereoselectivity. The iododiborons with different

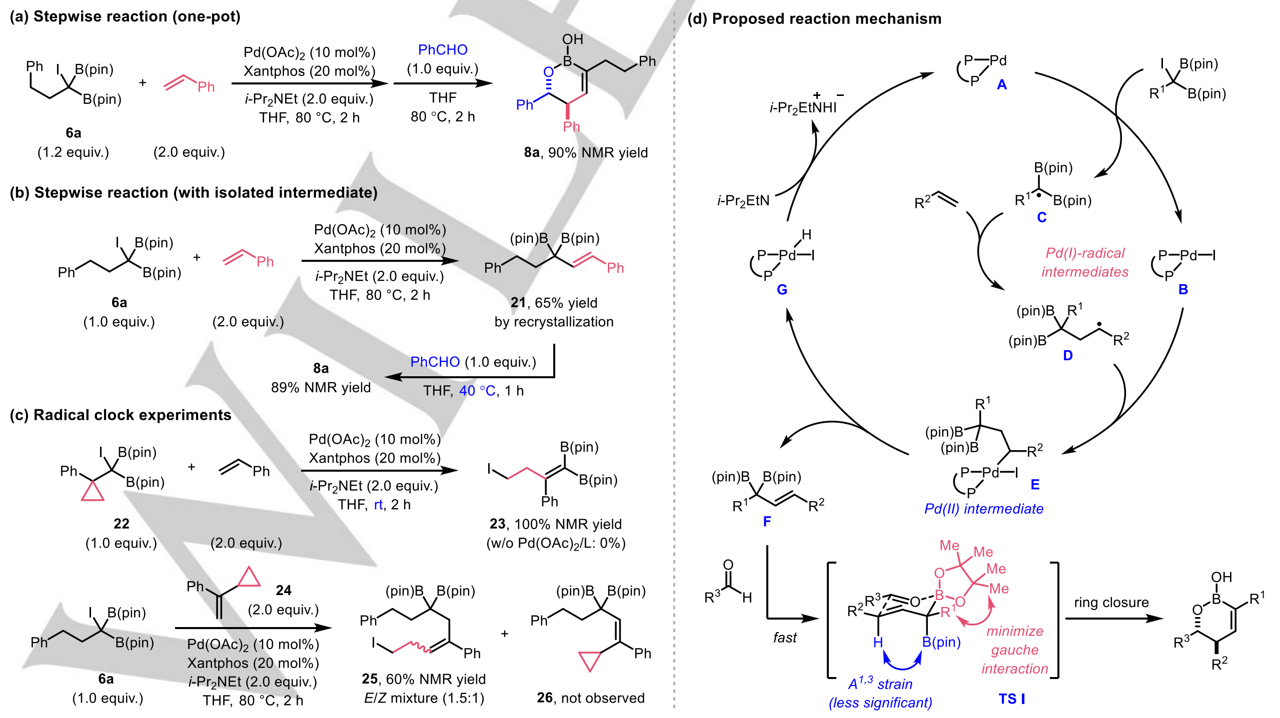
Table 3. Scope of Cascade Heck/Allylboration of Iododiborons, Alkenes and Silyl Imines.[a]



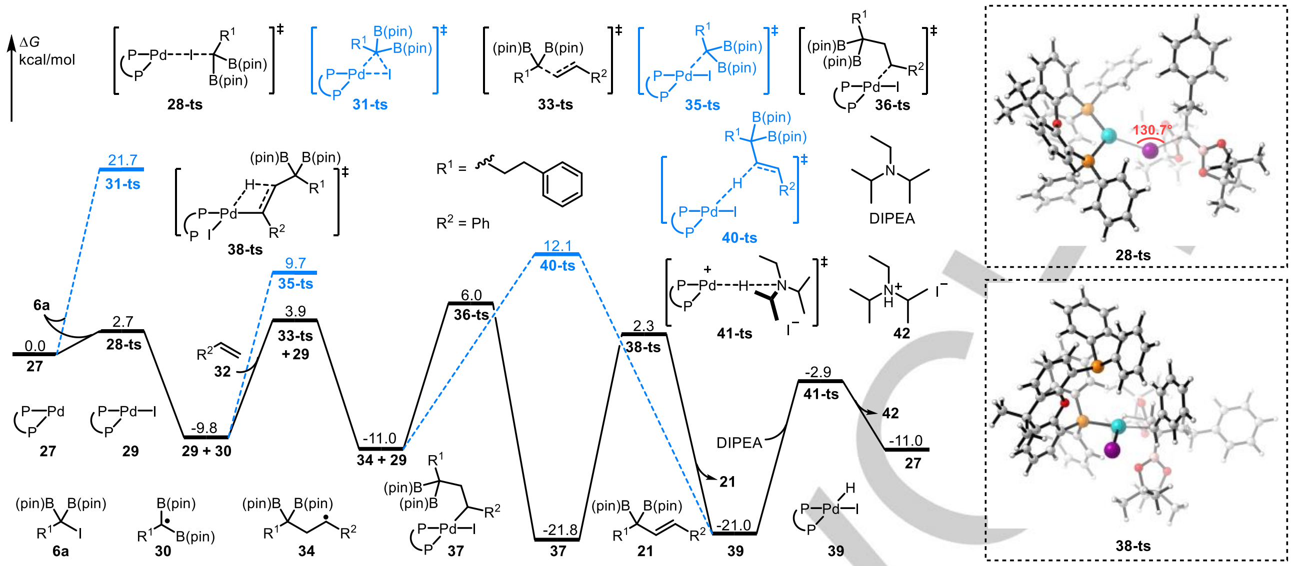
[a] Standard conditions: iododiboron (0.12 mmol), alkene (0.2 mmol), *N*-TMS imine (0.1 mmol), Pd(OAc)₂ (0.01 mmol), Xantphos (0.02 mmol), *N,N*-diisopropylethylamine (0.2 mmol), THF (0.1 mL), toluene (0.9 mL), 80 °C, 2 h, then protecting reagent (0.2 mmol), rt, 1 h. Isolated yields. [b] The Heck reaction was conducted under the standard conditions, then *N*-TMS imine (0.10 mmol), 80 °C, 1 h. [c] The hydroxyl group in the iododiboron substrate was TBS-protected.



Scheme 2. Gram-scale Experiments and Utilization of Products.



Scheme 3. Brief Mechanistic Survey and Proposed Reaction Mechanism.



Scheme 4. Computational Study of Cross-Coupling.

substituents all proceeded well (**9o–t**). Lastly, one advantage of using silyl-protected imine is that the resulting amino group can be acylated with a variety of different acyl donors at the endpoint. For instance, we could switch pivaloyl chloride to benzoyl chloride (**9u**), acetic anhydride (**9v**), and trifluoroacetic anhydride (**9w**). This feature could also be utilized to directly tether complex molecules such as the acid chloride derivative from ursodeoxycholic acid (**9x**). This strategy was also powerful for installing protecting groups like Boc and Cbz (**9y** and **9z**).

Gram-scale Experiments and Utilization of The Products. The robustness of our method was demonstrated by conducting the reaction on gram-scale without loss of efficiency. As depicted in Scheme 2a, **8a** and **9u** could both be synthesized on 5 mmol scale under the standard conditions. The slightly lower yield of **8a** was attributed to the extended period of time on silica gel chromatography. As noted at the outset, boronates are extremely versatile intermediates in organic synthesis.[13] A variety of transformations using **8a** were examined to further prove the value of our method (Scheme 2b). Silver-catalyzed protodeboronation was found to deliver the deuterated compound **10** in the presence of D_2O.[20] The treatment of I_2 and NaOH provided the vinyl iodide **11** in good yield.[21] In the presence of a palladium catalyst, **8a** could readily participate in a range of cross-coupling reactions with vinyl, aryl, and alkynyl halides. Lastly, a concise synthesis of compound **20**, a potent acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor,[22] was developed to further demonstrate the synthetic potential of our method (Scheme 2c). Compared with the literature, this modular synthetic route is much shorter, and it allows the facile introduction of substituents in the four reaction components, therefore rapidly accessing a wide variety of analogs for efficient evaluation of biological activity.

Brief Mechanistic Survey. To shed light on the mechanism of the transformation, a few mechanistic experiments were performed. The two-step sequence of the cascade reaction was unambiguously supported by running the reactions stepwise either in a one-pot fashion or with the isolation of the intermediate **21** (Scheme 3a and 3b). Notably, the allylboration was accomplished within 1 hour at 40 °C, which was much more expeditious than expected, considering **21** is a sterically congested allylboration reagent. This also indicated that, at least for the model reaction, the allylboration is not the rate-determining step. We then sought to elucidate the detailed mechanism of the cross-coupling. Due to the steric hindrance of the geminal diboryl groups, the classic Pd(0)/(II) catalytic cycle of Heck reaction seems questionable. It has come to our attention that alkyl halides, including the sterically encumbered tertiary halides, can undergo Heck-type coupling in the presence of a palladium catalyst under visible light irradiation.[23,15] In these reports by Alexanian, Gevorgyan and others, mechanism involving Pd(I)/alkyl-radical intermediates were generally proposed. Although unactivated alkyl halides or mono-boryl alkyl halides were incompetent under our irradiation-free conditions, we surmised that the existence of the two boryl groups could help lower the activation barrier. To confirm the radical nature of our intermediates, radical-clock experiments were performed (Scheme 3c). The reaction with substrate **22** bearing a cyclopropyl group resulted in the quantitative formation of the ring-opening product **23**. In another experiment, replacing styrene with radical clock **24** solely provided the ring-opening coupling product **25** as a mixture of *E*/*Z* isomers, and the coupling adduct possessing an intact cyclopropane unit (**26**), was not detected, which was a significant piece of evidence for the generation of radical intermediates.

Proposed Reaction Mechanism. Based on the mechanistic experiments and the proposals in the literature,[15] a putative Pd(I)-radical mechanism is proposed for the Heck cross-coupling (Scheme 3d). First, an active Pd(0) catalyst **A** is generated by *in situ* reduction of $Pd(OAc)_2$. Due to the steric hindrance, it fails to undergo a regular oxidative addition into the iododiboron substrate. Instead, the catalytic cycle commences with an iodine atom abstraction by the Pd(0) catalyst through a single electron transfer (SET) process, creating a Pd(I) species **B** and a geminal diboryl carbon-centered radical **C**. The latter is stabilized by the π-donation between the radical and the vacant *p* orbital of the boron atoms, which has been widely proposed.[24,25] **C** then reacts with the alkene to form a benzylic-type radical **D**, which is able to reunite with the Pd(I) species **B** to form a Pd(II) intermediate **E**, on which *β*-H elimination proceeds to give the cross-coupling product **F** and complex **G**, which can regenerate **A** through a base-assisted reductive elimination. Overall, a Pd(0/I/II) cycle is operative, which is fundamentally distinct from the conventional Pd(0/II) scenario. Meanwhile, the allylic *gem*-diboron species **F**

can immediately react with the aldehyde to undergo allylboration through a six-membered chairlike transition state **TS I**. According to the studies by Murakami and Chen,[7] one B(pin) moiety needs to be placed at the pseudoaxial position to avoid the gauche interaction of the two boryl groups. The resulting $A^{1,3}$ strain is considered less significant, therefore inducing the high diastereoselectivity. The allylboration product subsequently undergoes a ring closure to deliver the final product.

Mechanistic Computational Studies. Lastly, DFT calculations were used to evaluate the proposed pathway in the cross-coupling reaction between iododiboron **6a** and styrene as the model substrates. The calculated free energy profiles are shown in Scheme 4, where the Pd(0) catalyst is chosen as the relative zero. The iodine-atom transfer from iododiboron **6a** to Pd(0) in catalyst **27** could occur via a linear transition state **28-ts** with an energy barrier of only 2.7 kcal/mol to afford Pd(I) iodide **29** and diboryl alkyl radical **30**. In the transition state **28-ts**, the bond angle of Pd–I–C is 130.7º. The computational results showed that the activation free energy of direct oxidative addition of Pd(0) with the C–I bond in **6a** is as high as 21.7 kcal/mol via three-membered ring type transition state **31-ts**. Therefore, this pathway can be excluded due to the high barrier. Styrene **32** and Pd(I) iodide **29** compete for radical addition of diboryl alkyl radical **30** via the corresponding transition states **33-ts** and **35-ts**, respectively. The energy barrier via the latter was 5.8 kcal/mol higher, which indicates an unfavorable process. The generated new alkyl radical intermediate **34** could react with Pd(I) iodide **29** through radical-type oxidative addition to give Pd(II)-alkyl intermediate **37**. The calculated free energy barrier of this step is 17.0 kcal/mol via transition state **36-ts**. It clearly revealed that when the steric hindrance is reduced in a newly generated alkyl radical **34** comparing with **30**, the calculated free energy barrier of radical type oxidative addition onto the common Pd(I) intermediate **29** using alkyl radical **34** is 2.5 kcal/mol lower than that using diboryl alkyl radical **30**. Subsequently, the *β*-hydride elimination takes place via a four-membered ring-type transition state **38-ts** with an energy barrier of 24.1 kcal/mol to yield C–C bond coupling product **21** and form a Pd(II)-hydride species **39**. In transition state **38-ts**, the dissociation of partial phosphine ligand is necessary to provide vacancy for the hydride. This process can also be considered as synthetic hydrogen atom abstraction from alkyl radical **34** by Pd(I) iodide **29** via transition state **40-ts**. The calculated energy barriers are 6.1 kcal/mol higher than that of stepwise *β*-hydride elimination. Therefore, this pathway is expelled. The Pd(II)-hydride species **39** can be further deprotonated by the base of DIPEA to regenerate Pd(0) catalyst via transition state **41-ts** with an energy barrier of 18.1 kcal/mol to complete the catalytic cycle.

Conclusion

In summary, we have disclosed the first example of a transition metal-catalyzed three-component reaction of iododiboron compounds, demonstrating their synthetic potential as ambiphilic synthons. The cascade process consists of a Heck cross-coupling and a subsequent allylboration, and is highly efficient and compatible with various functional groups, and a wide range of heterocycles. We also conducted mechanistic studies using radical-clock experiments and DFT calculation, and our results suggested that the cross-coupling reaction proceeds through an unconventional Pd(I)-radical mechanism. By providing straightforward access to a broad array of polyfunctionalized boronates, and thereby to diverse families of complex compounds through subsequent functionalization, our catalytic method may have a substantial impact in many fields of organic chemistry.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Ambiphilic Reagent • Multicomponent Reaction • Iododiboron • Organoboron • Synthetic Methods

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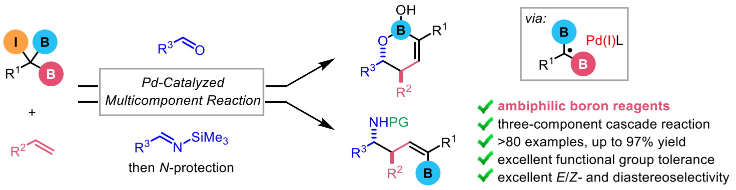

- ✓ **ambiphilic boron reagents**
- ✓ three-component cascade reaction
- ✓ >80 examples, up to 97% yield
- ✓ excellent functional group tolerance
- ✓ excellent *E*/*Z*- and diastereoselectivity

The ambiphilic reactivity of iododiboron compounds was disclosed by palladium-catalyzed three-component reactions of iododiborons, alkenes and aldehydes/imines. The reaction features mild conditions, broad scope, excellent diastereoselectivity and functional group tolerance. An unconventional Pd(0/I/II) catalytic cycle is operative, supported by mechanistic experiments and DFT calculations.