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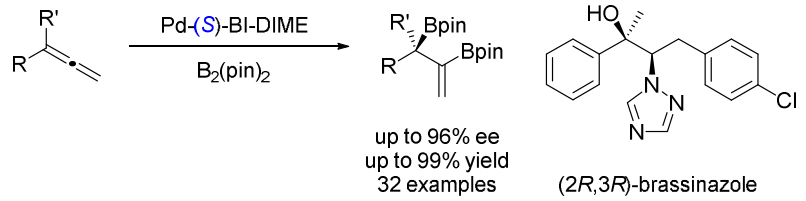

- chiral tertiary boronic ester
- perfect regioselectivity
- Pd loading as low as 0.2 mol %
- excellent yields and enantioselectivities
- first enantioselective synthesis of brassinazole
- concerted oxidative addition and allene insertion

Enantioselective palladium-catalyzed diboration of 1,1-disubstituted allenes is developed for the first time by employing a P-chiral monophosphorus ligand BI-DIME.

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EDGE ARTICLE

Enantioselective Palladium-Catalyzed Diboration of 1,1-Disubstituted Allenes

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A practical and enantioselective palladium-catalyzed diboration of 1,1-disubstituted allenes is developed by employing a P-chiral monophosphorus ligand BI-DIME to form a series of diboronic esters containing a chiral tertiary boronic ester moiety in excellent yields and ee's with the palladium loading as low as 0.2 mol %. DFT calculations revealed a concerted mechanism of oxidative addition of bis(pinacolato)diboron and allene insertion, as well as a critical dispersion effect on the origins of the enantioselectivity. The method is successfully applied to a concise and enantioselective synthesis of brassinazole.

Chiral boronic esters have become versatile building blocks in synthetic organic chemistry.[1] Synthesis of chiral tertiary boronic esters have attracted considerable interests recently and some notable methods are developed (Figure 1) including Aggarwal-Matteson lithiation-borylation methodology from chiral secondary alcohols,[2] asymmetric hydroboration of 1,1-disubstituted alkenes,[3] and asymmetric borylation of allylic carbonates,[4] Michael acceptors,[5] as well as tertiary halides.[6] The asymmetric diboration of 1,1-disubstituted alkenes or allenes[7] would not only provide a chiral tertiary boronic ester moiety, but also form an additional boronic ester component for further transformations. Work by Morken on asymmetric diboration[8,9] with various transition metal catalysts (Rh, Pt, or Pd) has provided significant progress in forming secondary boronic ester products with excellent ee's. However, the asymmetric diboration of 1,1-disubstituted alkenes or allenes to form chiral tertiary boronic esters remains challenging with either low ee's or low yields.[9b] Herein we communicate our results on palladium-catalyzed asymmetric diboration of 1,1-disubstituted allenes that have led to a series of diboronic esters containing a chiral tertiary boronic ester moiety in excellent enantioselectivities and yields with the employment of a P-chiral monophosphorus ligand BI-DIME. The chiral diboronic ester products are useful chiral building blocks which have led to the first enantioselective synthesis of a specific brassinosteroid biosynthetic inhibitor—brassinazole.[19]

Figure 1. Formation of chiral tertiary boronic esters by asymmetric diboration.

We chose to use buta-2,3-dien-2-ylbenzene (**1a**) as the substrate to investigate the palladium-catalyzed asymmetric diboration of 1,1-disubstituted allenes (Table 1). The reactions were carried out at rt in cyclohexane for 24 h with bis(pinacolato)diboron as the reagent in the presence of $Pd_2(dba)_3$ (1 mol %) and a chiral phosphorus ligand (2.5 mol %)

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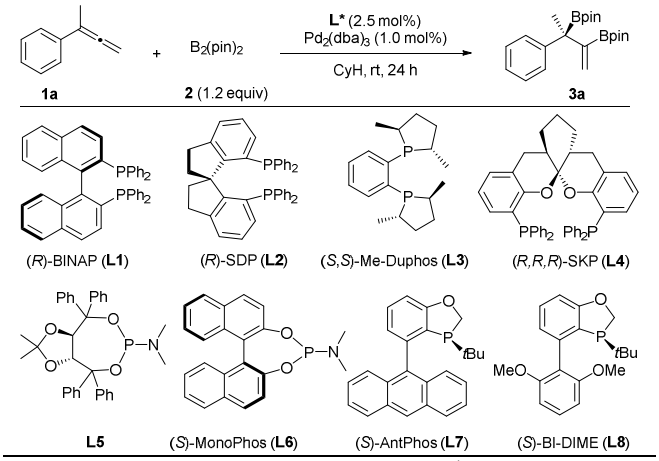
(Table 1). It was found that chelating phosphorus ligands such as BINAP and SDP did not provide any reactivities (entries 1-2).

Table 1. Enantioselective Pd-catalyzed diboration of buta-2,3-dien-2-ylbenzene (**1a**) with bis(pinacolato)diboron (**2**)



Entry[a]	L*	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	CyH	0	--
2	**L2**	CyH	0	--
3	**L3**	CyH	15	52
4	**L4**	CyH	95	59
5	**L5**	CyH	76	79
6	**L6**	CyH	45	12
7	**L7**	CyH	60	91
8	**L8**	CyH	98	94
9	**L8**	toluene	82	92
10	**L8**	THF	51	91
11	**L8**	Dioxane	27	92
12	**L8**	DCM	0	--
13[d]	**L8**	CyH	33	92
14[e]	**L8**	CyH	97	94

[a]Unless otherwise specified, the reactions were performed under nitrogen at rt for 24 h with **1a** (0.20 mmol), **2** (0.24 mmol), **L*** (2.5 mol %) and $Pd_2(dba)_3$ (1.0 mol %) in the specified solvent. Product **3a** was the only detectable product. The *R* absolute configuration of **3a** was determined by comparing its optical rotation with reported data.[14] [b]Isolated yields. [c]Determined by HPLC on a chiral IC-3 column. [d]$Pd(OAc)_2$ instead of $Pd_2(dba)_3$ was employed as the precursor. [e]**1a** (36.0 mmol), $Pd_2(dba)_3$ (0.1 mmol %), **L8** (0.25 mmol %), 72 h.

A low yield (15%) and ee (52% ee) were observed when Me-DuPhos was employed as the ligand (entry 3). It should be noted that the diboration occured exclusively on the substituted double bond of the allene, provided the prouct **3a** containing both a tertiary boronic ester and an alkenyl boronic ester moieties. Interestingly, the SKP ligand[10] (**L4**) with a large bite angle led to an excellent yield (95%) and a moderate ee (59% ee) (entry 4). We thus predicted that the reaction could be better promoted with a monophosphorus ligand, as observed by Morken in diboration of monosubstituted allenes.[9] Thus, a TADDOL-derived monophosphoramidite ligand **L5** led to the formation of **3a** in 76% yield and in 79 % ee (entry 5). Another monophosphoramite ligand **L6** derived from a chiral BINOL backbone proved to be less effective, indicating the importance of the ligand scaffold on both reactivity and enantioselectivity of the reaction. Encouragingly, the P-chiral monophosphorus ligand AntPhos[11] (**L7**) provided a moderate yield (60%) and an excellent ee (91% ee) (entry 7). Further study of the P-chiral phosphorus ligands developed in our laboratory showed that BI-DIME[12] (**L8**) provided an almost quantitative yield and a highest ee (94%) (entry 8). Screening of the solvent showed the reaction was facilitated with a nonpolar and non-coordinating solvent, as a diminished yield was observed in either toluene, THF or dioxane. No reaction was observed when dichloromethane was employed (entries 8-12). A Pd(0) precursor appeared to be advantageous for the reaction since a diminished yield was observed when $Pd(OAc)_2$ was applied (entry 13). Finally, the diboration was studied at a low catalytic loading (0.2 mol % Pd, 0.25 mol % **L8**) and at a gram scale (36 mmol **1a**, 4.8 g). The product **3a** (13.6 g) was obtained in 97% yield and in 94% ee (entry 14), demonstrating the practicality of this asymmetric transformation.

The substrate scope of this asymmetric diboration was then investigated. As depicted in Table 2, a series of diboronic esters with various electronic properties and substitution patterns on the benzene ring (**3b**-**p**) were smoothly formed at rt in excellent ee's and yields with Pd-**L8** as the catalyst. The enantioselectivities obtained were slightly higher with substrates having electron-donating substituents, but substituents such as fluoro (**3d**) and trifluoromethyl group (**3g**) were well applicable. Substrates with an *ortho* substituent (**3n**-**p**) were also tolerable. The reactions of both 1- and 2-naphthyl substrates provided excellent yields and ee's (**3q**-**r**). A chiral furyl product **3s** was also synthesized successfully. Substrates with multiple substituents on the benzene ring were equally effective for the transformation (**3t**-**u**). In order to test the chemoselectivity between an allene and an olefin, a substrate containing both moieties was subjected for diboration and only the allene moiety was reactive under the current conditions to form product **3v** in 99% yield and 96% ee. Both cyclic and heterocyclic substrates were applicable to smoothly afford **3w** and **3x**, respectively, in excellent yields and ee's. Switch of the methyl substituent with an ethyl group on allene resulted in an inferior ee (72% ee, **3y**). Introduction of a cyclopropyl group instead of the methyl substituent was less effective (**3z**). 1,1-Dialkylallenes were also applicable. While a moderate ee (67%) was obtained on product **3aa** bearing two primary alkyl substituents on the quaternary stereocenter, high ee's (87% and 91%) were obtained on products **3ab** and **3ac** containing both a methyl and a secondary alkyl groups at the chiral center. A good ee was also achieved on **3ad** bearing a tertiary alkyl group. Finally, the diboration of 1,1-diarylallenes were studied. While a low ee was obtained on product **3ae** indicating little difference between a phenyl substituent and a *para*-tolyl group, a moderate ee (75%) was achieved on product **3af** bearing both a phenyl and an *ortho*-tolyl substituents at the quaternary stereocenter.

To understand the mechanism of this catalytic asymmetric reaction, the diboration of **1a** was investigated with a scalemic mixture of ligand **L8**. A perfect linear relationship between ee of **L8** and ee of product **3a** was observed, indicating the reaction catalyzed by a palladium catalyst composed of a

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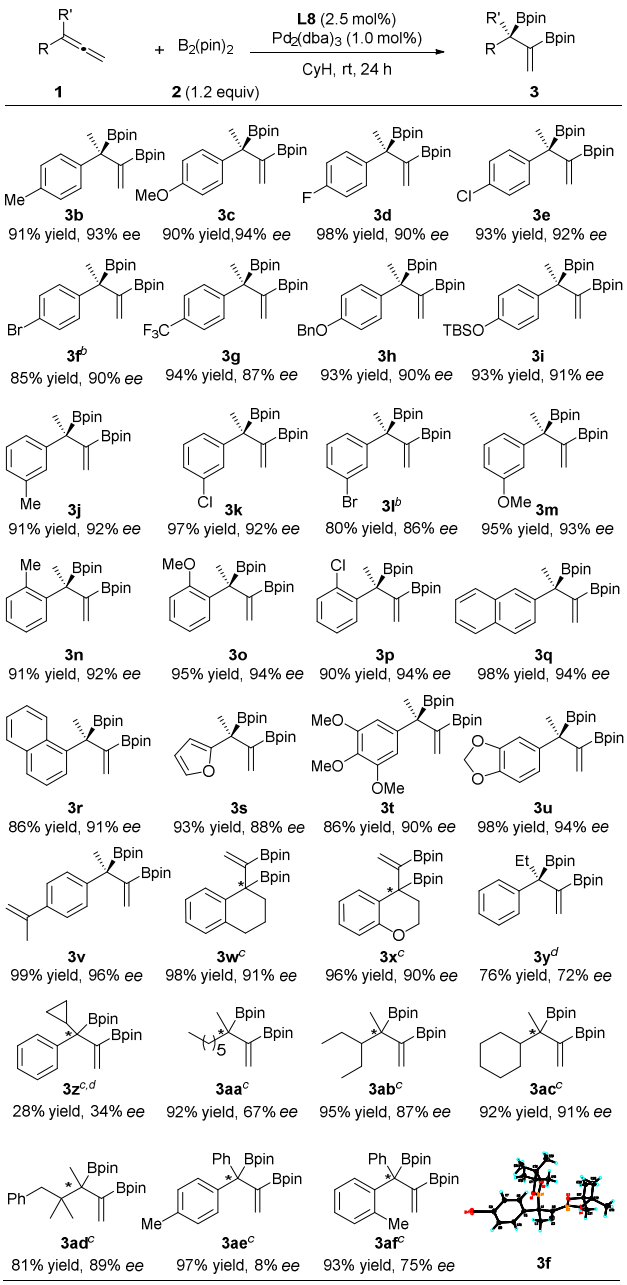
single monophosphorus ligand **L8**. Variation of the Pd:**L8** ratio from 1:1, 1:2, and 2:1 did not lead to a significant change of both the yield and the enantioselectivity, further demonstrating the

Table 2. Enantioselective Pd-catalyzed diboration of 1,1'-disubstituted allenes[a]



[a]Unless otherwise specified, the reactions were performed under nitrogen at rt for 24 h with **1** (0.20 mmol), **2** (0.24 mmol), **L8** (2.5 mol %) and $Pd_2(dba)_3$ (1.0 mol %) in cyclohexane (2.0 mL). The yields of isolated products were shown here. The ee values were determined by HPLC on a chiral column. The *R* absolute configuration of **3f** was determined by X-ray crystallographic analysis,[13] the others were assigned by analogy. [b]$Pd_2(dba)_3$ (2.0 mol %) and **L8** (5.0 mol %) were employed. [c]The absolute configurations were not determined. [d]Incomplete conversions.

composition of a single **L8** in the active palladium catalyst. To understand the perfect regioselectivity and the stereochemical model of this asymmetric diboration, energetics of the catalytic transformation was calculated at B3LYP-D3/6-31G(d)+SDD level. As shown in Figure 2a, the reaction initiates from the palladium species **RC**, which undergoes oxidative addition of bis(pinacolato)diboron concerted with allene insertion where the boryl group migrates to the middle carbon of the allene to give an *η3* Pd(II)-allyl intermediate **INT$_{Si}$** or **INT$_{Re}$**. Notably, this initial oxidative boryl migration[16] is in well agreement with the perfect regioselectivity of diboration on the internal double bond of allene, and such process is an irreversible and stereo-determining step of the transformation.[15] **TS1$_{Re}$** is computed to be lower in free energy than **TS1$_{Si}$** by 1.4 kcal/mol, in qualitative agreement with the observed enantioselectivity (ΔGexp: 2.1 kcal/mol).

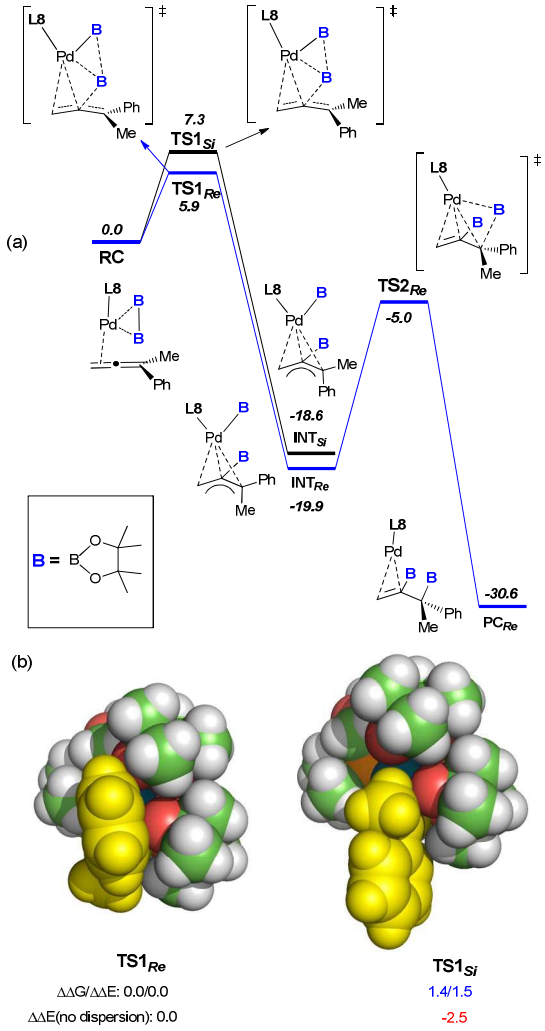


Figure 2. (a) Free-energy profile (in kcal/mol) for the Pd-catalyzed asymmetric diboration of buta-2,3-dien-2-ylbenzene (**1a**) with (*S*)-BI-DME (**L8**) as the ligand at B3LYP-D3/6-31G(d)+SDD level.[15] (b) VDW representation of the optimized

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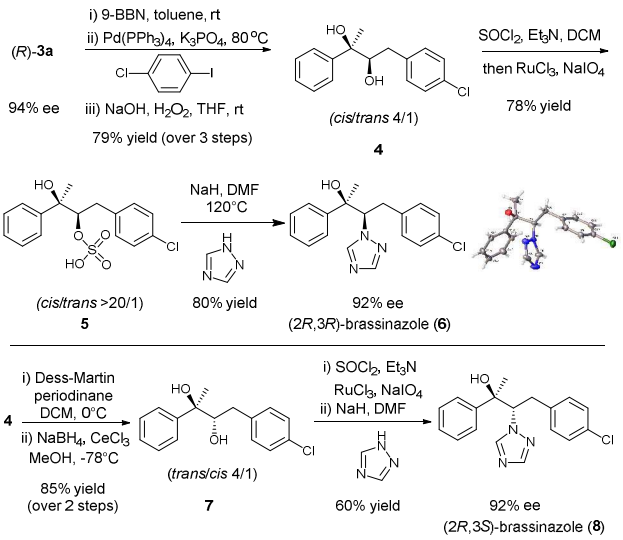
TS1$_{Re}$ and **TS1$_{Si}$** with relative free and electronic energies in kcal/mol

Distortion/interaction analysis[17] reveals that there is a greater dispersion interaction between the phenyl group[17b] on the allene and one boryl group in **TS1$_{Re}$** than **TS1$_{Si}$**, which is considered as the key factor for the enantioselectivity (Figure 2b).[15] When excluding the dispersion contribution, the enantioselectivity is computed to be reversed. Finally, the reductive elimination via **TS2$_{Re}$** proceeds from **INT$_{Re}$** to produce **PC$_{Re}$** with a barrier of about 14.9 kcal/mol. Apart from Morken's proposal where the oxidative addition of diboron to Pd proceeded prior to migratory insertion and the oxidative addition of diboron to Pd was computed as the rate-determining step,[9l] our calculations on diboration of **1a** revealed a concerted mechanism of oxidative addition of bis(pinacolato)diboron and allene insertion, provided the first computational insight on the origins of the enantioselectivity (molecular details and a critical dispersion effect), and disclosed the final reductive elimination step as the rate-determining step.

The chiral diboronic ester products are versatile building blocks in organic synthesis. For example, Aggarwal reported a stereospecific allylation between the diboronic ester (*S*)-**3a** and benzaldehyde to form a tetrasubstituted alkene after a Suzuki-Miyaura cross-coupling.[14,18,9k] To further explore the synthetic applications of such chiral diboronic esters, an enantioselective synthesis of brassinazole,[19] a specific inhibitor of brassinosteroid biosynthesis, was studied with (*R*)-**3a** as the starting material (Scheme 1). Surprisingly, despite its significant biological properties, its enantioselective synthesis was not reported to our knowledge. We envisioned that the diboration product (*R*)-**3a** would provide a rapid and efficient access to brassinazole through simple transformations. Thus, (*R*)-**3a** was subjected to a one-pot, three step sequence: a) hydroboration by treatment with 9-BBN;[20] b) Suzuki-Miyaura coupling with 1-chloro-4-iodobenzene; and c) oxidation under conditions of H_2O_2/NaOH. The chiral diol **4** was formed smoothly at a *cis*/*trans* ratio of 4:1 in 79% overall yield. Under Ley's conditions,[21] the diol **4** was readily oxidized to form the corresponding sulfate **5**, which was isolated as a pure *cis* product in 78% yield. Finally, treatment of sulfate **5** with 1,2,4-triazole under conditions of NaH/DMF yielded (2*R*,3*R*)-brassinazole (**6**) in 80% yield, whose absolute configurations were confirmed by X-ray crystallography.[13] It should be noted that the sulfate **5** proceeded first through an intramolecular S_N2 reaction to form an epoxide, which was subsequently attacked by 1,2,4-triazole to undergo a 2nd S_N2 reaction, yielding product **6** with the net retention of stereochemistry. Compound **4** was also transformed to its diastereomer **7** through an oxidation-reduction procedure, which ultimately led to the formation of (2*R*,3*S*)-brassinazole (**8**) via sulfate formation and nucleophilic substitution. Thus, we accomplished a concise and first enantioselective synthesis of brassinazole.

Conclusions

In summary, we have developed a practical and enantioselective palladium-catalyzed diboration of 1,1-disubstituted allenes which have led to the synthesis of a series of diboronic esters containing a chiral tertiary boronic ester in excellent yields and enantioselectivities with the palladium loading as low as 0.2 mol %. The reaction enjoys a broad substrate scope and good functional group compatibility. The chiral ligand BI-DIME has proven to be crucial for the success of the reaction. DFT calculations have identified a concerted mechanism of oxidative addition of bis(pinacolato)diboron and allene insertion, and revealed a critical dispersion effect on the origins of the enantioselectivity. Finally, the application of the chiral diboronic ester to a concise and first enantioselective synthesis of brassinazole has been successfully demonstrated.



Scheme 1. Asymmetric synthesis of brassinazole

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