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. A series of diboronic esters containing a chiral tertiary boronic ester moiety are formed 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 the concise and enantioselective synthesis of brassinazole.

Chiral boronic esters have become versatile building blocks in synthetic organic chemistry.1 The synthesis of chiral tertiary boronic esters has attracted considerable interest recently and some notable methods have been developed (Fig. 1), including the Aggarwal–Matteson lithiation–borylation methodology from chiral secondary alcohols,2 asymmetric hydroboronation of 1,1-disubstituted allenes,3 and asymmetric borylation of allylic carbonates4 and Michael acceptors,5 as well as tertiary halides.6 The asymmetric diboration of 1,1-disubstituted allenes or alkenes7 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 diboration8,9 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 allenes or alkenes 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 (Table 1). The reactions

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Table 1. Summary of asymmetric diboration of 1,1-disubstituted allenes.

| Substrate | Palladium Catalyst | Ligand | ee (%) | Yield (%) |
|-----------|--------------------|--------|--------|-----------|
| 1a        | Pd(II)             | BI-DIME | 95     | 92        |
| 1b        | Pd(II)             | BI-DIME | 88     | 85        |

Fig. 1 Formation of chiral tertiary boronic esters by asymmetric diboration.
were carried out at rt in cyclohexane for 24 h with bis(pinacolato)diboron as the reagent in the presence of Pd₂(db₃)(1 mol%) and Pd₂(db₃)(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. Isolated yields. Determined by HPLC on a chiral IC-3 column. Pd(OAc)₂ instead of Pd₂(db₃) was employed as the precursor. 1a (36.0 mmol), Pd₂(db₃)(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 occurred exclusively on the substituted double bond of the allene, providing product 3a, which contains both a tertiary boronic ester moiety and an allenyl boronic ester moiety. Interestingly, the SKP ligand (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 the diboration of mono-substituted allenes. Thus, a TADDOL-derived monophosphoramidite ligand, L5, led to the formation of 3a in 76% yield and 79% ee (entry 5). Another monophosphoramidite ligand, L6, derived from a chiral BINOL backbone, proved to be less effective, indicating the importance of the ligand scaffold for both the reactivity and enantioselectivity of the reaction. Encouragingly, the P-chiral monophosphorus ligand AntPhos (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 (L8) provided an almost quantitative yield and the highest ee (94%) (entry 8). Screening of the solvent showed that the reaction was facilitated with a nonpolar and non-coordinating solvent, as a diminished yield was observed in 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 practicability 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 groups (3d) and trifluoromethyl groups (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 to diboration and only the allene moiety was reactive under the current conditions, forming product 3v in 99% yield and 96% ee. Both cyclic and heterocyclic substrates were applicable to smooth formation 3w and 3x, respectively, in excellent yields and ee’s. Switching the methyl substituent on the allene with an ethyl group resulted in an inferior ee (72% ee, 3y). The introduction of a cyclopropyl group instead of the methyl substituent was less effective (3z). 1,1-Dialkyllallenes were also applicable. While a moderate ee (67%) was obtained for product 3aa, bearing two primary alkyl substituents on the quaternary stereocenter, high ee’s (87% and 91%) were obtained for products 3ab and 3ac, respectively, which contain both a methyl and a secondary alkyl group at the chiral center. A good ee was also achieved for 3ad, bearing a tertiary alkyl group. Finally, the diboration of 1,1-diarylallenes was studied. While a low ee was obtained for product 3ae, indicating little difference between the phenyl substituent and the para-tolyl group, a moderate ee (75%) was achieved for product 3af, bearing both a phenyl and an ortho-tolyl substituent 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 the ee of $L8$ and the ee of product $3a$ was observed, indicating that the reaction was catalyzed by a palladium catalyst composed of a 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 in either the yield or the enantioselectivity, further demonstrating the presence of a single $L8$ in the active palladium catalyst. To understand the perfect regioselectivity and the stereochemical model of this asymmetric diboration, the energetics of the catalytic transformation were calculated at the B3LYP-D3/6-31G(d)+SDD level. As shown in Fig. 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 $\eta^2$ Pd(II)-allyl intermediate, $\text{INT}^{\text{Si}}$ or $\text{INT}^{\text{Re}}$. Notably, this initial oxidative boryl migration is in

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

| $R^1$ | $R^2$ | $\text{L8} (5.0 \text{ mol})$ | $\text{B}_2(\text{pin})_2$ | $\text{Pd}_2(\text{dba})_3 (1.0 \text{ mol})$ |
|-------|-------|----------------|----------------|----------------|
| $1a$  | $1a'$ | $5.0 \text{ mol}$ | $1.0 \text{ mol}$ | $2.0 \text{ mol}$ |

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 $\text{Pd}_2(\text{dba})_3$ (1.0 mol%) in cyclohexane (2.0 mL). The yields of the isolated products are 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; the others were assigned by analogy. $^a$ $\text{Pd}_2(\text{dba})_3$ (2.0 mol%) and $L8$ (5.0 mol%) were employed. $^b$ The absolute configurations were not determined. $^d$ Incomplete conversions.

Fig. 2. (a) Free-energy profile (in kcal mol$^{-1}$) for the Pd-catalyzed asymmetric diboration of buta-2,3-dien-2-ylbenzene ($1a$) with (S)-BI-DME ($L8$) as the ligand at the B3LYP-D3/6-31G(d)+SDD level. (b) VdW representation of the optimized $\text{TS}^{\text{Re}}$ and $\text{TS}^{\text{Si}}$, with relative free and electronic energies in kcal mol$^{-1}$. 
good agreement with the perfect regioselectivity of diboration on the internal double bond of the allene, and this process is an irreversible and stereo-determining step of the transformation.\textsuperscript{15} TS1\textsubscript{Re} is computed to be lower in free energy than TS1\textsubscript{Si} by 1.4 kcal mol\textsuperscript{-1}, which is in qualitative agreement with the observed enantioselectivity (ΔG\textsubscript{exp} 2.1 kcal mol\textsuperscript{-1}).

Distortion/interaction analysis\textsuperscript{17} reveals that there is a greater dispersion interaction between the phenyl group\textsuperscript{19} on the allene and a boryl group in TS1\textsubscript{Re} than in TS1\textsubscript{Si}, which is considered as the key factor for the enantioselectivity (Fig. 2b).\textsuperscript{17} When excluding the dispersion contribution, the enantioselectivity is computed to be reversed. Finally, the reductive elimination via TS2\textsubscript{Re} proceeds from INT\textsubscript{Re} to produce PC\textsubscript{Re}, with a barrier of about 14.9 kcal mol\textsuperscript{-1}. In contrast to Morken’s proposal that the oxidative addition of diboron to Pd proceeded from prior to migratory insertion and that the oxidative addition of diboron to Pd was computed as the rate-determining step,\textsuperscript{14} our calculations on the diboration of 1a revealed a concerted mechanism of oxidative addition of bis(pinacolato)diboron and allene insertion, provided the first computational insight into the origins of the enantioselectivity (molecular details and a critical dispersion effect), and disclosed the final reductive elimination step as the rate-determining step.

Chiral diboronic ester products are versatile building blocks in organic synthesis. For example, Aggarwal reported a stereo-specific allylation between the diboronic ester (S)-3a and benzaldehyde to form a tetrasubstituted allene after a Suzuki–Miyaura cross-coupling.\textsuperscript{14,18,34} To further explore the synthetic applications of such chiral diboronic esters, an enantioselective synthesis of brassinazole,\textsuperscript{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 had not been reported to our knowledge. We envisioned that the diboration product (R)-3a would provide 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;\textsuperscript{20} (b) Suzuki–Miyaura coupling with 1-chloro-4-iodobenzene; and (c) oxidation under conditions of NaOH/NaOAc. The chiral diol 4 was formed smoothly with a cis/trans ratio of 4 : 1 in 79% overall yield. Under Ley’s conditions,\textsuperscript{21} 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 (2R,3R)-brassinazole (6) in 80% yield. The absolute configuration was confirmed by X-ray crystallography.\textsuperscript{13} It should be noted that sulfate 5 proceeded first through an intramolecular S\textsubscript{N}2 reaction to form an epoxide, which was subsequently attacked by 1,2,4-triazole to undergo a second S\textsubscript{N}2 reaction, yielding product 6 with 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 (2R,3S)-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 the practical and enantioselective palladium-catalyzed diboration of 1,1-disubstituted allenes. This has led to the synthesis of a series of diboronic esters containing a chiral tertiary boronic ester with 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 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.

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