Communication

# Site- and Stereo-selective trans-Hydroboration of 1,3-Enynes Catalyzed by 1,4-Azaborine-Based Phosphine-Pd Complex

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# Site- and Stereo-selective *trans*-Hydroboration of 1,3-Enynes Catalyzed by 1,4-Azaborine-Based Phosphine-Pd Complex

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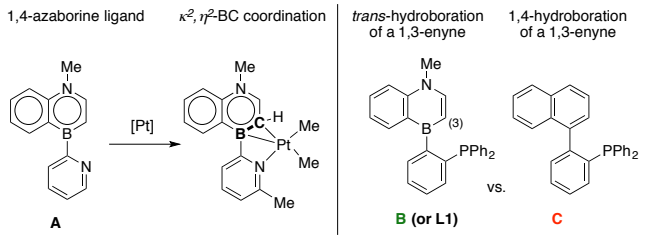
*Supporting Information Placeholder*

**ABSTRACT:** A concise synthesis of monobenzofused 1,4-azaborine phosphine ligands (Senphos) is described. These Senphos ligands uniquely support Pd-catalyzed *trans*-selective hydroboration of terminal and internal 1,3-enynes to furnish corresponding dienylboronates in high efficiency and diastereoselectivity. X-ray structural analysis of the Senphos-Pd(0) complex reveals a $\kappa^2$-*P*-$\eta^2$-BC coordination mode, and this isolated complex has been shown to serve as a competent catalyst for the *trans*-hydroboration reaction. This work demonstrates that the expanded chemical space provided by the BN/CC isosterism approach translates into the functional space in the context of stereoselective catalytic transformations.

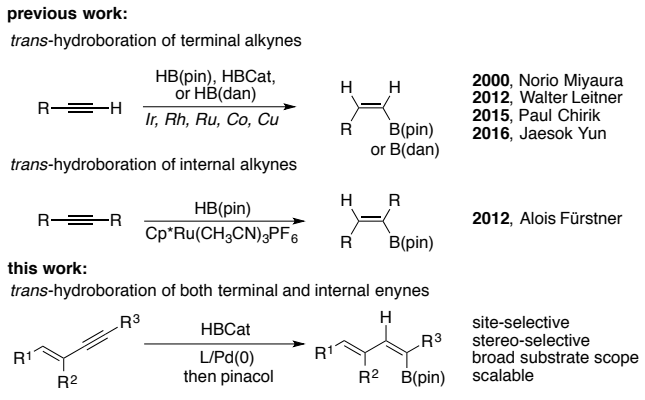
BN/CC isosterism, i.e., the replacement of a CC bond unit with the isoelectronic and isosteric BN bond unit, has recently emerged as a viable strategy to increase the structural diversity of organic molecules.[1] While early applications have appeared in the area of materials science[2] and biomedical research,[3] efforts taking advantage of expanded chemical space provided by BN/CC isosterism in ligand-supported catalysis for organic synthesis have lagged behind.[4-6] This is surprising in view of tremendous opportunities for achieving new reactivity and selectivity in catalytic transformations that the electronic tuning through BN/CC isosterism could potentially provide. In a recent example, we disclosed that the 1,4-azaborine-based pyridine ligand **A** (Scheme 1) exhibits a $\kappa^2$-$\eta^2$-BC coordination with group 10 transition metals and that the phosphine derivative **B** in conjunction with Pd could uniquely catalyze the hydroboration of a terminal enyne in a *trans*-selective fashion.[7] In contrast to **B**, the corresponding carbonaceous phosphine ligand isostere **C** behaves more similarly to a monodentate phosphine such as $PPh_3$ in terms of hydroboration selectivity and yield, producing preferentially allenes via 1,4-hydroboration; bisphosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe) furnish *syn*-hydroboration products exclusively.[8] Despite this promising preliminary result, our *trans*-hydroboration reaction still needed optimization with regard to yield and selectivity. More importantly, we wondered whether we could develop a *trans*-hydroboration protocol for internal enynes, a substrate class that is considered significantly more challenging (*vide infra*).

To date, only a handful of metal-catalyzed systems have been demonstrated to achieve *trans*-hydroboration of alkynes.[9] Miyaura reported the first example in 2000 using Ir or Rh catalysts (Scheme 2).[10] In 2012, Leitner showed that a Ru/PNP pincer complex can produce *Z*-vinylboronates via *trans*-hydroboration of alkynes with H-Bpin,[11] and Chirik introduced a Co-based system in 2015.[12] What these systems have in common is that they require the presence of the terminal alkyne proton due to the operating reaction mechanisms. Metal vinylidene species have been proposed for the Miyaura[10] and Leitner[11] catalysts whereas the Chirik system involves a Co-alkynyl[12] intermediate. Thus, internal enynes would not be suitable substrates for these systems. Lee and Yun reported very recently a Copper(I)–thiophene-2-carboxylate/DPEphos catalyzed *trans*-hydroboration of terminal aryl-alkynes in which the terminal alkyne proton does not undergo a migration that is observed in the Miyaura, Leitner, and Chirik systems.[13] To the best of our knowledge, the only metal-catalyzed system that can achieve the trans-hydroboration of internal alkynes is the $[Cp^*Ru(MeCN)_3]PF_6$ system by Fürstner.[14] This system works particularly well with symmetrical internal alkynes, and enynes have been pointed out as a problematic substrate for Fürstner's Ru catalyst.

**Scheme 1. An application of BN/CC isosterism in catalysis**



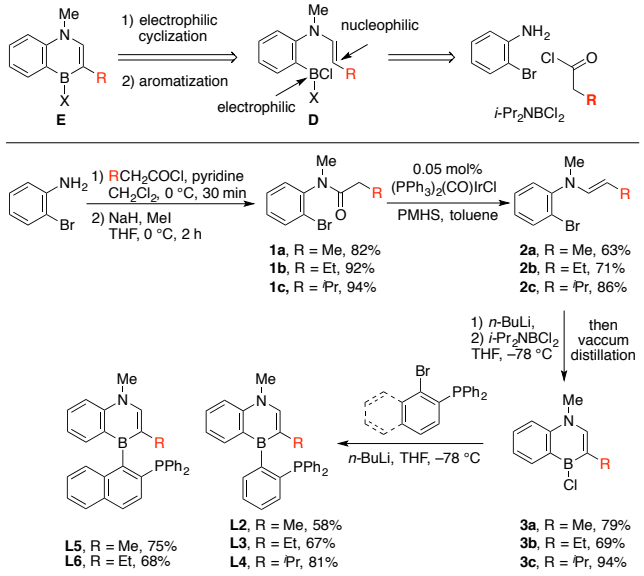

**Scheme 2. Transition-metal catalyzed *trans*-selective hydroboration of alkynes**




In this communication, we disclose a Pd-catalyzed *trans*-selective hydroboration of both terminal *and* internal 1,3-enynes with high site- and stereo-selectivity that is supported by 1,4-azaborine-based phosphine ligands. Key to the successful development of this reaction is a new, concise synthesis of monobenzofused 1,4-azaborine phosphines (Senphos), which we report here as well.

Our original synthesis of Senphos-type ligands via ring-closing metathesis[7] was unfortunately not amenable to scale-up[15] and ready modification of the C(3) position, which we believe could play an important role due to its proximity to the catalytically active Pd metal. This synthetic limitation significantly hampered our ability to develop a general and versatile *trans*-hydroboration protocol. Recognizing that *N*-vinyl-*B*-Cl intermediate **D** (Scheme 3, top) contains a nucleophilic enamine and an electrophilic boron atom, we envisioned that **D** could be poised to undergo intramolecular electrophilic cyclization[16] to furnish C3-substituted monobenzofused 1,4-azaborine **E** after aromatization, thus circumventing the limiting ring-closing-metathesis approach. Intermediate **D** should be accessible from commercially available 2-bromoaniline, a variety of acyl chlorides, and (diisopropylamino)boron dichloride.

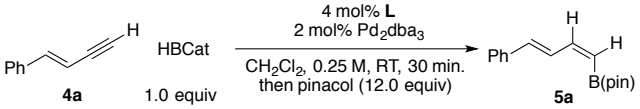
**Scheme 3. Retro-synthetic analysis and preparation of Senphos Ligands L2-L6**




With a new synthetic strategy in hand, we began our synthesis of a library of ligands with the acylation and methylation of 2-bromoaniline to provide amides **1a-c**. The critical enamine functionality was introduced using a protocol developed by Nagashima.[17] Treatment of **1** with polymethylhydrosiloxane (PHMS) in the presence of 0.05 mol% of Vasaka's complex $(PPh_3)_2(CO)IrCl$ as a catalyst furnished the corresponding enamines **2a-c** in 63-86% yield. Subsequent lithium-halogen exchange followed by addition of *i*-$Pr_2NBCl_2$ and distillation of the resulting reaction mixture under attenuated pressure afforded directly the versatile *B*-Cl-substituted monobenzofused 1,4-azaborines **3a-c**.[18] The structure of **3a** is further unambiguously confirmed by single crystal X-ray diffraction analysis (see supporting information). Finally, the substitution reaction of **3a-c** with phosphine-containing organolithium nucleophiles gave targeted SenPhos ligands **L2-6**.

We chose terminal *E*-1,3-enyne **4a** as our initial substrate to probe the effects of the ligand structure on the *trans*-hydroboration selectivity. In the presence of 4 mol% catalyst "**L1** (= **B**)/Pd(0)", reaction of **4a** with 1 equivalent of catecholborane (HBCat) in $CH_2Cl_2$ at room temperature and subsequent transesterification with pinacol[19] afforded the corresponding *trans*-hydroboration product **5a** with decent *trans*-hydroboration stereo-selectivity (93 : 7) in 59% yield (Table 1, entry 1). No background reaction was observed in the absence of the catalyst under otherwise identical reaction conditions. The C3-substituent in **L** plays an important role in the optimization of stereo-selectivity. For example, when **L4**, which bears the sterically more demanding *i*-Pr group at the C3 position, is used as the ligand, the reaction gave superior (> 98:2) *trans*-hydroboration selectivity compared to those with the smaller substituents (Table 1, enty 4 vs. entries 1-3). Switching the boron substituent from *o*-diphenylphosphinophenyl to 2-diphenylphosphinonaphth-1-yl group did not result in obvious trends in terms of both reactivity and stereo-selectivity (Table 1, entries 2 vs. 5, and entry 3 vs. 6). The isolated yield of dienylboronate ester **5a** could be elevated to 86% when 1.5 equivalents of CatBH is used instead of 1.0 equivalent (Table 1, entry 7).

**Table 1. Ligand survey of *trans*-hydroboration of terminal 1,3-enyne 4a catalyzed by L/Pd(0)**

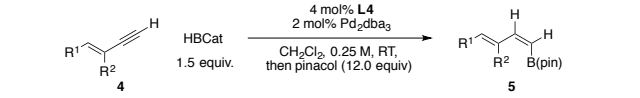


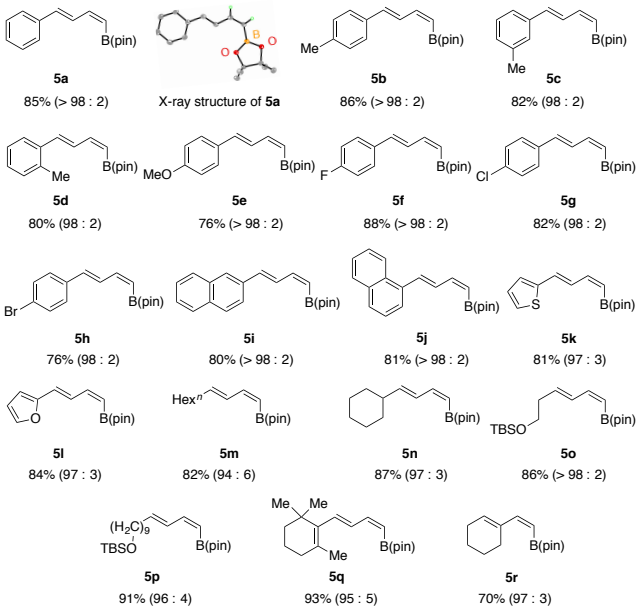

| entry | L | trans-hydroboration selectivity[a] | yield (%)[b] |
|---|---|---|---|
| 1 | **L1** | 93:7 | 59 |
| 2 | **L2** | 92:8 | 60 |
| 3 | **L3** | 96:4 | 56 |
| 4 | **L4** | >98:2 | 62 |
| 5 | **L5** | 96:4 | 59 |
| 6 | **L6** | 94:6 | 68 |
| 7[c] | **L4** | >98:2 | 86 |

[a]The diastereomeric ratio was determined by $^1$H NMR of crude material before addition of pinacol; [b]Yield of isolated product, based on **4a**; [c]1.5 equiv of HBCat was applied. dba: dibenzylidineacetone.

Under optimized reaction conditions, various terminal *E*-1,3-enynes **4** were subjected to the *trans*-selective hydroboration, and the results are summarized in Table 2. High yield and *trans*-selectivity were observed consistently with an array of electronically and sterically different substituents on the alkene. The stereochemistry of dienylboronate **5a** was confirmed by single crystal X-ray diffraction analysis (Table 2).

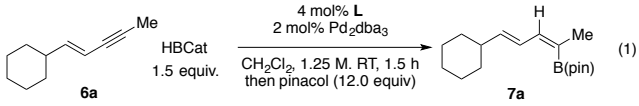
**Table 2. *Trans*-hydroboration of terminal 1,3-enynes 4 catalyzed by L4/Pd(0)**




Yield of isolated product (average of 2 runs), based on **4**. The diastereomeric ratio in parenthesis was determined by $^1$H NMR of crude material before addition of pinacol.

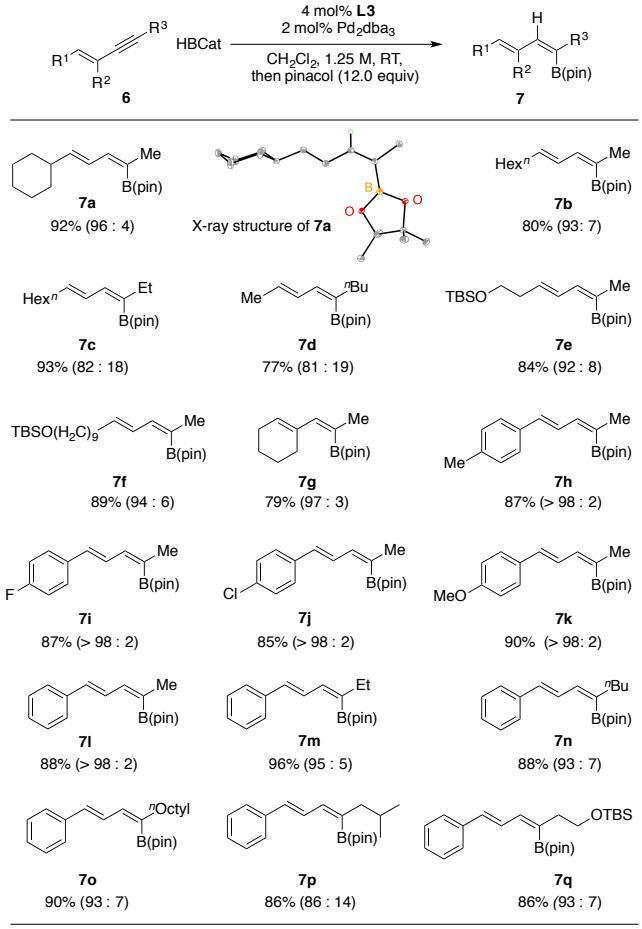
The metal-catalyzed *trans*-hydroboration of internal 1,3-enynes is a significantly more demanding problem and has currently no precedent in the literature. Internal 1,3-enynes are generally less reactive toward hydroboration, and the control of both site- and stereoselectivity is more challenging.[20] Gratifyingly, when the concentration of the reaction is increased from 0.25 M to 1.25 M,[21] the reaction of internal *E*-1,3-enyne **6a** with CatBH (see eq 1) in the presence of 4 mol% **L1**/Pd was complete within 90 minutes at room temperature, affording **7a** in 89% yield with 90:10 *trans*-hydroboration selectivity after treatment with pinacol. Other regioisomers were not observed. Further optimization with regard to the ligand structure revealed that the C3-ethyl substituted **L3** was the best performing ligand producing **7a** in 92% yield and 96:4 *trans*-hydroboration selectivity.[22]




**6a** **7a** (1)

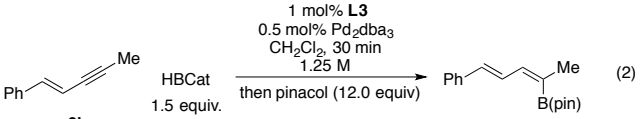
The substrate scope for the *trans*-hydroboration of internal 1,3-enynes is summarized in Table 3. In general, 1,4-disubstituted 1,3-eynes **6** bearing an aryl group at $R^1$ position gave superior *trans*-hydroboration selectivity than alkyl groups (Table 3, entries **7h**-**7l** vs. **7a**-**7g**). Increasing the substituent size of the $R^3$ substituent in **6** reduces *trans*-hydroboration selectivity (Table 3, entries **7l**-**7p**, in particular **7l** vs. **7p**). The bond connectivity of dienylboronate **7a** and the hydroboration stereoselectivity were unambiguously confirmed by the solid-state structure of **7a** (Table 3).

**Table 3. *Trans*-hydroboration of internal 1,3-enynes 6 catalyzed by L3/Pd(0)**




Yield of isolated product (average of 2 runs), based on **6**.The diastereomeric ratio in parenthesis was determined by $^1$H NMR of crude material before addition of pinacol.

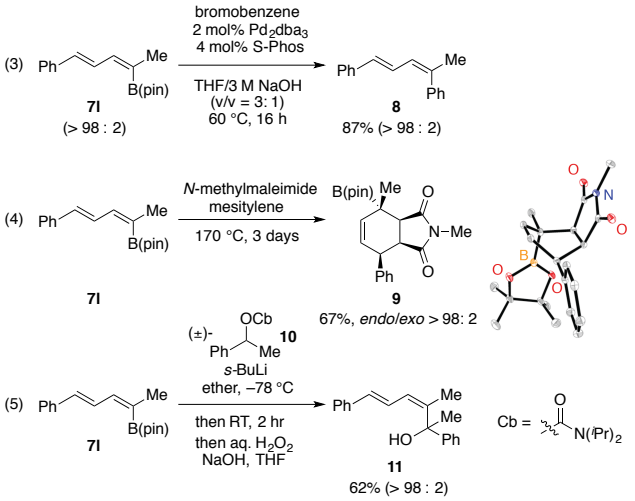
Our method is amendable to scale up. As can be seen from eq 2, *trans*-hydroboration of 1,3-enyne **6l** (1.138 g, 8.0 mmol) with a reduced catalyst loading (1 mol% Pd) furnished the desired product **7l** in 89% yield (1.819 g) without erosion of stereo-selectivity.




**6l** 1.138 g **7l** 89% (> 98 : 2) 1.819 g (2)

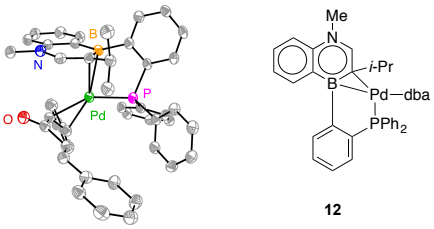
Dienylboronate esters such as **7l** are versatile intermediates in organic synthesis,[23] and Scheme 4 illustrates that **7l** is capable in engaging in subsequent C-C bond forming transformations stereospecifically. For example, **7l** undergoes Pd catalyzed Suzuki-Miyaura[24] coupling with bromobenzene to furnish 1,3-diene **8** in 83% yield with complete retention of the olefin stereochemistry (Scheme 4, eq 3). Furthermore, Diels-Alder reaction of **7l** with *N*-methylmaleimide afforded bicyclic **9** containing 4 stereogenic centers with high diastereoselectivity (endo/exo>98:2) in 67% yield (Scheme 4, eq 4).[25] Finally, homologation of **7l** with deprotonated carbamate **10** followed by oxidation furnished corresponding dienol **11** in 62% yield (Scheme 4, eq 5).[26]

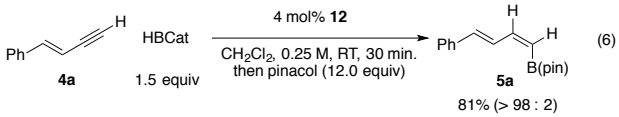
**Scheme 4. Functionalization of hydroboration product 7l**




We were able to obtain the single crystal X-ray structure of Senphos **L4** bound to Pd(0)dba. Scheme 5 shows that the $\kappa^2$-*P*-$\eta^2$-BC coordination mode to Pd(0) in complex **12** is preserved even with the sterically demanding *i*-Pr group at the C(3) position.[27,28] Complex **12** is a chemically and kinetically competent catalyst. *Trans*-hydroboration of substrate **4a** with the isolated Pd(0) complex **12** as the catalyst furnished the desired product **5a** in the same amount of yield and diastereoselective within 30 minutes as described in Table 1.

**Scheme 5. Isolated Pd(0) complex 12 is a competent catalyst for trans-hydroboration**




**4a** **5a** 81% (> 98 : 2) (6)

In summary, we have developed a modular and concise synthesis of monobenzofused 1,4-azaborine-based phosphine ligands. Their Pd(0) complexes have been found to catalyze *trans*-hydroboration of both terminal and internal *E*-1,3-enynes with high site- and stereo-selectivity under mild conditions. The method is also amendable to gram-scale synthesis without erosion of selectivity. Mechanistic studies including the origin of *trans*-hydroboration selectivity and further application of Senphos ligands in catalytic transformations are currently underway in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org."

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### Notes

The authors declare no competing financial interests.

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(15) Two relatively expensive catalysts were involved that had to be used at relatively high catalyst loadings: Grubbs second generation catalyst at 10 mol% loading, and $[(PPh_3)_3(CO)(Cl)RuH]$ at 2 mol% loading.

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(18) Compounds **3a-c** are formed after the exchange of the *B*-N*i*-$Pr_2$ group with the *in situ* generated HCl.

(19) In order to isolate dienylboronate, the catecholboronate was converted to pinacolboronate prior to column chromatography using similar procedures in reference 10. No erosion of stereochemistry was observed after transesterification.

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(21) At 0.25 M concentration, the reaction was sluggish.

(22) The use of an analogous carbonaceous ligand **CC-L3** as the supporting ligand in the hydroboration reaction of **6l** led to incomplete conversion and significant formation of *cis*- and 1,4-hydroboration byproducts, see Supporting Information for details.

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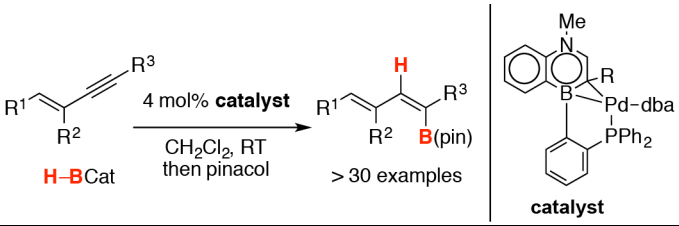
R3
R1
R2
H–BCat
4 mol% catalyst
CH2Cl2, RT
then pinacol
H
R3
R1
R2
B(pin)
> 30 examples
Me
N
R
B
Pd–dba
PPh2
catalyst