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Metal-free P-directed borylation of C(sp²)-H bonds

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In memory of Suning Wang

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Abstract: Spectacular progress has recently been achieved in transition metal-catalyzed C–H borylation of phosphines as well as directed electrophilic C–H borylation. As shown here, P-directed electrophilic borylation provides a new, straightforward, and efficient access to phosphine-boranes. It operates under metal-free conditions and leverages simple, readily available substrates. It is applicable to a broad range of backbones (naphthyl, biphenyl, *N*-phenylpyrrole, binaphthyl, benzyl, naphthylmethyl) and gives facile access to various substitution patterns at boron (by varying the boron electrophile or post-derivatizing the borane moiety). NMR monitoring supports the involvement of P-stabilized borenium cations as key intermediates. DFT calculations reveal the existence and stabilizing effect of π -arene/boron interactions in the (biphenyl)(*i*-Pr)₂P→BBr₂⁺ species.

Introduction

Over the past 15 years, phosphine-boranes have attracted tremendous interest and gained considerable importance as Frustrated Lewis Pairs for small molecule activation and metal-free catalysis,^[1] as well as ambiphilic ligands for transition metal/Lewis acid cooperative catalysis.^[2] Unimolecular P–B derivatives are generally prepared from ω -functionalized (halogenated) phosphines which are metalated and then reacted with boron electrophiles (ionic coupling).^[3] The drive to increase chemical diversity has stimulated the search for alternative routes to these derivatives, such as the hydroboration and carboboration of vinyl and alkynyl phosphines extensively developed by Erker *et al.*^[4] The last few years have also witnessed spectacular progress in transition metal-catalyzed C–H borylation of phosphines (Figure 1a).^[5,6] This P-directed approach was pioneered by Clark in 2014 with Ir complexes.^[7] First applied to the C(sp²)–H borylation of benzyl phosphines and biaryl-type phosphines, the methodology was then extended by Shi and Takaya to the *ortho*-borylation of aryl phosphines using Rh and Ru catalysts,^[8] and lately, to the borylation of C(sp³)–H and C(sp³)–X bonds.^[8a,9] The P-directing group can also be installed on phenols to direct *ortho*-borylation (Figure 1b).^[10]

Metal-free approaches for C–H borylation have also impressively advanced and now represent a powerful alternative and complement to TM-mediated methods.^[11] A few FLPs have proven capable to catalyze the C–H borylation of hetero-arenes.^[12,13] In addition, electrophilic C–H borylations directed by N-containing functional groups, pyridines and *N*-acyl/*N*-carbamate moieties in particular, have been shown to efficiently trigger the formation of C–B bonds from arenes and hetero-arenes.^[14-16]

Surprisingly, as highlighted in recent reviews,^[11c,d] P-directing groups have been very rarely used in metal-free C–H borylation. To the best of our knowledge, there is indeed only one

precedent. Vedejs reported the borylation of phenols under metal-free conditions, reacting $\text{ArOP}i\text{-Pr}_2$ phosphinites with BH_3 and then HNTf_2 (Figure 1b).^[17] We envisioned another approach based on the affinity of phosphines for electrophilic boranes. In the absence of steric shielding, strong $\text{P} \rightarrow \text{B}$ Lewis adducts are formed and halide dissociation from boron may open the way to electrophilic C–H borylation. This strategy is all the more promising given that P-stabilized boreniums have recently been shown to form readily and display rich reactivity.^[18]

Herein, we report that P-directed electrophilic borylation provides a straightforward and efficient entry to phosphine-boranes (Figure 1c). It operates under metal-free conditions, works with a variety of substrates and the boron center can be easily post-derivatized. Reaction monitoring supports the involvement of P-stabilized borenium cations^[19] as key intermediates for which DFT calculations substantiate the possible existence of some arene/B interactions.

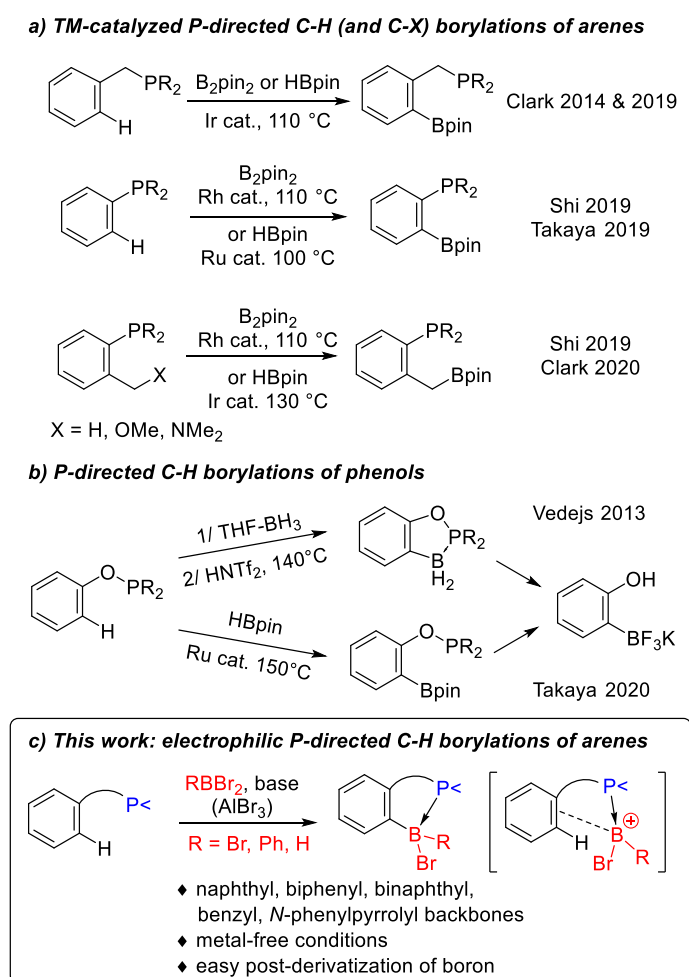
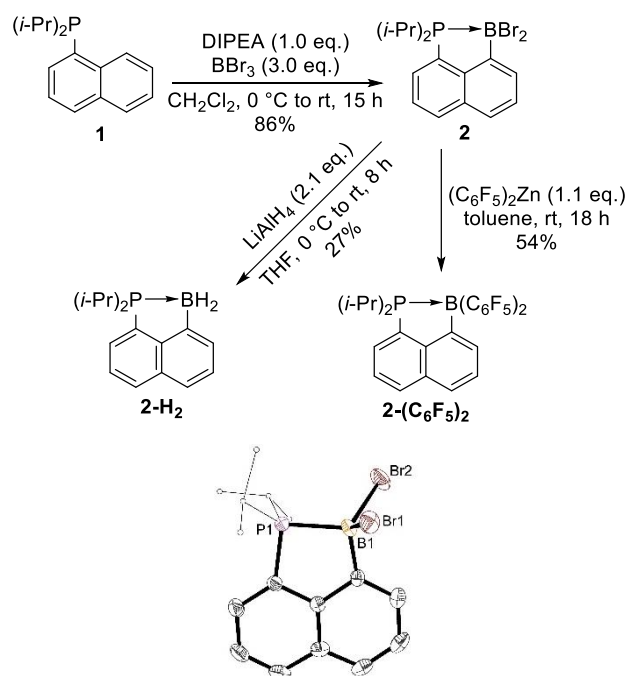


Figure 1. Phosphine-directed intramolecular C–H borylations.

Results and Discussion

Reaction development and scope

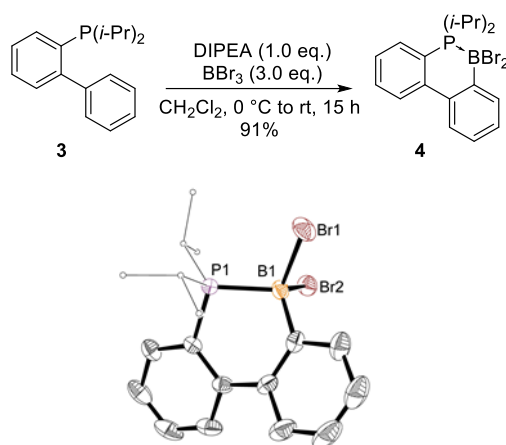
Mixed P–B compounds featuring a rigid (ace)naphthalene backbone display rich chemistry as a result of geometrically enforced P→B interactions.^[20] This prompted us to test the direct electrophilic borylation of naphthyl phosphines as an alternative to the previously used ionic coupling approach, starting from *peri*-halogenated substrates.^[21] The C–H borylation of **1** proceeded readily using 3 eq. of BBr₃ and 1 eq. di-*iso*-propylethylamine (DIPEA) in CH₂Cl₂. The reaction is complete within 15 hours at 25 °C (Scheme 1). The resulting *peri*-bridged phosphine-borane **2** (86% isolated yield) was characterized by multi-nuclear NMR spectroscopy, high-resolution mass spectrometry and X-ray crystallography.^[22] Additionally, we found that it could be subsequently derivatized by exchange of the bromides at boron for hydrides (with LiAlH₄) or C₆F₅ groups (with Zn(C₆F₅)₂) to give the corresponding phosphine-boranes **2-H₂** and **2-(C₆F₅)₂** (Scheme 1).



Scheme 1. Synthesis of the naphthyl-bridged phosphine-borane **2** by P-directed C–H borylation of **1** and post-functionalization at boron to provide **2-H₂** and **2-(C₆F₅)₂**. Molecular structure of **2**. Ellipsoids are shown at 50% probability; hydrogen atoms are omitted; *i*-Pr are simplified for clarity.

To probe the generality of this electrophilic C–H borylation strategy, we then attempted the reaction with a less preorganized phosphine substrate. To this end, we shifted to the more flexible biphenyl scaffold, where intramolecular P→B interaction is not geometrically enforced,

and the resulting adduct would form a 6-membered ring. Gratifyingly, the reaction worked equally well with **3** under identical conditions (Scheme 2). Complete conversion is achieved within 15 hours at 25 °C and the corresponding phosphine-borane **4** was isolated in 91% yield. Note that there are only seldom precedents of biphenyl-bridged phosphine-boranes. Wagner *et al.* unexpectedly obtained a polyfluorinated derivative upon reacting *ortho*-lithiated triphenylphosphine with $\text{HB}(\text{C}_6\text{F}_5)_2$ (the biphenyl C–C bond was formed by nucleophilic aromatic substitution of a fluorine in the *ortho* position relative to boron).^[23] In addition, Clark *et al.* have taken advantage of the Ir-catalyzed P-directed borylation approach to synthesize some P-Bpin derivatives from biphenyl phosphines.^[7]

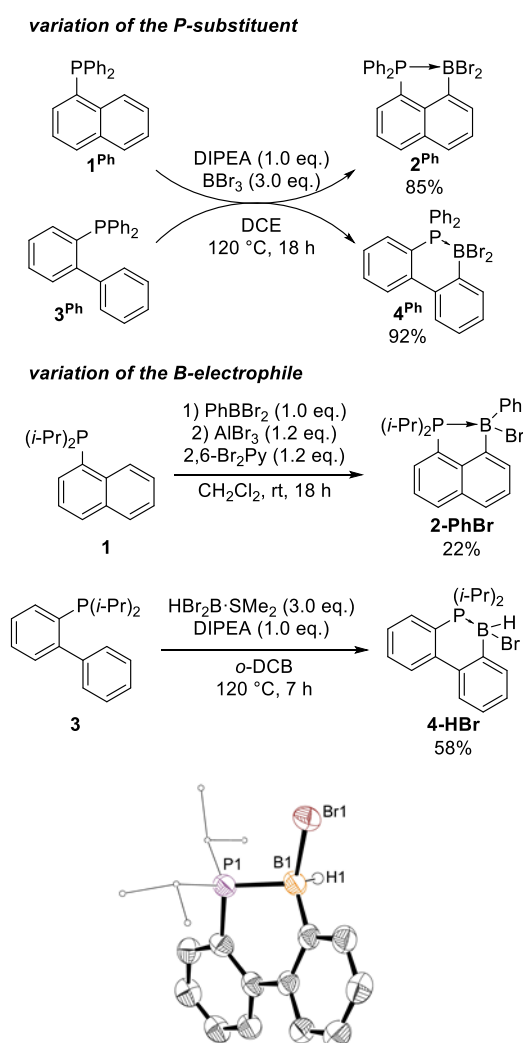


Scheme 2. P-directed C–H borylation of the biphenyl phosphine **3**. Molecular structure of the ensuing phosphine-borane **4**. Ellipsoids are shown at 50% probability; hydrogen atoms are omitted; *i*-Pr are simplified for clarity.

The reaction conditions for the borylation of phosphines **1** and **3** merit additional comments. We found that, an excess of BBr_3 is needed as it acts as both the borylation agent and bromide abstractor. DIPEA functions as a base, trapping the proton released upon electrophilic C–H borylation, while its steric hindrance prevents quenching of BBr_3 . While the reaction also proceeds in the absence of a base, the transformation is not as clean. Under base-free conditions, the isolated phosphine-borane product is contaminated with a PH phosphonium salt, due to the starting phosphine substrate itself acting as a Brønsted base (Table S1). Similar behavior has been observed in N-directed electrophilic C–H borylations, especially with BCl_3 , where the $\text{N} \rightarrow \text{BCl}_3$ adduct is in equilibrium with the free species.^[11d]

To further assess the generality of the transformation, we then varied the P-substituent and the boron electrophile (Scheme 3). PPh_2 , instead of $\text{P}i\text{-Pr}_2$, also works as a directing group for both the naphthyl and biphenyl spacers. However, C–H borylation requires heating in this case. The corresponding phosphine-boranes **2^{Ph}**/**4^{Ph}** are obtained in high yield (85/92%) within 18

hours at 120 °C in 1,2-dichloroethane (DCE). Formation of the key P-stabilized borenium intermediate is probably less favored with less electron-donating phosphines. On the other hand, attempted borylations of **1** with PhBBr₂ (excess) and DIPEA failed. Modifying the reaction conditions, we were nevertheless able to obtain **2-PhBr** in 22% yield by direct C–H borylation. After addition of 1 eq. of PhBBr₂ to **1**, we used a stronger Lewis acid, AlBr₃, in combination with 2,6-dibromopyridine (2,6-Br₂Py) to generate the requisite borenium intermediate and trigger borylation. The combination of sterically hindered pyridines and Al-based Lewis acids have been previously used by Ingleson *et al.* for challenging electrophilic C–H borylations, in particular with indoles.^[24] Remarkably, HBr₂·SMe₂ is an efficient borylating agent under the same conditions as BBr₃, but heating at 120°C in *ortho*-dichlorobenzene (*o*-DCB) for 7 hours, as illustrated by the preparation of the phosphine-borane **4-HBr** (58% isolated yield).



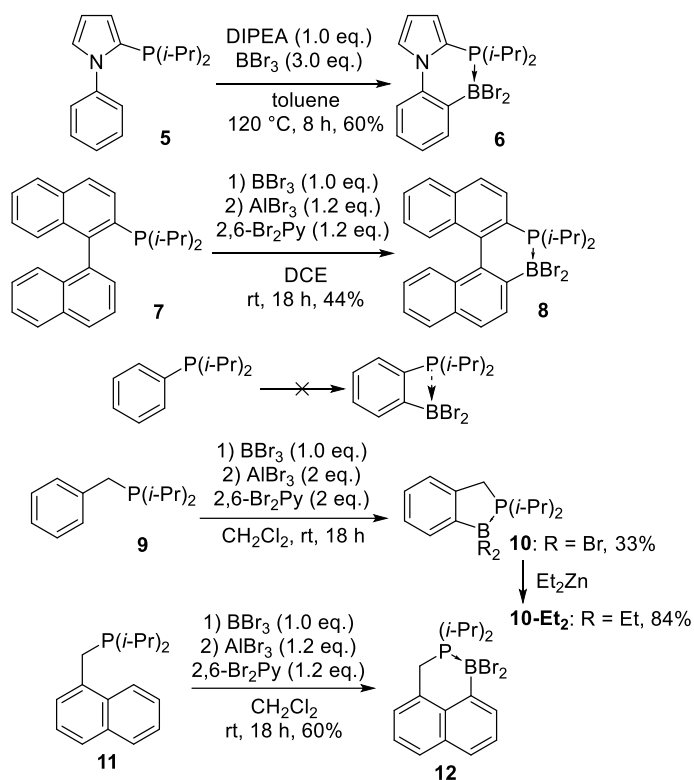
Scheme 3. Scope of the metal-free P-directed C–H borylation: variation of the P-substituent and B electrophile. Molecular structure of the phosphine-borane **4-HBr**. Ellipsoids are shown at

50% probability; hydrogen atoms are omitted except the one at boron; *i*-Pr are simplified for clarity.

We were then interested in diversifying the phosphine backbone (Scheme 4, Figure 2). The biphenyl framework was first replaced by an *N*-phenylpyrrole moiety. Pleasingly, phosphine **5** was efficiently borylated with BBr₃/DIPEA at 120 °C in toluene. More conformationally constrained biaryl backbones are also tolerated, as illustrated by the C–H borylation of the binaphthyl phosphine **7** with BBr₃ (1.0 eq.) and then AlBr₃/2,6-dibromopyridine (1.2 eq. each) at 25 °C, leading to the phosphine-borane **8**. The reaction does not work with phenyl-phosphines such as (*i*-Pr)₂PPh. Here, unfavorable geometric constraints most likely prevent electrophilic attack of the corresponding borenium at the *ortho* position. In contrast, the analogous benzyl phosphine **9** does undergo electrophilic borylation using the BBr₃/AlBr₃/2,6-Br₂Py system (1/2/2 eq., respectively) at 25 °C in CH₂Cl₂. The corresponding phosphine-borane **10** was obtained in moderate yield (33%) and was derivatized to **10-Et₂** (with Et₂Zn) to prevent deborylation. 1-naphthyl-CH₂-phosphine **11** was found to also react smoothly with BBr₃ (1.0 eq.) and then AlBr₃/2,6-dibromopyridine (1.2 eq. each) at 25 °C. C–H borylation exclusively occurs at the *peri*-position of the naphthyl ring. Phosphine-borane **12** was isolated in 60% isolated yield with no trace of the *ortho*-functionalized product detected. Notably, treating phosphines **7**, **9** and **11** with BBr₃ (excess) and DIPEA at 25 °C or 120 °C does not enable efficient borylation.

Only a few phosphine-boranes akin to **6**, **8**, **10** and **12** have been reported so far. A few benzyl-bridged P–B compounds have been prepared by ionic coupling from *ortho*-metalated benzyl phosphines R₂PCH₂(*o*-Ph)M.^[25,26] Clark *et al.* have also prepared some P-Bpin derivatives with benzyl and *N*-phenylpyrrole backbones *via* the P-directed TM-catalyzed borylation approach,^[7] but to the best of our knowledge, phosphine-boranes with binaphthyl and 1-naphthylmethyl frameworks are unprecedented.^[27]

variation of the phosphine backbone



Scheme 4. Scope of the metal-free P-directed borylation: variation of the phosphine backbone.

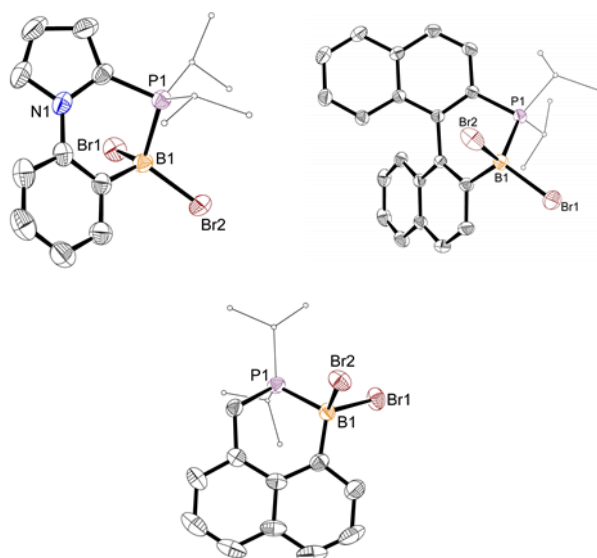
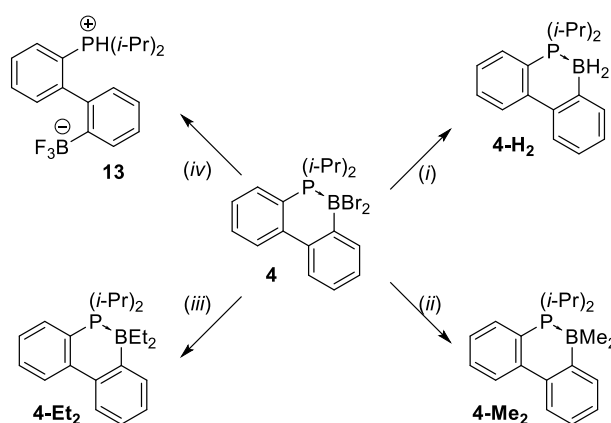


Figure 2. Molecular structures of the phosphine-boranes **6** (top left), **8** (top right) and **12** (bottom). Ellipsoids are shown at 50% probability; hydrogen atoms are omitted; *i*-Pr are simplified for clarity.

The possibility to chemically derivatize the phosphine-boranes obtained by C–H borylation, as pointed out for **2** and **10**, was further investigated on the biphenyl-bridged product **4** (Scheme 5). Despite a relatively strong P→B interaction (see below), the bromides at boron can be readily substituted for hydrogen atoms or organic groups, as substantiated by reactions with LiAlH₄, AlMe₃ and Et₂Zn. Notwithstanding the reduced Lewis acidity of boron, the intramolecular P→B interactions are retained in the resulting phosphine-boranes **4-H₂**, **4-Me₂** and **4-Et₂**, as apparent from ¹¹B NMR spectroscopy and X-ray diffraction analysis (for **4-Me₂**). In addition, treatment of **4** with KHF₂ quantitatively affords the corresponding PH-phosphonium/trifluoroborate zwitterion **13**. Here, the P and B groups rotate away to each other, and no intramolecular H⋯F bonding is observed crystallographically.^[28]



Scheme 5. Chemical derivatization of the biphenyl-bridged phosphine-borane **2**. (i) LiAlH₄ (2.1 eq.), THF, 0 °C to rt, 5 h, 41%. (ii) AlMe₃ (2.2 eq.), toluene/CH₂Cl₂, rt, 1.5 h, 99%. (iii) Et₂Zn (1.1 eq.), toluene, rt, 2 h, 65%. (iv) KHF₂ (3.3 eq.), MeOH/H₂O, 70 °C, 2 h, 99%.

The P-directed C–H borylation approach is thus applicable to a broad range of substrates. Besides the metal-free and relatively mild conditions in which it proceeds, it is synthetically attractive in that it does not require pre-functionalization and makes use of simple, readily available substrates. Providing ready access to various substitution patterns at boron, it complements the synthesis of P-Bpin derivatives *via* TM-catalyzed borylation.^[7,8]

Characterization/structure of the phosphine-borane products

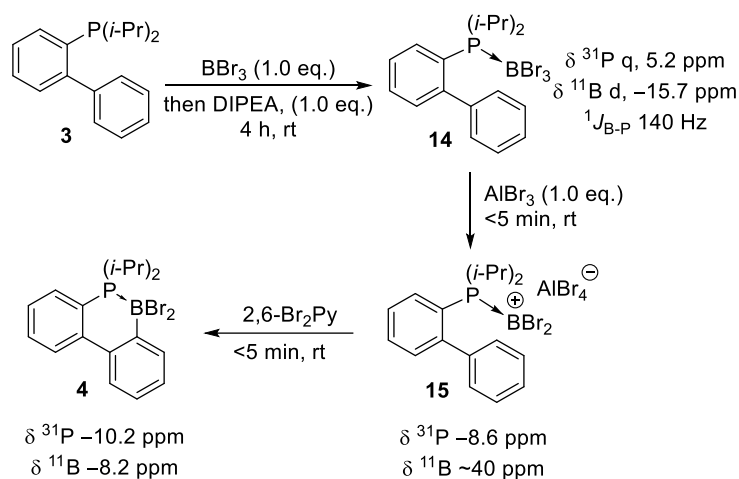
Having in hand a series of structurally related phosphine-boranes gave us the opportunity to compare their geometric and spectroscopic data, so that some structure-property relationships could eventually be delineated. All the borylation products and post-derivatized compounds were characterized by multi-nuclear NMR spectroscopy. Of note, the ¹¹B NMR spectroscopy signals for the P→BBr₂ borylation products (Table S2)^[22] fall in a narrow range (δ from –5 to –

10 ppm). They are systematically shifted to lower field (by 6 to 9 ppm) compared to those of the initially formed P→BBr₃ adducts ($\delta \sim -14.5$ ppm). The only exception is the benzyl-phosphine **9**. Its borylation product **10**, displays an ¹¹B NMR signal at $\delta +3$ ppm, shifted by 19 ppm from that of the P→BBr₃ adduct ($\delta -15.5$ ppm). Comparing the ³¹P NMR resonances of the P→BBr₃ adducts and P→BBr₂ borylation products showed opposite trends for the formation of 5- and 6-membered rings. The ³¹P NMR signal is deshielded for the former (by up to +25.5 ppm for **9**→**10**) but shielded for the latter (by up to -15.4 ppm for **7**→**8**). Diagnostic of the P-directed borylation is the systematic decrease of the ¹J_{B-P} constant, by 30 Hz on average. From 133–147 Hz in the P→BBr₃ Lewis adduct, it drops to 111–116 Hz in the P→BBr₂ borylation product. This probably conveys some decrease in the P→B donor-acceptor interaction as a result of the reduced electrophilicity of boron and geometrical constraints. The geometric data derived from XRD analyses were also analyzed (Tables S3 and S4).^[22] Phosphine-boranes with P→B interactions embedded in 5-membered rings (compounds **2**, **2-H₂**, **2-(C₆F₅)₂**, **2^{Ph}**, **2-PhBr**) display P–B distances of 1.96–2.07 Å (2.00 Å on average, to compare with the sum of the covalent radii^[29] of 1.91 Å). Slightly shorter values, 1.94–1.98 Å (1.95 Å on average), were found for related compounds with 6-membered rings (compounds **4**, **4-HBr**, **4-Me₂**, **4^{Ph}**, **6**, **8**, **12**). As for boron pyramidalization, minimal variations were observed in the sum of the bond angles $\sum B_{\alpha}$, 336 ± 4° for 5-membered rings vs 332 ± 2° for 6-membered rings. A more distinct difference was found when referring to the tetrahedral character (THC), as defined by Höpfl,^[30] to evaluate N→B interactions: 72 ± 5° for 5-membered rings vs 85 ± 2° for 6-membered rings. Overall, P→B interactions appear slightly stronger in the 6-membered ring phosphine-boranes. The higher flexibility of the backbone most likely helps to accommodate the optimal geometry.

Mechanistic details

In line with the mechanism underpinned computationally for N-directed electrophilic C–H borylation reactions,^[14a-c,e] we presume the reaction of the phosphine starts by formation of a P→BBr₃ Lewis adduct. Bromide dissociation would then lead to a P-stabilized borenium cation, which could participate in an electrophilic aromatic substitution. Here, the strong affinity of P for B combined with the powerful ³¹P NMR spectroscopic probe give a chance to characterize and authenticate reaction intermediates.^[31] In all the cases we studied, the P→BBr₃ adducts formed readily and were unequivocally identified spectroscopically. With the aim of characterizing the active P→BBr₂⁺ species generated prior to borylation,^[32] the Lewis adduct of the biphenyl-phosphine, **14**, was isolated and treated with one equivalent of AlBr₃ (Scheme 6). Upon addition of AlBr₃, the solution immediately turns from colorless to orange. ³¹P NMR spectroscopy shows instantaneous disappearance of the characteristic quartet signal at δ 5.2 ppm for the P→BBr₃

adduct ($^1J_{B-P} = 140$ Hz) to give a broad signal at $\delta -8.6$ ppm. The ^{11}B NMR spectrum displays a broad signal at $\delta \sim 40$ ppm, in the typical zone for boreniums.^[19,31,33] Upon addition of 2,6-dibromopyridine as a base, the solution immediately turns back to pale yellow. C–H borylation occurs spontaneously to give the phosphine-dibromoborane **4**, as confirmed from the respective ^{31}P and ^{11}B NMR spectroscopic signatures. Monitoring the reaction of the naphthyl phosphine **1** with BBr_3 , then AlBr_3 and finally 2,6-dibromopyridine also enabled to detect spectroscopically the different intermediates en route to the *peri*-bridged phosphine-borane **2**.^[22]



Scheme 6. Characterization of reactive intermediates along the C–H borylation of **3**.

To shed light on the structure of the P-stabilized borenium intermediate **15**, DFT calculations (B3PW91-D3(BJ)/6-31G**) were carried out on the actual species, as well as the corresponding $\text{P} \rightarrow \text{BBr}_3$ adduct **14**, for comparison.^[22] We were particularly intrigued by the possible existence and stabilizing contribution of some arene/borenium interaction.^[35] Indeed, geometry optimization led to a ground-state structure (Figure 3a) with the biaryl moiety facing the electron-deficient center (*syn* conformer). The boron center maintains a trigonal planar geometry ($\sum B_\alpha$ 359.2°), but it is engaged in two short contacts with C_{ipso} (2.844 Å) and one C_{ortho} (2.984 Å),^[36] suggesting η^2 -coordination of the remote aryl ring to boron. Of note, inspection of the potential energy surface provided another energy *minimum* in which the biaryl moiety is rotated away from the borenium (Figure 3b). This *trans* conformer is located 5.0 kcal/mol higher in energy, while it is the ground-state structure for the corresponding $\text{P} \rightarrow \text{BBr}_3$ phosphine-borane (it is more stable than the respective *syn* conformer by 2.3 kcal/mol).

Bonding analyses^[22] further corroborate the presence of an arene/borenium interaction in **15**. The NBO analysis shows a significant donor-acceptor $\pi(\text{CC}) \rightarrow \text{B}$ interaction ($\Delta E(2)$: 24.6 kcal/mol) and the corresponding NLMO displays some tail towards boron (Figure 3c). Consistently, AIM analysis (Figure 3d) locates a bond critical point between C_{ipso} and B with a

non-negligible electron density $\rho(r) = 0.016 \text{ e.bohr}^{-3}$. The computational study was extended to the related $\text{N} \rightarrow \text{BBr}_2^+$ borenium **A** isolated by Aldridge *et al.* (Figure 4).^[34] Here, the C_{ipso} atoms of the mesityl wings are somewhat enforced to interact with the electrophilic boron center while C–H borylation is prevented by the Me substituents at C_{ortho} . Our bonding analysis showed that the borenium is engaged in two mesityl \rightarrow B donor-acceptor interactions ($\Delta E(2) \pi(\text{CC}) \rightarrow \text{B}$ 10.4 + 12.5 kcal/mol, Table S6) which are together of similar magnitude to the biphenyl \rightarrow B interaction in **15**. It is also worth noting that π -arene coordination somewhat similar to that met in the borenium **15** are quite common in low-valent transition metal complexes deriving from biaryl phosphines. To compare the involved arene/B and arene/TM interactions, bonding analyses were performed on representative Pd and Au complexes **B1,2**^[37] and **C**^[38] (Figure 4). According to NBO analyses, the bonding situation in **15** most resembles that encountered in the T-shape biaryl phosphine Pd(II) complex **B1** ($\Delta E(2) \pi(\text{CC}) \rightarrow \text{Pd}$ 17.5 (σ_{Pd}) + 36.7 (σ^*_{PdBr}) kcal/mol).

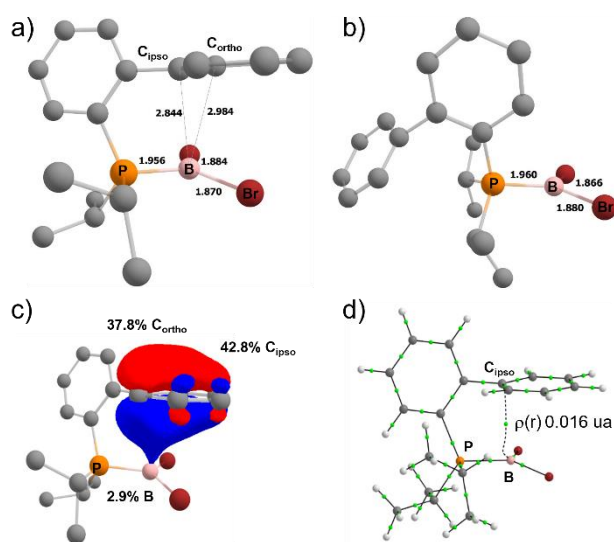


Figure 3. Optimized geometries of the P-stabilized borenium intermediate **15**, *syn* (a) and *trans* (b) conformers (main distances in Å). NBO and AIM analyses of the arene/B π -interaction in the *syn* conformer: (c) NLMO plot (cutoff: 0.04) with contributions of the main atoms (%) involved; (d) molecular graph, only the bond path relative to the arene/B interaction is shown for clarity.

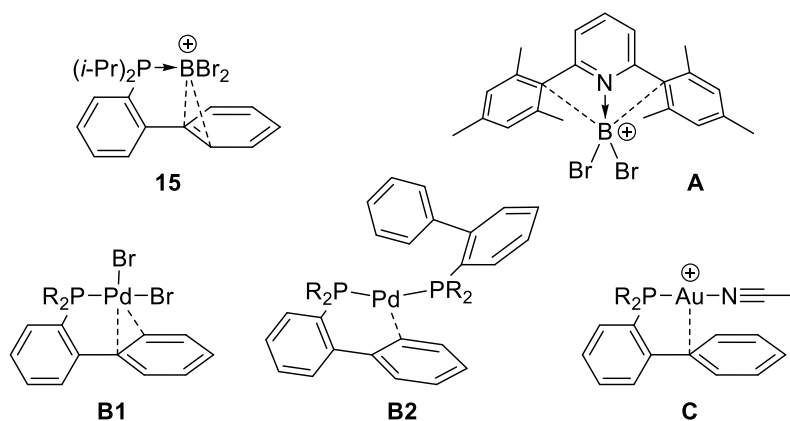


Figure 4. π -Arene interactions in boreniums and Pd/Au complexes.

The arene/borenium interaction, as observed in **15**, is expected to be the initial stage of the C–H borylation. The potential energy surface was scrutinized to locate an arenium form with the boron center σ -bonded to one of the *ortho* positions. The energy profile of the reaction sequence **3** \rightarrow **14** \rightarrow **15** \rightarrow **4** was also computed. To this end, all reaction partners (BBr_3 , AlBr_3 and 2,6-dibromopyridine) were included, counter-anion and solvents effects were taken into account. Accordingly, an arenium form **15'** with a short $\text{C}_{ortho}\text{--B}$ distance (1.814 Å) and a pyramidalized boron center (ΣB_α 328.5°) was found to sit slightly above the arene/borenium intermediate (ΔG 3.3 kcal/mol).^[22] The transformation **3** \rightarrow **4** is highly exergonic (ΔG – 80.4 kcal/mol) and all steps are fairly downhill in energy: the borylation by 35.7 kcal/mol, the bromide abstraction by 26.0 kcal/mol and the electrophilic aromatic substitution by 18.7 kcal/mol.^[22]

Conclusion

When steric shielding remains moderate, phosphines readily form strong $\text{P}\rightarrow\text{B}$ adducts with electrophilic boranes. Consequently, a halide may dissociate from boron to give P-stabilized borenium cations. These highly electrophilic 3-coordinate boron cations may act as powerful borylation reagents, as substantiated in this work. This P-directed electrophilic borylation of $\text{C}(\text{sp}^2)\text{--H}$ bonds proceeds under metal-free and relatively smooth conditions. In contrast to ionic coupling, the route most commonly used to access P–B derivatives, no pre-functionalized substrate is needed. The reaction is applicable to a broad range of phosphines, with alkyl as well as aryl substituents, and naphthyl, biphenyl, *N*-phenylpyrrole, binaphthyl, benzyl and naphthylmethyl backbones. The substitution pattern at boron can be easily and widely varied, either using BBr_3 as boron electrophile followed by post-derivatization, or directly using electrophiles such as PhBBr_2 or HBBr_2 .

The involvement of a P-stabilized borenium as key intermediate has been supported by monitoring the borylation of the biphenyl phosphine **3** by NMR spectroscopy. DFT calculations have provided evidence for a stabilizing π -arene/B interaction in the (biphenyl)(*i*-Pr)₂P→BBr₂⁺ species, whose nature is reminiscent of the π -arene/TM interactions encountered in some Pd complexes.

Essentially N-based directing groups, and occasionally NHC moieties, had been used so far in electrophilic C–H borylations. Here, phosphines are shown to also be powerful directing groups in this chemistry, affording straightforward and efficient access to phosphine-boranes. This new synthetic methodology will contribute to expand the variety of P–B derivatives and to further develop their applications as frustrated Lewis pairs,^[1] ambiphilic ligands,^[2] as well as chromophores.^[39]

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Keywords: borenium • C–H borylation • metal-free reactions • phosphine-boranes • P-directing groups

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