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Essential role of phosphines in organocatalytic β-boration reaction†

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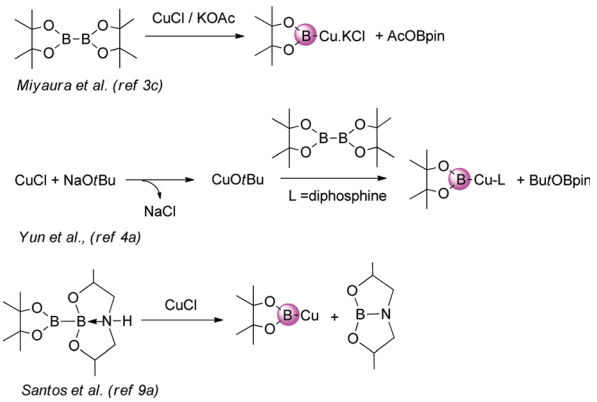
The use of phosphines to assist the organocatalytic β-boration reaction of α,β-unsaturated carbonyl compounds has been demonstrated with a selected number of substrates. The new method eludes the use of Brönsted bases to promote the catalytic active species and PR_3 becomes essential to interact with the substrate resulting in the formation of a zwitterionic phosphonium enolate. This species can further deprotonate MeOH when B_2pin_2 is present forming eventually the ion pair [α-(H),β-(PR_3)-ketone]$^+$-[B_2pin_2·MeO]$^-$ that is responsible for the catalysis.

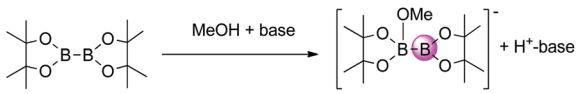
Introduction

Catalytic β-boration of activated olefins has gained an important recognition in synthetic chemistry since Norman, Marder and co-workers discovered the first Pt mediated 1,4-diboration of α,β-unsaturated ketones.[1] Further development of the reaction has been characterised by the use of alternative metal complexes to catalyse this selective transformation with the common feature that the addition of a base seems to be required for efficiency.[2–9] The role of the base has been discussed to some extent to accelerate the reaction assisting transmetallation between the metal species and the diboron reagents (Scheme 1). But the most recent approaches based on organocatalytic β-boration reaction[10] have postulated that the base could directly be involved in the activation of the diboron reagent (Scheme 2),[11] replacing the catalytic role of the metals in the activation of the B–B bond.

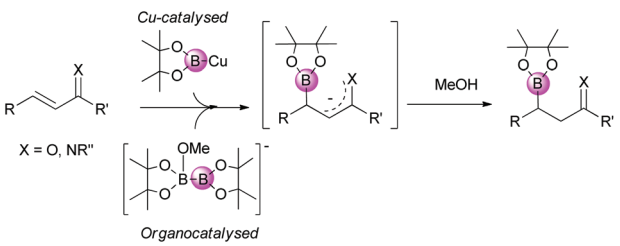
The enhanced nucleophilicity of the Bpin moiety,[12] in the Cu-catalysed and organocatalysed versions, is responsible for the selective attack at the β-position of α,β-unsaturated ester, ketone, amide and imine substrates.[13] The resulting borylated carbanionic intermediate is readily protonated in the protic medium (MeOH) to form the expected β-borated product (Scheme 3). Since base seems to be the key point in the formation of the nucleophilic Bpin moiety, we present here a



Scheme 1 Representative examples of the role of the base in promoting the active "Cu-Bpin" species for β-boration.



Scheme 2 Activation of diboron reagent B_2pin_2 by a base.



Scheme 3 Nucleophilic attack of the Bpin moiety *via* Cu-catalysed and organocatalysed reactions followed by protonation.

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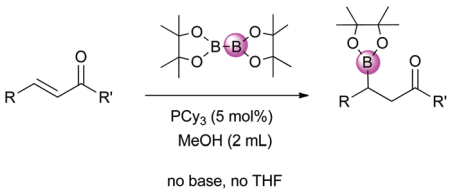


Scheme 4 Phosphine assisted β-boration reaction of α,β-unsaturated carbonyl compounds in MeOH.

novel method where base is replaced by PR_3 to assist the organocatalytic β-boration (Scheme 4).

Results and discussion

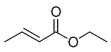
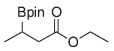
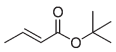
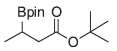
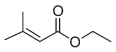
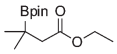
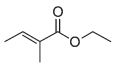
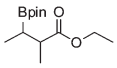
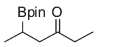
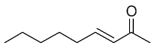
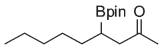
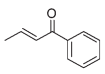
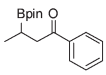
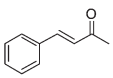
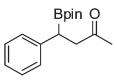
In order to prove the viability of the new phosphine assisted base-free β-boration reaction, we chose a series of α,β-unsaturated substrates and B_2pin_2 as the diboron source. Table 1 shows that within 6 h, at 70 °C, all the substrates tested were quantitatively converted, except those with α-substituted and β-disubstituted methyl groups using 5 mol% of PCy_3 and methanol as the unique solvent.

Aimed at unravelling the role of the phosphine, the first target was to establish unequivocally whether phosphines could activate the diboron reagent B_2pin_2, like alkoxides do. Characterization of the hypothesized adduct $[B_2pin_2{\cdot}PR_3]$ (R = Me, Cy, Ph) was not possible either theoretically[14] or by NMR experiments. No change in the B_2pin_2 signal (30.5 ppm, s) in $^{11}B\{H\}$ NMR could be observed when PR_3 was added to a solution of the diboron compound in MeOH. This simple experiment clearly showed that, unlike the methoxide anion, phosphines do not form any stable adduct with B_2pin_2, independently of the nucleophilic character of the phosphine. This is in good agreement with Marder and co-workers' observations[15] since a more acidic diboron compound, such as $[B(1,2\text{-}S_2C_6H_4)_2]_2$, is required to afford mono and bis-phosphine adducts, with both PMe_2Ph and PEt_3. A subtle balance dictates these weak B–P interactions: bis(catecholato)diboron (B_2cat_2) does not form any adduct and B_2pin_2 either. In a more recent example,[16] acidity on the boron was achieved by introducing halogen atoms directly bonded to one boron moiety.

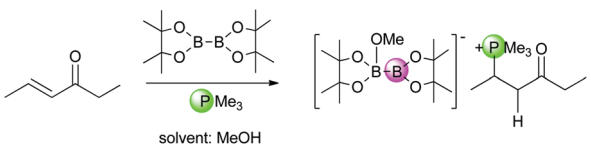
Among the possible interactions between the phosphine and MeOH, the phosphine acting as a Brönsted base is unlikely. Previous experimental and theoretical studies demonstrated that strongly basic trialkyl phosphines do not deprotonate MeOH.[17] We showed that the presence of the diboron reagent increases the Brönsted acidity of MeOH, because the conjugate base MeO^- is stabilized by forming the $[B_2pin_2{\cdot}MeO]^-$ adduct.[11a] Nevertheless, deprotonation of MeOH does not occur even in the presence of B_2pin_2 (see NMR studies in ESI†).

Next we focused on possible interactions between the phosphine and the substrate, since it is known that trivalent phosphines react as nucleophiles with some α,β-unsaturated compounds to form phosphonium enolates.[17–19] A series of

Table 1 Phosphine assisted organocatalytic β-boration of α,β-unsaturated carbonyl compounds[a]

Entry	Substrate	Product	Conv.[b] (%)	I.Y.[b] (%)
1			99	86
2			87	80
3			27	—
4			43	34
5			99	88
6			99	89
7			81	69
8			99	86
9			99	90
10			93	85
11			99	87
12			99	91

[a] Standard conditions: substrate (0.5 mmol), B_2pin_2 (0.55 mmol), PCy_3 (0.02 mmol), MeOH (2 mL), 70 °C, 6 h. [b] Conversion calculated using ^1H NMR spectroscopy and GC.



Scheme 5 Ion pair formation at stoichiometric level.

stoichiometric experiments were conducted to explore the formation of new species upon mixing stoichiometrically PMe_3, (*E*)-hex-4-en-3-one and B_2pin_2 in MeOH (Scheme 5, Fig. 1). Quantitative formation of a new species was observed: complete disappearance of the PMe_3 signal at −62.0 ppm in the $^{31}P\{^1H\}$-NMR spectrum, and appearance of a new signal at 30.4 ppm. In the $^{11}B\{^1H\}$-NMR, the signal of B_2pin_2 (broad s, 30.5 ppm) completely disappeared, and two new broad peaks at +35 ppm and +1.3 ppm were detected, as is shown in Fig. 1 and Table 2. These two new boron signals correspond to the sp^2 and sp^3 boron atoms of the well known $[B_2pin_2{\cdot}MeO]^-$ anionic adduct.[11] NMR data thus suggest the formation of a new ion-pair species, in which the anion is the $[B_2pin_2{\cdot}MeO]^-$

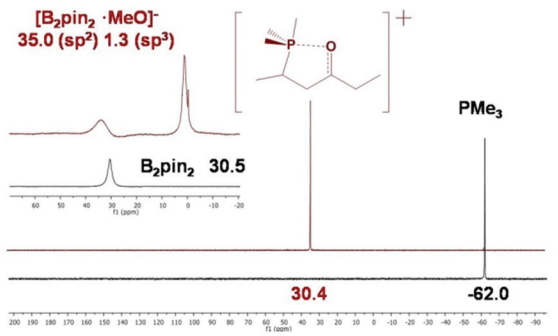
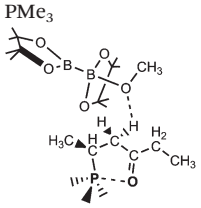


Fig. 1 ^{11}B–{^1H}-NMR and ^{31}P–{^1H} for: (*red*) the interaction of PMe_3 and (*E*)-hex-4-en-3-one in MeOH, in the presence of B_2pin_2 (1 mL, [PMe_3] = 0.5 M, [(*E*)-hex-4-en-3-one] = 0.5 M); (*black*) same mixture of PMe_3, B_2pin_2 in MeOH without the substrate (1 mL, [PMe_3] = 0.5 M, [B_2pin_2] = 0.5 M).

Table 2 Computed and experimental ^{11}B and ^{31}P NMR chemical shifts (in ppm) for several species

	NMR chemical shifts (ppm)			
	Computed		Experimental	
Species	^{11}B	^{31}P	^{11}B	^{31}P
B_2pin_2	30.5		30.5	
PMe_3		−63.0		−62.0
	1.5(sp^3)–33.0(sp^2)	31.4	1.3(sp^3)–35.0(sp^2)	30.4

adduct, and the cationic counterpart is the [α-(H),β-(PR_3)-hexanone]$^+$. Further ESI-MS experiments confirmed the mass for the cation (see values in ESI†). Consequently, the new peak at 30.4 ppm in the $^{31}P\{^1H\}$-NMR spectrum corresponds to a phosphonium salt, which should derive from the nucleophilic attack of the phosphine at the β-carbon of the substrate, followed by the protonation of the zwitterionic phosphonium enolate by MeOH. It is important to remark that quantitative formation of this phosphonium species requires the presence of the diboron reagent.

The molecular structure of the ion-pair ([α-H,β-PR_3-3-hexanone]$^+$[B_2pin_2·MeO]$^-$) is shown in Fig. 2. This structure was fully characterized computationally as a global minimum in the potential energy surface, taking into account its conformational flexibility. The computed NMR chemical shifts for this structure precisely coincide with the measured NMR shifts in both ^{11}B and ^{31}P NMR (Table 2).

The study of the formation of ion-pair species has revealed interesting features. Fig. 3 shows the computed reaction energy profile for the formation of **I2** from acrolein. Values for energy activation barriers are rather reasonable and reflect distinct behaviour for each phosphine. Actually, formation of **I2** is exothermic for PMe_3 only, which is precisely the phosphine

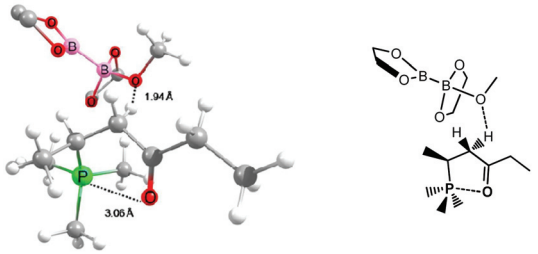


Fig. 2 DFT derived molecular structure of ion-pair: ([α-H,β-PMe_3-3-hexanone]$^+$[B_2pin_2·MeO]$^-$. Methyl groups of the B_2pin_2 are omitted for clarity.

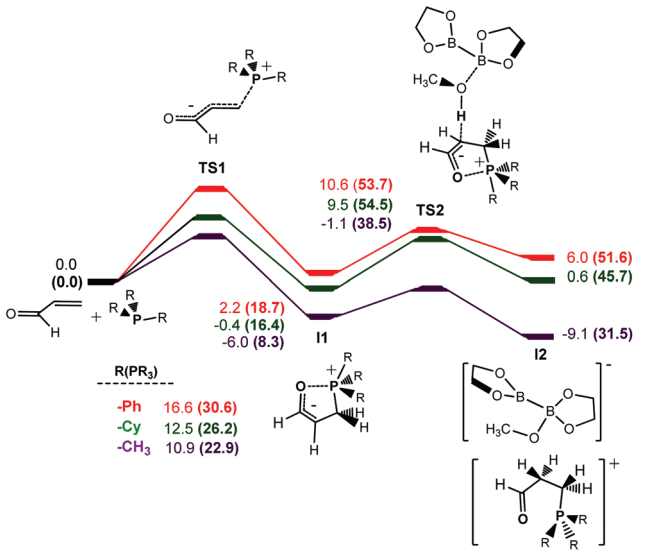


Fig. 3 Reaction energy profile for the formation of ([α-H,β-PR_3-propionaldehyde]$^+$[B_2pin_2·MeO]$^{-2}$. Purple: PMe_3; green: PCy_3; red: PPh_3. Electronic and Gibbs free energies (in parentheses) computed at BP86 are given in kcal mol^{-1}.

that enabled quantitative formation of **I2** in the NMR experiments. For PCy_3, the reaction is thermoneutral whereas for PPh_3 it is slightly endothermic. These values reflect well the equilibrium between free phosphine and **I2** observed in NMR. Using a metahybrid exchange–correlation potential that includes dispersion corrections, such as M06 (see details in ESI†), the general picture does not change although the reaction is exothermic for all the three phosphines. We must point out that the assembly of four molecular entities implies an entropic cost, which is apparently huge as ΔG values reflect. Note the exaggerated accumulated value for **TS2**, for instance. Solvent effects introduced through continuous solvent models do not take into account the entropy gain/loss due to solvent reorganization, a component that can partly compensate the entropy loss of merging two species. We evaluated an average value of 12 units in Gibbs free energy per encounter, so roughly 36 kcal mol^{-1} in excess are accumulated in **TS2** and **I2**. We will show below that formation of the final β-borated product, in the next reaction steps, largely overcomes the cost of forming **I2**. Reaction energy profiles exhibit a clear trend (PMe_3 < PCy_3 < PPh_3) that does not coincide either with

Brönsted basicity[20] or with the Tolman angle.[21] The most basic PCy_3 phosphine also displays the largest bulkiness, so a combination of stereo-electronic effects determines this reactivity.

The structure of the **I1** intermediate in Fig. 3 corresponds to the most stable conformation of the zwitterionic phosphonium enolate species, in which a dative bond between the oxygen and the formally positively charged pentavalent phosphorus compound is formed. Topological analysis of electronic charge density revealed the existence of a P–O bond critical point.[22] The Laplacian of the charge density (see values in ESI†) indicated that the P–O bond is mainly dative. A similar system was studied previously with MP2 based methods[23] in the context of the phosphine-catalyzed hydroalkoxylation of enones and α,β-unsaturated substrates,[18] although the cyclic most stable form was not considered in that study. The pentavalent phosphorus atom adopts a trigonal bipyramid coordination, thus favouring the localization of the negative charge in C_α. The highest coefficient of C_α in the HOMO can be clearly visualized in Fig. 4. The P–C bond length between the phosphorus atom and the carbon in the axial position is slightly longer than the other two (Table 3, $P–C_{ax}$ = 1.90 Å with respect to $P–C_1$ = 1.84 and $P–C_2$ = 1.84). We also observed that the P–O bond length slightly changes with the type of substituent in the phosphorus centre. The shortest P–O bond length for PPh_3 can be rationalized by the fact that the phenyl groups have higher electron density than the alkyl groups. Since the two tested trialkyl phosphines present almost equal P–O distances, electronic effects rather than sterics might control the establishment of this P–O bond.

At this point we wondered how basic **I1** species are, and how is their reactivity compared to that of a very strong organic base, such as Verkade's. In the alcohol–base system, Verkade's superbase showed the best performance for deprotonating methanol.[11a] The C_α position is by far the most basic spot in these zwitterionic species, and hence will be the atom that becomes protonated. By using the computational protocol described in the Computational details section, we computed pK_a values for some **I1** species as well as for the Verkade's base (Table 3). According to the pK_a values, the zwitterionic species **I1** are very strong bases, as strong or even stronger than Verkade's base. The trend clearly identifies the most basic phosphine and the highest pK_a value.

Data collected up to this point clearly showed that the phosphine could interact with the substrate through a nucleophilic attack at the β-carbon of the activated olefin. Then, the very strong base formed *in situ*, *i.e.*, the zwitterionic phosphonium enolate species **I1**, deprotonates MeOH assisted by B_2pin_2, forming the ion-pair **I2**. This conclusion is crucial, since it suggests that catalytic amounts of phosphine are enough to guarantee the formation of methoxy ions, which eventually activate the diboron reagent. This is clearly important as we found that phosphines can replace the standard bases used in previous work (Cs_2CO_3, NaO*t*Bu, NaOMe, Verkade, *etc.*).

Stoichiometric experiments in Schlenk and in NMR tube, and monitoring the reaction by ^{11}B NMR, ^{31}P NMR, and

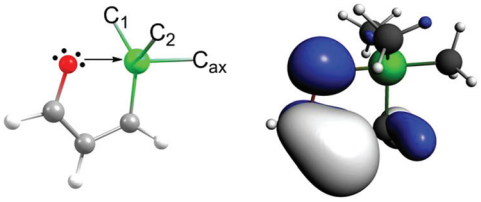


Fig. 4 Molecular structure and plot of the HOMO of the zwitterionic phosphonium enolate, **I1**.

Table 3 Computed pK_a values in dimethylsulfoxide (DMSO) and bond distances for some **I1** species. All distances are given in Å

Species	pK_{aDMSO}	d(P–O)	d(P–Cax)	d(P–C_1)	d(P–C_2)
I1–PCy_3	29.0	2.07	1.96	1.91	1.89
I1–PMe_3	27.6	2.02	1.90	1.84	1.84
I1–PPh_3	25.8	1.98	1.92	1.85	1.83
 Verkade	23.4 (exp. value: 26.8)				

CG-MS led to new discoveries. As we mentioned above, when mixing 1 equiv. of PMe_3 with 1 equiv. of B_2pin_2 and 1 equiv. of (*E*)-hex-4-en-3-one in 1 mL of MeOH ([reactants] = 0.25 M), we observed complete formation of an **I2** ion-pair by ^1H NMR, ^{31}P NMR, ^1H–^{31}P correlation NMR and ^{11}B NMR. Upon increasing the temperature to 70 °C, no conversion to the desired β-borated product was observed even after heating overnight. However, addition of an excess of substrate facilitated the formation of the β-borated product. After 1 h at 70 °C, with 3 equiv. of substrate, 1 equiv. of PMe_3 and 1 equiv. of B_2pin_2 in 1 mL of MeOH ([reactants] = 0.25 M, except for [(*E*)-hex-4-en-3-one] = 0.75 M) complete conversion was observed by ^{11}B NMR and GC (see ESI† for more details).

Experiments above demonstrated that: (i) **I2** species does not evolve to the β-borated product directly and (ii) the reaction proceeds from **I2** with an additional substrate. All these experiments might indicate that 1 equiv. of substrate with respect to the amount of phosphine is sacrificed to promote formation of the nucleophilic sp^2 B and consequently the nucleophilic boron attack. This idea derives in a new methodology for β-borating α,β-unsaturated carbonyl compounds replacing the required Brönsted bases, thus using only phosphine/methanol.

With all this information in hand, following the energy profile from Fig. 3, we envisioned a mechanism starting with the attack of a phosphine on the β-position of the α,β-unsaturated carbonyl compound (**TS1**, Fig. 5).

Attack of the trivalent phosphorus nucleophile on the most electrophilic carbon of the α,β-unsaturated compound results in the formation of the phosphonium enolate (**I1**). This species can further deprotonate MeOH. On the basis of our NMR studies described above, this process is favoured by the presence of B_2pin_2 that stabilizes the MeO^- anion forming the

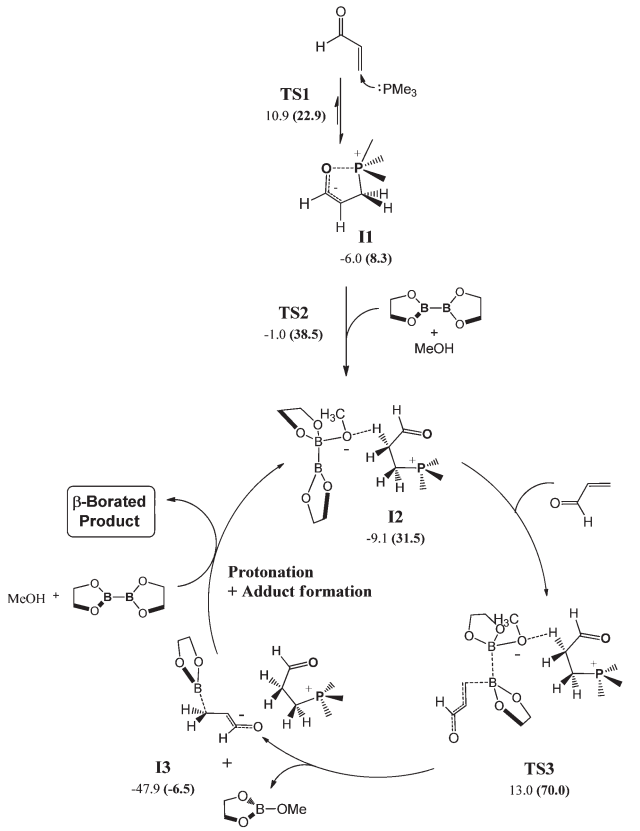


Fig. 5 Suggested catalytic cycle for the new base-free organocatalytic β-boration reaction. Electronic energy (kcal mol^{-1}) and Gibbs free energy (kcal mol^{-1}; in parentheses) computed at the BP86 level relative to two molecules of acrylaldehyde, MeOH, B_2pin_2 plus PMe_3. Methyl groups of the B_2pin_2 are omitted for clarity.

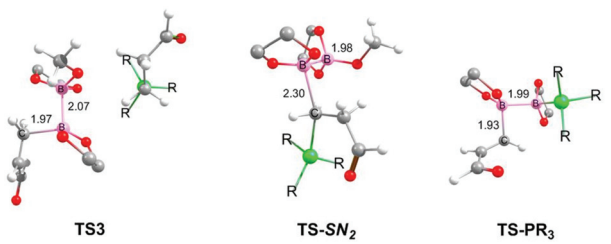


Fig. 6 Transition state structures for alternative C–B bond forming steps. Selected interatomic distances in Å.

$[B_2pin_2{\cdot}MeO]^-$ adduct. Therefore, the second transition state (**TS2**) of our mechanistic proposal involves the protonation of **I1** in a concerted manner with the interaction of the MeO^- with the B_2pin_2 to provide a phosphonium intermediate type with the nucleophilic $[B_2pin_2{\cdot}MeO]^-$ adduct as a counter-ion, (**I2** ion-pair). In the next step (**TS3**), the sp^2 boryl unit of the activated diboron reagent in the *in situ* formed ion-pair (**I2**) attacks the C_β of another molecule of the substrate. From **TS3**, it releases the "(pin)BOMe" byproduct and leads directly to the formation of an enolate ion-pair **I3**. Protonation of the enolate partner in **I3** results in the formation of the β-borated product and regeneration of **I2**, since the protonation is assisted by another molecule of B_2pin_2 that stabilizes the generated MeO^-. Note that the overall process is strongly exothermic (ΔE = −47.9 kcal mol^{-1}) and exergonic (ΔG = −6.5 kcal mol^{-1}), **TS3** being the most energetically demanding transition state in the catalytic cycle (22.1 kcal mol^{-1} with respect to **I2**). The mechanism in Fig. 5 resembles that proposed by Toste *et al.* for the phosphine-assisted alkoxylation of activated olefins.[18]

We also consider two alternative reaction pathways: the intramolecular attack of the nucleophilic sp^2 boryl unit of the adduct $B_2pin_2{\cdot}MeO^-$ towards the C_β of the phosphonium salt by an SN_2 type of reaction (**TS-SN$_2$**), and the direct addition of the nucleophilic boryl unit to the alkene, assisted by the phosphine (**TS-PR$_3$**) (Fig. 6). The computed energy barriers for the alternative mechanisms (see ESI† for details) demonstrated that the reaction pathways through **TS-SN$_2$** or **TS-PR$_3$** are more energetically demanding than the intermolecular attack *via* **TS3**.

Conclusions

Novel reaction conditions for the organocatalytic β-boration reaction of α,β-unsaturated carbonyl compounds using only phosphine and alcohol are presented here for the first time. The sole use of catalytic amounts of phosphine catalyses the β-boration reaction. No Brönsted base is required to activate the diboron reagent bis(pinacolato)diboron, B_2pin_2. The scope of the reaction is demonstrated, and includes esters, acyclic and cyclic ketones.

The development of this novel transformation is based on convergent spectroscopic, stoichiometric and theoretical evidence of *in situ* formed reactive species. The phosphine directly attacks the most electrophilic carbon of the α,β-unsaturated carbonyl compound resulting in the formation of a strongly basic zwitterionic phosphonium enolate species. This intermediate is further protonated by the excess of MeOH, a process that is particularly favoured by the presence of bis(pinacolato)diboron that stabilizes the MeO^- anion, thus forming the Lewis acid–base $[B_2pin_2{\cdot}MeO]^-$ adduct.

A considerable interest in this organocatalytic transformation can be expected due to the simplicity of the methodology. The results presented demonstrate that β-boration can be performed by the unique presence of catalytic amounts of phosphine in MeOH. The simplicity of the system and the understanding of the role of the phosphine open now an unlimited palette of possibilities and could have wider implications to other organocatalytic β-boration approaches.

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