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Asymmetric metal free β-boration of α,β-unsaturated imines assisted by (*S*)-MeBoPhoz†

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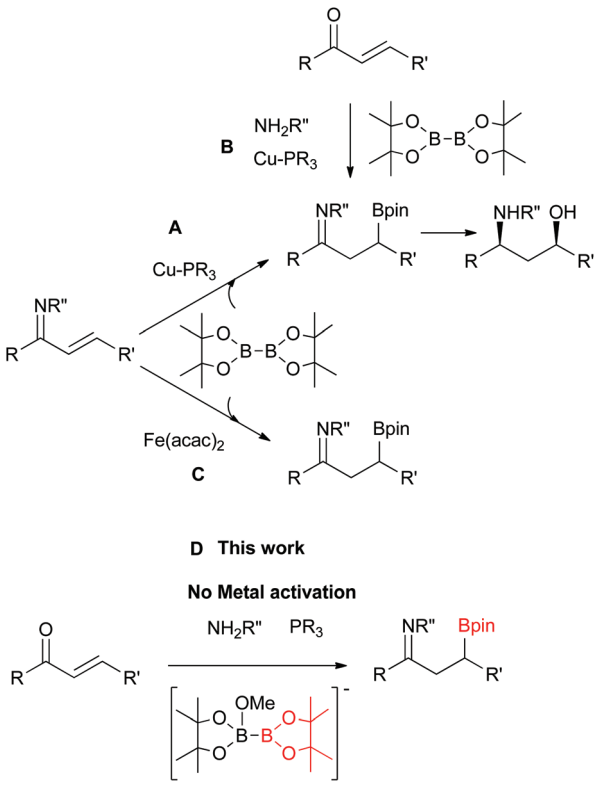
The adduct [MeO → Bpin–Bpin]$^-$ efficiently mediates the β-boration of α,β-unsaturated imines formed *in situ*. The use of chiral phosphines as additives, and in particular the chiral phosphine (*S*)-MeBoPhoz, enables the catalytic asymmetric reaction to proceed with higher enantioselectivity than the analogue copper(I) mediated reaction.

Metal-free activation of diboron reagents has gained significant momentum, particularly to generate C–B bonds in an organocatalytic context.[1–3] However, the development of a general, highly efficient asymmetric version of this reaction is still an important goal[4] with only limited successful examples.[2,3] Therefore, Cu(I) catalysts have become the most widely used for inducing asymmetry in β-boration, since Yun *et al.*[5] discovered that copper catalysts modified with chiral phosphines can activate diboron reagents, such as bis(pinacolato)diboron (B_2pin_2), and catalyze the borylation of α,β-unsaturated carbonyl compounds with high levels of enantioselectivity, in the presence of MeOH.[6] In this context, we have found that this approach might enable efficient access to γ-aminoalcohols from the corresponding α,β-unsaturated imines.[7] The optimal combination an amine (for imine formation), a copper source and a chiral ligand, followed by careful selection of a reducing reagent has provided a convenient methodology to obtain γ-aminoalcohols in a highly diastereo- and enantioselective manner (Scheme 1, pathways **A** and **B**).[7] The unique attempt to perform the β-boration of (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)-methanamine, in the absence of Cu(I) salts as precatalysts, required the substrate preactivation by Lewis acidic Fe(II) and Fe(III) salts (Scheme 1, pathway **C**).[8]



Scheme 1 (A) Cu catalyzed β-boration of α,β-unsaturated imines (ref. 7*a*,*b*,*c*); (B) Cu catalyzed β-boration of *in situ* formed α,β-unsaturated imines (ref. 7*d*,*e*,*f*); (C) Fe(II) activation of α,β-unsaturated imines towards the β-boration reaction (ref. 8); (D) organocatalytic β-boration reaction (this work).

Here, we have developed an asymmetric organocatalytic approach to generate C–B bonds at the β-position of an unsaturated imine, *i.e.* Scheme 1, pathway **D**, as an alternative strategy to synthesize γ-aminoalcohols. Towards this end, we focus our efforts on the *in situ* generation of a model α,β-unsaturated imine, *i.e.* (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine, from 4-phenyl-3-buten-2-one (**1**) and benzylamine in THF with the dehydrating reagent, MK10.[7a,d] After 6 hours, the

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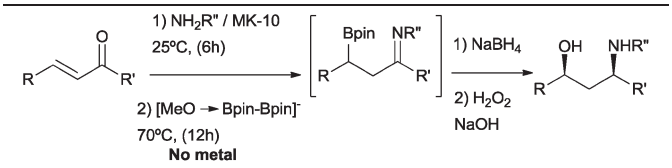
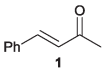
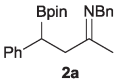
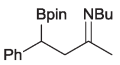
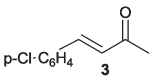
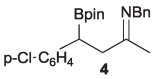
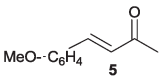
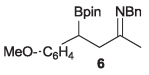
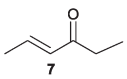
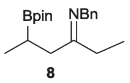
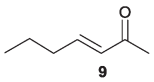
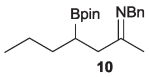
Table 1 *In situ* α,β-unsaturated imines formation followed by organocatalytic β-boration with B_2pin_2 [a]



Entry	Substrate	Additives	Product	% Conv.[b] [IY][c]
1	 1	—	 2a	—
2	〃	Cs_2CO_3/MeOH	〃	—
3	〃	PCy_3/Cs_2CO_3/MeOH	〃	99 [56]
4	〃	PCy_3	〃	—
5[d]	〃	PCy_3/Cs_2CO_3/MeOH	 2b	90 [66]
6	 3	PCy_3/Cs_2CO_3/MeOH	 4	99 [47]
7	 5	PCy_3/Cs_2CO_3/MeOH	 6	96 [37]
8	 7	PCy_3/Cs_2CO_3/MeOH	 8	95 [51]
9	 9	PCy_3/Cs_2CO_3/MeOH	 10	99 [68]
10	 11	PCy_3/Cs_2CO_3/MeOH	 12	97 [30]

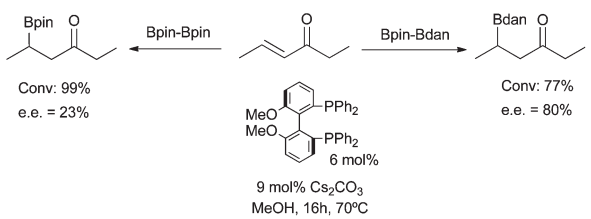
[a] Standard conditions: ketone (0.5 mmol), NH_2Bn (0.5 mmol), THF (2 mL), MK-10 (140 mg), B_2pin_2 (1.1 eq.), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), PCy_3(10 mol%). [b] Conversion determined by ^1H NMR spectroscopy. [c] Isolated yield calculated for *syn*-γ-amino alcohol (see ESI for reaction conditions). [d] NH_2Bu (0.5 mmol).

boron reagent bis(pinacolato)diboron (B_2pin_2) is added to the intermediate α,β-unsaturated imine; however, even when the reaction was performed at 70 °C, no β-borated product **2a** was observed (Table 1, entry 1). The addition of a base and MeOH to activate the diboron, *via* quaternization, was also insufficient at promoting the β-boration (Table 1, entry 2), unless a small amount of phosphine (10 mol% PCy_3) was added to the reaction (see Table 1, entry 3). However, the replacement of the base by the phosphine alone was not enough to activate the diboron (Table 1, entry 4). It seems, therefore, that the base/MeOH combination is essential for the diboron activation and that the role of the phosphine could be related to a similar pre-activation of the substrate as we have previously observed in the analogue metal-free β-boration of α,β-unsaturated carbonyl compounds, which is also assisted by phosphines.[9] Isolated yields were obtained for the corresponding γ-amino alcohols by reduction with $NaBH_4$ in methanol and oxidation with H_2O_2 in NaOH.

With these preliminary results in hand, we extended this observation to other ketone and amine combinations, to develop a general organocatalytic methodology for the β-boration of α,β-unsaturated imines. Interestingly, *n*$BuNH_2$ was also a versatile amine for the imine formation with **1**, and was compatible with the organocatalytic β-boration to produce quantitatively the β-borated imine **2b** (Table 1, entry 5). Electron accepting and electron releasing substituents at the *para*-position of the phenyl group of the ketone substrates **3** and **5**, respectively, did not change the reaction outcome (Table 1, entries 6 and 7). Even α,β-unsaturated ketones with alkyl moieties at the β-position were equally susceptible to quantitative β-boration, whether cyclic or acyclic (Table 1, entries 8–10). Hence, it can be seen that the organocatalytic β-boration of *in situ* formed α,β-unsaturated imines is a general and indeed new methodology for the formation of β-borylated imines in a one-pot reaction.

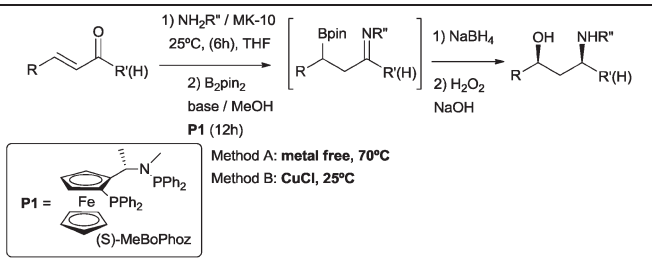
In the next step we considered the possibility of inducing asymmetry into the formation of the new C–B bond using this organocatalytic approach. Hence, we proposed that chiral phosphine additives might interact with the substrate and provide an asymmetric environment for the β-boration with the Lewis acid–base adduct [*i.e.* $MeO^- \rightarrow$ Bpin–Bpin]. This concept had already been successfully demonstrated in the β-boration of α,β-unsaturated ketones with B_2pin_2 [2a,d] or BpinBdan (dan = 1,8-diaminonaphthalene) (Scheme 2),[2e] and the hypothesis of the role of the phosphine in the asymmetric induction has also been postulated from both an experimental and theoretical point of view.[9]

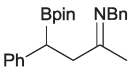
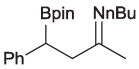
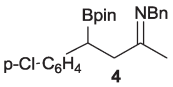
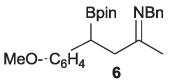
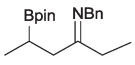
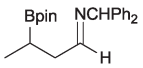
However, since imine functionality is more sterically hindered and less polarized than the carbonyl group, we were interested to ascertain whether asymmetric induction would be more or less efficient. Hence, we initiated our studies with substrate **1** and conducted the imine formation with benzylamine, followed by β-boration with the Lewis acid–base [$MeO^- \rightarrow$ Bpin–Bpin] adduct in the presence of a series of chiral diphosphines. Preliminary results using chiral Josiphos-type of diphosphines did not provide any significant asymmetric induction, which contrasts with the efficient trends observed with the corresponding ketones.[2a] Remarkably, however, when the [$MeO^- \rightarrow$ Bpin–Bpin] adduct was used with the dipho-



Scheme 2 β-Boration of α,β-unsaturated ketones with B_2pin_2 and BpinBdan (dan = 1,8-diaminonaphthalene), assisted by chiral phosphines.

Table 2 Asymmetric organocatalytic *versus* asymmetric Cu(I) catalyzed β-boration of *in situ* formed α,β-unsaturated imines with (*S*)-MeBoPhoz[a]



Entry	β-Borated imine	Method	% Conv.[b]	% ee[c]	% I.Y.[d]
1		A	90	54	59
2	**2a**	B	99	32	40
3		A	94	53	47
4	**2b**	B	80	32	40
5		A	98	50	49
6	**4**	B	95	45	43
7		A	96	70	61
8	**6**	B	88	61	57
9		A	99	51	48
10	**8**	B	92	33	57
11		A	99	57[e]	73
12	**14**	B	95	29[e]	52

[a] Conditions for method A: ketone or aldehyde (0.5 mmol), amine (0.5 mmol), THF (2mL), MK-10 (140 mg), B_2pin_2 (1.1 eq.), Cs_2CO_3 (15 mol%), MeOH (2.5 eq.), (*S*)-MeBoPhoz (10 mol%), 70 °C; for method B: same as method A + CuCl (3 mol%), 25 °C. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity determined from HPLC-MS. [d] Isolated yield for the corresponding *syn* γ-aminoalcohol (see ESI for reaction conditions). [e] ee calculated on the 4-(*N*-benzhydrylacetamido)butan-2-yl acetate derivative.

sphine (*S*)-MeBoPhoz (**P1**), total conversion was observed together with moderate enantioselectivity of the β-borated product (54% ee, Table 2, entry 1). When subtle changes were made to the reaction conditions, such as a lower base loading or a different reaction temperature, conversions and enantioselectivities remained essentially unchanged. However, when the β-boration was carried out in the presence of CuCl (3 mol%), conversions from **1** to **2a** were high but lower ees were observed (32% ee, Table 2, entry 2). Note that the isolated yields of the product are given for the final *syn*-γ-aminoalcohol after a highly stereoselective reduction protocol with $NaBH_4$ in MeOH, as reported previously,[7b] followed by oxidation with H_2O_2 in NaOH.

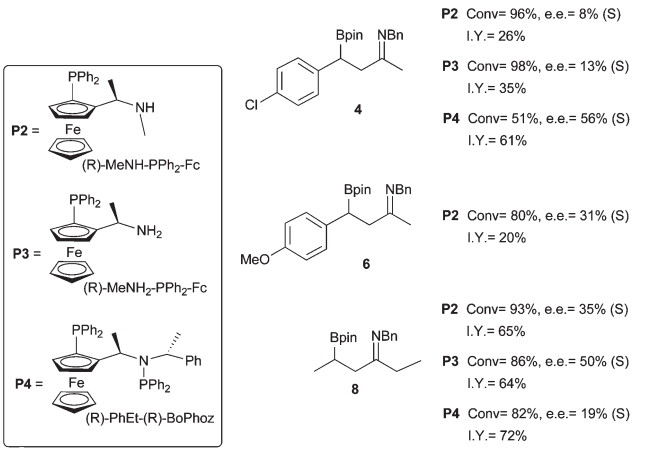
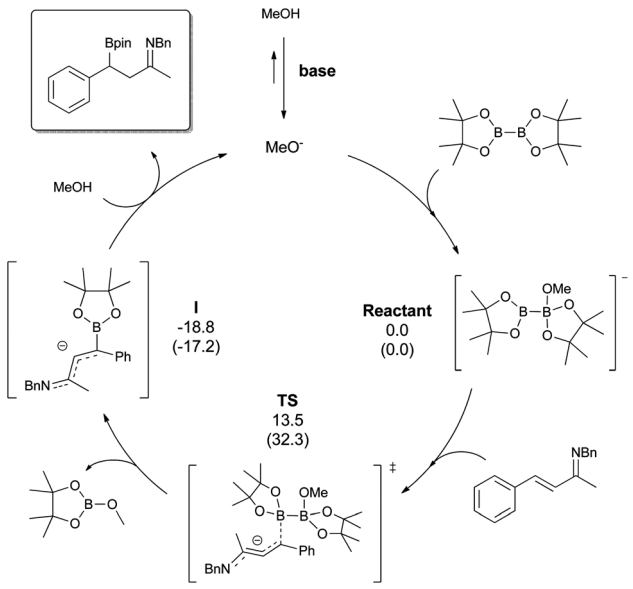


Fig. 1 Comparison of the chiral phosphine additives **P2–P4** for asymmetric β-boration of α,β-unsaturated imines **4**, **6** and **8**.

Since (*S*)-MeBoPhoz has been shown to be the most active and enantioselective additive for accessing β-boryl imines, in this metal free context, we extended this study to other similar chiral phosphines, *i.e.* **P2–P4**. We concluded that (*R*)-PhEt-(*R*)-BoPhoz (**P4**) provides comparable asymmetric induction than the close phosphine **P1**, and higher than the enantioselectivities provided by the other analogues, *i.e.* **P2** and **P3**, in which the amine is either mono- or di-substituted (Fig. 1).

To gain a deeper insight into the reaction mechanism and compare with other substrates that we reported previously,[1b] we conducted DFT-based theoretical studies (Scheme 3).

Initially, we postulated that the methoxide ion can quaternize a boron atom of the B_2pin_2 molecule forming the activated adduct [MeO → Bpin–Bpin]$^-$ (chosen as the origin of the



Scheme 3 Mechanistic proposal on the organocatalytic β-boration of imines. Electronic energies and Gibbs free energies (in parentheses) of the involved species in relation to the [MeO → Bpin–Bpin]$^-$ adduct are shown. All energies are in kcal mol^{-1}.

energies). This adduct can then react with the model α,β-unsaturated imine through a transition state **TS**, which corresponds to the nucleophilic attack of the sp^2 boron atom on the β-carbon of the α,β-unsaturated imine. The structural features of the **TS** show the cleavage of the B–B bond (Δd_{B-B} = 0.257 Å) and the formation of the new B–C bond (d_{B-C} = 2.078 Å). After this transition state (**TS**), a negatively charged intermediate **I** is formed. Also in this step, a molecule of (pin)B–OMe is released as the by-product. The anionic intermediate **I** is then protonated in the presence of an excess of B_2pin_2 and MeOH, regenerating again the active species [MeO → Bpin–Bpin]$^-$ and hence the β-borated product. At this point, it is interesting to compare energy values computed herein, with those obtained for the metal-free β-boration of ketones, esters and aldehydes.[1b] For the model imine (*E*)-1-phenyl-*N*-(4-phenylbutan-2-ylidene)methanamine, (**2a**), the transition state **TS** is higher ($\Delta G^{\neq}$ = 32.3 kcal mol^{-1}) than that found for acrolein ($\Delta G^{\neq}$ = 16.7 kcal mol^{-1}), 3-buten-2-one ($\Delta G^{\neq}$ = 18.7 kcal mol^{-1}), methyl acrylate ($\Delta G^{\neq}$ = 21.5 kcal mol^{-1}) and styrene ($\Delta G^{\neq}$ = 25.1 kcal mol^{-1}), but lower in energy than propylene ($\Delta G^{\neq}$ = 35.9 kcal mol^{-1}). This fact can be explained by the lower electrophilicity of the C_β of the α,β-unsaturated imine which makes it less reactive towards the nucleophilic attack. Moreover, the intermediate **I** for the imine (ΔG = –17.2 kcal mol^{-1}) is energetically more stable than the reactants, as expected, but less stable than the corresponding analogues for the activated alkenes.[1b] This can be also rationalized by the fact that the negative charge that is generated is more stabilized by the oxygen atom than the nitrogen due to their different electronegative characters. It is worth mentioning that the reaction energies computed for this model α,β-unsaturated imine substrate are in a similar range to those previously computed for ketones, aldehydes and esters, thus justifying the similarity in the reaction conditions (T = 70 °C) as described above.

Finally, we addressed the role of the chiral phosphine in not only mediating the catalytic reaction but importantly, guiding the asymmetric C–B bond formation. A possible interaction between a model phosphine of reduced steric congestion PMe_3, and the α,β-unsaturated imine **2a**, is to form a phosphonium enolate intermediate (Fig. 2).[10–12] We compared

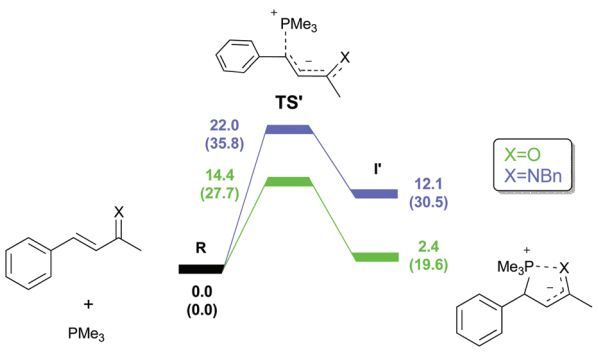
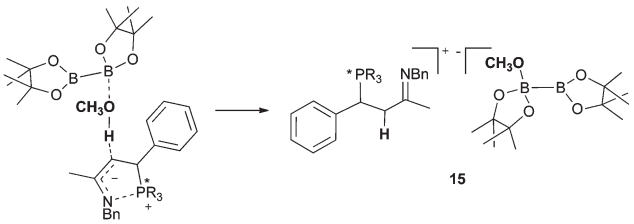


Fig. 2 Reaction energy profile for the formation of phosphonium enolates. Electronic and Gibbs free energies (in parentheses) are given in kcal mol^{-1}.



Scheme 4 Suggested formation of the ion pair ([α-H,β-PR_3-4-phenylbutylaldimine]$^+$[B_2pin_2·MeO]$^-$).

this with the corresponding α,β-unsaturated ketone-derived enolate species (Fig. 2). Interestingly, the imine-derived phosphonium enamide formed from PMe_3 and **2a** is higher in energy than the corresponding ketone-derived phosphonium enolate intermediate, which explains why that reaction has to be carried out at 70 °C, and does not proceed readily at lower temperature. Hence, the origin of the asymmetric induction when using (*S*)-MeBoPhoz may result from the protonation of the zwitterionic phosphonium enamide with MeOH, and formation of a tight ion-pair between the resulting [B_2pin_2·MeO]$^-$ adduct and the chiral phosphonium imine, *i.e.* as in **15** (Scheme 4), as we have postulated before.[9]

Conclusions

In conclusion, we have developed the first example of metal-free β-boration of *in situ* formed α,β-unsaturated imines, highlighting the compatibility of the organocatalytic Bpin addition with the imine formation in the presence of both ketone and amine. The reaction shows little dependence upon substrate electronics and shows consistently high conversion. Importantly, the use of chiral phosphines, such as the diphosphine (*S*)-MeBoPhoz, enables the catalytic asymmetric version to be realized with moderate asymmetric induction. Interestingly, the enantioselectivity is higher than that induced by the same chiral phosphines when modified using the corresponding Cu(I)-based catalytic system. The mechanism of the organocatalytic β-boration of these α,β-unsaturated imines has been postulated from a theoretical point of view, and seems to necessarily involve quaternization of the diboron reagent with methoxide. The role of the phosphine has been regarded to the ion pair formation and further work to elucidate this issue will be reported in due course.

Acknowledgements

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Notes and references

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