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

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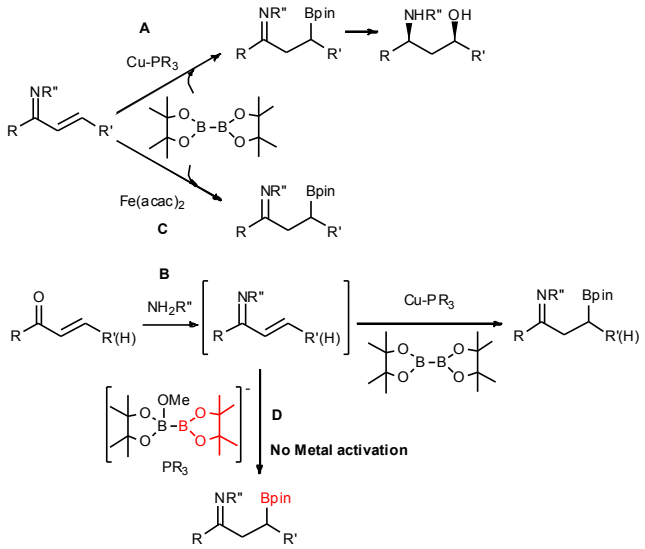
Abstract: The adduct [MeO→Bpin-Bpin]$^-$ efficiently mediates the β-boration of α,β-unsaturated imines formed "in situ". The use of chiral phosphines as additives, and in particular the chiral phosphine MeBoPhoz, enables the catalytic asymmetric reaction to proceed with moderate to good enantioselectivity.

Metal–free activation of diboron reagents has gained significant momentum, particularly to generate C-B new 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 that context, we found that this approach might enable efficient access to γ-aminoalcohols from the corresponding α,β-unsaturated imines.[7] The optimal combination of copper source, chiral ligand, amine and reducing reagent has provided a convenient methodology to obtain γ-aminoalcohols in a highly diastereo- and enantio-selective 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, was partially successful, however, the substrate was preactivated by Lewis acidic Fe(II) and Fe(III) salts (Scheme 1, pathway **C**).[8]
Recently, we became interested in trying to develop an asymmetric organocatalytic approach to generating C-B bonds in 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 focused 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 boron reagent bis(pinacolato)diboron (B_2pin_2), was added to the intermediate α,β-unsaturated imine. However, even when the reaction was performed at 70 ºC, no β-borated product **2a** was observed (Table 1, entry 1). The addition of 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) on its own. It seems, therefore, that the base/MeOH is essential for the diboron activation and the role of the phosphine could be

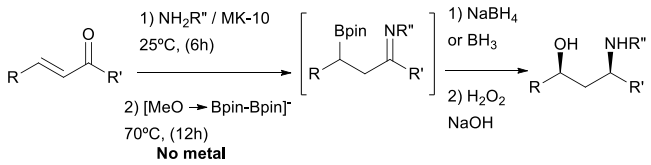
related to a similar pre-activation of the substrate as we have previously observed in the analogue metal-free β-boration of α,β-unsaturated carbonyl compounds, assisted by phosphines.[9]

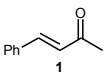
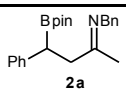
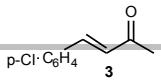
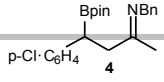


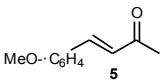
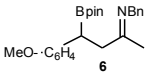
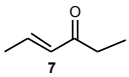
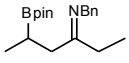
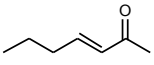
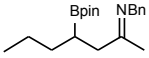
Scheme 1. A) Cu catalyzed β-boration of α,β-unsaturated imines (*ref 7a,b,c*), B) Cu catalyzed β-boration of "in situ" formed α,β-unsaturated imines (ref *7d,e,f*), C) Fe(II) activation of α,β-unsaturated imines towards the β-boration reaction (*ref 8*), D) organocatalytic β-boration reaction (*this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

With these preliminary results in hand, we extended this observation to other ketones 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 on 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 in 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 new methodology for the formation of β-borylated imines, in a one-pot reaction.

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



Entry	Substrate	Amine	Additives	Product	%Conv[b][IY][c]
1	 **1**	$BnNH_2$	-----	 **2a**	-----
2	"	$BnNH_2$	Cs_2CO_3 MeOH	"	-----
3	"	$BnNH_2$	PCy_3 Cs_2CO_3 MeOH	"	99 [56][d]
4	"	$BnNH_2$	PCy_3	"	-----
5	"	$BuNH_2$	PCy_3 Cs_2CO_3 MeOH	"	90 [66]
	 **3**			 **4**	

6		$BnNH_2$	PCy_3 Cs_2CO_3 MeOH		99 [47]
7	 **5**	$BnNH_2$	PCy_3 Cs_2CO_3 MeOH	 **6**	96 [37]
8	 **7**	$BnNH_2$	PCy_3 Cs_2CO_3 MeOH	 **8**	95 [51]
9	 **9**	$BnNH_2$	PCy_3 Cs_2CO_3 MeOH	 **10**	99 [68]
10	 **11**	$BnNH_2$	PCy_3 Cs_2CO_3 MeOH	 **12**	97 [30]

[a] Standard conditions: ketone (0.5 mmol), amine (0.5 mmol), THF (2mL), MK-10 (140 mg), B_2pin_2 (1.1eq), Cs_2CO_3 (15 mol%), MeOH (2.5 eq), PCy_3(10 mol%). [b] Conversion determined by ^1H NMR spectroscopy. [c] Reduction with $NaBH_4$, isolated yield calculated as syn-γ-amino alcohol. [d] Reduction with BH_3

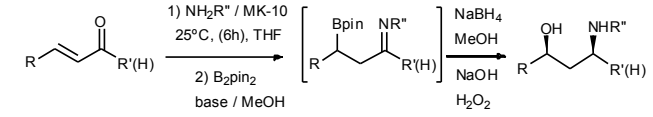
Our next step considered the possibility of inducing asymmetry into the formation of the new C-B bond using the organocatalytic approach. Hence, we proposed that chiral phosphine additives might interact with the substrate and provide an asymmetric environment for the β-boration with the Lewis acid-base adduct [*i.e.* MeO^-→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,[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 an 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^-→Bpin-Bpin] adduct in the presence of a series of chiral diphoshines. Preliminary results using chiral Josiphos-type of diphosphines did not provide any asymmetric induction, which contrasts with the efficient trends observed with the corresponding ketones.[2a] Remarkably however, when the [MeO^-→Bpin-Bpin] adduct was used with the diphosphine (*S*)-MeBoPhoz (**P1**), total conversion was observed together with moderate enantioselectivity of the β-borated product (54% e.e., Table 2, entry 1).

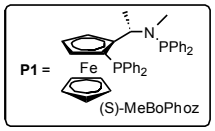
When subtle changes were made to the reaction conditions, such as lower base loading or reaction temperature, conversions and enantioselectivities remained essentially unchanged. However, when the β-boration was carried out in the presence of CuCl (3 mol%), conversions from **1** to **2a** were high but lower ees were observed (32% e.e., 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.

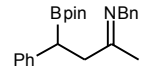
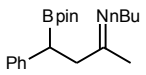
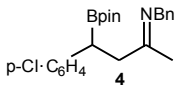
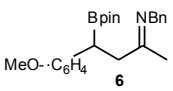
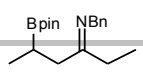
When the study of the asymmetric β-boration assisted by (*S*)-Me-BoPhoz was extended to other ketone or aldehyde and amine combinations, and compared with the Cu-(*S*)-MeBoPhoz-mediated reaction, it could be concluded that, in general, the conversions were comparable for metal-free and Cu-mediated β-borations (Table 2). However, the enantioselectivities *via* the organocatalytic reaction showed a general trend providing higher enantioselectivites than that for the copper-catalyzed process, achieving up to 70% e.e. for the β-borated imine **6** (Table 2, entry 7). For the metal-free β-boration of 2-but-2-enal, benzhydrylamine was used instead of benzylamine, to guarantee the completely chemoselective 1,4-addition *versus* 1,2-addition (as optimized in our previous studies[7e]). Hence, in the presence of (*S*)-MeBoPhoz, the substrate was quantitatively transformed into the β-borylated aldimine **14**, with an enantioselectivity significantly superior (e.e. =57%) to the same reaction carried out using Cu(I) (e.e. = 29%) (Table 2, entries 11 and 12).

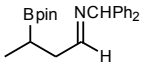
Table 2. Asymmetric organocatalytic versus asymmetric Cu(I) catalyzed β-boration of *in situ* formed α,β-unsaturated imines with (S)-MeBoPhoz.[a]





Method A: **metal free, 70ºC**
Method B: **CuCl, 25ºC**

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

10		B	92	33	57
11	 **14**	A	99	57	73
12		B	95	29	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 (1.1eq), Cs_2CO_3 (15 mol%), MeOH (2.5 eq), (S)-MeBoPhoz (10 mol%), 70ºC; for method **B**: same as method **A** + CuCl (3mol%), 25ºC. [b]Conversion determined by ^1H NMR spectroscopy. [c]Enantioselectivity determined from HPLC-MS. [d]Isolated Yield as the corresponding *syn* γ-aminoalcohol (see SI for reaction conditions). [e]e.e. calculated on the 4-(*N*-benzhydrylacetamido)butan-2-yl acetate derivative

Since (*S*)-MeBoPhoz has been shown to be the most active and enantioselective additive for accessing the β-boryl imine, in this metal free context, we extended this study to other similar chiral phosphines, **P2-P4**, and we concluded that (*R*)-PhEt-(*R*)-BoPhoz (**P4**), which is similar to **P1**, provides comparable asymmetric induction 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 (Figure 1).

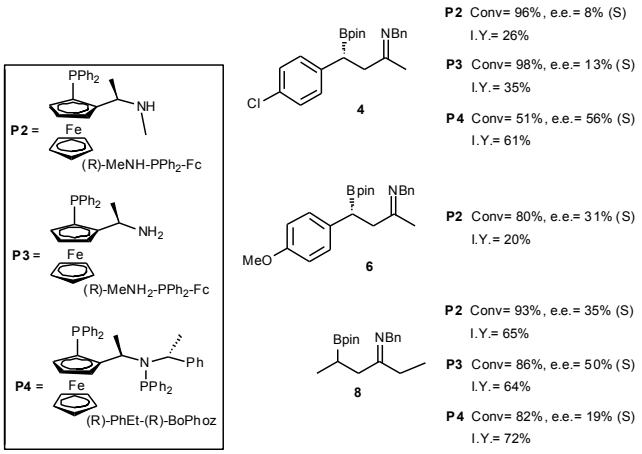
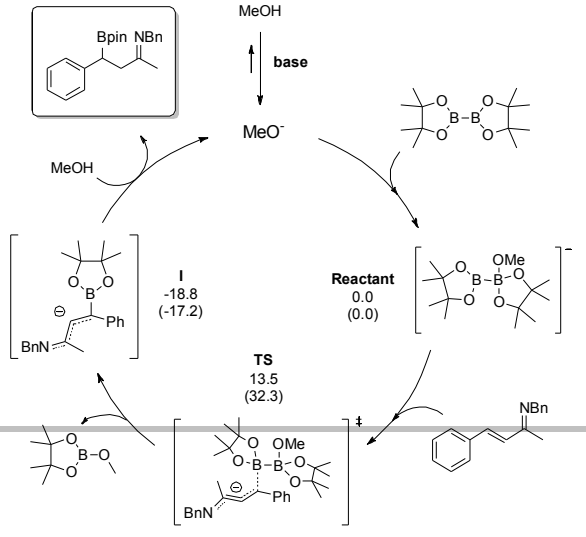


Figure 1. Comparison of the chiral phosphine additives **P2**-**P4** for asymmetric β-boration of α,β-unsaturated imines **4**, **6** and **8**

To get deeper insight into the reaction mechanism and compare with other substrates that we reported previously,[1b] we conducted DFT-based theoretical studies (Scheme 2). Initially we postulate that the methoxide ion quaternizes a boron atom of the B_2pin_2 molecule forming the activated adduct [MeO→Bpin-Bpin]$^-$ (chosen as the origin of the 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 to the C_β of the imine. The structural features of the **TS** show the cleavage of the B-B bond ($\Delta d_{B\text{-}B}$= 0.257 Å) and the formation of the new B-C bond ($d_{B\text{-}C}$= 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 a byproduct. The anionic intermediate **I** is then protonated in the presence of the excess of B_2pin_2 and MeOH, regenerating again the active species [MeO→Bpin-Bpin]$^-$ and the β-borated product.



Scheme 2. 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}.

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 the one 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 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 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=70ºC) described above.

We addressed the possible interactions between the model phosphine PMe_3 and the α,β-unsaturated imine **2a**, to form phosphonium enolates,[10-12] and we compared with the corresponding α,β-unsaturated ketone. Despite the fact that the phosphonium enolate between PMe_3 and **2a** is higher in energy than the corresponding values for the analogue ketone, the fact that the reaction is carried out at 70ºC, but not at lower temperature, might justify the formation of this intermediate. The interaction of the chiral phosphines with the substrate could be the explanation for the assistance of (*S*)-MeBoPhoz to the asymmetric induction observed, via the protonation of the zwitterionic phosphonium enolate species with MeOH, favoured by the presence of bis(pinacolato)diboron that stabilizes the MeO− anion, thus forming the Lewis acid–base [B_2pin_2·MeO]− adduct.[9]

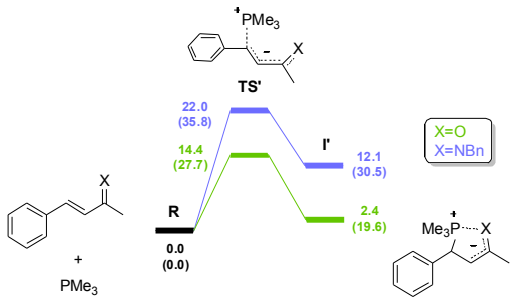


Figure 2. Reaction energy profile for the formation of phosphonium enolates Electronic and Gibbs free energies (in parentheses) computed at BP86 are given in kcal mol^{-1}.

In conclusion, we have developed the first example of a metal-free β-boration of α,β-unsaturated imines, which were formed in situ, highlighting the compatibility of the organocatalytic Bpin addition with the imine formation in the presence of the ketone and the amine. The reaction shows little dependence upon substrate electronics and shows consistently high conversion. The mechanism of the organocatalytic β-boration of the α,β-unsaturated imines, has been postulated from a theoretical point of view. Importantly, the use of chiral phosphines, such as MeBoPhoz diphosphine, 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 Cu(I) catalytic systems are employed. The role of the phosphine has been regarded to the ion pair formation and current work to disclose this issue will be reported in due course.

Experimental Section

Experimental Details.

Acknowledgements

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Keywords: β-boration • α,β-unsaturated imines • Me-BoPhoz • DFT • asymmetric induction

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