Asymmetric metal free $\beta$-boration of $\alpha,\beta$-unsaturated imines assisted by (S)-MeBoPhoz

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The adduct [MeO$\rightarrow$Bpin$\rightarrow$Bpin]$^-$ efficiently mediates the $\beta$-boration of $\alpha,\beta$-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. However, the development of a general, highly efficient asymmetric version of this reaction is still an important goal with only limited successful examples. Therefore, Cu(I) catalysts have become the most widely used for inducing asymmetry in $\beta$-boration, since Yun et al. discovered that copper catalysts modified with chiral phosphines can activate diboron reagents, such as bis(pinacolato) diboron (B$_2$pin$_2$), and catalyze the borylation of $\alpha,\beta$-unsaturated carbonyl compounds with high levels of enantioselectivity, in the presence of MeOH. In that context, we found that this approach might enable efficient access to $\gamma$-aminoalcohols from the corresponding $\alpha,\beta$-unsaturated imines. The optimal combination amine (for imine formation) then copper source and chiral ligand, followed by careful selection of reducing reagent, has provided a convenient methodology to obtain $\gamma$-aminoalcohols in a highly diastereo- and enantioselective manner (Scheme 1, pathways A and B). The unique attempt to perform the $\beta$-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).

Here, we develop an asymmetric organocatalytic approach to generate C-B bonds in the $\beta$-position of an unsaturated imine, i.e. Scheme 1, pathway D, as an alternative strategy to synthesize $\gamma$-aminoalcohols. Towards this end, we focus our efforts on the in situ generation of a model $\alpha,\beta$-unsaturated imine, i.e. (E)-1-phenyl-$N$-(4-phenylbutan-2-ylidene)methanamine, from 4-phenyl-3-buten-2-one (I) and benzylamine in THF with the dehydrating reagent, MK10. After 6 hours, the boron reagent bis(pinacolato) diboron (B$_2$pin$_2$), is added to the intermediate $\alpha,\beta$-unsaturated imine, however, even when the reaction was performed at 70 $^\circ$C, no $\beta$-bortonked 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 $\beta$-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 $\beta$-boration of $\alpha,\beta$-unsaturated carbonyl compounds, which is also assisted by phosphines. Isolated yields were given on the corresponding $\gamma$-amino alcohols by reduction with NaBH$_4$ in methanol and oxidation with H$_2$O$_2$ in NaOH.
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 
acrylic (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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Additives</th>
<th>Product</th>
<th>%Conv(^\circ) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>—</td>
<td>Ph</td>
<td>95 [30]</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Cs(_2)CO(_3)/MeOH</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>99 [56]</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>PC(_3)_2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5(^\text{c})</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>90 [66]</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>99 [47]</td>
</tr>
<tr>
<td>7</td>
<td>MeO-PhEt</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>96 [37]</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>95 [51]</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>99 [68]</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>PC(_3)_2C(_2)O(_3)/MeOH</td>
<td>—</td>
<td>97 [30]</td>
</tr>
</tbody>
</table>

\(^c\)Standard conditions: ketone (0.5 mmol), NH\(_2\)BH\(_3\) (0.5 mmol), THF (2 mL), MK-10 (140 mg), B-pin (1.1 eq), Cs\(_2\)CO\(_3\) (15 mol%), MeOH (2.5 eq), PC\(_3\)_2 (10 mol%). 
\(^\circ\)Conversion determined by \(^1\)H NMR spectroscopy.

Our next step 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\(_2\)-Bpin-Bpin. This concept had 
already been successfully demonstrated in the β-boration of α,β- 
unsaturated ketones with B\(_2\)pin\(_2\)\(2e\) 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. \(^9\)

\[\text{Bpin-Bdan}\] \(\text{MeOH, 16h, 70°C}\] \(\text{Conv. 77%}\) \(\text{e.e. = 85%}\)

Scheme 2. β-boration of α,β-unsaturated ketones with B\(_2\)pin\(_2\) and 
BpinBdan (dan=1,8-diaminonaphthalene), assisted by chiral phosphines.

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\(_2\)–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\(_2\)-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 a lower base loading or different reaction 
temperature, conversions and enantioselectivities remained 
esentially 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 \(\text{syn-γ-aminoalcohol}\) after a highly stereoselective reduction 
protocol with NaBH\(_4\) in MeOH, as reported previously, \(^h\) 
followed by oxidation with H\(_2\)O\(_2\) in NaOH.

Since (S)-MeBoPhoz has been shown to be the most active and 
enantioselective additive for accessing β-aryl 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 (Figure 1).
Table 2. Asymmetric organocatalytic versus asymmetric Cu(I) catalyzed β-boration of in situ formed α,β-unsaturated imines with (S)-MeBoPhoz.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-borated imine</th>
<th>Method</th>
<th>%Convb</th>
<th>% e.e.c</th>
<th>% I.Y.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bpin NBin A</td>
<td>90</td>
<td>54</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bpin Ph 2a B</td>
<td>99</td>
<td>32</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bpin NnBu A</td>
<td>94</td>
<td>53</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bpin NnBu B</td>
<td>80</td>
<td>32</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Bpin NBin A</td>
<td>98</td>
<td>50</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>p-Cl-C6H4 B</td>
<td>95</td>
<td>45</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Bpin NBin A</td>
<td>96</td>
<td>70</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MeO-C6H4 B 6</td>
<td>88</td>
<td>61</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Bpin NBin A</td>
<td>99</td>
<td>51</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bpin NBin B</td>
<td>92</td>
<td>33</td>
<td>57</td>
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<td>11</td>
<td>Bpin NBin A</td>
<td>99</td>
<td>57*</td>
<td>73</td>
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<tr>
<td>12</td>
<td>Bpin NBin 14</td>
<td>95</td>
<td>29*</td>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

*Conditions for method A: ketone or aldehyde (0.5 mmol), amine (0.5 mmol), THF (2mL), MK-10 (140 mg), B(pin) (1.1 eq), Cs2CO3 (15 mol%), MeOH (2.5 eq), (S)-MeBoPhoz (10 mol%), 70°C; for method B: same as method A + CuCl (3 mol%), 25°C. bConversion determined by 1H NMR spectroscopy. cEnantioselectivity determined from HPLC-MS. dIsolated Yield as the corresponding syn γ-aminoalcohol (see SI for reaction conditions). e.e. calculated on the 4-(N-benzhydrylacetamido)butan-2-yl acetate derivative.

To get a deeper insight into the reaction mechanism and compare with other substrates that we reported previously,[19] we conducted DFT-based theoretical studies (Scheme 3).

Initially, we postulated that the methoxide ion can quaternize a boron atom of the B(pin)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 sp2 boron atom to the β-carbon of the α,β-unsaturated imine. The structural features of the TS show the cleavage of the B-B bond (d_{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 the excess of Bpin and MeOH, regenerating again the active species \([\text{MeO} \rightarrow \text{Bpin} \rightarrow \text{MeO}]^+\) and hence the \( \beta \)-borated product. At this point, it is interesting to compare energy values computed herein, with those obtained for the metal-free \( \beta \)-boration of ketones, esters and aldehydes.\(^{[10]}\) For the model imine \((E)-1\)-phenyl-N-(4-phenylbutan-2-ylidene) methanamine, \((2a)\) the transition state \( \text{TS} \) is higher \((\Delta G^r=32.3 \text{ kcal mol}^{-1}) \) than that found for acrolein \((\Delta G^r=16.7 \text{ kcal mol}^{-1})\), 3-butene-2-one \((\Delta G^r=18.7 \text{ kcal mol}^{-1})\), methyl acrylate \((\Delta G^r=21.5 \text{ kcal mol}^{-1})\) and styrene \((\Delta G^r=25.1 \text{ kcal mol}^{-1})\), but lower in energy than propylene \((\Delta G^r=35.9 \text{ kcal mol}^{-1})\). This fact can be explained by the lower electronegativity of the C\( \beta \) of the \( \alpha,\beta \)-unsaturated imine which makes it less reactive towards nucleophilic attack. Moreover, the intermediate \( I \) for the imine and \((2a)\) is energetically more stable than the reactants, as expected, but less stable than the corresponding analogues for the activated alkenes.\(^{[11]}\) 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 \( \alpha,\beta \)-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 \((T=70^\circ \text{C})\) as described above.

Finally, we addressed the role of the chiral phosphine in, not only mediating the catalytic reaction but importantly, in controlling the asymmetric C-B bond formation. A possible interaction between a model phosphine of reduced steric congestion PMe\( \alpha \), and the \( \alpha,\beta \)-unsaturated imine \( 2a \), is to form a phosphonium enolate intermediate (Figure 2).\(^{[10]-[12]}\) We compared this with the corresponding \( \alpha,\beta \)-unsaturated ketone-derived enolate species (Figure 2). Interestingly, the imine-derived phosphonium enamide formed from PMe\( \alpha \) and \( 2a \) is higher in energy than the corresponding ketone-derived phosphonium enolate intermediate, which explains why this 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 \((S)-\text{MeBoPhoz}\) may result from protonation of the zwitieronic phosphonium enamide with MeOH, and formation of a tight ion-pair between the resulting \([\text{Bpin}_2\text{MeO}]^+\)– adduct and the chiral phosphonium imine, i.e. as in 15 (Scheme 4), as we have postulated before.\(^9\)

**Figure 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 \([\alpha,\beta-\text{H,PR}_{2}\text{-4-phenylbutyldimine}]^{[\text{Bpin};\text{MeO}]}\).