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Base-free $\beta$-boration of $\alpha,\beta$-unsaturated imines catalysed by Cu$_2$O with concurrent enhancement of asymmetric induction

Adam D. J. Calow, [b] Cristina Solé, [a] Andrew Whiting,*[b] Elena Fernández*[a]

Introduction

Cu(I) catalysed asymmetric $\beta$-boration reactions have received considerable attention since Yun et al. discovered that CuCl (3 mol%) modified with bidentate Josiphos-type chiral ligands (3 mol%) could activate B$_2$pin$_2$ in the presence of base (9 mol%), to deliver the Bpin moiety enantioselectively to the $\beta$-position of $\alpha,\beta$-unsaturated nitrile compounds (Scheme 1a).[1] Further efforts have been devoted to increase the scope of application of this convenient methodology to polyfunctional organoboron compounds.[2,3] We became interested in, and focussed on, the preparation of $\gamma$-amino alcohols in a highly enantio- and diastereoselective manner via a Cu(I) mediated $\beta$-boration of $\alpha,\beta$-unsaturated imines followed by a boron-assisted in situ imine reduction and B-C oxidation steps (Scheme 1b).[4] We extended this strategy using in situ formation of the $\alpha,\beta$-unsaturated imines from $\alpha,\beta$-unsaturated aldehydes and ketones, trapping them using the $\beta$-boration.[5] In addition, for certain water-soluble $\gamma$-amino alcohol products especially, a further protection step could be performed in situ to give the readily isolated 1,3-oxazine derivatives in a 5 step-one pot sequence (Scheme 1c).[5]

For all the Cu-mediated $\beta$-bortations of electron deficient olefins reported to date, the addition of base has always been required,[6] unless preformed (NHC)CuOR species (NHC= N-heterocyclic carbene ligands) and Cu(OH)$_2$/L are used to activate the B$_2$pin$_2$[7,8] or sp$^2$-sp$^3$ hybridised mixed diboron reagents transmetallate with CuCl to provide the CuBpin reactive species.[9] We became interested in exploring the use of Cu$_2$O as precursor of the active catalytic system for the $\beta$-boration of $\alpha,\beta$-unsaturated imines. Most importantly, this could potentially allow access to cyclic and acyclic $\beta$-boryl imines. The reaction was also followed using in situ IR spectroscopy, demonstrating the imine formation / $\beta$-boration sequence and that the new catalytic system is superior to those employed for this reaction previously.

Scheme 1. Strategies of precise C-B bond formation with CuCl: a) ref. 1, b) ref. 4a, c) ref. 5.
behave as a novel base-free system, as well as potentially being asymmetric when used in the presence of suitable compatible chiral ligands. This hypothesis is based on the possibility that CuO could interact with MeOH to generate a Cu(I) alcoholate or hydroxide species. To the best of our knowledge, there is only one example of asymmetric induction upon C-B bond formation mediated by CuO in the β-boration of α,β-unsaturated N-acryloxazolinidones using a chiral bicyclic 1,2,4-triazolium salt (Scheme 2) and CuClO₂ base.⑧⑨ Our objective was to investigate, and highlight, the benefits of CuO as a cheap catalyst precursor, avoiding the addition of an external base, and modify the CuO with commercially available chiral ligands, such as (R)-BINAP, to promote an efficient enantioselective catalytic system.

**Scheme 2.** CuO mediated β-boration of N-cinnamoyloxazolinid-2-one with chiral triazolium salt.

**Results and Discussion**

Our study began with the β-boration of 4-phenyl-3-buten-2-one (1) as a model substrate, and bis(pinacolato) diboron (B₂pin₂) as the diboron reagent. Two Cu(II) sources were selected; CuCl (3 mol%) and Cu₂O (1.5 mol%), in order to compare their relative activities as catalyst precursors, in the presence of (R)-BINAP. In an initial set of experiments, the substrate 1 was not converted into the β-borated ketone 2 in the absence of BnNH₂ (Table 1, entries 1 and 6), however, with the increasing addition of BnNH₂ (10 – 100 mol%) progressive formation of the β-borated imine 3a occurred with different efficiency, depending on the copper source. When the CuO-(R)-BINAP catalytic system was used, the β-borated ketone 2 was still the main product at low amine loadings (Table 1, entries 2-3). When the percentage of amine increased from 50 to 100% in the CuO mediated reaction, only β-borated imine 3a was observed, although substrate 1 still remained even in the presence of 100% of BnNH₂ (Table 1, entries 4-5). Remarkably however, when the Cu₂O-(R)-BINAP catalyst system was used for the β-boration of 1, the percentage of the β-borated imine 3a formed was, in all cases, close to the percentage of amine present (Table 1, entries 7-10). This shows that Cu₂O favours trapping of the "in situ" formed α,β-unsaturated imine by catalysing its transformation into the corresponding β-borated ketone 3a. In addition, the beneficial influence of Cu₂O could also be extended to the asymmetric induction of the C-B bond formation step. While the CuCl-(R)-BINAP catalytic system provided the β-borated imine with e.e. values around 85-89%, the Cu₂O-(R)-BINAP system promoted the enantioselective formation on 3a in up to 99% of e.e. (Table 1). It is noteworthy also that the remaining β-borated ketone 2 was obtained always with e.e. values between 16-22%, and that an excess of (R)-BINAP in the reaction media did not change the reaction outcome (Table 1, entry 11). The same was also found to be the case with higher loadings of CuO. (Table 1, entry 12). Interestingly, when a Cu(II) source was used instead, i.e. CuCl, the catalytic system CuO-(R)-BINAP did convert the α,β-unsaturated ketone 1 into the β-borated imine 3a, however, with only 71% of conversion and only moderate e.e.s (Table 1, entry 13). Apart from the previous reports of Cu(II) catalysed β-boration of α,β-unsaturated carbonyl compounds,⑧⑨ to the best of our knowledge, this is the first example of Cu(II) catalysing the β-boration of α,β-unsaturated imines. It is also interesting to observe that the nature of the amine used in the reaction seems to be crucial for the enantioselection. Hence, when the β-boration of 1 with Cu₂O-(R)-BINAP was carried out in the presence of 100 mol% of NH₄Bu, the β-borated imine 3b was quantitatively formed, but only with 27% e.e. (Table 1, entry 14).

![Diagram of catalyst system](image-url)

**Table 1.** Cu(II)-BINAP mediates β-boration of activated olefins.⑬⑭

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(II)</th>
<th>R NH₂</th>
<th>Conv (%)</th>
<th>2 (%)</th>
<th>e.e (%)</th>
<th>3(%)</th>
<th>3(%)&lt;sub&gt;[IY]%&lt;/sub&gt;</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl</td>
<td>...</td>
<td>0</td>
<td>0</td>
<td>...</td>
<td>0</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuCl</td>
<td>BnNH₂</td>
<td>24</td>
<td>21</td>
<td>(S)</td>
<td>3</td>
<td>nd</td>
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<td>3</td>
<td>CuCl</td>
<td>BnNH₂</td>
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<td>32</td>
<td>22 (S)</td>
<td>3</td>
<td>nd</td>
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<td>BnNH₂</td>
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<td>...</td>
<td>...</td>
<td>36</td>
<td>89 (S)</td>
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<td>5</td>
<td>CuCl</td>
<td>BnNH₂</td>
<td>71</td>
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<td>...</td>
<td>71</td>
<td>85 (S)</td>
<td>...</td>
</tr>
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<td>6</td>
<td>CuO</td>
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<td>0</td>
<td>...</td>
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<td>...</td>
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<td>...</td>
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<td>7</td>
<td>CuO</td>
<td>BnNH₂</td>
<td>43</td>
<td>37</td>
<td>16 (S)</td>
<td>6</td>
<td>99 (S)</td>
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<td>CuO</td>
<td>BnNH₂</td>
<td>53</td>
<td>32</td>
<td>22 (S)</td>
<td>21</td>
<td>99 (S)</td>
<td>...</td>
</tr>
<tr>
<td>9</td>
<td>CuO</td>
<td>BnNH₂</td>
<td>57</td>
<td>11</td>
<td>nd</td>
<td>46</td>
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<tr>
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<td>BnNH₂</td>
<td>&gt;99</td>
<td>0</td>
<td>nd</td>
<td>99</td>
<td>95 (S)</td>
<td>...</td>
</tr>
<tr>
<td>11</td>
<td>CuO</td>
<td>BnNH₂</td>
<td>&gt;99</td>
<td>0</td>
<td>nd</td>
<td>99</td>
<td>93 (S)</td>
<td>...</td>
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<td>BnNH₂</td>
<td>&gt;99</td>
<td>0</td>
<td>nd</td>
<td>&gt;99</td>
<td>95 (S)</td>
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<td>13</td>
<td>CuO</td>
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<td>0</td>
<td>nd</td>
<td>71</td>
<td>73 (S)</td>
<td>...</td>
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<td>14</td>
<td>CuO</td>
<td>n-BuNH₂</td>
<td>&gt;99</td>
<td>...</td>
<td>...</td>
<td>99</td>
<td>27&lt;sup&gt;⑭&lt;/sup&gt; (S)</td>
<td>...</td>
</tr>
</tbody>
</table>

⑬ Reaction conditions: substrate (0.25 mmol), CuCl (3 mol%) or CuO (1.5 mol%), (R)-BINAP (3 mol%), B₂pin₂ (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL), 25 °C, 16 h. ⑭ Conversion and selectivity calculated from consumed substrate by ⑯ NMR. ⑮ E.e. calculated by HPLC-UV as an average of two results. ⑬ CuO (1.5 mol%), (R)-BINAP (6 mol%), (R)-BINAP (3 mol%), (R)-BINAP (3 mol%), (R)-BINAP (3 mol%), (R)-BINAP (3 mol%). ⑯ CuO (3 mol%), (R)-BINAP (6 mol%). ⑰ E.e. calculated on the hydrolysed ketone via HPLC-MS.
To confirm the benefits of Cu$_2$O-(R)-BINA P on the enantioselective formation of the β-borated imines 3, we became interested in isolating the α,β-unsaturated imines, such as (E)-1-phenyl-N-(4-phenylbut-3-en-2-ylidene)ethanamine (4a), and performing the β-boration on that substrate to compare with the reactions carried out from the in situ reaction of α,β-unsaturated ketone 1 + BnNH$_2$. In the absence of base, Cu$_2$O-(R)-BINA P catalysed the formation of 3a with high enantioselectivity, while CuCl-(R)-BINA P was inactive (Table 2, entries 1 and 2). The addition of 10 mol% NaOEt or Bu$_3$CO$_2$ to the CuCl-(R)-BINA P catalytic system favoured the formation of 3a, but resulting in a racemic product (Table 2, entries 4 and 5). However, the addition of 10 mol% BnNH$_2$ as base did not favour the β-boration of the imine. The role of the base is expected to favour transmetalation from the hydrolysed ketone via HPLC E.e. calculated by HPLC at 25 ºC, 16 h. The substrate scope of Cu$_2$O-(R)-BINA P catalysed β-boration of activated olefins was significantly higher as shown in Table 2.

Table 2. Cu-(R)-BINA P mediates β-boration of activated olefins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Cu[I]</th>
<th>Base (mol%)</th>
<th>Conv (%)</th>
<th>e.e (%)</th>
<th>Conv (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (%)</td>
<td>6 (%)</td>
<td>[IY (%)]</td>
</tr>
<tr>
<td>1</td>
<td>4a</td>
<td>Cu$_2$O</td>
<td>---</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>87 (S)</td>
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<tr>
<td>2</td>
<td>&quot;</td>
<td>CuCl</td>
<td>---</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>CuCl</td>
<td>BnNH$_2$ (10)</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>CuCl</td>
<td>CsCO$_2$ (10)</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>CuCl</td>
<td>NaOEtBu (10)</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>(CH$_2$CN)$_2$CuPF$_6$</td>
<td>---</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>85 (S)</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>Cu$_2$O</td>
<td>---</td>
<td>15</td>
<td>15</td>
<td>69 (S)</td>
</tr>
<tr>
<td>8</td>
<td>4b</td>
<td>Cu$_2$O</td>
<td>---</td>
<td>99</td>
<td>99</td>
<td>74 (S)</td>
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<tr>
<td>9</td>
<td>&quot;</td>
<td>(CH$_2$CN)$_2$CuPF$_6$</td>
<td>---</td>
<td>99</td>
<td>99</td>
<td>84 (S)</td>
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<tr>
<td>10</td>
<td>&quot;</td>
<td>CuCl</td>
<td>---</td>
<td>&lt;5</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

[1] Reaction conditions: α,β-unsaturated imine (0.25 mmol), CuCl (3 mol%)/(R)-BINA P (6 mol%), (CH$_2$CN)$_2$CuPF$_6$ (3 mol%)/(R)-BINA P (6 mol%) or CuO (1.5 mol%)/(R)-BINA P (3 mol%), Bpin$_2$ (1.1 equiv.), MeOH (2.5 equiv.), THF (1 mL) 25 ºC, 16 h. [2] Conversion calculated from consumed substrate by $^1$H NMR. [3] E.e. calculated by HPLC-UV as an average of two results. [4] E.e. calculated from the hydrolysed ketone via HPLC-MS.

The lack of a coordinating anion on the Cu(I) catalytic system appears to be the key factor in avoiding the need for additional base in the β-boration. This is clearly demonstrated by using Cu(CH$_2$CN)$_2$PF$_6$ modified with (R)-BINA P to catalyse the asymmetric β-boration of 4a (Table 2, entry 6), which is similar to using Cu$_2$O, though Cu$_2$O is significantly cheaper. Interestingly, when Cu(I) was also explored for catalysing the reaction, we observed that the Cu$_2$O-(R)-BINA P catalytic system was almost inactive towards the β-boration of 4a (Table 2, entry 7). If we compare the latter result with the Cu$_2$O-(R)-BINA P catalysed β-boration of 1 in the presence of 1 eq. of BnNH$_2$ (Table 1, entry 13), we can conclude that the Cu(I) catalytic system studied needs a base to activate the diboron source. From these observations, it is clear that the use of Cu$_2$O is especially beneficial because it can be used in the absence of bases to promote the desired β-boration reaction. As far as the influence of the N-substituent is concerned, when Cu$_2$O-(R)-BINA P mediated the β-boration of (E)-N-(4-phenylbut-3-en-2-ylidene)butan-1-amine (4b), also without base the β-borated imine 3b was quantitatively formed but with low enantioselectivity (Table 2, entry 8). Similar behaviour was observed when Cu(CH$_2$CN)$_2$PF$_6$ was the copper source, although CuCl resulted inactive (Table 2, entries 9 and 10). The observation of low enantioselectivity in entries 8 and 9 (Table 2) also confirms the important role of the N-substituent in achieving high asymmetric induction.

The synergy between Cu$_2$O and (R)-BINA P (L0) was further demonstrated when we explored the influence of alternative bidentate chiral ligands such as (R)- Tol-BINA P (L1), (R)-Ph-MeOiBiphep (L2), Josiphos (L3, L4) and Mandiphos (L5) type ligands. Remarkably, the cheapest ligand, (R)-BINA P, provided the best influence on the enantioselective Cu$_2$O-catalysed β-boration of 4-phenyl-3-buten-2-one 1, in the presence of 1 eq. of BnNH$_2$ and Bpin$_2$ (Figure 1).

The substrate scope of the β-boration of α,β-unsaturated imines, formed in situ from the corresponding α,β-unsaturated ketones and BnNH$_2$, was surveyed using the Cu$_2$O-(R)-BINA P catalytic system and compared also with the influence of alternative chiral ligands. For the transformation of 4-(p-MeO-phenyl)-3-buten-2-one (1) into the β-borated imine 6 (Table 3, entry 1), the Cu$_2$O-(R)-BINA P and Cu$_2$O-(R)-Tol-BINA P catalytic systems provided moderate conversions but high e.e.s. On the contrary, the CuO-(R)-BINA P and Cu$_2$O-(R)-Et$_2$N catalytic systems provided only moderate enantioselectivity. When the substrate studied was the more electron deficient olefin 4-(p-CI-phenyl)-3-buten-2-one (7) (Table 3, entry 2), all the catalytic systems explored provided a quantitative β-borated product 8 with only moderate enantioselectivity.

Having examined acyclic substrates, the β-boration of cyclic α,β-unsaturated imine substrates was also studied. Towards this end, we found that cyclohexenone (9) could be efficiently converted
into the desired product 10 with Cu₂O-modified by (R)-BINAP (L0), (R)-Tol-BINAP (L1) and MeOBpheph (L2), however, the enantioselectivity was only moderate (Table 3, entry 3). In contrast, when the influence of a Walphos-type ligand L6 was explored, we observed that although conversion to the product 10 was low (20%), the e.e. was the highest for this substrate (92%) (Table 3, entry 3). It is important to note that although this is the first approach to the enantioselective formation of cyclic β-boryl imine derivatives, the base-free asymmetric induction provided by Cu₂O modified with ligands L0, L1 and L6 is in complete agreement with the previous work of Yun and co-workers,[20] who reported that CuCl base mediated the enantioselective β-boration of cyclohexenone (Table 3, entry 4). Since the corresponding α,β-unsaturated cyclic imine, 1-phenyl-N-(cyclohexenyl)methanamine, could not be isolated to be β-borated, the alternative in situ formation of the imine, followed by β-boration trapping by means of the Cu₂O-based system, represents a simple method to obtain an enantiomerically enriched β-borated imine 10.

Table 3: Substrate scope for the Cu₂O mediated asymmetric β-boration of in situ-formed α,β-unsaturated imines.[4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ligand</th>
<th>Conv (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP (L0)</td>
<td>L0  67 [45]</td>
<td>66 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1   71</td>
<td>82 (S)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>L2   85 [60]</td>
<td>49 (R)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L5   99</td>
<td>35 (R)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(R)-BINAP (L0)</td>
<td>L1  99 [87]</td>
<td>48 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L2   99 [85]</td>
<td>58 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L5   99</td>
<td>35 (S)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(R)-BINAP (L0)</td>
<td>L0  99 [89]</td>
<td>39 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1   99</td>
<td>65 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L2   97</td>
<td>30 (S)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L6   20</td>
<td>92 (R)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(R)-BINAP (L0)</td>
<td>L0  93 (2 h)</td>
<td>40 (R)</td>
<td></td>
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<td>L1   93 (2 h)</td>
<td>63 (S)</td>
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<td></td>
<td></td>
<td>L6   90 (24 h)</td>
<td>90 (S)</td>
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</tbody>
</table>

[4] Reaction conditions: α,β-unsaturated imine (0.25 mmol), Cu₂O (3 mol%), L (6 mol%), B(pin) (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 °C, 16 h. Conversion calculated from consumed substrate by 1H NMR spectroscopy. E.e. calculated by HPLC-UV as an average of two results. Calculated on the hydrolysed β-borated ketone via HPLC-MS. Ref. 2, CuCl (3 mol%), NaOtBu (3 mol%), L (3 mol%).

Another set of substrates we were keen to explore as suitable candidates for the in situ imine formation, followed by β-boration in the presence of Cu₂O/L, were the aliphatic, open-chain, α,β-unsaturated ketones, 4-hexen-3-one (11), 3-hepten-2-one (13) and 3-nonen-2-one (15). The corresponding α,β-unsaturated imines could also not be isolated in order to perform a copper-catalysed β-boration, and hence the in situ protocol gave us an alternative approach towards the aliphatic β-borated imines (see Table 4). In all cases, a secondary product (β-amino ketone) could be identified due to the competitive aza-Michael addition reaction of the amine to the α,β-unsaturated ketones.[12] Therefore, the selectivity of the desired β-borated imine varied from moderate to high, depending on the substrate and the nature of the chiral ligand. When the substrate was 3-hepten-2-one 13, the two-step reaction occurred efficiently to give a high conversion to the β-borated imine (up to 93%, Table 4, entry 2). The bidentate chiral ligand that induced the highest enantioselectivity in the Cu₂O mediated imine formation / β-boration of ketones 13 and 15 was the Josiphos-type ligand L7 (e.e.s up to 92%, Table 4).

Table 4: Substrate scope for the Cu₂O mediated asymmetric β-boration of in situ-formed α,β-unsaturated imines from aliphatic open chain α,β-unsaturated ketones.[4]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ligand</th>
<th>Conv (%)</th>
<th>Sel(%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINAP</td>
<td>L0  99</td>
<td>55 [35]</td>
<td>66 (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1   99</td>
<td>63 [32]</td>
<td>61 (+)</td>
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<td>L2   99</td>
<td>54 [36]</td>
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<td>L7   99</td>
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[4] Reaction conditions: α,β-unsaturated imine (0.25 mmol), Cu₂O (3 mol%), L (6 mol%), B(pin) (1.1 equiv.), MeOH (2.5 equiv.), THF (1.3 mL) 25 °C, 16 h. Conversion calculated from consumed substrate by 1H NMR spectroscopy. Selectivity calculated by 1H NMR spectroscopy, with the β-amino ketone as by-product. Calculated via HPLC-MS.

We further examined the base-free Cu₂O-L1-Bpin catalytic system and the analogous CuCl-L1-Bpin system, by following the in situ imine formation / β-boration reaction between 1 (1 eq.) and BnNH₂ (1 eq.) using in situ IR spectroscopy (ReactIR, Figs. 2 and 3 respectively). We were intrigued by the different roles of Cu₂O versus CuCl in the intrinsic α,β-unsaturated imine formation and subsequent β-boration to produce the β-boryl imine 3a. In each case, the initial 20 min period was cropped to allow for addition and mixing of reagents, imine formation, and then addition of MeOH which initiates the β-boration (as measured by the rate-of-decrease of the Bpin₂ blue line in both Figs. 2 and 3).

Using the Cu₂O system for the in situ formed α,β-unsaturated imine 4a, the reaction follows a first-order-like reaction profile (Fig. 2a), reaching completion after ca. 10 h (Note: subsequent addition of borohydride-MeOH can be followed readily by ReactIR, with the imine reduction clearly visible, see ESI). The
Cu₂O system does not seem to catalyse the imine formation. Interestingly, the formation of 3a almost mirrors the rate-of-decrease of the B₂pin₂ (see Fig. 2b: the direct graphical output of Fig. 2a) and is faster than the rate of decrease of enone 1 under direct borylation conditions, thus providing further evidence that the reaction proceeds through imine formation / β-boration sequence, and not β-boration of 1 followed by subsequent imine formation.

![Figure 2. a] ReactIR derived reaction profile showing synchronous in situ imine 4a formation from ketone 1 and CuO-L1 catalysed borylation, forming β-borylated imine 3a. Due to overlapping C=O (substrate) and C=N (product) stretches, an alternative stretch at 1532 cm⁻¹ was followed to monitor the formation of 3a. b) The corresponding ReactIR graphical output (with 2nd derivative base-line correction) showing synchronous in situ imine 4a formation from ketone 1 and CuO-L1 catalysed borylation, forming β-borylated imine 3a.

These results highlight that α,β-unsaturated imines are considerably more reactive than the corresponding α,β-unsaturated ketones, in the Cu-catalysed β-boration reaction. In stark contrast, when the identical reaction is carried out using CuCl (Fig. 3) in place of Cu₂O, the reaction shows completely different kinetic behaviour and does not proceed to completion (even after 24 h, see ESI). However, when base was added (NaOt-Bu, 10 mol%) at 4 h, the key role of the base was demonstrated, resulting in the rapid and complete loss of the B₂pin₂ and full conversion of 4a to the β-borylated imine 3a.

Next, we explored the efficiency of the base-free Cu₂O-L1-B₂pin₂ catalytic system in the in situ imine formation-borylation of the aliphatic cyclic α,β-unsaturated ketone 9. We became interested to determine the rate of formation of β-borylated imine 10 and compare it with the previously observed for the formation of β-borylated imine 3a. With the in situ IR spectroscopy (ReactIR) data shown in Fig. 4, similar behaviour of the in situ cyclohexenone-derived imine β-boration to that of the chalcone-ketone derivative substrate was observed, i.e. the decrease of substrate 9 and B₂pin₂ was synchronous to the increase in β-boryl imine 10. However, the reaction was slightly faster, being complete in essentially 6 h (for 10) vs. 10 h (for 3a). This strongly suggests that: 1) N-Cu chelation is not necessary for the α,β-unsaturated imine β-boration reaction; 2) an s-cis conformation of the activated imine more reactive towards β-boration is not required. Indeed, the fixed s-trans conformation derived from the cyclohexenone imine is more reactive, clearly illustrating this point.

![Figure 3. ReactIR derived reaction profile showing synchronous in situ imine 4a formation and borylation to give the resulting imine 3a [CuCl-L1+] the addition of NaOt-Bu (10 mol%) after 4 h. The peak fluctuation at 4 h is a result of the mixing upon addition of base.

![Figure 4. ReactIR derived reaction profile showing synchronous in situ imine derivative of ketone 9 and CuO-L1 catalysed borylation, forming β-borylated imine 10.](image-url)
Scheme 3 illustrates, in hypothesis A, a plausible interaction between Cu₂O, MeOH and Bpin₂, to provide the corresponding CuBpin nucleophilic species and an additional Cu(OH) species ready to transmetallate further with Bpin₂. In this hypothetical view, the NH·Bn seems to be exclusively involved in imine formation. However, when CuCl is used as the copper source, the BnNH₂ may have a partial role in inefficiently activating MeOH and forming the imine (Scheme 3, hypothesis B). This would explain why the reactions carried out without base addition and using CuCl do not proceed to completion effectively and low or zero activity that is observed in the β-boration of the isolated imine. Of course, as shown in Fig. 3, the addition of base is able to recover the catalytic activity, but even this does not match the newly developed efficient Cu₂O system, as demonstrated by Fig. 2. In addition, the enantioselectivity could be increased by the absence of external base which favors background reactions.

Experimental Section

Experimental procedure for the copper/(R)-BINAP catalysed β-boration of in situ formed α,β-unsaturated imines with bis(pinacolato)diboron.

Cu(I) salts (1.5-3 mol%), (R)-BINAP (3-6 mol%, 0.0075-0.015 mmol, 4.7-9.3 mg) were transferred to a Schlenck tube and dissolved in THF (1 mL) under Ar. After 15 min, bis(pinacolato)diboron (70 mg, 0.28 mmol, 1.1 equiv.) was added to the solution and stirred during 10 min. Then, benzylamine (0.25 mmol, 27 µl) and α,β-unsaturated ketone (0.25 mmol) were added at the same time. Finally, MeOH (0.55 mmol, 25 µl, 2.5 equiv.) was added and the reaction mixture was left to stir overnight at RT. The reaction products and conversions were determined by ¹H NMR. The e.e.s were determined directly by HPLC-UV or HPLC-MS for the hydrolysed β-borated ketone.

Screening of chiral ligands for the asymmetric Cu₂O/L catalysed β-boration of α,β-unsaturated imines formed in situ.

Cu₂O (3 mol%, 0.0075 mmol, 1 mg), chiral diphosphine (6 mol%, 0.015 mmol) and THF (1 mL) were transferred into a Radley’s Carousel 12 place reactor under Ar. The mixture was stirred for 15 min at room temperature. Bis(pinacolato)diboron (0.28 mmol, 70 mg, 1.1 equiv.) was added and the solution was stirred for 10 min. Then benzylamine (0.25 mmol, 27 µl, 1 equiv.) and the α,β-unsaturated ketone (0.25 mmol) were added simultaneously, followed by the addition of MeOH (0.55 mmol, 25 µl, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The products obtained were analyzed by ¹H NMR spectroscopy to determine the conversion towards the desired β-boryl imine products. The enantiomeric excess of 3a, 6 and 8, were determined directly by HPLC-UV; otherwise, the enantiomeric excess of the other β-boryl imines 3b, 10, 12, 14, 16 was determined by HPLC-MS from the corresponding β-boryl ketone derivative obtained by hydrolysis.

ReactIR All in situ IR spectroscopy experiments (ReactIR) were carried out on the following instrument: ReactIR 15 with MCT detector; HappGenzel, DiComp (Diamond) probe connected via AgX 9.5 mm – 2 m fiber (Silver Halide); Sampling 2500 to 650 cm⁻¹, 8 wave number resolution. Reaction performed on a 1 mmol scale using the standard protocol.

Conclusion

In conclusion, we have found that Cu₂O guarantees the clean and efficient β-boration of unsaturated imines in the absence of bases. Both the in situ formation of the α,β-unsaturated imine and concurrent β-boration of this intermediate can be readily followed by in situ IR spectroscopy, which shows a clean and rapid pseudo first order reaction, which is slightly faster for a cyclic enone-derived imine compared with the acyclic system. The activation of the diboron reagent, Bpin₂, with Cu₂O does not need external base to form the CuBpin moiety, and indeed, this system behaves similarly to the CuO system once base is added, though the Cu₂O system is more efficient, particularly as revealed by in situ IR. The modification of Cu₂O with commercially available chiral ligands, such as (R)-BINAP, enhances the asymmetric induction on the C-B bond formation, principally when the Bn group is attached to the imine.

Acknowledgements

We thank the EPSRC for a grant to A. D. J. C., MEC for funding (CTQ2010-16226) and C. S. for FP grant. We thank AllyChem and Solvias for the donation of diboron reagents and chiral auxiliaries.

Keywords: α,β-unsaturated imines • β-boration • Cu₂O • ReactIR • β-boryl imines


The activation of the diboron reagent, Bpin₂, with Cu₂O does not need external base to form the CuBpin moiety. We have demonstrated that Cu₂O-Ligand guarantees the \(\alpha,\beta\)-unsaturated imine formation from chalcone-ketone derivatives, aliphatic cyclic and acyclic ketones, but also efficiently \(\beta\)-borate the \(\alpha,\beta\)-unsaturated imine formed with high values of conversion. The modification of Cu₂O with commercially available chiral ligands, such as (R)-BINAP, enhances the asymmetric induction on the C-B bond formation, principally when the Bn group is attached to the imine. The in situ IR spectroscopy shows a clean and rapid pseudo first order reaction for Cu₂O, which is slightly faster for a cyclic enone-derived imine compared with an acyclic substrate.
Supporting information

Base-free $\beta$-boration of $\alpha,\beta$-unsaturated imines catalysed by $\text{Cu}_2\text{O}$ with concurrent enhancement of asymmetric induction

Adam D. J. Calow,[b] Cristina Solé,[a] Andrew Whiting,*[b] Elena Fernández*[^a]

Contents

1. Instrumentation and chemicals.
2. Experimental procedure for copper/(R)-BINAP catalyzed $\beta$–boration of $\alpha,\beta$–unsaturated imines with bis(pinacolato)diboron.
3. Screening of chiral ligands for the asymmetric $\text{Cu}_2\text{O}/\text{L}$ catalysed $\beta$–boration of $\alpha,\beta$–unsaturated imines formed in situ.
5. Analysis of the enantiomeric excess by HPLC.
6. ReactIR
7. References.

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1. Instrumentation and chemicals

All reactions and manipulations were carried out under an argon atmosphere by using Schlenk-typetechniques or Radleys Carousel 12 Reaction. Dry solventswere dried using MBRAUN Solvent Purification System (MB-SPS). Bis(pinacolato)diboron was used as purchased from AllyChem. \((R)-(S)-\text{Mandyphos}, \,(R)-(S)-\text{Taniphos,}\,(R)-\text{Ph-MeOBiphep,}\,(R)-(R)-\text{Walphos and}\,(R)-(S)-\text{Josiphos type ligands}\) were kindly supplied by Solvias. The \((R)-\text{Binap and (R)-Tol-Binap ligands were used as purchased from Strem.}\)

All other materials were purchased directly from standard chemical suppliers and used without further purification, unless stated otherwise.

High performance liquid chromatography (HPLC) was carried out using a Shimadzu Class VP model equipped with an autosampler and UV detector or Hewlett-Packard HP 5989 MS at an ionizing voltage of 70 eV. Chiralpak AD-H column (dimensions 250 × 4.6 mm), Chiralpak IA-H column (dimensions 250 x 4.6 mm) were used to determinate enantiomeric excesses.

Deuterated chloroform (CDCl\textsubscript{3}) was used as solvents for routine NMR measurements. NMR spectra were obtained using a Varian Mercury 400 spectrometer. \(^1\text{H}\) NMR and \(^13\text{C}\) NMR chemical shifts are reported in ppm (\(\delta\)) relative to tetramethylsilane, referenced to the chemical shift of residual solvents resonances. \(^{11}\text{B}\ \{^1\text{H}\}\) NMR chemical shifts are reported in ppm (\(\delta\)) relative to BF\textsubscript{3}·OEt\textsubscript{2} (\(\delta\) \(^{11}\text{B}=0.00\) ppm) as the external reference. Chemical shift values (\(\delta\)) are given in ppm, coupling constants (\(J\)) are given in Hz, and NMR peaks are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m).
2. Experimental procedure for copper/(R)-BINAP catalysed β–boration of α,β–unsaturated imines with bis(pinacolato)diboron.

Copper(I) salts (1.5-3 mol%), (R)-BINAP ligand (3-6 mol%, 0.0075-0.015 mmol, 4.7-9.3 mg), were transferred into a Schlenck tube and dissolved in THF (1 mL) under Ar. After 15 min, bis(pinacolato)diboron (70 mg, 0.28 mmol, 1.1 equiv.) was added to the solution and stirred during 10 min. Then benzylamine (0.25 mmol, 27 µl) and 4-phenyl-3-buten-2-one (1) (0.25 mmol, 36.5 mg) were added at the same time (or the corresponding isolated (E)-1-phenyl-N-(4-phenylbutyl-2-ylidene)methanamine (4a)¹ (0.25 mmol, 59 mg)), followed by the addition of MeOH (0.55 mmol, 25 µl, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The reaction products and conversion to the desired β–boryl imine was determined by ¹H NMR and the enantiomeric excess was determined directly by HPLC-UV.

3. Screening of chiral ligands for the asymmetric Cu₂O/L catalysed β–boration of α,β–unsaturated imines formed in situ.

Cu₂O (3 mol%, 0.0075 mmol, 1 mg), chiral diphosphine (6 mol%, 0.015 mmol) and THF (1 mL) were transferred into a Radley's Carousel 12 place reactor under Ar. The mixture was stirred for 15 min at room temperature. Bis(pinacolato)diboron (0.28 mmol, 70 mg, 1.1 equiv.) was added and the solution was stirred for 10 min. Then benzylamine (0.25 mmol, 27 µl, 1 equiv.) and the α,β–unsaturated ketone (0.25 mmol) were added simultaneously, followed by the addition of MeOH (0.55 mmol, 25 µl, 2.5 equiv.). The reaction mixture was stirred overnight at RT. The products obtained were analyzed by ¹H NMR spectroscopy to determine the conversion towards the desired β–boryl imine products. The enantiomeric excess of 3a, 6 and 8, were determined directly by HPLC-UV, otherwise, the enantiomeric excess of the other β–boryl imines 3b, 10, 12, 14, 16 was determined by HPLC-MS from the corresponding β–boryl ketone derivative obtained by hydrolysis. Purification was carried out by silica gel column chromatography (see below in section 4).

The hydrolysis protocol: To determine enantiomeric excesses of the β–boration products, some of the β–boryl imines obtained in the above procedures were converted into the corresponding β–boryl ketones following the procedure: Distilled water (1 mL) was added to the crude reaction product (cc. 0.25 mmol) in THF (1 mL). The reaction mixture was stirred vigorously for 2 h at RT. Then diluted with dichloromethane and extracted (3 x 2 mL). The combined organic phases were dried over Mg₂SO₄ and concentrated. The β–boryl ketones derived were dissolved in isopropanol solvent and analysed by chiral HPLC-MS to determine the enantiomeric excess.

4.1 Synthesis of (S,E)-1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine (3a)

Using the procedure described in section 3 and (R)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 90%; \(^{1}\)H NMR (\(\text{CDCl}_3,\ 400\ \text{MHz}\)) \(\delta\) 7.37 – 7.26 (m, 4H), 7.24–7.11 (m, 5H), 7.05 (t, \(J = 7.2\) Hz, 1H), 4.86 (d, \(J = 15.2\) Hz, 1H), 4.72 (d, \(J = 15.2\) Hz, 1H), 3.09 (dd, \(J = 19.6, 8\) Hz, 1H), 2.89 (dd, \(J = 19.6, 8\) Hz, 1H), 2.33 (t, \(J = 8\) Hz, 1H), 1.99 (s, 3H), 0.99 (s, 6H), 0.87 (s, 6H); \(^{13}\)C NMR (\(\text{CDCl}_3,\ 100.6\ \text{MHz}\)) \(\delta\) 189.9, 146.7, 135.9, 128.7, 128.1, 127.7, 127.6, 127.4, 123.8, 79.63, 49.5, 26.9, 26.3, 24.6, 19.3. \(^{11}\)B NMR (\(\text{CDCl}_3,\ 128.3\ \text{MHz}\)) \(\delta\) 21.2. MS m/z (ESI+) 364.24 (M+1). The spectroscopic data match those reported previously.

4.2 Synthesis of (S,E)-N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (6)

Using the procedure described in section 3 and (R)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 45%; \(^{1}\)H NMR (400 MHz, \(\text{CDCl}_3\)) \(\delta\) 7.38–7.28 (m, 5H), 7.12 (d, \(J = 8.4\) Hz, 2H), 6.79 (d, \(J = 8.4\) Hz, 2H), 4.86 (d, \(J = 14.8\) Hz, 1H), 4.73 (d, \(J = 14.8\) Hz, 1H), 3.75 (s, 3H), 3.05 (dd, \(J = 19.6, 8.4\) Hz, 1H), 2.27 (t, \(J = 8\) Hz, 1H), 1.99 (s, 3H), 0.99 (s, 6H), 0.90 (s, 6H); \(^{13}\)C NMR (\(\text{CDCl}_3,\ 100.6\ \text{MHz}\)) \(\delta\) 184.53, 156.42, 138.72, 135.97, 129.09, 128.81, 127.66, 127.36, 113.90, 113.09, 79.59, 55.21, 49.45, 46.53, 27.01, 26.34, 24.81, 19.32; \(^{11}\)B NMR (\(\text{CDCl}_3,\ 128.3\ \text{MHz}\)) \(\delta\) 19.21. MS m/z (ESI+) 394.25 (M+1). The spectroscopic data match those reported previously.
4.3 Synthesis of (S,E)-N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (8)

Using the procedure described in section 3 and (R)-BINAP as a ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:1, 10% anhydrous triethylamine); isolated yield 87%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 – 7.27 (m, 5H), 7.15 (d, $J$ = 8.4, 2H), 7.06 (d, $J$ = 8.4, 2H), 4.84 (d, $J$ = 15.2 Hz, 1H), 4.72 (d, $J$ = 15.2 Hz, 1H), 2.99 (dd, $J$ = 20.4, 8 Hz, 1H), 2.79 (dd, $J$ = 20.4, 8 Hz, 1H), 2.29 (t, $J$ = 8 Hz, 1H), 1.99 (s, 3H), 0.97 (s, 6H), 0.87 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 189.84, 145.27, 135.75, 129.52, 129.36, 128.78, 128.58, 127.63, 127.56, 127.43, 79.72, 49.49, 26.97, 26.32, 24.57, 19.29.$^{11}$B NMR (CDCl$_3$, 128.3 MHz) $\delta$ 18.93. MS m/z (ESI+) 398.19 (M+ 1). The spectroscopic data match those reported previously.$^3$

4.4 Synthesis of (S,Z)-1-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexylidene)methanamine (10)

Using the procedure described in section 3 and (R)-BINAP as ligand, the title compound was isolated as an colorless oil by chromatography (dry silica, DCM:hexane v:v =1:3, 10% anhydrous triethylamine); isolated yield 89%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 – 7.20 (m, 5H), 4.59 (m, 2H), 2.35 – 2.17 (m, 4H), 1.72 – 1.51 (m, 2H), 1.69 – 1.49 (m, 2H), 1.45 – 1.29 (m, 1H), 1.24 (s, 12H); $^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$ 189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 54.82, 48.85, 43.70, 26.77, 24.84, 24.69, 17.60; $^{11}$B NMR (CDCl$_3$, 128.3 MHz) $\delta$ 22.15. MS m/z (ESI+) 314.24 (M+ 1).
4.5 Synthesis of (E)-1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine (12)

Using the procedure described in section 3 and (R)-BINAP as a ligand, the title compound was isolated as an pale yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 35%; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.38–7.27 (m, 2H), 7.25–7.19 (m, 2H), 7.18–7.05 (m, 1H), 4.73 (d, $J$ = 15.2 Hz, 1H), 4.58 (d, $J$ = 15.2 Hz, 1H), 2.93 (dd, $J$ = 22.4, 6.8 Hz 1H), 2.47 (t, $J$ = 7.6 Hz, 1H), 2.19 (q, $J$ = 7.6 Hz, 2H), 2.09 (dd, $J$ = 22.4, 3.5 Hz, 1H), 1.25 (d, $J$ = 7.6 Hz, 3H), 1.13(s, 6H), 1.09 (s, 6H), 0.81 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 189.80, 136.76, 128.60, 127.47, 114.20, 78.98, 48.85, 43.70, 26.77, 24.84, 17.60, 9.26. $^{11}$B NMR (CDCl$_3$, 128.3 MHz) $\delta$ 13.83. MS m/z (ESI+) 316.25 (M+1).

4.6 Synthesis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-ylidene)methanamine (14)

Using the procedure described in section 3 and (R)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 63%; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.29–7.23 (m, 4H), 7.18–7.15 (m, 1H), 4.71 (d, $J$ = 15.2 Hz, 1H), 4.60 (d, $J$ = 15.2 Hz, 1H), 2.74 (m, 1H), 2.48 (t, $J$ = 6.6 Hz, 1H), 2.19 (dd, $J$ = 19.7, 3.5 Hz, 1H), 1.84 (s, 3H), 1.52-1.34 (m, 2H), 1.29-1.23 (m, 2H), 1.13 (s, 6H), 1.10 (s, 6H), 0.82 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 189.86, 143.18, 136.25, 128.64, 128.52, 128.36, 128.15, 128.01, 127.54, 127.16, 127.05, 126.78, 79.05, 46.46, 34.43, 27.00, 26.42, 24.83, 22.83, 19.29, 14.36. $^{11}$B NMR (CDCl$_3$, 128.3 MHz) $\delta$ 13.99. MS m/z (ESI+) 329.25 (M+1).
4.7 Synthesis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-ylidene)methanamine (16)

Using the procedure described in section 3 and (R)-BINAP as ligand, the title compound was isolated as an yellow oil by chromatography (dry silica, DCM:hexane v:v =1:2, 10% anhydrous triethylamine); isolated yield 56%. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29-7.25 (m, 4H), 7.18-7.16 (m, 1H), 4.71 (d, $J = 15.2$ Hz, 1H), 4.59 (d, $J = 15.2$ Hz, 1H), 2.74 (dd, $J = 19.7$, 8.0 Hz, 1H), 2.46 (t, $J = 6.6$ Hz, 1H), 2.26 (dd, $J = 19.7$, 3.5 Hz, 1H), 1.81 (s, 3H), 1.63-1.56 (m, 2H), 1.29-1.18 (m, 6H), 1.14 (s, 6H), 1.10 (s, 6H), 0.87 (t, $J = 6.4$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 189.79, 143.25, 136.27, 128.63, 128.50, 128.35, 128.14, 128.01, 127.55, 127.15, 127.03, 126.87, 126.75, 79.03, 46.49, 32.13, 29.66, 27.02, 25.28, 24.73, 22.81, 19.28, 14.18; $^{11}$B NMR (CDCl$_3$, 128.3 MHz) $\delta$ 14.26. MS m/z (ESI+) 357.20 (M+1)
5. Analysis of the enantiomeric excess by HPLC.

5.1 Analysis of (S,E)-1-phenyl-N-(4-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)methanamine (3a)

The enantiomeric excess were obtained by chiral HPLC analysis of 3a using an AD-H column (iPrOH-hexane, 95:5, 1mL/min, UV detection at 254 nm); (S)-isomer $t_r$ = 7.9min and (R)-isomer $t_r$ = 9.1min. Specific rotation of 3a: $[\alpha]_D^{25} + 40.9$ (c 0.95 in CHCl$_3$ for a (S)-enantiomerically enriched sample of 93ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding β-borated ketone compound obtained after hydrolysis of the boronate product: $[\alpha]_D^{25} + 34.6$ (c 1.02 in CHCl$_3$). Value found in the literature$^1$: $[\alpha]_D^{20} - 34.2$ (c 1.06, CHCl$_3$ for a (R)-enantiomerically enriched sample of 96:4 er).

\begin{align*}
\text{Racemic} & & 95\% \text{ ee} \\
\end{align*}
5.2 Analysis of (S or R,E)-N-(4-(4-methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-ylidene)-1-phenylmethanamine (6)

The enantiomeric excess were obtained by chiral HPLC analysis of 6 using an AD-H column (iPrOH-hexane, 97:3, 1mL/min, UV detection at 254 nm); (S)-isomer $t_r$ = 8.3min and (R)-isomer $t_r$ = 8.9min.

Specific rotation of 6: $[\alpha]_D^{25}$ +52.5 (c 1.08 in CHCl$_3$ for a (S)-enantiomerically enriched sample of 86ee%) and $[\alpha]_D^{25}$ -26.6 (c 1.00 in CHCl$_3$ for a (R)-enantiomerically enriched sample of 49ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding β-borated ketone compound obtained after hydrolysis of the boronate product: $[\alpha]_D^{25}$ +36.1 (c 0.70 in CHCl$_3$). Value found in the literature$^1$: $[\alpha]_D^{20}$ -29.1 (c 1.07, CHCl$_3$ for a (R)-enantiomerically enriched sample of 96:4 er).

- **Racemic**
- **86% ee of (S)-isomer**
- **49% ee of (R)-isomer**
5.3 Analysis of (S,E)-N-(4-(4-chlorophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaboralan-2-yl)butan-2-ylidene)-1-phenylmethanamine (8)

The enantiomeric excess were obtained by chiral HPLC analysis of 8 using an AD-H column (iPrOH-hexane, 99:1, 1mL/min, UV detection at 254 nm); (S)-isomer t_r= 8.4min and (R)-isomer t_r= 9.2min. Specific rotation of 8: [α]_D^{25} +18.02 (c 0.88 in CHCl_3) for a (S)-enantiomerically enriched sample of 48ee%) and [α]_D^{25} +30.8 (c 1.5 in CHCl_3 for a (S)-enantiomerically enriched sample of 58ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding β-borated ketone compound obtained after hydrolysis of the boronate product: [α]_D^{25} +27.5 (c 0.80 in CHCl_3). Value found in the literature: [α]_D^{20} -12.0 (c 0.12, CHCl_3 for a (R)-enantiomerically enriched sample of 95:5 er).
5.4 Analysis of (S or R,Z)-1-phenyl-N-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexylidene)methanamine (10)

The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product ((R)-4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-2-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); (S)-isomer $t_r=13.8$min and (R)-isomer $t_r=16.8$min. Specific rotation: $[\alpha]_D^{23} -2.5$ (c 1.07 in CHCl$_3$ for a (S)-enantiomerically enriched sample of 39ee%).

The absolute configuration was assigned by comparison of the optical rotation of the corresponding β-borated ketone compound obtained after hydrolysis of the boronate product: $[\alpha]_D^{25} -4.4$ (c 0.50 in CHCl$_3$). Value found in the literature: $^4 [\alpha]_D^{20} +6.2$ (c 1.29, CHCl$_3$ for a (R)-enantiomerically enriched sample of 83:17 er).
5.5 Analysis of (E)-1-phenyl-N-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-ylidene)methanamine (12)

The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product (5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); the major isomer $t_r = 5.29$ min and the minor isomer $t_r = 5.7$ min. Specific rotation: $[\alpha]_D^{23} +49.7$ (c 1.00 in CHCl$_3$ for a sample of 66ee%) and $[\alpha]_D^{25} +35.7$ (c 0.53 in CHCl$_3$ for a sample of 50ee%).

Racemic

66% ee
88% ee

26% ee (other enantiomer)
5.6 Analysis of (E)-1-phenyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-ylidene)methanamine (14)

The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptan-2-one) using an IA-H column (iPrOH-hexane, 0.5:99.5, 1mL/min, HPLC-MS); the major isomer $t_r = 5.56$ min and the minor isomer $t_r = 6.1$ min. Specific rotation: $[\alpha]_D^{23} +45.5$ (c 1.3 in CHCl$_3$ for a sample of 62ee%) and $[\alpha]_D^{25} +48.4$ (c 1.3 in CHCl$_3$ for a sample of 64ee%).
86% ee

10% ee (other enantiomer)
5.7 Synthesis of \((\text{E})-1\text{-phenyl-}N\text{-}(4\text{-}(4,4,5,5\text{-tetramethyl-}1,3,2\text{-dioxaborolan-2-yl)nonan-2-ylidene})\text{methanamine (16)}\)

The enantiomeric excess were obtained by chiral HPLC analysis of the corresponding hydrolysed product \((4\text{-}(4,4,5,5\text{-tetramethyl-}1,3,2\text{-dioxaborolan-2-yl)nonan-2-one})\) using an AD-H column (iPrOH-hexane, 0.2:99.8, 0.3mL/min, HPLC-MS); the major isomer \(t_r=29.4\text{min}\) and the minor isomer \(t_r=32.4\text{min}\). Specific rotation: \([\alpha]_D^{23}+56.2\) (c 0.53 in CHCl\(_3\) for a sample of 70\% ee\%) and \([\alpha]_D^{23}+52.5\) (c 0.53 in CHCl\(_3\) for a sample of 64\% ee\%).

\textit{Racemic} \hspace{1cm} 71\% ee
92% ee

66% ee (other enantiomer)
6. ReactIR

All in situ IR spectroscopy experiments (ReactIR) were carried out on the following instrument: ReactIR 15 with MCT detector; HappGenzel, DiComp (Diamond) probe connected via AgX 9.5 mm – 2 m fiber (Silver Halide); Sampling 2500 to 650 cm⁻¹, 8 wave number resolution.

Reaction performed on a 1 mmol scale using the standard protocol as outlined in Section 2.

Scheme 1.

a)

\[
\text{Ph} = \text{C} = \text{O} + \text{BnNH}_2 \xrightarrow{\text{Cu}_2\text{O} (3\%), (R')-\text{tol-BINAP} (6\%)} \text{pinB} \underbrace{\text{N}}_{\text{Bn}} \xrightarrow{\text{NaBH}_4, \text{MeOH}} \text{pinB} \underbrace{\text{H}}_{\text{N}} \underbrace{\text{Bn}}
\]

b)

\[
\text{Ph} = \text{C} = \text{O} + \text{BnNH}_2 \xrightarrow{\text{CuCl} (6\%), (R')-\text{tol-BINAP} (6\%)} \text{pinB} \underbrace{\text{N}}_{\text{Bn}} \xrightarrow{\text{MeOH} (2.5 \text{ equiv.}), \text{THF}}
\]

c)

\[
\text{Ph} = \text{C} = \text{O} + \text{BnNH}_2 \xrightarrow{\text{CuCl} (6\%), (R')-\text{tol-BINAP} (6\%)} \text{pinB} \underbrace{\text{N}}_{\text{Bn}} \xrightarrow{\text{MeOH} (2.5 \text{ equiv.}), \text{THF}, \text{NaOtfBu} (10\%) \text{ after 4h}}
\]

d)

\[
\text{Ph} = \text{C} = \text{O} + \text{BnNH}_2 \xrightarrow{\text{Cu}_2\text{O} (3\%), (R')-\text{tol-BINAP} (6\%)} \text{pinB} \underbrace{\text{N}}_{\text{Bn}} \xrightarrow{\text{MeOH} (2.5 \text{ equiv.}), \text{THF}}
\]

Peak overlap is placed between the C=O stretch of the starting enone and the C=N [a) and b]) of the product β-bprated imine. Therefore, alternative bands were trended for the imine product (1532 cm⁻¹).

The images overpage have been unedited.
ReactIR real time plot of Scheme 1a
Showing initial mixing (<1 h), reaction (1-12 h), reduction (>20 h)).

ReactIR real time plot of Scheme 1a – as used in the main paper.
ReactIR graphical output from Scheme 1a
(Spectrum Math = 2\textsuperscript{nd} Derivative, corrects for baseline fluctuations over time).

ReactIR real time plot of Scheme 1b
Showing initial mixing (<1 h), reaction (1-24+ h).
ReactIR graphical output from Scheme 1b
(Spectrum Math = 2\textsuperscript{nd} Derivative, corrects for baseline fluctuations over time).

ReactIR real time plot of Scheme 1c
(Spectrum Math = 2\textsuperscript{nd} Derivative, corrects for baseline fluctuations over time).
**ReactIR real time plot of Scheme 1c – as used in the main paper.**
(Spectrum Math = 2\textsuperscript{nd} Derivative, corrects for baseline fluctuations over time).

**ReactIR real time plot of Scheme 1d**
Showing initial mixing (<0.5 h), reaction (1-6 h).
ReactIR real time plot of Scheme 1d - as used in the main paper.

ReactIR graphical output from Scheme 1d
(Spectrum Math = 2\textsuperscript{nd} Derivative, corrects for baseline fluctuations over time).
7. References


