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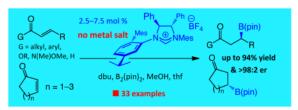
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# Metal-Free Catalytic Enantioselective C–B Bond Formation: (Pinacolato)boron Conjugate Additions to $\alpha,\beta$ -Unsaturated Ketones, Esters, Weinreb Amides and Aldehydes Promoted by Chiral N-Heterocyclic Carbenes

Hao Wu, Suttipol Radomkit, Jeannette M. O'Brien, and Amir H. Hoveyda<sup>\*</sup>
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill,
Massachusetts 02467

# **Abstract**

The first broadly applicable metal-free enantioselective method for boron conjugate addition (BCA) to α,β-unsaturated carbonyls is presented. The C–B bond forming reactions are promoted in the presence of 2.5–7.5 mol % of a readily accessible C<sub>1</sub>-symmetric chiral imidazolinium salt, which is converted, in situ, to the catalytically active diastereo- and enantiomerically pure Nheterocyclic carbene (NHC) by the common organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu). In addition to the commercially available bis(pinacolato)diboron  $[B_2(pin)_2]$ , and in contrast to reactions with the less sterically demanding achiral NHCs, the presence of MeOH is required for high efficiency. Acyclic and cyclic α,β-unsaturated ketones, as well as acyclic esters, Weinreb amides and aldehydes can serve as suitable substrates; the desired  $\beta$ -boryl carbonyls are isolated in up to 94% yield and >98:2 enantiomer ratio (er). Transformations are often carried out at ambient temperature. In certain cases, such as when the relatively less reactive unsaturated amides are used, elevated temperatures are required (50–66 °C); nonetheless, reactions remain highly enantioselective. The utility of the NHC-catalyzed method is demonstrated through comparison with the alternative Cu-catalyzed protocols; in cases involving a polyfunctional substrate, unique profiles in chemoselectivity are exhibited by the metal-free approach (e.g., conjugate addition vs reaction with an alkyne, allene or aldehyde).



### 1. Introduction

We recently reported the discovery of the first metal-free catalytic protocol for the formation of C–B bonds. We demonstrated that N-heterocyclic carbenes (NHCs), a class of organic molecules commonly used to catalyze C–C bond formation, promote reactions between bis(pinacolato)diboron [B<sub>2</sub>(pin)<sub>2</sub>; 1] and an assortment of cyclic and acyclic  $\alpha$ ,  $\beta$ -unsaturated ketones and esters. Such processes deliver  $\beta$ -boryl carbonyls, which are versatile

amir.hoveyda@bc.edu.

intermediates in chemical synthesis.<sup>3,4</sup> The NHC-catalyzed (pinacolato)boron conjugate addition (BCA) reactions were shown to be mechanistically distinct, allowing them to be complementary to the more extensively examined Cu-catalyzed variants<sup>5</sup> (e.g., distinct chemoselectivity profiles, see below). A subsequent study focused on the use of chiral phosphines to promote enantioselective BCA.<sup>6</sup> Additions to a limited number of acyclic esters and ketones were performed at 70 °C, affording products in 76:24–97.5:2.5 enantiomer ratio (er); reaction with cyclohexenone was shown to proceed to 62% conversion (16 h, 70 °C), generating the cyclic  $\beta$ -boryl ketone in 68:32 er. In our initial disclosure, <sup>1a</sup> we proposed that the metal-free reactions are initiated by formation of an NHC•B<sub>2</sub>(pin)<sub>2</sub> complex, wherein the B–B bond is activated due to association of the Lewis basic heterocycle; <sup>7</sup> support for the aforementioned hypothesis and the associated structural changes has more recently been provided through X-ray crystallography.<sup>8</sup>

Herein, we report the enantioselective version of the NHC-catalyzed BCA process. From the outset, our goal was to develop an efficient catalytic C–B bond forming process that is applicable to a wide substrate range. Accordingly, as illustrated in Scheme 1, the method described can be performed with acyclic  $\alpha$ , $\beta$ -unsaturated ketones, esters, Weinreb amides or aldehydes; in some cases, NHC-catalyzed variants have not been previously reported (including with achiral catalysts; e.g., additions to amides and enals). We show that metal-free catalytic BCA may be performed with cyclic enones of different ring sizes. Conjugate additions proceed in the presence of 2.5–7.5 mol % of a readily accessible  $C_1$ -symmetric chiral imidazolinium salt, a common organic base and commercially available  $B_2(pin)_2$  (1), delivering a wide range of products in up to 94% yield and >98:2 er. The NHC-catalyzed BCA reactions furnish chemoselectivity profiles that are unavailable through the use of alternative Cu-catalyzed variants, and thus represent a valuable addition to the arsenal of transformations that generate organoborons in high enantiomeric purity.

# 2. Results and Discussion

# 2.1. Identification of optimal conditions and catalysts

We began by probing the ability of the NHC derived from chiral imidazolinium salt 3a to effect reactions of unsaturated carbonyls with  $B_2(pin)_2$  (1). The basis for such a starting point was the finding that the latter heterocyclic carbene is effective in promoting the corresponding enantioselective silyl conjugate additions with (dimethylphenylsilyl)boronic acid pinacol ester. 9 Under conditions that result in efficient transformations when achiral NHCs are utilized, <sup>1a</sup> as illustrated in entry 1 of Table 1, there is hardly any product generated in the presence of **3a** and NaO*t*-Bu after 14 hours at ambient temperature. Inefficient BCA is not due to the inability of the relatively more sterically congested chiral NHC (vs the smaller achiral variants) to associate with 1;<sup>10</sup> as with the previously illustrated cases involving achiral heterocyclic carbenes, 1,8,9 spectroscopic studies point to rapid (within 15 min) generation of NHC•1 complexes. Ongoing studies aimed at elucidating the exact nature of the catalytically active species indicate that in reactions promoted by chiral NHCs, formation of a less sterically demanding complex (i in Figure 1), generated by the exchange of a pinacolato unit with a common alcohol, can facilitate catalysis through the pathway originally proposed in 2009. <sup>1a,11</sup> Accordingly, we chose to probe the effect of MeOH as an additive.

With 20 equivalents of the alcohol present (entry 2, Table 1), there is indeed 24% conversion to the desired β-boryl ketone **4a**, which is generated in 86.5:13.5 er. Use of the more robust and user-friendly organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu; vs NaOt-Bu) leads to similar reactivity and enantioselectivity (31% conv, 90:10 er; entry 3). There is enhancement in BCA efficiency when the amount of dbu is increased to 20 mol % (47% conv, 92:8 er; entry 4). The positive influence of the larger concentration of dbu could

arise from a more efficient generation of chiral NHC and/or it might be because exchange of pinacol with MeOH is base-catalyzed (cf. formation of **i** in Figure 1). Such issues are the subjects of continuing investigations designed to clarify these and other mechanistic intricacies of the metal-free process. It is nonetheless worthy of note that, in contrast to the formerly reported NHC-catalyzed silyl conjugate additions, water cannot be utilized as the additive (vs MeOH), and only a complex mixture of products is generated under such conditions (data not shown).

We thus took advantage of the facility with which chiral imidazolinium salts can be structurally modified, 12 and began search for a chiral NHC that can furnish higher conversion and promote the C-B bond forming reaction enantioselectively. Since studies aimed at elucidating the identity of the active chiral catalyst, required for outlining an appropriate stereochemical model, remain in progress, we turned to the systematic screening of  $C_2$ - and  $C_1$ -symmetric imidazolinium salts. Representative findings, depicted in Table 2, demonstrate that alteration of the structure of the chiral NHC has a notable influence on the reaction outcome. Comparison of the activity of 3b and 3c-d demonstrates that similar conversion and er values can be obtained with  $C_2$ -and  $C_1$ -symmetric carbenes, with the catalyst bearing two phenyl heterocyclic substituents affording somewhat higher er values (3c vs 3d, entries 2–3, Table 2). Overall, the NHC derived from  $C_1$ -symmetric 3h, bearing a sizeable mesityl at its dissymmetric N-Ar moiety furnishes the highest reactivity and enantioselectivity (Table 2, entry 7; 81% conv, 95:5 er). Catalytic BCA with 3f (entry 5), an imidazoliumum salt that carries a smaller phenyl unit at the same site, is less discriminating (76:24 vs 95:5 er). Subsequent optimization studies led us to establish that the presence of 60 equivalents of MeOH results in optimal reactivity and selectivity (>98% conv and 95:5 er); such a requirement points to the possible significance of the requisite ligand exchange mentioned above (pinacol with MeOH; cf. i, Figure 1).

An additional attribute of  $C_1$ -symmetric catalysts merits mention. Although it is possible that the  $C_2$ -symmetric chiral variants of certain highly hindered imidazolinium salts such as  $\bf 3h$  could give rise to improved enantioselectivity, synthesis of such sterically encumbered heterocycles is typically inefficient; this shortcoming is largely due to minimal yields obtained for the formation of the C-N bond required for installment of the second hindered N-Ar moiety. The more readily accessible  $C_1$ -symmetric NHCs that contain a single sterically demanding dissymmetric aryl unit, can be more easily synthesized and thus offer an attractive option.

# 2.2. NHC-Catalyzed Enantioselective BCA

### 2.2.1 Reactions with aryl- and alkyl-substituted acyclic α,β-unsaturated

**ketones**—Under the optimal conditions, the NHC derived from **3a**, optimal for catalytic silyl conjugate additions, promotes BCA to enone **2a** (cf. Table 1), affording **4a** in 82% yield and 92:8 er (entry 1, Table 3). However, when **3h** serves as the catalyst precursor (Table 3, entry 2), the reaction is more facile (>98% conv and 92% yield vs 87% conv and 82% yield), and the desired product is obtained with higher enantiomeric purity (96:4 vs 92:8 er). <sup>13</sup> As the additional data in Table 3 illustrate, an array of acyclic α.β-unsaturated ketones can be used as substrates. Enantioselective formation of **4b** (Table 3, entry 3), in spite of the presence of a sterically demanding *o*-tolyl substituent is worthy of note. Synthesis of enantiomerically enriched **4b** (entry 3), however, necessitates that the BCA is performed at 50 °C; ~15% conversion is observed when the NHC-catalyzed reaction is carried out at 22 °C. The findings in Table 3 indicate that, in general, electron-rich enones are superior substrates; indeed, as illustrated in entry 4 (Table 3), enantioselective addition to **2c** can be performed with 2.5 mol % **3h** and 10 mol % dbu under otherwise identical conditions with little or no loss of efficiency (90% conv, 80% yield, 94:6 er).

Catalytic BCA with bromophenyl-substituted ketone **2d** (entry 5, Table 3) affords **4d** in 43% yield (60% conv, 92:8 er). As the findings in Scheme 2 indicate, the relative inefficiency corresponds to a variety of halogen-substituted substrates. Thus, reaction of *p*-fluorosubstituted **2k**, under the conditions employed for the transformations in Table 2, although exceedingly enantioselective (98:2 er), results in only 27% conversion after 14 hours; NHC-catalyzed BCA of chloro-substituted **2l** is similarly inefficient. Our attempts to address the above complications led to the finding that increasing the amount of the organic base (dbu) from 20 mol % to one equivalent leads to substantial improvements in efficiency with similar or higher enantioselectivity (Scheme 2). Such an advance was made based on the assumption that a more efficient generation of the NHC catalyst or the aforementioned methanol/pinacol exchange (cf. **i**, Figure 1) might demand larger amounts of base, thus allowing the enantioselective pathway to become more competitive. <sup>15,16</sup>

The transformations in entries 7–8 show that alkyl-substituted  $\alpha$ ,  $\beta$ -unsaturated ketones, including those that bear a relatively hindered moiety (e.g., i-Pr in 2g) are suitable BCA substrates. Enones with an n-alkyl, an i-propyl or an aryl substituent at the carbonyl carbon can be efficiently converted to the  $\beta$ -boryl ketones through the NHC-catalyzed transformation (Table 3, entries 9–11). Some of the more sterically demanding electrophiles require 7.5 mol % 3h (Table 3, entry 10; 68% conv, 66% yield, 90:10 er with 5 mol %) or somewhat longer reaction times (entry 11). It should be pointed out that the positive influence of stoichiometric quantities of dbu is not limited to the catalytic transformations depicted in Scheme 2. As illustrated through improved yields obtained for BCA processes that give rise to the formation of furyl-substituted  $\beta$ -boryl methyl ketone 4e and phenyl-substituted phenylketone 4f, the same strategy can be applied to other types of substrates as well.

with 20 mol % dbu: 75% conv, 73% yield, 92:8 er with 100 mol % dbu:

with 20 mol % dbu: 82% conv, 72% yield, 93.5:6.5 er with 100 mol % dbu: >98% conv, 80% yield, 93.5:6.5 er

#### 2.2.2 Reactions with aryl- and alkyl-substituted acyclic α,β-unsaturated esters

—α,β-Unsaturated esters can be used in NHC-catalyzed BCA (Table 4); the desired products are generated in 62–87% yield and 94:6–98:2 er. In certain cases, such as those involving an electron-deficient aryl substituent (entry 2) and the sizeable *t*-butyl-ester (entry 3), additions require elevated temperatures (43% conv and 96.5:3.5 er and 57% conv and 98:2 er respectively, at 22 °C). In spite of the more forcing conditions in entries 2–3 (Table 4), enantioselectivities remain high (94:6–98:2 er).<sup>17</sup>

# 2.2.3 Reactions with aryl- and alkyl-substituted acyclic $\alpha,\beta$ -unsaturated

**amides**— $\alpha$ , $\beta$ -Unsaturated amides and aldehydes are two substrate classes that have received relatively scant attention in connection with catalytic enantioselective BCA. There are no reported examples of reactions with the aforementioned substrate types under any metal-free catalytic conditions. Accordingly, we set out to investigate their respective NHC-catalyzed BCA processes.

We first examined the transformations involving the versatile Weinreb amides, for which only one example of Cu-catalyzed enantioselective BCA has thus far been reported. As the data in Table 5 indicate, reactions with amides require relatively higher catalyst loadings (7.5 mol %), elevated temperatures (50–66 °C) and longer reaction times (up to 36 h); nonetheless, aryl- and alkyl-substituted  $\beta$ -boryl amides are obtained in 60–92% yield after

purification and high enantioselectivities are observed in most cases (86.5:13.5–95:5 er). It is noteworthy that sterically demanding substrates **7e** and **7f** (Table 5, entries 5–6) are converted to the desired products in 60–73% yield and 95:5 er. In the case of electron-deficient amide **7b** (Table 5, entry 2), shorter reaction times and reduced amounts of MeOH are preferred (30 vs 60 equiv), since the undesired proto-deboration <sup>14</sup> (cf. **6b**, entry 2, Table 4) as well as formation of the corresponding  $\beta$ -boryl methyl ester is otherwise significantly more competitive <sup>19</sup> (~70% byproduct formation with 60 equiv MeOH). Control experiments indicate that it is the  $\beta$ -boryl Weinreb amide that is subsequently converted to the ester (vs generation of the unsaturated ester directly from the unsaturated amide followed by BCA); the resident Lewis acidic  $\beta$ -boron likely activates the amide group towards reaction with MeOH.<sup>20</sup>

#### 2.2.4 Reactions with alkyl-substituted $\alpha,\beta$ -unsaturated aldehydes— $\alpha,\beta$ -

Unsaturated aldehydes are another set of substrates that have been less extensively examined in the context of Cu-catalyzed BCA. Part of the complication with NHC-Cu-catalyzed BCA reactions involving aldehydes is that the corresponding 1,2-addition to the carbonyl group can be efficient.<sup>21</sup> In one study, synthesis and isolation of an (achiral) NHC-Cu-OMe complex proved necessary, since the presence of base had to be avoided if efficient generation of  $\beta$ -boryl aldehydes were to be achieved. <sup>22</sup> In another example, an NHC–Cucatalyzed BCA of cinnamaldehyde is shown to afford the desired product in 70:30 er (86% conv; yield of isolated product was not reported).<sup>23</sup> Finally, a protocol for Cu-catalyzed enantioselective BCA to enals was reported most recently; transformations proceed through in situ-generated chiral  $\alpha,\beta$ -unsaturated iminiums formed from reaction with an enantiomerically pure amine (20 mol %).<sup>24</sup> Although high efficiency and enantioselectivities can be achieved through the latter method, and reactions can be carried out with aryl- as well as alkyl-substituted enals may, use of air- and moisture-sensitive Cu(OTf)<sub>2</sub> and 10 mol % of a Brønsted acid (o-FC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H) are required. Furthermore, the β-boryl aldehydes obtained were not isolated, but were directly functionalized (e.g., Wittig olefin synthesis).

The NHC derived from imidazolinium salt **3h** promotes enantioselective BCA to alkyl-substituted enals, as indicated by the examples shown in Table 6. As illustrated in entry 1, when  $C_2$ -symmetric **3a** is used in the reaction, under otherwise identical conditions, **10a** is obtained in 81% yield (>98% conv) and 84:16 er; catalytic BCA with **3h** delivers **10a** in 72% yield and the desired product is generated in significantly higher enantioselectivity (95:5 vs 84:16 er; entry 2, Table 6). Thus, reactions generally proceed to 95% conversion, are often performed at 22 °C, and afford the desired  $\beta$ -boryl aldehydes in 63–72% yield after isolation and purification and in 91:9–95:5 er.

Attempts to carry out catalytic conjugate addition with aryl-substituted variants resulted in the formation of a complex product mixture. Alternative pathways that might render transformations of aryl-substituted enals inefficient are addition of the NHC to an enal, which can lead to substrate homocoupling or generation of the derived saturated ester, <sup>25</sup> reaction with a  $\beta$ -boryl aldehyde product, or methoxide conjugate addition26 (a minor byproduct generated in the reaction shown in entry 2 of Table 6).

**2.2.5 Reactions with cyclic**  $\alpha$ ,  $\beta$ -unsaturated carbonyls—The final class of substrates examined involved cyclic enones.  $^{5c-d}$  As already mentioned, only one case of a phosphine-catalyzed BCA has been reported (cyclohexenone, 68:32 er). Preliminary studies indicated that NHCs derived from **3a** and **3h** promote additions to cyclopentenone efficiently (93% conv, 79% yield and >98% conv, 95% yield, respectively), but with diminished enantioselectivity; for example,  $\beta$ -boryl cyclopentanone **12** (Scheme 3) is obtained in 67:33 and 78.5:21.5 er with **3a** and **3h**, respectively. The relatively low

stereoselectivity is consistent with the fact that BCA to Z-2a delivers 4a in 55:45 er with 3h serving as the NHC precursor (vs 96:4 for the E isomer; see entry 2, Table 3). <sup>27</sup> Catalyst screening led us to establish that use of imidazolinium salt 3i (Scheme 3) promotes the BCA with similar efficiency (90% conv, 80% yield) but with improved enantioselectivity (92:8 er). Several additional examples, involving enones of different ring sizes are provided in Scheme 3. <sup>28</sup> Enantioselectivities are lower than those obtained with acyclic enones; future studies, supported by a better appreciation of the mechanistic nuances of the catalytic cycle, will be aimed at identification of catalysts that furnish higher er. Nevertheless, efficient formation of 13, involving the reaction of sterically congested cyclopentenone, is particularly noteworthy, since a previous report involving the use of chiral Cu–phosphine catalysts indicates <2% conversion with a similarly substituted cyclohexenone. <sup>5c</sup> Additions to lactones are hampered by adventitious cleavage of the heterocyclic ring (MeOH/dbu) and formation of various byproducts. Nonetheless, as the example regarding the conversion of 5e to 16 indicates (Scheme 3), such cyclic  $\beta$ -boryl esters can be readily accessed by means of BCA of the acyclic unsaturated ester, followed by an efficient cyclization.

# 2.3. Comparison with Cu-Catalyzed Variants. Complementarity in Chemical Synthesis

An impetus for performing the present studies was to develop a catalytic protocol that offers distinct advantages to the more established Cu-catalyzed versions. <sup>1a,5</sup> Such an expectation has been based on the principle that, since metal-free BCA reactions proceed through an entirely different pathway compared to the processes promoted by organocopper complexes, they can deliver certain complementarities that would otherwise remain unavailable. Certain distinctions, above all in connection with reactions of enals, have been already mentioned. Additional revealing examples, underlining some of the distinct attributes of the NHC-catalyzed processes are illustrated in Scheme 4. The chiral catalyst used as representative of Cu-based approaches was introduced in previous studies (with *S,R*-Josiphos as the chiral ligand). <sup>5a-b,f</sup>

Whereas NHC-catalyzed BCA to alkyne-substituted enone 17 proceeds with complete chemoselectivity to afford 18 in 95% yield and 94:6 er (Scheme 4a), under Cu-catalyzed conditions, 10% of  $\beta$ -vinylboron product (19),29 derived from Cu-B addition addition/ protonation of the alkyne, is observed as well. A more notable dissimilarity manifests itself in the context of reactions with alkyne-substituted enal 20 (Scheme 4b). In contrast to the NHC-catalyzed reaction, which affords  $\beta$ -boryl aldehyde 21 in 71% yield, when Josiphos— Cu complex is employed, the desired product is isolated in 50% yield; the diminished efficiency is likely the result of competitive 1,2-addition. <sup>1a</sup> The greater degree of chemoselectivity that is feasible through NHC-catalyzed BCA is further illustrated by the reaction of unsaturated ketone 2a in the presence of one equivalent of benzaldehyde (Scheme 4c). Although the efficiency of the NHC-catalyzed process is somewhat diminished, probably as a result of reversible NHC addition to the aldehyde<sup>30</sup> resulting in partial sequestration of the catalytically active heterocycle, the negative impact on the Cucatalyzed reaction is significantly more severe (32% conv and 16% yield vs 65% conv and 56% yield under NHC-catalyzed conditions). 31,32 As further illustrated in Scheme 4d, the presence of phenol (1.0 equiv) leads to a more significant rate reduction in the BCA promoted by the Cu-based catalyst (70% conv and 55% yield vs 98% conv and 88% yield with the NHC-catalyzed process); due to reduced Lewis basicity of the oxygen atom (vs an alkoxide), the intermediate Cu-OPh is likely more reluctant to undergo reaction with B<sub>2</sub>(pin)<sub>2</sub> to regenerate the active Cu–B(pin) complex. Finally, whereas Cu-catalyzed processes involving an allene<sup>33</sup> appear to be significantly more favored (Scheme 4e), leading to complete consumption of the available  $B_2(pin)_2$  and the formation of byproducts, the NHC-catalyzed BCA proceeds readily to afford the desired 4a in 74% yield (vs <5% yield).<sup>34</sup> It should be mentioned that, in certain aspects, the state-of-the-art in Cu-catalyzed

BCA is superior. The latter class of metal-catalyzed reactions typically require lower catalyst loading and shorter reaction times and the corresponding additions to cyclic enones are generally more enantioselective. Nonetheless, the examples provided in Scheme 4 clearly indicate that the availability of the NHC-catalyzed enantioselective BCA can serve as a set of transformations that provide a useful complement to the highly effective metal-catalyzed variants.

#### 3. Conclusions

The present account puts forth the first general metal-free protocol that can be used for enantioselective synthesis of a variety of  $\beta$ -boryl carbonyls. These studies emphasize the substantially higher activity of NHCs as BCA catalysts (vs phosphines<sup>6</sup>), as indicated in the initial disclosure. <sup>1a</sup> A significantly wider range of substrates participate in the C–B bond forming reactions, including those that contain sterically demanding substituents (e.g., **2g** in Table 3, 7f in Table 5, 9d in Table 6, 13 in Scheme 3). Conjugate additions are more facile (e.g., elevated temperatures are not needed for acyclic enones<sup>35</sup>) and generally proceed with superior enantioselectivity with a chiral NHC serving as the catalyst than when phospines are utilized. <sup>6</sup>

The metal-free catalytic method possesses attributes that are complementary to the Cucatalyzed alternatives: <sup>5</sup> in a polyfunctional molecule, highly chemoselective boron addition is more likely under the Cu-free conditions. In certain cases, such as reactions with alkyl-substituted enals (cf. Table 6) or sterically hindered cyclic enones (cf. Scheme 3), the NHC-catalyzed protocol offers a milder, more efficient and/or selective alternative to the Cu-catalyzed approach.

A critical finding disclosed in this report relates to the central role of methanol, as otherwise there is minimal transformation when sterically hindered chiral NHC are used (vs the originally disclosed achiral variants <sup>1a</sup>). Studies to shed light on various mechanistic aspects of the enantioselective metal-free process will be assisted by such findings, as well as by the variations in the levels and profiles in reactivity and selectivity observed during the screening of a wide range of chiral NHCs. Thus, a mechanistic scenario must provide a rationale as to why the aforementioned conditions are required for achieving efficient and highly enantioselective BCA reactions; it must also account for the dependence of the levels of reactivity and enantioselectivity on specific steric and electronic attributes of the chiral NHC catalysts.

Details of ongoing mechanistic investigations regarding NHC-catalyzed BCA will be reported in due course. The design and development of other NHC-catalyzed processes and applications to total synthesis of complex molecules are additional goals of future investigations.

# **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

# **Acknowledgments**

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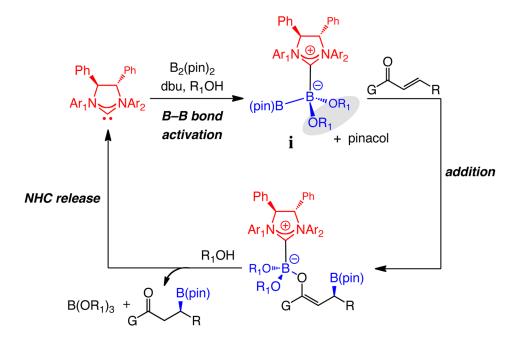
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- 10. For example, treatment of imidazolinium salt **3h** (see Table 2) with  $B_2(pin)_2$  at 22 °C leads to the clean formation of a new complex (11B NMR:  $\delta$  33.57 ppm and  $\delta$  12.20 ppm vs  $\delta$  30.10 ppm for **1** in  $d_8$ -thf at 22 °C). See the Supporting Information for details.
- 11. Details of the pathways that lead to the proposed NHC•diboron complex **i** and the role of such an intermediate in the context of a catalytic cycle and the reasons for its higher reactivity will be the subject of a detailed upcoming disclosure.
- 12. For a study that highlights the significance of easily modifiable  $C_1$ -symmetric chiral N-heterocyclic carbenes in enantioselective synthesis, see: Lee, K-s; Hoveyda, AH. J Org Chem. 2009; 75:4455–4462. [PubMed: 19445467] For application of such entities in other catalytic enantioselective processes, see: (b) Ref 5e. (c) Ref 9.
- 13. Although  $C_2$ -symmetric imidazolinium salt **3a** typically gives rise to less efficient and enantioselective (pinacolato)boron conjugate addition than the  $C_1$ -symmetric **3h**, it can be prepared by a shorter synthesis route (three vs five steps in 25–40% yield). See the Supporting Information for details.
- 14. Proto-deboration of the β-boryl ketone products can occur when the substrates carry an aryl group with a relatively strong electron withdrawing substituent. As an example, formation of p-bromophenyl-substituted **4d** is accompanied with ~10% of the saturated β-aryl ketone (Table 3, entry 5). Indeed, re-subjection of pure β-boryl ketone **4d** to the reaction conditions (22 °C, 14 h) leads to >98% conversion to the saturated ketone. It is plausible that protonation of the C–B bond occurs via the borate derived from addition of MeOH, followed by intramolecular protonation of the C–B bond. Thus, the more electrophilic boron atoms of a (pinacolato)boron unit adjacent to an electron-withdrawing aryl substituent, where polarization inherent in the protonation process might be better stabilized, are expected to be more prone towards participating in this undesired reaction pathway. In support of the significance of an electron-withdrawing unit to the degree of proto-deboration, BCA leading to the formation of p-fluoroaryl **4k** is typically accompanied with <2% of the saturated ketone (stronger hyperconjugative electron donation by F vs Br). Finally, it is

- also possible that a small amount (corresponding to the catalyst loading) of proto-deboration is caused by the tetrafluoroboron counter-ion of the imidazolinium salt. See: Nave S, Sonawane RP, Elford TG, Aggarwal VK. J Am Chem Soc. 2010; 132:17096–17098.Lennox AJJ, Lloyd-Jones GC. J Am Chem Soc. 2012 doi:10/1021/ja300236k.
- 15. Use of excess dbu, while substantially improving the yield of isolated β-boryl ketones, in some cases increases the amount of proto-deboration product as well (e.g., 4% vs 28% and 10 vs 21% protodeboration for **4l** and **4d** with 20 mol % and 100 mol % dbu, respectively). The latter observation is congruent with the aforementioned proposal regarding the role of MeOH in causing the protonation of the C–B bond, since borate formation is expected to be more facile under more basic conditions.
- 16. Performing the reactions shown in Scheme 2 with 20 mol % dbu but at 50 °C (vs 22 °C) also leads to a more rapid rate of substrate consumption. The product mixture, however, contains larger amounts of the proto-deboration product. For example, under such conditions, **4d** is obtained in 40% yield and 89:11 er along with ~60% of the saturated ketone.
- 17. Unlike acyclic enones, when 100 mol % dbu is used with reactions of α,β-unsaturated esters, somewhat lower conversion levels are observed. For instance, in the reaction to generate **6b**, there is 87% conversion to the desired product along with 27% of the saturated carboxylic ester (vs >98% conv and a similar degree of proto-deboration).
- 18. Hirsch-Weil D, Abboud KA, Hong S. Chem Commun. 2010; 46:7525–7527. For one example of catalytic enantioselective (pinacolato) boron conjugate addition to an α,β-unsaturated N,N-dimethylamide, see: (b) Ref 4a.
- 19. As with the unsaturated esters, when 100 mol % dbu is used, the desired  $\beta$ -boryl amides are formed with less efficiency (larger degree of ester formation and similar amounts of protodeboration).
- 20. For examples of chelation between a carbonyl group and a β-boron, influencing the course of a catalytic process, see: Sandrock DL, Jean-Gerard L, Chen CY, Dreher SD, Molander GA. J Am Chem Soc. 2010; 132:17108–17110.Ohmura T, Awano T, Suginome M. J Am Chem Soc. 2010; 132:13191–13193. [PubMed: 20822146] (c) Ref 5j.
- 21. Laitar DS, Tsui EY, Sadighi JP. J Am Chem Soc. 2006; 128:11036-11037. [PubMed: 16925416]
- 22. Bonet A, Lillo V, Ramírez J, Mar Diaz-Requejo M, Fernández E. Org Biomol Chem. 2009; 7:1533–1535. [PubMed: 19343238]
- Lillo V, Prieto A, Bonet A, Mar Díaz-Requejo M, Ramírez J, Pérez PJ, Fernández E. Organometallics. 2009; 28:659–662.
- 24. Ibrahem I, Breistein P, Córdova A. Angew Chem, Int Ed. 2011; 50:12036-12041.
- 25. For examples of NHC-catalyzed homocoupling reaction, see: Burstein C, Glorius F. Angew Chem, Int Ed. 2004; 43:6205–6208.Sohn SS, Rosen EL, Bode JW. J Am Chem Soc. 2004; 126:14370–14371. [PubMed: 15521753] For NHC-catalyzed conversion of unsaturated aldehydes to the saturated ester derivatives, see: Chan A, Scheidt KA. Org Lett. 2005; 7:905–908. [PubMed: 15727471] For examples of both types of processes, see: Sohn SS, Bode JW. Org Lett. 2005; 7:3873–3876. [PubMed: 16119920]
- 26. For a recent study regarding NHC-catalyzed conjugate addition of alcohols to α.β-unsaturated ketones, see: Phillips EM, Riedrich M, Scheidt KA. J Am Chem Soc. 2010; 132:13179–13181. [PubMed: 20809579]
- 27. In addition, control experiments, with chiral NHC excluded, indicate that BCA of the relatively more strained cyclic enones is promoted more readily by dbu (e.g., ~25% conv with cyclopentenone under the conditions used to synthesize 12 in Scheme 3). In contrast, there is 10% conversion under the same conditions with the acyclic substrates.
- 28. The absolute sense of enantioselectivity in NHC-catalyzed silyl conjugate additions (ref 9) is opposite to those illustrated in Scheme 3. The basis for this reversal of selectivity will be addressed in the upcoming account regarding the mechanism of these classes of transformations.
- 29. For catalytic hydroborations of alkynes, which involve Cu–B additions, see: Takahashi K, Ishiyama T, Miayura N. J Organomet Chem. 2001; 625:47–52.Lee JE, Kwon J, Yun J. Chem Commun. 2008; 44:733–734.Kim HR, Jung IG, Yoo K, Jang K, Lee ES, Yun J, Son SU. Chem Commun. 2010; 46:758–760.Kim HR, Yun J. Chem Commun. 2011; 47:2943–2945.Jang H,

- Zhugralin AR, Lee Y, Hoveyda AH. J Am Chem Soc. 2011; 133:7859–7871. [PubMed: 21526827]
- 30. DiRocco DA, Oberg KM, Rovis T. J Am Chem Soc. 2012; 134:6143-6145. [PubMed: 22455368]
- 31. With 5.0 mol % catalyst loading (1.1 equiv  $B_2(pin)_2$ , 60 equiv MeOH, 22 °C, 14 h), the NHC-catalyzed reaction affords the desired  $\beta$ -boryl ketone product in 48% yield (54% conv) and in 95:5 er. The Josiphos–Cu-catalyzed BCA, under the same conditions, proceeds to 22% conversion to afford **4a** in 15% yield and 85:15 er.
- 32. Treatment of benzaldehyde to the BCA conditions (with 5.0 mol % **3h** without an  $\alpha$ , $\beta$ -unsaturated carbonyl in otherwise identical conditions as described for reaction is Table 3) leads to <5% conversion.
- 33. For Cu-catalyzed hydroborations of allenes, see: Jung B, Hoveyda AH. J Am Chem Soc. 2012; 134:1490–1493. [PubMed: 22214185]
- 34. With 5.0 mol % catalyst loading (1.1 equiv  $B_2(pin)_2$ , 60 equiv MeOH, 22 °C, 14 h), the NHC-catalyzed reaction affords the desired  $\beta$ -boryl ketone product in 44% yield (52% conv) and in 95:5 er. The Josiphos–Cu-catalyzed BCA, under the same conditions, proceeds to >98% conversion to afford **4a** in 15% yield and 85:15 er.
- 35. In one case involving a sterically demanding *o*-tolyl-substituted substrate (enone **2b** in entry 3, Table 3), NHC-catalyzed BCA is performed at 50 °C for optimal results. However, with 100 mol % dbu (vs 20 mol % used in the reaction in Table 3), this transformation can be performed at ambient temperature to afford **4b** in 93% yield (>98% conv) and 88:12 er.



**Figure 1.** Catalytic cycle proposed for NHC-catalyzed BCA; exchanging a B(pin) with smaller alkoxides could lead to a faster rate of reaction.

G = alkyl, aryl, alkoxy, amino or H

$$R = alkyl \text{ or } H$$
 $R = alkyl \text{ or } H$ 
 $R = alkyl \text{ or } A$ 
 $R = al$ 

enantioselectivity?

Scheme 1. NHC-Catalyzed Enantioselective BCA to Unsaturated Carbonyls

with 20 mol % dbu: 27% conv, 18% yield, 98:2 er with 100 mol % dbu: >98% conv, 91% yield, >98:2 er

with 20 mol % dbu: 34% conv, 19% yield, 91:9 er with 100 mol % dbu: >98% conv, 65% yield, 95:5 er

with 20 mol % dbu: 60% conv, 43% yield, 92:8 er with 100 mol % dbu: 90% conv, 62% yield, 93:7 er

Scheme 2. Influence of Amine Base on BCA Efficiency

Scheme 3. NHC-Catalyzed Enantioselective BCA to Cyclic Enones

# Scheme 4. Functional Group Tolerance: Differences Between NHC- and Cu-Catalyzed $\mathsf{Protocols}^a$

"NHC-catalyzed conditions: Reactions (a), (b), and (d): 5.0 mol % **3h**, 20 mol % dbu, 1.1 equiv  $B_2(pin)_2$ , thf, 60 equiv MeOH, 22 °C, 14 h; reactions (c) and (e): 7.5 mol % **3h**, 30 mol % dbu, 1.1 equiv  $B_2(pin)_2$ , thf, 60 equiv MeOH, 50 °C, 14 h. Cu-catalyzed conditions: Reactions (a), (b), and (d): 5.0 mol % Josiphos, 5.0 mol % CuCl, 5.0 mol % NaO*t*-Bu, 1.1 equiv  $B_2(pin)_2$ , thf, 1.0 equiv MeOH, 22 °C, 14 h; reactions (c) and (e): 7.5 mol % Josiphos, 7.5 mol % CuCl, 7.5 mol % NaO*t*-Bu, 1.1 equiv  $B_2(pin)_2$ , thf, 1.2 equiv MeOH, 50 °C, 14 h. Conversion values relate to the percent starting material consumed and were determined through analysis of the 400 MHz <sup>1</sup>H NMR spectra of the unpurified mixtures ( $\pm$ 5%). Yield

values refer to isolated and purified  $\beta$ -boryl products ( $\pm 2\%$ ). See the Supporting Information for details.

Table 1

Study of Reaction Conditions with 3a as the Chiral NHCa

	₹	5.0 mol % Ph BF4  3a Ph  7.5-20 mol % base. 1.1 equiv B₂(pin)₂ (1), thf,	BF <sub>4</sub> And Me  Me  Me  Me  Me  Me  Me  Me  Me  Me	B(pin) 4a
ntry	base; mol %	additive; equiv	conv (%)	$\mathrm{er}^{\mathcal{C}}$
	NaOt-Bu; 7.5	none	<5	na
- \	NaOt-Bu; 7.5	MeOH; 20	24	86.5:13.5
	dbu; 10	MeOH; 20	31	90:10
_	dbu; 20	MeOH; 20	47	92:8

 $^{\it a}_{\it Reactions}$  were performed under N2 atmosphere.

 $^b$  Determined through analysis of 400 MHz  $^1\mathrm{H}\:\mathrm{NMR}$  spectra of unpurified mixtures (±5%).

Cetermined by HPLC analysis (±2%); see the Supporting Information for details. na = not applicable; dbu = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2

Initial Examination of Chiral NHC Catalysts<sup>a</sup>

Me Ha	OBF4 PPN EN SON SON SON SON SON SON SON SON SON SO	3g Ar = Mas, R = H 3h Ar = Mas, R = H 3h Ar = Mas, R = i-Pr
5.0 mol % chiral imidazolinium salt 20 mol % cbu, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, 20 equiv MeOH, 22 °C, 14 h	BE4 PH CONTROL OF THE	Mes -
Me 500 mo 2a 20 mo 3	OBF. Ph. NOON Ph.	36 R = H 36 R = H

entry	imidazolinium salt	q(%) and	$\mathrm{er}_{\mathcal{C}}$
1	3b	35	82:18
2	3c	37	81:19
3	3d	30	69:31
4	Зе	10	56:44
5	3f	78	76:24
9	3g	30	94:6
7	3h	18	95:5

 $^{a-c}$ See Table 1. Mes = 2,4,6-(Me)3C6H2.

Table 3

Wu et al.

NHC-Catalyzed Enantioselective BCA to Acyclic Enones<sup>a</sup>

B(pin)	4a-j
5.0 mol % chiral imidazolinium salt	20 mol % dbu, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, 60 equiv MeOH, 22 °C, 14 h
	Za-j

	\ \ \	0.0	5.0 mol % chiral imidazolinium sait		≺ -<	
	2a-j	20 mo	20 mol % dbu, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, 60 equiv MeOH, 22 °C, 14 h		4a-j	
ntry	$\mathbf{R}^1$ ; $\mathbf{R}^2$		imidazolinium salt	conv(%)b	yield $(\%)^{\mathcal{C}}$	$e^{rd}$
	Me, Ph	2a	За	87	82	92:8
	Me; Ph	<b>2a</b>	3h	>68	92	96:4
	Ме; <i>о</i> -МеС <sub>6</sub> Н₄ <sup>е</sup>	2b	3h	95	06	85.5:14.5
	Me; $p ext{-MeOC}_6 ext{H}_4^f$ 2c	<b>2</b> c	3h	06	08	94:6
	Me; $p ext{-BrC}_6 ext{H}_4\mathcal{S}$	2 <b>d</b>	3h	09	43	92:8
	Me; 2-furyl	<b>3</b> e	3ћ	75	73	92:8
	Me; n-pentyl	<b>2f</b>	3h	>98	94	94.5:5.5
	Me; <i>i</i> -Pr	$^{2g}$	3h	>68	93	94:6
	<i>n</i> -Bu; Ph	2 <b>h</b>	3h	81	92	91:9
0	$i$ -Pr; Ph $^h$	<b>2i</b>	3h	94	06	90:10
1	Ph; Ph <sup>j</sup>	2j	3h	82	72	93.5:6.5
I		ĺ				

 $^{\it a}_{\rm Reactions}$  were performed under N2 atmosphere.

 $^{b}$ Conversion determined through analysis of 400 MHz  $^{1}$ H NMR spectra of unpurified mixtures (±5%).

<sup>C</sup>Yields of isolated purified products ( $\pm 2\%$ ).

 $d_{\rm Bnantiomeric}$  ratio (er) determined by GLC or HPLC analysis ( $\pm 2\%$ ); see the Supporting Information for details.

 $^e\mathrm{Reaction}$  performed at 50 °C.

 $f_{\rm Reaction}$  performed with 2.5 mol %  ${\bf 3h}$  and 10 mol % dbu.

gn addition, ~10% proto-deboration (saturated ketone) product is formed (determined by analysis of 400 MHz <sup>1</sup>H NMR spectrum of the unpurified mixture).

Page 19

 $^{h}$ Reaction performed with 7.5 mol % 3h and 30 mol % dbu.

 $^{j}$ Reaction time = 18 h.

Table 4

NHC-Catalyzed Enantioselective BCA to Acyclic Unsaturated Esters<sup>a</sup>

O B(pin)	6a-d	conv (%) $^b$ yield (%) $^c$ er $^a$
5.0–7.5 mol % <b>3h</b>	20–30 mol % dbu, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, 60 equiv MeOH, 22 or 50 °C, 10–14 h	mol % 3h time (h); temp (°C) co
	5a-d	$\mathbf{R}^1$ ; $\mathbf{R}^2$

Eard         Fand         Fand<		1	ĵ,		5.0-7.5 mol % 3n	<b>₹</b>	°C	
3n         mol % 3h         time (h); temp (°C) $conv$ (%) b         yield (%) c $3r$ $5n$ $14; 22$ $>98$ $87$ $3r$ $7.5$ $10; 50$ $>98$ $62$ h $5c$ $5.0$ $14; 50$ $88$ $80$ entyl $5d$ $30$ $30$ $30$		5a-d	Ł	20–30 mol % db 60 equiv MeC	u, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, JH, 22 or 50 °C, 10–14 h	6a-d	÷	
$\mathbf{5a}$ $5.0$ $14;22$ $>98$ $87$ $\mathbf{rc}_6H_4[^e]$ $\mathbf{5b}$ $7.5$ $10;50$ $>98$ $62$ nnyl $\mathbf{5c}$ $5.0$ $14;50$ $88$ $80$ nnyl $\mathbf{5d}$ $5.0$ $14;22$ $83$ $80$	entry	$\mathbf{R}^1$ ; $\mathbf{R}^2$		mol % 3h	time (h); temp (°C)	q(%) auoo	yield $(\%)^{\mathcal{C}}$	$e^{rd}$
10,50     >98     62       14,50     88     80       14,22     83     80	1	Me, Ph	5a	5.0	14; 22	86<	87	98:2
5c     5.0     14;50     88     80       5d     50     14;22     83     80	2	Me; $p ext{-BrC}_6 ext{H}_4[^{e}]$	<b>S</b> b	7.5	10; 50	86<	62	94:6
<b>5d</b> 5.0 14;22 83 80	3	-Bu; Ph	5c		14; 50	88	80	98:2
	4	Me; mentyl	<b>2</b> q	5.0	14; 22	83	08	95:5

e Approximately 30% of the proto-deboration byproduct is generated (determined by analysis of 400 MHz <sup>1</sup>H NMR spectrum of the unpurified mixture).

Table 5

NHC-Catalyzed Enantioselective BCA to Acyclic Unsaturated Amides<sup>a</sup>

	Me	,	7.5 mol % <b>3h</b>	Me	B(pin)	
	OMe 7a-f	r	30 mol % dbu, 1.1 equiv $B_2(pin)_2$ (1), thf, 60 equiv MeOH, 50 or 66 °C, 10–36 h	oin) <sub>2</sub> (1), thf, 2, 10–36 h	OMe 8a-f	
entry R	R		time (h); temp (°C) conv (%) $^b$ yield (%) $^c$ er $^d$	q(%) auoo	yield $(\%)^{\mathcal{C}}$	$p^{\mathrm{Ja}}$
_	$Ph^e$	7a	36; 50	98	61	86.5:13.5
2	$p ext{-BrC}_6 ext{H}_4^{~e}$	<b>J</b> b	10; 50	>98	70	94:6
3	n-pentyl	7c	14; 50	77	74	95:5
4	(CH <sub>2</sub> ) <sub>2</sub> OTBS	<b>1</b> 4	24; 66	96	92	93:7
5	<i>i</i> -Bu	7e	24; 66	78	73	95:5
9	<i>j</i> -Pr	<b>J</b> Ł	24; 50	29	09	95:5

a-dSee Table 3.

 $^{e}$ Reaction performed with 30 equivalents of MeOH.

Table 6

NHC-Catalyzed Enantioselective BCA to Unsaturated Aldehydes<sup>a</sup>

B(pin)	10a-d
5.0-7.5 mol % imidazolinium salt	20–30 mol % dbu, 1.1 equiv B <sub>2</sub> (pin) <sub>2</sub> (1), thf, 60 equiv MeOH, 22 or 50 °C, 7.0–14 h
	9a-d

			9a-d	20–30 mol % dbu, 1.1 equiv $B_2(pin)_2$ (1), thf, 60 equiv MeOH, 22 or 50 °C, 7.0–14 h	equiv $B_2(pin)_2$ (1), thf, or 50 °C, 7.0–14 h	10a-d		
ntry R	æ		imidaz	olinium salt; mol %	imidazolinium salt; mol $\%$ time (h); temp (°C) conv (%) $^b$ yield (%) $^c$ er $^d$	q(%) auoo	yield $(\%)^{\mathcal{C}}$	$er^d$
	<i>n</i> -propyl <b>9a 3a</b> ; 5.0	9a	<b>3a</b> ; 5.0		14; 22	86<	81	84:16
	n-propyl	9a	<b>3h</b> ; 5.0		14; 22	95	72	95:5
	$(CH_2)_2 Ph^{\mathcal{C}}$	96	<b>3h</b> ; 7.5		7.0; 50	86<	65	95:5
	<i>j</i> -Bu	96	<b>3h</b> ; 5.0		14; 22	95	63	94:6
	<i>j</i> -Pr	<b>9</b> d	<b>9d 3h</b> ; 5.0		14; 22	>98	72	91:9

 $^{-d}$ See Table 3.

In addition, 18% of the derived  $\beta$ -methoxy aldehyde is obtained (determined by analysis of the 400 MHz  $^1$ H NMR spectrum of the unpurified mixture).