

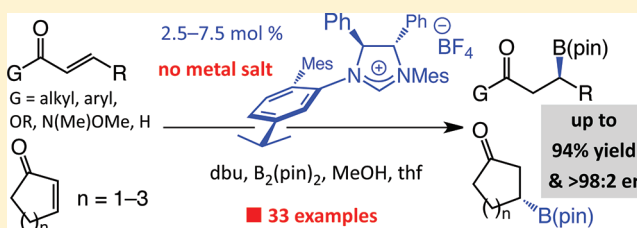
Metal-Free Catalytic Enantioselective C–B Bond Formation: (Pinacolato)boron Conjugate Additions to α,β -Unsaturated Ketones, Esters, Weinreb Amides, and Aldehydes Promoted by Chiral N-Heterocyclic Carbenes

Hao Wu, Suttipol Radomkit, Jeannette M. O'Brien, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

S Supporting Information

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_1 -symmetric chiral imidazolium salt, which is converted, in situ, to the catalytically active diastereo- and enantiomerically pure N-heterocyclic 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 [$B_2(\text{pin})_2$], 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 β -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.¹ We demonstrated that N-heterocyclic carbenes (NHCs), a class of organic molecules commonly used to catalyze C–C bond formation,² promote reactions between bis(pinacolato)diboron [$B_2(\text{pin})_2$; **1**] and an assortment of cyclic and acyclic α,β -unsaturated ketones and esters. Such processes deliver β -boryl carbonyls, which are versatile intermediates in chemical synthesis.^{3,4} The NHC-catalyzed (pinacolato)boron conjugate addition (BCA) reactions were shown to be mechanistically unique, allowing them to be complementary to the more extensively examined Cu-catalyzed variants⁵ (e.g., distinct chemoselectivity profiles, see below). A subsequent study focused on the use of chiral phosphines to promote enantioselective BCA.⁶ 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 β -boryl ketone in 68:32 er. In our initial disclosure,^{1a} we proposed that the metal-free reactions are initiated by formation of an $\text{NHC}\cdot B_2(\text{pin})_2$ complex, wherein the B–B bond is activated due to association of the Lewis basic heterocycle;⁷ support for the aforementioned

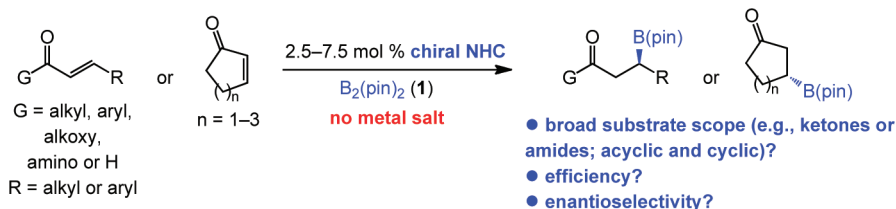
hypothesis and the associated structural changes has more recently been provided through X-ray crystallography.⁸

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 α,β -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 imidazolium salt, a common organic base, and commercially available $B_2(\text{pin})_2$ (**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.

Received: March 26, 2012

Published: May 4, 2012

Scheme 1. NHC-Catalyzed Enantioselective BCA to Unsaturated Carbonyls



2. RESULTS AND DISCUSSION

2.1. Identification of Optimal Conditions and Catalysts. We began by probing the ability of the NHC derived from chiral imidazolium salt **3a** to effect reactions of unsaturated carbonyls with $B_2(\text{pin})_2$ (**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,^{1a} as illustrated in entry 1 of Table 1, there is hardly any product

Table 1. Study of Reaction Conditions with **3a** as the Chiral NHC Precursor^a

entry	base; mol %	additive; equiv	conv (%) ^b	er ^c
1	NaOt-Bu; 7.5	none	<5	na
2	NaOt-Bu; 7.5	MeOH; 20	24	86.5:13.5
3	dbu; 10	MeOH; 20	31	90:10
4	dbu; 20	MeOH; 20	47	92:8

^aReactions were performed under N_2 atmosphere. ^bDetermined through analysis of 400 MHz 1H NMR spectra of unpurified mixtures ($\pm 5\%$). ^cDetermined by HPLC analysis ($\pm 2\%$); see Supporting Information for details. na = not applicable; dbu = 1,8-diazabicyclo[5.4.0]undec-7-ene.

generated in the presence of **3a** and NaOt-Bu after 14 h 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**;¹⁰ 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.^{1a,11} Accordingly, we chose to probe the effect of MeOH as an additive.

With 20 equiv 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

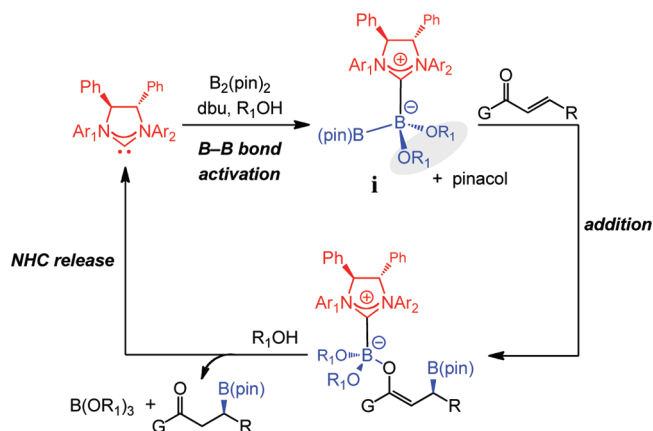
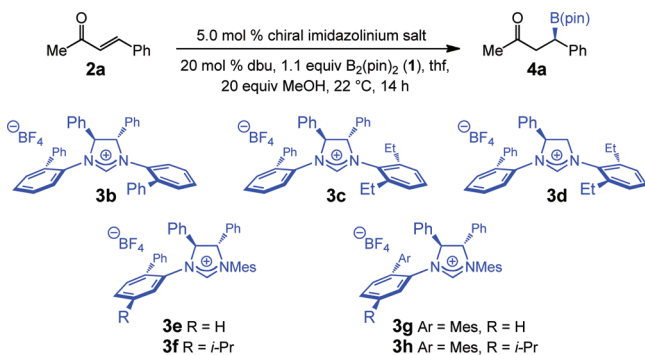


Figure 1. Catalytic cycle proposed for NHC-catalyzed BCA; exchanging a B(pin) with smaller alkoxides could lead to a faster rate of reaction.

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,⁹ 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 imidazolium salts can be structurally modified¹² and began search for a chiral NHC that can furnish higher conversion and promote the C–B bond-forming reaction enantioselectively. Because 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 imidazolium 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 and 3, Table 2). Overall, the NHC derived from C_1 -symmetric **3h**, bearing a sizable 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 imidazolium 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

Table 2. Initial Examination of Chiral NHC Catalysts^a

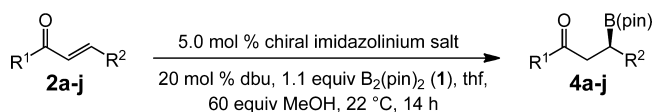
	imidazolium salt	conv (%) ^a	er ^a
1	3b	35	82:18
2	3c	37	81:19
3	3d	30	69:31
4	3e	10	56:44
5	3f	78	76:24
6	3g	30	94:6
7	3h	81	95:5

^aSee Table 1. Mes = 2,4,6-(Me)₃C₆H₂.

equiv 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 C₁-symmetric catalysts merits mention. Although it is possible that the C₂-symmetric chiral variants of certain highly hindered imidazolium salts such as **3h** could give rise to improved enantioselectivity, synthesis of these 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 C₁-symmetric NHCs that contain a single sterically demanding dissymmetric aryl unit are 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**, most suitable 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).¹³ 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), despite 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 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).

Table 3. NHC-Catalyzed Enantioselective BCA to Acyclic Enones^a

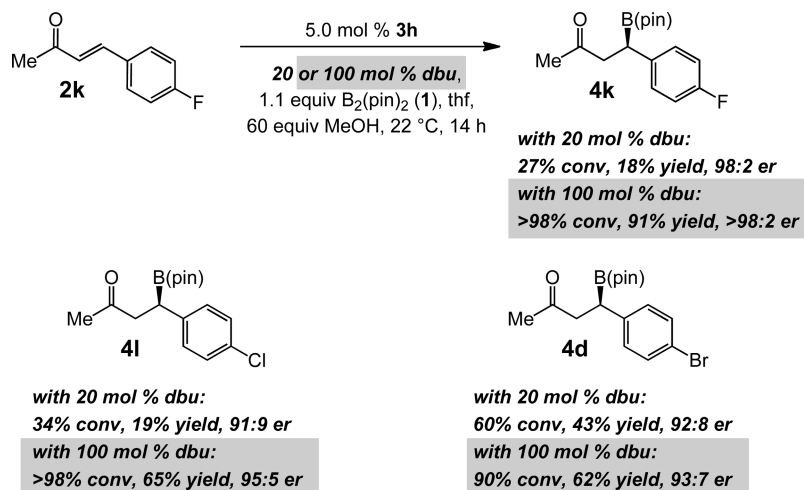
entry	R ¹ ; R ²		imidazolium salt	conv (%) ^b	yield (%) ^c	er ^d
1	Me; Ph	2a	3a	87	82	92:8
2	Me; Ph	2a	3h	>98	92	96:4
3	Me; <i>o</i> - MeC ₆ H ₄ ^e	2b	3h	95	90	85.5:14.5
4	Me; <i>p</i> - MeOC ₆ H ₄ ^f	2c	3h	90	80	94:6
5	Me; <i>p</i> - BrC ₆ H ₄ ^g	2d	3h	60	43	92:8
6	Me; 2-furyl	2e	3h	75	73	92:8
7	Me; <i>n</i> -pentyl	2f	3h	>98	94	94.5:5.5
8	Me; <i>i</i> -Pr	2g	3h	>98	93	94:6
9	<i>n</i> -Bu; Ph	2h	3h	81	76	91:9
10	<i>i</i> -Pr; Ph ^h	2i	3h	94	90	90:10
11	Ph; Ph ⁱ	2j	3h	82	72	93.5:6.5

^aReactions were performed under N₂ atmosphere. ^bConversion determined through analysis of 400 MHz ¹H NMR spectra of unpurified mixtures ($\pm$ 5%). ^cYields of isolated purified products ($\pm$ 2%). ^dEnantiomeric ratio (er) determined by GLC or HPLC analysis ($\pm$ 2%); see Supporting Information for details. ^eReaction performed at 50 °C. ^fReaction performed with 2.5 mol % **3h** and 10 mol % dbu. ^gIn addition, ~10% proto-deboration (saturated ketone) product is formed (determined by analysis of 400 MHz ¹H NMR spectrum of the unpurified mixture). ^hReaction performed with 7.5 mol % **3h** and 30 mol % dbu. ⁱReaction time = 18 h.

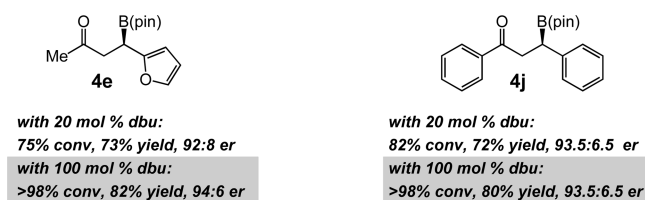
Catalytic BCA with bromophenyl-substituted ketone **2d** (entry 5, Table 3) affords **4d** in 43% yield (60% conv, 92:8 er). As the findings in Scheme 2 indicate, the relative inefficiency corresponds to a variety of halogen-substituted substrates. Thus, reaction of *p*-fluoro-substituted **2k**, under the conditions employed for the transformations in Table 2, although exceedingly enantioselective (98:2 er), results in only 27% conversion after 14 h; NHC-catalyzed BCA of chloro-substituted **2l** is similarly inefficient.¹⁴ Our attempts to address the above complications led to the finding that increasing the amount of the organic base (dbu) from 20 mol % to 1 equiv 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.^{15,16}

The transformations in entries 7 and 8 show that alkyl-substituted α,β -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 isopropyl, or an aryl substituent at the carbonyl carbon can be efficiently converted to the β -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

Scheme 2. Influence of Amine Base on BCA Efficiency



processes that give rise to the formation of furyl-substituted β -boryl methyl ketone **4e** and phenyl-substituted phenylketone **4j**, the same strategy can be applied to other types of substrates as well.



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 sizable *tert*-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). Despite the more forcing conditions in entries 2 and 3 (Table 4), enantioselectivities remain high (94:6–98:2 er).¹⁷

2.2.3. Reactions with Aryl- and Alkyl-Substituted Acyclic α,β -Unsaturated Amides. α,β -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.¹⁸ As the data in Table 5 indicate, reactions with amides require relatively

Table 5. NHC-Catalyzed Enantioselective BCA to Acyclic Unsaturated Amides^a

entry	R	time (h); temp (°C)	conv (%) ^a	yield (%) ^a	er ^a
1	Ph ^e	7a, 36; 50	86	61	86.5:13.5
2	<i>p</i> -BrC ₆ H ₄ ^e	7b, 10; 50	>98	70	94:6
3	<i>n</i> -pentyl	7c, 14; 50	77	74	95:5
4	(CH ₂) ₂ OTBS	7d, 24; 66	96	92	93:7
5	<i>i</i> -Bu	7e, 24; 66	78	73	95:5
6	<i>i</i> -Pr	7f, 24; 50	67	60	95:5

^aSee Table 3. ^eReaction performed with 30 equiv of MeOH.

higher catalyst loadings (7.5 mol %), elevated temperatures (50–66 °C), and longer reaction times (up to 36 h); nonetheless, aryl- and alkyl-substituted β -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

Table 4. NHC-Catalyzed Enantioselective BCA to Acyclic Unsaturated Esters^a

$$\text{R}^1\text{O}-\text{C}(=\text{O})-\text{CH}=\text{CH}-\text{R}^2 \xrightarrow[\text{20-30 mol \% dbu, 1.1 equiv B}_2(\text{pin})_2 \text{ (1), thf, 60 equiv MeOH, 22 or 50 }^\circ\text{C, 10-14 h}]{\text{5.0-7.5 mol \% 3h}} \text{R}^1\text{O}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}(\text{B}(\text{pin}))-\text{R}^2$$

entry	R ¹ ; R ²		mol % 3 h	time (h); temp (°C)	conv (%) ^a	yield (%) ^a	er ^a
1	Me; Ph	5a	5.0	14; 22	>98	87	98:2
2	Me; <i>p</i> -BrC ₆ H ₄ ^b	5b	7.5	10; 50	>98	62	94:6
3	<i>t</i> -Bu; Ph	5c	5.0	14; 50	88	80	98:2
4	Me; <i>n</i> -pentyl	5d	5.0	14; 22	83	80	95:5

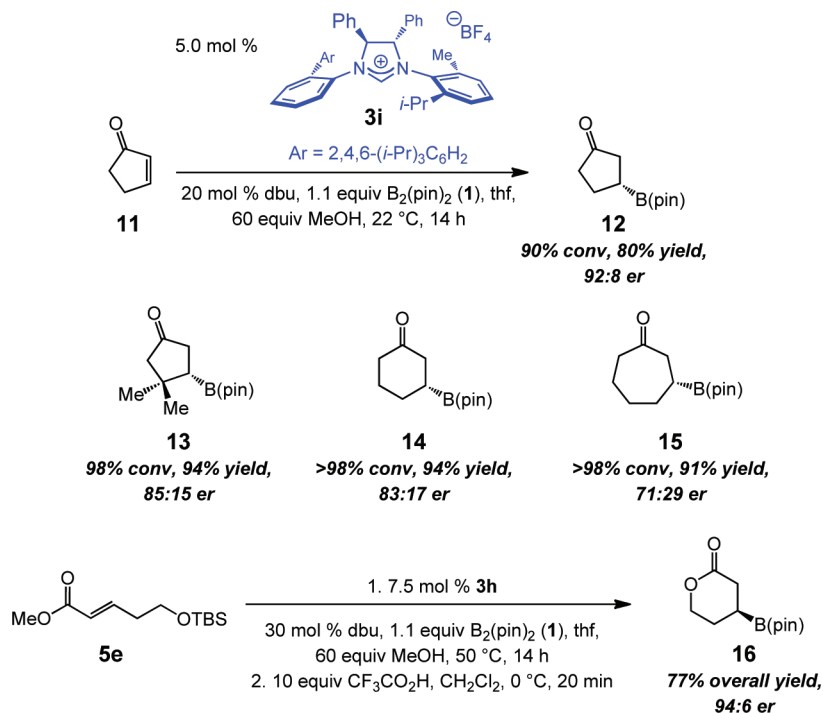
^aSee Table 3. ^bApproximately 30% of the proto-deboration byproduct is generated (determined by analysis of 400 MHz ¹H NMR spectrum of the unpurified mixture).

Table 6. NHC-Catalyzed Enantioselective BCA to Unsaturated Aldehydes^a

entry	R	imidazolium salt; mol %	time (h); temp (°C)	conv (%) ^a	yield (%) ^a	er ^a
1	<i>n</i> -propyl	3a ; 5.0	14; 22	>98	81	84:16
2	<i>n</i> -propyl	3h ; 5.0	14; 22	95	72	95:5
3	(CH ₂) ₂ Ph ^b	3h ; 7.5	7.0; 50	>98	65	95:5
4	<i>i</i> -Bu	3h ; 5.0	14; 22	95	63	94:6
5	<i>i</i> -Pr	3h ; 5.0	14; 22	>98	72	91:9

^aSee Table 3. ^bIn addition, 18% of the derived β -methoxy aldehyde is obtained (determined by analysis of the 400 MHz ¹H NMR spectrum of the unpurified mixture).

Scheme 3. NHC-Catalyzed Enantioselective BCA to Cyclic Enones

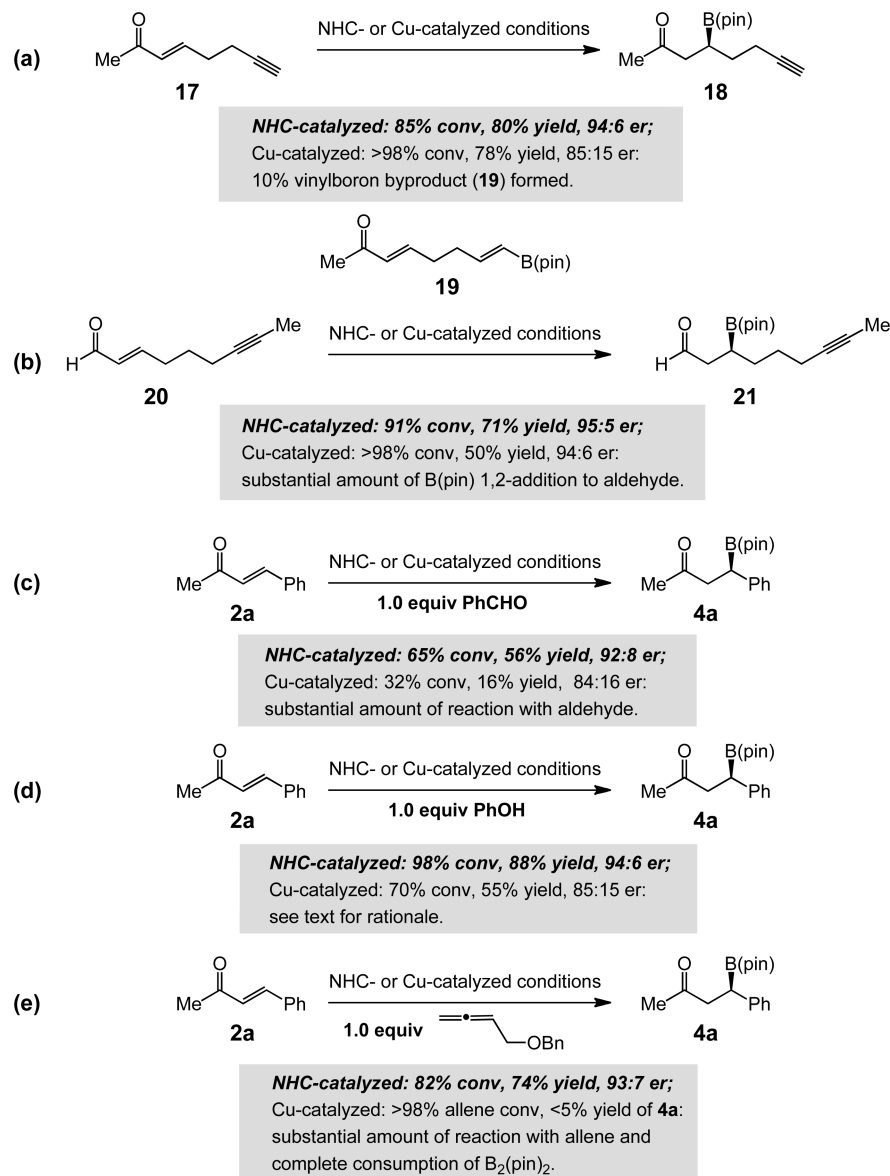


7e and **7f** (Table 5, entries 5 and 6) are converted to the desired products in 60–73% yield and 95:5 er. In the case of electron-deficient amide **7b** (Table 5, entry 2), shorter reaction times and reduced amounts of MeOH are preferred (30 vs 60 equiv), because the undesired proto-deboration¹⁴ (cf., **6b**, entry 2, Table 4) as well as formation of the corresponding β -boryl methyl ester is otherwise significantly more competitive¹⁹ (~70% byproduct formation with 60 equiv of MeOH). Control experiments indicate that it is the β -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 β -boron likely activates the amide group toward reaction with MeOH.²⁰

2.2.4. Reactions with Alkyl-Substituted α,β -Unsaturated Aldehydes. α,β -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.²¹ In one study, synthesis and isolation of an (achiral) NHC–Cu–OMe complex proved necessary, because the

presence of base had to be avoided if efficient generation of β -boryl aldehydes were to be achieved.²² In another example, an NHC–Cu-catalyzed BCA of cinnamaldehyde is shown to afford the desired product in 70:30 er (86% conv; yield of isolated product was not reported).²³ Finally, a protocol for Cu-catalyzed enantioselective BCA to enals was reported most recently; transformations proceed through in situ-generated chiral α,β -unsaturated iminiums formed from reaction with an enantiomerically pure amine (20 mol %).²⁴ 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, use of air- and moisture-sensitive Cu(OTf)₂ and 10 mol % of a Brønsted acid (*o*-FC₆H₄CO₂H) are required. Furthermore, the β -boryl aldehydes obtained were not isolated but were directly functionalized (e.g., Wittig olefin synthesis).

The NHC derived from imidazolium salt **3h** promotes enantioselective BCA to alkyl-substituted enals, as indicated by the examples shown in Table 6. As illustrated in entry 1, when C₂-symmetric **3a** is used in the reaction, under otherwise identical conditions, **10a** is obtained in 81% yield (>98% conv)

Scheme 4. Functional Group Tolerance: Differences between NHC- and Cu-Catalyzed Protocols^a

^aNHC-catalyzed conditions: Reactions a, b, and d: 5.0 mol % **3h**, 20 mol % dbu, 1.1 equiv of B₂(pin)₂, thf, 60 equiv of MeOH, 22 °C, 14 h; reactions c and e: 7.5 mol % **3h**, 30 mol % dbu, 1.1 equiv of B₂(pin)₂, thf, 60 equiv of MeOH, 50 °C, 14 h. Cu-catalyzed conditions: Reactions a, b, and d: 5.0 mol % Josiphos, 5.0 mol % CuCl, 5.0 mol % NaOt-Bu, 1.1 equiv of B₂(pin)₂, thf, 1.0 equiv of MeOH, 22 °C, 14 h; reactions c and e: 7.5 mol % Josiphos, 7.5 mol % CuCl, 7.5 mol % NaOt-Bu, 1.1 equiv of B₂(pin)₂, thf, 1.0 equiv of MeOH, 50 °C, 14 h. Conversion values relate to the percent starting material consumed and were determined through analysis of the 400 MHz ¹H NMR spectra of the unpurified mixtures (±5%). Yield values refer to isolated and purified β-boryl products (±2%). See Supporting Information for details.

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 β-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,²⁵ reaction with a β-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 α,β-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).⁶ 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, β-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).²⁷ Catalyst screening led us to establish that use of imidazolium salt **3i** (Scheme 3) promotes the BCA with similar efficiency (90% conv, 80% yield) and with improved enantioselectivity (92:8 *er*). Several additional examples, involving enones of different ring sizes are provided in Scheme 3.²⁸ 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, because a previous report involving the use of chiral Cu-phosphine catalysts indicates <2% conversion with a similarly substituted cyclohexenone.^{5c} 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 β -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.^{1a,5} Such an expectation has been based on the principle that, because metal-free BCA reactions proceed through an entirely different pathway compared to the processes promoted by organocopper complexes, they can deliver complementarities that would otherwise remain unavailable. Certain distinctions, above all in connection with reactions of enals, have been already mentioned. Additional revealing examples, underscoring some of the specific 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).^{5a,b,f}

Whereas NHC-catalyzed BCA to alkyne-substituted enone **17** proceeds with complete chemoselectivity to afford **18** in 80% yield and 94:6 *er* (Scheme 4a), under Cu-catalyzed conditions, 10% of β -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 β -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.^{1a} 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 1 equiv 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 aldehyde³⁰ resulting in partial sequestration of the catalytically active heterocycle, the negative impact on the Cu-catalyzed 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 B₂(pin)₂ to regenerate the active Cu–B(pin) complex. Finally, whereas Cu-catalyzed processes involving an allene³³ appear to be significantly more favored (Scheme 4e), leading to complete consumption of the available B₂(pin)₂ and the formation of byproducts, the NHC-catalyzed BCA proceeds readily to afford the desired **4a** in 74% yield (vs <5% yield).³⁴ It should however 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 loading and shorter reaction times, and the corresponding additions to cyclic enones are generally more enantioselective.⁵ 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 β -boryl carbonyls. These studies emphasize the substantially higher activity of NHCs as BCA catalysts (vs phosphines⁶), as indicated in the initial disclosure.^{1a} 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 enones³⁵) and generally proceed with superior enantioselectivity with a chiral NHC serving as the catalyst than when phosphines are utilized.⁶

The metal-free catalytic method possesses attributes that are complementary to the Cu-catalyzed alternatives:⁵ 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^{1a}). Studies to shed light on various 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.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and spectral data for substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

amir.hoveyda@bc.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to the memory of Professor Robert J. Silbey. Financial support was provided by the NIH (GM-57212) and the NSF (CHE-1111074). We thank Dr. K.-s. Lee and Dr. F. Haeffner for helpful discussions, and Frontier Scientific for gifts of bis(pinacolato)diboron.

■ REFERENCES

- (1) (a) Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255. (b) Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 12766.
- (2) For representative reviews on NHC-catalyzed processes in chemical synthesis, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.
- (3) For a review regarding the significance of enantioselective conjugate additions with B- and Si-based nucleophiles, see: Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, 47, 7917–7932.
- (4) For an application of enantioselective Cu-catalyzed (pinacolato)boron conjugate addition to synthesis of a biologically active molecule, see: (a) Chea, H.; Sim, H.-S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855–858. For a related example, see: (b) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4560–4563.
- (5) For representative examples of Cu-catalyzed enantioselective (pinacolato)boron conjugate additions, see: (a) Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. (b) Sim, H.-S.; Feng, X.; Yun, J. *Chem.—Eur. J.* **2009**, *15*, 1939–1943. (c) Feng, X.; Yun, J. *Chem. Commun.* **2009**, 6577–6579. (d) Chen, I.-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665. (e) O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10633. (f) Feng, X.; Yun, J. *Chem.—Eur. J.* **2010**, *16*, 13609–13612. (g) Chen, I.-H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098–4101. (h) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruck, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008–5011. (i) Moure, A. L.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2011**, 47, 6701–6703. (j) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nature Chem* **2011**, *3*, 894–899.
- (6) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5130–5134.
- (7) For a review on NHC–borane complexes, see: Curran, D. P.; Solov'yev, A.; Makhlof Brahm, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10294–10317.
- (8) Kleeberg, C.; Crawford, A. G.; Batsanov, A. S.; Hodgkinson, P.; Apperley, D. C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Org. Chem.* **2012**, *77*, 785–789.
- (9) O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7712–7715.
- (10) For example, treatment of imidazolium salt **3h** (see Table 2) with B₂(pin)₂ at 22 °C leads to the clean formation of a new complex (¹¹B NMR: δ 33.57 ppm and δ 12.20 ppm vs δ 30.10 ppm for **1** in thf-d₈ at 22 °C). See 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 C₁-symmetric chiral N-heterocyclic carbenes in enantioselective synthesis, see: (a) Lee, K.-s.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *75*, 4455–4462. For application of such entities in other catalytic enantioselective processes, see: (b) Reference 5e. (c) Reference 9.
- (13) Although C₂-symmetric imidazolium salt **3a** typically gives rise to less efficient and enantioselective (pinacolato)boron conjugate addition than that of the C₁-symmetric **3h**, it can be prepared by a shorter synthesis route (three vs five steps in 25–40% yield). See 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, resubjection 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 toward 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 by <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 counterion of the imidazolium salt. See: (a) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096–17098. (b) Lennox, A. J. J.; Lloyd-Jones, G. C. *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, because 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) (a) Hirsch-Weil, D.; Abboud, K. A.; 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) Reference 4a.
- (19) As with the unsaturated esters, when 100 mol % dbu is used, the desired β -boryl amides are formed with less efficiency (larger degree of ester formation and similar amounts of proto-deboration).
- (20) For examples of chelation between a carbonyl group and a β -boron, influencing the course of a catalytic process, see: (a) Sandrock, D. L.; Jean-Gerard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108–17110. (b) Ohmura, T.; Awano, T.; Sugimoto, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191–13193. (c) Reference 5j.

(21) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036–11037.

(22) Bonet, A.; Lillo, V.; Ramírez, J.; Mar Díaz-Requejo, M.; Fernández, E. *Org. Biomol. Chem.* **2009**, *7*, 1533–1535.

(23) Lillo, V.; Prieto, A.; Bonet, A.; Mar Díaz-Requejo, M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659–662.

(24) Ibrahim, I.; Breistein, P.; Córdova, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 12036–12041.

(25) For examples of NHC-catalyzed homocoupling reaction, see: (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205–6208. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. For NHC-catalyzed conversion of unsaturated aldehydes to the saturated ester derivatives, see: (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905–908. For examples of both types of processes, see: (d) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873–3876.

(26) For a recent study regarding NHC-catalyzed conjugate addition of alcohols to α,β -unsaturated ketones, see: Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 13179–13181.

(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 $\leq 10\%$ 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: (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47–52. (b) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, *44*, 733–734. (c) Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, *46*, 758–760. (d) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943–2945. (e) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859–7871.

(30) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.

(31) With 5.0 mol % catalyst loading (1.1 equiv of $B_2(\text{pin})_2$, 60 equiv MeOH, 22 °C, 14 h), the NHC-catalyzed reaction affords the desired β -boryl ketone product in 48% yield (54% conv) and 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 α,β -unsaturated carbonyl in otherwise identical conditions as described for the reaction in Table 3) leads to <5% conversion.

(33) For Cu-catalyzed hydroborations of allenes, see: Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490–1493.

(34) With 5.0 mol % catalyst loading (1.1 equiv of $B_2(\text{pin})_2$, 60 equiv of MeOH, 22 °C, 14 h), the NHC-catalyzed reaction affords the desired β -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.