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Efficient C−B Bond Formation Promoted by N-Heterocyclic Carbenes: Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,*β*-Unsaturated Carbonyls

Kang-sang Lee, Adil R. Zhugralin, and Amir H. Hoveyda*

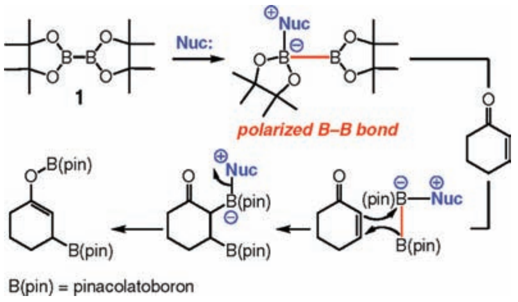
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

Received April 10, 2009; E-mail: amir.hoveyda@bc.edu

Development of metal-free catalytic processes is critical to the advancement of modern chemical synthesis; such protocols are valuable even in cases where a metal-catalyzed variant is available. The two reaction classes often proceed by mechanistically distinct pathways and can give rise to complementary reactivity and selectivity patterns. It is thus noteworthy that C−B bond formation has remained exclusively in the domain of metal-based catalysis.[1] Pt-,[2] Rh-,[3] Ni-,[4] and Cu-catalyzed[5] conjugate additions of diborons[6] with unsaturated esters have been disclosed; these transformations are largely or entirely limited to reactions of acyclic substrates (with achiral and chiral catalysts, respectively). In only three cases has the formation of quaternary B-substituted carbons been reported (all with acyclic enones).[4] Herein, we introduce a method for efficient C−B bond formation through transformations that are catalyzed by a readily available N-heterocyclic carbene (NHC) present at 2.5−10 mol %. Cyclic and acyclic α,*β*-unsaturated ketones or esters serve as substrates; *β*-boryl carbonyls with tertiary or quaternary B-substituted carbons are obtained in up to >98% yield. We illustrate that boron conjugate addition under metal-free conditions delivers reactivity and site-selectivity levels not attainable through the use of a Cu-catalyzed variant.[5]

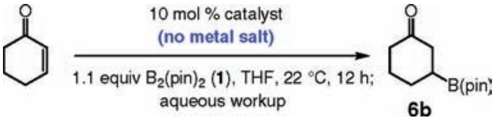
The present investigations are based on the principle that a nucleophilic NHC[7] might associate with the Lewis acidic boron atoms of commercially available bis(pinacolato)diboron (**1**) (Scheme 1).[8] The resulting electronic reorganization[9,10] could lead to activation of the B−B bond, promoting the reaction with an appropriate electrophilic site through the general pathway in Scheme 1.

Scheme 1. Proposed Model for Bis(pinacolato)diboron Activation and Conjugate Addition to an Enone

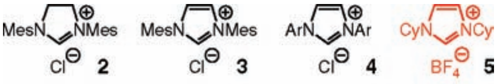


To initiate our studies, we subjected cyclohexenone and **1** to a premixed solution of commercially available imidazolinium salt **2** and NaO*t*-Bu (10 mol % each) in THF at 22 °C. As shown in entry 1 of Table 1, 66% conversion to the desired boronate **6b** was achieved in 12 h. Use of unsaturated **3** led to a more efficient process (92% conv; entry 2); the more sterically demanding **4** promoted 45% conversion to **6b** under the same conditions (entry 3). Complete reaction was obtained when the carbene derived from Cy-substituted imidazolium salt **5** served as the catalyst (>98% conv; entry 4).[11] The activity of the latter carbene is substantially superior to those corresponding to **2**−**4**: with only 2.5 mol % **5** (vs 10 mol % in Table 1), formation of **6** was complete within 1 h (vs 12 h). The findings in entries 5−7 of Table 1, indicating no reaction with 10 mol % NaO*t*-Bu, PPh_3, or PCy_3 in 12 h, underline the exceptional catalytic activity of the NHC catalysts. A relatively sluggish conjugate addition was observed with triphenylphosphine oxide (entry 8), suggesting an alternative and potentially effective avenue for catalyst development.

Table 1. Activation of Bis(pinacolato)diboron and Conjugate Additions with Various Catalysts[a]



entry	heterocyclic salt or phosphine	base; mol %	conv (%)[b]
1	**2**	NaO*t*-Bu; 10	66
2	**3**	NaO*t*-Bu; 10	92
3	**4**	NaO*t*-Bu; 10	45
4	**5**	NaO*t*-Bu; 10	***>98***
5	none	NaO*t*-Bu; 10	<2
6	PPh_3	none	<2
7	PCy_3	none	<2
8	$OPPh_3$	none	50



Mes = 2,4,6-trimethylphenyl; Ar = 2,6-di-*i*-propylphenyl

[a] Performed under a N_2 atm. [b] Conversion to product was determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures.

The following experiments were carried out to gauge the validity of the proposed scenario regarding NHC activation of **1** (Scheme 1): (1) Density functional theory (DFT) calculations[12] on a complex arising from association of **1** and the carbene derived from **5** were performed. The partial atomic charges (Scheme 2) indicate that complexation of an NHC with **1** results in polarization of the B−B bond and diminished electrophilic character of the two B atoms; the unassociated boron bears a lower positive charge than the one with which the NHC interacts (the electron density of the B−B bond is strongly polarized toward the unbound B center). Carbene association leads to weakening of the B−B bond, as evidenced by an increase in this bond length [1.703 Å in $B_2(pin)_2$ vs 1.749 Å in the NHC·**1** complex]. (2) Coordination of the highly effective carbene derived from **5** with diboron **1** was investigated by ^{11}B NMR spectroscopy; complete disappearance of the signal for **1** was observed within 5 min (22 °C). Consistent with the aforementioned hypothesis, significant upfield shifts were observed for the boron atom signals (Scheme 2), with one being more strongly shielded (from δ 30.1 to 4.5 and 6.3 for the sp^3- and sp^2-hybridized B centers, respectively). The same experiment with the less effective

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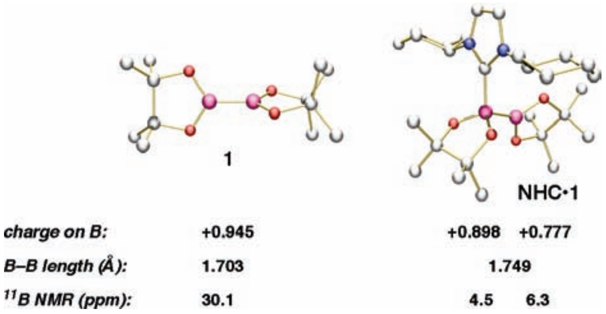
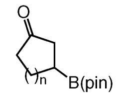
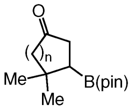
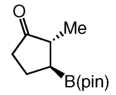
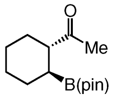
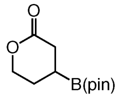
Scheme 2. DFT Calculations and ^{11}B NMR Studies of **1** and the Derived NHC Complex[a]



[a] DFT calculations were performed on the complex of **1** with the carbene derived from imidazolium salt **5**. Spectroscopic studies were performed with the carbenes derived from **4** and **5**. See the Supporting Information for additional details.

carbene derived from **4** led to the appearance of signals at δ −1.8 and 8.2 (∼20% conv in 1 h; additional transformation not observed after 12 h).

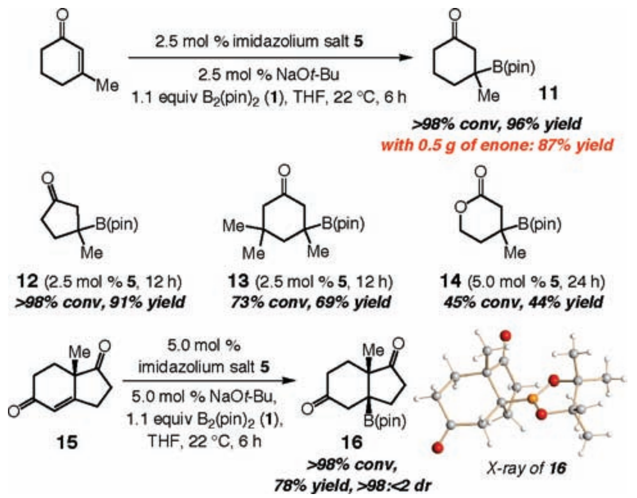
Table 2. Synthesis of Tertiary B-Substituted Carbons by NHC-Catalyzed Boron Conjugate Additions to Cyclic Enones[a]

entry	product		yield (%)[b]
1		n = 1 (**6a**)	93
2		n = 2 (**6b**)	91
3		n = 3 (**6c**)	93
4		n = 4 (**6d**)	89
5		n = 1 (**7a**)	97
6		n = 2 (**7b**)	98
7[c]		**8**	88
8[d]		**9**	90
9[e]		**10**	95

[a] Performed under a N_2 atm with 2.5 mol % **5** at 22 °C for 1.0 h; >98% conv in all cases. [b] Yield of purified products. [c] dr = 1.6:1. [d] dr = 7.1:1. [e] Performed with 5 mol % **5** for 24 h.

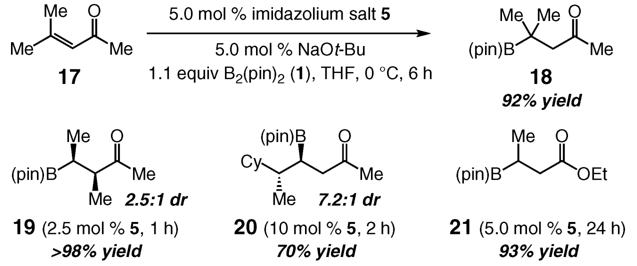
Reaction for 1 h with 2.5 mol % NHC catalyst was sufficient to give >98% conversion of five-, six-, seven-, and eight-membered-ring enones to **6a−d** in 89−93% yield (Table 2, entries 1−4). The transformations in entries 5 and 6 illustrate that the addition proceeds readily in cases where the *β* carbon of the unsaturated carbonyl is sterically congested. The efficient formation of boronates **8** and **9** demonstrates that tertiary C−B bonds are generated by facile catalytic additions to trisubstituted cyclic enones. The low and moderate diastereoselectivity in which **8** and **9** were obtained (1.6:1 and 7.1:1, respectively) are likely kinetically controlled, arising from aqueous quenching of the boron enolates. *β*-Boryl lactone **10** (Table 2, entry 9) was isolated in 95% yield; higher catalyst loading (5 mol % **5**) and longer times were required because of the diminished reactivity of the unsaturated lactone (24 vs 1 h).

Scheme 3. Synthesis of Quaternary B-Substituted Carbons by NHC-Catalyzed Boron Conjugate Additions to Cyclic Enones



Efficient formation of B-substituted quaternary carbon centers underlines one of the more noteworthy aspects of the present protocol. With 2.5 mol % catalyst, **11** and **12** were obtained in 96 and 91% yield, respectively (Scheme 3). The catalytic process can be used to obtain significant quantities of *β*-boroketones: reaction with 0.5 g (4.54 mmol) of *β*-methylcyclohexenone delivered 0.94 g of **11** after purification (87% yield). Synthesis of **13**, bearing two additional methyl units that are expected to retard the rate of reaction, proceeded to 73% conversion in 12 h (69% yield). The limitation of the method is manifested by the relatively inefficient formation of lactone **14**; a comparison of the conversion level (45%) and yield of the isolated product (44%), however, illustrates that the transformation proceeds with minimal byproduct formation. Reaction of the commercially available, enantiomerically pure bicyclic enone **15** (Scheme 3), which delivered boronate **16** in 78% yield as a single diastereomer (X-ray analysis), represents another process involving a particularly congested *β*-substituted enone.

Scheme 4. NHC-Catalyzed Boron Conjugate Additions to Acyclic Enones[a]

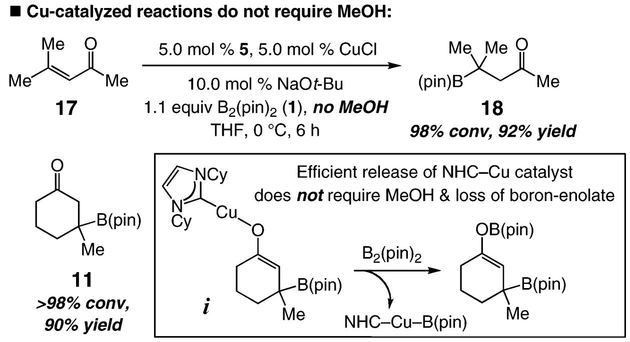


[a] Performed at 22 °C (except for **17** → **18**); >98% conv in all cases, except 88% for **20** (conv to the desired product by 400 MHz ^{1}H NMR). Yields of purified products are given.

NHC-catalyzed transformations can be performed with acyclic substrates (Scheme 4). Synthesis of **18** (92% yield), bearing a B-substituted quaternary carbon, required 5 mol % **5** at 0 °C[13] for 6 h. Formation of **19** proceeded in >98% yield via a tetrasubstituted boron enolate. Catalytic generation of **20**, which was isolated in 70% yield and 7.2:1 diastereomeric ratio (dr), illustrates that additions with acyclic substrates can proceed with useful stereoselectivity levels. The synthesis of *β*-boryl ester **21** (93% yield) shows that the metal-free protocol can be used to obtain products accessed by the recently disclosed Cu-catalyzed procedures.[5]

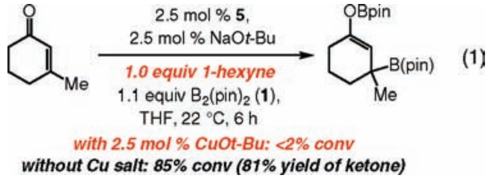
To identify some of the special attributes of the metal-free method, we briefly investigated the corresponding Cu-catalyzed process, likely the most advanced variant promoted by a metal complex.[5] With CuO*t*-Bu and the carbene from **5**, the additions proceeded as efficiently as in the NHC-catalyzed transformations; two examples are shown in Scheme 5. Unlike certain phosphine Cu-catalyzed processes[5h] and in contrast to reports regarding NHC

Scheme 5. Comparison of the Metal-Free and NHC−Cu-Catalyzed Processes

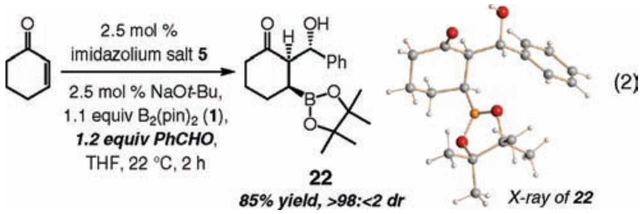


Cu complexes,[5g] MeOH was *not* required for efficient transformation. Additions promoted by a Cu complex, similar to the NHC-catalyzed processes, can furnish the boron enolate products (vs protonation with MeOH to afford ketones). This advantage likely arises from higher reactivity of Cu enolates bearing a strong σ-donor NHC (e.g., ***i*** in Scheme 5 vs the less Lewis basic P-based ligands), allowing for facile reaction with **1**.

Initial studies indicate that the NHC-catalyzed process can be more functional-group-tolerant than the Cu-catalyzed variant. Whereas the presence of 1 equiv of 1-hexyne led to complete inhibition of the Cu-catalyzed reaction,[14] the metal-free transformation gave 85% conversion (81% yield) (eq 1). Association of NHC−Cu-B(pin) with π-Lewis acidic alkynes likely leads to inhibition of the metal complex's catalytic activity. Thus, at least in some cases, site-selective C−B formation and boron enolate generation by conjugate addition to an alkyne-bearing enone can only be achieved through Cu-free catalysis.



The NHC-catalyzed reactions furnish molecules not easily accessible by alternative protocols. For example, oxidation of **11** delivered the corresponding tertiary alcohol in 94% yield.[15] As illustrated in eq 2, when addition to cyclohexenone was performed in the presence of benzaldehyde, the resulting boron enolate participated in an aldol addition, affording **22** as a single diastereomer (85% yield):



The outcome of the tandem conjugate addition/aldol process, established by X-ray crystallography, indicates that the reaction occurs from the *more* sterically hindered boron enolate face (C−C bond formation syn to boronate). The aldehyde approach might be directed through carbonyl association[16] with the adjacent C-bound boron atom. Generation of **22** was unaccompanied by products resulting from benzoin condensation, a Stetter-type process,[7] or aldehyde diboration (<2%).[1d] When the transformation in eq 2 was performed with 2.5 mol % CuO*t*-Bu, in addition to **22** (31%; >98:<2 dr), there was 19% benzaldehyde diboration (and 26% yield of an unidentified byproduct). A more efficient aldol addition could be achieved by introducing the aldehyde subsequent to the Cu-catalyzed process (to avoid its diboration). The above findings, however, illustrate that boron addition to an aldehyde-containing enone would proceed with high efficiency and site-selectivity only under the Cu-free conditions. Studies to establish the basis of the chemoselectivity furnished by the NHC catalyst are in progress.

A C−B bond can be converted to a C−O, C−N,[17] or C−C[17b,18] bond by various procedures, including catalytic cross-coupling reactions; the present protocol thus allows access to an assortment of valuable molecules. Development of the enantioselective variants and elucidation of the mechanistic details of the NHC-catalyzed reactions are underway.

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Supporting Information Available: Experimental procedures, spectral and analytical data for all reaction products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For details about the DFT calculations and ^{11}B NMR studies, see the Supporting Information.
(13) The lower reaction temperature for synthesis of **18** (0 °C vs 22 °C for formation of **19**−**21**) was due to formation of unidentified byproducts at 22 °C.
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