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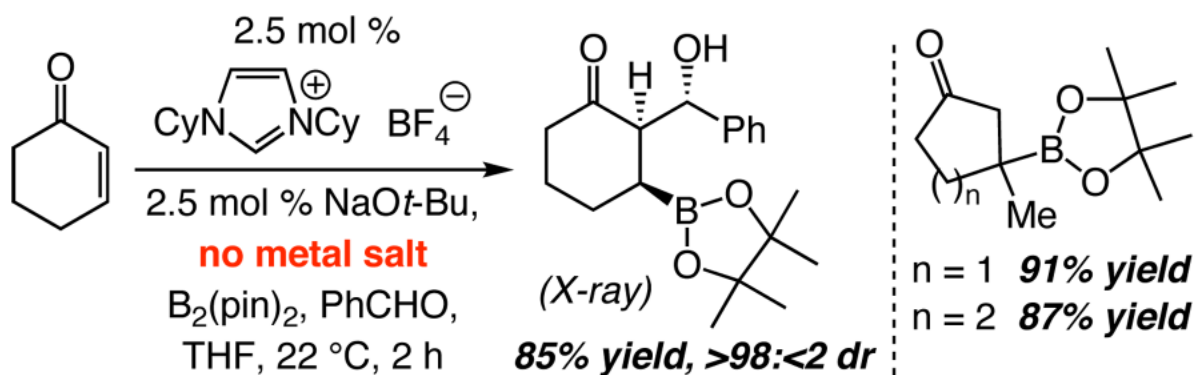
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Efficient C–B Bond Formation Promoted by *N*-Heterocyclic Carbenes. Synthesis of Tertiary and Quaternary B-Substituted Carbons through Metal-Free Catalytic Boron Conjugate Additions to Cyclic and Acyclic α,β -Unsaturated Carbonyls

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Abstract



Metal-free, nucleophilic activation of a B–B bond has been exploited in the development of a highly efficient method for conjugate additions of commercially available bis(pinacolato)diboron to cyclic or acyclic α,β -unsaturated carbonyls. Reactions are readily catalyzed by 2.5–10 mol % of a simple *N*-heterocyclic carbene (NHC). A variety of cyclic and acyclic unsaturated ketones and esters can serve as substrates. Transformations deliver β -boryl carbonyls bearing tertiary as well as quaternary B-substituted carbons in up to >98% yield. Preliminary studies indicate that, although related Cu–NHC-catalyzed reactions are equally efficient, the metal-free variant is more functional group tolerant; in contrast to the Cu-catalyzed reactions, the metal-free processes proceed readily in the presence of a terminal alkyne and do not promote concomitant diboration of an aldehyde. Representative functionalization of the resulting boron enolates demonstrates the strong influence of the Lewis acidic B of the β -boronate.

Development of metal-free catalytic processes is critical to 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-catalyzed⁵ conjugate additions of diborons⁶ 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 is the formation of quaternary B-substituted carbons reported (all with acyclic enones).⁴ Herein, we introduce a method for efficient C–B bond formation through transformations that are catalyzed by 2.5–10 mol % of a readily available *N*-heterocyclic carbene (NHC). 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 NHC⁷ might associate with a Lewis acidic boron 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 reaction with an appropriate electrophilic site through the general pathway in Scheme 1.

To initiate our studies, we subjected cyclohexenone and bis(pinacolato)diboron (**1**) to a premixed solution of commercially available imidazolium salt **2** and NaO*t*-Bu (10 mol % of each) in THF at 22 °C. As shown in entry 1 of Table 1, 66% conversion to the desired boronate **6b** is achieved in 12 h. Use of unsaturated **3** leads to a more efficient process (entry 2, 92% conv); the sterically more demanding **4** promotes 45% conversion to **6b** under the same conditions (entry 3, Table 1). Complete reaction is obtained when the carbene derived from Cy-substituted imidazolium salt **5** serves 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** is complete within one hour (vs 12 h). The findings in entries 5–7 of Table 1, indicating no reaction with 10 mol % NaO*t*-Bu, PPh₃ or PCy₃ in 12 hours, underline the exceptional catalytic activity of the NHC catalysts. A relatively sluggish conjugate addition is observed with triphenylphosphine oxide (entry 8), suggesting an alternative and potentially effective avenue for catalyst development.

The following experiments were carried out to gauge the validity of the proposed scenario regarding NHC activation of **1** (Scheme 1): (1) Theoretical studies (DFT)¹² of a complex arising from association of the carbene derived from **5** and **1** were performed. The partial atomic charges (Scheme 2) indicate that complexation of an NHC with **1** results in polarization of B–B bond and a diminished electrophilic character of both B atoms; the unassociated boron bears a lower positive charge than the one with which the NHC interacts (electron density of the B–B bond is strongly polarized towards 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 B₂(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 ¹¹B NMR spectroscopy; complete disappearance of the signal for **1** is observed within 5 min (22 °C). Consistent with the aforementioned hypothesis, significant upfield shifts are observed for boron atom signals (Scheme 2), with one being more strongly shielded (from δ 30.1 to δ 4.5 and 6.3 for the sp³- and sp²-hybridized B centers, respectively). The same experiment with the less effective carbene derived from **4** leads to the appearance of signals at δ –1.8 and 8.2 (~20% conv in 1 h; additional transformation not observed after 12 h).

One hour and 2.5 mol % of the NHC catalyst is sufficient for >98% conversion of five-, six-, seven- and eight-membered ring enones to **6a–6d** in 89–93% yield (entries 1–4, Table 2). Transformations in entries 5–6 (Table 2) illustrate that addition proceeds readily in cases where the β carbon of the unsaturated carbonyl is sterically congested. Efficient formation of boronates **8–9** 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** are obtained (1.6:1 and 7.1:1, respectively) are likely kinetically controlled, arising from aqueous

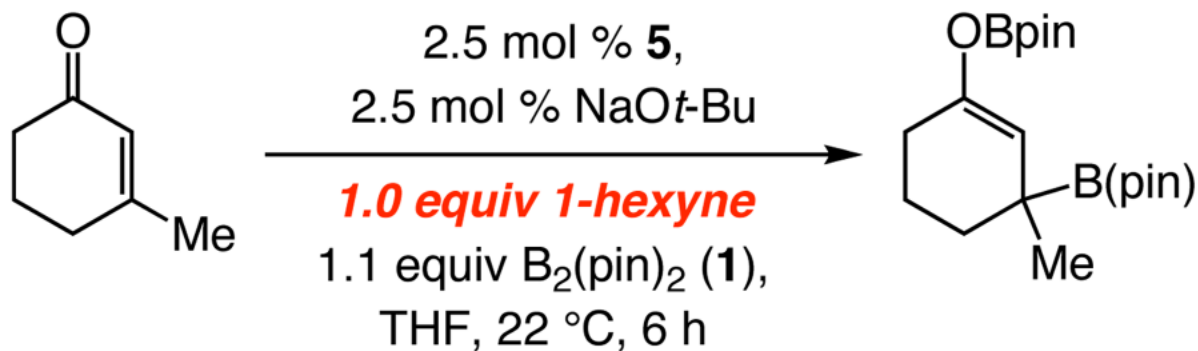
quench of the boron enolates. β -Boryl lactone **10** (entry 9, Table 2) is isolated in 95% yield; higher catalyst loading (5 mol % **5**) and longer time are required due to diminished reactivity of the unsaturated lactone (24 vs 1 h).

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** are 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 gram (4.54 mmol) of β -methylcyclohexenone delivers 0.94 g of **11** after purification (87% yield). Synthesis of **13**, with two additional methyl units, expected to retard the rate of reaction, proceeds to 73% conversion in 12 hours (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), delivering boronate **16** in 78% yield as a single diastereomer (X-ray analysis), represents another process involving a particularly congested β -substituted enone.

NHC-catalyzed transformations can be performed with acyclic substrates (Scheme 4). Synthesis of **18** (92% yield), bearing a B-substituted quaternary carbon, requires 5 mol % **5** at 0 °C¹³ for 6 h. Formation of **19** proceeds in >98% yield via a tetrasubstituted boron-enolate. Catalytic generation of **20**, isolated in 70% yield and 7.2:1 diastereomeric ratio, illustrates that additions with acyclic substrates can proceed with useful stereoselectivity levels. 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 CuOt-Bu and the carbene from **5**, additions proceed as efficiently as with NHC-catalyzed transformations; two examples are shown in Scheme 5. Unlike certain phosphine-catalyzed processes,^{5h} and in contrast to reports regarding NHC–Cu-catalyzed additions,^{5g} MeOH is *not* required for efficient transformation. Additions promoted by a Cu complex, similar to the NHC-catalyzed processes, can furnish the boron-enolate products (vs protonated ketones with MeOH). 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**.

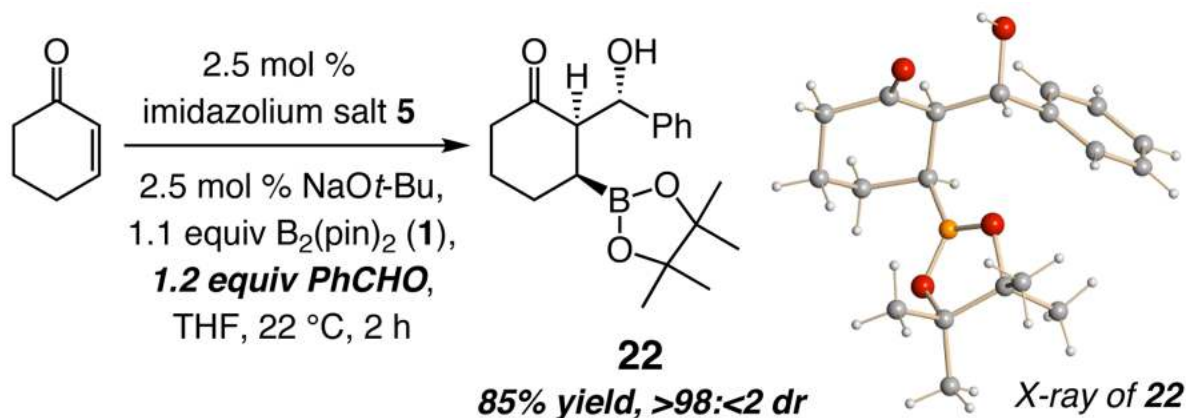
Initial studies indicate that the NHC-catalyzed process can be more functional group tolerant than the Cu-catalyzed variant. Whereas the presence of one equiv of 1-hexyne leads to complete inhibition of the Cu-catalyzed reaction (eq 1),¹⁴ the metal-free transformation proceeds to 85% conversion (81% yield). Association of NHC–Cu–B(pin) with π -Lewis acidic alkyne 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.



with 2.5 mol % CuOt-Bu: <2% conv
without Cu salt: 85% conv (81% yield of ketone)

(1)

The NHC-catalyzed reactions furnish molecules not easily accessible by alternative protocols. Oxidation of **11** delivers the corresponding tertiary alcohol in 94% yield.¹⁵ As illustrated in eq 2, when addition to cyclohexenone is performed in the presence of benzaldehyde, the resulting boron enolate participates 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 reaction occurs from the sterically *more* hindered boron-enolate face (C–C bond formation *syn* to boronate). Aldehyde approach might be directed through carbonyl association¹⁶ with the adjacent C-bound boron. Generation of **22** is unaccompanied by products resulting from benzoin condensation, a Stetter-type process⁷ or aldehyde diboration (<2%).⁵¹ When the transformation in eq 2 is performed with 2.5 mol % CuOt-Bu, in addition to **22** (31%; >98:<2 dr), there is 19% benzaldehyde diboration (and 26% of an unidentified byproduct).^{Error! Bookmark not defined.} A more efficient aldol addition can be achieved if the aldehyde is introduced 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 for the chemoselectivity furnished by the NHC catalyst are in progress.



A C–B bond can be converted to a C–O, C–N¹⁷ or a 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 are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

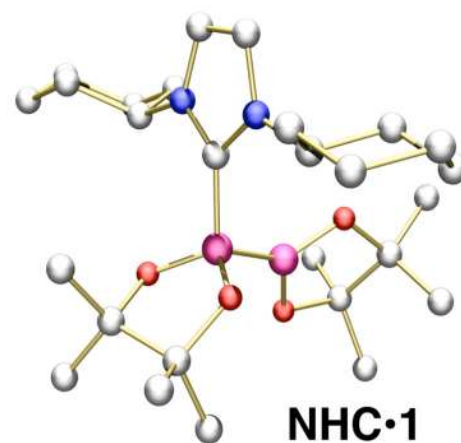
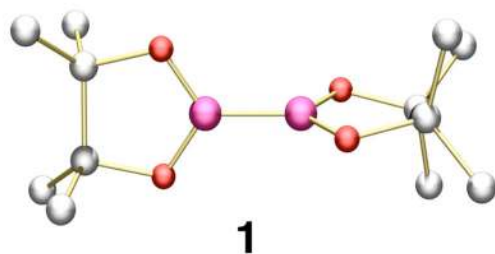
Acknowledgments

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11. Control experiments indicate that the change in the counterion of the imidazolium and imidazolium salts is not responsible for variation in activity.
12. For details of DFT calculations and ¹¹B 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**) is due to formation of unidentified byproducts at 22 °C.
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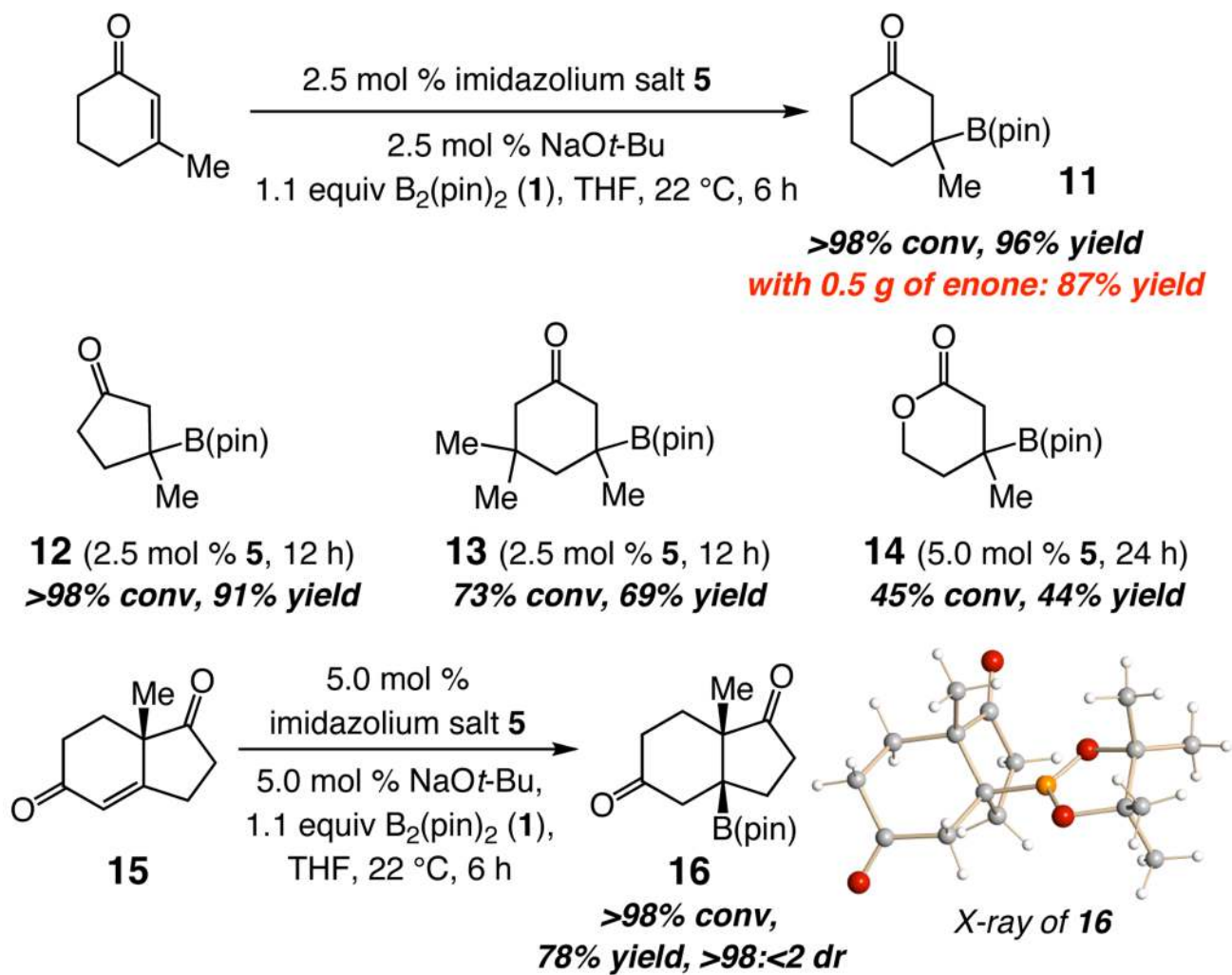


charge on B:	+0.945	+0.898	+0.777
B-B length (Å):	1.703	1.749	
¹¹B NMR (ppm):	30.1	4.5	6.3

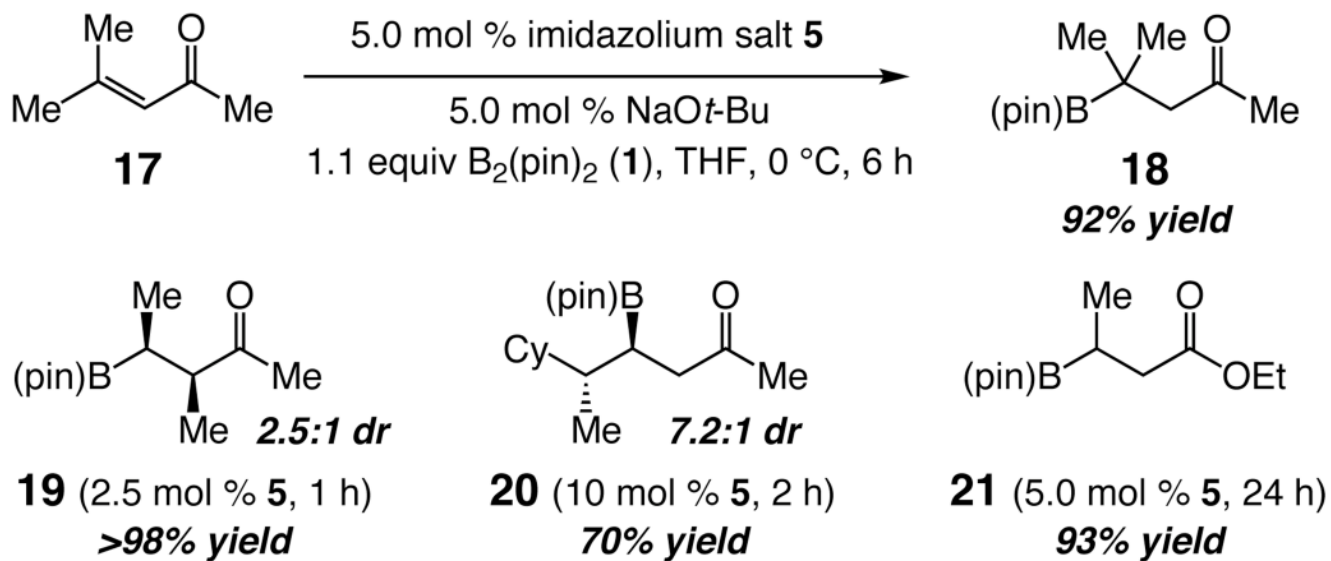
Scheme 2.

DFT Calculations and ¹¹B NMR Studies on **1** and the Derived NHC Complexa

^aDFT calculations were performed on a complex with the carbene derived from imidazolium salt **5**. Spectroscopic studies were performed with the carbene derived from **4-5**. See Supporting Information for additional details.

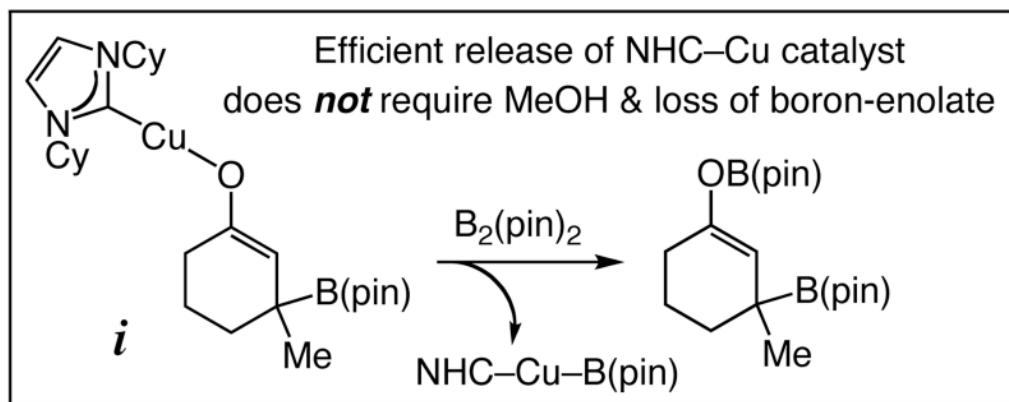
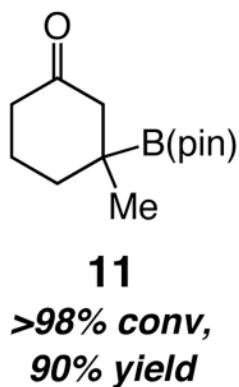
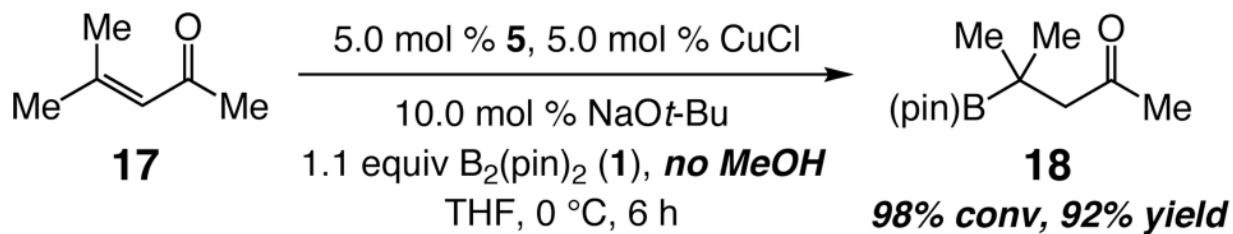


Scheme 3.
 Synthesis of Quaternary B-Substituted Carbons by NHC-Catalyzed Boron Conjugate Additions to Cyclic Enones

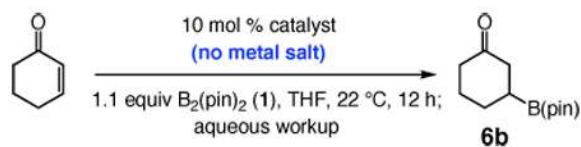
**Scheme 4.**

NHC-Catalyzed Boron Conjugate Additions to Acyclic Enones

^aPerformed at 22 °C (except for **17**→**18**); >98% conv in all cases, except 88% for **20** (conv to the desired product by 400 MHz ¹H NMR). Yields of purified products. dr = diastereomeric ratio.



Scheme 5.
 Comparison of Metal-Free with NHC–Cu-Catalyzed Processes

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

entry	heterocyclic salt or phosphine	base; mol %	conv (%) ^b
1	2	NaOt-Bu; 10	66
2	3	NaOt-Bu; 10	92
3	4	NaOt-Bu; 10	45
4	5	NaOt-Bu; 10	>98
5	none	NaOt-Bu; 10	<2
6	PPh ₃	none	<2
7	PCy ₃	none	<2
8	OPPh ₃	none	50

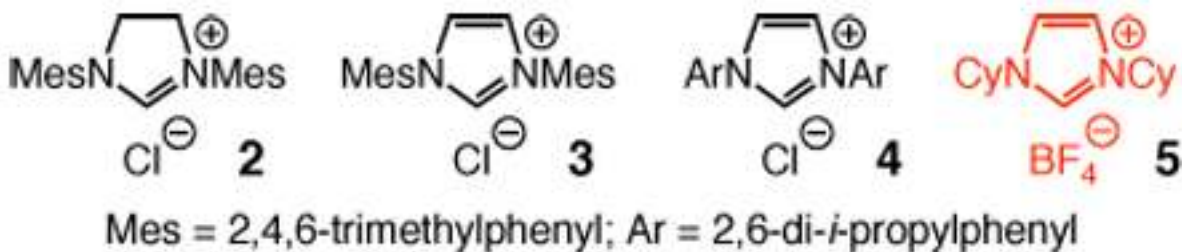
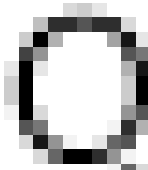
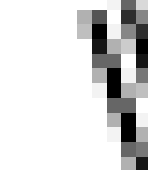
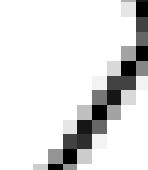
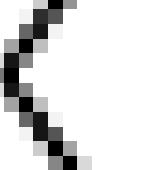
Mes = 2,4,6-trimethylphenyl; Ar = 2,6-di-*i*-propylphenyl^aPerformed under N₂ atm.^bConversion to product determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures.

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

Entry	product	yield
1		n =
2		n =
3		n =
4		n =

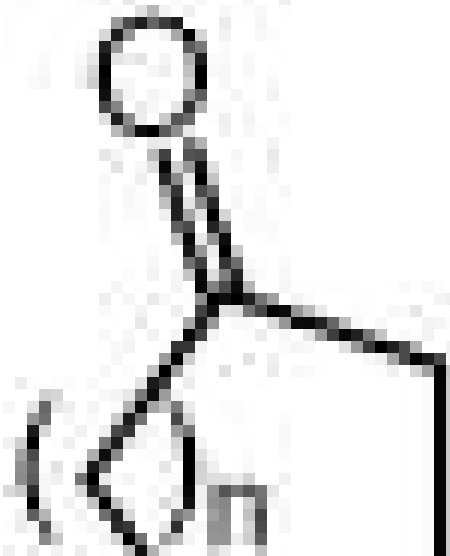
Entry

product

yield

5

n =



6

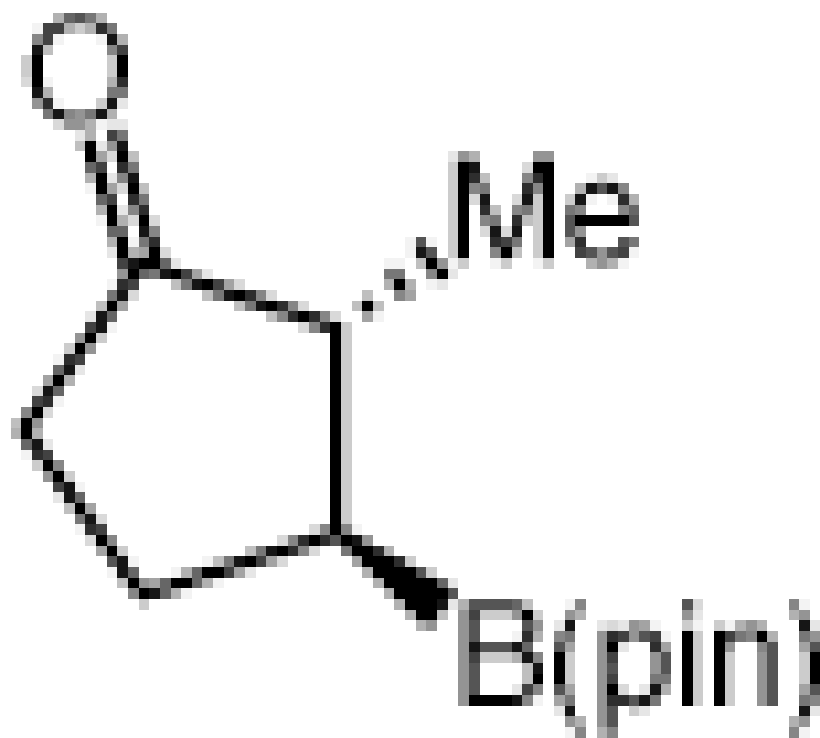
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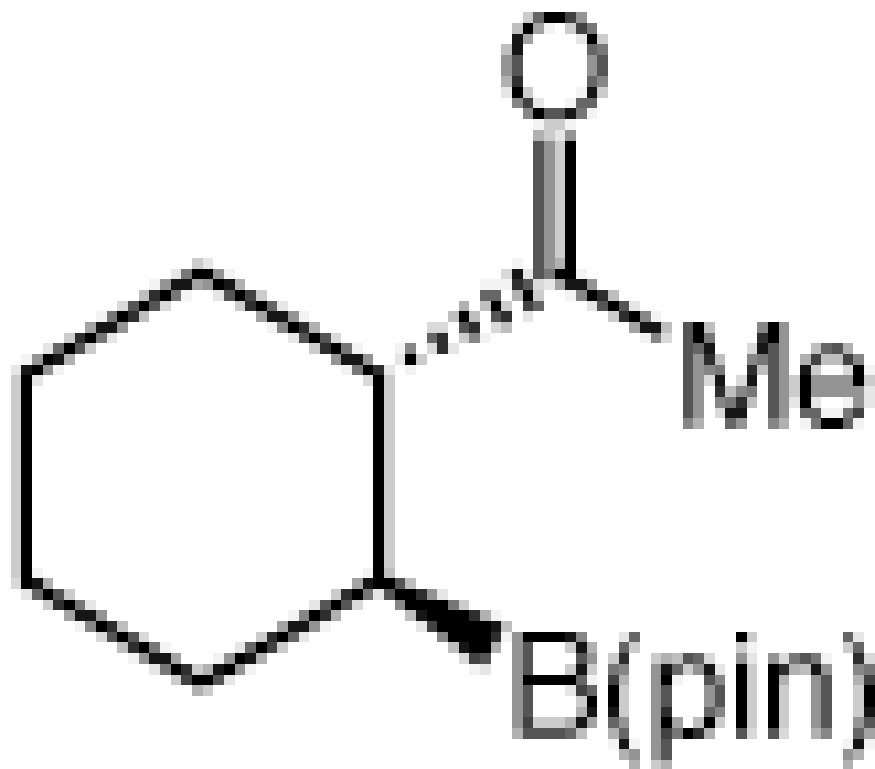
Entry

product

yield

7^c

8

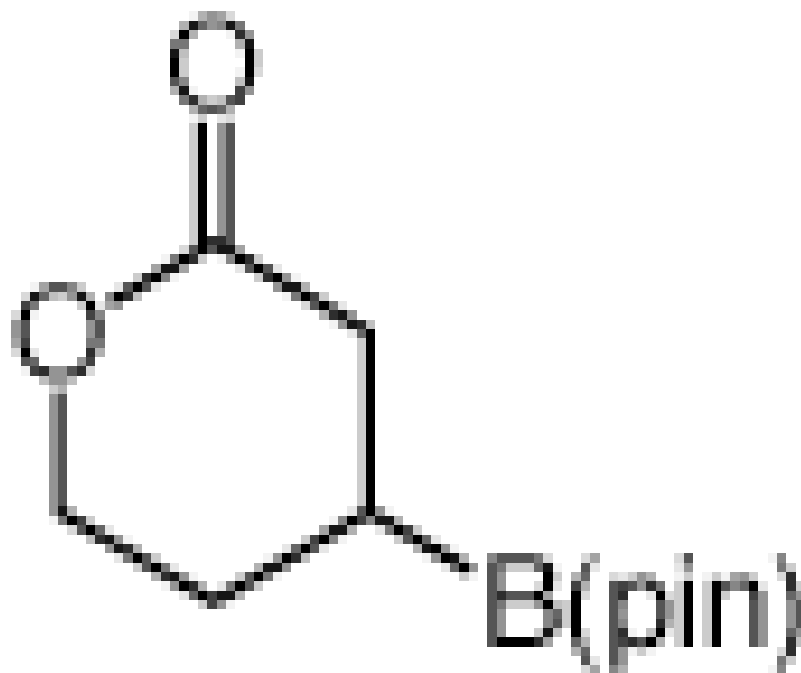
8^d

9

Entry

product

yield

 9^e **10**

^a Performed under N₂ atm with 2.5 mol % **5**, 22 °C, 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**, 24 h.