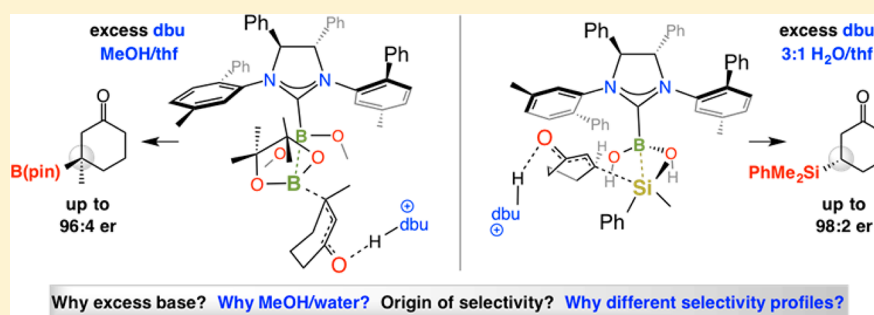


Mechanism of NHC-Catalyzed Conjugate Additions of Diboron and Borosilane Reagents to α,β -Unsaturated Carbonyl Compounds

Hao Wu, Jeannette M. Garcia, Fredrik Haeffner, Suttipol Radomkit, Adil R. Zhugralin, and Amir H. Hoveyda*

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

S Supporting Information



ABSTRACT: Broadly applicable enantioselective C–B and C–Si bond-forming processes catalyzed by an N-heterocyclic carbene (NHC) were recently introduced; these boryl and silyl conjugate addition reactions (BCA and SCA, respectively), which proceed without the need for a transition-metal complex, represent reaction pathways that are distinct from those facilitated by transition-metal-containing species (e.g., Cu, Ni, Pt, Pd, or Rh based). The Lewis-base-catalyzed (NHC) transformations are valuable to chemical synthesis, as they can generate high enantioselectivities and possess unique chemoselectivity profiles. Here, the results of investigations that elucidate the principal features of the NHC-catalyzed BCA and SCA processes are detailed. Spectroscopic evidence is provided illustrating why the presence of excess base and MeOH or H₂O is required for efficient and enantioselective boryl and silyl addition reactions. It is demonstrated that the proton sources influence the efficiency and/or enantioselectivity of NHC-catalyzed enantioselective transformations in several ways. The positive, and at times adverse, impact of water (biphasic conditions) on catalytic enantioselective silyl addition reactions is analyzed. It is shown that a proton source can facilitate nonenantioselective background reactions and NHC decomposition, requiring the catalyst to surpass such complications. Stereochemical models are presented that account for the identity of the observed major enantiomers, providing a rationale for the differences in selectivity profiles of BCA and SCA processes.

INTRODUCTION

The landscape of organic chemistry would be considerably more limited were it not for the multifaceted attributes of organoboron compounds. Also important are Si-containing organic molecules, entities that have significantly impacted the art of chemical synthesis. Accordingly, development of reliable catalytic enantioselective processes that generate C–B^{1–7} or C–Si^{8,9} bonds remains a compelling goal of research in modern chemistry. One area of activity relates to boryl and silyl conjugate addition (BCA and SCA, respectively) reactions that are facilitated by different transition-metal species¹⁰ and, in particular, Cu-based chiral complexes.^{11–13} For example, cyclic β -hydroxyl carbonyl products as well as acyclic or cyclic variants that contain a tertiary alcohol may be prepared by catalytic BCA methods (after C–B bond oxidation); these entities, which cannot be accessed through catalytic enantioselective aldol addition or related approaches,¹⁴ facilitate synthesis of a variety of biologically active molecules.

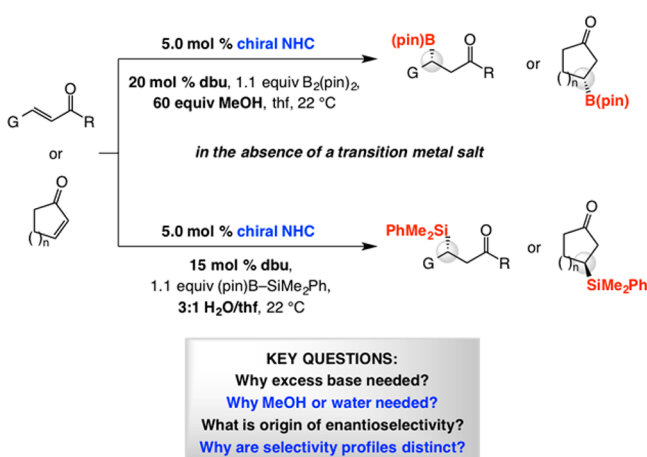
It was reported in 2009 that achiral N-heterocyclic carbenes¹⁵ (NHCs) can catalyze the addition of (pinacolato)-

diboron to α,β -unsaturated carbonyl compounds (Scheme 1).^{16,17} Enantioselective variants¹⁸ including those promoted by chiral phosphines¹⁹ and transformations involving a borosilyl reagent (to give a C–Si bond)²⁰ were subsequently introduced. Phosphine-²¹ and NHC-catalyzed boryl additions to tosylimines and yrones soon followed.²² Activation of B–B bonds by an external²³ and then a neighboring Lewis-basic alkoxide²⁴ were later exploited to effect diboron additions to unactivated alkenes, and related transformations involving propargyl alcohols were outlined.²⁵ Metal alkoxides have been shown to catalyze reactions of silylboren reagents with organohalide substrates, affording the corresponding silanes.²⁶ In the significant majority of Lewis-base-catalyzed boryl and silyl additions, the presence of a proton source (typically MeOH) is necessary; in many instances, excess base is needed for optimal efficiency and/or stereoselectivity. Nonetheless, a rigorous mechanistic basis for the latter requirements is lacking.

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Scheme 1. Catalytic Processes and the Key Mechanistic Questions

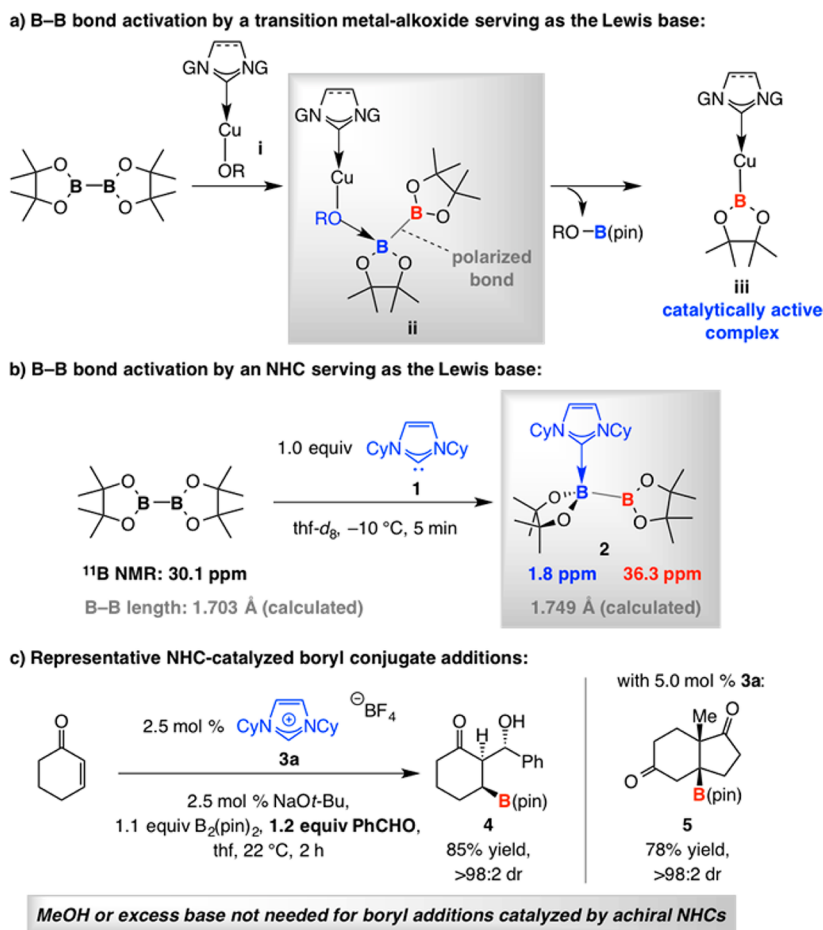


Boryl and silyl conjugate additions that are facilitated by transition-metal-free Lewis-base catalysts mark a new chapter in organoboron and organosilicon chemistries; these are mechanistically distinct reactions that offer complementary functional group compatibility profiles (vs those promoted by organometallic species). However, in addition to the aforementioned issues vis-à-vis the need for a proton source and excess base, a

number of questions regarding the details of the catalytic cycles for C–B and C–Si bond formation (Scheme 1), including those that are promoted by NHCs, remain unaddressed.²⁷ An appreciation of such attributes will be crucial to the success of future endeavors regarding catalyst and method development in this emerging area of research. Herein, we detail the results of studies performed aimed at finding a plausible answer for the above issues and various other questions relating to the inner workings of NHC-catalyzed boryl and silyl conjugate additions.

■ BACKGROUND

The viability of Lewis-base-catalyzed BCA is manifested in the manner with which initial activation of a B–B bond might occur by the oxygen atom of an NHC– or phosphine–Cu–OR complex (i → iii via ii, Scheme 2a).²⁸ In addition to increasing Cu Lewis acidity, according to the well-established tenets of Lewis-base enhancement of Lewis acidity,²⁹ the Lewis base (e.g., an NHC) elevates the nucleophilicity of the alkoxide ligand, facilitating the formation of ii, which is the principal player in a Cu–boryl addition. The question would then be whether efficient activation can be achieved directly by an organic Lewis-basic molecule. This notion finds support in X-ray crystallographic investigations showing that adducts derived from association of bis(catecholato)diboron and bis-(thiocatecholato)diboron with 4-methylpyridine and dimethyl-

Scheme 2. Discovery of NHC-Catalyzed Boryl Conjugate Addition^a

^aG = alkyl or aryl group; B(pin) = (pinacolato)boron.

phenylphosphine, respectively, cause perceptible weakening of B–B bonds.^{30,31}

We initially established that NHC·B₂(pin)₂ complexes can be readily generated. Spectroscopic analysis pointed to the formation of a Lewis-base-bound B atom (cf. **2** derived from NHC **1**, Scheme 2b), and calculations indicated B–B bond lengthening. The validity of the originally suggested NHC–diboron complex **2** was afterward substantiated by the notable X-ray crystallographic studies of Marder and co-workers.³²

While formation of a Lewis-base–diboron complex does not guarantee a catalytic process, we soon discovered that NHCs do promote BCA reactions. The multicomponent transformation in Scheme 2c, affording **4** as a single stereoisomer, is illustrative;^{16a} this reaction underscores the functional group compatibility of the NHC-catalyzed processes versus those promoted by Cu-based complexes (vs 31% yield with NHC–Cu species due to boryl addition to the aldehyde). We found that phosphines are catalytically less active,^{18a} and alkoxides (e.g., NaOt-Bu) proved to be less capable promoters (e.g., compared to i).^{16a}

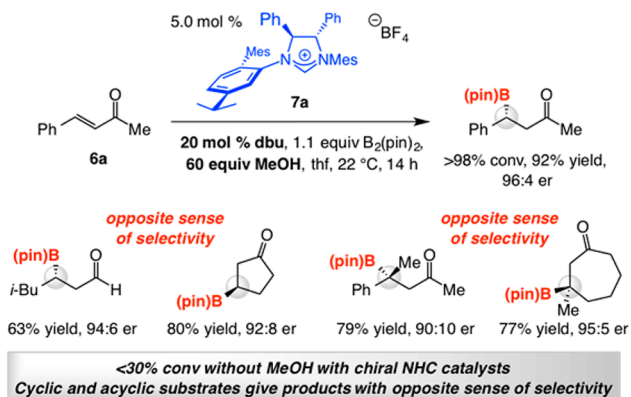
Enantioselective boryl additions to α,β -unsaturated carbonyl compounds (acyclic and cyclic enones, esters, Weinreb amides, or enals) can be performed with chiral NHC catalysts and 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) as the base (Scheme 3a).^{18a,33} The high er values are mechanistically revealing: they clearly indicate that an NHC-bound chiral complex is responsible for the C–B bond-forming process. Further, enantioselective addition to the more challenging trisubstituted enones is feasible; this is exemplified by the transformation promoted by the enantiomerically pure NHC derived from **7b** (Scheme 3b).^{18b} The BCA en route to natural product crassinervic acid proceeded readily despite the presence of a phenol and an aryl aldehyde, moieties that greatly diminish the activity of phosphine- or NHC–Cu complexes.³⁴ NHC-catalyzed enantioselective BCA reactions afford products that cannot be easily prepared otherwise in high enantioselectivity (e.g., acetate aldol products that contain a Weinreb amide³³ and ketone aldol products such as **8**^{18b} in Scheme 3b) and are practical and robust; contrary to reactions with Cu complexes, use of a drybox is not needed.

The above progress raises several fundamental questions. (1) Why is it that, unlike additions promoted by achiral NHC catalysts, the presence of MeOH is required for high conversion in enantioselective BCA reactions? (2) Why is excess base (dbu), beyond what is necessary for NHC formation, generally needed for achieving high yields of the desired products? (3) If the transferred boryl group is not the one that is associated with the NHC catalyst then precisely how is a high degree of stereochemical induction observed with the Lewis-base promoter being at a relatively remote site? (4) Why is the sense of addition to the acyclic substrates opposite to that of the cyclic enones (cf. Scheme 3a)?

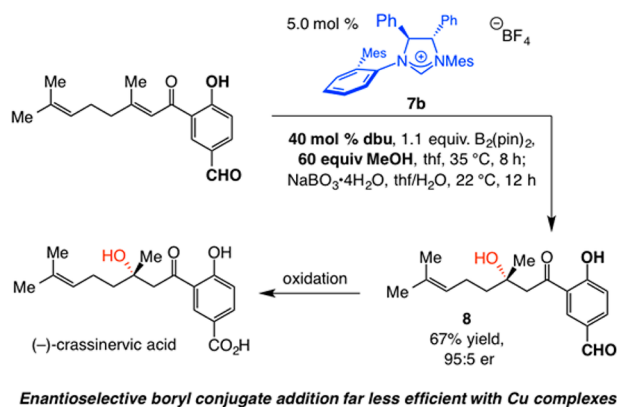
NHC-catalyzed silyl conjugate addition (SCA) with dimethylphenylsilylpinacolboron [PhMe₂Si–B(pin); Scheme 4]³⁵ further broadens the scope of the approach and, on several fronts, is distinct from the related boryl additions. Unlike the BCA processes, regardless of whether an achiral or a chiral NHC is involved, there is minimal conversion without a protic additive.²⁰ Not only is a proton source needed in SCA reactions, water is the superior choice (vs MeOH with BCA; cf. Scheme 4). Similar to the boryl additions, excess dbu enhances efficiency, but in further contrast to BCA processes, the same sense of absolute stereochemistry is generated in the C–Si

Scheme 3. Enantioselective NHC-Catalyzed Boryl Conjugate Additions^a

a) Higher efficiency in the presence of excess MeOH when chiral NHC used:



b) Representative application to natural product synthesis (see also ref 33):



Enantioselective boryl conjugate addition far less efficient with Cu complexes

^aMes = 2,4,6-Me₃-C₆H₂. The er values for some of the β -boryl ketones in Scheme 3a correspond to reactions with NHC catalysts that are slight structural variants of **7a**; see ref 18 for details. The stereoselectivity profiles, however, are as shown.

bond-forming reactions regardless of whether cyclic or linear α,β -unsaturated carbonyl compounds are employed.

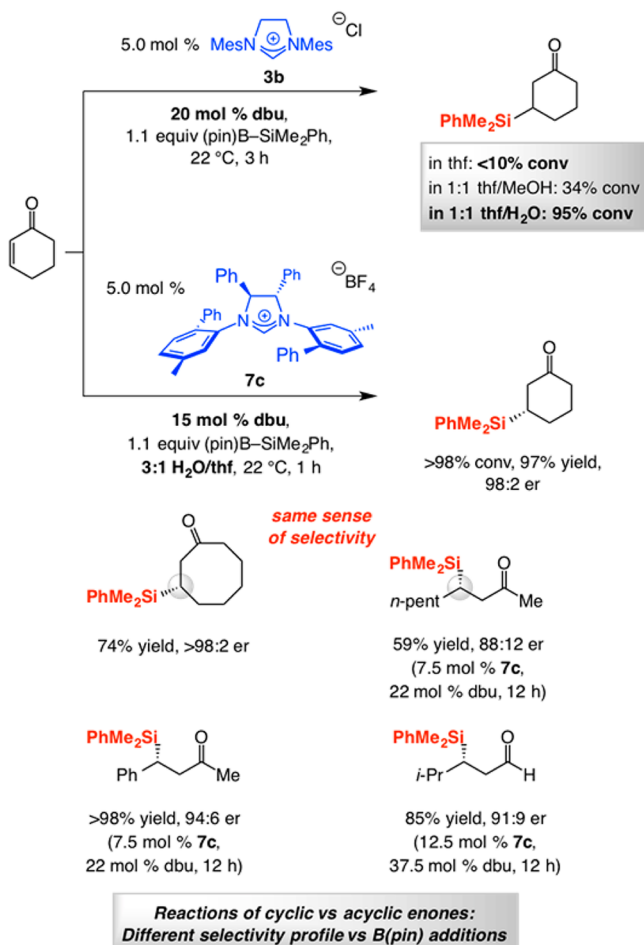
RESULTS AND DISCUSSION

1. Probing the Possibility of a Radical-Based Mechanism.

We began by looking into whether the NHC-catalyzed BCA or SCA reactions involve odd-electron intermediates, a scenario that may find support in the pioneering investigations of Curran, Malacria, and co-workers. The latter researchers provided convincing evidence that NHC–borane complexes are capable of facilitating a C–H and C–C bond-forming transformations by radical-based routes.³⁶ We judged the possibility of a radical pathway to be especially relevant because the calculated homolytic bond dissociation energy (BDE) for B–B bonds in B₂(pin)₂ and NHC·B₂(pin)₂ (NHC = 1,3-dimethylimidazol-2-ylidene) is 104 and 63 kcal/mol, respectively [at unrestricted B97D/6-31+G(d,p) level of theory].³⁷ The aforementioned values are lower than those calculated^{36a} for BDE of B–H bonds in NHC–BH₃ complexes (~74–80 kcal/mol), which are within the range measured for established radical precursors (e.g., 74 kcal/mol for *n*-Bu₃Sn–H).³⁸

Subjection of 3-cyclopropyl-cyclohexenone **9** to the BCA conditions afforded β -boryl ketone **10** in 85% yield without any detectable amounts of **11** (Scheme 5a), which would be formed

Scheme 4. NHC-Catalyzed Silyl Conjugate Addition

Higher efficiency in the presence of H₂O when chiral NHC used:

if a carbon radical were generated at the carbon β to the carbonyl group. A similar observation was made with the cyclopropyl moiety positioned at the site adjacent to the C=O bond: **12** was isolated in 67% yield as a single stereoisomer without any cyclopropyl cleavage. To ascertain that a radical mechanism is not in effect, we examined the reactions of the derived diphenylcyclopropane; here, the corresponding odd-electron species would undergo cleavage at a rate that is above the rate of diffusion-controlled processes.³⁹ We did not detect any **13**, likely because of steric hindrance, but did obtain β -boryl ketone **14** in 45% yield. Again, the product resulting from rupture of the cyclopropyl moiety was not observed. The identity of the BCA product was further substantiated by determination of the crystal structure of **15**, generated from reaction of **14** with atmospheric oxygen (Scheme 5a). NHC-catalyzed C-Si bond formation does not seem to involve odd-electron intermediates either, as the conversion of **16** to β -silyl ketone **17** and complete absence of **18** indicates (Scheme 5b).

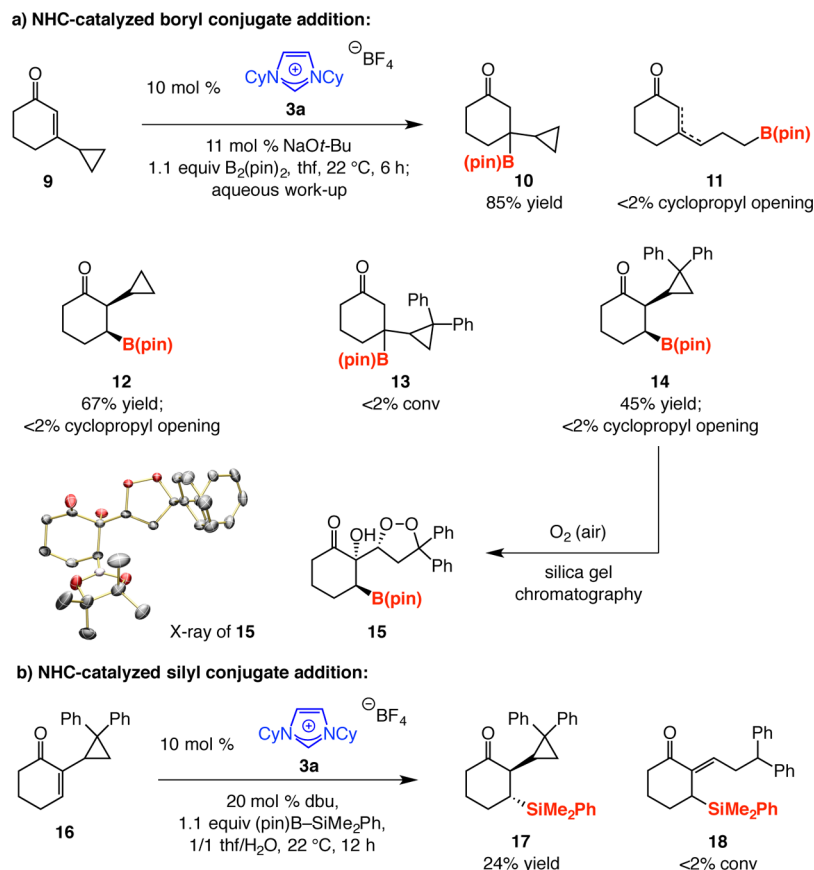
2. Influence of Excess Base and MeOH on Boryl Conjugate Additions. We then turned to addressing the question of why BCA reactions with achiral NHCs can be performed without MeOH (e.g., with **3a** in Scheme 2c), whereas when the corresponding chiral catalysts are used, an excess amount of a proton source is required (cf. Scheme 3a). When we made an inquiry regarding the possible association of the chiral NHC derived from imidazolium salt **7c** with B₂(pin)₂ in the absence of MeOH, we did not detect any

change in the ¹¹B NMR spectrum (6.0 h, 25 °C; Scheme 6); this is in contrast to when achiral NHC **1** was employed, where there was >98% conversion within just 5 min. In the case of the chiral NHC, only after 30 equiv of MeOH and 6 equiv of dbu were introduced were we able to detect 20–30% of a new signal at 5.1 ppm (¹¹B NMR), likely arising from NHC-diboron complex **19a** and/or **19b** (Scheme 6). (As will be detailed below, the aforementioned signal is not due to the derived methoxy complex.)

Concurrent availability of base and MeOH likely causes one of the pinacolato units of B₂(pin)₂ to rupture, producing a more accessible boron center (Scheme 7a).⁴² With MeOH, but in the absence of base, B₂(pin)₂ remains unaltered (Scheme 7b). The structurally modified and sterically less hindered boron site can readily associate with the more sizable chiral NHC (e.g., **7a-c**). Thus, with the smaller achiral NHC, complex formation and B-B bond activation do not require a priori cleavage of the pinacolato ring. Utilization of less congested diboron derivatives [vs B(pin)] to boost reactivity is an established strategy in organoboron chemistry;⁴⁰ in situ conversion of a B(pin) unit to a more accessible derivative was recently illustrated.⁴¹ The B(pin) moiety within the BCA product is more immune to reaction with MeOH probably because of the shorter B-C bond (1.5 vs 1.7 Å for B-B bond) as well as the presence of a neighboring sp³-hybridized C (vs an sp²-hybridized B).

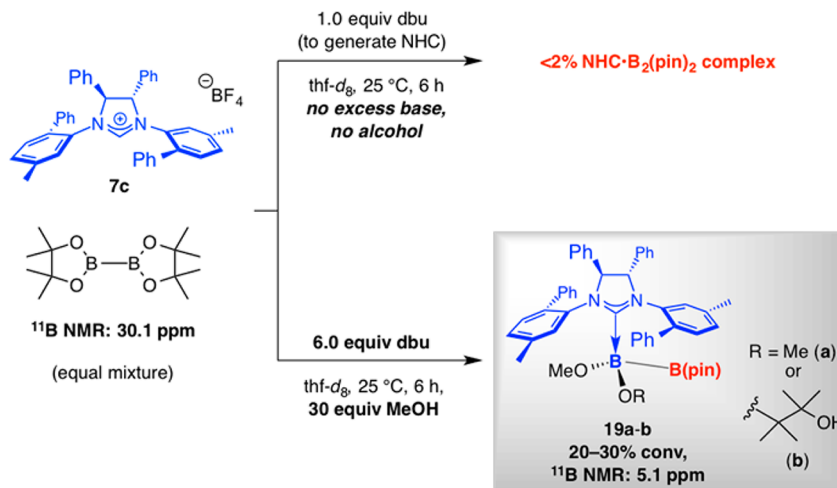
Spectroscopic analysis provided additional information about the role of excess base and alcohol. Reaction of B₂(pin)₂ with dbu and MeOH generated free pinacol, as indicated by analysis of ¹H NMR spectra of the unpurified mixtures,⁴² and resulted in a peak at 7.5 ppm in the ¹¹B NMR spectrum, a signal that may be attributed to the methoxy-bound diboron species **23a-b** (peak a, Figure 1); the intensity of the signal increased with time. Additionally, two broad peaks appeared between 25–35 ppm (b and c, Figure 1). The more upfield peak b may be attributed to the B atom undergoing hybridization change due to the rapid equilibrium between B₂(pin)₂ and **20**. As the sample was cooled to -10 °C, signal b shifted upfield toward ~10 ppm, indicating an increasing preference for the formation of borate **20** (Figure 1). The large and broad peak c almost certainly corresponds to the sp²-hybridized B atoms of B₂(pin)₂ and other species such as **20**, **22a-b**, and **23a-b**. The most upfield small signal (marked by a blue box), which can only be detected at ≤10 °C, is likely derived from association of the more weakly Lewis-basic and larger dbu (vs methoxide) with the diboron species (**24a-b**); thus, the more weakly held complex is more readily dissociated. As will be described, the amount of this latter entity increases in the presence of a highly Lewis-basic NHC. Methoxide activation of a B-B bond via **20** or **23a-b** points to the possibility of methoxide-catalyzed boryl addition.^{23,24} Accordingly, treatment of enone **6a** (Scheme 3) with 1.1 equiv of B₂(pin)₂, 20 mol % of dbu, and 60 equiv of MeOH generated ~20% of the corresponding *rac*- β -boryl ketone after 14 h (22 °C). The chiral NHC catalyst must overcome this latter competitive background process since high enantioselectivity can be attained.

3. Details of the Formation of Chiral NHC-diboron Complex. Spectroscopic studies with samples that contain enantiomerically pure imidazolium salt **7c** shed light on the interaction of various Lewis bases with in situ-generated sterically accessible/more reactive diboron species (Figure 2). Within 30 min at 25 °C, a peak at 7.5 ppm (c) and another at 6.5 ppm (b) could be detected. After 2 h, the two signals grew

Scheme 5. Probing the Possibility of a Radical-Based Mechanism^a

^aCatalytic BCA reactions leading to **12** and **14** were performed with 20 mol % **3a** and 22 mol % NaOtBu. See the [Supporting Information](#) for details.

Scheme 6. Probing the Effect of Base and MeOH on B–B Bond Activation

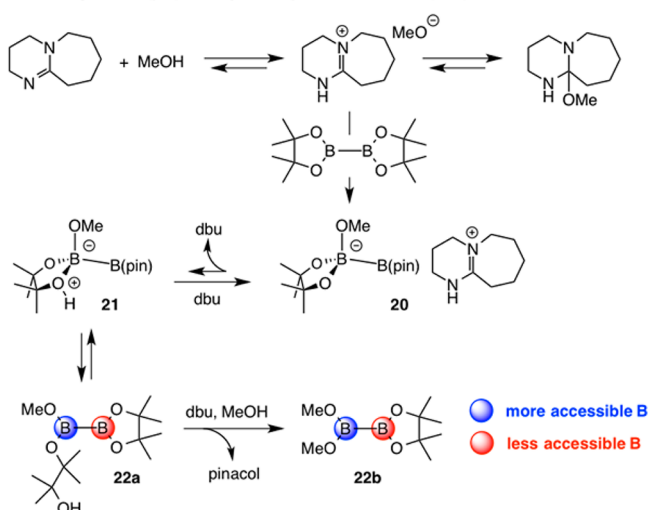
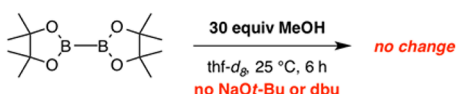


in strength and another upfield singlet emerged at 5.0 ppm (a). In 6 h, the intensity of the three peaks (a–c) increased extensively. The chemical shift at 7.5 ppm (c) corresponds to the methoxy-bound B atoms of diboron species **23a–b**, as established by the experiments depicted in [Figure 1](#), and the signal at 5.0 ppm arises from the NHC·diboron complexes **19a–b**, based on the spectroscopic observations illustrated in [Scheme 6](#). The signal at 6.5 ppm (b, [Figure 2](#)) is attributable to dbu-diboron complexes **24a–b**; as before, though this particular peak could not be detected at 25 °C in the absence

of the NHC (cf. [Figure 1](#)), it could be seen by cooling the sample to below 10 °C (cf. [Figure 1](#)). The signal corresponding to **24a–b** also appears as a much smaller peak in the spectra in [Figure 1](#) recorded at ≤ 10 °C; this difference in signal intensity is to be expected because the sterically less demanding methoxide can more effectively compete with dbu (vs chiral NHC). The increased abundance of **24a–b** in the presence of NHC suggests that the Lewis base accelerates B(pin) cleavage,⁴³ likely in the same manner as illustrated in [Scheme 7a](#) for a methoxide ion, to provide a higher concentration of the

Scheme 7. Susceptibility of B₂(pin)₂ to Alcohol and Base

a. Cleavage of a B(pin) moiety in the presence of base (dbu) and MeOH:

b. B₂(pin)₂ does not react with MeOH in the absence of a base:

dbu-diboron complex. The broad signals d–f in Figure 2 have been already analyzed (cf. signals b and c, Figure 1).

Variable-temperature NMR experiments showed that if the sample is allowed to warm from –10 to 40 °C (Figure 3), a

Lewis base (methoxy, dbu, or NHC) may begin to dissociate from its diboron host. Accordingly, signals a and b disappeared and peak d became visible at 40 °C, pointing to a shift in equilibrium in favor of sp²-hybridized B atoms. Methoxide complexes 23a–b (signal c) proved to be more resistant toward dissociation (vs 19a–b or 24a–b), as the signal at 7.5 ppm persisted at elevated temperatures. Such stability profiles may be partly due to the smaller size of a methoxide (less steric relief upon dissociation), which is congruent with the faster appearance of the corresponding peak versus those that relate to NHC- (a) or dbu-based diboron complexes (b) (cf. Figure 2 at 0.5 and 2 h). As mentioned vis-à-vis peak b in Figure 1 for MeO·diboron species 20, higher temperatures led to conversion of Lewis-base-diboron complexes to the free diboron species that contain only sp²-hybridized B atoms; this is evidenced by the downfield movement of signal e in Figure 3 when the sample was allowed to warm from –10 to 40 °C.

The above spectroscopic studies show that electronic variations extend beyond changes in the chemical shift of the B(pin) group that is directly bound to a Lewis base. Spectral data point to increased Lewis acidity at the unbound boron site (sp² hybridized). Thus, there is a chemical shift change from the B atoms of B₂(pin)₂ (30.1 ppm in ¹¹B NMR) to the more downfield signal for the uncoordinated sp²-hybridized B atom of the NHC-diboron complex derived from carbene 1a (36.3 ppm; cf. Scheme 2b). The electronic influence of Lewis-base activation is further manifested by the most downfield signals in Figure 3 (a and b, red); these peaks may be attributed to the sp²-hybridized B atoms of NHC-, methoxide-, and dbu-bound

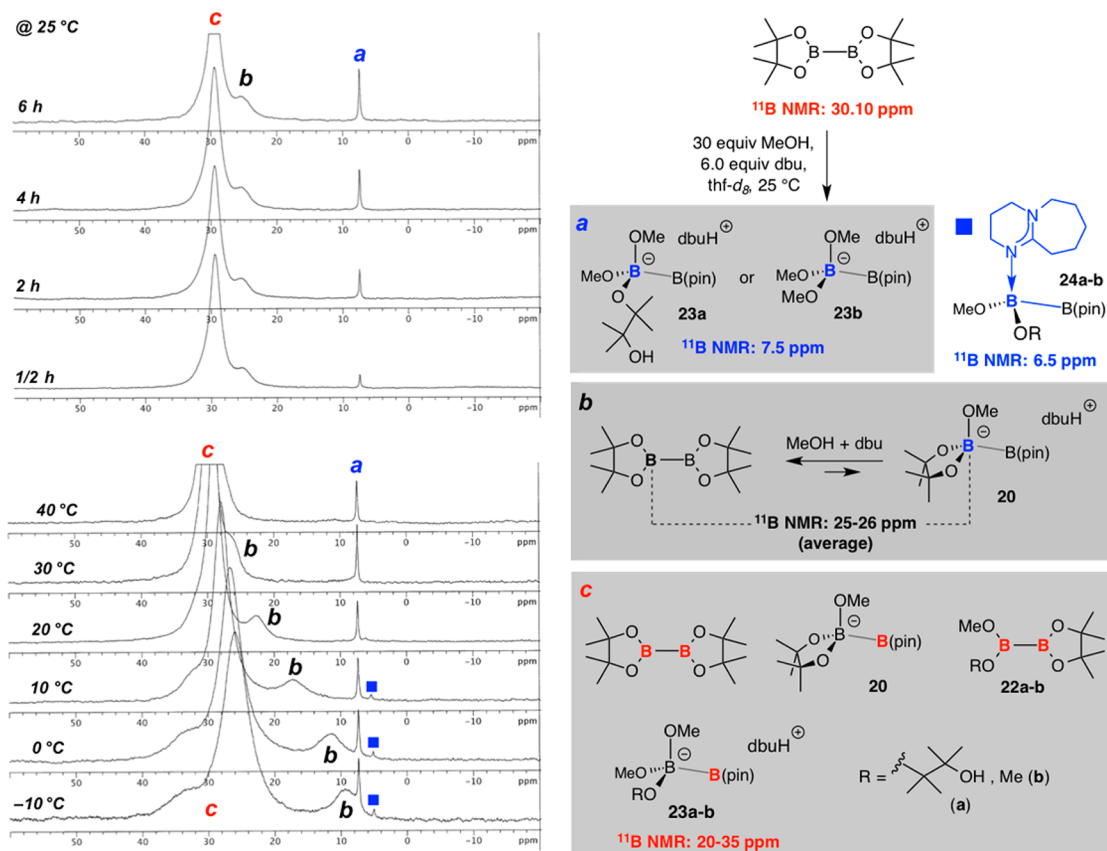


Figure 1. Effect of dbu on loss of pinacol and association of Lewis-basic groups with the more exposed B center.

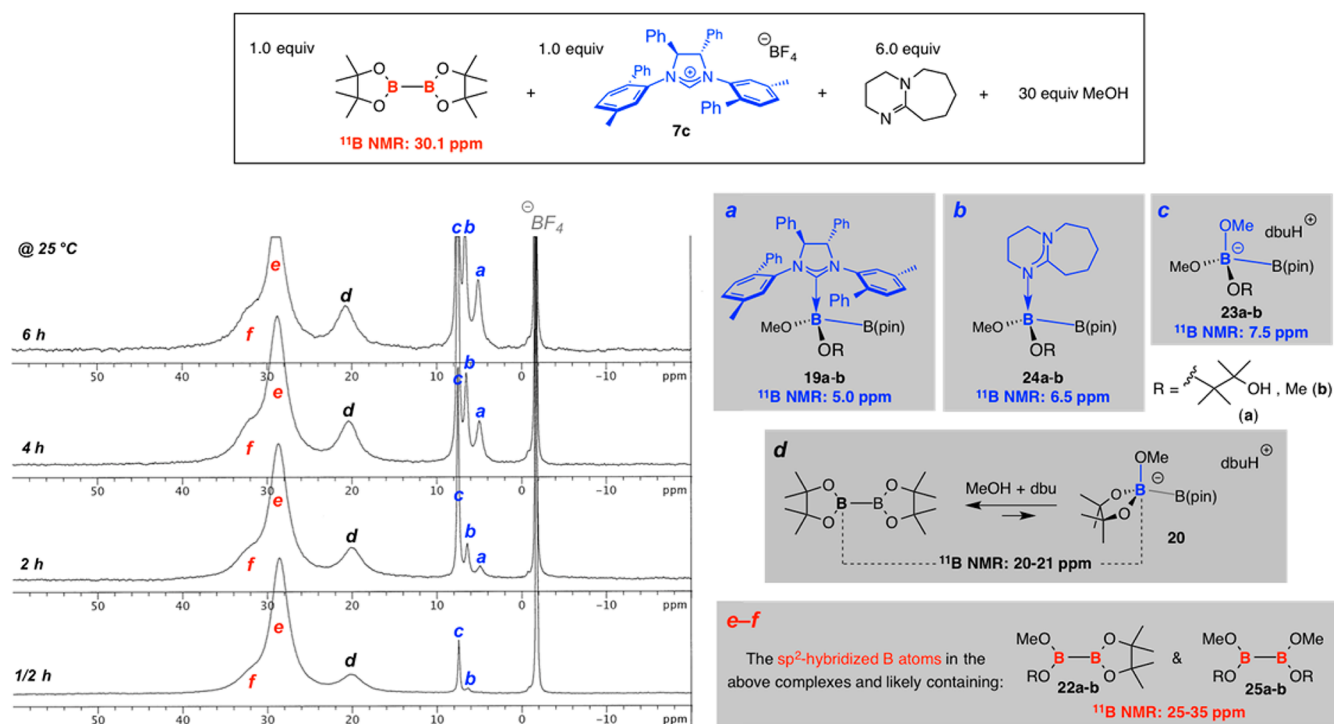


Figure 2. ^{11}B NMR spectra for reaction of $\text{B}_2(\text{pin})_2$ with 100 mol % of **7c** with 6.0 equiv of **dbu** and 30 equiv of **MeOH** (thf-d_8 , 25 °C).

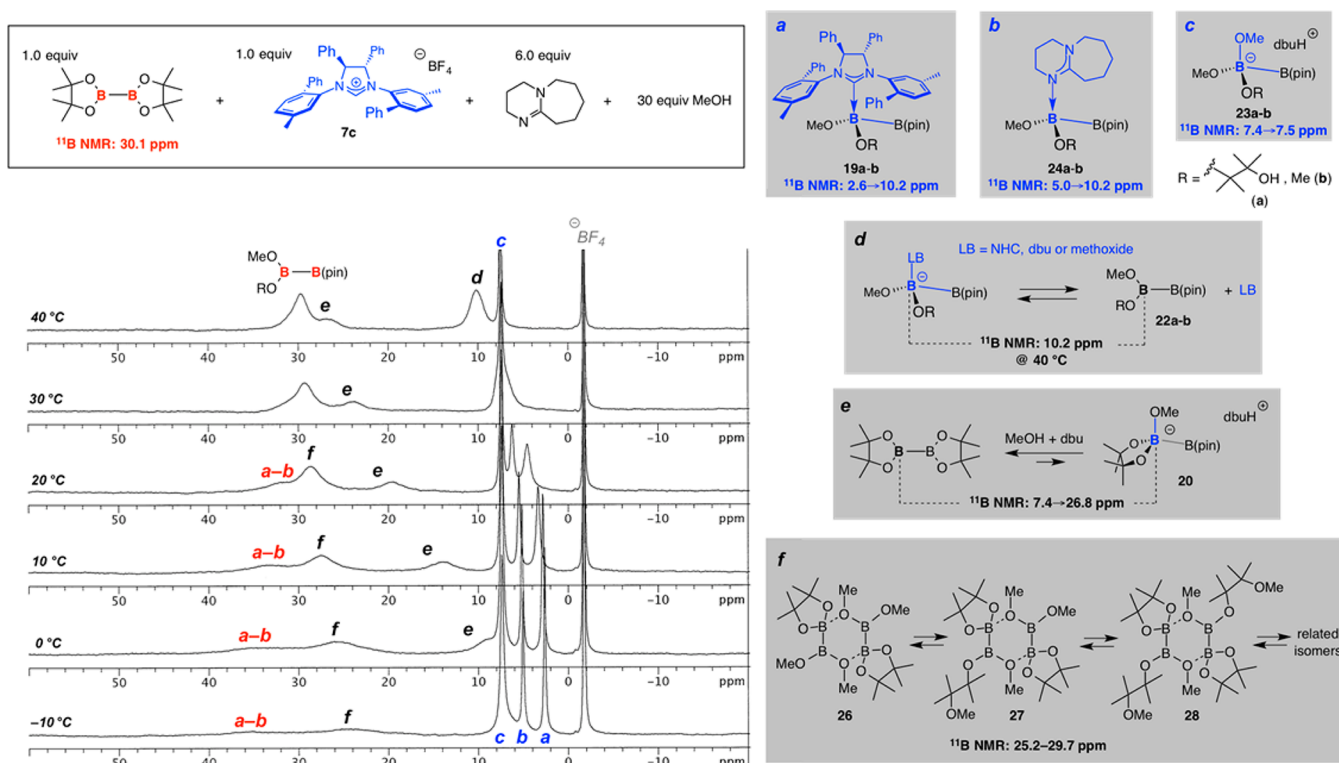
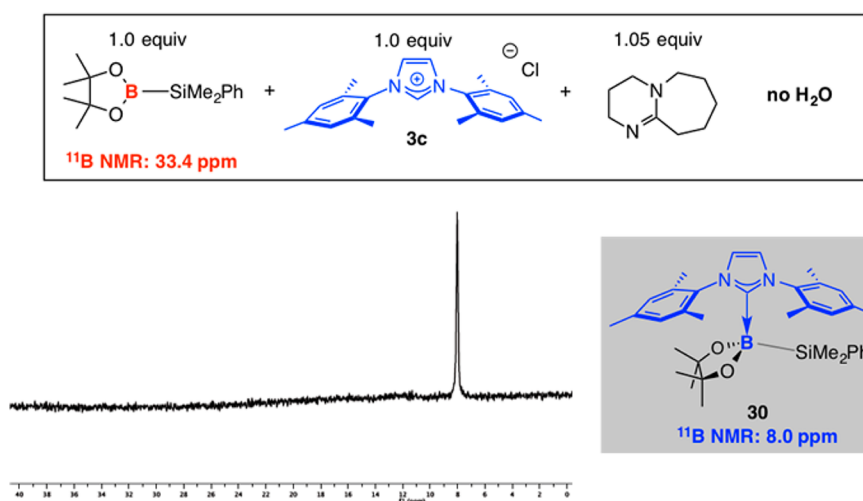
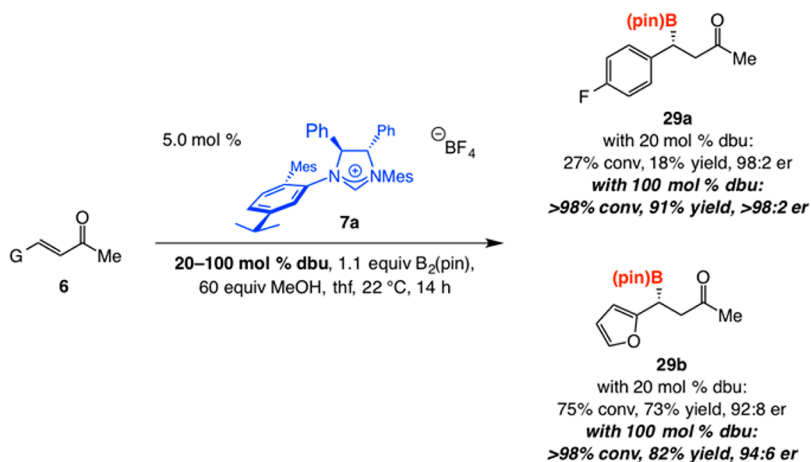


Figure 3. ^{11}B NMR spectra at different temperatures for reaction of $\text{B}_2(\text{pin})_2$, 100 mol % **7c** with 6.0 equiv of **dbu**, and 30 equiv of **MeOH** after 6 h (thf-d_8).

complexes **19**, **23**, and **24**. These findings are again consistent with the principles of Lewis-base activation of Lewis acids,^{29,43} indicating that alteration of electron density extends to the neighboring $\text{B}(\text{pin})$ unit as well (net increase at the more electronegative O atoms). The increase in Lewis acidity of the unbound boron atom, caused by association of a Lewis base to

the diboron compound, should not be expected to have an adverse effect on the rate of a BCA process, as it is the electron density of the more polarized B–B bond that likely kick-starts that C–B bond-forming process. It might be suggested that the enhancement in Lewis acidity of the uncoordinated boron might cause it to associate with a Lewis base as well. However,

Scheme 8. Influence of the Amount of Base on NHC-Catalyzed Boryl Additions

Figure 4. ^{11}B NMR spectrum for reaction of $(\text{pin})\text{B}-\text{SiMe}_2\text{Ph}$ with an achiral NHC in the presence of only dbu (thf- d_8 , 25 °C).

DFT calculations clearly indicate³⁷ that a doubly coordinated species would be substantially higher in energy probably as a result of steric congestion (severe eclipsing interactions) caused by vicinal fully substituted B atoms. Furthermore, the resulting B–B bond would be less polarized, and the activation barrier toward addition to an enone would be more energetically demanding.

The above studies provide valuable clues regarding optimization of the experimental conditions, namely, that increasing the amount of Lewis base (e.g., dbu) should lead to faster cleavage of a B(pin) unit of $\text{B}_2(\text{pin})_2$. NHC-diboron complex formation would then be facilitated, and B–B bond activation and an increase in the efficiency of the BCA process would ensue. Such expectations are supported by the representative data in Scheme 8. Whereas with 20 mol % of dbu there was 27% and 75% conversion to **29a** and **29b**, respectively, after 14 h (22 °C) with 100 mol % of base the BCA proceeded to full conversion. This enhancement in enantioselectivity suggests that, at lower concentration of dbu and with less efficient chiral NHC binding, there is likely residual catalysis by an achiral Lewis base (most likely the methoxide ion).^{23,24}

4. Influence of Excess Base and H_2O on NHC-Catalyzed Silyl Conjugate Additions. There are several key differences between NHC-catalyzed BCA and SCA

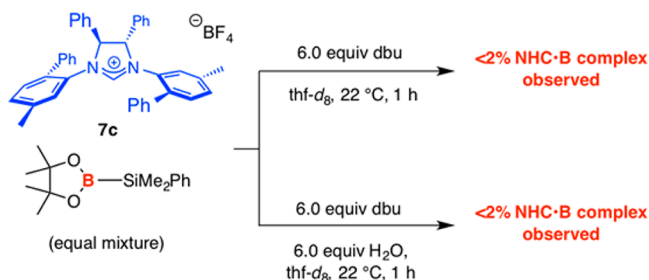
reactions. Unlike boryl additions, there is no C–Si bond formation without a protic additive despite involvement of a smaller achiral NHC. Moreover, SCA reactions are less efficient when carried out in the presence of MeOH; transformations proceed readily when conducted in a water/thf mixture that is turned emulsive due to the presence of the borosilane reagent. It is therefore possible that activation of a more sterically demanding borosilane [vs $\text{B}_2(\text{pin})_2$] requires a more accessible B(OH)₂ unit and/or a medium that can better accommodate the formation of polar intermediates and transition states.

Inefficient generation of a Lewis-base-borosilane complex is not the reason why SCA processes are slow when they are performed in the absence of a proton source. Treatment of imidazolium salt **3c** with $(\text{pin})\text{B}-\text{SiMe}_2\text{Ph}$ at 25 °C with 1.05 equiv of dbu (without any H_2O) led to complete loss of the signal for the borosilane reagent (33.4 ppm, ^{11}B NMR spectrum) in 5 min (Figure 4); this time, a broad peak appeared at 8.0 ppm that may be attributed to NHC-borosilane complex **30**.⁴⁴ It is therefore more likely that because of the bulkier dimethylphenylsilyl moiety [vs B(pin) of $\text{B}_2(\text{pin})_2$], efficient association of a species such as **30** with an enone substrate requires the conversion of the pinacolato group to a B(OH)₂ unit.

Hydrolysis of the B(pin) group is likely to be equally (if not more) critical when the more sizable chiral NHC catalysts are

involved. In the presence of chiral imidazolium salt **7c** and excess amounts of dbu (6.0 equiv) and 6.0 equiv of H₂O, the borosilane reagent was completely consumed in 1 h. Still, a signal corresponding to the NHC·borosilane complex could not be detected (Scheme 9).⁴²

Scheme 9. Probing the Association of Chiral NHC with (pin)B–SiMe₂Ph



To gain insight regarding the possible influence of water on NHC·borosilane association, we first examined the fate of (pin)B–SiMe₂Ph when treated with 6.0 equiv of dbu and H₂O in thf at 22 °C. Within 30 min, the reagent was entirely consumed and two types of B-containing species were generated (Scheme 10a). A signal at 21.5 ppm is likely due to formation of boronate **31**, Me₂PhSiH (characteristic peak in ¹H NMR spectrum at 4.4 ppm), and complex **32** [in equilibrium with (pin)B–SiMe₂Ph, H₂O, and dbu], while

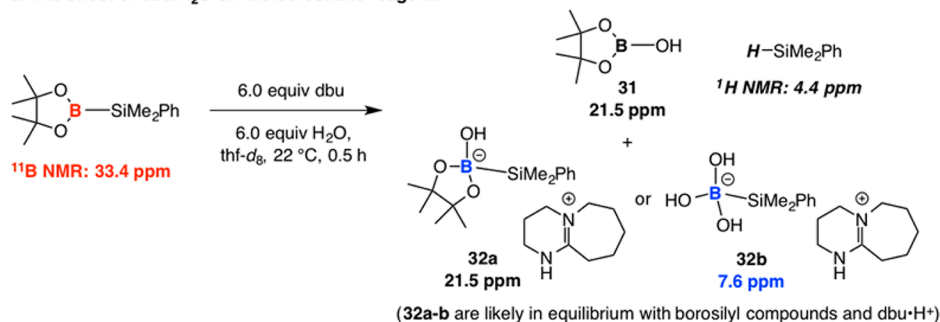
another at 7.6 ppm is because of the tetravalent B atom of **32b**; these complexes may form by pathways similar to those shown in Scheme 7a [involving B₂(pin)₂ and MeOH].

Through another experiment, summarized in Scheme 10b, we established that although (pin)B–SiMe₂Ph is relatively stable in aqueous media, soon after the addition of dbu it is swiftly consumed and SCA takes place efficiently (34% conversion in 2 min and 86% conversion in 30 min to β-silyl ketone **33b**). Moreover, we were able to isolate and obtain the X-ray crystal structure of borate complex **34**, resulting from the loss of the pinacol group, an event that likely leads to a more reactive borosilane derivative (e.g., **32b**) and facile SCA, regardless of whether an achiral (cf. **3b**, Scheme 4) or a larger chiral NHC (cf. **7c**, Scheme 4) is involved. These observations illustrate that a highly effective enantioselective SCA catalyst must be sufficiently active to overcome the somewhat rapid background processes that afford racemic β-silylcarbonyl compounds.

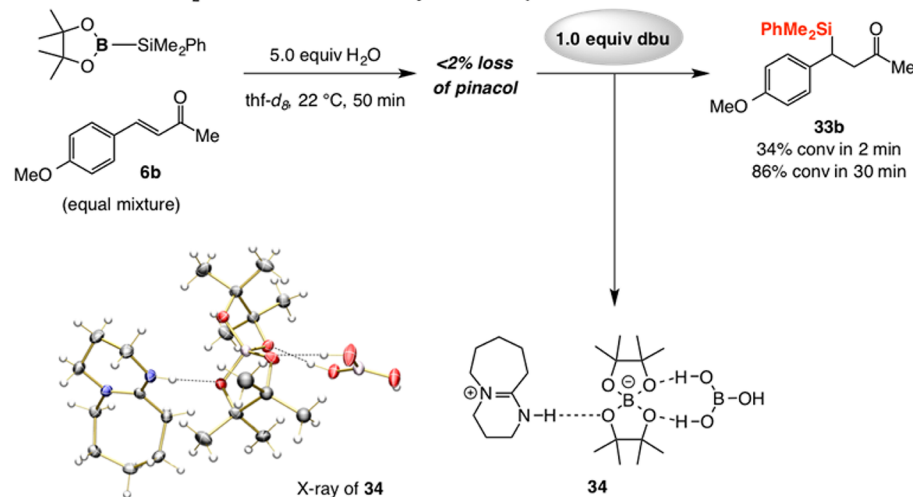
We resorted to spectroscopic analysis (¹¹B NMR) in our quest to gain information regarding the details of borosilyl activation by a chiral NHC. A mixture of (pin)B–SiMe₂Ph together with an equivalent of chiral imidazolium salt **7c**, 6.0 equiv of dbu, and 6.0 equiv of H₂O, shown in Figure 5, led to generation of different products, many of which contain an sp³-hybridized B atom (peaks a and b relating to **35a-b** and **32b**, respectively). The assignment of the signals at 4.4 and 7.7 ppm are based on formerly reported values⁴⁴ and the experiment performed in the absence of an NHC (cf. Scheme 10a),

Scheme 10. Influence of Base and H₂O on (pin)B–SiMe₂Ph and SCA Reactions^a

a. The effect of dbu/H₂O on the borosilane reagent:



b. The effect of dbu/H₂O on the enantioselectivity of the SCA process:



^aSee the Supporting Information for details.

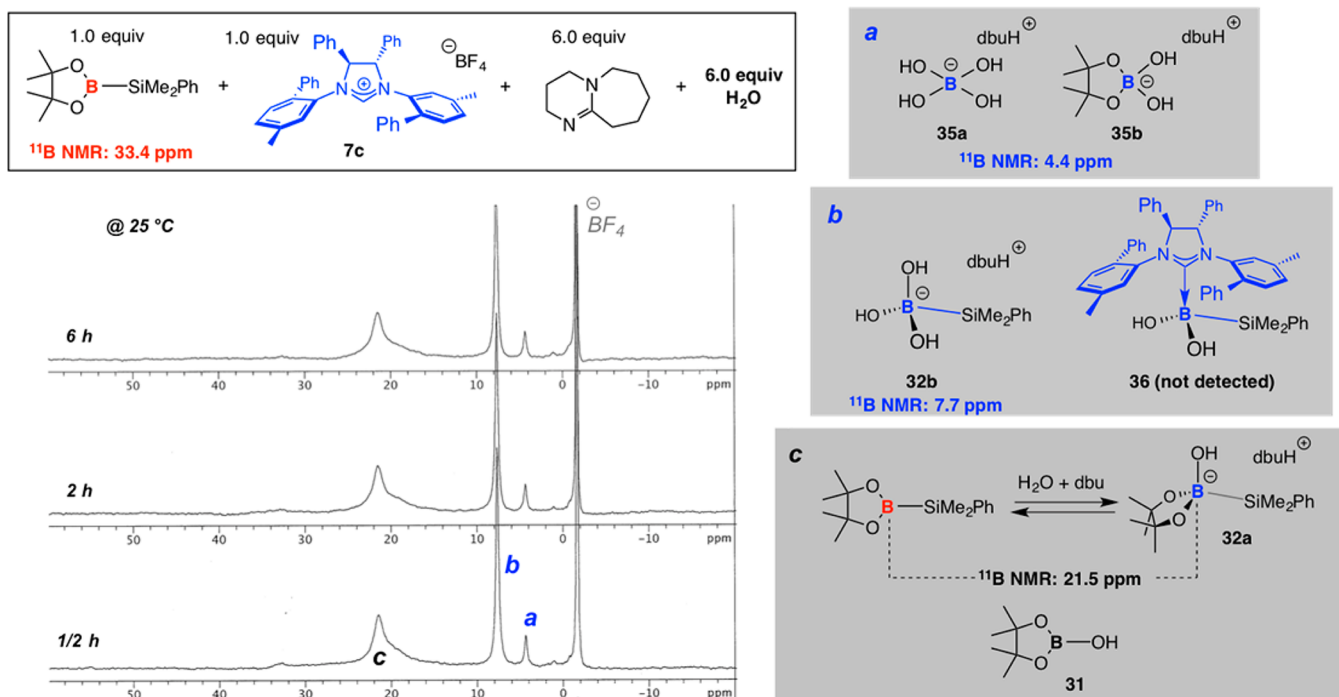


Figure 5. ¹¹B NMR spectra for reaction of (pin)B-SiMe₂Ph with a chiral NHC in the presence of H₂O and dbu (thf-*d*₈, 25 °C).

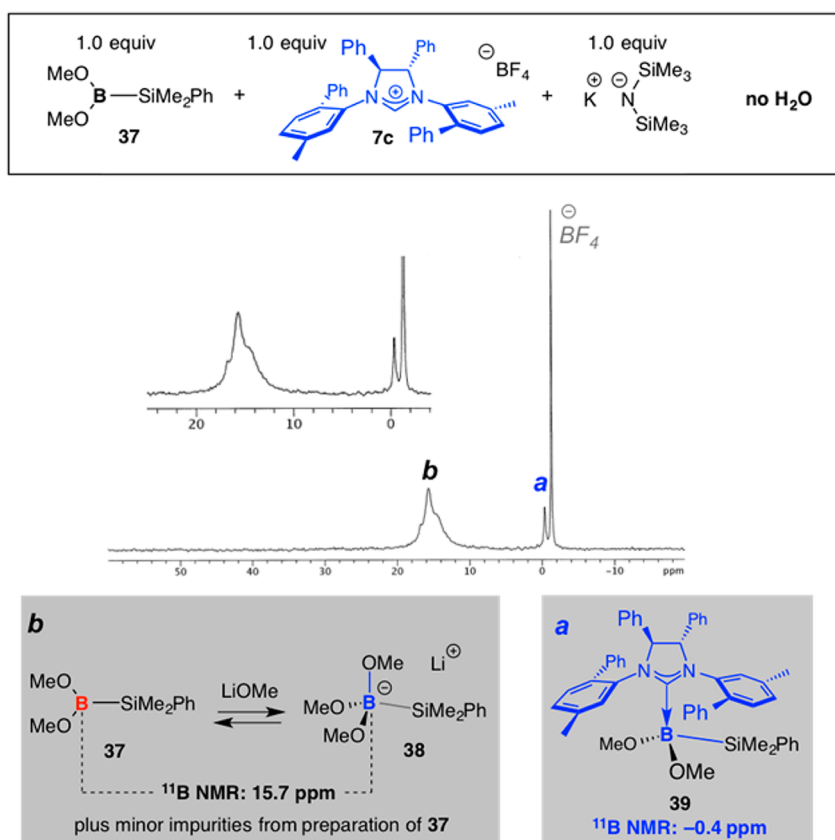


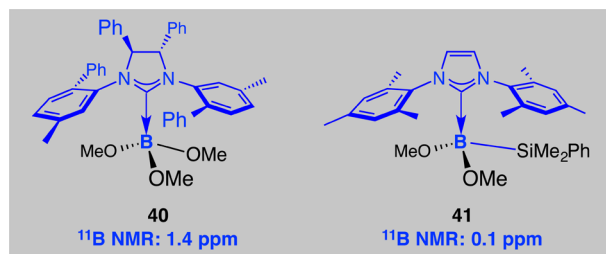
Figure 6. ¹¹B NMR spectrum for reaction of (MeO)₂B-SiMe₂Ph with a chiral NHC (thf-*d*₈, 25 °C).

respectively; that is, a distinct signal that may be confidently attributed to NHC-borosilane complex **36** could not be formed. Considering the differences in the electron donor abilities of an OH and an NHC ligand and the aforementioned influence of such characteristics on the chemical shift for the signals of the

associated boron atoms, the possibility that the signal for **36** might be hidden behind the peak at ~8 ppm is remote. It is noteworthy that the NHC-borosilane complex that is responsible for promoting SCA reactions with high enantioselectivity in the face of a somewhat swift background process

and at significantly lower concentrations (e.g., 5.0 vs 100 mol %) is difficult to observe. It is reasonable to suggest, however, that the lifetime of the borosilyl reagent or **36** is substantially increased under biphasic conditions (i.e., 3:1 H₂O/thf vs 6.0 equiv of H₂O in thf), as these species probably spend much of their time in the organic layer. Otherwise, extended reaction times (e.g., 12 h in Scheme 4) would not be productive.

To detect a chiral NHC·borosilane complex spectroscopically, we prepared dimethylphenylsilyl(dimethoxy)boron **37** (confirmed by HRMS), a species that is easier to synthesize and handle than the corresponding bis(hydroxy)boron derivative. Treatment of a sample of **37**, after filtration to remove solid residues, with 1.0 equiv of imidazolium salt **7c** and 1.0 equiv of potassium hexamethyldisilazide (KHMDS, to ensure rapid and complete kinetic deprotonation) at 25 °C in thf-*d*₈ for 30 min led to the appearance of a singlet in the ¹¹B NMR spectrum at −0.4 ppm (Figure 6). This signal likely belongs to complex **39**, and its broad shape indicates a rapid equilibrium between the chiral NHC·borosilane complex and the unbound borosilane. To ensure that the aforementioned peak does not originate from association of the NHC with trimethoxyborane used for preparation of **37**, we obtained the ¹¹B NMR spectrum of the suspected complex (**40**), establishing that the associated peak appears at 1.4 ppm. Furthermore, when the dimethoxyborosilane reagent **37** was reacted with the achiral NHC derived from bis(mesityl)imidazolium salt **3c**, the resulting NHC·boryl species (**41**) manifested itself with a signal at 0.1 ppm. Control experiments indicate that the reason for

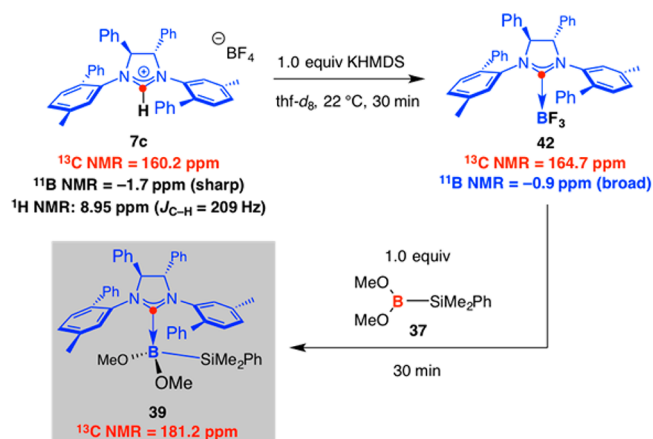


formation of the NHC·borosilyl complex is not the use of a stronger base (i.e., KHMDS vs dbu) as opposed to the availability of a more sterically accessible borosilane partner; treatment of **7c**, KHMDS (1.0 equiv), and (pin)B–SiMe₂Ph does not lead to any detectable amounts of a chiral NHC·borosilane complex (400 MHz ¹H NMR analysis).

To explore the formation of the chiral NHC·borosilyl complex **39** further, we prepared a ¹³C-labeled sample of imidazolium salt **7c** and converted it to the corresponding NHC·BF₃ complex **42** by the addition of 1.0 equiv of KHMDS at 22 °C in thf-*d*₈ for 30 min (Scheme 11). At ambient temperature, trifluoroboron species **42** may be identified by peaks at 164.2 and −0.9 ppm in the ¹³C and ¹¹B NMR spectra, respectively.⁴⁵ The latter signal is broad, indicative of rapid equilibrium between the free carbene and the BF₃ complex. Subsequent addition of 1.0 equiv of bis(methoxy)borosilane **37** to the sample containing **42** resulted in the formation of **39**, which was marked by the appearance of a new signal at 181.2 ppm in the ¹³C NMR spectrum (¹¹B NMR signal at −0.4 ppm). The above findings imply that the catalytically active NHC·borosilane is probably formed and capable of promoting substantial amounts of transformation prior to its decomposition.

Imidazolium salt **7c** is stable in monophasic 3:1 H₂O/thf solution (spectroscopic analysis). Incorporation of 22 equiv of

Scheme 11. Probing the Formation of a Chiral NHC·Borosilane Complex by Spectroscopic Analysis of a ¹³C-Labeled Chiral NHC^a

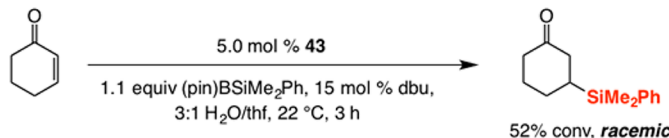
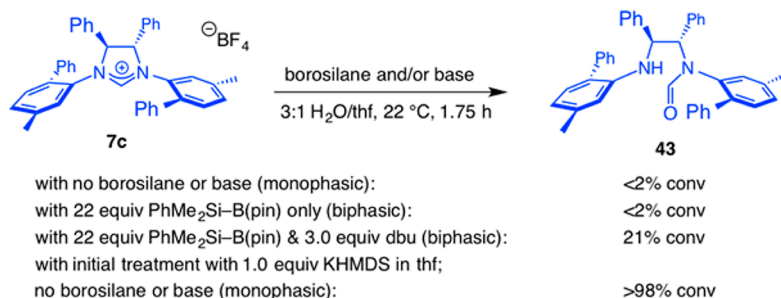


^aSee the Supporting Information for details.

PhMe₂Si–B(pin) (to emulate catalytic reaction conditions) caused the aqueous thf mixture to become biphasic, and **7c** remained unaltered (Scheme 12); however, when 3.0 equiv of dbu was added, there was ~20% decomposition to acyclic formamide **43** (Scheme 12). When **7c** was first treated with 1.0 equiv of potassium hexamethyldisilazide (KHMDS, thf) before being placed in an aqueous thf solution that does not contain either the borosilane reagent or any dbu (monophasic), complete conversion to **43** occurred in less than 2 h. The above experiments demonstrate that whereas the imidazolium salt precursors are relatively stable, the NHC species, formed upon addition of dbu, can slowly decompose under the reaction conditions. Formamide **43** promotes SCA but nonenantioselectively (Scheme 12). Facile and highly enantioselective silyl additions therefore imply that the biphasic nature of the medium retards the rate of formamide generation, and an NHC·borosilane complex is probably longer living than an unbound NHC.

5. Effect of Hydroxide Ion Permeability on Efficiency and Enantioselectivity of Conjugate Silyl Additions.

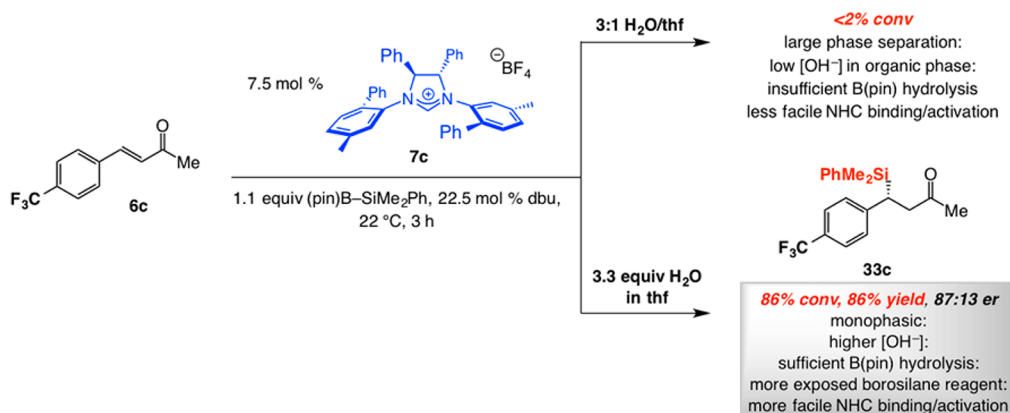
Through the studies described above we demonstrated that the presence of water can have a positive [increasing activity by B(pin) hydrolysis] or a deleterious effect (NHC and/or borosilane decomposition) on NHC-catalyzed SCA reactions, and the degree and nature of the influence of water depends on the amount of dbu present (cf. Scheme 10b). With a better understanding of such factors, we can rationalize the origin of otherwise perplexing observations, and conditions may be modified leading to significant improvement in reaction outcomes. One noteworthy case relates to SCA to *p*-trifluoromethylphenyl-substituted enone **6c**, which proved to be notoriously inefficient despite the substrate's significant electrophilicity. Indeed, in our initial disclosure, we reported that the expected β-silyl ketone could not be observed after 3 h in the biphasic 3:1 mixture of H₂O and thf (Scheme 13).²⁰ We reasoned that the presence of three fluorine atoms might cause enhanced phase separation, diminishing the concentration of the hydroxide in the organic phase (cf. Scheme 10b) needed to facilitate B(pin) removal, NHC·borosilane complex formation, and efficient SCA. Indeed, as shown in Scheme 13, when reaction with **6c** was performed with only 3.3 equiv of H₂O in thf (monophasic), we were able to obtain **33c** in 86% yield after

Scheme 12. Decomposition of an Imidazolium Salt in an Aqueous Medium^a

The enantiomerically pure formamide is a competent but non-enantioselective catalyst.

^aSee the [Supporting Information](#) for details.

Scheme 13. Influence of Ratio of Water/thf on the Efficiency of NHC-Catalyzed SCA

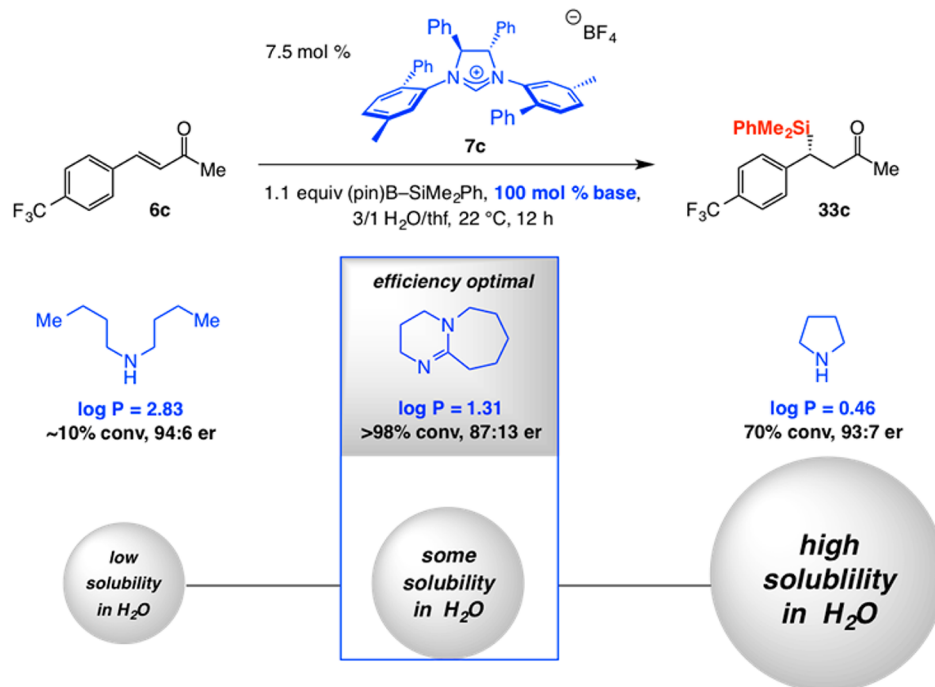


only 3 h. We must note that the latter conditions do not translate to efficient SCA with other, less electrophilic, enones—it is in the case of highly active substrates that a relatively small amount of water is sufficient to generate enough B(pin) hydrolysis for efficient silyl conjugate addition.

Another notable implication of the biphasic reaction medium and the role of in-situ-generated hydroxide in facilitating a catalytic SCA process is that the optimal base must be adequately soluble in the aqueous as well as the organic phase. The base (e.g., dbu) can then penetrate the aqueous phase to generate the appropriate amount of hydroxide salt (e.g., H⁺dbu⁻OH) that is lipophilic enough to enter the organic layer and promote B(pin) hydrolysis. The findings in [Scheme 14](#) shed light on these issues.

Firstly, with 100 mol % of dbu, SCA with trifluoromethyl-phenyl-substituted enone **6c** proceeded to >98% conversion, affording **33c** enantioselectively (87:13), even in biphasic 3:1 H₂O/thf ([Scheme 14](#)); this is in stark contrast to <2% conversion when 22.5 mol % of dbu was used (cf. [Scheme 13](#)). Secondly, efficiency variations with amine bases that possess different solubility properties indicate that with a more lipophilic base or one that has higher hydrophilicity than dbu, SCA efficiency suffers [(~10% and 70% conversion with (*n*-Bu)₂NH (log *P* = 2.83⁴⁶) and pyrrolidine (log *P* = 0.46), respectively, vs >98% conversion with dbu (log *P* = 1.31)]. Thirdly, enantioselectivity is higher when an amine base that is less water soluble is present [94:6 er for (*n*-Bu)₂NH] or when a base that is more hydrophilic than dbu is used (93:7 er for

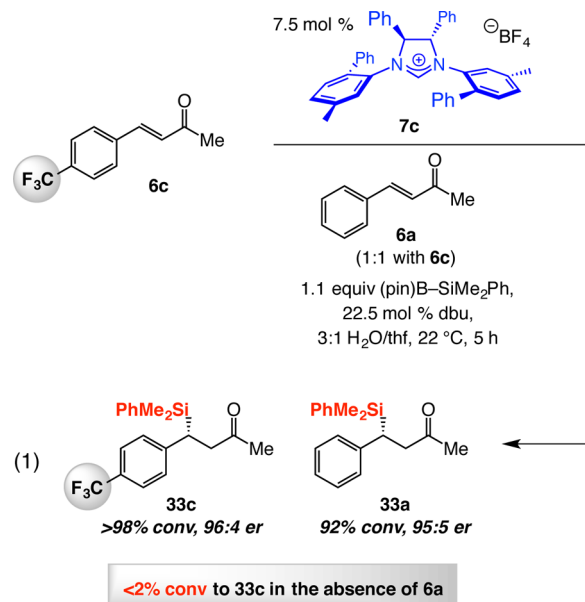
Scheme 14. Effect of Solubility of Different Amine Bases on the Efficiency of Catalytic SCA Reactions



pyrrolidine vs 87:13 er with dbu). In either instance, the concentration of hydroxide in the organic layer, where **6c** can be found, would be lower (vs with dbu), resulting in reduced generation of *rac*-**33c** (cf. Scheme 10b). For SCA with (*n*-Bu)₂NH, there is insufficient base penetration into the aqueous layer, and with pyrrolidine there would be less partitioning of the ammonium hydroxide into the organic layer.

Higher efficiency of exchange between the phases is not caused by the nature of the amine base only. The presence of a suitably polar organic molecule can accelerate an otherwise inert enone as well. As previously mentioned (cf. Scheme 13), there was <2% conversion when **6c** was subjected to 7.5 mol % of **7c**, 1.1 equiv of (pin)B–SiMe₂Ph, and 22.5 mol % of dbu in 3:1 H₂O/thf after 12 h. Nevertheless, with an equal amount of phenyl-substituted enone **6a** simultaneously present (identical catalyst loading for total enone concentration; cf. eq 1), the more lipophilic trifluoromethylphenyl-substituted enone **6c** was fully consumed in 5 h and **33c** was obtained in 96:4 er. The higher er in the latter transformation (vs 87:13 er, Scheme 13) is due to the presence of **6a**, which can increase hydroxide ion concentration enough so that SCA is facilitated but not to the extent that would lead to production of *rac*-**33c** (due to NHC decomposition; cf. Scheme 12).

6. Kinetic Studies and Stereochemical Models. Initial rate measurements involving representative enantioselective NHC-catalyzed BCA and SCA reactions indicate that transformations are first order in the NHC, the α,β -unsaturated carbonyl substrate, as well as B₂(pin)₂ and (pin)B–SiMe₂Ph reagents, respectively; no dependence on dbu was observed.⁴⁷ With the assumption that NHC-diboron and NHC-borosilane complex formation are rapidly reversible under the reaction conditions (22 °C; steady state approximation), a premise supported by the broad signals in the ¹¹B NMR spectra (see above) that may be sharpened at lower temperatures,^{16b,32a} the latter findings point to the C–B and C–Si bond-forming steps as turnover limiting. Accordingly, we set out to develop a



rationale for the observed stereochemical outcomes of NHC-catalyzed enantioselective BCA and SCA processes.

To begin with, several general scenarios for BCA and SCA reactions were explored by means of DFT calculations [B97D/6-31+G(d,p) level of theory], most of which entailed initial B–B or B–Si bond activation by an NHC catalyst.³⁷ Among the pathways examined were those proceeding via intermediates derived from NHC insertion into the B–B or B–Si bonds.⁴⁸ These investigations indicated that the originally suggested route, namely, the addition of polarized NHC-diboron or NHC-borosilane complexes to unsaturated carbonyl compounds, is energetically the more favorable possibility.

Model for Additions to Acyclic Substrates. The lowest energy transition state structures for boryl and silyl conjugate additions to an acyclic enone are presented in Figure 7. For the

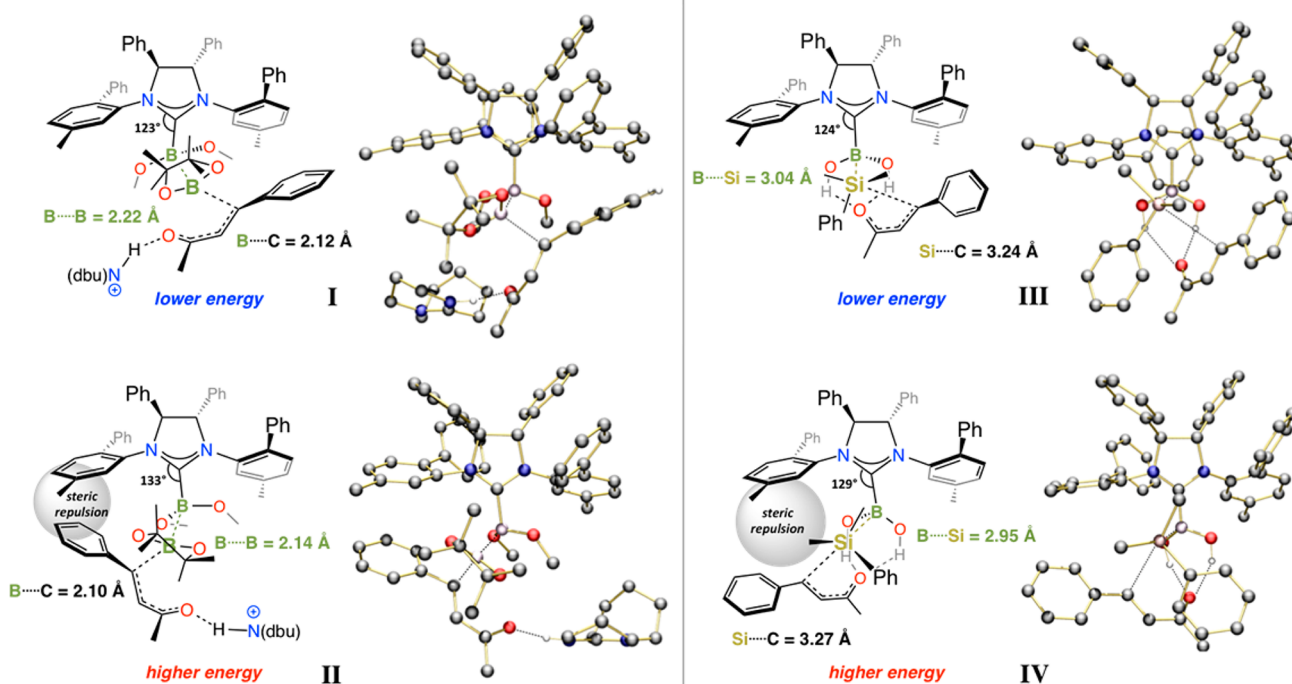


Figure 7. Transition state models for NHC-catalyzed enantioselective BCA and SCA reactions of acyclic enones obtained by DFT calculations.

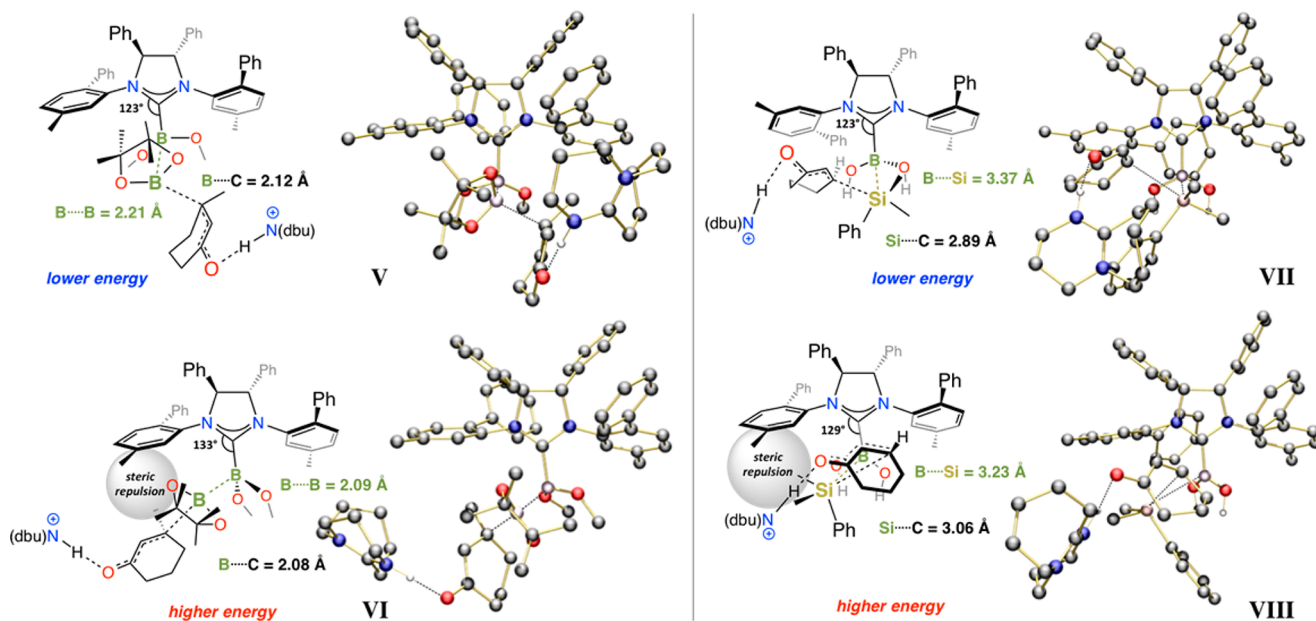


Figure 8. Transition state models for NHC-catalyzed enantioselective BCA and SCA reactions of cyclic enones obtained by DFT calculations.

BCA reactions, unlike **I**, complex **II** suffers from a destabilizing steric repulsion between the alkenyl substituent of the electrophile and the NAr moiety of the chiral NHC. This is consistent with experimental findings, indicating that the size of the meta substituent of the NAr group influences BCA enantioselectivity (Me in **I** and **II**, *i*-Pr in the optimal catalyst derived from **7a**; cf. Scheme 3). A larger ortho substituent within the NAr unit can cause the aromatic plane to tilt, so that the coordinating substrate is more readily accommodated (e.g., Mes in **7a** vs Ph in **I** and **II**).⁴⁹

DFT calculations point out that the N–C–B angle in the less favorable **II** is bent by $\sim 10^\circ$ (133° vs 123° in **I**); this allows minimization of the destabilizing interactions between the

aforementioned NAr group and the enone substituent (Ph in **II**). The transition states calculated for SCA transformations, **III** and **IV**, generally resemble those obtained for the BCA processes; the same arguments provided for **I** and **II** apply here as well. Widening of the N–C–B angle is less in the case of the borosilane complexes ($124^\circ/129^\circ$ in **III/IV** vs $123^\circ/133^\circ$ in **I/II**) perhaps because the longer B...Si engenders a lower degree of steric repulsion with the NHC. A difference between silyl and boryl additions is the possibility of H-bonding interactions between the B–OH within the NHC–borosilane ensemble and the substrate carbonyl group in **III** and **IV**. Such interactions alleviate the accumulation of electron density at the carbonyl oxygen that is developed after conjugate addition; the same

type of stabilization may be provided externally by a protonated dbu or a MeOH molecule in the NHC-catalyzed boryl additions (cf. I and II); the zero-order rate dependence on dbu suggests that either MeOH, which is available in great excess, largely serves as the proton source or association with Hdbu^+ is fast and precedes the turnover-limiting step.

Model for Additions to Cyclic Substrates. As mentioned before, unlike transformations involving acyclic substrates, BCA and SCA reactions with cyclic enones proceed with the *opposite* sense of enantioselectivity. DFT calculations⁵⁰ support the experimentally observed trend, indicating that whereas mode of addition V (Figure 8) is preferred for the C–B bond-forming processes (vs VI), those that afford β -silyl carbonyl compounds probably proceed via VII (vs VIII). One reason for this distinction might be the size differences among the B(pin), the Hdbu-bound substrate, and the especially larger Me_2SiPh moiety. Another factor could be the shorter $\text{B}\cdots\text{B}$ versus $\text{B}\cdots\text{Si}$ distance in the transition state structure (e.g., 2.21 vs 3.37 Å in V and VII, respectively). It is therefore plausible that the B(pin) moiety would be preferentially situated in the vicinity of the sterically less demanding front/left-hand quadrant of the chiral complex V. In the SCA process, on the other hand, the Me_2SiPh group would be situated more distally from the aforementioned N–Ar group, reducing the degree of repulsion between the NHC's N–Ar unit and the dbuH- or MeOH-bound enone. Another feature of the structures shown in Figure 8 is the absence of internal H bonding between the $\text{B}(\text{OH})_2$ and the carbonyl unit (cf. III and IV in Figure 7);⁵¹ such interactions would be a great deal more geometrically demanding in cyclic α,β -unsaturated carbonyl compounds, which are locked into a *s-cis* conformation (vs *s-trans* conformers in Figure 7).

CONCLUSIONS

The investigations detailed herein shed light on the following key mechanistic principles in regard to NHC-catalyzed enantioselective boryl and silyl conjugate addition reactions, which we show do not involve single-electron pathways.

- Excess base MeOH and dbu are needed for BCA reactions promoted by the larger chiral NHC catalysts because conversion of the relatively hindered B(pin) unit to a more accessible $\text{B}(\text{OMe})_2$ or $\text{B}(\text{OMe})$ ($\text{OC-Me}_2\text{CMe}_2\text{OH}$) facilitates diboron bond activation and NHC-diboron complex formation.
- Initial rate studies and DFT calculations have resulted in the development of models that provide a plausible rationale for the different stereoselectivity profiles for boryl addition processes.
- The lack of efficiency of silyl conjugate additions with the more diminutive achiral NHC (vs the corresponding BCA processes) in the absence of water is not because the necessary Lewis-base-borosilane species cannot be generated. Rather, it might be due to the resulting NHC·B(pin) complex being too hindered, rendering approach by an α,β -unsaturated carbonyl compound energetically prohibitive.
- The origin of high efficiency in SCA reactions in water with excess dbu is rapid hydrolysis of the sterically demanding B(pin) unit, allowing for the formation of a more sterically accessible and thus more reactive borosilane; this results in the more efficient NHC·

borosilane complex generation and a more rapid initiation of a catalytic cycle.

- For the silyl addition processes, the chiral NHC must be sufficiently active to overcome borosilane reagent decomposition as well as its own breakdown, which can yield a catalytically active but nonenantioselective acyclic formamide derivative.
- The positive role of dbu in an NHC-catalyzed SCA is a culmination of a sensitive balance achieved regarding the solubility of the base in two phases of the reaction mixture (typically, 3:1 $\text{H}_2\text{O}/\text{thf}$; biphasic nature caused by the borosilane reagent). Hydroxide ions must be transported into the organic layer in the form of $\text{Hdbu}^+\cdot\text{OH}^-$ in amounts that are sufficient for converting the B(pin) group of the silylboron reagent to its derived $\text{B}(\text{OH})_2$, which is critical for NHC activation of the B–Si bond. At the same time, the base must not cause too high an increase in hydroxide ion concentration in the organic layer or a substantial degree of reagent and catalyst decomposition results.
- Initial rate studies and DFT calculations demonstrate that the opposite sense of enantioselectivity for BCA reactions involving cyclic enones versus SCA transformations originate from the larger size of a Me_2SiPh moiety and a more elongated B–Si bond in the corresponding transition states.

Lewis-base-catalyzed reactions involving an NHC, a phosphine, or an alkoxide species, particularly those that generate a C–B bond, have emerged as a potentially significant set of transformations that provide reactivity, functional group compatibility, and stereoselectivity profiles and/or levels that are complementary to the more widely examined transition-metal-catalyzed systems. An understanding of the key mechanistic factors that facilitate such processes and/or render them highly selective allows for a more clear analysis of the existing data and is crucial if future initiatives in this burgeoning area are to achieve maximal success. The findings described above offer some of this needed insight.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06745.

Cystallographic information (CIF)

Cystallographic information (CIF)

Cystallographic information (CIF)

Experimental details for all reactions and analytic details for all enantiomerically enriched products (PDF)

AUTHOR INFORMATION

Corresponding Author

*amir.hoveyda@bc.edu

Notes

The authors declare no competing financial interest.

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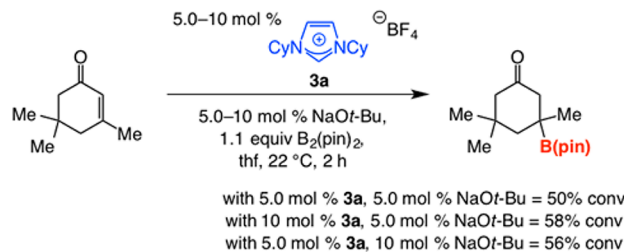
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