A Boron Alkylidene-Alkene Cycloaddition Reaction: Application to the Synthesis of Aphanamal

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Abstract

We describe an unusual net 2+2 cycloaddition reaction between boron alkylidenes and unactivated alkenes. This reaction provides a new method for construction of carbocyclic ring systems bearing versatile organoboronic esters. In addition to surveying the scope of this reaction, we provide details about the mechanistic underpinnings of this process, and examine application to the synthesis of the natural product aphanamal.

COMMUNICATION
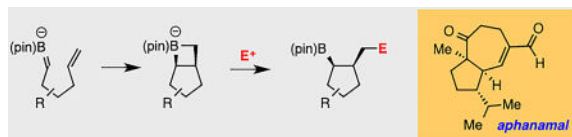
Two plus two, or not two plus two, that is the question: Boron alkylidenes are generated by alkoxide induced deborylation of geminal bis(boronates). These alkene analogs are shown to undergo a net 2+2 cycloaddition reaction with tethered alkenes and the resulting boronate complex can be trapped with electrophiles to generate substituted carbocyclic products. Mechanistic studies and application to synthesis are described.

Keywords

Cyclization; Boron; Total Synthesis; Alkenes; Reaction mechanisms

Geminal bis(boronates) are readily available reagents[1] that engage in an array of functional group transformations under catalytic[1b,g,i,j, 2] and non-catalytic[1e, 3] conditions. In recent studies, it was found that metal-alkoxide-induced deborylative alkylation (eq. 1, Scheme 1) of these compounds can be brought about under mild conditions, even for relatively hindered substrate pairings.[3b] Mechanistic investigations suggested that these reactions proceed through the intermediacy of a boron-stabilized carbanion (i.e. **3**), a compound that is generated upon reaction of the bis(boronate) **1** with the metal alkoxide. Spectroscopic study of the boron-stabilized carbanion revealed significant π-bonding between the carbanionic carbon and the three-coordinate boron center indicating that the anion can alternately be represented as boron alkylidene structure **4**, a compound related to other[4] boron

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alkylidenes. To probe the reactivity of the boron alkylidene, we examined deborylative alkyation of bis(boronate) **5**, a compound bearing a tethered alkene. In the presence of an alkyl halide electrophile, alkoxideinduced deborylation of **5** furnished alkylation product **6** without involvement of the tethered olefin. In this manuscript, we report that an alternate reactivity mode operates when the electrophile is omitted from deborylation of alkene-containing substrates such as **5**: in this circumstance, a deborylative cyclization reaction is observed that is consistent with a net 2+2 cycloaddition between the tethered, unactivated alkene and the boron alkylidene giving **7** (eq. 3).[5] After 14 hours, addition of an electrophile furnishes **8**. Overall, this unusual mode of reactivity results in net non-catalyzed carboboration[6] of an unactivated alkene, a process that has some resemblance to hexenyllithium and related cyclization reactions[7], but as far as we are aware, does not find precedent in reactions of stabilized carbanion equivalents. Importantly, this reaction provides a compound with a new carbocyclic ring system and has the capacity to establish three new stereocenters from simple precursor building blocks. Herein, we describe mechanistic and synthetic features of this process and examine the utility of this reaction in the construction of the terpene-derived natural product aphanamal.

Studies of the 2+2 reaction in eq. 3 began with the observation that treatment of geminal bis(boronate) **5** with sodium *tert*-butoxide furnished a small amount (13% yield) of cyclopentane-containing product **9** (Figure 1). Notably, while the cyclization product was formed in low yield, it was furnished as a 13:1 ratio of diastereomers. After optimization (see Supporting Information, Table S1), it was determined that KO*t*-Bu gave improved yield of the reaction product. It was also found that while the reaction efficiency was higher in toluene solvent at room temperature, when THF was employed as the reaction solvent, an efficient reaction and a higher level of diastereoselectivity was generally observed. Subsequently, we surveyed other substrates and electrophiles. As depicted in Figure 1, when deborylative cyclization of **5** was followed by addition of either D_2O, NBS, or I_2, electrophilic trap[8] of the reaction intermediate occurred and delivered **10, 11**, and **12**, respectively. It merits mention that relative to the example with protic work-up, the diastereoselectivity in formation of compounds **10–13** is considerably enhanced (>20:1 dr vs. 4:1 dr). The enhanced diastereoselection in production of **10–13** relative to **9** appears to result from protonolysis of the minor *trans* diastereomer prior to addition of electrophile such that electrophilic trap of the remaining *cis* isomer furnishes isomerically-enriched product.[9] As noted in Figure 1, reactions of other substrates show that a tethered styrene can also engage in the reaction (product **15**) and that with substitution on the alkene, a third stereocenter can be generated with useful levels of stereocontrol (product **16**). Also of note, prospective internally-coordinating Lewis bases such as benzyl ethers (product **14**) and silyl ethers (**18**) are tolerated. Similarly, substrates bearing substituents at the alkylidene center ranging from large aliphatic groups (products **17, 19**) to a simple proton (**20**) provide cyclic products in reasonable yields and selectivity. Lastly, a tethered diene engages in the reaction and furnishes an internal alkene upon protic work-up (**22→23**).

We propose that the deborylative cyclization proceeds through the intermediacy of a 5-borata-[3.2.0]-bicycloheptane "ate" complex **7** (Scheme 1). Structure **7** explains the following observations: (1) a carbanion equivalent (boron "ate" complex) is formed and is

stable enough that it persists for the duration of the first step (up to 14 h) such that it may be trapped with an electrophile; (2) only one stereoisomer of cyclization intermediate (*syn*) appears to be stable and subject to trap with the electrophile, while the other is protonated prior to addition of trapping reagent. To gain evidence for the intermediacy of complexes such 7, the experiments in Figure 2A were conducted. In the first, ^{13}C-labeled compound 24 was subjected to KO*t*Bu in THF-d$_8$ and the reaction followed by proton-decoupled ^{13}C NMR spectroscopy.[10] Over the course of the reaction, the ^{13}C resonance for the starting material (20.1 ppm; broad due to the boron quadrupole) was replaced by a broad resonance at 44.0 ppm (assigned to 25).[11] Upon quench of the reaction mixture with H$_2$O, the signal at 44.0 ppm was replaced with a broad resonance at 38.5 ppm. In a second experiment, reaction of ^{13}C-labeled 26 (δ = 114.0 ppm; sharp singlet) furnished a new structure that exhibits a broad resonance at 26.9 ppm (assigned to 27). Addition of H$_2$O to putative bicycle 27 furnishes a compound with a labeled methyl group resonating at δ = 18.0 ppm. The similar chemical shift and linewidth of the labeled carbons in 25 and 27 is suggestive of a related environment for both carbon atoms, a feature most readily accommodated by the intermediacy of the boracyclic compound.

To learn about the properties of the boron alkylidene/α-boryl carbanion, the experiments in Figure 2B were conducted. First, it was determined that deborylative alkylation of a non-racemic secondary alkyl bromide (29) occurs stereospecifically, furnishing 30 with inversion of configuration at the electrophilic carbon. Thus, in the context of an alkyl halide substitution reaction, the nature of the α-boryl carbanion is more consistent with a two-electron nucleophile as opposed to a single electron donor that undergoes alkylation by single-electron transfer to the alkyl halide, followed by fragmentation and radical combination.[12] In a second experiment, it was shown that a cyclopropyl group attached to the boron-stabilized carbanion center does not undergo fragmentation during the course of deborylative cyclization (31→32).[13] While these experiments suggest that the boron-stabilized carbanion does not have a proclivity to react by single-electron-transfer pathways, the concerted carbometallation pathway by which hexenyllithium[7a] undergoes cyclization does not appear to operate: cyclization/iodination of 33 (Figure 2C) leads to a 1:1 mixture of deuterium-labeled diastereomers 34 (epimeric at the iodination site). Assuming iodination of the ate complex is stereospecific[8a], this observation suggests that the cycloaddition is a non-concerted step-wise process, proceeding through an intermediate capable of bond rotation prior to closure to the boretane. We considered that a thermally-accessible open shell structure[14] such as 35 – formed by a process analogous to that proposed for dimerization of strained olefins[15] and for alleneyne intramolecular 2+2 reactions[16] – and closed-shell system 36 (see inset, Figure 2C) were most plausible intermediates; however, both raise questions. The radical-based pathway is not supported by experiments in Figure 2B, while addition of a stabilized carbanion to an unactivated alkene appears to have little precedent.[17] Nonetheless, the capacity for stereochemical scrambling at the reactive olefin site extends to other systems: cyclization/alkylation of *cis* and *trans* substrates 37 and 21 (Figure 2D) occurs with stereoconvergence – the intermediate "ate" complex is presumed to undergo stereoinvertive S_E2 alkylation[8] *via* 39 – furnishing 38 in excellent yield and stereoselection.

Key steps of the reaction mechanism were probed using density functional theory (DFT). As depicted in Figure 3, minimization of the α-boryl carbanion gives the structure **GS$_{SM}$** bearing a planar boron atom and a shortened B–C bond (1.46 Å) indicative of π-bonding. Cyclization of the boron alkylidene gives a non-stablized carbanion (**INT$_{cis}$**) by way of transition state **TS1$_{CIS}$** (calculated barrier = 20.7 kcal/mol) wherein the terminal carbon of the alkene undergoes pyramidalization as it accommodates a pair of electrons. An important feature of **INT$_{cis}$** is that the carbanion center does not yet exhibit bonding with the three-coordinate boron atom and therefore may be subject to bond rotation and stereoinversion, features required for stereoconvergence with styrene derivatives **18** and **39**, as well as the stereochemical scrambling observed with deuterium-labeled terminal alkene substrate **35**. As a final step in the reaction sequence, internal electrophilic trap of the carbanion in **INT$_{cis}$** by the adjacent boron atom occurs with stereoinversion at carbon and furnishes a stable four-membered boracyclic intermediate. Importantly, for the simplified model system used in these calculations, a similar reaction pathway is accessible for production of the *trans* product and the barrier is comparable to that observed for the *syn* compound (G$_{rel}$ TS1$_{TRANS}$ = +19.8 kcal/mol, INT$_{TRANS}$ = +9.4 kcal/mol, TS2$_{TRANS}$ = +15.1 kcal/mol); however, the *trans* boracycle is much less stable (PDT$_{TRANS}$ = +1.2 kcal/mol) and this feature may explain its inability to persist until the end of the reaction period. Overall, the mechanism that appears most consistent with experimental and computational observations is a step-wise 2+2 cycloaddition proceeding through the intermediacy of a carbanionic intermediate.

Considering the prevalence of cyclopentane-containing natural products (>49,000 according to the Reaxys database), it was of interest to study the cycloaddition in construction of natural product targets.[18] In this context, we addressed the natural product aphanamal, a bicyclic terpene isolated from the folk-medicine plant *chromolaena laevigata*.[19,20] As depicted in Figure 4, when geminal bis(boronate) **40** was subjected to deborylative 2+2 cycloaddition followed by trap with Eschenmoser salt[21], alkyl amine derivative **41** was isolated in good yield and with good levels of stereoinduction. Importantly, the tertiary boronate could be readily converted to methyl ketone **42** by a modified[22] Evans-Zweifel olefination. Subsequent, oxidation of the amine and Hoffmann elimination[23] furnished terminal alkene **43** in good yield. Finally, alkylation of the methyl ketone with methallyl iodide, followed by ring-closing olefin metathesis[24], and allylic oxidation[25] furnished the natural product.

In conclusion, the addition of a carbanion to an unactivated alkene is an uncommon event in organic chemistry. While the overall transformation of the boron alkylidene bears some similarity to transition metal alkylidene-based processes (i.e. in olefin metathesis)[26], the stepwise mechanism that operates with boron appears to be distinct from the concerted nature of transition metal-based 2+2 reactions and the energetic profile is much different, offering an opportunity to intercept the metallacyclobutane in alternate processes. This feature is likely to find use in construction of complex target structures from simple starting materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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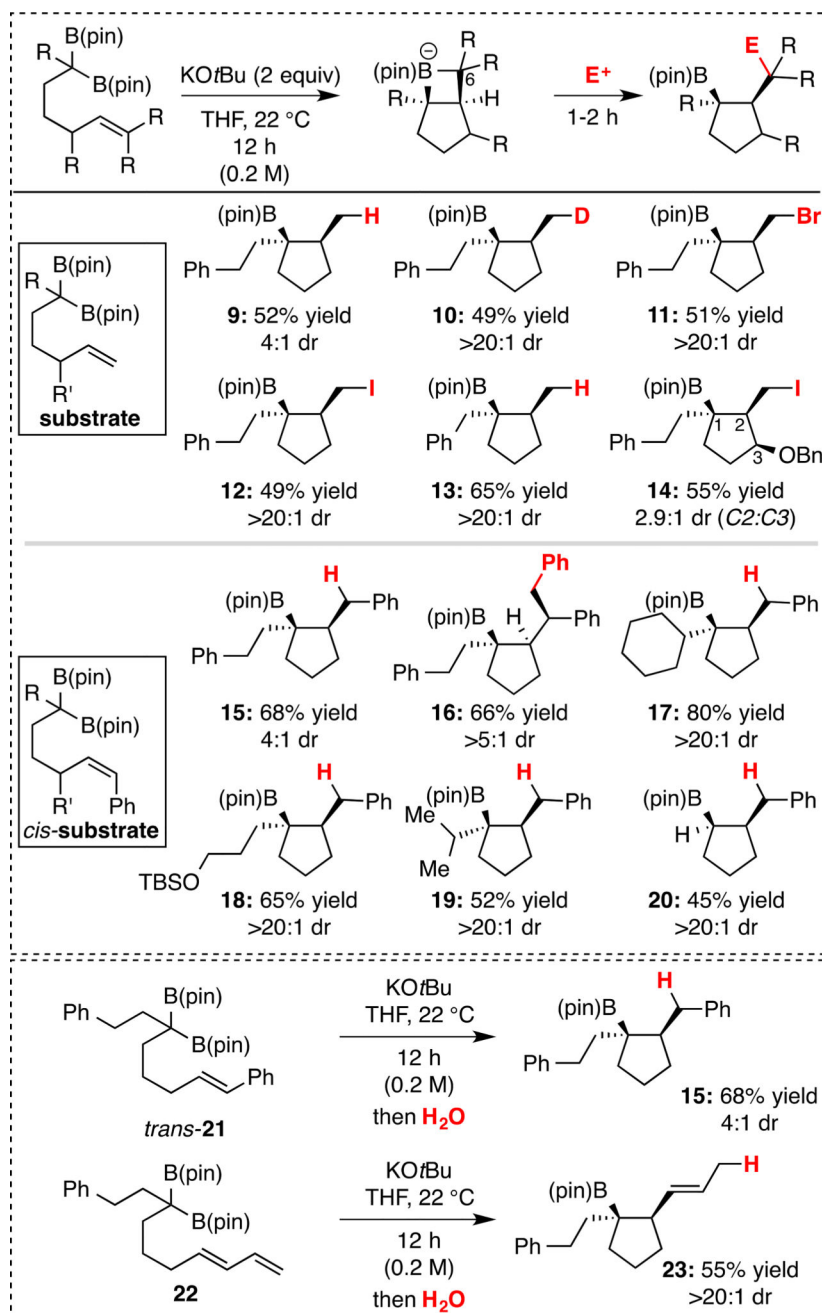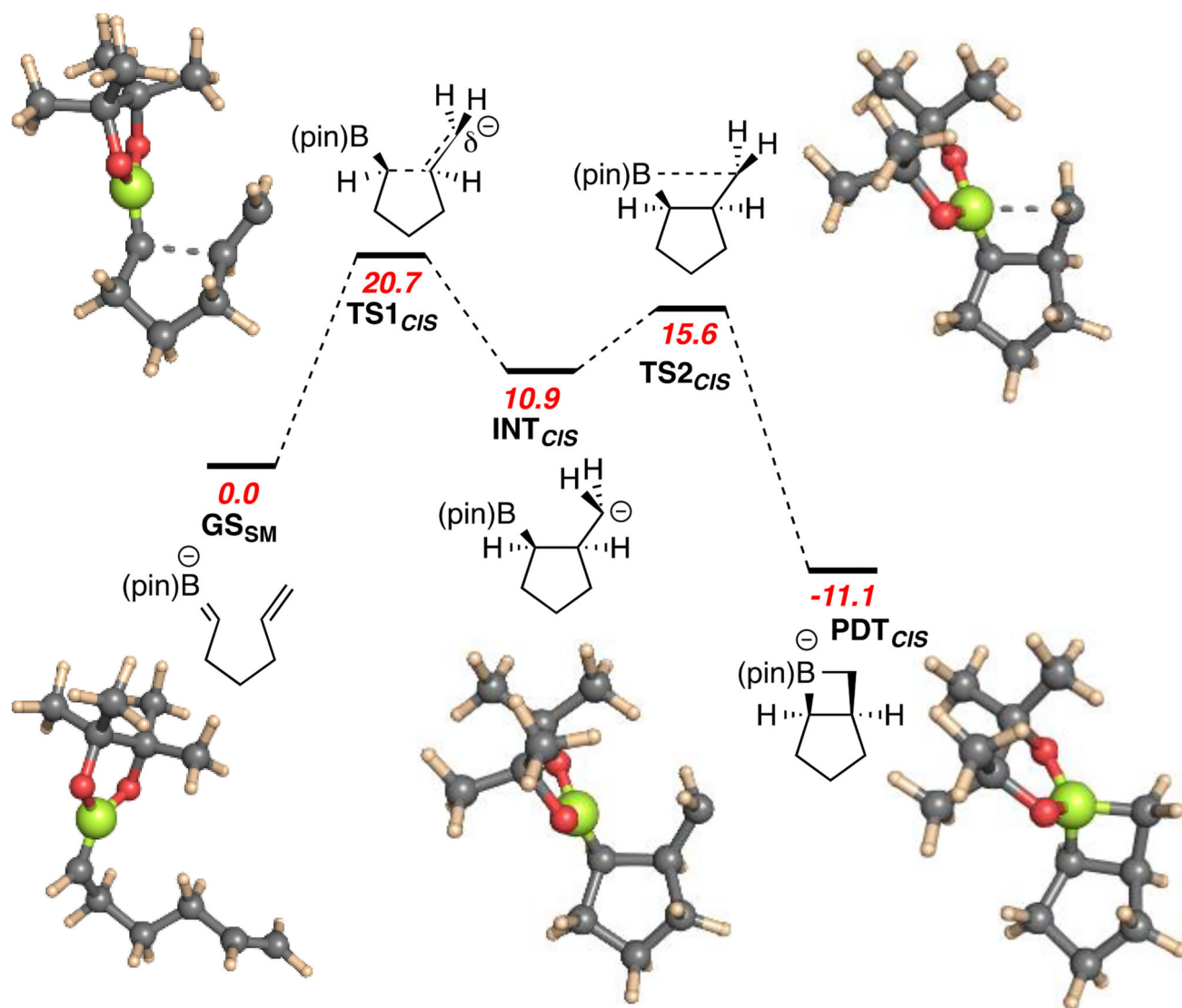
Figure 1.
Boron alkylidene-alkene 2+2 cycloaddition followed by reaction with an electrophile. After deborylative cyclization, the following electrophiles were employed: H_2O (**H**), D_2O (**D**), N-bromosuccinimide (**Br)**), I_2 (**I**), benzyl bromide (**CH₂Ph**).
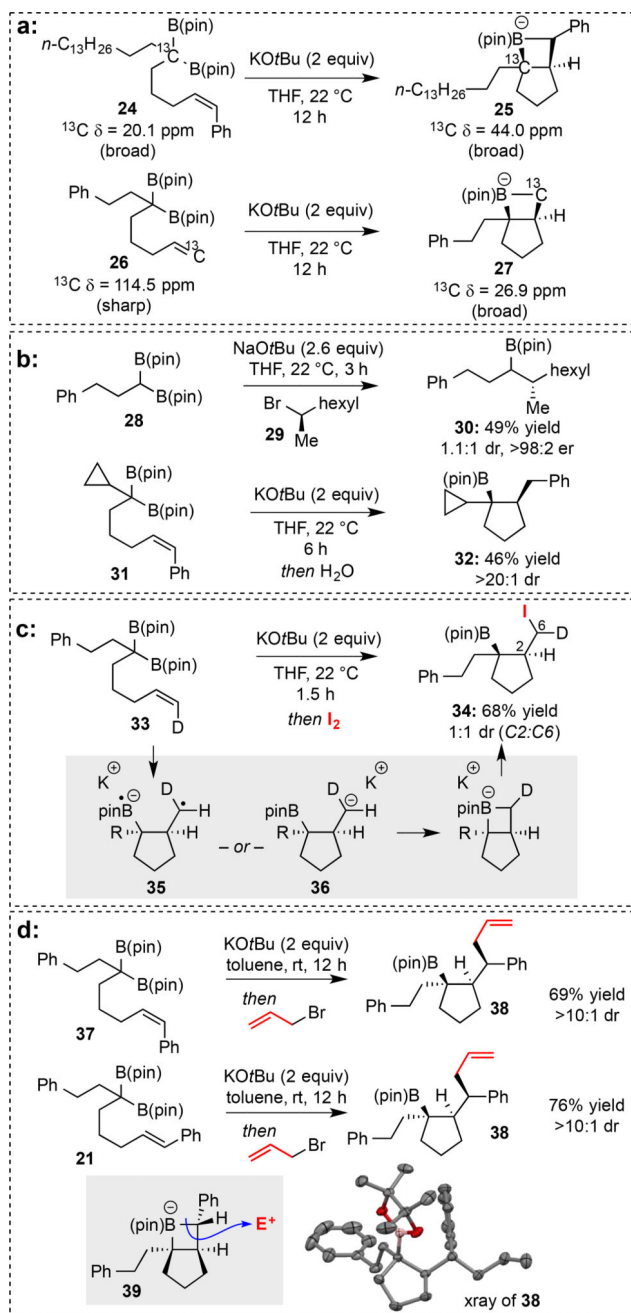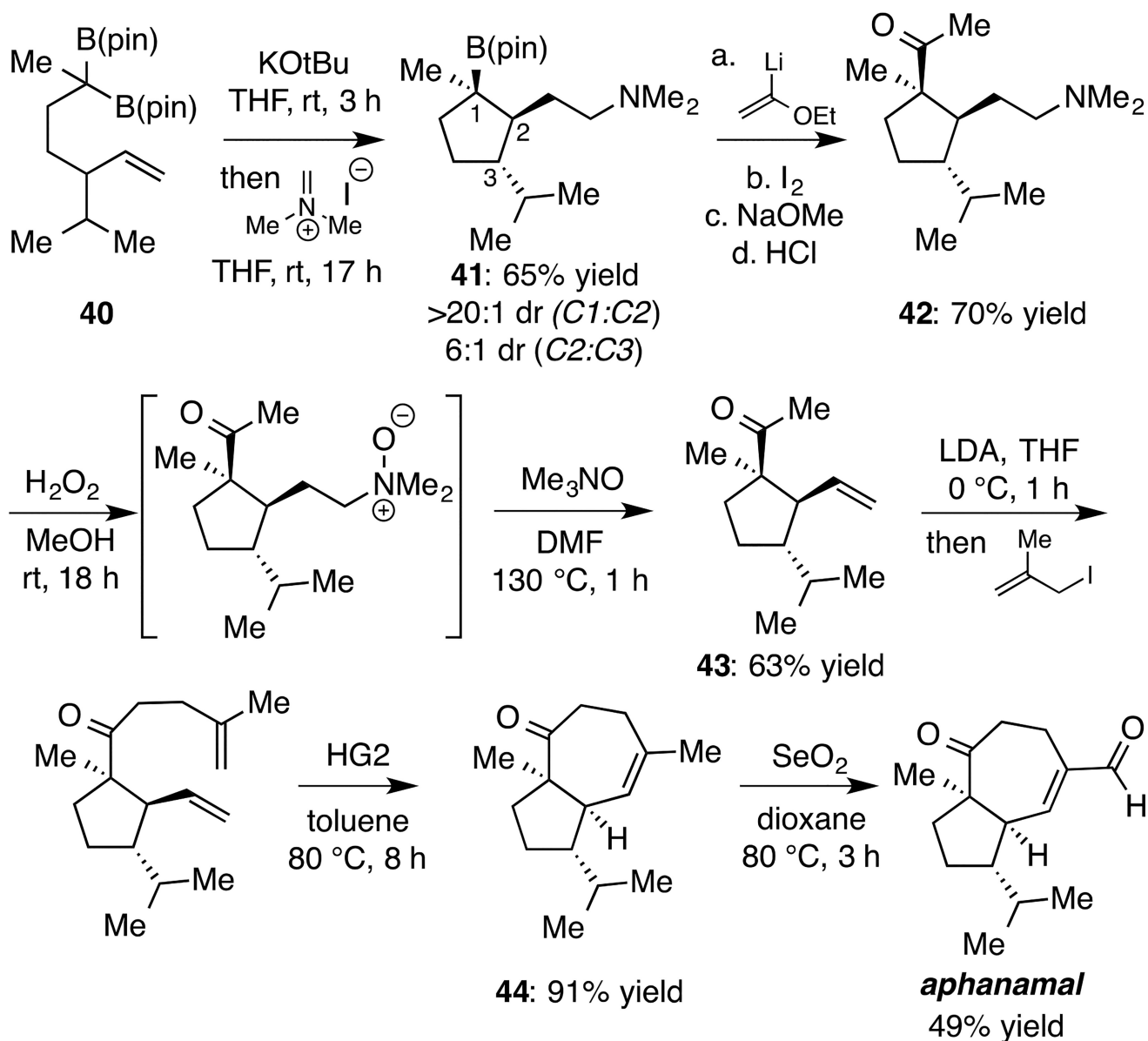
Figure 2.
Mechanistic investigation of the boron alkylidene/alkene cycloaddition reaction. (a) Isotope labeling studies support the intermediacy of a four-membered boretane. (b) Stereochemical and radical clock experiments suggest that radical intermediates may not be involved. (c) Use of a labeled alkene suggests the 2+2 reaction is not a stereospecific process. (d) The lack of stereospecificity in 2+2 reactions enables stereoconvergent reactions.

Figure 3.
DFT Analysis of the boron alkylidene/alkene cycloadddition reaction. Reaction to give the *syn* stereoisomer of product proceeds through an intermediate carbanion. Values are relative G in kcal/mol at 298 K; calculations performed by density functional theory (DFT; M06-2×/6–31+G* with PCM solvent model (THF).

Figure 1.
Stereoselective synthesis of aphanamal.

Scheme 1.