Boron Chemistry

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Transition-Metal-Free Diboration Reaction by Activation of Diboron Compounds with Simple Lewis Bases**

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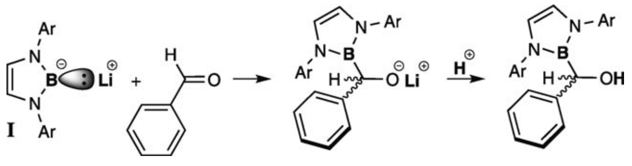
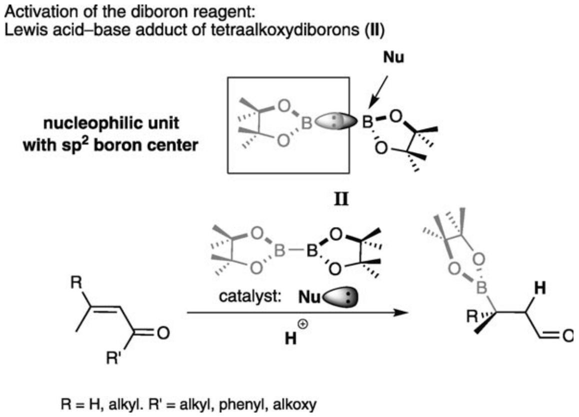
One of the most recent advances of organoboron chemistry is the isolation and synthetic applications of anionic sp^2 boron nucleophiles with sensitive carbene-type structures[1] (**I**, Scheme 1). Among other examples, **I** could be added to benzaldehyde to afford the corresponding α-borylbenzyl alcohol. This reactivity suggests a classic nucleophilic addition mechanism.



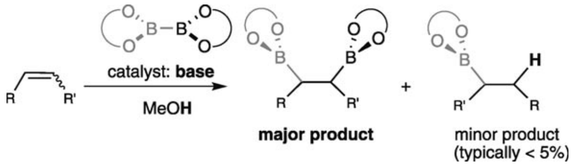
Scheme 1. Anionic "carbene-type" boron nucleophile **I** and its addition to benzaldehyde.

More recently, Hoveyda's and our research group independently recognized that sp^2 boron nucleophiles can also be generated in situ from easily accessible, chemically resistant diboron reagents and added to α,β-unsaturated carbonyl compounds[2,3] (Scheme 2). Upon interaction with Lewis bases, the diboron reagent becomes nucleophilic and is capable of transferring the "intact" sp^2 boryl group to activated olefins in nucleophilic conjugate additions. Importantly, in boron conjugate additions the electrophilic counterpart of the boron nucleophile is a proton, which usually derives from alcohol additives or aqueous workup.

Herein we demonstrate for the first time that the reactivity of the Lewis acid–base adducts **II** far exceeds that of common nucleophiles. By investigating the scope of catalysts, substrates, and reactions for this novel catalytic system, we discovered that, unlike ordinary nucleophilic reagents, the in situ formed adducts **II** attack non-activated, nucleophilic unsaturated substrates. Most importantly, although the reaction conditions are very similar to those we use for conjugate boron additions to activated olefins, the chemoselectivity is different. Despite the presence of the protic additive, usually MeOH, the electrophilic counterpart of the nucleophilic boryl unit also derives from the activated diboron reagent: the primary reaction is the Lewis base catalyzed diboration of the substrate (Scheme 3).



Scheme 2. Nucleophilic conjugate addition of an sp^2 boron unit to α,β-unsaturated carbonyl compounds.



Scheme 3. Nucleophilic diboration of non-activated olefins with diboron reagent, meditated by base/MeOH as catalyst.

The new reaction has several significant aspects. 1) The product is formed by a reaction between a nucleophilic substrate and a reagent that also has a pronounced nucleophilic character, representing an almost unknown reactivity. 2) Unlike in the case of conjugate additions, both boryl units of the reagent are introduced to the substrate, resulting in an atom-economic addition reaction of great practical importance. 3) Up to date, the only known method to add tetralkoxydiboron compounds to non-activated alkenes was the application of transition-metal complexes as catalysts.[4–8] Since organoboranes are very important in organic synthesis and biomedicine,[9–14] the transition-metal-free approach described herein might be a very appealing alternative.

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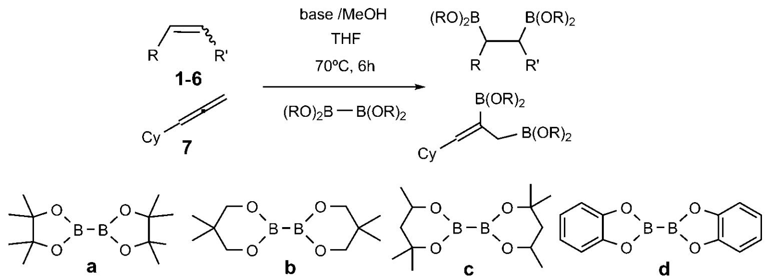
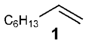
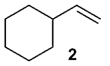
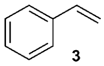
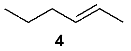
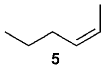
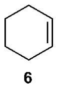
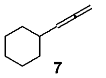
The catalytic system for the nucleophilic diboration of non-activated olefins is a combination of base and alcohol. Both additives are crucial to achieve high activity. After the screening of various bases and alcohols,[15] we have concluded that, in THF solutions, a combination of Cs_2CO_3 and MeOH provides synthetically useful conversions and chemoselectivities towards the diborated product. It is worth noting that various other bases, such as methoxides (Li^+, Na^+, K^+), or NaO*t*Bu give comparable results. Despite the fact that for optimal activities MeOH is added in excess with respect to the substrate, the formation of the "hydroborated" by-product rarely exceeds 5 mol%. This simple catalytic system is capable of mediating the addition of different diboron reagents to various non-activated unsaturated substrates. For example, in THF at 70°C, bis(pinacolato)diboron (**a**) could be added quantitatively to 1-octene (**1**) in the presence of 15 mol% Cs_2CO_3 and 5 equivalents of MeOH, within 6 h (Table 1, entry 1). Only traces of the "hydroborated" by-product could be observed by GC analysis. Changing the *n*-hexyl substituent to cyclohexyl (**2**) did not influence the reactivity of the C=C double bond significantly; 92% of the vinylcyclohexane was converted with close to complete chemoselectivity into the desired diborated product (Table 1, entry 2). Diboron reagents formed from 1,3-diols and catechol (**b**, **c**, **d**) are less reactive than bis(pinacolato)-diboron (**a**; Table 1, entries 2–5). The diboration of styrene (**3**) required milder reaction conditions than that of the aliphatic alkenes to obtain high selectivity (Table 1, entry 6). The diboration of internal alkenes (**4**–**6**) provided crucial information on the mechanism of the reaction. Unlike many of the classic electrophilic additions such as halogenation of alkenes, the nucleophilic diboration of non-activated olefins always occurs in *syn* fashion. Thus, diboration of *trans*-hex-2-ene (**4**) gives the diborated product in a 3:97 *syn*/*anti* ratio, while *cis*-hex-2-ene (**5**) forms the corresponding diborated product in 95:5 *syn*/*anti* ratio. Similarly, the diboration of cyclohexene exclusively gives the *cis* diborated product (Table 1, entries 7–9). Another interesting finding is that nucleophilic diboration of allene **7** favors the formation of the 1,2-diborated product (Table 1, entry 10). This selectivity is in contrast to most transition-metal-catalyzed diborations of allenes, which usually provide the 2,3-diborated isomers as primary products.[16–18]

Table 1: Transition-metal-free diboration reaction of alkenes and allenes.[a]



Entry	Substrate	$B_2(OR)_4$	Base	Conv. [%]	Sel. [%][b]	Yield [%][c] (isol. [%])[d]
1	 1	a	Cs_2CO_3	98	99	97 (71)
2	 2	a	Cs_2CO_3	92	97	89 (71)
3	2	b	Cs_2CO_3	73	99	72 (59)
4	2	c	Cs_2CO_3	60	99	59 (56)
5	2	d	Cs_2CO_3	85[e]	99	84[e] (82)[f]
6[g]	 3	a	NaO*t*Bu	82	99	81 (74)
7	 4	a	Cs_2CO_3	74	96 [*syn*/*anti* 3:97]	69 (57)
8	 5	a	Cs_2CO_3	92	95 [*syn*/*anti* 95:5]	83 (69)
9[h]	 6	a	NaO*t*Bu	84	99	83 (65)
10[i]	 7	a	NaO*t*Bu	95	92 [1,2-diboron 87%]	76

[a] General conditions: substrate (0.5 mmol), diboron reagent (0.55 mmol), base (15 mol%), MeOH (2.5 mmol), THF (2 mL), $T = 70$°C, $t = 6$ h. [b] As well as the "hydroborated" by-product (<5%), in certain cases traces of vinyl boronic esters (<1%) could be identified by GC-MS analysis. [c] Yield of the diborated product determined by GC analysis. [d] Yield of isolated diborated product. [e] Based on an internal standard. [f] Isolated as the corresponding diol. [g] $T = 45$°C, $t = 15$ h. [h] $T = 70$°C, $t = 16$ h. [i] $T = 45$°C, $t = 20$ h.

To understand the reactivity of the Lewis acid–base adducts **II**, one has to take into account both 1) the structure of the tetraalkoxydiboron compounds and 2) the structural changes they undergo upon the interaction with appropriate Lewis bases. Tetraalkoxydiboron compounds do not have nucleophilic character, and their electrophilicity, which originates from the presence of the virtually empty p orbitals of the boron atoms, is also considerably suppressed as a result of electron donation from the nonbonding pairs of the oxygen atoms (Figure 1). Nevertheless, they can establish Lewis acid–base interactions with C,[2] N,[19–23] and O[24] nucleophiles. The structural changes generated by such interactions cannot be sufficiently represented with the classical Lewis formulae.

Considering the Lewis structure of adducts **II**, one would expect an increased negative charge density on the rehybridized, formally sp^3 boron atom. According to our DFT calculations carried out on bis(pinacolato)diboron and on its Lewis acid–base adduct with CH_3O^- anion, the sp^3 boron atom loses negative charge density upon the charge transfer from the Lewis base, while the sp^2, virtually intact boron atom unambiguously gains

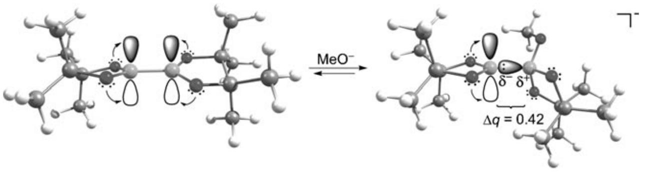
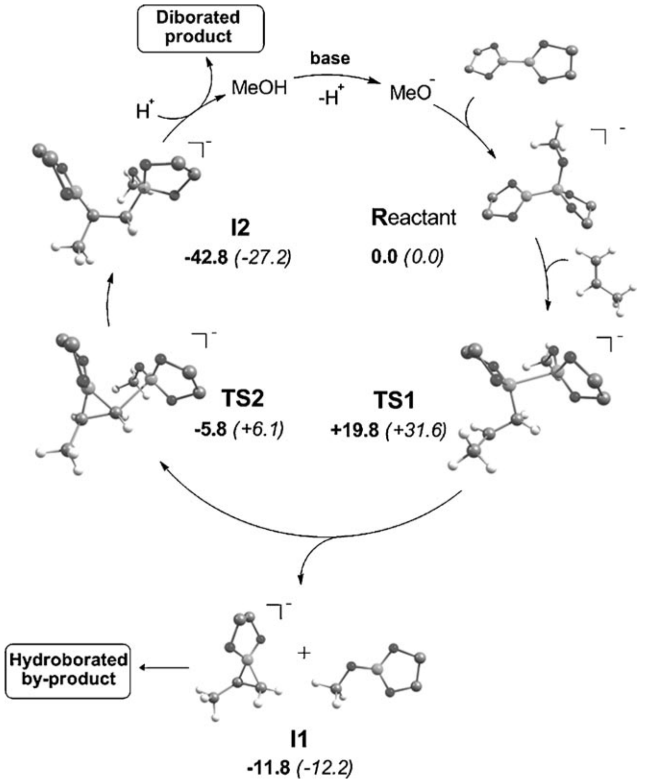


Figure 1. Polarization of the B–B bond upon formation of the Lewis acid–base adduct; Δq: difference between the Mulliken charges of the boron atoms of the adduct (see DFT calculations in the Supporting Information).[26–28]

electron density with respect to its partial charge in the intact bis(pinacolato)diboron. The loss of electron density on the sp^3 boron atom, despite the direct charge transfer from the Lewis base, can be rationalized by considering that upon rehybridization the boron atom loses the π-symmetric electron donation from the oxygen atoms of the pinacolate moiety. The net result of these structural changes is that in adducts **II** the B–B bond becomes considerably polarized, and the sp^2 boron atom gains a strong nucleophilic character.

We envisioned a mechanism for the organocatalytic diboration of olefins in which methoxide anion, generated in situ from MeOH with a catalytic amount of base, activates the diboron reagent (Scheme 4). A similar adduct formed from B$_2$pin$_2$ and KO*t*Bu was reported by Marder and coworkers.[25] To find evidence for the subsequent steps of the catalytic cycle, we studied the possible interactions between a model substrate propylene and the MeO$^-$→bis(pinacolato)diboron adduct using various DFT methods.[26–28]



Scheme 4. Suggested catalytic cycle. Electronic energy (kcal mol^{-1}) and Gibbs free energy (kcal mol^{-1}; in parentheses) computed at the M06 level relative to B$_2$pin$_2$·MeO$^-$ adduct plus propylene. Methyl groups of B$_2$pin$_2$ are omitted for clarity.

We identified two transitions states that can explain the formation of the product and the "hydroborated" by-product. In TS1 the sp^2 boron atom of the activated diboron reagent interacts with the unsubstituted carbon atom (C^1) of the C=C double bond, while the B–B bond weakens, and the negative charge density on the C^2 carbon increases. Importantly, we found that the interaction leading to TS1 is the overlap between the strongly polarized B–B σ bond (HOMO) of the activated diboron reagent and the antibonding π* orbital (LUMO) of the olefin. Hence, the reactivity between the reaction partners is clearly a nucleophilic attack of the reagent towards the substrate. The increased negative charge density on C^2 in TS1 results in considerable kinetic lability due to the positive inductive effect of the alkyl substituent. The negatively charged C^2 atom should be prone to attack any electrophilic site, and the closest one in TS1 is the attacking boron atom, which is losing the B–B bond as a result of nucleophilic attack. The distribution of the negative charge density among C^1, C^2, and the boron atom, might explain the connection between TS1 and the intermediate I1, as well as the formation of the second transition state structure TS2. Protonation of the intermediate I1 gives the "hydroborated" by-product.

Importantly, when electronic effects stabilize TS1 (increase its kinetic stability, and hence its lifetime) the "hydroboration" side reaction becomes competitive with the diboration reaction. This is the case when styrene (**3**) is the substrate, whereby the phenyl ring can stabilize the increased negative charge density on the C^2 atom. The electronic stabilizing effect is even more pronounced in the case of α,β-unsaturated carbonyl compounds as substrates, for which the "hydroborated" (β-borated) substrate is the only product of the reaction.

Upon nucleophilic attack, there is overlap between the strongly polarized B–B σ orbital and the C–C π* orbital, and the –B(pin)(OMe) moiety becomes electrophilic and is capable of interacting with the negatively charged olefin–B(pin) fragment. This interaction can be described with the second transition-state structure TS2, which directly leads to the methoxide adduct of the diborated main product (I2), rendering the overall process strongly exothermic ($\Delta G = -27.2$ kcal mol^{-1}). An interesting feature of the mechanism is that although the nucleophilic boron atom attacks at the C^1 atom, in the product it will be bonded to C^2. Actually, this sort of reaction sequence (R-TS1-TS2-I1,I2), which connects two transition states and two products, resembles what Houk called a bifurcation.[29]

In summary, we have reported a reaction that represents very rare reactivity: a reaction between a nucleophilic reagent and a nucleophilic substrate. The boron nucleophile is generated from easily accessible, chemically resistant diboron reagents, which also provide the electrophilic counterpart of the nucleophilic boron moiety. Precisely this structural feature, the possibility to subsequently create a nucleophilic and an electrophilic site on the activated diboron reagent along the reaction coordinate, makes this unusual reaction pathway possible. The net result is a new, Lewis base catalyzed diboration method, which, because of the simple reagents and catalysts, the complete atom economy, and the high synthetic value of the products, represents a great step towards a future industrial organoborane synthesis.

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