B–B Bond Activation

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Homolytic Cleavage of a B–B Bond by the Cooperative Catalysis of Two Lewis Bases: Computational Design and Experimental Verification

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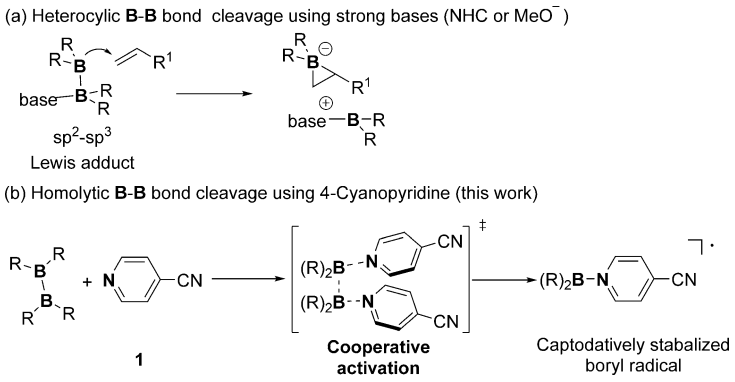
Abstract: *Density functional theory (DFT) investigations revealed that 4-cyanopyridine was capable of homolytically cleaving the B–B σ bond of diborane via the cooperative coordination to the two boron atoms of the diborane to generate pyridine boryl radicals. Our experimental verification provides supportive evidence for this new B–B activation mode. With this novel activation strategy, we have experimentally realized the catalytic reduction of azo-compounds to hydrazine derivatives, deoxygenation of sulfoxides to sulfides, and reduction of quinones with $B_2(pin)_2$ at mild conditions.*

Diborane compounds, $R_2B–BR_2$, are highly useful synthetic modules for concise synthesis of organoboronates,[1] which are versatile building blocks for the generation of new chemical bonds using the Suzuki–Miyaura crossing-coupling reactions.[2] Many transition-metal complexes are known to be able to effectively cleave the B–B bond of diborane and catalyze the borylation or diboration of unsaturated organic substrates.[3,4] On the other hand, transition-metal-free catalytic systems for activating the B–B bond of diborane compounds have also attracted much attention.[5]

Recently, the Lewis adducts of sp^2–sp^3 diborane compounds have been reported for the borylation or diboration of unsaturated substrates.[5–9] It has been shown that diborane compounds became a source of nucleophilic boryl moiety, when one of the boron atoms of the diborane was tetracoordinated to a strong base (Scheme 1 a). In such cases, the B(sp^2)–B(sp^3) bonds are always cleaved heterolytically.[6c,7b] In addition, reductive addition of diboranes to sterically hindered pyrazines in the presence of bipyridine derivatives has also been reported.[10] Nevertheless, the mechanistic details of this reaction are unclear yet. Owing to the high B–B bond dissociation energy (BDE) of diborane derivatives,[11] strong bases such as N-heterocyclic carbenes (NHC),[6] Cs_2CO_3, *t*-BuOK[7b] are usually used in the activation of diborane compounds. Given the considerable utility of diboranes in synthetic chemistry, it is highly desirable to develop new strategies for the activation of B–B bond.

Note that in the Lewis adducts of sp^2–sp^3 diborane compounds, there is another sp^2 hybridized boron atom. We envisioned that if the empty p orbital of the uncoordinated boron atom is associated with a second Lewis base, the B–B bond would be further weakened, and might be cleaved in a homolytic manner. With appropriate Lewis bases, the boryl radical generated from the homolytic cleavage of diborane B–B bond could be sufficiently stable, through the possible captodative effect.[12] Pyridines with electron-withdrawing substituents may act as appropriate Lewis bases to activate the B–B bond of diborane compounds as a result of their high boryl radical stabilization energies (see Scheme S1 in the Supporting Information). Herein, we report a computationally designed and experimentally verified catalyst which can homolytically cleave the B–B bond of $B_2(pin)_2$ via the cooperative Lewis base mechanism (Scheme 1 b).



Scheme 1. Representative transition-metal-free B–B bond activation modes. a) Heterolytic B–B bond cleavage using strong bases. b) Homolytic B–B bond cleavage with 4-cyanopyridine.

Before verifying our hypothesis experimentally, we performed density functional theory (DFT) calculations with the M06-2X functional[13] to determine whether the B–B bond of $B_2(pin)_2$ could be activated in this way. Computational details are given in the Supporting Information. The 4-cyanopyridine (**1**) was first selected to be the Lewis base. The free-energy profile of the reaction between 4-cyanopyridine and $B_2(pin)_2$

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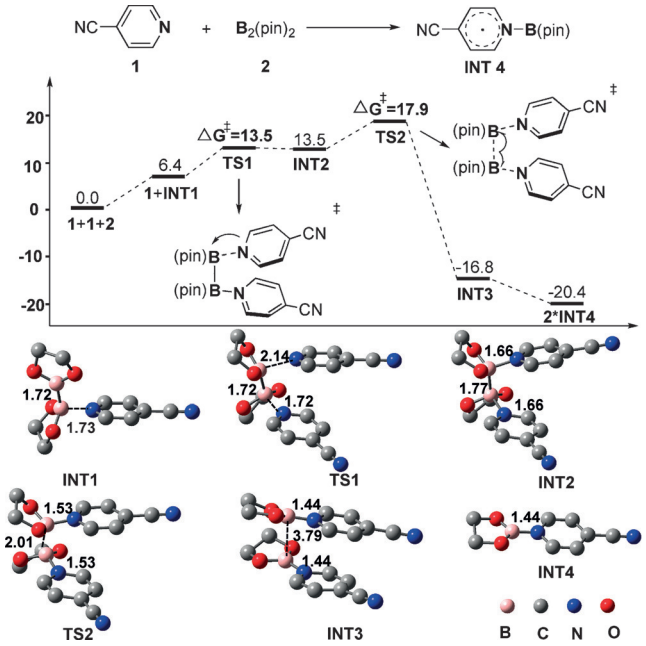
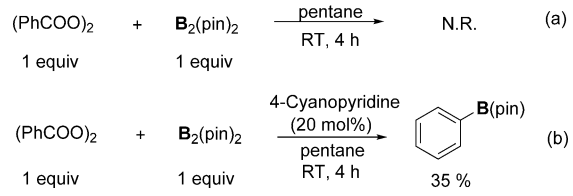


Figure 1. Computed Gibbs free energy (in kcal mol^{-1}) profile for the 4-cyanopyridine catalyzed homolytic B–B bond cleavage in $B_2(pin)_2$ in the solvent (benzene). Hydrogen atoms and the methyl group of pinacol boron are omitted for clarity. Interatomic distances are in Å.

(**2**) is shown in Figure 1 (see Supporting Information for details). First, the coordination of 4-cyanopyridine to one boron atom of $B_2(pin)_2$ generates the sp^2–sp^3 diborane (**INT1**). Then, a second 4-cyanopyridine molecule is coordinated to the sp^2 boron atom of **INT1** to form a possible intermediate (**INT2**) via **TS1**, with a barrier of 13.5 kcal mol^{-1}. Owing to the formation of two strong B–N bonds, this intermediate is only 13.5 kcal mol^{-1} in free energy above the separated reactants. Then, the homolytic cleavage of the B–B bond in **INT2** occurs via **TS2** with a barrier of 17.9 kcal mol^{-1} (relative to the separated reactants) to generate a diradical species (**INT3**), in which two radicals are loosely bound via the π–π stacking interaction. Our local correlation post-Hartree–Fock calculations[14] (see supporting information for details) also lead to a barrier of 18.2 kcal mol^{-1}, being very close to the M06-2X result (17.9 kcal mol^{-1}). Finally, this diradical species may readily dissociate into two boryl radicals (**INT4**). The rate-determining step in this process is the homolytic B–B bond cleavage, and the whole process is exothermic by 20.4 kcal mol^{-1} (with respect to the separated reactants). The reactions of $B_2(pin)_2$ and other substituted pyridines were also investigated theoretically. Our calculations suggested that 4-cyanopyridine is the most effective Lewis base for B–B bond activation, which has the lowest activation barrier.

Subsequently, we performed free-radical trapping experiments to verify whether the B–B bond of $B_2(pin)_2$ could be homolytically cleaved with 4-cyanopyridine to generate the boryl radical (**INT4**). In the absence of 4-cyanopyridine, a 1:1 mixture of benzoyl peroxide (BPO) and $B_2(pin)_2$ was stirred at room temperature for 4 h, and no desired product was detected (Scheme 2a). However, the addition of 20 mol% 4-



Scheme 2. Free-radical trapping experiments.

cyanopyridine gave phenylboronate in 35% yield at the same reaction conditions (Scheme 2b). Our DFT calculations suggested that the boryl radical (**INT4**) could induce the homolytic O–O bond cleavage of BPO to form the benzoyloxy radical (see Figure S5). This experiment provides a supportive evidence for the homolytic cleavage of the B–B bond of $B_2(pin)_2$.

We also carried out electron paramagnetic resonance (EPR) experiments to examine the possibility of directly detecting the boryl radical (**INT4**). When $B_2(pin)_2$ (**2**) was added to a THF solution of 4-cyanopyridine, a spectrum at $g = 2.00319$ (298 K) was obtained, as shown in Figure 2. The

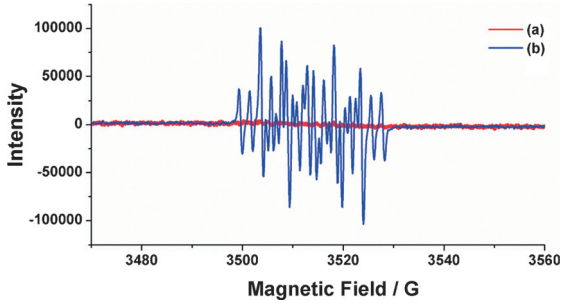


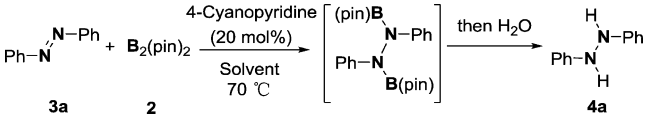
Figure 2. X Band EPR spectrum obtained in THF at 298 K. a) Spectrum of 0.1 M solutions of 4-cyanopyridine. b) Spectrum of a 1:1 mixture of 4-cyanopyridine and $B_2(pin)_2$.

hyperfine splittings (hfs) together with the spin-density distribution suggested that the unpaired electron of **INT4** was mainly delocalized over the 4-cyanopyridine moiety. The direct observation of the EPR signal of the boryl radical (**INT4**) provides a strong support for the proposed mechanism in Figure 1. Interestingly, in the chemistry of frustrated Lewis pairs (FLP)[15] or chemistry containing Lewis adduct of sp^2–sp^3 diboranes,[5–9] the Lewis bases are always regarded as an electron donor. On the contrary, 4-cyanopyridine behaves as a single-electron acceptor in the homolytic B–B bond cleavage of $B_2(pin)_2$.

Intrigued by the above computational and experimental results, we further attempt to explore whether this novel B–B activation mode can be employed in some chemical transformations. First, we focused our attention on the catalytic reduction of the N=N double bond of the azobenzene with $B_2(pin)_2$. The reductive diboration of N=N double bond has only been reported with rather specific diboron compounds.[16] Herein, we demonstrated that the catalytic reduction of azoarenes can be achieved with $B_2(pin)_2$ using 4-cyanopyridine as the catalyst. In the presence of 20 mol% of 4-cyanopyridine, product **4a** was obtained at 70 °C in 73%

yield (Table 1, entry 4). After further screening, the highest yield of **4a** (99%) was obtained with 1.5 equivalent of $B_2(pin)_2$ in pentane (entry 7). Some solvents (CH_2Cl_2 and CH_3CN) were found to be not suitable for this reaction, probably because of their greater stabilization for the free-radical intermediate (**INT4**).

Table 1: Optimization of the reaction conditions.[a]



3a 2 4a

Entry	Cat. [mol%]	$B_2(pin)_2$ [equiv]	Solvent	Yield [%][b]
1	none	1.2	pentane	n.d.
2	20	1.2	CH_2Cl_2	trace
3	20	1.2	CH_3CN	trace
4	20	1.2	THF	73
5	20	1.2	hexane	85
6	20	1.2	pentane	88
7	20	1.5	pentane	99

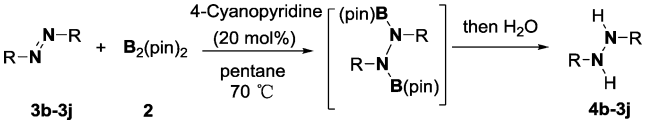
[a] Reaction conditions: azobenzene (0.20 mmol), solvent (1.0 mL), 24 h. Catalyst loading relative to azobenzene. [b] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard.

Under the optimal reaction conditions, we further examined the substrate scope of this catalytic reaction with various azo-compounds (Table 2). The azoarenes with electron-donating groups (**3b–d**) as well as electron-withdrawing groups (**3e–j**) on the phenyl were reduced in the reaction, affording the corresponding diaryl hydrazines in good to excellent yields (75–99%). Meanwhile, the position of substituents on the phenyl showed little influence on the reactivity (**3b–g**). Interestingly, for the substrate with ester groups (**3j**), only the N=N double bond of azobenzene was reduced. The halide (F, Cl, Br) groups were also well tolerated (**3e–i**).

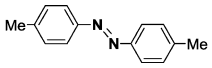
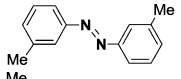
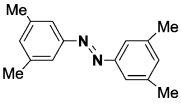
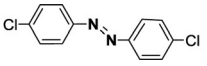
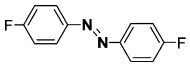
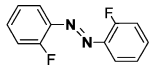
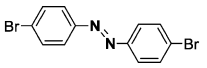
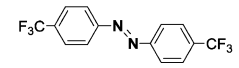
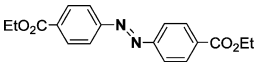
The possible mechanism for the reduction of azobenzene was also investigated using DFT calculations. The most probable pathway is shown in Scheme 3 (the structures of all stationary points are listed in Figure S4 of the Supporting Information). As shown in Scheme 3, the reduction of azobenzenes occurs via a successive boryl radical migration mechanism. The rate-determining step in this reaction (via **TS3**) has a barrier of 18.9 kcal mol^{-1}, and the whole process is exothermic by 19.2 kcal mol^{-1} (with respect to the reactants **3a** and **INT4**). The calculated results are consistent with the mild experiment conditions (at 70 °C). The experimental results and DFT calculations showed that the reduction of the N=N double bond of azo-compounds could be achieved at mild conditions via the proposed new B–B bond activation mode.

With the 4-cyanopyridine/$B_2(pin)_2$ system, we also investigated the reductive deoxygenation of sulfoxides to sulfides (Scheme 4). In the presence of the catalytic amount of 4-cyanopyridine, diphenyl or phenyl methyl sulfoxides bearing electron-withdrawing groups (Br, Cl, CN) were reduced at 80 °C to afford the desired sulfides in moderate isolated yields

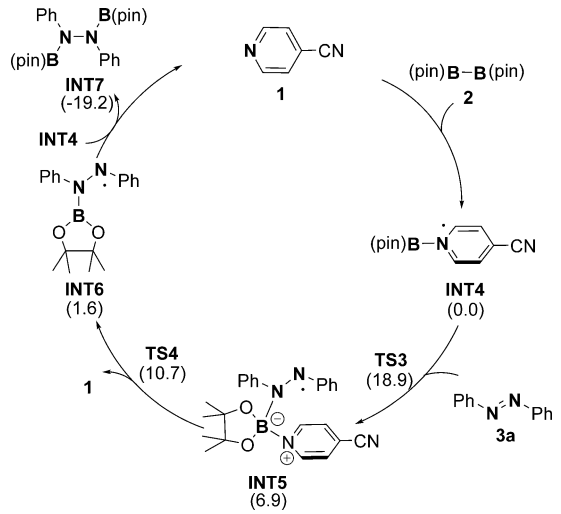
Table 2: Scope of the catalytic reduction of azo-compounds.[a]



3b-3j 2 4b-3j

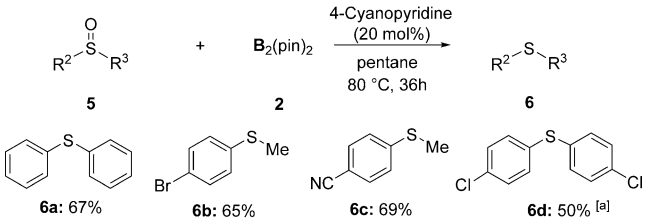
Substrates		Products	Yield [%][b]
3b		**4b**	77
3c		**4c**	99
3d		**4d**	96
3e		**4e**	87
3f		**4f**	98
3g		**4g**	99
3h		**4h**	99
3i		**4i**	75
3j		**4j**	99

[a] Reaction conditions: azoarenes (0.20 mmol) with $B_2(pin)_2$ (0.30 mmol) in pentane (1.0 mL) at 70 °C for 24 h. Catalyst loading relative to azobenzene. [b] Yields were determined by ^{1}H NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard.



Scheme 3. The suggested catalytic cycle for the reduction of the azobenzene with $B_2(pin)_2$ using 4-cyanopyridine as catalyst. The relative Gibbs free energies (relative to **3a** and **INT4**) are given in parentheses (in kcal mol^{-1}).

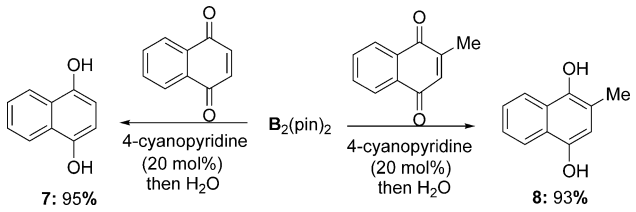
(50–69%). Although many methods have been developed for deoxygenation of sulfoxides,[17] some of these processes have used moisture-sensitive reagents, [17a] or transition metals.[17b] The possible reaction pathway for this type of reaction was



Scheme 4. 4-Cyanopyridine-catalyzed deoxygenation of sulfoxides to sulfides with $B_2(pin)_2$. [a] The reaction was performed in toluene.

also explored with DFT calculations, with the diphenyl sulfoxide as the substrate. Our calculations suggest that this reaction occurs via a stepwise mechanism (see Figure S6). The rate-limit step of the whole reaction has a barrier of 16.0 kcal mol^{-1}, and the whole process is exothermic by 79.8 kcal mol^{-1}. Therefore, the use of $B_2(pin)_2$ as reducing reagents may represent a practical method for deoxygenation of sulfoxides to sulfides, owing to the low toxicity, high stability of $B_2(pin)_2$.

Furthermore, the 4-cyanopyridine/$B_2(pin)_2$ system was applied to achieve the catalytic reduction of quinones. The reduction of 1,4-naphthoquinone and 2-methylnaphthalene-1,4-dione with $B_2(pin)_2$ in the presence of 4-cyanopyridine occurred at 50 °C to afford 1,4-diboration quinones, which were then hydrolyzed to yield hydroquinones in excellent yields (Scheme 5). The reduction of quinones has been



Scheme 5. 4-Cyanopyridine-catalyzed reduction of the quinones with $B_2(pin)_2$.

investigated by chemical, photochemical, and enzymatic methods because of its biological and industrial significance.[18] In these processes, metal complexes or coenzyme NADH were used as electron donors. However, our experimental and theoretical investigations suggested that the boryl radical intermediate (**INT4**) may act as a novel electron donor for the reduction of quinones (see Scheme S5). Therefore, the present Lewis base/$B_2(pin)_2$ system provides a new strategy for the reduction of quinones.

In summary, a novel B–B bond activation mode has been designed computationally and verified experimentally. In this new mode, two Lewis bases are coordinated to the two boron atoms of $B_2(pin)_2$, and then the B–B bond is homolytically cleaved to generate two boryl radicals. 4-Cyanopyridine can act as the Lewis base, as a result of its ability to form a strong N–B bond with $B_2(pin)_2$. The captodative effect is responsible for the stability of the generated boryl radical. Free-radical trapping and EPR experiments provide strong support for the generation of the boryl radical. With this novel activation mode, we have realized the catalytic reduction of azo-compounds and quinones, and deoxygenation of sulfoxides to sulfides, with 4-cyanopyridine and $B_2(pin)_2$ at mild conditions. Further studies to find more efficient Lewis bases for homolytic B–B bond activation, and explore other diborane involved transformations are underway.

Acknowledgements

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