Substrate Specific Metal-Ligand Cooperative Binding: Considerations for Weak Intramolecular Lewis Acid/Base Pairs

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Supporting Information Placeholder

ABSTRACT: Metal-ligand cooperative binding modes were interrogated in a series of zinc bis(thiophenoxide) complexes. A weak B-S binding interaction is observed in solution between the weakly Lewis basic thiophenoxide ligands and an appended trialkylborane. The energy of this binding event is dependent upon the strength of the Lewis acid and its proximity to the zinc-thiophenoxide.

Many new vistas employed by synthetic systems for small molecule binding/activation attempt to rely not only on a central metal active site, but also on a metal's surrounding environment.[1] Such secondary coordination sphere groups often use cooperative interactions to facilitate substrate coordination, stabilize high-energy transition states, and facilitate charge transfer.[2] Although commonly encountered within metalloenzyme active sites as regulatory components, design principles that enable synthetic systems to reliably exploit secondary sphere acidic groups are challenging to translate.

The use of added Lewis acids to facilitate substrate binding and activation have demonstrated improvements in selectivity and activity for a variety of organic,[3] organometallic,[4] and electrochemical reactions.[5] However, many such reactions use highly Lewis acidic reagents (e.g. BF_3 or $B(C_6F_5)_3$)[6] or exhibit product inhibition by generating an irreversible acid base adduct, and thereby limiting efficient catalysis.[7] Alternatively, designed ligands containing intramolecular (tethered) Lewis acids can facilitate substrate binding and can direct reactivity.[8]

A challenge associated with synthetic systems that use extremely electrophilic acids, or feature high rigidity, is that the acidic interactions are rendered strong and stagnant. The result is that synthetic acidic/basic residues are often either directed[9] and too strong—preventing subsequent reactivity—or lack the acidity/basicity required to change the thermodynamic landscape of substrate binding/activation.[10] Synthetic molecular scaffolds whose acidic groups are flexible, and thereby mobile, may hold key advantages over rigid platforms.[11] Particularly, entropic penalties can be used to favor (or disfavor) cooperative interactions at a metal center and may be determined by the size and shape of a substrate/product. In cases where the ligand scaffold is pre-organized for favorable interactions with a metal-substrate, even modest strength Lewis acids (weaker enthalpy of acid-base binding) can impart large differences to both binding and activation of a given substrate.[12] Because the substrate shape and binding modes necessarily impact metal/Lewis acid cooperativity,[13] systematic studies to categorize distance effects are needed for substrates across multiple binding modes.

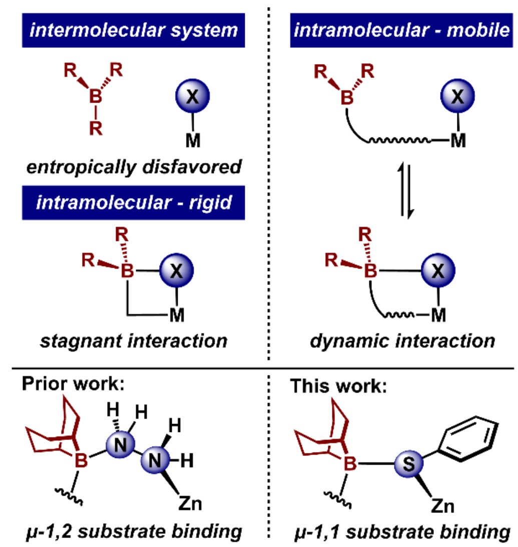
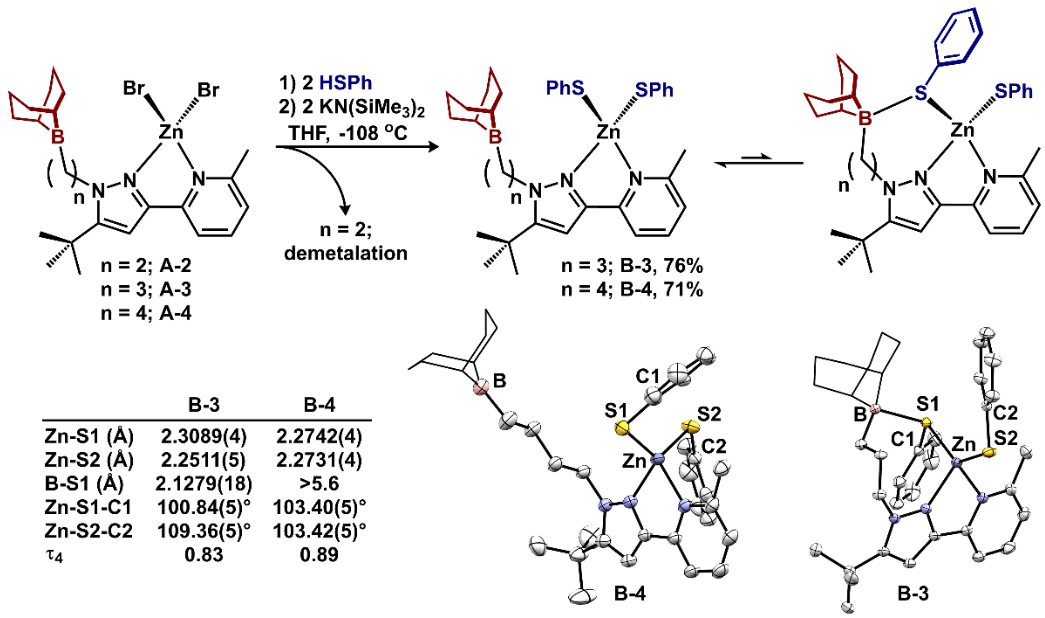


Fig. 1 Top: A dynamic binding regime enabled by a mobile Lewis acid design contrasts typical approaches that involve intermolecular acids or highly rigid systems. Bottom: specific substrates' binding modes interrogated with this framework.

Recently, our lab investigated a key design component of metal-ligand cooperativity: distance dependent binding/activation.[14] By varying the physical separation between zinc and a flexibly appended boron Lewis acid by ca. 1 Å increments (Fig. 1), we found that the binding mode and extent of activation/acidification were systematically



	B-3	B-4
Zn-S1 (Å)	2.3089(4)	2.2742(4)
Zn-S2 (Å)	2.2511(5)	2.2731(4)
B-S1 (Å)	2.1279(18)	>5.6
Zn-S1-C1	100.84(5)°	103.40(5)°
Zn-S2-C2	109.36(5)°	103.42(5)°
τ_4	0.83	0.89

Fig. 2 Synthesis of **B-3** and **B-4** and solution dynamic process. The molecular structures of **B-3** and **B-4** are displayed with 50% probability ellipsoids. All hydrogen atoms are omitted and the 9-BBN substituents are displayed in wireframe for improved clarity.

altered. While these methodical variations heightened our understanding of the system's ability to accommodate a μ-1,2-substrate, we recognized that these guiding principles may not necessarily be applicable across substrates that vary in size, shape, and electronics.

An inherent challenge in predicting the formation and favorability of a Lewis acid/base adduct is that Lewis acidities are substrate dependent: a consequence of both hard/soft-acid/base and steric considerations.[15] For analysis/optimization of a ligand's secondary sphere environment, combinations of acids/bases that form *strong* adducts (i.e. strong Lewis acids, or strong Lewis bases) provide limited insight into the geometric requirements needed for reversible binding when using an intramolecular tethered Lewis acid.[16] We selected thiophenoxides, substrates that we previously identified to exhibit dynamic binding with borane Lewis acids.[17] For example, modest binding energies for the $[Ni(CO)_3SPh]^-/BMe_3$ adduct ($\Delta H = -4$ kcal/mol) were calculated.[12] Herein, we describe our investigation to systematically evaluate the effects of Lewis acid proximity and strength on cooperative Zn-SPh-BR_3 binding by using a series of bidentate 2-(pyrazol-3-yl)pyridine ligands.

We initiated our studies with a set of complexes, ($^{n\text{-}BBN}NN^{tBu}$)$ZnBr_2$ (n = 2, 3, 4; complexes **A**),[14, 18] that differ only in the number of methylene units connecting the 2-(1-({CH_2}-BBN)-5-(*tert*-butyl)-1*H*-pyrazol-3-yl)-6-methylpyridine ligand to the appended 9-borabicyclo[3.3.1]nonane (BBN) Lewis acid (Fig. 2). Treating complexes **A** with two equiv. thiophenol followed by two equiv. potassium bis(trimethylsilyl)amide at low temperature produced divergent results. For **A-3** and **A-4** (e.g. **A** denotes compound series; **3** denotes number of methylene units), the bis(thiophenoxide) product, ($^{n\text{-}BBN}NN^{tBu}$)$Zn(SPh)_2$ (**B-3** and **B-4**), were obtained in high yield as malodorous white powders. In contrast, the reaction with **A-2** resulted in rapid demetallation of the bidentate ligand, $^{2\text{-}BBN}NN^{tBu}$, and formation of an insoluble species, presumably of the type $[Zn(SPh)_2]_n$.[19] Attempts to form **B-2** through alternate synthetic methods were also unsuccessful (see SI for details).

To further understand the formation of complexes **B**, we performed variable temperature NMR experiments to probe whether pre-association between **A** and thiophenol occurred in solution prior to deprotonation. Treating each complex **A** with one equiv. thiophenol did not result in changes to the ^1H NMR spectrum at 25 °C (CD_2Cl_2). Similarly, no changes were observed (in comparison to samples not containing thiophenol, see SI) when cooling the samples (-80 °C) to favor a B-S interaction. These data suggest that a pre-association of thiophenol and the appended boron Lewis acid is not occurring prior to deprotonation. We also attempted to form mono(thiophenoxide) complexes of the type ($^{n\text{-}BBN}NN^{tBu}$)Zn(SPh)Br. These attempts were unsuccessful for all complexes **A**; NMR analysis of the reactions indicated primarily formation of complexes **B** with remaining unreacted **A**, highlighting a thermodynamic driving force to form $[Zn(SPh)_2]$.

Structural confirmation of complexes **B-3** and **B-4** was achieved via single crystal X-ray diffraction studies (Fig. 2). The solid-state structures of the tetrahedral zinc bis(thiophenoxide) (τ_4 = 0.83-0.89)[20] complexes differ significantly: **B-3** displays acid/base adduct formation between the trialkylborane and the thiophenoxide ligand while **B-4** does not. In **B-3**, the B-S interaction is evident by a deviation from planarity of the borane and a close B-S contact (ΣB_α = 316.31(11)°; 2.1279(18) Å) as compared to **B-4** (ΣB_α = 359.43(17)°; 5.62 Å). Comparing the two thiophenoxide ligands in **B-3** illustrates the consequences of Lewis-acid activation: 1) elongation of the Zn-S bond distance from

2.2511(5) to 2.3089(4) Å, and 2) increased bending of the Zn-S-C angles from 109.36(5) to 100.36(5)°.[21]

The solid-state structures clearly indicate a binding preference that is dependent on the tether length to the Lewis acid and that, for thiophenoxide, **B-3** may contain the most favorable host/guest interaction. In related work with five-coordinate iron(II)-bis(thiophenoxide) complexes, the B-S interaction was estimated computationally to be thermodynamically disfavored by ca. 9 kcal/mol.[17] However, this value should be highly dependent on the identity of the metal, the geometry at the metal, and the Lewis acid/base proximity (i.e. tether length). The room temperature ^{1}H NMR spectra of complexes **B** are both C_s symmetric, indicating that the B-S interaction is either not present in solution or is dynamic. Upon cooling samples of **B** (+25 to -70 °C), resonances in the ^{1}H NMR spectra (CD_2Cl_2) exhibit slight broadening and shifting with those of **B-3** more pronounced than **B-4**. While we were unable to reach the coalescence temperature, the solution ^{1}H NMR data suggest, qualitatively, B-S adduct formation is more favorable for **B-3** than **B-4** (see SI).

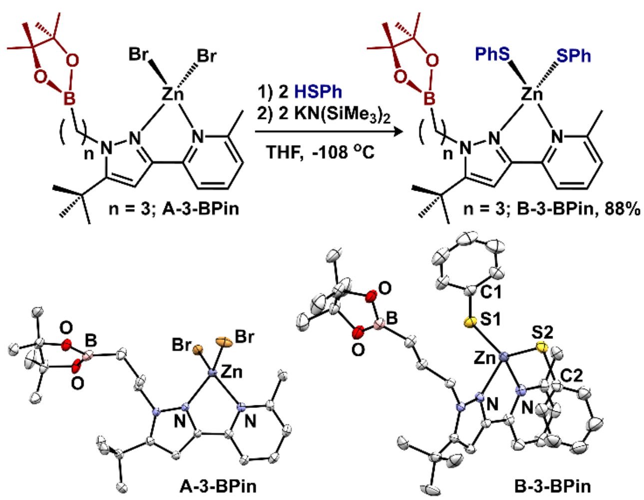
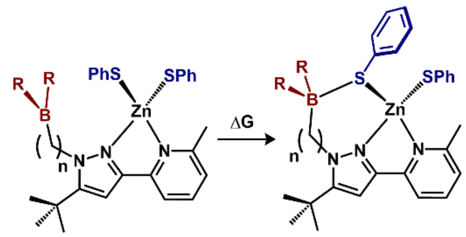


Fig. 3 Synthesis of **B-3-BPin** from **A-3-BPin**. The molecular structures of each compound are displayed with 50% probability ellipsoids. All hydrogen atoms are omitted for improved clarity.

We hypothesize that a greater entropic penalty is the origin of the differences observed in the B-S binding favorability. An alternate approach to favor (or disfavor) an acid/base adduct is to alter the Lewis acidity rather than the tether length.[22] The Lewis acidities of **A-3** and **A-4** were experimentally measured to be identical.[14] We hypothesized that by exchanging the moderately acidic 9-BBN in complexes **A** for a weakly acidic $-BO_2C_2Me_4$ (BPin), an *enthalpic* penalty would disfavor a B-S interaction. To probe this hypothesis, we synthesized a new ligand, 2-(1-({CH_2}-BPin)-5-(*tert*-butyl)-1*H*-pyrazol-3-yl)-6-methylpyridine, which was metalated with zinc(II) bromide to afford ($^{3\text{-BPin}}$NN$^{t\text{Bu}}$)$ZnBr_2$ (**A-3-BPin**; Fig. 3).[23] Treating **A-3-BPin** with two equiv. of each thiophenol and potassium bis(trimethylsilyl)amide afforded the bis(thiophenoxide) product, ($^{3\text{-BPin}}$NN$^{t\text{Bu}}$)Zn(SPh)$_2$ (**B-3-BPin**).

To ascertain the effect of the weakened Lewis acidity in **A-3-BPin** vs **A-3** (decreased acceptor number by *ca.* 20)[14, 24] to interact with thiophenoxide, we analysed **B-3-BPin** by single crystal X-ray diffraction. Data refinement of the tetrahedral bis(thiophenoxide) zinc complex (τ_4 = 0.85) revealed the absence of a B-S interaction, with a long B-S distance (>5.3 Å) and a trigonal boron (ΣB_α = 359.9(4)°). These data directly contrast those observed for **B-3**: decreased Lewis acidity in **B-3-BPin** disallows a B-S interaction. This is further borne out by VT ^{1}H NMR spectroscopy. Cooling samples of **B-3-BPin** to -71 °C does not have an effect on the NMR resonances (CD_2Cl_2) suggesting a greater barrier to form a B-S interaction as compared to **B-3** (see SI).



Compound	ΔG	ΔH
($^{3\text{-BBN}}$NN$^{t\text{Bu}}$)$ZnBr_2$	+10.3 kcal/mol	+4.3 kcal/mol
($^{4\text{-BBN}}$NN$^{t\text{Bu}}$)$ZnBr_2$	+17.5 kcal/mol	+12.3 kcal/mol
($^{3\text{-BPin}}$NN$^{t\text{Bu}}$)$ZnBr_2$	+22.4 kcal/mol	+18.8 kcal/mol

Fig. 4 DFT calculated thermodynamics associated with a B-S interaction.

To further elucidate the thermodynamic consequences on the dynamic B-S bonding regime, we undertook a DFT survey of complexes **B** (Fig. 4). For each complex, we calculated the change in free energy associated with a Lewis acid/base interaction by optimizing the molecules' geometries with and without a B-S interaction at the B3LYP/6-31G(d) (PCM: CH_2Cl_2) level of theory. The calculations support our experimental analysis: B-S bond formation is least unfavorable for **B-3** (ΔG = +10.3 kcal/mol). Upon increasing the distance between the Lewis acid and the thiophenoxide by one methylene unit (**B-4**), the B-S interaction becomes less favorable by an additional 7.2 kcal/mol. Enthalpically, the difference between **B-3** and **B-4** was greater than initially anticipated. While an additional *gauche* interaction in the alkyl chain of **B-4** may account for an upper limit of 4 kcal/mol of decreased favorability,[25] greater penalties are incurred by deformations of the primary coordination sphere that are necessary to accommodate a B-S interaction. In the optimized structure of **B-4** (B-S = 2.128 Å), a long Zn-pyrazole distance is observed (2.1765 Å) as a result of an increased pyridine-pyrazole dihedral angle (12.49° for the B-S bound species, compared to 4.50° in the B-S unbound **B-4** X-ray structure)—we propose these phenomena are a direct consequence of the imposed B-S interaction. Therefore, the increased ΔG for B-S binding in **B-4** is complicated and likely due to a composite of contributions beyond a simple boron-sulfur distance argument.

The discrepancies observed between the optimized structures of **B-3** and **B-4** are not observed when comparing **B-3** and **B-3-BPin**. In agreement with the experimental NMR studies and prior computed examples,[12] B-S bond formation in **B-3-BPin** is least favorable of all by a wide margin (ΔG = +22.4 kcal/mol). The difference between the ΔG and ΔH values in **B-3-BPin** suggest B-S binding is governed primarily by enthalpic considerations. These results highlight a necessity for secondary coordination sphere groups to be matched in both acidity/basicity and in proximity.

We have described a system where proximity and strength can be used to regulate the bonding dynamics between a tri-coordinate borane and a metal-bound thiophenoxide. In this system, a three-methylene spacer between the appended borane and the ligating-portion of the ligand was found to afford an ideal fit for a weakly basic thiophenoxide ligand. Less optimal bonding situations resulted from expanding the tether length or decreasing the Lewis acidity. These studies contribute to research that is challenging to investigate: modulating Lewis acidity by changing the entropic term in addition to the enthalpic term.[11c] We anticipate that this approach may enable a tethered Lewis acid to facilitate substrate-matched cooperative capture and product release—key features needed for catalytic turnover.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website and contains

Experimental procedures and spectroscopic characterization of all species (PDF).

Accession Codes

CCDC 2073450-2073453 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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The authors declare no competing financial interest.

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21. In **B-3**, the B-S distance is longer and the Zn-S-C angle is more obtuse than in the related five-coordinate complex. See ref. 17.
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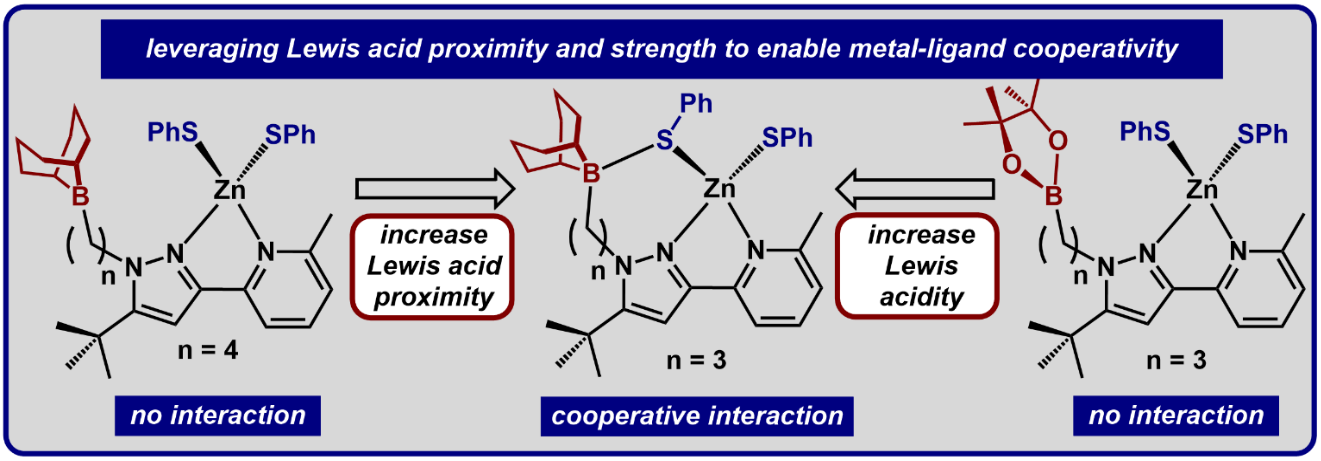
leveraging Lewis acid proximity and strength to enable metal-ligand cooperativity
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