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From the Design of a Chiral Lewis Acid Catalyst to Metal-Catalyzed Coupling Reactions

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In this Perspective, I describe my group's nonobvious path from an interest in chiral Lewis acid catalysis to a project focused on the development of new palladium and nickel catalysts for carbon-carbon bond-forming reactions.

I. Design of a Versatile Chiral Lewis Acid Catalyst

The origin of our program in palladium- and nickel-catalyzed couplings can be traced to a research proposal that I put together as part of my search for an academic position in the fall of 1992. At the time, the field of chiral Lewis acid chemistry was just beginning to take off. Although noteworthy progress had been described, the development of highly versatile catalysts still represented an important and exciting challenge.¹

Devising an effective Lewis acid catalyst for the enantioselective addition of nucleophiles to carbonyl compounds is a particularly interesting objective. For nearly all Lewis acids that have been reported to date, the carbonyl π system is activated through a σ -symmetry interaction between an oxygen lone pair and an empty metal orbital (Figure 1).² If this is the only interaction between the Lewis acid and the substrate, then all of the rotamers (around the M–O bond) are equally activated electronically; thus, a Lewis acid of this type provides a multitude of reactive substrate-catalyst complexes.^{3,4} We hypothesized that, if we could in fact *couple* activation of the substrate with organization of the resulting complex, we would considerably improve our prospects for developing a highly versatile and enantioselective chiral Lewis acid catalyst. We therefore decided to pursue a design wherein the Lewis acid interacts not only with an oxygen lone pair, but also with the π system, of the carbonyl group (Figure 2).

Thus, if the Lewis acid bears an empty π -symmetry orbital, interaction with the filled π system of the carbonyl group can further activate the substrate toward nucleophilic addition. Maximizing this second mode of activation requires that the π -symmetry orbitals of the substrate and the catalyst be parallel; this constraint obviates the generation of a multitude of comparably reactive rotamers (e.g., Figure 1). Therefore, with the dual-activation design outlined in Figure 2, activation and organization have indeed been coupled.

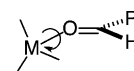


FIGURE 1. Activation via a σ -symmetry interaction between a Lewis acid and a carbonyl group.

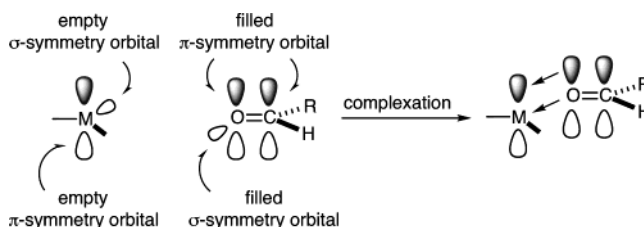
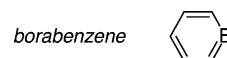
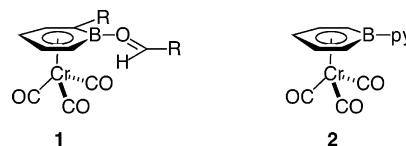


FIGURE 2. Dual activation via σ - and π -symmetry interactions between a Lewis acid and a carbonyl group.

After considering an array of frameworks, we decided to pursue the possibility that borabenzene⁵ might serve as the divalent Lewis acid of Figure 2, since the boron bears a vacant σ -symmetry, as well as a reasonably low-lying π -symmetry, orbital. Although borabenzene had not been isolated in the unbound state, an adduct with a Lewis base (pyridine) had been synthesized and crystallographically characterized.⁶



With respect to the development of a *chiral* Lewis acid catalyst, the structure of borabenzene suggested to us that the use of a *planar-chiral* derivative might be particularly effective (e.g., **1**).⁸ Significantly, in 1985, Schmid had reported a synthesis of a Cr(CO)₃-bound borabenzene (**2**).⁹



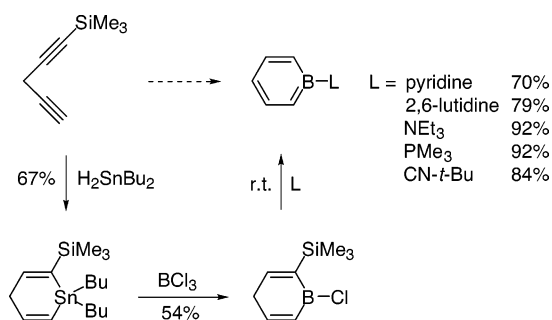
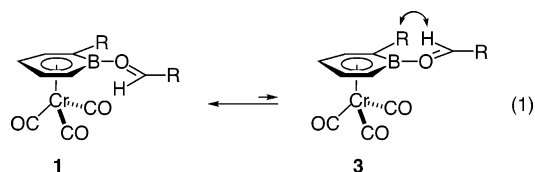
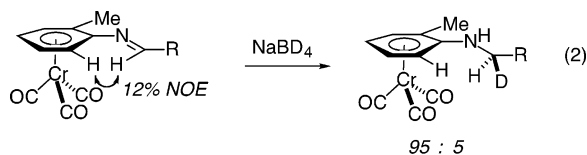


FIGURE 3. Synthesis of an array of neutral borabenzene-L complexes.

Based on three considerations, we hypothesized that the conformer depicted as complex **1** should in fact be the one that reacts with a nucleophile. First, boron will bind preferentially on the side of less-bulky H, rather than R.¹⁰ Second, the aldehyde and the borabenzene ring will be coplanar, to maximize overlap of their π systems. Third, **1** will be favored relative to **3**, since it avoids a destabilizing steric interaction (eq 1).



Collectively, these three constraints define a unique reactive conformation for a complex between the chiral Lewis acid and an aldehyde (**1**). We anticipated that the $\text{Cr}(\text{CO})_3$ group would effectively block attack of a nucleophile on the bottom face of the aldehyde, thereby leading to high stereoselection. Indeed, both NMR and reactivity studies of an isoelectronic system furnish support for this analysis (eq 2).¹¹



II. Development of More Versatile Routes to Borabenzene and Boratabenzenes

In pioneering studies, Maier, Paetzold, and Schmid had reported the synthesis of borabenzene-pyridine and its $\text{M}(\text{CO})_3$ complexes ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$; e.g., **2**);⁶ at the time that we initiated our program, these were the only neutral borabenzene-L adducts that had been characterized.¹² We were able to simplify the original route and to expand its scope, thereby providing ready access to multigram quantities of a range of neutral borabenzene complexes (Figure 3; nitrogen-, phosphorus-, and carbon-bound ligands),¹³ including a $\text{Cr}(\text{CO})_3$ -bound aldehyde adduct (**4**; Figure 4).¹⁴ An X-ray crystallographic analysis of **4** revealed that the boron is positioned syn to the aldehyde hydrogen and that the borabenzene ring and the aldehyde are coplanar (dihedral angle: $<5^\circ$) with a very short B-O bond distance (1.451 Å), consistent with a significant π -symmetry interaction (cf. **1** in eq 1).¹⁵

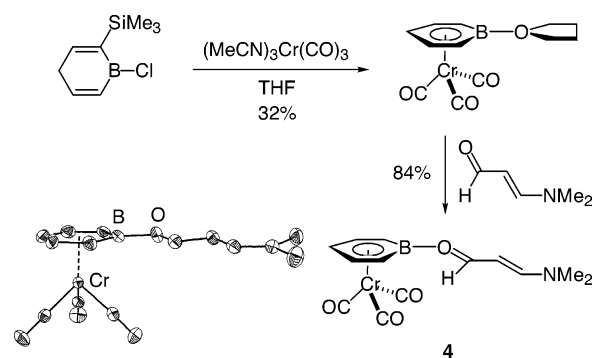


FIGURE 4. Synthesis and X-ray crystal structure of a $\text{Cr}(\text{CO})_3$ -bound borabenzene-aldehyde adduct (thermal ellipsoids are drawn at the 35% probability level).

TABLE 1. Synthesis of 1-Substituted Boratabenzenes via Substitution of Borabenzene- PMe_3

Nucleophile	Product	Yield (%)
LiAlH_4	$\left[\text{C}_6\text{H}_5\text{B-H} \right]^-$	71
$\text{Li-C}\equiv\text{SiMe}_3$	$\left[\text{C}_6\text{H}_5\text{B-C}\equiv\text{SiMe}_3 \right]^-$	68
Li-NMe_2	$\left[\text{C}_6\text{H}_5\text{B-NMe}_2 \right]^-$	78
Na-OEt	$\left[\text{C}_6\text{H}_5\text{B-OEt} \right]^-$	78
K-PPh_2	$\left[\text{C}_6\text{H}_5\text{B-PPh}_2 \right]^-$	91

In view of the somewhat limited scope of the approaches that had been reported for the synthesis of anionic boratabenzenes (BB-L^-),^{5a,16} we decided at this juncture to postpone our development of a chiral Lewis acid catalyst and to pursue the possibility that we could generate an electronically diverse array of boratabenzenes through substitution reactions of a neutral borabenzene-L adduct. Boratabenzenes are of interest to organometallic chemists since, being anionic six-electron donors, they can serve as surrogates for the ubiquitous cyclopentadienyl ligand.¹⁷

We were pleased to discover that borabenzene- PMe_3 (Figure 3) functions as a versatile precursor to a variety of boratabenzenes, reacting with nucleophiles in good yield (Table 1).¹⁸⁻²⁰ Since these were the first examples of substitution reactions of a borabenzene complex, we were of course interested in elucidating their mechanism (for some possibilities, see Figure 5). Through labeling studies, we ruled out substitution via dissociation of PMe_3 or by way of a borabenzynes. Indeed, all of the data that we have accumulated to date are consistent with an associative pathway (Figure 5).

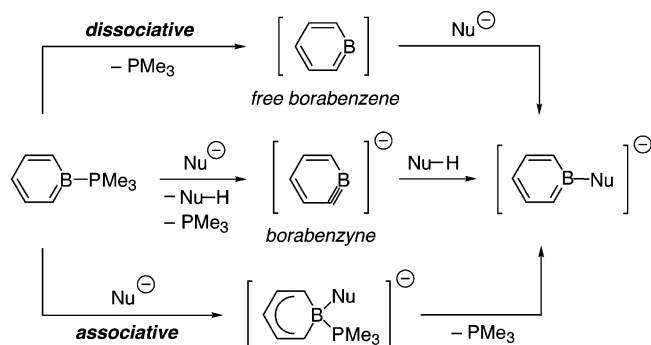


FIGURE 5. Three of the possible mechanisms for substitution of boratabenzene–PMe₃.

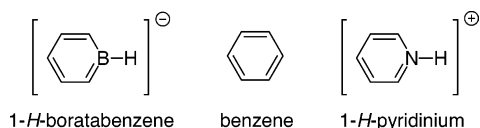


FIGURE 6. 1-*H*-Boratabenzene: a new addition to an isoelectronic series.

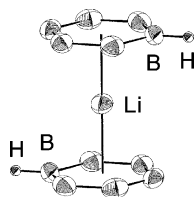


FIGURE 7. ORTEP drawing of Li(1-*H*-boratabenzene)₂·Li·(THF)₄ (thermal ellipsoids are drawn at the 35% probability level; for the sake of clarity, the Li(THF)₄ is not shown).

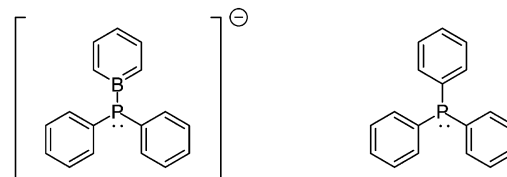
III. 1-*H*-Boratabenzene and 1-(Diphenylphosphido)boratabenzene

Of the new boratabenzenes that we produced (Table 1), two immediately attracted our attention: 1-*H*-boratabenzene and 1-(diphenylphosphido)boratabenzene. 1-*H*-Boratabenzene, which is isoelectronic with two very well-studied aromatic molecules,²¹ benzene and 1-*H*-pyridinium (Figure 6), had not previously been synthesized, although Ashe had examined the chemistry of an iron-bound adduct.²² We were able to crystallographically characterize the lithium salt of 1-*H*-boratabenzene as a sandwich structure composed of two boratabenzene rings with a lithium ion at the center of symmetry of the complex (Figure 7).²³ The X-ray data are consistent with 1-*H*-boratabenzene being aromatic. With regard to reactivity, we determined that the boron-bound hydrogen is hydridic, reducing *n*-dodecanal to 1-dodecanol and reacting with water to generate H₂.

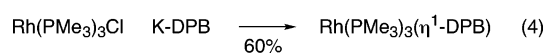
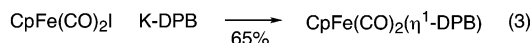
The other boratabenzene that was particularly intriguing to us was 1-(diphenylphosphido)boratabenzene (DPB). Because it is a negatively charged, isoelectronic, and essentially isosteric variant of triphenylphosphine (one of the most ubiquitous ligands in transition metal chemistry), we felt that comparison of corresponding DPB and PPh₃ complexes could furnish interesting insights into electronic and charge effects on reactivity, with steric

factors kept nearly constant.

1-(diphenylphosphido)boratabenzene (DPB)



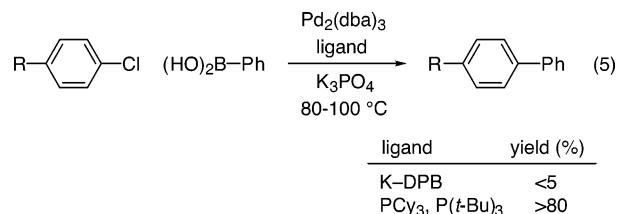
However, at the outset there was uncertainty as to whether we would be able to pursue the desired studies with DPB, since all previous transition-metal adducts of boratabenzenes, including amidoboratabenzenes, had involved π -complexation of the heterocycle, not σ -complexation through the substituent on boron. Fortunately, as we had hoped, DPB reacts with a variety of transition metal electrophiles to generate phosphorus-bound adducts (eqs 3 and 4).²⁴ On the basis of spectroscopic and X-ray crystallographic data for corresponding PPh₃ and DPB complexes, we concluded that DPB does indeed furnish a more electron-rich transition metal.



IV. Palladium-Catalyzed Coupling Reactions

Of course, we were interested in exploiting the electron-richness of DPB to enhance the activity of a transition-metal catalyst. By 1997, Pd/PPh₃-based complexes had been shown to effectively catalyze a variety of coupling reactions of aryl bromides and iodides;²⁵ on the other hand, there were relatively few examples of couplings of aryl chlorides.²⁶ The low reactivity of chlorides was generally ascribed to their reluctance to oxidatively add to Pd(0). Although aware of the mechanistic complexity of coupling reactions, we decided to pursue the simplistic hypothesis that replacement of PPh₃ with anionic, isosteric DPB might furnish a more electron-rich palladium complex that would be more prone to oxidatively add an aryl chloride.²⁷

Initially, we focused our attention on Suzuki cross-couplings, because at the time there were no efficient palladium-based catalysts for reactions of unactivated aryl chlorides. Unfortunately, Pd/DPB proved to be ineffective for such couplings, affording essentially none of the desired biaryl (eq 5). However, control experiments led us to the surprising observation that commercially available, electron-rich, sterically demanding phosphines such as PCy₃ and P(*t*-Bu)₃ furnish very effective catalysts (eq 5)!



Building on this unanticipated discovery, we developed

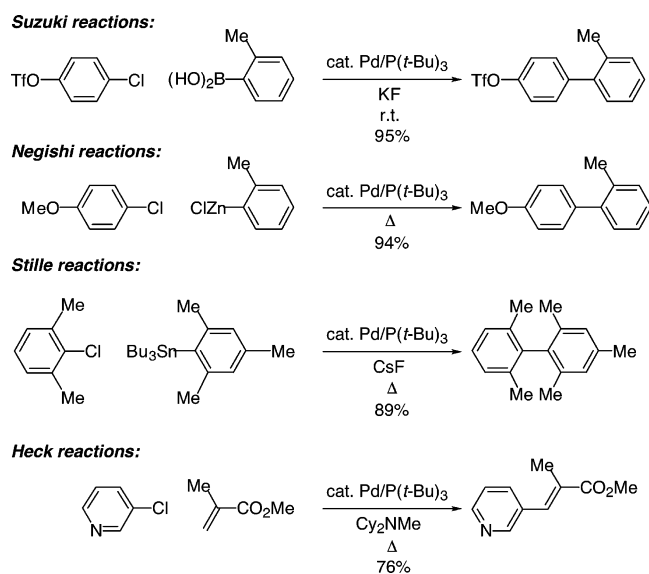


FIGURE 8. Pd/P(*t*-Bu)₃-catalyzed coupling reactions of aryl chlorides.

relatively mild and versatile methods for achieving an array of palladium-catalyzed couplings of a variety of aryl halides, including challenging aryl chlorides (Figure 8).^{28,29} More recently, we have turned our attention to a new frontier: the development of effective catalysts for cross-coupling *alkyl* electrophiles (Figure 9).³⁰ We believe that the achievement of this objective could have a

significant impact on strategic planning in synthetic organic chemistry.³¹

V. Summary

In this Perspective, I have described how a project that is directed at developing a versatile boron-based chiral Lewis acid catalyst gave birth to a seemingly unrelated program that is focused on palladium- and nickel-catalyzed coupling reactions. Interestingly, in some respects these two projects reflect two extremes in the methods-development spectrum: the chiral Lewis acid program involves the design of a catalyst (based on a relatively “exotic” framework) for which there is a clear hypothesis regarding the transition state of the key stereochemistry-determining step; in contrast, for the cross-coupling project, which relies upon commercially available catalyst components, the composition (much less the structure) of key intermediates in the catalytic cycle is not yet known. More broadly, although rational design is the ideal approach to methods development, for some processes, our current level of understanding is simply too unsophisticated for this to be the most effective strategy.

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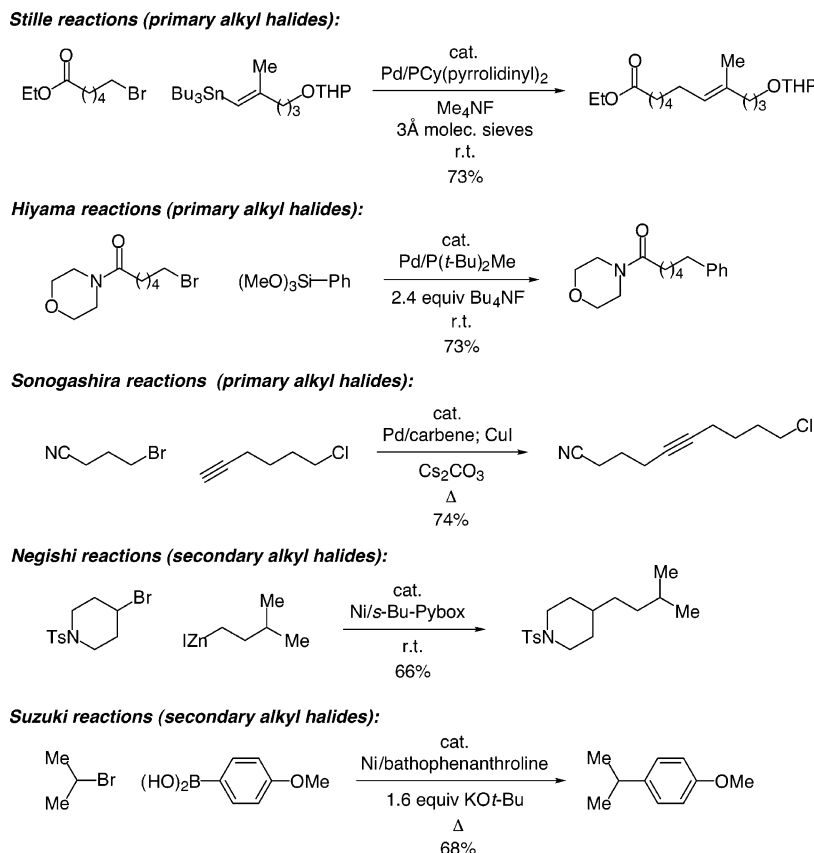


FIGURE 9. Cross-coupling reactions of alkyl electrophiles.

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