# Multifaceted Substrate–Ligand Interactions Promote the Copper-Catalyzed Hydroboration of Benzylidenecyclobutanes and Related Compounds

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**ABSTRACT:** A unified synthetic strategy to access tertiary four-membered carbo/heterocyclic boronic esters is reported. Use of a Cu(I) catalyst in combination with a modified dppbz ligand enables regioselective hydroboration of various substituted benzylidenecyclobutanes and carbo/heterocyclic analogs. The reaction conditions are mild, and the method tolerates a wide range of medicinally relevant heteroarenes. The protocol can be conveniently conducted on gram-scale, and the tertiary boronic ester products undergo facile diversification into valuable targets. Reaction kinetics and computational studies indicate that the migratory insertion step is turnover-limiting and accelerated by electron-withdrawing groups on the dppbz ligand. Energy decomposition analysis (EDA) calculations reveal that electron-deficient *P*-aryl groups on the dppbz ligand enhance the T-shaped $\pi/\pi$ interactions with the substrate and stabilize the migratory insertion transition state.

**INTRODUCTION.** Four-membered carbo/heterocycles are prized motifs in medicinal chemistry.[1] The unique properties and advantages of cyclobutanes, azetidines, oxetanes and other types of four-membered rings have recently been highlighted in numerous publications. For example, larger, saturated heterocycles tend to be more lipophilic and are cleared more rapidly relative to their four-membered ring counterparts.[2] In addition, four-membered rings can increase water solubility, reduce p$K_a$ and be used as bioisosteres.[3] For these reasons, numerous four-membered-ring-containing compounds have been developed to treat various medical indications, including PF-03654746,[4] linsitinib,[5] baricitinib,[6] and GNE-317[7] (Figure 1A). Despite the importance of four-membered ring motifs, preparative methods to access these structures remain relatively few in number, particular in comparison to the available methodology to synthesize five- and six-membered ring motifs. Specifically, appending a tertiary-substituted four-membered ring onto a target molecule of interest remains challenging.

Owing to their synthetic versatility, carbo/heterocyclic tertiary boronic esters have attracted significant attention in academia and industry (Figure 1B). For example, Hall and Pfizer co-workers recently demonstrated asymmetric copper-catalyzed 1,4-hydroboration of conjugated cyclobutenones to afford enantioenriched tertiary cyclobutylboronates.[8] In addition, decarboxylative and deoxygenative radical borylation of cyclobutyl precursors has been independently demonstrated by the Aggarwal, Baran, and Studer groups.[9] Deborylative alkylation developed by Morken and co-workers has also been used to access tertiary cyclobutylboronic esters from bis- or tris(boronate) precursors.[10] More recently, Aggarwal and Studer groups independently published elegant methods to generate both tertiary cyclobutyl and azetidinyl boronic esters from highly strained alkyl lithium intermediates through a 1,2-metallate rearrangement.[11,12] Additionally, the Brown group showed one example of a nickel-catalyzed arylboration of a benzylideneazetidine substrate to afford a tertiary azetidinylboronic ester product.[13] Although these existing methods are impressive and highly valuable, they also have limitations in terms of requiring harsh reaction conditions, employing air/moisture sensitive reagents, relying on precursors that are difficult to prepare, and exhibiting narrow substrate scope (e.g., heterocycle incompatibility). Moreover, to the best of our knowledge, a synthetic method to access tertiary boronic esters with a four-membered ring containing oxygen, sulfone or gem-difluoro groups has not been described.

We thus sought to develop a mild, heterocycle-tolerant, and unified method to afford various types of tertiary four-membered cyclic boronic esters. In this context, the Shi group and our laboratories have independently demonstrated copper–boryl catalytic systems with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as the ligand that can functionalize benzylidenecyclopropanes to afford tertiary cyclopropylboronic esters (Figure 1C).[14, 15] The reaction conditions are mild, and a wide variety of heterocycles are tolerated. Based on these precedents, we questioned whether copper–boryl catalysis could grant access to four-membered-ring variants. At the outset, however, we recognized a major challenge in the form of the strain energy difference between three- and four-membered ring systems. In the previous cyclopropane system, strain energy was used as a major driving force to achieve borylative addition to sterically

hindered trisubstituted alkenes. On the other hand, the estimated strain energy difference between benzylidenecyclobutane and cyclobutane itself (2.7 kcal/mol) is significantly smaller than the difference between benzylidenecyclopropane and cyclopropane (13.5 kcal/mol).[16] Therefore, functionalizations of benzylidenecyclobutane are expected to suffer from a much lower thermodynamic driving force due to the decreased ring strain energy release. Indeed, the Shi group reported that benzylidenecyclobutane did not react well under their reaction conditions for aminoboration of benzylidenecyclopropanes.[14a]

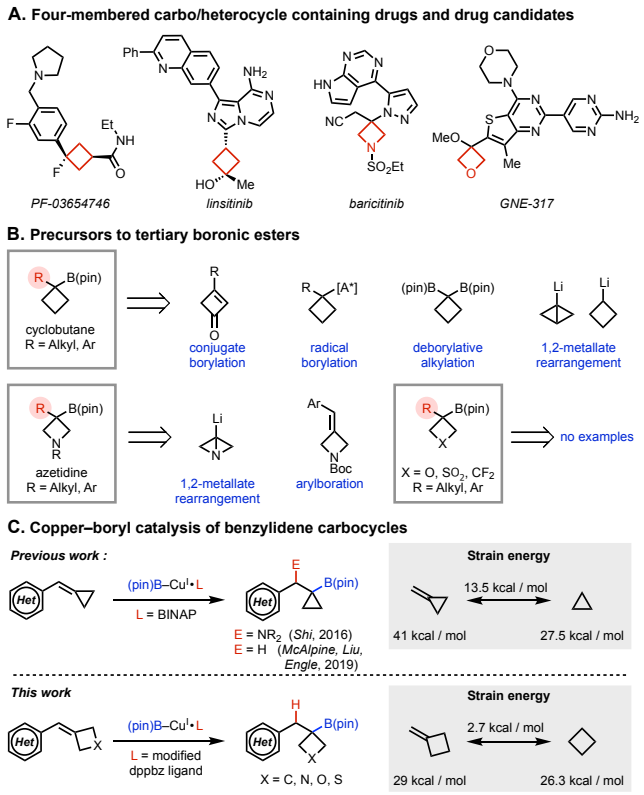
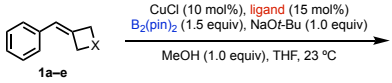


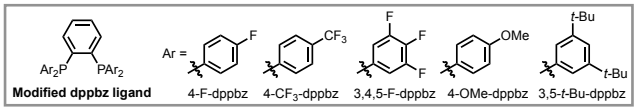

**Figure 1**. Overview of Proposed Approach to Preparation of Tertiary Boronic Esters.

**LIGAND OPTIMIZATION.** With these considerations in mind, we reasoned that the low reactivity of benzylidenecyclobutanes could be overcome through the use of a tailored ancillary ligand on the Cu catalyst, which would fine-tune its steric and electronic properties and enhance non-covalent interactions with the substrate.[17] To this end, we conducted two-dimensional screening with diverse phosphine ligands and five representative benzylidene carbo/heterocycles: cyclobutane (**1a**), azetidine (**1b**), oxetane (**1c**), thietane 1,1-dioxide (**1d**), 3,3-difluorocyclobutane (**1e**) (Table 1). It is worth mentioning that these substrates were synthesized through simple Wittig reactions from inexpensive and commercially available starting materials. Under the previously published hydroboration reaction conditions, the simplest ligand, triphenylphosphine ($PPh_3$), gave only trace amounts of products (entry 1).[14b] Notably, tri(pentafluorophenyl)phosphine ($(C_6F_5)_3P$) and BINAP, which were successfully used for our previous cyclopropane system, were ineffective in the cyclobutane system, although BINAP gave moderate yields for more electronically activated **1b** and **1c** (entries 2–3).[14b] After further screening with bis-phosphine ligands (entries 4–6), we found that 1,2-bis(diphenylphosphino)benzene ligand (dppbz) gave improved results for all substrates. Inspired by recent reports describing the use of modified dppbz ligands in related transformations,[18] we envisioned that modification of the electronic property of dppbz ligands without changing the 1,2-bis(phosphino)benzene backbone could enhance the product yields. Indeed, *para*-fluorine substituted dppbz ligand (4-F-dppbz, entry 7) increased the yields of desired products for all substrates. More strongly electron-withdrawing 4-$CF_3$-dppbz ligand further increased the product yield with the cyclobutane substrate but decreased the yields with substrates **1d** and **1e** (entry 8). Additional fluorine substitution on the *meta*-position (entry 9) led to diminished yields. Notably, introduction of an electron-donating group (entry 10) or a sterically bulky *tert*-butyl group in the *meta*-position (entry 11) significantly decreased the yield of the reaction. Across these optimization experiments, we did not observe any evidence of undesired side reactions, such as ring-opening; typically only unreacted starting materials along with the desired products could be detected.

**Table 1. Ligand optimization with representative substrates**




| | | product in % yield ($^1$H NMR) | | | | |
|---|---|---|---|---|---|---|
| entry | ligand | 1a | 1b | 1c | 1d | 1e |
| 1 | $PPh_3$ | 2 | 4 | 3 | 6 | < 1 |
| 2 | $(C_6F_5)_3P$ | < 1 | < 1 | < 1 | 10 | < 1 |
| 3 | BINAP | 2 | 66 | 61 | 4 | 5 |
| 4 | dppe | 36 | 45 | 79 | 33 | 4 |
| 5 | dppp | 10 | 50 | 85 | 26 | 12 |
| 6 | dppbz | 49 | 88 | 91 | 34 | 29 |
| 7 | **4-F-dppbz** | 62 | 95 | 97 | 53 | 74 |
| 8 | **4-$CF_3$-dppbz** | 74 | 99 | 99 | 29 | 33 |
| 9 | 3,4,5-F-dppbz | 15 | 72 | 67 | 6 | 32 |
| 10 | 4-OMe-dppbz | 17 | 39 | 13 | 45 | 18 |
| 11 | 3,5-*t*-Bu-dppbz | < 1 | 9 | 5 | 41 | 52 |



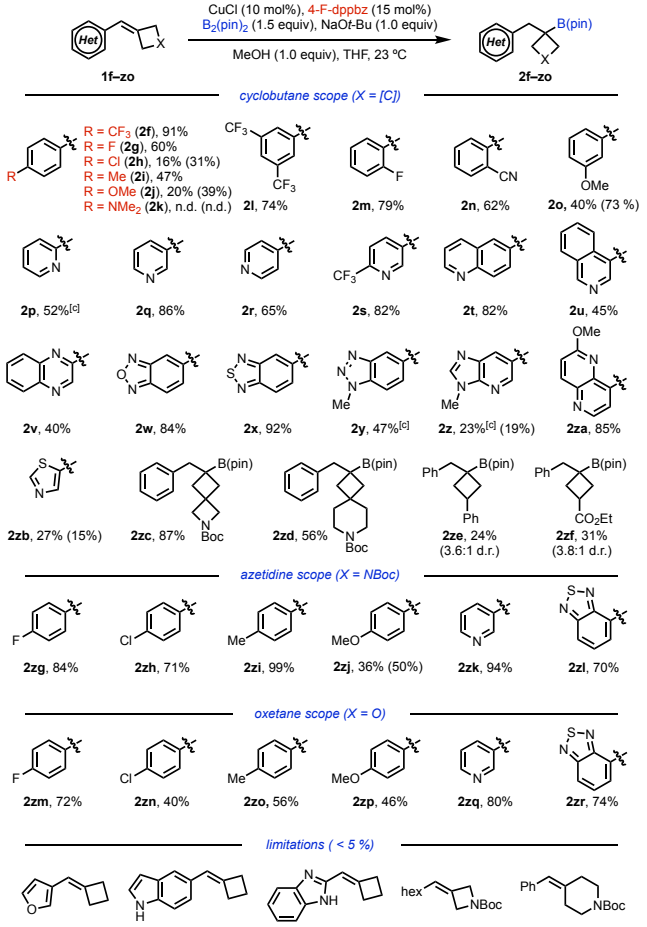

[a]Reaction conditions: 1 (0.2 mmol), CuCl (10 mol%), ligand (15 mol%), $B_2(pin)_2$ (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature. [b]Yields were determined by $^1$H NMR with the use of 1,3,5-trimethoxybenzene as an internal standard.

**SUBSTRATE SCOPE** We explored the arene substituent scope using 4-F-dppbz as the ligand. Interestingly, we observed a clear trend that electron-deficient aryl groups gave higher yields of the desired products than electron-rich aryl groups. Substrates containing electron-withdrawing trifluoromethyl or fluoride groups gave the desired products in good to excellent isolated yields (**2f**, **2g**, **2l** and **2m**). On the other hand, more electron-donating substituents resulted in diminished reactivity (**2h**–**2j**); in particular, the highly electron-rich -$NMe_2$ substrate was unreactive (**2k**). For low-yielding cases, unreacted starting material was observed as the major component of the crude reaction mixture. The cyano group was well-tolerated (**2n**), and an electron-donating -OMe group at the *meta*-position also delivered moderate yield (**2o**). In certain low-yielded cases, the 4-$CF_3$-dppbz ligand provided moderately higher yields (**2h**, **2j** and **2o**; yields with 4-$CF_3$-dppbz as ligand in parentheses).

Many heterocycles commonly employed in drug discovery were well tolerated under the reaction conditions. *Ortho*-, *meta*-, and *para*-substituted pyridines, the most common nitrogen-containing heterocycle, gave the products in good to excellent yields (**2p**–**2s**). We further explored more complex heterocycles, namely quinoline (**2t**), isoquinoline (**2u**), quinoxaline (**2v**), benzoxadiazole (**2w**), benzothiadiazole (**2x**), benzotriazole (**2y**), imidazolopyridine (**2z**), 1,5-naphthyridine (**2za**), and thiazole (**2zb**), which gave corresponding products in synthetically viable to excellent yields. In addition, benzylidene spirocyclic compounds also performed well under the reaction condition (**2zc** and **2zd**). Substrates containing substituted cyclobutanes also furnished the desired products, albeit in low yields with moderate d.r. (**2ze** and **2zf**).

In general, azetidine and oxetane substrates provided higher yields than cyclobutane substrates, presumably because the alkenes are more electronically activated due to the inductive effect of the heteroatom. Both azetidine and oxetane substrates containing *para*-fluoro, chloro, methyl, and methoxy substituents gave moderate to excellent yields (**2zg**–**2zj** and **2zm**–**2zp**), and heterocycles were compatible as well (**2zi**, **2zj** and **2zo**, **2zr**). The method is not without its limitations; notably, substrates containing an electron-rich furan ring or NH-containing azaheterocycles proved to be unreactive (<5% $^1$H NMR yield). Similarly, alkylidene azetidine and benzylidenepiperidine substrates could not be functionalized under these conditions.

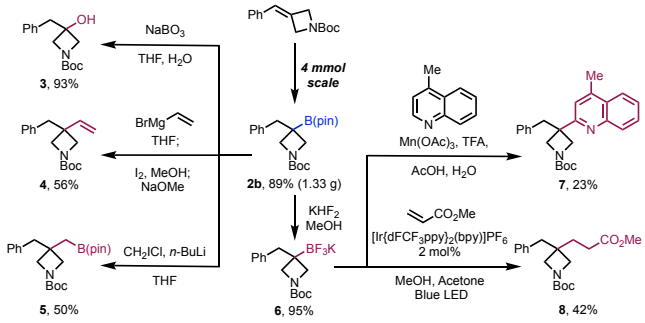
**Scheme 1. Hydroboration scope with substituted arenes and heterocycles.**




[a]Reaction conditions: **1** (0.2 mmol), CuCl (10 mol%), 4-F-dppbz (15 mol%), $B_2(pin)_2$ (0.3 mmol), NaO*t*-Bu (0.2 mmol), MeOH (0.2 mmol) in THF (0.5 mL) at room temperature. Percentages refer to the isolated yields of products. [b]The values in parentheses correspond to isolated yields with 4-$CF_3$-dppbz as ligand in place of 4-F-dppbz; d.r.=diastereomeric ratio. [c]The final product was oxidized to the corresponding alcohol for ease of isolation.

**PRODUCT DERIVATIZATIONS.** To highlight the utility of the tertiary boronic ester products, we prepared product **2b** on gram scale and demonstrated several diversification reactions. Oxidation to the corresponding tertiary alcohol **3** occurred in 93% yield.[19] A Zweifel–Aggarwal vinylation delivered desired product **4**, and a Matteson homologation furnished primary boronic ester **5** in modest yield.[20, 21] Conversion to the tertiary trifluoroborate salt **6** occurred in 95% yield.[22] In addition, using trifluoroborate **6** as a tertiary radical precursor, Minisci[23] and Giese reactions[24] were performed to give the corresponding C–C coupled products **7** and **8** in synthetically useful yields.

**Scheme 2. Selected derivatization reaction with tertiary boronic ester 2b.**




**REACTION KINETICS.** The crucial importance of the modified dppbz ligands and the pronounced reactivity trends based on substrate electronic properties prompted us to examine the mechanism of this transformation through kinetic and computational studies. First, in order to establish the turnover-limiting step, we measured the initial rates of four electronically different benzylidenecyclobutane substrates (**1a**, **1f**, **1i** and **1j**) by $^1$H NMR. Mirroring the yield trends noted above, substrate **1f** containing an electron-withdrawing group reacted with faster initial rate than electron-neutral **1a** or electron-rich **1i** and **1j**. This trend indicates that negative charge builds up at the benzylic carbon during the turnover-limiting step in the catalytic cycle, consistent with this step being migratory insertion since it is the only step in the catalytic cycle that would be expected to be accelerated by an electron-withdrawing group on the arene. We visualized this rate data using a Hammett plot and observed a positive ρ-value. The data deviated from linearity in the case of substrate **1f**, suggesting that the turnover-limiting step may have changed in the case of **1f**, where migratory insertion is presumably fast. We next studied the effect of ligand modifications on the initial rate of **1a** by comparing plain dppbz and modified dppbz ligands. 4-$CF_3$ and 4-F-dppbz ligands clearly showed faster initial rates than plain dppbz ligand (see Figure S3 in the SI). Additionally, we attempted to examine ligand effects by preparing and characterizing the Cl-bridged Cu–ligand complexes with each of these three ligands. However, we did not observe clear trends from comparison of the X-ray crystal structures and $^{31}$P NMR shifts(see Table S11 in the SI).

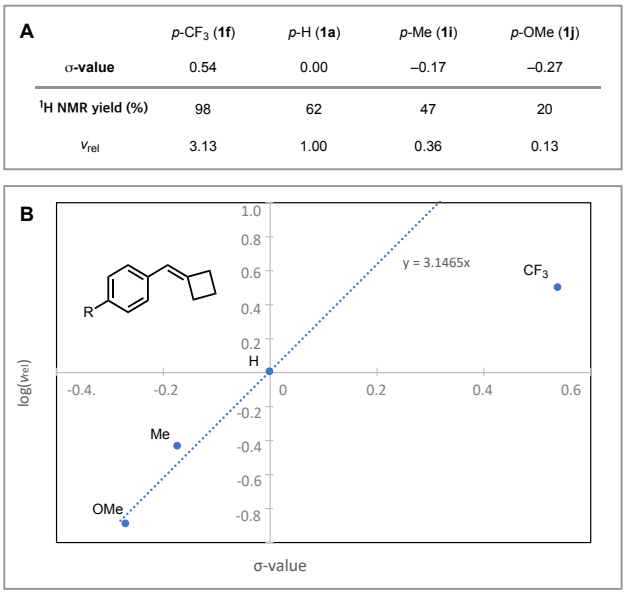
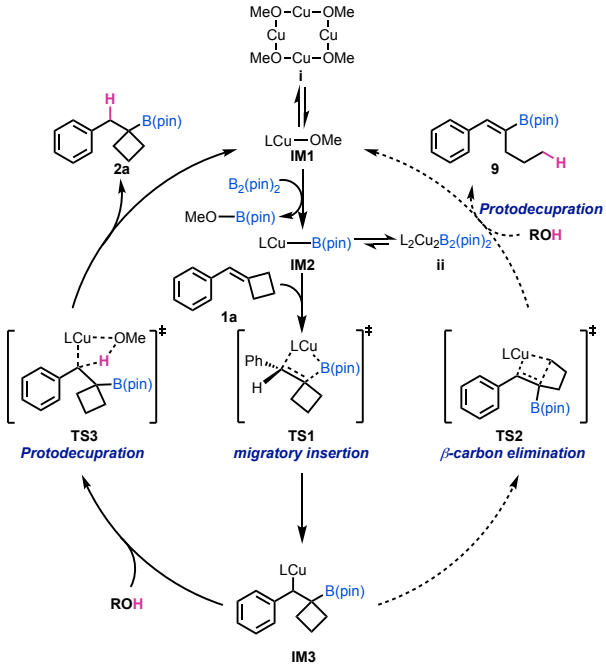



**Figure 2**. Hammett analysis of hydroboration of substituted benzylidenecyclobutanes.

**COMPUTATIONAL STUDIES.** To investigate the reaction mechanisms and the origin of ligand and substrate effects on reactivity, we performed density functional theory (DFT) calculations at the M06/SDD-6-311+G(d,p)/SMD(THF)//M06L/LANL2DZ-6-31G(d) level of theory. We computed the reaction energy profiles based on the proposed reaction mechanisms shown in Scheme 3 (see Figure SX in the SI). The productive catalytic cycle involves the σ-bond metathesis of LCuOMe (**IM1**) with $B_2(pin)_2$ to form copper(I)–boryl species **IM2**, which undergoes migratory insertion of **1a** to form benzylic Cu(I) intermediate **IM3**. Protodecupration of **IM3** yields the boronic ester and regenerates the copper(I)–alkoxy complex **IM1**.

**Scheme 3. Proposed reaction mechanism of hydroboration of benzylidenecyclobutanes.**




We first investigated the origins of product selectivity in the hydroboration of benzylidenecyclobutanes. Unlike the previously reported hydroboration of benzylidenecylcopropanes,[14b] the above experiments reveal that benzylidenecyclobutanes do not readily undergo β-carbon elimination (**TS2**, Scheme 3) from the benzylic Cu(I) intermediate **IM3** to form the putative ring-opened alkenyl boronate products (**9**), despite the similar ring strain energies of cyclopropane and cyclobutane rings (27.5 and 26.3 kcal/mol, respectively). Our calculations on the reaction energy profiles of the hydroboration of benzylidenecyclobutane **1a** with 4-$CF_3$-dppbz-supported Cu catalyst suggest the β-carbon elimination (**TS2a**) is disfavored by 1.3 and 11.3 kcal/mol in terms of activation free energy and activation enthalpies, respectively, compared to the competing protodecupration pathway (**TS3a**). Although both **TS3a** and **TS2a** adopt a tetrahedral geometry around the copper center, the β-carbon elimination transition state (**TS2a**) is more sensitive to steric effects from the ligand due to a greater substrate binding angle ($\angle$ CCuO = 74.4° in **TS3a** compared to $\angle$ CCuC = 88.2° in **TS2a**). Therefore, steric repulsions between the substrate and the ligand destabilize the protodecupration transition state (Figure 3). (For the full reaction energy profiles and a more detailed comparison of benzylidenecyclobutanes (BCBs) to benzylidenecyclopropanes (BCPs), see SI).

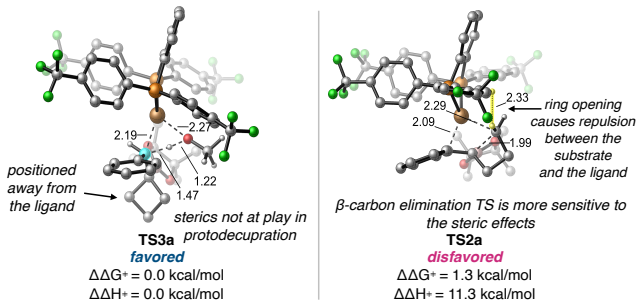



**Figure 3**. Protodecupration (left) and β-carbon elimination (right) transition states with 4-$CF_3$-dppbz ligand.

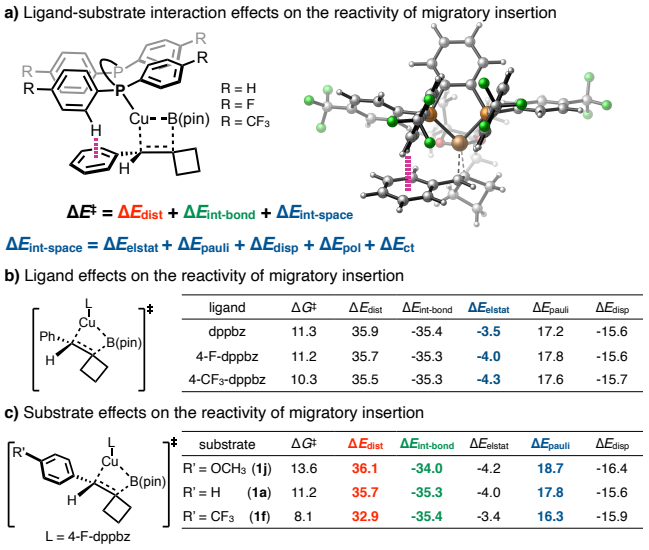
Next, we turned our attention to the origins of ligand and substrate effects on the barriers to alkene migratory insertion, since the experimental mechanistic studies (*vide infra*) suggested this is the turnover-limiting step of the catalytic cycle. Previous reports and our DFT calculations (see SI) indicated several stable dimeric and oligomeric copper(I)–alkoxide[25] or copper(I)–boryl species (e.g. i and ii, see Scheme 3) may be the off-cycle resting state(s) before the migratory insertion step. The computed energies required to convert these off-cycle complexes to the monomeric copper(I)–boryl species (**IM2**) do not correlate with the experimental reactivity, indicating the observed reactivity trend is not a result of dimer or oligomer dissociation. On the other hand, the calculated activation free energies of the migratory insertion transition states with respect to the monomeric copper(I)–boryl species agree well with the experimentally determined relative reactivities (Figure 4b and 4c), indicating the reactivity is mainly affected by the stability of the migratory insertion transition state. To gain more insights into factors that promote the catalyst/substrate interactions in this step, we sought to understand the differences in reactivity via the ligand–substrate interaction model analysis. Using an energy decomposition approach reported earlier,[17a, 17b] the computed activation energy for each reaction is dissected using the following equation:

$$\Delta E^{\ddagger} = \Delta E_{\text{dist}} + \Delta E_{\text{int-bond}} + \Delta E_{\text{int-space}}$$

where the distortion energy ($\Delta E_{dist}$) is the sum of the energies required to distort the LCuB(pin) complex and the substrate into their transition state geometries. The through-space interaction energy between the phosphine ligand and the benzylidenecyclobutane substrate ($\Delta E_{int\text{-}space}$) is calculated from the interaction energy of a hypothetical supramolecular complex of the ligand and the substrate at the transition state geometry in the absence of the CuB(pin) moiety. The rest of the catalyst/substrate interaction energy is defined as the through-bond interaction ($\Delta E_{int\text{-}bond}$) between the LCuB(pin) and the substrate in the transition state. Using the second-generation ALMO-EDA method implemented in Q-Chem 5.2, the through-space interaction energy ($\Delta E_{int\text{-}space}$) is further dissected according to the following equation:

$$\Delta E_{int\text{-}space} = \Delta E_{elstat} + \Delta E_{pauli} + \Delta E_{disp} + \Delta E_{pol} + \Delta E_{ct}$$

where $\Delta E_{elstat}$, $\Delta E_{pauli}$, $\Delta E_{disp}$, $\Delta E_{pol}$, and $\Delta E_{ct}$ correspond to several different types of non-covalent interactions, namely electrostatic, Pauli repulsions, dispersion interactions, intrafragment polarization, and interfragment charge transfer, respectively.




| ligand | ΔG‡ | ΔEdist | ΔEint-bond | ΔEelstat | ΔEpauli | ΔEdisp |
|---|---|---|---|---|---|---|
| dppbz | 11.3 | 35.9 | -35.4 | -3.5 | 17.2 | -15.6 |
| 4-F-dppbz | 11.2 | 35.7 | -35.3 | -4.0 | 17.8 | -15.6 |
| 4-CF3-dppbz | 10.3 | 35.5 | -35.3 | -4.3 | 17.6 | -15.7 |

| substrate | ΔG‡ | ΔEdist | ΔEint-bond | ΔEelstat | ΔEpauli | ΔEdisp |
|---|---|---|---|---|---|---|
| R' = OCH3 (1j) | 13.6 | 36.1 | -34.0 | -4.2 | 18.7 | -16.4 |
| R' = H (1a) | 11.2 | 35.7 | -35.3 | -4.0 | 17.8 | -15.6 |
| R' = CF3 (1f) | 8.1 | 32.9 | -35.4 | -3.4 | 16.3 | -15.9 |

**Figure 4**. Summary of ligand-substrate interactions and energy decomposition analysis.

The EDA calculations revealed the dominant factors that control the reactivity trends in reactions with different ligands (Figure 4b) and with different *para*-substituted benzylidenecyclobutanes (Figure 4c). The higher reactivity with the 4-$CF_3$-dppbz ligand (entry 8, Table 1) compared to those with dppbz and 4-F-dppbz is primarily due to the more favorable electrostatic interactions between the ligand and the substrate ($\Delta E_{elstat}$, Figure 4b). Examination of the migratory insertion transition state geometries indicated an edge-to-face (T-shaped) interaction between one of the *P*–Ar groups on the ligand and the phenyl group on the substrate (Figure 4a). Therefore, an electron-withdrawing substituent on the "edge" arene (i.e., on the ligand) would enhance the T-shaped $\pi/\pi$ interaction through more favorable electrostatic interactions.[26] On the other hand, when the electron-withdrawing substituent is installed on the "face" arene (i.e., on the benzylidenecyclobutane), the T-shaped $\pi/\pi$ interaction becomes weaker, as evidenced by the slightly less favorable $\Delta E_{elstat}$ term in the reaction with **1f** (R' = $CF_3$) than that with **1a** (R' = H) and **1j** (R' = $OCH_3$) (Figure 4c). Therefore, although the ligand effects on reactivity are controlled by the T-shaped $\pi/\pi$ interaction between the ligand and the substrate, such interactions are not the dominant factor leading to the higher reactivity of electron-deficient benzylidenecyclobutanes (Figure 2). The EDA calculations show that the transition state with **1f** (R = $CF_3$) is stabilized by multiple factors, including smaller distortion energy ($\Delta E_{dist}$) and Pauli repulsion energy ($\Delta E_{pauli}$), as well as more favorable through-bond interaction energy ($\Delta E_{int\text{-}bond}$) (Figure 4c). These results indicate that the reaction with **1f** (R = $CF_3$) has an earlier transition state with diminished catalyst/substrate distortion and steric repulsions. Although the transition state is early, the bonding interaction ($\Delta E_{int\text{-}bond}$) between LCuB(pin) and the electron-deficient benzylidenecyclobutane (**1f**) is still the strongest among the three substrates because of the more electron-deficient π-cloud that promotes migratory insertion.[27]

**CONCLUSIONS.** In conclusion, we have demonstrated that copper catalyzed hydroboration of benzylidene four-membered rings to afford synthetically useful tertiary boronic ester products. The role of modified 4-F and 4-$CF_3$-dppbz ligands in enhancing catalytic reactivity was elucidated through kinetic and computational studies. Specifically, DFT and EDA calculations revealed the T-shaped $\pi/\pi$ interactions between the ligand and the substrate influence the reactivity with different modified dppbz ligands. On the other hand, the reactivity differences of substituted benzylidenecyclobutane substrates are mainly affected by the through-bond interactions between the catalyst and the substrates with varying electronic properties. A refined understanding of these types of non-covalent interactions in catalysis offers exciting opportunities in rationally designing ligands that incorporate requisite substrate recognition motifs to amplify reactivity.

## ASSOCIATED CONTENT

### Supporting Information

Detailed experimental and computational procedures, compound characterization, Cartesian coordinates of the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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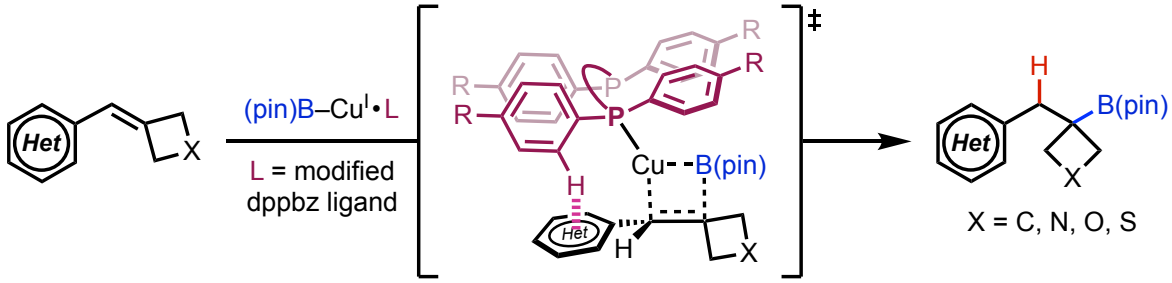


***Substrate–Ligand $\pi$–$\pi$ Interactions***

***• regioselective • mild conditions • diverse heterocycle compatibility***