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σ-Bond Hydroboration of Cyclopropanes

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ABSTRACT: Hydroboration of alkenes is a classical reaction in organic synthesis, in which alkenes react with boranes to give alkylboranes, with subsequent oxidation resulting in alcohols. The double bond (π-bond) of alkenes can be readily reacted with boranes owing to its high reactivity. However, the single bond (σ-bond) of alkanes has never been reacted. To pursue the development of σ-bond cleavage, we selected cyclopropanes as model substrates since they present a relatively weak σ-bond. Herein, we describe an iridium-catalyzed hydroboration of cyclopropanes, resulting in β-methyl alkylboronates. These unusually branched boronates can be derivatized by oxidation or cross-coupling chemistry, accessing "designer" products that are desired by practitioners of natural product synthesis and medicinal chemistry. Furthermore, mechanistic investigations and theoretical studies revealed the enabling role of the catalyst.

■ INTRODUCTION

Carbon–boron bonds (C–B) are very useful in organic chemistry because they are stable but can be coaxed into a host of reactions, resulting in carbon–carbon bonds (C–C) and carbon–heteroatom bonds (C–X). While the reactivity of aromatic carbon–boron bonds (C_{sp2}–B) is a mature topic that is widespread in all areas of chemical application,[1] the generation and reaction of aliphatic carbon–boron bonds (C_{sp3}–B) is still a growing facet of organic synthesis.[2,3] The conventional synthesis and use of alkylborane species was pioneered by H. C. Brown,[4] who reacted alkenes with boranes to give alkylboranes, which in turn can be oxidized to give alcohols.[5] In this classical transformation, the carbon–carbon double bond (C=C) of alkenes is readily reacted with electrophilic boranes to give alkylboranes (a C=C to C–B transformation; Figure. 1A). This transformation relies on the electron-rich and reactive nature of the π-bond present in the alkene, and therefore cannot be replicated when alkane C–C σ-bonds are used as the substrate. Instead of overcoming this limitation, chemists have worked around this problem in the generation of C_{sp3}–B bonds, resulting in the borylation of Grignard reagents (C_{sp3}–X to C_{sp3}–B via C_{sp3}–MgX) and the direct borylation of C–H bonds (C_{sp3}–H to C_{sp3}–B).[6,7] Furthermore, recognizing the specific importance of alkylboronate intermediates in organic synthesis, many methods in transition-metal-catalyzed hydroboration of alkenes have also been developed.[8] Although these methods have expanded the scope of boron chemistry, we surmised that a hydroboration of *alkanes* would be a more direct way to generate C_{sp3}–B bonds, all the while generating alkyl boron products that might be different from the classical hydroboration (Figure. 1B). This hypothesis, however, resulted in an arduous task because C–C σ-bonds lack the reactivity of C=C π-bonds, and thus had not been reacted with boranes. Exceptions to this rule only

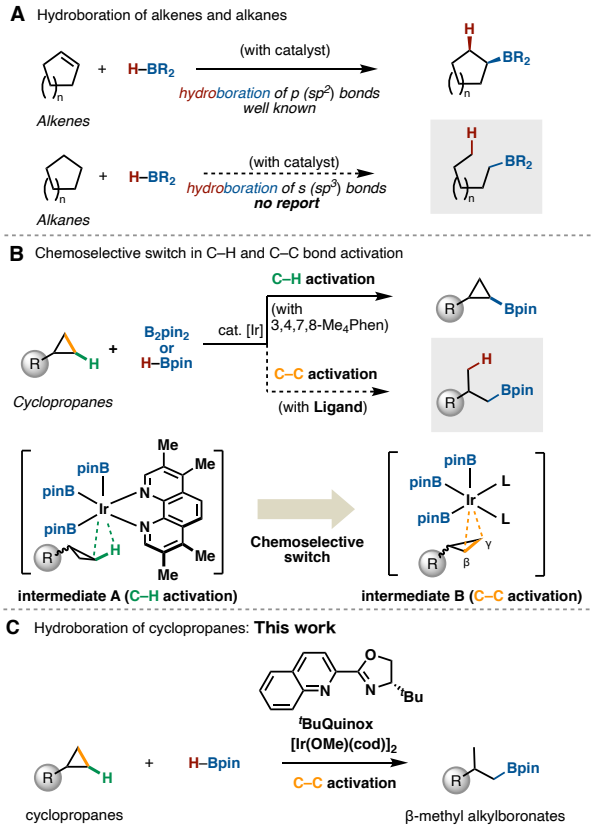


Figure. 1. (**A**) Hydroboration of alkenes and alkanes. (**B**) Chemoselective switch in C–H and C–C bond activation. (**C**) Hydroboration of cyclopropanes.

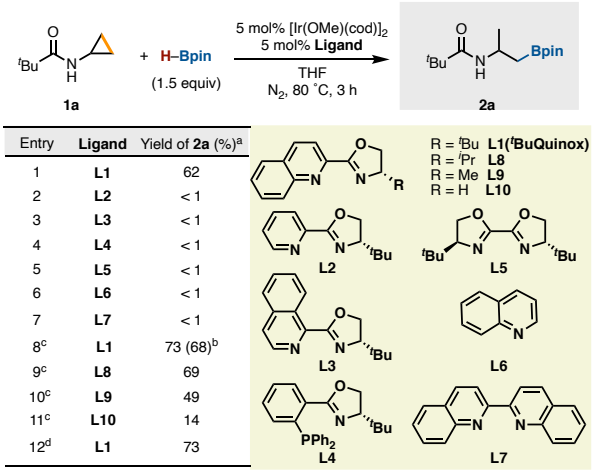
exist when extremely strained C–C σ-bonds are forced into reaction with boranes by guidance from adjacent π-bonds, such as biphenylene[9] or alkylidenecyclopropane.[10] Resulting from a desire to render this C–B bond formation more general, but keeping in mind the reality of C–C bond reactivity,[11-13] we demonstrate herein a σ-bond hydroboration of cyclopropanes.

Recently, several chemists including our group reported an iridium-catalyzed C–H borylation of cyclopropanes.[14] In one report, cyclopropanes were reacted with iridium complexes with a nitrogen bidentate ligand, 3,4,7,8-tetramethylphenanthroline (3,4,7,8-tetraMephen), which engendered a cyclopropane carbon–*hydrogen* activation to afford borylated cyclopropanes (Figure. 1B). With the aim of achieving cyclopropane carbon–*carbon* activation, we forged a blueprint for selective bond activation. If an appropriate ligand were used, it might be possible to perform a "chemoselectivity switch" from C–H (intermediate **A**) to C–C (intermediate **B**) bond activation in which the selectivity of C–C activation could be achieved by reaction of the catalyst with the sterically less hindered Cβ–Cγ bond. [15–18] With these goals in mind, we conducted an extensive screening of ligands, and by using 2-[4-(1,1-dimethylethyl)-4,5-dihydro-2-oxazolyl]quinoline (*t*-Bu-Quinox), we achieved the first iridium-catalyzed σ-bond hydroboration of cyclopropanes (Figure. 1C).

■ RESULTS AND DISCUSSION

Discovery and Screening of Optimized Conditions for Hydroboration of *N*-Cyclopropylpivalamide. We initiated our study by finding a suitable ligand for the target reaction, consisting of *N*-cyclopropylpivalamide (**1a**) as a model mono-substituted cyclopropane (Table 1). **1a** was reacted with pinacolborane (H–Bpin: 1.5 equiv) in the presence of Ir dimer $[Ir(OMe)(cod)]_2$ (5 mol%) and ligands (5 mol%) in THF at 80 °C under nitrogen atmosphere. After an extensive screening of ligands,[19] it was found that *t*-BuQuinox (**L1**) effects the cleavage of the σ-bond and forms hydroboration product **2a** in 62% NMR yield (entry 1). The reaction enabled hydroboration at the Cβ–Cγ bond selectively, as the adduct arising from the cleavage of the Cα–Cβ bond could not be obtained.[20,21] More surprisingly, when **L1** was changed from quinolin-2-yl to pyridyl (**L2**: entry 2) or isoquinolin-1-yl (**L3**: entry 3), the reaction did not work at all. Triphenylphosphine–oxazoline (**L4**: entry 4) and bis-oxazoline (**L5**: entry 5) ligands were not effective. Simple quinoline (**L6**) as well as bis-quinoline (**L7**) did not give any product. Changing the ratio of Ir dimer:**L1** from 1:1 to 2:1, even when using half the original amount of **L1** (5 mol% to 2.5 mol%), gave better results (73% NMR yield, 66% isolated yield, entry 8). In contrast, when the original amount of **L1** was increased, the yield of **2a** decreased significantly, and **1a** was recovered in greater amounts.[19] Although the reason for the metal-to-ligand ratio effect is unclear at present, we conjecture two possible reasons: 1) Due to the short lifetime of the catalyst, it is necessary to have a constant supply of Ir metal; 2) coordination of the oxazoline moiety might be weak, and thus it is necessary to make sure that Ir and **L1** make a 1:1 complex.[22] These conditions can also be applied on gram-scale, albeit with slightly lower yield (53% isolated yield).[19] When the *t*-butyl substituent of **L1** was altered to isopropyl (**L8**), methyl (**L9**), and hydrogen (**L10**), the yield of **2a** gradually decreased (entries 9–11). The catalyst loading can be reduced to 2 mol% Ir dimer and 1 mol% **L1** while maintaining the yield (entry 12). Under the established conditions [5 mol% $[Ir(OMe)(cod)]_2$, 2.5 mol% *t*-BuQuinox (**L1**), THF, 80 °C, 3 h], the substrate scope for σ-bond hydroboration of cyclopropanes was examined (Scheme. 1A).

Table 1. Screening of the ligand for the hydroboration of cyclopropane (1a).



Entry	Ligand	Yield of **2a** (%)[a]
1	**L1**	62
2	**L2**	< 1
3	**L3**	< 1
4	**L4**	< 1
5	**L5**	< 1
6	**L6**	< 1
7	**L7**	< 1
8[c]	**L1**	73 (68)[b]
9[c]	**L8**	69
10[c]	**L9**	49
11[c]	**L10**	14
12[d]	**L1**	73

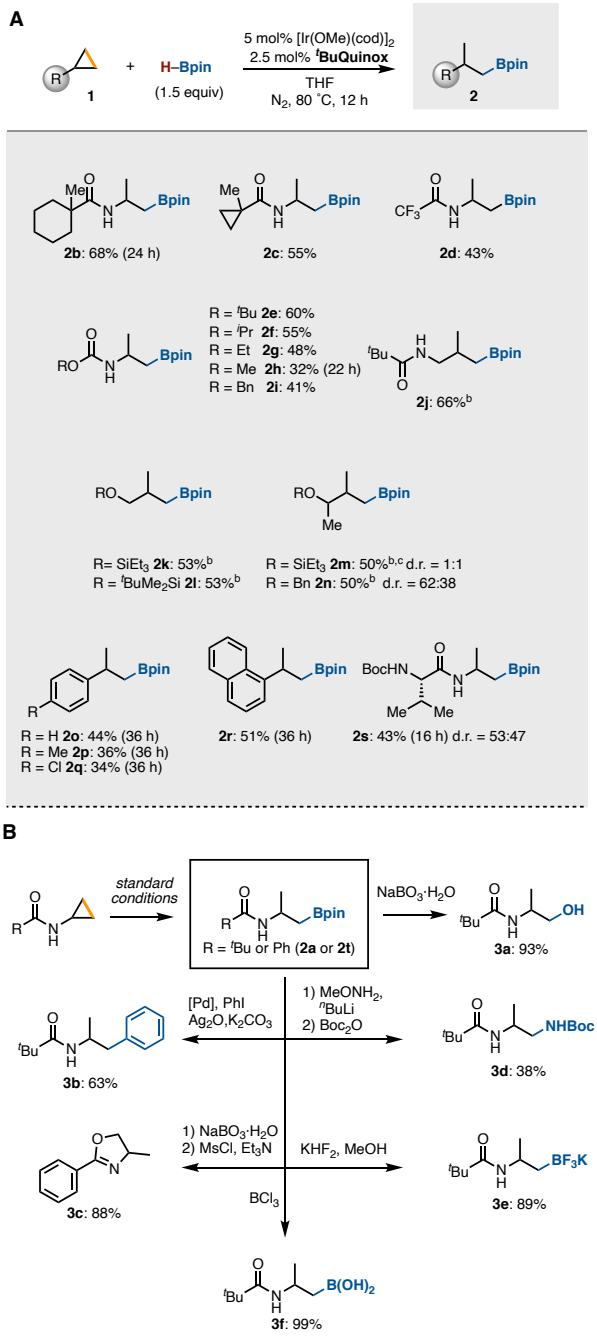
Reaction conditions: **1a** (0.35 mmol, 1.0 equiv), HBpin (1.5 equiv), $[Ir(OMe)(cod)]_2$ (5 mol%), ligand (5 mol%),THF (1.75 mL) at 80 °C for 3 h. [a] Yields of **2a** determined by crude ^{1}H NMR using dibromomethane as an internal standard. [b] Isolated yield. [c] 2.5 mol% of *t*BuQuinox was employed. [d] 2 mol% of $[Ir(OMe)(cod)]_2$ and 1 mol% *t*BuQuinox were employed. See the Supporting Information for full details of the effect of reaction parameters.

Substrate Scope and Synthetic Applicability of Products. The *t*-butyl substituent on the amide group was changed to methylcyclohexane to give the corresponding product **2b** in 68% yield. The reaction can distinguish between two cyclopropyl groups, reacting only with the aminocyclopropane component chemoselectively to afford **2c** in 55% yield. Substrates with substituents such as CF_3, *t*-butoxy, *i*-propoxy, ethoxy, methoxy, and benzyloxy gave the corresponding products **2e**–**2i** in moderate yields. The aminocyclopropane motif can be homologated to aminomethylcyclopropane, yet still react to form **2j** in 66% yield. The amine group was actually found to be unnecessary, as oxymethyl units can react to give **2k**–**2n** in moderate yields. Even in the absence of a Lewis basic functional group, hydroboration of phenyl-, tolyl-, 4-chlorophenyl- and naphthylcyclopropanes was achieved to give the corresponding products **2o**–**2r** without any C–H borylated products on the arene and cyclopropane, albeit in lower yields. A valine derivative was tolerated under the reaction conditions to provide the desired product **2s** in 43% yield while retaining its enantiopurity (>99% ee, dr = 53:47). Furthermore, we demonstrated the synthetic applicability of this product (Scheme 1B): **2a** or **2t** can be oxidized to give the corresponding alcohol **3a** in 93% yield (43% in one pot), or coupled with phenyl iodide to furnish the coupling product **3b** in 63% yield. Additionally, the derivatization of the product successfully generated, oxazoline **3c**, amine **3d**, trifluoroborate **3e**, and boronic acid **3f** in moderate to excellent yields.

Mechanistic Investigation. Next, we investigated how this C–C bond-breaking reaction takes place even though previous Ir-catalyzed cyclopropane transformations effected C–H bond activation. At the outset, we proposed three routes for the formation of

hydroboration adduct **2** (Figure 2A). In Route I, C–H borylation of the cyclopropane proceeds first, followed by C–C bond activation (ring opening); in Route II, the ring opening takes place first to give an alkene (or an Ir-alkene complex), followed by hydroboration; in

Scheme 1 (A) Hydroboration of cyclopropanes.[a] (B) Synthetic applicability of the product.



Reaction conditions: [a] **1** (0.35 mmol, 1.0 equiv), HBpin (1.5 equiv), $[Ir(OMe)(cod)]_2$ (5 mol%), *t*BuQuinox (2.5 mol%),THF (1.75 mL) at 80 °C for 12 h. [b] [Ir(acac)(cod)] (5 mol%) was used. [c] Diastereomeric mixtures.

Route III, C–C bond activation and formal allylic borylation afford a borylalkene (or an Ir-boryl alkene complex), followed by hydrogenation. To elucidate the reaction mechanism, several reactions using plausible intermediates experiments were conducted (Figure 2B–2D). When C–H borylation product **4a** was reacted under the standard conditions, **4a** was recovered completely unchanged (Figure 2B, formula 1), indicating that Route I is not operational. In contrast, both *N*-cyclopropylbenzamide (**1t**) and the corresponding alkene **5** reacted with H–Bpin under the standard conditions, affording the same hydroboration product **2t** (44% yield from **1t**; 38% NMR yield from **5**) along with hydrogenated product **2t'** (18% NMR yield from **1t**; 16% NMR yield **5**) and diborylated product **2t"** (5% NMR yield from **1t**; 0% yield from **5**, Figure 2B, formula 2). It is worth noting that the synthesis of enamine **5** was complex and lengthy, wherein only one procedure succeeded in transforming 2-methyloxirane to **5** in four steps.[23] Next, both cyclopropylbenzene (**1o**) and boryl alkene **6**[24] reacted with H–Bpin under the standard conditions, affording the same hydroboration product **2o** (44% yield from **1o**; 37% NMR yield from **6**) along with hydrogenated product **2o'** (21% NMR yield from **1o**; 0% yield **6**) and diborylated product **2o"** (12% NMR yield from **1o**; 46% yield from **6**, Figure 2B, formula 3). These results support the mechanism described in Route II or Route III. Additionally, deuterium labeling experiments of **1a** and possible intermediates were conducted (Figure 2C). Hydroboration of cyclopropylamine **1a** was conducted using deuterated pinacolborane (D-Bpin; Figure 2C, formula 4). After oxidation and capping with a protecting group (which helped facilitate product isolation and analysis), the incorporation of deuterium on three carbons on **7** was observed (D^1:45%, D^2: 27%, and D^3: 28%), indicating a reversible insertion of the Ir–H/D species onto the olefin.[25] We also examined hydroboration of **5** and **6**, which are possible intermediates of this reaction, using D-Bpin (Figure 2C, formula 5 and 6). As a result, similar incorporation of deuterium on three carbons for both **8** and **9** were observed (D^1: 34%, D^2: 42%, and D^3: 16% for **8**; D^1: 36%, D^2: 34%, and D^3: 20%). However, the ratios of deuterium incorporation are not completely consistent with each other, suggesting that the hydroboration of **1a** could be both through Route II and Route III. Furthermore, we investigated the byproducts of this reaction thoroughly (Figure 2D). The hydrogenated product **2a'** was obtained in 19% NMR yield, but it is unclear whether it was obtained by protodeborylation from **2a** or direct hydrogenation. For other cyclopropane **1**, the hydrogenated form **2'** was found to be similarly obtained. Additionally, linear products **linear-2a** (the adduct arising from the cleavage of the Cα–Cβ bond) and its hydrogenated form **linear-2a'** were also obtained in around 4% NMR yield as an inseparable mixture, when the reaction was conducted on large scale. Additionally, diborylated product **2a"** was also detected (6% NMR yield). Lastly, since this reaction uses a chiral ligand, we attempted to see if it could be applied to enantioselective reactions (Figure 2F). The results showed that the enantioselectivity was 16% *ee* under our standard conditions, while optimizations yielded (S)-**2a** in up to 30% yield and 36% *ee*. Although further optimization was performed, unfortunately, both the yield and the enantioselectivity did not improve. This result also supports the existing reaction pathways.

Plausible Mechanism and Theoretical Calculations. To complement the above experimental investigations of the cyclopropane hydroboration, we turned our attention to elucidate key mechanistic features through theoretical calculations (for details of the com-

putational methods, see Supporting Information). A plausible mechanism of the hydroboration of cyclopropanes, as well as the C–H borylation of cyclopropanes, is shown in Figure 3A. The calculations supported a 5-coordinate Ir complex **B** as the active catalyst for both reactions.[26] The Cβ–Cγ bond oxidative addition

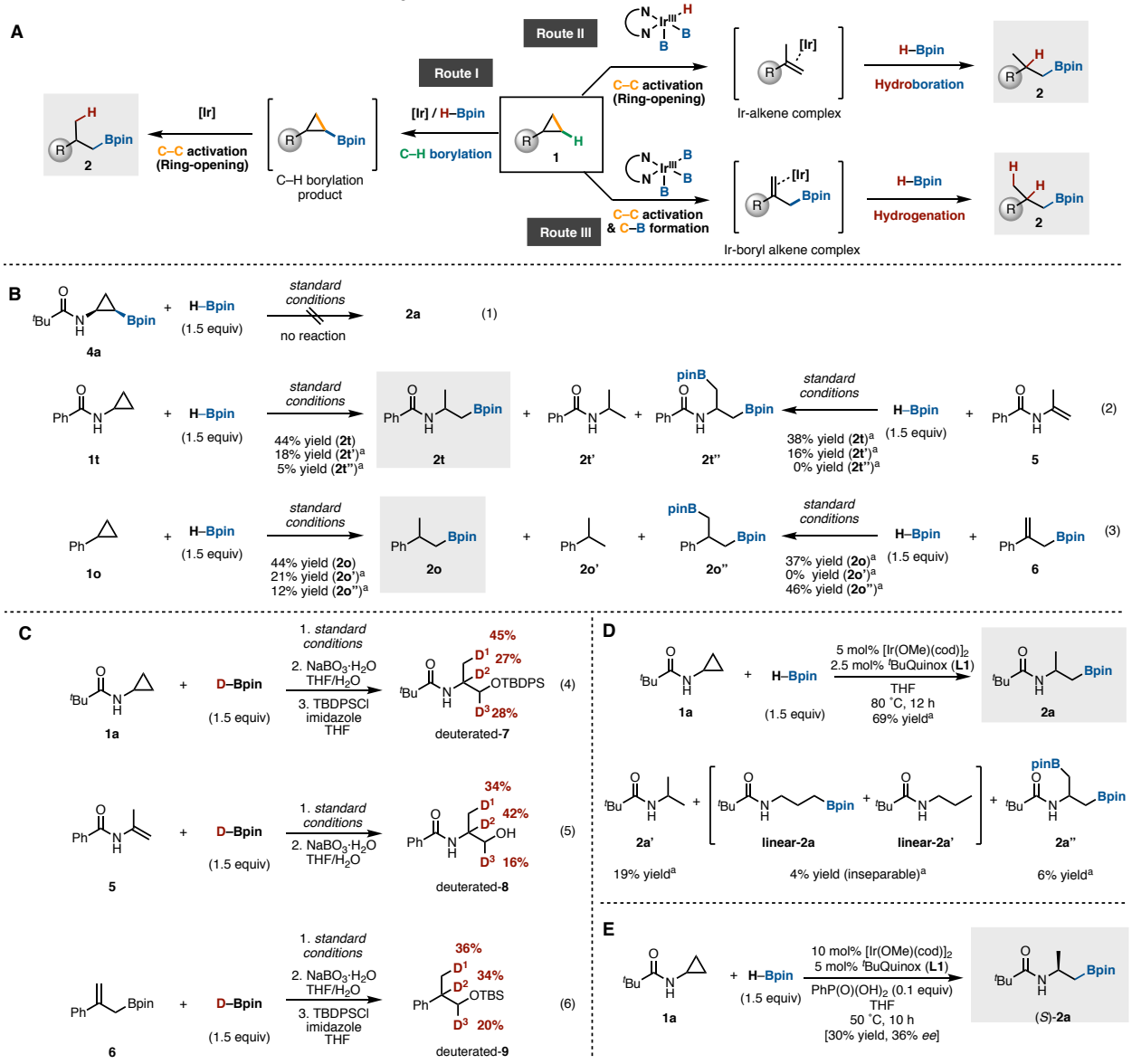


Figure 2. (A) Possible routes for the hydroboration of cyclopropanes. (B) Mechanistic investigations. (C) Deuterium labeling experiments. (D) Investigation of the reaction side products. (E) Attempt toward an enantioselective hydroboration. [a] Yields determined by crude ^{1}H NMR using dibromomethane as an internal standard.

mono-substituted cyclopropanes **1** to Ir complex **B** gives intermediate **C**, from which reductive elimination produces complex **D** (8.3 kcal/mol). From **D**, there are three pathways to afford complexes **E**, **D'**, and **D''** which exist in equilibrium with each other. Although hydroborylated product **2** can be produced from all three pathways, the most favorable one is the reaction through complex **E** (5.4 kcal/mol, Figure 3B). Through reductive elimination of complex **E**, hydroborylated product **2** can be obtained, and catalyst **B** is recovered. In an alternative pathway (mechanism for Route I), C–H borylation might occur from the same active species **B** by C–H activation of **1**, followed by reductive elimination to form **F**. The produced Ir complex **A** can then react with H-Bpin and then reform catalyst B by releasing a molecule of H_2. The free energy diagram for the reaction with *t*-BuQuinox ligand is shown in Figure 3B. Because the activation energies are around 20 kcal/mol, C–C and C–H activations are both possible under the experimental conditions, which is not consistent with experimental results. The reason why *t*-BuQuinox ligand only catalyzes the C–C activation pathway is currently unclear.

Some of the ligands from Table 1 (3,4,7,8-tetraMephen, **L2**, and **L10**) effect C–H activation, while *t*-BuQuinox (**L1**) effects C–C activation. To discuss this difference, we computed the activation free energies in C–C and C–H activation steps (ΔG_a(C − C) and ΔG_a(C − H), respectively). As shown in Figure 4A, ΔG_a(C − H) is smaller than ΔG_a(C − C) in the cases of 3,4,7,8-tetraMephen, **L2**, and **L10** ligands, which is consistent with the experimental data. In particular, ΔG_a(C − C) of **L2** and **L10** is much larger than ΔG_a(C − C) of 3,4,7,8-tetraMephen and **L1**.

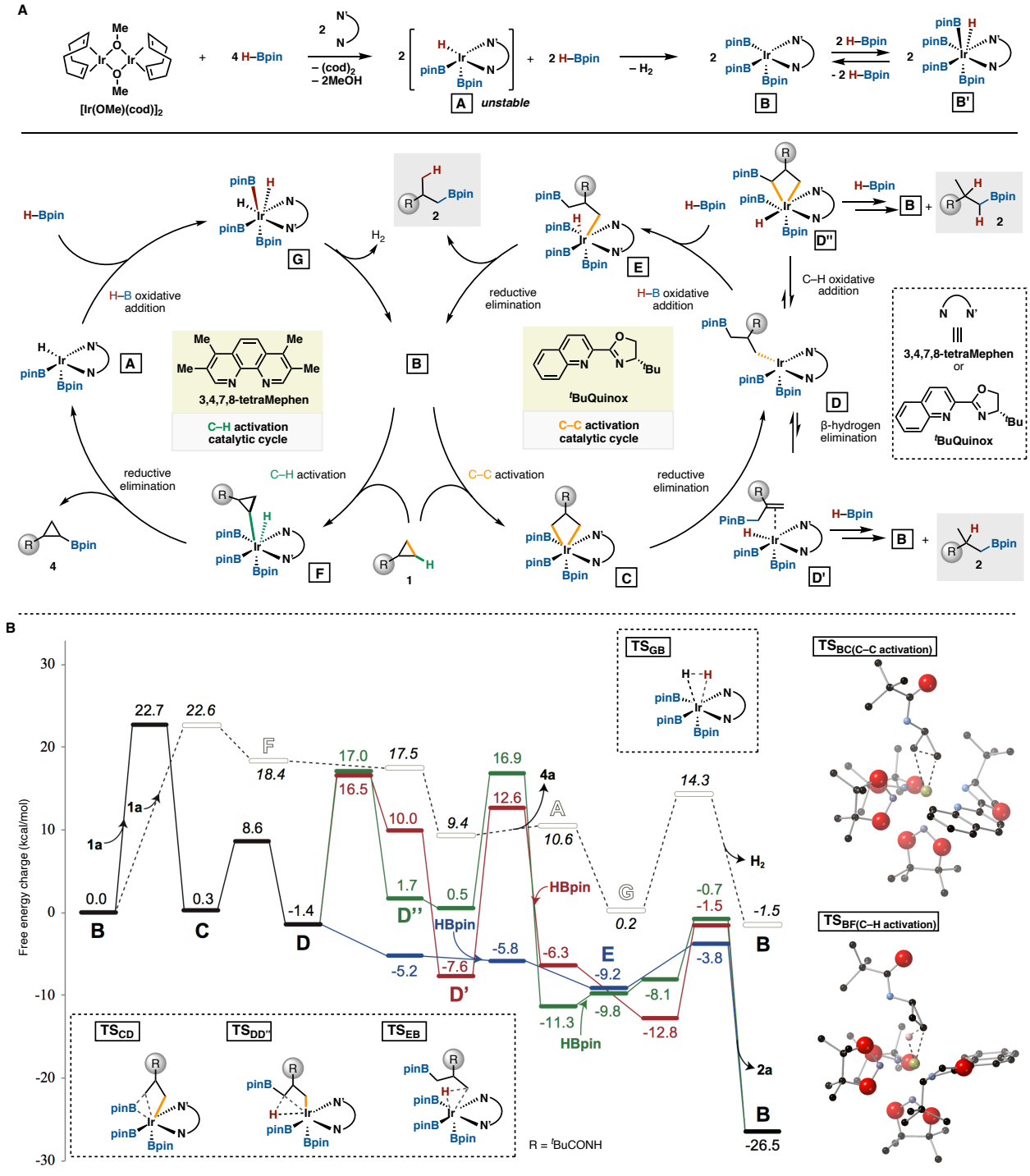


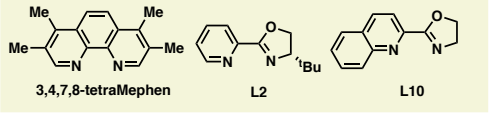
Figure 3. (A) Proposed mechanism: hydroboration and C–H borylation of cyclopropanes. (B) Free energy diagram of hydroboration and C–H borylation of cyclopropanes using *t*BuQuinox as the ligand. grey = C–H activation pathway, black+red = C–C activation through D', black+blue = C–

C activation through E, and black+green = C–C activation through D" (Other chemical structures of calculated energies are shown in supporting information).

By computing the activation energy using a model reactant, we found that the large difference in ΔG_a(C − C) mainly comes from steric repulsion between Bpin and reactant (Figure 4B, see the Supporting Information in details). The origin of the steric repulsion can be seen in the distances between the Me groups in Bpin and the reactant (C_1–C_a and C_1–C_b), which are shown in Figure 4B. In the case of **L1**, the distances C_1–C_a and C_1–C_b are around 4.3 Å, while the distance of C_1–C_b is around 4.1 Å in **L2** and **L10**. The small distance between Bpin and reactant causes a large steric repulsion in **L2** and **L10**. This steric repulsion is the reason why we can achieve selective bond activation by changing the ligands

A

Ligand	DG_a (C–C) kcal/mol	DG_a (C–H) kcal/mol
3,4,7,8-tetraMephen	27.2	21.8
L1 (^{t}BuQuinox)	22.7	22.6
L2	43.5	19.5
L10	40.0	18.0



B

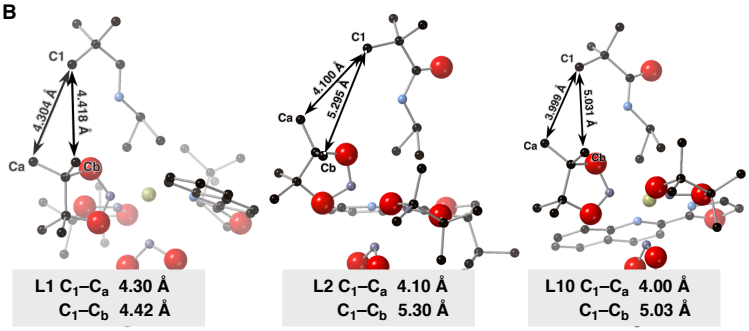


Figure 4. (A) Activation free energies (ΔG_a) computed with MP2 (SCS-MP2) in the step TS_{BC} (C–C activation) and TS_{BF} (C–H activation). (B) The distances between the Me groups in Bpin and the reactant (C_1–C_a and C_1–C_b) with **L1**, **L2**, and **L10**.

■ CONCLUSION

In summary, we have developed the first general hydroboration of cyclopropanes. An iridium catalyst, particularly bound to a *t*-BuQuinox ligand, was essential for this transformation, otherwise the reaction did not proceed or the C–H borylation of cyclopropanes occurred. The established conditions formed a variety of alkyl boranes via C–C bond activation, with downstream functionalizations for versatile use. We also elucidated key mechanistic features of this newly developed reaction by experimental investigations as well as theoretical calculations. Further optimization of the catalyst and reaction conditions to achieve broader scope and enantioselectivity is ongoing in our laboratory.

■ EXPERIMENTAL SECTION

General Procedure for Ir-catalyzed hydroboration

A 20-mL glass vessel tube equipped with a J. Young® O-ring tap containing a magnetic stirring bar was dried with a heat gun under reduced pressure and filled with nitrogen after cooling to room temperature. To this vessel were added cyclopropane (0.35 mmol) and (*S*)-4-(*tert*-butyl)-2-(quinolin-2-yl)-4,5-dihydrooxazole (^{t}Bu-Quinox: 2.2 mg, 8.8 μmol) under nitrogen, after which it was introduced inside an argon atmosphere glovebox. In the glovebox, [Ir(OMe)(cod)]$_2$ (11.6 mg, 0.018 mmol) and THF (1.0 mL) were added. After 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin: 76.2 μL, 0.53 mmol) and THF (0.75 mL) were added, the glass vessel was sealed with the O-ring tap and then taken out of the glovebox. The mixture was stirred at 80 °C for 12 h, cooled to room temperature and concentrated *in vacuo*. The residue was purified by MPLC to give the hydroboration product **2**.

■ ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and spectroscopic data for compounds including ^{1}H-, ^{13}C NMR spectra (PDF)

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Notes

No competing financial interests have been declared.

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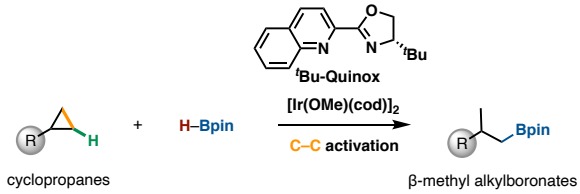

New C–C bond activation: addition of borane to Cβ–Cγ bond of cyclopropanes
Ligand accelerated reaction : *t*-Bu Quinox was essential for this transformation
Broad scope: applicable to acylamines, aminomethyl, oxymethyls, aromatics, amino acids
Synthetic utility: alcohols, oxazolines, amines, boronates
High chemoselectivity: no C–H boryaltion of the cyclopropanes and the aromatics