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.

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_{sp^2} –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_{sp^3} –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 was readily reacted with electrophilic boranes to give alkylboranes (a C=C to C–B transformation; Fig. 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_{sp^3} –B bonds, resulting in the borylation of Grignard reagents (C_{sp^3} –X to C_{sp^3} –B via C_{sp^3} –MgX) and the direct borylation of C–H bonds (C_{sp^3} –H to C_{sp^3} –B).^[6–10] Furthermore, recognizing the specific importance of alkylboronate intermediates in organic synthesis, many methods in transition-metal-catalyzed hydroboration of alkenes have also been developed.^[11,12] 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_{sp^3} –B bonds, all the while generating alkyl boron products that are different from the classical hydroboration adducts (see Fig. 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 exist when extremely strained C–C σ -bonds are forced into reaction with

boranes by guidance from adjacent π -bonds, such as biphenylene^[13] or alkylidenecyclopropane.^[14,15] Resulting from a desire to render this C–B bond formation more general, but keeping in mind the reality of C–C bond reactivity^[16–18], we demonstrate herein a σ -bond hydroboration of cyclopropanes.

Recently, several chemists including our group reported an iridium-catalyzed C–H borylation of cyclopropanes^[19–21]. 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 (Fig. 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 C β –C γ bond^[22–24]. 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 (Fig. 1C).

We initiated our study by finding a suitable ligand for the target reaction, consisting of *N*-cyclopropylpivalamide (**1a**) as a model mono-substituted cyclopropane. **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 (see Supplementary Materials), it was found that *t*-BuQuinox (**L1**) effects the cleavage of the σ -bond and forms hydroboration product **2a** in 62% yield

(entry 1). The reaction enabled hydroboration at the C β –C γ bond selectively, as the adduct arising from the cleavage of the C α –C β bond could not be obtained [25,26]. 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% yield, 66% isolated yield, entry 8). These conditions can also be applied on gram-scale, albeit with slightly lower yield (53% isolated yield; see Supplementary Materials). When the *t*-butyl substituent of **L1** was altered to isobutyl (**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).

Fig. 1. (A) Hydroboration of alkenes and alkanes. (B) Chemoselective switch in C–H and C–C bond activation. (C) Hydroboration of cyclopropanes. Reaction conditions: **1a** (0.35 mmol, 1 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 ¹H NMR using dibromomethane as an internal standard. [b] Isolated yield. [c] 2.5 mol% of ^tBuQuinox was employed. [d] 2 mol% of [Ir(OMe)(cod)]₂ and 1 mol% ^tBuQuinox were employed. See the Supplementary Materials for full details of the effect of reaction parameters.

Under the established conditions [5 mol% [Ir(OMe)(cod)]₂, 2.5 mol% ^tBuQuinox (**L1**), THF, 80 °C, 3 h], the substrate scope for σ -bond hydroboration of cyclopropanes was examined (Fig. 2A).

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 CF₃, *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 (Fig. 2B): **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.

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 3A). 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 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, reactions using plausible intermediates and a deuterium labeling experiment were conducted (Fig. 3B).

When C–H borylation product **4** was reacted under the standard conditions, **4** was recovered completely unchanged (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**; 36% yield from **5**; formula 2). It is worth noting that the synthesis of enamine **5** was complex and lengthy, wherein only one procedure succeeded in its preparation from 2-methyloxirane in four steps [27]. Next, both cyclopropylbenzene (**1o**) and boryl alkene **6** [28] reacted with H–Bpin under the standard conditions, affording the same hydroboration product **2o** (44% yield from **1o**; 37% yield from **6**; formula 4). These results might support the mechanism described in Route II or Route III. Lastly, hydroboration of cyclopropylamine **1a** was conducted using deuterated pinacolborane (D–Bpin; formula 5). 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 (D¹:45%, D²: 27%, and D³: 28%), indicating a reversible insertion of the Ir–H/D species onto the olefin [29].

To complement the above experimental investigation of the cyclopropane hydroboration, we turned our attention to elucidate key mechanistic features through theoretical calculations (for details of the computational methods, see Supplementary Materials). A plausible mechanism of the hydroboration of cyclopropanes as well as the C–H borylation of cyclopropanes is shown in Figure 4A. The calculations supported a 5-coordinate Ir complex **B** as the active catalyst for both reactions [30]. The Cβ–Cγ bond oxidative addition of 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 4B). Through reductive elimination of complex **E**, hydroborylated product **2** can be obtained, and catalyst **B** is recovered.

Fig 3. (A) Possible route for hydroboration of cyclopropanes (B) Mechanistic Investigations.

Fig 4. (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''. (C) Activation free energies (ΔG_a) computed with MP2 (SCS-MP2) in the step TS_{BC} (C–C activation) and TS_{BF} (C–H activation).

In an alternative pathway (mechanism for Route 1), 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 4B. Because the activation energies are around 20 kcal/mol, both pathways are possible under the experimental conditions. Although both mechanistic cycles are possible *kinetically*, the C–C activation cycle is *thermodynamically* favorable. On the other hand, in the case of the 3,4,7,8-tetraMephen ligand, the C–H activation cycle is thermodynamically and kinetically favorable (Figure 4C). The use of L2 and L10 were difficult to go through C–C bond activation because these required significantly high free energies. This is the reason why we can achieve the selective bond activation by changing the ligands.

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.

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 1H -, ^{13}C NMR spectra (PDF)

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Notes

No competing financial interests have been declared.

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REFERENCES

1. D. G. Hall, Ed., *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, vols. 1 and 2, Wiley-VCH (2011).
 2. D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed. Engl.* **54**, 1082–1096 (2015).
 3. C. Li et al., *Science*, eaam7355 (2017).
 4. H.C. Brown, *Tetrahedron* **12**, 117–138 (1961).
 5. M. B. Smith, J. March, Eds., *March's advanced organic chemistry: Reactions, mechanism and structure*, John Wiley & Sons, Inc., Hoboken (2007).
 6. K. M. Waltz, J. F. Hartwig, *Science* **277**, 211–213 (1997).
 7. H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **287**, 1995–1997 (2000).
 8. J. He, Q. Shao, Q. Wu, J.-Q. Yu, *J. Am. Chem. Soc.* **139**, 3344–3347 (2017).
 9. I. A. I. Mkhaliid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **110**, 890–931 (2010).
 10. J. F. Hartwig, *Chem. Soc. Rev.* **40**, 1992 (2011).
 11. I. Beletskaya, A. Pelter, *Tetrahedron* **53**, 4957–5026 (1997).
 12. C. M. Crudden, D. Edwards, *Eur. J. Org. Chem.* 4695–4712 (2003).
 13. T. Matsuda, H. Kirikae, *Organometallics* **30**, 3923–3925 (2011).
 14. I. Namamura, Y. Yamamoto, *Adv. Synth. Catal.* **344**, 111–129 (2002).
 15. S. Simaan, A. F. G. Goldberg, S. Rosset, I. Marek, *Chem. Eur. J.* **16**, 774–778 (2010).
 16. M. Murakami, N. Chatani, Eds., *Cleavage of Carbon–Carbon Single Bonds by Transition Metals*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim (2016).
 17. G. Fumagalli, S. Stanton, J. F. Bower, *Chem. Rev.* **117**, 9404–9432 (2017).
 18. Y. Xia, G. Lu, P. Liu, G. Dong, *Nature*, **539**, 546–550 (2016).
 19. C. W. Liskey, J. F. Hartwig, *J. Am. Chem. Soc.* **135**, 3375–3378 (2013).
 20. R. Murakami, K. Tsunoda, T. Iwai, M. Sawamura, *Chem. Eur. J.* **20**, 13127–13131 (2014).
 21. S. Miyamura, M. Araki, T. Suzuki, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed. Engl.* **54**, 846–851 (2015).
 22. M. Murakami, H. Amii, K. Shigeto, Y. Ito, *J. Am. Chem. Soc.* **118**, 8285–8290 (1996).
 23. S. C. Bart, P. J. Chirik, *J. Am. Chem. Soc.* **125**, 886–887 (2003).
 24. Z. He, A. K. Yudin, *Org. Lett.* **8**, 5829–5832 (2006).
 25. M. H. Shaw, W. G. Whittingham, J. F. Bower, *Tetrahedron* **72**, 2731–2741 (2016).
 26. H. Kondo, K. Itami, J. Yamaguchi, *Chem. Sci.* **8**, 3799–3803 (2017).
 27. J. P. Wolfe, J. E. Ney, *Org. Lett.* **5**, 4607–4610 (2003).
 28. W. Ma, J. Fang, J. Ren, Z. Wang, *Org. Lett.* **17**, 4180–4183 (2015).
 29. C. Mazet, D. Gérard, *Chem. Commun.* **47**, 298–300 (2011).
 30. H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **125**, 16114 (2003).
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