Catalytic, Undirected Borylation of Tertiary C–H Bonds in Bicyclo[1.1.1]pentanes and Bicyclo[2.1.1]hexanes

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Abstract:

Catalytic borylations of sp^3 C–H bonds occur with high selectivities for primary C–H bonds or secondary C–H bonds that are activated by nearby electron-withdrawing substituents. The catalytic borylation at tertiary C–H bonds has not been observed. We describe a broadly applicable method for the synthesis of boron-substituted bicyclo[1.1.1]pentanes (BCPs) and (hetero)bicyclo[2.1.1]hexanes (BCHs) by an iridium-catalyzed borylation of the bridgehead tertiary C–H bond. This reaction is highly selective for the formation of bridgehead boronic esters and is compatible with a broad range of functional groups (>35 examples). The method is applicable to the late-stage modification of pharmaceuticals containing this substructure and the synthesis of novel bicyclic building blocks. Kinetic and computational studies suggest that C–H bond cleavage occurs with a modest barrier and that the turnover-limiting step of this reaction is an isomerization that occurs prior to reductive elimination that forms the C–B bond.

Main

Recent developments in iridium-catalyzed borylation have made the undirected borylation of alkyl C–H bonds an increasingly practical method to access alkyl boronic esters.[1-6] Generally, metal-catalyzed borylation occurs at primary C–H bonds or, in the absence of accessible primary C–H bonds, at secondary C–H bonds activated by ring strain or electron-withdrawing substituents. Even recent radical-based borylations of C–H bonds, which could be expected to occur at tertiary C–H bonds, occurred at primary and secondary over tertiary C–H bonds.[7] The catalytic borylation of tertiary C–H bonds has not occurred (Fig. 1a). Our recent discovery of an iridium complex formed from 2-methylphenanthroline (2-mphen, **L1**) that catalyzes the borylation of primary and secondary alkyl C–H bonds with the alkane as the limiting reagent[5]

raised the question of whether the borylation of tertiary C–H bonds could be achieved. For this proposed reaction to occur and to be practical, the C–H functionalization must occur cleanly at a class of C–H bonds typically unreactive toward C–H activation forming metal-carbon bonds, with minimal deleterious C–C bond cleavage, and with the substrate as the limiting reagent.

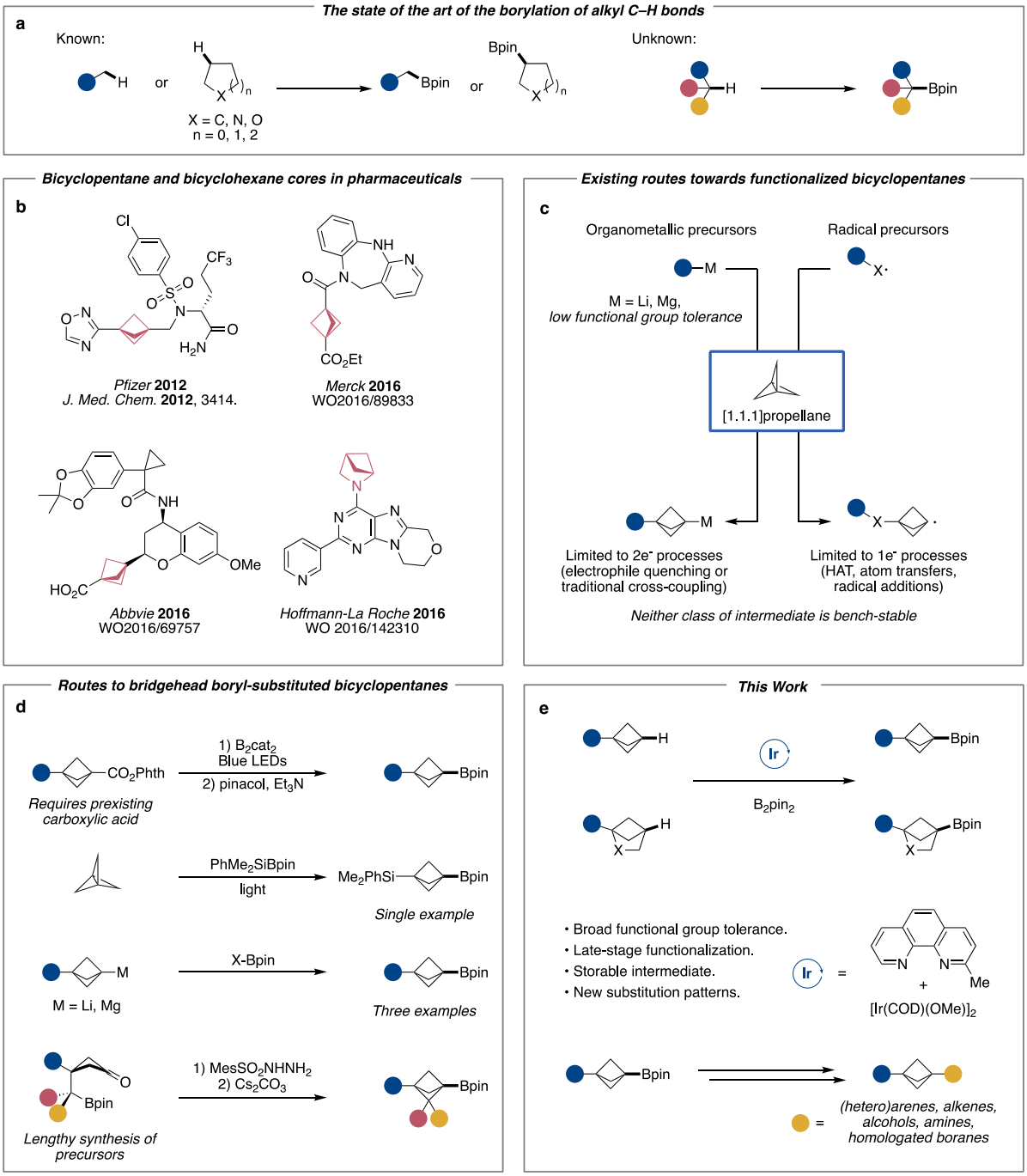

Fig. 1: State of the borylation of alkyl C–H bonds, applications of BCPs, and routes for their synthesis relevant to this study. (a) The borylation of primary and secondary C–H bonds are known, while the borylation of tertiary C–H bonds is unprecedented. (b) Selected examples of drug candidates exhibiting bioisosteric replacement of para-disubstituted benzenes and pyrrolidines by BCPs and (hetero)BCHs. (c) Summary of existing approaches towards 1,3-disubstituted BCPs. Addition of organometallic nucleophiles to propellane results in bicyclopentyl organometallic species, which can be quenched or cross-coupled with electrophiles. Addition of radicals to propellane results in bicyclopentyl radical species, which can participate in atom transfer reactions or additions to radical acceptors. Neither bicyclopentyl intermediate is bench-stable. (d) Approaches

toward bridgehead-substituted boryl-BCPs. Examples are either limited in scope or require lengthy syntheses prior to installation of the boryl substituent. (e) Approach and synthetic opportunities of the current work.

Since Lovering's seminal paper[8] introducing the concept of "escape from flatland," the synthetic community has become increasingly interested in the incorporation of sp^3-rich fragments into drug candidates. In particular, the highly strained bicyclo[1.1.1]pentane (BCP) motif is being applied as a potential bioisostere to mono- and *para*-disubstituted benzenes,[9-12] internal alkynes,[13] and *tert*-butyl groups.[14,15] Related bicyclo[2.1.1]hexanes (BCHs) and oxa- and aza-bicyclo[2.1.1]hexanes (XBCHs) have been proposed as possible bioisosteres to *ortho*- and *meta*- disubstituted benzenes[16,17] and conformationally constrained equivalents of pyrrolidine, respectively.[18,19] In many cases, bioisosteric substitution of disubstituted benzenes and pyrrolidines for these saturated bicycles imparted greater rigidity, increased solubility, and improved metabolic stability for drug candidates (Fig. 1b).

The increased demand for functionalized BCPs has led to a surge in the development of methods for the construction of substituted BCPs. Prevailing methods usually involve the manipulation of [1.1.1]propellane. Radical addition to the central bond of [1.1.1]propellane is well-known and is part of radical chain and photoredox pathways to substituted BCPs.[20-30] The addition of organometallic compounds, such as Grignard reagents, to [1.1.1]propellane is also well precedented, and the resulting bicyclo[1.1.1]pentyl organometallic intermediates can be quenched by electrophiles or used as nucleophiles in cross-coupling reactions.[13,31-37] The insertion of donor-acceptor carbenes into the bridgehead C–H bond of BCPs also has been reported.[38] While these methods allow access to 1,3-disubstituted BCP derivatives, the intermediate bicyclopentyl species are not bench-stable, and the limited scope of reaction partners that are compatible with the harsh reagents and with the conditions to install the second substituent makes rapid diversification of the scaffold difficult. Furthermore, most of these methods are limited to the synthesis of BCP derivatives and cannot be extended to BCHs and (hetero)BCHs (XBCHs) (Fig. 1c).

An alternative and unifying strategy towards the construction of diverse BCP, BCH, and XBCH building blocks is to enlist boronic esters, which are stable synthetic intermediates (Fig. 1c). The boronic ester motif could be derivatized into a variety of carbo- and heteroatom-based functional groups through well-established synthetic procedures. In this vein, Aggarwal developed a decarboxylative borylation of redox-active esters, including ester derivatives of BCPs,[39,40] Uchiyama reported the direct silaboration of propellane,[41] Qin reported a Barluenga−Valdés-inspired cyclization that forges the BCP core from cyclobutanones,[42] and the Anderson, Aggarwal, and Walsh groups demonstrated the feasibility of trapping *in situ*-generated BCP organometallic species with boron electrophiles.[25,36,43,44] Many of these routes rely on the handling of [1.1.1]propellane or the lengthy synthesis of either a prefunctionalized BCP or cyclobutanone scaffold prior to installation of the boryl group, thereby limiting the general applicability of these groups to the preparation of the boronic esters of BCHs and XBCHs (Fig. 1d). A direct and straightforward strategy to construct these coveted boronic esters would be to repurpose existing, but underutilized, stable and commercially available 1-substituted strained building blocks via the direct functionalization of the bridgehead C–H bond (Fig. 1e).

Herein, we report the iridium-catalyzed borylation of the bridgehead tertiary C–H bonds of BCPs, BCHs and XBCHs. This reaction occurs selectively at this type of tertiary C–H bond over unactivated primary and secondary C–H bonds and tolerates a wide variety of functional groups. This C–H bond reacts with rates that are similar to those observed with cyclopropanes,

leading to the broad scope, and the boronic ester products of this method undergo a wide variety of reactions to form 1,3-disubstituted bicyclic building blocks.

Results and Discussion

Reaction Development of the Borylation of Bridgehead C–H Bonds

We initiated our investigation of the borylation of the bridgehead, tertiary C–H bonds of BCPs by testing reactions of the model substrate 4-*tert*-butylphenylbicyclopentane **1b** in the presence of a series of catalysts reported for the borylation of alkyl C–H bonds (Fig. S2).[4,5,45] Studies on reaction times, stoichiometries and ligands for iridium showed that the iridium system formed from 2-mphen (**L1**) and (mesitylene)Ir(Bpin)$_3$ catalyzed the borylation of **1b** to form **1a** in high yield with the substrate as the limiting reagent and exclusively at the bridgehead tertiary C–H bond. Reactions conducted with 2,9-dimethylphenanthroline (2,9-dmphen, **L2**) also occurred in a high yield, albeit measurably lower than those with **L1**, and reactions conducted with 3,4,7,8-tetramethylphenanthroline (tmphen, **L3**) or 2,2'-((3-fluorophenyl)methylene)dipyridine (**L5**)[4] occurred in moderate to low yields. Reactions conducted with ligands used primarily for the borylation of aromatic C–H bonds, such as 4,4'di-*tert*-butylbipyridine (dtbpy, **L4**)[46] or 5-methyl-2-(thiophen-3-yl)pyridine (**L6**),[45] as ancillary ligands did not form product. Control experiments showed that both the ligand and the iridium precursor are necessary for the formation of the product, and reactions conducted with the commercially available precatalyst [Ir(COD)(OMe)]$_2$ were similar to those with (mesitylene)Ir(Bpin)$_3$. The use of HBpin or alternate diboron reagents in place of B_2pin_2 as the boron source resulted in lower yields. Although the desired boronic ester was obtained with **L2**, **L3**, or **L5** as ligand, we used 2-mphen as the ligand for further studies on reaction scope because the reaction times could be shorter, and these faster rates would likely reduce competing reactions with auxiliary functional groups and afford the products in superior yields (Fig. S3).

With conditions for the borylation of model substrate **1b** in hand, we explored the scope of the undirected borylation of monosubstituted BCPs with B_2pin_2 catalyzed by [Ir(COD)(OMe)]$_2$ and 2-mphen. All substrates underwent borylation exclusively at the bridgehead C–H bond or concomitantly at the bridgehead and at an aryl or acidic primary alkyl C–H bond if those C–H bonds were not sufficiently hindered. (Fig. 2a) Competitive reactions at primary and secondary C–H bonds with fully substituted α-carbons were not observed, presumably due to steric hindrance. Arene, sulfide, stannane, bromide, and ester functionalities did not interfere with borylation at the bridgehead, tertiary C–H bond (**1a**-**5a**, **8a**-**10a**). Alcohols were tolerated following an in situ protection procedure (**6a**, **7a**).[5] Reactions of BCPs containing sulfone and sulfonamide units gave products from borylation at the tertiary C–H bond (**11a**-**14a**); borylations at the methyl C–H bonds of a methyl sulfone and at the N–H bonds of the primary sulfonamide were observed, but the B–C and B–N bonds at those positions were labile and were selectively hydrolyzed upon workup to afford the product containing a boronic ester solely at the bridgehead position (**11a**, **12a**). Imides, amides and Boc-protected cyclic amines also underwent borylation at the tertiary C–H bond (**15a**-**18a**). A substrate containing sterically accessible aryl C–H bonds underwent borylation of both the aryl and bridgehead C–H bonds (**19a**). (Fig. 2b)

The broad functional group compatibility of this method prompted us to apply it to the late-stage borylation of complex molecules containing the BCP fragment and to test the reaction on larger scale. Exclusive borylation at the bridgehead C–H bond was observed for derivatives of abietic acid and valproic acid (**20a**, **21a**). (Fig. 2c) The method was easily amenable to

syntheses on a gram scale. The borylation of **11b** on a 4.0 mmol scale gave the corresponding boronic ester in 58% yield (631 mg), which was comparable to that of the reaction on smaller scale (0.25 mmol, 64%), and the borylation of **16b** on a 4.0 mmol scale formed the functionalized product in 95% yield (1.89 g), which was also comparable to that of the reaction on smaller scale (0.25 mmol, 94%).

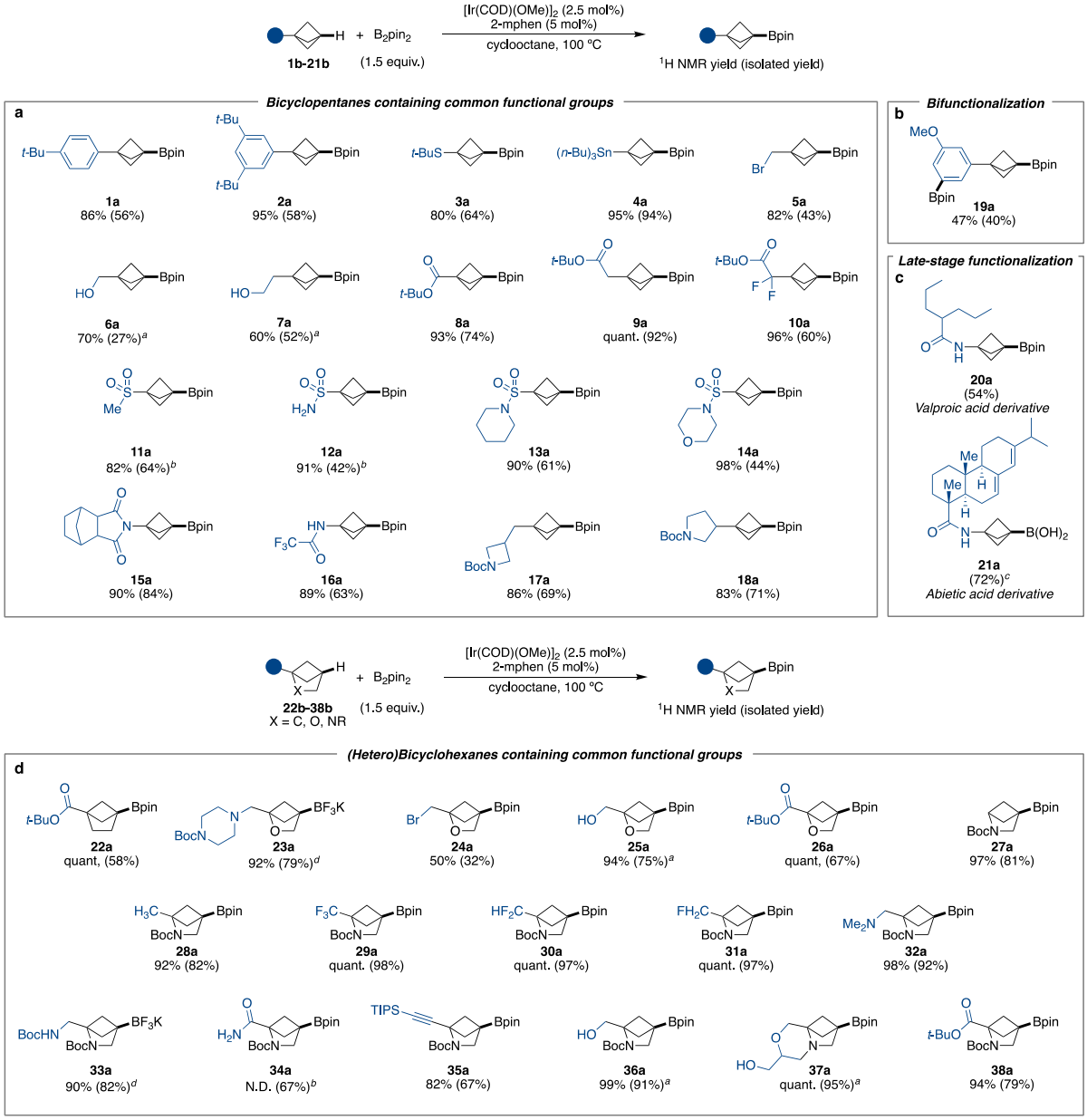

Fig. 2: Examples of bicyclo-[1.1.1]-pentanes and (hetero)bicyclo-[2.1.1]-hexanes that undergo borylation of the bridgehead C–H bond. (a) Examples of bicyclopentanes that undergo borylation of the bridgehead C–H bond. (b) Example of an arylbicyclopentane that undergoes borylation of both the aryl and the bridgehead C–H bonds. (c) Examples of complex molecules that contain the BCP substructure that undergo exclusive borylation of the bridgehead C–H bond. (d) Examples of (hetero)bicyclohexanes that undergo borylation of the bridgehead C–H bond. Reactions were conducted at 0.10-0.25 mmol scale. ^{1}H NMR yields were determined relative to an internal standard of dibromomethane, and the isolated yields are given in parenthesis. Standard conditions: substrate (0.10-0.25 mmol), B_2pin_2 (1.5 equiv), $[Ir(COD)(OMe)]_2$ (2.5 mol%), 2-mphen (5.0 mol%), cyclooctane (100 µL/mmol), 100 ºC. [a] Substrate treated with HBpin (1.3 equiv) prior to the reaction. [b] Conducted with 3 equivalents of B_2pin_2. [c] Spontaneous hydrolysis to the corresponding boronic acid upon purification. [d] Crude reaction mixture treated with 5 equivalents of KHF_2 after completion of the borylation reaction.

This reactivity extended to additional strained bi- or tri-cyclic systems containing activated tertiary C–H bonds. The all-carbon bicyclo-[2.1.1]-hexane **22a**, the oxabicyclo-[2.1.1]-hexanes (**23a**-**26a**), and the azabicyclo-[2.1.1]-hexanes (**27a**-**38a**) all reacted cleanly at the tertiary C–H bonds to afford the corresponding boronic esters. (Fig. 2d) The methylene C–H bonds within the bicyclo-[2.1.1]-hexane cores were unreactive, which we attribute, again, to steric crowding of the methylene hydrogens by the quaternary centers vicinal to this position. Bicyclohexanes possessing esters, alcohols, bromides, and amides underwent borylation at the tertiary C–H bond to afford the corresponding products (**22a-31a**, **33a**, **36a-38a**). The borylations of these bicycles were also compatible with a tertiary amine (**32a**), a primary amide (**34a**), and a TIPS-protected alkyne (**35a**). Reactions conducted with bicyclo-[1.1.0]-butane and cubane structures gave complicated mixtures, while the less strained bicyclo-[2.2.1]-heptane (norbornane) did not react under our conditions. (Fig. S4)

Derivatization and Applications of the Bridgehead Boronic Esters

The bridgehead pinacol boronic ester fragments in the products of these borylation reactions are primed for conversion to a variety of functional groups (Fig. 3). The 3-boryl BCPs were readily converted to trifluoroboronates and boronic acids for use when more reactive boron derivatives were needed. Addition of bifluoride formed the corresponding trifluoroborate salts (**1c**, **11c**, **16c**), and addition of methyl boronic acid formed the corresponding boronic acids[47] (**1d**, **11d**). This set of 3-boryl BCPs underwent reactions at the B–C bond to form new C–C bonds. Cross-coupling with aryl electrophiles occurred under either metallaphotoredox conditions[40] to form the 3-aryl BCP **1f** from the trifluoroborate **1c** or by activation with *t*-BuLi followed by Pd-catalyzed coupling[41] to form the 3-aryl BCP **1g** from boronic ester **1a**. An intermolecular Barluenga−Valdés coupling[48] afforded **1e** from boronic acid **1d**, Zweifel olefination afforded the 3-vinyl BCP **11e** from boronic ester **11a**, heteroarylation afforded the 3-heteroaryl BCP **13c** from boronic ester **13a**, and Matteson homologation formed the homologated boronic ester **1h** from boronic ester **1a**. The 3-boryl BCPs also underwent reactions to form heteroatom-substituted BCPs. For example, oxidation of boronic ester **16a** occurred with urea hydrogen peroxide to afford the 3-hydroxy BCP **16d**, and amination of the trifluoroborate **16c** occurred under Matteson's conditions[49] to afford the benzyl amine **16e**.

The examples in Fig. 3 also showcase the value of our method for medicinal chemistry. For example, **16d** and **16e** are analogs of electron-rich arenes, such as 4-aminophenol or 4-aminoanilines, and **11e** and **13c** represent examples of substitution patterns that would be difficult to access with existing methods.

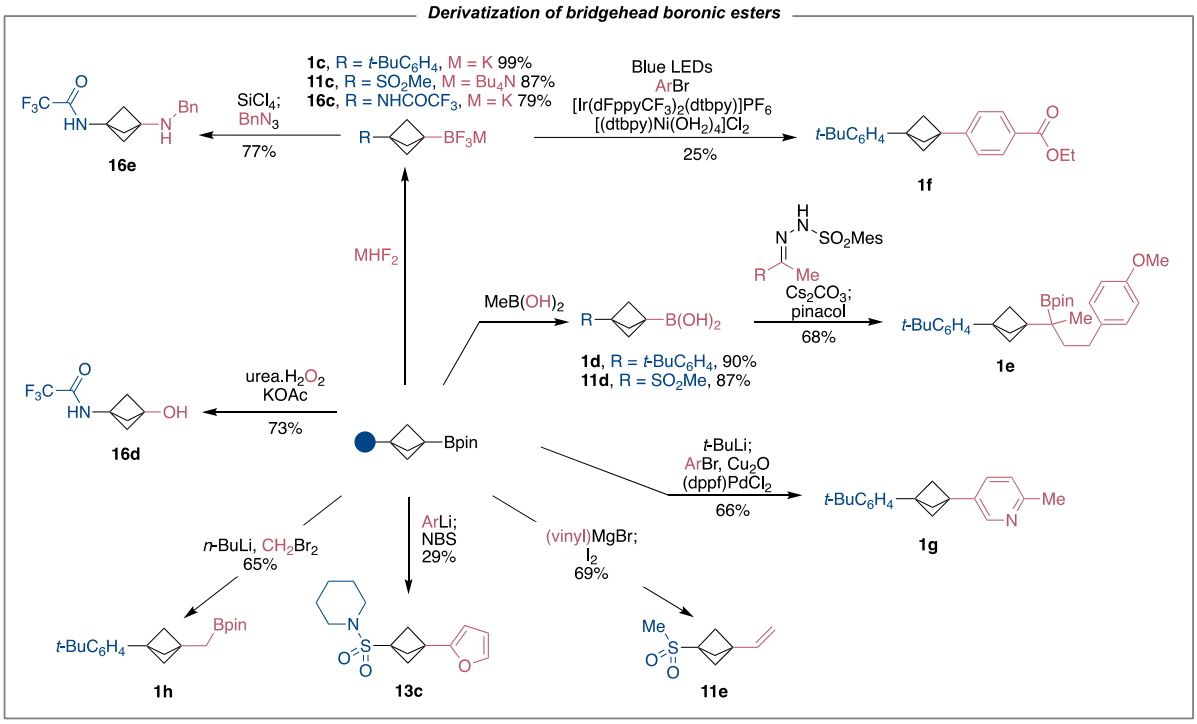

Fig. 3: Conversion of 3-boryl-bicyclo-[1.1.1]-pentanes into various functional groups. See SI for detailed experimental conditions.

Investigation of the Mechanism of the Tertiary C–H Borylation

This new borylation presented an opportunity to compare the mechanism of the borylation at tertiary C–H bonds to those at primary C–H bonds and to assess the magnitude of the effect of strain on the borylation of C–H bonds. To obtain preliminary understanding of the functionalization of the tertiary C–H bond in BCPs under our conditions, we compared the relative rates for the borylation the tertiary C–H bond in 4-*tert*-butylphenylbicyclopentane (**1b**) versus sp^2 and other sp^3 C–H bonds through a series of intermolecular competition studies (Fig. 4a). The borylation of the bridgehead tertiary C–H bonds of BCP **1b** occurred at a much slower rate than that of the aryl C–H bond of 1,3-dichlorobenzene, at roughly the same rate as that of the strained secondary C–H bonds of *tert*-butyl cyclopropanecarboxylate, at a much higher rate than those of the unactivated secondary C–H bonds of tetrahydrofuran and cyclohexane, and at a much higher rate than that of the unactivated primary C–H bonds of *tert*-butyloctyl ether.

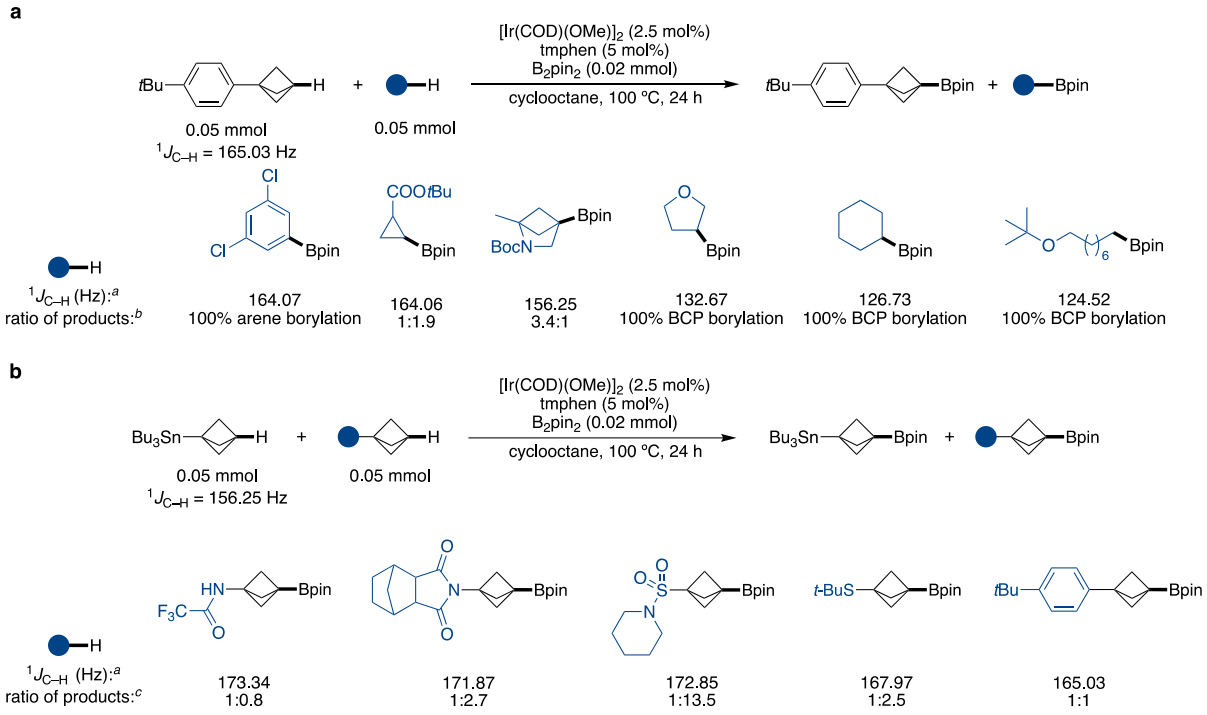

Fig. 4: Competition experiments and measurement of $^1J_{C–H}$ coupling constants. (a) Competition experiments between BCPs and typical substrates for C–H borylation. (b) Competition experiments between BCP substrates. [a] $^1J_{C–H}$ coupling constant of the C–H bond that underwent borylation. [b] Ratio of products determined by GC analysis. [c] Ratio of products determined by NMR analysis.

We reasoned that the high activity of the BCPs towards borylation could be rationalized by the high degree of *s*-character in the C–H bond, which in turn has been shown to correlate with increased acidity.[50] To investigate the origin of the high levels of activity of the BCP substrates observed for the borylation reaction, relative to the low reactivity of typical tertiary C–H bonds, we measured the $^1J_{C–H}$ coupling constants of various BCPs and non-BCP substrates. We also measured the relative rates of reaction for various BCPs containing different substituents in the 1-position. (Fig. 4b) Indeed, the measured $^1J_{C–H}$ coupling constants of BCPs and XBCHs were comparable to those of aryl and cyclopropyl C–H bonds. However, no clear correlation was observed between the relative rates of reaction of individual BCPs versus the variation of the $^1J_{C–H}$ coupling constants within the set of BCPs. Thus, the generally high reactivity of these C–H bonds toward undirected borylation can be explained by *s*-character of the C–H bond, but the more precise reactivity of the individual BCPs required a deeper mechanistic evaluation.

Kinetic isotope effect (KIE) data in previous reports on the borylation of aryl and alkyl C–H bonds suggested that cleavage of the C–H bond is likely irreversible and turnover-limiting.[1,3,51] Yet, other studies have suggested that reductive elimination to form product or isomerization of an intermediate prior to reductive elimination is turnover-limiting.[52-54] Because we observed no clear trend between the relative rates of reaction and the electronic properties of the substituents on the BCPs and because the steric properties of the BCP substrates are similar, oxidative addition is unlikely to be turnover-limiting.

To test further whether oxidative addition of the C–H bond was turnover-limiting, we measured the kinetic isotope effect (KIE) of the bridgehead C–H bond of the BCP on the reaction. While direct measurements of the rates of reactions initiated with 2-mphen were hampered by a significant induction period, we obtained a KIE value from a pair of competition experiments.

In separate flasks, a mixture of 3,5-di(*tert*-butyl)phenylbicyclopentane (**2b**) and either 4-*tert*-butylphenylbicyclopentane (**1b**) or 4-*tert*-butylphenylbicyclopentane-d_1 (**1b-*d*$_1$**) was allowed to react in the presence of B_2pin_2, $[Ir(COD)OMe]_2$, and 2-mphen (Fig. 5a, see the SI for details). These experiments yielded a KIE value of 1.8 ± 0.1, which is more consistent with an equilibrium isotope effect than a primary, kinetic isotope effect.

We conducted analogous rate measurements with tmphen as the ligand. The reaction with this ligand on iridium is slower than that with 2-mphen, but it occurred without a significant induction period, thereby enabling us to obtain clear kinetic data. The KIE value obtained from the initial rates of separate reactions initiated with tmphen as the ancillary ligand and either *tert*-butylphenylbicyclopentane (**1b**) or *tert*-butylphenylbicyclopentane-d_1 (**1b-*d*$_1$**) was, again, 1.8 ± 0.1 (Fig. 5b). The reaction with this catalyst was found to be first order in the BCP, first order in the catalyst, and zero order in the diboron reagent (Fig. 5c). These results imply that the BCP and the iridium catalyst are involved in the turnover-limiting step, but the low KIE value and the lack of correlation between the $^1J_{C–H}$ coupling constants and rate of reaction of the BCPs suggest that oxidative addition is not likely to be turnover-limiting and is likely reversible.

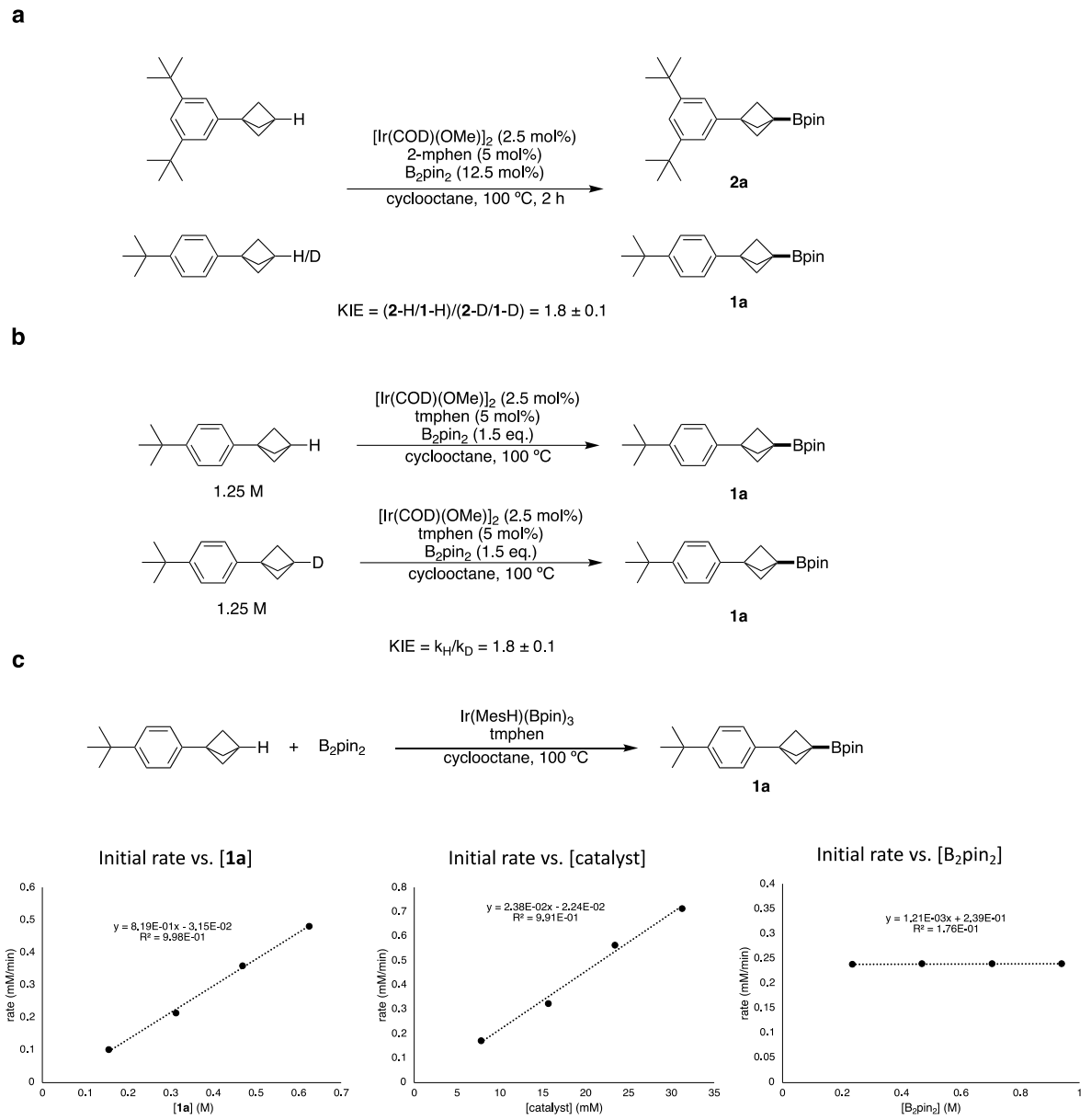

Fig. 5: Mechanistic Experiments. (a) Kinetic isotope effect obtained via competition experiments with 2-mphen as the ligand. (b) Kinetic isotope effect obtained via measurement of rates in separate vessels with tmphen as the ligand. (c) Reaction orders obtained via the method of initial rates.

To understand the low KIE value and to determine the turnover limiting step of the C–H borylation process, we conducted density functional theory (DFT) calculations on the borylation of unsubstituted bicyclopentane as a model substrate with tmphen as the ligand on iridium. The computed energy diagram for the reaction process is shown in Fig. 6. These calculations predict that oxidative addition of bicyclopentane (**R-H**) to the trisboryl species (tmphen)Ir(Bpin)$_3$ (**[Ir](Bpin)$_3$**) will be reversible with a barrier of 23.3 kcal/mol to form intermediate **[Ir](Bpin)$_3$(R)(H)**. This intermediate would then undergo an isomerization with a barrier of 17.9 kcal/mol that lies 30.1 kcal/mol above the starting complex and free substrate to form intermediate ***iso*-[Ir](Bpin)$_3$(R)(H)**. Reductive elimination from ***iso*-[Ir](Bpin)$_3$(R)(H)** occurs with a barrier of just 3.6 kcal/mol to afford the product. Turnover with B_2pin_2 then

regenerates **[Ir](Bpin)$_3$**. The KIE value of the reaction by this path was computed to be 2.03 for bicyclopentane as the substrate, which is in good agreement with the experimental value of 1.8 for 4-*tert*-butylphenylbicyclopentane. A discussion of pathways involving Ir(I) species or alternative isomerization pathways is included in the SI.

Based on our experimental and computational data, we propose that the borylation of BCPs occurs by initial, reversible oxidative addition of the bridgehead C–H bond to **(tmphen)Ir(Bpin)$_3$** to generate the 7-coordinate Ir(V) species **(tmphen)Ir(R)(H)(Bpin)$_3$**. Turnover-limiting isomerization of this intermediate leads to the 7-coordinate intermediate ***iso*-(tmphen)Ir(R)(H)(Bpin)$_3$**, from which facile reductive elimination occurs to afford **(tmphen)Ir(H)(Bpin)$_2$** and the borylated product. The catalyst is then regenerated by reaction between **(tmphen)Ir(H)(Bpin)$_2$** and B_2pin_2 with HBpin as the byproduct.

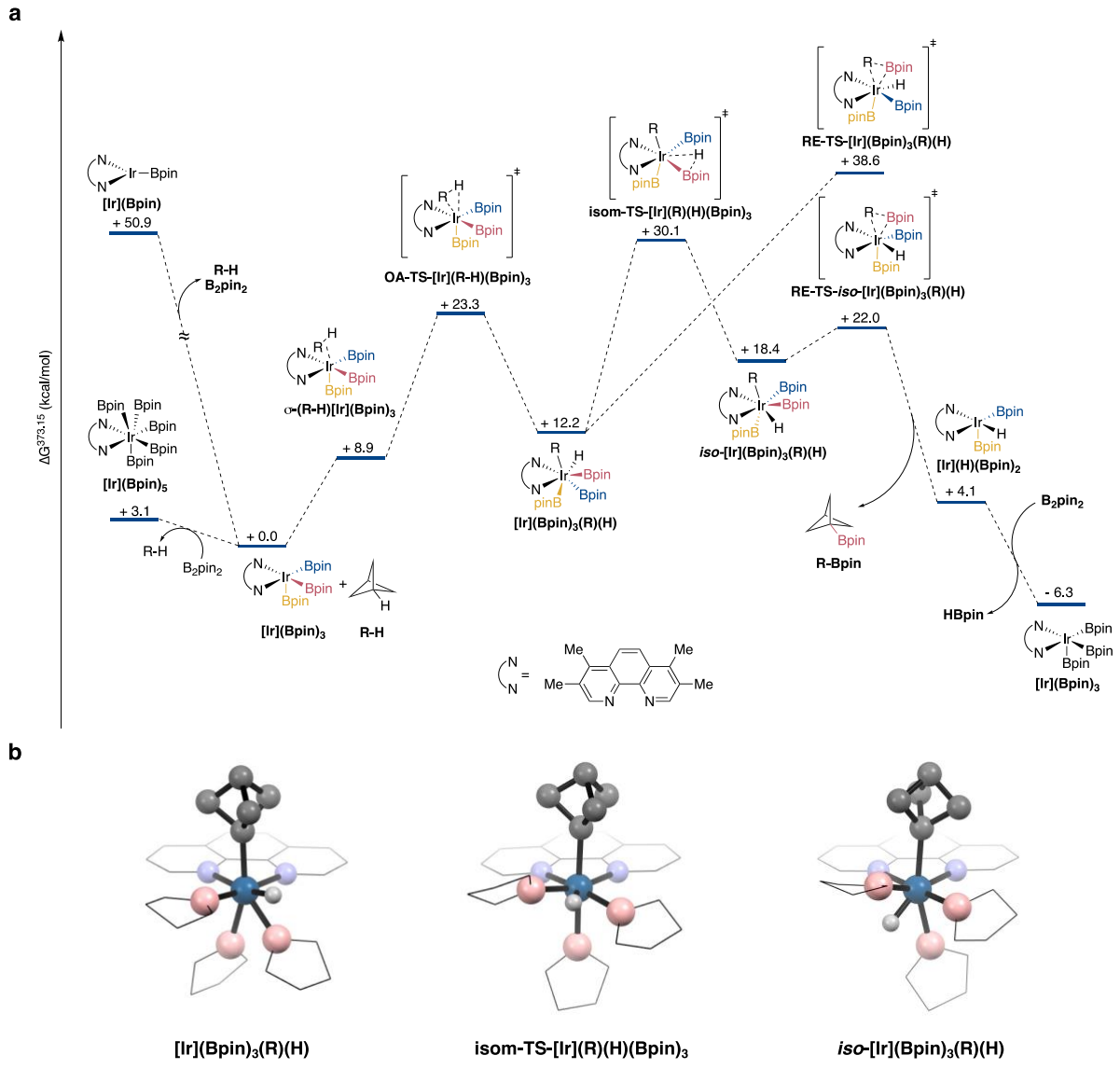

Fig. 6: DFT studies. (a) Energy diagram obtained via density functional theory. Energies are given in kcal/mol at 373.15 K. See SI for computational details and structures. Boryl groups have been color-coded for clarity. (b) Ball-and-stick structures of the key isomerization process. For clarity, peripheral methyl groups and hydrogen atoms have been omitted, and the phenanthroline ligand and boryl groups are represented as wireframes. The geometry of [Ir](Bpin)$_3$(R)(H) is roughly pentagonal bipyramidal in which one nitrogen and the boryl ligand that later undergoes reductive elimination occupying axial positions. The geometry of iso-[Ir](Bpin)$_3$(R)(H) is also roughly pentagonal bipyramidal in which the other nitrogen and boryl ligands now occupy occupy axial positions. The BCP alkyl and boryl ligands that are poised to undergo reductive elimination are in the equatorial plane.

Conclusion

The undirected borylation of C–H bonds, which is known to occur at aryl, primary alkyl, and some secondary alkyl C–H bonds, now has been shown to occur at a tertiary C–H bond. Although tertiary C–H bonds are typically inert under the conditions for the borylation of C–H bonds, the high strain in BCPs, BCHs and XBCHs and the resulting sp^2 character of these C–H bonds lead to mild activation and functionalization, despite the steric hindrance of a tertiary position. This reactivity enables a new synthesis of BCP and BCH and XBCH structures via the undirected borylation of the bridgehead C–H bonds and provides a direct method to these valuable building blocks from commercial or readily accessible reactants. As a result, this method tolerates a wide variety of functional groups of relevance to drug discovery and can be applied to the late-stage elaboration of complex structures containing these strained units. Mechanistic and computational studies show that the rate of reaction is relatively independent of the electronic properties of substituents on the BCP structures because the turnover-limiting step of the reaction is isomerization of the intermediate, 7-coordinate Ir complex, rather than C–H bond cleavage. Mechanistic insights gained in this study and the demonstration that a tertiary C–H bond can undergo undirected C–H bond functionalization by chemistry known to occur without radical intermediates should help guide future studies at hindered and typically unreactive alkyl C–H bonds.

Methods

In a nitrogen glovebox, a 4 mL vial was sequentially charged with 2-mphen (2.43 mg, 12.5 μmol, 5.00 mol%), $[Ir(COD)(OMe)]_2$ (6.25 μmol, 2.50 mol%), substrate (0.250 mmol, 1.00 equiv.), and B_2pin_2 (95.2 mg, 0.375 mmol, 1.50 equiv.) (If the substrate was a liquid, it was added last.). A magnetic stir bar and 0.2 mL of cyclooctane were added to the vial, and the vial was tightly sealed with a Teflon lined cap. The vial was brought out of the glovebox and heated at 100 ºC in a preheated aluminum heating block for the specified time. After cooling to ambient temperature, $CDCl_3$ and CH_2Br_2 (internal standard) were added to the vial, and a sample was taken and analyzed by ^1H NMR spectroscopy to quantify the conversion. The mixture was then co-evaporated with MeOH (5 mL x 3) at 45 ºC (Caution: vigorous gas evolution upon addition of MeOH!). The crude residue was purified by flash column chromatography (silica or C18 reverse phase) to give the borylated product.

Data availability

Complete experimental procedures and compound characterization data are available in the Supplementary Information; any other data is available from the authors on request.

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Contributions

J.F.H, A.M. and D.M.V. conceived and created an initial design of the research. I.F.Y, J.L.M, A.M. and A.D-v. performed the synthetic experiments. I.F.Y. conducted the computational and kinetic studies. J.L.M. conducted the competition studies. I.F.Y, A.M, A.E.P, S.V.R, and D.M.V. selected and prepared the bicyclic reagents used in this study. I.F.Y, J.L.M, A.M, D.M.V, and J.F.H. designed and analyzed the experiments and prepared the initial manuscript. All authors contributed to or approved the final version of the manuscript.

Ethics declarations

Competing interests

A.E.P, S.V.R., and D.M.V. are employees of Enamine, which is a chemical supplier of reagents used in the studies in this manuscript.