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Transfer C-H Borylation of Alkenes under Rh(I)-Catalysis: Insight into the Synthetic Capacity, Mechanism & Selectivity-Control

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SUMMARY

Transfer C–H borylation of alkenes bears the potential to unlock a range of attractive transformations for modular synthesis and late-stage derivatization of complex molecules. However, its scarce precedence and a limited mechanistic understanding hinders the development of practical synthetic protocols. Here we report a Rh(I)-catalyzed transfer C–H borylation that is applicable to various terminal and internal alkenes and compatible with a plethora of functional groups, including often problematic motifs. The successful late-stage borylation of bioactive molecules, including derivatives of macrocyclic Zearalenol and the drug Brompheniramine, underscores its synthetic capacity. A thorough mechanistic investigation involving a series of catalytic and stoichiometric experiments as well as computational studies gave insight into the full catalytic cycle employing a b-boryl elimination, which is unprecedented for Rh-catalysis, and elucidated the features controlling the activity and the selectivity. This work sets the stage for the development of other hydrogen-for-functional group exchange reactions undergoing similar pathways.

Borylation, C-H functionalization, alkene, olefin, transfer catalysis, xantphos-rhodium complex, alkenyl boronate, shuttle catalysis, functional group transfer.

INTRODUCTION

Given the pharmacophoric properties of boronic acid derivatives^{1–3} as well as the multitude of methods to convert a C–B bond into a C–C or C–X bond,^{4–7} the ability to install a boronic ester group by a selective functionalization of one of the C–H bonds in available starting materials is highly appealing for both modular synthesis of functional materials and late-stage functionalization of complex molecules.⁸ While the borylation of aromatic and aliphatic C–H bonds has been extensively studied,^{9–14} the direct borylation of vinylic C–H bonds remains underdeveloped with no general method being available, despite the presence of these motifs in various synthetic and natural compounds (Figure 1a).^{15–17} In that context, alkene cross-metathesis employing a simple vinyl boronate ester as a reagent^{18–22} enables formal C–H bond borylation of terminal alkenes under mild conditions and with high atom-economy (Figure 1b); thereby the strategy has found numerous applications in fine-chemical synthesis.^{23–27} However, when the initial carbon skeleton is to be maintained, the approach is unsuitable for the borylation of substrates bearing internal alkenes, e.g., many (macrocyclic) natural products. In contrast, the boryl-Heck^{28–30} and dehydrogenative^{31–44} protocols were reported to be applicable to the C–H borylation of terminal and internal alkene starting materials. Still, the synthetic utility of these

reactions is often limited. In the case of the boryl-Heck reaction, the use of Cl-Bcat or Br-Bcat as the borylation reagent leads to the inevitable incompatibility with many nucleophilic functional groups, including soft nucleophiles, such as enolizable ketones or esters, in addition to amines or alcohols. Also, the involvement of multiple reagents and a post-synthetic transesterification of unstable Bcat products further diminishes the atom-economy of the protocol. In turn, dehydrogenative borylation methods often suffer from competitive hydrogenation and hydroboration side-reactions. In addition, these processes involve high-valent metal-hydride intermediates, which need to be either quenched by a sacrificial reagent or undergo an extrusion of dihydrogen. Therefore, starting materials bearing functional groups of high reactivity towards such metal-hydrides are inherently incompatible.

Functional group transfer catalysis⁴⁵ that would mediate the exchange of hydrogen for a boryl group between starting materials could enrich the scope of strategies for C–H bond borylation by being applicable to both terminal and internal alkene starting materials, while at the same time employing a benign reagent as a boryl group donor, ensuring a tolerance toward a broad range of functional groups and high atom-economy of the process (Figure 1c).⁴⁶ Although, Marciniak^{47,48} and Wu⁴⁴ reported a boryl group transfer between boryl group donors and alkenes in the presence of $[\text{RuHCl}(\text{CO})(\text{PCy}_3)_2]$ or $[\text{Cp}_2\text{ZrH}_2]$, the reported scopes of these methods remain restricted to simple monosubstituted alkenes, such as styrene and its derivatives bearing a limited range of functional groups (i.e., halogens, alkyl, and alkoxy substituents).^{44,47,49–51} For instance, no examples of starting materials containing an internal double bond or bearing other common functional groups, such as alkynes, aldehydes, ketones, amides, or any heterocycles, were reported to be productive, and thus these methods found no practical applications in fine-chemical synthesis so far. Further, limited mechanistic insight into the boryl group transfer catalysis hinders rational development of these protocols toward synthetic applications.⁵²

We hypothesized that phosphine-Rh(I)-complexes would be the catalysts of choice for a chemoselective boryl group transfer that would occur in a proposed catalytic cycle involving a series of alkene insertion and β -elimination steps, as shown in Figure 1c. Our reasoning was as follows: (i) In stoichiometric experiments, a Rh(I)-boryl complex reacted with styrene to form Rh(I)-hydride and styryl boronate ester,⁵³ indicating the feasibility of two elementary steps of the proposed catalytic cycle (steps 1,2). In turn, (ii) Rh(I)-hydrides are known to react selectively with alkenes to form Rh(I)-alkyl species tolerating a broad range of functional groups (step 3).^{54–57} (iii) Although the final elementary step, the β -boryl elimination, (step 4), is unreported for Rh-complexes, microscopic reversibility for the reverse step, i.e., an alkene insertion into a Rh(I)-B bond,^{53,58} supported its feasibility.^{59–61} (iv) Lastly, the engagement of only low-valent Rh(I)-intermediates obviates otherwise impeding side-reactions based on reductive-elimination reactivity of high-valent complexes, such as competitive hydroboration or hydrogenation. The chemoselectivity of the alkene insertion into a Rh(I)-B bond remained an open question.^{62–67}

Here we report our studies establishing the development, mechanism, and key features of transfer C–H borylation of alkenes under Rh(I)-catalysis. The method proved to be applicable not only to terminal but also to so far challenging internal alkene starting materials and compatible with a broad range of functional groups, including motifs that are typically problematic using established approaches. A series of experimental mechanistic studies, corroborated by DFT calculations, provided insight into the details of the catalytic cycle that introduces the thus far unreported yet relatively fast β -boryl elimination step engaging the Rh(I)-(b-borylalkyl) intermediate. Further, the studies revealed the rate and selectivity determining

aspects of the reaction. The studies set the stage for developing other valuable hydrogen-for-functional group exchange transformations for fine-chemical synthesis.

RESULTS AND DISCUSSION

Catalyst formulation

We commenced our studies by evaluating the feasibility of the devised reactivity in a model reaction of styrene **1a** with vinyl boronate pinacol ester **2** forming product **3a**. To identify a suitable catalyst, we considered precursors that could form the prospective species that operate in the catalytic cycle, i.e., either a Rh(I)-hydride or a Rh(I)-boryl complex (Figure 1c). We selected phosphine-Rh(I)-alkoxide complexes, which were reported to form coordinatively unsaturated Rh(I)-hydride species through migratory insertion of an olefin into the Rh–O bond and subsequent β -hydride elimination.^{68,69}

Upon evaluation of a range of complexes of different phosphine ligands and conditions (Table 1, Tables S1-S5), we found that the model reaction of **1a** with **2** (1.5 equiv) in the presence of [Rh(cod)OMe]₂ and xantphos formed product **3a** in 92% NMR yield (81% yield of isolated material; entry 1), confirming the successful reaction design. Importantly, no other isomers of the product were observed. It should be noted that, because this isodesmic reaction is merely exergonic ($\Delta G^\circ = -0.57$ kcal/mol),⁷⁰ the release of the gaseous ethene by-product is a driving force of the reaction. The formation of ethene was confirmed by in situ NMR spectroscopy (Figure S17).⁷⁰

The phosphine-Rh(I)-alkoxide complex is key to the catalytic activity, as confirmed in a series of control experiments (Table 1). No reaction was observed with [Rh(cod)Cl]₂ in place of [Rh(cod)OMe]₂ (entry 2). However, the catalytic activity was recovered when [Rh(cod)Cl]₂ was used with a variety of alkoxide salts (entries 3-4 and Table S1) that formed the rhodium(I)-alkoxide complexes in situ. No reaction occurred in the absence of the rhodium precursor (entry 5), but low activity of the rhodium(I)-alkoxide precursor was maintained in the absence of any phosphine ligand (18% yield, entry 6).

The formation of a catalytic Rh(I)-hydride species via migratory insertion of an alkene into the Rh(I)-alkoxide bond and β -hydride elimination was confirmed in stoichiometric NMR experiments (Scheme 1a); however, the process is not quantitative. As judged by the characteristic hydride signal at -12.4 ppm in the ¹H NMR spectrum, up to 16% of a Rh-hydride species was formed after 2 h at 22 °C in the stoichiometric reactions of alkene **1a** with xantphos-Rh(I)-alkoxide containing either the MeO or tBuO ligand (see section 3.6 of the SI and Figures S18-S21). No increase of the yield of the Rh-hydride was observed upon further reaction at this or elevated temperatures, but a mixture of other unidentified complexes was formed as judged by ³¹P NMR spectroscopy.⁷⁰

We found that catalytic amounts of B₂pin₂ are beneficial for the rate of the catalytic reaction (Figure S16). Most likely, the addition of B₂pin₂ enables an alternative pathway of the pre-catalyst activation by the facile formation of the other catalytic intermediate of the cycle, i.e. the Rh(I)-Bpin complex, in a sequence of oxidative addition of B₂pin₂ and reductive elimination of MeOBpin (Scheme 1b).⁷¹ Noteworthy, a control catalytic reaction of **1a** with a stoichiometric amount of B₂pin₂ in the absence of vinyl Bpin **2** formed only trace of product **3a**, in line with B₂pin₂ acting as a pre-catalyst activator rather than an alternative stoichiometric boryl group

donor. Most importantly, the use of co-catalytic amounts of B₂pin₂ additive enables to lower the catalyst loading substantially (Table 1, entries 1 and 8-10, and Table S7).

Synthetic Capacity

With the established conditions in hand, we evaluated the reaction with respect to its functional group compatibility, its applicability to sterically and electronically varied olefines, including natural products and bioactive materials, as well as its ability to transfer different boryl groups (Figure 2). We established the following:

- The method is compatible with a broad variety of functional groups (**1b-1q**) and heteroaromatic moieties (**1r-1u**). Particularly noteworthy is the compatibility with aldehydes **1b**, alkynes **1p**, **1q**, amines **1c**, **1d**, and pyridines **1r**, **1s**, which are often problematic in borylation protocols,¹⁵ due to either their ability to inhibit the catalyst or their intrinsic incompatibility with reagents (e.g., HBpin) or catalytic intermediates (e.g., Ru(II)- or Rh(III)-hydrides). We found that although acidic NH, OH, or CH groups are problematic (Figure S44), they can be effectively protected, as observed in experiments with alkenes **1d**, **1k**, **1l**, and **1q**. It is worth noting that in initial reactions of alkynes **1p** or **1q** with donor **2**, a competitive ene-yne coupling was observed,^{72,73} however, the use of vinyl (*E*)-1,2-bisboronate **4** in place of donor **2** prevented these side-reactions. Inter se, alkene **1v** that contains an alkyl-benzyl alkyne moiety reacted to form boryl derivative **3v** bearing a (non-borylated) 1,3-diene motif, revealing the alkyne-isomerization activity⁷⁴ of this Rh-catalyst as well as a high selectivity of the catalyst towards terminal mono alkenes over dienes.
- The method is applicable to a range of olefins bearing electronically (**1w-1aa**) and sterically (e.g., **1ab**) varied double bonds and different substitution patterns, including 1,1- and 1,2-disubstituted alkenes **1ac-1an**. It is noteworthy that the borylation of enamides like **1x-1aa** have been thus far rather underdeveloped, with only a single substrate being borylated in a synthetically useful yield.^{37,38,47,75} In reactions of starting materials **1ab-1an**, the presence of co-catalytic B₂pin₂ was essential for the efficient catalytic activity; presumably alkenes **1ab-1an** are not able to activate the pre-catalyst efficiently due to their hindered insertion into the Rh–O bond. In case of 1,1-disubstituted alkenes, the stereoselectivity of the reaction seems to be controlled by steric effects. Unsymmetric alkenes **1ag-1aj** bearing two aryl rings of similar size, that is, phenyl rings with varied substituents in (remote) para or meta positions, reacted to form close to equimolar mixtures of stereoisomeric products irrespectively of the electronic effects. On the other hand, alkenes **1ac**, **1ae**, and **1ak** bearing one phenyl and one methyl, trifluoromethyl, or 2-thiophene ring furnished one isomer of the product preferentially with a synthetically useful stereoselectivity (77 to 90%). Similarly, 1,2-disubstituted alkenes **1al-1n** reacted with a substantial stereoselectivity (77 to >95%); however, the electronic effect on the selectivity was pronounced. While both (*E*)- and (*Z*)-*b*-methylstyrene **1al** reacted to form the same stereoisomer of **3al** with 83% selectivity (39% yield), (*E*)-methylisoeugenol **1am** furnished **3am** with excellent selectivity (>95%), with only traces of the other isomer. It should be noted that internal aliphatic alkenes, such as cyclooctene, alkenes that tend to isomerize to internal or trisubstituted alkenes, such as 1-octene or *a*-ethylstyrene, or alkenes bearing highly congested double bonds, such as *a*-tert-butylstyrene, failed to form the target products in substantial amounts, establishing the current limitations of the method (for details, see Figure S44).

- The method is applicable to transfer different boronate ester groups, including Bmac (**3ao**), or the chiral α -pinene-based Bpnd group (**3ap**), providing an easy access to boronic acid derivatives of varied reactivity for tailored synthetic applications.^{76–79} It is also worth noting that the method employs only simple readily available reagents and is easily scalable (1.1 g of **3aq** (76% yield) furnished using just 0.24 mol% of [Rh(cod)OMe]₂).
- Typical motifs of drug molecules with multiple strongly coordinating *N*- or *S*-sites that could chelate to the metal center and hence impede the reaction, often represent a significant challenge in transition metal catalysis (Figure 3). Nonetheless, we observed that derivatives of antihistamine Brompheniramine **1ar**, antipsychotic Chlorpromazine **1as**, and agonist of retinoid receptor CD3254 **3au** underwent transfer borylation efficiently, establishing a powerful entry point for the synthesis of large libraries of such bioactive molecules. Additionally, boronic acids are bioisosteres of carboxylic acids that find diverse applications in pharmacology.^{1–3} In this context, the protocol proved effective in the concise synthesis of the boronic acid bioisostere of antiplatelet drug Ozagrel **5** through its Bpin ester **3at**.
- Complex natural products of macrocyclic structure are particularly challenging. Gratifyingly, our protocol furnished boryl derivative **3av** of Zearalenol, a nonsteroidal mycoestrogen found in *Fusarium spp.* Albeit the product was formed in modest yield, this example demonstrates the unique synthetic capacity of the transfer borylation strategy for the late-stage functionalization of complex substrates.

Experimental mechanistic studies

Having established the boryl group transfer between alkenes under phosphine-Rh(I)-alkoxide catalysis and its broad applicability with an excellent functional group tolerance, open questions arose regarding the mechanistic aspects of the reaction that could assist further rational development of the method. In particular, we wondered whether the reaction occurred in the proposed catalytic cycle involving Rh(I)-hydride and Rh(I)-boryl intermediates with the Rh(I)-(b-borylalkyl) intermediates engaging in the so far unreported b-boryl elimination step (see Figure 1c) or whether an alternative mechanism involving a Rh-alkoxide mediated C(sp²)-H bond activation was operating.^{82–84} The origin of the excellent regio- and stereoselectivity remained to be solved as well. To shed light on the above questions, we performed a series of experimental studies, which we further corroborated by DFT calculations.

Probing Alternative Catalytic Cycles. Stereochemical considerations for the formation of the product involving either a sequence of alkene insertion into a Rh-B bond and b-hydride elimination or a direct C-H activation implied different fate of the olefinic hydrogen atoms of alkene **1a** depending on the mechanism of the reaction (paths I-II, Figure 4a). Furthermore, because the earlier mechanism operates through the formation of a Rh-H species, this pathway might also lead to a proton scrambling throughout different positions of the alkene starting materials, depending on selectivity, rates, and reversibility of alkene insertion steps (paths III-IV, Figure 4a). To differentiate between these scenarios, we performed catalytic experiments with deuterium-labeled starting materials (Figure 4b). The reaction of (*E*)-b-deuteriostyrene **1a-b-d** furnished product **3a** that partially retained deuterium labeling, which was scrambled between both vinylic C-H bonds (reaction 1). This outcome of **3a** maintaining some deuterium is inconsistent with the mechanism involving a direct C-H bond activation by the Rh(I)-alkoxide species (path II, Figure 4a), but it is consistent with the mechanism involving an alkene insertion into the Rh(I)-Bpin followed with a b-hydride elimination to form the product and a Rh-hydride

(path I). In this reaction, the deuterium scrambling results most likely from a fast and reversible alkene insertion into the Rh-H bond (paths III-IV). In fact, both (*E*)- or (*Z*)-b-deuteriostyrene **1a-β-d** reacted with **2** forming product **3a** with similar content and relative distribution of deuterium at the a- and b-sites (reactions 1-2). Furthermore, in situ NMR spectroscopy and GC-MS analysis of the reaction of styrene-*d*₈ **1a-d₈** with **2** revealed the extensive hydrogen/deuterium scrambling not only throughout the a- and b-sites of product **3a**, but also between both alkene starting materials **1a-d₈** and **2** occurring already early in the process (reactions 3-4). This result indicates that the reversible insertions into the Rh-H/Rh-D bonds are faster than the actual transfer of the boryl group. We also found that the product re-enters the cycle during the catalytic reaction. Compound **3t**, the analogue of **3a** bearing a different aryl ring, added to the reaction of **1a-d₈** and **2** as a 'spectator' underwent partial deuterium incorporation into its a- and b-positions, implying its reversible insertion into the Rh-H/Rh-D bond occurring also early in the process (3 h; reaction 5). Lastly, utilizing compound **3a** as the boryl group donor instead of vinyl boronate **2** in the reaction of 4-chlorostyrene **1f**, we observed the formation of **3f**, 4-chloro analogue of **3a**, and styrene **1a** (reaction 6), indicating the reversibility of all steps of the catalytic cycle. It should be noted that these experiments confirmed the reversibility of all steps in the catalytic cycle forming **3a**, i.e., (*E*)-product; however, the relative rates between the steps (e.g., alkene insertion into the Rh-B versus b-boryl elimination) as well as the feasibility of the catalytic cycle forming alternative products, i.e., (*Z*)- and a-isomers, had yet to be investigated.

Insight into the Rate Limiting Step. With the observed fast hydrogen/deuterium scrambling (Figure 4b), we considered that both the insertion of alkenes into the Rh(I)-hydride and b-hydride elimination must be fast, and hence the overall rate of the reaction is limited by either the alkene insertion into the Rh(I)-boryl intermediate or the b-boryl elimination step (Figure 1c). To differentiate between these scenarios, we studied the reactivity of the independently prepared Rh(I)-boryl intermediate, **LRhBpin** (Figure 5).^{70,71} First, we found that **LRhBpin** reacted with alkene **1a** to form product **3a** gradually in time, implying a rather slow alkene insertion into the Rh-B bond (Figure 5a). In turn, we observed that **LRhBpin** is catalytically active in the model reaction, with similar rates of the formation of **3a** early in the reaction, i.e., before the first catalytic turnover, and later in the reaction, i.e., after the first catalytic turnover (Figure 5b). Most importantly, the formation of **3a** before the first turnover involves only the insertion of alkene into the Rh-B bond of *starting* **LRhBpin** (and the fast b-hydride elimination), while the formation of **3a** in the later phase of the reaction requires all steps of the cycle, including the b-boryl elimination step. Thus, similar rates in the different phases of the reaction indicate that the alkene insertion into the Rh-B bond is slower than the b-boryl elimination, and hence is most likely the rate-limiting step of the catalytic process.

Probing Stereo- and Regiocontrol of the Reaction. Because product **3a** is more stable than isomers (*Z*)-**3a** and (a)-**3a** (0.0 vs. +4.2 and +5.0 kcal/mol, respectively),⁷⁰ the stereo- and regioselectivity of the reaction might be either under thermodynamic control, that is, when the formation of different isomers of the product is similarly fast, but isomers quickly interconvert to form the product of the lowest energy, or under kinetic control, that is, when the formation of one isomer is much faster than that of the other isomers. To shed light on these scenarios, we studied the reactivity of independently prepared isomers (*Z*)-**3a** and (a)-**3a** under catalytic conditions. We observed that stereoisomer (*Z*)-**3a** underwent fast conversion to (*E*)-isomer **3a**,

when present as a spectator of a catalytic reaction of substrate **1aq** under otherwise standard conditions (Figure 6, reaction 1). This observation indicates that stereoselectivity might be indeed thermodynamically controlled.^{28,35} However, the quick formation of (*Z*)-**3a** along with **3a** would need to be confirmed to exclude the possibility of kinetic control operating, where the reaction forms **3a** much faster than (*Z*)-**3a**. In contrast, in an analogous experiment, the a-regioisomer of **3a**, (a)-**3a** was rather reluctant to the isomerization: only 11% of (a)-**3a** converted to **3a** after 3 h, while at the same time the (b-selective) catalytic reaction was nearly finished (84% yield of **3m**; Figure 6, reaction 2). This experiment clearly showed that the formation of (*E*)-isomer is much faster than the formation of the a-isomer, in line with kinetic control of the regioselectivity. Overall, the conversions of (*Z*)-**3a** and (a)-**3a** to **3a** indicate that both prospective products of the reaction can enter the catalytic cycle, and hence, due to the principle of microscopic reversibility, they could be formed in the reaction as well. However, the slower conversion of the a-isomer to the (*E*)-isomer compared to the rate of the actual catalytic formation of the (*E*)-isomer implies that the regioselectivity of the reaction is kinetically controlled, a rather unusual feature in functional group transfer catalysis.⁸⁵ Most importantly, because the kinetic control depends on the catalyst, the data suggest the feasibility of accessing different isomers using different catalysts.

Computational mechanistic studies

The experimental mechanistic findings were corroborated by DFT calculations performed at the M06-L/def2-TZVP_(SMD,1,4-dioxane)/M06-L/def2-SVP level of theory. The computed free energy surfaces for the formation of **3a**, (*Z*)-**3a** and (a)-**3a** (Figure 7) demonstrated the feasibility of the initially considered catalytic cycle (Figure 1c) and further supported the alkene insertion into the Rh–B bond as the rate-limiting step of the reaction. Importantly, our computations not only support that the regioselectivity is kinetically controlled but also suggested that the stereoselectivity is also under kinetic control. Additionally, we provided a detailed analysis on the unprecedented b-boryl elimination process (section 4.3 of the SI), as well as an insight into the preferential P–P coordination mode of xantphos during the reaction (section 4.2 of the SI). Specifically, the initial xantphos-Rh(I)-hydride complex coordinated by boryl group donor **2**, **LRhH**(h²-**2**) is predicted to readily form the Rh(I)-boryl intermediate, **LRhBpin**(h²-ethene) in an exergonic process (DG_{rel} = -6.0 kcal/mol) through an alkene insertion (via transition state 1, **TS-1**) – b-boryl elimination (**TS-2**) sequence with a low free energy barrier of +5.6 kcal/mol. Noteworthy, the oxygen atom of the xantphos ligand does not interact with the metal center during the process, while such an interaction was found to be important in other Rh-catalyzed reactions.⁶⁷ Parallel calculations indicate that such a pathway would lead to a significantly higher free energy barrier (DG_{rel} = +10.5 kcal/mol vs +5.6 kcal/mol; see section 4.2 of the SI). Therefore, the activity of the **xantphos**-Rh(I) complex originates most likely from the distinct wide bite angle of the ligand rather than the presence of the oxygen atom. In accordance, no activity was observed for the analogous complex bearing flexible **dpephos** (cf. Table 1).

The borylation of **1a** with the thus-formed **LRhBpin**(h²-ethene) intermediate embarks upon a ligand exchange to form **LRhBpin**(h²-**1a**) (along with the extrusion of ethene), which is the lowest energy intermediate of the catalytic cycle (DG_{rel} = -9.0 kcal/mol; see section 4.4 of the SI for full discussion on olefin exchange processes). The subsequent alkene insertion into its Rh(I)–B bond is predicted to be rate-limiting with the free energy barrier of +12.6 kcal/mol (**TS-3**). The following b-hydride elimination to form product **3a** through **TS-4** proceeds with a low

barrier (+4.5 kcal/mol). Product **3a** is released from **LRhH(h²-3a)** upon the ligand exchange with another molecule of **2**, closing the catalytic cycle. Notably, the alternative b-hydride elimination step toward the formation of stereoisomeric product (*Z*)-**3a** involves a significantly higher energy barrier (**TS-4^Z**), even greater than that for the alkene insertion into the Rh-B bond (**TS-3**), accounting for the overall barrier of +20.4 kcal/mol (from **LRhBpin(h²-1a)**; dotted blue line in Figure 7), in line with kinetic control of the stereoselectivity. Further, the reaction pathway toward the formation of regioisomeric product (*a*)-**3a** involves higher energy transition states for both alkene insertion (**TS-3^a**) and b-hydride elimination (**TS-4^a**) with the overall barrier of +21.8 kcal/mol (grey line in Figure 7), in line with kinetic control of the regioselectivity. Noteworthy, computations also predict that both (*Z*)-**3a** and (*a*)-**3a** can enter the catalytic cycle with energy barriers of +6.9 and +9.4 kcal/mol, respectively. These results correlate well with the observed interconversions of (*Z*)-**3a** and (*a*)-**3a** to product **3a**, which were found to be fast and slow in comparison to the rate of the actual catalytic reaction, respectively (cf. Figure 6). Overall, although isomer **3a** is thermodynamically more stable than (*Z*)-**3a** and *a*-**3a**, the calculations suggest that its formation is kinetically controlled.

It is worth mentioning that a stepwise analysis of the b-boryl elimination process revealed that prior to the transition state, there is an intermediate engaging an interaction between boron and Rh atoms, which leads to the C–B bond weakening and its elongation prior to the bond breaking event, and hence facilitating this unprecedented elementary reaction (see section 4.3 of the SI). For full discussions, including all higher-energy pathways, further details, and structures of all transition states and intermediates, see section 4 of the SI.

Summarized Mechanistic Proposal

Based on the collected data we propose that Rh(I)-catalyzed transfer borylation of alkenes occurs as shown in Figure 8. The key mechanistic features are:

1. The Rh(I)-alkoxide pre-catalyst enters the catalytic cycle either through the alkene insertion into the Rh–O bond – b-hydride elimination sequence forming the catalytic Rh-hydride species (path a) or through its reaction with co-catalytic B₂pin₂ additive to form the catalytic Rh(I)-boryl complex along with pinBOMe under B₂pin₂-based activation (path b).
2. In the catalytic cycle, the Rh(I)-hydride intermediate with coordinated Bpin-donor **2**, **LRhH(h²-2)**, reacts readily to form the Rh(I)-boryl species, **LRhBpin(h²-ethene)**, through an alkene insertion into the Rh–H bond – b-boryl elimination sequence (steps I–II).
3. **LRhBpin(h²-1)**, formed upon olefin exchange of ethene for starting material **1**, is the lowest energy intermediate of the catalytic cycle (step III), which is in equilibrium engaging other alkenes in the mixture (step III'). The complex undergoes rate-limiting regioselective alkene insertion (step IV), followed by a fast and stereoselective b-hydride elimination (step V), and the release of product **3** through an olefin exchange, which completes the cycle (step VI).
4. The relatively low free energy barriers for all steps of the catalytic cycle forming the (*E*)-isomer of the product have two main consequences: First, many elementary steps are reversible, which can lead to isomerization and scrambling processes (through steps I' and IV'). Second, the free energy surface for the overall transformation is relatively flat, which is essential for effective catalysis in isodesmic processes with a limited energetic driving force. However, the study shows that a catalyst might impose high energy

barriers (e.g., competitive steps IV' or V') for the formation of different isomers of the products, creating the prospects for the kinetic control of selectivity in functional group transfer catalysis.⁸⁵

CONCLUSIONS

In conclusion, the herein disclosed Rh(I)-catalyzed boryl group transfer reaction proved to be applicable not only to simple alkenes but also to more complex settings of polyfunctionalized molecules with multiple groups that could inhibit the catalyst. Therefore, such reactivity together with an excellent functional group tolerance indicates its possible applicability to late-stage modifications of complex fine chemicals. Further, the mechanistic studies provided insight into the features controlling the selectivity setting the stage for the development of methods to access different regio- and stereoisomers of the products by C–H borylation; a feature that remains elusive with current strategies.

The studies revealed that an uncommon β -boryl elimination step engaged in the reaction is notably easy, especially in contrast to the well-documented reverse step – an alkene insertion into a Rh–B bond. Considering the number of known alkene insertion elementary reactions into different metal-heteroatom bonds, the mechanistic approach carries the potential for the development of other hydrogen-functional group exchange reactions of high value to organic synthesis. The research to uncover the full capacity of the strategy continues in our laboratories.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead author, Paweł Dydio (dydio@unistra.fr).

Materials availability

This study did not generate new material/reagents.

Data and code availability

This study did not generate any datasets

SUPPLEMENTAL INFORMATION

Supplemental information can be found at online at XXXX

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AUTHOR CONTRIBUTIONS

L.V. and P.D. conceived the project. L.V. performed the initial experiments. L.V. and H.A.G. performed the subsequent experiments and the experimental mechanistic studies. S.M. performed the DFT calculations. C.A. assisted with NMR experiments. P.D. supervised the project and wrote the manuscript with the comments from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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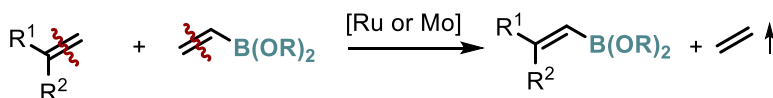
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(a) Desired features for alkene C–H borylation strategies



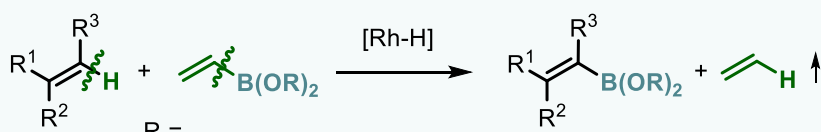
Compatible with common functional groups?
Applicable to terminal & internal (cyclic) alkenes?
Site-, regio-, and stereoselectivity?

(b) Borylation by well-established olefin cross-methathesis

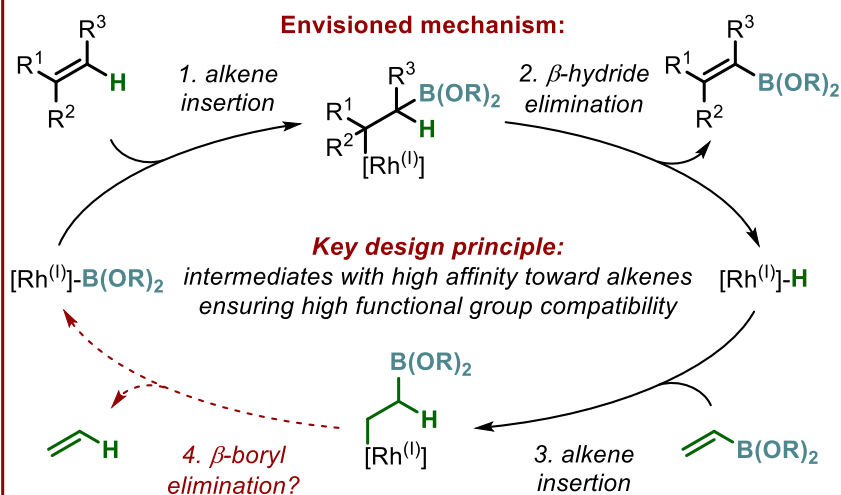


cleavage of carbon-carbon bond precludes borylation of internal (cyclic) alkenes without skeleton modification

(c) This study: boryl group transfer strategy under Rh(I)-catalysis



terminal, 1,1- & 1,2-disubstituted alkenes



Key features of this study:

- ◆ Support for the mechanism with an unprecedented β -boryl elimination
- ◆ Detailed insight into the selectivity-controlling features
- ◆ Compatibility with common functional groups & transfer of different boryl groups (e.g., alkyne, aldehyde, amine, pyridine & Bpin, Bmac, Bpnd)
- ◆ Applicability to a variety of terminal & internal alkenes confirmed

Figure 1. Context of this work. (a) C–H borylation of alkenes with appealing features for fine-chemical synthesis, (b) state of the art – alkene cross-metathesis, (c) transfer borylation reaction under Rh(I)-catalysis – summary of this work. * When thermodynamically favored, the isomerization of the double bond across an alkyl group is detrimental for the reaction.

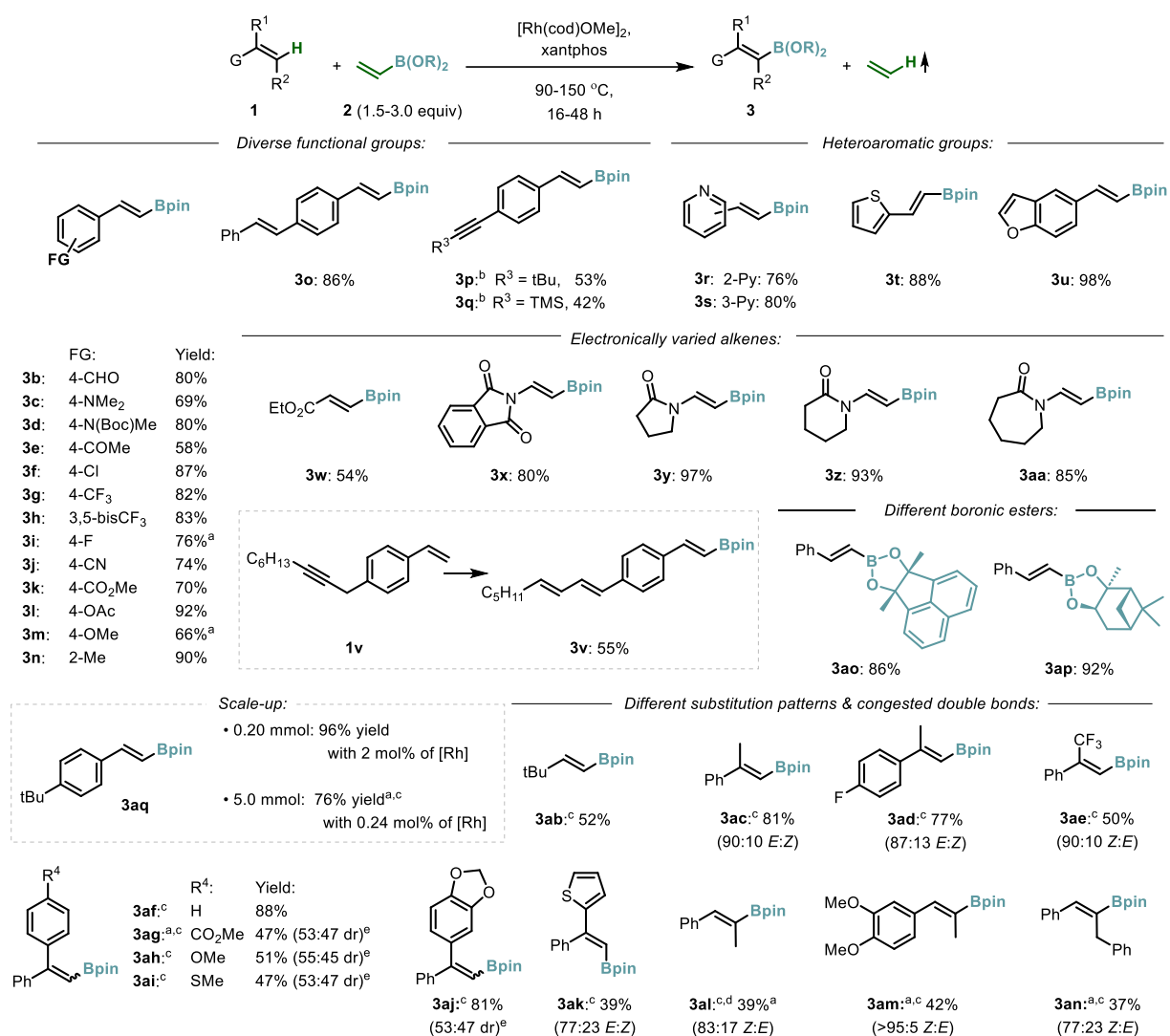


Figure 2. Compatibility of the method with different functional groups, heteroaromatic motifs, electronically and sterically varied terminal and internal alkenes, and different boronic esters. For an overview of the reaction conditions, including the comparison between the analytical yields determined by ¹H NMR analysis of the reaction mixture with an internal standard and the yields of isolated materials, see Table S10 and Figures S43-S44. Because vinylboronic esters tend to partially decompose during chromatography on silica gel,^{28,80,81} the analytical yields are reported here to indicate the actual reaction performance; for all experimental details, and product characterization, sections 6-8 of the SI; ^a isolated yield; ^b **4** (1.0 equiv) instead of **2**; ^c B₂pin₂ as an additive; ^d starting from *cis*-**1al**, starting from *trans*-**1al**: 38% isolated yield (83:17 *Z:E*); ^e dr, diastereomeric ratio between (*E*)- and (*Z*)-products; major stereoisomer was not assigned.

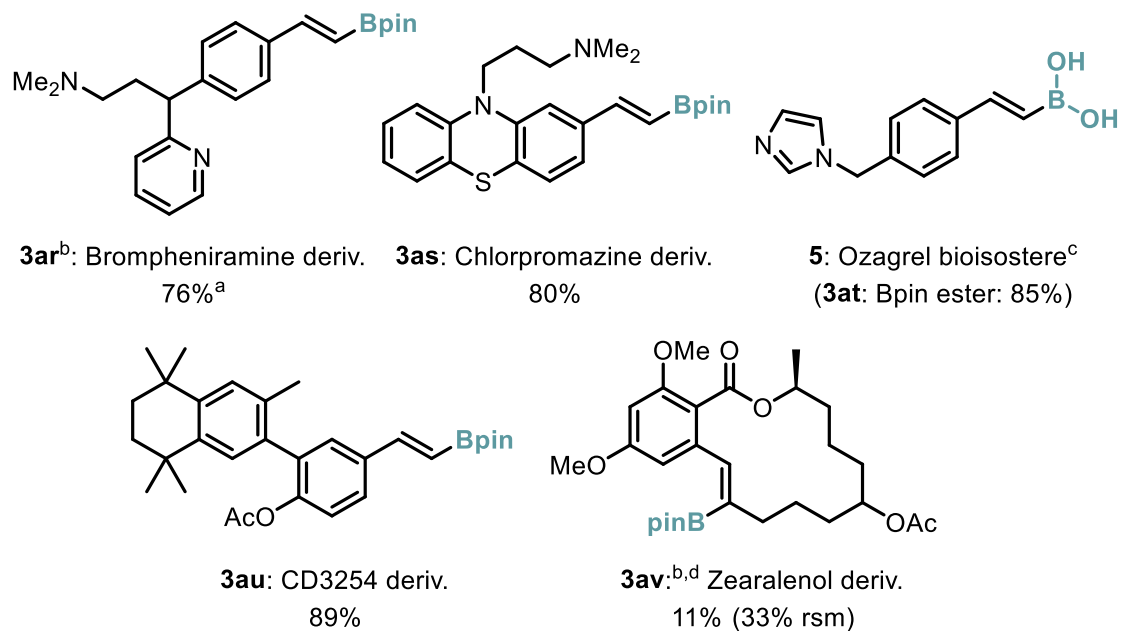
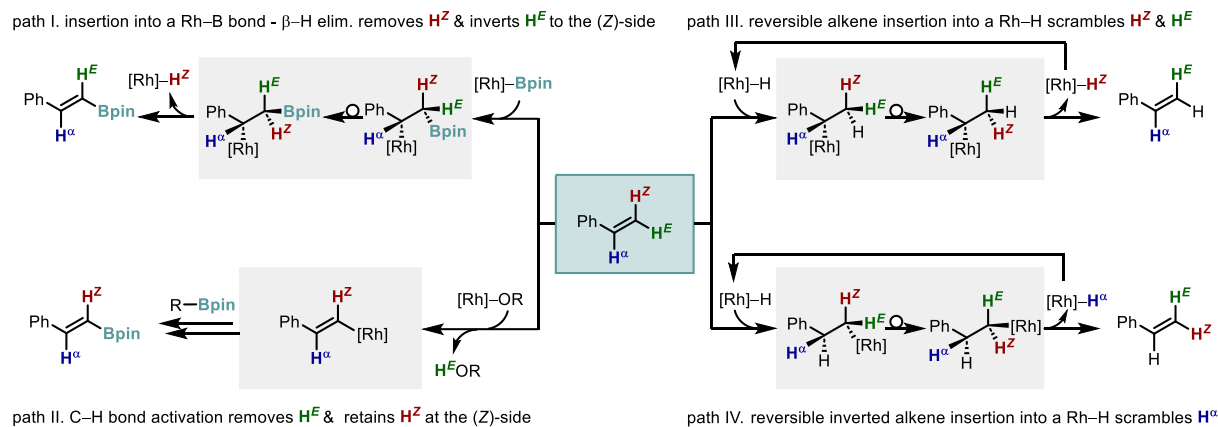


Figure 3. Compatibility of the method with polyfunctionalized bioactive compounds. ^a isolated yield; ^b B₂pin₂ as an additive; ^c The ester **3at** was readily hydrolyzed to the boronic acid **5** (68% yield);⁷⁰ ^d the catalyst solution was added portion-wise (in total 8.75 mol% of Rh-precursor);⁷⁰ deriv, derivative, rsm, recovered starting material.

(a) Implications of alkene insertion & β -elimination sequence or alternative C–H bond activation mechanism



(b) Experiments with isotope-labeled starting materials probing the mechanism of the reaction

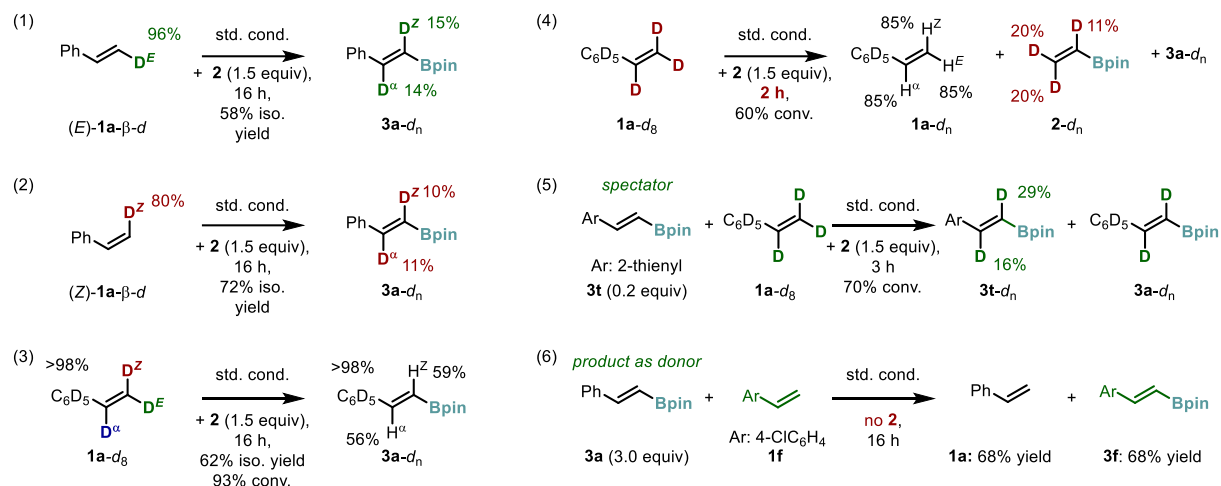
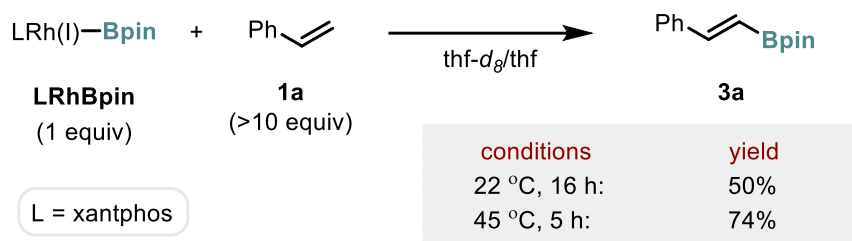


Figure 4 Mechanistic experiments probing the prospective catalytic cycle for the boryl group transfer. (1-2): Partial deuterium retaining in **3a** in the reaction of (E) -1a-b-d is consistent with the mechanism involving alkene insertion into a Rh–B bond & b-hydride elimination sequence; (1-4): H/D scrambling between starting materials indicates fast & reversible alkene insertion into the Rh–H intermediate; (5): Deuterium incorporation into **3t** indicates that the product re-enters the cycle; (6): Boryl group transfer between **3a** and **1f** indicates that the reaction is reversible. For standard conditions, see Table 1; for further details, see the SI and Figures S1-S13.

(a) Reactivity of Rh(I)-Bpin intermediate with an alkene



(b) Catalytic activity of Rh(I)-Bpin intermediate

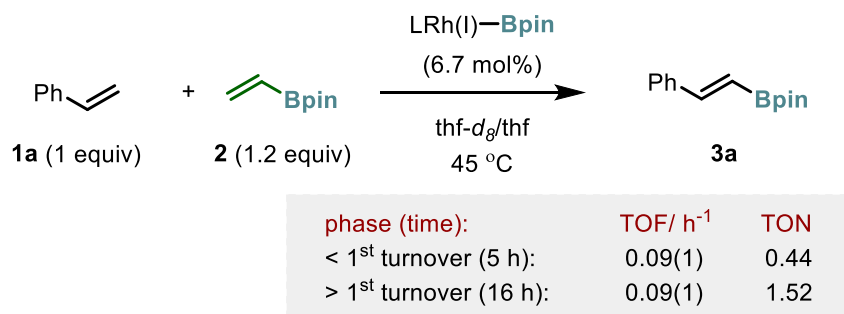
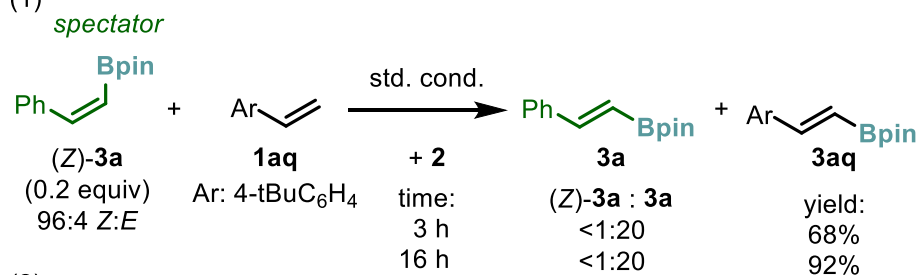


Figure 5. Reactivity of independently prepared xantphos-Rh(I)-Bpin intermediate. LRhBpin reacts with 1a rather slowly and is catalytically active under similar conditions; the formation of 3a with similar rates in the different phases of the catalytic reaction suggests that the alkene insertion is rate-limiting. TOF, turnover frequency; TON, turnover number; for full experimental details, see section 3.8 of the SI and Figures S22-S37.

(1)



(2)

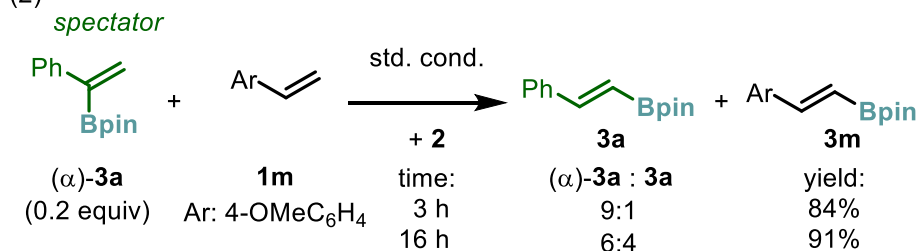


Figure 6. Mechanistic experiments probing the pathways toward formation of stereo- and regioisomeric products. (1): Fast isomerization of (Z)-3a to 3a indicates that the stereoselectivity of the reaction might be thermodynamically controlled or kinetically controlled at the b-hydride elimination step. (2): As the isomerization of (α)-3a to 3a is slower than the catalytic reaction, the regioselectivity is controlled kinetically. For standard conditions, see Table 1; for details, see section 3.2 of the SI and Figures S14-S15.

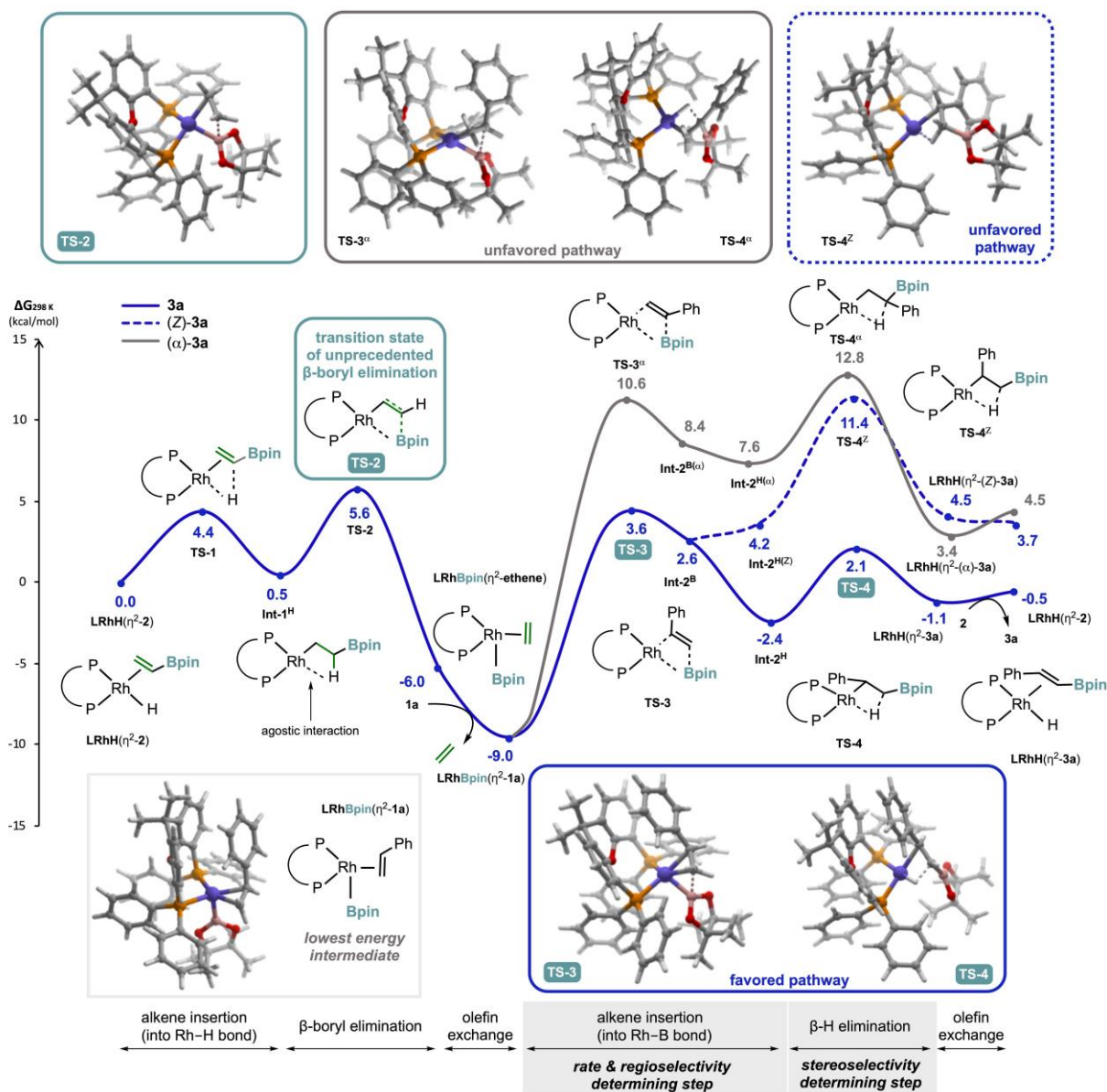


Figure 7. DFT investigation of the free energy surfaces for the reaction pathways leading to products **3a**, **(Z)-3a**, or **(α)-3a**. Calculations have been performed at the M06-L/def2-TZVP(SMD)//M06-L/def2-SVP level of theory in 1,4-dioxane as solvent (SMD solvation model); SMD, solvation model based on density; Int, intermediate, TS, transition state. For full discussions, structures of all transition states and intermediates, and further details, see the SI and Figures S38-S42.

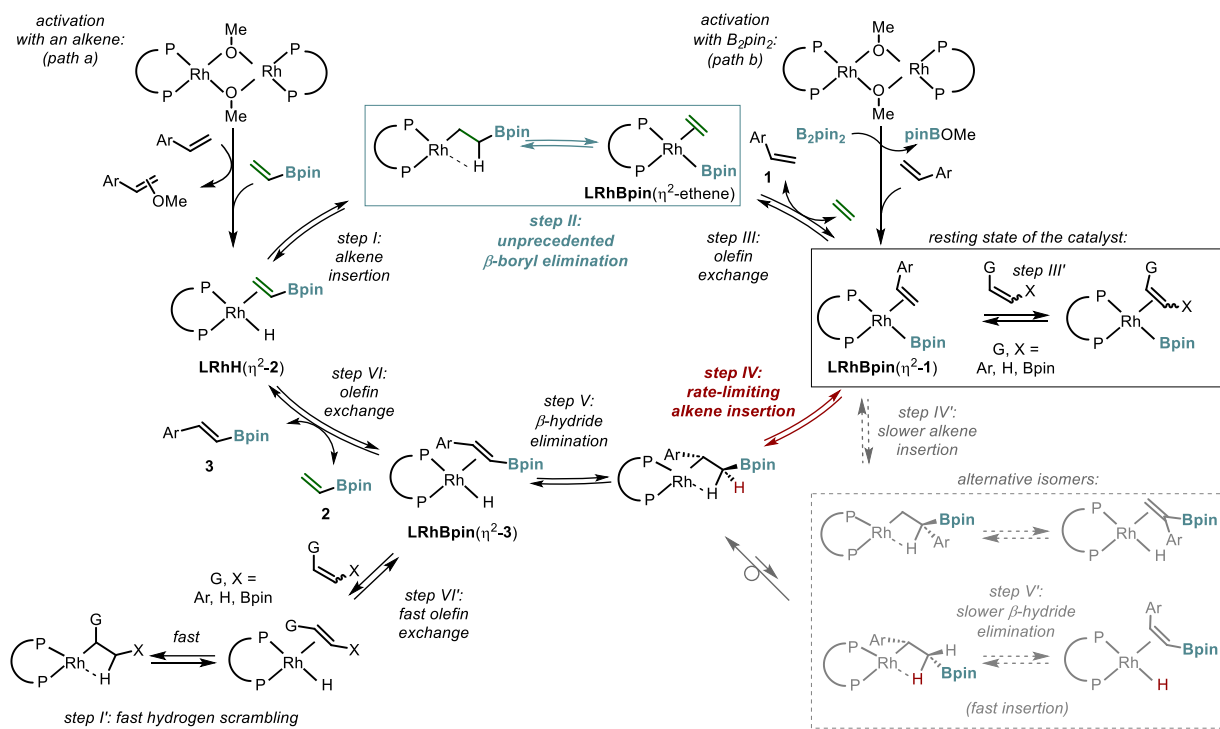
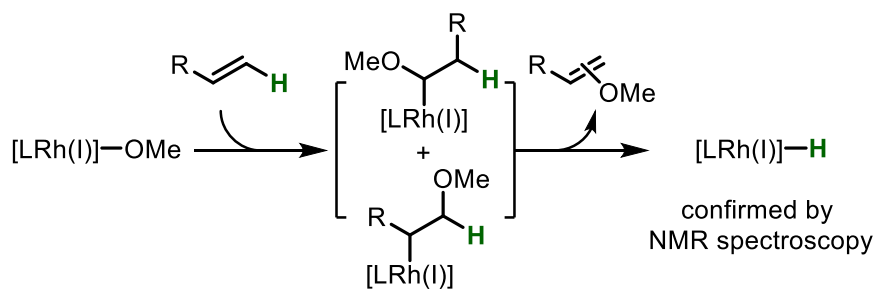
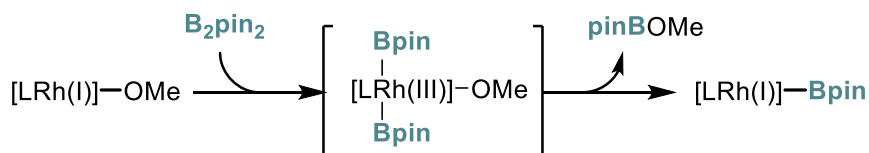


Figure 8. Full proposal of the mechanism of Rh(I)-catalyzed transfer borylation of alkenes.

(a) Pre-catalyst activation with alkene:

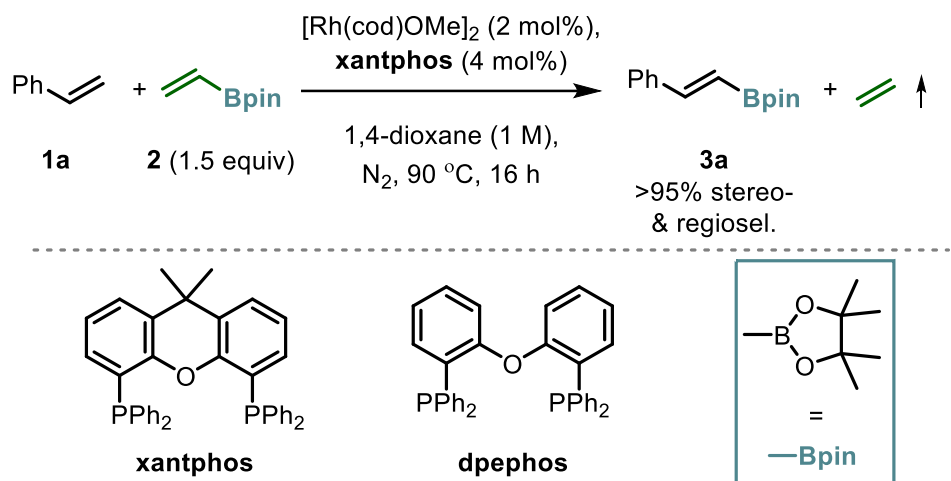


(b) Pre-catalyst activation with B_2pin_2 :



Scheme 1. Different modes of pre-catalyst activation

Table 1. Evaluation of reaction conditions



entry	variations from standard conditions	yield (%) ^a
1	none	92 (81) ^b
2	[Rh(cod)Cl] ₂ as precursor ^c	<2
3	[Rh(cod)Cl] ₂ + NaOMe as precursor ^c	92
4	[Rh(cod)Cl] ₂ + NaOtBu as precursor ^c	92
5	no [Rh(cod)OMe] ₂	<2
6	no xantphos	18
7	dpephos instead of xantphos	<2
8	1/2 cat. loading	<2
9	1/2 cat. loading + 5 mol% B ₂ pin ₂	92
10	1/8 cat. loading + 1.2 mol% B ₂ pin ₂	81

^a Yield determined by ¹H NMR analysis of the reaction mixture with an internal standard;

^b yield of isolated material by a column chromatography purification; ^c instead of [Rh(cod)OMe]₂; 1 : 1 ratio of Rh to sodium alkoxide. For reactions with other phosphine ligands and reaction conditions, see also Table S1-S9 and Figure S16.