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Research Article

Rhodium-Catalyzed Regiodivergent Synthesis of Alkylboronates via Deoxygenative Hydroboration of Aryl Ketones: Mechanism and Origin of Selectivities

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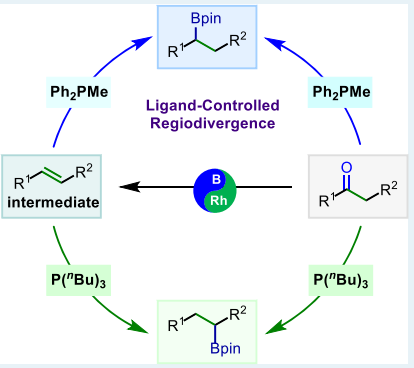
ABSTRACT: Here, we report an efficient rhodium-catalyzed deoxygenative borylation of ketones to synthesize alkylboronates, in which the regioselectivity can be switched by the choice of the ligand. The linear alkylboronates were obtained exclusively in the presence of $P(^nBu)_3$, and PPh_2Me favored the formation of branched alkylboronates. The protocol also allows access to 1,1,2-triboronates from the readily available ketones. Mechanistic studies suggest that this Rh-catalyzed deoxygenative borylation of ketones goes through an alkene intermediate, which undergoes regiodivergent hydroboration to afford linear and branched alkylboronates. The different steric effects of PPh_2Me and $P(^nBu)_3$ were found to be responsible for product selectivity by density functional theory calculations. The alkene intermediate can alternatively undergo sequential dehydrogenative borylation and hydroboration to deliver the triboronates.



KEYWORDS: *boron, ketones, rhodium, regiodivergence, deoxygenative borylation*

INTRODUCTION

Alkylboron compounds are among the most versatile in organic synthesis and are extensively applied in pharmaceutical, material sciences, and agrochemical via diverse carbon−boron bond transformations.[1−6] The hydroboration of alkenes is among the most straightforward strategies to access alkylboronates[7−11] and has been well-established since the pioneering work of Brown and Rao.[12] The control of the regioselectivity has been the core issue in this reaction. Generally, the catalyzed and uncatalyzed hydroboration of alkenes gives anti-Markovnikov products,[7−11,13−17] although the metal-catalyzed hydroboration of vinylarenes usually leads to Markovnikov regioselecitivity.[18−22] However, ligand-, borane-, and/or catalyst-controlled regiodivergent hydroboration of alkenes is rare (only six examples, Figure 1A).[23−28] These existing protocols for divergently controlling regioselectivity in hydroboration were realized by varying the catalyst, borane, and/or the ligand, and provide access to divergent anti-Markovnikov and Markovnikov products. Of particular note is that the regiodivergent synthesis of linear and branched alkylboronates from readily available starting materials except alkenes is yet to be reported to the best of our knowledge. To this end, the development of catalytic protocols to regiodivergently synthesize alkylboronates from abundant chemical feedstock other than alkenes is highly desirable.

Recently, we have demonstrated a rhodium-catalyzed deoxygenation and borylation of ketones for the selective synthesis of alkenes, vinylboronates, and vinyldiboronates (Figure 1B).[29] Mechanistically, the ketones undergo a Rh-catalyzed deoxygenation using B_2pin_2 as a deoxygenative reagent[30−34] to deliver the alkenes, followed by a Rh-catalyzed dehydrogenative borylation to give vinylboronate products.[35−40] We surmise that if the intermediate **A** in deoxygenative borylation of ketones[41−47] underwent protodemetalation[48] (Figure 1B) instead of β-hydride elimination, the hydroboration product would be obtained, leading to a practical approach for the preparation of alkylboronates from ketones. Moreover, it would be an important complement and extension to the existing protocols for the synthesis of linear or branched alkylboronates if the regioselectivity of hydroboration could be controlled by ligands. The key to achieving this assumption is to identify an appropriate catalyst system that can not only catalyze the deoxygenation of ketones to produce olefins but also enable regiodivergent hydroboration of alkenes. In view of our previous success in Rh-catalyzed deoxygenation of ketones to form alkenes,[29] we decided to explore whether rhodium catalyst would allow for regiodivergent deoxygenative borylation of ketones. However, the Rh-catalyzed hydroboration of alkenes generates Markovnikov

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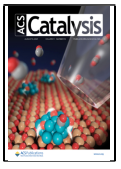

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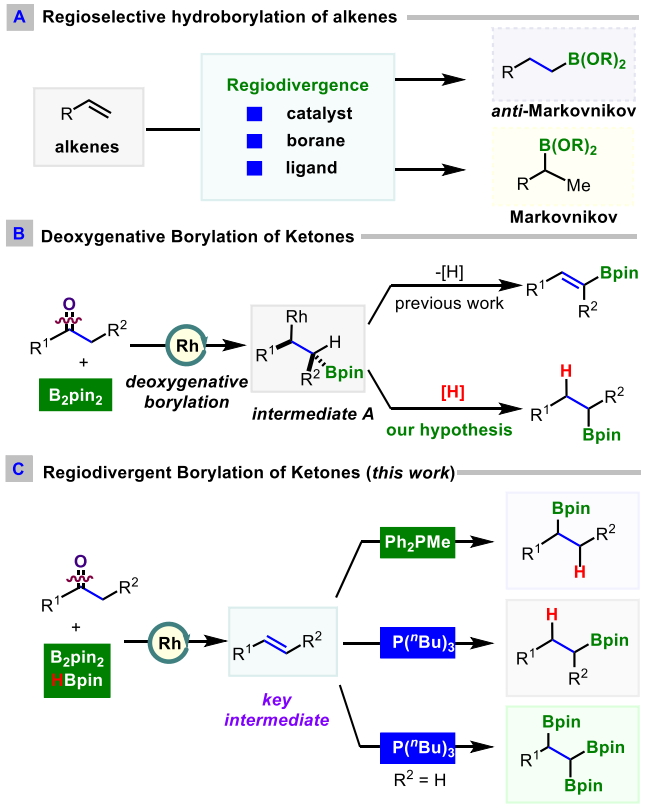


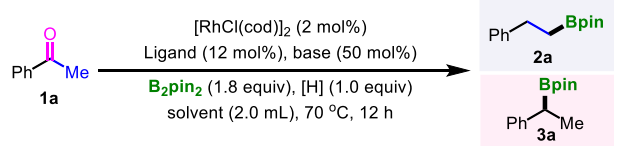
Figure 1. (a) Regioselective hydroborylation of alkenes, (b) deoxygenative borylation of ketones, and (c) regiodivergent borylation of ketones.

products or mixtures in most cases,[9,13,18,48−51] making our hypothesis more challenging. Herein, we disclose a ligand-controlled, regiodivergent synthesis of alkylboronates via Rh-catalyzed deoxygenative borylation of ketones (Figure 1C), allowing access to linear and branched alkylboronates as well as 1,1,2-triboration products in high regioselectivity.

RESULTS AND DISCUSSION

Optimization of Reaction Parameters. To test our hypothesis, we began our investigation with acetophenone **1a** as the model substrate. In light of our previous success in Rh-catalyzed deoxygenative borylation of ketones, we initially treated **1a** with $[RhCl(cod)]_2/P(^nBu)_3$ and B_2pin_2 in tetrahydrofuran (THF) and used MeOH as the proton source to protonate the intermediate **A**. Expectedly, the desired alkylboronate **2a** was obtained, albeit with low yield (36%, Table 1, entry 1), and no branched alkylboronate **3a** was observed. Other solvents such as hexane, 1,2-dimethoxyethane (DME), and IPE were also examined, and IPE gave the best result to provide the product **2a** in 63% (entries 2−4). Next, various bases were evaluated (see more details in Supporting Information). To our delight, the desired product **2a** was obtained in 82% yield in the presence of HCO_2K (entries 5−7). We then turned our attention to the proton source. As shown, ^{i}PrOH was chosen as the proton source for further studies as it proved superior in comparison with MeOH and ^{t}BuOH (entries 7−9). In addition, much lower yields were observed when PEt_3 and PCy_3 were employed, indicating that this reaction is highly sensitive to the bulkiness of the ligands (entries 9−11). Surprisingly, the regioselectivity of the deoxygenative hydroboration product was reversed to afford

Table 1. Optimization of Reaction Conditions



Entry	Ligand	Base	Solvent	H sourse	Yield (%)[a] 2a	3a
1	$P(^nBu)_3$	LiOAc	THF	MeOH	36	0
2	$P(^nBu)_3$	LiOAc	hexane	MeOH	60	0
3	$P(^nBu)_3$	LiOAc	DME	MeOH	20	0
4	$P(^nBu)_3$	LiOAc	IPE	MeOH	63	0
5	$P(^nBu)_3$	KOAc	IPE	MeOH	65	0
6	$P(^nBu)_3$	HCO_2Li	IPE	MeOH	44	0
7	$P(^nBu)_3$	HCO_2K	IPE	MeOH	82	0
8	$P(^nBu)_3$	HCO_2K	IPE	^{i}PrOH	85(73)	0
9	$P(^nBu)_3$	HCO_2K	IPE	^{t}BuOH	80	0
10	PEt_3	HCO_2K	IPE	^{i}PrOH	45	0
11	PCy_3	HCO_2K	IPE	^{i}PrOH	trace	0
12	PPh_2Me	HCO_2K	IPE	^{i}PrOH	5	30
13[b]	PPh_2Me	KOAc	IPE	^{i}PrOH	0	10
14[b]	PPh_2Me	CF_3CO_2K	IPE	^{i}PrOH	0	32
15[b]	PPh_2Me	CF_3CO_2K	THF	^{i}PrOH	0	33
16[b]	PPh_2Me	CF_3CO_2K	CyH	^{i}PrOH	0	31
17[b]	PPh_2Me	CF_3CO_2K	THF:CyH=1:4	^{i}PrOH	0	65
18[b, c]	PPh_2Me	CF_3CO_2K	THF:CyH=1:4	HBpin	0	87(78)

[a]Yields determined by ^{1}H NMR analysis using CH_2Br_2 as an internal standard. Isolated yield in parentheses. [b]Room temperature and 24 h. [c]B_2pin_2 (1.2 equiv). cod = 1,5-cyclooctadiene, pin = pinacol, IPE = 2-isopropoxypropane, DME = 1,2-dimethoxyethane, CyH = cyclohexane.

the product **3a**, albeit in 30% yield when PPh_2Me was used. Encouraged by this exciting result, we then devoted to the development of regiodivergent deoxygenative hydroboration of ketones to give linear and branched alkylboronates. To this end, the base and solvent were optimized using PPh_2Me as the ligand. However, no better results were obtained when KOAc and CF_3CO_2K were applied as the bases or THF and CyH were used as the solvents (entries 13−16). Pleasingly, the yield could be improved to 65% when a mixed solvent of THF and CyH (1:4) was used (entry 17). Furthermore, the use of HBpin instead of ^{i}PrOH provided the desired product **3a** in 87% yield (entry 18),[52,53] which was identified as the optimal conditions for the formation of branched alkylboronates.

With the optimized reaction conditions in hand, we next investigated the scope of ketone for the synthesis of linear alkylboronates. As shown in Table 2, a variety of ketones with different substituents at different positions all successfully participated in this deoxygenative hydroboration to afford the corresponding products in good yields and excellent regioselectivities (l/b > 20/1). The reaction tolerated a wide range of functional groups including electron-donating groups and electron-withdrawing groups, such as SMe (**2d**), OTBS (**2f**), NMe_2 (**2g**), Bpin (**2h**), F (**2j**), OBn (**2e**), and OTs (**2k**), allowing access to the alkylboronates in good yields. The substituents at ortho- and meta-positions such as OMe (**2l**, **2o**) and CF_3 (**2n**) were also compatible. Remarkably, the

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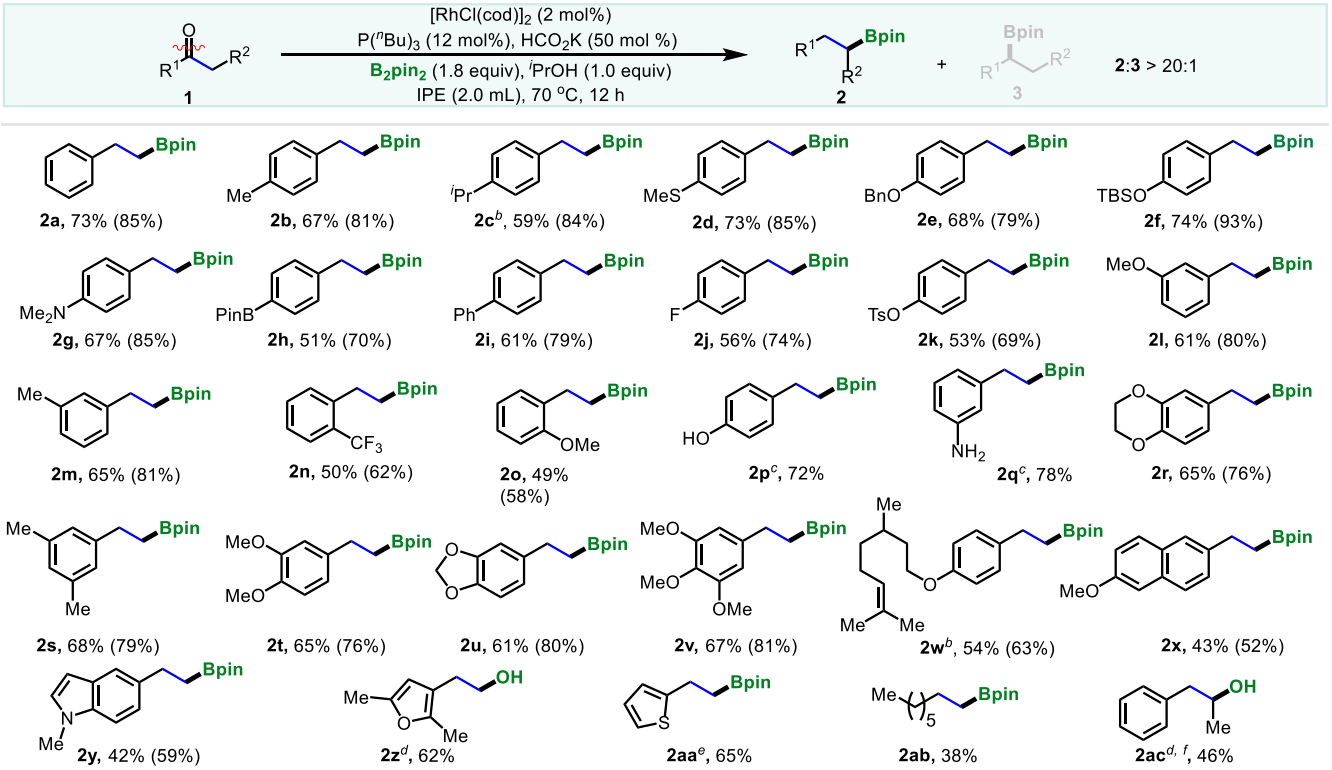
Table 2. Synthesis of Linear Alkylboronates[a]



[a]Standard conditions A: **1** (0.5 mmol), $[Rh(cod)Cl]_2$ (2 mol %), $P(^nBu)_3$ (12 mol %), HCO_2K (50 mol %), B_2pin_2 (1.8 equiv), ^{i}PrOH (1.0 equiv), IPE (2.0 mL), 70 °C, 12 h. Isolated yields. ^{1}H NMR yields are shown in the parentheses using CH_2Br_2 as the internal standard. [b]24 h. [c]No ^{i}PrOH. [d]Overall isolated yield after oxidation. [e]$P(Oct)_3$ as the ligand. [f]$P(^tBu)_3{\cdot}HBF_4$ (12 mol %), HCO_2Li (50 mol %).

substrates with free OH and NH_2 were competent to afford the products **2p** and **2q** in 72 and 78% yields, respectively. Additionally, the ketones with a multisubstituted phenyl group were applicable to deliver the desired products (**2r**−**2v**). The substrates derived from citronellol proceeded smoothly to afford **2w** in 54% yield. Other arenes including naphthalene (**2x**), indole (**2y**), furan (**2z**), and thiophene (**2aa**) were all successfully incorporated into the products in high efficiency. Noticeably, a methyl alkyl ketone such as 2-octanone also worked well under the standard reaction conditions to yield the desired product **2ab**. Moreover, the ketone other than methyl aryl ketones such as propiophenone is also a suitable substrate to provide the product **2ac** in reasonable yield when $P(^tBu)_3$ was used as the ligand.

The generality of ketones was then examined. As shown in Table 3, a diverse set of ketones reacted smoothly to afford the branched alkylboronate **3′** in moderate to good yields and good to excellent regioselectivities (the rations of *l*/*b* are shown in the parentheses, and these regioisomers are inseparable by column chromatography). It is worth noting that the mild reaction conditions were compatible with a series of functional groups, including OMe, SMe, OTBS, NMe_2, Bpin, F, Cl, morpholine, SO_2Me, CF_3, and CO_2Me (**3c′**−**3o′**). Remarkably, the substrates with free OH and NH_2 were competent to afford the products **3p′** and **3q′** in 67 and 81% yields, respectively. The aryl methyl ketones with the functional group at ortho- and meta-positions could also be smoothly transformed to the corresponding products in good yields (**3r′**−**3t′**). Additionally, the multisubstituted phenyl groups were suitable in this reaction (**3u′**−**3w′**). Other aromatic rings including naphthalene, indole, carbazole, furan, and thiophene all proceeded smoothly to furnish the alkylboronate products in moderate to good yields (**3w′**−**3aa′**). We were especially intrigued to find that the ketones derived from citronellol, menthol, and estradiol were all competent substrates to produce **3ab′**−**ad′** in high efficiency. Particularly noteworthy, in addition to methyl aryl ketones, the substrates with longer alkyl chain lengths are viable reaction partners (**3ae′**−**3ag′**), and the functional group OTBS on the alkyl chain was also compatible (**3ah′**). However, dialkyl ketones are inapplicable to the standard reaction conditions. For instance, the anti-Markovnikov product instead of the Markovnikov product was obtained in 36% yield when 2-octanone was treated with $[RhCl(cod)]_2/PPh_2Me$.

Triboronates are attractive building blocks for organic synthesis as three C−B bonds are provided for the construction of multiple new C−C or carbon−heteroatom bonds. However, their applications are much less explored probably due to the paucity of general and practical methods for their preparation.[47,54−56] As a result, it is highly desirable to develop efficient approaches for their preparation from readily available starting materials. 1,1,2-Triboronate was detected in some cases by gas chromatography (GC)−mass spectrometry when we optimized the reaction conditions for the synthesis of linear alkylboronate **2**. Further optimization revealed that the 1,1,2-triboration product could be obtained in 72% yield when the amount of B_2pin_2 was increased with fine-tuning of other reaction parameters. We next explored the substrate scope of this protocol. As depicted in Table 4, a range of aryl methyl ketones participated in this triboration reaction to give the corresponding products in moderate to good yields. Commonly used functional groups, such as OMe, F, CF_3,

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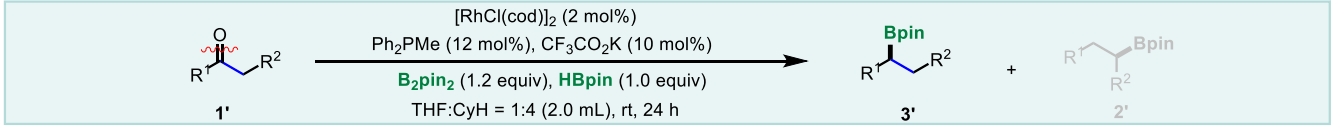
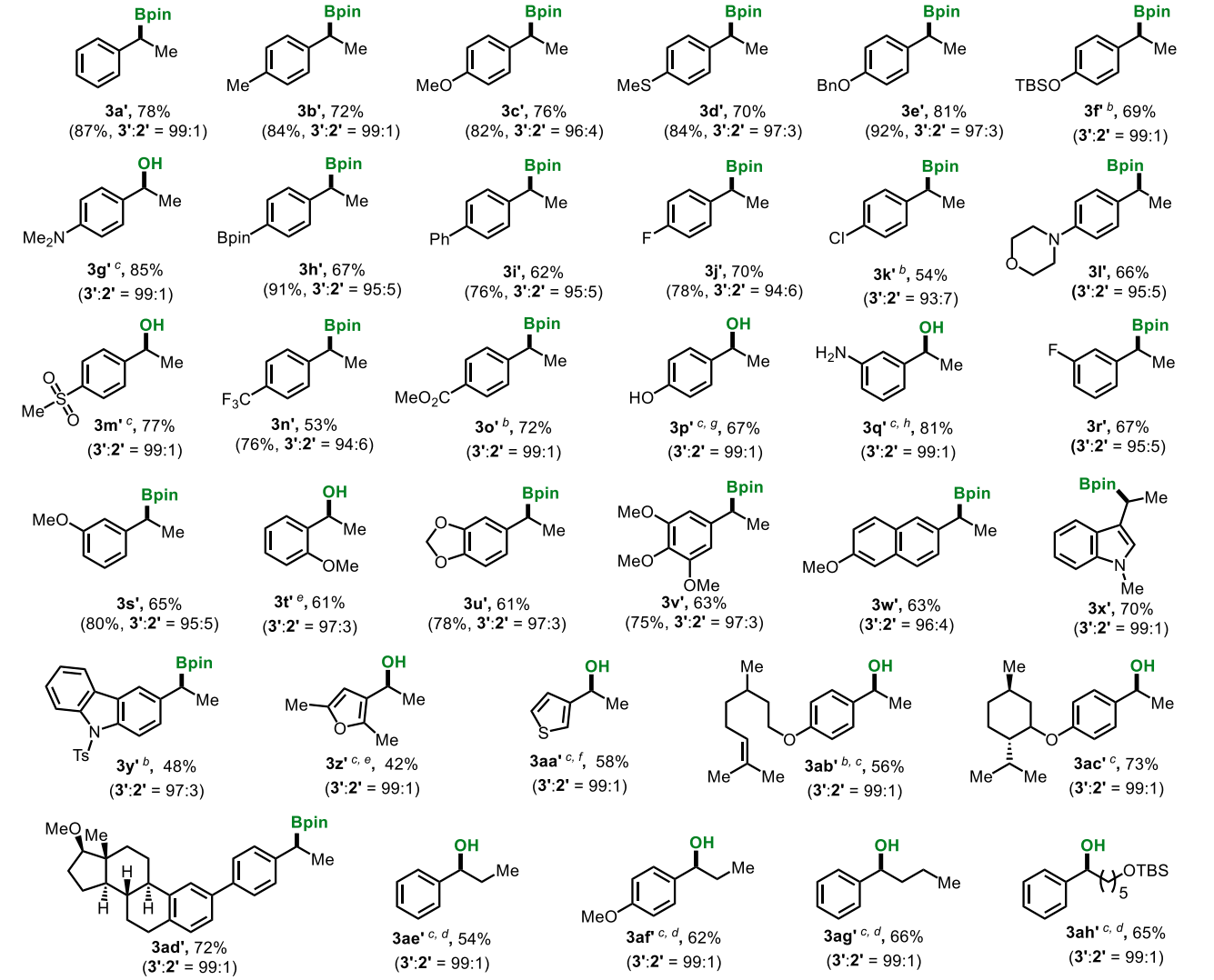
Table 3. Synthesis of Branched Alkylboronates[a]





[a]Standard conditions B: **1'** (0.3 mmol), $[Rh(cod)Cl]_2$ (2 mol %), PPh_2Me (12 mol %), CF_3CO_2K (10 mol %), B_2pin_2 (1.2 equiv), HBpin (1.0 equiv), THF (0.4 mL), CyH (1.6 mL), rt, 24 h. Isolated yields. ^1H NMR yields are shown in the parentheses using CH_2Br_2 as the internal standard. The ratio of *b*/*l* was determined by ^1H NMR analysis of the crude reaction mixtures. [b]B_2pin_2 (1.5 equiv) was used. [c]Overall isolated yield after oxidation. [d]$(4\text{-}^tBuC_6H_4)_2PMe$ as the ligand. [e]48 h. [f]50 °C. [g]HBpin (1.5 equiv), 70 °C. [h]B_2pin_2 (3.0 equiv), no HBpin. CyH = cyclohexane.

Bpin, and CO_2Me are compatible with the reaction conditions (**4b**−**4f**). Remarkably, the substrates with free OH and NH_2 were competent to afford the products **4g** and **4h** in 70 and 86% yields, respectively. The position and number of substituents had no effect on the yields of the 1,1,2-boronate products (**4i**−**4k**). Furthermore, the ketones with naphthalene and indole engaged readily in this triboration to yield **4l** and **4m**. Pleasantly, product **4n** with the estradiol skeleton was successfully prepared in 57% isolated yield.

To demonstrate the synthetic applications of this regiodivergent deoxygenative borylation, further diversifications of alkylboronate **2a** and **3a′** prepared on a gram scale were investigated (Figure 2). First, the iodination of **2a** with NIS was carried out, affording the product **5a** in 74% yield.[57] The reaction of **2a** with dichloromethane gave the *α*-chloroboronate **5b** in good yields. The couplings of **2a** with 3,4,5-trimethoxyiodobenzene and furan were also explored, which furnished the products **5c** and **5d** in 88 and 84% yields, respectively.[58,59] The transformations of **3a′** were then examined and are demonstrated in Figure 2. We treated **3a′** with vinylmagnesium bromide, I_2, and MeONa, delivering vinylation product **5e** in 74% yield.[60] The Matteson homologation of **3a′** followed by oxidation provided alcohol **5f** in excellent yield.[61] The conversion of C−B bonds to C−C bonds was also achieved by treating **3a′** with *para*-ethoxyiodobenzene and furan to give **5g** and **5h** in good yields.[59,62]

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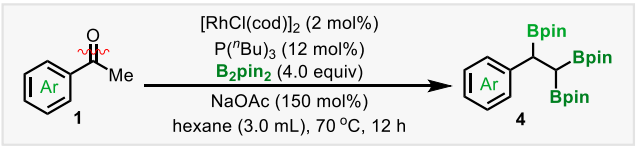
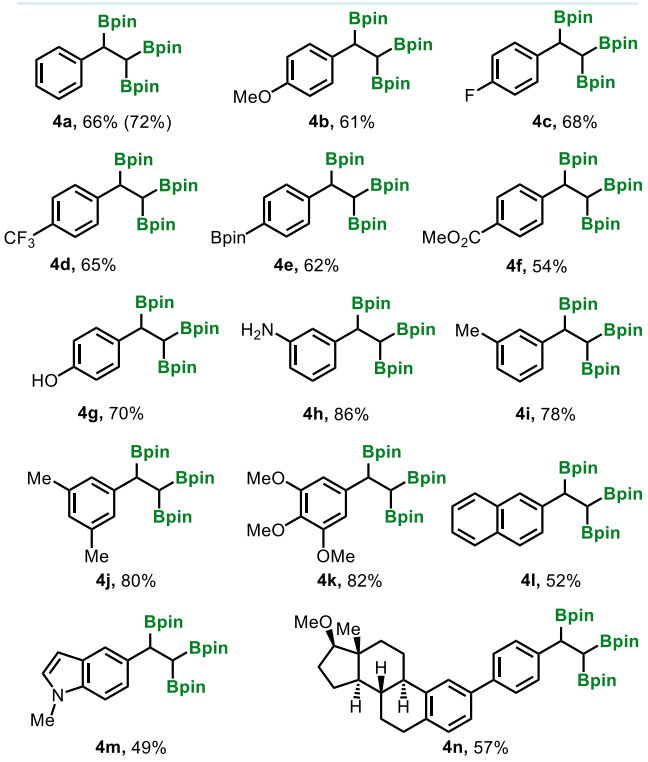
Table 4. Synthesis of 1,1,2-Triboronates[a]





[a]Standard conditions C: **1** (0.3 mmol), $[Rh(cod)Cl]_2$ (2 mol %), $P(^nBu)_3$ (12 mol %), NaOAc (150 mol %), B_2pin_2 (4.0 equiv), hexane (3.0 mL), 70 °C, 12 h. Isolated yields. GC yields are shown in the parentheses using dodecane as the internal standard.

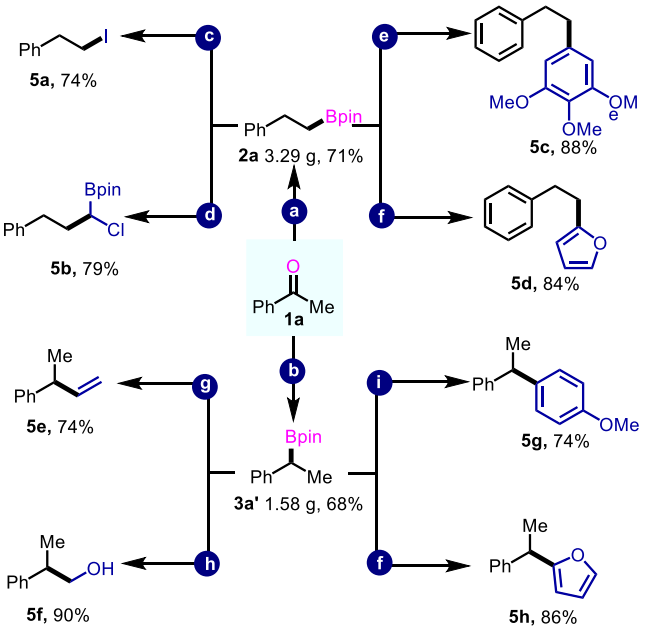


Figure 2. Synthetic applications. Reaction conditions: (a) **1a** (20 mmol), $[Rh(cod)Cl]_2$ (1 mol %), $P(^nBu)_3$ (6 mol %), HCO_2K (50 mol %), B_2pin_2 (1.8 equiv), ^{i}PrOH (1.0 equiv), IPE (50 mL), 70 °C, 12 h. (b) **1a** (10 mmol), $[Rh(cod)Cl]_2$ (2 mol %), PPh_2Me (12 mol %), CF_3CO_2K (10 mol %), B_2pin_2 (1.0 equiv), HBpin (1.0 equiv), THF (8.0 mL), cyclohexane (32 mL), rt, 24 h. (c) (3, 5-$CF_3C_6H_3$)Br (1.5 equiv), ^{n}BuLi (1.5 equiv), NIS (1.5 equiv), THF, −78 °C, 2 h. (d) CH_2Cl_2 (5 equiv), LDA (1.4 equiv), $ZnCl_2$ (1.5 equiv), THF, −78 °C, 5 h. (e) $Pd_2(dba)_3$ (2 mol %), RuPhos (4 mol %), NaO^{t}Bu (3.0 equiv), (3,4,5-$OMeC_6H_2$)Br (1.0 equiv), toluene/H_2O, 80 °C, 24 h. (f) Furan (2.0 equiv), ^{n}BuLi (1.5 equiv), NBS (1.5 equiv), THF, −78 °C, 3 h. (g) Vinylmagnesium bromide (4.0 equiv), I_2 (4.0 equiv), MeONa (8.0 equiv), THF, −78 °C, 3 h (h) $ClCH_2Br$ (2.0 equiv), ^{n}BuLi (1.5 equiv), THF, −78 °C—rt, 4 h, then NaOH/H_2O_2. (i) $Pd_2(dba)_3$ (5 mol %), PPh_3 (40 mol %), Ag_2O (1.4 equiv), (4-$OMeC_6H_4$)I (1.0 equiv), THF, 80 °C, 24 h.

MECHANISTIC STUDIES

To gain more insights into the reaction mechanism, a series of control experiments was carried out (Scheme 1). The mechanism for the formation of linear alkylboronate **2** was first studied (Scheme 1A). The deuterium-labeled acetophenone ***d*-1a** was subjected to the standard conditions A, and deuterated product ***d*-2a** was obtained in 68% yield with 60% deuterium incorporation at the α-position (eq 1). A crossover experiment using a mixture of ***d*-1a** and 4-methoxyacetophenone was also conducted, allowing access to the H/D scrambled products ***d*-2a** and ***d*-2c′** in 66 and 62% yield, respectively (eq 2). Moreover, the treatment of **1a** with deuterated isopropanol led to the generation of ***d*-2a** with 35 and 32% deuterium incorporation at α- and β-positions, respectively (eq 3). These results indicated that the two H atoms at the α-position in **2** are derived from the isopropanol and the α-H in **1**. In addition, we discovered that ^{i}PrOH is not necessarily required during our optimization, and the subjection of ketone **1a** to a mixture B_2pin_2 and HBpin (1:1) provided the product **2a** in 78% yield (eq 4), which could rule out the possibility that the Rh−C bond undergoes the protonation to yield the alkylboronate. Furthermore, the possible intermediate styrene was treated with the standard conditions A (eq 5), and the desired product **2c′** was isolated in 76% yield. Given that the styrene may undergo uncatalyzed hydroboration, the hydroboration of styrene was carried out in the absence of $[RhCl(cod)]_2$. However, the product **2a** was obtained only in 28% yield (eq 6), suggesting that the Rh was involved in the hydroboration. We also observed that the Hs at α- and β-positions in ***d*-2a** were deuterated when styrene was treated with deuterated isopropanol (eq 6). The deuterium incorporation at the β-position of ***d*-2a** in eq 6 should be caused by the formation of deuterated styrene via migratory insertion and β-hydride elimination of Rh−H. To verify this hypothesis, we performed the Rh-catalyzed hydroboration of styrene in the presence of ^{i}PrOD and recovered ***d*-6a** in 64% yield with deuterium incorporation at both the α- and β-positions after 1 h (eq 8), suggesting the Rh-catalyzed H/D exchange of styrene.

Next, we carried out the mechanistic studies on the formation of branched alkylboronate **3′**. As shown in Scheme 1B, the deuterated ***d*-1a** underwent Rh-catalyzed deoxygenative borylation to give ***d*-3a′** with 76 and 57% D incorporation at the α- and β-positions, respectively (eq 9). However, no H/D exchange was observed when ***d*-1a** and **1c′** were subjected to the standard conditions B (eq 10). Besides, the use of DBpin delivered 9 and 51% deuterium incorporation at the α- and β-positions (eq 11). These results suggested that the α- and β-H in **3′** are from the methyl group of **1** and HBpin, respectively.

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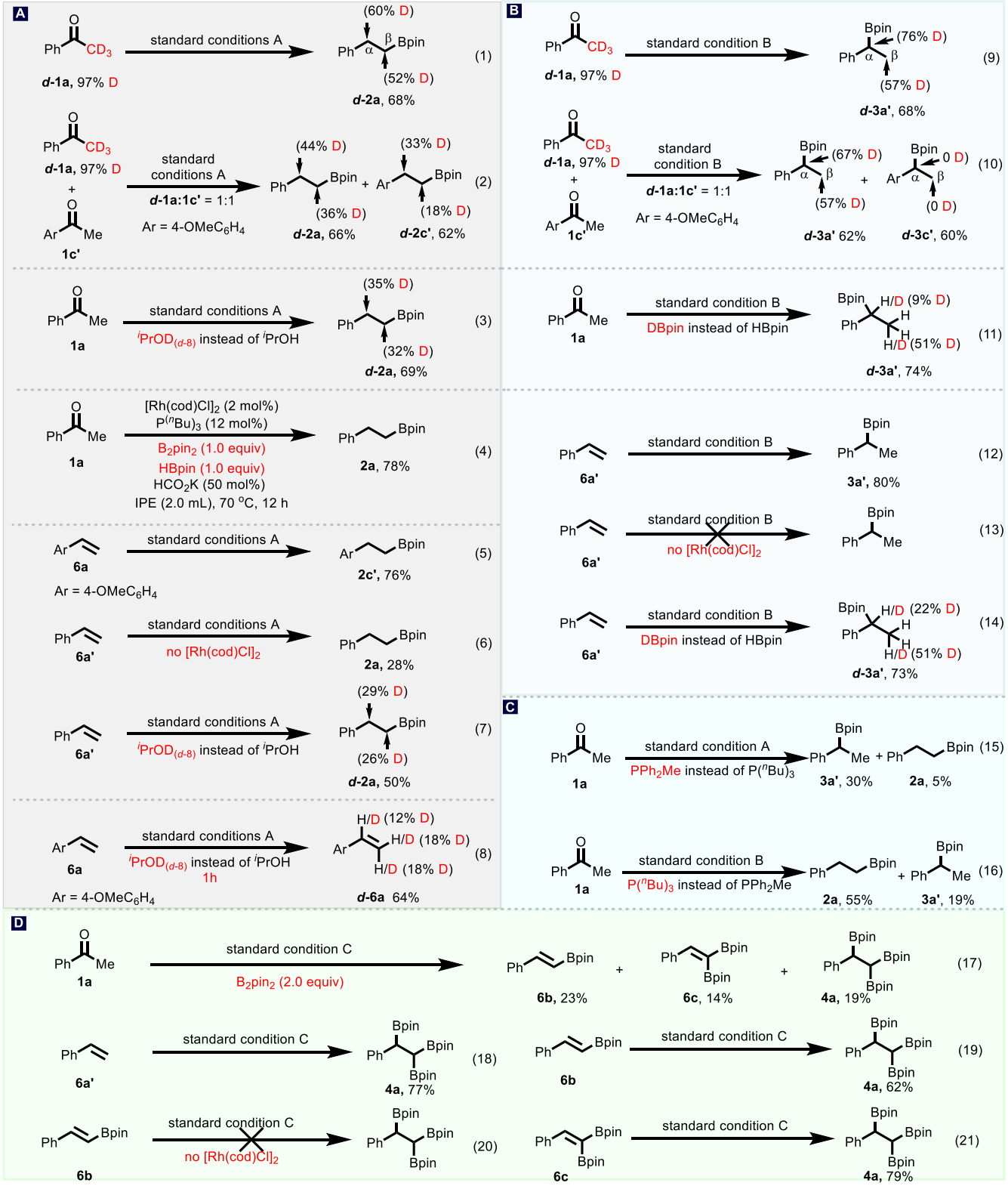
Scheme 1. Mechanistic Studies[a]



[a]Standard conditions (A) $[Rh(cod)Cl]_2$ (2 mol %), $P(^nBu)_3$ (12 mol %), HCO_2K (50 mol %), B_2pin_2 (1.8 equiv), ^iPrOH (1.0 equiv), IPE, 70 °C, 12 h. Standard conditions (B) $[Rh(cod)Cl]_2$ (2 mol %), PPh_2Me (12 mol %), CF_3CO_2K (10 mol %), B_2pin_2 (1.2 equiv), HBpin (1.0 equiv), THF/CyH = 1:4, rt, 24 h. Standard conditions (C) $[Rh(cod)Cl]_2$ (2 mol %), $P(^nBu)_3$ (12 mol %), NaOAc (150 mol %), B_2pin_2 (4.0 equiv), hexane, 70 °C, 12 h.

To probe the possibility of alkenes as intermediates, we treated the styrene with the standard conditions B and found that the alkylboronate **3a′** was obtained in 80% yield (eq 12). However, no desired **3a′** was formed in the absence of $[RhCl(cod)]_2$ (eq

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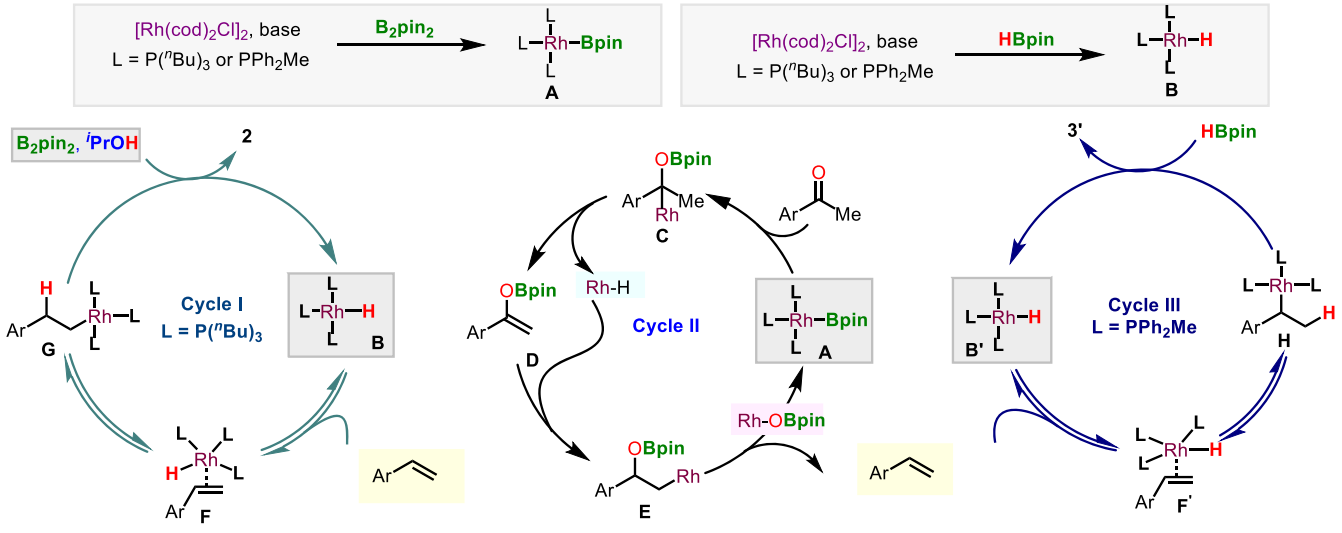

Figure 3. Proposed mechanism.

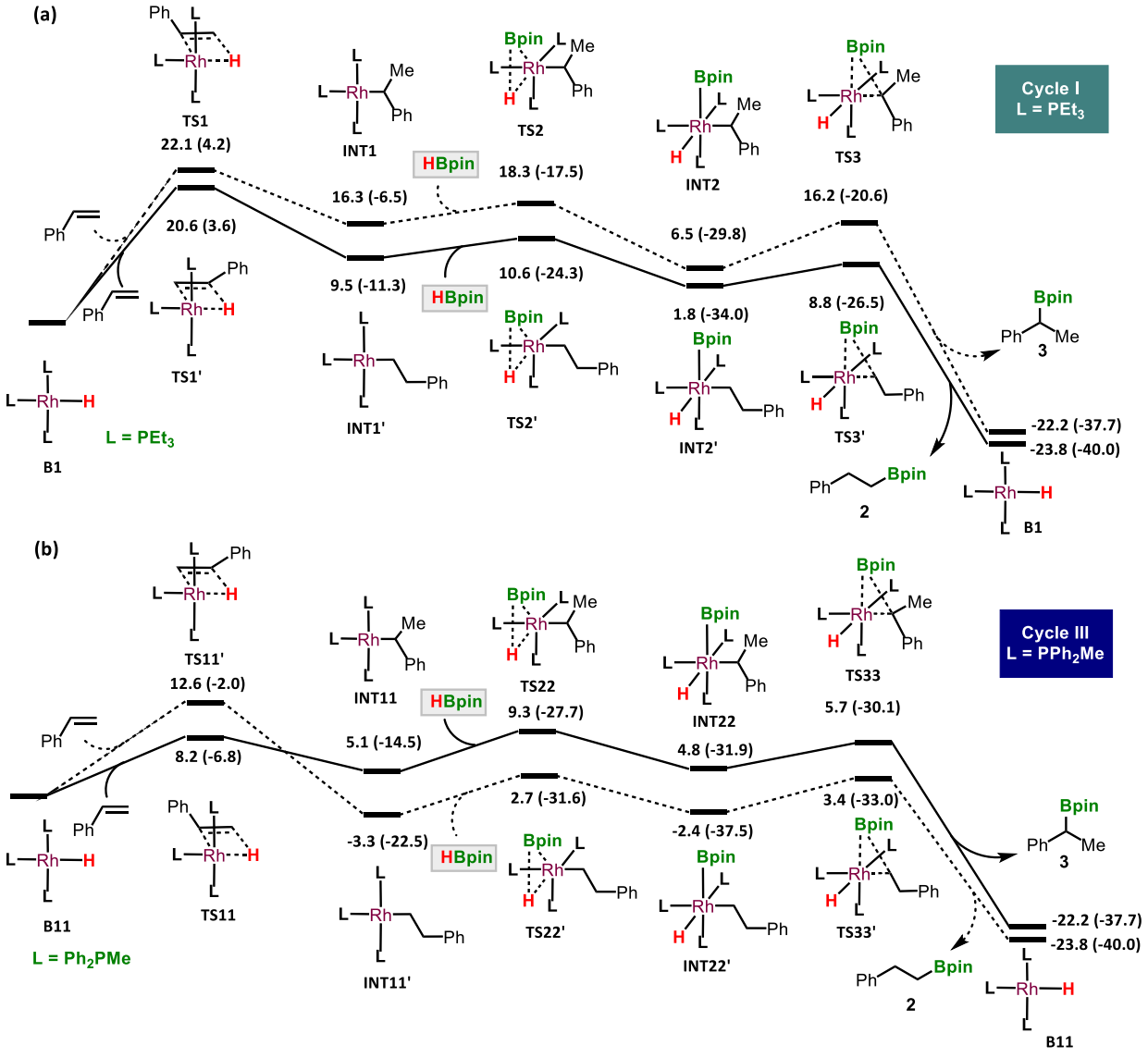

Figure 4. Energy profiles calculated for hydroboration of styrene with HBpin catalyzed by (a) $(PEt_3)_3$Rh-H and (b) $(PPh_2Me)_3$Rh-H. Relative free energies and electronic energies (in parentheses) are given in kcal·mol^{-1}.

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13). Additionally, the reaction of styrene with DBpin produced ***d*-3a′** with the same D incorporation at the β-position (51%) as acetophenone **1a** did (eq 14). These results are consistent with the intermediate of an alkene in the deoxygenative borylation. With regard to the control of regioselectivity, it is worth noting that the switch of regioselectivity was observed when PPh_2Me was employed instead of $P(^nBu)_3$ under the standard conditions A, providing **3a′** as the major product (eq 15). Likewise, the linear alkylboronate **2a** was dominant when $P(^nBu)_3$ was utilized as the ligand under the standard conditions B (eq 16). These results showed that the regioselectivities were mainly controlled by the ligands.

We then turned our attention to investigate the triboration mechanism. The vinylboronate **6b** and 1,1-vinyldiboronate **6c** were obtained in 23 and 14% yields, respectively, when **1a** was treated with 2 equiv of B_2pin_2 (eq 17). Moreover, the triboration of styrene gave the product **4a** in 77% yield under the standard conditions C (eq 18). The treatment of vinylboronate **6b** with the standard conditions C furnished the triboronate **4a** in 62% yield (eq 19), and no desired **4a** was formed in the absence of $[RhCl(cod)]_2$ (eq 20). Furthermore, the vinyldiboronate **6c** was subjected to the standard conditions C, providing the triboronate **4a** in 79% yield (eq 21). These results illustrated that the formation of triboronates involved the Rh-catalyzed deoxygenation of ketones to alkenes, double dehydrogenative borylation of alkenes, and hydroboration (or diboration−protodeboration) of vinylboronates.

Based on the results of mechanistic studies, we propose a plausible mechanism for this regiodivergent deoxygenative borylation of ketones (Figure 3). As demonstrated in Figure 3, the Rh−B bond generated from $[RhCl(cod)]_2$ and B_2pin_2 in the presence of the base[63,64] undergoes a sequential reaction process including 1,2-insertion, β-hydride elimination, and β-oxygen elimination to give alkenes (cycle II), which is consistent with our previous work. The resulting alkenes then went through Rh-catalyzed hydroboration with HBpin to afford alkylboronate products, in which the regioselectivities were controlled by the ligands. In the presence of $P(^nBu)_3$ (cycle I), the styrene first coordinated with Rh complex **B** to form intermediate **F**, which then underwent the anti-Markovnikov hydroboration (migratory insertion and reductive elimination) to yield the linear alkylboronate **2**. In cycle III (L = PPh_2Me), the coordination of styrene with Rh complex **B′** formed the intermediate **F′**. The subsequent migratory insertion of the Rh−H bond, oxidative addition of HBpin, and reductive elimination gave the Markovnikov product **3** and regenerated Rh−H **B′**.

In our previous work, we have computationally studied and validated cycle II in Figure 3 related to the deoxygenation process, leading to the generation of the intermediate styrene. To investigate how phosphine ligands affect the regioselectivity in the hydroboration of the intermediate styrene (cycles I and III in Figure 3), we performed density functional theory (DFT) calculations at the ωB97X-D level of theory (employed in the previous work),[29] considering [Rh]−H ([Rh] = $(PR_3)_3Rh$) as the active species, which can be easily generated in the presence of the HBpin reagent. Figure 4 shows the energy profiles calculated for hydroboration of styrene with HBpin catalyzed by $(PEt_3)_3Rh$−H (Figure 4a) and $(PPh_2Me)_3Rh$−H (Figure 4b; here we used Et as the model for ^{n}Bu for theoretical simplicity and computational cost reduction).

As expected, the hydroboration mechanism consistently/simply involves insertion of olefin into [Rh]−H bond, followed by oxidative addition of HBpin and then C−B bond-forming reductive elimination. Interestingly, in each pathway, the olefin insertion product [Rh]−alkyl does not undergo a direct one-step σ-bond metathesis with HBpin to give an alkyl-Bpin product. Instead, a two-step process consisting of oxidation addition and reductive elimination is found. Clearly, an [Rh]−C σ bond involving an sp^3-carbon center considerably compromises its accessibility to σ-bond metathesis with HBpin. On the contrary, boryl, alkyl, and hydride ligands are strongly σ-electron releasing, which are able to stabilize an Rh(III) oxidation state, as evidenced by the reported *fac*-$[(PMe_3)_3Rh(B(cat))_3]$[65] and *fac*-$[Rh(H)(Bpin)_2(PEt_3)_3]$,[63] which promotes the two-step process.

From Figure 4, we found that the C−B bond-forming reductive elimination is very facile, a result due to which the presence of the empty p-orbital on boron promotes the migration of the alkyl ligand to the boron center of the boryl ligand.[66] The elimination process is basically an empty-p-orbital-assisted 1,2-migration of alkyl to the boron center of the boryl ligand.

The DFT results also show that the olefin insertion is the regioselectivity-determining step. The olefin insertion process (into the Rh−H bond) can be formally viewed as a nucleophilic attack of the M−H σ-bond on one olefinic carbon. Therefore, among the two olefinic carbons, the less π-electron-rich carbon is expected to be preferentially attacked during the migratory insertion process.[67−69] Indeed, for the case when the phosphine PPh_2Me is used, the regioselectivity preference shown in Figure 4b is consistent with this commonly accepted view as the phenyl substituent on styrene is π-electron accepting. For the case when the phosphine PEt_3 is used, the regioselectivity preference shown in Figure 4a reverses. The steric effect provides a reasonable explanation for these observations. In PPh_2Me, the relative orientation of two planar phenyl substituents allows to create a less sterically hindered pocket for styrene to approach the rhodium metal center to facilitate the insertion. In PEt_3 (or P^nBu_3), such a flexibility is no longer possible. The argument here is also consistent with the fact that the insertion barriers calculated for the PEt_3 case (Figure 4a) are all noticeably greater than those calculated for the PPh_2Me case (Figure 4b).

In the energy profiles shown in Figure 4, the parts associated with HBpin oxidative addition and C−B reductive elimination resemble each other in both the PPh_2Me and PEt_3 cases, suggesting that the electronic properties of the primary versus secondary alkyl play dominant roles in the relative preference between the two insertion modes.

CONCLUSIONS

In summary, we have developed an efficient Rh-catalyzed regiodivergent deoxygenative borylation of ketones for the synthesis of linear and branched alkylboronates as well as triboronates. This protocol represents the first example of regiodivergent preparation of anti-Markovnikov and Markovnikov alkylboronates from readily available starting materials other than alkenes and offers an important complement to the existing protocols for their synthesis. In addition, this method features mild reaction conditions, good functional group tolerance, and broad substrate scope. The utilities of this approach were also demonstrated by the gram-scale reactions and various transformations of alkylboronates. Preliminary

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mechanistic studies and DFT calculations revealed that the ketones first undergo the deoxygenation to give alkenes, which then go through ligand-controlled hydroboration to furnish linear and branched alkylboronates, respectively. The very different steric effects of PPh_2Me and $P(^nBu)_3$ were found to be responsible for the product selectivity. Alternatively, the resulting alkenes can react with HBpin or B_2pin_2 via dehydrogenative borylation and hydroboration to afford the triboronates. This protocol will hopefully find applications in synthetic chemistry and materials science via the versatile transformations of organoboron compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02685.

Experimental procedures, characterization, and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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