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FULL PAPER

Experimental and density functional theory studies on hydroxymethylation of phenylboronic acids with paraformaldehyde over a Rh—PPh_3 catalyst

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The synthesis of benzyl alcohols (BAs) is highly vital for their wide applications in organic synthesis and pharmaceuticals. Herein, BAs was efficiently synthesized via hydroxymethylation of phenylboronic acids (PBAs) and paraformaldehyde over a simple Rh—PPh_3 catalyst combined with an inorganic base (NaOH). A variety of BAs with the groups of CH_3^-, CH_3O^-, Cl^-, Br^-, and so on were obtained with moderate to good yields, indicating that the protocol had a good universality. Density functional theory (DFT) calculations proposed the Hayashi-type arylation mechanism involved the arylation step of PBA and $Rh(OH)(PPh_3)_2$ catalyst to form Rh(I)-bound aryl intermediates and the hydrolysis step of Rh(I)-bound aryl intermediates and HCHO to generate BA product (the rate-determining step). The present route provides a valuable and direct method for the synthesis of BAs and expands the application range of paraformaldehyde.

KEYWORDS
hydroxymethylation, paraformaldehyde, Rh-catalyzed mechanism, Rh—P catalyst, synthesis

1 | INTRODUCTION

Benzyl alcohol (BA) derivatives are kinds of valuable building blocks in organic synthesis and fine-chemical industries such as cosmetics, dyes, coatings, inks, and polymers.[1–4] BA is also an important structural motif in many bioactive natural products and pharmaceuticals.[5,6] For example, benzyl benzoate, salix, and beneate hydrochloride contain the BA motif, which are widely used in anti-infective for dermatology,[7] antipyretic analgesia,[8] and treatment of ulcer disease,[9] respectively (Figure 1). Generally, BAs can be obtained from reduction of benzaldehydes,[10,11] hydrolysis of benzyl chloride,[12] electrochemical catalyzed oxidation of toluene,[13]

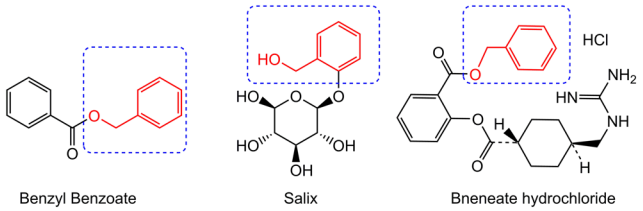
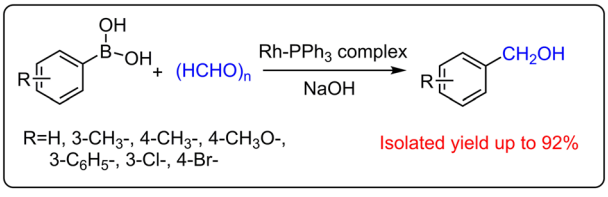


FIGURE 1 Examples of drug molecules with a benzyl alcohol motif

reduction of carboxylic acids,[14] etc. Intrigued by the wide applications and development of downstream products, to develop more routes for the synthesis of BAs is highly important.

As well known, the hydroxymethylation is an important reaction for introduction of a hydroxymethyl group into a molecular.[15–22] It has been reported that BAs could be synthesized via hydroxymethylation of aryl halides and triflates[23]; however, the catalyst was rather complicated and high loadings (the combination of 5 mol % Pd $(dba)_2$, 12 mol% Ru-phos, and 1.5 equiv. Na_2CO_3), and the reactants were expensive resulting in a high-cost route. The hydroxymethylation of organoboron compounds and formaldehyde has also been reported for synthesizing of BAs by using Pd and a complex ligand (bromo-substituted 1,3-diaryl-imidazoline carbene ligand) or a NHC ligand.[1,24] Besides BAs, lots of important chemicals were synthesized via hydroxymethylation by using HCHO as a C1 source, including isoquinoline alkaloid decumbenine B,[25] (2-(pyridin-2-yl)phenyl) methanol,[11] and 5-hydroxymethyl furans.[26]

Herein, a hydroxymethylation method, similar to the Hayashi–Miyaura reaction,[27–29] was developed to synthesize BAs by using paraformaldehyde and phenylboronic acids (PBAs) as the reactants over a simple homogeneous Rh—PPh_3 complex catalyst with an inorganic base (Scheme 1). The reaction proceeded efficiently and had a good tolerance for the substitute groups under the given conditions. Density functional theory (DFT) calculations suggested the Hayashi-type arylation pathway was the possible mechanism. The present approach provided a straightforward approach to synthesize BAs and utilization of formaldehyde.



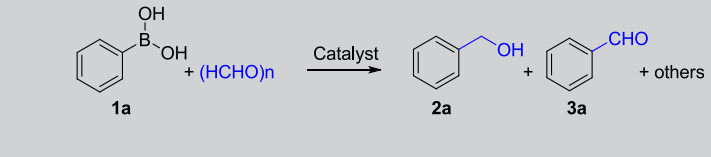
SCHEME 1 Rh-catalyzed hydroxymethylation of arylboronic acids with paraformaldehyde

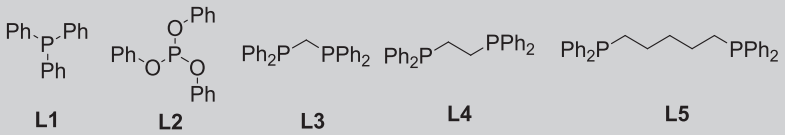
2 | RESULTS AND DISCUSSION

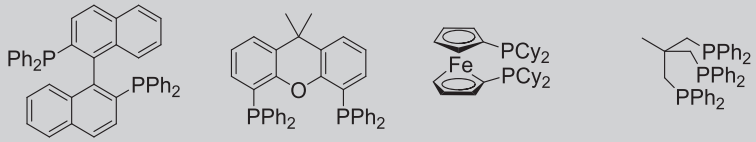
To establish the catalytic procedure, we chose commercially available PBA **1a** as a model substrate to react with paraformaldehyde. Initially, we investigated different catalysts for the reaction as shown in Scheme 1 (Table 1). No product was detected when the catalyst was absent, indicating that the reaction could not occur spontaneously (Table 1, Entry 1). The catalytic system of $RhCl_3$ combined with PPh_3 and NaOH showed the best results, which gave BA with 87% isolated yield (Table 1, Entry 2; GC and GC–MS spectra for the reaction of Entry 2 in Table 1 are given in the Supporting Information). Contrastively, when NaOH was absent, only 2% of BA was obtained, indicating that the base is necessary for the reaction (Table 1, Entry 3). Despite NaOH was indispensable, when it was used alone, the reaction proceeded badly with only 6% yield of BA (Table 1, Entry 4). Following that, various metal catalysts including $PdCl_2$, $RuCl_3$, $CoCl_2$, $CuCl_2$, and $ZnCl_2$ were evaluated in the reaction. However, all of them exhibited low activities (Table 1, Entries 5–9). Phosphine ligand is very important in homogeneous organic reaction as reported.[23,30–32] In this work, we examined effects of phosphine ligands on the catalytic performances (Table 1, Entries 10–17). Notably, all the other ligands (L2–L9) gave low yields than that of PPh_3 (L1). After that, we studied the effect of various bases on the catalytic performances, including Na_2CO_3, K_2CO_3, Cs_2CO_3, and CsF, and organic bases such as Et_3N and diaza(1,3)bicyclo[5.4.0]undecane (DBU) (Table 1, Entries 18–23). They gave moderate yields to target products except for DBU and Et_3N, which gave product in only 1% and 26% yields, respectively. This was probably because organic bases were ineffective in promoting transmetalation, which need to form a M—OH intermediate and/or M-bound aryl intermediates. NaOH gave the highest yield to BA, which is significantly superior to the other bases, and thus, we chose it as the optimum one for the reaction under the given conditions. As a result, we chose the $RhCl_3$—PPh_3—NaOH catalytic system for further use in the reaction.

We also investigated the dependence of reaction conditions on the yield of BA, including reaction temperature, reaction time, and the dosages of base and paraformaldehyde. The results are given in Figure 2. The BA yield increased with increasing the temperature from 50°C to 130°C, indicating that the temperature affected the reaction efficiency remarkably. However, the yield was dropped with further elevating the

TABLE 1 Catalytic performances of various catalysts on hydroxymethylation of phenylboronic acid (PBA) and paraformaldehyde







Entry	Catalyst	Ligand	Additive	Yield[a] (%) 2a	3a	Others[b]
1	—	—	—	0	0	0
2	$RhCl_3$	L1	NaOH	93 (87)	0	0
3	$RhCl_3$	L1	—	2	2	0
4	—	—	NaOH	5	6	0
5	$PdCl_2$	L1	NaOH	14	3	0
6	$RuCl_3$	L1	NaOH	15	8	0
7	$CuCl_2$	L1	NaOH	12	0	0
8	$CoCl_2$	L1	NaOH	3	0	0
9	$ZnCl_2$	L1	NaOH	6	1	0
10	$RhCl_3$	L2	NaOH	38	0	0
11	$RhCl_3$	L3	NaOH	3	3	0
12	$RhCl_3$	L4	NaOH	40	0	0
13	$RhCl_3$	L5	NaOH	42	0	0
14	$RhCl_3$	L6	NaOH	53	0	0
15	$RhCl_3$	L7	NaOH	42	0	0
16	$RhCl_3$	L8	NaOH	3	2	0
17	$RhCl_3$	L9	NaOH	3	6	0
18	$RhCl_3$	L1	Na_2CO_3	43	0	0
19	$RhCl_3$	L1	K_2CO_3	50	0	0
20	$RhCl_3$	L1	Cs_2CO_3	41	2	0
21	$RhCl_3$	L1	CsF	49	0	0
22	$RhCl_3$	L1	DBU	1	0	0
23	$RhCl_3$	L1	Et_3N	26	0	0

Note. Reaction conditions: PBA, 1 mmol; paraformaldehyde, 7 mmol (based on C-molar); catalyst, 4.8×10^{-3} mmol; ligand/catalyst metal 8/1, 130°C, 6 h, base 0.72 mmol; THF, 2 ml.

[a]GC yield and the isolated yield are indicated in brackets.

[b]Mainly benzyl formate.

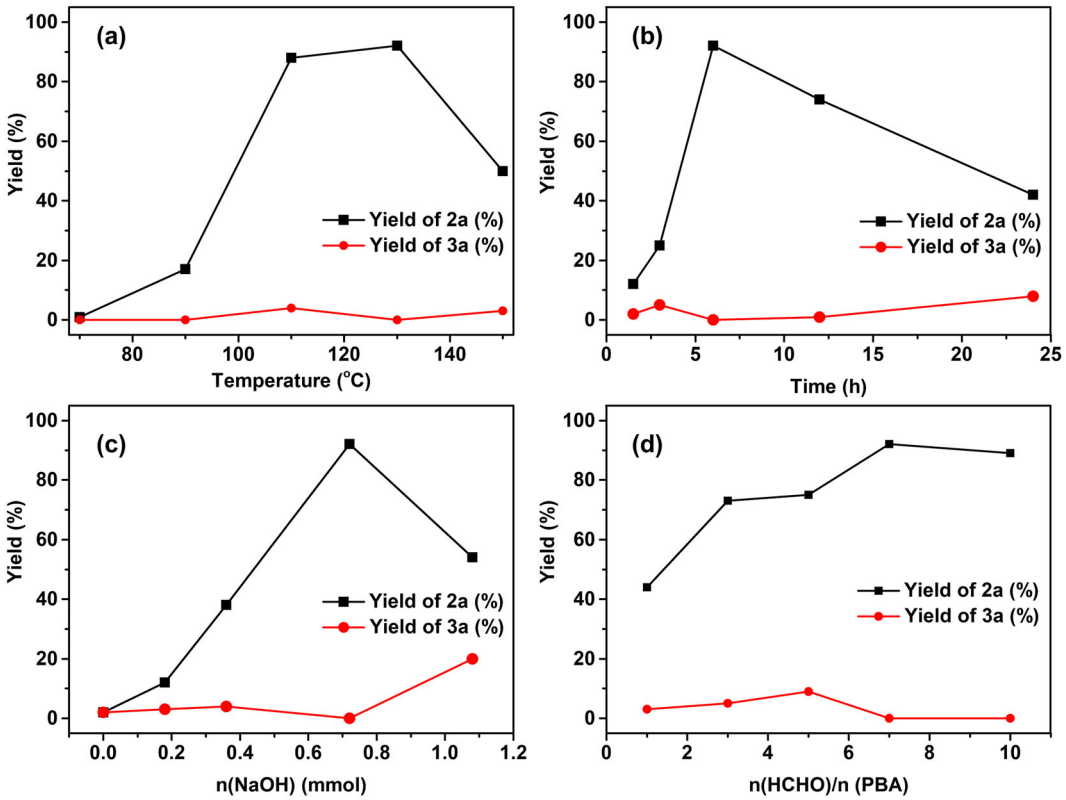


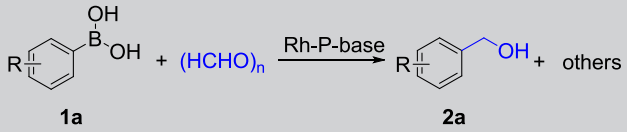
FIGURE 2 Effects of reaction conditions on hydroxymethylation of phenylboronic acid (PBA) with paraformaldehyde. The conditions are similar to that of Entry 2 in Table 1

temperature. The reaction time also affected the catalytic performances under the given conditions. The BA yield increased initially and then fell to 43% after 24 h. Thus, we chose 6 h as the optimized reaction time (Figure 2b).

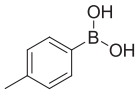
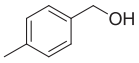
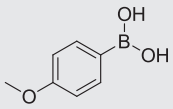
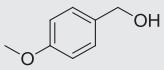
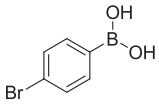
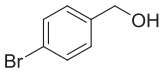
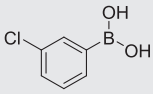
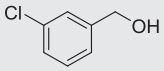
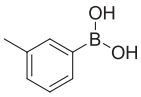
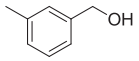
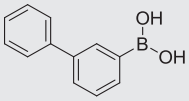
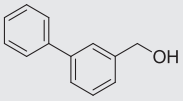
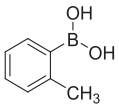
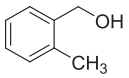
As mentioned above, the base is highly vital for the reaction, probably resulting from the neutralization of in situ generated boric acid (see the following proposed mechanism). Figure 2c shows the effect of base dosage on the reaction, and it could be found 0.72 mmol of NaOH exhibited the best performance. The molar ratio of paraformaldehyde (based on C-atom) to phenyl boronic acid affected the yield of BA, and the best result was obtained at the ratio was 7/1 (Figure 2d). During our experiments, the higher molar ratio resulted in depolymerization of formaldehyde in the reactor. As a result, to obtain a high yield of BA, the optimal reaction conditions were 0.72 mmol of NaOH, 7 mmol of paraformaldehyde (based on HCHO) at 130°C for 6 h. Then, we studied the effect of solvent on the catalytic performances of Rh—PPh_3—NaOH catalytic system. Various solvents including DMF, DMSO, acetonitrile, dichloromethane, cyclohexane, water, and toluene were studied, and THF showed the best performance (Figure S1 vs. Entry 2, Table 1).

With the optimized reaction conditions in hand, the universality of the present protocol to synthesize BAs was investigated. A variety of PBAs reacted well with paraformaldehyde and gave moderate to excellent isolated yields to the corresponding products (Table 2). In particular, the electron-donating groups at 4-position of PBA, such as CH_3^- and CH_3O^-, exhibited higher than 90% yield to the target products (Table 2, Entries 1 and 2). The electron-withdrawing groups, such as Br^- and Cl^- impeded the reaction. For example, 4-bromophenylboronic acid gave 71% yield to **2ha**, and 3-chlorophenylboronic acid generated **2da** with the yield of 62% even at a higher temperature (Table 2, Entries 3 and 4). The CH_3^- group at 3-position produced 76% yield to **2ea** after 12 h, and phenyl group at 3-position gave **2fa** with the yield of 71% at 150°C, respectively (Table 2, Entries 5 and 6). The strong steric resistance hindered the reaction remarkably, and this was validated by the instance of 2-methylphenylboronic acid, which gave only 53% yield even under harsh conditions (Table 2, Entry 7). Based on these results, the hydroxymethylation of PBAs with paraformaldehyde could be accomplished under the catalyzing of Rh—PPh_3 complex combined with NaOH as the base with satisfactory yields. To obtain the feasibility and generality of the present

TABLE 2 General applicability study of the reaction of phenylboronic acids and paraformaldehyde over Rh—P-base catalytic system

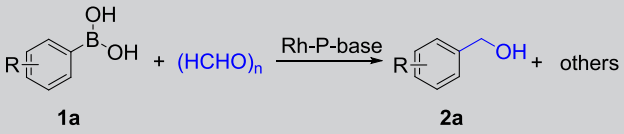


1a 2a

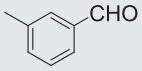
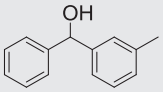
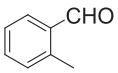
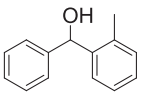
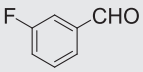
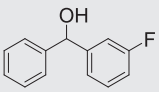
Entry	Substrate	Product	Yield[a]
1	**1aa** 	**2aa** 	91
2	**1ba** 	**2ba** 	92
3	**1ca** 	**2ca** 	71
4[c]	**1da** 	**2da** 	62
5[b]	**1ea** 	**2ea** 	76
6[c]	**1fa** 	**2fa** 	71
7[c]	**1ga** 	**2ga** 	53

(Continues)

TABLE 2 (Continued)



1a 2a

Entry	Substrate	Product	Yield[a]
8[d]	**1ha** 	**2ha** 	87
9[d]	**1ia** 	**2ia** 	52
10[d]	**1ja** 	**2ja** 	78

Note. Reaction conditions: PBAs, 1 mmol; paraformaldehyde 7 mmol (based on C-molar); $RhCl_3$, 4.8×10^{-3} mmol; P/Rh 8/1, 130°C, 6 h; NaOH, 0.72 mmol.
[a]Isolated yield.
[b]12 h, 130°C.
[c]12 h, 150°C.
[d]Aldehyde, 7 mmol. NMR data for the products are given in the Supporting Information.

Rh—P catalyst, more types of aldehydes have been tested (Table 2, Entries 8–10). Interestingly, these aldehydes can also exhibit high yield, demonstrating that the Rh—P catalyst is applicability in the hydroxymethylation. The present findings provide a practical and direct method to synthesize BAs and utilize of formaldehyde.

Next, some control experiments were performed to investigate the catalytic mechanism, which are listed in Table 3. Initially, in consideration of aromatic aldehyde that was detected in the products, we wondered whether the BA was obtained from benzaldehyde. Thus, benzaldehyde was used instead of PBA to react with paraformaldehyde under the conditions of Entry 2 in Table 1. However, no product was detected even prolonging the reaction time to 12 h (Table 3, Entries 1 and 2), demonstrating that BA was not produced from Cannizzaro reaction. We also used HCOOH, methanol, and methyl formate as the C1 source to react with PBA, respectively. However, no corresponding product was detected

TABLE 3 Control experiments of hydroxymethylation for different reactants

Entry	Reactants		2a Yield[a] (%)
1	Benzaldehyde	$(HCHO)_n$	0
2[b]	Benzaldehyde	$(HCHO)_n$	1
3	PBA	CH_3OH	0
4	PBA	HCOOH	0
5	PBA	$HCOOCH_3$	0
6	PBA	Formalin	72
7[c]	PBA	$(HCHO)_n$	0
8[d]	PBA	$(HCHO)_n$	0

Note. Reaction conditions were similar to Entry 2, Table 1.
Abbreviation: PBA, phenylboronic acid.
[a]GC yield.
[b]The reaction time was 12 h.
[c]Water as solvent.
[d]Water as solvent, and TPPTS was used as phosphine ligand with the same P/Rh molar ratio.

(Table 3, Entries 3–5). Interestingly, when formalin, an aqueous solution of individual formaldehyde molecule without polymerized trioxymethylene or paraformaldehyde, was used, the reaction proceeded with 72% yield (Table 3, Entry 6), which was lower than the highest yield (93%). The results indicated that formaldehyde was applied as the true C1 source for hydroxymethylation of BPA, which was decomposed from paraformaldehyde; thus, we chose formaldehyde as the reactant in the following DFT calculations.

Water was then used as the solvent, however, no product was detected (Table 3, Entry 7). In consideration of the low solubility of PPh_3 ligand in water, the water-solubility of TPPTS (sodium salt of tris(m-sulfophenyl) phosphine) was applied with the same P/Rh molar ratio. However, the reaction did not take place at all (Table 3,

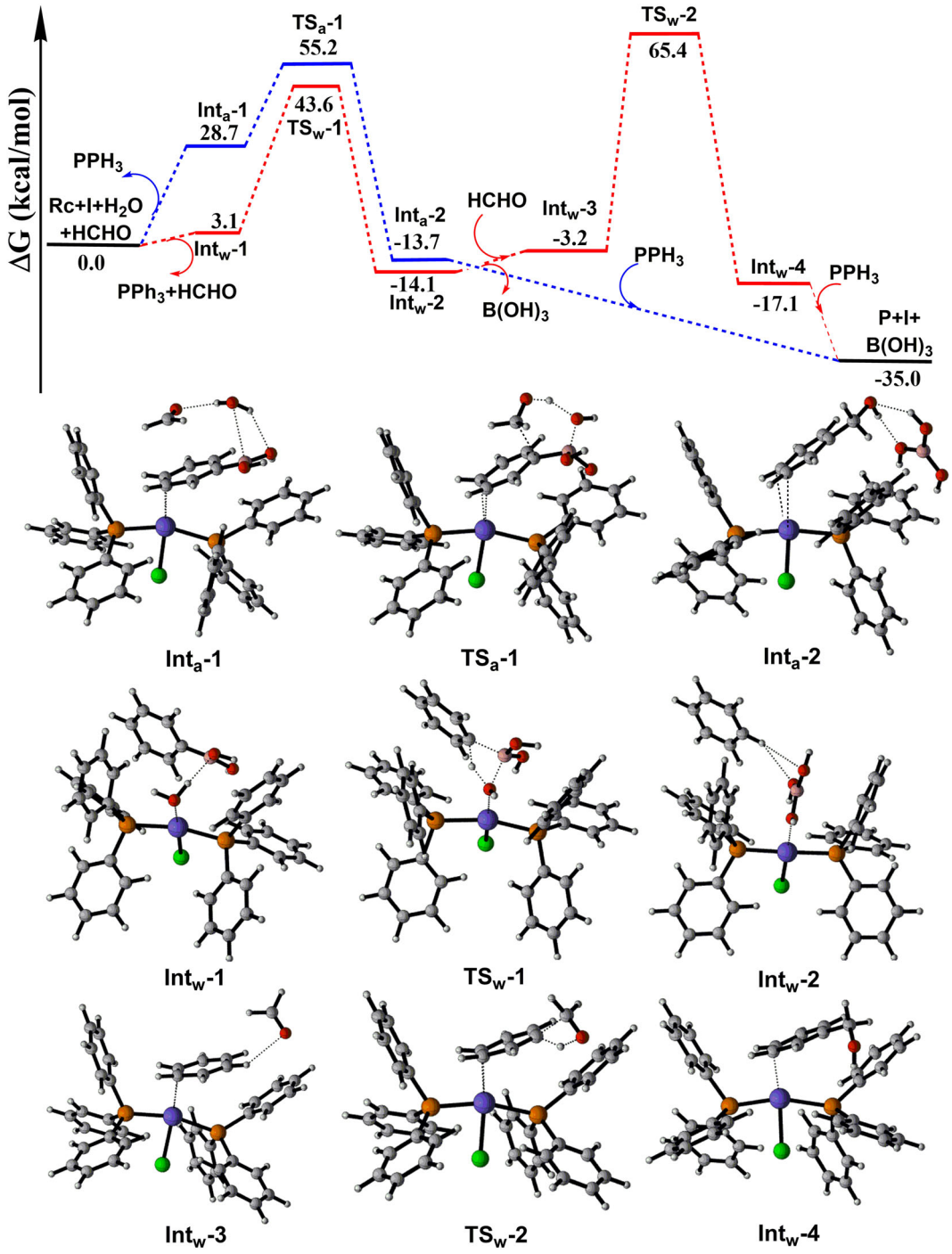
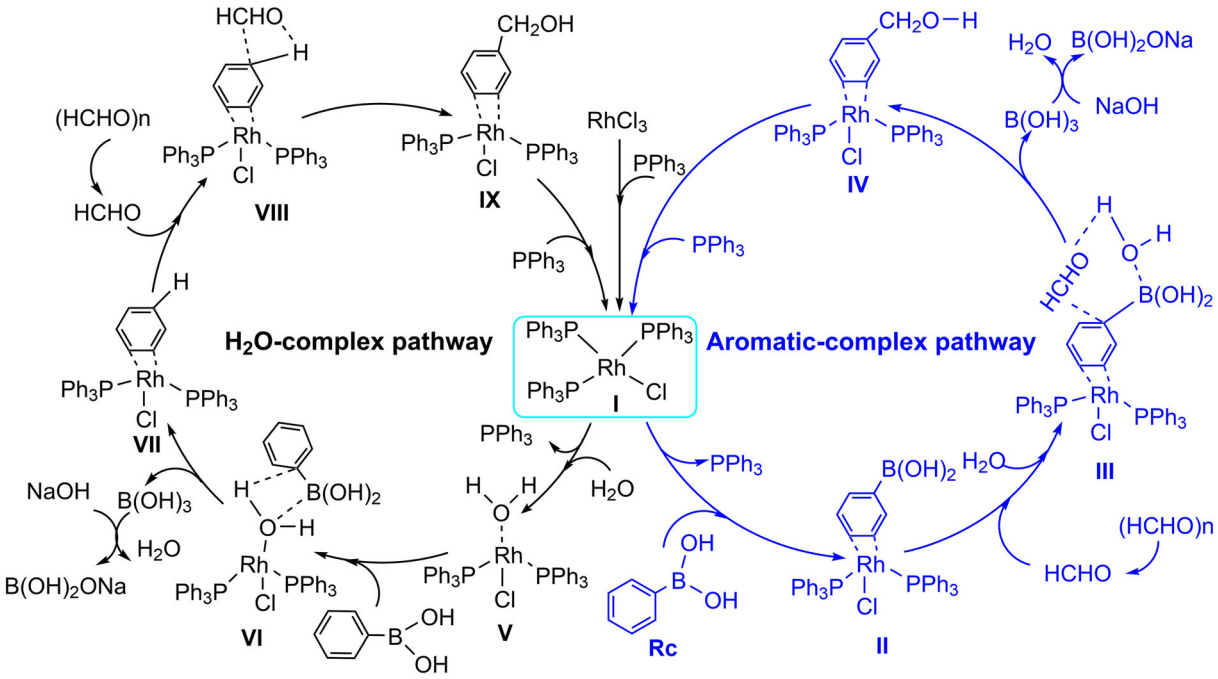


FIGURE 3 Density functional theory (DFT) computed energy surface and optimized structures of two Rh-catalyzed pathways for the hydroxymethylation of phenylboronic acids and HCHO with $RhCl(PPh_3)_3$



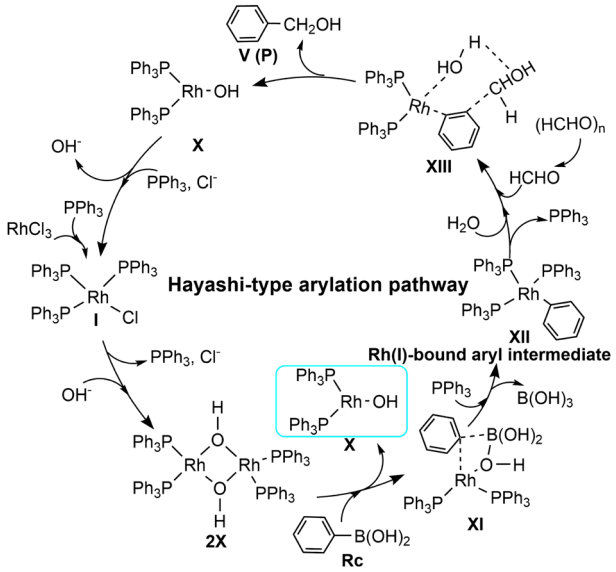
SCHEME 2 Proposed catalytic mechanisms for thehydroxymethylation of phenylboronic acid (PBA) and paraformaldehyde with $RhCl(PPh_3)_3$

Entry 8). The result indicated that the great amount of water prevented the reaction from proceeding. Indeed, small amount of water was generated in the depolymerization of paraformaldehyde[33] and neutralization of NaOH with boric acids and also existed in THF solvent, which was proved to have a slight effect on the catalytic performances in the experimental results.

On the basis of the obtained results, we further studied the mechanism of the reaction using formaldehyde as C1 source by DFT/M06-2X (conductor-like polarizable continuum model [CPCM]) calculations, and details for the calculation are given in following computational sections. The titled reaction of PBA with the highest yield was chosen as a calculation model (Table 1, Entry 2), in which Rh—PPh_3 complex could efficiently catalyze the hydroxymethylation of PBA and paraformaldehyde. Generally, $RhCl_3$ in the presence of triphenylphosphine (L1, PPh_3) can reduced to Rh(I)—P catalyst **I** ($RhCl(PPh_3)_3$). Based on the conclusions, two mechanisms with $RhCl(PPh_3)_3$ were proposed in the present work, that is, Rh-aromatic complex pathway and Rh—H_2O complex pathway, which were verified by DFT computations and shown in Scheme 2.

Starting with the Rh catalyst (**I**), PBA (**Rc**), HCHO, and H_2O (in situ formed in the reaction or existed in the solvent), the Rh-catalyzed reaction processes through an aromatic complex pathway and an H_2O complex pathway are given in Scheme 2. DFT-computed energy surface and transition state structures in two pathways are shown in Figure 3. In the former case, a new aromatic Rh—P complex (**II**) is firstly formed by the release of PPh_3 and the complex of **Rc** in Rh catalyst **I**, which is next approached by H_2O and HCHO to generate intermediate $\mathbf{Int_a\text{-}1}$ (**III**). This process is endergonic by 28.7 kcal mol^{-1} in solution (Figure 3). Next, the hydroxymethylation process ($\mathbf{Int_a\text{-}1} \rightarrow \mathbf{Int_a\text{-}2}$) involves a six-ring transition state ($\mathbf{TS_a\text{-}1}$) with the free energy barrier of 26.5 kcal mol^{-1} for producing the intermediate $\mathbf{Int_a\text{-}2}$. Finally, the product **P**, $B(OH)_3$, and Rh-catalyst **I** are released by the dissociation of $\mathbf{Int_a\text{-}2}$. The whole titled reaction is exergonic by 35.0 kcal mol^{-1} in solution (THF).

Interestingly, after the release of PPh_3, Rh catalyst **I** can also combine firstly by H_2O to form a new an H_2O—Rh—P complex (**V**), and this pathway is denoted as the H_2O complex pathway. Compared with the aromatic Rh—P complex pathway, it involves two processes, that is, the hydrolysis of **Rc** and the hydroxymethylation of HCHO, partly due to the high steric hindrance with the approach of **Rc** and HCHO to the H_2O complex **V**; the reaction energy of **Rc** and **V** to form $\mathbf{Int_w\text{-}1}$ is slightly higher (3.1 kcal mol^{-1}), indicating the formation of $\mathbf{Int_w\text{-}1}$ is much easier than that of $\mathbf{Int_a\text{-}1}$ (28.7 kcal mol^{-1}, right cycle) at the beginning of the reaction. For the hydrolysis step of **Rc** ($\mathbf{Int_w\text{-}1} \rightarrow \mathbf{Int_w\text{-}2}$), the free energy barrier through $\mathbf{TS_w\text{-}1}$ is 40.5 kcal mol^{-1} relative to $\mathbf{Int_w\text{-}1}$. After $\mathbf{Int_w\text{-}2}$ releases $B(OH)_3$, a phenyl complex Ph—Rh—P ($\mathbf{Int_w\text{-}3}$) is formed, which is similar



SCHEME 3 The Hayashi-type arylation mechanism for the hydroxymethylation of phenylboronic acid (PBA) and paraformaldehyde with $Rh(OH)(PPh_3)_2$

to our previous work.[34] Next, the hydroxymethylation step (**Int$_w$-3** → **Int$_w$-4**) takes place through **TS$_w$-2** with a very high free energy barrier of 68.6 kcal mol^{-1} for producing the intermediate **Int$_w$-4**, indicating that the H_2O complex pathway is severely unlikely to occur. Obviously, the aromatic complex pathway is more favorable Rh-catalyzed pathway in the hydroxymethylation of PBA and HCHO with $RhCl(PPh_3)_3$. However, this pathway may be restricted by the formation of pre-intermediate **Int$_a$-1** (endergonic by 28.7 kcal mol^{-1}).

In view that the titled reaction is similar to Hayashi–Miyaura reaction,[27–29] the Hayashi-type arylation mechanism by Rh(I)-bound aryl intermediates is also studied in the present work. The Rh-catalyzed reaction processes through the Hayashi-type arylation pathway are given in Scheme 3. Hayashi et al.[29] found that the identical hydroxorhodium complex coordinated with $[Rh(OH)(binap)]_2$ can be readily obtained by the reaction of $[RhCl((S)\text{-binap})]_2$ with KOH in aqueous THF. Then, an isolated hydroxo complex $1/2[Rh(OH)(binap)]_2$ and PBA in THF can generate a Rh(I)-bound aryl intermediate to further proceed the hydroxymethylation. Similarly, $[RhCl(PPh_3)_2]_2$, which is formed by combined two molecular catalyst **I** after the release of a PPH_3, can also be transformed $[Rh(OH)(PPh_3)_2]_2$ (**IX**) with NaOH in aqueous THF (Scheme 3). Next, the transmetalation of a phenyl group from PBA to hydroxorhodium of an isolated hydroxo complex $Rh(OH)(PPh_3)_2$ (**X**) can regenerate the phenylrhodium complex (Rh(I)-bound aryl intermediate, **XII**). Then, the hydrolysis of oxa-π-allyl complex (a complex of HCHO and **XII**) can finally generate the product **P** and hydroxo-Rh catalyst **X**; thus, the catalytic cycle can be achieved.

DFT calculations are also carried out to verify the Hayashi-type arylation mechanism by Rh(I)-bound aryl intermediates. And the computed free energy profile and the corresponding optimized geometries are shown in Figure 4. After catalyst **I** is introduced hydroxyl with the dechlorination to form $Rh(OH)(PPh_3)_2$ (**X**),[29] the arylation of PBA and **X** takes place through TS_H-1 with a low free energy barrier of 10.5 kcal mol^{-1} to generate aryl intermediate **Int$_H$-2** (**Int$_H$-1** → **Int$_H$-2**). Moreover, **Int$_H$-1** is low in free energy than PBA and **X** by 18.4 kcal mol^{-1}, indicating that which the intermediate **Int$_H$-1** are more favorable to generate in the hydroxymethylation of PBA. Next, **Int$_H$-2** release $B(OH)_3$ to form **XII′** (Rh(I)-bound aryl intermediate after the release of a PPh_3 ligand in **XII**), which is consistent with the observed results of ^{31}P NMR experiments.[29,35] For the hydrolysis of oxa-π-allyl by inserted HCHO in **XII′** (**Int$_H$-3** → **Int$_H$-4**), the free energy barrier through **TS$_H$-2** is 24.8 kcal mol^{-1} relative to **Int$_H$-3**, which is slightly lower than the pathway via TS_a-1 (26.5 kcal mol^{-1}). Moreover, the free energy of **TS$_H$-2** (15.6 kcal mol^{-1}, relative to zero potential energy surface in Figure 4) is much lower than that of **TS$_a$-1** (55.2 kcal mol^{-1}, relative to zero-potential energy surface in Figure 3), implying that the Hayashi-type arylation pathway is more favorable than the aromatic complex pathway from the energy point of view.

For probing the effect of Rh—P catalyst on the titled reaction, the direct hydroxymethylation pathway of PBAs and HCHO is calculated and shown in Figure S2. The free energy barrier of the direct pathway (**IM1** → **IM2**) takes place through **TS1** is 33.5 kcal mol^{-1}, which is approximately 12 kcal mol^{-1} higher than that of the boronate complex pathway (**Int$_b$-1** → **Int$_b$-2**). Therefore, the Hayashi-type arylation pathway is the most favorable hydroxymethylation way kinetically.

Apparently, Rh—P catalyst **X** could effectively promote the hydroxymethylation of PBA with HCHO via the Hayashi-type arylation pathway. However, the participation of hydroxide (i.e., KOH or NaOH) is a necessary condition of the conversion of Rh—P catalyst **I** into Rh—P catalyst **X**.[26] Compared with the obtained only 2% of BA without NaOH (Table 1, Entry 3), the BA with high 87% isolated yield (Table 1, Entry 2) is achieved in the existence of NaOH. DFT-predicted results could explain well the experimental observation and can deeply explore the role of NaOH in the hydroxymethylation of PBA. The hydroxymethylation of PBA in the presence of NaOH is more likely to go through the Hayashi-type arylation pathway with $Rh(OH)(PPh_3)_2$ catalyst, whereas that in the absence of NaOH may only occur through the aromatic complex pathway with $RhCl(PPh_3)_3$ to hinder the

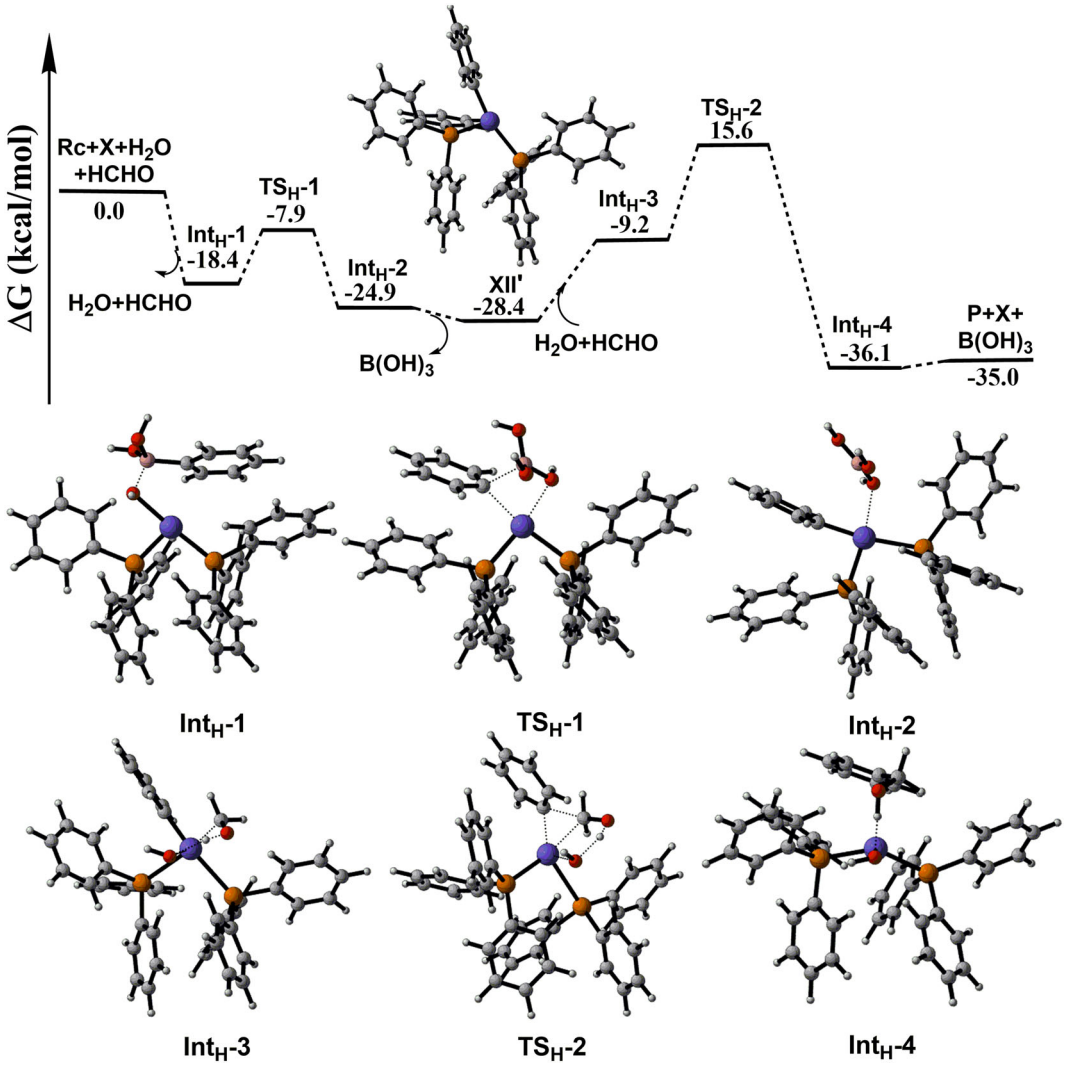


FIGURE 4 Density functional theory (DFT) computed energy surface and optimized structures of three Rh-catalyzed pathways for the hydroxymethylation of phenylboronic acids and HCHO with $Rh(OH)(PPh_3)_2$

formation of product BA, which are in well agreement with the experimental results. Thus, we suppose that NaOH may not only play a role in dissociating paraformaldehyde and neutralizing the generated $B(OH)_3$ to regulate the acid-base property but also provide a more favorable $Rh(OH)(PPh_3)_2$ catalyst for the titled reaction.

3 | CONCLUSIONS

In conclusion, we developed a highly efficient protocol to synthesize BAs from PBAs and paraformaldehyde via hydroxymethylation. The Rh—PPh_3 catalytic system exhibits high activity and selectivity for the reaction. A variety of benzylalcohols were synthesized with moderate to good isolated yields, demonstrating that the route has a good universality. Importantly, paraformaldehyde, an optional alternative for the toxic CO, is used for the hydroxymethylation of PBAs. DFT calculations indicated $Rh(OH)(PPh_3)_2$ catalyst could efficiently achieve the hydroxymethylation of PBA via the Hayashi-type arylation pathway. The present route encourages a more efficiency synthesis of BAs and opens a new way to utilize formaldehyde.

4 | EXPERIMENTAL SECTIONS

4.1 | Chemicals

PBA (97%), CsF (99%), L4 (98%), 2-tolyboronic acid (98%), and DBU (99%) were provided by Beijing Innochem Sci-Tech Co., Ltd. PPh_3 (99%), L3 (97%), L5 (97%), L6 (98%), L7 (98%), L8 (98%), 4-methoxyphenylboronic acid (98%), benzaldehyde (99%), 4-tolyboronic acid (98%), 3-tolyboronic acid (98%),

biphenyl-3-boronic acid (98%), 4-bromophenylboronic acid (97%), and methyl formate (98%) were obtained from Adamas Reagent Co., Ltd. Et_3N (99%), NaOH (96%), $CoCl_2$ (99%), $CuCl_2$ (99%), formic acid (88%), and Na_2CO_3 (99.8%) were purchased from Guangdong Guanghua Sci-Tech Co., Ltd. 3-Chlorophenylboronic acid (97%) and L9 (97%) were obtained from Shanghai Aladdin Bio-Chem Technology Co., Ltd. $RhCl_3$ (98%), $PdCl_2$ (98%), and $RuCl_3$ (95%) were provided by J&K Chemicals. Paraformaldehyde (95%) was bought from Tianjin Fuchen Chemical Reagents Factory. All other chemicals were purchased from commercial sources and used without further purification.

4.2 | Hydroxymethylation of PBA with paraformaldehyde

The reaction was performed in a 16-ml Teflon-lined stainless-steel reactor with a magnetic stirrer.[36] The typical procedures for hydroxymethylation were carried out as follows: PBA (0.1220 g, 1 mmol) and paraformaldehyde (0.2100 g, 7 mmol, based on C-atom), $RhCl_3$ (1.0 mg, 4.8×10^{-3} mmol), PPh_3 (10.0 mg, 3.8×10^{-2} mmol), and NaOH (28.8 mg, 0.72 mmol) were added into the autoclave, and then it was closed and flushed with N_2 for three times to remove air. The mixture was heated to 130°C and reacted for 6 h. Upon reaction completion, the reactor was cooled in an ice bath to 0°C, and the liquid phase was analyzed by GC (Agilent 7890B, HP-INNOWAX, 30 m × 0.32 mm × 0.25 μm) with undecane as an internal standard. The products were separated by a silica gel column chromatography with ethyl acetate and petroleum ether as eluent.

4.3 | Computational sections

All calculations were implanted in Gaussian 09 software,[37] and images of the optimized structures were displayed and prepared with CYLview software.[38] Geometry optimization and frequency analysis were performed in THF solvent with the CPCM[39,40] using M06-2X and a mixed basis set of LanL2DZ[41] for Rh and 6-31G(d,p) for other atoms (C, H, O, B, P, and Cl) (All optimized structural information is given in the Supporting Information). Intrinsic reaction coordinate (IRC) computations validated the connections between reactants, transition states, and products.

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AUTHOR CONTRIBUTIONS

Jie Lan: Conceptualization; data curation; formal analysis; investigation; methodology. **Zhen-Hong He:** Conceptualization; data curation; funding acquisition; project administration; resources; validation. **Zhe Cao:** Conceptualization; formal analysis; investigation; methodology. **Weitao Wang:** Formal analysis; investigation; methodology. **Yang Yang:** Data curation; project administration; resources. **Zhao-Tie Liu:** Conceptualization; funding acquisition; project administration; resources; software; supervision; validation.

CONFLICT OF INTEREST

There are no conflicts to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Additional supporting information may be found online in the Supporting Information section at the end of this article.

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REFERENCES

[1] T. Yamamoto, T. Furusawa, Z. Zhumagazin, T. Yamakawa, Y. Oe, T. Ohta, *Tetrahedron* **2015**, *71*, 19.
[2] S. Zhu, Y. Cen, M. Yang, J. Guo, C. Chen, J. Wang, W. Fan, *Appl. Catal. B-Environ.* **2017**, *211*, 89.
[3] S. H. Lee, T. Jeong, K. Kim, N. Y. Kwon, A. K. Pandey, H. S. Kim, J. M. Ku, N. K. Mishra, I. S. Kim, *J. Org. Chem.* **2019**, *84*, 2307.
[4] T. Suppan, H. P. Mahendran, S. Jeyaraj, K. Ohanta, R. R. Bhattacharjee, *Appl. Catal. A. Gen.* **2020**, *603*, 117734.
[5] R. L. Bis, S. M. Singh, J. Cabello-Villegas, K. M. G. Mallela, *J. Pharm. Sci.* **2015**, *104*, 407.
[6] F. P. Wu, J. B. Peng, X. Qi, X. F. Wu, *J. Org. Chem.* **2017**, *82*, 9710.
[7] N. P. Bachewar, V. R. Thawani, S. N. Mali, K. J. Gharpure, V. P. Shingade, G. N. Dakhale, *Indian J. Pharm.* **2009**, *41*, 9.
[8] A. Ahmed, W. A. Shah, S. Akbar, D. Kumar, V. Kumar, M. Younis, *J. Pharm. Res.* **2011**, *4*, 1067.
[9] J. M. Lee, J. Y. Lim, Y. Kim, Y. J. Kim, H. S. Choi, E. S. Kim, B. Keum, Y. S. Seo, Y. T. Jeen, H. S. Lee, S. H. Um, C. D. Kim,

H. S. Ryu, D. Sul, J. Hong, H. J. Chun, *Exp. Ther. Med.* **2016**, *12*, 573.
[10] Y. Ma, G. Xu, H. Wang, Y. Wang, Y. Zhang, Y. Fu, *ACS Catal.* **2018**, *8*, 1268.
[11] Y. Wu, B. Zhou, *ACS Catal.* **2017**, *7*, 2213.
[12] T.-T. Wang, T.-C. Huang, M.-Y. Yeh, *Chem. Eng. Commun.* **1990**, *92*, 139.
[13] H. Ma, B. Wang, Y. Liang, *Cat. Com.* **2004**, *5*, 617.
[14] J. A. Fernández-Salas, S. Manzini, S. P. Nolan, *Adv. Synth. Catal.* **2014**, *356*, 308.
[15] Y.-Y. Gui, N. Hu, X.-W. Chen, L.-L. Liao, T. Ju, J.-H. Ye, Z. Zhang, J. Li, D.-G. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 17011.
[16] J. Yang, D. Xie, H. Zhou, S. Chen, J. Duan, C. Huo, Z. Li, *Adv. Synth. Catal.* **2018**, *360*, 3471.
[17] M. Holmes, L. A. Schwartz, M. J. Krische, *Chem. Rev.* **2018**, *118*, 6026.
[18] V. J. Garza, M. J. Krische, *J. Am. Chem. Soc.* **2016**, *138*, 3655.
[19] B. Sam, T. P. Montgomery, M. J. Krische, *Org. Lett.* **2013**, *15*, 3790.
[20] M.-Y. Ngai, E. Skucas, M. J. Krische, *Org. Lett.* **2008**, *10*, 2705.
[21] F. Zhou, L. Zhang, Q. Wu, F. Guo, S. Tang, B. Xu, M. Yuan, H. Fu, R. Li, X. Zheng, H. Chen, *Appl. Organomet. Chem.* **2019**, *33*, e4646.
[22] A. Jagtap, B. M. Bhanage, *Appl. Organomet. Chem.* **2018**, *32*, e4478.
[23] Y. Zhang, Z. Yang, L. Guo, W. Li, X. Cheng, X. Wang, Q. Wang, L. Hai, Y. Wu, *Org. Chem. Front.* **2018**, *5*, 1604.
[24] T. Yamamoto, A. Zhumagazin, T. Furusawa, R. Tanaka, T. Yamakawa, Y. Oe, T. Ohta, *Adv. Synth. Catal.* **2014**, *356*, 3525.
[25] T. Wendling, E. Risto, T. Krause, L. J. Goossen, *Chem. – Eur. J.* **2018**, *24*, 6019.
[26] M. Sajid, G. Kehr, C. G. Daniliuc, G. Erker, *Chem. – Eur. J.* **2015**, *21*, 1454.
[27] M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229.
[28] Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, M. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.
[29] H. Tamio, T. Makoto, T. Yoshiaki, O. Masamichi, *J. Am. Chem. Soc.* **2002**, *124*, 5052.
[30] Y. C. Hsu, V. C. Wang, K. C. Au-Yeung, C. Y. Tsai, C. C. Chang, B. C. Lin, Y. T. Chan, C. P. Hsu, G. P. A. Yap, T. Jurca, T. G. Ong, *Angew. Chem., Int. Ed.* **2018**, *57*, 4622.
[31] R. Sang, P. Kucmierczyk, K. Dong, R. Franke, H. Neumann, R. Jackstell, M. Beller, *J. Am. Chem. Soc.* **2018**, *140*, 5217.
[32] Z. Wang, T. Hayashi, *Angew. Chem., Int. Ed.* **2018**, *57*, 1702.
[33] T. Suenobu, Y. Isaka, S. Shibata, S. Fukuzumi, *Chem. Commun.* **2015**, *51*, 1670.
[34] X. Yang, X. Jiang, W. Wang, Q. Yang, Y. Ma, K. Wang, *RSC Adv.* **2019**, *9*, 34529.
[35] N. Tokunaga, K. Yoshida, T. Hayashi, *PNAS* **2004**, *101*, 5445.
[36] Z.-H. He, N. Li, K. Wang, W. Wang, Z.-T. Liu, *Mol. Catal.* **2019**, *470*, 120.
[37] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc. Gaussian 09, Revision B.01, Wallingford, CT, **2010**.
[38] C. Y. Legault, CYLview, Université de Sherbrooke, Sherbrooke, Canada, **2009**, http://www.cylview.org
[39] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.
[40] M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003**, *24*, 669.
[41] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299.

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