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Ruthenium-catalyzed regio- and site-selective *ortho* C–H borylation of phenol derivatives

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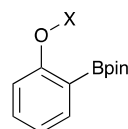
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Efficient synthesis of *o*-borylphenols is achieved through the Ru-catalyzed regio- and site-selective sp^2C-H borylation of aryl diphenylphosphinites followed by removal of the phosphorus directing group. A successful application to aryl phosphites enables practical one-pot borylation of phenols, demonstrating high synthetic utility of this protocol.

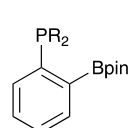
Phenols are important structural motifs found in many natural products, pharmaceuticals, agrochemicals, polymers, and functional materials. Therefore, development of efficient methods to synthesize a variety of functionalized phenol derivatives is of great importance in synthetic chemistry. As one of promising approaches for that, transition metal-catalyzed sp^2C-H bond transformation reactions of phenols and their derivatives have been extensively investigated.¹ In particular, a transition metal-catalyzed, directed *ortho* C–H borylation reaction of phenol derivatives having a removable directing group on the oxygen atom is highly useful for the synthesis of *o*-borylphenols, which serve as useful synthetic building blocks through various C–B bond transformations.² These are useful complements to classical electrophilic borylation reactions with aryllithium compounds generated by *ortho*-lithiation³ and direct electrophilic borylation reactions of phenol derivatives⁴ in terms of functional group compatibility and atom efficiency. Previously reported reactions employed Ir complexes as catalysts and silane ($-SiEt_2H$),⁵ carbamate ($-CONEt_2$),⁶ thiomethyl ether ($-CH_2SMe$),⁷ and boronic ester ($-B(OR)_2$)⁸ as directing groups (Figure 1-a).⁹ These directing groups control high *ortho*-selectivity through coordination to Ir,^{6,7} oxidative addition of a Si–H bond to Ir,⁵ and an electrostatic interaction with Ir⁸ although the regioselectivity of these reactions are not necessarily perfect in some cases due to the high reactivity of Ir

catalysts that undergo sp^2C-H borylation even without directing groups.¹⁰ On the other hand, ruthenium has also been recognized as an alternative transition metal catalyst for sp^2C-H borylation.^{11–13} However, its use in synthetic chemistry is rather limited compared with those of iridium and rhodium possibly due to poor substrate generality. Previously reported reactions required nitrogen-based coordinative directing groups such as pyridine^{11c,d,e} and imine^{11f}, and a specific substrate such as perylene diimide.^{11a,b} Recently, we have developed a Ru-catalyzed *ortho* C–H borylation reaction of arylphosphines as a facile method for late-stage derivatization of tertiary phosphines, demonstrating new synthetic utility of the Ru catalyst in C–H borylation chemistry (Figure 1-b).¹⁴ Moreover, interesting site-selectivity for borylation was also disclosed, where the borylation occurred at the particular

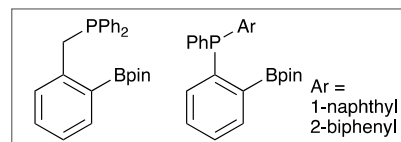
 a) Transition metal-catalyzed *ortho*-selective borylation of phenols


- Ir catalyst
- X = removable or traceless directing group
SiEt₂H, CONEt₂, CH₂SMe, B(OR)₂
- Regioisomers in some cases

b) Our previous work –Ru-catalyzed C–H borylation of tertiary phosphines–

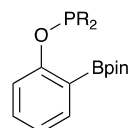


with Ru catalyst



site-selective borylation

c) This work



- Ru-catalyzed *ortho*-selective borylation of aryl phosphinites (R = Ph) and phosphites (R = OAr)
- Excellent regio- and site-selectivity
- One-pot borylation of phenols

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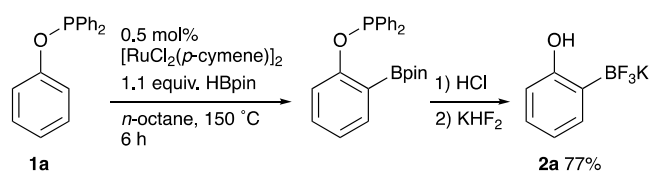
Electronic Supplementary Information (ESI) available: Details of experimental procedures, spectral data, and analytical data. See DOI: 10.1039/x0xx00000x

Fig. 1 Directed borylation of phenol derivatives

C–H bond selectively according to the following order; at an sp^2 C–H bond of a benzyl group > a phenyl group > 1-naphthyl and 2-biphenyl groups on phosphorus.

Herein we report a Ru-catalyzed regio- and site-selective borylation reaction of aryl diphenylphosphinites, which are easily available phenol derivatives having a $-PPh_2$ group on the oxygen atom as a removable directing group (Figure 1-c).¹⁵ We anticipated that the borylation proceeds selectively only at an *ortho*-position of the phenoxy moiety, not at C–H bonds of the $-PPh_2$ moiety, based on the privileged site-selectivity of the Ru-catalysis mentioned above. Hydrolysis of the resulting borylation products affords *o*-borylphenols, thus realizing regioselective *ortho*-borylation of phenols with Ru-catalysis.

We found that the borylation of phenyl diphenylphosphinite **1a** with 1.1 equiv. of pinacolborane (HBpin) proceeded smoothly in the presence of 0.5 mol% of $[RuCl_2(p\text{-cymene})]_2$ in *n*-octane at 150 °C (Scheme 1). After acidic hydrolysis of the obtained crude mixture followed by treatment with KHF_2 , *o*-hydroxyphenyl trifluoroborate **2a** was obtained as white solids in 77% yield. The reaction did not proceed in benzene at 100 °C, which are the reaction conditions employed for the borylation of arylphosphines.¹⁴ The formation of double borylation product and other regioisomers reacted at *meta*- or *para*-positions were not observed at all.¹⁶ Moreover, the borylation occurred only at the phenoxy ring, not at the PPh_2 moiety, thus demonstrating excellent regio- and site-selectivity of this reaction.

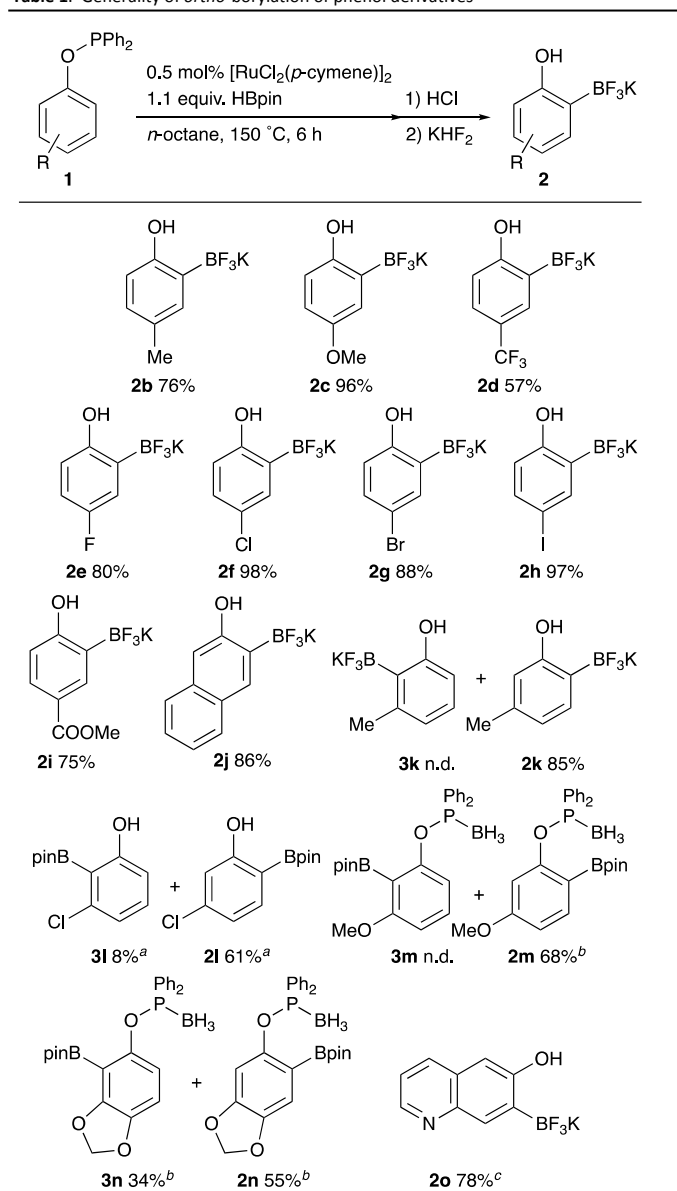


Scheme 1. Reaction of phenyl diphenylphosphinite

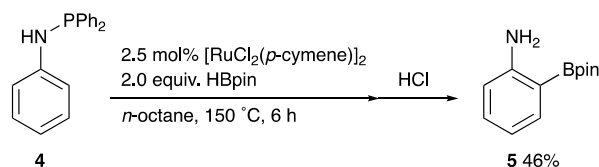
This borylation reaction is applicable to various aryl phosphinite derivatives (Table 1). Aryl phosphinites bearing an electron-donating or -withdrawing substituent at the *para*-position of the phenoxy ring were borylated smoothly under the optimized reaction conditions to afford corresponding *o*-borylphenol derivatives **2b–d** in good yields. Various halogen substituents (F, Cl, Br, I) were tolerated under the reaction conditions, giving 2-hydroxy-5-halophenyl trifluoroborates **2e–2h** selectively in 80–98% yields. It should be noted that iodophenol derivatives have never been employed as a substrate in the previously reported Ir-catalyst systems. Therefore, this result demonstrates good functional group compatibility of the Ru-catalysis. Moreover, the presence of an ester group was also no problem, giving the product **2i** in high yield. Concerning substrates having two adjacent C–H bonds to be borylated, 2-naphthyl phosphinite afforded 3-boryl-2-naphthol **2j** selectively in 87% yield. The borylation of *meta*-substituted aryl phosphinites proceeded at the less hindered position, *para* to the substituent, preferentially, affording **2k–m** in good yields. 3,4-Methylenedioxyphenyl phosphinite gave a mixture of two regioisomers **2n** and **3n** in good yield. In the

cases of **2m**, **2n**, and **3n**, these products were isolated as phosphinites protected with BH_3 to avoid protodeborylation of the resulting C–B bonds during the acidic hydrolysis. Borylation of 6-quinolyl diphenylphosphinite proceeded smoothly to give the borylation product **2o** in good yield, demonstrating a certain level of tolerance to heteroaromatic compounds.¹⁷ Moreover, phenyl phosphinous amide **4** was also employable as a substrate to give *o*-aminophenylboronic ester **5** in moderate yield after acidic hydrolysis (Scheme 2), indicating a promising applicability of this method to the synthesis of various *o*-borylaniline derivatives. In all cases, the borylation occurred only at *ortho*-positions of the $-OPPh_2$ directing group due to its

Table 1. Generality of *ortho*-borylation of phenol derivatives

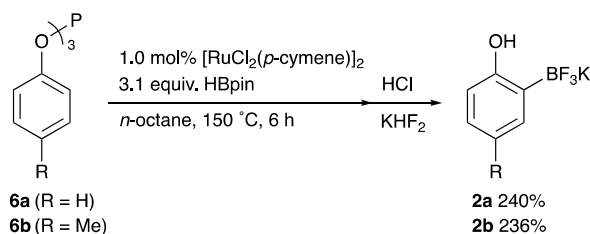


^a Isolated as an *o*-hydroxyarylboronic ester after hydrolysis without the treatment with KHF_2 . ^b Isolated as BH_3 -protected phosphinites without hydrolysis. ^c 1.0 mol% $[RuCl_2(p\text{-cymene})]_2$, 1.5 h. KHF_2 was added without acidic hydrolysis.

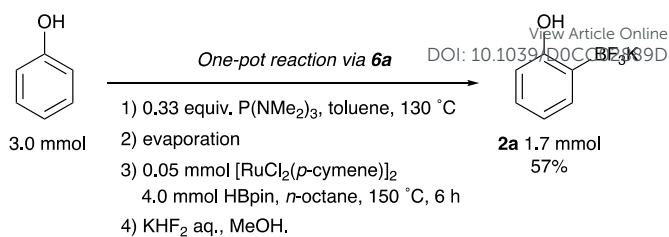
Scheme 2. *ortho*-Borylation of an aniline derivative

high coordination ability, and no borylation at *meta*- and *para*-positions were observed. Additionally, the phosphorus directing group can be easily removed by the acidic hydrolysis while more harsh conditions are required to remove some directing groups employed in the previous Ir systems.¹⁸ These results demonstrate high synthetic utility of the Ru-catalysis with the diphenylphosphinite directing group in the C–H borylation chemistry.

Furthermore, we also found that not only phosphinite, but also phosphite can also work as a good substrate for this Ru-catalyzed borylation reaction. The reaction of phenyl phosphite **6a** with 3.1 equiv. of HBpin under the standard reaction conditions proceeded smoothly to give the borylation product **2a** in 240% yield based on **6a** after acidic hydrolysis and the treatment with KHF₂ (Scheme 3). This result clearly supports that three phenoxy groups on boron in **6a** can be borylated efficiently although the substrate becomes sterically more demanding as the borylation proceeds. The reaction of *p*-methylphenyl phosphites **6b** also proceeded without any problems, affording the corresponding borylphenol **2b** in good yield. It is worth noting that the phosphite group is more atom economical as a removable directing group than phosphinite because all three phenoxy groups in a single phosphite molecule can be utilized in this Ru-catalyzed reaction. Furthermore, the successful borylation with phosphite substrates lead to the development of a practical one-pot *ortho*-borylation protocol using phenol as a starting material directly (Scheme 4). Treatment of phenol with 0.33 equiv. of P(NMe₂)₃ in toluene at 130 °C afforded phenyl phosphite **6a** quantitatively. After the evaporation of volatile HNMe₂ and toluene, the Ru-catalyzed borylation under the slightly optimized reaction conditions was carried out in the same flask, giving the borylation product **2a** in 57% yield (based on phenol). This one-pot reaction is highly promising as a practical method for the synthesis of *o*-borylphenol derivatives.

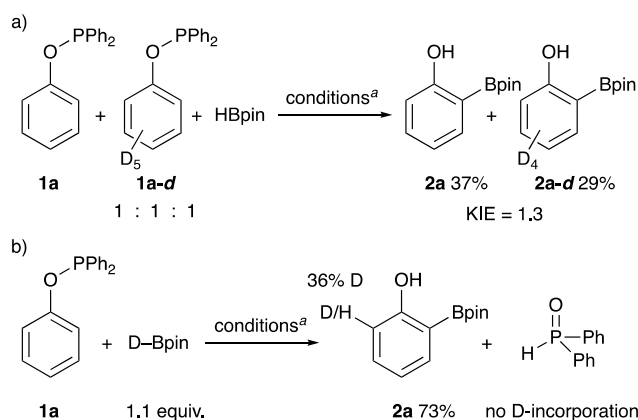


Scheme 3. Reaction of phosphites



Scheme 4. One-pot borylation of phenol

As a preliminary mechanistic study, we conducted an intermolecular competition experiment using phenyl phosphinite **1a** and phenyl-*d*₅ phosphinite **1a-d** as substrates under the standard reaction conditions (Scheme 5-a). The reaction afforded the borylation products **2a** and **2a-d** in 37% and 29% yields, respectively. Therefore, the intermolecular KIE value was calculated to be 1.3, indicating that the C–H activation step could be involved in the rate-determining step. Moreover, the reaction of phenyl phosphinite **1a** with DBpin afforded the product **2a**, in which the remaining *ortho* C–H bond is partially deuterated with 36% deuterium incorporation (Scheme 5-b). This result clarifies that the C–H activation at *ortho*-positions of the phenoxy group is reversible, and the generated ruthenium hydride species undergoes H/D exchange with deuterium originated from DBpin. Therefore, we propose that the C–H activation is a pre-equilibrium before the rate-determining step.¹⁹ Moreover, in the reaction with DBpin, no H/D exchange was observed on the –PPh₂ moiety as confirmed by ¹H NMR of diphenylphosphine oxide formed after the hydrolysis. This result supports that the C–H activation occurs selectively on the phenoxy group on phosphorus over the phenyl groups, leading to the excellent site-selectivity for the C–H borylation. This site-selectivity could arise from the different stability of the ruthenacycle intermediates formed by C–H activation. More detailed mechanistic studies are ongoing in our group, and the results will be reported in due course.



^a 0.5 mol% [RuCl₂(*p*-cymene)]₂, *n*-octane, 150 °C, 6 h, then HCl aq.

Scheme 5. Deuterium labeling experiments

In conclusion, we have developed an efficient method for the synthesis of *o*-borylphenols through the Ru-catalyzed regio- and site-selective $\text{sp}^2\text{C-H}$ borylation of aryl phosphinites utilizing phosphorus as a removable directing group. The reaction was also applicable to aryl phosphites, enabling a highly useful one-pot borylation reaction using phenol as a starting material. These results open up new utilization of ruthenium catalysis in the directed C-H borylation chemistry.

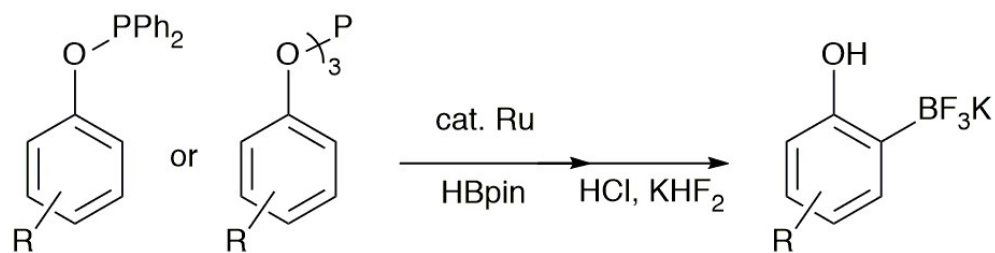
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Conflicts of interest

There are no conflicts to declare.

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- A double borylation product was not formed possibly due to steric repulsion in the second C-H activation step. The excellent selectivity for the mono-borylation was also observed in the borylation of arylphosphines (ref 14).
- The reaction of 2-pyridyl diphenylphosphinite did not proceed.
- Strong reductant and oxidant such as LiAlH_4 and I_2 are used for the removal of carbamate and thiomethyl ether groups in ref 6 and 7.
- A similar mechanism involving a reversible C-H activation step was also proposed in the previously reported C-H borylation reaction of tertiary phosphines. See ref 14.



Ru-catalyzed regio- and site-selective ortho C-H borylation of phenols

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