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Ruthenium-Catalyzed *ortho* C–H Borylation of Arylphosphines

Kazuishi Fukuda[a], Nobuharu Iwasawa[a], and Jun Takaya*[a][b]

Abstract: Efficient, phosphine-directed *ortho* C–H borylation of arylphosphine derivatives was achieved using Ru catalysts for the first time. The reaction is applicable to various tertiary arylphosphine and arylphosphinite derivatives to give (*o*-borylaryl)phosphorus compounds in high yields. This reaction enables easy access to a variety of functionalized phosphine ligands and ambiphilic phosphine-boronate compounds, realizing new late-stage modification of phosphorus compounds.

Transition metal-catalyzed, phosphine-directed intermolecular C–H bond transformation of tertiary phosphines is a promising approach for design and synthesis of new phosphine compounds, which can be widely utilized in the field of organic synthesis, organometallic chemistry, and materials science.[1] However, such reactions have rarely been developed, and in particular, the phosphine-directed *ortho*-functionalization of arylphosphines, such as PPh_3, remained unexplored.[2] The difficulties of the phosphine-directed C–H functionalization stem from 1) deactivation of the catalysts by strong coordination of phosphines to transition metal complexes and 2) formation of unfavorable four-membered metallacycle intermediates in the case of *ortho*-functionalization of arylphosphines.[3] To overcome these problems, phosphine oxides and sulfides-directed reactions have been developed although an additional reduction step is required to access tertiary phosphines (Figure 1-a).[4,5] As a direct route, Clark reported Ir-catalyzed phosphine-directed sp^2C–H borylation of benzylphosphine and biarylphosphine derivatives with rather limited substrate scope (Figure 1-b).[6] Recently, Rh-catalyzed direct C–H arylation reactions of biarylphosphines and 1-naphthylphosphines were developed by Shi's and Yu and Che's groups.[7,8] However, these reactions occurred at γ- or δ-position of the directing $–PR_2$ group via five- or six-membered metallacycle intermediates, thus limiting the substrates to benzyl, biaryl, and 1-naphthyl derivatives.[9]

Herein we report the first example of phosphine-directed *ortho* C–H borylation of arylphosphines catalyzed by ruthenium complexes. The C–H borylation is the most suitable reaction for the late-stage modification of phosphines since the resulting C–B bonds can be transformed to various substituents and functional groups.[10] This reaction exhibited high efficiency and wide substrate generality, enabling easy access to a variety of functionalized phosphine ligands and ambiphilic phosphine-boronate compounds.

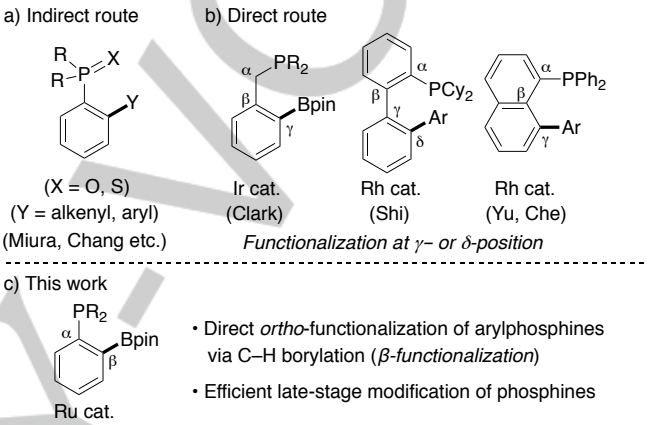

Figure 1. Phosphine-directed intermolecular C–H bond transformation of tertiary phosphines

It was found that *ortho*-borylation of triphenylphosphine with 1.0 equivalent of pinacolborane (HBpin) proceeded in the presence of various ruthenium complexes in *n*-octane at 150 ˚C (Table 1). The commercially available $[RuCl_2(p\text{-cymene})]_2$ turned out to be the best catalyst among tested to afford the *o*-borylphenyl(diphenyl)phosphine **1a** in 63% yield (Entry 7). The yield was further improved by carrying out the reaction in benzene at 100 ˚C with 1.1 equivalent of HBpin, giving **1a** in 80% yield after purification by silica gel column chromatography even with 0.5 mol% $[RuCl_2(p\text{-cymene})]_2$ (Entry 8).[11] The borylation occurred selectively at the *ortho*-position of one of the phenyl rings under the reaction conditions. Ru-catalyzed sp^2C–H borylation reactions have been rather rare and required pyridine, imine, or amide as directing groups.[12,13] It should be noted that the Clark's Ir-catalyst did not promote C–H borylation of PPh_3 at all,[6] thus demonstrating unique reactivity of the Ru catalyst.

This reaction is applicable to various arylphosphine derivatives (Table 2). Triarylphosphines bearing an electron-donating or -withdrawing substituent at the 4-position were smoothly borylated under the optimized conditions to afford the (*o*-borylphenyl)phosphine derivatives **1b-d** in good yields. It should be noted that various halogens and ester substituents were tolerated under the reaction conditions, giving functionalized triarylphosphine derivatives in 75-93% yields (Entries 4-7). The borylation of *meta*-substituted triarylphosphines proceeded at the less hindered position, *para* to the substituent, preferentially, affording **2a-c** in moderate to

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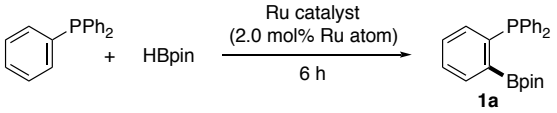
Table 1. Screening of reaction conditions.



1a

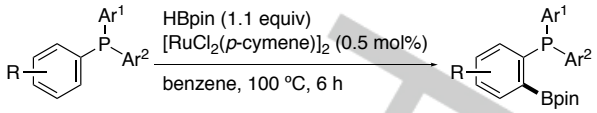
Entry	Ru catalyst	Conditions[a]	Yield[b]
1	None	A	0%
2	$RuCl_3•3H_2O$	A	trace
3	$Ru_3(CO)_{12}$[c]	A	35%
4	$(Cp^*RuCl_2)_n$	A	25%
5	$RuCl_2(dmso)_4$	A	50%
6	$[RuCl_2(cod)]_n$	A	59%
7	$[RuCl_2(p\text{-cymene})]_2$	A	63%
8	$[RuCl_2(p\text{-cymene})]_2$[d]	B	91% (80%)[e]

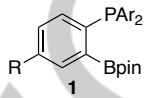
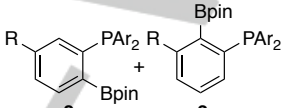
[a] Conditions A: HBpin (1.0 equiv) in *n*-octane at 150 ˚C. Conditions B: HBpin (1.1 equiv) in benzene at 100 ˚C. [b] NMR yield. [c] $Ru_3(CO)_{12}$ (2 mol%). [d] $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%). [e] Isolated yield.

good yields (Entries 8-10). Furthermore, this reaction can be applied not only to triarylphosphines but also to more electron rich $(alkyl)_n(aryl)_{3-n}$phosphines. The reaction of various alkyl(diphenyl)phosphines (alkyl = *i*Pr, Cy, *t*Bu, Et) afforded tertiary phosphines **4a-d** having three different substituents on phosphorus in moderate to good yields (Table 3, Entries 1-4). Borylation of diethyl(phenyl)phosphine also proceeded with 1.5 mol% of $[RuCl_2(p\text{-cymene})]_2$, giving diethyl(*o*-borylphenyl)phosphine **5a** in 37% yield (Entry 5). Notably, the reaction of phosphinite derivative, (–)-menthyl diphenylphosphinite, proceeded without problem to afford an (*o*-borylphenyl)phosphinite derivative **6** in good yield (dr = 50:50, Entry 6).

Next, the site-selectivity of this Ru-catalyzed C–H borylation was investigated with substrates having two different aryl moieties to be borylated. Diphenyl(1-naphthyl)phosphine reacted at one of the two phenyl rings, not at the 8-position of the naphthyl group, to give the *ortho*-borylation product **7** selectively in 73% yield (Scheme 1-a). The borylation of 2-biphenyl(diphenyl)phosphine also proceeded at the phenyl group to give **8** although the catalyst efficiency was not satisfactory due to large steric repulsion (Scheme 1-b). These results demonstrated different regioselectivity from that reported in the Rh-catalyzed C–H arylation reactions.[7,8] On the other hand, the reaction of benzyl(diphenyl)phosphine proceeded smoothly at the benzyl group to give benzyl(2-borylbenzyl)phenylphosphine **9** in 74% yield (Scheme 1-c). Notably, the Ru-catalyst enabled double borylation at 2,6-position of the benzyl group to give **10** in 82% yield by using 3 equivalent of HBpin.[14] Therefore, the site-selectivity for the

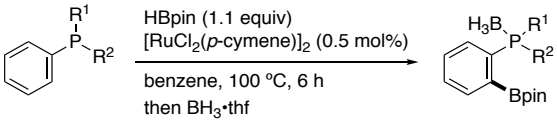
Table 2. Borylation of triarylphosphines.

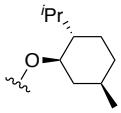


Entry	Product	R	Yield
1[a]		Me **1b**	83%
2		CF_3 **1c**	quant.
3		MeO **1d**	79%[b]
4	**1**	F **1e**	84%
5	(Ar = 4-RC_6H_4)	Cl **1f**	93%
6		Br **1g**	75%
7		COOMe **1h**	87%
8[a]		Me **2a**	91% (0%)[c]
9		Cl **2b**	57% (6%)[c]
10	**2** **3**	MeO **2c**	54% (8%)[c]
	(Ar = 3-RC_6H_4)		

[a] HBpin (1.5 equiv). [b] Isolated after BH_3-protection. [c] Yield of isomer **3** was shown in the parenthesis.

Table 3. Borylation of other phosphines and phosphinites.



Entry	R^1	R^2		Yield
1[a]	Ph	*i*Pr	**4a**	62%
2	Ph	Cy	**4b**	50%
3[b]	Ph	*t*Bu	**4c**	32%
4[a]	Ph	Et	**4d**	32%
5[b]	Et	Et	**5a**	37%
6[c]	Ph		**6**	68%[d]

[a] HBpin (1.5 equiv). [b] $[RuCl_2(p\text{-cymene})]_2$ (1.5 mol%), HBpin (1.5 equiv). [c] In *n*-octane at 150 ˚C. [d] dr = 50:50.

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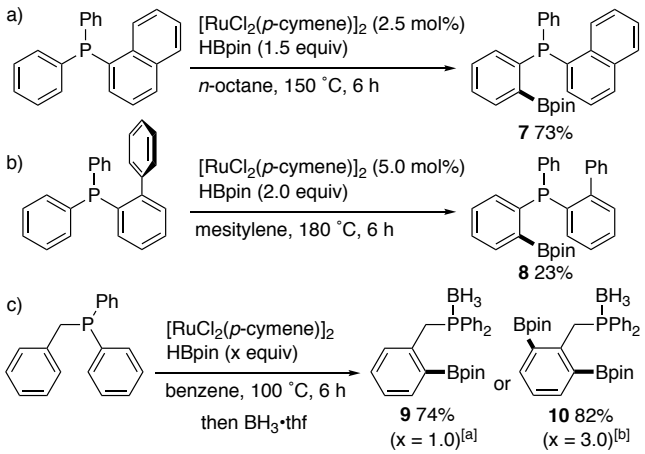
Ru-catalyzed borylation is demonstrated as benzyl > phenyl >> 2-biphenyl, 1-naphthyl. Further investigation on the origin of the site-selectivity is underway and will be reported in due course.



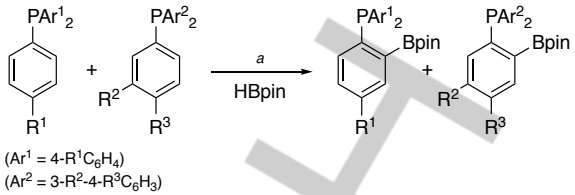
[a] $[RuCl_2(p\text{-cymene})]_2$ (1.0 mol%), HBpin (1.0 equiv), benzene, 100 ˚C, 6 h. [b] $[RuCl_2(p\text{-cymene})]_2$ (3.0 mol%), HBpin (3.0 equiv), benzene, 100 ˚C, 6 h.

Scheme 1. Site-selectivity for the C–H borylation.

To shed light on the mechanism, the effect of electronic nature of triarylphosphines on the reactivity was investigated. A set of competition experiments among PPh_3, $P(4\text{-}CF_3C_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$, and $P(3\text{-}MeOC_6H_4)_3$ revealed that the reaction was faster with $P(4\text{-}CF_3C_6H_4)_3$ > $P(4\text{-}MeOC_6H_4)_3$ > PPh_3 > $P(3\text{-}MeOC_6H_4)_3$ (Table 4). These results suggested that the electronic nature of the phosphorus atom did not affect the reactivity, and the reaction rate increased as the *ortho*-carbon to be borylated became electron deficient. On the other hand, deuterium labeling experiments with $PPh_3/P(C_6D_5)_3$ exhibited a KIE of 2.0 from two parallel reactions and 2.2 from an intermolecular competition (Scheme 2-a and 2-b). An intramolecular KIE was also observed in the reaction of $PPh_2(C_6D_5)$ (k_H/k_D = 1.3, Scheme 2-c). Furthermore, H/D exchange at the *ortho*-position of $P(C_6D_5)_3$ was observed with HBpin, thus suggesting that the C–H activation step is reversible (Scheme 2-d). These results support that the C–H activation could be involved as a pre-equilibrium before a rate-determining step.[15] The substituent effect demonstrated in Table 4 can be partly explained as the pre-equilibrium C–H activation is accelerated by the electron deficient *ortho*-carbon although the rate-determining step is not clear yet.[16] Further investigation on the reaction mechanism through detailed kinetic studies and characterization of intermediates is in progress.

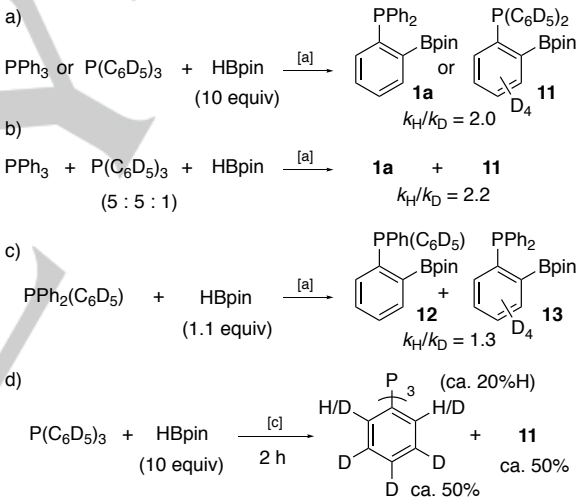
Finally, transformation of the borylation product enabled easy access to various tertiary phosphines (Scheme 3). Oxidation of the C–B bond of BH_3-protected **1a** with H_2O_2 afforded (*o*-hydroxyphenyl)phosphine derivative **14** quantitatively. Bench-stable trifluoroborate **15** was obtained by the treatment of **1a** with KHF_2.[17] Moreover, Pd-catalyzed cross coupling reaction of boronic acid **16** with PhI proceeded using SPhos as a ligand

Table 4. Competition Experiments.



Entry	R^1	R^2	R^3		Yield[b]
1	H	H	CF_3	**1a** 18%	**1c** 76%
2	H	H	MeO	**1a** 16%	**1d** 53%
3	CF_3	H	MeO	**1c** 64%	**1d** 16%
4	H	MeO	H	**1a** 52%	**2c** 14%

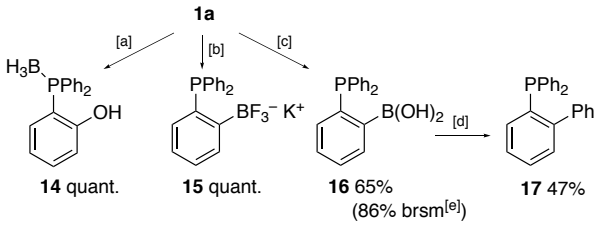
[a] PAr^1_3:PAr^2_3:HBpin=5:5:1, $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol% relative to the amount of HBpin), benzene, 100 ˚C, 6 h. [b] NMR yield in the crude products.



[a] $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%), benzene, 100 ˚C, 6 h. [b] $[RuCl_2(p\text{-cymene})]_2$ (1.5 mol%), HBpin (10 equiv), $[D_6]$benzene, 100 ˚C, 2 h.

Scheme 2. Deuterium Labeling Experiments.

to give (*o*-biphenyl)diphenylphosphine **17** in 47% yield.[18] In addition to these derivatization, the (*o*-borylphenyl)phosphine derivatives themselves are also highly useful as ambiphilic phosphine-boronate compounds, which have been reported to exhibit unique reactivity for small molecule activation and catalysis.[19,20] These strategies, the direct borylation of easily available phosphines and transformation of the resulting C–B bond, would expand structural diversity of tertiary phosphines, leading to their new utilization in synthetic chemistry.



[a] 1) BH_3•thf, 2) H_2O_2, NaOH aq., rt, 12 h. [b] KHF_2, MeOH, rt, 3 h. [c] $(HOCH_2CH_2)_2NH$, Et_2O, rt, 18 h. [d] $Pd(dba)_2$ (10 mol%), SPhos (12 mol%), PhI (1.5 equiv), K_3PO_4 (1.5 equiv), 1,4-dioxane, 100 ˚C, 6 h. [e] Based on recovered starting material.

Scheme 3. Transformation of **1a**.

In conclusion, we have developed Ru-catalyzed, phosphine-directed *ortho* sp^2C–H borylation of arylphosphines for the first time.[21] The high efficiency and wide substrate generality enabled easy access to various tertiary (*o*-borylphenyl)phosphines, which are highly useful as precursors to various functionalized phosphines and ambiphilic phosphine-boronate compounds. These results demonstrated unique reactivity of the Ru-catalyst for C–H borylation distinct from Ir. Further utilization of the borylated tertiary phosphines are underway in our group.

Acknowledgements

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Keywords: Phosphine • C–H activation • Borylation • Ruthenium • Late-stage modification

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[11] CAUTION! This reaction should be conducted inside an explosion-proof wall. This is performed in a sealed glass tube at 100 ˚C which is over the boiling point of benzene, and H_2 is generated during the reaction.

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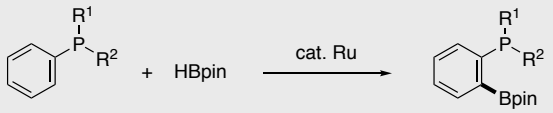
Layout 2:

COMMUNICATION



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Ruthenium-catalyzed *ortho* C–H Borylation of Arylphosphines

Efficient, phosphine-directed *ortho* C–H borylation of arylphosphine derivatives was achieved using Ru catalysts. The reaction is applicable to various tertiary arylphosphine and arylphosphinite derivatives to give (*o*-borylaryl)phosphorus compounds in high yields. This reaction enables easy access to a variety of functionalized phosphine ligands and ambiphilic phosphine-boronate compounds, realizing new late-stage modification of phosphorus compounds.