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Rhodium-Catalyzed Borylation of Aryl 2-Pyridyl Ethers through Cleavage of the Carbon−Oxygen Bond: Borylative Removal of the Directing Group

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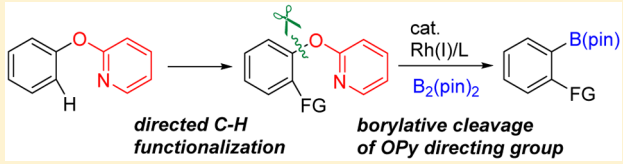
Supporting Information

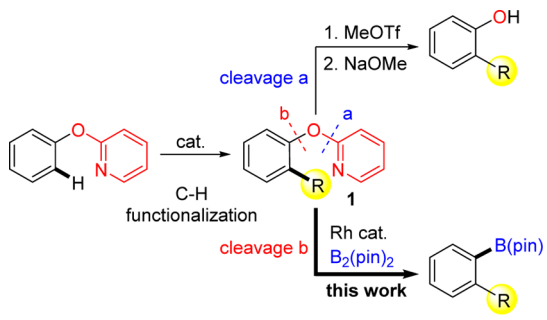
ABSTRACT: The rhodium-catalyzed reaction of aryl 2-pyridyl ethers with a diboron reagent results in the formation of arylboronic acid derivatives via activation of the C(aryl)−O bonds. The straightforward synthesis of 1,2-disubstituted arenes was enabled through catalytic ortho C−H bond functionalization directed by the 2-pyridyloxy group followed by substitution of this group with a boryl group. Several control experiments revealed that the presence of a sp^2 nitrogen atom at the 2-position of the substrate and the use of a boron-based reagent were crucial for the activation of the relatively inert C(aryl)−O bond of aryl 2-pyridyl ethers.



INTRODUCTION

Transition-metal-catalyzed transformation of C−H bonds has emerged as a powerful synthetic method, because it eliminates the need for preactivation of the starting materials.[1,2] Although the ubiquitous nature of C−H bonds makes this strategy highly versatile, this ubiquity results in a regioselectivity issue: which C−H bond reacts. Although the regioselectivity has often been controlled by the differentiation in the electronic and steric nature of the C−H bonds, these factors are substrate-dependent.[1] An alternative way to realize regioselective C−H functionalization involves the use of a directing group.[2,3] Metal-coordinating groups, such as ketones, amides, esters, nitriles, and alcohols, have been used as directing groups, which control the regioselectivity by forming stable metallacyclic intermediates. Among these metal-coordinating groups, the pyridine ring is a frequently used motif, and 2-phenylpyridine is a privileged substrate for investigating new ortho C−H bond functionalization reactions.[4,5] The utility of the 2-pyridyl moiety is attributable in part to the strong coordination ability of the sp^2 nitrogen atom and its stability under various transition-metal-catalyzed conditions. Despite the outstanding performance of 2-phenylpyridine substrates in C−H bond functionalization reactions, the utility of the products is severely limited because it is nontrivial to remove and functionalize the 2-pyridyl moiety. To overcome this limitation, several modified 2-pyridyl groups have been developed.[6] The 2-pyridylsilyl group is a suitable directing group in several catalytic ortho C−H transformations, and can subsequently be converted to a reactive group, such as a halide.[7] However, introduction of this useful directing group requires the tedious preparation of organosilicon compounds. 2-Aminopyridine can also serve as a removable directing group,[8−10] although the aniline product requires activation, such as diazotization, for further elaboration. Perhaps the most useful metal-coordinating group is 2-pyridyloxy (OPy), which serves as an excellent ortho directing group in a number of C−H bond functionalization reactions[11] and can subsequently be removed. The only available method to remove the pyridine ring in 2-OPy involves (1) *N*-methylation and (2) cleavage of the C(pyridinium)−O bond by NaOMe to give the corresponding phenol (Scheme 1, cleavage a).[11c] Although the development of this method has significantly increased the synthetic utility of the OPy directing group, several aspects of the method require improvement: (1) the use of a strong methylating reagent and a strong base limits applicable functional groups, (2) the protocol for the removal of the pyridine ring requires two steps, and (3) an additional

Scheme 1. 2-Pyridyloxy Group as an Ortho Directing Group in C−H Bond Functionalization and Its Subsequent Derivatization



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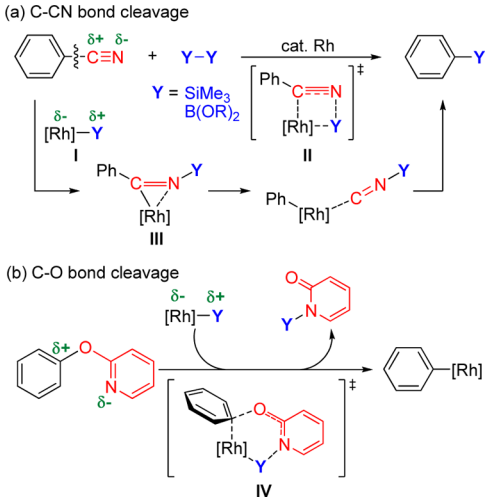
step is required for further elaboration of phenols (e.g., conversion to triflates). In this Article, we report a new method for the conversion of the OPy group by substituting the OPy group with a synthetically useful boryl group in a single step and in a catalytic manner (Scheme 1, cleavage b).[12] In this reaction, the relatively electron-rich C(aryl)−O bond in ether **1** is selectively cleaved over the electron-deficient C(pyridyl)−O bond.[13,14] This borylation proceeds under neutral conditions and is operationally simple.

RESULTS AND DISCUSSION

Previously, we developed a series of rhodium-catalyzed transformation reactions of nitriles through the cleavage of the C−CN bonds in the presence of organosilicon[15] or diboron[16] reagents. Stoichiometric[17] and theoretical studies[18,19] revealed that the silylrhodium or borylrhodium species **I** (depicted as [Rh]−Y) generated in situ mediates the cleavage of the C−CN bond through iminoacyl intermediate **III** (Scheme 2a).[20] The key feature of catalytically active species

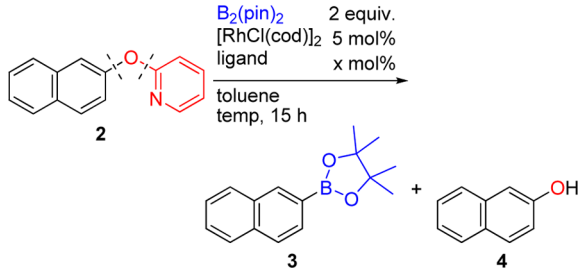
Scheme 2. Mechanism of Silylrhodium- or Borylrhodium-Mediated C−CN Bond Cleavage and Working Hypothesis for Application to C−O Bond Cleavage



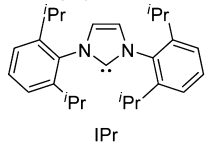
I is the Lewis acid nature of the silyl[21,22] or boryl ligand,[23,24] which favors binding to the Lewis base nitrogen of the cyano group in transition state **II**. This polarity-driven interaction allows for the formation of iminoacyl intermediate **III**, which eventually results in the cleavage of the carbon−carbon bond. These mechanistic considerations led us to hypothesize that the unique polarity of **I** could be applied to the activation of the C−OPy bond via cyclic transition state **IV**, in which the boron−nitrogen interaction facilitates the otherwise difficult C−O bond cleavage (Scheme 2b).

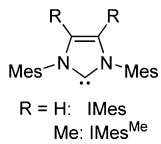
We began our study by investigating the reaction of aryl pyridyl ether **2**, which was easily prepared from 2-naphthol and 2-bromopyridine, with bis(pinacolato)diboron ($B_2(pin)_2$) in the presence of a rhodium(I) catalyst (Table 1). Pleasingly, it was found that the use of the rhodium(I) catalyst in conjunction with PPh_3 gave arylboronate **3** via the cleavage of the C(sp^2)−O bond (Table 1, entry 1). Considering the widespread use of the OPy group as a directing group in C−H bond activation reactions,[11] it is notable that the ortho C−H bonds remained unchanged under these conditions. However, the conversion of **2** was low (54%), and the selectivity of the

Table 1. Optimization Study of the Borylation of 2[a]



entry	ligand (mol %)	temp (°C)	NMR yields (%) 3	4	2
1	PPh_3 (30)	130	26	9	46
2	$P(4\text{-}MeOC_6H_4)_3$ (30)	130	35	9	37
3[b]	$P(4\text{-}MeOC_6H_4)_3$ (30)	130	30	35	16
4	PCy_3 (30)	130	65	0	0
5	PCy_3 (30)	100	89	0	0
6	PCy_3 (30)	80	4	0	89
7	IPr (20)	130	33	2	4
8	IMes (20)	130	70	0	0
9	IMes(10)	130	36	0	0
10	IMes (20)	100	27	0	72
11	$IMes^{Me}$ (20)	130	59	0	0


IPr



[a]Reaction conditions: **2** (0.50 mmol), $B_2(pin)_2$ (1.0 mmol), $[RhCl(cod)]_2$ (0.025 mmol), ligand, toluene (0.50 mL) for 15 h. [b]Bis(neopentylglycolato)diboron was used instead of $B_2(pin)_2$.

cleavage of the two C−O bonds was moderate (**3**:**4** = 3:1). Attempts to improve the reactivity and selectivity by introducing electron-donating or -withdrawing groups on the pyridine ring and by replacing the 2-pyridyl moiety with other nitrogen-containing heteroaromatics were unsuccessful.[25]

Next, we turned our attention to the effect of the ligand. It was found that the use of a more electron-rich phosphine ligand was better in terms of both conversion and selectivity (Table 1, entry 2). The selectivity dramatically decreased when bis(neopentylglycolato)diboron was used in place of $B_2(pin)_2$ (entry 3). When the reaction was performed using PCy_3 as the ligand, the highest conversion was achieved, and **3** was obtained as the only product (entry 4). Further improvement in the yield was achieved by decreasing the temperature to 100 °C, with **3** being formed in 89% yield (entry 5). The use of *N*-heterocyclic carbene (NHC) ligands, such as IMes, was also effective for selectively forming **3**, although the yield was slightly lower than that obtained with PCy_3 (entry 8).

Having identified PCy_3 as the optimal ligand for the rhodium-catalyzed borylative cleavage reaction of **2**, we next applied the optimized protocol to other substrates. However, unfortunately, the optimized conditions in Table 1 were ineffective for several other less reactive substrates. For example, the borylation of pyridyl ether **5** using the PCy_3 ligand did not give borylated product **6** (Table 2, entry 1). This prompted us to reinvestigate the reaction conditions for less reactive substrates, such as **5**. Inspired by the result that the use of IMes gave the borylated product in 22% yield (entry 3), we focused on modification of the IMes ligand. Introduction of

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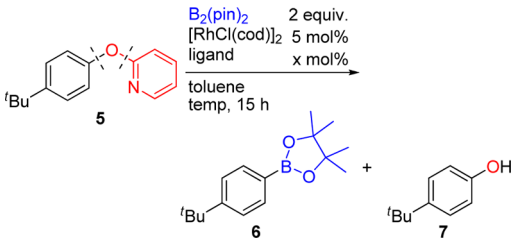
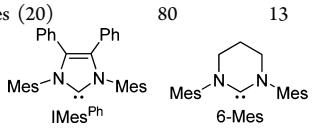
Table 2. Optimization Study of the Borylation of 5[a]



			NMR yields (%)		
entry	ligand (mol %)	temp (°C)	6	7	5
1	PCy_3 (30)	100	0	38	21
2	PCy_3 (30)	130	18	34	30
3	IMes (20)	130	22	3	7
4	IMes (20)	100	0	0	99
5	$IMes^{Me}$ (20)	130	77	0	0
6[b]	$IMes^{Me}$ (20)	130	76	0	0
7	$IMes^{Me}$ (20)	100	31	0	54
8	$IMes^{ph}$ (20)	130	56	0	0
9	6-Mes (20)	130	15	4	1
10	6-Mes (20)	80	13	2	15



[a]Reaction conditions: **5** (0.50 mmol), $B_2(pin)_2$ (1.0 mmol), $[RhCl(cod)]_2$ (0.025 mmol), ligand, toluene (0.50 mL) for 15 h. [b]$[RhCl(C_2H_4)_2]_2$ was used as the Rh source.

substituents at the 4- and 5-positions of the imidazolidene core of IMes dramatically improved the yield of **6** (entries 5–8). Among the substituted IMes ligands, $IMes^{Me}$[26] was found to be optimal, with **6** being obtained in 77% yield with no **7** being generated (entry 5). A similar result was also obtained when $[RhCl(C_2H_4)_2]_2$ was used as the catalyst precursor (entry 6). Other NHC ligands containing a six-membered framework were ineffective for this borylation reaction (entries 9 and 10).

With the two different sets of conditions (condition A, PCy_3, 100 °C; condition B, $IMes^{Me}$, 130 °C), we then investigated the scope of the rhodium-catalyzed borylation reaction using a variety of aryl pyridyl ether substrates (Table 3). Condition B was successful for pyridyl ethers containing a range of functional groups, including simple ethers (entries 3, 4, and 22), fluorinated substituents (entries 5, 6, and 9), and amines (entry 17). It should be noted that this catalytic system exhibited excellent selectivity for reactions containing different C–O bonds. The Ar–OPy bond was exclusively borylated with the Ar–OMe (entry 3), Ar–OPh (entry 4), Ar–OPiv (entry 13), and Ar–$OCONMe_2$ (entry 15)[27] groups remaining completely intact under these catalytic conditions, although all of the latter C–O bonds have been reported to be reactive toward nickel-catalyzed reactions.[28] Condition B proved to be unsuitable for substrates containing carbonyl functionalities (entries 12, 14, 16, and 36). This issue was addressed by using condition A, which allows for the borylation of pyridyl ethers containing esters (entries 11 and 13), carbamates (entries 15 and 34), and amides (entry 35). This borylation reaction was found to be relatively sensitive to steric effects: ortho substituted substrates gave the corresponding products in relatively lower yields (entries 18 and 20). The decrease in the yields of the borylated products was found to be due to the formation of a reductive cleavage product.[25] These results indicate that an ortho substituent does not significantly inhibit the C(aryl)–O activation process but rather retards the subsequent oxidative addition of $B_2(pin)_2$ (**D** → **F** in Scheme 4, below). To accelerate this step, we designed a new NHC ligand that should serve as a stronger σ-donor than $IMes^{Me}$. As a result, a methoxy-substituted analogue $IMXy^{Me}$ was found to be a better ligand for ortho-substituted substrates.[25] Under the reoptimized conditions using $IMXy^{Me}$ (condition C), the yields from substrates **19** and **20** were increased to 63% (entry 19) and 70% (entry 21), respectively. Although ketones and aldehydes were incompatible in this catalytic system, the use of an acetal protecting group (entry 25) allows application to such substrates. A range of heteroaromatic substrates, including quinoline (entry 28), indole (entry 31), carbazole (entry 32), and thiophene (entry 33), successfully underwent the borylation reaction. This protocol can also be applied to complex molecules derived from tyrosine (entry 34) and proline (entry 35). In addition, the $C(sp^3)$–OPy bond in benzyl alcohol derivatives can be activated in this Rh/diboron system (entries 37 and 39).

Because aryl 2-pyridyl ethers can be readily obtained from the corresponding phenol and 2-bromopyridine, and can readily undergo a number of ortho C–H bond functionalization reactions, the present borylation should provide a new strategy for the synthesis of a range of 1,2-disubstituted arenes from simple phenol derivatives (Scheme 3). For example, the ruthenium-catalyzed reaction of **15** with ethyl acrylate[11g] followed by hydrogenation gave ortho alkylated product **33**, which can be borylated via the loss of a OPy group to form arylboronate **34**. Similarly, introduction of an ortho aryl group via ruthenium catalysis[11d] followed by borylation via rhodium catalysis allows for the straightforward synthesis of 2-arylphenylboronic acid derivatives starting from phenol. The OPy directing group can also promote ortho alkoxylation by palladium catalysis to form **37**,[11k] which eventually leads to the borylated product **38** using our method. When the palladium-catalyzed reaction was performed in a carbon monoxide atmosphere, an ester group could also be installed at the ortho position to form **39**.[11j] The OPy moiety was again converted to the boryl group under the same rhodium-catalyzed conditions to give **40**. Thus, highly functionalized arylboronates, such as **34**, **36**, **38**, and **40**, can be synthesized and serve as useful building blocks that are amenable to further elaboration.[29] For example, compound **40**, which contains an ortho ester group, can be annulated with alkyne to form indenone derivative **41** in a single step under palladium catalysis.[30]

The elementary steps involved in the present rhodium-catalyzed borylation of aryl 2-pyridyl ethers are outlined in Scheme 4. The chlororhodium(I) precursor **A** initially generates borylrhodium(I) species **C** via the sequence of oxidative addition of $B_2(pin)_2$/reductive elimination of ClB(pin).[19b] Borylrhodium(I) complex **C** subsequently mediates the activation of the C(aryl)–O bond in the aryl 2-pyridyl ether, which should lead to the formation of arylrhodium(I) complex **D**, along with *N*-boryl-2-pyridone **E** or its tautomer **E′**.[31] 2-Hydroxypyridine, which can be formed by the hydrolysis of **E** or **E′**, was observed by ^1H NMR spectroscopy of the crude reaction mixture (ca. 55%).[32] The intermediate **D** eventually forms a borylated product by the reaction with $B_2(pin)_2$ with concomitant regeneration of borylrhodium **C**. The process of the generation of the catalytically active species (**A** → **B** → **C**) and the process of product formation and

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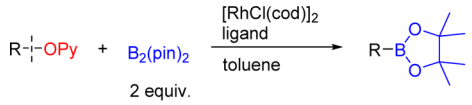
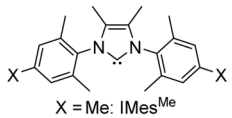
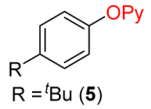
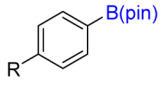
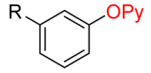
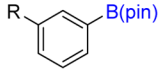
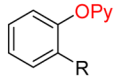
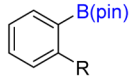
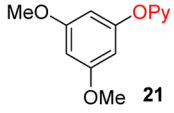
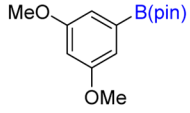
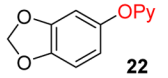
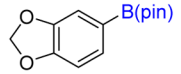
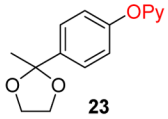
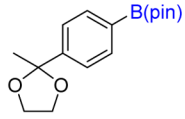
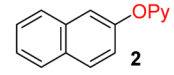
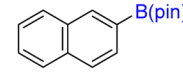
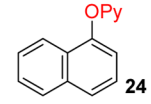
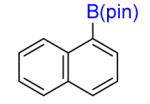
Table 3. Rh-Catalyzed Borylation of Aryl Pyridyl Ethers with $B_2(pin)_2$



condition A: PCy_3, 100 °C
condition B: $IMes^{Me}$, 130 °C
condition C: $IMXy^{Me}$, 160 °C



entry	ether	product	condition[a]	yield (%)
				
1	R = ^{t}Bu (**5**)		B	77
2	Ph (**8**)		B	80
3	OMe (**9**)		B	68
4	OPh (**10**)		B	71
5	OCF_3 (**11**)		B	62
6	F (**12**)		B[b,c]	70
7	Cl (**13**)		A	21[d]
8			B	0
9	CF_3 (**14**)		A[e]	65
10			B	61
11	CO_2Et (**15**)		A[e]	75
12			B	30
				
13	R = OPiv (**16**)		A[b,e]	72
14			B	0
15	$OCONMe_2$ (**17**)		A[b,e]	66
16			B	0
17	NMe_2 (**18**)		B	68
				
18	R = Me (**19**)		B[f]	42
19			C	63
20	Ph (**20**)		B[f]	50
21			C	70
22			B	40
23			A[c,e]	53
24			B	30
25			B	60

entry	ether	product	condition[a]	yield (%)
26			A	89
27	**2**		B	59
28			A	61
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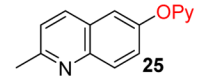
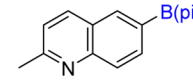
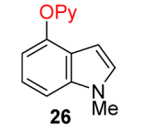
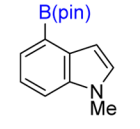
30			B	82
	25			
31			B	60
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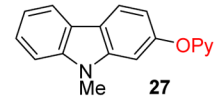
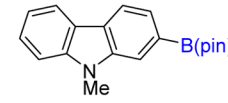
32			B	60
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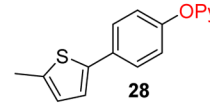
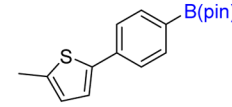
33			B[b,c]	65
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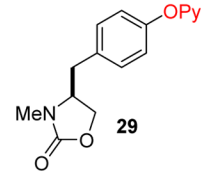
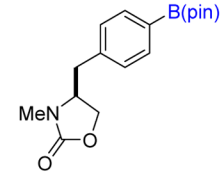
34			B	66
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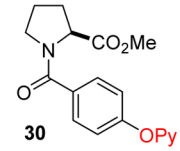
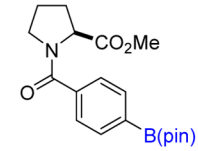
35			A	68
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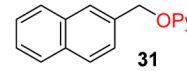
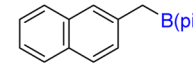
37			A	62
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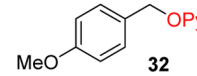
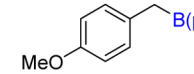
39			B	68
	32			

[a]Condition A: substrate (0.50 mmol), $B_2(pin)_2$ (1.0 mmol), $[RhCl(cod)]_2$ (0.025 mmol), PCy_3 (0.15 mmol), toluene (0.50 mL) for 15 h at 100 °C. Condition B: substrate (0.50 mmol), $B_2(pin)_2$ (1.0 mmol), $[RhCl(cod)]_2$ (0.025 mmol), $IMes^{Me}$ (0.10 mmol), toluene (0.50 mL) for 15 h at 130 °C. Condition C: substrate (0.50 mmol), $B_2(pin)_2$ (1.5 mmol), $[RhCl(cod)]_2$ (0.050 mmol), $IMXy^{Me}$ (0.20 mmol), toluene (0.50 mL) for 15 h at 160 °C. [b]3 equiv of $B_2(pin)_2$ was used. [c]Run for 48 h. [d]71% of substrate was recovered. [e]Run at 120 °C. [f]Run ar 160 °C.

catalyst turnover (**D** → **F** → **C**) are basically the same as those involved in the previously reported borylation reaction of nitriles, where the feasibility of these processes was demonstrated by computational studies.[19] Accordingly, the key issue is the mode of action of borylrhodium complex **C** in the C(aryl)−O bond activation step (**C** → **D**).

To gain insight into the mechanism for C(aryl)−O bond activation in the present catalytic reaction, several control experiments were performed. First, the rhodium-catalyzed reactions of the aryl 2-pyridyl ethers **2** and **5** were performed with either Si_2Me_6 or $PhB(OH)_2$ in place of $B_2(pin)_2$ to investigate whether the corresponding silyrhodium[15,22,33] or phenylrhodium[34] species can mediate the activation of a C(aryl)−O bond in a similar manner (Scheme 5). However, in all cases, none of the C(aryl)−O bond cleavage products were observed, and the starting material was quantitatively recovered.

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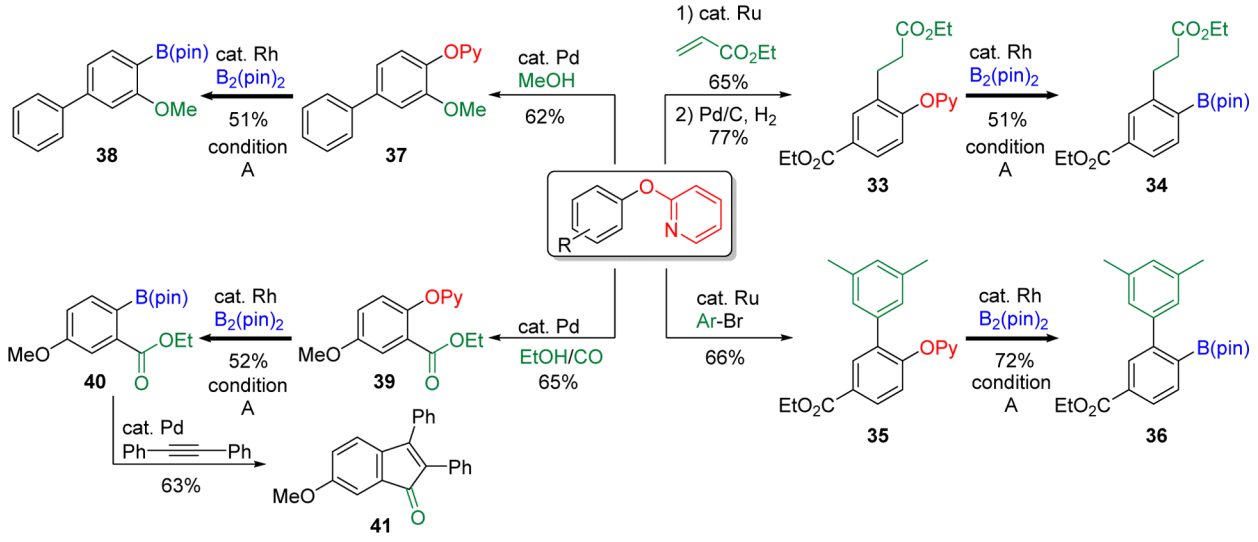
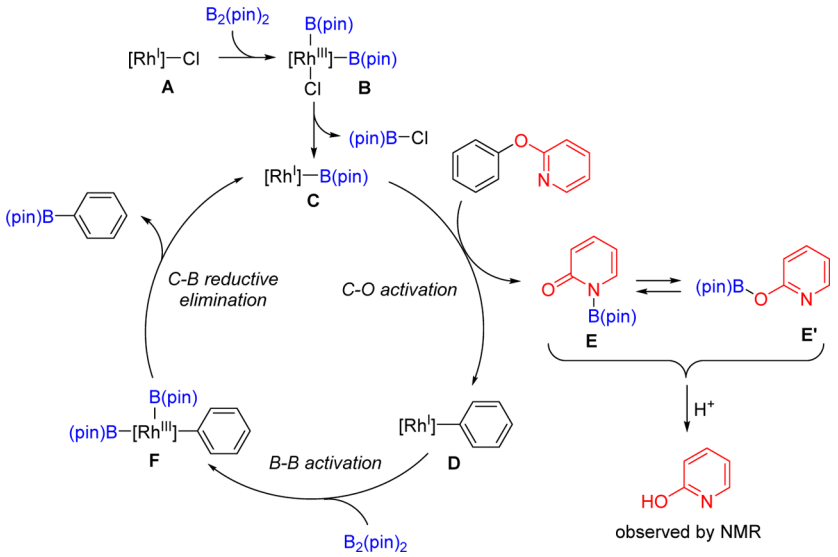
Scheme 3. Sequential Functionalization of Ortho C−H Bond/Borylation of Pyridyl Ethers



Scheme 4. Plausible Catalytic Cycle



These results clearly indicate that the boryl ligand on the rhodium center is crucial for the activation of aryl 2-pyridyl ethers. It was also confirmed that the reactions of the corresponding 4-pyridyl ethers **42** and **43** did not give the C(aryl)−O bond cleavage products, but rather resulted in cleavage of the C(4-pyridyl)−O bond to form 2-napthol and 4-*tert*-butylphenol, respectively (Scheme 6).[35] Moreover, no reaction occurred with conformationally restricted cyclic substrate **44** under the current optimized reaction conditions. These results suggest that the presence of a nitrogen atom at the appropriate position in the substrate is essential for the formation of the transition state for the desired C(aryl)−O bond activation.

Another interesting issue is the selectivity between the activation of an ortho C−H bond and C(aryl)−O bond. Despite a number of reported examples of ortho functionalization of aryl 2-pyridyl ethers using palladium[11b,c,f,h−k] and ruthenium[11a,d,g] catalysts, no ortho borylated products were observed with all substrates investigated under the current reaction conditions. Interestingly, deuterium incorporation at the ortho position was observed when the reaction was performed in toluene-d_8.[36,37] For example, the rhodium-catalyzed reaction of **5** with $B_2(pin)_2$ in toluene-d_8 was found to involve H/D exchange between the aromatic C−H bonds of **5** and **6** and the deuterated solvent (Scheme 7). At the time of 35% conversion of **5**, deuterium was incorporated at 17% and 28% of the ortho C−H bonds of **6** and the recovered substrate **5**, respectively. This observation indicates that activation of the ortho C−H bond by the rhodium catalyst did occur under the current reaction conditions. However, the rate of C−H activation was relatively slow compared with that for activation of the C(aryl)−O and C(pyridyl)−H bonds. Importantly, H/D exchange occurred to a similar extent when the reaction was performed in the absence of $B_2(pin)_2$. Thus, these non-productive C−H bond activation reactions were not mediated by borylrhodium species **C**, which is responsible for the desired borylation of the C(aryl)−O bond, but rather by a simpler rhodium species, such as RhCl(cod)(IMes^{Me}).[38]

On the basis of the above-mentioned control experiments and the observed H/D exchange, we believe that C(aryl)−O bond activation is initiated by the Lewis acid/base interaction between the boryl ligand and the 2-pyridyl moiety (Scheme

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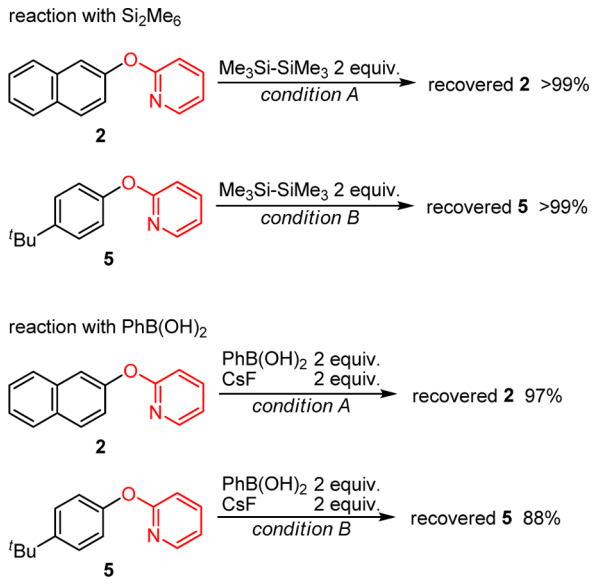
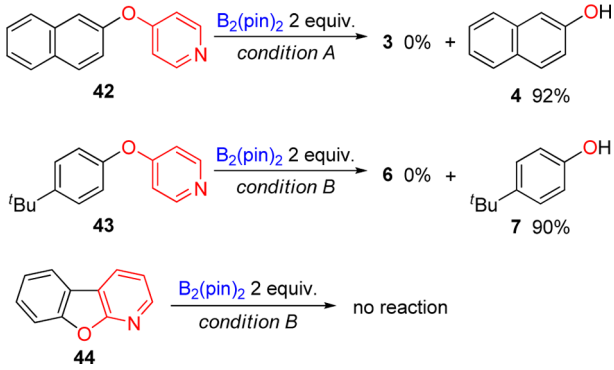
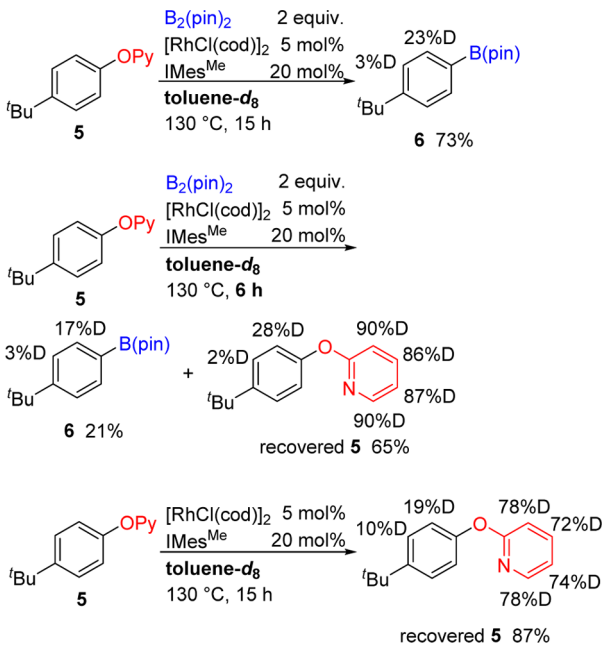
Scheme 5. Reaction with Silylrhodium and Phenylrhodium Species



Scheme 6. Control Experiments

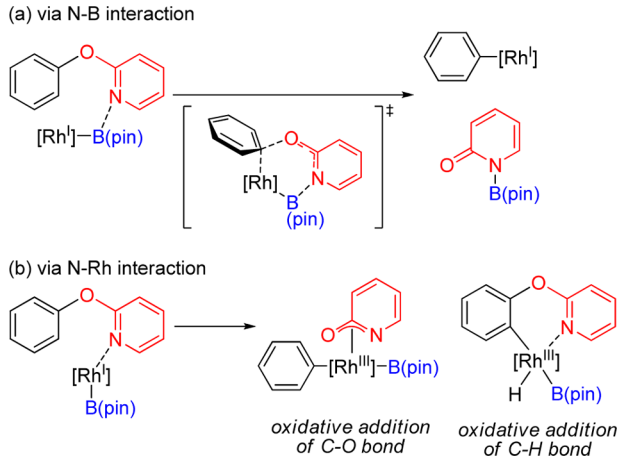


Scheme 7. H/D Exchange with Deuterated Solvent



8a).[39] This interaction not only brings the rhodium center close to the C(aryl)−O bond, but also makes the 2-pyridyloxy group

Scheme 8. Two Possible Mechanisms for the Cleavage of the Ar−OPy Bond



a better leaving group by imparting pyridinium-like character. Collectively, C(aryl)−O bond activation proceeds via a six-membered cyclic transition state, as we initially envisioned. However, we cannot completely exclude an oxidative addition pathway,[24c,d] which may be facilitated by the coordination of the pyridine ring to the rhodium center (Scheme 8b). This mode of coordination could also facilitate oxidative addition of an ortho C−H bond, which allows for the formation of a relatively stable six-membered metallacyclic intermediate. However, considering that ortho C−H bond activation is relatively slow compared with C(aryl)−O bond activation under the current reaction conditions, we prefer the possible mechanism shown in Scheme 8a over that shown in Scheme 8b.

CONCLUSIONS

We have developed a rhodium-catalyzed borylation reaction for aryl 2-pyridyl ethers through the selective cleavage of C(aryl)−OPy bonds. This reaction proceeds under neutral conditions and can be applied to a wide range of substrates that can be easily obtained from the corresponding phenol derivatives. Mechanistic studies revealed that this reaction was specifically catalyzed by a borylrhodium species, and the 2-pyridyl group plays a crucial role in the C(aryl)−O activation step. This method allows for the use of the OPy group as a convertible directing group in C−H bond activation reactions. Further investigation of new catalytic transformations using the unique polarity of borylrhodium(I) species, such as **C**, is currently underway in our laboratory.[40]

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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