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Tomohiro Yasuhisa, Koji Hirano,* and Masahiro Miura*

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Rhodium-Catalyzed Electrophilic Amination of Arylboronic Acids with Secondary Hydroxylamines

Tomohiro Yasuhisa, Koji Hirano,* and Masahiro Miura*
Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871

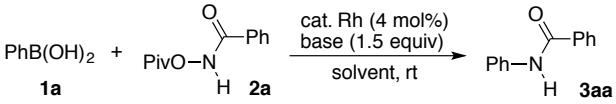
(E-mail: miura@chem.eng.osaka-u.ac.jp)

A rhodium(III)-catalyzed electrophilic amination of arylboronic acids with secondary hydroxylamines has been developed. The rhodium catalysis is compatible with heteroarylboronic acids as well as acyl and alkoxycarbonyl protecting groups on the nitrogen of *O*-acylhydroxylamines, and the corresponding secondary anilines are obtained in good to excellent yields.

Aryl- and heteroarylamines are prevalent motifs in many pharmaceutical targets, natural products, and functional materials.[1] The palladium-catalyzed amination of aryl (pseudo)halides with amines (Buchwald-Hartwig amination)[2] and copper-mediated oxidative coupling of arylboronic acids with amines (Chan-Lam coupling)[3] are representative powerful and convergent approaches to such important target structures. These processes are fundamentally based on the nucleophilic character of amine components (nucleophilic amination). On the other hand, the umpolung, electrophilic amination[4] of arylmetal reagents with chloro- and hydroxylamines has received significant attention as a unique alternative to the above nucleophilic amination reactions. Particularly, the catalytic electrophilic amination of arylboronic acids is quite attractive from the viewpoints of functional group compatibility, less toxicity, and commercial availability associated with the boronic acid derivatives. In 2012, our group[5] and Lalic[6] independently reported a copper-catalyzed electrophilic amination of arylboronates with *O*-benzoylhydroxylamines. Although the copper catalysis accommodated sterically and electronically diverse functional groups, the amination reagents were largely limited to tertiary hydroxylamines. Later, the research group of Lalic developed the second generation copper catalyst system, in which some secondary hydroxylamines could be employed; however, bulky substituents such as *i*-Pr and *t*-Bu groups and a higher reaction temperature (>60 ˚C) were still necessary.[6b] Moreover, the use of hydroxylamines with easily removal acyl and alkoxycarbonyl protecting groups on nitrogen still remains elusive. Liebeskind reported the electrophilic amination of arylboronic acids with such challenging secondary hydroxylamines, but a stoichiometric copper(II) salt was essential for a good conversion.[7] Thus, there still remains a large demand for further development of the catalytic electrophilic amination of arylboron reagents with acyl or alkoxycarbonyl substituted secondary hydroxylamines.[8,9] Herein, we report a rhodium(III)-catalyzed electrophilic amination of arylboronic acids with secondary *O*-acylhydroxylamines: the rhodium catalysis tolerates the above carbonyl-based protecting groups on the nitrogen, and the corresponding secondary anilines are obtained in good to excellent yields.

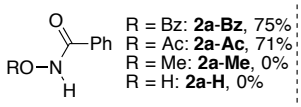
On the basis of recent advances in the rhodium-catalyzed amination of aromatic C–H bonds[10] and alkenylboronic acids,[11] we first focused on the potent activity of Cp*Rh(III) catalysts for the electrophilic amination of phenylboronic acid (**1a**) with *N*-benzoyl-*O*-pivaloyl secondary hydroxylamine **2a** as representative substrates (Table 1).[12] In an early experiment, treatment of **1a** (0.38 mmol) with **2a** (0.25 mmol) in the presence of $[Cp^*RhCl_2]_2$ (4 mol% Rh) and NaOAc (0.38 mmol) in MeOH at room temperature formed the corresponding secondary aniline **3aa** in 75% GC yield (entry 1). The choice of catalysts was critical: a common Rh(I) complex, $[RhCl(cod)]_2$ was totally ineffective (entry 2), while a cationic Rh(III) complex, $Cp^*Rh(MeCN)_3(SbF_6)_2$ showed comparable reactivity (entry 3). On the other hand, $Cp^*Rh(OAc)_2$ promoted the reaction even in the absence of the external base, albeit with lower efficiency (entry 4).[13] We next tested some inorganic bases. Several acetate-type bases accelerated the reaction (entries 5–8), with NaOPiv proving to be optimal (entry 7). Additional solvent screening (entries 9–11) found the combination of CsOAc and CH_2Cl_2 to be best, and the desired **3aa** was obtained in 99% isolated yield (entry 11). The use of $Cp^*Rh(OAc)_2$ could decrease the amount of CsOAc to 20 mol% albeit with somewhat lower efficiency (81% GC yield; entry 12). Some additional observations are to be noted: the use of *O*-benzoyl- and *O*-acetylhydroxylamines **2a**-**Bz** and **2a**-**Ac** also formed **3aa** in comparable yields, although no reaction occurred with *O*-methyl- and unprotected hydroxylamines **2a**-**Me** and **2a**-**H**; among other boronic acid derivatives tested, only triphenylboroxine afforded **3aa** in a synthetically useful yield.

Table 1. Optimization studies for rhodium-catalyzed electrophilic amination of phenylboronic acid (**1a**) with secondary hydroxylamine **2a**.[a]



Entry	Rh	Base	Solvent	Yield[b]/%
1	$[Cp^*RhCl_2]_2$	NaOAc	MeOH	75
2	$[RhCl(cod)]_2$	NaOAc	MeOH	trace
3	$Cp^*Rh(MeCN)_3(SbF_6)_2$	NaOAc	MeOH	63
4	$Cp^*Rh(OAc)_2$	none	MeOH	56
5	$[Cp^*RhCl_2]_2$	KOAc	MeOH	90
6	$[Cp^*RhCl_2]_2$	CsOAc	MeOH	83
7	**$[Cp^*RhCl_2]_2$**	**NaOPiv**	**MeOH**	**93**
8	$[Cp^*RhCl_2]_2$	CsOPiv	MeOH	92
9[c]	$[Cp^*RhCl_2]_2$	CsOAc	THF	76
10[c]	$[Cp^*RhCl_2]_2$	CsOAc	toluene	74
11[c]	**$[Cp^*RhCl_2]_2$**	**CsOAc**	**CH_2Cl_2**	**99 (99)**
12[d]	$Cp^*Rh(OAc)_2$	CsOAc	CH_2Cl_2	81

• yields of **3aa** under conditions of entry 1



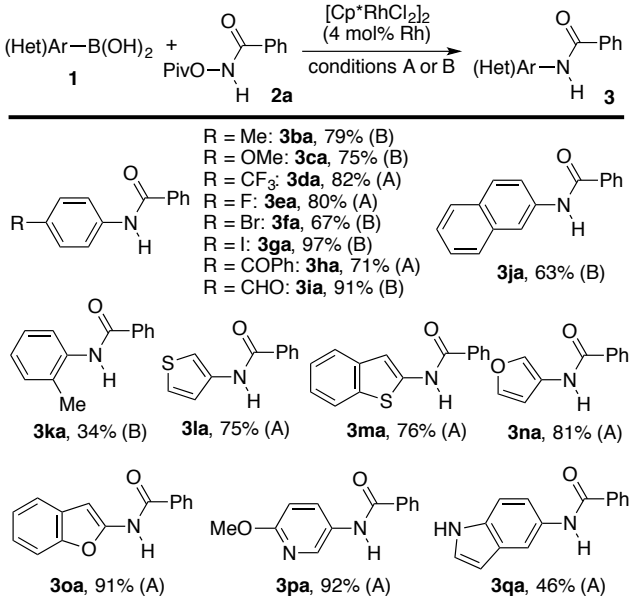
• yields of **3aa** under conditions of entry 11

PhBpin	PhBneo	PhB(MIDA)
0%	trace	0%

$PhBF_3K$	$(PhBO)_3$
9%	97%

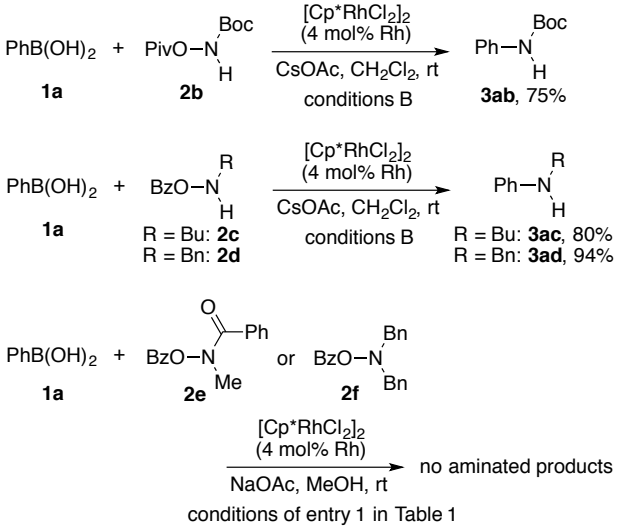
[a] Conditions: Rh catalyst (0.010 mmol on Rh), base (0.38 mmol), **1a** (0.38 mmol), **2a** (0.25 mmol), solvent (1.0 mL), r.t., 1–6 h, N_2. [b] Estimated by GC method. Isolated yield is in parentheses. [c] With 0.25 mmol of CsOAc. [d] With 0.10 mmol of CsOAc.

With the conditions of entries 7 and 11 in Table 1 (conditions A and conditions B, respectively), we subsequently performed the rhodium-catalyzed electrophilic amination of various arylboronic acids **1** with **2a**. Notably, the best conditions were highly dependent on the steric and electronic nature of the boronic acids; as a general trend, electron-neutral and -rich substrates coupled with **2a** more smoothly under conditions B, whereas electron-deficient and heteroaromatic systems necessitated conditions A for a satisfactory yield. Representative products are illustrated in Scheme 1. The $[Cp^*RhCl_2]_2$-based catalyst system was compatible with electronically diverse functional groups at the para position, including methyl, methoxy, trifluoromethyl, halogens, ketone, and aldehyde (**3ba**–**3ia**). Particularly, the aryl C–I bond completely retained (**3ga**), which can be a useful synthetic handle for further manipulations by conventional Pd-catalyzed cross-coupling reactions. The naphthalene moiety could also be employed (**3ja**). However, the more sterically demanding ortho methyl substituent decreased the reaction efficiency (**3ka**). Notably, several heteroaromatic substrates also underwent the electrophilic amination: thiophene, benzothiophene, furan, and benzofuran were equally aminated to deliver the corresponding *N*-benzoyl heteroarylamines **3la**–**3oa** in good to high yields. Furthermore, even more challenging pyridine- and N-unprotected indole boronic acids participated in the reaction, and **3pa** and **3qa** were isolated in 92% and 46% yields, respectively.



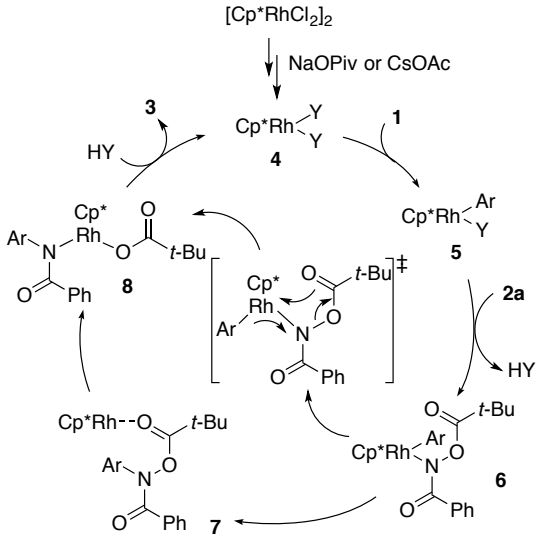
Scheme 1. Rhodium-catalyzed electrophilic amination of various (hetero)arylboronic acids **1** with secondary hydroxylamine **2a**. Isolated yields are shown. The conditions used (A or B) are in parentheses. Conditions A: $[Cp^*RhCl_2]_2$ (0.0050 mmol), NaOPiv (0.38 mmol), **1** (0.38 mmol), **2a** (0.25 mmol), MeOH (1.0 mL), r.t., 3–6 h, N_2. Conditions B: $[Cp^*RhCl_2]_2$ (0.0050 mmol), CsOAc (0.25 mmol), **1** (0.38 mmol), **2a** (0.25 mmol), CH_2Cl_2 (1.0 mL), r.t., 1–6 h, N_2.

The scope of hydroxylamines was also briefly investigated (Scheme 2). In addition to *N*-benzoyl **2a**, *N*-Boc-**2b** and *N*-alkylhydroxylamines **2c** and **2d** also reacted with phenylboronic acid (**1a**) under conditions B to form the corresponding secondary anilines in good yields. In contrast, tertiary hydroxylamines such as **2e** and **2f** afforded no detectable amount of aminated products.[14] These trends complement the precedented electrophilic amination by copper catalysis.[5–8]



Scheme 2. Rhodium-catalyzed electrophilic amination of phenylboronic acid (**1a**) with various hydroxylamines **2**.

Based on the above findings and literature information,[10-12,15] we are tempted to assume the reaction mechanism of **1** with **2a** as follows (Scheme 3). The catalyst precursor, $[Cp^*RhCl_2]_2$ is initially converted to an active rhodium acetate-type species **4** with the aid of NaOPiv or CsOAc. Subsequent transmetalation with **1** (**4** to **5**) is followed by an acetate-ligand-promoted proton abstraction from **2a** to form ArRh(III)-amide **6**. This process can be supported by the unsuccessful results with tertiary hydroxylamines **2e** and **2f** (Scheme 2). Then, C–N forming reductive elimination provides product-coordinated Rh(I) intermediate **7**. Oxidation of Rh(I) into Rh(III) via N–O bond oxidative addition (**7** to **8**) and release of product **3aa** upon protonolysis with HY regenerate the starting rhodium catalyst **4** to complete the catalytic cycle. However, an alternative mechanism including concerted C–N formation/N–O cleavage (**6** to **8**) cannot be completely excluded at present.



Scheme 3. Plausible mechanism. Y = OPiv or OAc.

In conclusion, we have developed a rhodium(III)-catalyzed electrophilic amination of arylboronic acids with secondary *O*-acylhydroxylamines. The rhodium catalysis is compatible with both acyl and alkyl substituents on the nitrogen of the hydroxylamines. These features complement the previous electrophilic amination catalysis based on copper.[5-8] Additionally, the reaction proceeds well even at room temperature and accommodates a diverse set of functionalized aromatic rings including halogen and carbonyl groups as well as generally challenging N-containing heterocycles.[16] Further development of related electrophilic amination reactions by rhodium catalysis is ongoing in our laboratory.

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