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# Ruthenium-catalyzed *ortho*-arylation of acetanilides with aromatic boronic acids: an easy route to phenanthridines and carbazoles

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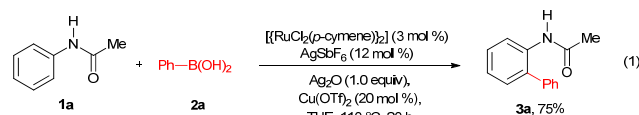
The highly regioselective *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of Ru(II) complex (3 mol %), AgSbF<sub>6</sub> (12 mol %), Cu(OTf)<sub>2</sub> (20 mol %) and Ag<sub>2</sub>O (1.0 eq) is described. Later, *ortho*-arylated acetanilides were converted into phenanthridine and carbazole derivatives by using Ph<sub>3</sub>PO and Tf<sub>2</sub>O or palladium or Cu(OTf)<sub>2</sub> catalyst.

*ortho*-Arylation of heteroatom substituted aromatics with aromatic electrophiles or organometallic reagents catalyzed by metal complexes via chelation-assisted C-H bond activation is one of the efficient method to synthesize biaryl derivatives.<sup>1</sup> Various chelating groups such as ketone, oxime, amide, acetamino (NH-COR), 2-pyridyl, cyano, ester, carboxylic acid and amine are efficiently used for the arylation reaction. Among them, acetamino (NH-COR) directed *ortho*-arylation of aromatics has gained much attention in organic synthesis.<sup>2-3</sup> Since, the derived *ortho*-arylated *N*-substituted anilines are key synthetic intermediates for various organic transformations and synthesizing heterocyclic moieties.<sup>2-3</sup> Metal-catalyzed *ortho*-arylation of acetamino directed aromatics with aromatic electrophiles has been extensively studied in the literature.<sup>2</sup> However, in the reaction of symmetrical acetanilides with aromatic electrophiles, a mixture of *mono*- and *di*-arylated acetanilides were observed. The diarylated compounds cannot be suppressed in the reaction, but, it can be suppressed by doing arylation using aromatic organometallic reagents.<sup>3-4</sup> Aromatic boranes, aromatic stannenes and aromatic silanes are commonly used arylating agents in the coupling reaction. Among them, organoborane reagents display multifarious advantages and the observed boron-derived byproducts are not harmful unlike other organometallic reagents.<sup>4</sup>

In 2007, Shi's group demonstrated *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of palladium complex.<sup>3a</sup> In the reaction, *N*-substituted anilides (Ph-NRCOR) showed good reactivity and selectivity. But, *N*-H free anilides (Ph-NHCOR) showed poor reactivity and selectivity with the formation of *N*-arylated anilide as a major by-product. Subsequently, the same group has reported *ortho*-arylation of *N*-H free anilides (Ph-NHCOR) with trialkoxy phenylsilanes in the presence of palladium complex.<sup>3b</sup> However, an excess amount of oxidants such as AgF (2.0 equiv) and Cu(OTf)<sub>2</sub> (2.0 equiv) were used and the availability of trialkoxy phenylsilanes is also limited. Recently, Lipshutz's group reported *ortho*-arylation of aryl ureas (Ph-NH-CONR<sub>2</sub>) with phenylboronic acids in the

presence of a cationic palladium complex.<sup>3c</sup> However, in the reaction of symmetrical aryl ureas with aromatic boronic acids, a minor amount of *di*-arylated compounds were observed.

Owing to the extraordinary reactivity and selectivity, [{RuCl<sub>2</sub>(*p*-cymene)}<sub>2</sub>] complex has been efficiently used as a catalyst for various C-H bond functionalization reactions.<sup>5-6</sup> Ru(II)-catalyzed arylation of 2-pyridyl, oxazoline, azole, amide and oxime substituted aromatics with aromatic electrophiles has been elaborately studied in the literature.<sup>5</sup> Very recently, we have reported a ruthenium-catalyzed *ortho*-arylation of benzamides with boronic acids.<sup>6a</sup> In the reported ruthenium-catalyzed arylation reactions, directing groups having a better coordinating nitrogen atom such as 2-pyridyl, oxime, oxazoline, azole and amide are explored. But, directing groups having a less coordinating oxygen atom are not explored. Herein, we wish to report a less coordination oxygen atom directed *ortho*-arylation of acetanilides with aromatic boronic acids in the presence of Ru(II) catalyst. The catalytic reaction was compatible with various functional groups such as electron-rich, electron-deficient and halogen substituted aromatic anilides and aromatic boronic acids. In the reaction, no diarylated products or *N*-arylated acetanilides were observed. Further, *ortho*-arylated anilides were converted into useful heteroaromatics such as phenanthridine and carbazole derivatives by using Ph<sub>3</sub>PO and Tf<sub>2</sub>O or palladium catalyst.<sup>7</sup>



Treatment of acetanilide (1a) with phenylboronic acid (2a) in the presence of [{RuCl<sub>2</sub>(*p*-cymene)}<sub>2</sub>] (3 mol %), AgSbF<sub>6</sub> (12 mol %), Ag<sub>2</sub>O (1.0 mmol) and Cu(OTf)<sub>2</sub> (20 mol %) in tetrahydrofuran (THF) at 110 °C for 20 h gave *ortho*-arylated anilide 3a in 75% isolated yield (eq. 1). The catalytic reaction is highly selective, only *mono*-arylation product was observed.

To optimize the arylation reaction, various additives, solvents and oxidants were examined in the reaction of 1a with 2a in the presence of [{RuCl<sub>2</sub>(*p*-cymene)}<sub>2</sub>] (3 mol %) at 110 °C for 20 h. First, the catalytic reaction was tested with various solvents such as THF, MeOH, AcOH, Toluene, DCE, DME, and DMF in the presence of catalyst, AgSbF<sub>6</sub> (12 mol %) and Ag<sub>2</sub>O (1.0 equiv). Among them, THF solvent was the best, providing coupling product 3a in 71% GC yield. The remaining solvents were totally ineffective. Next, the catalytic reaction was tested with various

oxidants such as Ag<sub>2</sub>O, AgOTf, AgOAc, AgF, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, oxone and Cu(OAc)<sub>2</sub>. Among them, Ag<sub>2</sub>O was very effective, giving **3a** in 71% GC yield. AgOTf, AgOAc and AgF were less effective, giving **3a** in 15, 10, and 5% GC yields, respectively. Remaining oxidants were totally ineffective. A variety of additives such as AgSbF<sub>6</sub>, AgBF<sub>4</sub>, AgOTf and KPF<sub>6</sub> were also tested. Among them, AgSbF<sub>6</sub> was very effective, giving **3a** in 71% GC yield. AgBF<sub>4</sub> and AgOTf were moderately effective, giving **3a** in 60% and 55% GC yields, respectively. But, KPF<sub>6</sub> was totally ineffective. Further, the reaction was tested with 1.0 equiv and 20 mol % of Cu(OTf)<sub>2</sub>. In the reaction, **3a** was observed 82 and 83% GC yields, respectively. It is believed that Cu(OTf)<sub>2</sub> increases the rate of C-H bond activation and stabilizes the active catalyst. The catalytic reaction was also tested without AgSbF<sub>6</sub>, only with Ag<sub>2</sub>O (1.0 equiv) and Cu(OTf)<sub>2</sub> (20 mol %). In the reaction, **3a** was observed in 68% GC yield.

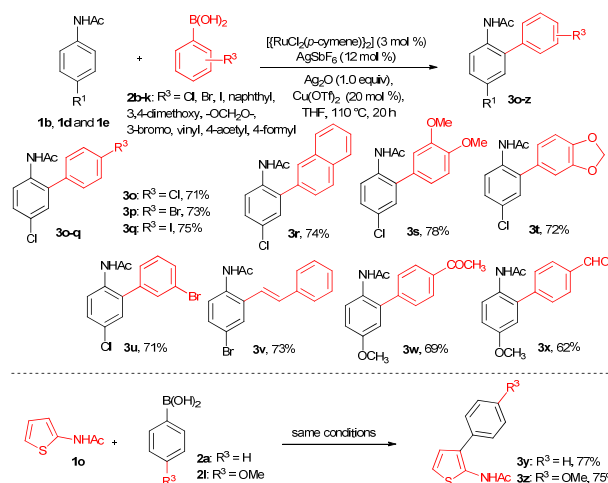
**Table 1** *ortho*-Arylation of anilides **1b-n** with phenylboronic acid (**2a**)<sup>d</sup>

Entry	<b>1b-n</b>	Product <b>3b-n</b>	Yield (%) <sup>b</sup>
1	<b>1b</b> : R <sup>1</sup> = OMe	<b>3b</b> : R <sup>1</sup> = OMe	71
2	<b>1c</b> : R <sup>1</sup> = Me	<b>3c</b> : R <sup>1</sup> = Me	73
3	<b>1d</b> : R <sup>1</sup> = Br	<b>3d</b> : R <sup>1</sup> = Br	75
4	<b>1e</b> : R <sup>1</sup> = Cl	<b>3e</b> : R <sup>1</sup> = Cl	76
5	<b>1f</b> : R <sup>1</sup> = F	<b>3f</b> : R <sup>1</sup> = F	73
6	<b>1g</b> : R <sup>1</sup> = CN	<b>3g</b> : R <sup>1</sup> = CN	68
7	<b>1h</b> : R <sup>1</sup> = NO <sub>2</sub>	<b>3h</b> : R <sup>1</sup> = NO <sub>2</sub>	65
8	<b>1i</b> : R <sup>1</sup> = CO <sub>2</sub> Me	<b>3i</b> : R <sup>1</sup> = CO <sub>2</sub> Me	70
9			72
10			76
11	<b>1l</b> : R <sup>2</sup> = Et	<b>3l</b> : R <sup>2</sup> = Et	59
12	<b>1m</b> : R <sup>2</sup> = <i>tert</i> -Bu	<b>3m</b> : R <sup>2</sup> = <i>tert</i> -Bu	5 <sup>c</sup>
13	<b>1n</b> : R <sup>2</sup> = CF <sub>3</sub>	<b>3n</b> : R <sup>2</sup> = CF <sub>3</sub>	0

<sup>a</sup>All reactions were carried out using **1b-n** (1.0 mmol), phenylboronic acid (**2a**) (1.5 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (3 mol %), AgSbF<sub>6</sub> (12 mol %), Ag<sub>2</sub>O (1.0 mmol) and Cu(OTf)<sub>2</sub> (20 mol %) in THF (3.0 mL) at 110 °C for 20 h. <sup>b</sup> Isolated yield. <sup>c</sup>GC yield.

To explore the scope of the arylation reaction, various substituted aromatic acetanilides **1b-n** were examined (Table 1). Thus, electron-donating and halo groups such as 4-methoxy, 4-methyl, 4-bromo, 4-chloro and 4-fluoro substituted acetanilides **1b-f** reacted efficiently with phenylboronic acid (**2a**) providing *ortho*-arylated acetanilides **3b-f** in excellent to moderate 71%, 73%, 75%, 76% and 73% yields, respectively (entries 1-5). Interestingly, a less reactive electron-withdrawing groups such as 4-cyano, 4-nitro and 4-methylester substituted acetanilides **1g-i** also efficiently participated in the coupling reaction, giving arylated products **3g-i** in 68%, 65% and 70% yields, respectively (entries 6-8). It seems the catalytic reaction is insensitive to the electronic effect of acetanilides. Next, the reaction was tested with unsymmetrical acetanilides such as 3-bromoacetanilide (**1j**) and 2-naphthylacetanilide (**1k**) with **2a**. In the reaction, coupling

products **3j** and **3k** were observed in 72% and 76% yields, respectively (entries 9 and 10). In the reaction, there are two *ortho* C-H bonds for arylation. Regioselectively, arylation takes place at a sterically less hindered side. Meanwhile, the effect of changing substituent on the *N*-group of anilides such as Et, *tert*-Bu and CF<sub>3</sub> instead of methyl was studied (entries 11-13). Ethyl **1l** and *tert*-Bu **1m** substituted anilides reacted with **2a** giving products **3l** and **3m** in 59% and 5% yields, respectively. CF<sub>3</sub> substituted anilide **1n** was not effective for the reaction.

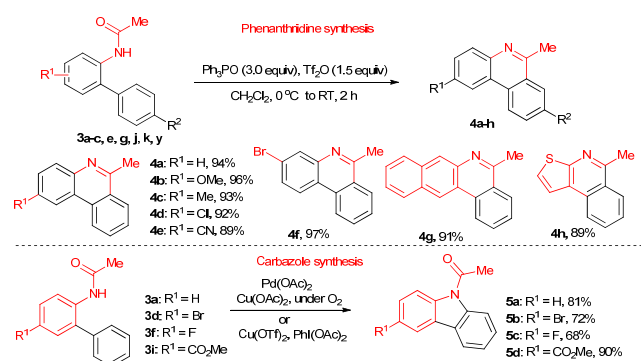


**Scheme 1** Scope of the aromatic boronic acids

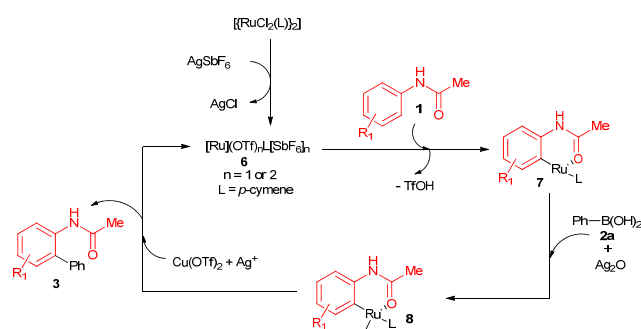
The present arylation reaction was successfully extended with substituted aromatic boronic acids **2b-l** (Scheme 1). Halogen groups such as 4-chloro, 4-bromo and 4-iodo substituted phenylboronic acids **2b-d** underwent coupling with **1e** giving coupling products **3o-q** in 71%, 73%, 75% yields, respectively. Nicely, sterically hindered 2-naphthylboronic acid (**2e**), 3,4-dimethoxyphenylboronic acid (**2f**) and 3,4-methylenedioxyphenylboronic acid (**2g**) yielded products **3r-t** in excellent 74%, 78%, 72% yields, respectively. 3-Bromophenylboronic acid (**2h**) was also nicely participated in the reaction, yielding product **3u** in 71% yields. Further, the coupling of 4-vinylphenylboronic acid (**2i**) with **1d** was tested. However, in the reaction, a Heck-type alkenylation product **3v** in 73% yield with the cleavage of boronic acid was observed. Interestingly, electron-deficient 4-acetylphenylboronic acid (**2j**) and 4-formylphenylboronic acid (**2k**) also reacted efficiently with 4-methoxyacetanilide (**1b**) affording coupling products **3w** and **3x** in 69% and 62% yields, respectively. It is important to note that a very sensitive functional groups such as I, Br, Cl, OR, COMe and CHO substituted phenylboronic acids were compatible for the reaction. The catalytic reaction was also tested with acetamino substituted heteroaromatic (Scheme 1). Thus, thiophen-2-acetamide **1o** underwent coupling with **2a** or 4-methoxyphenylboronic acid (**2l**) yielding arylation products **3y** and **3z** in excellent 77% and 75% yields, respectively.

To show the utility of *ortho*-arylated acetanilides **3** in organic synthesis, we have tried intramolecular cyclization of *ortho*-arylated acetanilides **3** in the presence of Ph<sub>3</sub>PO and Tf<sub>2</sub>O (Scheme 2).<sup>7a</sup> The intramolecular cyclization of **3a**, **3b**, **3c** and **3e** proceeded smoothly in the presence of Ph<sub>3</sub>PO and Tf<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C to r.t for 2 h, yielding phenanthridine derivatives

**4a-d** in 94%, 96%, 93% and 92% yields, respectively. Similarly, **3g, 3j** and **3k** underwent intramolecular cyclization under similar reaction conditions, giving **4e-g** in 89%, 97% and 91% yields, respectively. Nicely, *ortho* arylated thiophen-2-acetamide **3y** was also nicely participated in the reaction, giving product **4h** in excellent 89% yield (Scheme 2). Meanwhile, *ortho*-arylated acetanilides **3a, 3d, 3f** and **3i** were converted into carbazole derivatives **5a-d** in 81%, 72%, 68% and 90% yields, respectively, in the presence Pd(OAc)<sub>2</sub> (5 mol %) and Cu(OAc)<sub>2</sub> (1.0 equiv) under O<sub>2</sub> or Cu(OTf)<sub>2</sub> (5 mol %) and PhI(OAc)<sub>2</sub> (1.5 equiv).<sup>7b-c</sup> It is important to note that phenanthridine and carbazole scaffolds present in natural products and biologically active molecules.<sup>7a-c</sup>



**Scheme 2** Synthesis of phenanthridines and carbazole



**Scheme 3** Proposed mechanism

On the basis of known metal-catalyzed C- a plausible reaction mechanism is proposed in Scheme 3. The first step likely involves the removal of Cl ligand from Ru catalyst by AgSbF<sub>6</sub> providing a cationic ruthenium complex **6**. Coordination of the carbonyl oxygen of acetanilide **1** to the cationic ruthenium complex followed by *ortho*-metalation gives a ruthenacycle intermediate **7**. Transmetalation of phenylboronic acid (**2a**) into intermediate **7** in the presence of base AgO<sup>-</sup> provides intermediate **8**. Reductive elimination of intermediate **8** in the presence of Cu(OTf)<sub>2</sub> and Ag<sup>+</sup> affords product **3** and regenerates the active ruthenium species. In the reaction, Ag<sub>2</sub>O acts as an oxidant to oxidize the catalyst from Ru(0) to Ru(II) and base to cleave boronic acid moiety of **2**. It is believed that Cu(OTf)<sub>2</sub> plays an important role to regenerate the active catalyst in the presence of oxidant Ag<sup>+</sup>.

In conclusion, we have demonstrated a ruthenium-catalyzed *ortho*-arylation of acetanilides with aromatic boronic acids via an oxygen atom directed C-H bond activation. The catalytic reaction was compatible with various anilides and aromatic boronic acids.

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## Notes and references

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