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Regioselective *Ortho*-Arylation and Alkenylation of *N*-Alkyl Benzamides with Boronic Acids via Ruthenium-Catalyzed C−H Bond Activation: An Easy Route to Fluorenones Synthesis

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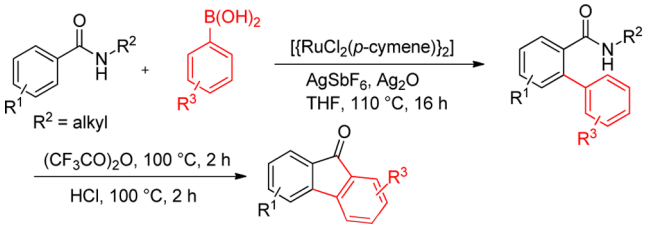
ABSTRACT



A highly regioselective ruthenium-catalyzed *ortho*-arylation of substituted *N*-alkyl benzamides with aromatic boronic acids in the presence of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$, and Ag_2O is described. Further, *ortho*-arylated *N*-alkyl benzamides were converted into fluorenones in the presence of trifluoroacetic anhydride and HCl.

The transition-metal-catalyzed heteroatom-directed *ortho*-arylation of substituted aromatics with aryl electrophiles or organometallic reagents by C−H bond activation is one of the most efficient and environmentally friendly methods to synthesize biaryl derivatives with minimum waste.[1,2] The biaryl structural unit is present in various natural products, drug and agrochemical molecules, and also key intermediates in various material syntheses.[3] Palladium-, rhodium-, or ruthenium-catalyzed *ortho*-arylations of heteroatom group substituted aromatics with aryl electrophiles such as aryl halides and aryl pseudohalides have been extensively studied by the groups of Miura, Daugulis, Yu, Cheng, Sanford, Ackermann, and others.[4,5]

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An alternative strategy such as *ortho*-arylation by using aryl organometallic reagents has not been well explored in the literature. Organoborons, organosilanes, and organostannanes are commonly used transmetallating agents in this type of reaction. Among them, organoboron reagents display multifarious advantages including availability, air and moisture stability, low toxicity, and easy removal of boron-derived byproducts unlike other organometallic reagents.[6]

In 1998, Oi et al. reported a rhodium-catalyzed direct arylation of 2-aryl pyridines with arylstannanes.[7] In 2003, Kakiuchi et al. reported a ruthenium-catalyzed direct arylation of aromatic ketones with aryl boronates.[8] Later, Yu's group showed several palladium-catalyzed direct alkylations and arylations of substituted aromatics with organostannanes and organoboron reagents.[9] Subsequently, Shi's group and other research groups demonstrated palladium-catalyzed arylation of acetanilides and aromatic oximes with arylboronic acids.[10] In most of the reported C−H bond activation reactions, the palladium complex has been used as a catalyst. In contrast, a ruthenium catalyst was found to be suitable only for C−H bond activation of aromatic ketones. In addition, in most of the reported reactions, organoboronates have been widely used as a coupling partner.[7,8] The corresponding organoboronic acid was not a suitable coupling partner for the reaction, mainly with ruthenium-catalyzed reactions. Therefore, hydroxy groups of boronic acid were masked and the masked reagent was used. Due to the vast availability and easy preparation of boronic acids, if a new arylation reaction is developed by an organoboronic acid, it would be very useful in organic synthesis. However, the major challenge in this reaction is to suppress other competitive reactions such as homocoupling of boronic acids, addition of boronic acid to the directing groups, and decomposition of directing groups by *in situ* generated proton of boronic acid.[10c]

Recently, the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex has been widely used as a catalyst in various C−H bond activation reactions due to remarkable reactivity, compatibility, and the low cost of the complex.[11,12] In this communication, we wish to report a highly regioselective *ortho*-arylation of *N*-alkyl benzamides with substituted aromatic boronic acids in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$, and Ag_2O. An *ortho*-alkenylation of *N*-alkyl benzamides with substituted alkenylboronic acids was also shown. Later, the *ortho*-arylated *N*-alkyl benzamides were successfully converted into fluorenones in the presence of $(CF_3CO)_2O$ and HCl.

The reaction optimization was carried out with 4-methoxy *N*-methylbenzamide (**1a**) (1.0 mmol) and phenylboronic acid (**2a**) (1.50 mmol) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (3 mol %) and $AgSbF_6$ (12 mol %) in THF at 110 °C for 16 h. The reaction was first tested with various terminal oxidants such as $Cu(OAc)_2$, AgOTf, $AgBF_4$, AgOAc, AgO_2CCF_3, Ag_2O, AgCl, AgBr, Ag_2CO_3, $AgClO_4$, and AgF. Among them, Ag_2O was very effective for the reaction, giving **3a** in 87% yield. The yield of **3a** was determined based on the ^1H NMR integration method using mesitylene as an internal standard. Ag_2CO_3, AgOTf, and $AgBF_4$ were less effective giving **3a** in 50%, 40%, and 21% yields, respectively. The remaining silver salts AgOAc, AgO_2CCF_3, $Cu(OAc)_2$, AgCl, AgBr, $AgClO_4$, and AgF were totally ineffective for the reaction. Next, the reaction was tested with various solvents such as 1,4-dioxane, DCE, DMF, CH_3CN, CH_3COOH, THF, MeOH, *tert*-BuOH, DMSO, and toluene. Of the solvents tested, THF was the most effective, affording **3a** in 87% yield. 1,4-Dioxane was also effective, providing **3a** in 45% yield. Other solvents such as DMF and *tert*-BuOH were less effective, providing **3a** in 25% and 15% yields, respectively. The remaining solvents such as DCE, CH_3CN, CH_3COOH, MeOH and DMSO were totally ineffective. Next, the reaction was tested with different amounts of Ag_2O (0.5, 1.0, 1.5, and 2.0 equiv). The coupling reaction showed a better yield of 87% in 1.0 equiv of Ag_2O. In the remaining reactions, product **3a** was observed only in 75−55% yields. Further, the reaction was tested without $AgSbF_6$ and only in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ and Ag_2O. However, in this reaction, coupling product **3a** was not observed. The catalytic reaction was also tested with a stoichiometric amount of $AgSbF_6$ (1.0 equiv) without Ag_2O under similar reaction conditions. In this reaction as well, no coupling product **3a** was observed. These results clearly revealed that both $AgSbF_6$ (12 mol %) and Ag_2O (1.0 equiv) were crucial for the reaction. The optimization studies revealed that $AgSbF_6$ (12 mol %) was the best additive, Ag_2O (1.0 equiv)

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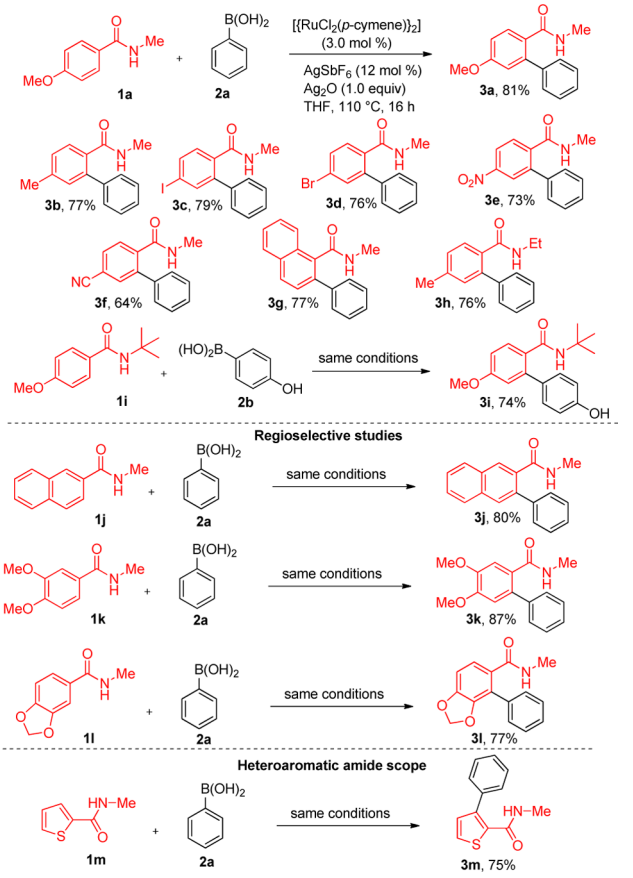
was the best terminal oxidant, and THF was the best solvent at 110 °C for 16 h for the present catalytic reaction. Under the optimized reaction conditions, **1a** reacted with **2a** providing coupling product **3a** in 81% isolated yield (Scheme 1).

Scheme 1. Scope of Substituted Amides



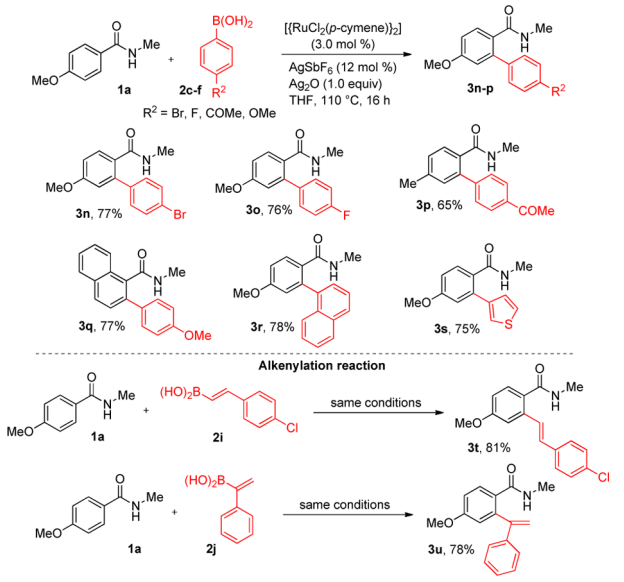
Under the optimized reaction conditions, various substituted *N*-methyl benzamides **1b**–**h** reacted efficiently with phenylboronic acid (**2a**) to give the corresponding *ortho*-arylated compounds **3a**–**h** in good to excellent yields (Scheme 1). Thus, 4-methyl *N*-methylbenzamide (**1b**) afforded the corresponding *ortho*-arylated product **3b** in 77% yield. Halogen group substituted benzamides such as 4-iodo *N*-methylbenzamide (**1c**) and 4-bromo *N*-methylbenzamide (**1d**) provided coupling products **3c** and **3d** in 79% and 76% yields, respectively. Interestingly, electron-withdrawing group substituted benzamides such as 4-nitro *N*-methylbenzamide (**1e**) and 4-cyano *N*-methylbenzamide (**1f**) also efficiently participated in the reaction giving the corresponding *ortho*-arylated products **3e** and **3f** in 73% and 64% yields, respectively. Bulky *N*-methyl-1-naphthamide (**1g**) was also successfully involved in the reaction providing coupling product **3g** in 77% yield. The effect of changing substituents on the *N*-group of the benzamides to Et and *tert*-Bu was also tested. Thus, 4-methyl *N*-ethylbenzamide (**1h**) reacted with phenylboronic acid (**2a**) to give coupling product **3h** in 76% yield. Similarly, 4-methoxy *N*-*tert*-butylbenzamide **1i** reacted with 4-hydroxyphenylboronic acid (**2b**) to give the corresponding *ortho*-arylated product **3i** in 74% yield. A sensitive-free hydroxy group on the benzene ring of boronic acid **2b** was not affected in the reaction. The coupling reaction was also tested with various *N*-phenyl substituted benzamides. However, no coupling product was observed in the reaction.

We next examined the scope of the regioselectivity of the present reaction (Scheme 1). Thus, the coupling reaction was tested with various unsymmetrical benzamides **1j**–**l**. *N*-Methyl-2-naphthamide (**1j**) underwent arylation reaction with phenylboronic acid (**2a**) affording coupling product **3j** in 80% yield in a highly regioselective manner. In this reaction, there are two *ortho* C–H bonds for arylation. Regioselectively, arylation takes place at the sterically less hindered C–H bond of **1j**. Similarly, 3,4-dimethoxy *N*-methylbenzamide (**1k**) also regioselectively reacted with **2a** at the sterically less hindered C–H bond of the **1k** moiety exclusively providing coupling product **3k** in 87% yield. In contrast, 1,3-dioxol group substituted benzamide **1l** reacted with **2a** giving coupling product **3l** in 77% yield by reverse regiochemistry. In this reaction, arylation takes place selectively at the sterically hindered C–H bond of the **1l** moiety. The catalytic reaction was also tested with a heteroaromatic group substituted amide (Scheme 1). Thus, *N*-methylthiophene-2-carboxamide (**1m**) underwent coupling with **2a** to afford **3m** in 75% yield.

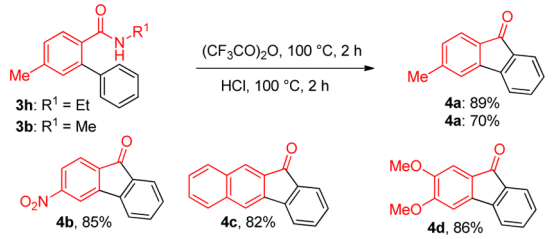
The scope of the present *ortho*-arylation reaction was further examined with various substituted aromatic and heteroaromatic boronic acids (Scheme 2). Thus, electron-withdrawing group substituted boronic acids such as 4-bromophenylboronic acid (**2c**), 4-fluorophenylboronic acid (**2d**), and 4-acetylphenylboronic acid (**2e**) reacted efficiently with **1a** or 4-methyl *N*-methylbenzamide (**1b**) providing coupling products **3n**–**p** in 77%, 76%, and 65% yields, respectively. 4-Methoxyphenylboronic acid (**2f**) coupled nicely with bulky *N*-methyl-1-naphthamide (**1g**) yielding biaryl derivative **3q** in 77% yield. Similarly, bulkier 1-naphthoboronic acid (**2g**) also efficiently coupled with **1a** to give the corresponding biaryl derivative **3r** in 78% yield. A heteroaromatic boronic acid was also compatible for the reaction. Thus, 3-thienylboronic acid (**2h**) efficiently participated in the coupling reaction with **1a** affording substituted 3-phenylthiophene derivative **3s** in 75% yield. Subsequently, the present coupling reaction was tested with alkenylboronic acids **2i** and **2j** (Scheme 2). Thus, 4-chlorostyrylboronic acid (**2i**) underwent coupling with **1a** to give the corresponding alkene derivative **3t** in 81% yield in a highly *E*-stereoselective manner. Surprisingly, highly sterically hindered 1-phenylvinylboronic acid (**2j**) also efficiently reacted with **1a** to yield an alkene derivative **3u** in 78% yield. It is noteworthy to say that various functional groups such as I, Br, Cl, F, CN, NO_2, OMe, S, COMe, and OH on the amides or boronic acids were compatible for the present reaction.

To demonstrate the synthetic utility of *ortho*-arylated *N*-alkylbenzamides **3** in organic synthesis, we carried out

Scheme 2. Scope of Boronic Acids

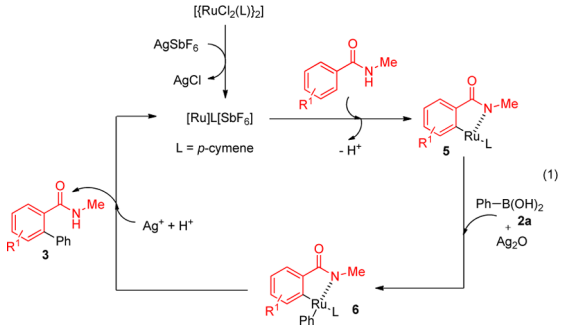


Scheme 3. Fluorenones Synthesis



intramolecular cyclization of *ortho*-arylated *N*-alkylbenzamides in the presence of trifluoroacetic anhydride and HCl (Scheme 3). The intramolecular cyclization of **3h** proceeded smoothly in the presence of $(CF_3CO)_2O$ at 100 °C for 2 h followed by HCl hydrolysis at 100 °C for another 2 h yielding fluorenone derivative **4a** in 89% yield, whereas **3b** underwent intramolecular cyclization under similar reaction conditions, giving **4a** only in 70% yield. Similarly, *ortho*-arylated *N*-ethyl benzamides of **3e**, **3j**, and **3k** also nicely converted into substituted fluorenone derivatives **4b**–**d** in excellent 85%, 82%, and 86% yields, respectively (Scheme 3). Fluorenone is an important structural scaffold present in various natural products and biologically active molecules.[5h]

On the basis of known metal-catalyzed C–H bond activations, a possible reaction mechanism is proposed to account for the present *ortho*-arylation reaction (eq 1). The first step involves removal of the chloride ligand from the ruthenium complex by $AgSbF_6$ providing the cationic ruthenium complex. Coordination of the carbonyl oxygen of benzamide **1** to the cationic ruthenium species followed by *ortho*-metalation gives ruthenacycle intermediate **5**.[5] Transmetalation of boronic acid **2** into intermediate **5** in the presence of Ag_2O provides intermediate **6**. Subsequent reductive elimination of intermediate **6** in the presence of Ag_2O affords product **3** and regenerates the active ruthenium species for the next catalytic cycle. While the exact role of Ag_2O is unclear, we think Ag_2O might play a dual role in the reaction. It acts as a base to accelerate transmetalation of boronic acid **2** into intermediate **5**. In addition, the Ag^+ ion acts as a terminal oxidant to oxidize Ru(0) to Ru(II).



In conclusion, we have described a ruthenium-catalyzed highly regioselective *ortho*-arylation of substituted *N*-alkylbenzamides with substituted aromatic and heteroaromatic boronic acids in the presence of $AgSbF_6$ and Ag_2O. Later, the observed coupling products were further converted into fluorenones in the presence of trifluoroacetic anhydride and HCl. Further extension of *ortho*-arylation of directing group substituted aromatics with other organometallic reagents and a detailed mechanistic investigation are in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.