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Pd-Catalyzed C−H Functionalizations of *O*-Methyl Oximes with Arylboronic Acids

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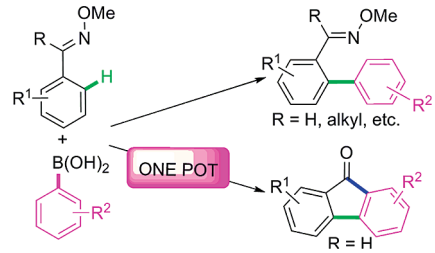
ABSTRACT



Useful methods have been developed to construct *ortho*-arylated aryl aldoximes, aryl ketoximes, and fluorenones via Pd(II)-catalyzed direct C−H arylation by using arylboronic acids as arylating reagents based on the analysis of the pathways of direct functionalization of aryl aldoximes.

Direct C−H functionalization is the most straightforward pathway to construct useful and complicated natural and synthetic molecules. Recently, many efforts have been made to pursue this goal.[1] Among those methods, functional group oriented *ortho* C−H activation is a common strategy to address this problem.[2] Actually, the *O*-methyl oximyl group has been successfully applied for *ortho* acetoxylation and amination.[3] Very recently, arylation followed by further transformation with aryl iodides to synthesize fluorenones has also been successfully developed.[4]

Compared with direct arylation with arylboronic acids directed by other anchoring groups, the arylation oriented by C=X (X = O, N) remains challenging.[5] The major issue

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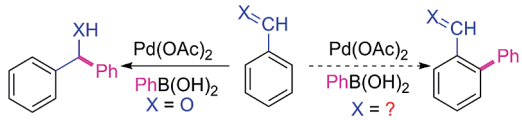
is to avoid the direct addition of arylboronic acids to the C═X group in the presence of Pd(II) species, which has been well studied (Scheme 1).[6] On the other hand, arylboronic

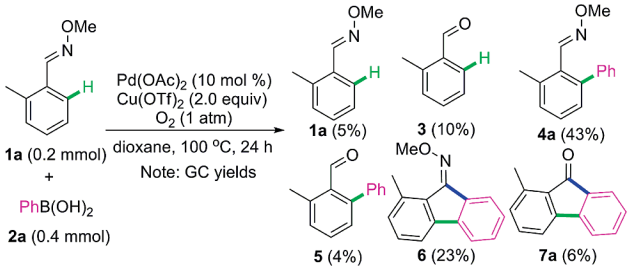
Scheme 1. Competition of Arylation of C═X and the *ortho* sp^2 C−H Bond



acid and the in situ generated proton may lead to the decomposition of oxime groups. Herein we demonstrated systematic investigations of various transformations between aldoximes/ketoximes and arylboronic acids.

We initially tested our idea with *O*-methyl (*E*)-2-methylbenzaldoxime **1a** with phenylboronic acid **2a** in the presence of $Pd(OAc)_2$ and $Cu(OTf)_2$. The reaction produced a complicated mixture. After careful analysis of this mixture, we found six compounds, accompanied by small amounts of biphenyl and benzene generated from **2a** (Scheme 2).

Scheme 2. Complication of Arylation of **1a** with Boronic Acid **2a** via Pd(II) Catalysis



Besides the recovery of **1a**, the desired *ortho* phenylated product **4a** was observed in a moderate yield. As predicted, both **1a** and **4a** were partially hydrolyzed to the corresponding aldehydes **3** and **5**. Unexpectedly, annulated product **6** and its hydrolyzed 9*H*-fluoren-9-one **7a** were also observed in low yields. It is very important to note that the arylation of C═X (X = O or N) was completely inhibited during this process.

Further efforts have been made to unveil the relationships among all those compounds. Compound **4a** was first synthesized through traditional Suzuki−Miyaura coupling from the corresponding halide.[7] When **4a** was submitted to the same condition for *ortho* C−H arylation, the desired annulated product **6** was observed, accompanied by a small amount of **7a**. Interestingly, the corresponding aldehyde **5** could not be transformed into **7a** directly under the same condition. Ketone **7a** could be produced from **6** by hydrolysis with excellent efficiency. Further studies indicated that **5** could not be obtained from **3** by direct arylation. Thus, **7a** was obtained through the pathway from the intermediates **4a** and **6**. During these transformations, Pd(II), Cu(II), and the in situ generated acid might play vital roles to promote different transformations. Thus, we envisioned that these complicated transformations could be selectively controlled at different stages to afford the desired products by tuning the reaction parameters.

With this idea in mind, we conducted many trials to approach our goals (Table S1, Supporting Information). After the systematic screening, we found that, when 2 6-dimethoxypyridine (DMOP) was used as a base, the arylation occurred in high efficiency, and the desired *ortho* phenylated product **4a** was isolated in an 86% yield. The proper steric hindrance and basicity of DMOP might trap the proton generated in situ and at the same time did not inhibit the cyclopalladation of *O*-methyl aldoxime.

The substrate scope was further surveyed (Figure 1). Various boronic acids **2** were tested. We found that: (1) the

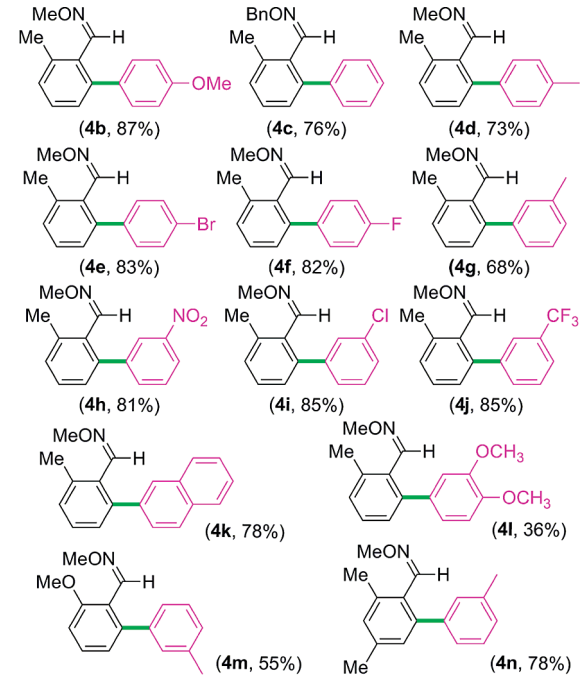


Figure 1. Direct arylation of benzaldoximes via Pd-catalyzed C−H activation. All the reactions were carried out in 0.2 mmol scale. Islolated yields.

electronic property of different substituents on the aryl rings did not affect this transformation very much, and arylboronic acids bearing both electron-donating groups and electron-withdrawing groups worked well; (2) the survival of the halogen substituents, such as C−Br and C−Cl, offered a great opportunity to functionalize the products further (**4e**, **4i**); (3) arylboronic acids with various substituents at both

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para and *meta* positions were good substrates (**4d**, **4g**); however, an *ortho* substituted arylboronic acid was not a suitable substrate, which may arise from the steric hindrance; (4) polysubstituted arylboronic acids were also suitable substrates despite the lower reaction efficiency due to the protonation of boronic acid. Different substituents on the aryl oxime scaffold were also examined. O-Substituents of oximes were of great importance for this transformation. Besides *O*-methyl oxime, *O*-benzyl oxime also worked well (**4c**). However, the unprotected oxime is not a suitable substrate for this transformation. On the other hand, *ortho* substituents of the *O*-methyl oximes showed good reactivity and selectivity for monoarylation. An increase of the electron density with the *o*-methoxyl group seemed to make the reaction messy and decreased the isolated yield substantially (**4m**). However, 2,4-dimethyl substituents did not affect the efficiency (**4n**).

The condition of direct *ortho* arylation of aldoximes could not be directly applied to aryl ketoximes. The *ortho* arylated product formed but with incomplete conversion and low yield, which may arise from the relatively high steric hindrance. To our delight, the desired *ortho* arylated product was obtained in an excellent yield in the absence of DMOP (Figure 2, **10a**). Similarly, different *O*-substituents of acetophenone oximes were tested. *O*-Benzyl 2′-methyl acetophenone oximes conducted the same arylation under the standard condition (**10b**). However, *O*-phenyl or *O*-acyl 2′-methyl acetophenone oximes completely decomposed under the same conditions (**10c**−**10f**).

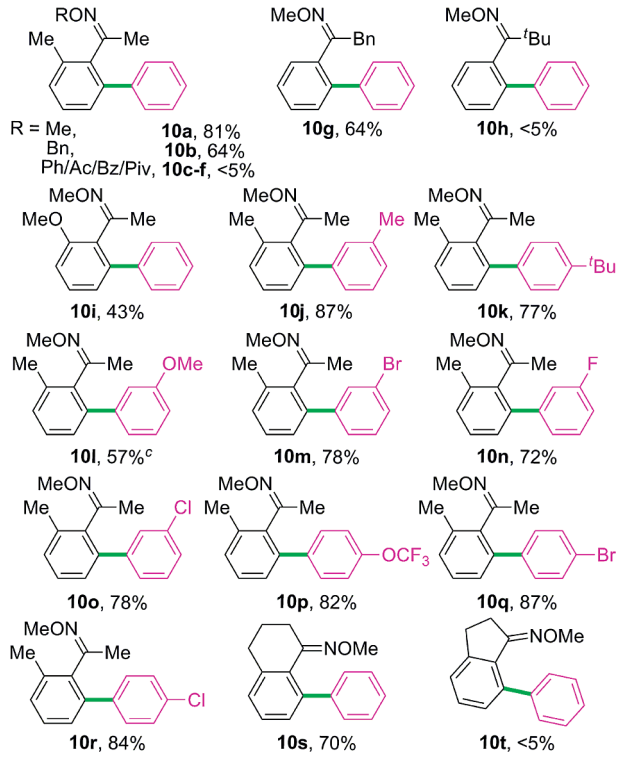

Figure 2. Direct *ortho* arylation of acetophenone oxime derivatives with various arylboronic acids. All the reactions were carried out in 0.2 mmol scale. Isolated yields. The corresponding arylboronic acids were added in batches by 0.5 equiv every 2 h.

The reactions of various *O*-methyl aryl ketoximes with phenylboronic acid were carried out (Figure 2). Moreover, *O*-methyl 2′-methoxy acetophenone oxime gave moderate yields (**10i**). To our delight, the benzyl group facilitated *ortho* arylation of the substrate and inhibited the generation of the diarylation product (**10g**). However, the *O*-methyl ketoxime derived from *tert*-butyl phenyl ketone provided arylated products in low yields due to a steric effect (**10h**). Arylboronic acids bearing alkyl and electron-withdrawing groups gave the corresponding *ortho* arylated products in good to excellent yields (**10j**, **10k**, and **10m**−**10r**). However, arylboronic acids bearing electron-donating groups afforded the desired products in relatively lower efficiencies (**10l**). Similarly, the survival of the halogen substituents, even the C−Br group, on the boronic acids offered the possibility for further functionalizations (**10m**−**10o** and **10q**−**10r**). Moreover, six-membered cyclic aryl ketoxime gave desired products in moderate yields (**10s**), while five-membered cyclic aryl ketoxime did not undergo this process (**10t**).

In analyzing the pathways, we proposed that the desired **7a** could become the major product by tuning the reaction parameters if hydrolysis of **1a** and **4a** could be inhibited. Since 9*H*-fluoren-9-one is an important structural scaffold, existing in many natural products and synthetic drugs[8] as well as intermediates in materials chemistry,[9] our attention was further drawn into a one-pot method to access polyfunctionalized 9*H*-fluoren-9-ones.

To prove our assumption, we added different acids after the first step (Table S2, Supporting Information). To our delight, after adding 1.0 equiv of HOTf and lengthening the reaction time at 90 °C for another 24 h, **4a** was converted completely, and cyclization products **6** and **7a** were obtained in 26% and 61% yield, respectively (entry 5, Table S2, Supporting Information). To obtain the sole desired product **7a**, hydrochloric acid was required to reach complete hydrolysis of **6**. Finally, **7a** was isolated in 62% yield after three steps in one pot. Under the same conditions, polysubstituted 9*H*-fluoren-9-ones **7a**−**7h** were obtained in moderate to good yields (Figure 3). In this transformation, steric hindrance did not affect the reaction efficiency. In contrast, the electronic effect played a key role. Alkyl groups were beneficial for this transformation; however, the alkoxy group promoted the reaction rate, while the yield of **7** decreased, which might arise from the instability of the intermediates and the final products under this acidic and oxidative condition. Moreover, the substrates bearing an electron-withdrawing group were not conducive to this transformation to produce the final 9*H*-fluoren-9-one perhaps due to the diminished electron density of arylated intermediates.

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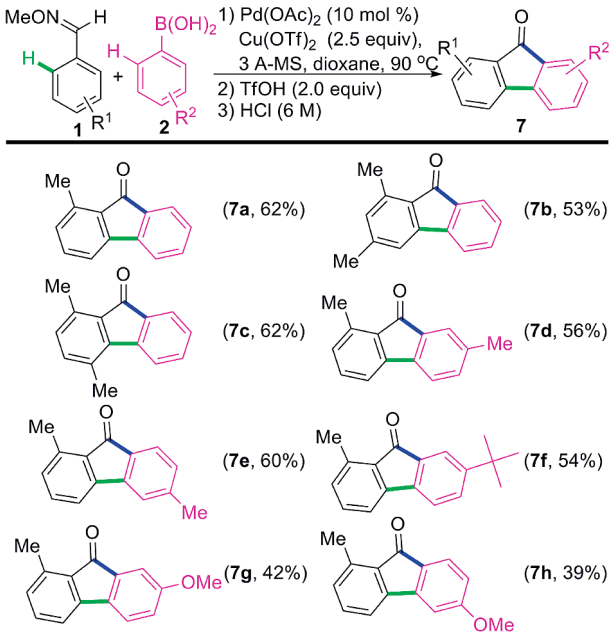

Figure 3. Cascade reaction to produce polysubstituted 9*H*-fluoren-9-ones **7** via Pd-catalyzed C−H activation. All the reactions were carried out in 0.2 mmol scale. Isolated yields.

Mechanistically, the transformation was initiated from *ortho* cyclopalladation directed by *O*-methyl oxime to generate cyclopalladium species ***A***, which underwent transmetalation with arylboronic acids to produce diaryl Pd species ***B*** (Scheme 3).[10] Reductive elimination of ***B*** produced the desired *ortho* arylated product **4**. Pd(0) was further reoxidized to Pd(II) by Cu(II) species and/or co-oxidant to fulfill the catalytic cycle. In the presence of proper DMOP for the arylation of aryl aldoximes, the transformation was terminated at this stage. With the addition of TfOH, this arylated product was further transformed to product **6**. Furthermore, **6** was hydrolyzed to give 9*H*-fluoren-9-one **7** under strongly acidic conditions. Thus, starting from the same reagents, different pathways have been developed to approach different scaffolds by tuning the reaction conditions.

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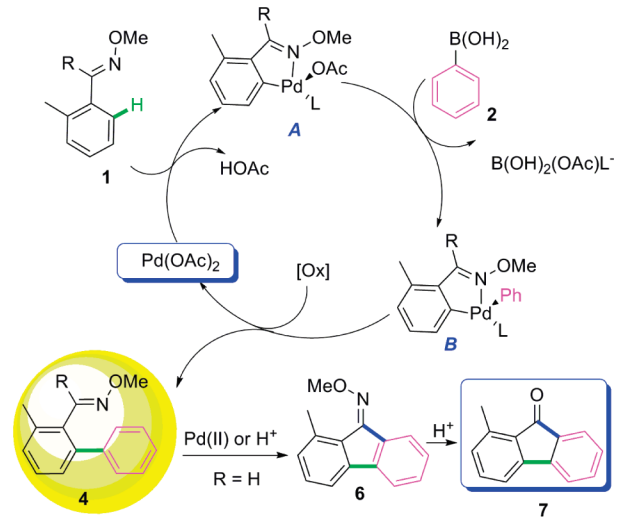
Scheme 3. Proposed Mechanism for Pd(II)-Catalyzed Arylation and Cascade Transformation to Fluorenone



In conclusion, we have developed novel methods to construct *ortho* arylated aryl aldoximes and ketoximes via Pd(II)-catalyzed direct C−H arylation by using arylboronic acids. On the basis of the analysis of *ortho* arylation of aryl aldoximes, cascade transformations toward interesting fluorenone scaffold were conducted by switching the reaction pathways through changing the reaction parameters. These studies showed various transformations to functionalize aryl carbonyl compounds starting from simple chemicals.

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Supporting Information Available: Brief experimental detail and other spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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