C–H Activation

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Synthesis of Phenanthridinones from *N*-Methoxybenzamides and Arenes by Multiple Palladium-Catalyzed C–H Activation Steps at Room Temperature**

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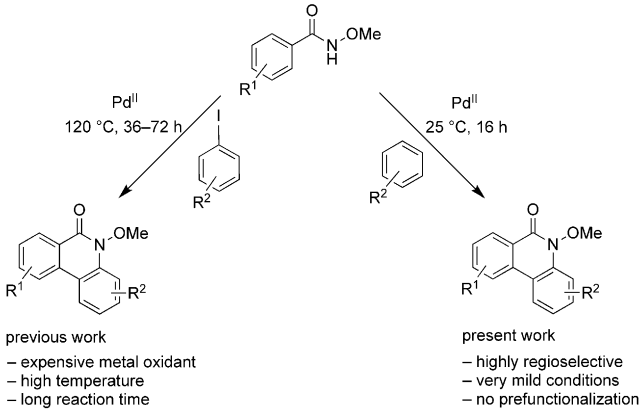
The phenanthridinone unit is often found in alkaloids, many of which have shown various biological activities.[1] Despite the existence of several methods for the synthesis of phenanthridinone derivatives,[2,14] versatile and flexible methodologies to construct phenanthridinones are still desirable.

Transition-metal-catalyzed oxidative C–H coupling of two different arenes has emerged as a powerful method for the construction of C–C bonds and functionalized biaryl linkages in organic synthesis.[3,4] Despite the increasing attention given to this area, most of these reactions still require a high temperature, powerful oxidants, and/or long reaction times, all of which significantly limit the scope and functional-group tolerance of these reactions. Thus, it is highly desirable to develop a milder, more efficient, environmentally benign, and atom-economical method for metal-catalyzed C–H functionalization reactions. Recently, palladium-catalyzed directing-group-assisted *ortho* functionalization of aromatic C–H bonds has been explored by coupling with simple arenes.[4e–l] Various substrates, such as pyridines,[4e–f] pyridine-*N*-oxide,[4g] anilides,[4h–i] amides,[4j] imines,[4k] and *o*-phenylcarbamates,[4l] have been employed for the palladium-catalyzed arylation with simple arenes. We have also investigated the synthesis of fluorenones from aldoxime ethers and arenes by multiple palladium-catalyzed C–H functionalization reactions.[5] Apart from the above-mentioned functional groups, only a few examples are known to have CONHOMe as a directing group for the activation of C(sp^2)–H and C(sp^3)–H bonds.[6–10] In 2008, Yu and co-workers first reported the use of CONHOMe as a directing group for the palladium-catalyzed functionalization of a C(sp^3)–H bond with aryl and alkyl boronic acids.[7] Subsequently, the same research group developed a palladium-catalyzed synthesis of biologically active lactam derivatives by intramolecular oxidative C–H activation and C–N formation using benzhydroxamic acids as substrates.[8] In 2010, Wang and Yuan reported a palladium-catalyzed alkoxylation of *N*-methoxybenzamides.[9] Very recently, Wang et al. demonstrated the synthesis of phenanthridinone from *N*-methoxybenzamides with aryl iodides using a palladium catalyst and metal oxidant at elevated temperatures (Scheme 1).[10] To the best of our knowledge, multiple C–H activation reactions of *N*-methoxybenzamides with simple arenes at ambient temperatures have not been reported to date. However, recent efforts have shown that palladium complexes can catalyze the C–H functionalization at room temperature.[11]



Scheme 1. Synthesis of phenanthridinone derivatives.

Our continuing efforts in metal-catalyzed C–H activation and cyclization reactions[12] prompted us to explore the reaction of *N*-methoxybenzamides with arenes. Herein, we report a palladium-catalyzed highly regioselective dehydrogenative cyclization of *N*-methoxybenzamides with arenes to give biologically active phenanthridinone derivatives through multiple oxidative C–H activation and C–C/C–N formation steps in one pot under mild conditions.

Treatment of *N*-methoxybenzamide **1a** with toluene **2a** in the presence of $Pd(OAc)_2$ (10 mol%) and $K_2S_2O_8$ (2.0 equiv) in TFA (20 equiv) at 25 °C for 16 h gave phenanthridinone **3a** in 92% yield (Table 1, entry 1). It is important to note that the reaction is highly regioselective with respect to **1a** and **2a**; we did not observe any regioisomer of **3a**. The transformation appears to include three C–H and N–H activation steps, and C–C/C–N formation steps. The identity of product **3a** was confirmed by $^1H/^{13}C$ NMR spectroscopy and mass spectrometry. Among the various oxidants examined, $K_2S_2O_8$ was most effective, and its use resulted in the formation of **3a** in 92% yield. Other oxidants, such as *meta*-chloroperoxybenzoic acid (*m*CPBA), oxone, and $Na_2S_2O_8$, were also active but led to **3a** in only 42%, 52%, and 78% yield, respectively.

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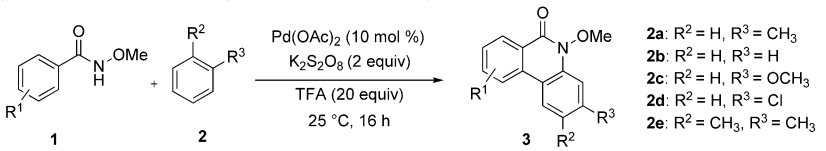
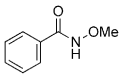
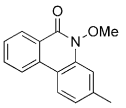
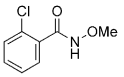
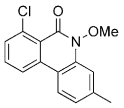
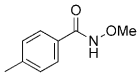
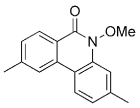
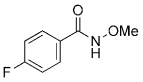
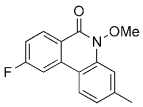
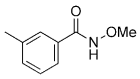
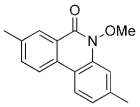
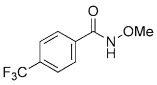
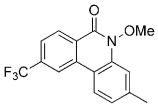
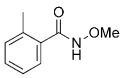
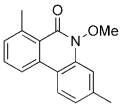
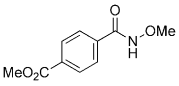
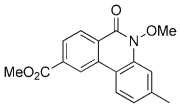
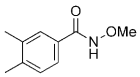
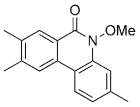
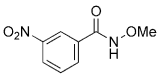
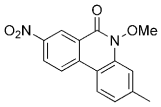
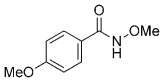
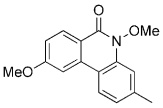
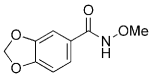
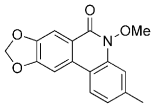
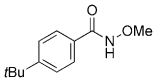
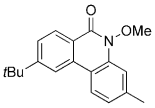
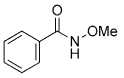
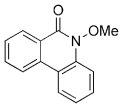
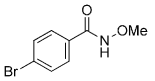
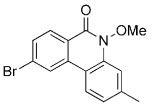
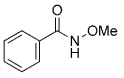
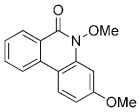
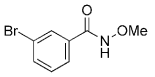
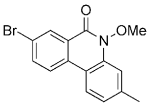
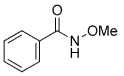
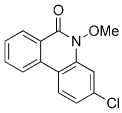
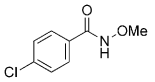
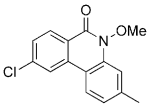
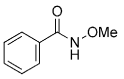
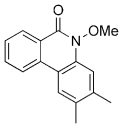
Table 1: Results of the catalytic reaction of *N*-methoxybenzamides with simple arenes.[a]



Entry	1	2	Product 3	Yield [%][b]	Entry	1	2	Product 3	Yield [%][b]
1		**1a** **2a**		**3a** 92	11		**1k** **2a**		**3k** 70
2		**1b** **2a**		**3b** 90	12		**1l** **2a**		**3l** 90
3		**1c** **2a**		**3c** 86	13		**1m** **2a**		**3m** 85
4		**1d** **2a**		**3d** 80	14		**1n** **2a**		**3n** 89
5		**1e** **2a**		**3e** 84	15		**1o** **2a**		**3o** 64
6		**1f** **2a**		**3f** 81	16		**1p** **2b**		**3p** 71
7		**1g** **2a**		**3g** 78	17		**1a** **2b**		**3q** 90
8		**1h** **2a**		**3h** 86	18		**1a** **2c**		**3r** 86
9		**1i** **2a**		**3i** 74	19		**1a** **2d**		**3s** 65
10		**1j** **2a**		**3j** 89	20		**1a** **2e**		**3t** 83

[a] Unless stated otherwise, all reactions were carried out using an *N*-methoxybenzamide **1** (0.70 mmol) and an arene **2** (17.5 mmol) in the presence of $Pd(OAc)_2$ (10.0 mol%) and $K_2S_2O_8$ (1.40 mmol) in TFA (140 mmol) at 25 °C for 16 h. [b] Yield of isolated product. TFA = trifluoroacetic acid.

Replacement of the oxidant with silver or copper salts did not lead to product **3a**. The choice of palladium catalysts was also crucial for this reaction. Use of $Pd(OAc)_2$ provided the highest yield for the catalytic reaction. Use of other palladium catalysts, such as $Pd(acac)_2$ (acac = acetylacetonate) and $Pd(TFA)_2$, was also effective and afforded **3a** in 58% and 64% yield, respectively. The presence of an acid is important to the catalytic reaction. Among the acids tested, TFA was most effective; toluene-*p*-sulfonic acid (PTSA, 2 equiv) afforded product **3a** in 47% yield. The other acids surveyed, including CH_3COOH, DMSO, and pivalic acid, were totally ineffective. The amount of TFA is also crucial for the yield of the product; the use of more or less than 20 equivalents of TFA led to a lower yield of **3a**. Control experiments showed that the reaction did not proceed in the absence of either palladium or TFA. The reaction proceeded at elevated temperatures, but the yield of **3a** decreased because of the decomposition of the starting material. For example, the yield of **3a** was only 79% when the reaction was carried out at 110 °C.

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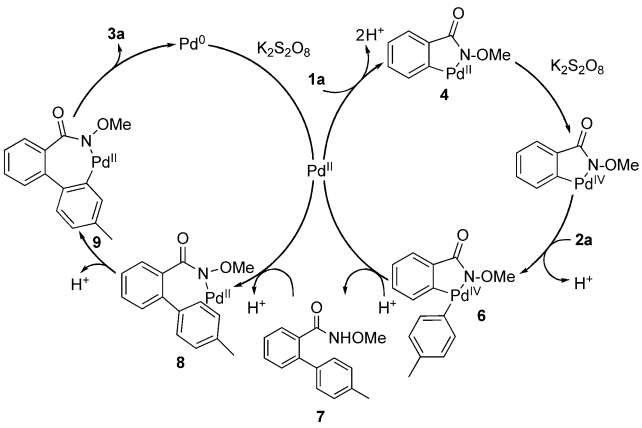
With the optimized reaction conditions established (see Table 1, footnote), we examined the reaction of various substituted *N*-methoxybenzamides (**1b–o**) with toluene (**2a**). Gratifyingly, excellent yields and high regioselectivities were generally observed for most of these substrates (Table 1). Thus, 4-methyl-, 3-methyl-, 2-methyl-, 3,4-dimethyl-, and 4-methoxy-*N*-methoxybenzamides (**1b–f**) afforded products **3b–3f** in excellent yields (Table 1, entries 2-6). The incorporation of the sterically demanding 4-*tert*-butyl substituent in **1g** did not affect the reaction with **2a** to a great extend, and product **3g** was afforded in 78% yield (Table 1, entry 7). In a similar manner, 4-bromo-, 3-bromo-, 4-chloro-, 2-chloro-, and 4-fluoro-*N*-methoxybenzamides (**1h–1l**) also underwent the reaction smoothly to give products **3h–3l** in 86%, 74%, 89%, 70%, and 90% yield, respectively (Table 1, entries 8–12). Comparison of these results indicates that the product yield is slightly affected by the position of the substituent in **1**. As shown in Table 1, entries 2–4 and 10–11, the yield for the methyl- or chloro-substituted substrate **1** follows the order: *para* > *meta* > *ortho*. The observed trend may be rationalized on the basis of the steric effect of the substituent. For *meta*-substituted substrates **1**, there are two possible C–H activation sites C2 and C6, but the activation occurs only at C6. The C–H activation at C2 is less likely because the steric repulsion between the *meta*-substituent and the palladium center is stronger, if the activation process takes place at C2 (Table 1, entries 3, 5, 9, and 15).

Finally, the present catalytic reaction is compatible with a wide scope of functional groups. Compounds **1** with either electron-withdrawing substituents, such as 4-F, 4-CF_3, 4-CO_2Me, and 3-NO_2 groups (Table 1, entries 12, 13, 14, and 15), or electron-donating groups, such as 4-methyl, 3,4-dimethyl, 4-methoxy, and 3,4-methylenedioxy groups (Table 1, entries 2, 5, 6, and 16) react smoothly with arenes to give the expected products **3**.

To further explore the scope of the reaction, various arenes **2b–e** were employed to react with **1a** under the optimized conditions. Treatment of **1a** with benzene **2b** afforded phenanthridinone **3q** in 90% yield (Table 1, entry 17). The reaction of electron-rich anisole (**2c**) with **1a** was highly regioselective and gave product **3r** in 86% yield (Table 1, entry 18). The reaction of **1a** with *o*-xylene (**2e**; Table 1, entry 20) also gave only one regioisomeric product (**3t**) in 83% yield. It is noteworthy that chlorobenzene **2d** also reacted with **1a** to afford the cyclization product **3s** in moderate yield (Table 1, entry 19). Thus, the present method provides an efficient way to a fast assembly of phenanthridinones with diverse substituents.

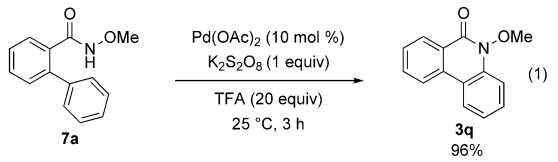
On the basis of known metal-catalyzed directing-group-assisted C–H activation reactions, a plausible mechanism for the reaction of **1a** with **2a** to give **3a** is proposed in Scheme 2. The arylation of *N*-methoxybenzamides most likely proceeds through a pathway similar to the *para*-selective arylation of amides with simple arenes,[4j] a reaction in which a persulfate salt is used as the oxidant and which proceeds through a $Pd^{II/IV}$ pathway. Similarly, the acetoxylation of oximes[13a] and anilides,[13b] the alkoxylation of *N*-methoxybenzamides,[9] and the dimerization of 2-phenylpyridines[13c] in the presence of persulfate salt was proposed to also proceed via $Pd^{II/IV}$



Scheme 2. Proposed mechanism for the catalytic reaction of *N*-methoxybenzamide (**1a**) with toluene (**2a**).

species. Michael and co-workers also suggested that the *para*-selective arylation proceeds via a Pd^{IV} species.[13d–e] The initial step involves the coordination of **1a** to a Pd^{II} species, and is followed by an *ortho* C–H activation to form a five-membered palladacycle **4**, and the release of protons. The oxidation of **4** by persulfate gives Pd^{IV} species **5**, which is arylated by substrate **2a** to afford intermediate **6**. Reductive elimination leads to *ortho*-arylated product **7** and a Pd^{II} species. Subsequent deprotonation of the N–H group in **7** and coordination of the nitrogen atom to a Pd^{II} species forms intermediate **8**. Further C–H activation gives the seven-membered palladacycle **9**. Reductive elimination of **9** affords **3a** and a Pd^0 species, which is oxidized by $K_2S_2O_8$ to regenerate the active Pd^{II} species for the next catalytic cycle.

To support the intermediacy of **7**, we prepared **7a** and examined its reactivity under various conditions. First, **7a** was treated with $Pd(OAc)_2$ (10 mol%) and $K_2S_2O_8$ (1 equiv) in TFA (20.0 equiv) at 25 °C for 3 h, and cyclization product **3q** was obtained in 96% yield [Eq. (1)]. When the same reaction was carried out in the absence of $K_2S_2O_8$, **3q** was obtained in 8% yield. These observations suggest that $Pd(OAc)_2$ and TFA can convert **7a** into final product **3q**. The observations also indicate that $K_2S_2O_8$ acts as an oxidant to transform Pd^0 to Pd^{II}.



The present methodology appears to be very useful for the synthesis of natural products that contain the phenanthridinone core. For example, crinasiadine (**9a**, Scheme 3) can be very conveniently synthesized by reaction of *N*-methoxybenzamide **1p**. Reaction of **1p** with benzene under the standard catalytic conditions gave **3p** in 71% yield. Photolysis of **3p** in methanol afforded crinasiadine in 90% yield.[14] This

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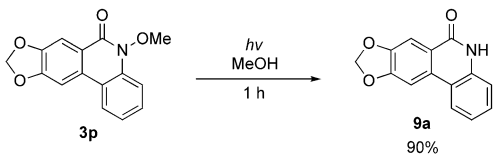

Scheme 3. Synthesis of crinasiadine (**9a**) from **3p**.

product, which has been isolated from *Crinum asiaticum*, belongs to the class of *amaryllidaceae* alkaloids.[15]

In conclusion, we have successfully demonstrated the palladium-catalyzed synthesis of phenanthridinone derivatives from *N*-methoxybenzamides and arenes through multiple oxidative C–H activation and C–C/C–N formation steps in one pot at room temperature. This method allows the rapid generation of phenanthridinone derivatives with diverse substituents (demonstrated with the synthesis of natural product crinasiadine) that are of importance in biochemistry and medicinal chemistry.

Experimental Section

General procedure for the palladium-catalyzed synthesis of phenanthridinones. A sealed tube (20 mL) containing $Pd(OAc)_2$ (0.070 mmol, 10.0 mol%), *N*-methoxybenzamide (0.70 mmol), and $K_2S_2O_8$ (1.40 mmol) was evacuated and purged three times with nitrogen gas. Toluene (17.5 mmol, 1.95 mL) and TFA (14.0 mmol, 1.1 mL) were added to the mixture by syringe. The reaction mixture was stirred at 25 °C for 16 h, then diluted with dichloromethane and stirred in air for 10 min. The mixture was filtered through Celite and silica gel pads and washed with dichloromethane. The filtrate was concentrated and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate as eluent to afford the desired product **3a** (154 mg) in 92% yield.

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