C–H Activation

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One-Pot Formation of C–C and C–N Bonds through Palladium-Catalyzed Dual C–H Activation: Synthesis of Phenanthridinones**

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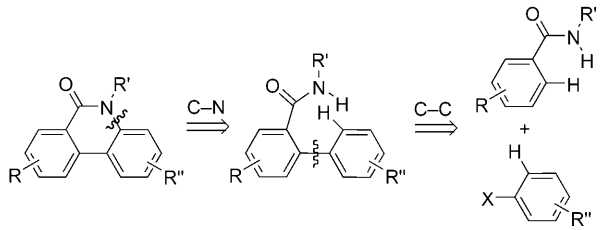
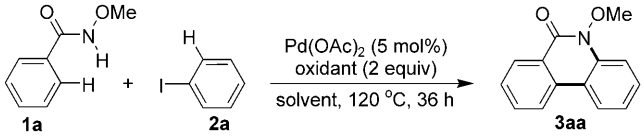
Palladium-catalyzed C–H activation has emerged in recent years as one of the most sustainable and intriguing protocols to construct C–C, C–O, C–N, C–S, and C–X (X = halogen) bonds, and has been employed in the synthesis of pharmaceuticals and natural products.[1] A directing group is commonly required to achieve high regioselectivity in a C–H activation reaction. Among the directing groups, the utilization of the CONHOMe group in the arylation of sp^3 C–H bonds through palladium-catalyzed C–C bond formation was first discovered by Yu and co-workers.[2] Subsequently, Wasa and Yu exploited the same directing group in intramolecular cyclization reactions, thus affording lactam derivatives through the palladium-catalyzed formation of C–N bonds.[3] Nevertheless, the cascade formation of C–C and C–N bonds through palladium-catalyzed C–H activation in one pot is quite challenging.[4] In continuation of our interest in the C–H activation of *N*-methoxybenzamides,[5] we envision that a palladium-catalyzed intermolecular C–C bond formation could be coupled with another palladium-catalyzed intramolecular C–N bond formation for a rapid synthesis of biologically important phenanthridinones (Scheme 1). Herein we report the one-pot cascade synthesis of phenanthridinones by the palladium-catalyzed reaction of *N*-methoxybenzamides and aryl iodides with this strategy. This reaction results in the breaking of four bonds and formation of two bonds.



Scheme 1. Retrosynthesis of phenanthridinones.

Aryl iodides have been widely employed in palladium-catalyzed ligand-directed arylation reactions.[6] Therefore, we chose the reaction of *N*-methoxybenzamide (**1a**) with phenyl iodide (**2a**) catalyzed by $Pd(OAc)_2$ as the model reaction to verify our assumption and to screen the optimal conditions. Silver salts have been widely used as oxidants in palladium-catalyzed arylation and lactamization reactions.[2,3,6] We first examined the model reaction with AgOAc as the oxidant and CF_3COOH as the solvent. However, the desired product **3aa** was not obtained (Table 1, entry 1). Other solvents such as 1,4-dioxane, 1,2-dichloroethane, and toluene were also ineffective. When AcOH was used as the solvent, product **3aa**

Table 1: Screening conditions for the palladium-catalyzed reaction of *N*-methoxybenzamide and phenyl iodide.[a]



Entry	Oxidant	Yield [%]	Entry	Oxidant	Yield [%]
1[b]	AgOAc	Trace	6[c]	Ag_2O	68
2	AgOAc	61	7[d]	Ag_2O	66
3	Ag_2SO_4	29	8	$K_2S_2O_8$	13
4	AgOTf	23	9	Oxone	13
5	Ag_2O	76	10	$Cu(OAc)_2$	12

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and oxidant (1.0 mmol) in AcOH (5 mL) at 120 °C for 36 h. [b] CF_3COOH was used as the solvent. [c] 0.5 mmol of **2a** was used. [d] 0.5 mmol of Ag_2O was used.

was isolated in 61% yield (entry 2). Silver salts Ag_2SO_4 and AgOTf could also promote the reaction, albeit in much lower yields (entries 3 and 4). It turned out that Ag_2O performed best; the yield was improved to 76% (entry 5). Decreasing the quantity of **2a** or Ag_2O from 2 equivalents to 1 equivalent resulted in a lower yield of 68% and 66%, respectively (entries 6 and 7 vs. entry 5). Disappointingly, when $K_2S_2O_8$, oxone, or $Cu(OAc)_2$ was employed as the oxidant, the product was isolated in very low yield (entries 8–10). In addition, the reaction did not occur without oxidant or with $PhI(OAc)_2$ and benzoquinone as the oxidant. Therefore, 1 equivalent of **1a**, 2 equivalents of **2a**, and 2 equivalents of Ag_2O were chosen as the best conditions for the palladium-catalyzed reaction of **1a** with **2a** in AcOH at reflux.

With the optimal conditions in hand, we next explored other *N*-methoxybenzamides and aryl iodides to examine the scope and limitation of the current reaction. The results are summarized in Scheme 2. Benzamides with either electron-

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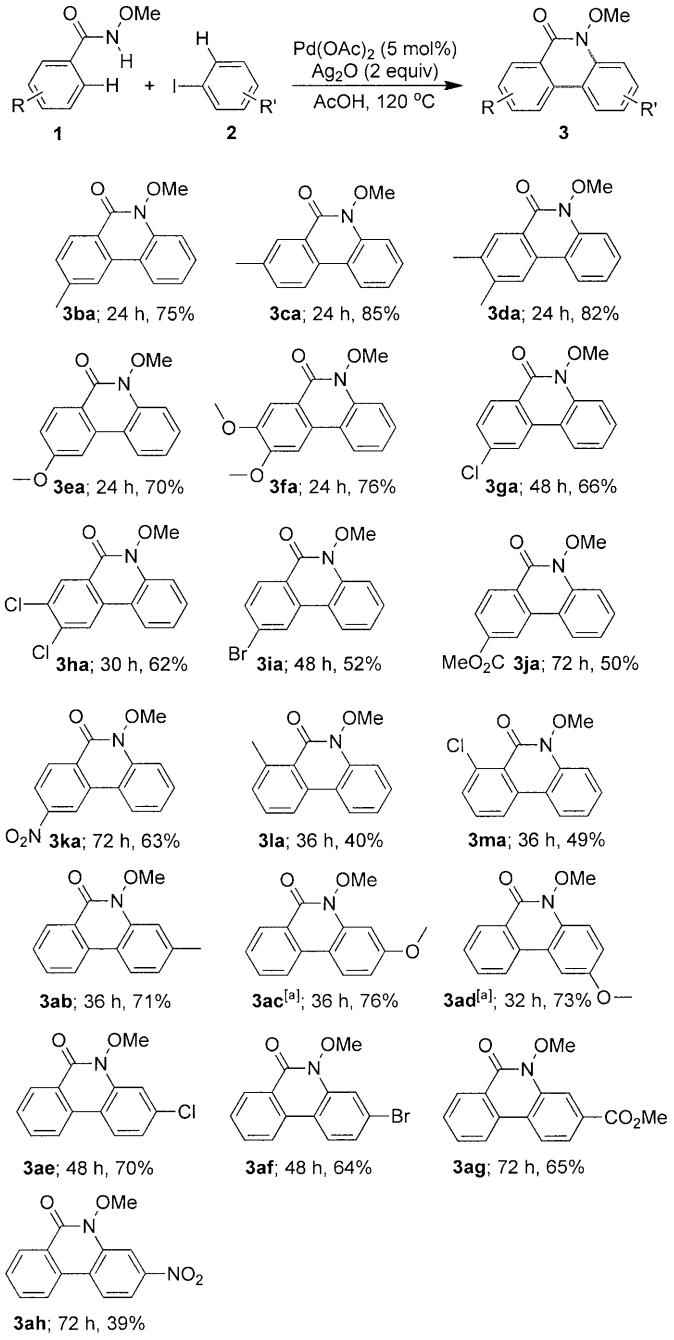


Scheme 2. Synthesis of phenanthridinones by palladium-catalyzed reaction of *N*-methoxybenzamides with aryl iodides. Unless otherwise specified, all reactions were carried out with of **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), and of Ag_2O (1.0 mmol) in AcOH (5 mL) at 120 °C. [a] 0.6 mmol of **2** and 100 °C were employed.

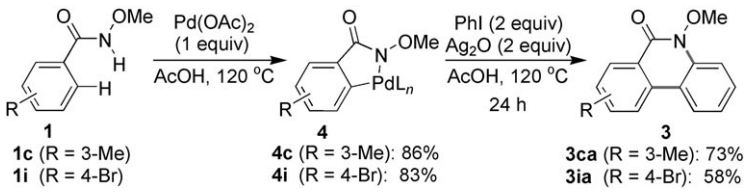
donating or electron-withdrawing groups furnished the desired products **3ba**–**3ma** in moderate to good yields. Benzamides containing electron-donating groups at the *meta* position and/or *para* position of the phenyl ring were generally more reactive and afforded higher yields than those bearing electron-withdrawing groups (70–85% for **3ba**–**3fa** vs. 50–66% for **3ga**–**3ka**). It should be emphasized that benzamide **1k** with a strong electron-withdrawing *p*-NO_2 group was also utilized, and a reasonably good yield (63%) was obtained. *Ortho* substitution on phenyl rings is known to hamper the palladium-catalyzed *ortho*-C–H functionalizations.[5,7] Thus, it was not surprising that the *o*-Me and *o*-Cl substitution on the phenyl rings of **1l** and **1m** reduced the product yields significantly relative to their *p*- and *m*-substituted counterparts. As another reaction partner, aryl iodides containing either electron-donating or electron-withdrawing groups could be employed to afford the products **3ab**–**3ah**. Similarly, aryl iodides bearing electron-donating groups were more reactive and gave better yields than those with electron-withdrawing groups. Nevertheless, the reaction with *ortho*-substituted aryl iodides such as 2-methyliodobenzene and 2-chloroiodobenzene gave a complex mixture with very low conversion, thus reflecting the extremely low efficiency of the cross-coupling step, which is probably the result of the steric hindrance of the *ortho* substituent. Furthermore, heteroaryl iodides such as 2-iodothiophene and 3-iodopyridine were unreactive while 1-iodonaphthalene gave a complex mixture under our standard reaction conditions.

As seen in Scheme 2, the halo, ester, ether, and nitro groups in either of the two phenyl rings were tolerated under our reaction conditions. The inert property of the chloro and bromo groups is consistent with the failed attempts to extend the substrates from aryl iodides to aryl bromides and chlorides. For the *meta*-substituted benzamides (**1c**, **1d**, **1f**, and **1h**) and *m*-methoxyiodobenzene (**2d**), the regioselectivity for the C–C and C–N bond formation was probably governed by steric factors.

Palladium-catalyzed C–H amination reactions have not been extensively investigated, and reports on the intramolecular[3,8] and intermolecular[9] aminations of aromatic C–H bonds are very limited because of the lack of suitable directing groups and oxidants. The formation of both C–C and C–N bonds by palladium-catalyzed cross-coupling reactions through aromatic C–H activation is known to be very sensitive to the directing groups[3,6a,c,d,f–h,7a,8c–e,10] and oxidants.[8a,d–f] Indeed, further intramolecular aminations were not observed after arylation of substrates with amides and amines as directing groups.[2,6a,c,d,f–h,10] Therefore, our synthesis of phenanthridinones through one-pot C–C and C–N bond formation under simple $Pd(OAc)_2/Ag_2O$ catalysis, which is operative simultaneously for two distinct processes, is unusual and intriguing.

To gain insight into the reaction mechanism we performed additional experiments. We found that treatment of benzamides **1** with $Pd(OAc)_2$ led to palladacycles **4**. For example, the reaction of **1c** with 1 equivalent of $Pd(OAc)_2$ in acetic acid at 120 °C generated palladacycle **4c** in 86% yield, while **1i** gave **4i** in 83% yield. These palladacycles could react with PhI and Ag_2O to afford products **3ca** and **3ia** in 73% and 58% yield, respectively (Scheme 3). The structure of a representative palladacycle was unequivocally established by the X-ray single-crystal analysis of a crystal of **4i** (Figure 1a)[11] grown in acetonitrile. These results hinted that palladacycle **4** should be a reaction intermediate.

The reaction of palladacycle **4** with aryl iodide could produce, in principle, **5** and **6** as the precursor of the final product through the formation of C–C and C–N bonds,



Scheme 3. Formation of palladacycle **4** and subsequent transformation to phenanthridinones **3**.

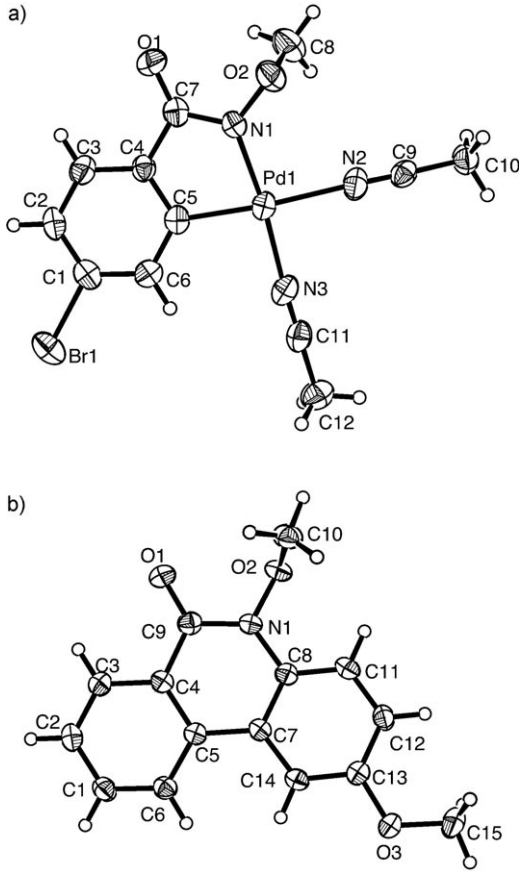
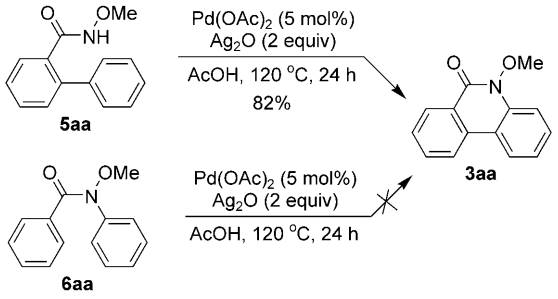


Figure 1. X-ray crystal structures of (a) palladacycle **4i**·$(CH_3CN)_2$ and (b) product **3ad**. Thermal ellipsoids are drawn at 35% probability level.

respectively. When **5aa** and **6aa** were treated with $Pd(OAc)_2$ (5%) and Ag_2O (2 equiv), only **5aa** led to product **3aa** (Scheme 4). Thus, the reaction of palladacycle **4** with aryl iodide resulted in the generation of **5** rather than **6** as the intermediate. The molecular structure of product **3**, as proved by the X-ray crystallography of **3ab** (see the Supporting Information) and **3ad** (Figure 1b),[11] could only be generated by the C–C and C–N bond-formation sequence, not vice versa. Furthermore, diaryl compound **5** was observed and could be isolated during the palladium-catalyzed reaction of **1** with **2**.

Based on the aforementioned results, a possible reaction mechanism has been proposed (Scheme 5). The reaction of benzamide **1** with $Pd(OAc)_2$ forms the five-membered palladacycle **4**, which is oxidized to the Pd^{IV} species **7** by aryl iodide.[1,6a–d] Reductive elimination of **7** in the presence of Ag_2O and AcOH gives diaryl **5** and AgI accompanied by the regeneration of $Pd(OAc)_2$. A control experiment using an equimolar equivalent of $Pd(OAc)_2$ in the absence of Ag_2O resulted in a lower yield of the product, thus indicating that Ag_2O is not only an oxidant, but it also could abstract a halide. Palladation of **5** with $Pd(OAc)_2$ results in the seven-membered palladacycle **8**.[8a,b,e] The C–N bond-forming reductive elimination from **8** affords **3** and



Scheme 4. Attempted palladium-catalyzed cyclization of **5aa** and **6aa**.

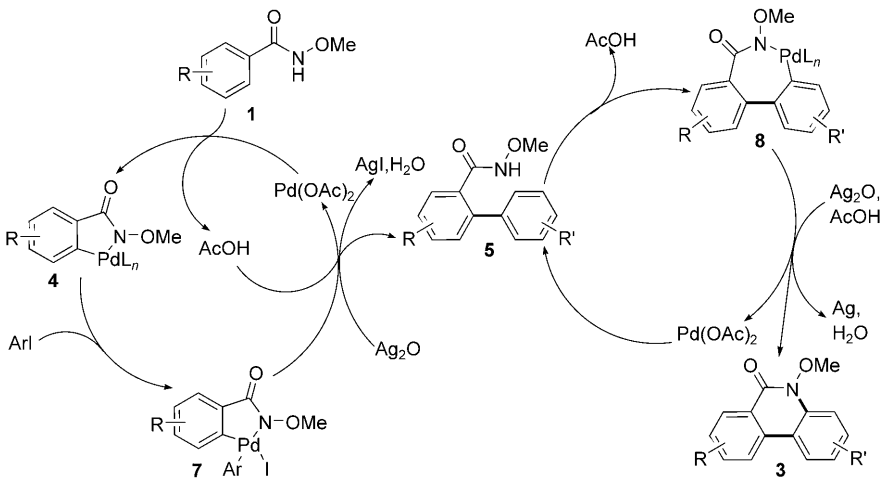
Pd^0, which regenerates Pd^{II} by the oxidation of Ag_2O. The alternative Heck-like or Wacker-like process[8d] for the formation of **3** is unlikely in our case because **2d** bearing a methoxy group at the *meta* position was more reactive than **2c** with a methoxy group at the *para* position.[12]

Phenanthridinones **3** can be further transformed into other diverse derivatives.[13] Photolysis of **3aa** in methanol efficiently gave the simplest phenanthridinone **10aa** (Scheme 6), which is the precursor of PJ34.[13a,b] Both **10aa** and PJ34 have been widely employed in biological studies.[13,14] Photolysis of **3ba** afforded **10ba** in 92% yield (Scheme 6). Product **10ba** is called phenaglydon, a natural product isolated from the lipophilic leaf extract of *Glycosmis cyanocarpa* (Rutaceae).[15]

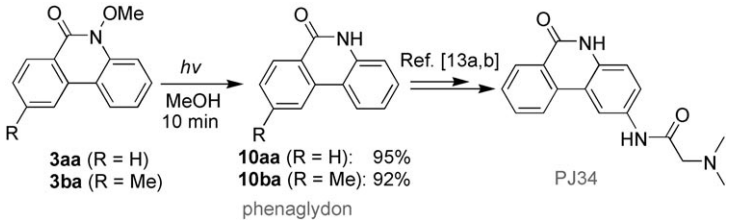
In summary, we have demonstrated that the synthesis of biologically important phenanthridinones can be achieved by palladium-catalyzed dual C–H activation through the one-pot formation of C–C and C–N bonds. This reaction sequence involves the rupture of two C–H bonds, one C–I bond, and one N–H bond, as well as the formation of one C–C bond and one C–N bond. The Pd^{II}-Pd^{IV}-Pd^{II} and Pd^{II}-Pd^0-Pd^{II} catalytic cycles operate simultaneously in our system. The replacement of benzamides **1** with non-MeO-substituted benzamides did not afford satisfactory results. The further development of this latter strategy and of other one-pot cascade reactions through palladium-catalyzed C–H activation is currently under way.

Experimental Section

General procedure for the synthesis of **3**: Ag_2O (231.7 mg, 1 mmol) was added to a stirred solution of *N*-methoxybenzamide **1** (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and aryl iodide **2** (1 mmol, 0.6 mmol for **2c** and **2d**) in AcOH (5 mL) at 120 °C (100 °C for **2c** and **2d**). The reaction was monitored by TLC. Upon completion, the solvent was evaporated in vacuo. The residual was separated by column chroma-



Scheme 5. Proposed reaction mechanism. L_n = ligand.



Scheme 6. Photolysis of **3aa** and **3ba** and subsequent conversion.

tography on silica gel with petroleum ether/ethyl acetate 6:1 as the eluent to afford product **3**.

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