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Deamidation Coupling

Practical Synthesis of Phenanthridinones by Palladium-Catalyzed One-Pot C–C and C–N Coupling Reaction: Extending the Substrate Scope to *o*-Chlorobenzamides

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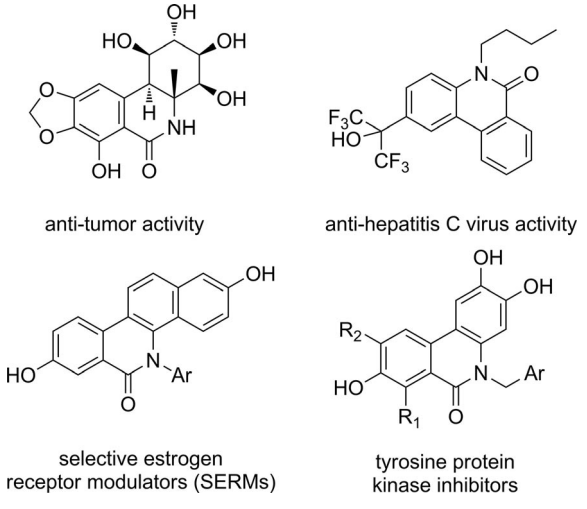
Abstract: A highly efficient construction of phenanthridinone derivatives from *o*-halobenzamides was developed by using a phosphine-free palladium catalyst in *N*,*N*-dimethylacetamide. The domino reaction proceeds through a sequential C–C and C–N bond-formation process in one pot. This protocol exhibits broad substrate scope and affords a series of phenanthridinones in up to 93 % yield. Importantly, the protocol could also be applied for the less reactive *o*-chlorobenzamides. The approach constitutes the first example of the synthesis of phenanthridinones from this kind of substrate. Moreover, the success of a gram-scale reaction demonstrated that this operationally simple process is scalable.

Introduction

Phenanthridinones composed of three fused six-membered rings are the key motifs of Amaryllidaceae alkaloids, which have potent biological activity, including antitumor and antivirus activities, and acetylcholinesterase inhibition (Scheme 1).[1] The development of synthetic methods for the construction of phenanthridinones and their derivatives has been an area of intense research. The conventional synthetic methods usually require multiple steps or harsh reaction conditions.[2] Therefore, an efficient and practical protocol for the preparation of phenanthridinones remains in demand. In recent years, palladium-mediated coupling reactions have developed into one of the most powerful tools in organic synthesis because of its high efficiency in the assembly of new compounds. In this context, a palladium-catalyzed approach has been developed to provide an alternative access to phenanthridinones.[3,4] For instance, palladium-catalyzed intramolecular direct arene arylation,[3b] Suzuki–Miyaura cross-coupling of (2-aminophenyl)boronic acid with *o*-halobenzoate,[3l] decarboxylative coupling of 2-(2-bromo-*N*-methylbenzamido)benzoic acid,[3m] double or multiple C–H activation starting from *N*-methoxybenzamide and aryl iodide or simple arenes have been reported.[3p,3q] Readily available *o*-halobenzamide derivatives have frequently been used as starting materials. These compounds can be annulated by arynes[3k] or cyclized with *ortho*-substituted iodoarenes in the presence of norbornene[3a] to afford the phenanthridinones. Recently, important studies reported by Catellani, Kan, and Porée revealed that two molecules of *o*-halobenzamide could be coupled to form phenanthridinone by palladium-catalyzed C–N deamidation and C–C coupling reaction involving *ipso*-substitution, respectively.[3f–3j] However, these reaction systems require either air-sensitive phosphine ligands or malodorous norbornene as additives. Furthermore, the scope of the reactions is usually limited to *o*-bromo(iodo)benzamides (Scheme 2); the use of more challenging but less expensive *o*-chlorobenzamides as substrates have not been reported. These problems stimulated us to find alternative catalytic systems for the synthesis of phenanthridinone derivatives. Herein, we report a phosphine-free palladium-catalyzed system for the construction of the phenanthridinone derivatives from *o*-bromo(chloro)-benzamides.



Scheme 1. Selected examples of phenanthridinone derivatives as natural products or key skeleton of bioactivity.

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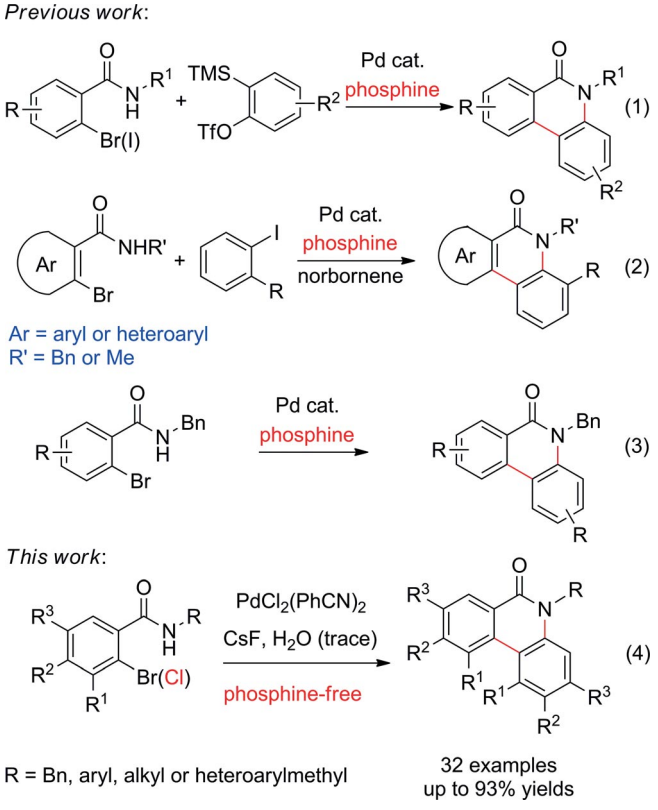


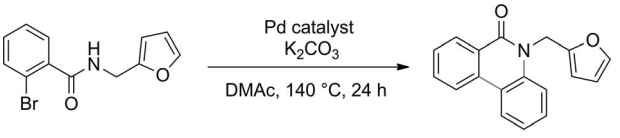
Scheme 2. Palladium-catalyzed C–N deamidation coupling reaction and C–C coupling reaction.

Results and Discussion

Initially, we carried out the reaction in *N*,*N*-dimethylacetamide (DMAc) at 140 °C, in the presence of 2 mol-% of $PdClC_3H_5dppb$ and K_2CO_3, in an attempt to construct azepinone, a seven-membered lactam, from compound **1a** by Pd-catalyzed direct intramolecular C–H arylation.[5] However, possibly due to the extremely low reactivity of the furan C3–H group,[6] no expected azepinone was detected. Instead, phenanthridinone derivative **1b** was obtained in 56 % yield (Table 1, Entry 1). The result turned our focus towards developing an efficient way to synthesize phenanthridinone derivatives. The optimization of reaction conditions are shown in Tables 1 and 2.

Upon testing several other Pd salts, it was found that $Pd(OAc)_2$ and $PdCl_2$ gave much lower yields (Table 1, Entries 3 and 4), whereas the use of $Pd_2(dba)_3$ or $PdCl_2(PhCN)_2$ resulted in comparable yields (Entries 2 and 5). Therefore, we subsequently used a phosphine-free palladium catalyst $PdCl_2(PhCN)_2$ for further optimization. The nature of the base was also found to be important for the reaction. Although it was shown by other groups that the carbonate base was necessary for the reaction to proceed,[3i,3j] our base screening investigation demonstrated that CsF and K_3PO_4 were also suitable for our system, affording **1b** in 71 and 62 % yield, respectively. The yield was further enhanced to 85 % by using 4.0 equiv. CsF (Table 2, Entry 6). The reason why CsF is so effective might be that it enhances deprotonation of the N–H group by hydrogen-bond formation. Further optimization led to the discovery that

Table 1. Optimization of Pd catalyst.[a]

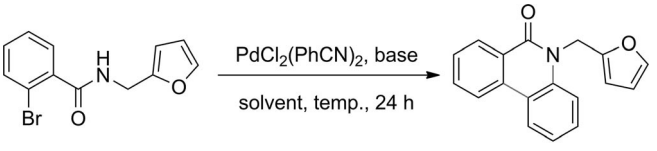


1a **1b**

Entry	Pd source	Yield of **1b** [%][b]
1	$PdClC_3H_5dppb$	56
2	$Pd_2(dba)_3$	55
3	$PdCl_2$	35
4	$Pd(OAc)_2$	37
5	*$PdCl_2(PhCN)_2$*	*58*

[a] Reaction conditions: Pd catalyst (2 mol-%), **1a** (0.5 mmol, 1 equiv.), K_2CO_3 (3 equiv.), DMAc (2 mL), 140 °C, 24 h. [b] Detected by NMR spectroscopic analysis using an internal standard.

Table 2. Optimization of the reaction conditions.[a]



1a **1b**

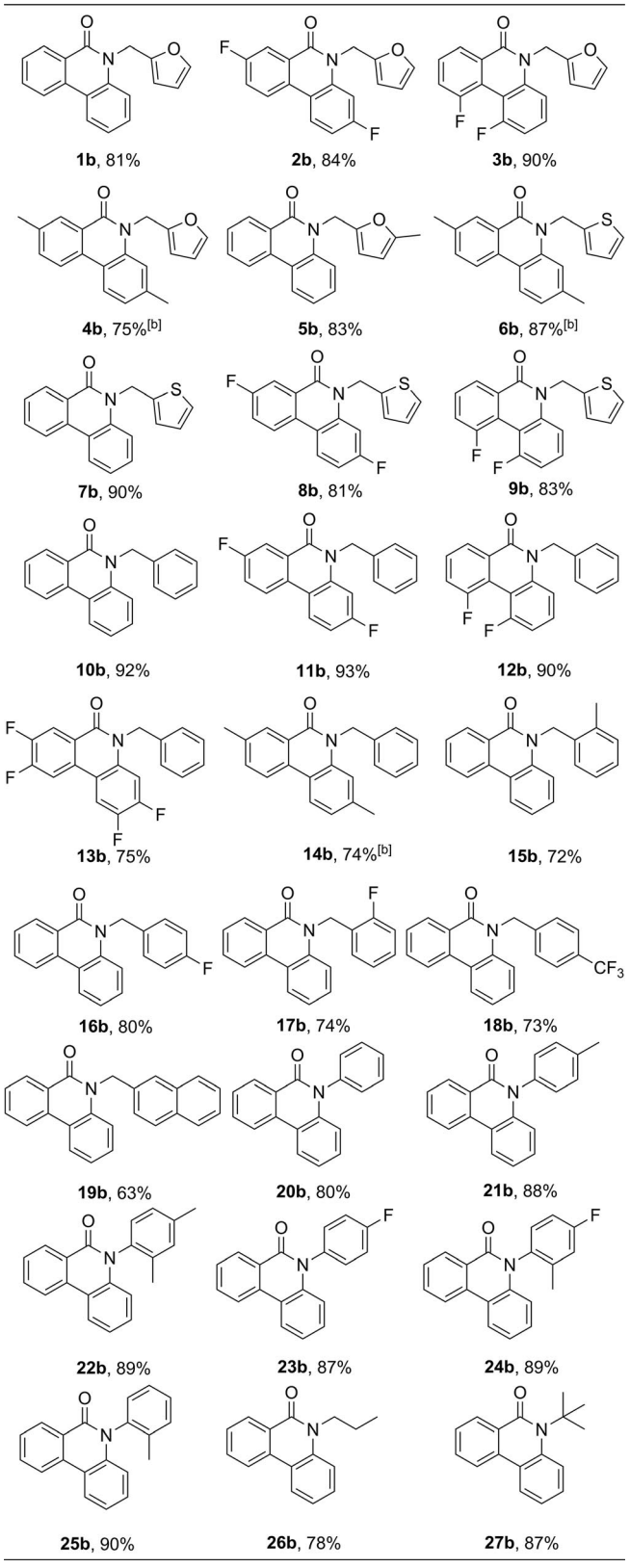
Entry	Base (equiv.)	Additive (μL)	Solvent	Yield of **1b** [%][b]
1	K_2CO_3 (3)	–	DMAc	58
2	KOAc (3)	–	DMAc	9
3	K_3PO_4 (3)	–	DMAc	62
4	KF (3)	–	DMAc	66
5	CsF (3)	–	DMAc	71
6	CsF (2)	–	DMAc	48
7	CsF (4)	–	DMAc	85
8	CsF (5)	–	DMAc	48
9	CsF (4)	H_2O (1)	DMAc	78
10	CsF (4)	H_2O (2)	DMAc	92
11	CsF (4)	H_2O (3)	DMAc	88
12	CsF (4)	H_2O (4)	DMAc	34
13	CsF (4)	H_2O (2)	xylene	32
14	CsF (4)	H_2O (2)	NMP	61
15	CsF (4)	H_2O (2)	diglyme	42
16	CsF (4)	H_2O (2)	DMF	72
17[c]	CsF (4)	H_2O (2)	DMAc	68
18[d]	CsF (4)	H_2O (2)	DMAc	80

[a] Reaction conditions: $PdCl_2(PhCN)_2$ (2 mol-%), **1a** (0.5 mmol, 1 equiv.), solvent (2 mL), 140 °C, 24 h. [b] Based on NMR spectroscopic analysis using an internal standard. [c] 120 °C. [d] 160 °C.

the presence of water has a great influence on the yield. A detailed investigation on the effect of the amount of water revealed that 2 μL of water is optimal, improving the yield to 92 % (Entry 9). Solvent screening and temperature variation experiments showed that the best solvent was DMAc, and the best temperature was 140 °C. Consequently, the catalytic system was established as: 2 mol-% of $PdCl_2(PhCN)_2$ and 4.0 equiv. of CsF, with 2 μL of water as additive in DMAc. These conditions were used to investigate the scope of the reaction.

Under the optimized reaction conditions, we set out to test the scope of the reaction with respect to amides (Table 3). A diverse range of *N*-heteroaromatic, *N*-aromatic and *N*-alkyl-*o*-

Table 3. Scope of the reaction with respect to bromo-substituted substrate.[a]



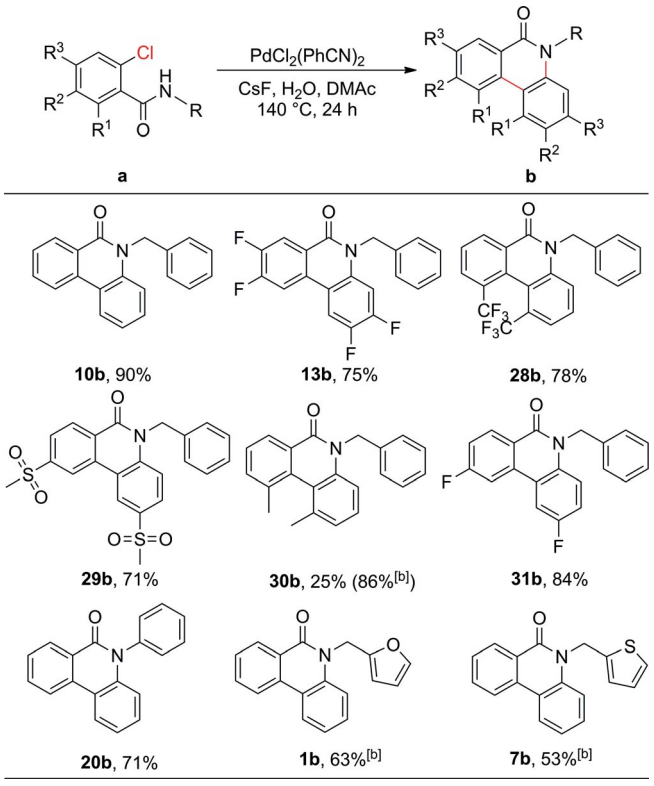
[a] Reaction conditions: $PdCl_2(PhCN)_2$ (2 mol-%), substrate (0.25 mmol, 1 equiv.), CsF (4 equiv.), DMAc (1 mL), H_2O (1 μL), 140 °C, 24 h. Isolated yields. [b] $PdCl_2(PhCN)_2$ (4 mol-%).

bromoarylamides were found to be suitable substrates. When the N-substituted groups of R were heteroaromatics (**1b**–**9b**), good yields (81–90 %) were obtained. Notably, the thiophene-substituted substrates, which contain a sulfur atom, did not appear to poison the palladium catalyst (**6b**–**9b**). *N*-Benzylarylamides provided the corresponding phenanthridinone derivatives **10b**–**19b** in 63–93 % isolated yields. *N*-Phenyl- and *N*-alkylarylamides also reacted smoothly and gave the product in excellent yields (**20b**–**27b**). The electron nature of the aromatic ring in *o*-bromobenzamide affected the outcome of the reaction to a certain extent. Electron-neutral and electron-deficient substrates all afforded the expected products in high yields (**1b**–**3b**, **5b**, **7b**–**13b**, and **15b**–**27b**).[7] In the case of the electron-rich substrates (e.g., $R^2 = CH_3$), an increase in the amount of catalyst to 4 mol-% was required to achieve good yields (**4b**, **6b**, and **14b**). This phenomenon differed from the previously reported results, for which the reaction efficiency depended strongly on the electronic nature of the substrates, and the scope of the reaction was limited to electron-rich *o*-bromobenzamides.[3g,3i,3j] In contrast, electron-withdrawing groups such as F and CF_3 were compatible with our system. To our surprise, when F was present *ortho* to the bromine atom, good results could still be obtained despite the increased steric hindrance (**3b**, **9b**, and **12b**). We expect that this catalytic system will be an effective complementary approach to existing processes.

Aryl chlorides remain an uncommon reagent in Pd-catalyzed coupling reactions because of the low reactivity of the relatively inert C–Cl bond. However, because of their lower cost and wider diversity, aryl chlorides are always attractive substrates in place of their bromo counterparts. We were pleased to find that *o*-chlorobenzamide derivatives were also reactive under the established catalytic conditions, albeit requiring a higher catalyst loading of 4 mol-% (Table 4). To our knowledge, the use of chlorobenzamide as substrate to construct phenanthridinone by Pd-catalyzed aryl–aryl and N–aryl coupling has not been reported. Selected examples are outlined in Table 4.

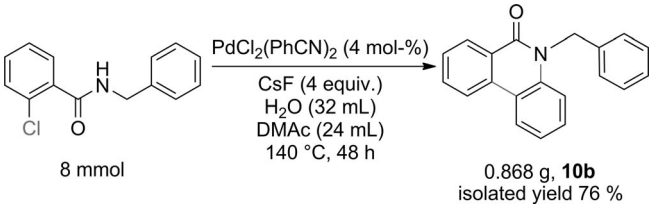
N-Substituted *o*-chlorobenzamides were investigated to study the effect of the R group on the reaction. Both benzyl and phenyl groups afforded the corresponding products in good to excellent yields (Table 4; **10b** vs. **20b**). The amide core can be electron-neutral and electron-deficient. For example, both benzamide and arylamides containing a fluoro, methylsulfonyl, or trifluoromethyl group generated the corresponding products in good yields (71–84 %). Interestingly, even *N*-benzyl-2-chloro-3-(trifluoromethyl)benzamide, bearing a sterically demanding 3-CF_3 substituent, resulted in a 78 % yield of **28b**. In contrast, substrate *N*-benzyl-2-chloro-3-methylbenzamide, bearing a weak electron-donating 3-CH_3 group, gave the corresponding desired product **30b** in only 25 % yield. The use of $PCy_3{\cdot}HBF_4$ as a promoter, which is a popular ligand,[8] greatly improved the yield of **30b** to 86 %. In contrast to the result obtained with *o*-bromo-*N*-heteroaromatic-substituted substrates, relatively low yields were induced when the *o*-chloro derivative had a heteroaryl group attached to the N atom, which led mainly to recovery of starting material. However, it is notable that the reaction proceeded with moderate yields in the presence of the PCy_3 ligand (**1b** and **7b**).

Table 4. Scope of the reaction with respect to chloro-substituted substrates.[a]



[a] Reaction conditions: $PdCl_2(PhCN)_2$ (4 mol-%), substrate (0.25 mmol), CsF (4 equiv.), DMAc (1 mL), H_2O (1 μL), 140 °C, 24 h. Isolated yields. [b] $PCy_3{\cdot}HBF_4$ (8 mol-%).

A scaled-up experiment (Scheme 3) was performed on a gram-scale reaction of *N*-benzyl-2-chlorobenzamide under the same conditions. Scaled up by 32 times to 8 mmol, the reaction proceeded as expected to give the desired product **10b** in 76 % isolated yield, demonstrating the practicality of this method.



Scheme 3. Scaled-up version of the reaction.

Conclusions

We have reported a highly efficient system for the construction of phenanthridinones from *N*-substituted 2-halobenzamides through a palladium-catalyzed domino process involving C–C coupling and C–N deamidation. Compared with previous approaches, this novel protocol exhibits broad substrate scope and operational simplicity, because it avoids the use of air-sensitive phosphine ligand. More importantly, the less reactive *N*-substituted 2-chlorobenzamides could also been used in this catalytic system.

Experimental Section

General Remarks: All reactions were carried out in dried Schlenk tubes under argon. Unless otherwise indicated, reagents obtained from commercial sources were used without further purification. DMAc, DMF, xylene and NMP were dried and distilled under reduced pressure and stored over molecular sieves (4 Å). NMR spectra were recorded with a Bruker Avance II (400 MHz) spectrometer. HR mass spectra (ESI) were recorded with a Waters Q-TOF Premier spectrometer.

General Procedure for the Synthesis of Substrates (Amides): 2-Bromobenzoic acid (1 mmol, 201 mg, 1 equiv.) or its derivative was dissolved in CH_2Cl_2 (5 mL); then Et_3N (1.1 mmol, 154 μL, 1.1 equiv.) was added dropwise followed immediately by the dropwise addition of isobutyl chloroformate (1.1 mmol, 143 μL, 1.1 equiv.) at 0 °C. The mixture was stirred for 15 min; then amine (1.2 mmol, 1.2 equiv.) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. Upon complete consumption of 2-bromobenzoic acid, the mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc/CH_2Cl_2, 5:1:2 or 9:1:2) to afford the desired compound.

Typical Procedure for the Palladium-Catalyzed C–N Deamidation Coupling Reaction and C–C Coupling Reaction of 2-Bromo-*N*-(furan-2-ylmethyl)benzamide (1a): $PdCl_2(PhCN)_2$ (0.01 mmol, 3.8 mg), 2-bromo-*N*-(furan-2-ylmethyl)benzamide (**1a**; 0.5 mmol, 140.1 mg), CsF (2 mmol, 304 mg), and H_2O (2 μL, 0.11 mmol) were added to a Schlenk flask, and the mixture was dissolved in anhydrous DMAc (2 mL) under nitrogen. The reaction mixture was stirred at 140 °C for 24 h; then ethyl acetate was added to dissolve the mixture as much as possible (except for inorganic salts). Celatom was used to filter undissolved substances. The solvent was then evaporated under vacuum, and the mixture was purified by column chromatography on silica gel (petroleum ether/EtOAc/CH_2Cl_2, 5:1:2) to afford **1b** (55.7 mg, 81 %) as a pale-yellow solid.

Acknowledgments

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Keywords: Palladium · Domino reactions · C–C coupling · C–N coupling · Synthetic methods

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