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Synthesis of Phenanthridinones and Phenanthridine Derivatives through Palladium-catalyzed Oxidative C–H Coupling of Benzanilides

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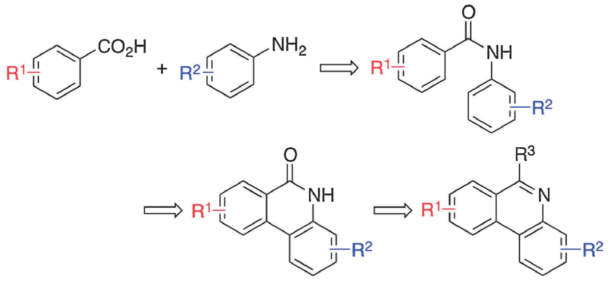
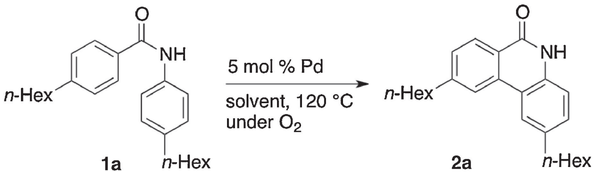
A palladium-catalyzed oxidative C–H coupling reaction of benzanilides using molecular oxygen as the oxidant furnishes phenanthridinones. The palladium-catalyzed reaction in combination with simple derivatization provides an efficient access to a phenanthridine skeleton starting from readily available benzoic acids and anilines.

Phenanthridine is an important structural motif which is found in a number of natural products[1] and fluorescent chromophores.[2] Although a number of reactions to construct a phenanthridine skeleton have been reported,[3,4] the search for better properties with such compounds requires more efficient synthetic methods equipped with structural diversity using readily available building blocks. This led us to envisage a synthetic pathway starting from benzoic acids and anilines leading to phenanthridines via phenanthridinones, as shown in Scheme 1. Benzanilide is readily synthesized by condensation of benzoic acid and aniline. Phenanthridinone is obtained by an oxidative C–H coupling reaction of benzanilide, for which a palladium/tin cocatalyst system is known to be effective.[5–7] The secondary amide moiety of phenanthridinone can be activated by triflation for further transformations, leading to the synthesis of 6-substituted phenanthridines. Since a wide variety of anilines and benzoic acids are available from commercial sources, this synthetic pathway would give rise to significant structural diversity. In this paper, we describe the tin-free palladium-catalyzed oxidative C–H coupling reaction of *N*-H benzanilides and its application to the synthesis of phenanthridine derivatives.



Scheme 1. Synthetic pathway to phenanthridines.

Table 1. Optimization of reaction conditions[a]



1a **2a**

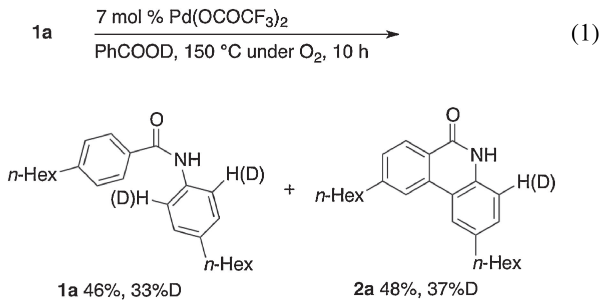
Entry	Pd	Solvent	Yield/%[b]
1	$Pd(OAc)_2$	AcOH	14
2	$Pd(OCOCF_3)_2$	AcOH	27
3	$Pd(OCOCF_3)_2$	*t*-BuCOOH	12
4	$Pd(OCOCF_3)_2$	CF_3COOH	not detected
5	$Pd(OCOCF_3)_2$	PhCOOH	42
6[c]	$Pd(OCOCF_3)_2$	PhCOOH	92 (91)

[a]Reaction conditions: 0.10 mmol **1a**, 5 mol % Pd, 1.0 mL solvent or 1.0 g PhCOOH, 120 °C, 24 h, O_2 atmosphere (1 atm) unless otherwise noted. [b]NMR yield. Isolated yield is in parentheses. [c]7 mol % $Pd(OCOCF_3)_2$, 150 °C, 48 h.

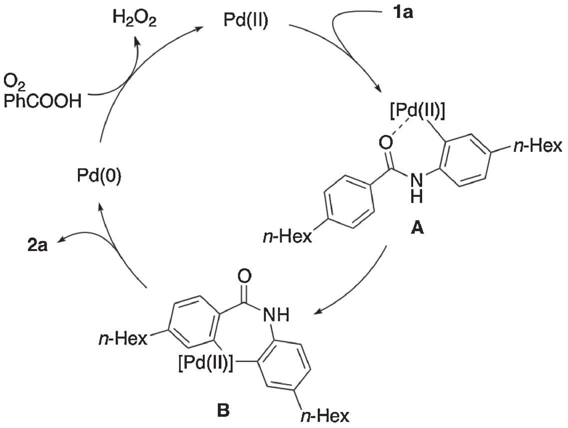
We initially reexamined the reaction conditions for palladium-catalyzed oxidative C–H coupling of benzanilide (Table 1). When **1a** was heated at 120 °C for 24 h in the presence of $Pd(OAc)_2$ (5 mol %) under an oxygen atmosphere (1 atm) in acetic acid, phenanthridinone **2a** was formed in 14% NMR yield (Entry 1). Palladium(II) trifluoroacetate was more reactive than $Pd(OAc)_2$, giving **2a** in 27% yield under otherwise identical conditions (Entry 2). The yield varied depending on the solvents and we found that melted benzoic acid afforded a relatively good result. In particular, when benzanilide **1a** was heated at 150 °C for 48 h in the presence of 7 mol % of $Pd(OCOCF_3)_2$ under an oxygen atmosphere (1 atm) in melted benzoic acid, phenanthridinone **2a** was obtained in 91% isolated yield (Entry 6). In contrast, only a small amount of **2a** was produced when other nonprotic solvents such as toluene, DCE (1,2-dichloroethane), and NMP (*N*-methylpyrrolidone) were employed and 5 equiv of benzoic acid was added therein.

For comparison, we conducted oxidative C–H coupling of **1a** under the reaction conditions which were previously reported for analogous oxidative C–H coupling of anilides.[5–7] With a $Pd(OCOCF_3)_2/Sn(OAc)_2$ cocatalyst system reported by Åkermark,[5b] **2a** was obtained in 38% yield. The catalytic systems for cross-coupling of anilides with benzenes developed by Shi (5 mol % $Pd(OAc)_2$, 10 mol % $Cu(OTf)_2$, EtCOOH, O_2, 120 °C, 24 h)[6a] and Buchwald (5 mol % $Pd(OAc)_2$, 10 mol % DMSO, 5 equiv CF_3COOH, benzene, O_2, 120 °C, 24 h)[6b] gave **2a** in 11% and <5% yields, respectively. No reaction was observed when **1a** was subjected to the reaction conditions reported by Dong[7] (10 mol % $Pd(OAc)_2$, 4 equiv $Na_2S_2O_8$, 5 equiv CF_3COOH, DCE, 70 °C). Thus, our conditions proved to be efficient and environmentally friendly in comparison with the reported conditions.

Next, the palladium-catalyzed oxidative C–H coupling reaction of **1a** was carried out in melted PhCOOD in order to gain mechanistic insight (eq 1). When the reaction at 150 °C was stopped after 10 h, a mixture of benzanilide **1a** (46% recovery) and phenanthridinone **2a** (48% yield) was obtained. Deuterium incorporation was detected by integration values in the ^{1}H NMR spectra of both compounds. With recovered benzanilide **1a**, 33% deuterium incorporation was observed at



the *ortho*-positions of the anilide moiety and no deuterium was incorporated onto the benzoyl moiety. With the cyclized product **2a**, deuterium was also incorporated only at the *ortho*-position of the anilide moiety (37% incorporation).



Scheme 2. Proposed mechanism.

On the basis of these results, we propose a possible mechanism, which is described in Scheme 2. The amide group of benzanilide **1a** acts as a directing group and the carbonyl oxygen coordinates to palladium to promote *ortho*-palladation of the anilide moiety of **1a**, resulting in the formation of arylpalladium species **A**.[8] We assume that the palladation occurs by an electrophilic aromatic substitution mechanism[9] and that the process is reversible. In the deuterium experiment mentioned above, protonation of **A** with PhCOOD gives benzanilide **1a** deuterated at the *ortho*-position of the anilide moiety. Uncoordination of the carbonyl group of the intermediate **A** and the rotation of the amide bond places the *ortho*-position of the benzoyl moiety in close proximity to the palladium center, leading to the second aromatic palladation to generate intermediate **B**. Reductive elimination gives phenanthridinone **2a** with release of palladium(0), which is reoxidized to palladium(II) by molecular oxygen with the assistance of benzoic acid.[10]

Various benzanilides were subjected to the palladium-catalyzed oxidative cyclization reaction and the results are shown in Chart 1.[11] Nonsubstituted benzanilide **1b** afforded phenanthridinone (**2b**) in 89% yield. A 4-methoxy group on the benzoyl moiety (**2c**), 3-trifluoromethyl groups on both the anilide and the benzoyl moieties (**2d** and **2e**), and a 4-ethoxycarbonyl group of the anilide moiety (**2f**) were tolerated and the corresponding phenanthridinones were obtained in yields ranging from 57 to 78%. Chloro groups (**2g** and **2h**) remained intact under the reaction conditions. On the other hand, bromo and cyano substituents were not tolerated under the reaction conditions.

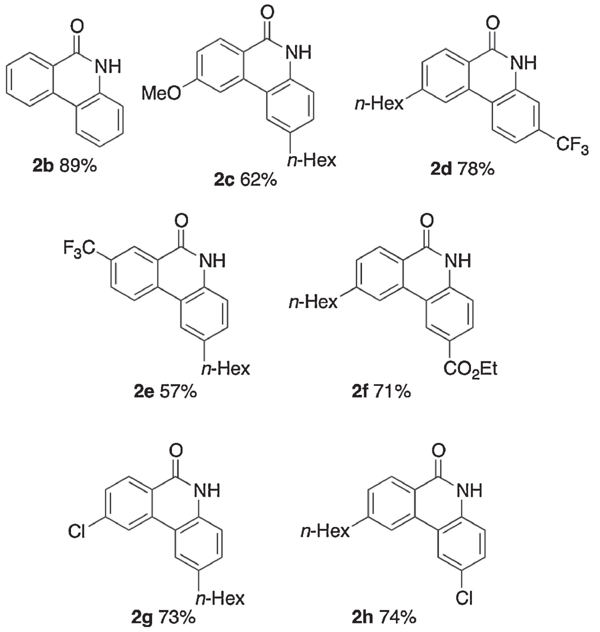
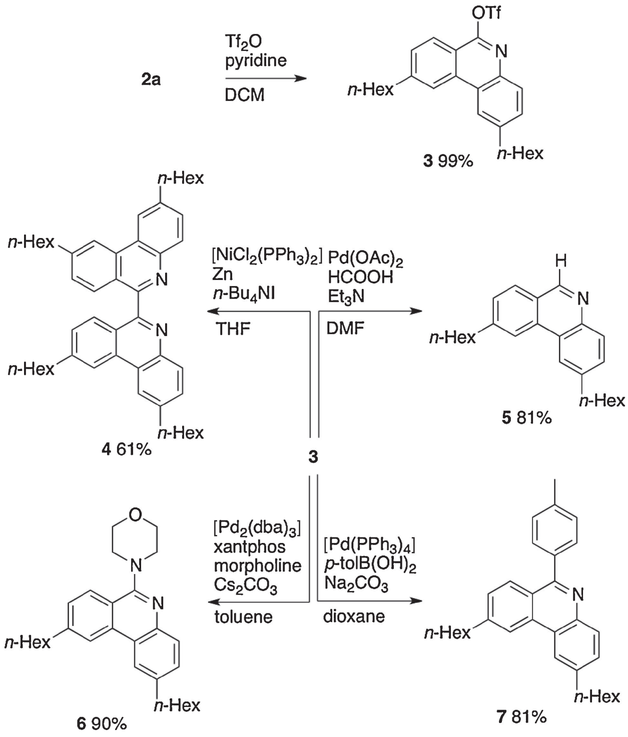


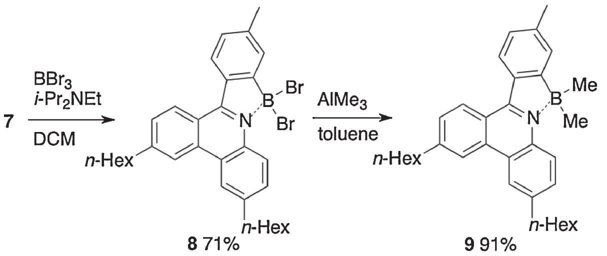
Chart 1. Synthesized phenanthridinones.



Scheme 3. Synthesis of phenanthridine derivatives.

We next examined derivatization of phenanthidinone **2a** to various phenanthridines via phenanthridine triflate **3** (Scheme 3). Initially, the phenanthridinone **2a** was treated with trifluoromethanesulfonic anhydride to give triflate **3** in quantitative yield. The triflate **3** served as a useful building block for the synthesis of a variety of phenanthridines. Homocoupling of **3** proceeded in the presence of a nickel catalyst, yielding bi(phenanthridine) **4** in 61% yield.[12] Palladium-catalyzed reduction of **3** with formic acid afforded phenanthridine **5** in 81% yield. An aryl substituent as well as an amine substituent was introduced by the palladium-catalyzed coupling reactions to produce the corresponding coupling products **6** and **7** in 90 and 81% yields, respectively.

6-Tolylphenanthridine **7** was further applied to the synthesis of an intramolecular borane complex (eq 2), which was expected to be potent light-emitting material with a considerably low-lying LUMO level.[13] According to the method we recently reported,[14] **7** was treated with boron tribromide to provide phenanthridine–dibromoborane complex **8** in 71% yield. Methylation of **8** with trimethylaluminum furnished the phenanthridine–borane complex **9**, which exhibited blue fluorescence ($\lambda = 422\,\text{nm}$, $\Phi = 0.58$ in CH_2Cl_2) and less negative reduction potential ($E_{\text{red}} = -1.56\,\text{V}$)[15] than Alq_3 ($E_{\text{red}} = -2.36\,\text{V}$).[16]



(2)

In summary, we have developed a catalytic reaction which oxidatively cyclizes benzanilides into phenanthridinones. The palladium-catalyzed reaction in combination with simple derivatization provides an efficient access to a phenanthridine skeleton starting from readily available benzoic acids and anilines.

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