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Palladium-Catalyzed Oxidative Insertion of Carbon Monoxide to *N*-Sulfonyl-2-aminobiaryls through C−H Bond Activation: Access to Bioactive Phenanthridinone Derivatives in One Pot

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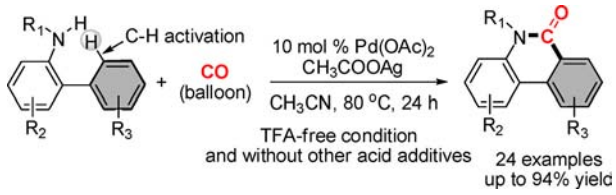
ABSTRACT



Palladium-catalyzed oxidative carbonylation of *N*-sulfonyl-2-aminobiaryls through C−H bond activation and C−C, C−N bond formation under TFA-free and milder conditions has been developed. The reaction tolerates a variety of substrates and provides biologically important phenanthridinone derivatives in yields up to 94%.

The structural moiety of phenanthridinones is widely occurring in a variety of natural products and biologically active drug intermediates (Figure 1).[1] Since the molecular skeleton has biological importance, such as antitumor activity, antiviral activity, and cytotoxicity, the development of a more straightforward synthetic method has been an attractive topic of research.[2] The transition-metal-catalyzed C−H bond activation strategy has grown as an efficient method for constructing C−C, C−N, C−O bonds and has been extensively used to synthesize various natural products and bioactive molecules.[3] Independent reports by Cheng and Wang's research groups have recently displayed the Pd- and Rh-catalyzed synthesis of

[†] These authors contributed equally.

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phenanthridinones from *N*-methoxy benzamides with aryl iodides or arylboronic acids via dual C−H bond activations (Scheme 1).[4]

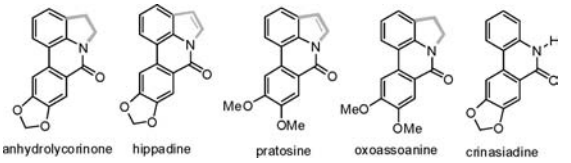


Figure 1. Naturally occurring phenanthridone-based natural products.

In this context, transition-metal-catalyzed carbonylation of organic compounds has turned into one of the most important approaches in C−C, C−N bond-forming processes.[5] In this regard, Yu et al.[6] have demonstrated the *ortho* carbonylation of anilides and carboxylic acids through Pd(II)-catalyzed C−H bond activation under a CO atmosphere. A recent report by Chatani, Rovis, Booker-Milburn and co-workers revealed the synthesis of phthalimides[7] through oxidative carbonylation of benzamides via Pd-, Ru-, and Rh-mediated C−H bond activation, respectively. Similarly, Pd-catalyzed oxidative dual C−H functionalization/carbonylation of diaryl ethers for the synthesis of xanthones was achieved by Lei.[8] We recently reported the annulation of benzamides and *N*-sulfonyl-2-aminobiaryls with [60]fullerene through Pd(II)-catalyzed C−H bond activation that afforded [60]fulleroisoquinolinones and [60]fulleroazepines, respectively.[9] There are a number of strategies through which phenanthridines[10] and carbazoles[11] have been synthesized from 2-aminobiaryl systems; however, insertion of CO for making phenanthridinones has yet to be explored further. We anticipated that if the C_{60} in our previous work[9c] were replaced with CO, we would access exclusively bioactive phenanthridinone derivatives (Scheme 1). Owing to the synthetic values of the phenanthridinone structure and our continuing interests in the Pd-catalyzed C−H activation reactions, herein we report the oxidative insertion of carbon monoxide with *N*-sulfonyl-2-aminobiaryls through C−H bond activation under trifluoroacetic acid (TFA)-free and milder conditions (Scheme 1).

Scheme 1. Approaches for Synthesis of Phenanthridinones through C−H Bond Activation

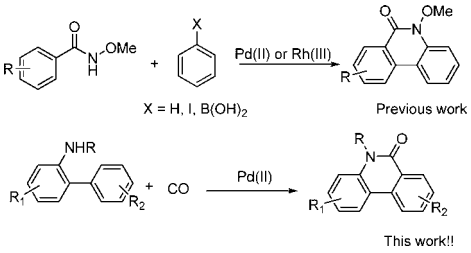
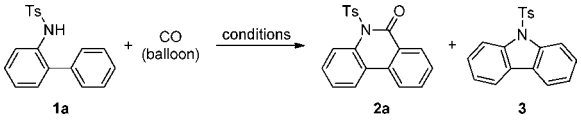


Table 1. Optimization of Reaction Conditions[a]



entry	oxidants (equiv)	solvent (mL)	temp (°C), time (h)	yield of **2a** (%)[b]	yield of **3** (%)[b]
1	CH_3COOAg (2)	DMSO (4)	100, 4 h	36 (57)	28
2	CH_3COOAg (2)	THF (4)	70, 4 h	45 (85)	trace
3	CH_3COOAg (2)	CH_3CN (4)	80, 24 h	40 (89)	–
4	CH_3COOAg (3)	CH_3CN (4)	80, 24 h	79 (98)	–
5	CH_3COOAg (4)	CH_3CN (4)	80, 24 h	90 (98)	–
6	**CH_3COOAg (5)**	**CH_3CN (4)**	**80, 24 h**	**94 (100)**	–
7	$Cu(OAc)_2$ (2)	CH_3CN (4)	80, 20 h	44 (66)	–
8	Ag_2O (2)	CH_3CN (4)	80, 20 h	46 (64)	–
9	BQ (2)	CH_3CN (4)	80, 20 h	0	–
10	$KHSO_5$ (2)	CH_3CN (4)	80, 20 h	35 (66)	25
11	$K_2S_2O_8$ (2)	CH_3CN (4)	80, 20 h	0	17
12	CH_3COOAg (2)	Bu-CN (4)	110, 24 h	0	49
13[c]	CH_3COOAg (5)	CH_3CN (4)	80, 24 h	81 (99)	–
14[d]	CH_3COOAg (2)	CH_3CN (4)	80, 24 h	18 (89)	–

[a] All the reactions were performed with **1a** (50 mg, 0.154 mmol), 10 mol % of $Pd(OAc)_2$ (3.47 mg, 0.015 mmol) under CO balloon. [b] Yields were measured by ^1H NMR spectroscopy, using mesitylene as an internal standard. Values in parentheses are based on converted **1a**. [c] 15 mol % of $Pd(OAc)_2$ was employed. [d] $PdCl_2(PPh_3)_2$ was used as a catalyst.

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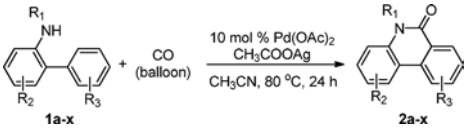
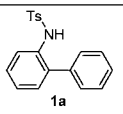
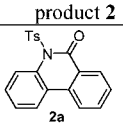
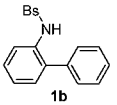
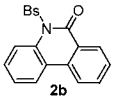
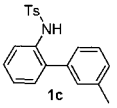
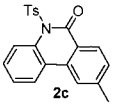
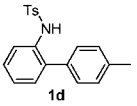
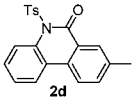
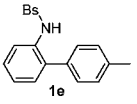
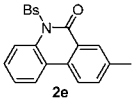
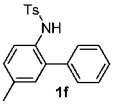
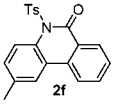
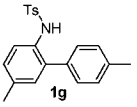
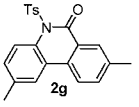
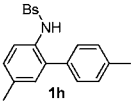
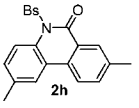
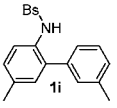
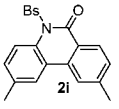
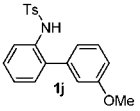
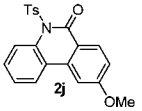
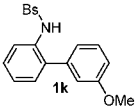
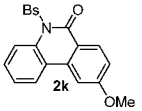
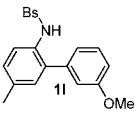
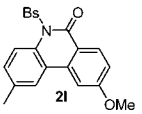
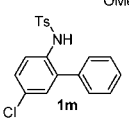
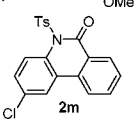
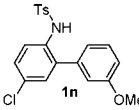
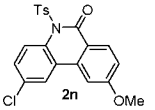
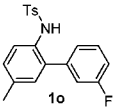
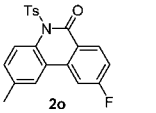
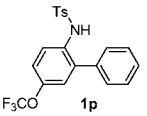
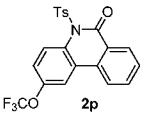
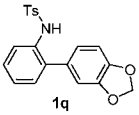
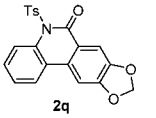
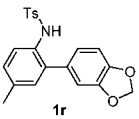
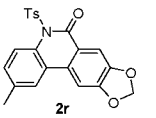
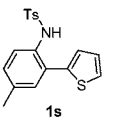
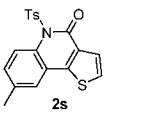
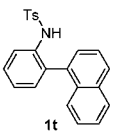
Table 2. Palladium-Catalyzed Synthesis of Phenanthridinone Derivatives[a]



entry	substrate **1**	product **2**	yield (%)[b]
1			94 (100)
2			84 (97)
3			87 (98)
4			87 (94)
5			82 (92)
6			82 (96)
7			76 (100)
8			71 (80)
9			89 (98)
10			94 (98)
11			86 (99)
12			91 (100)
13			89 (98)
14			86 (98)
15			88 (97)
16			93 (100)
17			81 (95)
18			82 (100)
19			86 (96)
20			90 (96)
21			62 (76)
22			58 (91)
23			56 (73)
24			76 (93)

[a] All reactions were carried out with substrate **1** (50.0 mg), $Pd(OAc)_2$ (10 mol %), and CH_3COOAg (5 equiv) in 4 mL of anhydrous CH_3CN at 80 °C for 24 h under CO balloon. [b] Isolated yields. Values in parentheses are based on converted **1**.

We initiated our studies to understand the nature of the present carbonylation reaction by performing a series of optimization reactions using *N*-tosyl-2-aminobiphenyl (**1a**) as a model substrate, and the results are summarized

in Table 1. We used the tosyl group in this study because it can direct the palladium center to activate the *ortho* C−H bond of the other aryl ring with ease for later deprotection as compared to *N*-alkyl groups,[11c] and it may provide the opportunity for further elaboration via *ortho* C−H activation on the other aryl ring through sulfonyl group modification.[12] At first, we performed the reaction of **1a** with CO in the presence of 10 mol % $Pd(OAc)_2$ and 2 equiv of CH_3COOAg in DMSO at 100 °C for 4 h. Surprisingly, we found the formation of desired product **2a** in 36% yield together with 28% of *N*-tosyl carbazole **3** as byproducts (Table 1, entry 1). We then tested various reaction conditions so that the formation of **3** is lessened in the reaction through direct amination. When we switched the solvent to THF, we isolated the compound **2a** in 45% yield with trace amounts of **3** (entry 2). The use of anhydrous CH_3CN extensively reduced the byproduct formation and produced the desired product **2a** in 40% yield (entry 3). After controlling the formation of **3** in the reaction, we proceeded next to screen conditions to increase the reaction yield. We concluded through our observations that the choice of solvents and amounts of oxidizing agent are important for the present carbonylation reaction. When the use of CH_3COOAg was increased from 2 to 3 equiv, the desired product **2a** was isolated in good yield (79%, entry 4). Then, we performed the reaction with a higher amount of silver acetate such as 4 and 5 equiv; the product **2a** was isolated in excellent yields, 90 and 94%, respectively (entries 5 and 6). Other metal oxidizing agents, such as $Cu(OAc)_2$ or Ag_2O, were not effective for this carbonylation reaction (entries 7 and 8). No reaction occurred when the reaction was performed with benzoquinone as oxidants (entry 9). Product **2a** and **3** were formed in 35 and 25% yields, respectively, when the reaction was tested with $KHSO_5$ (entry 10), while the reaction with $K_2S_2O_8$ was totally ineffective (entry 11). When solvent CH_3CN was replaced with butyronitrile, the reaction selectivity was also changed; we observed the formation of **3** exclusively in 49% yield (entry 12). Further, increasing catalytic amounts of $Pd(OAc)_2$ was not useful for increasing reaction yields (entry 13). Another palladium source, $PdCl_2(PPh_3)_2$, was rather less effective for this transformation (entry 14).

After obtaining the optimal reaction conditions, we next proceeded to examine the substrate scope of the present carbonylation reaction, and the results are summarized in Table 2. Under standard reaction conditions, substrates **1a**−**b** having no substitutions underwent carbonylation smoothly to give phenanthridinone derivatives **2a**−**b** in good yields, 94 and 84%, respectively (Table 2, entries 1−2). It was found that the substrates, **1c**−**i**, bearing an electron-donating methyl group on aryl rings reacted smoothly to deliver corresponding phenanthridinones **2c**−**i** in good to excellent yields, 71−94% (entries 3−9). We isolated phenanthridinone derivatives **2j**−**l** in 94, 86, 91% yields, respectively, in very high regioselectivity from **1j**−**l** under our optimal reaction conditions (entries 10−12). Further, substrates **1m**−**p** equipped with strong electron-withdrawing groups, such as chloro, fluoro, and trifluoromethoxy, afforded the desired products **2m**−**p** in good to excellent yield, 89, 86, 88, and 93%, respectively (entries 13−16). Highly electron-rich substrates such as **1q**−**r** gave the corresponding carbonylated products **2q**−**r** in good yields, 81 and 82%, respectively, and in excellent yields based on converted starting materials (entries 17 and 18). Further, the present carbonylation reaction is applicable to a heteroaromatic system, such as substrate **1s** with a 2-thienyl moiety, which produced **2s** in 86% yield (entry 19).[13] In a similar way, the polyaromatic substrates **1t**−**x** gave the corresponding products **2t**−**x** in moderate to excellent yields (entries 20−24). Further, we achieved the detosylation[14] of **2c**, **2o**, and **2q** using TBAF that produced **2c′**, **2o′**, and crinasiadine **2q′** in 97, 77, and 82% yields, respectively. Thus, the present oxidative carbonylation reaction provides an efficient way to access bioactive phenanthridinone derivatives under milder reaction conditions with a wide range of substrates. The rational reaction pathway for the present carbonylation is proposed on the basis of our experimental results and known metal-mediated C−H bond activation reactions.[15]

In conclusion, we have established an efficient Pd-catalyzed oxidative carbonylation of *N*-sulfonyl-2-aminobiaryls *via* one N−H and C−H bond cleavage and one new C−C and C−N bond formation under TFA-free and milder conditions with a tolerence for a large number of substrates in excellent yields. The present carbonylation reaction brings into existence a straightforward way to access phenanthridinone derivatives which are a structural moiety existing widely in *amaryllidaceae* alkaloids, various natural products, and bioactive molecules.

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Supporting Information Available. Detailed experimental procedures and spectral characterization of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Urones, B.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**10.1021/ol400206k.

(13) The present standard condition is not applicable to the heterocyclic examples with the pyridyl moiety such as 4-methyl-*N*-(2-(pyridin-2-yl)-phenyl)-, 4-methyl-*N*-(2-(pyridin-3-yl)phenyl)-, 4-methyl-*N*-(2-(pyridin-4-yl)phenyl)benzenesulfonamides. No corresponding CO insertion products were observed, likely due to their electron-defficient and unreactive nature.

(14) (a) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2012**, *14*, 2304–2307. (b) Péron, F.; Fossey, C.; Cailly, T.; Fabis, F. *Org. Lett.* **2012**, *14*, 1827–1829. (c) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900–3903.

(15) See the Supporting Information for the proposed reaction mechanism (Scheme S1). During the preparation of this manuscript, the $Pd(MeCN)_2Cl_2$ catalyzed carbonylation of unprotected *o*-arylanilines was reported. Reaction conditions: *o*-Arylanilines (0.2 mmol), $Pd(MeCN)_2Cl_2$ (5 mol %), $Cu(TFA)_2$ (1.0 equiv), TFA (1.0 equiv), CO balloon (1 atm), dioxane (1.0 mL), 110 °C, 7−65 h. Liang, D.; Hu, Z.; Peng, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 173–175.

The authors declare no competing financial interest.