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Palladium/Silver Synergistic Catalysis in Direct Aerobic Carbonylation of C(sp^2)−H Bonds Using DMF as a Carbon Source: Synthesis of Pyrido-Fused Quinazolinones and Phenanthridinones

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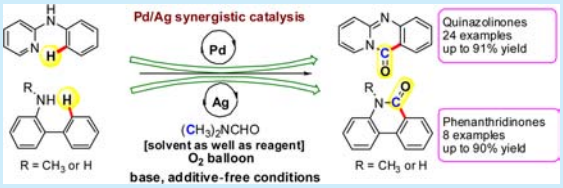
Supporting Information

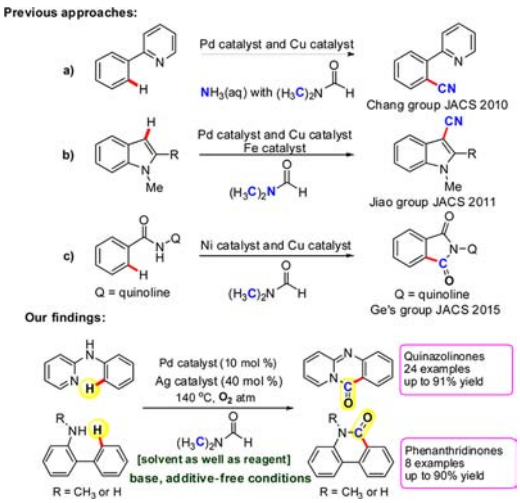
ABSTRACT: An unprecedented Pd/Ag synergistic catalysis in the direct carbonylation of C(sp^2)−H bonds utilizing DMF as the carbon source under oxygen is described and demonstrated in the synthesis of pyrido-fused quinazolinone and phenanthridinone scaffolds. Control experiments indicated that the "C" of the carbonyl group is derived from the methyl group of DMF and "O" originates from oxygen as in the case of Ge's recent work. This transformation offers an alternative avenue for "CO-free" carbonylations.



Transition-metal-catalyzed C−H functionalization/activation has experienced tremendous development over the past decade.[1] The development of synthetic methods, efficient catalysts focusing on reaction efficiency, and the avoidance of waste generation are of particular relevance. Concerning sustainability, methods based on direct derivatization of (hetero)-arenes in an extremely site-selective manner by avoiding prefunctionalization in the coupling reactions have become highly efficient strategies in organic synthesis. Among them, transition-metal-catalyzed direct carbonylation has attracted considerable attention in recent years due to the ubiquitous presence of the carbonyl group in organic molecules. For example, Pd-, Co-, Rh-, or Ru-catalyzed processes have been well established for carbonylation of (hetero)-arenes by using toxic carbon monoxide gas.[2] In recent decades, researchers have paid attention to carbonylation reactions in which a safer source of CO replaces the toxic carbon monoxide gas by using different metal carbonyls.[3] Several CO surrogates have also been introduced to carbonylation processes,[4] and these are alternatives for the preparation of carbonyl compounds by *in situ* generating the CO gas. Most of the methods are carried out in an autoclave or two-chamber system, and this limits the applications of the methods. Therefore, to avoid entirely replacing gaseous carbon monoxide, it would be highly desirable if nontoxic, safe, and inexpensive reagents, preferably the organic solvents, could serve as the carbon source of the carbonyl group.

In recent years, researchers have focused on the development of safer and novel reaction conditions with new reactivities of aryl or heteroaryl C−H bonds for various transformations. In this regard, DMF (*N*,*N*-dimethylformamide) was utilized as a cheap, efficient, and safe reagent for regioselective cyanation of different aromatic/heteroaromatic C−H bonds under bimetallic conditions such as Pd/Cu or Ni/Cu, in which the carbon originates from DMF.[5] In 2015, Ge et al. reported an unusual carbonylation reaction for the synthesis of succinimides, in which the carbon originates from DMF under atmospheric oxygen with Ni/Cu catalysis (Scheme 1).[6] Inspired by these observations and continuing with the development of new processes,[7] we herein describe an unprecedented Pd/Ag synergistic catalysis in the direct carbonylation of C(sp^2)−H bonds utilizing DMF as the carbon source of a carbonyl group under atmospheric oxygen. The usefulness of the method is demonstrated in the synthesis of pharmaceutically important heterocycles, pyrido-fused quinazolinones, and phenanthridinones. An external base, oxidant, and additives were not required for this process. Atmospheric oxygen is utilized as the terminal oxidant, and Pd/Ag catalysts are used catalytically.

Scheme 1. Utilization of CH_3 Group as a Carbon Source from DMF for Various Transformations



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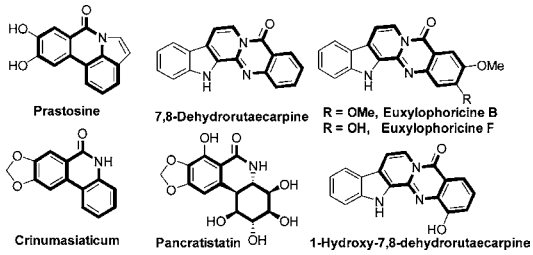


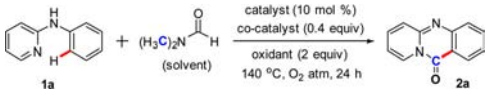
Figure 1. Biologically active phenanthridinone and pyrido-fused quinazolinone natural products.

These pyrido-fused quinazolinone[8] and phenanthridinone[9] scaffolds are present in many biologically active natural products and are recognized as a useful class of compounds in medicinal chemistry that exhibit unique biological and pharmaceutical properties (Figure 1).[10]

Our investigation began with direct carbonylation of *N*-phenylpyridin-2-amine (**1a**) in DMF via palladium/silver bimetallic catalysis under atmospheric oxygen (Table 1). After an extensive screening of the Pd-catalysts, 11*H*-pyrido[2,1-*b*]quinazolin-11-one (**2a**) was obtained in 10% yield by the combination of catalytic amounts of $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (0.4 equiv) with 2 equiv of $K_2S_2O_8$ as the terminal oxidant (entry 1). Next, the screening of the terminal oxidant instead of $K_2S_2O_8$ was carried out, and no further improvement in the product yield was observed (entries 2–5) (see Supporting Information). Interestingly, no difference in the product yield was found by carrying out the reaction in the absence of a terminal oxidant, indicating that Ag_2CO_3 is acting as a synergistic catalyst in the presence of O_2 as the terminal oxidant (entry 6). Next, the screening of the different Ag catalysts was carried out, with the finding that AgOTf as the catalyst provided the highest yield of the product **2a** (91%, entries 7–14). By replacing AgOTf with $Cu(OTf)_2$ as a cocatalyst, the product was isolated in 60% yield (entry 15). By using $Ni(OAc)_2$ as the catalyst instead of $Pd(OAc)_2$, the efficiency of the reaction is much lower (entry 16), and with $Cu(OAc)_2$ or $Co(OAc)_2$ as the catalyst the reaction was not working (entries 17, 18). Reaction using the combination of Ni/Cu as catalysts resulted in a 20% isolated yield of the product **2a** (entry 19). In the absence of $Pd(OAc)_2$ as the catalyst the reaction was not working, and also in the absence of AgOTf as the catalyst the reaction was not working, indicating that both Pd and Ag catalysts are essential for this reaction (entries 20–21). When using Ge's standard catalytic system (NiI_2/$Cu(OTf)_2$/O_2; TBAB/Li_2CO_3 in DMF, 160 °C, 24 h), the desired product (**2a**) was isolated in 60% yield.[6] For complete screening of optimization, see Supporting Information.

Next, we tested the response with analogues of DMF and observed that none of the indicated reagents were giving better yields (Scheme 2).

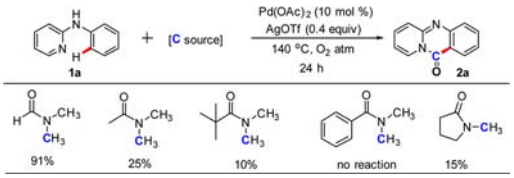
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	cocatalyst	oxidant	yield[b] (%) **2a**
1	$Pd(OAc)_2$	Ag_2CO_3	$K_2S_2O_8$	10
2	$Pd(OAc)_2$	Ag_2CO_3	$Na_2S_2O_8$	15
3	$Pd(OAc)_2$	Ag_2CO_3	$PhI(OAc)_2$	10
4	$Pd(OAc)_2$	Ag_2CO_3	BQ	20
5	$Pd(OAc)_2$	Ag_2CO_3	oxone	5
6	$Pd(OAc)_2$	Ag_2CO_3	–	10
7	$Pd(OAc)_2$	Ag_2O	–	30
8	$Pd(OTf)_2$	AgOAc	–	45
9	$Pd(OAc)_2$	Ag_2SO_4	–	25
10	$Pd(OAc)_2$	$AgSbF_6$	–	60
11	$Pd(OAc)_2$	$AgNO_3$	–	n.r.
12	$Pd(OAc)_2$	AgF	–	15
13	$Pd(OAc)_2$	AgTFA	–	62
14	**$Pd(OAc)_2$**	**AgOTf**	–	**91**
15	$Pd(OAc)_2$	$Cu(OTf)_2$	–	60
16	$Ni(OAc)_2$	AgOTf	–	10
17	$Cu(OAc)_2$	AgOTf	–	n.r.
18	$Co(OAc)_2$	AgOTf	–	n.r.
19	$Ni(OAc)_2$	$Cu(OTf)_2$	–	20
20	–	AgOTf	–	n.r.
21	$Pd(OAc)_2$	–	–	n.r.

[a]Reaction conditions: *N*-phenylpyridin-2-amine (1.0 equiv), catalyst (10 mol %), cocatalyst (0.4 equiv), oxidant (2 equiv), DMF (2 mL), 140 °C, 24 h, O_2 atm. [b]Isolated yield; n.r. = no reaction.

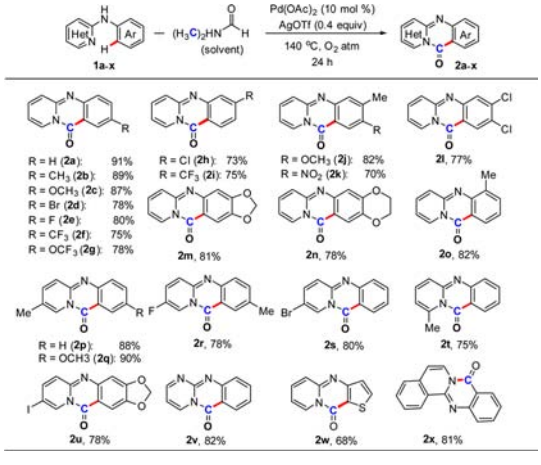
Scheme 2. Scope of the Reaction with Analogues of DMF[a]



[a]Reaction conditions: *N*-phenylpyridin-2-amine (1.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOTf (0.4 equiv), analogues of DMF (2 mL), 140 °C, 24 h, O_2 atm. Isolated yields.

With these optimized reaction conditions in hand, we probed the substrate range for the pyrido-carbonylation. As shown in Scheme 3, in general, both electron-rich or -poor substituted *N*-arylpyridin-2-amines (**1a–x**) were transformed into valuable 11*H*-pyrido[2,1-*b*]quinazolin-11-one (**2a–x**) scaffolds in moderate to good yields. The aromatics which have electron-rich and electron-poor functional groups in the para position afforded coupling products in good yields, 75–89% (**2b–2g**). Electron-

Scheme 3. Scope of the Pd/Ag Catalyzed Pyrido Carbonylation of 1a–x[a]



[a]Reaction conditions: **1a–x** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOTf (0.4 equiv), DMF (2 mL), 140 °C, 24 h, O_2 atm.

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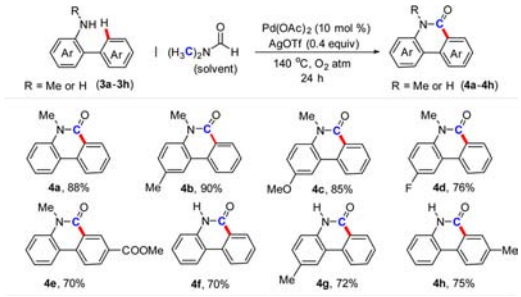
donating groups containing aromatics gave higher yields than those with electron-withdrawing groups. This indicates that a nucleophilic addition step might be involved in this process. For meta-substituted substrates, the reactions proceeded with high regioselectivity and with good yields, 73−75% (**2h−i**), and in both cases the pyridocarbonylation occurred exclusively at the sterically less hindered position of the arenes. Disubstituted substrates (**1j** and **1k**) bearing methyl, methoxy, and nitro groups at the 3- and 4-positions provided the respective products (**2j** and **2k**) in good yields, 70−82%, and with 3,4-dichloroarene 77% of the product **2l** was obtained. Then we tested the reaction with benzo[*d*][1,3]-dioxole, and 2,3-dihydrobenzo[*b*][1,4]dioxine provided the corresponding products with high regioselectivity (**2m** and **2n**) in good yields, 78−81%. It is worth noting that ortho methylated arene systems undergo smooth coupling at the ortho position of the arene in high yield (**2o**, 82%). Next, we tested the substitution effect on the pyridine ring at different positions with different substituents. It was observed that, in all cases tested, the corresponding products (**2p−2u**) were isolated in good yields (75−90%). It is worth mentioning that previously developed methods give lower yields for pyridine substituted derivatives. Notably, the fluoro, chloro, bromo, and even iodo halogen functional groups remained intact under these optimized reaction conditions. The heterocyclic substrate **1w** underwent reaction to produce product **2w** in 68% yield. Whereas in the case of pyridine derivative *N*-(pyridin-3-yl)pyridin-2-amine, the reaction is sluggish and no product formation was observed. By utilizing *N*-phenyl pyrimidin-2-amine and *N*-phenyl isoquinolin-1-amine under optimized reaction conditions, the corresponding products **2v** and **2x** were obtained in 82% and 81% yields, respectively, indicating that this method can be applicable to other heterocycles.

Encouraged by these results, we applied our optimized reaction conditions for the synthesis of medicinally important phenanthridinones. The influence of substituents on both of the phenyl rings was investigated (Scheme 4). A range of functional groups

Scheme 4. Scope of the Pd/Ag Catalyzed Amino Carbonylation of 3a−h[a]

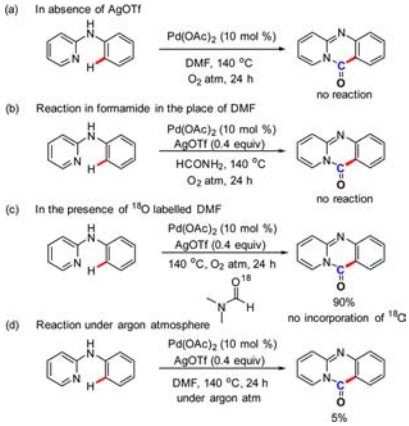


[a]Reaction conditions: **3a−h** (1.0 equiv), $Pd(OAc)_2$ (10 mol %), AgOTf (0.4 equiv), DMF (2 mL), 140 °C, 24 h, O_2 atm.

with various electronic properties including Me, OMe, F, and COOMe were well tolerated, providing the corresponding *N*-methylated phenanthridinones **4a−e** in 70−90% yields. When compared with the electron-donating groups, the electron-withdrawing groups gave relatively lower yields. Without any protection on the aniline moiety for the synthesis of free (NH)-phenanthridinones, the isolated yields of the products (**4f−h**) are lower as compared with *N*-methylated phenanthridinones, being 70%, 72%, and 75%, respectively.

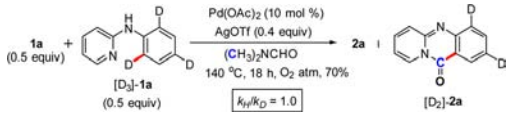
To gain insight into the mechanism of the reaction, a series of control experiments were conducted; it has been reported that DMF releases carbon monoxide at high temperature, and thus the released CO could potentially participate in this process as the carbonyl source.[11]To clarify this, we performed a series of experiments. (a) Reaction in the absence of AgOTf under standard reaction conditions revealed that, in the absence of AgOTf, product formation was not observed, indicating that AgOTf acts as a cocatalyst for this reaction. (b) Reaction in the presence of formamide as a solvent instead of DMF afforded no product, indicating that the methyl group of DMF may be involved in this process. To clarify, further DMF ($C{=}O^{18}$) was used as the solvent to replace unlabeled DMF. (c) It was found that there is no incorporation of O^{18} in the product, confirming that the incorporated carbonyl group mainly comes from the methyl group of DMF. (d) Finally, reaction under an argon atmosphere in the place of an oxygen atmosphere provided the product in 5% yield, suggesting that an O_2 environment is required for this process, and "O" is coming from oxygen. All these factors indicated that Pd/Ag synergistic catalysis is involved in this process (Scheme 5).

Scheme 5. Control Experiments



The kinetic isotope effect was also determined in parallel to the control experiments. A 1:1 mixture of [D_3]-**1a** and **1a** was treated under standard reaction conditions. No kinetic isotope effect (KIE; $K_H/K_D = 1$) was obtained (Scheme 6), indicating that C−H bond cleavage of the arenes is not the rate limiting step.

Scheme 6. Deuterium-Labelling Experiment of C(sp^2)−H Activation



On the basis of our observations and earlier precedents, a plausible reaction pathway is proposed in Scheme 7.[5,6,8] Although details about the mechanism are still unclear, a pathway for this reaction can be proposed as follows. The first step is most probably the coordination of Pd(II) to the nitrogen atom from the pyridine substrate followed by a chelate-directed C−H activation to form the six-membered cyclopalladated intermediate [**A**]. Simultaneously, an iminium species [**B**] is generated in situ from DMF via a sequential decarbonylation, nucleophilic addition, and elimination process under silver catalysis with oxygen as the external

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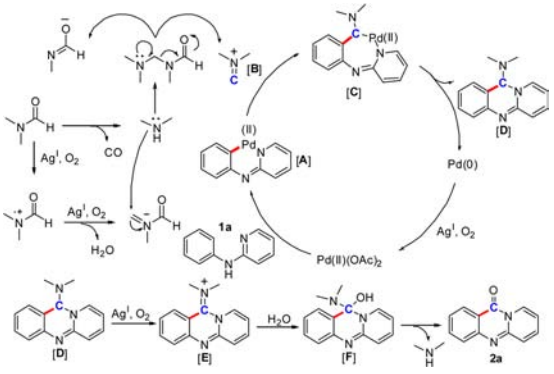
Scheme 7. Plausible Reaction Mechanism



oxidant.[12] Nucleophilic addition of the intermediate **A** to the iminium ion intermediate **B** provided the intermediate **C**. Reductive elimination produces intermediate **D** and Pd(0), and the latter is oxidized by Ag in the presence of terminal oxidant O_2, thus completing the catalytic cycle. Intermediate **D** then produces the product **2a** via oxidation and hydrolysis. The formation of phenanthridinones also took place by following a similar pathway.

In summary, we have established a cooperative Pd/Ag-catalyzed carbonylation of C(sp^2)−H bonds by employing *N*,*N*-dimethylformamide (DMF) as the carbon source of the carbonyl group under atmospheric O_2. The process is general in delivering medicinally important pyrido-fused quinazolinones and phenanthridinones with challenging substitution patterns. Mechanistic studies suggested that this reaction proceeded via palladium/silver synergistic catalysis, with the palladium species initiating the C−H activation of substrates to generate a nucleophile and DMF, providing an electrophile by utilizing the silver salt. With the easy availability of the substrates, economic DMF as the carbonyl source, excellent functional group tolerability, and easy to handle CO-free reaction conditions, this procedure is expected to complement current methods. Detailed mechanistic studies and further substrate scope study are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01292.

Full experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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