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Rhodium-Catalyzed Direct Oxidative Carbonylation of Aromatic C−H Bond with CO and Alcohols

Zheng-Hui Guan,[†,‡] Zhi-Hui Ren,[†] Stephen M. Spinella,[‡] Shichao Yu,[‡] Yong-Min Liang,*[,†] and Xumu Zhang*[,‡]

Department of Chemistry and Chemical Biology and Department of Pharmaceutical Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8066, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

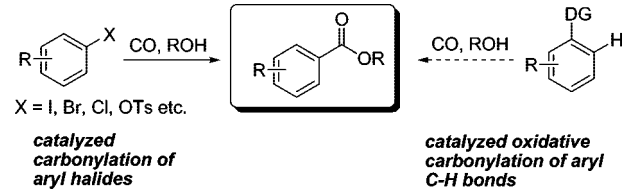
Received September 10, 2008; E-mail: xumu@rci.rutgers.edu

Abstract: A general protocol for the rhodium-catalyzed oxidative carbonylation of arenes to form esters has been developed. A broad substrate scope has been demonstrated allowing carbonylation of electron-rich, electron-poor, and heterocyclic arenes, and the reaction shows wide functional group tolerance and excellent regioselectivities. Up to 96% yield of *ortho*-substituted aryl or heteroaryl carboxylic esters were obtained with this methodology. The possible mechanism for the rhodium-catalyzed oxidative carbonylation reaction was proposed in this article. Studies show that Oxone play an important role in the transformation.

Introduction

Aryl carboxylic acids and derivatives are valuable commodity chemicals. Transition metal-catalyzed carbonylation[1] of aryl iodides, bromides and triflates is a well-known method for the regioselective installation of carbonyl functional groups on arenes.[2] Recent advances have allowed the use of the readily available aryl chlorides and aryl tosylates,[3] but an ideal and environmentally friendly method to construct aryl carboxylic acids functional groups would be direct carbonylation of aryl C−H bonds in regioselective manner (Scheme 1). There are a few reports of Pd-catalyzed carbonylation of aromatic amines to form benzolactams, however problems in regiocontrol of the carbonylation reaction remain challenging.[4]

Scheme 1. Transition Metal Catalyzed Carbonylation Reaction



Activation[5] and functionalization of C−H bonds is one of the most challenging tasks in organic chemistry.[6,7] Recently, Pd-catalyzed direct functionalizations of aryl C−H to form C−C and C-heteroatom bonds have been investigated intensively.[8] Pd has proved to be one of the most effective catalyst in this transformation.[9−14] However, Pd-catalyzed *ortho*-selective C−H bond carbonylation is exceedingly difficult because the depal-

[†] State Key Laboratory of Applied Organic Chemistry.
[‡] Rutgers, The State University of New Jersey.

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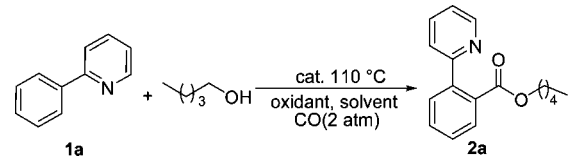
ladation process is often complicated by the reduction of Pd(II) to Pd(0) under CO atmosphere.[15−17] In the past decade, Rh[18] and Ru[19] complexes have emerged as very effective catalysts in the activation and functionalization of C−H bonds. And Rh−CO complexes are the most active species for carbonylation reactions, such as Monsanto acetic acid process[20] and hydroformylation of alkenes.[21] In connection with Rh and Ru-catalyzed reductive coupling of aryl C−H bonds with alkenes or CO/alkenes,[22] we envision that it may be possible to conduct direct oxidative carbonylation using a simple Rh−CO catalyst under CO atmosphere. Prior to our work, mild, highly efficient and regioselective carbonylation through direct C−H bond functionalization with CO and alcohol has not been realized. In this article, we report an unprecedented protocol for regioselective Rh-catalyzed oxidative carbonylation to form esters using a directed C−H bond activation coupled with an inexpensive and environmentally benign terminal oxidant.

Table 1. Optimization of Direct Oxidative Carbonylation of Arenes[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	$[Rh(COD)Cl]_2$	$Cu(OAc)_2$	toluene	48
2	$[Rh(COD)Cl]_2$	BQ	toluene	nd[c]
3	$[Rh(COD)Cl]_2$	CAN	toluene	32
4	$[Rh(COD)Cl]_2$	$K_2S_2O_8$	toluene	75
5	$[Rh(COD)Cl]_2$	Oxone	toluene	82
6	$[Rh(COD)Cl]_2$	Tempo	toluene	nd[c]
7	$[Rh(COD)Cl]_2$	Oxone	1,4-dioxane	<5
8	$[Rh(COD)Cl]_2$	Oxone	*n*-pentanol	<5
9	$[Rh(COD)Cl]_2$	Oxone	DMF	<5
10	$[Rh(COD)Cl]_2$	Oxone	THF	15
11	$Pd(OAc)_2$[d]	Oxone	toluene	<5
12	$Ru_3(CO)_{12}$[d]	Oxone	toluene	<5

[a] Reaction conditions: **1a** (0.1 mmol), *n*-pentanol (5 equiv), oxidant (3 equiv), and catalyst (2 mol %) in solvent (2 mL) under CO (2 atm) at 110 °C for 8 h. [b] Isolated yield. [c] Not detected. [d] Reaction was performed with 5 mol % catalyst.

Results and Discussion

Compounds containing heteroatoms are prevalent in nature. The syntheses of these compounds have attracted much attention in industrial and academic research due to desirable biological and pharmaceutical properties. Our experiment was initially conducted by treating 2-phenylpyridine **1a** with *n*-pentanol (5 equiv), $[Rh(COD)Cl]_2$ (2 mol %), $Cu(OAc)_2$ (3 equiv) in toluene under CO (2 atm) (Table 1, entry 1). We were pleased to find that after 8 h at 110 °C, the reaction resulted in 48% yield of the carbonylation product **2a**. Further experiments showed that $Cu(OAc)_2$ is not a good oxidant for the C−H activation carbonylation. We reasoned that the coordination of Cu(II) to the pyridine moiety might prevent the carbonylation reaction, which is in agreement with the results reported by Yu.[16] Therefore, a variety of other oxidants were screened for better efficiency in this transformation. To our delight, Oxone ($2KHSO_5KHSO_4K_2SO_4$) was found to be a particularly effective terminal oxidant in this Rh-catalyzed direct carbonylation reaction. Inexpensive, safe, and environmentally benign Oxone also makes this transformation more practical. After treatment of **1a** (0.1 mmol) with *n*-pentanol (5 equiv), Oxone (3 equiv), and $[Rh(COD)Cl]_2$ (2 mol %) in toluene at 110 °C under CO (2 atm) for 8 h, **2a** was obtained in 82% yield (Table 1, entry 5). Other oxidants such as BQ (benzoquinone), CAN (ammonium cerium (IV) nitrate), $K_2S_2O_8$, and TEMPO (2, 2, 6, 6-tetramethylpiperidine-*N*-oxyl radical) are less effective for this Rh-catalyzed reaction (Table 1, entries 2−4, 6). We have also tested a number of solvents; toluene was found to be most effective (Table 1, entries 7−10). Low conversion was observed when $Pd(OAc)_2$ or $Ru_3(CO)_{12}$ was employed as the catalyst in the oxidative carbonylation reaction (Table 1, entries 11−12).

Under the optimized conditions, for this direct carbonylation process, we have explored the substrate scope (Table 2). This new carbonylation procedure displayed good functional group tolerance. Arenes with ester, trifluoromethyl, and ether groups

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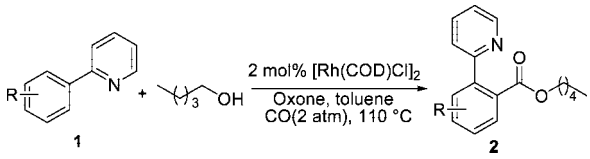
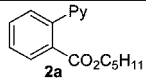
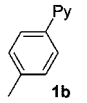
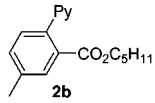
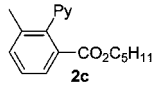
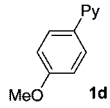
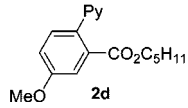
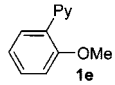
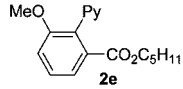
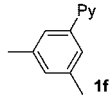
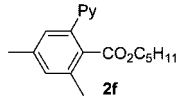
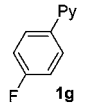
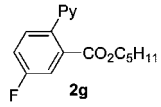
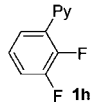
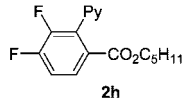
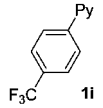
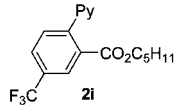
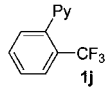
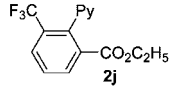
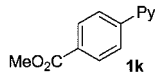
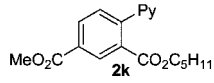
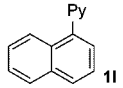
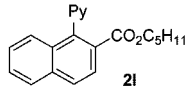
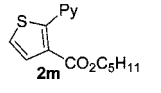
Table 2. Rh-Catalyzed Carbonylation of Aromatic C−H Bonds[a]



entry	substrate **1**	product **2**	yield (%)[b]
1	 **1a**	 **2a**	82
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	63
5	 **1e**	 **2e**	61
6	 **1f**	 **2f**	70
7	 **1g**	 **2g**	75
8	 **1h**	 **2h**	90
9	 **1i**	 **2i**	80
10	 **1j**	 **2j**	38[c]
11	 **1k**	 **2k**	83
12	 **1l**	 **2l**	78
13	 **1m**	 **2m**	96

[a] Reaction conditions: all reactions were carried out with **1** (0.1 mmol), *n*-pentanol (5 equiv), Oxone (3 equiv), and $[Rh(COD)Cl]_2$ (2 mol %) in toluene (2 mL) under CO (2 atm) at 110 °C for 8 h. [b] Isolated yield. [c] Reaction was performed with ethanol (10 equiv).

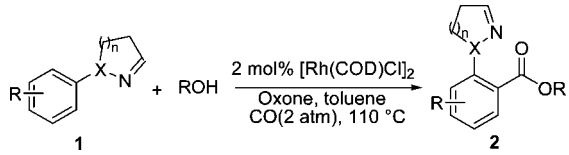
all gave high yields of corresponding esters (Table 2, entries 4, 5, 9−11). An aryl C−F bond was tolerated under the reaction conditions; **2g** and **2h** were obtained in high yields and without any products of C−F bond carbonylation (Table 2, entries 7, 8). For the electronic effects of this transformation, we found that electron-rich arenes show more reactivity and gave slightly higher yields than electron-deficient arenes (Table 2, entries 2, 3, 7, 9, and 11). Slightly lower yields were achieved for the carbonylation reaction of 2-(4-methoxyphenyl)pyridine **1d** and 2-(2-methoxyphenyl)pyridine **1e** due to partial decomposition of the substrates in the carbonylation reaction (Table 2, entries 4, 5). Hetero arenes exhibit higher reactivity than arenes. The carbonylation product **2m** was obtained in excellent yield from 2-(thiophen-2-yl)pyridine **1m** (Table 2, entry 13). In addition, the synthesis of ester derived from low molecular weight alcohol was also achieved, albeit the yield was limited by the boiling point of the alcohol.[3a] Ethyl 2-(pyridin-2-yl)-3-(trifluoromethyl)benzoate **2j** was obtained in moderate yield with 56% of the starting material **1j** recovered (Table 2, entry 10).

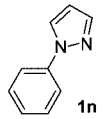
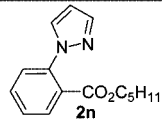
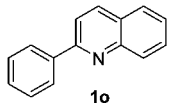
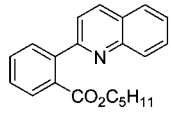
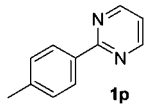
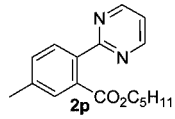
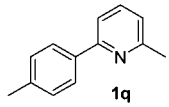
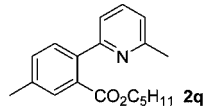
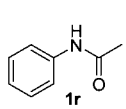
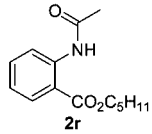
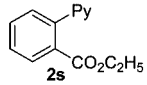
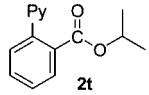
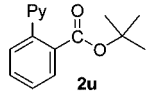
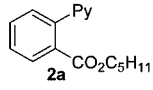
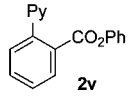
Furthermore, different directing groups and different alcohols were tested for this oxidative carbonylation reaction (Table 3). Nitrogen heterocycles, such as pyrazole and quinoline, can serve as efficient directing groups and generate the carbonylation products in moderate to good yields under the optimal conditions (Table 3, entries 1, 2). It is interesting to note that the monocarbonylation products were obtained in all cases from the corresponding substrates. Even with pyrimidine as the directing group, the monocarbonylation product **2p** was formed exclusively from 2-*p*-tolylpyrimidine **1p** (Table 3, entry 3). The steric hindrance of a directing group played an important role in the transformation. The carbonylation product **2q** was achieved in only 45% yield when 6-methylpyridyl group was used as the directing group (Table 3, entry 4). Even when the catalyst loading was doubled, the yield did not improve. It has been recently reported that acetanilide shows a good reactivity in Pd-catalyzed C−H activation.[10b,12a] However, only very low conversion was observed when acetanilide was employed as the substrate in this Rh-catalyzed oxidative carbonylation reaction (Table 3, entry 5). An extensive investigation of the reaction shows that both steric hindrance and boiling point of the alcohol played the important role in the transformation. Ethanol and 2-propanol gave lower yields of the carbonylation products (Table 3, entries 6, 7). Only very low conversion was observed when *t*-BuOH was employed (Table 3, entry 8). Additionally, phenol exhibited no reactivity under the carbonylation reaction conditions (Table 3, entry 10).

Although the exact mechanism of the reaction remains unclear, two mechanisms were proposed on the basis of our own observation and other related studies[6a,d,18a] for this oxidative carbonylation reaction (Scheme 2). In one case, first, coordination of the *ortho*-directing group and oxidative addition of an aromatic C−H bond to Rh(I) gives a Rh(III) complex **A**.[23] Next, insertion of CO in the resulting C−Rh bond to form an acylrhodacycle intermediate **B**, followed by coordination of alcohol to form intermediate **C**. The acylrhodacycle intermediate **C** is assumed to be oxidized by Oxone to give the Rh(III) complex **D** (path a) and undergoes a subsequent reductive elimination to afford the active catalyst species Rh(I) **F** and the carbonylation product **2**. An alternative mechanism (path **b**) is alcoholysis[24] of acylrhodium species **C** to give the Rh−H

(23) (a) Boyd, S. E.; Field, L. D.; Partridge, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 9492. (b) Rosini, G. P.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1994**, *116*, 9498.

Table 3. Carbonylation of Aromatic C−H Bonds with Different Directing Groups and Different Alcohols[a]

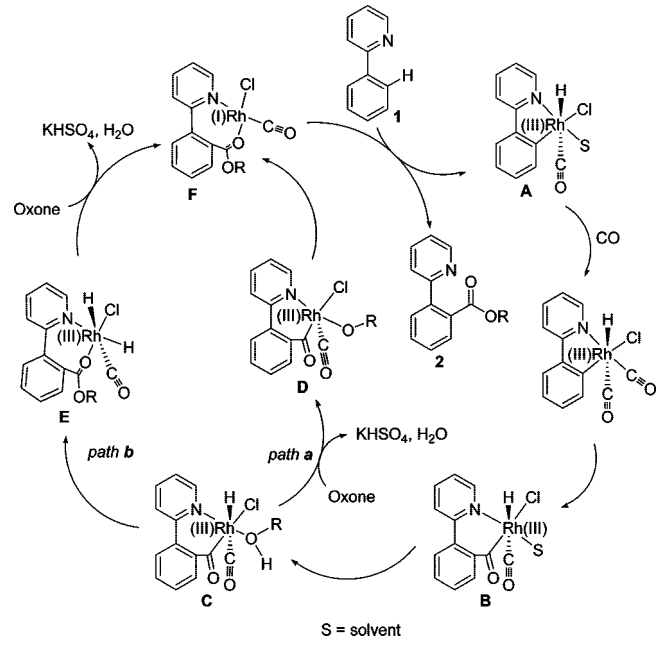


entry	substrate **1**	product **2**	yield (%)[b]
1	 **1n**	 **2n**	66
2	 **1o**	 **2o**	52
3	 **1p**	 **2p**	80
4	 **1q**	 **2q**	45
5	 **1r**	 **2r**	<5
6	 **1a**	 **2s**	40
7	 **1a**	 **2t**	35
8	 **1a**	 **2u**	<5
9	 **1a**	 **2a**	82
10	 **1a**	 **2v**	<5

[a] Reaction conditions: all reactions were carried out with **1** (0.1 mmol), alcohol (5 equiv), Oxone (3 equiv), and $[Rh(COD)Cl]_2$ (2 mol %) in toluene (2 mL) under CO (2 atm) at 110 °C for 8 h. [b] Isolated yield.

species **E**. The latter is assumed to be oxidized by Oxone to afford the active catalyst species Rh(I) **F**.[18f,25] If the reaction is proceeded though path **b**, we will expect to observe the reaction when a stoichiometric $[Rh(COD)Cl]_2$ is used. Therefore, a study was carried out to establish the fundamental steps of this catalytic cycle and the role of Oxone therein. Indeed, this

Scheme 2. Possible Mechanism of Rh-Catalyzed Oxidative Carbonylation Reaction



reaction does not occur at all in the absence of Oxone even when the stoichiometric $[Rh(COD)Cl]_2$ was used. This observation indicates that the path **b** is less likely.

Conclusion

In summary, we have developed a mild and general procedure for the Rh-catalyzed oxidative carbonylation of arenes and heteroarenes with carbon monoxide and alcohols. This Rh-catalyzed oxidative carbonylation reaction shows high regioselectivity and good functional group tolerance. Up to 96% yield of *ortho*-substituted aryl or heteroaryl carboxylic esters were obtained with this methodology. The use of Oxone as an inexpensive and environmentally benign terminal oxidant makes this unprecedented transformation attractive in organic synthesis. A possible mechanism was proposed in this article, and the study provides a new avenue for the direct carbonylation of aryl C−H bonds. Current research is focused on extending the scope and gaining more detailed information on the exact mechanism of the reaction.

Experimental Section

General Methods. Column chromatography was carried out on silica gel. ^1H NMR spectra were recorded on 500 or 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on 125 or 100 MHz in $CDCl_3$. All new products were further characterized by HRMS; copies of their ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra are provided in the Supporting Information. Unless otherwise stated, all arenes and solvents were purchased from commercial suppliers and used without further purification. Other substrates (**1c, 1d, 1e,**

(24) (a) van Leeuwen, P. W. N. M.; Zuideveld, M. A.; Swennenhuis, B. H. G.; Freixa, Z.; Kamer, P. C. J.; Goubitz, K.; Fraanje, J.; Lutz, M.; Spek, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 5523, and references cited therein. (b) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428. (c) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640.
(25) (a) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407.

1f, 1 g, 1 h, 1i, 1j, 1p, 1q, 1r) were prepared according to the literature procedures.[26]

Typical Procedure for Carbonylation of 1 with CO and Alcohol. $[Rh(COD)Cl]_2$ (2 mol %, 1 mg,) was added to a solution of arene **1** (0.1 mmol), alcohol (0.5 mmol), and Oxone (185 mg, 0.3 mmol) in toluene (2 mL) in a vial (5 mL). The resulting solution was then transferred into a steel autoclave and charged with CO (2 atm). After stirring at 110 °C for 8 h, the CO was released carefully. The suspension was filtered through a Celite pad and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The desired products **2** were obtained in the corresponding yields after purification by flash chromatography on silica gel with hexane, ethyl acetate, and triethylamine.

(26) (a) Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907. (b) Kitamura, Y.; Sako, S.; Udzu, T.; Tsutsui, A.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Commun.* **2007**, 5069.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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