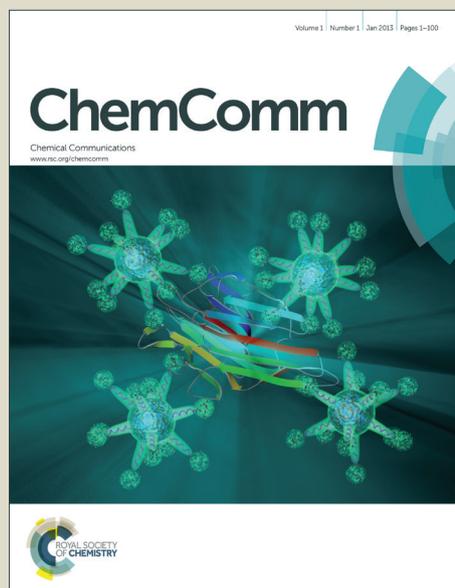


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COMMUNICATION

Palladium-catalyzed Oxidative Carbonylation of the hydrazides : Synthesis of 1,3,4-oxadiazol-2(3H)-ones

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A novel palladium-catalyzed oxidative carbonylation reaction was developed via the carbon monoxide insertions between amine group and carbonyl group to realize the intramolecular cyclization, which provides an efficient access to 1,3,4-oxadiazol-2(3H)-ones with wide range of substrates under mild conditions, resulting in good to excellent yields.

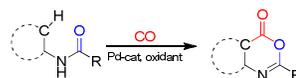
Since the work pioneered by Heck and co-workers in 1974,¹ transition-metal-catalyzed carbonylations have been recognized as an efficient and straightforward method to synthesize carbonyl derivatives,² which increases the carbon number and is in agreement with the green chemistry principle at the same time.³ However, amounts of transition-metal-catalyzed carbonylations are performed in high CO pressure and relatively high temperature.⁴ Then, the oxidative carbonylations of CO increasingly become an efficient solution to meet these harsh and inaccessible conditions.⁵ In addition, the carbonylated derivatives, instead of using R-X as the electrophiles which are prepared from the corresponding nucleophiles to realize the carbonylation, can be obtained from two nucleophiles with the assistance of oxidants which are used in oxidative carbonylations.^{5c, 6}

1,3,4-oxadiazol-2(3H)-one core is an important scaffold found in medicinal chemistry, which is widely used as Hormone-sensitive lipase (HSL) inhibitions,⁷ herbicides, fungicides,⁸ and function tools in chemical science.⁹ Thus, various methods were developed for the synthesis of 1,3,4-oxadiazol-2(3H)-ones involving the participations of propylene oxide, carbonic dichloride and phenanthrenequinones.¹⁰ To the best of our knowledge, although amine groups and carbonyl groups are frequently used as nucleophiles in palladium-catalyzed oxidative carbonylations respectively (Scheme 1a and 1b),^{11,12} no example has been reported on the CO insertion between these two nucleophiles for the intramolecular cyclocarbonylation. Encouraged by previous works, we aimed to synthesize 1,3,4-

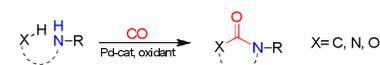
Scheme 1. Carbonylation cyclizations via nucleophiles (amine groups and carbonyl groups)

Previous work:

a) intramolecular palladium-catalyzed cyclocarbonylations via carbonyl group act as nucleophiles



b) intramolecular palladium-catalyzed cyclocarbonylations via amine group act as nucleophiles



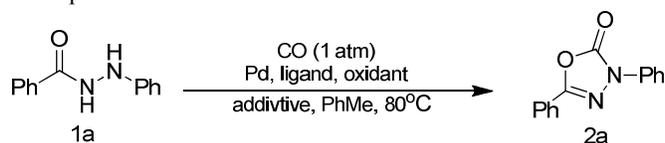
This work:

c) intramolecular palladium-catalyzed cyclocarbonylation between amine group and carbonyl group



oxadiazol-2(3H)-ones by using more straightforward method under mild conditions. Hence, we develop a convenient Pd-catalyzed oxidative cyclocarbonylation of hydrazides via the CO insertions between amine group and carbonyl group for the formation of 1,3,4-oxadiazol-2(3H)-ones (Scheme 1c), which could be considered as an environmentally friendly approach to these species.^{2b,5b-c}

Evaluation of this palladium-catalyzed CO insertion strategy began with exposure of benzoyl 2-phenylhydrazide to a series of palladium catalysts under CO atmosphere (Table 1). Unfortunately, the reaction failed to provide the desired product 2a in the presence of PdCl₂ (Table 1, entries 1-2). In screening of Pd-catalysts, including Pd(PPh₃)₂Cl₂, [PdCl₂(dppf)]CH₂Cl₂ and Pd(OAc)₂, [PdCl₂(dppf)]CH₂Cl₂ showed good activity to this transform and a 46% product yield of 2a was obtained (Ta-

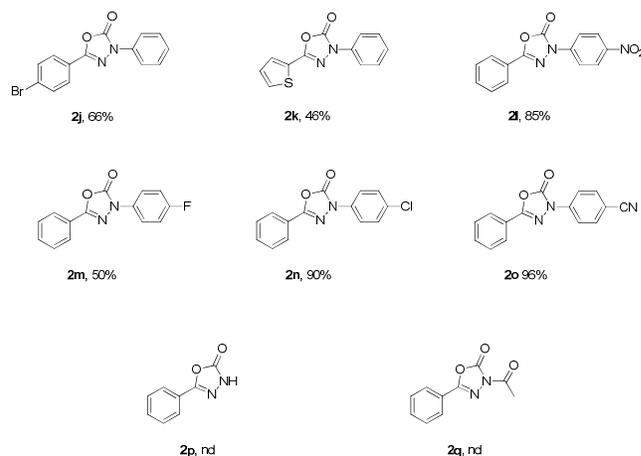
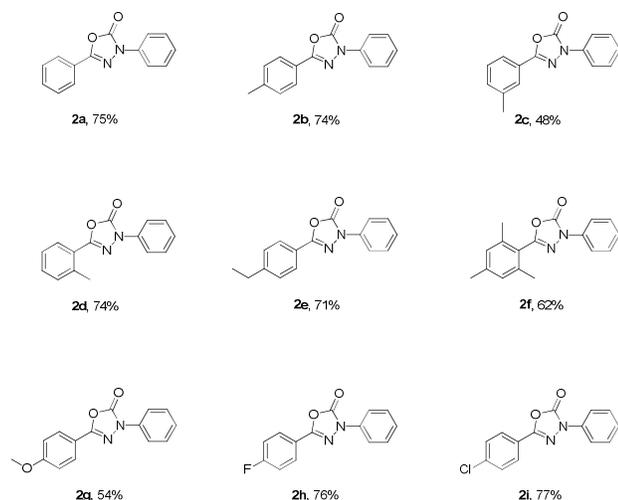
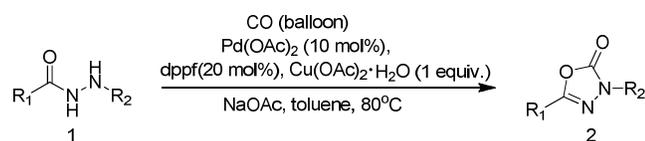
Table 1. Optimization of the Reaction Conditions^a

Entry	Catalyst	Ligand	Oxidant	Additive	Yield[%] ^b
1	PdCl ₂	-	CuCl ₂	-	nd
2	PdCl ₂	-	Cu(OAc) ₂ ·H ₂ O	-	trace
3	Pd(PPh ₃) ₂ Cl ₂	-	Cu(OAc) ₂ ·H ₂ O	-	33
4	[PdCl ₂ (dppf)]CH ₂ Cl ₂	-	Cu(OAc) ₂ ·H ₂ O	-	46
5	Pd(OAc) ₂	-	Cu(OAc) ₂ ·H ₂ O	-	trace
6	PdCl ₂	dppf	Cu(OAc) ₂ ·H ₂ O	-	21
7	Pd(OAc)₂	dppf	Cu(OAc)₂·H₂O	-	61
8	Pd(OAc) ₂	1,10-Phen	Cu(OAc) ₂ ·H ₂ O	-	trace
9	Pd(OAc) ₂	X-Phos	Cu(OAc) ₂ ·H ₂ O	-	26
10	Pd(OAc) ₂	XantPhos	Cu(OAc) ₂ ·H ₂ O	-	trace
11	Pd(OAc) ₂	Tri(1-naphthyl)phosphine	Cu(OAc) ₂ ·H ₂ O	-	23
12	Pd(OAc) ₂	Tri(3-Tolyl)phosphine	Cu(OAc) ₂ ·H ₂ O	-	trace
13	Pd(OAc) ₂	dppf	CuCl ₂	-	nd
14	Pd(OAc) ₂	dppf	K ₂ S ₂ O ₄	-	nd
15	Pd(OAc) ₂	dppf	AgOAc	-	25
16	Pd(OAc) ₂	dppf	CuO	-	nd
17	Pd(OAc) ₂	dppf	Cu(OAc) ₂ ·H ₂ O	NaOPiv	73
18	Pd(OAc) ₂	dppf	Cu(OAc) ₂ ·H ₂ O	KI	29
19	Pd(OAc)₂	dppf	Cu(OAc)₂·H₂O	NaOAc	75^[a]/57^[c]
20	Pd(OAc) ₂	dppf	Cu(OAc) ₂ ·H ₂ O	KOAc	35

^a Reaction conditions: hydrazide **1a** (0.2 mmol), catalyst (10 mol%), ligand (20 mol%), oxidant (1 equiv.), additive (1 equiv.), toluene (2 mL), at 80 °C under CO atmosphere (balloon pressure).

^b Isolated yields

^c Pd(OAc)₂ (5 mol%), dppf (10 mol%) were used as catalyst and ligand.

Scheme 2. Palladium-catalyzed carbonylation reaction of hydrazides **1**^a

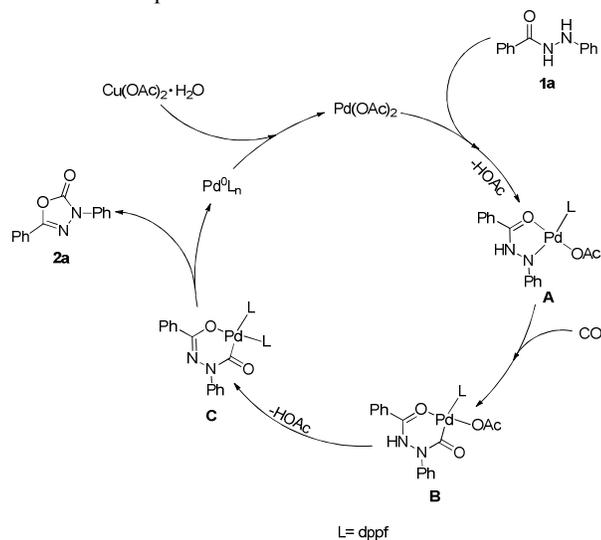
^a Reaction conditions: **1** (0.2 mmol), Pd(OAc)₂ (10 mol%), Cu(OAc)₂·H₂O (1.0 equiv.), CO balloon (1 atm), PhMe (2.0 mL), 80 °C, isolated yields of **2**, for 36 h.

ble **1**, entries 3-5). As expected, with PdCl₂ and Pd(OAc)₂ as catalysts, the yield of **2a** was improved to 21% and 61% when dppf was added as ligand (Table 1, entries 6-7). Various ligands, such as 1,10-Phen, X-Phos, XantPhos, Tri(1-naphthyl)phosphine, and Tri(3-tolyl)phosphine, were also tested and dppf was still the most effective ligand (Table 1, entries 8-12).

Meanwhile, better results were not observed when other oxidants were employed including CuCl_2 , $\text{K}_2\text{S}_2\text{O}_8$, AgOAc , and CuO (Table 1, entries 13-16). To our delight, through the study the effect of additives (such as NaOPiv , KI , NaOAc , and KOAc), NaOAc was shown improvement of the palladium-catalyzed carbonylation, thus giving **2a** in 75% yield.^{12f, 13} (Table 1, entries 17-20)

With the optimized reaction condition in hand, we then extended the reaction to a range of substrates. A wide variety of substitution patterns and functionalities were tolerated, as shown in Scheme 2. According to the results, benzoyl 2-phenylhydrazide substituted with electron-withdrawing groups (**2h-j**, **2l-o**) proceeded efficiently in good to excellent yields (50-96%). It was worth mentioning this reaction was compatible with various functional groups such as halogens (F, Cl, and Br) and cyano (**2h-j**, **2m-n**), which could be subjected to further synthetic transformation. On the other hand, hydrazide substitutions with electron-donating groups reacted smoothly and presented the corresponding products (**2b-g**, **2k**) in 46-74% yields. However, to our disappointment, N-Acetyl benzoylhydrazide and Benzoyl hydrazine failed to provide the desired products **2q-r**. Unfortunately, including 1-Acetyl-2-phenylhydrazine, Styryl N-phenylhydrazide, Phenylethynyl N-phenylhydrazide, 4-hydroxy-phenyl N-phenylhydrazide, N-tert-butyl benzoylhydrazide and N-benzyl benzoylhydrazide, show totally inactive to this reaction.

Scheme 3. Proposed mechanism for the reaction.



Based on previous reports as well as our results,^{11, 12, 14} a possible mechanism for this carbonylation is proposed as outlined in Scheme 3. With assistance of carbonyl group of **1a**, its N-H activation by $\text{Pd}(\text{OAc})_2$ forms the intermediate A.¹⁵ Insertion of a coordinated CO into the N-Pd bond affords the intermediate B. The formation of the palladacycle C via the release of HOAc. Subsequently, reductive elimination of C provides the desired product **2a** and Pd^0 species regenerate via reoxidized to the Pd(II) catalyst. The dpfp ligand is likely

promoted reductive elimination of Pd(II) from palladacycle C due to the wide bite angle of bis-phosphine.¹⁶

In summary, a highly efficient palladium-catalyzed carbonylation of hydrazides for the synthesis of 1,3,4-oxadiazol-2(3H)-ones was developed, which takes place smoothly under atmospheric pressure of CO. This is the first example of using both a amine group and a carbonyl group within one molecule as the two nucleophiles in a CO insertion cyclization reaction, to which further investigation is currently underway.

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Notes and References

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