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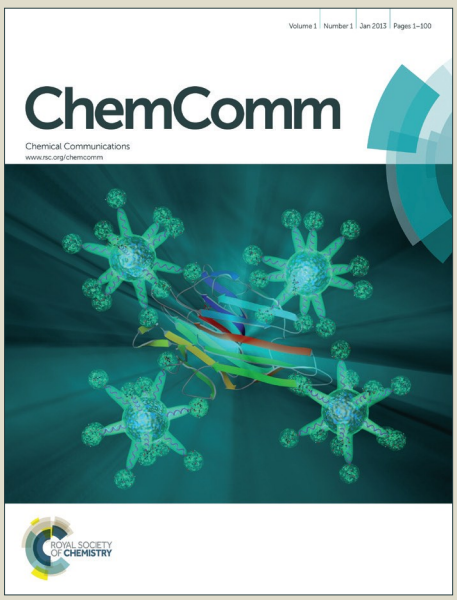

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ARTICLE TYPE

Pd-Catalyzed Carbonylative Cycloamidation of Ketoimines for Synthesis of Pyrido [1, 2-a] Pyrimidin-4-Ones **

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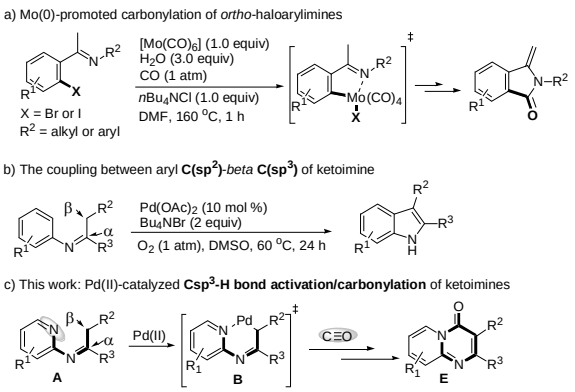
Introduction

Transition metal-catalyzed carbonylation of organic molecules such as aryl halides, [1] alkenes [2] and alkynes [3] etc, provides a powerful tool to construct carbon-carbon and carbon-heteroatom bonds. Among the various carbonylations, chelation-assisted C-H functionalization is emerging as an ideal site-selective carbonylation strategy due to its atom- and step-economy. In this regards, various heteroatom-containing functional groups such as amides, [4] nitrogen heterocycles, [4a, 4b, 5] hydroxy group,[6] amines,[7] and carboxylic acids [8] etc., have been widely employed as directing group to enhance Csp^2-H carbonylation. Moreover, several breakthrough in functional group-directed Csp^3-H carbonylation, has also been achieved through Pd(II) or Ru(0)-catalyzed carbonylative Csp^3-H functionalization of aliphatic amides or amines by Yu,[9] Gaunt [10] and Chatani, [11] respectively. Consequently, developing new type of ligand-directed carbonylations will continue to be more desirable.

On the other hand, as the versatile synthon, imines are of great importance in organic chemistry, transition metal-catalyzed C-X (X= C, N etc.) coupling reactions derived from imines are widely utilized in constructing kinds of nitrogen-containing compounds, [12] but the carbonylation involving imines was rarely reported. Up to now, only Iwasawa ever developed a molybdenum-promoted carbonylative cyclization of ortho-haloarylimines, in which carbonylation insertion occurred through oxidative addition of Mo(0) to Csp^2-halogen bond (Scheme 1a).[13] Recently, Yoshikai and co-workers reported that Pd(II) could directly catalyze the intramolecular oxidative cyclization of N-aryl ketoimine to construct indoles via aryl C (sp^2)-alkyl C (sp^3) coupling (Scheme 1b).[14] More recently, we developed a Pd-catalyzed pyridine-directed oxidative [3+2] cycloaddition reaction for assembling a multisubstituted pyrrole skeleton from readily available 2-(*N*-pyridyl)ketoimines and internal alkynes.[15] Yoshikai's and our work indicated that β-C(sp^3) of ketoimines could be directly coupled with unsaturated carbon atoms. Considering that carbon monoxide also belongs to an important unsaturated C1 source, and in connection with our continuing efforts to explore novel reactions starting from imines to construct nitrogen-containing compounds, [15, 16] we envisioned that a six-membered cyclopalladium species (**B**) which derived from 2-pyridine ketoimine **A**, will be possibly trapped by unsaturated carbon atom-containing CO *via* carbonyl insertion process, and result in the occurrence of carbonylation reaction (Scheme 1c). To identify this hypothesis, herein we report a novel Pd-catalyzed pyridine-directed carbonylation to rapidly assembly pyrido [1, 2-a] pyrimidin-4-ones (PPO) derived from *N*-(2-pyridyl)-ketoimines, which was ever employed to treat with isocyanates to furnish PPO,[17] most of PPO analogues are potent biological and drug molecules in medical chemistry.[18]



Scheme 1. Ketoimines as a catalysis platform for *N*-heterocycle synthesis

Results and Discussion

Initially, the carbonylation of *N*-(2-pyridyl)-ketoimine (**1a**) was investigated as a model system. First attempts were performed to screen palladium catalysts in the presence of MnO_2, K_2CO_3 and additive KI under an atmospheric pressure of CO in DMF at 80 °C (Table 1, entries 1-5), and we quickly found that $Pd(OAc)_2$ was an effective catalyst which could provide the desired carbonylation product 2-phenyl-pyrido[1,2-a]pyrimidin-4-one (**2a**) in 32% yield (entry 5). To further improve the reaction outcome, we conducted this reaction for optimizing oxidants including $Na_2S_2O_8$, and $PhI(OAc)_2$ *etc* (entries 5-10). Among the tested oxidants, $Cu(OAc)_2$ was a suitable oxidant for this transformation, and gave an improved yield of 36% (entry 10). Subsequently, we continued to further evaluate the effect of various bases on this carbonylation reaction for achieving satisfying yields (entries 10-14), and found the yield of product **2a** could be increased to 50% with the use of 1.0 equiv of DABCO (1, 4-diazabicyclo [2.2.2] octane) (entry 14). It is worth to note that not employing KI as additive resulted in significantly

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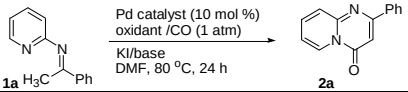
decreased yield possibly due to that iodide anions could enhance the carbonylation efficiency (compare entry 14 with 15).[19] Finally, to our delight, increasing the reaction temperature from 80 °C to 100 °C significantly enhanced the carbonylation reaction, and provided **2a** in up to 88% isolated yield (entry 17). Notably, lowering the reaction temperature to 60 °C led to poorer conversion (compare entries 14 and 17 with 16) [see Supporting Information (SI) for more details].

Table 1. Optimization of the reaction parameters [a]

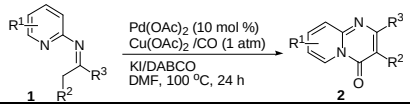


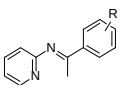
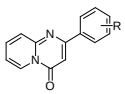
Entry	Catalyst	Oxidant	Base	Yield (%) [b]
1	$PdCl_2$	MnO_2	K_2CO_3	18
2	$Pd(TFA)_2$	MnO_2	K_2CO_3	trace
3	$PdCl_2(CH_3CN)_2$	MnO_2	K_2CO_3	trace
4	$PdCl_2(PPh_3)_2$	MnO_2	K_2CO_3	5
5	$Pd(OAc)_2$	MnO_2	K_2CO_3	32
6	$Pd(OAc)_2$	$Na_2S_2O_8$	K_2CO_3	14
7	$Pd(OAc)_2$	$PhI(OAc)_2$	K_2CO_3	10
8	$Pd(OAc)_2$	AgOAc	K_2CO_3	22
9	$Pd(OAc)_2$	BQ [c]	K_2CO_3	trace
10	$Pd(OAc)_2$	$Cu(OAc)_2$	K_2CO_3	36
11	$Pd(OAc)_2$	$Cu(OAc)_2$	$NaHCO_3$	31
12	$Pd(OAc)_2$	$Cu(OAc)_2$	Cs_2CO_3	10
13	$Pd(OAc)_2$	$Cu(OAc)_2$	NaOAc	14
14	$Pd(OAc)_2$	$Cu(OAc)_2$	DABCO	50
15	$Pd(OAc)_2$	$Cu(OAc)_2$	DABCO	27 [d]
16	$Pd(OAc)_2$	$Cu(OAc)_2$	DABCO	32 [e]
17	$Pd(OAc)_2$	$Cu(OAc)_2$	DABCO	88 [f]

[a] Unless otherwise noted, all the reactions were carried out using ketoimine (**1a**) (0.10 mmol), KI (1.0 equiv) and CO (balloon pressure) with Pd catalyst (10 mol %) in the presence of oxidant (1.0 equiv) and base (1.0 equiv) in DMF (1.0 mL) at 80 °C for 24 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield. [c] BQ stands for 1, 4-benzoquinone. [d] The reaction was run in the absence of KI. [e] The reaction temperature is 60 °C. [f] The reaction temperature is 100 °C.

With the optimized conditions in hand, we further examined the scope and limitations of the pyridine-directed Csp^3-H activation/carbonylation reaction. As shown in Table 2, common functional groups on the benzene rings attached to the ketoimine carbon, were tolerated in this transformation to furnish the corresponding carbonylation products in moderate to excellent yield (entries 1-14), including electron-donating groups, such as alkyl (**2b-2d**), alkyoxyl (**2e**), and acetal group (**2n**), and electron-withdrawing groups including halogen (**2f-2j**), nitrile (**2k**), ester (**2l**), and nitro groups (**2m**). It should be noted that *meso* or *ortho*-substituted benzene ring led to a lower yield possibly due to the increased steric hindrance around the ketoimine (**2b-2d**; **2g-2i**). Moreover, heteroaryl (HetAr) substituted ketoimines (HetAr = 2-thiophene, 2-furan, 4-pyridyl, and 3-pyridyl) also allowed for this transformation and produced the desired 2-heterocycle-substituted pyrido[1,2-a]pyrimidin-4-ones (**2o - 2r**) in 45-61% yields (entries 15-18). Importantly, this reaction protocol could still smoothly convert phenylpropone-derived ketoimine **1s** to the corresponding 3-methyl-2-phenyl-pyrido[1,2-a]pyrimidin-4-one **2s** (entry 19). Subsequently, we further investigated the substitution effects from pyridine ring of ketoimines on this transformation, and found electron–rich ketoimines offered higher yield of products except *N*-(3-methoxyl pyridine)-substituted ketoimine (**1w**) with stronger steric hindrance around the reaction center; While electron-deficient substrates inhibited cyclocarbonylation performance (entry 20-24, compare **2t** with **2u** and **2w**). Unfortunately, bromine-containing substrates were sensitive to this transformation in which bromine atom would be removed (**1j** and **1v**).

Table 2. Substrate scope for the Pd(II)-catalyzed carbonylative Csp^3-H bond cycloamidation of ketoimines [a]



Entry	Ketoimine (**1**)	Product (**2**)	Yield [b]
			
1	**1a:** R = H	**2a:** R = H	88
2	**1b:** R = *p*-Me	**2b:** R = *p*-Me	90
3	**1c:** R = *m*-Me	**2c:** R = *m*-Me	84
4	**1d**: R = *o*-Me	**2d**: R = *o*-Me	68
5	**1e**: R = *p*-MeO	**2e**: R = *p*-MeO	91
6	**1f**: R = *p*-F	**2f**: R = *p*-F	75
7	**1g**: R = *p*-Cl	**2g**: R = *p*-Cl	79
8	**1h**: R = *m*-Cl	**2h**: R = *m*-Cl	62
9	**1i**:R = *o*-Cl	**2i**: R = *o*-Cl	54
10	**1j**: R = *p*-Br	**2a**: R = *p*-H	82

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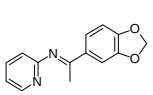
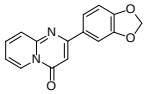
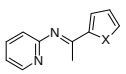
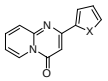
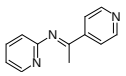
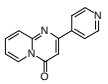
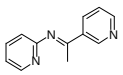
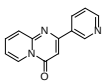
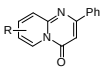
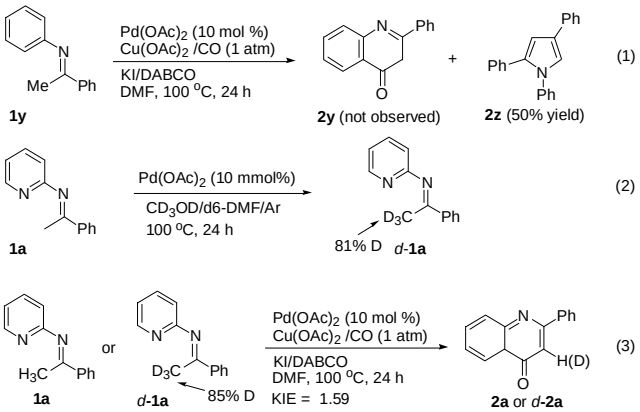
11	**1k**: R = *p*-CN	**2k**: R = *p*-CN	65
12	**1l**: R = *p*-CO_2Me	**2l**: R = *p*-CO_2Me	71
13	**1m**: R = *p*-NO_2	**2m**: R = *p*-NO_2	64
14	 **1n**	 **2n**	94
15	 **1o**: X = O	 **2o**: X = O	52
16	**1p**: X = S	**2p**: X = S	61
17	 **1q**	 **2q**	58
18	 **1r**	 **2r**	45
19	 **1s**	 **2s**	17
20	 **1t**: R = 5-Me	 **2t**: R = 5-Me	80
21	**1u**: R = 5-Cl	**2u**: R = 5-Cl	62
22	**1v**: R = 5-Br	**2a**: R = 5-H	60
23	**1w**: R = 3-MeO	**2v**: R = 3-MeO	60
24	**1x**: R = 5-CO_2Me	**2w**: R = 5-CO_2Me	50

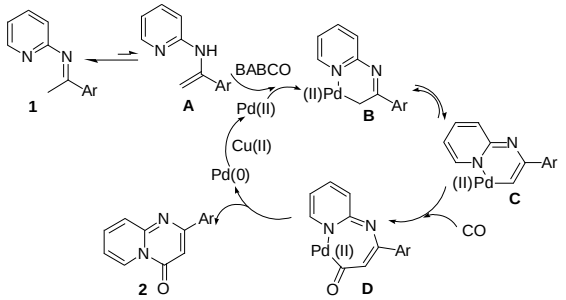
[a] All the reactions were carried out using ketoimine (**1a**) (0.10 mmol), KI (1.0 equiv) and CO (balloon pressure) with $Pd(OAc)_2$ (10 mol %) in the presence of $Cu(OAc)_2$ (1.0 equiv) and DABCO (1.0 equiv) in DMF (1.0 mL) at 100 ˚C for 24 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield.

To gain preliminary insight into the reaction mechanism, we conducted several controlled experiments. First, we tried the carbonylative cycloamidation of *N*-phenyl ketoimine (**1y**) under our standard conditions, no desired cyclocarbonylation product **2y** was detected by the ^{1}H NMR and GC-MS methods. On the contrary, only 50% yield of cascade cyclization product **2z** was produced [Scheme 2. Eq. (1)]. [20] This result remarkably demonstrated that pyridyl nitrogen played a key chelating site in this carbonylation process. Subsequently, when *N*-(2-pyridyl) ketoimine **1a** was subjected to Pd(II)/CD_3OD/Ar system for 24 h in the absence of carbon monoxide, 81% deuterium incorporation was observed at the imino methyl group of **1a** [Eq. (2)] (see SI for more details),[21] this experiment indicated that imine-enamine tautomerization is facile under the reaction conditions. Finally, kinetic isotope effect experiments were conducted under the standard conditions [Eq. (3)], and the corresponding KIE value (K_H/K_D = 1.59) indicated that imine-enamine equilibrium just influence, but not solely dominate the reaction rate (see SI for more details).



Scheme 2. Preliminary mechanistic studies

Based on the above experimental results, a possible mechanism that involved a Pd(II)/Pd(0) redox process can be proposed as shown in Scheme 3. Enamine **A** derived from imine/enamine-isomerization [14, 22] can be electrophilically attacked by Pd(II) to produce a palladacycle intermediate **B** which can isomerize to form palladacycle intermediate **C**. Subsequently, coordination and the migratory insertion of CO into the N-Pd bond of intermediate **C** affords a seven-membered palladacycle **D**, which can further lead to the formation of carbonylative cycloamidation product **2** through Pd(II) reductive elimination and generate a Pd(0) species which can be oxidized by Cu(II) salts to generate the catalytically active Pd(II) catalysts.



Scheme 3. Possible mechanism for the reaction

Conclusions

In summary, we have developed an efficient method for the synthesis of pyrido[1,2-a]pyrimidin-4-ones through Pd(II)-catalyzed carbonylative cycloamidation of *N*-(2-pyridyl) ketoimines under an atmospheric pressure of CO. This transformation tolerates a variety of functionalities including nitrile, chloride, alkyloxycarbonyl, nitro, and heteroaryl etc., which could be further employed as useful synthetic blocks for constructing more complex biological molecules. Further

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studies on substrate scope and investigations into the mechanism about this reaction are under way in our laboratory.

Acknowledgments

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