Tetrahedron Letters 53 (2012) 2465–2468

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

'Ligand-free' palladium-catalyzed direct C–H bond oxidative acyloxylation of 2-arylpyridines with aromatic carboxylic acids

Chao-Jun Hu [a], Xiao-Hong Zhang [a,*], Qiu-Ping Ding [a,b], Ting Lv [a], Shao-Peng Ge [a], Ping Zhong [a,c,*]

[a] College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China
[b] College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330027, China
[c] Oujiang College, Wenzhou University, Wenzhou 325035, China

ARTICLE INFO

Article history:
Received 26 October 2011
Revised 28 February 2012
Accepted 6 March 2012
Available online 14 March 2012

Keywords:
'Ligand-free'
Palladium-catalyzed
Acyloxylation
2-Arylpyridines

ABSTRACT

A palladium-catalyzed direct C–H bond oxidative acyloxylation of 2-arylpyridines with aromatic carboxylic acids is described. Several 2-arylpyridines derivatives and aromatic carboxylic acids participate in the reaction, providing a series of mono-acyloxylated products in moderate to good yields. Importantly, the reaction can be conducted without using any ligands in a lower temperature.

Introduction

In the past decades, tremendous efforts have been paid to develop mild methods for the direct functionalization of C–H in complex organic substrates to construct C–C,[1] C–N,[2] C–O[3] and C–S bonds.[4] Among them, transition-metal catalyzed acyloxylation of the C–H bond is one of the most attractive processes. For example, Sanford,[5] Kwong,[6] Pelcman[7] and Chen[8] illustrated acetoxylation of sp^2 C–H bond based on different aromatic substances using $PhI(OAc)_2$ as terminal oxidants. $K_2S_2O_8$ and $Cu(OAc)_2$ were also employed as oxidants to achieve the similar reaction by Wu and co-workers[9] and Zhang and co-workers,[10] respectively. However, most of the reported acyloxylation is almost restricted to acetoxylation[9,11] and different oxidants are required to fulfill the catalytic cycle. Additionally, the benzoxylation via transition-metal catalyzed C–H bond is rarely reported. In view of this situation, Cheng's group[12] had developed a rhodium-catalyzed *ortho*-benzoxylation of sp^2 C–H bond to afford the benzoxylated products without using any oxidant in 2009. In an attempt to expand the diversity of the available starting materials and the catalysts, copper(II)-catalyzed *ortho*-benzoxylations of 2-arylpyridine with anhydride[13] and acyl chloride,[14] respectively were reported by the same group.

Yet, Cheng's procedures required either expensive ligands or high temperature and the carboxylic anhydrides are not commercially available. All of these limited the development of C–H functionalization. We noted that Shi and co-workers has recently developed a new method for the direct *ortho*-benzoxylation of *O*-methyl oximes with various carboxylic acids using Pd as the catalyst.[15] So we envisioned that the direct *ortho*-benzoxylation of 2-arylpyridine with carboxylic acids could proceed in mild condition using Pd as the catalyst. Herein, we wish to demonstrate a new process of direct C–H bond oxidative benzoxylation of 2-arylpyridines via the palladium-catalyzed reaction with aromatic carboxylic acids. Importantly, the reaction can be conducted without using any ligands at lower temperature.

Results and discussion

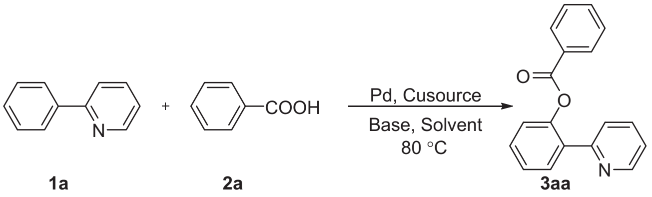
Our investigation started with the reaction of 2-phenylpyridines and benzoic acid under air atmosphere to screen the optimal reaction conditions (Table 1). First, in the presence of CuI, three commonly used catalyst precursors for the oxidative acyloxylation were surveyed when Ag_2CO_3 was used as the base and toluene as the solvent. It was found that $Pd(OAc)_2$ gave better yield of the product than $PdCl_2$ and $Pd_2(dba)_3$ (entries 1–3). The yield was dropped sharply to less than 5% in the absence of Pd catalyst (entry 4). Notably, no product was formed in the absence of a Cu source (entry 5), which showed that the Cu source played an indispensable role in the reaction. The behavior of the Cu source can be seen in the possible mechanism (Scheme 1). Evaluation of additional Cu

---

* Corresponding authors. Tel./fax:+86 0577 86689338.
E-mail addresses: kamenzxh@163.com (X.-H. Zhang), zhongp0512@163.com (P. Zhong).

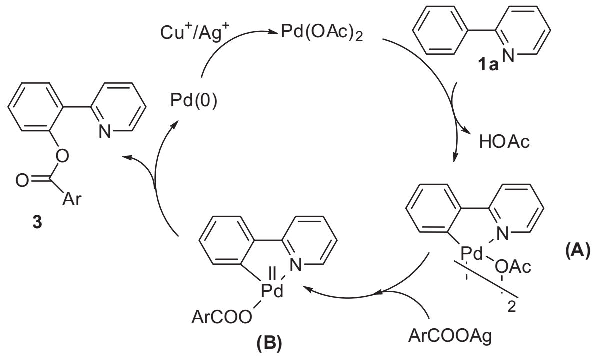
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.022

Table 1
Effects of Pd catalyst, Cu sources, bases, and solvents[a]



Entry	[Pd] (mol %)	[Cu] (equiv)	Base (equiv)	Solvent	Yield[b] (%)
1	$PdCl_2$ (10)	CuI (2)	Ag_2CO_3 (2)	Toluene	26
2	$Pd_2(dba)_3$ (10)	CuI (2)	Ag_2CO_3 (2)	Toluene	31
3	$Pd(OAc)_2$ (10)	CuI (2)	Ag_2CO_3 (2)	Toluene	43
4	—	CuI (2)	Ag_2CO_3 (2)	Toluene	<5
5	$Pd(OAc)_2$ (10)	—	Ag_2CO_3 (2)	Toluene	—
6	$Pd(OAc)_2$ (10)	CuBr (2)	Ag_2CO_3 (2)	Toluene	12
7	$Pd(OAc)_2$ (10)	CuCl (2)	Ag_2CO_3 (2)	Toluene	12
8	$Pd(OAc)_2$ (10)	Cu_2O (2)	Ag_2CO_3 (2)	Toluene	20
9	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (2)	Ag_2CO_3 (2)	Toluene	27
10	$Pd(OAc)_2$ (10)	$CuCl_2$ (2)	Ag_2CO_3 (2)	Toluene	9
11	$Pd(OAc)_2$ (10)	$CuBr_2$ (2)	Ag_2CO_3 (2)	Toluene	23
12	$Pd(OAc)_2$ (5)	CuI (2)	Ag_2CO_3 (2)	Toluene	23
13	$Pd(OAc)_2$ (10)	CuI (0.5)	Ag_2CO_3 (2)	Toluene	38
14	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (2)	Toluene	61
15	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	Toluene	67 (45[c], 70[d])
16	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (0.5)	Toluene	49
17	$Pd(OAc)_2$ (10)	CuI (1)	—	Toluene	23 (<5[c])
18	$Pd(OAc)_2$ (10)	CuI (1)	K_2CO_3 (1)	Toluene	37
19	$Pd(OAc)_2$ (10)	CuI (1)	$NaHCO_3$ (1)	Toluene	19
20	$Pd(OAc)_2$ (10)	CuI (1)	Na_2CO_3 (1)	Toluene	42 (<5[c])
21	$Pd(OAc)_2$ (10)	CuI (1)	$K_3PO_4{\cdot}3H_2O$ (1)	Toluene	28
22	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	DCE	79
23	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	CH_2Cl_2	51
24	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	THF	33
25	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	DMSO	12
26	$Pd(OAc)_2$ (10)	CuI (1)	Ag_2CO_3 (1)	CH_3COOH	17, (60[e])

[a] 2-Phenylpyridine (0.2 mmol), benzoic acid (0.6 mmol) in a sealed tube, 80 °C, 17 h.
[b] Isolated yields.
[c] Under N_2.
[d] Under O_2.
[e] The yield of phenyl acetate.



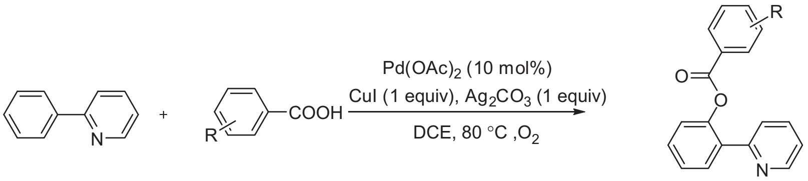
Scheme 1. Plausible mechanism.

sources, including Cu(I) and Cu(II), such as CuBr, CuCl, Cu_2O, $Cu(OAc)_2$, $CuCl_2$ and $CuBr_2$, provided conditions that gave a much lower yield of the benzoxylated product relative to CuI (entries 6–11). Remarkably, among the amounts of $Pd(OAc)_2$ and CuI screened (entries 12–14), the combined amounts of 10 mol % $Pd(OAc)_2$ and 1 equiv CuI turned out to be the best (entry 14). The amount of base affected the reaction: a higher yield was observed when the amount of Ag_2CO_3 was decreased to 1 equiv than 2 equiv Ag_2CO_3, while lowering the amount of Ag_2CO_3 to 0.5 equiv decreased the yield of **3aa** to 49% (entries 15 and 16).

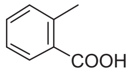
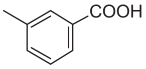
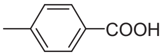
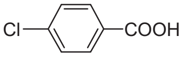
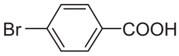
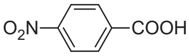
When Ag_2CO_3 was replaced with K_2CO_3, $NaHCO_3$, Na_2CO_3 and $K_3PO_4{\cdot}3H_2O$, lower yields of **3aa** were obtained (entries 18–21). In the absence of Ag_2CO_3, the desired product was obtained only in 23% yield (entry 17). We envisioned that Ag_2CO_3 might play more important roles than just a simple base. When the experiments proceed under N_2, the corresponding yields of entry 15 was decreased to 45%, while less than 5% yield of aimed product was obtained in the absence of Ag_2CO_3 (entries 17 and 20). Replacing air and N_2 by O_2 favored the benzoxylations slightly (entry 15). Finally, different solvents were also screened, and DCE was shown to be most suitable for this transformation (entries 22–26), while phenyl acetate was generated in 60% yield when CH_3COOH was used as the solvent (entry 26).

With the preliminary optimized reaction in hand, the scope of aromatic acids was next discussed. The results were summarized in Table 2. As expected, various aromatic acids worked well under the reaction condition. A series of functional groups, such as methyl, chloro and bromo groups, were tolerated in this process. However, the yield can be affected by steric hindrance. For instance, 78% **3ac** and 75% **3ad** were isolated, while the yield of **3ab** was decreased to 53% (entries 1–3). It was also found that the reaction seemed to be sensitive to electronic effects of the aromatic acids. The electron-donating group, such as methyl, was beneficial for the transformation, but the electron-withdrawing group, such as chloro and bromo, decreased the efficiency (entries 3–5), while 4-nitro benzoic acid gave the benzoxylated product in less

Table 2
Ortho-benzoxylation reaction of 2-phenylpyridine with aromatic acids

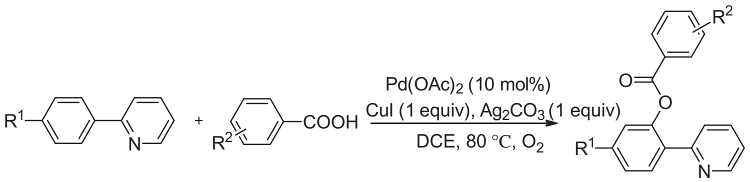


1a **2** **3**

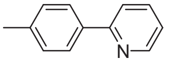
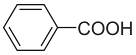
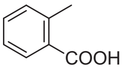
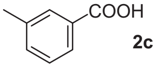
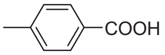
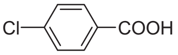
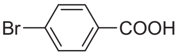
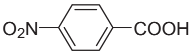
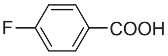
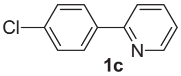
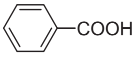
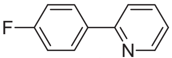
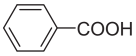
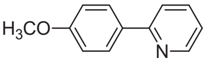
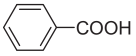
Entry	Aromatic acids **2**	Products	Yield[a] (%)
1	 **2b**	**3ab**	53
2	 **2c**	**3ac**	78
3	 **2d**	**3ad**	75
4	 **2e**	**3ae**	61
5	 **2f**	**3af**	62
6	 **2g**	–	<5
7	CH_3COOH **2h**	**3ah**	75

[a] Isolated yields.

Table 3
Ortho-benzoxylation reaction of 2-arylpyridines with aromatic acids



1b-1f **2** **3**

Entry	2-Arylpyridine **1**	Aromatic acids **2**	Products	Yield[a] (%)
1	 **1b**	 **2a**	**3ba**	77
2	**1b**	 **2b**	**3bb**	55
3	**1b**	 **2c**	**3bc**	69
4	**1b**	 **2d**	**3bd**	71
5	**1b**	 **2e**	**3be**	64
6	**1b**	 **2f**	**3bf**	62
7	**1b**	 **2g**	–	<5
8	**1b**	 **2i**	**3bi**	69
9	 **1c**	 **2a**	**3ca**	53
10	 **1d**	 **2a**	**3da**	59
11	 **1e**	 **2a**	**3ea**	65

[a] Isolated yields.

than 5% yield (entry 6). The alkyl carboxylic acid, such as acetic acid, can tolerate the reaction well (entry 7).

Subsequently, promoted by the successful palladium-catalyzed direct C–H bond oxidative acyloxylation of 2-phenylpyridine, we explored the reaction of several 2-arylpyridines with aromatic acids and the results were shown in Table 3.

Initially, the substrate of 2-(4-methylphenyl)pyridine was treated with different aromatic acids, giving similar results with 2-phenylpyridine. Steric hindrance and electronic effects of the aromatic acids both affected the reaction. For example, **2b** gave a lower yield of 55% than **2c** and **d** (entries 2–4). The electron-donating group, such as methyl group, was also beneficial for the transformation, but the electron-withdrawing group, like chloro, bromo, fluoro, and nitro, decreased the efficiency (entries 5–8). Moreover, the yield of **3ba** was nearly the same with **3aa**, indicating that the methyl group of the aryl ring had little influence on the reaction (entry 1). Next, the reaction of a variety of 2-arylpyridines, such as 2-(4-chlorophenyl)pyridine, 2-(4-fluorinphenyl)pyridine and 2-(4-methoxylphenyl)pyridine with benzoic acid were conducted under the optimal conditions. The arenes possessing electron-donating functional groups, like methyl and methoxyl, were found to be more reactive and gave slightly higher yields than those of electron-withdrawing groups, such as chloro and fluoro groups (entries 1, 9–11).

A possible mechanism for the present palladium(II)-catalyzed *ortho*-oxidative acyloxylation of 2-phenylpyridines (**1a**) with aromatic carboxylic acids is proposed in Scheme 1. First, the reaction of $Pd(OAc)_2$ with 2-phenylpyridine (**1a**) by removing HOAc affords a cyclopalladated intermediate (A), which was actually confirmed by many related reports[16] and was also detected by HRMS in our lab. This intermediate reacted with the in-situ generated silver carboxylate from the reaction of carboxylic acid with Ag_2CO_3 to give the ligand exchanged product (B), in which occurs the reductive elimination to release the acyloxylated product. The resulting Pd^0 intermediate is then reoxidized by Ag(I) and Cu(I) salts to regenerate the Pd(II) catalyst.[10,17]

In summary, we have developed a novel palladium-catalyzed direct C–H bond oxidative acyloxylation method, which allows the reaction between 2-arylpyridines and aromatic carboxylic acids for the synthesis of mono-acyloxylated products in moderate to good yields. Importantly, the reaction can be conducted without using any ligands at lower temperature.

Acknowledgments

The authors thank the National Natural Science Foundation of China (No. 20972114), the Zhejiang Provincial Natural Science Foundation of China (Y4100578) and the Opening Foundations of Zhejiang Provincial Top Key Discipline (100061200106 and 100061200140).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.022.

References and notes

1. For selected reports on the construction of C–C via direct functionalization of C–H, see: (a) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706; (b) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207; (c) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35; (d) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607; (e) Saha, D.; Adak, L.; Ranu, B. C. *Tetrahedron Lett.* **2010**, *51*, 5624; (f) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 1248.
2. For selected reports on the construction of C–N via direct functionalization of C–H, see: (a) Beccalli, E. M.; Broggini, G.; Fasana, A.; Rigamonti, M. *J. Organomet. Chem.* **2011**, *696*, 277; (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560; (c) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194; (d) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603; (e) Guo, S. M.; Xie, Y. J.; Xia, C. G.; Huang, H. H. *Org. Lett.* **2011**, *13*, 522; (f) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.
3. For selected reports on the construction of C–O via direct functionalization of C–H, see: (a) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247; (b) Kalber, E. W.; Whitfield, S. R.; Sanford, M. S. *J. Mol. Catal. A: Chem.* **2006**, *251*, 108; (c) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.
4. For selected reports on the construction of C–S via direct functionalization of C–H, see: (a) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147; (b) Xu, R. S.; Wan, J. P.; Mao, H.; Pan, Y. J. *J. Am. Chem. Soc.* **2010**, *132*, 15531; (c) Fukuzawa, S.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374; (d) Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1411; (e) Jaseer, E. A.; Prasad, D. J. C.; Dandapat, A.; Sekar, G. *Tetrahedron Lett.* **2010**, *51*, 5009; (f) Fang, X. L.; Tang, R. Y.; Zhong, P.; Li, J. H. *Synthesis* **2009**, *24*, 4183; (g) Pezzella, A.; Palma, A.; Iadonisi, A.; Napolitano, A.; d'Ischia, M. *Tetrahedron Lett.* **2007**, *48*, 3883.
5. (a) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285; (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300; (c) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2005**, *24*, 482; (d) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584; (e) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *26*, 1365; (f) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.
6. Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80.
7. Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B. *J. Org. Chem.* **2009**, *74*, 7195.
8. Gu, S. J.; Chen, C.; Chen, W. Z. *J. Org. Chem.* **2009**, *74*, 7203.
9. Wang, G. W.; Yuan, T. T.; Wu, X. L. *J. Org. Chem.* **2008**, *73*, 4717.
10. Liang, Z. J.; Zhao, J. L.; Zhang, Y. H. *J. Org. Chem.* **2010**, *75*, 170.
11. (a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050; (b) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530; (c) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790; (d) Wang, D. H.; Hao, X. S.; Wu, D. F.; Yu, J. Q. *Org. Lett.* **2006**, *8*, 3387.
12. Ye, Z. S.; Wang, W. H.; Luo, F.; Zhang, S. H.; Cheng, J. *Org. Lett.* **2009**, *11*, 3974.
13. Wang, W. H.; Luo, F.; Zhang, S. H.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415.
14. Wang, W. H.; Pan, C. D.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 3978.
15. Sun, C. L.; Liu, J.; Wang, Y.; Zhou, X.; Li, B. J.; Shi, Z. J. *Synlett* **2011**, 0883.
16. (a) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634; (b) Yu, W. Y.; Sit, W. N.; Zhou, Z. Y.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174; (c) Li, W.; Yin, Z. W.; Jiang, X. Q.; Sun, P. P. *J. Org. Chem.* **2011**, *76*, 8543.
17. (a) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1378; (b) Kim, D.; Hong, S. *Org. Lett.* **2011**, *13*, 4466.