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Palladium-Catalyzed Aryl C−H Bonds Activation/Acetoxylation Utilizing a Bidentate System

Fa-Rong Gou,[†] Xiang-Chuan Wang,[†] Peng-Fei Huo,[†] Hai-Peng Bi,[†] Zheng-Hui Guan,[†] and Yong-Min Liang*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China, and State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou 730000, People's Republic of China

liangym@lzu.edu.cn

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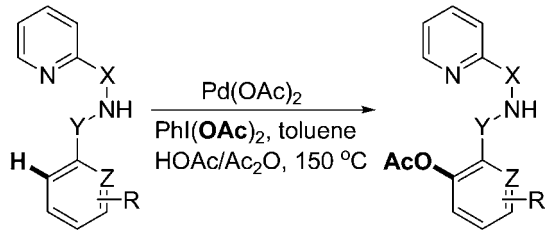
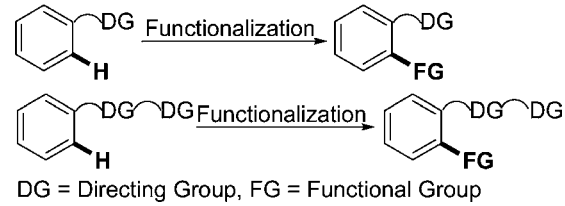
ABSTRACT



A palladium-catalyzed aryl C−H bonds activation/acetoxylation reaction utilizing a bidentate system has been explored. This transformation has been applied to a wide array of pyridine and 8-aminoquinoline derivatives and it exhibits excellent functional group tolerance.

The development of transition metal-catalyzed C−H activation reactions directed by directing functional groups has seen substantial progress in recent years.[1,2] These reactions allow for the highly site-selective transformations of a C−H bond proximal to a coordinating directing group (DG) into a new C−X bond (X = O,[3] C,[4] N,[5] X,[6] S[7]). A wide range of metal catalysts, including Ru, Rh, and Pd, have been exploited with varying degrees of success.[1] And a wide variety of directing groups, such as ketone, ester, amide, pyridine, oxazoline, imine, cyano groups, etc., have been reported to function as directing groups.[1,2] In most cases reported to date, a monodentate system has been utilized. However, rare examples of such transformations utilizing a bidentate system have been described (Scheme 1). Recent elegant work has begun to

Scheme 1. Monodentate and Bidentate Systems



[†] Lanzhou University.
[‡] Chinese Academy of Science.

(1) For reviews, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (f) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

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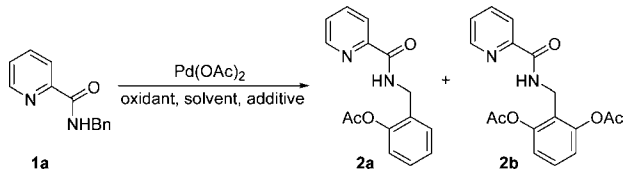
successfully address some of these challenges,[8] but the C−H activation/acetoxylation reaction that utilizes this bidentate system has thus far remained elusive. As part of our ongoing interest in developing methods for C−H activation reactions[9] via organometallic catalysis, we herein wish to report the details of this Pd-catalyzed aryl C−H bond activation reaction.

We initiated our investigations by examining whether the analogous pyridine derivatives can direct this Pd-catalyzed C−H activation/acetoxylation reaction. We discovered that the combination of 1.0 equiv of substrate *N*-benzylpicolinamide **1a** with 5 mol % of $Pd(OAc)_2$ and $PhI(OAc)_2$ (1.5 equiv) in toluene at 110 °C for 12 h produced a 3:4 ratio of the expected monoacetoxylated product **2a** and diacetoxylated product **2b** in 63% isolated yield (Table 1, entry 1).

Table 1. Optimization of the Pd-Catalyzed Acetoxylation of Pyridine **1a**[a]



entry	oxidant	solvent	time (h)	isolated yield (%)	ratio **2a/2b**[b]
1	$PhI(OAc)_2$	toluene	12	63	3:4
2[c]	$PhI(OAc)_2$	toluene	6	n.r.[d]	
3		toluene	6	n.r.[d]	
4	$PhI(OAc)_2$	HOAc	3	−[e]	
5	$PhI(OAc)_2$	$HOAc/Ac_2O$ (1:1)	3	−[e]	
6	TBHP	toluene	6	n.r.[d]	
7	AgOAc	toluene	6	n.r.[d]	
8	Oxone	toluene	12	trace[f]	
9[g]	$PhI(OAc)_2$	toluene	10	70	<1:99
10[h]	$PhI(OAc)_2$	toluene	6	77	<1:99

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent with 1.0 equiv of **1a**, 1.5 equiv of oxidant, and 0.05 equiv of [Pd] at 110 °C. [b] The ratio was determined by the isolated yields of the products. [c] No catalyst. [d] n.r. = no reaction. [e] Decomposed. [f] A trace amount of **2b** was isolated. [g] With 2.0 equiv of $PhI(OAc)_2$ and 1.0 equiv of $HOAc/Ac_2O$ (1:1). [h] The reaction was conducted with 2.0 equiv of $PhI(OAc)_2$ and 1.0 equiv of $HOAc/Ac_2O$ (1:1) at 150 °C.

Although the NMR spectroscopic data support the formation of acetoxylated products **2**, the structure was unambiguously confirmed through an X-ray crystal structure analysis of **2b**.[10]

Encouraged by the promising results, we attempted to optimize the reaction conditions. Utilizing **1a** as a reactant, the reaction parameters (i.e., oxidants, solvents, additives, and temperature) were varied to achieve this goal. Key results are shown in Table 1. The control experiment in the absence of catalyst resulted in complete recovery of **1a**, and no reaction was observed in the absence of $PhI(OAc)_2$ (Table 1, entries 2 and 3). Compared with other solvents, such as HOAc and $HOAc/Ac_2O$ (1:1) (entries 4 and 5), toluene was more effective. During a survey of the effect of various oxidants, it was determined that $PhI(OAc)_2$ was superior to others (entries 6−8). We envisioned that $PhI(OAc)_2$ might be playing other roles than just a simple oxidant; it might also serve as an acetate source.

Significant improvement was achieved by the use of 2.0 equiv of $PhI(OAc)_2$ and 1.0 equiv of $HOAc/Ac_2O$ (1:1) resulting in clean formation of the diacetoxylated product **2b** in 70% yield (entry 9). Furthermore, conducting the above reaction at 150 °C for 6 h furnished 77% yield of the product **2b** (entry 10). This meant that higher temperatures were beneficial for both the rate and the yield of the reaction. Herein, the optimum reaction conditions thus far developed employ 1.0 equiv of substrate, 5 mol % of $Pd(OAc)_2$, 2.0 equiv of $PhI(OAc)_2$, and 1.0 equiv of $HOAc/Ac_2O$ (1:1) in toluene at 150 °C. It should be noted that the rigorous exclusion of air/moisture is not required in any of these transformations, and comparable results are obtained in the presence and absence of air, as well as in freshly distilled versus commercial solvents. As such, this represents an exceedingly convenient method for functional group-directed functionalization of C−H bonds.

With the optimized conditions in hand, the reaction generality was investigated with various pyridines. The results are summarized in Table 2. Our initial attempt to acetoxylate the unactivated sp^3 C−H bond of substrate **1b** failed to provide any product (entry 2, Table 2). When the benzylic position of amine was substituted with a methyl

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(3) For selected recent examples, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (c) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (d) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (e) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (f) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (g) Gu, S. J.; Chen, C.; Chen, W. Z. *J. Org. Chem.* **2009**, *74*, 7203. (h) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717.

(4) For selected references, see: (a) Dipannita, K.; Deprez, N. R.; Deprez, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (c) Deng, G. J.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (d) Zhao, X. D.; Yu, Z. K. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (e) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316. (f) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.

(5) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048.

(6) (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (b) Wan, X. B.; Ma, Z. X.; Li, B. J.; Zhang, K. Y.; Cao, S. K.; Zhang, S. W.; Shi, Z. J. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215.

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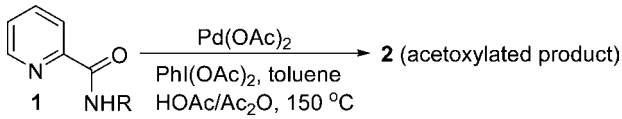
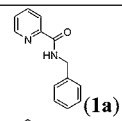
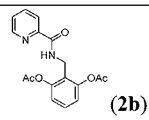
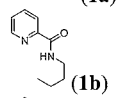
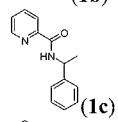
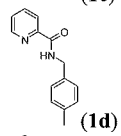
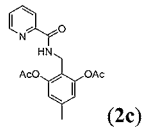
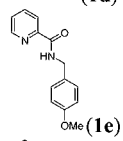
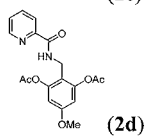
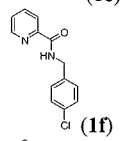
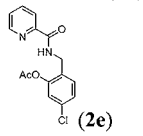
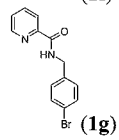
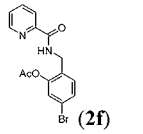
(9) (a) Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729. (b) Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464.

(10) Structure of **2b** is listed in the Supporting Information.

Table 2. Pd-Catalyzed Acetoxylation of Pyridines **1**[a]



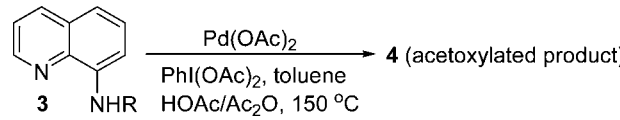
entry	pyridine	product	time (h)	isolated yield (%)
1	 (**1a**)	 (**2b**)	6	77
2	 (**1b**)	n.r.[b]	6	-
3	 (**1c**)	n.r.[b]	6	-
4	 (**1d**)	 (**2c**)	20	70
5	 (**1e**)	 (**2d**)	20	62 (93)[c]
6	 (**1f**)	 (**2e**)	24	43 (75)[c]
7	 (**1g**)	 (**2f**)	24	46 (81)[c]

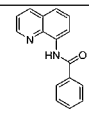
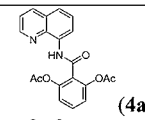
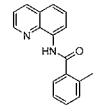
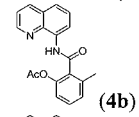
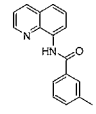
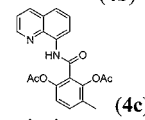
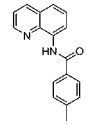
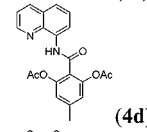
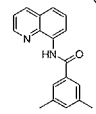
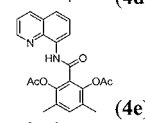
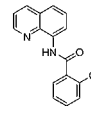
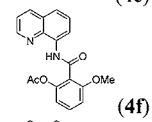
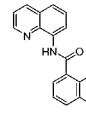
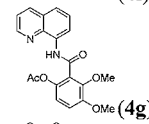
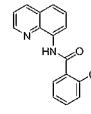
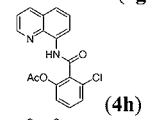
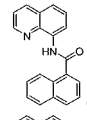
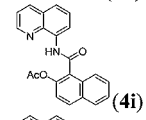
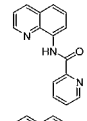
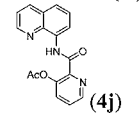
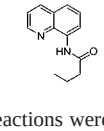
[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of toluene with 1.0 equiv of **1**, 2.0 equiv of $PhI(OAc)_2$, 1.0 equiv of $HOAc/Ac_2O$ (1:1), and 0.05 equiv of [Pd] at 150 °C. [b] n.r. = no reaction. [c] Conversions are indicated in parentheses.

group, surprisingly no reaction occurred, leading to 93% recovery of starting material (entry 3). This might be due to the steric effect. The additional functional groups such as methoxy, chloro, and even bromo substituents did not interfere with the palladium-catalyzed C−H activation reaction, showing good group tolerance. However, a significant influence of the substituents on the reactions was observed. The use of the substrates containing electron-donating substituents afforded moderate yields of the diacetoxylated products (entries 4 and 5). But the efficiency of these transformations was much lower in the presence of an electron-withdrawing substituent, affording comparatively low yields of monoacetoxylated products after longer reaction times (entries 6 and 7). Perhaps the low electron density on the phenyl ring reduces the tendency for C−H activation.

The results encouraged us to extend our protocol to investigate this new C−H activation reaction. We envisioned that a similar approach might be applied to the acetoxylation of 8-aminoquinoline derivatives. In this regard substrate **3a** was surveyed under the optimized reaction conditions. To our delight, the results exceeded our expectations, and were somewhat better than those for the pyridines. Although a longer reaction time was needed, the desired diacetoxylated product **4a** formed in 81% yield (Table 3, entry 1). We found

Table 3. Pd-Catalyzed Acetoxylation of 8-Aminoquinolines **3**[a]



entry	8-aminoquinoline	product	time (h)	isolated yield (%)
1	 (**3a**)	 (**4a**)	12	81
2	 (**3b**)	 (**4b**)	18	63
3	 (**3c**)	 (**4c**)	20	60
4	 (**3d**)	 (**4d**)	24	54
5	 (**3e**)	 (**4e**)	18	68
6	 (**3f**)	 (**4f**)	8	65
7	 (**3g**)	 (**4g**)	3	92
8	 (**3h**)	 (**4h**)	24	60 (74)[b]
9	 (**3i**)	 (**4i**)	24	52 (77)[b]
10	 (**3j**)	 (**4j**)	24	55 (81)[b]
11	 (**3k**)	n.r.[c]	6	-

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of toluene with 1.0 equiv of **3**, 2.0 equiv of $PhI(OAc)_2$, 1.0 equiv of $HOAc/Ac_2O$ (1:1), and 0.05 equiv of [Pd] at 150 °C. [b] Conversions are indicated in parentheses. [c] n.r. = no reaction.

that this methodology was broadly applicable to a variety of amides, affording acetoxylated products in synthetically valuable yields. All of the substrates bearing either an electron-donating group or an electron-withdrawing group at the ortho-, meta-, and the para-positions of the phenyl groups formed the desired products. Generally, the reactions of substrates with methyl groups at the ortho- and meta-positions afforded much better results than the para-substituted ones (entries 2−5). The substrate with a stronger electron-donating group at the ortho-position also worked well and afforded product **4f** in 65% yield after 8 h (entry 6). Excitingly, an extremely fast and efficient reaction was observed in the case of 2,3-dimethoxy-substituted amide **3g**, product **4g** being obtained in high yield after 3 h (92%, entry 7). It is not surprising that the 2-chloro-substituted substrate **3h** exhibited a similar effect to pyridines **1f** and **1g**. The presence of an electron-withdrawing substituent was no benefit in this transformation (entry 8). Comparing 1-naphthyl-substituted substrate **3i** with the less sterically hindered substrate **3a**, the efficiency of the reaction was reduced dramatically, only 52% yield of product was formed (entry 9). With the purpose of acetoxylation of heteroaromatic compound, pyridine **3j** was tested. Rewardingly, the reaction furnished the desired product in 55% yield (entry 10). An additional attempt to acetoxylate the sp^3 C−H bond of substrate **3k** failed (entry 11).

Then we proposed the mechanism of this Pd-catalyzed C−H bond activation with a series of pyridine derivatives. Pyridines having shorter or longer carbon chains, as in **5**, **6**, and **7**, did not give any desired products. Furthermore, no reaction was observed when the corresponding *N*-methyl-substituted substrate **8** was employed (Figure 1).

The above results indicate that the coordination in an *N*,*N* fashion is a key step, and substrates having shorter or longer carbon chains were not effective. Furthermore, a free NH is necessary for the process. The C−H activation of the resulting acetoxylated products could be easily realized due to the selective coordination of substrate bearing a *N*,*N* donor with the palladium catalyst, formation of two five-membered palladacyles,[8] followed by an unstable Pd(IV) specie[3] that decompose via a reductive elimination pathway. Subsequent functionalization would be possible (Scheme 2).

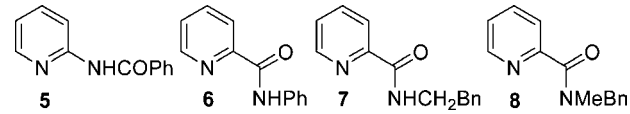
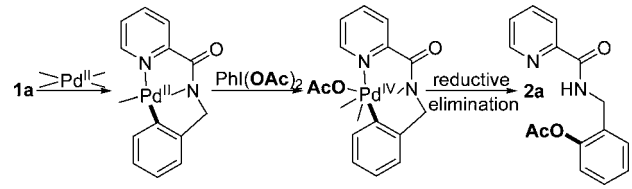


Figure 1. The exploration of the analogous pyridines.

Scheme 2. Possible Reaction Mechanism



In conclusion, a new and highly regioselective C−H activation/acetoxylation of amides possessing a directing pyridine and 8-aminoquinoline group was developed. This kind of bidentate system has large potential for the exploration of new reactions that have not been achieved by general monodentate-assisted systems. Current studies are focused on further exploration of the substrate scope and synthetic utility of this bidentate system.

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Supporting Information Available: Typical experimental procedure, characterization data for all products, and X-ray data for **2b**, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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