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Palladium-Catalyzed Acylation of sp^2 C−H bond: Direct Access to Ketones from Aldehydes

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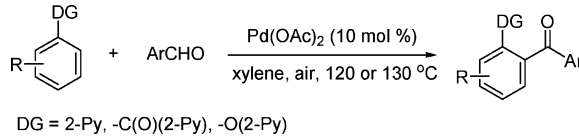
ABSTRACT



DG = 2-Py, -C(O)(2-Py), -O(2-Py)

A palladium-catalyzed direct access to ketones from aldehydes via C−H cleavage of arenes is described. The procedure utilizes air as a clean and free terminal oxidant.

Selective C−H bond functionalization has been a longstanding goal in organic synthesis since it obviates the prefunctionalization of substrates.[1,2] The combination of transition metals and directing groups is a useful strategy to facilitate C−H bond cleavage, which affords valuable transformations of C−H bonds to C−C,[3] C−X,[4] C−O[5] and C−N bonds.[6] Although the reaction of C−H bond with unsaturated bond should be highly valuable, such transformations are only limited to C−C double bonds[7] and triple bonds.[8] To the best of our knowledge, the reaction of a C−H bond with the C-hetero unsaturated bonds, such as C═O bonds, remains rare. Moreover, from the synthetic point of view, the direct and catalytic introduction of carbonyl functional groups into the phenyl via C−H bond cleavage is attractive in organic chemistry. For example, in 1996, Murai described a $Ru_3(CO)_{12}$-catalyzed acylation of imidazoles with CO and olefins.[9] In 2004, Orito reported $Pd(OAc)_2$-catalyzed direct aromatic carbonylation, providing benzolactams.[10] In 2008, Yu de-

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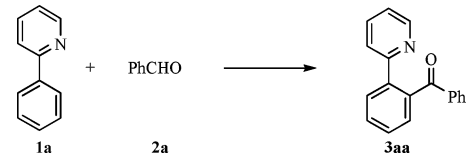
scribed a palladium-catalyzed oxidative ethoxycarbonylation of an aromatic C−H bond with diethyl azodicarboxylate for *ortho*-selective ethoxycarbonylation of aromatic C−H bonds.[11] Recently, Yu also reported the synthesis of 1,2- and 1,3-dicarboxylic acids via Pd(II)-catalyzed carboxylation of aryl and vinyl C−H bonds.[12] Very recently, Kakiuchi reported ruthenium-catalyzed amino- and alkoxycarbonylations with carbamoyl chlorides and alkyl chloroformates via aromatic C−H bond cleavage.[13] However, the generality of the applicable carbonyl functional groups via C−H bond cleavage is still limited. It occurred to us that the commercially available, inexpensive aldehydes could serve as the acylation reagents for C−H bond functionalization.

Herein, we report palladium-catalyzed regioselective acylations of aromatic C−H bonds using aldehydes in the presence of air as the ideal oxidant, affording the aromatic ketones in moderate to good yields.

Our initial investigations focused on the acylation of 2-phenylpyridine with benzaldehyde, and the results outlined in Table 1. Disappointingly, no desired product was obtained in the reaction of 2-phenylpyridine with 1.5 equiv of benzaldehyde under the combined system of $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2$ (2 equiv) at 110 °C in air for 24 h. Benzoquinone was also ineffective for this transformation. Since aldehydes are sensitive to some oxidants, the choice of oxidants is crucial for this transformation. Gratifyingly, employing air as the sole oxidant resulted in the sp^2 C−H acylation of 2-phenylpyridine to afford the desired product phenyl(2-(pyridin-2-yl)phenyl)methanone **3aa**, albeit in only 10% yield (Table 1, entry 4). The reaction temperature and solvent were also crucial for the reaction, and the yield sharply improved to 78% under air by replacing toluene with xylene as the solvent at 120 °C (Table 1, entry 6). Under an O_2 atmosphere, part of benzaldehyde was oxidized into benzoic acid and the yield decreased to 47%, while only 12% of the desired product was isolated when the reaction was performed under N_2 atmosphere. Among the Pd(II) catalysts tested, $Pd(OAc)_2$ turned out to be the best, while no product could be detected in the absence of Pd(II). Pd(0) was totally ineffective for the reaction.

From these preliminary explorations, the optimized conditions for this sp^2 C−H acylation were found as following:

Table 1. Screening for the Optimal Conditions[a]



1a 2a 3aa

entry	palladium	oxidant	solvent	yield (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	<5[b]
2	$Pd(OAc)_2$	$CuBr_2$	toluene	<5[b]
3	$Pd(OAc)_2$	benzoquinone	toluene	<5[b]
4	$Pd(OAc)_2$		toluene	10[b]
5	$Pd(OAc)_2$		dioxane	42[b]
6	$Pd(OAc)_2$		xylene	78
7	$Pd(OAc)_2$		DMF	<5
8	$Pd(OAc)_2$		NMP	<5
9	$Pd(acac)_2$		xylene	60
10	$Pd(OCOCF_3)_2$		xylene	49
11	$PdCl_2$		xylene	53
12	$Pd_2(dba)_3$		xylene	<5
13			xylene	<5

[a] 2-Phenylpyridine (0.2 mmol), benzaldehyde (0.3 mmol), Pd (10 mol %), indicated oxidant, air, dry solvent (2 mL), 120 °C, 24 h. Isolated yield. [b] At 110 °C.

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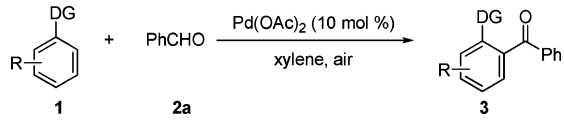
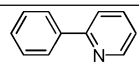
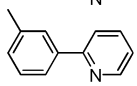
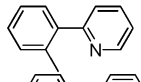
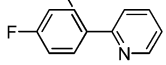
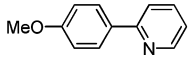
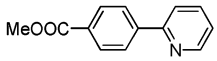
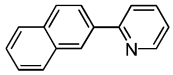
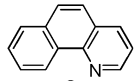
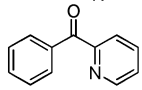
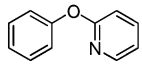
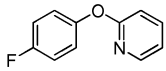
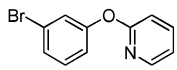
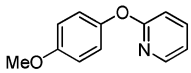
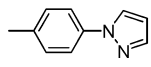
10 mol % of $Pd(OAc)_2$ as the catalyst, and a 1:2 mol ratio of 2-phenylpyridine and aldehyde substrates in dry xylene (2 mL) at 120 °C under air. Notably, neither strong bases/acids nor expensive ligands were required for this transformation. Moreover, the employment of air as the terminal oxidant significantly improved the practicality of this C−H functionalization reaction.

With the optimized conditions in hand, the acylations of 2-arylpyridines by benzaldehyde were tested, as shown in Table 2.

Table 2. Acylation Reaction with Benzaldehyde[a]



1 2a 3

entry	2-arylpyridine **1**		product	yield (%)
1		**1a**	**3aa**	78
2		**1b**	**3ba**	53
3		**1c**	**3ca**	79
4		**1d**	**3da**	55
5		**1e**	**3ea**	70
6		**1f**	**3fa**	67
7		**1g**	**3ga**	50
8		**1h**	**3ha**	90
9		**1i**	**3ia**	40[b]
10		**1j**	**3ja**	56[b]
11		**1k**	**3ka**	50[b]
12		**1l**	**3la**	60[b]
13		**1m**	**3ma**	54[b]
14		**1n**	**3na**	65[b]

[a] 2-Arylpyridine (0.2 mmol), benzaldehyde (0.3 mmol), $Pd(OAc)_2$ (10 mol %), dry xylene (2 mL), air, 120 °C, 24 h. Isolated yield. [b] At 130 °C, 48 h.

As expected, a series of functional groups on the phenyl ring of the 2-arylpyridines, such as methyl, methoxy, fluoro and COOMe, were compatible under this procedure, and the acylation products were isolated in moderate to good yields (Table 2, entries 2−6). Generally, the reaction efficiency was not sensitive to the electronic property of the substituents, as both electron-donating groups (Table 2, entries 2, 3 and 5) and electron-withdrawing groups could be employed in the reaction (e.g., Table 2, entry 6). However, the acylation of highly electron-deficient 2-(4-nitrophenyl)pyridine failed. We reasoned that this reaction may be blocked by the electrophilic attack of the Pd(II) center to the phenyl ring. The hindrance on the aryl group of 2-arylpyridine had a quite limited effect on the yield of the reaction. For example, the *ortho*-substituted substrate **1c** delivered a 79% yield of **3ca** (Table 2, entry 3). When benzo[h]quinoline **1h** was subjected to the procedure, a 90% yield of the acylation product was isolated (Table 2, entry 8). Interestingly, while 2-(naphthalen-1-yl)pyridine failed to undergo the acylation reaction, 2-(naphthalen-2-yl)pyridine ran smoothly under the standard conditions and produced the β-acylation product **3ga** in 50% yield (Table 2, entry 7).[14] Evidently, the regioselectivity in the acylation of *meta*-substituted substrates was dominated by steric effects, and only the less hindered ortho position of 2-arylpyridine was acylated. No regioisomeric products were observed by GC-MS and ^{1}H NMR spectroscopy (Table 2, entries 2 and 12).[15] It is also worth noting that phenyl(pyridin-2-yl)methanone **1i**, 2-aryloxypyridine **1j** and 1-phenyl-1H-pyrazole **1k** substrates could also provide the acylation products in moderate yields at an elevated temperature with prolonged reaction time (Table 2, entries 9−14). Disappointingly, the alkyl aldehydes did not work under the current condition.

Next, the acylations of **1a** and **1j** by various aldehydes were investigated (Table 3). In general, aldehydes possessing electron-withdrawing groups on the phenyl ring gave higher yields than those with electron-donating groups. While 4-methoxybenzaldehyde failed to deliver the acylation product under this procedure, the reaction of 4-formylbenzonitrile **2e** could lead to a 79% yield of **3ae** (Table 3, entry 4).[16] The procedure tolerated functional groups such as CN, Cl, COOMe, and NO_2. Importantly, aryl bromides were also applicable, albeit only moderate yields of the acylation products **3ad** and **3jd** were isolated (Table 3, entries 3 and 9). This is notable as on one hand the aryl bromide substrates are often very reactive in $Pd^{0/II}$ catalytic cycles, and on the other hand the bromo products could be easily further modifiable.

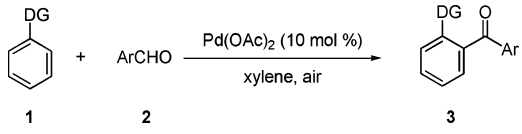
More experiments were carried out to gain a better understanding the mechanism. Following the reported procedure, palladacycle **A** was obtained in 80% yield.[11]

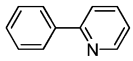
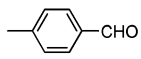
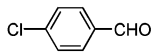
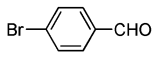
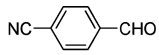
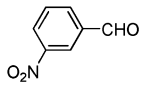
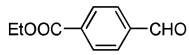
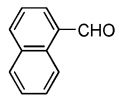
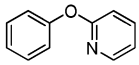
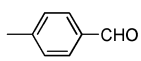
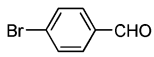
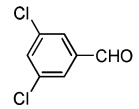
(14) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.

(15) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (c) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (d) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (e) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.

(16) The electronic effect observed in our reaction was consistent with the previously reported rhodium-catalyzed arylation reaction, which involved the insertion of an aryl rhodium species to the C=O bond in the catalytic cycle, see: Pucheault, M.; Darses, S.; Genet, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.

Table 3. Reaction of 2-Phenylpyridine with Aldehydes[a]



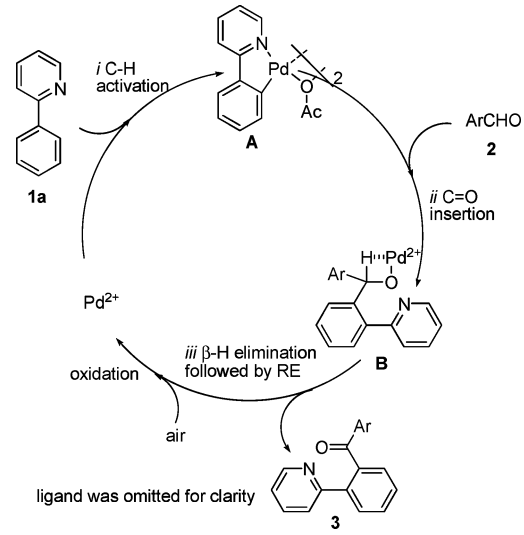
entry	1	aldehyde 2		product	yield (%)
1			**2b**	**3ab**	50
2	**1a**		**2c**	**3ac**	69
3			**2d**	**3ad**	45[b]
4			**2e**	**3ae**	79[c]
5			**2f**	**3af**	53[c]
6			**2g**	**3ag**	70[c]
7			**2h**	**3ah**	85[c]
8			**2b**	**3jb**	45[d]
9	**1j**		**2d**	**3jd**	43[d]
10			**2i**	**3ji**	44[d]

[a] 2-Phenylpyridine (0.2 mmol), aldehyde (0.4 mmol), $Pd(OAc)_2$ (10 mol %), dry xylene (2 mL), air, 120 °C, 24 h. Isolated yield. [b] Aldehyde (0.2 mmol). [c] Aldehyde (0.3 mmol). [d] At 130 °C, 48 h.

Complex **A** catalyzed the formation of **3aa** in 81% isolated yield in xylene under air at 120 °C (see Supporting Information). This result indicated that palladacycle **A** may be an active species during this catalytic cycle. The kinetic isotope effects of 2-phenylpyridine were studied. The k_H/k_D was found to be 3.6 (see Supporting Information). The observed intramolecular kinetic isotope effect indicates slow C−H bond activation.

Based upon the experimental results, a plausible mechanism is outlined in Scheme 1. Step (i) involves the chelate-directed C−H activation of 2-phenylpyridine to afford a

Scheme 1. Plausible Mechanism



cyclopalladated intermediate **A**. The high regioselectivity as well as the high catalytic activity of the isolated cyclopalladated complex **A** provides strong evidence to support this step. In step (ii), insertion of the C═O bond of the aldehyde into the C−Pd bond of cyclopalladated intermediate **A** produces intermediate **B**. The final step (iii) consists the β-H elimination of intermediate **B** to release the product along with a Pd(II) species. Then the Pd(II) species undergoes reductive elimination to produce a Pd(0) species, which is oxidized by air to regenerate the Pd(II) catalyst.

In conclusion, we have demonstrated an efficient palladium-catalyzed acylation of arene C−H bonds. The reaction provides a very convenient and atom-economic method for the synthesis of aromatic ketones directly from aldehydes. Ongoing work seeks to gain further insights into the mechanism of this reaction and to expand the scope to the acylation of unactivated sp^3 C−H bonds.

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Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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