JOC*Note*

Direct Ortho-Acetoxylation of Anilides via Palladium-Catalyzed sp^2 C−H Bond Oxidative Activation

Guan-Wu Wang,* Ting-Ting Yuan, and Xue-Liang Wu

Hefei National Laboratory for Physical Sciences at Microscale, Joint Laboratory of Green Synthetic Chemistry, and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, People's Republic of China

gwang@ustc.edu.cn

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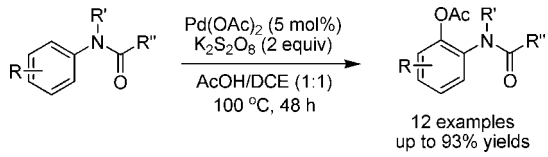

Various anilides have been directly ortho-acetoxylated through a $Pd(OAc)_2$-catalyzed C−H bond activation process. The amide group in anilides was found to functionalize as an elegant directing group to convert aromatic sp^2 C−H bonds into C−O bonds in high regioselectivity with acetic acid as the acetate source and $K_2S_2O_8$ as the oxidant.

During the past decades, the development of transition metal-catalyzed reactions for the direct functionalization of unactivated carbon−hydrogen bonds to construct carbon−carbon or carbon−heteroatom bonds remained a tremendous challenge in organic chemistry and attracted the interest of many organic chemists.[1] Since the discovery of σ-chelation directed C−H bond cleavage,[2] numerous endeavors have been focused on the application of this useful process.[3] Recent studies have led to many methods that directly functionalize C−H bonds of arenes to form C−C, C−N, C−O, and C−X bonds with transition metal catalysts; among them palladium-mediated C−H activation of arenes is one of the most attractive processes.[4] Significant progress in the development of Pd-catalyzed C−H functionalization reactions with use of directing groups has been achieved by many groups including Sanford, Daugulis, Yu, and others.[5,6]

Recent studies revealed that the Pd^{II}/Pd^{IV} catalysis may generate different series of products[7–9] compared with the traditional $Pd^{0/II}$ catalysis. Oxidants such as hypervalent iodine reagents,[5a,d] benzoyl peroxide,[5c] and Oxone[8] were often employed to convert Pd^{II} to Pd^{IV}. The formation of Pd^{IV} species has been confirmed by X-ray crystal structures.[9] This brand new catalyst system opens up a great opportunity to form carbon−heteroatom and carbon−carbon bonds directly from unactivated C−H bonds to produce novel organic molecules that cannot be achieved by common catalysts. With the acetamino group as a

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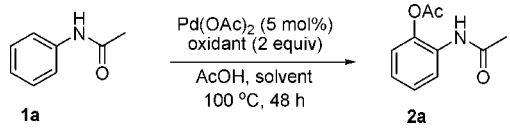
TABLE 1. Screening Reaction Conditions for the $Pd(OAc)_2$-Catalyzed Direct Ortho-Acetoxylation of Acetanilide 1a[a]



1a **2a**

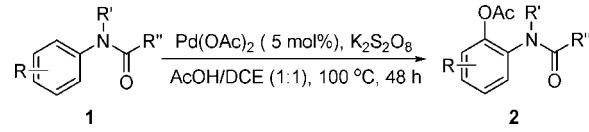
entry	oxidant	solvent	yield[b]
1	$PhI(OAc)_2$	DCE	trace
2	Oxone	DCE	11%
3	MCPBA	DCE	trace
4	^{t}BuOOH	DCE	44%
5	O_2	DCE	trace
6	$K_2S_2O_8$	DCE	77%
7	$K_2S_2O_8$[c]	DCE	43%
8	$K_2S_2O_8$[d]	DCE	55%
9	$K_2S_2O_8$[e]	DCE	72%
10	$K_2S_2O_8$	CH_3CN	trace
11	$K_2S_2O_8$	PhMe	39%
12	$K_2S_2O_8$	dioxane	42%
13	$K_2S_2O_8$		42%
14	$K_2S_2O_8$[f]	DCE	44%
15	$K_2S_2O_8$[g]	DCE	61%

[a] Unless otherwise specified, all the reactions were carried out in the presence of 1 mmol of **1a**, 0.05 mmol of $Pd(OAc)_2$, 2 mmol of oxidant in 5 mL of AcOH, and 5 mL of solvent at 100 °C for 48 h. [b] Isolated yields. [c] 1 mmol of $K_2S_2O_8$ was employed. [d] 1.5 mmol of $K_2S_2O_8$ was employed. [e] 2.5 mmol of $K_2S_2O_8$ was employed. [f] 2 mol % of $Pd(OAc)_2$ was used. [g] 3 mol % of $Pd(OAc)_2$ was used.

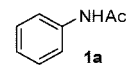
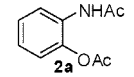
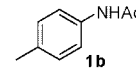
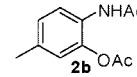
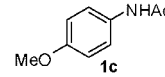
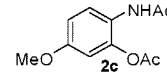
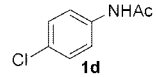
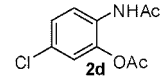
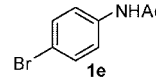
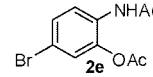
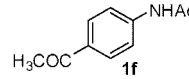
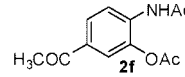
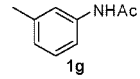
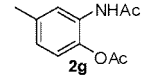
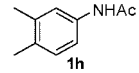
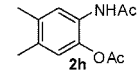
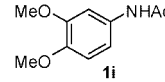
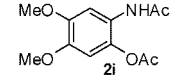
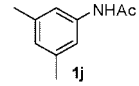
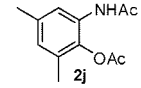
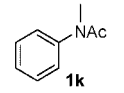
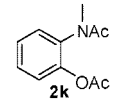
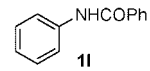
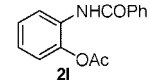
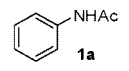
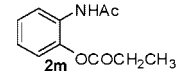
directing group, the *o*-C−H of acetanilide could be highly regioselectively functionalized. Selective oxidative couplings of anilides with alkyl halides,[10a] olefins,[10b–d] haloolefins,[10e] trialkoxyarylsilanes,[10f] arylboronic acids,[10g] arenes,[10h] and aryl iodides[10i] to construct C−C bonds have been reported. The C−N[10j] and C−X (X = Cl, Br)[6b] bond formations of acetanilides have also been demonstrated. However, the selective C−O bond formation process of anilides has remained unknown until now. Herein, we present the direct ortho-acetoxylation of anilides through $Pd(OAc)_2$-catalyzed sp^2 C−H bond oxidative activation.

In our initial study, we examined the $Pd(OAc)_2$-catalyzed acetoxylation with various oxidants and solvents to optimize the reaction conditions. Acetanilide **1a** was chosen as a model compound. The results are summarized in Table 1. $PhI(OAc)_2$ that was used as a privileged oxidant in Sanford's systems[7,8] was first investigated. However, only trace product was observed (entry 1, Table 1). When Oxone was employed, the acetoxylation reaction did proceed, yet giving product **2a** in 11% isolated yield (entry 2, Table 1). While *m*-chloroperoxybenzoic acid was unable to promote the reaction, peroxide alcohol TBHP facilitated it successfully with moderate yield (entries 3 and 4, Table 1). The reaction failed when molecular oxygen was used as the terminal oxidant (entry 5, Table 1). Much to our pleasure, when potassium persulfate was employed, the ortho-acetoxylated product **2a** was obtained in 77% yield (entry 6). Reducing the oxidant loading decreased the yield dramatically, while increasing the loading did not improve it (entries 7−9, Table 1). The above reactions were performed in acetic acid with 1,2-dichloroethane as cosolvent. Other cosolvents such as acetonitrile, toluene, and dioxane were also screened; all of them proved to be deleterious to the reaction (entries 10−12, Table 1). Reaction performed in pure acetic acid also gave a decreased yield (entry 13, Table 1). When the loading of $Pd(OAc)_2$ was reduced, the yield was compromised visibly (entries 14 and 15). As a result, when the reaction was carried out in the presence of 5 mol % of $Pd(OAc)_2$ with 2 equiv of $K_2S_2O_8$ as the oxidant and AcOH/DCE 1:1 as the solvent at 100 °C, the best result was achieved.

TABLE 2. Pd-Catalyzed Direct Ortho-Acetoxylation of Anilides[a]



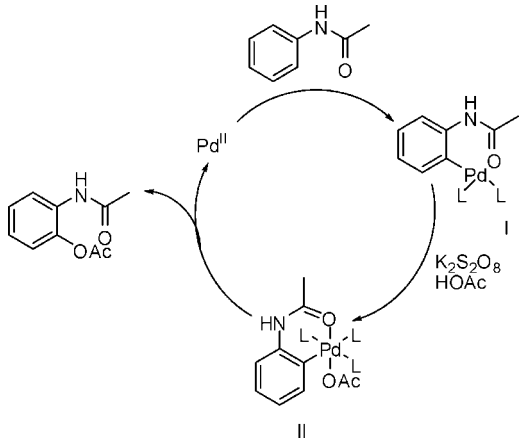
1 **2**

entry	substrate	product	yield/%[b]
1	 **1a**	 **2a**	77
2	 **1b**	 **2b**	77
3	 **1c**	 **2c**	41
4	 **1d**	 **2d**	60
5	 **1e**	 **2e**	42
6	 **1f**	 **2f**	55
7	 **1g**	 **2g**	93
8	 **1h**	 **2h**	92
9	 **1i**	 **2i**	81[c]
10	 **1j**	 **2j**	60
11	 **1k**	 **2k**	22
12	 **1l**	 **2l**	45
13	 **1a**	 **2m**	46[d]

[a] Unless otherwise specified, all the reactions were carried out with 1 mmol of **1**, 0.05 mmol of $Pd(OAc)_2$, 2 mmol of $K_2S_2O_8$ in 5 mL of AcOH, and 5 mL of DCE at 100 °C for 48 h. [b] Isolated yields. [c] The reaction was performed at 80 °C for 24 h. [d] $CH_3CH_2CO_2H$ was used instead of AcOH and the reaction time was 72 h.

With the optimized conditions in hand, the reaction generality was investigated with various substituted anilides. The results are summarized in Table 2. We found that the amide group-directed C−H bond functionalization protocol was broadly applicable to a variety of anilides, affording the acetoxylated products in synthetically valuable yields. Acetanilides with either electron-donating or electron-withdrawing groups furnished the expected products (entries 2−10, Table 2). It is noteworthy that the presence of the halogen, ether, and ketone substituents (entries 3−6, Table 2) did not interfere with the palladium-

SCHEME 1. Possible Reaction Mechanism



catalyzed oxidative activation reaction under our conditions. Acetoxylation of the acetanilide with a methyl group at the meta-position afforded product **2g** in pretty high yield (93%, entry 7, Table 2). It is not surprising that 3,4-dimethylacetanilide was also acetoxylated in comparably high yield (92%, entry 8, Table 2). Interestingly, when the substrate with strong electron-donating groups at 3,4-positions was employed, an accelerated reaction was observed, giving product **2i** in 81% yield after 24 h at 80 °C (entry 9 vs entry 3, Table 2). When the 3,5-positions of acetanilide were substituted with a methyl group, the reaction yield was reduced dramatically, probably ascribed to the steric hindrance (entry 10, Table 2). Nevertheless, the reaction with ortho-substituted acetanilides such as 2-methylacetanilide and 2-chloroacetanilide gave a complex mixture with very low conversion. To expand the scope of anilides, we then examined the reaction with *N*-methylated acetanilide (**1k**) and *N*-benzoylated aniline (**1*l***), and found that lower yields were obtained in both cases (entries 11 and 12 vs entry 1, Table 2). Much lower efficiency was also reported for the chlorination,[6b] olefination,[10c] and arylation[10f] of anilides with acyl groups other than the acetyl group. The yield for the olefination of **1k** was even 0%.[10c] These results along with our own data indicate the significant influence of the directing groups on the reactions. Other acyloxylation was also explored. The $Pd(OAc)_2$-catalyzed propionoxylation of acetanilide **1a** afforded the desired product **2m** in only moderate yield, quite lower than that of the corresponding acetoxylation (entry 13 vs entry 1, Table 2). Because of the unsatisfactory results shown in entries 11−13 of Table 2, no efforts had been made to investigate the acetoxylation of other *N*-alkylated anilides and *N*-acylated anilines as well as the propionoxylation of other anilides.

The Pd-catalyzed acetoxylation of aromatic compounds has been previously reported.[11,12] The originally proposed formation of Ar-OAc via the addition of Pd(II)-OAc across an arene C=C bond[11] was later revised as through a reductive elimination from an ArPd(IV)OAc intermediate.[12] Even though we do not have any evidence for the reaction mechanism of this ortho-acetoxylation reaction, we propose a possible pathway (Scheme 1) based on the well-documented literature for the acetoxylation reaction of various types of compounds via a Pd^{II}/Pd^{IV} mechanism,[5,7a,b,d,g,m,o,p,9a] and especially those with Oxone as a terminal oxidant.[8a,b] First, Pd(II) coordinated with the oxygen atom of the anilide, which induced the formation of a cyclopalladated intermediate I by chelate-directed C−H activation. This Pd(II) intermediate was oxidized by $K_2S_2O_8$ in the presence of acetic acid to afford a hexacoordinated Pd(IV) intermediate II, which proceeded through a reductive elimination process to furnish the final ortho-acetoxylated product and regenerated the Pd(II) catalyst. The formed Pd(IV) intermediate evidently deactivated the arene ring for further substitution and disfavored overoxidation,[12] and thus explained the failure of obtaining bisacetoxylated products in our experiments. It should be noted that a mechanism involving the common Pd(0)−Pd(II) catalytic cycle could not be completely excluded.

In conclusion, we have successfully developed an amide group-directed ortho-acetoxylation of anilides catalyzed by $Pd(OAc)_2$ with cheap $K_2S_2O_8$ as a terminal oxidant. This protocol was convenient, efficient, and applicable for various substituted anilides. Further investigations on other palladium-catalyzed direct C−H bond functionalizations are now underway.

Experimental Section

General Procedure for the Direct Ortho-Acetoxylation of Anilide 1a (1b−1m) Catalyzed by $Pd(OAc)_2$. To a stirred solution of anilide **1a** (**1b−1m**, 1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), and $K_2S_2O_8$ (540 mg, 2 mmol) in DCE (5 mL) at 80 °C was added AcOH (5 mL). The reaction was monitored by TLC. Upon completion, the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 2/1 as the eluent to get the desired product **2a** (**2b−2m**).

Compounds **2a**,[13] **2d**,[14] **2e**,[13] **2g**,[15] and **2j**[16] have been previously reported and their identities were confirmed by the comparison with their reported spectral data.

2-Acetamido-5-methylphenyl Acetate (2b). White solid, mp 154−155 °C. IR (KBr) ν 3356, 2926, 1740, 1688, 1594, 1523, 1367, 1307, 1210, 1111, 1025, 897, 814, 667, 594, 562 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (1H, d, J = 8.1 Hz), 7.08 (1H, br), 7.03 (1H, d, J = 8.1 Hz), 6.93 (1H, s), 2.34 (3H, s), 2.32 (3H, s), 2.15 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 168.5, 141.3, 135.3, 127.1 (2C), 123.7, 122.6, 24.2, 21.0, 20.9; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{11}H_{13}NO_3$, 207.0895, found 207.0900.

2-Acetamido-5-methoxyphenyl Acetate (2c). White solid, mp 117−120 °C. IR (KBr) ν 3294, 1763, 1662, 1607, 1560, 1511, 1420, 1373, 1203, 1122, 1022, 901, 818, 772, 716, 580, 509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (1H, d, J = 2.4 Hz), 7.22 (1H, dd, J = 8.7, 2.4 Hz), 7.13 (1H, br), 6.89 (1H, d, J = 8.7 Hz), 3.80 (3H, s), 2.31 (3H, s), 2.12 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 168.7, 147.8, 139.5, 131.6, 118.6, 115.8, 112.6, 56.2, 24.1, 20.8; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{11}H_{13}NO_4$ 223.0845, found 223.0847.

2-Acetamido-5-acetylphenyl Acetate (2f). White solid, mp 150−153 °C. IR (KBr) ν 3339, 2919, 2850, 1740, 1680, 1607, 1523, 1487, 1419, 1363, 1281, 1221, 1127, 1021, 931, 821, 687, 594, 485 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, J = 8.6, Hz), 7.80 (1H, dd, J = 8.6, 1.5 Hz), 7.76 (1H, d, J = 1.5 Hz), 7.36 (1H, br), 2.57 (3H, s), 2.42 (3H, s), 2.23 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.30, 168.60, 168.54, 139.64, 134.46, 133.03, 127.10, 122.19, 121.30, 26.43, 24.74, 21.07; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{12}H_{13}NO_4$ 235.0845, found 235.0851.

2-Acetamido-4,5-dimethylphenyl Acetate (2h). White solid, mp 157−160 °C. IR (KBr) ν 3346, 2922, 1740, 1684, 1599, 1525, 1453, 1401, 1367, 1311, 1225, 1194, 1089, 1020, 918, 884, 675, 584

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cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, s), 6.98 (1H, br), 6.88 (1H, s), 2.33 (3H, s), 2.23 (3H, s), 2.21 (3H, s), 2.16 (3H, d, J = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.4, 139.4, 134.9, 134.0, 127.0, 125.0, 122.9, 24.3, 21.0, 19.5 (2C); HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1054.

2-Acetamido-4,5-dimethoxyphenyl Acetate (2i). White solid, mp 181−184 °C. IR (KBr) ν 3228, 1772, 1648, 1517, 1445, 1409, 1364, 1265, 1206, 1116, 1017, 909, 879, 856, 526 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, s), 6.95 (1H, br), 6.65 (1H, s), 3.88 (3H, s), 3.84 (3H, s), 2.30 (3H, s), 2.16 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.4, 146.9, 146.2, 134.8, 122.5, 107.4, 105.9, 56.3 (2C), 24.3, 21.0; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{12}H_{15}NO_5$ 253.0950, found 253.0954.

2-(*N*-Methylacetamido)phenyl Acetate (2k). White solid, mp 61−63 °C. IR (KBr) ν 2930, 1767, 1662, 1495, 1430, 1378, 1309, 1193, 906, 877, 820, 780, 597, 499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.17 (4H, m), 3.16 (3H, s), 2.29 (3H, s), 1.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 168.8, 146.9, 136.8, 129.2, 129.1, 127.3, 123.9, 36.0, 21.8, 20.7; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0893.

2-Benzamidophenyl Acetate (2*l*). White solid, mp 112−113 °C. IR (KBr) ν 3232, 3060, 2926, 1758, 1652, 1597, 1524, 1496, 1443, 1370, 1311, 1286, 1214, 1185, 1105, 928, 754, 713, 587 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, d, J = 8.1 Hz), 7.94 (1H, br), 7.85 (2H, d, J = 7.6 Hz), 7.60−7.49 (3H, m), 7.33−7.26 (1H, m), 7.21−7.15 (2H, m), 2.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 165.5, 141.4, 134.8, 132.1, 129.9, 129.0 (2C), 127.1 (2C), 126.7, 125.2, 123.4, 122.2, 21.1; HRMS (EI-TOF): m/z [M$^+$] calcd for $C_{15}H_{13}NO_3$, 255.0895; found, 255.0897.

2-Acetamidophenyl Propionate (2m). White solid, mp 66−69 °C. IR (KBr) ν 3240, 2980, 1762, 1661, 1607, 1537, 1488, 1455, 1373, 1310, 1187, 1142, 1105, 1078, 1007, 890, 758, 466 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, J = 7.2 Hz), 7.26−7.12 (4H, m), 2.66 (2H, q, J = 7.3 Hz), 2.17 (3H, s), 1.31 (3H, t, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 168.4, 141.0, 129.8, 126.4, 124.9, 123.3, 122.1, 27.8, 24.5, 9.2; HRMS (EI-TOF) m/z [M$^+$] calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0893.

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Supporting Information Available: NMR Spectra of **2a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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