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Palladium-Catalyzed Regioselective C–H Bond *ortho*-Acetoxylation of Arylpyrimidines

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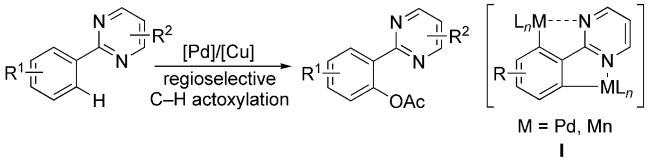
Keywords: Nitrogen heterocycles / C–H activation / Palladium / Regioselectivity

An efficient and regioselective palladium-catalyzed *ortho* C–H acetoxylation reaction was developed to afford *ortho* monoacetoxylated arylpyrimidines in good to excellent yields by using cupric trifluoroacetate as a cocatalyst. A wide variety of oxygenated arylpyrimidines were prepared with high regioselectivity and functional group tolerance.

Introduction

During the past decades, the development of transition-metal-catalyzed C–H activation reactions, which are directed by functional groups, has witnessed considerable progress.[1–3] A wide range of metal catalysts including ruthenium, rhodium, platinum, and palladium have been exploited with varying degrees of success. Among these reactions, metal-catalyzed oxidative functionalization of sp^2 and sp^3 C–H bonds can proceed regioselectively with the assistance of various directing groups, such as amides,[4] carbamates,[5] oxazolines,[6] oxime ethers,[7] pyridines,[8] and pyrimidines.[8a,9] These ligand-directed C–H functionalization reactions have made a great contribution to the mild and selective construction of C–C, C–halo, C–N, C–O, and C–S bonds.[1a] Recently, Sanford[8c,8d] and Yu[10] reported the acetoxylation of aryl C–H bonds by using pyridine as the directing groups, in which palladium acetate and copper acetate were used as catalyst precursors, respectively. Palladium(II)-catalyzed acetoxylation reactions proceed typically by using *tert*-butyl hydroperoxide, $PhI(OAc)_2$, Oxone, or $K_2S_2O_8$ as oxidants, and often proceed through a Pd^{II}/Pd^{IV} mechanism.[11] The formation of Pd^{IV} species has been confirmed by the Sanford group by X-ray structure analysis.[11e,11g] Yu also proposed a cation–radical intermediate that was formed by single-electron transfer from the aryl ring to the coordinated Cu^{II} center during the Cu^{II}-catalyzed C–H functionalizations.[10] However, high regioselectivity was sometimes difficult to achieve when the substrate contained more than one *ortho* C–H bond. On the basis of the previous investigations and results we considered whether the combination of Pd^{II} and Cu^{II} catalysts would have a positive effect on both the reactivity and regioselectivity of C–H functionalizations.

Pyrimidines and their derivatives are important motifs in materials and medicinal chemistry and have attracted much attention.[12] Thus, the development of readily available functionalized arylpyrimidines in a regioselective manner would find significant application in the preparation of this class of molecules. However, only few examples involving pyrimidine as a directing group for C–H activation have been reported.[3g,8a,9,13] One of the reasons may be due to the formation of dual metal complex **I** (Scheme 1),[14] which leads to low regioselectivity in C–H functionalization. Recently, Sanford[8a] and Chen[9] reported an *ortho*-oxygenation reaction of benzylpyrimidine and 2-phenoxypyrimidine, respectively. More recently, we reported a palladium-catalyzed C–H bond halogenation reaction to give a wide variety of *ortho*-halogenated arylpyrimidines with high monoselectivity and functional group tolerance by using calcium halides as crucial halogenating agents and cupric trifluoroacetate as the oxidant in the presence of air.[15] As part of our research aimed at the efficient construction of nitrogen-containing heterocycles,[15,16] we herein report a palladium-catalyzed highly monoselective C–H *ortho*-acetoxylation of arylpyrimidines by using cupric trifluoroacetate as cocatalyst under mild conditions (Scheme 1).



Scheme 1. Palladium-catalyzed regioselective C–H *ortho*-acetoxylation of arylpyrimidines.

Results and Discussion

Initially, we examined the reaction of phenylpyrimidine (**1a**) in the presence of $Pd(OAc)_2$ and Oxone in a mixed solvent of acetic anhydride and acetic acid at 75 °C. The

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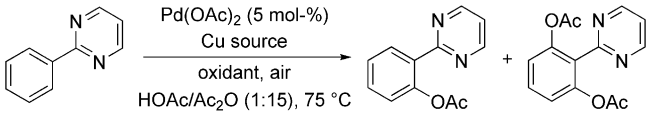
reaction gave mono- and diacetoxylated products in 38 and 29% yield, respectively (Table 1, Entry 1). When $Cu(OAc)_2$ was added, the reaction was promoted to afford monoacetoxylated product **2a** in 57% yield within 4 h (Table 1, Entry 2). Other oxidants such as $K_2S_2O_8$, *m*-CPBA, and benzoquinone (BQ) gave worse results (Table 1, Entries 3–5), whereas $PhI(OAc)_2$ afforded **2a** in 68% yield (Table 1, Entry 6); higher amounts of the oxidant accelerated the reaction (Table 1, Entry 7). When $Cu(OTFA)_2$ was employed instead of $Cu(OAc)_2$ at 75 °C, the yield of **2a** increased to 72% and high selectivity of *ortho*-acetoxylation was achieved (Table 1, Entry 8). Further screens concerning the reaction temperature (Table 1, Entries 9 and 10) and the ratio of acetic acid and acetic anhydride in the mixed solvent (Table 1, Entries 11 and 12) gave no significant effects on the reaction. Changing the loading of $Cu(OTFA)_2$ and $PhI(OAc)_2$ caused a dramatic decrease in the *ortho* regioselectivity (Table 1, Entries 13–15 vs. Entry 8). A low yield and poor regioselectivity of monoacetoxylated product **2a** were afforded in the absence of palladium (Table 1, Entry 16), and a trace amount of the product was detected without the addition of $PhI(OAc)_2$ (Table 1, Entry 17). The reaction did proceed sluggishly in the absence of $Cu(OTFA)_2$, but the yield of **2a** dropped to 42% and diacetoxylated product **2a′** was also isolated in 40% yield (Table 1, Entry 18), which indicated that catalytic Cu^{II} was crucial to control the monoselectivity of the reaction. When the reaction was conducted under an atmosphere of nitrogen (Table 1, Entry 19) or with the use of oxygen as the oxidant (Table 1, Entry 20) no better results were achieved.

Table 1. Reaction optimization for the C–H acetoxylation of **1a**.[a]



1a **2a** **2a'**

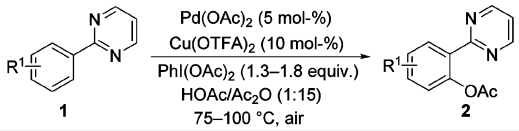
Entry	Oxidant (equiv.)	Cu source (mol-%)	*T* [°C]	Time [h]	Yield [%][b] **2a/2a′**
1	Oxone (1.1)	–	75	24	38:29
2	Oxone (1.1)	$Cu(OAc)_2$ (10)	75	4	57:29
3	$K_2S_2O_8$ (1.1)	$Cu(OAc)_2$ (10)	75	24	33:0
4	*m*-CPBA (1.1)	$Cu(OAc)_2$ (10)	75	24	20:0
5	BQ (1.1)	$Cu(OAc)_2$ (10)	75	24	trace[c]
6	$PhI(OAc)_2$ (1.1)	$Cu(OAc)_2$ (10)	75	24	68:17
7	$PhI(OAc)_2$ (1.3)	$Cu(OAc)_2$ (10)	75	19	65:25
8	*$PhI(OAc)_2$ (1.3)*	*$Cu(OTFA)_2$ (10)*	*75*	*22*	*72:20*
9	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	90	22	70:24
10	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	60	24	70:21
11	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	75	22	62:25[d]
12	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	75	22	67:19[e]
13	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (20)	75	24	66:27
14	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (5)	75	28	61:26
15	$PhI(OAc)_2$ (1.5)	$Cu(OTFA)_2$ (10)	75	14	55:35
16	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	75	48	14:0[f]
17	–	$Cu(OTFA)_2$ (10)	75	48	trace
18	$PhI(OAc)_2$ (1.3)	–	75	48	42:40
19	$PhI(OAc)_2$ (1.3)	$Cu(OTFA)_2$ (10)	75	23	48:28[g]
20	O_2	$Cu(OTFA)_2$ (10)	75	48	trace[h]

[a] Reaction conditions: **1a** (0.3 mmol), $Pd(OAc)_2$ (5 mol-%), $HOAc/Ac_2O$ (0.3 mL/4.5 mL) in air. BQ = benzoquinone, $Cu(OTFA)_2$ = cupric trifluoroacetate, *m*-CPBA = *m*-chloroperbenzoic acid. [b] Isolated yield. [c] Substrate **1a** was recovered. [d] $HOAc/Ac_2O$, 0.4:4.0 mL. [e] $HOAc/Ac_2O$, 0.2:4.0 mL. [f] Without $Pd(OAc)_2$, and 77% of **1a** was recovered. [g] Under an atmosphere of nitrogen. [h] Starting material **1a** was recovered quantitatively.

Encouraged by the successful monoacetoxylation of **1a**, we then extended the reaction to a range of substituted arylpyrimidines. We found that this pyrimidine-directed C–H acetoxylation protocol was broadly applicable to a variety of arylpyrimidines and afforded the corresponding monoacetoxylated products in good to excellent yields. The results are summarized in Table 2. Arylpyrimidines with electron-donating (Table 2, Entries 2–11, 13) or electron-withdrawing groups (Table 2, Entries 14–20) at the *ortho*, *meta*, and *para* positions of the phenyl group furnished the desired products smoothly. For those electron-rich substrates with *ortho* or *meta* substitution, the products were usually obtained in high yields (Table 2, Entries 4–9, 11, 13), whereas *para*-substituted arylpyrimidines gave products **2b** and **2c** in only moderate yields (Table 2, Entries 2 and 3). It is worth noting that the regioselectivity of this reaction was mainly controlled by steric effects and that the acetoxylation occurred at the less sterically hindered site (Table 2, Entries 6 and 7, 12 and 13, 19 and 20). Substrates bearing polysubstitutions on the aryl ring afforded products in good to excellent yields within a few hours (Table 2, Entries 8–11). In addition, the presence of functional groups such as acetal (Table 2, Entry 13), halogen (Table 2, Entries 14 and 15, 19), tosylate (Table 2, Entry 16), and ester (Table 2, Entry 18) were all compatible with this reaction under the optimized conditions. It should be noted that a strongly electron-deficient nitro-group-containing substrate, which is rarely used for C–H activation reactions, also worked well and afforded monoacetoxylated product **2t** in good yield (Table 2, Entry 20).[15]

This *ortho*-acetoxylation reaction could also proceed well for substrates with substitution at the 4- and 5-positions of the pyrimidine ring, and the results are summarized in Table 3. Substitution with methyl and phenyl groups afforded corresponding products **4a**–**c** in good yields under the optimized reaction conditions (Table 3, Entries 1–3). A substrate bearing a free amino group gave *N*-acetyl product **4d** in 32% yield (Table 3, Entry 4), whereas the protection of the substrate with an *N*-acetyl group afforded corresponding product **4d** in 57% yield (Table 3, Entry 5). It should be noted that substrate **3b**, which has two potential *ortho*-acetoxylation positions derived from the coordination of palladium and two nitrogen atoms (Scheme 2), gave exclusive product **4b** in 65% yield (Table 3, Entry 2). The identity of **4b** was determined by spectral analysis and further confirmed by X-ray crystallography from the corresponding deacetylated product 2-(4-phenyl-pyrimidin-2-yl)-phenol (**5b**).[17] The given results indicate that *ortho*-acetoxylation proceeds more easily when the phenyl group is attached to the 2-position (Scheme 2, attack a) instead of the 4-position (Scheme 2, attack b) of pyrimidine.

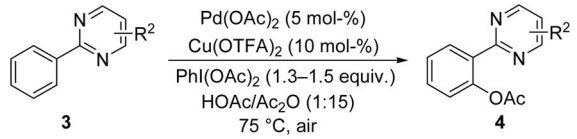
Table 2. Pyrimidine directed C–H acetoxylation reaction.[a]



Entry	Substrate R	Product	Time [h]	Yield [%][b]
1	H	**2a**	22	72
2	4-Me	**2b**	22	65
3	4-OMe	**2c**	18	63
4	2-Me	**2d**	10	92
5	2-OMe	**2e**	5	87
6	3-Me	**2f**	9	87
7	**1a–g**	**2g**	16	72
8	**1h**	**2h**	2	93
9	**1i**	**2i**	4.5	88
10	**1j**	**2j**	1.5	78
11	**1k**	**2k**	1.5	95
12	**1l**	**2l**	10	64
13	**1m**	**2m**	4	88
14	**1n**	**2n**	25	68
15	**1o**	**2o**	26	54[c]
16	**1p**	**2p**	24	62
17	**1q**	**2q**	14	50[d]
18	**1r**	**2r**	13	57[c]
19	**1s**	**2s**	16	73[c]
20	**1t**	**2t**	35	60[e]

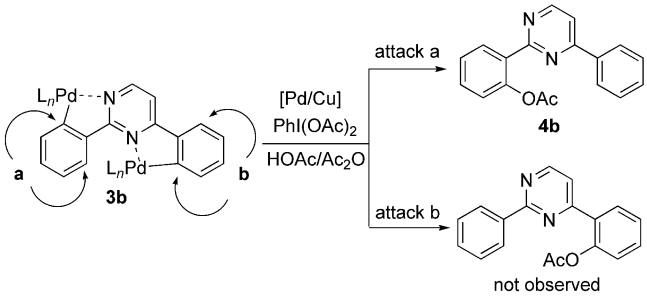
[a] Reaction conditions: **1** (0.4 mmol), $Pd(OAc)_2$ (5 mol-%), $Cu(OTFA)_2$ (10 mol-%), $PhI(OAc)_2$ (1.3–1.8 equiv.), $HOAc/Ac_2O$ (0.3:4.5 mL) in air. [b] Isolated yield. [c] $PhI(OAc)_2$ (1.4 equiv.). [d] $PhI(OAc)_2$ (1.6 equiv.), 85 °C. [e] $Pd(OAc)_2$ (10 mol-%), $PhI(OAc)_2$ (1.8 equiv.), in the absence of $Cu(OTFA)_2$, 100 °C.

Table 3. Reaction scope of substituted arylpyrimidines.[a]



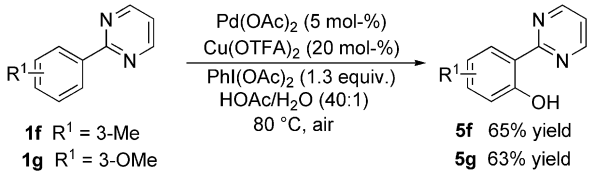
Entry	Substrate	Product	Time [h]	Yield [%][b]
1	**3a**	**4a**	8	50
2	**3b**	**4b**	22	65
3	**3c**	**4c**	23	57
4	**3d**	**4d**	10	32[c]
5	**3e**	**4d**	6	57

[a] Reaction conditions: **3** (0.4 mmol), $Pd(OAc)_2$ (5 mol-%), $Cu(OTFA)_2$ (10 mol-%), $PhI(OAc)_2$ (1.3–1.5 equiv.), $HOAc/Ac_2O$ (0.3:4.5 mL) in air. [b] Isolated yield. [c] 1.5 equiv. of $PhI(OAc)_2$ was used.



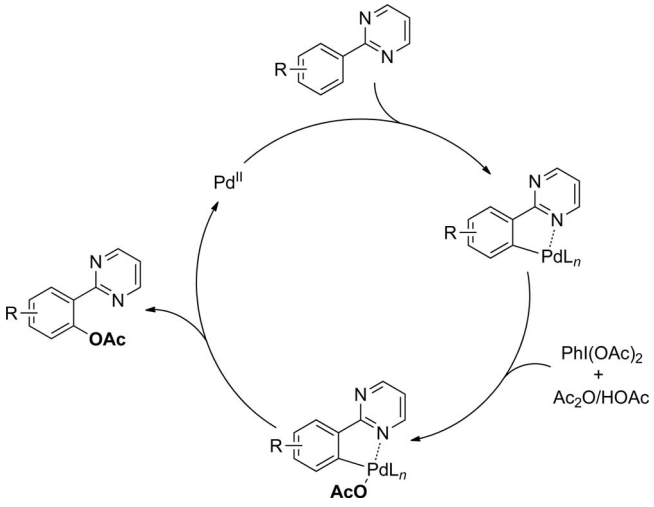
Scheme 2. Regioselective C–H acetoxylation of **3b**.

To our delight, when we used acetic acid as the solvent and water as the additive, *ortho*-hydroxy products **5f** and **5g** could be obtained in moderate yields (Scheme 3).[18] This one-pot reaction provided a convenient and useful approach for aryl hydroxylation through directed C–H bond activation, which is rarely reported in the literature.[10,19]



Scheme 3. One-pot *ortho*-hydroxylation of arylpyrimidines.

A plausible reaction mechanism is proposed, which proceeds through a Pd^{II}/Pd^{IV} pathway that is based on well-documented literature (Scheme 4).[2f,6–8,11] Pd^{II} coordinates to one of the nitrogen atoms of the arylpyrimidine to afford a palladacycle intermediate by chelation-directed C–H activation. This Pd^{II} intermediate is then oxidized by $PhI(OAc)_2$ in the presence of Ac_2O and HOAc to form the Pd^{IV} intermediate, which further furnishes the *ortho*-acetoxylated product through reductive elimination and regeneration of the active Pd^{II} species. Currently, we cannot exclude the mechanistic possibility for the existence of Pd^0/Pd^{II} or Pd^{III} intermediates in the present regioselective acetoxylation reaction.[20,21] The exact role of cupric trifluoroacetate in this reaction is not at present clear, and one of the possible reasons may be due to the initial formation of a copper complex, in which the Cu^{II} ions preferentially bonds to the N1 atom of the arylpyrimidine.[22]



Scheme 4. Proposed catalytic cycle.

Conclusions

In conclusion, an efficient and regioselective pyrimidine-directed C–H acetoxylation reaction was developed to afford *ortho* monoacetoxylated arylpyrimidines in good to high yields under the catalysis of palladium acetate and cupric trifluoroacetate. The characteristics of high monoselectivity, excellent functional group tolerance, and easy derivatization from the final products will give the described protocol a broad utility in organic synthesis. Further insights on the mechanism, reaction scope, and other pyrimidine-directed C–H functionalizations are now under investigation in our laboratory and will be reported in due course.

Experimental Section

Preparation of 2-(Pyrimidin-2-yl)phenyl Acetate (2a) as a Representative Procedure for the *ortho*-Acetoxylation of Arylpyrimidines: To a dried 25-mL round-bottom flask containing $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), $Cu(OTFA)_2$ (8.7 mg, 0.03 mmol), and $PhI(OAc)_2$ (125.6 mg, 0.39 mmol) in $HOAc/Ac_2O$ (0.2:3.0 mL, v/v = 1:15), was added 2-phenylpyrimidine (**1a**; 46.8 mg, 0.3 mmol), and the mixture was heated at 75 °C for 22 h in air. After removal of the solvent under reduced pressure, the residue was diluted with saturated $NaHCO_3$ solution (15 mL), extracted with EtOAc (3×30 mL), washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The given crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 4:1) to give **2a** (46.1 mg, 72%) as a light yellow oil.

Supporting Information (see footnote on the first page of this article): Experimental details; spectroscopic characterization data; copies of the ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra for all compounds; and X-ray crystal structure for compound **5b**.

Acknowledgments

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