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Ortho-Functionalization of 2-Phenoxypyrimidines via Palladium-Catalyzed C−H Bond Activation

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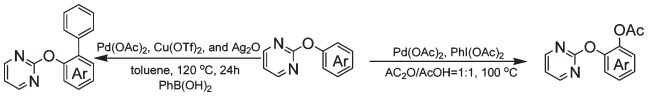

The palladium-catalyzed direct acetoxylation and arylation of 2-aryloxypyrimidine has been described. The aromatic C−H bonds may be functionalized in moderate to excellent yields providing a facile method for the synthesis of phenol derivatives, which show antimycobacterial and herbicidal activities.

Transition-metal-catalyzed direct C−H bond functionalization has emerged as a powerful method to afford valuable transformations of sp^2-hybridized C−H bonds to C−O,[1] C-X,[2] C−C,[3] C−N,[4] and C−S bonds.[5] In this context, many arenes containing a directing group such as pyridine, oxazoline, and aminomethyl can be regioselectively functionalized via cyclometalated intermediates under palladium, ruthenium, or rhodium catalysis. The direct ortho C−H activation of aromatic carboxylic acids[6] and amilides[7] can be similarly realized because of the functions of the β-positioned oxygen and nitrogen, whereas the regioselective ortho functionalization of aldehydes and ketones have been achieved via aldehydes and ketones directly or via their imine derivatives.[8] Although mono- and diarylation reactions of 2-phenylphenols and naphthols with aryl halides have been known to occur at the second phenyl ring,[9] the direct functionalization of simple phenols is not accessible because phenols are not able to form 5- or 6-membered metallacycles due to lack of directing groups at the β- or γ-positions. Introduction of a temporary directing group would be a possible passway leading to ortho C−H activation and subsequent functionalization. Actually, this strategy has been successful by using phosphites or phosphinites through reversible in situ transesterification of phenols. However, the rhodium-catalyzed protocol was not applicable to 2-position unsubstituted phenols, and the yields were low for less sterically hindered 2-alkylphenols.[10] This disadvantage could be partly overcome by using hexamethylphosphorous triamide.[10b,11] Herein, we present the direct ortho-acetoxylation and ortho-arylation of 2-phenoxypyrimidine derivatives through $Pd(OAc)_2$-catalyzed ortho C−H bond activation.

Phenols can be easily transformed to 2-phenoxypyridine or 2-phenoxypyrimidine by their copper-catalyzed C−O coupling reactions with 2-halopyridine or 2-halopyrimidine. The C−H activation of the resulting ethers could be easily realized due to formation of six-membered palladacyles.[12] Thus, subsequent functionalization would be possible (Scheme 1). We first tested $Pd(OAc)_2$-catalyzed acetoxylation of 2-naphthyloxypyrimidine **1a** with various oxidants and solvents. When air, $K_2S_2O_8$, benzoxyl peroxide, and silver salts were employed as oxidants, the desired functionalized product was not observed, and the pyrimidyl ether could be recovered. However, the ortho-acetoxylated product **2a** could be obtained in 87% yield using $PhI(OAc)_2$ as an oxidant under the conditions adopted by Sanford et al.[13] Then we tested $Pd(OAc)_2$-catalyzed acetoxylation of 2-phenoxypyridine and 2-phenoxypyrimidine using

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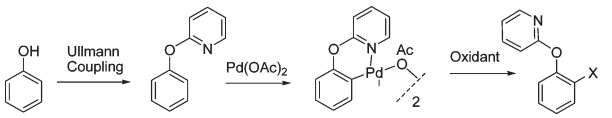
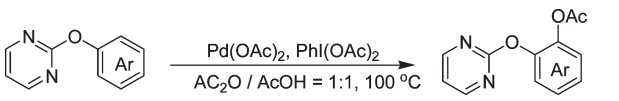
SCHEME 1. Illustration of Phenol Functionalization via C−H Activation



$PhI(OAc)_2$ as an oxidant in mixed Ac_2O/AcOH solvent. The results showed that pyridine and pyrimidine have the same directing function; thus, pyrimidine drivatives were chosen for further studies since they can be more easily obtained by C−O coupling reactions. In addition, these heteroaryl ethers have been known to show antimycobacterial and herbicidal activities.[14]

The successful functionalization of **1a** encouraged us to explore the possibility of other pyrimidyl ethers. We found that the pyrimidine group directed C−H bond functionalization protocol is broadly applicable to a variety of heteroaryl ethers affording corresponding acetoxylated products in good to excellent yields (Table 1). For example, 2-phenoxypyrimidine was converted to 2-(pyrimidin-2-yloxy)phenyl acetate in a yield of 50% together with a small amount of diacetoxylated product by using 1.1 equiv of $PhI(OAc)_2$. However, when 3.0 equiv of $PhI(OAc)_2$ was employed for the same reaction, the yield of the double-acetoxylated product (**2d**) was increased to 84% (entry 4). All of the substrates bearing either an electron-donating group or an electron-withdrawing group at the ortho-, meta-, and para-postions of phenyl groups could be applied to form the desired products (Table 1, entries 5−17). However, the efficiency of this transformation was comparatively low when an electron-withdrawing substituent is present. Probably the low electron density on the phenyl ring would reduce the tendency of C−H oxidative addition (Table 1, entries 5−8). For substrates containing two ortho C−H bonds like 2-(*p*-tolyloxy)pyrimidine, the reaction gave monoacetoxylated product in moderate yield when 2% $Pd(OAc)_2$ was used (Table 1, entry 9). For the sterically hindered substrates with substituents at the ortho- and meta-positions, the reaction yields were reduced (Table 1, entries 11 and 12). The polysubstituted diaryl ethers were also investigated, and the expected products were obtained in excellent yields (Table 1, entries 13 and 14). It is worth pointing out that the regioselectivity of this reaction was controlled by the steric effect. The acetoxylation always occurred at the less sterically hindered site (entries 15 and 16). In addition, the additional functional groups such as halogen, methoxyl, and carboxylate (entries 5−8 and 17) did not interfere with the palladium-catalyzed oxidative activation reaction showing good group tolerance. When two ortho positions are blocked by two methyl groups, the substrate **1p** was inert toward cyclopalladation, and thus, only the starting material was recovered. The ether, **1q**, was also inert probably because the coordination of two heteroarene would prevent cyclopalladation. It was expected that **1r** would be easily double acetoxylized since double cyclopalladation might happen simutaneously. Surprisingly, the functionalization of **1r** did not occur.

TABLE 1. $Pd(OAc)_2$-Catalyzed Acetoxylation of Heteroaryl Ethers[a]



1 2

Entry	Substrate	Product	Yield (%)
1	**1a**	**2a**	87
2	**1b**	**2b**	86
3	**1c**	**2c**	50
4[b]	**1c**	**2d**	84
5	**1d**	**2e**	24
6	**1e**	**2f**	29
7	**1f**	**2g**	27
8[b]	**1g**	**2h**	29
9	**1h**	**2i**	55
10[b]	**1h**	**2j**	83
11	**1i**	**2k**	45
12	**1j**	**2l**	62
13	**1k**	**2m**	82
14	**1l**	**2n**	81
15	**1m**	**2o**	81
16	**1n**	**2p**	69
17	**1o**	**2q**	42
18	**1p**	-	-
19	**1q**	-	-
20	**1r**	-	-

[a]Conditions: 2 mol % of $Pd(OAc)_2$, 1.1 equiv of $PhI(OAc)_2$, 0.125 M in AcOH/Ac_2O, 100 °C, 2−12 h. [b]Conditions: 5 mol % of $Pd(OAc)_2$, 3.0 equiv of $PhI(OAc)_2$, 0.125 M in AcOH/Ac_2O, 100 °C, 4 h.

The success in the highly regioselective acetoxylation of 2-phenoxypyrimidine derivatives by using the pyrimidine-directed C−H activation approach prompted us to explore the possibility of direct C−H arylation. The Suzuki−Miyaura-type

(14) (a) am Ende, C. W.; Knudson, S. E.; Liu, N.; Childs, J.; Sullivan, T. J.; Boyne, M.; Xu, H.; Gegina, Y.; Knudson, D. L.; Johnson, F.; Peloquin, C. A.; Slayden, R. A.; Tonge, P. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3029. (b) Yu, S.-R.; Cho, J.-H.; Ho, C.-U.; Lee, H.-S.; Hong, S.-M.; Kim, H.-U.; Im, J.-S.; Kim, J.-S. KR 9,511,418, **1995**.

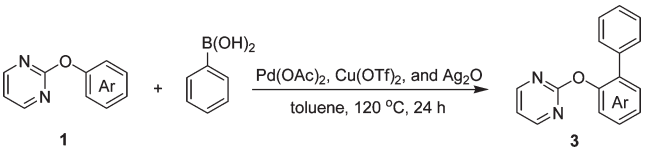
arylation of **1a** was first examined using phenylboronic acid as arylation reagent and $Pd(OAc)_2/Cu(OTf)_2/Ag_2O$ as catalyst. We were pleased to obtain the arylated product **3a** in 51% yield at 120 °C within 24 h. The arylation reaction was successfully extended to various pyrimidyl ethers bearing different substituents at the aromatic rings. As shown in Table 2, the Suzuki−Miyaura type coupling reactions of the ethers could proceed smoothly giving corresponding ortho arylated ethers in good yields by using 5 mol % of $Pd(OAc)_2$, 1 equiv of $Cu(OTf)_2$, and 1 equiv of Ag_2O. We found that both $Cu(OTf)_2$ and Ag_2O are essential for the catalytic cycle. Other combinations of copper and silver salts led to much lower yields of arylation products.

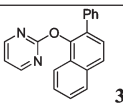
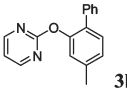
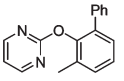
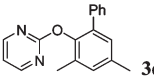
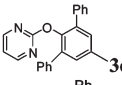
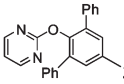
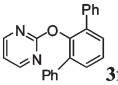
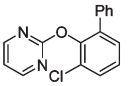
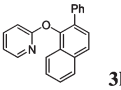
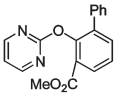
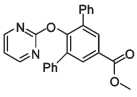
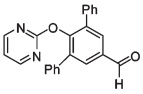
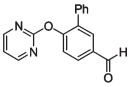
The scope of this reaction with respect to the heteroaryl ether substrates was screened. The results in Table 2 showed that the coupling reactions of electron-rich arylethers were more efficiently achieved. This observation is not surprising because C−H oxidative addition is preferred for substrates bearing electron-donating groups. Although the aromatic ethers bearing chloride, aldehyde, and carboxylate groups could be arylated, the yields are relatively low. In the cases of unsubstituted and *para*-substituted ethers that possess two *o*-C−H bonds, good yields of the double coupled products **3e**, **3f**, and **3j** were obtained upon addition of 3.0 equiv of $Cu(OTf)_2$, 3.0 equiv of Ag_2O, and 15 mol% $Pd(OAc)_2$ (Table 2, entries 6, 7, and 11). The coupling reaction of *meta*-substituted ether occurred at the less sterically hindered position (Table 2, entries 2 and 3). The X-ray crystallographic analysis of the arylation product **3b** verified the regioselectivity of this coupling reaction. The structure of **3b** is given in Figure S1 of the Supporting Information. In addition, unique functional group tolerance is observed, and the C−Cl bond on the substrate is tolerated (Table 2, entry 8), although in this case the yield is somewhat reduced. The product **3g** provides possibility for further C−C coupling reaction to construct more complex structure. Under the standard conditions, the direct arylations reaction could be scaled up to 0.5 mmol of **1** using 1.0 mmol of phenylboronic acid, and 0.025 mmol of $Pd(OAc)_2$ in 4 mL of toluene (Table 2, entries 13−15). The corresponding products **3c**, **3d**, and **3h** were readily isolated in 50%, 66%, and 58% yields, respectively.

A series of substituted phenylboronic acids as coupling partners were also investigated under the conditions used above. For the sake of products isolation, 2-(2,4-dimethylphenoxy)pyrimidine **1l** was chosen for evaluation. The results of the coupling reactions of **1l** with different phenylboronic acids are summarized in Table 3. Both electron-rich and electron-deficient arylboronic acids gave monoarylated products in good yields under the mild conditions. However, the relatively hindered boronic acid, 2-tolylboronic acid, demonstrated only poor reactivity (Table 3, entry 4). Among these reactants, 4-chlorophenylboronic acid is more interesting because the resultant products **4d** bears additional halide offering an opportunity for the construction of more complex compounds (Table 3, entry 5).

In summary, we have successfully developed ortho-acetoxylation and ortho-arylation of phenol derivatives through $Pd(OAc)_2$-catalyzed C−H bond activation. This protocol was convenient, efficient, and applicable to various substituted phenol and naphthol derivatives. 2-Phenoxypyrimidine derivatives have good herbicidal activities; thus, this route may provide a simaple procedure for the preparation of such herbicides.

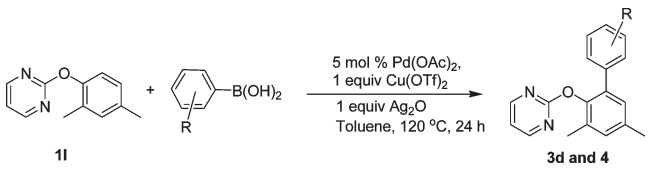
TABLE 2. Suzuki−Miyaura Coupling of Various Ethers with Phenylboronic Acid[a]

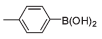
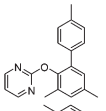
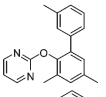
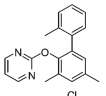
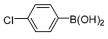
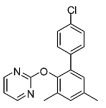
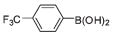
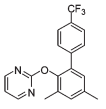


Entry	Substrate	Product	Yield (%)
1	**1a**	 **3a**	51
2	**1m**	 **3b**	42
3	**1n**	 **3c**	54
4	**1l**	 **3d**	73
5	**1h**	 **3e**	30
6[b]	**1h**	 **3e**	75
7[b]	**1c**	 **3f**	70
8	**1d**	 **3g**	38
9	**1b**	 **3h**	59
10	**1f**	 **3i**	33
11[b]	**1g**	 **3j**	70
12[b]	**1s**	 **3k**	29
		 **3l**	18
13[c]	**1n**	**3c**	50
14[c]	**1l**	**3d**	66
15[c]	**1b**	**3h**	58

[a]The reactions were carried out with **1** (0.2 mmol) and phenylboronic acid (0.4 mmol) in the presence of $Pd(OAc)_2$ (5.0 mol %), $Cu(OTf)_2$ (1.0 equiv), and Ag_2O (1.0 equiv). [b]Conditions: $Pd(OAc)_2$ (15 mol %), $Cu(OTf)_2$ (3.0 equiv), Ag_2O (3.0 equiv), and phenylboronic acid (5 equiv). [c]The reactions were carried out with 1 (0.5 mmol) and phenylboronic acid (1.0 mmol) in the presence of $Pd(OAc)_2$ (5.0 mol %), $Cu(OTf)_2$ (1.0 equiv), and Ag_2O (1.0 equiv).

TABLE 3. Arylation of C−H Bonds of 1l with Various Arylboronic Acids[a]



Entry	$RB(OH)_2$	Product	Yield (%)
1		**3d**	73
2		 **4a**	58
3		 **4b**	55
4		 **4c**	17
5		 **4d**	41
6		 **4e**	60

[a]All the reactions were carried out with **1l** (0.2 mmol) and phenylboronic acid (0.4 mmol) in the presence of $Pd(OAc)_2$ (5.0 mol %), $Cu(OTf)_2$ (1.0 equiv), and Ag_2O (1.0 equiv).

Experimental Section

General Procedure for the Direct Ortho-Acetoxylation of 2-Phenoxypyrimidine Derivatives. A solution of diaryl ether (0.5 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), and $PhI(OAc)_2$ (178 mg, 0.55 mmol) in AcOH (2.0 mL) and Ac_2O (2.0 mL) was stirred in a 20 mL Schlenk tube at 100 °C. The reaction was monitored by GC. Upon completion, the solvent was evaporated to dryness in vacuo. The residual was separated via thin-layer chromatography with petroleum ether/ethyl acetate (3/1) as the eluent to give the desired product (**2a**−**q**).

1-(Pyrimidin-2-yloxy)naphthalen-2-yl acetate (2a): pale yellow solid; mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 2H), 7.98−7.95 (m, 1H), 7.92−7.89 (m, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.52−7.49 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.07 (t, J = 4.8 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.1, 159.9, 139.5, 139.0, 132.5, 128.2, 127.9, 126.8, 126.2, 121.9, 121.7, 116.5, 20.6; HRMS (ESI, m/z) calcd for $C_{16}H_{12}N_2O_3Na$ 303.0746 (M + Na)$^+$, found 303.0740.

General Procedure for the Direct Ortho-Arylation of 2-Phenoxypyrimidine Derivatives. $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ether 1 (0.2 mmol), $Cu(OTf)_2$ (72.4 mg, 0.2 mmol), Ag_2O (46.4 mg, 0.2 mmol), arylboronic acid (0.4 mmol), and freshly distilled toluene (2 mL) were added to a dry Schlenk tube. The reaction mixture was heated and stirred for 24 h at 120 °C. Upon completion, the solvent was evaporated to dry in vacuo, the saturated sodium sulfide aqueous solution (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was washed twice with brine. The resulting organic layer was dried over $MgSO_4$ and concentrated. Purification of the crude mixture by thin-layer chromatography (petroleum ether/ethyl acetate) gave the desired product.

2-(2-Phenylnaphthalen-1-yloxy)pyrimidine (3a): pale yellow solid; mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 4.8 Hz, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 8.0 Hz, 3H), 7.53−7.46 (m, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.24−7.20 (m, 1H), 6.83 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 159.5, 145.1, 137.8, 134.2, 130.7, 129.3, 128.2, 128.1, 127.9, 127.2, 126.7, 126.4, 126.0, 122.1, 115.7; HRMS (ESI, m/z) calcd for $C_{20}H_{14}N_2ONa$ 321.1004 (M+Na)$^+$, found 321.0999.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.