Palladium-Catalyzed Regioselective *ortho*-Acetoxylation of 3-Aryl-1,2,4-Benzotriazines via C–H Activation

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Abstract: A highly regioselective *ortho*-acetoxylation has been achieved in the presence of 10 mol% $Pd(OAc)_2$ and a stoichiometric amount of $PhI(OAc)_2$ in a mixture of acetic anhydride and acetic acid via C–H activation to produce the corresponding acetoxy-substituted 3-aryl-1,2,4-benzotriazines derivatives in good yields.

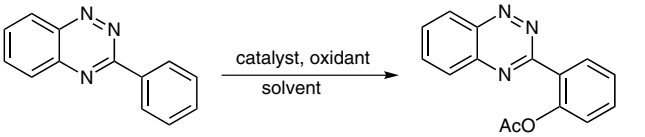
Key words: palladium catalyst, acetoxylation, C–H activation, 3-aryl-1,2,4-benzotriazines

The direct conversion of C–H bonds into C–O, C–N, C–S, C–halogen, and C–C bonds has been actively investigated in organic synthesis.[1] Great efforts have been devoted to the development of efficient methods for the direct C–H bond functionalization because of their potential in forming diverse derivatives.[2] Transition-metal complexes have been widely used as catalysts in C–H bond activation, and palladium catalysts are particularly attractive. Generally, the directing group possesses a lone-pair electron and coordinates the transition-metal catalyst via a five- or six-membered metallacycle to direct an *ortho* functionalization.[3] In recent years, the development of regioselective C–O bond formation via C–H activation received significant attention of organic chemists.[4]

1,2,4-Benzotriazine contains three nitrogen atoms and belongs to a special class of aromatic heterocycles, it is usually considered more significant than simple pyridine and quinoline rings.[5] It has been involved in many compounds and reactions such as aza nucleosides and aza nucleotides,[6] ligands,[7] herero Diels–Alder reactants,[8] herbicidal,[9] and metal-ion adsorption,[10] and it has been found in various agrochemicals, functional materials, and biologically active compounds.[11] Moreover, as a directing group, 1,2,4-benzotriazine is a useful building block for its potentially bioactive phenyl derivatives. Herein, we report a suitable and efficient method for the C–O bond formation on a phenyl ring via 1,2,4-benzotriazine-directed C–H activation with palladium catalysts.

Initially, we examined the reaction of 3-aryl-1,2,4-benzotriazine (**1a**) with $PhI(OAc)_2$ in AcOH–Ac_2O (1:1) catalyzed by $PdCl_2$ at 100 °C (Table 1, entry 1). Gratifyingly, the desired 2-{benzo[*e*][1,2,4]triazin-3-yl}phenyl acetate (**2a**) was obtained in 45% yield after six hours. Among the Pd sources we examined, $Pd(OAc)_2$ showed the highest activity for this reaction (Table 1, entries 2–4). Then several other oxidants were evaluated, and the results showed that $PhI(OAc)_2$ was superior to Oxone, $K_2S_2O_8$, 1,4-benzoquinone (BQ), and $Cu(OAc)_2$ (Table 1, entries 5–8). Thus, $PhI(OAc)_2$ was chosen as the oxidant for further optimization. Moreover, we have performed the reaction in various solvents. The reaction was sluggish either in MeCN or in Ac_2O (Table 1, entries 9 and 13). The use of 1,2-dichloroethane (DCE), toluene, and AcOH did not improve the yield of the product relative to AcOH–Ac_2O (Table 1, entries 10–12). Furthermore, changing the ratio of AcOH vs. Ac_2O did not improve the yield (Table 1, entries 14 and 15). Other than oxidant and solvent, the reaction temperature and time were also crucial for the reaction, the yield of **2a** decreased at both higher and lower temperature than 100 °C (Table 1, entry 16: 80 °C, entry 17: 120 °C); and the yield also decreased at longer and shorter reaction time than six hours (Table 1, entries 18: 4 h, 19: 8 h). Therefore, the optimized conditions were identified (Table 1, entry 4).

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield (%)
1	$PdCl_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	45[b]
2	$Pd(Ph_3P)_2Cl_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	28[b]
3	$PdCl_2C_4H_6N_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	39[b]
4	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	72[b]
5	$Pd(OAc)_2$	Oxone	AcOH–Ac_2O	6	42[b]
6	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH–Ac_2O	6	51[b]
7	$Pd(OAc)_2$	BQ	AcOH–Ac_2O	6	n.d.[b]
8	$Pd(OAc)_2$	$Cu(OAc)_2$	AcOH–Ac_2O	6	n.d.[b]
9	$Pd(OAc)_2$	$PhI(OAc)_2$	MeCN	6	trace
10	$Pd(OAc)_2$	$PhI(OAc)_2$	DCE	6	53

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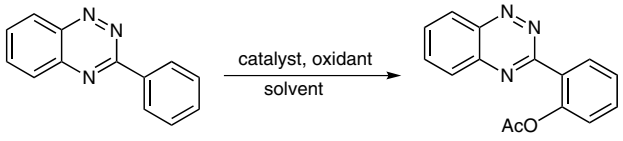
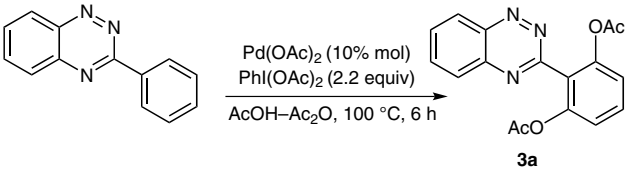
Table 1 Optimization of the Reaction Conditions[a] (continued)



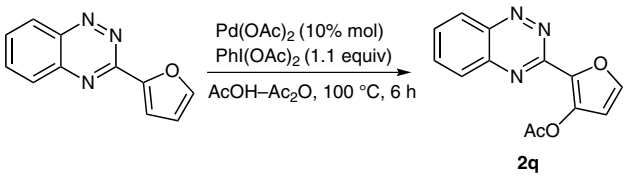
Entry	Catalyst	Oxidant	Solvent	Time (h)	Yield (%)
11	$Pd(OAc)_2$	$PhI(OAc)_2$	toluene	6	47
12	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH	6	34
13	$Pd(OAc)_2$	$PhI(OAc)_2$	Ac_2O	6	11
14	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	38[c]
15	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	23[d]
16	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	53[b,e]
17	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	6	48[b,f]
18	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	4	43[b]
19	$Pd(OAc)_2$	$PhI(OAc)_2$	AcOH–Ac_2O	8	59[b]

[a] Reaction conditions: The reaction was carried out using **1a** (0.2 mmol), catalyst (0.02 mmol), and oxidant (0.22 mmol) in solvent (1 mL) under air for 6 h at 100 °C.
[b] Yield for AcOH–Ac_2O (1:1).
[c] Yield for AcOH–Ac_2O (2:1).
[d] Yield for AcOH–Ac_2O (1:2).
[e] Yield for a reaction temperature of 80 °C.
[f] Yield for a reaction temperature of 120 °C.

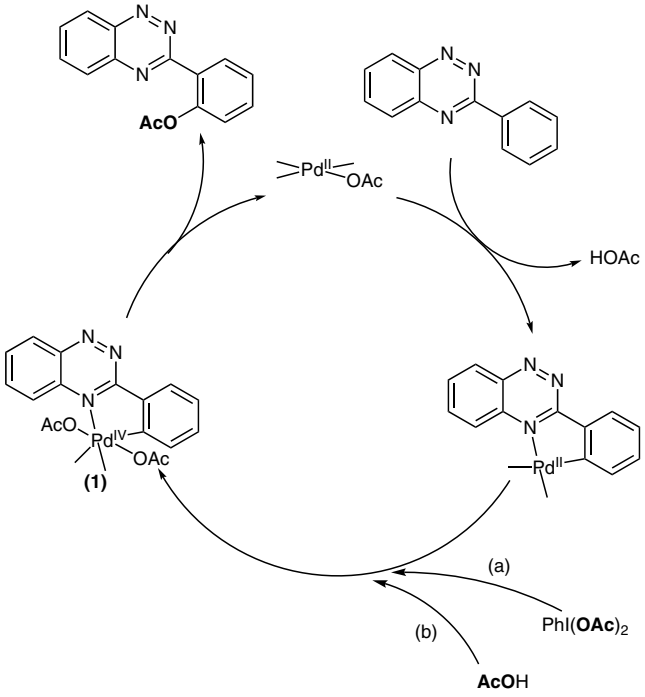
3-Aryl-1,2,4-benzotriazine presents two *ortho* C–H bonds that can coordinate with Pd at both 2,6-positions, but with 1.1 equivalents of $PhI(OAc)_2$ the monosubstituted product was obtained in good yield (Table 2, entry 1). When increase the feed of $PhI(OAc)_2$ to 2.2 equivalents, only the disubstituted product was detected (Scheme 1, 3a). Using the optimized conditions, we also examined a series of 3-aryl-1,2,4-benzotriazine compounds to establish the scope and limitations of this process. Generally, the reaction of 3-aryl-1,2,4-benzotriazine bearing either electron-withdrawing or electron-donating groups proceeded smoothly and afforded the corresponding desired product **2** in moderate to good yields (Table 2). However, the compounds with electron-donating functional groups on the aryl ring (Table 2, entries 1–4) generally gave higher yields than those with electron-withdrawing groups (Table 2, entries 5 and 6; 72–84% for **2a**–**d** vs. 58–60% for **2e**–**f**). Interestingly, methyl groups on the aryl ring seem to facilitate the reaction (Table 2, entries 2–4), and the 4-methyl-substituted compound gave the highest yield (Table 2, entry 2: 84%). However, the stronger electron-donating methoxy group on the aryl ring gave the product in low yield (Table 2, entry 7). To our surprise, the compound with the strong electron-withdrawing nitro group at the *meta* position gave the product in 31% yield (Table 2, entry 9). However, the compound with the nitro group at the *para* position may not be suitable for the process as the desired product was not isolated, and only a trace amount of the product was detected on silica gel (Table 2, entry 8). Furthermore, for substitution on the 1,2,4-benzotriazine, electron-donating substituted compounds (Table 2, entry 10: 70%, entry 11: 63%) gave slightly higher yields than those with electron-withdrawing substituents (Table 2, entry 12: 62%), but dimethyl substitution did not give better yield than single methyl substitution. For compounds with substitution at both phenyl and aryl rings, electron-rich 3-aryl-1,2,4-benzotriazines showed better reactivity and achieved higher yields than electron-deficient ones (Table 2, entries 13–17). Notably, 3-fury-1,2,4-benzotriazines can also undergo this transformation, albeit in 14% yield (Scheme 2, **2q**).



Scheme 1 Synthesis of 2-{benzo[*e*][1,2,4]triazin-3-yl}-1,3-phenylene diacetate from 3-aryl-1,2,4-benzotriazine

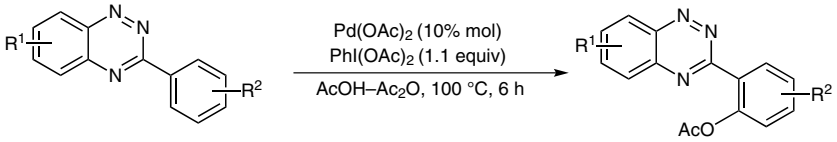


Scheme 2 Synthesis of 2-{benzo[*e*][1,2,4]triazin-3-yl}furan-3-yl acetate from 3-fury-1,2,4-benzotriazine



Scheme 3 Proposed reaction mechanism

Table 2 Substrate Scope of 3-Aryl-1,2,4-benzotriazines[a]



Entry	R^1	R^2	Product	Yield (%)
1	H	H	**2a**	72
2	H	4-Me	**2b**	84
3	H	3-Me	**2c**	82
4	H	3,5-Me_2	**2d**	78
5	H	4-Cl	**2e**	60
6	H	3-Cl	**2f**	58
7	H	4-MeO	**2g**	36
8	H	4-O_2N		trace
9	H	3-O_2N	**2h**	31
10	4-Me	H	**2i**	70
11	4,5-Me_2	H	**2j**	63
12	4-Cl	H	**2k**	62
13	4,5-Me_2	4-Me	**2l**	73
14	4-Cl	4-Me	**2m**	64
15	4-Me	4-Cl	**2n**	65
16	4-Me	3-Cl	**2o**	56
17	4,5-Me_2	4-Cl	**2p**	53

[a] Reaction conditions: The reaction was carried out using **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), and $PhI(OAc)_2$ (0.22 mmol) in AcOH–Ac_2O (1 mL) under air for 6 h at 100 °C.

A plausible reaction mechanism based on the results obtained above combined with previous reports[12] has been proposed in Scheme 3. We assume that the reaction may undergo according to the following procedures. 1,2,4-Triazine-directed C–H activation generates a five-membered cyclopalladated intermediate,[13] the intermedium palladacycle is stabilized with the 1,2,4-triazine group to induce the *ortho* acetoxylation.[14] The resulting Pd^{II} could be converted into Pd^{IV} by $PhI(OAc)_2$ to complete the catalytic cycle (Scheme 3, a).[15] An alternative peroxide-based oxidant may also give the key Pd^{IV} intermediate **1** when employing an external acetate source such as acetic acid (Scheme 3, b).[16]

In conclusion, we have developed a direct palladium-catalyzed method for the synthesis of 2-{benzo[*e*][1,2,4]triazin-3-yl}phenyl acetate derivatives form 3-aryl-1,2,4-benzotriazines using 10 mol% $Pd(OAc)_2$ and with $PhI(OAc)_2$ as oxidation agent in AcOH–Ac_2O in air in a one-pot manner, involving the cleavage of a C–H bond and the formation of a C–O bond. A variety of substituents are tolerated in this reaction, which proceeds smoothly in moderate to good yields. Additionally, the approach provides a new access to a variety of acetoxy-susbstituted 3-aryl-1,2,4-benzotriazines derivatives which may be important in medicinal chemistry for drug discovery and development. The application of 1,2,4-benzotriazines as a directing group to construct carbon–heteroatom bonds, and other further investigations, are under way in our laboratory.

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(17) **Typical Procedure for the Preparation of 2-{Benzo[*e*][1,2,4]triazin-3-yl}phenyl Acetate**
A test tube was charged with **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), and $PhI(OAc)_2$ (0.22 mmol). Then AcOH–Ac_2O (1 mL) was added to the reaction system. The reaction was stirred at 100 °C under air for 6 h. After cooling to r.t., the solvent was diluted with EtOAc (10 mL) and washed with brine (5 mL) and dried over anhyd Na_2SO_4. After the solvent was evaporated in vacuo, the residues were purified by column chromatography, eluting with PE–EtOAc to afford 38 mg (72%) pure **2a** as yellow solid, mp 102–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d d, *J* = 8.0 Hz, 1.6 Hz, 2 H), 8.07–8.05 (m, 1 H), 8.01–7.97 (m, 1 H), 7.89–7.85 (m, 1 H), 7.62–7.58 (m, 1 H), 7.51–7.47 (m, 1 H), 7.27 (d d, *J* = 8.0 Hz, *J* = 1.6 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 159.3, 149.7, 145.8, 140.6, 135.6, 132.1, 132.1, 130.6, 129.5, 128.9, 128.6, 126.5, 124.2, 21.2. IR (neat): 3070, 2924, 2853, 1768, 1514, 1458, 1372, 1322, 1198, 1100, 1012, 769 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{15}H_{11}N_3O_2$ $[M + H]^+$: 266.0930; found: 266.0922.

