

Palladium-Catalyzed Cascade Oxidation/ sp^2 C–H Acylation of Azoarenes with Aryl Methanes

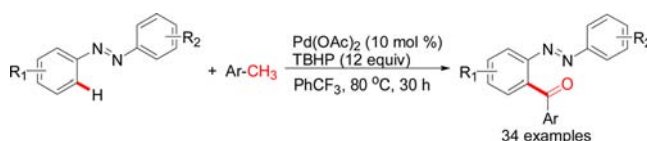
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ABSTRACT



A Pd-catalyzed cascade oxidation/ sp^2 C–H bond acylation of azoarenes was developed in which readily available aryl methanes were used as the *in situ* generated acyl sources. This reaction provides a convenient access to *ortho*-acyl azoarenes under mild conditions.

The regio- and chemoselective C–H bond activation of organic molecules by transition metal catalysts provides an atom-economic access to the construction of carbon–carbon or carbon–heteroatom bonds, which could further lead to simple and efficient synthetic strategies for the functionalization of organic compounds.¹ Since the discovery of directed *ortho* metalation of organic compounds

by Ryabov,² most elegant work has demonstrated that cyclometalated intermediates which have derived from substrates containing a nitrile,³ ketone,⁴ carboxylic acid,⁵ alcohol,⁶ triazone,⁷ pyridine,⁸ ester,⁹ amide,^{4b,10} aldehyde,^{9a,11} imine,¹² or oxazoline¹³ directing group, etc., could be easily trapped by appropriated electrophiles or nucleophiles and realized a versatile C–H functionalization. However, although significant attention has been recently focused on the above-mentioned directing groups, there are rare reported cases using the azo group as a directing group to accelerate the C–H activation/functionalization process.¹⁴

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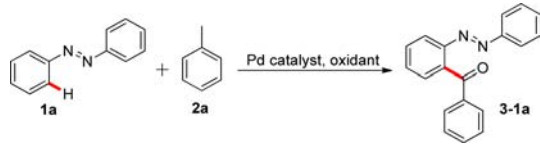
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Azo-substituted aryl ketones are fundamental building blocks which are widely utilized in the field of photochemical materials, biosensors, medicinal chemistry, and food additives.¹⁵ For the synthesis of these compounds, many methodologies have been established to make them *via* the coupling of diazonium salts with arenes or the oxidation of the corresponding azo-containing secondary alcohols.¹⁶ However, these methodologies suffered from tedious reaction steps and a relatively limited substrate scope. Therefore, developing an efficient synthetic approach to the direct catalytic C–H acylation of azoarenes by employing easily available acylating agents becomes more desirable. Considering that readily available aryl methanes could be used as an ideal *in situ* generated acylated reagent for constructing *ortho* acylated arene derivatives with the assistance of a pyridine or an amide directing group¹⁷ and, more recently, Wang reported that Pd(II) catalysts could realize the direct acylation of azoarenes using prefunctionalized aldehydes as acyl sources,^{14d} herein we further investigated the possibility that the Pd-catalyzed cascade oxidation/C–H acylation of azoarenes with no prefunctionalized aryl methanes as the simple acylating agents provides *ortho*-acylated azoarenes.

Our initial investigation began with the direct C–H acylation of azobenzene (**1a**) (0.15 mmol) with toluene (**2a**) (2.0 equiv) in the presence of 10 mol % PdCl₂ and stoichiometric TBHP (4.0 equiv) in CH₃NO₂ at 110 °C for 30 h (Table 1, entry 1). As expected, the desired product **3-1a** was obtained in 10% yield, and further solvent screening indicated that trifluorotoluene was the best solvent which led to the formation of **3-1a** in 17% yield (compare entries 1–4 with 5). Subsequently, we investigated the effect of various oxidants on this transformation and found that TBHP was the most suitable oxidant (22% yield), with other oxidants, such as DDQ, MnO₂, Na₂S₂O₈, etc., affording poorer reactivities (compare entries 6–9 with 5). Moreover, Pd catalyst screening showed that PdCl₂ and Pd(OAc)₂ possess similar catalytic activities while Pd(TFA)₂ and PdCl₂(MeCN)₂ gave only a trace amount of desired product **3-1a** (compare entries 10–11

with 5 and 12). The above-obtained positive results encouraged us to further change the reaction temperature and the ratio of **1a**/**2a**/TBHP for achieving satisfying yields (entries 13–17). Gratifyingly, the reaction system of **1a** (0.15 mmol)/**2a** (36.0 equiv)/TBHP (12.0 equiv) was most productive using Pd(OAc)₂ (10 mol %) as the catalyst and PhCF₃ as the solvent, providing **3-1a** in 77% yield at 80 °C for 30 h (entry 16). Afterwards, we also ran this transformation under solvent-free conditions^{17c} which only afforded a 60% yield of **3-1a** (entry 18). Further increasing or lowering the reaction temperature resulted in poorer yields (see Supporting Information (SI) for more details).

Table 1. Optimization of the Pd-Catalyzed *ortho*-Acylation of Azobenzene with Toluene^a



entry	PdX ₂	oxidant	solvent	yield (%) ^b
1	PdCl ₂	TBHP	CH ₃ NO ₂	10
2	PdCl ₂	TBHP	DCE	15
3	PdCl ₂	TBHP	DMSO	trace
4	PdCl ₂	TBHP	dioxane	trace
5	PdCl ₂	TBHP	PhCF ₃	17
6	PdCl ₂	DDQ	PhCF ₃	0
7	PdCl ₂	MnO ₂	PhCF ₃	0
8	PdCl ₂	Na ₂ S ₂ O ₈	PhCF ₃	0
9	PdCl ₂	O ₂	PhCF ₃	0
10	PdCl ₂ (MeCN) ₂	TBHP	PhCF ₃	trace
11	Pd(TFA) ₂	TBHP	PhCF ₃	trace
12	Pd(OAc) ₂	TBHP	PhCF ₃	22
13	Pd(OAc) ₂	TBHP	PhCF ₃	55 ^{c,d}
14	Pd(OAc) ₂	TBHP	PhCF ₃	60 ^{c,e}
15	Pd(OAc) ₂	TBHP	PhCF ₃	67 ^{c,f}
16	Pd(OAc) ₂	TBHP	PhCF ₃	77 ^{c,g}
17	Pd(OAc) ₂	TBHP	PhCF ₃	80 ^{c,h}
18	Pd(OAc) ₂	TBHP	–	60 ^{i,j}

^a Unless otherwise noted, the reactions were carried out using azobenzene (**1a**) (0.15 mmol) and toluene (**2a**) (0.30 mmol) with a palladium catalyst (10 mol %) in the presence of oxidant (4.0 equiv) in solvent (1.0 mL) at 110 °C under Ar for 30 h in a sealed reaction tube, followed by flash chromatography on SiO₂. ^b Isolated yield. ^c Reaction temperature: 80 °C. ^d 12.0 equiv of toluene and 12.0 equiv of TBHP were used. ^e 24.0 equiv of toluene and 12.0 equiv of TBHP were used. ^f 24.0 equiv of toluene and 24.0 equiv of TBHP were used. ^g 36.0 equiv of toluene and 12.0 equiv of TBHP were used. ^h 36.0 equiv of toluene and 24.0 equiv of TBHP were used. ⁱ 1.0 mL of PhCF₃ was not used. ^j 36.0 equiv of toluene were used.

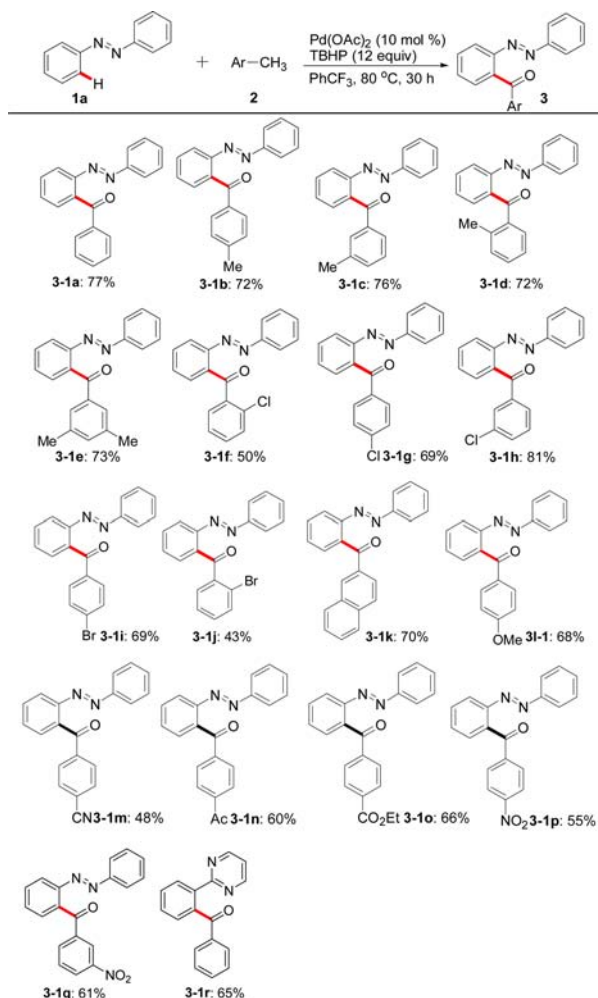
Having established an efficient reaction protocol that enables the *ortho*-acylation of azobenzene with toluene, we next investigated its scope with regard to aryl methanes as the acyl source. As shown in Scheme 1, the C–H acylation of azobenzene with various aryl methanes could proceed smoothly and furnish the corresponding acylated products. The substitution on the benzene ring showed no deleterious electronic effects; the substrates with a *para*- or *meta*-electron donating group (4-MeO, 4-Me, 3-Me) and a

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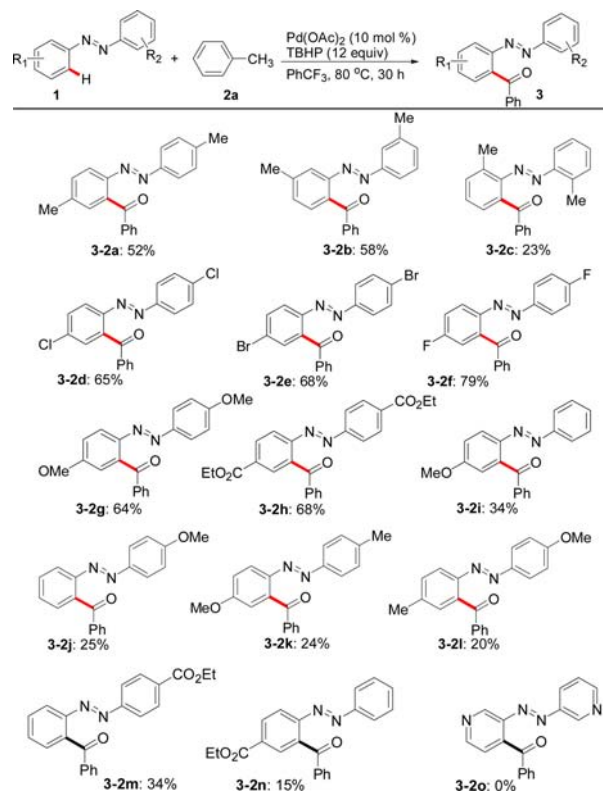
Scheme 1. Scope of Aryl Methanes^a

^a Unless otherwise noted, the reactions were carried out using azobenzene (1a) (0.15 mmol) and aryl methane (2) (36.0 equiv) with Pd(OAc)₂ (10 mol %) in the presence of TBHP (12.0 equiv) in PhCF₃ (1.0 mL) at 80 °C for 30 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO₂. ^b Isolated yield.

para- or *meta*-electron withdrawing group (such as 4-Cl, 3-Cl, 4-Br, 4-NO₂, 3-NO₂, 4-CN, 4-Ac, 4-CO₂Et) on the phenyl ring afforded the desired products in moderate to excellent yields (3-1a–3-1c, 3-1e, 3-1g–3-1i, 3-1l–3-1p). It is worth noting that the bromo group remained intact in this reaction system (3-1i and 3-1j). Meanwhile, the *ortho*-substituted phenyl methanes gave poorer yields of acylated products possibly due to their higher steric hindrance (3-1f–3-1g and 3-1i–3-1j).¹⁸ Moreover, we also tried the pyrimidyl group containing arenes using our reaction conditions. To our delight, the Pd-catalyzed oxidative acylation of 2-phenylpyrimidine with toluene could also proceed smoothly to furnish the corresponding *ortho*-acylated arenes (3-1r) in 65% yields.

(18) Unfortunately, no reaction occurred for 2-nitrotoluene, 3-methylpyridine, and 3-methylfuran even after increasing the reaction temperature to 110 °C or extending the reaction time to 72 h, and azobenzene 1a was completely recovered.

The scope of the procedure with regard to azoarenes was then explored with toluene as an acylating agent. The results from Scheme 2 demonstrated that no significant electronic effect of the *para*-substituted azoarene was found (3-2a, 3-2d–3-2h). Yet, *ortho*-substituted azobenzene gave an inferior product yield to that of *para*- or *meta*-substituted azobenzene (compare 3-2c with 3-2a and 3-2b) due to the “*ortho*-substituent” effect. Moreover, we also investigated the electronic effect of various substituents on the regioselectivity of the *ortho*-acylation of unsymmetric azoarenes and found *ortho*-acylation reactions took place mainly on the electron-rich azo aromatic rings (compare 3-2i, 3-2k, and 3-2m with 3-2j, 3-2l, and 3-2n, respectively). Subsequently, we tried to use 3-azopyridine as a substrate, but no *ortho*-acylation was observed under our reaction conditions (3-2o).

Scheme 2. Scope of Azoarenes^a

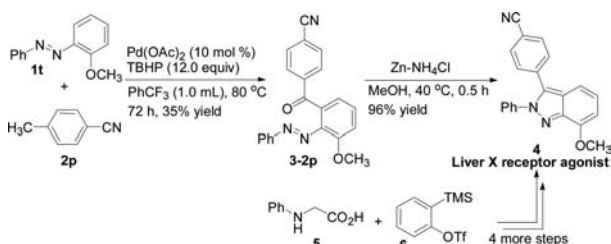
^a Unless otherwise noted, the reactions were carried out using azoarene (1) (0.15 mmol) and toluene (2) (36.0 equiv) with Pd(OAc)₂ (10 mol %) in the presence of TBHP (12.0 equiv) in PhCF₃ (1.0 mL) at 80 °C for 30 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO₂. ^b Isolated yield.

Indazole 4 belongs to an inhibitor of liver X receptor-mediated cardiovascular disease.¹⁹ The present synthetic method of 4 involved tedious steps using α -amino acid 5 and 2-(trimethylsilyl)phenyl derivative 6 as starting materials.²⁰ The *ortho*-regioselective acylation of unsymmetric azoarene

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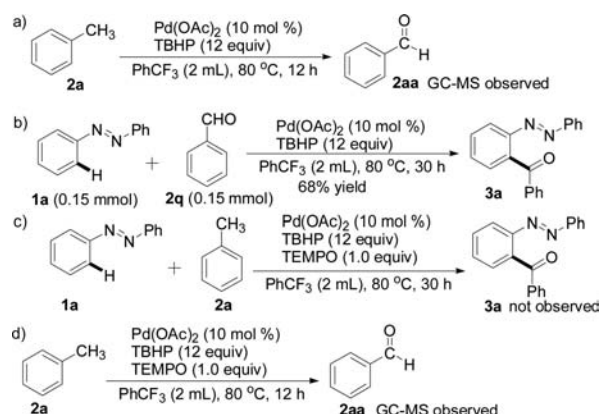
1t with 4-methyl-benzonitrile **2p** could afford the corresponding acylated intermediate **3-2p** in 35% yield, and then the following reductive cyclozation of **3-2p** occurred upon treatment with Zn/NH₄Cl to give the inhibitor **4** in 96% yield.^{14d} This procedure was accomplished in just two steps with an overall 34% yield from readily available starting materials (Scheme 3).

Scheme 3. Synthetic Application of This Transformation



To further probe the reaction mechanism, the mixture of toluene (1.0 mL)/Pd(OAc)₂ (10 mol %)/TBHP (12 equiv) in the absence of azobenzene was conducted and monitored using GC-MS spectra. After the reaction was carried out at 80 °C for 12 h, we could observe the formation of benzaldehyde (Scheme 4a) (see SI for the corresponding GC-MS spectra). Then benzaldehyde **2q** was employed as the acyl source instead of toluene **2a**, and a 68% yield of **3a** resulted (Scheme 4b). Moreover, we ran the Pd-catalyzed C–H acylation of azobenzene with toluene in the presence of TEMPO under our reaction conditions; unfortunately, no acylated **3a** was observed possibly due to the fact that TEMPO suppressed the acylation process instead of the formation of aldehyde intermediate **2aa** (Scheme 4c and 4d). These controlled experiments indicated that a radical process was involved in this reaction system.

Scheme 4. Controlled Reactions



Taking previous reports on Pd-catalyzed *sp*² C–H acylation into account,^{8c,14d,17c,21} and in combination with the results from the above-mentioned controlled reactions, we proposed a plausible reaction mechanism for this transformation, in which Pd(OAc)₂ reacted with azobenzene (**1a**) by *sp*² C–H activation to form a palladacyclic intermediate **A** (Figure 1).^{14d} Then **A** reacted with acyl radical **B** which was *in situ* generated from aryl methanes under oxidizing conditions to produce either Pd(IV)²² or Pd(III)²³ species **C**. Finally, the species **C** underwent reductive elimination to afford the acylated product **D** with the release of the Pd(II) species.

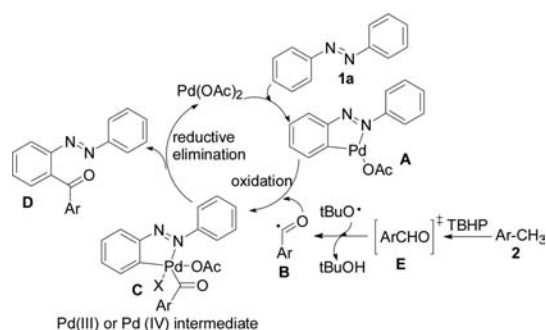


Figure 1. Proposed reaction mechanism.

In conclusion, we have developed a Pd(II)-catalyzed cascade oxidation/*sp*² C–H acylation of azoarenes with aryl methanes using TBHP as an oxidant. This protocol allows us to use simple and readily available aryl methanes as acyl sources and provides a convenient access to the synthesis of an *ortho*-acylazoarenes library. Further transformation of these azoarenes into other biologically active molecules is currently underway in our laboratory.

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Supporting Information Available. Details for experiments conditions, characterization data, and copies of ¹H and ¹³C NMR spectra for all isolated compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.