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Ortho Arylation of Acetanilides via Pd(II)-Catalyzed C−H Functionalization

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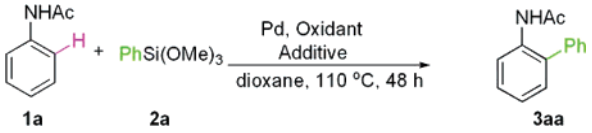
Palladium-catalyzed coupling with silyl reagents is a very useful method to construct a C−C bond in organic synthesis.[1] With much effort in the past, these couplings could be conducted with different substitutions, such as iodide, bromide, triflate, and even inexpensive but hard chloride.[2] As a potential green and efficient process to construct complicated structures from simple and commercially available chemicals, the sp^2 C−H bond may be functionalized to construct C−C via Pd-catalyzation.[3] Direct arylation of aromatic C−H has also been studied with or without directing groups.[4] With the acetamino group as a directing group, ortho C−H of acetanilide could be highly regioselectively functionalized.[5] Herein we first demonstrate a new development to form the C−C bond through aryl C−H activation by coupling with (trialkyoxyl)phenylsilane directed by an acetamino group.

In our recently reported ortho halogenation, the palladacycle formed through acetyl group-assisted electrophilic attack by Pd(II) cation was proposed as a key intermediate.[5i] We envisioned that the same intermediate might undergo coupling with silyl reagents under proper conditions. We first tried Hiyama coupling between acetanilide **1a** and (trimethoxy)phenylsilane **2a** in the presence of a stoichiometric amount of $Pd(OAc)_2$ with TBAF in dioxane. Unfortunately, no desired product was observed. Gratifyingly, the desired coupling product **3aa** was observed in a low yield monitored by GC when AgF was used as a fluoride source (entry 2, Table 1). Further studies indicated that a catalytic amount of $Pd(OAc)_2$ also made this transformation happen, but the efficiency was lower. We envisioned that AgF might play more roles than just a simple fluoride source; it may also serve as an oxidant to oxidize a Pd(0) species back to Pd(II) to fulfill the catalytic cycle. Thus, we hypothesized that the key point for this transformation is a proper oxidant. After many trials, we found that $Cu(OTf)_2$ was the best choice (entry 3, Table 1). Other organic and inorganic oxidants were not helpful for this transformation. The amount of $Cu(OTf)_2$ could be decreased to 1.0 equiv (entry 4, Table 1); however, the increase of $Cu(OTf)_2$ is helpful to inhibit the homocoupling of phenylsilane to produce diphenyl as a byproduct.

Table 1. Ortho Arylation via C−H Activation under Different Conditions[a]

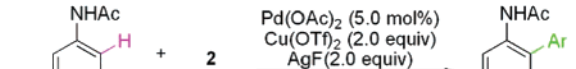


1a 2a 3aa

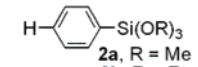
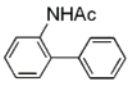
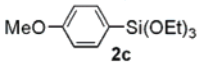
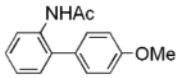
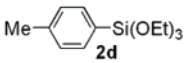
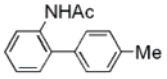
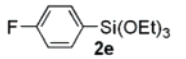
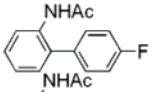
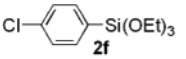
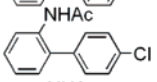
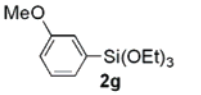
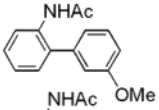
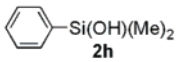
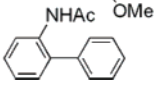
entry	Pd (mol %)	oxidant (equiv)	additive (equiv)	3aa[b]
10	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (2.0)		37
2	$Pd(OAc)_2$ (5.0)		AgF (2.0)	8
3[c]	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (2.0)	AgF (2.0)	86 (74)
4	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	AgF (2.0)	68
5	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (2.0)	AgF (1.0)	56
6	$PdCl_2$ (5.0)	$Cu(OTf)_2$ (2.0)	AgF (2.0)	19
7	$Pd(OTFA)_2$ (5.0)	$Cu(OTf)_2$ (2.0)	AgF (2.0)	67
8	$Pd(PPh_3)_2Cl_2$(5.0)	$Cu(OTf)_2$ (2.0)	AgF (2.0)	66
9	$Pd(PhCN)_2Cl_2$ (5.0)	$Cu(OTf)_2$ (2.0)	AgF (2.0)	73
10	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (2.0)	CsF (2.0)	11
11	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	CuF_2 (2.0)	15
12	$Pd(OAc)_2$ (5.0)	$Cu(OTf)_2$ (1.0)	TBAF (2.0)	<5
13	$Pd(OAc)_2$ (5.0)	$CuCl_2$ (2.0)	AgF (2.0)	<5
14	$Pd(OAc)_2$ (5.0)	$CuBr_2$ (2.0)	AgF (2.0)	<5

[a] All the reactions were carried out in the presence of 0.2 mmol of **1a** and 0.4 mmol **2a** in 5 mL of dioxane at 110 °C for 48 h. [b] GC yields with *n*-decane as an internal standard. [c] Isolated yield in parentheses.

Table 2. Ortho Arylation with Different Silyl Reagents via C−H Activation[a]



1a 3

entry	2	3	Yield (%)[b]
1	 **2a**, R = Me **2b**, R = Et		**3aa** (74)
2			(74)
3	 **2c**		**3ac** (71)
4	 **2d**		**3ad** (62)
5	 **2e**		**3ae** (63)
6	 **2f**		**3af** (61)
7	 **2g**		**3ag**(52)
8	 **2h**		**3aa** (33)

[a] All the reactions were carried out in 0.2 mmol scale. [b] Isolated yields.

On the basis of this observation, different trialkyloxyarylsilanes were surveyed (Table 2). The coupling occurred to produce the desired products **3** in moderate to excellent yields with (trimethoxy)-phenylsilanes, regardless electron withdrawing group or electron-donating group was introduced on the phenyl ring of the phenylsilane. However, phenyl silanol was not a good reagent for this transformation under the same condition and the product **3aa** was obtained in much lower efficiency (entry 8, Table 2). It was important to note that C−Cl on phenylsilane was compatible with this system, which could be further transformed into different functionalities (entry 6, Table 2).[2c]

The scope of acetanilides was also investigated (Table 3). Other than acetyl, benzoyl and formyl could be used as directing groups

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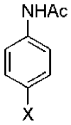
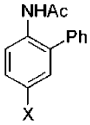
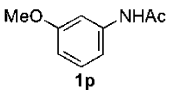
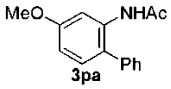
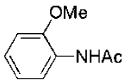
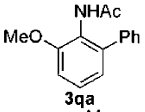
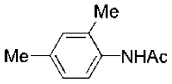
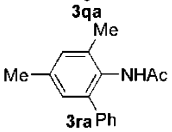
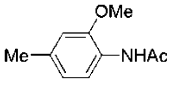
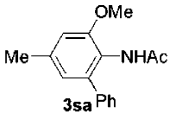
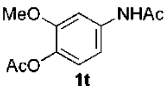
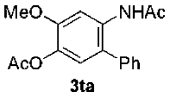
Table 3. Ortho Arylation of Actanilides with **2a** via C−H Functionalization[a]

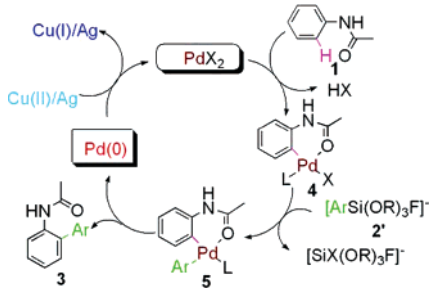
Entry	1	3	Yield(%)[b]
1	**1a**, R = Ac	**3aa**	74
2[c]	**1b**, R = HCO	**3ba**	12
3	**1c**, R = PhCO	**3ca**	38
4[c]	 **1d**, R = Boc	 **3da**	0
5[c]	**1e**, R = Ts	**3ea**	0
6[c]	**1f**, R = Me	**3fa**	0
7[c]	**1g**, R = TFAc	**3ga**	0
8	**1h**, R = PhPr	**3ha**	46
9[c]	**1i**, R = AcAc	**3ia**	0
10	**1j**, X = OMe	**3ja**	68
11	 **1k**, X = OAc	 **3ka**	66
12	**1l**, X = OBz	**3la**	64
13	**1m**, X = Me	**3ma**	71
14[d]	**1n**, X = Cl	**3na**	42
15[d]	**1o**, X = Ac	**3oa**	59
16	 **1p**	 **3pa**	52
17	 **1q**	 **3qa**	80
18	 **1r**	 **3ra**	73
19	 **1s**	 **3sa**	65
20	 **1t**	 **3ta**	62

[a] All the reactions were carried out in the presence of 0.2 mmol of **1**, 0.4 mmol of **2a**, 0.01 mmol of $Pd(OAc)_2$, 0.4mmol of $Cu(OTf)_2$, and 0.4 mmol of AgF in 5 mL of dioxane at 110 °C for 48 h. [b] Isolated yields.[c] GC yields with *n*-decane as an internal standard. [d] Reaction run in the presence of 10.0 mol % of $Pd(OAc)_2$ in these reactions, and some starting materials were recovered.

with lower efficiency (entries 2 and 3). The other groups, such as tosyl, acetacetyl, and trifluoroacetyl were not beneficial for this transformation (entries 4, 6, and 9). *N*-alkylated and free anilines were not fit for this transformation. Either the electron-donating groups or electron-withdrawing groups introduced to the phenyl group of acetanilides could be applied to form desired products (entries 10−16). However, the efficiency of this transformation was decreased by electron-withdrawing groups, perhaps arising from the decrease of electron density on the phenyl ring (entries 14−15). Furthermore, benzoyl, acetyl, and methyl groups could serve as a protecting group of phenol, and the regioselectivity was not affected by these functionalities (entries 10−12). The polysubstituted acetanilides were also investigated, and the expected products were obtained in good yields (entries 18−20). It is worthy pointing out that the regioselectivity of this arylation was also controlled by the steric effect with substituents at the meta position of acetanilides (entries 16 and 20).

This coupling may go through the following catalytic process (Scheme 1). After the ortho electrophilic attack by Pd(II) cation with the assistance of the acetamino group, the aryl group from silicate **2′** assisted by fluoride was transmetalated to palladacycle

Scheme 1. Proposed Mechnism of Ortho Arylation by Coupling via Pd(II)-Catalyzed C−H Activation



4 to form diaryl palladium species **5**, which underwent reductive elimination to produce the coupling product. Pd(0) was oxidized back to Pd(II) by either Ag(I) or Cu(II) or both to complete the catalytic cycle. Thus, electron-donating groups on acetanilides were helpful for this transformation. The prepared palladacycle **4** could stoichiometrically transform to the coupling product, which offered a further proof for this proposed mechanism.[5c]

In summary, we developed a novel transformation to realize ortho arylation of acetanilides with trialkoxyarylsilanes through direct C−H functionalization. Further investigation to clearly understand this transformation and expand the application of this chemistry is underway in our laboratory.

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Supporting Information Available: Brief experimental details and other spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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