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Highly Selective C−H Functionalization/Halogenation of Acetanilide

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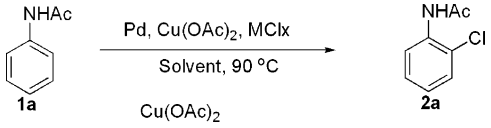
Aryl halides are broadly utilized to construct complex structures in organic syntheses via transition-metal-catalyzed coupling reactions (such as Suzuki coupling, Negishi coupling, and Buchwald/Hartwig amination/amidation).[1,2] The sp^2 C−X units are also important structural motifs in many natural products and synthetic drugs.[3] However, previous halogenations of arenes, such as direct electrophilic halogenations[4] and halogenations of aryldiazonium salts (Sandmeyer reaction), which are generally produced from anilines,[5] bear some disadvantages, including low regioselectivity as well as tedious and sometimes dangerous procedures. Thus, new methods that can selectively construct C−X groups are of importance. A useful method to achieve highly regioselective halogenation of arenes has been developed by Snieckus et al. through the *ortho* metalation followed by nucleophilic halogenation.[6] Herein we report a new process to construct C−X bonds with high regioselectivity through palladium-mediated aryl C−H group functionalization.

Recent studies have led to many methods that directly functionalize C−H groups of arenes to construct C−C bonds with transition metal catalysts.[7] Palladium-mediated C−H activation of arenes is one of the most important processes.[8] Formations of C−O/N bonds via C−H bond activation catalyzed by palladium species have also been reported by Sanford, Buchwald, and others.[9] Under Sanford's conditions, the highly regioselective halogenation of electron-deficient arenes, such as benzo[*h*]quinoline, can be achieved with NBS/NCS as the electrophilic halogen sources in CH_3CN.[9a] Subsequently, Yu's development of iodination of alkyl groups offers a useful method to functionalize the sp^3 C−H with oxazoline as the directing group.[10] In addition, Hartwig and co-workers have reported the stoichiometric reductive eliminations of aryl halides from palladium(II) species with special bulky phosphine ligands.[11] On the basis of these preliminary studies, we postulated that, with proper directing groups and halogen sources, direct catalytic C−X formation of arenes could be possible through C−X reductive elimination via Pd-mediated C−H functionalization.

With this in mind, we first tested the chlorination of acetanilide (Table 1), a starting material previously employed to form C−C bonds via C−H functionalization catalyzed by Pd(II) species.[8h−j] We found that the chlorination took place in the presence of a stoichiometric amount of $Pd(OAc)_2$ with 2 equiv of $CuCl_2$ as the chloride source in toluene. Further studies showed that $Pd(OAc)_2$ could be used in catalytic amounts with $Cu(OAc)_2$ as an oxidant, although the catalytic efficiency was relatively low (entry 4). The use of polar solvents, such as DMF, CH_3CN, and dioxane, terminated the chlorination. However, the reaction was very efficient in 1,2-dichloroethane (entry 5). Importantly, *ortho*-chlorinated acetanilide was produced with high regioselectivity during this process, which was predominantly controlled by the acetamino group. It is noteworthy that strong bases/acids and expensive ligands are not required for this practical method. Further studies indicated that (i) both $Cu(OAc)_2$ and $CuCl_2$ are required for the reaction; and (ii) $Pd(OAc)_2$, $Pd(OTFA)_2$, and $Pd(PhCN)_2Cl_2$ are superior to other Pd species as the catalyst perhaps due to their better solubility and enhanced electrophilicity. It should be noted that the chlorination of acetanilide occurred in the Friedel−Crafts manner with *para*-chloroacetanilide as the major product in the presence of palladium catalyst under Sanford's conditions, which may be due to the high electron density of arenes used (entry 16).[9a]

Table 1. Selective Chlorination of Acetanilide **1a**[a]



1a **2a**

entry	Pd (10 mol %)	$Cu(OAc)_2$ (equiv)	MCl_x (equiv)	solvent	**2a** (%)[b]
1[c]	$Pd(OAc)_2$	2.0	$CuCl_2$ (2.0)	dioxane	<5
2[c]	$Pd(OAc)_2$	2.0	$CuCl_2$ (2.0)	DMF	<5
3[c]	$Pd(OAc)_2$	2.0	$CuCl_2$ (2.0)	MeCN	<5
4	$Pd(OAc)_2$	2.0	$CuCl_2$ (2.0)	toluene	27
5	**$Pd(OAc)_2$**	**2.0**	**$CuCl_2$ (2.0)**	**DCE**	**80**
6	$Pd(OAc)_2$	2.0	LiCl (3.0)	DCE	14
7	$Pd(OAc)_2$	2.0	TBAC (3.0)	DCE	<5
8[c]	$Pd(OAc)_2$	2.0		DCE	<5
9	$Pd(OAc)_2$		$CuCl_2$ (4.0)	DCE	36
10	$Pd(OTFA)_2$	2.0	$CuCl_2$ (2.0)	DCE	79
11	$Pd(PPh_3)_2Cl_2$	2.0	$CuCl_2$ (2.0)	DCE	<5
12	$Pd(PhCN)_2Cl_2$	2.0	$CuCl_2$ (2.0)	DCE	77
13	$PdCl_2$	2.0	$CuCl_2$ (2.0)	DCE	56
14	PdI_2	2.0	$CuCl_2$ (2.0)	DCE	<5
15	$Pd(dba)_2$	2.0	$CuCl_2$ (2.0)	DCE	30
16[d]	$Pd(OAc)_2$	2.0	NCS (2.0)	DCE	46

[a] All the reactions were carried out at 90 °C for 48 h under N_2. [b] Isolated yields. [c] GC yields with *n*-decane as an internal standard. [d] *para*/*ortho*-Isomers = 6:4.

The scope of substrates was further explored as shown in Table 2. We found that the pivalyl group could be utilized as a directing group in addition to the acetyl group, albeit with a slight decrease of the chlorination efficiency. However, formyl, benzoyl, tosyl, and trifluoroacetyl did not serve as proper directing groups. It is important to note that 3′-phenylpropionyl group could also be employed as a directing group for this transformation without observable chlorination of the sp^3 C−H groups at the benzylic position and of the sp^2 C−H groups on the phenyl ring at the 3′-position (entry 9, Table 2). Starting from different acetanilides, the C−H chlorination could be broadly applied to yield the chlorinated acetanilides with high regioselectivity. The regioselectivity of chlorination of *meta*-substituted acetanilides was dominated by steric

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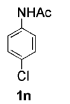
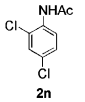
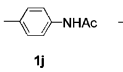
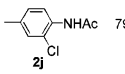
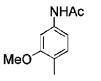
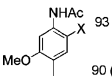
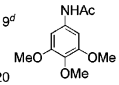
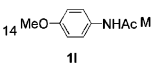
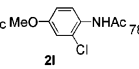
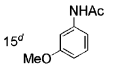
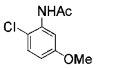
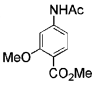
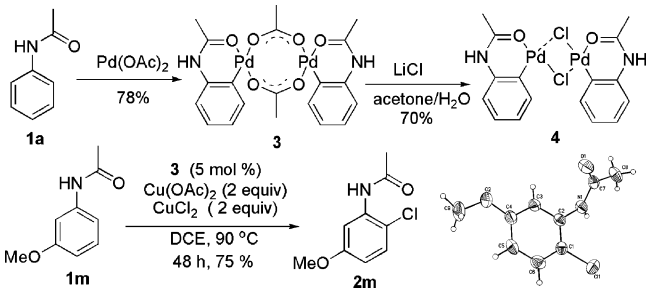
Table 2. Highly Selective Halogenation of Substituted Acetanilides[a]

entry	substrate **1**	product **2**	yield(%)[b]	entry	substrate **1**	product **2**	yield(%)[b]
1	**1a**, R = Ac	**2a**	80	16[e]	 **1n**	 **2n**	27
2[c]	**1b**, R = HCO	**2b**	< 5				
3	**1c**, R = PhCO	**2c**	26				
4[c]	 **1d**, R = Boc	 **2d**	< 5				
5[c]	**1e**, R = Ts	**2e**	< 5				
6[c]	**1f**, R = Me	**2f**	< 5				
7[c]	**1g**, R = CF_3CO	**2g**	<5				
8	**1h**, R = Piv	**2h**	67				
9	**1i**, R = 3'-PhPr	**2i**	55				
11	 **1j**	 **2j**	79	17[d]	 **1o**	 **2o**	93 (X = Cl, **2oa**)
12[d]			96 (X = Cl, **2ka**)	18			90 (X = Br, **2ob**)
13	**1k**	**2k**	86 (X = Br, **2kb**)	19[d]	 **1p**	 **2p**	66 (X = Cl, **2pa**)
14	 **1l**	 **2l**	78	20			91 (X = Br, **2pb**)
15[d]	 **1m**	 **2m**	78	21[e]			30 (X = Cl, **2qa**)
				22	**1q**	**2q**	87 (X = Br, **2qb**)
				23[d]	 **1r**	 **2r**	95

[a] All the reactions were carried out in the presence of 0.5 mmol of **1**, 0.05 mmol of $Pd(OAc)_2$, 1.0 mmol of $Cu(OAc)_2$, and 1.0 mmol of $CuCl_2$ in 4 mL of DCE at 90 °C for 48 h. [b] Isolated yields. [c] GC yields with *n*-decane as internal standard. [d] 5 mol % of $Pd(OAc)_2$ was employed in these reactions. [e] 5 mol % of $Pd(OAc)_2$ or $Pd(OTFA)_2$ was employed in these reactions; however, the yields were not enhanced obviously.

Scheme 1



effects, and only the less hindered *ortho*-chlorinated acetanilides were produced (entries 12, 15, and 17, Table 2). The exact structures of products **2a** and **2m** were further determined by single-crystal X-ray crystallography (S26, Supporting Information). When polysubstituted acetanilides were employed as substrates, the corresponding chlorinated acetanilides were produced in poor to good yields depending on substrates (entries 17, 19, and 21, Table 2). *ortho*-Chlorination of 4-chloro-acetanilide was also tested, and the corresponding product was obtained with the original C−Cl bond untouched (entry 16, Table 2). The relatively low yield of this reaction might be due to the weak electron-withdrawing effect of the chloride substituent. In addition, we found that the method could be applied to construct C−Br groups in relatively electron-rich acetanilides (entries 13, 18, 20, and 22, Table 2). Fused rings, such as **1r**, also serve as good substrates (entry 23, Table 2).

We conducted further studies to probe the mechanism of this C−H functionalization/halogenation reaction. It is well-known that cyclopalladation of acetanilide can be achieved under mild conditions in the presence of $Pd(OAc)_2$.[12] Following the reported procedure, palladacycles **3** and **4** were obtained in 78 and 70% isolated yields, respectively. Complex **3** could catalyze the formation of **2m** from **1m** in 75% isolated yield in the presence of 2.0 equiv of $Cu(OAc)_2$ and $CuCl_2$ (Scheme 1). It indicated that palladacycle **3** could also be an active species during this catalytic cycle. Furthermore, product **2a** could be produced from palladacycles **3** and **4** in poor yields in the presence of oxidative chloride sources, such as $FeCl_3$ or $CuCl_2$. With LiCl as a chloride source, **2a** was also observed from **4** with much lower efficiency. However, combining $PhI(OAc)_2$ with LiCl increased the efficiency of this transformation, and **2a** was obtained from **4** in 40% isolated yield. Obviously, the use of a proper oxidant is important for the efficient formation of C−X in this transformation. Thus, the catalytic pathway may go through a Pd(IV) intermediate C−Pd−X that reductively eliminates to afford the final product. It should be noted that a mechanism involving the common Pd(0)−Pd(II) catalytic cycle could not be completely excluded, in which copper salts may play a role in oxidizing Pd(0) species to Pd(II) to complete the catalytic cycle.

In summary, we have developed a highly regioselective halogenation of acetanilide via palladium-mediated C−H functionalization. Further investigations to understand this catalytic transformation and to evaluate the process with a broader scope of substrates and to construct complex structures are in progress in our lab.

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Supporting Information Available: Experimental details, X-ray structures of **2a**, **2m**, and other spectral data for products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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