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Palladium-Catalyzed C−H Aminations of Anilides with *N*-Fluorobenzenesulfonimide

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Supporting Information

ABSTRACT: The first amide-directed, palladium-catalyzed, intermolecular, highly selective C−H aminations with the non-nitrene-based nitrogen source *N*-fluorobenzenesulfonimide have been developed. This methodology might provide a new pathway for directed metal-catalyzed aromatic C−H amination.

Transition-metal-catalyzed direct carbon−hydrogen bond functionalization appears to be highly appealing, especially if high selectivity for a unique C−H bond can be achieved.[1] Accordingly, directed metalation[1,2] is a powerful approach for the selective functionalization of C−H bonds in complex substrates. However, all previously reported directed palladium-catalyzed C−H functionalizations of arenes provided *o*-C−H functionalized products. Therefore, the development of new methodologies that override the popular *o*-C−H selectivity to realize meta or para aromatic and benzylic C−H functionalization remains a great challenge.[3] Recently, an amide-group-directed, copper-catalyzed *m*-C−H arylation reaction was reported by Gaunt and co-workers.[3a] Yu and co-workers[3b] studied the palladium-catalyzed *m*-C−H olefination of electron-deficient arenes using 2,6-dialkylpyridine ligands. In addition, our group developed an amide-directed, palladium-catalyzed benzylic C−H amination with *N*-fluorobenzenesulfonimide (NFSI).[4] However, to date, directed, metal-catalyzed, highly selective *p*-C−H functionalization has not been realized.

Direct aromatic C−N bond formation is of immense interest because aromatic amines and their derivatives are common in pharmaceuticals, agrochemicals, dyes, herbicides, and conducting polymers.[5] Accordingly, the area of catalytic C−H amination has led to significant results arising both from the discovery of simple, efficient nitrene transfers and the combination of transition-metal-catalyzed C−H activation with C−N bond formation.[6] Although intramolecular oxidative aminations of arenes with amine derivatives had been reported,[7] intermolecular aromatic C−H amination could not be realized unless in situ-generated, highly active nitrene intermediates were employed as nitrogen sources (Scheme 1, amination product **B**).[8] Recently, a remarkably interesting work by Hartwig and co-workers[9] showed that intramolecular C−H amination via a Pd^0/Pd^{II} manifold can be achieved using a non-nitrene-based nitrogen source, oxime ester, which contains a N−O bond as a built-in oxidant. However, the analogous intermolecular C−H amination remains a challenge.

Similar to oxime ester, an active $FPdN(SO_2Ph)_2$ species was suggested to be formed via the oxidative addition of Pd(0) to the N−F bond of NFSI,[10] and therefore, as a starting point we sought to use NFSI as a nitrogen source to perform palladium-catalyzed intermolecular C−H amination reactions. As shown in Scheme 1, we supposed that a novel electrophilic palladation of in situ-generated $FPdN(SO_2Ph)_2$ with arene might form a dearomatized spiro-cyclopalladium intermediate **C**, which could undergo nucleophilic amination followed by hydrogen elimination to provide ortho-amination products **D** (path **I**) or para-amination products **E** (path **II**) depending on the electronic and steric effect of the arene substituents. In the present work, the first amide-directed, palladium-catalyzed, intermolecular, highly selective C−H aminations with the non-nitrene nitrogen source NFSI were efficiently realized.

Initially, we found that *N*-phenylacetamide failed to undergo the amination reaction upon treatment with $Pd(OAc)_2$ (10 mol %) and NFSI at 80 °C, and *N*-phenylacetamide was recovered after 24 h. Starting from *N*-*p*-tolylacetamide, a benzylic amination product was obtained in 71% yield.[4] Surprisingly, when *N*-(4′-methylbiphen-4-yl)acetamide **1a** was employed, *o*-C−H amination product **2a**[11] was obtained in 87% yield (Table 1, entry 1). No reaction occurred in the absence of the palladium catalyst (entry 2). KF was as effective as $NaHCO_3$ (entry 3). With solvents such as acetonitrile, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), no desired **2a** was obtained (entries 7−9). Other solvents, such as nitroethane, dichloromethane, nitrobenzene, and chlorobenzene were not as effective as dichloroethylene (DCE) (entries 10−13). In addition, the use of $Pd(TFA)_2$ and $Pd(dba)_2$ as the catalyst gave **2a** in 84 and 70% yield, respectively (entries 14 and 15). It should be noted that the transformation from **1a** to **2a** represents the first palladium-catalyzed intermolecular aromatic C−H amination with a non-nitrene nitrogen source.

With the optimized conditions in hand (Table 1, entry 1), we turned to an examination of the generality of this C−H amination reaction. As described in Table 2, the tested biphenyl derivatives **1b**−**h** were smoothly reacted with NFSI to afford **2b**−**h** in moderate to good yields. In addition, with various acyl group substrates **1i**−**l**, **2i**−**l** could also be obtained. Moreover, the reaction worked with carbamate, although the yield was only moderate. The 4-OR-substituted substrates **1m**−**q** were also successfully reacted with NFSI to afford **2m**−**q** in good to excellent yields. Starting from 4-amide-substituted substrate **1r**, **2r** could be obtained in 74% yield within 1.5 h. However, starting

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Scheme 1. Directed Palladium-Catalyzed Aromatic C−H Amination

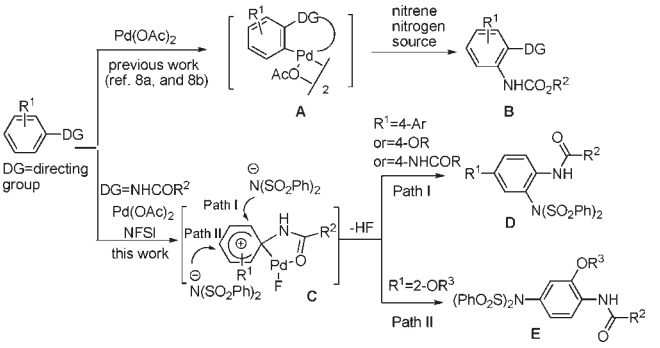
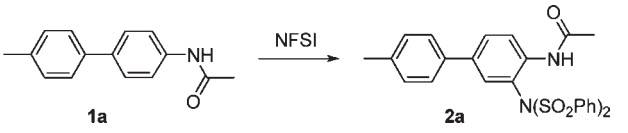


Table 1. C−H Amination of 1a with NFSI[a]



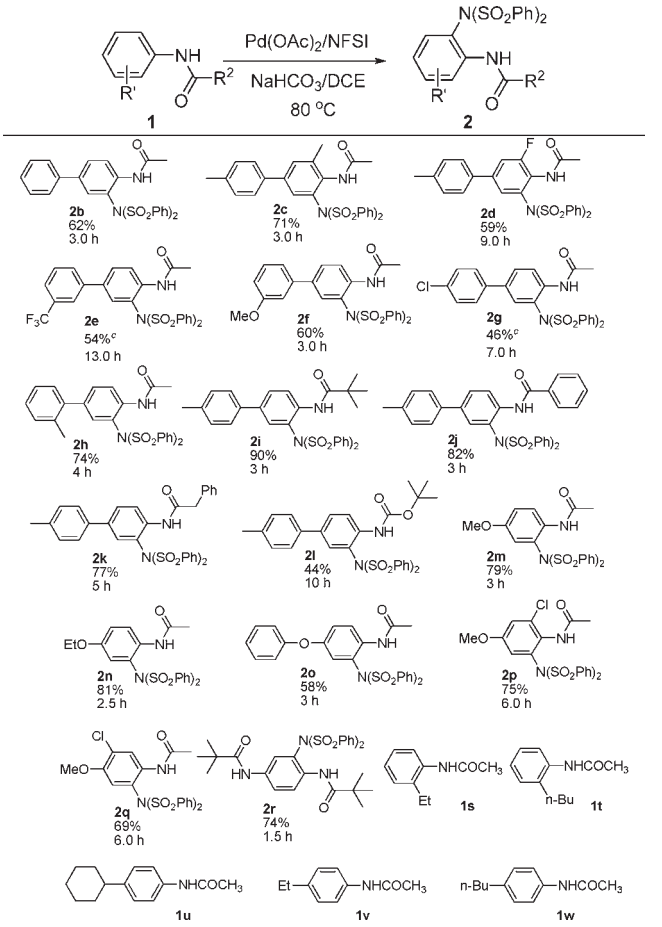
entry	catalyst	solvent	additive (2.0 equiv)	time (h)	yield of **2a** (%)[b]
1	**$Pd(OAc)_2$**	**DCE**	**$NaHCO_3$**	**2.5**	**87**
2	none	DCE	$NaHCO_3$	10.0	0
3	$Pd(OAc)_2$	DCE	KF	2.5	87
4	$Pd(OAc)_2$	DCE	none	4.0	81
5	$Pd(OAc)_2$	DCE	$NaHCO_3$	2.5	88[c]
6	$Pd(OAc)_2$	DCE	$NaHCO_3$	2.5	0[d]
7	$Pd(OAc)_2$	CH_3CN	$NaHCO_3$	10.0	0
8	$Pd(OAc)_2$	DMF	$NaHCO_3$	10.0	0
9	$Pd(OAc)_2$	DMSO	$NaHCO_3$	10.0	0
10	$Pd(OAc)_2$	$C_2H_5NO_2$	$NaHCO_3$	10.0	43[e]
11	$Pd(OAc)_2$	CH_2Cl_2	$NaHCO_3$	10.0	54[f]
12	$Pd(OAc)_2$	$PhNO_2$	$NaHCO_3$	2.5	81
13	$Pd(OAc)_2$	PhCl	$NaHCO_3$	3.0	43
14	$Pd(TFA)_2$	DCE	$NaHCO_3$	3.0	84
15	$Pd(dba)_2$	DCE	$NaHCO_3$	3.0	70

[a] Reactions were carried out with **1a** (0.5 mmol), Pd catalyst (10 mol %), and NFSI (2.0 equiv) at 80 °C. [b] Yield of the isolated product. [c] The reaction was performed at 110 °C. [d] The reaction was performed at 50 °C. [e] With recovery of 29% of **1a**. [f] With recovery of 26% of **1a**.

from 2-alkyl-substituted substrates **1s** and **1t** and 4-cyclohexyl-substituted substrate **1u**, no reactions occurred (Table 2). Starting from 4-alkyl-substituted substrates **1v** and **1w**, unseparated mixtures without main products were obtained (Table 2).

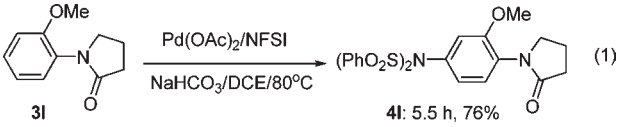
To our surprise, when 2-OMe-substituted substrate **3a** was tested under the optimal conditions (Table 1, entry 1), the para-amination product **4a** was obtained in 92% yield (Table 3). Indeed, the transformation from **3a** to **4a** represents the first directed palladium-catalyzed highly selective para aromatic C−H amination. Gratifyingly, 2-OR-substituted substrates **3b**−**f** provided **4b**−**f** in good to excellent yields (Table 3).[11] In addition, starting from 2-OMe-substituted acetamide and benzamide substrates **3g**−**k**, **4g**−**k** could also be obtained in good to

Table 2. *o*-C−H Amination of 1b−w with NFSI[a,b]



[a] Reactions were carried out with **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NFSI (2.0 equiv), and $NaHCO_3$ (2.0 equiv) in DCE (4 mL) at 80 °C. [b] Yields of isolated products are shown. [c] The reaction was performed at 110 °C.

excellent yields. **4f** and **4g** could be obtained even starting from substrates **3f** and **3g** having substituents at both ortho positions. Notably, starting from cyclic substrate **3l**, para-substituted product **4l** could also be obtained in 76% yield (eq 1):



(1)

However, no reaction occurred from diacetamide substrate **3m** or **3n** or from substrate **3o** with a strongly electron-withdrawing nitro group on the aromatic ring. Also, no reaction occurred starting from substrate **3p**. Surprisingly, instead of the *p*-C−H amination product, the *m*-C−H amination product **5q** was obtained in 77% yield starting from **3q** (eq 2),[12] which might be attributed to the steric effect.

To understand the mechanims of these aromatic C−H amination reactions, ortho-substituted cyclopalladium(II) intermediate **F** was prepared from **1m** (eq 3).[13] No desired **2m** was obtained when the reaction of **F** and NFSI was performed under conditions identical to those described in Table 1, entry 1. In addition, there was no obvious effect on the C−H amination of **1m** by addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),

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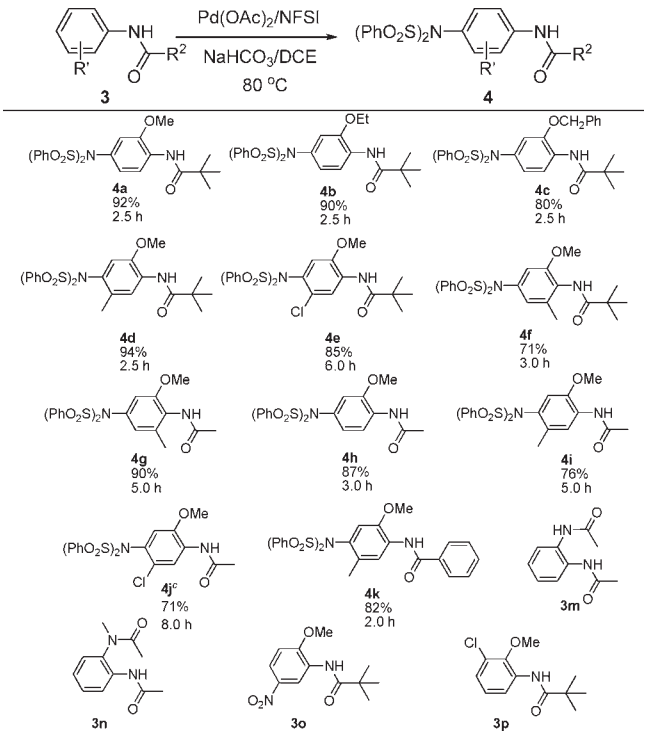
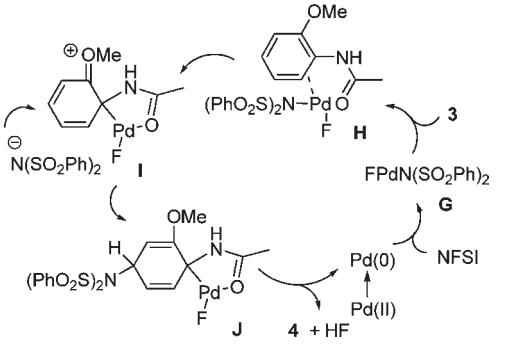
Table 3. *p*-C−H Amination of 3a−k and 3m−p with NFSI[a,b]



[a] Reactions were carried out with **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), NFSI (2.0 equiv), and $NaHCO_3$ (2.0 equiv) in DCE (4 mL) at 80 °C. [b] Yields of isolated products are shown. [c] With recovery of 11% of **3j**.

Scheme 2. Proposed Mechanism for the Formation of 4



which suggests that a radical mechanism was not operating. Also, on the basis of the result that *p*-C−H amination products **4f** and **4g** (Table 3) could also be obtained starting from substrates **3f** and **3g** (without ortho aromatic hydrogens), we propose a possible catalytic cycle for the formation of **4** (Scheme 2). The suggested initial step is the formation of intermediate **G** with a N−Pd(II) bond via the oxidative addition of Pd(0) to the N−F bond of NFSI.[10] The electrophilic palladation of intermediate **H** would provide dearomatized spiro-palladacycle intermediate **I**, which would undergo an amination reaction to give intermediate **J**. The next hydrogen elimination would provide the amination product **4**. Notably, for the spiro-palladacycle intermediate **I** in the above proposed mechanism (Scheme 2), the carbons of the functionalized C−H bond were not directly connected to palladium as in the pattern for the widely accepted cyclopalladium intermediate **A** (Scheme 1). Therefore, this methodology might provide a new pathway for directed metal-catalyzed aromatic C−H functionalization.

In conclusion, an unprecedented amide-directed, palladium-catalyzed, intermolecular, highly selective C−H amination reaction using the non-nitrene-based nitrogen source NFSI that might provide a new pathway for aromatic C−H amination has been developed. Further investigations of the mechanism for the formation of the novel key dearomatized spiro-palladacycle intermediates and the application of this methodology for directed C−H functionalization are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, spectral data for new compounds, and crystallographic data for **2a** and **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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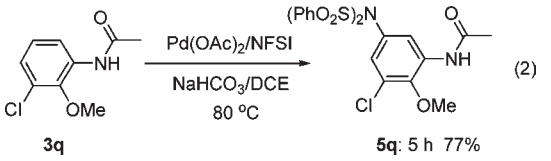
(11) Crystallographic details for **2a** and **4b** are provided in the Supporting Information.

(12) In this reaction, 21% of **3q** was recovered, and even when the reaction time was prolonged to 20 h, the same result was obtained.



3q **5q**: 5 h 77% (2)

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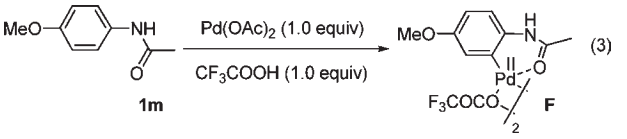

1m **F** (3)

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