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Pd-Catalyzed Intermolecular *ortho*-C−H Amidation of Anilides by *N*-Nosyloxycarbamate

Ka-Ho Ng, Albert S. C. Chan, and Wing-Yiu Yu*

State Key Laboratory for Chirosciences and The Institute of Molecular Technology for Drug Discovery and Synthesis, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

Received July 18, 2010; E-mail: bcwyyu@inet.polyu.edu.hk

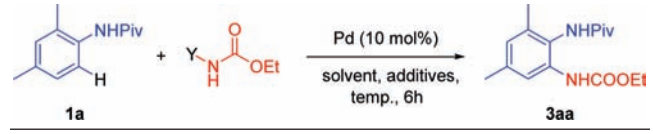
Abstract: A palladium-catalyzed *ortho*-C−H amidation of anilides by *N*-nosyloxycarbamates was developed for the synthesis of 2-aminoanilines. This reaction can be carried out under relatively mild conditions and exhibits excellent regioselectivity and functional group tolerance. The amidation reaction is probably initiated by rate-limiting C−H cyclopalladation (k_H/k_D = 3.7) to form an arylpalladium complex, followed by nitrene functionalization.

2-Aminoanilines are essential precursors for benzimidazoles, 1,5-benzodiazepines, quinoxalines, and benzotriazoles, which are common scaffolds of many pharmaceutical products.[1] Notable examples include omaprazoles (Nexium), olanzapine (Zyprexa), and bromonidine (Alphagan P) with a combined global sales value of over $6.5 billion in 2008.[2] Conventionally, 2-aminoanilines are prepared from 2-fluoronitrobenzenes via a nucleophilic substitution−nitro group reduction sequence;[1c,3] methods for direct amination of substituted aromatics are rare. Recently, Pd-catalyzed aromatic C−H bond functionalizations proved to be an effective strategy for C−C bond formation.[4] With the assistance of a donor group (e.g., pyridyl, imino, amido, carboxylato), highly *ortho*-selective direct arylation and vinylation have been achieved.[5,10b] To devise a straightforward synthesis of 2-aminoanilines, a protocol for catalytic *ortho*-C−H amidation of anilides should be highly desirable because of the improved synthetic efficiency.

Catalytic aromatic C−H amidation has been a subject of extensive investigation.[6] Since the pioneering work by Buchwald and co-workers,[7g] Pd-catalyzed oxidative intramolecular amidation has achieved significant advances.[7] A majority of these transformations may proceed by initial arene C−H palladation, followed by C−N bond formation probably via the Pd^{II}/Pd^{IV} manifold. Recently, Hartwig and co-workers showed that the Pd^0/Pd^{II} catalysis can also effect the intramolecular aromatic C−H amination with oxime esters.[8] Yet, the analogous intermolecular amidation/amination remains a challenge.[9] Motivated by our earlier findings that intermolecular coupling of organopalladium with nitrene would lead to C−N bond formation,[10e] herein we describe a Pd-catalyzed protocol for intermolecular C−H amidation of anilides by *N*-nosyloxycarbamate.

Initially, we found that *N*-pivalanilide **1a** failed to undergo amidation reaction upon treatment with $Pd(OAc)_2$ (10 mol %), ethyl carbamate, and $K_2S_2O_8$ (5 equiv) in DCE at 100 °C, and the starting anilide was completely recovered. While there are many successful examples of *ortho*-C−H cleavage of the anilides by Pd(II) catalysis,[11] we sought to overcome the amidation problem by searching for more effective reagents. After screening several reagents, gratifyingly **3aa** was obtained in 57% yield with ethyl *N*-tosyloxycarbamate and $Pd(OAc)_2$ (10 mol %) in dioxane with AcOH (20 equiv) as additive at 100 °C (entry 1). Previously, Lebel and co-workers reported that *N*-tosyloxycarbamates are effective reagents for the Rh-catalyzed intermolecular nitrene insertion of aliphatic C−H bonds.[12a] As shown in Table 1, the *N*-pivalate (OPiv) and *N*-pentafluorobenzoate (OPFB) derivatives are ineffective reagents for the amidation reaction (entries 2 and 3); the best result (70% yield) was achieved with ethyl *N*-nosyloxycarbamate **2a** (entry 4). Without $Pd(OAc)_2$, no **3aa** was formed under the same experimental conditions (entry 5).

Table 1. Reaction Optimization[a]



1a **3aa**

entry	Pd	Y	additive (20 equiv)	solvent	temp (°C)	yield[b] (%)
1	$Pd(OAc)_2$	OTs	AcOH	dioxane	100	57
2	$Pd(OAc)_2$	OPFB	AcOH	dioxane	100	<5
3	$Pd(OAc)_2$	OPiv	AcOH	dioxane	100	0
4	$Pd(OAc)_2$	ONs	AcOH	dioxane	100	70
5	--	ONs	AcOH	dioxane	100	0
6	$Pd(OAc)_2$	ONs	AcOH	dioxane	80	84
7	$Pd(OAc)_2$	ONs	AcOH	DCE	80	67
8	$Pd(OAc)_2$	ONs	AcOH	toluene	80	58
9	$Pd(OAc)_2$	ONs	AcOH	THF	80	34
10	$Pd(OAc)_2$	ONs	AcOH	DMA	80	12
11	$Pd(OAc)_2$	ONs	AcOH	DMF	80	28
12	$Pd(OAc)_2$	ONs	AcOH	CH_3CN	80	0
13	$Pd(OAc)_2$	ONs	--	dioxane	80	76
14	$Pd(TFA)_2$	ONs	--	dioxane	80	78
15	$PdCl_2(MeCN)_2$	ONs	--	dioxane	80	56
16	$Pd(OPiv)_2$	ONs	--	dioxane	80	86
17	$Pd(OTs)_2(MeCN)_2$	ONs	--	dioxane	80	86
18[d]	$Pd(OTs)_2(MeCN)_2$	ONs	--	dioxane	80	90[c]

[a] Conditions: 2′,4′-dimethylpivalanilide (0.2 mmol), *N*-oxycarbamate (1 equiv), Pd (10 mol %), solvent (2 mL), 6 h. [b] Yields determined by ^1H NMR. [c] Isolated yield = 84%. [d] 1.2 equiv of ethyl *N*-nosyloxycarbamate was used.

Employing $Pd(OAc)_2$ (10 mol %) and **2a** (1 equiv), changing the solvent systems (e.g., DCE, toluene, THF, DMA, MeCN) did not lead to more favorable outcomes (entries 7−12). Yet, the amidation reaction was mostly suppressed in the MeCN/AcOH system (entry 12). Interestingly, the $Pd(OAc)_2$-catalyzed amidation was found to be equally effective at 80 °C in dioxane without AcOH, and **3aa** was obtained in 76% yield (entry 13). Inspired by the recent works of Yu[11a] and Llyod-Jones[11c] on the C−H carbonylation of anilides and *N*-phenylureas, we found that treating **1a** with $Pd(OTs)_2(MeCN)_2$ (10 mol %) and **2a** (1.2 equiv) in dioxane at 80 °C for 6 h would furnish 90% of **3aa** (entry 18).

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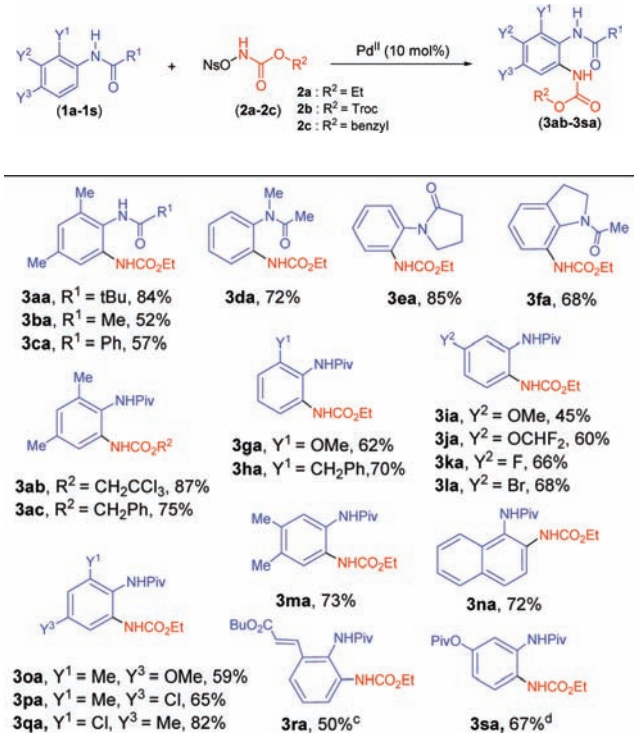
With the optimized conditions in hand, we turned to examine the scope and generality of the Pd-catalyzed amidation reaction (Table 2). Acetanilides and benzamides can be converted to their respective amides **3ba** (52%) and **3ca** (57%); however, pivalanilides apparently produced better product yields (**3aa**: 84% yield) presumably due to its favorable conformational properties. Parallel with this finding, substrates with a tertiary amide group would undergo facile *ortho*-C−H amidation in 68−85% yields for **3da**−**3fa**. We considered that this C−H amidation reaction would become synthetically useful if amide groups of orthogonal reactivity can be introduced to the anilides. Thus, further transformations of the anilide scaffolds can be pursued by selective manipulation of the nitrogen protecting groups.[13] In this work, we studied the C−H amidation reaction with 2,2,2-trichloroethyl (Troc) *N*-nosyloxycarbamate **2b** and benzyl *N*-nosyloxycarbamate **2c** as reagents. When **1a** was treated with **2b**/**2c** (1.2 equiv) and $Pd(OTs)_2(MeCN)_2$ (10 mol %) in dioxane at 80 °C for 6 h, the corresponding amides **3ab** and **3ac** were obtained in 87% and 75% yield, respectively. According to the literature, the *N*-Troc and *N*-benzyl groups can be selectively removed by Zn reduction and hydrogenolysis without affecting the *N*-pivaloyl group.[13]

Table 2. Substrate Scope Studies[a,b]

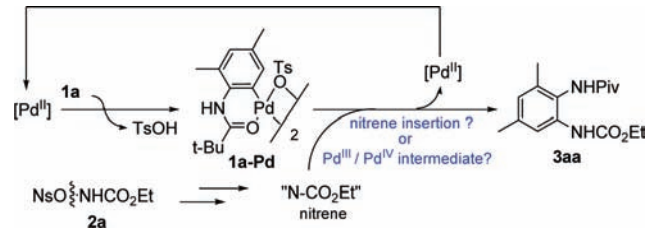


[a] Conditions: anilide (0.2 mmol), *N*-nosyloxycarbamate (1.2 equiv), $[Pd(OTs)_2(MeCN)_2]$ (10 mol %), 1,4-dioxane (2 mL), 80 °C, 6 h. [b] Isolated yields. [c] Batchwise addition of **2a** (2 × 1.2 equiv/6 h),12 h; 40% starting anilide was recovered. [d] Reaction run for 12 h.

As shown in Table 2, electron-donating (Me, benzyl, OMe) and -withdrawing (F, Cl, Br) groups are tolerated under the amidation conditions. Interestingly, anilides bearing a vinyl substituent can be transformed to the expected amide **3ra** in 50% yield. Note that 40% of the starting anilide was recovered after the reaction; this reaction exhibits a mass balance of ca. 85%. Liu and Xu reported earlier that *O*-pivaloyl esters would undergo Pd-catalyzed *ortho*-C−H arylations.[14] In this work, treating the pivalanilide containing a pivaloyl ester moiety with **2a** afforded **3sa** exclusively in 67% yield, suggesting that the amide group is a stronger directing group than the ester group. In all cases, only monoamidation products were obtained exclusively under our experimental conditions.[15]

It is plausible that the amidation reaction would be initiated by cyclopalladation of **1a** (Scheme 1). By means of competitive experiments with acetanilide and acetanilide-d_5 as substrates, a primary kinetic isotope effect (k_H/k_D) = 3.7 was obtained; this value is compatible with the rate-determining C−H activation step.[16] Consistent with this notion, the cyclopalladated complex **1a-Pd**[17] is an effective catalyst for the amidation reaction. It is noteworthy that the stoichiometric reaction of **1a-Pd** with **2a** alone would afford **3aa** in only 45% yield. However, when **1a-Pd** was treated with **2a** (2 equiv) in the presence of free **1a** (2 equiv), **3aa** was formed in 70% yield.[18] While the role of the free **1a** is unclear, however, the added anilide may be needed to stabilize some reactive Pd species after the C−N bond forming step.

Scheme 1. Proposed Mechanism



To probe the nature of the reactive nitrogen species,[19] we performed the stoichiometric reaction in the presence of inorganic bases (e.g., K_2CO_3). It is known that treatment of arylsulfonyloxycarbamates with inorganic bases would spontaneously produce reactive nitrene species.[20] As expected, treatment of **1a-Pd** (1 equiv) and **1a** (2 equiv) with **2a** (2 equiv) in the presence of K_2CO_3 (2 equiv) in dioxane at 80 °C, furnished **3aa** in 74% yield. Based on this finding, it is possible that the *N*-nosyloxycarbamate produced nitrene, which would then undergo formal nitrene insertion to the cyclopalladated complex via a metal-nitrene pathway.[21] Alternatively, the C−N bond formation may involve the formation of a Pd(IV)[22b,c] or a dimeric Pd(III) complex,[18a,22a] and its subsequent reductive elimination would afford the product amide. A detailed mechanistic investigation is underway.

In summary, we developed an intermolecular *ortho*-C−H amidation of anilides using *N*-nosyloxycarbamate and have demonstrated its high functional group tolerance, regioselectivity, and scope under relatively mild conditions. In view of the synthetic utility of 2-aminoanilines, this reaction would be of broad interest to synthetic chemistry.

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Supporting Information Available: Experimental procedures, characterization data, and experimental data for reaction optimization. This material is available free of charge via the Internet at http://pubs.acs.org.

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