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Palladium-catalyzed intermolecular C–H amidation of indoles with sulfonyl azides

Ziwei Hu, Shuang Luo* & Qiang Zhu*

State Key Laboratory of Respiratory Disease; Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510530, China

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A new kind of intermolecular indole C–H amidation reaction catalyzed by the most frequently used palladium catalyst has been developed. Sulfonyl azide was employed as an innovative nitrogen source and environmentally benign nitrogen was produced as the only byproduct.

C–H amidation, indole, palladium, sulfonyl azide

1 Introduction

Methods of C–N bond formation have attracted particular attention of organic chemists due to the fact that nitrogen-containing molecules are ubiquitous in pharmaceuticals, agricultural chemicals, natural products and synthetic materials [1]. Among them, Ullmann reaction [2] and Buchwald-Hartwig amination [3] have been extensively investigated as efficient strategies using readily available pre-functionalized haloarenes. In recent years, transition metal-catalyzed direct amination of C–H bonds has emerged as a powerful tool without the need for pre-functionalized arenes [4,5]. However, this process usually requires external oxidants to complete the catalytic cycles [6]. Alternatively, electrophilic aminating agents [7], such as halogenated amines, have been successfully employed in C–H amination of arenes. However, generation of stoichiometric halogenated waste cannot be avoided. Recently, Chang's group [8] has demonstrated that sulfonyl azides could be used as novel amidation agents with environment benign N_2 as the sole byproduct in the absence of additional oxidants. After that, a surge of sulfonyl azide participated C–H amidation reactions have appeared in literatures [9,10]. Typically, these reactions are catalyzed by Rh, Ru and Ir using various directing groups. Palladium, the most frequently used transition-metal in C–H activation, has been absent from the feast.

Indole and its derivatives are always hot topics because of their wide existence in biologically relevant compounds [11]. As a result, much effort has been made to synthesis of indole through either construction or decoration of the indole cores [12]. The electron-rich character of indoles allows them to undertake direct C–H bond functionalization resulting in the formation of carbon-carbon or carbon-heteroatom bonds at C2 or C3 position. Previously, we have reported palladium-catalyzed C–H functionalization of indoles followed by isocyanide insertion [13]. Considering the electronic similarity between carbene and nitrene, we envisioned that C–H amidation of indoles with sulfonyl azide might take place using palladium catalyst (Scheme 1) [14].

2 Results and discussion

To test our hypothesis, we initiated the study by investigating the reaction of 2-phenylindole **1a** with *p*-methylbenzen-

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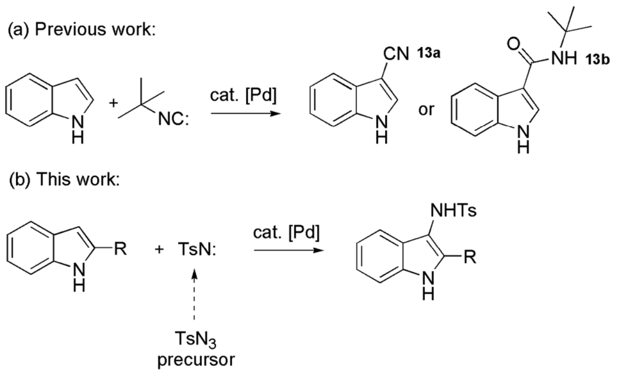
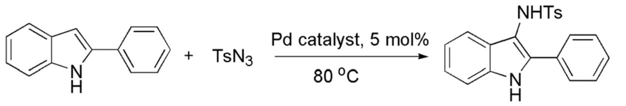
*Corresponding authors (email: luo_shuang@gibh.ac.cn; zhu_qiang@gibh.ac.cn) esulfonyl azide (TsN_3) **2a** in the presence of $Pd(TFA)_2$ in THF at 80 °C and found no desired product appeared (Entry1, Table 1). Intriguingly, the target product **3a** was generated in 32% yield by addition of PPh_3 (Entry 2). Screening of solvents indicated that non-polar solvents were more suitable than polar ones and *m*-xylene was the optimal solvent of choice (Entries 3–8). Other tested palladium salts including $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(acac)_2$ were obviously less effective than $Pd(TFA)_2$ (Entries 9–12). Control experiments showed the palladium catalyst was required for the transformation (Entry 13). Only trace or even no product was detected by replacing PPh_3 with other phosphine or nitrogen ligands (Entries 14–19). Both acid and base additives inhibited the reaction apparently (Entries 20, 21). To our delight, the addition of 10 equivalent of water increased the yield to 95% (Entry 22). In particular, argon atmosphere didn't change the yield obviously, which suggested that no external oxidant was involved.



Scheme 1 Reaction between indole and carbene or nitrene.

Table 1 Optimization of the reaction conditions a)



1a 2a 3a

Entry	Pd	Ligand	Additive	Solvent	Yield (%) b)
1	$Pd(TFA)_2$	–	–	THF	nd
2	$Pd(TFA)_2$	PPh_3	–	THF	32
3	$Pd(TFA)_2$	PPh_3	–	Toluene	71
4	$Pd(TFA)_2$	PPh_3	–	DCE	68
5	$Pd(TFA)_2$	PPh_3	–	CH_3CN	trace
6	$Pd(TFA)_2$	PPh_3	–	DMF	trace
7	$Pd(TFA)_2$	PPh_3	–	*m*-xylene	76
8	$Pd(TFA)_2$	PPh_3	–	mesitylene	73
9	$PdCl_2$	PPh_3	–	*m*-xylene	nd
10	$Pd(OAc)_2$	PPh_3	–	*m*-xylene	14
11	$Pd(PPh_3)_2Cl_2$	PPh_3	–	*m*-xylene	trace
12	$Pd(acac)_2$	PPh_3	–	*m*-xylene	14
13	–	PPh_3	–	*m*-xylene	nd
14	$Pd(TFA)_2$	PCy_3	–	*m*-xylene	nd
15	$Pd(TFA)_2$	dppm	–	*m*-xylene	nd
16	$Pd(TFA)_2$	dppf	–	*m*-xylene	nd
17 c)	$Pd(TFA)_2$	TMEDA	–	*m*-xylene	nd
18 c)	$Pd(TFA)_2$	Phen	–	*m*-xylene	nd
19 c)	$Pd(TFA)_2$	*L*-proline	–	*m*-xylene	nd
20 d)	$Pd(TFA)_2$	PPh_3	PivOH	*m*-xylene	53
21 e)	$Pd(TFA)_2$	PPh_3	Na_2CO_3	*m*-xylene	24
22 f)	$Pd(TFA)_2$	PPh_3	H_2O	*m*-xylene	95
23 f, g)	$Pd(TFA)_2$	PPh_3	H_2O	*m*-xylene	95

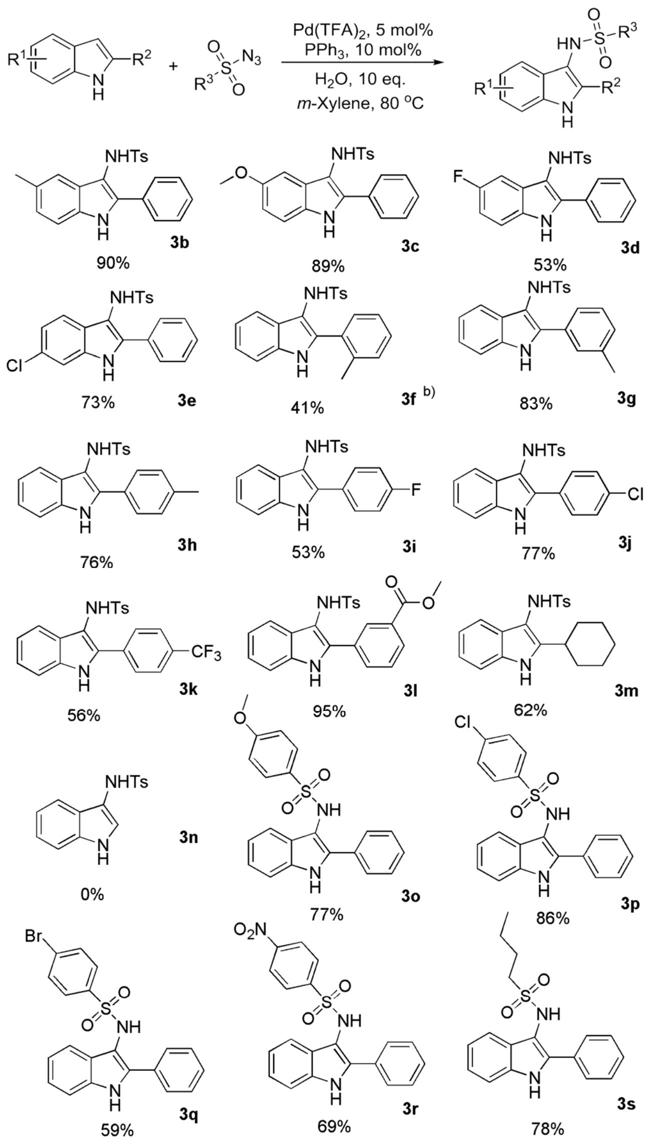
a) All reactions were carried out at 0.2 mmol scale, with Pd catalyst (5 mol%), ligand (10 mol%), in solvent (1 mL), at 80 °C, in air; b) isolated yield; c) 5 mol% ligand was used; d) 1.0 equiv. of PivOH was added; e) 1.0 equiv. of Na_2CO_3 was added; f) 10 equiv. of H_2O was added; g) in argon atmosphere.

With the optimized conditions in hand, we next explored the generality of this transformation using a variety of indoles with **2a** (Scheme 2). Both electron-donating (CH_3, OMe) (**3b**, **3c**) and withdrawing (F, Cl) (**3d**, **3e**) substituents on the indole core were compatible with the newly established protocol. Indoles bearing different tolyl groups (**3g**, **3h**) at C2 position were amidated efficiently. The yield of **3f** was relatively low probably due to steric hindrance. Substrates with electron-withdrawing *para*-fluorophenyl group (**3i**), *para*-chlorophenyl group (**3j**), *para*-trifluoromethylphenyl (**3k**) and *meta*-methoxylcarbonylphenyl group (**3l**) at C2 position of indole afforded the corresponding products in good to excellent yields. Satisfyingly, we found that the amidation reaction of C2 cyclohexyl substituted substrate (**3m**) proceeded smoothly as well. However, C2 unsubstituted indole (**3n**) did not react under the developed conditions and the starting material was completely recovered.

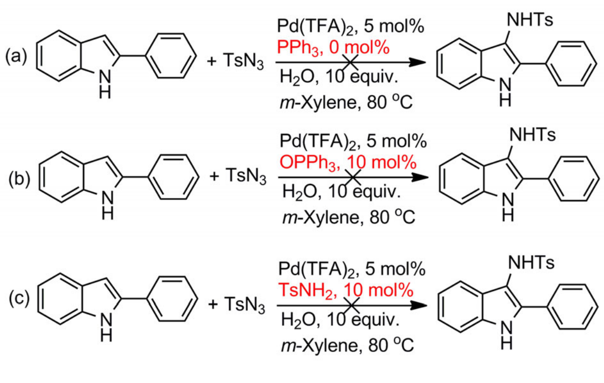
The scope of different sulfonyl azides with **1a** was investigated subsequently. Electron-donating and electron-withdrawing substituted arylsulfonyl azides reacted efficiently, generating the corresponding products (**3o**–**3s**) in good yields. To our delight, aliphatic sulfonyl azide also gave good yield of the desired product (**3t**).

In order to evaluate the function of PPh_3, we conducted the reaction under the identical conditions by omitting PPh_3 and found no product was detected (Scheme 3(a)). As the Staudinger reaction might take place between TsN_3 and PPh_3, reactions were operated by replacing PPh_3 with $OPPh_3$ (Scheme 3(b)) and $TsNH_2$ (Scheme 3(c)) respectively. No desired product was detected in both cases. Although the true function was not clear at the present stage, these results indicated that PPh_3 played a requisite role in the transformation.

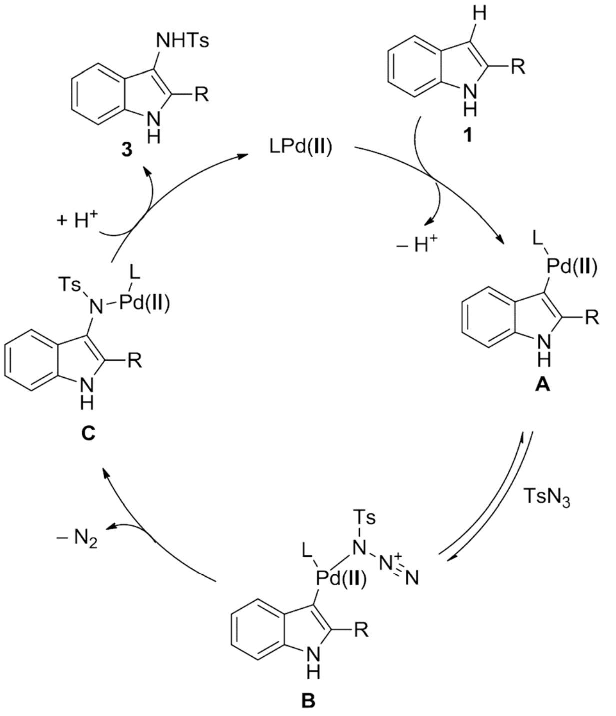
A possible mechanism was proposed on the basis of these experimental results and relative literatures (Scheme 4). Ligand chelated Pd(II) species facilitates C–H bond activation to give intermediate **A**. Coordination of azide to **A** leads to **B**, followed by the subsequent insertion of a sulfonamido moiety into the C–Pd bond through concerted migratory insertion driven by releasing of N_2 to genernate intermediate **C**. Stepwise intrenoid path involving Pd(IV) species is also possible. Protonolysis of **C** delivers the final product **3** and dissociates Pd(II) for the next catalytic cycle.



Scheme 2 Scope of the catalytic intermolecular C–H amidation. Conditions: **1** (0.2 mmol), sulfonyl azide **2** (0.3 mmol), $Pd(TFA)_2$ (5 mol%), PPh_3 (10 mol%), H_2O (10 equiv.), in *m*-Xylene (1 mL), 80 °C, 5 h, isolated yield of **3**; a) 8 h.



Scheme 3 Evaluation of the function played by PPh_3.



Scheme 4 Proposed reaction mechanism of the intermolecular indole C–H amidation reaction.

3 Conclusions

In summary, we have developed a new kind of intermolecular indole C–H amidation reaction. The reaction, which is catalyzed by the most frequently used palladium catalyst, is different from the published reactions [14] using sulfonyl azides as amidating reagents. Sulfonyl azide was employed as an innovative nitrogen source and environmentally benign nitrogen was produced as the only byproduct.

Supporting information

The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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