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Palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides followed by isocyanide insertion: synthesis of 2-substituted 1*H*-indole-3-carboxamides†

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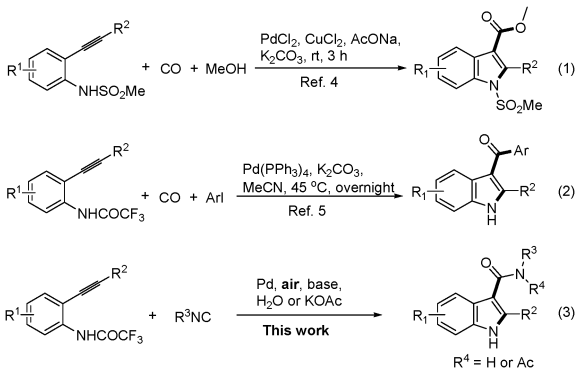
A base-controlled synthesis of 2-substituted secondary and tertiary 1*H*-indole-3-carboxamides through $PdCl_2$-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides followed by isocyanide insertion has been developed. The reaction proceeds smoothly at ambient temperature using O_2 in air as the sole oxidant of the palladium catalyst.

The indole nucleus is present in a wide range of natural products and synthetic pharmaceutical agents with varied bioactivities.[1] Consequently, substantial synthetic methods have been developed for the preparation of indole derivatives since more than a century ago. Among them, palladium-catalyzed cyclization of *o*-alkynylanilides followed by trapping of the resulting σ-indolylpalladium intermediate with various nucleophiles has emerged as a powerful and versatile strategy toward 2,3-disubstituted indoles.[2,3] When the reaction is performed in a carbon monoxide atmosphere, carbonylation of the indole scaffold at the C3 position will take place through an σ-indolylpalladium intermediate upon CO insertion.[4] For example, 2-substitued methyl indole-3-carboxylates were formed *via* $PdCl_2$-catalyzed cyclization of *o*-alkynylmesylanilides in the presence of CO in methanol by using $CuCl_2$ as a stoichiometric oxidant (eqn (1), Scheme 1).[5] A similar three-component synthesis of 2-substituted 3-acylindoles was developed starting from *o*-alkynyltrifluoroacetanilides, aryl iodides and carbon monoxide (eqn (2), Scheme 1).[6]

Isocyanides have been recognized as versatile building blocks in Lewis or Brønsted acid-promoted reactions, including Passerini and Ugi mutlicomponent reactions, complex amide synthesis and others.[7] However, their application in transition metal-catalyzed imination,[8] carboxyamidation[9] and amidination[10] reactions, acting as isoelectronic equivalents of CO, is relatively undervalued. It is anticipated that when isocyanide is present instead of CO, isocyanide will insert into the 3-indolylpalladium intermediate following palladium-catalyzed cyclization of *o*-alkynylanilide. The resulting 3-indoimidoylpalladium intermediate can be trapped by water and acetate to produce 2-substituted secondary and tertiary 1*H*-indole-3-carboxamides upon tautomerization, respectively (eqn (3), Scheme 1). Very recently, we have developed a novel method for the preparation of 2-unsubstituted 3-carboxamidated indoles through Pd-catalyzed sequential C–H activation and isocyanide insertion of indoles.[11] Herein, we would like to report an unprecedented and general approach to 2-substituted secondary and tertiary 1*H*-indole-3-carboxamides through Pd-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides followed by isocyanide insertion. The current method not only widens the application of isocyanides in palladium-catalyzed reactions, but also provides an efficient method for the synthesis of 2-substituted indole-3-carboxamides,[12] which exist in many biologically active molecules.[13]



Scheme 1 Synthesis of C3 carbonylated indoles by palladium-catalyzed cyclization of *o*-alkynylanilides.

To test the hypothesis, we commenced the investigation in DMSO with *o*-(phenylethynyl)trifluoroacetanilide **1a** and *tert*-butylisocyanide **2a** (1.5 equiv.) as model substrates catalyzed by $PdCl_2$ (5 mol%) in the presence of K_2CO_3 (1.0 equiv.) in a balloon pressure of O_2. The expected product, *N*-*tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide **3aa**, was obtained successfully in 68% yield at ambient temperature (entry 1, Table 1). It was notable that the trifluoroacetyl protecting group was removed simultaneously during the reaction. The carbonyl oxygen was believed to originate from moisture in the reaction system, which was confirmed by adding 10 equivalents of H_2O^{18} to the reaction (see ESI for details†). Other palladium sources,

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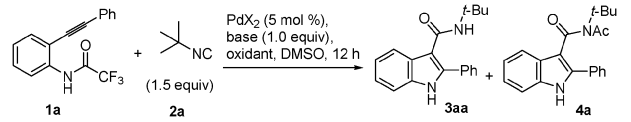
Table 1 Optimization of the reaction conditions[a]



Entry	Pd source	Base	Oxidant	Temp./°C	Yield[b] (%) 3aa	4a
1	$PdCl_2$	K_2CO_3	O_2	rt	68	—
2	$Pd(OAc)_2$	K_2CO_3	O_2	60	58	—
3	$Pd(TFA)_2$	K_2CO_3	O_2	60	51	—
4	$Pd(PPh_3)_2Cl_2$	K_2CO_3	O_2	60	54	—
5	$Pd(acac)_2$	K_2CO_3	O_2	60	75	—
6	—	K_2CO_3	O_2	rt	N.R.[e]	—
7	$PdCl_2$	K_2CO_3	Air	rt	67	—
8[c]	$PdCl_2$	K_2CO_3	—	rt	trace	—
9	$PdCl_2$	Na_2CO_3	Air	rt	**92**	—
10	$PdCl_2$	Cs_2CO_3	Air	rt	61	—
11	$PdCl_2$	K_3PO_4	Air	rt	48	—
12	$PdCl_2$	KOAc	Air	rt	—	75
13[d]	$PdCl_2$	KOAc	Air	rt	—	**86**
14	$PdCl_2$	—	Air	rt	N.R.[e]	—

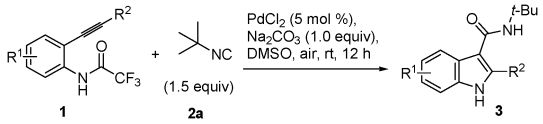
[a] All the reactions were carried out at 0.2 mmol scale of **1a**, *tert*-butylisocyanide **2a** (0.3 mmol), palladium catalyst (5 mol%), base (1.0 equiv.) in DMSO (1 mL), in O_2 (1 atm) or air for 12 h. [b] Yields of isolated **3aa** and **4a**. [c] In Ar. [d] 1.2 equiv. of KOAc. [e] N.R. = no reaction.

including $Pd(OAc)_2$, $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(acac)_2$, were also effective at elevated temperature (entries 2–5). A control experiment in the absence of a palladium catalyst resulted in no product formation at all (entry 6). The reaction proceeded equally well in air, but it was completely shut down in an argon atmosphere. To our delight, the yield of **3aa** was improved significantly to 92% by simply changing the base to Na_2CO_3 (entry 9). Screening of other bases led to an interesting finding that *N*-acetyl-*N*-*tert*-butyl-2-phenyl-1*H*-indole-3-carboxamide **4a** was isolated as a sole product in 75% yield when KOAc was employed (entries 10–12). The yield of **4a** was improved further to 86% with 1.2 equiv. of KOAc. Neither **3aa** nor **4a** were detected when a base additive was absent (entry 14).

Under the optimized conditions, the generality of the reaction for different *o*-alkynyltrifluoroacetanilides was investigated first (Table 2). Gratifyingly, substrates with electron-donating (CH_3) or withdrawing (CF_3, F, Cl, Br) substituents on the aniline ring produced the corresponding products in good to excellent yields (entries 1–6). A variety of functional groups on the arylalkynyl moiety, including OMe, NHAc, $COCH_3$, COOMe, Cl and Br, were compatible with the reaction conditions (entries 7–15). These functionalities provide handles for further elaboration of the products. In general, electron-donating substituents on the aryl ring are more beneficial to the reaction than electron-withdrawing ones, which need higher reaction temperatures to drive the reaction to completion. This tendency indicates that the electron density on the acetylene moiety is essential for complexation with the palladium catalyst. In addition, 2-heteroaromatic and 2-alkyl substituted *N*-1*H*-indole-3-carboxamides **3qa–3sa** were also obtained by following this methodology.

Isocyanides other than *tert*-butylisocyanide **2a**, such as *n*-butyl, isopropyl, cyclohexyl and 2,6-dimethylphenyl isocyanides,

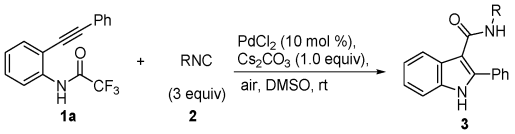
Table 2 The scope of substrate **1**[a]



Entry	Substrate **1**	Product **3**	Time/h	Yield (%)
1	**1b**, R^1 = 4-Me, R^2 = Ph	**3ba**	12	88
2	**1c**, R^1 = 4-CF_3, R^2 = Ph	**3ca**	12	77
3	**1d**, R^1 = 4-F, R^2 = Ph	**3da**	12	88
4	**1e**, R^1 = 4-Cl, R^2 = Ph	**3ea**	12	85
5	**1f**, R^1 = 4-Br, R^2 = Ph	**3fa**	12	84
6	**1g**, R^1 = 4,6-diMe, R^2 = Ph	**3ga**	48	69
7	**1h**, R^1 = H, R^2 = 4-$CH_3C_6H_4$	**3ha**	12	94
8	**1i**, R^1 = H, R^2 = 4-$MeOC_6H_4$	**3ia**	12	91
9	**1j**, R^1 = H, R^2 = 4-$AcNHC_6H_4$	**3ja**	12	82
10	**1k**, R^1 = H, R^2 = 4-AcC_6H_4	**3ka**	12	76[b]
11	**1l**, R^1 = H, R^2 = 4-$MeO_2CC_6H_4$	**3la**	6	68[b]
12	**1m**, R^1 = H, R^2 = 4-ClC_6H_4	**3ma**	12	76
13	**1n**, R^1 = H, R^2 = 4-BrC_6H_4	**3na**	16	86
14	**1o**, R^1 = H, R^2 = 2-ClC_6H_4	**3oa**	12	79
15	**1p**, R^1 = H, R^2 = 3-ClC_6H_4	**3pa**	16	76
16	**1q**, R^1 = H, R^2 = 2-thienyl	**3qa**	12	75
17	**1r**, R^1 = H, R^2 = *n*-butyl	**3ra**	12	88
18	**1s**, R^1 = H, R^2 = cyclohexyl	**3sa**	24	87

[a] Conditions: **1** (0.2 mmol), *tert*-butylisonitrile **2a** (0.3 mmol), $PdCl_2$ (5 mol%), Na_2CO_3 (1.0 equiv.), in DMSO (1 mL) under air, rt, yield of isolated **3**. [b] Reaction conducted at 50 °C.

Table 3 The scope of substrate **2**[a]



Entry	Substrate **2**	Product **3**	Time/h	Yield (%)
1	**2b**, R = n-butyl	**3ab**	24	51
2	**2c**, R = isopropyl	**3ac**	24	63
3	**2d**, R = cyclohexyl	**3ad**	30	61
4	**2e**, R = 2,6-diMePh	**3ae**	12	57[b]
5	**2f**, R = adamantyl	**3af**	12	98[c,d]

[a] Conditions: **1a** (0.2 mmol), isocyanide **2** (0.6 mmol), $PdCl_2$ (10 mol%), Cs_2CO_3 (1.0 equiv.), in DMSO (1 mL) under air, rt, yield of isolated **3**. [b] 50 °C. [c] $PdCl_2$ (5 mol%), isocyanide **2f** (1.5 equiv.) was applied. [d] Na_2CO_3 (1.0 equiv.) was employed instead of Cs_2CO_3.

were also applied in this process under modified conditions (Table 3). However, the corresponding *N*-1*H*-indole-3-carboxamides **3ab–3ae** were formed in lower yields than when employing *tert*-butylisocyanide as a substrate. It is notable that sterically hindered 1-adamantylisocyanide was a feasible coupling partner, leading to the corresponding amide **3ae** almost quantitatively.

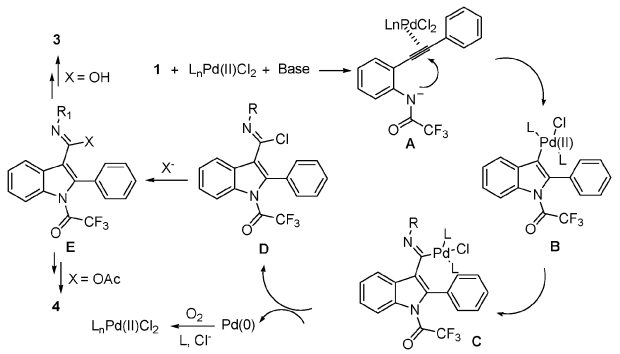
Finally, some *N*-acetyl-*N*-*tert*-butyl-2-aryl-1*H*-indole-3-carboxamides were prepared by applying KOAc as a base (Table 4). No significant electronic effect on the aniline ring was observed (**4b** *vs.* **4c**), while an electron-donating OMe (**4e**) on another aryl ring favored the reaction much more than electron-withdrawing COOMe (**4f**) and Br (**4g**).

A plausible mechanism involved in the present process is illustrated in Scheme 2. Initial coordination of isocyanide

Table 4 Synthesis of tertiary 1*H*-indole-3-carboxamides **4**[a]

Entry	Substrate **1**	Product **4**	Time/h	Yield (%)
1	**1b**, R^1 = 4-Me, R^2 = H	**4b**	12	84
2	**1c**, R^1 = 4-CF_3, R^2 = H	**4c**	12	81
3	**1f**, R^1 = 4-Br, R^2 = H	**4d**	18	73
4	**1i**, R^1 = H, R^2 = OMe	**4e**	12	93
5	**1l**, R^1 = H, R^2 = COOMe	**4f**	16	56[b]
6	**1n**, R^1 = H, R^2 = Br	**4g**	18	55

[a] Conditions: **1** (0.2 mmol), *tert*-butylisocyanide **2a** (0.3 mmol), $PdCl_2$ (5 mol%), KOAc (1.2 equiv.), DMSO (1 mL), air, rt, yield of isolated **4**. [b] Reaction conducted at 50 °C.



Scheme 2 Proposed reaction mechanism.

ligated Pd(II) with carbon–carbon triple bond triggers intramolecular nucleophilic attack of the nitrogen anion across the triple bond. Isocyanide insertion to the resulting σ-indolylpalladium intermediate **B** yields the imidoylpalladium intermediate **C** followed by reductive elimination. The unstable imidoylchloride intermediate **D** undergoes nucleophilic substitution by water or acetate to give corresponding final products **3** or **4** *via* intermediate **E** upon tautomerization. Oxidation of concurrently formed Pd(0) by air regenrates the active Pd(II) species. An alternative direct ligand exchange of Cl with water or acetate in the intermediate **C** is also possible.

In summary, we have developed an efficient method for the construction of 2-substituted 1*H*-indole-3-carboxamides *via* $PdCl_2$-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides followed by isocyanide insertion. A variety of 2-substituted secondary and tertiary 1*H*-indole-3-carboxamides are formed selectively by the choice of bases. The reaction proceeds smoothly at ambient temperature using dioxygen in air as the sole oxidant for the palladium catalyst.

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