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Aminopalladation-Triggered Carbene Insertion Reaction: Synthesis of 2-(1*H*-Indol-3-yl)acetates

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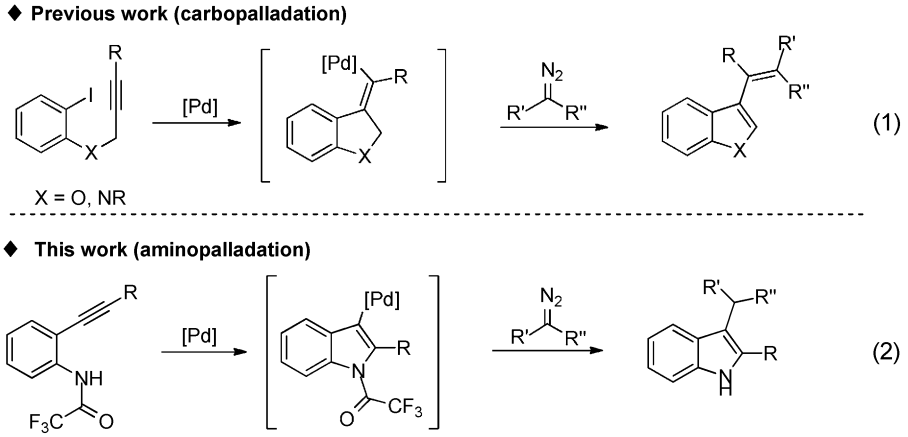
Abstract: The first example of a nucleopalladation-triggered carbene insertion reaction for the synthesis of C-3 alkylated indole derivatives from *ortho*-alkynyltrifluoroacetanilides and α-diazoacetates is presented; it involves a palladium catalyst and a weak base in the open air. Yields range from 49–88% with excellent functional group tolerance. The reaction proceeds through intramolecular aminopalladation of alkynes followed by carbene insertion. Migratory insertion of the carbene into the σ-indolylpalladium intermediate was favored over N–H insertion.

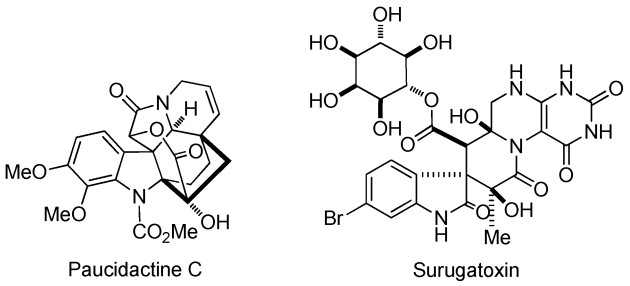
Keywords: acetates; carbene insertion; indoles; nucleopalladation; palladium

To some extent, the versatility of palladium chemistry relies on the fact that unsaturated small molecules, such as alkenes,[1] alkynes,[2] CO,[3] and isocyanides[4] can insert into X–Pd bonds (X = C or heteroatom), generating X–C and C–Pd bonds for further transformations. During the past decade, diazo compounds have been recognized as another class of small molecules applicable in these migratory insertion reactions which were first developed by Van Vranken[5] and then systematically investigated by Wang and others.[6] The key palladium carbene intermediates can be generated by Pd(II)-facilitated decomposition of stabilized diazo compounds, or transformation of *N*-tosylhydrazones as precursors of non-stabilized diazo compounds. Subsequently, migratory insertion of the carbene moiety into R–Pd bond would create a new C–Pd σ-bond which can be utilized for further transformations including β-H elimination, protonation, or cross-coupling.[6] This novel C–C bond-forming strategy greatly expands the synthetic application of diazo compounds to many conventional transformations, such as X–H (X = C or heteroatom) insertion, cyclopropanation, ylide formation, and others useful reactions.[7] The RPdX species used for carbene complex formation can be generated mainly through two pathways including oxidative addition of aryl, alkenyl, benzyl or allylic halides to Pd(0),[8] and ligand exchange or transmetallation of terminal alkynes or arylboronic acids with Pd(II).[9] On the other hand, nucleopalladation of alkynes activated by Pd(II) species is a well-established strategy for alkyne difunctionalization, which is particularly useful in heterocycle synthesis.[10] Very recently, intramolecular carbopalladation of alkynes followed by carbene insertion reactions have been reported for the synthesis of 3-vinylindoles and 3-vinylbenzofurans [Eq. (1), Scheme 1].[11] Herein we report an aminopalladation-triggered carbene insertion reaction for the synthesis of 2-(1*H*-indol-3-yl)acetates under mild conditions [Eq. (2), Scheme 1].

The indole scaffold exists ubiquitously in natural products, biologically active molecules, pharmaceuticals, and agrochemicals.[12] As a result, developing practical methods for the synthesis of indole derivatives has been a long-lasting interest. In recent years, palladium-catalyzed tandem processes for indole synthesis have attracted great attention.[13] Among them, intramolecular aminopalladation of *ortho*-alkynylanilides followed by trapping with various nucleophiles is a prominent approach for the construction of substituted indole derivatives. According to our recent reports on the synthesis of 2-substituted 1*H*-indole-3-carboxamides[14] and 2-substituted 1*H*-indole-3-carboxamidines[15] through isocyanide insertion, we envisioned that indole derivatives containing a C-3 alkyl-substituted acetate moiety could be obtained through palladium-catalyzed intramolecular aminopalladation of *ortho*-alkynylanilides followed by carbene insertion, although competitive N–H insertion is a foreseeable side reaction in this process. Furthermore, it is



Scheme 1. Nucleopalladation-triggered carbene insertion reactions.



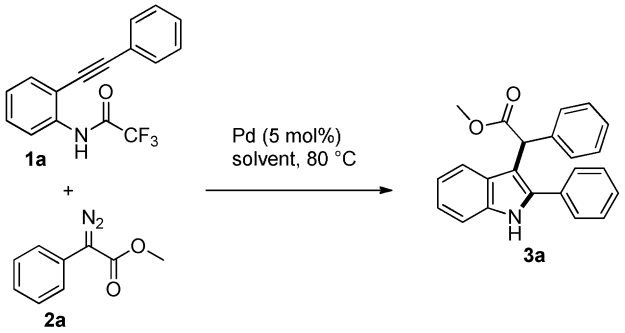
Scheme 2. Natural products containing the 2-(indol-3-yl)acetate moiety.

worthy of note that the skeleton of the resulting products can be found in natural products (Scheme 2).

To test the hypothesis, we initiated the study by reacting *ortho*-(phenylethynyl)trifluoroacetanilide **1a** and methyl α-phenyldiazoacetate **2a** in the presence of $PdCl_2$ (5 mol%) and Na_2CO_3 (1.0 equiv.) at 80 °C in DMSO in the open air (Table 1). Gratifyingly, the expected product, methyl 2-phenyl-2-(2-phenyl-1*H*-indol-3-yl)acetate **3a**, was isolated in 54% yield (entry 1). DMF was found to be the most suitable solvent for the reaction after extensive screening (entries 1–7). A screen of bases was also conducted, and Na_2CO_3 gave better results than K_2CO_3, Cs_2CO_3, NaOAc and K_3PO_4 (entries 8–11). Increasing the amount of Na_2CO_3 to 1.2 equivalents afforded the target compound **3a** in an improved 88% yield, and no reaction occurred in the absence of base (entries 12 and 14). A control reaction under argon suggested that dioxygen was unnecessary for this reaction (entry 13). Other palladium catalysts gave inferior or comparative results to $PdCl_2$ (entries 15–18). However, no product was detected in the absence of a palladium catalyst (entry 19).

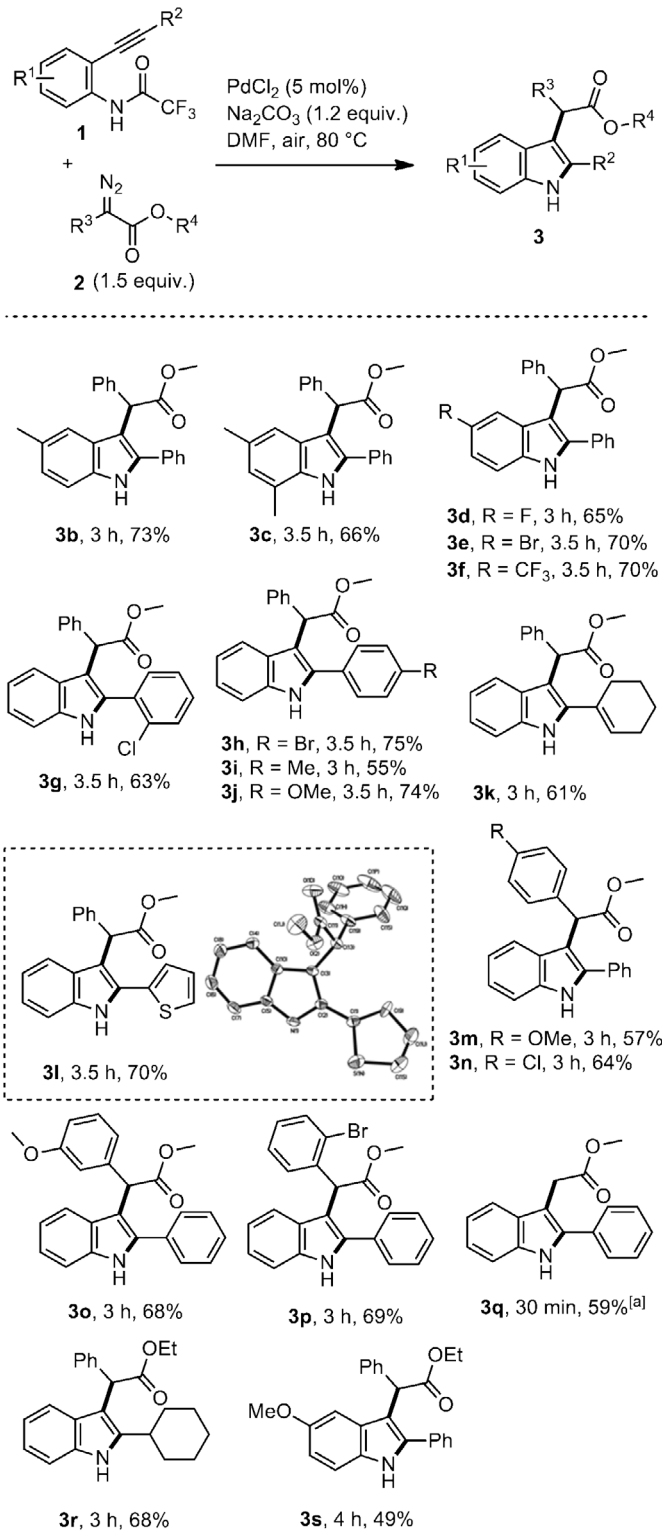
With the optimized conditions in hand, the substrate scope was then investigated (Scheme 3). Unfortunately, no desired product was detected when *ortho*-(phenylethynyl)aniline or *ortho*-(phenylethynyl)acetanilide was used as substrate, which indicated the necessity of the trifluoroacetamide group in

Table 1. Optimization of the reaction conditions.[a]



Entry	Pd	Base/equiv.	Solvent	Yield [%][b]
1	$PdCl_2$	Na_2CO_3/1.0	DMSO	54
2	$PdCl_2$	Na_2CO_3/1.0	toluene	trace
3	$PdCl_2$	Na_2CO_3/1.0	dioxane	trace
4	$PdCl_2$	Na_2CO_3/1.0	DCE	trace
5	$PdCl_2$	Na_2CO_3/1.0	CH_3CN	50
6	$PdCl_2$	Na_2CO_3/1.0	DMF	79
7	$PdCl_2$	Na_2CO_3/1.0	C_2H_5OH	37
8	$PdCl_2$	K_2CO_3/1.0	DMF	38
9	$PdCl_2$	Cs_2CO_3/1.0	DMF	68
10	$PdCl_2$	NaOAc/1.0	DMF	57
11	$PdCl_2$	K_3PO_4/1.0	DMF	75
12	$PdCl_2$	Na_2CO_3/1.2	DMF	88
13[c]	$PdCl_2$	Na_2CO_3/1.2	DMF	88
14	$PdCl_2$	–	DMF	trace
15	$Pd(OAc)_2$	Na_2CO_3/1.2	DMF	72
16	$Pd(TFA)_2$	Na_2CO_3/1.2	DMF	78
17	$Pd(acac)_2$	Na_2CO_3/1.2	DMF	78
18	$Pd(MeCN)Cl_2$	Na_2CO_3/1.2	DMF	87
19	–	Na_2CO_3/1.2	DMF	nr

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.3 mmol, 1.5 equiv.), Pd catalyst (5 mol%), base, solvent (1 mL), air, 3 h, 80 °C.
[b] Isolated yield. nr = no reaction.
[c] Argon atmosphere.



[a] A solution of ethyl diazoacetate **2q** in 0.5 mL of DMF was added to the reaction mixture through a syringe pump in 20 min, and the mixture was stirred for an additional 10 min.

Scheme 3. Substrate scope. *Reaction conditions:* **1** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv.), $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), Na_2CO_3 (25 mg, 0.24 mmol, 1.2 equiv.), DMF (1 mL), air, 80 °C.

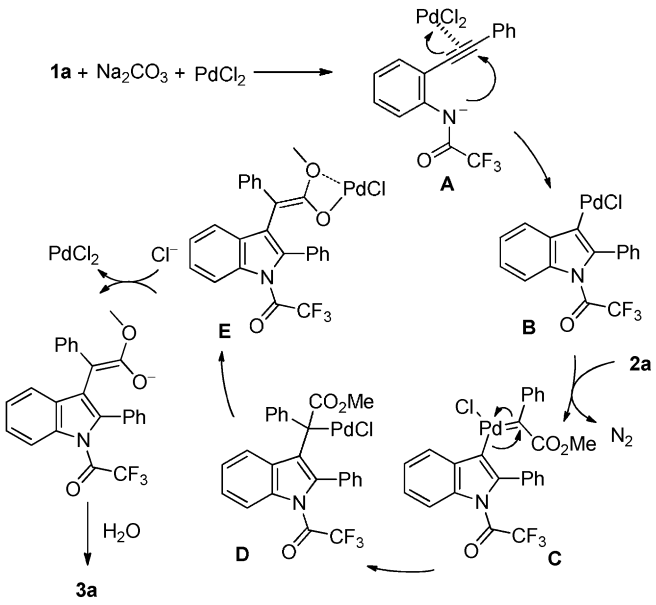
the substrates. *ortho*-(Phenylethynyl)trifluoroacetanilides **1** with electron-donating substituents (Me, OMe) or electron-withdrawing substituents (F, Br, CF_3) on the anilinic ring were tested, and the corresponding products were obtained in moderate to good yields (**3b**–**3f**, **3s**). A range of functional groups on the arylalkynyl moiety, including *p*-Me, *p*-OMe, *p*-Br, and *o*-Cl was tolerated under the reaction condition (**3g**–**3j**). In addition, 2-alkenyl- and 2-heteroaryl-substituted products (**3k** and **3l**) can also be obtained with moderate yields by following the current procedure. The structure of **3l** was confirmed by X-ray diffraction.[16] Fortunately, an alkylsubstituted substrate could also survive the reaction conditions and afforded the 2-alkyl-subsituted product (**3r**) in moderate yield.

Then, a variety of α-aryldiazoacetates with *p*-MeO, *p*-Cl, *m*-MeO, or *o*-Br substituents was explored. These functional groups were compatible with the reaction conditions, and afforded the corresponding aryl-substituted methyl 2-(2-phenyl-1*H*-indol-3-yl)acetates **3m**–**3p** in 57–69% yields. When unsubstituted ethyl diazoacetate was used, the corresponding alkylated indole derivative, ethyl 2-(2-phenyl-1*H*-indol-3-yl)acetate **3q**, was isolated in 59% yield under slightly modified conditions. It is notable that in all of the cases, no side product derived from carbene insertion to the N–H bond was formed. On the contrary, carbene insertion to the N–H bond occurred exclusively when *N*-tosylhydrazone was used as the carbene precursor.

In order to probe the reaction mechanism, 2-phenylindole **4** and α-phenyldiazoacetate **2a** were subjected to the standard reaction conditions. 2-Phenylindole was completely recovered, while α-phenyldiazoacetate **2a** decomposed. The result ruled out the possibility of 2-phenylindole being a reaction intermediate.

Based on the above experiments, a plausible mechanism is proposed (Scheme 4). First, substrate deprotonation by Na_2CO_3 and the alkyne moiety activation by $PdCl_2$ generate a palladium complex **A**. Then, intramolecular aminopalladation of **A** forms the key σ-indolylpalladium intermediate **B**. Decomposition of α-phenyldiazoacetate **2a** by **B** leads to a palladium carbene species **C** with concomitant release of gaseous nitrogen. Migratory insertion of the carbene moiety into the C–Pd bond of σ-indolylpalladium intermediate **C** generates a new C–Pd bond in intermediate **D**, which tautomerizes to a more stabilized enol **E**. Ligand exchange of **E** with chloride anion delivers the final product **3a** after protonation and deprotection during work-up.

In summary, we have developed an efficient method for the construction of 2-(1*H*-indol-3-yl)acetate derivatives through a Pd-catalyzed carbene migratory insertion reaction in air. This is the first example of a nucleopalladation-triggered carbene insertion



Scheme 4. Plausible reaction mechanism.

reaction for the synthesis of C-3 alkylated indole derivatives. The current reaction would expand the application of the migratory insertion of palladium carbene in C–C bond formation. No N–H insertion reaction was observed under our reaction conditions.

Experimental Section

Typical Procedure for the Preparation of 3a

A mixture of *ortho*-ethynyltrifluoroacetanilide **1a** (0.2 mmol), $PdCl_2$ (0.01 mmol, 5.0 mol%, 1.8 mg), Na_2CO_3 (0.24 mmol, 1.2 equiv., 25 mg) and diazoacetate **2a** (0.3 mmol, 1.5 equiv.) in DMF (1 mL) was stirred at 80 °C for 3 h. After complete consumption of **1a** as monitored by TLC analysis, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography on silica gel using petroleum ether/ethyl acetate as eluent to afford the product **3a** as a white solid ; yield: 60 mg (88%).^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.51 (br s, 1H), 7.50 (m, 4H), 7.42 (m, 3H), 7.29 (m, 2H), 7.22 (m, 3H), 7.12 (m, 1H), 6.96 (m, 1H), 5.38 (s, 1H), 3.58 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.3, 139.5, 137.0, 136.6, 132.5, 129.2, 128.8, 128.7, 128.6, 128.5, 127.6, 127.1, 122.0, 120.4, 119.7, 111.9, 108.0, 52.4, 48.1; IR (KBr): ν = 3387, 1723, 1453 cm^{-1}; HR-MS (ESI): *m/z* = 342.1486, calcd. for $C_{23}H_{20}NO_2$ $[M+H]^+$: 342.1489.

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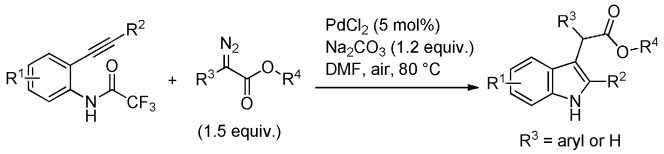
[16] CCDC 1017169 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

6 Aminopalladation-Triggered Carbene Insertion Reaction: Synthesis of 2-(1*H*-Indol-3-yl)acetates



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