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Palladium-Catalyzed Regioselective Domino Spirocyclization of Carbamoyl Chlorides with Alkynes and Benzynes

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Abstract: A palladium-catalyzed domino spirocyclization of carbamoyl chlorides with alkynes and benzynes, involving intramolecular C–H activation to afford valuable oxindole scaffolds bearing spiro quaternary stereocenters, has been developed. This one-step synthesis of spirooxindole is both step- and atom-economic, proceeding with high regioselectivity in moderate to excellent yields.

Keywords: Palladium; Domino reaction; Spirooxindoles; Carbamoyl chlorides; C–H activation

Spirooxindoles are privileged structural units, with diverse applications in numerous bioactive natural products and pharmaceuticals (Figure 1).[1] Their promising performance in the relevant areas and complex skeleton have encouraged the development of various synthetic strategies.[2] The key structural characteristic of these compounds is the spirocyclic scaffold with quaternary carbon center; it is still of great of interest to develop new strategies to construct this scaffold. Among many accessible approaches based on the stepwise elaboration of two rings, one-step, direct formation of spirocycles with a quaternary center is undoubtedly an efficient and attractive approach.[3] Alternatively, domino reactions are cost- and time-effective and can streamline the construction of complex molecules *via* formation of two or more bonds in a single batch without

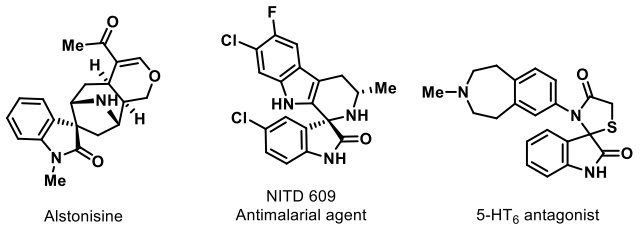

Figure 1. Selected examples of natural products and pharmaceuticals.

the addition of extra catalysts and reagents, and are broadly applied in the pharmaceutical and other bulk chemical industry.[4] Furthermore, transition-metal-catalyzed domino transformations have made notable achievements in the last few decades.[5-7]

Henin and co-workers demonstrated that alkene-tethered carbamoyl chloride could undergo a Pd-catalyzed intramolecular Heck reaction to afford α-methylene γ-lactam.[8-9] Since then, the intermolecular reaction pattern of the transition metal-catalyzed cascade cyclization/anion capture sequences of alkene tethered carbamoyl chlorides have been widely explored for the synthesis of valuable oxindole employing a variety of coupling components, including organometallic reagents,[10] B_2pin_2,[11] hexamethyldisilane,[12] aldehyde,[13] iodide[14] and carbene[15] generated *in situ* (Scheme 1A). Domino Heck transformation is an astounding development and the discovery of the ability of transition metals to interact with intermolecular alkynes in the domino spirocyclization would be an elegant progress in organometallic chemistry.[16]

Recently, we disclosed a Pd-catalyzed domino-Heck reaction of carbamoyl chlorides to achieve the regiodivergent synthesis of oxindoles, obviating the use of prefunctionalized vinyl organometallics reagents (Scheme 1B). [17] Notably, when the substitution group on the styrene moiety is an aromatic group, the alkyl palladium intermediate, generated *via* the initial Heck type insertion, undergoes a subsequent 1,4-palladium shift[18] to provide the aryl palladium intermediate, and affords the desired product *via* a second Heck reaction process. We envisaged capturing the palladacycle intermediate with suitable reaction component to tune the 1,4-Pd migration process. Herein, we report a Pd-catalyzed domino process

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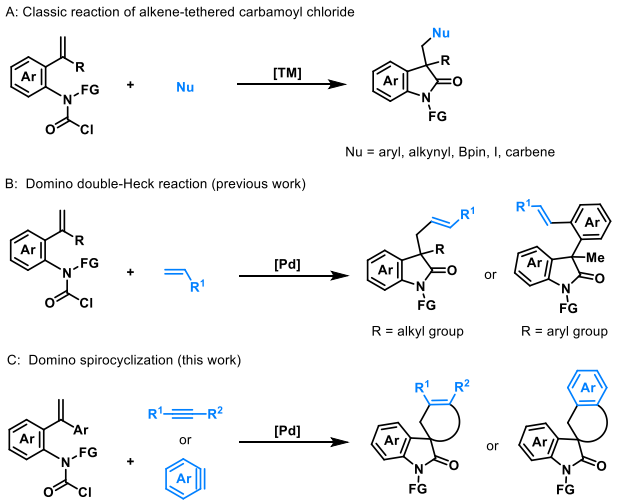
using carbamoyl chlorides as a relay switch and a highly regioselective insertion of unsymmetrical external alkyne to afford spirooxindole scaffolds (Scheme 1C), exhibiting distinctive selectivity and reactivity.

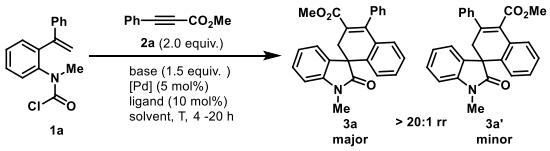


Scheme 1. Synthesis of spirooxindoles from carbamoyl chlorides.

To investigate the feasibility of our hypothesis, we initially performed the reaction of carbamoyl chlorides (**1a**) and methyl 3-phenylpropiolate (**2a**) as model substrates under the following conditions: **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.20 mmol, 2.0 equiv.), Pd_2dba_3 (0.0025 mmol, 2.5 mol%), IPr·HCl (0.01 mol, 10 mol%) and Cs_2CO_3 (0.15 mmol, 1.5 equiv.) in toluene (0.1 M) at 110 °C for 4 h, delivering the expected product **3a** in 55% yield (Table 1, entry 1). It should be noted that a small amount of decarbonylation by-product **7** formation was detected (Scheme 2). The regioselectivity of **3a** to **3a'** is more than 20:1. Amongst various ligand screening, it was found that the commercially available $Pd(PPh_3)_2Cl_2$ provided the highest yield (Table 1, entries 2-6). Under the standard conditions, the desired product **3a** was obtained with 72% isolated yield. Next, we investigated the base screening: the yield of product **3a** significantly dropped down when K_3PO_4 was employed as the inorganic base (Table 1, entry 7); When CsOPiv, a common base for C-H activation was used, no desired product formation was observed, and the same scenario applied to NaOMe (Table 1, entries 8 and 9), indicating the nucleophilicity of alkoxy group was too strong, causing decomposition of the starting material **1a**. The solvent screening revealed that toluene is the optimal solvent for this domino transformation (Table 1, entries 10-12). Finally, lowering the reaction temperature to 80 °C resulted in sluggish conversion of **1a** and 66% yield could be obtained by extending reaction time to 20 h (Table 1, entry 13).

With the optimized conditions in hand, we investigated the applicability of domino spirocyclization for spirooxindole synthesis (Table 2). Unless otherwise stated, the ratio of regioisomers in all spirooxindoles are greater than 20:1. The substituent

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



Entry	[Pd]/Ligand	Base	Solvent	T [°C]	Yield [%][b]
1[c]	Pd_2dba_3/IPr•HCl	Cs_2CO_3	toluene	110	55
2[c]	Pd_2dba_3/PPh_3	Cs_2CO_3	toluene	110	28
3	$Pd(OAc)_2$/PPh_3	Cs_2CO_3	toluene	110	48
4	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	110	61
5	$Pd(dppf)Cl_2$	Cs_2CO_3	toluene	110	25
6	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	toluene	110	78 (72[d])
7	$Pd(PPh_3)_2Cl_2$	K_3PO_4	toluene	110	28
8	$Pd(PPh_3)_2Cl_2$	CsOPiv	toluene	110	N.D.
9	$Pd(PPh_3)_2Cl_2$	NaOMe	toluene	110	N.D.
10	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	CH_3CN	110	trace
11	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	xylene	110	61
12	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	benzene	110	52
13[e]	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	toluene	80	66

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (2.0 equiv.), base (1.5 equiv.), [Pd] catalyst (5 mol%), ligand (10 mol%), solvent (0.1 M), 110 °C, 4 h.
[b] Corrected GC yield.
[c] $Pd_2(dba)_3$ (2.5 mol%), ligand (10 mol%).
[d] Isolated yield.
[e] 20 h.

effect on the internal alkynes was first examined. Generally, the optimized reaction conditions were found to be suitable for various alkynes possessing different electronic properties. For instance, the substituted methyl 3-arylpropiolate containing both electron donating (-OMe) and electron-withdrawing groups (-Cl) on the aryl rings could be tolerated and provided **3b** and **3c** in good isolated yields. 1,3-Diphenylprop-2-yn-1-one was incorporated to give **3d** in 63% yield. The reaction proceeded well with alkyl-substituted acetylate delivering the corresponding products **3e** and **3f** in good to excellent isolated yields (82–93%). Notably, it was found that the conjugated enyne **2g**, selective insertion of alkyne with the maintenance of alkene functionality, to provide **3g** in 50% yield, albeit with longer reaction time. The less reactive diarylacetylene cannot participate this domino reaction, and only low yield of the desired product (13% crude ^1H NMR yield) was observed when diethyl acetylenedicarboxylate was employed under the standard conditions. The reaction worked efficiently on the oxindole containing methoxy (**3h**) or chloride (**3i**) functionality. Interestingly, the substrate bearing bromide was well-tolerated and gave moderate reaction yield (**3j**). Furthermore, access to the *ortho*-fluoro substituted spirooxindole (**3k**) indicated the steric effect is inconspicuous. Product with *para*-methyl group at the phenyl ring (**3l**) was formed in good yields. Moreover, electron-withdrawing ester and nitro groups (**3m, 3n**) were tolerated under the standard conditions with 80%, 44% isolated yields. The change of substituent on the nitrogen atom to *N*-substituted benzyl substrate produced the desired products (**3o**) in 66% yield. The *para*-substitute effect

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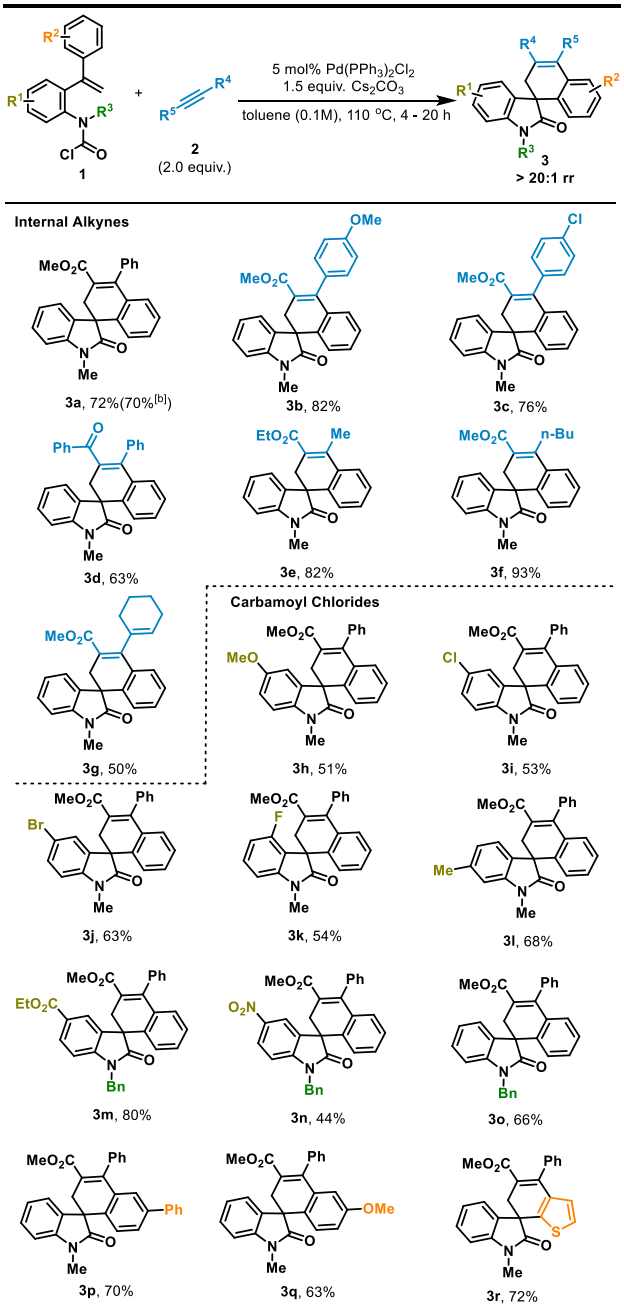
on the aromatic ring did not affect the selective 1,4-Pd migration, affording the desired product **3p** and **3q** in good yield. It is notable that the heterocycle thiophene substitution could smoothly undergo the domino 1,4-Pd shift as well to provide an expedient access of hetero-substituted spirooxindole **3r** in 72% isolated yield.

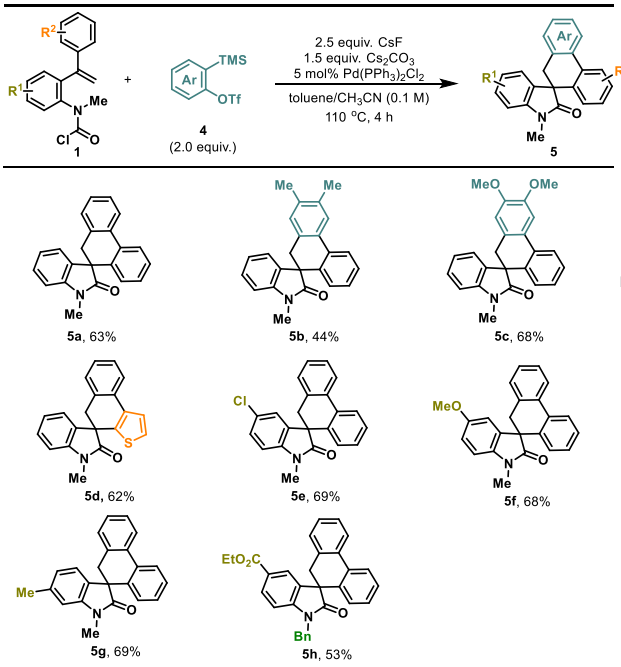
Table 2. Reaction scope with internal alkynes.[a]



[a] Standard conditions: **1** (1.0 equiv.), **2** (2.0 equiv.), Cs_2CO_3 (1.5 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), toluene (0.1 M), 110 °C, 4-20 h.
[b] 1.0 mmol scale reaction.

The 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, initially developed by Kobayashi in 1983,[19] has become an powerful aryne precursor and was widely applied in organic synthesis.[20] However, these highly reaction aryne intermediate is easy to undergo the undesired cyclotrimerization with the transition metal catalyst to furnish triphenylene byproduct.[21] To overcome this challenge, a series solvent and palladium source screenings were performed, and the yield of triphenylenes byproduct was formed less than 5% under the optimized conditions (see the Supporting Information). It was found that the combination of Cs_2CO_3 and CsF was the crucial for this domino reaction, **5a** was obtained in 63% isolated yield. The substrate scope with arynes were then carried out (Table 3). The reaction with substrates bearing methyl (**5b**) or methoxy group (**5c**) worked well, affording the desired products in moderate yields. To our delight, thiophene substitution (**5d**) could also undergo the domino migration and insertion reactions to generate the desired products in 62% yield. Next, the functionality of the carbamoyl chloride was investigated. It was found that various functional group could be tolerated with this cascade benzyne insertion, including chloride (**5e**), methoxy (**5f**), methyl (**5g**) and ester (**5h**) group, to generate the products **5e–h** in 53–69% isolated yield.

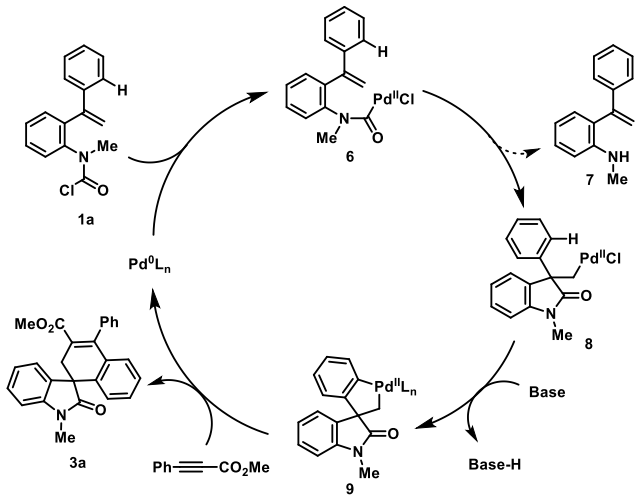
Table 3. Reaction scope with arynes.[a]



[a] Standard conditions: **1** (1.0 equiv.), **4** (2.0 equiv.), Cs_2CO_3 (1.5 equiv.), CsF (2.5 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%) toluene/CH_3CN (v/v = 1:1, 0.1 M), 110 °C, 4 h

A plausible mechanism is shown in Scheme 2. The domino spirocyclization commences with oxidative addition of carbamoyl chlorides (**1a**) to Pd^0 to afford the carbamoyl-Pd intermediate **6**. Accompanied by decarbonylation to give the side product **7**, **6** undergoes the intramolecular Heck reaction with tethered alkene to generate the alkyl-palladium(II) intermediate **8**. The alkyl-Pd intermediate **8** subsequently performs an intramolecular C–H

activation to afford a five-membered palladacycle (**9**), which undergoes a selective scission of C(sp^2)-Pd bond under kinetic control *via* the regioselective migratory insertion to the activated alkynes,[16e] followed by a final reductive elimination to provide the desired product **3a**.



Scheme 2. Plausible mechanism.

In conclusion, we have demonstrated a mild and efficient palladium-catalyzed domino spirocyclization of carbamoyl chlorides with alkynes and arynes. Distinguished by remarkable regioselectivity and diverse set of substitution patterns, this protocol is a novel strategy for synthesizing spirooxindoles and may provide further application value in complex agrochemicals and pharmaceuticals.

Experimental Section

General Experimental Procedure for the Synthesis of Spirooxindoles 3

An oven-dried vial charged with carbamoyl chlorides **1** (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), and Cs_2CO_3 (1.5 equiv.) was evacuated and backfilled with N_2 (This process was repeated three times). Internal alkynes **2** (2.0 equiv.) and toluene (0.1 M) were subsequently added to the reaction mixture. The tube was sealed with Parafilm, and allowed to stir for 4–20 h at 110 °C. The mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The separated organic layer was washed twice with water and once with brine, then dried over anhydrous Na_2SO_4, the resulting organic layer was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel column (PE/EtOAc) to afford the desired spirooxindoles **3**.

General Experimental Procedure for the Synthesis of Spirooxindoles 5

An oven-dried vial charged with carbamoyl chlorides **1** (1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), and Cs_2CO_3 (1.5 equiv.) CsF (2.5 equiv.) was evacuated and backfilled with N_2 (This process was repeated for three times). Aryne precursor **4** (2.0 equiv.) and toluene/CH_3CN (v/v = 1/1, 0.1 M) were subsequently added into the reaction mixture. The tube was sealed with Parafilm, and allowed to stir for 4 h at 110 °C. The mixture was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The separated organic layer was washed twice with water and once with brine, then dried over anhydrous Na_2SO_4, the resulting organic layer was concentrated under reduced pressure, and the crude product was purified by chromatography on silica gel column (PE/EtOAc) to afford the desired spirooxindoles **5**.

Acknowledgements

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