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Synthetic Methods

Domino Carbopalladation/C–H Functionalization Sequence: An Expedient Synthesis of Bis-Heteroaryls through Transient Alkyl/Vinyl–Palladium Species Capture

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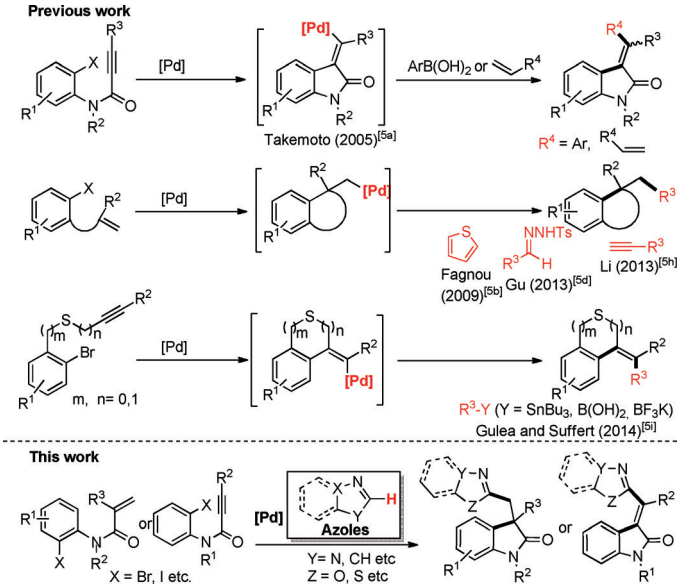
Abstract: A microwave-assisted highly efficient intermolecular domino carbopalladation/C–H functionalization sequence has been developed to access bis-heteroaryl frameworks in a single operation. The reaction involves carbopalladation of the halogenated acrylamides or phenylpropiolamides by the Pd(0) catalysis, followed by the direct (hetero)arylation to give products with good to excellent yields. The synthetic utility of this method was also extended towards the application of the Ugi-adduct as the starting material.

The rapid generation of complex (bis)heterocyclic frameworks has always been challenging and has received considerable attention due to several inherent benefits.[1] Recent advances in C–H functionalization[2] of arenes and heteroarenes have begun to alter the way organic chemists execute synthesis of such complex structures. One such interesting approach is the amalgamation of transition-metal-catalyzed C–H bond functionalization with another C–C bond formation step. By triggering such domino reactions with well-defined functionalities in the structure of the starting material, these reactions increase the efficiency and modularity of the synthetic protocol, allowing the rapid generation of molecular diversity in a minimum number of steps.[3] It has already been established that the carbopalladation of the halogenated acrylamides or phenylpropiolamides can generate the transient σ-alkyl/vinyl–palladium(II) intermediates, which are living species, and the reaction is only terminated by exchanging the Pd–X bond with an anion or nucleophile followed by reductive elimination.[4]

In this regard, considerable progress has been achieved towards capturing of these σ-alkyl/vinyl–palladium(II) intermediates by anionic, neutral, as well as organometallic species (Scheme 1).[5] However, these intermediates are rarely intercepted by the intermolecular C–H functionalization.[5b] In the course of our ongoing research on domino reactions[6] and the direct C–H functionalization[7] of heteroarenes, we wondered if such transient vinyl- or alkylpalladium(II) species could activate the sp^2 C–H bond of azoles in a domino process. The heteroaryl azole skeleton[8] is a key structural unit in a number of biologically active compounds and finds profound applications in medicinal chemistry as well as material sciences.[9] In recent years, considerable progress has been achieved in the direct arylation, alkenylation, and alkynylation of azoles using aryl halides or pseudohalides as coupling partners.[10] However, similar strategies for the construction of heteroaryl–heteroaryl scaffolds, such as the oxindole–azole framework, remain far less explored. Moreover, 3,3-oxindoles and 3-alkylideneoxindoles are known versatile compounds in terms of their biological activity and synthetic applicability (Figure 1).[11]



Scheme 1. Cross-coupling reactions by vinyl- or alkylpalladium species.

To develop this domino protocol, the conditions must be carefully selected to avoid the direct heteroarylation as an

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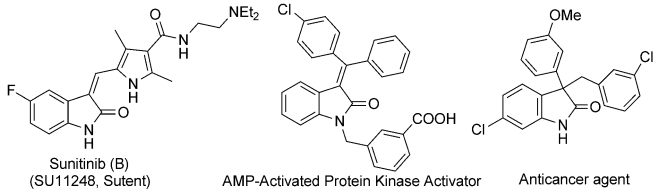
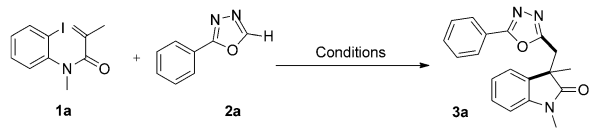


Figure 1. Important molecules containing the 3-vinylidene or 3,3-disubstituted oxindole framework.

unwanted side reaction. We started our investigations for the synthesis of indolinone–azole framework by attempting the intermolecular cyclization using **1a**, which was easily prepared from 2-iodoaniline,[5d] and 2-phenyl-1,3,4-oxadiazole (**2a**) as model substrates in toluene for 12 h at 100 °C (Table 1). $[Pd(PPh_3)_4]$ proved to be a superior catalyst to $Pd(OAc)_2$ for the reaction (entries 1–5). The product yield was significantly improved (89%; entry 6) when the temperature was increased to 110 °C; however, further rising the temperature resulted in a decreased yield (entry 7). In the presence of other inorganic bases, such as *t*BuOLi, K_2CO_3, Na_2CO_3, and K_3PO_4, low yields of the product were obtained, while no reaction was observed with Et_3N (entries 8–12). Similarly, no improvement in the yield was observed upon changing the reaction time (entries 13 and 14). Follow-up reactions revealed that running the reaction in acetonitrile at 110 °C provided the best yield (entries 15–18). Shifting from the conventional heating to microwave irradiation, considerably lowered the reaction time[12] from 12 h to 30 min without compromising the yield (entries 18–20). Moreover, decreasing the catalytic loading of $[Pd(PPh_3)_4]$ to 5 mol% still allowed the domino reaction to occur smoothly, providing the desired product **3a** in 97% isolated yield (entry 21). However, a further decrease of the catalyst to 3 mol% resulted in a reduced yield (entry 22).

With the optimized reaction conditions in hand (Table 1, entry 21), we evaluated the scope of this methodology (Table 2). Initially, the one-pot reaction was applied to a series of 2-iodoanilines, all giving the corresponding products (**3a**–**3e**) in good to excellent yields. Acrylamide (**3f**), derived from the atropic acid, gave a relatively low yield, which could be attributed to the steric factors. Next, the influence of the azole subunit on the reaction outcome was examined. Different 1,3,4-oxadiazoles with electron-donating- or -withdrawing

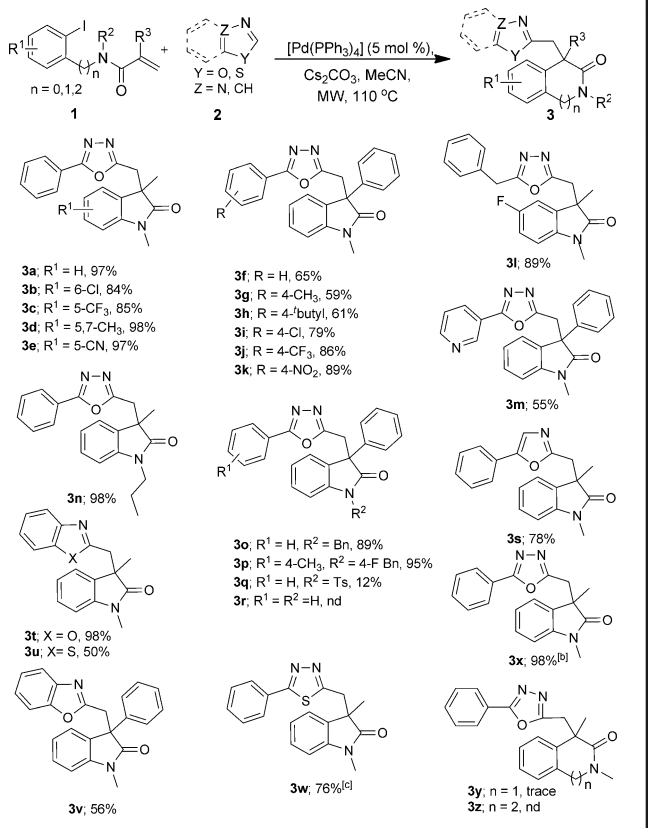
Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Ligand	Base	Solvent	*T* [°C]	Yield [%][b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	100	19
2	$Pd(OAc)_2$	XantPhos	Cs_2CO_3	toluene	100	40
3	$Pd(OAc)_2$	DPEPhos	Cs_2CO_3	toluene	100	33
4	$Pd(OAc)_2$	DBPF	Cs_2CO_3	toluene	100	24
5	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	toluene	100	51
6	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	toluene	110	89
7	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	toluene	120	61
8	$[Pd(PPh_3)_4]$	–	LiO*t*Bu	toluene	110	17
9	$[Pd(PPh_3)_4]$	–	K_2CO_3	toluene	110	22
10	$[Pd(PPh_3)_4]$	–	Na_2CO_3	toluene	110	21
11	$[Pd(PPh_3)_4]$	–	K_3PO_4	toluene	110	24
12	$[Pd(PPh_3)_4]$	–	Et_3N	toluene	110	nd
13[c]	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	toluene	110	67
14[d]	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	toluene	110	80
15	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	*o*-xylene	110	87
16	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	DCE	110	74
17	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	DMSO	110	39
18	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	MeCN	110	100 (97)
19[e]	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	MeCN	110	100 (98)
20[f]	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	MeCN	110	100 (97)
21[f,g]	**$[Pd(PPh_3)_4]$**	**–**	**Cs_2CO_3**	**MeCN**	**110**	**100 (97)**
22[f,h]	$[Pd(PPh_3)_4]$	–	Cs_2CO_3	MeCN	110	51

[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (10 mol%), ligand (20 mol%), and base (0.4 mmol) in solvent (1 mL) at the indicated temperature for 12 h under N_2 atmosphere. [b] Yield determined by ^1H NMR using 3,4,6-trimethoxy benzaldehyde as internal standard; isolated yields in parenthesis. [c] Reaction run for 10 h. [d] Reaction run for 16 h. [e] Microwave irradiation for 1 h at 100 W maximum power. [f] Microwave irradiation for 30 min. [g] Catalyst (5 mol%). [h] Catalyst (3 mol%).

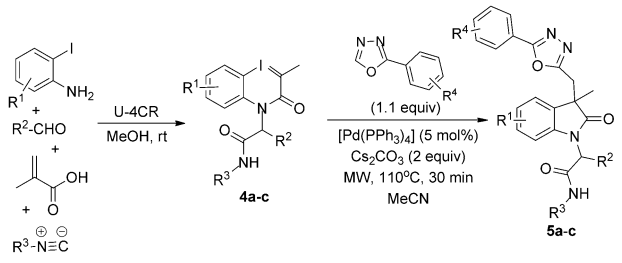
Table 2. Scope of domino carbopalladation/C–H functionalization sequence by an alkyl–Pd species.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (1.1 equiv), $[Pd(PPh_3)_4]$ (5 mol%), and Cs_2CO_3 (2 equiv) in MeCN (1.5 mL) under N_2 atmosphere at 110 °C for 30 min under microwave irradiation at 100 W maximum power. [b] *N*-(2-*b*romophenyl)-*N*-methylmethacrylamide used as substrate. [c] Conventional reaction for 12 h.

groups on the aryl ring were well tolerated (**3g**–**3k**). Replacement of the phenyl ring of the oxadiazole with a benzyl group (**3l**) or 3-pyridyl ring (**3m**) led to the desired products in satisfactory yields. Also, the alkyl (**3n**) or benzyl substitutions (**3o** and **3p**) on the nitrogen atom were well tolerated. However, the electron-withdrawing tosyl group (**3q**) provided only 12% yield, while the unsubstituted indole was incompatible under these conditions (**3r**). To further demonstrate the catalytic efficacy, we expanded the scope of this protocol to other azole derivatives, resulting in good to moderate yields of the products (**3s**–**3w**). Also, the acrylamide, with a bromo group instead of iodo, worked equally well under these conditions (**3x**). It is worth noting that our efforts for the ring expansion by employing the higher homologues of acrylamide **1** failed (**3y** and **3z**) and heteroarylated products, resulted by the competitive direct arylation reaction, were observed instead. This could be attributed to the more difficult formation of seven- or eight-membered palladacycle intermediates.

To enhance the practical utility of our methodology, compounds **4a**–**c** were synthesized by the Ugi four-component reaction (Ugi-4CR)[13] and subjected to the optimized reaction conditions, which led to the facile synthesis of indolinones **5a**–**c** in good yields as diastereomeric mixtures (Scheme 2).

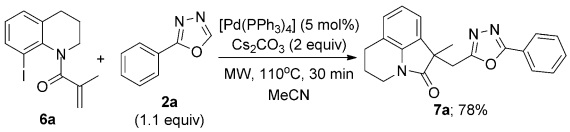


5a; R^1 = H, R^2 = iso-butyl, R^3 = *t*-Bu, R^4 = H, 98% (d.r. 1:1.3)
5b; R^1 = 4-Me, R^2 = 4-Cl Ph, R^3 = 1,1,3,3-tetramethylbutyl, R^4 = 4-Me, 67% (d.r. 1:2)
5c; R^1 = H, R^2 = R^2 = 4-Me Ph R^3 = *t*-Bu, R^4 = 4-Cl, 97% (d.r. 1:2)

Scheme 2. Expansion of the reaction scope to post-Ugi tandem-domino carbopalladation/C–H functionalization.

Further, the above protocol was successfully extended to a domino reaction starting from 1-(8-iodo-3,4-dihydroquinolin-1-yl)-2-methylprop-2-en-1-one **6a** (derived from 8-iodo-1,2,3,4-tetrahydroquinoline) that delivered compound **7a** in 78% yield (Scheme 3).

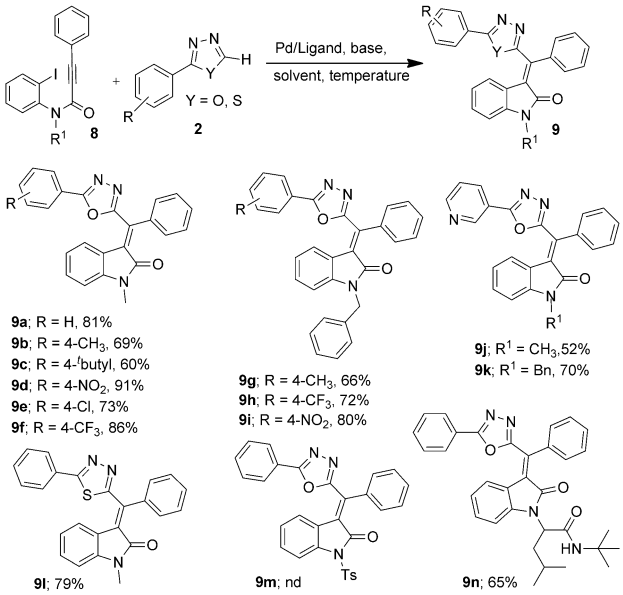
Next, we targeted the synthesis of a 3-ethylidene indolinone–azole framework using *N*-(2-*i*odophenyl)-*N*-methyl-3-phenylpropiolamide (**8a**) as the substrate. However, employment



Scheme 3. Expansion of the reaction scope to a tetrahydroquinoline derivative.

of the conventional heating proved better than the microwave irradiation for this transformation. After careful examination, it was ascertained that the best conditions for this domino reaction were $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Cs_2CO_3 (2 equiv) in toluene at 100 °C for 24 h under N_2 (see Table S1 in the Supporting information) that provided the desired product **9a** in 81% yield as a single isomer. The *E*-configuration of the obtained isomer was deduced from NOESY experiments (for **9b** and **9j**, see the Supporting Information). The observed double-bond geometry is due to the regioselective *syn* insertion of the arylpalladium species to the triple bond of the propiolamide. The optimized reaction conditions were applied to evaluate the scope of the method (Table 3). To our satisfaction,

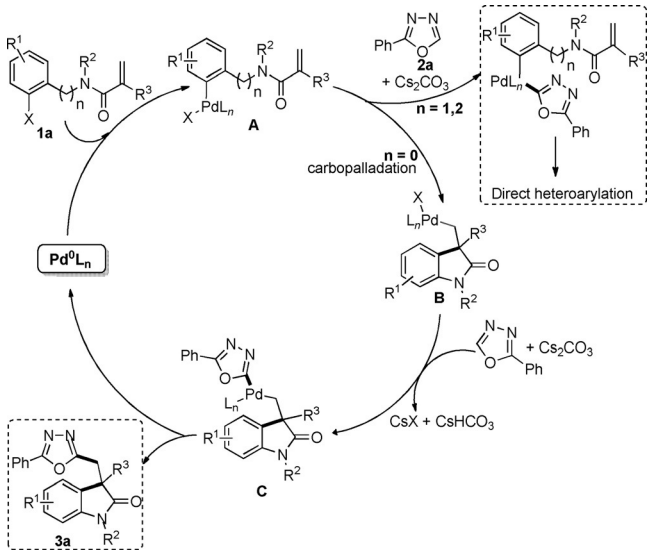
Table 3. Scope for domino carbopalladation/C–H functionalization sequence by a vinyl–Pd species.[a]



[a] Reaction conditions: all reactions were performed with **8** (0.2 mmol), **2** (1.1 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Cs_2CO_3 (2 equiv) in toluene (1.5 mL) under N_2 atmosphere at 100 °C for 24 h.

a wide range of substituents with different electronic properties on the aryl ring of 1,3,4-oxadiazoles (**9a**–**9f**), provided the corresponding products in moderate to good yields. Also, benzyl substitution (**9g**–**9i**) on the nitrogen was well tolerated; however, the electron-withdrawing tosyl group (**9m**) was incompatible under these conditions. Moderate to good yields were obtained with 3-pyridyl-substituted oxadiazoles (**9j** and **9k**) and 2-phenyl-1,3,4-thiadiazole (**9l**). A highly substituted compound derived from the Ugi-4CR underwent facile reaction to provide **9n** in moderate yield.

A mechanism for the synthesis of the indolinone–azole framework was proposed involving the formation of a σ-alkylpalladium intermediate (Scheme 4). Initially, the oxidative addition of acrylamide **1a** by the ligated Pd(0) species, generates the Pd(II) complex **A**. This is followed by the intramolecular



Scheme 4. Proposed mechanistic pathway for the indolinone–azole framework.

cyclization to form complex **B**, which could be trapped by the oxadiazole **2a** through a base-assisted halide exchange to give **C**. Finally, reductive elimination from **C** delivers product **3a** and regenerates the Pd(0) catalyst.

In summary, we have developed a domino carbopalladation/C–H activation approach for the synthesis of the indolinone–azole framework through trapping of the σ-alkyl/vinyl–palladium intermediate with azoles resulting in the generation of two C–C bonds in a single catalytic cycle. In terms of practical utility, the reaction involves relatively mild conditions, shows remarkable selectivities, displays a broad substrate scope, and high product yields.

Experimental Section

Method A: Synthesis of 3,3-substituted indolinone–azole framework

In an oven-dried microwave vial (10 mL) equipped with a magnetic stirring bar was added acrylamide **1** (0.2 mmol, 1 equiv), azole **2** (1.1 equiv), Cs_2CO_3 (0.4 mmol), $[Pd(PPh_3)_4]$ (5 mol%), and MeCN (1.5 mL). The vial was degassed, backfilled with nitrogen and heated under microwave irradiation (100 W) for 30 min at 110 °C. After completion of the reaction as monitored by TLC analysis, the mixture was filtered, concentrated, and the resulting crude product was purified by column chromatography on silica gel using heptane/EtOAc as eluent. The products were further identified by ^{1}H NMR, ^{13}C NMR, and HRMS and were all in good agreement with the assigned structures.

Method B: Synthesis of 3-ethylidene indolinone–azole framework

To an oven dried screw cap vial (10 mL) equipped with a magnetic stirring bar was added propiolamide **8** (0.2 mmol), azole **2** (1.1 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (0.4 mmol), and toluene (1.5 mL). The mixture was degassed and stirred under nitrogen at 100 °C for 24 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (5 mL) and passed through a small bed of celite. The filtrate was concentrated under vacuum to provide the crude product, which was purified by column chromatography on silica gel using heptane/EtOAc as eluent. The products were further identified by ^{1}H NMR, ^{13}C NMR and HRMS, and were all in good agreement with the assigned structures.

Acknowledgements

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Keywords: C–H activation · domino reactions · heterocycles · microwave chemistry · palladium

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