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Palladium-Catalyzed Domino Heck / Intermolecular Cross-Coupling: Efficient Synthesis of 4-Alkylated Isoquinoline Derivatives

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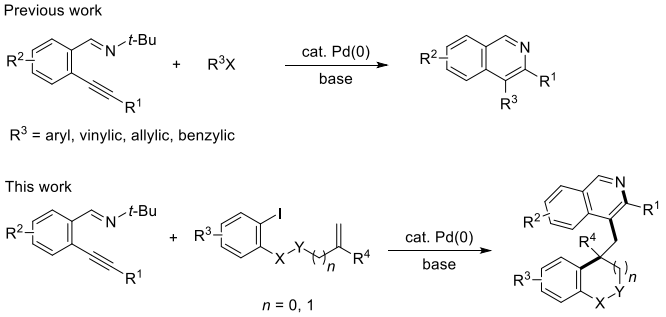
A highly efficient Pd-catalyzed Heck-type cascade process with 2-(1-alkynyl)benzaldimines has been developed, which provides access to a broad range of 4-alkylated isoquinoline derivatives in moderate to good yields. The *σ*-alkylpalladium(II) intermediate in the Heck reaction activates alkynes toward intramolecular nucleophilic attack. This is the first example of a *σ*-alkylpalladium(II) intermediate promoting the cyclization of alkynes containing a proximate nucleophilic center.

The organopalladium-promoted cyclization of alkynes containing proximate nucleophilic centers is a very effective strategy for heterocyclic ring construction.[1] This strategy has been successfully applied in the synthesis of 2,3-disubstituted indoles,[2] 2,3-disubstituted benzofurans,[3] 3,4-disubstituted isoquinolines[4] and other cyclic compounds.[5] However, previous studies have focused on the construction of $C(sp^2)$–$C(sp^2)$ bonds [*via* arylpalladium(II) or vinylpalladium(II) intermediates]. Introducing alkyl-$C(sp^3)$-substituents in heterocyclic ring construction is particularly desirable. Benzylation and allylation in heterocyclic ring construction has been realized *via* benzylpalladium and π-allylpalladium intermediates.[4a,6] These palladium intermediates are relatively more stabilized and show higher activities compared with *σ*-alkylpalladium intermediates, so cyclization involving *σ*-alkylpalladium intermediates is still a challenge.

The intramolecular Heck reaction of 1,1'-disubstituted olefins is known to be highly efficient for the construction of benzo-fused saturated nitrogen / oxygen heterocycles with a carbon quaternary center *via* an *n-exo*-trig cyclization.[7] We envisioned that the resulting neopentyl-type *σ* Pd(II) complex may activate alkynes toward intramolecular nucleophilic attack. Herein we report the development of a palladium-catalyzed domino Heck / intermolecular cross-coupling process for the synthesis of 4-alkylated isoquinolines. To the best of our knowledge, this is the first example of a *σ*-alkylpalladium(II) intermediate promoting cyclization of alkynes containing a proximate nucleophilic group.



Scheme 1 Palladium-catalyzed synthesis of 4-substituted isoquinolines.

Our study of this Pd-catalyzed Heck-type cascade reaction commenced with (*E*)-*N*-*tert*-butyl-1-[2-(phenylethynyl)phenyl]methanimine (**1a**) and 1-iodo-2-((2-methylallyl)oxy)benzene (**2a**) as model substrates under the following conditions: **1a** (1.2 equiv), **2a** (0.2 mmol), $Pd(dba)_2$ (5 mol %), PPh_3 (10 mol %) and Na_2CO_3 (3.0 equiv) in DMF (5 mL) at 100 °C under argon for 16 h (Table 1). The desired isoquinoline **3a** was isolated in a 52% yield. The structure of **3a** was unambiguously confirmed by X-ray crystallography. A side product was also observed, which was identified as 3-phenylisoquinoline (**4**). The 3-phenylisoquinoline was believed to be formed by either the thermal or Pd(II)-catalyzed cyclization of imine **1a**. Various bases were then screened and K_2CO_3 was the best in promoting the reaction, affording the desired **3a** in a 66% isolated yield (entries 1-5). When the reaction was performed using BINAP as the ligand and K_2CO_3 as the base, a much lower yield of **3a** was obtained (entry 6). The replacement of $Pd(dba)_2$ plus Ph_3P by $Pd(PPh_3)_4$ did not improve the yield of **3a**, but reduced the amount of the side product 4 (3-phenylisoquinoline) (entry 7). Shortening the reaction time to 6 h increased the yield of **3a** to 71% (entry 8). No improvement in the yield of **3a** was achieved when increasing the amount of **1a** (entry 9). Reducing the volume of DMF or lowering the reaction temperature led to lower yields of **3a** (entries 10 and 11).

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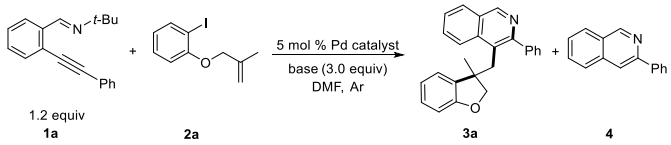
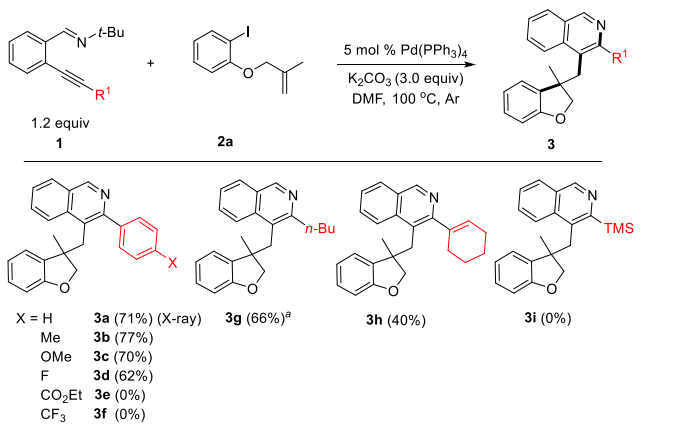
Table 1. Optimization for the reaction conditions [a]



Entry	Pd catalyst	Base	Temp (°C)	Time (h)	% Yield [b] 3a : 4
1	$Pd(dba)_2$/2 PPh_3	Na_2CO_3	100	16	52 : 17
2	$Pd(dba)_2$/2 PPh_3	K_2CO_3	100	16	66 : 21
3	$Pd(dba)_2$/2 PPh_3	Cs_2CO_3	100	16	31 : 17
4	$Pd(dba)_2$/2 PPh_3	NaOAc	100	16	61 : 35
5	$Pd(dba)_2$/2 PPh_3	Et_3N	100	16	55 : 28
6	$Pd(dba)_2$/1 BINAP	K_2CO_3	100	16	7 : 8
7	$Pd(PPh_3)_4$	K_2CO_3	100	16	66 : 10
8	$Pd(PPh_3)_4$	K_2CO_3	100	6	71 : 8
9	$Pd(PPh_3)_4$	K_2CO_3	100	6	67 : 10 [c]
10	$Pd(PPh_3)_4$	K_2CO_3	100	6	58 : 11 [d]
11	$Pd(PPh_3)_4$	K_2CO_3	80	6	35 : 12

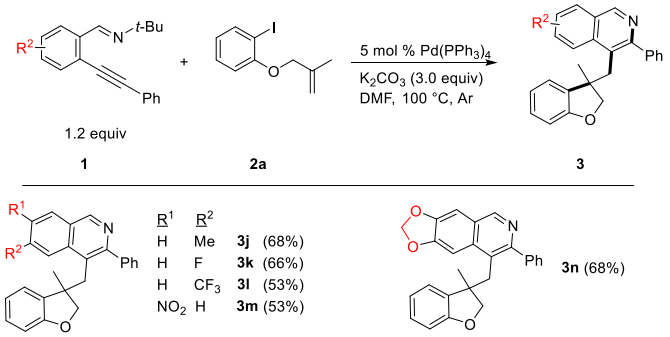
[a]Representative procedure: **1a** (1.2 equiv), **2a** (0.20 mmol), Pd catalyst (5 mol %), ligand when applied, base (3.0 equiv) and DMF (5 mL) were placed in a 4-dram vial, and the reaction was stirred at the indicated temperature under argon. [b]Isolated yield. [c]1.5 equiv of **1a**. [d]3 mL of DMF.

With the optimum conditions [$Pd(PPh_3)_4$ (5 mol %), K_2CO_3 (3.0 equiv) in DMF (c0.04 M) at 100 °C for 6 h] in hand, the scope of the substituents on the terminus of the acetylene was examined first (Scheme 2). When R^1 is a phenyl group or a phenyl-containing electron-donating groups or halogen, the reactions worked well (**3a**-**d**). However, when R^1 is an aryl group containing a strong electron-withdrawing ester or trifluoromethyl group, no desired isoquinoline products were observed (**3e** and **3f**) and the starting material **2a** was consumed. This observation is consistent with Larock's, since arylpalladium(II) and π-allylpalladium intermediates did not promote the cyclization of 2-(1-alkynyl)benzaldimine **1** when R^1 is an aryl group containing a strong electron-withdrawing group.[4] 1-Alkenyl- and alkyl-substituted acetylenes have proven successful in this transformation, generating isoquinolines **3g** and **3h** in moderate yields. Unfortunately, no desired product was obtained when R^1 is a TMS group (**3i**). This might be explained by the steric effect of the bulky silyl group, which presumably prevents the formation of intermediate **V** (see Scheme 5).



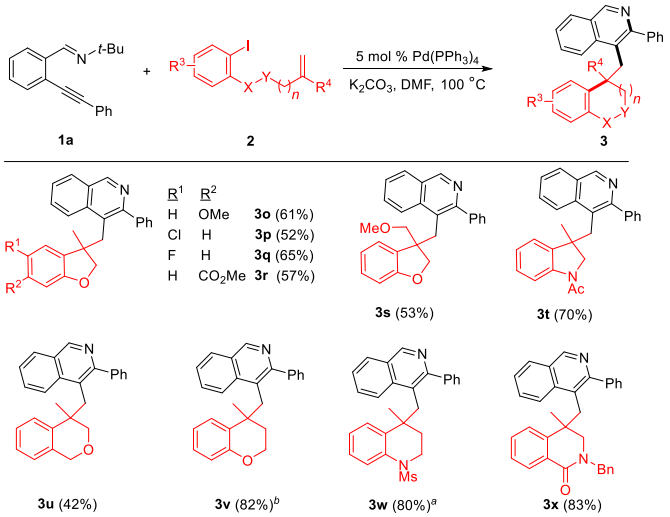
Scheme 2. Scope of the substituents on the acetylene. [a]2.0 equiv of **1**.

The electronic effects of the substituents attached to the aromatic ring of the imine have also been examined (Scheme 3). The presence of an electron-withdrawing or –donating group was well tolerated (**3j**-**n**). The electron-rich imine substrates displayed better reactivity, affording slightly higher yields of the desired isoquinolines than electron-deficient imines.

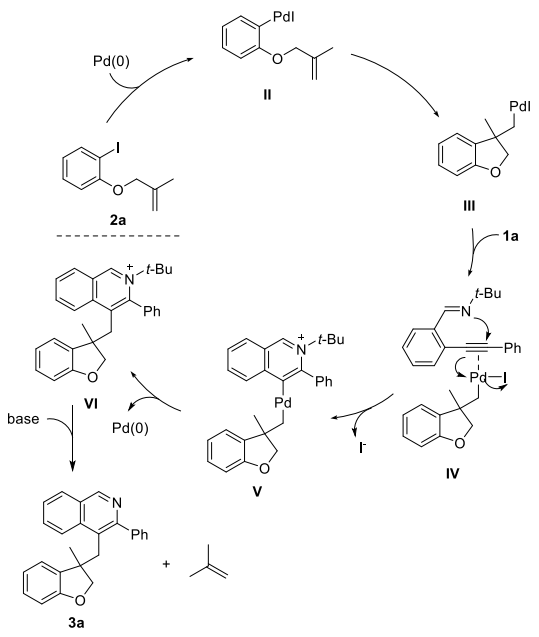


Scheme 3. Scope of the substituents on the aromatic ring of the imine.

The generality of this domino process was explored by employing various aryl halides (Scheme 4). Substrates bearing an electron-withdrawing or –donating group underwent a smooth reaction to afford the corresponding product in good yield (**3o**-**r**). The substrates with an electron-donating group generally gave slightly higher yields than an electron-withdrawing group. We were gratified to find that 1-iodo-2-((2-(methoxymethyl)allyl)oxy)benzene with a OMe group on the *β*-position of the double bond also worked well in this transformation and generated isoquinoline **3s** in a moderate yield. A nitrogen-containing substrate can be used in this domino reaction to generate indoline product **3t**. Six-membered ring substituted isoquinolines can be equally efficiently prepared in this transformation. Thus isochromane- (**3u**), chromane- (**3v**), tetrahydroquinoline- (**3w**) and dihydroisoquinolinone- (**3x**) containing isoquinolines have been prepared in good yields.



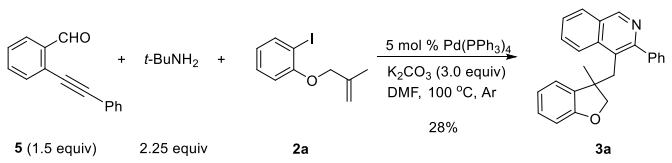
Scheme 4. Scope of the aryl halide. [a]2.0 equiv of **1a**



Scheme 5. Proposed mechanism

The mechanism shown in Scheme 5 is proposed for this palladium-catalyzed Heck / intermolecular cross-coupling process. Oxidative addition of **2a** to the Pd(0) catalyst generates arylpalladium species **II**, which undergoes an intramolecular Heck-type reaction to form alkylpalladium species **III**. Coordination of the alkylpalladium intermediate **III** to the triple bond of **1a** activates the triple bond toward intramolecular nucleophilic attack of the nitrogen atom of the imine to generate palladium intermediate **V**. Reductive elimination of intermediate **V** produces the isoquinolinium salt **VI** and simultaneously regenerates the Pd(0) catalyst. Finally, fragmentation of the *tert*-butyl group of **VI** generates product **3a**.[8]

A three-component reaction of aldehyde **5,** *tert*-butylamine and aryl iodide **2a** has also been examined (Scheme 6). The reaction afforded the expected isoquinoline **3a** in a 28% yield under unoptimized reaction conditions through imination and palladium-catalyzed domino Heck / intermolecular cross-coupling.



Scheme 6. Palladium-catalyzed domino Heck / annulation of an alkynyl aldehyde with *tert*-butylamine.

In conclusion, the first palladium-catalyzed domino Heck reaction / intermolecular cross-coupling reaction for the synthesis of 4-alkylated isoquinolines has been developed. The reaction is operationally simple and affords 4-alkylated isoquinolines in moderate to good yields. Efforts toward further expanding the reaction scope (e.g., alkylated benzofurans, indoles *etc*.) are underway in our laboratory.

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