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Halopalladation/Decarboxylation/Carbon−Carbon Forming Domino Process: Synthesis of 5-Halo-6-substituted Benzo[*b*]naphtho[2,1-*d*]furans

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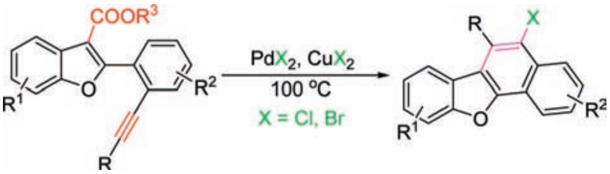
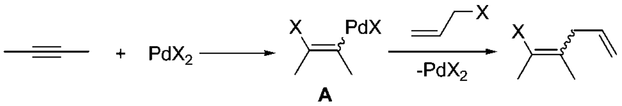
ABSTRACT



A novel and general halopalladation/decarboxylation/carbon−carbon forming domino protocol is described for the synthesis of 5-halo-6-substituted benzo[*b*]naphtho[2,1-*d*]furans. The protocol represents the first example of trapping the σ-vinylpalladium intermediate, generated from halopalladation of alkynes, by the decarboxylative coupling reaction.

Scheme 1. Mechanism of Halopalladation of Alkynes with Allyl Halides



Halopalladation of alkynes has been proven to be an extremely important and convenient method for the construction of both the carbon−carbon and carbon−halide bonds in one step.[1−4] Halopalladation of alkynes will generate a versatile reactive σ-vinylpalladium intermediate **A** (Scheme 1).[1] Until now, how to capture the σ-vinylpalladium intermediate is still a highly challenging area because the capture reagents are often limited to allyl halides, alkynes, conjugated dienes, and carbon monoxide. Recently, we found that the σ-vinylpalladium intermediate could be trapped by some nucleophilic *ortho*-groups in the arylalkyne moiety.[3] This prompted us to explore other nucleophilic groups for the purpose. Accidently, we found that arylcarboxylates were

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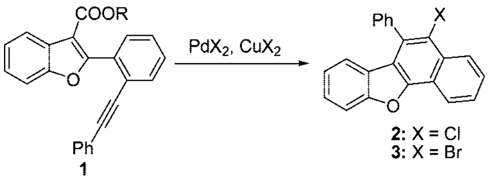
an available alternative to the traditional capture reagents to trap the σ-vinylpalladium complexes.[5] In the presence of $PdCl_2$ and CuX_2 (X = Cl, Br), a variety of 2-(2-(2-substituted ethynyl)phenyl)-benzofuran-3-carboxylates could undergo an intramolecular decarbonylative coupling reaction to capture the σ-vinylpalladium intermediate in situ. In this paper, we report our preliminary results on the first example of trapping the σ-vinylpalladium intermediate by the decarboxylative coupling reaction (eq 1). It is noteworthy that the products, polycyclic aromatic furans, are prominent structural units found in a wide range of natural products, pharmaceuticals, and materials as well as important intermediates in organic synthesis.[6]

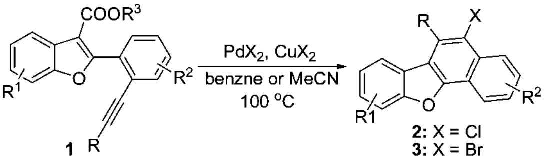
Ethyl 2-(2-(2-phenylethynyl)phenyl)benzofuran-3-carboxylate (**1a**) was treated with $PdCl_2$ and $CuCl_2$ to screen the optimal reaction conditions, and the results are summarized in Table 1. Initially, a set of solvents were examined, and benzene was found to be the most effective solvent (entries 1−6). Treatment of substrate **1a** with $PdCl_2$ and $CuCl_2$ in benzene afforded the corresponding target product **2a** in a 69% yield (entry 1). Identical results were obtained using toluene as the solvent (entry 2). However, other solvents, such as $ClCH_2CH_2Cl$, CH_3CN, THF, and cyclohexane, decreased the yield to some extent (entries 3−6). Subsequently, the amount of $CuCl_2$ was tested (entries 7−9). We found that 1 equiv of $CuCl_2$ reduced the yield to 55% (entry 7), and 5 equiv of $CuCl_2$ provided the same yield as that of 3 equiv of $CuCl_2$ (entry 8). However, a trace amount of **2a** was observed without either $CuCl_2$ or $PdCl_2$ (entries 9 and 11). It is worth noting that no reaction is observed using LiCl instead of $CuCl_2$ (entry 10), and room temperature gives a low yield after 24 h (entry 12). The screening results demonstrated that two analogs, *i*-propyl 2-(2-(2-phenylethynyl)phenyl)benzofuran-3-carboxylate (**1b**) or benzyl 2-(2-(2-phenylethynyl)phenyl)-benzofuran-3-carboxylate (**1c**), were also suitable for the halopalladation/decarbonylation/carbon−carbon forming reaction with $PdCl_2$ and $CuCl_2$ in moderate yields (entries 13 and 14). To our delight, the reaction of substrate **1a** with $PdBr_2$ and $CuBr_2$ was conducted successfully in MeCN to afford the corresponding 5-bromo-6-phenylbenzo[*b*]-naphtho[2,1-*d*]furan (**3a**) in 59% yield (entry 16).

Table 1. Screening Optimal Conditions[a]



entry	R	CuX_2 (equiv)	solvent	*t* (h)	yield (%)[b]
1	Et (**1a**)	$CuCl_2$ (3)	benzene	16	69 (**2a**)
2	Et (**1a**)	$CuCl_2$ (3)	toluene	23	70 (**2a**)
3	Et (**1a**)	$CuCl_2$ (3)	$ClCH_2CH_2Cl$	6	60 (**2a**)
4	Et (**1a**)	$CuCl_2$ (3)	CH_3CN	24	20 (**2a**)
5	Et (**1a**)	$CuCl_2$ (3)	THF	16	24 (**2a**)
6	Et (**1a**)	$CuCl_2$ (3)	cyclohexane	23	54 (**2a**)
7	Et (**1a**)	$CuCl_2$ (1)	benzene	24	55 (**2a**)
8	Et (**1a**)	$CuCl_2$ (5)	benzene	16	70 (**2a**)
9	Et (**1a**)	−	benzene	24	trace (**2a**)
10	Et (**1a**)	LiCl (3)	benzene	16	0 (**3a**)
11[c]	Et (**1a**)	$CuCl_2$ (3)	benzene	24	trace (**2a**)
12[d]	Et (**1a**)	$CuCl_2$ (3)	benzene	24	16 (**2a**)
13	*i*-Pr (**1b**)	$CuCl_2$ (3)	benzene	16	59 (**2a**)
14	Bn (**1c**)	$CuCl_2$ (3)	benzene	16	65 (**2a**)
15	Et (**1a**)	$CuBr_2$ (3)	benzene	16	35 (**3a**)
16[e]	Et (**1a**)	$CuBr_2$ (3)	MeCN	16	59 (**3a**)

[a] Reaction conditions: **1** (0.3 mmol), $PdCl_2$ (10 mol %), and $CuCl_2$ (3 equiv) in solvent (5 mL) at 100 °C. [b] Isolated yield. [c] Without $PdCl_2$. [d] At room temperature. [e] $PdBr_2$ (10 mol %) instead of $PdCl_2$.



(1)

As shown in Table 2, we examined the scope of the halopalladation/decarboxylation/carbon−carbon bond forming process with respect to ethyl carboxylate substrates under the standard conditions. Substituents at the terminal alkynic moiety of 2-(2-(ethynyl)phenyl)benzofuran-3-carboxylates were first evaluated in the presence of PdX_2 and CuX_2 (X = Cl, Br) (entries 1−13). While carboxylates **1d**−**1f** bearing electron-rich aryl groups were treated with PdX_2 and CuX_2 (X = Cl or Br) in good yields (entries 1−6), substrates **1g**−**1k**, having either electron-deficient aryl or alkyl groups, reduced the yields to some extent (entries 7−12). Ethyl 2-(2-(2-*o*-tolylethynyl)phenyl)benzofuran-3-carboxylate (**1e**), for instance, underwent the tandem reaction with $PdCl_2$ and

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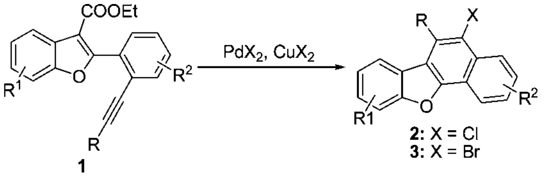
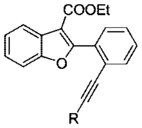
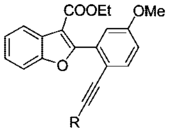
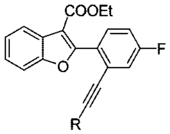
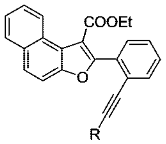
Table 2. Halopalladation/Decarboxylation/Carbon−Carbon Forming Reactions of **1** with PdX_2 and CuX_2[a]

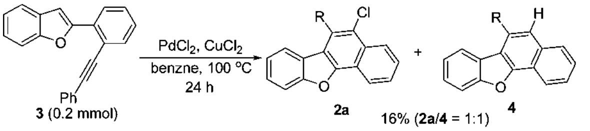


entry	substrate **1**	*t* (h)	CuX_2	yield (%)[b]
				
1	R = *p*-MeC_6H_4 (**1d**)	10	$CuCl_2$	76 (**2d**)
2[c]	R = *p*-MeC_6H_4 (**1d**)	10	$CuCl_2$	76 (**2d**)
3	R = *o*-MeC_6H_4 (**1e**)	16	$CuCl_2$	82 (**2e**)
4[d]	R = *o*-MeC_6H_4 (**1e**)	4	$CuBr_2$	89 (**3e**)
5	R = *p*-$MeOC_6H_4$ (**1f**)	18	$CuCl_2$	73 (**2f**)
6[d]	R = *p*-$MeOC_6H_4$ (**1f**)	5	$CuBr_2$	79 (**3f**)
7	R = *p*-$NO_2C_6H_4$ (**1g**)	16	$CuCl_2$	48 (**2g**)
8	R = *n*-C_8H_{17} (**1h**)	7	$CuCl_2$	47 (**2h**)
9	R = *n*-C_5H_{11} (**1i**)	5.5	$CuCl_2$	58 (**2i**)
10[c]	R = *n*-C_5H_{11} (**1i**)	5.5	$CuCl_2$	64 (**2i**)
11	R = 2-cyclohexenyl (**1j**)	5.5	$CuCl_2$	52 (**2j**)
12	R = hydroxymethyl (**1k**)	4	$CuCl_2$	15 (**2k**)
13	R = thiophen-2-yl (**1l**)	18	$CuCl_2$	51 (**2l**)
				
14	R = C_6H_5 (**1m**)	30	$CuCl_2$	69 (**2m**)
15	R = *n*-C_5H_{11} (**1n**)	12	$CuCl_2$	42 (**2n**)
				
16	R = C_6H_5 (**1o**)	7	$CuCl_2$	45 (**2o**)
17	R = *n*-C_5H_{11} (**1p**)	7	$CuCl_2$	46 (**2p**)
				
18	R = C_6H_5 (**1q**)	12	$CuCl_2$	70 (**2q**)
19	R = *n*-C_5H_{11} (**1r**)	9	$CuCl_2$	57 (**2r**)

[a] Reaction conditions: **1** (0.3 mmol), $PdCl_2$ (10 mol %), $CuCl_2$ (3 equiv) in benzene (5 mL) at 100 °C. [b] Isolated yield. [c] In toluene. [d] $PdBr_2$ (10 mol %) and $CuBr_2$ (3 equiv) in MeCN (5 mL).

$CuCl_2$ in 82% yield (entry 3) and with $PdBr_2$ and $CuBr_2$ in 89% yield (entry 4). The reaction of substrate **1g**, bearing an electron-deficient NO_2 group, with $PdCl_2$ and $CuCl_2$ afforded the target product **2g** in only 48% yield (entry 7). The alkyl groups, including octyl, hexyl, and 2-cyclohexenyl at the alkyne moiety, also provided the corresponding products in moderate yields (entries 8−11), and the hydroxymethyl groups resulted in a low yield (entry 12). It is noted that the reactions of substrates **1d** or **1i** can be conducted efficently in toluene (entries 2 and 10). Gratifyingly, the standard conditions were compatible with the thiophen-2-yl group, providing a moderate yield (entry 13). It was found that two groups, OMe and F, on the 2-aryl moiety were perfectly tolerated under the standard conditions (entries 14−17). Ethyl 2-(5-methoxy-2-(2-phenylethynyl)phenyl)benzofuran-3-carboxylate (**1m**), for example, underwent the reaction with $PdCl_2$ and $CuCl_2$ smoothly in 69% yield (entry 14). Remarkably, naphtho[2,1-*b*]furan-1-carboxylates **1q** and **1r** were suitable substrates providing good yields under the same conditions (entries 18 and 19).

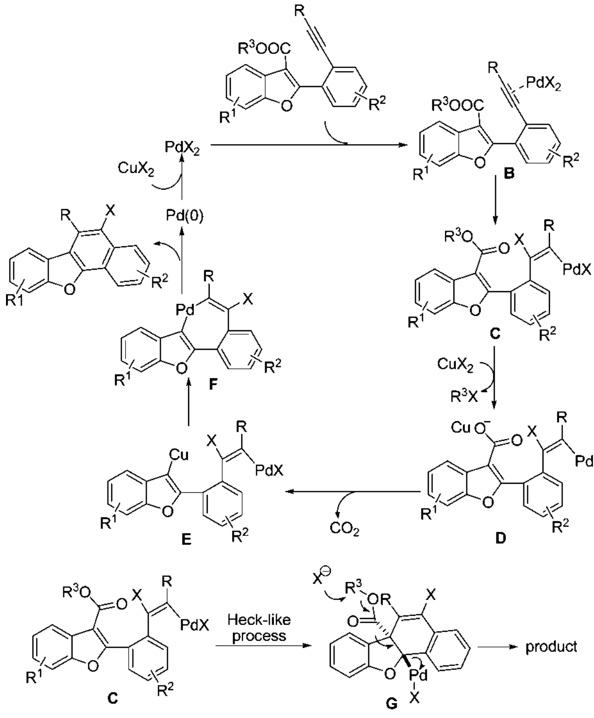
The reaction of 2-(2-(2-phenylethynyl)phenyl)-benzofuran (**3**) was also tested under the standard conditions, and a mixture was observed by GC-MS analysis (eq 2). In the presence of $PdCl_2$ and $CuCl_2$, 30% of substrate **3** was consumed after 24 h to provide a mixture of the desired product **2a** and another hydroarylation product **4** in 16% total yield.



(2)

Two possible mechanisms as outlined in Scheme 2 were proposed for the present reaction on the basis of the previously reported mechanism.[1−5] Complexation of PdX_2 with the carbon−carbon triple bond affords intermediate **B**, followed by *trans*-addition to give intermediate **C**, the σ-vinylpalladium intermediate.[1−3] Intermediate **C** undergos

Scheme 2. A Working Mechanism



anion exchange with Cu to produce intermediate **D**. Intermediate **E** is formed from decarboxylation of intermediate **D**.[5] Subsequently, intramolecular transmetalation of intermediate **E** takes place to give intermediate **F**. Finally, reductive elimination of intermediate **F** yields both the target product and Pd(0) species. The Pd(0) species are oxidized by CuX_2 to regenerate the active PdX_2 species. Another possible pathway is a Heck-like mechanism. Insertion of the vinylpalladium species **C** into benzofuran via a Heck-like process forms intermediate **G**, which subsequently undergoes decarboxylative β-carbo-elimination to give the desired product.

We deduced that three roles of CuX_2 are played in the process: (1) as a halide source; (2) as a cocatalyst to react with carbonyls generating the Cu intermediate in the decarbonylation process; and (3) as a cocatalyst to cleave the C−Pd σ-bond and regenerate the active PdX_2 species in the halopalladation reaction. Study of the real function of CuX_2 is in progress.

In summary, we have developed a new and general protocol for the synthesis of polycyclic aromatic furans by a halopalladation/decarboxylation/carbon−carbon forming domino process. In the presence of $PdCl_2$ and CuX_2, a variety of 2-(2-(2-substitutedethynyl)phenyl)benzofuran-3-carboxylates underwent the reaction to afford 5-halo-6-substituted benzo[*b*]naphtho[2,1-*d*]furans in moderate to good yields. It is noteworthy that these products with a halide (Cl or Br) provide an attractive and useful route to introduce new groups for the synthesis of new natural products. Work to apply the reaction in organic synthesis is currently underway.

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products **2** and **3**; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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