JOC Note

Synthesis of (*E*)-3-(Isobenzofuran-3(1*H*)-ylidene)-indolin-2-ones by the Palladium-Catalyzed Intramolecular C−H Functionalization Process

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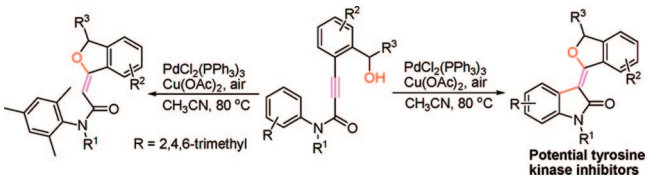

A novel and selective protocol has been developed for the synthesis of (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)indolin-2-ones by Pd-catalyzed oxidative intramolecular C−H functionalization reactions of various 3-(2-(hydroxymethyl)aryl)-*N*-methyl-*N*-arylpropiolamides in moderate yields. Mechanisms involving a C−H activation process were proposed for this transformation on the basis of the observed values of kinetic isotope effects.

The indolin-2-one skeleton is a prevalent motif found in many naturally occurring products and biologically active compounds.[1] Two 3-methyleneindolin-2-ones, SU11248 and tenidap, were commercialized as medicines by Pfizer Inc. The traditional method for synthesizing these compounds is the Knoevenagel reaction, but it is sometimes limited due to its low stereoselectivity.[1,2] Recently, much attention has been paid on transition metal-catalyzed transformations.[3−5] Despite the high selectivity and efficiency of these transition metal-catalyzed methods, many require the use of expensive 2-haloanilides or 2-(alkynyl)phenylisocyanates as the starting materials.[3] Direct C−H functionalization has emerged as a promising and economically attractive alternative for the direct cyclization of *N*-arylpropiolamides with an electrophile[4] or a nucleophile.[5] Zhu and co-workers have first reported a Pd(0)-catalyzed intermolecular domino carbopalladation/C−H activation/C−C bond-forming reaction that employs both an anilide sp^2 C−H bond and an electrophilic reagent (aryl iodide) as the coupling partners.[4] However, only carbon atoms were introduced to the triple bond to form carbon−carbon bonds. Many bioactive 3-methyleneindolin-2-ones include the carbon−heteroatom bonds at the terminal of the 3-methylene group. Recently, we described several protocols for constructing carbon−carbon bonds or carbon−heteroatom bonds at the terminal of the 3-methylene group by the Pd(II)/Pd(IV)-catalyzed intermolecular C−H functionalization of *N*-arylpropiolamides with a nucleophilic reagent (phthalimide, an acid, or an aryliodonium salt). However, these oxidative approaches suffer the limitation of requiring noneasily accessible iodine(III) salts as the oxidants.[5] Therefore, a novel strategy, involving the use of inexpensive and environmentally benign oxidants, able to carry out the C−H functionalization to construct carbon−heteroatom bonds, would be highly desirable.[6−9] Here, we report the first example of Pd(II)-catalyzed intramolecular C−H activation reactions of 3-(2-(hydroxymethyl)aryl)-*N*-phenylpropiolamides to prepare (*E*)-3-(isobenzofuran-3(1*H*)-

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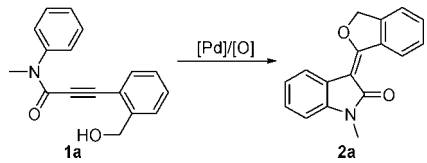
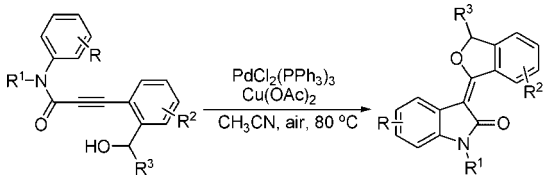
TABLE 1. Screening Optimal Conditions[a]



entry	catalyst	[O]	solvent	t (h)	yield (%)[d]
1[c]	$PdCl_2(PPh_3)_2$		MeCN	10	0
2	$PdCl_2(PPh_3)_2$	air	MeCN	10	trace
3[c]	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$	MeCN	25	trace
4	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	MeCN	10	68
5[d]	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2/O_2$	MeCN	25	65
6	$PdCl_2(PPh_3)_2$	$Cu(OTf)_2$/air	MeCN	10	mixture
7	$PdCl_2(PPh_3)_2$	$CuCl_2$/air	MeCN	10	mixture
8[e]	$PdCl_2(PPh_3)_2$	air	MeCN	10	25
9[f]	$PdCl_2(PPh_3)_2$	air	MeCN	10	mixture
10[e]	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	MeCN	10	39
11[g]	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	MeCN	10	60
12	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	THF	10	48
13	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	dioxane	10	42
14	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	DMF	10	61
15	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$/air	CH_2ClCH_2Cl	10	41
16	$PdCl_2/PPh_3$	$Cu(OAc)_2$/air	MeCN	10	56
17	$Pd(OAc)_2/PPh_3$	$Cu(OAc)_2$/air	MeCN	10	44
18	$PdCl_2/PCy_3$	$Cu(OAc)_2$/air	MeCN	10	40
19	$PdCl_2/P(o\text{-tol})_3$	$Cu(OAc)_2$/air	MeCN	10	10
20[h]	$PdCl_2$/IMes	$Cu(OAc)_2$/air	MeCN	10	51
21	$PdCl_2$/bipyridinyl	$Cu(OAc)_2$/air	MeCN	10	35
22	$PdCl_2$	$Cu(OAc)_2$/air	MeCN	10	8
23		$Cu(OAc)_2$/air	MeCN	10	0

[a] Reaction conditions: **1a** (0.2 mmol), [Pd] (5 mol %), [Cu] (10 mol %), solvent (2 mL) at 80 °C under air atmosphere. [b] Isolated yield. [c] Under argon atmosphere. [d] Under oxygen atmosphere. [e] $PhI(OAc)_2$ (1.5 equiv) was added. [f] Oxone (1.5 equiv) was added. [g] $Cu(OAc)_2$ (1 equiv). [h] IMes = 1,3-dimesitylimidazol-2-ylidene.

ylidene)indolin-2-ones using a catalytic amount of $Cu(OAc)_2$combined with air as the oxidant (eq 1). (*E*)-3-(Isobenzofuran-3(1*H*)-ylidene)indolin-2-ones have also been proven to display high bioactivity as potential tyrosine kinase inhibitors.[1g]



(1)

As shown in Table 1, 3-(2-(hydroxymethyl)phenyl)-*N*-methyl-*N*-phenylpropiolamide (**1a**) was selected as the model substrate to screen the optimal reaction conditions. Initially, we sought effective oxidants. We found that $Cu(OAc)_2$ combined with air provided the best results. No reaction was observed in the absence of oxidants (entry 1). While trace amounts of the target (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)-1-methylindolin-2-one (**2a**)[10] were determined by GC-MS analysis with either air or $Cu(OAc)_2$ as the oxidant alone (entries 2 and 3), $Cu(OAc)_2$ combined with air increased the yield of **2a** sharply to 68% (entry 4). The yield was reduced slightly with oxygen instead of air (entry 5). We found that the other oxidant systems, such as $Cu(OTf)_2$/air, $CuCl_2$/air, $PhI(OAc)_2$/air, oxone/air, and $Cu(OAc)_2/PhI(OAc)_2$/air, were less effective (entries 6−10). The amount of $Cu(OAc)_2$ was also evaluated, and 1 equiv of $Cu(OAc)_2$ decreased the yield to some extent (entry 11). Subsequently, the effect of solvent was examined, and it turned out that MeCN was the most effective solvent in terms of yield (entries 4 and 12−15). Finally, a number of other Pd catalytic systems, including $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, $PdCl_2/PCy_3$, $PdCl_2/P(o\text{-tol})_3$, $PdCl_2$/Imes, $PdCl_2$/bipyridinyl, and $PdCl_2$, were investigated, and they were less efficient than $PdCl_2(PPh_3)_2$ (entries 16−22). It is noted that the reaction does not take place without Pd (entry 23).

We next explored the scope of the reaction under the standard conditions, and the results are summarized in Table 2.[10] The results demonstrated that various 3-(2-(hydroxymethyl)aryl)-*N*-phenylpropiolamides **1b**−**r** were suitable to afford the corresponding (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)indolin-2-ones in moderate yields under the standard conditions. Gratifyingly, the *N*-methyl group can be replaced for a benzyl group without affecting the yield in the presence of $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and air (entry 1).

Subsequently, substitutents on the *N*-aryl rings were tested (entries 2−11). We found that both electron-withdrawing and electron-donating substitutents, such as methyl, butyl, methoxy, fluoro, chloro, bromo, ester, and trifluoromethyl, were tolerated well (entries 2−11). It is noteworthy that the reaction of the amide **1k** bearing a *m*-methyl group gives the corresponding 6-aryl C−H activated product **2k** regiospecifically in 40% yield (entry 10). Gratifying, the reaction conditions are compatible with ether, halide, and ester functional group (entries 4−9). The substitution in the alkynylarene moiety was investigated under the standard conditions (entries 12−17). We found that 3-(4,6-disubstituted aryl)propiolamides **1m** and **1n** could also undergo the reaction with $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and air smoothly in moderate yields (entries 12 and 13). It was interesting to diclose that heteroarylpropiolamides **1o**−**q** were also suitable substrates (entries 14−16). 3-(3-(Hydroxymethyl)thiophen-2-yl)-*N*-methyl-*N*-phenylpropiolamide (**1o**), for instance, was treated with $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and air to gave the target product in 73% yield (entry 14). Notably, 17% yield was still achieved from a tertiary benzyl alcohol after 22 h (entry 17).

As shown in Scheme 1, a mixture of products including 1-methyleneisobenzofuran (**3s**) was isolated from the reaction of substrate **1s** with $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and air. However, both amine **1t** and ester **1u** were unsuitable for the reaction with a mixture of products being formed.

To elucidate this transformation further, kinetic isotope effect studies as outlined in Scheme 2 were conducted. The results demonstrated that this reaction exhibited significant intermolecular ($k_H/k_D = 2.2$) and intramolecular ($k_H/k_D = 4.3$) hydrogen/deuterium kinetic isotope effects. These data are in a range of

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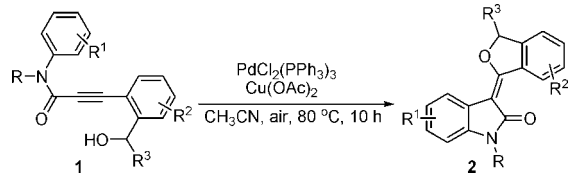
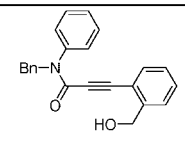
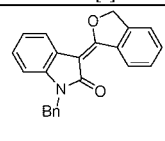
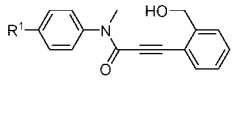
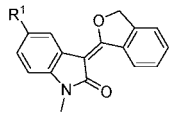
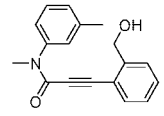
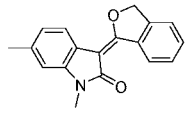
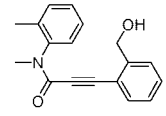
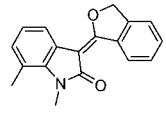
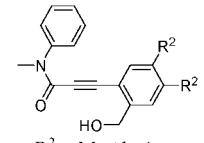
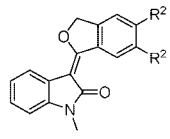
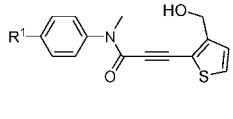
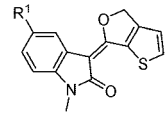
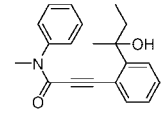
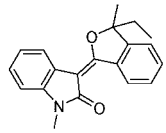
(10) The structure and the *E*-configuration of the products **2** were unambiguously assigned by X-ray analysis of the product **2c** (Figure 1), see the Supporting Information for details.

(11) In Zhu's and our reported results, the intermolecular k_H/k_D value is 1, and the intramolecular k_H/k_D value is about 2.8 to 3.4, see refs 4 and 5.

TABLE 2. Palladium-Catalyzed Intramolecular Cyclization of Amides 1 in the Presence of $PdCl_2(PPh_3)_2$, $Cu(OAc)_2$, and Air[a]



Entry	Substrate	[I][a]	Yield (%)[b]
1	 (**1b**)	 (**2b**)	61
2	 R^1 = Me (**1c**)	 R^1 = Me (**2c**)	67%
3	R^1 = *n*-Bu (**1d**)	R^1 = *n*-Bu (**2d**)	53%
4	R^1 = MeO (**1e**)	R^1 = MeO (**2e**)	48%
5	R^1 = F (**1f**)	R^1 = F (**2f**)	55%
6	R^1 = Cl (**1g**)	R^1 = Cl (**2g**)	58%
7	R^1 = Br (**1h**)	R^1 = Br (**2h**)	60%
8	R^1 = CO_2Me (**1i**)	R^1 = CO_2Me (**2i**)	30%
9	R^1 = CF_3 (**1j**)	R^1 = CF_3 (**2j**)	50%
10	 (**1k**)	 (**2k**)	40%
11[c]	 (**2l**)	 (**2l**)	10%
12	 R^2 = Me (**1m**)	 R^2 = Me (**2m**)	42%
13	R^2 = MeO (**1n**)	R^2 = MeO (**2n**)	47%
14	 R = H (**1o**)	 R = H (**2o**)	73%
15	R = Me (**1p**)	R = Me (**2p**)	67%
16	R = Cl (**1q**)	R = Cl (**2q**)	60%
17	 (**1r**)	 (**2r**)	17

[a] Reaction conditions: **1** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), $Cu(OAc)_2$ (10 mol %), and MeCN (2 mL) at 80 °C under air atmosphere for 10 h. [b] Isolated yield. The substrate **1** was consumed completely, and some decomposed products by the cleavage of two C−N bons were determined by GC-MS analysis. [c] For 22 h.

the kinetic isotope effects observed for the reactions proceeding via the Pd-catalyzed aromatic C−H functionalization pathways, i.e., the C−H functionalization step is the rate-determining step in the present reaction and the mechanism of C−H activation is incompatible with the SEAr mechanism.[7] It is noteworthy

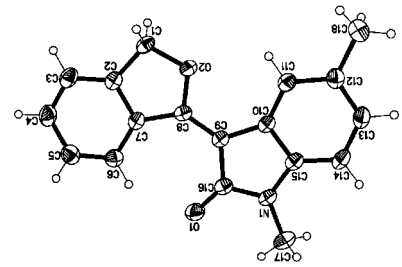
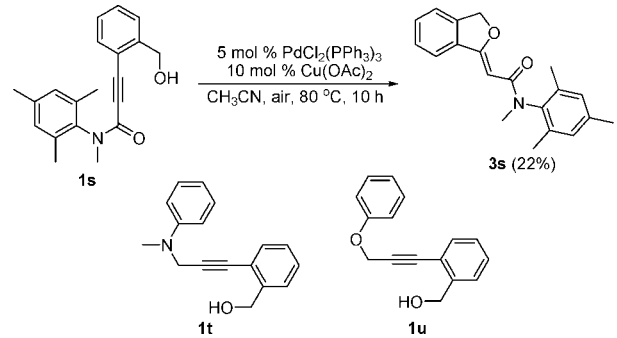
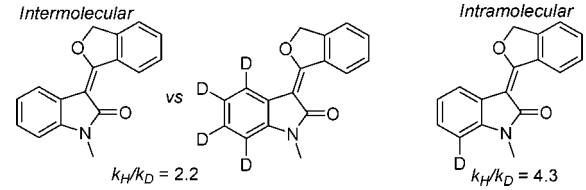


FIGURE 1. X-ray structure of **2c**.

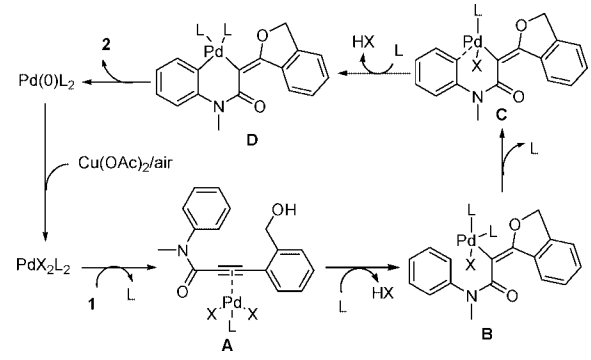
SCHEME 1. The Reactions of Other Substrates



SCHEME 2. Kinetic Isotope Effect Experiments



SCHEME 3. A Working Mechanism



that these kinetic isotope effects are different from those of Zhu's and our reported intermolecular C−H activation reactions.[4,5,11]

Accordingly, a possible mechanisms as shown in Scheme 3 is proposed on the basis of the reported and present results.[4−10] Complexation of the triple bond with the active Pd(II) species readily occurs to afford intermediate **A**.[6−9] Intermediate **A** undergoes the intramolecular cis-addition of Pd and −OH to the triple bond to give intermediate **B**.[6−9] Oxidative C−H activation/reductive elimination of intermediate **B** affords **2** and a Pd(0) species. The active Pd(II) species are regenerated from oxidation of the Pd(0) species by $Cu(OAc)_2$ and air to start a new catalytic cycle. In the process, the propiolamido group may facilitate the activation of the *o*-arene C−H bond.[6b,12]

(12) For selective papers, see: (a) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (b) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949.

In summary, we have developed a new route to selectively construct two heterocyclic rings in one step by an intramolecular C−H functionalization protocol. This protocol allows selective cyclization of various 3-(2-(hydroxymethyl)aryl)-*N*-methyl-*N*-arylpropiolamides possessing electron-rich and electron-deficient aryl rings into the corresponding (*E*)-3-(isobenzofuran-3(1*H*)-ylidene)indolin-2-ones. Mechanisms involving the C−H activation process have been proposed for this transformation on the basis of the observed values of kinetic isotope effects.

Experimental Section

Typical Experimental Procedure for the Palladium-Catalyzed Intramolecular C−H Functionalization Process. A mixture of *N*-arylpropiolamides **1** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), $Cu(OAc)_2$ (10 mol %), and MeCN (2 mL) was stirred at 80 °C under air atmosphere for 10 h until complete consumption of starting material as monitored by TLC. Then the mixture was washed with saturated NaS_2O_3 and extracted with diethyl ether. The organic layers were dried with Na_2SO_3 and evaporated under vacuum, then the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product **2**.

(*E*)-3-(Isobenzofuran-1(3*H*)-ylidene)-1-methylindolin-2-one (2a): [1g] yellow solid, mp 157.2−159.3 °C (uncorrected); ^{1}H NMR (500 MHz, CD_3Cl) δ 9.77 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.50−7.48 (m, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 5.58 (s, 2H), 3.29 (s, 3H); ^{13}C NMR (125 MHz, CD_3Cl) δ 168.0, 167.6, 143.2, 140.4, 132.0, 131.6, 128.5, 128.4, 126.1, 123.7, 123.0, 121.4, 120.2, 106.9, 103.1, 75.6, 25.7; IR (KBr, cm^{-1}) 1683; LRMS (EI, 70 eV) *m*/*z* (%) 263 (M^+, 91), 234 (100); HRMS (EI) for $C_{17}H_{13}NO_2$ (M^+) calcd 263.0946, found 263.0946.

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Supporting Information Available: General experimental procedures, characterization data for **2**, copies of spectra, and a CIF file of the product **2c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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