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Sequential Intermolecular Aminopalladation/*ortho*-Arene C–H Activation Reactions of *N*-Phenylpropiolamides with Phthalimide

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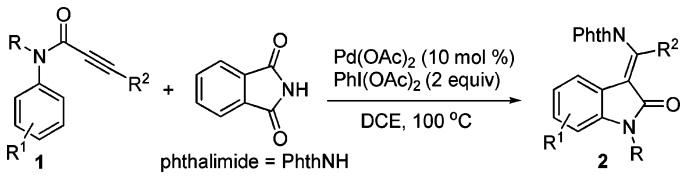
ABSTRACT



A novel palladium-catalyzed intermolecular aminopalladation/C–H activation method for selectively synthesizing (*E*)-(2-oxindolin-3-ylidene)-phthalimides has been developed. In the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$, alkynes were difunctionalized with a phthalimide and an arene sp^2 C–H bond to selectively synthesize (*E*)-(2-oxoindolin-3-ylidene)phthalimides, which products are of great potential pharmaceutical value products in many major therapeutic areas, such as oncology, inflammation, neurology, immunology, and endocrinology. To the best of our knowledge, the reaction serves as the first example of intermolecular aminopalladation/C–H activation reactions of alkynes.

Aminopalladation of an alkyne with an amine or an amide provides a convenient route to the prevalent Pd(II) σ-vinyl intermediates, which are frequently utilized in the synthesis of a variety of biologically active and natural N-containing compounds.[1−3] Despite significant efforts that have been devoted to this area, only two papers have been reported on intermolecular aminopalladation of alkynes (eq 1).[3]

Moreover, rapid protonolysis of these Pd(II) σ-vinyl intermediates, particularly in the intermolecular aminopalladation process, creates a substantial hindrance for the second functionalization of the alkynes, which limits their application in organic synthesis.[1−3] Thus, our aim is to utilize the Pd(II) σ-vinyl intermediate **A** for a new C−C bond (eq 2). After a series of trials, we developed a mild method for achieving this goal based on some recent reports showing that Pd−C σ-bonds are readily oxidized by iodine(III)-based

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(1) (a) For reviews, see: (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley−Interscience: New York, 2002. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Alonso, F.; Beletskava, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (e) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (g) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874. (h) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407.

(2) For very recent papers on the intramolecular aminopalladation reactions of alkynes, see: (a) Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C. H.; Lu, B. Z. *Org. Lett.* **2006**, *8*, 3573. (b) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083. (c) Lu, B. Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271. (d) Shen, Z.; Lu, X. *Tetrahedron* **2006**, *62*, 10896. (e) Tang, Z.-Y.; Hu, Q.-S. *Adv. Synth. Catal.* **2006**, *348*, 846. (f) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Perez, A.; Fananas, F. J. *J. Org. Chem.* **2007**, *72*, 5113. (g) Tang, S.; Xie, Y.-X.; Li, J.-H.; Wang, N.-X. *Synthesis* **2007**, 1841.

(3) (a) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670. (b) Shimada, T.; Bajracharya, G. B.; Yamamoto, Y. *Eur. J. Org. Chem.* **2005**, 59.

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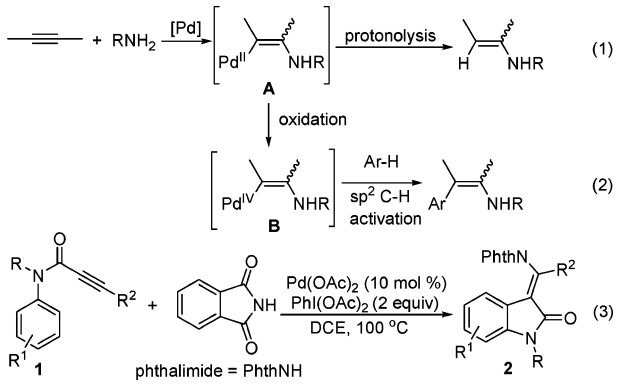
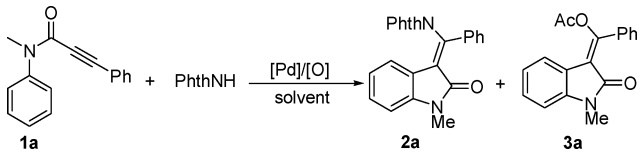
oxidants.[4] Here, we report the first examples of intermolecular aminopalladation/C−H activation reactions of alkynes with a phthalimide and an *ortho*-arene sp^2 C−H bond in the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$ (eq 3).



As demonstrated in Table 1, the reaction of *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) with phthalimide was chosen to screen the optimal conditions.[5] Initially, a series of palladium catalysts combined with oxidants were tested in $ClCH_2CH_2Cl$ (DCE). Without any oxidants, the reaction of amide **1a** with phthalimide and $Pd(OAc)_2$ did not occur (entry 1). Identical results were also obtained using either 1,4-benzobenzoquinone (BQ) or O_2 as the oxidant (entries 2 and 3). Gratifyingly, a trace amount of the target aminopalladation product **2a** could be observed by GC−MS analysis in the presence of $Cu(OAc)_2$ (entry 4). This prompted us to evaluate other oxidants, such as $K_2S_2O_8$, oxone, and $PhI(OAc)_2$ (entries 5−7). While 11−14% yield of **2a** was isolated using $K_2S_2O_8$ or oxone as the oxidant (entries 5 and 6), $PhI(OAc)_2$ enhanced the yield of **2a** sharply to 61% together with a 4% yield of an acetoxypalladation product **3a** (entry 7). Two other palladium catalysts, $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$, were subsequently tested, and the results showed that their catalytic activities were reduced to some extent (entries 8 and 9). Note that no reaction takes place without Pd catalysts (entry 10).

Table 1. Screening Conditions[a]



entry	[Pd]/[O]	isolated yield (%) 2a	3a
1	$Pd(OAc)_2$	0	0
2	$Pd(OAc)_2$/BQ	0	0
3	$Pd(OAc)_2/O_2$	0	0
4	$Pd(OAc)_2/Cu(OAc)_2$	trace	0
5	$Pd(OAc)_2/K_2S_2O_8$	14	0
6	$Pd(OAc)_2$/oxone	11	0
7	$Pd(OAc)_2/PhI(OAc)_2$	61	4
8	$PdCl_2/PhI(OAc)_2$	56	7
9	$Pd(CH_3CN)_2Cl_2/PhI(OAc)_2$	57	8
10	$PhI(OAc)_2$	0	0

[a] Reaction conditions: **1a** (0.2 mmol), phthalimide (0.6 mmol), [Pd] (10 mol %), [O] (0.4 mmol) and DCE ($ClCH_2CH_2Cl$; 3 mL) at 100 °C for 4 h.

With the standard conditions in hand, a variety of *N*-phenylpropiolamides were surveyed to explore scope of the oxidative carboamination/C−H activation reaction (Table 2).[6] We were happy to find that *N*-benzyl-*N*,3-diphenylpropiolamide (**1b**) selectively underwent the desired reaction with phthalimide, $Pd(OAc)_2$ and $PhI(OAc)_2$ in a 51% yield (entry 1). However, trace amounts of products **2** were observed from the analogous amides with the benzyl group replaced by a hydrogen or an acetyl group (entries 2 and 3). To our delight, a number of *N*-methyl-*N*-phenylpropiolamides **1e**−**l** bearing various functional groups, such as methyl, fluoro, chloro, bromo, and ester, on the N-aryl ring were tolerated well (entries 4−11). Amide **1k** having a 2-bromo group, for instance, successfully reacted with phthalimide, $Pd(OAc)_2$, and $PhI(OAc)_2$ to afford the target product **2k** in a 50% yield (entry 10). It is noteworthy that *N*-(3-substituted aryl)propiolamide (**1f**) regioselectively provides the 6-position C−H activated product **2f** in 50% yield due to its lower steric hindrance (entry 5). However, the target product **2l** from substrate **1l** includes a mixture of (*E*)- and (*Z*)-isomers (entry 11). Gratifyingly, alkynes **1m**−**o** bearing aryl groups, electron-rich or electron-deficient, at the terminus of the alkyne also worked with phthalimide smoothly under the standard conditions, but the steric hindrance and an electron-withdrawing group reduced the yield to some extent (entries 13 and 14). While 4-methoxyphenylalkyne **1m** afforded the target product **2m** in a 77% yield, 2-methoxyphenylalkyne **1n** provided only 42% yield of the corresponding product **2n** (entries 12 and 13). Unfortunately, *N*-phenylpropiolamides **1p** and **1q** bearing a hydrogen or methyl group at the terminus of the alkyne were not suitable substrates under the standard conditions (entries 15 and 16).

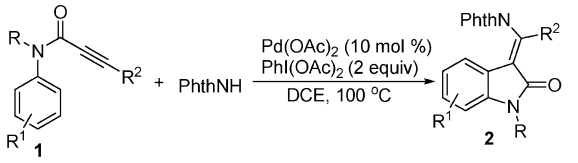
As listed in Scheme 1, the earlier reports on palladium-catalyzed transformations for the synthesis of 3-(diphenylmethylene)oxindoles proceed via (i) the reaction of *N*-(2-iodophenylpropiolamides or 2-(alkynyl)phenylisocyanates with arylboronic acids,[7a−d] and (ii) the reaction of *N*-phenyl-

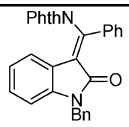
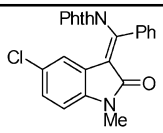
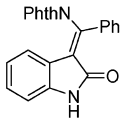
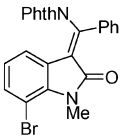
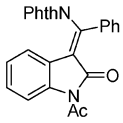
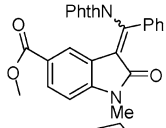
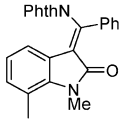
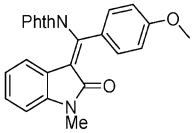
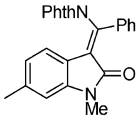
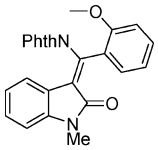
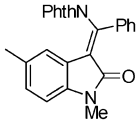
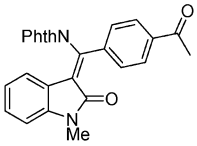
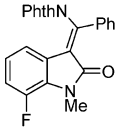
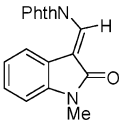
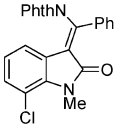
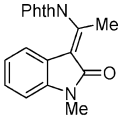
(4) For selected papers on the Pd^{II}/Pd^{IV} process in the presence of iodine(III)-based oxidants, see: (a) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (c) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (d) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (e) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (f) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. (g) Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *26*, 1365. (h) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (i) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (j) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836.

(5) The other three solvents (MeCN, THF, and HOAc) and two additives (NaOAc and $AgBF_4$) were evaluated, and they disfavored the aminopalladation reaction to some extent. The detailed data were summarized in Table S1 (Supporting Information).

(6) The products **2** were selectively obtained as (*E*)-isomers except for the product **2l**. The *E*-configuration of the tretrasubstituted double bond was determined according to COSY and NOESY spectroscopy of **2n**, and the authoritative 5-H and/or 8-H shift data of oxindoles in ref 7.

Table 2. $Pd(OAc)_2$-Catalyzed Carboamination/C−H Activation of *N*-Phenylpropiolamides **1** with Phthalimide[a]

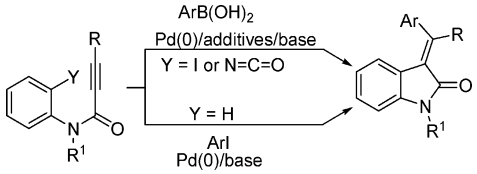


Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1		51 (**2b**)	9		71 (**2j**)
2		trace (**2c**)	10		50 (**2k**)
3		trace (**2d**)	11[c]		83 (**2l**)
4		60 (**2e**)	12		77 (**2m**)
5		50 (**2f**)	13		42 (**2n**)
6		70 (**2g**)	14		43 (**2o**)
7		43 (**2h**)	15		<5 (**2p**)
8		70 (**2i**)	16		<5 (**2q**)

[a] Reaction conditions: **1** (0.2 mmol), phthalimide (0.6 mmol), $Pd(OAc)_2$ (10 mol %), $PdI(OAc)_2$ (0.4 mmol), and DCE (3 mL) at 100 °C for 3−10 h. [b] Isolated yield. [c] The ratio of *E*:*Z* is 3:1 as determined by ^1H NMR spectra.

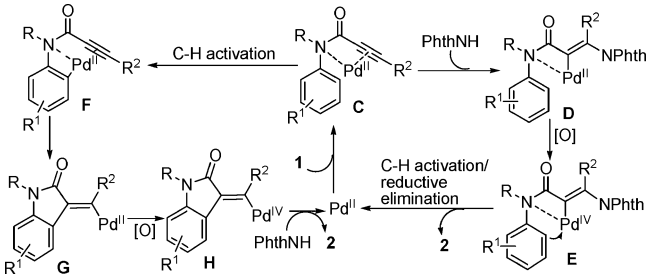
propiolamides with aryl iodides.[7e−f] Compared with these reported transformations, the present protocol is clearly different: (i) all these reported transformations worked in the presence of a Pd(0) catalyst and a base. In contrast, the present protocol was conducted with the aid of a Pd(II) catalyst and an oxidant ($PhI(OAc)_2$), and no bases were required. (ii) Zhu's method proceeded via an addition of alkyne with an electrophilic aryl iodide reagent, whereas the present protocol is attack of alkyne with a nucleophilic amide reagent.

Scheme 1



To elucidate the present results, a working mechanism as outlined in Scheme 2 was proposed on the basis of the

Scheme 2. Possible Mechanisms



previously proposed mechanism, in particular the Pd^{II}/P^{IV}-catalyzed amination of olefins mechanism.[1−4,7] Complexation of Pd(II) with both C≡C and nitrogen occurs to afford intermediate **C** followed by *cis*-aminopalladation of **C** with phthalimide to generate intermediate **D**. The Pd(II) intermediate **D** can be oxidized readily to generate Pd(IV) intermediate **E** by $PhI(OAc)_2$.[4] The *ortho*-arene sp^2 C−H bond on the N-aromatic ring is then activated by the Pd(IV) species to form a new C−C bond,[4a−d,g,h] and regenerate the active Pd(II) species. The results showed that the traditional Pd(0)/Pd(II) oxidants, such as $Cu(OAc)_2$, BQ, and O_2, were ineffective for the present transformation, which ruled out the Pd(0)/Pd(II) mechanism. Although no arylamine product was observed in the present transformation,[10] we cannot rule

(7) For papers on the synthesis of 3-(diphenylmethylene)oxindoles from the reactions of *N*-phenylpropiolamides, see: Pd: (a) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972. (c) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (d) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (e) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (f) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. In/Pd: (g) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825. Rh: (h) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799.

(8) For a patent on the synthesis of 3-(aminomethylene)oxindoles, which also display high pharmaceutical value, see: Burgdorf, L. T.; Bruge, D.; Greiner, H.; Kordowicz, M.; Sirrenberg, C.; Zenke, F. PCT Int. Appl. WO 2006131186 (CAN 146:62590; AN 2006:1312199), 2006.

(9) For selected papers, see: (a) Mohammadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B. K.; Hubbard, S. R.; Schlessinger, J. *Science* **1997**, *276*, 955. (b) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem.* **1999**, *42*, 5120. (c) Hare, B. J.; Walters, W. P.; Caron, P. R.; Bemis, G. W. *J. Med. Chem.* **2004**, *47*, 4731. (d) Noble, M. E. M.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *203*, 1800. (e) Liao, J. J.-L. *J. Med. Chem.* **2007**, *50*, 409.

(10) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

out another possible mechanism, which is initiated by arene C−H bond palladation to yield intermediate **F** followed by *cis*-addition with alkyne to give vinylpalladation intermediate **G**. Pd(IV) intermediate **H** is generated by oxidation of the Pd(II) intermediate **G**. Pd(IV) intermediate **H** undergoes reductive elimination with PhthNH to generate the product **2** and the active Pd(II) species.

In summary, we have developed a novel palladium-catalyzed carboamination/C−H activation of the alkyne method for selectively synthesizing (*E*)-(2-oxindolin-3-ylidene)phthalimide. In the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$, *N*-phenylpropiolamides successfully underwent the difunctionalization reactions with a phthalimide and an aryl sp^2 C−H bond in moderate to good yields. Importantly, we have developed a novel route to the synthesis of new types of oxindoles,[7,8] and oxindoles are of great potential pharmaceutical value products in many major therapeutic areas, such as oncology, inflammation, neurology, immunology, and endocrinology.[8,9] Work to probe the detailed mechanism, determine the bioactivities of these compounds, and apply the reaction in pharmaceutical synthesis is 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 for the intramolecular electrophilic *ipso*-iodocyclization reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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