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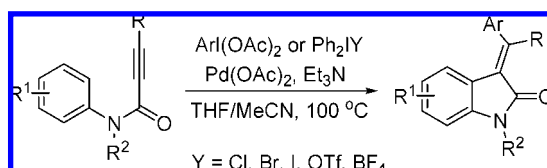
Palladium-Catalyzed C–H Functionalization of N-Arylpropiolamides with Aryliodonium Salts: Selective Synthesis of 3-(1-Arylmethylene)oxindoles

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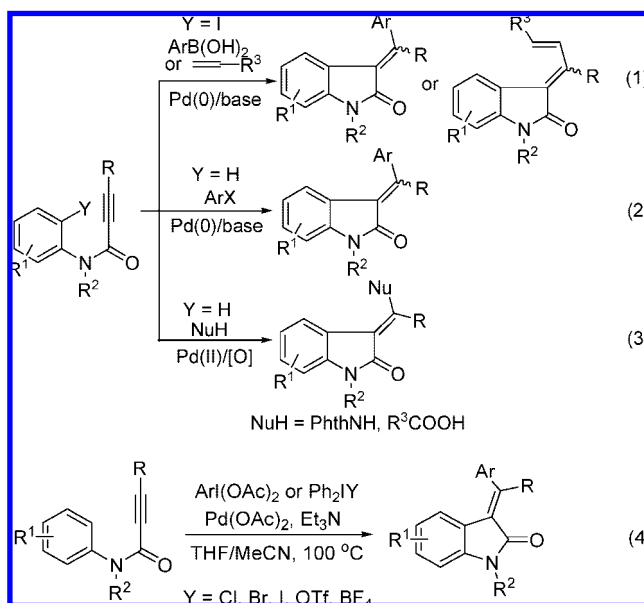


A selective and efficient method for the synthesis of 3-(1-arylmethylene)oxindoles by palladium-catalyzed C–H functionalization of anilides with aryliodonium salts has been developed. In the presence of Pd(OAc)₂ and Et₃N, a variety of anilides underwent the reaction with aryliodonium salts to afford the corresponding 3-(1-arylmethylene)oxindoles in moderate to good yields. It is noteworthy that the reaction can be conducted providing moderate yields even without bases. The mechanism of the reaction was also discussed.

Introduction

The construction of the oxindole skeleton is of immense interest in organic synthesis due to the prevalence of this structure motif in a myriad of biological and pharmaceutical compounds, and these compounds display potential utilizations in many major therapeutic areas, such as oncology, inflammation, CNS, immunology, and endocrinology.¹ As a result, considerable effort has been devoted to the development of new and efficient methods for the synthesis of 3-methyleneindolin-2-ones.^{1,2,3,4} One of the reliable approaches for the preparation of this class of compounds is

SCHEME 1. Three Protocols for the Synthesis of Oxindoles with Pd Catalysts



palladium-catalyzed domino reactions (Scheme 1).² Player and co-workers,^{2a} for instance, demonstrated a Heck-car-

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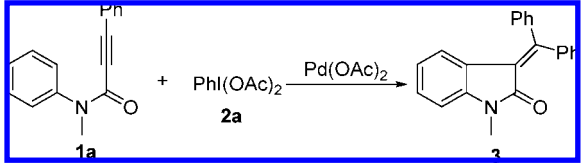
(1) (a) Mohammadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B. K.; Hubbard, S. R.; Schlessinger, J. *Science* **1997**, 276, 955. (b) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. *J. Med. Chem.* **1999**, 42, 5120. (c) Hare, 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**, 304, 1800. (e) Liao, J. J.-L. *J. Med. Chem.* **2007**, 50, 409. (f) *Drugs Future* **1990**, 15, 898. (g) Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, 39, 10. (h) Andreani, A.; Burnelli, S.; Granaola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Kunkel, M. W. *J. Med. Chem.* **2006**, 49, 6922. (i) Graczyk, P. P. *J. Med. Chem.* **2007**, 50, 5773.

bocyclization/Suzuki-coupling sequence protocol for the synthesis of (*E*)-3,3-(diarylmethylene)indolinones in the presence of $\text{Pd}(\text{PPh}_3)_4$ and CuTC (copper(I) thiophene-2-carboxylate), but the selectivity is not desirable. Subsequently, Takemoto and co-workers^{2b} have reported a selective method for the synthesis of oxindoles by $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ -catalyzed Heck/Suzuki, Heck/Heck, and Heck/carbonylation/Suzuki domino reactions of *N*-(2-iodophenyl)propionamides with arylboronic acids or alkenes. However, the above two methods require the use of 2-iodoanilides as the starting materials besides the requirement of some additives, such as phosphine ligands and CuTC (eq 1 in Scheme 1). To overcome these drawbacks, Zhu and co-workers have developed a $\text{Pd}(\text{OAc})_2$ -catalyzed domino carbopalladation/C–H activation/C–C bond-forming process that uses an anilide sp^2 C–H bond as one of the coupling partners for selectively synthesizing 3-(diarylmethylene)oxindoles (eq 2).^{2c,d} Very recently, we developed a novel palladium-catalyzed C–H functionalization process for the preparation of (*E*)-(2-oxindolin-3-ylidene)phthalimides and (*E*)-(2-oxindolin-3-ylidene)methyl acetates in the presence of $\text{PhI}(\text{OAc})_2$ (eq 3).^{2i,j} We were interested to observe that 3-(1-phenylmethylene)oxindoles were isolated as byproduct in our previous experiments. This prompts us to explore the feasibility of the use of both anilides and arylidonium salts as the coupling partners to construct the oxindole skeleton. Here, we wish to report a simple and efficient protocol for the synthesis of 3-(1-arylmethylene)oxindoles by palladium-catalyzed C–H functionalization of anilides with arylidonium salts (eq 4).

Results and Discussion

As listed in Table 1, the optimal reaction conditions for the reactions of *N*-methyl-*N*,3-diphenylpropionamide (**1a**) with $\text{PhI}(\text{OAc})_2$ (**2a**) were screened. In the presence of 5 mol % of $\text{Pd}(\text{OAc})_2$, treatment of amide **1a** with **2a** in MeCN at 80 °C afforded the target product **3** in a 17% yield after 10 h (entry 1, Table 1). The results showed that both the reaction temperature and the amount of $\text{PhI}(\text{OAc})_2$ affected the yield to some extent (entries 2–4, Table 1). It turned out that 100 °C combined with 2 equiv of $\text{PhI}(\text{OAc})_2$ was the best reaction conditions for the reaction, and both further increasing temperature and loading

TABLE 1. Screening Optimal Conditions^a



entry	additive	<i>t</i> (°C)	solvent	yield (%)
1 ^b		80	MeCN	17
2 ^b		100	MeCN	35
3		100	MeCN	54
4		120	MeCN	55
5 ^c		100	MeCN	55
6		100	$\text{ClCH}_2\text{CH}_2\text{Cl}$	5
7		100	THF	53
8		100	THF/MeCN (1:4)	59
9	NaOAc	100	THF/MeCN (1:4)	57
10	NaHCO_3	100	THF/MeCN (1:4)	51
11	Et_3N	100	THF/MeCN (1:4)	79
12	NMP	100	THF/MeCN (1:4)	19
13 ^d	Et_3N	100	THF/MeCN (1:4)	76
14 ^e	Et_3N	100	THF/MeCN (1:4)	77
15 ^f	Et_3N	100	THF/MeCN (1:4)	60
16 ^g	Et_3N	100	THF/MeCN (1:4)	0

^a Reaction conditions: **1a** (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), $\text{PhI}(\text{OAc})_2$ (2 equiv), and additive (2 equiv) in solvent (3 mL) at 100 °C for 10 h. ^b $\text{PhI}(\text{OAc})_2$ (1.2 equiv). ^c $\text{PhI}(\text{OAc})_2$ (3 equiv). ^d PdCl_2 (5 mol %) instead of $\text{Pd}(\text{OAc})_2$. ^e $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (5 mol %) instead of $\text{Pd}(\text{OAc})_2$. ^f $\text{Pd}(\text{PPh}_3)_4$ (5 mol %) instead of $\text{Pd}(\text{OAc})_2$. ^g Without $\text{Pd}(\text{OAc})_2$.

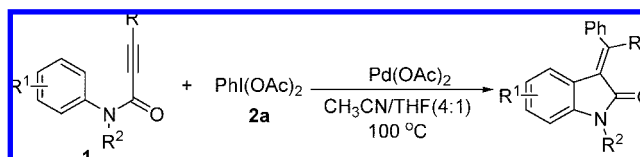
of $\text{PhI}(\text{OAc})_2$ affected the reaction slightly. Subsequently, the solvent effect was examined (entries 5–8, Table 1). We found that a mixture of THF and MeCN provided the best results (entry 8, Table 1). A number of bases, such as NaOAc, NaHCO_3 , Et_3N , and NMP (4-(*N,N*-dimethyl)pyridine), were also tested (entries 9–12, Table 1). NaOAc, the reported efficient base, displayed no activity for the reaction (entry 9, Table 1), and Et_3N provided the best results (entry 11, Table 1). To our surprise, both NaHCO_3 and NMP disfavored the reaction (entries 10 and 12, Table 1). Finally, a series of other Pd catalysts, including PdCl_2 , $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, and $\text{Pd}(\text{PPh}_3)_4$, were investigated (entries 13–15, Table 1). Identical results to those of $\text{Pd}(\text{OAc})_2$ were obtained by using PdCl_2 or $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, but $\text{Pd}(\text{PPh}_3)_4$ was less efficient. It is noteworthy that no reaction takes place without Pd catalysts (entry 16, Table 1).

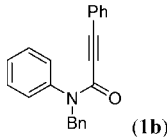
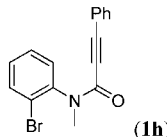
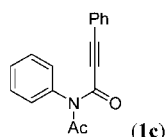
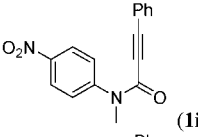
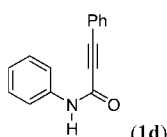
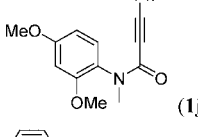
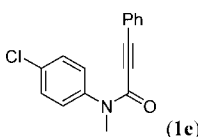
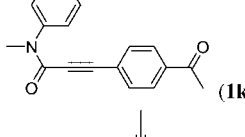
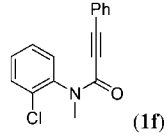
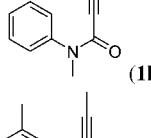
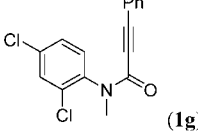
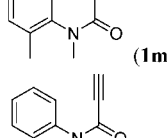
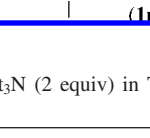
With the standard reaction conditions in hand, we then focused on the examination of scope of *N*-arylpropionamides by reacting with $\text{PhI}(\text{OAc})_2$ (Table 2). We found that *N*-benzyl-*N*,3-diphenylpropionamide (**1b**) still underwent the reaction with $\text{PhI}(\text{OAc})_2$, $\text{Pd}(\text{OAc})_2$, and Et_3N in THF/MeCN to afford the target product **4** in 82% yield (entry 1, Table 2), but the *N*-benzyl group replaced by the acetyl or hydrogen group was found to be unsuitable for the C–H functionalization reaction (entries 2 and 3, Table 2). Subsequently, the effect of substitutes on the *N*-aryl ring was evaluated, and the results demonstrated that a series of functional substitutes, such as chloro, bromo, nitro, methoxy, or methyl groups, on the aromatic motif were tolerated well. Amides **1f–j**, bearing a chloro group or two chloro groups on the *N*-aryl ring, all worked with $\text{PhI}(\text{OAc})_2$ well in good yields under the standard conditions (entries 4–6, Table 2). The C–H functionalization reaction of substrate **1h** having an *o*-bromo group was still conducted successfully in 53% yield (entry 7, Table 2). To our delight, the other amides with either electron-deficient or electron-rich *N*-aryl groups underwent the reaction smoothly to afford the corresponding target products

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(3) For papers on the synthesis of oxindoles with Rh as the catalysts and 2-alkynylaryl isocyanates as the substrates, see: (a) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, 8, 4799. (b) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, 8, 5075. (c) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, 10, 1743.

(4) For papers on the other methods for the synthesis of oxindoles, see: (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 20, 1133. (b) Sun, L.; Liang, C.; Shirazian, S.; Zhou, Y.; Miller, T.; Cui, J.; Fukuda, J. Y.; Chu, J.-Y.; Nematala, A.; Wang, X.; Chen, H.; Sistla, A.; Luu, T. C.; Tang, F.; Wei, J.; Tang, C. *J. Med. Chem.* **2003**, 46, 1116. (c) Wang, L.; Zhang, Y.; Hu, H.-Y.; Fun, H. K.; Xu, J.-H. *J. Org. Chem.* **2005**, 70, 3805. (d) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, 47, 4683. (e) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099. (f) Yang, T.-M.; Liu, G. *J. Comb. Chem.* **2007**, 9, 86.

TABLE 2. Palladium-Catalyzed C–H Functionalization Reactions of Amides **1** with $\text{PhI}(\text{OAc})_2$ (**2a**)^a

Entry	Amide	Time (h)	Yield (%)	Entry	Amide	Time (h)	Yield (%)
1	 (1b)	8	82 (4)	7	 (1h)	7	53 (10)
2	 (1c)	20	trace (5)	8	 (1i)	10	75 (11)
3	 (1d)	15	<5 (6)	9	 (1j)	22	74 (12)
4	 (1e)	7	81 (7)	10	 (1k)	6	78 (13)
5	 (1f)	7	84 (8)	11	 (1l)	5	80 (14)
6	 (1g)	8	83 (9)	12	 (1m)	25	73 (15)
				13	 (1n)	5	trace (16)

^a Reaction conditions: **1** (0.2 mol), $\text{Pd}(\text{OAc})_2$ (5 mol%), $\text{PhI}(\text{OAc})_2$ (2 equiv), and Et_3N (2 equiv) in $\text{THF}/\text{CH}_3\text{CN}$ (v/v 1:4, 3 mL) was stirred under air at 100 °C.

in good yields (entries 8 and 9, Table 2). For example, *N*-(2,4-dimethoxyphenyl)-*N*-methyl-3-phenylpropionamide (**1j**), a bulky and electron-rich amide, was treated with $\text{PhI}(\text{OAc})_2$, $\text{Pd}(\text{OAc})_2$, and Et_3N providing 74% yield (entry 9, Table 2). Finally, substituents at the terminal of the $\text{C}\equiv\text{C}$ bond of *N*-methyl-*N*-arylpropionamides were also evaluated. The results showed that *N*-methyl-*N*-arylpropionamides **1k–m**, having either a aryl group or a alkyl group, underwent the reaction with $\text{PhI}(\text{OAc})_2$ in good yields (entries 10–12, Table 2). However, *N*-methyl-*N*-phenylpropionamide (**1n**) was not a suitable substrate under the standard conditions (entry 13, Table 2).

The scope of arylidonium diacetates was also explored, and the results are summarized in Table 3. The results showed that a variety of arylidonium diacetates, either electron-deficient or electron-rich, all underwent the C–H functionalization reaction with *N*-methyl-*N*,3-diphenylpropionamide (**1a**) and $\text{Pd}(\text{OAc})_2$ smoothly in moderate to good yields (entries 1–9, Table 3). (*p*-Methylbenzene)iodonium diacetate (**2b**), for instance, was treated with amide **1a** smoothly to afford the target

product **17** in 75% yield (entry 1, Table 3). Interestingly, the bulky iodonium diacetate **2j** reacted with amide **1a** was still conducted successfully in 27% yield (entry 9, Table 3). The other amide, *N*-methyl-*N*-phenylbut-2-ynamide (**1m**), was also reacted with (*p*-acetylbenzene)iodonium diacetate (**2i**) smoothly in 60% yield under the standard conditions (entry 10, Table 3).

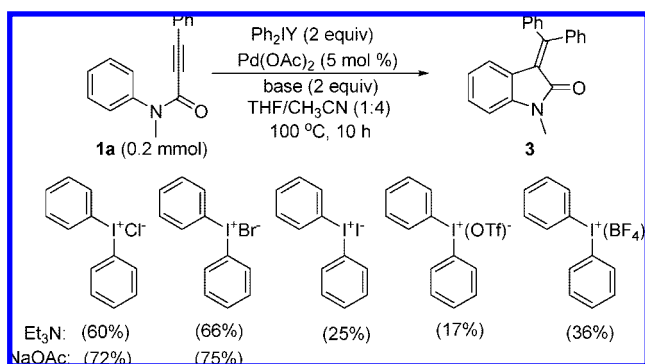
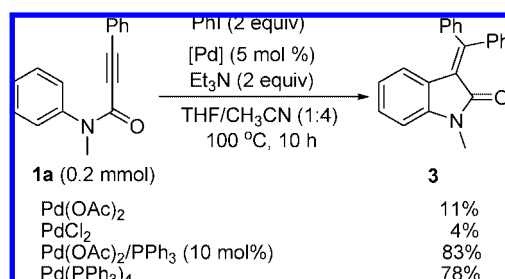
As demonstrated in Scheme 2, a series of diphenyliodonium salts were also tested in the presence of $\text{Pd}(\text{OAc})_2$. The results indicated that both diphenyliodonium chloride and diphenyliodonium bromide also displayed high efficient activity for the C–H functionalization reaction with *N*-methyl-*N*,3-diphenylpropionamide (**1a**) with Et_3N as the base. However, the other diphenyliodonium salts, including $[\text{Ph}_2\text{I}]\text{I}$, $[\text{Ph}_2\text{I}]\text{OTf}$, and $[\text{Ph}_2\text{I}]\text{BF}_4$, were less active in terms of the yields. Interestingly, both diphenyliodonium chloride and diphenyliodonium bromide are more efficient when Et_3N was replaced by NaOAc .

Four controlled reactions were conducted to elucidate the mechanism, and the results are summarized in Scheme 3. We found that treatment of *N*-methyl-*N*,3-diphenylpropionamide (**1a**)

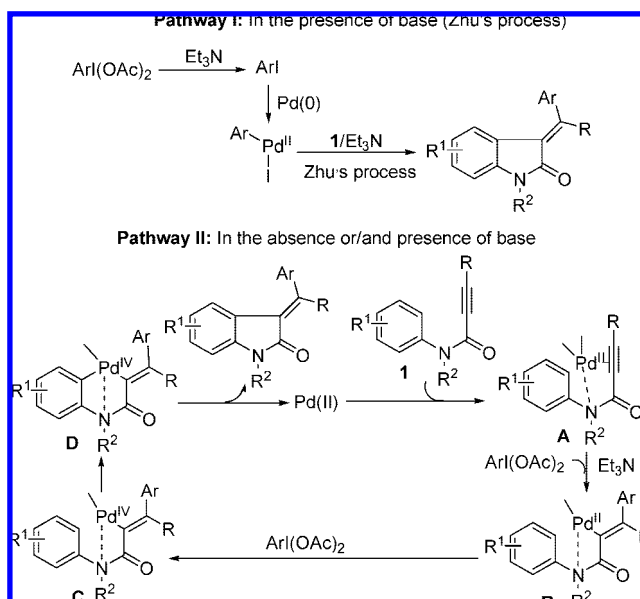
TABLE 3. Palladium-Catalyzed C–H functionalization Reactions of Amides (1) with Aryliodonium Diacetates (2)^a

entry	R	Ar	time (h)	isolated yield (%)
1	Ph (1a)	<i>p</i> -CH ₃ C ₆ H ₄ (2b)	9	75(17)
2	Ph (1a)	<i>o</i> -CH ₃ C ₆ H ₄ (2c)	20	54(18)
3	Ph (1a)	<i>p</i> -CH ₃ OC ₆ H ₄ (2d)	20	73(19)
4	Ph (1a)	<i>o</i> -CH ₃ OC ₆ H ₄ (2e)	24	48(20)
5	Ph (1a)	<i>p</i> -NO ₂ C ₆ H ₄ (2f)	24	63(21)
6	Ph (1a)	<i>o</i> -ClC ₆ H ₄ (2g)	15	82(22)
7	Ph (1a)	<i>m</i> -CH ₃ COC ₆ H ₄ (2h)	24	56(23)
8	Ph (1a)	<i>p</i> -CH ₃ COC ₆ H ₄ (2i)	24	65(24)
9	Ph (1a)	2,4,6-(CH ₃) ₃ C ₆ H ₄ (2j)	48	27(25)
10	Me (1n)	<i>p</i> -CH ₃ COC ₆ H ₄ (2i)	24	60(26)

^a All reaction were run under the following conditions: **1** (0.2 mol), Pd(OAc)₂ (5 mol %), ArI(OAc)₂ **2** (2 equiv), and Et₃N (2 equiv) in THF/CH₃CN (v/v 1:4, 5 mL) under air at 100 °C.

SCHEME 2. Palladium-Catalyzed C–H Functionalization Reactions of *N*-Methyl-*N*,3-diphenylpropiolamide(1a**) with Ph₂IY (**2**)**

SCHEME 3. Four Controlled Reactions


with iodobenzene and Pd(OAc)₂ afforded the desired product **3** in 11% GC yields under the present conditions (Zhu's conditions: Pd(OAc)₂, NaOAc, and DMF at 110 °C),^{2c} and PdCl₂ provided only 4% GC yield of **3** after 10 h. While satisfactory yields were obtained from the reaction of amide **1a** with PhI by using Pd(OAc)₂/PPh₃ or Pd(PPh₃)₄ as the catalyst (Zhu's conditions: Pd(PPh₃)₄, NaOAc, and DMF at 110 °C),^{2d} the results of Table 1 showed that Pd(PPh₃)₄ instead of Pd(OAc)₂ reduced the yield of the reaction between amide **1a** with PhI(OAc)₂ (entry 15, Table 1). Compared with the Zhu's results, the results suggested that the present reaction is conducted via a different process from that of Zhu to some extent. To further elucidate the mechanism, the reaction of PhI(OAc)₂ with Et₃N

SCHEME 4. Two Possible Mechanisms


was determined in situ by ¹H NMR analysis.⁷ The reaction of PhI(OAc)₂ with 2 equiv of Et₃N was conducted in CDCl₃ at room temperature. The results showed that 38% of PhI(OAc)₂ was decomposed by Et₃N to PhI after about 1 h, and 75% of PhI(OAc)₂ was decomposed after 10 h.

Based on the previously reported mechanisms^{2,3,5} and the present results,⁷ the C–H functionalization reaction may proceed via two possible processes as outlined in Scheme 4. In the presence of base (Et₃N), ArI(OAc)₂ is readily decomposed to generate ArI, and ArI then reacts with amide **1** via Zhu's process to afford the target product. However, we cannot rule out another possible process because the reaction can occur without bases: Coordination of Pd^{II} with alkyne and nitrogen readily occurred to afford intermediate **A**, followed by cis-addition of intermediate **A** with Pd and ArI(OAc)₂ to afford intermediate **B** in the absence or presence of Et₃N. The Pd^{II} intermediate **B** is then oxidized by ArI(OAc)₂ to give a Pd^{IV} intermediate **C**. The Pd^{IV} intermediate **D** is formed by activation of the *o*-C–H bond of intermediate **C**.⁵ The reductive elimination of intermediate **D** occurs readily to yield the target product and the active Pd^{II} species.

Conclusions

In summary, we have developed a novel protocol for the synthesis of 3-(1-arylmethylene)oxindoles via palladium-catalyzed C–H functionalization of *N*-arylpropiolamides with

(5) For selected recent reviews and papers on the Pd^{II}/Pd^{IV} process, see: (a) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4042. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (c) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (d) Liu, G.; Stahli, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (e) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (f) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (g) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (h) Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (i) Muniz, K.; Hovellmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

(6) The structure of the products were unambiguously assigned by X-ray analysis of the product **3**, see the Supporting Information. The configuration of the tetrasubstituted double bond was determined according to the authoritative 5-H and/or 8-H shift data of oxindoles in refs 2–4.

(7) ¹H NMR spectra of the reaction of PhI(OAc)₂ with Et₃N are summarized in the Supporting Information.

aryliodonium salts. In the presence of $\text{Pd}(\text{OAc})_2$ and Et_3N , a variety of anilides underwent the reaction with aryliodonium salts to afford the corresponding 3-(1-arylmethylene)oxindoles in moderate to good yields. Efforts to study the detailed mechanism and extend the application of the transformation in organic synthesis are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Palladium-Catalyzed C–H Functionalization of *N*-Arylpropiolamides with Aryliodonium Salts. A mixture of propiolamides **1** (0.2 mmol), aryliodonium salt **2** (2 equiv), $\text{Pd}(\text{OAc})_2$ (5 mol %), and Et_3N (2 equiv) in THF/ CH_3CN (v/v 1:4, 3 mL) was stirred under air at 100 °C for the desired time until complete consumption of starting material as monitored by TLC. Then the mixture was washed with saturated NaCl and extracted with diethyl ether. The organic layers were dried with Na_2SO_4 and evaporated under vacuum, the residue was purified by flash column chromatography to afford the pure product (hexane/ethyl acetate).

1-(*p*-Methylbenzyl)-3-(diphenylmethylene)indolin-2-one (4**).** Yellow solid, mp 171.2–172.3 °C (uncorrected); ^1H NMR (400 MHz) δ 7.44–7.42 (m, 3H), 7.38–7.32 (m, 7H), 7.22 (d, J = 8.0

Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.63 (t, J = 7.2 Hz, 1H), 6.40 (d, J = 7.6 Hz, 1H), 4.88 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz) δ 166.8, 154.9, 142.5, 141.4, 139.9, 137.1, 133.3, 130.2, 129.4 (2C), 129.2, 129.0, 128.7, 128.4, 127.9, 127.5, 124.1, 123.4, 123.2, 121.4, 108.7, 43.3, 21.1; LRMS (EI, 70 eV) m/z (%) 401 (M^+ , 100); HRMS (EI) for $\text{C}_{29}\text{H}_{23}\text{NO}$ (M^+) calcd 401.1780, found 401.1779.

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Supporting Information Available: General experimental procedures, characterization data for compounds **3**, **4**, **7–15**, and **17–26**, and copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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