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Synthesis of (2-Oxoindolin-3-ylidene)methyl Acetates Involving a C−H Functionalization Process

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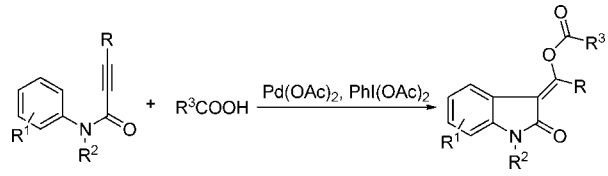
ABSTRACT



A novel palladium-catalyzed oxidative C−H functionalization protocol for the synthesis of (2-oxoindolin-3-ylidene)methyl acetates has been developed. In the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$, a variety of *N*-arylpropiolamides underwent the C−H functionalization reaction with acids to afford the corresponding (*E*)-(2-oxoindolin-3-ylidene)methyl acetates selectively in moderate to excellent yields.

3-Methyleneindolin-2-ones are pharmacologically important compounds that display great potential utilizations in many major therapeutic areas, such as oncology, inflammation, CNS, immunology, and endocrinology.[1] For example, SU11248 was commercialized by Pfizer, Inc. in 2006 to treat renal cell carcinoma and gastrointestinal stromal tumors (Figure 1). The traditionally synthetic method for these compounds is via the intermolecular condensation of an oxindole with a diaryl ketone.[1,2] However, the method is

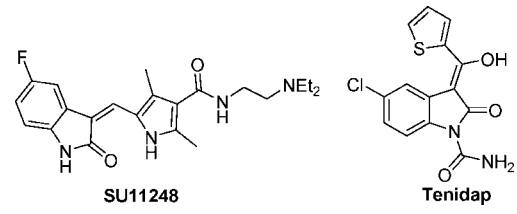


Figure 1. Two commercial medicines.

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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**, *203*, 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) Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Frye, S. V.; Gampe, R. T., Jr.; Harris, P. A.; Hassell, A.; Holmes, W. D.; Hunter, R. N.; Lackey, K. E.; Lovejoy, B.; Luzzio, M. J.; Montana, V.; Rocque, W. J.; Rusnak, D.; Shewchuk, L.; Veal, J. M.; Walker, D. H.; Kuyper, L. F. *J. Med. Chem.* **2001**, *44*, 4339. (i) Graczyk, P. P. *J. Med. Chem.* **2007**, *50*, 5773.

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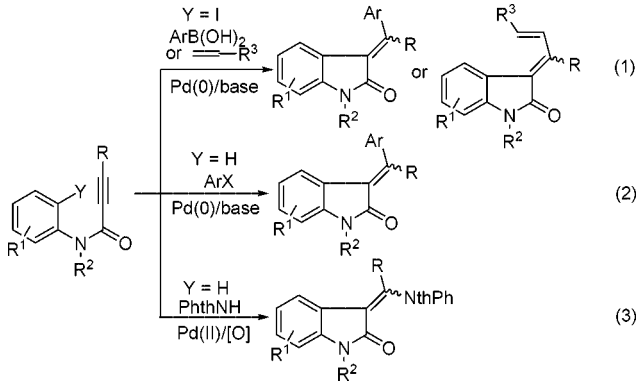
limited due to its low selectivity and tedium. Recently, considerable effort has been devoted to develop transition metals, in particular, palladium-catalyzed domino reactions for the synthesis of 3-methyleneindolin-2-ones to solve these drawbacks (Scheme 1).[3,5] However, most of these reactions

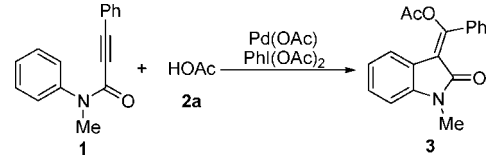
Scheme 1. Three Protocols for the Synthesis of Oxindoles



require the use of 2-haloanilides or 2-(alkynyl)phenylisocyanates as the starting materials (eq 1 in Scheme 1). An interesting approach is the palladium-catalyzed domino carbopalladation/C−H activation/C−C bond-forming reaction that uses an anilide sp^2 C−H bond as one of the coupling partners (eq 2).[3c,d] Although all the reported palladium-catalyzed transformations provided an efficient and selective route to the synthesis of methylenyloxindoles, only carbon atoms were introduced to the triple bonds to form two carbon−carbon bonds in all cases.[3]

Many bioactive 3-methyleneindolin-2-ones include the carbon−heteroatom bonds at the terminal of the 3-methylene group.[1f–h] Tenidap (commercialized in 1993; Pfizer, Inc.), for instance, is an anti-inflammatory medicine for the therapy of arthritis, etc. (Figure 1).[1f] Thus, the development of new palladium-catalyzed routes to synthesize these indolin-2-ones is of considerable importance. Very recently, we developed a novel protocol for constructing two bonds, a C−C bond and a C−N bond, via a sequential intermolecular aminopalladation/*ortho*-arene C−H activation process (eq 3 in Scheme 1).[4] As a continuing interest in constructing the oxindole skeleton, we report herein that (2-oxoindolin-3-ylidene)-methyl acetates could be prepared successfully by the acetoxypalladation/C−H functionalization of anilides in the presence of $PhI(OAc)_2$.

Table 1. Screening Conditions[a]



entry	$PhI(OAc)_2$ (equiv)	solvent	time (h)	yield (%)[b]
1[c]	2.0	MeCN	10	trace
2[d]	2.0	MeCN	10	56
3[e]	2.0	MeCN	10	80
4	2.0	MeCN	10	89
5	2.0	HOAc	2	91
6	1.2	HOAc	2	90
7[f]	1.2	HOAc	5	89
8[g]	1.2	HOAc	5	0
9[h]	1.2	HOAc	2	38
10[i]	1.2	HOAc	2	88

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ and HOAc (10 equiv) in solvent (3 mL) at 80 °C. [b] Isolated yield. [c] Without HOAc, a 17% yield of 1-methyl-3-(diphenylmethylene)indolin-2-one (**4**) was isolated. [d] HOAc (2 equiv). A 6% yield of **4** was isolated. [e] HOAc (5 equiv). [f] $Pd(OAc)_2$ (5 mol %). [g] Without $Pd(OAc)_2$. [h] At room temperature. [i] At 100 °C.

As demonstrated in Table 1, *N*-methyl-*N*,3-diphenylpropiolamide (**1**) was employed as the starting substrate to explore the optimal conditions.[5] Initially, the amount of HOAc was examined, and the results showed that the amount of HOAc has a fundamental influence on the reaction in terms of yield and rate (entries 1−5). Without HOAc, a trace amount of the target acetoxypalladation product **3** was detected by GC-MS analysis from the reaction of amide **1** with $Pd(OAc)_2$ and $PhI(OAc)_2$ in MeCN (entry 1), and the product **3** was enhanced sharply to 56% in the presence of 2 equiv of HOAc (entry 2).[6] In the presence of 5 equiv of HOAc, the yield of **3** was increased to 80% (entry 3). To our delight, substrate **1** was consumed completely in 2 h, providing a 91% yield using HOAc as the medium (entry 5). We were happy to discover that a good yield of **3** was still isolated even in the presence of 1.2 equiv of $PhI(OAc)_2$ using HOAc as the medium (entry 6). Noteworthy is that the reaction can be conducted in good yields even at a loading of 5 mol % of Pd after prolonged reaction time (entry

(2) (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.; Nematalla, 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.

(3) 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) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (d) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (e) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (f) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (g) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. In/Pd: (h) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825. Rh: (i) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (j) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *8*, 5075.

(4) Tang, S.; Peng, P.; Pi, S.-F.; Liang, Y.; Wang, N.-X.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1179.

(5) The detailed experimental data are summarized in Table S1 in Supporting Information.

(6) The structure of the products and the *E*-configuration of the tetrasubstituted double bond were determined according to the COSY and NOESY of the products **12** and **16** and were unambiguously assigned by X-ray analysis of the products **9** and **14** (see Supporting Information).

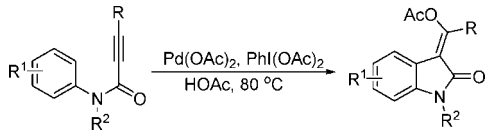
7). However, no reaction was observed without $Pd(OAc)_2$ (entry 8). Finally, the temperature effect was investigated, and a higher temperature favored the reaction (entries 9 and 10).

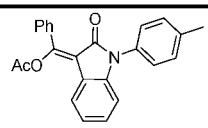
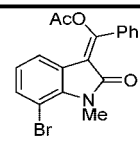
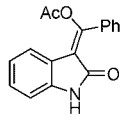
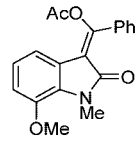
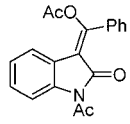
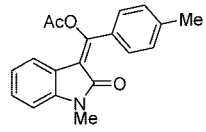
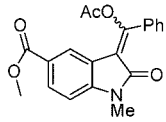
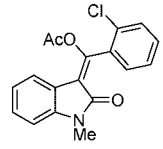
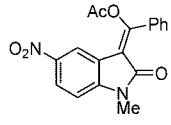
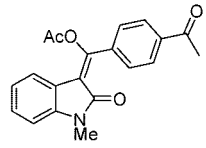
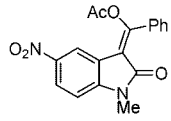
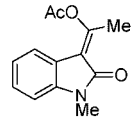
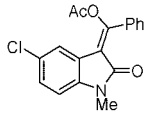
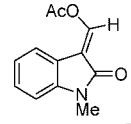
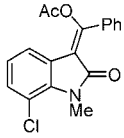
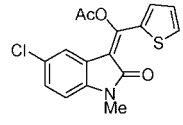
Subsequently, a variety of anilides were surveyed to investigate the scope of the reaction with HOAc under the standard reaction conditions (Table 2). In the presence of $Pd(OAc)_2$ and $PhI(OAc)_2$, *N*-benzyl-*N*,3-diphenylpropiolamide could also afford the target (*E*)-product (**5**) in a 69% yield (entry 1). However, both *N*-acetyl-*N*,3-diphenylpropiolamide and *N*,3-diphenylpropiolamide were unsuitable substrates for the reaction (entries 2 and 3). We were delighted to disclose that several functional groups, such as the ester, nitro, chloro, bromo, and methoxy group, on the *N*-phenyl group were tolerated well, but the yields were reduced to some extent when the steric hindrance was presented (entries 4−11). While *N*-(4-chlorophenyl)-*N*-methyl-3-phenylpropiolamide, for instance, was treated with $Pd(OAc)_2$, $PhI(OAc)_2$, and HOAc smoothly to afford the corresponding (*E*)-**10** in a 91% yield (entry 7), only a 28% yield of (*E*)-**13** was isolated from the reaction of the bulky substrate, *N*-(2-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (entry 10). Gratifyingly, *N*-methyl-*N*-phenylpropiolamides bearing either electron-deficient or electron-rich aryl groups at the terminal alkyne underwent the reaction successfully in moderate to good yields under the standard conditions (entries 11−13). We found that *N*-methyl-*N*-phenylbut-2-ynamide, having a methyl group at the terminal of alkyne, also gave the (*E*)-**18** in a 93% yield (entry 14). Unfortunately, attempts to cyclize *N*-methyl-*N*-phenylpropiolamide failed (entry 15). It is noteworthy that a tenidap analogue **19** can be synthesized in one step (entry 16).

N-Methyl-3-phenyl-*N*-*m*-tolylpropiolamide (**20**) was chosen to test the regioselectivity of the reaction. As shown in Scheme 2, it was selectively *para*-cyclized to afford (*E*)-(1,6-dimethyl-2-oxoindolin-3-ylidene)(phenyl)methyl acetate (**21**) in 90% yield together with an *ortho*-cyclized product (**22**) in <5% GC yield.

We then turned our attention to examine suitable acids for the reaction. The results in Table 3 show that a variety of acids **2b**−**i**, either aryl or alkyl acids, all worked well with amides in moderate to good yields. Moreover, the reaction tolerated a series of functional groups including nitro, bromo, fluoro, iodo, vinyl, or acetyl groups on the aromatic ring of aryl acids. For example, treatment of amide **1** (0.2 mmol) with 4-nitrobenzoic acid (**2b**) (5 equiv), $Pd(OAc)_2$ (10 mol %), and $PhI(OAc)_2$ (2 equiv) in MeCN afforded the corresponding product **23** in 81% yield (entry 1). However, the yield of **23** was reduced to 47% in the presence of 10 equiv of 4-nitrobenzoic acid (**2b**) (entry 2). The other amide **26** with an acid **2e** bearing an iodo group was also reacted successfully to give the target product **28** in 55% yield (entry 5). Note that a bulky acid **2h** can still react with anilide **26** to give the target product **31** in 77% yield under the standard conditions (entry 8).

Table 2. $Pd(OAc)_2$-Catalyzed Cyclizations of Various Amides with HOAc in the Presence of $PhI(OAc)_2$[a]



Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1		69 (**5**)	9		63 (**12**)
2		trace (**6**)	10		28 (**13**)
3		trace (**7**)	11[c]		91 (**14**)
4		69 (**8**)	12		77 (**15**)
5		38 (**9**)	13		60 (**16**)
6		87 (**9**)	14		93 (**17**)
7		91 (**10**)	15		<5 (**18**)
8		45 (**11**)	16		65 (**19**)

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.2 equiv), and HOAc (3 mL) at 80 °C for 2−5 h. [b] Isolated yield. [c] HOAc/MeCN (1:4, 3 mL).

Scheme 2. Reaction of *N*-Methyl-3-phenyl-*N*-*m*-tolylpropiolamide

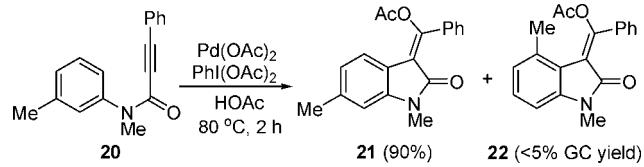
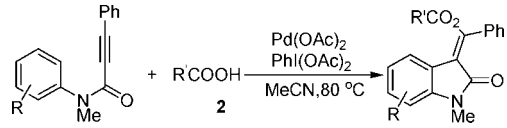


Table 3. Screening Suitable Acids (**2**)[a]

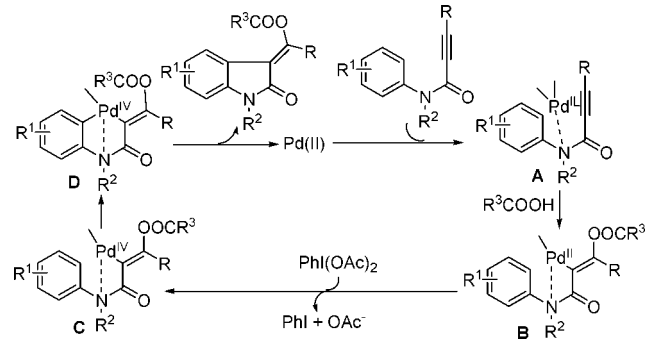


entry	R	R′	time (h)	yield (%)[b]
1	H (**1**)	4-$NO_2C_6H_4$ (**2b**)	2	81 (**23**)
2[c]	H (**1**)	4-$NO_2C_6H_4$ (**2b**)	2	47 (**23**)
3	2-Cl (**24**)	2-Br-4-FC_6H_3 (**2c**)	3	57 (**26**)
4	4-Me (**26**)	4-BrC_6H_4 (**2d**)	3	77 (**27**)
5	4-Me (**26**)	2-IC_6H_4 (**2e**)	4	52 (**28**)
6	4-Me (**26**)	4-vinylC_6H_4 (**2f**)	5	52 (**29**)
7	4-Me (**26**)	2-$CH_3COC_6H_4$ (**2g**)	2	75 (**30**)
8	4-Me (**26**)	*t*-Bu (**2 h**)	6	77 (**31**)
9	4-Me (**26**)	$C_6H_5CH_2CH_2$ (**2i**)	3	75 (**32**)

[a] Reaction conditions: **1** (0.2 mol), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2 equiv), and R′COOH (5 equiv) in CH_3CN (3 mL) at 80 °C. [b] Isolated yield. [c] R′COOH (10 equiv).

A working mechanism as outlined in Scheme 3 was proposed on the basis of the previously proposed mechanisms[3,4,7,8] and the results of the kinetic isotope effect.[9] Coordination of Pd^{II} with alkyne and nitrogen is readily occurs to afford intermediate **A**, followed by acetoxypalladation of intermediate **A** with acid to afford intermediate **B**. The Pd^{II} intermediate **B** is then oxidized by $PhI(OAc)_2$ to give a Pd^{IV} intermediate **C**. The Pd^{IV} intermediate **D** is formed by activation of the *ortho*-C−H bond of intermediate **C**. The reductive elimination of intermediate **D** occurs readily to yield the target product and the active Pd^{II} species. However, we cannot rule out the possibility of a Pd^{II}/Pd^0 mechanism because the target product could be obtained in the presence of $Cu(OAc)_2$, a traditional Pd^{II}/Pd^0 oxidant.[5,8]

Scheme 3. Possible Mechanism



In summary, we describe here the first example of constructing (1-substituted-2-oxoindolin-3-ylidene)methyl acetates via a $Pd(OAc)_2$-catalyzed C−H functionalization reaction in the presence of $PhI(OAc)_2$. Work to probe the detailed mechanism and 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 and typical procedure for the acetoxypalladation/C−H functionalization reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) 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) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (d) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (e) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (f) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (g) Liu, G.; Stahi, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (h) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906. (i) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836. (j) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (k) Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (l) Muniz, K.; Hovelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763.

(8) (a) The Pd^{II}/Pd^{II}-catalyzed hydroacetoxylation of 2-alkynoic amides has also been reported using some specified additives such as LiX, LiOAc, bipyridine, and Et_3N. However, no desired product **3** was observed using $Pd(OAc)_2$ combined with the specified additives in the reaction of **1**. Lu, X.; Zhu, G.; Ma, S. *Tetrahedron Lett.* **1992**, *33*, 7205. (b) Wakabayashi, T.; Ishii, Y.; Murata, T.; Mizobe, Y.; Hidai, M. *Tetrahedron Lett.* **1995**, *36*, 5585. (c) Han, X. L.; Liu, G. X.; Lu, X. Y. *Chin. J. Org. Chem.* **2005**, *25*, 1182.

(9) The results of the kinetic isotope effect are summarized in the Supporting Information.