JOC Note
pubs.acs.org/joc

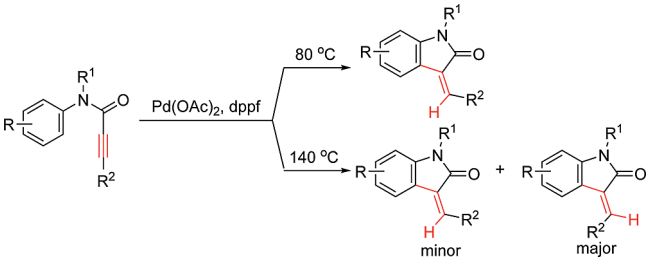
Palladium-Catalyzed Intramolecular 5-*exo-dig* Hydroarylations of *N*-Arylpropiolamides: Thermodynamics-Controlled Stereoselective Synthesis of 3-Methyleneoxindoles

Tao-Shan Jiang, Ri-Yuan Tang, Xing-Guo Zhang, Xin-Hua Li, and Jin-Heng Li*

College of Chemistry and Materials Science, Wenzhou University, Wenzhou 325035, China

jhli@hunnu.edu.cn

Received September 12, 2009



Palladium-catalyzed intramolecular hydroarylation of *N*-arylpropiolamides has been developed for the stereoselective synthesis of 3-(monosubstituted methylene)oxindoles. In the presence of $Pd(OAc)_2$ and dppf, a variety of *N*-arylpropiolamides successfully underwent the intramolecular hydroarylation reaction to afford the corresponding 3-(monosubstituted-methylene)oxindoles in moderate to excellent yields. It is noteworthy that the stereoselectivity of the reaction can be controlled by varying the reaction temperature.

The construction of the oxindole skeleton is a continuing hot topic in the field of organic chemistry[1−4] as a result of a wide range of biological and pharmacological interest.[1] Among these efficient methods,[1−4] palladium-catalyzed C−H bond activation with a subsequent C−C bond-forming process is particularly effective and economic (Scheme 1).[2,3] Zhu and co-workers have developed a $Pd(OAc)_2$-catalyzed tandem process for the preparation of 3-(diarylmethylene)-oxindoles under basic conditions using both an anilide sp^2 C−H bond and an electrophile (aryl iodides) as the coupling partners.[2] We have also reported a novel protocol for selectively constructing the 3-(disubstituted methylene)-oxindole skeleton by palladium-catalyzed oxidative C−H functionalization of *N*-arylpropiolamides with nucleophiles.[3] However, many bioactive oxindoles involve the (*Z*)-3-(monosubstituted methylene)oxindole moiety.[1] Thus, the synthesis of (*Z*)-3-(monosubstituted methylene)oxindoles by the C−H functionalization is still interesting. We envisioned that the intramolecular hydroarylation of *N*-arylpropiolamides might realize the goal.[5−8] In 2000, Fujiwara and co-workers reported the first example of hydroarylation of arylacetylenes.[5,6] Since then, considerable efforts have been paid to the hydroarylation of alkynes, and two processes were observed: (1) the intramolecular *6-endo-dig* hydroarylation under acidic conditions,[5−7] and (2) 5-*exo-dig* hydroarylation under neutral conditions.[8] Fujiwara and co-workers, for example, have described that arylalkynes could undergo the palladium-catalyzed intramolecular hydroarylation reaction in acids to afford the corresponding

(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 Fut.* **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.; Granaiola, 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.

(2) (a) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927. (b) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (c) Pinto, A.; Neuville, L.; Zhu, J. *Tetrahedron Lett.* **2009**, *50*, 3602. (d) Song, R.-J.; Liu, Y.; Li, R.-J.; Li, J.-H. *Tetrahedron Lett.* **2009**, *50*, 3912.

(3) (a) Tang, S.; Peng, P.; Zhong, P.; Li, J. H. *J. Org. Chem.* **2008**, *73*, 5476. (b) Pi, S. F.; Liang, Y.; Wang, N. X.; Li, J. H. *Org. Lett.* **2008**, *10*, 1179. (c) Tang, S.; Peng, P.; Wang, Z. Q.; Tang, B. X.; Deng, C. L.; Li, J. H.; Zhong, P.; Wang, N. X. *Org. Lett.* **2008**, *10*, 1875. (d) Peng, P.; Tang, B.-X.; Pi, S.-F.; Liang, Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 3569. (e) Tang, D.-J.; Tang, B.-X.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 6749.

(4) For selected papers on the other methods for the synthesis of oxindoles see: (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) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (f) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825. (g) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (h) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2007**, *8*, 5075. (i) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 1743. (j) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, *20*, 1133. (k) 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. (l) Wang, L.; Zhang, Y.; Hu, H.-Y.; Fun, H. K.; Xu, J.-H. *J. Org. Chem.* **2005**, *70*, 3805. (m) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683. (n) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099. (o) Yang, T.-M.; Liu, G. *J. Comb. Chem.* **2007**, *9*, 86. (p) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2587. (q) Kamijo, S.; Sasaki, Y.; Kawazawa, C.; Schubeler, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7718. (r) Mao, Z.; Baldwin, S. W. *Org. Lett.* **2004**, *6*, 2425. (s) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (t) Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 6473. (u) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477. (v) Park, J. H.; Kim, E.; Chung, Y. K. *Org. Lett.* **2008**, *10*, 4719.

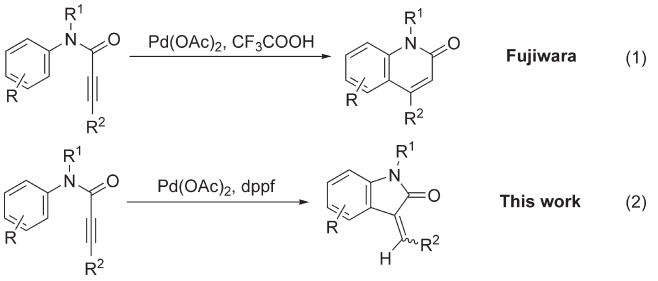
(5) For reviews on the intramolecular hydroarylation of alkynes, see: (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Soc.* **2001**, *34*, 633. (b) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (c) Fairlamb, I. J. S. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2006**, *102*, 50.

(6) For papers on palladium-catalyzed 6-*endo-dig* hydroarylation of alkynes, see: (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (c) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516. (d) Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **2000**, *2*, 2927. (e) Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc.* **2003**, *125*, 4518. (f) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752. (g) Ahlquist, M.; Fabrizi, G.; Cacchi, S.; Norrby, P.-O. *J. Am. Chem. Soc.* **2006**, *128*, 12785.

Published on Web 10/22/2009 DOI: 10.1021/jo901963g

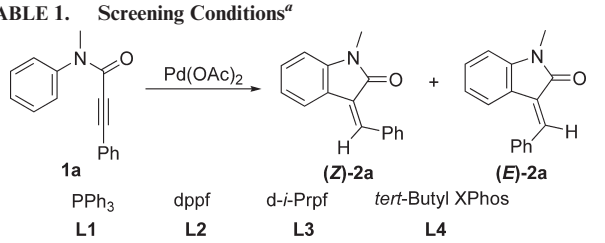
6-*endo-dig* cyclization products (eq 1 in Scheme 1).[6] Recently, Gevorgyan and Chemyak reported that under neutral conditions an exclusive 5-*exo-dig* hydroarylation reaction of *o*-alkyne biaryls could take place in the presence of $Pd(OAc)_2$/d-*i*-Prpf (1,1′-bis(diisopropylphosphino)ferrocene), providing the corresponding 5-*exo-dig* cyclization products (9-benzylidene-9*H*-fluorene derivatives) in moderate to excellent yields.[8] Here, we report a simple and efficient protocol for the stereoselective synthesis of (*Z*)- and (*E*)-3-(monosubstituted methylene)oxindoles by $Pd(OAc)_2$/dppf-catalyzed hydroarylation of *N*-arylpropiolamides (eq 2 in Scheme 1).

SCHEME 1. Hydroarylation Reaction Involving a C−H Activation Process



The hydroarylation reaction of *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) was conducted to screen the optimal conditions, and the results are summarized in Table 1. Initially, a series of phosphine ligands, including PPh_3 (**L1**), dppf (1,1′-bis(diphenyphosphino)ferrocene; **L2**), d-*i*-Prpf (**L3**), and *tert*-butyl Xphos (2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl; **L4**), were tested for the reaction of substrate **1a** with $Pd(OAc)_2$ in xylene at 120 °C (entries 1−5). Without ligands, a trace amount of the target products was observed by GC−MS analysis together with a rather low conversion (entry 1). To our delight, amide **1a** could be consumed completely to afford the two isomers (*Z*)-**2a** and (*E*)-**2a** in good total yields using ligands **L1**−**L3** (entries 2−4). Treatment of substrate **1a** with $Pd(OAc)_2$ and **L2**, for instance, gave the target products (*Z*)-**2a** and (*E*)-**2a** in 93% total yield (entry 3). However, **L4** has no activity for the reaction (entry 5). Interestingly, the selectivity was shifted toward (*E*)-**2a** at higher temperature (entries 6 and 7). At 140 °C in xylene, (*E*)-**2a** was obtained as a major product in 76% yield along with 21% yield of (*Z*)-**2a** from the reaction of amide **1a** with $Pd(OAc)_2$ and **L2** (entry 6). We found that the selectivity toward (*E*)-**2a** was increased to some extent using toluene solvent at 140 °C (entry 7). We were pleased to discover selectivity toward (*Z*)-**2a** when the reaction temperature was decreased in toluene (entries 8−11). Whereas 100 °C provided 83% of (*Z*)-**2a** and 15% of (*E*)-**2a** (entry 8), 80 °C afforded the desired (*Z*)-**2a** alone in 86% yield (entry 9). Although the target (*Z*)-**2a** was still isolated exclusively at lower temperatures, both the conversion and yield were reduced even prolonging the reaction time (entries 10 and 11). The structure of (*Z*)-**2a** was unambiguously assigned by the X-ray single-crystal diffraction analysis, and the configuration of the trisubstituted carbon−carbon double bond was determined according to the authoritative ^1H NMR and ^{13}C NMR spectra of both (*E*)-**2a** and (*E*)-**2b**.[4u,v,9]

TABLE 1. Screening Conditions[a]



						yield (%)	
entry	ligand	solvent	*T* (°C)	*t* (h)	conv (%)[b]	(*Z*)-**2a**	(*E*)-**2a**
1		xylene	120	10	< 5	trace	trace
2	**L1**	xylene	120	10	100	32	49
3	**L2**	xylene	120	10	100	52	41
4	**L3**	xylene	120	10	100	38	50
5	**L4**	xylene	120	10	< 5	trace	trace
6	**L2**	xylene	140	8	100	21	76
7	**L2**	toluene	140	8	100	17	83
8	**L2**	toluene	100	10	100	83	15
9	**L2**	toluene	80	12	100	86	0
10	**L2**	toluene	60	24	58	55	0
11	**L2**	toluene	25	36	30	28	0

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), and ligand (5 mol %) in solvent (1 mL). [b]The conversion was determined by GC−MS analysis.

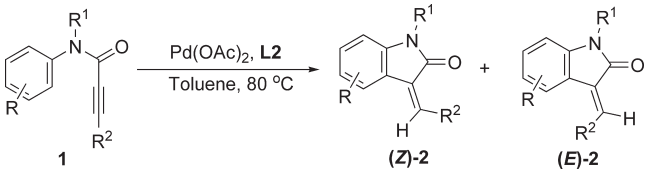
With the standard conditions in hand, both the scope of *N*-arylpropiolamides and the selectivity at different temperature were investigated (Tables 2 and 3). As shown in Table 2, the hydroarylation reactions of various *N*-arylpropiolamides at 80 °C were first examined to prepare (*Z*)-3-(arylmethylene)oxindoles. In the presence of $Pd(OAc)_2$ and dppf (**L2**), the analogous amides with the *N*-methyl group replaced by either a benzyl or an acetyl group underwent the hydroarylation reaction smoothly to afford the corresponding products **2b** and **2c** in moderate yields (entries 1 and 2). However, *N*-unsubstituted propiolamide (**1d**) was not suitable for the reaction under the same conditions (entry 3). To our delight, several functional groups, such as methoxy, methyl, fluoro, and chloro, on the aromatic ring of *N*-arylpropiolamides were tolerated well. MeO-substituted substrate **1e**, for instance, smoothly underwent the reaction with $Pd(OAc)_2$ and **L2** in 80% yields (entry 4). Although substrates **1f**−**1i**, bearing an *o*-methyl group

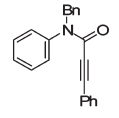
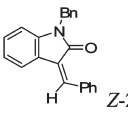
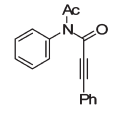
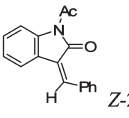
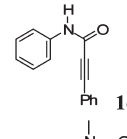
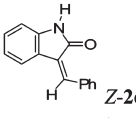
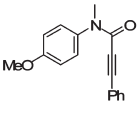
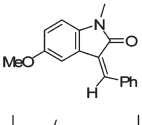
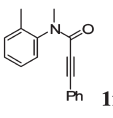
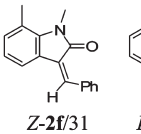
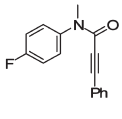
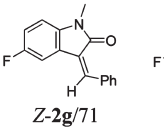
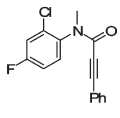
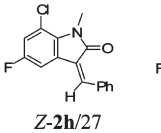
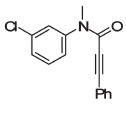
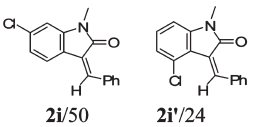
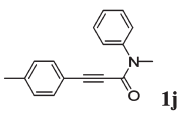
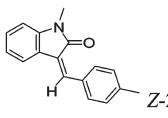
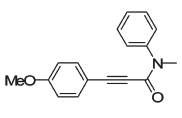
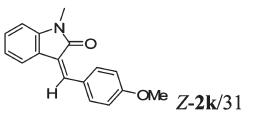
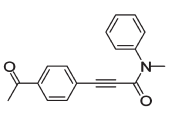
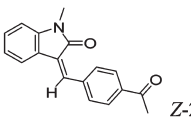
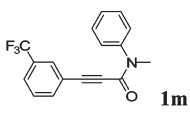
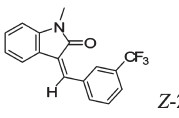
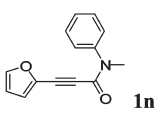
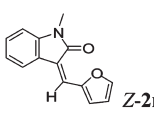
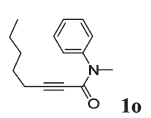
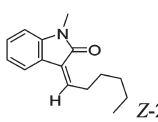
(7) For selected papers on other transition-metal-mediated 6-*endo-dig* hydroarylation of alkynes, see: (a) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440. (b) Soriano, E.; Marco-Contelles, J. *Organometallics* **2006**, *25*, 4542. Pt: (c) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (d) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556. (e) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155. Au: (f) Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485. (g) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669. (h) England, D. B.; Padwa, A. *Org. Lett.* **2008**, *10*, 3631. Fe: (i) Li, R.; Wang, S. R.; Lu, W. *Org. Lett.* **2007**, *9*, 2219. Re: (j) Kuninobu, Y.; Kikuchi, K.; Tokunaga, Y.; Nishina, Y.; Takai, K. *Tetrahedron* **2008**, *64*, 5974. Rh: (k) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1980**, 507. (l) Boese, W. T.; Goldman, A. S. *Organometallics* **1991**, *10*, 782. (m) Aulwurm, U. R.; Melchinger, J. U.; Kisch, H. *Organometallics* **1995**, *14*, 3385. Ru: (n) Hong, P.; Cho, B.-R.; Yamazaki, H. *Chem. Lett.* **1979**, 339. (o) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. Lewis acid: (p) Song, C. E.; Jung, D.-u.; Choung, S. Y.; Roh, E. J.; Lee, S.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 6183. (q) Yoon, M. Y.; Kim, J. H.; Choi, D. S.; Shin, U. S.; Lee, J. Y.; Song, C. E. *Adv. Synth. Catal.* **2007**, *349*, 1725.

(8) (a) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (b) Chernyak, N.; Gevorgyan, V. *Adv. Synth. Catal.* **2009**, *351*, 1101.

(9) The selectivity toward the *E*-isomer under the optimized conditions (entry 7 in Table 1) is higher than that of eq 3 because isomerization of olefins to the *E*-isomer can take place in the presence of Pd(II); see: Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.

TABLE 2. Palladium-Catalyzed 5-*exo-dig* Hydroarylation Reactions of *N*-Arylpropiolamides (1) at 80 °C[a]



Entry	Amide **1**	Product **2**/Yield (%)
1	 **1b**	 *Z*-**2b**/75
2	 **1c**	 *Z*-**2c**/34
3[b]	 **1d**	 *Z*-**2d**/mixture
4	 **1e**	 *Z*-**2e**/80
5[c]	 **1f**	 *Z*-**2f**/31 *E*-**2f**/65
6	 **1g**	 *Z*-**2g**/71 *E*-**2g**/22
7	 **1h**	 *Z*-**2h**/27 *E*-**2h**/35
8	 **1i**	 **2i**/50 **2i'**/24
9	 **1j**	 *Z*-**2j**/81
10[d]	 **1k**	 *Z*-**2k**/31
11	 **1l**	 *Z*-**2l**/88
12	 **1m**	 *Z*-**2m**/85
13	 **1n**	 *Z*-**2n**/56
14	 **1o**	 *Z*-**2o**/20

[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), and **L2** (5 mol %) in toluene (1 mL) at 80 °C for 12 h. [b]For 36 h. [c]At 120 °C for 12 h. [d]At 120 °C for 24 h.

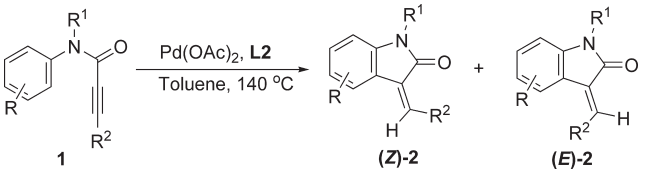
or electron-withdrawing groups, afforded a mixture of *Z*- and *E*-isomers, the total yields are still satisfactory (entries 5−8). Substituents at the terminal alkyne were subsequently investigated (entries 9−14). The results demonstrated that the property of substituents affected the reaction to some extent. Substrate **1j** with a 4-MeC_6H_4 group was successfully reacted with $Pd(OAc)_2$ and **L2** in 81% yield (entry 9), whereas propiolamide **1k** having a stronger electron-donating group, a 4-$MeOC_6H_4$ group, afforded only 31% yield (entry 10). We were pleased to find that substrates **1l** and **1m**, bearing electron-deficient groups, displayed higher activity under the standard conditions (entries 11 and 12). It is noteworthy that amide **1n** with a furan-2-yl group is still a suitable substrate for the reaction (entry 13). However, substrate **1o** bearing an aliphatic group was less efficient, affording **2o** in a low yield (entry 14).

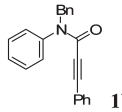
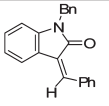
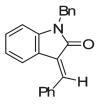
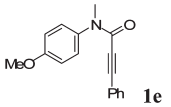
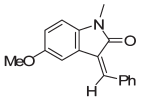
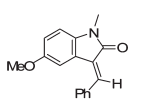
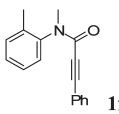
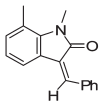
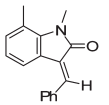
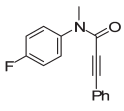
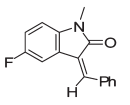
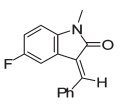
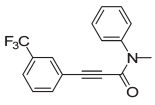
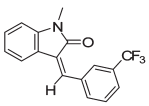
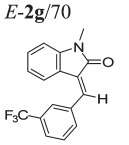
As shown in Table 3, the reaction at 140 °C was explored to shift the stereoselectivity toward (*E*)-3-(monosubstituted methylene)oxindoles. As expected, treatment of substrate **1b** with $Pd(OAc)_2$ and **L2** at 140 °C afforded a mixture of (*Z*)-**2b** and (*E*)-**2b**, and (*E*)-**2b** was the major product in 59% yield along with 30% of (*Z*)-**2b** (entry 1). Identical results were observed from the reactions of other substrates **1e**−**1f** and **1m** (entries 2−5).

To elucidate the mechanism, the reaction of (*Z*)-**2a** was heated in toluene at 140 °C (eq 3 in Scheme 2). The result showed that the *Z*-isomer could be converted to the *E*-isomer at higher temperature without catalysts. After 10 h, (*E*)-**2a** was isolated in 75% yield and (*Z*)-**2a** was recovered in 21% yield.[9] The results of computational study revealed that the energies of (*Z*)-**2a** and (*E*)-**2a** are −20205.207 and −20205.053 eV, respectively, and the energy difference is only 3.562 kcal/mol (calculated by the HF method in the Gaussian program). Therefore, (*E*)-**2a** could be obtained easily from (*Z*)-**2a** at 140 °C. The deuterium-labeled experiment was also carried out in toluene at 80 °C, affording the H- and D-substituted products (*Z*)-**3a-D1** (eq 4 in Scheme 2).[10] The results

(10) See Supporting Information for detailed results.

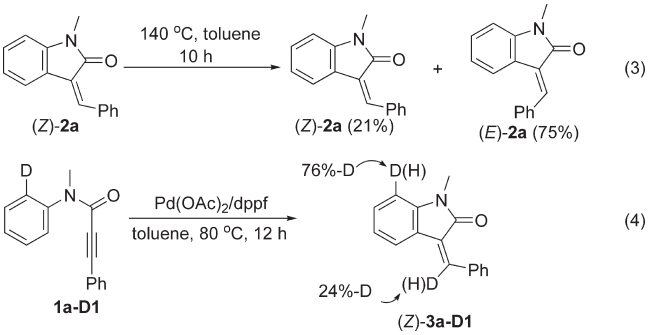
TABLE 3. Palladium-Catalyzed Hydroarylation Reactions at 140 °C[a]



Entry	Amide **1**	Product **2**/Yield (%)	
1	 **1b**	 *Z*-**2b**/30	 *E*-**2b**/59
2	 **1e**	 *Z*-**2e**/21	 *E*-**2d**/71
3	 **1f**	 *Z*-**2f**/8	 *E*-**2f**/86
4	 **1g**	 *Z*-**2g**/26	 *E*-**2g**/70
5	 **1m**	 *Z*-**2m**/25	 *E*-**2m**/62

[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %) and **L2** (5 mol %) in toluene (1 mL) at 140 °C for 12 h.

SCHEME 2. Controlled Reactions

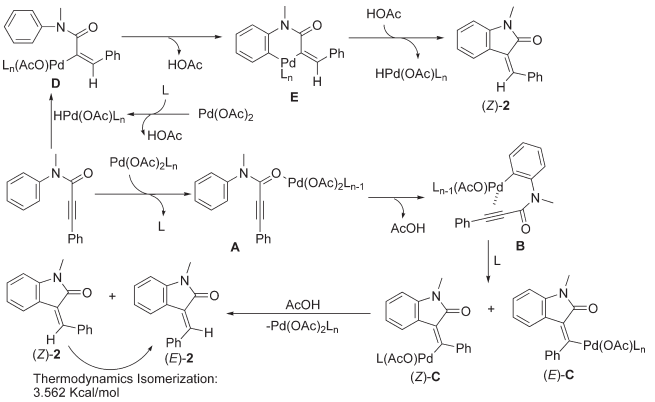


suggested that the deuterium atom of methylene was from the *ortho*-position of anilide via a Pd-catalyzed aromatic C−H activation pathway.

Two possible mechanisms were proposed as outlined in Scheme 3 on the basis of the reported mechanism and the present results.[5−9,11] Sequential C−H activation/complexation with alkyne affords intermediate **B**, followed by *cis*- and/or *trans*-addition to yield intermediates (*Z*)-**C** and/or (*E*)-**C**.[9] Protonation of intermediates **C** takes place to give

(11) (a) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (b) Amatore, C.; Jutant, A.; Meyer, G.; Carelli, I.; Chiarotto, I. *Eur. J. Inorg. Chem.* **2000**, 1855.

SCHEME 3. Possible Mechanism



the desired products (*Z*)-**2** and/or (*E*)-**2**. The products (*Z*)-**2** can be converted to (*E*)-**2** under thermodynamics control. Another route cannot be rule out: $HPd(OAc)L_n$ is generated *in situ* from the reaction of $Pd(OAc)_2$ with ligand,[11] followed by *cis*-hydropalladation of alkyne to afford intermediate **D**. Sequential C−H activation/reductive elimination of intermediate **D** gives the product (*Z*)-**2**.

In summary, we have developed a novel and facile method for the stereoselective synthesis of 3-(monosubstituted methylene)oxindoles in moderate to excellent yields by $Pd(OAc)_2$/dppf (**L2**)-catalyzed 5-*exo*-*dig* hydroarylation of *N*-arylpropiolamides. Importantly, we found that the stereoselectivity of the products was thermodynamics-controlled, which provided an attractive route to the conversion of (*Z*)-olefins into (*E*)-olefins in organic synthesis.

Experimental Section

Typical Experimental Procedure for the Palladium-Catalyzed Intramolecular Hydroarylation of *N*-Arylpropiolamides (1). To a flame-dried Schlenk tube was added *N*-arylpropiolamides **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), dppf (10 mol %), and toluene (1 mL). The mixture was stirred at the indicated temperature (80 or 140 °C) for the indicated time until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the mixture was filtered by a crude column with ethyl acetate as eluent and evaporated in vacuum. The residue was purified by flash column chromatography on a silica gel using EtOAc/petroleum ether (1:15) as eluent to give the product **2**.

(*Z*)-1-Acetyl-3-benzylideneindolin-2-one (2c). Yellow solid, mp 104.1−106.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, J = 8.2 Hz, 1H), 7.90 (s, 1H), 7.73−7.65 (m, 3H), 7.51−7.47 (m, 3H), 7.36−7.27 (m, 1H), 7.05−7.03 (m, 1H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 168.6, 140.2, 138.7, 134.4, 131.8, 130.3, 130.1, 129.2, 128.8, 128.4, 124.5, 122.1, 116.7, 26.9. IR (KBr, cm^{-1}): 2915, 1684, 1595, 1449, 1114. LRMS (EI, 70 eV) m/z (%): 263 (M^+, 32), 221 (100), 220 (67), 144 (39). HRMS (ESI) $C_{17}H_{13}NO_2Na$ $[M + Na]^+$: calcd 286.0843, found 286.0840.

Acknowledgment. We thank authors thank the National Natural Science Foundation of China (No. 20872112), Program of Science and Technology of Wenzhou (No. G20090080), Zhejiang Provincial Natural Science Foundation of China (Nos. Y407116 and Y4080169), and Wenzhou University (No. 2007L004) for financial support.

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