DOI: 10.1002/adsc.201600767

Advanced Synthesis & Catalysis

Palladium(II) Acetate-Catalyzed Dual C–H Functionalization and C–C Bond Formation: A Domino Reaction for the Synthesis of Functionalized (*E*)-Bisindole-2-ones from Diarylbut-2-yne-diamides

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Received: July 17, 2016; Revised: August 30, 2016; Published online: ■■ ■■, 0000

Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600767.

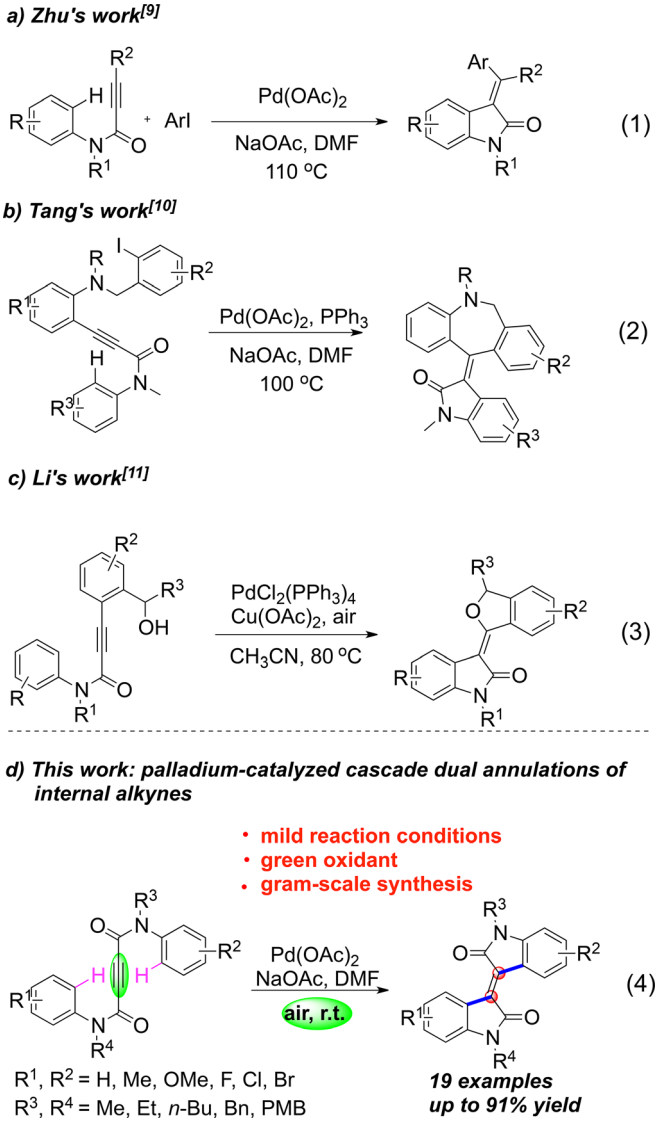
Abstract: A domino reaction of palladium(II)-catalyzed dual C–H functionalization with subsequent intramolecular annulation is presented. This method provides a convenient synthesis of a range of symmetrical and unsymmetrical biologically important (*E*)-bisindole-2-ones under extremely mild reaction conditions – room temperature, green oxidant and no additive. The reaction mechanism is elucidated in light of the yield values as well as additional control experiment results.

Keywords: domino reaction; intramolecular annulation; mild reaction conditions; palladium(II)-catalyzed process

The bisindole-2-one skeleton is an important structural framework found not only in natural products but also in a number of synthetic bioactive compounds[1] including Meisoindigo and Natura, which have been demonstrated as successful drugs for treating leukemia (Figure 1).[2] Additionally, bisindol-2-ones have recently emerged as promising scaffolds for the preparation of conjugated polymers,[3,4] many of which have found applications in organic photovoltaics as key components in the active layers of organic solar cells.[3] For example, isoindigo has been used in the design of low-band gap semiconductor materials.[4]

The transition metal-catalyzed C–H functionalization and C–C bond formation process is undoubtedly a powerful tool for the construction of N-containing heterocycles.[5] During the past few years, our laboratories have developed novel strategies for forming heterocycles under conditions both with[6] and without[7] transition metals. As starting substrates, alkyne amides have been recognized as a class of useful building blocks for the assemblage of the oxindole skeleton *via* palladium-catalyzed C–H functionalization followed by intramolecular annulation reactions.[8–11] In 2006, Zhu reported a domino reaction[12] for the synthesis of 3-(diarylmethylenyl)oxindoles from alkyne amides and aryl iodides, which involves a palladium-catalyzed carbopalladation, C–H activation and two C–C bond formations [Scheme 1, Eq. (1)].[9] Lately, Tang realized the construction of a framework that simultaneously contains an oxindole and a dibenzoazepine moiety starting from arylpropiolamide compounds [Scheme 1, Eq. (2)].[10] This process involves a sequential intramolecular arylation of the alkynyl moiety and an annulation reaction between the vinyl carbon and an aryl ring carbon. In 2012, Li reported a synthetic route to selectively build two heterocyclic rings from various arylpropiolamides by palladium-catalyzed C–O bond formation with

Figure 1. Representative compounds containing a bisindole-2-one moiety.

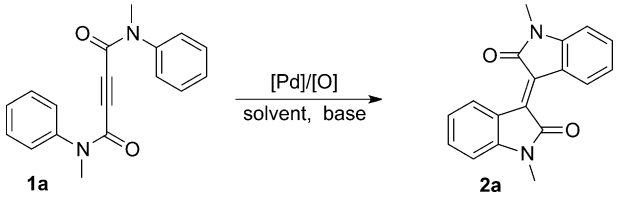


Scheme 1. Formation of oxindoles *via* intramolecular annulation of alkyne amides.

subsequent oxidative intramolecular C–C bond formation [Scheme 1, Eq. (3)].[11] Here, we report the first intramolecular annulation of diarylbut-2-ynediamides *via* a palladium-catalyzed double annulation processes leading to a convenient synthesis of versatile biologically intersting bisindole-2-one compounds [Scheme 1, Eq. (4)].

N^1,*N*^{4}-Dimethyl-*N*^{1},*N*^{4}-diphenylbut-2-ynediamide **1a** was selected as a model substrate in the search for the ideal reaction conditions. Results are summarized in Table 1. Our investigation began with having **1a** reacting with 0.1 equivalent of $Pd(OAc)_2$, 3 equivalents of $Cu(OAc)_2$, and 2 equivalents of Cs_2CO_3 in DMF at room temperature[8–11] (Table 1, entry 1). To our delight, the target product **2a** was obtained in 58% yield (Table 1, entry 1). Further control experiments indicated that the palladium reagent was indispensable

Table 1. Optimization of the reaction conditions.[a]



Entry	[Pd]	Base (3 equiv.)	Time [h]	Yield [%][b]
1[c]	$Pd(OAc)_2$	Cs_2CO_3	4	58
2[c]	–	Cs_2CO_3	12	0[d]
3	$Pd(OAc)_2$	Cs_2CO_3	6	68
4[e]	$Pd(OAc)_2$	Cs_2CO_3	6	69
5	$PdCl_2$	Cs_2CO_3	6	66
6	$PdCl_2(PPh_3)_2$	Cs_2CO_3	6	50
7	$Pd(PPh_3)_4$	Cs_2CO_3	6	5
8	$Pd(OAc)_2$	Na_2CO_3	6	61
9	$Pd(OAc)_2$	Et_3N	6	40
10	$Pd(OAc)_2$	K_3PO_4	6	64
11	**$Pd(OAc)_2$**	**NaOAc**	**5**	**78**
12[f]	$Pd(OAc)_2$	NaOAc	5	43
13[g]	$Pd(OAc)_2$	NaOAc	5	23
14[h]	$Pd(OAc)_2$	NaOAc	5	17
15[i]	$Pd(OAc)_2$	NaOAc	5	21
16	$Pd(OAc)_2$[j]	NaOAc	18	67

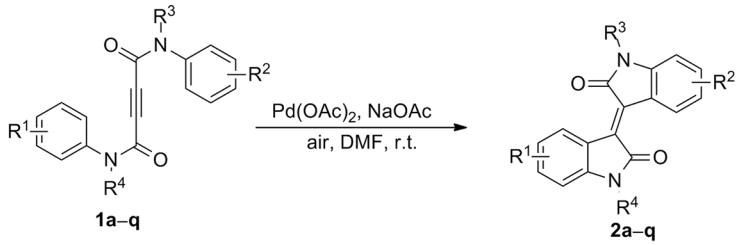
[a] *Reactions conditions:* **1a** (0.5 mmol), [Pd] (10 mol%), air as the oxidant and base (2 equiv.) in DMF ($c = 0.05$ M) at room temperature unless otherwise stated.
[b] Isolated yield.
[c] $Cu(OAc)_2$ (3 equiv.) as the oxidant.
[d] No reaction occurred.
[e] O_2 (in balloon) as the oxidant.
[f] The reaction was run in DMSO.
[g] The reaction was run in CH_3CN.
[h] The reaction was run in DCM.
[i] The reaction was run in toluene.
[j] $Pd(OAc)_2$ (5 mol%).

for the conversion, as no reaction occurred in the absence of $Pd(OAc)_2$ (Table 1, entry 2). To our surprise, the reaction with no added $Cu(OAc)_2$ afforded the product **2a** in a slightly improved yield (Table 1, entry 3). This observation indicated that oxygen in the air could adequately serve as the oxidant for this process. Counterintuitively, the yield did not improve when pure oxygen gas was supplied (Table 1, entry 4).

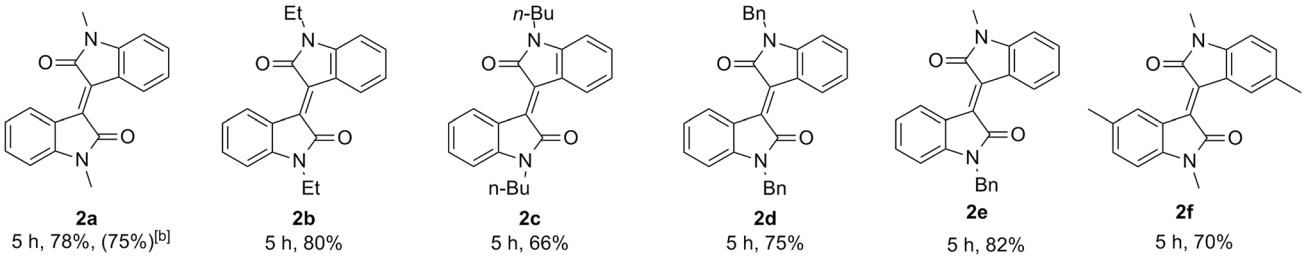
Under these initial conditions, several palladium catalysts including $PdCl_2$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ were examined. Results showed that none of them gave better yields than $Pd(OAc)_2$ (Table 1, entries 5–7). Our next study for identifying an effective base showed that NaOAc was the best to promote the reaction as with it the desired product was obtained in the highest yield (78%) (Table 1, entries 8–11). The solvent screening study suggested that DMF was by far the most appropriate solvent among all the solvents put to test, including DMSO, CH_3CN, toluene

and DCM (Table 1, entries 12–15). Reducing the loading of $Pd(OAc)_2$ to 5 mol% resulted in a sluggish reaction and a decreased yield of 67% (Table 1, entry 16). Based on these results, the best conditions were concluded to be: 10 mol% of $Pd(OAc)_2$, 2 equivalents of NaOAc in DMF and air as the oxidant at room temperature (Table 1, entry 11).

Table 2. Synthesis of functionalized bisindole-2-ones.[a]



1a–q 2a–q



2a 5 h, 78%, (75%)[b]

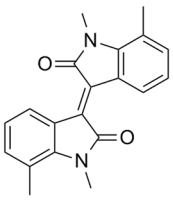
2b 5 h, 80%

2c 5 h, 66%

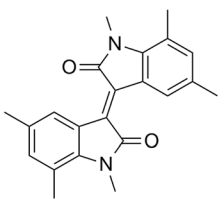
2d 5 h, 75%

2e 5 h, 82%

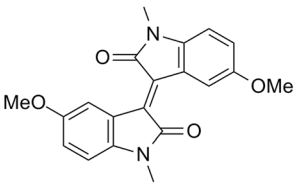
2f 5 h, 70%



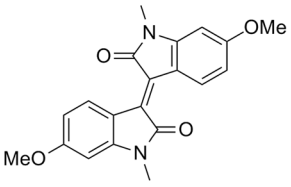
2g 8 h, 56%[c]



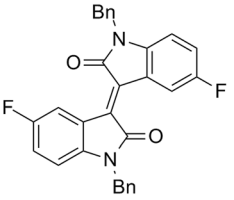
2h 8 h, 50%[c]



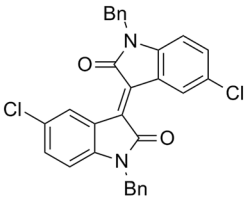
2i 6 h, 68%



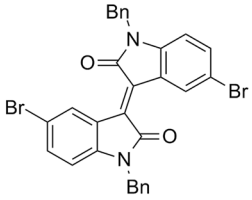
2j 7 h, 23%[d,e]



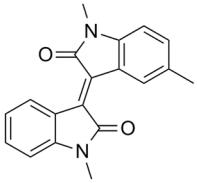
2k 3.5 h, 67%



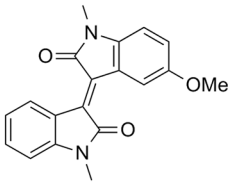
2l 3.5 h, 70%



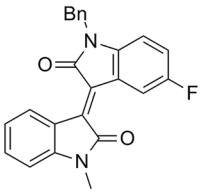
2m 3.5 h, 65%



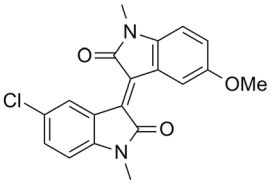
2n 5 h, 77%



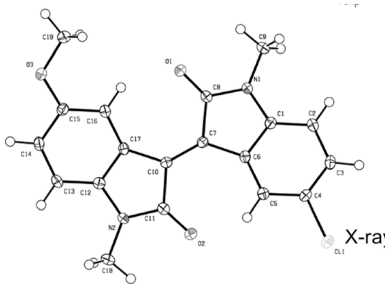
2o 5 h, 60%



2p 4 h, 83%



2q[f] 4 h, 91%



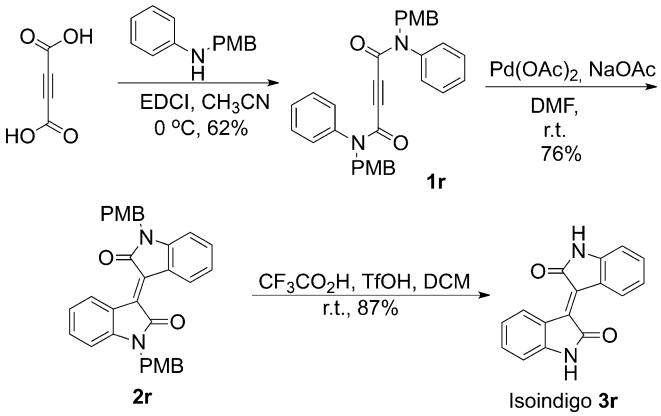
2q[f] X-ray single-crystal

[a] *Conditions:* **1** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), NaOAc (1.0 mmol) in dry DMF ($c = 0.05$ M) at room temperature.
[b] Yield of gram scale reaction in parentheses (see the Supporting Information for details).
[c] The reaction was carried out using 0.2 equiv. of $Pd(OAc)_2$.
[d] Some unidentified by-products were formed.
[e] The yield was 10% when the reaction was carried out at −10 °C for 24 h.
[f] The structure of **2q** was assigned by X-ray single crystal diffraction analysis.[13]

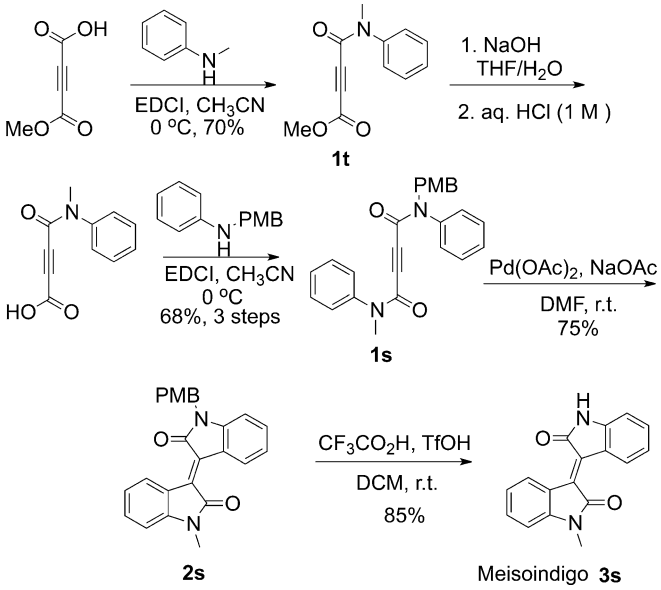
Our next step was to investigate the generality of this newly established protocol. A variety of diarylbut-2-ynediamides **1a–q** were investigated under the optimized conditions (Table 2). The method worked well with symmetrical substrates bearing an ethyl, *n*-butyl and benzyl groups as R^3 and R^4 (Table 2, **2b–d**). The method showed to be equally applicable to unsymmetrical substrates, as **1e** was successfully converted into the corresponding unsymmetrical bisindole product **2e** in very good yield. For symmetrical substrates bearing the same R^1 and R^2 groups, similar yields were obtained for those bearing a methyl or dimethyl R^1/R^2 groups (Table 2, **2f–h**), with the *o*-substituted substrate **2g** giving a relatively lower yield. On the contrary, drastically different yields (68% *vs.* 23%) were observed between substrates with R^1/R^2 being *p*-OMe and *m*-OMe (Table 2, **2i** *vs.* **2j**[14]). With regard to substrate **1j**, the low yield was probably caused by the formation of some unidentified by-products during the reaction. We tried to further improve the yield by restricting the side reactions at a lower temperature, however, the yield was reduced to 10% when the reaction was carried out at −10 °C after 24 h. Those substrates bearing electron-withdrawing halogen groups – F, Cl, and Br – all gave the desired products **2k–m** in nearly identical, satisfactory yields of 65–70%. For the unsymmetrical, mono-substituted substrates (R^1 = H, R^2 = Me, OMe, and F), reaction yield was the highest when the substrate was F-substituted (83%) while the lowest for the MeO-substituted (60%) (Table 2, **2n–p**). The highest yield of all (91%) was obtained from **1q**, which bears an electron-donating (OMe) and an electron-withdrawing (Cl) group at the R^1/R^2 positions (Table 2, **2q**). During the process of the reaction, the substrates (**1a–q**) were completely consumed in each case, accompanied by the occurrence of different degrees of side reactions.

Isoindigo and Meisoindigo, two important pharmaceutical agents found to offer effective treatment for chronic myeloid leukemia (CML),[2] could be synthesized by using our method in a fairly straightforward manner. As illustrated in Scheme 2, the coupling of the acetylenedicarboxylic acid with aniline afforded substrate **1r**, and palladium-catalyzed intramolecular cyclization followed by the removal of the *para*-methoxybenzyl ether (PMB) protective group afforded isoindigo **3r** in an overall yield of 41%. Likewise, as depicted in Scheme 3, Meisoindigo **3s** could be synthesized from readily available 4-methoxy-4-oxobut-2-ynoic acid in 6 steps (30% overall yield) (see the Supporting Information for details).

On the basis of previous reports,[8–11,15] we tentatively postulated two mechanistic pathways for this domino reaction. As illustrated in Scheme 4, the first step is the carbopalladation between the triple bond moiety and $Pd(OAc)_2$. The resulted complexation in-

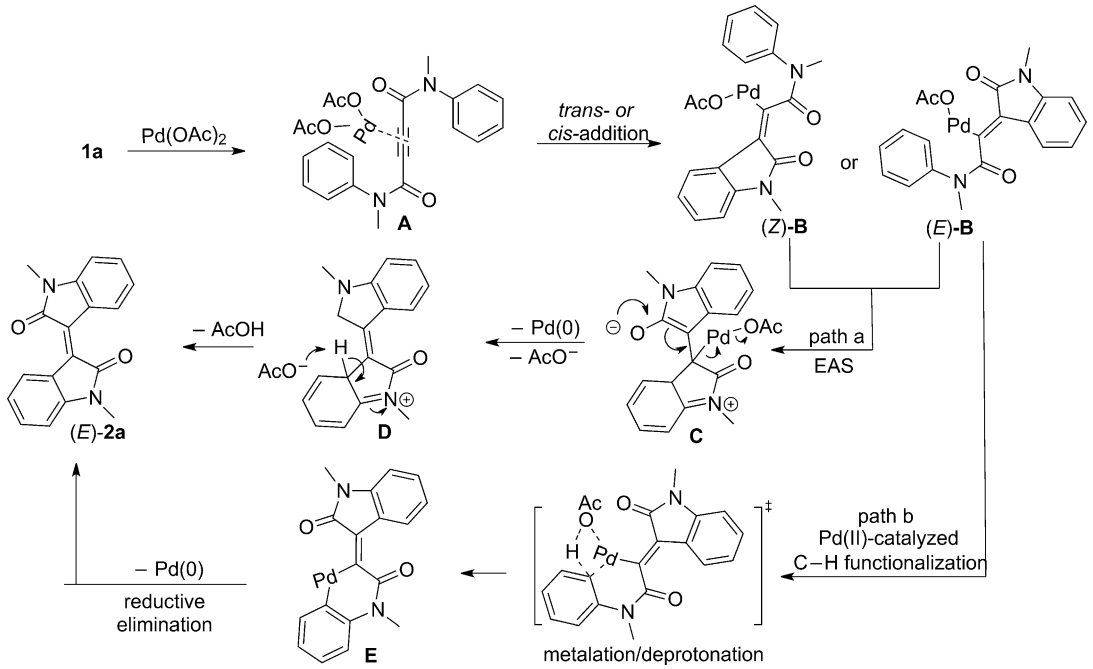


Scheme 2. Synthesis of Isoindigo **3r**.

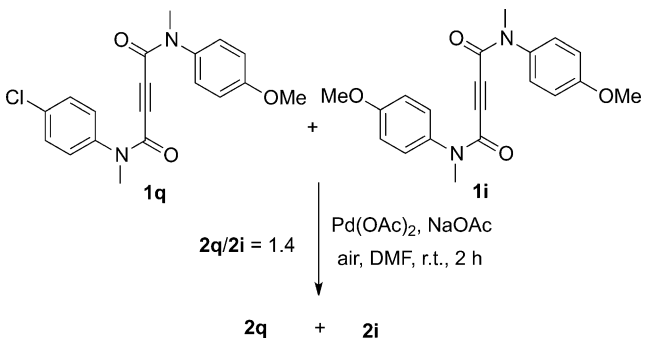


Scheme 3. Synthesis of Meisoindigo **3s**.

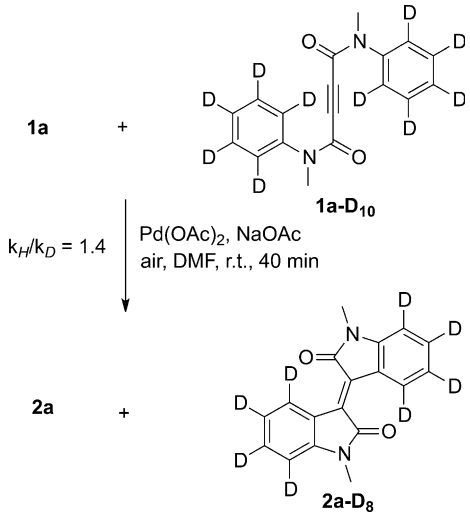
termediate **A** then undergoes *cis*- or *trans*-addition to the triple bond realizing the first annulation *via* an electrophilic aromatic substitution (EAS) mechanism. In path a, the EAS product (*E*)-**B** or (*Z*)-**B** undergoes a second intramolecular EAS reaction to form intermediate **C**. By losing the leaving group as Pd(0) and the acetate ion, intermediate **C** is converted to intermediate **D**, which further gives rise to the final product (*E*)-**2a** after deprotonation. However, the pathway is inconsistent with the result of the competitive experiment (Scheme 5) involving **1i** and **1q**, in which **2q** was formed in much higher yield (with ratio of **2q**:**2i** = 1.4). As is known, the EAS mechanism prefers electron-rich aryls, so the second EAS steps proposed in path a would then predict a preference for substrates with electron-donating (R^1 = OMe) substituents; yet in contrast, the lower yields were observed in **2i** (Scheme 5) with R^1 being a methoxy group.



Scheme 4. Plausible mechanistic pathways.



Scheme 5. Kinetic experiment for electronic effect study.



Scheme 6. Kinetic isotope effect experiments.

In the second pathway (path b), after the first EAS step, intermediate (*E*)-**B** undergoes a Pd(II)-catalyzed C–H functionalization with an aryl hydrogen, passing through a concerted metalation/deprotonation[16,17] step to form the Pd(II) complex **E**. Reductive elimination of Pd(0) eventually leads to the final product (*E*)-**2a**. As an electron-withdrawing substituent would increase the acidity of the aryl-H and consequently decrease the energy of the transition state for the concerted metalation/deprotonation,[18] the pathway is consistent with the competitive experiment results (Scheme 5) which indicated that the higher yield from **2q** was probably due to the electron-withdrawing R^1 = Cl group (which would favor the second annulation step). Competitive experiments of **1a** *vs.* its deuterated analog (**1a-D$_{10}$**) provided the k_H/k_D value close to 1.4 (Scheme 6), suggesting that the C–H functionalization might not be the rate-determining step.

It is worth noting that the generated Pd(0) species could be reoxidized by the oxygen in the air back to Pd(II) and enter a new catalytic cycle.

In summary, we have disclosed an unprecedented approach for the construction of a series of (*E*)-bisindole-2-ones from the diarylbut-2-ynediamides *via* a palladium(II)-catalyzed intramolecular C–H functionalization and C–C bond formation protocol. The method is practically useful and operationally convenient to perform. The reaction proceeds under mild reaction conditions and can be run on a gram-scale, and the products have important applications as pharmaceuticals, dyes and electronic devices.

Experimental Section

General Procedure

In a 50-mL round-bottom flask, diarylbut-2-ynediamide (0.5 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF, 10 mL). $Pd(OAc)_2$ (0.05 mmol, 0.1 equiv.) and NaOAc (1 mmol) were added to the solution. The mixture was then stirred in the open air at room temperature. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water (40 mL) and then extracted with EA (40 mL × 5). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel.

Acknowledgements

We acknowledge the National Natural Science Foundation of China (21472136, 21302136) and the National Basic Research Project (2014CB932201, 2015CB856500), Tianjin Research Program of Application Foundation and Advanced Technology (15JCZDJC32900) and Tianjin Natural Science Foundation (13JCQNJC04800) for financial support.

References

[1] For selected examples, see: a) T. Maugarda, E. Enauda, P. Choisyb, M. D. Legoya, *Phytochemistry* **2001**, *58*, 897–904; b) P. Polychronopoulos, P. Magiatis, A. Skaltsounis, V. Myrianthopoulos, E. Mikros, A. Tarricone, A. Musacchio, M. Roe, L. Pearl, M. Leost, P. Greengard, L. Meijer, *J. Med. Chem.* **2004**, *47*, 935–946; c) L. Rui, K. F. Reardon, T. K. Wood, *Appl. Microbiol. Biotechnol.* **2005**, *66*, 422–429; d) M. Sassatelli, F. Bouchikhi, B. Aboab, F. Anizon, D. Fabbro, M. Prudhomme, P. Moreau, *Anti-Cancer Drugs* **2007**, *18*, 1069–1074; e) L. J. Stanislav, H. Petra, L. Antonín, *Dyes and Pigments* **2010**, *85*, 171–176; f) Y. Y. Gui, J. Yang, L. W. Qi, X. Wang, F. Tian, X. N. Li, L. Peng, L. X. Wang, *Org. Biomol. Chem.* **2015**, *13*, 6371–6379.

[2] For selected examples, see: a) X. M. Liu, L. G. Wung, H. Y. Li, X. I. Ji, *Biochem. Pharmacol.* **1996**, *51*, 1545–1551; b) F. Bouchikhi, F. Anizon, P. Moreau, *Eur. J. Med. Chem.* **2008**, *43*, 755–762; c) X. K. Wee, W. K. Yeo, B. Zhang, V. Tan, K. M. Lim, T. E. Tay, M. L. Go, *Bioorg. Med. Chem.* **2009**, *17*, 7562–7571; d) Z.-H. Wang, T. Wang, S.-N. Yao, J.-C. Chen, W.-Y. Hua, Q.-Z. Yao, *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 160–166; e) P. Zhao, Y. H. Li, G. W. Gao, S. Wang, Y. Yan, X. P. Zhan, Z. G. Liu, Z. M. Mao, S. X. Chen, L. Q. Wang, *Eur. J. Med. Chem.* **2014**, *86*, 165–174.

[3] For selected examples, see: a) J. G. Mei, K. Graham, R. Stalder, J. Reynolds, *Org. Lett.* **2010**, *12*, 660–663; b) G. B. Zhang, Y. Y. Fu, Z. Y. Xie, Q. Zhang, *Macromolecules* **2011**, *44*, 1414–1420; c) R. Stalder, J. Mei, J. R. Reynolds, *Macromolecules* **2010**, *43*, 8348–8352.

[4] For selected examples, see: a) B. Liu, Y. P. Zou, B. Peng, B. Zhao, K. L. Huang, Y. H. He, C. Y. Pan, *Polym. Chem.* **2011**, *2*, 1156–1162; b) T. Lei, Y. Cao, Y. L. Fan, C. Liu, J. Pan, S. C. Yuan, J. Pei, *J. Am. Chem. Soc.* **2011**, *133*, 6099–6101; c) J. G. Mei, D. H. Kim, A. L. Ayzner, M. F. Toney, Z. Bao, *J. Am. Chem. Soc.* **2011**, *133*, 20130–20133; d) R. Stalder, C. Grand, J. Subbiah, F. So, J. R. Reynolds, *Polym. Chem.* **2012**, *3*, 89–92; e) R. S. Ashraf, A. J. Kronemeijer, D. I. James, H. Sirringhau, I. McCulloch, *Chem. Commun.* **2012**, 48, 3939–3941; f) P. Sonar, H. S. Tan, S. Sun, Y. M. Lam, A. Dodabalapur, *Polym. Chem.* **2013**, *4*, 1983–1994.

[5] For selected examples, see: a) L. L. Welbes, T. W. Lyons, K. A. Cychosz, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837; b) K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541–6544; c) X. B. Wan, D. Xing, Z. Fang, B. J. Li, F. Zhao, K. Y. Zhang, L. P. Yang, Z.-J. Shi, *J. Am. Chem. Soc.* **2006**, *128*, 12046–12047; d) M. Y. Yang, B. Su, Y. Wang, K. Chen, X. Y. Jiang, Y.-F. Zhang, X.-S. Zhang, G. Y. Chen, Z. C. Cao, Q.-Y. Guo, L. S. Wang, Z.-J. Shi, *Nat. Commun.* **2014**, *5*, 4707; e) Q. Xiao, W.-H. Wang, G. Liu, F.-K. Meng, J.-H. Chen, Z. Yang, Z.-J. Shi, *Chem. Eur. J.* **2009**, *15*, 7292–7296; f) Y. Y. Ma, Z. Y. Yan, C. L. Bian, K. Li, X. W. Zhang, M. F. Wang, X. L. Gao, H. Zhang, A. W. Lei, *Chem. Commun.* **2015**, *51*, 10524–10527; g) M. Chen, Y. Weng, M. Guo, H. Zhang, A. W. Lei, *Angew. Chem.* **2008**, *120*, 2311–2314; *Angew. Chem. Int. Ed.* **2008**, *47*, 2279–2282; h) W. Li, C. Liu, H. Zhang, K. Y. Ye, G. H. Zhang, W. Z. Zhang, Z. L. Duan, S. L. You, A. W. Lei, *Angew. Chem.* **2014**, *126*, 2475–2478; *Angew. Chem. Int. Ed.* **2014**, *53*, 2443–2446; i) D. Y. Qian, J. Zhang, *Chem. Commun.* **2012**, *48*, 7082–7084; j) J. B. Zhang, X. L. Han, *Adv. Synth. Catal.* **2014**, *356*, 2465–2470; k) K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126–1136; l) H. H. Cui, W. Wei, D. S. Yang, J. M. Zhang, Z. H. Xu, J. W. Wen, H. Wang, *RSC Adv.* **2015**, *5*, 84657–84661; m) O. Jackowski, J. P. Wang, X. M. Xie, T. Ayad, Z. G. Zhang, V. Ratovelomanana-Vidal, *Org. Lett.* **2012**, *14*, 4006–4009; n) Z.-C. Ding, H.-T. Tang, R.-H. Li, L.-C. Ju, Z.-P. Zhan, *J. Org. Chem.* **2015**, *80*, 9307–9313; o) X.-H. Ouyang, R.-J. Song, B. Liu, J.-H. Li, *Chem. Commun.* **2016**, *52*, 2573–2576; p) R. Shintani, T. Yamagami, T. Hayashi, *Org. Lett.* **2006**, *8*, 4799–4801; q) Y. Q. Deng, W. Gong, J. He, J.-Q. Yu, *Angew. Chem.* **2014**, *126*, 6810–6813; *Angew. Chem. Int. Ed.* **2014**, *53*, 6692–6695; r) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059; s) T.-S. Mei, X. S. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807; t) T. Piou, A. Bunescu, Q. Wang, L. Neuville, J. P. Zhu, *Angew. Chem.* **2013**, *125*, 12611–12615; *Angew. Chem. Int. Ed.* **2013**, *52*, 12385–12389.

[6] a) W. Liu, Q. Yu, L. Hu, Z. Chen, J. Huang, *Chem. Sci.* **2015**, *6*, 5768–5772; b) H. Zhong, D. Yang, S. Wang, J. Huang, *Chem. Commun.* **2012**, *48*, 3236–3238; c) Q. Yu, N. Zhang, J. Huang, *Chem. Eur. J.* **2013**, *19*, 11184–11188; d) W. Bi, X. Yun, Y. Fan, X. Qi, Y. Du, J. Huang, *Synlett* **2010**, 2899–2904.

[7] a) S. Shang, D. Zhang-Negrerie, Y. Du, K. Zhao, *Angew. Chem.* **2014**, *126*, 6330–6333; *Angew. Chem. Int. Ed.* **2014**, *53*, 6216–6219; b) X. Zhang, C. Yang, D.

Zhang-Negrerie, Y. Du, *Chem. Eur. J.* **2015**, *21*, 5193–5198; c) X. Zhang, W. Hou, D. Zhang-Negrerie, K. Zhao, Y. Du, *Org. Lett.* **2015**, *17*, 5252–5255; d) L. Liu, H. Lu, H. Wang, C. Yang, X. Zhang, D. Zhang-Negrerie, Y. Du, K. Zhao, *Org. Lett.* **2013**, *15*, 2906–2909; e) C. Yang, X. Zhang, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem.* **2015**, *80*, 5320–5328.

[8] a) X.-H. Yang, K. Li, R.-J. Song, J.-H. Li, *Eur. J. Org. Chem.* **2014**, 616–623; b) D.-J. Tang, B.-X. Tang, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 6749–6755; c) T.-S. Jiang, R.-Y. Tang, X.-G. Zhang, X.-H. Li, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 8834–8837; d) S. Tang, P. Peng, P. Zhong, J. H. Li, *J. Org. Chem.* **2008**, *73*, 5476–5480; e) S. Tang, P. Peng, Z.-Q. Wang, B.-X. Tang, C.-L. Deng, J.-H. Li, P. Zhong, N.-X. Wang, *Org. Lett.* **2008**, *10*, 1875–1878; f) S. Tang, P. Peng, S.-F. Pi, Y. Liang, N.-X. Wang, J.-H. Li, *Org. Lett.* **2008**, *10*, 1179–1182; g) S. Balalaie, H. Motaghedi, M. Bararjanian, D. Tahmassebi, H. R. Bijanzadeh, *Tetrahedron* **2011**, *67*, 9134–9141.

[9] A. Pinto, L. Neuville, R. Pascal, J. P. Zhu, *Org. Lett.* **2006**, *8*, 4927–4930.

[10] T. Zou, X. G. Zhang, J.-H. Li, C. L. Deng, R. Y. Tang, *Adv. Synth. Catal.* **2012**, *354*, 889–898.

[11] P. Peng, B. X. Tang, S. F. Pi, Y. Liang, J.-H. Li, *J. Org. Chem.* **2009**, *74*, 3569–3572.

[12] Selected reviews on the palladium-catalyzed domino reactions: a) N. T. Patil, Y. Yamamoto, *Synlett* **2007**, *13*, 1994–2005; b) R. Grigg, V. Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65–87; c) A. de Meijere, S. Bräse, *J. Organomet. Chem.* **1999**, *576*, 88–110; d) C. J. Ball, M. C. Willis, *Eur. J. Org. Chem.* **2013**, 425–441; e) N. T. Patil, Y. Yamamoto, *Top. Organomet. Chem.* **2006**, *19*, 91–113.

[13] CCDC 1482689 (**2q**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Formula: $C_{19}H_{15}ClN_2O_3$, unit cell parameters: $a=7.1145(15)$ $b=18.993(3)$ $c=23.116(5)$ $C2/c$.

[14] Product **2j** was stable under the reaction conditions, as no reaction occurred when **2j** was stirred under the same reaction conditions [$Pd(OAc)_2$ (0.05 mmol), NaOAc (1.0 mmol) in dry DMF ($c=0.05$ M) at room temperature] for 12 h.

[15] a) M. Hatano, M. Terada, K. Mikami, *Angew. Chem.* **2001**, *113*, 255–259; *Angew. Chem. Int. Ed.* **2001**, *40*, 249–253; b) A. Pinto, L. Neuville, J. P. Zhu, *Angew. Chem.* **2007**, *119*, 3355–3359; *Angew. Chem. Int. Ed.* **2007**, *46*, 3291–3295.

[16] a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem.* **2008**, *120*, 7340–7343; *Angew. Chem. Int. Ed.* **2008**, *47*, 7230–7233; b) A. M. Echavarren, B. Gómez-Lor, J. J. González, Ó. Frutos, *Synlett* **2003**, 585–597.

[17] a) D. Garcia-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067; b) D. Garcia-Cuadrado, P. D. Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

[18] C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639.