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Synthesis of 3-(Diarylmethylenyl)oxindole by a Palladium-Catalyzed Domino Carbopalladation/C–H Activation/C–C Bond-Forming Process

Artur Pinto, Luc Neuville, Pascal Retailleau, and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

zhu@icsn.cnrs-gif.fr

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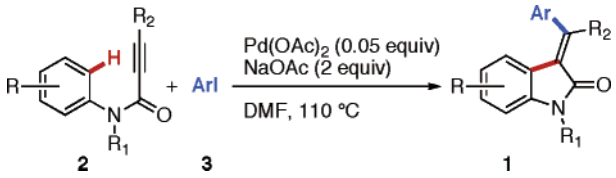
ABSTRACT



2 3 1

A highly efficient palladium-catalyzed synthesis of unsymmetrically substituted 3-(diarylmethylenyl)indolinones from readily accessible starting materials is developed. The domino reaction involves a sequence of intermolecular carbopalladation, C–H activation, and C–C bond formation. A plausible mechanistic pathway for the reaction is discussed on the basis of the kinetic isotope effect [K_H/K_D (intermolecular) = 1, K_H/K_D (intramolecular) = 2.7] as well as the electronic effect.

3-Alkylideneoxindoles are attractive synthetic targets because of their significant biological activities[1] as well as their proved utilities as valuable intermediates in the elaboration of complex naturally occurring alkaloids and drug candidates.[2] Whereas (3-arylidenyl)indolinone is easily accessible,[3] methods allowing a rapid and reliable access to stereochemically defined unsymmetrically substituted 3-(diarylmethylenyl)indolinones (**1**) are scarce.[4−7] Furthermore, the reported transformations required the use of 2-iodoanilides[4−6] or 2-(alkynyl)phenylisocyanates[7] as starting materials. We have recently reported a synthesis of tetracyclic heterocycles by a palladium-catalyzed domino sequence involving a key C−H functionalization step.[8] As a continuation of this research program, we report herein a novel and efficient synthesis of **1** that involves a palladium-catalyzed domino intermolecular carbopalladation/C−H activation/C−C bond-forming process (Scheme 1).[9,10] Besides being conceptually novel, this approach allows the use of anilides (**2**) that are

(1) Noble, M. E. M.; Endicott, J. A.; Johnson, L. N. *Science* **2004**, *303*, 1800−1805.

(2) (a) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666−5667. (b) Ma, D.; Wu, Q. *Tetrahedron Lett.* **2000**, *41*, 9089−9092. (c) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347−6355.

(3) (a) Fielding, M. R.; Grigg, R.; Urch, C. J. *Chem. Commun.* **2000**, 2239−2240. (b) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511−2514. (c) Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477−3480. (d) Kalinski, C.; Umkehrer, M.; Schmidt, J.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W.; Hoffmann, S. D. *Tetrahedron Lett.* **2006**, *47*, 4683−4686 and references therein. See also: (e) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099−2103.

(4) Indium-mediated cyclization/Pd-catalyzed cross-coupling: Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825−2828.

(5) Pd-catalyzed Heck cyclization/Suzuki−Miyaura coupling: (a) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741−3744. (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972−6975.

(6) Pd-catalyzed Heck cyclization/Sonogashira coupling: D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153−158.

(7) Kamijo, S.; Sasaki, Y.; Kanazawa, C.; Schüsseler, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7718−7721.

(8) (a) Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774−4777. (b) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475−14484.

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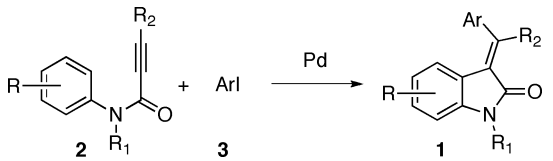
Scheme 1. Synthesis of 2-Oxindoles by a Sequence of Carbopalladation/C−H Activation/C−C Bond Formation



readily synthesized from cheap and easily accessible anilines and arylpropiolic acid.

The reaction between *N*-(4-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (**2a**, R = 4-MeO, R_1 = Me, R_2 = Ph)[11] and 1-iodo-2-nitrobenzene (**3a**) was initially examined. After a brief survey of reaction conditions, it was observed that the reaction was best performed under ligandless conditions using $Pd(OAc)_2$ as a catalyst and NaOAc as a base. DMF was found to be a superior solvent to ethanol and toluene. Overall, under optimized conditions [5 mol % of $Pd(OAc)_2$, NaOAc, DMF, 110 °C, 3 h], reaction of **2a** and **3a** afforded **1a** (R = 4-OMe, Ar = 2-nitrophenyl, R_2 = phenyl) in 82% yield as a single stereoisomer (Figure 1). The *E*-configuration

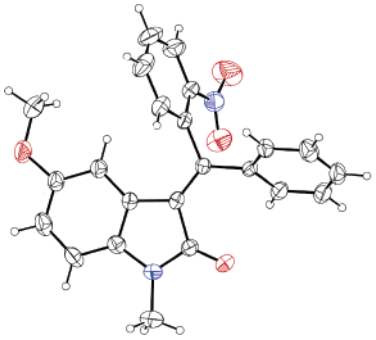
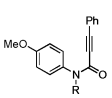
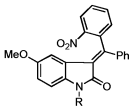
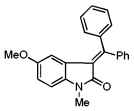
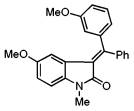
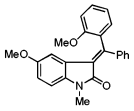
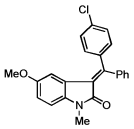
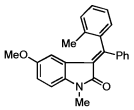
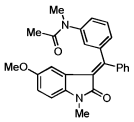
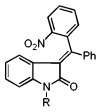
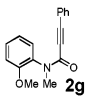
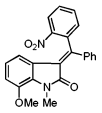
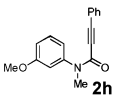
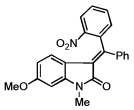
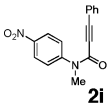
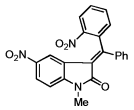


Figure 1. X-ray structure of oxindole **1a**.

of the tetrasubstituted double bond was deduced from NOE studies and was unambiguously assigned by X-ray analysis.

(9) For a selected Domino process involving C−H functionalization, see: (a) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157−160. (b) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedron Lett.* **1995**, *36*, 8137−8140. (c) Grigg, R.; Loganathan, V.; Sridharan, V. *Tetrahedron Lett.* **1996**, *37*, 3399−3402. (d) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310−2311. (e) Karig, G.; Moon, M. T.; Thassana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115−3118. (f) Masselot, D.; Charmant, J. P. H.; Gallagher, T. *J. Am. Chem. Soc.* **2006**, *128*, 694−695. (g) Rahman, S. M. A.; Sonoda, M.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2003**, *5*, 3411−3414. (h) Mauleón, P.; Núñez, A. A.; Alonso, I.; Carretero, J. C. *Chem.−Eur. J.* **2003**, *9*, 1511−1520. (i) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103−5106. (j) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149. (k) Bour, C.; Suffert, J. *Org. Lett.* **2005**, *7*, 653−656. (l) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722−723. (m) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506−11507. (n) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460−7461. (o) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1873−1875. (p) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 5340−5348 and references therein.

Table 1. Synthesis of 3-Alkylideneoxindoles through Domino Carbopalladation/ C−H Functionalization[a]

entry	aniline	aryl iodide	product		yield[b]
1				**1a** R = Me	82%
2		**3a**		**1b** R = H	<10%
3				**1c** R =SEM	93%
4	**2a** R = Me	 **3b**		**1d**	62%
5	**2a** R = Me	 **3c**		**1e**	64%
6	**2a** R = Me	 **3d**		**1f**	59%
7	**2a** R = Me	 **3e**		**1g**	61%
8	**2a** R = Me	 **3f**		**1h**	62%
9	**2a** R = Me	 **3g**		**1i**	68%
10		**3a**		**1j** R = Me	83%
11	**2e** R = Me **2f** R = Bn			**1k** R = Bn	92%
12	 **2g**	**3a**		**1l**	81%
13	 **2h**	**3a**		**1m**	64%
14	 **2i**	**3a**		**1n**	68%[c]

[a] Reaction conditions: aniline (1.0 equiv), iodoarene (1.1 equiv), $Pd(OAc)_2$ (5 mol %), and NaOAc (2.0 equiv), in DMF (*c* 0.75 M), at 110 °C. [b] Isolated yield. [c] Both *E*- and *Z*-isomers were isolated in a 2.3:1 ratio.

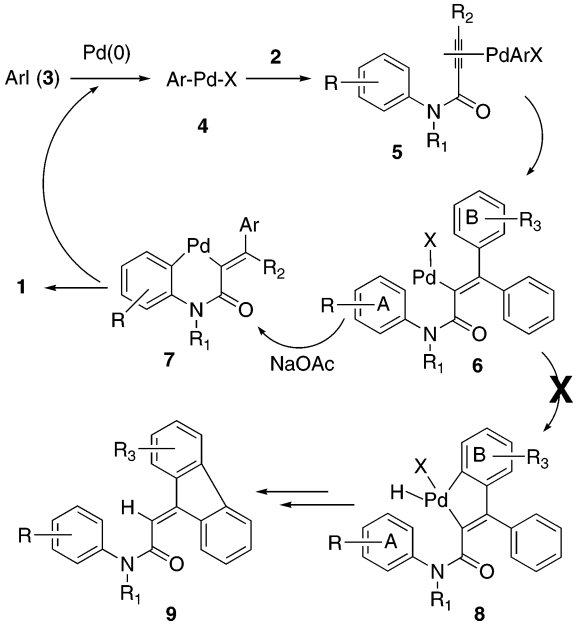
The regioselective syn insertion of the arylpalladium species to the triple bond of the propiolamide can account for the observed double bond geometry.[12]

The generality of this novel domino transformation was examined by varying the electronic and steric properties of both reactants (Table 1). With respect to anilides, it was noted that a tertiary amide has to be used to ensure the smooth occurrence of the annulation reaction because the reaction

of the secondary anilide **2b** (R_1 = H) afforded the corresponding oxindole **1b** in less than 10% yield, most probably for conformational reasons. The N-benzylated anilides **2f** participated in the reaction without the occurrence of competitive C−H functionalization of the benzyl group that would otherwise produce an isoquinolinone derivative. The N-SEM protecting group is tolerated under these reaction conditions providing **1c** in 93% yield that is readily converted to oxindole **1b** with a free NH function. When *N*-(3-methoxyphenyl)-*N*-methyl propiolamide **2h** was employed, the 6-methoxy-3-alkylideneoxindole was obtained at the expense of the 4-methoxy isomer (entry 13). Interestingly, electron-poor *N*-(4-nitrophenyl)-*N*-methyl anilide participated well in this reaction with **3a** to afford oxindole **1n** (entry 14). Interestingly, in this case, both *E*- and *Z*-isomers were isolated in a ratio of 2.3:1.[13] As far as aryl iodide (**3**) was concerned, the electron-poor aryl iodide tended to give better results than the electron-neutral or electron-rich counterpart. Reaction of 4-iodo-chlorobenzene **3e** with **2a** is chemoselective leading to a chlorinated compound (**1g**) that could in principle be further functionalized by way of transition-metal-catalyzed reaction of aryl chloride.[14]

A possible reaction scenario that accounts for the formation of oxindole **1** is shown in Scheme 2. Oxidative addition of aryl iodide to palladium(0) would give the arylpalladium-(II) species (**4**) that would subsequently coordinate to the triple bond of propiolamide. The syn carbopalladation would then take place to afford vinylpalladium intermediate **6**. The high regioselectivity observed in this carbopalladation process is somehow unexpected because it is well-known that the regioselectivity of such a reaction is insensitive to electronic effects and is predominantly affected by steric factors.[12,15] We reasoned that the observed selectivity is inherent to the propiolamide structure and results from the combination of coordination power and steric influence of the amide group. Similar high regioselectivity is seen in Lu's domino carbopalladation/intramolecular Heck reaction/anion capture sequence.[16]

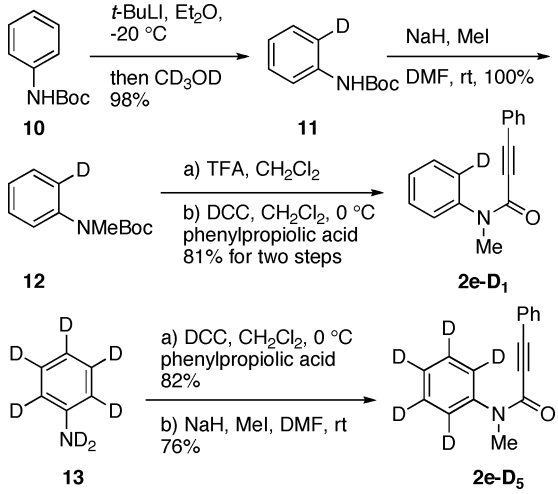
Scheme 2. Proposed Reaction Mechanism



Two benzenoid C−H's, those of ring A and ring B in intermediate **6**, are available for activation. Activation of the ring B C−H followed by vinyl to aryl migration of palladium and cyclization according to Larock[17] would produce a fluorene derivative (**9**) via an intermediate (**8**). However, this sequence did not take place even in the case of the reaction between **2a** and 3-(*N*-methyl-*N*-acetyl)iodobenzene **3g** wherein ring A and ring B (R_3 = *m*-acetamido) in the intermediate (**6**) have a very similar electronic and steric environment. The C−H activation of ring A occurred instead to provide a six-membered palladacycle **7**. Reductive elimination would then lead to the formation of **1** with the concomitant regeneration of Pd(0).

To probe the reaction mechanism, we set out to examine the kinetic isotope effect of this reaction. Toward this end,

Scheme 3. Synthesis of Deuterated Anilides



(10) For reviews on C−H activation, see: (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403−424. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. (d) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1770. (f) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (g) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533−538. (h) Catellani, M. *Synlett* **2003**, 298−313. (i) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253−1264.

(11) **2a** is synthesized by DCC-mediated coupling of *N*-methyl-*N*-(4-methoxyphenyl)amine with phenylpropiolic acid. **2e**, **2g**, and **2h** are similarly prepared. **2c** and **2f** are synthesized by alkylation of the corresponding secondary amides with BnBr and SEMCl, respectively. **2i** is synthesized by acylation of *N*-methyl-*N*-(4-nitrophenyl)amine with phenylpropiolyl chloride. See also refs 4−6.

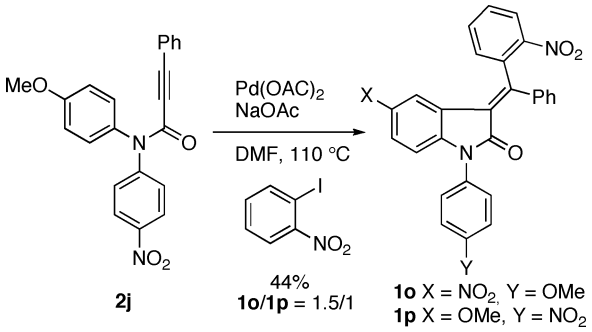
(12) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920.

(13) The structure of the *Z*-isomer was determined by X-ray analysis (cf. Supporting Information). However, we do not know at the present stage of development if the *Z*-isomer was produced during the reaction sequence or by isomerization of the *E*-isomer. A control experiment indicated that *E*-**1n** is partially isomerized to *Z*-**1n** in a $CDCl_3$ solution at room temperature and vice versa.

(14) For a review, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(15) For a leading reference, see: Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765−3777 and references therein.

Scheme 4. Electronic Effect on the Domino Process



the deuterated anilides **2e-D$_1$** and **2e-D$_5$** were synthesized (Scheme 3). Ortho lithiation of *N*-Boc aniline **10** followed by quenching with CD_3OD afforded the deuterated derivative **11** in 98% yield with 90% deuterium incorporation according to the ^{1}H NMR spectrum. A three-step sequence involving N-methylation, removal of *N*-Boc function, and DCC-mediated amide formation provided **2e-D$_1$** in excellent overall yield. **2e-D$_5$** was synthesized from the commercially available D_7-aniline (**13**) in two steps involving: (a) DCC-mediated coupling with phenylpropiolic acid and (b) N-methylation.

A competitive experiment of **2e** and its pentadeuterated derivative (**2e-D$_5$**) provided an intermolecular K_H/K_D value of 1. This result indicated that the C−H functionalization (from intermediate **6** to product) is not the rate-determining step of this domino process. On the other hand, an intramolecular isotope effect of 2.8 was obtained[18] in the cyclization of **2e-D$_1$** indicating that the mechanism of C−H activation is incompatible with the S_EAr mechanism.

We also designed an intramolecular competition experiment using anilide **2j** as a substrate and found that electronic effects influenced only weakly the *regio*selectivity of the C−H functionalization step (Scheme 4). Actually, the cyclization occurred preferentially at the electron-poor benzene ring (**1o**/**1p** = 1.5:1) that is again incompatible with the S_EAr mechanism for the C−H activation step.[19] According to these observations and in light of the recent computational studies, we think that proton abstraction via either σ−H bond metathesis (**14**) or formation of an agostic C−H intermediate (**15**) followed by H-transfer to palladium bond acetate provided the best explanation for the C−H activation mechanism.[20] Figure 2 shows a possible C−H activation mechanism.

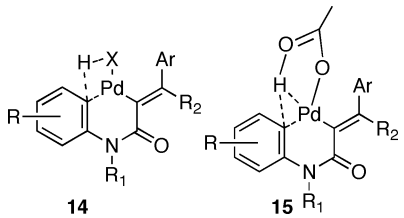


Figure 2. Possible C−H activation mechanism.

In summary, we have disclosed a novel synthesis of 3-(diarylmethylenyl)indolinones (**1**) by developing a palladium-catalyzed domino carbopalladation/C−H functionalization process. Experimental data revealed that the C−H activation is not the rate-determining step and that it proceeded most probably through a proton abstraction mechanism.

Acknowledgment. We thank CNRS and this institute for financial support. A.P. thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a doctoral fellowship.

Supporting Information Available: General experimental procedure, product characterization for **1a**−**p** and determination of the kinetic isotope effects and X-ray analyses of *E*-**1a** and *Z*-**1n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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