DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of [3.4]-spirooxindoles through cascade carbopalladation of skipped dienes

Hamid Azizollahi,[a,b] Marta Pérez-Gómez,[a] Vaibhav P. Mehta[a] and José-Antonio García-López[a]*

[a] Grupo de Química Organometálica, Universidad de Murcia, Campus de Espinardo, 30100, Murcia (Spain) joangalo@um.es
[b] Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, 91775-1436, Mashhad, (Iran)

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. A synthetic route to [3.4]-spirooxindoles based on cascade carbopalladation reactions of 1,4-dienes is described. While carbopalladation of alkenes have been used to access mainly [4.4]- or [4.5]-spirocycles, 4-*exo-trig* carbopalladation has not been yet applied to the synthesis of relevant [3.4]-spirooxindole scaffolds bearing a cyclobutyl ring. In addition, the cascade reaction generates an exocyclic double bond that can serve as a platform to further diversify the substitution pattern of the spirooxindole nuclei.

Keywords: spirooxindole; palladium; cascade; carbopalladation; cyclobutyl

Spirooxindoles are privileged scaffolds present in numerous pharmaceuticals and natural products.[1–4] One of the factors influencing the biological activity of this type of compounds is the size of the ring that conforms the spirocyclic structure at the 3-position of the oxindole moiety.[1] In recent years, a plethora of synthetic methods giving rise to spirooxindoles with different substitution patterns has been reported in the literature.[3,5–11] Thus it is possible to incorporate rings from 3 to 8 members at the 3-position of the aforementioned nuclei. More specifically, the introduction of conformationally constrained cyclobutyl rings confer interesting properties to many bioactive molecules and drugs.[12–15] Some examples of 3,3-cyclobutyl-spirooxindoles include the marine alkaloid welwitindolinone A isonitrile which shows antifungal properties,[16] compounds with RSV antiviral activity,[17] or bromodomain[18] and p38α inhibitors,[19] among others (Figure 1). Notwithstanding the relevance of [3.4]-spirooxindoles bearing a cyclobutyl moiety in their core structure, the studies focused on their synthesis are relatively scarce. The main methods reported in the literature include: a) 3,3-dialkylation of the oxindole skeleton with 1,3-dihalopropane (route **a**, Scheme 1);[20] b) the

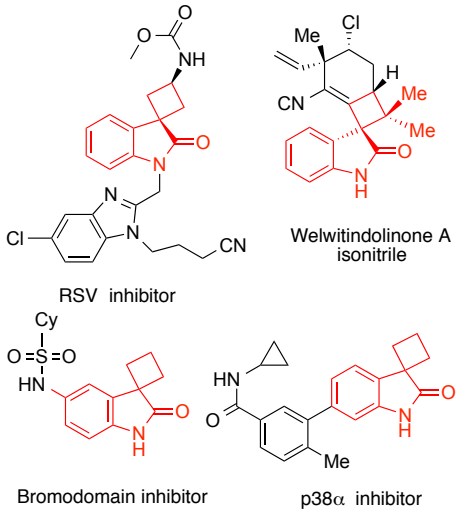
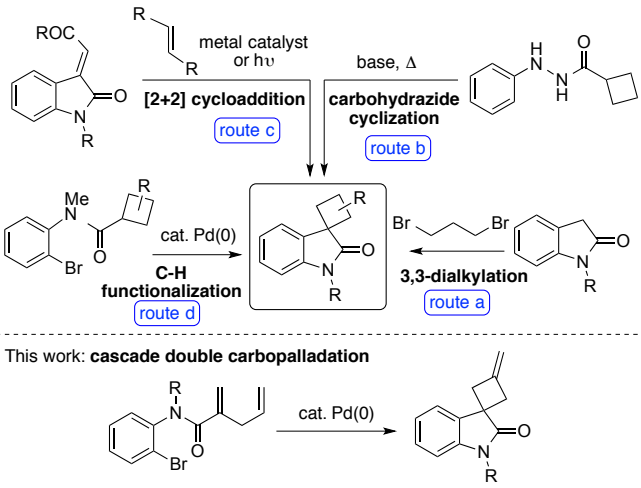


Figure 1. Biologically relevant spirooxindoles bearing a cyclobutyl unit in the spirocyclic core.

intramolecular cyclization of *N*'-phenylcyclobutanecarbohydrazide at high temperature (route **b**, Scheme 1);[19] and c) [2+2] cycloaddition reactions based on the use of activated 3-methylene oxindole derivatives (route **c**, Scheme 1).[21–25] Other approaches based on Pd-catalyzed or mediated intramolecular C–H functionalization afford spirooxindoles where two carbons of the cyclobutyl ring belong to an aryl group (route **d**, Scheme 1).[7,26] In addition, several strategies have been applied to the construction of the cyclobutyl ring present in the core of the welwitindolinone A isonitrile.[27–30]
Inspite of the available synthetic methods, a general route which incorporates different range of substitution patterns from readily synthesized starting materials is highly desirable.

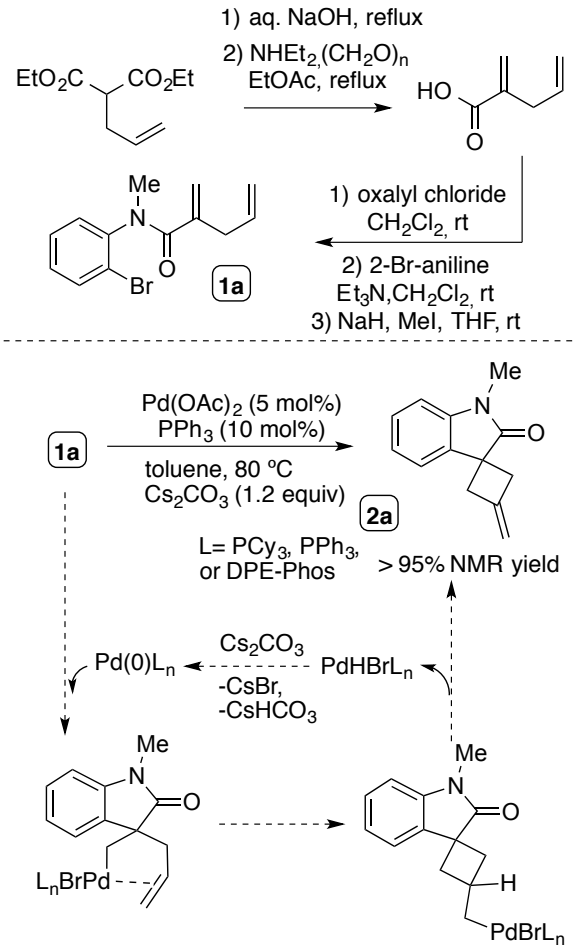


Scheme 1. Routes to get 3,3-cyclobutyl-spirooxindoles.

Our group is interested in the study of cascade reactions involving the intramolecular carbopalladation of alkenes.[26,31–34] Noteworthy, carbopalladation cascade reactions are not limited to the use of alkenes, they have also been successfully implemented in substrates bearing alkynyl fragments.[35] These reactions have been widely used in the synthesis of [4.4]- and [4.5]-spirocycles.[10,36–50] Nevertheless, their application to get the related [3.4]-spirooxindole derivatives has not been studied, what is likely related to the scarce number of reported examples dealing with 4-*exo*-*trig*-carbopalladations.[51–54]

We reported recently a ligand-controlled Pd-catalyzed reaction taking place on 2-haloarylethers bearing a 1,4-diene tethered chain.[32] We found that bulky monodentate ligands such as PCy_3 promoted a sequential double carbopalladation of the 1,4-diene moiety, affording interesting [3.4]-spirodihydrofuranes. Given the importance of the 3,3-cyclobutylspirocyclic oxindole structures, we have now sought to apply the Pd-catalyzed cascade strategy to their synthesis in order to enhance the variability of the substitution pattern of these cores (Scheme 1).

The starting amide substrate **1a** could be easily obtained from commercially available anilines and 2-methylenepent-4-enoic acid, prepared in turn from 2-allyl-diethylmalonate ester (Scheme 2).[54] We submitted the amide **1a** to the cyclization reaction by generating Pd(0) in situ from $Pd(OAc)_2$ (2.5 mol%) and PPh_3 (5 mol%) in toluene at 80 ºC in the presence of Cs_2CO_3 (entry 1, Table 1). Gratifyingly, the spirooxindole **2a**, bearing a 3-methylene-cyclobutyl ring, was the main product of the crude reaction mixture, along with some unreacted starting material. Different bases such as NEt_3, K_2CO_3 or NaOAc did not improve the yield of **2a** (entries 3-5, Table 1). The increase of the $Pd(OAc)_2$ loading to 5 mol% afforded nearly full conversion of **1a** into the desired spirocyclic product **2a**. We tested different mono-



Scheme 2. Substrate synthesis and proposed mechanistic pathway for its cyclization reaction.

Table 1. Screening of conditions for the cascade reaction leading to the spirooxindole **2a** from **1a**.

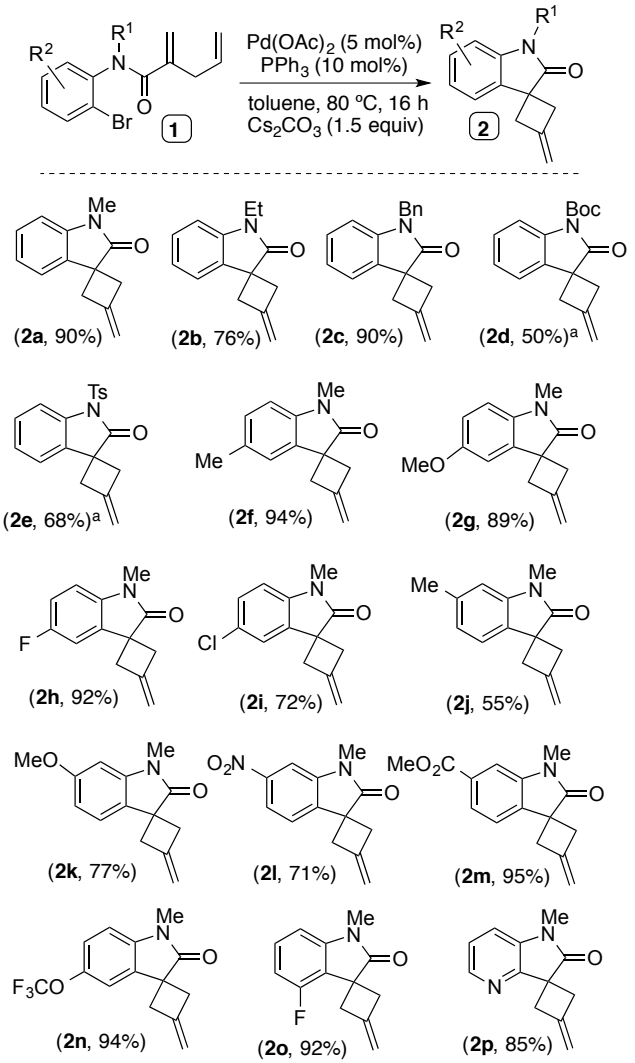
Entry	$Pd(OAc)_2$ (mol%)	Ligand (mol%)	Base (equiv)	Yield (%)[a]
1	2.5	PPh_3 (5)	Cs_2CO_3 (1.5)	85
2[b]	2.5	PPh_3 (5)	Cs_2CO_3 (1.5)	41
3	2.5	PPh_3 (5)	K_2CO_3 (1.5)	76
4	2.5	PPh_3 (5)	NaOAc (1.5)	72
5	2.5	PPh_3 (5)	Et_3N (1.5)	70
6	5	PPh_3 (10)	Cs_2CO_3 (1.5)	98 (90)
7	5	PPh_3 (5)	Cs_2CO_3 (1.5)	83
8	5	PCy_3 (5)	Cs_2CO_3 (1.5)	97
9	5	DPE-Phos (5)	Cs_2CO_3 (1.5)	98
10	5	-		0
11	-	PPh_3 (5)	Cs_2CO_3 (1.5)	0

Unless otherwise stated, the reactions were carried out with 0.2 mmol of **1a**, in toluene (3 mL) under N_2 atmosphere, at 80 ºC for 16 h. a) ^{1}H-NMR yield of **2a** using trimethylbenzene-1,3,5-tricarboxylate as standard, isolated yield in brackets. b) Reaction carried out at 60 ºC. DPE-Phos = bis-[2-(diphenylphosphino)phenyl]ether.

and bidentate phosphine ligands (entries 8-9, Table 1) to check any possible effect on the outcome of the catalytic process, as observed previously for related ether derivatives.[32] Nevertheless, in this occasion the reaction proved insensitive to the use of different phosphines, producing the spirocycle **2a** in all the cases. Likely, the cascade process starts with the oxidative addition of the C–Br bond to Pd(0), what triggers the sequential double carbopalladation of the skipped diene moiety. Final β-hydrogen elimination would generate the exocyclic alkene in the spirocyclic structure (Scheme 2).

We proceeded to study the scope of the reaction using $Pd(OAc)_2$ (5 mol%)/PPh_3 (10 mol%) as a readily available precatalyst system. Substrates **1a–e** bearing different substituents on the nitrogen atom afforded the corresponding cyclized products **2a–e** (Scheme 3). The reaction gave good yields for *N*-alkylated amides (**2a**, Me; **2b**, Et; **2c**, Bn). Nevertheless, the generation of the *N*-Boc (**2d**) or *N*-Tosyl (2**e**) derivatives required higher $Pd(OAc)_2$ loading (10 mol%) to reach a moderate conversion, perhaps due to the competing coordination of these groups to Pd. The introduction of electron-donating groups (Me, OMe) at the 4- and 5-position of the aromatic ring was well tolerated (products **2f**, **2g**, **2j**, and **2k,** Scheme 3). The starting materials bearing an electron-withdrawing substituent (F, Cl, OCF_3, CO_2Me, NO_2) afforded the corresponding products in good yields (**2h**, **2i**, **2l**, **2m, 2n** and **2o,** Scheme 3). The catalytic cascade reaction also proceeded smoothly for the pyridine derivative **1p**, giving the spirocompound **2p** in 85% yield.

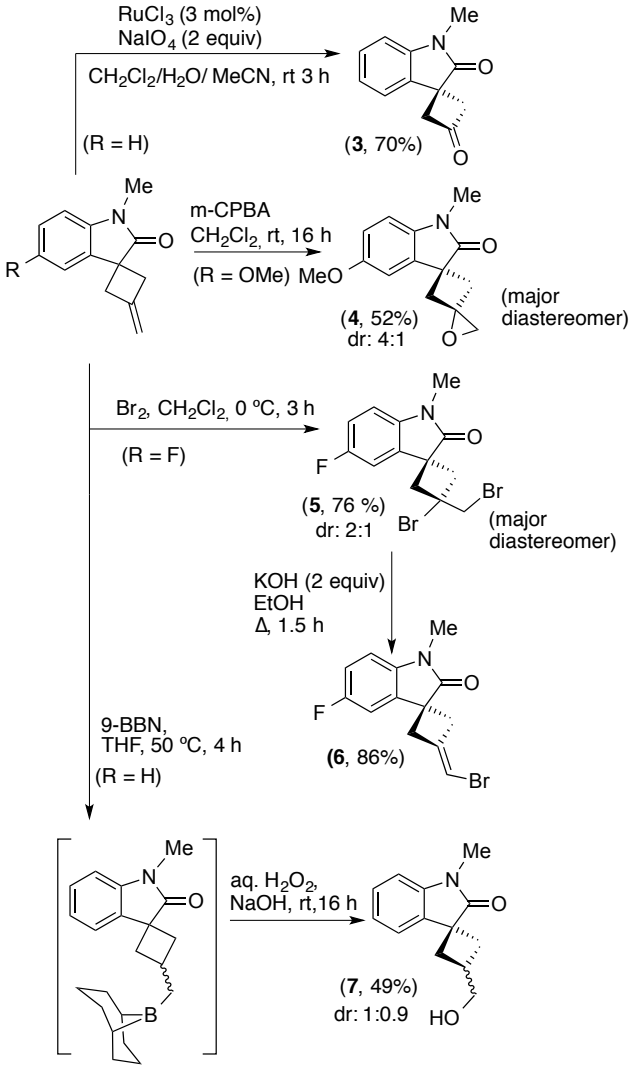
The Pd-catalyzed cascade reaction of amides **1** leading to the cyclized derivatives **2** offers an additional synthetic advantage for further functionalization over other methods to get related 3,3-cyclobutyl-spirooxindoles. The generation of a terminal olefin represents a useful handle that can serve as a platform to obtain a family of derivatives through its functionalization, what can result interesting for the generation of libraries of compounds including the spirocyclobutyl unit.
For instance, the compound **3,** bearing a cyclobutanone ring, could be smoothly obtained through the Ru-catalyzed oxidation of the olefin present in the spirooxindole **2a** with $NaIO_4$.
Similarly, an epoxidation step of compound **2g** was carried out with *m*-CPBA, affording the [4.3.2]-polyspirocycle **4** as a 4:1 mixture of diastereomers. The major diastereomer of this mixture was isolated in a 52% yield upon column chromatography separation. A NOESY NMR experiment did not show clearly the sterochemical configuration of the major diastereomer (see S. I). We propose that the major diastereomer should place the oxygen atoms (from the amide group and the epoxy ring) in opposite sides of the plane containing the cyclobutyl unit, since this is the observed stereochemistry for the derivative **5** (see below). In addition, we developed optimized 3D molecular structures for the two possible diastereomers with the software Spartan 14. The model predicted the structure proposed for the major diasteromer of **4** to be around 5 KJ/mol more stable than the diasteromer where the amide group and the epoxy ring are in the same side of the plane containing the cyclobutyl unit.
The halogenation of compound **2h** with Br_2 afforded the derivative **5** in 76% yield as a 2:1 mixture of diastereomers. In this case, the sterochemistry of the major one could be unequivocally determined through a NOESY NMR experiment. It located the Br atom on the quaternary carbon in the opposite side of the amide group. Probably, the path leading to this diastereomer minimizes electronic repulsion of the lone pairs of the heteroatoms, as in the case of the derivative **4**. Compound **5** could be easily transformed in the spirocycle **6** by simple reflux in the presence of KOH. The bromo vinyl fragment in **6** may serve as a handle for further derivatization *via* transition-metal cross-coupling reactions.



Scheme 3. Scope of the cascade double carbopalladation reaction. a) Products **2d** and **2e** were obtained using 10 mol% of $Pd(OAc)_2$ and 20 mol% of PPh_3.

Finally, regioselective hydroboration of **2a** afforded the alkylborane intermediate which could be oxidized with H_2O_2 to give the alcohol **7** in 49% overall yield as a 1:0.9 mixture of diastereomers.

In summary, we have applied a Pd-catalyzed cascade strategy to the straightforward synthesis of [3.4]-spirooxindoles incorporating a 3-methylene-cyclobutyl unit. This route relies on the sequential double carbopalladation of arylamides bearing a skipped diene fragment. The presence of a terminal double bond in the spirooxindole nuclei generated *via* this method offers interesting opportunities for further derivatization, broadening the accessibility to different substitution patterns in this type of scaffolds



Scheme 4. Further derivatization of the spirooxindole core.

Experimental Section

Representative procedure for the synthesis of [3.4]-spirooxindoles 2. Synthesis of compound **2a**. A Carius tube was charged with the substrate **1a** (280 mg, 1 mmol), $Pd(OAc)_2$ (11 mg, 5 mol%), PPh_3 (28 mg, 10 mol%), Cs_2CO_3 (490 mg, 1.5 mmol, 1.5 eq) and a magnetic stirrer. Under nitrogen atmosphere, dry toluene (3 mL) was added and the tube was sealed. The reaction mixture was stirred in a pre-heated oil bath at 80 ºC for 16 h. After cooling the tube, the crude was diluted with CH_2Cl_2 (20 mL) and filtered through a Celite pad. The filtrate was concentrated and the crude was purified by column chromatography (silica gel, n-hexane/EtOAc, gradient from 0 to 10 % EtOAc) to afford the spirooxindole **2a** (179 mg, 0.9 mmol, 90% yield).

Acknowledgements

Financial support from MICINN (grant PGC2018-100719-B-I00-with FEDER funding) and Fundación Séneca-Agencia de Ciencia y Tecnología de la Región de Murcia (grant 19890/GERM/15) is gratefully acknowledged. V.P. Mehta thanks the Fundación Séneca for a "Jimenez de la Espada" research stay fellowship.

References

[1] B. Yu, D. Q. Yu, H. M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673–698.

[2] C. V Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8778–8758.

[3] T. L. Pavlovska, R. G. Redkin, V. V. Lipson, D. V. Atamanuk, *Mol. Diversity,* **2016**, *20*, 299–344.

[4] N. Ye, H. Chen, E. A. Wold, P. Y. Shi, J. Zhou, *ACS Infect. Dis.* **2016**, *2*, 382–392.

[5] D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, *ACS Catal.* **2014**, *4*, 743–762.

[6] L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023–1052.

[7] D. Katayev, Y. X. Jia, A. K. Sharma, D. Banerjee, C. Besnard, R. B. Sunoj, E. P. Kündig, *Chem. - Eur. J.* **2013**, *19*, 11916–11927.

[8] B. Niu, X. Y. Wu, Y. Wei, M. Shi, *Org. Lett.* **2019**, *21*, 4859–4863.

[9] R. Samineni, J. Madapa, P. Srihari, G. Mehta, *Org. Lett.* **2017**, *19*, 3119–3122.

[10] H. Yoon, M. Rölz, F. Landau, M. Lautens, *Angew. Chem. Int. Ed.* **2017**, *56*, 10920–10923. *Angew. Chem.* **2017**, *129*, 11060 –11063.

[11] S. Guo, P. Dong, Y. Chen, X. Feng, X. Liu, *Angew. Chem. Int. Ed.* **2018**, *57*, 16852–16856; *Angew. Chem.* **2018**, *130*, 17094–17098.

[12] V. M. Dembitsky, *J. Nat. Med*. **2008**, *62*, 1–33.

[13] E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257–8322.

[14] Y. Y. Fan, H. Zhang, Y. Zhou, H. B. Liu, W. Tang, B. Zhou, J. P. Zuo, J. M. Yue, *J. Am. Chem. Soc.* **2015**, *137*, 138–141.

[15] R. F. Sweis, M. Pliushchev, P. J. Brown, J. Guo, F. Li, D. Maag, A. M. Petros, N. B. Soni, C. Tse, M. Vedadi, M. R. Michaelides, G. G. Chiang, W. N. Pappano, *ACS Med. Chem. Lett.* **2014**, *5*, 205–209.

[16] K. Stratmann, R. E. Moore, G. M. L. Patterson, R. Bonjouklian, J. B. Deeter, S. Shaffer, T. A. Smitka, C. D. Smith, *J. Am. Chem. Soc.* **1994**, *116*, 9935–9942.

[17] A. Tahri, S. M. H. Vendeville, T. H. M. Jonckers, P. J.-M. B. Raboisson, S. D. Demin, L. P. Mans, WO2014/060411, **2014**.

[18] R. K. Ujjinamatada, S. Hosahalli, S. Samajdar, C. Abbineni, WO2015/092118, **2015**.

[19] P. Eastwood, J. González, E. Gómez, B. Vidal, F. Caturla, R. Roca, C. Balagué, A. Orellana, M. Domínguez, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4130–4133.

[20] F. C. Stevens, W. E. Bloomquist, A. G. Borel, M. L. Cohen, C. A. Droste, M. L. Heiman, A. Kriauciunas, D. J. Sall, F. C. Tinsley, C. D. Jesudason, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6270–6273.

[21] Y. Q. Zou, S. W. Duan, X. G. Meng, X. Q. Hu, S. Gao, J. R. Chen, W. J. Xiao, *Tetrahedron* **2012**, *68*, 6914–6919.

[22] L. W. Qi, Y. Yang, Y. Y. Gui, Y. Zhang, F. Chen, F. Tian, L. Peng, L. X. Wang, *Org. Lett.* **2014**, *16*, 6436–6439.

[23] K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691.

[24] Y. H. Jiang, R. Y. Yang, J. Sun, C. G. Yan, *Heterocycl. Commun.* **2016**, *22*, 151–156.

[25] L. L. Wu, G. H. Yang, Z. Guan, Y. H. He, *Tetrahedron* **2017**, *73*, 1854–1860.

[26] M. Pérez-Gómez, L. Navarro, I. Saura-Llamas, D. Bautista, M. Lautens, J. A. García-López, *Organometallics* **2017**, *36*, 4465–4476.

[27] J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska, J. L. Wood, *Angew. Chem. Int. Ed.* **2004**, *43*, 1270–1272; *Angew. Chem*. **2004**, *116*, 1290–1290.

[28] P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404–408.

[29] J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938–17954.

[30] S. E. Reisman, J. M. Ready, M. M. Weiss, A. Hasuoka, M. Hirata, K. Tamaki, T. V. Ovaska, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100.

[31] M. Pérez-Gómez, J. A. García-López, *Angew. Chem. Int. Ed.* **2016**, *55*, 14389–14393; *Angew. Chemie* **2016**, *128*, 14601.

[32] H. Azizollahi, V. P. Mehta, J. A. García-López, *Chem. Commun.* **2019**, *55*, 10281–10284.

[33] M. Pérez-Gómez, S. Hernández-Ponte, D. Bautista, J. A. García-López, *Chem. Commun.* **2017**, *53*, 2842–2845.

[34] I. Franzoni, H. Yoon, J. A. García-López, A. I. Poblador-Bahamonde, M. Lautens, *Chem. Sci.* **2018**, *9*, 1496–1509.

[35] a) M. Pawliczek, T. F. Schneider, C. Maaß, D. Stalke, D. B. Werz. *Angew. Chem. Int. Ed.* **2015**, *54*, 4119–4123*; Angew. Chem.* **2015**, 127, 4192–4196; b) S. Blouin, V. Gandon, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.,* 2016, 55, 7208–7211; *Angew. Chem.,* **2016**, *128*, 7324–7327. *c)* D. A. Petrone, I. Franzoni, J. Ye, J. F. Rodríguez, A. I. Poblador-Bahamonde, M. Lautens. *J. Am. Chem. Soc.* **2017**, *139*, 3546–3557; d) A. Reding, P. G. Jones, D. B. Werz, *Angew. Chem. Int. Ed.* **2018**, *57*, 10610–10614. *Angew. Chem.* **2018**, *130*, 10770–10774. For a review see: A. Düfert, D. B. Werz, *Chem. Eur. J.* **2016**, *22*, 16718–16732.

[36] R. T. Ruck, M. A. Huffman, M. M. Kim, M. Shevlin, W. V. Kandur, I. W. Davies, *Angew. Chem. Int. Ed.* **2008**, *47*, 4711–4714; *Angew. Chem.* **2008**, *120*, 4789–4782.

[37] R. Grigg, V. Sridharan, *Tetrahedron Lett.* **1993**, *34*, 7471–7474.

[38] R. Grigg, P. Fretwell, C. Meerholtz, V. Sridharan, *Tetrahedron* **1994**, *50*, 359–370.

[39] A. Casaschi, R. Grigg, J. M. Sansano, D. Wilson, J. Redpath, *Tetrahedron* **2000**, *56*, 7541–7551.

[40] S. Jaegli, J. Vors, L. Neuville, J. Zhu, *Tetrahedron* **2010**, *66*, 8911–8921.

[41] H. Hu, F. Teng, J. Liu, W. Hu, S. Luo, Q. Zhu, *Angew. Chem. Int. Ed.* **2019**, *58*, 9225–9229; *Angew. Chem.* **2019**, *131*, 9323 –9327.

[42] A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. - Eur. J.* **2007**, *13*, 961–967.

[43] T. Piou, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11561–11565; *Angew. Chem.* **2012**, *124*, 11729 –11733.

[44] J. Ye, M. Lautens, *Nat. Chem.* **2015**, *7*, 863–870.

[45] L. E. Overman, D. J. Poon, *Angew. Chem. Intl. Ed. Engl.* **1997**, *36*, 518–521.

[46] S. Jaegli, W. Erb, P. Retailleau, J. Vors, L. Neuville, J. Zhu, *Chem. - Eur. J.* **2010**, *16*, 5863–5867.

[47] R. Grigg, I. Köppen, M. Rasparini, V. Sridharan, *Chem. Commun.* **2001**, 964–965.

[48] J. H. Seo, G. D. Artman, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8891–8900.

[49] G. Satyanarayana, M. E. Maier, *J. Org. Chem.* **2008**, 5410–5415.

[50] For reviews on Pd-catalyzed intramolecular Heck cyclizations see: a) V. P. Mehta, J. A. García-López, *ChemCatChem*, **2017**, *9*, 1149. b) S. Blouin, G. Blond, M. Donnard, M. Gulea, J. Suffert, *Synthesis*, **2017**, 1767; c) H. A. Döndas, M. G. Retamosa and J. M. Sansano, *Organometallics*, **2019**, *38*, 1828; c) Y. Ping, Y. Li, J. Zhu, W. Kong, *Angew. Chem. Int. Ed.* **2019**, *58*, 1562–1573; *Angew. Chem.* **2019**, *131*, 1576–1587.

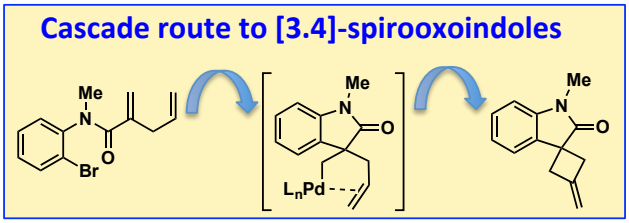
[51] S. Bräse, *Synlett* **1999**, 1654–1656.

[52] J. Hitce, O. Baudoin, *Adv. Synth. Catal.* **2007**, *349*, 2054–2060.

[53] G. Albarghouti, R. Kotikalapudi, D. Lankri, V. Valerio, D. Tsvelikhovsky, *Chem. Commun.* **2016**, *52*, 3095–3098.

[54] K. T. Yip, N. Y. Zhu, D. Yang, *Org. Lett.* **2009**, *11*, 1911–1914.

Synthesis of [3.4]-spirooxindoles through cascade carbopalladation of skipped dienes



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Hamid Azizollahi, Marta Pérez-Gómez, Vaibhav P. Mehta, José-Antonio García-López*