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Spirocyclization by Palladium-Catalyzed Domino Heck–Direct C–H Arylation Reactions: Synthesis of Spirodihydroquinolin-2-ones

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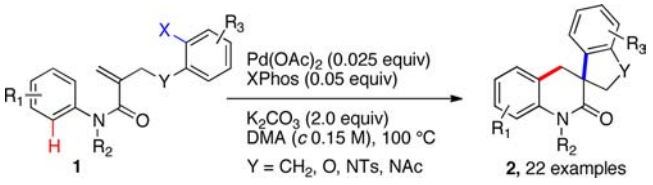
ABSTRACT



Treatment of a DMA solution of anilide 1 with a catalytic amount of palladium acetate (0.025 equiv) and XPhos (0.05 equiv) in the presence of potassium carbonate (2.0 equiv) at 100 °C afforded dihydroquinolin-2-ones spiro-fused to dihydrofuranyl, indolinyl, and indanyl 2 in good to excellent yields. The reaction went through a domino sequence involving a 5-*exo*-trig Heck cyclization followed by an intramolecular direct C–H functionalization.

The spirocycle is a key structural unit found in many bioactive natural products. The unique three-dimensional orientation of the spirocycle escaped from the aromatic flatland often encountered in many drug development programs,[1] and as a consequence, this structure has attracted the attention of medicinal chemists for its potential as an important pharmacophore.[2] The fascinating molecular architecture and the proven biological activities of spirocycles have made them attractive targets, and numerous synthetic strategies have been developed for their synthesis in recent years.[3]

Construction of the quaternary carbon center[4] and the spirocyclic scaffold are two key issues that need to be addressed in developing any new method for the synthesis of spirocycles. While many existing methods relied on the elaboration of a preconstructed monocycle, the strategy involving the concurrent formation of two cycles with the creation of a quaternary center in one operation is without a doubt the most appealing.[5] Since the intramolecular Heck reaction of 1,1′-disubstituted olefin is known to be highly efficient for the creation of all carbon quaternary centers *via* an *n-exo*-trig cyclization,[6] the trapping of the resulting neopentyl-type σ Pd(II) complex by a properly

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positioned internal nucleophile would therefore constitute an efficient approach for the construction of spirocycles with the simultaneous creation of a quaternary carbon. Based on this strategy, we have recently reported syntheses of spiropyrrolidinyloxindoles by formation of C−C and C−N bonds across the terminal double bond.[7] In continuation of our ongoing research on palladium-catalyzed domino reactions,[8,9] we became interested in combining the Heck reaction with the C−H activation/C−C bond formation[10] for the construction of spirocycles.[11] We report herein an efficient synthesis of dihydroquinolin-2-ones spiro-fused to dihydrofuranyl, indolinyl, and indanyl at the 3,3′-position (Scheme 1). Interesting biological activities of the 3,3′-disubstituted 3,4-dihydroquinolin-2(1*H*)-ones have been documented.[12]

We began our studies using the easily accessible 2-[2-(iodophenoxy)methyl]-*N*-methyl-*N*-phenylacrylamide (**1a**)[13] as a model substrate for the survey of reaction conditions. As shown in Table 1, the double cyclization of **1a** proceeded efficiently in the presence of palladium acetate (0.1 equiv), PPh_3 (0.2 equiv), and Cs_2CO_3 (2.0 equiv) at 120 °C to afford 1′-methyl-1′*H*,2*H*-spiro[benzofuran-3,3′-quinolin]-2′(4′*H*)-one (**2a**) in 85% yield (entry 1, Table 1). Using tri-*n*-butylamine as a base under otherwise identical conditions afforded only a trace amount of **2a** (entry 2). When the reaction was performed using XPhos as a ligand and potassium carbonate as a base, **2a** was isolated in an excellent yield (97%, entry 4). The reaction is nevertheless only slightly ligand-dependent as it proceeded even in the absence of a phosphine ligand (91%, entry 5). Finally, the domino cyclization occurred with only slightly reduced efficiency at a lower catalyst loading [$Pd(OAc)_2$, 0.025 equiv] and lower reaction temperature (100 °C, entry 6).

Scheme 1. Palladium-Catalyzed Double Cyclization to Spirodihydroquinolin-2-ones

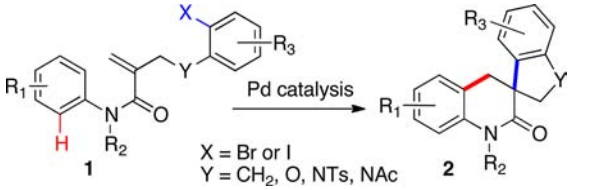
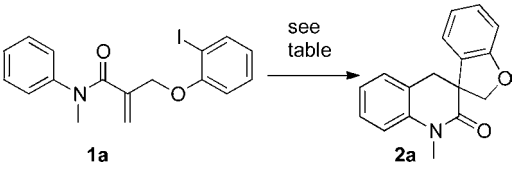


Table 1. Survey of Reaction Conditions[a]



entry	Pd source	ligand	base	*t* (°C)	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	120	85
2	$Pd(OAc)_2$	PPh_3	NBu_3	120	trace
3	$Pd(PPh_3)_2Cl_2$	–	Cs_2CO_3	120	78[c]
4	$Pd(OAc)_2$	XPhos	K_2CO_3	120	97
5	$Pd(OAc)_2$	PivOH	K_2CO_3	120	91
6	$Pd(OAc)_2$	XPhos	K_2CO_3	100	85[d]

[a] Reactions were carried out under an argon atmosphere using **1a** (1.0 equiv), catalyst (0.1 equiv), ligand (0.2 equiv), base (2.0 equiv), and DMA (*c* 0.15 M), 6 h). [b] Isolated yield. [c] Reaction performed in DMF (*c* 0.15 M). [d] Reaction was performed using $Pd(OAc)_2$ (0.025 equiv), XPhos (0.05 equiv), 12 h.

With the optimum conditions [$Pd(OAc)_2$ (0.025 equiv), XPhos (0.05 equiv), K_2CO_3 (2.0 equiv), in DMA (*c* 0.15 M) at 100 °C] in hand, the scope of the domino process was next examined. The results are summarized in Tables 2 and 3.

As shown in Table 2, the use of tertiary amide was mandatory to ensure the occurrence of the domino reaction since treatment of secondary amide 2-[2-(iodophenoxy)-methyl]-*N*-phenylacrylamide (**1b**) under identical conditions failed to produce the spirocycle (entry 1, Table 2). The *N*-benzyl derivative afforded the corresponding spirodihydroquinolin-2-one **2c** in 90% yield. The presence of an electron-withdrawing or -donating group at the *para*-position of anilides was tolerated (entries 3−7). When *N*-*meta*-tolylacrylamide was employed, an inseparable

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(10) For recent reviews on C−H activation, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (f) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(11) For Pd-catalyzed domino Heck/C−H functionalization, see: (a) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V. *Tetrahedon Lett.* **1995**, *36*, 8137. (b) Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Kandur, W. V.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4711. (c) Hu, Y.; Song, F.; Wu, F.; Cheng, D.; Wang, S. *Chem.—Eur. J.* **2008**, *14*, 3110. (d) Hu, Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5448. (e) Hu, Y.; Ouyang, Y.; Qu, Y.; Hu, Q.; Yao, H. *Chem. Commun.* **2009**, 4575. (f) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560. (g) Satyanarayana, G.; Maichle-Mössmer, C.; Maier, M. E. *Chem. Commun.* **2009**, 1571. (h) Jayanth, T. T.; Zhang, L.; Johnson, T. S.; Malinakova, H. C. *Org. Lett.* **2009**, *11*, 815. (i) Kim, K. H.; Lee, H. S.; Kim, S. H.; Kim, S. H.; Kim, J. N. *Chem.—Eur. J.* **2010**, *16*, 2375. (j) Tietze, L. F.; Hungerland, T.; Düfert, A.; Objartel, I.; Stalke, D. *Chem.—Eur. J.* **2012**, *18*, 3286.

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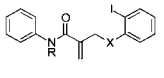
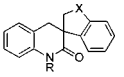
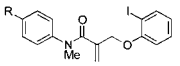
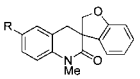
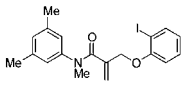
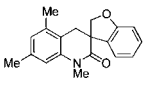
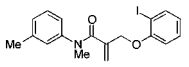
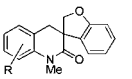
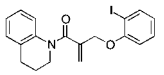
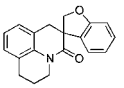
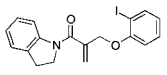
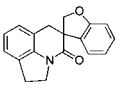
(13) Synthesized by reaction of 2-(bromomethyl)-*N*-methyl-*N*-phenylacrylamide with 2-iodophenol under basic conditions (NaH, THF, room temperature; see Supporting Information).

mixture of regioisomers **2j** and **2j'** (1.2/1 ratio) was isolated in 96% overall yield in favor of the 6-substituted spirodihydroquinolin-2-one (entry 9). Cyclization of the anilides derived from tetrahydroquinoline and indoline furnished pentacyclic spiroquinolinones **2k** and **2l** in 48% and 38% yields, respectively (entries 10 and 11). An attempt to perform the reaction under forcing conditions (120 °C) afforded **2k** and **2l** in reduced yields.

Table 2. Scope of the Domino Intramolecular Heck Reaction/C−H Functionalization: Variation on the Aniline[a]

entry	substrate (**1**)	product (**2**)	yield (%)[b]
1 2			**2b**, R = H, X = CH_2, 0 **2c**, R = Bn, X = O, 90
3 4 5 6 7			**2d**, R = OMe, 97 **2e**, R = Me, 92 **2f**, R = CN, 76 **2g**, R = F, 44 **2h**, R = CO_2Me, 91
8			**2i**, 93
9			**2j**, R = 6-Me **2j'**, R = 4-Me 96 (**2j**/**2j'** = 1.2/1)
10			**2k**, 48
11			**2l**, 38

[a] General conditions: $Pd(OAc)_2$ (0.025 equiv), XPhos (0.05 equiv), K_2CO_3 (2.0 equiv), DMA, 100 °C. [b] Isolated yield.

Variation on the aryl halide was evaluated next (Table 3). Under the standard conditions, aryl bromides can be used, albeit with a reduced yield (61%, entry 1, Table 3). While XPhos proved to be a suitable ligand in cross-coupling reactions of aryl chlorides and aryl sulfonates,[14] the desired spirodihydroquinolinone was not formed when **1n** (X = Cl) and **1o** (X = OTf) were submitted to our reaction conditions (entries 2 and 3, Table 3). Substrates having substituents of different electronic properties such as ester, cyanide, phenyl, *tert*-butyl, methyl, and methoxy groups cyclized smoothly to provide the corresponding spirodihydroquinolinones (**2p**−**2r** and **2v**−**2x**) in good to excellent yields (entries 4−6 and 10−12). Cyclization of 4-(2-iodophenyl)-*N*-methyl-2-methylene-*N*-phenylbutanamide,[15] lacking the heteroatom in the chain, underwent the cyclization without event to afford the 3,3′-spiroindenyldihydroquinolin-2-one **2s** (entry 7). Linear bis-anilides underwent double cyclizations to furnish the corresponding spiroindolinyldihydroquinolin-2-ones (**2t**−**2y**) in good to excellent yields (entries 8−13).

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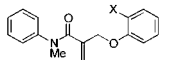
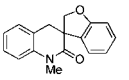
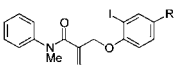
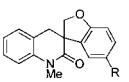
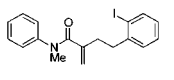
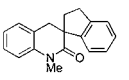
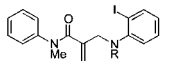
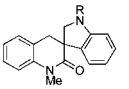
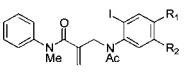
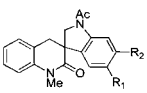
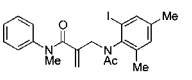
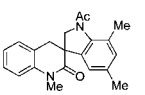
(15) For details of its synthesis, see Supporting Information.

Table 3. Scope of the Domino Intramolecular Heck Reaction/C−H Functionalization: Variation at the Aryl Halide Part[a]

entry	substrate (**1**)	product (**2**)	yield (%)[b]
1[c] 2[c] 3			**2a**, X = Br, 61 **2a**, X = Cl, 0 **2a**, X = OTf, 0
4 5 6			**2p**, R = CO_2Me, 97 **2q**, R = Ph, 83 **2r**, R = *t*Bu, 76
7			**2s**, 53
8 9[c]			**2t**, R = Ac, 92 **2u**, R = Ts, 80
10 11 12			**2v**, R_1 = H, R_2 = OMe, 95 **2w**, R_1 = CN, R_2 = H, 60 **2x**, R_1 = Me, R_2 = H, 94
13			**2y**, 69

[a] General conditions: $Pd(OAc)_2$ (0.025 equiv), XPhos (0.05 equiv), K_2CO_3 (2.0 equiv), DMA, 100 °C. [b] Isolated yield. [c] $Pd(OAc)_2$ (0.05 equiv), XPhos (0.1 equiv), K_2CO_3 (2.0 equiv), DMA, 120 °C.

Enantioselective intramolecular Heck reactions including the 5-*exo*-trig cyclization are known. Although most of them implicated a trisubstituted olefin,[16] enantioselective Heck cyclization involving a terminal olefin also existed.[17] Therefore, the spirocyclization of aryl iodide (X = I) and aryl triflate (X = OTf) were investigated in the presence of a variety of chiral ligands.[18] However, all the catalytic conditions employing different chiral ligands afforded essentially the racemic compound. The complete lack of enantioselectivity, together with the fact that the reaction occurred even in the absence of a phosphine ligand (cf. entry 5, Table 1), indicated that a "ligandless" species might be involved in the stereodetermining carbopalladation step.[19]

A proposed catalytic cycle for the domino Heck/C−H functionalization reaction is shown in Scheme 2. Oxidative addition of aryl halide to Pd(0) provided intermediate **A**. The intramolecular Heck reaction proceeded selectively in a 5-*exo*-trig cyclization mode to afford a stable σ-alkylpalladium complex **B**. Activation of the neighboring aromatic

(16) (a) Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (c) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

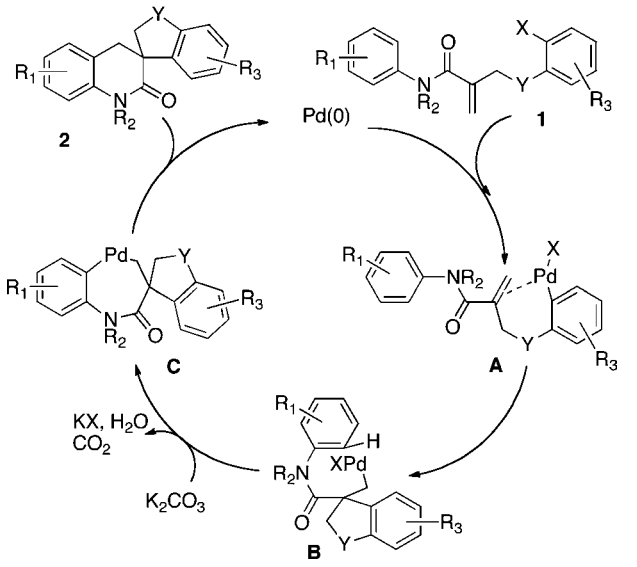
(17) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961.

(18) For a list of the chiral ligands examined, see Supporting Information.

(19) We thank one of the referees for this insightful view. For mechanistic studies on a "ligandless" Heck reaction, see: Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 79.

C−H bond led to the formation of a seven-membered palladacycle **C**, which upon reductive elimination provided the spiro-fused dihydroquinolin-2-one **2**.

Scheme 2. Possible Reaction Pathway of Domino Heck/C−H Functionalization Process[a]

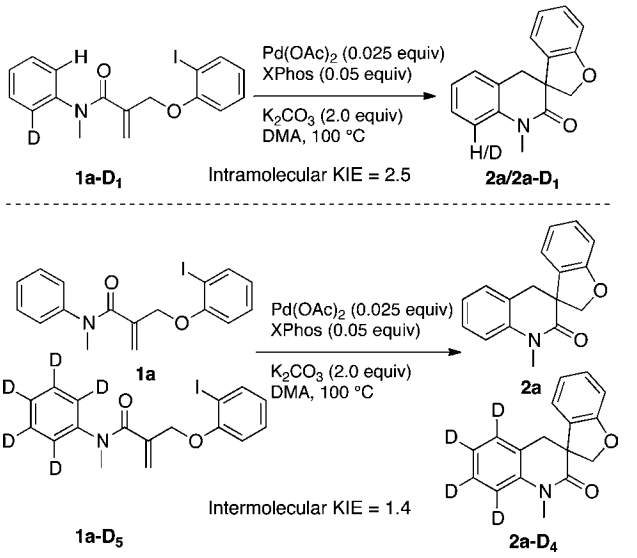


[a] Ligand on Pd was omitted for clarity.

The fact that the formation of a spirocycle is insensitive to the electronic properties of the aniline unit (for example, see entry 3 vs 7, Table 2) led us to assume that the C−H activation proceeded through the base-induced concerted metalation−deprotection mechanism[20] instead of an electrophilic aromatic substitution reaction (S_EAr mechanism). To gain further information, the kinetic isotope effect of this reaction was examined.

Compounds **1a-D$_1$** and **1a-D$_5$** were synthesized following the literature procedure.[21] Submitting **1a-D$_1$** to our standard spirocyclization conditions afforded **2a-D$_1$**/**2a** in a ratio of 2.5, hence a KIE value of 2.5 (Scheme 3).[22] This result is again incompatible with the S_EAr mechanism, favoring therefore a C−H activation process. On the other hand, an intermolecular competition experiment using an equimolar amount of **1a** and its penta-deuterated derivative

Scheme 3. Palladium-Catalyzed Spirocyclization to Spirodihydroquinolin-2-ones: Kinetic Isotope Effect



(**1a-D$_5$**) provided an intermolecular KIE value of 1.4.[23] Such a value indicated that the C−H functionalization (from intermediate **B** to product) might not be the turnover-controlling step of this domino process.[24]

In conclusion, a palladium-catalyzed spirocylization was developed, allowing a direct access to dihydrofuranyl, indolinyl, and indanyl spiro-fused to dihydroquinolin-2-ones at the 3,3′-position from linear substrates. The domino process, involving an intramolecular Heck reaction and a C−H functionalization step, allowed the one-pot creation of two cycles and one quaternary center in a highly efficient manner.

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Supporting Information Available. Supporting Information includes experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The reaction was stopped at 30% conversion.

(24) Side-by-side kinetic experiments have to be performed in order to firmly establish whether the C−H activation was the turnover-controlling step or not (*cf.* ref 22d). This will be included in our forthcoming report on this subject.

The authors declare no competing financial interest.