Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201401129

A Further Decrease in the Catalyst Loading for the Palladium-Catalyzed Direct Intramolecular Arylation of Amides and Sulfonamides

Nerea Conde,[a] Fátima Churruca,[a] Raul SanMartin,[a,*] María Teresa Herrero,[a] and Esther Domínguez[a,*]

[a] Department of Organic Chemistry II, Faculty of Science and Technology, University of the Basque Country (UPV-EHU), 48940 Leioa, Spain
Fax: (+34)-946012748; phone: (+34)-946015435; e-mail: raul.sanmartin@ehu.es or qopdopee@lg.ehu.es

Received: December 3, 2014; Revised: February 19, 2015; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201401129.

Abstract: The direct arylation of *N*-substituted *o*-bromobenzanilides and benzenesulfonamides *via* C–H bond functionalization has been developed using very low catalyst loadings. This novel cost-effective and more sustainable method relies on a PCN-type palladium pincer complex as a highly active palladium source, providing a general and efficient access to phenanthridinones, biaryl sultams and related heterocyclic systems. The beneficial effect of water as cosolvent has been observed in this process, which is not seriously influenced by electronic effects at the arene moieties or sterically demanding substituents at the amide or sulfonamide nitrogen. In addition, a number of experiments (kinetic plot, poisoning assays, TEM, ESI) have been performed in order to understand the role of the employed palladium complex in this reaction.

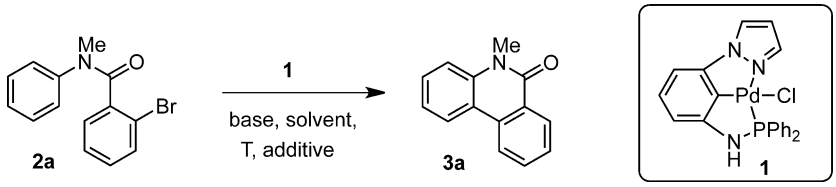
Keywords: biaryl sultams; C–H arylation; palladium; phenanthridinones; pincer complexes

Palladium-catalyzed direct functionalization of C–H bonds has emerged over the last years as a modern and sustainable tool in organic synthesis.[1] The increasing demand for green chemistry in industry as well as in academia has lead to the development of innovative, environmentally friendly and highly efficient synthetic strategies.[2] Thus, regarding both atom and step economy, the formation of carbon–carbon bonds through C–H functionalization has appeared as a convenient methodology with broad application in total synthesis and medicinal chemistry.[3]

Phenanthridinones are important structural scaffolds found in many natural products that exhibit remarkable biological and pharmaceutical properties.[4] In the last years, novel alternative synthetic approaches have been developed to the synthesis of the phenanthridinone core and related lactams, most of them based on palladium-catalyzed direct functionalization of arenes.[5] Although recent efforts have been focused on the discovery of complementary routes in order to avoid the substantial costs associated to the relative big amounts of catalysts required (2–10 mol%),[6] still, the palladium-catalyzed intramolecular direct C–H arylation reaction has proved to be one of the most versatile, reliable and efficient method for the access of phenanthridinones. Furthermore, related heterobiaryls and biaryl heterocyclic compounds as well as biaryl sultams have been successfully prepared under equivalent direct arylation procedures.[6a,7a–c] Therefore, it would be desirable to develop a novel palladium-catalyzed approach for the direct functionalization of arenes using very low catalyst loadings,[7d–e] which would provide a cost-effective and environmentally very attractive procedure for the preparation of such compounds. Moreover, considering the problems associated to the minute quantities of metal particles usually detected in the products of transition metal catalyzed reactions,[8] such method would prevent metal contamination of the product and therefore be of added interest regarding its potential application in medicinal chemistry.

Our group has ample experience in the synthesis and application of pincer-type palladium complexes as very active catalysts or pre-catalysts (cat. loading $\leq$ 0.1 mol%) in a variety of chemical transformations.[9] The power of pincer complexes lies in their unique balance of stability vs reactivity, which confers them extraordinary catalytic performance.[10] Thus, we en-

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst [Pd]	Base	Additive	Solvent	Yield [%][b]
1	0.1 mol %	NEt_3		DMPU	
2	0.1 mol %	DBU		DMA	–[c]
3	0.1 mol %	KO*t*Bu		DMF	–[c]
4	0.1 mol %	K_2CO_3	-	DMA	–[c]
5	0.1 mol %	K_2CO_3	20 mol % PivOH	DMA	<5
6	0.1 mol %	KOAc	-	DMA	24
7	0.1 mol %	KOAc	-	DMF	–[c]
8	0.1 mol %	KOAc	-	DMPU	8
9	0.1 mol %	KOAc	-	DMI	–[c]
10	0.1 mol %	K_2CO_3	20 mol % benzoic acid	DMA	17
11	0.1 mol %	KOAc	20 mol % BA[d]	DMA	<5
12	0.1 mol %	KOAc	25 mol % surfactant[e]	DMA	7–18
13	0.1 mol %	KOAc	25 mol % TBAB	DMA	19
14	0.1 mol %	KOAc	–	DMA/*o*-xylene (1:1)	23
15	0.1 mol %	KOAc	–	DMA/DMSO (1:1)	–[c]
16	0.1 mol %	KOAc	–	DMA/THF (1:1)	51
17	0.1 mol %	KOAc	–	DMA/H_2O (9.5:0.5)	57
18	0.1 mol %	KOAc	–	DMA/H_2O (9:1)	68
19	0.1 mol %	KOAc	–	DMA/H_2O (7.5:2.5)	<5
20[f]	0.1 mol %	KOAc	–	DMA/H_2O (9:1)	68
21 [g]	0.1 mol %	KOAc	–	DMA/H_2O (9:1)	75
22 [f], [g]	0.1 mol %	KOAc	–	DMA/H_2O (9:1)	83
23	0.05 mol %	KOAc	–	DMA/H_2O (9:1)	<5
24 [g]	0.05 mol %	KOAc	–	DMA/H_2O (9:1)	70
25 [f,g]	**0.05 mol %**	**KOAc**	–	**DMA/H_2O (9:1)**	**89 (88)**
26 [f,g,h]	0.03 mol %	KOAc	–	DMA/H_2O (9:1)	78
27 [f,g,i]	0.01 mol %	KOAc	–	DMA/H_2O (9:1)	57
28 [f,g]	$PdCl_2$ (0.1 mol %)	KOAc	–	DMA/H_2O (9:1)	29
29 [f,g]	$Pd(OAc)_2$ (0.1 mol %)	KOAc	–	DMA/H_2O (9:1)	33
30 [f,g]	$PdCl_2$ (0.05 mol %)	KOAc	–	DMA/H_2O (9:1)	10
31 [f,g]	$Pd(OAc)_2$ (0.05 mol %)	KOAc	–	DMA/H_2O (9:1)	11
32 [f,g]	$PdCl_2$ (0.05 mol %)	KOAc	–	DMA	<5
33 [f,g]	$Pd(OAc)_2$ (0.05 mol %)	KOAc	–	DMA	<5

[a] Reaction conditions: **2a** (0.3 mmol), **1** (0.1 mol %), base (1.5 equiv), solvent (0.06 M), 130 °C, sealed tube, 20 h under Ar unless otherwise noted. DMPU: *N*,*N*′-Dimethylpropyleneurea; DMI: 1,3-Dimethyl-2-imidazolidinone.
[b] Determined by ^{1}H NMR spectroscopy. Diethylene glycol dimethyl ether was used as internal standard. Isolated yield is displayed in parentheses.
[c] Recovery of starting material.
[d] BA: Brønsted acids (pivaloic acid, benzoic acid and *p*-toluensulfonic acid).
[e] CTAB: Hexadecyltrimethylammonium bromide; DDA: Dimethyldioctadecylammonium bromide.
[f] 3.0 equiv of KOAc were used
[g] Solvent (0.3 M)
[h] Reaction time: 48 h.
[i] Reaction time: 96 h.

visaged that such palladium complexes would be a suitable tool to achieve a more efficient direct arylation of arenes.[11] Herein we report an unprecedented palladium-catalyzed intramolecular direct arylation of *N*-substituted *o*-bromobenzanilides and benzosulfonamides for the general access of phenanthridinones and related biaryl sultams using palladium pincer complex **1** under very low catalyst loadings.

A series of screening experiments were conducted by employing a set of palladium pincer complexes

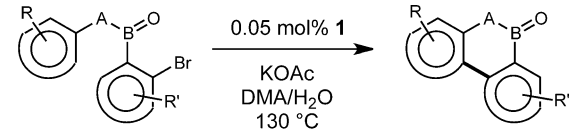
prepared by our group[9] in only 0.1 mol% with *N*-methyl-*N*-phenyl-2-bromobenzamide[12] **2a** as substrate (Table 1, entries 1–7). In contrast with other bases/solvents assayed, the use of PCN catalyst **1** produced the desired phenanthridinone **3a** in a 24% yield using KOAc as base in DMA (entry 6). Encouraged by this initial result, we proceeded to optimize the reaction conditions.

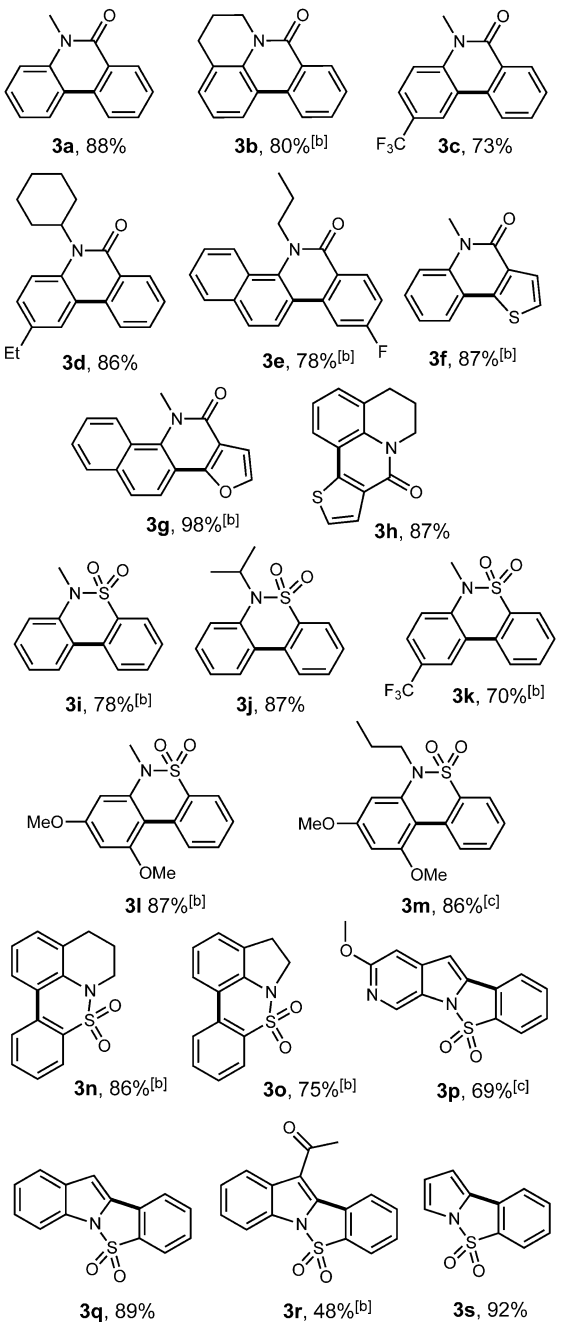
Tentative attempts to employ alternative solvents with the same base resulted ineffective (entries 7-9), as also occured by the addition of Brønsted acids such as pivalic acid (PivOH), benzoic or *p*-toluenesulfonic acid (entries 10–11). Similarly, the use of tetrabutylammonium bromide or cationic surfactants CTAB and DDA as additives did not benefit the reaction (entries 12–13). In contrast, the mixture of solvents as THF or water with DMA did improve the conversion rate (entries 16–18), obtaining the best results when 10% of water in DMA was employed (68%, entry 18). Other variables such as the amount of base, solvent concentration and especially the catalyst loadings were also examined (entries 20–27). In addition, control experiments carried out with commercially available palladium sources ($PdCl_2$ and $Pd(OAc)_2$) confirmed the convenience of palladacycle **1** and water as co-solvent (entries 28–33). Thus, after careful experimentation, we succeeded to obtain phenanthridinone **3a** in a very good yield (88%, entry 25) with only 0.05 mol% of palladium pincer complex **1** using 3 equiv of KOAc in a relatively concentrated solution of DMA/H_2O (9:1, 0.3 M). Moreover, a further decrease of the catalyst loading down to 0.01 mol% was also possible, affording desired phenanthridinone **3a** although at the cost of lower yields (78% and 57%, entries 26–27) even at longer reaction times. To the best of our knowledge, these values represent the lowest catalyst loadings achieved so far not only for the direct arylation of *N*-substituted *o*-halobenzanilides, but for any biaryl coupling of an aryl halide with a nonfunctionalized arene.[13] To relate this to the previous state of art, the elegant procedure reported by Fagnou and co-workers[5a] afforded a turnover number (TON) of 41.5 for **3a**, significantly lower than our TONs of 1760 (entry 17) and 5700 (entry 19). It should be also pointed out that the latter reactions were carried out in an air atmosphere with no effect on the reaction yield, thus providing an additional advantage from a practical point of view.

With the establishment of an optimal catalyst loading of 0.05 mol% as the most effective, the generality and scope of the reaction were initially studied with a variety of *o*-bromo-*N*-alkyl-*N*-aryl(hetero)arylcarboxamides **2b–g**.[12]

As summarized in Table 2, the functional tolerance of this procedure was observed by synthesizing various phenanthridinones and related heterocyclic quinolinones with good to excellent yields. The electronic nature of the substituents seemed to have a little effect on the product yields, according to the slightly

Table 2. Intramolecular direct arylation of arenes.[a]





[a] Reaction conditions: **2** (0.3 mmol), **1** (0.05 mol%), KOAc (3 equiv), DMA-H_2O (9:1, 0.3 M), 130 °C, sealed tube, 20 h under air. Isolated yields.
[b] 1.5 equiv of KOAc were used.
[c] 0.09 mol% of **1** was used.

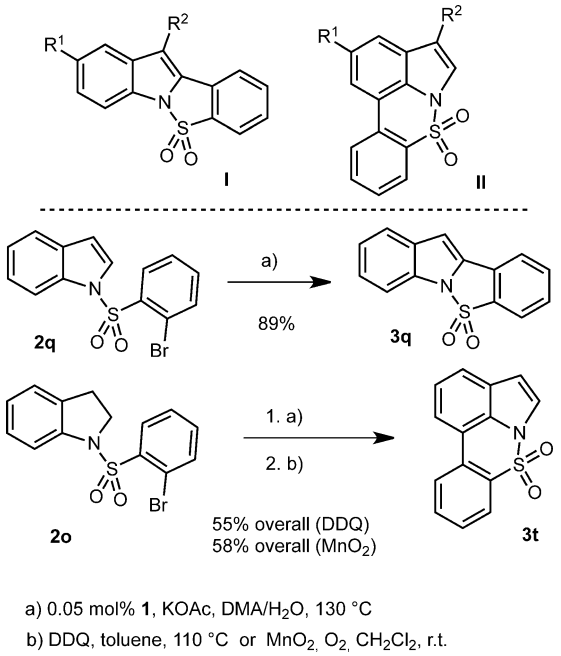
lower yield obtained for the phenanthridinone **3c** containing the electron-withdrawing CF_3 group on the *N*-aryl ring (73%). Besides, the reaction with different aromatics as naphthalene and heterocycles such as furan, thiophene or tetrahydroquinoline proceeded selectively in this C(sp^2)-H arylation (78–98%). Even sterically hindered substrates as *N*-cyclohexyl amide **2d** afforded the desired product **3d** in an 86% yield.

Considering the excellent activity of the pincer-type complex **1** to access biaryl lactams and as an attempt to further extend the potential of our approach, we investigated the applicability of this protocol to structurally related *o*-halo-*N*-arylsulfonamides. Sulfonamide group is one of the most important pharmacophores, and sulfonamide containing compounds, including sultams, display a vast array of biological activity.[14] While the recent application of palladium-catalyzed direct coupling reactions has significantly improved the access of biaryl sultams in terms of versatility and efficiency, considerably high loadings of palladium catalyst are still required (1-10 mol%).[5a,7c]

Accordingly, a series of *o*-bromo-*N*-(hetero)arylbenzenesulfonamides **2i–s** were readily prepared[12] and reacted with only 0.05 mol% pincer catalyst **1** (Table 2). To our delight, the direct functionalization of *N*-(hetero)arylsulfonamides with such low catalyst loadings afforded regioselectively the corresponding biaryl sultams. It is worth mentioning the good results obtained for the construction of benzopyrroloisothiazole-, benzoisothiazolindole- and benzo[4,5]isothiazolopyrrolopyridine *S*,*S*-dioxides **3p–s** bearing a more constrained 5-membered sultam ring. To date, the preparation of such tetracyclic systems have been only possible in moderate to good yields (<70%),[15] illustrating the difficulty to perform this particular intramolecular cyclization.

Therefore, although the yields obtained in our case are in accordance with literature precedents and, on average, not as high as the ones obtained for the corresponding 6-membered ring sultams **3h–o**, the significantly smaller amounts (0.05–0.09 mol%) of catalyst required make our protocol into the most effective approach to benzoisothiazoloindoles and related heterocycles.

In the last years, indole derivatives with constrained sulfonamide ring have gained interest as novel 5-HT_6 receptor ligands, which play an important role in CNS disorders such as schizophrenia, dementia, Alzheimer's disease and Parkinson's disease.[15,16] In particular, benzoisothiazoloindoles and benzothiazinoindoles of general structure **I**[16a] and **II**[16b] respectively (Scheme 1) have been reported as potent 5-HT_6 receptor ligands with good affinity towards 5-HT_6R and selectivity over known GPCRs. Having established the direct arylation of *N*-(*o*-bromobenzenesulfonyl)indoles mediated by palladium pincer complex **1** as an efficient and straightforward access to benzo[4,5]isothiazolo[2,3-*a*]indole *5*,*5*-dioxides (see for instance transformation of **2q** into **3q** in Scheme 1), we envisaged a complementary protocol to access the benzo[5,6]thiazino[4,3,2-*hi*]indole 7,7-dioxide framework. Indeed, whereas the intramolecular direct arylation of 2-substituted indoles affords the desired benzothiazinoindoles, a 7-bromoindole derivative has been described as essential for the selective preparation of unsubstituted benzothiazinoindoles in C2 position.[17] Alternatively, we carried out the oxidation of benzothiazinoindoline **3o**, readily available from *N*-(*o*-bromobenzenesulfonyl)indoline **2o**, to afford the target indole derivative **3t** in a good yield over two steps (Scheme 1).



a) 0.05 mol% **1**, KOAc, DMA/H_2O, 130 °C
b) DDQ, toluene, 110 °C or MnO_2, O_2, CH_2Cl_2, r.t.

Scheme 1. Access to the benzoisothiazoloindole 5,5-dioxide and benzothiazinoindole 7,7-dioxide skeletons.

As mentioned above, one of the major drawbacks of transition metal catalyzed reactions in drug discovery is the presence of trace metals contaminants in the products, as only residual palladium levels below <10 ppm are allowed in drug products.[8] We predicted that the use of a highly active palladium source like **1** in such a low amount (0.05 mol%) would avoid such contamination issues while still accomplishing the desired transformations. Accordingly, the measurement of the palladium content in benzothiazinodihydroquinoline **3n** was conducted using IPC-MS[12] and determined as low as 0.29 ppm. Therefore, our method not only provides a cost-effective and more sustainable access to biaryl amide and sultam containing heterocycles, but also offers an additional benefit regarding the avoidance of scavenger resins or further purification steps[8] in order to suppress metal contamination in the products.

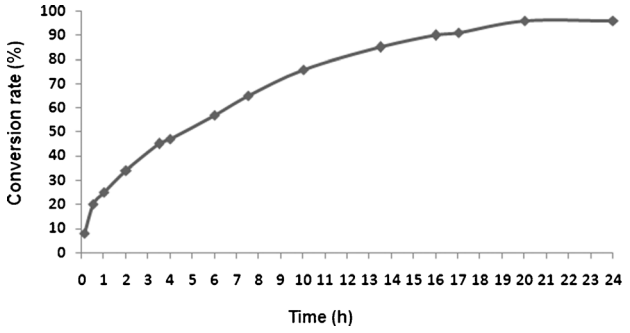


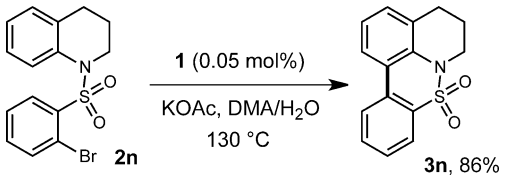
Figure 1. Conversion rate (%) of 1-((2-bromophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoline **2n** vs time.

A number of experiments were then performed to shed light on the high catalytic profile observed for pincer complex **1**. Recycling or reuse of the reaction media containing the catalytic species was initially examined. After submitting sulfonamide **2n** to the optimized reaction conditions, water was added, the mixture was extracted with ethyl acetate and the aqueous layer was concentrated to dryness. To this crude oil **2n**, KOAc and DMA were added and the reaction repeated. However, a significant drop in the conversion rate was observed (24%), and further runs provided negligible results.

The possible presence of palladium nanoparticles was also evaluated by examination of transmission electron microscopy (TEM) images from the reaction crude. The interference caused by the presence of stoichiometric amounts of potassium bromide was avoided by using a cationic exchange resin in order to remove selectively potassium ions. No such Pd nanoparticles were detected in the organic or aqueous layers after initial work-up, even when TEM was combined with Energy-dispersive X-ray spectroscopy (EDS).[12] In addition, conversion vs time curve (Figure 1) showed neither sigmoidal shape nor induction time, thus suggesting the intermediacy of homogeneous catalysts.[18] Nevertheless, the results from a series of poisoning assays (Table 3) account for the possible participation of heterogeneous species.

The somewhat puzzling outcome from the latter recycling, TEM, kinetic and poisoning measurements might be related to a mechanistic pathway based on a cocktail of in situ generated and preformed catalysts[20] after steady decomposition of **1**. A tentative proposal for the formation of benzothiazinodihydroquinoline **3n** is shown in Scheme 2. Hydrolysis[21] of phosphinoamine **A** generates 3-(1*H*-pyrazol-1-yl)aniline **B** and diphenylphosphine oxide or its tautomer diphenylphosphinous acid **C**, which upon complexation with Pd(0) species provides phosphine oxide complex(es) **D**.[22,23] After oxidative addition of aryl halide **2n** and formation of palladacyclic intermediate **F**, reductive elimination renders target **3n** and releases Pd(0) species that re-enter the catalytic cycle. The above intermediates **A**–**F** were detected by electrospray ionization mass spectrometry (ESI-MS).[12] In addition, the use of diphenylphosphine oxide as ligand along with $Pd(OAc)_2$ (0.05 mol%) under optimized conditions (KOAc, DMA/H_2O, 130 °C) provided a 54% yield of **3n** from *o*-bromosulfonamide **2n**.

Table 3. Summary of poisoning experiments.



Entry	Poisoning additive	Conv. [%][a]
1	Hg (one drop)[b]	0
2	CS_2 (0.5 equiv per metal atom)	2
3	CS_2 (2.0 equiv per metal atom)	0
4	PPh_3 (0.03 equiv per metal atom)	76
5	PPh_3 (0. 3 equiv per metal atom)	71
6	PPh_3 (4.0 equiv per metal atom)	70
7[c]	Py (150 equiv per metal atom)	8
8[d]	PVPy (300 equiv per metal atom)	88

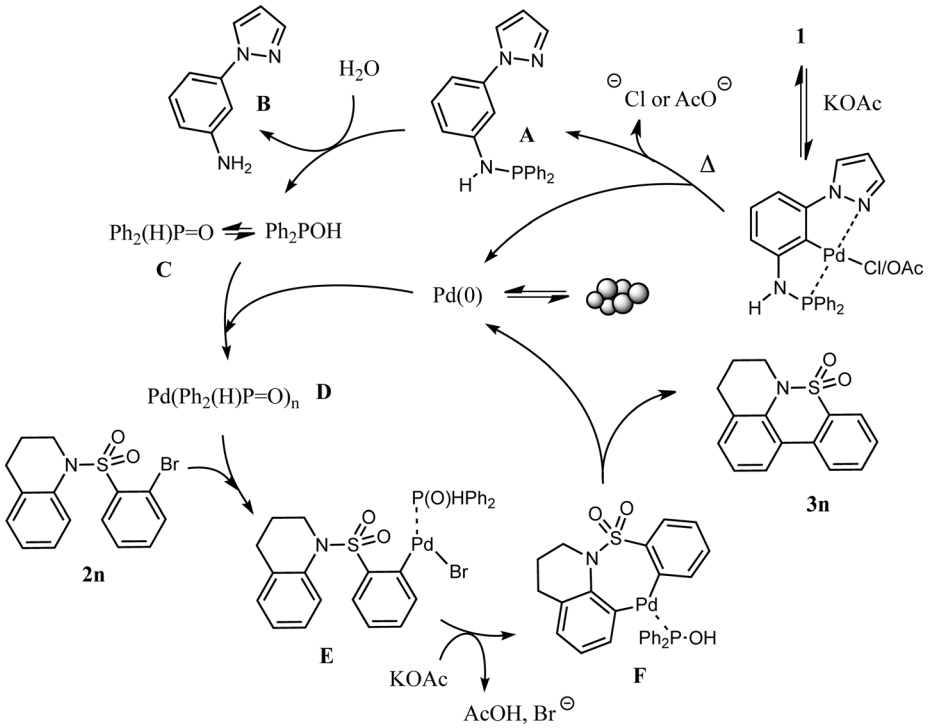
[a] Measured by ^{1}H NMR. Diethyleneglycol dimethyl ether was used as internal standard.
[b] See ref. 19 for further details on the use of Hg drop test.[19]
[c] Py: Pyridine
[d] PVPy: Polyvinylpyridine.

In summary, we have developed a method for the intramolecualr direct arylation of arenes *via* C–H bond functionalization at very low catalyst loadings. With only 0.05 mol%, palladium pincer complex **1** promotes efficiently the direct functionalization of a series of *N*-arylbenzanilides and *N*-arylsulfonamides providing a novel versatile and sustainable access to phenanthridinones, biaryl sultams and related heterocyclic derivatives. A number of experiments indicate a relatively complex mechanism that might involve different catalytically active species and cooperative catalysis between them. Further studies on the scope of the substrates, applications, and the precise mechanism are ongoing in our laboratory.

Experimental Section

General procedure for the direct arylation of arenes

DMA (0.8 mL) and water (0.1 mL) were added to a heavy-wall pressure tube charged with substrate **2** (0.35 mmol) and KOAc (1.05 mmol) at room temperature. Then, a solution of pincer complex **1** in DMA (1.75 mM, 0.1 mL, 0.175 μmol of **1**) was added, the tube was closed and it was heated to 130 °C for 20 h. After cooling, the crude reaction mixture was diluted with H_2O (2 mL) and washed with EtOAc (2×



Scheme 2. Proposed mechanism for the direct intramolecular coupling of *o*-bromosulfonamide **2n** in the presence of palladium complex **1**.

3 mL). The combined organic phase was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc in hexane) to give the desired product **3**.

Acknowledgements

This research was supported by the Basque Government (IT-774–13), the Spanish Ministry of Economy and Competitiveness (CTQ2013–46970-P) and the University of the Basque Country (UFI QOSYC 11/12). N.C. thanks the Basque Government for a predoctoral scholarship. The authors also thank Petronor, S. A. for generous donation of hexane. Finally, technical and human support provided by SGIker (UPV/EHU, MICINN, GV/EJ, ESF) is gratefully acknowledged.

References

[1] For selected recent reviews see: a) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; b) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4771; c) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17–117.

[2] M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter, H. F. Sneddon, *J. Med. Chem.* **2013**, *56*, 6007–6021.

[3] J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem.* **2012**, *124*, 9092–9142; *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.

[4] For selected recent applications see: a) D. C. Hegan, Y. Lu, G. C. Stachelek, M. E. Crosby, R. S. Bindra, P. M. Glazer, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 2201–2206; b) H. Aoyama, K. Sugita, M. Nakamura, A. Aoyama, M. T. A. Salim, M. Okamoto, M. Baba, Y. Hashimoto, *Bioorg. Med. Chem.* **2011**, *19*, 2675–2687; c) F. Moroni, A. Cozzi, A. Chiaguri, L. Formentini, E. Camaioni, D. E. Pellegrini-Giampietro, Y. Chen, S. Liang, M. M. Zaleska, C. Gonzales, A. Wood, R. Pellicciari, *British J. Pharma.* **2012**, *165*, 1487–1500.

[5] a) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590; b) G.-W. Wang, T.-T. Yuan, D.-D. Li, *Angew. Chem.* **2011**, *123*, 1416–1419; *Angew. Chem. Int. Ed.* **2011**, *50*, 1380–1383; c) L. Zhang, M. Geng, P. Teng, D. Zhao, X. Lu, J.-X. Li, *Ultrason. Sonochem.* **2012**, *19*, 250–256; d) G. Zhang, X. Zhao, Y. Yan, C. Ding, *Eur. J. Org. Chem.* **2012**, 669–672; e) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem. Commun.* **2013**, *49*, 173–175; f) J. K. Laha, K. P. Jethava, N. Dayal, *J. Org. Chem.* **2014**, *79*, 8010–8109.

[6] a) B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar, S. Kumar, *Org. Lett.* **2012**, *17*, 2838–2841; b) S. De, S. Mishra, B. N. Kakde, D. Dey, A. Bisai, *J. Org. Chem.* **2013**, *78*, 7823–7844.

[7] a) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, C. Zoni, *Eur. J. Org. Chem.* **2005**, 2091–2096; b) T. Harayama, T. Sato, A. Hori, H. Abe, Y. Takeuchi, *Heterocycles* **2005**, 527–530; c) C. B. Bheeter, J. K. Bera, H.

Doucet, *Adv. Synth. Catal.* **2012**, *354*, 3533–3538; for two examples of direct intermolecular arylation of heteroarenes with very low catalyst loadings, see d) H. Y. Fu, L. Chen, H. Doucet, *J. Org. Chem.* **2012**, *77*, 4473–4478; e) J. Roger, H. Doucet, *Adv. Synth. Catal.* **2009**, *351*, 1977–1990.

[8] a) USP-NF <232> and <233> **2013**; b) A. Thayer, *Chem. Eng. News* **2005**, *83*, 55–58; see also: c) M. Benaglia (Ed.), *Recoverable and Recyclable Catalysts*, John Wiley & Sons, Chichester, **2009**; d) S. Phillips, P. Kauppinen, *Platinum Metals Rev.* **2010**, *54*, 69–70.

[9] a) F. Churruca, R. SanMartin, B. Inés, I. Tellitu, E. Domínguez, *Adv. Synth. Catal.* **2006**, *348*, 1836–1840; b) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez, *Tetrahedron Lett.* **2006**, *47*, 3233–3237; c) B. Inés, R. SanMartin, F. Churruca, E. Dominguez, M. K. Urtiaga, M. I. Arriortua, *Organometallics* **2008**, *27*, 2833–2839; d) B. Inés, I. Moreno, R. SanMartin, E. Domínguez, *J. Org. Chem.* **2008**, *73*, 8448–8451; e) G. Urgoitia, R. SanMartin, M. T. Herrero, E. Domínguez, *Green Chem.* **2011**, *13*, 2161–2166.

[10] *The Chemistry of Pincer Compounds*, 1st ed., (Eds.: D. Morales-Morales, C. M. Jensen), Elsevier, Amsterdam, **2007**.

[11] For the synthesis of phenanthridinones catalyzed by palladacycles using relatively high catalyst loadings, see ref. 5d.

[12] For more details, see Supporting Information.

[13] For the only example of biaryl coupling of an aryl halide with a nonfunctionalized arene using <1 mol% catalyst see: L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187.

[14] For selected recent applications see: a) K.-C. Tsai, L.-W. Teng, Y.-M. Shao, Y.-C. Chen, Y.-C. Lee, M. Li, N.-W. Hsiao, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5665–5669; b) G. Compain, A. Martin-Mingot, A. Maresca, S. Thibaudeau, C. T. Supuran, *Bioorg. Med. Chem.* **2013**, *21*, 1555–1563; c) A.-B. Nørholm, P. Francotte, L. Olsen, C. Krintel, K. Frydenvang, E. Goffin, S. Challal, L. Danober, I. Botez-Pop, P. Lestage, B. Pirotte, J. S. Kastrup, *J. Med. Chem.* **2013**, *56*, 8736–8745.

[15] V. S. N. Ramakrishna, K. Ramasastri, K. Prabhakar, K. Jagadishbadu, R. B. Thrinath, G. Parandhama, A. Sobhanadri, P. G. Narasimhareddy, K. S. Anil, D. D. Amol, D. Adireddy, K. C. Anil, K. D. Pramod, *J. Enzyme Inhib. Med. Chem.* **2012**, *27*, 443–450.

[16] a) V. Jasti, V. S. N. Ramakrishna, R. S. Kambhampati, S. R. Battula, A. Veeraraeddy, V. S. V. V. Rao (Suven Life Sciences Ltd.), WO 2004/000849 A1, **2003**; b) V. S. N. Ramakrishna, R. S. Kambhampati, V. S. Shirsath, V. Jasti (Suven Life Sciences Ltd.), WO 2005/005439 A1, **2005**; c) A. Ishtiyaque, V. S. N. Ramakrishna, *Neuroscience & Medicine* **2011**, *2*, 87–92.

[17] a) V. S. N. Ramakrishna, V. S. Shirsath, R. S. Kambhampati, A. D. Deshpande, P. Kothmirkar, V. Jasti (Suven Life Sciences Ltd.), WO 2006/095360 A1, **2006**; b) K. Ramasastri, K. Prabhakar, D. D. Amol, A. Sobhanadri, R. K. Kameswara, R. G. P. Narasimha, K. S. Anil, V. S. N. Ramakrishna, *Synth. Commun.* **2008**, *38*, 2419–2428.

[18] Kinetic plots with clear sigmoidal shapes and induction periods are often associated to the catalytic participation of heterogeneous species. For a discussion on the different parameters to be analyzed in the determination of the nature of the catalytic species see: a) E. Bayram, J. C. Linehan, J. L. Fulton, J. A. S. Roberts, N. K. Szymczak, T. D. Smurthwaite, S. Özkar, M. Balasubramanian, R. G. Finke, *J. Am. Chem. Soc.* **2011**, *133*, 18889–18902; see also: b) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A: Chem.* **2003**, *198*, 317–341; c) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609–679; d) K. Sommer, W. Yu, J. M. Richardson, M. Weck, C. W. Jones, *Adv. Synth. Catal.* **2005**, *347*, 161–171.

[19] The suitability on Hg drop test has been questioned in other palladacycle-mediated reactions like Suzuki coupling due to the ability of Hg(0) to react with Pd(II) centers of palladacycles and so promote their decomposition; see: O. N. Gorunova, M. V. Livantsov, Y. K. Grishin, M. M. Ilyin, K. A. Kochetkov, A. V. Churakov, L. G. Kuz′mina, V. N. Khrustalev, V. V. Dunina, *J. Organomet Chem.* **2013**, *737*, 59–63.

[20] For a discussion on the interconversion of catalytic species in Heck-type reactions, see: A. S. Kashin, V. P. Ananikov, *J. Org. Chem.* **2013**, *78*, 11117–11125.

[21] For the hydrolysis of phosphinoamine derivatives, see: S. Priya, M. S. Balakrishna, J. T. Mague, S. M. Mobin, *Inorg. Chem.* **2003**, *42*, 1272–1281.

[22] For a review on metal complexes of substituted phosphinites, see: D. M. Roundhill, R. P. Sperline, W. B. Beaulieu, *Coord. Chem. Rev.* **1978**, *26*, 263–279.

[23] For the participation of palladium-diphenylphosphine oxide complexes in cross-coupling reactions, see: a) J. Jiménez-Bülle, R. Gaviño, *Catal. Commun.* **2008**, *9*, 826–830; b) I. Pryjomska, H. Bartosz-Bechowski, Z. Ciunik, A. M. Trzeciak, J. J. Ziółkowski, *Dalton Trans.* **2006**, 213–220.