DOI: 10.1002/chem.201000312

Palladium-Catalyzed Domino Process to Spirooxindoles: Ligand Effect on Aminopalladation versus Carbopalladation

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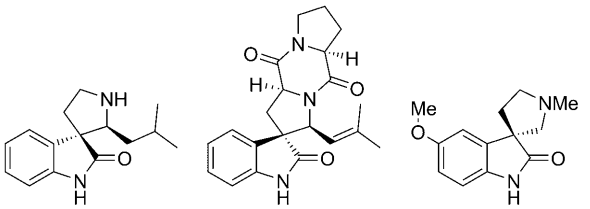
The spiropyrrolidine-3,3′-oxindole skeleton is present in a number of bioactive natural products[1] and is a sought after structural motif for the development of pharmaceuticals and agrochemicals.[2] This class of compounds can be as simple as elacomine (**1**)[3] or present additional structural complexity as seen in spirotryprostatine (**2**)[4]. The synthesis of such heterocycles has received considerable attention in recent

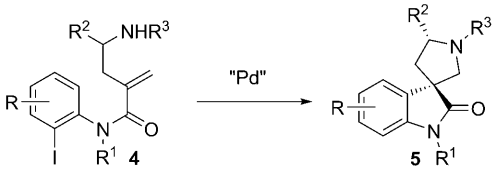


Elacomine (**1**) Spirotryprostatine A (**2**) Horsfiline (**3**)

years.[5] However, most of these approaches rely upon the stepwise construction of two rings and examples of the simultaneous formation of the spirocycle and the quaternary carbon remain rare.[6]

Palladium-catalyzed double addition across an alkene is a well-documented reaction.[7] Heck/anionic-capture sequences have been extensively developed and a variety of nucleophiles have been used to trap the intermediate σ-alkylpalladium complex.[8] Starting from appropriately functionalized dienes, Overman[6b] and Takemoto[6c] reported the synthesis of spiro[indoline-3,3′-pyrrolidine] by a Pd-catalyzed Heck/allylic-substitution sequence. Although C–N bonds are formed in these transformations, they do not involve the capture of a σ-alkylpalladium complex by a nucleophilic nitrogen. Indeed such a capture would require a reductive elimination between an sp^3 carbon atom and a heteroatom, which has little precedent.[9] On the other hand, palladium-catalyzed, intramolecular carboamination of alkenes has recently emerged as an attractive method for the construction of heterocycles.[10,11] Whereas this process has been well studied for intra/intermolecular sequences, little is known about the related intra/intramolecular one.[12]

We recently reported a facile method for accessing functionalized 3-alkyl-3-cyanomethyl-2-oxindoles by a palladium-catalyzed, domino intramolecular-Heck/cyanation process and applied it to the total syntheses of both physostigmine and horsfiline (**3**).[13] In connection with our previous work on palladium-catalyzed domino reactions involving either multiple C–C bond formation[14] or C–C and C–N bond formation,[15] we became interested in developing a one-step synthesis of spiropyrrolidine-3,3′-oxindoles **5**. Herein, we report an efficient palladium-catalyzed spirocyclization of linear anilides **4** that leads to the formation of compounds **5** in good to excellent yields (Scheme 1). Preliminary results indicated that the domino process[16] was initiated by aminopalladation instead of by an intramolecular Heck reaction.



Scheme 1. Synthesis of spirooxindole **5** by a palladium-catalyzed spirocyclization of anilide **4**.

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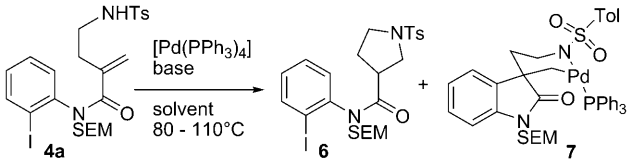
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000312.

The cyclization of **4** under the influence of palladium is challenging, since a number of competitive reactions could occur: a) β-Hydride elimination α to the amine; b) intra- or intermolecular *N*-arylation of the amine; or c) intramolecular Michael addition leading to pyrrolidine formation. Other challenges arise because of the interplay between carbopalladation (the Heck reaction) and aminopalladation and, even if the desired sequence occurs, the transformation poses interesting questions regarding regio- and stereoselectivity.

We selected *N*-tosyl derivative **4a** (R^1=SEM, R^2=H, R^3=Ts)[20] as a probe for a survey of reaction conditions. In our initial studies, various bases and solvents were screened by using [$Pd(PPh_3)_4$] (10 mol%) as the catalyst. Performing the reaction in solvents such as toluene, dioxane, or acetonitrile in the presence of a weak base (K_2CO_3) resulted in low conversion (<30%) and none of the desired product was formed. In DMF, in the presence of K_2CO_3 or a stronger base (K_3PO_4 or PhONa), high conversion (>90%) was observed, but led to the formation of pyrrolidine **6** as the main product instead of the desired spiro compound (Scheme 2).



Scheme 2. Preliminary observations.

Further experiments indicated that **6** was formed, even in an apolar solvent, if a strong base (K_3PO_4 or PhONa) was used. The formation of pyrrolidine **6** can be explained by an intramolecular Michael addition through 5-*endo*-trig cyclization. A related cyclization has recently been reported, although such a process is disfavored according to Baldwin's rules.[17] Furthermore, a control experiment showed that palladium is not involved in the formation of **6** as K_2CO_3 alone, in DMF, promoted the cyclization of **4a** to afford pyrrolidine **6** in 80% yield.

In these preliminary experiments, we consistently isolated another product, in addition to **6**, in about 10% yield. Based on the spectroscopic data (see the Supporting Information), we assigned the structure of this product to be palladacycle **7** (Scheme 2). A control experiment, performed with a stoichiometric amount of tetrakis(triphenylphosphane)palladium(0), in toluene, at reflux, afforded, after flash column chromatography, palladacycle **7** in 78% yield. Such σ-alkyl palladium complexes, resulting from Heck reactions, have been documented in the literature.[18] The reactivity of complex **7** was examined next, in an attempt to induce the formation of the C–N bond.[19] Heating the complex at 110°C for a prolonged period of time (15 h) both in the presence or absence of additional ligands (PPh_3, *t*BuMePhos)[20] led to full recovery of the starting complex; this was also the case if the reaction was performed in the presence of benzoquinone or $Cu(OTf)_2$,[20] whereas complete degradation was observed if $PhI(OAc)_2$ was used as the oxidant.[21]

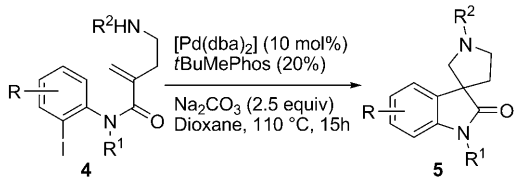
From these preliminary results, we concluded that: 1) the use of either polar or apolar solvents combined with a strong base should be avoided in order to suppress the formation of pyrrolidine **6**; 2) the Heck pathway is a viable route but was unproductive due to the high stability of palladacycle **7**. Therefore, we hypothesized that, to achieve the desired spirocyclization, the Heck manifold has to be avoided and conditions that favor carboamination were sought.

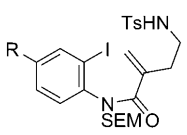
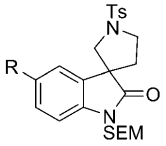
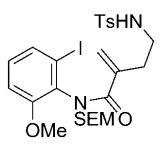
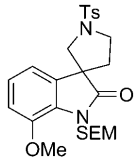
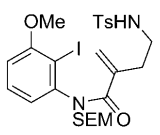
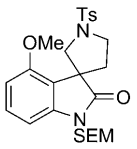
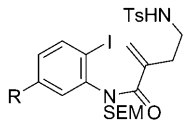
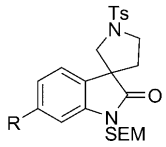
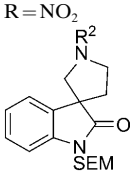
First, the effect of the ligand structure was examined.[22] Using tri-*tert*-butylphosphane as a supporting ligand allowed us to isolate spirooxindole **5a** in 5% yield, thus demonstrating the feasibility of the spirocyclization (for details see the Supporting Information). Bidentate ligands (BINAP, Xantphos,[23] and dppf)[20] were inefficient for the reaction. Further screening of biaryl-type phosphanes[24] showed that the use of sterically encumbered, electron-rich phosphanes containing the di-*tert*-butylphosphinyl group was necessary to allow the spirocyclization. Among them, *t*BuMePhos gave spirocycle **5a** in the highest yield (19%).

With the optimum ligand in hand, we set out to further optimize the conditions by varying the palladium source, the base, and the solvent. Although $PdCl_2$ was ineffective, both [$Pd(tfa)_2$][20] and [$Pd(dba)_2$][20] displayed catalytic activity, with the latter providing slightly better results. The base also considerably affected the reaction outcome. Whereas strong bases (*t*BuOK, NaHMDS,[20] NaOH) and tertiary amines (DIPEA)[20] were clearly inefficient, carbonated bases generally gave superior results, with Na_2CO_3 showing the best activity. Under otherwise identical conditions, reactions performed in toluene or dioxane provided much better results than those performed in polar solvents, such as CH_3CN, DMSO and NMP. Overall, the optimum reaction conditions were found to be as follows: 10 mol% [$Pd(dba)_2$], 20 mol% *t*BuMePhos, and 2.5 equivalents of Na_2CO_3 in toluene or dioxane, at 110°C, *C* 0.20 M. Under these conditions, spiropyrrolidine-3,3′-oxindole **5a** was isolated in 45% yield (67% based on conversion).[25]

The scope of this novel spirocyclization was then examined by using the established conditions. A variety of spiropyrrolidine-3,3′-oxindoles, containing an electron-donating (OMe, Me) or -withdrawing group (CN, NO_2, halogen) on the aniline, were readily synthesized in good to excellent yields (Table 1, entries 2–9). The presence of a substituent at the *ortho*-, *meta*-, or *para*-position of the aniline was well tolerated. Extraneous halogens, such as chlorine or fluorine, were unaffected by the reaction (Table 1, entries 4 and 5), providing the potential for further functionalization of the skeleton.[26] The effect of the protecting group on the primary amine was next examined (Table 1, entries 10–13). It is interesting to note that, under these optimized conditions, the *N*-Boc[20] and *N*-Cbz[20] derivatives (**4j** and **k**, Table 1, entries 10 and 11) underwent the desired spirocyclization, although less efficiently than their *N*-tosyl counterpart. Other *para*-substituted benzenesulfonyl groups (NO_2 and OMe, Table 1, entries 12 and 13) can also be used and give the spi-

Table 1. Spirocyclization of substituted anilides.



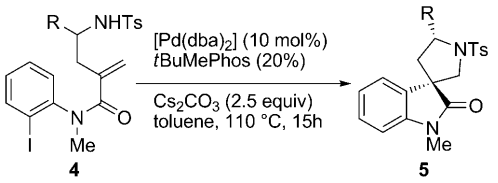
	Anilide **4**		Product **5**		Yield [%][a]
					
1	R = H	**4a**	R = H	**5a**	45 (67)[b]
2	R = OMe	**4b**	R = OMe	**5b**	57 (75)[b]
3	R = CN	**4c**	R = CN	**5c**	72
4	R = Cl	**4d**	R = Cl	**5d**	76
5	R = F	**4e**	R = F	**5e**	73
					
6		**4f**		**5f**	67 (85)[b]
					
7		**4g**		**5g**	64 (80)[b]
					
8	R = Me	**4h**	R = Me	**5h**	81
9	R = NO_2	**4i**	R = NO_2	**5i**	52 (75)[b]
					
10	R^2 = Boc	**4j**	R^2 = Boc	**5j**	32 (45)[b]
11	R^2 = Cbz	**4k**	R^2 = Cbz	**5k**	19 (45)[b]
12	R^2 = *p*-$NO_2C_6H_4SO_2$	**4l**	R^2 = *p*-$NO_2C_6H_4$ SO_2	**5l**	32 (55)[b]
13	R^2 = *p*-$OMeC_6H_4$ SO_2	**4m**	R^2 = *p*-OMe-$C_6H_4SO_2$	**5m**	42 (62)[b]

[a] Refers to chromatographically pure product. [b] Isolated yield based on conversion appears in parentheses.

rooxindole in reduced or comparable yields. However, the *N*-benzylated derivative is incompatible with the proposed reaction sequence.[27] Substitution of the amide was also examined and, as expected, *N*-Me amides cyclized efficiently to give the corresponding spirooxindoles in good to excellent yields (see Table 2).

To further extend the scope of this spirocyclization, substrates containing a substituent α to the terminal tosylamine were investigated (Table 2). Unfortunately, low conversion (<20%) was observed when compound **4n** (R = *i*Pr) was submitted to the standard reaction conditions. Fortunately,

Table 2. Spirocyclization of α-substituted tosylamines.



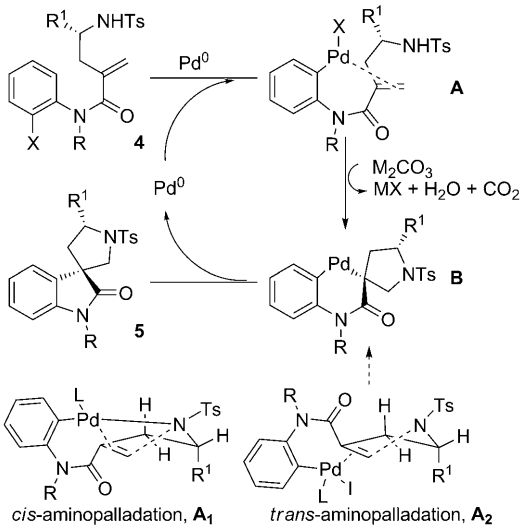
	Anilides **4**		Products **5**		Yield [%][a]
1	R = *i*Pr	**4n**	R = *i*Pr	**5n**	90
2	R = H	**4o**	R = H	**5o**	57[b]
3	R = CH_3	**4p**	R = CH_3	**5p**	58
4	R = *t*Bu	**4q**	R = *t*Bu	**5q**	80
5	R = CH_2OBn	**4r**	R = CH_2OBn	**5r**	48
6	R = Ph	**4s**	R = Ph	**5s**	54
7	R = *p*-$MeOC_6H_4$	**4t**	R = *p*-$MeOC_6H_4$	**5t**	58
8	R = *p*-ClC_6H_4	**4u**	R = *p*-ClC_6H_4	**5u**	58
9	R = *p*-Ph-C_6H_4	**4v**	R = *p*-Ph-C_6H_4	**5v**	63
10	R = CO_2*t*Bu	**4w**	R = CO_2*t*Bu	**5w**	40[c]

[a] Refers to chromatographically pure product. [b] Na_2CO_3 was used as the base. [c] 1/1 mixture of diastereoisomers.

simply changing the base from Na_2CO_3 to Cs_2CO_3 allowed the reaction to reach full conversion and led to spirooxindole **5n**, as a single diastereomer, in 90% isolated yield (Table 2, entry 1). Therefore, we applied this new protocol to other substrates. As can be seen in Table 2, substrates bearing an alkyl side chain were successfully converted to spirooxindoles (Table 2, entries 1–5). Steric hindrance was, to a certain extent, beneficial as seen for the isopropyl and *tert*-butyl derivatives (**4n** and **q**, Table 2, entries 1 and 4), which afforded the spirocyclic product in higher yields than **4o** and **p** (R = H and Me, respectively, Table 2, entries 2 and 3). Aromatic ring substituents with various electronic properties were also tolerated at the 4-position of the 4-(*N*-tosyl)aminobutanamides (Table 2, entries 6–9). It should be noted that, in most cases, the diastereoselectivity was excellent as only one stereoisomer could be detected in the ^{1}H NMR spectra of the crude products. Of these types of compound we only observed the presence of a second diastereoisomer for compound **5t** (R = 4-MeOPh, major/minor = 15:1). In contrast, cyclization of compound **4w**, containing an ester functionality, afforded two diastereoisomers in a 1:1 ratio (Table 2, entry 10). A control experiment performed by separately resubmitting each diastereoisomer of **5w** to the reaction conditions revealed that complete epimerization α to the ester function occurs in this compound. The relative stereochemistry of the substituted spiropyrrolidine-3,3′-oxindoles was found to be *cis*, based on detailed NOE correlations for compound **5q** and confirmed by X-ray crystallographic analysis of compound **5v**.[28]

Several possible reaction pathways could explain the formation of these spirooxindoles. In principle, pyrrolidines **6**

could be converted to spirooxindoles by palladium-catalyzed α-arylation of the amide group[29] and, indeed, this process has been used for the preparation of spiropiperidine-3,3′-oxindoles.[30] However, this pathway was ruled out in our system, since resubmitting pyrrolidine **6** to the reaction conditions only led to recovery of the starting materials. The second pathway to be considered is one that is initiated by the Heck reaction. Isolation of palladacycle **7** supports the feasibility of this pathway. However, the fact that $C(sp^3)$–N bond-forming reductive elimination did not take place from this complex allows us to infer that this pathway is not conducive to product formation. A third mechanism, which most probably accounts for the formation of spirooxindoles, involves aminopalladation of the double bond as the initial step (Scheme 3). Thus, after oxidative addition of the arylhalide to Pd^0, aminopalladation via the coordinated intermediate **A** leads to palladacycle **B**; reductive elimination of this complex then provides the spirooxindoles. Both *trans*- and *cis*-aminopalladation are known to occur.[31,32] In our case, *cis*-aminopalladation would involve the unfavorable formation of a nine-membered chelate; nevertheless, the entropic penalty could, in part, be compensated for by the additional alkene coordination in this intermediate (Scheme 3). However, if *cis*-aminopalladation operates, transition state $\mathbf{A_1}$, in which the R^1 substituent adopts a pseudo axial position would be preferred, since this avoids unfavorable allylic-1,2 strain with the tosyl group;[33] this would provide a diastereomer of the spirooxindoles **5** that was barely detectable under our reaction conditions. Alternatively, *trans*-aminopalladation through the preferred transition state $\mathbf{A_2}$ would provide, via intermediate **B**, spirooxindoles **5** with the relative stereochemistry that is in accord with experimental observations. It is interesting to note that dihydropyrroles, which would result from β-Hydride elimination of **B**, were not observed under our reaction conditions.



Scheme 3. Possible mechanism and rationale for the stereoselectivity; X = halide.

In summary, we have developed a novel palladium-catalyzed, domino spirocyclization process for the formation of biologically relevant spiropyrrolidine-3,3′-oxindoles. Experimental results indicate that both Heck and aminopalladation processes were viable pathways from amide **4** and the route that occurs is dependent upon the ligand chosen. However, only the latter process is conducive to the spirocyclization and the use of *t*BuMePhos as the ligand is required for the success of this palladium-catalyzed process. Excellent diastereoselectivity was obtained for cases in which α-substituted terminal sulfonamides are used, which can be accounted for by a *trans*-aminopalladation process.

Experimental Section

Typical procedure: Anilide **4a** (50.0 mg, 0.083 mmol, 1.0 equiv) and *t*BuMePhos (5.2 mg, 0.017 mmol, 0.20 equiv) were added to a stirred suspension of $[Pd(dba)_2]$ (4.8 mg, 0.0083 mmol, 0.10 equiv) in dioxane (0.40 mL) under argon. This was followed by the addition of the base (Na_2CO_3; 28.8 mg, 0.208 mmol, 2.5 equiv). The reaction mixture was then heated to reflux and stirred overnight. The reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, heptane/EtOAc, 2:1) afforded **5a** as a white solid (17.8 mg, 45%, 67% based on conversion); m.p. 73–74 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.76$ (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 7.28 (dt, $J = 7.7$, 1.0 Hz, 1H), 7.11 (dd, $J = 7.7$, 0.9 Hz, 1H), 7.05–7.02 (m, 2H), 5.12 (d, $J = 10.9$ Hz, 1H), 5.08 (d, $J = 10.9$ Hz, 1H), 3.78–3.73 (m, 1H), 3.57 (d, $J = 9.7$ Hz, 1H), 3.55–3.49 (m, 3H), 3.44 (d, $J = 9.7$ Hz, 1H), 2.47 (s, 3H), 2.32–2.25 (m, 1H), 2.07–2.02 (m, 1H), 0.89 (t, $J = 8.7$ Hz, 2H), −0.04 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 177.3$, 143.9, 141.0, 133.4, 131.9, 129.8, 128.6, 127.7, 123.6, 122.9, 109.8, 69.5, 66.1, 56.3, 52.7, 47.3, 36.6, 21.6, 17.7, −1.5 ppm; IR ($CHCl_3$): $\tilde{\nu} = 3056$, 2950, 2890, 1721, 1613, 1487, 1467, 1348, 1246, 1228, 1163, 1081 cm^{-1}; HRMS (ES+): *m*/*z* calcd for $C_{24}H_{32}N_2O_4NaSSi$: 495.1750; found: 495.1762.

Acknowledgements

Financial support from the CNRS, the Bayer CropScience (Doctoral fellowship to S.J.) and the "Ministère de l'Enseignement Supérieur et de la Recherche" (Doctoral fellowship to W.E.) is gratefully acknowledged.

Keywords: aminopalladation · carbopalladation · domino reactions · oxindoles · palladium · spiro compounds

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Received: February 4, 2010
Published online: April 13, 2010

