Palladium-Catalyzed Intramolecular Coupling of Aryl Halides and Ketone Enolates: Synthesis of Hexahydro-2,6-methano-1-benzazocines

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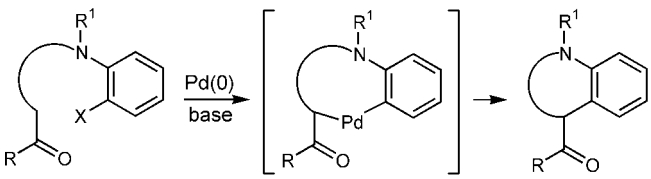
Abstract: The palladium-catalyzed intramolecular coupling of 2-haloanilines and ketone enolates is a useful methodology for the synthesis of hexahydro-2,6-methano-1-benzazocine derivatives. A study about the reaction conditions of the process is reported.

Keywords: cyclization; homogeneous catalysis; nitrogen heterocycles; palladium; synthetic methods

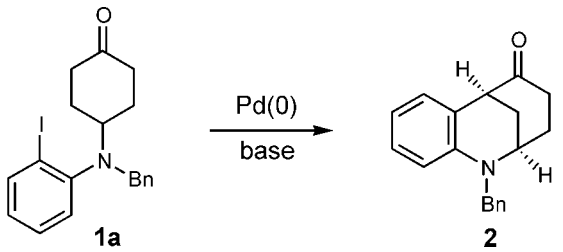
The palladium-catalyzed intermolecular coupling of aryl halides and ketone enolates has been widely investigated during the last years and is now recognized to be a useful methodology for the synthesis of α-aryl ketones.[1] In contrast, the intramolecular version of this reaction,[2] which is a promising procedure to construct complex polycyclic compounds, has received little attention, and examples of this palladium-catalyzed annulation process are scarce.[2,3,4]

As part of our ongoing program on the synthesis of natural products, we recently reported the palladium-catalyzed intramolecular coupling of vinyl halides and ketone enolates as a suitable methodology for the synthesis of nitrogen heterocycles.[5,6] Given the success of this palladium-catalyzed chemistry, we started to explore the applicability of our reaction conditions to the intramolecular coupling of 2-haloanilines and ketones (Scheme 1). In this communication we describe our preliminary results in this annulation process on nitrogen-containing derivatives.



Scheme 1. Pd-catalyzed intramolecular coupling of aryl halides and ketone enolates.

The palladium-catalyzed cyclization of 2-iodoaniline (**1a**)[7] (Scheme 2 and Table 1) was chosen as the initial model system for our study since its annulation would afford a synthetic entry to the hexahydro-2,6-methano-1-benzazocine framework (**I**),[8] which is a bridged ring system present in some natural products such as aspernomine[9] and strychnochromine.[10]



Scheme 2.

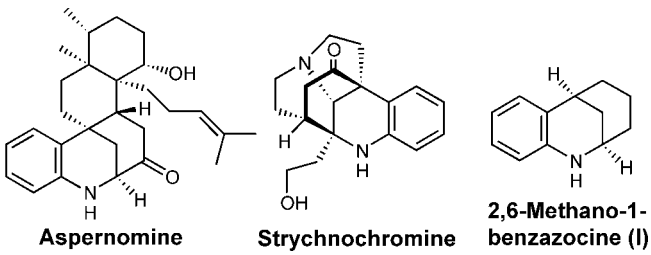


Figure 1.

When reaction conditions were employed that have been used in much of our previous work[5] with vinyl halides [0.2 equiv. of $Pd(PPh_3)_4$ and 3 equiv. of KO*t*-Bu in refluxing THF, entry 1], aryl iodide **1a** underwent cyclization to give hexahydro-2,6-methano-1-benzazocine (**2**)[11] in 84% yield. A variety of reactions was run in order to investigate further the synthesis of this bridged aniline. The use of smaller amounts of $Pd(PPh_3)_4$ (entries 2 and 3), otherwise with the same reaction conditions, resulted in lower yields. Using $PdCl_2[P(o\text{-tolyl})_3]_2$ as the catalyst,[5] the cyclized product **2** was also obtained, although in worse yield (entry 4).

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Table 1. Pd-Catalyzed cyclization of **1a**.

Entry	Catalyst (equiv.)	Base (equiv.)/Additive (equiv.)[a]	*T*/time	Yield [%][b]
1	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (3)	reflux/3.5 h	84
2	$Pd(PPh_3)_4$ (0.1)	KO*t*-Bu (3)	reflux/3.5 h	63
3	$Pd(PPh_3)_4$ (0.05)	KO*t*-Bu (3)	reflux/3.5 h	57
4	$PdCl_2[P(o\text{-Tol})_3]_2$ (0.1)	KO*t*-Bu (3)	reflux/3 h	36
5	$PdCl_2$(*R*)-BINAP (0.1)	KO*t*-Bu (3)	reflux/3.5 h	98
6	$Pd(OAc)_2$ (0.2)/$P(t\text{-Bu})_3$ (0.2)	KO*t*-Bu (3)	rt/48 h	41
7	$PdCl_2(PPh_3)_2$ (0.2)	KO*t*-Bu (3)/*n*-Bu_4NCl (1)	reflux/3 h	99
8	$PdCl_2(PPh_3)_2$ (0.1)	KO*t*-Bu (3)/*n*-Bu_4NCl (1)	reflux/5 h	93
9	$PdCl_2(PPh_3)_2$ (0.2)	Cs_2CO_3 (3)	100 °C/12 h[c]	58
10	$Pd(PPh_3)_4$ (0.2)	K_3PO_4 (3)	110 °C/24 h[c]	76

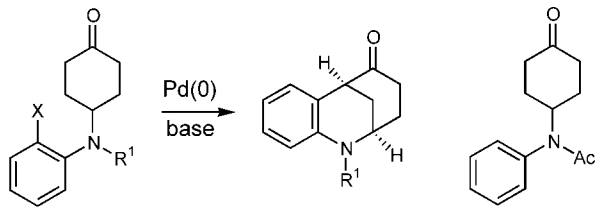
[a] All reactions have been carried out in THF.
[b] Yield refers to pure isolated product.
[c] Sealed tube.

Given that ketone **1a** is a prochiral substrate, the use of a Pd catalyst with enantiopure ligands might differentiate between the two enantiotopic methylene groups, thus allowing the synthesis of bridged ketone **2** in enantiopure form. Nevertheless, although Pd-catalyzed cyclization of **1a** in the presence of $PdCl_2$(*R*)-BINAP[12] gave ketone **2** in high yield (entry 5), the product was racemic.[13]

The annulation reaction could be accomplished at room temperature by using $P(t\text{-Bu})_3$ as the ligand[14] although in moderate yield (entry 6). On the other hand, addition of *n*-Bu_4NCl[15] to the otherwise standard cyclization conditions of **1a** increased the yield of annulation (entries 7 and 8). We also studied the influence of other bases on this process. Changing the base for sodium *tert*-butoxide[1b] (using the reaction conditions of entry 1) did not effect the yield of **2** significantly, while when Cs_2CO_3 [2,16] (entry 9) or K_3PO_4 [1b] (entry 10) were used, the Pd-catalyzed cyclization of **1a** required higher temperatures and long reaction times. In some cyclization mixtures, 4-(*N*-benzyl-*N*-phenylamino)cyclohexanone (the side product from hydrodehalogenation[17] of **1a**) was detected, although not quantified.

In order to study the effect of the halide and the nature of the substituent at the nitrogen atom on the course of the cyclization reaction we prepared bromide **1b**, acetanilide **3**, and carbamate **6**.[7] The results of the optimization studies carried out with **1a** led us to use three general reaction procedures for the cyclization of these compounds: Method A, 0.2 equiv. of $Pd(PPh_3)_4$ and 3 equiv. of KO*t*-Bu in THF at reflux for 3.5 h; Method B, 0.2 equiv. of $PdCl_2(PPh_3)_2$ and 3 equiv. Cs_2CO_3 in THF in a sealed tube at 100 – 110 °C for 24 h; Method C, 0.2 equiv. of $Pd(PPh_3)_4$ and 3 equiv. K_3PO_4 in THF in a sealed tube at 100 – 110 °C for 24 h.

In general, no significant effect was observed in the cyclization reaction when changing the halide from iodide to bromide (compare entries 1, 9, and 10 in Table 1 with entries 1, 2, and 3 in Table 2, respectively). In contrast, varying the substituent at the nitrogen had a marked effect on the cyclization. In general,



1b X = Br, R^1 = Bn
3 X = I, R^1 = Ac
6 X = I, R^1 = COOMe
2 R^1 = Bn
4 R^1 = Ac
7 R^1 = COOMe
5

Scheme 3.

carbamate **6** was more efficient in the intramolecular coupling than amide **3**. Thus, when KO*t*-Bu was used as the base, acetamide **3** gave complex reaction mixtures[18] and no cyclization product was obtained (entry 4), while carbamate **6** afforded tricyclic ketone **7** as the only isolable product although in moderate yield (entry 8). However, the Pd-catalyzed cyclization

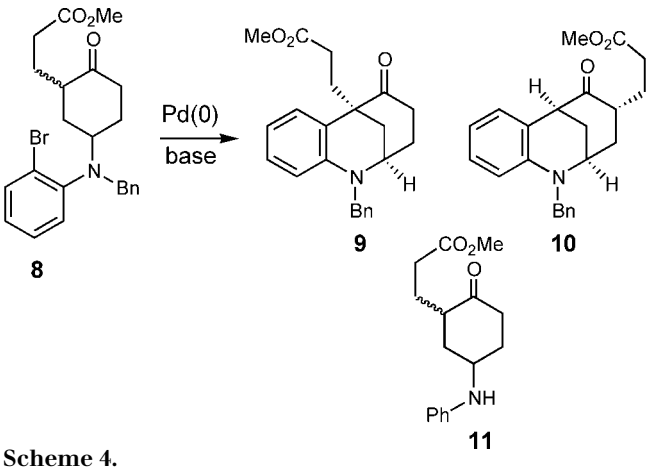
Table 2. Pd-catalyzed cyclization of **1b**, **3**, and **6**.

Entry	Substrate	Method[a]	Products (yield) [b]
1	**1b**	A[c]	**2** (67%)
2	**1b**	B	**2** (60%)
3	**1b**	C[d]	**2** (78%)
4	**3**	A	—
5	**3**	B	**4** (33%), **5** (<5%)
6	**3**	B[e]	**4** (35%), **5** (33%)
7	**3**	C	**4** (38%), **5** (<5%)
8	**6**	A	**7** (48%)
9	**6**	A[e]	**7** (34%)
10	**6**	B[f]	**7** (92%)
11	**6**	C	**7** (35%)

[a] Method A: $Pd(PPh_3)_4$ (0.2 equiv.), KO*t*-Bu (3 equiv.), THF, reflux, 3.5 h. Method B: $PdCl_2(PPh_3)_2$ (0.2 equiv.), Cs_2CO_3 (3 equiv.), THF, 100 – 110 °C, sealed tube, 24 h. Method C: $Pd(PPh_3)_4$ (0.2 equiv.), K_3PO_4 (3 equiv.), THF, 100 – 110 °C, sealed tube, 24 h.
[b] Yield refers to pure isolated products.
[c] $Pd(PPh_3)_4$ (0.1 equiv).
[d] 48 h.
[e] *n*-Bu_4NCl (1 equiv.).
[f] $PdCl_2(PPh_3)_2$ (0.3 equiv.), 48 h.

of amide **3** was accomplished by using Cs_2CO_3 or K_3PO_4 as the base (entries 5 – 7), resulting in a moderate yield and the isolation of different amounts of the dehalogenated acetanilide **5**. It is noteworthy that the addition of *n*-Bu_4NCl, which had a positive effect on the cyclization of **1a** (entries 7 and 8, Table 1), now resulted in the formation of a considerable amount of **5** (entry 6). On the other hand, Pd-catalyzed cyclization of carbamate **6** using either Cs_2CO_3 or K_3PO_4 as the base (entries 10 and 11) afforded ketone **7** as the only isolable product in moderate to excellent yield. Addition of *n*-Bu_4NCl (entry 9) resulted in a decrease in the yield of the cyclization, but in this case no dehalogenation by-product was formed.

At this point, once the usefulness of the Pd-catalyzed intramolecular arylation of ketone enolates for the construction of the hexahydro-2,6-methano-1-benzazocine ring system[19] had been demonstrated, we decided to investigate the regioselectivity of the annulation process in a ketone with both an enolizable methylene and methine group. In this context, 2-bromoanilino ketone **8** was prepared.[20] When **8** was submitted to the reaction conditions of method A of Table 2, a complex mixture of products was obtained, and no cyclization product was detected. In contrast, ketone **8** reacted under the reaction conditions of method B to give a clean reaction mixture from which bridged anilines **9** (30%) and **10** (15%) were obtained, together with a significant amount (10%) of secondary amine **11**,[21] the latter being formed by hydrodehalogenation and debenzylation of the starting material. The use of $Pd(PPh_3)_4$ (0.2 equiv.) as the catalyst under the same reaction conditions afforded the same three products in similar yields. The regioselectivity of the annulation process, although moderate (2:1), resulted in the predominant formation of the regioisomer bearing a quaternary center. When the cyclization was carried out under the reaction conditions of method B in the presence of *n*-Bu_4NCl (1 equiv.), aniline **11** became the main product (37%) and the cyclization compounds **9** and **10** were obtained in low yield (20%, 2:1). Once again, the addition of *n*-Bu_4NCl resulted in an increase of the hydrodehalogenation side reaction.



Scheme 4.

In summary, we have developed a methodology for the synthesis of hexahydro-2,6-methano-1-benzazocine derivatives based on the palladium-catalyzed intramolecular coupling of 2-haloanilines and ketone enolates. Further studies directed both to the synthesis of natural products embodying this bridged ring system and the application of the above methodology to the synthesis of other nitrogen heterocycles are in progress and will be reported in due course.

Experimental Section

Representative Procedures for the Pd-Catalyzed Intramolecular Coupling of 2-Haloanilines and Ketone Enolates

Method A: To a solution of ketone **1a** (126 mg, 0.31 mmol) in dry THF (15 mL) were added $Pd(PPh_3)_4$ (36 mg, 0.03 mmol) and KO*t*-Bu (0.95 mmol, 0.95 mL of a 1 M solution in *t*-butyl alcohol) under argon. The solution was heated at reflux for 3.5 h. After cooling to room temperature, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give ketone **2**; yield: 54 mg (63%).

Method B: To a solution of ketone **3** (102 mg, 0.28 mmol) in dry THF (10 mL) were added $PdCl_2(PPh_3)_2$ (39 mg, 0.05 mmol) and Cs_2CO_3 (276 mg, 0.85 mmol). The mixture was stirred at 100 °C in a sealed tube for 24 h. After cooling to room temperature, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH) to give ketone **4** (21 mg, 33%) and amide **5** (3 mg, 5%).

Method C: To a solution of ketone **1a** (100 mg, 0.25 mmol) in dry THF (10 mL) were added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and K_3PO_4 (160 mg, 0.75 mmol). The mixture was stirred at 110 °C in a sealed tube for 24 h. After cooling to room temperature, the mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give ketone **2**; yield: 52 mg (76%).

1-Benzyl-1,3,4,6-tetrahydro-2,6-methano-1-benzazocin-5(2*H*)-one (2)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.80–1.94 (m, 1H), 2.15–2.30 (m, 3H), 2.36–2.54 (m, 2H), 3.70–3.77 (m, 2H, H-2 and H-6), 4.61 (d, *J* = 17.4 Hz, 1H, NCH_2Ar), 4.79 (d, *J* = 17.4 Hz, 1H, NCH_2Ar), 6.56 (d, *J* = 8.4 Hz, 1H), 6.59 (td, *J* = 7.5 and 1 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.05 (ddd, *J* = 8.4, 7.5, and 1.5 Hz, 1H), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 29.4 (CH_2), 33.6 (CH_2), 34.5 (CH_2), 51.5 (CH), 51.8 (CH),

52.5 (CH_2), 110.2 (CH), 115.7 (CH), 118.5 (C), 125.9 (CH), 127.0 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 138.2 (C), 144.6 (C), 209.8 (CO).

1-Benzyl-6-[2-(methoxycarbonyl)ethyl]-1,3,4,6-tetrahydro-2,6-methano-1-benzazocin-5(2*H*)-one (9)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.88 (m, 1H), 1.97 (dd, *J* = 12.8 and 2.4 Hz, 1H, H-11), 2.16 (dt, *J* = 12.8 and 3.3 Hz, 1H, H-11), 2.22–2.58 (m, 7H), 3.68 (s, 3H, OCH_3), 3.74 (br s, 1H, H-2), 4.58 (d, *J* = 17.3 Hz, 1H, NCH_2Ar), 4.74 (d, *J* = 17.3 Hz, 1H, NCH_2Ar), 6.53 (d, *J* = 8.4 Hz, 1H), 6.59 (td, *J* = 7.5 and 1 Hz, 1H), 7.01 (ddd, *J* = 8.4, 7.5, and 1.5 Hz, 1H), 7.06 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.23–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 27.5 (CH_2), 29.1 (CH_2), 33.4 (CH_2), 33.5 (CH_2), 35.1 (CH_2), 50.3 (C-6), 51.7 (CH_3), 52.3 (C-2), 53.0 (NCH_2Ar), 110.7 (C-10), 115.9 (C-8), 120.4 (C-6a), 125.9 and 128.7 (*o*-C and *m*-C), 126.3 (C-7), 127.0 (*p*-C), 128.4 (C-9), 138.2 (*ipso*-C), 145.6 (C-10a), 174.0 (COO), 208.9 (C-5).

1-Benzyl-4-[2-(methoxycarbonyl)ethyl]-1,3,4,6-tetrahydro-2,6-methano-1-benzazocin-5(2*H*)-one (10)

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.46–1.64 (m, 1H), 1.95–2.10 (m, 1H), 2.15–2.58 (m, 7H), 3.59 (s, 3H, OCH_3), 3.73 (br s, 1H), 3.77 (br s, 1H), 4.63 (d, *J* = 17.3 Hz, 1H, NCH_2Ar), 4.77 (d, *J* = 17.3 Hz, 1H, NCH_2Ar), 6.56 (d, *J* = 8.4 Hz, 1H), 6.58 (td, *J* = 7.5 and 1 Hz, 1H), 7.01 (dd, *J* = 7.5 and 1.5 Hz, 1H), 7.05 (ddd, *J* = 8.4, 7.5 and 1.5 Hz, 1H), 7.22–7.40 (m, 5H); 13C NMR ($CDCl_3$, 75.5 MHz): δ = 24.3 (CH_2), 30.0 (C-11), 31.6 (CH_2), 41.0 (C-3), 42.0 (C-4), 51.5 (C-6), 51.8 (CH_3), 52.7 (C-2), 52.8 (NCH_2Ar), 110.4 (C-10), 115.7 (C-8), 118.9 (C-6a), 126.0 and 128.7 (*o*-C and *m*-C), 127.0 (*p*-C), 128.5 (C-7), 129.0 (C-9), 138.3 (*ipso*-C), 144.5 (C-10a), 173.8 (COO), 210.7 (C-5).

Acknowledgements

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[16] K_2CO_3 did not cause any reaction.

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[18] The failure of the cyclization might be attributed to the acid hydrogens of the acetamido group. For the Pd-catalyzed intramolecular α-arylation of 2-haloacetamides using NaO*t*-Bu as the base, see ref.[4a].

[19] Interestingly, in this work about δ-(2-haloaryl) ketones we have not observed processes of nucleophilic addition, recently reported in a series of β- and γ-(2-haloaryl) ketones: L. G. Quan, M. Lamrani, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 4827–4828.

[20] Compound **8** was obtained from **1b**, by imine formation ($BnNH_2$, 4 Å MS), followed by reaction with methyl acrylate and imine hydrolysis (AcOH, H_2O, 60 °C) in 43% yield, as an epimeric mixture (*cis/trans* ratio approximately 2:1).

[21] Compound **11** was obtained as an epimeric mixture, *cis/trans* ratio approximately 2.2:1.