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Published on Web 01/18/2003

Intramolecular Pd-Mediated Processes of Amino-Tethered Aryl Halides and Ketones: Insight into the Ketone α-Arylation and Carbonyl-Addition Dichotomy. A New Class of Four-Membered Azapalladacycles

Daniel Solé,*,† Lluís Vallverdú,† Xavier Solans,‡ Mercè Font-Bardía,‡ and Josep Bonjoch†

Contribution from the Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, and Departament de Cristal.lografia, Mineralogia i Dipòsits Minerals, Universitat de Barcelona, Martí i Franquès s/n, 08028-Barcelona, Spain

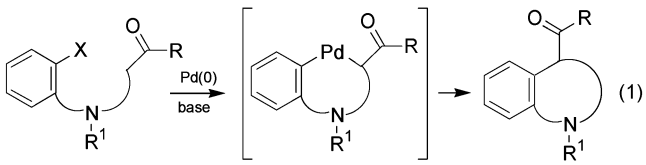
Received October 28, 2002; E-mail: dsole@farmacia.far.ub.es

Abstract: An exploration of the scope and limitations of Pd(0)-catalyzed intramolecular coupling reactions of amino-tethered aryl halides and ketones has been conducted. Two different and competitive reaction pathways starting from ω-(2-haloanilino) alkanones, enolate arylation and addition to the carbonyl group, have been observed, while ω-(2-halobenzylamino) alkanones exclusively underwent the enolate arylation process. The dichotomy between ketone α-arylation and carbonyl-addition in the reactions of ω-(2-haloanilino) alkanones has been rationalized by the intermediacy of unprecedented four-membered azapalladacycles, from which X-ray data and chemical behavior are reported.

Introduction

A growing interest in the application of transition metal promoted processes to the synthesis of heterocyclic systems has been seen in recent years.[1] Besides its synthetic application, transition metal chemistry involving heteroatom-containing compounds is of interest from the mechanistic point of view due to its unique characteristics stemming from the heteroatom present in the substrates.[2]

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.[3] Continuing our research on this palladium chemistry, we decided to extend the carbocyclization process to the intramolecular coupling of amino tethered aryl halides and ketones (eq 1).



(1)

The palladium-catalyzed coupling reaction of aryl halides and enolates has been widely investigated in the past few years. However, while the intermolecular version[4−8] of this reaction has been extensively studied and is now recognized to be a useful methodology for the synthesis of α-aryl carbonyl compounds, the intramolecular processes have received less attention. The first examples of this latter type of cyclization reaction were reported by Ciufolini in 1988, who described the intramolecular arylation of soft enolates catalyzed by zerovalent palladium complexes.[9] Later on, coinciding with the development of the intermolecular processes, Muratake reported the

† Laboratori de Química Orgànica, Universitat de Barcelona.
‡ Departament de Cristal.lografia, Universitat de Barcelona.

(1) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*: *A Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000.
(2) For some examples in which the coordination of N with the metal controls or modifies the course of transition metal promoted processes, see: (a) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442. (b) Mauleón, P.; Alonso, I.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1291−1293. (c) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544−549. (d) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133−12134.
(3) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228.
(4) For reactions starting from ketones, see: (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108−11109. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382−12383. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370. (e) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967−5974. (f) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284−3290. (g) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261−1268. (h) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209−217. (i) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2002**, *4*, 1591−1594. (j) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053−4056.
(5) For reactions starting from aldehydes, see: Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101−104.
(6) For reactions starting from esters, see: (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996−8002. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410−8411. (c) Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557−12565.
(7) For reactions starting from amides, see: Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546−6553.

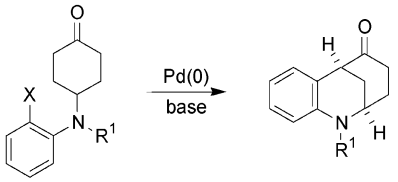
intramolecular α-arylation of ketones,[10,11] and Hartwig described the synthesis of oxindoles[7,12] by means of the Pd-catalyzed α-arylation of amides.[13,14] Finally, very recently, Buchwald has reported the intramolecular α-arylation of α-amino acid esters.[15]

In this paper, we present a full account of the scope and limitations of the palladium-mediated intramolecular coupling of aryl halides and ketone enolates as a methodology for the synthesis of nitrogen heterocycles as well as the discovery of a new class of four-membered azapalladacycles, the formation of which allows the behavior of *ω*-(2-haloanilino) alkanones in their Pd(0)-catalyzed reactions to be understood.

Results and Discussion

Our initial studies were focused on developing an optimum set of reaction conditions for the palladium-catalyzed intramolecular coupling of amino tethered aryl halides and ketone enolates. The reactions of 2-haloanilines **1a**, **1b**, **3**, and **5** were chosen as the model systems to optimize the annulation process because their cyclization would afford a synthetic entry to the hexahydro-2,6-methano-1-benzazocine framework (Table 1).[16] This is a bridged ring system present in some natural products such as aspernomine[17] and strychnochromine[18] and is closely related to the 2-azabicyclo[3.3.1]nonane framework successfully prepared in our earlier work.[3] The most representative results of the studies carried out with the aforementioned models are summarized in Table 1. Thus, in the presence of 0.2 equiv of $Pd(PPh_3)_4$ and 3 equiv of KO*t*-Bu in refluxing THF (entry 1), aryl iodide **1a** underwent the desired cyclization reaction to give ketone **2** in good yield. The annulation reaction could also be carried out by using Cs_2CO_3 (entry 2) or K_3PO_4 (entry 3) as the base, but in these cases higher temperatures and long reaction times were required. No significant effect was observed in the cyclization reaction when the halide was changed from iodide to bromide (compare entries 1−3 with entries 4−6, respectively). In contrast, varying the substituent at the nitrogen atom had a marked effect on the cyclization. Thus, when KO*t*-Bu was used as the base, acetamide **3** gave a complex reaction mixture, and no cyclization product was obtained (entry 7),[19]

Table 1. Pd(0)-Catalyzed Cyclization of 2-Haloanilino Ketones **1a**, **1b**, **3**, and **5**



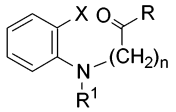
1a, X = I, R^1 = Bn
1b, X = Br, R^1 = Bn
3, X = I, R^1 = Ac
5, X = I, R^1 = COOMe

2, R^1 = Bn
4, R^1 = Ac
6, R^1 = COOMe

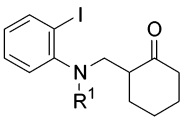
entry	substrate	method[a]	product (yield)[b]
1	**1a**	A	**2** (84%)
2	**1a**	B	**2** (68%)
3	**1a**	C	**2** (76%)
4	**1b**	A[c]	**2** (67%)
5	**1b**	B	**2** (60%)
6	**1b**	C[d]	**2** (78%)
7	**3**	A	
8	**3**	B	**4** (33%)[e]
9	**3**	C	**4** (38%)[e]
10	**5**	A	**6** (48%)
11	**5**	B[f]	**6** (92%)
12	**5**	C	**6** (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] 4-(*N*-Acetyl-*N*-phenylamino)cyclohexanone (∼5%) was also isolated. [f] $PdCl_2(PPh_3)_2$ (0.3 equiv), 48 h.

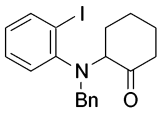
Chart 1. Type I: 2-Haloanilino Alkanones



7, X = I, R^1 = Bn, R = CH_3, n = 3
11a, X = I, R^1 = Bn, R = CH_3, n = 2
11b, X = Br, R^1 = Bn, R = CH_3, n = 2
13, X = I, R^1 = Ac, R = CH_3, n = 2
15, X = I, R^1 = CO_2Me, R = CH_3, n = 2
18, X = I, R^1 = Bn, R = Et, n = 2
20, X = I, R^1 = CO_2Me, R = Et, n = 2
22, X = I, R^1 = Me, R = *t*-Bu, n = 2
29, X = I, R^1 = Bn, R = CH_3, n = 1



24, R^1 = CH_3
26, R^1 = CO_2Me



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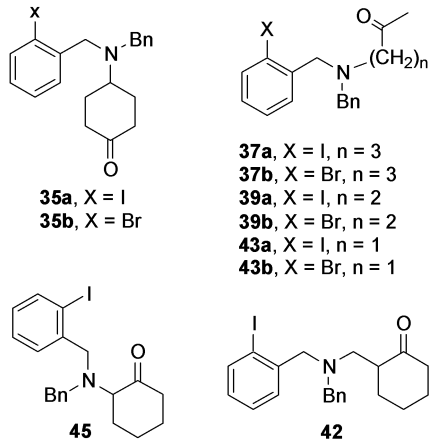
while carbamate **5** afforded tricyclic ketone **6** as the only isolable product, although in moderate yield (entry 10). The Pd-catalyzed cyclization of amide **3** could be accomplished by using Cs_2CO_3 (entry 8) or K_3PO_4 (entry 9) as the base, although in moderate yield and isolating small amounts of the dehalogenated amide.[20] On the other hand, under the same reaction conditions (entries 11 and 12), carbamate **5** afforded ketone **6** as the only isolable product.

Once we had developed a set of reaction conditions for the intramolecular coupling, we planned to extend the carbocyclization process to the construction of other nitrogen heterocycles by varying the relative position of the 2-haloaryl moiety and the ketone carbonyl group. Two types of amino-tethered 2-haloaryl alkanones were chosen for this study (Charts 1 and

(8) For reactions starting from methylene active carbonyl compounds,[8a] nitroalkanes,[8b] and nitriles,[8c] see: (a) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541−555. Kashin, A. N.; Mitin, A. V.; Beletskaya, I. P.; Wife, R. *Tetrahedron Lett.* **2002**, *43*, 2539−2542. Aramendía, M. A.; Borau, V.; Jiménez, C.; Marinas, J. M.; Ruiz, J. R.; Urbano, F. J. *Tetrahedron Lett.* **2002**, *43*, 2847−2849. Kondo, Y.; Inamoto, K.; Uchiyama, M.; Sakamoto, T. *Chem. Commun.* **2001**, 2704−2705. See also ref 4c. (b) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106−111. (c) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330−9331.
(9) Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149−4151.
(10) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581−7582.
(11) For the Pd-catalyzed intramolecular coupling of aryl halides and aldehyde enolates, see: Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355−2358.
(12) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415.
(13) (a) Freund, R.; Mederski, W. W. K. R. *Helv. Chim. Acta* **2000**, *83*, 1247−1255. (b) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193−195. (c) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363−1365.
(14) For the extension of the α-arylation of amides to the synthesis of *δ*-lactams, see: Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631−633.
(15) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465−475.
(16) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439−442.
(17) Staub, G. M.; Gloer, J. B.; Dowd, P. F.; Wicklow, D. T. *J. Am. Chem. Soc.* **1992**, *114*, 1015−1017.
(18) Quetin-Leclercq, J.; Angenot, L.; Dupont, L.; Dideberg, O.; Warin, R.; Delaude, C.; Coune, C. *Tetrahedron Lett.* **1991**, *32*, 4295−4298.
(19) The failure of the cyclization of acetanilide **3** under these reaction conditions might be attributed to the acid hydrogens of the acetamido group. In fact, the Pd-catalyzed intramolecular α-arylation of 2-haloacetanilides using NaO*t*-Bu as the base has been reported; see refs 7 and 12.

(20) The formation of hydrodehalogenation byproducts has been reported; see for example refs 7, 10, and 14.

Chart 2. Type II: 2-Halobenzylamino Alkanones



2), 2-haloanilino alkanones (type I) and 2-halobenzylamino alkanones (type II). In both cases, γ-amino-, β-amino-, and α-amino ketones were studied.

We began by studying the intramolecular coupling of the (2-haloanilino) alkanone derivatives (type I, Table 2),[21] which was attempted under reaction conditions similar to those we successfully used for the synthesis of 2,6-methano-1-benzazocines (methods A, B, and C, Table 1). However, when the above compounds were submitted to the reaction conditions of method A, no cyclization products were obtained, and only compounds arising from hydrodehalogenation and degradation of the amino ketone moiety were isolated.[22] On the other hand, we found that using the reaction conditions of method B led to two different and competitive cyclization pathways, enolate arylation and the addition to the carbonyl group, depending on the structure of the starting amino ketone. As can be seen from the results summarized in Table 2, Pd-catalyzed intramolecular coupling of γ-(2-iodoanilino) ketone **7** in the presence of $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in THF at 110 °C (entry 1) took place exclusively at the α-position to give quinolines **8** and **9**, although in low yield, together with the hydrodehalogenated compound **10**. The alcohol **9** is formed by oxidation of **8** under the cyclization conditions; in fact, longer reaction times (72 h) resulted in the formation of alcohol **9** as the major reaction product. The lower yield in the cyclization reaction of γ-anilino ketone **7** when compared with **1a** could be interpreted on conformational grounds. Thus, the higher conformational freedom of the open chain γ-anilino ketone **7** might thwart the coordination of the enolate with the σ-arylpalladium moiety, allowing competing reactions (e.g., reduction) to occur extensively.

In contrast, under the same reaction conditions, β-(2-haloanilino) ketone **11a** exclusively afforded alcohol **12** in 40% yield, as a result of the addition process to the ketone carbonyl group (entry 2, Table 2). The unexpected outcome[23,24] led us to study the Pd-catalyzed cyclization of β-(2-haloanilino) ketone **11a**. During the course of these studies, we found that when using K_2CO_3 as the base instead of Cs_2CO_3, alcohol **12** was obtained in similar yield, whereas with Et_3N, no reaction took place, and the starting material was recovered. On the other hand, it should be noted that purification of alcohol **12** was hampered by the formation of considerable amounts of γ-butyrolactone when using THF as the solvent in the reaction (vide infra). Interestingly, addition of Et_3N (2 equiv) to the otherwise standard cyclization conditions resulted in very clean reactions by avoiding the formation of γ-butyrolactone. Finally, it was also found that the use of toluene as the solvent instead of THF, in combination with Et_3N, slightly increased the yield of the addition reaction (entry 3).

Bromide **11b** was less efficient in the addition to the carbonyl group than iodide **11a**, and in the same reaction conditions it afforded *N*-benzyl-2-bromoaniline as the main product, resulting from the retro-Michael fragmentation of the starting material (entry 4).

The palladium-catalyzed intramolecular addition to the carbonyl proceeded smoothly from other β-(2-iodoanilino) ketones to give the corresponding alcohols in moderate to good yields (entries 5−15). The use of THF as the solvent instead of toluene always gave inferior results, and in some cases it resulted in the formation of considerable amounts of the retro-Michael decomposition compounds (entry 7 vs 8, and 12 vs 13).

The effect of the amine protecting group in the addition reaction was also examined in these series. Acetanilide **13** exclusively gave alcohol **14** (entry 5), whereas carbamate **15** afforded alcohol **16** in 44% yield, and 3-acetylindole **17** in 29% yield (entry 6), the latter resulting from the oxidation, under the reaction conditions, of the 3-acetylindoline initially formed by intramolecular arylation of the ketone enolate. Thus, changing the substituent at the nitrogen atom from alkyl to methoxycarbonyl had a marked effect on the cyclization and resulted in the formation of significant amounts of the product from α-arylation of the ketone. The same behavior was observed in carbamate **26**, which afforded a mixture of alcohols **27**-*cis* and **27**-*trans*, and ketone **28**, the latter resulting from the arylation of the enolate (entries 14 and 15). A noteworthy exception was the Pd(0)-catalyzed cyclization of carbamate **20** that exclusively afforded alcohol **21**, although in low yield (entries 9 and 10).

The cyclization reactions of β-(2-iodoanilino) ketones **24** and **26** merit some additional comments. Thus, while Pd(0)-catalyzed intramolecular addition to the carbonyl in **24** took place stereoselectively to give alcohol **25**-*cis* as the major isomer (cis/trans ratio 3.5:1), the reaction of **26** took place with the inverse selectivity to give alcohol **27** as a 1:2 mixture of the cis and trans isomers. On the other hand, no significant effect was observed in either the stereoselectivity (cis/trans) or the chemoselectivity (α-arylation/carbonyl addition) of the reaction of **26** after changing the solvent from THF to toluene (compare entries 14 and 15).

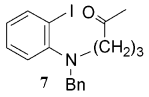
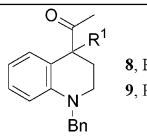
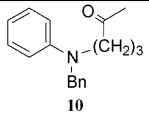
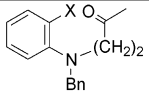
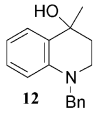
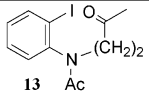
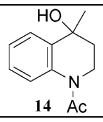
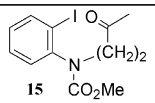
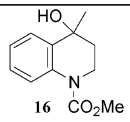
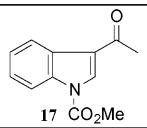
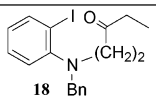
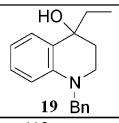
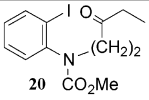
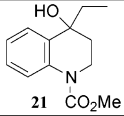
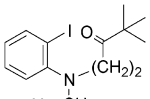
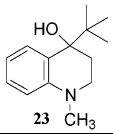
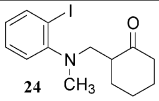
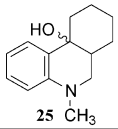
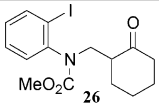
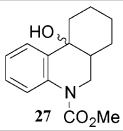
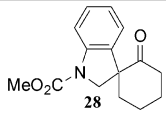
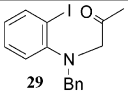
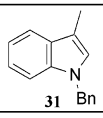
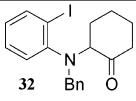
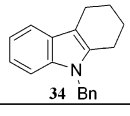
(21) For a preliminary account of part of our studies with ω-(2-haloanilino) alkanones, see: Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888−1889.

(22) For example, under reaction conditions of method A, β-anilino ketones **11a** and **18**, and α-anilino ketones **29** and **32**, afforded *N*-benzylaniline as the only isolable product.

(23) The intramolecular addition of aryl palladium halides to ketones is an uncommon transformation that has not been described until very recently, see: Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827−4828.

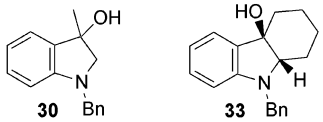
(24) For the intramolecular addition of vinyl palladium intermediates to ketones,[24a,b] aldehydes,[24b,c] and nitriles,[24d] see: (a) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545−3546. (b) Vicente, J.; Abad, J.-A.; López-Peláez, B.; Martínez-Viviente, E. *Organometallics* **2002**, *21*, 58−67. (c) Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579−4583. Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089−4092. (d) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238−3239.

Table 2. Pd(0)-Catalyzed Cyclization of 2-Haloanilino Ketones[a]

Entry	Substrate	Solvent	Additive[b]	Products (yield)[c]
1	 **7**	THF	---	 **8**, R^1 = H (20%) **9**, R^1 = OH (9%)  **10** (25%)
2	 **11a**, X = I **11b**, X = Br	THF	---	 **12** (40%)
3		Toluene[d]	Et_3N (2)	(45%)
4		Toluene[d]	Et_3N (2)	(15%)[e]
5	 **13**	Toluene[d]	Et_3N (2)	 **14** (65%)
6	 **15**	Toluene[d]	Et_3N (2)	 **16** (44%)  **17** (29%)
7	 **18**	THF[f]	Et_3N (10)	 **19** (60%)[g]
8		Toluene	Et_3N (10)	(84%)
9	 **20**	THF	Et_3N (10)	 **21** (18%)
10		Toluene	Et_3N (10)	(25%)
11	 **22**	Toluene	Et_3N (10)	 **23** (63%)
12	 **24**	THF	Et_3N (10)	 **25** (65%, *cis*/*trans* ratio 3.5:1)[h]
13		Toluene	Et_3N (10)	(73%, *cis*/*trans* ratio 3.5:1)
14	 **26**	THF	Et_3N (10)	 **27** (32%, 1:2)[i]  **28** (24%)
15		Toluene	Et_3N (10)	(45%, 1:2)[i] (31%)
16	 **29**	THF[f]	Et_3N (10)[j]	 **31** (66%)
17		Toluene[d]	Et_3N (10)[j]	(83%)
18	 **32**	THF[f]	Et_3N (10)[j]	 **34** (86%)
19		Toluene[d]	Et_3N (10)[j]	(87%)

[a] Reaction run with 0.2 equiv of $PdCl_2(PPh_3)_2$ and 3 equiv of Cs_2CO_3 in a sealed tube at 100−110 °C for 48 h. [b] (equiv). [c] Yield refers to pure isolated products. [d] 24 h. [e] *N*-Benzyl-2-bromoaniline (46%) was also isolated. [f] 65 h. [g] *N*-Benzyl-2-iodoaniline (34%) was also isolated. [h] *N*-Methyl-2-iodoaniline (30%) was also isolated. [i] Cis/trans ratio. [j] After the cyclization reaction, the crude mixture was treated with TFA.

The intramolecular addition to the carbonyl was also the reaction pathway observed in the palladium-catalyzed cyclization of α-(2-iodoanilino) ketones **29** and **32**, which exclusively afforded alcohols **30** and **33** (Figure 1), respectively, as was confirmed by careful analysis of the crude reaction mixtures. These alcohols could not be characterized due to their instability and were converted to the corresponding indoles **31** and **34** by treatment with TFA[25] (entries 16−19).

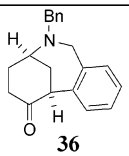
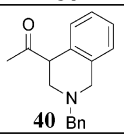
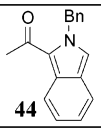


30 **33**

Figure 1.

The use of K_3PO_4 as the base (method C) in the palladium-catalyzed reaction of type I compounds resulted in the same reaction pathway obtained when using Cs_2CO_3, but always gave

Table 3. Pd(0)-Catalyzed Cyclization of 2-Halobenzylamino Ketones[a]

Entry	Substrate	Products (yield)[b]	
1	**35a**	 **36**	36%[c]
2	**35b**		45%
3	**37a**	 **38**	75%[d]
4	**37b**		68%[e]
5	**39a**	 **40**	80%[f]
6	**39b**		55%[f]
7	**42**	---	
8	**43a**	 **44**	52%
9	**43b**		22%
10	**45**	---	

[a] Reaction run with 0.2 equiv of $PdCl_2(PPh_3)_2$, 3 equiv of Cs_2CO_3, and 3 equiv of Et_3N in a sealed tube at 100−110 °C for 24 h. [b] Yield refers to pure isolated products. [c] 4-(*N*,*N*-Dibenzylamino)cyclohexanone (∼10%) was also isolated. [d] 48 h. [e] 63 h. [f] 4-Acetyl-2-benzyl-2*H*-isoquinolin-1-one (**41**)[28] was also isolated (∼5%).

inferior results. Thus, for example, after 3 days under the reaction conditions of method C, γ-(2-haloanilino) ketone **7** afforded a 3:1:1 mixture of the starting material, α-arylation compound, and the reduction product. On the other hand, under the same reaction conditions, β-(2-haloanilino) ketone **11a** afforded alcohol **12** in 15% yield.

At this point, we extended the studies on the palladium-catalyzed intramolecular coupling to the 2-halobenzylamino alkanones (type II compounds, Table 3). Once again, no cyclization compound could be obtained when KO*t*-Bu was used as the base. Interestingly, when the Pd-catalyzed reactions of type II compounds were run using Cs_2CO_3 as the base, a behavior different from that of type I compounds was observed. Thus, under these reaction conditions, either γ- or β- and α-(2-halobenzylamino) ketones afforded the α-arylation compound as the only cyclization product, and the addition to the carbonyl was never observed. As shown in Table 3, the formation of seven-, six-, and five-membered rings was accomplished in moderate to high yields.[26] It is noteworthy that α-(2-halobenzylamino) ketones **43a** and **43b** directly afforded isoindole **44**, as a result of the oxidation, under the reaction conditions, of the α-arylation product initially formed.[27] Generally, aryl bromides gave worse results than iodides, an exception being the formation of the bridged azatricyclic ketone **36** (entries 1 and 2), in which the iodide gave a lower yield and afforded a significant amount of the hydrodehalogenation product. This latter result could be understood considering that as the cyclization giving the bridged system proceeds more slowly than the formation of fused compounds, the use of the less reactive bromide prevents an extensive occurrence of competing reactions (i.e., reduction).

Both β-amino ketone **42** and α-amino ketone **45** failed to afford the cyclization products. These results could be understood considering that the enolization to the α-methine position generates a more hindered enolate, which would react more slowly in the cyclization reaction, allowing degradation processes to occur. It should be noted, however, that α-arylation of carbamate **26** took place at the α-methine position to afford **28**, although in moderate yield (entries 14 and 15, Table 2). Both the formation of a five-membered ring and the lower tendency of carbamates to give the retro-Michael fragmentation could facilitate the cyclization reaction in this case. Finally, the use of K_3PO_4 as the base for the Pd(0)-catalyzed cyclization of type II compounds afforded only products of α-arylation, but, once again, yields were very low, and it was impossible to drive reactions to completion.

At this point, we turned our attention to the "anomalous" behavior of type I compounds, which in some cases intriguingly changed the reaction pathway from α-arylation to addition to the carbonyl group. Although both the intramolecular enolate arylation[10] and the addition of aryl halides to ketones[23] catalyzed by Pd(0) have been previously reported in the carbocyclic series, these two reactions seem to operate quite independently of each other, and no competition between the two processes has been described.[29,30] Considering the similarity of the reaction conditions and the structural analogy, it is interesting to compare the results obtained by Muratake in the carbocyclic series[10] and those obtained in this work from type I compounds (Scheme 1). This comparison suggests the origin of the change in the reaction pathway lies in the nitrogen atom, and, as a hypothesis, we considered that this change could be caused by the ability of the nitrogen to chelate the palladium atom.

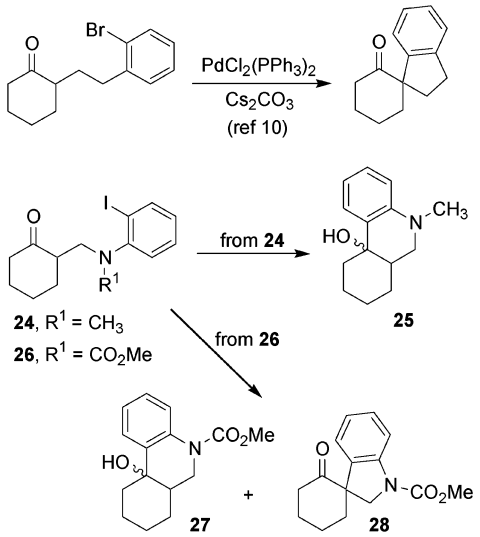
Hoping to gain more insight into the above Pd(0)-catalyzed carbocyclizations, we attempted the isolation of the σ-aryl palladium complexes, the purported intermediates in these reaction, to study their chemical behavior. Gratifyingly, γ-(2-iodoanilino) ketone **7** reacted with $Pd(PPh_3)_4$ (1:1 molar ratio) in benzene (room temperature, 72 h) to give a mixture of the four-membered palladacycles **46** and **47**, which were isolated by flash chromatography in 56 and 15% yield, respectively (Scheme 2). A shorter reaction time afforded a mixture in which a third compound was observed together with small amounts of palladacycles **46** and **47**. The NMR data suggested that it

(25) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767−3776.
(26) Especially interesting is the preparation of the novel benzazepine **38**, whose use in the synthesis of Crinane-type alkaloids is now being studied.
(27) Aromatization of existing rings is an important means of synthesis of isoindoles, see: Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119−206.
(28) It is interesting to note that on standing in solution isoquinoline **40** partially oxidizes to isoquinolone **41**.

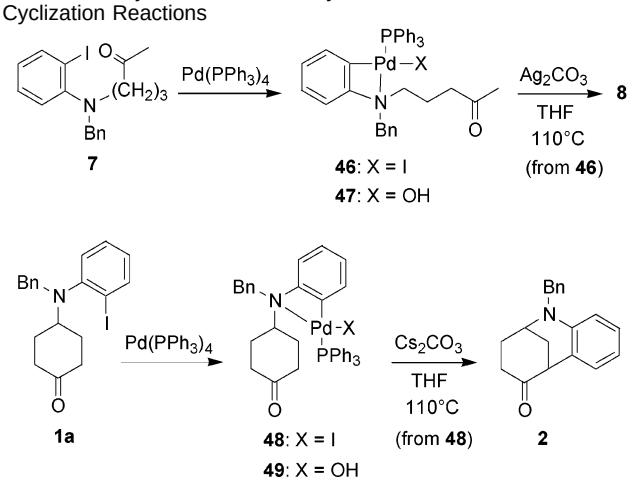
41

(29) Muratake had observed some competition between the enolate arylation and the carbonyl arylation in Pd(0)-catalyzed reactions of aldehydes.[11] The formation of the carbonyl arylation compounds was explained by means of the insertion of σ-arylpalladium species into the formyl C−H bond, a reaction that is not possible from ketones.
(30) A careful analysis of the haloaryl ketones studied by Yamamoto[23] reveals that the substitution pattern of the majority prevents the α-arylation reaction from taking place.

Scheme 1



Scheme 2. Synthesis of Palladacycles **46** and **48**, and Their Cyclization Reactions



could be the corresponding *trans*-bis(triphenylphosphane)-palladium complex.[31] Unfortunately, this compound could not be isolated and characterized, because on standing in solution it turned into palladacycles **46** and **47**. Palladacycle **46** was also obtained, in 84% yield, by using $Pd_2(dba)_3$ and PPh_3 (0.55:1 molar ratio) instead of $Pd(PPh_3)_4$, the hydroxopalladium complex **47** not being detected under these reaction conditions.

Similar reactions were observed starting from γ-(2-iodoanilino) ketone **1a**, which on treatment with $Pd_2(dba)_3$ and PPh_3 afforded the four-membered palladacycle **48** in 65% yield. The use of $Pd(PPh_3)_4$ as the zerovalent palladium complex resulted in the formation of considerable amounts of hydroxopalladium complex **49**, together with palladacycle **48**. The isolation of the hydroxopalladium complexes **47** and **49** only when $Pd(PPh_3)_4$ was used as the zerovalent palladium source, and the fact that palladacycle **46** was recovered unchanged after several days at room temperature in different solvents (benzene, THF, ...), suggested that these hydroxopalladium species were formed

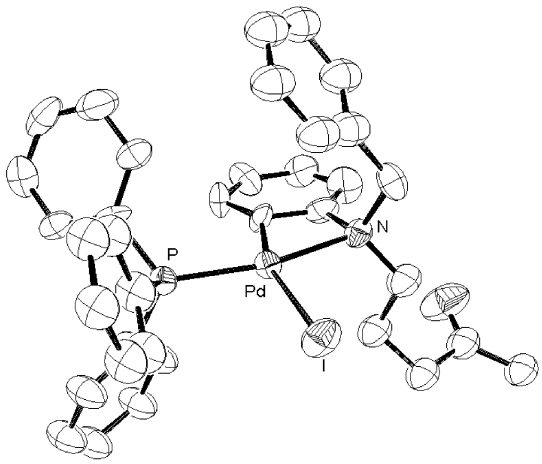


Figure 2. ORTEP drawing for **46**.

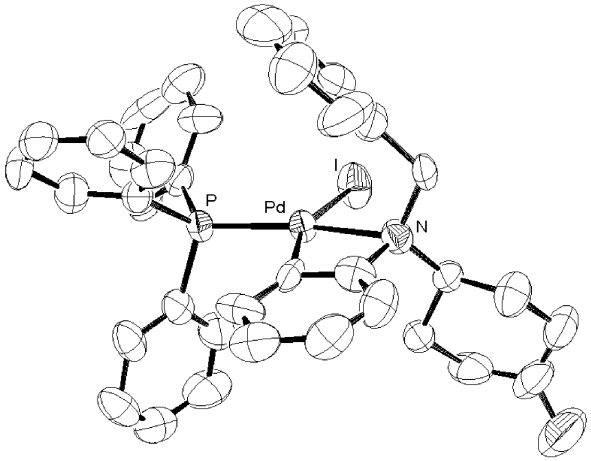


Figure 3. ORTEP drawing for **48**.

from the transient bis(triphenylphosphane)palladium complexes initially generated when using $Pd(PPh_3)_4$.[32,33]

The structures proposed for palladacycles **46** and **48** on spectroscopic grounds have been unambiguously confirmed by X-ray crystallography (Figures 2 and 3).[34] The four-membered metallacycle of **48** is planar (largest deviation to mean plane 0.004(4) Å in the C bonded to the Pd atom). The dihedral angle between this ring and the adjacent phenyl ring is 1.4(2)°. The electronic coupling due to the planarity of the $Pd(C_6H_4)N$ moiety in **48** produces the shortening of the Pd−C(Ar) bond length (1.989(3) Å, average value for the shortest Pd−C in CCDC database 2.07(2) Å,[35] range 2.022−2.102 Å) and decreases the N−Pd−C bond angle (65.91(13)°, average value 67.8(7)°, range 66.33−70.76°). The steric hindrance produced by this geometric

(31) The ^{31}P NMR spectrum of this bis(triphenylphosphane)palladium complex shows a singlet at δ 19.5. On the other hand, the ^1H NMR spectrum of this compound shows a singlet at δ 4.46, corresponding to the nondiastereotopic NCH_2Ar protons, and all of the protons of the palladated aromatic ring are between δ 6 and 7. These NMR data are very different from those recorded for the azapalladacycles **46** and **47** (see the Supporting Information).

(32) These reactions were carried out without precautions against the presence of moisture. So, as long reactions times are required, adventitious water could account for the formation of the hydroxopalladium(II) complexes. For the formation of hydroxopalladium complexes, see: (a) Getty, A. D.; Goldberg, K. I. *Organometallics* **2001**, *20*, 2545−2551. (b) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461−470.

(33) It is interesting to note that the N atom could play an important role in the formation of these hydroxopalladium complexes because they have not been observed during the preparation of the bis(triphenylphosphane)palladium complexes of the non-nitrogen-containing haloaryl ketones. So, the hydrolysis reaction could occur by deprotonation by the amino group of the more acidic coordinated water. For a related process, see: Albéniz, A. C.; Espinet, P.; Manrique, R.; Pérez-Mateo, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2363−2366.

(34) Detailed crystallographic and spectroscopic data of **46** and **48** are provided in the Supporting Information.

(35) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, 31−37.

shortening produces the lengthening of the Pd−N bond length (2.228(3) Å, average value 2.03(2) Å, range 2.006−2.084 Å), the Pd−C−C bond angle (99.5(3)°, average value 89(2)°, range 86.5−92.6°), and the N−C−C bond angle (109.6(3)°, average value 105.5(17)°, range 101.9−108.4°).

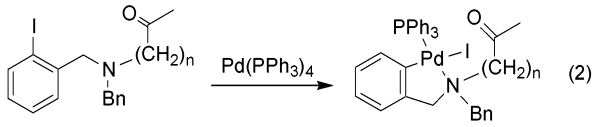
The formation of palladium complexes **46** and **48** is noteworthy. Contrary to what might be expected, these four-membered azapalladacycles are robust compounds that can be purified by flash chromatography without decomposition (see the Supporting Information). On the other hand, although nitrogen-containing palladacycles are a widely investigated class of organopalladium compounds, the most common are those with five- or six-membered rings,[36] and, to the best of our knowledge, these are the first reported examples of four-membered azapalladacycles fused with an aromatic ring. Moreover, the formation of these palladacycles contrasts with the results recently reported by Vicente et al.,[37] who have prepared several *trans*-bis(triarylphosphane)(2-aminophenyl)-iodopalladium complexes by oxidative addition of *o*-iodoaniline to "Pd(dba)$_2$" in the presence of arylphosphines. The two types of iodoanilines differ in that our compounds bear two alkyl groups at the nitrogen. The subsequent steric hindrance, forcing the nitrogen substituents out of the plane and directing the nonbonding electron-pair toward the palladium, together with an increase in the basicity of the N atom could facilitate the coordination of the amino group with the palladium atom to afford the otherwise unfavorable four-membered palladacycle.

The intermediacy of azapalladacycles **46** and **48** in the Pd-catalyzed intramolecular α-arylation of γ-(iodoanilino) ketones **7** and **1a** was confirmed by treating these Pd-complexes with bases to promote the carbocyclization reaction (Scheme 2). Thus, for example, treatment of **48** with Cs_2CO_3 in THF at 110 °C in a sealed tube for 24 h afforded **2** (75%) together with small amounts of the hydrodehalogenation compound. On the other hand, when azapalladacycle **46** was treated with Ag_2CO_3, which increases the electrophilicity of the palladium center by removal of the iodide ligand while simultaneously bringing about the enolization of the ketone, the cyclization compound **8** was obtained as the only reaction product in nearly quantitative yield.

Interestingly, when both β-(anilino) ketone **11a** and α-(anilino) ketones **29** and **32** were treated with equimolecular amounts of zerovalent palladium sources to obtain the corresponding azapalladacycles, a reaction behavior different from that of γ-(anilino) ketones **1a** and **7** was observed. Thus, the reaction of **11a**, **29**, and **32** with either $Pd_2(dba)_3$ and PPh_3 or $Pd(PPh_3)_4$ in benzene at room temperature afforded alcohols **12**, **30**, and **33**, respectively, in quantitative yields, the four-membered azapalladacycles not being isolated. It is worth noting that azapalladacycle **46** did not undergo the intramolecular addition to the carbonyl group, neither when submitted to high temperatures in the absence of a base nor when treated with Tl(TfO) to remove the iodo ligand and facilitate the coordination of the carbonyl group.

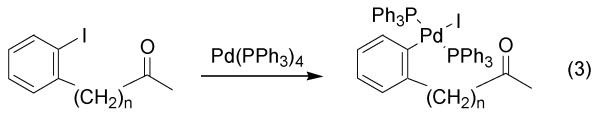
To confirm that bringing the carbonyl and iodoaryl groups closer together, which was achieved when changing from γ- to β- and α-anilino ketones, is not enough to promote the addition to the carbonyl and that the formation of the four-membered azapalladacycles is required, we attempted the isolation of the σ-arylpalladium complexes from 2-iodobenzylamines **37a** and **43a**, and from the non-nitrogen-containing compounds **50**−**53**.

2-Iodobenzylamines **37a** and **43a** reacted with either $Pd_2(dba)_3$ and PPh_3 or $Pd(PPh_3)_4$ in benzene at room temperature (3−4 days) to give the five-membered azapalladacycles **54** and **55**,[38] respectively, as the only isolable products (eq 2). The intermediacy of these azapalladacycles in the Pd-catalyzed intramolecular α-arylation of γ-(2-iodobenzylamino) ketones **37a** and **43a** was also confirmed. Thus, for example, treatment of **54** with Cs_2CO_3 (3 equiv) in THF at 110 °C in a sealed tube for 21 h afforded **38** in quantitative yield. Interestingly, the α-arylation reaction from azapalladacycle **55** took place even in the absence of Cs_2CO_3. Thus, when palladacycle **55** was heated in THF at 100 °C in a sealed tube, no addition to the carbonyl was observed, and instead isoindole **44** was obtained in 70% yield.

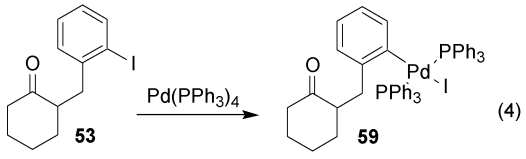


37a, n = 3 **54**, n = 3
43a, n = 1 **55**, n = 1 (2)

On the other hand, iodoaryl ketones **50**−**53** reacted with $Pd(PPh_3)_4$ (1:1 molar ratio) in benzene (room temperature, 3−4 days) to give the *trans*-bis(triphenylphosphane)aryliodopalladium complexes **56**−**59**[38] (eqs 3 and 4).[39] These σ-aryl palladium complexes are stable solids that, although they decomposed thermally in solution, in no case afforded the alcohols resulting from the intramolecular addition to the carbonyl group.



50, n = 3 **56**, n = 3
51, n = 2 **57**, n = 2
52, n = 1 **58**, n = 1 (3)



53 **59** (4)

The above results confirm that the formation of the four-membered azapalladacycles is the origin of the addition to the ketone carbonyl group process in the aniline series. Because the Lewis acidity of the Pd atom must be very similar in both α-amino ketone compounds, the only significant difference between five-membered azapalladacycle **55** and the transient four-membered azapalladacycle from iodoaniline **29** is the size of the chelate ring. So, although we have been unable to obtain

(36) For a recent review: Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917−1927.
(37) Vicente, J.; Abad, J.-A.; Frankland, A. D.; Ramírez de Arellano, M. C. *Chem.-Eur. J.* **1999**, *5*, 3066−3075.
(38) The moderate yield in the preparation of palladium complexes **55** and **59** (see the Supporting Information) is due to the difficulty of separating these complexes from PPh_3 and dba.
(39) Palladium complexes **56** and **58** were also obtained, in similar yields, by using $Pd_2(dba)_3$ and PPh_3 (0.55:2 molar ratio) instead of $Pd(PPh_3)_4$.

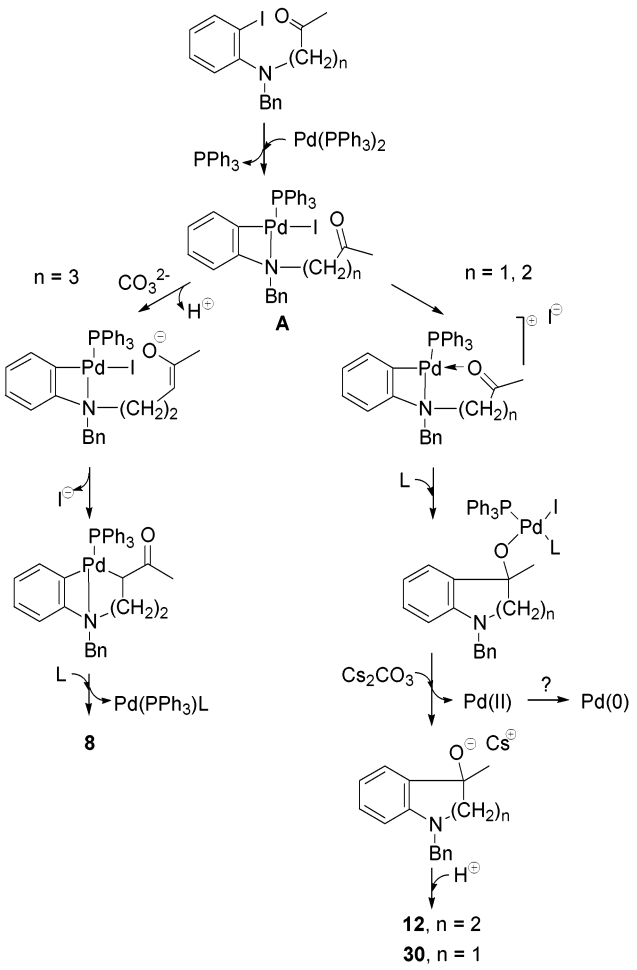


Figure 4. Proposed mechanisms for the intramolecular Pd(0)-catalyzed α-arylation and ketone carbonyl addition of 2-haloanilino ketones.

experimental evidence for the formation of the four-membered azapalladacycles from iodoanilines **11a**, **29**, and **32**, and hence it remains speculative, their participation as intermediates in the carbonyl-addition reaction appears reasonable on chemical grounds.

Moreover, the dichotomy between ketone α-arylation and carbonyl-addition in the intramolecular Pd-catalyzed processes from *ω*-(2-iodoanilino) alkanones could also be rationalized by the intermediacy of four-membered azapalladacycles **A** (Figure 4). Thus, for *β*- and α-anilino ketones ($n = 2$ and 1, respectively), the purported four-membered azapalladacycles undergo facile addition (even at room temperature) to the carbonyl group. This easy addition is a consequence of the coordination of the amino group to the palladium atom, which brings the carbonyl nearer to the metal atom, facilitating the formation of a transient C═O chelated intermediate,[40] which by means of a carbopalladation reaction would afford the corresponding Pd(II) alkoxide. The formation of this C═O chelated intermediate[41] would be easy when $n = 1$ or 2, as a new five- or six-membered ring is formed. On the contrary, it would be difficult when $n = 3$ (*γ*-anilino ketones),[42] and as a consequence the corresponding four-membered azapalladacycles (i.e., **46**) would be stable compounds which undergo the expected α-arylation reaction[43] in the presence of Cs_2CO_3. The α-arylation reaction, which is an easy process in the azapalladacycles when $n = 3$, would be thwarted when $n = 1$ and 2, as three- and four-membered rings, respectively, would be formed.[44]

Finally, it should be noted that as little is known about the mechanism of the Pd-catalyzed intramolecular addition of arylhalides to ketones,[23,24] the results obtained in this work contribute to clarify some of the steps in the mechanism. The catalytic cycle does not seem to demand a base but a salt (K_2CO_3 or Cs_2CO_3 in this work, and Na_2CO_3 or NaOAc in studies by Yamamoto[23]) that would transmetalate the oxypalladium intermediate into an alkoxide, which after protonolysis during the workup would give the corresponding alcohol. Additionally, Pd(II) obtained in the above step must undergo reduction to Pd(0). Proof of a redox process was obtained from the isolation of considerable amounts of *γ*-butyrolactone when the reaction was carried out in THF.[45]

In summary, we have reported that two different structure-depending reaction pathways can operate in the Pd-catalyzed intramolecular coupling of amino-tethered aryl halides and ketones, enolate arylation and addition to the carbonyl group. The formation of unprecedented four-membered azapalladacycles, from which X-ray data are reported, sheds light on the behavior of *ω*-(2-haloanilino) alkanones in their Pd(0)-catalyzed reactions, which are governed by the coordination of the amino group with the palladium atom.

Acknowledgment. This work was supported by MCYT, Spain (Project BQU2001-3551). Thanks are also given to the DURSI (Catalonia) for Grant 2001SGR-00083 and a fellowship to L.V.

Supporting Information Available: Experimental procedures for Pd(0)-catalyzed cyclization reactions and preparation of compounds. Characterization data for all new compounds and crystallographic data for complexes **46** and **48** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA029114W

(40) The coordination ability of intramolecular ketone carbonyl groups has already been observed: Vicente, J.; Abad, J.-A.; Martínez-Viviente, E.; Ramírez de Arellano, M. C.; Jones, P. G. *Organometallics* **2000**, *19*, 752−760.

(41) We agree with the reviewer who suggests that the formation of the C═O chelated intermediate could take place via a pentacoordinated Pd(II) complex (not illustrated in Figure 4). For a related proposal, see: Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499.

(42) The carbopalladation reaction probably requires an eclipsed arrangement that may not be likely when $n = 3$. See: Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813−1819.

(43) For the isolation and study of the reductive elimination reaction of aryl palladium enolates, see: Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816−5817.

(44) The behavior of carbamates that afford products from both α-arylation and addition to the ketone carbonyl group (entries 7, 8, 14, and 15 in Table 2) could be rationalized taking into account the intermediacy of *σ*-arylpalladium complexes with a coordinated carbonyl oxygen.[12] These six-membered palladacycles would be more stable and less prone to give the addition to the carbonyl than the four-membered azapalladacycles, and so the α-arylation process could occur to some extent. However, *σ*-arylpalladium complexes from the carbamates could not be isolated. For example, carbamate **26** on treatment with either $Pd_2(dba)_3$ and PPh_3 or $Pd(PPh_3)_4$ directly afforded alcohols **27**-*cis* and **27**-*trans*, although in moderate yields.

(45) When reactions were run in the presence of Et_3N (entries 3−19, Table 2), no *γ*-butyrolactone was obtained. It is known that tertiary amines with α-hydrogens could be the reductants in Pd-catalyzed reactions, see: Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179−3182. Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348−350.