JOC*Note*

Nitrogen Heterocycles by Palladium-Catalyzed Cyclization of Amino-Tethered Vinyl Halides and Ketone Enolates

Daniel Solé,* Faïza Diaba, and Josep Bonjoch*

Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain

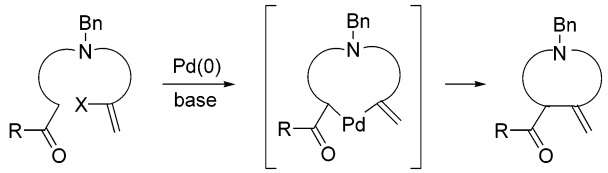
dsole@farmacia.far.ub.es

Received March 7, 2003

Abstract: The scope and limitations of Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone enolates as a methodology for the synthesis of nitrogen heterocycles have been studied. This reaction constitutes a synthetic procedure to obtain bridged, condensed, and monocyclic nitrogen-containing compounds.

The development and implementation of new procedures to assemble nitrogen heterocycles is still a challenge for organic synthesis.[1] Particularly interesting are cyclization processes in which the formation of a C−C bond occurs simultaneously with the installation of an exocyclic double bond, since a significant number of natural products bear a 3-alkylidenepiperidine motif in their skeleton (e.g., indole alkaloids of several structural types: strychnine,[2] ervitsine,[3] deplancheine,[4] and subincanadines;[5] as well as pumiliotoxins and related alkaloids from *Dendrobates* frogs[6]). Among the several cyclization methodologies leading to alkylidene-bearing nitrogen heterocycles,[7−9] the use of vinyl halides as starting materials has a wide range of application. Their cyclization can be performed upon alkenes using different methodologies, palladium-catalyzed processes (Heck-type reaction),[10] nickel-promoted reactions,[11] or radical cyclizations,[12] and upon aldehydes by means of a chromium-promoted reaction (Nozaki−Hiyama−Kishi reaction).[13]

SCHEME 1. Pd-Catalyzed Intramolecular Coupling of Vinyl Halides and Ketone Enolates



In this paper, we present a full discussion of our studies on the Pd-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone enolates (Scheme 1) in the search for a suitable methodology for the synthesis of nitrogen heterocycles incorporating an alkylidene side chain.[14] The reaction exploits the electrophilic character of the palladium atom, and it is presumed to proceed by sequential oxidative addition and enolization, followed by conversion to a palladacycle, which undergoes a simple reductive elimination.

At the beginning of our work, there were only two examples of this Pd(0)-catalyzed coupling process, developed by Piers in the carbocyclic series and then successfully applied by himself to the synthesis of the diterpenoid crinipellin B.[15] Contemporaneously with our preliminary studies, Cook reported another example of this Pd-catalyzed coupling process in the context of the total synthesis of the alkaloid (+)-vellosimine.[16]

Continuing our studies on the synthesis of compounds embodying the 2-azabicyclo[3.3.1]nonane framework,[17,18] we have focused our efforts on the Pd(0)-catalyzed cycliza-

(1) (a) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (c) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929 and references therein.

(2) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455.

(3) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.

(4) Itoh, T.; Enomoto, Y.; Ohsawa, A. *Heterocycles* **2001**, *55*, 1165 and references therein.

(5) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449.

(6) (a) Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505. (b) Kibayashi, C.; Aoyagi, S.; Wang, T.-C.; Saito, K.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157 and references therein.

(7) For tandem processes involving iminium salts, see: (a) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (c) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

(8) For nickel-catalyzed cyclizations of ynals or alkynyl enones, see: (a) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. J. *Tetrahedron* **1997**, *53*, 16449. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950.

(9) For radical-promoted cyclizations, see: (a) Baldwin, J. E.; Mackenzie Turner, S. C.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9425. (b) Cossy, J.; Cases, M.; Gomez Pardo, D. *Synlett* **1996**, 909. (c) Alcaide, B.; Rodríguez-Campos, I. M.; Rodríguez-López, J.; Rodríguez-Vicente, A. *J. Org. Chem.* **1999**, *64*, 5377. (d) Hoepping, A.; George, C.; Flippen-Anderson, J.; Kozikowski, A. P. *Tetrahedron Lett.* **2000**, *41*, 7427. (e) Cossy, J.; Bouzide, A.; Leblanc, C. *J. Org. Chem.* **2000**, *65*, 7257. (f) Prévost, N.; Shipman, M. *Tetrahedron* **2002**, *58*, 7165.

(10) (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685. (c) McAlonan, H.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1996**, *37*, 7151. (d) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146. (e) Larock, R. C.; Han, X. *J. Org. Chem.* **1999**, *64*, 1875. (f) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655. (g) Lee, C.-W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213. (h) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324.

(11) (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (b) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017. (c) Cancho, Y.; Martín, J. M.; Martínez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A.; *Tetrahedron* **1998**, *54*, 1221. (d) Yu, S.; Berner, O. M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827. (e) Reference 10h.

(12) (a) Kuehne, M. E.; Wang, T.; Seraphin, D. *Synlett* **1995**, 557. (b) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307. (c) Kuehne, M. E.; Bandarage, U. K.; Hammach, A.; Li, Y.-L.; Wang, T. *J. Org. Chem.* **1998**, *63*, 2172. (d) Reference 10h.

(13) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393.

(14) For a preliminary account of part of these results: Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225.

(15) (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454. (b) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11.

(16) (a) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057. (b) Liu, X.; Wang, T.; Xu, Q.; Ma, C.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 6299. (c) For further applications in the indole alkaloid synthesis, see: Yu, J.; Wearing, X. Z.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543 and references therein.

(17) (a) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230. (b) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968. (c) Reference 10f.

(18) For previous synthesis of 2-azabicyclo[3.3.1]nonan-6-ones, see: (a) Bosch, J.; Bonjoch, J. *J. Org. Chem.* **1981**, *46*, 1538. (b) Boger, D. L.; Patel, M.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4559. (c) Teuber, H.-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1990**, 781. (d) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans 1* **1999**, 1157.

10.1021/jo034299q CCC: $25.00
Published on Web 06/07/2003

tion of amino-tethered vinyl halides and ketones[19,20] that would afford compounds bearing different alkylidene substituents on the aforementioned bridged system (Table 1). After optimization studies with vinyl bromide **1a**, in which different bases, Pd sources, and solvents were examined,[14] we found that the combination of KO-*t*-Bu (1.5 equiv) and $Pd(PPh_3)_4$ (0.2 equiv) in THF at reflux gave the best results. Under these reaction conditions, **1a** afforded 2-azabicyclo[3.3.1]nonan-6-one **6** in 40−50% yield, together with minor amounts of dimer **7** (entry 1). The formation of the latter can be explained by the Pd-catalyzed coupling of **1a** with the alkyne **8** formed by elimination of HBr from the starting vinyl bromide. In fact, minor amounts of alkyne **8** were obtained in some runs where the amount of KO-*t*-Bu was increased.[14]

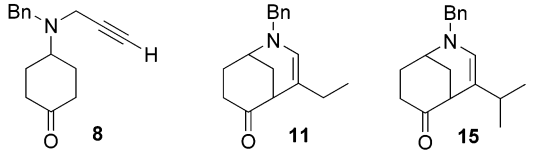
As expected, vinyl iodide **1b** was more efficient in the intramolecular coupling than **1a** and, under the standard cyclization conditions (entry 2), gave **6** in 55−60% yield, the dimer **7** not being obtained. Starting from vinyl bromide **2**, bicycle **9** was obtained in 24% yield as a 1.5:1 mixture of diastereomers (entry 3). The lower yield of the cyclization could be interpreted on conformational grounds. Thus, the introduction of a bulkier substituent at the nitrogen atom hampers the conformational change previous to the cyclization, allowing degradation processes to occur. In this context, it is noteworthy that 4-[*N*-(α-methylbenzyl)amino]cyclohexanone was also detected in the reaction mixtures.[21] On the other hand, the low diastereoselectivity of the cyclization reaction could be explained taking into account the scarce control of the chiral auxiliary in the enolization process.

The influence of the substitution pattern on the double bond was also studied. When starting from the *E* vinyl iodide **3**, the bridged compound **10** was obtained in good yield (entry 4). However, this compound, which is the only one detected in the reaction mixture, could not be completely characterized because on standing in solution it isomerizes to the enamine **11**. Under the same reaction conditions, the isomeric *Z* vinyl iodide **4b** gave a mixture of the cyclization compound **12** and alkyne **13** (entry 5), due to a decrease in the rate of the oxidative addition reaction as well as a greater tendency to undergo the E2 elimination of *Z* vinyl iodides with respect to the *E* isomers. When starting from **5b**, in which the elimination process is not possible, azabicyclic compound **14** was obtained as the only isolable product in good yield (entry 7). The latter is also an unstable compound and isomerizes to the enamine **15** in dichloromethane solution as well as during flash chromatography on SiO_2. In contrast with the results obtained with iodides **4b** and **5b**, vinyl bromides **4a** and **5a** were inefficient in the cyclization process, since, under essentially the standard reaction conditions, **4a** exclusively afforded alkyne **13** (entry 6), while **5a** was recovered unchanged (entry 8).

TABLE 1. Synthesis of 4-Alkylidene-2-azabicyclo-[3.3.1]nonan-6-ones by Pd-Catalyzed Cyclization of Vinyl Halides and Ketones[a]

entry	substrate	time	products (yield)	
1	**1a**, X = Br	30 min	**6** (40-50%)	**7** (≈5%)
2	**1b**, X = I	30 min	**6** (55-60%)	
3	**2**	1.5 h	**9** (24%, 1.5:1)[b]	
4	**3**	30 min	**10** (75%)	
5	**4b**, X = I	45 min	**12** (41%)	**13** (24%)
6	**4a**, X = Br	3 h		**13**[c]
7	**5b**, X = I	1 h[d]	**14** (74%)[e]	
8	**5a**, X = Br	6 h[d]	**5a**[c]	

[a] Reactions were carried out with 0.2 equiv of $Pd(PPh_3)_4$ and 1.5 equiv of KO-*t*-Bu in THF at reflux. [b] 4-[*N*-(α-Methylbenzyl)amino]cyclohexanone was also detected in the reaction mixture. [c] This was the only compound observed in the reaction mixture although it was not quantified. [d] KO-*t*-Bu (1.75 equiv). [e] After the usual workup, flash chromatography was carried out on Al_2O_3.



The tendency of the 4-alkylidene-2-azabicyclo[3.3.1]-nonan-6-ones **10** and **14** to undergo isomerization to the corresponding enamines can be accounted for considering the $A^{(1,3)}$ strain between the methyl group of the (*Z*)-ethylidene or isopropylidene side chain and the hydrogens at C-3 of the bicyclic ring. Although the 2-azabicyclo-[3.3.1]nonane framework is a conformationally mobile system, compounds **10** and **14** in either of their CC

(19) For the intermolecular vinylation of ketone enolates, see: Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

(20) For related Pd-catalyzed intramolecular coupling of aryl halides and ketone enolates, see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581. (b) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355. (c) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439. (d) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888. (e) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587. For Pd-catalyzed intramolecular coupling of aryl halides and amide enolates, see: (f) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (g) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (h) Freund, R.; Mederski, W. W. K. R. *Helv. Chim. Acta* **2000**, *83*, 1247. (i) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193. (j) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363. (k) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631. For a Pd-catalyzed intramolecular coupling of aryl halides and α-amino acid esters, see: (l) Gaertzen O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.

(21) The formation of deallylated products has also been reported by Cook.[16b]

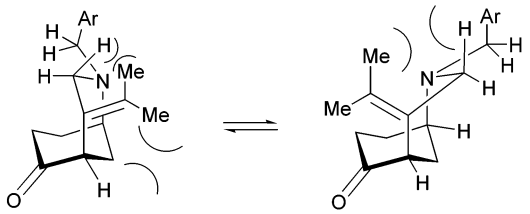


FIGURE 1. Conformational analysis of **14**.

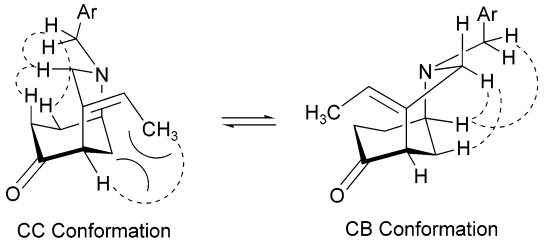


FIGURE 2. Conformational analysis and selected NOESY correlations of 2-azabicyclo[3.3.1]nonan-6-one **12**.

(chair−chair) or CB (chair−boat) conformations cannot relieve the aforementioned allylic strain (Figure 1) and, since they cannot gain a greater stability through a conformational equilibrium, follow an isomerization pathway to furnish enamines **11** and **15**. In contrast, (*E*)-ethylidene-bearing azabicycle **12** in its CB conformation can avoid the $A^{(1,3)}$ strain, and consequently is a constitutionally stable compound.[22] The conformational equilibrium in **12** between the CC and CB conformations is supported by NMR studies (NOESY data, Figure 2), which also showed that methylene derivative **6** prefers the CC conformation, as occurs in the 2-azabicyclo[3.3.1]-nonanes lacking steric interactions.[23]

After studying the 2-azabicyclo[3.3.1]nonane series, we decided to extend the Pd-catalyzed intramolecular coupling of vinyl halides and ketone enolates to the synthesis of other nitrogen heterocycles bearing alkylidene substituents. On treatment with 0.2 equiv of $Pd(PPh_3)_4$ and 1.5 equiv of KO-*t*-Bu in refluxing THF (method A in Table 2), vinyl iodide **16** gave the 2-azabicyclo[4.3.1]decanone **22**, although in low yield (entry 1).[24]

3,4-Disubstituted piperidine derivatives could also be obtained by this annulation process. Starting from vinyl bromide **17**, a 1:7 mixture of piperidine **23** and tetrahydropyridine **24** was obtained (entry 2), the latter arising from the initially formed annulation product **23** when this undergoes an isomerization to the more stable conjugated ketone under strongly basic reaction conditions.[25] It should be noted that in some runs minor amounts of alkyne **25** and dimer **26** were obtained together with the cyclization compounds. On the contrary, the Pd-catalyzed cyclization of vinyl iodide **18** exclusively afforded piperidine **27** (entry 3), and no isomerization compound was detected.

TABLE 2. Synthesis of Nitrogen Heterocycles by Pd-Catalyzed Cyclization of Vinyl Halides and Ketones

entry	substrate	method[a]	products (yield)	
1	**16**	A	**22** (23%)[b]	
2	**17**	A[c]	**23**	**24** (41%, 1:7)
3	**18**	A[c]	**27** (49%)	
4	**19**	A	**28**	**29** (32%, 1:1)
5	**19**	B		**29** (45%)
6	**20**	A		**31** (12%)[d]
7	**20**	B	**30**	**31** (34%, 2:3)
8	**21**	A	**32** (62%)	
9	**21**	B	**32** (26%)	

[a] Method A: KO-*t*-Bu (1.5 equiv), $Pd(PPh_3)_4$ (0.2 equiv), THF reflux, 30 min. Method B: Cs_2CO_3 (3 equiv), Et_3N (3 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), toluene 110 °C, sealed tube, 24h. [b] Alkyne **8** was also detected in the reaction mixture along with several unidentified products. [c] *N*-Benzyl-2-cyclohexenylamine (29%) was also isolated. [d] 4 h.

The synthesis of five-membered nitrogen heterocycles was also examined. In this series, the Pd-catalyzed cyclization could be accomplished by using either KO-*t*-Bu or Cs_2CO_3[26] as the base. When KO-*t*-Bu was used, vinyl bromide **19** afforded a reaction mixture in which the only product detected was pyrroline **28**, although a 1:1 mixture of **28** and pyrrole **29** was obtained after column chromatography (entry 4). Meanwhile, the use of Cs_2CO_3 resulted in the direct formation of pyrrole **29** (entry 5). Similar results were obtained from vinyl bromide **20**, which underwent cyclization to afford mixtures of hydroindoles **30** and **31**, although in lower yields (entries 6 and 7). It should be noted that pyrrolidines **28** and **30** could not be completely characterized because on standing in solution they easily suffer air oxidation to pyrroles **29** and **31**, respectively.[27]

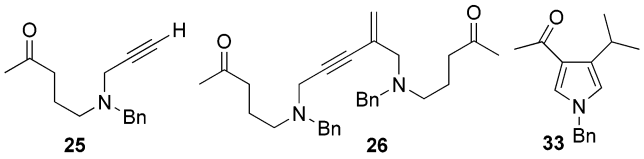
(22) In fact, all indole alkaloids bearing a 20-ethylidene side chain in the piperidine ring shows an *E* configuration: Bosch, J.; Bennasar, M. L. *Heterocycles* **1983**, *20*, 2471.

(23) Casamitjana, N.; Bonjoch, J.; Gràcia, J.; Bosch, J. *Magn. Reson. Chem.* **1992**, *30*, 183.

(24) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179.

(25) The isomerization of the initially formed annulation products to the conjugated enones under the reaction condition was also observed by Piers.[15a]

(26) It should be noted that no cyclization product was obtained in none of the series leading to six-membered rings when Cs_2CO_3 was used as the base.



Finally, Pd-catalyzed cyclization of vinyl iodide **21** exclusively afforded pyrrolidine **32** with either KO-*t*-Bu or Cs_2CO_3 (entries 8 and 9), and no isomerization compound was detected. However, it should be noted once again that on standing in solution **32** slowly oxidizes to pyrrole **33**. Interestingly, in contrast to what happens in the bridged azabicyclic compounds, in the monocyclic series the isopropylidene derivatives are more stable than the methylene analogues, which easily isomerize to the conjugated enones.

In summary, we have developed a methodology for the synthesis of nitrogen heterocycles based on the palladium-catalyzed intramolecular coupling of vinyl halides and ketone enolates. These processes have shown to work better when using vinyl iodides, rather than bromides, except in the methylene series where the halogen influence is weak. When planning to use this synthetic methodology it should be borne in mind that in some substrates side reactions can occur, such as the elimination of HX from the starting material to give an alkyne and the isomerization of the initially formed annulation product to the conjugated ketone or enamine. Nevertheless, looking at the full picture, the Pd(0)-catalyzed reaction here described constitutes a promising methodology for the synthesis of heterocycles. Further studies directed to the synthesis of natural products embodying the 2-azabicyclo[3.3.1]nonane framework using this methodology are in progress and will be reported in due course.

Experimental Section

Representative Procedure for the Pd(0)-Catalyzed Intramolecular Coupling Using KO-*t*-Bu as the Base (Table 1, Entry 2). To a solution of $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) in dry THF (5 mL) were added under argon a solution of vinyl bromide **1b** (100 mg, 0.27 mmol) in dry THF (2 mL) and KO-*t*-Bu (0.4 mmol, 0.4 mL of 1 M solution in *tert*-butyl alcohol). The solution was heated at reflux for 30 min. After being cooled to room temperature, the mixture was diluted with ether and washed with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, 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 azabicyclic compound **6** (39 mg, 60%).

Representative Procedure for the Pd(0)-Catalyzed Intramolecular Coupling Using Cs_2CO_3 as the Base in Toluene (Table 2, Method B: Entry 5). A solution of vinyl bromide **19** (100 mg, 0.34 mmol), Cs_2CO_3 (332 mg, 1.02 mmol), Et_3N (0.14 mL, 1.02 mmol), and $PdCl_2(PPh_3)_2$ (49 mg, 0.07 mmol) in dry toluene (10 mL) was stirred at 110 °C in a sealed tube for 24 h. After being cooled to room temperature, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue was purified by flash chromatography (Al_2O_3, from hexane to 8:2 hexane/AcOEt) to give pyrrole **29** (33 mg, 45%).

2-Benzyl-4-methylene-2-azabicyclo[3.3.1]nonan-6-one (6):[28] IR (film) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.72 (dddd, J = 14.5, 10.5, 8, 4.5 Hz, 1H, H-8ax), 1.97 (dt, J = 13, 2.7 Hz, 1H, H-9α), 2.24 (dm, J = 13 Hz, 1H, H-9β), 2.25−2.33 (m, 1H, H-8eq), 2.45 (dd, J = 17.5, 8.5 Hz, 1H, H-7eq), 2.59 (ddd, J = 17.5, 10.5, 8.5 Hz, 1H, H-7ax), 3.08 (br s, 1H, H-1), 3.24 (br s, 1H, H-5), 3.34 (s, 2H, H-3), 3.70 (d, J = 13.5 Hz, 1H, NCH_2Ar), 3.77 (d, J = 13.5 Hz, 1H, NCH_2Ar), 4.84 (s, 1H, =CH), 4.91 (s, 1H, =CH), 7.22−7.36 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.4 (C-8), 32.7 (C-9), 37.9 (C-7), 49.9 (C-1), 53.5 (C-5), 53.7 (C-3), 59.8 (NCH_2Ar), 112.6 ($=CH_2$), 127.1 (*p*-C), 128.5 and 128.7 (*o*-C and *m*-C), 139.0 (*ipso*-C), 141.0 (C-4), 210.5 (C-6). Anal. Calcd for $C_{16}H_{19}NO$ (241.3): C, 79.63; H, 7.94; N, 5.80. Found: C, 79.34; H, 7.79; N, 5.45.

2-Benzyl-4-[(*Z*)-ethylidene]-2-azabicyclo[3.3.1]nonan-6-one (10): flash chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH); IR (film) 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.52 (dd, J = 7, 1.2 Hz, 3H), 1.60−1.80 (m, 1H), 1.94 (dt, J = 12.8, 3 Hz, 1H), 2.23 (dq, J = 12.8, 3.4 Hz, 1H), 2.26−2.44 (m, 1H), 2.43 (dd, J = 17.2, 8.2 Hz, 1H), 2.58 (ddd, J = 17.2, 10.6, 8 Hz, 1H), 3.08 (br s, 1H), 3.13 (br s, 1H), 3.23 (d, J = 14.6 Hz, 1H), 3.61 (d, J = 14.6 Hz, 1H), 3.79 (s, 2H), 5.43 (qm, J = 7 Hz, 1H), 7.20−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, DEPT) δ 13.0 (CH_3), 25.5 (CH_2), 32.8 (CH_2), 38.0 (CH_2), 48.4 (CH_2), 50.2 (CH), 54.4 (CH), 59.9 (CH_2), 122.3 (CH), 127.5 (CH), 128.3 (CH), 128.6 (CH), 131.5 (C), 139.0 (C), 211.2 (C); HRMS calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1627.

2-Benzyl-4-[(*E*)-ethylidene]-2-azabicyclo[3.3.1]nonan-6-one (12):[28] flash chromatography (SiO_2, from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH); IR (film) 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.62 (d, J = 7 Hz, 3H, CH_3), 1.67 (dddd, J = 14, 11.5, 7.5, 4 Hz, 1H, H-8ax), 1.91 (dt, J = 13.5, 3 Hz, 1H, H-9α), 2.14 (ddm, J = 14, 8 Hz, 1H, H-8eq), 2.26 (dq, J = 13.5, 3.5 Hz, 1H, H-9β), 2.35 (dd, J = 16.5, 7.5 Hz, 1H, H-7eq), 2.75 (ddd, J = 16.5, 11.5, 8 Hz, 1H, H-7ax), 3.08 (br s, 1H, H-1), 3.25 (d, J = 13.5 Hz, 1H, H-3ax), 3.31 (d, J = 13.5 Hz, 1H, H-3eq), 3.51 (br s, 1H, H-5), 3.71 (d, J = 13.5 Hz, 1H, NCH_2Ar), 3.76 (d, J = 13.5 Hz, 1H, NCH_2Ar), 5.42 (q, J = 7 Hz, 1H, =CH), 7.22−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.9 (CH_3), 27.9 (C-8), 31.6 (C-9), 37.4 (C-7), 47.5 (C-5), 51.1 (C-1), 54.7 (C-3), 60.5 (NCH_2Ar), 122.5 (=CH), 127.0 (*p*-C), 128.2 and 128.7 (*o*-C and *m*-C), 132.1 (C-4), 138.9 (*ipso*-C), 210.6 (C-6); HRMS calcd for $C_{17}H_{21}NO$ 255.1623, found 255.1615. Anal. Calcd for $C_{17}H_{21}NO{\cdot}H_2O$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.29; H, 8.06; N, 4.79.

2-Benzyl-4-isopropylidene-2-azabicyclo[3.3.1]nona-6-one (14):[28] flash chromatography (Al_2O_3, from hexane to 8:2 hexane/AcOEt); IR (film) 1704 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.15 (dddd, J = 13.5, 12, 6.3, 3.3 Hz, 1H, H-8ax), 1.27 (s, 3H, CH_3), 1.42 (dt, J = 13.2, 3 Hz, 1H, H-9α), 1.66 (s, 3H, CH_3), 1.67 (ddm, J = 13.5, 8 Hz, 1H, H-8eq), 1.92 (dq, J = 13.2, 3.5 Hz, 1H, H-9β), 2.15 (br dd, J = 15.3, 6.3 Hz, 1H, H-7eq), 2.58 (br t, J = 3 Hz, 1H, H-1), 2.67 (ddd, J = 15.3, 12, 8 Hz, 1H, H-7ax), 3.20 (s, 2H, H-3), 3.44 (s, 2H, NCH_2Ar), 3.45 (br s, 1H, H-5), 7.04−7.28 (m, 5H); ^{13}C NMR (C_6D_6, 75.5 MHz) δ 20.2 (CH_3), 20.6 (CH_3), 29.4 (C-8), 31.1 (C-9), 37.0 (C-7), 48.7 (C-1), 49.5 (C-3), 51.2 (C-5), 61.1 (NCH_2Ar), 125.9 (C), 127.3 (*p*-C), 128.6 and 128.8 (*o*-C and *m*-C), 128.7 (C), 139.9 (*ipso*-C), 208.2 (C-6); HRMS calcd for $C_{18}H_{23}NO$ 269.1780, found 269.1771.

Acknowledgment. This work was supported by MCYT, Spain (Project BQU2001-3551). Thanks are also given to the DURSI (Catalonia, 2001SGR-00083).

Supporting Information Available: Characterization data for all new compounds and experimental procedures for preparation of starting materials. Conformational analysis and NOESY correlations for compounds **6** and **14**. ^1H and ^{13}C NMR spectra for compounds **1b**, **4a**,**b**, **6**−**12**, **14**, **15**, **18**, **20**−**22**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034299Q

(27) For easy air oxidation of 3-acylpirrolines to 3-acylpyrroles, see: Chou, S.-S. P.; Yuan, T.-M. *Synthesis* **1991**, 171.

(28) The signals in the ^1H and ^{13}C NMR spectra of this compound were unambiguously assigned with the aid of 2D-NMR experiments (COSY and HSQC) and NOESY.