Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3131–3135
Tetrahedron Letters

Palladium-catalysed intramolecular coupling of vinyl or aryl halides and β,γ-unsaturated nitronates

Daniel Solé,* Xavier Urbaneja and Josep Bonjoch

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

Received 15 January 2004; revised 9 February 2004; accepted 17 February 2004

Abstract—Both vinyl and aryl halides effectively undergo intramolecular coupling with amino-tethered allylic nitro moieties in the presence of a palladium catalyst and base. The reaction constitutes a useful methodology for the synthesis of bridged nitrogen-containing compounds.

During the last years a number of studies have been devoted to the development of palladium-catalysed coupling reactions of aryl halides and enolates or related anions, so it is now possible to introduce an aromatic unit to a broad range of enolate-type nucleophiles.[1] In contrast, the analogous coupling reactions involving vinyl halides, although described as early as 1990,[2] have received little attention, and the few examples of these processes so far reported only deal with the α-alkenylation of ketone enolates.[3–5]

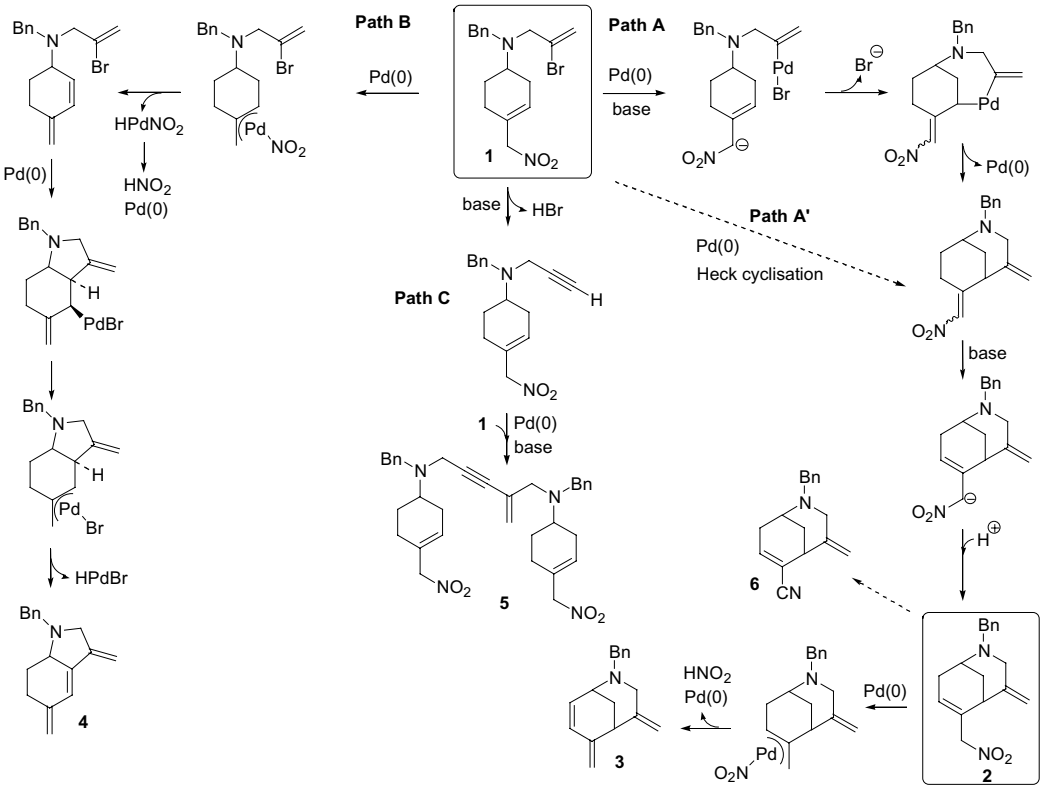
In our group, we have been working on the development of palladium-catalysed intramolecular coupling reactions of amino-tethered vinyl[4] or aryl halides[6] and ketone enolates. Continuing our research in this chemistry, we decided to explore the feasibility of using the anion derived from an allylic nitro compound,[7] an α,β-unsaturated nitronate, as the enolate-type nucleophile in these coupling reactions.[8] We anticipated that the use of a nitro derivative[9–11] could be of special interest in reactions of vinyl halides, because the low pK_a of nitro compounds would allow the use of a mild base, thus avoiding the competitive elimination of HX from the starting vinyl halide, which is the major side reaction of these annulation processes.[2a,4a,b] In order to develop a useful protocol for the new palladium-catalysed cyclisation process, we focused our efforts on the elaboration of the 2-azabicyclo[3.3.1]nonane ring system.[12] In this context, the cyclisation reaction of vinyl bromide **1**[13] was studied with the aim of obtaining the bridged nitro compound **2** (Scheme 1).

The results of the cyclisation reactions from **1** are summarised in Table 1 and Scheme 1, in which plausible reaction mechanisms for the formation of compounds **2**–**5** are depicted.[14,15] As can be seen, three reaction pathways (A, B and C) can operate depending on both the kind and amount of base used.

When vinyl bromide **1** was treated with $Pd(PPh_3)_4$ (0.2 equiv) and Cs_2CO_3 (3.2 equiv) in THF at reflux for 3 h, bicyclic compounds **3** (28%) and **4** (34%) were obtained, instead of the expected nitro derivative **2** (entry 1). The bridged compound **3** is probably formed by means of reaction pathway A (vide infra). Thus, the sequential deprotonation of the nitro alkyl moiety and oxidative addition of the vinyl bromide to Pd(0), followed by nucleophilic substitution on the palladium atom, reductive elimination[16] and base promoted isomerisation would give the allylic nitro compound **2**. As the latter is not quantitatively deprotonated due to the mild base used,[17] it undergoes oxidative addition to Pd(0) to give a π-allyl palladium complex, which in the absence of any nucleophile undergoes a 1,4-elimination reaction[18] to yield **3**. On the other hand, hydroindole **4** is the product of reaction path B, which becomes the major pathway when the nitronate anion is not quantitatively generated whether because the base used is not strong enough or the amount of base is low. Thus, oxidative addition of the allylic nitro compound to Pd(0) gives a π-allyl palladium complex, which then undergoes the 1,4-elimination reaction to give a

Keywords: Alkenylation; Arylation; Nitro compounds; Catalysis; Palladium.
* Corresponding author. Tel.: +34-934024540; fax: +34-934024539; e-mail: dsole@ub.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.086



Scheme 1.

Table 1. Pd-catalysed cyclisation of vinyl bromide **1**, see Scheme 1

Entry	Catalyst (equiv)	Base (equiv)	Time (h)[a]	Products (Yield)[b]
1	$Pd(PPh_3)_4$ (0.2)	Cs_2CO_3 (3.2)	3	**3** (28%), **4** (34%)
2	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (1.5)	2	**3** (67%), **4** (5%)
3	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (2.5)	2	**5** (67%)
4	$Pd(PPh_3)_4$ (0.2)	PhOK (2.5)	0.5	**2** (49%)[c]
5	$Pd(PPh_3)_4$ (0.1)	PhOK (2.5)	1	**2** (46%)[c]
6	$Pd(PPh_3)_4$ (0.05)	PhOK (2.5)	1.5	**2** (44%)[c]

[a] Reactions were carried out in THF at reflux.
[b] Yields refer to pure isolated products.
[c] In some runs minor amounts of **3** (<5%) and nitrile **6** (<5%) were also obtained.

conjugated diene. Finally, a Heck-type cyclisation from the latter leads to hydroindole **4**.

The use of a stronger base such as *t*-BuOK (1.5 equiv), under essentially the same reaction conditions, afforded bridged compound **3** as the main product, together with minor amounts of **4** (entry 2). Increasing the amount of *t*-BuOK to 2.5 equiv, in order to avoid the Pd(0)-catalysed 1,4-elimination reaction by quantitative deprotonation of the initially formed allylic nitro compound **2**, resulted however in the formation of dimer **5** as the only isolated compound (entry 3). Thus, in presence of an excess of strong base, there is considerable elimination of HBr from the vinyl bromide (Path C), and the resulting alkyne competes with the nitronate anion for the palladium-catalysed coupling process.[19] The use of amounts of *t*-BuOK between 1.5 and 2.5 equiv resulted in the formation of different mixtures of **2**, **3** and **5**, while less than 1.5 equiv of *t*-BuOK gave considerable amounts of **4**.

Finally, to our satisfaction we found that when the base potassium phenoxide was used, path A became the main process and the allylic nitro compound **2** was obtained in acceptable yields, although in some runs minor amounts of **3** and nitrile **6** were also isolated (entries 4–6).[20] Moreover, PhOK allowed the amount of the catalyst to be reduced to 0.05 equiv without any significant effect on the yield of the cyclisation product.

An alternative reaction mechanism for the formation of **2** involving a Heck reaction upon the allylic nitro moiety seems to be less likely, although it cannot be completely rejected. In this context, it is noteworthy that when **1** was treated under the same reaction conditions using Et_3N, AcONa, TMG or DBU as the base instead of PhOK, the cyclisation product **2** was obtained in ≈20% yield, which corresponded to the amount of $Pd(PPh_3)_4$, and the remaining starting material was recovered regardless of the length of reaction times. In these cases the reaction pathway leading to **2** could be the Heck

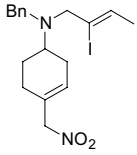
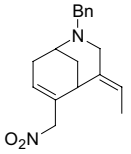
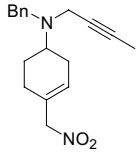
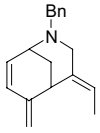
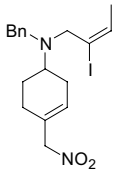
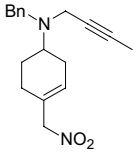
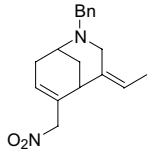
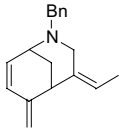
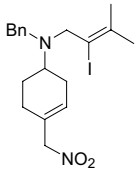
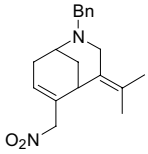
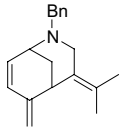
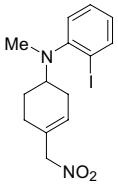
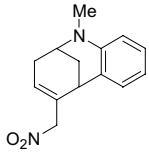
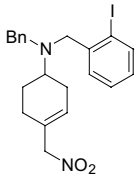
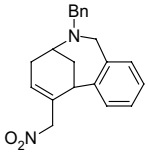
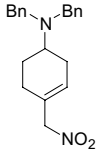
cyclisation (Path A′),[21] although after the first run the palladium seemed unable to establish a catalytic cycle.

At this point, the intramolecular coupling of several amino-tethered vinyl or aryl halides and α,β-unsaturated nitronates were investigated under the optimised reaction conditions (Table 2).

We found that in the reactions starting from vinyl halides **7**, **11** and **14**, similar yields of cyclisation compounds were obtained using either *t*-BuOK or PhOK as the base (entries 1–6). The main difference between the two bases was that the use of PhOK avoids the formation of alkynes, and allows the amount of catalyst to be reduced to 0.1 equiv. It is interesting to note that, in contrast to what happens when starting from **1**, in the cyclisation reactions from **7**, **11** and **14** using *t*-BuOK as the base, the corresponding nitro compounds could now be obtained. This different behaviour is due to the fact that the amount of *t*-BuOK could be increased because the Sonogashira-type coupling (Path C) is not possible.

On the other hand, in the reactions starting from aryl halides very different results were obtained depending on

Table 2. Pd-catalysed cyclisation of vinyl and aryl halides

Entry	Substrate	Catalyst (equiv)	Base (equiv)	Time (h)[a]	Products (Yield)[b]		
1	 **7**	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (1.75)	1	 **8** (30%)	 **9** (22%)	 —
2	**7**	$Pd(PPh_3)_4$ (0.1)	PhOK (2.5)	1	**8** (37%)	—	**10** (10%)
3	 **11**	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (1.75)	1	 **9** (5%)	 **12** (34%)	 —
4	**11**	$Pd(PPh_3)_4$ (0.1)	PhOK (2.5)	1	—	**12** (30%)	**13** (5%)
5	 **14**	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (2.5)	2	 **15** (50%)		 —
6	**14**	$Pd(PPh_3)_4$ (0.2)	PhOK (2.5)	1	**15** (45%)		**16** (10%)
7	 **17**	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (2.5)	3		 **18** (<5%)	
8	**17**	$Pd(PPh_3)_4$ (0.2)	PhOK (2.5)	1		**18** (80%)	
9	**17**	$Pd(PPh_3)_4$ (0.1)	PhOK (2.5)	1.5		**18** (82%)	
10	 **19**	$Pd(PPh_3)_4$ (0.2)	*t*-BuOK (2.5)	2	 —		 **21** (40%)
11	**19**	$Pd(PPh_3)_4$ (0.2)	PhOK (2.5)	44	**20** (66%)		—

[a] Reactions were carried out in THF at reflux.
[b] Yields refer to pure isolated products.

which base was used. Thus, while PhOK gave the cyclisation compounds in good yields (entries 8, 9 and 11), *t*-BuOK proved completely ineffective, giving either complex reaction mixtures (entry 7) or the hydrodehalogenation product (entry 10) instead of the cyclisation compound.

In summary, α,β-unsaturated nitronates have been found to be efficient terminators in the palladium-catalysed intramolecular coupling with amino-tethered vinyl or aryl halides. Potassium phenoxide is the base of choice in these reactions. Further studies directed towards the application of this methodology to the synthesis of natural products embodying the 2-azabicyclo[3.3.1]nonane framework, and to explore the use of the base PhOK in related Pd(0)-catalysed processes are in progress and will be reported in due course.

Acknowledgements

This research was supported by the MCYT (Spain) through Grant BQU2001-3551.

References and notes

1. For a recent review: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.
2. (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454–3455; (b) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11–13.
3. (a) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057–2059; (b) Liu, X.; Wang, T.; Xu, Q.; Ma, C.; Cook, J. M. *Tetrahedron Lett.* **2000**, *41*, 6299–6303; (c) Cao, H.; Yu, J.; Wearing, X. Z.; Zhang, C.; Liu, X.; Deschamps, J.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 8013–8017.
4. (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225–2228; (b) Solé, D.; Diaba, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746–5749; (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387–8390.
5. Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897–1900.
6. (a) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439–442; (b) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888–1889; (c) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587–1594.
7. For the use of nitro compounds in organic synthesis, see: Ono, N. *The Nitro Group in Organic Synthesis*; Willey-VCH: New York, 2001.
8. Allylic nitro compounds have been used as substrates for Pd(0)-catalysed allylic substitution by nucleophiles: (a) Tamura, R.; Kai, Y.; Kakihana, M.; Hayashi, K.; Tsuji, M.; Nakamura, T.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4375–4385; (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423–434, and references cited therein.
9. For the intramolecular palladium-catalysed arylation of nitroalkanes, see: Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355–2358.
10. For the intermolecular palladium-catalysed arylation of nitroalkanes, see: Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106–111.
11. For the palladium-catalysed coupling of 4-alkylnitrobenzenes and aryl bromides, see: Inoh, J.-I.; Satoh, T.; Pivsa-Art, S.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 4673–4676.
12. This azabicyclic ring system is found in more than 200 natural products. For recently isolated alkaloids embodying this ring system, see: Madangamines: (a) Kong, F.; Graziani, E. I.; Andersen, R. J. *J. Nat. Prod.* **1998**, *61*, 267–271; (b) Daphnezomines: Morita, H.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 6637–6641; (c) Calyciphylline A: Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895–2898.
13. The allylic nitro compounds have been prepared by reaction of the corresponding ketones with nitromethane: Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1982**, 551–552; (b) Tamura, R.; Sato, M.; Oda, D. *J. Org. Chem.* **1986**, *51*, 4368–4375.
14. General procedure for the Pd(0)-catalysed cyclisation using PhOK as the base: To a stirred solution of **1** (100 mg, 0.28 mmol) and phenol (79 mg, 0.84 mmol) in freshly distilled THF (10 mL) were added under argon *t*-BuOK (0.7 mmol, 0.7 mL of 1 M solution in *tert*-butyl alcohol) and $Pd(PPh_3)_4$ (32 mg, 0.027 mmol). The solution was heated at reflux for 1 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2) to give **2** (36 mg, 46%).
15. All new compounds were characterised by IR, ^1H NMR, ^{13}C NMR, HR-MS and/or microanalysis. NMR data for selected compounds of Scheme 1: (**2**) ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (dt, $J = 12$ and 3 Hz, 1H), 2.07 (ddd, $J = 12$, 3 and 2.4 Hz, 1H), 2.18 (d, $J = 18.6$ Hz, 1H), 2.50 (d, $J = 18.6$ Hz, 1H), 2.96–3.05 (m, 3H), 3.10 (m, 1H), 3.59 (d, $J = 13.5$ Hz, 1H), 3.67 (d, $J = 13.5$ Hz, 1H), 4.70–4.86 (m, 4H), 6.08 (t, $J = 3$ Hz, 1H), 7.22–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.6 (CH_2), 32.0 (CH_2), 39.8 (CH), 49.1 (CH), 51.0 (CH_2), 58.8 (CH_2), 79.9 (CH_2), 109.7 (CH_2), 127.0 (CH), 128.3 (CH), 128.7 (CH), 130.4 (C), 133.8 (CH), 138.7 (C), 143.9 (C). (**3**) ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (dt, $J = 12$ and 3.2 Hz, 1H), 1.95 (dt, $J = 12$ and 2.8 Hz, 1H), 3.01 (d, $J = 13$ Hz, 1H), 3.10 (d, $J = 13$ Hz, 1H), 3.22 (t, $J = 2.8$ Hz, 1H), 3.33 (dt, $J = 6$ and 2.8 Hz, 1H), 3.48 (d, $J = 13$ Hz, 1H), 3.63 (d, $J = 13$ Hz, 1H), 4.62 (t, $J = 2$ Hz, 1H), 4.79 (t, $J = 2$ Hz, 1H), 4.90 (s, 1H), 4.91 (s, 1H), 5.86 (dd, $J = 9.6$ and 6 Hz, 1H), 6.52 (d, $J = 9.6$ Hz, 1H), 7.22–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.9 (CH_2), 44.5 (CH), 49.8 (CH), 52.5 (CH_2), 59.4 (CH_2), 107.4 (CH_2), 113.7 (CH_2), 125.5 (CH), 127.0 (CH), 128.3 (CH), 128.9 (CH), 133.4 (CH), 138.9 (C), 145.6 (C), 148.1 (C). (**4**) ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (dm, $J = 12$ Hz, 1H), 2.19 (dm, $J = 12$ Hz, 1H), 2.33 (br t, $J = 15$ Hz, 1H), 2.53 (dt, $J = 15$ and 3.6 Hz, 1H), 2.93 (dt, $J = 13.2$ and 3 Hz, 1H), 3.04 (br d, $J = 15$ Hz, 1H), 3.31 (d, $J = 12.9$ Hz, 1H), 3.54 (d, $J = 13.2$ Hz, 1H), 4.10 (d, $J = 12.9$ Hz, 1H), 4.87 (s, 1H), 4.91 (s, 1H), 4.94 (s, 1H), 5.35 (s, 1H), 6.43 (s, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 28.5 (CH_2), 28.6 (CH_2), 58.7 (CH_2), 59.1 (CH_2), 65.5 (CH), 103.0 (CH_2), 112.2 (CH_2), 119.9 (CH), 127.0 (CH), 128.2 (CH), 128.9 (CH), 138.6 (C), 141.8 (C), 142.9 (C), 143.1 (C).
16. For the isolation and subsequent reductive elimination of palladium complexes of enolate-type anions, see: (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817; (b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330–9331; (c) Wolkowski, J. P.;

Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4289–4291.
17. pK_a $MeNO_2$=10.2, and pK_a $NaHCO_3$=10.3.
18. Tsuji, J. *Palladium Reagents and Catalysts-Innovations in Organic Synthesis*; Willey: Chichester, 1995.
19. For a recent example of a copper-free Sonogashira coupling, see: Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. *Org. Lett.* **2003**, *5*, 4191–4194.
20. For the conversion of nitro compounds to nitriles, see: Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 7497–7498.
21. The change in the reaction pathway could be explained considering that in THF these bases cannot produce the proton transfer necessary to convert the nitro alkane into the nitronate anion: Boyle, P. H.; Convery, M. A.; Davis, A. P.; Hosken, G. D.; Murray, B. A. *J. Chem. Soc., Chem. Commun.* **1992**, 239–242.