Pergamon

Tetrahedron Letters 40 (1999) 4259–4262

TETRAHEDRON LETTERS

Nucleophile-Dependent Stereodivergence in the Pd-Catalyzed Intramolecular Cyclization of 2-(*p*-Tolylsulfinyl)allylacetates

Marielouise Henrich[†], Antonio Delgado[‡], Elies Molins[¶ §], Anna Roig[¶ §] and Amadeu Llebaria[*†]

† Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB-C.S.I.C) Jordi Girona 18-26, 08034 Barcelona, Spain.

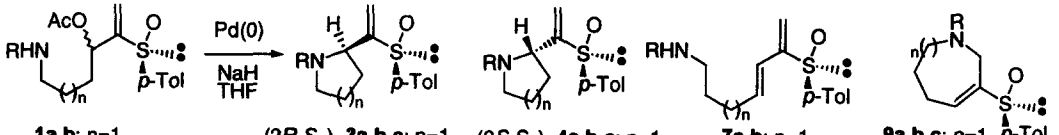
‡ Universitat de Barcelona, Facultat de Farmàcia, Unitat de Química Farmacèutica, Avgda. Joan XXIII, s/n, 08028 Barcelona, Spain.

¶ Institut de Ciencia de Materials de Barcelona (CSIC), Campus Universitari de Bellaterra, E-08193 Cerdanyola, Spain.

Received 25 February 1999; accepted 6 April 1999

Abstract: The palladium-catalyzed intramolecular cyclization of the sodium salts of *N*-Boc or *N*-trifluoroacetyl substituted 4-acetoxy-5-(*p*-tolylsulfinyl)-5-hexenylamines (**1a,b**) and 5-acetoxy-6-(*p*-tolylsulfinyl)-6-heptenylamines (**2a,b**) gives the corresponding 2-(1-(*p*-tolylsulfinyl)ethenyl)-pyrrolidines (**3a,b** and **4a,b**) and piperidines (**5a,b** and **6a,b**) in 50-88% yield and up to 90% diastereomeric excess. The major cycloadducts obtained in the trifluoroacetamide and NHBoc series were epimeric at the α-nitrogen stereogenic carbon, thus indicating a stereoselectivity dependence on the nitrogen anionic nucleophile.

The palladium-catalyzed allylation of nucleophiles is a versatile, selective and efficient methodology for Organic Synthesis.[1] Both inter- and intramolecular[2] palladium-catalyzed allylation reactions are known and efficient catalytic asymmetric versions have been developed.[3] The use of nitrogen nucleophiles[4,5] in the allylation reaction leads to allylic amines or derivatives thereof.[6] Cyclic nitrogen compounds arise from intramolecular reactions, and examples of diastereoselective[7] and enantioselective[8] synthesis have been described. The versatility of the sulfinyl group[9] as a chiral director in asymmetric synthesis led us to study the intramolecular cyclization of 2-(arylsulfinyl)allyl acetates with trifluoroacetamide or *t*-butylcarbamate anions under Pd catalysis.[10]



1a,b; n=1
2a,b; n=2

(2*R*,S$_S$), **3a,b,c**; n=1
(2*R*,S$_S$), **5a,b,c**; n=2

(2*S*,S$_S$), **4a,b,c**; n=1
(2*S*,S$_S$), **6a,b,c**; n=2

7a,b; n=1
8a,b; n=2

9a,b,c; n=1
10a,b; n=2

a, R=Boc; b, R= $COCF_3$; c, R=H

SCHEME 1

* Corresponding author; e-mail: alsqob@cid.csic.es.

§ X-Ray Structure Determination

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00701-7

The Pd-catalyzed cyclization occurred under uncommonly mild reaction conditions for this type of processes, giving moderate to good diastereoselectivities of the corresponding pyrrolidine or piperidine derivatives (Scheme 1, Table 1).

TABLE 1

			Cyclic Products						
Substrate	Catalyst.(*a*)	Temp (°C)	*exo*	dr (*b*)	% yield (*c*)	*endo*	% yield (*c*)	diene	% yield (*c*)
1a	A	r.t	**3a/4a**	90:10	88	**9a**	—	**7a**	—
1a	B	-10	**3a/4a**	85:15	85	**9a**	—	**7a**	—
1b	B	-5	**3b/4b**	10:90	53	**9b**	17	**7b**	—
1b	A	r.t.	**3b/4b**	40:60	61	**9b**	—	**7b**	—
1b	A	-5	**3b/4b**	20:80	41	**9b**	22	**7b**	—
1b	A	-20	**3b/4b**	5:95	38(*d*)	**9b**	38(*d*)	**7b**	—
2a	A	r.t.	**5a/6a**(*e*)	75:25	68	**10a**	—	**8a**	23
2b	B	r.t.	**5b/6b**(*e*)	45:55	74	**10b**	—	**8b**	18

(*a*) A, 10 mol% $Pd(OAc)_2$/20 mol% dppe; B, 10 mol % $Pd(PPh_3)_4$.
(*b*) Determined by ^{1}H-NMR and/or GC on the crude reaction mixture.
(*c*) Isolated yields
(*d*) Isolated as the corresponding amines **3c**, **4c** and **9c** after trifluoroacetamide hydrolysis.
(*e*) See footnote 12.
(*f*) Crude yield.

Since the starting materials **1a,b** and **2a,b** were obtained as a 1:1 inseparable mixture of epimers at the allylic carbon from (*R*)-*p*-tolylvinylsulfoxide, the above results seem to indicate that equilibration of either the diastereomeric π-allylpalladium intermediates (Figure 1) or the starting acetates[11] was faster than nitrogen alkylation. No epimerization of the cyclic compounds was ever detected under the reaction conditions and no allylation reaction took place in the absence of NaH, presumably this was required for the formation of carbamate and trifluoroacetamide sodium salts. In some instances, dienes **8a,b** were obtained as side products, especially in the piperidine series. These dienes were the main reaction products in the absence of the palladium catalyst, showing that the metal complex is essential for the success of the cyclization. In the trifluoroacetamide series, the strong influence of the reaction temperature on the diastereoselectivity and the formation of compounds **9b** and **10b**, arising from the uncommon *endo* cyclization mode are remarkable. Interestingly, the formation of **9b** and **10b** parallels the achievement of

high levels of diastereoselection in the cyclization. In the pyrrolidine series, the ($2R,S_S$) configuration of the stereogenic center relative to sulfur could be inferred from an X-ray analysis of a monocrystal from the major diastereomer **3a** obtained from the cyclization of **1a**.[12] Nitrogen deprotection of the major diastereomers obtained in the *N*-Boc and in the trifluoroacetamide series, gave diastereomeric pyrrolidines and piperidines epimeric at the α-nitrogen stereogenic carbon, this indicating *a surprising reversal of the stereoselectivity when moving from a trifluoroacetamide to the NHBoc anion as a nitrogen nucleophile.* Although the reasons for this difference in stereoselectivity remain unclear at this stage, a mechanistic proposal can be suggested. Thus, due to the presence of the stereogenic sulfur atom, four diastereomeric π-allylpalladium complexes in dynamic equilibria can be proposed as intermediates (Figure 1).

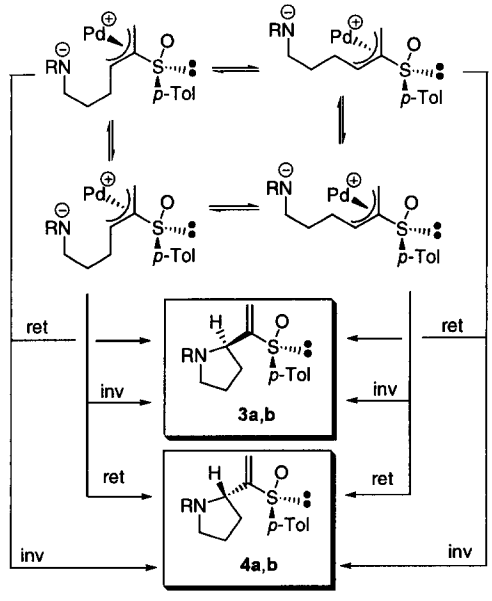


FIGURE 1

If we assume that nucleophilic attack from both the *N*-Boc and trifluoroacetamide anions take place with inversion, as is generally accepted for this kind of reaction, then different π-allyl-Pd intermediates should be considered in each series. However, an alternative interpretation would rely on the operation of different mechanistic pathways for each anion. Thus, whereas one of the anionic nucleophiles would attack the allyl-Pd intermediate with inversion, the other one could attack the metal first, being subsequently transferred to the allyl ligand with retention, *via* a reductive elimination process,[13] as is usually proposed for π-allylpalladium reactions with non stabilized nucleophiles.[14] In addition, the strong temperature dependence on the stereo- and regiochemical outcome in the trifluoroacetamidate allylation leading to *endo* cyclization products (not detectable in the *N*-Boc cyclizations) might also be mechanistically relevant.

In summary, the diastereomeric nature of the 2-(*p*-tolylsulfinyl)allylpalladium complexes has led to the discovery that apparently similar nitrogen nucleophiles can react in a stereodivergent manner. Further studies concerning the generality of the above results and the mechanistic rationale are open for future work.

Acknowledgements. We thank Comissionat per a Universitats i Recerca, Generalitat de Catalunya for support (Projects QF-95-4718, 1997SGR00140 and 1997SGR00021) and DAAD for a postdoctoral fellowship (to M.H.). We also thank Dr. Roberto Fernández de la Pradilla (Instituto de Química Orgánica General, CSIC, Madrid) for helpful discussions.

References and Notes

(1) a) Godleski, S.A. in *Comprehensive Organic Synthesis, Vol.4* (Eds.: Trost, B.M., Fleming, I.; Semmelhack, M.F.) Pergamon, Oxford, **1991**, pp. 586-661; b) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley, Chichester, **1995**; c) Takacs, J.M. in *Comprehensive Organometallic Chemistry II, Vol.12* (Eds.: Abel, E.W.; Stone, F.G.A.; Wilkinson, G.; Hegedus, L.S.), Pergamon, Oxford, **1995**, pp.785-904.

(2) a) Trost, B.M. *Angew. Chem. Int. Ed. Eng.* **1989**, 101, 1173-1192; b) Heumann, A.; Réglier, A. *Tetrahedron* **1995**, *51*, 975-1015.

(3) a) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395-422; b) Trost, B.M. *Acc. Chem. Res.* **1996**, *29*, 355-364.

(4) Metz, P. *Methoden Org. Chem. (Houben-Weyl)*, Vol.E21, pp. 5643-5668.

(5) Primary or secondary amines, or anionic nucleophiles such as azides and imide or sulfonamide salts are the usual nucleophiles, whereas the corresponding carbamate or carboxamide salts are recognized to be poor nucleophiles in reactions with π-allyl palladium intermediates. See, for example: a) Inoue, Y.; Taguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2721-2722; b) Takagi, M.; Yamamoto, K. *Chem. Lett.* **1989**, 2123-2124; see also ref. 7a.

(6) Johannsen, M.; Jorgensen, K.A. *Chem. Rev.* **1998**, *98*, 1689-1708.

(7) For Pd(0) catalyzed intramolecular carbamate cyclizations involving π-allyl-palladium intermediates, see: K. Takano, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681-5704. For Pd(II) catalyzed intramolecular cyclizations not involving π-allyl-palladium intermediates, see: a) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776-777; b) Yokoyama, H.; Otaya, K.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **1998**, *39*, 5971-5974.

(8) Trost, B.M.; Van Vranken, D.L. *J. Am. Chem. Soc.* **1993**, *115*, 444-458.

(9) Carreño, M.C. *Chem. Rev.* **1995**, *95*, 1717-1760.

(10) Reactions of sulfinyl-substituted π-allyl palladium complexes: a) Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153-156; b) Hiroi, K.; Onuma, H.; Arinaga, Y. *Chem. Lett.* **1995**, 1099-2000.

(11) At short reaction times or when NaH was absent, formation of the primary acetate resulting from 1,3-allylic rearrangement of the acetoxy group was observed. See: a) Trost, B.M.; Verhoeven, T.R.; Fortunak, J.P. *Tetrahedron Lett.* **1979**, 2301-2304 b) Trost, B.M.; Organ, M.G. *J. Am Chem. Soc.* **1994**, *116*, 10320-10321.

(12) We could temptatively assign the stereochemistry of the major piperidines as being the same as the major pyrrolidines in *N*-Boc and trifluoracetamide series, based on the assumption that a similar mechanism operated for 5 and 6 membered cyclizations. No suitable crystals for X-ray analysis could be obtained in the piperidine series. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication n° CCDC-102450. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

(13) Reductive elimination in palladium-catalyzed aryl amination: Mann, G.; Hartwig, J.F.; Driver, M.S.; Fernández-Rivas, C. *J. Am Chem. Soc.* **1998**, *120*, 827-828 and references therein. For a related aryl amidation, see: Wolfe, J.P.; Rennels, R.A.; Buchwald, S.L. *Tetrahedron* **1996**, *52*, 7525-7546.

(14) For an example of acetamide attack to a cyclic π-allyl Pd complex from the same face of the metal see: Larock, R.C.; Harrison, L.W.; Hsu, M.H. *J. Org. Chem.* **1984**, *49*, 3662-3664.