Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1681–1685

TETRAHEDRON: *ASYMMETRY*

# Stereoselective synthesis of α-aryl-2-benzofuranmethanamines and α-aryl-1*H*-indole-2-methanamines through palladium-mediated annulation of chiral α-arylpropargylamines

Flavia Messina,[a,†] Maurizio Botta,[a,*] Federico Corelli[a,*] and Claudio Villani[b]

[a]*Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Via A. Moro, 53100 Siena, Italy*
[b]*Dipartimento Scienze del Farmaco, Università di Chieti 'G. D'Annunzio', Via dei Vestini, Chieti Scalo, Chieti, Italy*

Received 21 February 2000; accepted 31 March 2000

**Abstract**

The title compounds, valuable chiral synthons for the synthesis of biologically active compounds, have been prepared in good yield and with high stereoselectivity through palladium-catalyzed heteroannulation of 2-iodophenol or 2-iodo-*N*-mesylaniline with enantiomerically pure or enriched α-arylpropargylamines.


## 1. Introduction

The transition metal-mediated annulation of alkynes has proven useful for the synthesis of a variety of hetero- and carbocyclic ring systems.[1] Methodology based on palladium is of special value, since the palladium complexes are readily available, generally not oxygen or moisture sensitive, and accommodate a number of different functional groups.[2] The synthetic potential of palladium-mediated carbon–carbon bond forming reactions, such as Suzuki, Stille, and Heck couplings, has been still further enhanced by their successful transfer to the solid-phase environment.[3]

In connection with our investigations on chiral, non-racemic imidazole compounds as antifungal and antiaromatase agents,[4,5] we have recently described the palladium-mediated heteroannulation of homochiral arylpropargylic alcohols to give aryl 2-benzofuranyl carbinols **1** and aryl 2-indolyl carbinols **2** (Fig. 1).[6] Pursuing the same research line, herein the first enantioselective synthesis of α-aryl-2-benzofuranmethanamine **3** and α-aryl-1*H*-indole-2-methanamine **4** through the palladium-mediated heteroannulation of chiral, non-racemic arylpropargylamines **5**[7] is reported. Some mechanistic aspects of the heteroannulation reaction are also briefly presented.

* Corresponding authors. E-mail: botta@unisi.it and corelli@unisi.it
† Present address: GlaxoWellcome, Medicines Research Centre, Verona, Italy.

0957-4166/00/$ - see front matter 
PII: S0957-4166(00)00131-2

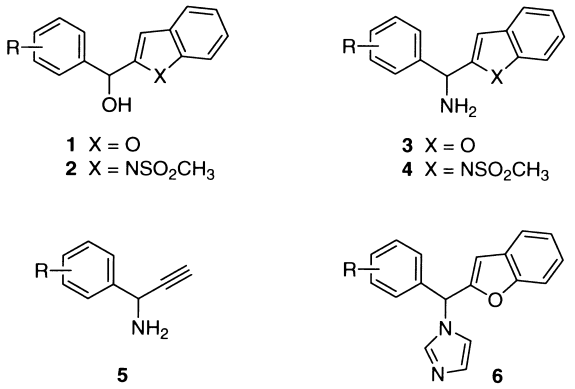
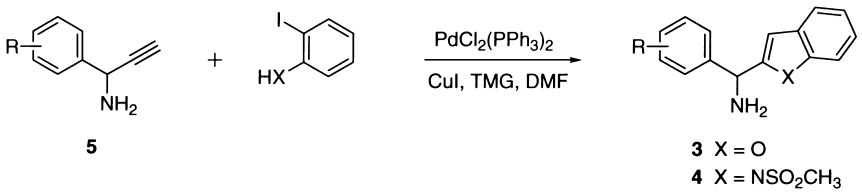



Figure 1.

Compounds **3** are valuable intermediates for the preparation of homochiral imidazole derivatives **6**,[8] some of which have been shown to be potent, enantioselective inhibitors of aromatase in vitro. On the other hand, racemic indolemethanamines **4** have been used as important building blocks in the synthesis of C-terminal inhibitors of HIV protease.[9]

## 2. Results and discussion

Racemic and enantiomerically pure or enriched arylpropargylamines **5** (1.0 mmol) were reacted with 2-iodophenol (1.0 mmol) in the presence of $PdCl_2(PPh_3)_2$ (0.025 mmol), CuI (0.025 mmol), and tetramethylguanidine (TMG, 3.0 mmol) in DMF at 40°C for 16–20 h while passing argon through the reaction mixture, according to the procedure developed for the corresponding alcohols, to afford the benzofuran derivatives **3** in good yield and with high stereoselectivity.[10] Analogously, reaction of **5** with 2-iodo-*N*-mesylaniline under the same experimental conditions gave α-aryl-1-methanesulfonyl-1*H*-indole-2-methanamines **4**. Experiments of this nature are described in Scheme 1 and Table 1.




Scheme 1.

Enantiomeric excesses were determined by HPLC analyses on a chiral column (Chiralcel, Daicel Chemical Co., Ltd), while the absolute configurations were assigned based on those of the corresponding propargylamines.[7] It should be pointed out that the enantiomeric excess of the resulting product was similar to that of the corresponding starting material: in no case was a loss of enantiomeric excess higher than 3% observed. Such a high stereospecificity of the palladium-mediated annulation is understandable since the stereogenic center of the substrate is not involved in the probable reaction mechanism outlined in Scheme 2.[11]

Table 1
Palladium-mediated cyclization of propargylamines **5** to benzofurans **3** and indoles **4**

| Product | R | Time (h) | Yield (%)[a] | Configuration[b] | $[\alpha]_D^{23c}$ | ee (%)/ee (%) of **5**[d] |
|---|---|---|---|---|---|---|
| **3a** | H | 20 | 70 | *R* | –10.1 (*c* 1.1) | 95/97 |
| **3b** | H | 20 | 82 | *S* | +11.9 (*c* 1.2) | 95/98 |
| **3c** | 4-Cl | 16 | 80 | *R* | –10.7 (*c* 1.1) | 74/76 |
| **3d** | 4-Cl | 16 | 71 | *S* | +10.9 (*c* 1.0) | 83/84 |
| **3f** | 4-F | 17 | 65 | *R* | –12.9 (*c* 1.0) | 96/97 |
| **3g** | 4-F | 17 | 76 | *S* | +12.6 (*c* 1.0) | 95/98 |
| **3h** | 3-F | 16 | 72 | *R* | –6.9 (*c* 0.9) | 80/82 |
| **3i** | 3-$CH_3$ | 16 | 69 | *R* | –12.6 (*c* 1.0) | 94/97 |
| **4a** | H | 20 | 73 | *R* | –15.4 (*c* 0.6) | 95/97 |
| **4b** | 4-Cl | 16 | 78 | *S* | +7.3 (*c* 0.7) | 95/98 |
| **4c** | 4-F | 20 | 69 | *R* | –14.8 (*c* 0.6) | 96/98 |
| **4d** | 3-$CH_3$ | 16 | 72 | *S* | +13.1 (*c* 0.8) | 93/96 |

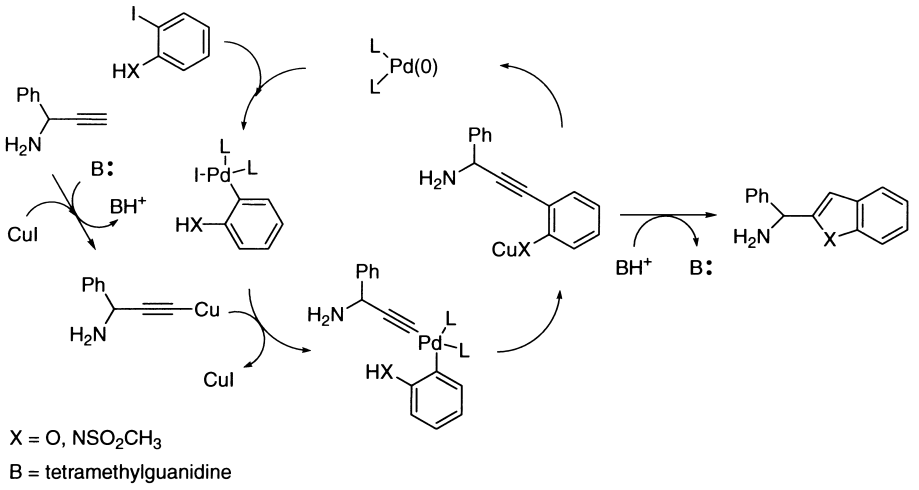
[a]Reaction yields refer to isolated and purified materials

[b]Absolute configurations were assigned based on those of the starting α-arylpropargylamines

[c]Measured in chloroform solution

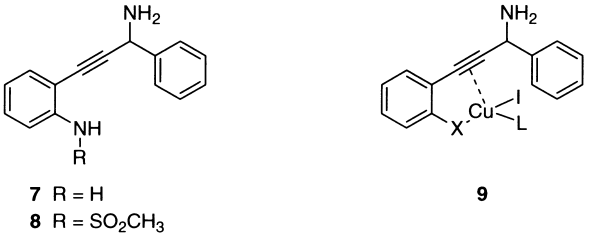
[d]Enantiomeric excesses were determined by HPLC analyses on chiral column Chiralcel OD (Daicel Chemical Co, Ltd.) (250 x 4.6 mm) eluting with *n*-hexane/2-propanol 80/20 (flow rate 0.8 mL/min)

The mesylation of 2-iodoaniline was crucial for the annulation reaction to occur, since 2-iodoaniline on reaction with propargylamine **5a** only gave the coupling product **7** (Fig. 2), which in turn could not be cyclized to the indole derivative **4a**. On the other hand, the intermediate **8**, which proved to be resistant to annulation under either palladium or base catalysis, was smoothly converted to indole **4a** by treatment with CuI and TMG in DMF at 40°C. Based on




Scheme 2.

these findings, we hypothesize that the heteroannulation step may be copper-catalyzed and, accordingly, the XH group of the aromatic substrate should be able to coordinate copper (structure **9**) in the presence of CuI and TMG.



**7** R = H
**8** R = $SO_2CH_3$

**9**

Figure 2.

It is interesting to note that, unlike propargylic alcohols, the corresponding propargylamines have not as yet found very extensive application in palladium-mediated heteroannulation reactions and, to the best of our knowledge, the reaction reported here is the first example involving homochiral α-arylpropargylamines.[12]

## Acknowledgements

We thank the Italian CNR and the University of Siena for financial support.

## References

1. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. T. *Chem. Rev.* **1996**, *96*, 635–662.
2. Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002–2009, and references cited therein.
3. Zhang, H.-C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804–1809, and references cited therein.
4. Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008–2015.

5. Botta, M.; Summa, V.; Trapassi, G.; Monteagudo, E.; Corelli, F. *Tetrahedron: Asymmetry* **1994**, *5*, 181–184.
6. Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263–1266.
7. Messina, F.; Botta, M.; Corelli, F.; Schneider, M.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767–3769.
8. Messina, F.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **1999**, *40*, 7289–7292.
9. Varney, M. D.; Appelt, K.; Kalish, V.; Reddy, M. R.; Tatlock, J.; Palmer, C. L.; Romines, W. H.; Wu, B.-W.; Musick, L. *J. Med. Chem.* **1994**, *37*, 2274–2284.
10. All the new compounds gave satisfactory microanalyses and showed spectroscopic data in accordance with the assigned structures.
11. Summa, E. PhD Thesis, University of Siena, Italy and University of Wuppertal, Germany, 1999.
12. For examples of annulation of achiral propargylamines both in solution and on solid support, see: Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307–2310.