Tetrahedron Letters,Vol.30,No.43,pp 5941-5944,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# SYNTHESIS OF ENANTIOMERICALLY PURE PROTECTED β-ARYL ALANINES

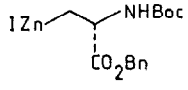
**Richard F.W. Jackson,*[a] Martin J. Wythes,[b] and Anthony Wood[a]**

[a] Department of Chemistry, Bedson Building, The University, Newcastle upon Tyne, NE1 7RU, UK

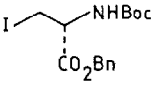
[b] Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK.

***Summary**: The organozinc reagent (1), prepared from the β-iodoalanine derivative (2), reacts with aryl iodides at 50 °C in the presence of catalytic bis(tri-o-tolylphosphine)palladium dichloride to give in moderate to good yields enantiomerically pure protected S-β-aryl alanine derivatives (4).*

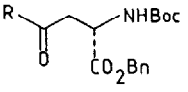
The asymmetric synthesis of α-amino acids remains an important challenge for organic chemists.[1] Many approaches rely on formation of one of the four possible bonds to the α-centre with control of the chirality by use of a second chiral centre, which is subsequently removed.[2] Methods for the functionalisation of existing amino acids in the asymmetric synthesis of more complicated amino acids have received less attention. The most common starting material in this approach has been serine.[3-8] We have recently reported that the organozinc reagent (1), prepared from the protected iodoalanine derivative (2) and zinc/copper couple in benzene/dimethylacetamide (15:1) using sonication, undergoes palladium catalysed reaction with acid chlorides to give high yields of protected enantiomerically pure γ-keto α-amino acids (3).[9] We now wish to report that the organozinc reagent (1) also reacts under palladium catalysis with a wide variety of aryl iodides to give enantiomerically pure protected S-β-aryl alanine derivatives (4). Numerous approaches to the synthesis of enantiomerically pure phenylalanine analogues have been reported, based either on the asymmetric reduction of dehydroarylalanine derivatives[10] or the reaction of chiral nucleophilic glycine equivalents with benzylic halides.[11] Our approach offers a useful alternative.



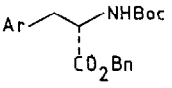

(1)




(2)



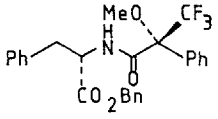

(3)



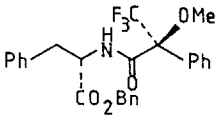

(4)

Previous work, in which coupling of less functionalised organozinc reagents was investigated,[12] suggested that $(Ph_3P)_2PdCl_2$ would not be an efficient catalyst for the coupling of the zinc reagent (1) with aryl iodides. Indeed, treatment of the organozinc reagent (1) with $(Ph_3P)_2PdCl_2$ and iodobenzene at 60 °C for 1h gave a low yield of protected phenylalanine (4a, 15%). Use of

lower reaction temperatures (which had proved satisfactory for coupling of **(1)** with acid chlorides) produced no protected phenylalanine **(4a)**. However, we were pleased to find that simple replacement of the catalyst by $[(o\text{-}CH_3C_6H_4)_3P]_2PdCl_2$ (5 mol. %), which had previously been shown to be an effective catalyst for coupling of less functionalised zinc reagents with aryl iodides,[12] allowed reaction to occur at 50 °C within 1h, yielding the protected phenylalanine derivative **(4a, 55%)**. Since the temperature used for this coupling reaction was slightly higher than that used for the coupling of acid chlorides (50 °C *versus* 40 °C), we considered it necessary to establish the optical purity of the product. We have therefore prepared the (*R*) and (*S*) Mosher amide[13] derivatives **(5a)** and **(6a)**, each of which was diastereoisomerically pure (as judged by 300 MHz proton n.m.r. spectral analysis), confirming that indeed no racemisation had occurred in the preparation of **(4a)**.

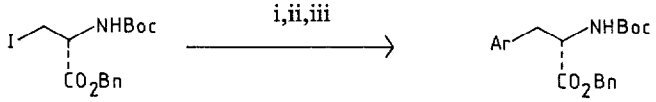



**(5a)**




**(6a)**

We have investigated the scope of this coupling reaction by using a range of commercially available aryl iodides (Scheme 1).[14] Our results are presented in the table.




**(2)** **(4)**

i, Zn/Cu couple, sonication; ii, $[(o\text{-tol})_3P]_2PdCl_2$; iii, ArI, 50 °C, 1 h.

**Scheme 1**

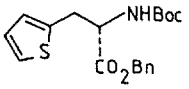
**TABLE. - Preparation of Protected (S)-β-Aryl Alanines**

| Aryl Iodide | Product | Ar | Yield, % | $[\alpha]_D$ (c in EtOH) |
|---|---|---|---|---|
| Iodobenzene | **(4a)** | $C_6H_5$ | 55 | -10.0° (1.0)† |
| 1-Iodonaphthalene | **(4b)** | 1-naphthyl | 64 | -16.6° (1.0) |
| 2-Acetoxy-1-iodobenzene | **(4c)** | $2\text{-}AcOC_6H_4$ | 12 | -11.0° (0.2) |
| 2-Fluoro-1-iodobenzene | **(4d)** | $2\text{-}FC_6H_4$ | 0 | |
| 1-Iodo-2-methoxybenzene | **(4e)** | $2\text{-}MeOC_6H_4$ | 40 | -10.9° (1.0) |
| 4-Acetoxy-1-iodobenzene | **(4f)** | $4\text{-}AcOC_6H_4$ | 53 | -17.7° (0.8) |
| 4-Bromo-1-iodobenzene | **(4h)** | $4\text{-}BrC_6H_4$ | 67 | -11.3° (1.0) |
| 4-Fluoro-1-iodobenzene | **(4i)** | $4\text{-}FC_6H_4$ | 36 | -22.0° (0.8) |
| 1-Iodo-4-methylbenzene | **(4j)** | $4\text{-}MeC_6H_4$ | 50 | -15.1° (1.0) |
| 1-Iodo-4-nitrobenzene | **(4k)** | $4\text{-}NO_2C_6H_4$ | 61 | -19.2° (1.0) |

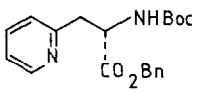
†An authentic sample of **(4a)** prepared from S-phenylalanine benzyl ester had $[\alpha]_D$ = -10.8° (c = 1.0, EtOH).

We have established the optical purity of several representative examples [(4e), (4h) and (4k)] by preparation of (*R*) and (*S*) Mosher amide derivatives, and we therefore feel confident of the optical purity of the other examples as well. Although several of the yields are only moderate, they have not been optimised. The main problems which remain concern aryl iodides with *ortho* substituents. Where this substituent can act as a leaving group (*e.g.* AcO (4c) or F (4d)), we obtain low or negligible yields, although 1-iodo-2-methoxybenzene does react satisfactorily. In all cases the mass balance is accounted for by recovery of N-Boc-alanine benzyl ester, which results from protonation of the zinc reagent (1) either during the reaction, or on quenching.

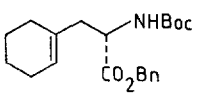
We have also briefly investigated the preparation of β-heteroaryl alanine derivatives. Reaction of 2-iodothiophene with the organozinc reagent (1) under our usual conditions ($[(o\text{-}CH_3C_6H_4)_3P]_2PdCl_2$, 50 °C, 1h) gave a poor yield (10%) of the desired protected β-(2-thienyl)alanine (7).[15] By contrast, 2-bromopyridine reacted satisfactorily with the organozinc reagent (1) under the conditions which we had previously used for coupling with acid chlorides [$(Ph_3P)_2PdCl_2$, 35 to 40 °C, 30 min] to give protected β-(2-pyridyl)alanine (8)[16] in good yield (59%).[17]




(7)




(8)




(9)

As a final example, we have also investigated the coupling of cyclohexen-1-yl triflate with (1). In a single unoptimised experiment treatment of the organozinc reagent (1) with cyclohexen-1-yl triflate and $(Ph_3P)_2PdCl_2$ at 50 °C for 1h gave the 2,3,4,5-tetrahydrophenylalanine derivative (9)[18] in 36% yield.

In summary, we have demonstrated that reaction of the organozinc reagent (1) with aryl iodides under palladium catalysis is an effective method for the preparation of a wide variety of enantiomerically pure analogues of phenylalanine. Moreover, the derivatives (4) are obtained with protecting groups which are ideally suited to peptide synthesis.

**Acknowledgements**: We thank the SERC for a CASE studentship to A.W., Dr. Keith James for helpful discussions, and Pfizer Central Research for support.

## References

1. R.M. Williams, P.J. Sinclair, D. Zhai, and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547; and references therein.
2. *α-Amino Acid Synthesis*; M.J. O'Donnell (Ed.) *Tetrahedron Symposium-in-Print*, Pergamon, London, 1988; Vol. 44, Issue 17.
3. P.J. Maurer, H. Takahata, and H. Rapoport, *J. Am. Chem. Soc.*, 1984, **106**, 1095.

4. J.A. Bajgrowicz, A. El Hallaoui, R. Jacquier, C. Pigiere, and P. Viallefont, *Tetrahedron,* 1985, **41**, 1833.
5. J.E. Baldwin, R.M. Adlington, and N.G. Robinson, *J. Chem. Soc., Chem. Commun.*, 1987, 153.
6. L.D. Arnold, J.C.G. Drover, and J.C. Vederas, *J. Am. Chem. Soc.,* 1987, **109**, 4649.
7. N.A. Sasaki, C. Hashimoto, and P. Potier, *Tetrahedron Lett.,* 1987, **28**, 6069.
8. T. Itaya and A. Mizutani, *Tetrahedron Lett.*, 1985, **26**, 347.
9. R.F.W. Jackson, K. James, M.J. Wythes, and A. Wood, *J. Chem. Soc., Chem. Commun,* 1989, 644; a recent report describes the use of a homologous amino acid derived zinc reagent: Y. Tamaru, H. Tanigawa, T. Yamamoto, and Z-i. Yoshida, *Angew. Chem., Int. Ed. Engl.,* 1989, **28**, 351.
10. For a review, see: K.E. Koenig in *Asymmetric Synthesis*, Vol. 5, pp. 71, J.D. Morrison (ed.), Academic Press, Orlando, 1987.
11. For example, see: U. Schöllkopf, U. Groth, C. Deng, *Angew. Chem., Int. Ed. Engl,* 1981, **20**, 798; R. Fitzi and D. Seebach, *Tetrahedron*, 1988, **44**, 5277; S. Ikegami, H. Uchiyama, T. Hayama, T. Katsuki, and M. Yamaguchi, *Tetrahedron*, 1988, **44**, 5333; R.M. Williams and M-N. Im, *Tetrahedron Lett.,* 1988, **29**, 6075; J.F. Dellario, Jr. and B.D. Santarsiero, *Tetrahedron Lett.,* 1988, **29**, 607. For use of a chiral phase transfer catalyst, see: M.J. O'Donnell, W.D. Bennett, and S. Wu., *J. Am. Chem. Soc.,* 1989, **111**, 2353.
12. Y. Tamaru, H. Ochiai, T. Nakamura, and Z-i. Yoshida, *Tetrahedron Lett.,* 1986, **27**, 955
13. J.A. Dale, D.L. Dull, and H.S. Mosher, *J. Org. Chem.,* 1969, **34**, 2543.
14. *Typical Procedure.* A solution of the protected β-iodoalanine derivative **(2)** (0.304 g, 0.75 mmol) in dry benzene (3 $cm^3$) and dry dimethylacetamide (0.25 $cm^3$) was added to zinc/copper couple (0.090 g, 1.38 mmol) in a dry flask under nitrogen. The mixture was sonicated in a Hillsonic FM 100 bath for 30 min, during which the temperature of the bath rose from 22 °C to 35 °C, and after which no **(2)** remained (t.l.c. analysis). Bis(tri-*o*-tolylphosphine)palladium dichloride (0.035 g, 0.04 mmol) was added, followed by the aromatic iodide (0.75 mmol). The resulting mixture was stirred at 50 °C for 1 h, and then allowed to cool. Ethyl acetate (50 $cm^3$) was added and the flask contents filtered. The filtrate was washed with dilute hydrochloric acid (1*M*, 20 $cm^3$) and water (3 x 20 $cm^3$), before being dried ($Na_2SO_4$). Solvent was removed on the rotary evaporator and the residue purified by flash chromatography using petroleum ether (b.p. 40-60 °C): diethyl ether as the eluent to give the protected β-aryl alanine **(4)**.
15. F.W. Dunn, *J. Org. Chem.,* 1956, **21**, 1525; A.W. Lipkowski and G. Flouret, *Pol. J. Chem.,* 1980, **54**, 2225.
16. K-H. Hsieh, E.C. Jorgensen, and T.C. Lee, *J. Med. Chem.,* 1979, **22**, 1199; C. Hoes, J. Raap, W. Bloemhoff, and K.E.T. Kerling, *Recl. Trav. Chim. Pays-Bas,* 1980, **99**, 99.
17. The palladium catalysed coupling of organozinc iodides with N-heteroaryl halides has been reported: T. Sakamoto, S. Nishimura, Y. Kondo, and H. Yamanaka, *Synthesis*, 1988, 485.
18. M.L. Snow, C. Lauinger, and C. Ressler, *J. Org. Chem.*, 1968, **33**, 1774.

(Received in UK 21 August 1989)