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# Preparation of (*S*)-2-Quinolylalanine by Asymmetric Hydrogenation

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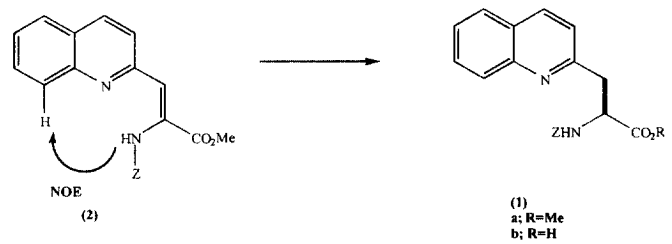
***Abstract***: The synthesis of (*S*)-2-quinolylalanine through asymmetric hydrogenation with (*S,S*)-Et-DuPHOS-Rh is described. The reaction has been extended to other 2-pyridylalanine derivatives. 

As part of a programme aimed at the preparation of inhibitors of zinc-dependent matrix metalloproteinase (MMP) enzymes for the treatment of arthritis and cancer,[3,4] we needed a synthesis of the protected amino acid (**1b**).[5] We envisaged that such a compound may be readily prepared through asymmetric hydrogenation of the enamide (**2**) (**scheme 1**). The DuPHOS range of catalysts are well known for giving high enantioselectivity (>95%) in the hydrogenation of a wide range of substrates.[6] The application of these catalyst systems to pyridylalanines and benzo analogues had not, however, previously been described. In this letter we report the successful implementation of this strategy and our preliminary results on other 2-pyridylalanine derivatives.




**Scheme 1**

The required enamide (**2**) was readily prepared in 58% yield, after recrystallisation, by treatment of quinoline-2-carboxaldehyde with the phosphonate (**3**).[7] The geometry of the enamide was confirmed as Z- by NOE studies. Compound (**2**) underwent facile reduction with the cationic rhodium complex $[(COD)Rh(DiPFc)]^{+}OTf^{-}$ to afford the racemate in 94% yield.[8] Gratifyingly we found that the asymmetric reduction with the cationic (*S,S*)-Et-DuPHOS-Rh catalyst in the presence of tetrafluoroboric acid gave the protected amino acid ester (**1a**) in 95% yield and 94% e.e.[9,10] Saponification of the ester with aqueous lithium hydroxide furnished the Z-protected acid (**1b**) in 91% yield (95% e.e.).[11]

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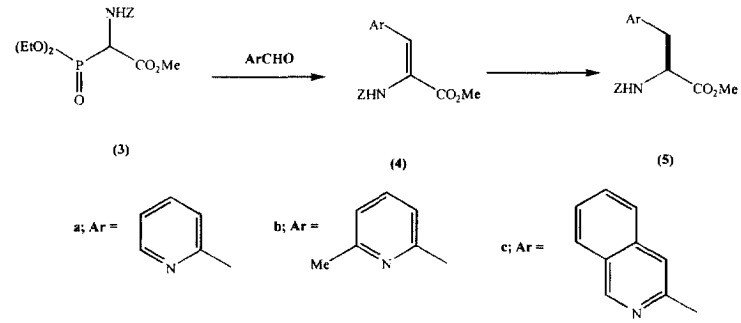
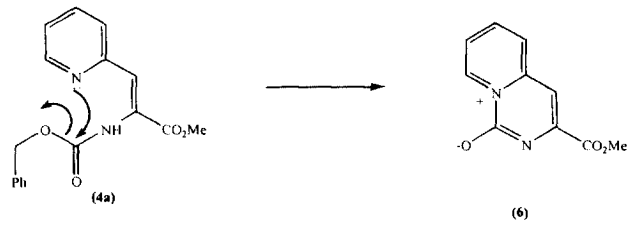
Given the success in the preparation of (**1b**) we sought to further examine the scope of the asymmetric hydrogenation reaction (**scheme 2**). Thus, while the preparation of 3- and 4-pyridylalanines by asymmetric hydrogenation is a well established process,[12] the preparation of 2-pyridylalanine itself has remained elusive. This has, in part, been due to difficulties in the preparation of the enamide. We have found that the enamide precursors (**4a**) and (**4b**) could be prepared by the route outlined in scheme 2 in 55 and 57% yield respectively. The latter compound underwent facile asymmetric hydrogenation to afford the 6-methyl-2-pyridyl amino acid ester (**5b**) in quantitative yield and 97% e.e. Even more surprisingly we found that this reaction proceeded in the *absence* of tetrafluoroboric acid without loss of enantioselectivity! Generally *N*-protonation is required to obviate catalyst inhibition through co-ordination of the heterocycle to the metal. In the present case, the 6-methyl group of (**4b**) apparently provides sufficient steric encumbrance to co-ordination.




**Scheme 2**

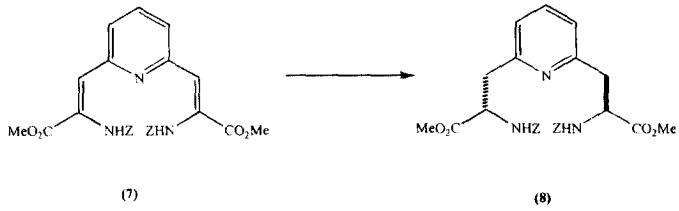
Compound (**4a**) failed to undergo asymmetric hydrogenation, even in the presence of tetrafluoroboric acid, although reduction with the highly active DiPFc-Rh catalyst gave the racemate (**5a**). We were able to isolate a compound from the attempted hydrogenation of (**4a**) with (*S,S*)-Et-DuPHOS-Rh after 24 hours and have tentatively assigned the rearranged structure (**6**) to this material on the basis of NMR and MS data.[13] We believe that compound (**6**) is formed by an initial nucleophilic attack by the pyridyl nitrogen atom on the carbonyl moiety of the Z-group, followed by elimination of benzyl alcohol and aromatisation to furnish (**6**) (**scheme 3**).




**Scheme 3**

The isoquinolyl derivative (**4c**)[14] was prepared (66% yield) and reduced to the protected racemic amino acid ester (**5c**) with the DiPFc-Rh catalyst (87% yield). Disappointingly asymmetric hydrogenation using Et-DuPHOS-Rh failed, again even in the presence of tetrafluoroboric acid.

We rationalised that successful hydrogenation of a 2-pyridylalanine derivative requires a reasonably bulky group in the $C_6$ position. To further demonstrate this effect we decided to prepare the $C_2$- symmetrical amino acid (**8**). Thus, the required dehydroamino acid ester (**7**) was obtained in 45% yield by reaction of 2,6-pyridinedicarboxaldehyde and the phosphonate (**3**). Asymmetric hydrogenation of (**7**) proceeded well to afford (**8**) in 78% yield and 95% e.e. (**scheme 4**).[15]




**Scheme 4**

These results have led us to postulate that if there is sufficient steric hindrance around the 2-pyridyl nitrogen atom then asymmetric hydrogenation will be successful; simple protonation of the nitrogen atom is not always sufficient. This work further extends the use of the DuPHOS range of catalysts in asymmetric synthesis and when combined with the phosphonate methodology gives rapid access to Z-protected 2-pyridylalanine derivatives.

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**References and Notes**

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9. HPLC e.e. assay for (**1a**): Chiralpak AD, 30% IPA/70% heptane, 1 ml/min., 210 nm.
10. The use of tetrafluoroboric acid was inferred from ref. 12a.
11. The acid was derivatised to the methyl ester with TMS diazomethane and analysed as ref. 9.
12. (a) Dobler, C.; Kreuzfeld, H.J.; Michalik, M. and Krause, H.W. *Tetrahedron: Asymmetry* **1996**, *7*, 117. (b) Cativiela, C.; Mayoral, J.A.; Melendez, E.; Oro, L.A.; Pinillos, M.T. and Uson, R. *J. Org. Chem.* **1984**, *49*, 2502. (c) Bozell, J.J.; Vogt, C.E. and Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584.
13. Selected data for (**6**): M/Z 205 ($MH^+$), 173 (M-OMe) and 146 ($M-CO_2Me$). $^{13}C$ NMR (100 MHz; $CDCl_3$) 164.9 (C), 153.3 (C), 151.0 (C), 149.2 (C), 138.3 (CH), 131.5 (CH), 125.5 (CH), 120.1 (CH), 100.7 (CH) and 53.2 ($CH_3$).
14. The aldehyde was prepared by reduction of the corresponding methyl ester with DIBAL.
15. HPLC e.e. assay for (**8**): Chiracel OJ, 65% EtOH (0.1% TFA)/35% heptane, 1 ml/min., 210 nm.