An Efficient and Diastereoselective Method for the Synthesis of (*R*)-1-Ferrocenylethylamines and 1-Ferrocenylethyl Acetate

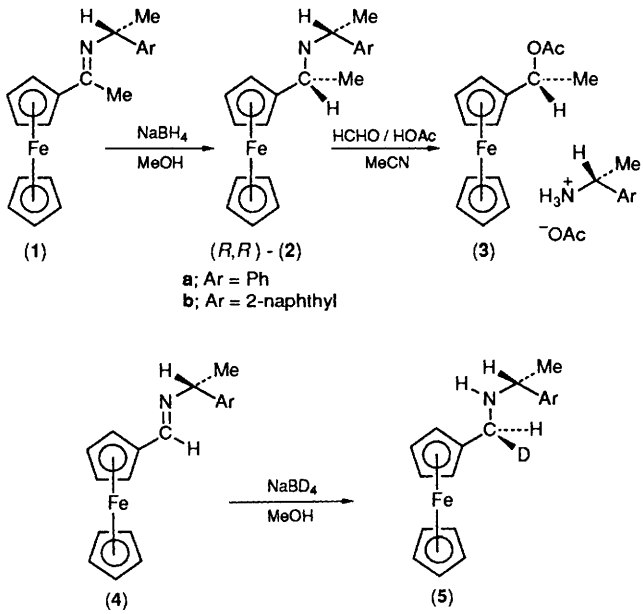
Dorothy M. David, Leon A. P. Kane-Maguire,* and Stephen G. Pyne*

Department of Chemistry, The University of Wollongong, PO Box 1144, Wollongong, NSW 2500, Australia

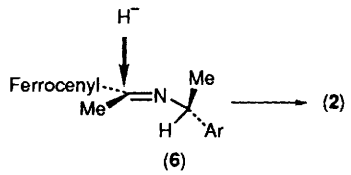
The imine formed from 1-acetylferrocene and (*R*)-(+)-1-phenylethylamine undergoes a highly diastereoselective reduction with sodium borohydride to give, after a single recrystallisation, diastereoisomerically pure (*R,R*) amine (**2a**), which has been converted to (*R*)-(−)-1-ferrocenylethyl acetate in high optical purity (>98%).

Chiral ferrocene derivatives are highly useful ligands for homogeneous asymmetric catalysis[1] and peptide synthesis.[2] They have been prepared using classical resolution techniques[3] and more recently by an enzymic kinetic resolution.[4] We now report an extremely efficient method for preparing 1-ferrocenylethyl acetate *via* a highly diastereoselective hydride reduction of the imine (**1**).

1-Acetylferrocene[5] was converted to the novel imine (**1a**) by treatment with (*R*)-(+)-1-phenylethylamine in the presence of 5Å molecular sieves and using diethyl ether as solvent.[6] The ^{1}H NMR spectrum of (**1a**) revealed that essentially (≥95%) a single geometric isomer had formed. Reduction of (**1a**) with sodium borohydride ($NaBH_4$) at 25°C in ethanol (Scheme 1) gave a 90 : 10 mixture of two diastereoisomeric amines. Simple recrystallisation of this mixture from light petroleum furnished, in 73% isolated yield, a diastereoisomerically pure material which was shown to have the (*R,R*) absolute stereochemistry depicted in (**2a**) by its conversion to (*R*)-(−)-1-ferrocenylethyl acetate (**3**).† Attempted reductive methylation of (**2a**) with sodium cyanoborohydride ($NaCNBH_3$) and formaldehyde in acetonitrile and acetic acid[7] gave a mixture of products in which the acetate (**3**) was the major component. When this reaction was repeated in the absence of $NaCNBH_3$, acetate (**3**) was obtained in 86% yield and high optical purity



† *Physical and spectral data* for (**2a**): m.p. 51—52 °C, $[\alpha]_D^{25}$ −18.8° (*c* 1.3, benzene); MS *m/z* 333 (M^+, 37%), 213 (100), 121 (42), 105 (76), 56 (44); satisfactory elemental analyses were obtained; ^{1}H NMR ($CDCl_3$) δ 7.35—7.27 (5H, m) 4.13 (3H, m) 4.07 (5H, s), 4.02 (1H, m) 3.82 (1H, q, *J* 6.7 Hz), 3.33 (1H, q, *J* 6.6 Hz), 1.39 (3H, d, *J* 6.7 Hz), 1.23 (3H, d, *J* 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 146.51, 128.31, 126.62, 93.82, 68.38, 67.94, 67.38, 66.90, 65.04, 55.37, 49.48, 25.38, 22.83.



(6)

{$[\alpha]_D^{25}$ −33.90° (*c* 1.05, ethanol); lit.[4] $[\alpha]_D^{25}$ −30.5° (*c* 1.3, ethanol)}.‡ This compound was determined to be >98% enantiomerically pure from ^{1}H NMR studies using chiral shift reagents. By analogy with previous work, the latter reaction is expected to involve nucleophilic addition of acetate ion to the 1-ferrocenylethyl carbocation with overall complete retention of configuration at the 1-ferrocenylethyl stereogenic centre.[8]

The 2-naphthyl analogue (**1b**) of (**1a**) also underwent stereoselective reduction with $NaBH_4$ to give (*R,R*)-(**2b**) as the major diastereoisomeric product (diastereoselectivity 90:10).

The imine (**4**) prepared from 1-formylferrocene[9] and (*R*)-(+)-1-phenylethylamine could only be obtained as a mixture of geometric isomers (*anti:syn* 80:20). Reduction of this mixture with $NaBD_4$, however, proceeded with apparent high diastereofacial selectivity, since an almost identical mixture (78:22) of diastereoisomeric amines (**5**) was obtained (Scheme 2). The stereochemical outcome of these reductions can be readily rationalized by attack of hydride on the conformation (**6**) (Scheme 3) in which allylic 1,3-strain is minimized.[10]

‡ The optical rotation of (**3**) must be measured immediately since (**3**) undergoes reaction with ethanol to give the corresponding ethyl ether quite rapidly.

In summary, a direct and highly diastereoselective method for the synthesis of chiral 1-ferrocenylethylamines and 1-ferrocenylethyl acetate has been developed. The latter is an immediate precursor to a host of enantiomerically pure 1-substituted ferrocenylethane derivatives.[8] The application of these compounds as reusable chiral templates for asymmetric synthesis is currently under investigation.

We thank the Australian Research Council for financial support.

Received, 15th March 1990; Com. 0/01155J

References

1 T. Hyshi, K. Kanehira, T. Hagihara, and M. Kumada, *J. Org. Chem.*, 1988, **53**, 113; S. D. Pastor and A. Togni, *J. Am. Chem. Soc.*, 1989, **111**, 2333; *Tetrahedron Lett.*, 1989, **30**, 1071.
2 I. Ugi, *Rec. Chem. Progr.*, 1969, **30**, 289.
3 D. Marquarding, H. Klysacek, G. Gokel, P. Hoffmann, and I. Ugi, *J. Am. Chem. Soc.*, 1970, **92**, 5389.
4 N. W. Boaz, *Tetrahedron Lett.*, 1989, **30**, 2061.
5 V. Weinmayr, *J. Am. Chem. Soc.*, 1955, **77**, 3009.
6 K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, 1971, **36**, 1570.
7 R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.
8 G. W. Gokel, D. Marquarding, and I. K. Ugi, *J. Org. Chem.*, 1972, **37**, 3052.
9 G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, 1958, 650.
10 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.