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Preliminary communication

Asymmetric synthesis of chiral amines via nucleophilic addition to ferrocenylalkyl substituted imines

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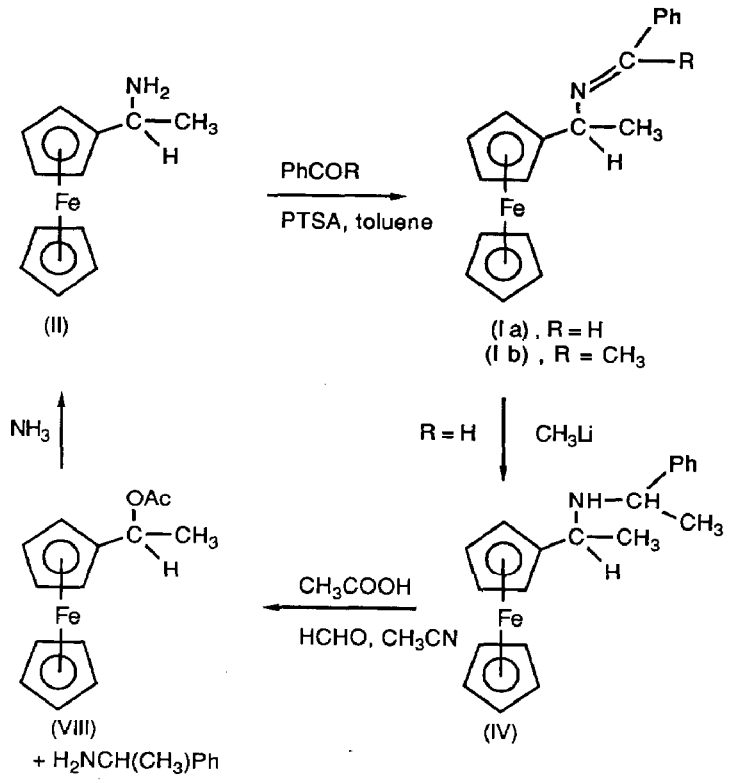
Abstract

The isomerically pure imine (**Ia**) formed from 1-ferrocenylethyl amine and benzaldehyde undergoes diastereoselective nucleophilic attack (Me^-, D^-) on the N=C double bond to give ca. 67/33 mixtures of diastereomeric amines. The stereochemical outcome can be rationalised in terms of nucleophilic attack on the conformation of **Ia** in which allylic 1,3-strain is minimised. The opposite stereochemistry is favoured in the reduction by hydride of the related imine (**Ib**) formed from 1-ferrocenylethyl amine and methylphenyl ketone. These processes provide a useful new method for the asymmetric synthesis of amines from which the chiral ferrocenyl auxiliary may be readily regenerated.

The asymmetric synthesis of chiral amines, including amino acid derivatives, attracts considerable current interest [1–3]. During an investigation of the use of chiral organometallic auxiliaries for such syntheses, we have devised a novel route to such amines involving the diastereoselective addition of nucleophiles to the imines (**Ia**, R = H; **Ib**, R = Me).

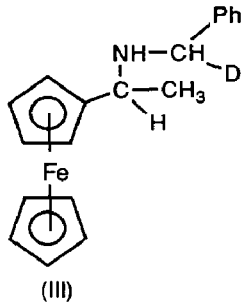
Imines **Ia** and **Ib** were obtained in almost quantitative yield by refluxing a solution of 1-ferrocenylethyl amine and benzaldehyde or methylphenylketone in toluene in the presence of *p*-toluenesulphonic acid as catalyst (Scheme 1). The ^1H NMR spectrum of imine **Ia** showed it to be essentially ($\geq 98\%$) one geometric isomer, assumed to be that depicted in Scheme 1.

Reduction of **Ia** with sodium borodeuteride in CD_3OD at room temperature gave the amine **III** as a 66 : 34 mixture of diastereomers. Similarly, addition of MeLi (THF, −78°C, then warmed to room temperature) to imine **Ia** gave a 67 : 33 mixture of two diastereomeric amines (**IV**) (Scheme 1). The major diastereomer was shown from its ^1H NMR spectrum [$CDCl_3$: 1.23 (3H, d, $J = 6.8$ Hz), 1.38 (3H, d, $J = 6.8$ Hz), 3.32 (1H, q, $J = 6.4$ Hz), 3.92 (1H, q, $J = 6.8$Hz), 4.02 (1H, m), 4.07 (5H, s) ppm; other signals masked by minor diastereomer] to be identical with the minor product (**Vb**) that we recently obtained [4] from the borohydride reduction of

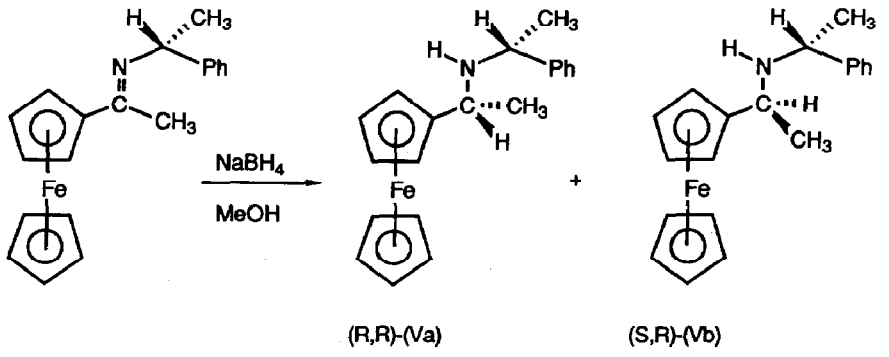


Scheme 1

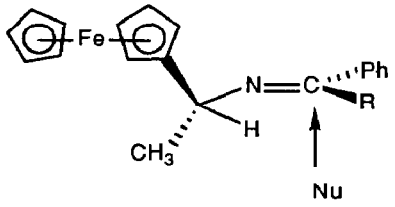
the related imine (**VI**) (Scheme 2). On the basis of the absolute stereochemistry established for **Vb**, the major (67%) diastereomer (**IVa**) can be identified as the enantiomeric $(S,R)/(R,S)$ pair.



Allylic 1,3-strain [5] in imine **Ia** is expected to be minimised in the conformation (**VII**; illustrated for the (*S*)-ferrocenyl alkyl case) with the H and R group eclipsed. The observed stereochemistry of methylation may therefore be explained in terms of attack by Me^- on the face of conformer **VII** (R = H) remote from the bulky ferrocenyl substituent. The lower stereoselectivity (67/33) in this reaction compared with that in the related reduction shown in Scheme 2 (ca. 95/5) may be associated with the greater distance of the bulky ferrocenyl group from the reaction centre in the former case.



Scheme 2



(VII)

The imine **Ib** (R = Me) was shown from its ^{1}H NMR spectrum to be a 91/9 mixture of geometric isomers, the major form being assumed to be that depicted in Scheme 1. Borohydride addition to this imine favours the formation of the (*R*,*R*)/(*S*,*S*) amine (**IVb**), i.e. the reverse stereochemistry to that noted above for **Ia** (R = H). This stereochemical outcome is also readily explicable in terms of attack by hydride on the conformer **VII** (R = Me).

Treatment of the amine product (**IV**) with an acetic acid/formaldehyde mixture in CH_3CN released the amine $H_2NCH(Me)Ph$ and regenerated the chiral ferrocenyl auxiliary as the acetate (**VIII**). This may be readily converted through known reactions [6] into the original 1-ferrocenylethyl amine. The sequence in Scheme 1 thus provides the basis for the asymmetric synthesis of amines from which the chiral auxiliary may be readily regenerated.

Further studies are in progress aimed at increasing the stereoselectivity in these processes, and extending their application to the asymmetric synthesis of other amines such as amino acid derivatives.

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References

1 R.M. Williams, P.J. Sinclair, D. Zhai and D. Chen, J. Am. Chem. Soc., 110 (1988) 1547 and references cited therein.

2 D.A. Claremon, P.K. Lumma and B.T. Phillips, ibid., 108 (1986) 8265 and references cited therein.
3 S.G. Pyne, P. Bloem and R. Griffith, Tetrahedron, 45 (1989) 7013 and references cited therein.
4 D.M. David, L.A.P. Kane-Maguire and S.G. Pyne, J. Chem. Soc., Chem Commun., in press.
5 R.W. Hoffmann, Chem. Rev., 89 (1989) 1841.
6 G.W. Gokel, D. Marquarding and I.K. Ugi, J. Org. Chem., 37 (1972) 3052.