Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 7, pp. 1027–1030, 1997

Printed in Great Britain
PII: S0957-4166(97)00092-X 0957-4166/97 $17.00 + 0.00

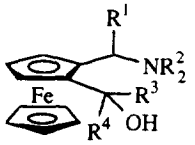
Lipase catalysed resolution of ferrocene cyanohydrin: access to novel ferrocenyl aminoalcohols and diamines

James A. S. Howell,[a,*] Kristina Humphries,[a] Patrick McArdle,[b] Desmond Cunningham,[b] Giovanni Nicolosi,[c] Angela Patti[c] and Martin A. Walsh[d]

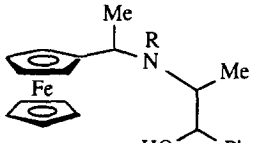
[a] Chemistry Department, Keele University, Keele, Staffordshire ST5 5BG, UK
[b] Chemistry Department, University College, Galway, Ireland
[c] Istituto CNR per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-farmaceutico, via del Santuario 110, 1-95028 Valverde CT, Italy
[d] European Molecular Biology Laboratory, c/o DESY, Notkestrasse 85, D-22603 Hamburg, Germany

Abstract: (R)-(+)-Ferrocene cyanohydrin acetate, obtained by enzymatic acylation of ferrocene cyanohydrin, may be transformed by reduction and alkylation into novel ferrocenyl β-aminoalcohols. Substitution of acetate by methanolic $HNMe_2$ proceeds with racemisation, but significant diastereoselection is observed on Strecker reaction using (−)-PhCH(Me)NHMe. © 1997 Elsevier Science Ltd

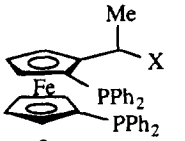
Amongst the many ferrocene-based ligands which have received recent attention as catalysts for asymmetric synthesis[1] are aminoalcohol derivatives of structures **1** and **2** which catalyse the enantioselective addition of dialkylzinc reagents to aldehydes.[2] Best case enantioselectivities for the two structural types are comparable (91–95% for reaction with PhCHO),[3] and debate continues over the relative importance of planar versus centrochirality. Additionally, phosphinated complexes of structure **3** function as ligands in a variety of asymmetric reactions, including Pd-catalysed alkylation and amination, Ag- and Au-catalysed aldol reactions, and Rh-catalysed hydrogenation.[4]



1



2 R = H, Me

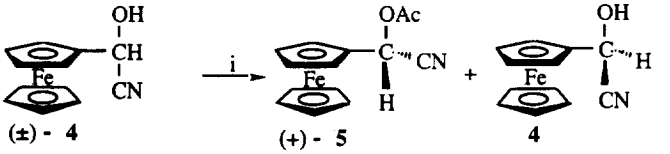


3

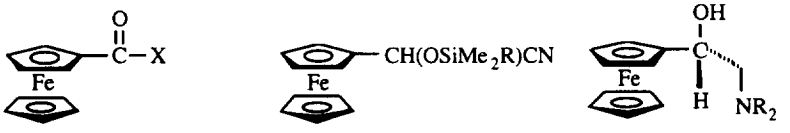
X=N(R)$(CH_2)_n$OH (n=2,3; R=H, Me)
X=N(R)CH_2CH_2N(R)Me (R=H, Me)

We wish to report that ferrocene cyanohydrin **4**[5] also provides access to novel β-aminoalcohols and diamines of possible catalytic interest. Lipase catalysed acylation of **4** to 50% completion provides, after chromatography, the acetate (+)-**5** of 84% e.e.[6] Recrystallisation provides material of >95% e.e. The substrate cyanohydrin was not isolated, decomposing slowly in solution and rapidly on chromatography [silica, alumina (grades I to IV)] to regenerate aldehyde **6** and small amounts of the acid cyanide **7**.[7] Chromatographic stability is markedly enhanced in the protected silyl derivatives **8** and **9**.[8] Assignment of the (R) configuration has been confirmed by X-ray crystal structure determination,[9] and is consistent with the results of lipase catalysed resolutions of organic cyanohydrins.[10]

* Corresponding author.

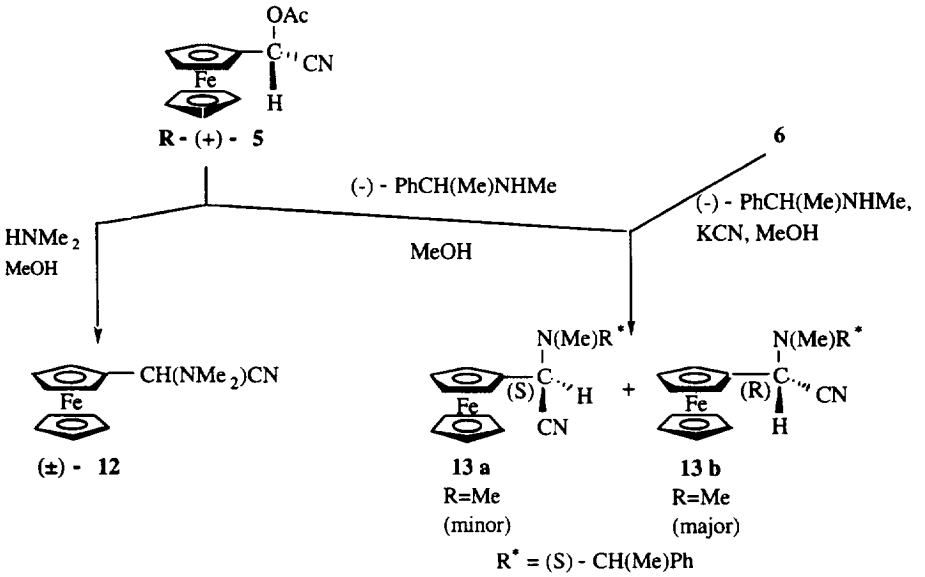


(i) *Pseudomonas cepacia*, vinyl acetate, 3 days



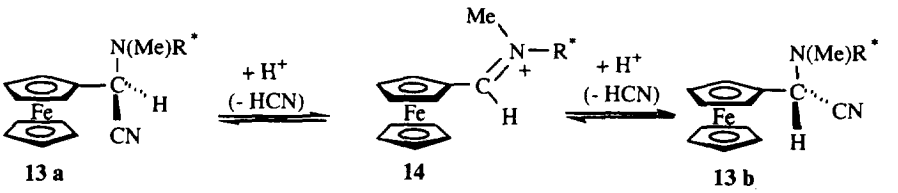
Reduction of (+)-**5** to (−)-**10**[11] followed by reductive dimethylation[12] gives (+)-**11** without loss of enantiomeric purity. The complex functions as an active catalyst for addition of Et_2Zn to benzaldehyde to give (S)-PhCH(OH)Et (360 minutes for 86% yield, <1% formation of $PhCH_2OH$, 33% e.e.). Structural modifications are currently in progress with a view to improving the enantioselectivity.

In view of the well established stereospecific retention of configuration on reaction of 1-ferrocenylethyl acetate with methanolic Me_2NH,[13] it is surprising to note that reaction of (+)-**5** under these conditions to give **12** gives **racemic** product **12**.

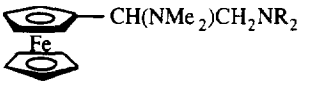


Reaction of (+)-**5** with (S)-(−)-PhCH(Me)NHMe[14] or a Strecker reaction[15] using **6** both yield a 1:2 mixture of the diastereoisomer pair **13a,b** from which **13a** may be isolated by crystallisation and shown to have the (S) configuration by X-ray crystal structure determination.[16]

Experiments with isolated **13a** show that it undergoes a rapid proton catalysed epimerisation in MeOH[17] to regenerate the 2:1 equilibrium mixture, a result which is most consistent with reversible dissociation to generate the iminium cation intermediate **14**.



The ready dissociation is no doubt enhanced by the well documented ability of the metal to stabilise positive charge in the α-position. This rapid epimerisation/racemisation process raises the possibility of a dynamic resolution of complexes such as **12**, which we are currently pursuing. Complex **12** may be reduced and reductively alkylated to the novel diamines **15** and **16**; we are currently extending this to single diastereoisomers of **13**.



(±) - **15** R = H

(±) - **16** R = Me

Acknowledgements

We thank Amano Chemical Corporation for the gracious gift of lipase enzymes.

References

1. A. Togni, T. Hayashi (editors), *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*, VCH, Weinheim, **1995**.
2. (a) G. Nicolosi, A. Patti, R. Murrone, M. Piatelli, *Tetrahedron: Asymmetry*, **1994**, *5*, 1639–42; (b) M. Watanabe, N. Hashimoto, S. Araki, Y. Butsugan, *J. Org. Chem.*, **1992**, *57*, 742–44; (c) M. Watanabe, S. Araki, Y. Butsugan, *J. Org. Chem.*, **1991**, *56*, 2218–24; (d) M. Watanabe, *Synlett*, **1995**, 1050–52; (e) M. Watanabe, *Tetrahedron Lett.*, **1995**, *36*, 8991–94; (f) M. Watanabe, S. Araki, Y. Butsugan, *Chem. Express*, **1990**, *5*, 661–64; (g) M. Watanabe, S. Araki, Y. Butsugan, *Chem. Express*, **1989**, *4*, 825–28.
3. (a) M. Watanabe, M. Uemura, N. Araki, Y. Butsugan, *Chem. Abstr.*, **1993**, *118*, 233625; (b) M. Watanabe, M. Uemura, N. Araki, Y. Butsugan, *Chem. Abstr.*, **1991**, *115*, 256398.
4. For reviews, see (a) Y. Butsugan, S. Araki, M. Watanabe, reference 1, pp. 143–69; (b) M. Sawamura, Y. Ito, *Chem. Rev.*, **1992**, *92*, 857–71; (c) T. Hayashi, *Pure Appl. Chem.*, **1988**, *60*, 7–12.
5. P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, G. M. Whitman, *J. Am. Chem. Soc.*, **1957**, *79*, 3416–21.
6. In a typical acylation (±)-**4** (1.6 g) and *Pseudomonas cepacia* lipase (1.6 g, Amano) were shaken in distilled, N_2 degassed vinyl acetate (35 ml) until NMR analysis of an aliquot (using C*H* resonances in $CDCl_3$ at 5.23 ppm and 6.25 ppm for **4** and **5** respectively) indicated 50% completion. After filtration and evaporation, the residue was chromatographed on 15% deactivated Al_2O_3 using 1:1 CH_2Cl_2: petroleum ether (40–60). Complex **5** eluted as the first orange band [0.74 g, 82%, NMR (C_6D_6): 3.97 (s, C_5H_5), 4.40, 4.05, 3.85, 3.78 (multiplets, C_5H_4), 6.17 (s, CH), 1.33 (s, OAc)]. Elution of a second orange–red band provided the aldehyde **6**. Enantiomeric excess was determined by integration of the OAc resonance in the presence of tris[(heptafluoropropylhydroxymethylene)-(+)-camphorato] Eu(III). Recrystallization from diethyl ether/petroleum ether (40–60) gave material with >95% e.e. and $[\alpha]_D^{25}$ +74 (c 2×10^{-3}, CH_3CN).
7. Identified by comparison with an authentic sample prepared from ferrocene carboxylic acid: K. Shimada, S. Orii, M. Tamaka, T. Nambara, *J. Chromatography*, **1986**, *352*, 329–35.

8. Prepared by reaction of (±)-**4** with RMe_2SiCl/imidazole/DMF: J. Brussee, W. T. Loos, C. G. Kruse, A. van der Gen, *Tetrahedron*, **1990**, *46*, 979–86. The acetate **5** exhibits no reaction under these conditions.
9. (R)-(+)-**5**: monoclinic, space group C2, a=20.799(3), b=7.4882(7), c=16.7000(10) Å, β=94.710(10)°, Z=8, R_1=0.0610, R_2=0.1709 for 361 parameters and 2825 observed reflections, absolute structure parameter=0.01(4).
10. For a review, see F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 1555–64.
11. $LiAlH_4$, 80%: K. Yamakawa, R. Sakaguchi, K. Osumi, *Chem. Pharm. Bull.*, **1974**, *22*, 576–82; (−)-(**10**): $[\alpha]_D^{25}$ −15 (c 2×10^{-3} ,CH_3CN).
12. $NaBH_3CN/ZnCl_2$/HCHO, 75%: S. Kim, C. H. Oh, J. S. Ko, K. H. Ahn, Y. J. Kim, *J. Org. Chem.*, **1985**, *50*, 1927–32; (+)-**11**: $[\alpha]_D^{25}$ +42 (c 3×10^{-3}, CH_3CN).
13. (a) Y. Matsumoto, A. Ohno, S. Lu, T. Hayashi, N. Ogoni, M. Hayashi, *Tetrahedron: Asymmetry*, **1993**, *4*, 1763–66; (b) G. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.*, **1972**, *37*, 3052–58.
14. H. Brunner, T. Scheck, *Chem. Ber.*, **1992**, *125*, 701–09.
15. C. R. Hauser, J. K. Lindsay, *J. Org. Chem.*, **1957**, *22*, 906–908.
16. **3a** $[\alpha]_D^{25}$ −85 (c 2×10^{-3}, CH_3CN); orthorhombic, space group $P2_12_12_1$, a=6.001 (3), b=12.107 (4), c=22.995 (5) Å, Z=4, R_1=0.0292, R_2=0.0718 for 219 parameters and 8936 observed reflections, absolute structure parameter=0.083 (10).
17. For **13a**⇌**13b**, K_{eq}=1.84, $k_1=1.25\times10^{-3}$ s^{-1}, $k_{-1}=6.78\times10^{-4}$ s^{-1} in MeOH; rate constants in benzene are $k_1=3.86\times10^{-6}$ s^{-1}, $k_{-1}=2.12\times10^{-6}$ s^{-1}.

(Received in UK 17 February 1997)