Pergamon

Tetrahedron: Asymmetry Vol 5, No. 7, pp. 1275-1280, 1994

0957-4166/94 $7.00+0.00

0957-4166(94)00177-4

Enzyme-promoted Kinetic Resolution of 1-Hydroxymethyl-2-dimethylaminomethylferrocene

Giovanni Nicolosi,* Angela Patti, Raffaele Morrone and Mario Piattelli

Istituto per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico
Via del Santuario 110, I-95028 Valverde CT, Italy

Abstract: Both enantiomers of 1-hydroxymethyl-2-dimethylaminomethylferrocene have been obtained in high enantiomeric excess by lipase-mediated irreversible acetylation using vinyl acetate as acyl donor.

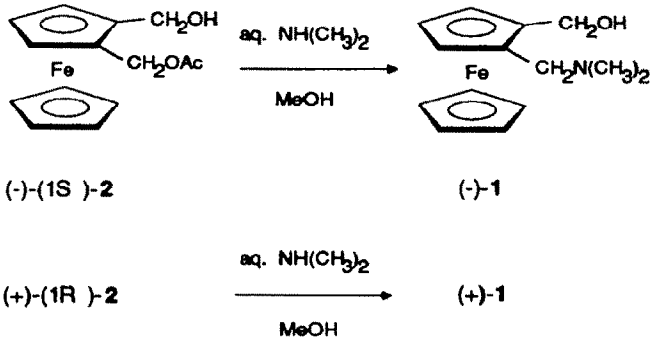
Introduction

Enantioselective addition of organometallic reagents to aldehydes, mediated by a variety of chiral auxiliaries such as aminoalcohols and diamines, has recently been developed as an important tool in synthetic organic chemistry.[1a,b] Many chiral catalysts providing in some cases a high degree of stereocontrol have been employed, among which are some homoannularly disubstituted ferrocenyl aminoalcohols, all possessing central and planar chirality at the same time.[2a-c] Schlögl *et al.* proposed that in these catalysts centrochirality dominates over planar chirality in determining the sense of asymmetric induction.[2c] To shed light on this question and, at the same time, develop effective catalysts stucturally more simple than those until now proposed, we resolved to study the preparation of enantiopure ferrocenyl aminoalcohols possessing just a plane or a center of asymmetry. Since enzymatic trasformations have become attractive for the preparation of nonracemic chiral compounds, including organometallics,[3a-m] we examined the possibility of obtaining the desired ferrocenyl derivatives *via* lipase-catalysed resolution of racemates.

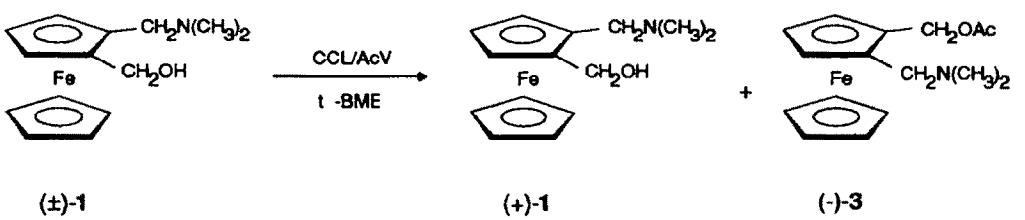
Here we wish to report the lipase-catalysed kinetic resolution of the planar chiral (±)-1-hydroxymethyl-2-dimethylaminomethylferrocene providing both enantiomers with excellent enantiomeric excess.

Results and Discussion

At the onset of the present work, reference samples of both enantiomers of 1-hydroxymethyl-2-dimethylaminomethylferrocene **1** were prepared in enantiomeric excess from the reaction of dimethylamine with (–)-(1*S*)- and (+)-(1*R*)-1-hydroxymethyl-2-acetoxymethylferrocene **2**, obtained from *meso*-1,2-bis(hydroxymethyl)ferrocene *via* enzymatic desymmetrization and avalaible from



previous work.[4] However, this procedure is not valid for preparative purposes, since 1,2-bis(hydroxymethyl)ferrocene has been synthesized from racemic **1** through *N*-methylation with methyl iodide followed by treatment with base.[5] Therefore, direct resolution of **1** appeared the best route to the target molecules. To this end, in initial experiments racemic **1** dissolved in toluene was subjected to enzyme catalysed transesterification with vinyl acetate as acyl donor in the presence of a lipase as catalyst. The acetate formed was analysed by ^{1}H-NMR spectroscopy in the presence of a chiral shift reagent to determine configuration and enantiomeric excess. From the results summarized in Table 1 it is readily apparent that *Pseudomonas cepacia* lipase (PSL) and porcine pancreatic lipase (PPL) both gave products with very poor, if any, enantiomeric excess; hence these enzymes were not investigated



further. The remaining lipases, immobilized *Mucor miehei* lipase (Lypozyme®), immobilized *Candida antarctica* lipase (Novozym 435®) and *Candida cylindracea* lipase (CCL), all gave products with significant enantiomeric excess. Remarkably, Lipozyme® yielded the *R* isomer, while Novozym 435® and CCL afforded the *S* isomer. At this point in order to optimize the conditions and enhance the e.e.'s,

the three active lipases were tested in different solvents (hexane, *tert*-amyl alcohol, diisopropyl ether, *tert*-butylmethyl ether). *Tert*-butylmethyl ether (*t*-BME) proved to be the best one, since the e.e. was increased from 20 to 38% when Novozym 435® was used, and from 60 to 92% in the CCL-catalysed reaction. Therefore, CCL in *t*-BME was selected for the kinetic resolution of (±)-**1** in larger scale. A run in which the reaction was quenched after 13 h, when conversion reached 42%, gave monoester (–)-**3** with 92% e.e., that upon alkaline hydrolysis yielded (–)-**1** without any loss of enantiomeric excess. The

Table 1. Enzyme mediated esterification of (±)-1-hydroxymethyl-2-dimethylaminomethylferrocene[a]

Catalyst	Solvent	Time(h)	Conversion[b] (%)	e.e.[c] (%)	Configuration
PSL	Toluene	48	12	0	--
PPL	Toluene	48	28	0	--
Lipozyme®	Toluene	40	40	35	1*R*
Lipozyme®	*t*-BME[d]	0.5	30	36	1*R*
Novozym 435®	Toluene	12	38	20	1*S*
Novozym 435®	*t*-BME	4	40	38	1*S*
CCL	Toluene	13	42	60	1*S*
CCL	*t*-BME	13	42	92	1*S*

[a]Experimental conditions: substrate 40 mg in 2 ml of solvent, vinyl acetate (5 molar equivalents), enzyme 60 mg/ml, 45 °C, 300 rpm. [b]Determined by HPLC. [c]Determined by ^{1}H-NMR in the presence of Pirkle's alcohol. [d]*t*-BME=*tert*-butylmethylether

enantiomer (+)-**1** was obtained in still better e.e. (>95%; chemical yield 32%) by prolonging the reaction time until the desired conversion (65% after 22 h) was reached.

In view of the known reversibility under appropriate conditions of the lipase catalysed reactions and the enantio-complementary nature of esterification and hydrolysis (or alcoholysis), we considered the "deacylation approach" as an alternative procedure to obtain (–)-**1** with high e.e. Since (±)-**3** is rather unstable in aqueous media,[6] we resorted to alcoholysis and accordingly (±)-**3** in *t*-BME was submitted to reaction with *n*-butanol in the presence of CCL as catalyst. After an incubation period of 48 h, (–)-**1** was isolated in good chemical yield (40%) and excellent enantiomer excess (e.e. >95%).

In conclusion, this report shows that biocatalysed transesterification is an effective route for the preparation of both enantiomers of a metallocene possessing only planar chirality, 1-hydroxymethyl-2-dimethylaminomethylferrocene, whose catalytic properties, currently under investigation, will be reported elsewhere. It is worth noting that **1** has structural features that allows access to a variety of homochiral ferrocenyl derivatives.[7] To this end, both functional groups can be manipulated in many ways and, in addition, the substituted ring can be metallated with butyllithium at the position adjacent to the dimethylaminomethyl group.[8a,b] Condensation of the resulting lithiated derivative with electrophilic compounds will lead to 1,2,3-trisubstituted ferrocenes with predetermined planar chirality.[9]

Experimental

General methods. ^{1}H- and ^{13}C-NMR were recorded at 250.13 and 62.9 MHz respectively in $CDCl_3$, unless otherwise stated, on a Bruker AC 250 spectrometer. Optical rotations were measured with a Jasco DIP-370 polarimeter. HPLC analyses were carried out on a Varian instrument fitted with an UV detector set at 250 nm using a Hypersil ODS column (150 x 4.6 mm) and mixtures of MeOH and 0.02M triethylammonium acetate buffer (pH 5) as eluent.

Materials. Lipozyme® (immobilized lipase from *Mucor miehei*) and Novozym 435® (immobilized lipase from *Candida antarctica*) are registered marks from Novo Nordisk. Lipase from *Candida cylindracea* (CCL) and porcine pancreatic lipase (PPL) were purchased from Sigma Chemical Co. Lipase from *Pseudomonas cepacia* (PSL) was obtained from Amano International Enzyme Co. All reagents were analytical grade. 1-Hydroxymethyl-2-dimethylaminomethylferrocene (±)-**1** was prepared according to the literature procedure[5] and its spectroscopic properties agreed with those reported.[10] Column chromatography was performed on LiChroprep Si Diol 40-63 μm (Merck). (–)-(*R*)-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle's alcohol) used as chiral shift agent was from Aldrich.

Reaction of 1-hydroxymethyl-2-acetoxymethylferrocene with dimethylamine. (–)-(1*S*)-1-Hydroxymethyl-2-acetoxymethylferrocene (–)-**2** (60 mg, e.e. 95%) was treated with aqueous dimethylamine (0.25 mL) in methanol (1 mL) at 45 °C for 2 h affording, after separation of the reaction mixture by column chromatography, (–)-(1*S*)-1-hydroxymethyl-2-dimethylaminomethylferrocene (–)-**1** (25 mg, 44% yield), $[\alpha]_D$ -30.5 (*c* 1.25, $CHCl_3$), e.e. 90%, and 1,2-bis(hydroxymethyl)-ferrocene (23 mg). The enantiomeric (+)-(1*R*)-1-hydroxymethyl-2-dimethylaminomethylferrocene (+)-**1**, prepared from (+)-(1*R*)-1-hydroxymethyl-2-acetoxymethylferrocene (+)-**2**, had $[\alpha]_D$ +29.8 (*c* 1.3, $CHCl_3$), e.e. 88%.

Preliminary experiments of enzymatic acylation. Racemic aminoalcohol (±)-**1** (40 mg) was dissolved in the solvent of choice (2 mL) and vinyl acetate (34 μL/mL) and lipase (120 mg) were added. The suspension was shaken in a stoppered vial at 45 °C under 300 rpm. The conversion of substrate was monitored by HPLC and the reaction was stopped at the times reported in table 1 by filtering out the enzyme. Column chromatography of the residue (gradient of *n*-hexane/ethyl acetate as eluent) gave unreacted aminoalcohol and its acetate. Enantiomeric excesses were measured by ^{1}H-NMR analysis in the presence of Pirkle's alcohol using the integrated areas of the resonances for each enantiomer relative to the unsubstituted cyclopentadienyl rings (Cp') or the dimethylamino groups. Also the singlets for the acetate group appear at distinctly different fields.

Lipase catalysed esterification of compound (±)-1. CCL (1.2 g) and vinyl acetate (0.68 mL) were added to a solution of (±)-**1** (400 mg, 1.46 mmol) in *t*-BME (20 mL) and the mixture incubated as above. When the conversion of the substrate was about 45% the reaction was quenched removing the enzyme by filtration and the filtrate dried in vacuo. Column chromatography of the residue afforded (–)-(1*S*)-1-acetoxymethyl-2-dimethylaminomethylferrocene [(–)-**3**; 175 mg, 38% yield], $[\alpha]_D$ -17.9 (*c* 2, $CHCl_3$), e.e. 92%. IR ν_{max} 3016, 2987, 2781, 2360, 1732, 1373, 1251, 1106, 1039. ^{1}H-NMR: δ

2.02 (s, 3H, CH_3CO-), 2.16 (s, 6H, -$N(CH_3)_2$), 3.24 and 3.39 (AB system, d, J=13.0 Hz, each 1H, -$CH_2N(CH_3)_2$), 4.09 (s, 5H, Cp'), 4.17 (t, 1H, J=2.5 Hz, Cp), 4.28 and 4.30 (m, each 1H, Cp), 4.94 (s, 2H, -CH_2OAc). This last signal appears as an AB system in CD_3OD (δ 4.77 and 4.88, d, J= 12.2 Hz, each 1H,) and in C_6D_6 (δ 4.94 and 5.07, J=12.2 Hz, each 1H). ^{13}C-NMR: δ 20.94 (CH_3CO-), 44.89 (-$N(CH_3)_2$), 56.92, 61.04, 67.85, 68.11, 69.97, 71.06, 81.00, 83.89, 170.86 (CH_3CO-). In addition, unreacted (+)-**1** (180 mg, 45% yield) was recovered with an optical purity of 75%.

Alkaline hydrolysis (NaOH in ethanol) of (–)-**3** (50 mg, 92% e.e.) afforded (–)-**1** (34 mg, 80% yield), $[\alpha]_D$ -31.4 (*c* 1.7, $CHCl_3$).

In a run with an incubation period of 22 h (conversion 65%) the unconverted (+)-**1** (125 mg, 32% yield) was recovered with excellent enantiomer excess (e.e >95%), $[\alpha]_D$ +32.9 (*c* 1.2, $CHCl_3$).

Alcoholysis of 1-acetoxymethyl-2-dimethylaminomethylferrocene (±)-3. Compound (±)-**3** (150 mg, 0.48 mmol), obtained by conventional chemical acetylation of (±)-**1**, was dissolved in *t*-BME (7.5 mL) containing *n*-BuOH (0.25 mL) and CCL (450 mg) was added. The reaction was carried out at 45 °C for 48 h (conversion of substrate 42%). Work up of the reaction mixture gave 60 mg (40% yield) of optically pure (–)-**1** (e.e >95%), $[\alpha]_D$ -32.5 (*c* 1.5, $CHCl_3$).

Acknowledgments.

Authors thank CNR Progetto "Chimica Fine e Secondaria". Thanks are due to Novo Nordisk for generous supplies of Lipozyme® and Novozym 435®.

References and notes

1. a) R. Noyori and M. Kisamura *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 and refs. therein. b) K. Soai and S. Niwa *Chem. Rev.* **1992**, *92*, 833 and refs. therein.

2. a) M. Watanabe, S. Araki and Y. Butsugan *J. Org. Chem.* **1991**, *56*, 2218. b) M. Watanabe, N. Hashimoto, S. Araki and Y. Butsugan *J. Org. Chem.* **1992**, *57*, 742. c) H. Wally, M. Widhalm, W. Weissensteiner and W. K. Schlögl *Tetrahedron: Asymmmetry* **1993**, *4*, 285.

3. a) A. D. Ryabov *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 931 and refs. therein. b) T. Izumi and S. Aratani *J. Chem. Techn. Biotechnol.* **1993**, *57*, 33. c) Y. Yamazaki and H. Kobayashi *Tetrahedron: Asymmmetry* **1993**, *4*, 1287. d) Y. Yamazaki, A. Maruyama, K. Hosono, T. Higashihara and H. Kobayashi *Z. Naturforsch.* **1993**, *48c*, 451. e) B. Malézieux, G. Jaouen, J. Salaun, J. A. S. Howell, M. G. Palin, P. McArdle, M. O'Gara and D. Cunningham *Tetrahedron: Asymmmetry* **1992**, *3*, 275. f) J. A. S. Howell, M. G. Palin, G. Jaouen, S. Top, H. El Hafa and J. M. Cense *Tetrahedron:*

Asymmmetry **1993**, *4*, 1241. h) C. Baldoli, S. Maiorana, G. Carrea and S. Riva *Tetrahedron: Asymmmetry* **1993**, *4*, 767. i) M. Uemura, H. Nishimura, S. Yamada, K. Nakamura and Y. Hayashi *Tetrahedron Lett.* **1993**, *34*, 6581. l) D. Lambusta, G. Nicolosi, A. Patti and M. Piattelli *Tetrahedron: Asymmetry* **1993**, *4*, 919. m) G. Nicolosi, A. Patti and M. Piattelli *J. Org. Chem.* **1994**, *59*, 251.

4. G. Nicolosi, R. Morrone, A. Patti and M. Piattelli *Tetrahedron: Asymmetry* **1992**, *3*, 753.

5. C. Moise and J. Tirouflet *Bull. Soc. Chim. Fr.* **1969**, *4*, 1182.

6. G. W. Gokel, D. Marquading and I. K. Ugi *J. Org. Chem.* **1972**, *37*, 3052.

7. G. Marr, B. W. Rockett and A. Rushworth *J. Organomet. Chem.* **1969**, *16*, 141.

8. a) D. W. Slocum, B. W. Rockett and C. R. Hauser *J. Am. Chem. Soc.* **1965**, *87*, 1241. b) D. Marquading, H. Klusacek, G. Gokel, P. Hoffmann and I. Ugi *J. Am. Chem. Soc.* **1970**, *92*, 5389.

9. N. Deus, G. Hübener and R. Herrmann *J. Organomet. Chem.* **1990**, *384*, 155.

10. The ^{13}C-NMR spectrum, previously unreported, displays resonances at δ 44.38, 58.27, 60.03, 65.34, 68.82, 69.55, 70.58, 84.46, 87.66.

(*Received in UK* 5 *April* 1994; *accepted* 23 *May* 1994)