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Enzymatic resolution of (±)-1-ferrocenylethylamine

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Abstract

(±)-1-Ferrocenylethylamine was resolved by a highly enantioselective acetylation catalyzed by *Candida antarctica* B lipase.

Over the last few years, ferrocene-based chiral compounds have gained a growing interest due to their usefulness as catalysts and reagents for asymmetric reactions.[1] In particular, among the molecules containing the ferrocene substructure, chiral ferrocenylalkylamine derivatives have proved to be highly efficient ligands in homogeneous asymmetric catalysis[2] and as precursors of optically active ferrocenyl compounds exhibiting planar chirality.[3] However, few concise asymmetric syntheses of ferrocenylalkylamines have been described, most of such preparations involving several steps. While in some of the reported preparations the stereoselectivity was attained through the asymmetric reduction of an imine bearing a chiral auxiliary[4] or by the diastereoselective alkylation of an optically active hydrazone,[5] in other more complex syntheses optically active 1-ferrocenylalkanols were prepared as precursors of 1-ferrocenyl-*N*,*N*-dimethylalkylamines.[6]

In recent years, we have been investigating the possibilities of enantioselective lipase-catalyzed aminolysis for the resolution of nitrogen-containing compounds, and this biotransformation has proved to be a simple and useful access to optically active amines, amides, carbamates and esters.[7] Taking into account the remarkable simplicity and efficiency of this enzymatic procedure, we decided to try the resolution of (±)-1-ferrocenylethylamine **1** using *Candida antarctica* B lipase (CAL-B) as the biocatalyst, due to its well-documented performance.[7]

In a first approach to the resolution of (±)-**1**,[8] the enzymatic aminolysis was carried out at 28°C and 200 rpm using ethyl acetate **2a** as the acylation reagent and the solvent (Scheme 1), and the biotransformation was studied at different reaction times.[9] In every case, after removal of the biocatalyst, the remaining amine (*S*)-**1** was isolated as its ammonium salt (*S*)-**4**, formed by treatment of the reaction mixture with 3N HCl (Scheme 1), and the product (*R*)-**3a** was purified by flash chromatography. Results collected in Table 1 (entries 1–3) reveal that CAL-B is an efficient catalyst for the resolution of (±)-**1** displaying a high enantioselectivity ($E > 200$),[10] the substrate

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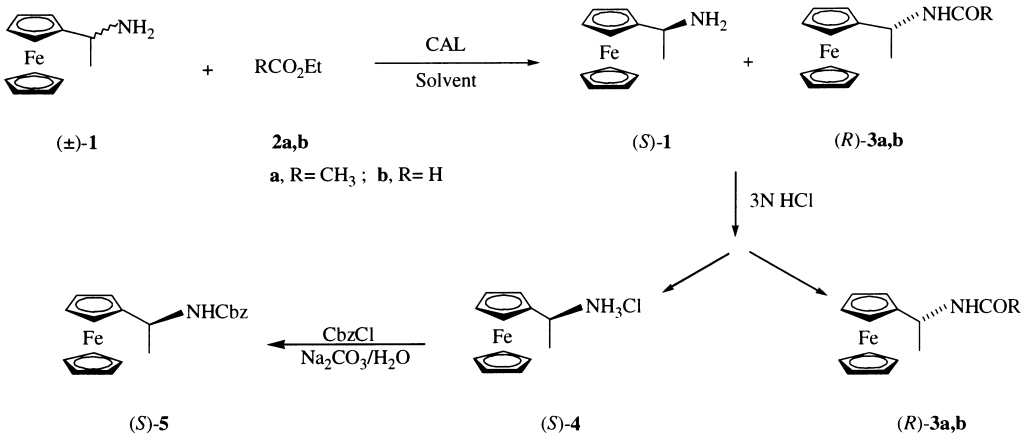

Scheme 1.

Table 1
CA lipase-catalyzed resolution of (±)-1-ferrocenylethylamine[a]

Entry	Acyl donor	Solvent	t, h	Amine (*S*)-**1** ee[b] (%)	Amide (*R*)-**3** ee[b] (%)	conv.[c] (%)	*E*[c]
1	**2a**	**2a**	2.5	52	99	34	> 200
2	**2a**	**2a**	5	71	99	42	> 200
3	**2a**	**2a**	12	87	98	47	> 200
4	**2b**[d]	1,4-dioxane	3	63	88	42	29
5	**2b**[e]	1,4-dioxane	24	> 99	63	61	30

[a] Typical procedure: see ref. 9. [b] For determination, see text. [c] See ref. 10. [d] **2b** (0.4 mL). [e] **2b** (0.8 mL).

(*S*)-**1** and the amide (*R*)-**3a** being obtained with high enantiomeric excesses even at high conversion (entry 3). In each case, the enantiomeric excesses of (*S*)-**1** and (*R*)-**3a** were determined by HPLC analysis using a Chiralcel-OD column; prior to the analysis, it was necessary to convert (*S*)-**1** into its Cbz-derivative (*S*)-**5**[11] (Scheme 1).

The configuration of the unreacted amine (*S*)-**1** was assigned by comparison of the sign of its specific rotation $\{[\alpha]_D^{20}$ +18.0 (*c* 2.7, EtOH) 87% ee} with reported data for this compound.[2c] Moreover, the comparison of the specific rotation obtained for (*R*)-**3a** $\{[\alpha]_D^{22}$ −86.5 (*c* 1.0, PhH) 99% ee} with that reported[5a] confirms the assignment.

The high enantioselectivity obtained in the acetylation described above prompted us to study the resolution by changing the acyl donor, and we chose ethyl formate **2b** because the formamide **3b** formed in the course of the biotransformation is a suitable precursor of optically active *N*-methyl-substituted ferrocenylethylamine. Prior to the enzymatic formylation, control experiments carried out in the absence of the lipase showed no appreciable conversion.

Two experiments were performed at different ethyl formate/amine ratios (Table 1, entries 4 and 5), using in both cases 1,4-dioxane as the solvent, due to its usefulness in enzymatic aminolysis processes.[7e] Results show that even though enzymatic formylations were carried out with a lower acyl donor content than the acetylation, they proceeded faster; however, a lower enantioselectivity was obtained ($E = 30$). After work-up of the reaction mixtures, which afforded

unreacted (*S*)-**1** isolated as its salt (*S*)-**4**, and amide (*R*)-**3b**, the enantiomeric excess of the former was again determined through HPLC analysis of its Cbz-derivative (*S*)-**5**. As attempts to analyze (*R*)-**3b** by HPLC using a Chiralcel-OD and a Chiralcel-OD-H column were unsuccessful, the formamide was then hydrolyzed with 1N KOH (reflux, 2 h) and the resulting amine (*R*)-**1** converted into its Cbz-derivative (*R*)-**5**.[12] Analysis of the specific rotation of the recovered amine (*S*)-**1** $\{[\alpha]_D^{20}$ +22.3 (*c* 3.0, EtOH) >99% ee$\}$ and of (*R*)-**5** $\{[\alpha]_D^{22}$ −24.5 (*c* 1.0, EtOH) 88% ee$\}$ allowed assignment of the absolute configurations.[13]

In the acylations studied here, CAL-B shows a preference towards the (*R*)-enantiomer of the racemic amine, which is in agreement with the behaviour displayed by this biocatalyst in previous reports by us.[7]

In summary, in this paper we describe a simple, efficient and concise method for the resolution of (±)-1-ferrocenylethylamine. The straightforward procedure presented herein appears as a convenient methodology to be extended to the preparation of other optically active ferrocenylalkylamines.

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9. In a typical procedure, CAL-B (75 mg) was added to a solution of (±)-**1** (2.5 mmol) in **2a** (8 mL) and the resulting mixture was shaken at 28°C and 200 rpm. When reaction times indicated in Table 1 were reached the lipase was filtered off, washed with dichloromethane and the resulting filtrate subjected to the work-up depicted in Scheme 1.
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11. Satisfactory spectral data were obtained for amides (*R*)-**3a**,**b** and for the new compound (*S*)-**5**: mp 71–73°C (from chloroform–*n*-hexane); $[\alpha]_D^{20}$ +28.3 (*c* 1.0, EtOH) >99% ee; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.49 (d, $J=7$ Hz, 3H, CH_3), 4.14–4.20 (m, 9H, $C_{10}H_9$), 4.62–4.69 (m, 1H, $CHCH_3$), 4.95 (s, 1H, NH), 5.15 (s, 2H, $CH_2C_6H_5$), 7.33–7.42 (m, 5H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3 (CH_3), 45.5 ($CHCH_3$), 65.7, 66.5, 67.0, 67.6, 67.9, 68.4, 91.5 ($C_{10}H_9$, CH_2Ph), 128.0 (CH, C_6H_5), 128.4 (CH, C_6H_5), 136.5 (C, C_6H_5), 155.3 (CO). Anal. calcd for $C_{20}H_{21}FeNO_2$: C, 66.11; H, 5.83; N, 3.86. Found: C, 65.73; H, 6.14; N, 3.79.

12. Conditions for chiral-HPLC (Chiralcel-OD column, hexane:propan-2-ol 90:10, 1 mL/min, 210 nm): for (±)-**5**, two peaks: t_R 11.56 and 18.72 min, $R_s = 4.7$; for (*S*)-**5**, t_R 11.51 min; for (*R*)-**5**, t_R 18.35 min. For (±)-**3a**, two peaks: t_R 12.26 and 18.77 min, $R_s = 3.7$; for (*R*)-**3a**, t_R 19.09 min.
13. As the specific rotation value determined for (*R*)-**3b** $\{[\alpha]_D^{22} +13.5$ (*c* 1.2, EtOH) 88% ee$\}$ differed from reported data (El-Shihi, T.; Siglmuller, F.; Herrmann, R.; Carvalho, M. F.; Pombeiro, A. J. L. *J. Organomet. Chem.* **1987**, *335*, 239), its configuration was confirmed through the specific rotation of (*R*)-**5**.