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# Enantiospecific Conversion of (*S*)-Alanine to (*R*)-α-Methyl Phenylalanine

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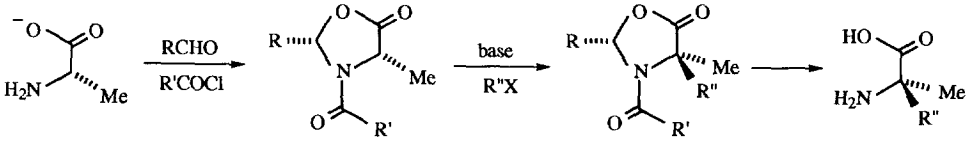
**Abstract:** Based on the strategy of self-reproduction of chirality, a practical enantiospecific conversion of (*S*)-alanine to (*R*)-α-methyl phenylalanine *via* the *N*-pivaloyl 1,3-oxazolidin-5-one derived from ferrocene carboxaldehyde and sodium alaninate is described.

Homochiral α-methyl-α-amino acids are of interest because of their innate pharmacological activities[1] and because of their increasing use as stabilising and structure determining components of pseudopeptides.[2] The method commonly used to access such α-methyl-α-amino acids utilises the self-reproduction of chirality strategy, an example of which is shown in Scheme 1, delineated by Seebach[3,4] and extended by others.[5]




**1** **2**

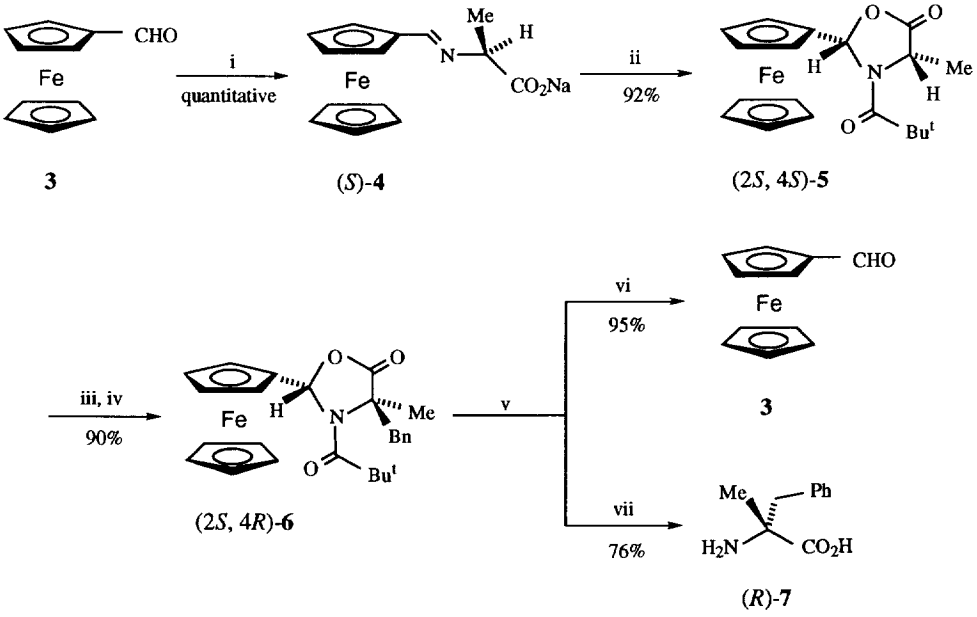
**Scheme 1**: Self reproduction of chirality

The practical limitations of this elegant strategy, however, curtail its usefulness.[3-5] Firstly, the formation of the initial *cis*-1,3-oxazolidin-5-one **1** is not particularly stereoselective and could lead to partial racemisation. Although both the *cis*- and *trans*-1,3-oxazolidin-5-ones alkylate highly stereoselectively in favour of **2**, any of the *trans*-diastereoisomer in **1** compromises the enantiomeric excess of the final α-methyl-α-amino acid. It is always necessary therefore to purify the oxazolidinones **1** by crystallisation or chromatography. Secondly, the 1,3-oxazolidin-5-ones **1** and **2** are relatively stable species requiring harsh conditions for their hydrolysis to liberate the product α-methyl-α-amino acids, conditions which are not compatible with the full range of substituents.

We describe herein our efforts to eliminate the above problems. Our approach is based on our kinetic resolution procedure for benzaldehyde chromium tricarbonyl complexes,[6] which relies on highly

diastereoselective *cis*-1,3-oxazolidine formation with valinol, and on the neighbouring group participation of the chromium in the solvolysis reactions of benzyl chromium tricarbonyl derivatives.[7] The high reactivity and instability of benzaldehyde chromium tricarbonyl complex precludes its use for the present purpose whereas the relatively stable and unreactive ferrocene carboxaldehyde **3**, which possesses the same relevant chemical properties, was deemed ideal.

Treatment of ferrocene carboxaldehyde **3** with sodium alaninate, derived from (*S*)-alanine, in absolute ethanol generated in quantitative yield the imine (*S*)-**4**, which was cyclised with pivaloyl chloride in dichloromethane to the *cis*-1,3-oxazolidin-5-one (2*S*, 4*S*)-**5** {$[\alpha]_D^{25}$ +21.5 (*c* 1, $CHCl_3$)} in 92% isolated yield (Scheme 2).[8] Treatment of (2*S*, 4*S*)-**5** with lithium di-isopropylamide (LDA) and benzyl bromide generated the 1,3-oxazolidin-5-one (2*S*, 4*R*)-**6** {$[\alpha]_D^{25}$ -195.0 (*c* 1, $CHCl_3$)} in 90% isolated yield as a single diastereoisomer.




**Scheme 2.** *Reagents and conditions* : i, (*S*)-(+)-$H_2N(Me)CHCO_2Na$, absolute EtOH, 4 Å molecular sieves, r.t., 5 h, **4**; ii, pivaloyl chloride, $CH_2Cl_2$, 4 Å molecular sieves, -18 °C to r.t., overnight, **5**, >98% d.e.; iii, LDA, THF, -78 °C; iv, BnBr, -78 °C to r.t., overnight, **6**, 100% d.e.; v, Amberlyst-15, acetone-$H_2O$ 9:1, overnight; vi, acetone-$H_2O$ 9:1, **3**; vii, 2% $NH_4OH$, **7**, >98% e.e.

1,3-Oxazolidin-5-ones **5** and **6** were shown to be diastereoisomerically pure by $^1H$ and $^{13}C$ nmr spectroscopy (d.e. >98%) and shown to be homochiral (e.e. >98%) by the use of the chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol. The relative configurations of the 2- and 4- stereogenic centres in both **5** and **6** were assigned unambiguously by nOe experiments and single crystal X-ray structure analyses.[9] The absolute configuration of **5** follows from that of the (*S*)-alanine starting material while that of **6** follows from the (2*S*)-centre of **5**.

Hydrolysis of (2*S*, 4*R*)-**6** on amberlyst-15 released the ferrocene carboxaldehyde **3** (95%), pivalic acid and the free α–methyl phenylalanine (*R*)-**7** (76% yield). The amino acid (*R*)-**7** was shown to be homochiral by derivatisation to the corresponding Mosher's amide[10] and $^{1}H$ and $^{19}F$ nmr spectroscopic analysis. The absolute configuration followed from that of (2*S*,4*R*)-**6** and was confirmed by comparison of the sign of the specific rotation $[\alpha]_{578}^{25}$ +17 (*c* 0.1, MeOH) with that in the literature $[\alpha]_{578}^{24}$ +20 (*c* 0.1, MeOH).[3]

In conclusion, we have presented practical methodology (all reactions have been performed on >3g scale) based on the self-reproduction of chirality strategy for the stereospecific conversion of (*S*)-alanine to (*R*)-α-methyl phenylalanine. We are currently extending this methodology to other α-methyl-α-amino acids and exploring chiral ferrocene carboxaldehyde derived 1,3-oxazolidin-5-ones as chiral glycine equivalents.

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8 All new compounds gave satisfactory spectroscopic data and elemental analyses. (2S,4S)-2-*Ferrocenyl*-4-*methyl*- 3-*pivaloyl*-1,3-*oxazolidin*-5-*one* **5**.- $[\alpha]_D^{25}$ +21.5 (*c* 1, $CHCl_3$) (Found: C, 61.98; H, 6.57; N, 3.77. $C_{19}H_{23}NO_3Fe$ requires C, 61.80; H, 6.28; N, 3.79%); $\nu_{max}$(KBr)/$cm^{-1}$

3097 (HC=C), 1796 (OC=O), and 1643 (NC=O); $\delta_H$ (200 MHz; $C_6D_6$) 0.90 (9 H, s, Bu$^t$), 1.26 (3 H, d, *J* 6.9, *Me*CH), 3.86-3.91 (2 H, m, Cp), 4.07 (5 H, s, Cp'), 4.11-4.12 (1 H, m, Cp), 4.23 (1 H, q, *J* 6.9, C*H*Me), 4.70-4.71 (1 H, m, Cp), and 7.10 (1 H, s, OCH); $\delta_H$ (200 MHz; $CDCl_3$) 1.27 (9H, s, Bu$^t$), 1.56 (3H, d, *J* 6.9, *Me*CH), 4.18-4.23 (3H, m, Cp), 4.25 (5H, s, Cp'), 4.59-4.61 (1H, m, CpH), 4.64 (1H, q, *J* 6.9, C*H*Me), and 7.07 (1H, s, OCH);$\delta_C$(200 MHz; $CDCl_3$) 20.0 (*Me*CH), 28.1 (*Me*$_3$C), 39.9 (*C*Me$_3$), 52.0 (*C*HMe), 65.3, 67.8, 68.4, 69.2, 85.0 (Cp, Cp'), 88.7 (OCHN), 173.5 (NC=O), and 175.8 (OC=O); *m/z* 371(M$^+$+2, 20%), 370 (M$^+$+1, 100), 369 (M$^+$, 28), 240 (39), 215 (13), and 156 (11).

(2S, 4R)-4-*Benzyl*-2-*ferrocenyl*-4-*methyl*-3-*pivaloyl*-1,3-*oxazolidin*-5-*one* **6**.- $[\alpha]_D^{25}$ -195.0 (*c* 1, $CHCl_3$) (> 99% e.e.) (Found: C, 67.79; H, 6.26; N, 3.28. $C_{26}H_{29}NO_3Fe$ requires C, 67.98; H, 6.36; N, 3.05); $\nu_{max}$ (KBr)/cm$^{-1}$ 3107 (HC=C), 1790 (OC=O), and 1629 (NC=O); $\delta_H$ (300 MHz; $CDCl_3$) 0.81 (9 H, s, Bu$^t$), 2.04 (3 H, s, MeC-N), 3.21, 3.81 (2 H, AB system, *J* 13.6, $CH_2$), 4.21, 4.25-4.26 (4 H, 2 m, Cp), 4.28 (5 H, s, Cp'), 6.10 (1 H, s, OCH), and 7.12-7.15, 7.24-7.28 (5 H, 2 m, Ph); $\delta_C$ (200 MHz; $CDCl_3$) 23.6 (*Me*CN), 28.1 (*Me*$_3$C), 40.8 (*C*Me$_3$), 41.3 ($CH_2$), 66.2, 67.9, 68.6, 68.7, 69.1, 69.3 (Cp), 86.7 (OCHN), 89.1 (Me*C*N), 176.1, and 176.6 (2 x C=O); *m/z* 461 (M$^+$+2, 23%), 460 (M$^+$+1, 100), 459 (M$^+$, 33), 331 (21), 330 (50), and 199 (27).

(R)-(+)-α-*Methylphenylalanine* **7**.- $[\alpha]_{578}^{25}$ +17 (*c* 0.1, MeOH) since this material proved difficult to dehydrate, showed a tendency to rehydrate, and was easily oxidized by air the elemental analysis was performed on its HCl salt (Found: C, 55.86; H, 6.77; N, 6.72. $C_{10}H_{14}NO_2Cl$ requires C, 55.69; H, 6.54; N, 6.49; $\nu_{max}$(KBr)/cm$^{-1}$ 3436 (N-H), 3034 (HC=C), 1619 ($CO_2^-$), and 1583 (C=C);$\delta_H$ (200 MHz; MeOD) 1.50 (3 H, s, Me), 2.92, 3.28 (2 H, AB system, *J* 14.0, $CH_2$), and 7.29 (5 H, m, Ph); $\delta_C$ (200 MHz, MeOD) 21.5 (Me), 42.6 ($CH_2$), 60.7 (*C*Me), 127.6, 128.7, 130.2, 134.1 (Ph), and 173.9 (CO); *m/z* 181 (M$^+$+2, 14%), 180 (M$^+$+1, 100), 179 (M$^+$, 6), 164 (6), 134 (16), 91 (6), 88 (21), and 60 (7).

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