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Diastereospecific oxidation of ferrocenyl aminoalcohols: synthesis of new chiral ligands

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Abstract

Oxidation of 1-[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]ethanol by manganese dioxide proceeds with complete diastereospecificity without any catalyst. New diastereopure and enantiopure ferrocenyl compounds were produced.

The synthesis of new chiral aminoalcohols is of great interest in modern synthetic organic chemistry, in particular for catalytic processes.[1,2] The usual route to synthesize optically active aminoalcohols is the asymmetric reduction of prochiral ketones or aldehydes.[3] In contrast, selective chemical oxidation of a mixture of aminoalcohols is, to the best of our knowledge, unknown. In our group, we have an ongoing interest in the synthesis of ferrocenyl aminoalcohols.[4] Here we report a diastereospecific oxidation of aminoalcohols, without any chiral oxidant or auxiliary. This reaction allows the isolation of new enantiomerically pure ferrocenyl ligands.

In a typical procedure,† alkylation by methyllithium of aldehyde **1**[5] leads to the formation of the two diastereomers of aminoalcohol **2**; the (1*RS*,1′*SR*):(1*RS*,1′*RS*) ratio is 73:27 (Scheme 1).[6]

These two diastereomers are difficult to separate. Oxidation of this mixture by manganese dioxide gives the expected ketone coming from the minor diastereomer (1*S*,1′*S*),(1*R*,1′*R*), but leaves intact the other diastereomer (1*S*,1′*R*),(1*R*,1′*S*) of **2**[7] (>98% d.e.). Aminoalcohol **2** and aminoketone **3** are easily separated by silica gel chromatography and recovered with the expected yields.

The application of this phenomenon to enantiopure **1** should give new homochiral compounds. This aminoaldehyde was resolved according to Nicolosi's procedure, using *Candida rugosa* lipases as

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† Typical procedure: To a solution of aldehyde **1** (271 mg, 1 mmol) in dry ether (20 ml) was added CH_3Li (1.6 M in Et_2O, 937 μl, 1.5 mmol) at rt under nitrogen. The mixture was reacted for 5 min, then quenched with H_2O (15 ml). The residue was purified by silica gel chromatography (ether:hexane:triethylamine, 7:2:1) to produce **2** (273 mg, 95%). This compound was oxidized by MnO_2 (83 mg, 10 equiv.) in CH_2Cl_2 at rt for 1 h. The solution was filtered on Celite and purified by silica gel chromatography (ether:hexane:triethylamine, 7:2:1) to give **3** (73 mg, 27%) and one diastereomer of **2** (191 mg, 70%).

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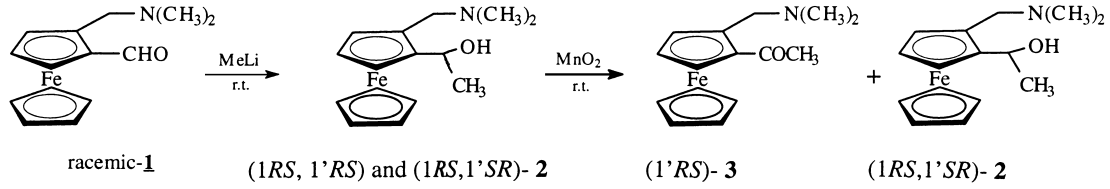
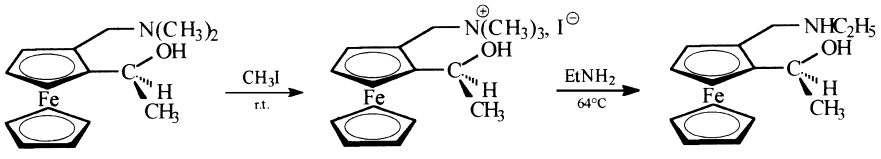


racemic-**1** (1*RS*, 1'*RS*) and (1*RS*,1'*SR*)- **2** (1'*RS*)- **3** (1*RS*,1'*SR*)- **2**

Scheme 1.

resolving agents.[8] The reaction of enantiopure (*R*)-**1** (>98% e.e., assessed by ^{1}H NMR with Pirkle's alcohol) according to the previous two-step procedure affords aminoalcohol (1*S*,1′*R*)-**2**[9] (>98% d.e.) and the (1′*R*)-**3**[10] (>98% e.e.) in 70% and 27% isolated yields, respectively.

Compound (1*S*,1′*R*)-**2** was further alkylated by methyl iodide, and the resulting ammonium salt was substituted by ethylamine‡ to give the enantio- and diastereomerically pure (>98% d.e.) aminoalcohol **5**[11] in 65% isolated yield (Scheme 2).



(1*S*,1'*R*)-**2** (1*S*,1'*R*)-**4** (1*S*,1'*R*)-**5**

Scheme 2.

In summary, oxidation of **2** by manganese dioxide is diastereospecific. The synthesis of new chiral aminoalcohols **2** and **5**, powerful potential chelating ligands, and aminoketone **3** has been presented. The application of this phenomenon for the creation of new chiral ligands and their use in catalysis are under development.

Acknowledgements

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2. Alkylation reaction: (a) Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem*. **1991**, *56*, 2218–2224. (b) Tanner, D.; Korno, H.; Guijarro, D.; Andersson, P. *Tetrahedron* **1998**, *54*, 14213–14232.
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‡ Experimental procedure: Aminoalcohol **2** (180 mg, 0.627 mmol) was dissolved in acetone (15 ml). Methyl iodide (1.17 ml, 18.8 mmol) was injected and the reaction was allowed to react for 1 h. The solvent was evaporated and the ammonium was dissolved in acetonitrile. Ethylamine (4 ml) and K_2CO_3 (895 mg, 0.627 mmol) were added and the tube was sealed. After 64 h at 45°C, the reaction was quenched with H_2O (10 ml) and afforded, after purification by silica gel chromatography (ether:hexane:triethylamine, 7:2:1), aminoalcohol **5** (115 mg, 64%).

6. The relative configurations were attributed according to Bau's results: Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakama, R. T.; Ugi, I. K. *J. Am. Chem. Soc.* **1973**, *95*, 482–486. The denomination '1*S*' or '1*R*' refers to the tetrahedral chirality and the '1′*S*' or '1′*R*' one refers to the planar chirality. The ratio was calculated by integration of the ^{1}H NMR resonances.
7. The purity of the unreactive alcohol was assessed by ^{1}H NMR, showing the disappearance of resonances corresponding to the minor diastereomer.
8. Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1275–1280.
9. Key data for **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.97 (q: *J*=6.5 Hz; 1H; C*H*CH_3); 4.23 (m; 1H; C_5H_3); 4.08–4.00 (m; 2H; C_5H_3); 4.04 (s; 5H; C_5H_5); 3.89 (d: *J*=12.5 Hz; 1H; C*H*(–H)N); 2.75 (d: *J*=12.5 Hz; 1H; C*H*(–H)N); 2.16 (s; 6H; $N(CH_3)_2$); 1.50 (d: *J*=6.5 Hz; 1H; C*H*$_3$CH). $[\alpha]_D^{20}$=−43.0 (*c* 0.285, $CHCl_3$).
10. Key data for **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.65 (m; 1H; C_5H_3); 4.54 (m; 1H; C_5H_3); 4.42 (m; 1H; C_5H_3); 4.15 (s; 5H; C_5H_5); 4.12 (d: *J*=12.8 Hz; 1H; C*H*(–H)N); 3.19 (d: *J*=12.8 Hz; 1H; C*H*(–H)N); 2.42 (s; 3H; $COCH_3$); 2.24 (s; 6H; $N(CH_3)_2$). $[\alpha]_D^{20}$=+403.2 (*c* 0.265, $CHCl_3$).
11. Key data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (q: *J*=6.6 Hz; 1H; C*H*CH_3); 4.22 (m; 1H; C_5H_3); 4.09 (m; 1H; C_5H_3); 4.05 (s; 5H; C_5H_5); 4.01 (m; 1H; C_5H_3); 3.86 (d: *J*=12.2 Hz; 1H; C*H*(–H)N); 3.45 (d: *J*=12.2 Hz; 1H; C*H*(–H)N); 2.62 (m; 2H; C*H*$_2$$CH_3$); 1.50 (d: *J*=6.6 Hz; 1H; C*H*$_3$CH); 1.06 (t: *J*=7.1 Hz; 1H; C*H*$_3$$CH_2$). $[\alpha]_D^{20}$=−53.2 (*c* 0.215, $CHCl_3$).