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The first example of an enantiopure planar chiral hydroxyferrocene ligand

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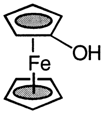
Abstract

Lithiation of 2-ferrocenyl-4,4-dimethyloxazoline followed by addition of bis(trimethylsilyl)peroxide led to the isolation of air-stable 2-(2-hydroxyferrocenyl)-4,4-dimethyloxazoline. Repetition of this procedure on (*S*)-2-ferrocenyl-4-(1-methylethyl)oxazoline gave the lithium salt of (*S*)-2-((${}_{p}S$)-2-hydroxyferrocenyl)-4-(1-methylethyl)oxazoline, a stable precursor to the first example of an enantiopure hydroxyferrocene ligand. © 1999 Elsevier Science Ltd. All rights reserved.

The recent resurgence of interest in 1,2-disubstituted ferrocene derivatives displaying planar chirality has resulted in numerous methods for their synthesis as single enantiomers.[1] These compounds are finding widespread application as ligands in asymmetric catalysis, particularly as P–N and P–P based bidentate ligands with phosphorus attached to the ferrocene nucleus.[2,3] Although ligands are also known with sulfur attached to the cyclopentadienyl ring,[4] related non-racemic hydroxy substituted ferrocenes have not been reported. This may be due in part to the aerobic instability of the parent hydroxyferrocene **1**[5] and 1,1′-dihydroxyferrocene **2**, decomposition of the latter in air giving rise to the formation of dicyclopentadienone.[6] Representative of the very few racemic hydroxyferrocene derivatives known are **3**[7] and **4**.[8] Both are reported to display intramolecular hydrogen bonding, and in the case of **3** this and the presence of the electron-withdrawing ester group are invoked to explain the unusual stability of this derivative. Given the extensive use of ferrocenyloxazolines for generating planar chirality via diastereoselective *ortho*-lithiation,[1,9] we were attracted by the possibilities offered by oxazolines for both generating and stabilising planar chiral hydroxyferrocene containing ligands. Our results are reported in this Communication.



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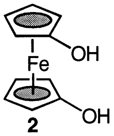

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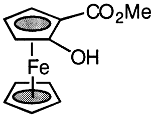

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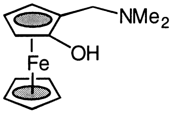

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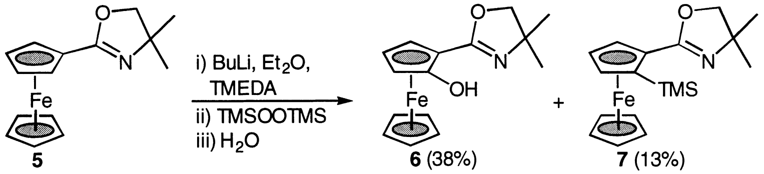
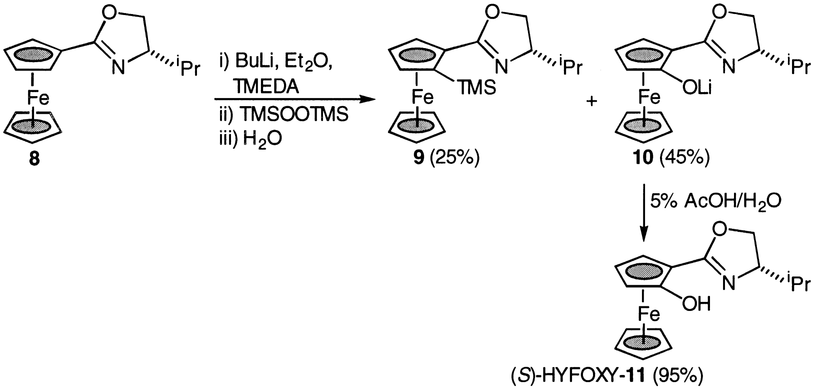
For the direct attachment of oxygen onto the ferrocene nucleus we chose bis(trimethylsilyl)peroxide[10] as this has been employed in the high yielding synthesis of trimethylsiloxyferrocene from ferrocenyllithium.[11] Thus, lithiation of **5** with 1.3 equivalents of BuLi was followed by addition of 1.1 equivalents of the peroxide leading to isolation of **6**[12,13] (38–44% accounting for recovered **5**) and **7** (13%) after an aqueous work-up (Scheme 1).



Scheme 1.

Crystalline hydroxyferrocene **6** is stable to air as are, for short periods (<1 h), solutions of **6** in either hexane or benzene. In contrast, dissolution of **6** in other common organic solvents ($CHCl_3$, EtOAc, CH_2Cl_2) leads to rapid decomposition. The presence of the expected intramolecular hydrogen bond in **6** is supported by the invariance of the hydroxyl proton resonance at 8.82 ppm in C_6D_6 at concentrations ranging from 0.008 M to 0.033 M, and this feature most likely accounts for the solubility and relative stability of **6** in non-polar solvents.

Our efforts to generate non-racemic **6** by replacing TMEDA with sparteine, or by attempting a kinetic resolution of the intermediate lithiated ferrocenyl oxazoline with a chiral oxaziridine, only resulted in isolation of racemic material. Instead we reverted to the known highly diastereoselective lithiation procedure for **8**[9d] followed by addition of bis(trimethylsilyl)peroxide as before.[12] To our surprise no hydroxyferrocene was present in the organic extract following an aqueous work-up, only recovered starting material **8** (18%) and **9** were obtained (Scheme 2). However, a large quantity of precipitate was noticed at the organic/aqueous interface, and isolation and drying of this material led to its identification as the lithium salt **10** (45–54% accounting for recovered **8**).[14] This material was converted to the parent hydroxyferrocenyloxazoline (HYFOXY) ligand **11** by shaking with 5% AcOH/H_2O followed by extraction into hexane (×3) and washing of the resultant yellow solution with aqueous saturated $NaHCO_3$.[15] Hexane and other solutions (Et_2O, THF, CH_2Cl_2) of **11** are stable when maintained under a nitrogen atmosphere; prolonged exposure (>15 min) to the air does result in significant decomposition.



Scheme 2.

In both reactions the desired C–O bond formation is accompanied by generation of trimethylsilyl derivatives **7** and **9**. This may result from the initially formed 2-trimethylsiloxyferrocenyloxazolines acting as sources of electrophilic silicon for lithiated ferrocenyloxazolines. The presence of recovered starting material in both reactions is likely due to the difficulty of entirely freeing the bis(trimethylsilyl)peroxide of CH_2Cl_2, the solvent in which it is formed.[10]

In summary, we have demonstrated that hydroxyferrocenyloxazoline complexes can be readily generated, and that the fortuitous isolation of the lithium salt **10** enables this to act as a stable and storable precursor to the first example of an enantiopure hydroxyferrocene ligand displaying planar chirality.

Acknowledgements

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12. To a solution of either **5** or **8** (7.0 mmol) and TMEDA (1.38 ml, 9.2 mmol) in Et_2O (50 ml) at −78°C was added a solution of BuLi in hexanes (3.84 ml, 9.2 mmol). After stirring at −78°C for 2 h bis(trimethylsilyl)peroxide (1.38 g, 7.7 mmol) was added and the reaction mixture allowed to warm to room temperature before the addition of water (100 ml) and hexane (50 ml). From **5**, separation of the organic phase followed by drying ($MgSO_4$) and chromatography (20% EtOAc/40–60 petroleum ether) gave (in elution order) **7** (0.32 g, 13%), **6** (0.19 g, 9%) and recovered **5** (0.29 g, 15%). After addition of concd HCl (0.25 ml) to the aqueous phase, further extraction with hexane followed by solvent evaporation gave **6** as a dark orange/brown crystalline solid (0.61 g, 29%). From **8**, separation of the organic phase followed by drying ($MgSO_4$) and chromatography (20% EtOAc/40–60 petroleum ether) gave (in elution order) **9** (0.64 g, 25%) and recovered **8** (0.37 g, 18%). Filtration of the aqueous phase, washing (H_2O and hexane) and drying gave **10** as a brown powder (1.0 g, 45%).
13. **6**: mp 92–94°C (hexane); (found: C, 59.88; H, 5.71; N, 4.60; $C_{15}H_{17}FeNO_2$ requires: C, 60.23; H, 5.73; N, 4.68%); ν_{max} (nujol)/cm^{-1} 1643; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, -CH_3), 1.40 (3H, s, -CH_3), 3.91 (1H, s, 4-Fc), 3.99 (1H, d, *J* 8.1, -OC*H*H-), 4.13 (6H, brs, C_5H_5 + -OCH*H*-), 4.24 (1H, s, 3-Fc), 4.42 (1H, s, 5-Fc); δ_C (100 MHz, C_6D_6) 26.46 (-CH_3), 27.50 (-CH_3), 54.77 (Fc), 56.79 (5-Fc), 59.55 (3-Fc), 61.60 (4-Fc), 65.70 (-$C(CH_3)_2$), 69.60 (C_5H_5), 77.45 (-OCH_2-), 167.67 (C=N); *m/z* (EI) 299 (M^+, 14%), 283 (52), 268 (38), 211 (31), 121 (100).
14. **10**: mp 216–218°C (dec.); (found: C, 58.08; H, 5.65; N, 4.12; $C_{16}H_{18}FeLiNO_2\cdot 2/3H_2O$ requires: C, 58.04; H, 5.88; N, 4.23%); ν_{max} (nujol)/cm^{-1} 1639; δ_H (400 MHz, d^6-DMSO) 1.07 (6H, brs, 2×-CH_3), 1.95 (1H, brs, -C$H(CH_3)_2$), 3.49 (2H, brs), 3.58 (1H, brs), 3.69 (1H, brs), 3.99 (5H, brs, C_5H_5), 4.11 (1H, brs), 4.26 (1H, brs); *m/z* (EI) 319 (M^+, 16%), 313 (72), 227 (71), 121 (100).
15. **11**: $[\alpha]_D^{20}=-47$ (*c* 0.334, hexane); ν_{max} (liquid film)/cm^{-1} 1641; δ_H (400 MHz, C_6D_6) 0.85 (3H, d, *J* 6.7, -CH_3), 0.93 (3H, d, *J* 6.7, -CH_3), 1.56 (1H, octet, *J* 6.6, -C$H(CH_3)_2$), 3.60–3.63 (1H, m, -C*H*N-), 3.72–3.82 (2H, m, -OCH_2-), 3.77 (1H, dd, *J* 2.7, 2.4, 4-Fc), 4.21 (5H, s, C_5H_5), 4.43 (1H, dd, *J* 2.7, 1.2, 3-Fc), 4.51 (1H, dd, *J* 2.4, 1.2, 5-Fc). δ_C (100 MHz, C_6D_6) 18.8 (-CH_3), 18.9 (-CH_3), 33.0 (-$CH(CH_3)_2$), 56.4 (Fc), 58.1 (5-Fc), 60.9 (3-Fc), 62.9 (4-Fc), 70.0 (-OCH_2-), 70.9 (C_5H_5), 71.6 (-*C*HN-), 170.0 (C=N); *m/z* (EI) 313 (M^+, 100), 227 (62), 205 (26), 121 (85), 55 (80); (found: M^+, *m/z* (EI) 313.0766. $C_{16}H_{19}FeNO_2$ requires: 313.0765).