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NEW CHIRAL THIO- AND SELENO-SUBSTITUTED FERROCENYLAMINES

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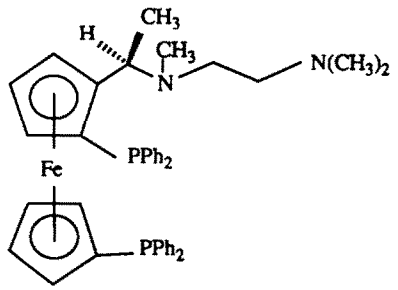
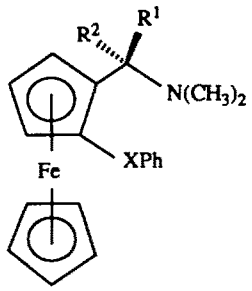
Abstract- A new class of chiral thio- and seleno-substituted ferrocenylamines were prepared by the dilithiation of R-(+)-N,N-dimethyl-1-ferrocenylethylamine followed by the reaction with either a disulfide or diselenide.

Since the pioneering work of Ugi *et al.* in 1970 directed towards the synthesis of ferrocenyl ligands possessing both central and planar chirality,[1] Hayashi and co-workers have exploited the modification of chiral ferrocenylphosphine ligands for use in transition-metal-catalyzed asymmetric synthesis.[2] Recently, Hayashi *et al.* have reported the use of the (*R*)-(*S*)-ferrocenylamine ligand **1** in an elegant synthesis of oxazolines using a gold(I) catalyzed aldol reaction with both high diastereo- and enantioselectivity.[3]



(*R*) - (S) - **1**



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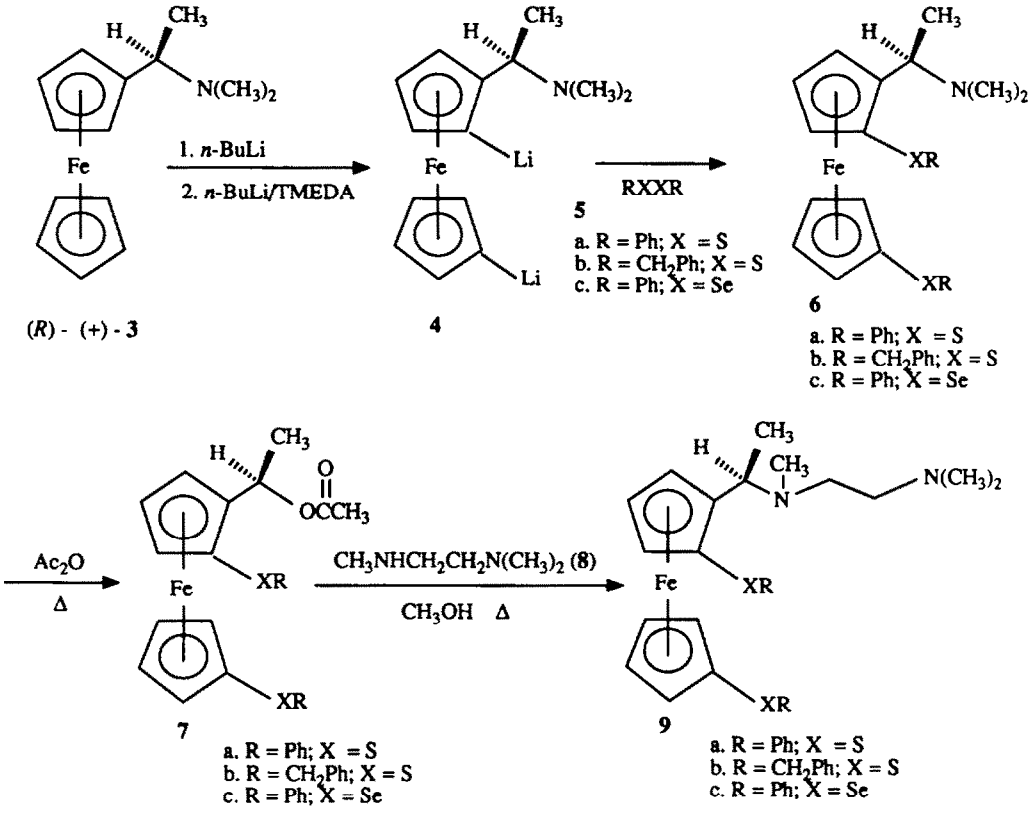
a. $R^1 = CH_3$; $R^2 = H$; X = S
b. $R^1 = H$; $R^2 = CH_3$; X = Se

The demonstrated importance of ferrocenyl ligands in transition-metal- catalyzed reactions has led to research efforts for the synthesis of ferrocenyl ligands with metal-chelating groups other than phosphorus. Simple ferrocenyl ligands with sulfur, selenium, and tellurium donor substituents have been described.[4-6] Quite recently, Brubaker *et al.* have reported the synthesis of the chiral ferrocenylamines **2a-b** containing a single sulfur- or seleno-substituent, which were effective catalysts for Grignard cross-coupling reactions.[7]

Our laboratory efforts have been directed towards the synthesis of chiral ferrocenylamine chelating ligands having either two sulfide or selenide donor groups. The procedure developed allows for their rapid preparation starting from the readily available (*R*)-(+)-ferrocenylethylamine **3**.[1] The (*R*)-(*R*)-dilithio-ferrocenylamine **4** was prepared by the sequential metalation of **3** in diethyl ether with *n*-butyllithium (*n*-BuLi) followed by *n*-BuLi with N,N,N',N'-tetramethylethylenediamine (TMEDA).[2a,8] The reaction of **4**, prepared *in situ*, with excess **5a-c** at reflux temperature gave the corresponding bisthio- and bisseleno-substituted

ferrocenylamines **6a-c**.[4] The reaction of **6a-c** with acetic anhydride[2a] at 100 °C gave the corresponding acetates **7a-c** as liquids. Chromatographic purification (neutral Al_2O_3) of the acetates resulted in partial hydrolysis to



the corresponding alcohol whereupon the mixture must be reesterified prior to further modification. The reaction of **7a-b** with N,N,N'-trimethylethylenediamine, **8**, in methanol at reflux[2a] gave the thio- and seleno-substituted ferrocenylamines **9a-c**, which are currently under study in our laboratory.

EXPERIMENTAL

All reactions were carried out in dried apparatus under a dry argon atmosphere. Woelm alumina N (activity 1), and Merck silica gel 60 (70-230 Mesh) were used for chromatography. All ^1H NMR spectra were obtained on a Bru ker 300 MHz spectrometer and chemical shifts are relative to TMS where a positive sign is downfield from the standard. The abbreviations used for peak multiplicity are s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Reagents were purchased from commercial laboratory supply houses. All solvents were dried prior to use. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY Corp.

(*R*)-N,N-Dimethyl-1-[(*S*)-1',2-bis(phenylthio)ferrocenyl]ethylamine, (6a): To a solution of 7.71 g (30 mmol) of (*R*)-(+)-**3** in 50 mL of anhydrous diethyl ether was added dropwise over 5 min 22.5 mL (36 mmol) of a 1.6 M hexane solution of *n*-BuLi. The reaction mixture was stirred for 7 h at 27 °C and then a solution[9] of 3.97 g (34.2 mmol) of TMEDA and 24.4 mL (39 mmol) of a 1.6 M hexane solution of *n*-BuLi in 30 mL of diethyl ether was added dropwise. The reaction mixture was stirred at room temperature for 5 h and then to the reaction mixture at 0 °C was added dropwise a solution of 19.65 g (90 mmol) of **5a** in 80 mL diethyl ether. The reaction mixture was heated at reflux for 76 h and then to the cooled reaction mixture was added 100 mL of saturated sodium bicarbonate followed by 50 mL of toluene and 50 mL of water. The organic phase was separated, was extracted with water, and was dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by chromatography twice (Al_2O_3, hexane followed by CH_2Cl_2 eluent and SiO_2,

acetone eluent). The residue was sequentially recrystallized from hexane and methyl alcohol to give 5.77 g (41 %) of a yellow crystalline solid, mp 85-86 °C; $[\alpha]^{22}_D$ -220.73° [c 0.545, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.49 (d, 3 H), 1.94 (s, $N(CH_3)_2$, 6 H), 3.92 (q, C<u>H</u>CH_3, 1 H), 4.29 - 4.48 (complex m, 6 H), 4.60 (m, 1 H), 7.00 - 7.27 (complex m, 10 H). Anal. Calcd for $C_{26}H_{27}FeNS_2$: C, 65.95; H, 5.75; N, 2.96. Found: C, 65.81; H, 5.73; N, 3.06.

(*R*)-N,N-Dimethyl-1-[(*S*)-1',2-bis(benzylthio)ferrocenyl]ethylamine, (6b): By the procedure used to prepare compound **6a**, compound **6b** was prepared from 7.71 g (30 mmol) of **3**, 22.5 mL (36 mmol) of a 1.6 M hexane solution of *n*-BuLi, a solution of 3.97 g (34.2 mmol) of TMEDA and 24.4 mL (39 mmol) of a 1.6 M hexane solution of *n*-BuLi, and 22.75 g (90 mmol) of **5b**. The residue was purified by chromatography three times (Al_2O_3, hexane followed by acetone eluent and twice SiO_2, acetone eluent) to give 2.37 g (15 %) of a viscous red liquid, R_f (acetone) 0.62; $[\alpha]^{22}_D$ -23.62° [c 0.635, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3 H), 2.20 (s, $N(CH_3)_2$, 6 H), 3.71 (s, Ph<u>C</u>H_2, 2 H), 3.93 (AB q, Ph<u>C</u>H_2, 2 H), 4.00 - 4.25 (complex m, 8 H), 7.03 - 7.30 (complex m, 10 H). Anal. Calcd for $C_{28}H_{31}FeNS_2$: C, 67.06; H, 6.23; N, 2.79; S, 12.78. Found: C, 67.19; H, 6.40; N, 2.77; S, 12.78.

(*R*)-N,N-Dimethyl-1-[(*S*)-1',2-bis(phenylseleno)ferrocenyl]ethylamine, (6c): By the procedure used to prepare compound **6a**, compound **6c** was prepared from 7.71 g (30 mmol) of **3**, 22.5 mL (36 mmol) of a 1.6 M hexane solution of *n*-BuLi, a solution of 3.97 g (34.2 mmol) of TMEDA and 24.4 mL (39 mmol) of a 1.6 M hexane solution of *n*-BuLi, and 28.09 g (90 mmol) of **5c**. The residue was purified twice by chromatography (Al_2O_3, hexane followed by acetone eluent and SiO_2, acetone eluent) to give 7.00 g (41 %) of a yellow crystalline solid, mp 58-59 °C; $[\alpha]^{22}_D$ -201.95° [c 0.514, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.47 (d, 3 H), 1.95 (s, $N(CH_3)_2$, 6 H), 3.92 (q, C<u>H</u>CH_3, 1 H), 4.28 (complex m, 2 H), 4.38 (complex m, 4 H), 4.53 (m, 1 H), 7.08 - 7.43 (complex m, 10 H). Anal. Calcd for $C_{26}H_{27}FeNSe_2$: C, 55.05; H, 4.80; N, 2.47. Found: C, 54.75; H, 5.02; N, 2.52.

(*R*)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(*S*)-1',2-bis(phenylthio) ferrocenyl]ethylamine, (9a): A mixture of 5.67 g (11.9 mmol) of **6a** and 35 mL of acetic anhydride was heated for 1 h at 100 °C. After concentration *in vacuo* and chromatography (Al_2O_3, CH_2Cl_2 eluent) to remove unreacted **6a**, the partially hydrolyzed **7a** was heated with 35 mL of acetic anhydride at 100 °C for 1 h. The volatiles were removed *in vacuo* and the resultant **7a** (4.30 g, 74 %) was used without further purification.[10]

A mixture of 4.30 g (8.8 mmol) of **7a** and 77 mL (594 mmol) of **8** in 200 mL of methyl alcohol was heated at reflux for 20 h. The volatiles were removed *in vacuo* and then a diethyl ether solution of the residue was extracted with saturated brine. The organic phase was dried over anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. The residue was purified by chromatography (SiO_2, 99:1 diethyl ether:triethylamine (Et_3N) followed by 99:1 CH_3OH:Et_3N eluent). The product was dissolved in toluene, was extracted with water, and the organic phase was dried with anhydrous $MgSO_4$. The volatiles were removed *in vacuo* to give 1.97 g (42 %) of a red viscous liquid, $[\alpha]^{22}_D$ -152.63° [c 0.494, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.40 (d, 3 H), 1.87 (m, CH_2, 2 H), 1.92 (s, NCH_3, 3 H), 2.02 (s, $N(CH_3)_2$, 6 H), 2.33 (m, CH_2, 2 H), 4.05 (q, C<u>H</u>CH_3, 1 H), 4.37 (complex m, 6 H), 4.55 (m, 1 H), 6.98-7.22 (complex m, 10 H). Anal. Calcd for $C_{29}H_{34}N_2FeS_2$: C, 65.65; H, 6.46; N, 5.28; S, 12.09. Found: C, 65.59; H, 6.47; N, 5.34; S, 12.01.

(*R*)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(*S*)-1',2-bis(benzylthio) ferrocenyl]ethylamine, (9b): By the procedure used to prepare **7a**, compound **7b** was prepared from 2.20 g (4.39 mmol) of **6b** and 13 mL of acetic anhydride. The resultant **7b** (2.23 g , 98 %) was used without further purification.

By the procedure used to prepare **9a**, compound **9b** was prepared from a mixture of 2.23 g (4.32 mmol) of **7b**, 38 mL (292 mmol) of **8**, and 98 mL of methyl alcohol. The residue was purified by chromatography (SiO_2; 99:1 diethyl ether:Et_3N followed by 99:1 CH_3OH:Et_3N eluent) to give 1.88 g (78 %) of a red viscous liquid, $[\alpha]^{22}_D$ -40.60° [c 0.564, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.33 (d, 3 H), 2.17 (s, NCH_3, 3 H), 2.19 (s, $N(CH_3)_2$, 6 H), 2.29 (complex m, 1 H), 2.42 (complex m, 1 H), 2.55 (complex m, 2 H), 3.71 (s, $PhCH_2$, 2 H), 3.83-4.23 (complex overlapping m, 10 H), 7.07-7.30 (complex m, 10 H). Anal. Calcd for $C_{31}H_{38}N_2FeS_2$: C, 66.65; H, 6.86; N, 5.01; S, 11.48. Found: C, 66.49; H, 6.72; N, 4.76; S, 11.49.

(*R*)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(*S*)-1',2-bis(phenylselen o)ferrocenyl]ethylamine, (9c): By the procedure used to prepare **7a**, compound **7c** was prepared from 6.80 g (12.7 mmol) of **6c** and 35 mL of acetic anhydride. The resultant **7c** (5.50 g , 74 %) was used without further purification.

By the procedure used to prepare **9a**, compound **9c** was prepared from a mixture of 5.50 g (9.4 mmol) of **7c**, 80 mL (630 mmol) of **8**, and 200 mL of methyl alcohol. The residue was purified by chromatography (SiO_2; 99:1 diethyl ether:Et_3N followed by 99:1 CH_3OH:Et_3N eluent) to give 4.10 g (70 %) of a red viscous liquid, $[\alpha]^{22}_D$ -167.99° [c 1.087, $CHCl_3$]; ^1H NMR ($CDCl_3$) δ 1.39 (d, 3 H), 1.94 (m, CH_2, 2 H), 1.95 (s, NCH_3, 3 H), 2.05 (s, $N(CH_3)_2$, 6 H), 2.34 (m, CH_2, 2 H), 4.04 (q, $C\underline{H}CH_3$, 1 H), 4.26 (complex m, 2 H), 4.38 (complex m, 4 H), 4.48 (m, 1 H), 7.08-7.38 (complex m, 10 H). Anal. Calcd for $C_{29}H_{34}N_2FeSe_2$: C, 55.79; H, 5.49; N, 4.49; Se, 25.29. Found: C, 55.54; H, 5.56; N, 4.54; Se, 25.00.

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9. Prepared in a separate flask by the addition of the *n*-BuLi to a solution of TMEDA in 30 mL of diethyl ether.
10. **7a**: $[\alpha]^{22}_D$ + 274.72 [c 0.992, $CHCl_3$]; IR ($CHCl_3$) ν 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (s, $CH_3C(=O)$, 3 H), 1.60 (d, CH_3, $^3J_{HCCH}$ = 7 Hz, 3 H), 3.37 - 5.53 (complex m, 7 H), 6.07 (q, $^3J_{HCCH}$ = 7Hz, 1 H), 7.03 (complex m, 10 H).