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An Efficient Diastereoselective Synthesis of Chiral Ferrocenyl Aldehydes‡

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Abstract: An efficient access to both enantiomers of ferrocenyl aldehyde **4** and their transformations to other optically active ferrocenyl aldehydes were described. © 1998 Elsevier Science Ltd. All rights reserved.

Ferrocenes with planar chirality are of increasing importance in the synthesis of chiral ligands used in asymmetric catalysis[1,2] as well as being building blocks in asymmetric synthesis.[3] The stereochemical aspects of chiral ferrocenes have been widely investigated.[4] So far, the most important method for preparing enantiopure planar chiral ferrocene derivatives relies upon a diastereoselective ortho-lithiation and subsequent reaction with an appropriate electrophile. The most prominent example of this methodology is based on the pioneering work of Ugi and his co-workers[5,6] (**Scheme 1**). This strategy, which involves the use of stereogenic ortho-directing groups, has been widely used in the synthesis of ferrocene derivatives.

Chiral ferrocenyl aldehydes, which bear a transformable formyl group, constitute a unique class of ferrocene derivatives. In 1993, Kagan reported a method of their preparation, starting from ferrocenyl aldehyde and employing the acetal of a chiral diol as the lithiation guide to introduce different substitution groups.[7] Recently, Togni *et al.* finished the synthesis of a formyl vinylferrocene, using Ugi's method of diastereoselective ortho-lithiation to obtain enantiopure alcohol followed by oxidation.[8] As we know, the reaction of organolithium compound with N,N'-dimethylformamide(DMF) has long been known as an efficient method for the preparation of aldehydes.[9,10] Herein, we report the first synthesis of both enantiomers of planar-chiral ferrocenyl aldehyde **4**, using Ugi's method of diastereoselective ortho-lithiation and DMF as the electrophile (**Scheme 2**).[11]

Through diastereoselective ortho-lithiation with *n*-BuLi and subsequent quenching with DMF, the enantiopure compounds (R)-(S)-**4** and (S)-(R)-**4** were obtained in 66% and 70% yields after chromatography, respectively, from optically pure **1**. Both products were dark red solids.

‡Dedicated to the memory of Professor Yu Wang (d. May 6, 1997).

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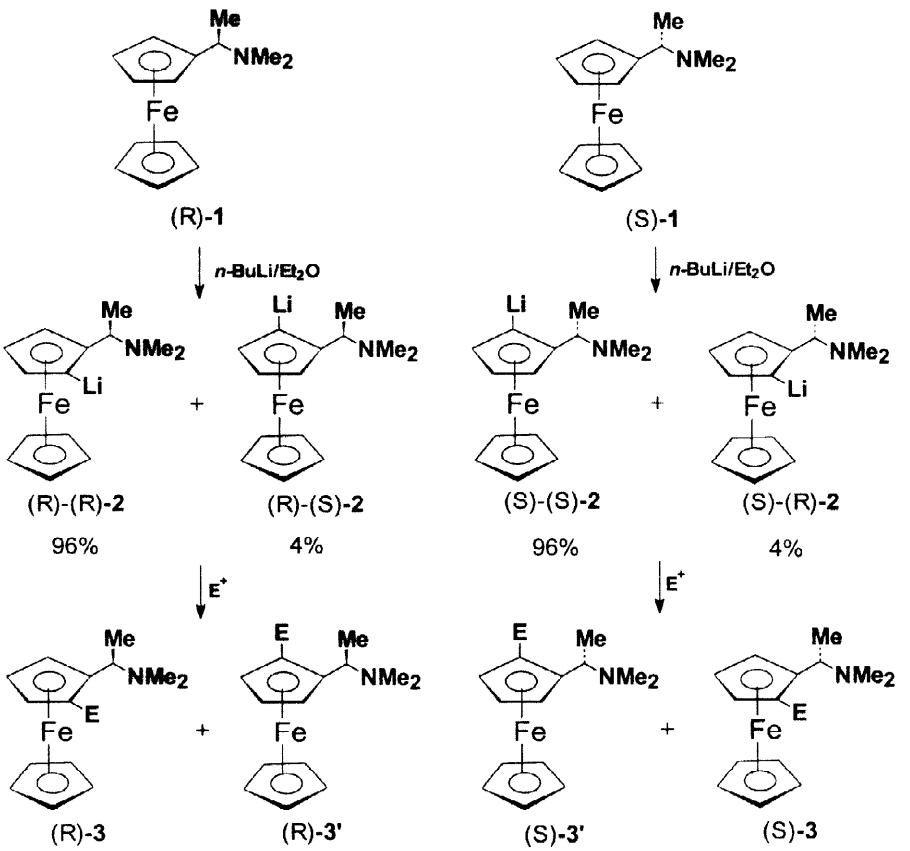
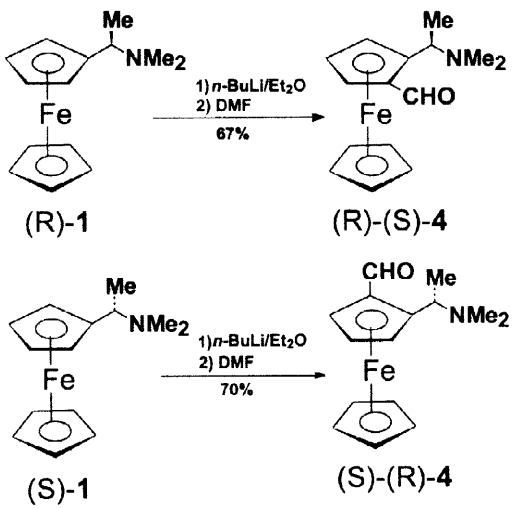
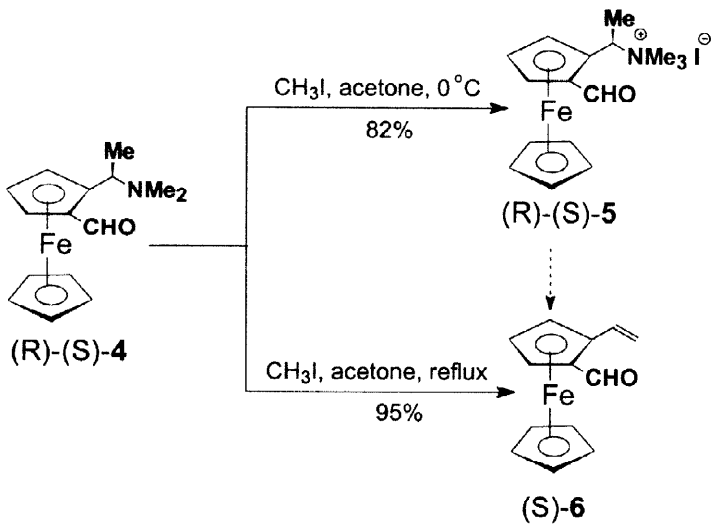


Scheme 1

While the ferrocenyl aldehyde (R)-(S)-**4** stirred with CH_3I at 0°C for 0.5h in acetone yielded the ammonium salt (R)-(S)-**5**, the reaction at reflux led to the complete conversion of (R)-(S)-**5** to the important imtermediate formyl vinyl ferrocene (S)-**6** in high yield (**Scheme 3**).

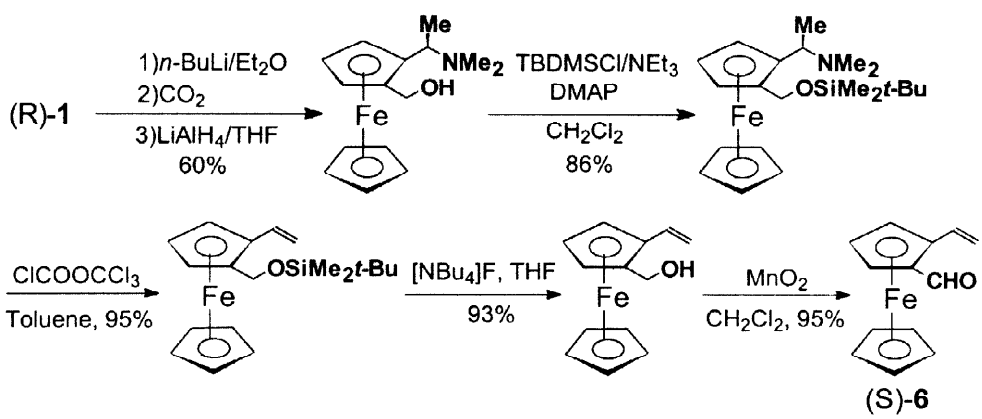


Scheme 2



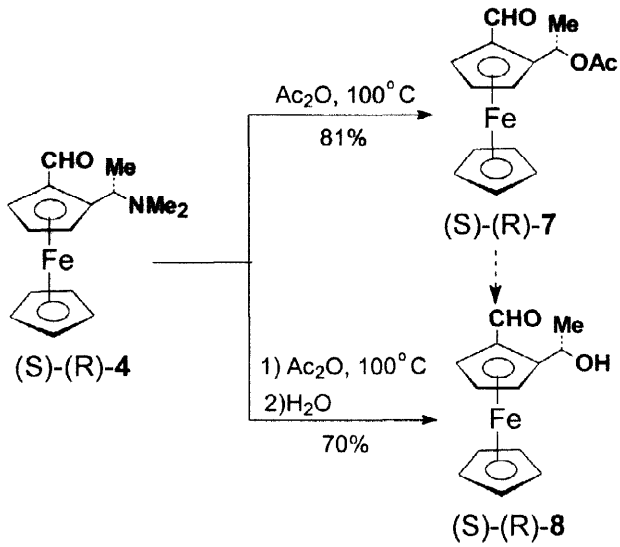
Scheme 3

(S)-**6** is the common precursor for the preparation, *via* Wittig method of planar-chiral conjugated donor-acceptor systems for nonlinear optics.[8,12] Togni *et al.* has reported its first synthesis in five steps with 43% overall yield, starting from the optically pure (R)-**1**[8] (**Scheme** 4). Compared with this strategy, our two-step synthesis of aldehyde (S)-**6** with 66% overall yield from the same starting amine is quite concise and efficient.



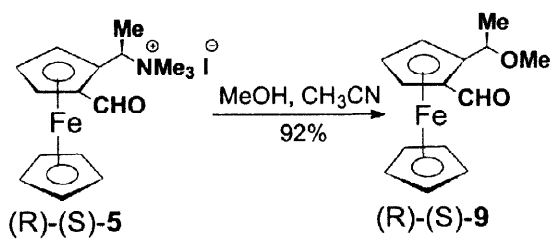
Scheme 4

Further transformations of (R)-(S)-**4** and (S)-(R)-**4** were also carried out, using the retentive nucleophilic displacements reaction of α-substituted alkylferrocene[13] (**Scheme 5**).



Scheme 5

Compound (S)-(R)-**7** was formed directly from the aldehyde (S)-(R)-**4** and using only a slight excess of acetic anhydride as the nucleophile, in the absence of a solvent at 100°C. By subsequent reaction with water, (S)-(R)-**8** was obtained in 70% yield. The amino group attached to the pseudobenzylic center of the ferrocene moiety can also be substituted by methoxy group in high yield just by stirring compound (R)-(S)-**5** in the mixture of methanol in acetonitrile (**Scheme 6**).



Scheme 6

In summary, we have developed an efficient access to both enantiomers of ferrocenyl aldehyde **4**. The synthesis of NLO intermediate (S)-**6** was thus greatly simplified. Further transformations of **4** to other optically active ferrocenyl aldehydes were also investigated.

EXPERIMENTAL

Infrared spectra were obtained with FTS-185 instrument. Proton magnetic resonance spectra were recorded with a Varian EM-390 or Bruker AM-300 spectrometer and were reported in ppm downfield of internal tetramethylsilane (δ units). Mass spectral data were taken on a Finnigan 4021 spectrometer and HRMS data were obtained on a Finnigan MAT 8430 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC instrument.

Optically active N,N'-dimethyl-(1-ferrocenylethyl) amines were obtained by resolution of the corresponding racemic compound.[5]

1-(R)-[1'-N,N-Dimethylaminoethyl]-2(S)-formylferrocene and 1-(S)-[1'-N,N-dimethylaminoethyl]-2(R)-formylferrocene ((R)-(S)-4 and (S)-(R)-4). General procedure:

To a solution of optically active N,N'-dimethyl-(1-ferrocenylethyl) amine **1** (2.90 g, 11 mmol) in Et_2O (10 mL) was added dropwise a solution of *n*-BuLi in hexane (1.6 M, 7.6 mL, 12.1 mmol). After stirrd at r.t. for 1.5 h, the mixture was cooled to -5°C (ice-salt bath), and DMF (1.6 g, 22 mmol) was dropped down over 20 mins. The resultant solution was stirred vigorously at r.t. and monitored by TLC until the reaction was complete. Water (15 mL) was added, and the aqueous phase was extracted with Et_2O (3x15 mL). Then the combined organic phases were dried ($MgSO_4$) and evaporated. Further purification by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate/triethyl amine = 6:2:1) gave the pure product as dark red solid (2.20 g, 70%).

(R)-(S)-**4**: mp: 66~68°C; $[\alpha]^{25}$ -350 (c 0.12, $CHCl_3$). IR (Nujol film): ν 2900, 1670, 1440, 1370, 1040, 820, 770, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.08 (s, 1 H), 4.80 (s, 1 H), 4.60 (m, 2 H), 4.30~4.10 (m, 6 H), 2.12 (s, 6 H), 1.52 (d, J = 6.83 Hz, 3H). EI-MS: m/z (%): 285 (M^+, 17.15), 270 (81.26), 242 (41.99), 212 (100.00), 121 (48.75), 72 (53.36). Anal Cacld for $C_{15}H_{19}FeNO$: C, 63.18; H, 6.71; N, 4.91; Found: C, 63.09; H, 6.82 ; N, 4.92.

(S)-(R)-**4**: mp: 67~68°C; $[\alpha]^{22}$ +360 (c 0.10, $CHCl_3$). IR (Nujol film): ν 2978, 2940, 1672, 1444, 1373, 1043, 823, 769, 719 cm^{-1}. ^1H NMR (300M Hz, $CDCl_3$): δ 10.08 (s, 1 H), 4.80 (s, 1 H), 4.60 (m, 2H), 4.30~4.10 (m, 6 H), 2.12 (s, 6 H), 1.52 (d, J = 6.72 Hz, 3 H). EI-MS: m/z (%): 285 (M^+, 35.33), 270 (100.00), 242 (18.08), 212 (54.81), 121 (23.56), 72 (28.50). HRMS Cacld for $C_{15}H_{19}FeNO$: 285.0816; Found: 285.0810.

1-(R)-[1'-(Trimethylammonium)ethyl]-2(S)-formylferrocene iodide ((R)-(S)-5):

A solution of (R)-(S)-**4** (285 mg, 1 mmol) in acetone (2 mL) was cooled to 0°C and methyl iodide (2.28 g, 16 mmol) was added dropwise. The mixture was stired at 0°C and monitord by TLC. After the reaction was complete, the resulting yellow-orange solid was collected by filtration and dried under vacuum. Recrystallized from acetone/ether gave the pure product (R)-(S)-**5** (350 mg, 82%); mp: 143~145°C; $[\alpha]^{24}$ +387 (c 0.36, acetone). IR (Nujol film): ν 1660,1440, 1410, 1300, 1260, 1000, 820 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 10.18 (s, 1 H), 5.42 (t, J = 6.91Hz, 1 H), 5.35 (s, 1 H), 5.14 (m, 1 H), 5.02 (m, 1 H), 4.50 (s, 5H), 3.02 (s, 9 H), 2.15 (m, 3 H). EI-MS: m/e (%): 240 (M^+-NMe_3I, 100.00), 212 (76.88), 186 (7.55), 146 (12.86), 121 (34.06), 58 (22.98). Anal Cacld for $C_{16}H_{22}FeINO$: C, 44.99; H, 5.19; N, 3.28; Found: C, 44.89; H, 5.20; N, 3.29.

(S)-1-Formyl-2-vinylferrocene ((S)-6):

To a solution of (R)-(S)-**4** (120 mg, 0.42 mmol) in acetone (10 mL) was added dropwise methyl iodide (1.5mL) at r.t.. The mixture was heated to reflux and monitored by TLC. After the reaction was complete, the solvent was removed and the resulting slurry was submitted to column chromatography on silica gel (eluent: petroleum ether /ethyl acetate = 10/1). Pure product (S)-**6** was obtained (96 mg, 95%); oil; $[\alpha]_D^{25}$ +586 (c 0.1, $CHCl_3$) [lit.[8] $[\alpha]_D$ +581 (c 0.18, $CHCl_3$). ^1H NMR (90 MHz, CCl_4, TMS): δ 10.10 (s, 1 H), 7.0 (dd, J = 18.0 and 12.0 Hz, 1 H), 5.50 (d, J = 18.0 Hz, 1 H), 5.20 (d, J = 12.0 Hz, 1 H), 4.80 (m, 2 H), 4.55 (m, 1 H), 4.20 (s, 5 H).

1-(S)-[1'-Acetylethyl]-2(R)-formylferrocene ((S)-(R)-7):

A mixture of (S)-(R)-**4** (168 mg, 0.58 mmol) and acetic anhydride (0.5 mL) was stirred at 100°C and monitored by TLC. After the reaction was complete, the excess acetic anhydride was removed under vacuum. Further purification by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 3 /1) gave (S)-(R)-**7** (144 mg, 81.5%); mp: 80~82 °C; $[\alpha]^{25}$ +459 (c 0.07, $CHCl_3$). IR (Nujol film): ν 2900, 1720, 1670, 1240, 1360, 1060, 940, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, 1 H), 6.15 (q, J = 6.34 Hz, 1 H), 4.90 (m, 1 H), 4.70~4.50 (m, 2 H), 4.20 (s, 5 H), 2.10 (s, 3 H), 1.70 (d, J = 6.34 Hz, 3 H). EI-MS: m/e (%): 300 (M^+, 66.09), 235 (65.65), 180 (100.00), 147 (30.88), 121 (51.91), 91 (26.21). HRMS Cacld for $C_{15}H_{16}FeO_3$: 300.0449; Found: 300.0455.

1-(S)-[1'-Hydroxyethyl]-2(R)-formylferrocene ((S)-(R)-8):

A mixture of (S)-(R)-**4** (350 mg, 1.23 mmol) and acetic anhydride (1 mL) was stirred at 100°C and monitored by TLC. After the reaction was complete, water (5 mL) and Et_2O (10 mL) were added subsequently and the resultant solution was stirred vigorously. The aqueous phase was extracted with Et_2O (3x15 mL), and

the combined organic phases were washed by saturated brine and dried ($MgSO_4$). The solvent was removed under vacuum, and the residue was submitted to column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2/1). Pure procuct (S)-(R)-**8** was obtained (240 mg, 70%);oil ; $[\alpha]^{25}$ -817 (c 0.15, $CHCl_3$). IR (neat): ν 3400~3200, 1650, 1440, 1280, 1240, 1080, 820cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 10.00 (s, 1 H), 4.80 (m, 2 H), 4.65 (m, 1 H), 4.50 (s, 5 H), 1.50 (d, J = 5.37 Hz, 3 H). MS: m/e (%): 258 (M^+, 97.32), 240 (14.76), 193 (33.22), 175 (100.00), 138 (30.53), 121 (26.10). HRMS Cacld for $C_{13}H_{14}FeO_2$: 258.0343; Found: 258.0333.

1-(R)-[1'-Methoxyethyl]-2(S)-formylferrocene ((R)-(S)-9):

A solution of (R)-(S)-**4** (43 mg, 0.1 mmol) in methanol (0.5 mL) and acetonitrile (0.5 ml) was stirred at r.t. and monitored by TLC. After the reaction was complete, water (10 mL) and Et_2O (10 mL) were added. The aqueous phase was extracted with ether (3x10 mL), and the combined organic phases were washed by saturated brine and dried ($MgSO_4$). Preparative TLC on silica gel (eluent: petroleum ether/ethyl acetate = 5/1) afforded the product; oil ; $[\alpha]^{25}$ +148 (c 0.39, $CHCl_3$). IR (neat): ν 2900, 1670, 1260, 1090, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (s, 1 H), 4.85~4.58 (m, 4 H), 4.22 (s, 5 H), 3.20 (s, 3 H), 1.62 (d, J = 5.50 Hz, 3 H). MS: m/e (%): 272 (M^+, 100.00), 242 (36.69), 213 (28.28), 175 (65.85), 147 (31.09), 122 (59.39). HRMS Cacld for $C_{14}H_{16}FeO_2$: 272.0500; Found: 272.0512.

ACKNOWLEDGEMENTS

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