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Enantioselective Synthesis of Sulfur-Containing 1,2-Disubstituted Ferrocenes[1]

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A significant number of transition-metal complexes containing sulfoxides and sulfides has been reported;[3] however, relatively few chiral complexes containing sulfur have been described,[3a,4] and in most of these cases, chiral sulfoxides were first synthesized and complexation with various transition-metal complexes was then carried out.[3a,4a,b] Chiral transition-metal complexes containing sulfides have not been reported. Furthermore, asymmetric catalysis utilizing chiral transition-metal complexes containing sulfur is relatively rare.[3a,4] We have studied the stereoselective synthesis of various chiral bi- and tridentates containing sulfur and their use in asymmetric catalysis. We now report a stereoselective synthesis of enantiomerically pure 2-substituted 1-(*tert*-butylsulfinyl)ferrocenes via the trapping of (S*R*,1*S*,2*R*)-1-(*tert*-butylsulfinyl)-2-lithioferrocene (**1**) with various electrophiles, subsequent conversion to sulfides and sulfones, and stereoselective addition to (S*R*,1*S*,2*R*)-1-(*tert*-butylsulfinyl)-2-formylferrocene.

Scheme 1

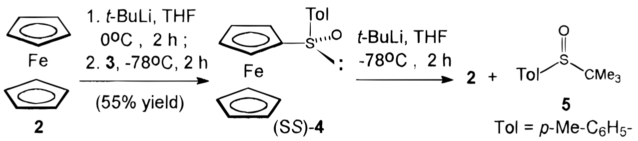
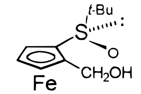
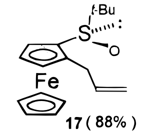
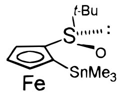
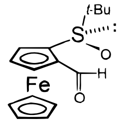
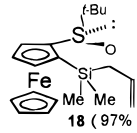
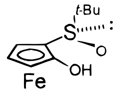
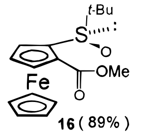
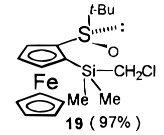
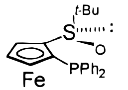
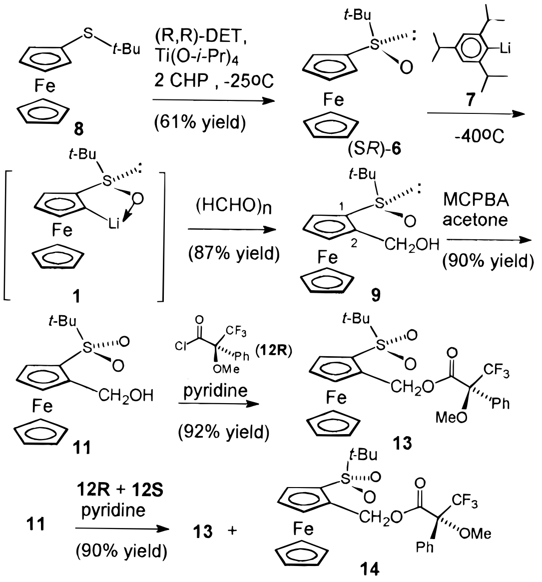


Table 1. Products and Yields of the Reactions of the Lithiated Anion of 6 with Various Electrophiles

Entry	Product (% yield)	Entry	Product (% yield)	Entry	Product (% yield)
1	 **9** (87%)	4	 **17** (88%)	7	 **20** (95%)
2	 **15** (98%)	5	 **18** (97%)	8	 **21** (66%)
3	 **16** (89%)	6	 **19** (97%)	9	 **22** (96%)

[a] Yields based on recovered starting sulfoxide **6** (5−25% recovery). [b] Reagents: entry 1, $(CH_2O)_n$; entry 2, EtOCHO; entry 3, $ClCO_2Me$; entry 4, $BrCH_2CH{=}CH_2$; entry 5, $ClSi(Me)_2CH_2CH{=}CH_2$; entry 6, $ClSi(Me)_2CH_2Cl$; entry 7, $ClSnMe_3$; entry 8, $Me_3SiOOSiMe_3$; entry 9, $ClPPh_2$.

Scheme 2



Our goal was to first synthesize a chiral ferrocenyl sulfoxide and then stereoselectively introduce a second functional group at C-2 of the ferrocene ring. For the synthesis of enantiomerically pure ferrocenyl sulfoxide, we initially investigated the direct sulfinylation of ferrocene (**2**) with *t*-BuLi in THF at 0 °C followed by the addition of (S*S*)-*l*-menthyl *p*-tolylsulfinate (**3**) at −78 °C for 2 h (Scheme 1). (S*S*)-(*p*-Tolylsulfinyl)ferrocene (**4**) was isolated in 55% yield with a specific rotation of +246° (*c* = 0.5, $CHCl_3$).[5] Kagan et al.[4d] reported a similar reaction in which sulfinate **3** was allowed to react with lithiated ferrocene at 0 °C yielding sulfoxide **4** with a specific rotation of +4° (*S*-configuration). From a later report by Kagan et al.[4f] describing the synthesis of **4** from the asymmetric oxidation of the corresponding sulfide, we realized that our product **4** is 81% ee. This partial racemization process[6] at −78 °C, resulting from nucleophilic attack by lithiated ferrocene on (S*S*)-**4** to provide (S*R*)-**4**, was proven by the treatment of our 81% optically pure (S*S*)-**4** with 1 equiv of lithiated ferrocene in THF at 0 °C for 1 h (derived from **2** and *t*-BuLi), which gave racemized **4** [$[\alpha]^{22}_{D} = +25.4°$; 8% ee]. Surprisingly, in contrast to the reported[4e] C-2 deprotonation of ferrocenyl sulfoxides with various bases (such as *n*-BuLi and LDA), treatment of **4** with *t*-BuLi in THF at −78 °C for 2 h resulted in the formation of *tert*-butyl *p*-tolyl sulfoxide (**5**; 41% yield) and ferrocene (**2**; 84% yield) from the nucleophilic displacement reaction at the sulfur center.[7] To avoid the nucleophilic displacement reaction, we investigated a bulkier sulfoxide, (S*R*)-(−)-(*tert*-butylsulfinyl)ferrocene (**6**),[4f] and a sterically hindered base, (2,4,6-triisopropylphenyl)-

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[1] Part of this work was presented in the 210th ACS National Meeting, Chicago, IL; Aug 20, 1995; Abstr. ORGN 185.

[2] To whom inquiries regarding the X-ray analysis should be addressed. Department of Geology, Southern Illinois University at Carbondale, Carbondale, IL 62901.

[3] Transition-metal complexes containing sulfoxides. For a review, see: (a) Kagan, H. B.; Roan, B. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; Ivlyu K. K.: Tokyo, Japan, 1992; Vol. 7, p 92. (b) Ibbotson, A.; Reduto dos Reis, A. C.; Saberi, S. P.; Slawn, A. M. Z.; Thomas, S. E.; Tustin, G. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans 1.* **1992**, 1251. Sulfoxides and sulfides: (c) Quiros Mendez, N.; Arif, A. M.; Gladysz, J. A. *Organometallics* **1991**, *10*, 2199. (d) Riley, D. P.; Oliver, J. D. *Inorg. Chem.* **1986**, *25*, 1814; (e) 1821. (f) Fritz, H. P.; Kreiter, C. G. *J. Organomet. Chem.* **1967**, *7*, 427. (g) Sato, M.; Sekino, M. *J. Organomet. Chem.* **1989**, *377*, 327.

[4] For a review, see: (a) Zassinovich, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051. (b) James, B. R.; McMillan, R. S. *Can. J. Chem.* **1977**, *55*, 3927 and references cited therein. (c) Herrmann, R.; Hubener, G.; Ugi, I. *Tetrahedron* **1985**, *41*, 941. (d) Rebiere, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, 3121. (e) Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568. (f) Diter, P.; Samuel, O.; Taudien, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **1994**, *5*, 549. (g) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1994**, *13*, 441. (h) Griffiths, S. L.; Perrio, S.; Thomas, S. E. *Tetrahedron: Asymmetry* **1994**, *5*, 545; (i) 1847.

[5] The substitution of **3** occurs with inversion of configuration at the sulfur center: Andersen, K. K. *Tetrahedron Lett.* **1962**, 93.

[6] This racemization process was not reported previously, and the optical purity of the products described in ref 4d, was not determined.

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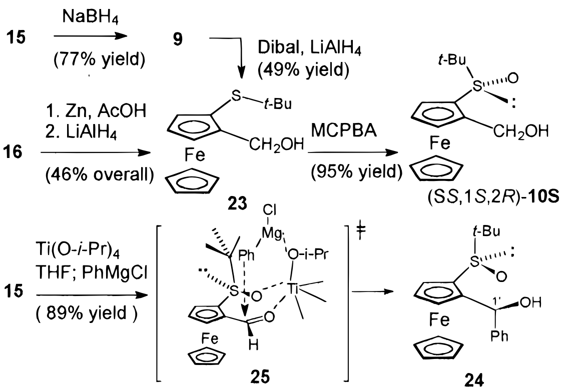
lithium (**7**).[8] Following Kagan's method[4f] using L-(*R*,*R*)-diethyl tartrate (DET), titanium tetraisopropoxide, and cumene hydroperoxide (CHP) in CH_2Cl_2 and H_2O at −25 °C for 72 h, we converted sulfide **8** into sulfoxide (S*R*)-**6** in 61% yield with specific rotation $[\alpha]^{22}_D = -357.8°$ (*c* 0.505, $CHCl_3$; ~100% ee) [lit.[4f] $[\alpha]^{22}_D = -339°$ (*c* 0.505, $CHCl_3$); *R*-configuration, 95% ee] (Scheme 2). Treatment of sulfoxide (S*R*)-**6** with the hindered base **7** in THF at −40 °C followed by trapping of the lithiated anion **1** with paraformaldehyde afforded an 87% yield (based on 5% unreacted **6**) of alcohol **9**. The absolute configuration of **9** was determined by a single-crystal X-ray analysis indicating an (S*R*,1*S*,2*R*)-configuration.[9a] The crystal has an acentric space group, $P2_12_12_1$ with $R = 0.048$ and $R_w = 0.042$.[9b] The ^{1}H NMR spectrum of crude **9** indicated the absence of the (S*R*,1*R*,2*S*)-isomer, **10R**. Its enantiomer, (S*S*,1*S*,2*R*)-**10S**, was unequivocally synthesized (*vide infra*), and its TLC and ^{1}H and ^{13}C NMR spectra were different from those of **9**. Apparently, the base **7** deprotonates **6** regioselectively to allow a chelation of the lithium ion with the sulfoxide oxygen as depicted in **1**.[10] The optical purity of **9** was determined to be >99% ee by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) to sulfone **11** (90% yield) followed by esterification with Mosher's acid chloride **12*R***[11] to give ester **13**. The ^{1}H NMR spectrum of crude **13** indicated only two doublets, one at δ 5.67 and the other at 5.32 ppm, assigned to the C*H*$_2$O of **13**. The Mosher derivatives of **11** from the reaction with racemic acid chloride (*R*,*S*)-(±)-**12** were also prepared, and the ^{1}H NMR spectrum of the products showed two sets of chemical shifts indicating two diastereomers; the resonances of C*H*$_2$O of diastereomer **14** appeared at δ 5.58 (doublet) and 5.36 (doublet).[12]

Various disubstituted ferrocenes were synthesized in excellent yields by reactions of anion **1** with a variety of electrophiles of carbon (ethyl formate, methyl chloroformate, allyl bromide), silicon ($CH_2{=}CHCH_2SiMe_2Cl$, $ClCH_2SiMe_2Cl$), tin (Me_3SnCl), and phosphorus (Ph_2PCl). The oxygen electrophile bis(trimethylsilyl) peroxide provided only a 66% yield. The results are summarized in Table 1. The regiochemistry and optical purity of aldehyde **15** and ester **16** were determined by the following correlations. Reduction of **15** with $NaBH_4$ in MeOH at 25 °C gave **9** (77% yield) (Scheme 3), whose NMR spectra and specific rotation were identical with those of the sample obtained from the reaction of **1** with $(HCHO)_n$. Reduction of **16** of the corresponding sulfide with zinc in acetic acid at 25 °C (48% yield; based on 3% recovery of **16**) followed by treatment with $LiAlH_4$ in ether (96% yield) gave alcohol **23**, whose spectral data and specific rotation were identical to those obtained from the product of the reduction of sulfoxide **9** with DIBALH and LAH in ether at 25 °C (49% yield).[13] Other disubstituted ferrocenes, **17**−**22**, were assumed to have the same regiochemistry. Sulfide **23** was stereoselectively oxidized with 1 equiv of *m*-CPBA in THF at 25 °C to give (S*S*,1*S*,2*R*)-**10*S*** (95% yield).

Scheme 3



Stereoselective addition of an organometallic reagent to aldehyde **15** was achieved by prechelation with Ti(O-*i*-Pr)$_4$ in THF followed by reaction with PhMgCl to give an 89% yield of alcohol (1′*S*)-**24**.[14] The stereochemistry of **24** was determined by single-crystal X-ray analysis. Without the addition of Ti(O-*i*-Pr)$_4$, **24** and its 1′*R*-isomer were produced in a 4.4:1 ratio. The transition state of this addition reaction, proposed in structure **25**, suggests attack by the phenyl group to the aldehyde function from the *si*-face[15a] of the aldehyde.[15b]

In summary, various enantiomerically pure bidentates were synthesized that contain a sulfinyl, sulfonyl, or sulfenyl moiety at C-1 and a carbon or heteroatom substituent at C-2 of the ferrocene ring. The use of these bidentates in asymmetric catalytic reactions is being investigated. (S*R*,1*S*,2*R*)-1-(*tert*-butylsulfinyl)-2-formylferrocene (**15**) has been shown to undergo stereoselective nucleophilic addition reactions with Grignard reagents under chelation control conditions.

Supporting Information Available: Procedures for the preparations and full characterization of **4**−**7**, **9**−**11**, and **13**−**24**, partial ^{1}H NMR spectra (the $CH_2OC{=}O$ region) of **13** and a mixture of **13** and **14**, and the ORTEP drawing of the X-ray crystallographically determined structure of **9** (20 pages).

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[7] Sulfoxide **5** has $[\alpha]^{22}_D = +1.0°$ (*c* 1.5, acetone) (lit.[7] $[\alpha]^{22}_D + 161°$ for *R*-configuration). Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958. The small amount of lithiated ferrocene, initially formed from the reaction of *t*-BuLi and (S*S*)-**4**, underwent displacement reaction with (S*S*)-**4** in a faster rate than that of *t*-BuLi to give racemic **4**, which then provided racemic **5** upon reaction with *t*-BuLi.

[8] Derived from the reaction of 1-bromo-2,4,6-triisopropylbenzene with *t*-BuLi in THF at −78 °C for 2.5 h. (a) Bonini, B. F.; Grossi, L.; Lunazzi, L.; Macciantelli, D. *J. Org. Chem.* **1986**, *51*, 517. Prepared from the bromination of 1,3,5-triisopropylbenzene by a method similar to that used with 1,3,5-mesitylene: (b) Smith, L. I. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, p 95.

[9] (a) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) The acentric space group implies that only one enantiomer is present if the compound is optically active. When the enantiomer of **9** was calculated using the collected X-ray data, the *R* factors increased to $R = 0.054$ and $R_w = 0.049$. This indicated that the enantiomer chosen is the correct one.

[10] Although this regioselective deprotonation reaction was reported by Kagan et al.[4e] with *n*-BuLi or LDA, the optical purity of their products as mentioned above (see ref 6) was not determined. An amido-directed enantioselective deprotonation of an amidoferrocene with *n*-BuLi−(−)-sparteine was reported recently: Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685. See references cited therein for other amino-directed selective deprotonation of substituted ferrocenes.

[11] Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[12] It should be noted that were the enantiomer of **11** present, it would have reacted with **12*R*** to produce the enantiomer of **14**. However, the NMR spectrum of **13** (derived from **11** and **12*R***) indicated only one diastereomer, implying that **11** is 100% optically pure.

[13] Diisobutylaluminum hydride (DIBALH) was used to prechelate the hydroxyl and sulfoxide moieties of **9**. Without the addition of Dibal, LAH alone gave only 25% yield of **23**. Reduction of **9** with Zn in AcOH was sluggish, and mainly starting material was recovered.

[14] The prechelation of sulfoxide with Lewis acid has been reported previously: (a) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72. (b) Solladie, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, 435.

[15] (a) The Izumi−Tai nomenclature is employed: Izumi, Y.; Tai, A. *Stereodifferentiating Reactions*; Kodansha Ltd.; Tokyo: Academic Press: New York, 1977; pp 68. (b) This result is contrary to those reported for the additions of other nonchelated 2-substituted 1-formylferrocenes with Grignard reagents: Taudien, S.; Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1995**, 3513.

[16] Financial support from Research Corporation and from the National Science Foundation, EPSCoR program, are gratefully acknowledged.