

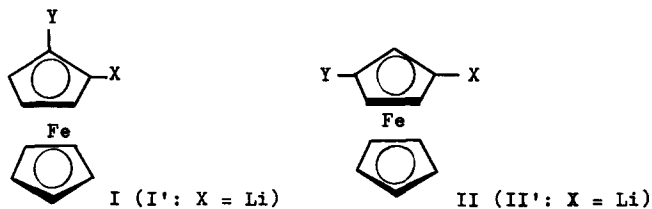
ASYMMETRIC LITHIATION OF FERROCENES

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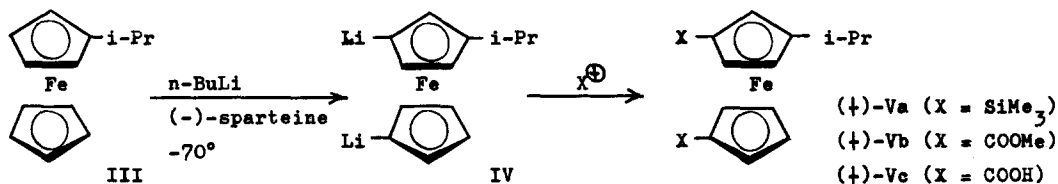
(Received in Japan 25 April 1969; received in UK for publication 5 May 1969)

Ferrocene derivatives are chiral when they have two different substituents X and Y in one cyclopentadienyl ring (I and II) and thus can be resolved into optical antipodes. This has been demonstrated by K. Schlögl et al. and the absolute configuration of about ninety compounds is now established (1). We wish to report the asymmetric syntheses of lithioferrocenes (I' and II') which serve as key compounds for the determination of the absolute configuration of some new ferrocene derivatives.



Ferrocene itself has been metallated with *n*-butyllithium-tetramethylethylenediamine complex to afford only 1,1'-dilithioferrocene in excellent yield (2). (-)-Sparteine as a bidentate ligand gives a modified organolithium reagent which induces the asymmetric syntheses of cyclic allenes (3a) and carbinols (3b). Lithiation of isopropylferrocene (III) was now effected by means of a mixture of *n*-butyllithium and (-)-sparteine (2.5 equivalents each) in hexane at -70° for 10 hr. and the reaction mixture was treated with excess trimethylchlorosilane. The product was subjected to gas chromatographic analysis (Apiezon L, 200°), which indicated the presence of the recovered III (15%) and 3-isopropyl-1,1'-bis(trimethylsilyl)ferrocene (Va, 80%) accompanied by the other isomeric mono- and bis-trimethylsilyl substituted ferrocenes (total 5%). This procedure is more advantageous than those in diethyl ether (4) in order to obtain 3,1'-dilithio-1-alkylferrocene. Furthermore the isolated Va showed optical activity, b.p. 135°/4 mm, $[\alpha]_D^{20} +0.7^\circ$ (c 5.9, benzene). The dilithioferrocene (IV) was fully carbonated and esterified with diazomethane to give (+)-dimethyl 3-isopropylferrocene-1,1'-dicarboxylate (Vb), m.p. 49-50°, $[\alpha]_D^{20} +2.5^\circ$ (c 1.9, benzene) (chromatography on alumina, 58% yield).

Hydrolysis of this (+)-diester gave (+)-3-isopropylferrocene-1,1'-dicarboxylic acid (Vc), m.p. $\sim 200^\circ$ (dec), $[\alpha]_D^{20} +3.8^\circ$ (c 1.3, methanol).



Since these compounds have been derivatized from the same dissymmetric dilithioferrocene IV they should have the same absolute configuration and the same optical purity. Among them, (+)-(1S)-3-isopropylferrocene-1,1'-dicarboxylic acid (Vc) is correlated with (+)-(1S)-3,1'-dimethylferrocene-1-carboxylic acid (VIIa) (5) as follows and the optical yield is calculated to be 3%. Dicarboxylic acid was resolved by means of (-)-phenethylamine salts to give (+)-Vc, $[\alpha]_D^{20} +110^\circ$ (c 0.68, methanol), and then esterified to diester (+)-Vb, $[\alpha]_D^{20} +77^\circ$ (c 0.78, benzene), which was reduced with a mixture of lithium aluminium hydride and aluminium chloride to yield (+)-1,1'-dimethyl-3-isopropylferrocene (VI), b.p. 110° (bath)/2 mm, $[\alpha]_D^{20} +2.0^\circ$ (c 1.0, cyclohexane). On the other hand, the enantiomer (-)-(1R)-VI, $[\alpha]_D^{20} -1.0^\circ$ (c 6.7, cyclohexane), was obtained upon similar reduction of (-)-(1S)-1- α -hydroxyisopropyl-3,1'-dimethylferrocene (VIIc), $[\alpha]_D^{20} -2.0^\circ$ (c 4.3, ethanol), which was alternatively prepared by the reaction of two equivalents of methyllithium on (+)-(1S)-methyl 3,1'-dimethylferrocene-1-carboxylate (VIIb), $[\alpha]_D^{20} +10^\circ$ (c 2.0, benzene) (45% optical purity) (5a).

Specific 2-lithiation of N,N-dimethylaminomethylferrocene and 1-ferrocenylmethylpiperidine has been recorded by Hauser et al. and ascribed to the intramolecular coordination of nitrogen lone pair to lithium atom forming a five membered chelate ring (6). We have synthesized (+)-(1S)-1-ferrocenylmethyl-2-methylpiperidine (VIII), m.p. $38-39^\circ$, $[\alpha]_D^{20} +70^\circ$ (c 2.0, ethanol), by the action of (+)-(1S)-2-methylpiperidine, $[\alpha]_D^{20} +33^\circ$ (neat, 93% optical purity) (7), on the methiodide of N,N-dimethylaminomethylferrocene in a 70% yield. This amine (+)-VIII was metallated with n-butyllithium in ether-hexane at room temperature for 40 hr. and the resulting lithioamine (IX) was completely carbonated. The amino acid (Xa: X = COOH) was quarterized with excess methyl iodide and the crude product was thoroughly reduced with sodium amalgam in water. Esterification with diazomethane, followed by chromatography on alumina, gave (-)-(1S)-1-carbomethoxy-2-methylferrocene (XIa) of 94% optical purity (Table I). This means

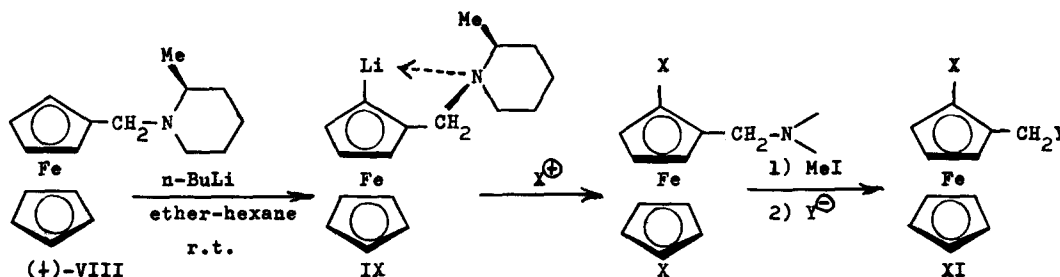


Table I. Asymmetric Lithiation of (+)-1-Ferrocenylmethyl-2-methylpiperidine (VIII)^a

Compound ^b	X	CH ₂ Y	Yield, %	$[\alpha]_D^{20}$, deg. ^c	\underline{c} , g/100 ml	b.p. [m.p.]
(-)-XIa	COOMe	CH ₃	24 ^d	-10 ^f	1.9 (benzene)	125°(bath)/1.5 mm
(+)-XIb	SiMe ₃	CH ₃	29 ^d	+3.0	3.7 (benzene)	135°(bath)/2 mm
(+)-XIc	SiMe ₃	CH ₂ OH	21 ^d	+1.3	5.2 (benzene)	[60-62°] ^g
(+)-XIId	SiMe ₃	CHO	63 ^e	+130	0.25(ethanol)	[67-70°] ^h

^a Optical purity was 93% (see text). ^b All compounds exhibited NMR and IR spectra consistent with the assigned structures and gave correct elemental analyses.

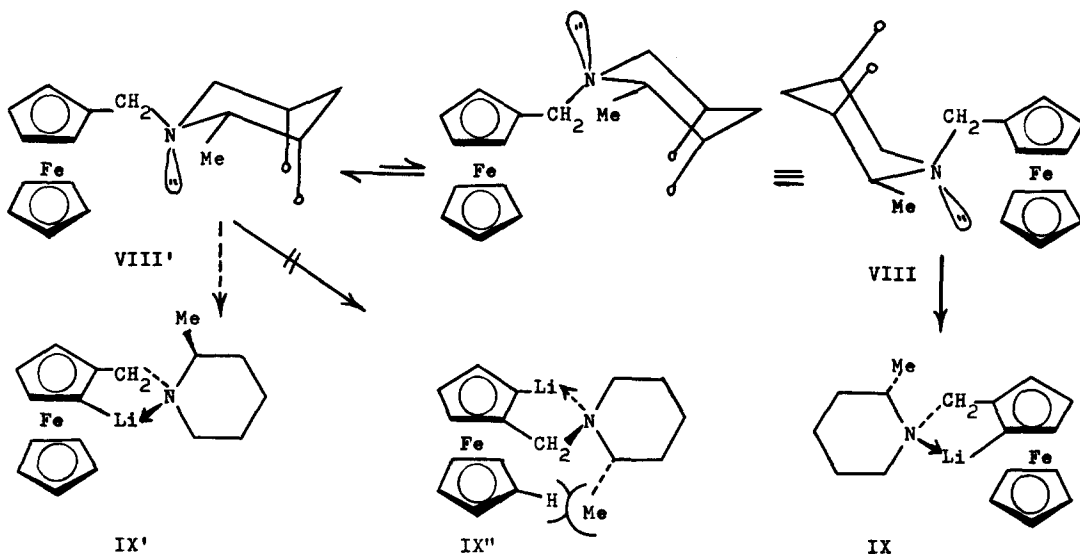
^c All rotations were measured with a 5 cm cell. ^d Based on VIII. ^e Based on XIc.

^f Optical purity was 94% (ref 8). ^g Ref 9. ^h The semicarbazone melted at 175-176°(dec).

that asymmetric synthesis of 2-lithioamine IX of the absolute configuration as shown is achieved in almost quantitative optical yield. The lithioamine IX was condensed with excess trimethylchlorosilane and the resulting silylamine (Xb: X = SiMe₃) (10) was quarterized with methyl iodide. The methiodide was treated with sodium amalgam in water to give (+)-(1S)-2-methyl-1-trimethylsilylferrocene (XIb). Hydrolysis of methiodide in the presence of aqueous sodium hydroxide yielded (+)-(1S)-2-hydroxymethyl-1-trimethylsilylferrocene (XIc), which was oxidized with active manganese dioxide to give (+)-(1S)-2-formyl-1-trimethylsilylferrocene (XIId).

The preference of 2-lithioamine IX over its diastereomer IX' may be explained as follows. The presumably stable conformer VIII' is expected to give IX' instead of IX" on the basis of model inspection, which reveals that considerable interaction exists between methyl group and aromatic hydrogens of the other ring. The inertness of VIII' towards this metallation should be ascribed to the fact that its lone pair is hindered by 1,3-diaxial hydrogens. Flipping on nitrogen (11) gives rise to less preferred conformer VIII, whose lone pair is appropriately directed to participate in 2-lithiation

process leading to IX stereoselectively.



REFERENCES

1. K. Schlögl, "Stereochemistry of Metallocenes" in Topics in Stereochemistry, edited by N. L. Allinger and E. L. Eliel, Vol. 1, p. 39, Interscience, New York (1967).
2. M. D. Rausch and D. J. Ciappenelli, J. Organometal. Chem. **10**, 127 (1967).
3. (a) H. Nozaki, T. Aratani and R. Noyori, Tetrahedron Letters, 2087 (1968);
(b) H. Nozaki, T. Aratani and T. Toraya, Tetrahedron Letters, 4097 (1968).
4. R. A. Benkeser and J. L. Bach, J. Am. Chem. Soc. **86**, 890 (1964). These authors also describe the identification of Va, b and c.
5. (a) G. Haller and K. Schlögl, Monatsh. Chem. **98**, 603 (1967); (b) O. L. Carter, A. T. McPhail and G. A. Sim, J. Chem. Soc. (A), 365 (1967).
6. (a) D. W. Slocum, B. W. Rockett and C. R. Hauser, J. Am. Chem. Soc. **87**, 1241 (1965);
(b) M. Hadlington, B. W. Rockett and A. Nelhans, J. Chem. Soc. (C), 1436 (1967).
7. H. Ripperger and K. Schreiber, Tetrahedron, **21**, 1485 (1965).
8. H. Falk, K. Schlögl and W. Steyer, Monatsh. Chem. **97**, 1029 (1966).
9. G. Marr, J. Organometal. Chem. **9**, 147 (1967).
10. (+)-Xb formed an oil, b.p. 140°/0.15 mm, $[\alpha]_D^{20} +71^\circ$ (c 1.5, ethanol). ORD (c 0.15, ethanol, 20°) of (+)-Xb: $[\phi]_{589} +260^\circ$, $[\phi]_{450} +790^\circ$ (shoulder), $[\phi]_{300} +2100^\circ$; that of (+)-VIII: $[\phi]_{589} +210^\circ$, $[\phi]_{490} +500^\circ$ (shoulder), $[\phi]_{300} +1300^\circ$.
11. J. B. Lambert, R. G. Keske, R. E. Carhart and A. P. Jovanovich, J. Am. Chem. Soc. **89**, 3761 (1967) and references cited therein.

Acknowledgement. The authors are grateful to Prof. K. Sisido for help and encouragement.