Highly Diastereoselective Ortho Lithiations of Chiral Oxazoline-Substituted Ferrocenes

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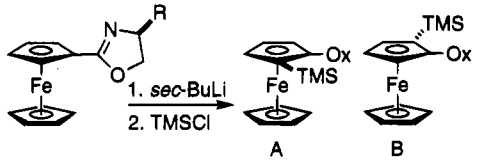
Received October 27, 1994

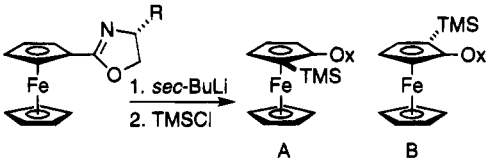
We have initiated a program to study methods of asymmetric synthesis using ferrocene complexes which possess planar chirality. Our studies require a versatile method for the synthesis of this class of molecules which will enable us to prepare a variety of derivatives with only minor modifications of the route. Ferrocene complexes which possess planar chirality have been known for some time and have most often been prepared in nonracemic form by classical resolution.[1-3] However, this method has practical limitations in that the resolution procedure must be modified for each substrate, and is consequently time consuming if a variety of molecules are to be synthesized. We have therefore investigated an asymmetric synthesis of these molecules which relies on the directed metalation of chiral ferrocenyloxazolines. We have been able to achieve high yields and high levels of diastereoselection in this reaction. While our work was in progress, Kagan described a related reaction which utilizes a chiral ferrocenyl acetal to direct the metalation.[4]

The ortho lithiation of ferrocenes is known to be directed by a variety of heteroatom-containing groups, including achiral oxazolines.[5] Chiral oxazolines have been shown by Meyers to be effective asymmetric inducing agents for a number of reactions,[6] and we reasoned that they may also induce asymmetry in the metallation of ferrocenes. We therefore synthesized the ferrocene derivatives shown in Table 1[7] and examined their diastereoselectivities in the metalation reaction. Standard metalation conditions were employed for all of these substrates. Accordingly, the chiral oxazolines were

Table 1



Cmpd	R	A : B
1	*tert*-butyl	36:1
2	*iso*-propyl	8:1
3	phenyl	6:1
4	benzyl	3:1
5	CH_2SMe	3:1
6	CH_2OMe	4:1
7	CH_2OTBS	2:1
8	CH_2OCH_2OMe	4:1



Cmpd	R	A : B
9	CMe_2OMe	1:19
10	CEt_2OMe	1:10

treated with 1.2 equiv of *sec*-butyllithium at −78 °C in THF for a period of 2 h followed by 5 min at 0 °C to ensure complete metalation. The lithiated species were then trapped with trimethylsilyl chloride at 0 °C, and the reaction mixture was allowed to warm to room temperature to produce the TMS-substituted ferrocene derivatives with the diastereoselectivities shown in Table 1. Some interesting trends are apparent from this data. First, the reaction seems to be governed predominantly by steric effects; as the group on the oxazoline becomes larger, the selectivity increases (compare entries 1–4), with a *tert*-butyl group providing the highest level of selectivity (36:1, 83–96% yield) and excellent yields. Second, additional heteroatom coordination does not appear to enhance the selectivity of this reaction (compare entries 4–8), a result which we found surprising in light of the work of Meyers where a substantial increase in selectivity has been observed upon heteroatom coordination.[6]

The sense of asymmetric induction was determined by correlation with an authentic sample prepared by the method of Ugi (Scheme 1). (*S*)-(−)-*N*,*N*-Dimethyl-1-ferrocenylethylamine ($[\alpha]_D = -11.3°$, $c = 5.1$ mg/mL, EtOH)[1] was metalated and trapped with methyl iodide.[8] The dimethylamino group was then substituted for an acetoxy group by treatment with acetic anhydride at room temperature. The acetate group was removed with LAH and the resulting alcohol oxidized to the ketone[9] with NMO in the presence of a catalytic amount of TPAP.[10] This material displayed a specific rotation of

(1) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389; Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. K. *J. Am. Chem. Soc.* **1973**, *95*, 482.

(2) For other methods of asymmetric synthesis of disubstituted ferrocenes which do not rely on classical resolution, see: (a) Ratajczak, A.; Misterkiewicz, B. *J. Organomet. Chem.* **1975**, *91*, 73. (b) Hayashi, T.; Mise, T.; Kumada, M. *Tetrahedron Lett.* **1976**, *48*, 4351. (c) Wang, Y.-F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C.-H. *J. Am. Chem. Soc.* **1988**, *110*, 7200. (d) Boaz, N. W. *Tetrahedron Lett.* **1989**, *30*, 2061.

(3) For lead references to the synthesis of chromium arene complexes possessing planar chirality, see: Aube, J.; Heppert, J. A.; Milligan, M. L.; Smith, M. J.; Zenk, P. *J. Org. Chem.* **1992**, *57*, 3563; Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182.

(4) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835. Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568.

(5) For examples of directed metalation of ferrocene compounds see: (a) Slocum, D. W.; Rockett, B. W.; Hauser, C. R. *J. Am. Chem. Soc.* **1965**, *87*, 1241. (b) Bolton, E S.; Pauson, P. L.; Sandhu, M. A.; Watts, W. E. *J. Chem. Soc. C* **1969**, *17*, 2260. (c) Marr, G. *J. Organomet. Chem.* **1967**, *9*, 141. (d) Schmitt, G.; Klein, P.; Ebertz, W. *J. Organomet. Chem.* **1982**, *234*, 63. For reviews of directed metalation of aryl compounds see: (e) Gilman, H.; Morton, J. W., Jr. J. W. *Org. React.* **1954**, *8*, 258. (f) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (g) Gschwend, H.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (h) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(6) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, 1984; Vol. 3, Part B, Chapter 3.

(7) The details of the synthesis of these complexes are contained in the supplementary material.

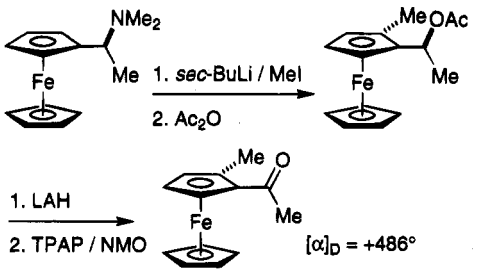
(8) Marquarding, D.; Burghard, H.; Ugi, I.; Urban, R.; Klusacek, H. *J. Chem. Res., Synop.* **1977**, 82.

(9) This ketone is a known compound (Marquarding, D.; Burghard, H.; Ugi, I.; Urban, R.; Klusacek, H. *J. Chem. Res., Synop.* **1977**, 82; *J. Chem. Res., Miniprint* 0915. Schlogel, K. In *Topics in Stereochemistry*; Elliel, E. L., Allinger, N. L., Eds.; Wiley: New York, 1967; pp 39–91); however, we wished to double check the stereochemistry by independent synthesis.

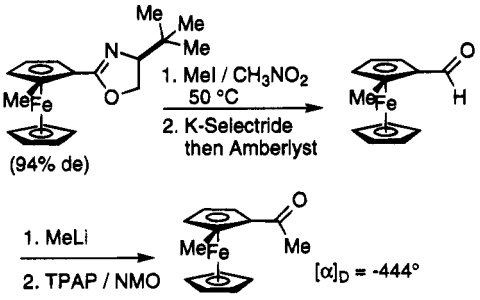
(10) Griffin, W. P.; Ley, S. V.; Whitecombe, G. P.; White, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

0022-3263/95/1960-0010$09.00/0

Scheme 1



Scheme 2



+486° (c = 8.69 mg/mL, CH_2Cl_2) and was compared with that derived from the *tert*-butyl-substituted ferrocenyloxazoline prepared by metalating and trapping with methyl iodide to provide the substituted ferrocene. The nitrogen of the oxazoline was then alkylated with methyl iodide in nitromethane at 50 °C and then reduced with K-Selectride (Aldrich) to provide a labile aminal which underwent hydrolysis to the corresponding aldehyde upon treatment with Amberlyst 15 in wet THF (Scheme 2).[11] Addition of methyllithium to this aldehyde provided a 4:1 mixture of diastereomeric alcohols which were oxidized to the desired ketone with NMO in the presence of a catalytic amount of TPAP. This material displayed a specific rotation of −444° (c = 2.3 mg/mL, CH_2Cl_2) indicating that the absolute stereochemistry is the opposite of that derived from the material prepared by the method of Ugi.[12]

In summary, the ferrocenyloxazoline derived from *tert*-leucine is a valuable precursor for the synthesis of asymmetrically disubstituted ferrocenes with planar chirality. It is easily synthesized by condensation of ferrocenecarbonyl chloride and *tert*-leucinol, followed by cyclization to the corresponding oxazoline. The directed ortho lithiation of this substrate proceeds with high levels of diastereotopic group selectivity, and the resulting lithiated intermediate can be trapped with a variety of electrophiles. The oxazoline can be subsequently removed in order to provide enantiomerically pure chiral ferrocene derivatives for use as chiral reagents or ligands. The origin of asymmetric induction in the metalation reaction and the use of ferrocene complexes in asymmetric synthesis are subjects of further investigations in our laboratory.

Acknowledgment. We gratefully acknowledge Professor Al Meyers for a gift of *tert*-leucine and for valuable discussions, and NSC Technologies, a Division of the Nutra Sweet Co., for a gift of *tert*-leucine. We thank the National Institutes of Health (GM48498), the Camille and Henry Dreyfus Foundation (New Faculty Award to T.S.), the American Cancer Society (Junior Faculty Research Award to T.S.), and the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research.

Supplementary Material Available: Complete spectral characterization and experimental details for the syntheses of all TMS-substituted ferrocenyloxazolines and their precursors and the correlation of planar chirality (23 pages).

JO941795T

(11) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531. Wilson, S. R.; Mao, D. T.; Khatri, H. N. *Synth. Commun.* **1980**, 17.

(12) A similar analysis of the material derived from **9** provides consistent results. Since the oxazoline of **9** has the opposite absolute stereochemistry of the oxazoline derived from L-*tert*-leucine, it provides the opposite enantiomer and the same enantiomer as the material prepared by the method of Ugi.