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An Enantioselective Synthesis of Optically Pure Azaferrocenyl Anions—First General and Practical Approach to Chiral Azaferrocenes

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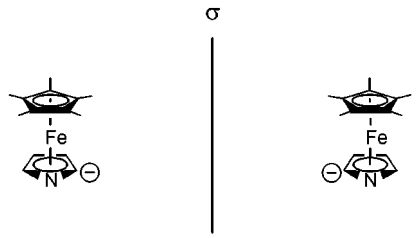
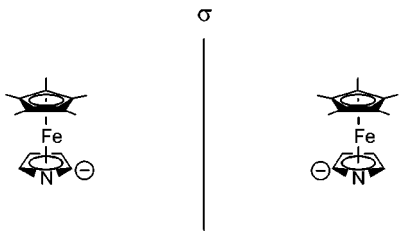
ABSTRACT



Herein we report a very simple route that allows the construction of a variety of optically pure azaferrocenyl compounds. The key feature is the preparation of optically pure 2-azaferrocenyl anions, which can serve as precursors for the construction of novel chiral azaferrocenyl complexes.

During the past decades the ferrocene moiety has proven to be one of the most efficient and generally applicable backbones in chiral ligands.[1] This is due in part to the diversity of ligand structure that is available in a straightforward manner from a single optically pure ferrocenyl (anion) building block.[2] Recently it has been shown by Fu et al. that the planar chiral azaferrocenyl group also is a very efficient chiral controller in asymmetric catalysis.[3] However, no general procedure for synthesizing optically pure azaferrocenes was available. Hitherto, such compounds (e.g., (+)-**4e**) have been synthesized as racemic samples, which were then resolved via crystallization or on a chiral stationary column.[4−6]

Herein, we report a very simple route that allows the construction of a variety of optically pure azaferrocenyl compounds. The key feature is the preparation of optically pure 2-azaferrocenyl anions, which exist as a pair of planar chiral enantiomers:



The first step in the synthesis and resolution of the new chiral building blocks involves a directed ortho lithiation of the pentamethylated azaferrocene **1**, giving solely the 2-lithi-

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(1) (a) Togni, A.; Hayashi, T. *Ferrocenes*; VCH: Weinheim, 1995. (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (c) Togni, A.; Halterman, R. L. *Metallocenes*; Wiley-VCH: Weinheim, 1998; Vol. 2, pp 685−721.

(2) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389; see also ref 1a−c.

(3) (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444. (c) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230. (d) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637. (e) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270.

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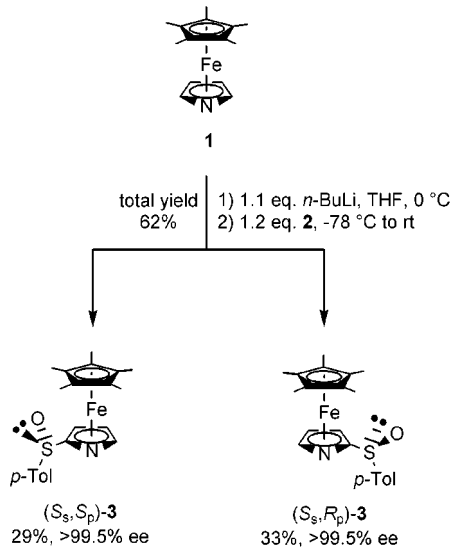
ated isomer, which is trapped by the addition of (1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate **2**.[7] To our satisfaction the reaction went well giving the two diastereomeric products (S_S,S_P)-**3** and (S_S,R_P)-**3**, both with a surprisingly high ee (>99.5%).[8−9] Initially we used a slow cannulation technique to transfer the lithiated azaferrocene to the sulfinate in order to avoid in situ racemization. However, it was soon realized that the simple addition of the solid sulfinate ester to the anion at −78 °C sufficed. After the reaction mixture was warmed to room temperature, the two diastereoisomers could easily be separated on a standard flash column, giving the enantiopure sulfoxides in 29% and 32% yield (62% total yield) (Scheme 1). We presume the clean inversion at sulfur

Scheme 1



is governed by the ortho stabilizing effect of the nitrogen atom. This finding could be of importance for the resolution of other related structures.

(4) For the first resolution of a chiral azaferrocene (2-methylazaferrocene) see: Bauer, K.; Falk, H.; Schlögl, K. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 135.

(5) During the final stage of this work Fu et al. reported on the successful flash column separation of two diasteromeric azaferrocenyl complexes, which could be used as precursors for his 2-hydroxymethyl azaferrocene catalysts. No experimental details were included, however. See ref 3a.

(6) We have observed that only a few of our azaferrocenes could be resolved on some of the most common analytical HPLC colums (vide infra).

(7) Earlier reports on the selective ortho lithiation of azaferrocenes describe problems with concomitant 1′,2-dilithiations and monolithiation of the Cp ring. By introducing a Cp* ring in the azaferrocene only monolithiation of the complex should be possible. For the ealier reports on ortho lithiation of azaferrocenes and related complexes see, e.g., (a) Zakrzewski, J. *Heterocycles* **1990**, *31*, 383. (b) Pyshnograeva, N. I.; Setkina, V. N.; Kursanov, D. N. *J. Organomet. Chem.* **1983**, *251*, C41. (c) Zakrzewski, J. *J. Organomet. Chem.* **1989**, *362*, C31.

(8) Previous attempts to add directly lithiated metallocenes and related benzene chromium tricarbonyl complexes to menthyl *p*-tolyl sulfinate gave partly racemized products with ee's in the range of 6−89%. The best procedure involved the cannulation of the metalated ferrocene to a 2-fold excess of the sulfinate, giving the product in 83% ee: (a) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511 (b) Davies, S. G.; Loveridge, T.; Fatima, M.; Teixeira, C. C.; Clough, J. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3405. (c) See also: Hua, D. H.; Lagneau, N. M.; Chen, Y.; Robben, P. M.; Clapham, G.; Robinson, P. D. *J. Org. Chem.* **1996**, *61*, 4508.

The absolute configuration of (S_S,S_P)-**3** and (S_S,R_P)-**3** were determined by X-ray analysis of both diasteromeric products (Figure 1).[10] The yellow-brown crystals used were stable for months when stored under nitrogen.

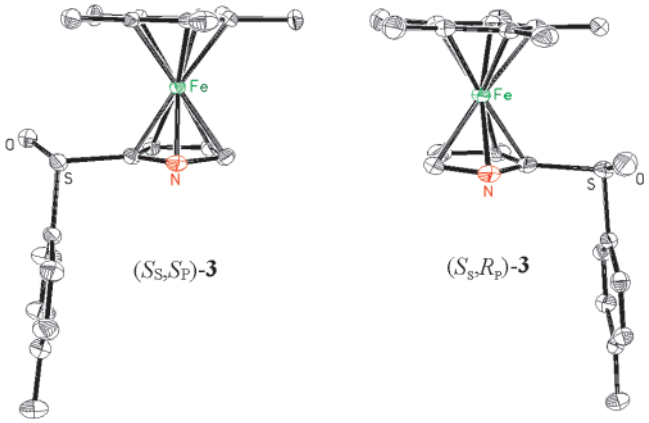
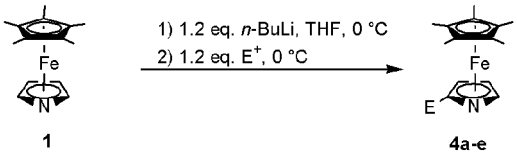


Figure 1. Drawing of the two azaferrocenes (S_S,S_P)-**3** and (S_S,R_P)-**3**. The thermal ellipsoids are at a 50% probability level. The hydrogen atoms have been omitted for clarity.

To expand the scope of the directed ortho lithiation of azaferrocene **1**, entrapment of the anion was carried out with a selection of electrophiles (Table 1).

Table 1. Directed Ortho Lithiation and Addition of Electrophiles E[a]



entry[a]	product	electrophile E	yield, %
1	**4a**	I_2	43
2	**4b**	n-Bu_3SnCl	59
3	**4c**	$ClPPh_2$	41
4	**4d**	TMSCl	60
5	**4e**	$(CH_2O)_n$[b]	49

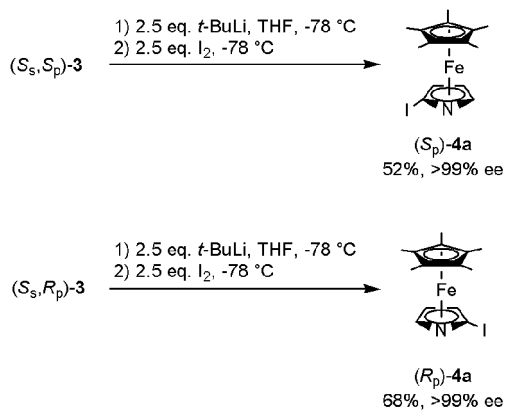
[a] Lithiation was carried out with 1.2 equiv of *n*-BuLi at 0 °C for 30 min in THF followed by the addition of 1.2 equiv of the electrophile and an additional 30 min of stirring before workup. [b] 10 equiv of the electrophile was used.

It has been demonstrated by Kagan et al. that the selective removal of the *p*-tolyl sulfoxide group from a chiral 1,2-substituted ferrocene can be accomplished with 1.1 equiv

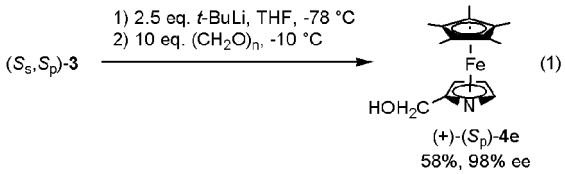
(9) The compounds are designated according to a slightly modified procedure of Schlögl. See ref 1a, pp 173−4. The azaferrocenes are viewed from the top, i.e., the ring to be assigned, and the nitrogen atom is given first priority followed by the ortho substituent. The subscript p is used for planar chirality and s for sulfur chirality.

of *tert*-butyllithium at −78 °C without any racemization.[8a] We found that a similar selective cleavage could be performed on our azaferrocenes; however, a slightly higher excess of *t*-BuLi was used in order to get the highest yield.[11] The optically pure azaferrocenyl anions were trapped with iodine as electrophile, giving the almost enantiopure 2-iodoazaferrocenes (*R*)- and (*S*)-**2** (Scheme 2).[12]

Scheme 2



The methodology should open up for the construction of a variety of new optically pure azaferrocene derivatives. As a simple example of our new methodology we chose to synthesize the chiral azaferrocene **4e**, which constitutes the backbone in the Fu-type nucleophilic catalysts.[3] Hitherto the absolute configuration of this compound was unknown. The optically pure sulfoxide (S_s,S_p)-**3** is dissolved in dry THF and treated with 2.5 equiv of *tert*-butyllithium at −78 °C for 5 min followed by a 10-fold excess of paraformaldehyde, which is added in one portion. The reaction is left to stir for 2 h while the temperature gradually reaches −10 °C. Standard workup gives the azaferrocene in 58% yield and with 98% ee. The optical rotation of the product is positive, allowing us to assign the Fu-type catalyst **4e** as (+)-(S_p)-2-hydroxymethyl-1′,2′,3′,4′,5′-pentamethylazaferrocene (eq 1).[13] We believe this finding will shed some light on the mechanism of the asymmetric reactions involving this catalyst.



In summary, we have developed a new and simple synthesis of optically pure azaferrocenyl anions, which may serve as modular building blocks in the construction of new chiral azaferrocene complexes and nucleophilic catalysts. The synthesis relies on two highly selective steps: the synthesis of the two enantiopure sulfoxides and the concomitant *t*-BuLi mediated cleavage followed by trapping of the anion with electrophiles without any racemization taking place. We plan to apply this new methodology in the synthesis of a range of optically pure azaferrocenes, as well as to extend the selective ortho lithiation and sulfoxide formation procedure for resolving other azaferrocene parent structures.

Acknowledgment. We thank The Danish Technical Research Council, Leo Pharmaceuticals, Direktør Ib Henriksens Fond and Familien Hede Nielsens Fond for generous support and Dr. Jørgen Ø. Madsen for MS measurements.

Supporting Information Available: Experimental procedures for compounds **3** and **4a**−**e** (both racemic and optically pure derivatives), compound characterization data, and X-ray crystallographical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) X-ray data for (S_S,S_P)-**3**: yellow-brown crystal, fw 395.33, crystal system monoclinic, space group $P2_1$, a = 7.2192(9) Å, b = 35.183(4) Å, c = 8.3476(11) Å, β = 115.226(12)°, V = 1918.0(4) Å^3, Z = 4, $R1$ = 0.0355, $wR2$ = 0.0792, data/parameters = 8406/451, GOF = 1.069, Flack parameter 0.006(11). X-ray data for (S_s,R_p)-**3**: yellow-brown crystal, fw 395.33, crystal system orthorhombic, space group $P2_12_12_1$, a = 8.351(2) Å, b = 11.469(2) Å, c = 19.629(4) Å, V = 1883.5(7) Å^3, Z = 4, $R1$ = 0.0241, $wR2$ = 0.0639, data/parameters = 4535/226, GOF = 1.033, Flack parameter 0.001(11). The crystallographic data will be available at Cambridge Crystallographic Database.

(11) Initially we used the conditions of Kagan et al. to accomplish the transformation; however, after some optimizations it was found that 2.5 equiv of *t*-BuLi gave the most gratifying results with respect to ee and yield: 1.1 equiv *t*-BuLi (15 min), 20% yield, >99.5% ee; 2.5 equiv *t*-BuLi (5 min), 50% yield, >99% ee; 4 equiv *t*-BuLi (15 min), 36% yield, 97% ee; 4 equiv *n*-BuLi (60 min), 22% yield, 40% ee.

(12) Iodine was the electrophile of choice since it gave a good separation on chiral HPLC. We were not able to separate the products obtained after reaction with *n*-Bu_3SnCl, PPh_2PCl, or TMSCl on our columns (Daicel OD-H, AD, and OJ). The results for these reactions will be reported on a later occasion.

(13) A referee made us aware of another determination of the absolute configuration of (R_p)-**4e**: Ruble, J. C. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, June, 1999.