Communications to the Editor

Direct and Highly Enantioselective Synthesis of Ferrocenes with Planar Chirality by (−)-Sparteine-Mediated Lithiation

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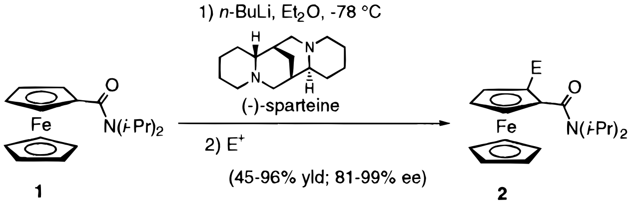
We report the first direct and highly enantioselective synthesis of ferrocenyl derivatives with planar chirality *via* a (−)-sparteine-mediated Directed ortho Metalation (DoM) process (**1** → **2**, Scheme 1). Although reports for the effective diastereoselective preparation of chiral 1,2-disubstituted ferrocenes using chiral Directed Metalation Group (DMG) auxiliaries have been rapidly accumulating (Scheme 2),[1] direct methods to obtain enantiomerically pure ferrocenyls,[2] unrestricted by requirement for substrate-specific resolution[1a,3] and chiral auxiliary removal,[1b−f] have not been hitherto described. Our work is a rational extension of DoM strategies[4] and is stimulated by the results of Hoppe[5a] and Beak,[5b] demonstrating that (−)-sparteine is an effective ligand for high asymmetric induction in lithiation−substitution reactions. In view of the increasing importance of ferrocenes with planar chirality[6a] in asymmetric catalysis,[6b] enantioselective synthesis,[6c] and diverse material science areas,[6d] significant utility and broad application of the present methodology may be anticipated.

Scheme 1



Scheme 2

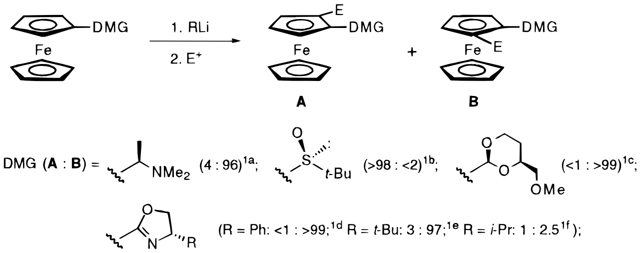


Table 1. *n*-BuLi/(−)-Sparteine-Induced Metalation of *N*,*N*-Diisopropyl Ferrocenecarboxamide (**1**): Electrophiles, Yields, and Enantioselectivities

E^+ [a]	E	product	yield, %[b]	ee, %
TMSCl	TMS	**2a**	96	98
MeI	Me	**2b**	91	94
Et_2CO	$Et_2C(OH)$	**2c**	45	99
Ph_2CO	$Ph_2C(OH)$	**2d**	91	99
$ClCH_2OCH_3$	CH_2OCH_3	**2e**	62	81
I_2	I	**2f**	85	96
$(PhS)_2$	PhS	**2g**	90	98[c]
$(PhSe)_2$	PhSe	**2h**	92	93[c]
Ph_2PCl	Ph_2P	**2i**	82	90[c]
$B(OMe)_3$	$B(OH)_2$	**2j**	89	85

[a] 2.2 equiv of *n*-BuLi/(−)-sparteine was used with the exception of E^+ = TMSCl, Et_2CO, and Ph_2CO (1.2 equiv of *n*-BuLi/(−)-sparteine). [b] All yields refer to isolated and purified (chromatographed) materials. [c] Compounds **2g**−**i** undergo slow racemization at room temperature (ref 12). Therefore, ee determination was carried out immediately after purification.

Deprotonation (1.2 equiv of *n*-BuLi/(−)-sparteine/Et_2O/−78 °C) of *N*,*N*-diisopropyl ferrocenecarboxamide (**1**)[7,8] followed byquenching with TMSCl, warming to room temperature, and standard aqueous NH_4Cl workup afforded the silylated product **2a** in 96% chemical yield and 98% ee (Table 1).[9] Similarly, sequential DoM and electrophile quench produced a variety of substituted ferrocenes **2b**−**j** in high yield and excellent enantioselectivity. For compounds **2b**,**e**−**j**, 2.2 equiv of *n*-BuLi/sparteine was required to achieve optimum chemical yield; in these cases, the change of stoichiometry did not lead to erosion of ee. Enantiomeric excess was established by comparison with racemic products, prepared by deprotonation with *n*-BuLi/TMEDA/Et_2O/−78 °C, using chiral HPLC.[10] The (*S*) absolute configuration of **2c** was established by single-crystal X-ray

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(6) (a) Togni, A., Hayashi, T., Eds. *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*; VCH: Weinheim, 1995. Illustrative examples: (b) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (c) Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1639. (d) Lion-Dagan, M.; Marx-Tibbon, S.; Katz, E.; Willner, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1604.

(7) Prepared from ferrocenecarboxylic acid (Aldrich) by sequential treatment with $COCl_2$/cat. DMF/CH_2Cl_2 and HN(i-Pr)$_2$ in 74% yield after recrystallization (hexane).

(8) For DoM chemistry of ferrocenes, see ref 1f.

(9) Metalation with *s*-BuLi/(−)-sparteine in Et_2O and *t*-BuOMe produced 94% and 97% yields and 74% and 67% ee, respectively.

(10) CHIRALCEL OD, CHIRALCEL OK, and CHIRALCEL OJ chiral columns were used. For details, see supporting information.

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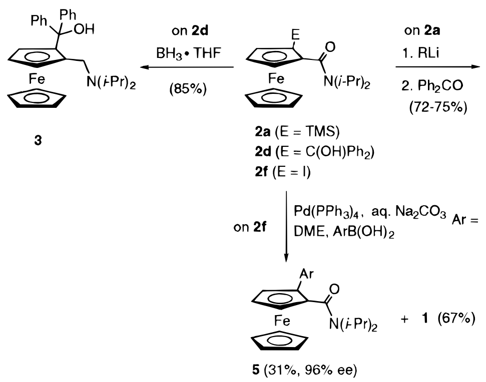
Scheme 3



crystallographic analysis.[11] In view of the configurational stability of the sp^2-hybridized ferrocenyl carbanion, enantioselective induction must occur at the deprotonation and not electrophile substitution step.[5b] On this basis, the corresponding configurational outcome can be provisionally assigned to all 1,2-disubstituted ferrocenes **2a**,**b**,**d**−**j**.

As depicted in Table 1, the electrophiles introduced provide diverse carbon (**2b**−**e**) and heteroatom (**2a**,**f**−**j**)-based[12] chiral ferrocenes, some of which (**2c**,**d**,**i**) are related to popular ligands for enantioselective catalysis.[6] In fact, reduction (BH_3/THF) of **2d** (Scheme 3) furnished **3**, whose use in asymmetric synthesis is under study.[13] Subsequent metalation of **2a** under achiral conditions (1.2 equiv of *n*-BuLi/THF or *s*-BuLi/Et_2O) and benzophenone quench resulted in exclusive formation of **4** (Scheme 3), a result suggesting that the amide DMG effect is overridden by steric hindrance factors in the substituted Cp ring.[14] In order to show the combined potential of DoM−cross-coupling reactions, a powerful strategy in aromatic and heteroaromatic chemistry,[15] the iodoferrocenyl amide **2f** was subjected to the Suzuki procedure with (2,4-dimethoxyphenyl)-boronic acid to afford **5** in low yield but unchanged enantiomeric excess together with the dehalogenation product **1** (Scheme 3).[16]

The present results demonstrate the first direct and highly efficient enantioselective synthesis of ferrocenyl carboxamide derivatives with planar chirality using sparteine-mediated DoM. Enantiomerically pure ferrocenes are thus available from achiral precursors without recourse to tedious methods of resolution and chemical manipulation of chiral DMG auxiliaries. Furthermore, aryl-substituted systems may be prepared by a combined DoM−cross-coupling regimen (**2f** → **5**). The ready availability of diverse DMG-bearing ferrocenes,[6] the rich functional group chemistry of ferrocenes, and the flourishing use of these ligands in asymmetric catalysis and synthesis suggest considerable utility of these findings.

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Supporting Information Available: Detailed description of experimental procedures for the preparation and reactions of **1**−**5** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[11] Crystal data for **2c**, $C_{22}H_{23}FeNO_2$, $M_r = 399.36$, orthorhombic, $P2_12_12_1$, $a = 7.4383(7)$ Å, $b = 9.8099(8)$ Å, $c = 28.763(2)$ Å, $V = 2098.8(3)$ Å^3, $Z = 4$, $D_c = 1.264$ g/cm^3, μ(Mo Kα) = 7.33 cm^{-1}, $F(000) = 856$, $T = 200$ K. Data were collected on a Siemens P4 diffractometer with Mo Kα radiation ($\lambda = 0.710\,73$ Å); 6866 reflections were measured giving 6130 independent reflections (unmerged Friedel opposites). The structure was solved using Patterson and Fourier routines (SHELXTL IRIS) and refined by full-matrix least squares on F resulting in final R, R_w and GOF (for 5006 data with $F > 6.0\sigma(F)$) of 0.0283, 0.0298, and 1.59, respectively, for solution using the S model. The corresponding values for solution of the R model were 0.0430, 0.0467, and 2.49.

[12] Compounds **2g**, **2h**, and **2i** undergo complete racemization in hexane: *i*-PrOH (98:2) at room temperature: *e.g.*, **2g** ($t_{1/2} \approx 24$ h); **2h** ($t_{1/2} \approx 60$ h). This intriguing observation may be tentatively rationalized by substituted Cp−aryl ligand exchange. For similar examples, see: Slocum, D. W.; Tucker, S. P.; Engelmann, T. R. *Tetrahedron Lett.* **1970**, 621. Roman, E.; Astruc, D.; des Abbayes, H. *J. Organomet. Chem.* **1981**, *219*, 211.

[13] Related chiral ferrocenyl amino alcohols are very efficient catalysts for the enantioselective addition of diethylzinc to aldehydes: Butsugan, Y.; Araki, S.; Watanabe, M. In *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, 1995; pp 143−169. See also ref 6c.

[14] Similar behavior with parallel implications has been observed in deprotonations of the TMS derivative of a chiral ferrocenyloxazoline (ref 1f).

[15] Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349 and references cited therein.

[16] Unoptimized yield. For similar dehalogenations observed during cross-coupling reactions, see: Nguyen, P.; Yuan, Z.; Agocs, L.; Lesley, G.; Marder, T. B. *Inorg. Chim. Acta* **1994**, *220*, 289 and references cited therein.