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(–)-Sparteine-Mediated Metalation of Ferrocenesulfonates. The First Case of Double Asymmetric Induction of Ferrocene Planar Chirality

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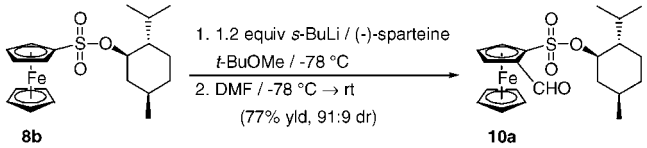
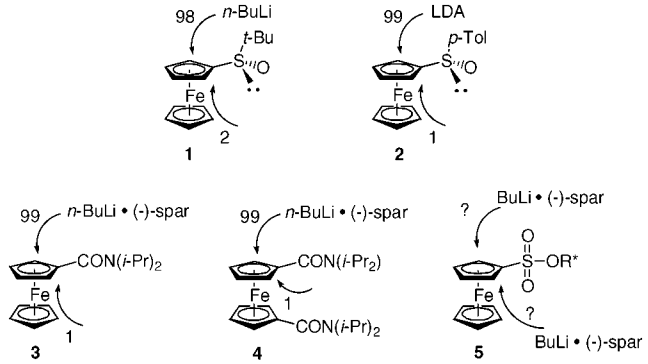
ABSTRACT



A new process for induction of planar chirality via a matched chiral-directed metalation group (DMG)/(–)-sparteine interaction is demonstrated. Thus, *s*-BuLi metalation of (–)-menthylferrocenesulfonate (8b) with (–)-sparteine constitutes a *matched pair* resulting in amplification of the dr in the 2-formyl product 10a.

The search for practical asymmetric synthesis of planar chiral ferrocenes[1] has produced directed *ortho* metalation (DoM) methods invoking (a) diastereoinduction of ferrocenes bearing carbon-based[2] chiral auxiliaries[3] and (b) enantioinduction using chiral lithium amide[4] and alkyllithium/(−)-sparteine[5] reagents. Availability of planar chiral ferrocenes with heteroatom-directed metalation groups (DMGs) has been limited to enantiomerically pure *tert*-butyl (**1**)[6] and *p*-tolyl (**2**)[7] sulfoxides for which preparation of enantiopure 1,2-disubstituted ferrocenes has been demonstrated (Scheme 1).[8] As part of efforts to expand the scope of the (−)-sparteine-mediated enantioinduction of planar chirality into ferrocenes beyond the promising amide DMGs (**3**, **4**),[5] we report our preliminary studies on ferrocenyl sulfonates, which demonstrate amplification of diastereoselectivity by induction of planar chirality via a *matched pair* interaction with a chiral DMG (**5**, R* = (+)- and (−)-menthyl).

Scheme 1. Lithiation Diastereoselectivites of Ferrocenyl Sulfur-Based and Carboxamide DMGs



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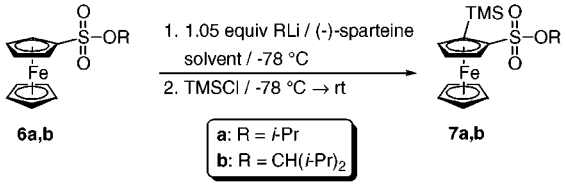
Cognizant of the pioneering studies on alkylsulfonate DMGs,[9] which showed that the SO_3i-Pr DMG is more powerful than the CON(i-Pr)$_2$ DMG,[10] we subjected isopropylferrocenesulfonate **6a**, prepared from ferrocenesulfonyl chloride[11a] (NaOi-Pr, Et_2O, rt), to (−)-sparteine-mediated metalation (1.05 equiv n-BuLi/(−)-sparteine, Et_2O, −78 °C) followed by a TMSCl quench to give product **7a** in moderate yield but low enantiomeric ratio (er) (Scheme 2).

Scheme 2. (−)-Sparteine-Mediated DoM of Alkyl Ferrocenesulfonates



Substrate	RLi	Solvent	Product	yld, %, **7**	er, **7**[a]
6a	*n*-BuLi	Et_2O	**7a**	53	67:33
6a	*iso*-BuLi	Et_2O	**7a**	61	53:47
6a	*s*-BuLi	Et_2O	**7a**	67	26:74
6a	*n*-BuLi	*t*-BuOMe	**7a**	72	54:46
6a	*s*-BuLi	*t*-BuOMe	**7a**	61	21:79
6b	*n*-BuLi	Et_2O	**7b**	67	67:33
6b	*iso*-BuLi	Et_2O	**7b**	58	65:35
6b	*s*-BuLi	Et_2O	**7b**	77	34:66

[a] Determined on a Chiralcel OD HPLC column and compared to racemic material.

Changing to successively bulkier alkyllithiums produced an interesting trend: *iso*-BuLi[12] provided **7a** in practically racemic form, whereas employing *s*-BuLi led to **7a** in substantially higher enantiomeric excess but *with the preferential production of the opposite enantiomer*. Repetition of these experiments in *t*-BuOMe afforded **7a** in the optimized 21:79 er. The same trend was observed for the bulkier, branched 2,4-dimethyl-3-pentylferrocenesulfonate **6b** (Scheme 2) and gave product **7b**.

We reasoned that the observed trend in er arose because the protons on the Cp ring and the sulfonyl oxygens of the DMG are necessarily diastereotopic[13] in the transition state leading to products. It followed that introducing a chiral auxiliary would make these positions diastereotopic in the starting material, thereby allowing amplification of stereoselectivity with (−)-sparteine. Notably, metalation of the same compound without (−)-sparteine would constitute a diastereoselective metalation akin to chiral sulfoxides (**1**, **2**).[14,15] The (+)-(1*S*,2*R*,5*S*)- and (−)-(1*R*,2*S*,5*R*)-menthylferrocenesulfonates (**8a** and **8b**, respectively) were chosen as test substrates because of the commercial availability of both enantiomers of menthol and the reported properties of $(S)_S$-(1*R*,2*S*,5*R*)-menthyl-*p*-toluenesulfinate.[16]

Metalation of (+)-(1*S*,2*R*,5*S*)-menthylferrocenesulfonate (**8a**) (*n*-BuLi, THF, −78 °C), followed by a DMF quench and $NaBH_4$ reduction of the crude aldehyde (for ease of dr determination), provided alcohol **9** in an expectedly low 59:41 dr (Scheme 3). Performing the same reaction with (−)-sparteine in Et_2O gave **9** in improved 70:30 dr, and switching to *s*-BuLi gave the opposite diastereomer in 39:61 dr, mirroring the trend observed for **6a** and **6b** (Scheme 2). However, the same series of experiments on (−)-(1*R*,2*S*,5*R*)-menthylferrocenesulfonate **8b**, to provide aldehyde **10a**, showed augmentation from 75:25 to 87:13 dr *favoring the same diastereomer*. The reaction in *t*-BuOMe afforded the best diastereoselectivity (77% yield, 91:9 de), paralleling the behavior **6a**.

The above results indicate that *s*-BuLi/(−)-sparteine always seems to favor the same relative stereochemistry during lithiation of both **8a** and **8b**. However, whereas the combination of *s*-BuLi/(−)-sparteine with **8b** constitutes a *matched pair* resulting in amplification of diastereoselectivity, the combination of *s*-BuLi/(−)-sparteine with **8a** is a *mismatched pair*, leading to even poorer selectivity than that obtained with achiral sulfonate **6a**. Interestingly, *n*-BuLi/(−)-sparteine does not seem to make matched or mismatched pairs with either **8a** or **8b**, as its use augments the dr for both products **9** and **10a**. The apparent ability of *s*-BuLi/(−)-sparteine to form matched or mismatched pairs with chiral substrates **8a**,**b** may be tentatively attributed to the chirality of *s*-BuLi itself, which upon complexation with (−)-sparteine forms a reagent that may exist predominantly in one of two possible diastereomeric forms.

In any case, extension to other electrophiles provided products **10b**−**e** in moderate to good yields and in similar drs (Scheme 4). The absolute configuration of phosphine **10d** was established by single-crystal X-ray analysis,[17] which

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(8) (a) Review: Kagan, H. B.; Diter, P.; Gref, A.; Guillaneux, D.; Masson-Szymczak, A.; Rebiere, F.; Riant, O.; Samuel, O.; Taudien, S. *Pure Appl. Chem.* **1996**, *68*, 29. (b) Achiral *tert*-butylferrocenyl sulfone, upon metalation with *n*-BuLi/chiral cyclohexanediamine complex, afforded only a racemic product; see: Nishibayashi, Y.; Arikawa, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1996**, *61*, 1172.

(9) Bonfiglio, J. N. *J. Org. Chem.* **1986**, *51*, 2833.

(10) Spangler, L. A. *Tetrahedron Lett.* **1996**, *37*, 3639.

(11) To date, we have avoided sulfonamide DMGs because ferrocenes are known to be sensitive to strongly acidic media that are normally used to hydrolyze sulfonamides; see: (a) Slocum, D. W.; Achermann, W. *Synth. React. Inorg. Met.-Org. Chem.* **1982**, *12*, 397 and references therein. However, the advent of the *N*-cumyl sulfonamide DMG makes this a more attractive pursuit; see: (b) Metallinos, C.; Nerdinger, S.; Snieckus, V. *Org. Lett.* **1999**, *1*, 1183.

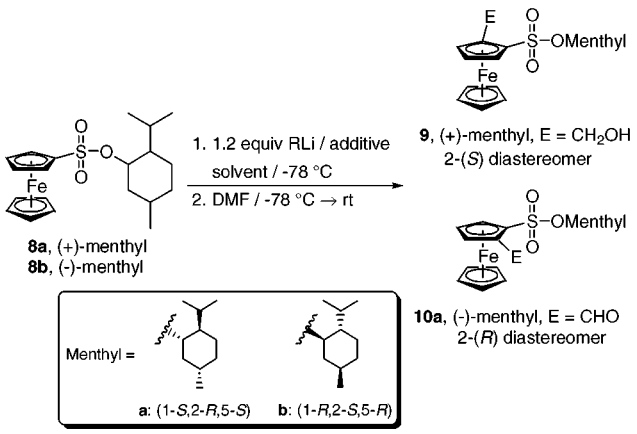
(12) *iso*-BuLi was made from *iso*-BuBr according to the method in: Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer-Verlag: New York, 1987; p 17.

(13) Discrimination of diastereotopic sulfonyl oxygens has been postulated to rationalize the observed stereoselectivity in chiral Lewis acid-mediated radical reactions; see: Watanabe, Y.; Mase, N.; Furue, R.; Toru, T. *Tetrahedron Lett.* **2001**, *42*, 2981.

(14) Amplification of the inherent selectivity of a chiral DMG may be tested by metalating both enantiomers in the presence of (−)-sparteine in the expectation of a matched auxiliary/chiral ligand pair effect, the classic phenomenon of double asymmetric induction. For a review, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1; *Angew. Chem.* **1985**, *97*, 32.

(15) For recent examples of matched/mismatched-pair effects in asymmetric synthesis, see: (a) Vetter, A. H.; Berkessel, A. *Tetrahedron Lett.* **1998**, *39*, 1741. (b) Koert, U.; Wagner, H.; Pidun, U. *Chem. Ber.* **1994**, *127*, 1447.

Scheme 3. (−)-Sparteine-Mediated D*o*M of Menthylferrocenesulfonates

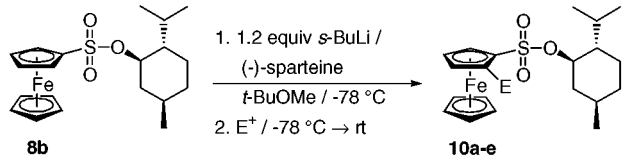


Substrate	RLi / additive	Solvent	Product	yld, %	dr[b]
8a	*n*-BuLi	THF	**9**	80[a]	59:41
8a	*n*-BuLi / (-)-spar	Et_2O	**9**	69[a]	70:30
8a	*s*-BuLi / (-)-spar	Et_2O	**9**	56[a]	39:61
8a	*s*-BuLi / (-)-spar	*t*-BuOMe	**9**	28[a]	38:62
8b	*n*-BuLi	THF	**10a**	65	60:40
8b	*n*-BuLi / (-)-spar	Et_2O	**10a**	86	75:25
8b	*s*-BuLi / (-)-spar	Et_2O	**10a**	69	87:13
8b	*s*-BuLi / (-)-spar	*t*-BuOMe	**10a**	77	91:9

[a] Overall yield after reduction of aldehyde with 4.7 equiv of $NaBH_4$ in MeOH/H_2O at rt. [b] Determined on a Chiralcel OD HPLC column.

revealed the 2-(*R*) absolute stereochemistry (Figure 1). The identity of the crystallized sample was confirmed from its ^{31}P NMR spectrum, which showed a signal (δ −21.7) corresponding to the major diastereomer when compared to the ^{31}P NMR spectrum of the initial diastereomeric mixture.

Scheme 4. (−)-Sparteine-Mediated D*o*M of (−)-(1*R*,2*S*,5*R*)-Menthylferrocenesulfonate



E^+	E	Product	yld, %, **10**	dr, **10**
DMF	CHO	**10a**	72-77	90:10-92:8[d]
PhNCO	CONHPh	**10b**	49	90:10[a]
TMSCl	TMS	**10c**	82	90:10[b]
Ph_2PCl	Ph_2P	**10d**	47	91:9[c]
$(MeS)_2$	MeS	**10e**	70	91:9[d]

[a] Determined by integration of peaks in the inverse-gated ^{13}C NMR. [b] Based on phosphine **11**. [c] Determined by integration of peaks in the ^{31}P NMR. [d] Determined on a Chiralcel OD HPLC column.

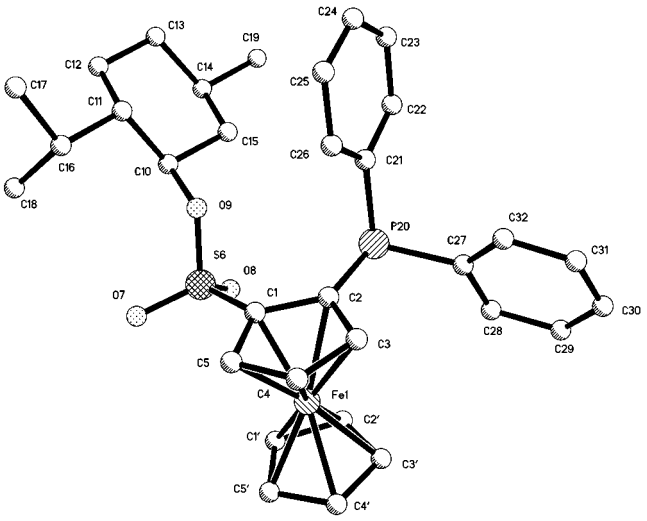
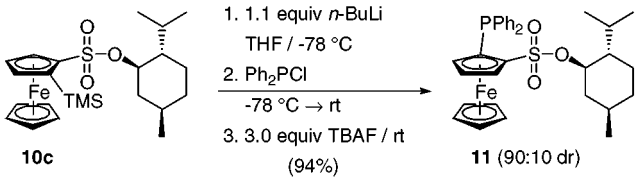


Figure 1. X-ray crystal structure of **10d**.

Metalation of the 2-TMS[18] sulfonate **10c** (1.1 equiv of *n*-BuLi, THF, −78 °C) followed by a Ph_2PCl quench gave the intermediate trisubstituted ferrocene that, without isolation, was treated with TBAF[19] to afford phosphine **11** in excellent yield and with a 90:10 dr as determined by ^{31}P NMR spectroscopy (Scheme 5). On the basis of the X-ray

Scheme 5. Preparation of Phosphine **11**



crystal structure analysis of **10d** (Figure 1) and ^{31}P NMR measurements of both diastereomers **10d** and **11**, the 2-(*R*) absolute stereochemistry is confidently assigned to products **10a**−**e**. This result allows the preparation of the diastereomeric series of potentially valuable ferrocenyl sulfonates **10a**−**e**, thus overcoming the commercial unavailability of (+)-sparteine.

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(17) Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162485. Copies of the data can be obtained free of charge upon application to: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, (+44) 1223−336−033; e-mail, deposit@ccdc.cam.ac.uk).

(18) (a) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372. (b) This experiment received encouragement from the observation that metalaton of **6a** using 2.2 equiv of *n*-BuLi/(−)-sparteine followed by a TMSCl quench afforded the 2,5-disilylated product in 69% yield: Metallinos, C. Ph.D. Thesis, Queen's University, Kingston, Ontario, 2001.

(19) Ahn, K. H.; Cho, C.; Baek, H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937.

In conclusion, the previously established (−)-sparteine-mediated D*o*M method for the induction of planar chirality[5] has been extended to sulfonate DMGs. Amplification of an otherwise low diastereoselectivity by induction of planar chirality via a *matched* chiral DMG/(−)-sparteine interaction has been demonstrated for (−)-(1*R*,2*S*,5*R*)-menthylferrocenesulfonate **8b**. This new process, which differs conceptually from diastereoselective[2,3] or enantioselective[4,5] induction of planar chirality, may serve as a paradigm for the development of similar reactions to induce planar chirality. Work to use phosphines similar to **10d** in enantioselective catalysis[20] and to extend the methodology to *N*-cumyl ferrocenesulfonamides[11] is under way.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) In a preliminary study, recrystallized phosphine **10d** was tested as a ligand for enantioselective Pd-catalyzed allylic substitution of (±)-phenylcinnamyl acetate (1.25 mol % [Pd(η^3-C_3H_5)Cl_2], 3.0 equiv of *N*,*O*-bis(trimethylsilyl)acetamide, 0.01 equiv of AcOLi, 3.0 equiv of $CH_2(CO_2Me)_2$, CH_2Cl_2, rt, 24 h) giving alkylated product in good yield, but low enantiocontrol (95% yield, 42% ee).