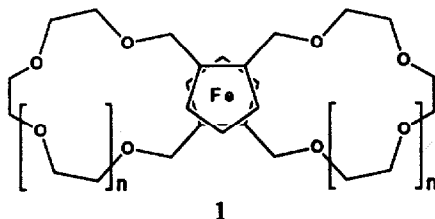


## Stereochemistry of Directed Lithiation of 1,1'-Bis(methoxymethyl)ferrocene

Russell C. Petter\* and Craig I. Milberg  
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

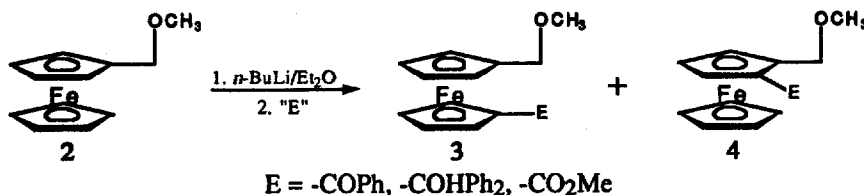
**Summary:** 1,1'-Bis(methoxymethyl)ferrocene undergoes stereoselective directed dilithiation in the presence of *t*-butyllithium. Evidence is presented to establish the stereochemistry of the products.

As part of a program of research directed toward potentially allosteric<sup>1</sup> ferrocene-dicoronand hosts (e.g., 1), we have need of efficient routes to tetrasubstituted ferrocene derivatives to act as central molecular pivots. Stereochemical control of the substitution pattern around the ferrocene nucleus is important in that different stereoisomeric ferrocene-dicoronands may lead to profoundly different allosteric interactions. Analogous metallocene-monocoronands are known to bind various ions with accompanying changes in dihedral angle about the central axis of the metallocene.<sup>2</sup>



Previous studies<sup>3-5</sup> on the directed lithiation of substituted ferrocenes suggested that new functionality may be introduced with some regio- and perhaps stereoselectivity.<sup>3</sup> For example, Slocum et al. treated methoxymethylferrocene (2) with *n*-butyllithium and quenched with a variety of electrophiles to give 1:1 mixtures of 3 and 4 as the only products.<sup>3</sup> The present work focuses on a related reaction which proceeds through stereoselective dilithiation of 1,1'-bis(methoxymethyl)ferrocene 8.

### Scheme I

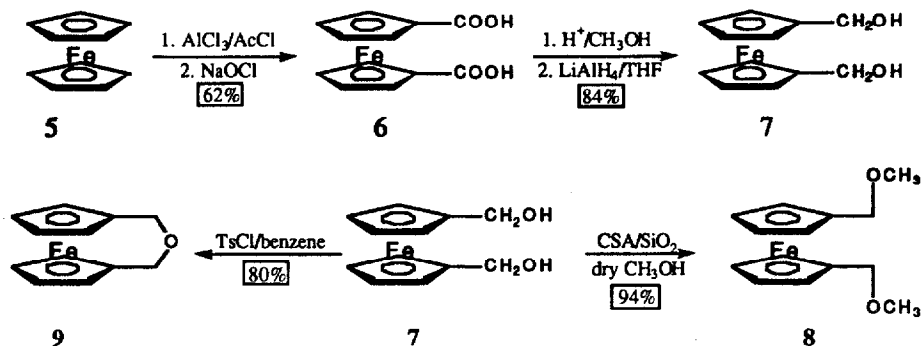


Diacetylation of ferrocene<sup>6</sup> (AcCl/AlCl<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>/25°) followed by oxidation<sup>7</sup> (NaOCl) gives 1,1'-ferrocenedicarboxylic acid 6. Esterification (H<sub>2</sub>SO<sub>4</sub>/CH<sub>3</sub>OH/Δ) and reduction (LiAlH<sub>4</sub>/THF/Δ) leads to 1,1'-ferrocenedimethanol 7 in 52% overall yield (75 g) from ferrocene (Scheme II). Acid-catalyzed exchange of OCH<sub>3</sub> for OH (CSA/CH<sub>3</sub>OH) is straightforward, producing diether 8 efficiently. Several investigators<sup>8</sup> have emphasized the extraordinary stability of the ferrocenylcarbanyl cation and in this case the hydrolysis is also clearly assisted by the ether oxygen of the opposing ring.<sup>9</sup> The cyclic ether 9 is a commonly observed by-product and can be produced cleanly with TsCl in benzene with removal of water.

Ferrocene requires 6 h at room temperature with *n*-butyllithium/TMEDA in hexanes to produce 1,1'-dilithioferrocene.<sup>10</sup> Deprotonation of 9 is also sluggish and the material is destroyed under these

conditions, presumably via deprotonation of the  $\alpha$ -position followed by Wittig rearrangement. Methoxyethoxymethylferrocene and 1,1'-bis(methoxyethoxymethyl)ferrocene (not shown) are also not stable to the deprotonation conditions. In contrast, exposure of **8** to 2.5 eq *t*-butyllithium in diethyl

**Scheme II**

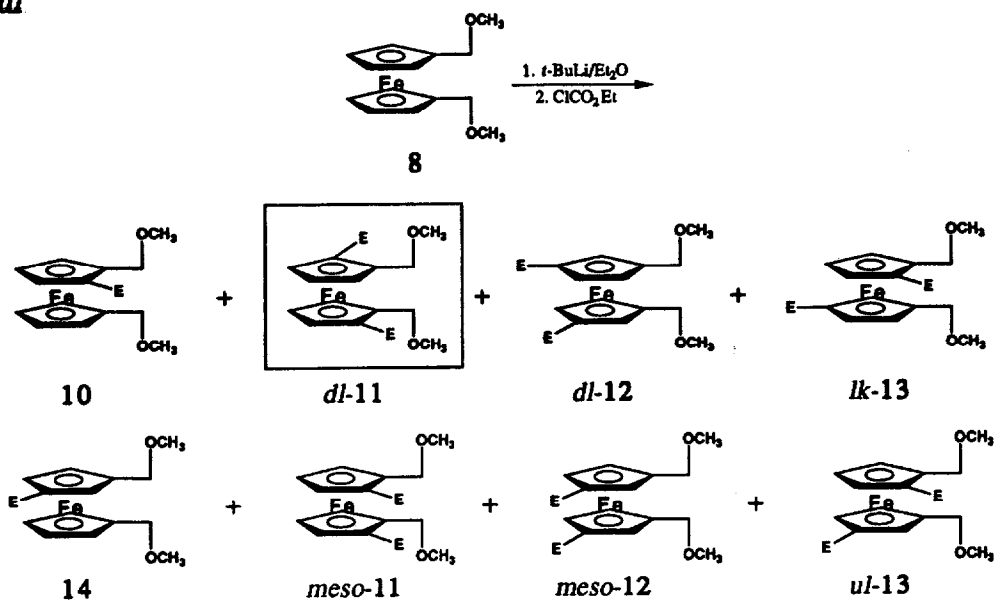


ether at 0 °C rapidly produces a deep red precipitate (ca. 2 min), an observation we find indicative of efficient deprotonation. Dimethyl carbonate quenches the reaction rather slowly, while ethyl and methyl chloroformate react rapidly and exothermically. Quenching with ethyl 4-nitrophenyl carbonate is rapid, but not obviously exothermic, and is thus preferred on a preparative scale. Preparative HPLC (22:78 EtOAc:hexanes,  $\text{SiO}_2$ , 8  $\mu\text{m}$ ) of the diethyl esters affords recovered **8** (41%) and three products which we have identified as the mono-acylated **10** (4%), an asymmetric di-acylated material (**13**, 7% yield), and a symmetric material **11** (*meso* and/or *dl*, 22%). The eight possible stereoisomeric products (two trisubstituted and six tetrasubstituted) are shown in Scheme III (E =  $\text{CO}_2\text{Et}$ ).

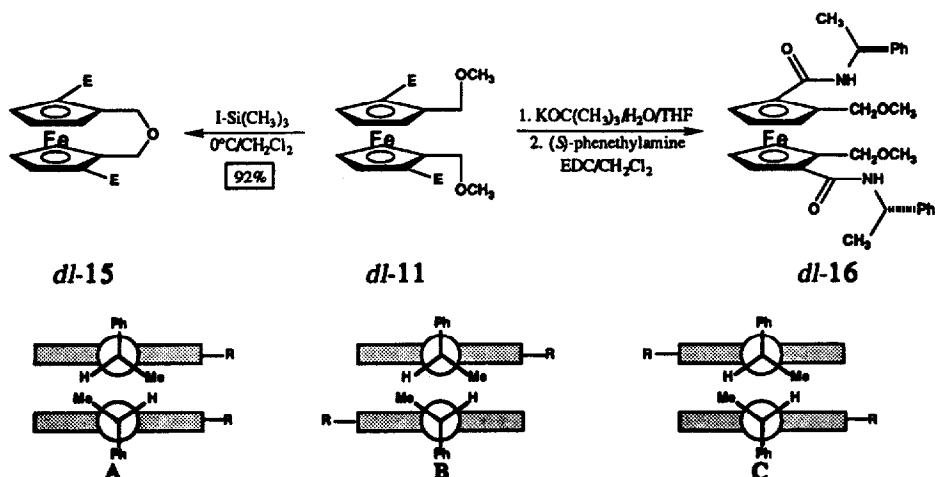
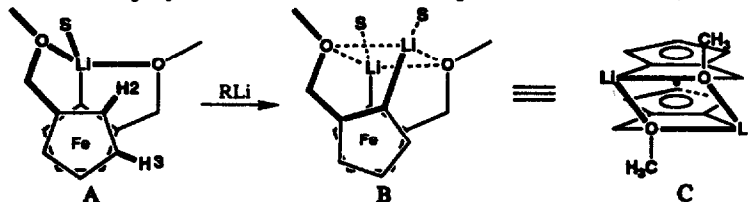
The structure of **10** was assigned on the basis of the coupling pattern for the Cp protons<sup>11</sup> ( $J_{\text{H}1,\text{H}2} \cong 2.5$  Hz,  $J_{\text{H}1,\text{H}3} \cong 1.5$  Hz). Because there is no apparent spin-spin interaction between the protons of the opposing Cp rings, we do not know which structure (*lk* or *ul*<sup>12</sup>) corresponds to the asymmetric tetrasubstituted ferrocene **13**, but the splitting pattern clearly indicates the presence of both types of Cp substitution (1,2 and 1,3). No product is observed which can be assigned as **12** or **14**. Analytical HPLC (22:78 EtOAc:hexanes,  $\text{SiO}_2$ , 5  $\mu\text{m}$ , 275 nm) of purified **11** shows a clean gaussian peak with **10** as an impurity (4%). Selective hydrolysis of **11** ( $\text{ISi}(\text{CH}_3)_3/\text{CH}_2\text{Cl}_2/0^\circ\text{C}$ ) gives cyclic ether-diester **15** (Scheme IV); the  $^1\text{H-NMR}$  spectrum of **15** at  $-91^\circ\text{C}$  (300 MHz,  $\text{CD}_2\text{Cl}_2$ ) exhibits reduced symmetry. At this temperature the ring flipping of the cyclic ether is slow,<sup>9</sup> so the  $\alpha$ -protons of the ether bridge emerge as a four spin system. The *meso* stereoisomer would still be a two spin system. This is consistent with our assignment of the stereochemistry of **11** as *dl*. To corroborate this conclusion we have hydrolyzed the esters of **11** (Gassman's conditions<sup>13</sup>) and coupled (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl/ $\text{CH}_2\text{Cl}_2$ ) the resulting diacid to (*S*)- $\alpha$ -phenethylamine. HPLC analysis (1:1 EtOAc:hexanes,  $\text{SiO}_2$ , 5  $\mu\text{m}$ ) of this material gives two diastereomers with a 1:1 ratio of areas (**B** and **C**, Figure 1).

This result has certain implications for the structures of the dilithio intermediates derived from **8**. A single methoxymethyl group exhibits no preference for homoannular vs. heteroannular lithiation,<sup>3</sup> implying that the two necessary geometries of the ferrocenyllithium intermediates (homo- and heteroannular ligation) are equally favored, either kinetically or thermodynamically. By extension, *both* ether oxygens of **8** may ligate a single lithium (Figure 2A) and produce the observed regioselectivity of **10** over **14** (not observed).

## Scheme III



## Scheme IV

Figure 1. Newman projections of stereoisomeric possibilities for **16** ( $\text{R} = \text{CH}_2\text{OCH}_3$ ).Figure 2. Proposed structures for lithiated derivatives of **8** ( $\text{S} = \text{solvent}$ ).

Complexation of a second *t*-butyllithium by the oxygens will place it near both protons H2 and H3 (see Figure 2A). Deprotonation at these positions will lead, upon trapping, to *dl*-11 and *ul*-13, respectively. The observed preference for *dl*-11 might derive from the formation of a cyclic Li-O-Li-O complex (Figure 2B,C). Models indicate that a dilithio species leading to *meso*-11 cannot assume such a geometry. The remaining ligation sites of the lithium ions may be filled by solvent, but we have no evidence to rule out higher order complexes.<sup>14</sup> In contrast to these observations, a very recent report on the bis-metalation of 1,1'-bis(dimethylaminomethyl)ferrocene<sup>15</sup> leads to a mixture (1:2) of *meso* and *dl* products.

**Acknowledgement:** This work has been generously supported by the NIH (GM39816).

### References and Notes

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