A General Asymmetric Synthesis of Ferrocenes with Planar Chirality

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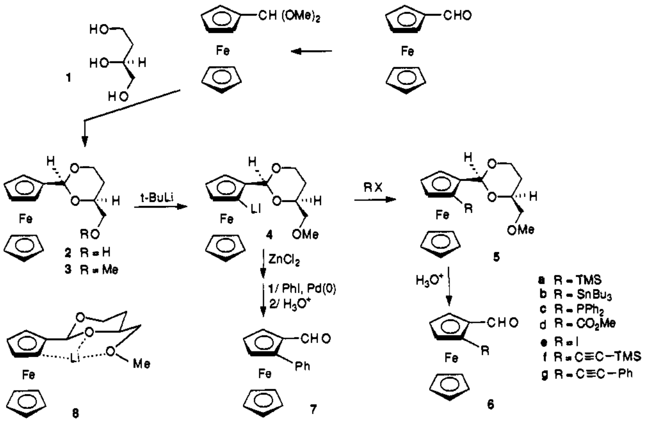
Ferrocene and its derivatives are widely used as structural units for devising unusual compounds or as components in material science.[1] Moreover, ferrocenes with planar chirality are of increasing importance in the synthesis of chiral ligands used in asymmetric catalysis[2,3] and asymmetric synthesis,[4] and the stereochemical aspects of chiral ferrocenes have been widely investigated.[5] Enantiopure ferrocenes are mainly obtained by resolution methods. The most common way is the resolution of *N*,*N*-dimethyl-(α-methylferrocenyl)ethylamine and its diastereoselective ortho-lithiation followed by electrophilic attack.[6–9] There are no convenient methods for the asymmetric synthesis of ferrocenes with planar chirality. We present here a general method for preparation of a number of enantiomerically pure ferrocenes (Scheme I).

Scheme I



The ferrocenyl acetal **2** was easily prepared from triol **1** (commercially available or synthesized from malic acid) by transacetalization of the known ferrocenyl dimethylacetal in chloroform using *p*-toluenesulfonic acid as catalyst.[10] The *cis*-1,3-dioxane structure **2** was established by ^{1}H NMR spectroscopy compared to a compound obtained by a similar reaction with benzaldehyde.[11] Only one epimer was observed by ^{1}H NMR and thin-layer chromatography after recrystallization in toluene (85% overall yield starting from commercially available formylferrocene). Dioxane **2** was obtained free of the isomeric dioxolanes present in minor quantities in the crude product. O-Methylation (NaH, MeI in THF at room temperature) gave **3** quantitatively. Deprotonation of **3** (0.2 M in diethyl ether) by 1.1 equiv of *t*-BuLi (1.7 M in hexane) at −78 °C for 15 min and then stirring of the solution for 2 h at room temperature and quenching the reaction with an electrophile (at −30 °C followed by warming to room temperature) led to ortho-substituted ferrocenes **5** with isolated yields between 80% and 90%.[12] In all the cases **5** is formed as a *single diastereomer* (>98% de), as shown by ^{1}H NMR on the crude product. Acidic hydrolysis of **5** cleanly releases chiral ferrocene carboxaldehydes **6** with a wide range of vicinal groups (90–95% isolated yields). The silane **6a** ($[\alpha]_D = -202$, EtOH) and the ester **6d** ($[\alpha]_D = +765$, EtOH) were isolated in 80% yield (calculated from **3**), and they are enantiomerically pure with an (*S*) configuration, as established by comparison with the known specific optical rotation and absolute configuration of these compounds.[13,14] Racemic α-(trimethylsilyl)ferrocene carboxaldehyde (**6a**) was synthesized. The ^{1}H NMR of **6a** in benzene-d_6 containing 5 equiv of Pirkle's alcohol ((trifluoromethyl)anthracenemethanol) showed two peaks for the unsubstituted cyclopentadienyl proton (5–6-Hz separation) with racemic **6a**, while (−)-**6a** prepared by asymmetric synthesis showed only one peak, a confirmation of ee ≥ 95%.

The key ferrocenyllithium **4** was transmetalated with ZnCl$_2$ and then was phenylated with iodobenzene in the presence of PdCl$_2$(PPh$_3$)$_2$/DIBAH catalyst.[15] In this way (*R*)-**7** was obtained. α-Iodoferrocene carboxaldehyde ((+)-**6e**) was converted in good yield into α-ethynylferrocene carboxaldehydes (*R*)-**6f** and (*R*)-**6g** by a coupling reaction with (trimethylsilyl)acetylene or phenylacetylene, respectively, in the presence of a palladium(II) catalyst.[16] The presence of an aldehydic group in compounds **6a**–**6g** allows one to prepare a wide range of chiral ferrocenes.[17] All the enantiopure ferrocenes with planar chirality (**6a**–**6g**, **7**) have a known absolute configuration, as established by chemical correlation in two cases and by the fact that the ortho-lithiated

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(12) The exception is **5d** (43% yield), which is separated from bis[α-(4-(methoxymethyl)-1,3-dioxan-2-yl)ferrocenyl] ketone (37% yield). This latter occured by a competitive reaction between **5d** and ferrocenyllithium **4**.

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(17) For example, treatment of **6c** by diiodosamarium[22] gives in high yield diastereomeric pinacols, reduction of **6c** by NaBH$_4$ gives quantitatively the corresponding hydroxyphosphine, and McMurry coupling of **6c** provides (*E*) and (*Z*) diphosphines. All these derivatives are under investigation in various areas of asymmetric catalysis. Samuel, O.; Riant, O.; Kagan, H. B. unpublished work.

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ferrocene **4** is their common precursor. The diastereoselectivity of the ortho-lithiation can be explained by the model **8**, assuming chelation by the methoxymethyl group, a process often encountered in asymmetric synthesis.[18,19] The alternative ortho-lithiation gives a less favorable chelation ring. It is possible that the steric effects are not the only reasons for the very high stereoselectivity (for example, electronic effects due to the oxygen atoms could also play a role). The ortho-lithiation is very likely under kinetic control; in order to reach the perfect diastereoselectivity, it is necessary to deprotonate **3** by *t*-BuLi at −78 °C. After the reaction mixture is warmed to room temperature, the initial stereoselectivity is retained. If the deprotonation step is performed at 0 °C, one gets only 90–95% de after quenching by various electrophiles.

In conclusion, the new method described above for the synthesis of chiral ferrocene derivatives is very efficient, uses a cheap and easily removable chiral auxiliary, and gives products with predictable absolute configuration. Moreover, both enantiomers of 1,2,4-butanetriol are commercially available, enlarging the scope of the reaction.[20] The present approach to such chiral ferrocenes with planar chirality now opens up a range of possibilities for the design of chiral ligands or chiral auxiliaries for asymmetric synthesis.[17]

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Supplementary Material Available: Detailed description of the experimental procedures and spectral characterization of the compounds described herein (4 pages). Ordering information is given on any current masthead page.

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