Ortho-lithiation of free ferrocenyl alcohols: a new method for the synthesis of planar chiral ferrocene derivatives†

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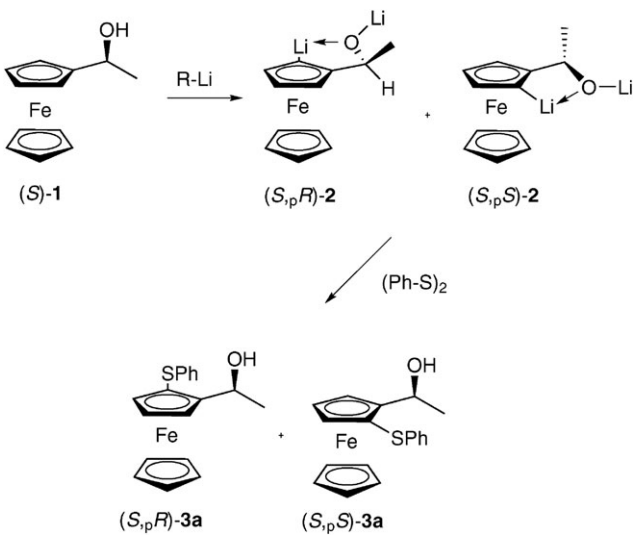
An *ortho*-metalation method for free ferrocenyl alcohols has been developed, which allows preparation of planar chiral ferrocene derivatives with high yields and diastereoselectivities.

Chiral ferrocene derivatives have attracted tremendous interest from academia as well as from industry over the last decades.[1] They have proven to be exceptionally useful as ligands in enantioselective processes, especially those that exhibit planar chirality.[2] Therefore, there is an ongoing search for new methods to introduce planar chirality into the ferrocene framework. By far the most used strategy to achieve this goal is the diastereoselective *ortho*-lithiation of central chiral ferrocene derivatives. The strategy of using an *ortho*-directing group is the key to achieve both regio- and diastereoselectivity in ferrocene metalation. Since the pioneering work of Ugi and Hayashi,[3] who reported *ortho*-lithiation of (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine (now known as *Ugi amine*), numerous *ortho*-directing groups have been explored, *i.e.* sulfoxides,[4] acetals,[5] oxazolines,[6] azepines,[7] pyrrolidines,[8] hydrazones,[9] sulfoximines,[10] *O*-methylephedrine derivatives,[11] imidazolines,[12] phosphinoxides[13] and oxazaphospholidines[14] found application in the synthesis of planar chiral ferrocene derivatives. All these directing groups feature a free electron pair, which coordinates to the Li atom and facilitates proton abstraction in the *ortho*-position. The diastereoselection is based on steric repulsion between the side chain and the ferrocene nucleus. Despite these impressive efforts, there is an ongoing interest in developing new methods for asymmetric synthesis of planar chiral ferrocene derivatives, in order to extend the variety of accessible derivatives.

Surprisingly, despite their easy availability in enantiopure form through kinetic resolution of a racemate or asymmetric reduction,[15] and the potential usefulness of the corresponding products, the *ortho*-lithiation of free ferrocenyl alcohols has not yet been described.[16] Herein, we report our efforts and results in achieving this goal. Racemic ferrocenyl-ethanol was prepared on a multigram scale by Friedel–Crafts acylation of ferrocene, which gave acetylferrocene, followed by $LiAlH_4$ reduction. Enantiopure alcohol (*S*)-**1** was subsequently prepared by kinetic enzymatic resolution of (*rac*)-**1**, utilising Novozyme 435®.[17] Since diastereoselective *ortho*-metalation of ferrocenyl alcohols was unknown when we started this work, (*S*)-**1** was subjected to different lithiation conditions, and the putative dilithiated intermediate ($S_{,p}R$)-**2** scavenged with diphenyl disulfide (Scheme 1, Table 1).

With *t*-BuLi, unselective lithiation was observed (after quenching with diphenyl disulfide), with deprotonation occurring on the substituted as well as on the unsubstituted cyclopentadienyl ring, leading to a mixture of several products. When we changed to the weaker base *n*-BuLi, better results were obtained, with the solvent playing a decisive role. *n*-BuLi in THF also led to an inseparable mixture of several isomers, while in cyclohexane two isomers were formed in a 60 : 40 diastereomeric ratio. The best results in terms of yield and diastereoselectivity were obtained with 2.2 equiv. of *n*-BuLi in Et_2O at −20 °C. Under these conditions smooth metalation occurred and the corresponding 1,2-disubstituted ferrocenyl alcohol **3a** was obtained in 79% yield and a diastereomeric ratio of 95 : 5.

About 10% of the 1,1′-substituted product, formed by lithiation of the unsubstituted 1′-cyclopentadiene ring, was also observed, but could be removed by column chromatography. Lowering the temperature to −50 °C resulted in even better diastereoselectivity (99 : 1), but the reaction became very slow and yielded only 25% of product. On the other hand, when performing the metalation at 0 °C, diastereoselectivity was again in the range of 95 : 5, but higher amounts (*ca.* 25%) of 1,1′-substituted product were observed, complicating product purification and reducing the overall yield.



Scheme 1 Metalation of (*S*)-1-ferrocenyl-ethanol.

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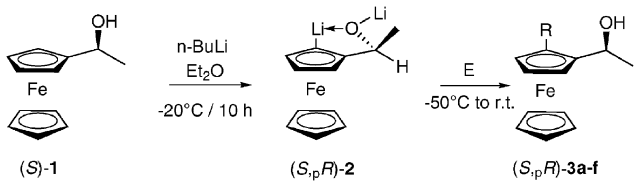
Table 1 Conditions applied for lithiation of 1-ferrocenyl-ethanol

Base	Solvent	Temp./°C	Time/h	Main product	*d.r.*[a]	Yield [%] (*S*,$_p$*R*)-**3a**
t-BuLi	Et_2O	−60	2	Several	n.d.	Inseparable
n-BuLi	THF	−60	2	Several	n.d.	Inseparable
n-BuLi	C_6H_{12}	5	2	(*S*,$_p$*R*)-**3a**	60 : 40	Inseparable
n-BuLi	Et_2O	−50	10	(*S*,$_p$*R*)-**3a**	99 : 1	25
n-BuLi	Et_2O	−20	10	(*S*,$_p$*R*)-**3a**	**95 : 5**	**79**
n-BuLi	Et_2O	0	10	(*S*,$_p$*R*)-**3a**	95 : 5	60

[a] Determined by HPLC and ^{1}H-NMR analysis.



Scheme 2 Synthesis of *ortho*-substituted ferrocenyl alcohols.

Encouraged by these results and with optimised conditions in hand, we tested the scope of our method by reacting the dilithiated ferrocenyl alcohol (*S*,$_p$*R*)-**2** with different electrophiles (Scheme 2, Table 2).

Yields were generally good, and the diastereomeric ratio was again in the range of 95 : 5. In the case of *t*-butyl sulfide **3c** only, low yield and massive formation of 1′-substituted by-product were observed, probably due to steric hindrance caused by the bulky *t*-butyl group. Comparison of the NMR spectra of **3b** and **3e** with literature values[18] proved their configuration to be (*S*,$_p$*R*), which is in accordance with the established stereochemical model for ferrocene lithiation.[19]

In this manner, a variety of interesting new planar chiral ferrocene derivatives were prepared, which could find use in asymmetric catalysis. Compounds **3a–e** feature a Lewis basic heteroatom in the 2-position as well as a free hydroxy group, which makes them promising candidates for the emerging field of hydrogen-bond assisted nucleophilic catalysis.[20] Chiral ferrocene diol **3f** could find application in reactions usually catalysed by Binol or Taddol derivatives.

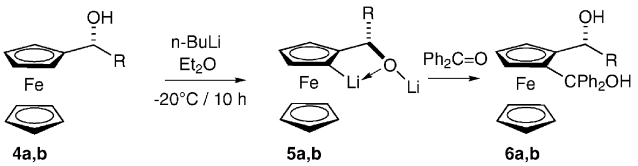
Next, we turned our attention to other ferrocenyl alcohols, to explore the generality of the lithiation method. Satisfyingly, phenyl- and cyclohexyl-ferrocenyl alcohols **4a** and **4b** gave single diastereomers in good yields after lithiation and quenching with benzophenone (Scheme 3, Table 3).

These compounds were prepared only in racemic form, and their configuration cannot yet be assigned. However, in analogy to compounds **3a–f** we assume their relative configuration to be also (*S*,$_p$*R*)/(*R*,$_p$*S*), respectively.

Table 2 Diastereoselective synthesis of *ortho*-substituted ferrocenyl alcohols

3	Electrophile	R	Yield [%]	*d.r.*
a	$(Ph\text{-}S)_2$	–S-Ph	79	95 : 5[ab]
b	$(Me\text{-}S)_2$	–S-Me	64	94 : 6[a]
c	$(t\text{-}Butyl\text{-}S)_2$	–S-*t*-butyl	21	n.d.
d	$(Ph\text{-}Se)_2$	–Se-Ph	77	95 : 5[a]
e	Ph_2PCl	$-P(Ph)_2$	63	>93 : 7[a]
f	$Ph_2C{=}O$	$-C(Ph)_2OH$	75	95 : 5[a]

[a] Determined by NMR spectroscopy. [b] Determined by HPLC analysis.



Scheme 3 Lithiation of phenyl- and cyclohexyl-ferrocenyl alcohols.

Table 3 Diastereoselective lithiation of phenyl- and cyclohexyl-ferrocenyl alcohols

6	R	Yield [%]	*d.r.*[a]
a	Phenyl	66	>95 : 5
b	Cyclohexyl	81	>95 : 5

[a] Determined by ^{1}H-NMR spectroscopy.

In summary, we have established the free hydroxy-function as a new *ortho*-directing group for diastereoselective *ortho*-metalation of ferrocene. This method opens up an efficient and flexible approach to novel planar chiral ferrocene derivatives. The easy preparation of enantiopure ferrocenyl-ethanol makes it an interesting alternative to the popular Ugi amine. The obtained planar chiral ferrocenyl alcohols can easily be elaborated further to known and new ligands, and are promising new lead structures for hydrogen bond assisted nucleophilic catalysis. Research along these lines is underway and will be reported in due course.

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