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New Chiral Ferrocenyl Building Blocks for Asymmetric Reactions

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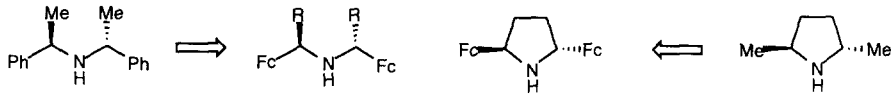
Abstract: *The new C_2-symmetrical ferrocenyl amines **2** and **3** are easily prepared starting from the ketones **4**. Their utility is demonstrated for enantioselective deprotonation reactions and highly diastereoselective alkylations of the amides **7**.* © 1997 Elsevier Science Ltd.

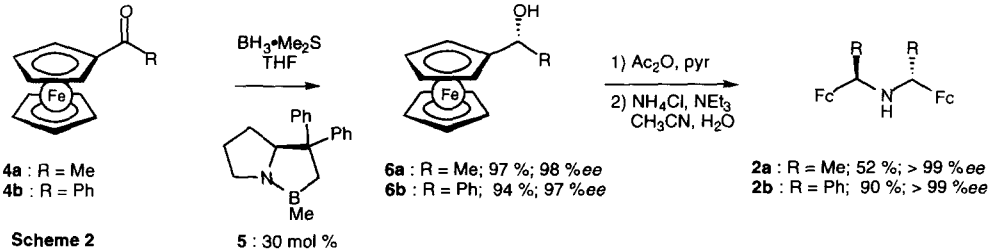
The preparation of new chiral ligands and auxiliaries for asymmetric synthesis is currently an important field of research.[1] Many of the successful chiral inductors contain a phenyl group as key organic moiety for achieving the stereodifferentiation.[2] We have envisioned that the replacement of a phenyl or methyl substituent by a ferrocenyl substituent (Fc) for example in the C_2-symmetrical amine **1** could be advantageous and may lead to new classes of versatile chiral ligands or auxiliaries (Scheme 1).



1 **2a** : R = Me **3**
2b : R = Ph

Scheme 1: Fc = ferrocenyl

The "3-dimensional nature" of a ferrocenyl group compared to the "2-dimensional steric hindrance" of a phenyl group may result in higher stereoselectivities. Furthermore, the introduction of an α-chiral ferrocenyl unit into a target structure is an easy synthetic operation, especially since a variety of α-functionalized chiral ferrocenyl diols can be prepared with high enantioselectivity by a CBS reduction[3] of the ketones obtained by acylation of ferrocene (RCOCl, $AlCl_3$) as described recently by us[4] and others.[5] Thus, a broad range of chiral ferrocenyl building blocks is available by a combinatorial approach[6] since the choice of the nature of R is nearly unlimited. Substitutions of the hydroxyl function by an ether, amino, phosphino or thioester group are well known reactions.[4,7] The ease of preparation and structural diversity of the chiral ferrocenyl building blocks make them attractive compared to the traditional approach using precursors from the chiral pool. Herein, we wish to report the first success of this strategy. We have prepared two new types of chiral auxiliaries **2a-b** and **3** by an expeditive route and have demonstrated their utility in asymmetric synthesis.
The CBS reduction[4,5] of the commercially available acylferrocenes **4a-b** (30 mol % catalyst **5**, BH_3·SMe_2, THF, 0 °C, 0.5 h) furnishes the desired ferrocenyl alcohols **6a-b** in 94-97 % yield and respectively 98 and 97 % *ee*. The corresponding acetates (Ac_2O, pyridine, rt, 12 h) were obtained quantitatively and were treated with NH_4Cl (2 equiv) and NEt_3 in CH_3CN:H_2O (4:1) furnishing the amines **2a** and **2b** in respectively 52 % and 90 % yield. Both crude diferrocenylamines **2a-b** contain less than 3 % of the *meso* compound and are > 99 % enantiomerically pure (Scheme 2). Diastereomerically pure material is obtained after chromatography.



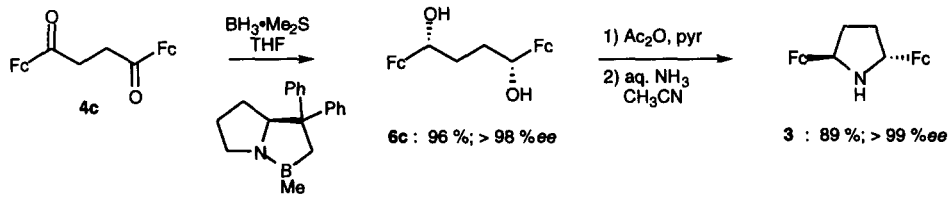
4a : R = Me
4b : R = Ph

6a : R = Me; 97 %; 98 %*ee*
6b : R = Ph; 94 %; 97 %*ee*

2a : R = Me; 52 %; > 99 %*ee*
2b : R = Ph; 90 %; > 99 %*ee*

Scheme 2

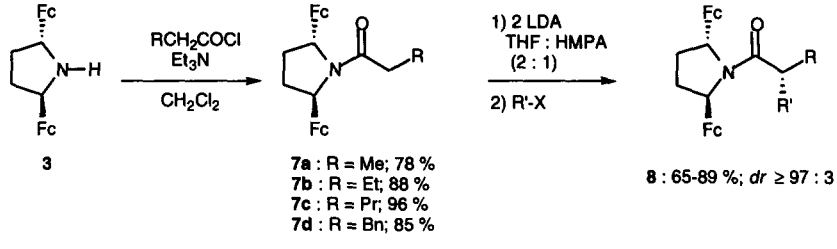
5 : 30 mol %

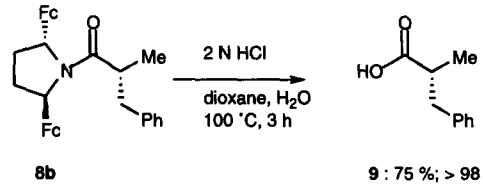


Scheme 3

Using the same methodology, the diferrocenyl-1,4-diketone **4c**[8] was reduced affording the 1,4-diol **6c** in 96 % yield in > 98 % *ee* containing 13 % of the corresponding *meso*-diol. The conversion of **6c** to the corresponding diacetate followed by treatment with aqueous NH_3 in acetonitrile gives the desired pyrrolidine derivative **3**[9] in 89 % yield (*cis*:*trans* ratio 12:78). The *cis*-isomer can be easily separated by chromatography affording the pure *trans*-pyrrolidine **3** (99 % *ee*).

The diferrocenylamines **2a-b** and **3** proved to be excellent chiral auxiliaries.[10] Thus, the acylation of **3** with an acid chloride RCH_2COCl (1.2 equiv, NEt_3, CH_2Cl_2, 25 °C, 10 min) provides the corresponding amides **7a-d**. The conversion of **7** to the lithium enolate with LDA (2 equiv) in THF : HMPA followed by the alkylation with an alkyl iodide or bromide furnishes the crystalline α-alkylated ferrocenyl amides **8** with high diastereoselectivity (≥ 97:3) (Scheme 4 and Table 1).[11,12]





Scheme 4

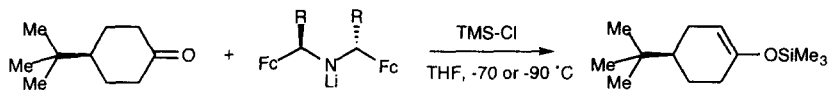
Especially remarkable compared to similar alkylations reported in the literature is the stereoselective alkylation of **7b** with MeI which proceeds with high diastereoselectivity (> 97:3).[12a] Both alkyl iodides and activated bromides react in satisfactory yields (65-89 %). The diastereomeric ratio can be further improved by simple chromatography allowing to reduce the other epimer to less than 0.5 %.

As an example, the alkylated amide **8b** has been hydrolysed by refluxing in 2 N HCl (dioxane : H_2O, 3 h) leading to the carboxylic acid **9** in 75 % yield and > 98 % *ee* (determined by derivatization with (*S*)-methyl mandelate). Like in the case of the removal of other chiral auxiliaries,[12] nearly no epimerization is observed. Attempts to use the non-cyclic C_2-symmetrical amines **2a-b** as chiral auxiliaries for the α-alkylation lead in the case of the methylation with MeI to moderate diastereoselectivities (80:20).

Table 1. α-Alkylated amides of type **8** obtained by the deprotonation of **7a-d** with LDA in THF:HMPA (2:1) and alkylation with R'X (X = Br, I).

entry	ferrocenyl amide **7**	R'-X	product **8**	diastereo-selectivity[a]	yield[b] (%)	$[\alpha_D]^c$ (°)
1	**7a**	EtI	**8a**	>99:1 (>99:1)	66	+144
2	**7a**	BnBr	**8b**	>98.5:1.5 (>99.5:0.5)	89	+77
3	**7a**	allyl-Br	**8c**	>98:2 (>99:1)	88	+113
4	**7a**	$PivOCH_2I$	**8d**	97:3 (98:2)	65	+113
5	**7b**	MeI	**8e**	>97:3 (>99:1)	71	+208
6	**7c**	MeI	**8f**	>97:3 (>99:1)	72	+220
7	**7d**	MeI	**8g**	>97:3 (>99.5:0.5)	75	+215

[a] The diastereomeric ratio indicated is that of the crude reaction mixture. The ratio in parenthesis corresponds to the diastereomeric ratio after chromatographical purification. The diastereoselectivity has been determined by ^1H- and ^{13}C-NMR analysis. [b] Isolated yield of analytically pure product. [c] Measured in $CDCl_3$ at room temperature.



11 **10a** : R = Me, **10b** : R = Ph (*R*)-**12** : up to 62 % ee

Scheme 5

In contrast, the chiral amine **2b** allows to perform enantioselective deprotonations.[13] Thus, treatment of the amines **2a-b** with *n*-BuLi affords the corresponding lithium amides **10a** (R = Me) and **10b** (R = Ph). The deprotonation of 4-*tert*-butylcyclohexanone (**11**) with these strong bases in the presence of Me_3SiCl (*in situ* quench conditions)[13e] affords the silyl enol ether **12** with modest selectivity with **10a** ((*S*):(*R*) 60:40 at - 70 °C), but a better selectivity is obtained with **10b** (27:73 at -70 °C and 19:81 at -90 °C). Interestingly the lithium amide derived from **3** gives no stereoselectivity in these deprotonation reactions.

In summary, we have prepared new chiral ferrocenyl amines in a very effective manner and have shown first applications of these auxiliaries for the performance of asymmetric alkylations and deprotonations. The design of these structures was driven by the idea of replacing a phenyl ring or a methyl group with a ferrocenyl moiety in already known chiral auxiliaries. Studies for extending this concept to the preparation of phosphorus containing chiral ligands for asymmetric catalysis are currently underway in our laboratories.

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[10] The phenyl-analogs of **2a-b** and **3** have been extensively used for asymmetric synthesis. For leading references see Ref. 9 and 12.

[11] **Typical procedure.** The amide **7a** (122 mg, 0.25 mmol) dissolved in THF (2 mL) and HMPA (0.5 mL) was dropwise added a 0.41 M solution of LDA (1.3 mL, 0.53 mmol). After 2 h at 0 °C, the reaction mixture was cooled to -78 °C and benzyl bromide (86 mg, 0.63 mmol) in THF (0.9 mL) was slowly added. After 30 min at -78 °C the solution was stirred 2 h at 0 °C and poured into 5 % HCl (20 mL). An extraction with ether (30 mL) was followed by washings with 5 % HCl (2 x 20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), concentrated and chromatographed (SiO_2, hexanes/*t*-BuOMe 6:1) to give the product **8b** (130 mg, 0.22 mmol, 89 %) as a brown solid (mp = 175 °C), $[\alpha]_D$ = 77.2 (c = 0.76 in $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.07-7.03 (m, 3H), 6.75-6.73 (m, 2H), 5.11 (d, *J* = 8.2 Hz, 1H), 4.83-4.82 (m, 1H), 4.11-3.86 (m, 18H), 2.70-2.09 (m, 7H), 0.85 (d, *J* = 5.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.4, 139.6, 128.8, 128.0, 125.5, 94.1, 88.1, 72.8, 68.6, 68.4, 67.5, 67.2, 66.8, 66.6, 65.9, 56.6, 56.0, 42.0, 40.8, 36.2, 29.6, 17.5; Anal. calcd for $C_{34}H_{35}Fe_2NO$: C 69.77, H 6.03, N 2.39. Found: C 69.43, H 6.15, N 2.23.

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