Stereochemical control in reactions of chiral ketone with 2-lithiated substituted ferrocene derivatives*

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The formation of a new chiral center in the reactions of ketone 4-$MeOC_6H_4CH(Et)C(O)Et$ with planar-chiral 2-lithio-1-methyl- and 1-chloro-2-lithioferrocenes proceeded stereoselectively to give two diastereomers in a ratio of ~3 : 2 or a single diastereomer, respectively, out of four possible diastereomeric 4-aryl-3-ferrocenylhexan-3-ols. The replacement of the hydroxy group in the resulting compounds by hydrogen under the conditions of ionic hydrogenation was studied. The configurations of the reaction products were established by X-ray diffraction analysis and ^{1}H NMR spectroscopy.

Key words: lithioferrocenes, planar and central chirality, 1,2-addition at the CO group, stereochemical control.

The regioselective introduction of substituents into monosubstituted ferrocenes proceeds primarily *via* 2-lithio intermediates, which are planar-chiral, like all homoannular differently substituted ferrocenes. Although many ferrocene derivatives are used to advantage in the asymmetric synthesis or catalysis,[1] the chiral plane in lithio derivatives is inefficient as a source of induction. Actually, our earlier study[2] of the stereochemistry of the reaction between chiral 4-(4-methoxyphenyl)hexan-3-one (**1**) and 1-dimethylaminomethyl-2-lithioferrocene (**2a**) has demonstrated that the chiral plane in lithioferrocenes poorly distinguishes both the diastereotopic and enantiotopic sides of the prochiral carbonyl group resulting in the formation of diastereomeric mixtures. An analogous stereochemical outcome was obtained in the reactions of compound **2a** or its α-methyl analog (**2a´**, R = $CH(Me)NMe_2$) with prochiral aldehydes.[3,4] The reaction between racemic compounds **1** and **2a** giving rise to products containing two asymmetric carbon centers (one center has already been present in compound **1**, whereas another center was generated in the reaction) and a chiral plane yielded only two of four possible racemic diastereomers in noticeable amounts, *viz*., **3a** and **4a**. These diastereomers have the $R_p{}^*S_{OH}{}^*R_{bn}{}^*$ and $R_p{}^*R_{OH}{}^*S_{bn}{}^*$ configurations, respectively.[2] The third diastereomer with unknown stereochemistry was isolated in trace amounts and characterized only by ^{1}H NMR spectroscopy.[5] The results obtained suggest that the reaction proceeds predominantly under stereochemical control of the chiral center of **1** according to the Felkin model.[6] This model considers the attack of the carbonyl group exclusively from the *anti* side with respect to the aryl group and assumes that the transition state is structurally similar to the starting reagents. The steric interactions only in the starting compound **1** are taken into account, whereas the properties of the lithium reagent (in our case, of substituted lithioferrocene) are not taken into consideration. Nevertheless, the assumption that the chiral plane in lithioferrocene can exert an effect on the stereochemistry of the reaction with ketone **1** must not be ignored.

With the aim of checking this assumption, we studied the stereochemistry of the reaction of ketone **1** with 2-lithio-1-methyl- (**2b**) and 1-chloro-2-lithioferrocenes (**2c**). Reagents **1** and **2b**,**c** were used as racemates. Compound **2b**, like **2a**, contains the electron-donating substituent, whereas the substituent in reagent **2c** possesses electron-withdrawing properties.

Results and Discussion

It was found that the reaction of more nucleophilic ferrocene **2b** with ketone **1** afforded a mixture of two

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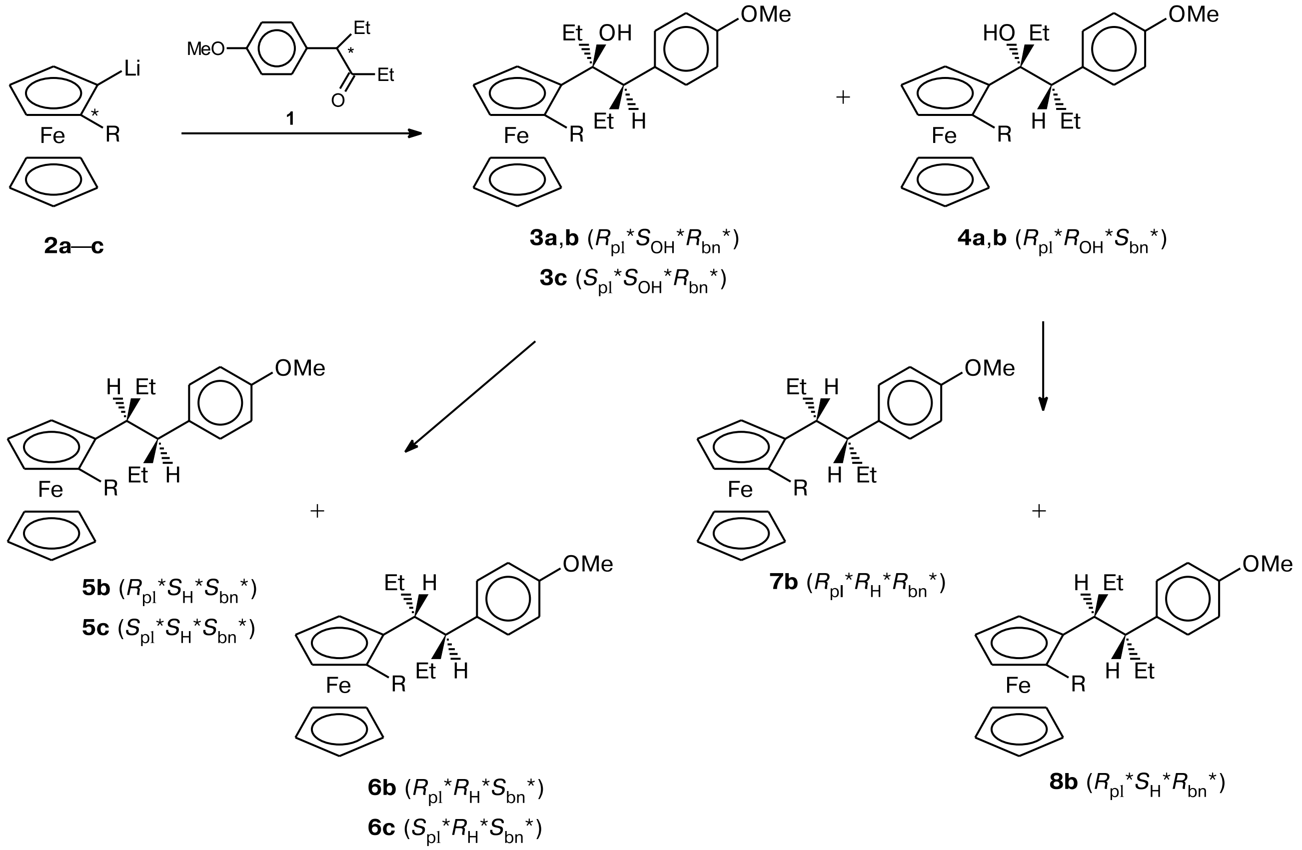
Scheme 1



R = CH_2NMe_2 (**a**), Me (**b**), Cl (**c**)

diastereomers (**3b** and **4b**) in a ratio of 62 : 38 in ~30% yield (Scheme 1). Less nucleophilic derivative **2c** reacted more slowly and the conversion was only 20%, but the reaction gave rise exclusively to diastereomer **3c**. The stereochemistry of the reaction product remained unchanged within 0.5 or 16 h after mixing of the reagents, hence the isomerization involving alkoxides did not occur. Most likely, the steric outcome of the reaction is determined in the earlier step of the generation of a complex of ketone **1** with the lithium derivative postulated for this type of reactions.

The fact that the reaction of ketone **1** with ferrocene **2b** afforded only two of four possible diastereomers is indicative of the induction by only one of the available elements of chirality. The diastereomerically pure product obtained in the reaction of **1** with **2c** provides evidence that the reaction pathway is stereochemically controlled by both the benzyl center of the ketone and the chiral plane of lithioferrocene.

Only the major diastereomer **3b** was isolated in the individual form from a mixture of diastereomers **3b** and **4b**. The structure and stereochemistry of this diastereomer were established by X-ray diffraction analysis. Another diastereomer **4b** was characterized only by ^{1}H NMR spectroscopy (Table 1).

Individual compounds **3b** and **3c** and a mixture of diastereomers **3b** + **4b** were subjected to ionic hydrogenation. Equally high reaction rates and low degrees of stereoselectivity were observed for all the reactions under consideration. The reaction of compound **3b** afforded a mixture of two products (**5b** and **6b**) in a ratio of 84 : 16, from which product **5b** was isolated in pure form. Its stereochemistry was established by X-ray diffraction analysis. The ^{1}H NMR spectrum of a reduction product of the mixture **3b** + **4b** revealed the presence not only of compounds **5b** and **6b** but also of two diastereomers (**7b** and **8b**) derived, apparently, from **4b**. These diastereomers differ from the products obtained upon ionic hydrogenation of **3b**. On the whole, compound **5b** substantially prevailed among the reaction products, compound **8b** was present in a noticeable amount, whereas compounds **6b** and **7b** were present as minor diastereomers. Ionic hydrogenation of **3c** gave rise to two diastereomers (**5c** and **6c**) in a ratio of 2 : 1. The spectroscopic characteristics of compounds **5c**, **6b**, **6c**, **7b**, and **8b** (see Table 1) were determined from the ^{1}H NMR spectra of the resulting mix-

Table 1. Data from ^{1}H NMR spectroscopy of diastereomeric 4-(4-methoxyphenyl)-3-(2-chloro- or 2-methylferrocenyl)hexan-3-ols

Compound	Configuration	δ (*J*/Hz)						
		$CH_3(1)$, $CH_3(6)$	$C\underline{H}_3C_5H_3$	CH	OCH_3	Cp	C_6H_4 (AB system)	Other
3a★	$R_p{}^*S_{OH}{}^*R_{bn}{}^*$	0.36 (t, 3 H, *J* = 7.3); 0.78 (t, 3 H, *J* = 7.3)	—	2.77 (m, 1 H)	3.80 (s, 3 H)	4.17 (s, 5 H)	6.63 and 7.26 (*J* = 8.7)	0.85 (m, 1 H); 1.17 (m, 1 H); 1.32 (m, 1 H); 1.95 (m, 1 H); 2.17 (s, 6 H); 2.71 (d, 1 H, *J* = 12.4); 2.77 (m, 1 H); 3.67 (d, 1 H, *J* = 12.3); 3.80 (s, 3 H); 3.90 (t, 1 H, *J* = 2.4); 4.10 (dd, 1 H, *J* = 2, *J* = 1.4); 4.15 (dd, 1 H, *J* = 2.4, *J* = 1.4); 4.17 (s, 5 H)
4a★	$R_p{}^*R_{OH}{}^*S_{bn}{}^*$	0.48 (t, 3 H, *J* = 7.3); 1.15 (t, 3 H, *J* = 7.3)	—	2.45 (m, 1 H)	3.77 (s, 3 H)	4.12 (s, 5 H)	6.76 and 7.15 (*J* = 8.7)	1.12 (m, 1 H); 1.4 (m, 1 H); 1.75 (m, 1 H); 2.13 (m, 1 H); 2.20 (s, 6 H); 2.45 (m, 1 H); 2.50 (d, 1 H, *J* = 12.1); 3.77 (s, 3 H); 3.93 (dd, 1 H, *J* = 2.4, *J* = 1.4); 3.96 (d, 1 H, *J* = 12, *J* = 0); 3.99 (dd, 1 H, *J* = 2.4, *J* = 1.4); 4.09 (t, 1 H, *J* = 2.4); 4.12 (s, 5 H)
3b	$R_p{}^*S_{OH}{}^*R_{bn}{}^*$	0.74 (t, 6 H, *J* = 7.2)	1.92 (s, 3 H)	2.69 (dd, 1 H, *J* = 12, *J* = 2.5)	3.82 (s, 3 H)	4.13 (s, 5 H)	6.78 and 7.07 (*J* = 8.6)	1.50—1.76, 1.85—1.93, 2.00—2.06, 2.35—2.55 (all m, 4 H, $C\underline{H}_2Me$); 2.30 (s, 1 H, OH)
4b	$R_p{}^*R_{OH}{}^*S_{bn}{}^*$	0.66 (t, 3 H, *J* = 7.2); 1.15 (t, 3 H, *J* = 7.4)	1.45 (s, 3 H)	2.79 (dd, 1 H, *J* = 13, *J* = 3.2)	3.75 (s, 3 H)	4.07 (s, 5 H)	6.68 (br.s)	3.86—3.87, 3.90—3.91, 3.97—3.99, 4.06—4.07, 4.08—4.10; 4.11—4.12 (all m, 3 H, C_5H_3)
3c	$S_p{}^*S_{OH}{}^*R_{bn}{}^*$	0.67 (t, 3 H, *J* = 7.3); 0.91 (t, 3 H, *J* = 7.3)	—	2.78 (dd, 1 H, *J* = 12.3, *J* = 2.9)	3.79 (s, 3 H)	4.24 (s, 5 H)	6.77 and 6.95 (*J* = 8.6)	1.50—1.76, 1.92—2.00, 2.10—2.25, 2.37—2.55, (all m, 4 H, $C\underline{H}_2Me$); 1.99 (s, 1 H, OH); 3.69 (dd, 1 H, C_5H_3, *J* = 2.4, *J* = 1.4); 3.99 (t, 1 H, C_5H_3, *J* = 2.4); 4.41 (dd, 1 H, C_5H_3, *J* = 2.4, *J* = 1.4)
5b	$R_p{}^*S_H{}^*S_{bn}{}^*$	0.66 (t, 3 H, *J* = 7.3); 1.12 (t, 3 H, *J* = 7.4)	2.00 (s, 3 H)	—	3.77 (s, 3 H)	3.97 (s, 5 H)	6.71 (br.s)	1.45—1.58 (m, 3 H, $C\underline{H}_2Me$, $CH\underline{H}Me$); 1.95—2.00 (m, 1 H, $CH\underline{H}Me$); 2.44—2.49 (m, 1 H, CH); 2.65—2.71 (m, 1 H, CH); 3.41 (m, 1 H, C_5H_3); 3.86 (m, 1 H, C_5H_3); 4.04 (m, 1 H, C_5H_3)
6b	$R_p{}^*R_H{}^*S_{bn}{}^*$	0.66 (t, 6 H, *J* = 7.2)	1.92 (s, 3 H)	—	3.82 (s, 3 H)	4.03 (s, 5 H)	6.83 and 7.07 (*J* = 8.3)	
7´b	$R_p{}^*S_H{}^*R_{bn}{}^*$	0.65 (t, 3 H, *J* = 7.0); 1.11 (t, 3 H, *J* = 7.0)	1.38 (s, 3 H)	—	—	4.02 (s, 5 H)	6.73 (q, *J* = 8.6)	1.31 (m, 2 H, $C\underline{H}_2Me$); 1.79 (m, 1 H, $C\underline{H}HMe$); 2.03 (m, 1 H, $C\underline{H}HMe$); 2.41 (q, 1 H, CH); 2.61 (q, 1 H, CH); 3.85 (m, 1 H, C_5H_3); 3.99 (m, 2 H, C_5H_3)
7b	$R_p{}^*S_H{}^*R_{bn}{}^*$	0.62 (t, 3 H, *J* = 7.3); 1.08 (t, 3 H, *J* = 7.3)	1.38 (s, 3 H)	—	3.78 (s, 3 H)	4.00 (s, 5 H)	6.74 and 6.78 (*J* = 6.9)	1.32—1.40, 1.60—1.70, 2.00—2.05 (all m, 4 H, $C\underline{H}_2Me$); 2.30—2.40 (m, 1 H, CH); 2.50—2.60 (m, 1 H, CH)
8b	$R_p{}^*R_H{}^*R_{bn}{}^*$	0.80 (t, 3 H, *J* = 7.3); 0.99 (t, 3 H, *J* = 7.3)	1.27 (s)	—	3.78 (s)	3.99 (s)	—	1.73—1.77 (m, $C\underline{H}_2Me$)
5c	$S_p{}^*S_H{}^*S_{bn}{}^*$	0.73 (t, 3 H, *J* = 7.4); 1.17 (t, 3 H, *J* = 7.4)	—	2.67—2.77 (m, 2 H)	3.77 (s, 3 H)	4.11 (s, 5 H)	6.71 and 6.75 (*J* = 8.9)	1.40—1.70 (m, 2 H, $C\underline{H}_2Me$); 1.70—2.00 (m, 2 H, $C\underline{H}_2Me$); 3.40 (m, 1 H, C_5H_3); 3.87 (m, 1 H, C_5H_3); 4.40 (m, 1 H, C_5H_3)
6c	$S_p{}^*R_H{}^*S_{bn}{}^*$	0.73 (t, 6 H, *J* = 7.4)	—	1.70—2.00, 2.35—2.49 (both m, 2 H)	3.80 (s, 3 H)	4.20 (s, 5 H)	6.84 and 7.17 (*J* = 8.7)	1.40—1.70 (m, 2 H, $C\underline{H}_2Me$); 1.70—2.00 (m, CH); 2.35—2.49 (m, 1 H, CH); 3.50 (m, 1 H, C_5H_3); 3.94 (m, 1 H, C_5H_3); 4.37 (m, 1 H, C_5H_3)

★ Ref. 2.

tures. It is of interest to compare these data with the results of ionic hydrogenation of alcohols **3a** and **4a**. In these reactions, the latter compounds exhibit complete stereospecificity, give opposite stereochemical outcomes (inversion of the configuration of the reaction center in the case of **3a** and its retention for **4a**), and show radically different reactivities.[7]

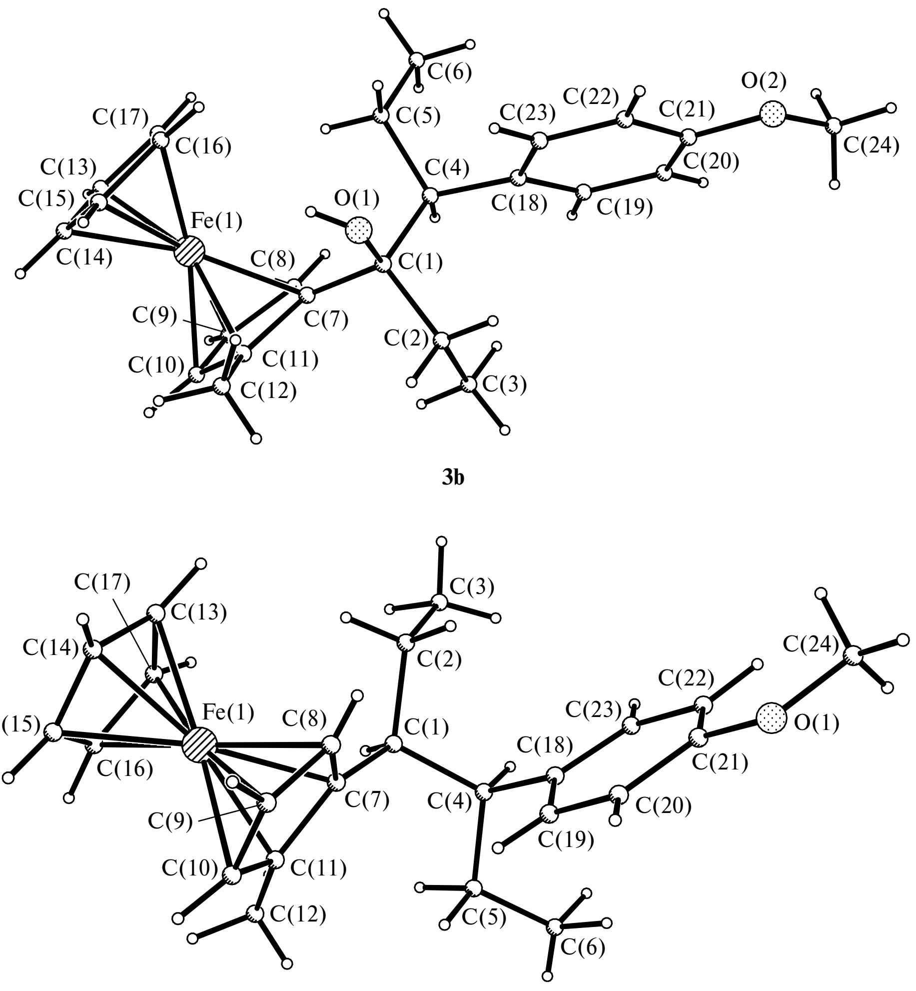
These results were interpreted based on the data on the stereochemistry of compounds **3b** and **5b** obtained from ^{1}H NMR spectroscopy and X-ray diffraction analysis.

The overall views of molecules **3b** and **5b** are shown in Fig. 1. The crystallographic data are given in Table 2.

The crystals of compounds **3b** and **5b** are centrosymmetric and contain equal amounts of the enantiomeric molecules $R_pS_{OH}R_{bn}$ and $S_pR_{OH}S_{bn}$ (**3b**) or $R_pS_HS_{bn}$ and $S_pR_HR_{bn}$ (**5b**). Based on these data, the relative $R_p{}^*S_{OH}{}^*R_{bn}{}^*$ and $R_p{}^*S_H{}^*S_{bn}{}^*$ configurations were assigned to **3b** and **5b**, respectively.

Molecules **3b** and **5b** adopt different overall conformations, the main differences being the orientations of the aryl ring and ethylene bridge (the C(11)C(7)C(1)C(4) and C(7)C(1)C(4)C(18) torsion angles are respectively 172.8(6) and 165.5(5)° in **3b** and 83.3(6) and 69.4(5)° in **5b**). Hence, the ethylene bridge (C(4) atom) in molecule **3b** is in the transoid position with respect to the Cp ring, whereas the Ar and Cp substituents are in *trans* positions with respect to the C(1)—C(4) ethylene bridge. In molecule **5b**, the analogous fragments are in cisoid positions in both cases.

In molecule **3b**, the H(1) atom of the hydroxy group is directed toward the Fe(1) atom (O(1) atom deviates from the plane of the Cp ring by 0.631 Å) and forms an intramolecular OH...Fe hydrogen bond (3.07(8) Å) as well as the very weak intermolecular O(1)H......O(1´) hydrogen bond (O(1)...O(1´) and H—O(1´) distances are 3.038(7) and 2.78(7) Å, respectively). Analogous metal—proton bonds were found in many molecules containing the FcC(OH)R^{1}R^2 fragment in which the configuration of the C(OH)R^{1}R^2 chiral center favors the deviation of the OH group from the plane of the Cp ring



3b

5b

Fig. 1. Crystal structures of compounds **3b** and **5b**.

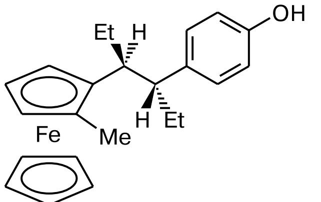
Table 2. Crystallographic data and details of the refinement of compounds **3b** and **5b**

Parameter	**3b**	**5b**
Molecular formula	$C_{24}H_{30}FeO_2$	$C_{24}H_{30}FeO$
Molecular weight	406.33	390.33
Space group	*Pbca*	$P2_1/c$
T/K	293(2)	
a/Å	8.091(2)	21.285(4)
b/Å	20.653(4)	7.989(2)
c/Å	25.314(5)	12.380(3)
α/deg	—	—
β/deg	—	104.30(3)
γ/deg	—	—
V/Å^3	4230(15)	2039.9(7)
Z	8	4
d_{calc}/g cm^{-3}	1.276	1.271
Color and habitus of crystals	Yellow needles	
Dimensions/mm	0.40×0.20×0.15	0.50×0.30×0.20
Diffractometer	Siemens P3/PC	Enraf—Nonius CAD4
Radiation	MoKα (λ = 0.71073 Å)	
μ/cm^{-1}	7.28	7.49
Scan mode	θ – 2θ	θ – 5/3θ
$2\theta_{max}$/deg	50	56
Total number of reflections	5644	5083
Number of independent reflections	3650	4883
R_1 (based on F for reflections with $I > 2\sigma(I)$)	0.0839 (1587 отр.)	0.0562 (1818 отр.)
wR_2 (based on F^2 for all reflections)	0.1614	0.1558
Number of refinable parameters	248	355
Weighting scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = 1/3(F_o^2 + 2F_c^2)$	
a	0.0457	0.0608
b	3.490	0.0000
GOOF	1.012	0.976
F(000)	1728	832

Note. Absorption was ignored.

toward the iron atom. The typical Fe......H and Fe......O distances are 3.00—3.20 and 3.45—3.65 Å, respectively. The structures of analogous molecules with the opposite configuration of the C(OH)R^{1}R^2 center are characterized by either the deviation of the OH group in the opposite direction with respect to the iron atom or the coplanar arrangement of this group and the plane of the Cp ring. In this case, no Fe......HO hydrogen bond is formed (Fe...O distance is larger than 4 Å). Among the FcC(OH)R^{1}CHR^{2}Ph molecules, which are analogous to **3b**, those with R^1 = R^2 = H and R^1 = Ph, R^2 = H[8] also contain the Fe......HO hydrogen bond. The IR spectroscopic data demonstrated that diastereomer **3b** exists as the only conformer with the Fe...HO hydrogen bond (ν_{OH} = 3560 cm^{-1}). It was of interest to compare these data with the results of X-ray diffraction analysis and IR spectroscopy of dimethylaminomethyl analog **3a**, for which two conformers were found.[2] This fact is associated with the formation of a strong intramolecular hydrogen bond between the hydroxy and amino groups.

Attempts to directly establish the configuration of the second diastereomer **4b** failed. A comparison of the results of ionic hydrogenation of **3b** and **4b** substantially helped in the determination of this configuration. It appeared that ionic hydrogenation of **3b** and **4b** afforded different pairs of reaction products (consequently, all possible diastereomers of 3,4-disubstituted hexane, *viz.*, **5b** + **6b** and **7b** + **8b**, respectively, were prepared). Of two diastereomeric products **5b** and **6b** derived from the R_p*S_{OH}*R_{bn}* diastereomer **3b**, the major diastereomer **5b** has the R_p*S_H*S_{bn}* configuration suggesting that the process proceeded predominantly with the inversion of the configuration of the carbon atom containing the HO group.* The second diastereomer, *viz.*, **6b**, can be formed only as a result of the retention of the configuration of this atom and has the relative R_p*R_H*S_{bn}* configuration. Hence, it can be conclusively stated that compound **4b** is not the R_p*R_{OH}*R_{bn}* diastereomer, because ionic hydrogenation of the latter should produce the diastereomeric products identical with those derived from **3b**. However, the results of ionic hydrogenation gave no way of assigning one of the remaining two configurations (R_p*S_{OH}*S_{bn}* or R_p*R_{OH}*S_{bn}*) to **4b**, because the non-stereoselective reactions of the corresponding diastereomers yield the same products having the R_p*R_H*R_{bn}* and R_p*S_H*R_{bn}* configurations. To establish the stereochemistry of **4b**, we carried out a comparative analysis of the ^{1}H NMR spectra of compounds **3—6b** and compound **7´b** having the R_p*S_H*R_{bn}* configuration. The latter compound, which has been described earlier,[6] is a phenol analog of compound **7b**, and its configuration follows from the chemical correlation with compound R_p*R_{OH}*S_{bn}*-**4a**.[6]



7´b

As can be seen from Table 1, the transformation of **3b** into **5b**, *i.e.*, the inversion of the configuration of the reaction center, was accompanied by the appearance of

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* The configuration symbols are the result of the formal application of the precedence rule to the substituents at the chiral center or chiral plane and provide no information on the stereochemical pathway of the reaction.

two signals (instead of one signal) of the terminal Me groups in the ^{1}H NMR spectra and a change in the type of the AB system for the aromatic protons, but had only a slight effect on the position of the signal of the Me group of the ferrocene moiety (δ 1.92 and 2.00 for **3b** and **5b**, respectively). In contrast, the transformation of **3b** into **6b** (the configuration of the reaction center remained unchanged) did not lead to noticeable changes in the positions and character of the above-mentioned signals. Besides, the ^{1}H NMR spectrum of **3b** differs substantially from that of **4b**, whereas δ for the signals of all the above-mentioned groups, except for the Me group in ferrocene, in the ^{1}H NMR spectra of compounds **4b**, **5b**, and **7´b** (δ 1.45, 2.00, and 1.38, respectively) are only slightly different.

The results obtained led to the following conclusions. First, the chemical shift δ of the Me group in the ferrocene moiety reflects the different (actual rather than formal) relative configurations of the chiral plane and benzyl center in compounds **3b**, **5b**, and **6b**, on the one hand, and in **4b** and **7´b**, on the other hand. In addition, the above-considered signals are insensitive to the replacement of the OH group by the hydrogen atom, their positions and character remaining virtually unchanged in the course of ionic hydrogenation, provided the configuration of the carbon atom that contained the HO group retained,* as in the transformation of **3b** into **6b**. Finally, as in the case of the transformation of **3b** into **5b**, it is the stereochemical modification, *i.e.*, the inversion of the configuration of the deoxygenated center, rather than its chemical modification, that leads to radical changes in the ^{1}H NMR spectrum.

Hence, the substantially different chemical shifts of the Me group of the ferrocene ring in **3b** and **4b** are indicative of the difference in the relative configurations of the chiral plane and the benzyl center (R_p*R_{bn}* in **3b** and R_p*S_{bn}* in **4b**). Based on the similarity of the ^{1}H NMR spectra of **4b** and **5b** and taking into account that the replacement of the hydroxy group by the proton has only a slight effect, an analogy can be drawn between the configurations of their asymmetric carbon atoms bearing the ferrocenyl substituent. Hence, the configuration of this center in **3b** is opposite to its configuration in compounds **4b** and **5b**, and, consequently, this center in **4b** has the R_{OH}* configuration. Based on the relative R_p*S_{bn}* configuration of the chiral center and benzyl center, the complete R_p*R_{OH}*S_{bn}* stereochemistry of diastereomer **4b** can be established. This stereochemistry is identical with that found for **4a** formed as the second product of the reaction of **1** with **2a**.[2]

On the whole, the reactions of **1** with **2a**,**b** follow the qualitatively identical stereochemical pathway, but the amounts of diastereomeric 4-aryl-3-ferrocenylhexan-3-ols and the ratios between compounds **3a**/**4a** and **3b**/**4b** (30 : 50 and 62 : 38, respectively) are different. The stereochemistry of ionic hydrogenation of compounds **3a** and **4a** also differs from that of **3b** and **4b**, primarily, in the degree of stereoselectivity. In addition, the reactions of **4b**, unlike those of **4a**, not only proceeded much more rapidly and non-stereoselectively but, apparently, were also accompanied by the predominant inversion of the configuration of the HO-bearing carbon atom instead of its retention.

The ^{1}H NMR spectroscopic data and the degree of their changes upon ionic dehydrogenation of alcohols were used also as a criterion for the configuration assignments of diastereomers **3c**, **5c**, **6c** and **7b**, **8b** (see Table 1).

Since we failed to obtain crystals of the only diastereomer **3c** formed in the reaction of **1** with **2c**, its structure could not be established directly. The IR spectrum of **3c** has an absorption band at ν 3576 cm^{-1} corresponding to the conformer with the Fe...HO hydrogen bond and a shoulder at ν 3596 cm^{-1} assigned to the Cl...HO hydrogen bond. Apparently, compound **3c** exists as two conformers (analogously to aminoalcohols **3a**).

In the ^{1}H NMR spectra of compounds **5c** and **6c** formed in a ratio of 2 : 1 upon ionic hydrogenation of **3c**, the chemical shifts of the signals for all protons, except for ferrocene, are very similar to those observed in the spectra of **5b** and **6b**. Taking into account that the latter are products of reduction of **3b**, it can be assumed that compounds **3c**, **5c**, and **6c** have the relative S_p*S_{OH}*R_{bn}*,* S_p*S_H*S_{bn}*, and S_p*R_H*S_{bn}* configurations, respectively, and that ionic hydrogenation of **3c** proceeded predominantly with the inversion of the configuration of the HO-bearing carbon atom.

Based on the results of the previous[2] and present studies, it can be conclusively stated that the stereochemistry of the alcohol center newly formed in the reactions of planar-chiral lithiated derivatives of ferrocene with chiral ketone is always determined by the chiral center of the ketone according to the Felkin model (Scheme 2), but the amount of the diastereomers and their ratio depend, evidently, on the nature of the substituent in the Li derivative of ferrocene. The attack occurs from the side opposite to the aryl group. However, as the donor properties of the substituent decrease in the series CH_2NMe_2 > Me > Cl, the degree of Li......O complex formation increases, the reagents approach each other, the transition state moves along the reaction coordinate thus becoming more structurally similar to its products, and the steric interactions between the substituent in ferrocene and the ethyl group in ketone begin to exert a noticeable effect, so that its chiral center gains the capacity to recognize the enanti-

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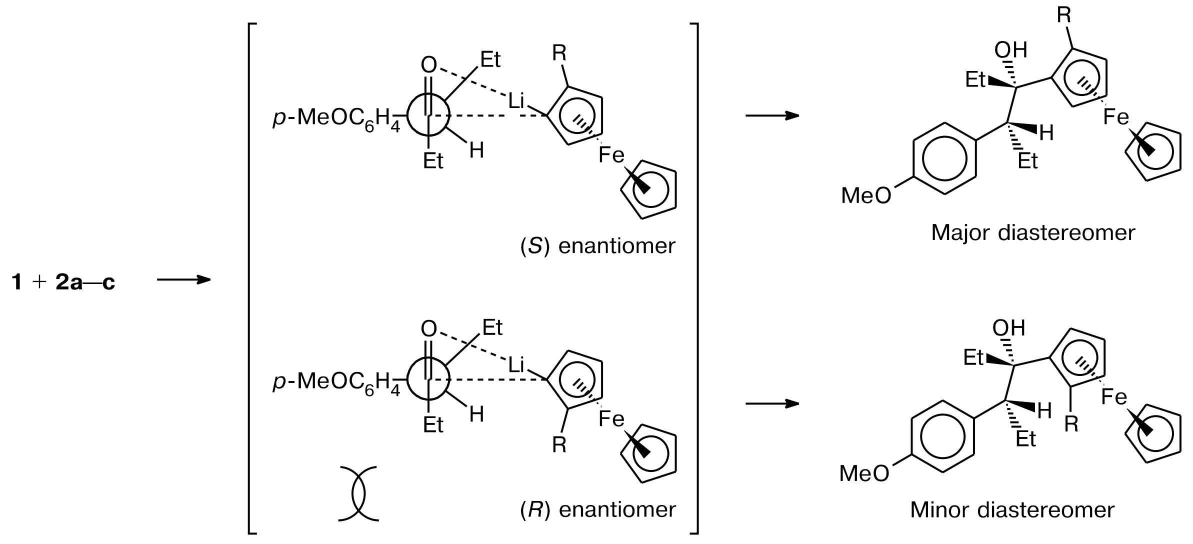
* This means that no inversion occurs rather than the (*R*,*S*) symbolism is changed.

* According to the precedence rule, the configuration symbols take into account the precedence of the chlorine atom.

Scheme 2



omers of 2-lithiochloroferrocene and reacts with one of them with high stereoselectivity.

Experimental

All experiments were carried out under an argon atmosphere. Organic solvents were purified according to standard procedures. The ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker WP-200-SY (200.13 MHz) and Bruker AM 250 spectrometers (standard program for protons, 299.9 MHz). The spectroscopic data are given in Table 1.

4-(4-Methoxyphenyl)-3-(2-methylferrocenyl)hexan-3-ols (3b, 4b). A 1.65 *M* Bu^{n}Li solution (0.43 mL, 0.7 mmol) in hexane was added to a solution of 1-bromo-2-methylferrocene[9] (100 mg, 0.35 mmol) in anhydrous diethyl ether (5 mL) at −70 °C. After 30 min, the reaction mixture was warmed to 0 °C, kept at this temperature for 30 min, and again cooled to −70 °C. Then a solution of compound **1** (143 mg, 0.7 mmol) in ether (1 mL) was added. The reaction mixture was kept at ~20 °C for ~12 h, hydrolyzed with water, and extracted with hexane. The hexane solution was dried with $MgSO_4$ and the solvent was evaporated to obtain an oil. The oil was subjected to repeated TLC (Silufol) using hexane as the eluent to obtain a mixture of the starting 1-bromo-2-methylferrocene and methylferrocene (60 mg), unconsumed **1** (77 mg, 53%), and a mixture of **3b** and **4b** (39 mg, 27.5%) in a ratio of 62 : 38 with traces of **1** as an oil. Crystallization of the oil from heptane afforded crystals of major diastereomer **3b**, m.p. 78 °C. These crystals were studied by X-ray diffraction analysis (Fig. 1, Table 2).

3-(2-Chloroferrocenyl)-4-(4-methoxyphenyl)hexan-3-ol (3c). A 2.4 *M* BuLi solution (4.5 mL) was added dropwise with stirring under argon to a solution of chloroferrocene[10] (1.1 g, 5 mmol) in anhydrous THF (30 mL) at 0 °C. After 1.5 h, the reaction mixture was cooled to −80 °C and a solution of compound **1** (2.06 g, 10 mmol) in THF was added. Then the reaction mixture was kept for 12 h, decomposed with water, and extracted with hexane. The hexane solution was dried with $MgSO_4$ and the solvent was evaporated to obtain an oil. The starting chloroferrocene and compound **1** (0.83 and 1.41 g, respectively) as well as **3c** (0.4 g, 18.5%) were isolated by chromatography on silica gel using successive elution with hexane and hexane—ether mixtures (50 : 1 and then 10 : 1).

4-(4-Methoxyphenyl)-3-(2-methylferrocenyl)hexanes (5—8b). ***A.*** A solution of compound **3b** (30 mg, 0.075 mmol) in CH_2Cl_2 was mixed with a 20-fold excess of $NaBH_4$. Then CF_3COOH was added with stirring at 30-min intervals (3×0.5 h) under argon at 0 °C. The reaction mixture was diluted with hexane and poured into an ice—sodium carbonate solution, after which ascorbic acid was added (to partially reduce ferrocenium that formed). Then the reaction mixture was extracted with hexane, the hexane solution was dried over $MgSO_4$, and the solvent was evaporated to obtain a mixture of **5b** and **6b** in a ratio of 5.5 : 1 in a yield of 25 mg (85%). Upon prolonged storage of a methanolic solution of **5b** and **6b** at −4 °C, crystals of **5b** (m.p. 70 °C) precipitated. These crystals were studied by X-ray diffraction analysis (Fig. 1, Table 2). Found (%): C, 73.95; H, 7.96. $C_{24}H_{30}FeO$. Calculated (%): C, 73.85; H, 7.75.

B. A mixture of **3b** and **4b** (2 : 1) (0.12 g, 0.3 mmol) was subjected to ionic hydrogenation according to the above-described procedure. Crystallization of the resulting mixture of diastereomers **5—8b** (0.1 g, 86%) from MeOH afforded **5b** containing approximately 10% of diastereomer **7b**. The fourth isomer **8b** was present in a substantial amount in the mother liquor (NMR), but we failed to isolate this isomer in the individual form.

3-(2-Chloroferrocenyl)-4-(4-methoxyphenyl)hexanes (5c, 6c). Ionic hydrogenation of **7** (0.395 g, 0.93 mmol) under the above-described conditions afforded a mixture of **5c** and **6c** in a ratio of 2 : 1 in a yield of 0.37 g (90%).

X-ray diffraction analysis. Yellow platelet-like crystals of **3b** and **5b** were obtained by crystallization from heptane and methanolic solutions, respectively.

The X-ray diffraction data sets were collected on four-circle automated diffractometers. The details of X-ray diffraction study and refinement are given in Table 2. The structures were solved by direct methods. All nonhydrogen atoms were located from difference Fourier syntheses and refined anisotropically by the full-matrix least-squares method based on F^2_{hkl}. All hydrogen atoms in **5b** and the H(1)O atom in **3b** were also revealed from electron density maps and refined isotropically. The hydrogen atoms in **3b** (except for the H(1)O atom of the OH group) were placed in geometrically calculated positions and refined using the riding model with isotropic thermal parameters $B_{iso}(H) = 1.2B_{equiv}(C)$ for the H atoms of the phenyl rings and CH_2 groups and $B_{iso}(H) = 1.5B_{equiv}(C)$ for the H atoms of the Me groups, where $B_{equiv}(C)$ is the equivalent isotropic thermal parameters of the carbon atoms to which the corresponding hydrogen atoms are attached.

All calculations were carried out using the SHELXTL PLUS 5 program package.[11] The atomic coordinates and all other structural characteristics were deposited with the Cambridge Structural Database.

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References

1. (a) T. Hayashi, in *Ferrocenes*, Eds. A. Tongi and T. Hayashi, VCHPubl., Weinheim, 1995, 105; (b) Y. Butsugan, S. Araki, and H. Watanabe, *ibid.*, 143.
2. M. Gruselle, B. Malezieux, L. L. Troitskaya, V. I. Sokolov, L. M. Epstein, Y. S. Shubina, and J. Vaissermann, *Organometallics*, 1994, **13**, 200.
3. C. Moise, D. Sautrey, and J. Tirouflet, *Bull. Soc. Chim. France*, 1971, **12**, 4562.
4. L. F. Battele, R. Bau, G. W. Gokel, R. T. Oyakawa, and I. K. Ugi, *J. Am. Chem. Soc.*, 1973, **95**, 482.
5. B. Malezieux, M. Gruselle, L. L. Troitskaya, and V. I. Sokolov, *Tetrahedron: Asymmetry*, 1998, **9**, 1.
6. (a) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 1968, 2199; (b) V. Cherest and H. Felkin, *ibid.*, 1968, 2205.
7. B. Malezieux, M. Gruselle, L. L. Troitskaya, V. I. Sokolov, and J. Vaissermann, *Organometallics*, 1994, **13**, 2979.
8. C. Glidewell, R. B. Klar, P. Lightfoot, C. M. Zakaria, and G. Ferguson, *Acta Crystallogr.*, *Sect. B (Str. Sci.)*, 1996, **52**, 110.
9. P. Bickert, B. Hildebrandt, and K. Hafner, *Organometallics*, 1984, **3**, 653.
10. V. A. Nefedov and M. N. Nefedova, *Zh. Obshch. Khim.*, 1966, **36**, 122 [*J. Gen. Chem. USSR*, 1966, **36** (Engl. Transl.)].
11. G. M. Sheldrick, *SHELXTL Ver. 5.0. Software Reference Manual*, Siemens Industrial Automation, Inc., Madison, 1995.

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