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Asymmetric Synthesis of Novel Ferrocenyl Ligands with Planar and Central Chirality**

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The application of ferrocenyl ligands possessing planar chirality to asymmetric catalysis has recently received considerable interest, especially in their use as P,P- and P,N-chelating systems.[1] Planar-chiral ferrocenes of the Kumada – Hayashi type **A**, which additionally possess a stereocenter in the α-position, have shown efficiency as catalysts for asymmetric synthesis both in research and industrial processes.[1, 2] We report here a straightforward asymmetric synthesis of planar-chiral ferrocenyl ligands of type **B** bearing a

A **B**

stereogenic center in the β-position of the side chain. The field of such planar-chiral ferrocenes has been little studied until now, since it was previously not possible to synthesize these compounds stereoselectively. In 1981 Kumada et al. described the only synthesis of ligand **B** ($E^1 = NMe_2$, $E^2 = PPh_2$), a homologue of diphenylphosphanylferrocenylethylamine (PPFA), which required separation of racemates and diastereoisomers.[3]

Our SAMP/RAMP-hydrazone method (SAMP and RAMP = (*S*)- and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine) seemed to be appropriate for the asymmetric synthesis of planar-chiral ligands bearing a stereogenic center at the β-position of the ferrocene backbone. Not only would the highly diastereoselective alkylation α to the hydrazone functional group be possible,[4] but also various heteroatom functionalities could be introduced with similar highly asymmetric inductions. In the context of ligand synthesis this would necessarily require the use of phosphorus,[5] sulfur,[6] and nitrogen electrophiles.[7] Since we have recently demonstrated that benzoylferrocene – SAMP-hydrazones may be easily functionalized at the *ortho* position with high diastereoselectivity,[8] it was decided to combine both synthetic strategies. Ferrocenyl ketones **1** with α-positioned acidic protons, which may be accessed simply by Friedel – Crafts acylation,[9] served as starting material. Because the ketones were only weakly electrophilic, owing to the electron-donating character of the ferrocenyl system, quantitative conversion into the *E*/*Z*-SAMP-hydrazone mixtures **2** ($E:Z \approx 3:1$) was achieved through activation with $AlMe_3$ (Scheme 1).[8, 10]

The regioselective metalation of the side chain was possible by the use of lithium diisopropylamide (LDA). After trapping the azaenolate with electrophiles, we first obtained *E*/*Z*-hydrazone mixtures **3** ($E:Z = 3:1$ to 1:3), in which the new stereogenic center in the *E* and *Z* isomers unexpectedly show the opposite configuration. It was therefore necessary to find conditions that would yield only one geometric hydrazone isomer. Accordingly, we examined the influence of base, solvent, cosolvent, additives, reaction time, reaction temperature, transition metal salts for transmetalation of the lithio azaenolates, and SAMP auxiliary derivatives on the *E*:*Z* ratio. We discovered that for metalation in diethyl ether at room temperature, the addition of $LiClO_4$ resulted in the desired high *E*:*Z* ratios. Without $LiClO_4$ the azaenolate formed a yellow-orange percipitate; however, with $LiClO_4$ orange-brown homogeneous solutions were obtained. It is well known that $LiClO_4$ leads to deaggregation of organolithium species, and this explains the differing solubilities and selectivities.[11] Through trapping of the metalated species at $-100\,^{\circ}C$ with the requisite electrophile, the desired α-functionalized hydrazones **3** were available in good yields and with *E*:*Z* ratios varying from 9:1 to 50:1. The *E* isomers were diastereomerically pure (Table 1).

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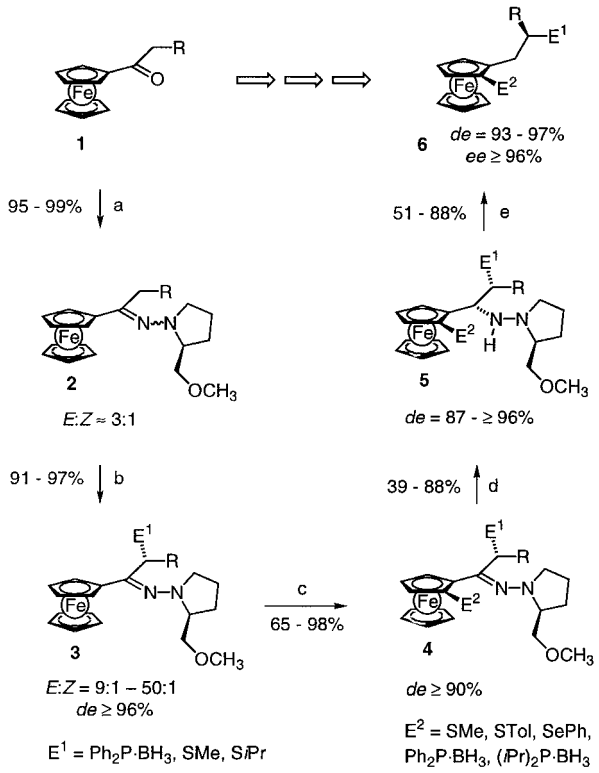

Scheme 1. Diastereo- and enantioselective synthesis of planar-chiral ferrocenyl ligands **6** with a stereogenic center in the position β to the ferrocene backbone. a) SAMP/$AlMe_3$ (2 equiv), toluene, reflux; b) 1. LDA (1.2 equiv), $LiClO_4$ (3 equiv), Et_2O, RT; 2. E^1X (1.3 equiv), $-100\,^\circ C$; c) 1. *t*BuLi, $LiClO_4$, THF, $-70\,^\circ C$; 2. E^2X; d) catecholborane, Et_2O/CH_2Cl_2, $-20\,^\circ C \rightarrow RT$; e) $NaBH_4$, TFA, CH_2Cl_2, $0\,^\circ C \rightarrow RT$ or 1. $HBF_4 \cdot OEt_2$ (2.5 equiv), CH_2Cl_2, $0\,^\circ C$; 2. $HBEt_3Li$ (5 equiv). RT = room temperature, Tol = tolyl = $CH_3C_6H_4$, X = Cl, Br, SR.

For our studies we chose alkyl, phosphorous, and sulfur electrophiles. The alkylation experiments served to optimize the reaction conditions with respect to *E*/*Z* selectivity. The BH_3-protected phosphorous derivatives undergo *E*/*Z* isomerization in diethyl ether or benzene at room temperature. To avoid this process, the completed reaction had to be worked up rapidly and at low temperature ($0\,^\circ C$). Purification by column chromatography was also avoided for this reason; filtration through silica gel and subsequent crystallization from *n*-hexane at $-26\,^\circ C$ yielded the analytically pure compounds. Relative to the BH_3-protected phosphanes, the unprotected phosphanes isomerize much faster. In addition, they undergo rapid oxidation; as a result the use of the protecting group was preferred since the protected compounds are highly robust. The sulfur derivatives did not show any tendency to undergo isomerization.

Table 1. Diastereoselective synthesis of ferrocenylketone – SAMP-hydrazones **3**.

3	R	E^1	*E*:*Z*	Yield [%]	*de* [%][a]	$[\alpha]_D^{25}$ ($CHCl_3$)
a	Me	$Ph_2P \cdot BH_3$	20:1	91	≥ 96	− 89.6
b	Et	$Ph_2P \cdot BH_3$	44:1	97	≥ 96	− 79.2
c	Me	SMe	12:1	95	≥ 96	+ 270.9
d	Et	SMe	28:1	93	≥ 96	+ 257.8
e	Me	S*i*Pr	50:1	92	≥ 96	+ 245.7
f	Et	S*i*Pr	9:1	97	≥ 96	+ 327.8

[a] The diastereomeric excesses of the *E* isomers were determined by ^1H NMR spectroscopy.

The regio- und diastereoselective metalation of **3** at the cyclopentadienyl (Cp) ring *ortho* to the directing hydrazone moiety in the presence of anion-stabilizing RS[12] and $R_2P \cdot BH_3$ substituents[13] was achieved through variation of the metalation conditions (Table 2). Again the use of $LiClO_4$, this time in combination with *t*BuLi/THF at $-70\,^\circ C$, turned out to be advantageous in that metalation of the side chain was completely avoided. In this step, the *E* isomers were further enriched, since the *E*-configured hydrazones **3** underwent *ortho*-metalation more readily than the *Z*-configured isomers. To achieve high yields with the $R_2P \cdot BH_3$-substituted hydrazones **3**, an excess of base was necessary (2.5 – 3 equiv); however, this did not have any negative influence on the regio- or diastereoselectivity. A double metalation was not observed in any case. It is noteworthy that the planar-chiral products do not show any tendency to undergo *E*/*Z* isomerization. The *ortho*-metalation of the alkylsulfanyl-substituted hydrazones **3** proceeded with only one equivalent of *t*BuLi. After the optimized reaction conditions had been found, we used various phosphorous, sulfur, and selenium electrophiles for ligand synthesis. The new method allows the successive, highly diastereoselective introduction of two different electrophiles. Unfortunately we have not yet been able to introduce two diphenylphosphanyl groups in acceptable yield: This is probably due to steric crowding.

Table 2. Diastereoselective synthesis of hydrazones **4**, hydrazines **5**, and ferrocenyl donor ligands **6**.

4–**6**	R	E^1	E^2	**4**			**5**			**6**			
				yield [%]	*de*[a] [%]	$[\alpha]_D^{25}$ ($CHCl_3$)	yield [%]	*de*[a] [%]	$[\alpha]_D^{25}$ ($CHCl_3$)	yield [%]	*de*[a] [%]	*ee* [%]	$[\alpha]_D^{25}$ ($CHCl_3$)
a	Me	$Ph_2P \cdot BH_3$	SMe	94	≥ 90	− 287.9	58	≥ 96	− 112.7	70	94	≥ 99[b]	+ 15.6
b	Et	$Ph_2P \cdot BH_3$	SMe	65	≥ 90	− 310.1	40	≥ 96	− 94.6	51	97	≥ 99[b]	− 22.4
c	Me	SMe	$Ph_2P \cdot BH_3$	86	96	+ 10.8	39	≥ 96	− 174.4	62	95	≥ 96[c]	− 149.4
d	Et	SMe	$Ph_2P \cdot BH_3$	77	≥ 96	− 35.2	82	≥ 96	− 154.2	72	97	≥ 96[c]	− 192.4
e	Et	SMe	$(iPr)_2P \cdot BH_3$	93	≥ 90	+ 52.6	55	≥ 96	+ 21.5	88	95	≥ 96[c]	+ 100.0
f	Et	SMe	SMe	98	≥ 90	− 432.3	75	87	− 211.4	77	94	≥ 99[d]	− 181.3
g	Me	S*i*Pr	$Ph_2P \cdot BH_3$	73	≥ 96	− 25.7	43	≥ 96	− 153.2	68	94	≥ 96[c]	− 86.9
h	Et	S*i*Pr	STol	89	≥ 90	− 219.7	88	≥ 96	− 86.7	84	97	≥ 99[b]	− 5.9
i	Et	S*i*Pr	SePh	98	≥ 96	− 440.0	68	≥ 96	− 81.7	70	≥ 96	≥ 99[b]	− 8.0

[a] Determined by ^1H NMR spectroscopy. [b] Determined by analytical HPLC on a chiral phase (Daicel Chiracel OD-H) with cyclohexane as eluent. [c] Determined by ^1H NMR spectroscopy with (−)-pirkle alcohol as chiral cosolvent. [d] Determined by gas chromatography on a chiral phase (Chirasil dex 25 m).

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Subsequently, the planar-chiral *E*-configured SAMP-hydrazones **4** could be transformed into the hydrazines **5** by reduction with the Lewis acidic catecholborane in diethyl ether/dichloromethane (1/1 – 2/1, Table 2). With hydride reducing agents such as $LiAlH_4$, $HBEt_3Li$, $NaBH_4$, and others no reaction was observed. The *Z*-hydrazones **4** also did not undergo reduction. Compounds bearing a BH_3-protected phosphanyl group in the side chain had to be deprotected with *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA) to achieve acceptable yields. As the reduction with catecholborane proceeds with high diastereoselectivity, the protocol described allows the stereocontrolled generation of two contiguous stereogenic centers at the α- and β-positions in addition to the planar chirality. The X-ray structure analysis of **5g** (Figure 1) proves the absolute configuration shown in

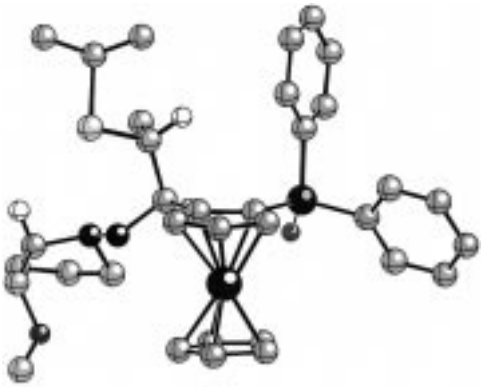

Figure 1. Crystal structure of **5g**.[14]

Scheme 1.[14] Since uniform reaction pathways may be assumed, all compounds **5** were assigned as bearing the same absolute configuration.

To remove the auxiliary group, the hydrazines **5** were protonated with HBF_4 or trifluoroacetic acid (TFA). The method of choice for the P,S ligands **6** was protonation with HBF_4 and trapping of the resulting carbocation with superhydride ($HBEt_3Li$). The S,S and S,Se ligands were obtained by the combination TFA/$NaBH_4$.[15] The cations of the latter systems turned out to be remarkably unstable; therefore, the presence of the hydride reagent was necessary during the acidic reaction conditions. In contrast, the cations of the P,S systems were so stable that they could only be trapped with the extremely nucleophilic $HBEt_3Li$. The title compounds **6** were synthesized in virtually enantiomerically pure form ($ee \geq 96\,\%$) and with high diastereoselectivity ($de = 94 - 97\,\%$, Table 2).

The asymmetric synthesis described opens up an efficient and very flexible approach to novel ferrocenyl ligands for asymmetric catalysis. Initial experiments indicate that the corresponding primary amines are accessible by reductive N–N cleavage of the hydrazines **5** with $BH_3 \cdot THF$.[16] The exchange of the hydrazino functional group by other nucleophiles with retention of configuration to build up tridentate or more rigid ligands is currently under investigation.

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[14] X-ray structure analysis of **5g**: $C_{34}H_{46}N_2OBPSFe$, $M_r = 628.45$; suitable crystals were obtained by crystallization from *n*-hexane; monoclinic, space group $P2_1$ (no. 4), $a = 9.410(1)$, $b = 17.313(8)$, $c = 11.183(3)$ Å, $\beta = 109.99(1)^\circ$, $Z = 2$, $\rho_{calcd} = 1.219\ g\,cm^{-3}$. Enraf-Nonius CAD4 diffractometer, $Mo_{K\alpha}$ radiation (graphite monochromator, $\lambda = 0.71069$ Å). The structure was solved by direct methods (SHELXS86).[17] Some of the hydrogen atoms could be localized, the rest were calculated; the hydrogen positions were not refined. A total of 6291 observed reflections ($I > 2\sigma(I)$) in the final full matrix least-squares refinement of 369 parameters, $R = 0.051$, $R_w = 0.039$ ($w = \sigma^{-2}$), min./max. residual electron density $-0.64/+0.59\ e\,Å^{-3}$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-116942. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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