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A straightforward and modular synthesis of enantiopure C_2- and C_1-symmetrical 2,2′′-phosphino-1,1′′-biferrocenes

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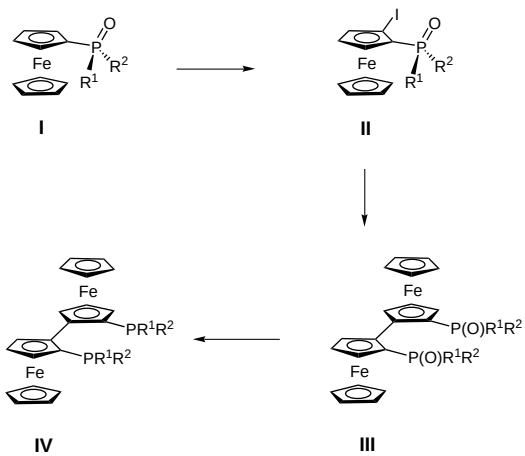
Abstract—A new practical and highly flexible synthesis of enantiopure C_2- and C_1-symmetrical 2,2′′-phosphino-1,1′′-biferrocenes is presented. The structural properties of two of their $PdCl_2$ complexes and preliminary Ru-catalysed hydrogenations using the biferrocene ligands, giving enantioselectivities of up to 82%, are described.

1. Introduction

Axially chiral diphosphines as exemplified by 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) are widely used in enantioselective catalysis.[1,2] Surprisingly little attention has been paid to their biferrocene analogues, although ferrocene based ligands have proved to be highly efficient in many catalytic enantioselective reactions.[3,4] Almost 10 years ago, Ito et al. described the synthesis of 2,2′′-bis(diphenylphosphino)-1,1′′-biferrocene (BIFEP),[5,6] but to the best of our knowledge neither structural nor catalytic results have been published. Only very recently a few additional examples with P-stereogenic phosphino substituents were synthesised by Nettekoven.[7] In allylic aminations using the ligands, products having up to 93% e.e. were obtained.[8]

Both the original synthesis of BIFEP and that of its P-stereogenic analogues followed a similar strategy to that outlined in Scheme 1. Ferrocenylphosphineoxide **I** was *ortho*-magnesiated and transformed into the respective 2-iodo-ferrocenylphosphineoxide **II**. A racemate was obtained for $R^1=R^2=Ph$, while diastereomers were formed in up to 94% d.e. in the case of $R^1\neq R^2$. Coupling of the iodides led to the 2,2′′-bis-(phosphinyl)-1,1′′-biferrocenes **III**, which on reduction with trichlorosilane gave the final products **IV**.



Scheme 1.

In the case of BIFEP, resolution of (±)-2,2′′-bis-(diphenylphosphinyl)-1,1′′-biferrocene was necessary, while both the coupling reaction of the P-stereogenic 2-iodoferrocenylphosphineoxides and the final reduction step led to partial epimerisation at phosphorus. These facts severely limit the applicability of this reaction sequence.

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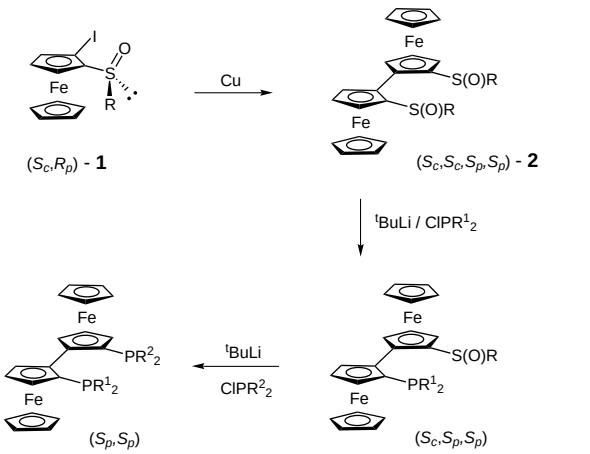
We now describe a new modular synthesis of BIFEP and analogues avoiding the need for a resolution step and allowing for the stepwise addition of different phosphino groups to an enantiopure biferrocene intermediate (Scheme 2). In a solid state reaction iodide **1**[9,10] was coupled with Cu powder giving enantiopure (S_c,S_c,S_p,S_p)-2,2″-bis-(*p*-tolylsulfinyl)-1,1″-biferrocene, **2**† (130°C, 16 h, yield 77%, $[\alpha]_D^{20}=-393.0$ ($c=0.50$, $CHCl_3$)), which served as the central intermediate allowing the stepwise replacement of both *p*-tolylsulfinyl units. Reaction of **2** in THF with *tert*-Bu-Li (1.2 equiv.) in THF (−78°C, 5 min) and quenching with chloro(diaryl)phosphine led to (S_c,S_p,S_p)-2-diarylphosphino-2″-*p*-tolyl-sulfinyl-1,1″-biferrocenes: R^1 = Ph, **3** (60%, $[\alpha]_D^{20}=+60.6$ ($c=0.50$, $CHCl_3$)); R^1 = 3,5-dimethylphenyl, **4** (80%, $[\alpha]_D^{20}=-27.0$ ($c=0.52$, $CHCl_3$)); R^1 = 3,5-dimethyl-4-methoxyphenyl, **5** (66%, $[\alpha]_D^{20}=-14.4$ ($c=0.50$, $CHCl_3$)). In a subsequent step the second sulfinyl group was removed by treatment of **3**–**5** in THF with *tert*-Bu-Li in THF (−78°C, 5 min) followed again by reaction with a chloro(diaryl)-phosphine.[10]



R^1= R^2= Ph **6**; 3,5-$(CH_3)_2$Ph **7**; R^1= 3,5-$(CH_3)_2$-4-(OCH_3)Ph, R^2= 3,5-$(CF_3)_2$Ph **8**; R = 4-(CH_3)Ph

R^1= Ph **3**; 3,5-$(CH_3)_2$Ph **4**; 3,5-$(CH_3)_2$-4-(OCH_3)Ph **5**

Scheme 2.

Depending on the phosphine used, either C_2- or C_1-symmetrical biferrocenes all of (S_p,S_p) configuration were obtained (C_2: $R^1=R^2$ = Ph, **6** (49%, $[\alpha]_D^{20}=+150.5$ ($c=0.22$, $CHCl_3$)); $R^1=R^2$ = 3,5-dimethylphenyl, **7**‡ (30%, $[\alpha]_D^{20}=+125.5$ ($c=0.40$, $CHCl_3$)); C_1: R^1 = 3,5-dimethyl-4-methoxyphenyl, R^2 = 3,5-trifluoromethylphenyl, **8** (42%, $[\alpha]_D^{20}=+1.63$ ($c=0.43$, $CHCl_3$))).§

The (S_p,S_p) absolute configuration of biferrocenes **2**–**8** follows directly from the absolute configuration of starting material **1**, known to be (S_c,R_p).[9]

With respect to their intended application in enantioselective catalysis the palladium dichloride complexes of biferrocenes **6** (**6**·$PdCl_2$) and **8** (**8**·$PdCl_2$) were prepared by reacting the respective ligands with $(CH_3CN)_2PdCl_2$ in benzene. Solvated single crystals suitable for X-ray diffraction could be obtained from both complexes on crystallisation from appropriate solvent mixtures (Figs. 1 and 2).

The X-ray study¶ not only proved the structural integrity of ligands **6** and **8** and the *cis*-coordination to Pd but also in both cases the (S_p,S_p) absolute configuration. A particularly interesting feature is the biferrocene conformation. Unlike for BINAP, at the laboratory time scale, for ligands **6**–**8** a free rotation about the biferrocene bond must be assumed. Hence, their $PdCl_2$ complexes may exist as two conformers differing in the biferrocene arrangement.

A comparison of the molecular structures depicted in Figs. 1 and 2 indeed shows that in complex **6**·$PdCl_2$ the biferrocene unit adopts a (*P*)-shaped conformation while **8**·$PdCl_2$ prefers an (*M*)-shaped biferrocene backbone. Obviously, the biferrocene shape in the preferred

† NMR data for **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 6H, CH_3), 4.01 (m, 2H, Cp-H), 4.37 (br s, 12H, Cp-H), 5.14 (m, 2H, Cp-H), 7.31 (d, J=8.1 Hz, 4H, Ph-H), 7.68 (d, J=7.8 Hz, 4H, Ph-H); MS (EI, 200°C) m/z=646 (M^+).

‡ NMR data for **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 12H, CH_3), 2.34 (s, 12H, CH_3), 3.97 (m, 2H, Cp-H), 4.00 (s, 10H, Cp-H), 4.51 (m, 2H, Cp-H), 4.90 (m, 2H, Cp-H), 6.26 (d, J=7.3 Hz, 4H, Ph-H), 6.45 (s, 2H, Ph-H), 7.03 (s, 2H, Ph-H), 7.20 (d, J=8.3 Hz, 4H, Ph-H); ^{31}P NMR δ −22.42; MS (EI, 100°C) m/z=850 (M^+).

§ NMR data for **8**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 6H, CH_3), 2.29 (s, 6H, CH_3), 3.38 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.85 (m, 1H, Cp-H), 3.96 (br s, 6H, Cp-H), 4.05 (s, 5H, Cp-H), 4.56 (m, 1H, Cp-H), 4.68 (m, 1H, Cp-H), 4.80 (m, 1H, Cp-H), 5.06 (m, 1H, Cp-H), 6.26 (d, J=7.0 Hz, 2H, Ph-H), 7.06 (d, J=5.6 Hz, 2H, Ph-H), 7.13 (d, J=8.1 Hz, 2H, Ph-H), 7.43 (s, 1H, Ph-H), 7.91 (d, J=7.0 Hz, 2H, Ph-H), 7.98 (s, 1H, Ph-H); ^{31}P NMR δ −25.93, −19.09; MS (FAB) m/z=1126 (M^+).

¶ Crystal data for **6**·$PdCl_2$·2$CHCl_3$·H_2O: $C_{46}H_{40}Cl_8Fe_2OP_2Pd$ (red prisms from $CHCl_3$/EtOH+H_2O), M=1172.42, monoclinic, a=10.270(3), b=22.142(6), c=10.282(3) Å, β=100.96(2)°, U=2296(1) Å^3, T=223 K, space group $P2_1$ (no. 4), Z=2, μ(Mo-K$_\alpha$)=1.58 mm^{-1}, 33075 reflections measured (λ_{max}=30°), 12764 unique (R_{int}=0.051) which were used in all calculations. The final $wR(F^2)$ was 0.1086 (all data). The investigated crystals were pseudo-merohedral twins (twin matrix 0 0 1/0 −1 0/1 0 0) showing orthorhombic pseudosymmetry with $C222_1$ as the pseudo-space group.

Crystal data for **8**·$PdCl_2$·solv.: $C_{54}H_{44}Cl_2F_{12}Fe_2O_2P_2Pd$ (solvent containing red prisms from $EtOEt/CH_2Cl_2$; solvent badly disordered and therefore omitted from chemical formula, M, and μ), M=1303.83, orthorhombic, a=13.883(3), b=15.914(3), c=26.242(5) Å, U=5798(2) Å^3, T=297 K, space group $P2_12_12_1$ (no. 19), Z=4, μ(Mo-K$_\alpha$)=1.49 mm^{-1}, 60296 reflections measured (λ_{max}=25°), 10183 unique (R_{int}=0.068), which were used in all calculations. The final $wR(F^2)$ was 0.1091 (all data).

conformer of bis(diarylphosphino)–biferrocene complexes depends on the steric requirements of the diarylphosphino groups. In solution, the presence of interconverting conformers cannot be excluded.

Although conformational flexibility of the biferrocenyl backbone might be considered a disadvantage, some preliminary, but promising, results in the hydrogenation of ethyl acetylacetate were obtained (Table 1). Ruthenium complexes prepared in situ from $[RuI_2(p\text{-cymene})]_2$ and ligands **6**–**8** were used and enantioselectivities of up to 82% could be reached.

When a 0.43 M solution of ethyl acetylacetate in ethanol containing a catalyst prepared in situ from $[RuI_2(p\text{-cymene})]_2$, **6** and HCl (1 M; 60 μL) was stirred under 80 bar pressure of H_2 at 80°C for 16 h, (*R*)-ethyl-3-hydroxybutyrate was produced in 82% e.e. and >99.5% yield. Interestingly, the application of catalysts with the C_2-symmetrical ligands **6** or **7** gave the hydrogenation product in markedly higher enantioselectivity than reactions with the C_1-symmetrical ligand **8** (20% e.e.). With the use of ligand **6** at the lower temperature of 60°C the enantiomeric purity of the hydrogenation product, (*R*)-ethyl-3-hydroxybutyrate, decreased from 82 to 70% e.e.

In summary, we have developed a straightforward synthesis of enantiopure 2,2″-phosphino-1,1″-biferrocenes via 2,2″-bis-(*p*-tolylsulfinyl)-1,1″-biferrocene as the intermediate. Consecutive replacement of the sulfinyl groups allowed the introduction of either equivalent or non-equivalent phosphino substituents. In general, this modular approach is also expected to be applicable to electrophiles other than phosphine. Preliminary asymmetric hydrogenations of ethyl acetylacetate with in situ prepared Ru catalysts gave the product in up to 82% e.e. X-Ray diffraction studies on two biferroceno–$PdCl_2$ complexes revealed that conformers with either a (*P*)- or a (*M*)-shaped biferroceno unit are accessible, depending on the substitution pattern of the phosphino units.

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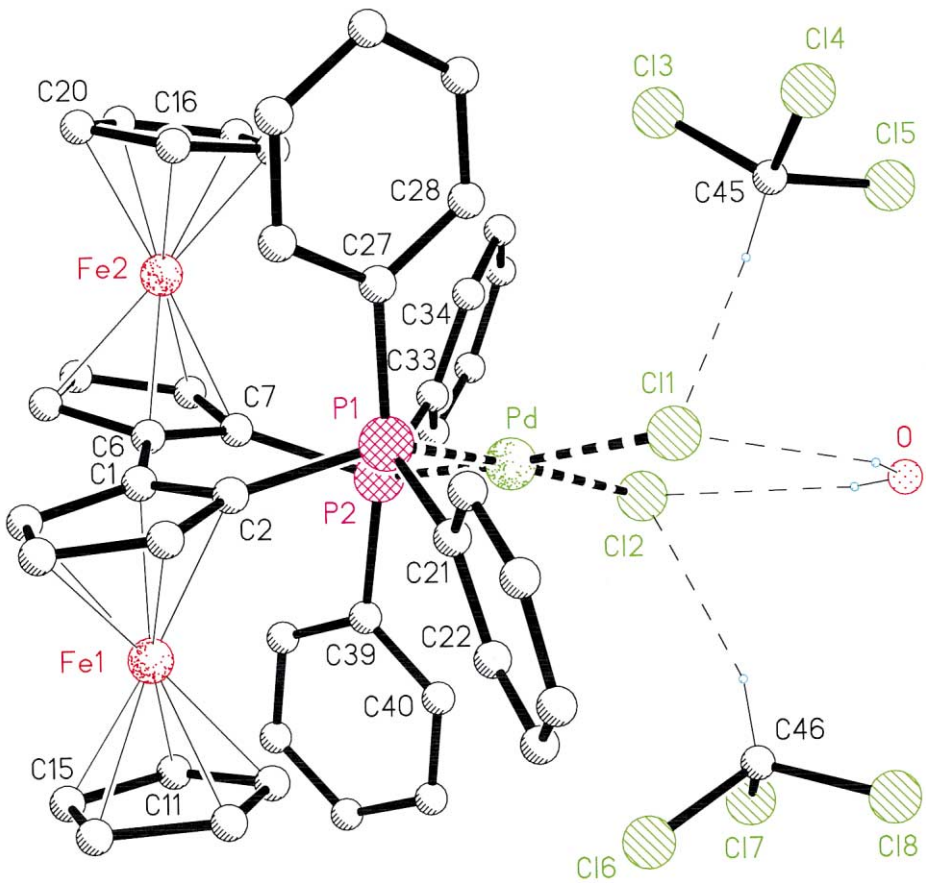

Figure 1. Molecular structure of C_2-symmetric **6**·$PdCl_2$ in **6**·$PdCl_2$·$2CHCl_3$·H_2O with hydrogen bonded $CHCl_3$ and H_2O molecules. Characteristic torsion angles: P(1)–C(1)–C(6)–P(2) = 32.8(3)°, C(2)–C(1)–C(6)–C(7) = 29(1)°.

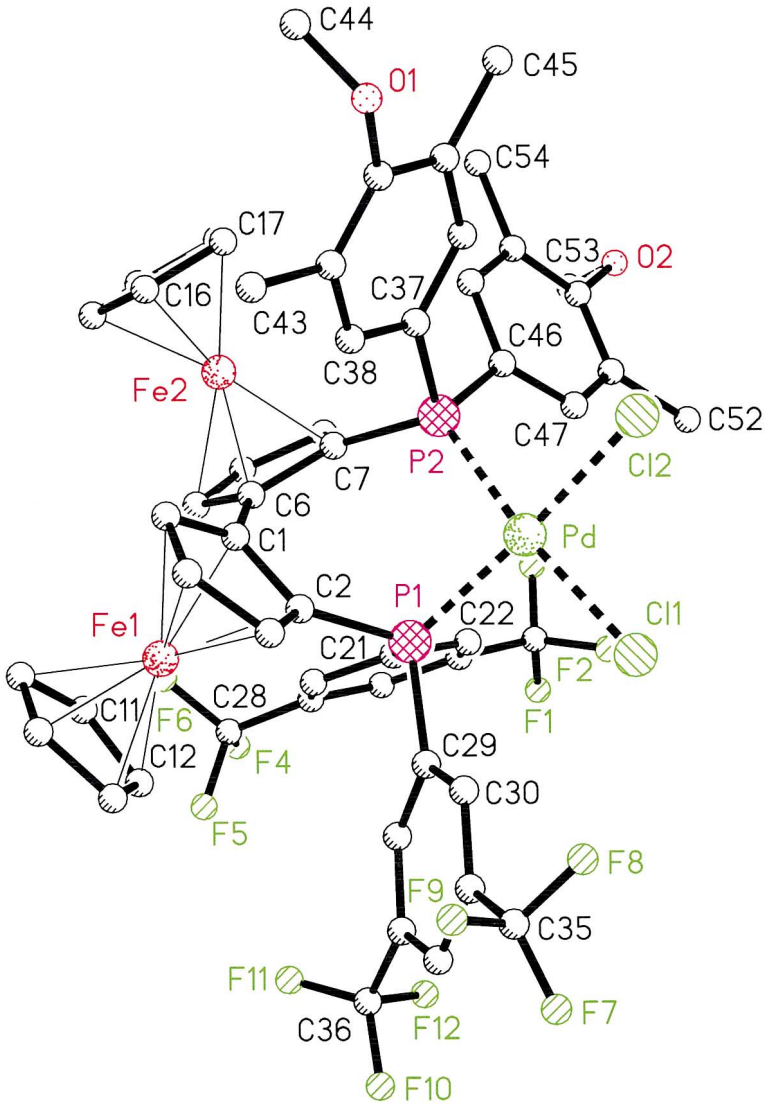

Figure 2. Molecular structure of C_1-symmetrical **8**·$PdCl_2$ in **8**·$PdCl_2$·solv. Characteristic torsion angles: P(1)–C(1)–C(6)–P(2) = −55.4(2)°, C(2)–C(1)–C(6)–C(7) = −58.4(7)°.

Table 1. Catalytic hydrogenation of ethyl acetylacetate with H_2/Ru/ligands **6**–**8**

Ligand	Temp. (°C)	Conversion (%)	E.e. (%)	Configuration
6	80	>99.5	82	*R*
6	60	>99.5	70	*R*
7	80	>98	68	*R*
8	80	96	20	*R*

Reaction conditions: ethyl acetylacetate: (0.84 g, 6.45 mmol); catalyst: $[RuI_2(p\text{-cymene})]_2$+Ligand (PP:Ru = 1.05); s/c: 1000; solvent: ethanol (15 mL); HCl (1 M, 60 μL); p(H_2): 80 bar; reaction time: 16 h.

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