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Diastereospecific addition of Grignard reagents to 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde

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Abstract—The reaction of both enantiomers of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde **1** with EtMgBr and PhMgBr has been studied. It has been found that addition of a Grignard reagent to the carbonyl group of **1** proceeds diastereospecifically. The configuration of the sp^3 stereogenic centre formed in this reaction has been determined by single crystal X-ray diffraction and can be explained assuming *exo*-attack of the nucleophile on the *s-cis*-conformation of **1**. The circular dichroism spectra of the product 1,1′-diphosphaferrocenyl alcohols are also reported and discussed.

1. Introduction

Diastereoselective nucleophilic addition to the carbonyl group attached to a planar chiral organometallic moiety has been observed in reactions of 2-substituted ferrocenyl,[1] (η^4-diene)tricarbonyliron,[3] (η^3-allyl)tricarbonyliron lactone,[3] (trimethylenemethane)tricarbonyliron,[3] (η^6-arene)chromium tricarbonyl[4] and phosphaferrocene[5] aldehydes and ketones with organometallic reagents. The stereoselectivity is usually attributed to the presence of a single reactive conformation of the carbonyl group and steric differentiation of its diastereotopic faces by the organometallic backbone.[3] These reactions constitute as a general entry to compounds with planar and central chirality elements, which have proven to be useful ligands in asymmetric catalysis.[1,2] They have also found applications in the syntheses of biologically interesting natural products.[3]

Continuing our research into the chemistry of 1,1′-diphosphaferrocenes, we have recently reported that nucleophilic addition of dimethylphosphite to the carbonyl group in 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde **1** results in formation of a single diastereomer of the corresponding hydroxyphosphonate.[6] The stereochemical outcome of this reaction has been explained as a result of the *exo*-attack of a nucleophile on the *s-cis* conformation of the starting aldehyde (Fig. 1).

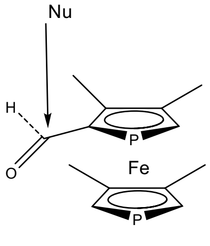

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Figure 1. The *exo*-attack of the nucleophile on the *s-cis* conformation of **1** (only one enantiomer of **1** is shown).

However, the addition of dialkyl phosphites to carbonyl compounds (Pudovik reaction) is a reversible process, which often leads not to the kinetic product, but to the thermodynamically stable compound.[7] We thought, therefore, that it would be of interest to study the stereochemistry of the addition of Grignard reagents to **1**, which proceeds under kinetic control (irreversibly). Although diastereoselective reactions may be studied using racemic substrates, we decided to use for our study enantiomerically pure (*R*)-**1** and (*S*)-**1**, which are available using a recently reported resolution method.[8] This enabled us to study the circular dichroism (CD) spectra of the products

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in order to evaluate the potential of this technique for configuration assignment of chiral 1,1′-diphosphaferrocenes.

2. Results and discussion

Reaction of enantiopure (S_p)-**1** with EtMgBr and PhMgBr in THF at rt afforded the corresponding alcohols (S,S_p)-**2a** and (S,S_p)-**2b**, which were isolated in 57% and 68% yield, respectively (Scheme 1). In both cases, ^{1}H and ^{31}P NMR spectra of the crude reaction mixture revealed the formation of only one diastereomer. The relatively low reaction yields of these reactions may be due to the possibility of the competitive nucleophilic attack at phosphorus,[9] which may lead to the decomposition of the metallocene moiety.

Alcohols (S,S_p)-**2a** and (S,S_p)-**2b** have been fully characterized by spectroscopic (^{1}H and ^{31}P NMR, IR) data and elemental analyses. They displayed $[\alpha]_D^{20}$ values of +30 and +22, respectively (in $CHCl_3$). The absolute configuration of (S,S_p)-**2b** was determined by single crystal X-ray diffraction after transformation of this compound into crystalline bis-W(CO)$_5$ derivative **3** via reaction with an excess amount of the photochemically generated labile complex $W(CO)_5(THF)$ (Scheme 1). The structure of one of the two crystallographically independent molecules, found in the unit cell of **3** (which differ only slightly in the conformation of the metallocene moiety) is displayed in Figure 2.[10]

Similarly, reaction of (R_p)-**1** with ethylmagnesium and phenylmagnesium bromides afforded alcohols (R,R_p)-**2a** and (R,R_p)-**2b**, which displayed $[\alpha]_D^{20}$ values of −30 and −22, respectively (in $CHCl_3$).

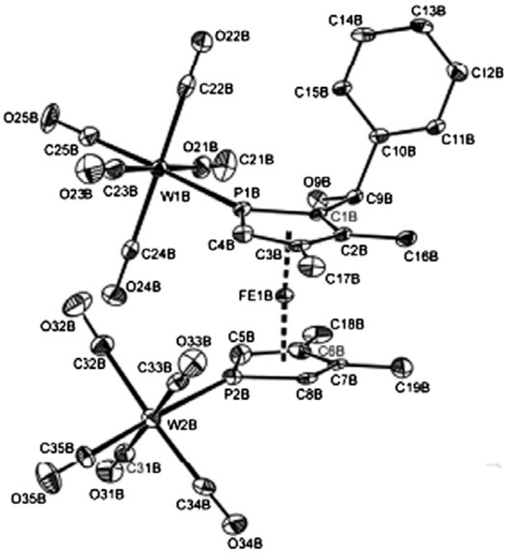
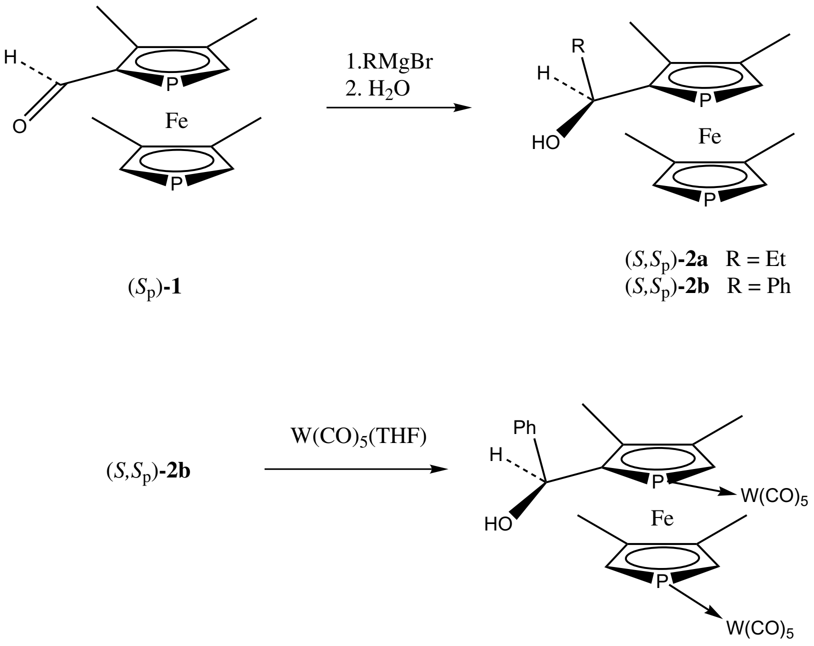


Figure 2. The molecular structure of one of the two crystallographically independent molecules of **3**.

The CD spectra of the enantiomeric pairs of alcohol products: (S,S_p)-**2a**, (R,R_p)-**2a** and (S,S_p)-**2b**, (R,R_p)-**2b** are shown in Figure 3. The enantiomeric relationship observed in the region of metallocene d–d and charge-transfer transitions (~300–500 nm)[11] is in accordance with the opposite planar metallocene chirality in both series of compounds.

Comparison of the spectra of ethyl-substituted alcohols (S,S_p)-**2a**, and (R,R_p)-**2a** with those of their phenyl analogues, (S,S_p)-**2b**, and (R,R_p)-**2b**, reveals that the latter



(S_p)-**1**

(S,S_p)-**2a** R = Et
(S,S_p)-**2b** R = Ph

(S,S_p)-**2b**

3

Scheme 1. Reaction of (S_p)-**1** with Grignard reagents and the synthesis of **3**.

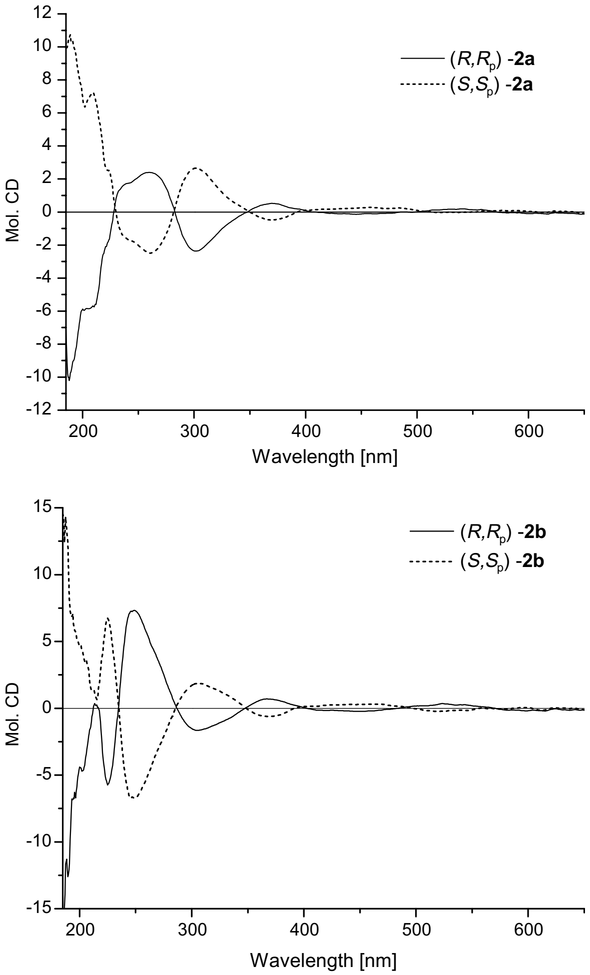


Figure 3. CD spectra of the product alcohols in acetonitrile.

shows strong Cotton effects at 226 and 249 nm, attributable to the π–π* transition in the phenyl substituent. The opposite signs of this effect for (S,S_p)-**2b**, (R,R_p)-**2b** are in accordance with the opposite configuration of the sp^3 stereogenic centre in both compounds.

The configuration of the sp^3 stereogenic centre formed upon the addition of the Grignard reagents to the carbonyl group of **1** is in full accordance with the model shown in Figure 1 (i.e., *exo*-attack of the nucleophile on the *s-cis* conformation of **1**). The *s-cis* conformation of a closely related phosphaferrocene aldehyde, 3,4-dimethyl-1-phosphaferrocene carboxaldehyde, in the solid state has been determined by X-ray crystallography.[12] The NOESY spectrum of **1** shows a considerable NOE interaction of the formyl proton with protons of one methyl group, which confirms the presence of the *s-cis* conformation of this compound in solution.

3. Conclusion

In conclusion, we have found that nucleophilic addition to the carbonyl group in enantiomers of planar chiral **1** can be used for stereoselective construction of stereogenic sp^3 centres in the lateral chains of the 1,1′-diphosphaferrocene system.

Acknowledgments

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10. 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 648210. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.htlm or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223336033 or deposit@ccdc.cam.ac.uk. Crystallographic data for **3**. $C_{29}H_{22}FeO_{11}P_2W_2$, $M = 1031.94$, $T = 193(2)$ K. Monoclinic, space group $P2_1$ with $a = 7.4691(5)$, $b = 19.7285(8)$, $c = 22.3465(14)$ Å, $\beta = 92.590(5)°$, $V = 3285.5(3)$ V/Å^{-3}, $Z = 4$, $D_x = 2.084$ g cm^{-3} ($Z = 4$), $F(000) = 1952$, absorption coefficient = 7.656 mm^{-1}, X-ray data were collected on a Stoe IPDS-II diffractometer[1] using Mo Kα X-ray source, (graphite crystal monochromator, $\lambda = 0.71073$ Å) using the φ-scan method; absorption corrections were applied. Refinement with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-97) using all data; final R indices $[I > 2\sigma(I)]$, $R(F)^a = 0.0242$, $wR(F^2)^b = 0.494$, R indices (all data), $R(F)^a = 0.0217$, $wR(F^2)^b = 0.0551$, $^a R(F) = \Sigma(|F_o - F_c|)/\Sigma|F_o|$, $^b wR(F^2) = [\Sigma w(|F_o - F_c|)^2/\Sigma|F_o|^2]^{1/2}$, $w = 1/[\Sigma^2(F_o^2) + 0.0346P^2]$, $P = [(F_o^2) + 2(F_c^2)]/3$. Flack parameter −0.009(5).
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