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Short Note

Formaldehyde-1,1″-(phenylphosphinidenesulfide)bis [(2*S*)-2-[(1*R*)-1-(methylamino)-ethyl]]ferrocene-aminal

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Abstract: In the course of an ongoing synthetic project, we observed an unprecedented reactivity of *N*-methyl groups in bis(*N*,*N*-dimethylaminoethylferrocenyl)phenylphosphinesulfide upon treatment with manganese dioxide (MnO_2). The intramolecular course of this reaction resulted in the formation of an unexpected homochiral diaza macrocycle. The target structure was accessible in two steps from known *N*,*N*-dimethylaminoethylferrocene.

Keywords: ferrocene; manganese dioxide; oxidation; planar chirality; diaza macrocycle; C–N bond formation

1. Introduction

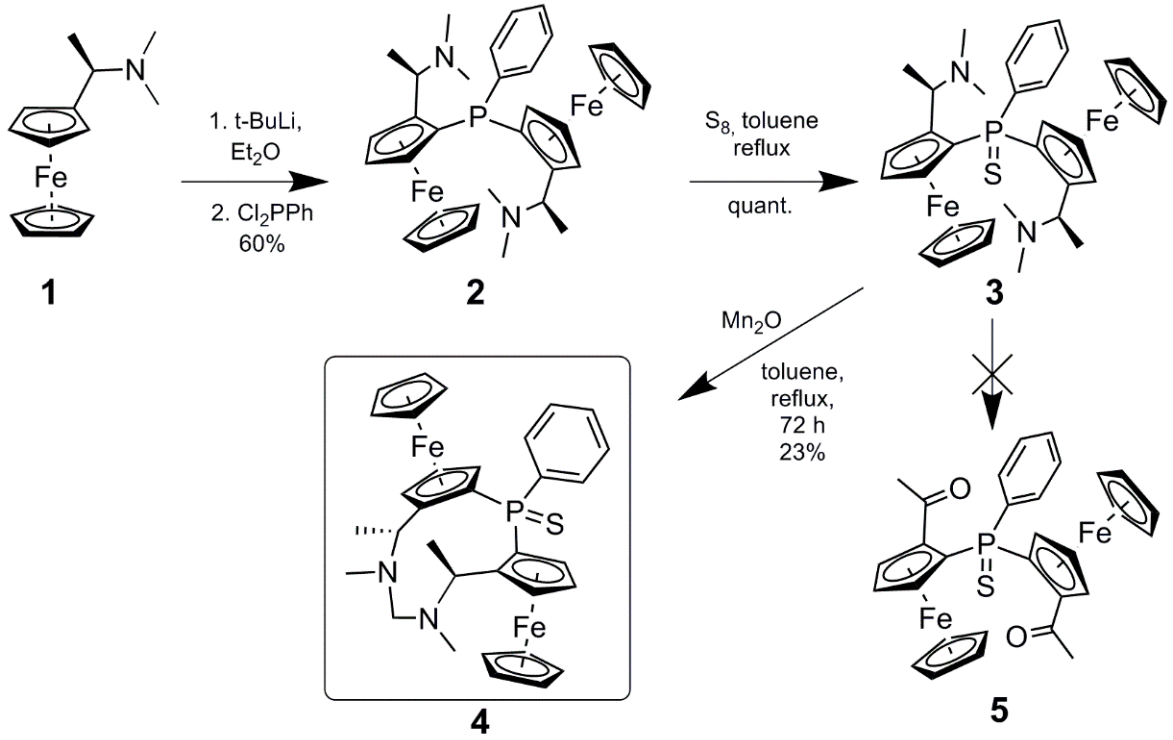
Ferrocene derivatives bearing at least two different substituents at the same ring are planar chiral and represent an important back bone frequently found in ligands for asymmetric catalysis. The ease of introducing a broad range of substituents with various heteroatoms and functional groups at C1 and C2 of the Cp ring has promoted the build-up of ligand libraries. Together with high chemical and configurative stability, ferrocene ligands are well established in asymmetric catalysis, academic research as well as in industry. A particular successful industrial application was the synthesis of the pesticide metolachlor applying the ferrocene-based P,P-ligand Xyliphos [1]. In several cases, the degree of asymmetric induction was further enhanced by the incorporation of a second ferrocene unit [2]. To date, diferrocenes have been used as asymmetric ligands for transition metal catalyzed hydrosilylations [3], hydride transfer reactions [4], acetalizations [5], hydroaminations [6], hydrogenations [7], hydroalkoxylations, [8], and allylic substitutions [2]. Moreover, ferrocene derivatives were also applied as organocatalysts for the Morita-Baylis-Hillman addition [9], Lu cyclization [10], and 1,3-dipolar cycloaddition [11].

As it was frequently observed that catalysts with well-defined geometry show a higher degree of enantioselectivity, we were interested in developing protocols to connect the two ferrocenes with a two to four atom bridge. For the resulting 7- to 8-membered diferrocenophospha macrocycles, a higher degree of rigidity can be expected. Similar structures have been reported by Togni et al. [8].

2. Results and Discussion

Scheme 1 presents the synthetic path. We prepared the known key intermediate **2** from enantiopure precursor **1** [12] via stereoselective *ortho*-lithiation [13,14] using a known protocol with *tert*-butyl lithium as the base [8]. The phosphino group was protected as a phosphine sulfide by reaction with elemental sulfur yielding compound **3** quantitatively. From here, we attempted to transform the side chains into ferrocenylmethyl ketones. These groups would enable ring closing via pinacol coupling,

benzoin coupling, or McMurry coupling to yield *trans*-diferroceno phosphepines potentially useful as asymmetric ligands.



Scheme 1. Synthesis of diazaphospha cycle **4**.

Fleischer et al. reported an oxidation procedure for aminomethylferrocenes to remove a chiral auxiliary oxidatively yielding aldehydes [15]. Therefore, we performed a modified MnO_2-driven oxidation with **3**, but instead of the desired diacetyl compound **5**, we recovered a product identified as aminal **4**, which was identified by NMR (see the supplementary materials) due to its striking similarity with precursor **3**, except for the loss of six aminomethyl signals in the ^{1}H NMR spectrum and the emergence of the CH_2 signal at 77.61 ppm in the ^{13}C spectrum, which corresponds closely to the expected shift of formaldehyde aminal carbons in a ring. It appears that one of the *N*-methyl groups was oxidized, closing the 10-membered ring by forming a C–N bond with the opposite amino group. Formally, one methyl group was lost, but the structure of this by-product was not investigated. Curiously, we recovered only product **4** with the methyl group oxidized instead of the more plausible quasi-benzylic one. This may be due to steric hindrance of the α-methyl group, however, in other experiments, we observed that these positions can in fact be substituted.

MnO_2 is well-known as a chemoselective reagent oxidizing benzylic and allylic alcohols or amines to carbonyls selectively. To our knowledge, however, only one work has mentioned a somewhat similar oxidation of aminal carbons to amide equivalents. While we report the activation of an Ar–C–N–**C**–**H** bond to form a C–N bond, Tobrmann et al. reported on an oxygen atom insertion into an Ar–N–**C**–**H** bond [16].

This raises questions about the mechanism. The aminoalkylation protocol reported here does not enable monitoring by NMR, but previously, MnO_2-based oxidations were found to take place via a radical mechanism as deduced from a chemically induced dynamic nuclear polarization (CIDNP) NMR experiment [17]. Therefore, we speculate that this novel chemoselective C–N bond formation might also take place via a radical mechanism. Why was the methylamine carbon activated and not the more stable carbon adjacent to ferrocene? The most plausible reason is the bulky, substituted ferrocene unit sterically hindering contact with the surface of the reactive MnO_2 particles and might be a consequence of the heterogeneous reaction type.

3. Materials and Methods

3.1. General

Reaction progress was monitored by TLC (SiO_2 or Al_2O_3 sheets with F 254 fluorescence indicator). Preparative column chromatography was carried out with a Biotage Isolera One automated flash chromatography instrument using self-packed columns (Macherey-Nagel silica gel 60 M, 40–63 µm). ^{31}P-NMR spectra were recorded in $CDCl_3$ using a 400 MHz Bruker AVIII 400 spectrometer operating 162.04 MHz (^{31}P). ^{1}H-NMR spectra, ^{13}C-NMR spectra, and 2D spectra were recorded either on a 600 MHz Bruker AVIII 600 spectrometer (Bruker Biospin, Billerica, MA, USA) operating at 600.25 MHz (^{1}H) and 150.95 MHz (^{13}C) or on a Bruker AVIII 700 spectrometer at 700.40 MHz (^{1}H) and 176.13 MHz (^{13}C), respectively. ^{13}C-NMR spectra were recorded in J-modulated mode. Chemical shifts δ were referenced to $CHCl_3$ or $CDCl_3$ at 7.26 ppm (^{1}H-NMR) or 77.00 ppm (^{13}C-NMR), respectively, and to 85% H_3PO_4 at 0.00 ppm (^{31}P-NMR). HRMS were recorded by a Bruker Maxis ESI oa-RTOF mass spectrometer equipped with a quadrupole analyzer ion guide.

3.2. Synthesis

1,1″-(Phenylphosphinidenesulfide)bis[(2S)-2-[(1R)-1-(dimethylamino)-ethyl]]ferrocene (**3**)

Diaminoferrocenylphosphine **2** [12] (315 mg, 0.51 mmol) and sulfur (100 mg, 3.12 mmol, 6.14 equiv.) were dissolved in toluene (4 mL) in a flame-dried Schlenk tube. The solution was degassed, set under Ar, and stirred under reflux for 4 h. After cooling, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (Et_3N/Et_2O, 1.5/98.5) to yield phosphinesulfide **3** (331 mg, quant.) as an orange oil. ^{1}H-NMR (600 MHz,) δ = 7.87 (dd, *J* = 12.8, 7.6 Hz, 2H); 7.37–7.29 (m, 3H); 5.07 (q, *J* = 6.7 Hz, 1H); 4.49 (m, 1H); 4.38 (s, 5H); 4.34 (q, *J* = 6.8 Hz, 1H); 4.32 (m, 2H); 4.29 (m, 1H); 4.26 (m, 1H); 4.21 (m, 1H); 3.78 (s, 5H); 2.26 (s, 6H); 1.42 (s, 6H); 1.38 (d, *J* = 6.8 Hz, 3H); 1.10 (d, *J* = 6.7 Hz, 3H) ppm. ^{13}C-NMR (151 MHz) δ = 138.19 (d, J_{CP} = 91.5 Hz, C_q); 131.17 (d, J_{CP} = 10.2 Hz, CH); 129.14 (d, J_{CP} = 2.5 Hz, CH); 126.47 (d, J_{CP} = 12.3 Hz, CH); 98.11 (d, J_{CP} = 11.8 Hz, C_q); 93.84 (d, J_{CP} = 11.4 Hz, C_q); 79.18 (d, J_{CP} = 96.6 Hz, C_q); 74.37 (d, J_{CP} = 11.6 Hz, CH); 74.07 (d, J_{CP} = 11.6 Hz, CH); 72.27 (d, J_{CP} = 94.2 Hz, C_q); 70.87 (CH); 70.59 (d, J_{CP} = 9.6 Hz, CH); 70.47 (CH); 70.44 (d, J_{CP} = 9.4 Hz, CH); 68.64 (d, J_{CP} = 9.7 Hz, CH); 66.57 (d, J_{CP} = 10.5 Hz, CH); 54.91 (CH); 53.67 (CH); 40.35 (CH_3); 38.55 (CH_3); 10.97 (CH_3); 8.95 (CH_3) ppm. ^{31}P-NMR δ = 40.55 (s) ppm. HRMS: *m/z* calculated for $C_{34}H_{41}Fe_2N_2PS$ $[M + H]^+$: 653.1505, found: 653.1507.

Formaldehyde-1,1″-(phenylphosphinidenesulfide)bis[(2S)-2-[(1R)-1-(methylamino)-ethyl]]ferrocene-aminal (**4**)

A suspension of phosphinesulfide **3** (57 mg, 0.09 mmol) and MnO_2 (96 mg, 1.10 mmol, 12.7 equiv.) in toluene (1.5 mL) was refluxed under Ar for 72 h. The reaction mixture was cooled to r.t. and the black material was filtered off. The remaining orange solution was washed with water (2 mL) and brine (2 mL), and dried over $MgSO_4$. The solvent was removed and the residue was subjected to column chromatography (Et_2O/Et_3N (98.5/1.5), 0→100%)/heptane) yielding diazaphospha cycle **4** (13 mg, 23%) as an orange solid. ^{1}H-NMR (700 MHz) δ = 7.66 (s, 2H); 7.42 (tq, *J* = 7.6, 1.3 Hz, 1H); 7.38–7.33 (m, 2H); 5.19 (m, 1H); 4.81 (m, 1H); 4.68 (m, 1H); 4.56 (s, 5H); 4.46 (m, 1H); 4.44 (m, 1H); 4.36 (m, 1H); 4.35 (s, 5H); 3.05 (d, *J* = 12.3 Hz, 1H); 2.84 (d, *J* = 12.3 Hz, 1H); 2.83 (q, *J* = 6.9 Hz, 1H); 2.33 (q, *J* = 6.8 Hz, 1H); 2.13 (s, 3H); 1.94 (s, 3H) ppm. ^{13}C-NMR (176 MHz) δ = 137.55 (d, J_{CP} = 90.1 Hz, C_q); 132.36 (d, J_{CP} = 10.9 Hz, CH); 130.82 (d, J_{CP} = 2.9 Hz, CH); 127.42 (d, J_{CP} = 12.6 Hz, CH); 97.55 (d, J_{CP} = 10.7 Hz, C_q); 93.72 (d, J_{CP} = 8.3 Hz, C_q); 78.31 (d, J_{CP} = 96.3 Hz, C_q); 77.67 (d, J_{CP} = 92.0 Hz, C_q); 77.61 (CH_2); 76.28 (d, J_{CP} = 15.4 Hz, CH); 72.81 (d, J_{CP} = 17.1 Hz, CH); 71.60 (CH); 70.82 (CH); 69.85 (d, J_{CP} = 8.2 Hz, CH); 69.78 (d, J_{CP} = 11.8 Hz, CH); 69.63 (d, J_{CP} = 9.4 Hz, CH); 69.15 (d, J_{CP} = 11.7 Hz, CH); 55.93 (CH); 50.18 (CH); 40.73 (CH_3); 34.54 (CH_3); 23.12 (CH_3); 10.53 (CH_3) ppm. ^{31}P-NMR δ = 54.44 (s) ppm. HRMS: *m/z* calculated for $C_{33}H_{37}Fe_2N_2PS$ $[M + H]^+$: 637.1192, found: 637.1174.

Supplementary Materials: The following are available online, Figure S1: ^{1}H-HMR spectrum of compound **3**, Figure S2: ^{13}C-NMR spectrum of compound **3**, Figure S3: ^{1}H-NMR spectrum of compound **4**, Figure S4: ^{13}C-NMR spectrum of compound **4**.

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