

DOI: 10.1002/ejoc.201201325

# Explanation of Different Regioselectivities in the *ortho*-Lithiation of Ferrocenyl(phenyl)methanamines

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Keywords: Directed metalation / Lithiation / Ferrocenes / Regioselectivity / Diastereoselective synthesis / NMR spectroscopy

Diastereoselective *ortho*-lithiation of ferrocenes is a principal strategy for the synthesis of chiral ferrocene ligands. Dilithiation of (*R*)-1-(2-bromophenyl)-1-ferrocenyl-*N*,*N*-dimethylmethanamine leads to a dilithium intermediate, which can be transformed to a Taniaphos ligand with (R, $R_p$ )-configuration. On the other hand, lithiation of (*R*)-1-phenyl-1-ferrocenyl-*N*,*N*-dimethylmethanamine affords a lithiated product with opposite configuration of the stereogenic plane. Pre-

#### sumably, the second lithium atom attached at the *ortho*-position of the phenyl ring is responsible for this difference through the intramolecular multicenter arrangement involving both lithium atoms and their adjacent carbon atoms, the iron atom of the ferrocenyl moiety, and the nitrogen atom of the amino group. This hypothesis has been supported also by quantum chemical calculations.

# Introduction

Directed ortho-metalation is a useful strategy for selective introduction of a large variety of substituents on aromatic compounds.<sup>[1]</sup> ortho-Metalation of substituted metallocenes results in the creation of a stereogenic plane, thus leading to planar chiral compounds. Planar chiral metallocenes.<sup>[2]</sup> ferrocene derivatives in particular, find great use in asymmetric catalysis.<sup>[3]</sup> Synthesis of most of them features diastereoselective ortho-lithiation as a crucial step for introducing important donor atoms stereoselectively.<sup>[4]</sup> In general, diastereoselective ortho-lithiation has been carefully studied by spectroscopic as well as theoretical methods.<sup>[5]</sup> On the other hand, considerably less attention has been devoted to dilithiations.<sup>[6]</sup> Dilithiations are, in comparison to monolithiations, much rarer, but still interesting for the synthesis of useful compounds.<sup>[7]</sup> Among several ferrocene derivatives that can be made by double lithiation,<sup>[8]</sup> the Taniaphos family of chiral ligands are representative examples.<sup>[9]</sup> In this case, the process of dilithiation consists of a stereoselective ferrocene deprotonation ortho-directed by the dimeth-

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ylamino group and a bromine–lithium exchange. As Taniaphos is one of the most widely used ferrocene ligands,<sup>[10]</sup> it is useful to investigate the course of its synthesis. Furthermore, the stereochemical outcome of the dilithiation in the synthesis of Taniaphos is different from that of the lithiation typically observed in related ferrocenyl methylamines.<sup>[11]</sup> It seems that the presence of two lithium atoms in the molecule leads to this particular stereochemical outcome. We therefore hypothesized that a lithium atom attached at the *ortho*-position of the phenyl ring forces a different conformation in the transition state through Fe–Li interaction. Interactions of iron atoms with carbocations, silylium ions, or metals are known;<sup>[12]</sup> therefore, it seems reasonable to suppose that Fe–Li interaction can occur during the dilithiation of the Taniaphos precursor.

In this context, we decided to investigate dilithiation of (R)-1-(2-bromophenyl)-1-ferrocenyl-N,N-dimethylmethanamine, which leads to the Taniaphos ligand family, and to compare it with the lithiation of related model substrates. Explanations suggested for different stereochemical outcomes are supported by quantum chemical calculations of transition states of lithiation.

# **Results and Discussion**

The Taniaphos ligand precursor, 2-bromobenzylamine (*R*)-1, was prepared by following the original Knochel procedure.<sup>[9b]</sup> Lithiation of 2-bromobenzylamine (*R*)-1 with *t*BuLi produced a dilithium intermediate, which, after reaction with chlorodiphenylphosphane, led to Taniaphos ligand ( $R, R_p$ )-2.<sup>[9]</sup> The Taniaphos ligand has been, for some

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time, wrongly depicted as having the  $(R, S_p)$ -configuration, although the correct X-ray structure of the Rh-Taniaphos complex was presented in the original report. Fukuzawa and co-workers provided additional proof of the absolute configuration of the dilithium intermediate by its oxidative coupling and thus also corrected the configuration of Taniaphos.<sup>[13]</sup> The fact that the lithiation of Ugi-type amine 3 led, through a monolithiated intermediate, to aminophosphane  $4^{[14]}$  with  $(R, S_p)$ -configuration may have contributed to the original confusion with the designation of proper configurations of Taniaphos ligands (Scheme 1). At the outset of our study, we obtained X-ray-quality crystals of Taniaphos itself and amino phosphane  $(R,S_p)$ -4. Crystal structure analysis confirmed their absolute configurations (Scheme 1). For details of X-ray structure determinations of compounds 2 and 4, see Supporting Information.



#### Scheme 1.

Although X-ray crystallographic analysis provides definite proof of the configuration, it is time-consuming and expensive. Furthermore, it depends on the availability of suitable crystalline material. Therefore, we sought a more convenient method that would provide insight into the facial selectivity of the lithiation. We first investigated lithiation of amines 1 and 3. Deuterated products, obtained by quenching lithiated intermediates with CD<sub>3</sub>OD or D<sub>2</sub>O, seem to be suitable for this purpose. Compounds  $d_1$ -3 and  $d_2$ -3, obtained in this way, are almost chemically identical, but they are distinguishable by using NMR spectroscopy (Scheme 2).



Scheme 2.

The positions of the deuterium atoms on the cyclopentadienyl (Cp) ring were unambiguously confirmed by the gHSQC spectrum (Figure 1). In compound  $d_2$ -3, the unsubstituted carbon atoms of the substituted Cp ring have signals at 66.5, 68.5, and 70.5 ppm, and in compound  $d_1$ -3 (see Supporting Information), the corresponding signals are at 66.5, 67.2, and 68.5 ppm. Carbon atoms bearing deuterium atoms show signals of lower intensity due to splitting to triplets. Therefore, in compound  $d_2$ -3 deuterium is in the *pro-S*<sub>p</sub> position, while in compound  $d_1$ -3 deuterium is in the *pro-R*<sub>p</sub> position.



Figure 1. Determination of the position of deuterium by HSQC in deuterated compound  $d_2$ -3.

Therefore an interesting question arises: What will be the major product of the dilithiation of derivative (R)-**5**? The lithiation of this compound should also proceed via a dilithiated intermediate, but stabilization through an intramolecular Fe–Li interaction is not possible in this case. Therefore, we performed the lithiation of amine (R)-**5**, and quenching with CD<sub>3</sub>OD gave dideuterated product  $d_2$ -**6** with a deuterium atom in the *pro-R<sub>p</sub>* position of the Cp ring (Scheme 3).



Scheme 3.

<sup>2</sup>H NMR spectroscopy can also provide information on the position of deuterium atoms. <sup>2</sup>H NMR spectra of compounds  $d_1$ -3 and  $d_2$ -6 show that deuterium atoms on the Cp ring have the same chemical shift (4.25 ppm). On the other hand, compound  $d_2$ -3 has one deuterium signal at 4.13 ppm. These spectra provide additional support to a different relative configuration and thus different regioselectivity of the lithiation (Figure 2). They also show that the lithiation of amine 5 follows the path followed by that of amine 3 and therefore further support the hypothesis that Fe–Li interaction plays a role in the different regioselecti-



vity of the lithiation of amine (*R*)-1. The gHSQC spectrum of  $d_2$ -6 also confirms the suggested stereochemistry (see Supporting Information).



Figure 2.  $^{2}$ H NMR spectra (92 MHz, [D<sub>6</sub>]acetone, 20 °C, TMS) of the deuterated products.

<sup>7</sup>Li NMR spectroscopy can provide direct insight into the nature of lithium intermediates. For practical reasons, the <sup>7</sup>Li NMR spectroscopic study was carried out in [D<sub>8</sub>]-THF and *n*BuLi instead of  $[D_{10}]Et_2O$  and *t*BuLi. The lithiation of substrate 1 consists of two steps. The first step, bromine-lithium exchange, proceeds quickly even at low temperature. The lithiation was usually completed within 20 min after treatment with *n*BuLi at -60 °C. The second step, diastereoselective *ortho*-lithiation of the substituted Cp ring directed by the dimethylamino group, requires higher temperatures. In the <sup>1</sup>H NMR spectrum, two broad singlets appear at 1.98 and 1.90 ppm (3 H each) corresponding to the chemically nonequivalent methyl groups of the dimethylamino group. The coordination of the lithium atom at the ortho-position of the Cp ring with the nitrogen atom from the amino group restrains free rotation around the C-N bond. In the case of compound 1, we obtained almost complete regio- and stereoselectivity of the lithiation with nBuLi.

The lithiation of substrates 3 and 5 occurs on the opposite *ortho*-position of the substituted Cp ring and partially on the unsubstituted Cp ring. The diastereoselectivity of the *ortho*-lithiation with *n*BuLi at 5 °C decreases in the order 1 > 5 > 3. The lithiation and subsequent deuteration of substrate 5 provided dideuterated amine  $d_2$ -6 with the diastereomeric ratio 3:1. Substrate 5, upon treatment with *n*BuLi in Et<sub>2</sub>O, formed an orange precipitate as the temperature rose above 0 °C. The precipitate was soluble in THF. This suggests the formation of intermolecular clathrates stabilizing the dilithiated intermediate. Amine 3 provided monodeuterated product  $d_1$ -3 with a diastereomeric ratio of 2:1 under the same reaction conditions. The substrate without the amino group was lithiated at -60 °C selectively on the phenyl ring by bromine–lithium exchange. No lithiation on the ferrocenyl moiety was observed in this case.

The lithiation of substrate 1 with *n*BuLi at -60 °C without allowing the temperature to rise, followed by quenching with CD<sub>3</sub>OD, provided only the phenyl deuterated product, similarly to the lithiation of 2-bromobenzylferrocene. Selective phenyl deuteration of compound **5** was achieved even after its treatment with *n*BuLi for 1 h at 0 °C.

The bromine–lithium exchange on the phenyl ring is manifested as a broad signal at 1.08–1.16 ppm in <sup>7</sup>Li NMR spectra of the lithiation of amines 1 and 5 (Figure 3, spectra of 7 and 9). This signal is missing in the spectrum for the lithiation of amine 3 (Figure 3, spectrum of 8). Increasing the temperature above 0 °C resulted in a resonance at 1.49 ppm corresponding to the lithium atom at the *ortho*position of the substituted Cp ring (Figure 3, spectra of 7 and 8).



Figure 3. <sup>7</sup>Li NMR spectra of lithium intermediates 7–9.

With the help of quantum chemical calculations at the DFT level BP-86/6-31G<sup>\*</sup>,<sup>[15]</sup> we identified possible transition states for the Cp ring lithiation of amine (*R*)-1 leading to both diastereomers of Taniaphos (Figure 4). Interestingly, both transition states show Fe–Li interaction, which is therefore probably not the main reason for the observed diastereoselectivity of the lithiation. However, transition state ( $R_p$ )-TS1, leading to the major diastereomer of Taniaphos, features additional quasidimeric arrangement of organolithium fragments. This quasidimeric arrangement is not possible in diastereomeric transition state ( $S_p$ )-TS1, because the phenyl group bearing the second lithium is too distant.

(S<sub>p</sub>)-**TS1** 



(R<sub>p</sub>)-**TS1** 

Calculated molecular orbitals of  $(R_p)$ -TS1 offer insight into the bonding in the transition state. HOMO-3 indicates the formation of the organolithium dimer, and HOMO-4 represents the Fe–Li interaction. The distance between the iron atom and the lithium atom on the phenyl ring is 2.72 Å, which corresponds roughly to the sum of the covalent radii of the two metal atoms (2.60 Å).<sup>[16]</sup> Figure 5 depicts molecular orbitals and orbital energies for transition state ( $R_p$ )-TS1.



Figure 5. Molecular orbitals and orbital energies for  $(R_p)$ -TS1.

Calculated transition states of the lithiation of amine (*R*)-3 show only steric interaction of the phenyl group with the unsubstituted Cp ring of the ferrocene. This gives preference for the  $S_p$ -configuration of the newly formed stereogenic plane (Figure 6).

The difference between transition states **TS1** and **TS2** is that **TS1** features additional stabilizing Fe–Li interaction. Furthermore, preferred transition state ( $R_p$ )-**TS1** is also stabilized with multicenter arrangement of organolithium fragments.



Figure 6. DFT (BP- $86/6-31G^*$ ) calculated diastereomeric transition states for the lithiation of amine **3**.

#### Conclusions

With X-ray structural analysis of Taniaphos and amino phosphane **4** we have confirmed their absolute configurations. NMR spectroscopic investigations of deuterated products provided readily applicable proofs of the direction of the lithiation. <sup>7</sup>Li NMR spectroscopy showed that a dilithium intermediate was indeed formed. Dilithiation of amine **5** proceeded with same facial selectivity as the monolithiation of amine **3**, therefore supporting the hypothesis that Fe–Li interaction and the dimeric arrangement of organolithium fragments are responsible for the different outcomes of the lithiation. Finally, with the help of quantum chemical calculations, a model explaining the course of the lithiation was developed.

# **Experimental Section**

**General:** All reactions were carried out in an inert atmosphere of Ar or N<sub>2</sub>. Solvents were dried and purified by standard methods before use.<sup>[17]</sup> NMR spectra were recorded with Varian Mercury plus (300 MHz for <sup>1</sup>H, 46 MHz for <sup>2</sup>H, 75 MHz for <sup>13</sup>C, 121 MHz for <sup>31</sup>P) and Varian NMR System 600 (600 MHz for <sup>1</sup>H, 92 MHz for <sup>2</sup>H, 150 MHz for <sup>13</sup>C, 233 MHz for <sup>7</sup>Li) instruments. Chemical shifts ( $\delta$ ) are given relative to tetramethylsilane for <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. A unified chemical shift scale was used for <sup>31</sup>P NMR (85% H<sub>3</sub>PO<sub>4</sub> as secondary standard) and <sup>7</sup>Li NMR (LiCl in D<sub>2</sub>O as secondary standard) spectroscopy. Specific optical rotations were measured with a Perkin–Elmer instrument and are given in deg cm<sup>3</sup>g<sup>-1</sup> dm<sup>-1</sup>. Melting points were measured in an open capillary tube.

**Typical Procedure for Dilithiations:** *t*BuLi (1.6 M in pentane, 400  $\mu$ L, 0.63 mmol) was added at -70 °C to a solution of amine (*R*)-1 (118 mg, 0.37 mmol) in anhydrous Et<sub>2</sub>O (3 mL). The mixture was stirred for 80 min while the temperature was raised to room temp. It was then cooled down to -70 °C and PPh<sub>2</sub>Cl (120  $\mu$ L, 0.67 mmol) was added. The resulting mixture was stirred at room temp. for 16 h. NH<sub>4</sub>Cl (sat. soln., 6 mL) and Et<sub>2</sub>O (5 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL) and brine (1 × 10 mL), dried with Na<sub>2</sub>SO<sub>4</sub>, and the solvents were evaporated. Products were isolated by column chromatography [SiO<sub>2</sub>, hexane/Et<sub>2</sub>O (3:1) + 1% Et<sub>3</sub>N].

For characterization data of amino phosphanes **2** and **4** see Supporting Information.



#### **Characterization Data for Deuterated Products**

 $(R, R_p)$ -1-(2-Deuterioferrocenyl)-N, N-dimethyl-1-phenylmethanamine: <sup>2</sup>H NMR (92 MHz, [D<sub>6</sub>]acetone, 20 °C, TMS):  $\delta = 4.25$  (D-C<sup>Fc</sup>) ppm. MS: m/z = 276.2 [M – NMe<sub>2</sub>]<sup>+</sup>.

(*R*,*S*<sub>p</sub>)-1-(2-Deuterioferrocenyl)-1-(2-deuteriophenyl)-*N*,*N*-dimethylmethanamine: <sup>2</sup>H NMR (46 MHz, [D<sub>6</sub>]acetone, 20 °C, TMS):  $\delta =$ 7.58 (D-C<sup>Ph</sup>), 4.13 (D-C<sup>Fc</sup>) ppm. MS: *m*/*z* = 277.2 [M – NMe<sub>2</sub>]<sup>+</sup>.

(*R*,*R*<sub>p</sub>)-1-(2-Deuterioferrocenyl)-1-(4-deuteriophenyl)-*N*,*N*-dimethylmethanamine: <sup>2</sup>H NMR (92 MHz, [D<sub>6</sub>]acetone, 20 °C, TMS):  $\delta =$  7.33 (D-C<sup>Ph</sup>), 4.25 (D-C<sup>Fc</sup>) ppm. MS: *m*/*z* = 277.2 [M - NMe<sub>2</sub>]<sup>+</sup>.

**2-Deuteriobenzylferrocene:** <sup>2</sup>H NMR (46 MHz, [D<sub>6</sub>]acetone, 20 °C, TMS):  $\delta = 7.24$  (D-C<sup>Ph</sup>) ppm. MS: m/z = 277.2 [M]<sup>+</sup>.

<sup>7</sup>Li NMR Spectroscopic Experiments: The reactants were mixed together in a carefully dried NMR tube under an argon atmosphere at -70 °C and stirred under a mild flush of dry argon. <sup>1</sup>H and <sup>7</sup>Li NMR spectra were recorded at -60 °C to avoid the broadening of the lithium signals because of dynamic processes in the reaction mixture observed at higher temperature.

#### X-ray Data Collection, Structure Solution, and Refinement

Measurements were taken with an Oxford Diffraction Gemini R  $\kappa$ -axis diffractometer<sup>[18]</sup> having graphite-monochromated Mo- $K_a$  radiation ( $\lambda = 0.71073$  Å) at 100 K by using  $\omega$  scans. Corrections for Lorentz, polarization, and absorption effects were applied by using the CrysAlisPro software. Both structures were solved by structure-invariant direct methods with SIR–2002<sup>[19]</sup> and refined with CRYSTALS.<sup>[20]</sup> The crystal data and details of data collection and refinement for compounds **2** and **4** are given in the Supporting Information (Table S1).

All non-hydrogen atoms were refined anisotropically as free atoms. The hydrogen atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The hydrogen atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry, after which their positions were refined with riding constraints.<sup>[21]</sup> The absolute structure was determined from anomalous dispersion effects by using Friedel difference restraints<sup>[22]</sup> for obtaining better convergence of the Flack *x* parameter. Additionally, the Hooft *y* factor<sup>[23]</sup> was calculated by CRYSTALS for comparison.

CCDC-878297 [for  $(R,R_p)$ -2] and -893171 [for  $(R,S_p)$ -4] contain the supplementary crystallographic data for this paper (including structure factors). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data\_request/cif.

**Computational Details:** Guess structures for transition states were obtained by modifying our earlier calculation of lithiations of ferrocenophanes.<sup>[24]</sup> These initial structures were optimized by using the semiempirical PM3 method and then fully geometrically optimized at the DFT BP-86 functional, 6-31G\* basis set level.<sup>[15]</sup> All transition states were characterized by one imaginary frequency. For coordinates of all calculated structures, see Supporting Information.

**Supporting Information** (see footnote on the first page of this article): Copies of the <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>31</sup>P NMR spectra, additional HSQC spectra and details of X-ray crystallographic and computational analyses.

### Acknowledgments

Financial support from the Slovak Grant Agency VEGA, grant no. VEGA 1/0623/12 is gratefully acknowledged. This publication is

the result of the project implementation 26240120025 supported by the Research & Development Operational Programme funded by the European Regional Development Fund (ERDF). NMR spectroscopy measurements were provided by the Slovak State Programme project no. 2003SP200280203. We also thank the Structural Funds, Interreg IIIA for the financial support for purchasing the diffractometer.

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Received: October 8, 2012 Published Online: November 20, 2012