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Synthesis of epimer of Taniaphos ligand

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ABSTRACT

The spatial arrangement of groups within a chiral ligand is essential for its catalytic performance. This work describes convenient synthesis of (R,S_p)-1-(2-(diphenylphosphano)ferrocenyl)-1-(2-diphenylphosphanophenyl)-*N*,*N*-dimethylmethanamine, a diastereomer of the well known (R,R_p)-Taniaphos ligand. The compound was prepared from the same homochiral amine as Taniaphos by sequential twofold lithiation followed by trapping with diphenyphosphane chloride. Sequential twofold lithiation, in contrast to simultaneous dilithiation, leads to the opposite configuration of the stereogenic plane. The structure and configuration of the (R,S_p)-diastereomer along with its CuBr-complex were confirmed by X-ray structural analysis. DFT calculations elucidated underlying effects controlling the stereochemical outcome of the lithiation.

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1. Introduction

Ferrocene is one of the prominent structural elements for building chiral ligands for asymmetric catalysis [1–6]. In particular, ferrocenyl phosphanes possessing elements of central and planar chirality represent an important group of ligands used in homogeneous asymmetric catalysis with transition metals [7,8]. Ferrocenyl phosphane, Taniaphos, introduced by Knochel and coworkers, is the highly useful type of chiral ligand [9]. Taniaphos proved helpful in the copper-catalyzed conjugate additions of organometallic reagents [10–18], copper-catalyzed allylic substitutions [19–22], or rhodium catalyzed hydrogenations [23–25].

Introduction and manipulation of stereogenic units during synthesis of chiral ferrocene ligands is an important topic [26]. Many chiral ferrocene ligands can be synthesized from suitable chiral amines. These homochiral α-amino derivatives often result from the resolution of corresponding racemic amines (Ugi's resolution) or stereoselective reduction of carbonyl compounds followed by a nucleophilic substitution with retention of the configuration. Stereoselective induction of the planar chirality is allowed by the *ortho*-directing amino group on α-carbon. Steric control of the lithiation leads predominantly to (R^*,S^*_p)- relative configuration of the product (Scheme 1) [27,28].

In this transition state model, the hydrogen atom on α-carbon occupies the space between the planes of ferrocenyl Cp rings relieving the steric interaction of bulkier groups with the ferrocenyl fragment. These substituents on stereogenic center are located above the plane of the substituted Cp ring, and the introduction of lithium atom is directed by the nitrogen of the amino group. This model of the lithiation applies even in such constrained systems as *N*,*N*-dimethyl-[5]ferrocenophan-1′-amine [29].

On the other hand, dilithiation of compound (R)-**1** and subsequent reaction with PPh_2Cl leads to diphosphane (R,R_p)-**3** (Taniaphos). The formation of a quasi-dimeric arrangement of lithium atoms in the transition state explains the configuration of the chiral plane (Scheme 1). Another factor, which further stabilizes this pathway may be an interaction of Li with Fe [30].

The presence of two lithium atoms in the transition state is essential to achieving the observed stereochemical result of the lithiation. Separating the lithiations in two distinct steps should, therefore, lead to the opposite configuration of the chiral plane similarly to other mono-lithiations.

Alternatively, Taniaphos-type ligands can also be synthesized by stereoselective *ortho*-lithiation of chiral ferrocenyl sulfoxides. Electrophilic quenching of the resulting Li-intermediate with 2-(diphenylphosphano)benzaldehyde provided two

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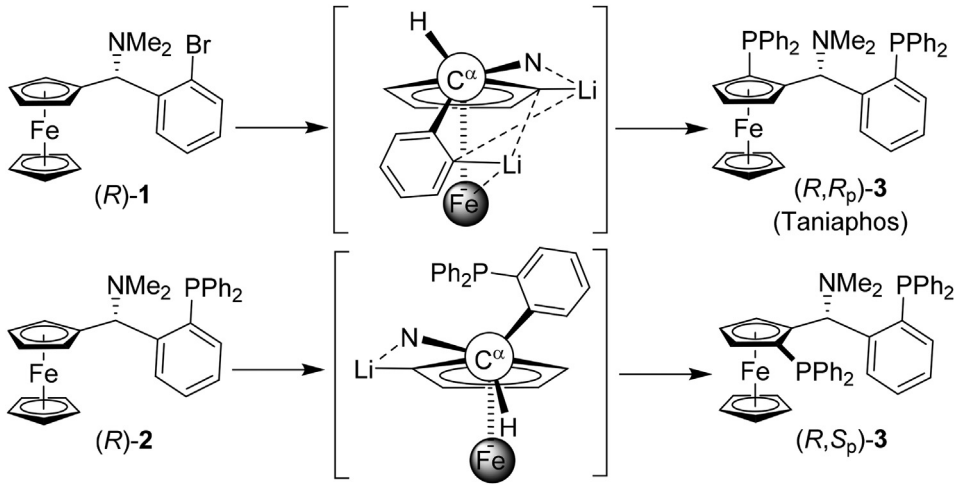


Scheme 1. Schematic representation of different course of double and step-wise lithiation.

diastereoisomeric alcohols with a different configuration of the chiral center on α-carbon formed in approximately equal amounts [31–34]. These alcohols were separated by chromatography and the sulfoxide group substituted with phosphano group. However, this method was not employed for the synthesis of (R,S_p)-configured diphosphane-amines [32].

In another approach, Fukuzawa and coworkers protected (*pro-S*) *ortho*-position of 1-ferrocenyl-*N*,*N*-dimethyl-1-phenylmethanamine with a trimethylsilyl group. Ensuing lithiation of the second *ortho*-position of Cp ring and phenyl ring helps to introduce two diphenylphosphano groups. After deprotection, they obtained (R,R_p)-Taniaphos [35,36].

In this context, we decided to investigate step-wise twofold lithiation for the synthesis of (R,S_p)-epimer of Taniaphos, compound (R,S_p)-**3**. To the best of our knowledge, the synthesis of diastereomer **3** was not accomplished, despite several attempts. We show that a careful control of reaction parameters enables one to perform the desired step-wise dilithiation and thus obtain epimer of Taniaphos.

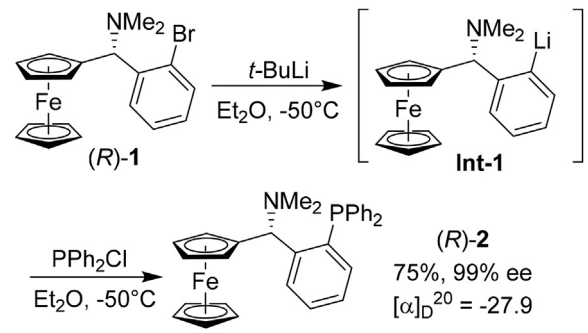
2. Results and discussion

2.1. Synthesis

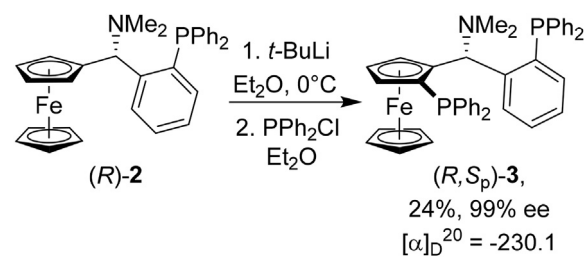
Enantioselective CBS-reduction of (2-bromobenzoyl)ferrocene afforded the starting amine (R)-**1**. Crystallization of alcohol from heptane provided the corresponding product in 99% enantiomeric excess. The resulting alcohol was acetylated, and acetoxy group subsequently substituted for dimethylamino group following the procedure of Knochel and coworkers [9]. The nucleophilic substitution in the α-position to ferrocenyl moiety proceeds with complete retention of the configuration on the stereogenic center as was well documented in many ferrocenyl compounds.

Exposure of compound (R)-**1** to *t*-BuLi resulted in an exchange of the bromine atom in *ortho*-position of the phenyl ring. This Br–Li exchange proceeded quickly even at low temperatures. Complete conversion of starting bromoamine **1** was achieved within one hour in THF at −50 °C. Lithiated intermediate **Int-1** is moisture sensitive and decomposes by protolysis to the corresponding debrominated amine. To minimize this side reaction, the starting material (R)-**1** should be dried carefully by heating above its melting point (m.p. 73 °C) under vacuum [23]. Quenching of the reaction with PPh_2Cl afforded aminophosphane (R)-**2** in 75% yield (Scheme 2).

The compound (R)-**2** is an orange crystalline compound, which



Scheme 2. Synthesis of phosphane **2**.



Scheme 3. Synthesis of (R,S_p)-**3**.

slowly decomposes in chloroform solution forming the paramagnetic particles. Satisfactory ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in d_6-acetone solution. The chemical shift of the phosphorus, a singlet at −17.2 ppm, is similar to that of the phenyl attached phosphorus in (R,R_p)-Taniaphos (doublet −16.7 ppm).

The subsequent lithiation of compound (R)-**2** proceeded slowly (Scheme 3). It required elevated reaction temperature and longer time. Lithium was stereoselectively directed to the preferred *ortho*-position of the substituted Cp ring by coordination to the nitrogen atom of the amino group (see Scheme 1). Trapping of the corresponding lithiated intermediate **Int-2** with PPh_2Cl afforded the compound (R,S_p)-**3**. The ^{31}P chemical shifts of phosphorus atoms in compound (R,S_p)-**3** (δ = −18.1 ppm for Ph-P and −27.0 ppm for Cp-P, J(P,P) = 39.6 Hz in $CDCl_3$ at 242.8 MHz) are similar to that of the phosphorus signals of diphosphane (R,R_p)-**3** (δ = −16.7 and −23.2 ppm, J(P,P) = 19.1 Hz in $CDCl_3$ at 81 MHz). Coupling with

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