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Diastereoselective *ortho*-lithiation of [5]ferrocenophanes

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ABSTRACT

Planarly chiral ferrocene derivatives with bridged cyclopentadienyl rings are interesting ligands in asymmetric catalysis. A planar stereogenic unit is conveniently introduced by diastereoselective *ortho*-lithiation. The directed lithiation of several [5]ferrocenophane derivatives followed by quenching with chlorodiphenylphosphane led to planarly chiral ligands. The sense of diastereoselection was studied by computational methods. Absolute configuration of methoxy phosphane was determined by single crystal X-ray diffraction study.

1. Introduction

Chiral ferrocene ligands belong to privileged ligand classes for transition-metal catalyzed enantioselective reactions [1,2]. Several ferrocenyl phosphanes, especially members of the *Josiphos* family [3], found also commercial applications. A number of ferrocene compounds proved useful in many enantioselective transformations [4]. Ferrocene derivatives with bridged cyclopentadienyl (Cp) rings were also successfully utilized in several asymmetric catalytic reactions and represent interesting alternatives to non-bridged compounds. An efficient access to planarly chiral ferrocenophane derivatives is, therefore, desired. Principal strategy for introduction of planar stereogennic unit is based on directed *ortho*-metalation. Selective *ortho*-metalations of aromatic compounds found widespread use in the synthesis of otherwise inaccessible derivatives [5–7]. This concept has later been applied to ferrocene derivatives as well, where it has important consequences in generation of another stereogenic unit (planar chirality) in the molecule. The majority of chiral ferrocene ligands possess planar chirality and it is generated by some form of *ortho*-metalation. After pioneering study of Ugi [8] a number of directing group were described. Most often nitrogen containing substituents, such as amines [9], oxazolines [10,11], imidazolines [12] were used as *ortho*-directing groups. However, several other functionalities such as acetal [13], sulfoxide [14] and oxazaphospholidine-oxide [15] were also described as suitable directing groups. Snieckus pioneered use of independent chiral molecule, sparteine, present in the reaction mixture, which is capable of inducing *ortho*-lithiation with high enantioselectivity [16,17].

The first planarly chiral ferrocenophane ligands were prepared by Widhalm and coworkers [18]. Their synthesis started from [3] ferrocenophane analog of Ugi amine **1**. The lithiation of **1** with *n*-BuLi followed by a reaction with chlorophosphanes afforded corresponding N,P-ligands. Erker used another [3]ferrocenophane derivative (**2**) for preparation of similar ligands [19]. In our laboratory, we showed that methylamino derivative can be dilithiated and thus transformed to phosphane-aminophosphane ligands [20]. Dimethylamino [5] ferrocenophane **3** can be diastereoselectively lithiated too (Fig. 1) [21].

In this paper we present results of our combined experimental and quantum-chemical study of diastereoselective *ortho*-lithiation of selected [5]ferrocenophane derivatives. The resulting phosphanes have potential use as chiral ligands.

2. Results and discussion

2.1. Synthesis

In an analogy to *ortho*-lithiation of Ugi amine [5] ferrocenophane derivative **3** can be similarly lithiated with *n*-BuLi in Et_2O.

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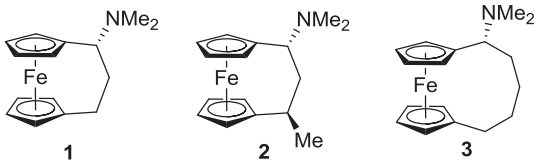
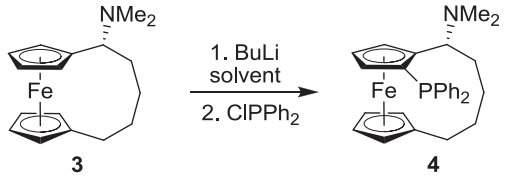


Fig. 1. Ferrocenophane amines suitable for ortho-lithiation.



Scheme 1. Lithiation of amine 3 followed by phosphanylation.

After quenching the lithiated intermediate with $ClPPh_2$, aminophosphane **4** was obtained (Scheme 1). Diastereoselectivity of this reaction typically ranged from 87 to 93% [21]. Although isolation and purification of major diastereoisomer (R,S_p)-**4** was feasible, it often resulted in substantial loses of material. This prompted us to investigate possibilities for increasing diastereoselectivity of the reaction.

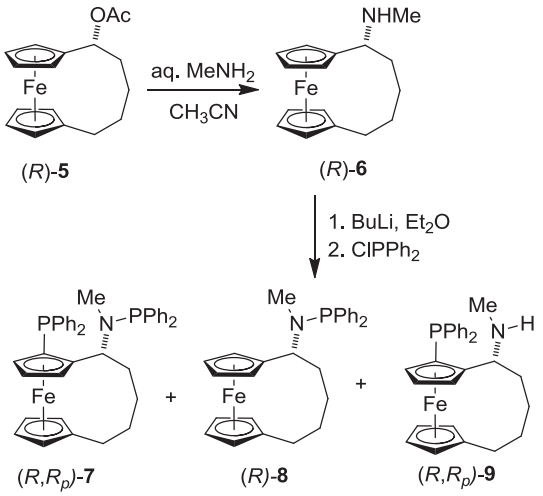
We screened several lithiation reagents in several ethereal solvents. The highest diastereoselectivity 99:1 was obtained with *s*-BuLi. However, the lithiation with *t*-BuLi is more interesting from a practical point of view. It afforded product **4** in the highest chemical yield (66%), while diastereoselectivity remained high (98:2). Attempts on use of Knochel's bases $(TMP)_2Zn.LiCl$ did not afford desired product. The results of lithiation of amine **3** are summarized in Table 1.

Aminophosphane-phosphane ligands, exemplified by *BoPhoz* ligand [22], are useful in a number of metal catalyzed reactions. Previously, we prepared [3]ferrocenophane aminophosphane-phosphane ligand by double lithiation. Therefore we tried this strategy also on [5]ferrocenophane derivative **6**. Compound **6** was synthesized from acetate **5** by a nucleophilic substitution with aqueous methylamine. Lithiation of amine **6** with more than 2 equivalents of *n*-BuLi resulted in a dianion formation, which after reaction with chlorodiphenylphosphane afforded compound **7** (Scheme 2). Product **7** was always accompanied by a mono-substituted compound **8**. Diastereoselectivity of this reaction is high, minor diastereoisomer of **7** was not observed. We also found that compound **7** was sensitive and decomposed to derivative **9** during chromatographic purification. When we have cleaved PPh_2 group from nitrogen on purpose, derivative **9** was obtained in 75% yield. Diphenylphophano group can be then reintroduced by reaction with $ClPPh_2$ and Et_3N. In this way cleaner crude product

Table 1
Lithiation of amine **3** followed by reaction with ClPPh2.

Base	Solvent	Temp. (°C)	Yield (%)[a]	d.r.[b]
n-BuLi	Et_2O	r.t.	58	93:7
n-BuLi	*t*-BuOMe	r.t.	51	90:10
n-BuLi	CpOMe	r.t.	48	93:7
s-BuLi	Et_2O	0 °C	45	>99:1
t-BuLi	Et_2O	0 °C	66	98:2
t-BuLi	Et_2O	−10 °C → 0 °C	54	97:3
$(TMP)_2Zn.LiCl$	Et_2O	0 °C	–	–
$(TMP)_2Zn.LiCl$	THF	r.t.	–	–

[a] Isolated yield of pure.
[b] Determined by ^{31}P NMR of the crude reaction mixture.



Scheme 2. Lithiation of amine 6 followed by phosphanylation.

Table 2
Lithiation of substrate **6** followed by quenching with ClPPh2.

Base	Temp. (°C)	Time (h)	**7**:**8**[a]
s-BuLi	0	4	66:34
t-BuLi	0	5	36:64
t-BuLi	r.t.	5	21:79
n-BuLi	r.t.	6	>99:1

[a] Determinedcted by ^1H NMR of the crude reaction mixture.

was obtained and it can be purified by crystallization to afford compound **7** in 53% yield (Table 2).

We established relative configuration of compound **9** by NOESY NMR, thus confirming also configuration of compound **7**. This experiment revealed strong NOE cross-peak of Cp-proton (3.03 ppm) with a proton located on C1 carbon (4.28 ppm) of the bridge that confirmed relative R_p configuration of planar stereogennic unit (Fig. 2).

Methoxy group as an *ortho*-directing group is also known [23]. We studied diastereoselectivity of the lithiation on *(R)*-1,1′-(1-methoxypentanediyl)ferrocene (**11**). The compound **11** was

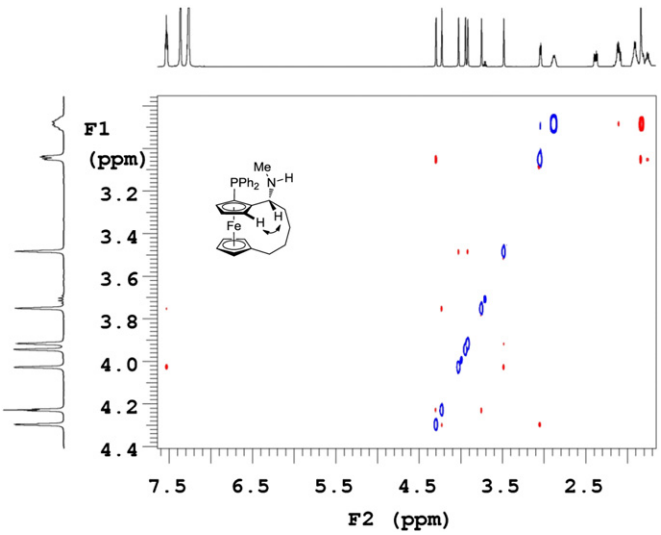


Fig. 2. NOESY NMR spectrum of **9**.