

Oxazaphospholidine-oxide as an Efficient *ortho*-Directing Group for the Diastereoselective Deprotonation of Ferrocene

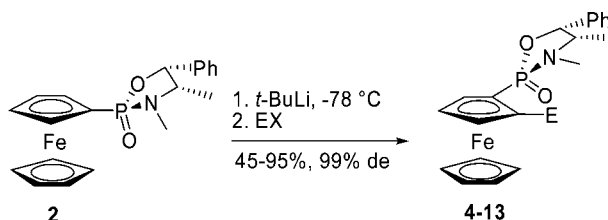
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ABSTRACT



Ortho-lithiation of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl[1,3,2]oxazaphospholidine 2-oxide **2** was carried out with diastereoselectivity of >99%, affording a new and efficient way for introducing planar chirality into the ferrocene backbone. Various electrophiles were used to quench the lithiated species, showing the wide applicability of the new *ortho*-directing group and its potential to generate ligands for use in asymmetric catalysis.

The development of asymmetric catalysis in recent years has resulted in an increasing demand for highly active and selective ligands.¹ In this context, planar chiral ferrocenes have emerged as a dominant class of compounds for many new catalytic processes.^{2,3}

Since the pioneering work of Ugi et al.,⁴ the synthesis of planar chiral ferrocenes has become of continuous interest. Enantiopure 1,2-disubstituted ferrocenes can be accessed by

a variety of stereoselective *ortho*-metalation reactions. A number of chiral *ortho*-directing groups have been developed and studied; these include sulfoxides,⁵ acetals,⁶ oxazolines,⁷ hydrazones,⁸ azepines,⁹ sulfoximines,¹⁰ pyrrolidine,¹¹ and *O*-methyl ephedrine derivatives¹² (Figure 1). *Ortho*-metala-

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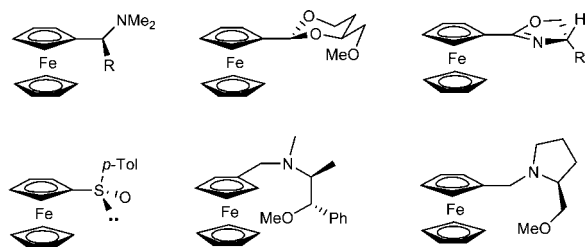
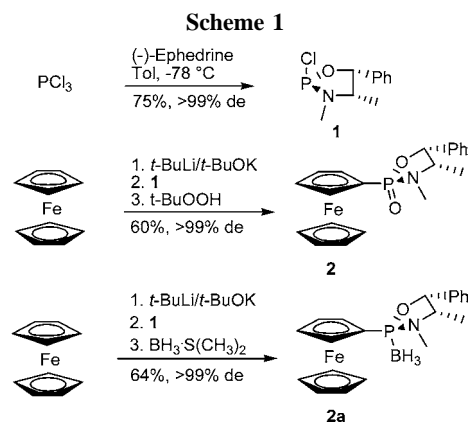


Figure 1. Ferrocene carrying *ortho*-directing groups.

tion directed by stereogenic phosphine oxides was also reported for the synthesis of ferrocenyl diphosphines;¹³ however, the metalation process was nondiastereoselective with organolithium reagents. Application of external chiral auxiliaries, e.g., (–)-sparteine,¹⁴ (1*R*,2*R*)-*N,N,N,N'*-tetramethylcyclohexane diamine,¹⁵ or chiral lithium amide¹⁶ bases in combination with achiral *ortho*-directing groups, has also been explored. However, most of these methodologies require laborious resolutions of the starting material or the use of expensive chiral reagents. Here we report an efficient, easily accessible chiral *ortho*-directing group, the oxazaphospholidine oxide, for the synthesis of diastereomerically pure 1,2-disubstituted ferrocenes.

The starting compound **2** is prepared in two steps from inexpensive (–)-ephedrine, with no resolution required.¹⁷ The first step is the nucleophilic attack of (–)-ephedrine on PCl_3 . Performing the reaction in toluene at -78°C in the presence of *N*-methyl morpholine leads to practically pure (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine **1** in 75% yield. The second step is the quenching of monolithiated ferrocene with previously prepared **1**. Here the monolithiation step is best performed according to slight modification of the procedure reported by Mueller–Westerhoff.¹⁸ *t*-BuLi (1.1 equiv) is added to a solution of ferrocene and *t*-BuOK in THF at -78°C . After 1 h of stirring at room temperature a fine red-brick precipitate is formed. The slurry is transferred via cannula to a solution of **1** (1.5 equiv) previously cooled to -78°C , and the reaction is allowed to reach room temperature. After overnight stirring, the mixture is cooled to 0°C and *t*-BuOOH (1.5 equiv) is added. Aqueous workup and purification by SiO_2 flash chromatog-



raphy gives **2** in 60% yield and over 99% de (Scheme 1). The $^3J_{\text{PH}}$ value of 6.5 Hz for the coupling between P and the 5-H proton on the ephedrine ring supports the configuration shown for **2**.¹⁹

Assuming that the oxidation step occurs with retention of configuration,²⁰ the substitution product is then formed with retention of configuration as well. Further support for this is found in the analogous reaction with $\text{BH}_3\cdot\text{S}(\text{CH}_3)_2$, the product of which was crystallized and analyzed by X-ray diffraction. The resolved structure of **2a** shows that the substitution occurred with retention of configuration (Figure 2). The BH_3 group points toward the other Cp ring, the

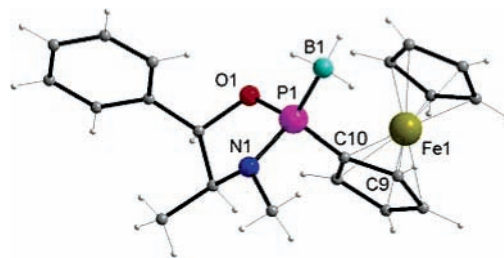


Figure 2. X-ray structure of **2a**. Selected bond lengths (\AA) and angles (deg): P1–B1 1.877(5), P1–N1 1.681(3), P1–O1 1.604(2), P1–C10 1.792(4); O1–P1–N1 94.69(14), O1–P1–B1 117.3(2), N1–P1–B1 115.1(2).

dihedral angle between the planes C9–C10–P1 and C10–P1–B1 being $11.5(1)^\circ$. The ephedrine ring adopts a half-chair conformation with its backbone pointing away from the ferrocene moiety.

The overall retention of configuration could be rationalized by a reaction sequence involving attack of FcLi on the electrophilic phosphorus followed by pseudorotation and termination by chloride elimination (eq 1, Scheme 2).^{21,22}

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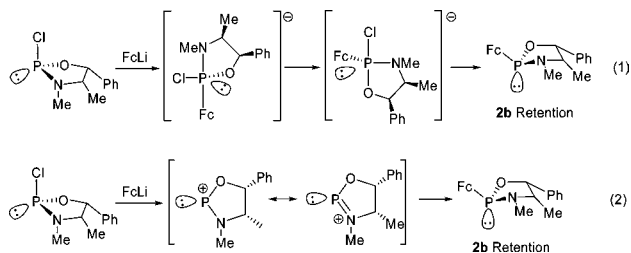
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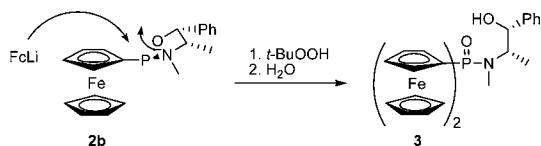
Scheme 2



Another less likely scenario could be the formation of a phosphonium ion intermediate from the dissociation of Cl^- in the presence of the Lewis acidic lithium (eq 2, Scheme 2). This intermediate could be particularly stabilized by the presence of a nitrogen atom, which would help to disperse the positive charge by resonance.²³ In such species, the nitrogen, oxygen, and phosphorus atoms and the phosphorus lone pairs would be in the same plane. The bottom face of the intermediate would be more hindered as a result of the configurations of the methyl and phenyl groups lying below the five-membered ring of the ephedrine skeleton. The nucleophile would then attack the phosphorus from the top, generating the substituted product with retention of configuration.

We also observed that using a lower concentration of **1** (1 equiv to the ferrocene), a mixture containing approximately 43% of **2** and 28% of a bisubstituted compound **3** was formed, as evidenced by the ^{31}P NMR of the crude product. Under these conditions the nucleophilic attack of the ferrocenyllithium at **1** competes with the attack at the newly formed **2b** (Scheme 3). With a lower amount of **1**,

Scheme 3

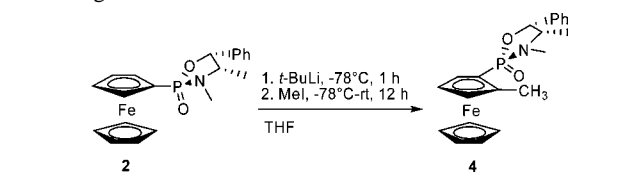


the reaction with ferrocenyllithium was also slowed in accord with a mechanism where the rate of the reaction was dependent on the concentration of the electrophile.

Solvents, source of lithium, and substrate/lithium ratios have been shown to play an important role in the diastereoselective deprotonation of ferrocene.^{6–16} To examine if the oxazaphospholidine oxide moiety could be used as an *ortho*-directing group, we first studied these parameters in the lithiation followed by reaction with an electrophile, MeI. All reactions were performed at -78°C to prevent deprotonation at the benzylic position on the phospholidine ring. It appeared quite clear from the beginning that THF was the best solvent. In fact, **2** was not soluble in hexane and only slightly soluble

in Et_2O at this temperature; only starting material was recovered from these reaction mixtures.

Using *n*-BuLi in THF, however, afforded 37% of the desired product **4** in 99% de and about 50% of a side product (Table 1). A careful examination of the ^1H and ^{31}P NMR

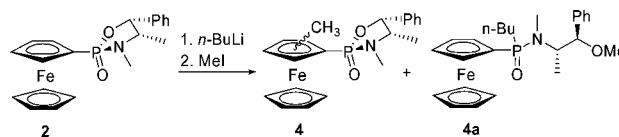
Table 1. Diastereoselective *ortho*-Lithiation of **2** under Various Screening Conditions^a

entry	solvent	RLi	isolated yield (%)	de ^b (%)
1	THF	<i>n</i> -BuLi	37	>99
2	THF	<i>s</i> -BuLi	66	>99
3	THF	<i>t</i> -BuLi	95	>99
4 ^c	THF	<i>t</i> -BuLi	77	>99

^a Reaction condition: 1 equiv of **2**, 1.5 equiv of RLi, 1.5 equiv of CH_3I , -78°C . ^b Determined by ^{31}P NMR; a value of >99% was assigned when the other diastereomer was not detected. ^c 2 equiv of RLi.

spectroscopic data revealed that some of the *n*-BuLi had attacked the phospholidine ring to cleave the P–O bond to give a Li-alkoxide species that had reacted with MeI to give **4a** (Scheme 4). This suggested that a more basic and less

Scheme 4



nucleophilic organolithium reagent was necessary. Accordingly, *s*-BuLi was able to afford 66% of **4**, and *t*-BuLi allowed an even more efficient deprotonation process on the Cp ring, affording the methyl derivative **4** with 95% isolated yield and over 99% de. Using 2 equiv of *t*-BuLi did not give better results because of competing deprotonation at the benzylic position (Table 1). The absolute configuration of **4** was determined from X-ray analysis (Figure 3).

The resolved structure shows that **4** is planar chiral with configuration *R*. The O2 atom lies *cis* to the C16 methyl and points down to the bottom Cp ring. The dihedral angle between the plane O2–P1–C11 and C15–C11–P1 amounts to $22.0(4)^\circ$. The corresponding torsion angle in the other crystallographically independent molecule is similar, at $13.1(4)^\circ$. This suggests possible assistance by O2 in the deprotonation at C15 by *t*-BuLi and stabilization of the resulting lithiated species by O2 coordination to lithium.

Using the conditions established, a variety of electrophiles were next examined in this reaction. A summary of the results obtained is reported in Table 2.

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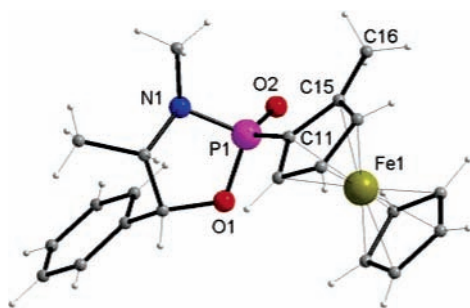
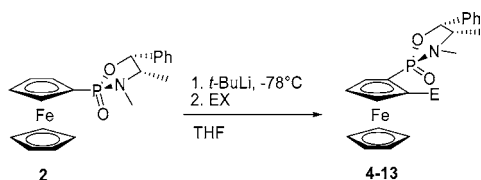


Figure 3. X-ray structure of (*R_p*)-**4**. Only one of the two crystallographically independent molecules is shown. Selected bond lengths (Å) and angles (deg): N1–P1 1.669(3), O1–P1 1.600(3), O2–P1 1.467(2), P1–C11 1.765(3); O2–P1–O1 116.40(14), O2–P1–N1 115.27(15), O1–P1–N1 95.03(14).

Our methodology was shown to be compatible with a number of functionalities: alkyls, halogens, boronates,

Table 2. Diastereoselective *ortho*-Lithiation of **2**^a



entry	E(X)	yield (%)	de ^b (%)	main product
1	Me(I)	95	>99	(<i>R_p</i>)- 4
2	I(I)	76	>99	(<i>S_p</i>)- 5
3	TMS(Cl)	94	>99	(<i>R_p</i>)- 6
4	TES(Cl)	70	>99	(<i>R_p</i>)- 7
5	Ph ₂ CO	61	>99	(<i>R_p</i>)- 8 ^c
6	B(OMe) ₃	73	>99	(<i>R_p</i>)- 9 ^d
7	PPh ₂ (Cl)	65	>99	(<i>R_p</i>)- 10
8	PCy ₂ (Cl)	68	>99	(<i>R_p</i>)- 11
9	P(pTFP) ₂ (Cl) ^e	72	>99	(<i>R_p</i>)- 12
10	P(pMOP) ₂ (Cl) ^e	45	>99	(<i>R_p</i>)- 13

^a Reaction condition: 1 equiv of **2**, 1.5 equiv of RLi, 1.5 equiv of EX, –78 °C. ^b Determined by ³¹P NMR; see Table 1. ^c E = Ph₂COH. ^d E = B(OH)₂. ^e See Figure 4 for structures.

silanes, alcohols, and phosphines. All reactions proceeded to completion, with all products being isolated as solids after SiO₂ flash chromatography purification. Assuming that the lithiation process is independent of the electrophile chosen, we assigned the absolute configuration based on the results obtained for **4**.

In conclusion, we have established a simple and convenient methodology for the synthesis of diastereomerically pure, functionalized ferrocenyl compounds. We found the oxazaphospholidine moiety to be a new and excellent *ortho*-directing group for the stereoselective deprotonation of ferrocene. With this methodology, we produced a range of 1,2-disubstituted ferrocene derivatives possessing planar chirality, including electronically and sterically diverse phosphines (Figure 4). Possible applications of the ligands

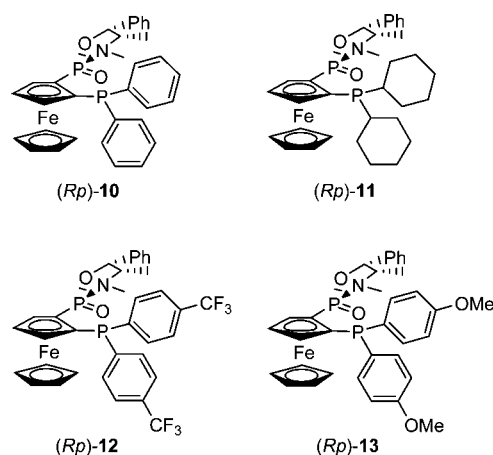


Figure 4. Planar chiral ferrocenyl phosphines.

in asymmetric catalysis are being pursued in our laboratory.

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Supporting Information Available: Experimental procedures and analytical data, including CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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