Tetrahedron: *Asymmetry* 21 (2010) 1199–1202

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Bis((2-methoxymethyl)pyrrolidine)phosphine as effective chiral auxiliary for the stereoselective synthesis of chiral ferrocenyl diphosphines

Matthias Lotz [a,*], Benoît Pugin [a,*], Martin Kesselgruber [a], Marc Thommen [a], Felix Spindler [a], Hans-Ulrich Blaser [a], Andreas Pfaltz [b], Marc Schoenleber [b]

[a] *Solvias AG, PO Box, CH-4022 Basel, Switzerland*
[b] *Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland*

ARTICLE INFO

Article history:
Received 31 March 2010
Accepted 14 May 2010
Available online 19 June 2010

Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The bis(2-methoxymethyl pyrrolidine)phosphine moiety is shown to be a very effective chiral auxiliary for the *ortho*- and diastereoselective lithiation of ferrocene, thereby allowing the highly selective attachment of various electrophiles to the cyclopentadienyl ring of ferrocene. The potential of the methodology is demonstrated by the synthesis of Kephos, a new family of ferrocenyl diphosphines and of OH-Taniaphos derivatives.

1. Introduction

Ferrocene-based chiral diphosphines are amongst the most versatile ligands for a variety of asymmetric catalytic transformations.[1] In most cases these compounds exhibit planar chirality, which renders their enantioselective synthesis non-trivial. The most common approach to solve this problem is the diastereoselective functionalization of chiral monosubstituted ferrocene derivatives via *ortho* lithiation followed by reaction with an electrophile.[2,3a] A variety of chiral *ortho*-directing groups has been reported and some representative examples are depicted in Figure 1. The majority of these groups are attached to the ferrocene via a carbon bond, one of the most versatile being the chiral amine introduced by Ugi in 1970,[4] which is now used to produce a number of commercial ligands.[5] Other well-known examples are Richards's[6] and Uemura's[7] chiral oxazolines or Kagan's chiral acetal.[8] An important property of these C-bound groups is the fact that they cannot be easily removed or replaced. Kagan[9] overcame this limit by using a chiral sulfoxide. After the stereoselective introduction of a first electrophile, the sulfoxide can be replaced relatively easily by another electrophile such as a PR_2 group. However, the yields are usually relatively low and the reaction is not easy to scale. Our goal was to find a suitable chiral ortho-directing P(III)-bound auxiliary that could be readily transformed into a phosphine after introduction of the electrophile. A similar approach had already been described by Nettekoven et al.[10] but the scope of the phosphine oxide auxiliary is rather narrow and restricted to P-chiral phosphines with bulky groups. When we already had filed our patents,[11–13] Xiao published a method using an ephedrine-based P(V) auxiliary.[14] In both cases, an (often problematic) reduction is required to obtain the desired PR_2 group.

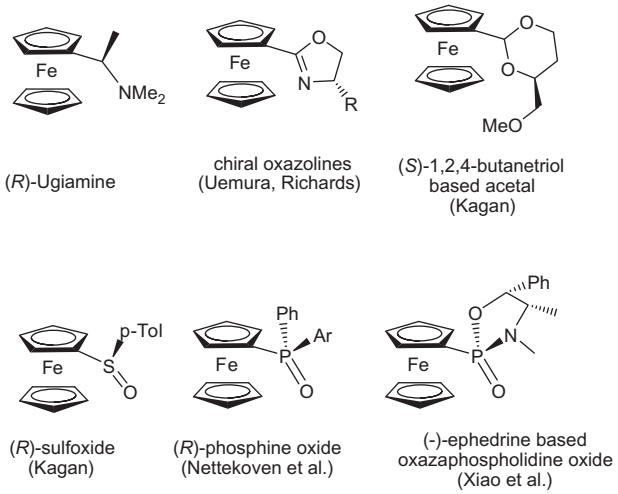


Figure 1. Chiral ferrocene derivatives used as starting material for various ligand syntheses.

Herein we report a new modular and versatile methodology based on a P(III) derivative of the commercially available (2-methoxymethyl)pyrrolidine auxiliary allowing the highly *ortho*- and diastereoselective functionalization of ferrocene with a variety of electrophiles as depicted in Figure 2. The versatility of this strat-

* Corresponding authors.
E-mail addresses: matthias.lotz@solvias.com (M. Lotz), benoit.pugin@solvias.com (B. Pugin).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.05.028

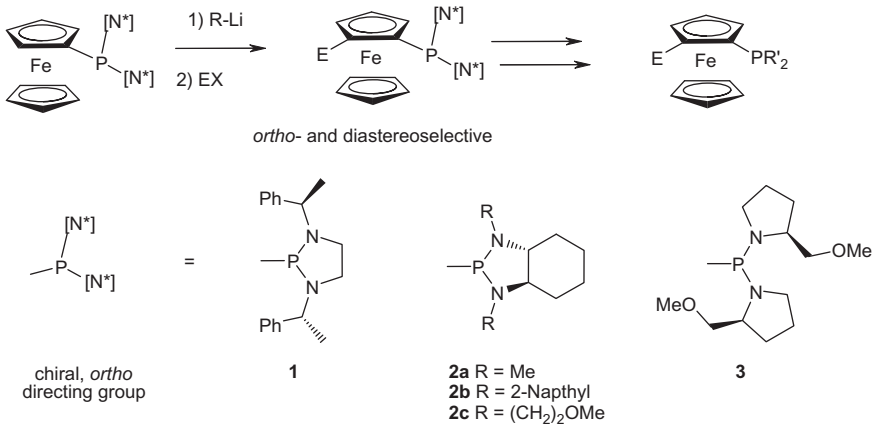


Figure 2. General strategy and structures of directing groups used in this work.

egy is demonstrated by the synthesis of Kephos, a new family of 1,2-substituted ferrocenyl diphosphines **7** (see Fig. 5,[8]), and of various Taniaphos[12,13,15] derivatives **10** (see Fig. 6).

2. Results and discussion

In order to find effective chiral auxiliaries and suitable reaction conditions several[3b] lithiation studies were carried out with various ferrocene diazaphospholidine derivatives (auxiliaries **1** and **2**) and bis((2-methoxymethyl)pyrrolidine)phosphine **3**. It turned out that the borane protection was required for stability reasons and that diazaphospholidine **2** moieties without an additional coordinating group (such as **1** or **2b**) did not give any lithiation of the ferrocene with *t*-BuLi (−25 °C in diethyl ether). Auxiliaries **2c** and **3** were more successful, allowing very selective *ortho* lithiation (>99% selectivity) with >98% de, when the corresponding BH_3 adducts of **4** and **5** were lithiated and treated with *tert*-butyllithium under optimized reaction conditions (see Fig. 3). Since both enantiomers of (2-methoxymethyl)pyrrolidine are commercially available, we carried out all further investigations with intermediate **5**.

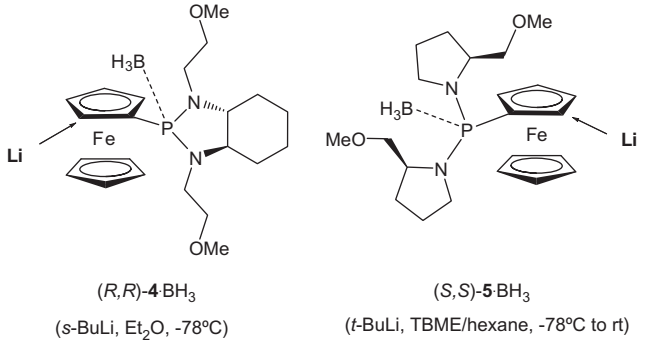


Figure 3. Lithiation of BH_3 adducts of **4** and **5**.

The synthesis of the key intermediate **5** will be described in detail (Fig. 4,[16]). In the first step, NEt_3 and then (*S*)-(2-methoxymethyl)pyrrolidine were added dropwise at 0 °C to a PCl_3 solution in THF (since most reagents and intermediates are air and water sensitive, all manipulations were carried out under argon). The resulting suspension was stirred overnight at rt. The precipitated salts were filtered off and solution **A** was directly used in the next step. Here, ferrocene and *t*-BuOK were dissolved in dry THF and cooled to −78 °C, followed by the dropwise addition of *t*-BuLi in hexane. The lithiated ferrocene was precipitated by the addition of *n*-heptane, thoroughly washed with *n*-heptane, and dissolved in THF. Solution **A** was then added dropwise at −78 °C and the reaction mixture stirred overnight at rt. The borane complex was prepared by the dropwise addition of $BH_3{\cdot}Me_2S$ followed by over night stirring at rt. After hydrolysis with a saturated NH_4Cl solution, extraction with TMBE and chromatography on silica gel (*S,S*)-**5** was obtained as an orange solid in 70% yield, which showed a broad multiplet signal at around 81 ppm in the ^{31}P NMR spectrum. Obviously, the *ortho*- and diastereoselective lithiation of (*S,S*)-**5**·BH_3 is the key step in our new synthesis of a variety of ferrocenyl diphosphine ligands. As mentioned above, it can be carried out in >99% selectivity under optimized conditions. The choice of the Li reagent (optimal *s*-BuLi), the temperature (−30 to −40 °C), the solvent (TMBE/hexane 1:1), and the absence of any coordinating agents such as TMEDA are important.

The potential of this methodology is illustrated by the preparation of a Kephos (Fig. 5) and a Taniaphos (Fig. 6) ligand. It is important to note that a variety of different analogues of both ligand families have been prepared with similar yields and described in several patent applications in some detail.[11–13] Intermediates **6** and **7** (Kephos synthesis), and **9** and **10** (Taniaphos synthesis) were characterized by ^{31}P NMR spectroscopy and used without further purification since only one isomer was detected. The lithiation of (*S,S*)-**5**·BH_3 and subsequent reaction with $ClPR_2$ took place with very high selectivity and in good yields to give (S_P)-**6**. Depending on the choice of the $ClPR_2$ reagent, the next reaction step, that is, the hydrolysis of the P–N bonds, occurs with different selectivity. When $ClPPh_2$ is used (as depicted in Fig. 5) the PCl_2 moiety obtained by reaction with HCl can be reduced to the desired PH_2 group without affecting the stable PPh_2 substituent. Reaction with the corresponding diol sulfates or tosylates allows the synthesis of mixed phospholane/diarylphosphino Kephos ligands **8**, which would be very difficult to make otherwise. With the appropriate choice of the absolute configuration of the chiral diol, both diastereomers (S_P,*S,S* and S_P,*R,R*)-**8** with R = Me, Et or *i*-Pr can be prepared in a controlled manner. Due to the presence of phospholane moieties, most Kephos ligands are relatively air sensitive and should be stored either in protonated form or as metal complexes.

Several synthetic approaches to the various Taniaphos ligand types with MeO, NR_2, or alkyl groups at the stereogenic center have been described,[5] but the corresponding OH derivatives seem not to be accessible via these routes. The OH derivative is of interest as a ligand in its own right but also because the OH group can be readily converted to an MeO or NR_2 substituent. A first attempt using Kagan's sulfoxide route gave the desired ligand but was not scalable. As shown in Figure 6, the new methodology gives ready access to these derivatives via reaction of the lithiated **5**·BH_3 with

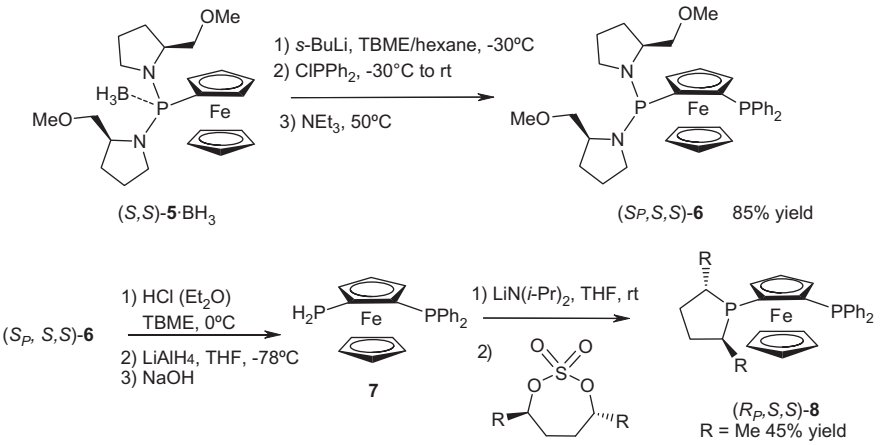


Figure 5. Synthesis of Kephos derivatives **8**.

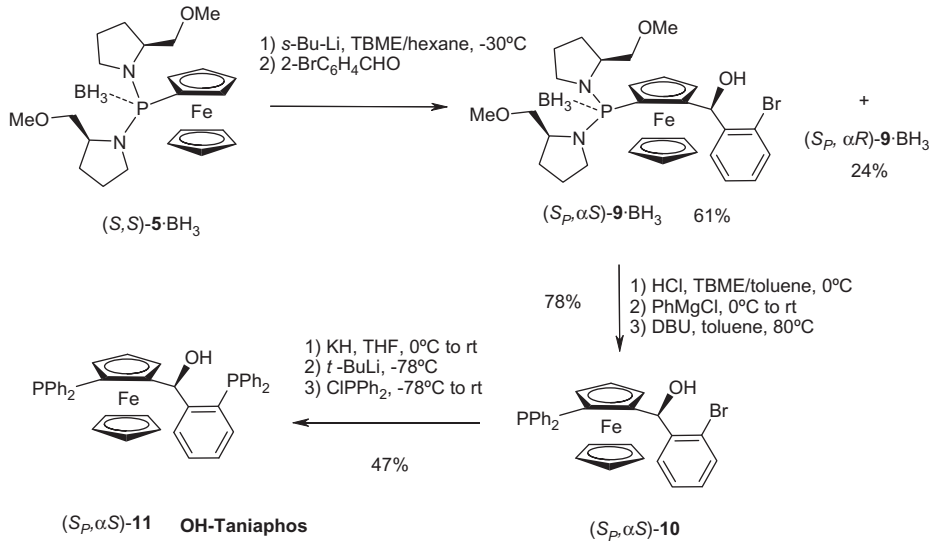


Figure 6. Synthesis of OH-Taniaphos derivative **11**.

2-Br-benzaldehyde. The reaction also occurs with this electrophile with very high *ortho*- and diastereoselectivity at the cp ring and high yields of the two diastereomeric adducts can be obtained. A mixture of (S_P,αS)-**9** and of (S_P,αR)-**9** was obtained (ca. 3:1), which could be readily separated by chromatography on a silica gel column. The absolute configuration at the stereogenic center for (S_P,αS)-**9** was confirmed by X-ray analysis.[17] In principle, this procedure allows the preparation of both diastereomeric ligands, which might lead to different catalytic properties. Reaction with HCl gives the PCl_2 derivative which can be reacted with Grignard

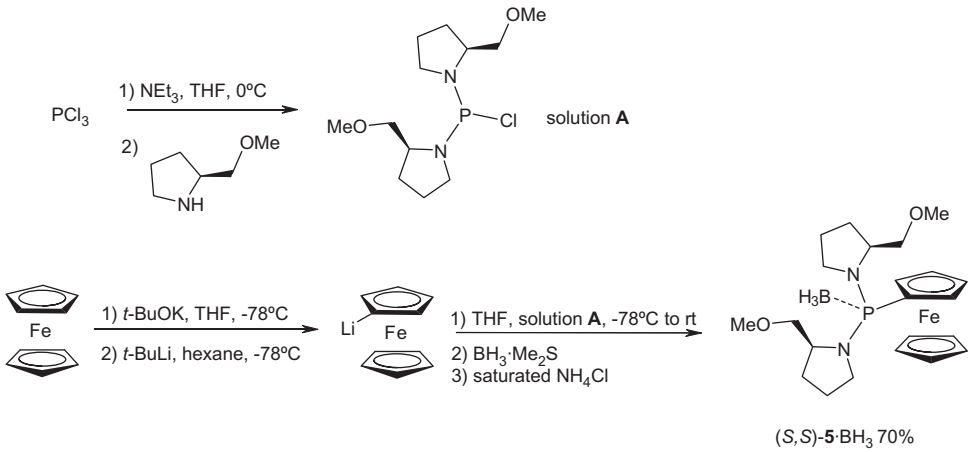
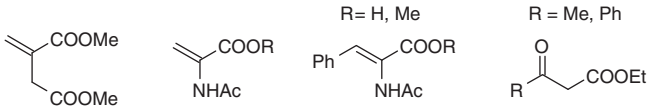


Figure 4. Synthesis of key intermediate **5**.



(R_P,S,S)-**8**	96-98%	50-60%	<30-87%	
(R_P,R,R)-**8**	70-80%	>99,9%	96-98%	
(S_P,αS)-**11**	>99%		>99%	97-98% (Ru)

Figure 7. Enantioselectivities obtained with Kephos and Taniaphos ligands.

reagents in conventional manner to give intermediate (S_P,αS)-**10.** The introduction of the second phosphino group via lithiation and reaction with $ClPAr_2$ requires first a deprotonation of the OH with KH but then proceeds reasonably well under the conditions originally described by Knochel.[5] Several mixed Ar/Ar′ derivatives have been prepared via this route with non-optimized yields of 45–88%.

Starting from (S,S)-**5**·BH_3, further alternative classes of ligands can be prepared, for example, if (S,S)-**5**·BH_3 is reacted with $ClP(NEt_2)_2$, both P substituents can be converted to the PH_2 group.[18] This intermediate allows access to ferrocenyl analogues of the well-known DuPhos diphospholane ligands in (non-optimized) yields of 40–52%. Also, it is possible to prepare 1,2-diphosphines with different PR_2/PR'_2 groups with only planar chirality as described by Kagan in his seminal paper[19] by reacting the PCl_2 intermediate after HCl hydrolysis of **6** with RMgBr as described for the synthesis of OH-Taniaphos.

The enantioselectivities for the hydrogenation of several test substrates using Rh and Ru complexes of various Kephos and Taniaphos derivatives are shown in Figure 7; more detailed results will be reported elsewhere. The results clearly demonstrate that these ligands have considerable potential for the Rh hydrogenation of activated alkenes and of β-keto esters (Ru complex, only OH-Taniaphos). As expected, the unsymmetrical Kephos ligands of type **8** exhibit a pronounced 'matched–mismatched' effect and interestingly, the optimal ligand for dimethyl itaconate is opposite the one for dehydro α-amino acid derivatives. The Rh catalysts showed quite good activities, allowing the hydrogenation of DMI with (R_P,S,S)-**8** with ee values of 97.8% and full conversion at an s/c ratio of 10,000 (1 bar, 40 °C, 1 h). With very few exceptions, the OH-Taniaphos ligands had similar performances as the analogous MeO derivatives which have been profiled extensively.[20]

3. Conclusions

The bis((2-methoxymethyl)pyrrolidine)phosphine moiety is very effective in directing the lithiation of ferrocene. The presence of the methoxy groups as well as the appropriate lithium reagent is required to give good selectivity. Electrophiles such as $ClPR_2$ or aldehydes can be introduced with good yields, allowing the preparation of a variety of 1,2-substituted ferrocene derivatives.

Acknowledgments

We thank the innovation promotion agency of Switzerland (CTI) and Umicore for partial financial support, Umicore for allowing publication of the Taniaphos results, and Reto Kellerhals and Cédric Raillard for excellent experimental work.

References

1. For a recent monograph see: *Chiral Ferrocene Ligands in Asymmetric Catalysis*; Dai, L., Hou, X.-L., Eds.; Wiley-VCH, 2010; For a recent review see: Gomez, A. R.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674.
2. Kagan, H. B.; Riant, O.. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press, 1997; Vol. 2, p 189.
3. Schönleber, M. Ph.D. Thesis, University of Basel, 2005. http://pages.unibas.ch/diss/2005/DissB_7189.pdf; (a) For a literature overview see pp 69–75; (b) Lithiation studies are described in detail on pp 76–133.
4. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
5. For an overview see: Chen, W.; Blaser, H. U. In *Trivalent Phosphorus Compounds in Asymmetric Catalysis: Synthesis and Applications*; Börner, A., Ed.; Wiley-VCH, 2008; p 359.
6. Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74.
7. Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79.
8. Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733.
9. Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568.
10. Nettekoven, U.; Widhalm, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Mereiter, K.; Lutz, M.; Spek, A. L. *Organometallics* **2000**, *19*, 2299.
11. Pfaltz, A.; Lotz, M.; Schoenleber, M.; Pugin, B.; Kesselgruber, M.; Thommen, M. PCT Int. Appl. WO 2005/056566, 2005 (assigned to Solvias AG).
12. Lotz, M.; Kesselgruber, M.; Thommen, M.; Pugin, B. PCT Int. Appl. WO 2005/056568, 2005 (assigned to Solvias AG).
13. Lotz, M.; Spindler, F. PCT Int. Appl. WO 2005/108409, 2005 (assigned to Solvias AG and Umicore AG).
14. Vinci, D.; Mateus, N.; Wu, X.; Hancock, F.; Steiner, A.; Xiao, J. *Org. Lett.* **2006**, *8*, 215.
15. For an overview on Taniaphos derivatives and their synthesis see Ref.[5].
16. Synthesis of bis((2-methoxymethyl)pyrrolidine)phosphine chloride.
In a 500 mL-Schlenk flask, PCl_3 (7.38 g, 53.75 mmol) was dissolved in dry THF (150 mL) under argon and the solution was cooled to 0 °C in an ice bath. Next, NEt_3 (11.97 g, 118.25 mmol, 2.20 equiv) was added dropwise, followed by the dropwise addition of (S)-(2-methoxymethyl)pyrrolidine (12.69 g, 110.19 mmol, 2.05 equiv). A white precipitate formed during the addition. The ice bath was removed and the resulting suspension was stirred at rt overnight (14 h). The precipitated white solid was filtered off under argon and washed with dry THF (2 × 25 mL). A ^{31}P NMR (C_6D_6, 121 MHz) spectrum of the yellowish filtrate was recorded: 154.3 (s). The obtained solution **A** was used without further purification.
Preparation of (S,S)-**5**·BH_3.
In a 1 L-Schlenk flask, ferrocene (10.00 g, 53.75 mmol) and KO*t*-Bu (754 mg, 6.72 mmol, 0.125 equiv) were dissolved in dry THF (100 mL) under argon. The solution was cooled to −78 °C and *t*-BuLi (1.5 M in hexane; 71.67 mL, 107.50 mmol, 2.00 equiv) was added within 45 min. After stirring the resulting solution for 1.5 h at −78 °C, heptane (75 mL) was added. The resulting precipitate was filtered off under argon and washed with heptane (60 mL) at −78 °C. This procedure was repeated three times. The obtained solid was dissolved in dry THF (50 mL) and solution **A** (53.75 mmol, 1.00 equiv) in THF (200 mL) was added at −78 °C within 1.5 h. The solution was allowed to warm to rt overnight (14 h). Borane–dimethylsulfide-complexes (5.10 mL, 53.75 mmol, 1.00 equiv) were added dropwise and the solution was stirred at rt overnight. The reaction was quenched with satd NH_4Cl-solution (50 mL) and the mixture was extracted with TBME (3 × 100 mL). The combined org. layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product (24.18 g) was purified by column chromatography (200 g silica gel, *n*-heptane/TBME 5:1). (S,S)-**5**·BH_3 (17.23 g, 37.60 mmol, 70%) was isolated as an orange solid. ^1H NMR (C_6D_6), selected characteristic signals: 4.22 (s, 5H cp), 3.11 (s, 3H, OMe), 3.04 (s, 3H, OMe). ^{31}P NMR (C_6D_6, 121 MHz): 81.7–80.4 (m, br).
17. Bats, J. W.; Doppiu, A.; Rivas Nass, A.; Hashmi, A. S. K. *Acta Crystallogr., Sect. E* **2008**, *64*, m1585.
18. The use of a chiral directing group is of course not optimal to make this symmetrical intermediate and, indeed, 1,2-bis(phosphino)ferrocene can be prepared using $-P(O)(OEt)_2$ as directing group. These results will be published elsewhere.
19. Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, *2893*.
20. Spindler, F.; Malan, C.; Lotz, M.; Kesselgruber, M.; Pittelkow, U.; Rivas-Nass, A.; Briel, O.; Blaser, H. U. *Tetrahedron: Asymmetry* **2004**, *15*, 2299.