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Preparation of Novel Enantiopure Ferrocenyl-Based Ligands for Asymmetric Catalysis

Thomas Sturm, Li Xiao, and Walter Weissensteiner*

Abstract: Novel enantiopure ferrocene-based aminophosphine and diphosphine ligands for asymmetric catalysts have been developed. In all cases a highly flexible synthetic approach allowed access to ligands with different ferrocenyl backbones and with a variety of functional group patterns. Procedures for the synthesis of six families of ligands with either a homo- or heteroannularly bridged ferrocene, ferrocenylmethyl, biferrocene, biferroceno-azepine or ferrocenyl-aryl framework are described in detail.

Keywords: Asymmetric catalysis · Ferrocenes · Phosphines

1. Introduction

Transition metal mediated asymmetric catalysis makes extensive use of enantiopure aminophosphine and diphosphine ligands [1]. A major role in this field is played by chelating bi- and multidentate ferrocene derivatives of both C_1 and C_2 symmetry [2]. Representative examples are ligands like *ppfa*, *josiphos* and *trap*, originally developed by Hayashi, Togni, and Ito [3–5] (Fig. 1).

The ease of synthesizing ppfa and josiphos has led to a plethora of analogous aminophosphine and diphosphine derivatives. Typically, a highly diastereoselective *ortho*-lithiation of easily accessible (*S*)- or (*R*)-(1-dimethylamino-ethyl) ferrocene (originally developed by Ugi and co-workers [6]), is followed by reaction with an electrophile. Further modification by nucleophilic substitution of the dimethylamino group leads to the final products (Scheme 1).

This synthetic strategy allowed the preparation of a huge number of ligands characterized by a variety of functional group patterns on a common ferrocenylethyl backbone. The enormous success of these ligands in asymmetric catalysis, both on the small laboratory scale as well as in industry [7] has led to a renewed interest in developing methods for the synthesis of new types of ferrocenyl ligands. Over the last years, research in this field has primarily focused on two subjects: (i) enantioselective methods for the preparation of enantiopure intermediates in order to avoid cumbersome separations of enantiomers [8] and (ii) on ligands with new structural frameworks [9].

Recognizing the need for new types of catalysts, we became interested in the development of ferrocenyl-based ligands with novel backbones. Herein we review procedures for the preparation of new

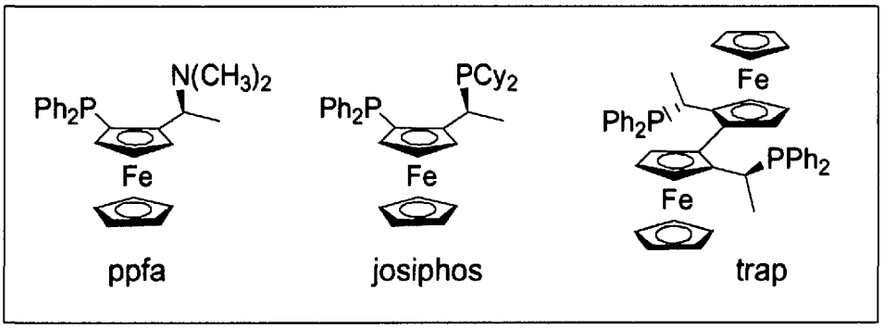
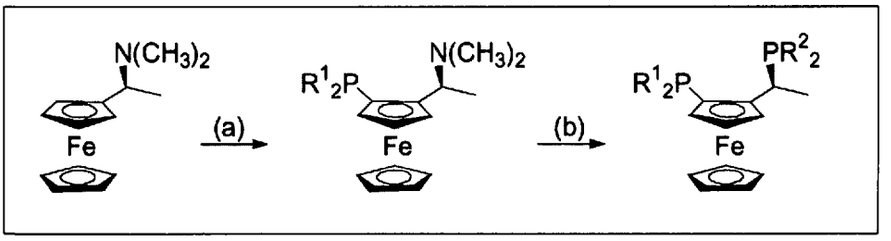


Fig. 1. Typical C_1 and C_2 symmetrical ferrocene ligands



Scheme 1. Synthesis of ppfa- and josiphos-type ligands. (a) BuLi, $ClPR^1_2$; (b) HPR^2_2, AcOH

*Correspondence: Dr. W. Weissensteiner
Universität Wien
Institut für Organische Chemie
Währinger Straße 38
A-1090 Wien
Tel.: +43 1 4277 52148
Fax: +43 1 4277 9521
E-Mail: walter.weissensteiner@univie.ac.at

families of enantiopure ferrocenyl aminophosphines and diphosphines as well as new synthetic approaches to already known ligands covering some recent work of our group [10].

2. Synthesis of Novel Ferrocene Ligands: General Considerations

Two groups of ligand families (**1–3** and **4–6**) have been investigated (Fig. 2). The first group, ligands **1–3**, represent framework analogues of josiphos-type diphosphines with the ethyl side chain integrated either into a homo- or heteroannular bridge (**1**, **2**) or into a methylene unit (**3**) while all ligands of the second group **4–6** are reminiscent of biaryl derivatives. It should be mentioned that members of **1**, **2**, **5**, and **6** constitute new classes of ligands while a few representatives of **3** and **4** have been described previously. For these latter types of ligands, new synthetic approaches are presented.

The synthesis of all groups of ligands follows the same principles: (i) first the enantiopure framework is constructed and (ii) the final functional groups are implemented stepwise. Whenever possible a modular approach was chosen. With the exception of **1**, all ligands were synthesized in a highly diastereoselective manner avoiding resolution of enantiomers.

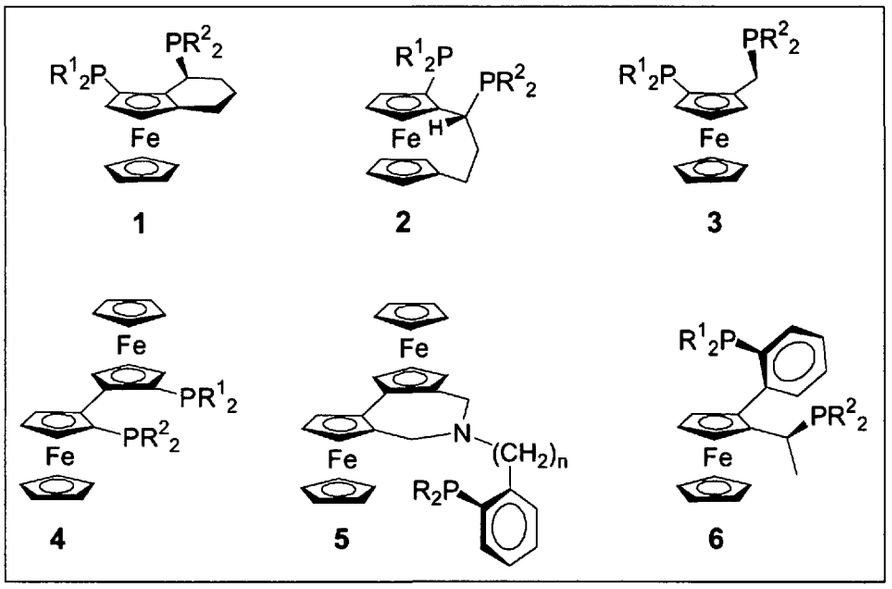


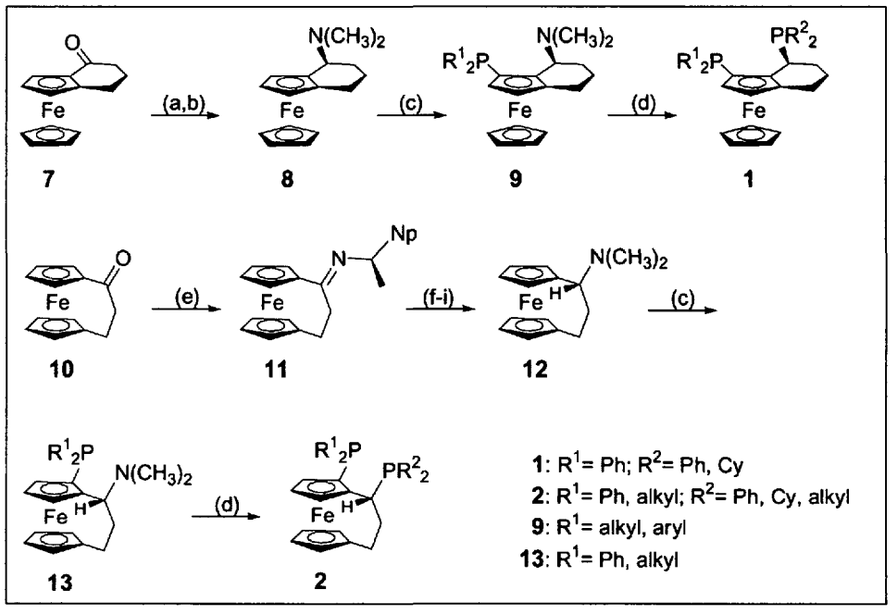
Fig. 2. List of ligands **1-6**

3. Framework Analogues of Josiphos-type Ligands 1-3

It is not uncommon that even small structural modifications, both of the ligating groups and the ligand backbone, significantly change the catalyst performance. With ligands **1–3** we intended to study the influence of the nature and flexibility of the side chain on the catalysis results. Compared to josiphos, ligands **1** and **2** restrict this flexibility while the opposite is expected for **3**.

3.1. *Synthesis of Homo- and Heteroannularly Bridged Ligands 1 and 2*

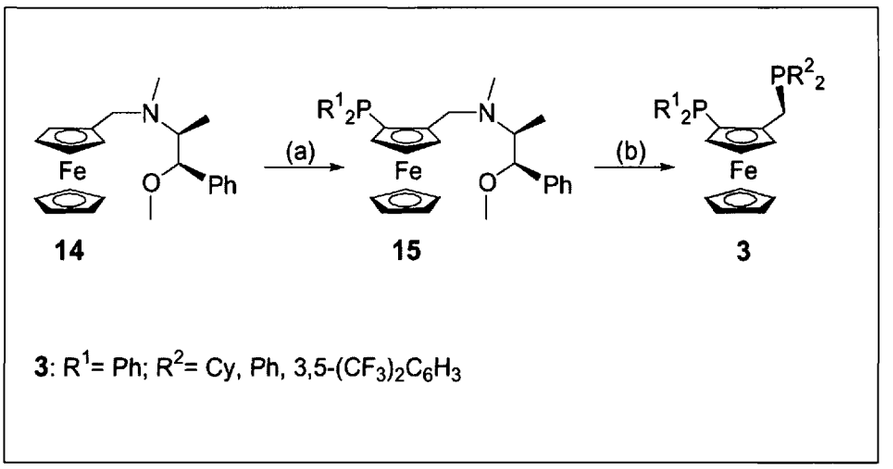
The structural similarity of **1** and **2** with josiphos is also reflected in their preparation procedures. In order to keep the synthetic flexibility as high as possible, the final steps in the synthesis of diphosphines **1** and **2** were carried out exactly as those described in Scheme 1 for josiphos-type ligands. *Ortho*-lithiation of enantiopure amines **8** or **12** and reaction with a proper electrophile such as a dialkyl or diaryl chlorophosphine gave the ppfa-analogous aminophosphines **9** or **13** (Scheme 2). A subsequent substitution of the dimethylamino group with a diaryl or dialkyl phosphine in acetic acid led to the final products, diphosphines **1** or **2**. As for the ferrocenylethyl-based ligands, this sequence allows a variety of functional groups to be attached to a given enantiopure homo- or heteroannular framework. While the last two steps in the synthesis of **1** and **2** are identical, the preparation of amines **8** and **12** differs significantly. Homoannular ketone **7** was prepared in its racemic form, enantiomers were separated by chromatography on triacetylcellulose as the chiral stationary phase and transformed in two steps to give **8** [11]. Amine **12**, however, was accessible in a multistep sequence from achiral heteroannular ketone **10** *via* a highly diastereoselective imine reduction (>99% d.e.) of intermediate **11** using 1-naphthylethyl amine as the chiral auxiliary [12]. Following the sequence outlined above, a number of aminophosphines, aminoalcohols [13] and diphosphines [10a] was prepared and structurally characterized. In addition, their coordination chemistry has been studied [14].



Scheme 2. Synthesis of homo- and heteroannular ligands **1** and **2**. (a) $LiAlH_4$; (b) $HN(CH_3)_2$, $AlCl_3$; (c) BuLi, $ClPR^1_2$; (d) HPR^2_2, AcOH; (e) $NpCH(CH_3)NH_2$; (f) $NaBH_4$; (g) $NaBH_4$, HCHO; (h) KOAc, AcOH; (i) $HN(CH_3)_2$

3.2. *Synthesis of Ligands 3 with a Ferrocenylmethyl Framework*

As is the case for **1** and **2**, diphosphines **3** are structurally related to josiphos. However, their preparation follows a slightly different route. Whilst the course of *ortho*-lithiation of Ugi's amine, **8** or **12**, is directed by the configuration of the stereogenic center of the side chain, in the case of **3** a chiral auxiliary is required. Recently, Kagan and co-workers reported the synthesis of such ligands [15] *via* a seven-step sequence starting from ferrocene carbaldehyde and an acetal as the chiral directing group [16]. Our approach makes use of O-methylephedrine as the *ortho*-directing group, a chiral auxiliary recently developed in our group [17]. Ferrocene derivative **14**, easily accessible in one step from O-methylephedrine and ferrocenylmethyl- trimethyl ammonium iodide, was found to react similarly to Ugi's amine. *Ortho*-lithiation with *tert*-BuLi in pentane and quenching with chlorophosphines gave aminophosphines **15** in 98% d.e. which could be transformed by nucleophilic replacement of the chiral auxiliary to the diphosphines **3** [18] (Scheme 3). It is interesting to note that, unlike with ppfa, the yield of this last step depends strongly on the nucleophilicity of the phosphine used (R^2 = $HPCy_2$ > $HPPh_2$ > $HP[3,5\text{-}(CF_3)_2)Ph]_2$). In summary, all ligands were obtained in three steps from commercially available ferrocenylmethyl-trimethyl ammonium iodide and O-methylephedrine in up to 77% overall yield (**3**: R^2 = Cy).



Scheme 3. Synthesis of diphosphines **3**. (a) *tert*-BuLi, $ClPR^1_2$; (b) HPR^2_2, AcOH

4. Biferrocene- and Ferrocene-Aryl-Based Ligands 4–6

Binaphthyl- and biphenyl-based derivatives, such as *binap* or *biphemp*, are very well established ligands for asymmetric catalysts. An analogous approach would be to replace their biaryl framework by a biferrocene or a ferrocene-aryl system. Although ligands with a biferrocene (e.g. *bifep* [19] or *trap* [5] ligands) or a ferrocenyl-aryl backbone (*e.g.* [20] [21]) are not entirely new, only a few representatives have been studied in asymmetric catalysis. For this reason, we intended not only to revisit the synthesis of bifep-type diphosphines (**4**) but also to prepare two groups of ligands with a new biferroceno or ferrocene-aryl backbone (**5** and **6**).

4.1. *Synthesis of 2,2''-Phosphino-Biferrocenes 4*

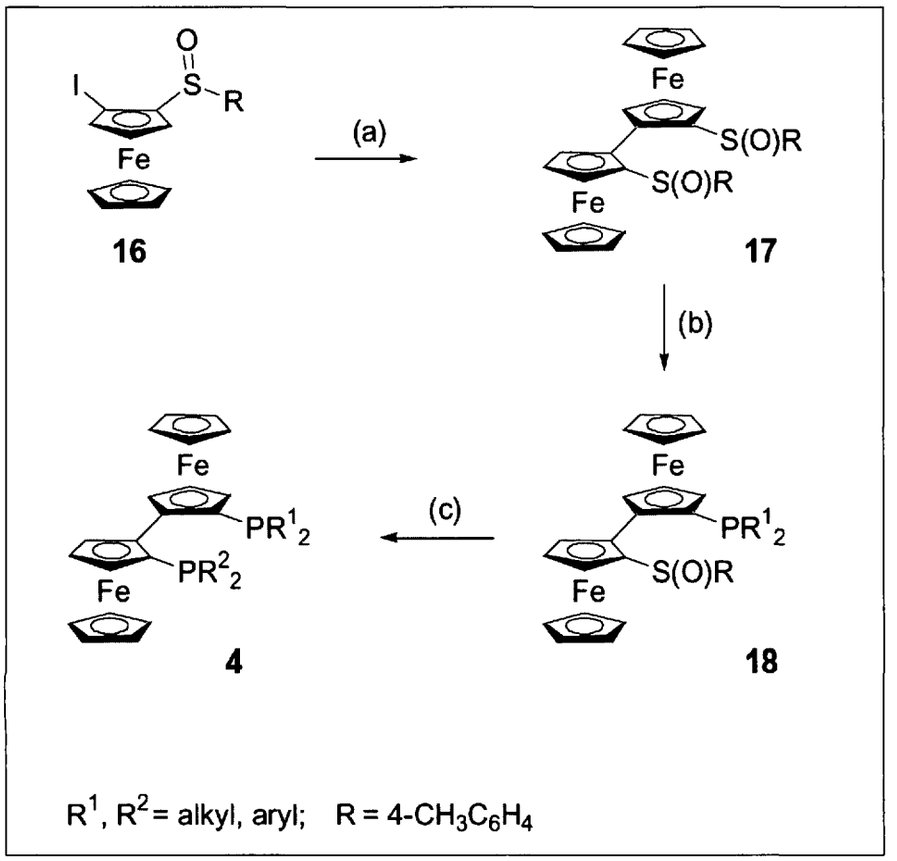
To the best of our knowledge, until now, only one example of 2,2''-diphosphino-biferrocenes, 2,2''-bis(diphenylphosphino)-1,1''-biferrocene (bifep) [19] and a few P-stereogenic analogues [22] have been described. In all cases the phosphino substituents were introduced to the ferrocene skeleton before the biferrocene unit was formed, thereby limiting the synthesis to C_2 symmetrical derivatives. In our new approach, we have inverted this order. By applying the elegant sulfoxide methodology originally developed by Kagan [23], it was possible to prepare enantiopure 2,2''-bis-(*p*-tolylsul-finyl)-1,1''- biferrocene **17** in one step from easily accessible **16** [23] and to subsequently replace the sulfinyl groups stepwise by phosphino substituents (**17**→**18**→**4**). Following this route, a number of C_1 and C_2 symmetrical diphosphines **4** were prepared [24] (Scheme 4). A conformational analysis of the $PdCl_2$ complex of bifep (**4**·$PdCl_2$; **4**: R^1 = R^2 = Ph) revealed that unlike the configurationally stable biaryl backbones of binap and biphemp the biferrocene unit of bifep is flexible. In solution, two differently populated P- and M-shaped conformers interconvert rapidly at room temperature. This behavior is not unexpected since the biferrocene unit lack proper substituents at the 5 and 5'' positions, thought to be required for configurational stability.

4.2. *Preparation of Biferroceno-azepine Ligands 5*

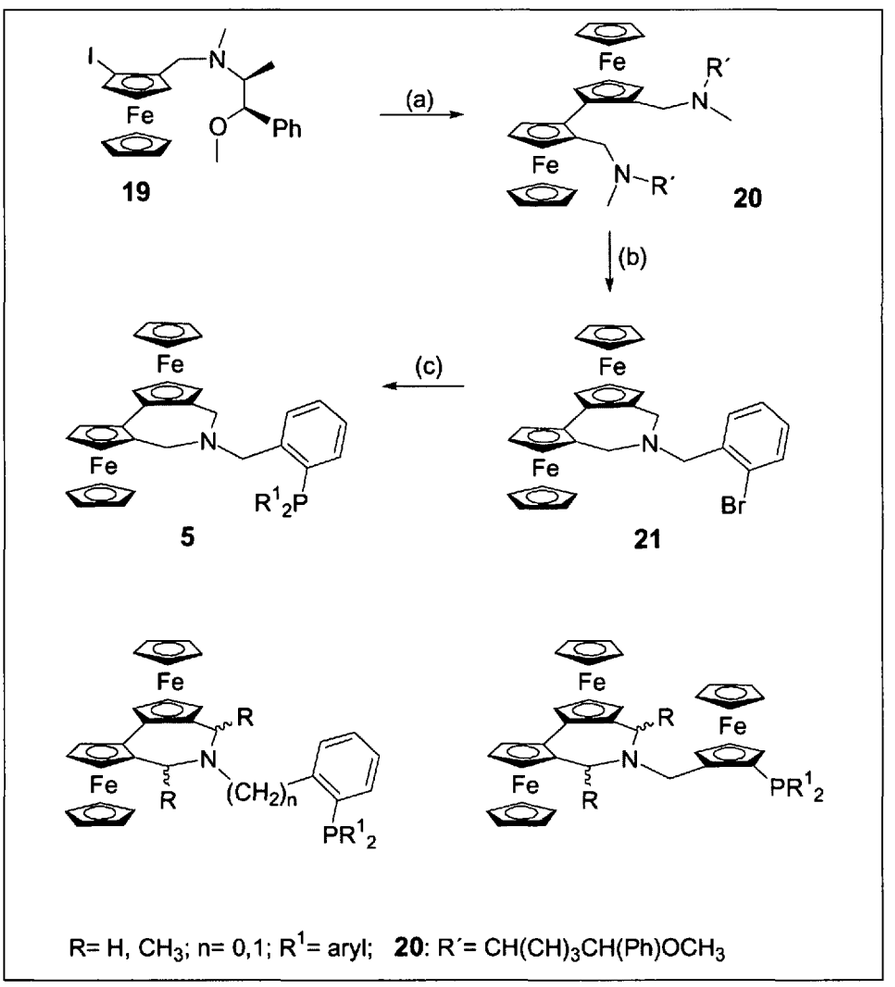
Although biaryl-azepine or the analogous P-compounds (especially binaphthyl derivatives [25][26]), are well known, their biferrocene counterparts are unprecedented. These ligands were synthesized following the modular sequence outlined in Scheme 5. Dimerization of iodo derivative **19**, accessible in one step from **14**, gave biferrocene intermediate **20**. Methylation with MeI, followed by a ring closure reaction with 2-bromobenzylamine led to azepine **21**. Exchange of bromide by proper phosphines resulted in the final products **5**. Structural variations were easily accessible by combining different ferrocene, amine and phosphino components (Scheme 5; bottom) [10b] [27]. We are confident that, with use of proper phosphines instead of amines, the corresponding P-compounds will also be accessible. As the biferrocenes **4**, ligands **5** do not correspond to their binaphthyl analogues from a structural point of view. This difference is especially pronounced for the conformation of their seven membered azepine rings, which are of local C_2 symmetry in the case of binaphthyl derivatives, whereas in ligands **5** C_1 symmetry with essentially coplanar ferrocene units is observed.

4.3. *Preparation of Ferrocenyl-Aryl Based Diphosphines 6*

The preparation of this new class of ligands starts from an enantiopure amine, *e.g.* from (1-dimethylaminoethyl)-ferrocene (Ugi's amine). In a Negishi coupling with 2-bromo-iodobenzene the ferrocenyl aryl backbone was formed (**22**). Subsequently, both the bromide (**23**) and the amino functionality (**24**) were replaced by phosphines. In order to prevent a ring closure reaction in step **23**→**24** the



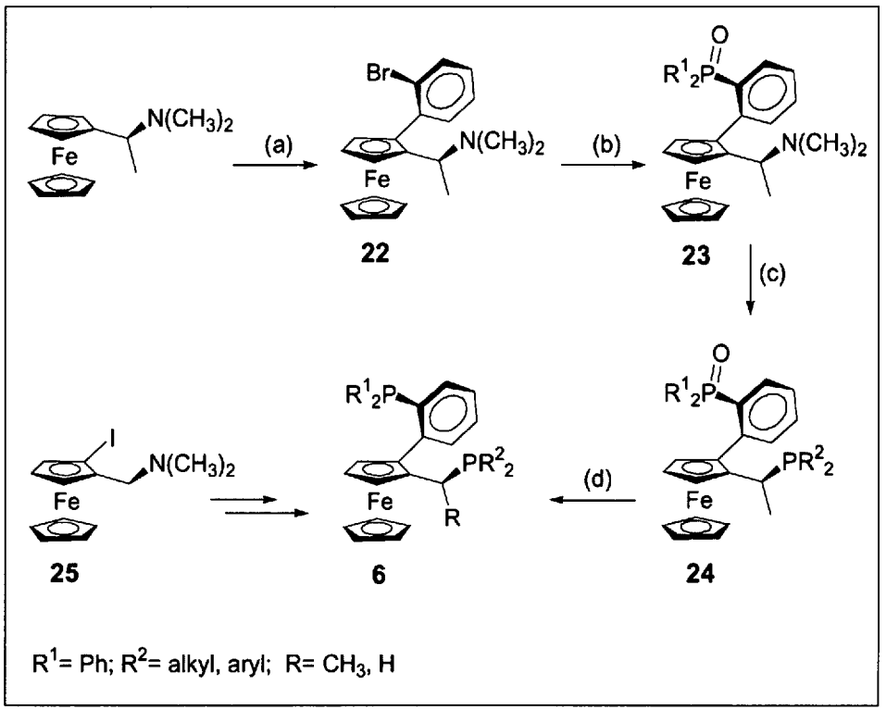
Scheme 4. Preparation of biferrocene ligands **4**. (a) Cu; (b) *tert*-BuLi, $ClPR^1_2$; (c) *tert*-BuLi, $ClPR^2_2$



Scheme 5. Preparation of biferroazepine ligands **5** and structural variations thereof (bottom). (a) Cu; (b) CH_3I, 2-$BrC_6H_4CH_2NH_2$·HCl; (c) BuLi, $ClPR^1_2$

phosphino functionality of **23** had to be oxidized to the corresponding phosphine oxide. Finally, reduction of **24** led to the desired diphosphines **6** (Scheme 6). A number of ligands with varying substituents R^2 = alkyl (Cy, *tert*-Bu) or aryl (Ph, 4-CH_3O-3,5-$(CH_3)_2C_6H_2$, 3,5 $(CF_3)_2C_6H_3$) was prepared [10a]. When this reaction sequence was started with enantiopure amine **25**, accessible in two steps from **14** [17], the corresponding ligands lacking centro chirality (Scheme 6, **6**: R = H) were obtained.

The molecular structure of complex **6**·$PdCl_2$ (**6**: $R^1 = R^2 = Ph$, $R = CH_3$) in the solid state shows the unique ligand geometry of this new ferrocenyl aryl diphosphines (Fig. 3) [10a][28].



Scheme 6. Preparation of ferrocenyl-aryl ligands **6**. (a) sec-BuLi, $ZnCl_2$, 1,2-BrC_6H_4I, $(Ph_3P)_2PdCl_2$; (b) BuLi, $ClPR^1_2$, H_2O_2; (c) HPR^2_2, AcOH; (d) $HSiCl_3$

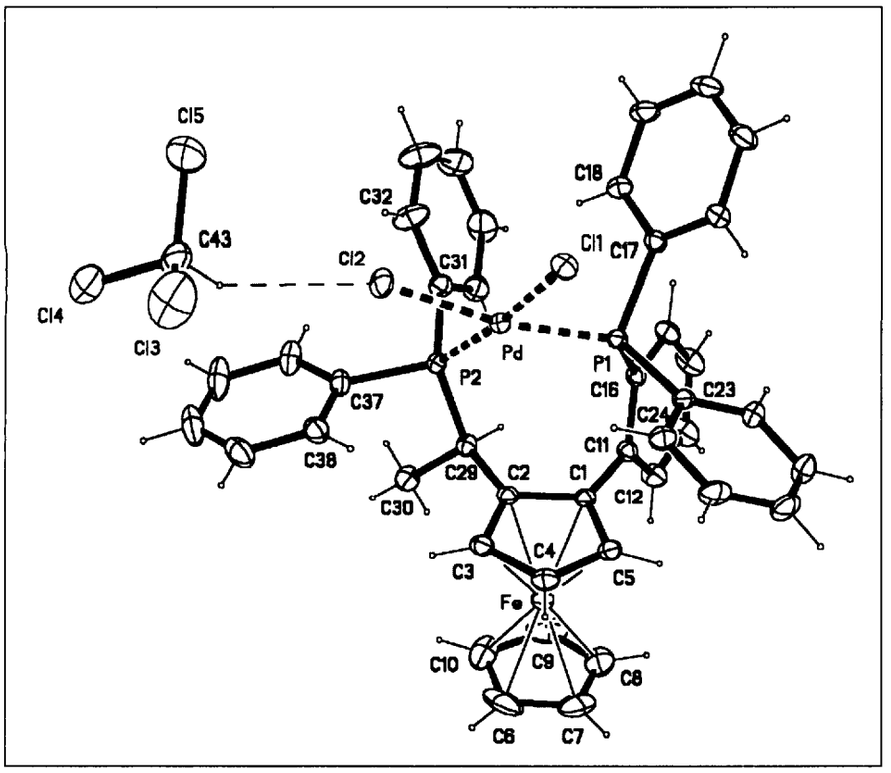


Fig. 3. Molecular structure of **6**·$PdCl_2$ (**6**: $R^1 = R^2 = Ph$, $R = CH_3$)

5. Summary

In conclusion, we have designed synthetic routes to six groups of ferrocene ligands for asymmetric catalysts. From a structural point of view, ligands **1–3** are closely related to josiphos-type derivatives, whilst **4–6**, based on biferroceno or ferrocenyl-aryl backbones, constitute independent classes of ligands not comparable to their biaryl analogues. For all groups of ligands extensive catalytic testing is in progress and will be published in due course.

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