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Towards new ferrocenyl ligands for asymmetric catalysis

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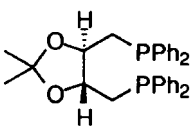
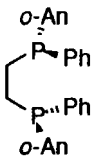
Abstract: Some new approaches for asymmetric synthesis of chiral ferrocenyl ligands are described. Many types of ferrocene compounds with planar chirality were prepared through diastereoselective ortholithiation, thanks to a chiral sulfoxide or chiral acetal auxiliary. Various mono- and diphosphines may be subsequently generated. In the sulfoxide route, a key intermediate is pure monolithioferrocene. A convenient procedure was set up, involving the isolation of stable tri-*n*-butylstannyl-ferrocene as a precursor of monolithioferrocene. The species Fc_2PH (Fc = ferrocenyl) and its borane protected derivative allowed to synthesize chiral diphosphines where the usual PPh_2 groups are replaced by the PFc_2 fragment.

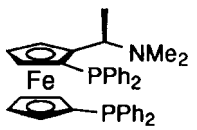
Asymmetric catalysis using organometallic complexes is in fast development and has reached its present state of high efficiency because of the availability of a wide range of chiral ligands coming either from the chiral pool or from synthetic transformations. Chiral chelating diphosphines played a special role in the early development of asymmetric catalysis (1). Some representative examples of chiral diphosphines are listed in Fig. 1, Diop (1971) being the first example and Duphos (1991) one of the very recent examples of important diphosphines. The chiral information arises from one or several asymmetric carbon or phosphorus atoms, or from axial or planar chirality. Moreover the chiral ligands can be of C_2 (Diop, Chiraphos, Binap or Duphos) or C_1 symmetry (Bppm, Bppfa or Norphos) and give excellent results in asymmetric catalysis.



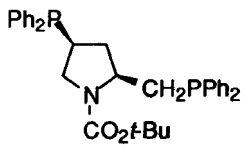
Diop, 1971 (2)
(C_2 symmetry)



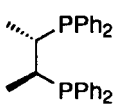
Dipamp, 1972 (3)
(C_2 symmetry)



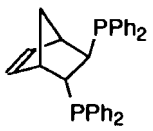
Bppfa, 1974 (4)
(C_1 symmetry)



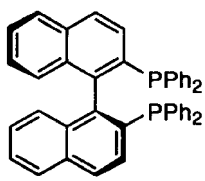
Bppm, 1975 (5)
(C_1 symmetry)



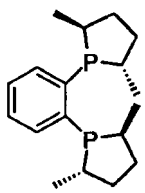
Chiraphos, 1977 (6)
(C_2 symmetry)



Norphos, 1979 (7)
(C_1 symmetry)



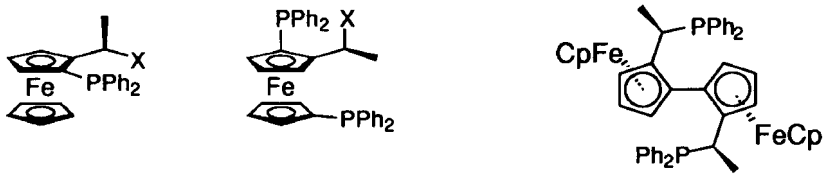
Binap, 1980 (8)
(C_2 symmetry)



Duphos, 1991 (9)
(C_2 symmetry)

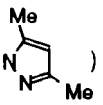
Figure 1. Chiral Diphosphines for Asymmetric Catalysis

In this article we shall concentrate on chiral ligands involving a *ferrocenyl fragment*. Many structural modifications are possible by combining central chirality and planar chirality. Some of the main compounds already prepared are indicated in Fig. 2.



Kumada, Hayashi, Ito 1975-1995
(X = NMe_2, OH, $NMe(CH_2)_2OH$, etc.)

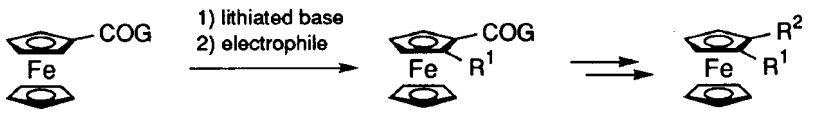
Ito 1991

Togni 1994
(X = PCy_2, 

)

Figure 2. Some Examples of Chiral Ferrocenylphosphines

We wanted to explore the possibility of creating new ferrocenyl structures by asymmetric synthesis, thus avoiding a resolution method. We also intended to use this approach to prepare new chiral ligands for asymmetric catalysis, especially chelating diphosphines. Our approach was based on the strategy of a chiral directing group for diastereoselective ortholithiation (Fig. 3).



COG = Chiral Orthodirecting Group

Figure 3. Chiral Orthodirecting Group Strategy

The chiral directing group should be removable, and if possible reusable. The classical route to ferrocene compounds with planar chirality is based on the pioneer work of Ugi *et al.* (10), who resolved the *N,N*-dimethyl-(ferrocenyl-eth-1-yl)-amine (Fig. 4) and realized a diastereoselective ortholithiation (92 % de). This amine, sometimes called the Ugi amine, was the immediate precursor of many chiral mono or diphosphines including the ferrocenyl moiety (5,11).

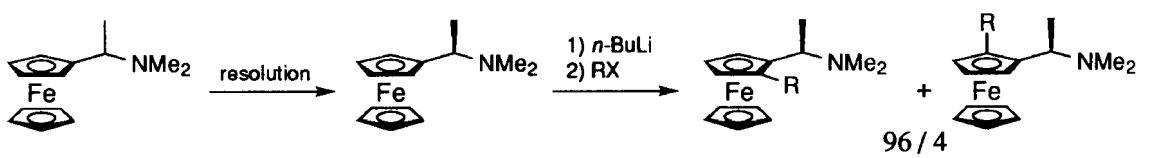


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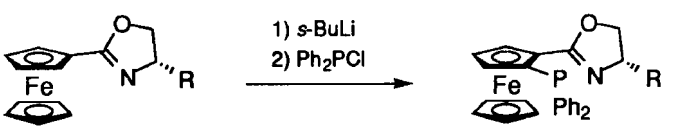
Figure 4. Diastereoselective Ortholithiation of the Ugi Amine

Subsequent to our work, diastereoselective ortholithiation of chiral ferrocenyl oxazolines has been described independently by three groups (12, 13, 14). In this way phosphinoferrocenyl oxazolines were prepared (Fig. 5), they are bidentate ligands.



R = *i*-Pr (95 % de)
R = *t*-Bu (84 % de)
R = Ph (99 % de)

Figure 5. Phosphinoferrocenyloxazolines via Diastereoselective Ortholithiation

ASYMMETRIC SYNTHESIS OF FERROCENES WITH PLANAR CHIRALITY

The chiral sulfite approach to ferrocenyl sulfoxides

We described in 1991 a new method to prepare chiral sulfoxides (15). It involves two successive nucleophilic substitutions at the sulfur of a chiral sulfite available in two steps from (*S*)-ethyl lactate. It is possible to isolate the sulfinate intermediate which is formed with full inversion of stereochemistry at sulfur. *t*-Butylmagnesium bromide reacts regioselectively as shown in Fig. 6. The corresponding *t*-butylsulfinate is an excellent starting material for the preparation of many *t*-butyl sulfoxides (15). By the use of monolithioferrocene it is possible to synthesize in high yield (*S*)-*t*-butyl-ferrocenyl-sulfoxide (ee > 99 %) (16), the absolute configuration being the result of an inversion of stereochemistry during the substitution, as observed in the Andersen method (17).

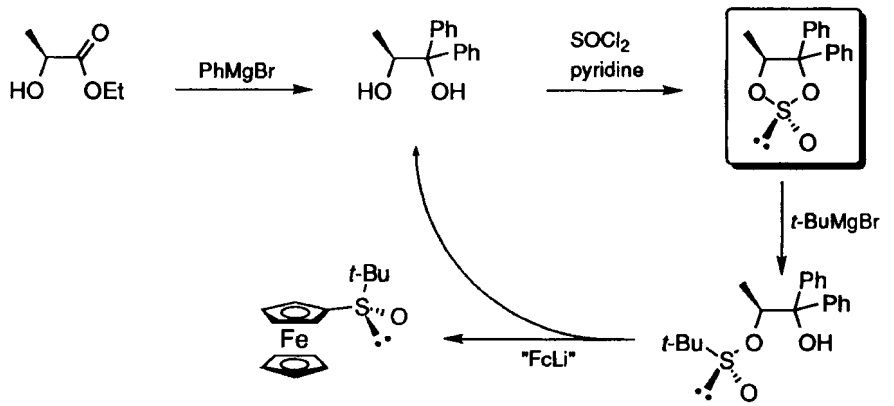


Figure 6. Cyclic Sulfite Route to Chiral Ferrocenyl Sulfoxides

The classical Andersen method was also applied to the synthesis of (*S*)-ferrocenyl-*p*-tolyl-sulfoxide (Fig. 7). However it was obtained with ee's ranging from 10 % to 90 %, depending on the experimental procedure. The best way is to carry out the reaction at low temperature (– 24 °C), and to avoid an excess of lithioferrocene (which reacts with the sulfoxide in a substitution process giving rise to racemization).

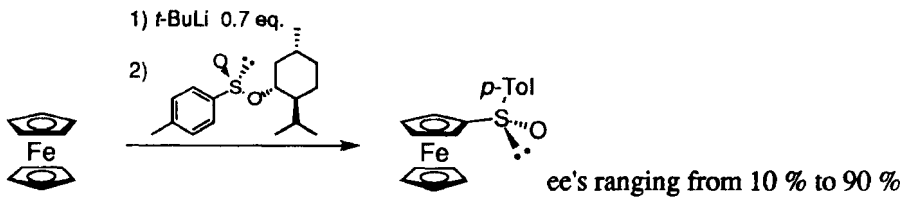


Figure 7. Reaction of Lithioferrocene with Andersen's Sulfinate

Ferrocenyl sulfoxides from oxidation of sulfides

We developed a method of asymmetric oxidation of sulfides by hydroperoxides in the presence of a stoichiometric amount of a chiral titanium complex (18). This complex was formed by the combination Ti(O*i*-Pr) / DET(diethyl tartrate) / H_2O = 1 / 2 / 1. This method was applied to the oxidation of various ferrocenyl sulfides (19). We discovered that the enantioselectivity could exceed 99 % ee (measured by hplc on a chiral Daicel OD-H stationary phase) by a careful control of the experimental conditions during the formation of the titanium complex (19). Some representative examples are indicated in Fig. 8. The starting sulfides were prepared by action of monolithioferrocene on various disulfides (RSSR).

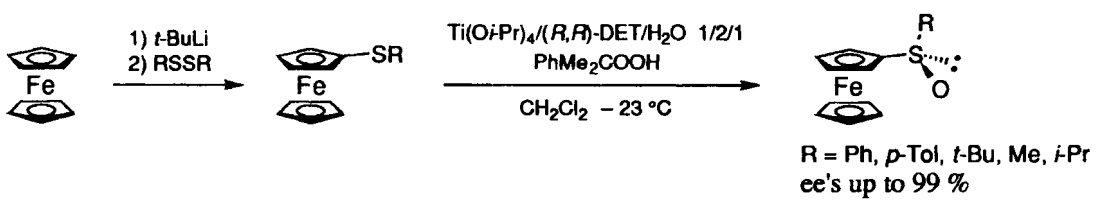


Figure 8. Asymmetric Oxidation of Ferrocenyl Sulfides

Induction of planar chirality by means of chiral ferrocenylsulfoxides

(*S*)-*t*-Butyl ferrocenyl sulfoxide was easily deprotonated in the ortho position with high diastereoselectivity (96 % de), as evidenced by quenching by various electrophiles. Methyl iodide led to *t*-butyl-(2-methyl-ferrocen-1-yl)-sulfoxide whose stereochemistry was established by X-ray analysis (16).

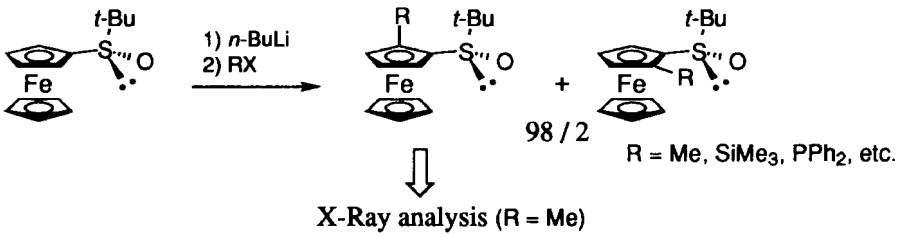


Figure 9. Diastereoselective Ortholithiation of Chiral Ferrocenyl Sulfoxides

The lithiation of (*S*)-*t*-butyl-ferrocenyl-sulfoxide by one or two equivalent of *n*-BuLi at – 78 °C provided the mono and diphosphines of Fig. 10. Catalytic hydrogenation of dehydroamino acids by a rhodium complex involving the diphosphine gave a low yield of racemic product. However, a palladium complex catalyzed the asymmetric allylic amination by benzylamine of an allylic acetate (40 % ee).

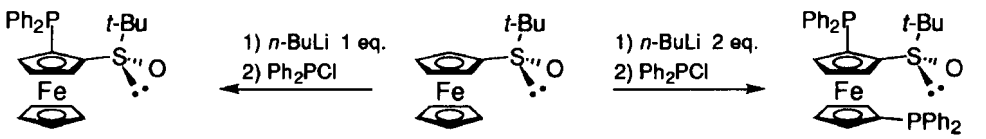


Figure 10. Diphenylphosphine Ligands

Ortholithiation of (*S*)-ferrocenyl-*p*-tolyl-sulfoxide by *n*-BuLi is not clean, but occurs with a high diastereoselectivity (98 % de) when using LDA (Fig. 11). There is here an additional and convenient route to prepare many ferrocenyl sulfoxides with planar chirality.

The sulfoxide group is a powerful diastereoselective and orthodirecting unit in the ferrocene family. However, in order to be fully general, the sulfinyl moiety has to be replaced when needed by an other group. We found that it is possible to do so in some cases (20), after oxidation to the sulfone (Fig. 11).

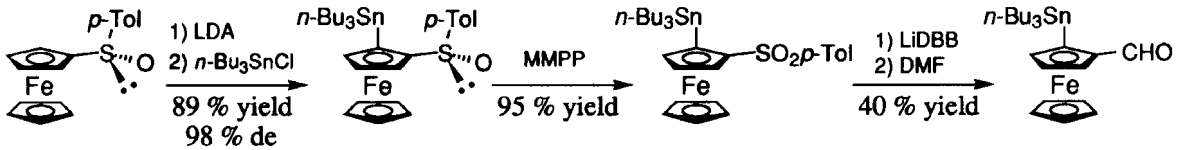


Figure 11. Replacement of the Sulfinyl Moiety

Chiral ferrocenyl acetal as a key precursor to ferrocenes with planar chirality

A more direct route to ferrocene with planar chirality was needed. This has been realized by the transformation of ferrocenecarboxaldehyde into a chiral acetal deriving from (*S*)-1,2,4-butanetriol (21) (Fig. 12). The remaining hydroxyl group was subsequently protected by O-methylation.

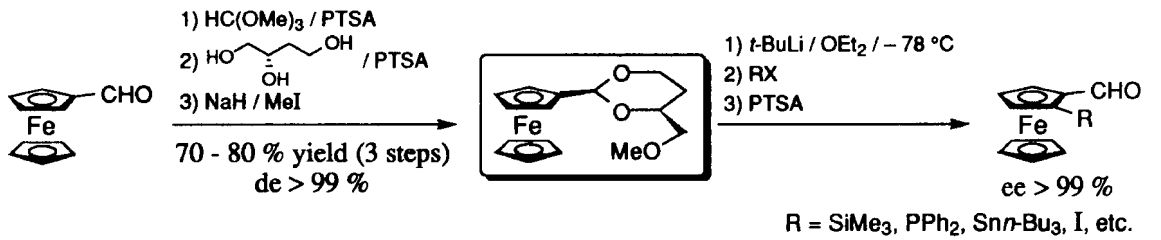


Figure 12. Chiral Acetal Route to Ferrocenes Bearing Planar Chirality

The methoxymethyl acetal was ortholithiated with *t*-BuLi in diethyl ether at – 78 °C. The resulting organolithium intermediate was trapped by a wide range of electrophiles. ^{1}H NMR analysis of the crude material showed only one diastereomer, meaning de > 99 %. A correlation was established with some reference compounds by the choice of the electrophilic reagent followed by acidic hydrolysis to generate the aldehyde function. The comparison of the specific rotation with the known (*S*)-2-formyl-1-trimethylsilyl-ferrocene (22) and (*S*)-1-carbomethoxy-2-formyl-ferrocene (23) gave the absolute configuration of the compounds and confirmed that the ee's (and de's) are higher than 98 – 99 %.

The aldehydes thus obtained could be further transformed through nucleophilic additions to the carbonyl group (24) or through palladium catalyzed cross-coupling reactions (when R = Sn*n*-Bu$_3$ or I). Some of the ferrocene derivatives with planar chirality which were synthesized by this route are indicated in Fig. 13.

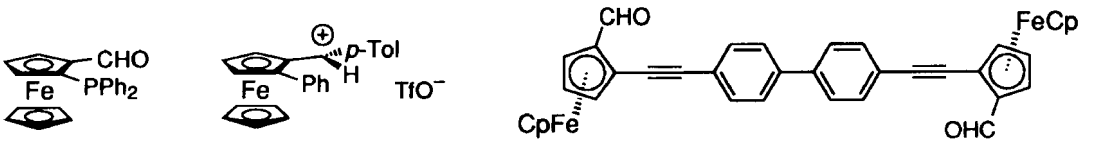


Figure 13. Some Chiral Ferrocenes Obtained by the Acetal Route

Amongst them is (*S*)-1-diphenylphosphino-2-formyl-ferrocene. This compound is a useful starting material for the preparation of many types of diphosphines. The pinacolization of the phosphinoaldehyde by diidosamarium, a powerful monoelectronic donor (25), occurred very rapidly (Fig. 14). A mixture of three diastereomeric diols was formed unselectively. The three dihydroxy diphosphines were separated by flash chromatography on silica gel. Each one was checked as ligand on *in situ* rhodium complex "RhClL". The three catalysts provided quite high ee's (90 %, 85 % and 80 % respectively) in asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid into (*R*)-*N*-acetyl-phenylalanine. The ketalization by acetone succeeded only on the diol diphosphine which gave above the most enantioselective catalyst. Unfortunately the corresponding rhodium complex provided only 45 % ee in the formation of (*R*)-*N*-acetyl-phenylalanine.

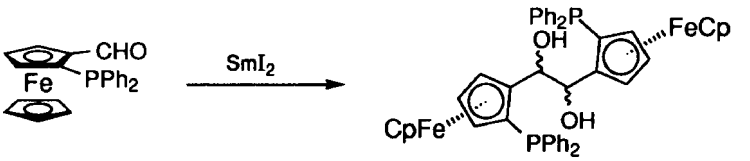


Figure 14. SmI_2 Mediated Pinacolization

The condensation of (*S*)-1-diphenylphosphino-2-formyl-ferrocene and 1,2-diaminoethane afforded a bis-diphenylphosphino bis-imine compound (Fig. 15) which gave ruthenium (II) and copper (I) complexes (26). ^{1}H and ^{31}P NMR unambiguously established that ruthenium is fully complexed by the two nitrogens and the two phosphorus, giving a C_2 symmetry chelate. An electrochemical study of the ruthenium complex was in full agreement with a tetradentate structure. The cyclic voltammogram showed two waves, a reversible oxidation at + 0.25 V (Vs AgCl/Ag) for ruthenium oxidation ($Ru^{2+} \rightarrow Ru^{3+}$) followed by the reversible iron oxidation ($Fe^{2+} \rightarrow Fe^{3+}$). ^{31}P NMR of the copper complex showed a broad singlet, which could be indicative of an equilibrium between two tridentate complexes.

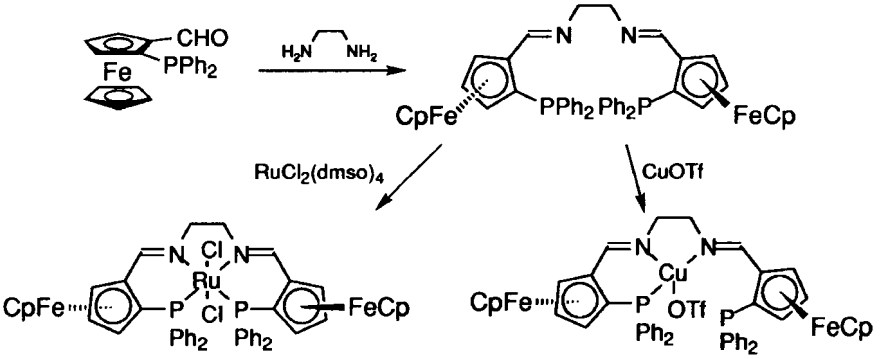


Figure 15. Complexes of a Ferrocenyl Ligand

IMPROVEMENT OF THE PREPARATION OF MONOLITHIOFERROCENE AND APPLICATION TO PHOSPHORUS CHEMISTRY

Lithioferrocene and tri-*n*-butylstannyl-ferrocene

As discussed above, monolithioferrocene is a key reagent in the preparation of ferrocenylsulfoxides. Unfortunately monolithiation of ferrocene is a difficult process, because of the competitive formation of 1,1'-dilithioferrocene. There are many reports of lithiation by *n*-BuLi/ether, with yields in the range of 25 % (for example see refs 27-28). We improved the yield in monolithioferrocene to a value of 60 % by using *t*-BuLi/THF at 0 °C (29). A further improvement was claimed to be afforded by lowering the temperature at – 20 °C (30). Finally we found recently that the best compromise is the system *t*-BuLi/THF/hexane at 0°C (31), giving around 70 % to 80 % of monolithioferrocene (however mixed with some dilithioferrocene and ferrocene). In many cases it is necessary to use a well defined quantity of monolithioferrocene (as in the Andersen method, *vida supra)*. We found that in our optimized conditions of monolithiation, electrophilic quenching by *n*-Bu_3SnCl allowed a clean separation of $FcSnn\text{-}Bu_3$ (Fig. 16). The compound was isolated by distillation under reduced pressure in 70 % yield, on a large scale. It is stable and can be be stored. It gives a smooth transmetalation with *n*-BuLi at – 78 °C, providing an exact amount of monolithioferrocene for further synthetic transformations into various monosubstituted ferrocenes.

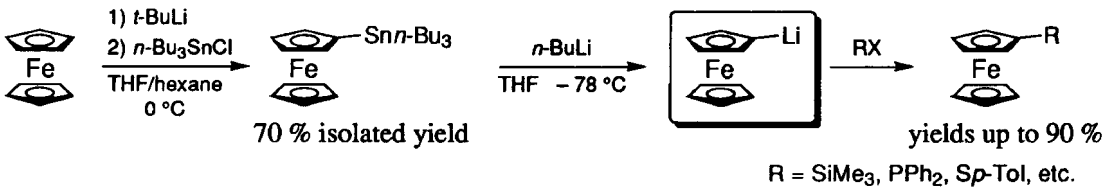


Figure 16. New Route to Monolithioferrocene

For example monolithioferrocene obtained in this way gave an excellent yield in the Andersen method, into (*S*)-ferrocenyl-*p*-tolyl-sulfoxide of 98 % ee (Fig. 17). Treatment by iodine gave iodoferrocene, and transformation into cuprate followed by oxidation according to the Lipshutz procedure (32) led to 1,1''-biferrocenyl.

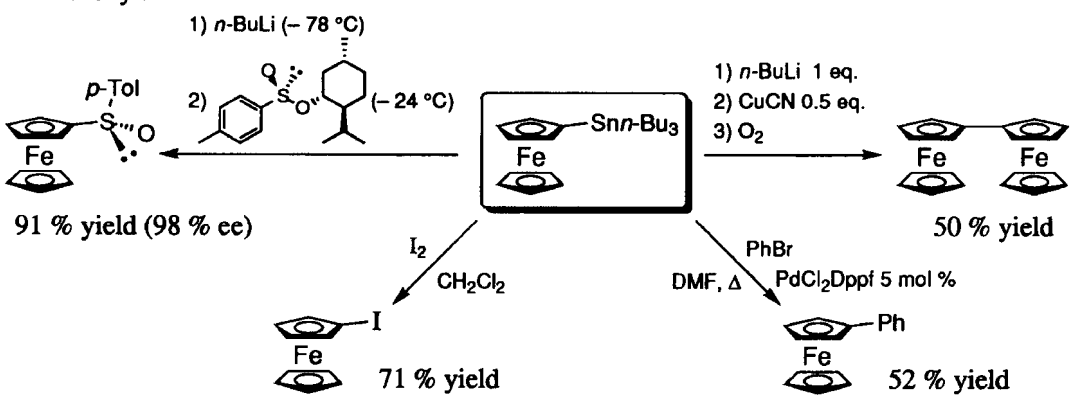


Figure 17. Chemistry of Tri-*n*-butylstannyl-ferrocene

Diferrocenylphosphine derivatives

We recently devised the preparation of diferrocenylphosphine, its borane protected derivative, as well as the deprotonated analogs (33). The key-step is the reaction of FcLi on controled amounts of $P(OPh)_3$ (Fig. 18). The borane deprotection occurred quantitatively by treatment with Dabco.

Formation of trisferrocenyl phosphine (Fc_3P) was also achieved by reaction of monolithioferrocene with $P(OPh)_3$.

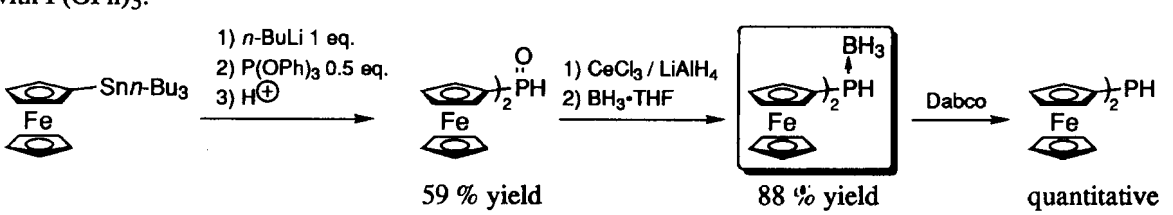


Figure 18. Synthesis of Diferrocenylphosphine Derivatives

The borane protected diferrocenyl phosphine was easily transformed into its potassium salt by *t*-BuOK (Fig. 19). This potassium phosphide has nucleophilic properties and allowed the preparation of the ferrocenyl analog of Diop in good yield, after removal of the borane protection by Dabco. An isolable cationic rhodium complex of this diphosphine was prepared. The complex catalyzed asymmetric hydrogenation of (*Z*)-α-acetamidocinnamic acid (40 % ee). This ligand is under examination in various asymmetric catalytic reactions. Synthesis of other ferrocenyl analogs of standard diphosphines such as Skewphos (Bdpp) are in progress, by using $Fc_2P(BH_3)K$ as the key reagent.

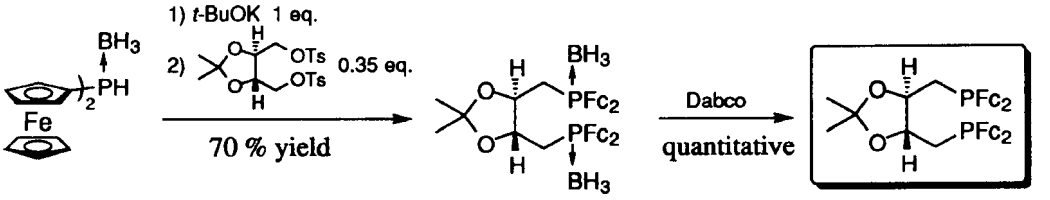


Figure 19. Chiral Bis(diferrocenylphosphines): New Ligands for Asymmetric Catalysis

CONCLUSION

The ferrocene skeleton is unique in allowing one to introduce chirality in a large variety of molecules interesting for their properties as ligands, as electrochemical derivatives, or as materials (34). The ferrocene chemistry developed above (35) allowed to prepare various classes of ferrocene compounds with planar chirality having very high enantiomeric excess and predictible absolute configuration. By this way new diphosphines or new types of chiral ligands become available. Monolithioferrocene is a key starting material for many syntheses of monosubstituted ferrocenes, the detour *via* FcSn*n*-Bu3 proved to be very valuable and also allowed to develop the synthesis of diferrocenylphosphine and derivatives. These later are useful reagents for introducing the diferrocenylphosphine moiety into chiral molecules.

Acknowledgements

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