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Recent advances in the generation of non-racemic ferrocene derivatives and their application to asymmetric synthesis

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Contents

1. Introduction

Until recently, the principle method available for synthesising non-racemic ferrocene derivatives utilises the highly diastereoselective lithiation of *N,N*-dimethyl-1-ferrocenylethylamine **1** followed by introduction of an appropriate electrophile, such as chlorodiphenylphosphine (Scheme 1). Depending upon the lithiation conditions, this can result in either the monophosphine **2** or diphosphine **3**, which

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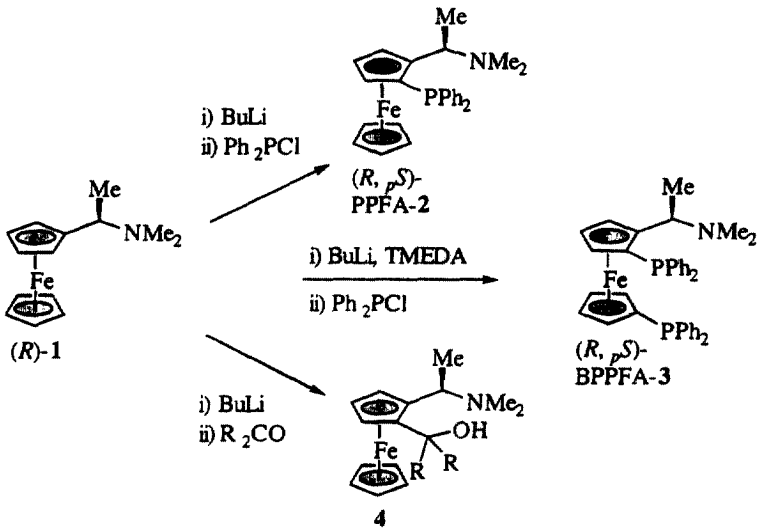
are themselves starting materials for a large array of derivatives obtained via stereospecific replacement of the dimethylamino unit. Such compounds have been successfully applied as ligands for numerous catalytic asymmetric reactions including organometallic cross-coupling, allylic alkylation, and especially the aldol reaction of α-isocyanocarboxylates. Alternatively, quenching the lithiation with ketones yields ferrocenyl amino alcohols **4**, many examples of which have been applied as catalysts for the addition of dialkylzincs to aldehydes. This and other aspects of the chemistry of chiral ferrocene derivatives have been extensively reviewed covering the literature up until 1993.[1]



Scheme 1.

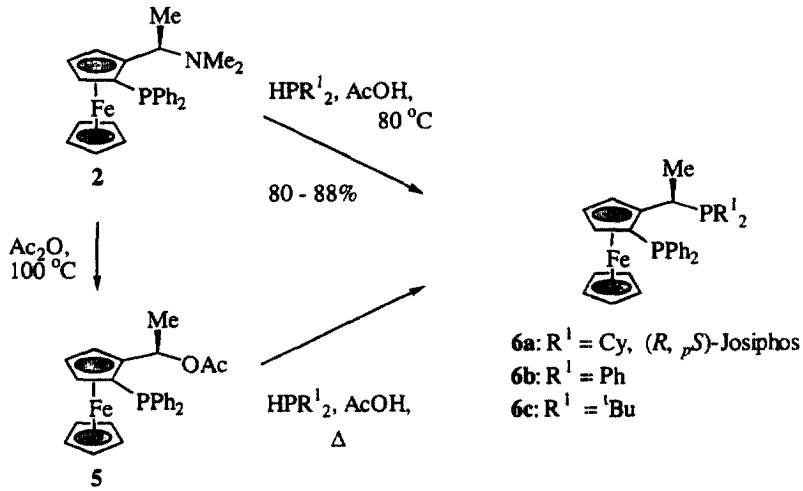
Since this date, there has been a resurgence of interest in the synthesis and application of chiral ferrocene derivatives. Although many of these methods also rely upon **1** as the starting material (Section 2), there has been a spate of publications on alternative *ortho*-directing groups for the synthesis of non-racemic ferrocenes displaying planar chirality (Section 3). In addition, several new methods have been reported for the highly enantioselective generation of α-stereogenic centres (Section 4). Overall, these new methods, together with lipase mediated resolutions (Section 5), have led to the synthesis of several new classes of ligands that are proving extremely effective in asymmetric catalysis, as are the heteroatom containing ferrocene derivatives (Section 6) and other miscellaneous diphosphines (Section 7). The aim of this work is to provide a comprehensive review of this recent activity covering the period from 1994 until the end of 1997.[2]

2. Ligands derived from *N,N*-dimethyl-1-ferrocenylethylamine

2.1. By nitrogen–phosphorus exchange

New asymmetric diphosphines **6** were prepared by heating the acetate **5** with an appropriate secondary phosphine in glacial acetic acid.[3] An improvement over this method, which does not require the intermediate acetate **5** (and therefore removes one step), involves the substitution of the amine **2**, directly to the diphosphines **6a–c** (Scheme 2).[4]

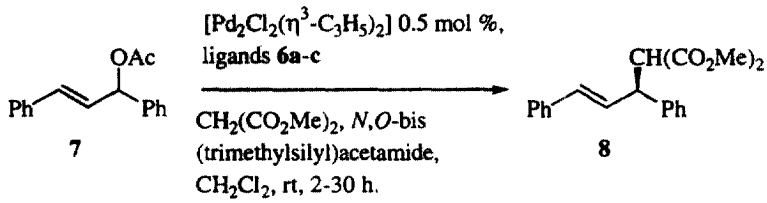
This route to ferrocenyldiphosphines allows the separate introduction of two different phosphorus groups and provides access to a large number of ligands with differing electronic and steric properties.[3]



Scheme 2.

This is not the case with the method for synthesising 1,1′-ferrocenyldiphosphine ligands such as **3**, as the phosphorus groups were introduced simultaneously in a one-pot reaction (Scheme 1).[1]

The new ligand **6a** (Josiphos) was subsequently applied to the Rh-catalysed asymmetric hydrogenation of methyl acetamidocinnamate, ethyl 3-oxobutyrate and dimethyl itaconate, all of which proceeded quantitatively and with excellent enantioselectivities (96–99% e.e.). The Rh-catalysed hydroboration of styrene also proceeded with an excellent degree of selectivity (91.5% e.e.). When the ligands **6a–c** were used in the catalytic allylic alkylation of **7** to give **8**, it was found that **6b** and **6c** exhibited significantly lower selectivities (66 and 81% e.e. respectively), and catalytic activities approximately one order of magnitude less than those exhibited by **6a** (93% e.e., Scheme 3).

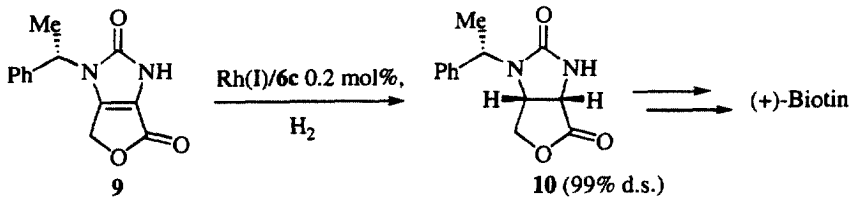


Scheme 3.

In the case of **6c**, the lower activity is thought to be due to the enhanced steric hindrance of the *tert*-butyl groups. However, this argument cannot be applied to **6b** as the phenyl and cyclohexyl groups are of similar size. Rather, it is thought that the modest enantioselectivity is a result of the electronic similarity of the two phosphorus moieties, and this illustrates the advantage of being able to introduce these separately.

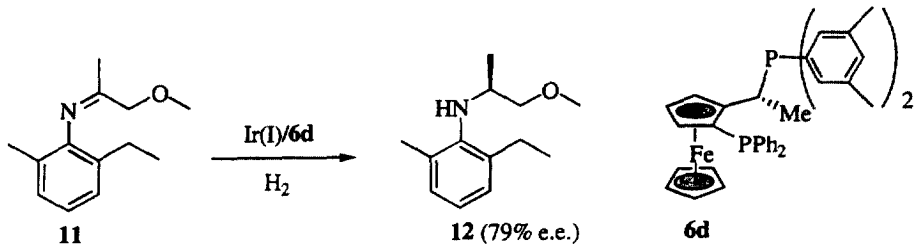
An example of the industrial importance of these ligands was recently revealed by Lonza, who used ligand **6c** in the industrial synthesis of (+)-Biotin, via the very high diastereoselective hydrogenation of **9** to give **10** (Scheme 4).[5]

A related ligand **6d** is the chiral component in the highly active Ir(I)-catalysed asymmetric hydrogenation of imine **11** to give **12**, an intermediate in the synthesis of (*S*)-Metolachlor, a commercially important herbicide. Although the enantiomeric excess is only 79%, this is tolerable for an agrochemical. More important though is the activity of the catalyst, as the ratio of the substrate to Ir(I) is >1,000,000:1 (Scheme 5).[6]



9 10 (99% d.s.)

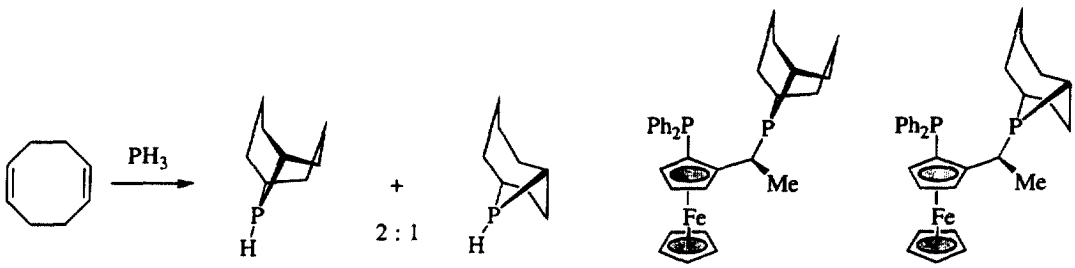
Scheme 4.



11 12 (79% e.e.) 6d

Scheme 5.

The replacement of the amine with phosphorus groups is not limited to the use of simple dialkyl- or diarylphosphines. Recently, the use of a 'forgotten' phosphine, 9-phospha-9*H*-bicyclo[3.3.1]nonane **13a** ('phobane'), as a sterically less bulky equivalent of dicyclohexylphosphine was reported.[7] The 'phobane' is produced from the reaction between 1,5-cyclooctadiene and phosphine (PH_3). This reaction yields a 2:1 mixture of the major [3.3.1] isomer **13a**, and the minor [4.2.1] isomer **13b** (Scheme 6).



13a 'Phobane' **13b** **14a** **14b**

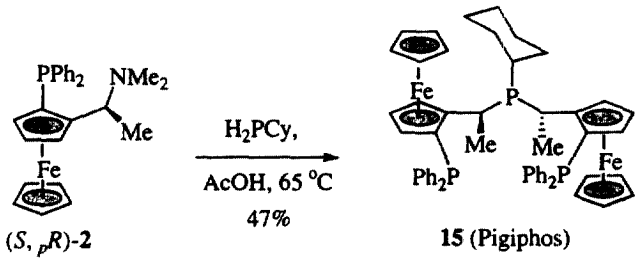
Scheme 6.

Use of two equivalents of this mixture with (S_pR)-**2** in hot acetic acid for two hours gave a 4:1 mixture of the ferrocenyldiphosphines **14a** and **14b**. However, repetition of the reaction with 10 equivalents of the secondary phosphine mixture led to exclusive, kinetically controlled, formation of **14a** which was isolated in 68% yield.

Ligand **14a** was employed in the palladium catalysed allylic alkylation between **7** and dimethyl malonate for which the highest enantioselectivity obtained (85% e.e.) is inferior to that obtained with **6a** (Josiphos, 93% e.e.).[4] This lower selectivity may be due to the conformational flexibility of palladium complexes of **14a**, as revealed by NMR studies, resulting in a less well defined environment around the metal during catalysis.[7]

Recently, the same group has applied the general method for the synthesis of 'phobane' and 'Josiphos' type ferrocenyldiphosphine ligands, to the synthesis of the chiral tridentate bisferrocenyl ligand **15** (Pigiphos).[8] The reaction simply consists of heating two equivalents of (S_pR)-**2** with cyclohexylphosphine in acetic acid at 65°C. Again the amine groups are replaced by the cyclohexylphosphine with retention of configuration to give the product in satisfactory yield (Scheme 7). A number of derivatives of **15** containing methyl and trifluoromethyl substituents on the diarylphosphine groups were later reported.[9]

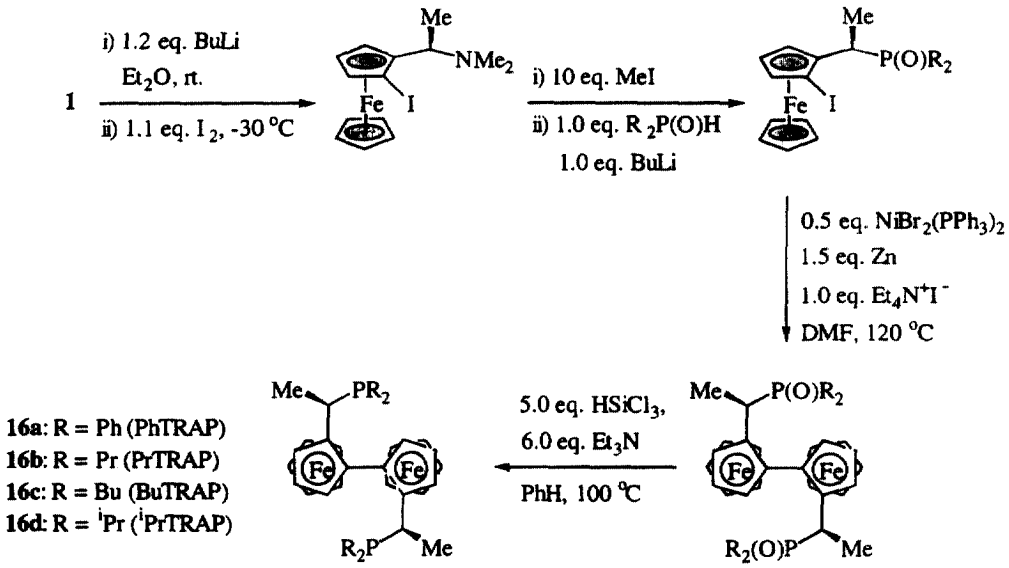
Together with **15** these ligands were used in the synthesis of cationic Ru(II) complexes containing chloride and acetonitrile ligands.



Scheme 7.

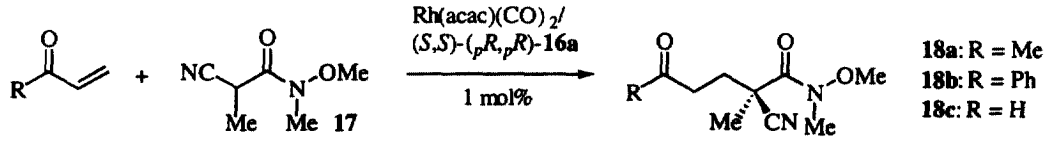
Their subsequent use in the asymmetric transfer hydrogenation of acetophenone in propan-2-ol, gave mostly poor enantiomeric excesses (5.6–21.0%), with two reasonable exceptions (64.6 and 71.7%) using {*fac*-[(*S*)-(*pR*)-Pigiphos]Ru(CH_3CN)$_3$}(PF_6)$_2$.

The principle of stereospecific replacement of the dimethylamino group by a phosphine was instrumental in the synthesis of *trans*-chelating diphosphine bisferrocene systems known as TRAP ligands **16** (Scheme 8).



Scheme 8.

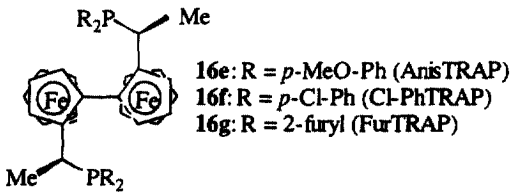
Shortly after the synthesis of **16a** (in 16% yield),[10] it was reported that it performed as an effective ligand for the Rh-catalysed asymmetric Michael addition of α-cyanocarboxylates to vinyl ketones and acrolein.[11,12] This reaction was extended to an α-cyano Weinreb amide **17**, from which the products **18** (89–94% e.e.) were readily converted into a range of other derivatives on amide manipulation (Scheme 9).[13]



Scheme 9.

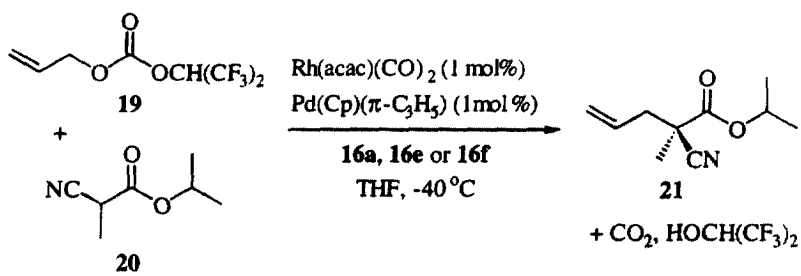
It was suggested that the bulkiness and rigidity of the phenyl substituents on the phosphorus atoms are not always required for asymmetric reactions, and that they may indeed prevent an effective interaction of reactants with the catalyst. This promoted the synthesis of a number of similar *trans*-chelating chiral diphosphine systems bearing flexible P-alkyl substituents, **16b**, **16c**, **16d** (25–34% from **1**), by the same method as that used for **16a** (Scheme 8),[14] the yields of these reactions being later improved to 51–56%.[15] The X-ray crystal structure of *trans*-[RhCl(CO)(BuTRAP)] revealed a nearly planar coordination geometry about the metal, with a P–Rh–P bite angle of 164.4°. This structure also revealed the chloride and carbonyl ligands to be deep within the cavities created by the bisferrocenyl backbone and the butyl groups. Both **16b** (R=Pr) and **16c** (R=Bu) gave 92% e.e. for the Rh(I)-catalysed asymmetric hydrosilylation of acetophenone, indicating that the terminal methyl groups of the BuTRAP are not important for stereoselectivity. Significantly, the reduction of acetophenone in the presence of ^{i}PrTRAP and PhTRAP, which carry bulkier substituents on the phosphorus atoms, was much less enantioselective (1 and 15% e.e. respectively). The BuTRAP ligand **16c** also proved effective for the hydrosilylation of saturated ketones containing one bulky substituent (80–95% e.e.). In addition, the corresponding EtTRAP[15] ligand has been successfully applied to rhodium catalysed ketone hydrosilylation of α-, β- and γ-keto esters (80–93% e.e.),[16] and to a variety of symmetrical diketones from which the resulting diols were obtained selectively (89–99% e.e.) together with a generally small amount of the *meso*-diol (4–31%).[17] Furthermore, EtTRAP and BuTRAP **16c** are also effective ligands with rhodium for the hydrogenation of (*Z*)- and (*E*)-β-disubstituted α-acetamidoacrylates respectively (77–86% e.e.),[18] and EtTRAP gives an e.e. of 96% for the product obtained on hydrogenation of dimethyl itaconate.[19]

More recently the same group has reported an improved synthesis of PhTRAP **16a** (51% from **1**), together with the synthesis of *para*-substituted PhTRAP ligands **16e/f** and a 2-furyl derivative **16g**,[20] and also the use of the ligands **16a**, **16e** and **16f** in the enantioselective Rh–Pd two-component catalysed allylic alkylation of activated nitriles.[21]



16e: R = *p*-MeO-Ph (AnisTRAP)
16f: R = *p*-Cl-Ph (Cl-PhTRAP)
16g: R = 2-furyl (FurTRAP)

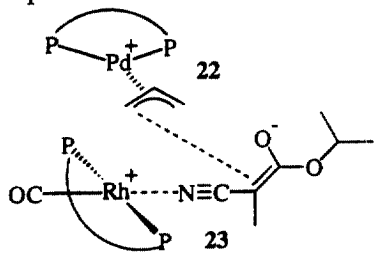
In this process, allylation of cyano ester **20** with the fluorinated carbonate **19** to produce **21**, proceeded with excellent enantioselectivities (93–99% e.e.) for ligands **16a** and **16e** (Scheme 10).



Scheme 10.

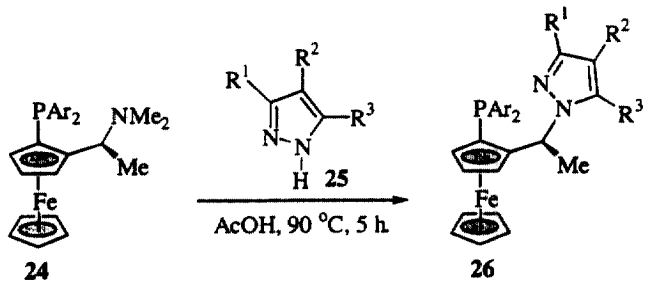
However, use of the electron-deficient ligand **16f** gave a much slower reaction with poor enantioselectivity (54% e.e.). It was thought that the electron withdrawing effects of the *para*-chloro groups reduced the nucleophilicity of the Rh(I)-coordinated enolate **23**, for the Pd(II)-allyl complex **22**. The high enantioselectivity of this reaction, resulting from excellent discrimination of the two faces of the

prochiral enolate, is entirely due to the ligand environment about rhodium. Control experiments revealed that the TRAP ligands coordinated to palladium do not contribute to the selectivity.



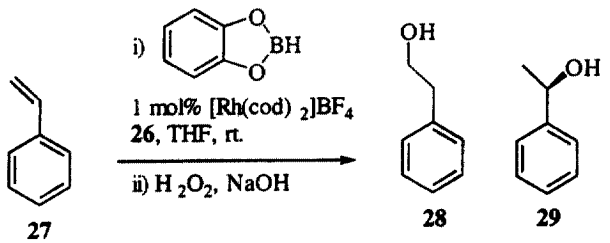
2.2. *By nitrogen–nitrogen exchange*

An alternative to the replacement of the amine group with dialkyl or diarylphosphines, is the incorporation of pyrazole rings at the α-stereogenic centre. The retentive nucleophilic substitution reactions are carried out by simply combining **24** and 1.2 equivalents of the appropriate pyrazole **25** in hot acetic acid to give the phosphinopyrazole ferrocene ligands **26** in moderate yields (38–67%) (Scheme 11).[22]



Scheme 11.

The advantage of replacing the amine group of ferrocenyl amino phosphines with the pyrazole is that this allows for the synthesis of a much wider variety of P,N-ligands with differing electronic and steric properties (due to the possibilities offered by three different functional groups at R^1, R^2 and R^3, together with differing aryl groups). During these studies, a total of 40 phosphinopyrazole ligands **26** were prepared and characterised.[23] For non-symmetrical pyrazoles containing different R^1 and R^3 substituents only one regioisomer of the resulting ligand was generally detected, with the nitrogen adjacent to the less bulky and/or less electron-withdrawing group acting as the nucleophilic centre. Ten of these ligands were used in an initial study of the Rh-catalysed hydroboration of styrene **27** with catecholborane, permitting a detailed investigation of ligand influences on the enantioselectivity of this reaction (Scheme 12).[22]

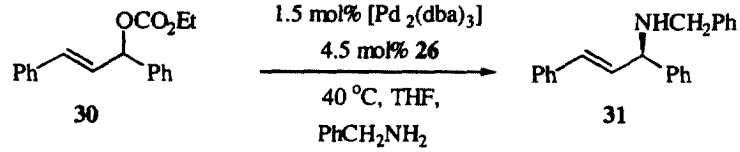


Scheme 12.

Although compared to some systems a high proportion (typically a third) of the linear alcohol **28** was formed, the selectivity for (*R*)-**29** was an unprecedented 98% e.e. using a ligand containing the

3,5-dimethylpyrazole fragment (R^1=R^3=Me, R^2=H) together with *para*-trifluoromethylphenyl groups on phosphorus. Of the examples studied, this ligand displayed the maximum electronic asymmetry, the pyrazole nitrogen acting as a good σ-donor with almost no π-accepting properties, the phosphorus ligand in contrast acting as a good π-acceptor. Attachment of trifluoromethyl groups at R^1 and R^3, reducing the pyrazole ligand's σ-donor ability whilst increasing its π-accepting capability, resulted in a significant drop in enantioselectivity (33.4% with Ar=Ph). A detrimental steric influence was also observed: use of ^{i}Pr substituents at R^1 and R^3 yielded a reduced e.e. of 91.6%. The electronic influence of these ligands was further confirmed with the establishment of a strong correlation between the enantioselectivities of hydroboration, and the stretching frequency of the carbonyl ligand in the corresponding [Rh(CO)Cl(P–N)] complexes.[24]

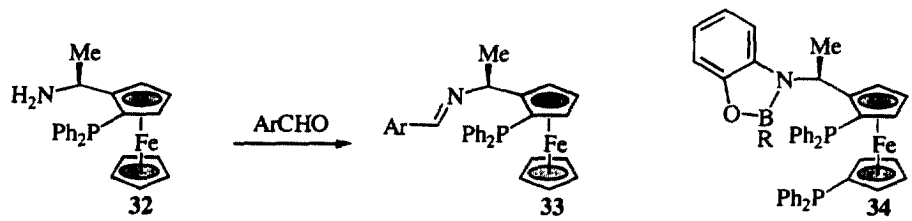
A number of the phosphinopyrazole ligands have also been reported to give excellent enantioselectivities in Pd-catalysed allylic aminations of **30**, with enantiomeric excesses greater than 94% being obtained for **31** when the pyrazole ligand contains a bulky R^1 group.[25] The best result was obtained for **26** with R^1 as a 1-adamantyl substituent, **31** being obtained in 99% e.e. (Scheme 13).



Scheme 13.

This study also reported in depth on the control by the ligand of the configuration of the intermediate η^3-allyl species, and the nature of subsequent site-selective nucleophilic attack. These results were later supported by crystallographic and NMR studies on related Pd(II)–allyl phosphinopyrazole ferrocene complexes,[26] together with computational studies on model palladium complexes,[27] to provide a detailed understanding of the origin of enantioselection in allylic amination. For this reaction, co-catalytic amounts of small hard anions such as F^- and BH_4^- were found to enhance the selectivity to >99.5% e.e. where the pyrazole fragment of **26** contained only a 1-adamantyl R^1 substituent (with Ar=Ph). In contrast, the non-coordinating PF_6^- anion reduced the e.e. to <10%.[28] A high enantioselectivity (99.3%) was also obtained with 1,1′-ruthenocendiyl as the R^1 substituent linking two components of **26** (with Ar=Ph). The high molecular weight of the corresponding two centred bimetallic palladium catalyst aids recovery and reuse with little loss of selectivity (98.5% e.e.).[29]

Treatment of (*S*,*pR*)-**5** by excess ammonia in an autoclave at 100°C gave **32** which was further modified into a series of ferrocenylphosphine–imine ligands **33**. These proved effective for rhodium catalysed hydrosilylation of aryl alkyl ketones, for which the highest e.e. of 90% was measured on (*S*)-1-phenylethanol obtained with a *meta*-trifluoromethylphenyl containing ligand **33** (Scheme 14).[30]



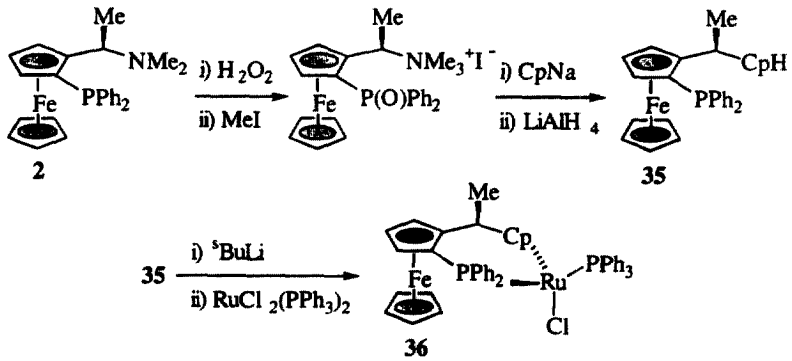
Scheme 14.

Initial nitrogen–nitrogen substitution between (*S*,*pR*)-**3** and 2-aminophenol, and further reaction with a series of boric acid derivatives, yielded the novel Lewis acidic ligands **34** from which platinum

and rhodium complexes have been prepared. Use of the latter for hydrogenation of methyl (Z)-α-acetamidocinnamate gave modest selectivity (up to 54% e.e.).[31]

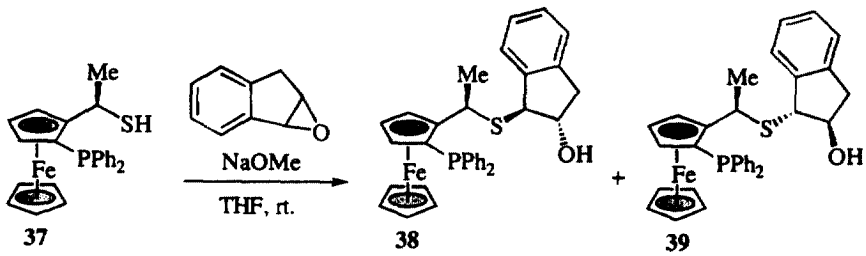
2.3. By nitrogen–carbon and nitrogen–sulfur exchange

Overall substitution of the dimethylamino group of **2** with the cyclopentadiene moiety to give **35** is reported to proceed in 46% overall yield by the route shown in Scheme 15. Formation of the cyclopentadienyl anion of **35** with ^{s}BuLi was followed by complexation to both rhodium(I), and ruthenium(II), which in the latter case gave **36** as a single diastereoisomer. Preliminary results on the use of **36** as a promoter of asymmetric reconstitutive condensation of allylic alcohols and terminal acetylenes are also reported in this work.[32]



Scheme 15.

Mercaptan **37**, readily prepared from **2** by stereospecific replacement of nitrogen by sulfur, has been used for the generation of sulfur linked derivatives of the Pigiphos ligand **15**.[9] In addition, **37** has been used for the synthesis of the P, S, O-ligands **38** and **39**, which were obtained from racemic *cis*-indene epoxide followed by chromatographic separation (Scheme 16).



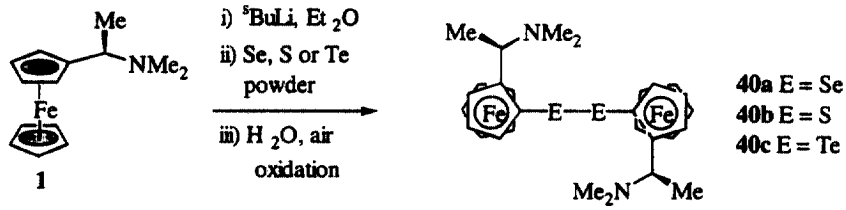
Scheme 16.

However, the enantiomeric excesses obtained for the Rh(I)-catalysed hydroboration of styrene with both ligands were poor (≈10%), and only moderate selectivity was obtained for allylic alkylation (55% e.e. with **39**).[33]

2.4. Ferrocenyl chalcogenides

In 1994, the first synthesis of diferrocenyl diselenide **40a** was reported via *ortho*-lithiation of **1** followed by the addition of selenium powder and aqueous oxidation (Scheme 17). After purification by column chromatography the pure diselenide was obtained in 77% yield.[34,35] Similarly prepared were the corresponding sulfur and telurium derivatives **40b** and **40c**,[36] and all three dichalcogenides were applied

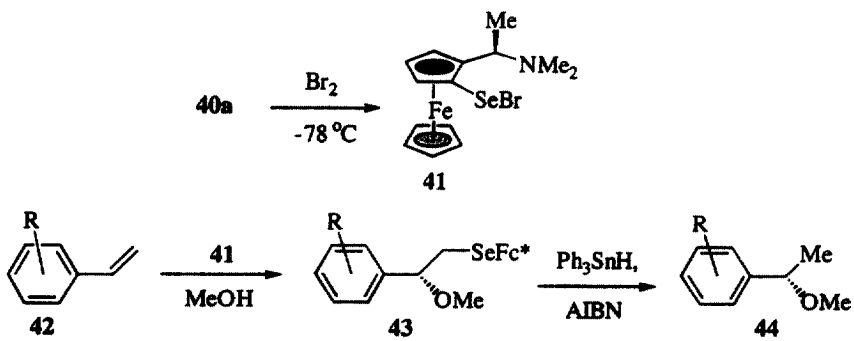
as ligands in the Rh(I)-catalysed asymmetric hydrosilylation of ketones, for which enantiomeric excesses of up to 88% were obtained with **40a** using alkyl aryl ketones as substrates.[37] These reactions are believed to involve a tetracoordinate rhodium–dichalcogenide complex with two selenium and two nitrogen atoms bound to the metal. Low to moderate selectivities were also obtained for the hydrosilylation of imines (up to 53% e.e.) and hydrogenation of α-acetamidocinnamic acid (69% optical purity).[38] Ligands **40a** also gave modest selectivity (e.g. 48% e.e. from acetophenone) for transfer hydrogenation catalysed by rhodium employing diphenylsilane and methanol.[39]



Scheme 17.

The diselenide **40a** has also been employed as a chiral selenium reagent for the preparation of vinyl selenides, which on *m*CPBA oxidation and selenoxide elimination gave chiral allenecarboxylic esters in up to 89% enantiomeric excess.[34,35] Similar oxidation of allylic selenides derived from **40a** resulted in an asymmetric [2,3] sigmatropic rearrangement to provide chiral allylic alcohols, again with up to 89% enantiomeric excess.[35] All of the dichalcogenides **40a–c**, have been applied to the asymmetric ring opening of *meso*-epoxides after reduction to their corresponding ferrocenyl chalcogenide anions with $LiAlH_4$. Selectivities of up to 69% d.e. were obtained using the anion derived from **40a** with cyclohexene oxide.[36] The resultant ferrocenylseleno amino alcohol is an efficient catalyst for the addition of diethylzinc to aryl aldehydes (up to 99% e.e.).[40]

This group has also reported the synthesis of the ferrocenylselenyl bromide **41** via the homolytic cleavage of **40a**. Addition of **41** to styrenes **42** in the presence of methanol, led to the resultant β-methoxyselenium derivatives **43** as single regioisomers and with diastereomeric excesses of up to 98%. Reduction of the carbon–selenium bond gave ethers **44** with enantiomeric excesses in up to 98%, although the yields were generally low (14–48%) (Scheme 18).[41] Improved yields were obtained with the selenium triflate obtained from **41** on treatment with silver triflate. Although this reagent gave reduced diastereoselectivities with styrene, and α-, *ortho*- and *meta*-methylstyrene, high diastereoselectivies returned with *trans*-alkenes and trisubstituted alkenes as substrates.[42]



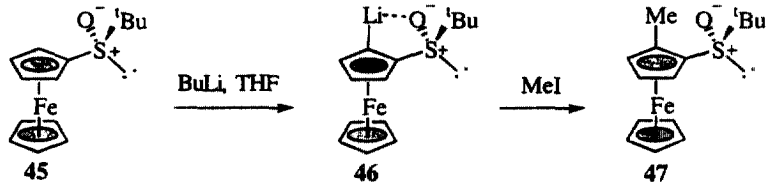
Scheme 18.

3. Alternative *ortho*-directing groups

Of particular significance during the period covered by this review has been the introduction of a variety of new methods for the generation of non-racemic planar chiral ferrocene derivatives. Although lithiation of **1** proceeds with high diastereoselectivity, the *N,N*-dimethyl-1-ethylamine unit must be retained or modified, and **1** itself must be obtained by resolution or asymmetric synthesis. The newer methods described below offer rapid access to a wider range of planar chiral derivatives and ligands, in which the source of chirality is normally a readily available chiral pool derived auxiliary or base.

3.1. *Sulfoxide and acetal* ortho-*directing groups*

The mechanism for *ortho*-lithiation of the sulfoxide **45** is thought to be similar to that of *N,N*-dimethyl-1-ferrocenylethylamine **1**, but with the lithium coordinating instead to the sulfoxide oxygen. The *tert*-butyl group prefers to be *anti* to the ferrocene moiety, thus directing lithiation to yield **46**, methylation of which gave **47** with a diastereoisomeric excess of >96% (Scheme 19).[43] The ferrocenyl sulfoxide **45** is itself readily available in 95% e.e. from $Ti(O^iPr)_4$/diethyl tartrate catalysed oxidation of the corresponding sulfide with cumene hydroperoxide.[44,45]



Scheme 19.

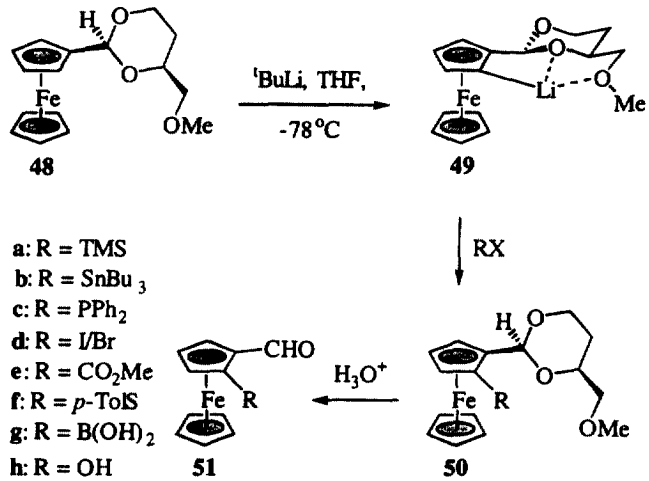
Of greater synthetic value is the acetal **48**, which is readily synthesised in 80% yield over three steps from commercially available ferrocenecarboxaldehyde and (*S*)-1,2,4-butanetriol. Addition of *tert*-butyl lithium at −78°C and warming of the reaction mixture to room temperature results in a kinetically controlled, highly diastereoselective lithiation (98% d.e.) rationalised by the transition state leading to **49**. This was treated with a wide range of electrophiles yielding an array of 2-substituted ferrocenecarboxaldehydes **51** in 98% e.e. after removal of the recoverable auxiliary from **50** (Scheme 20).[46,47] Transmetallation of **49** to mixed higher order cuprates and electrophilic amination has also provided a moderate yield of (*S*)-2-aminoferrocenecarboxaldehyde.

The diphenylphosphinocarboxaldehyde **51c** has been used for the preparation of a number of diphosphine ligands, most notable of which are the three separable diastereoisomers **52a–c** formed in a 4:3:3 ratio on pinacol coupling (Scheme 21). These gave between 85–89% enantiomeric excess for rhodium catalysed hydrogenation of α-acetamidocinnamic acid. The diphenylphosphinoacetal **50c** also gave 87% e.e. in this reaction.[47] Carboxaldehyde **51c** also gives a terdentate ligand on condensation with 1,2-diaminoethane.[48]

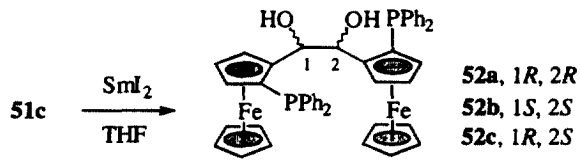
This acetal methodology has also been applied to the synthesis of **53** (94% e.e.), the starting material for both the ketone **54** and ester **55** which on Claisen ester condensation gave the C_2-symmetric 1,3-dicarbonyl **56** (Scheme 22).[49]

The 1:1 complex of **56** and yttrium isopropoxide (prepared in situ) was found to be a highly efficient Lewis acid catalyst. In the presence of 0.2 mol% of the catalyst, the asymmetric silylcyanation of benzaldehyde by TMSCN proceeded in 95% yield with an enantiomeric excess of 87%.

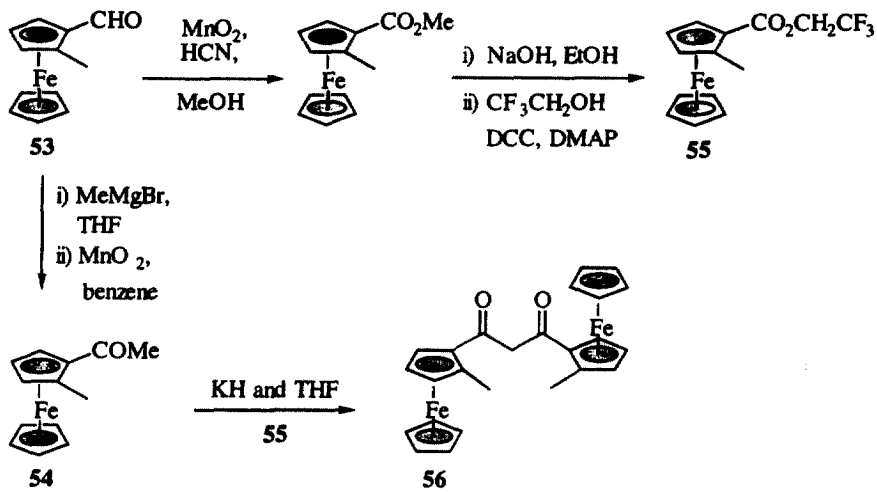
In combination with the in situ generation of a 1′-directing aminal moiety,[50] the acetal methodology has also been applied to the synthesis of enantiopure 1,2,1′-trisubstituted ferrocenes. Addition of lithium



Scheme 20.

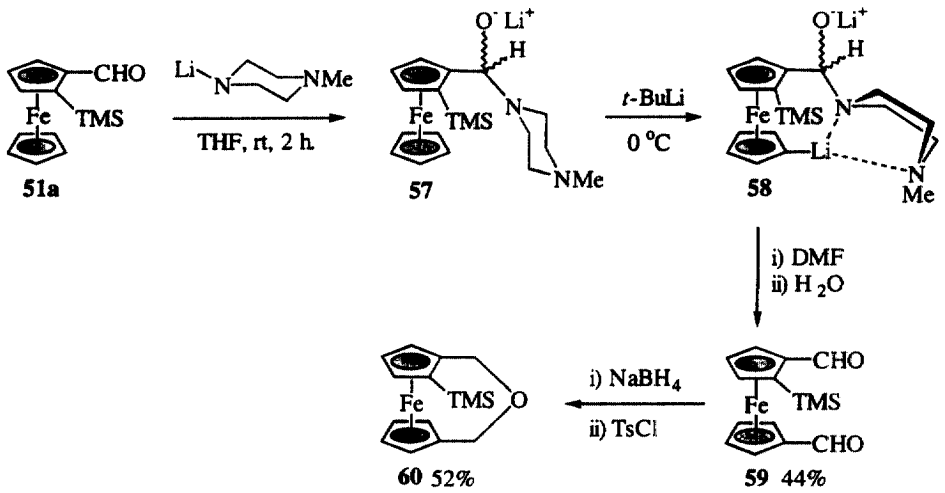


Scheme 21.



Scheme 22.

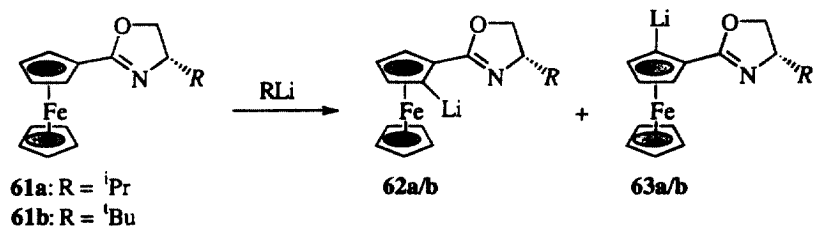
N-methylpiperazide to **51a**, and further addition to the resulting aminal anion **57** of ^{t}BuLi gave **58** with a >98:2 selectivity in favour of 1′-lithiation. Quenching of the reaction with chlorotributyltin gave three different substituents on the resulting isolated ferrocene. When instead DMF was added to **58**, the resulting dialdehyde **59** was used for the synthesis of **60**, the first example of an enantiopure oxaferrocenophane (Scheme 23).[51]



Scheme 23.

3.2. *Oxazoline* ortho-*directing groups*

An area that has generated a great deal of interest since 1995 is the synthesis of planar chiral ferrocene derivatives via the *ortho*-lithiation of ferrocenyloxazolines. These are readily synthesised from commercially available ferrocenecarboxylic acid and amino alcohols. The first reports of this chemistry appeared simultaneously from three groups who examined the ratio of diastereoisomers obtained on addition of BuLi or ^{s}BuLi followed by an appropriate electrophile.[52–54] Common to all three studies was the *iso*-propyl substituted ferrocenyl oxazoline **61a** for which the ratio of lithiated oxazolines **62a** to **63a** varied from 2.5:1 using BuLi at room temperature,[52] through 8:1 with ^{s}BuLi at −78°C in THF,[54] and finally 39:1 with ^{s}BuLi again used at −78°C but in Et_2O (Scheme 24).[53] Satisfyingly, all three papers reported the same configuration for the major product.



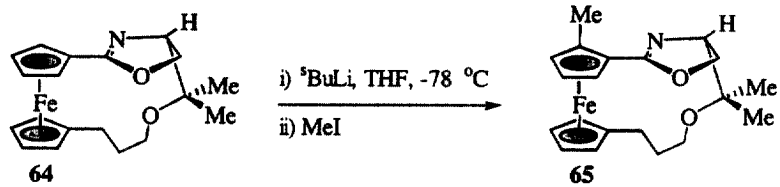
Scheme 24.

What is now the method of choice for this lithiation was discovered when additional ligands were added to the reaction to vary the nature of the metallating agent. Although the use of TMEDA with BuLi in THF had little effect (Table 1), when the reaction was carried out in Et_2O or hexanes, a dramatic increase in selectivity to 100:1 was obtained with **61a**. This ratio was still further increased when either ^{s}BuLi was employed with **61a** or the *tert*-leucine derived ferrocenyloxazoline **61b** was used in combination with either BuLi or ^{s}BuLi (Table 1).[55]

That these reactions are mediated by nitrogen rather than oxygen directed lithiation was proved via synthesis of the macrocyclic ferrocenyloxazoline **64** in which rotation about the ferrocene–oxazoline bond is prevented. Lithiation and subsequent quenching with methyl iodide led to the isolation of only one detectable diastereoisomer **65** with the new methyl group proximal to the nitrogen (Scheme 25). The oxygen in the tether of **64** is not thought to play a significant role in this reaction.[56]

Table 1
Lithiation of **61a** and **61b**

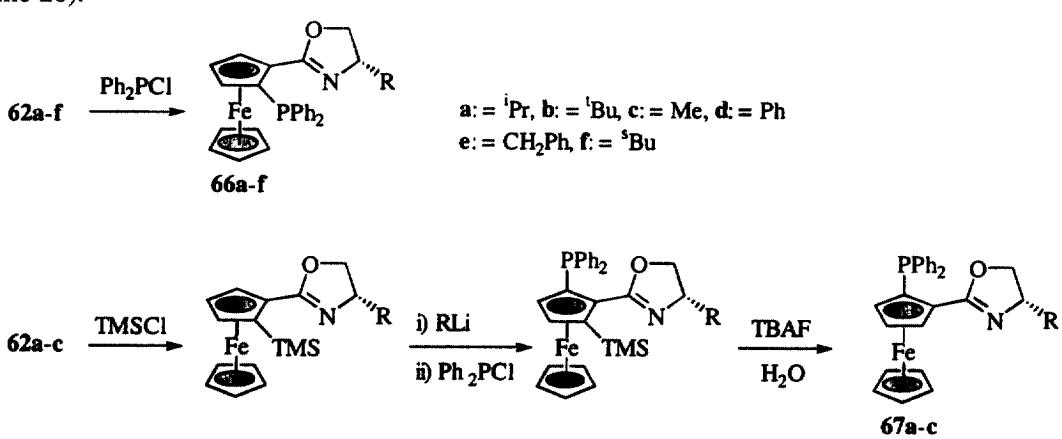
Compound	RLi	Solvent	Additive	62 : 63	Yield (%)
61a	BuLi	THF	TMEDA	3 : 1	>75
61a	BuLi	Et_2O	TMEDA	100 : 1	80
61a	BuLi	Hexanes	TMEDA	100 : 1	75
61a	^{s}BuLi	Hexanes	TMEDA	>500 : 1	94
61a	^{t}BuLi	Hexanes	TMEDA	28 : 1	>75
61b	BuLi	Hexanes	TMEDA	>500 : 1	>75
61b	^{s}BuLi	Hexanes	TMEDA	>500 : 1	>75
61b	^{t}BuLi	Hexanes	TMEDA	34 : 1	>75



Scheme 25.

With oxazolines **61a/b** the observed selectivity may be explained with a model in which the oxazoline substituent is similarly oriented towards the iron, allowing the nitrogen-coordinated alkyl lithium reagent to approach unconstrained from the opposite direction.[52,56] However, when ^{t}BuLi is employed in these lithiations, it is possible that the significantly lower selectivities observed (Table 1) are due to a competing and less sterically encumbered oxygen directed pathway.

Quenching these lithiations with chlorodiphenylphosphine has provided an array of ($S_p S$)-phosphinoferrocenyloxazoline (phosferrox) ligands **66a–f**. The corresponding ($S_p R$)-diastereoisomers **67a–c** have also been obtained through initial introduction of a removable trimethylsilyl blocking group (Scheme 26).[57,58]

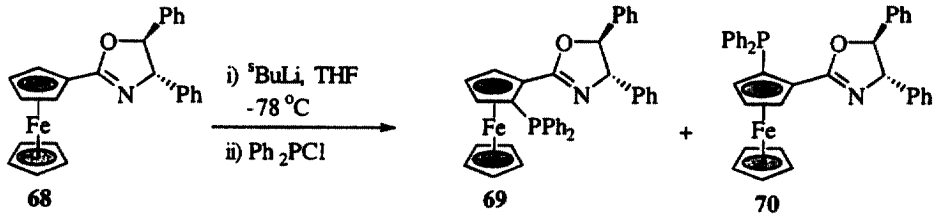


Scheme 26.

Both **66a** and **67a** have been applied to palladium catalysed Grignard cross-coupling of 1-phenylethylmagnesium chloride with (*E*)-β-bromostyrene. The former ligand gave the more encouraging result: use of 1 mol% of **66a**/$PdCl_2$ cleanly gave the cross-coupled product in 45% enantiomeric excess.[59] The X-ray crystal structures of **66a**/$PdCl_2$[58] and **67a**/$PdCl_2$[59] reveal the differences in these complexes due to the opposite configurations of their elements of planar chirality. Furthermore, addition of butylmagnesium chloride to enones is catalysed by 12 mol% of **66d** and 10 mol% CuI. Enantiomeric

excesses of 92% and 83% were obtained with cycloheptenone and cyclohexenone respectively in reactions that proceed with >100:1 selectivity for conjugate over 1,2-addition.[60]

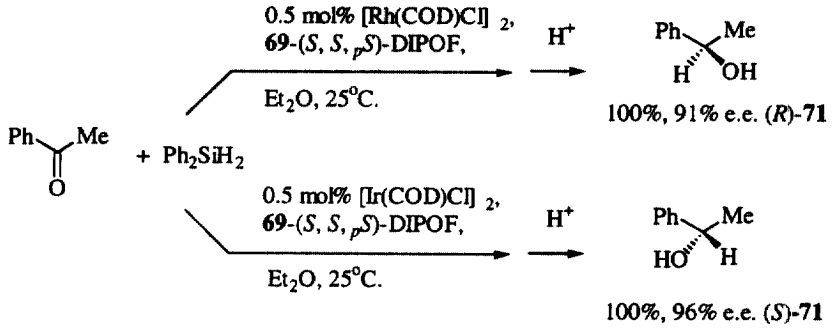
Ligands **66a** and **66d** have also been applied to rhodium catalysed asymmetric hydrosilylation of acetophenone, (*R*)-1-phenylethanol **71** being formed in 48% e.e. and 60% e.e. respectively. A significant improvement of this selectivity was obtained through introduction of an additional substituent on the oxazoline to give (*S*,*S*$_p$*S*)-DIPOF **69**.[61] This is obtained from (*S*,*S*)-**68** in 40% yield together with its diastereoisomer (*S*,*S*$_p$*R*)-DIPOF **70** in 28% yield (Scheme 27).[62]



68 **69** **70**

Scheme 27.

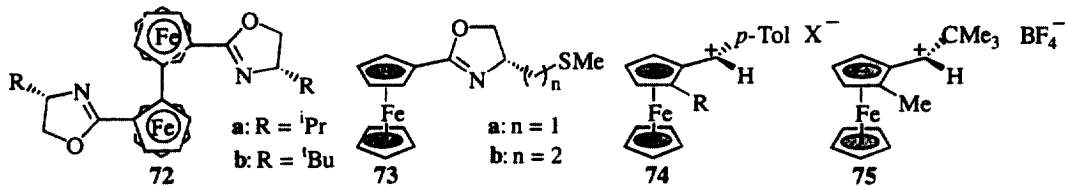
Reduction of acetophenone gave (*R*)-**71** in 91% e.e., and similar selectivities were obtained for other aryl methyl ketones (88–90% e.e.) and bulky alkyl methyl ketones (87–89% e.e.).[61] When Rh(I) was replaced by Ir(I) for the hydrosilylation of acetophenone, the absolute configuration of **71** was observed to change from (*R*) to (*S*) and the e.e. to increase to 96% (Scheme 28). This result represents the first highly enantioselective iridium catalysed hydrosilylation of a ketone, and the DIPOF/Ir(I) system has been successfully applied to the reduction of a number of other aryl methyl ketones (81–91% e.e.).[63]



Scheme 28.

The parent phosferrox ligands **66a–e** are all effective mediators of transfer hydrogenation from 2-propanol in conjunction with as little as 0.2 mol% of $RuCl_2(PPh_3)_3$ at 28°C. All these ligands give (*R*)-**71** in at least 90% e.e., **66d** giving 94% e.e. with good conversion. This has been further applied to a range of aryl methyl ketones and although electron rich and hindered ketones required reaction temperatures of up to 80°C, this resulted in no more than a 10% reduction in enantiomeric excess.[64]

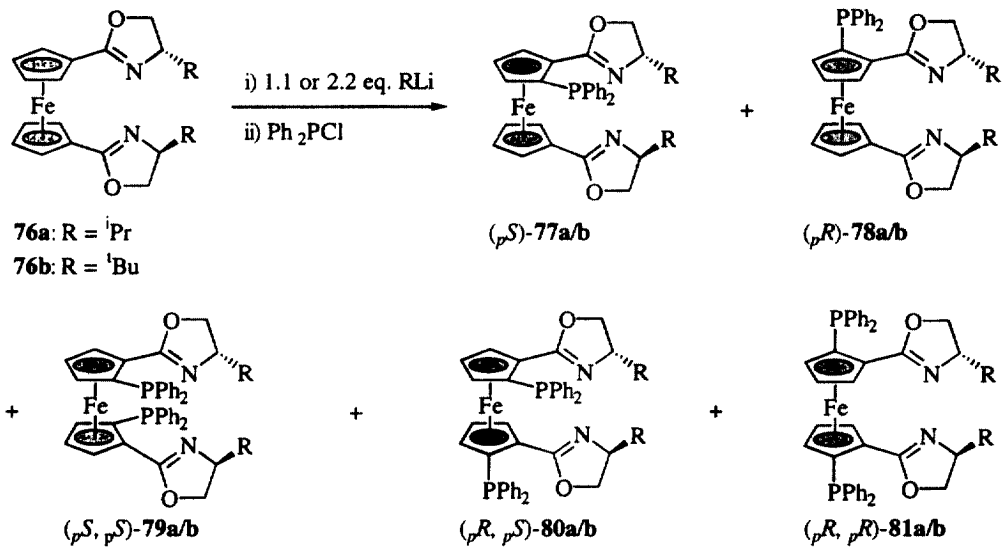
Lithiated oxazolines **62a/b** have also been converted to bisoxazolines **72a/b** via transmetallation to their corresponding ferrocenylcopper intermediates and oxidative dimerisation with oxygen. Further introduction of two trimethylsilyl groups on **72b**, by double BuLi mediated *ortho*-lithiation and addition of TMSCl, gave a ligand which was utilised with copper triflate for the asymmetric cyclopropanation of styrene. The resulting cyclopropanes were isolated in up to 99% e.e. with an *l*-menthyl derived diazoacetate, although with low (77:23) *trans*:*cis* selectivity.[65] Both 1- and 1,1′-ferrocenyloxazolines, for example **73a/b**, containing pendent thioether units have been prepared from cysteine and methionine. These nitrogen–sulfur chelating ligands have also been applied to the generation of **8**, with a maximum enantioselectivity of 93% being obtained.[66]



72 73 74 75

Both the acetal and oxazoline methodologies have been used for the synthesis of α-ferrocenylcarbenium ions **74**[67] and **75**[68] respectively, with a view to applying these cations as chiral trityl Lewis acid equivalents. Although Diels–Alder reactions are effectively catalysed in their presence, this is believed to be due to the presence of HX (e.g. HBF_4) as the products are always obtained as racemates.

A report on the lithiation and diphenylphosphination of the corresponding 1,1′-bis(oxazolinyl)-ferrocenes **76a/b** also first appeared in 1995[69] with two additional studies appearing shortly afterwards.[70,71] These bisoxazolines are readily synthesised from their corresponding amino alcohols and commercially available 1,1′-ferrocenedicarboxylic acid. Taken together, these studies reveal that the solvent and the type of butyl lithium reagent employed dictate which of the five possible products are obtained (Scheme 29). These results are summarised in Table 2 with **76a** as the starting material, in which for simplicity only the configuration of the planar chirality is given. A similar set of results has also been reported with **76b** as the starting material, the only significant difference being the ratio of **79b/80b** which is shown to be 85:15 (by NMR)[70] and 81:9 (isolated yields).[71]



76a: R = iPr
76b: R = tBu

($_pS$)-**77a/b** ($_pR$)-**78a/b**

($_pS$, $_pS$)-**79a/b** ($_pR$, $_pS$)-**80a/b** ($_pR$, $_pR$)-**81a/b**

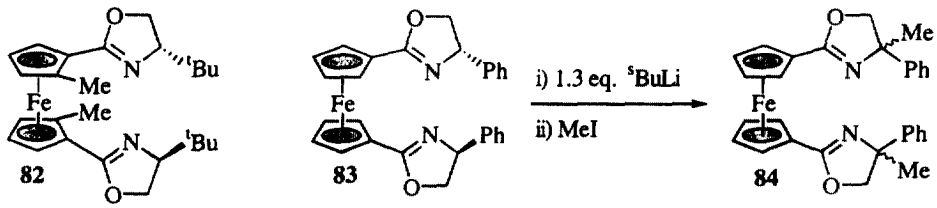
Scheme 29.

In support of these stereochemical assignments is an X-ray crystal structure of the 1:1 complex

Table 2
Percentage yields of **77–81** following lithiation of **76a**

Base(eq.)/Solvent	($_pS$)-**77a**	($_pR$)-**78a**	($_pS$, $_pS$)-**79a**	($_pR$, $_pS$)-**80a**	($_pR$, $_pR$)-**81a**
sBuLi(1.2)/Et_2O	3	81	-	6	9
sBuLi(1.2)/THF	72	6	6	7	1
sBuLi(2.2)/Et_2O	-	-	-	26	27
sBuLi(2.2)/THF	-	-	56	19	5
tBuLi(2.2)/Et_2O	-	-	-	60	-

between **80b** and $PdCl_2$ (in which the palladium is bound by N,P chelation with the oxazoline of (*R*)-configuration),[69] an X-ray structure of **82**, obtained under the same lithiation conditions that gave **79**,[70] and an X-ray structure of **78b**.[71] It should be noted that in the first work in this area **81** was incorrectly assigned as **79**,[69] and that the representation of the X-ray structure of **82** is of the wrong enantiomer.[70] Dilithiation and subsequent methylation of the phenyl substituted oxazoline **83** gave as the major component **84** (21%), obtained via base abstraction of the benzylic protons and subsequent methylation (Scheme 30).



Scheme 30.

The bisoxazoline ligands **77–81** were subsequently used in allylic alkylation with **7** to give **8** of (*S*) absolute configuration (Scheme 3) and the results obtained are summarised in Table 3 together with those of monooxazoline ligands **66a/b** and **67b**.[72,73] Where appropriate there is good agreement between the two sets of data, despite the different bases employed, revealing that complexes derived from **79a/b**, **80a/b** and **66a/b** are excellent catalysts for this reaction. Preliminary results suggest that the diphosphines may act in these reactions as P,P chelating ligands, and that the relative ineffectiveness of **77a/b** and **78a/b** may be due to the possibility of there being two possible P,N complexes formed with palladium.[73]

That a 1,1′-ferrocenyldiphosphine derived ligand is effective in this allylic alkylation was demonstrated with the synthesis of **85** by oxazoline ring opening of **79a** followed by transesterification (Scheme 31). Selectivities of up to 90% e.e. were obtained for (*S*)-**8** with this C_2-symmetric ligand.[74]

3.3. *Other auxiliary* ortho-*directing groups*

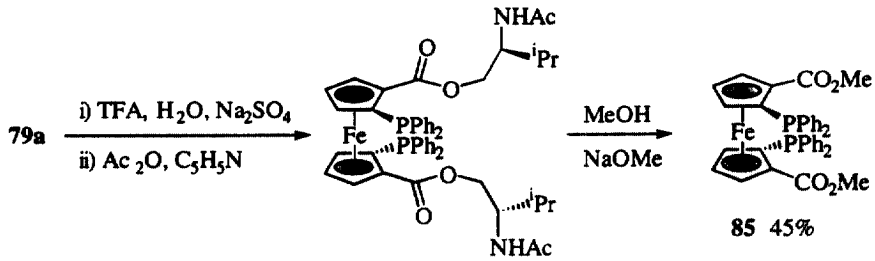
The reaction between the ammonium iodide **86** and (*S*)-2-methoxymethylpyrrolidine (SMP) **87** gave an 86% yield of (*S*)-(2-methoxymethylpyrrolidin-1-yl)ferrocene (FcSMP) **88**. Lithiation with ^{s}BuLi in Et_2O at −78°C and subsequent addition of Ph_2PCl led to the isolation of **89** with a diastereomeric excess of 98% (Scheme 32).[75]

The SMP group can be readily replaced, as was demonstrated by the synthesis of the ferrocenylmethanol **90** (Scheme 33). The ease of auxiliary replacement and the alcohol oxidation state of the resulting products nicely complements the acetal (aldehyde oxidation level) and the oxazoline (carboxylic acid oxidation level) methodologies described in Sections 3.1 and 3.2 respectively.

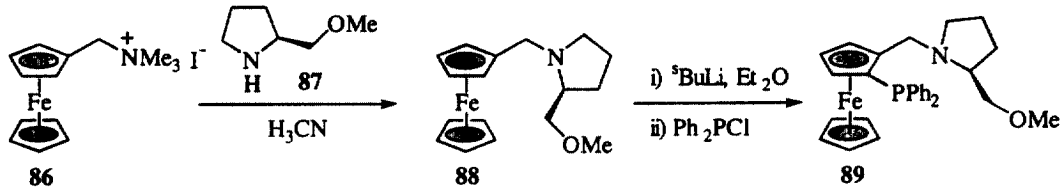
A method that also complements these existing protocols, for *ortho*-functionalisation at the ketone oxidation level, is the use of the SAMP hydrazone **91** prepared from benzoylferrocene in 73% yield

Table 3
Enantioselectivities of (*S*)-**8** formed on allylic alkylation with ferrocenyloxazoline ligands

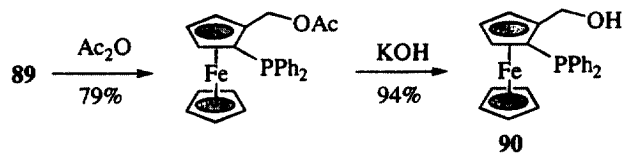
Reference	**66a**	**67a**	**77a**	**78a**	**79a**	**80a**	**81a**
72	93	-	-	-	96	96	-
73	90	-	-	77	-	99	38
	66b	**67b**	**77b**	**78b**	**79b**	**80b**	**81b**
72	-	-	-	-	99	-	-
73	>99	67	80	74	94	99	34



Scheme 31.

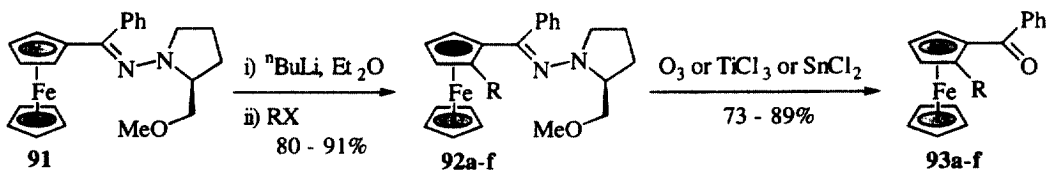


Scheme 32.



Scheme 33.

(Scheme 34).[76] Lithiation with BuLi in Et_2O at −70°C followed by quenching of the reaction with a variety of electrophiles gave adducts **92a–f** with high diastereoselectivities. Either oxidative cleavage of the hydrazone with ozone, or reductive cleavage with $SnCl_2$ or $TiCl_3$, provided a range of functionalised benzoylferrocenes **93a–f**. Although a little racemisation occurred on auxiliary cleavage, these ketones were obtained in high enantiomeric purity (90–96% e.e., with the exception of **93f**, 71% e.e.).



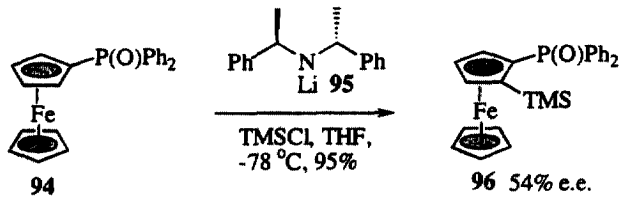
a: R = Me, **b**: R = TMS, **c**: R = Ph_2P, **d**: R = $C(OH)Ph_2$, **e**: R = CHO, **f**: R = I

Scheme 34.

3.4. *Non-auxiliary enantioselective* ortho-*functionalisation*

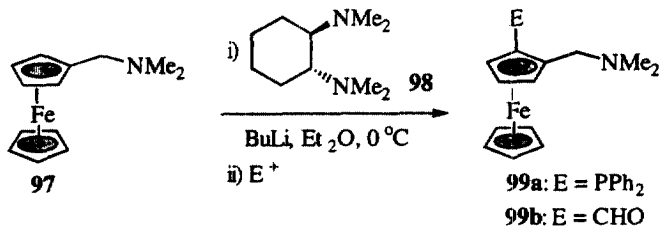
The first demonstration of enantioselective *ortho*-lithiation of a monosubstituted ferrocene utilised the chiral lithium amide **95**. Although this was insufficiently basic to deprotonate a wide range of functionalised ferrocenes, and gave racemic products from a sulfone and a diisopropylcarboxamide, the phosphine oxide **94** underwent clean conversion to **96** produced in 54% enantiomeric excess (Scheme 35).[77] Unfortunately further lithiation of **96** with alkyl lithiums was unsuccessful.

Higher selectivities were obtained on metallation of the aminoferrocene **97** with BuLi and two equivalents of the disymmetric diamine **98** in Et_2O at 0°C. Quenching of the reaction with Ph_2PCl gave **99a** in 62% e.e., and after two crystallisations this was obtained almost enantiopure in 25% yield. If



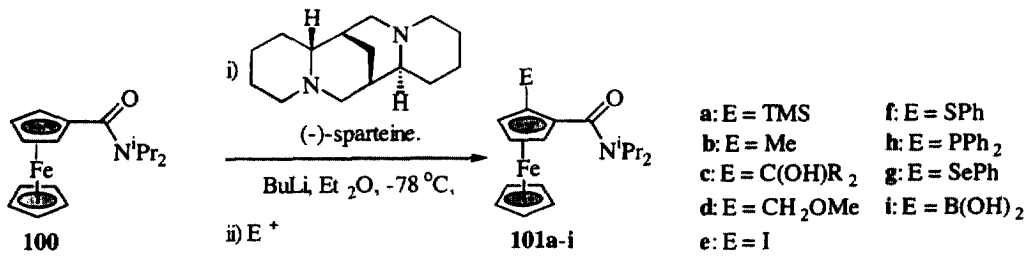
Scheme 35.

instead the reaction was quenched with DMF the resulting aldehyde **99b** was isolated with an 80% e.e. (Scheme 36).[78] Replacement of **98** by (−)-sparteine resulted in only a trace amount of the phosphine **99a**.



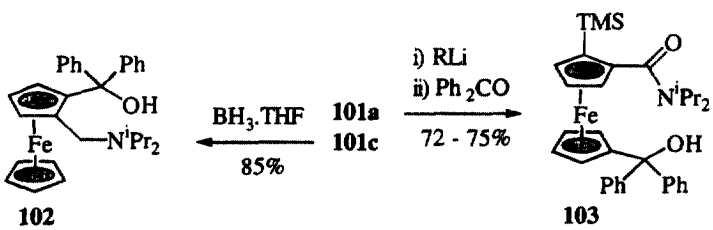
Scheme 36.

However, (−)-sparteine mediated lithiation of *N,N*-diisopropyl ferrocenecarboxamide **100** with BuLi in Et_2O at −78°C proceeds with very high enantioselectivity. Quenching of the reaction with a range of electrophiles gave amides **101a–i** with the following enantiomeric excesses (Scheme 37): **a**: 98%; **b**: 94%; **c**: 99%; **d**: 81%; **e**: 96%; **f**: 98%; **g**: 93%; **h**: 90%; and **i**: 85%.[79]



Scheme 37.

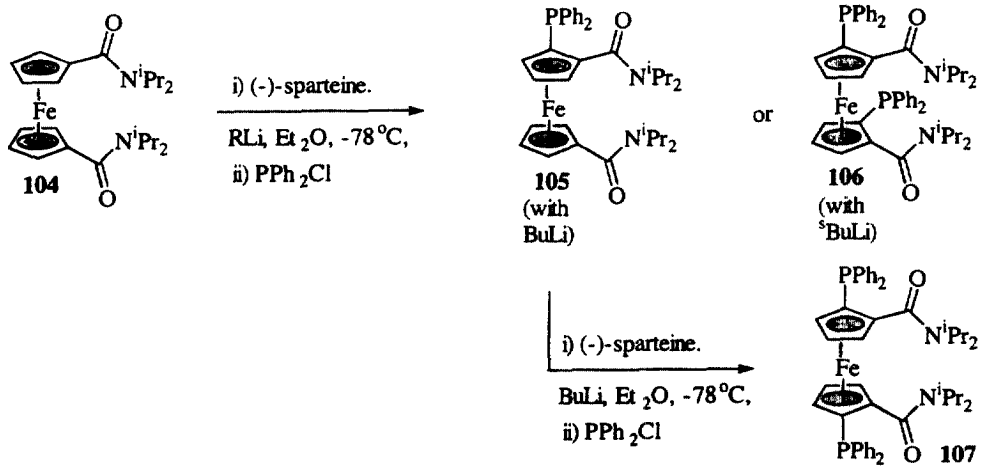
For **101c** (R=Ph), the amide functionality was cleanly reduced with borane–THF to give the replaceable aminomethyl group in **102**, suggesting that this method will be applicable for the synthesis of derivatives that can be further functionalised at the alcohol oxidation level (Scheme 38). Further lithiation (BuLi/THF or ^{s}BuLi/Et_2O) of the trimethylsilyl product **101a** and addition of benzophenone gave exclusive formation of **103**, revealing that the TMS group can not be used as a removable blocking group for the generation of enantiomers of **101**.



Scheme 38.

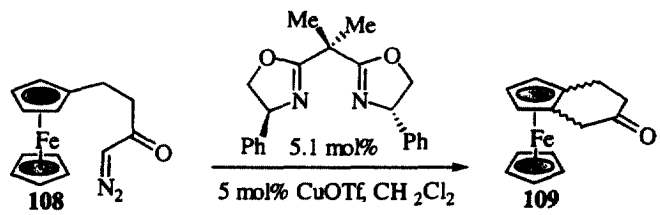
This (−)-sparteine mediated methodology has been further applied to the corresponding diamidoferrocene **104**. Only monodeprotonation occurred on addition of up to 4.4 equivalents of BuLi in Et_2O, together with an equimolar quantity of (−)-sparteine. After addition of Ph_2PCl, **105** (80% e.e.) was isolated and further purified on recrystallisation to give the product in 58% yield and 98.5% enantiomeric excess. Use of ^{s}BuLi in Et_2O gave an 85% yield of the crude (90% pure) *meso*-diphosphine **106**.

This problem was nicely circumvented by further (−)-sparteine mediated BuLi metallation of **105** in Et_2O which led to highly selective formation of **107** over **106** (between 93:7 and 97:3, Scheme 39). The excellent *enantioselectivity* of this second step was demonstrated on repetition with racemic **105** which gave a 1:1 ratio of **106** and **107** in which the latter diphosphine was isolated in 99% e.e.[80]



Scheme 39.

A recent and novel catalytic method for the synthesis of planar chiral ferrocenes employed diazoketone **108** in a copper triflate/bisoxazoline mediated carbenoid C–H insertion reaction. The cyclisation product **109**, for which the absolute configuration has not yet been determined, was isolated in 72% yield and an e.e. of 78% (Scheme 40).[81]



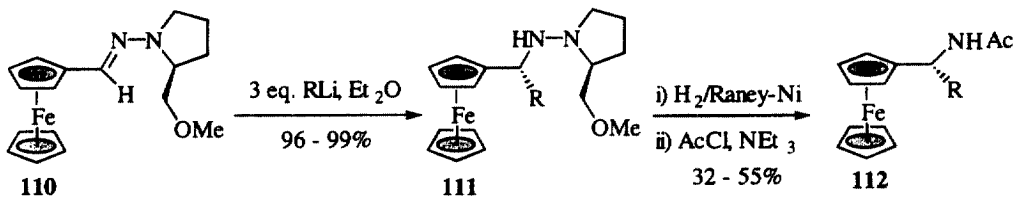
Scheme 40.

4. Generation and manipulation of α-stereogenic centres

As shown in Section 1, the stereospecific replacement of the dimethylamino group in **2** is a key feature of ferrocene chemistry. The importance and generality of this reaction has resulted in a number of new methods for the asymmetric synthesis of stereogenic centres α to ferrocene, and for new methods of substitution, especially with carbon nucleophiles.

4.1. Auxiliary mediated synthesis

The SAMP-hydrazone **110**, readily prepared from ferrocenecarboxaldehyde in 99% yield, undergoes highly diastereoselective (>99:1) addition of a number of alkyl lithium reagents to give **111**. Reductive N–N bond cleavage with Raney nickel gave (*R*)-1-ferrocenylalkylamides **112** of between 85–94% e.e., where this partial loss of enantiopurity could not be avoided (Scheme 41).[82] This method has been extended to the bis-SAMP hydrazone derived from ferrocenedicarboxaldehyde. Addition of 10 equivalents of a range of alkyl lithium reagents, followed by an improved method for reductive cleavage of the auxiliary using $BH_3 \cdot THF$, yielded 1,1′-bis(1-aminoalkyl)ferrocene derivatives in 90–98% e.e. and containing 5–20% of the *meso*-diastereoisomer.[83]

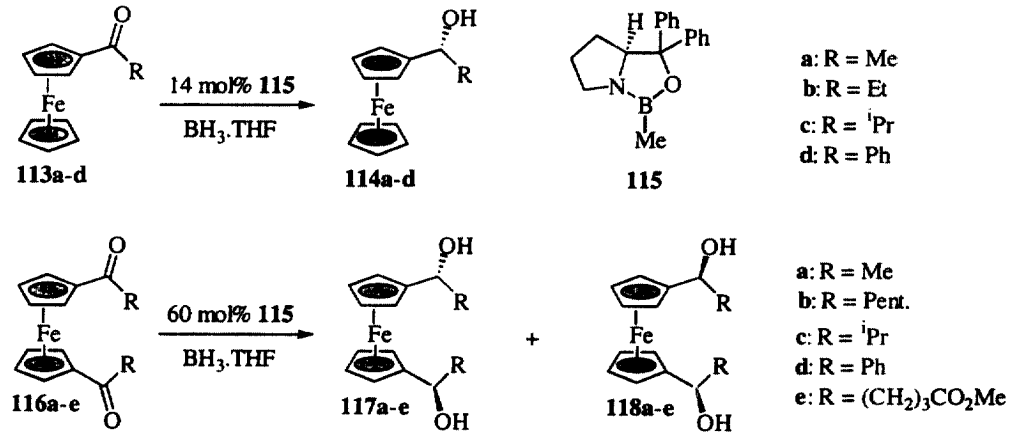


110 **111** **112**

Scheme 41.

4.2. Asymmetric reductions of ferrocenylketones

Due to the ease of ferrocene acylation, asymmetric reduction of ferrocenylketones **113** is an attractive route for the synthesis of α-ferrocenyl alcohols, from which an array of non-racemic ferrocene derivatives may be obtained. A breakthrough in this area came with the very efficient asymmetric reduction of **113** with borane–THF catalysed by 14 mol% oxazaborolidine **115**. The product α-ferrocenyl alcohols **114** were isolated in good yields and with excellent enantiomeric excesses (all >95%, Scheme 42).[84]

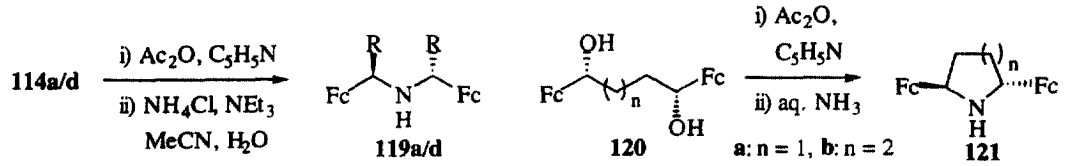


113a-d **114a-d** **115** **116a-e** **117a-e** **118a-e**

Scheme 42.

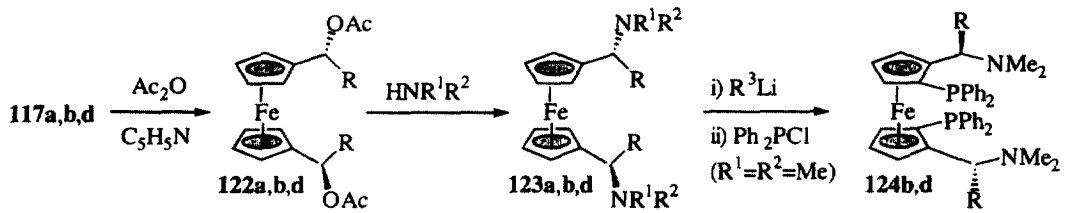
The same protocol was applied to the reduction of ferrocenyldiketones **116** from which were obtained the (*R*,*R*)-diols **117** with excellent enantioselectivities (98% e.e.) and good control of the relative stereochemistry, the *meso*-diols **118** comprising only 3–13% of the products. This reduction methodology was also applied to ferrocenyl ketones containing a pentamethylcyclopentadienyl (Cp*) group, and ruthenocenyl diketones, both classes of substrate giving high selectivities (94–98% e.e.).[85]

The alcohols **114a/d** have been cleanly converted into the C_2-secondary amines **119a/d** (Scheme 43) both of which have been employed as precursors to chiral lithium amide bases for enantioselective deprotonation of 4-*tert*-butylcyclohexanone (max. 62% e.e.).[86] The oxazaborolidine reduction methodology has also been used for the synthesis of diols **120a/b**, themselves precursors to the pyrrolidine and piperidine derivatives **121a/b**. The amination step leading to **121b** was found to be accelerated and higher yielding (from 58% to 65%) on exposure to ultrasound, a reaction that was also applied to the amination of other ferrocenylalkyl acetates.[87] Amides derived from **121a** undergo highly diastereoselective alkylation after deprotonation with LDA, and even the use of methyl iodide as an electrophile gave greater than 97:3 diastereoselection.[86]



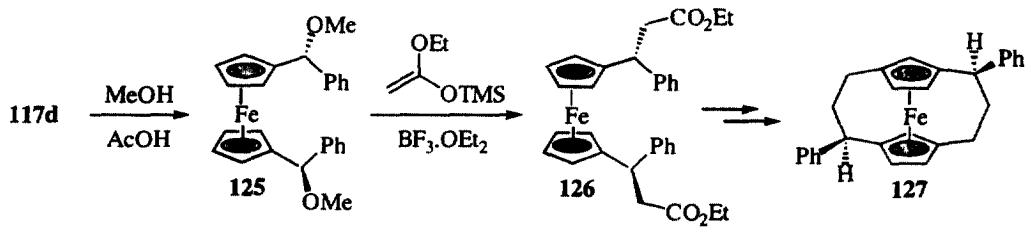
Scheme 43.

The use of the 1,1′-disubstituted diols **117** for ligand synthesis was neatly demonstrated by their quantitative conversion into acetates **122** followed by addition of either dimethylamine, methylamine or benzylamine, these substitutions proceeding with retention of configuration (Scheme 44). These secondary diamines **123**, together with the primary diamine produced on hydrogenolysis of the benzyl groups, were applied to the ruthenium catalysed transfer hydrogenation of aromatic ketones with ^{i}PrOH, selectivities of up to 90% e.e. being achieved.[88] The corresponding tertiary diamines (R^1=R^2=Me) underwent diastereoselective lithiation to give diphosphine ligands **124** after addition of Ph_2PCl.[85]



Scheme 44.

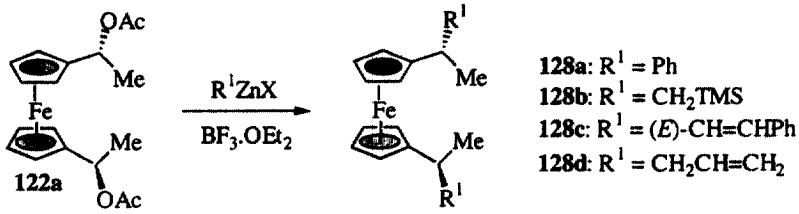
Treatment of diol **117d** with methanol and acetic acid readily provides the diether **125** via stereospecific replacement of –OH by –OMe. In turn, these methoxy groups are readily substituted using a silyl ketene acetal as a carbon nucleophile in the presence of $BF_3 \cdot OEt_2$ to give diester **126** in 96% enantiomeric excess.[89] This in turn has been further transformed into the disymmetric ferrocenophane **127** (Scheme 45).[90]



Scheme 45.

The diacetate **122a** also undergoes clean substitution with a range of organozinc reagents promoted by $BF_3 \cdot OEt_2$, and enantioselectivities of 92–98% e.e. were obtained for the resulting chiral ferrocenes

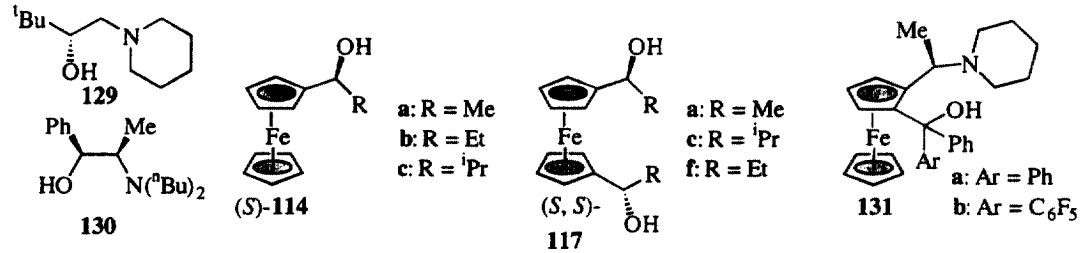
128 (Scheme 46).[91] Both this and the reaction outlined in Scheme 45, also work well on monosubstituted α-ferrocenyl acetates and ferrocenyl methyl ethers respectively.



Scheme 46.

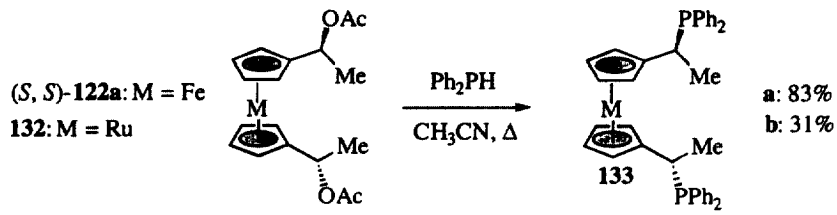
4.3. Addition of organozinc reagents to ferrocenecarboxaldehydes

In view of the success achieved utilising 1,2-disubstituted ferrocenyl amino alcohols as catalysts for the addition of dialkylzinc reagents to aldehydes, a logical extension of this work was the use of ferrocenecarboxaldehydes as substrates for this reaction. The first report of such a reaction utilised 5 mol% of amino alcohol **129** which catalysed the addition of diethylzinc to ferrocenecarboxaldehyde to give **114b** in greater than 96% enantiomeric excess.[92] Ruthenocenecarboxaldehyde gave the same result despite a longer reaction time (five versus two days). Methylation with dimethylzinc in diethyl ether over seven days gave **114a** of greater than 99% optical purity. This process has been extended to the 1,1′-ferrocenedicarboxaldehyde, catalysed by *N*,*N*-dialkylnorephedrines of which **130** was the most successful.[93] Use of 10 mol% and 50 mol% respectively of **130** with these two substrates gave a 97% yield of (*S*)-**114c** with an e.e. of 97.7%, but only a 39% yield of (*S*)-**117c**, albeit in 100% enantiomeric excess.

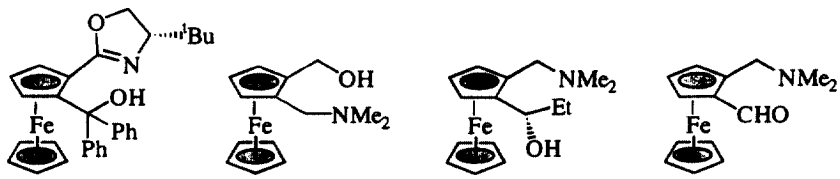


Furthermore, use of 2–5 mol% of ferrocenylaminoalcohol (−)-DFPE **131a** as a catalyst for the addition of dimethyl and diethylzinc to ferrocenecarboxaldehyde gave (*S*)-**114a** and (*S*)-**114b** in 96.6% and 99% e.e., reactions that also work equally well with ruthenocenecarboxaldehyde. Use of a modified ligand **131b** (used as an 83:17 mixture of diastereoisomers) increased the e.e. of (*S*)-**114a** to 98.4% and more than halved the reaction time to 1.5 h. at room temperature.[94] Catalyst **131a** was also successfully applied to the addition of dimethyl and diethylzinc to 1,1′-ferrocenedicarboxaldehyde (in CH_2Cl_2 and toluene respectively) to give (*S*,*S*)-**117a/f** both in >99% e.e. together with 5% of the *meso*-diols. Again these reactions worked equally well for the synthesis of the ruthenocenyldiols, and after acetylation the two acetates (*S*,*S*)-**122a** and **132** were substituted with diphenylphosphine to give the disymmetric ligands **133a/b** (Scheme 47).[95]

Generation of **62b** and addition of benzophenone has led to the synthesis of **134** in 87%, which is also an excellent catalyst (5 mol%) for the synthesis of (*R*)-**114b** formed in 95% e.e., this catalyst also producing an 87% e.e. for the addition of diethylzinc to heptanal.[96] Use of ferrocenylaminoalcohol **135**, possessing only planar chirality, in 10 mol% with diethylzinc gave a range of aryl and aliphatic (*R*)-alcohols in 64–83% e.e.[97]

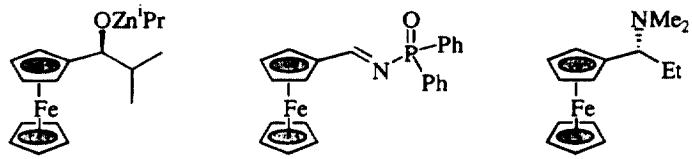


Scheme 47.



134 135 136 137

The related catalyst **136** is formed with greater than 99:1 selectivity on addition of diethylzinc to aldehyde **137**, a reaction that is complete in one minute at 20°C, in a process believed to proceed with intramolecular autocatalysis.[98] Use in turn of **136** for the addition of diethylzinc to benzaldehyde gave the (*R*)-alcohol in 62% e.e. (compare with 82% with **135**). Autocatalysis has also been reported for the addition of diisopropylzinc to ferrocenecarboxaldehyde, the product alkoxide **138** acting as a catalyst for its own formation with the same configuration in 35–39% enantiomeric excess.[99]



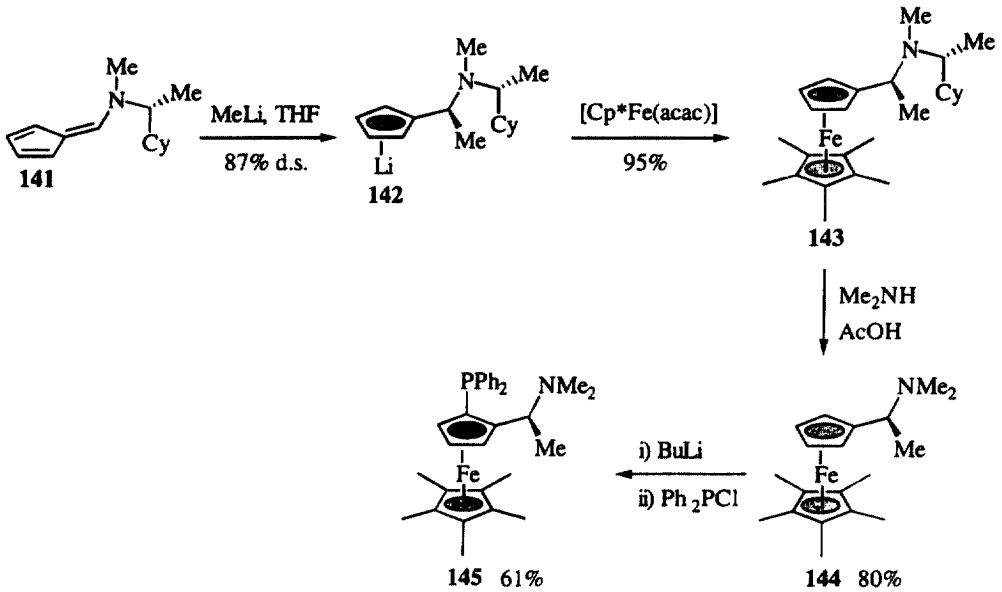
138 139 140

An alternative substrate for these reactions, the ferrocenyl imine **139**, gave amines in 76–90% e.e. on addition of dialkylzincs catalysed by **130** and related amino alcohols.[100] In an alternative synthesis of ferrocenylalkylamines, **140** was obtained from **114b** on acylation and addition of dimethylamine. This was then employed in the synthesis of the ethyl containing analogues of **2** and **3** (i.e. Et-PPFA and Et-BPPFA) which proved more effective ligands than **2** and **3** for Grignard cross-coupling and allylic substitution.[101]

4.4. Construction from chiral cyclopentadienylides

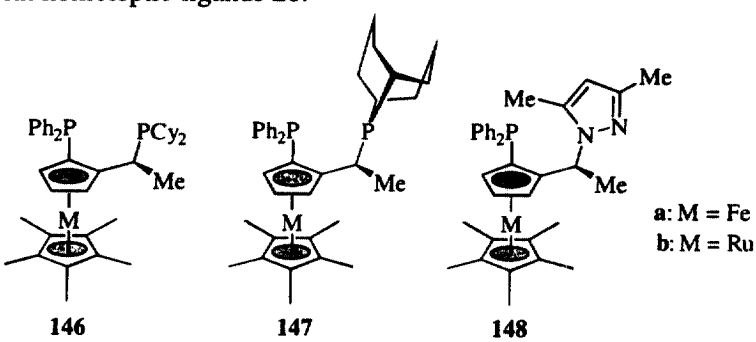
Rather than carrying out the formation of a new α-stereogenic centre on a metallocene itself, it has proved possible to construct these organometallics from appropriately substituted cyclopentadienyl anions. This technique is especially useful for the synthesis of heteroleptic systems and was first reported utilising fulvalene **141** synthesised in four steps from (*R*)-(1-cyclohexylethyl)amine. Addition of MeLi gave **142** and its diastereoisomer in a 93.5:6.5 ratio, such that on addition of [Cp*Fe(acac)] the resulting heteroleptic ferrocene **143** was formed in 95% yield. Following substitution with dimethylamine to give **144** in 75% e.e., lithiation with BuLi in Et_2O proceeds with greater than 99% diastereoselectivity to give **145** after addition of Ph_2PCl (Scheme 48). Enantiopure **145** is obtained readily as the racemate crystallises from methanol or hexane to leave an oil (>95% e.e.) that does not crystallise at room temperature.[102]

This methodology has also been applied to the ruthenocenyl analogue of **145**, and both have been



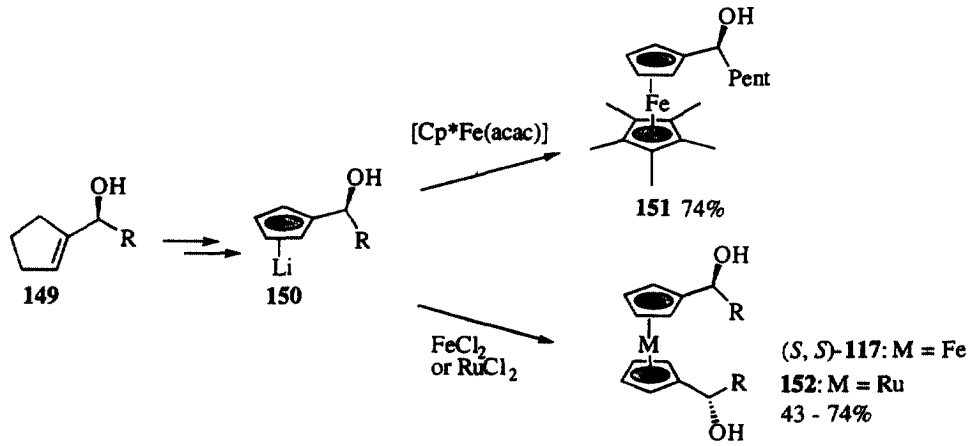
Scheme 48.

converted to ligands **146a/b–148a/b** by the routes described in Section 1. Lower activities and enantioselectivities were obtained with these ligands in palladium catalysed allylic alkylation of **7** to **8**, although **148a/b** gave 94% and 87% e.e. for the rhodium catalysed hydroboration of styrene, results comparable to those obtained with homoleptic ligands **26**.[103]

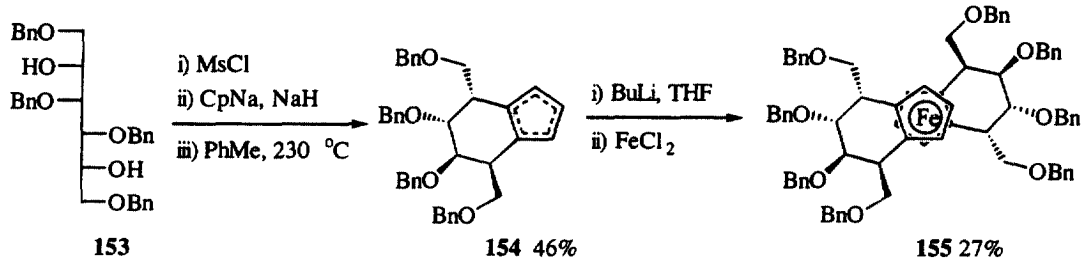


In a related method, allylic alcohols **149** produced by asymmetric (89–98% e.e.) addition of dialkylzincs to cyclopentenecarboxaldehyde, were converted in four steps to cyclopentadienyl dianions **150**. Reaction with Cp*Fe(acac) gave the heteroleptic ferrocene **151** of >96% e.e., or reaction with either $FeCl_2$ or $RuCl_3$ gave diols (*S,S*)-**117** and **152** with little (3–11%) contamination from the *meso* diastereoisomer, and a high (99%) e.e. for the two examples measured (Scheme 49).[104]

A more complex example of this methodology begins with 1,3,4,6-tetra-*O*-benzyl-D-mannitol **153** which after mesylation, undergoes double alkylation and thermolysis of the resultant spiro-annulated diene to give **154** as a mixture of three isomers. All of these are utilised in the synthesis of the highly functionalised tetrasubstituted C_2-symmetric ferrocene **155** (Scheme 50).[105]



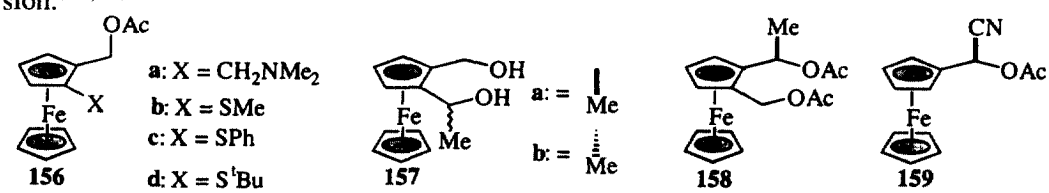
Scheme 49.



Scheme 50.

5. Lipase mediated resolutions

Lipases have been successfully utilised as catalysts for the kinetic resolution of a number of planar chiral 2-substituted hydroxymethylferrocenes. Use of vinyl acetate as an irreversible acyl donor with *Candida cylindracea* lipase (CCL) in *t*-butylmethyl ether gave **156a** in 92% e.e. at 42% conversion. This same lipase has also been used for kinetic resolution by deacylation, racemic **156a** being converted with butanol into **135** in 40% yield and 95% enantiomeric excess.[106] Similarly, the lipase from *Candida antarctica* (Novozyme®) has led to the isolation of **156b** (90% e.e. at 32% conversion), **156c** (88% e.e. at 45% conversion) and **156d** (76% e.e. at 30% conversion). For the latter substrate, improved resolution was achieved with the lipase from *Mucor miehei* (Lipozyme®) which gave 90% e.e. at 35% conversion.[107,108]

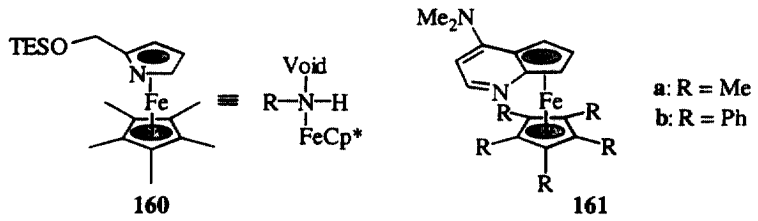


In a further application of this technique, both diastereoisomers **157a/b** were kinetically resolved to give the enantiomer drawn (**157a**: 27% yield, >97% e.e.; **157b**: 41% yield, 95% e.e.) with *Pseudomonas cepacia* lipase which recognises the opposite sense of planar chirality compared to the lipases applied to **156**, the primary hydroxyl group being acylated faster than the secondary hydroxyl group. For this lipase, the matched set of planar and central chirality elements also results in the isolation of diacetate **158** in 18% yield and 97% enantiomeric excess.[109] Furthermore, *Pseudomonas cepacia* catalyses

the kinetic resolution of ferrocene cyanohydrin, to give the acetate (*R*)-**159** isolated in 84% e.e. at 50% conversion.[110] For central chirality, Novozyme® also preferentially gives the (*R*)-acetate in high enantiomeric excess on kinetic resolution of racemic 1-hydroxyalkyl ferrocenes.[111]

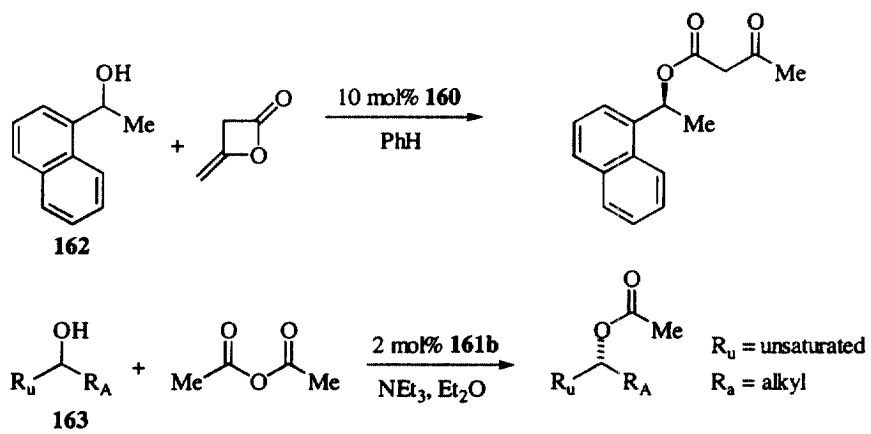
6. Heterocyclic ferrocene derivatives

A significant recent development in catalyst and ligand synthesis is the use of iron cyclopentadienyl bound heterocycles in which the heteroatom is a key component of the element of planar chirality in the resulting complex.



160 **161**

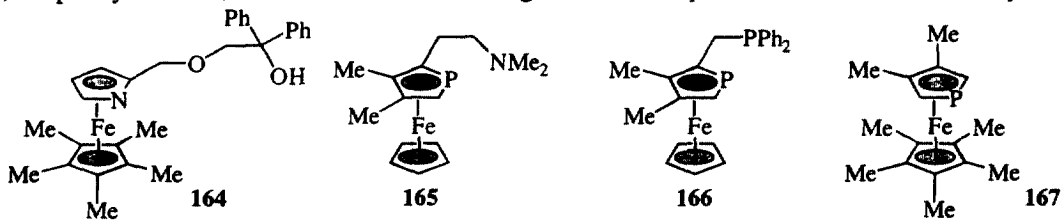
This is illustrated for the 2-substituted azaferrocene **160** with a representation of the view along its lone pair–nitrogen axis showing the differentiation of left from right, and of top from bottom. This complex is a nucleophilic catalyst for the acylation of secondary alcohols with diketene. Kinetic resolution of **162** with 10 mol% of (−)-**160** leaves (*R*)-**162** of 87% e.e. at 67% conversion (k_{fast}/k_{slow}=S=6.5, Scheme 51).[112]



Scheme 51.

Much greater levels of catalytic activity were obtained with the DMAP analogue **161a**, but no enantioselectivity was observed when 1-phenylethanol was treated with diketene in the presence of 2 mol% of (−)-**161**. This was solved with the synthesis of (−)-**161b** in which the extra bulk of the five phenyl substituents makes this an extremely efficient catalyst for the kinetic resolution of an array of secondary alcohols **163** with selectivity ratios (S) between 12 and 52 (Scheme 51). In addition, this method also utilises inexpensive acetic anhydride as the acylating agent. For example, for **162**, S equals 22, corresponding to an enantiomeric excess of 99.7% for the (*S*)-alcohol at 63% conversion.[113] These results represent a major advance in non-enzymatic kinetic resolution of alcohols by enantioselective acylation. Complexes **160** and **161** are also effective as catalysts for cyanosilylation of aldehydes and the addition of benzylalcohol to unsymmetrically substituted ketenes, although no enantioselectivities have yet been reported for these reactions. The free alcohol of (−)-**160** (a β-amino alcohol) has been used as

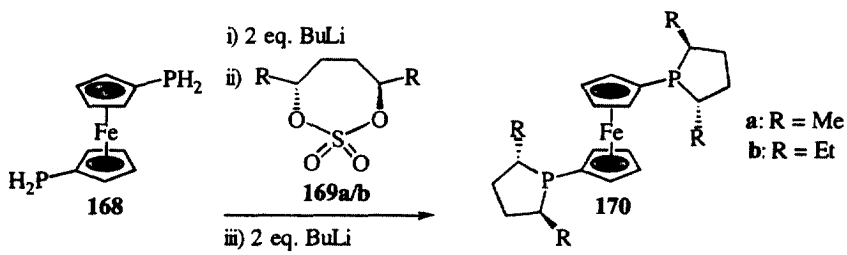
a catalyst (3 mol%) for the addition of diethylzinc to aldehydes, an e.e. of 51% being obtained for (*S*)-1-phenyl-1-propanol. This increased to 90% e.e. with the modified catalyst **164** obtained on *O*-alkylation with 1,1-diphenyloxirane, similar selectivities being obtained for *para*-substituted benzaldehydes.[114]



A series of related 2-substituted phosphaferrocenes have also been reported of which P,N and P,P chelates **165** and **166** are representative examples.[115,116] Several transition metal complexes of these ligands have also been reported, notably that between **165** and Cp*RuCl which is formed as a single diasteroisomer. All of these ligands are derived from a common 2-formylphosphaferrocene which has been resolved via column chromatography of its diastereomeric aminals derived from 1,2-di(*N*-methylamino)cyclohexane.[117] The achiral phosphaferrocene **167** has been reported to act as a nucleophilic catalyst for the ring opening of epoxides with trimethylsilyl chloride.[118]

7. Miscellaneous diphosphine ligands

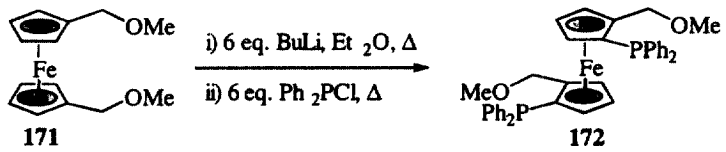
The two 1,1′-di(phospholano)ferrocene ligands **170a/b** are readily prepared in excellent overall yield in which the last reaction combines 1,1′-diphosphinoferrocene **168** with cyclic sulfates **169a/b** (Scheme 52).



Scheme 52.

After conversion to their corresponding rhodium catalyst precursors [(COD)Rh(**170a/b**)]$^+$TfO$^-$, they were found to give reasonable enantioselectivities for the hydrogenation of methyl *N*-α-acetamidoacrylate (**a**=64% e.e., **b**=83%) and dimethyl itaconate (**a**=72% e.e., **b**=83%). More significantly, the hydrogenation of the β-keto ester, methyl acetoacetate, was achieved under mild conditions (25°C, 60 psi H_2) although with modest selectivity (**a**=33% e.e., **b**=58%). This high catalytic activity is believed to be a result of the conformational flexibility of these electron rich phosphines. In contrast, conformationally restricted 1,2-phenylene derived DUPHOS ligands are ineffective for ketone reduction under these mild conditions.[119]

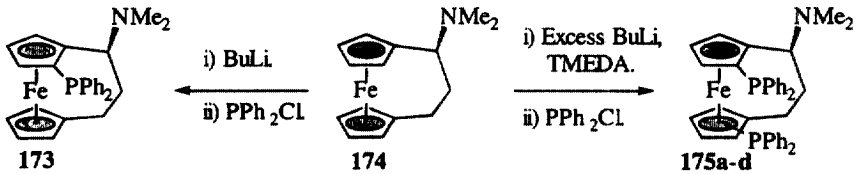
A highly diastereoselective, although not yet enantioselective, synthesis of disymmetric diphosphine **172** was reported from diether **171**, itself obtained in 82% overall yield from ferrocene. Addition of six equivalents of BuLi in Et_2O to **171** followed by heating at reflux for 14 h and addition of Ph_2PCl, gave racemic **172** in 63% yield with only 3% of the *meso*-diastereoisomer (Scheme 53). The two were readily separated by chromatography.[120]



171 172

Scheme 53.

Finally, the dimethylaminoferrocenophane **174**, a conformationally restricted varient of amine **1**, also undergoes highly selective lithiation although with the opposite sense of diastereoselection. Addition of Ph_2PCl gave **173** for which the $PdCl_2$ adduct has also been reported.[121] Repetition of this lithiation with excess BuLi–TMEDA led to the four separable aminodiphosphinoferrocenophanes **175a–d**: **a**=2,2′-(43.6%), **b**=2,3′- (6.3%), **c**=2,4′- (4.8%), **d**=2,5′-(6.8%) (Scheme 54). Each was further converted, by removal of the dimethylamino group in two or three steps, to its corresponding trimethylene bridged ligand.[122]



173 174 175a-d

Scheme 54.

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