The syntheses and catalytic applications of unsymmetrical ferrocene ligands

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Interest in the chemistry of ferrocene remains intense, largely due to applications within catalysis. New synthetic routes to unsymmetrical ferrocene ligands have provided another facet to this area, as substituents can be designed to be electronically- and/or sterically-distinct in order to affect the environment around the catalytically-active metal centre. This *critical review* provides a concise summary of the synthetic routes that have been applied to the synthesis of unsymmetrical ferrocene ligands, along with a systematic survey of the applications of these ligands in homogeneous catalysis. The aim is to help the reader select a suitable ferrocenediyl ligand for a particular synthetic application, and in the synthesis of ligands that require particular structural and/or electronic features. (186 references.)

1 Introduction and scope

Even though it was first discovered over 50 years ago, research into ferrocene-containing compounds continues apace, largely due to applications within catalysis and materials science.[1,2] In coordination chemistry, the ferrocene moiety has played a significant role as a backbone or a substituent in ancillary ligands due to (i) the specific and unique geometries that the ferrocene provides and (ii) its electronic (redox) properties, whereby the possibility of switching the redox state of the ferrocene backbone gives access to potential control of reactivity at a metal centre.

This review will focus on the application of unsymmetrical ligands with a ferrocene backbone to homogeneous catalysis—with regard to both organic synthesis and industry. Unsymmetrical ligands have many potential advantages in catalysis: the substituents may be designed to be electronically and sterically distinct in order to alter the environment around the catalytic metal centre in such a way as to increase the turnover or, in some cases, to allow the catalysis to happen at all. Enantiomerically pure versions of chiral unsymmetrical ligands may favour the formation of a product with a particular configuration so allowing asymmetric catalysis. Alternatively, a ligand that contains both substitutionally labile and

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Vernon Gibson was born in Grantham, England in 1958. He received his BSc degree from the University of Sheffield in 1980 and his DPhil degree from the University of Oxford in 1984 with Malcolm Green. He was a NATO postdoctoral fellow with John Bercaw at Caltech from 1984 to 1986 before being appointed to a lectureship in Inorganic Chemistry at the University of Durham, England. He was promoted to Professor at Durham in 1992, and in 1995 moved to Imperial College where he now holds the Sir Edward Frankland BP Chair of Inorganic Chemistry. His research interests include fundamental aspects of metal coordination and

organometallic chemistry, and applications of discrete metal complexes in polymer synthesis.

Nick Long, born in Bristol in 1965, obtained a BSc from the University of Durham and a PhD from the University of Exeter in 1989 under the supervision of Eddie Abel and Tony Osborne. He was a Demonstrator in Inorganic Chemistry in Exeter before moving to the University of Cambridge to become the Adrian Research Fellow with Darwin College. In January 1995, he was appointed to a lectureship in Inorganic Chemistry at Imperial College London and he is now a Reader in Inorganic Chemistry. His expertise lies in synthetic chemistry, particularly transition metal and lanthanide coordination and organometallic chemistry, and areas of interest within catalysis and materials science include multidentate, hemilabile N, S, P-donor ferrocene ligands, substituted phthalocyanines and aza-macrocycles, and transition metal alkynyl complexes.

Vernon Gibson (left) Rob Atkinson (centre) Nick Long (right)

substitutionally inert groups may act in a hemilabile fashion. The term "hemilabile" was first coined by Jeffrey and Rauchfuss in 1979.[3] The weakly coordinating group can stabilise coordination sites on a transition metal centre until displaced by a substrate molecule. The presence of the inert group means that the ligand remains anchored to the transition metal centre. These characteristics have meant that hemilabile ligands have found numerous applications in homogeneous catalysis.[4] Unsymmetrical systems utilising a variety of heteroatoms are known. For example, P/S,[5] P/O,[6] P/N[7–9] and N/O[10–12] systems have been employed in catalytic applications.

Since the 1970s, numerous ligands derived from ferrocene have been used in homogeneous catalysis—this review will concentrate on unsymmetrical ligands synthesised up to August 2003. It should be noted that, in some cases, the coordination mode of the ligand to the metal centre in a catalytic system has been established through the synthesis and characterisation of model metal complexes which provide mechanistic information about the catalytic process under study. However, in other cases the catalytic efficacy of the ligand has been determined with little evidence for the manner in which the ligand actually interacts with the catalytic metal centre—these ligands are also considered herein however. For completeness, unsymmetrical ligands featuring the same heteroatom donors are also considered as the steric and electronic effects of different substituents on a given heteroatom can greatly influence its coordinating strength and therefore the steric and electronic environment around the catalytic metal centre. Although this review focuses on ligands with at least one heteroatom directly bonded to the cyclopentadienyl ring of the ferrocene, a few examples with a carbon spacer between the heteroatom and the cyclopentadienyl ring are also included where noteworthy applications have been found in catalysis.

This review attempts to provide the reader with a concise summary of the synthetic routes that have been applied to the synthesis of unsymmetrical ferrocene ligands. A systematic survey of the applications of these ligands in catalysis is also presented, grouped according to the route by which the ligand was synthesised. This highlights the flexibility of the ligand syntheses that have been developed in producing a wide range of ligand types with varied applications from a common starting material. The modifications made to the standard ligand types to improve the performance of the ligands are analysed and conclusions drawn about the structural features common to successful ligands for selected catalytic processes. During the preparation of this review, an excellent review by Colacot[13] has been published detailing the applications of chiral ferrocenyl phosphines in homogeneous catalysis leading to organic synthesis. To complement this, we aim to provide an introduction to a wider range of ligand types and catalytic processes to aid the reader in the selection of a suitable

ferrocenyl ligand for a particular synthetic application, and in the synthesis of ligands with the required structural features for novel applications.

A brief mention must be made of the symmetrical ligand 1,1′-bis(diphenylphosphino)ferrocene [dppf], which has found wide application in organometallic cross-coupling reactions, hydroformylation, hydrogenation and hydrosilylation reactions. The applications of dppf and related symmetrical ferrocenyl bis-(phosphine) ligands in catalysis are well-known and have been reviewed separately elsewhere.[14,15]

2 General synthetic routes to unsymmetrical ferrocenes

There are two distinct classes of disubstituted unsymmetrical ferrocenyl ligand that have been utilised in catalysis. The two substitution patterns are shown in Fig. 1. 1,2-unsymmetrically

Fig. 1 The two types of disubstituted unsymmetrical ferrocene ligand.

disubstituted ligands possess planar chirality and as such may be synthesised in enantiomerically pure form. 1,1′-unsymmetrically disubstituted ligands are less common due to the difficulty in preventing either 1,2-substitution or symmetrical substitution to both cyclopentadienyl (Cp) rings. The main synthetic routes that have been employed in the synthesis of both 1,1′- and 1,2-unsymmetrical ferrocenes will be considered. The synthesis of 1,2-unsymmetrical ligands will only be covered briefly as this has been reviewed in more detail elsewhere.[16–21]

2.1 Synthetic routes to 1,1′-unsymmetrical ferrocenes

Controlled 1,1′-dilithiation of ferrocene by n-BuLi in the presence of the chelating diamine TMEDA is the usual method by which substituents are introduced to the 1 and 1′-positions. Three main synthetic methods have been developed for the synthesis of 1,1′-unsymmetrical ligands, as shown in Fig. 2. Cullen first utilised the ring opening of 1-phenyl-1-phospha-[1]-ferrocenophane 1 to synthesise unsymmetrical bis(phosphino)ferrocene derivatives.[22] In 1992, Adeleke utilised the selective transmetallation of 1,1′-bis(tri-n-butylstannyl)ferrocene 2 at low temperatures using n-BuLi followed by addition of an electrophile.[23] The selective lithium–halogen exchange of 1,1′-dibromoferrocene 3, first developed by Dong in 1994,[24] has been used by both Dong[25,26] and Butler,[27] amongst others, to synthesise a variety of unsymmetrical ferrocene
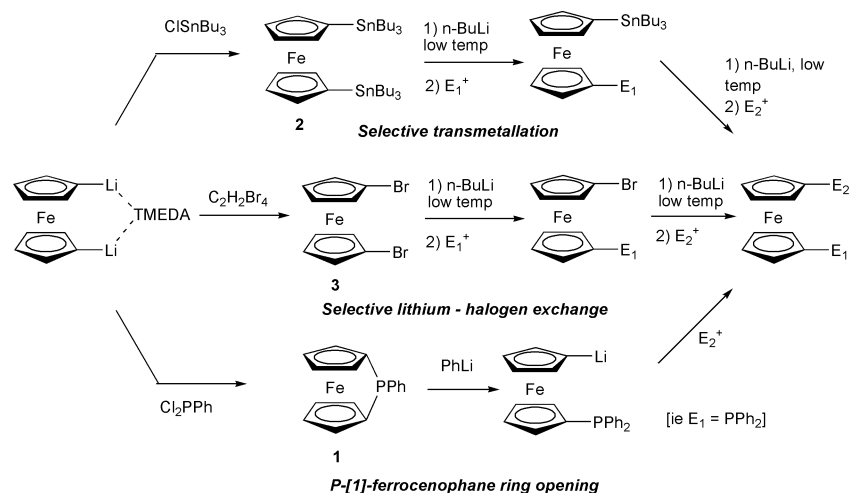

Fig. 2 Synthetic routes to 1,1′-unsymmetrical ferrocene ligands.

derivatives in high yields. An alternative route to sulfur-containing unsymmetrical ferrocenes has recently been developed by Long *via* a di(ferrocenyl)disulfide intermediate as shown in Fig. 3.[28,29] Very recently it has been shown that lithiation of Boc-protected 1-ferrocenylethylamine with two equivalents of *n*-BuLi results in selective *N*,1′-dimetalation. A variety of 1,1′-unsymmetrical ferrocenes have been synthesised by using different quenching agents.[30]

Section 3 details the particular ligands that have been synthesised and their catalytic applications. Although the primary focus of this review is the range of ligands that have been used in catalytic applications, because of the relative scarcity of 1,1′-unsymmetrical ligands, unsymmetrical ferrocenes whose catalytic potential has not yet been demonstrated are also included.

2.2 Synthetic routes to 1,2-unsymmetrical ferrocenes

2.2.1 Ligands derived from *N*,*N*-dimethyl-1-ferrocenylethylamine. The presence of a substituent containing a suitably located donor atom on one of the Cp rings directs lithiation to the adjacent position. Quenching the resulting lithioferrocene derivative with a suitable electrophile results in 1,2-substitution. The synthesis of enantiopure planar-chiral ferrocene derivatives requires diastereoselective *ortho*-lithiation. This was first achieved by Ugi who reported the asymmetric *ortho*-lithiation of enantiomerically pure *N*,*N*-dimethyl-1-ferrocenylethylamine **4** using *n*-BuLi in 1970,[31] as shown in Fig. 4. It was found that addition of a further equivalent of *n*-BuLi together with TMEDA induced lithiation on the other Cp ring forming a dilithiated species. A variety of electrophiles have been reacted with the lithiated species to form disubstituted ligands and selected examples are shown in Fig. 5. The NMe$_2$ moiety can undergo exchange reactions and in this way has been replaced by different heteroatoms to form other catalytically important ligands. Some catalytically important examples are shown in Fig. 6.

2.2.2 Ligand synthesis using other *ortho*-directing groups. Other *ortho*-directing groups have been utilised apart from the *N*,*N*-dimethylaminoethyl group. Chiral sulfoxide groups are thought to induce asymmetric lithiation *via* the same mechanism as that for the *N*,*N*-dimethylaminoethyl species with the bulky alkyl group preferring to orient itself away from the ferrocene ring.[32] The sulfoxide moiety may be reduced back to the thioether by reduction

with HSiCl$_3$ and Et$_3$N in refluxing toluene.[33] The acetal formed from the reaction between ferrocenecarboxaldehyde and (*S*)-1,2,4-butanetriol also induces asymmetric *ortho*-lithiation on the Cp ring. Subsequent acetal hydrolysis leads to a planar chiral 1,2-disubstituted ferrocenecarboxaldehyde derivative (Fig. 7).[34,35]

An important *ortho*-directing group is the oxazoline moiety. Ferrocenyloxazolines are readily synthesised *via* the reaction of ferrocenecarboxylic acid with amino alcohols. The diastereoselective *ortho*-lithiation of ferrocenyloxazolines to synthesise chiral 2-ferrocenyloxazolines was simultaneously discovered by Sammakia,[36] Richards[37,38] and Uemura.[39] The greatest diastereoselectivity is obtained using a mixture of *sec*-BuLi and TMEDA in hexane. The SAMP hydrazone shown in Fig. 8 also induces very diastereoselective *ortho*-lithiation. The hydrazone may be cleaved with ozone, SnCl$_2$ or TiCl$_3$ to unmask the benzoyl group.[40]

Finally, addition of an enantiopure chiral molecule to the reaction mixture may be used to bring about diastereoselective lithiation. Chiral lithiating agents such as a chiral lithium amide (Fig. 9) have been shown to induce *ortho*-lithiation.[41] (−)-Sparteine-mediated lithiation of *N*,*N*-di-*iso*-propyl ferrocenecarboxamide proceeds with very high stereoselectivity.[42]

To form one diastereomer in appreciable excess, an enantiomerically pure ferrocene starting material with a suitable stereogenic centre is normally crucial in directing the *ortho*-lithiation. The generation of a suitable enantiomerically-enriched ferrocenyl starting material may be achieved by chiral resolution or asymmetric synthesis.[17,43]

3 Examples of 1,1′-unsymmetrical ferrocene derivatives

This section describes examples of 1,1′-unsymmetrical ferrocenes that have been synthesised *via* the methods discussed in Section 2.1, and their applications within catalysis.

3.1 P/P Ligands

Fig. 10 illustrates some unsymmetrical 1,1′-P/P ligands that have been synthesised to date. The first unsymmetrical 1,1′-P/P ferrocene derivatives, 1-(diphenylphosphino), 1′-(di-*tert*-butylphosphino)ferrocene **15**[22] and 1-(diphenylphosphino), 1′-(di-*iso*-propylphosphino)ferrocene **16**[44] were synthesised by Cullen in 1985 *via* P-[1]-ferrocenophane ring opening. By reacting the P-
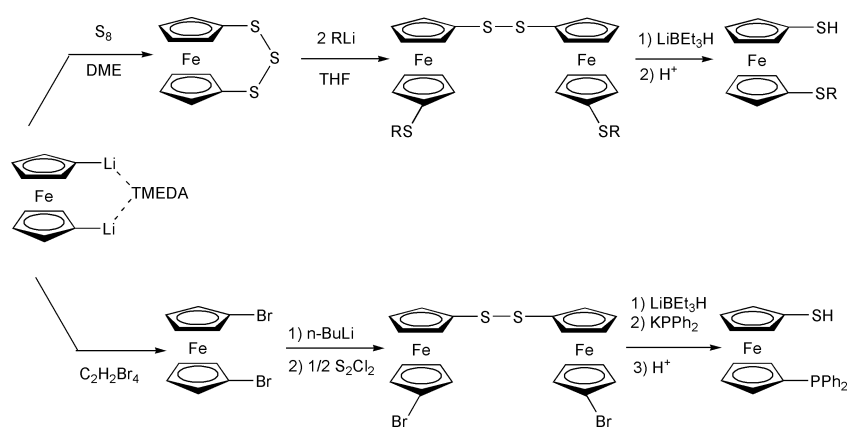

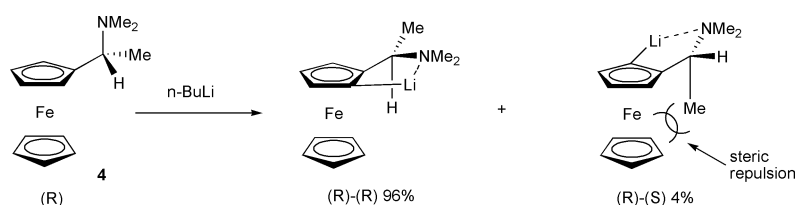**Fig. 3** Synthetic route to sulfur-containing ferrocene ligands *via* disulfides.

Fig. 4 Diastereoselective *ortho*-lithiation of (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine.
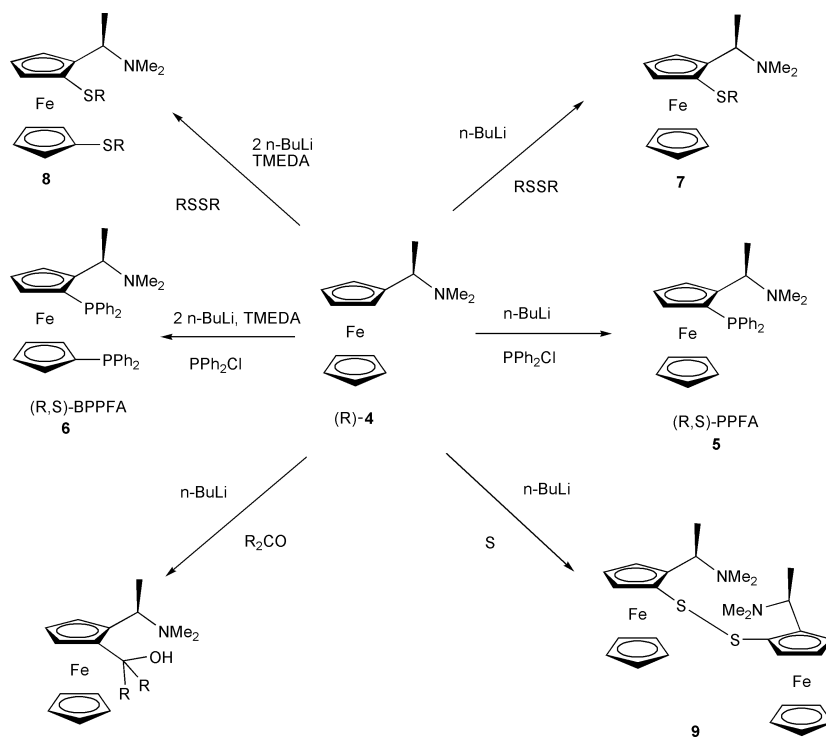
Fig. 5 Ligands derived from *N,N*-dimethyl-1-ferrocenylethylamine.
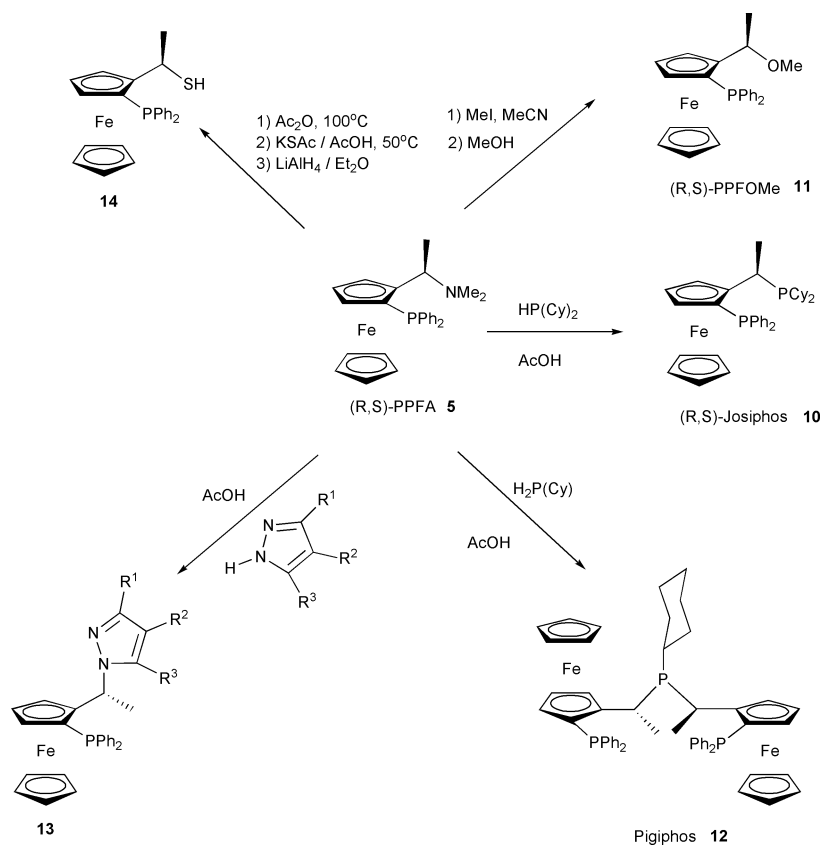

Fig. 6 Ligands derived from PPFA *via* nitrogen exchange reactions.
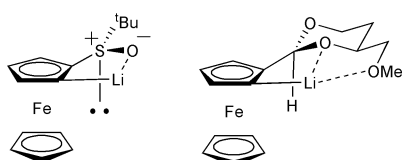

Fig. 7 Use of sulfoxide and acetal *ortho*-directing groups.

[1]-ferrocenophane (1,1′-ferrocenediyl)phenylphosphine **1** with *tert*-butyllithium, unsymmetrical ligands such as **17** were synthesised containing an asymmetrically substituted phosphine.[22] A cationic rhodium complex of **15**, [(**15**)Rh(NBD)]ClO$_4$, has been used as an olefin hydrogenation catalyst.[45] Boyes found that a palladium(II) complex of **16** was found to be a reasonable catalyst precursor for the Heck coupling of iodobenzene with methyl acrylate.[46] However, it should be noted that although **16** performed
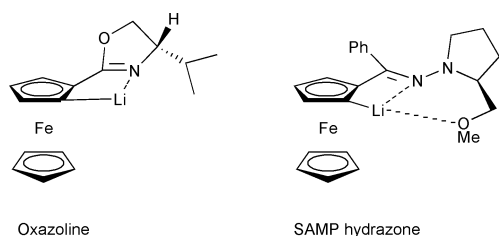
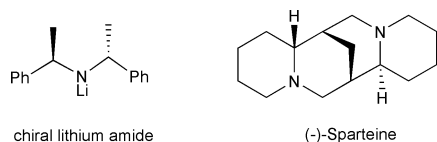Fig. 8 Use of oxazoline and SAMP hydrazone *ortho*-directing groups.

chiral lithium amide   (−)-Sparteine

Fig. 9 Use of chiral lithiating agents and (−)-sparteine-mediated lithiation.

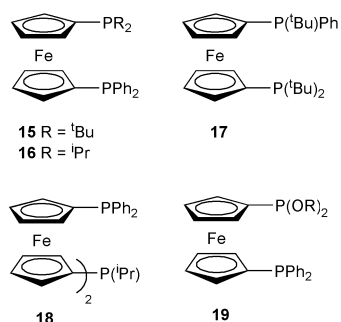15 R = ^{t}Bu
16 R = ^{i}Pr

17

18

19

Fig. 10 Unsymmetrical 1,1′-P/P ligands.

better than dppf, disoppf was a superior ligand to both indicating that the unsymmetrical nature of the ligand was not the most important factor. 16 has also been synthesised *via* selective lithium–halogen exchange by Dong.[26] In addition, this method was used by Butler to synthesise diferrocenyltriphosphine ligands such as 18.

1,1′-Unsymmetrical phosphine-phosphonite derivatives 19 have been synthesised by Broussier *via* ring opening of (1,1′-ferrocene-diyl)phenylphosphine with phenyllithium followed by addition of PCl$_3$. The resulting dichlorophosphine was reacted with various alcohols in the presence of NEt$_3$ to form the phosphine-phosphonite ligand.[47] Preliminary catalyst test data is reported for the corresponding Pd and Rh complexes of 19 showing promise for the Heck reaction and hydroformylation respectively.

Recently, phosphorus-chiral ferrocenyl diphosphines have been synthesised as shown in Fig. 11. 20, in which chirality is derived
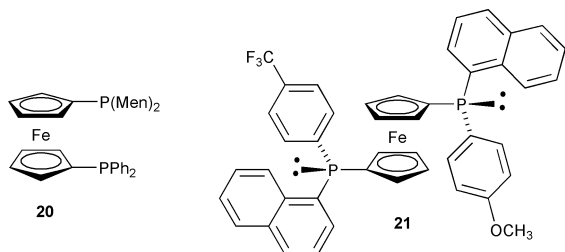

20

21

Fig. 11 P-Chiral ferrocenyl diphosphine ligands.

from the optically active (1R,3R,4S)-menthyl substituents, was synthesised *via* both selective lithium–halogen exchange and P-[1]-ferrocenophane ring opening.[48] A rhodium complex of 20 (generated *in situ*) was used as an asymmetric hydrogenation catalyst giving high yields but only moderate enantiomeric excess (ee) with a variety of substrates. The nickel-catalysed Grignard cross-coupling of 1-phenylethylmagnesium chloride with vinyl bromide was also investigated but 20 produced only a low ee.

The P-chiral diphosphine 21, synthesised *via* selective lithium–halogen exchange, has been used in rhodium-catalysed hydroformylation[49] and palladium-catalysed asymmetric allylic substitution.[50] (However, symmetrical ligands with different electronic properties in the former case or steric properties in the latter case were found to be more efficient.)

Finally, mixed phosphine-thiophosphine and phosphine-phosphine oxides have recently been synthesised (Fig. 12). The
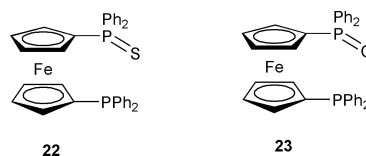

22   23

Fig. 12 Mixed phosphine-thiophosphine and phosphine-phosphine oxide ligands.

palladium complex of 22 (which itself is synthesised by the reaction of dppf with elemental sulfur) was tested as a catalyst for the Heck reaction[51] using the same conditions as Boyes (decribed previously)[46] and was found to show promising activity. Importantly, whereas Boyes found that dppf gave a 7% yield of product, the corresponding phosphine-thiophosphine ligand gave a 90% yield which is thought to be due to the hemilabilisation of dppf brought about by selective sulfination.

Grushin has recently developed a palladium-catalysed biphasic catalytic route to bis-phosphine monoxides (BPMOs) including the potentially hemilabile ferrocene 23 shown in Fig. 12.[52,53] Although 23 has not yet been applied in homogeneous catalysis, other BPMOs have proved useful in catalysis and therapeutic applications.

3.2 P/S Ligands

1,1′-P/S ferrocene derivatives that have been synthesised to date are shown in Fig. 13. The first 1,1′-P/S ferrocene 24 was synthesised in
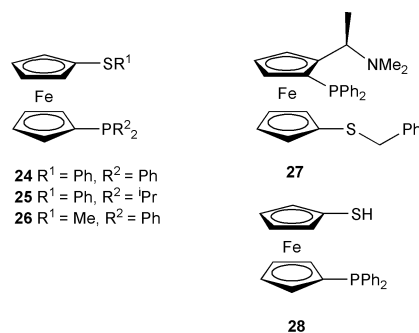

24 R^1 = Ph, R^2 = Ph
25 R^1 = Ph, R^2 = ^{i}Pr
26 R^1 = Me, R^2 = Ph

27

28

Fig. 13 Unsymmetrical 1,1′-P/S ligands.

1992 by Adeleke *via* the selective transmetallation route.[23] 24 was also synthesised by Dong *via* selective lithium–halogen exchange,[25] and 25 was prepared *via* the same method. 26, synthesised by both P-[1]-ferrocenophane ring opening and by direct reaction of dilithioferrocene with ClPPh$_2$ and Me$_2$S$_2$ followed by chromatographic purification,[54] has found application in conjunction with Pd$_2$(dba)$_3$ as a catalyst for the Suzuki cross-coupling reaction.[55] A *pseudo-C$_2$*-symmetric planar chiral version of 26 has been synthesised with CHEt$_2$ groups in the 2 and 2′ positions of the Cp rings. Poor enantioselectivity was obtained in Pd-catalysed allylic alkylation reactions, but it is interesting to note that better results were obtained than with the *C$_2$*-symmetric bisphosphine analogue.[56] 27 has been used to facilitate the copper-catalysed asymmetric addition of diethyl zinc to alkylidene malonates.[57] Whilst 28 is the first example of a ferrocenyl phosphine-thiol ligand,[29] any catalytic activity has yet to be demonstrated.

3.3 P/O Ligands

Very recently, 1,1′-P/O ferrocenyl ligands have been synthesised *via* selective lithium-halogen exchange as shown in Fig. 14. 29 and
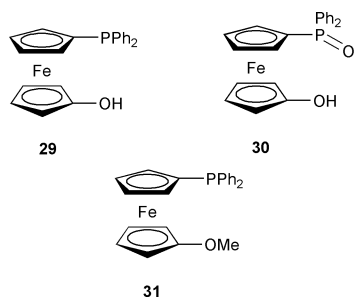

Fig. 14 Unsymmetrical 1,1′-P/O ligands.

30[58] are the only examples of 1,1′- unsymmetrical hydroxyferrocene ligands, whose applications in catalysis are currently under study. **31** is the only example of a 1,1′-unsymmetrical ferrocenyl ether ligand.[59] It is recently formed but its coordination chemistry has been extensively studied with transition metal precursors. Preliminary results show that it is an effective ligand for the Suzuki cross-coupling reaction in conjunction with Pd precursors.

3.4 1,1′-Ferrocenyloxazoline ligands

Recently, 1,1′-unsymmetrical ferrocenyloxazolines have been synthesised and the unsymmetrical substitution was achieved *via* the selective lithium–bromine exchange route to yield 1′-(bromo-)ferrocene-1-carboxylic acid. The corresponding acid chloride was then reacted with the aminoalcohol (*S*)-valinol to form the β-hydoxy amide which was subsequently cyclised to form the oxazoline.[60,61] The selective transmetallation route has also been utilised to synthesise similar derivatives[62] and examples that have found applications in catalysis are shown in Fig. 15.
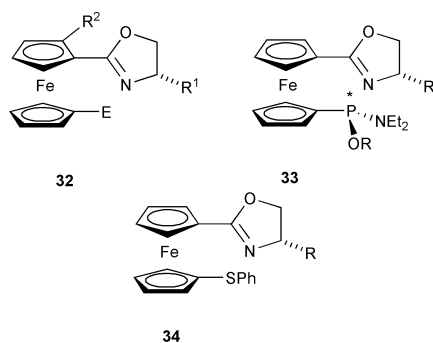

Fig. 15 Unsymmetrical 1,1′-ferrocenyloxazoline ligands.

32 (E = PPh$_2$, R^2 = H) and **34** have been used in Pd-catalysed asymmetric allylic alkylations. The thioether **34** gave lower yields and enantiomeric excesses (ee) than **32**[61,62] and the enantioselectivity may be tuned by the inclusion of methyl, trimethylsilyl or tributylstannyl groups in the 2 position.[63] **32** (E = PPh$_2$, R^2 = TMS, Me, SnBu$_3$) has also been used in Pd-catalysed asymmetric allylic amination[64] and asymmetric Heck reactions[65] whilst **33**, containing a stereogenic centre on the P atom, gives highly regio- and enantio-selective Pd-catalysed asymmetric allylic alkylation and amination of allylic acetates.[66] **32**, **33** and related 1,2-ferrocenyl oxazolines are the subject of a recent review by Hou and Dai[20] which discusses the role of planar chirality in allylic substitution and asymmetric Heck reactions.

32 (E = CPh$_2$OH, R^1 = t-Bu, R^2 = Me or H) has been synthesised recently by Hou and the influence of planar chirality on the catalytic addition of diethylzinc to aldehydes investigated. It was found that when the planar chiral ligand with R^2 = Me was

used, ee's of up to 95% were obtained whereas the ee dropped to 89% using **32** (R^2 = H) possessing solely central chirality.[67]

3.5 Other 1,1′-ferrocenes

1′-(diphenylphosphino)ferrocene-1-carboxylic acid **35** was synthesised by Stepnicka *via* P-[1]-ferrocenophane ring opening.[68] A 2-(trimethylsilyl)-substituted version **36** (Fig. 16) has recently been synthesised from the corresponding oxazoline by Hou and Dai.[69] When applied to the Pd-catalysed asymmetric allylic alkylation of cycloalkenyl acetates, this ligand was shown to give good yields and enantiomeric excesses.
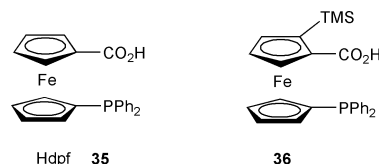

Fig. 16 Unsymmetrical 1,1′-ferrocenylcarboxylic acids.

Other 1,1′-unsymmetrical ferrocenes that have been synthesised *via* the selective lithium–halogen exchange route include those shown in Fig. 17. Although none of these have been used in catalytic applications, they demonstrate the wide applicability of this technique to synthesise 1,1′-N/C,[70] P/N[70] and P/C[26] ligands, and there appears to be excellent future scope.
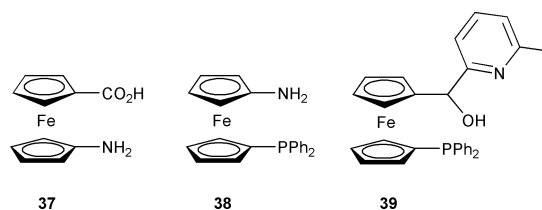

Fig. 17 Other 1,1′-unsymmetrical ligands synthesised *via* the selective lithium halogen exchange route.

4 Examples of 1,2-unsymmetrical ferrocenes

A large number of 1,2-unsymmetrical ligands have found application in a variety of catalytic processes. This section focuses only on ferrocenes that have been used in catalysis and classifies the ligands by their synthetic route detailing the catalytic processes they have been applied to.

4.1 Ligands derived from N,N-dimethyl-1-ferrocenylethylamine

4.1.1 P/N Ligands. PPFA **5** first synthesised by Kumada and Hayashi[71] has itself been applied to a number of catalytic processes. One of the earliest examples of the use of a chiral ferrocene ligand in asymmetric catalysis was demonstrated by Kumada and Hayashi in the Ni- or Pd-catalysed asymmetric cross-coupling of alkyl Grignard reagents with vinyl halides in up to 68% ee.[72] The asymmetric induction is thought to result from coordination of the amine nitrogen to the magnesium of the Grignard reagent so directing the cross-coupling. A Pd complex was isolated and characterised as a 1 : 1 PPFA : Pd P/N chelated complex. **5** was also used in the Pd catalysed preparation of optically-active allyl silanes using asymmetric Grignard cross-coupling in very high enantiomeric excess (93–95 % ee).[73] The Pd-catalysed asymmetric cross-coupling of *ortho*- and *meta*-substituted (arene)chromium carbonyl complexes with vinylic boronic acids was achieved in up to 44% ee using **5**. Although the enantiomeric excess was low, **5** outperformed other chiral ligands such as (*R*)-BINAP, (*S,S*)-DIOP and (*S*)-Valphos possessing only central chirality, suggesting that planar chirality might have been an important feature of **5**.[74] **5** performed less well in Ru-catalysed transfer hydrogenation, giving no enantioselectivity in the transfer hydrogenation of acetophenone.[75]

The postulated mechanism involves decomplexation of the N heteroatom: the hemilability of **5** with Ru means that the chiral induction is lost. The first asymmetric Suzuki cross-coupling of aryl halides and boronic acids to synthesise chiral binaphthalene derivatives was achieved most effectively using **5**.[76] The selectivity in this reaction is thought to arise from nitrogen-boron complexation directing the enantiomeric induction prior to transmetalation. (It should be noted that PPFOMe **11** gave much lower ee's because boron-oxygen complexation is not possible.)

Replacement of the NMe$_2$ group by a variety of other alkyldiamines or cycloamines or replacement of the PPh$_2$ group by other phosphines has been achieved in order to tune the catalytic properties of the ligand. Hybrid ligands of the general structure **40** (Fig. 18) have been used in the Pd-catalysed hydrosilylation of 1,3-dienes with good activity,[77] where the ligand contained a perfluroalkyl side chain giving increased solubility of the Pd complex at low temperature. Recently, Boaz has shown that the aminophosphine **40** (R^1 = Ph, R^3 = PR$_2$) gives very high activity and enantioselectivity in the Rh-catalysed asymmetric hydrogenation of amino acids, itaconic acids and α-ketoesters.[78] The ligand forms a 7-membered P/P chelate with Rh which was thought to be responsible for the high activity since it undergoes internal reorganisation faster than 5-membered analogues. The Pd catalysed arylation of *tert*-cyclobutanols leads to enantioselective C–C bond cleavage affording chiral ketones. This was achieved in up to 78% ee using **40** (R^1 = Ph, R^2 = Me, R^3 = Cy) by Uemura[79] but using **40** (R^1 = Ph, R^2 = Me, R^3 = Adamantyl) gives better ee's of up to 95%. PPFA-type ligands were compared with various other chiral P/N ligands and it was found that planar chirality was important together with a stereogenic centre of matched configuration. Although it was deduced that a 1 : 1 **40** : Pd complex was formed, no other information on the structure of the active catalyst has been found so far.[80] **41** has also been synthesised (although not derived from *N,N*-dimethyl-1-ferrocenylethylamine) with a methylene spacer between the stereogenic centre and Cp ring.[81] This was found to give much lower ee's in the Ni-catalysed Grignard cross-coupling reaction, however. The greater distance of the amino group from the planar chiral ferrocene moiety responsible for the enantiomeric induction makes the stereocontrol by coordination to the Mg atom of the Grignard reagent less effective and hence the enantiomeric excess is lowered.

BPPFA **6** and its derivatives with the general structure **42** (Fig. 18) have also found application in a wide variety of catalytic processes. The Au-catalysed aldol reaction developed by Ito has been used in the synthesis of chiral oxazolines, which are precursors for β-hydroxyamino acids. Although BPPFA gives almost racemic oxazolines,[82] by carefully tuning the amino group it is possible to synthesise enantiomerically pure oxazolines in up to 97% ee and 94% yield.[83] A wide variety of amine end groups were tested and it was found that a terminal amine provided a key role in forming an ammonium enolate with isocyanoacetate. **42** (R^1 = Me, R^2 = CH$_2$CH$_2$N-morpholine) was found to be the most effective ligand. The catalysed reaction and the postulated stereoselective transition state are shown in Fig. 19. Ito found that Au seemed
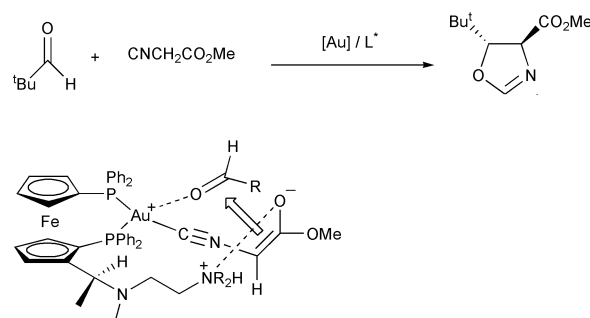

Fig. 19 The Au-catalysed aldol reaction and stereoselective transition state.

essential due to its high affinity for phosphorus whereas Cu and Ag formed undesirable species by coordinating to N atoms in the ligand disrupting the stereoselective transition state.[82] **42** (R^1 = Me, R^2 = CH$_2$CH$_2$N-cyclopentyl) was used in the aldol reaction between aldehydes and isocyanophosphonates which are important precursors to (1-aminoalkyl)phosphonic acid analogues of amino acids.[84] Togni showed that neutral Au complexes using the more readily available starting material Me$_2$SAuCl also give similar activity but lower ee's (80%).[85] A crystal structure of [{rac-**42**(R^1 = Me, R^2 = CH$_2$CH$_2$NMe$_2$)}$_2${AuCl}$_3$]·Et$_2$O was obtained confirming that there are no gold-nitrogen interactions. Changing R^1 in **42** from Me to Bz led to lower ee's and yields as the increased steric requirements of the *N*-benzyl substituents adversely affects the geometry of the stereoselective transition state.[86] Surprisingly, with some substrates such as tosyl methyl cyanides, Ag(ı) analogues were found to be better.[87] Hayashi later found that ee's of up to 90% were possible even with methylisocyanoacetate
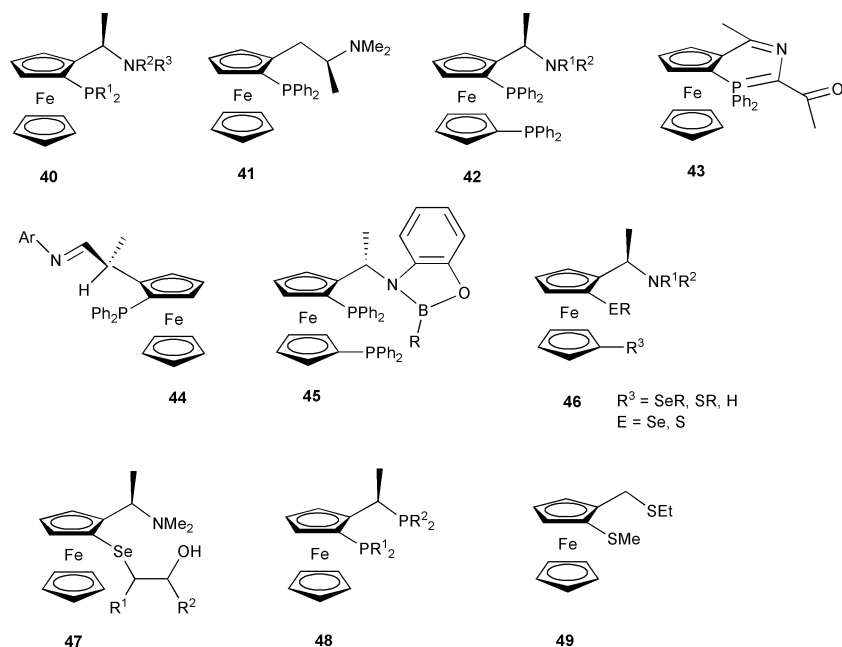

Fig. 18 Ligands derived from *N,N*-dimethyl-1-ferrocenylethylamine.

starting material if methylisocyanoacetate was added slowly over the period of one hour to a solution of the aldehyde and Ag(I) catalyst. This favoured the formation of a tri-coordinate Ag(I) species with a vacant site allowing the aldehyde to coordinate to the Ag centre: this is important to achieve good stereoselectivity.[88]

Another common application for chiral ferrocenes is in Pd-catalysed asymmetric allylic substitution reactions. A general reaction scheme is shown in Fig. 20 and the nucleophile may be
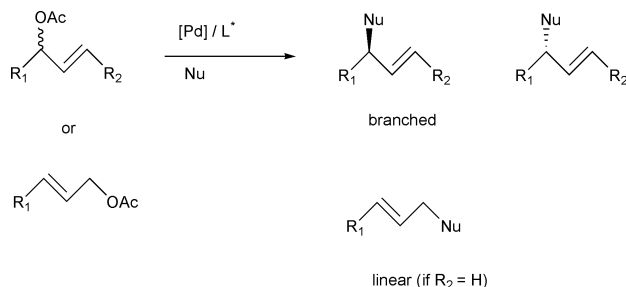

Fig. 20 A generalised Pd-catalysed allylic substitution reaction.

chosen to bring about alkylation or amination. When R^2 = H, the regioselectivity of the reaction is also important: the choice of ligand may affect the ratio of linear to branched product. Substitution in the 2-position of the substrate is usually more desirable as a stereogenic centre is generated—the ligand is chosen such that one enantiomer is preferred.

BPPFA has been used in Pd-catalysed allylic alkylation and amination reactions. Pd-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate was studied by Hayashi.[89] The best result was obtained using **42** (R^1 = Me, R^2 = CH_2CH_2OH) which gave ee's of up to 92%. It was thought that the pendant hydroxy group has an attractive interaction with the approaching nucleophile *via* hydrogen bonding thus inducing stereoselectivity to the reaction. The allylation of 2-acetylcyclopentanone and 2-acetylcyclohexanone with allyl acetate using monoaza- or diaza-crown ether modified BPPFA type ligands was studied by Ito.[90] The best ligand was found to be **42** (R^1 = Me, R^2 = CH_2CH_2N-diaza-crown-[6]) which gave up to 82% ee with 2-acetylcyclohexanone but an almost racemic product was obtained with 2-acetylcyclopentanone. Interestingly, this ligand was able to simultaneously activate an electrophile (allyl acetate or π-allyl-Pd(II) intermediate) and the approaching nucleophile (a potassium enolate). A similar reaction involving the attack of a sodium salt of a β-diketone on allyl acetate was achieved in up to 82% ee and 94% yield by Hayashi. Again, the best ligand was found to have a pendant hydroxy group to direct the approaching nucleophile.[91] Allylic amination of 1,3-diphenyl-2-propenyl acetate with benzylamine was achieved in 93% yield and 97% ee by Hayashi using **42** (R^1 = R^2 = CH_2OH).[92] The key role of the hydroxy groups in directing the stereoselective nucleophilic attack of benzylamine to a specific π-allyl carbon was demonstrated by X-ray diffraction and ^{31}P NMR studies which showed that one hydroxy was located close to one of the π-allyl carbons, and that the π-allyl group adopts one of two possible conformations in high selectivity in the equilibrium state. Rh-catalysed asymmetric hydrogenation has been studied using both **6**[93] and **42** (R^1 = Me, R^2 = CH_2CH_2N-cyclohexyl) which allowed the hydrogenation of unsaturated carboxylic acids.[94] The pendant amino group was thought to form an ammonium carboxylate with the substrate to attract it to the coordination sphere of the catalyst bringing about increased activity and stereoselectivity. Aza crown ether-modified BPPFA type ligands were synthesised by Landis[95] in an attempt to investigate interactions between the crown ether and ammonium cations in a similar manner as that already described for allylic alkylation catalysis. Unfortunately, although successful for the Rh-catalysed hydrogenation of simple substrates, the hydrogenation of allyl amines was not successful as the aza crown ether underwent substitution by allyl amine. Finally, derivatives of **6** containing a pendant hydroxy

group have been used in more specialised synthetic applications such as Pd-catalysed asymmetric bicycloannulation[96] and (3 + 2) cycloaddition[97] with good stereocontrol.

Other P/N ligands derived from PPFA are **13** and **43** whilst **44** is formed from **40** (where R^1 = Ph; R^2 = R^3 = H) *via* imine formation,[98] **45** is derived from **42** (R^1 = R^2 = H).[99] **13**,[100] containing a pyrazole group, and its derivatives have been used by Togni in the Rh-catalysed hydroboration of styrene.[101] Subsequent hydrolysis forms 2-phenylethanol in up to 98.5% ee and the carbonyl stretching frequency of the Rh(**13**)(CO)Cl catalytic complex was correlated with the observed enantioselectivity. Although it was found that electron withdrawing groups on the phosphine and electron donating groups on the pyrazole increased the stereoselectivity, it was not possible to formulate the exact origin of these effects in the absence of mechanistic information about the catalytic cycle. The Pd-catalysed asymmetric hydro-silylation of norbornene with $HSiCl_3$ using **13** was also successful in synthesising chiral alcohols in good yields and ee's after hydrolysis of the silane intermediate.[102] Again, electron with-drawing groups on the phosphine were most efficient, together with sterically bulky substituents on the pyrazole moiety. The allylic amination of 1,3-diphenyl-2-propenyl acetate with benzylamine was investigated by Togni using derivatives of **13** with substituted pyrazoles.[103] The Pd-ligand-substrate complexes were analysed by 2D-NMR and X-ray diffraction showing that too bulky a sub-stituent in the 4- position on the pyrazole disrupted the conforma-tion required for good stereoselectivity. It was also found that the carbon *trans* to P is attacked as the P substituent exerts a greater *trans*-influence. The different *trans*-influences of P and N heteroa-toms highlights the value of unsymmetrical ligands in this reaction in favouring nucleophilic attack at a particular allyl carbon. *Rac*-**43**, synthesised *via* the condensation of PPFA with ethane-1,2-dialde-hyde, has been used in the stereoselective Cu-catalysed cyclopropa-nation of styrene with ethyl diazoacetate to yield only the *trans* product in 100% yield.[104] Although the mechanism has not been elucidated thus far, this ligand is far superior to the bis-imine ligands used previously. **43** was also used in the Pd-catalysed allylic alkylation of 1,3-diphenyl-2-propenylacetate but with moderate ee's (50%).[105] An unusual N/O Pd chelate complex was isolated: a carbonyl oxygen normally being a poor ligand for an organome-tallic fragment. Interestingly, the Pd-catalysed allylic alkylation of terminal allyl acetates gave solely the linear product in 90% yield. A Mo(I) complex of **43** gave similar results and a W(I) complex showed the same selectivity but with lower yields (23%) and ligand **44** has been used in the Rh-catalysed hydrosilylation of ketones.[98] **45** was used in Rh-catalysed asymmetric hydrogenation/hydro-formylation.[99] It was hoped that secondary interactions between the Lewis Acidic boron and the Lewis basic functionality of a coordinated alkene would accelerate these catalyses but only moderate ee's were actually achieved.

4.1.2 S/N Ligands. The sulfur analogues of PPFA, **7** and **8**, have also been derivatised to produce hybrid ligands of the general structure **46** and tuned for various catalytic processes. Compounds **46** have been used by Brubaker in asymmetric Grignard cross-coupling. Using **46** (ER = SPh or SMe, R^1 = R^2 = Me, R^3 = H) in combination with Pd precursors gave good yields but poor ee's (up to 26% with ER = SMe).[106,107] This should be compared with ee's of 68% using the analogous phosphine **5**. It was also found that Pt complexes gave consistently higher ee's than the analogous Pd complex (although the best ee was still only 35%). Assuming the same mechanism as with **5**, although the metal–nitrogen bond is cleaved to form a nitrogen–magnesium interaction, the metal–sulfur bond remains intact and hence the stronger Pt–S bond should be more effective in keeping the ligand anchored to the metal.[108] Ni-catalysed reactions were also performed with a maximum ee of 45% using **46** (ER = S[t]Bu, R^1 = R^2 = Me, R^3 = S[t]Bu) and bulky thioethers were most effective in this case.[108] The Cu-catalysed substitution of allylic acetates with Grignard reagents has also been

achieved in excellent regioselectivity and in 64% ee (the highest ee reported for this process) using the air-sensitive anionic ligand **46** (ER = SLi, R^1 = R^2 = Me, R^3 = H).[109] The corresponding thioether gives a racemic mixture highlighting the importance of anionic coordination to copper. **46** (ER = S^{i}Pr, R^1 = R^2 = Me, R^3 = H) in combination with Pd precursors has been used in the selective hydrogenation of 1,3-cyclooctadiene to cyclooctene.[106] There is some doubt as to the exact nature of the catalyst however, as the system is inactive in dichloromethane solvent without the addition of water to form a heterogeneous system. Hydrogenation does occur in acetone solvent but solvent coordination to Pd has not been ruled out. The hydrogenations of 1,3-cyclooctadiene and 1,3-cyclohexadiene were found to proceed with better selectivity [up to 100% of the mono-unsaturated product when **46** (ER = SEt, R^1 = R^2 = Me, R^3 = H) was used] with Pd rather than Pt precursors. Converse to Grignard cross-coupling, metal–sulfur cleavage is important in selective hydrogenation and hence catalysts containing the weaker Pd–S bonds are more effective. Following the same reasoning, when selenium was used in place of sulfur, the catalysis failed completely due to the high strength of the metal–selenium bonds.[108,110] Derivatives of diferrocenyl dichalco-genides (like **9**) have also found applications in catalysis. **9** and its selenium analogue have been used in the Rh-catalysed hydro-silylation of ketones to form chiral alcohols in moderate to quantitative yields and in up to 88% ee.[111] A variety of derivatives were tested but the best results were achieved with the selenium-analogue of **9**. The Ir derivatives were found to favour products with the opposite configuration, the reasons for which are unclear. Isolation of a model Rh complex (also catalytically active) suggests a mechanism involving a single Rh(I) centre coordinated by 2 nitrogen and 2 selenium atoms with oxidative addition of a Si–H bond followed by C=O addition to the resulting Rh(III) hydride. Replacement of the NMe$_2$ group with OH did not give good results in this system. The same ligand was also used in Rh-catalysed transfer hydrogenation with good yields and up to 95% ee's.[112] The dichalcogenide bridge may be cleaved with alkyl halides forming other ligands. An example of this is **47** which gives good yields and ee (up to 99%) in the catalytic enantiomeric addition of Et$_2$Zn to benzaldehyde.[113]

4.1.3 P/P Ligands. Ligands derived from PPFA *via* nitrogen-phosphorus exchange are very important in catalysis. The most prevalent and important example is Josiphos **10** first synthesised by Togni.[114] Different phosphines have been used to synthesise a variety of unsymmetrical bisphosphine ligands represented by **48** in Fig. 18. Pd-catalysed alkoxycarbonylation of chloroarenes using carbon monoxide and a variety of alcohols and amines has been achieved in up to 99% yield and selectivity using both **10**[115] and **48** (R^1 = R^2 = Cy).[116] By combining **48** (R^1 = C$_6$H$_3$-*m*-[CF$_3$]$_2$, R^2 = Cy) with Pd(OAc)$_2$ and activating with BF$_3$·OEt$_2$, the co-polymerisation of carbon monoxide with propene was achieved with an activity of up to 1797 gg(Pd)$^{-1}$h^{-1} to form a highly regioregular and stereoregular isotactic co-polymer.[117] The high electronic differentiation between the two phosphine atoms ac-counts for the high activity: the electron withdrawing arylphos-phine decreases the electron density at the Pd centre leading to a higher rate of reaction. Pd-catalysed allylic alkylation was studied with both **10** and **48** (R^1 = Ph, R^2 = phobyl)[118] and the ferrocenyl-phobane catalyst gave a higher activity but lower ee than the parent Josiphos ligand. The bulkier PCy$_2$ substituent is more effective in creating a well-defined chiral environment around the Pd centre. Recently, Hartwig has used **48** (R^1 = Ph or Cy, R^2 = t-Bu) in the Pd-catalysed cross coupling of aryl tosylates with Grignard reagents or primary amines.[119] Aryl tosylates are desirably cheap and diverse starting materials for this reaction. The derivative where R^1 = Ph was found to be more effective with Grignard reagents giving up to 86% yield at 25 °C within 5 h, and the reaction was successful with electron withdrawing, unactivated or electron donating aryl tosylates. The more electron rich ligand, where R^1 =

Cy was more successful with amines, giving up to 74% yield at 25 °C within 2 h. Ru-catalysed asymmetric hydrogenation of a variety of substrates was accomplished with 100% conversion but only modest ee's using a P-chiral version of **48** where the R^2 substituents were non-identical.[120] Recently, the complex Ru(**10**)Cl$_2$(py)$_2$ has been shown to hydrogenate 1′-acetonaphthone with reasonable activity and with 98% ee. Although the activity was doubled when the pyridine substituents were replaced with (*R*,*R*)-diphenylethyle-nediamine, the ee was unchanged showing that **10** dominates the stereoselectivity.[121] **48** (R^1 = Cy, R^2 = Ph) has also been used in Rh-catalysed asymmetric hydroformylation of styrene.[122] The best results were obtained at high temperatures to give efficient conversions (84%) with moderate ee's (45%). The asymmetric ring-opening of oxabicyclic alkenes with either alcohols and amines[123,124] or organoboronic acids[125] has been achieved by Lautens using **48** (R^1 = Ph, R^2 = t-Bu) in high yields and excellent enantioselectivity thus providing a new enantioselective carbon-heteroatom bond forming process.

48 (R^1 = Ph, R^2 = Xyl) (Xyliphos) has been used in a number of Ir-catalysed reactions important in both organic synthesis and the chemical industry. For example, the hydrogenation of *N*-aryl imines was achieved in good yields and with moderate to good ee's.[126] The central and planar chirality of **48** must be correctly matched for good catalyst performance: unfortunately the optimal combination of R^1 and R^2 groups depends on the electronic demands of each *N*-aryl imine. The first enantioselective reductive alkylation of hindered anilines was also achieved using Xyliphos[127] and this is potentially applicable to the synthesis of metalolachlor (an active ingredient in grass herbicides). The hydroamination of norbonadiene[128] was achieved using a (Josiphos)IrCl dimer. For reasons that are not clear, the presence of "naked" fluoride anion additives was found to improve the activity and enantioselectivity of the process. **48** has also been attached to a dendrimer core and used in Rh-catalysed hydrogenation and hydroboration and Pd-catalysed allylic substitution with similar selectivity to the parent Josiphos ligand.[129,130] The dendrimer produced was large enough (≈ 3 nm) to be retained by a membrane support and a slight drop in ee was observed for each increasing generation of dendrimer.

Nitrogen–phosphorus exchange was also used to synthesise the Pigiphos ligand type, **12**, which is a rare example of a tridentate chiral phosphine. This has been used in Ru-catalysed asymmetric transfer hydrogenation but was found to give only moderate ee's of up to 72%.[131]

4.1.4 P/O Ligands. PPFOMe **11** synthesised from PPFA *via* nitrogen–oxygen exchange[71] has been used in racemic form by Buchwald in the Pd-catalysed aryl amination of aryl bromides with excellent conversions.[132,133] The P/O ligand was thought to remain coordinated to Pd throughout the catalytic cycle and to make the Pd centre less electron rich than with chelating diphosphine ligands, so increasing the rate of reductive elimination (to form the required coupled product) *versus* β hydride elimination. The related ligand (*S*)-(*R*)-*bis*(PPFOMe) has been used in the Pd-catalysed synthesis of axially chiral allenylsilanes in up to 90% yield and enantiomeric excess.[134] Asymmetric hydrosilylation of 1,3-dienes with di-fluorophenylsilane has been achieved in 60% yield and 72% ee using (*R*)-(*S*)-PPFOAc.[135] This ligand was found to perform more efficiently than **5** as the lone pair of the amino group on **5** was found to hinder the reaction. **11** has also been used to synthesise 1,1′-binaphthyls *via* asymmetric Ni-catalysed Grignard cross-coupling with up to 95% ee.[136] The ee was markedly better than that achieved with **5** as the O heteroatom is more effective in coordinating to the Mg atom of the Grignard nucleophile thereby orientating it to form one product enantiomer.

4.1.5 P/S Ligands. Nitrogen–sulfur exchange has been used to synthesise P/S ligands such as **14**. A derivative of **14** with a pendant amino group has been used in the Au-catalysed aldol reaction, but the S heteroatom was found to have no effect: substitution of the

sulfur atom for nitrogen was found to give similar yields and ee's.[137] The length of the side chain was found to be the crucial factor, as for **42** previously described. Reaction of **14** with epoxides has been used to synthesise P/S/O ligands but these gave poor results in Rh-catalysed hydroboration and Pd-catalysed alkylation.[138] The high conformational flexibility of the ligand was thought to be responsible for the poor ee's. The dithioether **49** was also synthesised from *N,N*-dimethyl-1-ferrocenylethylamine.[139] The ligand was tested in the Pd-catalysed hydrogenation of 1,3-cyclo-octadiene but the strong binding of the dithioether ligand meant that the hydrogenation was very slow.

4.1.6 Miscellaneous ligands. Fig. 5 shows that ferrocenes possessing bidentate N/O coordinating sites may be synthesised upon the *ortho*-lithiation of **4** followed by addition of an appropriate ketone, R_2CO. Although there is a carbon spacer between the O heteroatom and the Cp ring, these ligands are mentioned as they possess two hard donor groups and the sensitive nature of hydroxyferrocenes has meant that derivatives with an O heteroatom directly bonded to the Cp ring have not been studied extensively. Good results were obtained in the catalytic enantioselective addition of dialkylzincs to aldehydes with up to 100% ee being reported depending on the aldehyde substrate and nature of the amine group.[140,141]

4.2 Ligands derived from ferrocenyloxazolines

Section 3.4 describes 1,1′-ferrocenyloxazolines but numerous 1,2-ferrocenyloxazolines have also been synthesised and applied in catalysis.[21] **50** and **51** (Fig. 21) show the general structure of

50 E = SR, PR$_2$, CR^{6}R^{7}OH

51 E = PR$_2$

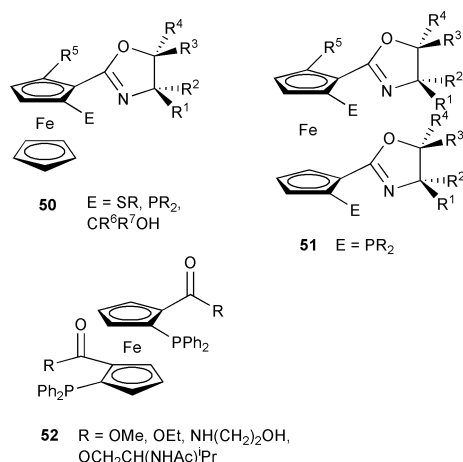**52** R = OMe, OEt, NH(CH$_2$)$_2$OH, OCH$_2$CH(NHAc)^{i}Pr

Fig. 21 Ligands derived from ferrocenyloxazolines.

1,2-ferrocenyloxazolines. A recent review by Hou and Dai describes the synthesis of these oxazolines, and the roles of planar and central chirality in allylic substitution and asymmetric Heck reactions.[20] It should be noted that **50** (E = SPh, R^2 = t-Bu, R^1 = R^3 = R^4 = R^5 = H) performed slightly better than **50** (E = PPh$_2$, R^2 = t-Bu, R^1 = R^3 = R^4 = R^5 = H) in Pd-catalysed allylic alkylation, the sulfur analogue giving ee's of 98% and the phosphorus analogue 95%.[142] A similar trend has been reported using **50** (E = SPh or PPh$_2$, R^2 = C*H(Ph)OSiMe$_2$(t-Bu), R^1 = R^3 = R^4 = R^5 = H) possessing two stereogenic centres.[143] Conversely, P derivatives of PPFA were found to give better stereocontrol than S derivatives. However, ligands **50** possessing only planar chirality (*i.e.* where R^1 = R^2 and R^3 = R^4) gave the same trend in stereocontrol as for PPFA derivatives: crystallographic and NMR analysis gave evidence for newly formed chirality on the S atom during complexation with Pd which disrupted the enantiocontrol. In all cases, the absolute configuration of the product was determined by the stereogenic centre, although the planar and central chirality must be matched for good ee's. **50** (E = PPh$_2$, R^2 = t-Bu, R^1 = R^3 = R^4 = R^5 = H) has been used

in the ring opening of oxabicylic alkenes in up to 98% ee.[144] Ni-catalysed asymmetric cross-coupling of 3-bromocyclohexadiene with Grignard reagents[145] and boronic acids[146] has been achieved using derivatives of **50** (E = PPh$_2$) in moderate yields and enantioselectivities. Better yields and ee's were obtained using Grignard nucleophiles and the results were poorer with acyclic substrates. Uemura has investigated the application of **50** in Rh- or Ir-catalysed asymmetric hydrosilylation and imine substrates were hydrosilylated in up to 89% ee by an iridium-oxazoline system.[147] Although better results were obtained with Ir rather than Rh or Ru, the products all had the same configuration regardless of the metal employed. Ketone substrates were hydrosilylated in up to quantitative yields by both Ir (96% ee)[148] and Rh (91% ee)[149] In this case, the opposite product configurations were achieved with Ir and Rh respectively, the ligand employed being **50** (E = PPh$_2$, R^2 = R^3 = Ph, R^1 = R^4 = R^5 = H) known as DIPOF. The Ru-catalysed hydrosilylation of ketones and a sec-imine was achieved with 97% and 88% ee respectively using **50** (E = PPh$_2$, R^2 = Ph, R^1 = R^3 = R^4 = R^5 = H).[150] No reaction was obtained with **6** under the same conditions. Modifications to **50** have been made to effect the Ru-catalysed transfer hydrogenation of arylalkyl and alkylmethyl ketones. Thus, using **50** (E = PPh$_2$, R^1 = i-Pr, Ph or t-Bu, R^2 = R^3 = R^4 = R^5 = H), remarkable ee's of up to 99.9% when R^1 = i-Pr or Ph.[151] Slightly lower ee's were achieved when R^1 = t-Bu.[152] and using **50** (E = PPh$_2$, R^3 = Ph, R^1 = R^2 = R^4 = R^5 = H), acetophenone was hydrogenated with up to 93% conversion and 94% ee.[153] In all cases the catalyst was thought to have the structure Ru(**50**)(PPh$_3$)Cl$_2$, the complex without PPh$_3$ being virtually unselective. The active species was thought to be a ruthenium dihydride complex—the substrate approaching to minimise steric interactions with the phenyl groups and chiral oxazolinyl substituent.[151] Recently, the complex Ru(**50**)(PPh$_3$)Cl$_2$ has been isolated (E = PPh$_2$, R^1 = i-Pr, R^2 = R^3 = R^4 = R^5 = H) and shown to be highly effective in catalysing the oxidative kinetic resolution of racemic alcohols.[154] The Cu-catalysed asymmetric conjugate addition of Grignard reagents to enones was achieved in up to 92% ee using **50** (E = PPh$_2$, R^3 = Ph or i-Pr, R^1 = R^2 = R^4 = R^5 = H).[155] The corresponding phenyl oxazolines gave much lower yields and an almost racemic product suggesting that either planar chirality or the ferrocene backbone was essential.

Section 4.1.6 describes the use of N/O ligands where there is a carbon spacer between the O heteroatom and the Cp ring. The analogous oxazoline ligands **50** (E = CR^{6}R^{7}OH) have been developed by Bolm and are included here due to their importance in Zn-catalysed asymmetric alkyl and aryl transfer reactions to aldehydes. **50** (E = CPh$_2$OH, R^2 = t-Bu, R^1 = R^3 = R^4 = R^5 = H) was found to give good results in the addition of ZnEt$_2$ to a variety of aldehyde substrates. By testing the ligand with opposite planar chirality, it was found that as in the case of Pd-catalysed allylic alkylation, matched planar and chiral elements are required for the best results.[156] Furthermore, it was found that phenyl transfer to aldehydes was possible using **50** (E = CPh$_2$OH, R^2 = t-Bu, R^1 = R^3 = R^4 = R^5 = H) and a mixture of ZnPh$_2$ and ZnEt$_2$ to synthesise a wide range of arylphenylmethanols with very high enantioselectivities.[157] This work has been extended to Zn-catalysed asymmetric aryl transfer from aryl boronic acids to aldehydes to allow the synthesis of other diarylmethanols with excellent yield and enantioselectivity.[158] Finally, polymer-supported versions have been developed allowing highly enantioselective phenyl transfer to aldehydes (with up to 97% ee) with facile catalyst-product separation and excellent recyclability, the ee dropping to only 95% after five cycles.[159]

The bis(oxazoline)s **51** have been used in Pd-catalysed allylic alkylation, and on mixing with a suitable Pd precursor, a **51**:2Pd P/N chelated complex is formed. Swapping the planar configuration of the P/N chelate ring gives similar ee's and the same absolute product configuration indicating that central chirality is more important. Slightly better ee's were obtained than with the corresponding mono(oxazoline),[160] and by changing R^5 = H to R^5

= TMS, a reversal in enantioselectivity is observed. Interestingly, a P/N chelate complex dominates with the (pR,pR)-**51** stereoisomer but with the (pS,pS)-**51** stereoisomer, P/P chelation is favoured.[161] Clearly, an increase in the number of possible ligand stereoisomers complicates the metal coordination chemistry in this case. Recently, the 1,1′-bis(diphenylphosphine) version of **50**(R² = t-Bu) has been developed and used in the Heck reaction of *N*-methoxycarbonyl-2-pyrroline with aryl triflates giving ee's of up to 99%. This is a logical development and should enable similar comparisons as have already been established between PPFA and BPPFA as described in section 4.1.1.[162] It should be noted that the oxazoline may be hydrolysed to form planar-chiral carboxylic acid derivatives. One example is **52**, which possesses only planar chirality, synthesised by Ikeda, which has been used in Pd-catalysed allylic alkylation with good ee's (up to 94%).[163] However, varying the R substituent was found to have little effect on the catalysis.

4.3 Ligands derived from sulfoxide and acetal precursors

As discussed in Section 2.2.2, the acetal formed from ferrocene-carboxaldehyde and (S)-1,2,4-butanetriol may be hydrolysed to reform the aldehyde once *ortho*-lithiation has taken place to form a 1,2-planar chiral derivative. Two equivalents of **53** (Fig. 22) have
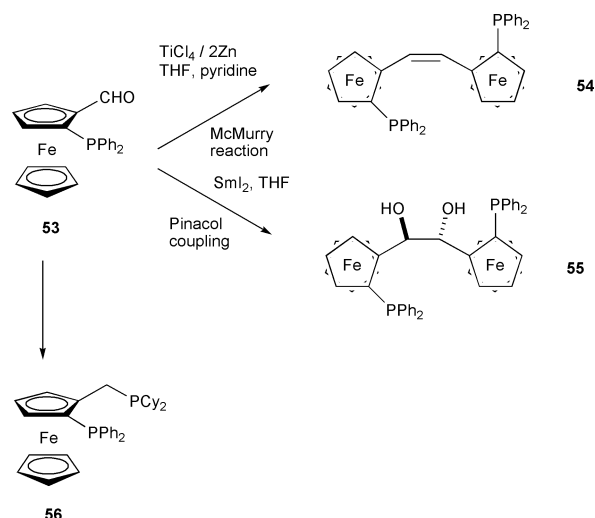

Fig. 22 Ligands derived from an acetal precursor.

been coupled *via* either McMurry or Pinacol coupling to give **54** and **55**.[35] **55** has been used in asymmetric Rh-catalysed hydrogenation giving good yields and ee's. Similar ee's were obtained using stereoisomers with a variety of configurations of the hydroxy groups suggesting that planar chirality dominated the stereocontrol.

56 was synthesised from **53**[164] and used in Rh-catalysed asymmetric hydrogenation with good yields and ee's. Similar results were obtained with **56** (possessing only planar chirality) and **10** (with central and planar chirality) suggesting that planar chirality is the most important for good stereocontrol. Both ligand types showed that an arylphosphine bound to the ferrocene ring and an alkylphosphine on the side chain worked most efficiently.

Chiral [(dialkylamino)methyl]phospholylferrocenes, containing a cyclic phosphole moiety, have been synthesised *via* a chiral acetal (as described in Section 2.2.2). Although the conversion was efficient, only moderate ee's (67%) were achieved in the Pd-catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate however.[165]

Ligands containing the sulfoxide *ortho*-directing group have found catalytic applications in their own right. For example, **57** (Fig. 23) has been used in the catalytic addition of ZnEt₂ to
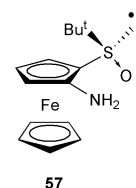

Fig. 23 1,2-Ferrocenyl sulfoxide ligand for catalytic addition of ZnEt₂ to aromatic aldehydes.

aromatic aldehydes[166,167] and it is a rare example of the use of a chiral ferrocenylamine in catalysis. Tertiary amine, amide and arylsulfonamide derivatives of **57** have also been synthesised. The best ligand was the *p*-methoxyphenylsulfonamide derivative which gave the product alcohol with up to 96% ee. The corresponding sulfide and sulfone (with an achiral sulfur atom) gave similar ee's as the *S*-chiral sulfoxide suggesting that planar chirality was the most important.

Ferrocenyl sulfoxides have also been used in the synthesis of 1,2-unsymmetrical P/P and P/S ligands and Kagan synthesised ligand **58** *via* the route shown in Fig. 24. The sulfoxide group was used to promote stereoselective *ortho*-lithiation before being removed *via* lithiation and replaced with a second phosphine moiety. **58** has been used in the Rh-catalysed C=C hydrogenation of dimethyl itaconate giving good yields and moderate to good ee's of up to 95%.[168] Crystal structure analysis showed bidentate coordination to Rh forming a 2:1 complex.

Carretero found that the sulfoxide could be reduced back to the corresponding thioether *via* reduction with HSiCl₃ and Et₃N in refluxing toluene. This method was employed in the synthesis of **59** *via* the route shown in Fig. 25 and the electronic and steric properties of the ligand may be tuned by varying the thioether and phosphine substituents. For Pd-catalysed allylic substitution, the bulkier SᵗBu and less electron rich PPh₂ substituents were best. A crystal structure of the Pd allyl complex showed that the Pd–C bond
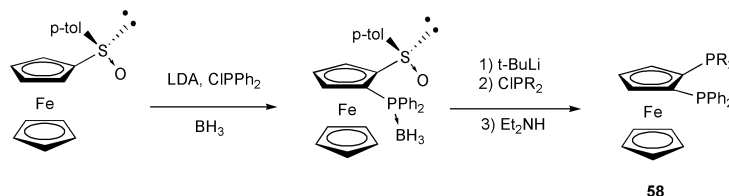

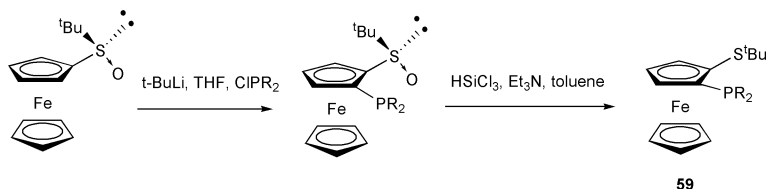**Fig. 24** Synthesis of 1, 2-unsymmetrical P/P ligands.

Fig. 25 Synthesis of 1,2-unsymmetrical P/S ligands.

trans to the phosphine was longer (as with **13**) so that the nucleophile attacks adjacent to the bulky thioether substituent enhancing the stereocontrol.[169] Among the best ee's to date (93–94%) for the Pd catalysed ring opening of oxabenzonorbornadienes were found with **59** substituted with electron rich phosphines.[33] **59** has also been employed in the construction of nitrogen heterocycles *via* a Cu-catalysed asymmetric aza Diels–Alder reaction of *N*-sulfonyl imines with Danishefsky's diene. A variety of Cu(I) complexes of **59** were synthesised demonstrating P/S bidentate coordination and it was found that a Cu(I) bromide dimeric complex containing a bulky phosphine (R = α-naphthyl) was most active giving 90% yield and 93% ee in 1 hour. Given the growing recent interest in chelating P/S ligands,[5] it can be confidently predicted that further important applications of **59** will be found in asymmetric synthesis demonstrating the usefulness of this ligand.

Recently, ferrocenyl sulfoxides have been used in the synthesis of **60** and **61** by Knochel (Fig. 26). The reaction of lithiated
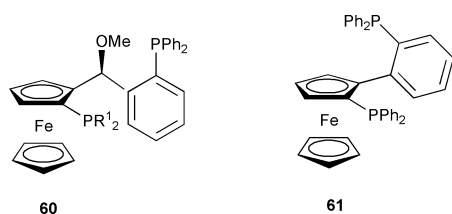

Fig. 26 Knochel's chiral bisphosphine ligands synthesised *via* a ferrocenyl sulfoxide.

ferrocenyl-(*p*-toluene)sulfoxide with 2-diphenylphosphanylbenzaldehyde furnished two diastereomeric alcohols which were separated and methylated, followed by replacement of the sulfoxide group with a second phosphine to yield **60**.[170] **60** forms diphosphine chelate complexes with Rh and Ru and gives up to 99% enantiomeric excesses in the Rh-catalysed C=C hydrogenation of a variety of substrates, and up to 99% enantiomeric excesses in Ru-catalysed C=O hydrogenation. The configuration of the stereogenic centre is very influential on the enantioselectivity: it is postulated that the *S* enantiomer of the ligand may shield the upper half of the diphosphine metal complex forcing the asymmetric reaction to occur from the sterically congested bottom face. After forming a 1,2-phosphine-sulfoxide as previously described, the sulfoxide moiety was substituted by ZnCl *via* a lithio-intermediate allowing an aryl group to be attached by Negishi coupling to liberate **61**. **61** forms an interesting axially-chiral Pd chelate complex with a well defined steric environment and locked conformation providing the chiral axis: hence Pd-catalysed allylic substitution and amination proceeds in up to 98% enantiomeric excess.

4.4 Miscellaneous ligands with catalytic applications

Unsymmetrical bisphosphines containing a homo- or heteroannularly bridged ferrocene, **62** and **63** respectively (Fig. 27), have been synthesised by Weissensteiner to investigate the effect of reducing the ligand's flexibility. The Rh- or Ir-catalysed hydrogenation of olefins[171] showed that the homoannularly-bridged ligands performed best, but neither outperformed **10** except in a few cases where the conversions and ee's were low anyway. The success of **10** was attributed to its flexibility allowing it to accommodate a variety of substrates whilst still retaining good stereocontrol on the catalysis. The Pt-catalysed hydroformylation of styrene proceeded with good conversion but low ee's and showed an interesting temperature dependence, with the favoured product configuration switching above 90 °C.[172] **64** was synthesised using a TiCl$_4$-catalysed Mannich-type C–C coupling reaction between diacetylferrocene and dimethylamine to form an unsaturated [3]-ferrocenophane. Directed lithiation and quenching with chlorodiphenylphosphine followed catalytic hydrogenation and replacement of the amino group using diphenylphosphine proceeded with retention of stereochemistry as with **5**. Treatment of

the ligand with Pd(OAc)$_2$ and activation with BF$_3$·OEt$_2$ formed an active catalyst system for the co-polymerisation of CO and ethylene. The activity was 250 gmmol[Pd]$^{-1}$ at 30 bar CO and 30 bar ethylene pressure. In addition, a Pd dichloride complex was isolated and activated with AgBF$_4$ but only gave approximately half the activity.[173]

Compound **65**,[174] containing a chiral pocket, has been used in Pd-catalysed allylic alkylation to form α-alkylated amino esters containing a chiral quaternary carbon centre in up to 75% ee. **66**[175] has been used in Pd-catalysed allylic alkylation and amination reactions with moderate ee's, but there is no significant increase in ee over the analogous phenyl derived ligand without planar chirality. A chiral, bulky amine was used to promote diastereoselective *ortho*-lithiation in the synthesis of **67** which has also been used in Pd-catalysed allylic alkylation with up to 71% ee's.[176] Knochel's **68** was synthesised from the relevant ferrocenyl ketone by Corey–Bakshi–Shibata asymmetric reduction to the chiral alcohol followed by replacement of the hydroxy group with a secondary amine *via* an acetate intermediate. Subsequent dilithiation and quenching with a chlorodiarylphosphine led to the diphosphine ligand.[177,178] Rh-catalysed C=C hydrogenation was achieved with up to 98% ee, Ru-catalysed C=O hydrogenation with up to 96.5% ee and Rh-catalysed C=N hydrogenation with moderate ee (67%) and conversion. Replacement of the amino group by a methyl substituent gave the opposite enantiomer of the product in many cases. The analogous **60** containing a methoxy group instead of an amine, already discussed, in fact gave slightly better ee's in Rh-catalysed C=C hydrogenation and Ru-catalysed C=O hydrogenation. The imine **69** has been used in Pd-catalysed allylic alkylation giving ee's of up to 82%[179] but polystyrene bound versions also synthesised showed poor recyclability. **70**, synthesised *via* the SAMP hydrazone method,[180] has the stereogenic centre on the β position of the alkyl side chain. This ligand gave good ee's in Pd-catalysed allylic alkylation (up to 97%)—amongst the best reported for a P/S ligand[181,182]—and a most interesting result given the poor performance of **41** as described earlier. Recently the phosphine-amidine derivative **71** has been synthesised and used in the Pd-catalysed allylic alkylation reaction with excellent results.[183] The interesting P,N,O-tridentate salicylaldimine ligand **72** has been used with excellent results in the Ru-catalysed asymmetric transfer hydrogenation of simple ketones. Up to 94% ee with 99% conversion was achieved using **72** (R^1 = R^2 = NO$_2$).[184] A range of P/N ligands utilising nitrogen-containing heterocycles have recently been developed by Knochel. One example is **73**. Interestingly, the Rh-catalysed hydroboration of styrene with catechol borane proceeded with either high regioselectivity (97 : 3 linear/branched ratio) or high enantioselectivity (92%) depending on the nature of the nitrogen heterocycle. Pd-catalysed allylic substitution reactions were also carried out with good results.[185]

5 Summary of the catalytic applications of unsymmetrical ferrocene ligands

Sections 2.3 and 2.4 give many examples of the use of unsymmetrical ferrocenyl ligands in catalytic applications. Catalysis with 1,1′-unsymmetrical ligands is an area of research that is still in its infancy and only preliminary results have been reported so far (apart from with the 1,1′-ferrocenyl oxazolines **32**, **33** and **34** which have related 1,2-counterparts). This is partly due to the fact that the selective monolithiation of dibromoferrocene, which represents a high yielding, general route to the synthesis of these ligand types, has only recently been developed.

By far the most common class of 1,2-unsymmetrical ligands are those derived from *N,N*-dimethyl-1-ferrocenylethylamine (although recent advances in the synthesis of other chiral ferrocene starting materials means that more recent research has focused on other synthetic routes). Some conclusions can be drawn by analysing the structural features of successful ligands derived from

N,N-dimethyl-1-ferrocenylethylamine. The different heteroatoms may provide unsymmetrical coordination or, since the geometry of ferrocene allows for more than two substituents, a suitable pendant substituent for orientating an approaching substrate to improve the stereocontrol of a reaction. For example, nitrogen–boron complexation is used to direct approaching boronic acids in Suzuki couplings, whereas oxygen–magnesium interaction is more effective for directing approaching Grignard reagents. By derivatising the side chain more effective stereocontrol can be achieved: a terminal amine is used to form ammonium carboxylates in the Au-catalysed aldol reaction whereas a terminal hydroxide is used to direct the nucleophile by hydrogen bonding in allylic substitution reactions for example. It should be noted that the use of high-throughput screening techniques has played a significant role in the selection of the most appropriate substituents for a particular application.

Table 1 presents a summary of the generalised ligand types that have been discussed in this review and selected catalytic processes to which they have been applied. It should be noted that the ferrocenyl oxazoline ligands **32**, **33**, **50** and **51** have been classed as P/N ligands as they have been shown to coordinate to metal centres through the P and N atoms.[64] Table 1 demonstrates that un-

symmetrical P/N and P/P ligands have found the most widespread applications in catalysis, particularly as **40**, **42** and **48** are general ligand types representing a whole series of different ligands. This is most likely to be due to the fact that P and N donor atoms are the most compatible with Pd, Ru, Rh, Ir and Au which are the most common metals to be employed in the catalytic processes studied to date. Indeed, there has been considerable recent interest in the synthesis and application of new P/P ligands such as **60**, **61**, **62** and **63**. The unsymmetrical nature of the ligands has often been employed to exert a degree of hemilability in a reaction: the N–Pd bond cleavage in Grignard cross-coupling reactions and S–Pd bond cleavage in selective hydrogenations for example. Alternatively, the different *trans* influence of phosphines and amines has been utilised to improve the stereocontrol in Pd-catalysed allylic substitution reactions, for example. (A comprehensive study has recently been carried out on ligands derived from **4** by Hou and Dai.[186]) In a few cases, S/N ligands have been more effective; for example, the anionic character of **43** (E = SLi) was important in Cu-catalysed allylic substitution. The S/N-substituted centrally chiral oxazoline ligands proved to be slightly better than the corresponding P/N derivatives. Recently developed synthetic methods allowing the convenient introduction of a wider range of
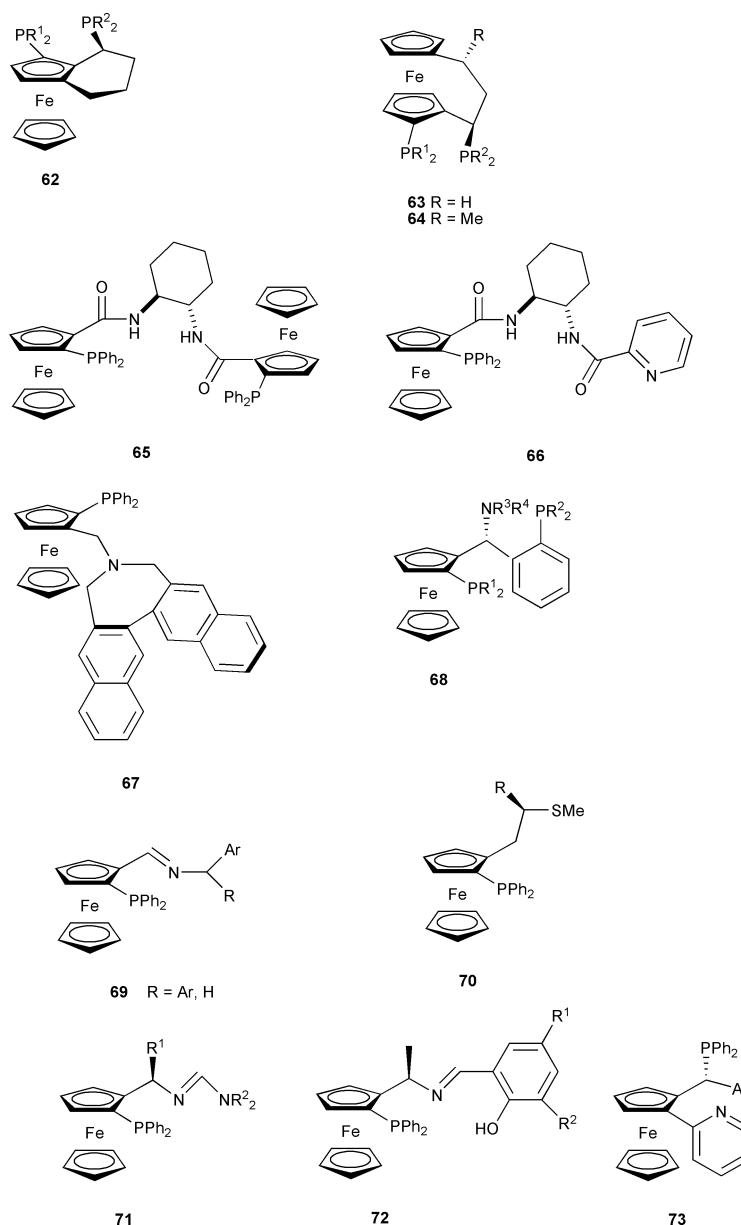

Fig. 27 Miscellaneous ligands with catalytic applications.

Table 1 Summary of Ferrocene Ligands used in Catalysis

	P/N	S/N	P/P	P/O	P/S	Other
Organometallic cross-coupling	5,40,41,50	46	16,19,20,22	11,31	26,27	
Hydrogenation	5,40,42,45,50,68	9	15,20,48,12,56,58,60,62,63	55		49
Allylic substitution	32,33,42,13,50,51,52,65,66,67,69	34	21,61	36	59,70	
Hydroformylation	45		19,21,48			
Au-, Ag-catalysed aldol reaction	42				14	

heteroatoms may allow the synthesis of ligands suited to the complexation of 'harder' early/mid-transition metals opening up a wider range of catalytic processes.

The ligands described here have been progressively derivatised since their original synthesis to tune the steric and electronic environment at the catalytic metal centre producing >99% ee and 100% conversion in some cases. Research continues apace to further improve the conversion and ee of less efficient catalyses. It can be confidently predicted that new applications will be found for unsymmetrical ferrocene ligands as their synthesis becomes easier and the range of derivatives widens.

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