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Ferrocene phosphane-heteroatom/carbon bidentate ligands in asymmetric catalysis

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Štefan Toma,[a] Jana Csizmadiová,[a] Mária Mečiarová,[a] and Radovan Šebesta* [a]

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Chiral ferrocene derivatives belong to privileged ligand classes for asymmetric transition metal catalysed reactions. Hetero-bidentate phosphane ligands are hybrid ligands, which combine properties of phosphorus with that of other donor atom. This feature creates further asymmetry around the metal centre, which may be helpful for increasing stereoinduction. Therefore, hetero-bidentate ligands are useful alternatives to homo-bidentate ligands. Ligands featuring phosphorus and nitrogen or sulphur are quite common. From among ferrocene catalysts, ferrocenyl amino phosphanes and phosphane oxazolines serve as excellent examples. Fesulphos and ThioClickFerrophos are notable P,S-ligand examples. On the other hand, combinations of phosphorus with oxygen or carbon are only beginning to show its potential in asymmetric catalysis. Another useful feature in ligands of this type is markedly different coordination properties of donor atoms, resulting in interesting opportunities in catalysis. Ferrocenyl MOP-analogues or a fascinating combination of phosphane and secondary phosphane-oxide would represent this ligand class. The last section of the review focus on phosphanes combined with carbon-based donor atoms that are phosphane-alkene and phosphane-carbene ligands. This review focuses on applications of these hetero-bidentate ferrocene ligands in asymmetric catalysis with a special emphasis on the most recent and influential works.

Introduction

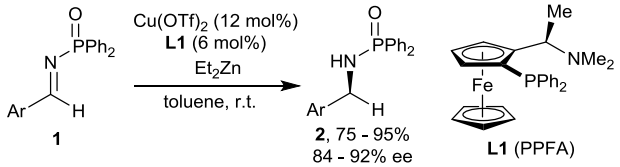
Chiral ferrocene ligands are one of the most prominent ligand classes in asymmetric catalysis. The importance of chiral ferrocene catalysts is highlighted by the fact that three books have been devoted to the synthesis and applications of these catalysts.[1-3] Ferrocene based catalysts have also been a topic of several review articles.[4-10] Some of the reviews deal mainly with synthesis and coordination properties of ferrocenyl ligands.[11, 12] Most emphasis, however, is placed on ferrocenyl diphosphanes, which are ligands with very diverse applications. There are also review articles focusing on other particular ferrocenyl classes, such as oxazolines,[13-15] carbenes,[16] or sulphur derivatives.[17] A combination of excellent coordinating properties of phosphorus with that of other donor atoms seems particularly effective for asymmetric catalysis. It results in additional asymmetry brought directly at the catalysing metal centre. Ligands of this type comprise combinations of phosphorus with nitrogen, sulphur, oxygen and even carbon as a donor atom. Apart from differences in bond lengths between phosphorus and other donor atoms, there are also differences in proportions of dative and back-bonding. Furthermore, many catalytically active transition metal complexes have square planar geometry and thus strong *trans*-effect of the phosphorus produce additional geometry distortions. There have been many exciting developments in the application of hetero-bidentate ferrocene ligands recently. Therefore, we think that it is useful to review applications of hetero-bidentate ferrocene ligands in asymmetric catalysis.

Ferrocene P,N bidentate ligands

Combination of soft and hard donor atoms such as phosphorus and nitrogen constitutes the most important type of hybrid ligands. Metal complexes with ferrocenyl bidentate P,N-ligands form diverse group of compounds with wide-ranging catalytic abilities. The research in this area begun with discoveries by Hayashi and Kumada, who showed that *N*,*N*-dimethyl-1-[2-(diphenylphosphano)ferrocenyl]ethylamine (**L1**, PPFA) can form catalytically active complexes with transition metals. For instance, Pd-PPFA complexes were efficient for hydrosilylation of alkenes,[18, 19] and corresponding Ni-complexes for cross-coupling with Grignard reagents.[20, 21] Detailed coverage of the early developments of ferrocenyl P,N-ligands can be found in several review articles[5, 6, 13] and book chapters.[22, 23] This section

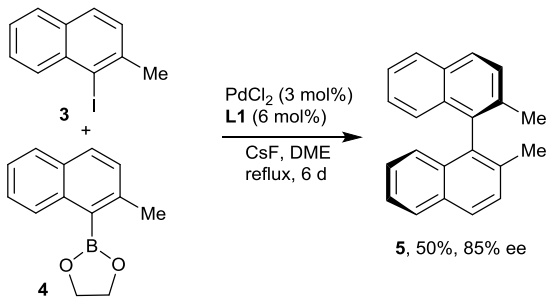
focuses on recent applications of ferrocenyl P,N-ligands in asymmetric catalysis.

The PPFA ligand (**L1**) was effective in a Cu-catalysed addition of diethyl zinc to *N*-diphenylphosphanoyl aromatic aldimines **1**. Corresponding amines **2** were isolated in high yields (75-95%) and high enantiomeric purities (84-92% ee) (Scheme 1).[24]



Scheme 1

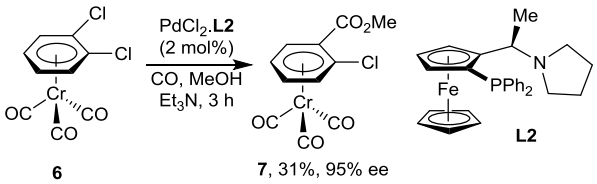
Palladium-catalysed Suzuki cross-coupling between aryl halides **3** and arylboronates **4** proceeded enantioselectively when PPFA ligand (**L1**) was used. Axially chiral binaphthyl products **5** were obtained in up 85% ee (Scheme 2). Although P,N-ligand was more enantioselective than a 1,1´-substituted diphosphane BPPFA ligand, authors used two equivalents of the PPFA ligand for palladium and thus forcing formation of a bis(phosphane) complex.[25, 26] Bringmann and co-workers utilized this methodology in the total synthesis of naphthylisoquinoline alkaloids ancistroealaine A and B.[27]



Scheme 2

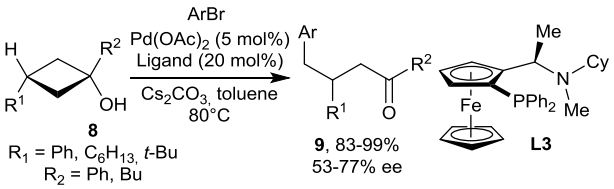
PPFA ligand (**L1**) worked well also in the similar Pd-catalysed cross-coupling, in which triorganoindiums were employed as organometallic donors. The corresponding, axially chiral diaryls were obtained in up to 86% ee.[28]

Amino phosphane ligand **L2** acted in a Pd-catalysed methoxycarbonylation of 1,2-dichlorobenzene tricarbonyl-chromium complex (**6**).[29] The desired monomethoxy-carbonylated product **7** was obtained in high enantiomeric purity (95% ee). Enantioselectivity of the reaction increased with longer reaction time, as a result of a subsequent kinetic resolution connected to the formation of a bis-methoxycarbonylated product (Scheme 3).



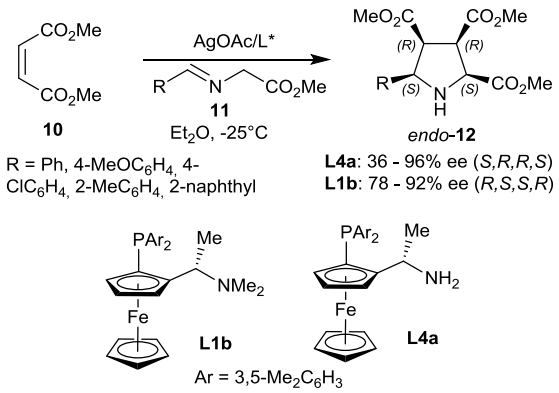
Scheme 3

Amino phosphane ligand **L3** with different substituents on the nitrogen was employed in a Pd-catalysed arylation of cyclobutanols **8** with aryl bromides. The corresponding ketones **9** with stereogenic centre in the β-position were isolated in high yields but with only medium enantiomeric purities (53-77% ee) (Scheme 4).[30]



Scheme 4

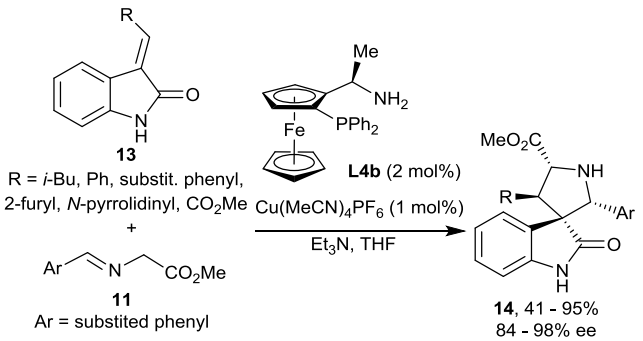
PPFA ligands were also useful in a silver-catalysed [3+2] cycloaddition of dimethyl maleate (**10**) with azomethine ylides generated from imines **11**. Interestingly, a ligand with dimethylamino group (**L1b**) and the amino group (**L4a**) afforded cycloaddition products **12** with opposite absolute configurations. Authors explained this behaviour by change in the organization of the transition state mediated by hydrogen bonds, which are only available in the ligand **L4a** (Scheme 5).[31]



Scheme 5

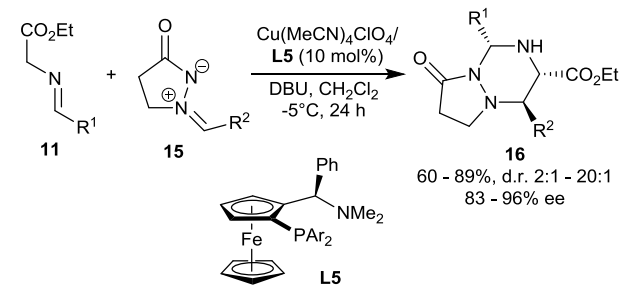
Recently Guo and co-workers discovered that PPFA-type ligands were efficient in a [6+3] cycloaddition of tropone with azomethine ylides. The resulting piperidine-fused bicyclic heterocycles were obtained in good yields, and diastereomeric purities were in the range of d.r. 4:1 to 20:1. Enantiomeric purities of these products were also high (87 - 96% ee). Screening of a variety of PPFA-type compounds showed that ligand **L1a** was the most competent one.[32]

Another PPFA-type ligand with NH_2-group (**L4b**) was excellent ligand in the Cu-catalysed [3+2] cycloaddition of 3-arylidene- or alkylideneoxindoles **13** with azomethine ylides.[33] A series of 3,3′-pyrrolidinyl-spirooxindoles **14** was isolated in good to excellent yields and enantiomeric purities (up to 98% ee) (Scheme 6).



Scheme 6

The ligand **L4b** was also used in a Ru-catalysed hydrogenation of aryl(methyl)ketones. Enantiomeric purities of the corresponding alcohols were only medium (up to 67% ee).[34]
Ferrocenyl aminophosphane ligands **L5** were efficient in the Cu-catalyzed [3+3] cycloaddition of azomethine ylides **11** with azomethine imines **15**. The corresponding bicyclic amides **16** were usually isolated in good yields and high diastereomeric and enantiomeric purities (Scheme 7).[35]



Scheme 7

Several other amino phosphane ligands **L6**-**L8** were synthesized and used in a Pd-catalysed allylic substitution (Figure 1).[36-38] Chen, Zhang and co-workers synthesized P,N,N-ligand **L9** (Figure 1) featuring pyridine moiety. This ligand was useful in an Ir-catalysed hydrogenation of ketones. Corresponding chiral alcohols were obtained with enantiomeric purities up to 87% ee.[39]

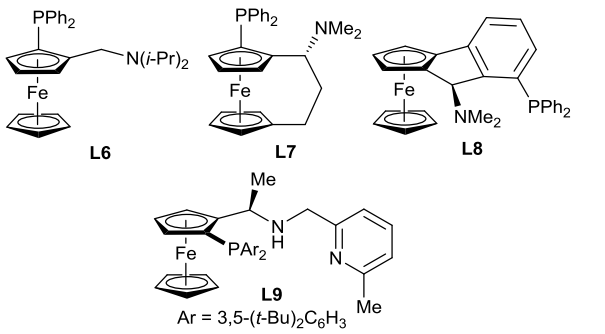


Figure 1

The most frequently used ferrocene P,N bidentate ligands are probably ferrocenyl oxazolines **L10**. Such ligands possess both central chirality on the oxazoline ring as well as planar chirality on ferrocene. Investigation of such ligands started by three independent research groups of Richards, Sammakia and Uemura, who almost at the same time described *ortho*-lithiation of ferrocenyl oxazolines as a way to obtain various oxazoline derivatives with planar chirality. Furthermore, ligands with both configurations of the planar stereogenic unit are available (S,S_p) and (S,R_p-**L10a**) (Figure 2).[40-42]

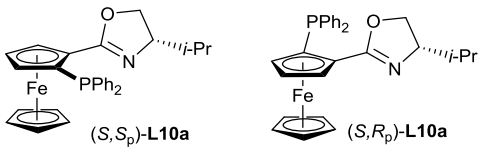
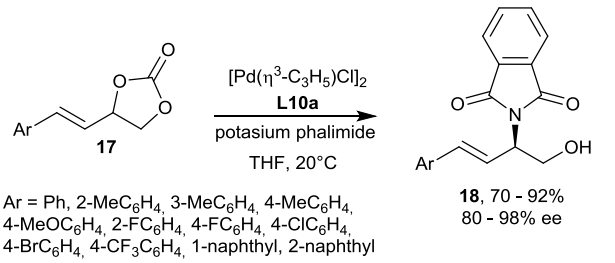


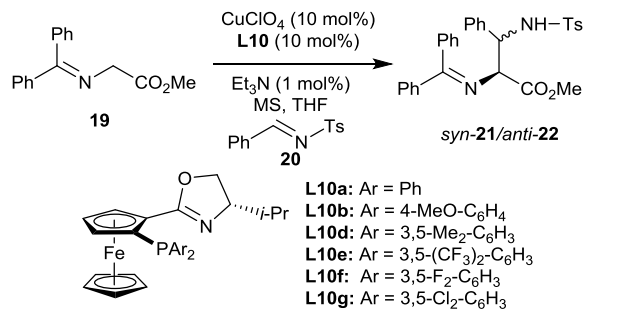
Figure 2

Planar-chiral ferrocenyl phosphane oxazolines (**L10,** Phosferrox**)** were used as excellent ligands in Pd-catalysed Grignard cross-couplings,[43] Pd-catalysed Tsuji-Trost allylic substitutions[44] and also in Cu-catalysed conjugate additions of Grignard reagents to cyclic enones.[45] Uemura and co-workers reported Ni-catalysed cross-coupling of allylic substrates with Grignard reagents[46] and arylboronic acids.[47]
Zhang and co-workers showed that Pd-**L10** complexes can effectively catalyse an allylic substitution on 4-aryl-1,3-dioxolan-2-ones **17** using potassium phthalimide as nucleophile.[48] The resulting unsaturated amino alcohols **18** were obtained in good yields and high enantiomeric purities (Scheme 8).



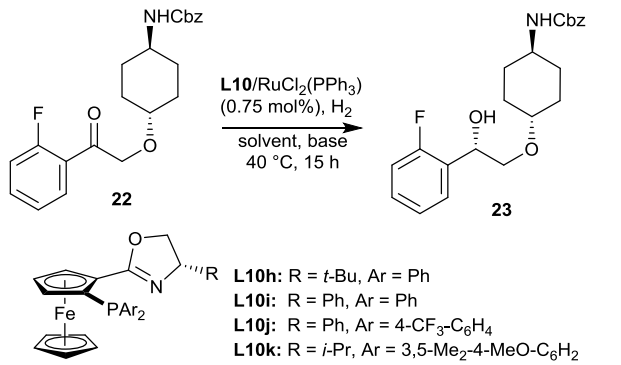
Scheme 8

Several oxazolines **L10** were successfully used in a Cu-catalysed Mannich reaction of enolates derived from glycine imines **19** with tosyl-protected imines **20** (Scheme 9). The reaction afforded products **21** in high yields (92–97%), with *syn/anti* ratios from 8:92 to 94:6 and enantiomeric purities up to 99% ee. Interestingly, the *syn/anti* ratio was strongly ligand dependent. For instance, ligand **L10a** led to the preferential formation of *anti*-**21** (*syn*/*anti* 8:92). On the other hand, ligand **L10e** afforded isomer *syn*-**21** (*syn*/*anti* 94:6).[49]



Scheme 9

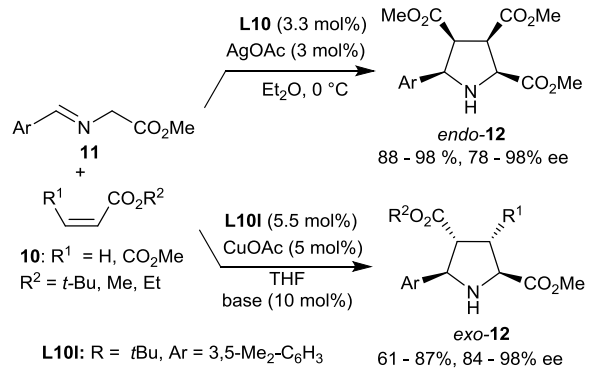
Ferrocenyl phosphane oxazoline ligands **L10** were useful in asymmetric hydrogenations. In one of the first reports on Phosferrox ligands, Sammakia used them in the Ru-catalysed hydrogenation of aryl(alkyl)ketones.[50] Later, Naud and co-workers developed and scaled-up this methodology up to a pilot level. Ferrocenyl oxazolines afforded chiral alcohols in enantiomeric excesses up to 99% and with very high substrate to catalyst ratios (S/C) of 10,000 – 50,000.[51, 52] Phosferrox ligands (**L10a**, **L10d, L10h-k**) were used in the Ru-catalysed hydrogenation of α-alkoxy substituted ketone **22**.[53] The reaction was performed under mild conditions and the corresponding alcohol **23** was obtained with the highest enantiomeric purity of 93% ee using ligand **L10h** (Figure 10).



Scheme 10

Phosferrox ligands **L10** were also useful in the Ir-catalysed hydrogenation of quinolines. The corresponding tetrahydroquinoline derivatives were obtained in high yields and enantiomeric purities up to 92% ee.[54] Uemura and co-workers showed that Rh-complex with ligand **L10** afforded in the hydrosilylation of acetophenone (*R*)-1-phenylethan-1-ol and Ir-complex led to (*S*)-enantiomer of this alcohol.[55] Phosferrox ligands **L10** participated also in the enantioselective Ru-catalysed hydrosilylation of ketoximes.[56]

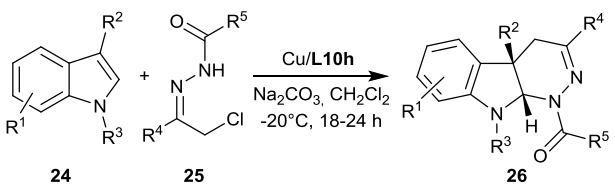
Oxazoline ligands **L10** were used in a Ag-catalysed *endo*-selective and enantioselective [3+2] cycloaddition of azomethine ylides formed from imines **11** with dimethyl maleate (**10**).[57] Cycloadduct **12** was obtained in high enantiomeric purities up to 98% ee. On the other hand, similar Cu-catalysed reaction with maleates and other alkenes was *exo*-selective. The adduct *exo*-**12** was also isolated in high enantiomeric purities (Scheme 11).[58]



Scheme 11

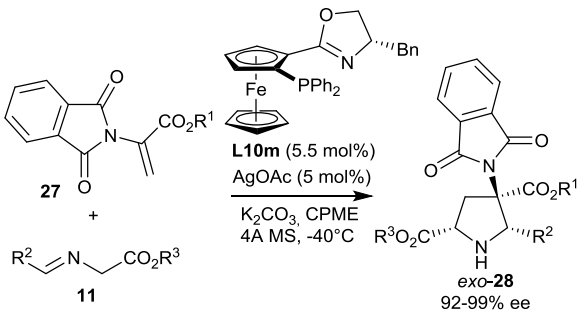
Ferrocenyl phosphane oxazoline ligands **L10** were also used in a 1,3-dipolar cycloaddition of azomethine ylides to β-nitrostyrenes.[59] Reactions went smoothly under $CuClO_4$ catalysis, although slightly higher catalyst loading (10 mol%) was necessary for obtaining acceptable yields. Chemical yields were in the range of 49–75%, *exo/endo* ratios varied greatly from 100:0 to 0:100 and enantiomeric purities of the *exo* product were up to 98% ee.

Wang and co-workers utilized Phospherrox ligand **L10h** in a Cu-catalysed inverse-electron-demand aza-Diels-Alder reaction of indoles **24** with azoalkenes **25**. The resulting [2,3]-fused indoline heterocycles **26** were obtained in high yields and enantiomeric purities (up to 99% ee) (Scheme 12).[60]



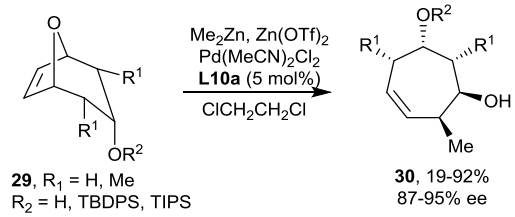
Scheme 12

Phosferrox ligands **L10** participated in an Ag-catalysed enantioselective 1,3-dipolar cycloaddition of azomethine ylides to α-aminoacrylates **27**. This catalytic system exhibited excellent *exo*-diastereoselectivity and enantioselectivity (92–99% ee). This process provided efficient access to useful 4-aminopyrrolidine-2,4-dicarboxylic acids **28** containing a unique quaternary α-amino acid unit (Scheme 13).[61]



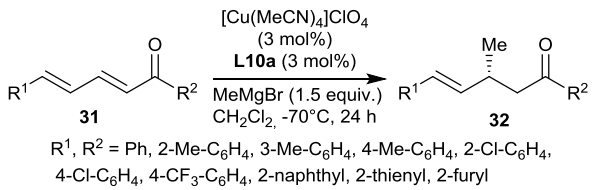
Scheme 13

Lautens and co-workers used Phosferrox ligand **L10a** in a Pd-catalysed ring opening of oxabicyclic alkenes **29** with dimethylzinc.[62] The corresponding cycloheptenyl alcohols **30** were obtained in good yields and enantiomeric purities up to 95% ee (Scheme 14).



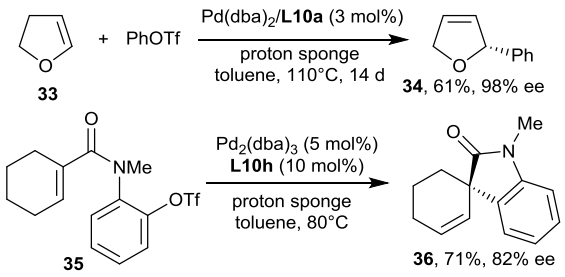
Scheme 14

Xie, Zhang and co-workers showed that the ligand **L10a** was highly efficient in the Cu-catalysed conjugate additions of methyl magnesium bromide to linear α,β,γ,δ-unsaturated ketones **31**.[63] The 1,4-addition products **32** were isolated in high yields. The addition was completely regioselective with respect to 1,4 vs. 1,6 addition pathway. The 1,4-addition was also highly enantioselective (up to 98% ee) (Scheme 15).



Scheme 15

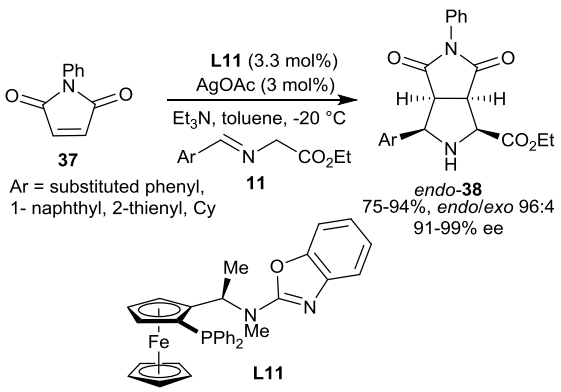
Guiry´s laboratory used the Phosferrox ligand **L10a** in a Pd-catalysed Heck reaction. The reaction between 2,3-dihydrofuran (**33**) and phenyl triflate required 14 days to give 61% of the coupling product **34**. It was, however, isolated with high enantiomeric purity of 98% ee.[64] Intramolecular Heck reaction in the amide **35** worked also well. With the ligand **L10h**, the product **36** was isolated in 72% yield and with enantiomeric purity 82% ee (Scheme 16).[65, 66]



Scheme 16

Lu and Hou have prepared BAR_F (BAR_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) salts of Ir-complexes of the ligands **L10** and used them in an asymmetric hydrogenation of α,β-unsaturated amides.[67] The reactions proceeded practically with complete conversion and high enantioselectivities (75–98% ee). Ligand **L10a** was also used in a regio- and stereoselective Cu-catalysed addition of Grignard reagents to 1,5-diarylpenta-2,4-dienones. The products of 1,4-addition were isolated in 69–92% yields. Enantioselectivity depended on the Grignard reagent, which was used. The MeMgBr afforded 1,4-adducts with the best results (98% ee). On the other hand, the reaction with EtMgBr proceeded with only medium enantioselectivity (66% ee).[63]

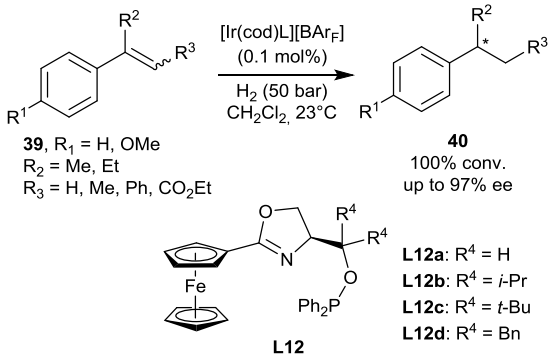
Hu and co-workers described an interesting amino phosphane ligand **L11** with benzoxazole moiety.[68] This ligand proved to be excellent in the Ag-catalysed 1,3-dipolar cycloadditions of azomethine ylides generated from imines **11** to *N*-phenyl maleimide (**37**) (Scheme 17). Bicyclic cycloaddition products **38** were obtained in high yield, *endo*/*exo*-selectivity and enantiomeric purities.



Scheme 17

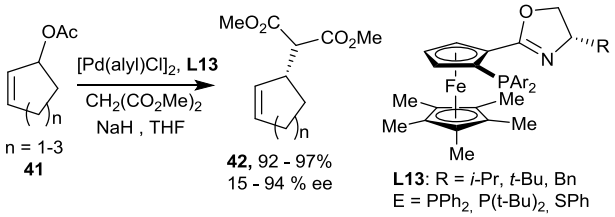
Jones and Richards prepared phosphinite-oxazoline P,N-ligand **L12** (Scheme 18) having phosphite group on the oxazolidine moiety and tested it in the Pd-catalysed allylic substitution.[69] Asymmetric induction was affected by stereocentre on the oxazolidine skeleton, and 90% ee was observed. Authors also described analogues having η^5-(pentaphenylcyclopentadiene-η^5-(cyclopentadiene)iron and η^4-(tetraphenyl cyclobutadiene)-η^5(cyclopentadiene)cobalt instead of ferrocene, but both ligands were less active.

Pfaltz and co-workers used ligand **L12b-d** in the Ir-catalysed hydrogenation of trisubstituted alkenes **39**. The corresponding alkanes **40** were obtained in enantiomeric purities up to 97% ee (Scheme 18).[70]



Scheme 18

Helmchen and co-workers described an interesting synthesis of bidentate ligands **L13** based on pentamethylferrocene backbone and used them in the Pd-catalysed allylic substitution of cycloalkenyl acetates **41** with dimethyl malonate.[71] The allylation products **42** were usually isolated in high yields, but its enantiomeric purities varied greatly. The ligand **L13b** afforded the best results (Scheme 19).

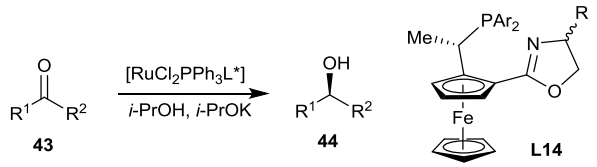


Scheme 19

Peters and co-workers synthesized related sterically demanding P,N-ligands based on pentaphenylferrocenyloxazolines. Corresponding phosphanes were obtained via diastereoselective *ortho*-lithiation. Interestingly, both epimers with respect to the planar stereogenic unit were obtained by altering an additive in the lithiation. The lithiation with *n*-BuLi and TMEDA led to the formation of (S,S_p)-isomer. On the other hand, bis(2-*tert*-butoxyethyl)ether afforded (S,R_p)-isomer. These ligands were useful in the allylic substitution on challenging cyclic substrates **41** (n=2). The resulting allylation products **42** were obtained in high yields and reasonable enantiomeric purities (84% ee).[72]

Weissensteiner and co-workers described a new ligands **L14** (Scheme 20), which exhibited excellent activity in the Ru-catalysed asymmetric hydrogenation of a range of alkyl(aryl)ketones.[73] All reactions proceeded with 99% conversion and the corresponding secondary alcohols were obtained with up to 99% ee.

Later on, Weissensteiner´s group undertook a detailed study of Ru-catalysed hydrogenation and transfer hydrogenation of aryl(alkyl)ketones **43**.[74] They compared a series of ferrocenyl oxazoline ligands. A range of ketone substrates was reduced with high enantioselectivity (**44**, up to 99% ee). A comparison of X-ray structure of Phosferrox (**L10**) and ligands **L14** showed that these compounds adopt different molecular structures. However, in asymmetric transfer hydrogenation, both ligands afforded chiral alcohols in similar enantiomeric purities (Scheme 20).



Scheme 20

Ikeda and co-workers described synthesis of ferrocene bidentate P,N ligands **L15** without planar chirality (Figure 3).[43] Starting from bis-(1,1´-tributylstannyl)ferrocene, they prepared 2-(1´-diphenylphosphino ferrocenyl)oxazolines **L15**, which were used as ligands in the Pd-catalysed allylic substitution of 1,3-diphenylallyl acetate with dimethyl malonate. The reaction afforded allylation products in high yields and enantioselectivity when bis(trimethysilyl)acetamide (BSA) with KOAc was used as a base. Surprisingly, ligand/Pd-source ratio was 2:1 in all experiments, although authors proved by NMR experiments that ligands **L15** acted as bidentate ligands (Figure 3).

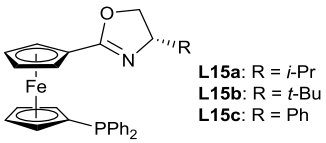


Figure 3

Structural motive of 1,1´-disubstitution was also exploited by others. More than a decade ago Dai et al. described synthesis of interesting P,N-ferrocene bidentate ligands **L16**, sometimes termed as SiocPhos. These ligands possess carbon central chirality on oxazoline ring, another stereogenic centre on phosphorus in the position 1´ on the ferrocene as well as the axial stereogenic unit on binaphthyl moiety (Figure 4).[75] Diastereoisomers of the ligand **L16** were separable by column chromatography. Interesting also is unusual stability of these ligands, which are stable on the air for 2 months.

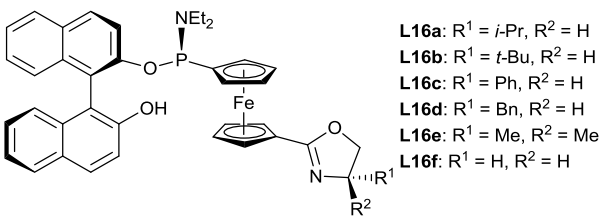
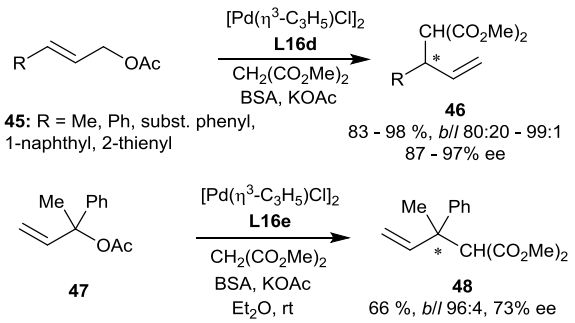


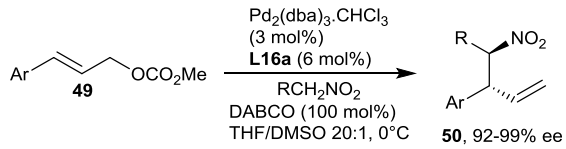
Figure 4

Ligand **L16** participated in the Pd-catalysed allylic alkylation of various allylic acetates **45**. The reactions worked well with preferential formation of branched product **46** (branched/linear (*b*/*l*) ratio was up to 99:1) and with good to excellent enantioselectivity (Scheme 21). Similar results were achieved in a Pd-catalysed amination of allylic acetates with benzylamine. Furthermore, ligand **L16e** was also used in the allylic substitutions of acetoxy derivatives **47**, which led to the formation of a quaternary stereogenic centre in compound **48** (Scheme 21).[76]



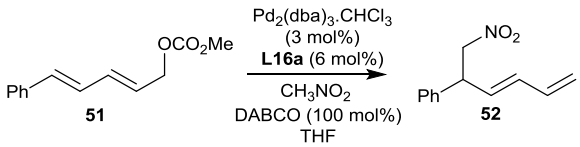
Scheme 21

Ligands **L16** were highly efficient also in the Pd-catalysed allylic alkylation of nitromethane[77] and other nitroalkanes with monosubstituted allylic substrates **49** (Scheme 22).[78] Allylation products were isolated in good yields (69-95%) as a mixture of γ-substitution and α-substitution product with ratios 80:20 – 97:3. Enantiomer purities of derivatives **50** were 92 – 99% ee. Diastereomeric ratios were in the range of 83:17 – 97:3.



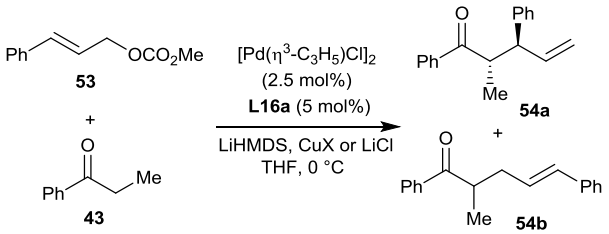
Scheme 22

In an extension to the study of allylic alkylation of nitroalkanes, Hou and co-workers explored use of dienyl carbonates **51** as allylic substrates.[79] This class of compounds brings additional challenge with another electrophilic reaction centre. The ligand (S_c,S_{phos},R_a)-**L16a** promoted the reaction in favour of ω-substitution (α/β/ω = 4:1:95) and the corresponding product **52** was isolated with enantiomeric purity of 87% ee (Scheme 23).



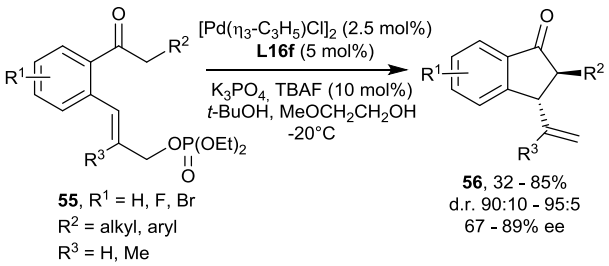
Scheme 23

The Hou laboratory used ligand **L16a** in a Pd-catalysed alkylation of enolates, generated from acyclic ketones **43**, with allyl methyl carbonates **53**. The corresponding allylation products **54** were isolated in 87–96% yields.[80] The ratio **54a**/**54b** varied from 0:100 to 98:2, *anti/syn* ratio of product **54a** was from 2:1 to 6:1 and enantiomeric purities of *anti*-**61a** were up to 98 % ee. It is of interest to note, that **54a**/**54b** ratio strongly depended on the anion of the additive. Using CuI the ratio (**54a**/**54b**) was 0:100, on the other hand with CuCl it was 94:6. The **54a**/**54b** ratio varied, depending on the solvent, from 84:16 up to 98:2, when LiCl was used as an additive (Scheme 24).



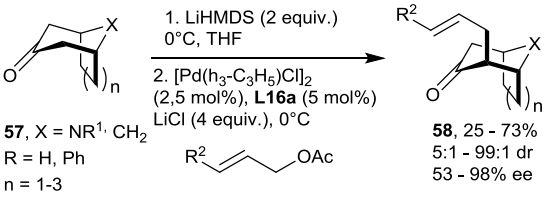
Scheme 24

Ketone **55** having adjacent allylic phosphonate group also participated in an intramolecular allylic alkylation catalysed by the Pd-**L16f** complex. A range of 2,3-disubstituted indanones **56** were obtained in good yields and enantiomeric purities (up to 89% ee) (Scheme 25).[81]



Scheme 25

Ketone enolates generated from symmetrical cyclic ketones **57** were desymmetrized via Pd-catalysed allylic alkylation with allylic acetates (Scheme 26). Hou´s ligand **L16a** was highly efficient in this transformation affording corresponding products **58** in yields 25 – 73%, diastereomeric ratio 5:1 – 99:1 and enantiomeric purities 53 – 98% ee.[82]

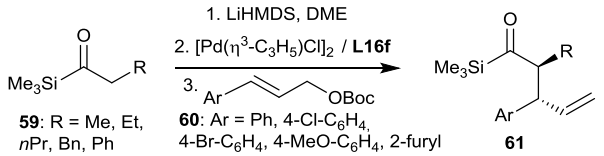


Scheme 26

Next paper dealt with alkylation of different aliphatic tertiary amides with allyl acetate.[83] The reaction with *N*,*N*-diphenyl amides using **L16a** gave good yields (75–99 %) of allylated products as well as high enantiomeric excesses (73–93 % ee).

Fang et al. have used ligands **L16a** in a Pd-catalysed *O*-alkylation of benzyl alcohol with Boc-protected allyl alcohols.[84] Chemical yields of the corresponding allylation products were up to 87 %. Using Cs_2CO_3 as a base branched/linear product ratio was 29:71–92:8. When *n*-BuLi was used as a base, only linear product was isolated in 75 % yield. The enantiomer purity of the branched product was in the range of 16–98 % ee.

A few years ago, Hou and co-workers described alkylation of acylsilanes **59** with monosubstituted allyl substrates **60**. The reactions proceeded well and products **61** were isolated in high yields (80–96 %), with branched/linear ratio from 88:12 to 99:1 and *anti/syn* 10:1–50:1.[85] Allylated acylsilanes **61** were obtained in excellent enantiomeric purities (up to 99 % ee). Interestingly, the central chirality on the oxazoline ring was not important for stereoinduction. The allylic substitution was highly enantioselective even if oxazoline ring bore no substituent (R = H, **L16f**) (Scheme 27).



Scheme 27

Ferrocenyl oxazolines offer interesting possibilities for structural variations. For instance, another stereogenic centre can be introduced easily. Balavoine, Haddou and co-workers used ligand **L17** for the Pd-catalysed allylic substitution (Figure 5). The allylation product was obtained in 82% yield and with 97% ee.[86] Another modification was reported by Moyano and co-workers, who synthesized ligand **L18** also for Pd-catalysed allylic substitution (63% yield, 96% ee) (Figure 5).[87]

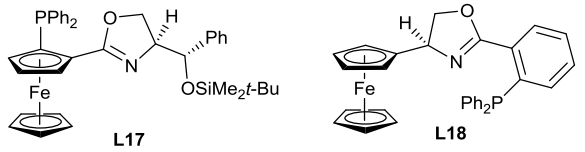
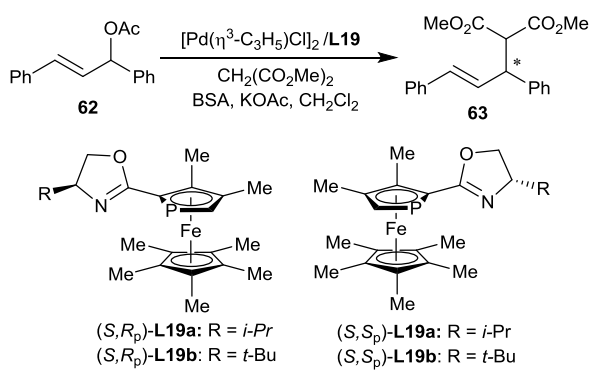


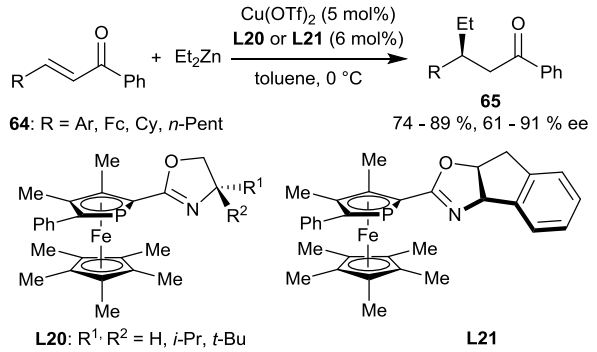
Figure 5

Fu and co-workers prepared a phosphaferrocene analogue of 2-ferrocenyloxazoline ligands **L19** and used them in the Pd-catalysed allylic substitution on acetate **62**, which proceeded with 80–94% yield and 68–82% ee (Scheme 28).[88] Planar chirality was dominant stereoinducing element in these ligands. Ligands (S,R_p)-**L19** afforded (*S*)-**63**, on the other hand, diastereoisomeric ligands (S,S_p)-**L19** led to the formation of (*R*)-**63**. The phosphaferrocene-oxazoline ligands **L19** were later applied in the Cu-catalysed 1,3-dipolar cycloaddition of azomethine imines with alkynes. The resulting bicyclic lactams were obtained in good yields and high enantiomeric purities.[89] Fu and co-workers adapted this reaction also into a kinetic resolution of chiral azomethine imines.[90]



Scheme 28

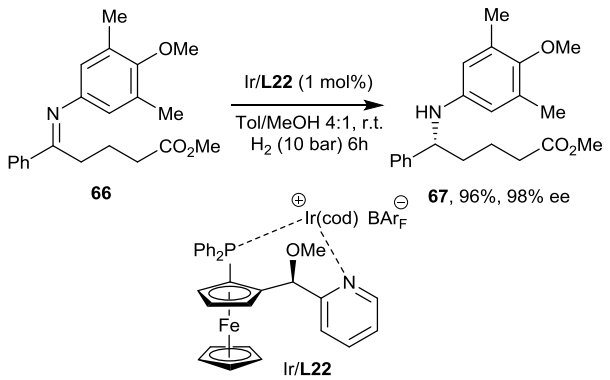
The Fu laboratory synthesized and also characterized a bigger series of similar ligands **L20** and **L21** and used them in a Cu-catalysed diethyl zinc addition to enones **64**.[91] Reactions worked well with ligands of both types and the corresponding products **65** were obtained in enantiomeric purities up to 91% ee (Scheme 29).



Scheme 29

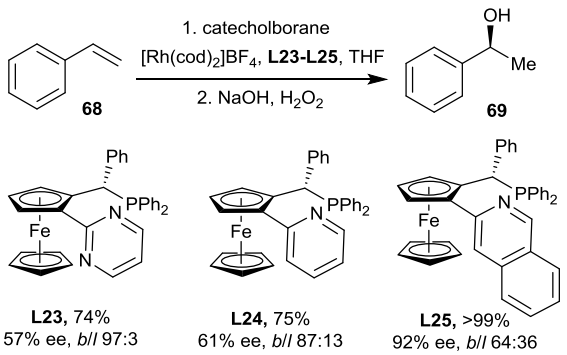
Ganter and co-workers described synthesis of analogous phosphaferrocene P,N-ligands without methyl groups on the cyclopentadienyl ring and with nitrogen donor atom on a side chain of the phosphacyclopentadiene ring.[92] Authors tested these ligands in the Pd-catalysed allylic substitution on acetate **62**, but enantioselectivity was only low (11–19% ee). Analogous ligands, having 1-imidazolyl or 2-imidazolyl moiety instead of 2-pyridyl substituent, have been prepared in the same laboratory and have been successfully used in the same reaction. The product **63** was obtained in yields greater than 90%, but again with only low or moderate enantioselectivities (19–42% ee).[93]

Knochel and co-workers synthesized another P,N-ligand featuring pyridine moiety **L22**. Iridium complex with this ligand was highly effective catalyst for the asymmetric reduction of imine **66**. The corresponding amine **67** was isolated in 96% yield and 98% ee (Scheme 30).[94]



Scheme 30

Knochel´s group also described P,N-ferrocene ligands **L23–L25**, in which phosphane group was located at the alkyl side chain and nitrogen in heterocycles located on the position 2 of ferrocene acted as N-donor.[95] All prepared ligands proved to be very good in the Rh-catalysed hydroboration of styrene (**68**). The reaction was analysed after oxidation to the corresponding alcohol **69**, which was obtained in high yields and enantiomeric purities up to 92% ee (Scheme 31).



Scheme 31

Other nitrogen heterocycles were employed in designing chiral P,N-ligands (Figure 6). Jin and co-workers synthesized imidazolidine-containing ligand **L26**, which was highly enantioselective in the Pd-catalysed allylic substitution.[96] Ligand **L27** was also used in the Pd-catalysed allylic substitution, but was less enantioselective.[97]

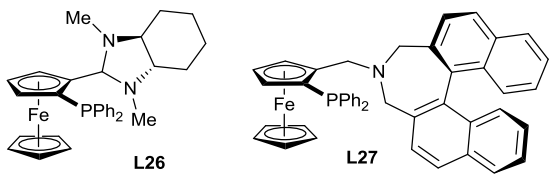
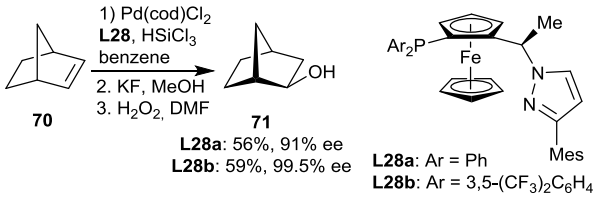


Figure 6

Enantioselective hydrosilylation of alkenes has traditionally been one of the areas where ferrocenyl P,N-ligands played an important role. Togni and co-workers showed that phosphane-pyrazole ligands **L28** participated in the Pd-catalysed hydrosilylation of alkenes. Bicyclic alkene **70** was effectively hydrosilylated and the corresponding alcohol **71** isolated after oxidation in high enantiomeric purity (Scheme 32).[98-100]



Scheme 32

Phosphane-pyrazole ligands **L28** have also been used in the Rh-catalysed hydroboration of alkenes with catecholborane.[101]

The Togni laboratory described P-stereogenic trifluoromethyl ligands **L29** (Figure 7) and used them successfully in the Pd-catalysed allylations.[102] The reactions ran up to full conversion of starting materials and excellent stereoselectivity (up to 94 % ee).

Fukuzawa and co-workers described so called ClickFerroPhos ligands **L30** (Figure 7) having 1-triazolyl group in α-position on the side alkyl chain.[103] ClickFerroPhos ligands **L30** were conveniently synthesized by a click reaction of a ferrocenyl azide with suitable alkyne. Ligands **L30** proved to be excellent ligands in the Ru-catalysed asymmetric hydrogenation of alkenes, β-keto esters, β-diketones as well as Pd-catalysed allylic substitution. Reactions proceeded with high yields and enantioselectivities up to 99 % ee.

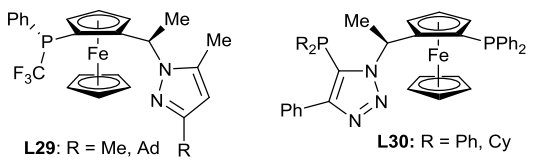


Figure 7

A range of ferrocenyl phosphane imine ligands **L31-L36** (Figure 8) were described. These ligands were typically used in Pd-catalysed allylic alkylations.

Ligands **L31** afforded the Pd-catalysed allylation of dimethyl malonate with ester **62** or 1,3-diphenylallyl pivalate with enantioselectivities up to 96% ee.[104] Even higher enantioselectivities afforded ketamine ligands **L32** (91–99% yield and up to 98% ee).[105] Ligands **L31-L33** were also studied in the Pd-catalysed allylic substitution of dimethyl malonate with cyclohexenyl acetate, but enantioselectivities were slightly lower (59–83% ee).[106]

Ligand **L34** with the hydroxyl group in the position 2 of the phenyl ring was used in addition of diethyl zinc to benzaldehyde and other aromatic aldehydes. Although yields were quite low, enantioselectivities up to 98% ee were achieved.[107]

Also ligands **L35** and **L36** were highly enantioselective allylic substitution (up to 99% ee).[108-110]

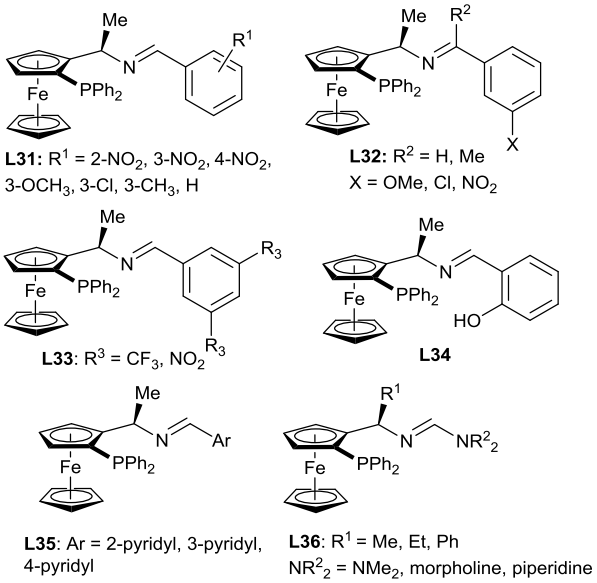
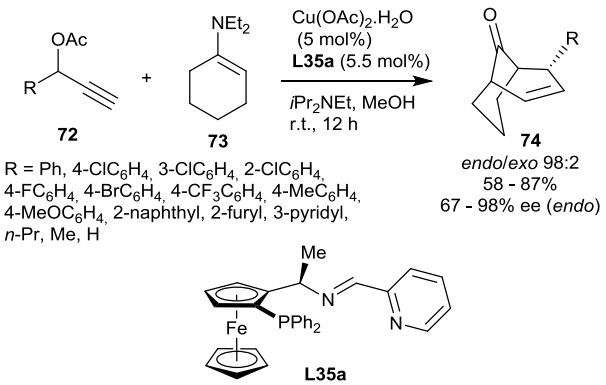


Figure 8

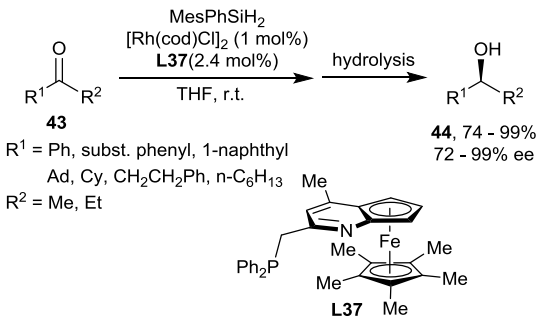
Zheng and co-workers reported application of the ligand **L35a** (Ar = 2-pyridyl) in a Ru-catalysed cyclopropanation. Styrene has been cyclopropanated using ethyl diazoacetate with up 90% ee for *trans* and 95% ee for *cis*-cyclopropane product. Ratio of *cis*/*trans* was typically 1:4.[111]

Hu and co-workers reported a formal [3+3] cycloaddition of propargyl esters **74** with cyclic enamines **75** (Scheme 33).[112] The reaction was catalysed by a Cu-complex with P,N,N-tridentate ligand **L38a** featuring pyridine moiety. The corresponding bicyclic ketones **76** were isolated as *endo*-isomers with high diastereoselectivity (typically 98:2) and high enantiomeric purities (up to 98% ee).



Scheme 33

Fu and Tao developed ferrocenyl P,N-ligand **L37** for the Rh-catalysed hydrosilylation of ketones. The corresponding alcohols were obtained in high yields and enantiomeric purities (Scheme 34).[113]



Scheme 34

Zhou and co-workers described quaternary ammonium salt-tagged ferrocenylphosphine-imine ligands **L38** (Figure 9) and applied them in the Pd-catalysed allylic substitutions.[114] The allylation of dimethyl malonate with 1,3-diphenylallyl acetate (**62**) worked best with the ligand with NMe_3 in the position 4 (up to 95% ee). These ligands worked similarly also in the allytion of benzylamine, but enantioselectivity of the reaction was lower (32–89% ee). Analogous ligand with diphenylphosphino groups on position 1 and 1´ of ferrocene was described by Dai *et al*.[115] but it acted as a P,P-ligand. In another attempt on immobilizing ferrocene P,N-ligand, Chung and co-workers attached imine-type ligand onto a polystyrene resin. The resulting ligand **L39** was applied in the Pd-catalysed allylic substitution. Enantiomeric purity of the allylation product was 73% ee, but ligand´s performance decreased after reuse.[116]

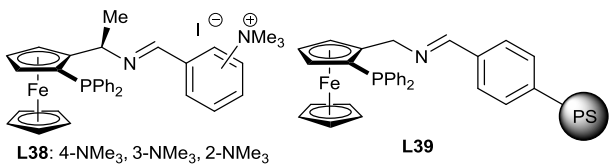


Figure 9

New ferrocenyl imine ligand **L40** was described by Van der Eycken and co-workers.[117] The ligand **L40** proved to be excellent ligands for the Pd-catalysed allylation of dimethyl malonate with 1,3-diphenylallyl acetate. The yields as well as enantiomeric excess were up to 99%.

Attar and co-workers described ferrocenylimine ligands **L41** (Figure 10), which had stereogenic centre not on α-, but on γ-carbon and tested them at the same allylic substitution.[118] The best reactivity, as well as selectivity, was observed with ligand **L41c** (99% conversion and 94% ee).

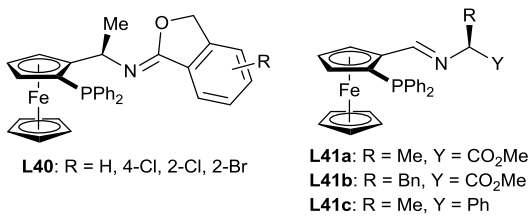
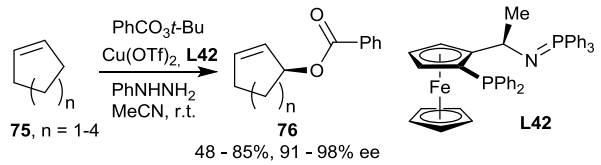


Figure 10

Kim and co-workers reported interesting iminophosphoranyl ferrocenes **L42** and applied them in the Rh-catalysed hydrogenation of methyl cinnamic acid, methyl (Z)-2-acetamidocinnamate and methyl (Z)-2-acetamidoacrylate.[119] These ligands afforded useful results also in a Cu-catalysed allylic oxidation of cyclic alkenes **75**. The corresponding allylic esters 7**6** were obtained in good yields and high enantiomeric purities (91 – 98% ee) (Scheme 35).[120]



Scheme 35

Mino and co-workers developed ferrocenyl P,N-ligand containing the hydrazine moiety (Figure 11). The ligand **L43** proved to be active in the Pd-catalysed allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate. The allylation product was afforded with high enantiomer purity (96% ee).[121] Manoury, Gouygou and co-workers synthesized a P,N-ligand **L44**, which has phosphorus heterocycle. This ligand was also applied in the Pd-catalysed allylic alkylation, but with only medium enantioselectivities (67% ee) (Figure 11).[122]

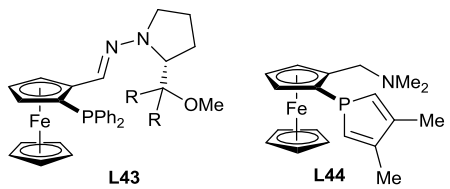


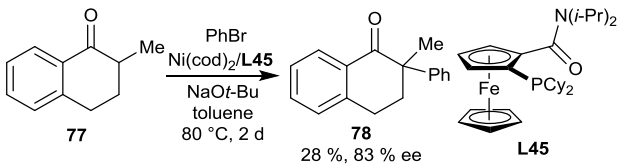
Figure 11

Johannsen and co-workers described synthesis of P,N-ligands having amino group on *ortho*-position of the phenyl group.[123] These ligands participated in the $Cu(OTf)_2$ catalysed diethyl zinc addition to chalcone. Reactions proceeded with 5–95 % yield and up to 58% ee.

Several types of ferrocenyl P,N-ligands stands out from a large variety of structurally diverse derivatives. Amino phosphanes based on PPFA (**1**) are undoubtedly one of the most successful ones, based on various reactions, in which these ligands can participate. PPFA-type ligands were useful for various Cu and Ag-catalysed cycloadditions as well as Cu-catalysed organometallic additions. Even more powerful structural motif seem to be the oxazoline ring, which has also been featured in a number of ferrocene P,N-ligands. The simplest implementation of this structural element is in 1,2-disubstituted ferrocenyl compounds such as ligands **L10**. Catalytic performance of these ligands can be easily tuned by varying substituents on the oxazoline ring as well as on the phosphorus. Ferrocenyl phosphane-oxazolines are useful for Cu-catalysed Mannich reactions, Pd-catalysed allylic substitutions, Cu and Ag-catalysed cycloadditions, Cu-catalysed additions of organometallic reagents and Ir and Ru-catalysed hydrogenations. 1,1´-Disubstitution of the ferrocene was successfully employed in another highly useful ferrocene oxazoline ligands SiocPhos **L16**. These compounds are highly efficient in various Pd-catalysed allylic substitutions. Importantly, ligands **L16** work well also on more challenging substrates than symmetrical acetate **62**. Other ligand types, such as compounds having nitrogen in different heterocycles or in the imine function also show some useful applications. Many of these P,N-ligands were tested in the Pd-catalysed allylic substitution on 1,3-diphenylpropenyl acetate **62**, sometimes with good results.

Ferrocene P,O bidentate ligands

Combination strongly coordinating phosphorus and weakly bound oxygen within one compound produces interesting class of hemilabile hybrid ligands.[124] Kwong and Chan reviewed hemilabile P,O-type ligands in cross-coupling reactions and several ferrocene P,O bidentate ligands were described there.[125] They have also mentioned their unpublished work describing synthesis of ligands **L45**, which was successfully used in a Ni-catalysed arylation of ketone enolate **77** (Scheme 36).



Scheme 36

However, the first ferrocene P,O bidentate ligand **L46** (Figure 12) was described by Kumada et al.[126] and it was used in the Ni-catalysed Grignard cross-coupling leading to axially chiral binaphthyls.[127] Ligand **L46** was also successfully employed in the Cu-catalysed 1,3-dipolar cycloaddition between naphthoquinone and azomethine ylides. Interestingly, this P,O-ligand was more efficient than corresponding P,N-ligand, such as **L1**. A range of isoindolines was obtained in high yields and high diastereomeric and enantiomeric purities (d.r. 20:1, 86-97% ee).[128]

Racemic form of the ligand **L46** was used by Buchwald in a Pd-catalysed coupling of secondary amines with bromoarenes.[129, 130] Pedersen and Johannsen have prepared an air stable ferrocene P,O ligand **L47** and its PPh_2 analogues.[131, 132] This ligand was effective in the Pd-catalysed hydrosilylation of styrene giving reasonable yields of the product having good enantioselectivity (Figure 12).

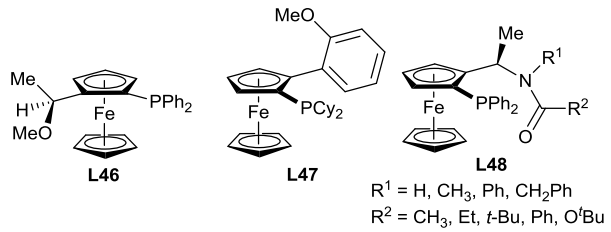


Figure 12

Ligand **L47** was successfully also used in the Pd-catalysed Suzuki cross-coupling of aryl chlorides as well as aryl bromides with boronic acids. For instance, 2-methyl-1-bromonaphthalene was coupled with 2-methyl-1-naphthylboronic acid in 62% yield and 43% ee.[133] Lang and Schaarschmidt prepared hybrid P,O-ligands featuring ferrocenyl-phenyl ether moiety. These ligands, although chiral, were synthesized and used as racemates in the Suzuki coupling. The ligands were remarkably active, as only 10 ppm of the corresponding Pd-catalyst was necessary for generation of hindered biaryls.[134]

Manoury and co-workers synthesized acetal-phosphane ligands, which afforded enantioselectivities up to 77% ee in the allylic alkylation of acetate **62**.[135]

Štěpnička has published a critical review on phosphano-carboxamides as ligands and also as potential pharmaceuticals.[136] The first ferrocenyl carboxamide ligands **L48** (Figure 12) was described by Boaz and co-workers, and it proved to be excellent for the allylic alkylation of dimethyl malonate.[137] The best yields (81–94%) as well as enantioselectivities (73–99% ee) were achieved, when R^1 = H and R^2 = Et.

Štěpnička and co-workers prepared planar chiral carboxamides **L49** and **L50** (Figure 13) and compared them as ligands in the Pd-catalysed allylic substitutions with 1,3-diphenylallyl acetate (**62**).[138, 139] High yields of the alkylation product as well as high enantioselectivity (up to 90%) were achieved with ligand **L49** (R = Bn). Much lower enantioselectivity (below 70% ee) was achieved with ligands **L50**, which apparently acted as a P,P-ligand. They also isolated Pd-complexes of both ligands and proved that ligand **L49** is P,O-ligand, while the corresponding diphosphane was a P,P-ligand. Dimitrov and co-workers showed that **L50** afforded enantioselectivities up to 82% ee in the allylic alkylation.[140] Higher enantiomeric excess (up to 89%) achieved Ikeda and co-workers with ligands **L51** (Figure 13).[141]

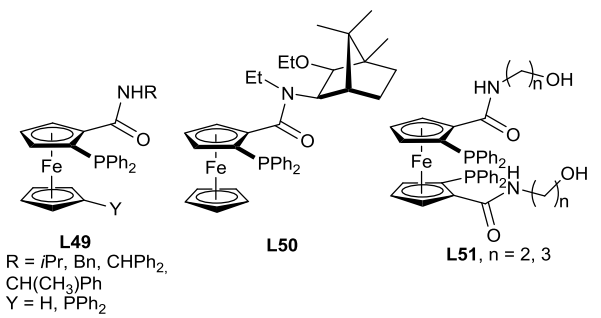


Figure 13

Štěpnička´s group also synthesized 2-phoshanyl ferrocene carboxamide ligands **L52** and **L53** (Figure 14) having both planar as well as central stereogenic unit. Ligands (R,S_p) and (S,S_p)-**L52** are analogues to ligands **L49**, but chiral amino acids were used for the amide preparation.[142, 143] The ligand **L53** have diphenylphosphanyl group in α-position of the alkyl group.[144] Ligands **L52** were used in the Cu-catalysed diethyl zinc addition to chalcones. Both conversions, as well as enantioselectivities, depended on the nature of the R-group. The best conversion (100 %) as well as enantioselectivity (84 % ee) were achieved when R = *i*-Pr. Ligands **L53** and its corresponding carboxylic acid took part in the Pd-catalysed allylation of dimethyl malonate. High yield (94 %) was achieved with the phosphane carboxylic acid, but the product was virtually racemic (10% ee). Using the ligand **L53** resulted in 42% conversion and mediocre enantioselectivity (43% ee).

Wang and co-workers synthesized pyrrolidinyl amide **L54** and used it in the Cu-catalysed addition of dialkylzinc to imines.[145] Interestingly, reduction of amide carbonyl group to CH_2 and thus producing a P,N-ligand resulted in a sharp decrease of the enantioselectivity of the addition (84% *vs.* 21% ee).

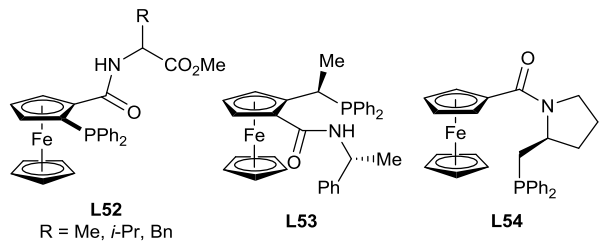


Figure 14

Carboxamido group can also serve as a handle for immobilization of ferrocenyl ligands on the ionic liquid moiety, which make substantially simpler recovery of the ligand as well as reuse of the catalytic system. Blaser and co-workers have prepared ligand **L55** (immobilized Josiphos) (Figure 15) and used it successfully in the Rh-catalysed hydrogenation of methyl acetamidoacrylate as well as dimethyl itaconate.[146] Conversion up to 100% and 30–99% ee were achieved.

Ligand **L56** (Figure 15) was successfully used in the Pd-catalysed allylation of dimethyl malonate in different ionic liquids.[147] The best results (97% yield and 92% ee) were achieved in ionic liquid [bmim]PF_6. It was possible to recycle catalytic system in [emim]SO_4Et three times with drop of yield but with only slight decrease in the enantioselectivity (from 89% to 69% ee). The ligand **L56** also participated in a Pd-catalysed allylation of potassium phthalimide, phenolate ions and sodium *para*-tolylsufinate in mixtures of various ionic liquids and organic solvents.[148] Both ligand **L55** and **L56**, however, are not P,O but P,P-ligands because of the presence of two phosphane groups.

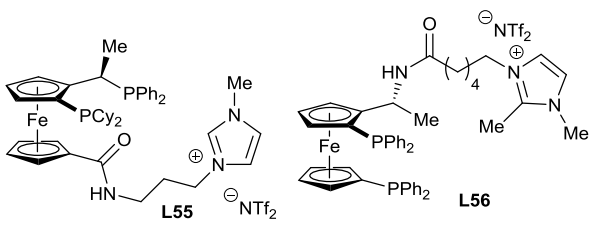
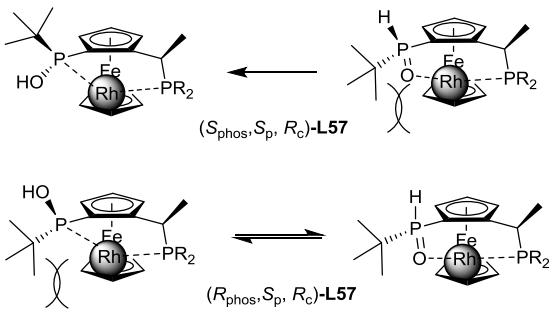


Figure 15

Scientists led by Pugin and Pfaltz described interesting P,O-ligands **L57** featuring a combination of a phosphane and secondary phosphane-oxide.[149] This Josiphos analogue **L57**, termed JoSPOphos, showed peculiar coordination behaviour, which depended on the absolute configuration on phosphorus. The ligand with (S_{phos},S_p,R_c) configuration showed predominantly P,P-coordination to rhodium as evidenced by ^{31}P NMR. On the other hand, (R_{phos},S_p,R_c)-**L57** was observed as a mixture of P,P and P,O-complexes. Authors argued that this behaviour was caused by steric hindrance of *t*-butyl group with cyclopentadienyl ring (Scheme 37). A range of prochiral alkenes has been hydrogenated with up to 99% ee using Rh-complexes of ligand **L57**. Authors also speculated that P,P complex rather than P,O complex was catalytically active, but no experimental evidence was available.



Scheme 37

From among P,O-ligands, mainly two types are present within ferrocene derivatives. Ferrocenyl ligands mostly feature amide functionality, which usually serves as O-ligand to transition metals. These P,O-ligands were usually tested on Pd-catalysed allylic substitution of acetate **62** with varying degree of success. Ligands with ether functionality are less populated but offer some interesting applications, such as Pd-catalysed cross-couplings and hydrosilylations. There is also an unusual, but highly promising application of the ligand **L46** in the Cu-catalysed dipolar cycloaddition.

Ferrocene P,S bidentate ligands

Combination of phosphorus and sulphur in one compound is another useful way of producing hetero-bidentate ligands. Several reviews focus on chiral ligands containing sulphur donor atoms. The review article by Masdeu-Bulto, Martin and co-workers concentrated mostly on characterisation of their complexes with different transition metals.[150] There are also general reviews covering chiral sulphur ligands only in part.[151, 152] The article of Bonini *et al*. described mostly synthetic methods for preparation of sulphur-containing chiral ferrocene derivatives, and P,S ferrocene ligands were only briefly mentioned.[17] In 2010, Chan and co-workers published a feature article on chiral P,S-ligands, in which ferrocene P,S-ligands were well covered.[153] In this section, we cover the most important ferrocenyl P,S-ligands from the point of view of their catalytic activity.

Enders and co-workers synthesized the first chiral ferrocene P,S ligands **L58** and **L59** (Figure 16) using their SAMP/RAMP methodology from acylferrocenes.[154, 155] They used these ligands in the Pd-catalysed allylic alkylation and amination.[156] The allylation of dimethyl malonate with acetate **62** worked very well with ligand **L58** (R^1 = Ph, R^2 = Me, R^3 = Et) (99% yield, 97% ee). Interestingly, the regioisomeric ligand **L59** afforded only racemic product, albeit in 99% yield. The enantioselective allylic amination of acetate **62** with benzylamine using the ligand **L58** (R^1 = Ph, R^2 = Me, R^3 = Et) proceeded also with high enantioselectivity (94% ee), but the allylation product was isolated in somewhat lower yield (50%). Several years later, Hou and Dai have prepared similar ligands **L60** and **L61** (Figure 16) from Ugi´s amine, which were also very active in the allylic substitution of 1,3-diphenylallyl acetate (**62**) with dimethyl malonate.[157] Application of the ligand **L60** in this reaction resulted in 90% yield of the product with (*S*) configuration (94% ee). On the other hand, the ligand **L61** gave the product with (*R*) configuration, although in slightly lower enantiomer purity (75% ee).

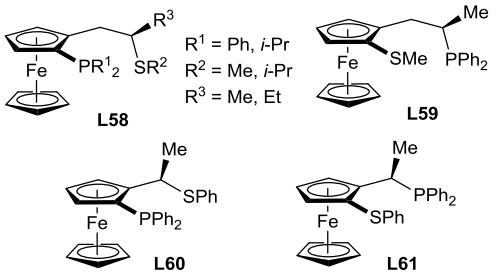


Figure 16

A break-through in the applications of ferrocene P,S ligands in asymmetric catalysis brought about work of Carretero and co-workers, who disclosed synthesis and application of FesulPhos ligands (**L62**) (Figure 17).[158, 159]

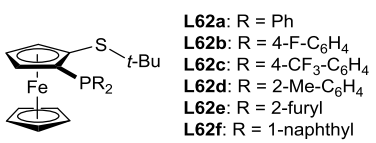
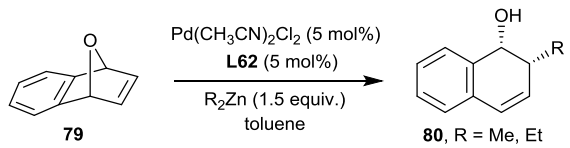


Figure 17

Fesulphos ligands (**L62**) were efficient in the Pd-catalysed allylation of dimethyl malonate with 1,3-diphenylallyl acetate (**62**). These ligands afforded high yields (60–96%) and

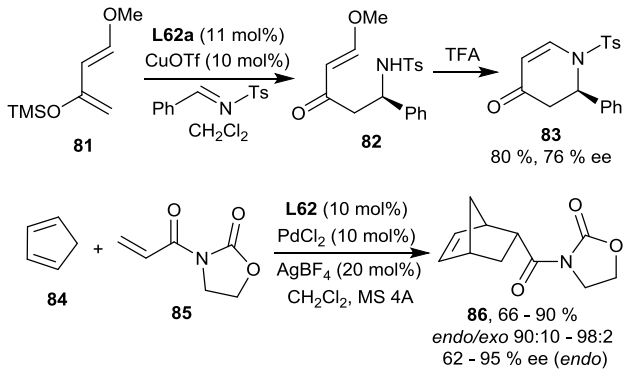
enantiomeric purities (up to 97% ee) of the allylation product when 4 mol% of palladium precursor and 6 mol% of the ligand **L62** were used. Not surprisingly, Fesulphos ligands **L62** were useful also in the related allylic amination with benzylamine (72–93% yield and enantiomer purity up to 99.5% ee) as well as potassium phthalimide (90% yield, 96% ee). Carretero´s laboratory described also (η^5-cyclopentadienyl)(η^4-cyclobutadiene)cobalt analogue of FesulPhos as a ligand for allylic substitutions.[160]

Usefulness of the Fesulphos ligands in the Pd-catalysed allylic substitution stimulated their evaluation also in a related Pd-catalysed enantioselective ring opening of heterobicyclic alkenes **79** with organozinc reagents (Scheme 38).[161, 162] Outcome of the reaction strongly depended on the phosphane substituent in the ligand. The best results (**80**, 68–70% yield, 88–94% ee) were achieved with ligands **L62a**, **L62b**, **L62e**, and **L62g**. Authors have also tested different sources of the catalyst. The reaction rate was much higher when pre-formed cationic palladium complex [**L62**Pd(Cl)(Me)] together with $NaB(Ar^F)_4$ was used. In this case, even at 0.2 mol% catalyst loading, full conversion could be still reached within 5 h at -25°C.



Scheme 38

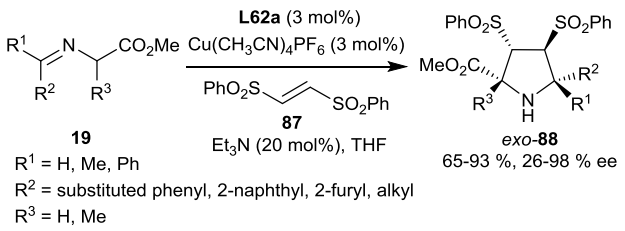
FesulPhos ligands were successfully used in cycloaddition reactions too. Copper-complexes with Fesulphos ligands **L62** were able to catalyse formal aza-Diels-Alder reactions of imines with Danishefsky´s diene. On the other hand, Pd–complexes were efficient for a typical Diels-Alder reaction of cyclopentadiene with *N*-enoyl oxazolidinones (Scheme 39).[163, 164]



Scheme 39

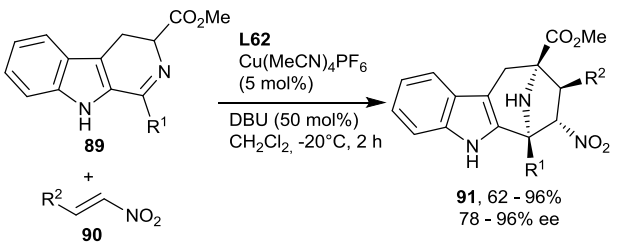
FesulPhos ligands **L62** were also effective in the Cu-catalysed 1,3-dipolar cycloadditions of azomethine ylides to *N*-phenylmaleinimide, dimethyl maleate, dimethyl fumarate, fumaronitrile, methyl acrylate, 2-butenolide, methacrolein and β-nitrostyrene.[165, 166] Catalytically active complexes were prepared *in situ* using $Cu(CH_3CN)_4ClO_4$. The reactions afforded cycloadducts in good yields and with high diastereomeric and enantiomeric purities (up to 99% ee).

Also α,β-unsaturated ketones, such as chalcone, cyclopentenone as well as acyclic enones, can be used as dipolarophiles under catalysis with Cu/Fesulphos complexes.[167] Chemical yields of the corresponding addition products were in the range of 45 to 79%, *endo/exo* ratios were up to 2:98 and enantiomeric purities for major *exo*-isomer were greater than 98% ee. The cycloadditions of azomethine ylides proceeded effectively also with *trans*-1,2-bisphenylsulfonyl ethylene (**87**) (Scheme 40).[168] The corresponding cycloadducts **88** were obtained in yields 65-93% and enantiomer purities 26-98% ee. The cycloaddition to dipolarophiles having different functional groups, such as methyl *cis*-3-phenylsulfonyl acrylate gave a mixture of two regioisomers in an 86:14 ratio.[169] The sulfonyl group mainly governed the regioselectivity and nearly exclusive formation of *exo* isomers with only minor enantioselectivity (20% ee) was observed.



Scheme 40

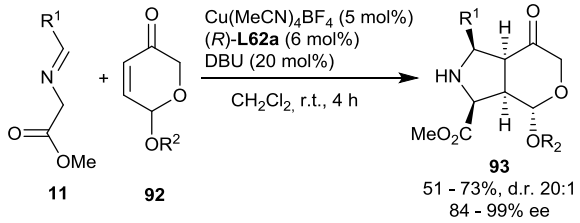
Waldmann, Antonchick and co-workers described highly enantioselective synthesis of tropane derivatives via [3+2] cycloaddition of 1,3-fused azomethine ylides, generated from imines **89**, with nitroalkenes **90**. Cu-Fesulphos complex was identified as the most effective chiral catalyst. A collection of densely substituted tropane compounds **91** was obtained in good yields and high enantiomer purities (Scheme 41).[170]



Scheme 41

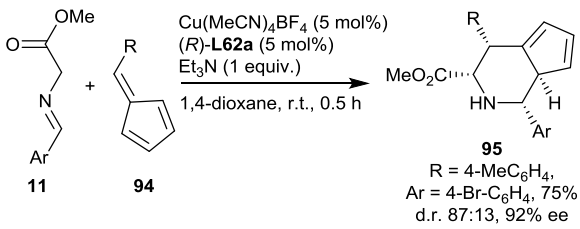
Fesulphos ligand was useful also in the Cu-catalysed 1,3-dipolar cycloaddition of glycine derived azomethine ylides **11** with oxodihydropyrans **92**. A range of cycloadducts **93** were isolated in good yields and excellent enantiomeric purities (up to 99% ee) (Scheme 42).[171] The Waldmann laboratory also showed that two-fold dipolar cycloaddition is possible if benzoquinone was used as the alkene component. Structurally

highly complex, chiral bis(pyrrolidine) compounds for biological tests were accessed via this reaction.[172]



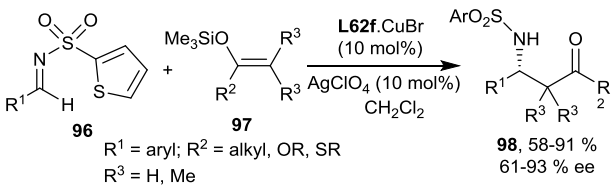
Scheme 42

Waldmann, Antonchick and co-workers also described a higher order cycloaddition, which was catalysed by the Cu/Fesulphos complex. An addition of azomethine ylides to fulvenes **94** gave excess to a collection of highly functionalized piperidines **95** (Scheme 43).[173]



Scheme 43

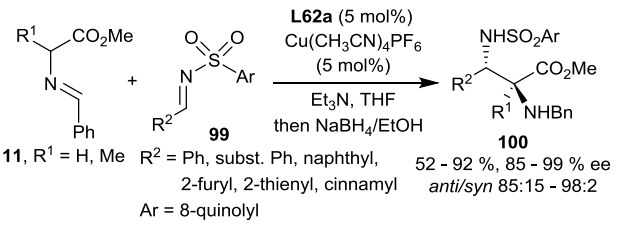
FesulPhos ligands **L62** proved to be effective also in Mannich type reactions. The additions of trialkyl silyl enol ethers **97** to *N*-sulfonyl imines **96** required 10 mol% of Cu/FesulPhos complex (Scheme 44).[174] The corresponding β-amino ketones **98** were obtained in good yields and enantiomeric excesses in the range of 61-93% ee.



Scheme 44

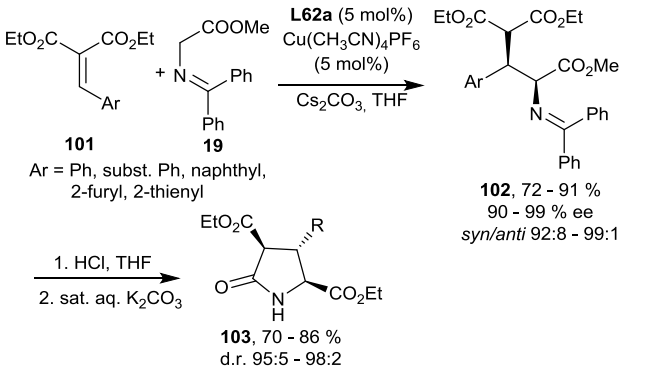
In an extension to this study, the Carretero laboratory showed that FesulPhos ligands were effective also in vinylogous Mannich reactions. Both acyclic silyl dienol ethers and 2-trimethylsilyloxyfuran were ample nucleophiles to imines.[175] The corresponding Mannich products were isolated in yields ranging from 62 to 91% and with enantiomer purities 77–95% ee.

In an attempt to further broaden the scope of Cu/FesulPhos catalysed Mannich reaction, Carretero´s group investigated also glycine imines **11** as pro-nucleophiles. The addition of these nucleophiles to imines **119** enabled access to important α,β-diaminoesters **120** (Scheme 45).[176, 177] α-Amido sulfones can also be used as precursors of aliphatic imines.



Scheme 45

Nucleophiles derived from glycine imines can add enantioselectively to *gem*-diactivated olefins (diethyl arylmetylene malonates). Copper(I) complex with FesulPhos ligand **L62a** was ample catalyst for this transformation.[178] The Michael additions afforded products **102** in 72–91% yields, with *syn/anti* ratio up to 99:1 and enantioselectivities 90–99% ee. The addition products that are β-branched α-aminoacids, can be easily converted into interesting chiral pyroglutamic acid derivatives **103** (Scheme 46). The work of Carretero´s research group was also covered in two perspective articles.[179, 180]



Scheme 46

The Carretero laboratory described the polymer supported FesulPhos ligands **L63** (Figure 18) and used them successfully in the 1,3-dipolar cycloadditions of azomethine ylides to *N*-phenyl maleimide (55–95% yield, >99% ee), allylation of dimethyl malonate with acetate **62** (82%, > 98% ee) as well as in the corresponding allylation of benzylamine (79%, 91% ee).[181] The catalyst can be recovered by simple filtration and had the same activity also in the third run, under strictly inert atmosphere.

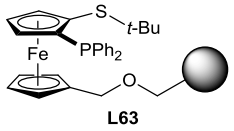


Figure 18

Manoury and co-workers prepared P,S ligands **L64** starting from chiral 2-diphenylphosphanoferrocencarbox-aldehyde (Figure 19).[182] These ligands were efficient in the allylic alkylation of dimethyl malonate (93–97% yield, 80–93% ee). An Ir-complex of the ligand **L64** worked also excellently in the

hydrogenation of alkyl aryl ketones.[183] The reduction of ketimines were less enantioselective.[184] Later, Manoury showed that ligand **L64** (R = Ph) can be covalently grafted on the dendrimer periphery and used in the allylic substitution.[185] The product was isolated in high yield, when reaction was carried out in dichloromethane (up to 93% ee). The ligand was easily recovered and used in the subsequent reaction. Unfortunately, it was necessary to prolong reaction time considerably, but still the yields as well as enantioselectivities decreased (88% yield, 81% ee).

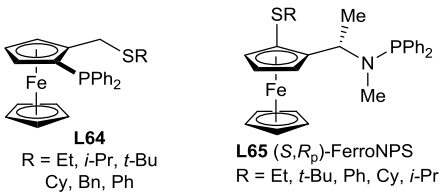


Figure 19

Chan and co-workers prepared new ferrocene N,P,S ligand **L65**, also termed as FerroNPS (Figure 19) starting from Ugi´s amine.[186] This ligand proved to be highly efficient in the allylic alkylation of dimethyl malonate. Enantioselectivity of the reaction increased upon addition of zinc acetate (97% yield, 92% ee, R = Et). FerroNPS ligands (**L65**) were effective also in an *O*-allylation of different aliphatic as well as substituted benzyl alcohols.[187] The reactions worked best when R on the ligand **L65** was cyclohexyl. Products of the reactions with different aliphatic alcohols were isolated in 58–98% yields with 83–96% ee. An exception was *tert*-butanol, which was unreactive under these conditions. Allylations of benzyl alcohols proceeded even better. Interestingly, authors observed LFER between enantioslectivity of the allylation and with Hammett´s substituent constants in alcohols.

Chan and co-workers synthesized ferrocenylmethyl heterocycles bearing alkyl- or arylsulfanyl group on the ferrocene moiety and phosphane group on the heterocycle. Ligands **L66-L68** (Figure 20) were used in the Pd-catalysed allylations of malonates.[188] All allylations afforded the corresponding products in high yields (up to 99%) and with excellent enantioselectivity (up to 96% ee). The most efficient catalysts comprised ligands **L66** (R = Et) and **L67**.

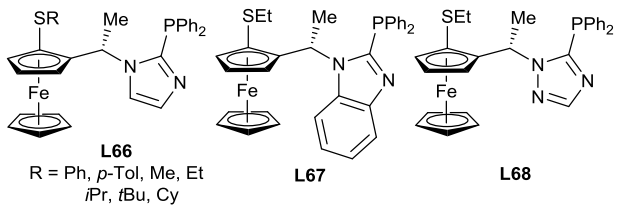


Figure 20

Hu *et al*. have prepared similar ligands **L69** and **L70** (Figure 21), just having phosphane group on ferrocene and sulfanyl groups on the heterocycle moiety.[189] These ligands were excellent in the Ag-catalysed 1,3-dipolar cycloadditions of azomethine ylides to dimethyl maleate. The corresponding cycloadducts were isolated in 26–95% yields, *endo/exo* ratio to 97:3 and enantiomeric purities of *endo*-isomer varied significantly 5–99%.

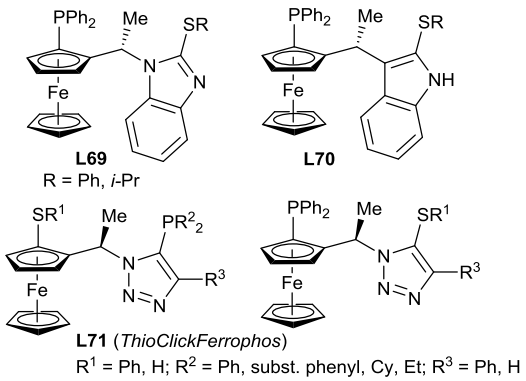
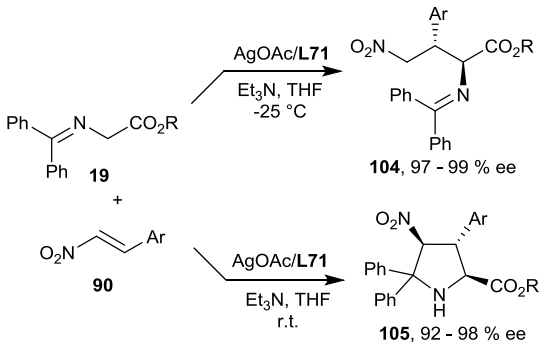


Figure 21

Fukuzawa and co-workers described synthesis of ThioClickFerrophos ligands **L71** (Figure 21) and used them in the Pd-catalysed allylic alkylations, etherifications, and aminations of 1,3-diphenylallyl acetate (**62**).[190] Reactions proceeded with high yields (95–99%), and with good enantioselectivities (70–90%). Ligands **L71** were also used in the allylic etherification of benzyl alcohol. Reactions proceeded with 15–95% yield and 45–82% ee. The Fukuzawa laboratory have used ligands **L71** in the Ag-catalysed 1,3-dipolar cycloadditions of azomethine ylides to (*E*)-benzalacetone.[191] The products were isolated in 61–85% yields having high *endo/exo* ratio of 68:32 to 90:10 and enantioselectivities up to 96%. Ligands **L71** were successfully applied also at Ag-catalysed dipolar cycloadditions of azomethine ylides to methyl acrylate. The reactions proceeded with 74–93% yield; *endo/exo* ratio was 98:2 and enantiomeric excess was up to 98%.[192] Similarly, Ag-catalysed [3+2] cycloaddition with aryl- and alkylidene malonates proceeded well.[193] The same ligands were used also in Mannich reactions, amination of glycine base and Michael addition of glycine imino ester **19** to β-nitrostyrenes **90** (Scheme 47).[194, 195] Enantioselective Michael addition to unsaturated malonates and enones worked also well.[196]



Scheme 47

There are also several chiral P,S-ligands, which feature 1,1´-disubstitution pattern. Alexakis and Benhaim described ligand **L72** (Figure 22) and used it the Cu-catalysed conjugate additions of dialkylzinc reagents to diethyl benzylidenemalonate.[197] Although, the reaction usually reached full conversion; the product was isolated with only 57% ee. Toru *et al*.[198] described ligand **L73** (Figure 22), which had just central chirality on sulphur. On the other hand, Kang et al. described ligand **L74** (Figure 21), which possess only planar chirality.[199] Toru have used ligand **L73** in the Pd-catalysed allylations of dimethyl malonate with 1,3-diphenylallyl acetate (**62**) as well as with cyclohex-2-yl acetate. These reactions afforded allylation product in good to excellent yields (45–99% yield) but with only mediocre enantioselectivity (32–68% ee). The reaction with cyclohex-2-yl acetate proceeded with 18% yield and only 40% ee. Kang have used ligand **L74** in the Pd-catalysed allylations of dimethyl malonate with 1,3-diphenylallyl acetate (**62**) and the product was isolated in high yield (up to 99%) but with a low enantioselectivity (38% ee). The same ligand was also used in the Pd-catalysed Heck reaction of 2,3-dihydrofuran with phenyltriflate, but yield of the product was low (34%) as well as enantioselectivity (34% ee).

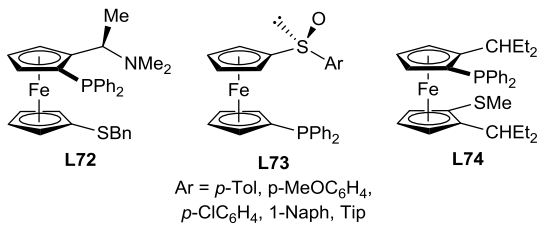


Figure 22

Ferrocenyl P,S-ligands feature sulphur mostly in the thioether unit. The most successful ligands here are undoubtedly members of the Fesulphos family **L62**. Behind the success of these ligands stands its ease of synthesis accompanied by possibilities for large structural variability obtained via modifications of substituent on the phosphorus and sulphur. Fesulphos ligands proved excellent in various Cu-catalysed Mannich reactions and cycloadditions. Other P,S-ligands such as ThioClickFerrophos (**L71**) were similarly efficient in the Cu and Ag-catalysed 1,3-dipolar cycloadditions. Combination of phosphorus and sulphur seems to be favourable also for Pd-catalysed reactions, such as allylic substitutions.

Ferrocene P,C bidentate ligands in asymmetric catalysis

Many achiral, as well as chiral ferrocene-based carbenes and their transition metal complexes, are already known.[16] Only a few of chiral ferrocene carbene complexes were successfully used in asymmetric catalysis. Chung and co-workers prepared and characterised ligands **L75a** and **L75b** (Figure 23).[200] The ligand **L75b** served in the Rh-catalysed hydrogenation of dimethyl itaconate. The reaction proceeded with full conversion; however the enatioselectivity was rather poor (13% ee).

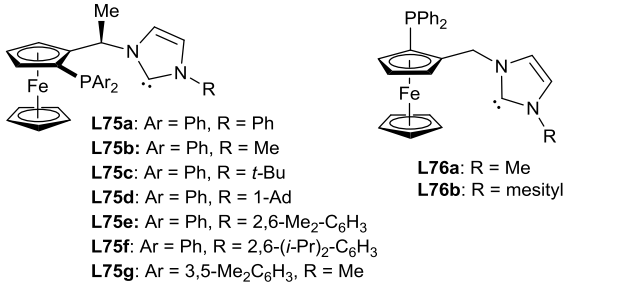
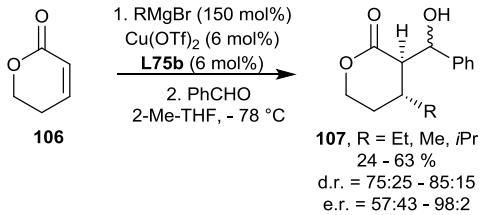


Figure 23

Ligands **L75c-f** (Figure 23) were efficient in the Pd-catalysed Suzuki-Myiaura cross-coupling. The reactions afforded coupling products in high yields up to 99% yield.[201] Poli and co-workers used ligands **L76** in an asymmetric version of this reaction. Here, 2-substituted-1-bromonaphthalenes were coupled with 1-naphthylboronic acid and the corresponding products were obtained in yields up to 95% but with only low enantiomeric purities 10-40% ee.[202]

Visentin and Togni have used ligands **L75b** and **L75c** (Figure 23) in kinetic studies of the Pd-catalysed allylation of benzylamine, but they did not give any information on the enantioselectivity of the reaction.[203] Copper-complexes with ferrocene carbene ligands **L75a**,**b** and **L75g** catalysed enantioselective 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds.[204] Although, virtually full conversions of the starting unsaturated derivatives were observed, products were isolated in lower yields (4–84%). In some cases, both products of 1,4- as well as 1,2-addition of Grignard reagents were isolated. Enantiomer purities varied greatly according to the substrate from 2 to 90% ee.

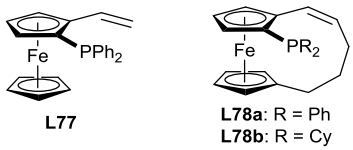
The ligand **L75b** participated also in a domino conjugate Grignard addition followed by reaction with imine or aldol reaction with benzaldehyde (Scheme 48).



Scheme 48

Alkenes are another group of carbon based donors, which can be a part of hetero-bidentate ligands. Štepnička and Cisařová have described the synthesis of 2-diphenylphosphino-1-vinyl ferrocene (**L77**) with planar chirality (Figure 24).[205] Its complexes with *ortho*-palladated benzylamine as well as with tetracarbonyl tungsten were fully characterised. The ligand **L77** was prepared from chiral 2-diphenyphosphino ferrocenecarboxaldehyde by a Wittig reaction. One year later,

Stemmler and Bolm prepared this ligand by a different way from Ugi´s amine. The ligand **L77** was evaluated it a Rh-catalysed addition of phenylboronic acid to cyclohexen-3-one.[206] The product was isolated in 96% yield with 53% ee.



L77 **L78a**: R = Ph **L78b**: R = Cy

Figure 24

Štěpnička´s group tested the ligand **L77** also in the Pd-catalysed allylation of dimethyl malonate.[207] Conversion of starting materials (58–100%) depended on the base, but enantioselectivity of the reaction was just medium (up to 44% ee). In our laboratory, we have prepared analogous [5]ferrocenophane ligands **L78** having C=C double bond in the bridge connecting two cyclopentadienyl rings (Figure 24).[208] Ligand **L78a** was more enantioselective than the analogous ligand **L77** in the addition of phenylboronic acid to cyclic α,β-unsaturated ketones and lactones compounds. The corresponding β-phenyl substituted products were isolated in good yields 56-81% and enantiomeric purities 62-92% ee.

Ferrocenyl phosphane ligands featuring carbon as the second donor atom are based on two types of compounds. Ferrocenyl phosphane-alkene ligands were utilized in Pd and Rh-catalysed reactions, but so far with either mediocre enantioselectivities or limited substrate scope. Similar situation is also in phosphane-carbene ligands, which are effective for some Cu-catalysed conjugate additions.

Conclusions

Ferrocene is a prominent framework for constructing chiral ligands for transition metal catalysed reactions. Hetero-bidentate ferrocenyl phosphane ligands are highly effective in a number of asymmetric transformations. Their catalytic activity is mainly governed by excellent coordination properties of phosphorus to late transition metals such as copper, palladium, rhodium, ruthenium or iridium. This feature is complemented by the second donor atom with different coordination properties. So far, practical utility found ligands with nitrogen, sulphur, oxygen and carbon as the second coordinating atom. Electronic differentiation influences the catalytic activity of the resulting metal complexes. Furthermore, different donor atoms embedded in the chiral backbone enhance asymmetry around the metal centre and thus improve transfer of the stereogenic information. In their catalytic profile, these ligands often complement ferrocenyl diphosphanes. Ferrocenyl P,N ligands are the largest group of hybrid ferrocenyl hetero-bidentate phosphane ligands. There are several notable examples such as PPFA-type amino phosphanes, oxazoline derivatives Phosferrox, and SiocPhos, which served well in Pd-catalysed allylic substitutions, Cu-catalysed cycloadditions and conjugate additions as well as some hydrogenations. Ferrocenyl P,O ligands were represented mainly by phosphane-ether ligands and phosphane-amide combination. However, catalytic utility of ferrocenyl P,O ligands seem still little explored. These derivatives were useful in Pd-catalysed cross-coupling reactions and allylic substitutions. On the other hand, P,S-ligands form the second largest group of ferrocenyl phosphane hetero-bidentate ligands. Particularly, FesulPhos family of ligands proved to be highly effective in a range of transformations. Ferrocenyl P,S-ligands participated in Cu-catalysed cycloadditions and Mannich reactions. Judging by their catalytic profile, P,N and P,S-ligands have similar properties. The last group of ferrocenyl hybrid ligands featuring carbons as donor atoms have also been only recently studied. Therefore, only a few applications of these ligands have been described until now. Conjugate additions, both Rh and Cu-catalysed, were primary applications of these ligands so far. By summarising and analysing such structurally diverse chiral catalysts, we believe that we help the scientific community in providing collection of recent information about these ligands. It is also worthwhile to note that ferrocenyl P,N and P,S ligands have been studied in depth and explored from various angles. On the other hand ferrocenyl P,O and P,C were studied in much lesser details. We, therefore, believe that this review will help stimulate further research in this area.

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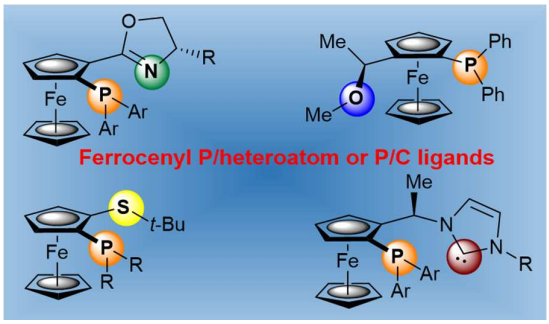
Table of contents entry

a) graphics



b) text

Review of chiral ferrocene ligands featuring combination of phosphorus and another element as donor atoms in the asymmetric catalysis.