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Review

Advanced Application of Planar Chiral Heterocyclic Ferrocenes

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Abstract: This manuscript is reviewing the superior catalytic activity and selectivity of ferrocene ligands in a wide range of reactions: reduction of ketones, hydrogenation of olefins, hydroboration, cycloaddition, enantioselective synthesis of biaryls, Tsuji–Trost allylation. Moreover, the correlation between a ligand structure and its catalytic activity is discussed in this review.

Keywords: ferrocene; asymmetric synthesis; heterocyclic ferrocene ligands

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1. Introduction

The ferrocene molecule, despite the "respectable age", attracts great interest from researchers [1–3]. An insatiable curiosity about ferrocene is driven by its sandwich structure and rigid framework, as well as by thermal and relative oxidative stability, and moisture tolerance. Another important feature is that ferrocene is prone to undergo reversible oxidation to ferrocenium ion through the transfer of electrons with subsequent formation of oxidation-reduction pair Fe(II)/Fe(III) [4–6].

Meanwhile, the steric effect of ferrocene offers an additional advantage for the synthesis of ligands possessing axial or spiro-central chirality and bearing different stereogenic elements [7]. One of the reasons why ferrocene derivatives are of particular concern, is that ferrocene has the potential to form compounds with planar chirality due to the incorporation of two or more versatile groups into one cyclopentadienyl ring (Cp) [8]. The resulting enantiomerically enriched products are commonly used as ligands for transformations, catalyzed by transition metals [9]. Over the past few years, a wide variety of ligands have been developed, occasionally possessing several elements of symmetry [10,11].

In the early 21st century oxazolinyl substituted ferrocenes were the most investigated class among ferrocene ligands [12]. Chiral oxazolines have shown a high capability of coordination of transition metals. Chiral mono- and bisoxazolines have been implemented in asymmetric reactions, catalyzed by transition metals [13,14]. Besides, oxazoline moieties were actively used as auxiliary groups in the diastereoselective synthesis of planar chiral ferrocenes [15]. Later on, not only five-membered indole and pyrrole, but also six-membered *N*-heterocycles and heterocyclic carbenes have been used for the creation of ferrocene asymmetric ligands.

Reactions, proceeding in the presence of ferrocene ligands, also have been developed. Until 2010 the catalytic activity of ferrocene ligands had mostly been studied in the Tsuji–Trost asymmetric allylation [13,14,16]. Over the past decade, the research interest has focused on the processes of reduction of ketones [17–19], hydrogenation of olefins, hydroboration, cycloaddition, amination [20], enantioselective synthesis of biaryls, and

especially on the utilization of enantiomeric pure ferrocenes in the kinetic resolution of racemates [21,22].

This review analyzes the influence of a ligand structure on its catalytic activity. A comprehensive revision on the application of planar chiral ferrocenes is also presented.

2. Application of Planar Chiral Heterocyclic Ferrocenes

2.1. Tsuji–Trost Reaction

Tsuji–Trost reaction is known to be an accepted model for the investigation of catalytic activity of planar chiral ferrocenes due to a wide scope of C-, N-, and O-nucleophiles employed in the transformations of allylic substrate. Additional incorporation of phosphine ligands has a beneficial effect on the reactivity of substrates and enantioselectivity of desired products.

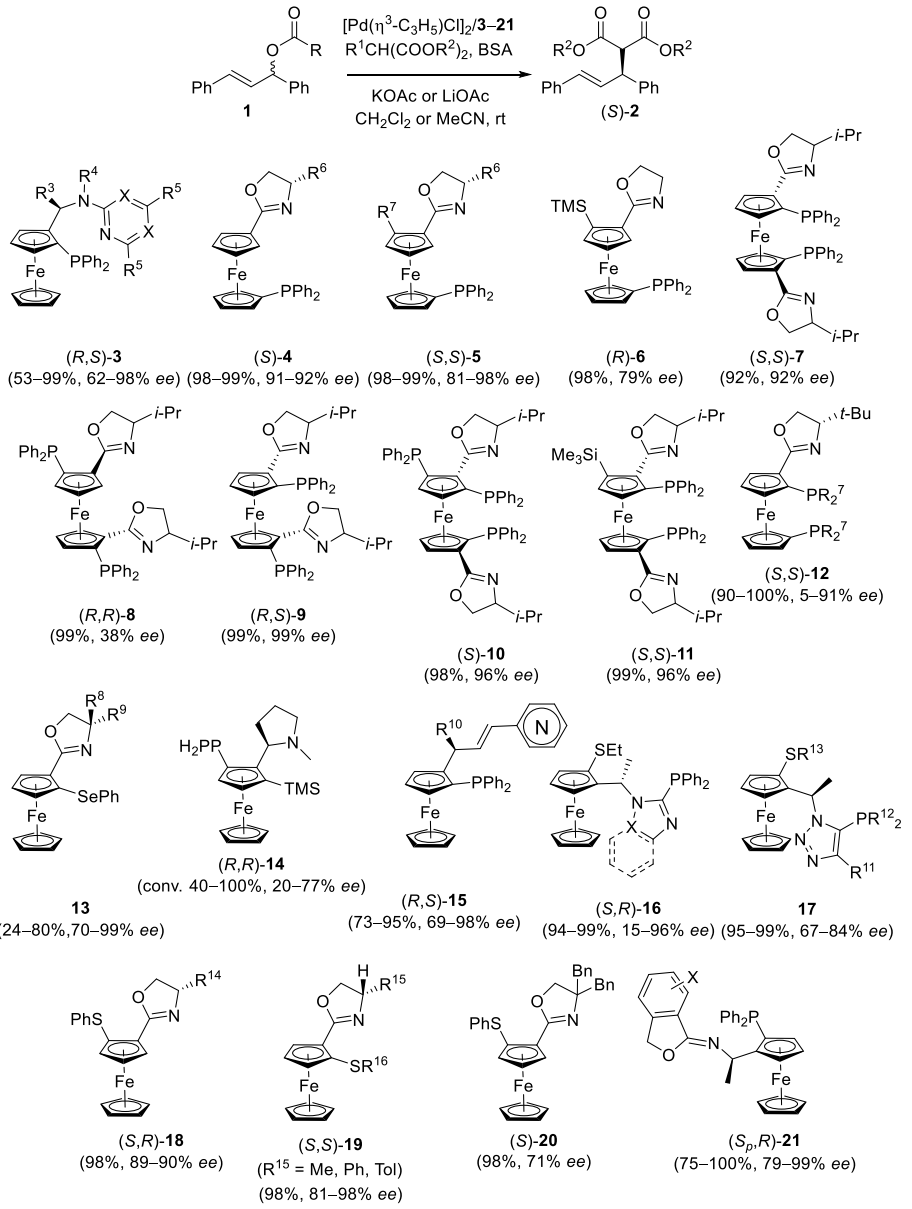
X.-P. Hu et al. investigated the effect of additional N-atoms in *P*,*N*-ligand structure on the yield and selectivity of allylic alkylation [23]. The catalytic activity of chiral ferrocene ligands **3** was demonstrated on Pd-catalyzed asymmetric allylic alkylation of esters **1** with malonates (Scheme 1). It was shown that enantioselectivity and reactivity enhanced with an increase of the number of N-atoms in *P*,*N*-ligands, and azine-containing moieties were the most effective. So the allylic alkylation reactions between (*R*,*S*)-**3** and 4,6-diphenoxy-1,3,5-triazine moiety provide 99% yields and enantioselectivity up to 99% *ee*. Incorporation of the diphenylphosphine fragment into another ring (**4**–**6**) leads to a slight decrease in enantiomeric excess to 92%. W.-P. Deng et al. determined that planar chirality in compounds **4**–**6** influenced the absolute configuration and enantiomeric enriching of the products **2** (Scheme 1) [24,25].

The Pd-catalyzed asymmetric allylic alkylation of esters **1** with malonates using phosphorylated **7**–**10** and silylated **11** ligands run with the selectivity up to 99% and led to the formation of (*S*)-**2** (Scheme 1) [26]. Planar chiral diphosphineoxazolinyl ferrocene ligands (*S*,*S*)-**12** have been successfully applied in Pd-catalyzed asymmetric allylic alkylation of esters **1** with malonates (Scheme 1) [27]. Ligands (*S*,*S*)-**12** bearing electron withdrawing or electron donor groups, demonstrated high reactivity. The product (*S*)-**2** was gained in quantitative yield. Electron withdrawing groups in the structure of ligands resulted in the increase of selectivity in the reaction of allylic alkylation up to 91%, meanwhile electron donating groups provided a decrease in enantiomeric enrichment up to 5%. Selenium containing oxazolinyl ferrocene ligands **13** underwent Pd-catalyzed asymmetric allylic alkylation of esters **1** with the formation of the product (*S*)-**2** in high yield and with enantiomeric enrichment up to 99% (Scheme 1) [28]. 1,2,3-Substituted ferrocene ligands **14** afforded a good conversion (40–100%) in these transformations, but a moderate enantioselectivity (20–77% *ee*) [29].

X. Hu et al. investigated a new class of phosphine-imine ligands on the base of ferrocene **15**, bearing a pyridine fragment (Scheme 1) [30]. The authors showed that the position of the N-atom in the pyridine fragment had a strong influence on both the catalytic activity of the Pd-complex and the selectivity of the process. Pd-complex of a 3-substituted pyridine ligand turned out to be the most efficient catalyst among phosphine-imine ligands and gave the product (*S*)-**2** with 99% selectivity. Ligand with 4-pyridine *N*-atom was less effective, and enantiomeric enrichment of the product reached 95%. Phosphine-imine ligand with 2-pyridine *N*-atom did not catalyze allylic alkylation.

Replacement of phosphine fragment with thioester does not cause a decrease in selectivity. The reaction of allylic alkylation in the presence of chiral *P*,*S*-ferrocene ligands **16** provides products **2** with *ee* up to 99% and 96% yield. The authors established that an increase of the substituent bulk at the S-atom gives rise to a decline in enantioselectivity (Scheme 1) [31]. H. Y. Cheung et al. alongside the authors from Japan investigated the catalytic activity of *P*,*S*-Thio ClickFerrophos **17** in Pd-catalyzed asymmetric allylic alkylation of esters **1** with malonates (Scheme 1) [32]. They also conclude that an increase of the substituent bulk at the S-atom decreases the selectivity, whereas the presence of more bulk

substituent at the P-atom and in the 5-position of the triazole cycle leads to an increase in the selectivity. S.-L. You et al. describe *S*,*N*-ferrocenyloxazoline ligands, as possessing only planar chirality, and giving lower enantioselectivity in allylic alkylation. Nevertheless, the products of allylic substitutions **2** in the presence of thioester ferrocenyloxazolines **18–20** were obtained with selectivity up to 98% and yields up to 98% [33].

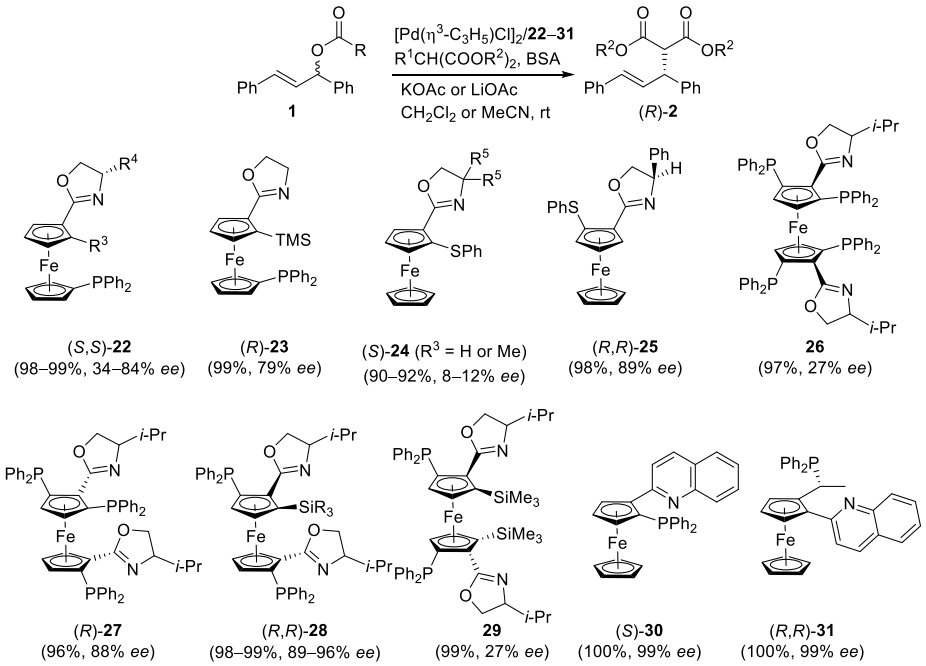


Scheme 1. Pd-catalyzed asymmetric allylic alkylation.

Embedding of O-containing heterocycles into a ferrocene fragment gives the opportunity to gain planar chiral optimal catalysts for asymmetric allylic alkylation. J. Van der Eycken et al. achieved enantiomerically pure product in (*S*)-configuration and with quantitative yield in conditions of Tsuji–Trost reaction using a synthesized chiral imidate-phosphanes (*Sp*,*R*)-**21**. However, embedding of a methyl group into the structure of nucleophile at CH-active atom, or using a cyclic substrate result in the (*R*)-product only (Scheme 1) [34].

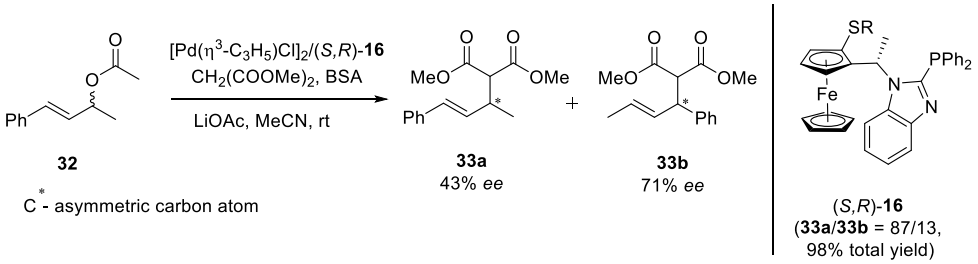
W.-P. Deng et al. compared the correlation between ligands' **4–6** (Scheme 1) and **22**, **23** (Scheme 2) planar chirality and absolute configuration and enantiomeric excess of the products of alkylation **2** [24]. In the presence of ligands **22**, **23** the product of alkylation **2**

was formed as (*R*)-isomer in the yields up to 99% and selectivity up to 84%. *S,N*-Ligands **24**, **25** afforded the products of allylic substitutions **2** in high yields up to 98% and selectivity up to 89% (Scheme 2). Meanwhile, *S,N*-ligands possessing only planar chirality turned out to be less effective than ligands **22** and **23**. Complexes for the asymmetric allylic alkylation reactions were synthesized from bis(η-allylpalladium chloride) and **26**, **27** in a 1:2 molar ratio. The product (*R*)-**2** was formed in the yield up to 99% and selectivity from 27% to 96% *ee* in all the cases (Scheme 2) [26]. Tetraphosphorylated ligands **26** and disilylated ligands **29** gave the products (*R*)-**2** with low selectivity. The results for the ligands **7**–**11** (Scheme 1) and **26**–**29** (Scheme 2) confirm that sterically bulky groups in the positions 3 and 3′ of cyclopentadienyl rings impact the selectivity of alkylation. Thus, sterically bulky substituents in position 3 elevate the reactivity of a ligand and lead to the (*R*)-product only. The Tsuji–Trost reaction has been shown to give a stereoselectively formed target product with quantitative yield in the presence of planar chiral ligands (S_p)-[2-(2-quinolin-2-yl)-ferrocen-1-yl]-diphenylphosphine **30** or (R_p)-1-(quinolin-2-yl)-2-(α-(*R*)-diphenylphosphinoethyl)ferrocene ligand **31** possessing planar and central chirality [35].



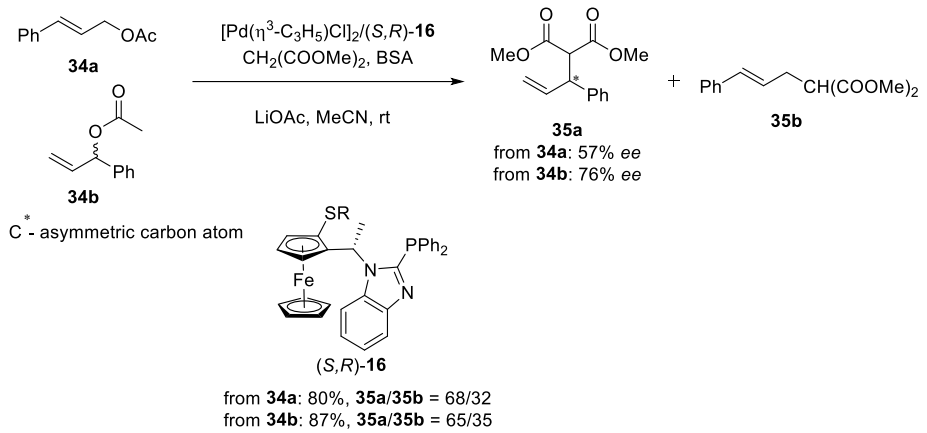
Scheme 2. Pd-catalyzed asymmetric allylic alkylation.

H. Y. Cheung et al. studied the regio- and enantioselectivity of the allylic substitution of unsymmetrical substrates **32** (Scheme 3) [31]. Alkylation of substrate **32** in the presence of [Pd]/**16** complex run with the high regioselectivity giving rise to a formation of two isomers **33a** and **33b** in an 87:13 ratio in 98% yield. Enantiomeric excesses turned out to be lower than 43% *ee* and 71% *ee* for **33a** and **33b**, respectively.



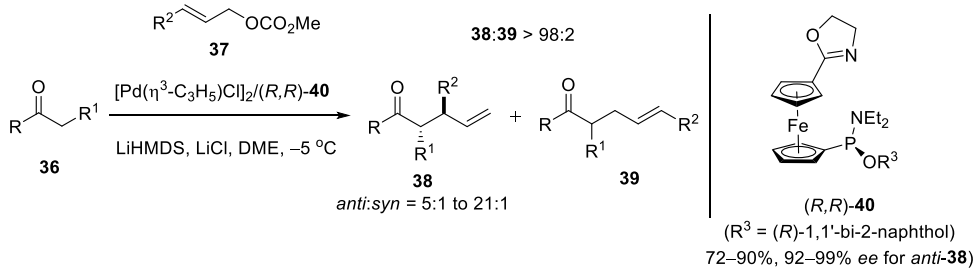
Scheme 3. Pd-catalyzed asymmetric allylic alkylation of unsymmetrical substrates.

Cinnamyl acetate substrate **34a** in the allylic alkylation reaction led to a mixture of the products **35a** and **35b** in a 68:32 ratio and an 80% yield (Scheme 4) [31]. The mixture of the same products **35a** and **35b** in a 65:35 ratio in 87% yield was gained in the presence of isomer **34b**, enantioselectivity of the main product **35a** increased from 57% to 76%.



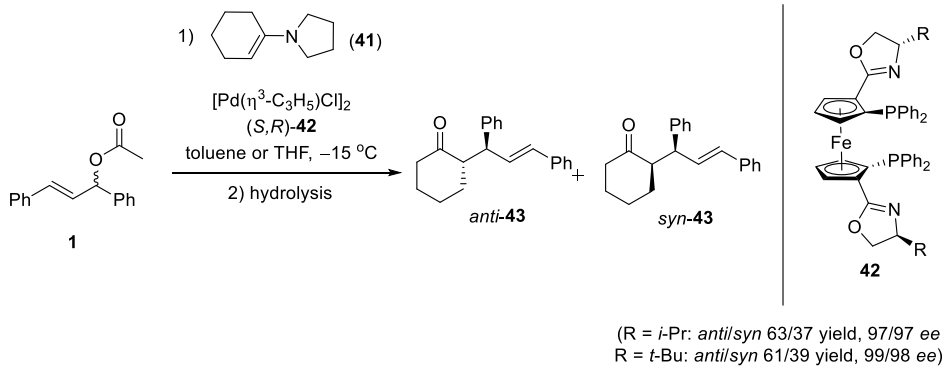
Scheme 4. Pd-catalyzed asymmetric allylic alkylation of unsymmetrical substrates.

W.-H. Zheng et al. established Pd-catalyzed asymmetric allylic alkylation of acyclic ketones **36** with monosubstituted allyl carbonates **37** (Scheme 5) [36]. Using of 1,1′-disubstituted ferrocenyloxazoline ligand **40** led the authors to the opportunity to obtain the products **38** with high regio-, diastereo- and enantioselectivity, whereas the *syn*-product was formed in traces amounts.



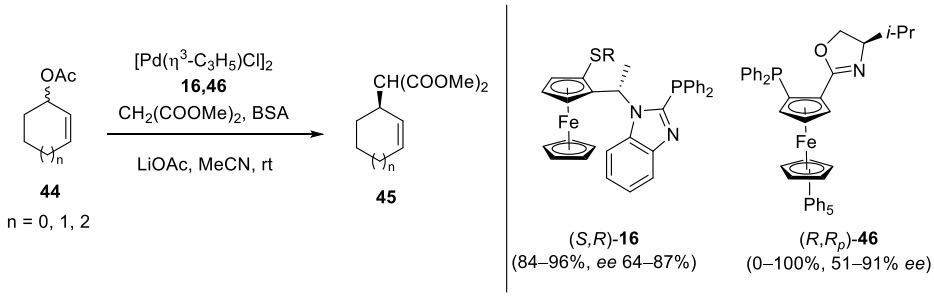
Scheme 5. Pd-catalyzed asymmetric allylic alkylation of acyclic ketones.

D. Liu et al. chose oxazolinylferrocene **42** as a ligand in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **1** with the enamine **41** and as the result, they obtained the increased amount of the product *syn*-**43** (Scheme 6) [37]. Nevertheless, the authors observed the high yields and enantioselectivity in the reactions with enamine **41** for both *anti*-**43** and *syn*-**43** configurations.



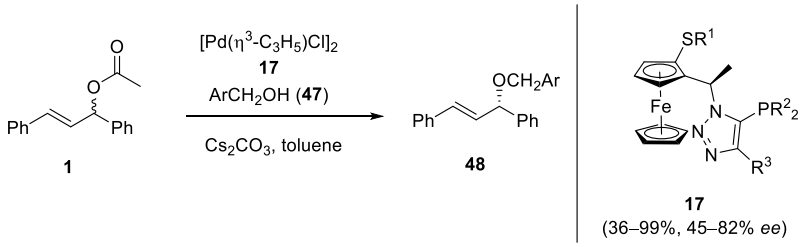
Scheme 6. Pd-catalyzed asymmetric allylic alkylation of esters **1** with enamine **41**.

The catalytic activity of planar chiral derivatives of ferrocene **16** and **42** was investigated in Pd-catalyzed asymmetric allylic alkylation of cycloalkenyl acetate substrates by dimethyl malonate. The ligand **16**, bearing benzimidazole fragment, exhibited high reactivity and selectivity in the enantioselective allylic alkylation reaction of non-sterically demanding cyclic substrates **40** (Scheme 7) [31]. The authors note, that oxazolinyl ferrocene **42** demonstrated relatively high effectivity in this transformation [38]. Cyclohexenyl acetate with a tetrasubstituted C atom at position 5 was significantly less reactive in comparison with the unsubstituted one. An increased steric bulk of the substrate reduces the enantioselectivity. An appropriate cycloheptenyl substrate demonstrated lower reactivity, and the desired yield and enantioselectivity were achieved after 12 h of the reaction. Enantioselectivity has been shown to be the highest in the presence of an electron-rich phosphine ligand due to the stability of the complexes of phosphines (Scheme 7).



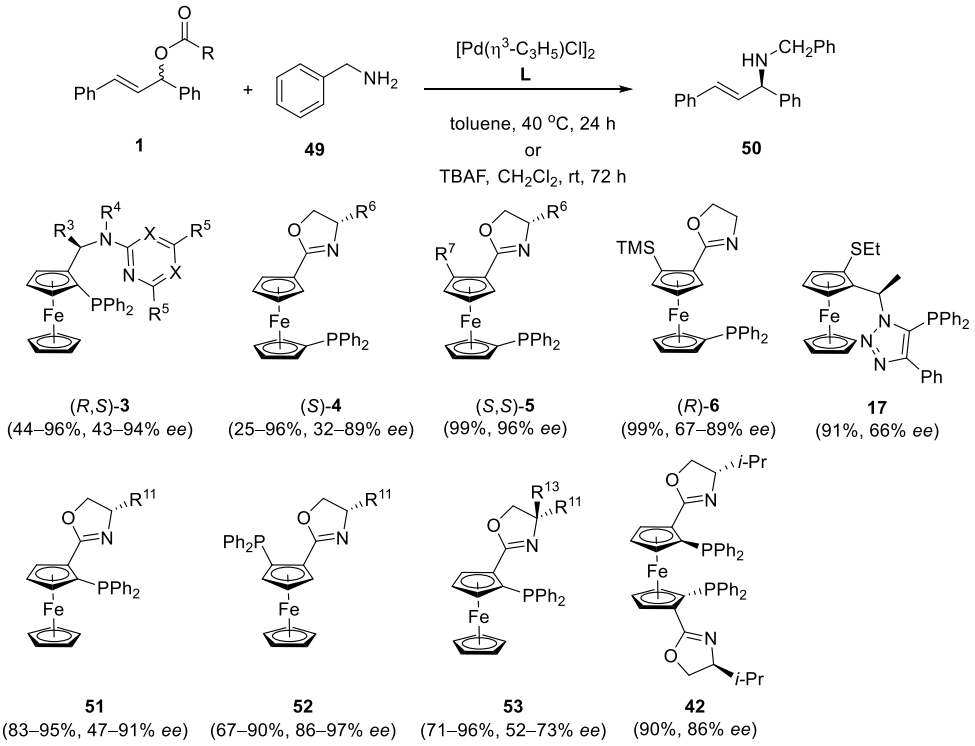
Scheme 7. Pd-catalyzed asymmetric allylic alkylation of cyclic substrates.

Pd-complexes of planar chiral thioesters **17** (ThioClickFerrophos) have effectively behaved as catalysts in the reaction of asymmetric allylic etherification between benzyl alcohol **47** and esters **1** (Scheme 8) [32]. The products of etherification **48** were obtained in high yields and with enantiomeric enrichment up to 82%.



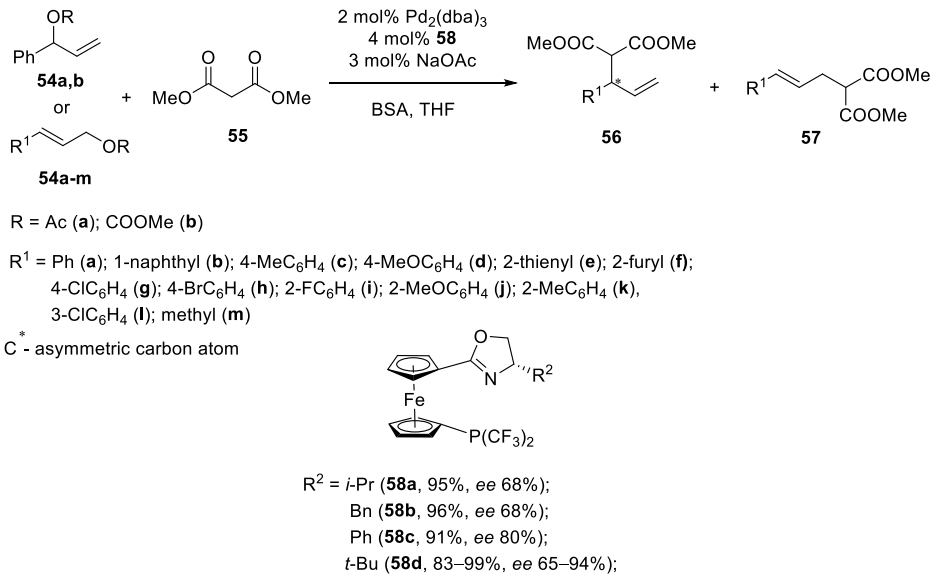
Scheme 8. Pd-catalyzed asymmetric allylic etherification.

The catalytic activity of ligands **3** was investigated in the Pd-catalyzed asymmetric allylic amination of 1,3-diphenylprop-2-en-1-yl pivalate **1** with benzylamine **49** (Scheme 9) [23]. In the reaction of allylic amination, these ligands exhibited lower reactivity and selectivity than in the reactions of allylic alkylation. Moreover, the purity of the initial benzylamine **49** affected the selectivity and yields of the product **50**. Pd-complex of **17** in the reaction of allylic amination of esters **1** with benzylamine led to the product **50** in yield 91% and 66% *ee* (Scheme 9) [32]. Ferrocenyl oxazolines **4–6** had a positive impact on the process and increased the yields and selectivity of the reaction of amination up to 99% and 96% *ee* respectively (Scheme 9) [25]. Ferrocenyl oxazoline *P*,*N*-ligands **51–53** in the Pd-catalyzed asymmetric allylic amination of 1,3-diphenylprop-2-en-1-yl pivalate **1** with benzylamine give the product **50** in yields up to 95% and selectivity 97% (Scheme 9) [33,39]. In contrast with ferrocenyl oxazolines **4–6**, the ligands **51–53** and **42** have been essential in controlling the enantioselectivity and absolute configurations of the product **50**.



Scheme 9. Pd-catalyzed asymmetric allylic amination.

Shu-Li You and co-workers studied the catalytic activity of 1-[bis(trifluoromethyl)phosphine-1′-oxazolinyl ferrocene ligands **58** in the reactions of allylic alkylation of carbonates **54a–m** by dimethyl malonate **55** catalyzed by Pd (Scheme 10) [40]. In this work, the ligands show high efficiency and give (*S*)-isomer with good yield and selectivity. The highest stereoselectivity (88% *ee*) demonstrated a catalyst derived from the ligand **58d** bearing a branched *t*-Bu fragment. The authors establish that the nature of a substrate (electron donating or electron withdrawing groups of the aromatic ring of the aryl allyl carbonates) has virtually no effect on the yield and selectivity of the reaction. In addition, a replacement of PPh_2 on $P(CF_3)_2$ in the second ferrocene ring leads to an increase in selectivity.

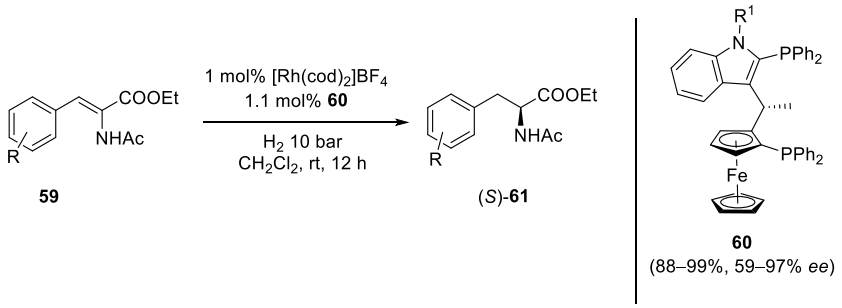


Scheme 10. Pd-catalyzed asymmetric allylic alkylation of carbonates.

Thus, in the reactions of allylic substitution, the ferrocenes bearing oxazoline fragments are the most often used. The enantioselectivity of the Tsuji–Trost reaction decreases after the replacement of the O-atom with carbon [29] or nitrogen [31,32] in the oxazoline moiety of ferrocenyl ligand. The incorporation of thioester fragment into the cyclopentadienyl ring of ferrocene slightly decreases the selectivity of the reaction. A more bulky substituent at S-atom negatively affects enantiomeric enrichment of the products of allylic alkylation [31,32]. Six-membered N-heterocycles positively influence both the reactivity and enantioselectivity [23,30].

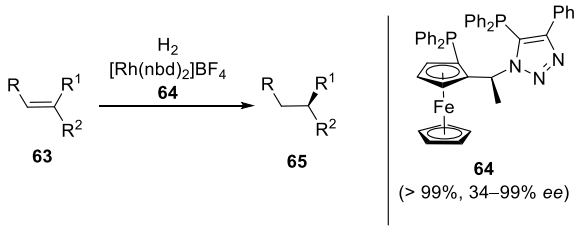
2.2. Asymmetric Hydrogenation

Catalytic hydrogenation of multiple bonds has enormous practical value for oil refining, petrochemistry, and in the hydrogenation of vegetable oils. Industrial hydrogenation is known to be based on heterogeneous catalysts, but another way of hydrogenation of olefins builds upon chiral ferrocene/indole-based diphosphine ligands, resulting in high yields and enantioselectivity. As reported by Z. Abbas et al., ferrocenyl indoles **60** exhibited a superior catalytic activity in reactions of asymmetric hydrogenation of *α*-enamides **59** (Scheme 11) [41]. The product (*S*)-**61** is formed with high enantioselectivity (up to 97% *ee*), the yield is not lower than 88%. Furthermore, ferrocene bearing *N*-unsubstituted indole showed the highest catalytic activity in these transformations.



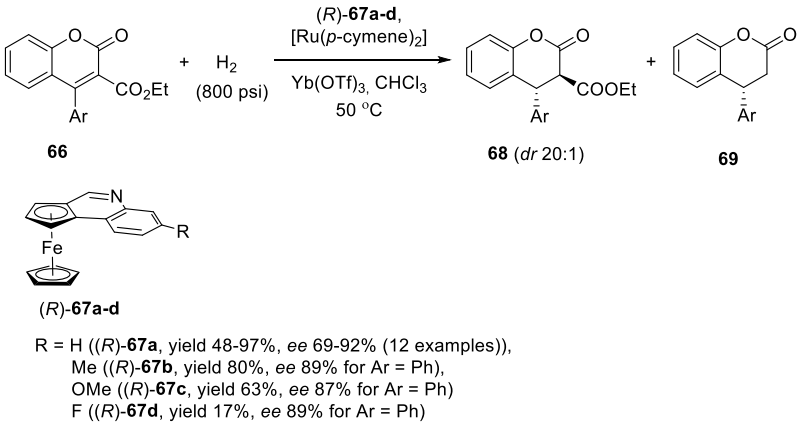
Scheme 11. Rh-catalyzed asymmetric hydrogenation of functionalized olefins.

ClickFerrophos **64** also demonstrated a high catalytic activity in asymmetric hydrogenation of alkenes **62** (Scheme 12) [42].



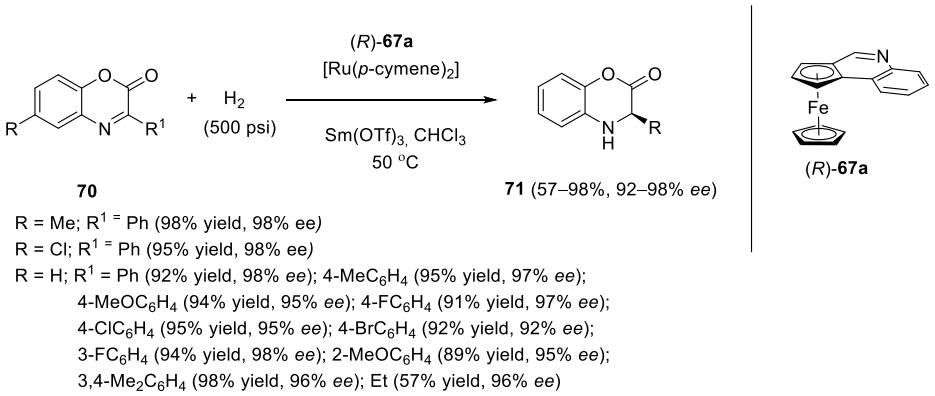
Scheme 12. Rh-catalyzed asymmetric hydrogenation of alkenes.

Rational design of chiral and regenerative analogues NAD(P)H based on planar chiral ferrocenes led to a realization of biomimetic asymmetric reduction of a double bond using stable Lewis acids as proton transfer catalysts. Thus, a wide variety of alkenes (Scheme 13) and imines (Scheme 14) have been reduced with up to 98% yield and 98% *ee* in the presence of analogues NAD(P)H (*R*)-**67** [43]. In search of the optimal catalyst the authors chose an asymmetric reduction of tetra substituted alkene **66** bearing phenyl substituent as the model reaction. Unsubstituted ferrocene (*R*)-**67a** in the presence of $Yb(OTf)_3$ as Lewis acid afforded the highest yield (97%) and stereoselectivity (90% *ee*) (Scheme 13). It was established that more bulky (Me, OMe) or electron withdrawing (F) substituents in the structure of a ligand resulted in a decrease of the yield and selectivity of the reaction.



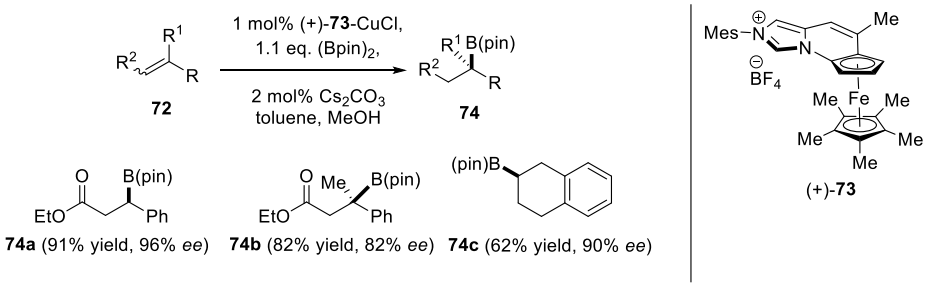
Scheme 13. Biomimetic asymmetric reduction of C=C bond.

Catalytic activity of the most effective ligand (*R*)-**67a** was also investigated in biomimetic asymmetric reduction of C=N bonds (Scheme 14). The reaction runs with high yields (89–98%) and enantioselectivity (92–98%) regardless of the nature of the substituent at the position 7 of the substrate **70**.



Scheme 14. Biomimetic asymmetric reduction of C=N bond.

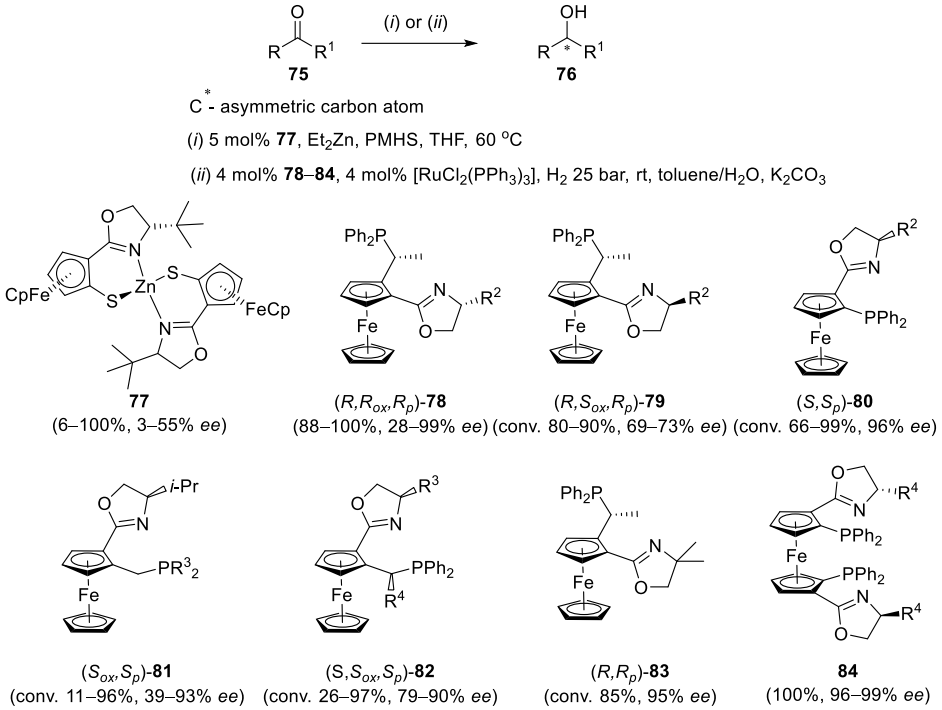
Borylation is one of the reactions for reduction of a C=C bond. Karl A. Scheidt et al. studied Cu-catalyzed borylation of olefins **72** in the presence of carbene **73**. The authors found that enantiomerically pure complex (+)-**73**-CuCl catalyzed the borylation of substrates and provided the products **74** with good yields and stereoselectivity without any optimizations of the reaction conditions (Scheme 15) [44,45].



Scheme 15. Asymmetric borylation of olefins.

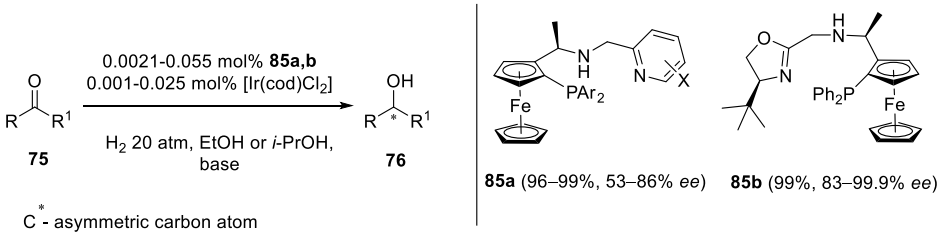
Asymmetric reduction of ketones via hydroboration and catalytic hydration remains a conventional approach to chiral alcohols, which represent an important structural element of natural and pharmaceutical products. Even so, S. Gérard et al. decided to apply

ferrocene catalyst **77** *N,S*-chelating with Et_2Zn in reactions of the enantioselective reduction of ketones in the presence of polymethylhydrosiloxane (PMHS) (Scheme 16) [46]. The products **76** were obtained with low selectivity. Utilizing of rhodium catalyst, based on *P,N*-chiral oxazolinyl ferrocenes **78–83** causes increasing of enantioselectivity of the reaction of reduction of ketones up to 99% *ee* [47,48]. Derivatives with (R_p)-configuration of the ferrocene fragment provide in the reaction secondary (*S*)-alcohols **76**, while (S_p)-ferrocenes give (*R*)-alcohols (Scheme 16). In addition, disubstituted C2-symmetrical ferrocenyl planar phosphinooxazoline ligands **84** revealed high efficiency in the Ru(II)-catalyzed asymmetric reduction of ketones. This type of ligands possesses two reactive centers. Optimization of the reaction conditions resulted in quantitative yield and enantioselectivity up to 99.7% *ee* [49].



Scheme 16. Enantioselective reduction of ketones.

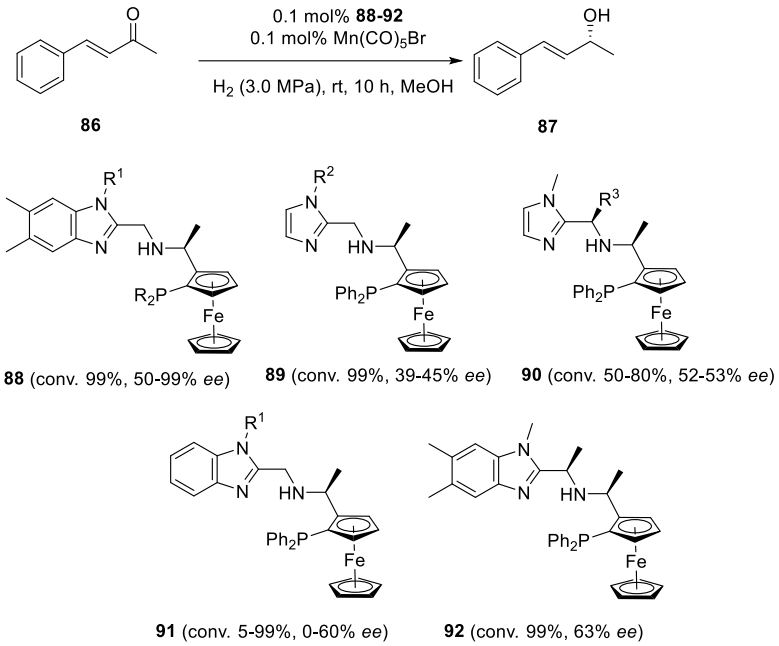
Substitution of oxazoline fragment by pyridine in the molecule of the ligand, as well as replacing Ru for Ir, result in good yields in asymmetric reduction of ketones, but enantioselectivity is dropped (Scheme 17) [50]. However, application of the ligand **85b** in asymmetric hydrogenation of ketones resulted in the secondary alcohols **76** with high enantiomeric excess and quantitative yields [51]. The replacement of pyridine (**85a**) with oxazoline (**85b**) moiety in ferrocene structure afforded the lowest catalyst loading.



Scheme 17. Asymmetric hydrogenation of ketones.

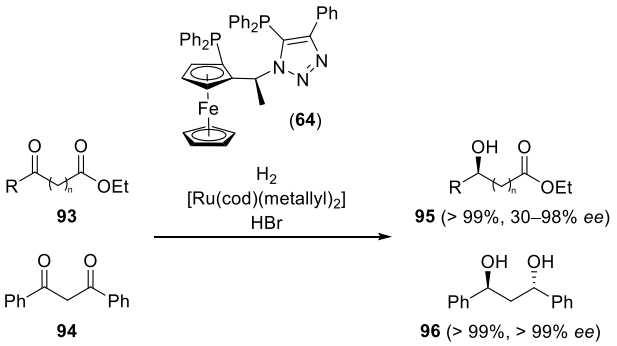
Asymmetric 1,2-reduction of α,β-unsaturated ketones using the reactions of hydroboration or catalytic hydrogenation constitutes conventional approaches to chiral allylic alcohols. At the same time, these transformations are accompanied by the rival processes

of 1,2- and 1,4-reduction. As reported in [52] a method of enantioselective Mn-catalyzed 1,2-reduction of *α,β*-unsaturated ketones **86** was developed. The authors disclosed that utilization of Mn-complexes of tridentate *P,N,N*-ligands **88–92**, bearing imidazole groups, led to a selective reduction of keto-group and formation of allylic alcohols **87** with high yields (96–99%) and good enantioselectivity (66–86% *ee*) (Scheme 18). This reaction demands mild conditions and gives rise to the key intermediates of cannabidiol.



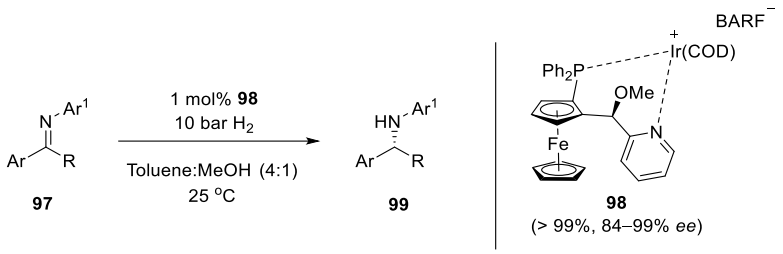
Scheme 18. Asymmetric hydrogenation of *α,β*-unsaturated ketones.

ClickFerrophos **64** demonstrated superior catalytic activity not only in the hydrogenation of olefins, but also in the ruthenium catalyzed asymmetric hydrogenation of ketoesters **93** and 1,3-diketones **94** (Scheme 19) [42]. Hydrogenation proceeded with the use of 0.5 mol% [Ru(cod(metallyl)$_2$]/HBr and ligand **64**, the products **95** and **96** were accessed with quantitative yields and high enantioselectivity (≥99% *ee*).



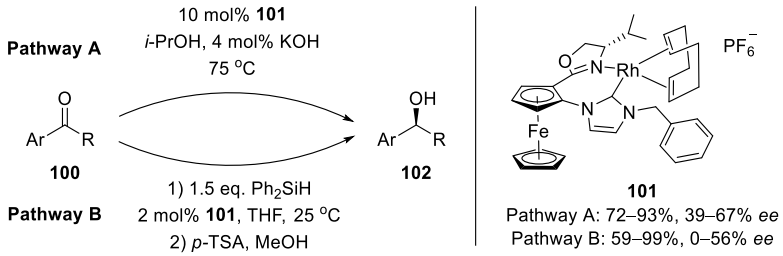
Scheme 19. Asymmetric hydrogenation of ketones.

Ferrocenyl *P,N*-ligands have been successfully applied for the hydrogenation of a C=N bond. For example, it was described that Ir-complex **98** acted as essential catalyst in the reaction of asymmetric hydrogenation of acyclic *N*-arylimines **97** producing chiral phenyl alkylamines **99** in quantitative yield (Scheme 20) [53]. Enantiomeric excess was not lower than 84% *ee*.



Scheme 20. Asymmetric hydrogenation of acyclic *N*-arylimines.

Chiral *N*-heterocyclic carbenes (NHCs) have been recognised as the prominent alternatives to chiral phosphine ligands due to their strong σ-donating and weak π-accepting properties. For example, carbene-Rh(I) complex **101** was applied to the asymmetric transfer hydrogenation of prochiral ketones (Scheme 21, Pathway A) [54]. The carbene-Rh(I) complex **101** catalyzed the hydrogenation reaction of aryl alkyl ketones **100**. All ketones **100** are readily transformed into the corresponding secondary alcohols in the presence of 10 mol% catalyst and 4 mol% KOH in 2-propanol at 75 °C. The yield and enantioselectivity were affected by the steric and electronic properties of the ketones. Secondary alcohols **102** were attained as the result of asymmetric hydrosilylation of ketones **100** in the presence of carbine-Rh(I) complex **101** (Scheme 21, Pathway B) [55,56]. The yields and selectivity of the products **102** were lower than those in asymmetric transfer hydrogenation of ketones (Scheme 21, Pathway A). The yield and enantioselectivity of the reaction were also affected by the steric and electronic properties of ketones.



Scheme 21. The asymmetric transfer hydrogenation of prochiral ketones.

Ferrocenes featuring five-membered as well as six-membered heterocycles appeared to be effective in the reactions of asymmetric hydrogenation. Furthermore, in this type of reactions ligands bearing imidazole- and triazole provide a selective reduction of the keto-group. Ferrocenes featuring five- or six-membered heterocycles appeared to be effective in the reactions of asymmetric hydrogenation of a C=C bond both in aliphatic and cyclic substrates. Oxazolinyl ferrocenes bearing phosphine fragment encourage hydrogenation of carbonyl group in ketones to proceed enantioselectively. 1,1′-Bisoxazolinyl ferrocene enables the highest yield in these transformations.

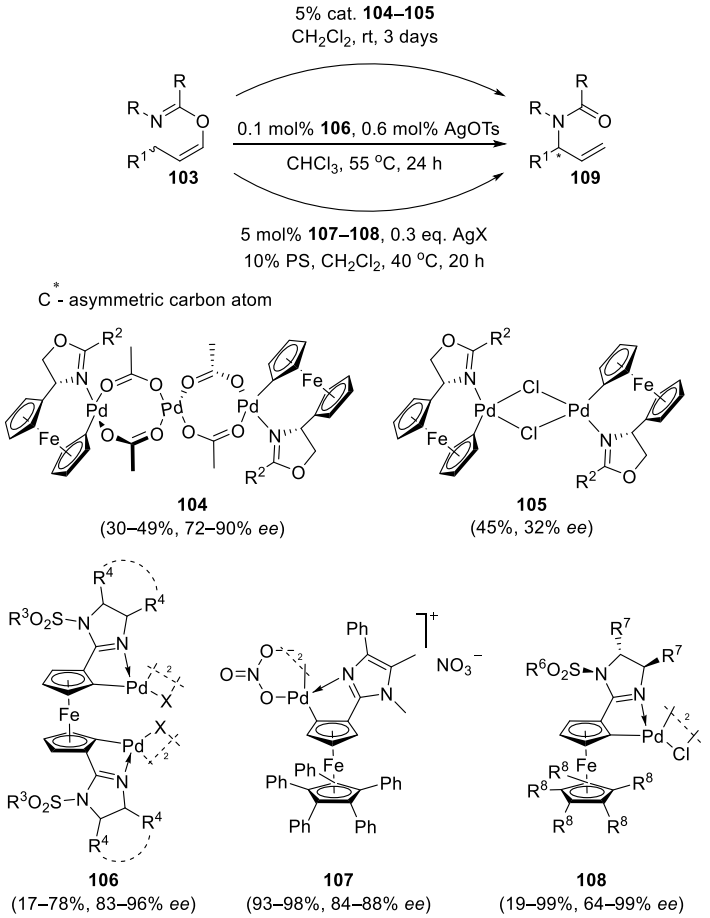
The replacement of the PPh_2-group with a thioester [46] or imidazole [54–56] in oxazolinylferrocenes, as well as the oxazoline moiety [47–49] with a pyridyl group [50] leads to a decrease of selectivity of the hydrogenation of ketones from 99% *ee* to 55–67% *ee*. However, pyridyl containing ligand readily hydrogenates a C=N bond [53]. It is worth noting, that ferrocenyl derivatives of imidazole enable regio- and enantioselective reduction of keto-group in *α*,*β*-unsaturated ketones, and benzimidazolyl ferrocene bearing electron donating groups proved to be the most effective [52]. Triazole cycle in diphenylphosphine ferrocene provides enantioselective reduction (up to 99% *ee*) of one or two keto-groups in high yields [42].

2.3. The Rearrangement

Research of molecular rearrangements affords a deep understanding of mechanisms of chemical reactions and implementing of direct organic synthesis. A wide number of rearrangements are applied in industrial processes such as isomerization of oil hydrocarbons for the producing of high octane motor fuel, conversion of cyclohexanone oxime to caprolactam, synthesis of organic semi-products and dyes.

A. Moyano et al. successfully applied tri- and bi-nuclear palladocycles **104** and **105** in the *aza*-Claisen reaction enabling various allylic amides **109** from the corresponding allylic alcohols **103** (Scheme 22) [57].

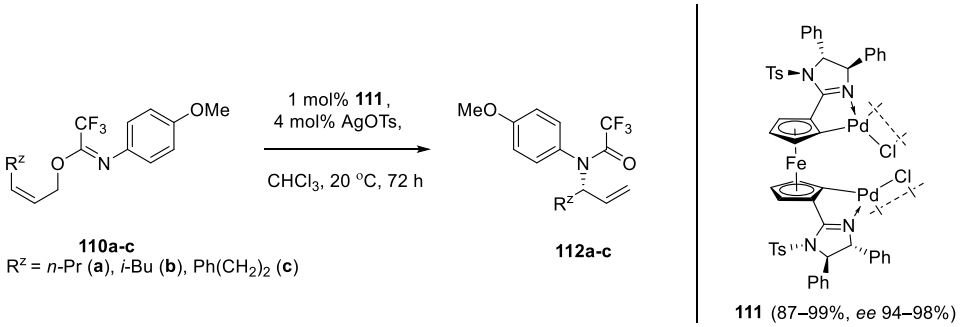
The use of trinuclear complexes **104** in the [3,3]-sigmatropic rearrangement of (*E*)-3-phenylallyl(*N*-phenyl)benzimidate **103** resulted in levorotatory enantiomer of **109** in 30–49% yields and selectivity 72–90%. Whereas, di-μ-chlorocomplex **105** gave dextrorotatory allylic amide **109** in 45%yield and 32% *ee*. The diastereomerically pure bispalladacycles **106** revealed high catalytic activity in *aza*-Claisen reaction (Scheme 22) [58]. As a result enantiomerically enriched allylic amines **109** featuring such substituents as ether-, carbonyl- or amino-group were gained in yields up to 94% and selectivity up to 96%. Complexes **107** and **108** were examined in the *aza*-Claisen rearrangement of allylic acetimidates **103** (Scheme 22) [59]. The *aza*-Claisen rearrangement proceeded in the presence of Ag salts (AgTFA or $AgNO_3$), complexes **107** or **108** and substoichiometric amounts of proton sponge (PS, *N*,*N*,*N*',*N*'-tetramethyl-1,8-diaminonaphthalene). This approach provides not only highly enantiomerically enriched primary allylic amines, but also secondary, tertiary and quaternary amines. In addition, the reaction conditions tolerate many important functional groups.



Scheme 22. The aza-Claisen rearrangement.

Pd-complex of imidazolyl ferrocene **108** bearing sulfo group that is adjacent to the nitrogen atom proved to be the most prominent in these transformations. A high enantioselectivity was also achieved in the reaction with disubstituted ferrocene **106** however, the yield of the target product was lower.

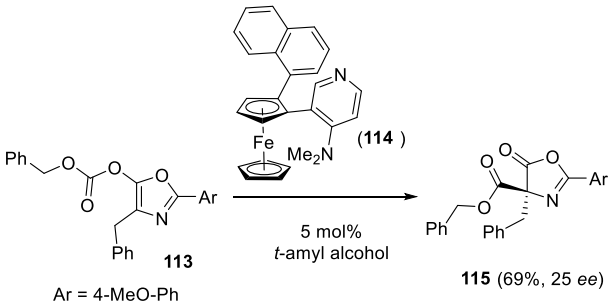
Nevertheless a planar chiral ferrocene bisimidazoline bispalladacycle **111** [60,61] demonstrated a high catalytic activity in the aza-Claisen rearrangement of Z-configured allylic *N*-aryltrifluoroacetimidates **110** (Scheme 23).



Scheme 23. The *aza*-Claisen rearrangement of Z-configured allylic *N*-aryltrifluoroacetimidates.

In this case, an intermetallic distance between equivalent catalytic centers is the decisive point. The main advantage of ferrocene moiety is apparently a partial rotational freedom around the Cp-Fe axis facilitating the two interacting metallic centers to activate two reacting substrates (or functional groups). The mentioned results exhibit that an appropriate catalyst for this type of reaction is ferrocene **114**, providing the rearrangement product **112** with high yields and enantioselectivity.

Ferrocenes featuring six-membered heterocycle were also investigated in rearrangements. Thus, product **115** was obtained as a consequence of the rearrangement of *O*-acylated azlactones **113** in the presence of pyridine-containing planar chiral ferrocene ligands **114**. The reaction was characterized by moderate yield 69% and low enantiomeric excess 25% *ee*) (Scheme 24) [62].



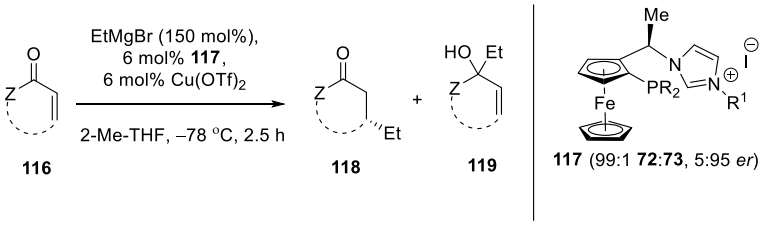
Scheme 24. The rearrangement of O-acylated azlactones.

As a short resume, it can be concluded that derivatives of five-membered heterocycles represent the most effective catalysts for asymmetric rearrangement. Additionally imidazolyl containing [57] ferrocenes revealed a higher catalytic activity compared to that of oxazolinyl ferrocenes [58,59].

2.4. Asymmetric Addition

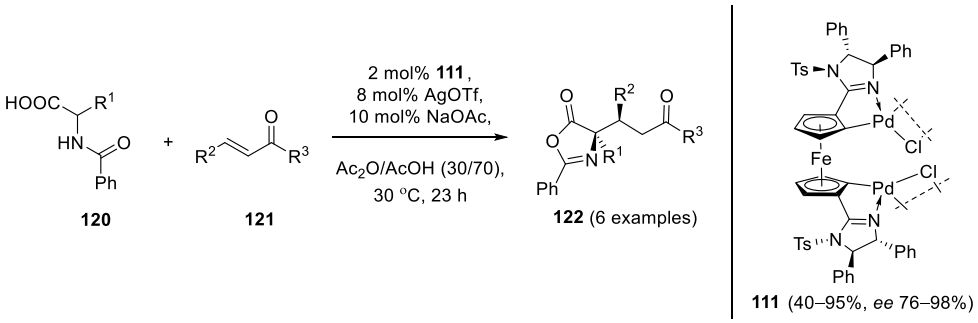
Conjugate additions of C-nucleophiles to *α,β*-unsaturated carbonyl compounds and lactones function as the valuable tool to create C-C bond in organic synthesis. In this regard applying of Grignard reagents in Cu-catalyzed 1,4-additon to Michael acceptors **116** represents a very attractive synthetic approach [63,64]. The authors established that reaction between *α,β*-unsaturated carbonyl compounds **116** and EtMgBr proceeded in the

presence of catalytic amounts of the ferrocene imidazolium phosphanes ligand **117** and copper (II) triflate in 2-Me-THF with high regio- and enantioselectivity (Scheme 25). Diphenyl phosphine ligand bearing a methyl substituent in the imidazole ring showed the best result in the reaction. Thus the main addition product **118** is formed with the conversion 100% and high regioselectivity 99:1 (**118**:**119**) and enantioselectivity *er* 5:95.



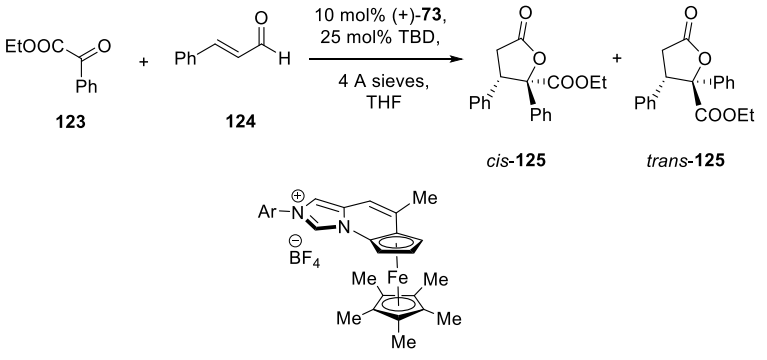
Scheme 25. Conjugate additions of EtMgBr to Michael acceptors.

1,1′-Disubstituted derivative of ferrocene **111** proved to be an effective catalyst of the *aza*-Claisen rearrangement and further demonstrated a catalytic activity in the reaction of 1,4-addition of azlactone generated in situ from racemic *N*-benzoylated α-amino acids **120** and acetic anhydride, to enones **121**. Potentially biologically active highly enantio-enriched (*ee* 76–98%) derivatives of α-amino acids **122** have been prepared in the presence of complex **111** with quantitative yield (up to 95%) (Scheme 26) [60].



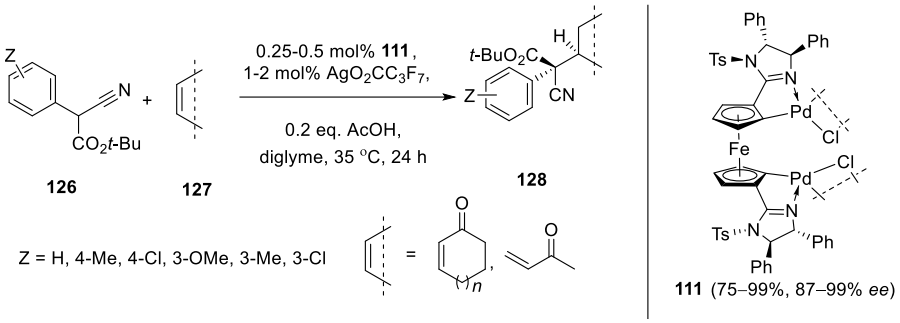
Scheme 26. Asymmetric 1,4-cycloaddition.

At the same time imidazolyl containing ferrocene azolium salt (+)-**73** has been less effective ligand in these reactions (Scheme 27) [44,45]. The target product of cyclization **125** is formed as the result of asymmetric homoenolate addition to α-ketoesters in 40–95% yields and enantioselectivity (32–70% *ee* for *cis* and 24–50% *ee* for *trans*).



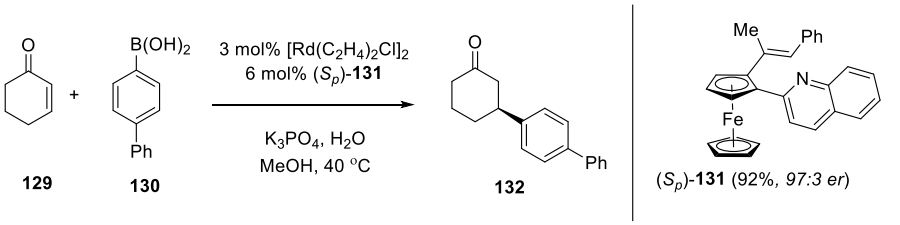
Scheme 27. The asymmetric homoenolate addition to α-ketoesters.

In addition, **111** functioned as an essential catalyst in the direct 1,4-addition of α-cyanoacetates **126** to enones **127**. Thus in the paper [60] the authors found that (S_p)-ferrocene **111** generated (*R,R*)-products **128** as the main diastereomers with high yields and enantioselectivity (Scheme 28).



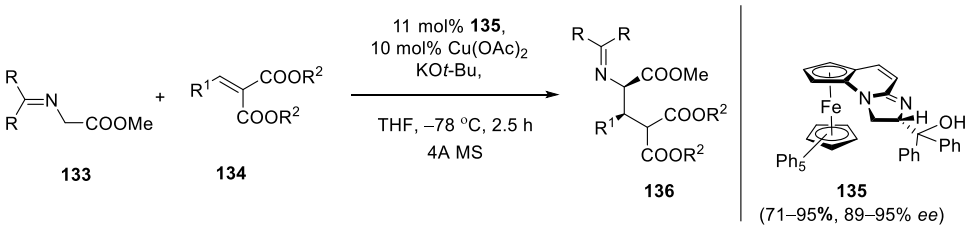
Scheme 28. The 1,4-addition of α-cyanoacetates to enones.

Ferrocenyl derivatives featuring six-membered *N*-heterocycles are known to possess superior catalytic activity. To demonstrate it, Z. Hou et al. have found that quinoline substituted ferrocene (S_p)-**131** containing olefin moiety exhibited high catalytic activity (97:3 *er*) in Rh-catalyzed 1,4-addition of arylboronic acid **130** to α,β-unsaturated ketone **129** (Scheme 29) [65].



Scheme 29. Rh-catalyzed asymmetric 1,4-addition.

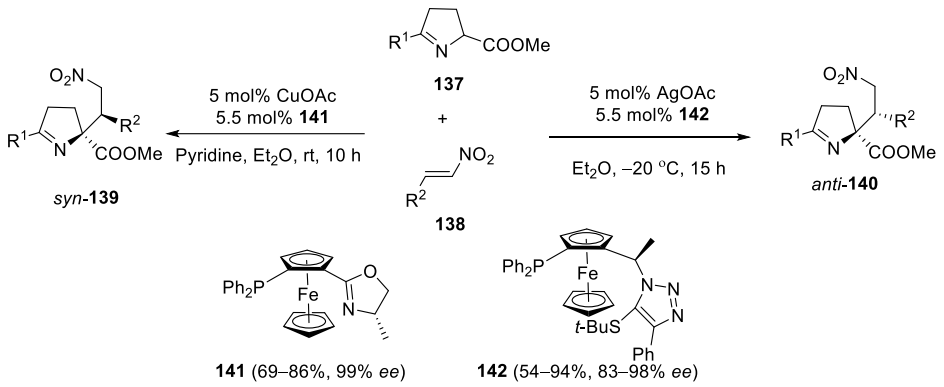
1,4-Michael addition of glycine derivatives to alkylidene malonates is a relevant tool because the following cyclization of the corresponding 1,4-adducts afforded 3-arylglutamic acids representing selective inhibitors of absorption of *L*-homocysteic acid (HCA) [66]. W.-P. Deng et al. showed that planar chiral ferrocene *N,O*-ligand **135** effectively catalyzed asymmetric Cu-catalyzed 1,4-addition of derivatives **133** to malonates **134** giving the corresponding 1,4-adducts **136** with high yields and enantioselectivity (up to 95% *ee*) with predominance of *anti*-adduct (Scheme 30) [67]. The reaction was identified to proceed readily with practically equal enantioselectivity (89–93% *ee*) if the substrates contained both electron withdrawing and electron donating groups.



Scheme 30. 1,4-Addition of glycine derivatives to alkylidene malonates.

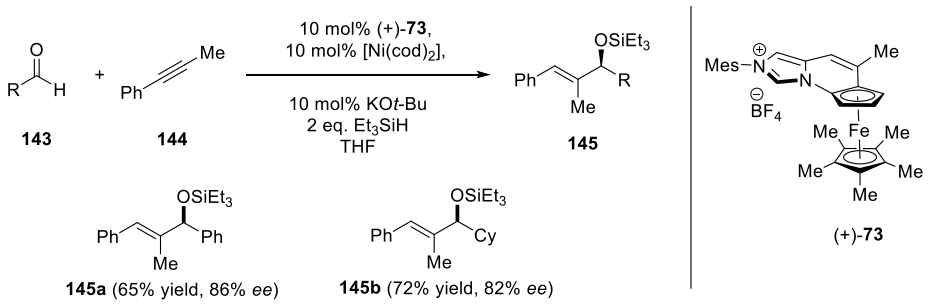
Imino esters of glycine constitute a good source of azomethine ylides for the following synthesis of derivatives of α-amino acids in 1,3-dipolar cycloaddition and conjugate addition with electron deficient alkenes. The authors proposed chiral oxazolinyl **141** and

triazolinyl ferrocene **142** complexes of copper and argentum as highly effective catalysts in the formation of enantiomerically enriched α-amino acids [68]. It has been concluded that *syn*-diastereoselective addition of 1-pyrroline esters **137** to nitroalkenes **138** occurred with good yields and enantioselectivity while using Cu-complex of oxazoline derivative **141** as a catalyst in the presence of pyridine (Scheme 31). At the same time, Ag-complex of ferrocene **142** facilitates of *anti*-diastereoselective conjugate addition in the absence of bases with high enantioselectivity. This method provides chiral derivatives of 1-pyrroline with various structures.



Scheme 31. Rh-catalyzed asymmetric 1,4-addition.

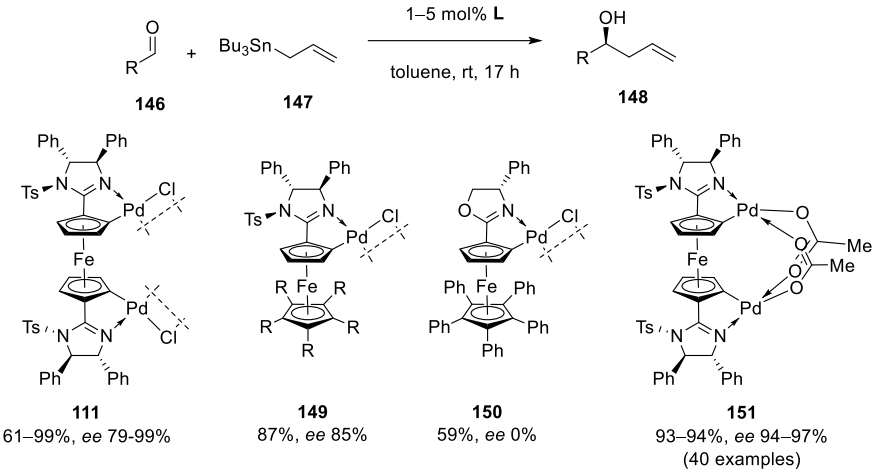
As reported by Montgomery et al. *N*-heterocyclic imidazolium carbenes demonstrated a prominent catalytic activity in Ni-catalyzed reductive couplings of alkines and aldehydes [69,70]. Simultaneously they showed that incorporation of ferrocenyl moiety into the carbene structure resulted in the increase of regio- and stereoselectivity of the process. Ni-catalyzed coupling of 1-phenyl-1-propine **144** with benzaldehyde **143** in the presence of a ligand (+)-**73** and triethylsilane as a reducing agent afforded the product **145** with excellent regioselectivity (>20:1 and 10:1) and enantiomeric excess (86% and 82% *ee*) (Scheme 32) [44,45].



Scheme 32. Ni-catalyzed reductive couplings.

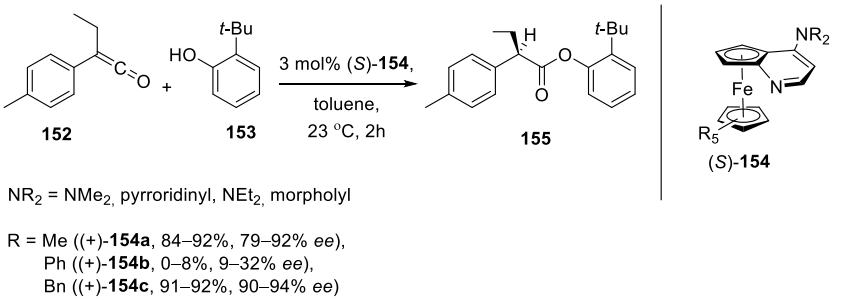
Affinity of aldehydes to Pd(II) is considered to be low making it very difficult to search of a highly active enantioselective catalyst. However, the application of Pd-catalyst creates new opportunities in transformation of substrates containing reactive functional groups. "Soft" palladacycles have an advantage over hard catalysts based on Lewis acids. Due to a lower oxophilicity, they are allowed to be used in conjunction with the substrates featuring highly reactive functional groups. The paper [71] indicates that ligand **111** exhibits high catalytic activity in Pd-pincer complex catalyzed reactions of nucleophilic allylation of aldehydes with allyltin reagents (Scheme 33). The authors reported that a model reaction of addition of allyltributyltin **147** to *p*-chlorobenzaldehyde **146** in the presence of 0.5 mol% bispalladacycle **111**, provided the product **148** in high yield and 94% *ee* (Scheme 33). The ligands based on sterically hindered 1′,2′,3′,4′,5′-pentaphenylferrocene

149 and **150** facilitate the reaction in moderate to high yields. However, the ferrocene **150** provided the alcohol **148** in racemic form. In the presence of compound **151** the reaction proceeds both with electron poor substituents in the structure of substrate and aromatic substrates equipped with σ- and π-acceptor substituents regardless of their position (ortho-, meta- or para-) and quantity (mono- and di-substituted).



Scheme 33. The Pd-pincer complex catalyzed the nucleophilic allylation of aldehydes.

The catalytic activity of attained by K. Yoshida et al. ferrocene-fused 4-dialkylaminopyridines (*S*)-**154** was investigated in the reaction of addition of 2-*t*-Bu-phenol **152** to ethyl(*n*-tolyl)ketene **153** which was likely to proceed according a mechanism catalyzed by Brønsted acid [72,73]. The superior catalytic activity has been typical for the derivatives of ferrocene bearing Bn substituent on the second cyclopentadienyl ring in comparison with the activity of pentamethyl-substituted ligand **154a**. The introduction of a phenyl fragment to ferrocenyl ligand structure (**154b**) dramatically reduces the activity of a catalyst (Scheme 34).

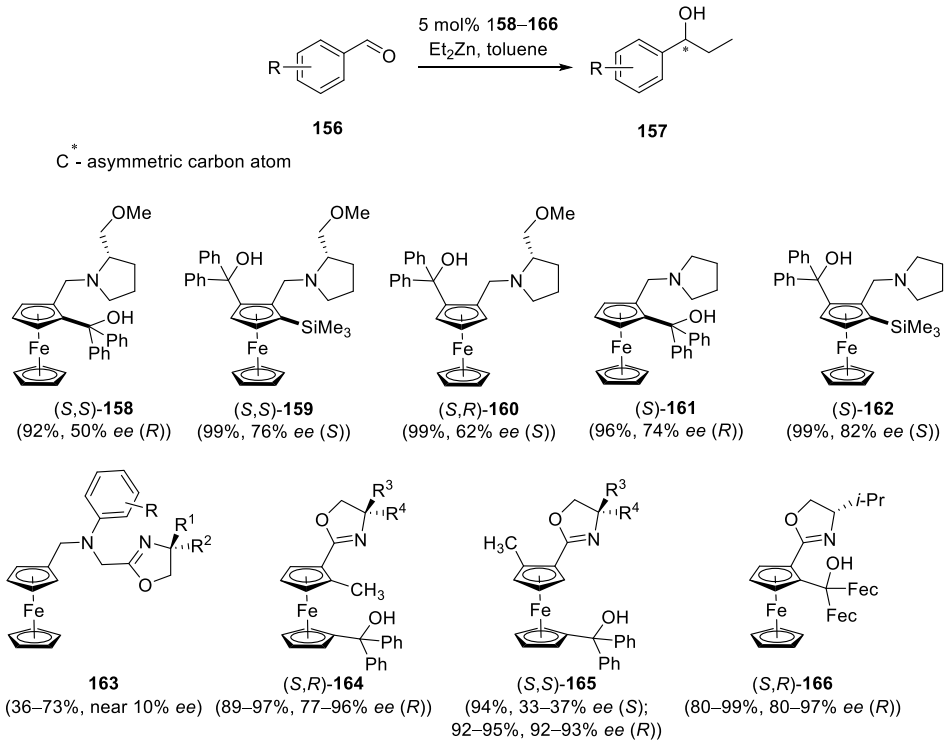


Scheme 34. Enantioselective addition of 2-*t*-Bu-phenol to ethyl(*p*-tolyl)ketene.

R. Šebesta et al. [74] presented an approach to the novel chiral amino-alcohol ferrocene ligands based on (*S*)-2-(methoxymethyl)pyrrolidine possessing central and planar chirality **158–160** as well as only planar chirality **161–162** (Scheme 35). While using ligands **158** and **160** the products of the enantioselective addition of diethylzinc **157** to benzaldehyde **156** were achieved with the selectivity 50% and 62% respectively. Absolute configuration of the obtained alcohols depended on the configuration of the planar chiral unit of the ligand. Ligand **159** containing trimethylsilyl fragment also reacted in the enantioselective addition of diethylzinc to benzaldehyde **156** leading to an increase of selectivity of the product **157** up to 76% (Scheme 35).

For a deep understanding of how the structure of ligands influences the selectivity of the addition of diethylzinc to benzaldehyde the ligands **161** and **162** have been synthesized. The ligands **161** and **162** possessing only the planar chirality proved to be more effective than the derivatives **158** and **159** (Scheme 35).

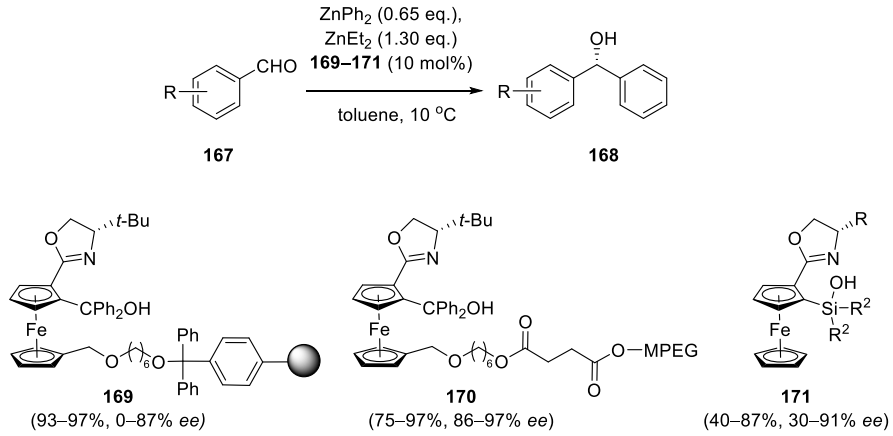
Ferrocenyl oxazolines **163** have also been used as ligands in the enantioselective addition and the product **157** was gained with the selectivity about 10% that was connected with steric hindrance of the nitrogen donor centres [75]. M. Li et al. showed that novel planar chiral 1,1′-*N*,*O*-ferrocenyl ligands **164**, **165** were very active in these transformations [76]. In the presence of a catalytic amount of ligand (*S*,*R*)-**164** the reaction proceeded readily providing the corresponding alcohol (*R*)-**157** with the yields up to 97% and enantiomeric enrichment up to 96%. The replacement of (*S*,*R*)-**164** with (*S*,*S*)-**165** led to a drastic decrease of a selectivity up to 33%. It could be related to a steric effect of substituents both on ferrocene and on oxazolyne ring. In the reaction with ferrocenyl oxazolyne (*S*,*R*)-**166** the product (*R*)-**157** was obtained with the yields up to 99% and selectivity upper 97% [77]. The authors explain the high yields and selectivity by occurrence of transition state, which is stabilized due to an interaction between the central-atom chirality of oxazolinyl substituent, the planar chirality of di-substituted ferrocene and a steric effect of the two additional ferrocenyl substituents which apparently leads to the formation of the (*R*)-product mainly.



Scheme 35. The enantioselective addition of diethylzinc to benzaldehyde.

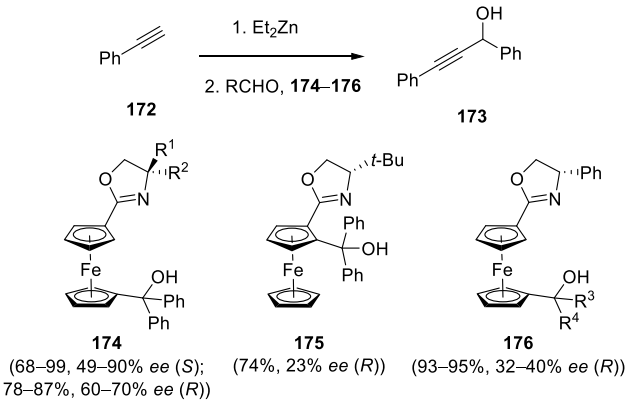
C. Bolm et al. focused on the synthesis of new polymer-supported ferrocenes and their use in asymmetric phenyl-to-aldehyde addition reactions [78]. In the result of applying of the resin-bound ferrocene **169** the product of addition of phenylzinc reagent **168** to *p*-chlorobenzaldehyde was obtained as a racemic mixture. In its turn an addition of diethylzinc to benzaldehyde **167** proceeded with the selectivity of 87%. MeO-PEG-supported ferrocene **170** in asymmetric phenyl transfer reaction provided the products **168** with the yields 75–97% and selectivity up to 97%. Then C. Bolm et al. investigated the possibility of utilization of the ligands **169**, **170** in asymmetric phenyl transfer reaction. It was shown that MeO-PEG-supported ferrocene **170** maintained the high levels of enantioselectivity over five consecutive cycles. Ferrocene-based organosilanols **171** similarly demonstrated

high catalytic activity in asymmetric phenyl-to-aldehyde addition (Scheme 36) [79]. The best results were obtained with *tert*-butyl substituted oxazoline ring and isopropyl groups in the silanol moiety. Surprisingly that in earlier works the enantioselectivity was achieved exceptionally in the presence of diphenyl hydroxymethyl substituent at the position 2 of a ferrocene ring.



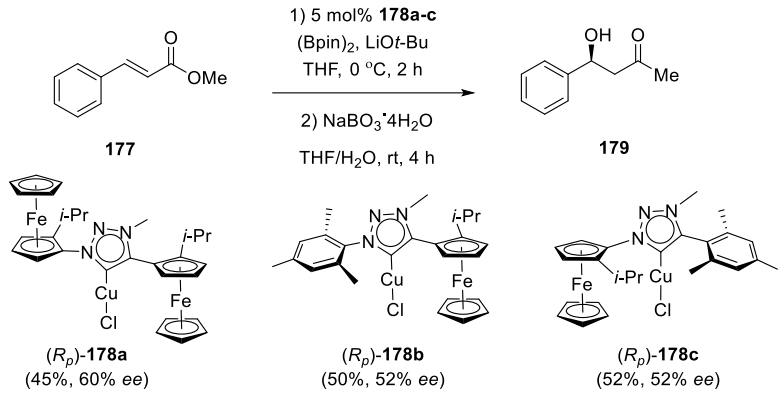
Scheme 36. Asymmetric phenyl-to-aldehyde addition reactions.

1,1′-Ferrocenyl oxazoline ligands **174–176** were applied in the addition reaction of phenylacetylene **172** to aldehydes (Scheme 37) [80]. It was shown that the framework and substituent in oxazoline ring of ligands had a great influence on the yields and selectivity of the reaction. Ligand **175** bearing *tert*-butyl substituted oxazoline ring demonstrated the best results.



Scheme 37. The addition reaction of phenylacetylene with aldehydes.

Recently chiral *N*-heterocyclic carbenes (NHCs) have been increasingly utilized as catalysts in asymmetric synthesis. R. Haraguchi et al. investigated application of ferrocenyl triazolylidene copper complexes (R_p)-**178ac** in the reaction of asymmetric borylation of methyl cinnamate (Scheme 38) [81]. Treatment of methyl cinnamate **177** by bis(pinacolato)diboron ((Bpin)$_2$) in the presence of derivatives (R_p)-**178a–c** and lithium *tert*-butoxide gives borylated intermediate which is oxidized by $NaBO_3 \cdot 4H_2O$ into methyl-3-hydroxy-3-phenylpropanoate **179** in good yield (45–52%) and selectivity (52–60% *ee*). Enantioselectivity is improved up to 60% *ee* in the presence of copper complex (R_p)-**178a** containg two planar-chiral ferrocenyl fragments.

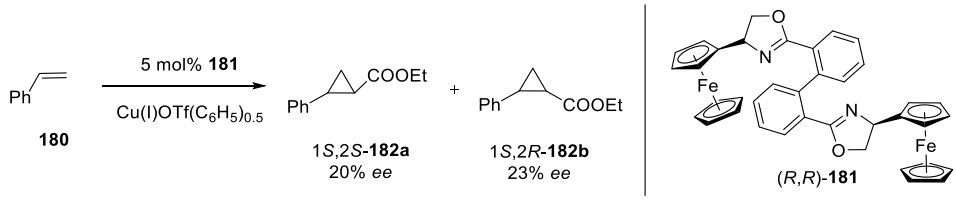


Scheme 38. Asymmetric borylation of methyl cinnamate with bis(pinacolato)diboron.

In the addition reactions, Pd-complexes of imidazolyl-containing ferrocene ligands exhibit the highest efficiency [60,71]. Similarly oxazolinyl ferrocenes show the high catalytic activity in these transformations [68,77]. However addition of a spacer between cyclopentadienyl ring and oxazoline moiety strongly reduces enantioselectivity of the reaction [75]. Benzimidazole annelated to ferrocene decreases efficiency of a ligand [67] whereas annelated quinolone [65] and pyridine [72,73] give the high enantioselectivity (86–99% *ee*) in these transformations.

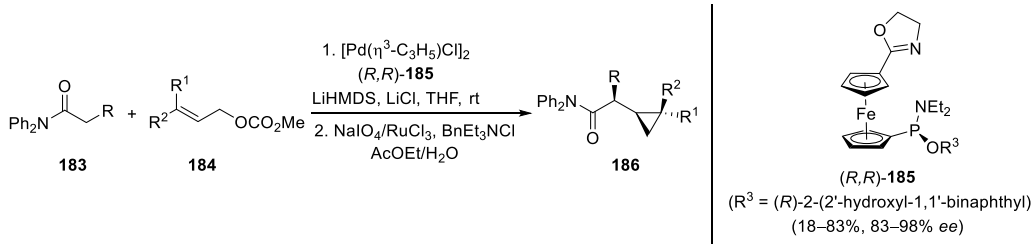
2.5. Annulation and Cycloaddition

Since Hegedus discovered the reaction of cyclopropane formation as the result of interaction of π-allylpalladium chloride with enolates of esters through the attack of nucleophiles on the central C atom [82] the reactions of asymmetric cyclopropanation with allylic reagent catalyzed by metals are still much less explored. However, complex (*R*,*R*)-**181** with [Cu(I)OTf(C_6H_5)$_{0.5}$] was successfully applied in asymmetric cyclopropanation reaction of styrene **180** (Scheme 39) [83]. As the result, a mixture of *trans*- and *cys*-2-phenylcyclopropanecarboxilate (**182**) in a ratio 65:35 was obtained. Nevertheless, enantioselectivity of the process was low and reached 20% *ee* (*trans*-) and 23% *ee* (*cis*-).



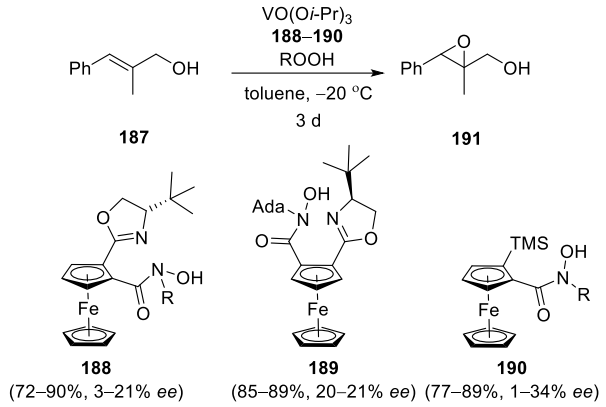
Scheme 39. Asymmetric cyclopropanation reaction of styrene.

Reaction of cyclopropanation of acyclic amides **183** with monosubstituted allyl carbonates **184** in the presence of Pd-complex of ligand (*R*,*R*)-**185** led to enantiomerically enriched derivatives of cyclopropane **186** possessing three chiral centers in 83% yield and up to 98% *ee* (Scheme 40) [84].



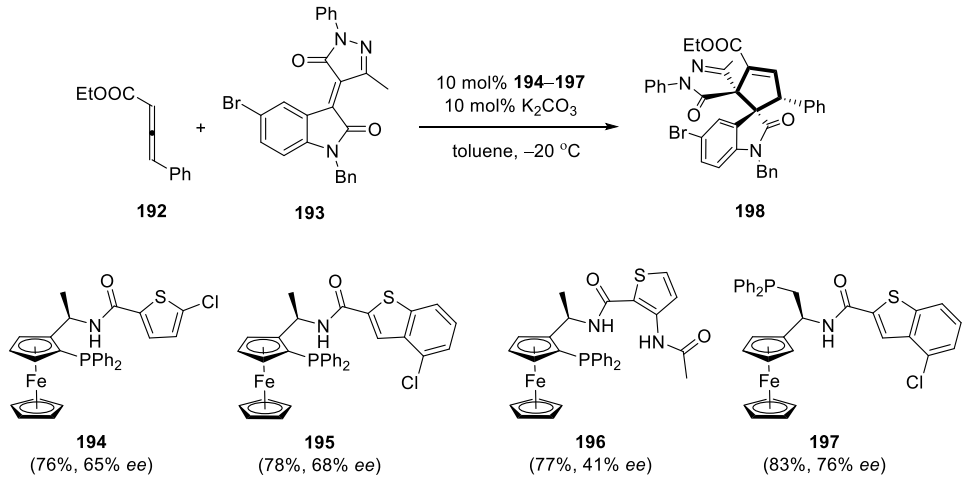
Scheme 40. The cyclopropanation of acyclic amides.

Elaborated by C. Bolm et al. asymmetric epoxidation of allylic alcohols **187** to three-membered epoxy compounds **191** in the presence of planar chiral hydroxamine acids based on ferrocenes **188–190** proceeded with low selectivity (1–34% *ee*). The yield of the reaction which was carried out in the presence of VO(O*i*-Pr)$_3$ and *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP) reached 72–90% (Scheme 41) [85].



Scheme 41. Asymmetric epoxidations of allylic alcohols.

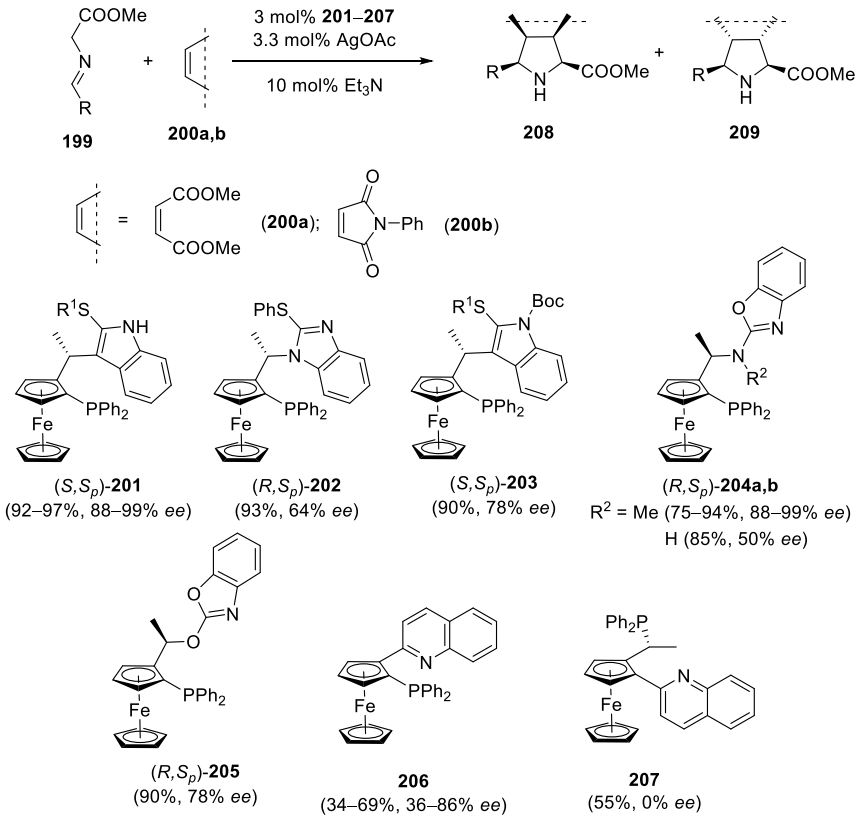
Spirocyclic compounds bearing at least one quaternary C-atom represent valuable structural motifs for biomedicinal natural molecules and pharmaceuticals [86]. In [87] the authors proposed a method of asymmetric [3 + 2]-annulation of tetra-substituted activated alkenes for the synthesis of compounds containing spirocyclopentene **198**, that binds oxindole and pyrazolone (Scheme 42). In the reaction of ethyl 4-phenylbuta-2,3-dienoate **192** and pyrazoloneyldiene oxindole **193** in the presence of bifunctional chiral ferrocenylphosphines **194** and **195** the product **198** is formed with moderate values of *ee* (65% and 68%) and in good yields (76–78%), while phosphine **196** provides only 40% *ee*. Incorporation of diphenylphosphine substituent into the pendant arm of the ligand (**197**) led to improved yield and selectivity (83%, 76% *ee*).



Scheme 42. Asymmetric [3 + 2]-annulation of tetra-substituted activated alkenes.

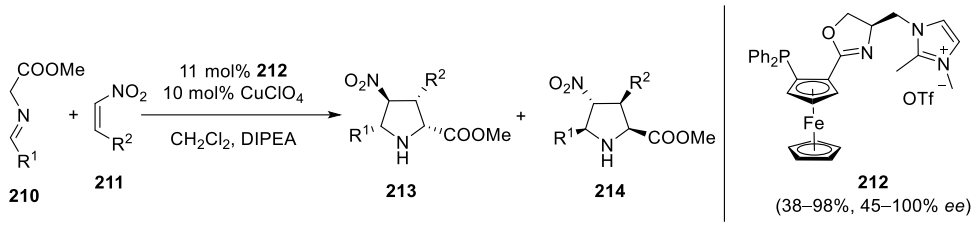
Asymmetric [3 + 2]-cycloaddition is a conventional tool for the asymmetric formation of five-membered cycles. The chiral ferrocenyl derivatives based on *N*,*N*-dimethyl-1-ferrocenylethylamine (Ugi's amine) reveal excellent diastereo/enantioselectivities in such transformations. The group of M.-L. Han et al. report that replacement of the amino-group with heterocycle fragment in ligand (**201–203**) in the reaction of imino esters **199** with dimethyl maleate **200a** leads to the high yields and selectivity (92–97%, 88–99% *ee*) [88]

(Scheme 43). The ferrocene ligand **201** bearing a phenylthio group demonstrated the highest catalytic activity in diastereo- and enantio-selectivity (endo/exo = 96/4 and 99% ee for endo-adduct). The presence of a proton at the N-atom in ligand is essential since the application of imidazoline derivative **202** and Boc-protected ligand **203** caused a dramatic drop of enantioselectivity from 88–99% *ee* to 64–78% *ee*. Subsequently, this group of scientists determined that chiral *P*,*N*-ligands with a benzoxazole ring as the N-donor moiety proved to be highly efficient ligands in Ag(I)-catalyzed asymmetric [3 + 2] cycloaddition of azomethine ylides with cyclic *N*-phenylmaleimide **200b** (Scheme 43) [89]. In comparison with the unsubstituted at N-atom ligand **204b** (85%, 50% *ee*), ferrocene **204a** bearing N-methyl substituent provides the corresponding *endo*-cycloadduct **208b** with high yields and diastereo- (95/5) and enantioselectivity (up to 95% *ee*). The replacement of the nitrogen atom with oxygen adjacent to stereogenic carbon center (**205**) leads to a decrease of enantioselectivity (87% *ee*). When the reaction proceeds with quinolone containing ferrocene ligands **206** and **207** the product of [3 + 2]-cycloaddition is formed with moderate yield and lower selectivity (to 86% *ee* for **206**; 0% *ee* for **207**) [90].



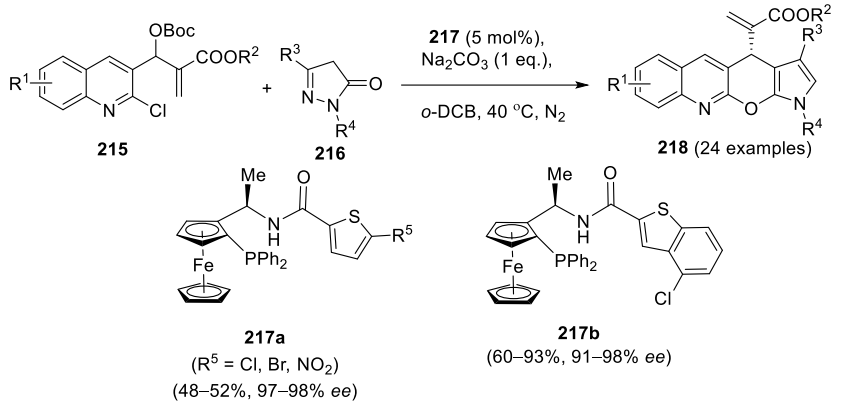
Scheme 43. Ag-catalyzed asymmetric [3 + 2] cycloaddition.

The reaction of 1,3-dipolar cycloaddition is a well-established strategy for the construction of heterocyclic compounds which in turn are used as building blocks for organic synthesis and as organic catalysts for asymmetric reactions. In particular, L. Dai et al. concentrated on the application of ferrocenyl oxazolinephosphine ligand **212** bearing imidazole fragment in the Cu-catalyzed cycloaddition of azomethine ylides **210** with nitroalkenes **211** to produce corresponding pyrrolidine products *endo*-selectively (Scheme 44) [91]. Thus, in the presence of a weak base the analogues of pyrrolidine **213** have been isolated with satisfying yields and excellent enantioselectivity (>99% *ee*). The authors established that ion effect between imidazole moiety and azomethinilide is the key factor for increasing the enantioselectivity. Furthermore, the ferrocene ligand **212** additionally acts as ionic liquid and, as a consequence, the reaction of asymmetric 1,3-dipolar cycloaddition proceeds in the system DCM/ionic liquids.



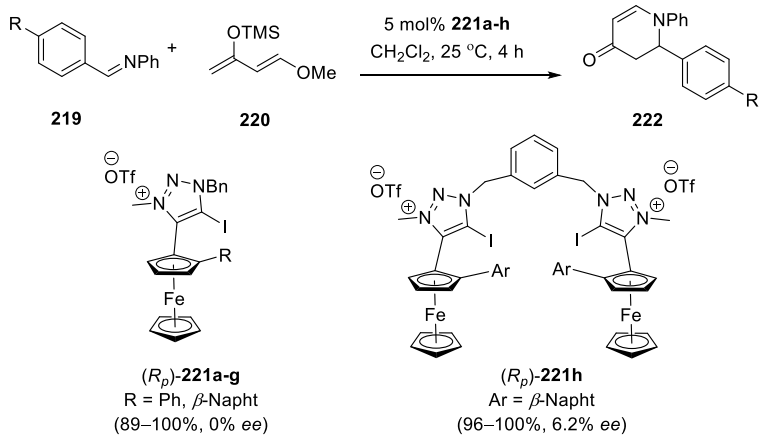
Scheme 44. Asymmetric 1,3-dipolar cycloaddition.

Phosphine-mediated annulation reactions provide optically pure derivatives of dihydropyran and pyrazole, possessing biological activity. Weihui Zhong and co-workers proposed a stereoselective method for alkylation/annulation of quinoline **215** containing a good-leaving group at the *ortho*-position by pyrazolones **216** in the presence of ferrocene-derived bifunctional phosphine catalysts **217a,b** (Scheme 45) [92]. So, thiophene containing derivatives of ferrocene enable optically active 1,4-dihydropyrazolo[4',3':5,6]thiopyrano[2,3-*b*]quinolones **218** with high selectivity (up to 98% *ee*). The authors determined that the replacement of electron withdrawing substituents in thiophene fragment of a ligand (Cl, Br, NO_2) with annelated benzene ring resulted in the increase of the yields of the products on average by 30% with the same value of *ee*.



Scheme 45. Phosphine-mediated annulation reaction.

However not all chiral triazoles possess catalytic activity. Thus, in the paper [93] is reported that in the presence of iodotriazolium triflates an *aza*-Diels-Alder reaction occurs with low asymmetric induction despite the high yield of the product. The best enantiomeric excess (*ee* 6.2%) was achieved with the use of ferrocene ligand (S_{Fc},S_{Fc})-**221h** (Scheme 46).

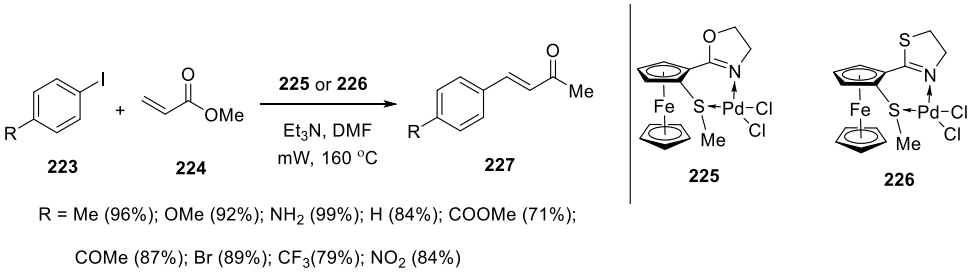


Scheme 46. Asymmetric *aza*-Diels-Alder reaction.

In the reactions of cyclopropanation the planar chiral oxazoline ferrocenes containing diphenylphosphine substituent are considered to be the superior catalysts [84]. The absence of PPh_2-group leads to a decrease of selectivity [83,85]. The replacement of oxazoline with thiophene [87,92] in the structure of a ligand affords spiro-compounds with moderate selectivity. In the reactions of [3 + 2] cycloaddition the ligand bearing indole moiety proved to be the most effective [88]. Derivatives of benzimidazole [88] and benzoxazole [89] ensure the moderate enantioselectivity in these transformations. The replacement of five-membered heterocycle with six-membered one (quinolone) leads to moderate yields and selectivity [90]. Incorporation of diphenyl phosphine into the structure of quinolone ferrocene by means of a spacer causes the loss of efficiency of a ligand and the lack of selectivity. Triazolylferrocenes give the low enantioselectivity in an *aza*-Diels-Alder reaction despite the high catalytic activity (yield 100%) [93].

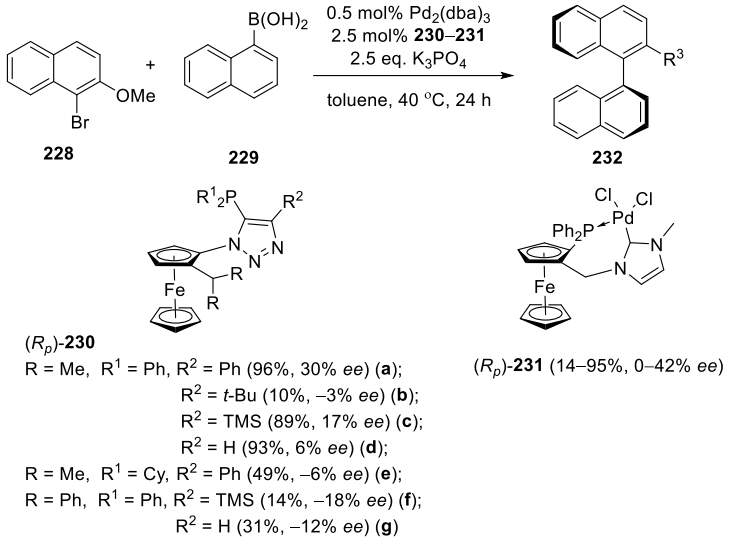
2.6. Cross-Coupling Reactions Catalyzed by Metals

Ferrocenyl derivatives decorated with five-membered heterocycles and oxazolines in particular have been the widespread ligands for the catalysts of asymmetric synthesis for over 20 years [94–96]. The replacement of oxazoline moiety with thiazoline makes it possible to change the catalytic reactivity of such a ligand. For example planar chiral Pd-complexes of oxazolinyl- **225** and thiazolinylferrocene **226** act as viable catalysts in Mizoroki-Heck reaction of aryl iodides with methyl acrylate assisted by microwave irradiation [97]. It was established that **226** revealed a higher catalytic activity relative to that of **225**. Thus the coupling products **227** are generated with good yields (71–99%) in the presence of a base NEt_3 and 0.05 mol% of **226** upon heating in DMF at 160 °C under microwave radiation (Scheme 47).



Scheme 47. The Mizoroki-Heck reaction of aryl iodides with methyl acrylate.

Azole fragments in the structure of ferrocene provide enantiomerically enriched biaryls in high yields but selectivity remains low. S. Sakai et al. reported that planar chiral monophosphine ligands bearing ferrocene-triazole backbones demonstrated a good catalytic activity in Suzuki-Miyaura coupling reaction of 2-bromo-3-methoxynaphthalene **228** with 2-naphthyl boronic acid **229** (Scheme 48) [98]. The best rates of the selectivity (30% *ee*) and yield (96%) were achieved when the ligand (R_p)-**230a** bearing phenyl substituents in triazole cycle was used.



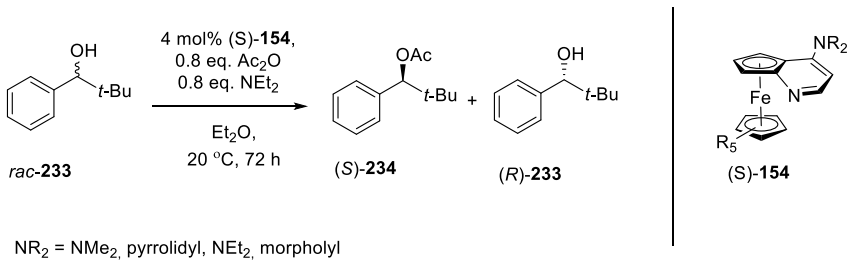
Scheme 48. Asymmetric Suzuki-Miyaura coupling reaction.

N. Debono et al. managed to increase enantioselectivity of this reaction up to 42% ee [99]. Pd-complex (R_p)-**231** bearing planar chiral ferrocenyl phosphine-N-heterocyclic carbene ligand demonstrated high activity in Suzuki-Miyaura reaction and provided the product of C-C coupling with yield up to 95% and moderate enantioselectivity (Scheme 48).

Lastly, among a small number of the reactions of asymmetric C-C cross-coupling oxazolinyl- [97] and thiazolinyl [97,98] ferrocenes bearing thioester group demonstrated the high catalytic activity and enantioselectivity.

2.7. Resolution of Enantiomers

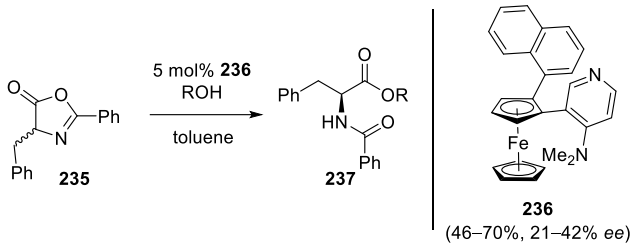
Chiral derivatives of ferrocene have found their usefulness not only as the catalysts of asymmetric synthesis but also for the resolution of racemic mixtures. Thus, in the earlier mentioned papers [72,73] the authors established that ferrocene-fused 4-dialkylaminopyridines (S)-**154** could be successfully applied for a kinetic resolution of the racemic secondary alcohol *rac*-**233**. Enantioselective acetylation of *rac*-**233** with acetic anhydride in the presence of (*S*)-**154** (4 mol%) produces mixture of ester (*S*)-**234** and initial alcohol (*R*)-**233** (Scheme 49). In its particular case the pentaphenyl substituted ligand showed the highest activity (enantioselectivity with *s* factors ranging from 13 to 69) in contrast to that of Me- (5–7) and Bn-containing (3.7–11) derivatives.



Scheme 49. Dynamic kinetic resolution of racemic alcohols.

The kinetic resolution in the presence of a ligand containing 4-morpholine fragment provided the best selectivity (*s* = 69). However, a lower electron-donating ability of this ligand decreases the catalytic activity of the ferrocene ligand overall.

J. G. Seitzberg et al. have accessed the ligand **236** based on ferrocene for dynamic kinetic resolution of azlactone **235** (Scheme 50) [62]. The kinetic resolution of azlactone **235** proceeded in the presence of nucleophiles (MeOH or *i*-PrOH) and catalyst **236**. The product **237** was obtained in 46–70% yields and 21–42% *ee*.



Scheme 50. Dynamic kinetic resolution of azlactone.

As for planar chiral heterocyclic derivatives of ferrocene are concerned, their participation in the kinetic resolution of racemic mixtures remains poorly studied. This field of research certainly has huge potential. Thus ferrocene featuring aniline annelated to cyclopentadienyl ring [72,73] shows a higher activity compared with the ligand in which a fragment of pyridine [62] adjacent to ferrocene via the C–C bond.

3. Conclusions

This review attempted to represent the development of the exploitation of planar chiral derivatives of ferrocene in the reactions of asymmetric synthesis over the last 20 years. During the first decade of the XXI century, a particular attention was drawn to the application of enantiomerically enriched ligands in the reactions of allylic substitution. The ligands providing an enantioselective synthesis of target products in the Tsuji–Trost reactions with quantitative yields have been developed as the result of substantial progress in this area. The most studied and prospective class of compounds used in this type of transformation are the ferrocenes bearing oxazoline fragments. After 2010 the sight of chemists was focused on the reactions of asymmetric hydrogenation, 1,4-addition and cycloaddition. Thus, ferrocenes containing five- and six-membered heterocycles have been successfully employed. Moreover, methods of selective reduction of unsaturated ketones have been developed.

It is worth noting that despite impressive progress achieved in the study of properties and application of chiral ferrocenes, not all challenges have been addressed. To date, the scope of asymmetric hetaryl ferrocenes in the reactions of C-C-coupling of (hetero)aromatic compounds has not been sufficiently explored. Kinetic resolution of isomers, determination of a structure, and absolute configuration of target products pose relevant issues. Therefore, future efforts should be aimed at the development of this field. Moreover, we firmly believe that in the near future special attention will be paid to a great number of step-economic strategies for the stereodivergent synthesis of new planar chiral ferrocene derivatives and recyclable catalysts.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

Ada adamantly;

Ar	aryl;
Bn	benzoyl;
Boc	*tert*-butyloxycarbonyl;
$(Bpin)_2$	bis(pinacolato)diborane;
BSA	bis(trimethylsilyl)acetamide;
t-Bu	*t*-butyl;
CHP	cumene hydroperoxide;
o-DCB	1,2-dichlorobenzene;
DIPEA	*N*,*N*-diisopropylethylamine;
DME	dimethoxyethane;
DMF	dimethylformamide;
ee	enantiomeric enriched;
eq.	equivalent;
er	enantiomeric ratio;
Et	ethyl;
HCA	*L*-homocysteic acid;
$[Ir(cod)Cl_2]$	bis(1,5-cyclooctadiene)diiridium(I) dichloride;
LiHMDS	lithium bis(trimethylsilyl)amide;
Me	methyl;
Mes	mesityl;
MPEG	methoxy polyethylene glycol;
NHCs	*N*-heterocyclic carbenes;
$[Ni(cod)_2]$	bis(cyclooctadiene)nickel(0);
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0);
Ph	phenyl;
PMHS	polymethylhydrosiloxane;
i-Pr	*i*-propyl;
PS	proton sponge, *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene;
$[Rh(cod)_2]BF_4$	bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate;
$[Rh(nbd)_2]BF_4$	bis(norbornadiene)rhodium(I) tetrafluoroborate;
$[Ru(p\text{-cymene})_2]$	dichloro(*p*-cymene)ruthenium(II) dimer;
TBAF	tetra-*n*-butylammonium fluoride;
TBD	triazabicyclodecene;
TBHP	*tert*-butyl hydroperoxide;
THF	tetrahydrofuran;
TMS	trimethylsilyl;
Tol	tolyl.

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