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Siva Sankar Murthy Bandaru, Jagrut Shah, Shatrughn Bhilare, Carola Schulzke, Anant R Kapdi, Julien Roger, Jean-Cyrille Hierso

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# Phosphine Ligands Based on the Ferrocenyl Platform:

## Advances in Catalytic Cross-Couplings

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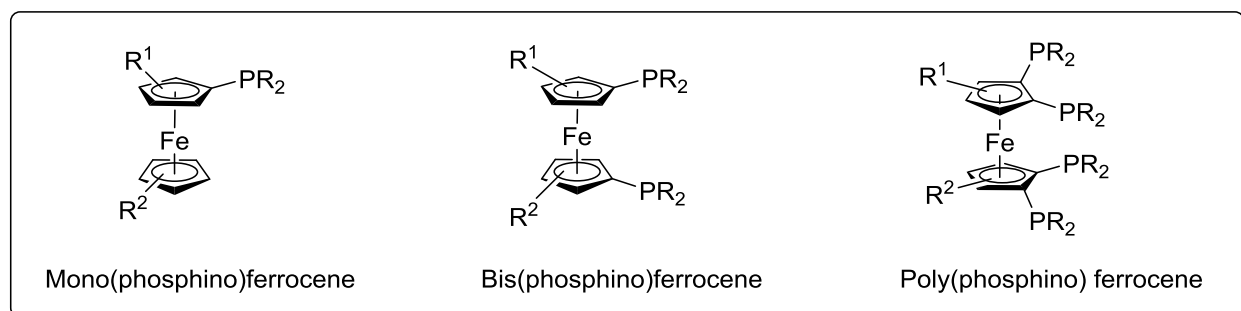
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## Abstract

Ferrocenyl skeletons tagged with a variety of donor atoms (metalloligands) have become popular in modern metal-catalyzed organic transformations, broadening the applications. Ferrocenylphosphines, such as 1'-bis(diphenylphosphino)ferrocene (dppf), have been widely used as metalloligands in academic and industrial research, motivating further investigation into novel ferrocenylphosphine ligands. The current review concentrated non-exhaustively on emblematic applications of different ferrocenylphosphine ligands in transition metal-catalyzed cross-coupling strategies. Initially, the stereochemical aspects of the ferrocenyl skeleton, nomenclature, and applications of chiral ferrocenyl phosphines in asymmetric synthesis are evoked. We simply classified ferrocenyl phosphine ligands, eventually further functionalized at cyclopentadienyl ( $C_p$ ) ring, into three types based on the number of phosphine donors on the ferrocenyl backbone: monophosphine, bisphosphine, and polyphosphine ferrocenyl ligands. Furthermore, the use of hybrid monophosphinoferrrocene type scaffolds (P, N)-, (P, O)-, (P, S)-, (P, NHC)-, and (P, X)- (X is polar/hydrophilic like guanidium) in cross-coupling is evoked. The latest advances in the chemistry of symmetric achiral di- and polyphosphine ferrocene-based ligands related to metal-catalyzed bond-forming reactions (C-C, C-N, and C-O bonds) are discussed, with a special emphasis on consolidating all important work in this area. A cumulative table is provided in the end, with a focus on compiling significant work in this field. The general structure and electronic features and effects of ferrocenylphosphine ligands on the selectivity and activity in catalysis is also briefly evoked. The literature cut-off date was in general ending of 2020.



Keywords: Ferrocenylphosphine; Structure; Transition metal catalysis; C–C cross-coupling; C–heteroelement bond formation

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## 1. Introduction

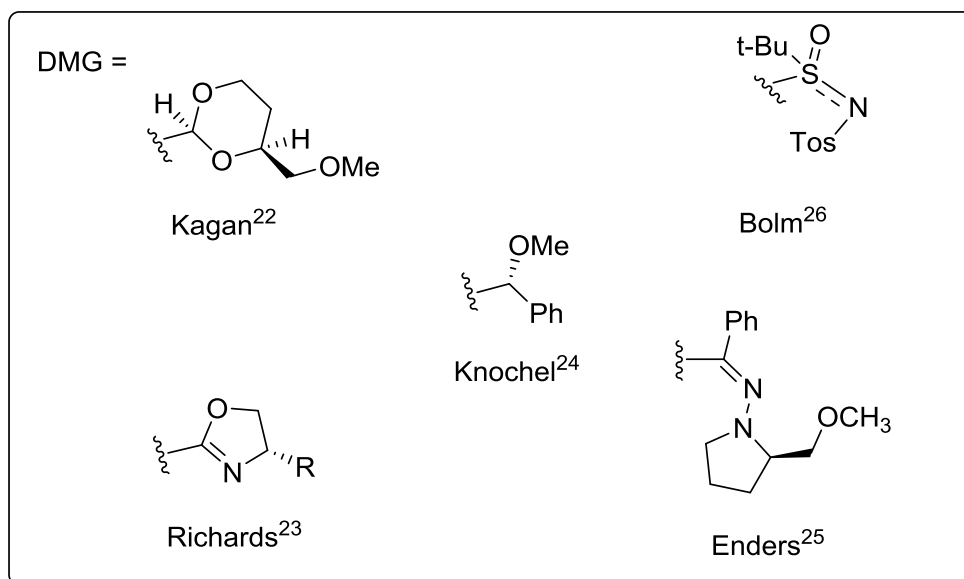
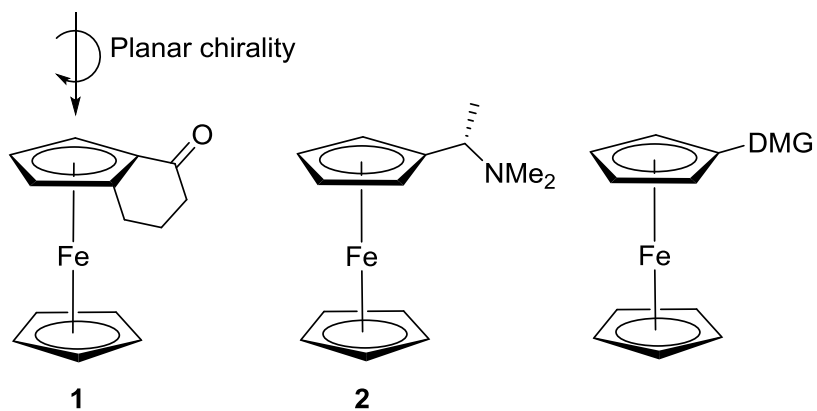
In 1951, a new era of organometallic chemistry was born with the discovery of ferrocene and the related metal-based “sandwich” compounds. Ferrocene has become a valuable building block for the synthesis of compounds with various properties, because of its high stability, and owing to the efficient synthetic methods established for its modification.[1] Selective functionalization of ferrocene with donor atoms like P, O, S, N, and others, led to the second generation of a useful class of chiral and achiral compounds mainly applied as ligands for transition metals.[2] In particular, these species showed outstanding efficiency in metal-catalyzed contemporary organic reactions.[3-6] Based on the impetus provided by the applications of the diphosphine 1,1'-bis(diphenylphosphino)ferrocene (dppf), the investigations directed towards the synthesis of new ferrocenylphosphines – sterically and electronically modified either at the ferrocenyl backbone or at the phosphorus atoms – are still of fundamental and industrial interest.[6] Many advances in the catalytic use of ferrocenylphosphines in cross-coupling, especially using palladium, emerged involving C–C as well as C–X bond formation (where X = O, N, S, P, halogens, etc.). Accordingly, we provide herein a tutorial review, which after remaining the basic knowledge to enter into the field, incorporates the prominent advances in metal-catalyzed cross-coupling reactions with ferrocenyl phosphines. Because of the enormous extent of this continuously developing field, a drastic selection illustrating concisely the themes was operated.

Chiral ligands play a decisive role in metal-catalyzed asymmetric reactions, where they induce the product's chirality and may provide the desired enantiomeric isomer with high optical purity.[7] Transition-metal catalyzed reactions in homogeneous conditions, often involving chiral phosphine ligands, provided high chiral induction as well as catalytic activity, which have been transferred into industrial scale asymmetric conversions. Different classes of chiral phosphine ligands have been designed and synthesized in the last decades; the metal complexes derived from bisnaphthol-, [8, 9] spirobiindane-, [10] biphenyl-, [11-13] and ferrocenyl-phosphine

ligands are clearly amongst the most numerous and efficient chiral catalysts. Accordingly, various types of essential chiral ferrocenyl phosphine scaffolds and their applications in asymmetric catalysis are known. Important reactions, such as the hydrogenation or hydration of unsaturated organics, have been early on covered in classical surveys by Togni and Hayashi (1995),[1] and Dai and Hou (2010),[14] which discussed the application of ferrocenyl-based phosphine ligands in asymmetric reactions. Notably, the ease with which phosphino groups could be introduced to the ferrocenyl backbone has driven the emergence of new classes of chiral and achiral organophosphines, both useful for metal-catalyzed asymmetric reactions and cross-couplings applications, respectively. Synthetic approaches and respective applications of chiral ferrocenyl phosphine ligands can be found in various reports from Hayashi.[3, 4] Previous reviews, book chapters and articles from Kagan[15], Richards,[16] Knochel,[17] Togni,[1] Ito,[3] Blaser,[18], Zhang,[19] or Lu,[20] describe synthetic applications of selected chiral ferrocenyl ligands in transition-metal catalyzed C–C bond formation.

## 2. Chirality introduced onto the ferrocenyl platform

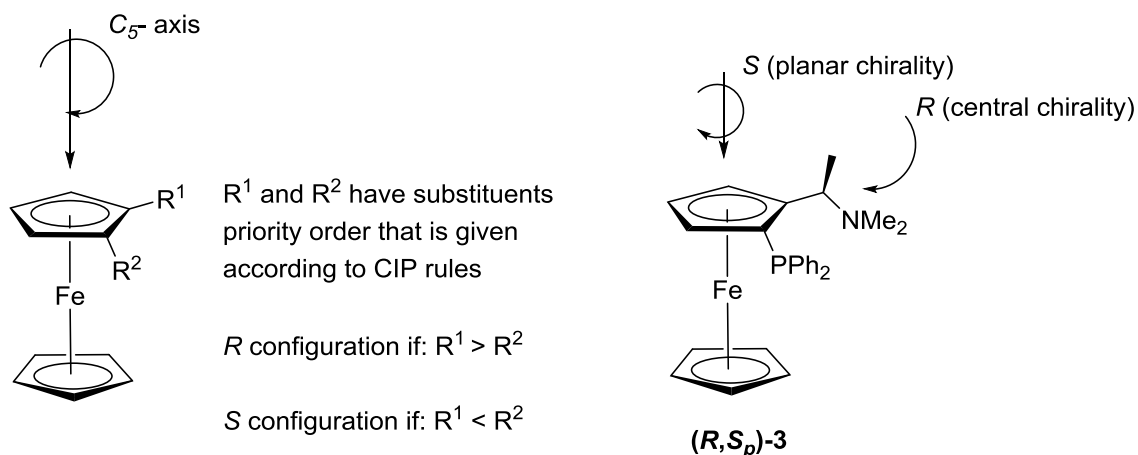
The planar chirality of ferrocene derived ligands is the significant factor that separates it from contemporary axial chiral ligand types, e.g. bis(naphthol), spirobiindane or biphenyl. The stereoselectivity of the catalyst is directly connected to the planar chirality of the ligand; therefore, it has been considered as the key parameter in ferrocene based asymmetric ligand design. The first optically active ferrocene (**1**) with planar chirality was synthesized by Thomson by chemical resolution (Figure 1).[21] Later, the discovery of N,N-dimethylferrocenylethylamine **2**, widely known as Ugi's amine, served as directing metalation group (DMG) in numerous varieties of planar chiral ferrocene ligands. Since then, similar DMGs on the ferrocenyl backbone were reported by many groups and many innovative ferrocene-based asymmetric ligands were produced [19]. Figure 1 depicts the examples for ferrocenyl ligands with different DMGs.[15, 22-26] All these DMG groups facilitate highly selective *ortho*-lithiation, subsequent reaction with electrophile ( $E^+$ ) resulting in diastereoselective substitution of E at a definite position, leading to additional planar chirality. Conversely, Snieckus directly synthesized highly enantioselective planar chiral ferrocenyl ligands by using optically active (–)-sparteine-mediated lithiation.[27]



**Figure 1:** The first optically active ferrocene **1** with planar chirality. Ugi's amine **2** as DMG. Selected examples of ferrocenyl ligands with various directing metalation groups (DMG).

Initially Cahn, Ingold and Prelog (CIP) [28] coined the term “planar chirality” for the cyclophane skeleton; later Schlögl [29] translated the concept to ferrocenes. However, the definition and respective planar chirality of CIP rules does not hold for the ferrocene class. According to Schlögl, the substitution of one cyclopentadienyl ( $C_p$ ) ring with one or two different groups perturb the plane of symmetry and introduce planar chirality. The absolute configuration notation for the ferrocene ligands was assigned by viewing the molecule from the above along the highly substituted  $C_p$  ring  $C_5$ -axis.[29] As shown in Figure 2 the “(R)” notation is assigned if the substituents  $R^1$  and  $R^2$  descend priority (according to CIP rules) in a clockwise arc, and “(S)” stereochemistry notation is given if the same groups descend priority in anti-clockwise

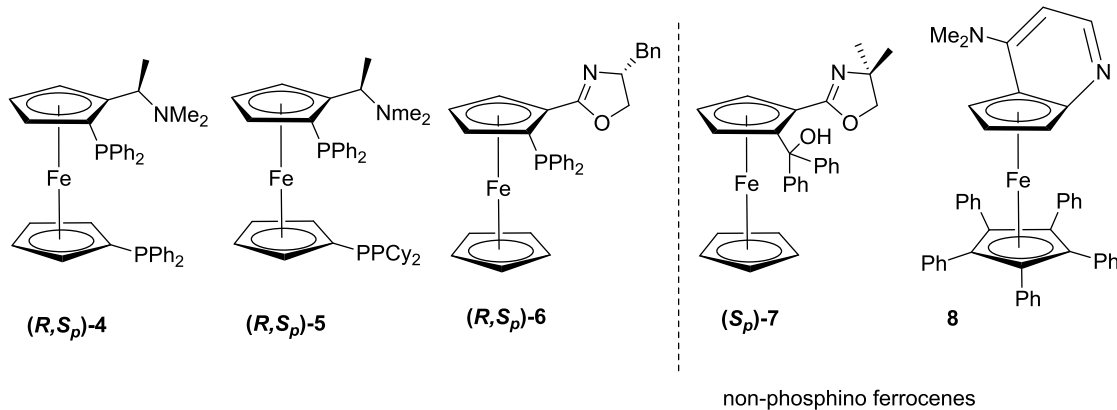
direction.[30] In order to avoid the ambiguity in chirality symbols between central chirality and planar chirality, the subscript of “p” was tagged to planar chirality notations (e.g.,  $R_p$ ,  $S_p$ ).[31] When ferrocenes bear multiple chirality sources, then the nomenclature of priority of the chiral elements follow the trend central>axial>planar (Figure 2). For example, compound **3** nomenclature is given as R (central) followed by  $S_p$  (planar).[32]



**Figure 2:** Assignment of chirality descriptors in ferrocene according to Schögl rules.

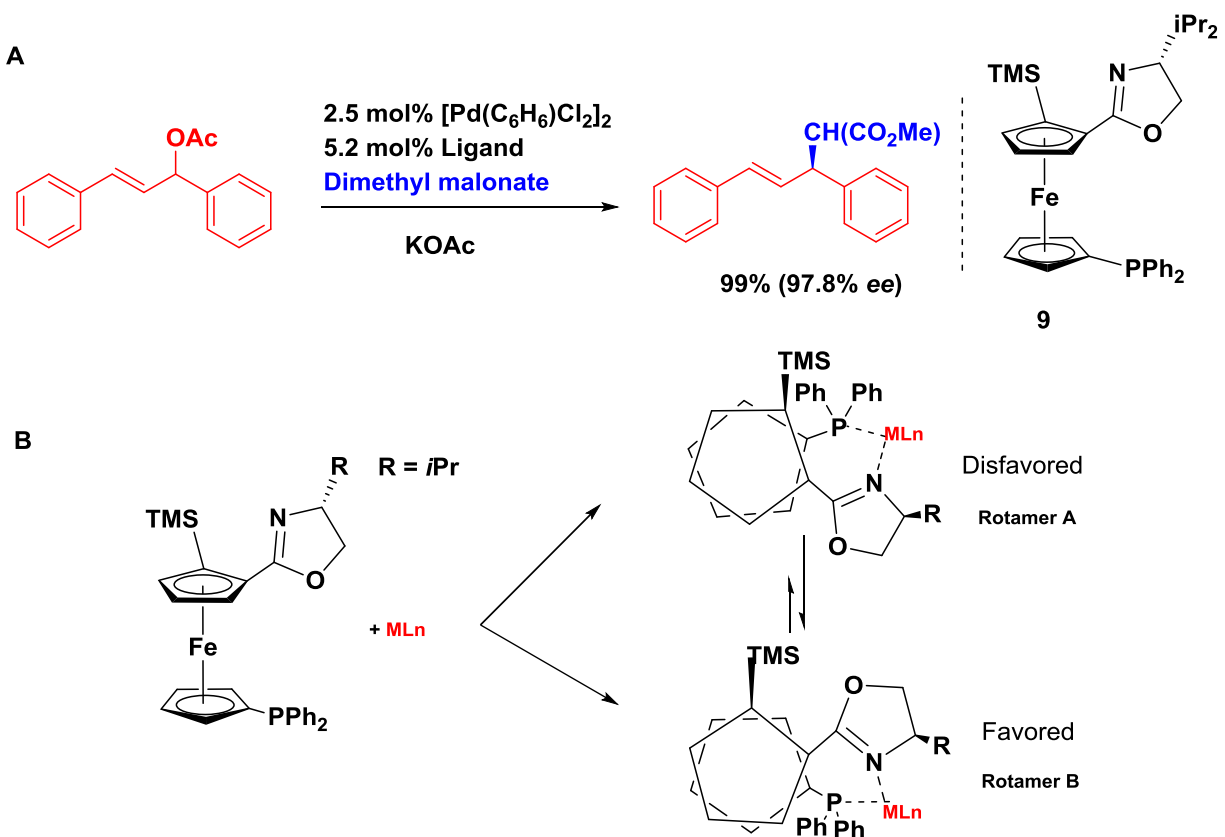
Since planar chiral ferrocenyl ligands can be derived with high diastereoselectivity from Ugi's amine and other DMG-substituted ferrocenes, the applications of the resulting ligands in asymmetric coupling reactions have been developed from fundamental [1, 33, 34] and industrial perspectives.[18, 35] Examples of chiral mono- or bis(phosphino)ferrocene having both planar and central chirality are depicted in Figure 3 (left). These ligands, because of their dual chirality, have been at the origin of noticeably high enantioselectivity performances.[21]





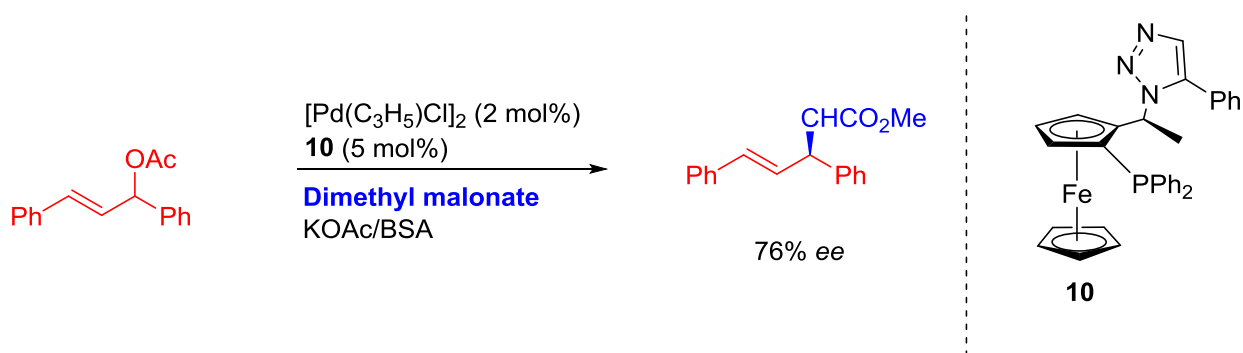
**Figure 3:** Mono- and bis(phosphino)ferrocene ligands with central and planar chirality (**4-6**, left), and ferrocene-based hydroxyloxazoline and azaferrocene-DMAP with only planar chirality and no phosphino group (**7, 8**, right).

For instance, the ligands (*R,S<sub>p</sub>*)-**4**, (*R,S<sub>p</sub>*)-**5** and (*R,S<sub>p</sub>*)-**6** with both central and planar chirality yielded the final products, from palladium-catalyzed allylic substitutions for instance, in good enantiomeric excess (ee), and the maximum diastereo- and enantioselectivity were obtained when the absolute configurations of planar chirality and central chirality are opposite.[5, 36-38] Conversely, some planar chiral ferrocene-based hydroxyloxazoline (*S<sub>p</sub>*-**7**, Figure 3, right), without phosphino groups and having no central chirality, led to a significant drop in enantiomeric excess.[39, 40] However, other non-phosphinoferrocene ligands, like the planar chiral azaferrocene-derivatives **8**, were found efficient in asymmetric catalysis.[41] Thus, a correlation between the type of chirality of the backbone and the end-product's enantioselectivity cannot be generalized. Nevertheless, the effect of the ferrocenyl ligand's planar chirality on the stereoselective outcome was illustrated with the planar plus central chiral P,N-oxazoline-ferrocenyl phosphine **9** (Scheme 1).[42] Ferrocene **9** promoted more than 90% ee in the palladium catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate (Scheme 1A).[42] The multiple chirality (central, planar and axial) of the palladium-coordinated ligand was analyzed via two rotamers **A** and **B**. The rotamer **A** formation is sterically disfavored regarding rotamer **B** (Scheme 1B).[43] In this example, the structural role of combined chirality is well-illustrated.



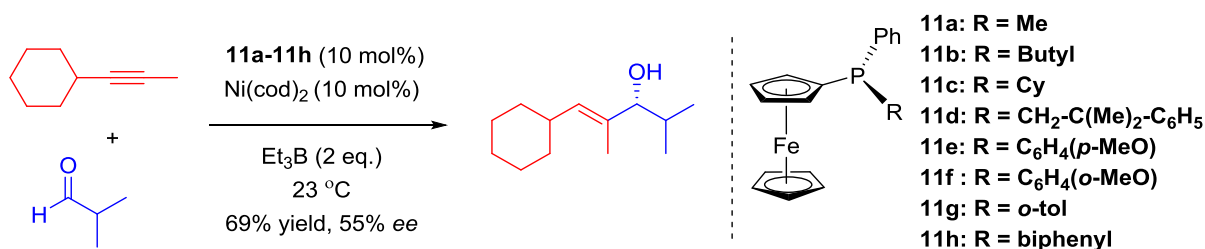
**Scheme 1:** Part A. Ferrocenyl phosphine **9**-promoted asymmetric palladium-catalyzed allylic alkylation. Part B. Axial chirality in metal coordinated 1,1'-disubstituted ferrocenyl-based ligand.

In another example, Satoshi and co-workers synthesized chiral triazole ferrocenyl-1,5-phosphine ligand **10** via click chemistry, and employed it in palladium-catalyzed allylic alkylation reactions (Scheme 2).[44] Ligand **10** achieved an enantioselectivity of 76% ee.[44]



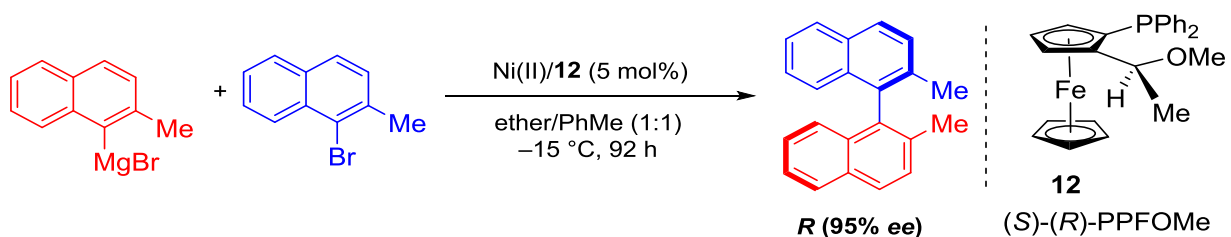
**Scheme 2:** Asymmetric catalysis by chiral triazole 1,5-ferrocenyl phosphine **10**.

Monophosphino P-chiral ferrocenyl ligands were synthesized and identified to be relevant for varied metal-catalyzed asymmetric carbon-carbon bond formation beyond palladium chemistry.[45] Chiral allylic alcohols were prepared with regio- and enantioselectivity of 55% ee via reductive coupling between aldehyde and alkyne in the presence of Ni(0) and monophosphino P-chiral ferrocenyl ligands **11a-h** (Scheme 3).[45] Simultaneously, these novel P-chiral ligands were found to be useful in other asymmetric catalytic conversions such as, dialkylzinc additions to aldehydes, allylic alkylations, and  $\alpha$ -isocyanocarboxylate aldol reactions.[45]



**Scheme 3:** Ni-catalyzed asymmetric synthesis of chiral alcohols through reductive coupling of aldehyde and alkynes by employing P-chiral ferrocenyl monophosphines.

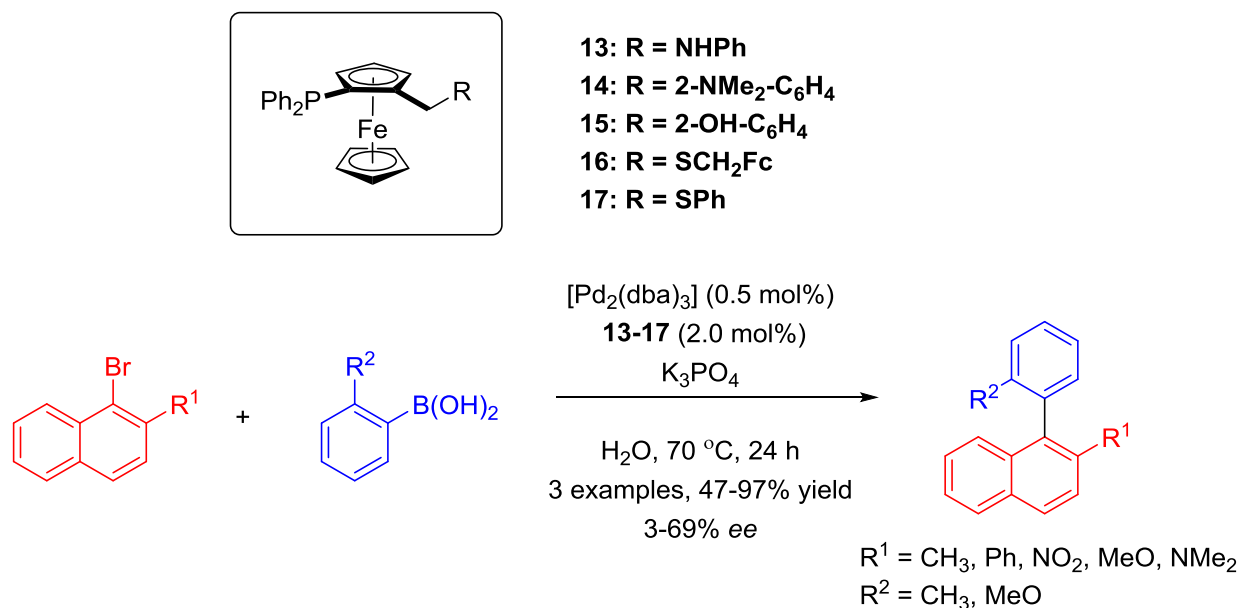
Optically active 1,1'-binaphthyl derivatives were synthesized by reacting (2-methyl-1-naphthyl)magnesium bromide with 2-methyl-1-naphthylbromide in the presence of 4 mol% of nickel(II) complex stabilized by the chiral ferrocenylphosphine **12** at -15 °C. This Kumada-Corriu asymmetric cross-coupling for the construction of bis-naphthyl structures provided the expected derivatives with high enantioselectivity up to 95% ee (Scheme 4).[3]



**Scheme 4:** Asymmetric C-C cross coupling in the presence of central-planar chiral mono(phosphino)ferrocene **12**.

In C-C bond formation by cross-coupling reactions, 1,2-disubstituted planar chiral ferrocenyl phosphines **13-17** were used in the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction to

produce highly hindered biaryl with atropisomeric features (Scheme 5).[46] In earlier reports, a maximum ee of 54% from a catalytic loading of Pd at 2 mol% was reported for the synthesis of analogous hindered biaryl.[47] The use of ferrocenyl phosphines **13-17** significantly improved the production of biaryl up to 97% isolated yield with an ee up to 69%. Notably, low catalytic loadings of 0.5 to 1.0 mol% were also effective in catalyzing this cross-coupling. The series of 1-(diphenylphosphino) ferrocene **13-17**, bearing methylene-bridged substitutions at position-2 of the cyclopentadienyl ring were prepared from their phosphine sulfide (S=P<sup>V</sup>) precursors via desulfurization/reduction with P(NMe<sub>2</sub>)<sub>3</sub>. Ferrocenylphosphine **14** with *o*-substituted NMe<sub>2</sub>-benzyl has shown the best catalytic conversion/enantioselectivity for the biaryl synthesis, with selectivity results ranging from 3 to 69% ee. The chirality transfer was attributed to the ferrocene-backbone planar chirality.[48]



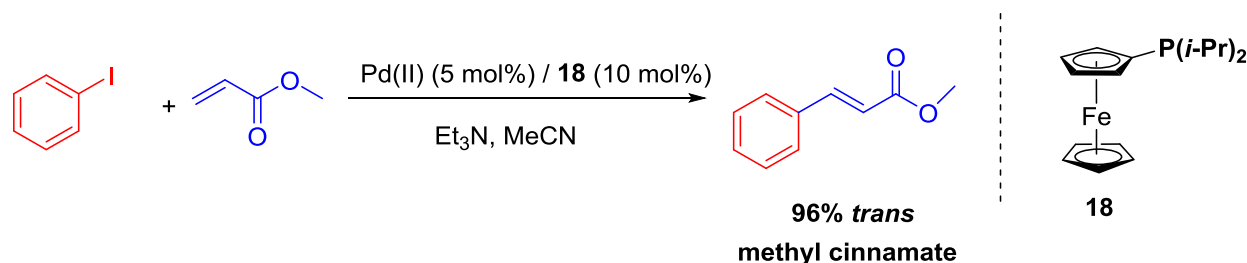
**Scheme 5:** Synthesis of biaryl via palladium-catalyzed Suzuki–Miyaura cross-coupling using the planar-chiral ferrocenyl phosphines **13-17**.

Further applications of chiral ferrocenyl phosphines have been reviewed in details and notably include enantioselective versions of asymmetric cross-couplings, aldol condensations, Morita-Baylis-Hillman reactions, allylic alkylations, hydrogenation and annulation reactions, *etc.*[ 16, 19, 20, 49, 50]

### 3. Monophosphine ligands with ferrocenyl skeleton

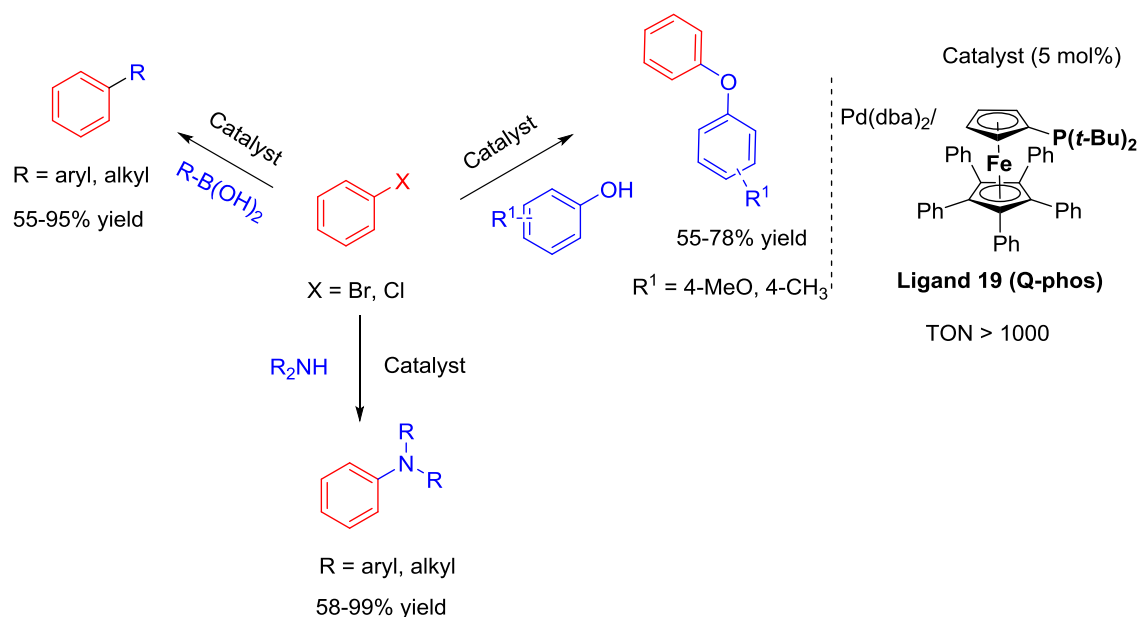
#### 3.1. Mono(phosphino)ferrocenes in carbon–carbon bond formation

Mono(phosphino)ferrocene ligands are widely applied in homogeneous catalysis for the synthesis of achiral cross-coupling products.[2, 50, 51, 52] Many examples have been reported, in which mono(phosphino)ferrocenes are successfully employed in C–C cross-coupling reactions with various transition metals, notably palladium. For instance, the bis(isopropyl)phosphine (P(*i*-Pr)<sub>2</sub>)-substituted ferrocenyl phosphine **18** provided in palladium-catalyzed Mizoroki–Heck coupling *trans*-methyl cinnamate in 96% isolated yields (Scheme 6).[53]



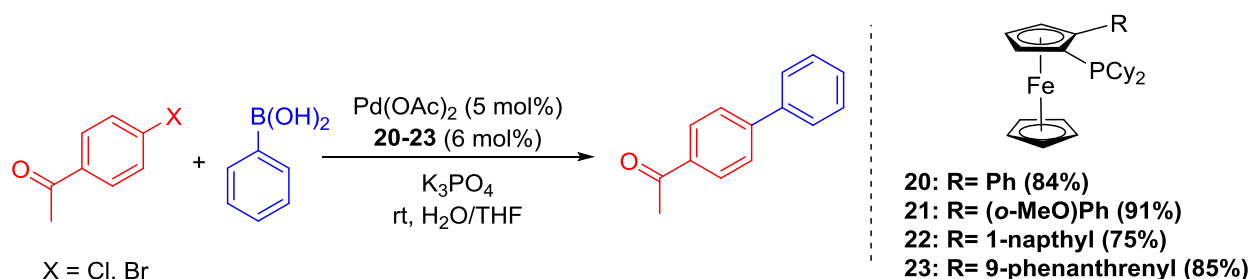
**Scheme 6:** Pd(II)-catalyzed Mizoroki–Heck cross-coupling using the ferrocenyl monophosphine **18**.

Di-*tert*-butylphosphinopentaphenylferrocenyl **19** (Scheme 7), named Q-phos, has been employed in Suzuki–Miyaura reactions between haloarene and primary alkylboronate ester partners. The cross-couplings of activated aryl halides extended to amine, phenol, and boronic acid substrates was achieved with TONs (turnover numbers) beyond 1000 (Scheme 7).[54] Palladium(0) complexes of **19**, because of its very protective steric hindrance, were found to exhibit remarkable air stability in the solid state, which possibly extend to solution conditions and explains the TOF obtained from 0.1 mol% catalyst employed.[54]



**Scheme 7:** C–C, C–N, and C–O palladium-catalyzed cross-coupling reactions using monophosphine **19**.

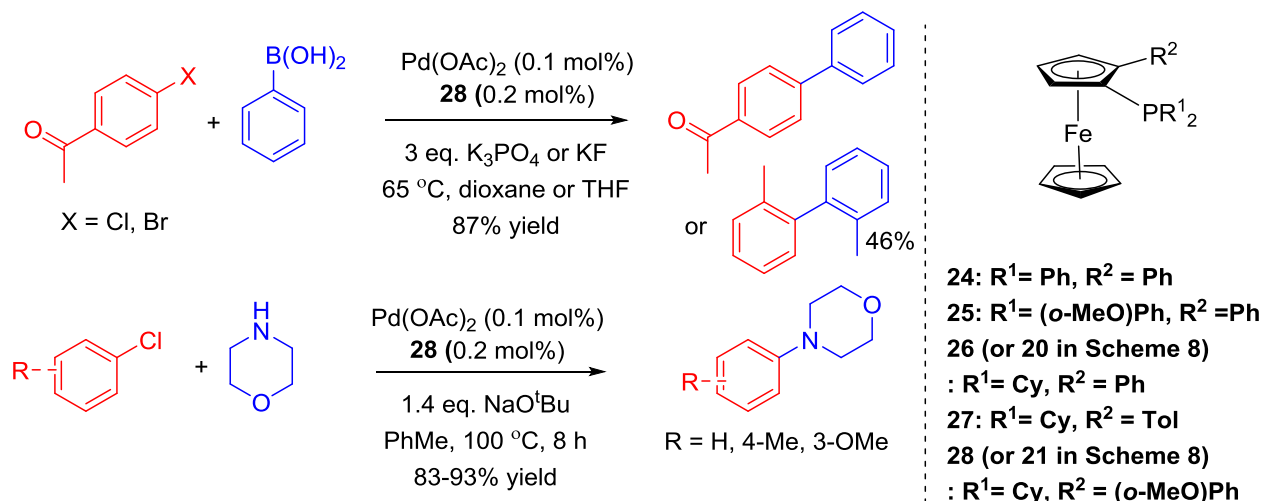
Johannsen, also reported the air-stability for aryl-mono(phosphino)ferrocenes (aryl-MOPFs) **20-23** (Scheme 8).[47] The catalyst derived from Pd(OAc)<sub>2</sub> and **21** efficiently activated the C–Cl bond in both electron-rich and electron-poor aryl chlorides at room temperature. The employment of these mono(phosphino)ferrocenes for the synthesis of optically pure 2,2'-dimethyl binaphthyl via Suzuki-Miyaura coupling resulted, as above mentioned, in 54% ee of the *R* isomer.[49]



**Scheme 8:** Pd-catalyzed Suzuki-Miyaura coupling using monophosphines **20-23**.

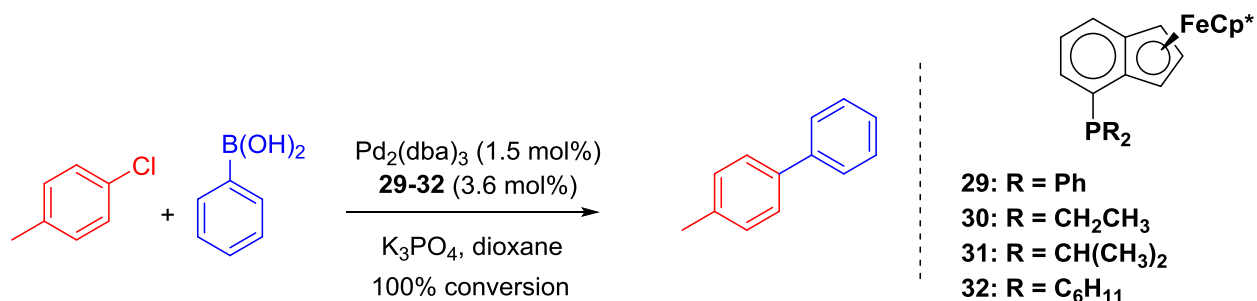
*o*-Arylated mono(phosphino)ferrocenes **24-28** (Scheme 9) were prepared as electron-donating ligands for the Pd-catalyzed arylation using aryl chlorides. Fairly low catalyst loadings (0.1 mol%), were employed in the synthesis of bis-*o*-substituted biaryl.[55] The palladium complexes

stabilized by **28** were also effective in the Buchwald-Hartwig catalytic amination of aryl chlorides with morpholine at low palladium loadings of 0.1 mol%, and furnished the coupled products in more than 80% isolated yields (Scheme 9).[55]



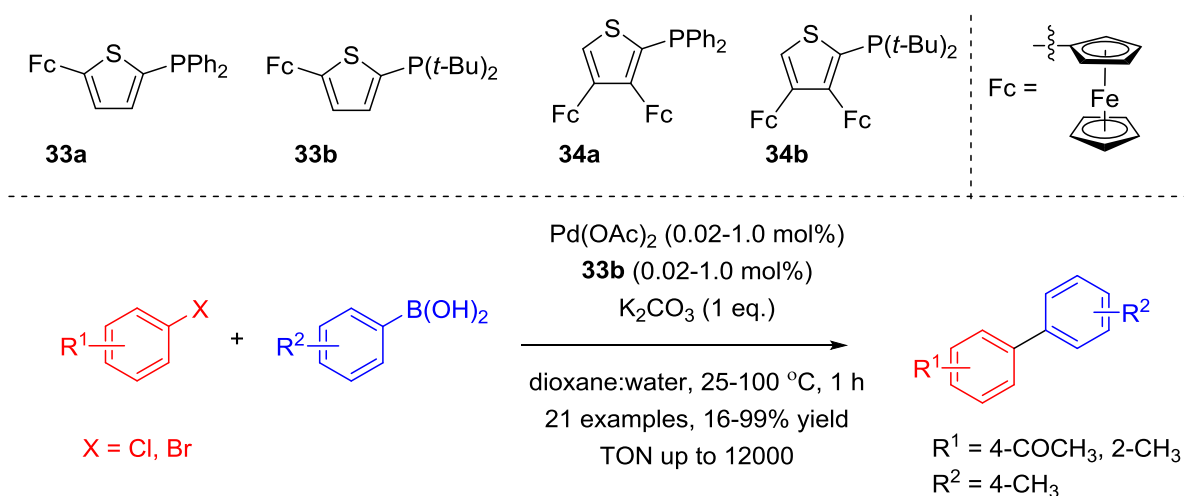
**Scheme 9:** Suzuki-Miyaura coupling of aryl bromides and amination of aryl chlorides in the presence of ligands **24-28**.

The (benzo)ferrocenyl phosphines **29-32** (Scheme 10) are also air-stable mono(phosphino)ferrocene ligands. Compound **32** provided the highest catalytic performance in the Suzuki-Miyaura coupling of aryl halides, facilitating conversions with quantitative isolated yields (Scheme 10). Some highly hindered biaryl compounds could be obtained in moderate to excellent yields in the presence of  $\text{Pd}_2(\text{dba})_3$  and **32** in dioxane.[56]



**Scheme 10:** Suzuki-Miyaura coupling catalyzed by novel (benzo)ferrocenyl phosphines **29-32** and Pd.

Phosphine substituted heterocycles, like thienyl phosphines, are recognized as ligands for transition metals: 2-(3-ferrocenylthienyl)Phosphines of the formula 2-PR<sub>2</sub>-3-Fc-C<sub>4</sub>H<sub>2</sub>S (R= Ph, **33a**; R= *t*-Bu, **33b**; Fc= ferrocene) and bis-ferrocenyl ligands **34a-b** were prepared from 3-ferrocenylthiophene.[57] These compounds combined with palladium in Suzuki-Miyaura coupling reactions of aryl bromides and chlorides with arylboronic acids in 1,4-dioxane:water at 100 °C, in the presence of cheap sodium carbonate, achieved very efficient cross-couplings (Scheme 11).[57] The highly  $\sigma$ -donating – P(*t*-Bu)<sub>2</sub> functionalized ferrocenyl thiophene derivative achieved the best conversions with electron-rich or electron-poor aryl bromides. The low catalytic loadings of 0.02 to 0.05 mol% of [Pd/**33b**] resulted in remarkable TONs, i.e. up to 12,000 with electron-deficient aryl bromides.

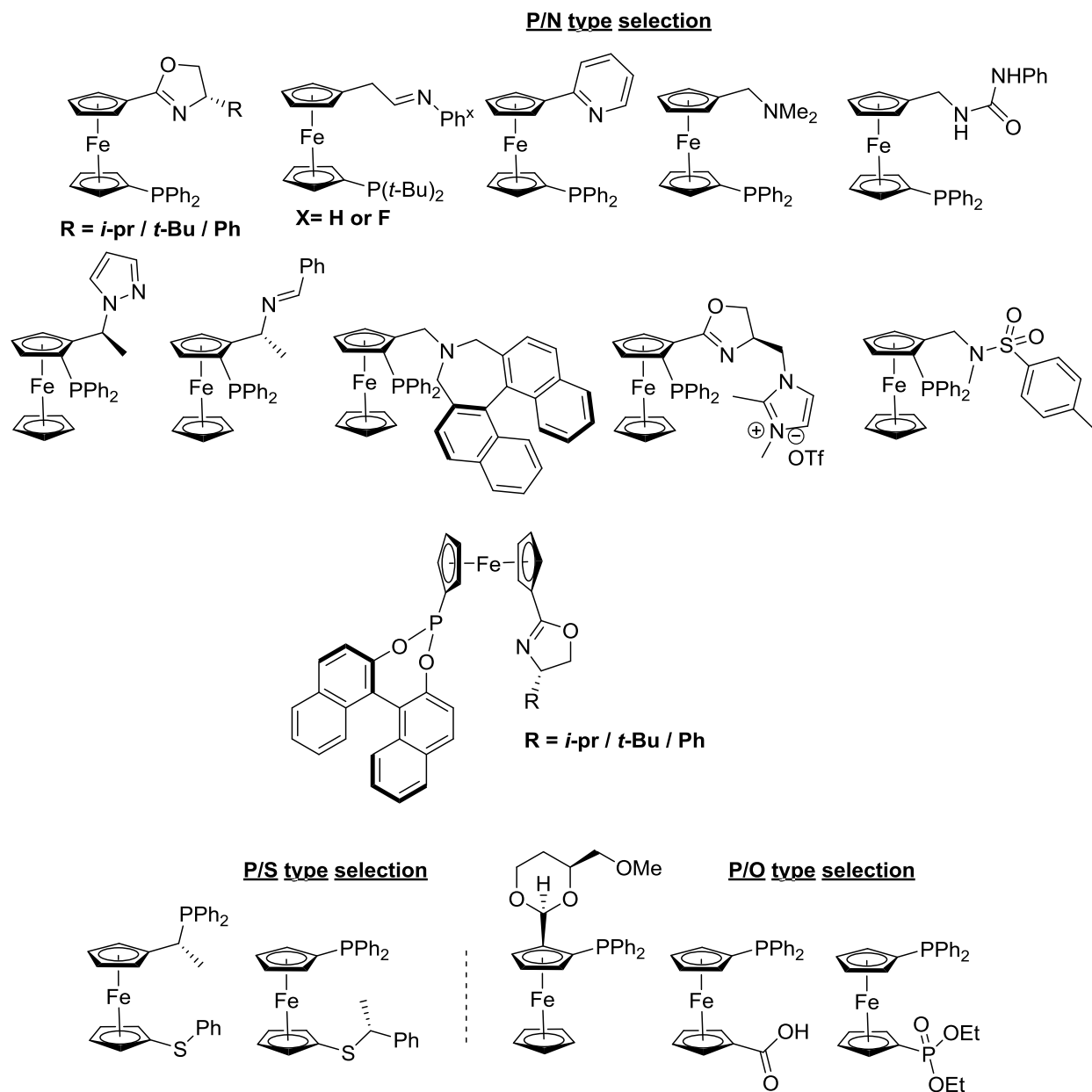


**Scheme 11:** Synthesis of biaryl derivatives employing (ferrocenylthienyl)phosphines **33-34** in Suzuki-Miyaura C–C couplings.

### 3.2. (P, N)–, (P, O)–and (P, S)–mono(phosphino)ferrocene ligands for metal catalyzed cross-coupling reactions: achiral and chiral approaches

Figure 4 illustrates typical mono(phosphino)ferrocenes bearing (P, N)–, (P, O)– or (P, S)–substitutions. These compounds were successfully employed as ligands in many achiral (and sometimes in chiral version) transition metal-catalyzed carbon-carbon bond formation processes.

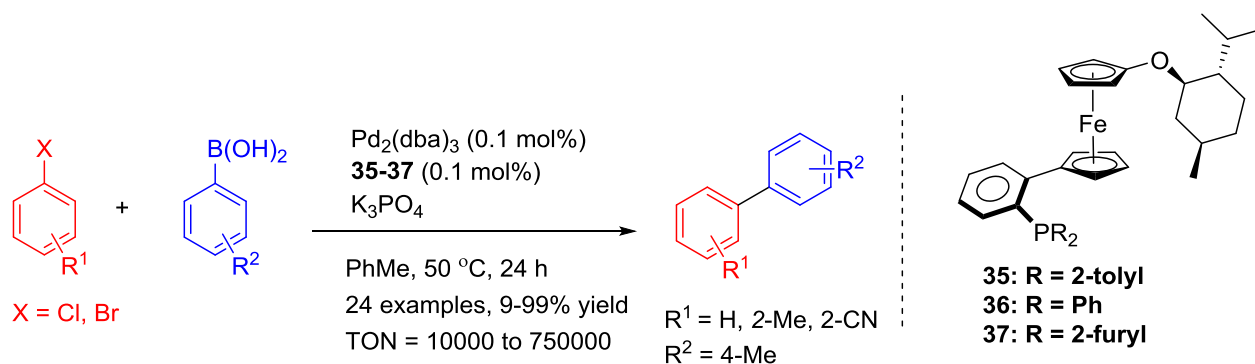




**Figure 4:** Selection of typical mono(phosphino) (P, N)-, (P, O)-, and (P,S)-ferrocenes used as ligands in coupling reactions.

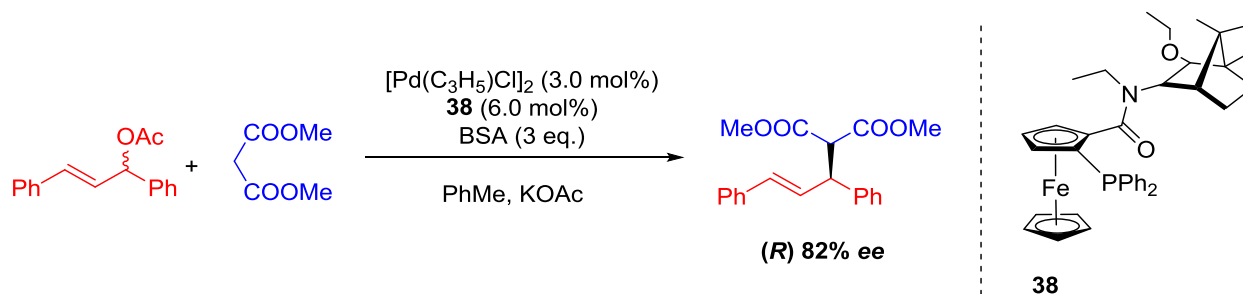
Monophosphines bearing heteroatoms (N, O, and S) with 1,2- and 1,1'-substitutions are efficient chelating ligands.[2, 52, 58, 59] Their differences in donor atoms may create an electronic dissymmetry around the coordinated central metal. Hybrid chiral P,O-ferrocenes were successfully employed in the Suzuki-Miyaura coupling reaction for the synthesis of sterically demanding biaryl (Scheme 12).[60] (P, O)-ferrocene ligands **35-37** combined efficiently with  $[Pd_2(dba)_3]$  for coupling unactivated aryl bromides with aromatic boronic acids

at low catalytic loadings ( $10^{-4}$  mol%). A TON of 750,000 for the coupling of 2-bromotoluene and a TON of 10,000 for the conversion of 2-chlorobenzonitrile were reported, while yielding the coupled products almost quantitatively (>96%) (Scheme 12).[60, 61] (P, O)-type mono(phosphino)ferrocenes efficiently activated bulky *o*-substituted chloroarenes, but *o*-substituted aromatic boronic acids resulted in only modest conversion. Apparently, the menthoxy moiety on the second Cp ring significantly enhances the catalytic activity in Suzuki-Miyaura coupling. The improvement in conversion was attributed to weak interactions existing between the palladium center and the menthoxy unit.[60] The monophosphino ferrocenes **35-37** despite their central chirality at menthyl group, failed in the challenging atroposelective Suzuki-Miyaura coupling of biphenyls using 1-bromo-2-methylnaphthalene and 2-methoxyphenyl boronic acid.



**Scheme 12:** Hybrid (P, O)-mono(phosphino)ferrocene **35-37** in Suzuki-Miyaura C–C couplings.

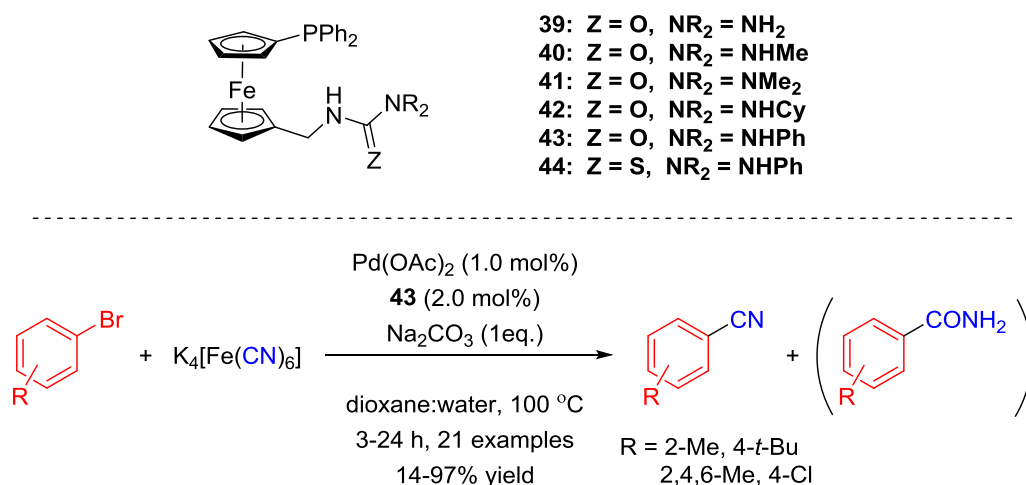
(P, heteroatom)-mono(phosphino)ferrocene ligands have gained also much importance in allylic alkylations. A series of planar chiral ferrocene and ferrocenophane-based amidophosphine ligands were prepared, and their catalytic performances were investigated in the palladium-catalyzed asymmetric allylic alkylation of racemic (E)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 13).[62]



**Scheme 13:** Chiral P,N-ferrocene based amidophosphine **38** used as ligand in Pd-catalyzed asymmetric allylic alkylations.

Catalytic loadings of 3.0 mol%  $[\text{Pd}(\text{C}_3\text{H}_5)_2\text{Cl}]_2$  and 6.0 mol% of monophosphino-ferrocene **38** in toluene efficiently coupled the allylic precursors with nucleophilic species (Scheme 13). Among the tested amidophosphine ligands, **38** favors the formation of the (*R*)-enantiomer up to 82% ee.[62]

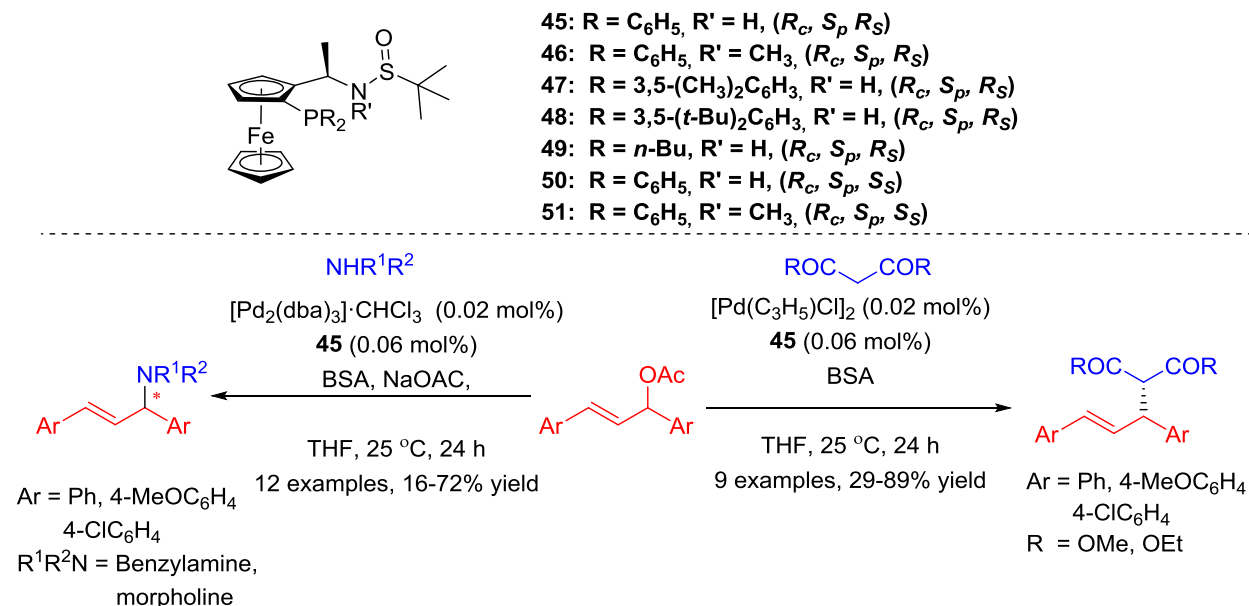
Ferrocenyl methyl-substituted urea derivatives were extensively studied in electrochemical sensing mechanisms.[63] Štěpnička and co-workers developed a series of 1'-(diphenylphosphino)-ferrocenes linked to various scaffolds of urea via a methylene spacer.[64] This novel class of ligands **39-44** was accessed either by addition of 1'-(diphenylphosphino)-aminoferrocene to isocyanates or by direct reactions of 1'-(diphenylphosphino)-carboxaldehyde.



**Scheme 14:** (P, N)-type(phosphino)ferrocene urea **39-44** in the Pd-catalyzed cyanation of aryl bromides.

The aforementioned scaffolds attached by soft donor (phosphine) to electron-rich metal centers, while the hydrophilic urea tags remained free to potentially engage in hydrogen bonding interactions.[52] The Pd-catalyst derived from **43** and Pd(OAc)<sub>2</sub> is active in the cyanation of aryl bromides with lesser toxic cyanide K<sub>4</sub>[Fe(CN)<sub>6</sub>] (up to 97% substitution yield, Scheme 14). Electron-rich bromoarenes produced moderate to excellent yields, but unactivated bromoarenes and amine substituted bromoarenes displayed moderate reactivity only, presumably due to the subsequent hydrolysis step induced by the Na<sub>2</sub>CO<sub>3</sub> base or the metal-scavenging nature of the amine, respectively.[65, 66]

Monophosphino-*tert*-butyl sulfonamide ferrocene ligands **45-51** were employed in enantioselective C–C and C–N bond formations (Scheme 15).



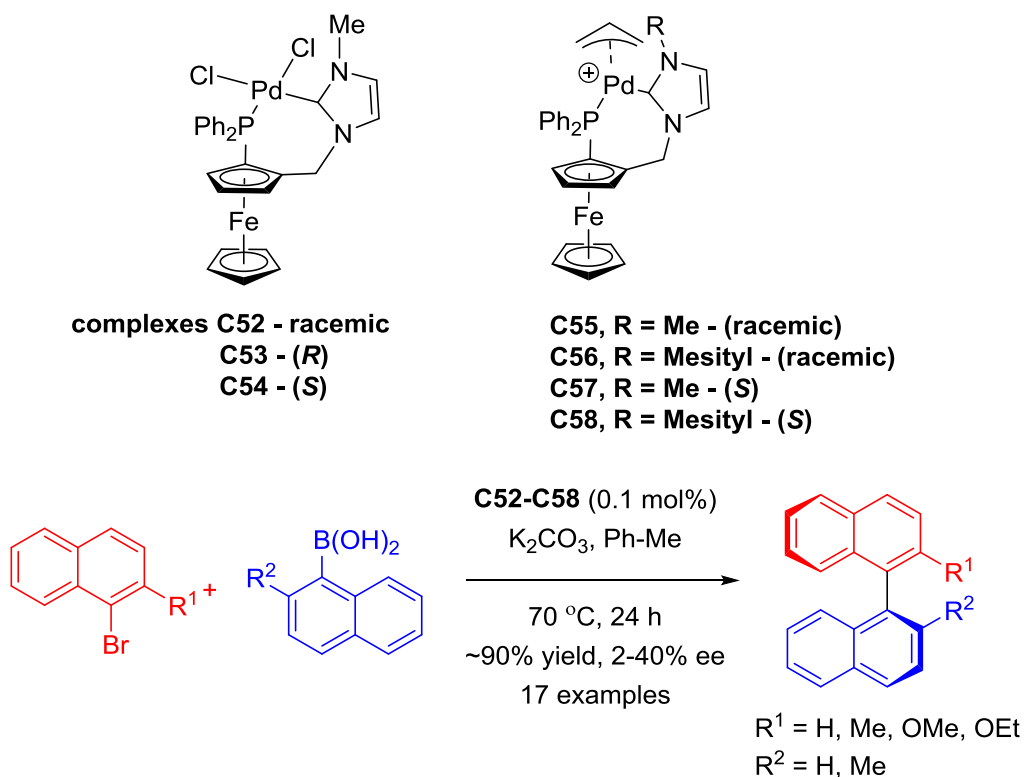
**Scheme 15:** (P, N)-ferrocene-based phosphine-*tert*-butyl sulfonamide **45-51** used in Pd-catalyzed asymmetric allylic substitution.

These compounds were diastereoselectively synthesized from (*R*)-Ugi's amine via lithiation followed by reaction with diarylphosphine chlorides. After subsequent *trans*-amination with ammonia, a final sulfinylation using enantiopure *tert*-butanethiosulfinate gave the desired compounds.[67] The palladium catalyst derived from ferrocenylphosphine **45** achieved the best conversions in asymmetric allylic substitution with dialkyl malonate and secondary amines. Highest enantioselectivity in both allylic C–C and C–N coupling reactions was obtained in the presence of N, O-bis(trimethylsilyl)acetamide as base in THF. The catalyst was also found to be

highly efficient in asymmetric allylic alkylations of challenging unhindered cyclic alkenes, with optical purity of products reaching up to 91% ee.

### 3.3. Mono(phosphino)ferrocene ligands bearing NHC-groups applied in cross-coupling reactions

N-heterocyclic carbenes (NHC) are highly  $\sigma$ -donating compounds with a very good potential of steric/electronic/geometric alteration. Accordingly, they are frequently employed in organometallic catalysis, including in the ubiquitous Suzuki-Miyaura cross-couplings and some chiral version.[68, 69] Thus, for instance, homochiral hybrid systems bearing both a phosphine and a NHC group on the same ring of a ferrocenyl platform have been synthesized. The coordination of the compounds **52-58** (Scheme 16) to two different palladium precursors, resulted in the formation of air-stable neutral and cationic complexes **C52-C58** (Scheme 16).[70]



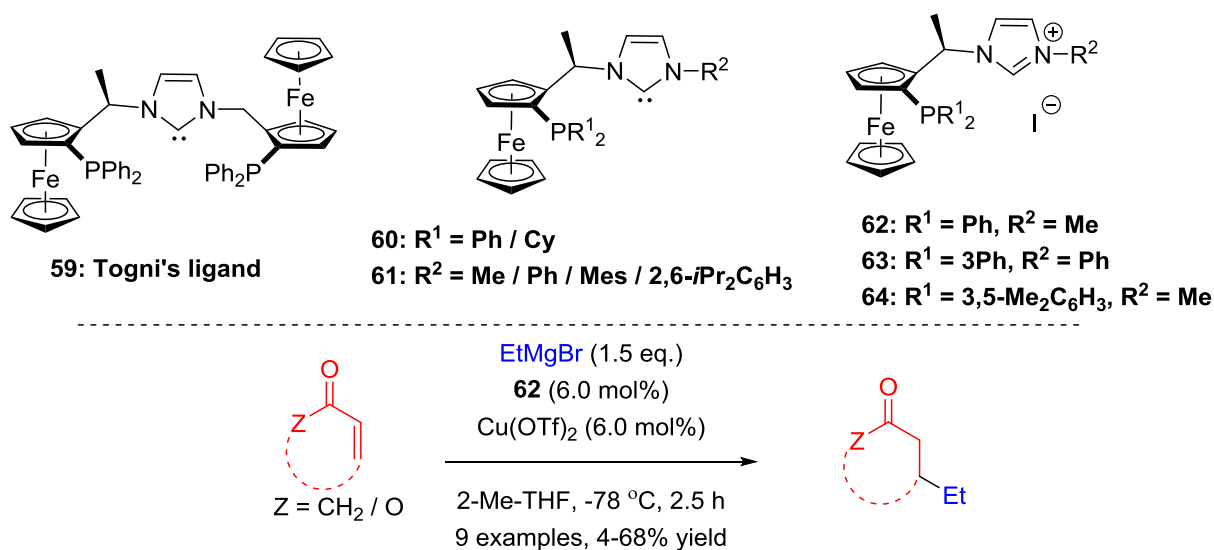
**Scheme 16:** Pd-complexes **C52-C58** for planar chiral ferrocenyl phosphine-NHC for the asymmetric Suzuki-Miyaura reaction.

In the palladium-catalyzed Suzuki-Miyaura reaction targeting the asymmetric synthesis of optically active *o*-substituted bisnaphthalene, the neutral complexes **C52-C54** were more useful

than their cationic congeners **C55-C58** (Scheme 16). Presumably, the increase of the steric environment around the palladium center in the cations may have a detrimental effect on the overall conversion and results in poorer enantioselectivity below 40% ee.

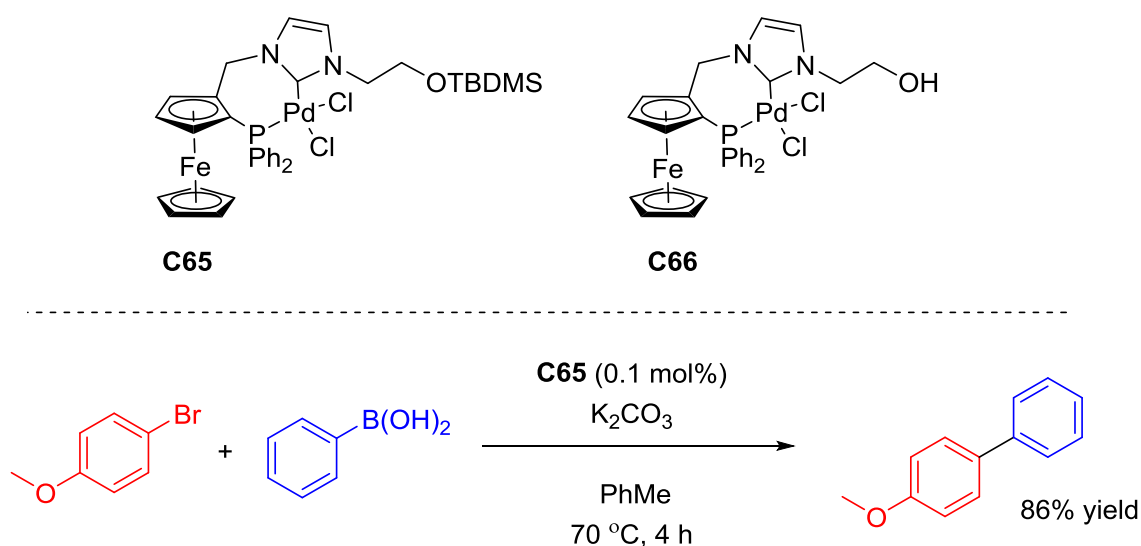
The conjugated addition of carbon nucleophiles to  $\alpha,\beta$ -unsaturated ketones is a methodology commonly used for C–C bond formation,[71-73] and copper-catalyzed asymmetric approaches are efficient tools in this respect.[71] The studies of Togni and coworkers were initially based on original tridentate phosphine-carbene-ferrocene ligands (Scheme 17, top),[74] and further attracted the interest in the use of (phosphino)ferrocene-NHC hybrids in asymmetric catalysis.[75] The works of Seo *et al.*,[76] Yu *et al.*,[77] Visentin and Togni,[78] settled various imidazolium/ferrocene and NHC-ferrocene derivatives (Scheme 17), for notably investigating their performance in asymmetric Suzuki-Miyaura cross-couplings, allylic amination, and hydrogenation reactions. Accordingly, their chelating coordination, notably to palladium, iridium and rhodium, was amply illustrated.

For instance, **62** (Scheme 17, bottom) was used for the asymmetric 1,4-conjugative addition of carbon nucleophile Grignard reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds and lactones.[79] The Cu-mono(phosphino)ferrocene catalyst derived from **62** in 6.0 mol% loading offered good conversion to 1,4-addition products with mostly high regioselectivity but moderate enantioselectivity (in general below 60:40) presumably because of ring opening side reactions.



**Scheme 17:** Typical (phosphino)ferrocene-NHC (top) and application in the copper-catalyzed asymmetric 1,4-additions of Grignard reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds (bottom).

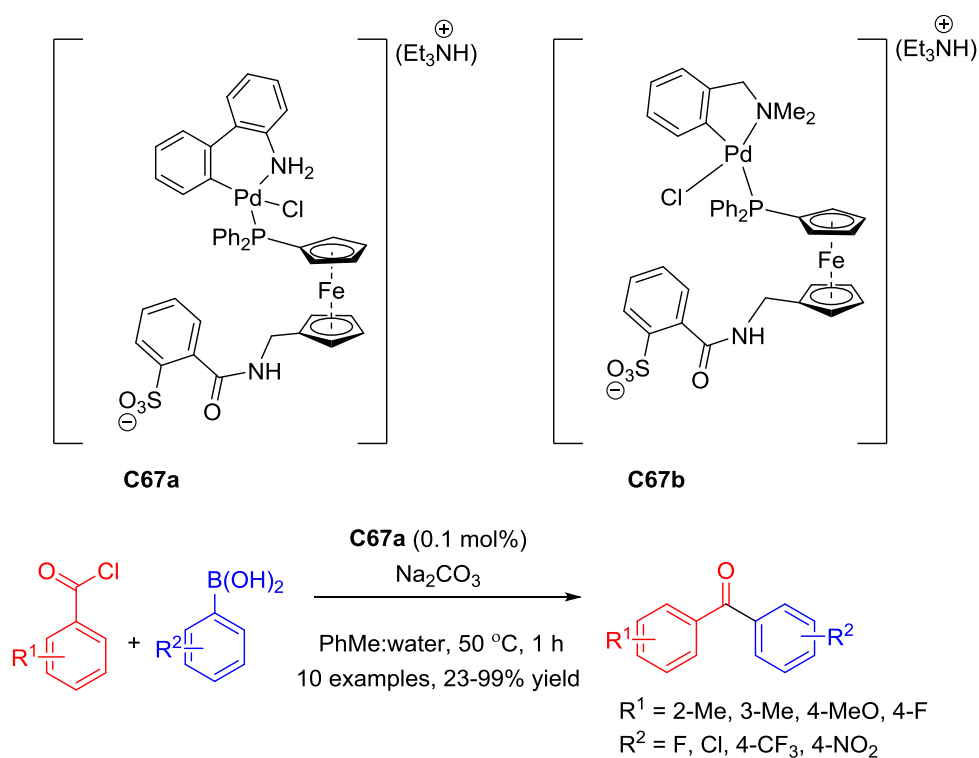
Chiral palladium complexes bearing bidentate phosphine-N-heterocyclic carbenes (NHC) were employed in the synthesis of sterically hindered biaryl via Suzuki-Miyaura coupling.[70,80] Ferrocenylphosphine-NHC ligands **65** and **66** were synthesized and coordinated with  $[\text{PdCl}_2(\text{MeCN})_2]$ , resulting in the complexes **C65** and **C66** (Scheme 18). The complex **C65** bears an ethylene chain with a terminal oxygen protected with the *tert*-butyldimethylsilyl group (TBDMS), which has a beneficial effect on the catalytic outcome compared to complex **C66** holding a free hydroxyl. However, complex **C66** has a reduced solubility in organic solvents, which limits its catalytic use in those conditions. The coupling of 1-bromo-2-methyl naphthalene with naphthyl boronic acid in the presence of 0.5 mol% of complex **C65** at 40 °C for 24 h resulted in biaryl derivative formation in 46% isolated yield. The kinetics of the Suzuki-Miyaura coupling of aryl bromides with aryl boronic acids under the applied catalytic conditions has shown a high dependency on the water presence in the reaction. This protocol compares well with those using some non-ferrocenic purely NHC ligands.[81, 82] Using analogous ferrocenyl phosphane-(benz)imidazol-2-ylidene ligands in enantiomerically pure form, asymmetric Suzuki-Miyaura reaction between 2-substituted  $\alpha$ -naphthyl bromides and  $\alpha$ -naphthylboronic acid has also been reported, the influence of the NHC structure on enantioselectivity was not entirely predictable and the best e.e. of 46% was obtained.[83]



**Scheme 18:** Mono(phosphino)ferrocene-NHC appended ligands for Pd-complexes **C65** and **C66** employed in the biaryl synthesis via Suzuki-Miyaura coupling.

### 3.4. Mono(phosphino)ferrocenes bearing polar functional groups (hydrophilic) and their applications in cross-coupling reactions

The group of Štěpnička prepared water-soluble mono(phosphino)ferrocene amidosulfonates via amide coupling with 1'-(diphenylphosphino)ferrocene-1-carboxylic acid.[84] These polar ligands were also synthesized via amidation of (phosphino)ferrocene amine with 2-sulfobenzoic anhydride.[85] Compound **67** (Scheme 19) featured a  $^{31}\text{P}$  NMR resonance at  $-15.8$  ppm along with characteristic  $^{13}\text{C}$  NMR signals of  $\text{C}=\text{O}$  at  $168.6$  ppm. The ligand were reacted with two different Pd(II) precursors and complexes **C67a** and **C67b** were obtained quantitatively. The P-donor coordination was confirmed by  $^{31}\text{P}$  NMR shifts to  $48.9$  and  $46.1$  ppm, respectively.



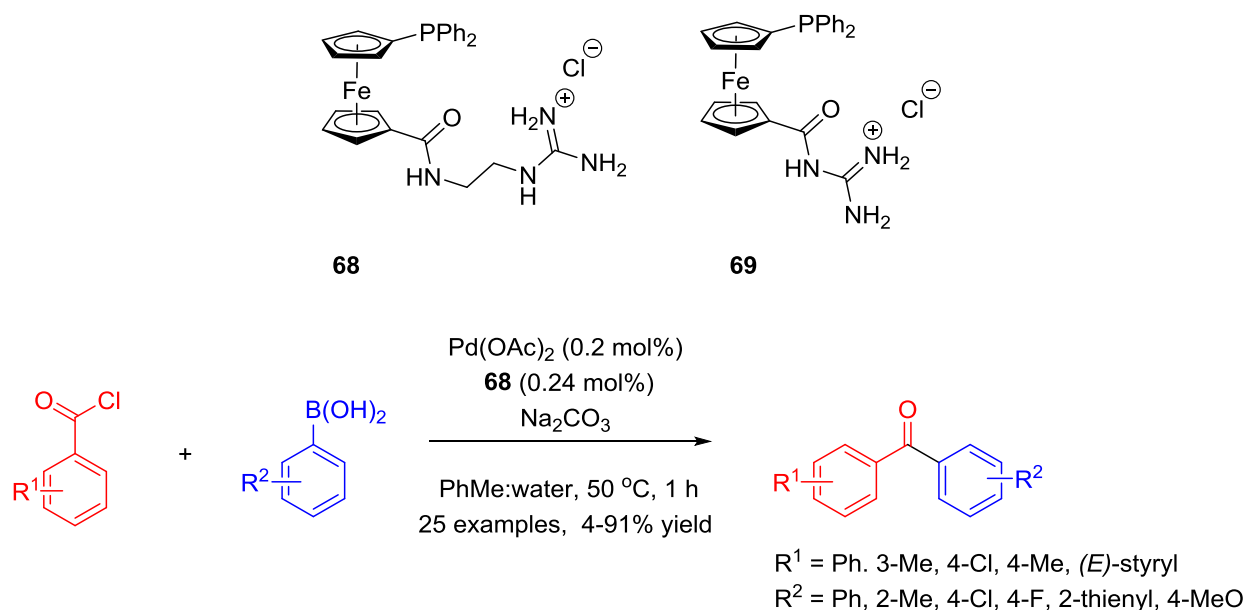
**Scheme 19:** Ferrocenylphosphino-amido sulfonate palladium complexes **C67a,b** used in the coupling of aromatic boronic acids and acyl chlorides in water.

Complexes **C67a** and **C67b** were tested in cross-couplings of aryl boronic acids with benzoyl chlorides, and this chemistry was extended to effective cyanation reactions with other (phosphino)ferrocene amidosulfonate derivatives.[86] As expected, the water solubility of the



polar species and substrates allowed the catalytic cross-coupling to be performed in aqueous media, with isolated yields up to 99% using **C67a** (Scheme 19). The high catalytic activity of complex **C67a** was attributed to either P, N- or P,O-chelation involving the amidosulfonate which facilitates Pd(II) reduction to Pd(0). The activity of isomeric phosphinobiphenyl amidosulfonates in Pd-catalyzed cyanation of aryl bromides was also reported.[87] Most recently, Štěpnička and Hierso groups further extended this chemistry to the synthesis and catalytic use in direct C2–H arylation of indoles in water using polar phosphinoferrocenes amidosulfonates bearing bulky substituents at the ferrocene backbone.[88]

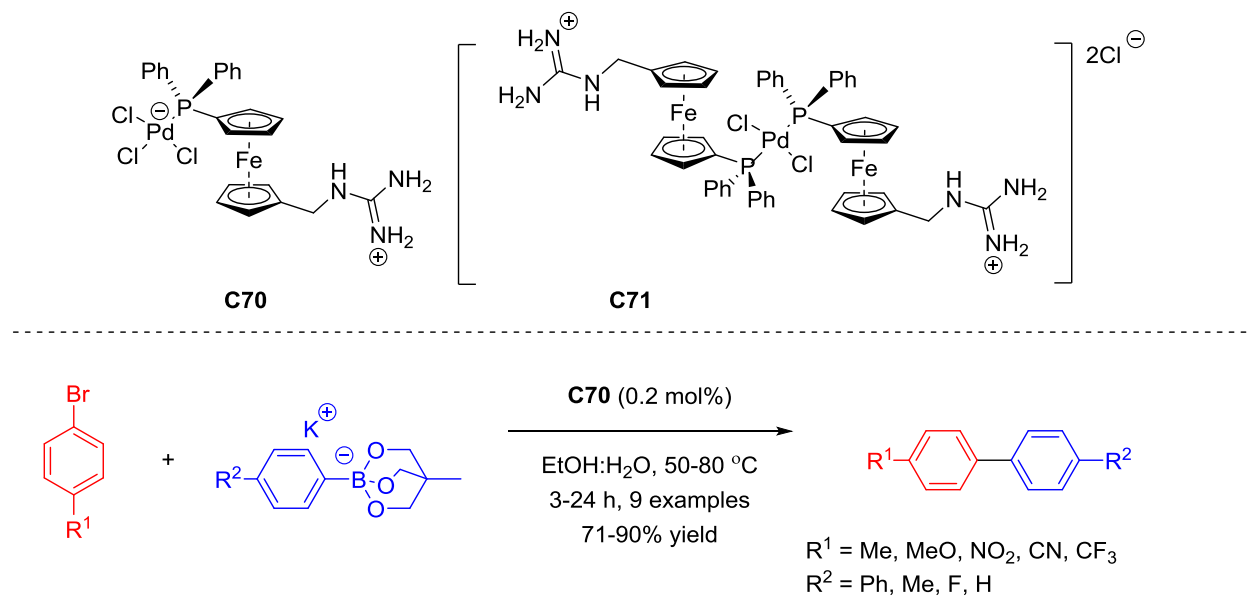
Further, polar mono(phosphino)ferrocenes carboxamide and carbohydrazide were synthesized,[89] extending to **68** and **69** that incorporate acyl guanidium salts (Scheme 20), this by amide coupling reactions between 1'-(di-phenylphosphanyl)ferrocene-1-carboxylic acid (Hdcpf) and N-(2-aminoethyl)guanidine.[90-92] The <sup>31</sup>P NMR spectra exhibit values at –19.0 ppm (DMSO) and –17.0 ppm (CDCl<sub>3</sub>) for **68** and **69**, respectively, which confirmed the presence of non-oxidized phosphino groups. The Pd(II) complexes were synthesized from **68** and **69** with the important ancillary ligands [2-(dimethylamino-κN)methyl]phenylκC<sup>1</sup>(L<sup>NC</sup>) and η<sup>3</sup>-allyl, from dinuclear palladium precursors.



**Scheme 20:** Phosphanylferrocenecarboxamides for the Pd-catalyzed cross-coupling of boronic acids with acyl chlorides.

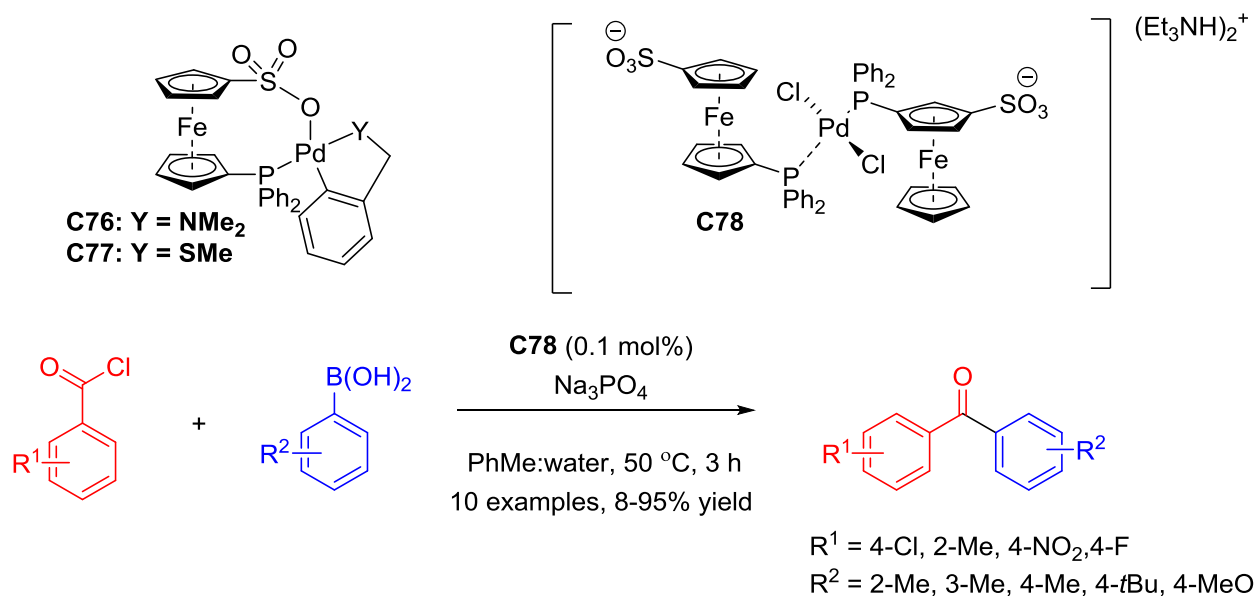
The presence of the polar groups in the complexes facilitates reactions in biphasic media. The employment of **68** in combination with Pd(OAc)<sub>2</sub> (1.2:1) in the cross-coupling of aryl boronic acids with aromatic acyl chlorides resulted in the formation of aryl ketones in moderate to high yields (Scheme 20). [90]

The group of Štěpnička also designed a family of phosphanylferrocene guanidium ligands in which the acylamide group was replaced by a non-coordinative flexible methylene bridge, and prepared the respective complexes after reacting with [Pd(Cl)<sub>2</sub>(MeCN)<sub>2</sub>].[93] Complexes **C70** and **C71** used in the Suzuki-Miyaura cross-coupling of anionic boron salts with aryl bromides in aqueous media gave the desired products (Scheme 21). The zwitterionic complex **C70** provided up to 90% isolated yields from low catalyst concentrations (0.2 mol%) at 50-80 °C without additional base, which provided an efficient protocol with fluorosubstituted salts of boronic esters. Finally, concerning related polar hybrid phosphinoferrocenes, Štěpnička reviewed the coordination and applied chemistry of phosphinoferrocene carboxamides.[94]



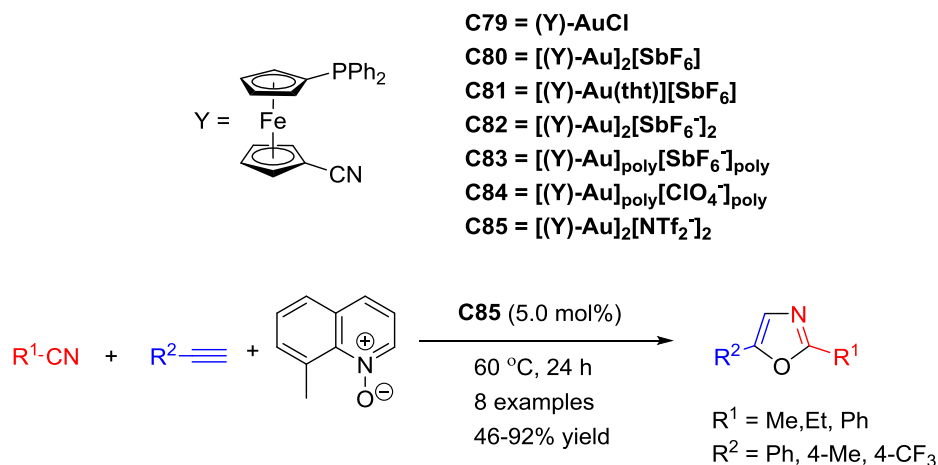
**Scheme 21:** Guanidium bearing mono(phosphino)ferrocene-Pd complexes **C70** used for Suzuki-Miyaura arylation of boron salts.

The polar ligand 1'-(diphenylphosphino)-1-sulfonic acid, also closely related to 1'-(diphenylphosphino)-1-carboxylic acid (Hdpf), has been introduced.[95] To elude the instability of the acid derivative, the corresponding triethylammonium salt of the sulfonic acid compound was prepared in 30-39% isolated yields via both direct sulfonation by the chlorosulfonic acid method,[96] and/or lithiation followed by functionalization with  $\text{SO}_3\cdot\text{NMe}_3$ .[97] The coordination with different palladium (II) precursors possessing ancillary ligands has then been achieved (Scheme 23). The P, O-chelating complexes **C76** and **C77** were structurally characterized by X-ray diffraction analysis. The anionic bis(phosphine) complex **C78**  $\text{trans}-(\text{HNEt}_3)_2[\text{PdCl}_2(\text{Ph}_2\text{PfcSO}_3\text{-}\kappa\text{P})_2]$  was prepared by reacting 2.0 equiv of ligand with  $[\text{PdCl}_2(\text{MeCN})_2]$ . These complexes were investigated in the palladium-catalyzed Suzuki-Miyaura type cross-coupling of acyl chlorides with boronic acids, resulting in corresponding biaryl ketones in excellent yields (>95%). Amongst the tested complexes, the anionic bis(phosphine) **C78** was found to provide superior performance compared to its neutral counterparts.



**Scheme 23:** 1'-(Diphenylphosphino)ferrocene-1-sulfonate **78** used as in Pd-catalyzed benzoyl chloride Suzuki-Miyaura coupling.

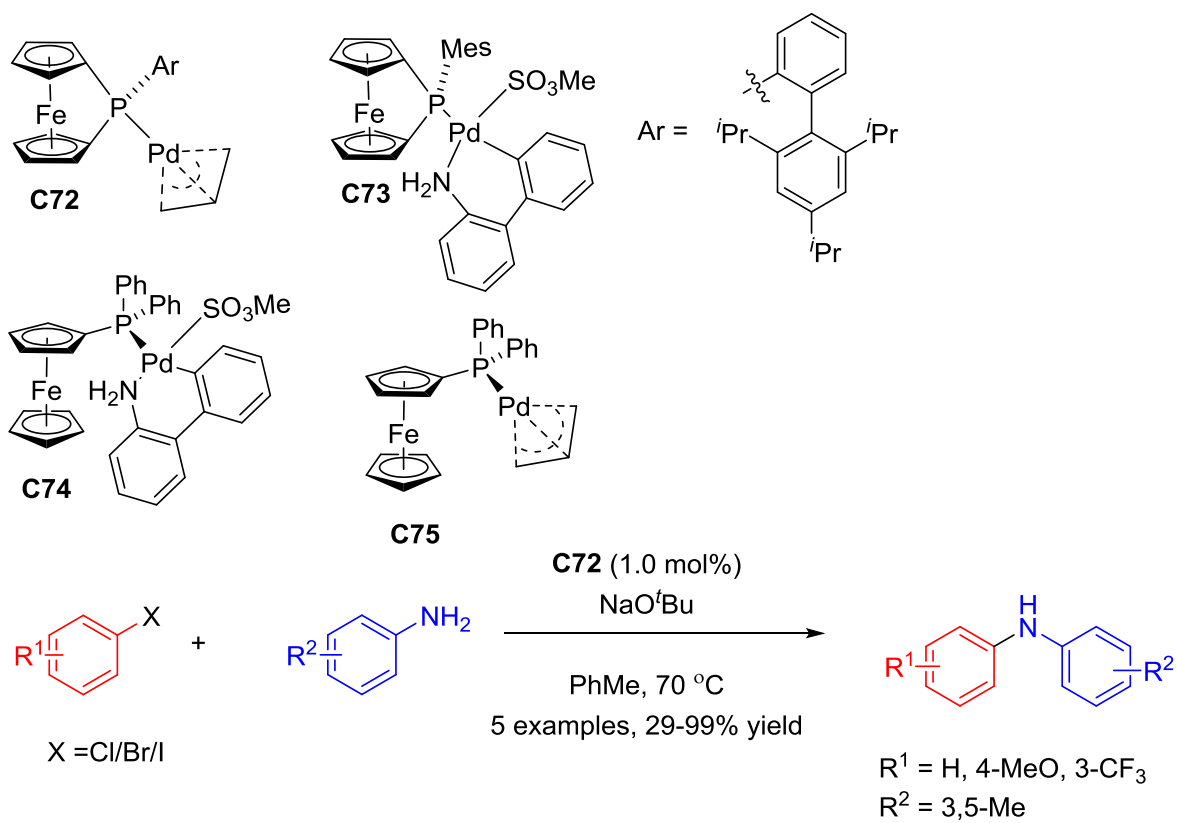
Štěpnička and co-workers further investigated the coordination behavior of 1'-(diphenylphosphanyl)-1-cyanoferrocene with copper,[98] and with Au(I) precursors (Scheme 24).[99]



**Scheme 24:** Three-component synthesis of 1,3-oxazoles using **C27** derived from 1'-(diphenylphosphino)-1-cyanoferrocene.

The series of cationic complexes **C79-C85** of formula [Au(Y)<sub>n</sub>]<sub>n</sub>X<sub>n</sub> were prepared as dimers or oligomers whose degree of association may be controlled by the counter anion (X<sup>-</sup>) species. Amongst all, the dimeric Au(I) complex **85** with the counter anion NTf<sub>2</sub><sup>-</sup> showed the highest catalytic activity towards oxidative cyclization of alkynes with nitriles to form 1,3-oxazoles (Scheme 24).[99]

Breher and co-workers examined the influence of the ferrocenyl moiety in the field of redox-switchable transition metal catalysis.[100,101] They synthesized bridged [1]phosphaferrocenophanes bearing aryl and biaryl substituents, as well as their non-bridged congeners, to form the palladium complexes **C72-C75** (Scheme 22). The palladium complexes derived from bridged [1]-phosphaferrocenophanes **C72** and **C73**, and non-bridged analogs **C74** and **C75**, were investigated as redox switchable catalysts in the Buchwald-Hartwig amination reaction of 3,5-dimethylaniline with bromobenzene derivatives.[101] The coupling was achieved with satisfactory yields (29-99%). The authors proposed that the oxidation of iron in redox-switchable ligands decreases the electron donor and/or increases the electron-acceptor nature of phosphine ligands, and thus creates a partial positive charge on the palladium center, which in turn reduces the energy barrier for the reductive elimination step.

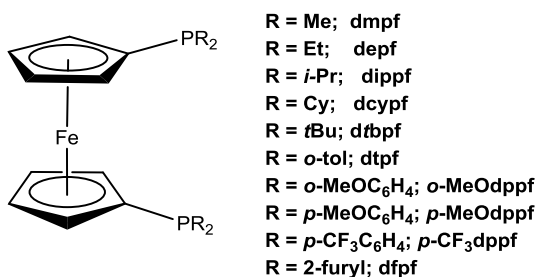


**Scheme 22:** Redox-switchable polar ferrocene-phosphine Pd-complexes used in Buchwald-Hartwig amination.

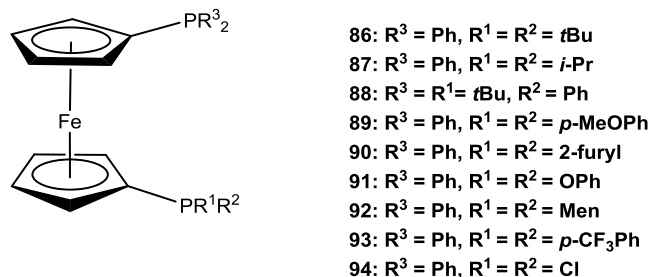
## 4. Bisphosphine ligands with ferrocenyl skeleton

Bis(phosphino)ferrocenes have emerged as a useful class of stabilizing, mostly chelating, ligands in chiral and achiral transition metal catalysis. Since Hayashi demonstrated the importance of the bite angles in  $C_2$ -symmetric metallocenes, the 1,1'-bis(diphenylphosphino)ferrocene (dppf) and its palladium complexes gained significant attention in carbon-carbon coupling reactions.[4] The dppf ligand and the application of its derivatives in a variety of metal-catalyzed transformations have previously been discussed in details.[1, 2, 6, 14, 102] The main relevant characteristics of bis(phosphino) ferrocenes are : i) their high stability allowing their facile purification –including as enantiopure compounds–, ii) their very large variety with diverse electronic and steric properties, iii) their ability to form stable metal complexes with virtually all the transition elements in a variety of coordination spheres.[103] Bis(phosphino)ferrocenes can be sorted according to their substitutions, such as 1,1'-bisphosphine, 1,2-bisphosphine, 1,3-bisphosphine, *etc.* Figure 5 illustrates typical structures for 1,1'-disubstituted symmetrical and unsymmetrical bis(phosphino)ferrocenes.[ 102, 104-107]

1,1'-disubstituted symmetrical bis(phosphino)ferrocenes



1,1'- disubstituted unsymmetrical bis(phosphino)ferrocenes



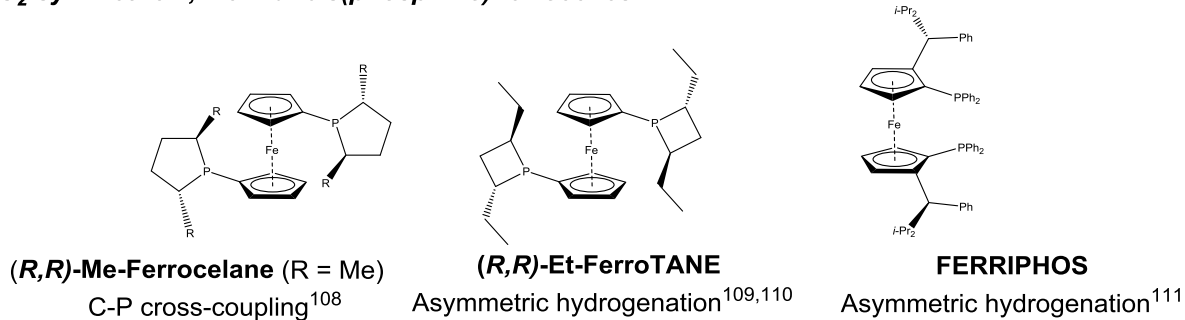
**Figure 5:** Typical 1,1'-disubstituted symmetrical and unsymmetrical bis(phosphino)ferrocenes.

### 4.1. Chiral bis(phosphino)ferrocenes and applications in metal catalyzed asymmetric reactions

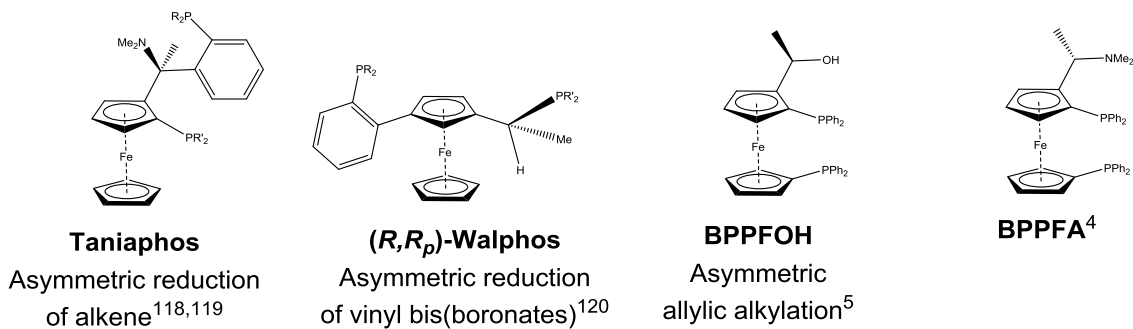
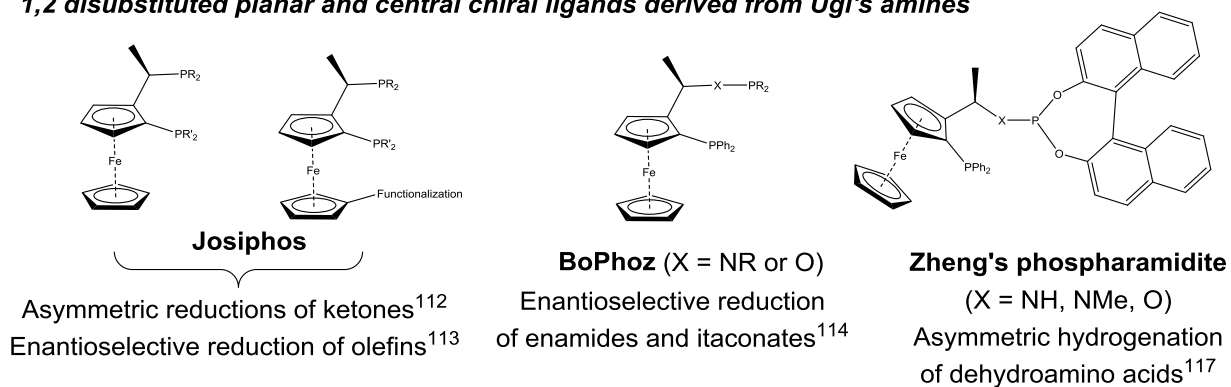
Bis(phosphino)ferrocenes designed for asymmetric catalysis can efficiently promote the transformation of a prochiral substrate into an enantio- or diastereopure product. Pioneeringly, the Hayashi and Kumada group,[4] and then others,[1] developed many classes of chiral

bis(phosphino)ferrocenes based on Ugi's amine chemistry. Selected emblematic examples of such chiral bis(phosphino)ferrocenes are depicted in Figure 6, together with their main applications in asymmetric catalysis. The  $C_2$ -symmetric 1,1'-disubstituted bis(phosphino)ferrocenes Ferrocene, [108] FerroTANE, [109, 110] FERRIPHOS, [17, 111] offered excellent enantioselectivity in asymmetric catalysis. Structural variations with 1,2-disubstituted planar and central chiral ligands Josiphos, [112, 113] BoPhoz, [114-116] Zheng's phosphine-phosphoramidite, [117] Taniaphos, [118, 119] Walphos, [120] have been widely applied in a variety of transition metal asymmetric reactions. Additionally, some bis(ferrocene)bis(phosphino) ligands as Bifep, [121, 122] or Zhang's ligand, [123] have been employed in selective metal-catalyzed asymmetric transformations. In the following, the bis(phosphino)ferrocenes are discussed in groups based on the type of cross-coupling they promote.

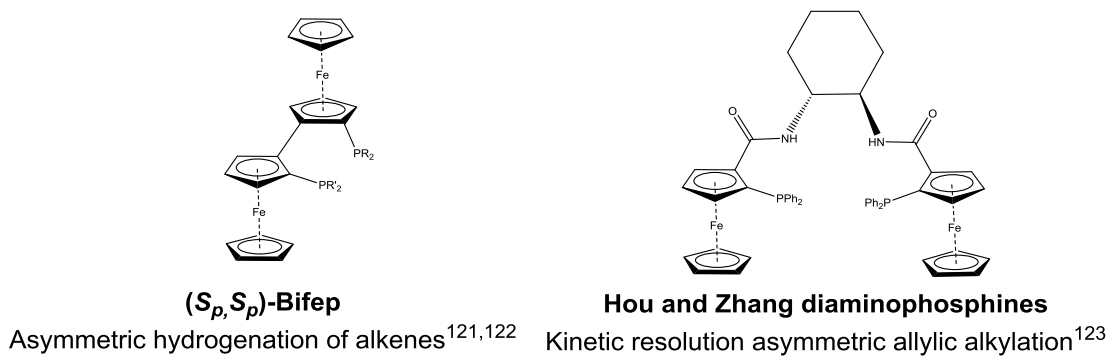
***C*<sub>2</sub>-symmetric 1,1'-chiral bis(phosphino) ferrocenes**



**1,2 disubstituted planar and central chiral ligands derived from Ugi's amines**



***Bis(ferrocene)bis(phosphino) asymmetric ligands for metal catalyzed asymmetric reactions.***

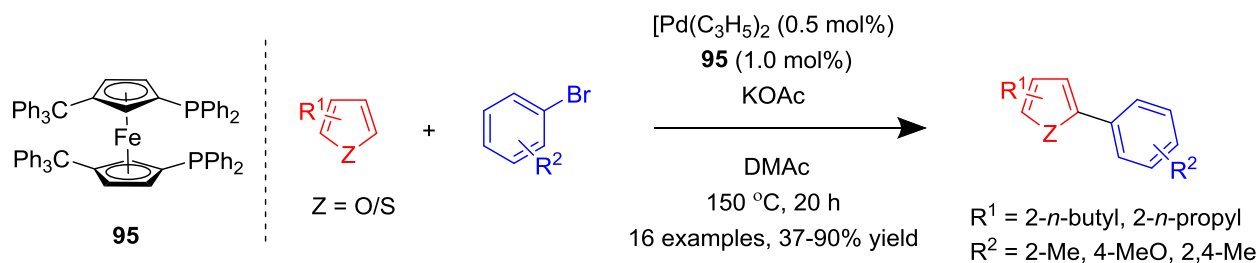


**Figure 6:** Selected examples of chiral bis(phosphino)ferrocenes and their application in asymmetric catalysis.



## 4.2. Bis(phosphino)ferrocenes in carbon-carbon cross-coupling

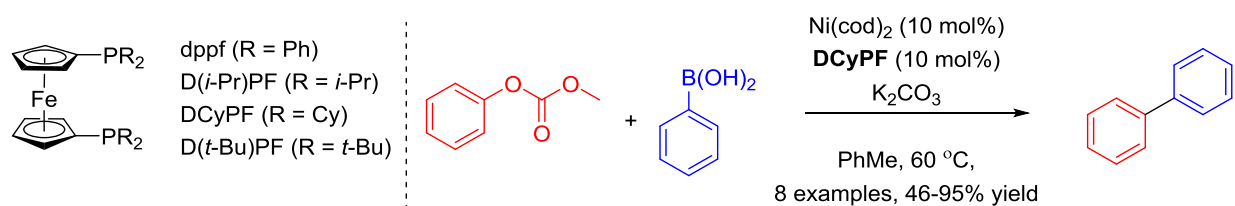
Besides traditional organometallic cross-coupling (Suzuki-Miyaura, Stille, Negishi, Kumada couplings, *etc.*), the activity of palladium complexes in the highly topical palladium-catalyzed arylation of substituted heteroaromatics via C–H bond direct functionalization attracted much attention. Such a reaction, which involves C–C bond formation, but does not result in the production of stoichiometric amounts of metallic waste and therefore contribute to a more sustainable chemistry. The Hierso and Doucet groups reported new highly hindered (triphenyl)methyl substituted ferrocenes, including the bisphosphine **95** (Scheme 25), for palladium catalyzed direct C–H arylation of furanes and thiophenes.[124] The conformation of the ferrocenyl backbone in **95** allowed a control over the final orientation of the phosphorus donors. This structuring effect originating from sterically hindering substituents was established by the analysis of “through-space” NMR  $J_{PP}$  spin-spin nuclear coupling. Then, ligand **95** was tested successfully in the palladium-catalyzed arylation of activated heterocycles via C–H bond activation and efficiently promoted the coupling of 2-substituted furans and thiophenes with bromoarenes, resulting in the targeted products in good yields (70 to 90%) with full C2-selectivity (Scheme 25).[124]



**Scheme 25:** Bistrityl-ferrocenyl bisphosphine **95** as ligand applied in palladium-catalyzed C–C cross coupling by sustainable direct C–H arylation.

Another sustainable approach is the exchange of precious metal (Pd) for more abundant catalysts (Ni). Ni-based catalytic system gained significant importance with application of more environmentally friendly aryl/alkenyl carboxylates and carbamates to Suzuki–Miyaura, Negishi, and Kumada–Corriu reactions to construct various biaryl scaffolds and highly substituted alkenes, or to activate aromatic esters.[125, 126] Accordingly, Ni(COD)<sub>2</sub> in combination with

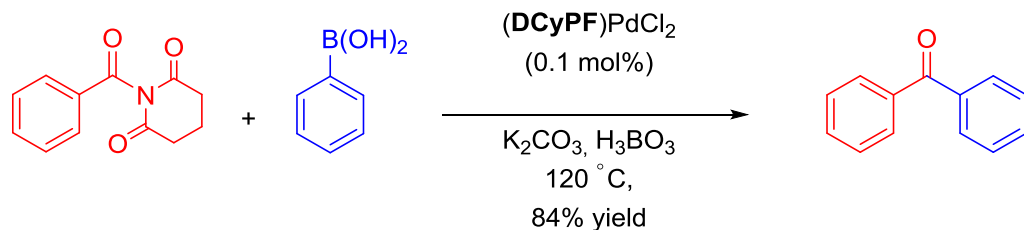
chelating bis-phosphine DCyPF (1,1'-bis(dicyclohexylphosphino)ferrocene) was investigated for the Suzuki-Miyaura coupling of aryl carbonates with aryl boronic acids (Scheme 26).[127] The catalyst offered an excellent conversion rate with moderate to good isolated yields of biaryl products, in the presence of potassium carbonate base in toluene at 60 °C (Scheme 26).



**Scheme 26:** Bis(phosphino) ferrocenes, Ni-catalyzed cross-coupling of aryl boronic acids with aryl carbonates.

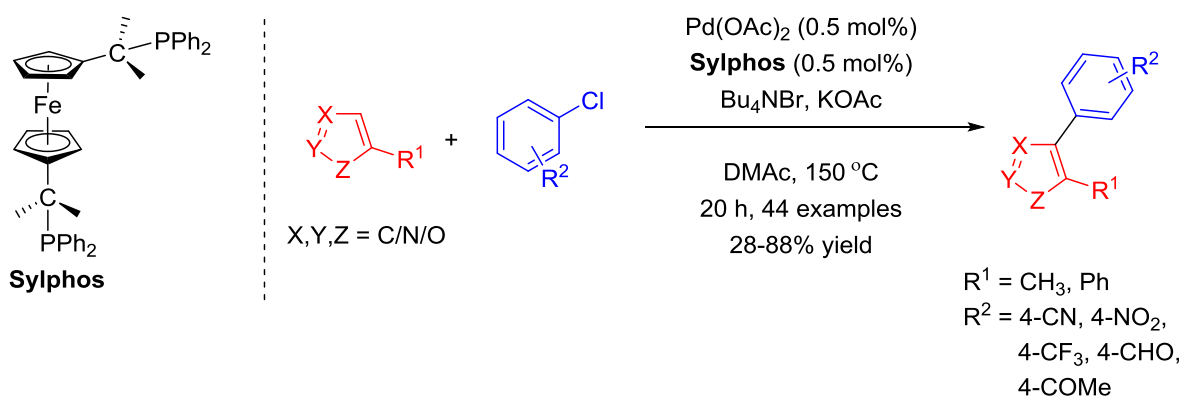
The *in situ* formed Ni-DCyPF catalyst well-tolerated both electron-deficient aryl carbonates as well as electron-rich boronic acids. Competitive experiments between aryl carbonates and aryl acetates with Ni/DCyPF, revealed the selectivity of the bis(phosphino) ferrocenes towards the activation of the aryl carbonate C–O bond. The previously used phosphine  $\text{PCy}_3$ [128] was not the preferable ligand to the nickel-catalyzed cross-coupling, indicating even that the monophosphine is useless for the reaction of aryl carbonates.[127]

In another study using DCyPF, the Pd(II) precatalyst prepared was found to be highly active in catalyzing the Suzuki-Miyaura cross-coupling of amides with aryl boronic acids. Interestingly,  $[(\text{DCyPF})\text{PdCl}_2]$  was found to be more effective than  $[(\text{dppf})\text{PdCl}_2]$ . In the presence of additive  $\text{H}_3\text{BO}_3$  in THF solution at 120 °C, the corresponding biarylketone were isolated in 84% yields (Scheme 27). Although 0.1 Mol%  $[(\text{DCyPF})\text{PdCl}_2]$  was found to be an active catalyst, further studies revealed in that case that the alternative  $[(\text{PCy}_3)_2\text{PdCl}_2]$  enables the desired N–C(O) cross-coupling at 50 ppm loadings with TONs of 12,600 to 19,200.[129]



**Scheme 27:** Suzuki-Miyaura Cross-Coupling of amides by using air-stable  $[(\text{DCyPF})\text{PdCl}_2]$  precatalyst.

The activation of aryl chlorides via congested electron-rich monodentate ligands such as PCy<sub>3</sub>, Cy<sub>2</sub>P-*o*-biphenyl, and *n*BuAd<sub>2</sub>P has been well-established. Because of their generally higher air-stability and robustness polydentate ferrocenyl phosphine ligands are attractive alternatives for the activation of unactivated C–Br and C–Cl bonds. The Hierso group prepared a novel sterically relieved and air- and moisture-stable bis(phosphino)ferrocene named Sylphos (Scheme 28), in which the ferrocenyl unit and the phosphine donor are connected via a methylene bridge.[130] The Sylphos ferrocene was synthesized in two steps from dimethyl fulvene.<sup>31</sup>P NMR signal was significantly shifted to 26.1 ppm compared to classical ferrocenylphosphines having a direct connection of phosphorus(III) to the cyclopentadienyl ring.

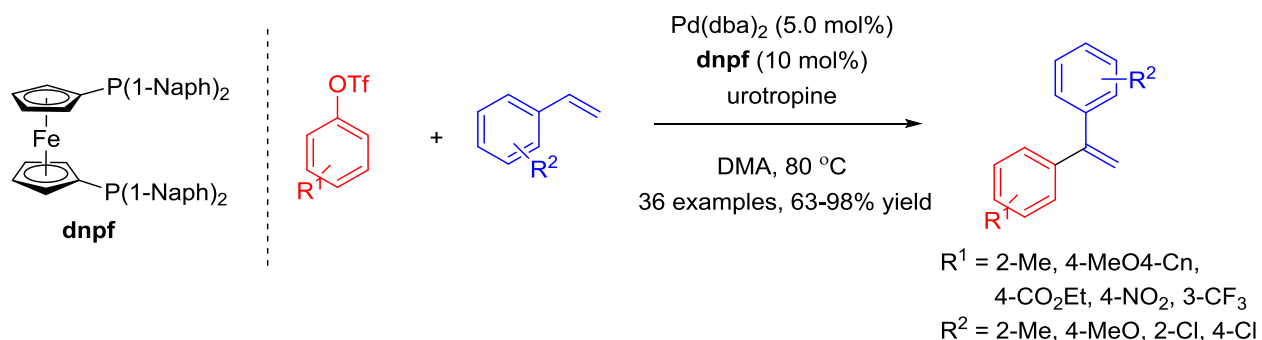


**Scheme 28:** Sterically relieved bis(phosphino)ferrocene Sylphos applied in the arylation of heteroaromatics with aryl chlorides.

The  $\sigma$ -donor property of the bis(phosphino)ferrocene was deduced from the <sup>31</sup>P NMR nuclear spin-spin coupling constant of 1,1'-(diphenylphosphinoselenide)ferrocene <sup>1</sup>J<sub>P=Se</sub> (728 Hz), where it is equivalent to <sup>1</sup>J<sub>P=Se</sub> in Se=PPh<sub>3</sub> (730 Hz). Besides, electrochemical investigations of Sylphos revealed that the electron-donating effect from the spacer methylene group was mainly directed towards the iron center and not to the -PPh<sub>2</sub> group. The catalyst combining Pd(OAc)<sub>2</sub>/Sylphos at 0.5 mol% loading in the presence of KOAc/Bu<sub>4</sub>NBr promoted the direct C–H arylation of heteroaromatics with electron-deficient aryl chlorides (Scheme 28).[130] Sylphos has shown to favor selectivity towards C3 or C5 positions in heterocyclic units such as oxazole, benzofuran, indole, and pyrazole, whereas, previously reported mono- or bisphosphines, and other phosphinoferrocene ligands, were found to be ineffective in providing such activity/regioselectivity. Aryl chlorides substituted with a variety of functional groups such as

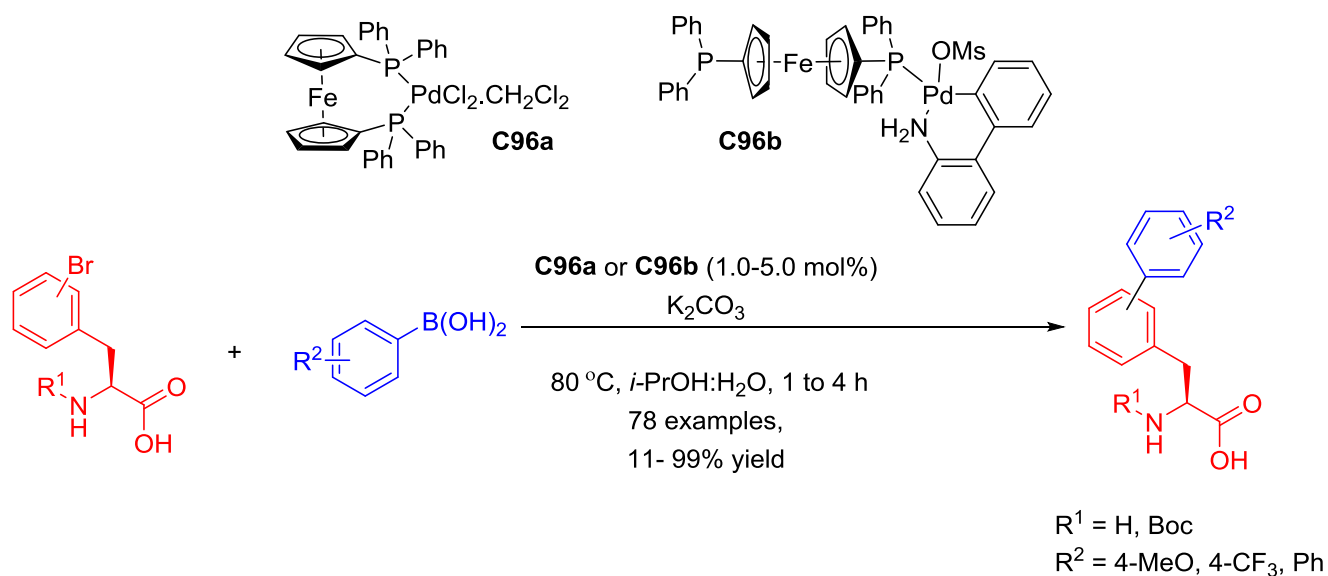
formyl, nitro, acetyl, or *ortho/meta/para*-trifluoromethyl were well-tolerated under the employed catalytic conditions.

Intermolecular Heck reactions in various conditions, *i.e.* decarboxylative, decarbonylative,[131] and oxidative,[132] proceed often with preferential  $\beta$ -selectivity.[133, 134] Therefore, directing the selectivity towards the  $\alpha$ -position in styrene derivative coupling may be fairly challenging. The 1,1'-bis(dinaphthylphosphino)ferrocene (dnpf) in the presence of urotropine base promoted Heck couplings with a ratio in  $\alpha/\beta$  selectivity >20:1, and almost quantitative yields (Scheme 29).[135] Other chelating ligands, including dppf (1,1'-bis(diphenylphosphino)ferrocene), and classical ligands such as 1,3-bis(diphenylphosphino)propane (dppp), butane-1,4-diylbis(diphenylphosphane) (dppb), (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (BINAP), (Oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEphos), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xanthphos), provided much lower selectivity. Vinyl arene substrates substituted with electron-withdrawing groups like Cl, CF<sub>3</sub> resulted in poorer selectivity (<10:1). The origin of the high  $\alpha$ -selectivity for the Pd/dnpf catalyst was attributed to atypical edge-to-edge  $\pi$ -interactions between two naphthyl rings in dnpf.



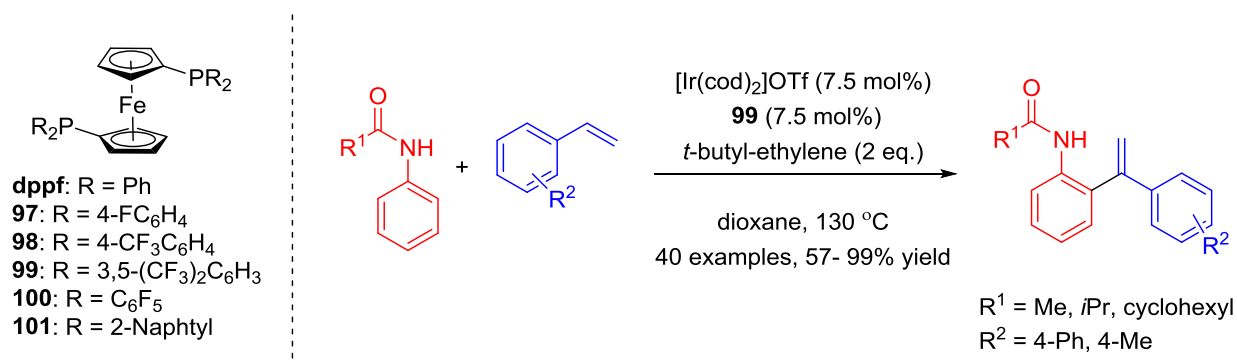
**Scheme 29:** Selective  $\alpha$ -arylation of vinylarenes via Pd-catalysis in the presence of the dnpf ligand.

Aqueous conditions (water, alcoholic, *etc.*), compatible with palladium catalysts, have been tested using complexes **C96a** and **C96b** in the Suzuki-Miyaura cross-coupling arylation of halogenated aminoacids (Scheme 30). The coupling of halogenated phenylalanine, tryptophane, and other dipeptide-containing amino acids with various (hetero)aromatic boronic acids was described under mild conditions.[136] Thereby, prior incorporation of halogenated amino acid side chains on the peptide backbone allowed their late-stage modifications.



**Scheme 30:** Dppf bisphosphine used in palladium-catalyzed Suzuki-Miyaura arylation of aminoacids and peptides in water.

1,1'-Bis(diphenylphosphino)ferrocene (dppf) and related compounds **97-101** were investigated in the coupling of anilide with styrene using  $[\text{Ir}(\text{COD})_2]\text{OTf}$  in dioxane solvent (Scheme 31).



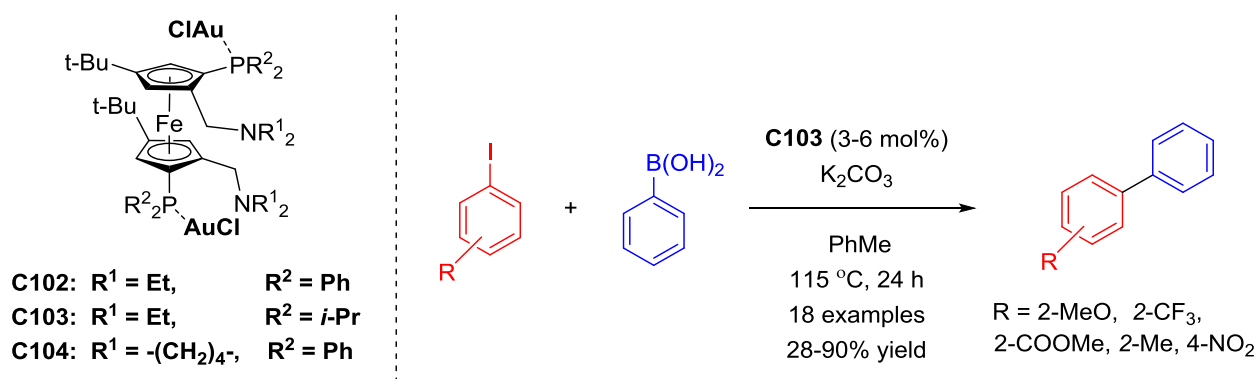
**Scheme 31:** Bis(phosphino)ferrocenes used for iridium-catalyzed dual oxidative C-H  $\alpha$ -coupling of anilides with olefins.

The high  $\alpha$ -selective arylation of styrene with acetanilide was demonstrated,[137] and the influence of bis(phosphino)ferrocene on the iridium center presumably increased the  $\alpha$ -selectivity by enforcing the alkene carbometallation catalytic step.[137] The aromatic core of the ligand influences the selectivity towards alkenylation ( $\alpha$ -arylation) compared to concurrent hydroarylation. The 3,5-trifluoromethylphenyl-bis(phosphino)ferrocene **99** gave with cationic

iridium a 8:2 selectivity of alkenylation vs. hydroarylation, in the presence of *tert*-butyl ethylene as oxidant.

#### 4.3. Polytopic N, N'-bis(phosphino)ferrocene ligands applied in gold-catalyzed Suzuki-Miyaura cross-coupling reaction

The synthetic application of gold complexes is well-explored in Lewis acid mediated catalytic processes involving the electrophilic activation of  $\pi$ -C–C bonds.[138, 139] The use of gold catalysis in cross-coupling reactions, in contrast, remains somehow underdeveloped.[140] Examples of molecularly well-defined gold catalysts were reported both for the Suzuki-Miyaura and Sonogashira coupling reactions. A major limitation to overcome is generally the homocoupling of nucleophilic reagents such as aryl boronic acids.[141-143] A class of dinuclear gold chloride tetradentate (N,N')-diamino-(P,P')-di(phosphino)ferrocenes was reported as catalysts for the Suzuki-Miyaura reaction promoted by gold (Scheme 31).[144] The diastereoselective synthesis of planar chiral tetradentate (N, N', P, P')-ferrocenyl ligands allowed the subsequent formation of dinuclear gold complexes **C102** to **C104**. Complex **C103**, in the presence of  $K_2CO_3$  base, afforded the desired cross-coupling product in 100% conversion and with 81% selectivity (Scheme 32).



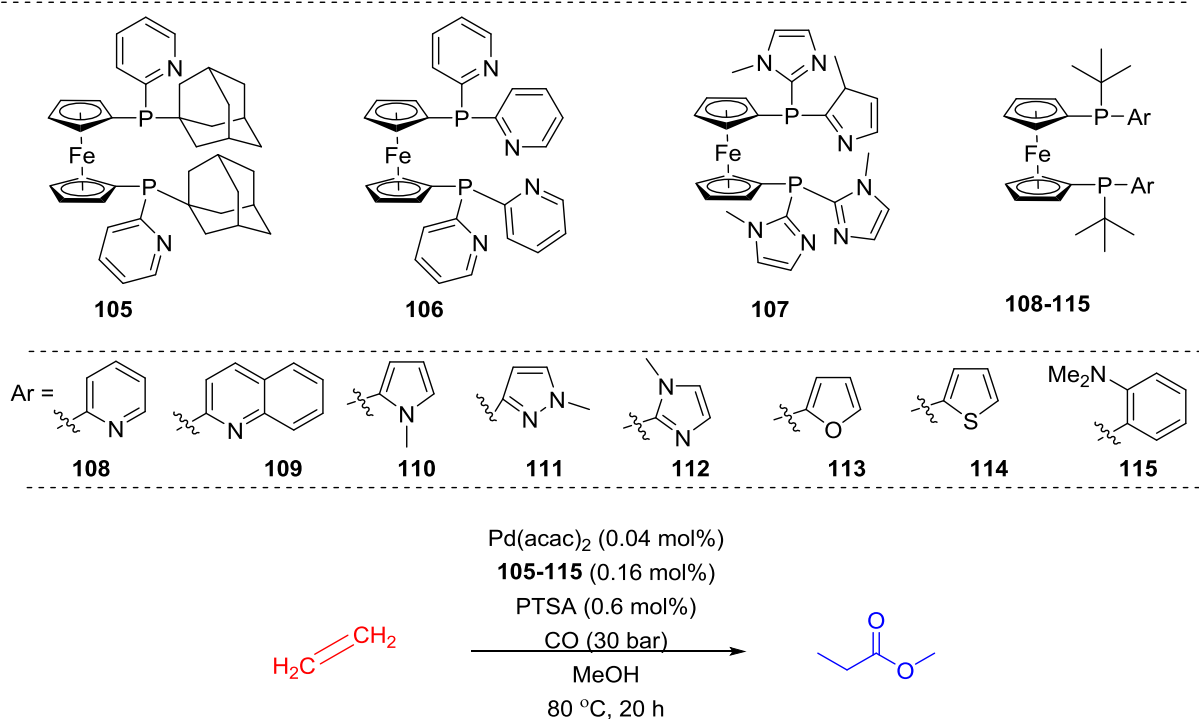
**Scheme 32:** Gold-bis(amino)bis(phosphino)ferrocene **C102-C104** employed in gold-catalyzed Suzuki-Miyaura cross-coupling.

The presence of highly electron-rich isopropyl groups on the phosphorus donor atom was found to be essential for optimum performance. The electron-poor aryl iodides gave better yields compared to electron-rich aryl iodides. In addition, the catalyst efficiently coupled demanding *o*-

substituted compounds and hindered polycycles (1-iodonaphthalene, 1-iodopyrene) with phenylboronic acid.

#### 4.4. Bis(phosphino)ferrocenes in olefin alkoxy carbonylation

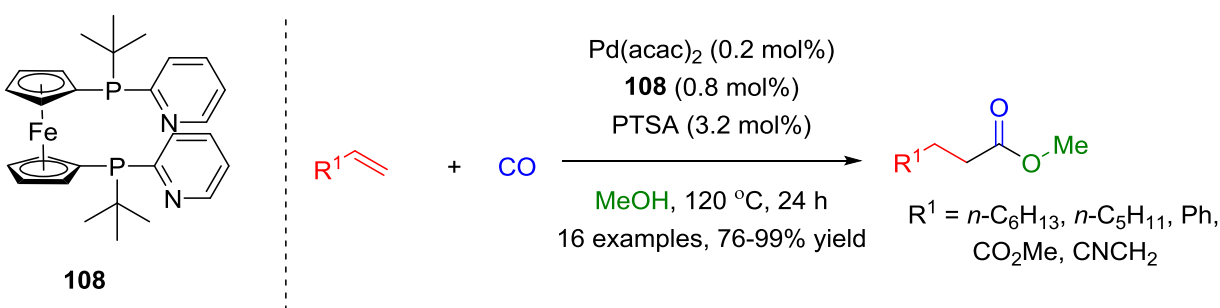
Olefin alkoxy carbonylation is an industrially relevant and frequently applied reaction.[145] Methyl methacrylate, which is the monomeric unit for manufacturing resins and plastics, was synthesized industrially from  $C_2H_4$ , CO,  $H_2CO$  compounds *via* methyl propionate Pd-catalyzed carbonylation and condensation on Cs/SiO<sub>2</sub> (Lucite  $\alpha$ -process, 2009).[146-148] Various classes of bis(phosphino)ferrocenes, **105-115** (Scheme 33), emerged for the methyl methacrylate synthesis from ethylene under CO pressure.



**Scheme 33:** C<sub>2</sub>-symmetric 1,1'-bis(phosphino)ferrocenes for palladium-catalyzed olefin alkoxy carbonylation.

Their P-donor atom is substituted both with sterically hindered groups and amphoteric nitrogen heterocycles.[149] These ligands in combination with palladium, have shown improved activity and productivity for the alkoxy carbonylation process compared to existing state-of-the-art

ligands such as 1,2-bis((di-*tert*-butylphosphino)methyl)benzene.[149] The substituents were introduced via classical lithiation of the ferrocenyl backbone followed by quenching with (hetero)arylphosphine chlorides. The ferrocene derivatives **105** and **108** exhibited high reaction kinetics and provided 99% conversion within ten minutes. The amphoteric character of the N-heterocycle was demonstrated via temperature-dependent reaction rate experiments, where the apparent activation energy of the catalyst based on ligand **108** is much lower than industrially used catalyst 1,2-bis ((di-*tert*-butylphosphino)methyl)benzene. The protocol was further extended to polysubstituted alkenes, yielding quantitatively the corresponding alkoxy esters with high selectivity (Scheme 34).[150] The catalyst tolerated cyclic olefins, ester and cyano substituted alkenes, and push-pull 1,1'-disubstituted alkenes, to yield the corresponding esters.



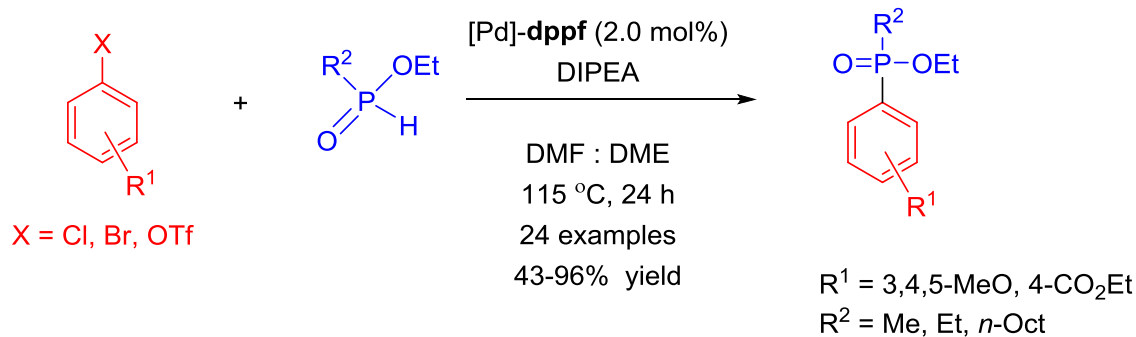
**Scheme 34:** Bis(phosphino-pyridyl)ferrocene **108** used as ligand in palladium-catalyzed methoxycarbonylation of alkenes

## 4.5. Bis(phosphino)ferrocenes in carbon-hetero atom cross-coupling reactions

### 4.5.1. C–P bond formation

Hirao's pioneering work showed that palladium-catalyzed cross-coupling between phosphorus reagents and  $\text{Csp}^2\text{-X}$  (where X = halide) was generally feasible,[151] and accordingly various phosphinylidene  $[\text{P}(\text{O})\text{H}]$  containing compounds, such as phosphinates  $[\text{ROP}(\text{O})\text{H}_2]$ , H-phosphinates  $[\text{R}^1\text{P}(\text{O})(\text{OR})\text{H}]$ , H-phosphonates  $[(\text{RO})_2\text{P}(\text{O})\text{H}]$ , and secondary phosphine oxides  $[\text{R}_2\text{P}(\text{O})\text{H}]$  were arylated using dppf bisphosphine as ligand for palladium. The cross-coupling of aryl chlorides was achieved with  $[\text{P}(\text{O})\text{H}]$  phosphorus reagents, using palladium-dppf catalyst, in the presence of (*i*-Pr<sub>2</sub>)<sub>2</sub>NEt, and dimethoxyethane (DME) in DMF (Scheme 35).[152]



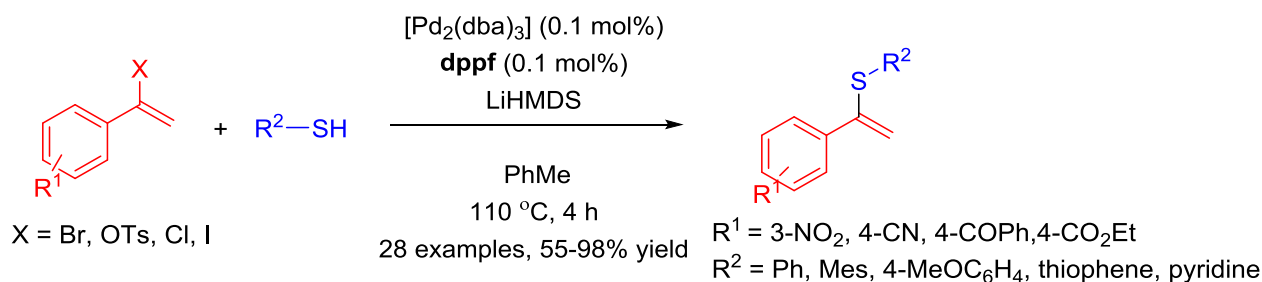


**Scheme 35:** Dppf stabilized palladium-catalyst for C–P bond formation from aryl halides and  $\text{R}_2\text{P(=O)H}$ .

Employing the large bite angle chelating ligand (dppf) slowed down the  $\beta$ -hydride elimination and impaired the competing hydrogen transformation side reaction. The developed protocol was extended to a wide range of electrophiles such as benzylic, alkenyl, allylic, heteroaryl chlorides and alkynylbenzene, and the respective coupling derivatives were isolated in moderate to excellent yields up to 96% (Scheme 35).

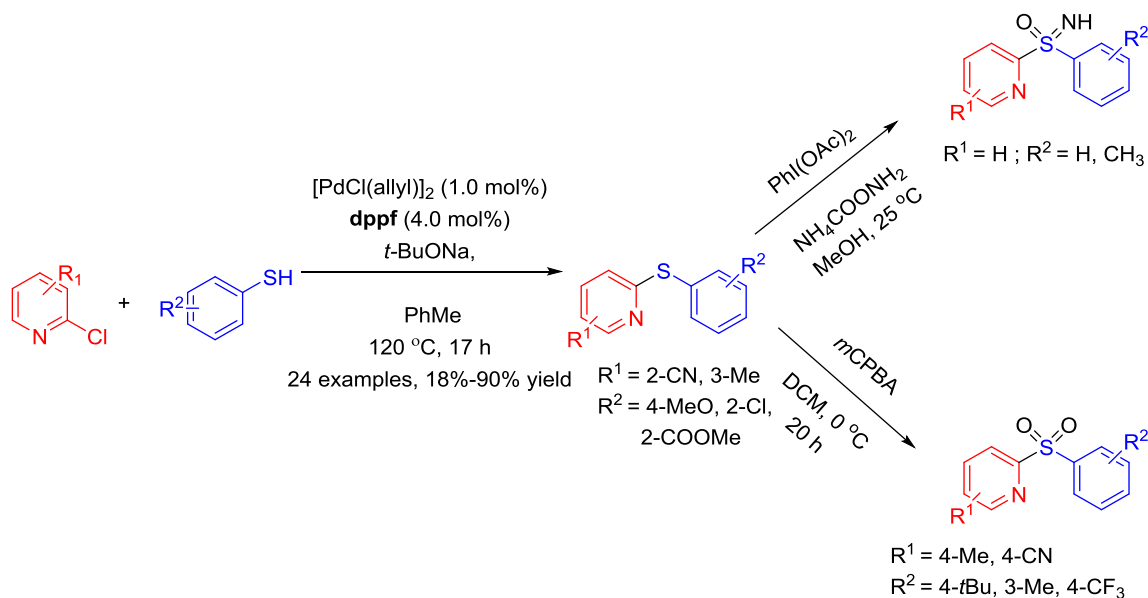
#### 4.5.2. C–S bond formation

Palladium combined with 1,1'-bis(diphenylphosphino)ferrocene has also proven efficient in the catalyzed cross-coupling of substituted alkenyl bromides with aryl and alkyl thiols (Scheme 36).[153] The reaction proceeded at low catalytic loading (0.01-0.25 mol%) and afforded high yields with a broad substrate scope, including sterically hindered alkyl or aryl thiols and alkene synthons. The thioetherification of  $\alpha/\beta$ -bromo- and  $\alpha$ -iodoalkenes was achieved in less than four hours at gram scale.[153]



**Scheme 36:** Thioetherification of alkenyl halide and tosylate catalyzed by [Pd]/dppf.

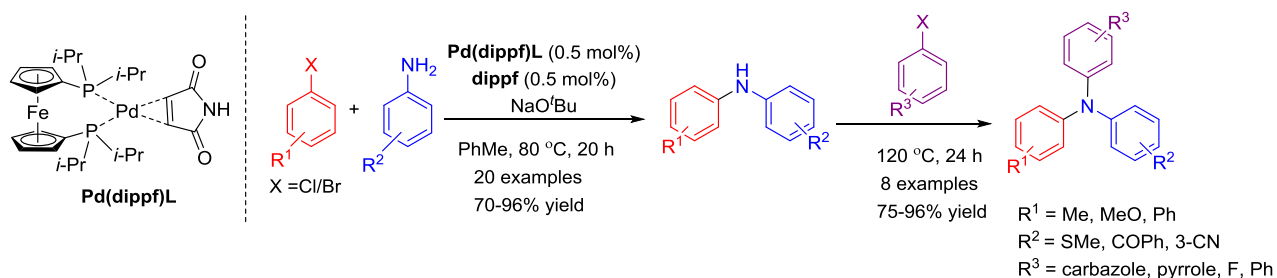
Alternatively, 1,1'-bis(diarylphosphino)ferrocene combined with  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  (1-2 mol%) catalyzed the C–S cross-coupling reaction between heteroaryl chlorides and aromatic thiols, resulting in heteroaryl thioethers amenable to sulfones and NH-sulfoximines (Scheme 37).[154] The protocol tolerated a variety of heteroaryl chlorides such as pyridine, pyrazine, and pyridazine. However, the highly electron-deficient thiols such as,  $4\text{-CF}_3\text{C}_6\text{H}_4\text{SH}$ ,  $p\text{-NO}_2\text{-C}_6\text{H}_4\text{SH}$  are challenging substrates. The lack of reactivity of these electron-poor thiols was attributed to the formation of stable stationary species of Pd–S dithiolate complexes.



**Scheme 37:** [Pd]-dppf catalytic system for C–S cross-coupling of heteroaryl chlorides with aromatic thiols.

### 4.5.3. C–N bond formation

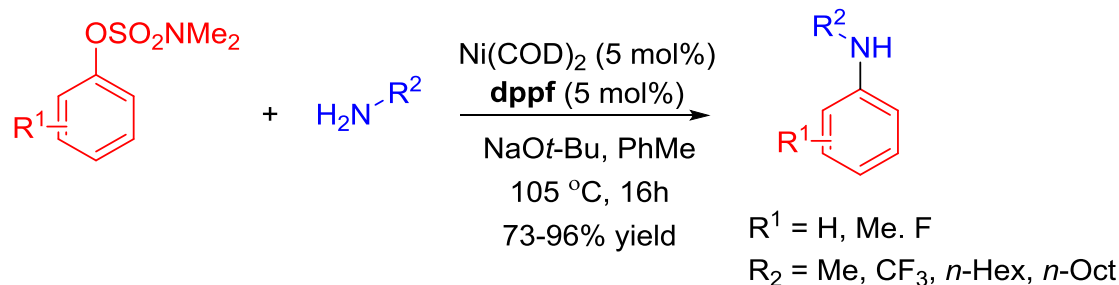
The palladium 1,1'-bis(diisopropylphosphino)ferrocene Pd(dippf)L catalyst promoted the selective and sequential diarylation of primary anilines (Scheme 38).[155] The air-stable [Pd(dippf)(maleimide)] complex was used at low 0.2 mol% catalytic loadings for the selective synthesis of various di- and tertiary amines, building blocks towards highly the formation of conjugated  $\pi$  electron-rich structures as OLED hole transporters.[129]



**Scheme 38:** Pd(dippf)L catalyst for sequential arylation of primary anilines.

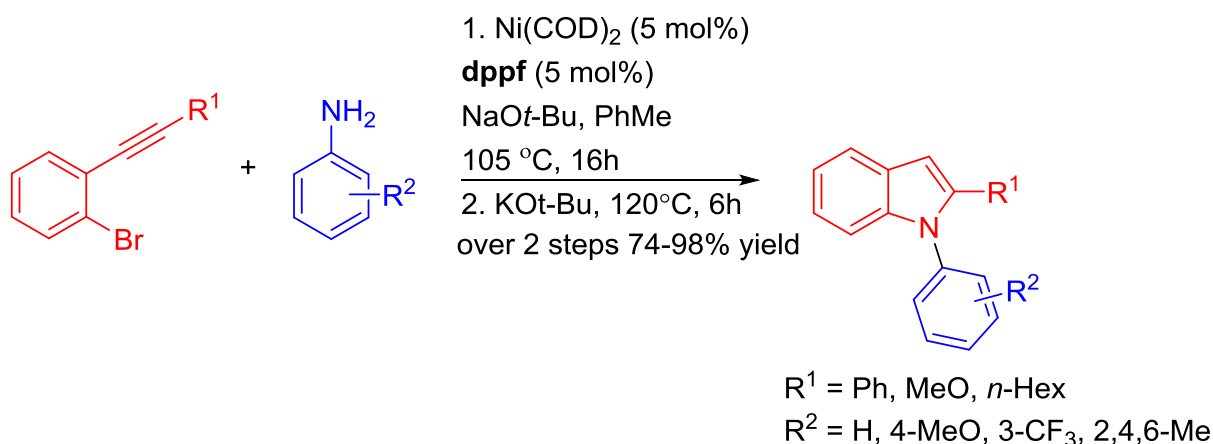
Although Pd- and Cu-catalyzed cross-couplings are well-established for C–heteroatom bond formation, Ni-catalysis employing the ancillary ligands usually useful in palladium catalysis has become competitive in the area of  $\text{Csp}^2\text{-N}$  bond formation. The Stradiotto's group provided a comprehensive summary of  $\text{Csp}^2\text{-N}$  cross-coupling reactions catalyzed by nickel and bisphosphine ligands.[156] From Wolfe and Buchwald reports on the application of the Ni/dppf catalyst for  $\text{Csp}^2\text{-N}$  bond formation,[157] especially using aryl chloride electrophiles, the chelating bis(phosphino)ferrocene dppf in combination with  $\text{Ni(COD)}_2$  gained considerable interest. Later, dppf was also combined with some Ni/C heterogeneous system for the amination of aryl chlorides with primary alkylamines, anilines, and secondary cyclic amines.[158, 159]

Ackermann and co-workers used air and moisture stable phenol derived aryl sulfamates as electrophilic coupling partners in Ni/dppf catalyzed C–N cross-coupling (Scheme 39).[160] The catalyst furnished the targeted cross-coupling products in excellent yields in the presence of  $\text{NaO}^t\text{Bu}$ . Moreover, electron-withdrawing and electron-donating substituents on aniline as well as challenging *n*-alkyl amines were well tolerated.



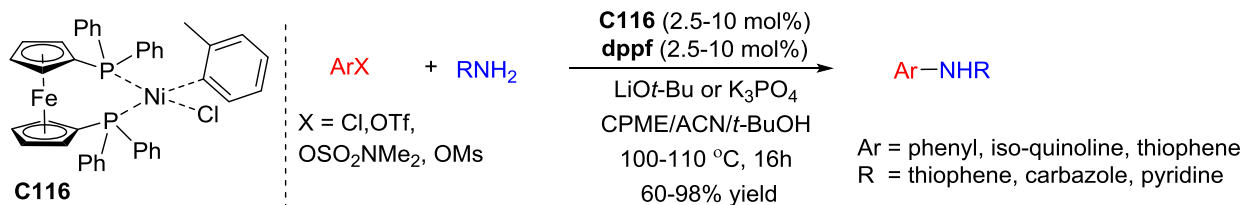
**Scheme 39:** Ni/dppf catalyst for the N-arylation of primary amines.

The same group prepared substituted indoles via a reaction sequence involving Ni/dppf catalyzed C–N cross-coupling and base mediated amination/hydroamination reactions.[161] The *o*-alkynyl haloarene was coupled with various aromatic amines bearing electron-withdrawing and electron-donating groups in the presence of the Ni/dppf catalyst and the addition of base promoted the cyclization of the coupled product to the indole derivatives via intramolecular hydroamination (Scheme 40).[161]



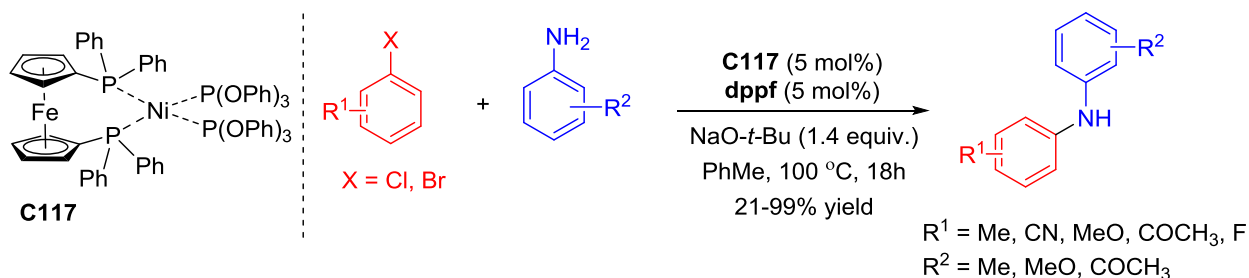
**Scheme 40:** Ni/dppf catalyzed indole synthesis.

Buchwald and his co-workers introduced an air stable Ni-precatalyst **C116** for C–N cross-coupling reactions. The catalyst exhibited a large substrate scope tolerance including both aryl and heteroaryl electrophiles and aryl, heteroaryl and alkyl amine nucleophiles (Scheme 41).[162] Complex **C116** was accomplished via ligand exchange reaction between  $(\text{PPh}_3)_2\text{Ni}(o\text{-tolyl})\text{Cl}$  and dppf. The precatalyst **C116** in the presence of additional dppf has proven effective in giving the corresponding C–N cross-coupled products in 60-98% isolated yields from aryl chlorides, as well as phenol-derived sulfamate, triflate and mesylate aryl electrophiles (Scheme 41).[162]



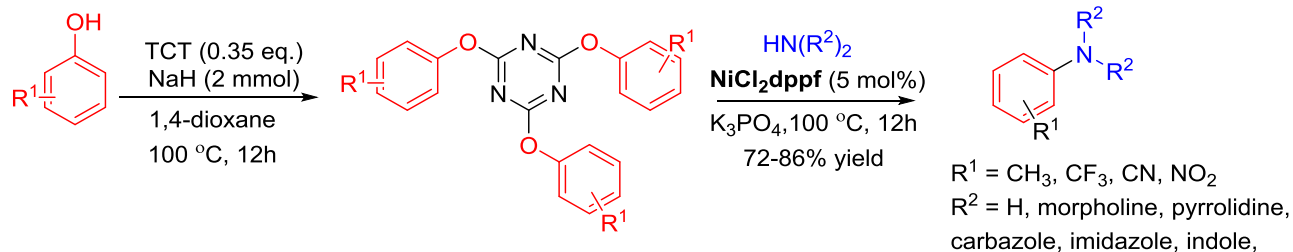
**Scheme 41:** Csp<sup>2</sup>-N bond formation via Ni(dppf)(*o*-tolyl)Cl (**C116**) precatalyst.

A similarly air-stable, but phosphite-based, precatalyst **C117** was developed by Stewart and co-workers for the amination of aryl halides (Cl/Br) with aniline and cyclic secondary amine derivatives [163]. The precatalyst **C117** was synthesized from nickelocene in good yields. The employment of mono-substituted dppf precatalyst (dppf)Ni[P(OPh)<sub>3</sub>]<sub>2</sub> (**C117**) in the presence of additional dppf improved the conversion rate, subsequently yielding the coupled products in moderate to excellent yields (Scheme 42).[163] Various substituted aryl or heteroaryl halides were used as electrophilic coupling partners; however, no correlation between reactivity and electronics of the substrates was observed.



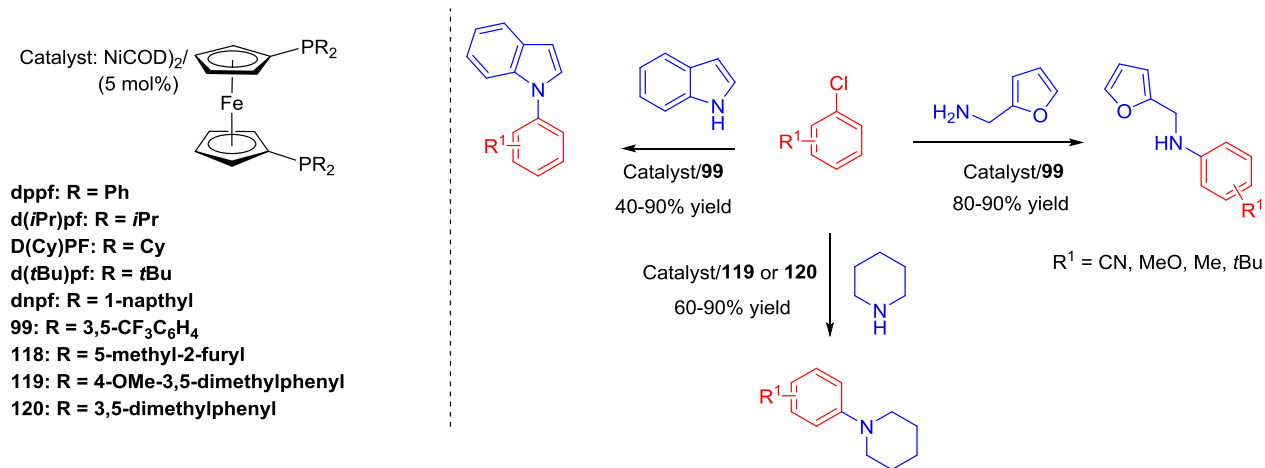
**Scheme 42:** N-arylation of aniline derivatives using Ni/dppf precatalyst **C117**.

2,4,6-Trichloro-1,3,5-triazine (TCT) was employed for the activation of phenolic C–O bonds, and the resulting aryl C–O electrophilic synthon was subsequently coupled with aryl amines and cyclic secondary amines, in the presence of NiCl<sub>2</sub>(dppf) catalyst, to yield the corresponding aryl amines in 72 to 86% yields (Scheme 43).[164] The developed methodology was applied to coupling differently substituted phenols with a variety of amines including, morpholine, piperidine, pyrrolidine, diethyl amine, imidazole, carbazole, benzylamines, aniline and indole. Moreover, using this protocol aromatic primary amines were synthesized in 70% isolated yields from phenols and ammonium carbonate as amine source.[164]



**Scheme 43:** Synthesis of aniline derivatives from phenol via Ni/dppf C–O bond activation.

Stradiotto and his co-workers systematically investigated a series of structurally varied 1,1'-bis(bis(alkyl/aryl)phosphino)ferrocene ligands in the Ni-catalyzed cross-coupling of (hetero)aryl chlorides with furfurylamine, morpholine and indole (Scheme 44).[165]

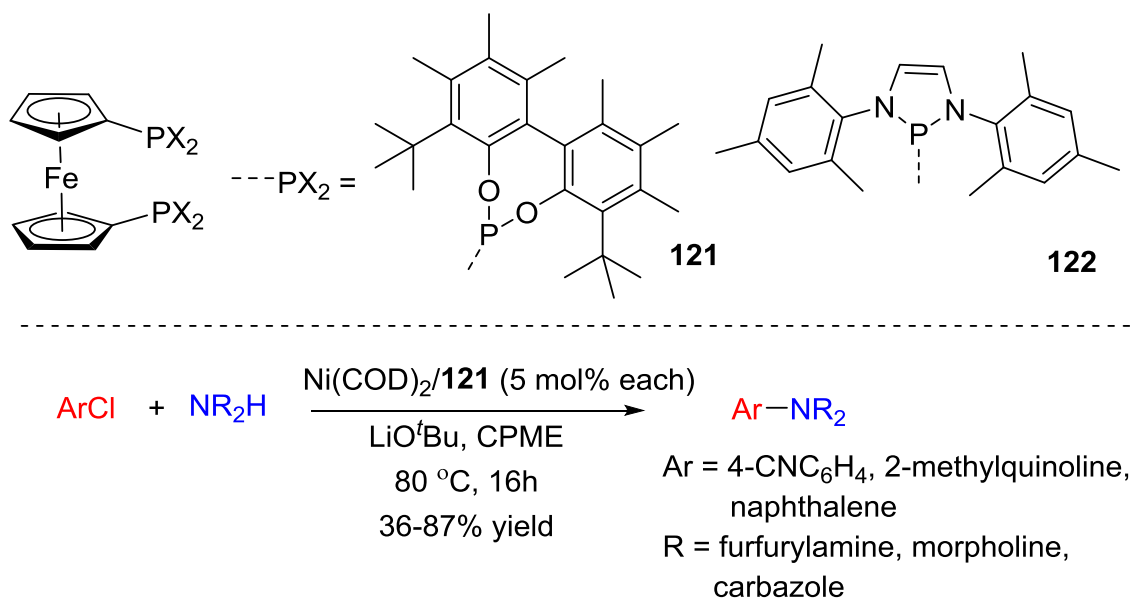


**Scheme 44:** 1,1'-bis(alkyl/aryl)phosphino)ferrocenes promoting Ni-catalyzed C–N cross-coupling.

The system combining dppf and nickel(0) catalyzed C–N bond formation, and the electron-deficient variant ligand **99** performed similarly to dppf in the N-arylation of indoles and furfuryl amines (Scheme 44).[165] Ligands **119** and **120** offered optimal catalytic conversions in the case of morpholine (Scheme 44). The comparable reactivity profiles of dppf, **99**, **119** and **120** ligands in Ni-catalyzed  $\text{Csp}^2\text{-N}_2$  coupling reactions suggests that the aryl substitutions on the phosphine ligand had only minor implication on the nickel-based chemistry described.[165]

More recently, the same group introduced two novel bis(phosphino)ferrocenes bearing bulky dioxaphosphepine (**121**) and diazaphospholene (**122**) for Ni-catalyzed  $\text{Csp}^2\text{-N}$  cross-couplings.[166] These ligands were synthesized in gram scale by reacting 1,1'-dilithio-ferrocene-

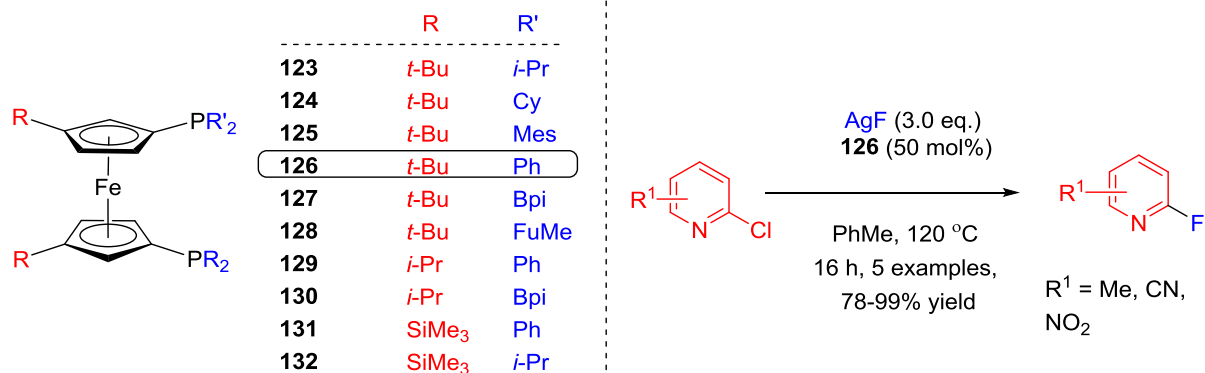
tetramethylethylenediamine with corresponding phosphine chloride derivatives in toluene. The Ni-catalyst derived from ligand **121** afforded useful synthetic conversions to desired C–N cross-coupled products. The cross coupling of furfurylamine, 2-thiophenemethylamine, or N-octylamine, with aryl chlorides using Ni(cod)<sub>2</sub>/**121** resulted in corresponding aryl amines in 36 to 87% isolated yields (Scheme 45).[166] The ligand **121** failed to couple electron-rich electrophiles such as 4-chloroanisole and 2-chloro-1,4-dimethyl-benzene to furfurylamine or indoles. The catalytic performance of ligand **121** is lower to dppf and its P-aryl derivatives in nickel-catalyzed C–N cross-couplings.



**Scheme 45:** 1, 1'-bis(dioxaphosphapine/diazaphosphalene)ferrocenes promoting Ni-catalyzed C–N cross coupling.

#### 4.5.4. C–F bond formation

The Hierso group developed various tetra-substituted alkylated bis(phosphino)ferrocenes, which were used in palladium-catalyzed C–C and C–heteroatom bond formation, including in the challenging nucleophilic C–F bond formation by direct *trans*-halogenation.[167] They reported the *rac*-bis(phosphino)ferrocenes **123-132**, in which the cyclopentadienyl rings are alkylated with more or less sterically demanding groups: i. e. *tert*-butyl, *iso*-propyl and trimethylsilyl, while the P-donor atoms are substituted with various alkyl, aryl, and heterocyclic or polycyclic moieties (Scheme 46).[167]



**Scheme 46:** Dialkylated bis(phosphino)ferrocenes promoting silver-mediated *trans*-fluorination of chloroquinolines.

*rac*-Bis(phosphino)ferrocene chiral ligands **123-132** were synthesized in a generally diastereoselective two-step sequence, in which the dilithiated ferrocene moiety reacted with the corresponding chlorophosphine electrophiles.[167] These air-stable and moisture insensitive bis(phosphino)ferrocenes achieved the fluorination of chloroquinolines in a *trans*-halogenation from AgF. The fluorination was more effective in the absence of palladium, and the nucleophilic fluorination was favored when 50 mol% of alkylated bis(phosphino)ferrocenes and three equivalents of AgF were employed (Scheme 46).

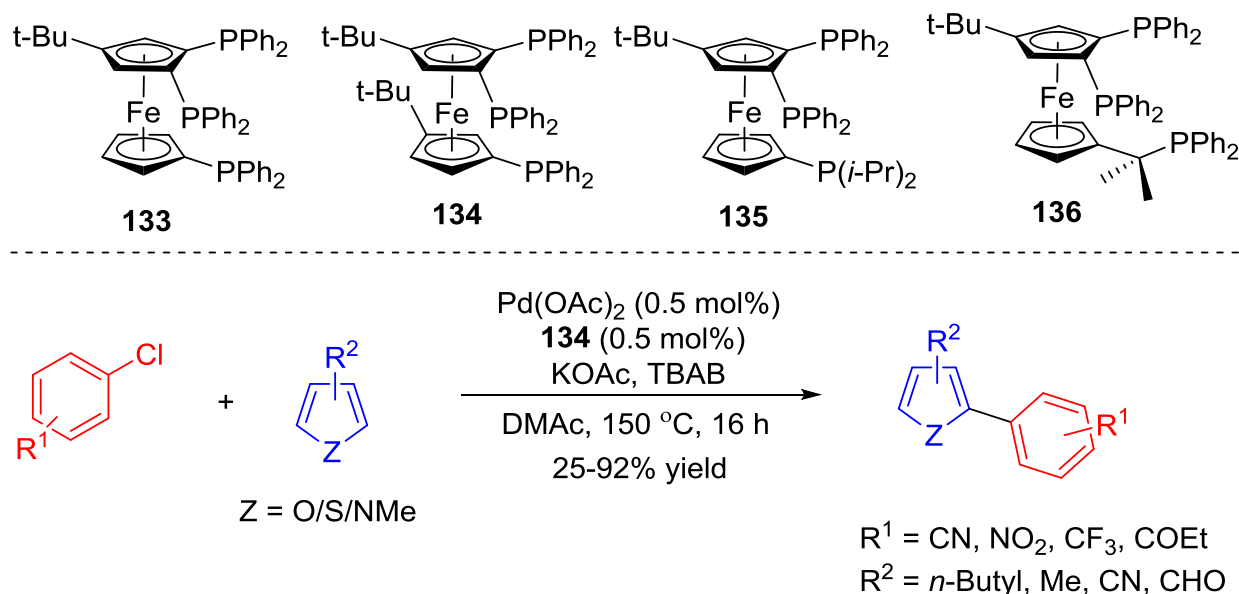
Overall, the mono- and di-functionalization of the ferrocenyl backbone is mainly achieved at 1,1'- or 1,2-positions with a large variety of alkyl, aryl and heterocyclic substituents. This allowed at finely tuning steric and electronic specific properties of ferrocene derivatives in their use as ligands for coupling reactions. The functionalization with groups including carbenes or other donor heteroatoms provided hybrid ligands used in reactions such as Suzuki-Miyaura cross-couplings under demanding conditions: i.e. unactivated substrates, reluctant halides, room temperature couplings, *etc.* The introduction of polar functional groups facilitated the use of aqueous media for catalytic couplings. The introduction of bulky groups either on the ferrocene backbone or as electron-rich substituents on phosphorus is a lever for controlling the conformation of the ferrocene and of the coordination sphere at the metal when used as ligand. This has important consequences in the regioselectivity and stereoselectivity of the catalyzed reactions. Finally, phosphinoferrocenes in combination with transition metals (mainly palladium, nickel, copper, iridium, gold, *etc.*) are clearly efficient in a broad range of cross-coupling reactions, including achiral/chiral C–C and C–X bond formation (X = N, O, P, S, and others).



Despite the organometallic nature of such ligands, robustness and air- and moisture-insensitivity are major features often encountered with these compounds, and as such are valued by synthetic chemists involved in catalytic cross-coupling research. No doubt also that in the future the redox switching of catalytic process offered by the couple Fe(II)/Fe(III), often reversible and non-destructive to the sandwich structure could be further explored and better exploited.

## 5. Polyphosphine ligands based on ferrocenyl platform

Ten positions of the two cyclopentadienyl rings are accessible to functionalize further the ferrocenyl backbone. Poly(phosphino)ferrocenes, *i.e.* functionalized with more than two phosphino groups, are polydentate ligands usable in catalysis. They offer diverse coordination modes to the metal centers [168, 169], and allow a significant lowering of the catalytic loadings in many cross-coupling reactions.[170] In general, the synthesis of such kind of ferrocene derivatives (Scheme 47, polyphosphines **133-136**) can be achieved by either the direct phosphination of the ferrocenyl backbone,[34, 171] or the reaction of iron halide salts with adequately substituted cyclopentadienyl rings.[170]

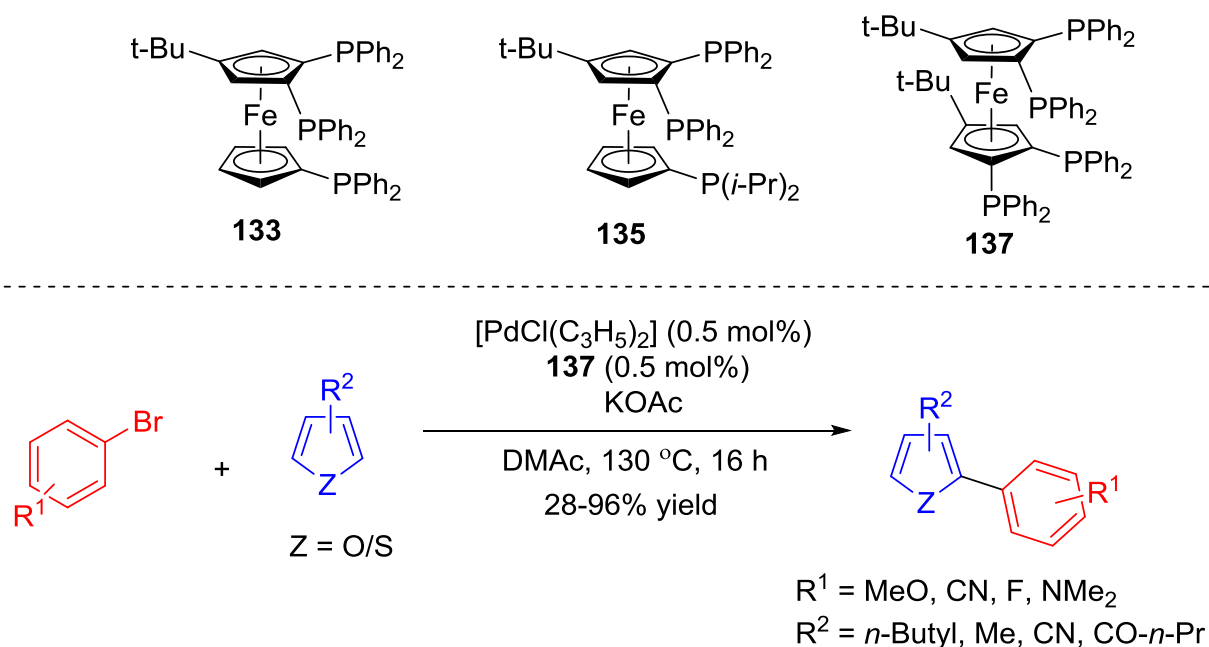


**Scheme 47:** [Pd/poly(phosphino)ferrocene]-catalyzed direct C–H arylation of heteroarenes with functionalized chloroarenes.

The polydenticy of poly(phosphino)ferrocene compounds promotes catalyst longevity, and allows to reduce catalytic loadings down low to  $10^{-1}$  to  $10^{-4}$  mol% levels in palladium-catalyzed C–C bond formation.[172] The direct arylation of heteroaromatic substrates using both C–H and C–Cl activation is an atom-economic general synthetic strategy for accessing valuable substituted organic heterocyclic compounds.[173, 174]

Hierso and Doucet groups investigated the performances of air- and moisture-stable, temperature resistant ferrocenyl polyphosphines **133-136** for palladium-catalyzed direct coupling of chloroarenes with heteroaromatics (Schemes 47-48). The ferrocenyl triphosphine ligand **134** exhibited higher efficiency than analogous mono- and bis(phosphino)ferrocene ligands (Scheme 47).[175] Catalyst concentrations ranging between 0.1 and 0.5 mol% were used for the arylation of electron-rich, electron-poor, and polysubstituted furans, thiophenes, pyrroles, and thiazoles. Formyl, nitro, nitrile, keto and ester groups were well-tolerated on aryl chloride substrates.

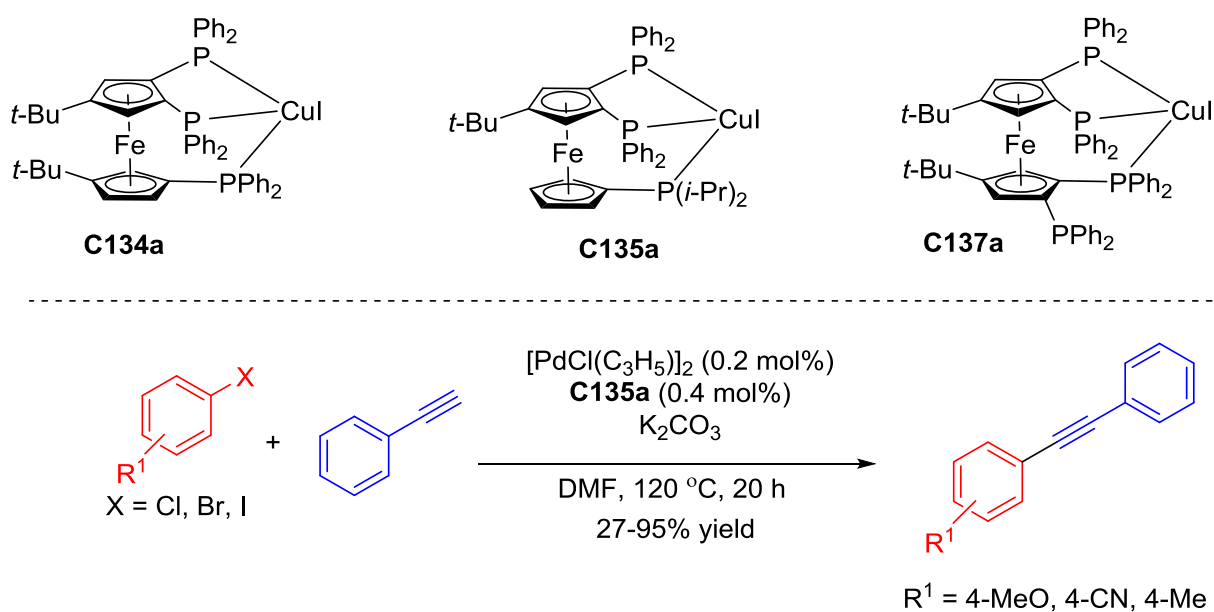
The performances of poly(phosphino)ferrocenes **133**, **135**, and **137**, bearing phenyl groups on P-donor atom, ddpf and 1,1'-bis(dimethylfurylphosphino)ferrocene were investigated for the direct arylation of bromoarenes using  $[\text{Pd}(\text{C}_3\text{H}_5)_2\text{Cl}_2]$  (Scheme 48).[176] The triphosphine ligand **137** gave comparably higher yields at catalytic loadings down to 0.1 mol%, in the presence of KOAc as base in dimethylacetamide at 130 °C.[176]



**Scheme 48:** Palladium-catalyzed C–H bond arylation of heterocycles using palladium stabilized with poly(phosphino)ferrocenes.

[Pd/**137**] effectively achieved the coupling of sterically hindered 1-bromonaphthalene, and 2-bromotoluene with alkylated furans, thiophenes, thiazoles, and benzoxazoles in moderate to excellent yields (up to 96%) but performed sluggishly with activated chloroarenes.

Poly(phosphino)ferrocene ligands were also employed for stabilizing copper(I) as well-defined species useful in the palladium and copper co-catalyzed Sonogashira-Hagihara cross-coupling of alkynes with deactivated aryl bromides and electron-poor aryl chlorides. These copper(I) iodide complexes stabilized with tri- or tetra(phosphino)ferrocenes were used at low loadings of 0.4 mol% in combination with [Pd(allyl)Cl]<sub>2</sub> (Scheme 49).<sup>[177]</sup> The low amount of copper used is particularly notable in contrast with much higher loadings of above 5 mol% usually employed in Sonogashira reactions.

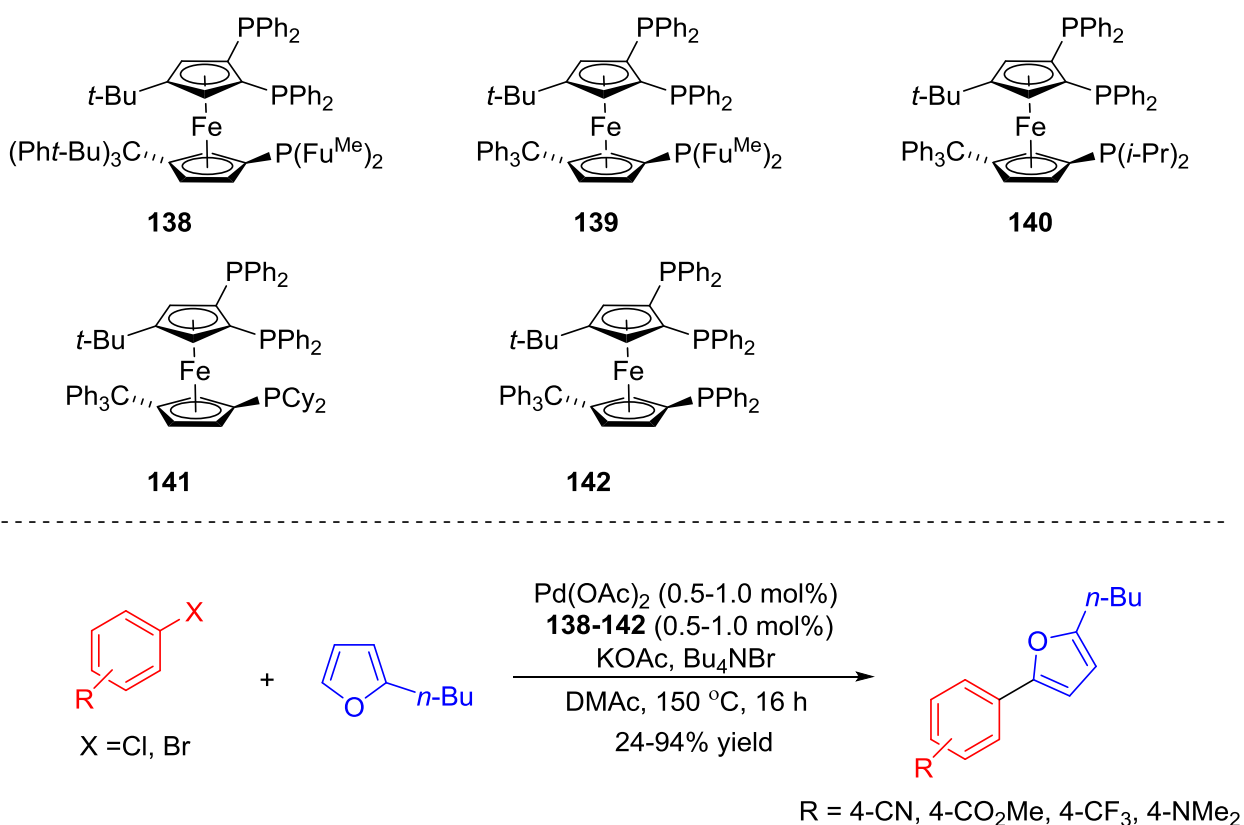


**Scheme 49:** Tricoordinate copper/poly(phosphino)ferrocene and Pd-catalyzed Sonogashira-Hagihara cross-coupling.

Demanding aryl bromides such as 4-bromoanisole, 2-bromonaphthalene, 2-bromotoluene, and 1,2-bromobenzene were successfully used, while the coupling of 4-chloroanisole failed. At higher catalyst loadings of [Pd/Cu] (2 mol%), the electron-poor chloroarenes gave moderate yields (65%). Interestingly, complex **C135a** promoted the coupling of electron-rich 4-iodotoluene with phenylacetylene in the absence of a palladium source. The coordination of these

polydentate ligands with copper and palladium in solution was examined by NMR, suggesting that ligand transfer from copper to palladium is viable. While **C137a** with a tetraphosphine was reluctant to undergo such ligand transfer process, the exchange was conversely found to be rapid with triphosphine complexes **C134a** and **C135a**.

The Hierso group also prepared very congested ferrocenyl polyphosphines **138-142** (Scheme 50), from substituted cyclopentadienyl assemblies, in which one cyclopentadienyl ring was substituted with two phosphino groups and one *tert*-butyl group, while the other ring is substituted with one phosphino group and one hindering branched group, (triphenyl)methyl or tri(4-*tert*-butyl)phenylmethyl (Scheme 50).[178]



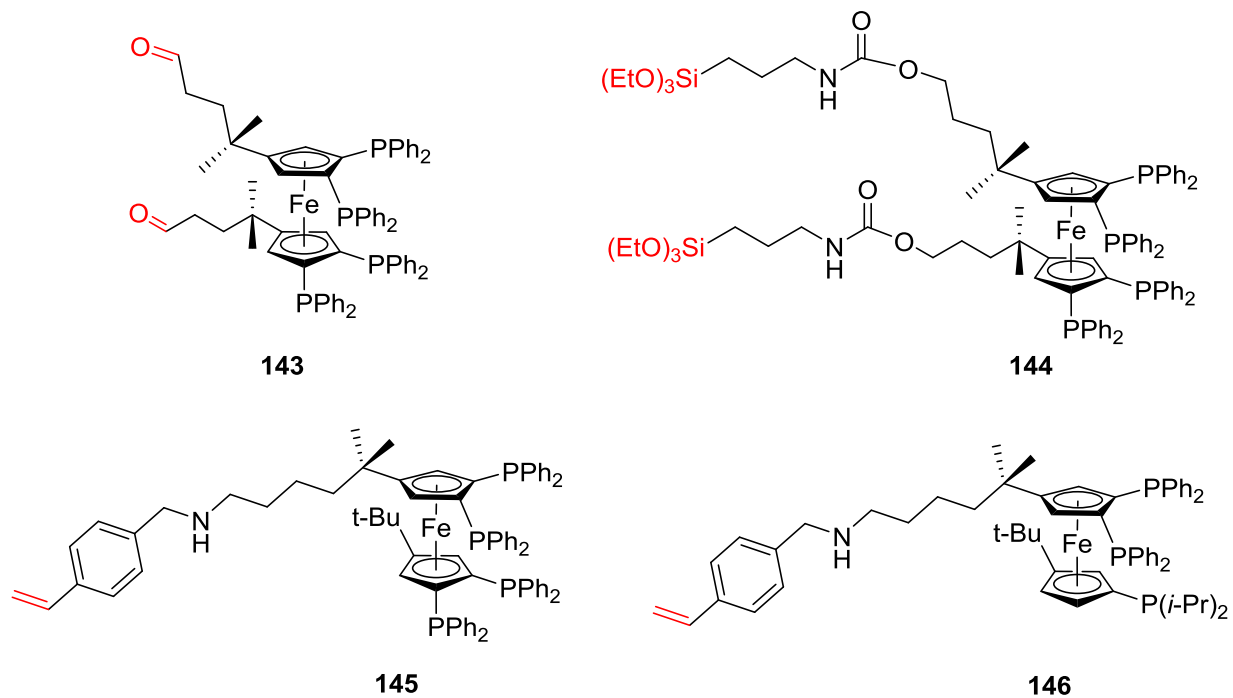
**Scheme 50:** Congested poly(phosphino)ferrocenes used in the Pd-catalyzed cross-coupling of chloroarenes and heteroarenes.

The resulting robust tris(phosphino)ferrocenes **138-142** were found to be air-stable even when P-donor atoms were substituted with electron-rich *i*-propyl and cyclohexyl groups. The poly(phosphino)ferrocenes with the electron-withdrawing furyl groups on the P-donor atom were also synthesized in good yields.

The conformational analysis by multinuclear NMR of the tris(phosphino)ferrocenes evidenced non-covalent “through-space” (TS) spin-spin  $^{31}\text{P}$ - $^{31}\text{P}$  nuclear couplings between heteroannular phosphorus atoms presumed to be in close proximity in solution. Values ranging up to  $^{\text{TS}}J_{\text{pp}} = 23$  Hz were reported.

Bis(phosphino) and tris(phosphino)ferrocene as ligands were investigated in the palladium-catalyzed direct arylation of heteroaromatics via C–H activation (Scheme 50).[178] The palladium catalysts derived from alkylated electron-rich tris(phosphino)ferrocenes **140** and **141** achieved the best conversions (Scheme 50). The catalysts promoted the coupling of deactivated bromoarenes, 4-chlorobenzonitrile, 4-chloronitrobenzene and 4-(trifluoromethyl)chlorobenzene with heterocyclic units at loadings of 0.5 to 1.0 mol%.

Beside lowering the catalyst metal loading down to  $10^{-4}$  mol%, the immobilization of molecular catalytic systems is an attractive strategy for effective separation and recycling towards more economical and environment-friendly industrial processes.[179-184]. The Hierso group further proposed polyphosphines immobilization for addressing a specific limitation in solid support catalysts, *i. e.* the unproductive high dispersion of coordinating donor-sites on supports.[169, 185] They synthesized ferrocenyl tri- and tetraphosphines **143-146** (Figure 7), as compounds ready for immobilization, with a controlled conformation, back-functionalized for their targeted implantation on various solid supports.

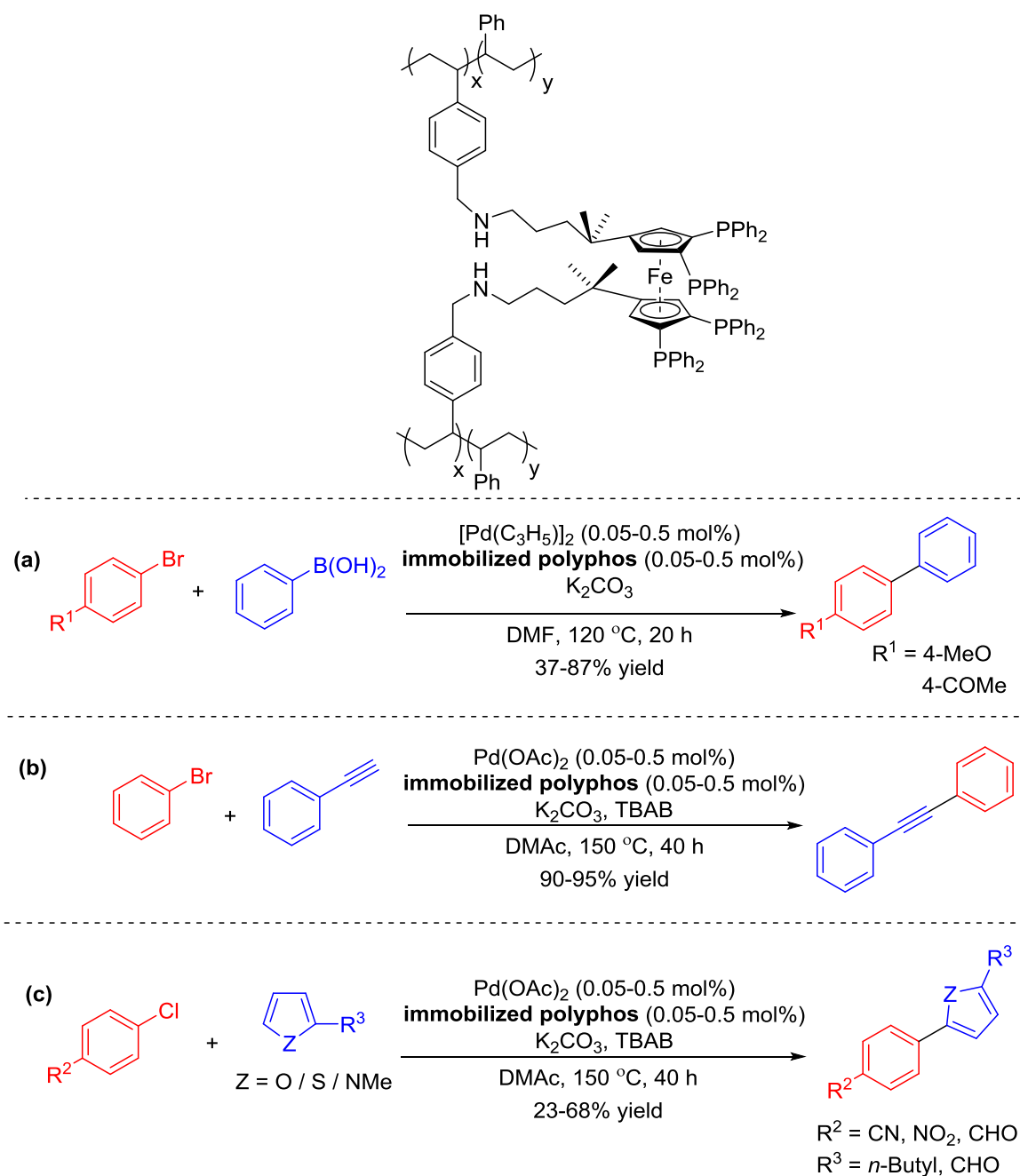


**Figure 7:** Back-functionalized poly(phosphino)ferrocenes ready for immobilization and controlled backbone conformation.

Ligand rigidity and close proximity of phosphorus donors on the ferrocene backbone were preserved by *gem*-dimethyl groups linked to cyclopentadienyl (Figure 7). Among others, immobilization of ligand **146** was realized utilizing its styrenyl unit anchored to tetra(phosphino)ferrocene via radical copolymerization with styrene (Scheme 51).[169, 185] The resultant solid has shown good solubility in many organic solvents except for methanol and hexane. The phosphorus concentration (1.05%) was measured by elemental analysis, and  $^{31}\text{P}$  NMR depicting two broad signals at  $-30.0$  and  $-34.0$  ppm evidencing the presence of internal and peripheral P-donor atoms in the polymer typical of the corresponding molecular tetraphosphine arrangement.

Similarly, ligand **144** (Figure 7) was efficiently immobilized on silica gel via siloxane condensation, resulting in insoluble brown-red beads, for which  $^{31}\text{P}$  NMR CP-MAS analysis indicated a broad singlet at  $-30$  ppm. Modified tris(phosphino)ferrocene, ligand **146** was also immobilized via radical polymerization with 60 equiv of styrene and 7 equiv of divinyl benzene, resulting in an insoluble polymer material with 1.05 % of phosphorus concentration.[169] These immobilized poly(phosphino)ferrocene compounds in the presence of palladium were employed

in Suzuki-Miyaura arene arylations (Scheme 51a), copper-free Sonogashira alkyne arylations (Scheme 51b), and in the C–H bond arylation of furan, thiophene and pyrrole substrates with chloroarenes (Scheme 51c).



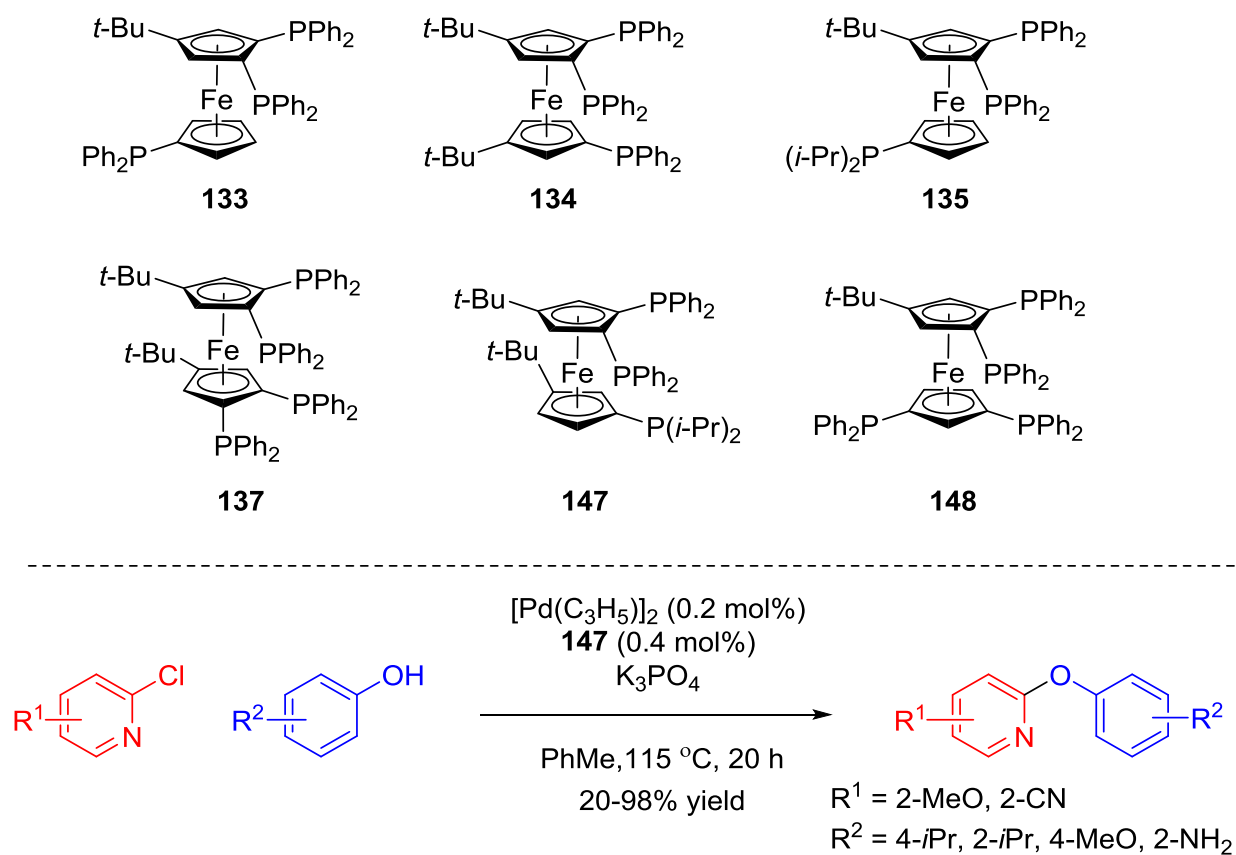
**Scheme 51:** a) Pd-catalyzed Suzuki-Miyaura, b) copper-free Sonogashira, and c) direct C–H arylation of heteroarenes with arylchlorides promoted by immobilized poly(phosphino)ferrocenes.

In the reactions investigated, the heterogeneous solid support catalysts offered moderate to excellent product conversions at very low palladium loadings (0.05-0.5 mol%) and maintained the regioselectivity in the case of heterocyclic C–H activation processes.

## 5.1. Poly(phosphino)ferrocene ligands in carbon–heteroatom cross-coupling reactions

### 5.1.1. C–O bond formation

Congested ferrocenyl polyphosphines **133-135**, **137**, **147** and **148** combined with palladium were tested for the C–O cross-coupling etherification of pyridine-based heteroaromatic halides (Scheme 52).[186]



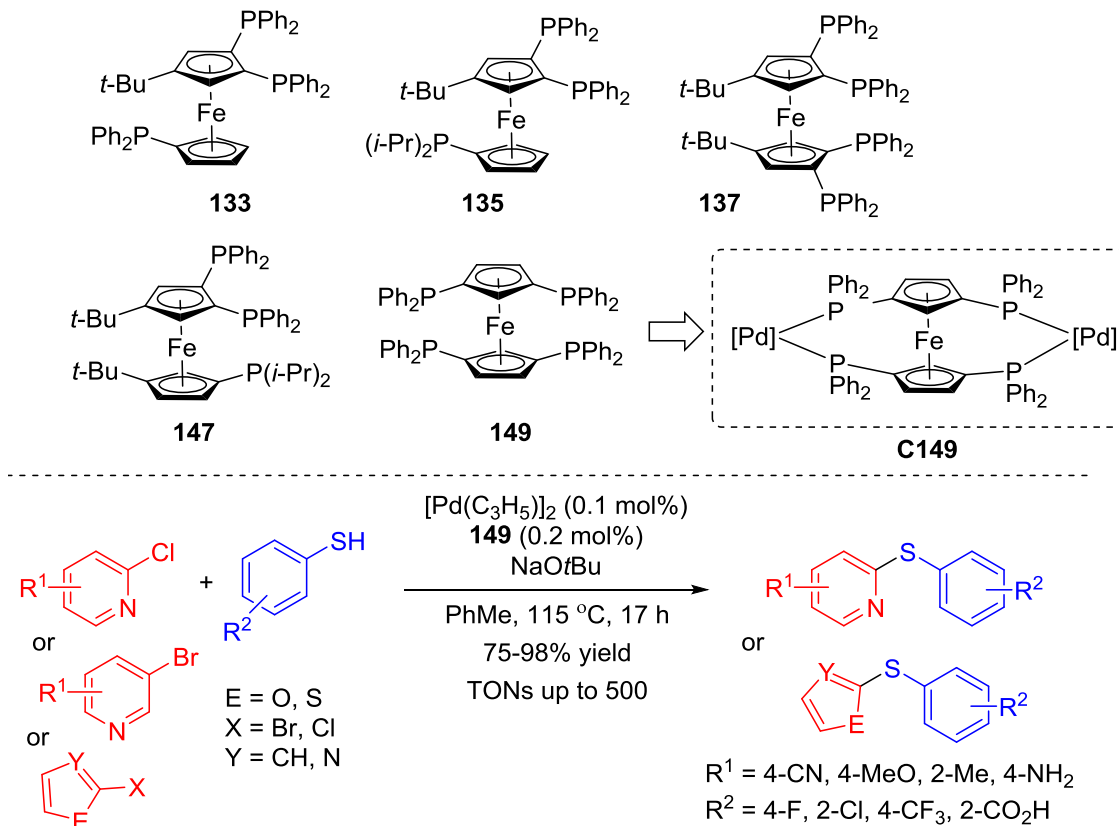
**Scheme 52:** Poly(phosphino)ferrocenes applied in Pd-catalyzed C–O cross-coupling for (heteroaryl)arylether formation.



At 0.2 mol% of the palladium catalyst derived from tris(phosphino)ferrocenes, **147** was found to be the most effective for coupling between 2-chlorinated substrates of pyridine, pyrimidine, hydroxypyridine, and quinolone with various phenols bearing electron-donating and electron-withdrawing groups in *ortho*, *meta* and *para*-positions. The ferrocenylpolyphosphines **147**, **134** and **137**, bearing two bulky *tert*-butyl groups, afforded supplementary conformational control at the ferrocene backbone, along with a high activity for palladium catalyzed C–O coupling for **147**. The DFT studies demonstrated that tris(phosphino)ferrocene **147** opens up new catalytic pathways involving the third electron-rich *iso*-propylphosphino group in the rate determining step that is C–O reductive elimination. The rate for one of these new pathways was calculated as *ca.* 1000 times faster than reductive elimination from a complex with a similar ferrocenyl ligand but without a phosphine group on the bottom cyclopentadienyl ring. The coordination of the third phosphino group to the palladium(II) center was evidenced to essentially stabilizing the transition state in this new pathway, thereby enhancing the reductive elimination rate.[186]

#### 5.1.2. C–S bond formation

The cross-coupling of thiophenols with heteroaryl halides is a challenging reaction, in which many state-of-the-art palladium- and copper-based catalytic systems achieved only limited turnover numbers.[187, 188, 189] However, poly(phosphino)ferrocenes in combination with palladium were employed for such challenging C–S bond formation reactions (Scheme 53).



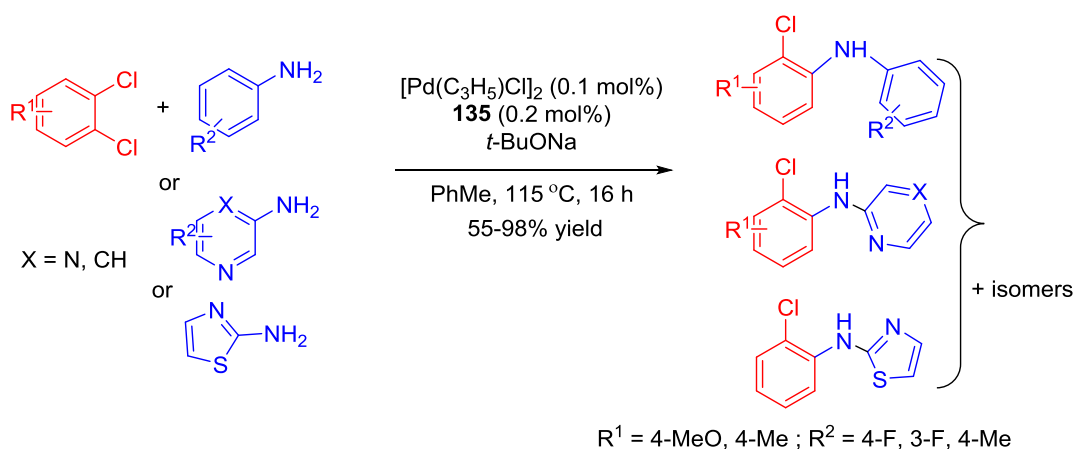
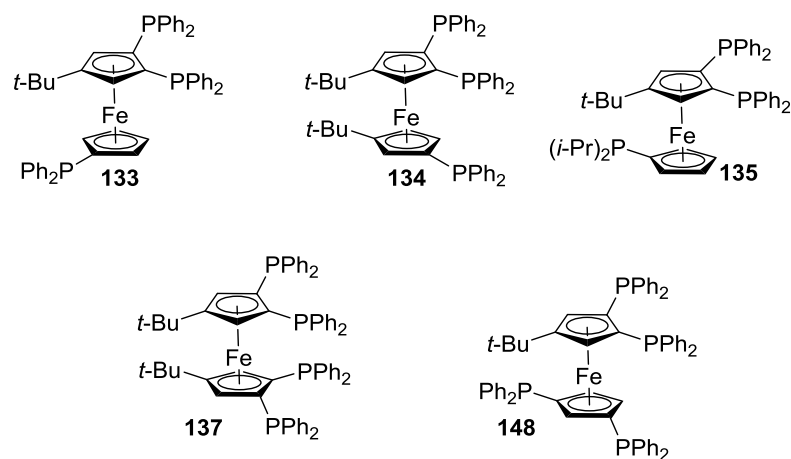
**Scheme 53:** Tetra(phenylphosphino)ferrocene **152** used in palladium-catalyzed C–S cross-coupling reactions.

The air-stable tetradentate 1,1',3,3'-tetrakis(diphenylphosphino)ferrocene **149** (Scheme 53), in combination with palladium, very efficiently catalyzed the coupling of a wide range of functionalized thiophenols with chloro- and bromoheteroaromatics. This included 2- or 3-pyridinyl, thiazolyl, furanyl and thienyl scaffolds with the highest TONs reported to date (Scheme 53).[190] Catalytic conditions involved  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\mathbf{149}$  at 0.1 and 0.2 mol%, respectively, in toluene with the base  $\text{NaO}^t\text{Bu}$ . The catalytic system tolerated electron-rich, electron-withdrawing, fluoro, unprotected amino or chloro-functionalized thiophenols, as well as six and five-membered 2-chloroheteroarenes, including pyridine, pyridazine, quinolone, pyrimidine, and others. The mode of coordination of ligand **149**, favored the formation of a locked binuclear palladium **C149** complex, in which **149** coordinates two palladium centers via a bis- $\kappa^2$  mode (Scheme 53), which resembles the classical 1,1'-coordination of dppf repeated on two opposite site directions. DFT studies attributed the good performance of such binuclear palladium catalyst to the decreased stability of thiolate-containing resting states [190]. Palladium

loading was as low as 0.2 mol%, which may be important for industrial application, and is a step forward in resolving catalyst activation/deactivation issues.

### 5.1.3. C–N bond formation

The cross-coupling between aryl chlorides and anilines (Buchwald-Hartwig reaction) has faced some shortcomings in terms of catalytic efficiency, sometimes due to the propension to catalyst deactivation by oxidation of the labile air-sensitive electron-rich phosphine ligands. The palladium-catalyzed C–N bond formation reaction employing air-stable robust polydentate ferrocenyl phosphines was investigated to address this issue (Scheme 54). A diverse set of polydentate ligands was tested for their efficiency and selectivity in the amination of dichloroarenes.[191] Among these ligands the air-stable electron-rich tridentate ferrocenylpolyphosphine 1,2-bis(diphenylphosphino)-1'-(diisopropylphosphino)-4-*tert*-butylferrocene **135** (Scheme 54) was successfully employed in 2 mol% loading in combination with 1 mol% of  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ ; it allowed an efficient and selective coupling, while such demanding substrates normally induce chloroarene homocoupling and/or dehalogenation processes. The scope of the system included electron-poor fluoroanilines (deactivated nucleophiles) and electron-rich methylated and methoxylated dichlorobenzenes (deactivated electrophiles), while regioselectivities between 1:1 to 1:10 were observed depending of the substrates.

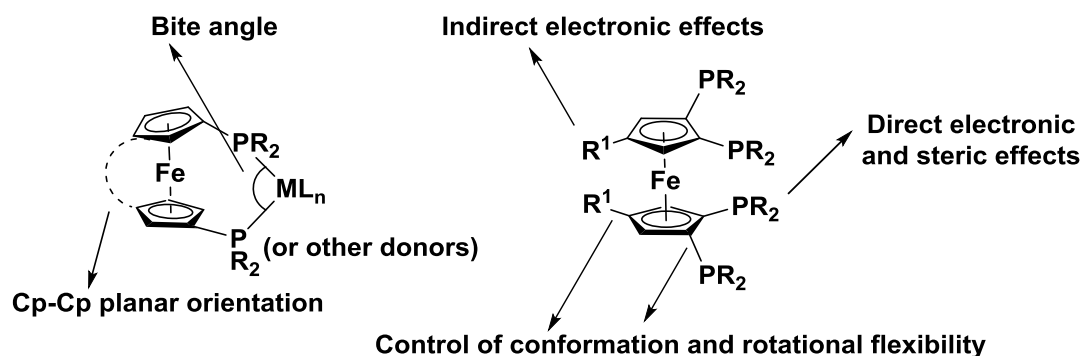


**Scheme 54:** Polyphosphinoferrocenes employed for Pd-catalyzed selective C–N cross-coupling of dichloroarenes.

## 6. Electronic properties and structural benefits of phosphinoferrocenyl scaffolds for catalysis

Ferrocenylphosphines widely used in homogeneous catalysis gained special attention due to their air-, moisture-, and temperature excellent stability. As a ligand, their conformational flexibility is also a benefit for adopting various coordination to metals, as the catalytic intermediate in the cycles are evolving in terms of coordination number and formal oxidation degree of the metal. Accordingly, ferrocenylphosphines, used as metalloligands, have a direct influence on the catalytic output in a variety of reactions –as it is illustrated in the previous sections–, which may be concisely exposed.[102] While the cause of the specific effects (*i.e.* electronic, steric, geometric, redox, *etc.*) in relation to reaction parameters and substrates may be delicate to

comprehend –and should be better individually explored in details [190]–, some essential structural features of diphosphine and polyphosphine ferrocene ligands may be depicted. We show in Figure 8 critical features: *i*) their chelating bite angle, *ii*) the Cp-Cp planar orientation, *iii*) the conformation control jointly from substituents on Cp rings and donor groups, *i*) the direct and indirect electronic effects of these substituents on the iron center and the coordinating donor groups.



**Figure 8:** Features influencing typical ferrocenyl ligand in catalysis

In ligand chemistry, bite angle is a determining parameter in the case of chelating bidentate coordination. The archetypal bidentate ferrocenylphosphine dppf complexes with various transition metals (Mn, Fe, Pd, Cu, Ni, Au, Ag) and the respective bite angles are generally reported and compared (in general from XRD or computed optimized structures).[1, 192, 193] In general, P–M–P bite angle values ranged from 90 ° to 120 °, which contributes to the flexibility in metal/ferrocenyl ligands complexes. The P–M–P bite angles may exert a control on the activity and selectivity for a specific transformation. For example, the PdCl<sub>2</sub>(dppf) with larger P–Pd–P bite angle of 96 ° outperformed its analogues catalysts derived from PPh<sub>3</sub>, dppe (diphenylphosphinoethane), or dppp (diphenylphosphinopropane) in Kumada type coupling of *sec*-butyl magnesium chloride with bromobenzene.[194] Dierkes and van Leeuwen reviewed the bite angle effects in relation with reaction rates of intermediate steps involved in catalytic cycles.[192] A smaller bite angle enhances the electron density at central metal atom, thus favoring the oxidative addition of polarized C–X bonds on the metal. Conversely, the larger bite angles enhanced the rate of the reductive elimination step. Therefore, a flexible range of bite angles satisfactory balances the individual rate of catalytic elementary steps.

The effect of the substrates on the stability of metal complex intermediates is also an important parameter. For instance, in studies involving Pd-catalyzed and dppf in Heck reactions that employ methyl acrylate and aryl halides, Jutand and Brown recognized that the alkene reactant (and products) are electrophilic substrates whose strong association to Pd(0) intermediates may diminish the overall turnover rate by enforcing a kinetically unfavorable process of oxidative addition [195]. These ligands reduced the electron-density at the palladium core, and hence slowed down the reactivity toward the substrate activation, as it has been early on discussed by Tolman in relation with large chelating bite angles.[196] Nevertheless, this stability enhancement can be also very profitable for low time life palladium(0) species and may provide lower TOFs but better TONs as demonstrated by the studies of the Hierso group.[197,198]

Additionally, the determining direct electronic effects on reaction kinetics of substituent on P-donors were illustrated, for instance, in C–C cross-coupling reactions by the preparation of an electron-poor bis-(difuryl)phosphino ferrocene  $\text{Fc}[\text{P}(\text{FuMe})_2]_2$  [199] (in general electron-rich ligands effects are very well-documented in the literature because of their recognized positive effect on oxidative addition, see for instance below the Colacot group work). The resultant active precatalyst  $\{\text{PdCl}_2(\text{Fc}[\text{P}(\text{FuMe})_2]_2)\}$  used for allylic amination, promoted exceptional TOFs (turnover frequencies) above  $10,000 \text{ h}^{-1}$  with full conversion and 96% monoamination selectivity at rt. Under same conditions dppf performed sluggishly (60% conversion with TOF  $150 \text{ h}^{-1}$ ). The low  $\sigma$ -electron-donating and more  $\pi$ -accepting nature of furyl groups on phosphorus in comparison to phenyl groups much increase the electrophilicity of the Pd(II)/allyl intermediate.[200] Thus, accelerating the outer-sphere amine nucleophilic attack, the assumed rate-limiting step.[201]

Notably, the reactivity is also influenced by the steric effects of the size of the substituents on phosphorus for polydentate,[197] bidentate,[102] and monodentate ferrocenylphosphine ligands,[202] also depending on the substrates impediment. For instance, Colacot and coworkers studied the activation of aryl chlorides in Suzuki-Miyaura reaction with a series of  $[\text{Cp}_2\text{Fe}(\text{PR}_2)_2\text{PdCl}_2]$  complexes, where R is a bulky and electron rich group (*i*-Pr and *t*-Bu). The comparison of the efficiency of these air-stable catalysts with the other commercial catalysts, such as  $[(\text{Ph}_3\text{P})_2\text{PdCl}_2]$ ,  $[(\text{Cy}_3\text{P})_2\text{PdCl}_2]$ , *etc.* was established. From 1 mol% catalyst loading of of

[di-*t*-BuPFcPdCl<sub>2</sub>] remarkable activation of chloroarenes occurred under standard Suzuki-Miyaura reaction conditions.[203] All other tested catalysts performed sluggishly, including [PdCl<sub>2</sub>(dppf)]. The increase in steric bulk and electron density of the phosphine ligand is shown to clearly increase the activity.

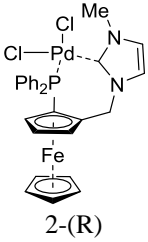
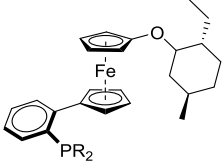
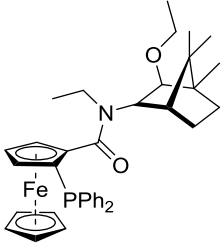
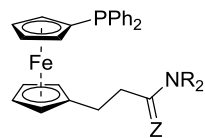
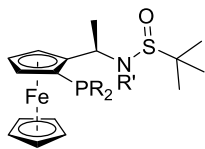
Polydentate ligands showed high performance at exceptionally low catalytic loadings of palladium ranging from 10<sup>-2</sup> to 10<sup>-4</sup> mol%.[205,206] The robustness of these class of polyphosphino ligands is attributed to their ability to form stable intermediate metal-phosphine catalytic species especially with low stability Pd(0) species, during the catalytic process, which as a result, reduces the catalyst degradation towards insoluble metal Pd(0) nanoparticle formation.[197,198] Finally, the "coordination-pressure" surrounding the metal core may accelerate some cross-coupling determining stages, including the reductive elimination at the origin of products releasing.[186]

## 7. Cross-coupling reaction cumulative table

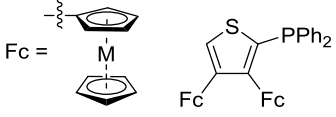
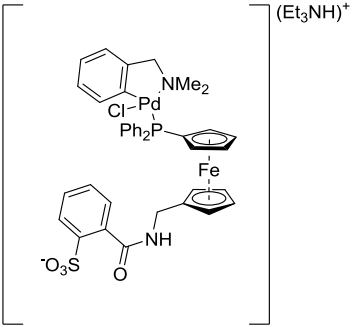
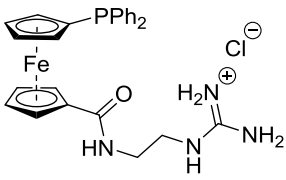
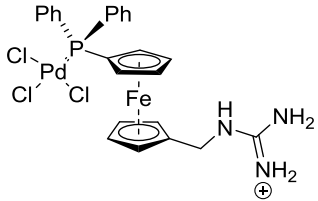
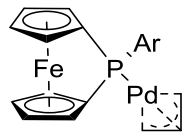
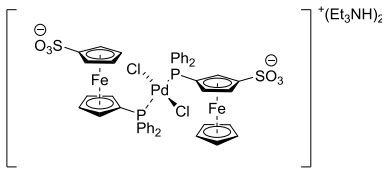
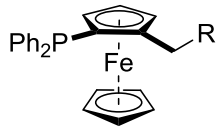
Currently, because of their commercial accessibility, robustness (for long-term conservation), and decisive metal-stabilizing properties, ferrocenyl phosphines are among the ligands of choice (together with triphenylphosphine and alkyl derivatives) in pharmaceutical and fine chemical industry relevant organic transformations. Olefin alkoxy carbonylation, Heck coupling, Stille coupling, asymmetric hydrogenation, allylic alkylation, Grignard cross coupling, aldol reactions, and many others are achieved using ferrocenyl phosphines.[46, 47, 63, 96, 110] More precisely, the advantages of these types of metalloligands include together steric bulkiness, large bite angles (90° to 120° for chelating ligands, see above section 6), and as previously mentioned, a relative air stability of even alkyl-substituted ferrocenyl phosphines (notably compared to *t*-Bu<sub>3</sub>P and PCy<sub>3</sub>). Furthermore, ferrocenyl phosphine ligands enable simple reductive elimination avoiding unwanted isomerization ( $\beta$ -hydrogen elimination), which sometimes results in undesired side-products. Many of the ligands, such as dppf or its  $-P(i\text{-Pr})$  and  $-P(t\text{-Bu})$  substituted analogs, are commercially available, and their air and moisture stabilities improved even more when complexed with palladium or other late transition metals. Today, more than 70 ferrocenyl phosphine ligands and/or precatalysts are commercially available from big

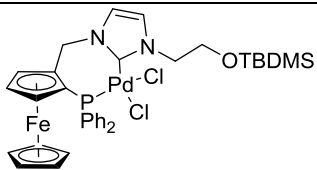
distributors, demonstrating their applicability and ease of use in the industry and academia. Beyond this brief account, it is of interest to get a rapid view of the opportunity in catalysis offered by ferrocenyl systems, and the following *Cumulative Table 1* fulfills this need. The reactions are presented with respect to metals involved in particular transformation.

**Table 1**

Ferrocenyl phosphine or metal complex	Metal Center	Type of Reaction	Ref.
 <p>2-(R)</p>	Pd	Asymmetric Suzuki-Miyaura reaction between naphthyl bromides and naphthylboronic acids	[70]
 <p>1, R = 2-tolyl 2, R = Ph 3, R = 2-furyl</p>	Pd	Suzuki-Miyaura C–C coupling	[60]
	Pd	Asymmetric allylic alkylation	[62]
 <p>Z = O, NR<sub>2</sub> = NPh</p>	Pd	Cyanation of aryl bromides	[64]
 <p>R = C<sub>6</sub>H<sub>5</sub>, R' = H, (R<sub>C</sub>, S<sub>F<sub>C</sub>'</sub>, R<sub>S</sub>)</p>	Pd	Asymmetric allylic alkylation & Allylic amination	[67]



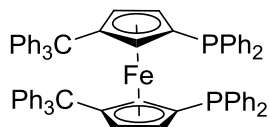
	Pd	Suzuki-Miyaura C–C coupling	[57]
	Pd	C – C cross-coupling of aryl boronic acids and acyl chlorides in aqueous medium	[85]
	Pd	C – C cross-coupling of aryl boronic acids with acyl chlorides	[89]
	Pd	Suzuki-Miyaura C–C coupling	[93]
	Pd	Buchwald–Hartwig coupling	[95]
	Pd	C – C cross-coupling of boronic acids with acyl chlorides	[96]
 <p>R = NPh</p>	Pd	Suzuki-Miyaura cross-coupling for the synthesis of <i>ortho</i> -substituted biaryl	[48]



Pd

Suzuki-Miyaura C–C coupling

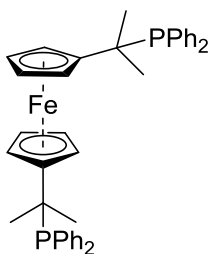
[80]



Pd

Heteroaromatics arylation by direct C–H activation

[124]

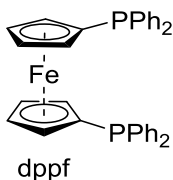


Sylphos

Pd

Direct C–H arylation of heteroaromatics with activated aryl chlorides

[130]



dppf

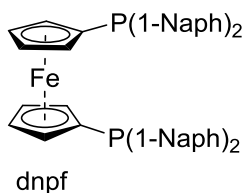
Pd

C – P cross-coupling of H-phosphinates and other P(O)H-containing compounds

[152]

Thioetherification of alkenyl halides and tosylates

[153]



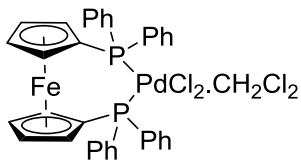
dnfp

Pd

 $\alpha$ -Arylation of vinyl arenes; Heck reaction of aliphatic olefins and aryl halides

[135]

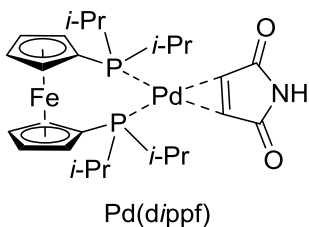
[204]



Pd

Suzuki–Miyaura diversification of amino acids and dipeptides in aqueous media

[136]



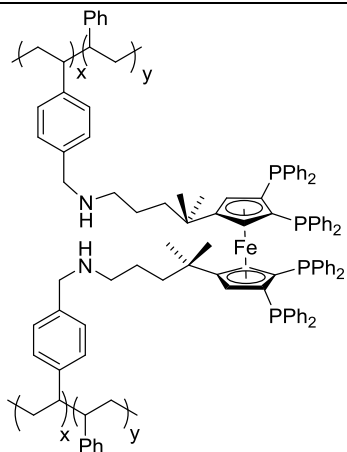
Pd(dippf)

Pd

Monoarylation of primary anilines

[155]

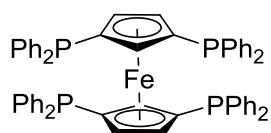
	Pd	Alkoxy carbonylation of bulky olefins	[149]
	Pd	Methoxy carbonylation of alkenes	[150]
	Pd	Direct C–H arylation of heteroarenes with chloroarenes	[205]
	Pd	Sonogashira-Hagihara coupling of alkynes with aryl bromides	[206] [177]
	Pd	Direct C–H arylation of heteroarenes with chloroarenes	[178]
	Pd	Etherification of functionalized phenols with chloroheteroarenes	[186]



Pd

C–C coupling and direct C–H arylation in heterogeneous and recycling conditions

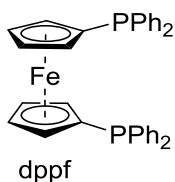
[169]



Pd

Thioetherification of chloroheteroarenes

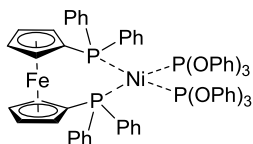
[190]



Ni

$C_{sp^2}$ –N cross-coupling

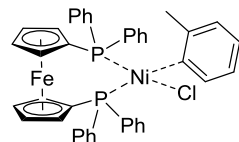
[160, 161, 164, 165]



Ni

*N*-arylation of amine

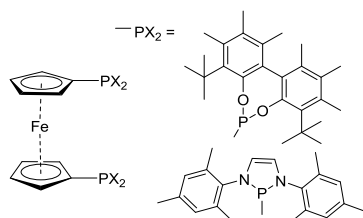
[162, 163]



Ni

*N*-arylation of amine

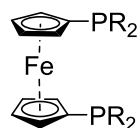
[166]

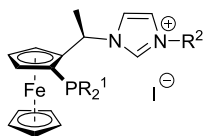


Ni

C–C cross-coupling of arylboronic acids with aryl carbonate

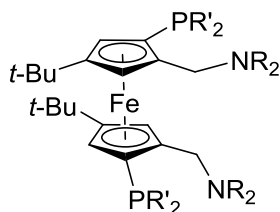
[127]





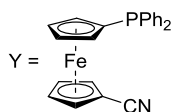
R<sup>1</sup> = Ph, R<sup>2</sup> = Me

Cu      Enantioselective 1,4-additions of Grignard reagents to  $\alpha,\beta$ -unsaturated carbonyl      [79]



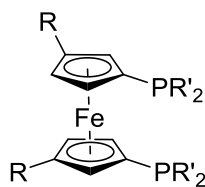
R = Et, R' = *i*-Pr

Au      Suzuki coupling of *ortho*-substituted hindered haloarenes      [144]



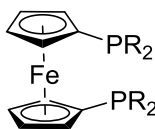
Au complex = [(Y)-Au]<sub>2</sub>[NTf<sub>2</sub>]<sub>2</sub>

Au      Oxidative cyclisation of terminal alkynes with nitriles to give 1,3-oxazoles      [100]



R	R'	R	R'
<i>t</i> -Bu	<i>i</i> -Pr	Ph	<i>i</i> -Pr
<i>t</i> -Bu	Cy	Bpi	<i>i</i> -Pr
<i>t</i> -Bu	Mes	Ph	SiMe <sub>3</sub>
<i>t</i> -Bu	Ph	<i>i</i> -Pr	SiMe <sub>3</sub>
<i>t</i> -Bu	Bpi		
<i>t</i> -Bu	FuMe		

Ag      Direct nucleophilic fluorination of chloroquinolines      [167]



R = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

Ir       $\alpha$ -Selective arylation of styrenes      [137]

## 8. Conclusion and Perspective

The overview of mono-, di- and polyphosphine ligands built on the ferrocene platform presented herein emphasizes the high potential of these compounds for providing innovative advances in varied transition metal catalysis. The usefulness of planar chiral functionalized ferrocene backbones has been amply demonstrated, and will certainly find further applications in producing optically active compounds. The synthetic shift from organometallic cross-coupling – archetypically the Suzuki-Miyaura coupling of boron-functionalized organometallics– to direct C–H activation has already begun with precious transition metals, such as palladium and iridium. It should be further alimented in the future with more widely accessible metals such as nickel and copper. Some first-row transition metals (cobalt, manganese, etc.) stabilized by ferrocenyl phosphines were, until now, notably underdeveloped –implying thus potential catalytic application. Their coordination chemistry warrants further exploration and development, as they hold considerable promise for cross-couplings leading to C–X bond formation (with X = P, N, O, S, Se, and halides including challenging F). In particular, the development of polytopic ferrocene ligands, either as polyphosphines or as hybrid ligands, hold promises for stabilizing by various chelation modes the elusive first-row transition metal centers. However, the propensity of these metals to achieve single-electron transfer, and the radical processes attached to these, is a difficulty to overcome when metalloligands like ferrocene are used. Indeed, the control of Fe(II)/Fe(III) oxidation state would be either a major issue or a beneficial lever towards some redox controlled chemistry. Finally, the robustness and facile functionalization of ferrocene for stabilizing strong donors like carbenes, phosphines and others is a key for atom-economic approaches aiming at the development of protocols employing only traces of metallic components as catalysts. Traces as low as ppm are accessible.

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