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Review

Performances of symmetrical achiral ferrocenylphosphine ligands in palladium-catalyzed cross-coupling reactions: A review of syntheses, catalytic applications and structural properties

Aziz Fihri *, Philippe Meunier, Jean-Cyrille Hierso **

ICMUB (Institut de Chimie Moléculaire de l'Université de Bourgogne)-UMR CNRS 5260, Laboratoire ARECO (Architecture, Réactivité, Electrochimie et Catalyse Organométallique)-Université de Bourgogne, 9 Avenue Alain Savary, 21078 Dijon, France

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Contents

Abstract

Ferrocene derivatives bearing donor atoms led to the generation of several classes of metallo-ligands, which collectively show an impressive diversity of applications, especially in metal-catalyzed modern organic reactions. Based on the impetus provided by the use of the diphosphine

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* Corresponding author. Present address: Laboratoire de Chimie et Biochimie des Centres Rédox Biologiques, UMR 5047, CEA/CNRS/Université Joseph Fourier, CEA-Grenoble, DRDC/CB, 17 rue des Martyrs, 38054 Grenoble Cedex 09, France. Tel.: +33 4 38 78 91 21; fax: +33 4 38 78 91 24.

** Corresponding author. Tel.: +33 3 80 39 61 06; fax: +33 3 80 39 36 82.

E-mail addresses: aziz.fihri@cea.fr (A. Fihri), jean-cyrille.hierso@u-bourgogne.fr (J.-C. Hierso).

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1,1′-bis(diphenylphosphino)ferrocene (dppf) the investigations directed towards the synthesis of new ferrocenylphosphines remain of fundamental and industrial interest. The present review aims to describe the performances in palladium-catalyzed cross-coupling reactions of *symmetrical achiral ferrocenylphosphine* ligands, mainly diphosphines. We specifically choose to restrict our review efforts to these species due to their wide accessibility to all the chemist community. First, the synthetic routes that have been applied to the synthesis of these ferrocene derivatives are overviewed. Then, the recent 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 thrust to consolidate all the important work in this area. Finally, the structural properties of these ligands are discussed in relation with their reactivity, in the light of the mechanistic studies reported on parameters like coordination bite angle, electronic, steric and geometric features of ligands, conformation, and multidentarity. The many achievements and new challenges on this topic are summarized within the article. The literature cut-off date was beginning 2006.

Keywords: Ferrocenylphosphine; Catalysis; Palladium; Cross-coupling (Heck, Suzuki, Kumada, Negishi, Sonogashira, cyanations, aminations, etherations); Structure; Mechanisms (bite angle, conformation, multidentarity)

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1. Introduction

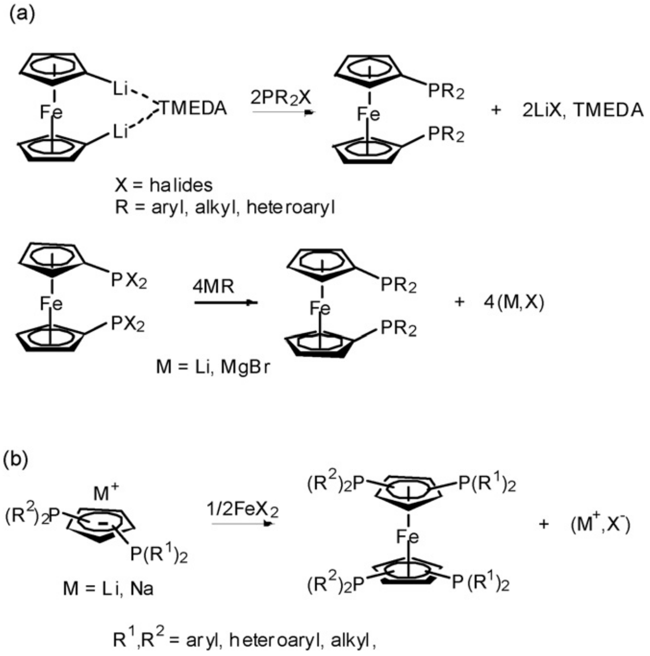
The discovery of ferrocene and the elucidation of its outstanding “sandwich”-structure, more than 50 years ago [1], initiated a new era of organometallic chemistry in the history of contemporary chemistry [2,3]. The selective functionalization of ferrocene derivatives with donor atom (P, S, N, etc.) led to a second generation of different classes of chiral and achiral molecular ligands. These ubiquitous species show important applications in metal-catalyzed modern organic reactions. 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/or electronically modified either at the ferrocenyl backbone or at the phosphorus atoms [4] – are still of fundamental and industrial interest.

The chemistry of ferrocene-based ligands has been intensively investigated, and a number of excellent reviews have appeared in the recent years [5]. They generally cover some particular aspects of ferrocenylphosphine chemistry: for instance, Bandoli and Dolmella reviewed in 2000 the coordination ability exhibited by the dppf ligand to transition metals [6]. In 2001 a concise review presented the applications of group 10 ferrocenylphosphine complexes in achiral coupling reactions [7]. More recently, Colacot and Atkinson et al. have reviewed the applications of chiral ferrocenylphosphines in homogeneous catalysis, and the syntheses and application of *unsymmetrical* ligands with a ferrocene backbone in homogeneous catalysis, respectively [8,9]. Bianchini and co-workers reported as well a review covering stereoselective catalysis by metal complexes with chiral ferrocenylphosphines in 2004 [10].

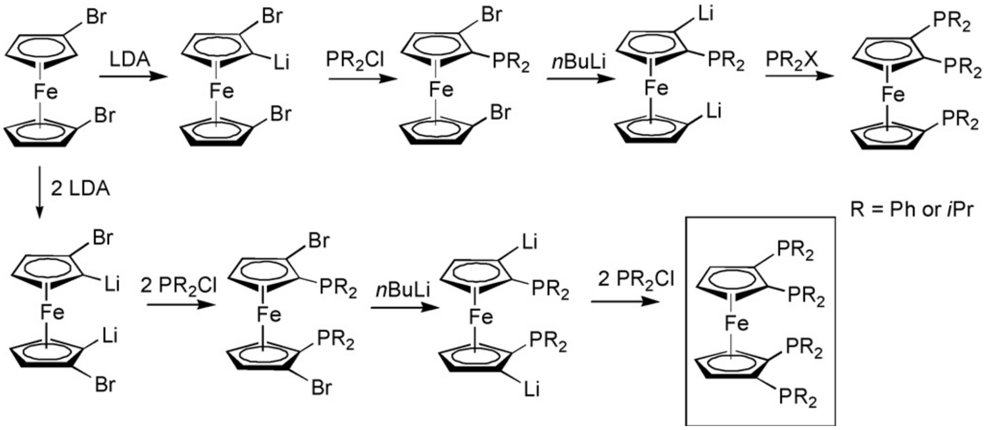
The present review aims to describe the performances in palladium-catalyzed cross-coupling reactions of symmetrical achiral ferrocenylphosphine ligands, mostly diphosphines. We specifically choose to restrict our review efforts to these species due to their wide accessibility to the entire chemist community [11] (including non-specialist of metallo-ligands synthesis) and particularly to researchers involved in catalyzed carbon–carbon bond formation or in total synthesis. The well-known general robustness of the ferrocene derivatives both at the solid state and in solution is an additional advantage, which makes all the more appealing, the ferrocenylphosphine ligands of easy access. The first section gives an overview of the synthetic routes that were applied to the synthesis of these ferrocene derivatives. In the following sections are presented the important applications of the ligands which were reported over the past decades in palladium (or nickel)-catalyzed cross-coupling reactions. The chemistry of the di- and polyphosphine ferrocene-based ligands in catalytic cross-coupling is detailed in carbon–carbon, carbon–nitrogen and carbon–oxygen bond-forming reactions. The last part is devoted to structural and mechanistic discussions with the view to highlight some critical properties of ferrocenyl ligands such as coordination bite angle, conformation, electronic and steric features and multidentarity effect.

2. Synthesis of symmetrical ferrocenylphosphine ligands

The synthesis of ferrocene-based phosphine ligands with identical substitutions on the two cyclopentadienyl rings (Cp) has been conducted following two general routes (Scheme 1a and b). The first one – which is also the most often employed –



Scheme 1.



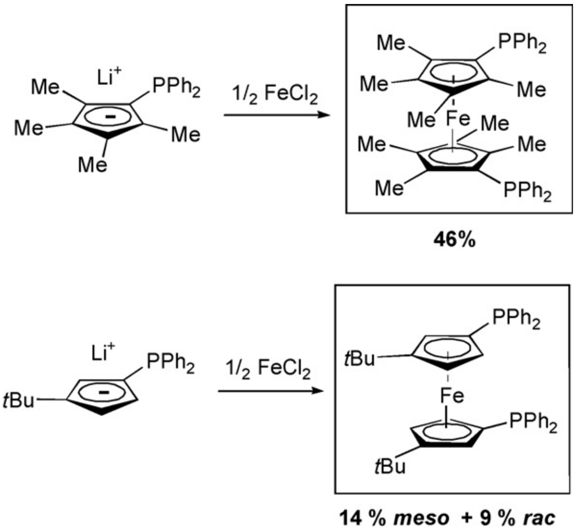
Scheme 2.

is the direct substitution of the ferrocene backbone *via* phosphorylation reactions by employing phosphine halides. The second route requires the synthesis of cyclopentadienyl salts adequately substituted to form the targeted ligand in one step with iron halides. A major difference between these two routes is that the direct functionalization of the ferrocene backbone is more convenient for the synthesis of disubstituted symmetrical ferrocenes, while the second method has been shown to be very powerful for the synthesis of polysubstituted ferrocenyl species (tri, tetrasubstituted or more).

The original studies on the dilithiation of the ferrocene and the quenching by halophosphines (Scheme 1a) were reported by Bishop et al. to yield the 1,1′-bis(diphenylphosphino)ferrocene, dppf [12]. This method (and the related versions) was used to produce a number of achiral symmetrical ferrocenyldiphosphines: the most employed in catalysis are listed in Table 1 [13–24].

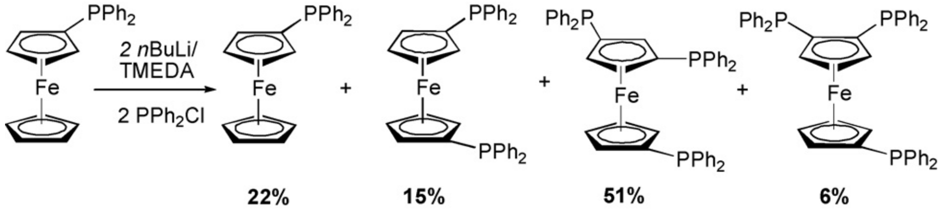
Following these studies, Butler and co-workers largely explored further phosphorylation of ferrocenylphosphine backbones through multistep synthetic procedures. They formed both symmetrical and unsymmetrical ferrocene-based polyphosphines by successive bromation and/or lithiation and phosphorylation reactions (Scheme 2) [25,26]. The role of bromide atoms as a directing-group for orthometallation, and the use of LDA as a selective base is of great significance since Butler showed at an early stage that a direct lithiation/phosphorylation sequence on diphenylphosphinoferrocene by using *n*BuLi gave unsatisfactory yields and selectivity (Scheme 3) [27].

The second route to ferrocenylphosphines is inspired by the synthesis of ferrocene derivatives from fulvenes (Scheme 1b)[28]. This methodology consists in the reaction of appropriate substituted-cyclopentadienyl salts with iron halides and was originally developed by Broussier and co-workers (Schemes 4 and 5) [29–31].



Scheme 4.

The synthesis of either ferrocenyldi- or tetra-phosphines ligands was performed in this way, but generally the yields for the diphosphine compounds were found much lower (>50% based on Cp). The most delicate part of this methodology is the synthesis of the desired substituted-cyclopentadienyl anions. The control on the substitution positions of the phosphorus atoms on the Cp ring (Scheme 5) – which is essential for subsequent applications – was achieved by using a *tert*-butylcyclopentadienyl



Scheme 3.

Table 1
Typical symmetric 1,1′-ferrocenyldiphosphines and their applications

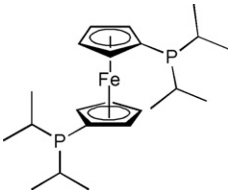
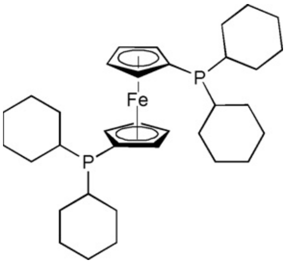
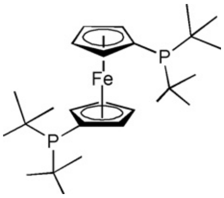
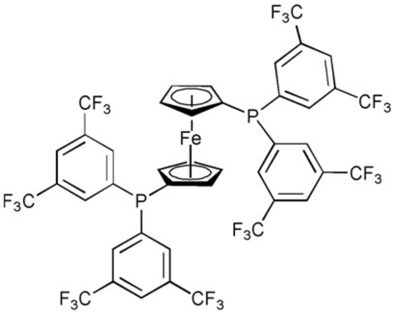
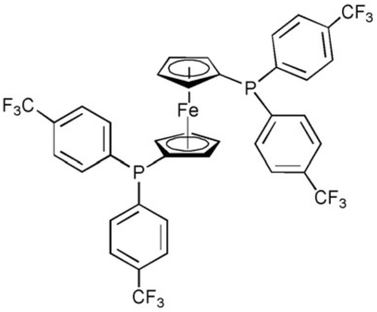
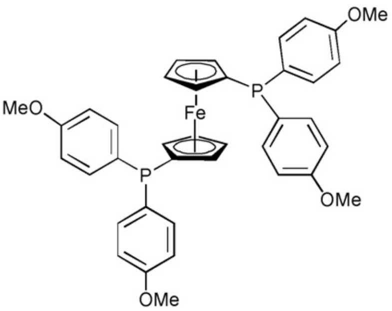
Ligand	References to synthesis	Applications
	[13]	Suzuki–Miyaura and Heck reactions; amidation; indolization; ethylene carbonylation, ketones hydrogenation; hydroamination
	[14]	Suzuki–Miyaura reaction; Buchwald–Hartwig amination; alkoxycarbonylation
	[15]	Suzuki–Miyaura reaction; Buchwald–Hartwig amination; amidation; arylation; indolization
	[16]	Hydroformylation; Buchwald–Hartwig amination
	[16,17]	Hydroformylation; Buchwald–Hartwig amination; etheration
	[16,18]	Buchwald–Hartwig amination; etheration

Table 1 (*Continued*)

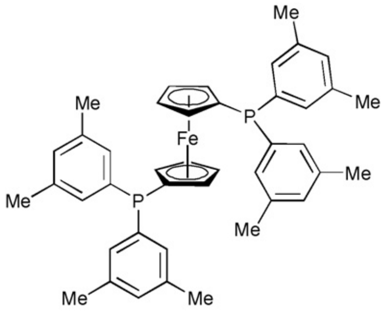
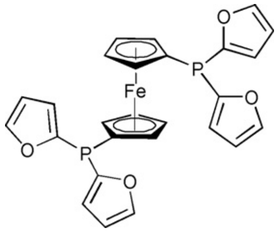
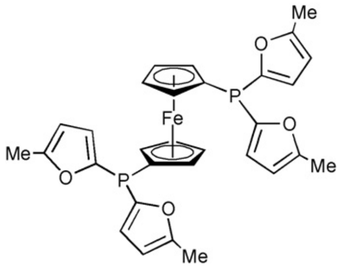
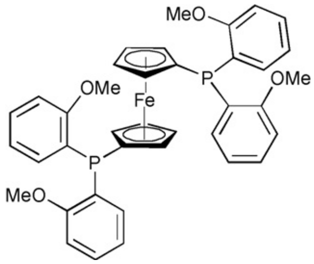
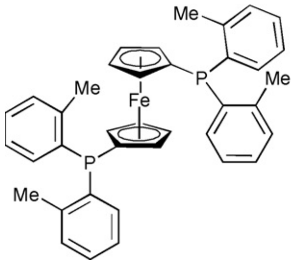
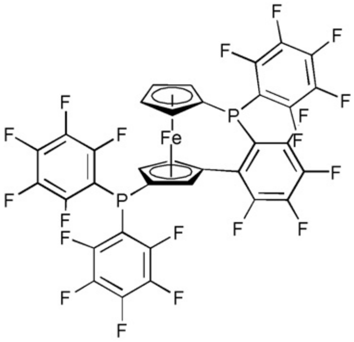
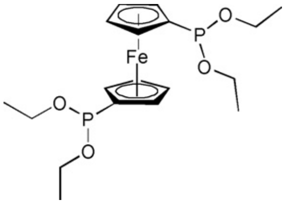
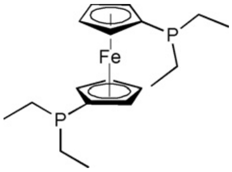
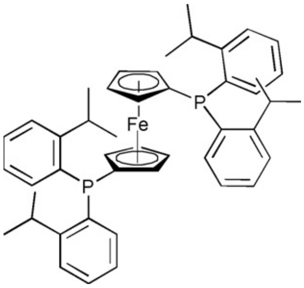
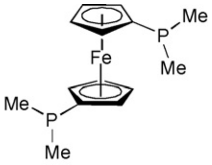
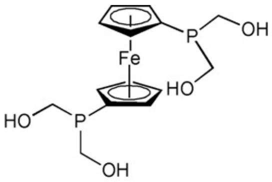
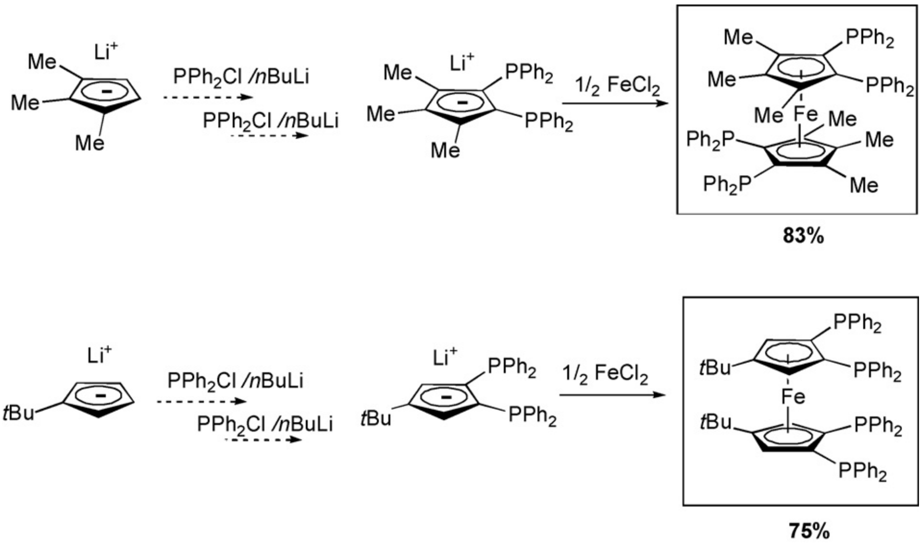
Ligand	References to synthesis	Applications
	[19]	Buchwald–Hartwig amination
	[19]	Buchwald–Hartwig amination
	[20]	Suzuki–Miyaura, Heck, and Sonogashira–Hagihara reactions; allylic amination
	[21]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction
	[21]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction

Table 1 (*Continued*)

Ligand	References to synthesis	Applications
	[21]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction
	[21]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction
	[21,22]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction; ethylene carbonylation
	[21,23]	Buchwald–Hartwig amination; Suzuki–Miyaura reaction; hydroformylation
	[12,22]	Ethylene carbonylation
	[24]	–

lithium salt by which a 1,2-phosphine disubstitution was directed. Alternatively, three adjacent positions can be blocked on the ring by employing a trimethylcyclopentadienyl lithium salt. On an unsubstitued-Cp ring, 1,3-disubstitution is obtained upon lithiations and consecutive quenching reactions. The Cp assembling methodology also allowed to produce various *unsymmetrical* polyphosphines (some examples are depicted in Scheme 6) [32].



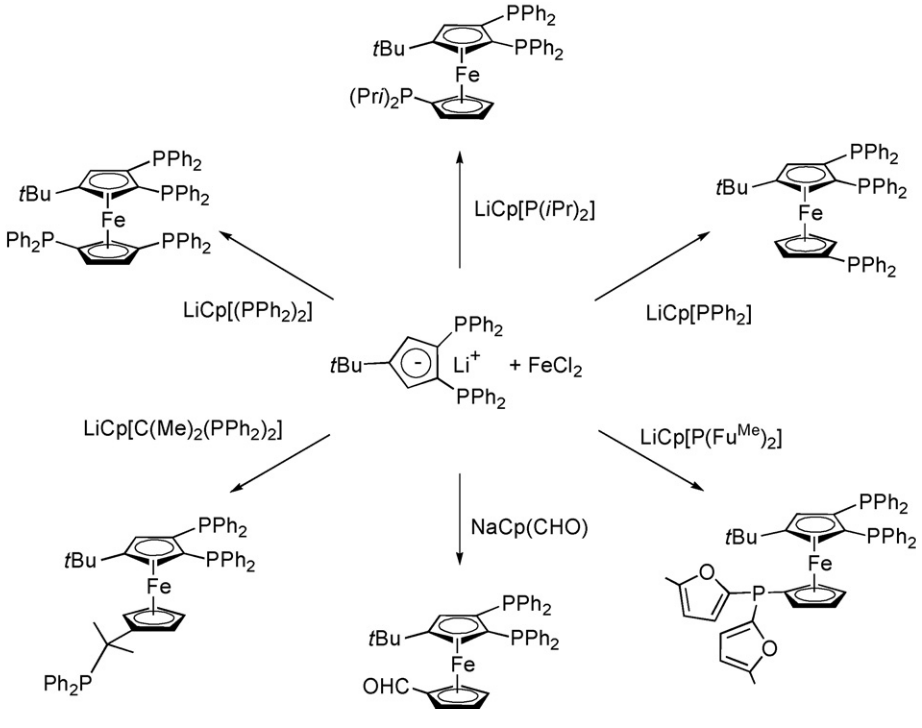
Scheme 5.

As mentioned in Section 1, the general synthesis of dppf and related symmetrical ferrocenyldiphosphine ligands is essentially easier than the multistep-syntheses reported to get optically pure chiral ferrocenylphosphines (or even sometimes to get simple unsymmetrical ferrocene derivatives) [10]. The formation of ferrocenyl*poly*phosphines of higher rank (tetraphosphines for instance) by Cp assembling requires several synthetic steps but is of relatively easy access and above all do not suffer from selectivity troubles. Nevertheless, the following sections that details the catalyst systems successfully used in cross-coupling reactions, show that only a few applications of these polyphosphine ligands have been explored. Thus, a great number of potential extensions and optimizations in catalytic applications are still possible for further studies.

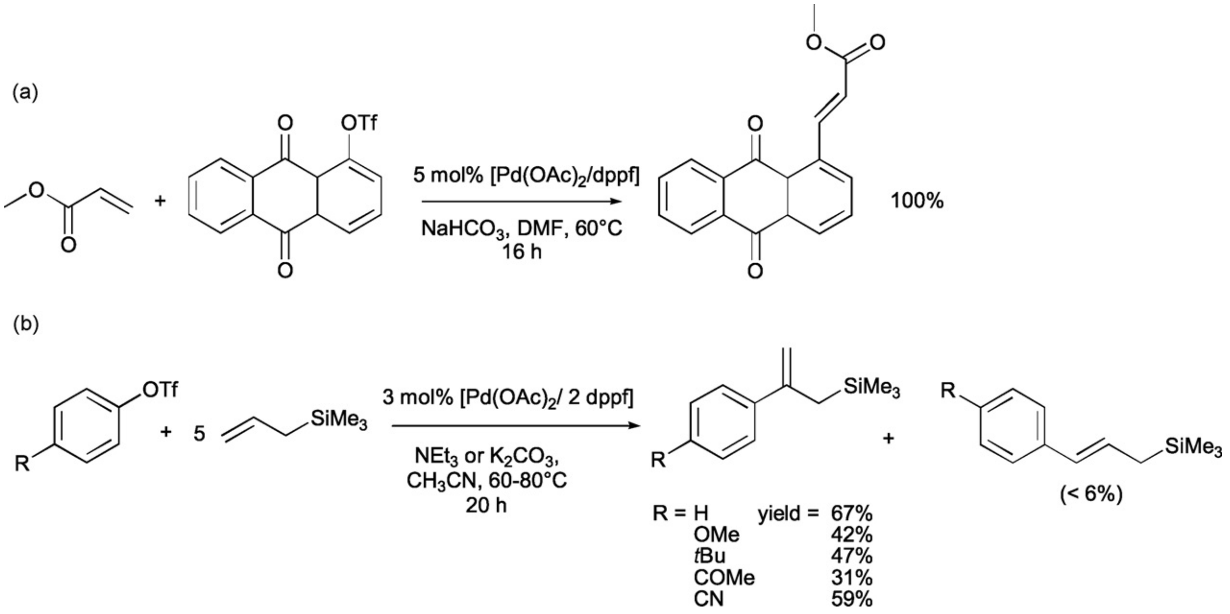
3. Carbon–carbon bond-forming reactions catalyzed by employing ferrocenylphosphines

3.1. Heck reaction

Heck coupling with systems combining palladium and ferrocenylphosphines ligands was surveyed by Colacot up to the year 1999 [7]. Herein, some essential studies are reviewed together with the results reported in the following period. Until the 1980s



Scheme 6.



Scheme 7.

the chelating diphosphines were reported not to form effective catalysts for the Heck reaction [33]. In the 1990s mechanistic investigations by Brown and co-workers provided spectroscopic evidence for a set of palladium alkenyl complexes which incorporate the dppf ligand; these species were considered as putative intermediaries in the Heck reaction (see also structure-reactivity discussion in Section 6) [34]. The coupling of an aryl triflate with an electron-poor olefin promoted by bidentate ligands was reported in 1991; a complete conversion and selectivity in the desired coupling product was obtained by employing a $Pd(OAc)_2$/dppf system at 60 °C in 16 h (Scheme 7a) [35].

Following these studies, the internal arylation of allyltrimethylsilane with various aryl triflates was selectively conducted in moderate to good yield by employing the same catalyst (Scheme 7b) [36]. Microwave activation allowed one to substantially shorten reaction times with a only slight lowering of regioselectivity.

The efficiency of the system $Pd(OAc)_2$/dppf was later confirmed with aryl halide substrates. Hii and co-workers reported the arylation of methyl acrylate with 4-bromoacetophenone, by employing 0.01 mol% of catalyst at 140 °C in DMF (96% yield, TON 9600) [37].

The complex $PdCl_2$(dppf) was also successful for solid-phase synthesis in the reaction of a resin-bound aryl iodide with ethyl acrylate (90% yield of product, in the presence of 20 mol% catalyst in DMF/water at 40 °C for 12 h); the other catalytic systems commonly used in the classical Heck reaction, such as $Pd(OAc)_2/PPh_3$ or $Pd(OAc)_2/P(o\text{-tol})_3$, were found ineffective [38].

More recently, some studies explored the electronic effects obtained in the Pd-catalyzed Heck reaction with catalytic systems which incorporate thiolate ligands such as $[Pd(SC_6F_5)_2(dppf)]$ [39]. The authors did not discuss the widely accepted Pd(0)/Pd(II) catalytic mechanism, and the nature of the Pd(0) catalyst remains unclear, especially regarding the genuine role of the thiolates after the first rotation of the catalytic cycle.

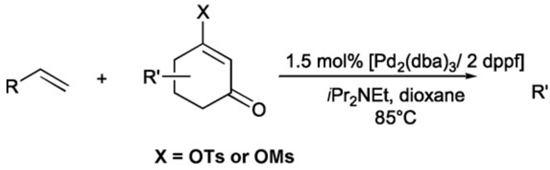
It is well-known and documented that the substitution of aryl groups for alkyl groups on phosphorus atoms of organic ligands allows significant improvement in catalytic cross-coupling reactions. In the case of the Heck reaction, Butler and co-workers reported the use of 1,1′-bis(diisopropylphosphino)ferrocene for the coupling of phenyl iodide to methyl acrylates [40]. As expected, this ligand led to significantly better conversions (40–96% yield) than the parent ligand dppf (4–7% yield), with a total selectivity in *trans* product.

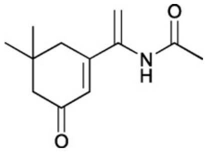
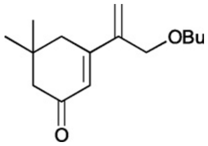
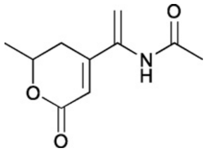
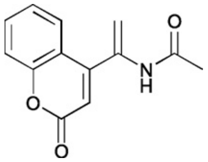
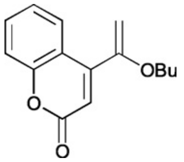
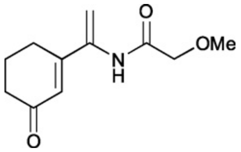
A recent exciting application of the system $[Pd_2dba_3]$/dppf (dba = dibenzylideneacetone) by Skrydstrup and Hansen, is the Heck coupling of α,β-unsaturated tosylates and mesylates to electron-rich olefins, as alternative to triflate substrates [41]. As displayed in Table 2 enamides and butyl vinyl ether were coupled in moderate to excellent yields by employing 1.5 mol% of Pd with 3 mol% of dppf; high regioselectivity (>19:1, branched:linear) were obtained. This method to produce unsaturated ketones is of great interest in terms of cost, since the price of starting materials relatively in euro/mol is the following: triflic anhydride (17) ≫ tosyl chloride (1.8) > mesyl chloride (1).

Besides the use of triflate-, halide-, tosylate- and mesylate substrates, aryl boronic acids were coupled to α,β-unsaturated esters in a reaction conducted in the presence of 3 mol% $RhCl_3$ and dppf [42].

The reactivity of another class of symmetric ferrocenylphosphine has been successfully explored in the Heck coupling. The system combining the ferrocenyl*tetra*phosphine 1,1′,2,2′-tetrakis(diphenylphosphino)-4,4′-di-*tert*-butylferrocene and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ was found to be an active catalyst for the vinylation of aryl halides with various alkenes (Scheme 8) [43]. The Heck reaction of aryl halides with ^{n}butyl acrylate, styrene and ^{n}butyl vinylether were carried out under conditions of very low loading of catalyst: with iodobenzene and ^{n}butylacrylate a very high TON of 1,000,000 was obtained. High TONs of 10,000 and 65,000 were achieved with the unactivated bromoanisole and ^{n}butyl acrylate and styrene, respectively. Even

Table 2
Heck coupling of unsaturated tosylates and mesylates



Product	Yield (%) from tosylate	Yield (%) from mesylate
	83	82
	75	67
	55	28
	73	Not reported
	91	Not reported
	Not reported	45

the electron-rich alkene ^{n}butylvinylether led to the expected coupling products in the presence of 0.1 mol% catalyst.

In this study the opportunity for the same metal atom to interact with the four phosphorus atoms of the tetraphosphine ligand was demonstrated by the dynamic behavior observed in variable-temperature ^{31}P NMR (see details in Section 6). The performance of this tetradentate ferrocenylpolyphosphine in carbon–carbon coupling catalysis would be in part due to the resulting stabilization provided to the palladium active species. Furthermore, that hypothesis would explain why, contrary to more fragile phosphine ligands, the tetraphosphine ligand can be used in such low concentrations. This concept favors the catalyst longevity with regard to the catalyst activity which dominates in the chemistry of electron-rich monophosphines. Therefore, in terms of cost and resources saving, this type of polydentate species of constrained geometry is promising.

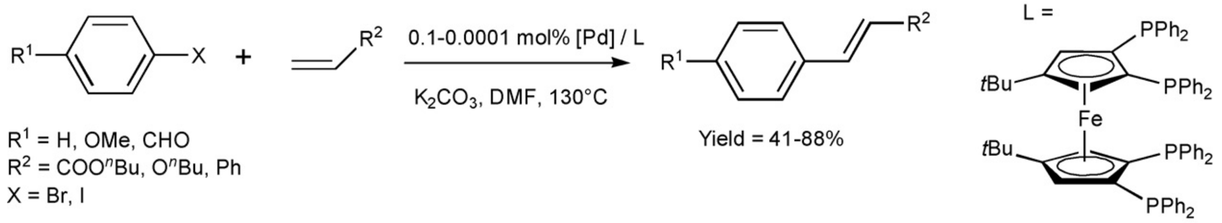
3.2. Coupling from boronic acids and esters (Suzuki–Miyaura reaction)

3.2.1. Suzuki coupling with dppf as the ligand

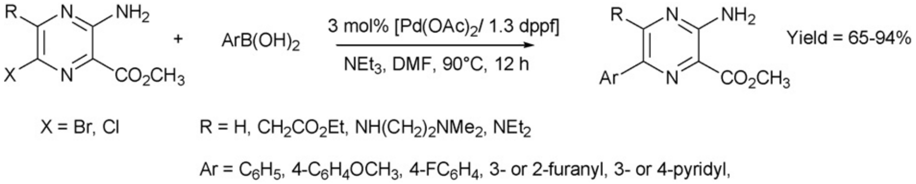
The Suzuki–Miyaura cross-coupling provides a general and convenient method for the formation of biaryls from aryl halides and aryl boronic acids or esters [44]. The first study demonstrating the interest of 1,1′-bis(diphenylphosphino)ferrocene-bonded palladium in Suzuki-type coupling on a large array of substrates was reported in 1988 by Thompson et al. [45] Substituted bromo- and chloropyrazinoate esters were efficiently coupled to aryl and heteroaryl boronic acids which incorporate, for instance, 4-fluorophenyl, 4-methoxyphenyl, 3-furanyl, 2-furanyl, 3- and 4-pyridinyl groups (Scheme 9). This system was found significantly more efficient than $Pd(PPh_3)_4$ or $Pd(OAc)_2$/2 P(*o*-tolyl)$_3$.

The usefulness of the method was further demonstrated in the convergent synthesis of a methyl derivative of milrinone, a cardiotonic drug [45].

Soon after, Suzuki, Miyaura and Oh-e disclosed that the complex $PdCl_2$(dppf) was also an efficient catalytic precursor for the coupling of 1-alkenyl- and aryl triflates with 9-alkyl-9-borabicyclo[3.3.1]nonane (9-*R*-9-BBN) derivatives [46]. High yields (above 75%) of coupling products were obtained in the presence of 2.5 mol% $PdCl_2$(dppf) and 1.5 equiv. of K_3PO_4 in THF at 65 °C, whereas $Pd(PPh_3)_4$ and Pd/tris(2,4,6-trimethoxyphenyl)phosphine catalysts were less effective. The authors postulated that triphenylphosphine-type ligands can react with triflates to give phosphonium salts, leading to the formation of palladium-black as a result of the decomposition of the catalyst [46b].

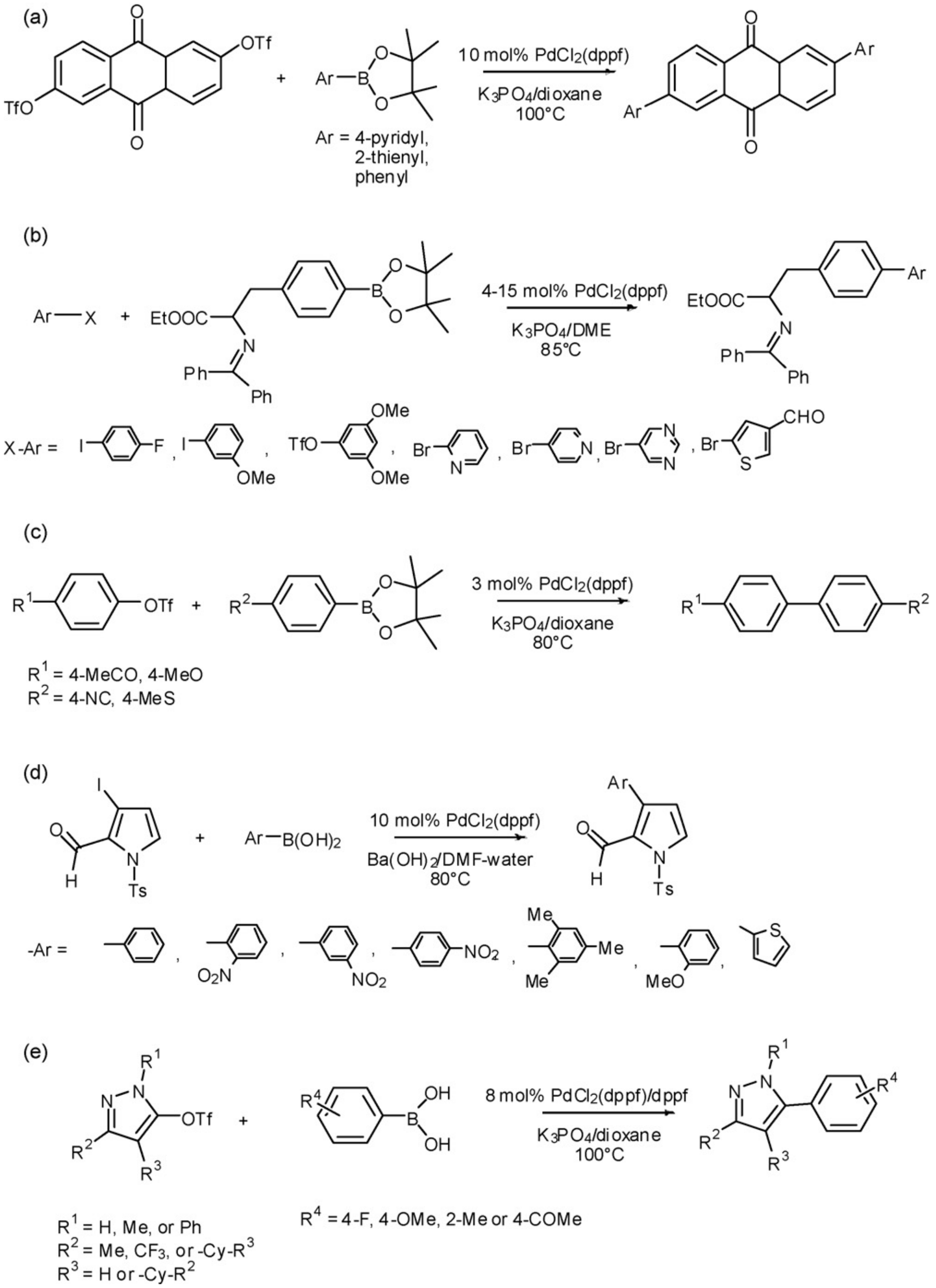


Scheme 8.



Scheme 9.

Following these pioneering studies, catalytic systems based on the complex $PdCl_2$(dppf) have been profusely employed: the successful reactions are summarized in Scheme 10. The coupling of phenyl- and heteroarylboronates to an anthraquinone triflate (Scheme 10a) was reported to proceed in 60–85% yields at a small scale (3 mmol) under rigorously anaerobic conditions [47]. 4-Substituted phenylalanine derivatives were obtained in 50–75% yields by coupling reaction of a (4-



Scheme 10.

pinacolylborono)phenylalanine ethyl ester derivative with some substituted aryl- and heteroaryl iodides, bromides and triflates (Scheme 10b) [48]. Unsymmetrical biaryls were produced in 65–95% yield from reaction of aryl triflates with pinacol boronic esters (Scheme 10c) [49]. A general synthesis of 2-formyl-3-aryl pyrroles was described from reaction of a variety of aryl boronic acids with 2-formyl-iodo pyrroles (Scheme 10d), yields of 60–100% were obtained, even for demanding substrates such as the polysubstituted mesityl boronic acid [50]. The coupling of a wide set of pyrazole triflates with aryl boronic acids was also possible in excellent yields above 75% (Scheme 10e) [51]. Similar conditions were employed for the coupling of these significantly different substrates: 3–15 mol% of the complex $PdCl_2$(dppf) in a polar solvent (typically dioxane) at 80–100 °C in the presence of K_3PO_4 as a base. In addition, in most of these studies, other catalytic systems have been tested that often showed poorer results: a significant example is the failure of the system including bulky electron-rich phosphine PCy_3 for the Suzuki coupling of pyrazole triflates to aryl boronic acids [51].

The diversity of substrates successfully employed for Suzuki coupling reactions with Pd/dppf systems is noticeable; several examples of single use in Suzuki reactions were reported with: bromoacetophenone [52], 2-bromophenyl tetrazole [53], 4-trifluoromethylsulfonyloxy-indole [54], resin-bound 3-phenoxy-4-iodophenyl β-lactam [38]. The Suzuki coupling using $PdCl_2$ (dppf) allowed also the synthesis of various oligomeric and polymeric species such as poly(phenylene)s, poly(binaphthyl) derivatives and sexithiophenes [55–57]. The synthesis of dityrosines and trityrosines [58], some incorporating peptides [59] were also reported using a similar Pd/dppf catalytic system.

Finally, the conditions to use $PdCl_2$(dppf) as an extremely active catalyst for the Suzuki reaction of aryl bromides in water were recently disclosed (Scheme 11) [60]. Substituted aryl boronic acids and electron-rich aryl bromides were efficiently coupled with TONs up to 870,000 (1-bromo-4-nitrobenzene with phenyl boronic acid). A single example of two recycling runs in 20% aqueous poly(ethyleneglycol) was given which showed good recycling with a slight deactivation. The cross-coupling of aryl chlorides was unfortunately unsuccessful under these conditions.

3.2.2. Suzuki coupling with other ferrocenylphosphine ligands

Palladium catalytic systems that include some other ferrocenyldiphosphines have been tested in Suzuki–Miyaura coupling (Scheme 12). The Suzuki cross-coupling of 4-amino-2-chloro-5-nitropyrimidine (Scheme 12a) to a wide variety of aryl boronic acids has been conducted very efficiently with a system combining 10 mol% Pd and 1,1′-bis(di-*tert*-butylphosphino)ferrocene (abbreviated D^{t}BPF) [61]. This system is optimal among those examined to promote the coupling of electron-rich and/or sterically hindered aryl boronic acids; it was also employed to couple various aminochloropyrimidines and aminochloropyridines with phenylboronic acid [62].

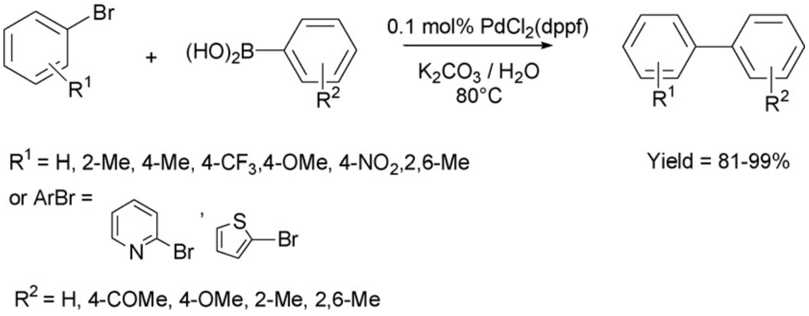
The ligand D^{t}BPF has also been tested in palladium-catalyzed cross-coupling of arene sulfonyl chlorides with boronic acids (Scheme 12b), with however less success than an imidazolium salt precursor of carbenes [63].

More classical substrates such as activated chlorides or activated and deactivated bromides have also been tested in the Suzuki reaction employing the 1,1′-bis(di-cyclohexylphosphino)ferrocene [64] and 1,1′-bis(di-furylphosphino)ferrocene [20] ligands, respectively (Scheme 12c and d). The 1,1′-bis(di-furylphosphino)ferrocene ligand provides a catalytic system which minimizes the consumption of expensive palladium since only low catalytic loading (0.01–0.001 mol%) is required to couple phenyl boronic acid and aryl bromides [20].

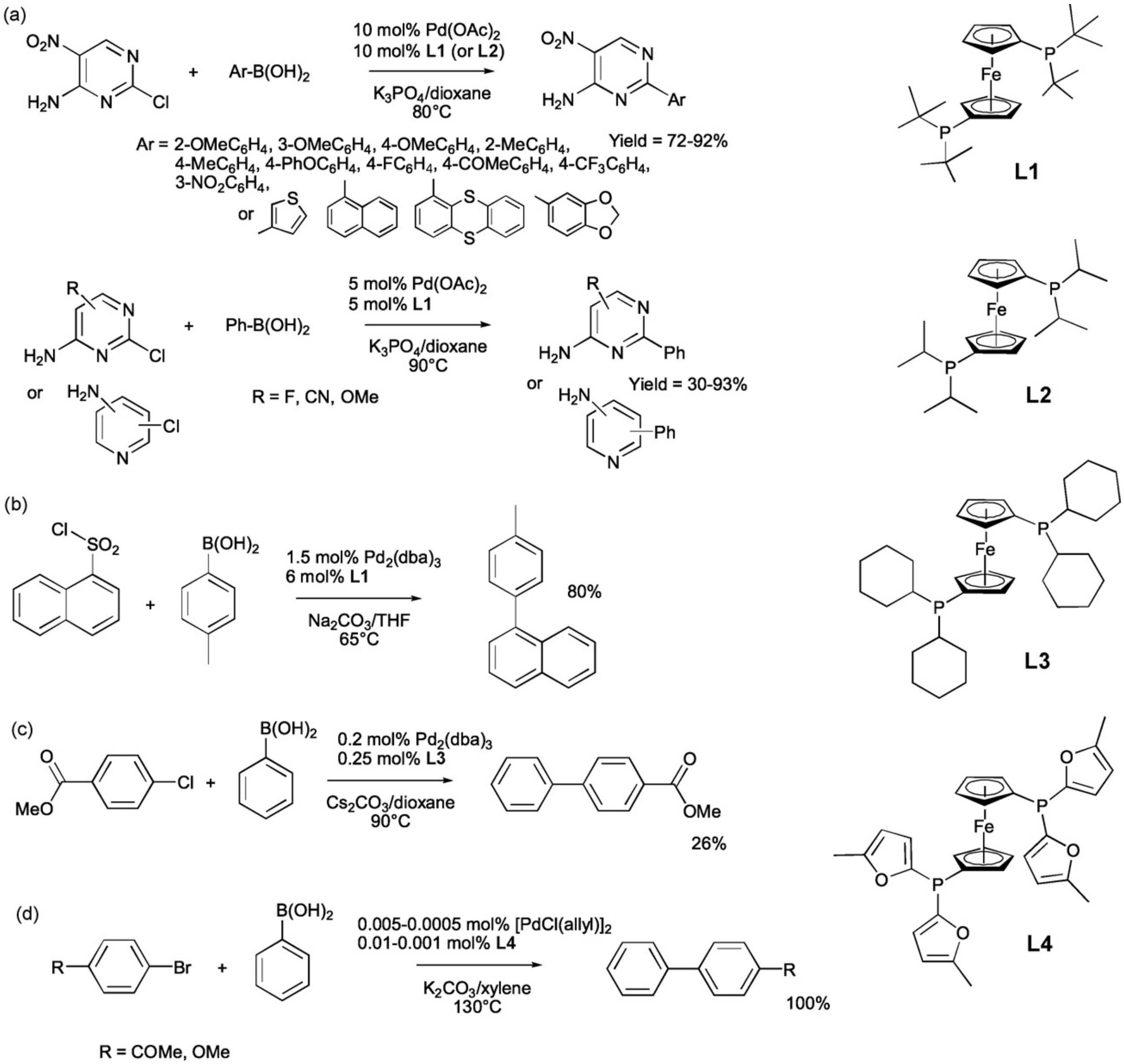
The use of a symmetric ferrocenyltetraphosphine has been also successfully achieved in Suzuki–Miyaura cross-coupling with aryl bromides and chlorides (Scheme 13, see also Section 3.1; "Heck coupling", and Section 6 for structure-reactivity discussion) [43]. A variety of chlorides were coupled in good yield with aryl boronic acids in the presence of 1–0.01% palladium/phosphine catalyst. The more reactive aryl bromides were coupled with aryl boronic acids in the presence of 0.01–0.0001% catalyst; The TONs obtained are ranging from 77,000 (4-bromoanisole with phenyl boronic acid) up to 150,000 (4-trifluoromethylbromobenzene with phenyl boronic acid).

3.2.3. Suzuki coupling with nickel-based catalyst systems

Investigations have been conducted to evaluate Suzuki cross-coupling by employing nickel catalysts instead of palladium catalysts: the main advantage would be the development of cost-saving conditions regarding palladium-based systems. The reactions seem in general more difficult to achieve, and from our own experience the reproducibility of results can be troublesome. Nevertheless, conditions based on nickel/dppf catalyst systems have been described to allow the arylation cross-



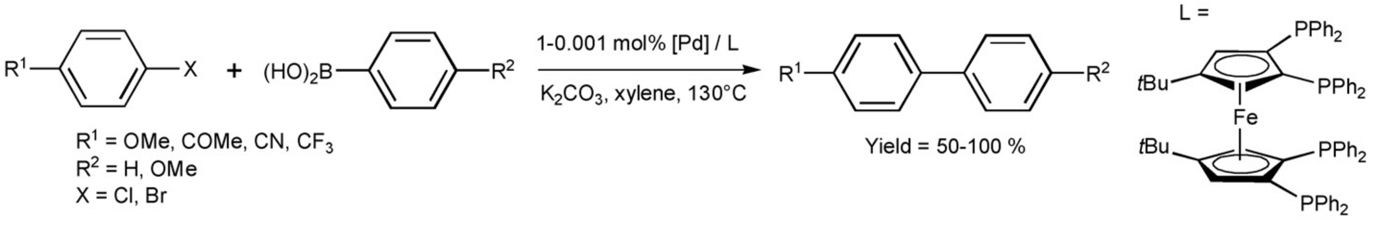
Scheme 11.



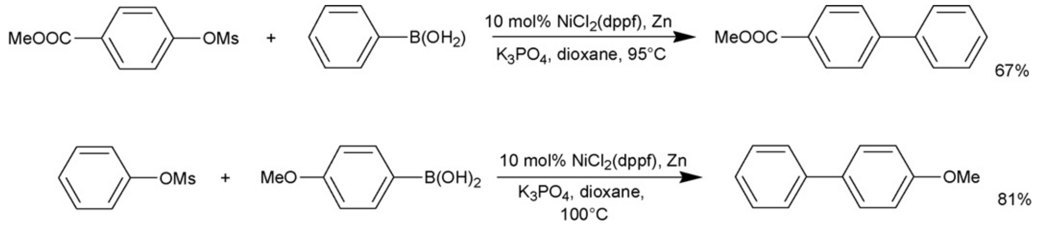
Scheme 12.

coupling. In 1995, Percec and co-workers reported that Ni/dppf can catalyze Suzuki couplings of various aryl sulfonates (including mesylates) with aryl boronic acids (Scheme 14) [65]. The Ni(0) catalyst was generated *in situ* from $NiCl_2$(dppf) and zinc powder.

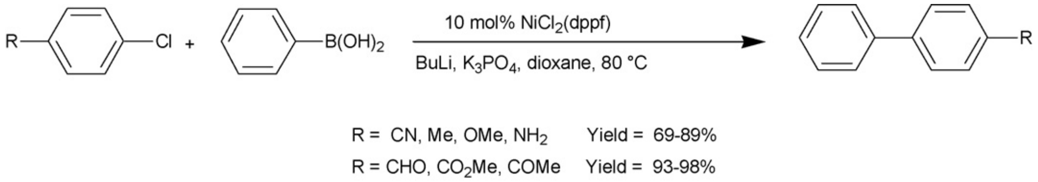
The influence on the reaction yield of the nature of the leaving group, of the solvent, and of the type of the base was studied. The highest yield (67%) in the cross-coupling reaction of methyl 4-[(methylsulfonyl)oxyl]benzoate with phenyl boronic acid was obtained by employing 10 mol% $NiCl_2$(dppf), 3 equiv. of K_3PO_4 and 1.7 equiv. of Zn in dioxane at 95 °C. Under these conditions the cross-coupling of phenyl mesylate with (4-methoxyphenyl)boronic acid gave 81% yield of 4-methoxybiphenyl.



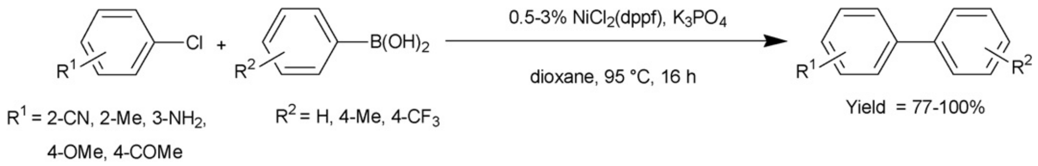
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

Miyaura and co-workers reported that phenyl boronic acid reacts with chloroarenes bearing either an electron-withdrawing or a electron-donating group in the presence of $NiCl_2$(dppf) (Scheme 15) [66]. The electron-deficient chloroarenes mostly gave biaryl yields exceeding 95%. In the reactions with substrates holding electron-donating groups the yields were slightly lower; however, they were surprisingly found greater for the nickel catalysis compared to palladium. The nickel(0) species was prepared *in situ* by treating the nickel chloride complexes with butyllithium.

The authors further extended the scope of this nickel-catalyzed cross-coupling reaction to the use of functionalized aryl boronic acids with some representative chloroarenes: chloroindole and chlorothiophene, for instance, smoothly coupled with phenyl boronic acid [67]. Aryl boronic acids holding electron-withdrawing groups resulted in lower yields of product due to deboronation.

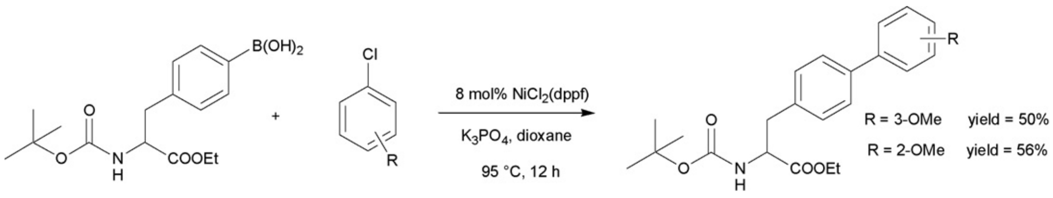
Another convenient procedure for Suzuki reaction promoted by a Ni/dppf system in the absence of zinc salt or BuLi was reported by Indolese (Scheme 16) [68]. Chloroarenes were coupled in high yield and apparently the catalytic system was able to reach turn over numbers up to 200, with a high efficiency when compared to the TONs around 10 obtained in the above-described studies. The underlying mechanisms responsible for such activity in the presence of low catalyst loading and in the absence of additional reducing reagent was unfortunately not evoked by the author.

Firooznia and co-workers reported the nickel-catalyzed preparation of 4-substituted phenylalanine ethyl ester derivatives by cross-coupling reactions of boronic acids with aryl chloride substrates (Scheme 17) by using the same catalyst system in a higher amount [69].

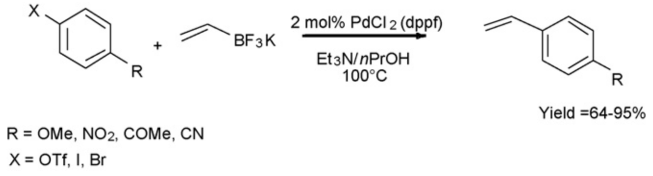
Finally, a recent report on hindered non-symmetric ferrocenylmethylphosphines indicated their potential for the room temperature nickel-catalyzed cross-coupling of aryl boronic acids with aryl chlorides and aryl arenesulfonates [70].

3.2.4. Related coupling and relevant trends

Organoboron compounds other than aryl boronic derivatives have been used in reactions related to the Suzuki cross-coupling. The cross-coupling reactions described below, which employed $PdCl_2$(dppf) as the catalyst, illustrate well the potential of ferrocenylphosphine ligands. Molander and co-workers have shown that organoboron coupling partners such as potassium alkenyltrifluoroborates can be efficiently employed with aryl- and alkenyl halides and triflates (Scheme 18) [71].



Scheme 17.



Scheme 18.

Alkyl boronic acids were coupled to heterocyclic internal-vinyl triflates compounds to give in moderate to high yields the corresponding alkyl-substituted heterocycles in the presence of Ag_2O together with a base in anhydrous toluene (Scheme 19) [72].

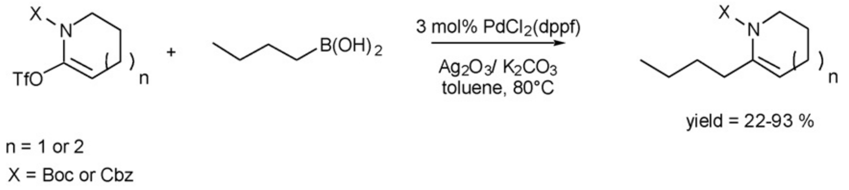
Concerning the relevant trends in this field, many examples of palladium- and nickel-catalyzed Suzuki cross-coupling surveyed in the present section clearly show that readily available systems incorporating dppf gives valuable results. For example, the ligand 1,1′-bis(di-*tert*-butylphosphino)ferrocene [61], and 1,1′-bis[di(5-methyl-2-furyl)phosphino] ferrocene [20], which hold electron-rich and electron-deficient phosphorus donors, respectively, have also allowed efficient coupling either for chloride activation, or high efficiency bromide coupling at low catalyst loading. Thus, a more systematic exploration of such a kind of dppf analogues could be of interest, especially concerning the reactions with demanding substrates or the catalysis in water.

The recent studies from Colacot and Shea illustrate this tendency: in a high-throughput screening approach, the catalytic systems using 1 mol% $PdCl_2$[1,1′-bis(di-*tert*-butylphosphino)ferrocene] in the presence of K_2CO_3 in DMF at 120 °C was the most active catalyst for Suzuki coupling of unactivated and sterically challenging aryl chlorides (together with the ferrocene analogues bearing isopropyl groups) [73]. The comparison was conducted with the commercial catalytic precursors $PdCl_2$(dppf), $PdCl_2(PPh_3)$, $PdCl_2(PCy_3)$, $PdCl_2$ (dppe = 1,2-bis(diphenylphosphino)ethane), $PdCl_2$(dppb = 1,4-bis(diphenylphosphino)butane) and $Pd[P(t\text{Bu})_3]_2$. Similarly the results reported by Gusev et al. (see the ligands in Table 1) [21], also showed that the diversity in ferrocenyldiphosphines provided relevant results in the Suzuki coupling of 4-bromotoluene and 4-(methoxyphenyl)boronic acid.

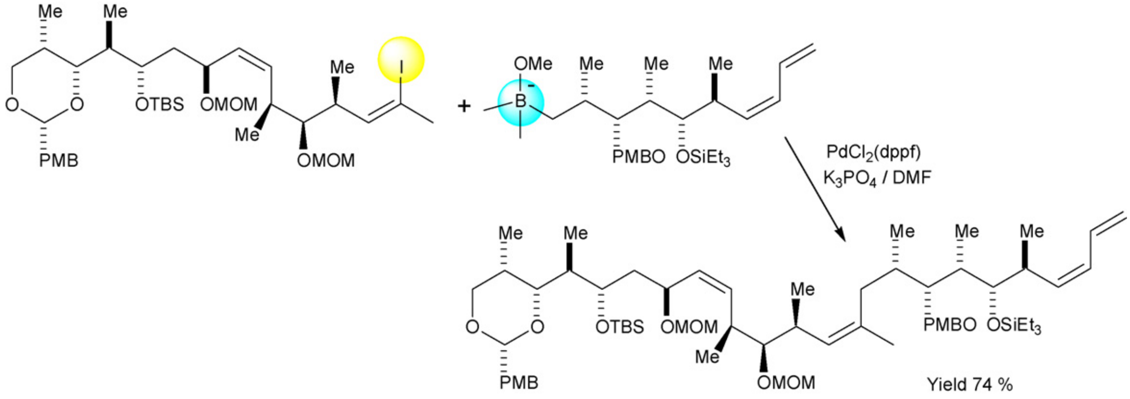
Suzuki–Miyaura coupling related to medical applications is also an increasing field of investigation. The use of ferrocenylphosphine as the ligands can be a valuable option, as illustrated by the two following examples: the first one concerns total synthesis and the second one radiopharmaceuticals. Marshall and Johns reported the total synthesis of (+)-discodermolide (potent immunosuppressant and possibly antitumoral) where the complete carbon backbone of the target product was obtained in a terminal Suzuki reaction (Scheme 20) [74].

The Suzuki coupling was also proved by Hostetler and co-workers to be a versatile method for the ^{11}C-labeling of functionalized toluene derivatives, opening the way to radiolabel highly functionalized pharmaceuticals (Scheme 21) [75].

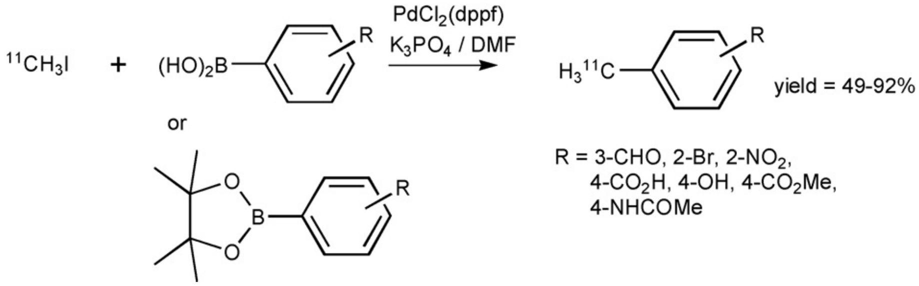
Finally, a complementary aspect of the use of palladium/ferrocenylphosphine catalytic systems in Suzuki coupling is their noticeable application for efficient synthesis of diverse biaryl products in solid-phase reactions [38]. The use of the complex $PdCl_2$(dppf) in Suzuki or Heck coupling with resin-bound material (out of the scope of the present discussion) has been successful in many aspects which were covered in another review [76].



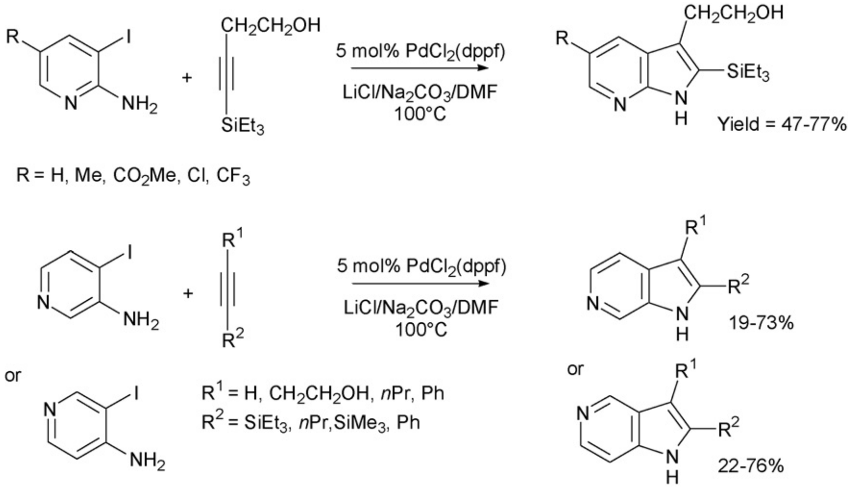
Scheme 19.



Scheme 20.



Scheme 21.



Scheme 22.

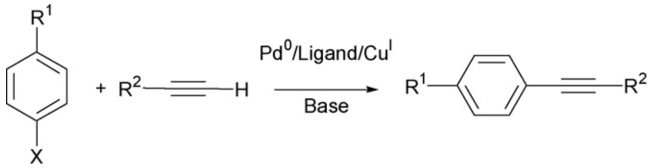
3.3. Alkynylation reactions (Sonogashira–Hagihara and Heck reactions)

The palladium-catalyzed alkynylation of aryl halides, known as Heck (palladium-catalyzed) or Sonogashira–Hagihara (palladium and copper co-catalyzed) cross-couplings, provides a powerful method to access conjugated aryl/alkynes [77]. In 1981, Kobayashi and Tanaka reported their studies concerning the catalytic activation of alkynes/aryl halides/CO mixtures to form acetylenic ketones by employing $PdCl_2(dppf)$ [78]. The interest of the complex $PdCl_2(dppf)$ in arylation of *internal* alkynes was investigated afterward by Ujjainwalla and Warner [79]. The multistep heteroannulation of various alkynes using *ortho*-iodoaniline allowed the synthesis of 5-, 6-, or 7-azaindoles (Scheme 22). The authors indicated the greater effectiveness of the system $PdCl_2(dppf)/LiCl$ compared to $Pd(OAc)_2/PPh_3$ used in previous studies [79].

Following these results, Lu and co-workers have reported a catalytic process combining $Pd(OAc)_2$ and 1,1′-bis(di-*tert*-butylphosphino)ferrocene for the synthesis of 2,3-substituted indole compounds from the heteroannulation of a variety of internal alkynes on 2-bromo and 2-chloroanilines (Table 3) [80]. The electron-rich ferrocenyldiphosphine ligand allowed the activation of chloroanilines, and makes the procedure economically attractive compared to the previously reported multistep heteroannulation of alkynes. A screening of catalysts has revealed a greater efficiency of the Pd/1,1′-bis(di-*tert*-butylphosphino)ferrocene system compared to other catalysts which incorporated either dppf, 1,1′-bis(diisopropylphosphino)ferrocene, $PtBu_3$, PCy_3 or some other electron-rich phosphines.

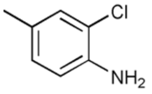
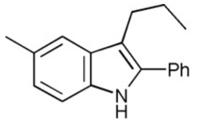
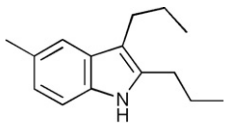
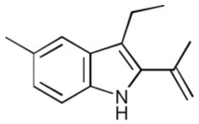
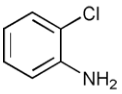
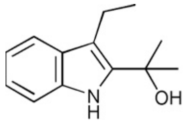
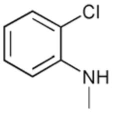
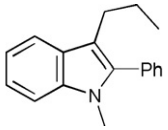
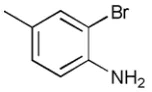
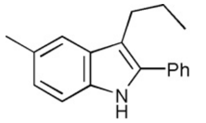
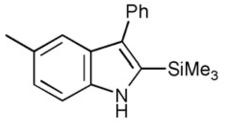
Besides these positive results, the catalysts based on the complex $PdCl_2(PPh_3)$ were more efficient than Pd/dppf systems in the classical single-step Sonogashira–Hagihara alkynylation of aryl halides (Scheme 23) [81] and in various related reactions (such as diyne formation or carbonylative coupling) [82,83], suggesting some limitations of this ferrocenyldiphosphine ligand.

Conversely, a highly efficient copper-free alkynylation (Heck reaction) of 4-bromoanisole and 4-bromoacetophenone with a Pd/1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene system was reported (Scheme 24) [20], this promising process employed an ultra-low concentration of catalyst (10^{-1} to 10^{-3} mol%) and would be further explored on more diverse substrates.



Scheme 23.

Table 3
2,3-Disubstituted indoles obtained by heteroannulation of internal alkynes using the catalytic system $Pd(OAc)_2$/1,1′-bis(di-*tert*-butylphosphino)ferrocene[a]

Aniline	Major product	Isolated yield
		76
		82
		60
		60
		68
		86
		63

[a] Selected results.

Pd/ferrocenyldiphosphines systems allowed some alkynylation reactions which have been conducted on unusual coupling partners or with unusual promoters: potassium alkynyltrifluoroborates were used as substrates (Scheme 25a) [84,85], the coupling of aryl boronic acids was performed in the presence of silver salts (Scheme 25b) [86], and 1,1-dibromo-1-alkenes were coupled to alkynyl silanes (Scheme 25c) [87].

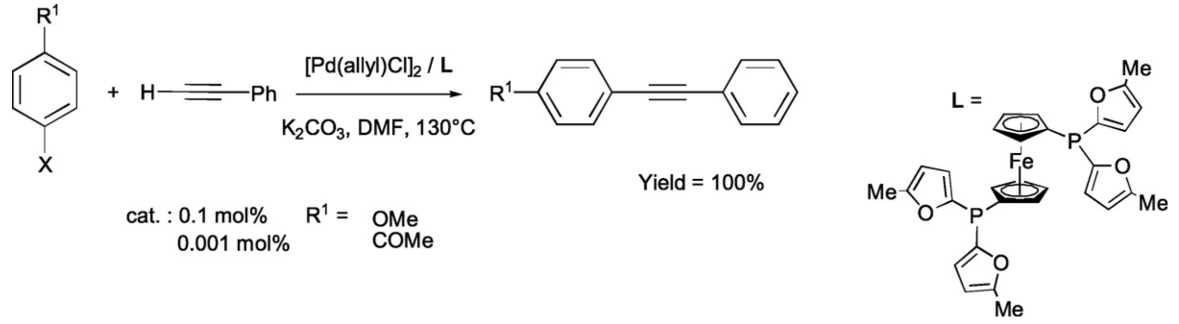
In summary, most of the studies concerning palladium/ferrocenyldiphosphine catalytic systems used for Heck–Sonogashira alkynylation reactions were conducted by employing dppf. In the classical procedures significant limitations were reported, possibly due to negative chelating effects. Nevertheless, very interesting activations of internal and terminal alkynes were reported with systems using the $PdCl_2$(dppf) complex, such as heteroannulation [78–80] or alkynyltrifluoroborates valorization [84]. In addition, unexpected good results have been obtained employing the electron-deficient ligand 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene for the alkynylation of activated or deactivated aryl bromides at very low catalyst concentration [20].

3.4. Coupling from zinc organometallics (Negishi reaction)

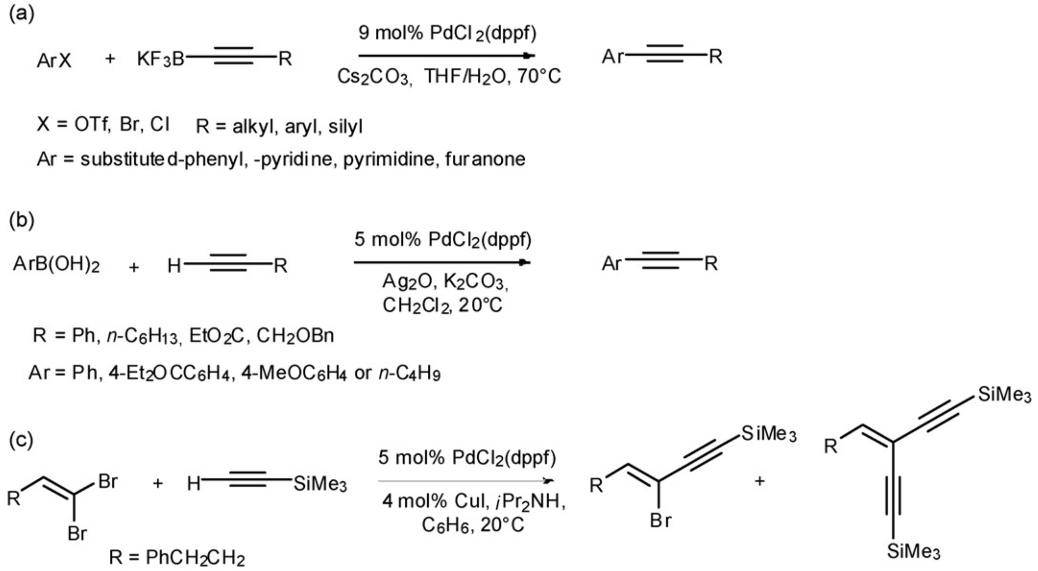
The cross-coupling reactions of organozinc reagents with organic halides in the presence of a palladium or a nickel catalyst, often called Negishi reaction has found a great number of valuable applications [88]. The excellent ability of organozinc species for transmetalation reactions permits one to perform Negishi cross-coupling under mild reaction conditions in the absence of air and water. This reaction has been apparently less intensively investigated than the Suzuki coupling for Pd/ferrocenylphosphine catalysts.

Bumagin and co-workers studied the reaction of 6-bromo-2-methylbenzothiazole with aryl zinc chloride in the presence of a catalytic amount of $PdCl_2$(dppf) complex [89]. This reaction led to 6-aryl-2-methylbenzothiazoles in high yields as shown in Scheme 26.

Knochel and co-workers developed reaction conditions in the presence of $Pd(dba)_2$/dppf that resulted in the selective coupling of aryl zinc reagents with aryl iodides at room temperature, and with aryl triflates at 65 °C (Scheme 27) [90]. Therefore, iodoaryl triflate substrates could be used as multi-coupling reagents with two different organozinc compounds. The $Pd(dba)_2$/dppf catalyst system was also used by the authors to promote aryl



Scheme 24.



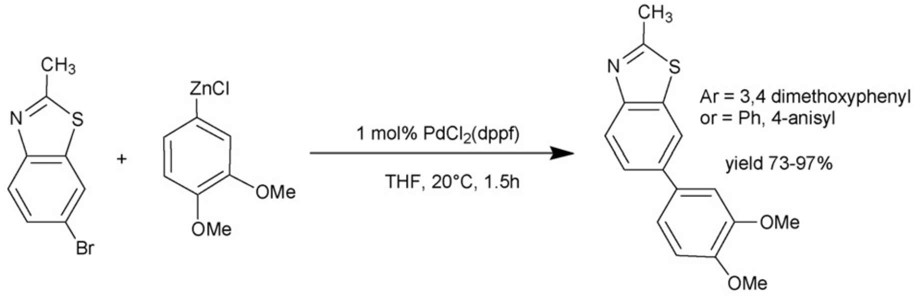
Scheme 25.

nonaflate substrates ($ArONf = ArOSO_2(CF_2)_3CF_3$) as a practical alternative to aryl triflates in Negishi cross-coupling, and also with organoboron and organostannanes reagents [91].

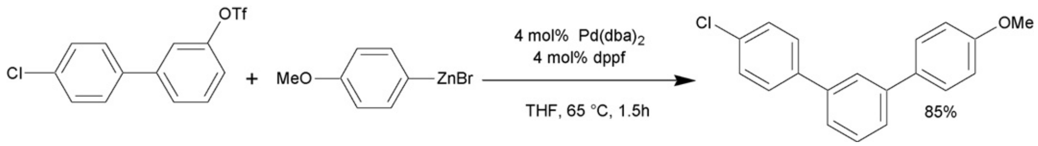
Miller and Farrell reported that the $PdCl_2$(dppf) complex efficiently allowed the cross-coupling of activated aryl chlorides with aryl zinc reagents yielding unsymmetrical biaryls (Scheme 28) [92].

They found that Pd/dppf provided a more active system than other Pd/monophosphine systems which incorporate ligands such as the racemic BINAP (*rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), P(*o*-tol)$_3$ or PPh_3 under similar conditions. The cross-coupling of phenylzinc chloride with 2-chlorobenzonitrile was possible in the presence of 2 mol% of $Ni(acac)_2$ and 2.2 mol% of dppf (room temperature for 18 h), the desired biaryl was obtained in 80% yield from cheap aryl chloride starting materials.

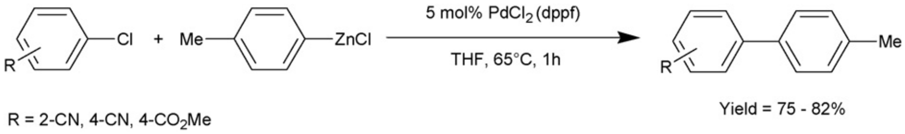
The palladium-catalyzed Negishi cross-coupling was used as the key step for the regiospecific synthesis of a range of substituted nitro and amino-fluorenes, from zinc-containing aromatics



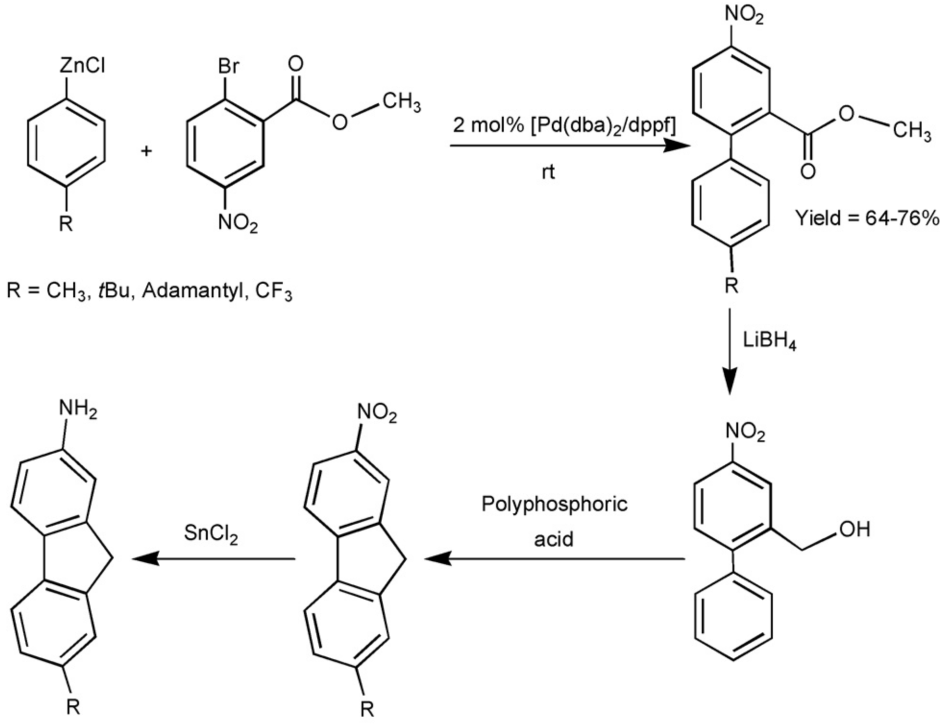
Scheme 26.



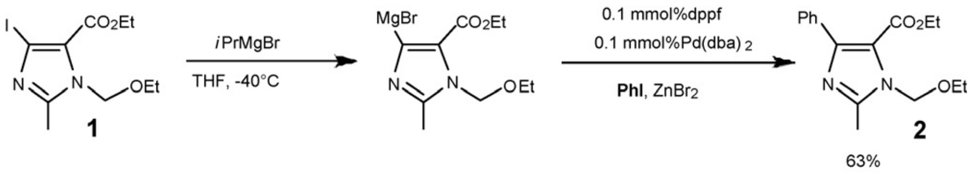
Scheme 27.



Scheme 28.



Scheme 29.

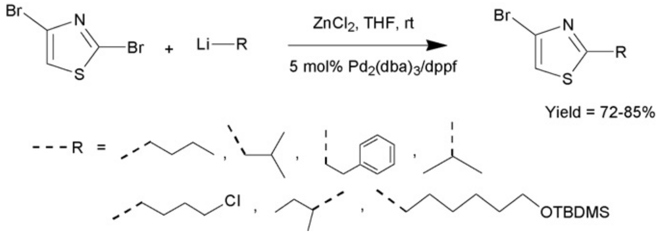


Scheme 30.

under very mild conditions of temperature and moderate catalyst loading (Scheme 29) [93].

The Negishi cross-coupling with Pd/dppf was also used in imidazole and thiazole heterocycle chemistry: 5-iodoimidazole **1**, upon halogen–magnesium exchange, reacts in a transmetalation process with $ZnBr_2$; the subsequent cross-coupling with iodobenzene gave product **2** in 63% yield (Scheme 30) [94].

The efficient cross-coupling of a dibromo-thiazole to alkyl lithium compounds via a transmetalation process with $ZnCl_2$ was effected in THF at room temperature (Scheme 31) [95]. Good yields of alkylated bromo-thiazole were obtained from 5 mol% Pd/dppf catalyst.



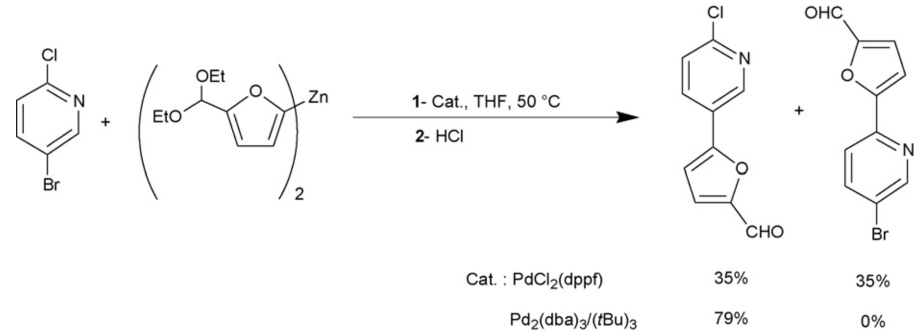
Scheme 31.

The applications of $PdCl_2$(dppf) in Negishi reaction from 2- and 3-chloropyridines with di(2-furyl)zinc substrates were reported [96]. The catalytic system was more effective for reactions involving 2-chloropyridine derivatives than 3-chloropyridines. The coupling of 5-bromo-2-chloropyridine in the presence of $PdCl_2$(dppf) afforded an unexpected 1:1 mixture of products as a result of both chloride and bromide activation; in contrast selective coupling *via* the bromide was observed by employing Pd/P(*t*Bu)$_3$ (Scheme 32).

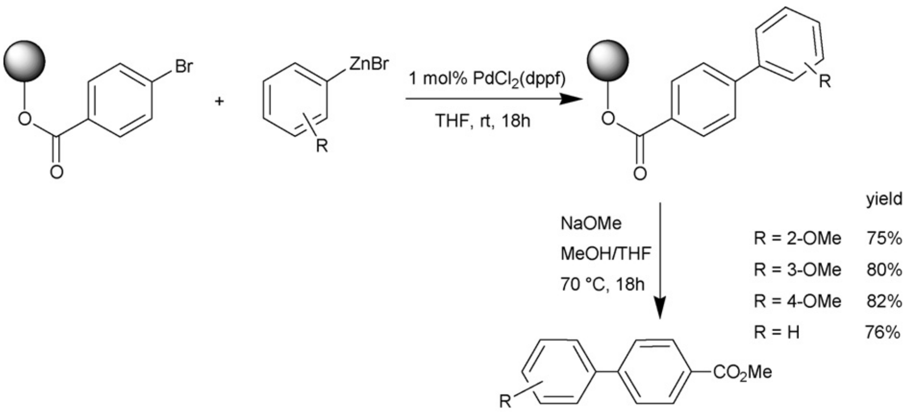
The cross-coupling of aryl zinc halides in solid-phase synthesis has also been reported by Marquals and Arlt [97]. An aryl halide containing an acidic function was linked to a Merrifield's resin (Scheme 33). After the cross-coupling reactions in the presence of $PdCl_2$(dppf), the biaryl products were cleaved from the resin by transesterification. This efficient method to perform aryl–aryl coupling on a solid support is a relevant alternative to the known Suzuki reactions on solid support.

3.5. *Coupling from magnesium organometallics (Kumada–Corriu reaction)*

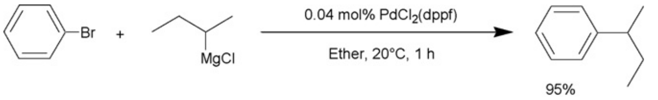
The transition metal-catalyzed cross-coupling of Grignard reagents with aryl- and vinyl halides or triflates was the sub-



Scheme 32.



Scheme 33.



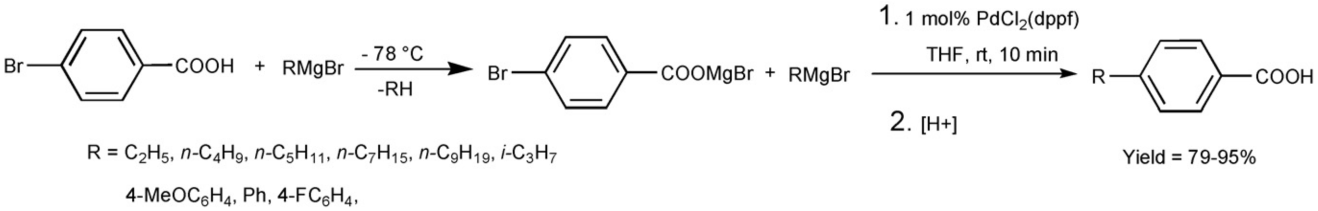
Scheme 34.

ject of studies at an early stage [98]. This methodology was, however, limited because of the incompatibility of magnesium organometallic reagents with several functional groups.

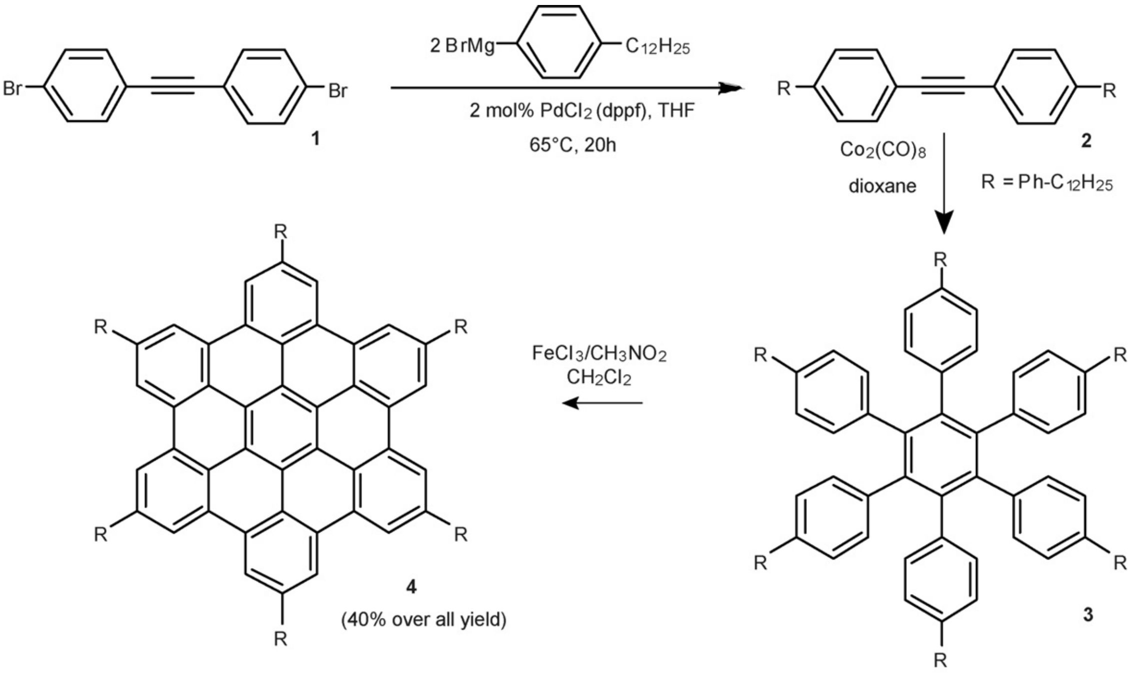
Hayashi et al. demonstrated the usefulness of $PdCl_2$(dppf) in the Kumada coupling of *sec*-butyl magnesium chloride with bromobenzene at room temperature [99]. For this model reaction a yield of 95% in coupling product was reported with no side reactions (Scheme 34). The authors proposed that the higher activity and selectivity of the complex compared to other classical systems (which incorporate PPh_3, dppe, dppp = 1,3-bis(diphenylphosphino)propane, etc.) could be ascribed to the large P–Pd–P bite angle in $PdCl_2$(dppf). The genuine role and influence on catalysis of the chelating bite angles in the ferrocenylphosphine chemistry is unfortunately unclear, with contradictory reports (see also structure–reactivity discussion in Section 6) [7].

It was later shown that Grignard reagents readily react with aryl bromides bearing carboxy-, hydroxy- and amino-groups in the presence of 1 mol% $PdCl_2$(dppf) as the catalyst and without any protection of the substituents [100], a two- or three-fold excess of organomagnesium compound was nevertheless required. For example, the acidic function of 4-bromobenzoic acid reacts with Grignard reagent to give bromomagnesium 4-bromobenzoate, which then can undergo the cross-coupling reaction for a product yield of 95% (see Scheme 35). Aniline and phenols were also arylated and alkylated by this method.

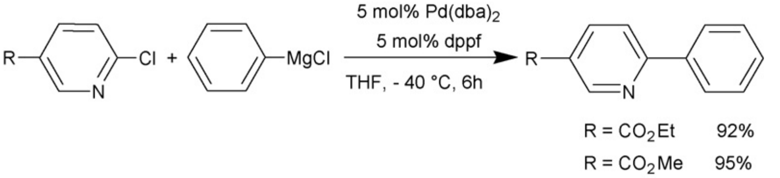
The Kumada–Corriu reaction was also a key step in the synthesis of a substituted hexa-*peri*hexabenzocoronene molecule for its optoelectronic properties [101]. As displayed in Scheme 36, 4,4′-dibromotolane **1** reacts with 4-*n*-dodecylphenylmagnesium bromide, in the presence of 2 mol% $PdCl_2$(dppf), to give di(4-*n*-dodecylbiphenyl)acetylene



Scheme 35.



Scheme 36.

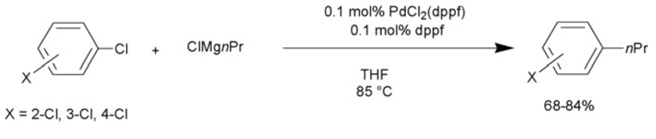


Scheme 37.

2 in 75% yield. Cyclotrimerization of **2**, afforded hexa(4-*n*-dodecylbiphenyl)benzene **3**, which finally lead to **4** in fairly good overall yield.

Besides the coupling of aryl bromides, the use of heteroaryl halides has also been investigated: Knochel and co-workers reported that bromopyridine derivatives react with functionalized arylmagnesium compounds under very mild conditions in the presence of $PdCl_2$(dppf) [102]. Under the same conditions, very good yields were also obtained with the analogous chloropyridine derivatives (Scheme 37). Low temperatures were required and esters were tolerated.

The first example of palladium-catalyzed Kumada cross-couplings of non-heteroaryl chlorides with alkyl Grignard reagents was performed in the presence of $PdCl_2$(dppf) as catalyst (Scheme 38) [103]. The cross-coupling of Grignard reagents RMgX (R = Me, Ph, Pr, $CHMe_2$, *n*-octyl, X = Cl; R = Et, X = Br) with dichlorobenzenes (*o*-, *m*-, *p*-) was described. Monoalkylated and arylated arenes *o*-, *m*-, and *p*-RC_6H_4Cl were selectively produced. The system was also effective for the cross-coupling of Grignard reagents incorporating reactive β-hydrogen atoms.

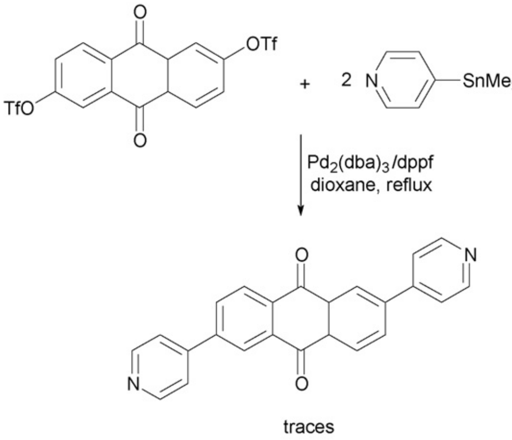


Scheme 38.

To the best of our knowledge, $PdCl_2$(dppf) was the only Pd/ferrocenylphosphine system found to be useful in classical Kumada–Corriu reactions. Aryl- and heteroaryl bromides and chlorides, including electronically deactivated dichlorobenzenes were efficiently coupled. The reaction is also an efficient synthetic tool in key steps of the production of some complex molecules.

3.6. Coupling from other organometallics: Stille (Sn) and Hiyama (Si) reactions

The cross-coupling reactions using organostannane compounds and silanes are commonly identified as Stille coupling and Hiyama coupling, respectively [104]. The pioneering studies by Farina and Krishnan on the relative initial rates in the coupling of iodobenzene to (vinyl)*n*-tri(butyl)tin catalyzed by Pd_2dba_3 at 50 °C in THF in the presence of chelating ligands, showed that Pd/dppf catalyst was inefficient in this reaction (5 times slower than Pd/PPh_3 and 50 times slower than Pd/dppp) [105]. These results were confirmed by Percec and co-workers in the reaction of various aryl sulfonates with (phenyl)*n*-tri(butyl)tin in the presence of different systems incorporating ferrocenylphos-



Scheme 39.

phine: $Pd(OAc)_2$/dppf, $PdCl_2$(dppf)/dppf or $NiCl_2$(dppf) [106]. Both mesylate and triflate substrates provided only low yields of coupling product (<25%).

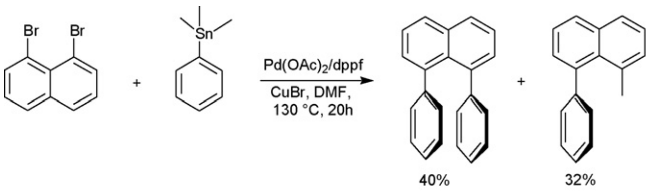
These general trends were once more confirmed by the subsequent studies, as briefly illustrated in the following, and no general conditions were disclosed that employ metal/ferrocenylphosphines for the coupling of a significantly broad range of organostannane substrates.

For example, Coudret and co-workers applied $Pd_2(dba)_3$/dppf as catalyst system in the cross-coupling of aryl triflates with 4-(trimethylstannyl) pyridine for the synthesis of polyaromatic molecules [47]. Under the various conditions explored the catalyst was not effective (Scheme 39), conversely the Suzuki reaction employing aryl boronates provided the desired product in good yield [107].

Fairlamb and co-workers reported that (dppf)Pd(N-succ)Br catalyzed the Stille cross-coupling of benzyl bromide with ethyl 3-(tributylstannyl)-2-*E*-propenoate in fairly good yield (Scheme 40) [108].

Wolf and co-workers have shown that $Pd(OAc)_2$/dppf complex catalyzed the coupling of 1,8-dibromonaphthalene with phenyltrimethylstannane. The catalyst provided the product in 40% yield but 32% of 1-methyl-8-phenylnaphthalene was also obtained (Scheme 41) [109]. In this reaction the best catalyst was $Pd(PPh_3)_4$ which gave the desired product in 58% yield.

Söderberg and Scott found that the best yield (although moderate) for the formation of a polysubstituted-biaryl precursor to carbazolones by Stille coupling (Scheme 42) was obtained using dppf as the ligand with $PdCl_2(PPh_3)_2$ [110].



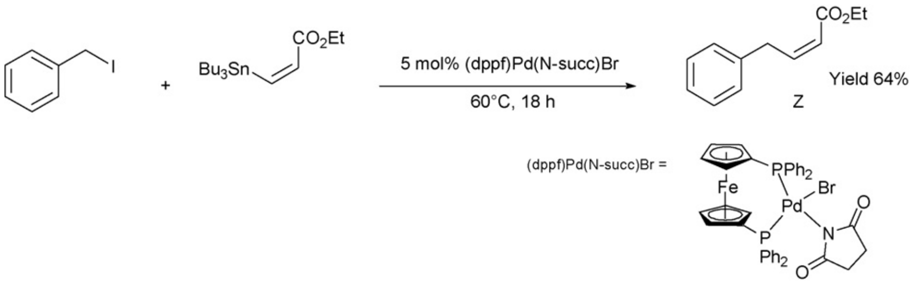
Scheme 41.

The relatively poor efficiency of the catalyst systems described above in the Stille reaction – especially when compared to the reports devoted to Suzuki coupling – might be associated with a more difficult transmetalation step [105,106]. Consistent with this postulated sluggishness several possible intermediates of the transmetalation step in the Stille and the Hiyama couplings were isolated and reported by Echavarren and co-workers by employing Pd/dppf systems (Scheme 43) [111,112]. These studies reveal another aspect of the usefulness of the ferrocenylphosphines as stabilizing ligands for mechanistic understanding (see Section 6 for structure-reactivity discussion).

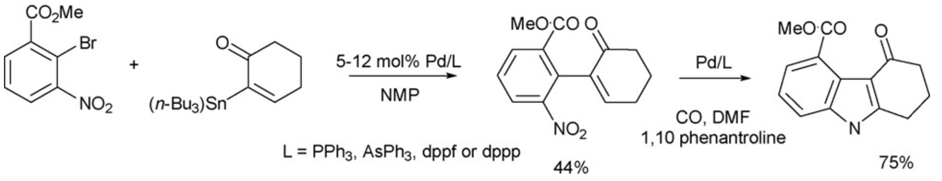
3.7. Cyanation reactions of aromatic halides

Because of the well-known limitations of nucleophilic aromatic substitution the metal-catalyzed cyanation of aromatic halides and pseudo-halides is of interest to produce a large array of alkyl-, alkoxy-, alkylthio-, hydroxyl-, acyl-, carboxyl- or amino-substituted aryl nitriles, as well as polycarbonitriles [113]. These arylnitriles form essential parts of many natural products and pharmaceuticals and can be useful intermediates in organic synthesis.

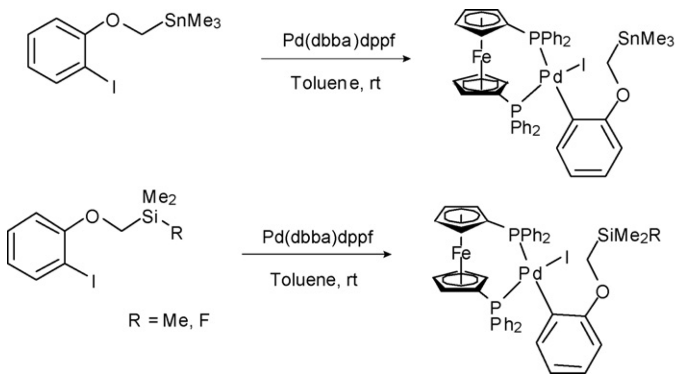
Takagi et al. have first disclosed that the reaction of unactivated aryl halides with cyanide ions in the presence of palladium salts was possible [114]. Fifteen years after this pioneering work, Takagi and co-workers reported that the system $[Pd_2(dba)_3]\cdot CHCl_3$/dppf is effective for the cyanation of various aryl iodides (Scheme 44a) and aryl triflates (Scheme 44b) using KCN as the source of cyanide [115]. In the absence of ligand the cyanation of aryl halides was not complete and more surprisingly, the presence of auxiliaries such as PPh_3, PBu_3, $P(O\mathit{i}Pr)_3$, dppp, 1,10-phenanthroline or 2,2′-bipyridyl even lowered the catalytic activity. The Pd/ferrocenylphosphine catalytic system was more effective for the cyanation of aryl iodides than aryl triflates which required a higher catalyst loading. The attempts to achieve cyanation of aryl bromides and chlorides were not



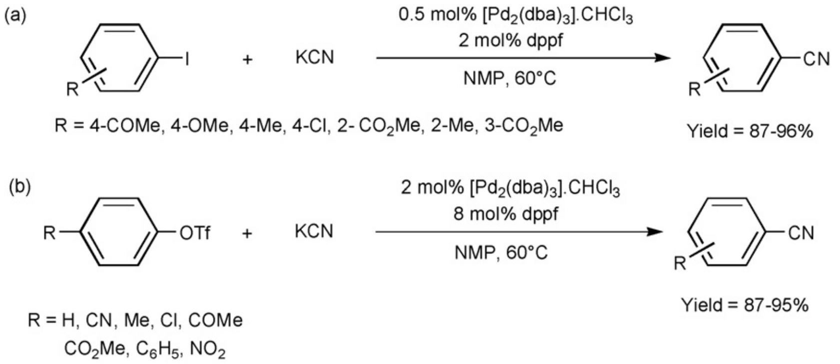
Scheme 40.



Scheme 42.



Scheme 43.

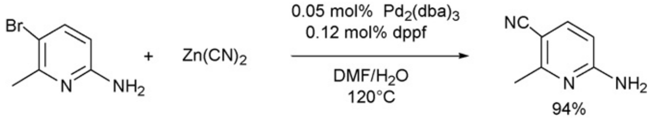


Scheme 44.

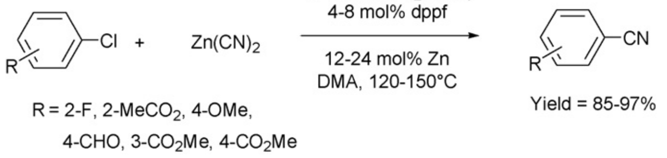
successful. The authors assumed that the efficiency of the dppf ligand was a result of a protective effect towards Pd, an effect not perturbed by cyanide anions attacks on the metal center [115].

The results from Takagi's group on the relative efficiency of phosphine auxiliary ligands were to some extent confirmed in the studies by Maligres et al. [116] in which the synthesis of 2-amino-5-cyano-6-picoline was carried out by cyanation of 2-amino-5-bromo-6-picoline with $Zn(CN)_2$ as cyanide ions source and a catalytic system combining $Pd_2(dba)_3$ and dppf (Scheme 45). They found that in comparison to dppf, phosphines such as PPh_3, dppe, dppp, dppb or BINAP were less effective. They revealed in addition, practical conditions for the conversion of bromobenzene, l-bromonaphthalene and 2-bromoanisole conversion into the corresponding arylnitriles in yields over 85%: ultimately, multi-kilogram cyanations were conducted at 120 °C in wet DMF (2% H_2O) in the presence of only 0.1 mol% Pd/dppf.

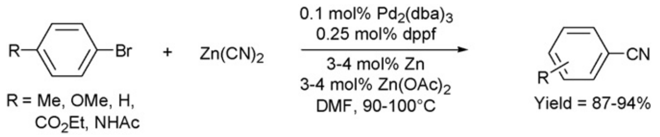
Jin and Confalone reported that the cyanation of either electron-deficient or electron-rich aryl chlorides was possible by employing a similar catalytic system with an additional amount of zinc powder (Scheme 46) [117]. In this study as well, $Zn(CN)_2$ was used as the cyanide source, confirming its superiority other NaCN or KCN salts [116]. The coupling of electron-rich aryl chlorides required higher Pd/dppf loading and a prolonged reaction time at 150 °C, nevertheless, the corresponding aryl nitriles were obtained in yields above 85%.



Scheme 45.



Scheme 46.



Scheme 47.

Chidambaram reported that $Pd_2(dba)_3$/dppf can be an effective system for the cyanation of activated and deactivated aryl bromides with excellent yields, by using KCN as the source of cyanide in the presence of zinc acetate and additional zinc powder (Scheme 47) [118]. Surprisingly, the catalyst did not effect the cyanation reactions of 4-aminobromobenzene and 4-nitro bromobenzene. The beneficial role attributed to the zinc powder and to the additional $Zn(OAc)_2$ is somewhat unclear in this study.

An additional interesting contribution regarding cyanation reaction with ferrocenylphosphine showed that the combination of dppf with $Pd_2(dba)_3$ can catalyze cyanation of 2-bromopyridine with KCN under mild conditions (80 °C, 0.5 mol% Pd/dppf) in the presence of 0.14 mol% Bu_3SnCl [119]. In addition, some less reactive halides such as 2-chlorobenzonitrile and 1,2-dichlorobenzene were fairly smoothly cyanated by employing nickel-catalyzed reaction with $NiBr_2$/dppf (3–4 mol% in hexamethylphosphoramide at 60 °C for 24 h) [120].

4. Carbon–nitrogen bond-forming reactions catalyzed by employing ferrocenylphosphines

4.1. Amination of aryl halides, triflates and sulfonates (Buchwald–Hartwig reaction)

4.1.1. Buchwald–Hartwig coupling with dppf as the ligand

Arylamines are common building blocks of many organic molecules and biologically active natural products. The first syntheses of arylamines were carried out by nitration of arenes followed by catalytic hydrogenation or a reduction with a metal salt. These procedures that employ strong acidic and oxidizing conditions are incompatible with many functional groups, and thus require the use of protective groups in multiple reaction step. The discovery of palladium-catalyzed aryl/amine bond-forming reactions procedures has enlarged the availability in excellent yields and selectivity of these important arylamine compounds.

Migita and co-workers described in 1983 a palladium-catalyzed coupling of bromobenzene with *N*,*N*-diethylaminotri-*n*-butyltin which afforded the corresponding *N*,*N*-diethylaminobenzene and tri-*n*-butyltin bromide as a stoichiometric by-product [121]. From this pioneering study, a tin-free palladium-catalyzed amination was reported independently by the groups of Hartwig and Buchwald [122]: $Pd_2(dba)_3$ combined with *o*-tolylphosphine allowed the coupling of secondary amines with aryl iodides and bromides in the presence of strong bases such as NaO*t*Bu.

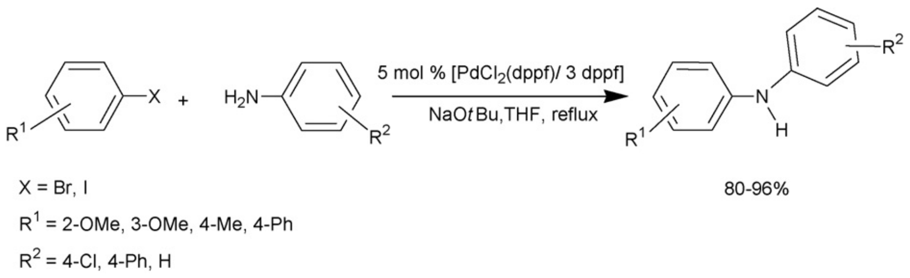
In 1996, Driver and Hartwig successfully employed $PdCl_2$(dppf) as a catalyst in the coupling of aryl halides with primary amine aniline derivatives (Scheme 48) [123]. This catalyst provided nearly quantitative yields for electron-rich, electron-poor, hindered or unhindered aryl bromides and iodides. The coupling of the secondary amine di-*n*-butylamine with 4-*tert*-butylbromobenzene was more difficult: only 40% of coupling product was obtained employing 5% $PdCl_2$(dppf)/15 mol% dppf, a number of other systems giving better results [124,125].

The catalytic amination of 2-halo-pyridines with various hydrazine substrates was reported using Pd/dppf as catalytic system and Cs_2CO_3 as the base (Scheme 49) [126,127]. This catalytic amination provided a direct route to protected bifunctional hydrazinopyridine as chelating *N*,*N*-ligands in relation to the chemistry of ^{99m}Tc and Re radiopharmaceuticals.

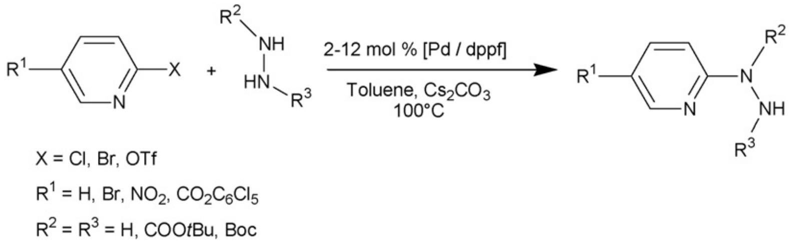
Beletskaya and Guilard have shown that a catalyst system combining $PdCl_2$(dppf) and dppf allows the monoarylation of 1,3-diaminopropane with 4-bromobiphenyl in good yield and high selectivity (Scheme 50) [128]. Tri- and tetra-amines were thus monoarylated, preferentially at the primary terminal amino position. This reaction is of great interest for the preparation of polyamines and linear or macrocyclic polyaza ligands.

N-Aryl azoles were synthesized employing dppf-ligated palladium in the presence of Cs_2CO_3 or NaO*t*Bu as a base (Scheme 51) [129]. These potentially biologically active molecules can be prepared in high yields from electron-rich, electron-neutral and electron-poor 4-substituted aryl bromides; long-term reactions at rather high temperature were required.

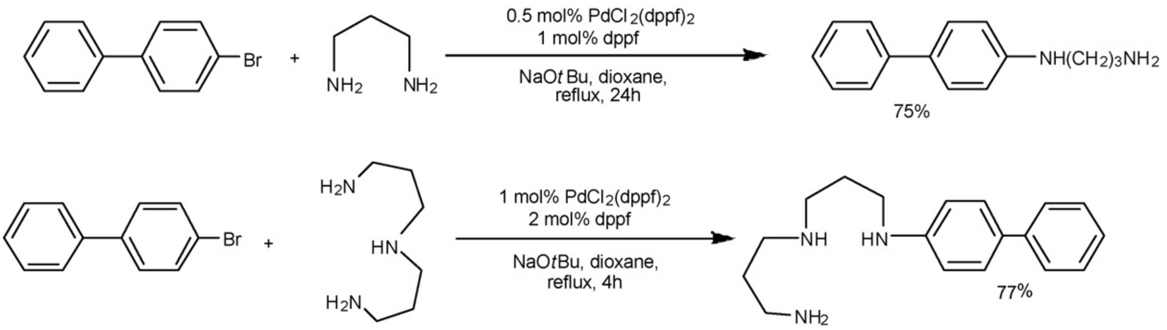
N-Substituted indole-2-carboxylates have been prepared by the intramolecular palladium-catalyzed amination reaction of didehydrophenylalanine iodo-derivatives in the presence of low amounts of $PdCl_2$(dppf) and KOAc as a base, in DMF at 90 °C (Scheme 52) [130]. The carboxylate function is preserved and further activation and substitution on the molecules can be performed.



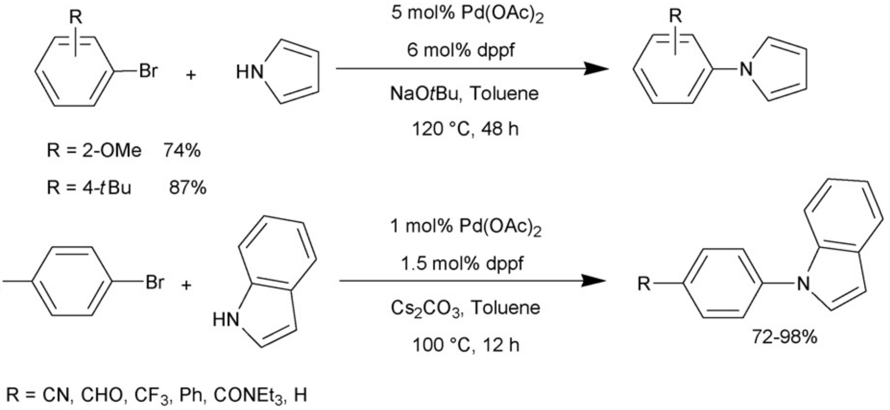
Scheme 48.



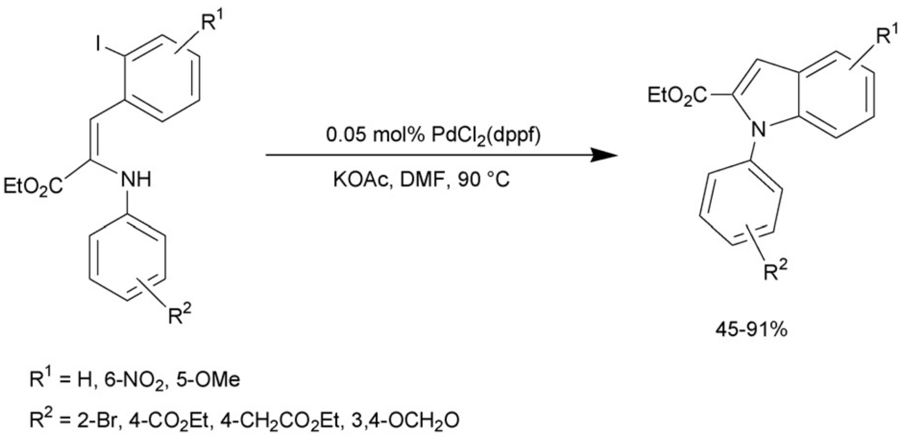
Scheme 49.



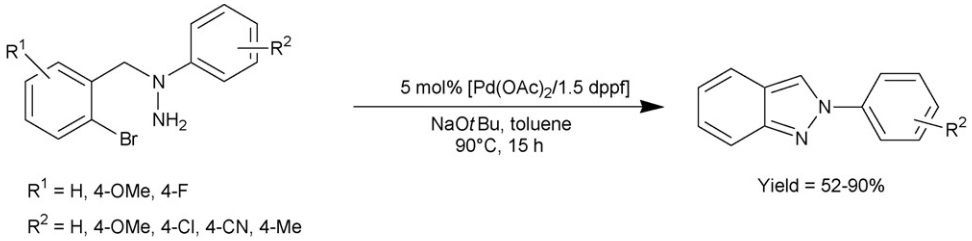
Scheme 50.



Scheme 51.



Scheme 52.



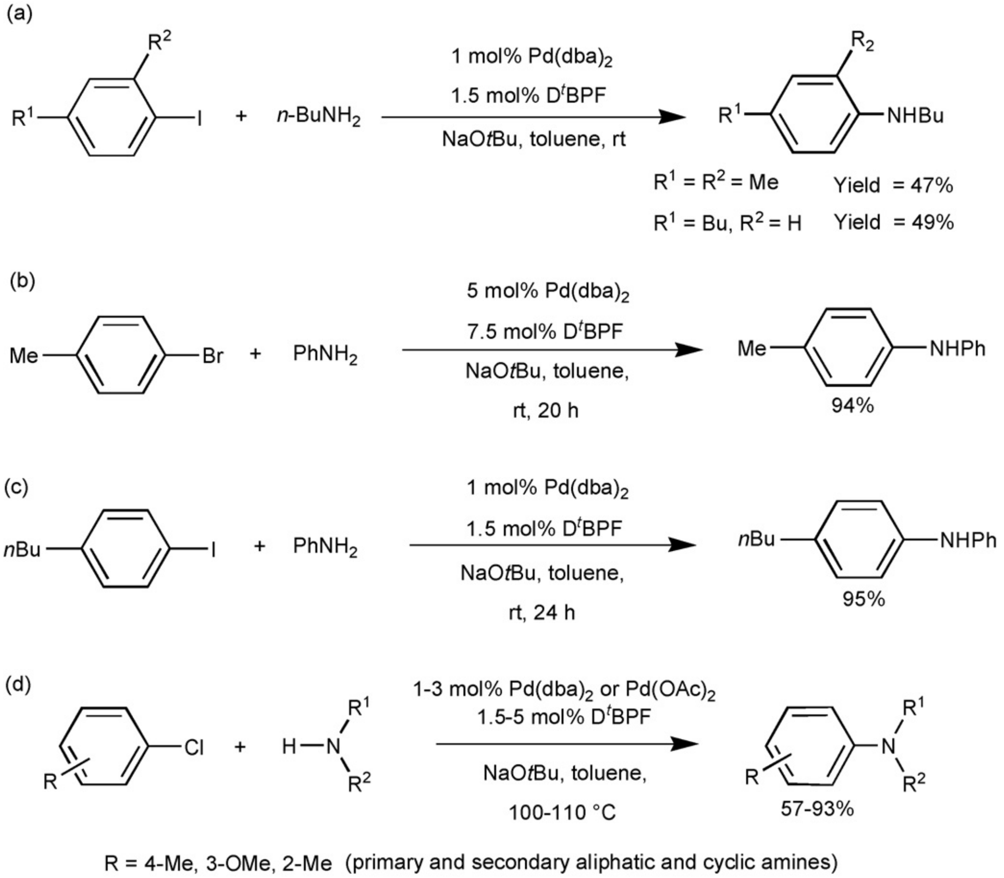
Scheme 53.

The intramolecular aryl amination reaction gave also access to various 2-aryl-2*H*-indazoles from *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines (Scheme 53) [131]. The arylated indazole nucleus, which can be a key subunit of pharmaceuticals, was obtained in fairly good to excellent yield by using a $Pd(OAc)_2$/dppf system. The dppf ligand was found more effective than monodentate and other bidentate ligands such as the *rac*-BINAP, PPh_3 or dppp. This system was applied to a range of substrates which incorporate electron-donating and electron-withdrawing substituents.

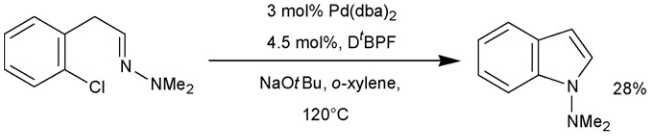
4.1.2. Buchwald–Hartwig coupling with other ferrocenylphosphines as the ligand

For amination of aryl halides, several successful studies were based on Pd/1,1′-bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF) systems. Hamann and Hartwig reported the palladium-catalyzed coupling of primary alkyl amines with deactivated aryl iodides at room temperature (Scheme 54a) in the absence of any additive [132]. The chelating electron-rich D^{t}BPF was also efficiently employed for the coupling of aniline with *p*-bromotoluene and *p*-(*n*-butyl)iodobenzene at room temperature (Scheme 54b and c). The amination of the comparatively inert aryl chlorides can even be achieved with Pd/D^{t}BPF catalyst systems under harsher conditions of temperature (Scheme 54d).

The high effectiveness of D^{t}BPF was attributed to a fine combination of electron-donating properties – which may facilitate the oxidative addition of halides to the active Pd(0) species – and steric hindrance, which may favor the reductive elimination step. Nevertheless, a Pd/D^{t}BPF system was employed with only little success in the Pd-catalyzed intramolecular cyclization of *o*-chloroarylacetaldehyde *N*,*N*-dimethylhydrazones in the presence of NaO*t*Bu, and in *o*-xylene as solvent (Scheme 55), some other ligands being more effective [133].



Scheme 54.



Scheme 55.

A systematic study aimed at determining the influence of the steric, geometric and electronic properties of dppf derivatives in aryl halide amination has been reported by Hamann and Hartwig (see detailed discussion in Section 6) [19]. The model reactions studied included amination of (4-bromobutyl)benzene with isobutylamine and *n*-butylamine, and amination of 4-bromo-*N*,*N*-dimethylaniline with aniline. Comparisons of the ratios of amine products to dehydrohalogenation products (see example in Scheme 56) showed that catalysts containing electron-rich, modestly hindered phosphines with small bite angles gave the best selectivity.

More recently, the use of the monodentate Ph$_5$FcP(*t*-Bu)$_2$ (pentaphenylated (di-*tert*-butylphosphino)ferrocene) as ligand provided a very efficient system for the palladium-catalyzed coupling aminations of activated and unactivated aryl bromides and chlorides with primary and secondary aromatic and aliphatic amines [134].

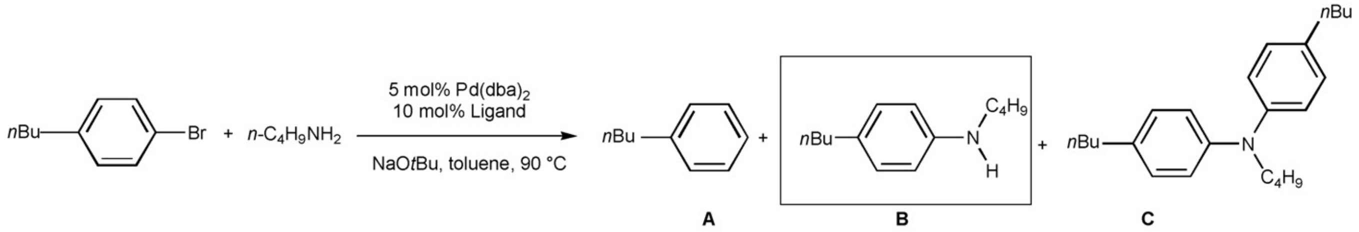
4.1.3. Buchwald–Hartwig coupling with nickel-based catalyst systems

Nickel-catalyzed amination has also been explored by employing ferrocenylphosphine ligands, with the view to produce cheaper catalytic systems. Wolfe and Buchwald disclosed that the combination of Ni(COD)$_2$ and dppf is an effective catalyst for the coupling of aryl chlorides with a broad range of amines (Scheme 57) [135]. A number of electron-rich and electron-poor aryl chlorides, as well as heteroaryls such as chloropyridine derivatives, were successfully used. A drawback of this procedure was the utilization of the air-sensitive and commercially expensive Ni(COD)$_2$ as a catalyst precursor; this problem has been partially addressed by an alternative procedure in the presence of NiCl$_2$dppf [135].

Lipshutz and co-workers have reported an interesting modification of this method by conducting the aminations of aryl chlorides in the presence of nickel on charcoal and LiO*t*Bu at high temperature (Scheme 58) [136]. LiO*t*Bu was used to reduce nickel, and dppf was present as the ligand; aryl amines were obtained in fairly good to excellent yields.

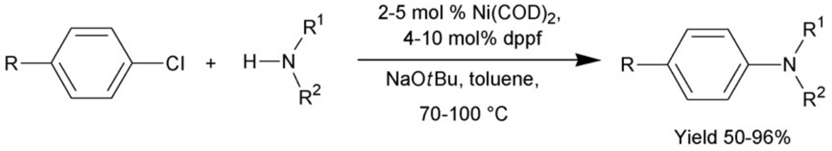
4.1.4. Amination of aryls from pseudo-halides sulfonates

The amination of aryl triflates have a significant synthetic value with regard to the diversity of available phenols (and aromatic chemistry of protected phenols) [137], and to the simple conversion of phenols to aryl triflates [138]. Pd(dba)$_2$ combined with dppf gave an effective catalyst for the amination of aryl triflates [113]. The reaction conditions are similar to those employed for the amination of aryl halides and led to very good yields. Some representative examples of amination of aryl triflates by aniline and alkyl amines are depicted in Scheme 59. However, electron-poor aryl triflates are susceptible to cleavage under basic conditions because of the stable phenolate formed. This problem has been overcome by the slow addition of the aryl triflate in the course of the reaction [139]. Alternatively,



Ligand	% A	% B	% C
p-MeOdppf	4	55	21
dppf	4	52	22
p-CF$_3$dppf	6	53	18
3,5-CF$_3$dppf	14	49	6

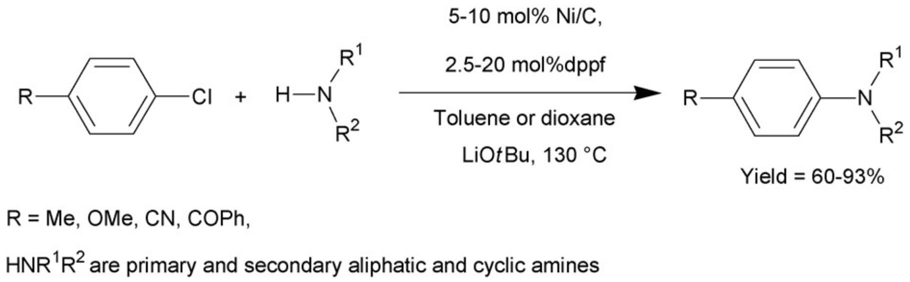
Scheme 56.



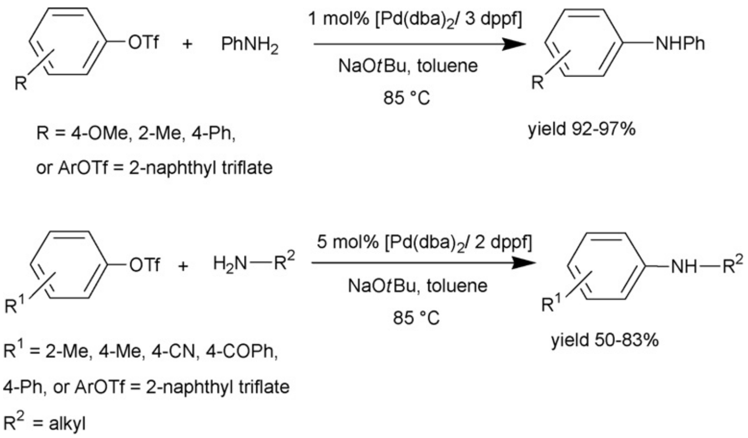
R = Me, OMe, CN, COPh,

HNR^{1}R^2 are primary and secondary aliphatic and cyclic amines

Scheme 57.



Scheme 58.



Scheme 59.

the problem of triflate cleavage can be reduced by the use of Cs_2CO_3 as the base [140,141].

Although the leaving group ability of tosylates is substantially lower than that of triflates, Hamann and Hartwig have shown that palladium combined with the electron-rich D^{t}BPF ligand generate an effective catalyst for the amination of aryl tosylates [132]. The cross-coupling reaction of aniline with the tosylate derivative of 4-cyanophenol illustrates well the potential of using this Pd/ferrocenyldiphosphine system to convert phenols into amines (Scheme 60).

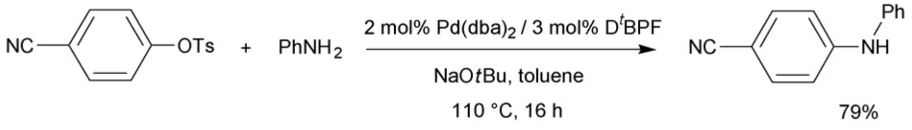
Klapars and co-workers reported that $Pd_2(dba)_3$ combined to 1,1′-bis(diisopropylphosphino)ferrocene provides an active catalyst for the stereoselective coupling of tosylates (from enols) with amides (Scheme 61) [142]. The procedure was applied to tosylated enols bearing an aryl substituent or an electron-withdrawing group in the β-position of the double bond. The tolerance towards steric hindrance in the tosylate substrate allowed a convenient synthesis of functionalized tri- and tetra-substituted enamides.

Pioneering studies have been reported concerning the solid-phase synthesis of aryl amines by palladium-catalyzed amination of resin-bound aromatic bromides in the presence of phosphine ligands, such as dppf, by using a Suzuki-type cross-coupling [143].

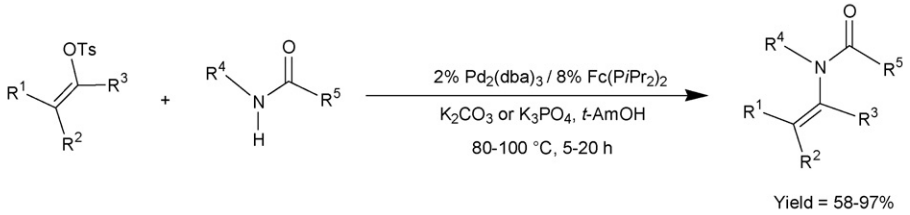
4.2. Amination of allylic acetates (nucleophilic substitution)

The discovery of the palladium-catalyzed allylic alkylation initiated an intense research effort towards the synthesis of useful allylic building blocks. Amination of allyl halides, acetates or malonates was efficient when conducted in the presence of 1–10 mol% palladium catalysts and phosphine auxiliaries. In the achiral version of these reactions, the efficiency of ferrocenylphosphine ligands was studied in relation to their stability – due to the robustness of the ferrocenyl backbone – and to their tunable activity (based on steric and electronic effects of phosphine substituents) [144]. The ligand 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene was found to promote nucleophilic allylic amination of allylic acetate at room temperature with unmatched turnover frequencies (Scheme 62).

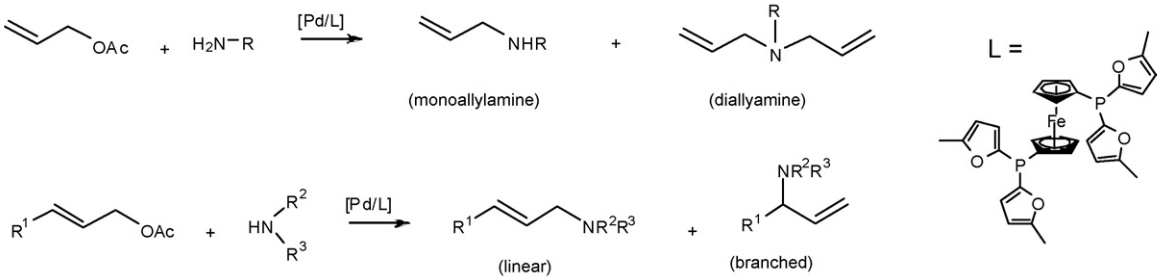
For instance, in the presence of 0.01 mol% catalyst the coupling of aniline with allyl acetate occurred at a TOF above



Scheme 60.



Scheme 61.



Scheme 62.

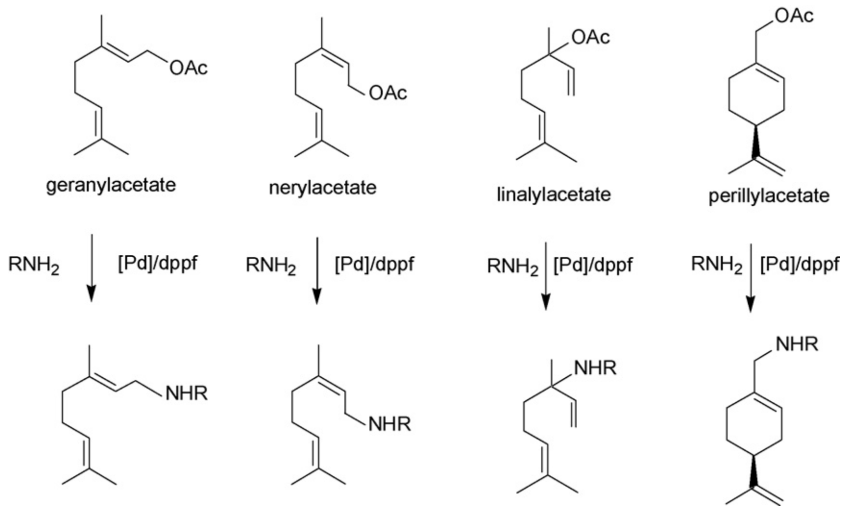
10,000 h^{-1} with a complete conversion and 96% selectivity in monoallylamine (Table 4). Under the same conditions, dppf as the ligand gave a conversion of 60% after 40 h at room temperature (TOF 150 h^{-1}). The monophosphines PPh_3 and PCy_3 were ineffective at such low concentration and temperature. Various aliphatic and cyclic primary or secondary amines of different steric and nucleophilic properties have been successfully employed for the amination of allyl acetate, cinnamyl acetate and hexenyl acetate (Table 4). The low concentrations of the catalytic system as well as the mild reaction conditions are especially notable (see Section 6 for structure-reactivity discussion) [20].

The same catalytic system was employed to investigate the allylic amination reaction with a substantially more demanding allylic acetate substrate. The sterically hindered monoterpene derivative geranyl acetate was chosen due to the industrial interest of monoterpenes [144]. The reaction of geranyl acetate with aniline at room temperature using 1 mol% Pd/furylphosphine

Table 4
Amination of allylic acetate with Pd/[furylphosphino]ferrocene

Allylic acetate	Amine	Ratio substrate/catalyst	Reaction conditions	Yield %	Selectivity %
Allyl acetate	H_2NPh	10,000	r.t.,[a] 1 h	100	96/4 (mono/di)
Allyl acetate	$–(CH_2)_4HN–$	10,000	r.t.,[a] 2 h	98	100
Allyl acetate	$–[O(CH_2)_4]HN–$	10,000	r.t.,[a] 2 h	85	100
Allyl acetate	H_2NCH_2Ph	10,000	r.t.,[a] 4h	73	75/25 (mono/di)
Allyl acetate	HN(*n*-octyl)$_2$	1,000	r.t., 20 h	100	100
		10,000		45	100
		100,000		5	100
Allyl acetate	HN(*i*-propyl)$_2$	1,000	80 °C,[a] 2 h	96	100
3-Phenylallyl acetate	$HNEt_2$	1,000	r.t., 20 h	100	94/6 (lin/brch)
		10,000		76	94/6
3-Phenylallyl acetate	$–(CH_2)_4HN–$	1,000	50 °C, 20 h	100	94/6 (lin/brch)
		10,000		26	94/6
3-Phenylallyl acetate	$–[O(CH_2)_4]HN–$	1,000	50 °C, 20 h	100	93/7 (lin/brch)
		10,000		48	93/7
E-Hex-2-en-1-yl acetate	$HNEt_2$	250	50 °C, 20 h	100	99/1 (lin/brch)
		1,000		76	99/1
E-Hex-2-en-1-yl acetate	$–(CH_2)_4HN–$	1,000	50 °C, 20 h	100	94/6 (lin/brch)
E-Hex-2-en-1-yl acetate	$–[O(CH_2)_4]HN–$	1,000	50 °C, 20 h	98	94/6 (lin/brch)
E-Hex-2-en-1-yl acetate	HN(*n*-octyl)$_2$	250	50 °C, 20 h	59	100
		1,000		11	100

Conditions: catalyst $[PdCl(\eta^3\text{-}C_3H_5)]_2/\mathbf{1}$:1/2. No additional base. Allylic acetate 1 equiv., amine 2 equiv., tetrahydrofuran.
[a] Carried out in toluene.



Scheme 63.

ferrocenic ligand yielded geranylaniline with a total selectivity in 75% yield after 20 h. Morpholine was coupled to geranyl acetate in the presence of 1 mol% Pd/1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene at room temperature with a 60% conversion in 1 h, and an almost total conversion after 20 h. The coupling of the more demanding diisopropylamine to geranyl acetate did not proceed satisfactorily in the presence of 1 mol% Pd/ligand [144].

Several monoterpene derivatives have been efficiently aminated using a ferrocenyl tetraphosphine (depicted Schemes 5, 8 and 13) or dppf with palladium at 1 to 10^{-1} mol% (Scheme 63) [145]. For the amination of nerylacetate, linalylacetate and perillylacetate, the readily available dppf looks very attractive since high selectivity was observed together with excellent conversion yields.

The studies devoted to the catalytic properties of dppf derivatives built with phosphorus donors bearing heterocyclic substituents are notably less developed than the studies concerning ferrocenylphosphines holding electron-rich phosphine groups (such as classical aryl or alkyl substituents). Therefore, the reports quoted above regarding nucleophilic amination interestingly highlight the potential interest of electron-poor ferrocenylphosphines ligands in some well-selected catalytic reactions, incorporating for instance nucleophilic substitution steps.

5. Carbon–oxygen bond-forming reactions catalyzed by employing ferrocenylphosphines

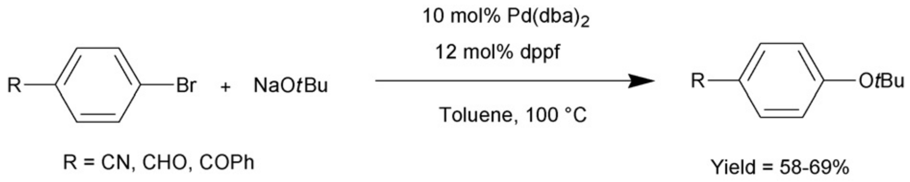
The synthetic efforts directed towards organic synthesis of natural substances have conducted to the formation of aryl ether blocks, in addition to the above-discussed aryl–aryl and aryl–amine units. The organic reactions that originally generated diaryl ethers from aryl halides were nucleophilic aromatic substitutions [146]. Ullmann coupling that employs copper powder or copper salts was also used [147]. The nucleophilic aromatic substitution suffer strong limitations regarding the fact that activated aromatic systems are unavoidably required. The Ullmann ether synthesis is conducted with aryl halides substrates under harsh conditions which are often damaging for functional groups. Therefore, the recent developments on palladium-catalysis have led to a much more convenient formation of aryl ethers. These aryl ethers, through carbon–oxygen bond-forming, provided building block for pharmaceuticals and active natural products [148,149].

The first example of intermolecular etheration of aryl halides was reported by Mann and Hartwig [150]. $Pd(dba)_2$ combined with dppf was used as the catalyst for the addition of NaO*t*Bu to the activated aromatic compounds 4-bromobenzophenone, 4-bromobenzaldehyde and 4-bromobenzonitrile, to provide the corresponding aryl ether in fairly good yield (Scheme 64). In contrast, when unactivated aryl bromides were used no formation of aryl ethers was observed. The *tert*-butyl ethers produced by this way can generate phenols by addition of acid to the crude reaction mixture after completion of etheration.

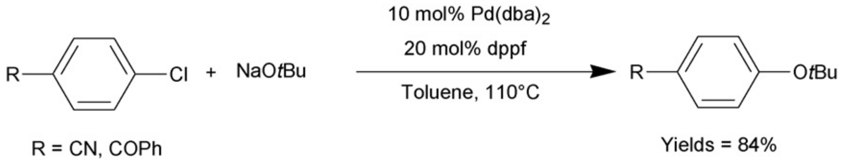
Palladium-catalyzed C–O bond formation was described from cheaper aryl chloride substrates incorporating electron-withdrawing substituents under slightly harsher conditions [151]. Pd/dppf catalyst systems allowed the coupling of aryl chlorides with NaO*t*Bu to generate *tert*-butyl aryl ethers in good yield (Scheme 65).

In the same study dealing with cheaper and convenient access to aryl ether, the nickel complex $Ni(COD)_2$ combined with dppf was successfully employed for the formation of alkyl- and silyl aryl ethers, in one step from aryl halides (Scheme 66) [151]. A range of different conditions and of nickel catalytic precursors was tested, which showed a large amount of Ni and ligand necessary for the reaction to proceed. *tert*-Butyl-, methyl-, and *tert*-butyldimethylsilyl-aryl ethers were obtained from the coupling of aryl bromides and chlorides with sodium alkoxides and sodium siloxides. The $Ni(COD)_2$/dppf combination provided higher yields of coupling product than the palladium systems for the formation of the silyl aryl ether, but lower yields for *tert*-butyl aryl ethers.

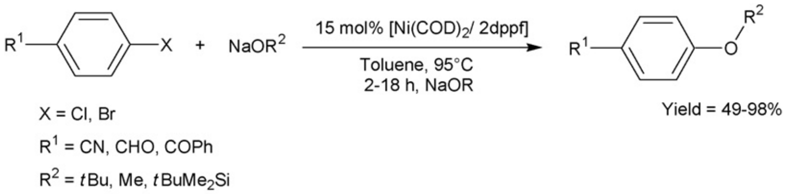
It is worth noting – even if it is out of the main scope of the present review [11] – that Hartwig and co-workers were able



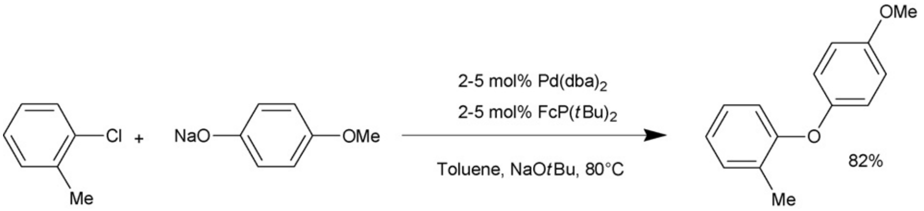
Scheme 64.



Scheme 65.



Scheme 66.



Scheme 67.

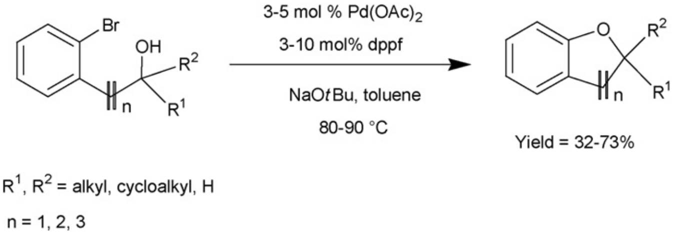
to generate C–O bond formation between deactivated electron-rich aryl chlorides and sodium aryloxides by employing the more electron-donor dissymmetric ferrocenyl*mono*phosphine (di-*tert*-butylphosphino)ferrocene, FcP(tBu)$_2$, as auxiliary ligand (Scheme 67) [152]. Interestingly, only aryl chlorides bearing an *ortho* substituent were activated. The beneficial effect of the *ortho* substituent might be due to acceleration – attributable to the steric pressure – of the reductive elimination step of the catalytic cycle, whereas the oxidative addition step might be favored by the electron-donor effect of the ligand. Consistently, under these conditions Pd/dppf and Pd/P(o-tol)$_3$ systems that lack either electron-richness or steric hindrance were ineffective.

FcP(tBu)$_2$ can undergo pentaarylation to generate Ph$_5$FcP(tBu)$_2$, which provides a more active palladium-based catalytic system than that furnished by FcP(tBu)$_2$ in the couplings of aryl bromides with alkoxides, siloxides, and sodium phenoxides at room temperature [153]. Complexes of this ligand also catalyzed the coupling of electron-poor aryl chlorides and sodium *tert*-butoxide at room temperature.

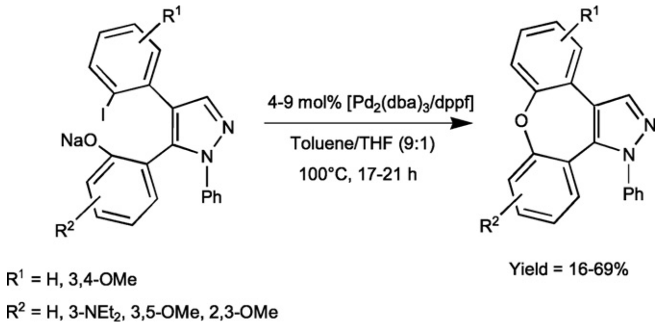
Buchwald and co-workers reported the palladium-catalyzed synthesis of cyclic aryl ethers from aryl halides bearing an alcohol function, in the presence of dppf (Scheme 68) [154]. These intramolecular cyclization reactions conducted with tertiary or secondary alcohols produced five-, six-, and seven-membered heterocycles. The authors assumed that the reaction occurs through oxidative addition of the aryl halide on the palladium center and subsequent formation of the palladium oxametallacycle and C–O bond formation after reductive elimination.

By using a related intramolecular palladium-catalyzed diaryl ether formation, Olivera et al. reported an efficient methodology for the preparation of dibenzoxepine compounds from iodide substrates (Scheme 69) [155].

Mann and Hartwig have shown that the electronic properties of the ligands can substantially affect the yields of formation of diaryl ethers [156]. The reaction of 4-bromobenzonitrile with sodium phenoxide catalyzed by a combination of Pd(dba)$_2$/dppf



Scheme 68.



Scheme 69.

or modified dppf ligands has been explored (Scheme 70). When dppf was used, a 51% yield was obtained. Interestingly, the yield was increased when the more electron-withdrawing derivative *p*-CF_3-dppf was employed, whereas when the electron-donating *p*-OMe-dppf was used the reaction proceeded in only 8% yield. A possible explanation is that the more electron-poor ligands accelerate the reductive elimination process and might increase the reaction yield when this step is determining [156].

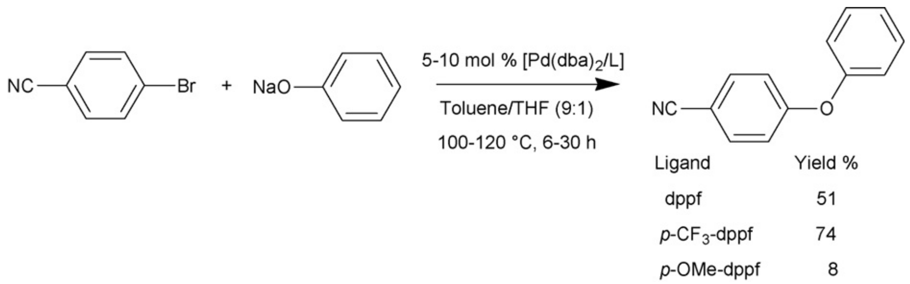
6. Structure-reactivity studies of ferrocenylphosphines related to catalysis performances

The large influence on reactivity and catalysis performances of the structure of ferrocenylphosphine ligands was clearly demonstrated by the numerous successful reactions described above. However, the origin of the specific effects with regard to substrates and reaction conditions is often difficult to rationalize.

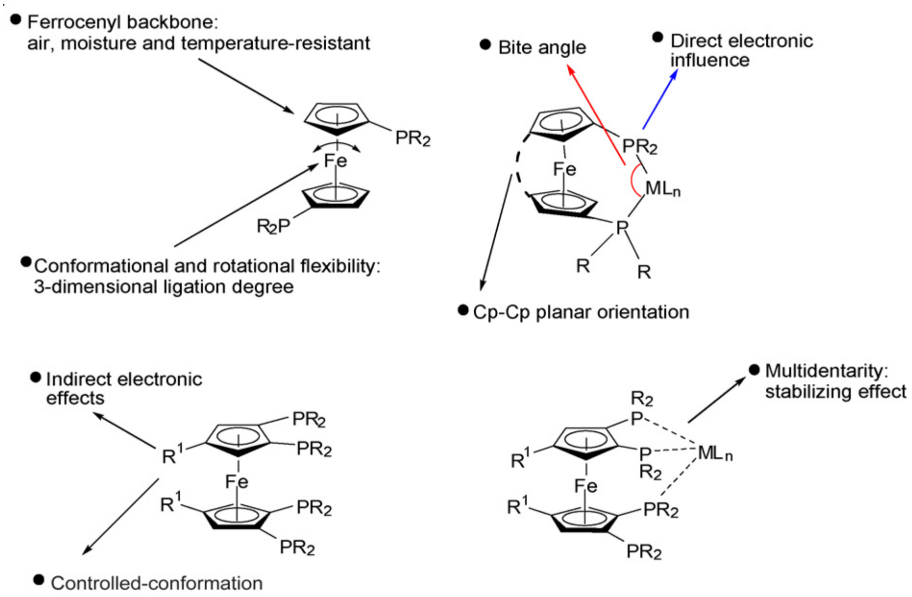
In the absence of systematic studies concerning the catalytic cycles to determine reaction mechanisms, rates and limiting steps, or catalytic intermediaries (experimentally or *via* computer modeling) understanding of ligand properties on a regular and "less-empirical" basis remains a challenge. Nevertheless, in the present section an attempt to point out the pivotal advantages provided by the structures of ferrocenylphosphines is provided, on the basis of the studies above mentioned in the sections devoted to catalytic reactivity.

In Scheme 71 are summarized the structural features we believe of decisive influence encountered in diphosphine and polyphosphine ferrocenic ligands and their metal coordination complexes.

The first practical advantages offered by the ferrocenyldiphosphines in homogeneous catalysis are the robustness



Scheme 70.



Scheme 71.

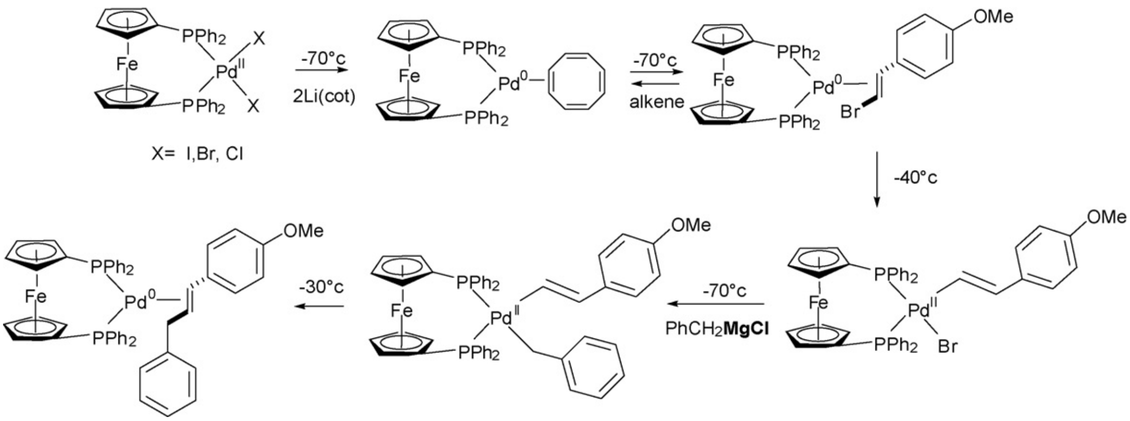
and conformational flexibility of the ferrocene backbone. Discussions concerning the influence of the steric and electronic parameters of the ferrocenylphosphine ligands on their corresponding metal complexes have been more controversial. This could probably be attributed in part to the general difficulty to define easily quantifiable parameters that describe ligand properties. Among the parameters commonly used in ligand chemistry, the bite angle is believed to be appropriate for bidentate phosphine ligands. However, when this parameter is employed it is of utmost importance to keep in mind some essential points: (i) changes in the bite angle can have both *steric* and *electronic* effects from ligand–ligand (or ligand–substrate) steric interactions, and from metal–ligand orbital hybridization modification, respectively [157], therefore this parameter cannot be considered only from a simplistic geometric perspective; (ii) depending on the conditions and on the goal of the studies the bite angle determination (and somewhat its definition) can differ from one report to another: for instance, bite angle calculation by molecular modeling and *standardized* bites angles recalculated by employing ligand P···P distances from crystallographic data are opposed to P–M–P "angles" directly measured in crystal structures (possibly different also from solution!) [158a]. With these precautions in mind it is possible to comment on the structure-reactivity studies reported on cross-coupling catalysis using ferrocenylphosphines.

The bite angles found for dppf in various transition metal complexes (Mn, Fe, Pd, Ni, Cu, Ag, Au) have been collected and compared [5,158a]. The values of the bite angles can be increased by opening the torsion angle along the axis described by the two centroids of the Cp rings (rotational flexibility, Scheme 71) and by opening the angle between the planes encompassing the Cp rings (Cp planar orientation, Scheme 71). As a consequence if the preferred P–M–P bite angle is centered around 96° (that corresponds to "ideal" coplanar Cp rings in a perfectly staggered conformation with a heteroannular C–P dihedral angle of 36°), the values ranging from 90° to 120° attest for the flexibility of the ligand.

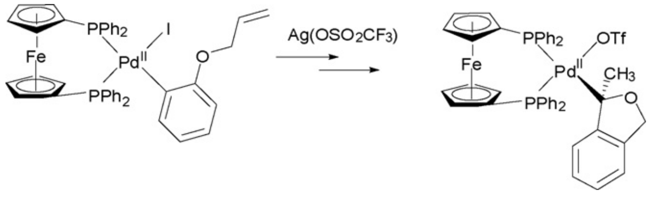
Hayashi et al. have reported at an early stage the usefulness of $PdCl_2$(dppf) in the Kumada coupling of *sec*-butyl magnesium chloride with bromobenzene (see Section 3.5) [99]. The authors proposed that the higher activity and selectivity of the complex compared to other classical systems incorporating PPh_3, dppe or dppp could be ascribed to the large P–Pd–P bite angle of 96° in $PdCl_2$(dppf). Later, Dierkes and van Leeuwen, in a very instructive review [158a], rather related the bite angle to the reaction rate with the view to give a more complex picture of Hayashi's results: the oxidative addition is supported by ligands having smaller bite angles because they increase the electron density on the metal center, while larger bite angles go along with decreased electron density on the metal and make the reductive elimination easier [158b]. Therefore, only a narrow range of bite angle values (96–102°) would preserve an equilibrium between the different steps of the cycle, at the origin of the good results obtained with dppf. In relation to that, the successive intermediaries formed in many palladium-catalyzed reactions have to accommodate very different geometries, mainly three- to five-coordinate geometries for which optimal bite angles range from 90° to 120°; consequently, the three-dimensional ligation degree (Scheme 71) and the flexibility of ferrocenylphosphine ligands would significantly help to achieve this requirement.

In the early 1990s Brown and co-workers provided the first mechanistic studies aiming to map step by step the reaction pathway in palladium-catalyzed coupling reactions based on Pd(dppf)L_n complexes (see related catalysis in Section 3.1) [34a,b,159]. A significant interest of these studies was the isolation and spectroscopic characterization (^{31}P NMR) of several Pd(0) and Pd(II)/dppf intermediates of Heck and cross-coupling reactions from experiments conducted under stoichiometric conditions [34a]. Species involved in the three fundamental steps of the cycle (oxidative addition–transmetalation–reductive elimination, Scheme 72) were identified and their relative stability (at least at low temperature) was established.

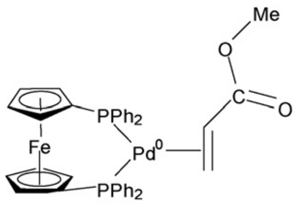
Another advantage of these ferrocenylphosphine ligands, thus, lies in their suitability for stabilizing the transient metal species of catalytic cycles. Extended Hückel calculations have been conducted in relation to the reductive elimination step presented in Scheme 72 [159]. The calculation confirmed that a migration pathway with an η^2-propene complex formed is energetically favored (1.3 eV *versus* 1.9 eV for a concerted reductive elimination) especially if the bite angle P–Pd–P is allowed to relax; that is possible if the chelating diphosphine palladium complex is not too rigid, restricting a bite angle constrained to



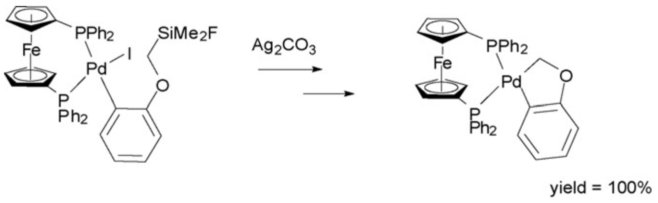
Scheme 72.



Scheme 73.



Scheme 74.



Scheme 75.

90°. The flexibility of the ferrocene backbone is in favor of this conclusion.

Brown and co-workers later reported the X-ray structure of the iodide palladium complex displayed in Scheme 73 which exhibit a “measured” (non-standardized) bite angle of 100.7°, slightly larger than the “classical” 96° (see discussion above) [34b]. This complex is thermally stable and in the absence of silver sulfonate salts activation, it showed no tendency for the intramolecular Heck cyclization studied.

Jutand et al. were also able to report the X-ray structure of the palladium(0) alkene complex depicted in Scheme 74 [160], which exhibits a (non-standardized) large bite angle of 104.5°: its rate constant *k* for oxidative addition of aryl triflates and iodides was found 4000 times lower than the one found for $Pd^0(PPh_3)_4$; in this case also the bite angle might be of influence (larger bite angles go along with decreased electron density on the metal, and thus more difficult oxidative additions).

Some studies devoted to the transmetalation step in cross-coupling with organometallics were conducted with Pd/dppf complexes. At an early stage, Farina and Krishnan reported a set of rate constants for iodobenzene coupling to the vinyltributylstannane using various Pd/ligand catalytic systems [105]. The effects of bidentate ligands invariably led to modest rates, from which dppf gave the worst. This was regarded as a proof that ligand dissociation is a key step in this transmetalation. In a similar way, the palladium(II) silane complex reported by Echavarren and co-workers (see Scheme 75) was found as a stable compound that does not undergo intramolecular Pd/Si transmetalation after being heated at 50 °C for 17 h in $CDCl_3$ or CD_3CN (smooth transmetalation occurred, however, in the presence of Ag_2CO_3 to give the corresponding oxapalladacycle in quantitative yield) [112a]; the stannane analogue, in contrast, was isolated as a moderately stable complex which undergoes rather rapid transmetalation [111].

Another important parameter investigated at an early stage in ferrocenylphosphines ligands for catalysis was the electronic influence of the groups hold by the phosphorus donor atoms (see Scheme 71). Unruh and Christenson reported a study on rhodium-catalyzed alkenes hydroformylation in the presence of dppf and of derivatives containing electron-withdrawing substituents on the phenyl groups: *p*-Cl, *m*-F, or *p*-CF_3 [17]. The position for substitution and the size of the substituents were chosen to reduce the eventual effect of changes in the steric environment at the immediate vicinity of the rhodium center. In the hydroformylation of 1-hexene it was shown that both rate and selectivity in linear heptanal (against formation of 2-methyl hexanal or isomerization towards 2-hexene) decreased with the electron-donicity of the ligand (Table 5). These results were reviewed by van Leeuwen et al. [161], who reported the catalytic results as a function of the frequently employed Tolman χ-parameter [4,162], as displayed in Table 5. The electronic influence of the ligand modification on the rate of the reaction is clearly detectable. From a general point of view, however, the increases remain moderate (maximum multiply by 2).

The influence of the electronic properties of the aryl groups held by the phosphorus atoms of dppf derivatives – chosen because of their effectiveness in the amination chemistry and the ease of modifying the substituents on phosphorus – has been

Table 5
Catalytic hydroformylation of 1-hexene with Rh/modified-dppf ligands

Aryl group on phosphorus	χ_i-Value (Ar)	Relative rate	Conversion yield (%)		
			Linear	Branched	Isomerization
p-CF_3-C_6H_4	6.3	1.92	92	2	6
m-F-C_6H_4	6.0	1.90	89	6	5
p-Cl-C_6H_4	5.6	1.29	87	8	5
Ph	4.3	1	81	15	4

The Tolman χ_i-parameter [4] is extracted for one substituent from $[\chi = \sum \chi_i]$ for $(R_i)_3P$, and χ is calculated from the measurement of the frequency $[\nu = 2056.1 + \chi]$ (where ν is the frequency of the A_1 carbonyl mode of $Ni(CO)_3[P(R_i)_3]$ in CH_2Cl_2, and 2056.1 the ν value for $P(t\text{-Bu})_3$ an extremely σ-donating (basic) phosphine symmetric ligand ($\chi = 0$)).

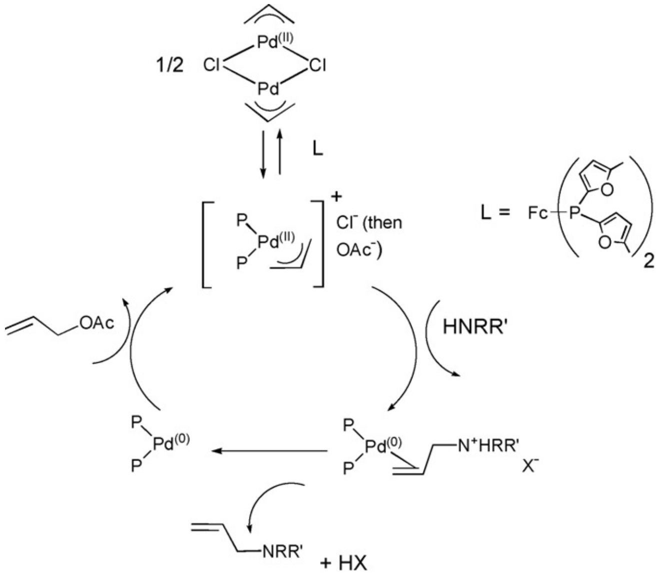
Table 6
Catalytic amination of 4-bromobutylbenzene with *n*-butylamine

Aryl group on phosphorus	χ_i-Value (Ar)	νCO[a] (NiCO$_2$dppf) (cm^{-1})	Conversion yield (%)		
			Arene	Monoamine	Diamine
m-CF$_3$-C$_6$H$_4$	–	2017	14 ± 2.5	49 ± 5.0	6
p-CF$_3$-C$_6$H$_4$	6.3	–	5.5 ± 0.5	53 ± 0.5	18
Ph	4.3	1999	4.0 ± 0.2	52 ± 2.5	22
p-OMe-C$_6$H$_4$	3.4[b]	2002	4.0 ± 0.6	55 ± 1.0	21

[a] From Ref. [19].
[b] From Ref. [4].

studied by Hamann and Hartwig [19]. The ratios of amine formation to dehydrohalogenation towards arenes were determined and compared in several reactions (see also Section 4.1.2). The influence of phosphine aryl group electronic properties was evaluated by employing ligands that contained electron-donating and electron-withdrawing groups: *p*-OMe, *p*-CF$_3$, or *m*-CF$_3$. The authors were originally expecting that electron-poor phosphines would accelerate the rate of reductive elimination and increase the aryl monoamine production against the side-products formation. As shown in Table 6, it appeared that reactions involving *p*-CF$_3$- or *p*-OMe-modified dppf gave only moderate variation in amination reaction compared to dppf: the related electronic parameters (Tolman χ-parameter or νCO frequencies in Ni carbonyl model complexes, Table 6) being in fact close to each other, suggest that the electronic modification remains minor. Reactions conducted with the more electron-poor ligand incorporating two *m*-CF$_3$ groups showed a more significant increase in dehydrohalogenation reaction against amination, that is consistent with more significant electronic modification as attested by the larger shift of νCO. However, as mentioned above about the study by Unruh and Christenson, it seems that these electronic changes, relatively far away from the metal center, perturb much less the activity and selectivity of reactions than steric and geometric modifications can do. Additionally, in this study it was shown for the reactions conducted, a more preeminent influence of the bite angle by comparison of the performances of dppf (and its analogs) with more efficient bidentate ligands (BINAP) having smaller angles than the dppf-family (around 90° against 99° for dppf derivatives). Nevertheless, in the absence of thorough kinetic data, a more in depth discussion on the relative rates of the fundamental steps (especially oxidative addition and reductive elimination) of the cycle would be rather speculative.

In relation with the determination of electronic effects of ligands, we reported the comparison of reactivity of dppf to the related ligand incorporating methylfuryl groups on phosphorus, 1,1′-bis[di(5-methyl-2-furyl)phosphino]ferrocene, Fc[P(FuMe)$_2$]$_2$, in various allylic amination of acetates (see Section 4.2 for catalytic results) [144]. Fc[P(FuMe)$_2$]$_2$ promoted nucleophilic allylic amination of allylic acetate at room temperature with high-turnover frequencies: the coupling of aniline with allyl acetate occurred at a TOF above 10,000 h^{-1} with a complete conversion and 96% selectivity in monoallylamine while under the same conditions, dppf as the ligand gave a conversion of 60% after 40 h at room temperature (TOF 150 h^{-1}). The X-ray structure of the complex PdCl$_2$(Fc[P(FuMe)$_2$]$_2$) was reported, a non-standardized P–Pd–P bite angle of 96.98(3)° (P–Pd = 2.261 Å) was found, a value closely similar to the data reported for the analogous complexes PdX$_2$(dppf). In addition, the X-ray structure showed that the heterocyclic methylfuryl groups are not sterically very different from phenyl groups. In contrast, the furyl group was reported to be significantly less σ-electron-donating (and therefore more π-accepting) [163] than phenyl; unfortunately, to the best of our knowledge, the Tolman χ_i-parameter has not yet been determined for furyl groups. These make this ligand interesting for approaching a comparison of electronic effects with dppf. Mechanistic studies on allylic amination by Kuhn and Mayr provided meaningful kinetic evidence on this reaction [164]: the use of various amines and 3-phenylallyl acetate in presence of either Pd/PPh$_3$ or with the poor σ-electron-donating/high π-accepting P(OPh)$_3$ conducted to global reaction rates two orders of magnitude higher in favor of Pd/P(OPh)$_3$ system. In the absence of kinetic data, we rationalized the results obtained with Fc[P(FuMe)$_2$]$_2$ through the simplified catalytic cycle depicted in Scheme 76. The high TOFs reported would be the result of: (i) the ability of the ligand to electronically increase the electrophilicity of the Pd(II)/allyl



Scheme 76.

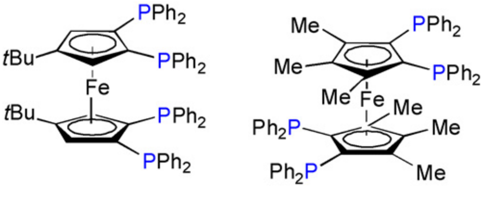
transient species, accelerating thus the nucleophilic attack which might be the rate-determining step (and also/or the step of dissociation of the olefin-ammonium [165]), and (ii) its ability to sterically stabilize the Pd^0 complex resulting from product elimination.

Finally, the steric effects due to the size of the substituents on phosphorus for bidentate [19] or monodentate [152] ferrocenylphosphine ligands were also shown to influence the reactivity, obviously depending on the hindrance of substrates (see *ortho*-substituent effects discussed in Section 5).

The structure-reactivity studies concerning ferrocenylpolyphosphine ligands have highlighted some other important features not encountered in ferrocenyldiphosphines. Scheme 71 illustrates the properties that should be taken into account. First, in the case of heteroannular polysubstituted species such like 1,1′,2,2′- or 1,1′,2-P substituted ferrocenes the preferred chelating conformation in coordination is to be determined. For nickel and palladium species with the example of tetraphosphines depicted in Scheme 71, the 1,2-P bonding to metal is preferred for mononuclear and dinuclear palladium and nickel stable and isolable complexes [166]. This induced into the reported complexes a relatively close bite angle ranging from 84° to 88° (non-standardized) [43,166]; about 10° less open than the traditional values for 1,1′-bonding in ferrocenyldiphosphines found around 96–98°. In the light of the studies previously discussed, this very different bite angle from 1,2-chelating bonding could probably be essential in the catalytic reactions studied (see Sections 3.1 and 3.2.2), and especially concerning the elementary reactions steps such as oxidative addition and reductive elimination.

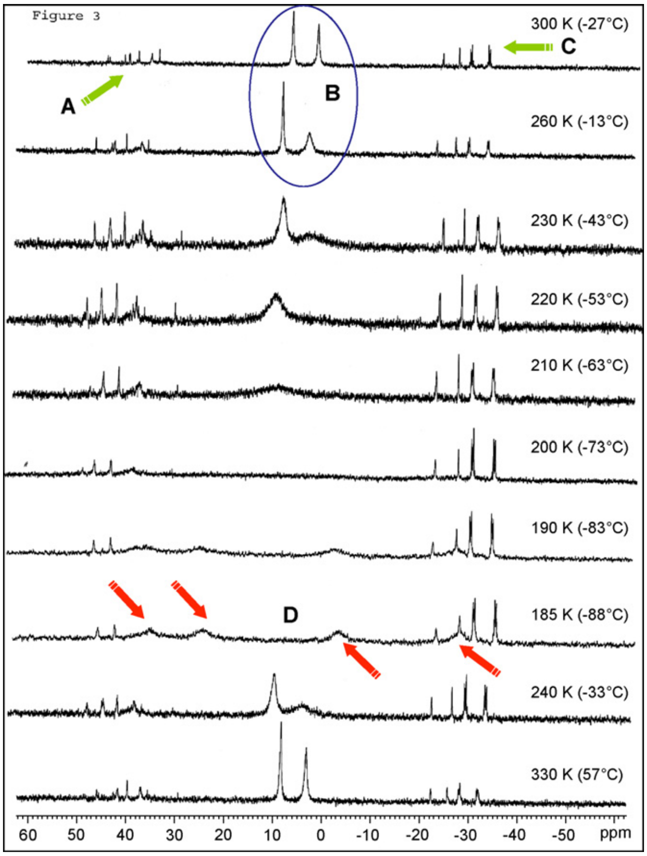
Another pivotal parameter in the chemistry of the polyphosphines reported [32,167], is the access to a blocked-conformation in solution due to hindrance of non-phosphorus substituents on Cp rings. For instance, in the tetraphosphine Fc(P)$_4$*t*Bu depicted in Scheme 77 the steric barrier of the two *tert*-butyl groups maintains (in solution and in the solid state) a restricted rotation of the cyclopentadienyl rings in a cisoid blocked-conformation, for which the four phosphorus atoms point towards the same direction.

Conversely, the methylated-tetraphosphine family product Fc(P)$_4$Me (Scheme 77) presents homoannular phosphorus pairs that face opposite spatial directions due to the unrestricted rotation of the Cp rings. The resulting catalytic performance of the two species is therefore very different [43,145]. The cisoid conformation for the *tert*-butylated-tetraphosphine is conserved in solution above 90 °C as attested by ^{31}P NMR in toluene-D_8. In the course of studies concerning the catalytic performances of Fc(P)$_4$*t*Bu, an intriguing phenomenon was identified by variable-temperature ^{31}P NMR [43]. Under the conditions used for Heck and Suzuki catalytic reactions for which 1 equiv. of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was reacted with 2.2 equiv. of tetraphosphine (ratio Pd:P ≈ 1:4), the occurrence of a dynamic behavior at the scale rate of NMR was observed in $CDCl_3$ (usual solvent for pre-catalyst preparation is CH_2Cl_2) at 300 K (B, Scheme 78).



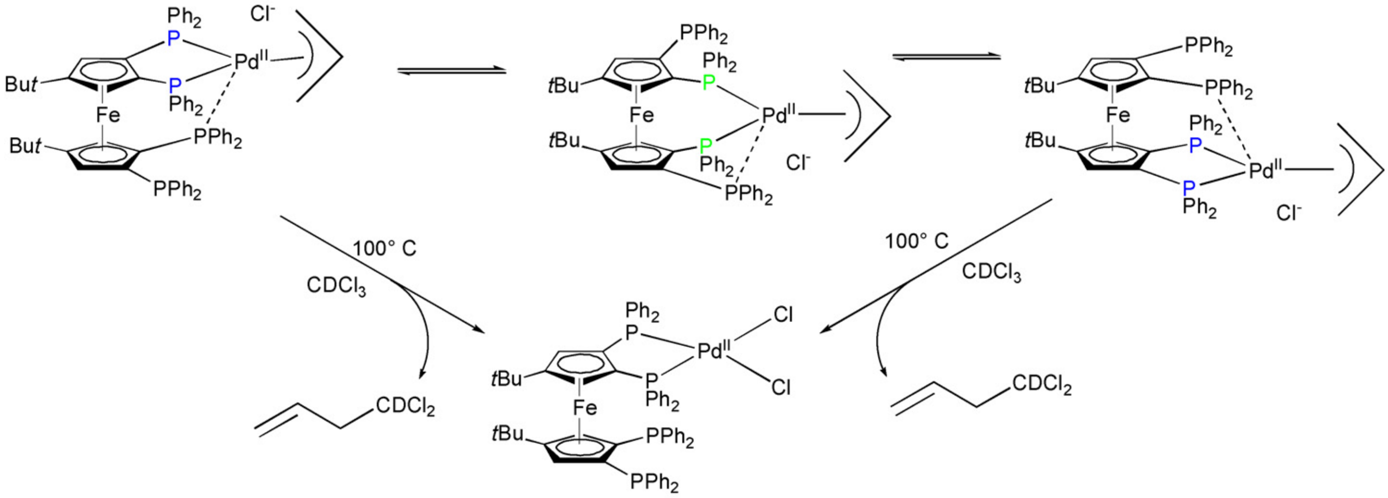
Fc(P)$_4$*t*Bu Fc(P)$_4$Me

Scheme 77.

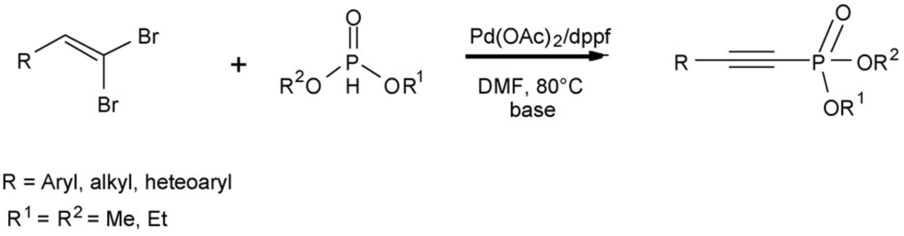


Scheme 78.

Two signals were detected between 0 and 10 ppm, an unusual range of chemical shift (CS) for $-PPh_2$ groups. Indeed, the CS for the signals of non-bonded phosphorus corresponding to free ligand and to biligated-$PdCl_2P_4$ is centered around −25 ppm (C, Scheme 78). Palladium-bonded phosphorus give signals centered around 40 ppm (A, Scheme 78). Therefore, we envisioned that the four phosphorus could be alternatively bonded and released from the palladium center: leading to large signals of average CS. Upon cooling, the characteristic behavior of labile compounds was confirmed with the two broad signals at 8.90 and 3.50 ppm slowly coalescing at 220 K to disappear at 200 K. At 190 K, four new very broad signals were detected (decoalescence, signals centered at 34.8, 24.2, −2.7 and −27.0 ppm, D in Scheme 78), which were even more clearly confirmed at 185 K. The dynamic phenomenon was reversible upon increasing back the temperature above the coalescence temperature; the labile species were stable until a temperature of 370 K was attained. After a few minutes at this temperature the mononu-



Scheme 79.



Scheme 80.

clear palladium biligated-$PdCl_2P_4$ thermodynamically favored was quantitatively formed. Scheme 79 gives a summarized picture of the observed phenomena. NMR experiments give evidence that at temperature above −70 °C the mainly formed species display a fluxional behavior which lead to detect two signals at an average CS between bonded and non-bonded phosphorus CS. Therefore, the most reasonable explanation (taking into account the ratio P:Pd = 4) is that the palladium center is "traveling" between the four phosphorus donors at a high exchange-rate.

This is a rarely reported phenomenon in multidentate compound chemistry, and we believe that this constitutes the first proof of the possibility for the catalytic palladium species to be further stabilized by the close vicinity of several coordinating atoms during the successive catalytic steps, statistically decreasing *de facto* the deactivation of catalysts by palladium-black formation. In addition, the "coordination-pressure" around the metal center might accelerate some determining steps in cross-coupling such as the reductive elimination of products. This hypothesis of an "active" multidentate behavior would explain why, contrary to more fragile systems, polyphosphine ligands can be combined and used with palladium in outstandingly low concentrations such as 10^{-2} to 10^{-4} mol%. Finally, the control of the conformation in this kind of multidentate ligands is, thus, possible, and can lead to very specific features potentially interesting for catalytic applications directed towards sustainable and economical catalytic processes.

7. Conclusions

A great part of the catalytic studies on cross-coupling reactions reviewed herein is concerned with the use of the ubiquitous metallo-ligand 1,1′-bis(diphenylphosphino)ferrocene, dppf. Its importance in modern carbon–carbon coupling catalysis might challenge in the future the place traditionally attributed to the triphenylphosphine ligand PPh_3. A reason for this success is probably its easy access and commercial availability. As shown in Section 2 of the present review a large number of dppf derivatives have been produced and are readily available. These compounds display a variety in electronic and geometric features that is promising for future development in applied catalysis. For instance, the high-turnover numbers obtained in aryl alkenylation and alkynylations reactions with various di-or tetraphosphines illustrate well this strong potential. From another perspective, mechanistic studies on Stille and Hiyama coupling have shown the interest to isolate stable intermediates of catalytic cycles, on this topic also the variety of ferrocenylpolyphosphine ligands might help in addition to the robustness of the ferrocene backbone. The structure-reactivity studies showed that the specific advantages of this family of ligand can be tuned through modifications in coordination bite angle, changes in steric and geometric features of the substituents at the phosphorus donors, changes in the substituents hold by the Cp rings, and by use of multidentate species of unusual conformation and properties.

Finally, the present review delivers only a limited overview focused on palladium or nickel-catalyzed C–C, C–N and C–O cross-coupling. The use of metal/ferrocenylpolyphosphine catalytic systems encompasses many other fascinating applications such as for instance the elegant C–P coupling to form alkynylphosphonates from 1,1-dibromo-1-alkenes (Scheme 80) [168].

Clearly, the powerful and rather cost and resources-saving aspect of the chemistry of metal/ferrocenylphosphines should provide in the future numerous fundamental and applied advances, at least equivalent to the progress accomplished for the last 50 years.

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