

# New concepts in multidentate ligand chemistry: effects of multidentarity on catalytic and spectroscopic properties of ferrocenyl polyphosphines

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This *tutorial review* devoted to ligand chemistry deals with the design and properties of ferrocenyl polyphosphines, an original class of multidentate ligands. The development of a varied library of ferrocenyl tetra-, tri- and diphosphine ligands is reviewed. The multidentate nature of these species has led to unique spectroscopic and catalytic properties, in which the spatial proximity of phosphorus atoms is crucial. Regarding their catalytic applications, the key issues of catalyst longevity and ultralow catalyst loadings are discussed. Another part is concerned with fundamental advances gained in physical chemistry for structure elucidation by the study of the intriguing “through-space” NMR spin–spin *J* couplings existing within several of these polyphosphines.

## 1 Introduction and scope

Ligand chemistry remains a pivotal science naturally connecting modern organic, inorganic, organometallic and coordination chemistry through an array of valuable applications, mainly catalysis based. Multidentate ligands represent a fascinating class of compounds that offer a variety of coordination modes, for which new structures are developed each year. Our efforts in this area are reviewed herein. Since the mid nineties we have been engaged in the development of ferrocenyl tetra-, tri-, and 1,1'- or 1,2-diphosphine ligands. New concepts which take advantage of this family of branched multidentate ligands have driven progress in homogeneous catalysis, as well as in fundamental physical chemistry related

to the comprehension of phosphorus nuclear spin couplings. The synthetic routes employed to generate a library of ligands are also detailed. The concepts of catalyst *longevity* and ultralow catalyst loadings (high TONs catalyst), based primarily on the multidentarity effect, in reactions such as palladium-catalysed C–N and C–C cross-couplings are reviewed. The last section is devoted to the intriguing spectroscopic properties of ferrocenyl polyphosphine species. Practical experimental guidance for the study of the nuclear spin–spin *nonbonded* scalar coupling phenomenon (“through-space” NMR *J* coupling), which is often neglected and unappreciated, is provided.

## 2 Synthesis of ferrocenyl polyphosphines

Among the chemical features provided by multidentate ligands to coordination complexes and organometallic species, the most noticeable is arguably the possibility to readily access multinuclear species, which include heterometallic complexes and clusters. In addition, dissymmetric chelating di- or

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polyphosphines exhibit interesting hemilability behaviour, often important in promoting certain steps in the catalytic cycles of many transition metal catalysed reactions. On this basis, we originally hypothesised that an examination of the chemistry of novel di-, tri- and tetraphosphines built on the robust ferrocenyl backbone, would be worth pursuing.

Fig. 1 summarizes some representative examples of the library of ligands developed by our group since 1995. Four classes of compounds can be broadly distinguished: 1,1'- and 1,2-diphosphines, triphosphines, and tetraphosphines. Nevertheless, in this chapter the synthetic strategy used to access these ligands is detailed facilitating the synthesis of two types of ferrocenyl polyphosphines: either symmetric or dissymmetric species, in which the two cyclopentadienyl rings (Cp) include, respectively, the same or different substituents. Two key complementary synthetic routes to the ferrocene derivatives have been employed: i) the direct phosphorylation of the ferrocenyl backbone; ii) the reaction of phosphorylated cyclopentadienyl salts with iron halide salts (see details in part 2.3). These approaches have been successfully applied in the synthesis of all the ferrocenyl polyphosphines described in this review.

### 2.1 Symmetric ferrocenyl phosphines synthesis

The ferrocenyl dilithium-TMEDA adduct **1** (Fig. 2) is a useful reagent for the synthesis of ferrocenyl bis(dialkyl)- and bis(diaryl)phosphines. This dilithiated derivative can also be employed in the synthesis of symmetric ferrocenyl diphosphine bearing heterocyclic substituents such as **2** (Fig. 1),<sup>1,2</sup> the procedure is different to that reported for the preparation of the parent compound 1,1'-bis(di-2-furylphosphino)ferrocene from 1,1'-bis(dichlorophosphino)ferrocene and 2-lithiofuran.<sup>3</sup> Attempts to prepare **2** by reaction of Cp salts with iron chloride resulted in poor yields.

Early on the direct phosphorylation of diphosphines to produce tri- or tetraphosphines was investigated by Butler and coworkers. They initially reported that selectivity problems leading to mixtures of polyphosphines were observed,<sup>4</sup> making this method less appropriate for the construction of complex structures incorporating several phosphorus donors. We

concluded that the synthesis of more intricate ferrocenyl polyphosphines might be accomplished by reaction of substituted Cp salts with iron halides. By this route, the synthesis of ferrocenyl diphosphines was also possible, such as **3**, obtained in good yield by reaction of the Cp salt **1a** with FeCl<sub>2</sub> in THF (Fig. 3).<sup>5</sup> In the case of dissymmetric salts such as **2a**, the formation of two diastereoisomers is expected—a *meso* form **4** and a racemic **5** (Fig. 4). These isomers were effectively separated by column chromatography.<sup>6</sup> The method was especially successful for the synthesis of symmetric ferrocenyl tetraphosphines such as **6**, **7** and **8**, which were isolated in a one-step reaction in a 70–80% yields (from precursors **3a**, **4a** and **5a** respectively, Fig. 5).<sup>6–8</sup>

### 2.2 Dissymmetric ferrocenyl phosphine syntheses

Dissymmetric ferrocenyl diphosphines have been accessed by successive phosphorylation of the ferrocene backbone. The monolithium salt **9**, which is obtained from the parent ferrocene dilithium salt **1**, is an essential intermediate in these syntheses (Fig. 6). Compound **9** reacts readily with diorganylphosphorus halides (route *i*) or with phosphorus trichloride (route *ii*) to form the intermediary species **10**.<sup>9</sup> The route (*i*) was employed in the synthesis of the ferrocenyl diphosphine **11** which incorporates both –P(furyl)<sub>2</sub> and –P(phenyl)<sub>2</sub> groups.<sup>2</sup> Additionally, compound **10** has been a useful building block in the synthesis of phosphonite derivatives **12**.<sup>9,10</sup> This strategy facilitated the obtention of a variety of 1,1'-substituted ferrocenyl phosphine derivatives which display significantly different electronic and steric properties at phosphorus. Consequently, these potentially useful ligands are expected to display hemilabile behaviour upon employment in catalytic reactions.

The assembly of two different phosphorylated Cp salts in the presence of an iron halide appeared to be a useful synthetic route to access original dissymmetric ferrocenes. The ferrocenyl phosphines **13–15** (obtained from Cp salts **1a**, **3a**, **4a** and **6a**, Fig. 7) were the first examples demonstrating the effectiveness of this approach.<sup>6,7</sup> Accordingly, we extended the methodology to more accessible and structurally promising Cp salts. For example, the addition of diverse Cp salts to a



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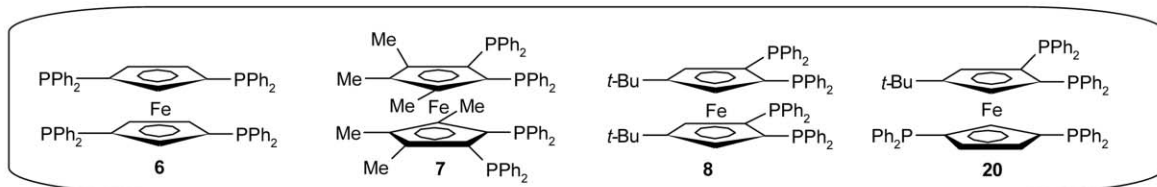
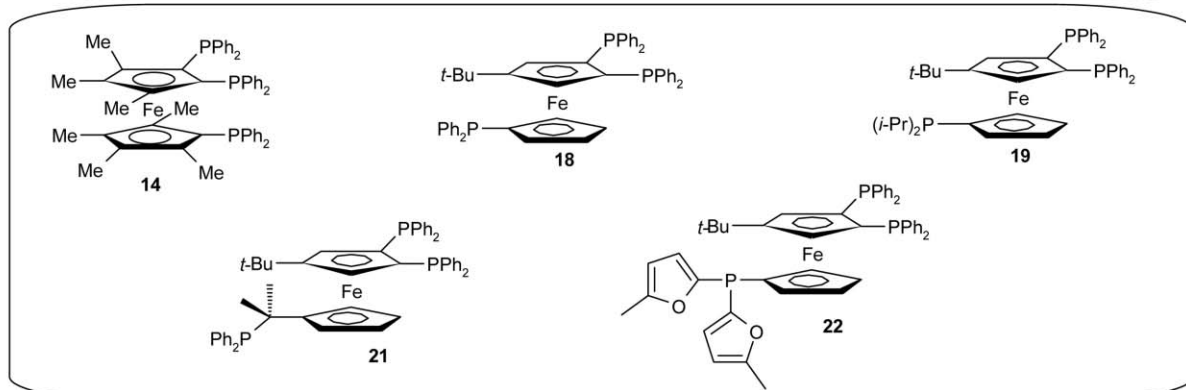
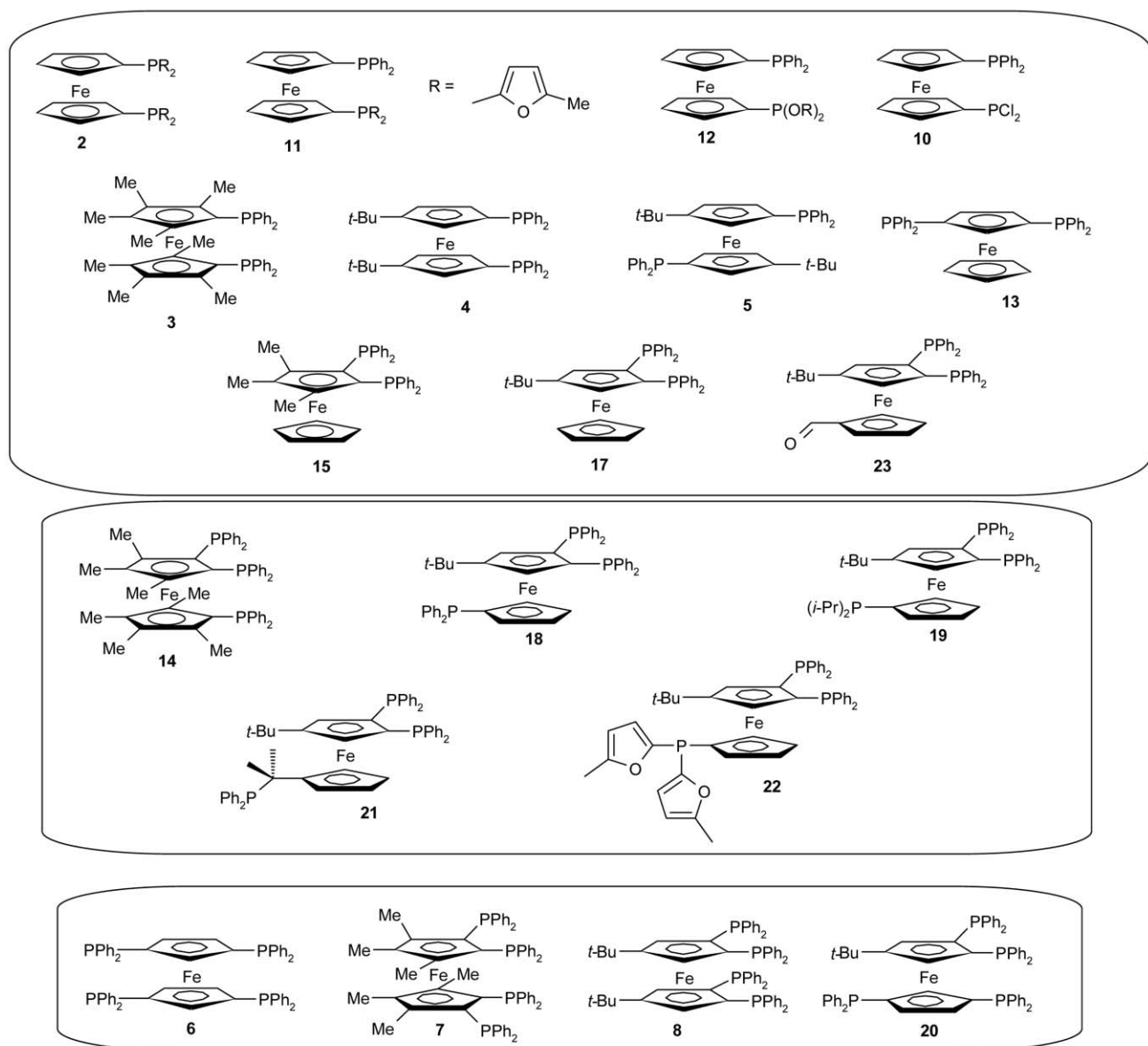


Fig. 1

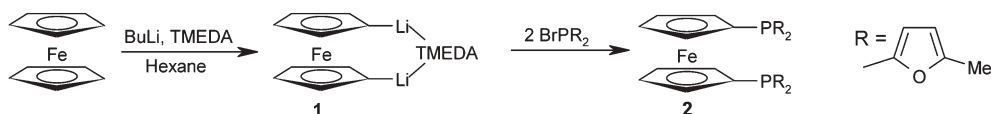


Fig. 2

preformed mixture of iron chloride and Cp salt **5a** (**16** in Fig. 8) allowed the synthesis of various dissymmetric ferrocenyl di-, tri- and tetraphosphines (**17–23** in Fig. 8, from Cp salts **6a–11a** in Table 1).<sup>6,11,12</sup>

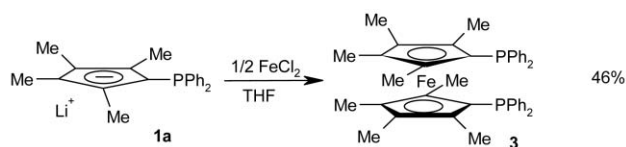


Fig. 3

The creation of these ferrocenyl phosphines are of interest, regarding their present application and/or in further investigations. For example, we established that the triphosphine **19**, which incorporates an electron-donating substituent,  $-P(iPr)_2$  group, is one of the most efficient catalytic auxiliary reported to date in the Heck–Sonogashira alkylation reaction (see part 3.2).<sup>13</sup> The parent triphosphines **18**, **21**, **22** display interesting structural features such as a flexible spacer at phosphorus (**21**) or in variance of furyl electron-withdrawing substituents (**22**). The ferrocenyl diphosphine **23** could pave the way for preparation of novel derivatives due to the possible

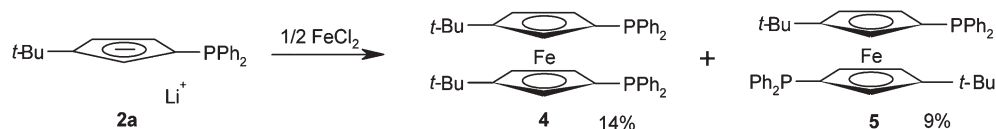


Fig. 4

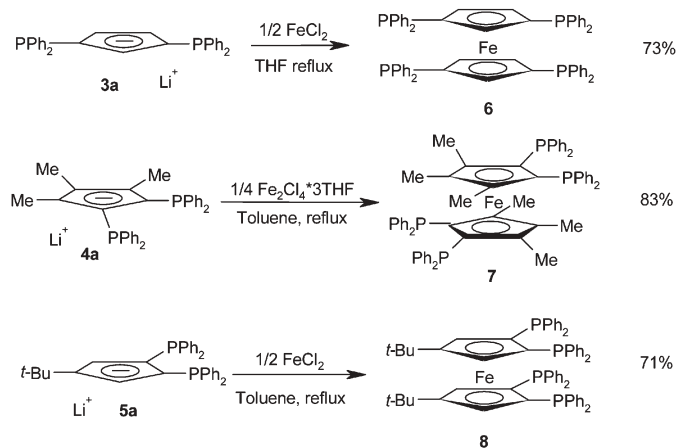
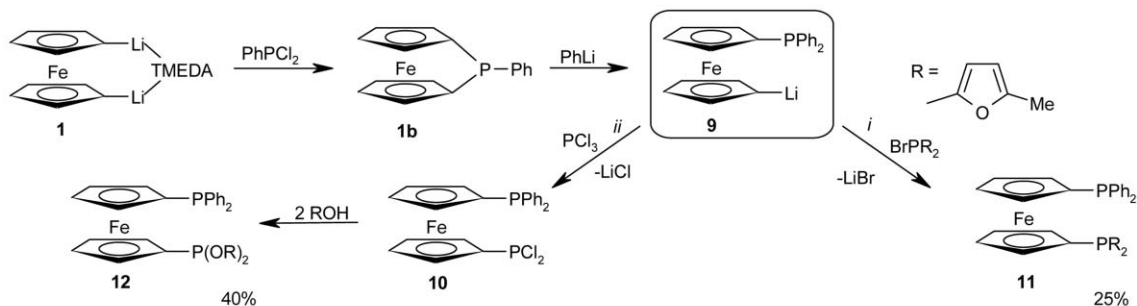


Fig. 5



ROH = Phenol, ethylene glycol, binaphtol (racemic and (R)),

Fig. 6

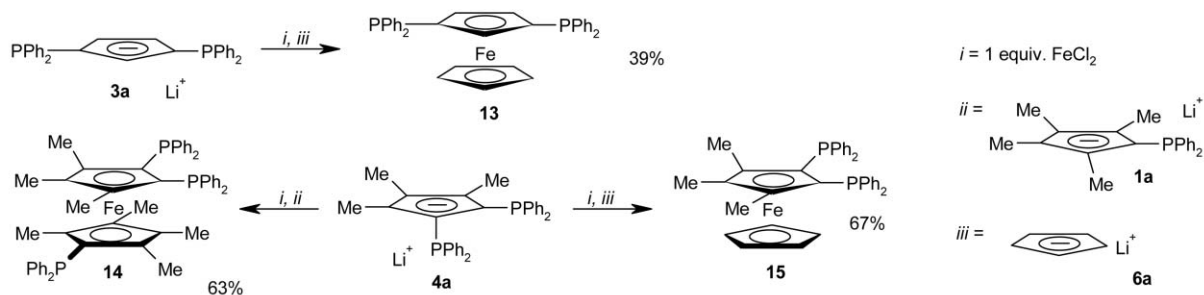


Fig. 7

derivatisation of the aldehydic function: including grafted polymeric or dendromeric ferrocenyl 1,2-diphosphines for heterogeneous catalysis. The tetraphosphine **20** is a unique model of 1,2,1',3'-substitution with unexpected "through-space"  $^{31}\text{P}$  spin coupling characteristics (see part 3.3).<sup>12</sup>

The yields of the dissymmetrical compound obtained by this method were superior than that expected from the apparent

statistical formation of three compounds (two symmetrical and one dissymmetrical species). From our observations and NMR measurements,<sup>11</sup> we believe this phenomenon is associated with the preliminary formation of a solvated complex of Cp salt **5a** with iron chloride (**16**). Finally, as indicated in Table 1, synthetic procedures for some of the ferrocenyl phosphines require improvements to the methodology. Nevertheless, this

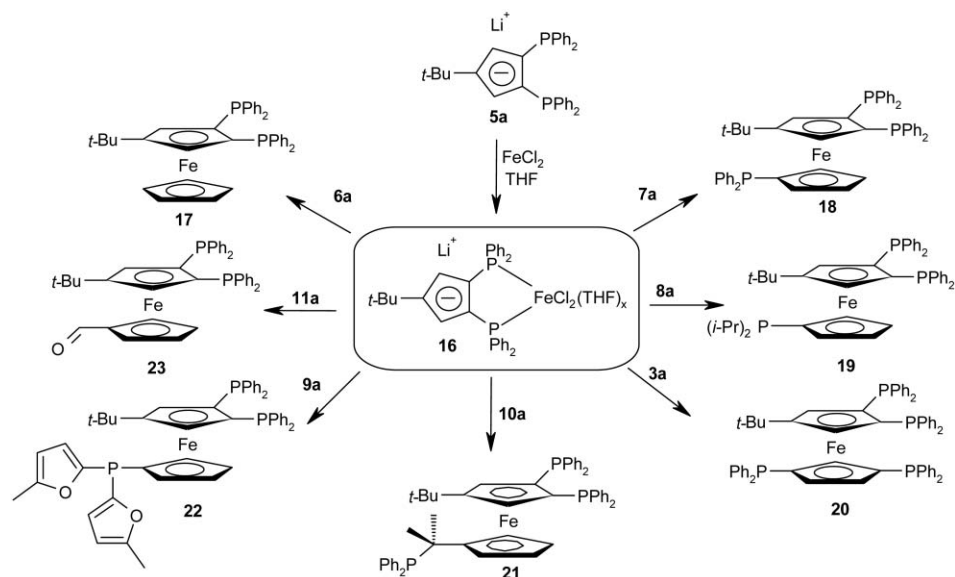


Fig. 8

**Table 1** Cyclopentadienyl anions employed for the synthesis of dissymmetric ferrocenylphosphines

Compound	17	18	19	20	21	22	23
Cp	6a			3a			
Isolated Yield(%)	68	85	70	45	15	3	20

method is useful and important for the selective synthesis of polysubstituted ferrocene compounds.

### 2.3 Synthesis of phosphorylated Cp-salts

As shown above, the method that consists in the assembling of adequately substituted phosphorylated Cp-salts with iron precursor salts is very attractive for the selective synthesis of ferrocenyl polyphosphines. Its usefulness is somewhat limited by the availability and reactivity of the functionalised Cp salts.

The common synthetic procedures used for Cp salt formation have been recently described in a thought-provoking review reported by Butenschön.<sup>14</sup> The synthetic routes used to access phosphorylated Cp salts, including at the time novel Cp salts, are elaborated upon below.

One of the first examples of monophosphorylated Cp salts that was employed in our studies was compound **1a**. The synthesis of this compound is described in Fig. 9.<sup>15</sup> The reaction proceeded in high yield and selectivity since only a unique position for substitution on the Cp ring is available, the other four being occupied by methyl groups (Cp salt **12a**). The

phosphorylation step leads to a solution mixture of isomers. Nevertheless, since the presence of isomers and their ratio does not affect the unique salt resulting from the lithiation step, the tautomeric forms of the cyclopentadienes will not be further elaborated upon. Synthetic chemistry based on this kind of phosphorylated salts is unattractive due to the numerous steps necessary to afford tri- or tetramethylated derivatives of cyclopentadiene.<sup>15,16</sup> The parent cyclopentadiene obtained directly by thermal cracking of dicyclopentadiene being much more accessible, we formed under mild conditions—at appropriate dilution and low temperature in non polar solvents—both novel and known monophosphorylated cyclopentadienyl salts by employing various halogenophosphines (Fig. 10).<sup>11,12,17–19</sup>

Salt **7a** selectively undergoes a second phosphorylation and the substitution proceeds selectively for 3-position affording salt **3a** (Fig. 11). Unexpectedly, we found that **3a** can be formed as a by-product in 5 to 10% yield when the synthesis of **7a** is carried out under more forcing conditions (higher temperature and concentration of reagents). The formation

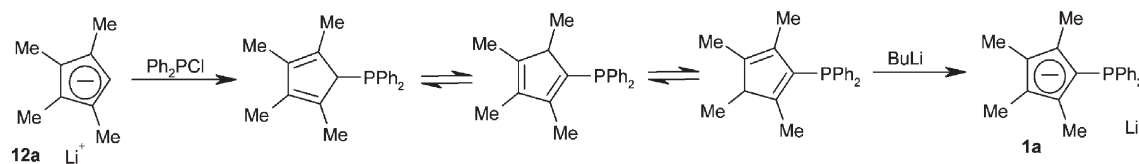


Fig. 9



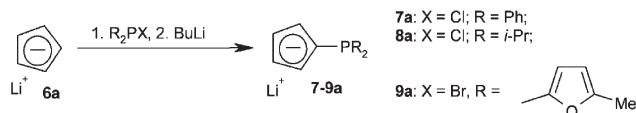


Fig. 10

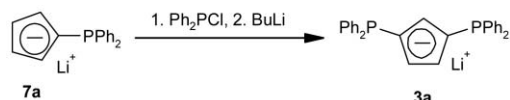


Fig. 11

of a double phosphorylation product, which requires a second metalation, might occur *via* exchange-metalation between the initially formed diene and the unreacted Li-salt **6a**, as depicted in Fig. 12.

To meet the objective of preparing chelating multidentate ligands we envisioned that the synthesis of Cp salts bearing phosphine groups on adjacent substitution positions of the ring would be possible. The first strategy was based on the use of the 1,2,3-trimethylated Cp salt **13a** (Fig. 13). This was phosphorylated as expected to give Cp salt **14a**, Fig. 13.<sup>20</sup> However, as indicated above, the methylated derivatives of Cp salts such as **13a** are difficult to access, requiring several synthetic steps.<sup>20</sup> For this reason an alternative strategy based on the use of a directing group was carried out successively. Here, the hindered *tert*-butyl (*t*-Bu) group was selected to facilitate the formation of salt **15a** (Fig. 14).<sup>6</sup> Unlike **13a**, Cp salt **15a** is readily available in multigram scale by treatment of the well-known fulvene **24** with methyllithium.<sup>21</sup> It is pertinent to mention that salts **5a** and **4a** not only differ in their accessibility but also in their chemistry, attested by the physical and structural properties of their metallocene derivatives.

### 3 Properties of ferrocenyl polyphosphines

Amongst multidentate ligands various classes have demonstrated useful properties.<sup>22</sup> In the case of polyphosphines the

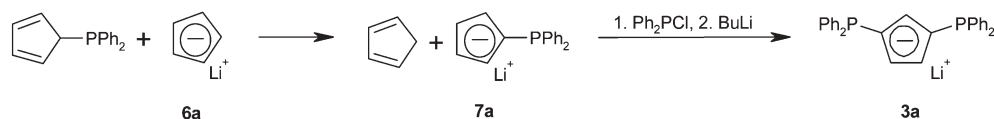


Fig. 12

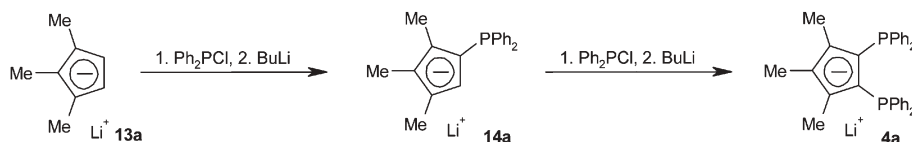


Fig. 13

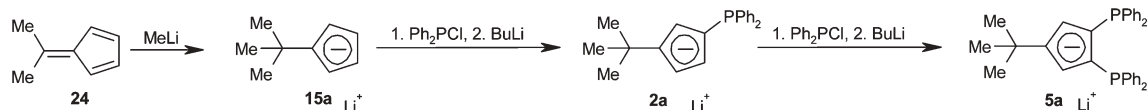


Fig. 14

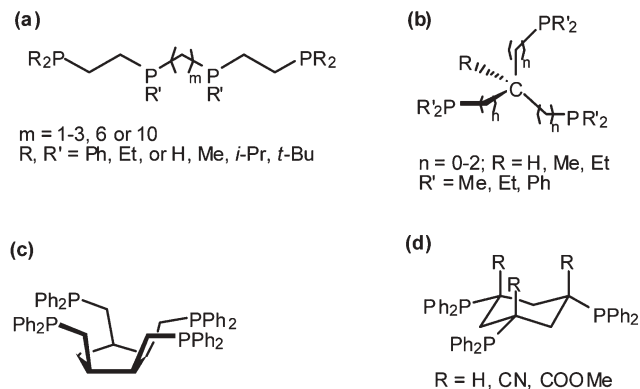


Fig. 15

first classes reported and predominantly studied were the *linear* (Fig. 15 (a)) and *tripodal* species (Fig. 15 (b)).<sup>22,23</sup> The ferrocenyl polyphosphines reviewed herein pertain to a different class, which could be categorized as *branched* polyphosphines. Other branched polyphosphines were reported by Santelli<sup>24</sup> and Mayer<sup>25</sup> (Fig. 15 (c) and (d)). In comparison to tripodal or linear multidentate ligands, specific properties appear to be associated with the branched structure.

We present in the following section the coordination chemistry of some representative examples of ferrocenic polyphosphines towards the transition metals Cr, Mo, W, Rh, Ni, Pd, Pt and Cu. The application of these ligands in catalysis, by employing systems which combines palladium and ferrocenic tetra-, tri- or diphosphines, has been achieved. In the optimised C–C and C–N coupling reactions, palladium/ligand loadings of a hundred- or a thousand-fold lower than the commonly reported amounts (1 to 10 mol%) have been employed. Here we discuss the origin of such high catalytic activity. The branched geometry of the ferrocenyl tetraphosphine combined with its rotational rigidity in solution, which results in close spatial vicinity of the phosphorus atoms, allowed us to gain evidence for the rarely observed phenomenon of nonbonded nuclear spin coupling. These specific

physical properties have been explored with the view to providing a simple and easily understandable model for the “through-space” spin coupling observed in ferrocenyl tetraphosphines derivatives.

### 3.1 Transition metal complexes incorporating di-, tri- and tetradentate ferrocenyl polyphosphines

The ferrocenyl backbone, due to its particular sandwich structure, displays a number of different conformations in the solid-state as in solution. Beside the classical eclipsed and staggered positions of the Cp rings, not discussed here, we were specifically interested in the mutual position adopted by phosphorus atoms. For example, the two tetraphosphines **7** and **8** revealed very different geometrical features. As shown by the X-ray structure, in the favoured solid state conformation for **7** (Fig. 16), the two potentially chelating pairs of phosphorus atoms are facing opposite directions. Conversely, in the preferred conformation found for **8** the four phosphorus atoms are pointing towards the same half-space due to steric factors attributed to the hindering *t*-Bu groups as well as interlocking of the phenyl groups. In solution, NMR spectroscopic experiments allowed us to verify that the conformation of **8** is restricted, similar to the solid state, exhibiting a AA'BB' spin system, even at temperatures up to 90 °C in toluene.<sup>8</sup> Therefore, as shown in the following section, the coordination properties of the ferrocenyl polyphosphines not only depend on the chelating possibilities but also on the rotational features of the ferrocenic backbone—an unexploited facet prior to these studies.

**3.1.1 Group 6 and 7 transition metals.** The coordination properties of the various classes of ligands that form the library of ferrocenyl phosphines were studied with group 6 metal carbonyls and with the manganese organometallic complex [MnCp(CO)<sub>3</sub>]; shown in Fig. 17 are selected representative examples. Monodentate and bidentate compounds were obtained with 1,1'-, 1,2-, 1,1',2- and 1,1',2,2'-coordination frameworks. The complexes **25**, **25b** and **26**, which incorporate a permethylated ferrocenyl diphosphine,

were obtained by a photochemical route as a mixture which can be separated by chromatography.<sup>5</sup> The bis(monoligated) dinuclear complex **25b** can be preferentially formed upon a stoichiometric adjustment.

Depending on the type of tetraphosphine ligand, either 1,2-biligated (**27**) or 1,1',2-triligated (**28**) mononuclear complexes can be obtained with metal carbonyls.<sup>7,26</sup> As mentioned previously, the blocked cisoid conformation of the tetraphosphine **8** in solution is at the origin of the unusual triligated coordination in complexes **28**. Upon complexation with [MnCp(CO)<sub>3</sub>] the tetraphosphine appeared to be both a heteroannular 1,1'- and a homoannular 1,2-biligate ligand. The two products **29** and **30** were obtained in a 1 : 1 ratio under the photochemical irradiation conditions employed. The complexes were easily separated by using their very different solubility properties. From these compounds it appears feasible to access original heterometallic polynuclear complexes.

**3.1.2. Group 9 and 11 transition metals.** The study of the coordination complexes of transition metals from groups 9 and 11 was connected with our interest in catalysis, and particularly in hydroformylation reactions, which were essentially conducted with rhodium complexes. We were especially interested in the performance of dinuclear bridged rhodium species since some very impressive results of dinuclear cooperating effects have been reported by other groups.<sup>27–29</sup> The complexes **31** and **32** (Fig. 18) that present a rare “quasi-close bridging” A-frame are of interest on a fundamental level since only the dppe analogue was known prior to their synthesis.<sup>10,30</sup> Compounds **31** were synthesized from a dissymmetric phosphine-menthylphosphonite whereas in most of the dinuclear rhodium complexes reported; the metal centres present identical coordination spheres. Independent of the reaction, one may reasonably anticipate that cooperating effects would be more apparent from homodinuclear species presenting electronically and sterically different environments at the metal centres, as expected and observed in the heterodinuclear metal complexes. In addition, while phosphite ligands have been intensively studied as auxiliaries

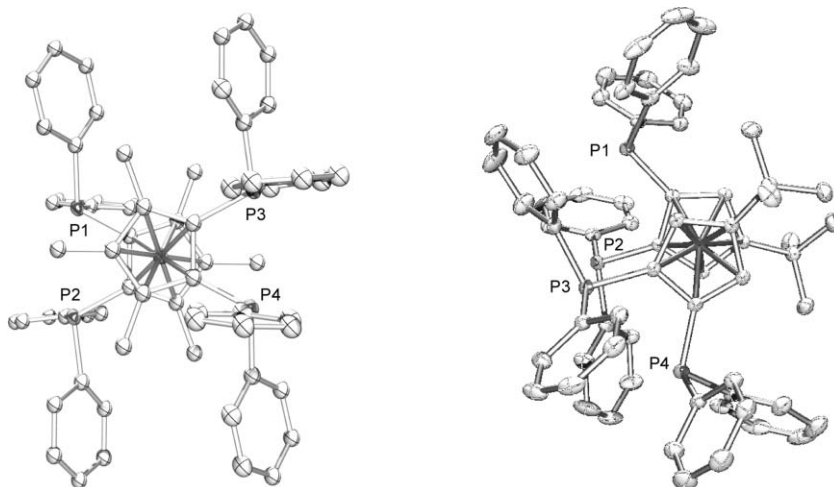


Fig. 16

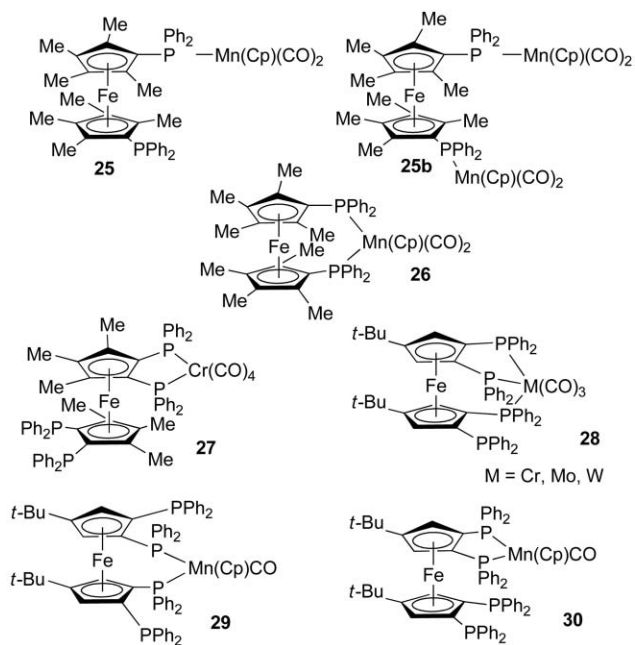


Fig. 17

for catalytic hydroformylation, only a few reports have been concerned with phosphonite auxiliaries. For these reasons preliminary tests of our compounds in olefin hydroformylation were conducted. The activity of **31** was deceptively low, but good TONs of *ca.* 1700 were possible using **31b** (*t*-BuS bridged). However, the genuine monomeric or dimeric nature of the catalyst remain to be determined and the selectivity was poor.<sup>10</sup> Mononuclear rhodium complexes, such as **33**, which incorporate other dissymmetric phosphine-phosphonite ligands, have been reported.<sup>9</sup>

The activity of **34**, obtained from a mixed bidentate (P=S) ferrocenyl ligand, and from which hemilability can be expected as well, was tested in the carbonylation of methanol without success.<sup>31</sup>

The tetraphosphine **8** appeared as a ubiquitous ligand for the formation of rhodium complexes since, contrary to group 10 metals (Pd and Ni), a number of different coordination modes were established (see compounds **35**, **36**, **37**). These complexes were synthesized independently under certain conditions to favour one coordination mode.<sup>8</sup>

The preliminary exploration of the coordination of polyphosphines to copper (in relation with the studies concerning Sonogashira alkylation) appeared much more difficult, even though triligated compounds such **38** have been unambiguously identified.<sup>32</sup>

**3.1.3 Group 10 transition metals.** The coordination complexes of transition metals from group 10, mainly of palladium but not only, were of substantial interest for us since their application in cross-coupling processes represents one of our objectives. Chelating mononuclear metal compounds were obtained from 1,1'- and 1,2-ferrocenyl diphosphines, such as **39**, **39b** and **40** for which X-ray structure determinations were reported (Fig. 19).<sup>1,33,34</sup> The palladium and platinum halide complexes obtained displayed classical square planar geometry.

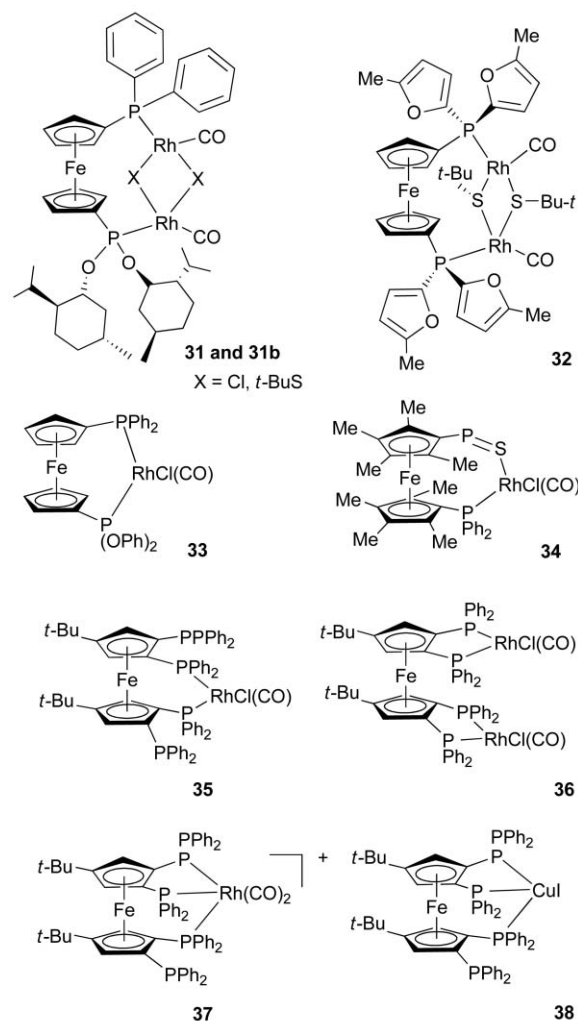


Fig. 18

The coordination behaviour of the 1,1',2,2'-ferrocenyl tetraphosphines **7** and **8** are of special interest. Upon control of the metal stoichiometry, mononuclear and dinuclear coordination species were obtained (Fig. 20).<sup>35</sup> The X-ray structure characterization revealed the preferential coordination of nickel and palladium halides to phosphorus atoms within a chelating -1,2 framework (**41**, **42** and **41b**, **42b** respectively mononuclear and dinuclear Ni and Pd complexes, Fig. 20). Under the conditions adopted no heteroannular coordination was detected.

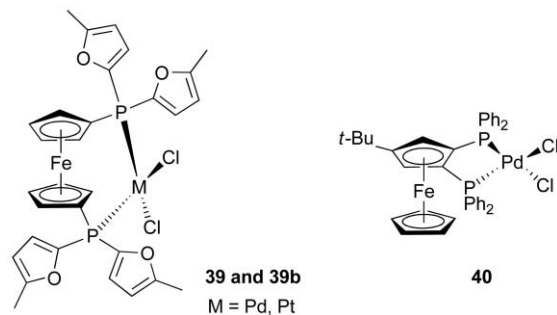


Fig. 19



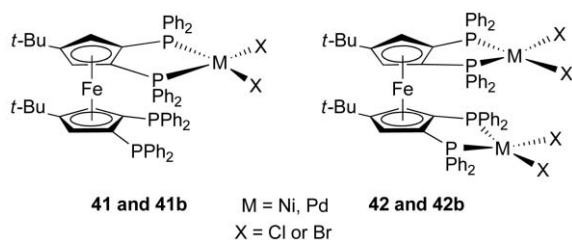


Fig. 20

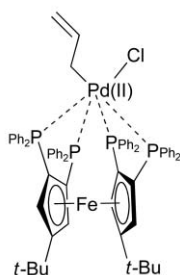


Fig. 21

The formation of palladium complexes **41b** and **42b** was also established by NMR spectroscopy as thermodynamically favoured from a long-standing evolution of the mixture of **8** with  $[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2$  in solution.<sup>35</sup> Interestingly, variable-temperature NMR spectroscopic studies highlighted a dynamic phenomenon rarely observed in ligand chemistry. The interaction of two equivalents of **8** with the dimeric palladium complex  $[\text{Pd}(\eta^3\text{-allyl})\text{Cl}]_2$  clearly showed that at ambient temperature the four phosphorus interact with one palladium centre, leading at the NMR scale rate to observe an average spectrum with a reversible coalescence–decoalescence behaviour upon cooling. This very significant observation illustrates the restricted conformation of ligand **8**, allowing proximity in space for the four phosphorus which is sufficient for interaction with the same metal nucleus, as depicted in Fig. 21. This flexibility and labile behaviour amplify the

possibility of the metallic species to be stabilized by a phosphorus donor group, in addition to an increase in steric congestion around the metal centre. We believe that these properties would strongly contribute to the outstanding results obtained within several catalytic systems described below.

### 3.2 High-performance palladium catalytic systems based on ferrocenyl polyphosphines

**3.2.1 Ultralow loading catalysts and catalyst longevity concepts.** In the last few decades much progress in metal-catalysed cross-coupling reactions has been accomplished through the synthesis and recognition of efficient auxiliary ligands. Regarding organic substrates, significant advances have been reported on the activation of the relatively inert aryl bromides and chlorides (by comparison to their iodide analogues). The low reactivity of such substrates has been often ascribed to their reluctance to perform the oxidative addition to palladium. Therefore, improved catalytic activities were detected from catalyst systems combining palladium to hindered strongly  $\sigma$ -electron-donating ligands such as trialkylphosphines. Additionally, the success of bulky phosphines has been suggested to be derived from the ability of these ligands to promote geometrically driven coordinative unsaturation important to transmetalation and reductive elimination steps.

From a different perspective, several groups have attributed the spectacular turnover numbers they observed not to a specific high activity of their catalyst but more to an outstanding longevity in catalyst lifetime.<sup>36,37</sup> This concept of catalyst longevity, and consequently of stability of the catalytic species in the reaction conditions, was specially evoked as an explanation for the activity in a broad range of palladium-catalyzed reactions in the presence of the multidentate tetraphosphine ligand *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Fig. 15(c)).<sup>38</sup> Table 2 summarizes some selected representative results of high-efficiency C–C and C–N palladium-catalyzed cross-couplings, obtained with di- or tetraphosphine ligands, and that are detailed in the following.

**Table 2** Performances of ferrocenyl polyphosphines in palladium-catalyzed arylation or allylation<sup>a</sup>

Reaction	Ligand	Aryl halides or allyl acetates	Substrate	TON or TOF (h <sup>-1</sup> )	
Suzuki	<b>8</b>	4-bromoacetophenone	phenylboronic acid	100,000	
		4-cyanobromobenzene		100,000	
		4-trifluoromethylbromobenzene		150,000	
Heck	<b>8</b>	4-bromoanisole	<i>n</i> -butylacrylate	77,000	
		iodobenzene		1,000,000	
		4-bromoanisole		10,000	
Sonogashira <sup>b</sup>	<b>19</b>	4-fluorobromobenzene	styrene	65,000	
		4-bromoacetophenone		20,000	
		4-bromobenzonitrile		250,000	
Tsuji–Trost	<b>2</b>	allylacetate	phenylacetylene	46,000	
				aniline	10,000 h <sup>-1</sup>
				pyrrolidine	4,900 h <sup>-1</sup>
		morpholine		4,250 h <sup>-1</sup>	
		benzylamine		1,825 h <sup>-1</sup>	
		3-phenylallylacetate		7,600	
pyrrolidine	2,600				
morpholine	4,800				

<sup>a</sup> Representative selected results obtained in the presence of 10<sup>-2</sup> to 10<sup>-4</sup> mol% Pd per ligand. <sup>b</sup> Copper-free Sonogashira (Heck alkylation) was also described.

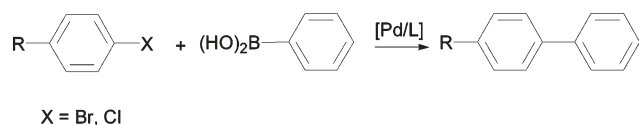


Fig. 22

**3.2.2 C–C cross-coupling: Suzuki, Heck and Sonogashira reactions.** The first reaction that was explored by our group under conditions of ultralow loading catalyst was the arylation of aryl halides with aryl boronic acids, usually known as the Suzuki–Miyaura cross-coupling reaction (Fig. 22).<sup>35</sup> With the view to deliver more economical catalytic systems, we tested nickel catalysts ([NiCl<sub>2</sub>], [NiCOD<sub>2</sub>]) with the multidentate tetraphosphine **8** under various conditions without success. Conversely, the results obtained employing the system [Pd( $\eta^3$ -allyl)Cl]<sub>2</sub> combined with **8** were very interesting. High-reaction rates were obtained with aryl bromides. TONs above 100,000 were found for the coupling of phenylboronic acid with the activated aryl bromides 4-bromoacetophenone and 4-cyano-bromobenzene and of 150,000 and 77,000 with the deactivated 4-trifluoromethylbromobenzene and 4-bromoanisole, respectively. The coupling of activated chlorides, although successful, did not allow the obtention of such TONs.<sup>35</sup>

The Heck reactions (Fig. 23) of aryl iodides and bromides with *n*-butyl acrylate, styrene and *n*-butyl vinyl ether were effected under very low catalyst loadings.<sup>35</sup> Reaction of iodobenzene and *n*-butylacrylate gave a very high TON of 1,000,000. With the unactivated bromoanisole in the presence of *n*-butyl acrylate or styrene, high TONs (10,000 and 65,000, respectively) were observed. Even the electron-rich alkene *n*-butyl vinyl ether led to the corresponding adducts in the presence of 0.1% catalyst.

The scope and limitations of the tridentate ferrocenyl phosphine ligand **19** for the Sonogashira alkylation of a variety of aryl bromides with terminal alkynes was also established (Fig. 24).<sup>39</sup> When activating substituents are present on the aryl bromide, high reaction rates were observed. For example, the coupling of 4-fluorobromobenzene, 4-bromoacetophenone and 4-bromobenzonitrile with phenylacetylene using 0.001 mol% palladium complex led to the coupled products in 20,000, 250,000 and 46,000 TONs, respectively. The quantitative conversion of the strongly deactivated 4-bromoanisole requires a higher catalyst loading (0.4 mol%) and resulted in a lower TON of 520. Reactions with activated aryl chlorides such as 4-chlorobenzonitrile and 4-chloroacetophenone in the absence of copper promoter led to the desired

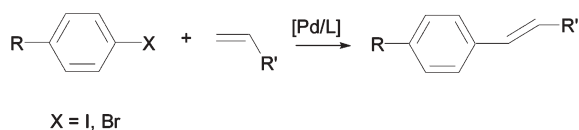


Fig. 23

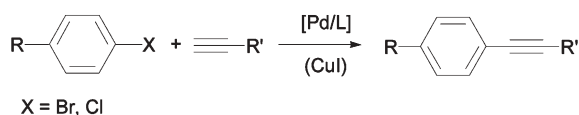


Fig. 24

products in TONs of 540 and 205, respectively, and in very good yields using 0.4 mol% catalyst. Aliphatic alkynes such as dec-1-yne or but-1-yn-4-ol were coupled to 4-bromoacetophenone with good TONs of 620 and 460, respectively.

**3.2.3 Allylic amination from allyl acetates.** Amination of allyl acetates or malonates has been proved to be efficient to form useful allyl amine blocks when conducted in the presence of 1 to 10 mol% palladium catalysts combined to phosphine auxiliaries (Tsuji–Trost type reactions).

With the view to test more efficient catalytic systems in terms of atom economy we employed the ligand 1,1'-bis[di(5-methyl-2-furyl)phosphino]ferrocene **2**, as well as the related dissymmetric compound **11**, with palladium under low catalyst loading conditions.<sup>1,2</sup> As a result, nucleophilic amination of an allylic acetate was performed at room temperature with unprecedented turnover frequencies (Fig. 25). Various aliphatic and cyclic primary or secondary amines of different steric and nucleophilic properties were successfully employed for the amination of allyl acetate, cinnamyl acetate and hexenyl acetate, using low concentrations of catalyst under mild conditions. In the presence of 0.01 mol% catalyst Pd/**2** the coupling of aniline to allyl acetate occurred at a high 10,000 h<sup>-1</sup> TOF with a complete conversion and 96% selectivity in monoallylamine. An excellent 98% conversion was achieved from the cyclic secondary amine pyrrolidine (TOF 4,900 h<sup>-1</sup>). Only a slightly decreased conversion of 85% was obtained with the less nucleophilic cyclic morpholine (TOF 4,250 h<sup>-1</sup>). Under the same conditions, morpholine was quantitatively converted in three hours at ambient temperature. The coupling of primary amine benzylamine appeared more difficult and less selective (TOF 1,825 h<sup>-1</sup> and 75% selectivity for the monoallylation product). In addition to primary amines and cyclic secondary amines, also more challenging aliphatic secondary amines such as *n*-dioctylamine, were coupled efficiently. Complete conversion of the sterically demanding diisopropylamine was possible at 80 °C in the presence of 0.1 mol% catalyst in 2 h (TOF 480 h<sup>-1</sup>), and of the long alkyl chain-bearing dioctylamine at ambient temperature after a longer reaction time, with the best TOF being 250 h<sup>-1</sup>.

This new catalytic system was also found to be remarkably active and selective for the more difficult amination of substituted allylic acetates.<sup>1</sup> Using the same pool of amines, we focused our catalytic investigations on coupling reaction of 3-phenylallyl acetate and *E*-hex-2-en-1-yl acetate at 0.1 and 0.01 mol% Pd/**2**, at a moderate reaction temperature and for a short period of time. Starting from diethylamine, pyrrolidine

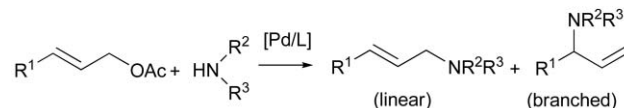
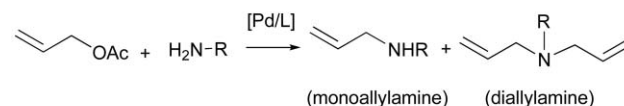


Fig. 25

and morpholine complete conversion was obtained from 0.1 mol% catalyst. Lowering the catalyst loading to 0.01 mol% resulted in TONs of 7,600, 2,600 and 4,800, respectively. In each case, good regioselectivity was observed for the linear product (93–94%), especially concerning the primary amine: HNEt<sub>2</sub>; for which monoallylation occurs exclusively (for primary amines, theoretically five different products could be obtained: linear/branched mono or diallylic product combinations). The selectivity is even higher in linear monoallylamine for the coupling of HNEt<sub>2</sub> to the *E*-hex-2-en-1-yl acetate (99%). For the cyclic secondary amines these coupling reactions proceeded in >90% yields using as little as 0.1 mol% catalyst (94% selectivity for the linear product). Finally, only in the course of the addition of dioctylamine (for which lower TONs and TOFs were observed) was higher catalyst-loading required (0.4 mol%). The results obtained were obviously not the result of a stabilizing multidentate ligand effect, but were more likely attributed to a high activity in the nucleophilic substitution step of the cycle, and provided by the electron-withdrawing furyl groups on phosphorus atoms of the ligands.<sup>1</sup> The comparison of activity with a catalyst system incorporating the ligands dppf, PPh<sub>3</sub> or PCy<sub>3</sub> confirmed this hypothesis.

**3.2.4 Trends in rationally designed ferrocenyl phosphine ligands for catalysis.** The developed ferrocenyl phosphine species present several features which are useful in the rational design of a large number of new metallo-ligands. Fig. 26 summarizes some of these benefits to identify and realise adaptable systems of high-efficiency for appropriate catalytic reactions:

(i) the first common feature of these polyphosphines species is the robustness of their ferrocenyl backbone which allows their handling and storage under air for years without any need for precaution. Additionally, non-glove box conditions and temperatures above 120 °C have been used in longer reactions (over 20 h) without deactivation;

(ii) the possibility of using the assembly method to access polysubstituted Cp rings was decisive in controlling the conformation of the ferrocene. Current investigations have

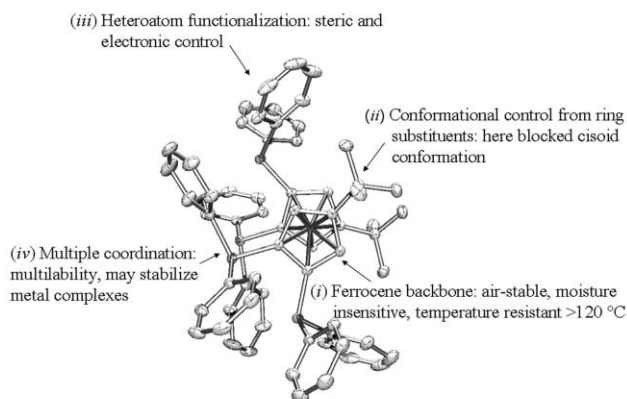


Fig. 26

extended the substitution possibilities, besides methyl and *tert*-butyl groups;

(iii) the nature of the substituent on the phosphorus atoms can be modified for either more electron-donating groups, *e.g.* isopropyl groups, or more electron-withdrawing, *e.g.* furyl groups; other than the classical phenyl moiety which are, however, interesting in terms of steric bulk for blocked conformations and for exerting steric pressure on metal complexes. Other donor-atoms such as nitrogen might be explored for catalysis with other metals such as copper;

(iv) multiple coordination to the metal centre allows stabilization of some catalytic systems, leading to more efficient catalysis with lower loadings of precious metal. Therefore other polysubstituted ligands would be of interest to assess.

Concerning the potentialities of this class of ligand, it should be added that the role of the iron nucleus from ferrocene might be non-innocent in catalysis (role, for example, of the most extended orbitals of the metal?). Further important fundamental studies could be developed, *e.g.* (i) electrochemistry with the ferrocene as a probe and for the characterization of Pd intermediaries in catalysis, and (ii) enantioselective catalysis involving the chiral atropoisomery of some of the polyphosphines presented herein. The metallo-ligands build on ferrocene display another interesting potentiality, which is the influence of the iron redox-active centre on catalysis. Indeed, promising developments are linked to the study of the catalytic activity of all the ferrocenium derivatives available from ferrocene-based ligands.<sup>40</sup>

### 3.3 “Through-space” nuclear spin–spin $J_{PP}$ coupling in multidentate ferrocenyl phosphines

**3.3.1 Introduction.** Currently the indirect nuclear spin–spin coupling  $J$  provides important data for the characterization of organic and biological molecules. For many years this electron-mediated coupling has been commonly thought as only originating from clearly covalently bonded magnetic nuclei. Nevertheless, experimental and theoretical reports highlighted the existence of  $J$  coupling nonbonded by nature (also called “through-space”, TS, couplings).<sup>41</sup> These non-bonded couplings constitute one of the under-explored fields of modern NMR and therefore is an emerging topic of investigation.<sup>42</sup>

We have reported on <sup>31</sup>P–<sup>31</sup>P nuclear spin–spin coupling constants of the tetraphosphine **8** (Fig. 5) and its nickel and palladium complexes **41** and **42** (Fig. 20) in solution.<sup>43</sup> The  $J_{PP}$  constants were accurately determined through NMR iterative simulation based on the second order spectra obtained for the compounds. The eclectic array of puzzling NMR patterns obtained was finally established as being due to the existence of unexpected  $J_{PP}$  “through-space” nuclear spin–spin coupling, previously not reported in the coordination chemistry literature at that time. We provided a rationale to the coupling constants observed between the different phosphorus atoms, clearly demonstrated to be a result of nonbonded interactions.

**3.3.2 Requirements for “through-space” nuclear spin coupling.** The empirical requirements for the detection of nonbonded

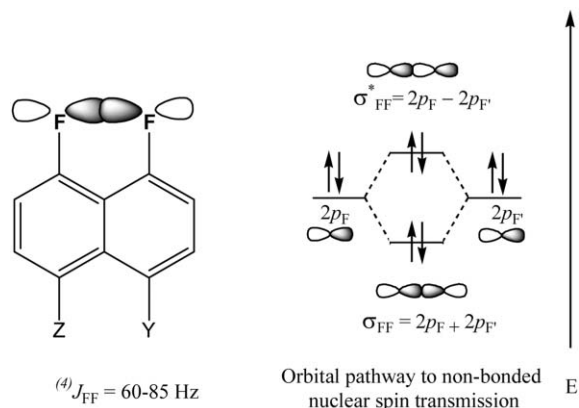


Fig. 27

coupling constants in organic compounds can be derived from the pioneering studies concerning (FF), (NF), (HF) or (CF) spin–spin couplings (Fig. 27), and occasionally (PX), with X = P, Se, F.<sup>44–46</sup>

The first requirement is trivial but involves in practice some architectural difficulties. In order to easily and directly detect a coupling constant when the nuclei are identical in nature, they have to be anisochronous. Therefore, the molecule must be dissymmetric or more precisely the involved nuclei must display magnetic inequivalence (see Fig. 27).

The second requirement is that the nuclei must be in *close proximity* in solution. In our case the tetraphosphine species described here have a locked-conformation in solution even at temperatures above 90 °C.

A last requirement invoked by Mallory and coworkers for organic species is the presence of *two* lone-pairs of electron involved in a mutual overlap: from that, “through-space” coupling has been analyzed using a simple but powerful perturbation model (Fig. 27).<sup>44</sup>

The “through-space” couplings result from overlap interactions between lone-pair orbitals on the two crowded elements. The nonbonding distances are short and the two lone-pair orbitals experience a  $\sigma$ -directed overlap. The overlap between these lone-pair orbitals is expected to afford an in-phase and out-of-phase combination. As both orbitals are occupied (two-orbitals, four-electrons interaction), no net bonding is observed. However, it provides an adequate pathway for transmitting spin information between the coupled nuclei *via* electron spin polarization. The magnitude of coupling depends on the extent to which the two lone-pair orbitals interact due to their overlap.

This model, initially qualitative, led to a breakthrough when the overlap interaction was quantitatively estimated for a family of 1,8-difluoronaphthalene through an exponential relationship between the *ab initio* calculated internuclear distances and the observed  $J_{FF}$  coupling constant.<sup>47</sup> We proposed to extend this model to phosphorus nuclear  $^{31}\text{P}$ – $^{31}\text{P}$  spin–spin “through-space” interactions, and to complete it with the case of metallo-organic species.

### 3.3.3 Advances in the modelling of TS couplings provided by ferrocenyl phosphines.

A dataset to investigate by NMR spectroscopy the nuclear-spin interactions in our ferrocenylpolyphosphine coordination complexes has been generated (Fig. 28): four mononuclear and dinuclear nickel complexes  $[\text{NiCl}_2\{\text{Fc}(\text{P})_4^t\text{Bu}\}]$  and  $[\text{Ni}_2\text{Cl}_4\{\text{Fc}(\text{P})_4^t\text{Bu}\}]$  (**41b**, **42b** and their bromine analogs), have been synthesized and characterized by X-ray crystallography.<sup>43</sup> These extended on the palladium congeners  $[\text{PdCl}_2\{\text{Fc}(\text{P})_4^t\text{Bu}\}]$  and  $[\text{Pd}_2\text{Cl}_4\{\text{Fc}(\text{P})_4^t\text{Bu}\}]$  (**41** and **42**) reported during the course of the catalysis studies.<sup>35</sup> The conformational rigidity of all these species in solution allowed us to correlate their geometric features in the solid-state and their spin–spin  $J_{PP'}$  coupling constants in solution (see Table 3 relating to Fig. 28).

In the case of this class of tetraphosphine ferrocenyl derivatives the shortest “through-bond” interactions between phosphorus pairs can be considered as  $^3J_{PP'}$  and  $^4J_{PP'}$  coupling constants. It clearly appears from Table 3 that the values of  $J_{PP'}$  present a strong inverse dependence on  $\text{P}\cdots\text{P}$  distances. Whatever the compound, for  $\text{P}\cdots\text{P}$  distances above 4.60 Å no detectable  $J_{PP'}$  is observed. On the other hand, for distances below 4.00 Å,  $J_{PP'} > 20$  Hz were systematically obtained.

We examined the compounds according to the model developed by Mallory (Fig. 27).<sup>44,46</sup> It was established that to observe “through-space” nuclear spin coupling in the complexes, *two lone-pair orbitals are not required*. One lone-pair orbital with an appropriate orientation can interact with a bonding electron-pair shared between a phosphorus atom and a metal and thus transmit “through-space” nuclear spin  $\text{P}\cdots\text{P}$  information.

Thus, the “through-space” interaction involved a three-centre system composed of P and P'–M (M = Ni, Pd). The Fig. 29 presents an important corollary to the model developed for fluorinated purely organic compounds (Fig. 28). For simplicity, only the three localized orbitals involved in the “through-space” interaction are sketched. The metal–ligand bond between P1 and M is considered as coming from the

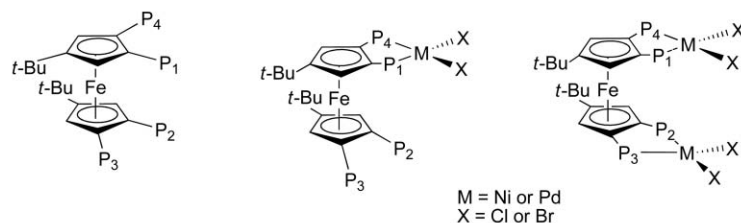


Fig. 28



**Table 3** Correlation between  $^{31}\text{P}$  NMR  $J_{\text{PP}}$  coupling constants and corresponding nuclei “through-space” distances (from X-ray crystallographic data)

$\text{P}\cdots\text{P}$ distances ( $\text{\AA}$ )/Coupling constant (Hz)	Ferrocenyl tetraphosphine derivative				
	$\text{Fc}(\text{P})_4^t\text{Bu}$	$\text{PdCl}_2\text{Fc}(\text{P})_4^t\text{Bu}$	$\text{Pd}_2\text{Cl}_4\text{Fc}(\text{P})_4^t\text{Bu}$	$\text{NiCl}_2\text{Fc}(\text{P})_4^t\text{Bu}$	$\text{Ni}_2\text{Cl}_4\text{Fc}(\text{P})_4^t\text{Bu}$
$\text{D P}_1\cdots\text{P}_2/J_{\text{PP}}^a$	3.728(2)/59.8	3.842(1)/24.0	4.985(5)/ $N$	3.644(3)/31 <sup>b</sup>	4.987(8)/ $N$
$\text{D P}_1\cdots\text{P}_3/J_{\text{PP}}^a$	4.861(2)/ $N$	4.698(2)/ $N$	5.372(5)/ $N$	5.397(3)/ $N$	5.382(8)/ $N$
$\text{D P}_4\cdots\text{P}_2/J_{\text{PP}}^a$	4.861(2)/ $N$	4.440(1)/6.4	5.351(4)/ $N$	4.429(3)/ $N$	5.373(9)/ $N$
$\text{D P}_4\cdots\text{P}_3/J_{\text{PP}}^a$	6.633(2)/ $N$	6.292(2)/ $N$	6.582(5)/ $N$	6.740(3)/ $N$	6.577(8)/ $N$
$\text{D P}_1\cdots\text{P}_4/J_{\text{PP}}^a$	3.364(2)/74.5	3.035(2)/15.7	3.113(5)/13.0	3.002(3)/67 <sup>b</sup>	2.950(7)/76.3
$\text{D P}_2\cdots\text{P}_3/J_{\text{PP}}^a$	3.364(2)/74.5	3.515(2)/14.3	3.018(5)/13.0	3.765(3)/ $N$	3.067(7)/76.3

<sup>a</sup> Values from simulated spectra at  $\pm 0.1$  Hz. <sup>b</sup>  $J_{\text{PP}}$  is given at  $-80$  °C due to a broadening at ambient temperature.  $N$  = coupling constant null or  $< 0.5$  Hz.

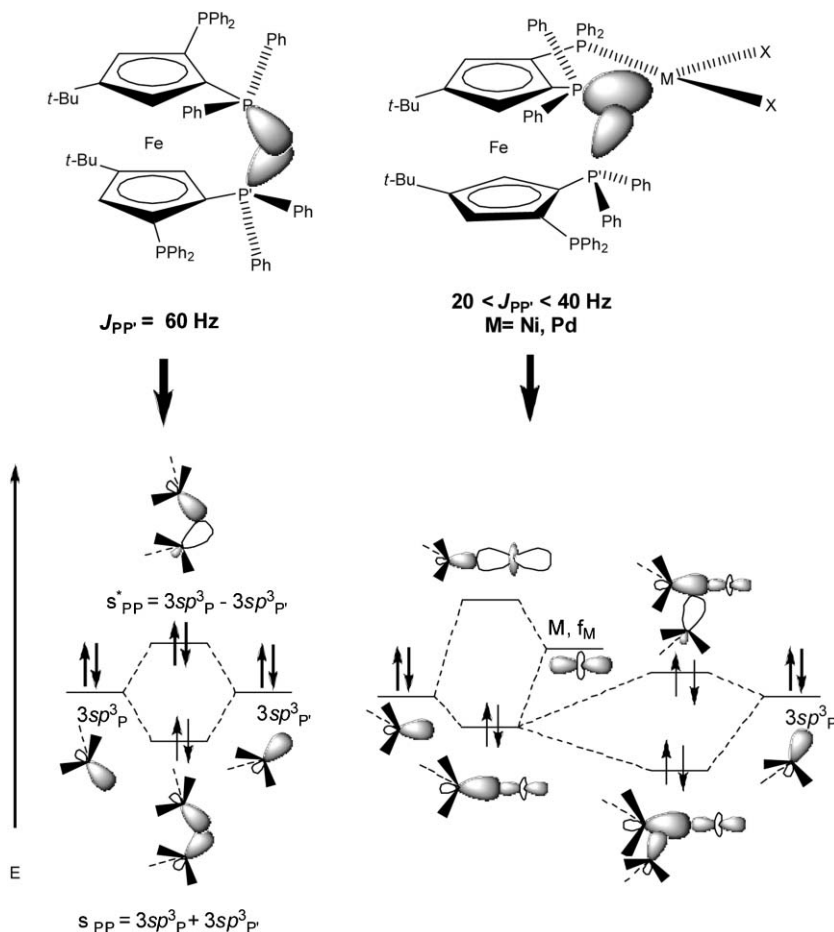
$\sigma$ -overlap between a  $3\text{sp}^3$  and a metallic d orbital. To account for the fact that nuclear spin information is transmitted between the phosphorus atoms, two filled molecular orbitals have been constructed which incorporate a contribution from the metal. The qualitative orbital ordering, as well as the symmetry of the interacting orbitals allow this schematic view.

In addition, a semi-quantitative correlation of the distance-dependence of  $^{31}\text{P}$ - $^{31}\text{P}$  coupling in coordination complexes was furnished from the plot constructed by using the data collected in Table 3. The data points were plotted as  $J_{\text{PP}}$  vs  $d\text{P}\cdots\text{P}$  (Fig. 30). A very good fit was obtained for an exponential curve expressed by eqn (1), in which  $J_{\text{PP}}$  is in

units of hertz and  $d\text{P}\cdots\text{P}$  in units of angstroms (regression coefficient  $R^2 = 0.975$ ).

$$J_{\text{PP}} = (9691.9)\text{e}^{-1.6102d\text{P}\cdots\text{P}} \quad (1)$$

It should be emphasized that the fitted data all correspond to experimentally determined values, which span a wide range of coupling constants (from 6 to 76 Hz) as well as distances (from 2.9 to 4.4  $\text{\AA}$ ). The semi-quantitative experimental formulation proposed is rather convenient, as it presents an intuitive correlation between “geometric parameters” and “through-space” nucleus spin-coupling, a more significant



**Fig. 29**

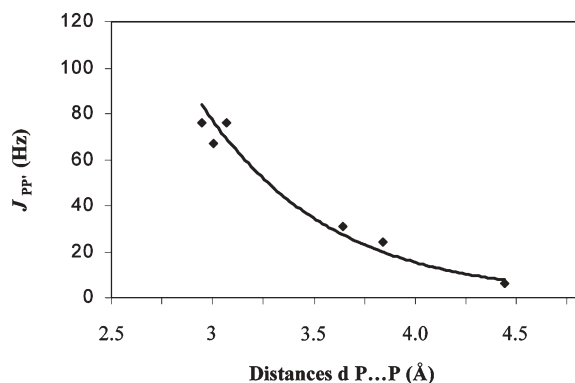


Fig. 30

correlation should probably be expressed in terms of orbitals overlap: taking into account the shape and the relative diffuse character of the electronic clouds. Consequently, further improvements should include quantitative orbital overlap effectiveness derived from molecular orbital calculations.

The proximity of the Cp rings in the ferrocene backbone which is at the origin of the P...P “through-space” coupling detected has led to identify in **19** a related phenomenon.<sup>11</sup> This remarkable feature in the <sup>13</sup>C NMR spectroscopic data is a net spin-spin nuclear coupling constants ( $J_{CP} = 5.5$  Hz) between the three carbon atoms of the *t*-Bu group and the phosphorus atom connecting the isopropyl groups (unambiguously demonstrated by selective phosphorus decoupling). The shortest distance between the involved nuclei is a five bond (C–C–C–Fe–C–P) distance that would not lead to a detectable <sup>5</sup> $J_{CP}$ . Consistently, no other coupling constant <sup>4</sup> $J_{CP}$  or <sup>5</sup> $J_{CP}$  are observed. The X-ray structure revealed the proximity in space of the atoms (shortest “through-space” distance  $d_{P...C} = 3.64$  Å), favoured by the staggered conformation of the ferrocene backbone. The lone-pair of the phosphorus was found to be directed towards the carbon atoms of the *t*-Bu group as drawn in Fig. 31: ascertaining then a strong  $J_{CP}$  coupling constant “through-space”.

To summarize this section we have reported for the first time “through-space”  $J_{PP}$  spin-spin couplings in ferrocenyl tetraphosphine derivatives involving a unique phosphorus lone-pair in the transmittal of the spin information; the ensuing study showed that analogous “through-space”  $J_{CP}$  also exists in ferrocenylpolyphosphines. A number of other ferrocenyl polyphosphines in which small <sup>31</sup>P TS couplings were detectable depending on their conformation was also studied.<sup>12</sup>

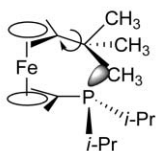


Fig. 31

Nuclear magnetic resonance is recognized as one of the most useful and innovative techniques available for chemists and biologists for studying a variety of molecular problems relating to high-resolution structure determination. The indirect nuclear spin-spin coupling  $J$  provides decisive data for characterization, and this whatever the nature (organic, organometallic) or the size (small molecules, pharmaceuticals, biomolecules) of the observed systems. For many years this electron-mediated scalar  $J$ -coupling has been commonly thought as only originating from clearly covalently bonded magnetic nuclei. Fortunately, a significant number of experimental and theoretical reports highlight now the existence of  $J$ -coupling nonbonded by nature.<sup>48</sup> These “through-space”  $J$ -coupling first encountered in small organic compounds incorporating <sup>19</sup>F, are demonstrated as a general phenomenon known now for nuclei as different as <sup>13</sup>C, <sup>14</sup>N, <sup>31</sup>P, and even <sup>1</sup>H involved in hydrogen bonding. The polyphosphine ligands and their metallic coordination complexes provide a set of unique examples in which close proximity of phosphorus atoms result in very diverse and very intense TS nuclear spin couplings.

## Summary

Over the period 1995–2005 the chemistry of the new class of the branched ligands ferrocenylpolyphosphines was proved to be rich from the perspective of both catalytic applications and fundamental knowledge in chemical physics related to nuclear spin couplings. The synthesis of new Cp-based reagents, of original di-, tri- and tetraphosphines, as well as their corresponding coordination complexes with group 6 to 11 transition metals has been described. Symmetric and dissymmetric species were obtained and many coordination modes were revealed. Their efficiency in catalytic applications under “green chemistry” conditions (ultralow metal/ligand concentration) has been proved in several C–C and C–N valuable cross-coupling reactions.

These results open the way to many prospective studies. Numerous catalytic optimizations and ligand developments are envisioned. Potentially interesting ferrocenic polyphosphines would incorporate more electron-rich substituents on phosphorus and/or on the Cp rings, and consequently might allow the activation of chloride substrates with the advantage of a preserved robustness. Concerning the perspective in ligand synthesis, higher-rank polyphosphines such as penta- or hexaphosphines should be rather easily reachable. *In particular, such kind of “enhanced multidentarity” would allow us to pursue the effort for stabilizing catalytic systems and promoting their longevity.* Other ligand modifications are currently being studied by our group, especially the heterogenisation of the polyphosphines using solid supports, and the control of their conformation *via ansa*-Cp bridging. The possibility of synthesizing water-soluble derivatives of this class of ligand is also appealing.

The library of ligands developed up to now could be of interest in other metal-catalyzed cross-coupling reactions, such as in the coupling from organozinc compounds (Negishi coupling) or organotin reagents (Stille reaction). Ultralow catalyst loadings can be used for some important C–C and

C–N bond forming processes with very demanding or water soluble substrates: carboxylic acids and arylpolyhalides could be primary targets. Concerning the coordination chemistry, the generation of active heterometallic polynuclear species might also constitute some appreciable further achievement, in especial to study some tandem-reactions which require several metals.

From a more fundamental point of view, the modelling of “through-space” nuclear spin–spin coupling is an interesting and very challenging issue for physical chemists. The advantages of the constrained geometry of the compounds and the existence of a data set of X-ray structures and complete NMR determination should help for theoretical modelling work. In particular, the determination of a fine model that would help separating the contribution of “through-bond” and “through-space” spin transmission is a priority. Then, the opportunity to link the intensity of spin-coupling between nuclei and their spatial arrangement in solution, taking into account quantitative orbital overlap effectiveness derived from molecular orbital calculations, would be very exciting.

Finally, we recently started mechanistic studies of the high-performance palladium catalytic cycle involving ferrocenyl tetraphosphines, by employing electrochemical tools. In particular the rate determination of palladium oxidative addition and the characterization of multidentate intermediates are targeted. These relevant studies will be reported in due time, we hope from these studies to efficiently orientate further ferrocenyl polyphosphine ligands modifications.

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