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Ultra-Low Catalyst Loading as a Concept in Economical and Sustainable Modern Chemistry: The Contribution of Ferrocenylpolyphosphane Ligands

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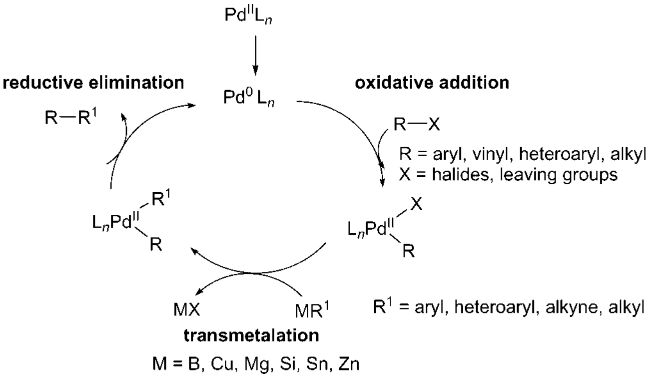
The challenge of sustainability in modern chemistry will be met with new technologies and processes provided significant progress is made in several key research areas, such as the expansion of chemistry from renewable feedstock, the design of environmentally benign chemicals and solvents, the minimization of depletive resources, and the development of high-performance catalysis. In this prospect, ligand chemistry is a pivotal science that links modern-organic, -inorganic, -organometallic, and -coordination chemistry through a vast number of valuable applications, precisely associated to catalysis. We review in this article our recent work on catalysis promoted by original ferrocenyl tetra-, tri-, and diphosphane ligands. New concepts, taking advantages of this family of branched multidentate ligands, have led to progress in homogeneous catalysis. The search for catalyst longevity and ultra-low catalyst loadings (high turnover numbers), on the basis of multidentarity effects and robustness of the ferrocenyl backbone were focused on high-value palladium-catalyzed C–C cross-couplings, such as Heck, Suzuki, and Sonogashira reactions. Low catalyst loading was also explored for C–N cross-coupling in the allylic amination of achiral substrates. The advantages of this newly born family of ligands in the class of multidentate compounds are discussed in light of the valuable information gathered up to now on their reactivity, structure, and mechanistic behavior.

Introduction and Scope

Sustainable chemistry is expected, at the beginning of this new century, to solve many of the global environmental challenges we must face. This major societal and economic matter is now a priority of the scientific research programs in many industrialized nations,[1] and a guidance for chemists on this multiparameter question is summarized by the twelve principles of green chemistry.[2] One of these principles, which concerns explicitly catalytic chemistry, states: "Catalytic reagents (as selective as possible) are superior to stoichiometric reagents". The underlying idea of this principle is that, owing to catalysis, the minimization of the resources consumed and the economy of atoms is effective. However, a practical overview of the huge field covered by the term "catalysis" shows that the so-called "catalyst amount" ranges from substoichiometric amounts (30 mol-%) to amazingly low quantities down to 10^{-6} mol-%.[3,4]

Among the most fertile and innovative fields in "catalysis" for the last three decades is the formation of carbon–carbon bonds by employing active transition metals (Scheme 1). In this prospect, palladium catalysts emerged as powerful tools in reactions aimed at the coupling of organic halides with organometallic substrates that are based mainly on boron- (Suzuki–Miyaura reaction), tin- (Stille reaction), zinc- (Negishi reaction), silicon- (Hiyama reaction), or magnesium reagents (Kumada–Corriu reaction).[5]



Scheme 1.

From an economic and financial point of view,[6] the catalyst turnover number (TON)[7] is a key parameter for industrial applications. Relevant recent reviews by Farina[8] and by Corbet and Mignani[5] illustrated that the efficient use of a catalytic system at less than 10^{-1} mol-% (TON ≥ 1000) can avoid its recovery and thus its recycling. Convergent benefits are found between industrial and sustainable development with the use of such kind of high-efficiency catalytic systems. As a consequence, in the last

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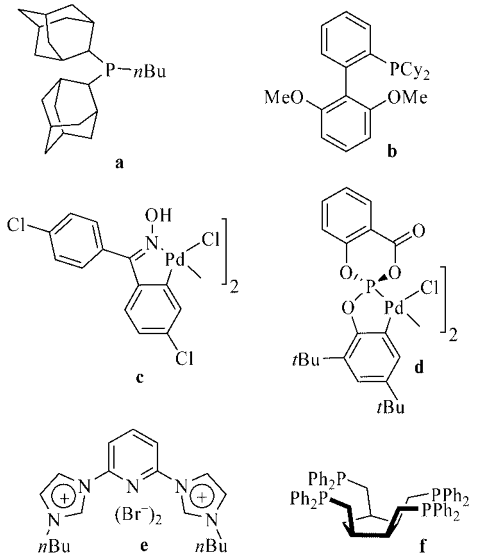
decade the progress on ligand chemistry became a major goal in the community of the organic chemist, and creativity partnered with a better understanding of the mechanistic necessities led to the emergence of several families of useful ligands for high-turnover palladium catalytic systems. For instance, and nonexhaustively: bulky electron-rich trialkylmonophosphanes,[9] (biaryl)dialkylphosphanes,[10] di- and tridentate pincers,[11] heterostructures at the origin of various palladacycles,[12,13] carbenes,[14] or multidentate polyphosphanes (Scheme 2) were found to be very efficient catalytic auxiliaries.[15]

On this basis and ongoing since the mid 1990s we developed the design, synthesis, and characterization of original di-, tri-, and tetraphosphanes built on the ferrocenyl backbone (some representative examples of the library of ligands developed are depicted in Scheme 3). Catalytic applications of a selection of these ligands with palladium in the formation of C–C and C–N bonds are reviewed herein. The reactions explored, namely Suzuki, Heck, and Sonogashira cross-couplings, as well as the amination of allylic acetates, led either to high TONs or high turnover frequencies (TOFs) depending on the reaction and on the ligands. The general advantages of this newly born family of ligands, in the class of multidentate species, are detailed and discussed in light of the gathered structural and mechanistic information. Finally, some of the trends and properties identified could serve as a privileged starting point for the further development of the promising concepts of catalyst *longevity* and ultra-low catalyst loading.



Scheme 2.

Milestones in Ultra-Low Catalyst Loadings

In 1995 Herrmann and coworkers reported "...new, structurally defined, easy-to-handle palladium complexes, that surpass all previously known catalysts of the Heck reaction as regards stability and lifetime."[16] The authors observed from kinetic measurements that standard catalytic systems combining 1 mol-% $Pd(OAc)_2$ with 2–6 mol-% of

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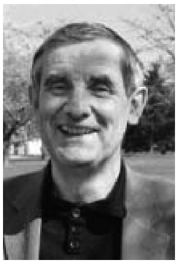
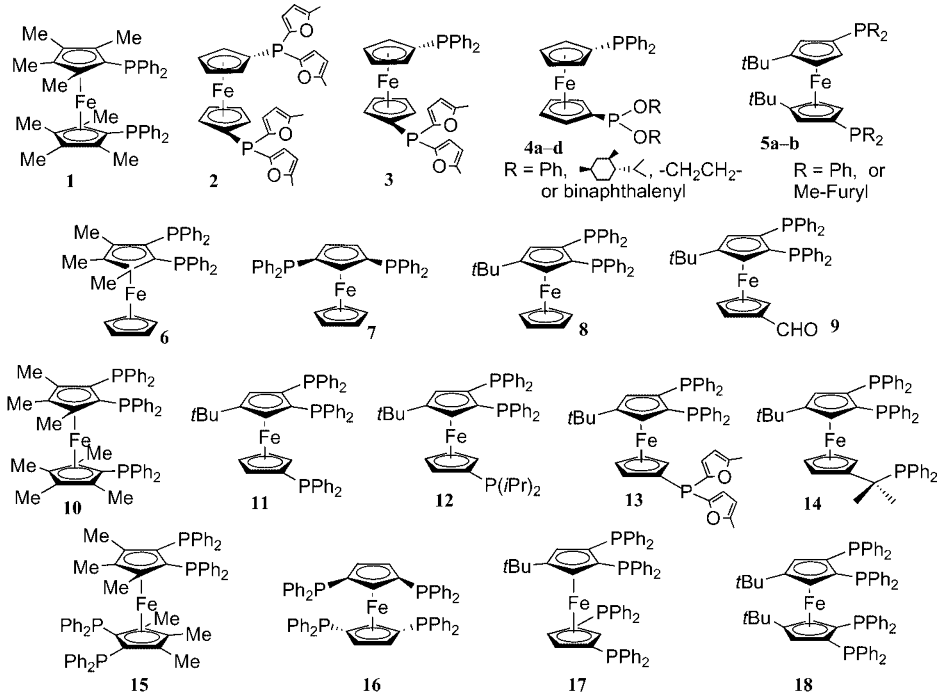
Matthieu Beaupérin was born in 1982 in Saint-Malo (France). In 2006, he graduated from the Graduate School of Chemistry and Chemical Engineering of Clermont-Ferrand (ENSCCF) specializing in organic chemistry. He is currently a Ph.D. student in the group of Prof. P. Meunier, where he is working under the supervision of J.-C. Hierso on the synthesis of ferrocenylphosphanes and their use in catalyzed cross-coupling reactions.

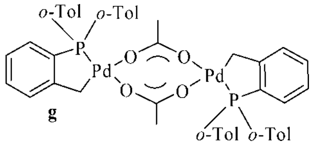


Prof. Philippe Meunier was born in Auxerre (France) in 1946. He obtained his Ph.D. (1979) in heterocyclic chemistry from the Université de Bourgogne after a long period of work in photoelectron spectroscopy and theoretical chemistry at the University of Pau. He then joined the group of organometallic chemistry at Dijon and began to work in group 4 organometallic chemistry. He became a full professor in 1992, and he is currently head of a research group in the Institute of Molecular Chemistry of the Université de Bourgogne (ICMUB-CNRS 5260). His research interests concern group 4 organometallic chemistry for synthesis and group 10 coordination chemistry for catalysis applications.



Scheme 3.

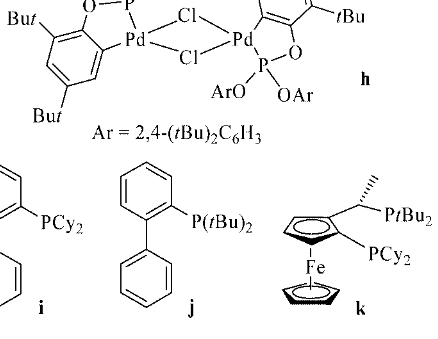
the triarylphosphane PPh_3 are rapidly deactivated in the Heck reaction between 4-bromoanisole and *n*-butyl acrylate above 120 °C; a temperature useful for the activation of demanding organic halides such as deactivated bromides and chlorides. The decomposition of the ligand ($P–C_{aryl}$ bond cleavage), as well as its oxidation [$P(O)Ph_3$ formation] were proposed to be responsible for the deposition of catalytically inactive palladium black. From the treatment of palladium(II) acetate with tris(*o*-tolyl)phosphane in toluene, cyclometalation afforded efficient palladacycle pre-catalyst **g** (Scheme 4).[16] In the Heck reaction of the activated 4-bromobenzaldehyde to *n*-butyl acrylate a TON of 200000 was obtained in a quantitative coupling achieved at 135 °C for 12 h (5×10^{-4} mol-% cat.).



Scheme 4.

This study can be considered as a starting point in the explicit recognition of the concepts of long-term stability and increased lifetimes of the catalysts in palladium-catalyzed cross-coupling-type reactions. The mechanistic involvement of palladacycles in cross-couplings is subject of severe controversy:[8] whether palladacycles upon catalysis remain quasiunchanged and react in Pd^{II}/Pd^{IV} processes, or only constitute slow-delivery reservoirs of active naked palladium, the result was a focus of the community on the ultra-low catalyst loading in C–C cross-coupling reactions.

After this work, the group of Beller[17] followed by Bedford[18] both confirmed the efficiency of palladacycles in the activation of aryl bromides for biaryl formation (in Suzuki coupling) under conditions of low catalyst loading. Palladacycle **g**, depicted in Scheme 4, allowed the coupling of phenylboronic acid to the electronically activated 4-bromoacetophenone with a TON of 74000 (yield 74%, in the presence of 10^{-3} mol-% cat. at 130 °C for 16 h) and to the electronically deactivated 4-bromoanisole with a TON of 7600 (yield 76%, in the presence of 10^{-2} mol-% cat.).[17] Orthopalladated triarylphosphite complex **h** (Scheme 5) was employed for the coupling of phenylboronic acid to 4-bromoacetophenone and 4-bromoanisole and resulted in the formation of coupling products with TONs of, respectively, 1000000 (yield 100%, in the presence of 10^{-4} mol-% cat. at 110 °C for 2 h) and 30000 (yield 30%, 10^{-3} mol-% cat. at 130 °C for 15 h).[18] The same phosphite palladacycle precatalyst allowed the Heck coupling of 4-bromoacetophenone to styrene, and 4-bromoanisole to *n*-butyl acrylate, with, respectively, TONs of 5700000 (yield 57%, 10^{-5} mol-% cat. at 180 °C for 69 h) and 9800 (10^{-2} mol-% cat. at 160 °C for 65 h).[19]



Scheme 5.

In 1999, Buchwald and coworkers disclosed a new family of ligands able to promote ultra-low loading catalysis with aryl bromides and chlorides.[20,21] (Biaryl)dialkylphosphanes **i** and **j** (Scheme 5) were the first of this class to be employed: the coupling of phenylboronic acid to the electronically activated 4-bromoacetophenone and the electronically deactivated 4-(*tert*-butyl)bromobenzene was effective with TONs of, respectively, 91000000 (yield 91%, 10^{-6} mol-% [Pd/2·**j**] at 100 °C for 24 h) and 18600 (yield 93%, 5×10^{-3} mol-% [Pd/2·**i**] at 100 °C for 16 h). In addition, phenylboronic acid was successfully coupled to the electronically activated 4-chloroacetophenone with a TON of 4600 (yield 92%, 2×10^{-2} mol-% [Pd/2·**j**] at 100 °C for 23 h), and to the electronically deactivated 4-chlorotoluene with a TON of 1860 (yield 93%, 5×10^{-2} mol-% [Pd/2·**i**] at 100 °C for 25 h). These results well-illustrate the difficulties encountered when organic chlorides are preferred to bromides for cross-coupling. Interestingly, Buchwald indicated also at that time that the coupling of the electronically activated 4-bromoacetophenone was possible with $Pd(OA_C)_2$ in the absence of a ligand with a TON of 100000 (yield 100%, 10^{-3} mol-% Pd at 100 °C for 19 h) while "...under these conditions, Suzuki coupling reactions of other substrates give little or no products in the absence of phosphane ligands.";[21] anticipating, therefore, the future studies on ligand-free palladium low loading catalyst (see below).

After 2000, a blooming of the high-turnover palladium catalysts for the reactions of Heck, Suzuki, Stille, and Sonogashira occurred in the literature, with systems based on, for instance, ligands such as trialkylmonophosphanes,[9] modified (biaryl)dialkylphosphanes,[10] oxime palladacycles,[12] strongly π-acidic orthopalladated diarylphosphite palladacycles,[13] or carbenes[14] (respectively, **a**, **b**, **c**, **d**, and **e** in Scheme 2). The use of ferrocenyl diphosphanes, such as the electron-rich josiphos (**k**; Scheme 5) was also successful in some other low catalyst loading cross-couplings,[22] following the seminal works published by Hayashi et al. for the Kumada–Corriu reaction.[23] The high performances of the aforementioned systems were thoroughly reviewed in many recent articles,[8,24–28] and their portrayal fall out of the scope of the present review; however, two important points appeared to us as conceptual landmarks: the efficiency and scope of the multidentate diarylalkylphosphane named tedicyp (**f**; Scheme 2), and the so-called "homeopathic" ligand-free catalysis.

At the end of 2000, the first study by Doucet and Santelli appeared on the catalytic activity of the tetradentate polyphosphane ligand *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane (tedicyp) in C–N cross-coupling reactions.[15,29] By employing this original ligand in the palladium-catalyzed amination of allyl acetates, a TON of 680000 was obtained for the coupling of dipropylamine to allylacetate (yield 68%, 10^{-4}mol-% cat. at 25 °C for 136 h). The authors intensively explored the catalytic performances of this multidentate ligand that is based on a cyclopentane alkyl backbone in the pallado-catalyzed reactions of allylic amination, Heck, Suzuki, and Sonogashira. This chemistry was reviewed recently,[4] nevertheless it is worthy of note that, in the reported corpus of more than 50 papers devoted to the activity of Pd/tedicyp in C–C and C–N cross-coupling, was described: (1) the coupling of phenylboronic acid to 4-bromoacetophenone and to 4-bromoanisole with TONs of, respectively, 96000000 (yield 96%, 10^{-6} mol-% cat. at 130 °C for 135 h) and 93000 (yield 93%, 10^{-3} mol-% cat. at 130 °C for 24 h);[30] (2) the Heck coupling of activated 3,5-bis(trifluoromethyl)bromobenzene to *n*-butyl acrylate with a remarkable TON of 210000000 (yield 21%, 10^{-7} mol-% cat. at 130 °C for 72 h) or with a TON of 78000000 and a better yield of 78% (10^{-6} mol-% cat. at 130 °C for 40 h), and the coupling of deactivated 4-bromoanisole to *n*-butyl acrylate with a TON of 82000 (yield 82%, 10^{-3} mol-% cat. at 130 °C for 72 h);[31] (3) the Sonogashira cross-coupling of phenylacetylene to 4-bromoacetophenone and 4-bromoanisole with TONs of, respectively, 700000 (yield 70%, 10^{-4} mol-% cat. at 140 °C for 20 h) and 3800 (yield 38%, 10^{-2} mol-% cat. at 140 °C for 20 h).[32] The scope and performances of tedicyp shed light on the interest of examining the activity of multidentate phosphanes for the development of ultra-low loading catalytic processes.

The term of "homeopathic" catalyst loading has been related to the ligand-free palladium-catalyzed Heck reaction and biaryl formation.[33] Whereas this expression is objectively inappropriate for several reasons,[34] the ligand-free catalysis results that are associated with it are interesting from an economic and environmental point of view. Ligand-free $Pd(OAc)_2$ can be used as a catalyst in the Heck reaction of aryl bromides as long as the amount of catalyst is kept between 10^{-1} to 10^{-2} mol-% (TONs ranging from 1000 to 10000). For instance, in the coupling of the activated 4-bromobenzaldehyde to *n*-butyl acrylate a TON of 2000 was obtained with a quantitative coupling achieved at 135 °C in only 1 h (5×10^{-2} mol-% cat.). As expected, the coupling of deactivated 4-bromoanisole to *n*-butyl acrylate was more difficult, leading to a TON of 1800 in 5 h at 135 °C (yield 91%, 5×10^{-2} mol-% cat.).[3] The authors believe that the corresponding concentration of palladium is low enough to preclude deactivation by palladium-black formation; conversely, a catalyst/substrate ratio lower than 10^{-2} mol-% lead to a conversion too slow to be practical. The limits of this interesting concept were found for couplings such as Negishi- (with zinc organometallics) and Kumada–Corriu reactions (with Grignard reagents), whereas the Suzuki reaction could be carried out with aryl bromides in the presence of 5×10^{-1} to 2×10^{-2} mol-% of $Pd(OAc)_2$: for instance, the coupling of phenylboronic acid to activated 4-bromoacetophenone was achieved with a TON of 4800 (yield 95%, 2.5×10^{-2} mol-% cat., at 90 °C in 4 h). These results illustrate that to reach the lowest catalyst loadings (below 10^{-2} mol-% cat.) the stabilization and steric/electronic activation provided by the ligand chemistry remain up to now unavoidable. Table 1 summarizes the short historical perspective given above through the example of the Suzuki reactions under ultra-low catalyst loading conditions.

Finally, to develop our projects on sustainable chemistry and ultra-low catalyst loading we were inspired by a study

Table 1. Historical perspective of C–C coupling under ultra-low catalyst loadings in Suzuki reactions (1995–2001[a]).

Coupling reagents	Catalyst or ligand	Class of ligand or catalyst	TON	Ref.
4-Bromoacetophenone/phenylboronic acid	**g**	palladacycle	74000	[17]
4-Bromoanisole/phenylboronic acid	**g**		7600	[17]
4-Bromoacetophenone/phenylboronic acid	**h**	phosphite palladacyle	1000000	[18]
4-Bromoanisole/phenylboronic acid	**h**		30000	[18]
4-Bromoacetophenone/phenylboronic acid	**j**	(biaryl)dialkylphosphane	91000000	[20]
4-*t*Bu-bromobenzene/phenylboronic acid	**j**		18600	[20]
4-Bromoacetophenone/phenylboronic acid	**f**	alkyl tetraphosphane	96000000	[28]
4-Bromoanisole/phenylboronic acid	**f**		93000	[28]
4-Bromoacetophenone/phenylboronic acid	**18**	ferrocenyl tetraphosphane	100000	[b]
4-Bromoanisole/phenylboronic acid	**18**		77000	[b]
4-Bromoacetophenone/phenylboronic acid	$Pd(OAc)_2$	ligand-free	4800	[31]
4-Bromoanisole/phenylboronic acid	$Pd(OAc)_2$	ligand-free	0	[21]

[a] Selected results from the first section, systematic ligand-free studies appeared after 2001. [b] Work reviewed herein.

reported in 2002 by Bedford on "...the importance of catalyst longevity".[13] The difficulties encountered in the coupling of halides other than iodides has often been ascribed to their reluctance to perform the oxidative addition to palladium. Improved catalytic activities were detected from systems that combine palladium to hindered strongly σ-electron-donating ligands (such as trialkylphosphanes); in addition, the success of bulky ligands has been suggested to be derived from the ability of these ligands to promote geometrically driven coordinative unsaturation important to the transmetalation and reductive elimination steps. The perspective of Bedford and coworkers was different when they attributed the spectacular TONs they observed (with poor σ-donor phosphonite ligand **d**; Scheme 2) not to a specific high activity of their catalyst but more to an outstanding *catalyst longevity*. This concept of catalyst longevity, and consequently the stability of the catalytic species under the reaction conditions, appeared primordial to us for sustainable chemistry and led us to employ the robust ferrocenyl backbone as a platform with a tunable flexibility to build new active ligands.

Performances of Ferrocenylphosphanes in Heck and Suzuki Reactions

Structural Considerations for Tetraphosphane Ferrocenic Ligands

The ferrocenyl backbone, owing to its peculiar sandwich structure, displays a number of different conformations that have to be elucidated for ferrocenyl derivatives both in the solid-state and in solution. We were specifically interested in the mutual positions adopted by the different phosphorus atoms. For instance, tetraphosphanes **15** and **18** [1,1′,2,2′-tetrakis(diphenylphosphanyl)-3,3′-4,4′,5,5′-hexamethylferrocene and 1,1′,2,2′-tetrakis(diphenylphosphanyl)-4,4′-di-*tert*-butylferrocene; Scheme 3] revealed very different geometrical features. As shown by the molecular structures in Figure 1, in the solid state the favored conformation for **15** (Figure 1, left) shows the two chelating pairs of phosphorus atoms that face opposite directions (staggered conformation).

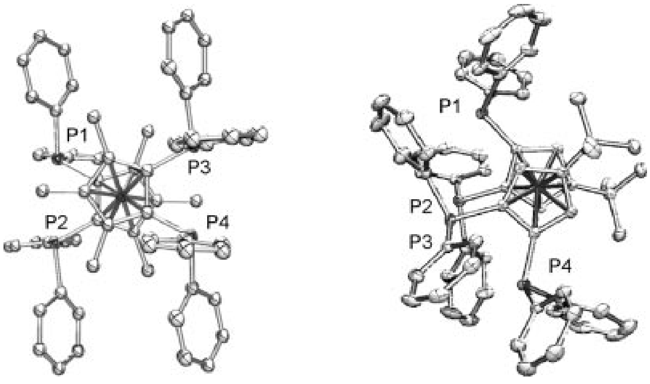


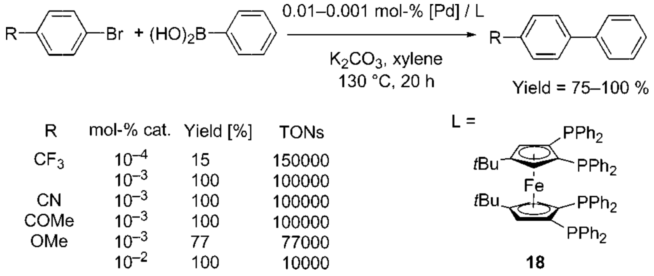
Figure 1. Molecular structures of **15** and **18** from X-ray diffraction studies (Povray illustration).

Conversely, in the favored conformation found for **18** (Figure 1, right) the four phosphorus atoms point towards the same half-space as a result of steric factors attributed to the hindering *tert*-butyl groups; the phenyl groups are also interlocked (P2 and P3 are in the eclipsed conformation).[35] In solution, NMR spectroscopic experiments indicated that the conformation of **18** is restricted, similarly to the solid state, exhibiting an AA′BB′ spin-system pattern. *The cisoid conformation for the tert-butylated tetraphosphane was conserved in solution above 90 °C, as attested by ^{31}P NMR spectroscopy in [D_8]toluene*. Therefore, in the multidentate ferrocenylphosphanes the coordination properties not only depend on the chelating possibilities of phosphorus (1,1′- or 1,2-P bonding) but also on the rotational features of the ferrocenic backbone, a rather unexploited facet prior to these studies.

Suzuki C–C Cross-coupling and Heck Vinylation with a Ferrocenyltetraphosphane

As detailed above, in the last decade much progress in metal-catalyzed cross-coupling reactions was accomplished in the synthesis and recognition of efficient auxiliary ligands. Regarding the organic substrates now, significant advances have been reported on the activation of the relatively inert aryl bromides and chlorides relative to their iodide analogues; indeed, the relative reactivity of the aryl halides is well-established as Ar–I (65 $kcal\,mol^{-1}$ of bond dissociation energies) >> Ar–Br (81 kcal mol^{-1}) > Ar–Cl (96 kcal mol^{-1}).[36] As a consequence, we focused our efforts in the coupling of bromides and chlorides more than iodides. We verified, however, that concerning the coupling of activated or deactivated iodides all the catalytic systems described herein shows an enhancement in the activity of one or two orders of magnitude relative to bromides.

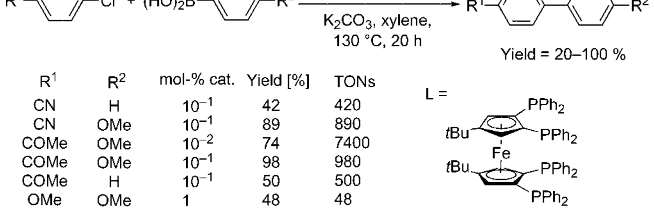
The first reaction we explored under conditions of ultra-low catalyst loading was the arylation of aryl halides with boronic acids (Scheme 6).[37] With the view to deliver more economical catalytic systems, we tested in priority nickel catalysts [$NiCl_2$, $Ni(cod)_2$, cod = 1,5-cyclooctadiene] with multidentate tetraphosphane **18** (Scheme 3), under various conditions, with unsuccessful results. Conversely, the results obtained by employing the system [$Pd(\eta^3\text{-}C_3H_5)Cl]_2$ combined with **18** were very interesting. High reaction rates were obtained with aryl bromides. TONs around 100000 were found for the coupling of phenylboronic acid to the activated 4-bromoacetophenone and 4-cyanobromobenzene (up to 150000 with 4-trifluoromethylbromobenzene) and a very good TON of 77000 was reached with deactivated 4-bromoanisole.



R	mol-% cat.	Yield [%]	TONs
CF$_3$	10^{-4}	15	150000
	10^{-3}	100	100000
CN	10^{-3}	100	100000
COMe	10^{-3}	100	100000
OMe	10^{-3}	77	77000
	10^{-2}	100	10000

Scheme 6.

The coupling of chlorides, although successful for electronically activated substrates, did not allow reach high TONs (Scheme 7); the catalytic activity of the system, nevertheless, compared favorably to the activity of classical ligands such as PPh_3 or dppe [1,2-bis(diphenylphosphanyl)ethane].[37] In the coupling of phenylboronic acid to electronically activated 4-chloroacetophenone, the systems combining [Pd/4 PPh_3] and [Pd/2 dppe] were found useless at low loadings of 0.1 mol-% cat. as less than 2% and only 22% yield, respectively, of the coupling products were obtained in 20 h. The catalyst [Pd/**18**] reached, under these conditions, a TON of 500 (yield 50%).

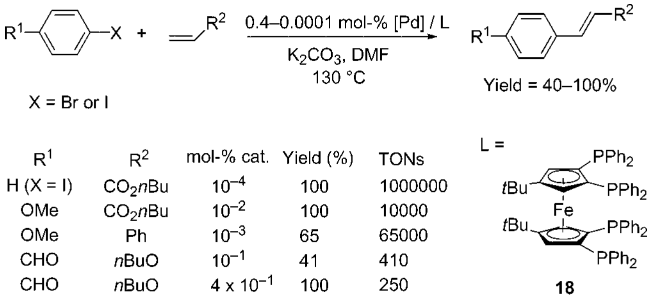


R^1	R^2	mol-% cat.	Yield [%]	TONs
CN	H	10^{-1}	42	420
CN	OMe	10^{-1}	89	890
COMe	OMe	10^{-2}	74	7400
COMe	OMe	10^{-1}	98	980
COMe	H	10^{-1}	50	500
OMe	OMe	1	48	48
OMe	H	1	20	20

Scheme 7.

The highest TON of 7400 was obtained for the coupling of 4-methoxybenzeneboronic acid with 4-chloroacetophenone (yield 74%, 10^{-2} mol-%, 130 °C, 20 h). The substrate 4-cyanochlorobenzene was also efficiently coupled to 4-methoxybenzeneboronic acid with a TON of 890 (yield 89%, 10^{-1} mol-%). Lower TONs were obtained for the couplings with electronically deactivated 4-chloroanisole, showing the limit of the ligand, which remains nevertheless among the most active phosphanes in the class of the ligands incorporating exclusively aryl groups on the phosphorus atom (poor electron donor relative to alkyl substituents).

With the same catalytic system employed for Suzuki coupling, the Heck vinylation of aryl iodides and bromides with *n*-butyl acrylate, styrene, and *n*-butyl vinyl ether were investigated under conditions of very low catalyst loading (Scheme 8).[37] In the coupling of unactivated iodobenzene to *n*-butylacrylate, a very high TON of 1000000 was obtained (yield 100%, 10^{-4} mol-%, 130 °C, 48 h). With electronically deactivated 4-bromoanisole, the coupling to *n*-butyl acrylate and to styrene proceeded with high TONs of 10000 (yield 100%, 10^{-2} mol-%, 130 °C, 48 h) and 65000 (yield 65%, 10^{-3} mol-%, 130 °C, 20 h), respectively. Even the strongly deactivated electron-rich alkene *n*-butyl vinyl ether led to the corresponding adducts in the presence of 0.1 mol-% catalyst with TONs ranging from 250 to 400.



R^1	R^2	mol-% cat.	Yield (%)	TONs
H (X = I)	CO$_2$nBu	10^{-4}	100	1000000
OMe	CO$_2$nBu	10^{-2}	100	10000
OMe	Ph	10^{-3}	65	65000
CHO	nBuO	10^{-1}	41	410
CHO	nBuO	4 x 10^{-1}	100	250

Scheme 8.

The characterization of the complexes involved in the catalytic cycles is important to understand the origin of their activities under conditions of ultra-low catalyst loading. The palladium precatalyst complexes formed under the conditions employed for the Heck and Suzuki reactions in chlorinated solvents (P/Pd = 4) were identified as being ex-

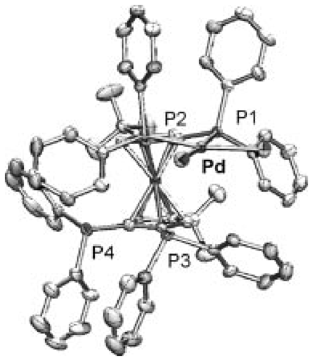


Figure 2. Molecular structure of [$PdCl_2$·**18**] from X-ray diffraction studies.

clusively 1,2-chelating P-bonded either mononuclear ([$PdCl_2$·**18**], see Figure 2, formed in majority above 90%) or dinuclear palladium chloride (<10%).[37]

NMR characterization in solution confirmed the solid-state X-ray analysis of the complexes, and clearly indicated that the phosphorus P3 atom is strongly oriented towards the (P1/Pd/P2) area of coordination (and especially its lone pair of electrons). The fine analysis of the unprecedented "through-space" coupling constants found between the phosphorus atoms was detailed,[38] and a theoretical model was proposed for nuclear spin transmitting.

In the course of the precatalyst characterization studies, an intriguing phenomenon was identified and investigated by variable-temperature ^{31}P NMR spectroscopy.[37] Under the starting conditions used for Heck and Suzuki catalysis (P/Pd = 4) was observed the occurrence of dynamic behavior at the scale rate of NMR spectroscopy. Two signals were detected between 0 and 10 ppm, an unusual range of chemical shift for the $-PPh_2$ groups (A in Figure 3).[39]

We envisioned that the four phosphorus atoms could be alternatively bonded and released from the palladium center, leading to large signals of average chemical shift. Upon cooling, the characteristic behavior of the labile compounds was confirmed with a coalescence and decoalescence (B in Figure 3) of the spin system. The dynamic phenomenon was reversible, and the labile species were stable up to 370 K. At this temperature the biligated mononuclear com-

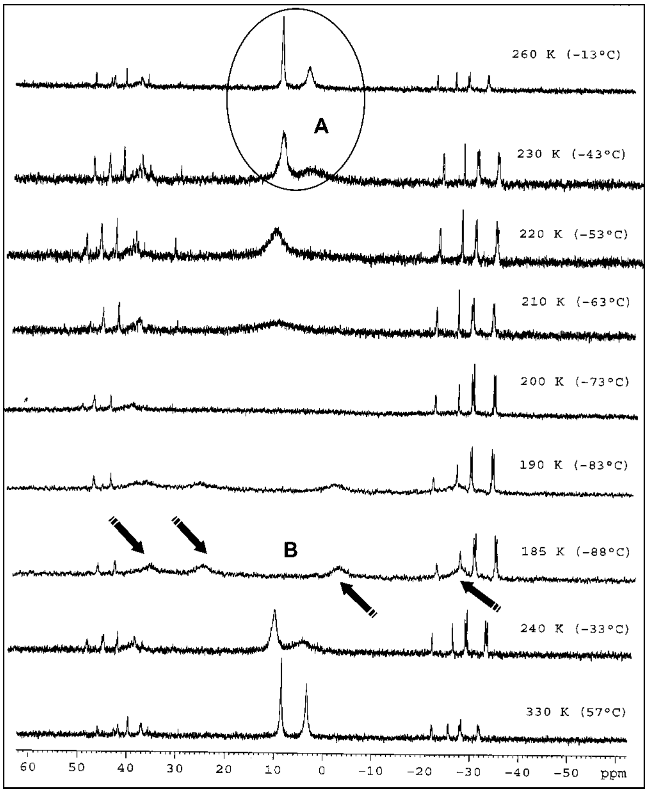
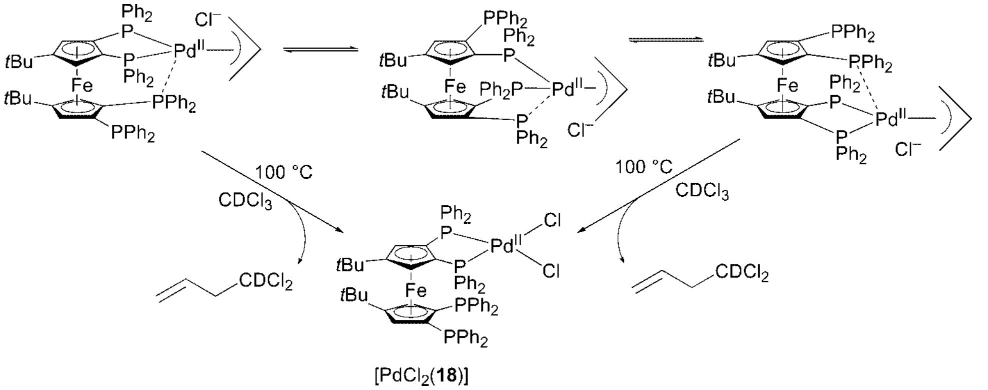
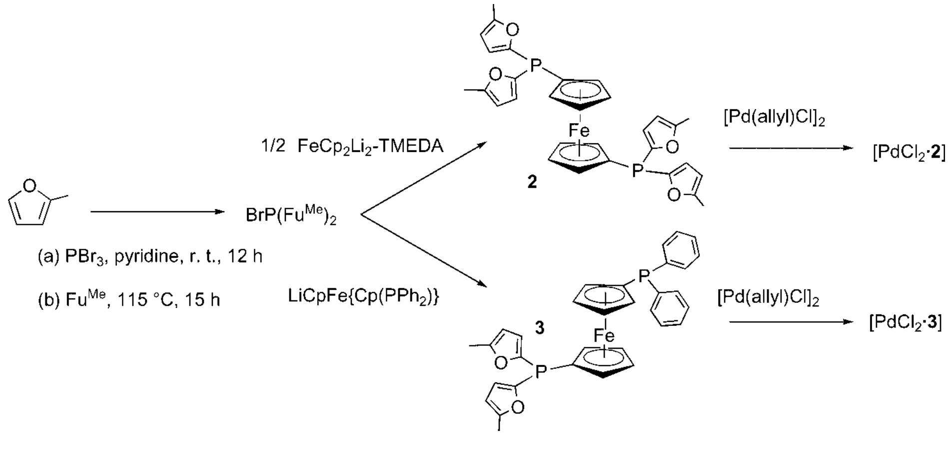


Figure 3. VT ^{31}P NMR spectrum of the [Pd/**18**] (1:1) catalytic system.



Scheme 9.



Scheme 10.

plex [$PdCl_2$·**18**] (Scheme 9) is quantitatively formed. Scheme 10 gives a summarized picture of the observed phenomena, which involves the chlorinated solvent.[37]

The most reasonable explanation, taking into account the ratio P/Pd, is that the palladium center "travels" between the four phosphorus donors at a high exchange rate. This constitutes a unique observation in the chemistry of multidentate compounds and 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. This would statistically decrease de facto the deactivation of catalysts by palladium-black formation. In addition, as postulated by Doucet and Santelli for their tetraphosphane, the "coordination pressure" around the metal center might accelerate some determining steps in cross-couplings such as the reductive elimination.[4] This "active" multidentate behavior would partly explain why, contrary to more fragile systems, polyphosphane ligands can be efficiently combined with palladium in low concentrations such as 10^{-2} to 10^{-4} mol-%.

Performances of a Bulky π-Acidic Ferrocenyldiphosphane in Suzuki and Heck Reactions

As mentioned above, bulky phosphane ligands with high σ-donor abilities emerged as powerful ligands. Their efficiency was initially surprising since strong σ-donor ligands would not be expected to facilitate the transmetalation and reductive elimination steps. These performances revealed the importance of oxidative addition steps, particularly with substrates containing strong carbon–halide bonds. Additionally, the success of bulky phosphanes was suggested to be derived from the ability of these ligands to promote *geometrically driven* coordinative unsaturation and palladium reactivity. These geometric features appear to be important to the transmetalation and reductive elimination steps when utilizing strongly electron-donating ligands. Conversely, high activity in the cross-coupling reactions of aryl bromides and chlorides has been reported in some cases with palladium complexes incorporating various strongly electron-withdrawing phosphite ligands.[40] As a consequence of the complexity in the prediction of a rate-limiting step, it did not appear unreasonable to us to test, in more depth, a range of cross-coupling reactions using a comparatively "forgotten" π-acidic bulky ferrocenylphosphane ligand. We choose to build a weakly σ-donor phosphane on the ferrocenic backbone with phosphorus bearing heterocyclic substituents, which are notably less developed than the corresponding ferrocenyldiphosphanes bearing aryl or alkyl substituents. The new ligand 1,1′-bis[bis(5-methyl-2-furyl)phosphanyl]ferrocene (**2**; Figure 4), is obtained in 80% isolated yield from reaction of lithiated ferrocene with bis(5-methyl-2-furyl)bromophosphane (see below, amination).[41] Ligand **2** was isolated in pure form on a 10-g scale, as a crystalline orange powder, insensitive to air and moisture (Scheme 10).

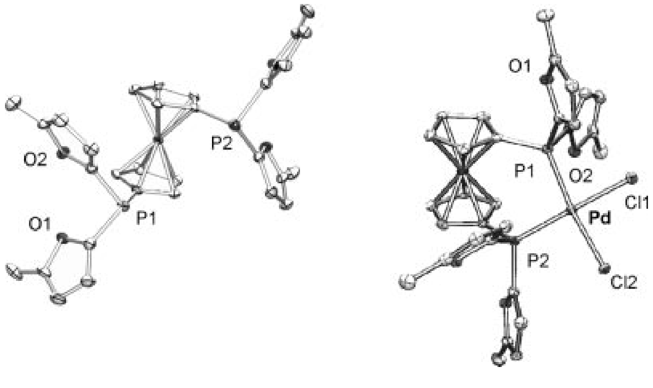
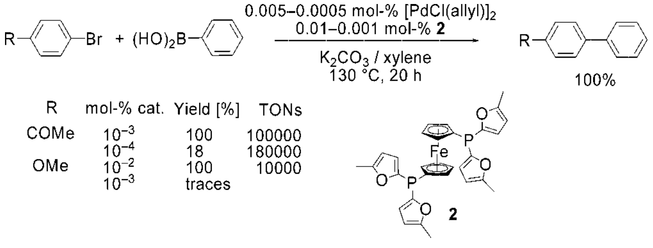


Figure 4. Molecular structures of **2** and [$PdCl_2$·**2**] from X-ray diffraction studies.

Suzuki cross-coupling with the use of activated substrate 4-bromoacetophenone with phenylboronic acid afforded the corresponding product in the presence of the in-situ-formed [$PdCl_2$·**2**] precatalyst and K_2CO_3 (Scheme 11).[41] Surprisingly, regarding the low basicity of phosphorus atoms, a high TON of 100000 with complete conversion was obtained in the presence of 10^{-3} mol-% catalyst: a result equivalent to that obtained with more electron-rich tetraphosphane **18** under identical conditions (Scheme 6). A TON of 180000 was obtained after 20 h (yield 18%, 10^{-4} mol-% cat. at 130 °C). Deactivated and electron-rich 4-bromoanisole gave a complete conversion with a TON of 10000 (10^{-2} mol-% catalyst), but disappointingly a lower concentration did not yield any product. Under identical conditions tetraphosphane **18** facilitated a TON of 77000, in the presence of 10^{-3} mol-% catalyst. The preliminary experiments on the Heck reaction were conducted by using 4-bromoanisole with *n*-butyl acrylate *without* the addition of tetraalkylammonium salts, which are often used to delay palladium black formation. Here, excellent conversions were obtained in the presence of 10^{-2} mol-% catalyst (TON 10000), but again lowering the concentration of one order of magnitude completely inhibited the reaction.



R	mol-% cat.	Yield [%]	TONs
COMe	10^{-3}	100	100000
	10^{-4}	18	180000
OMe	10^{-2}	100	10000
	10^{-3}	traces	

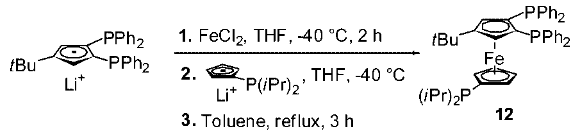
Scheme 11.

Except for the robustness of the ferrocenyl backbone, phosphane ligand **2** is very different from **18**, and obviously in this case no "multidentarity" effect was expected. To the best of our knowledge, only a few reports exist on the use of highly-efficient catalysts incorporating very poor σ-donating phosphane ligands in cross-coupling reactions.[40] One of our goals was to demonstrate the possibility of variation in the phosphorus substituents, and to explore its effects. Subtle changes in the rate-determining step *depending* *on the substrate* are probably at the origin of the results obtained. For more demanding substrates, the oxidative addition is rate-determining (and disfavored by poor σ-donating ligands such **2**). In contrast, for strongly activated substrates (aryl iodides and activated bromides) where the oxidative addition is comparatively facile, the same ligands would multiply the rates of transmetalation and reductive elimination. These results led us to exploit ligand **2** in other reactions for which its π-acidic character would reveal to be more useful (see below, C–N coupling).

Performances of Ferrocenylphosphanes in Sonogashira–Heck Alkynylations

Structural Considerations for Triphosphane Ferrocenic Ligands

We anticipated that "geometrically simpler" ferrocenyl*tri*phosphanes (relative to tetraphosphanes **15** or **18**) might lead, as well, to highly active systems in palladium-catalyzed C–C coupling. We developed therefore a methodology for the preparation of dissymmetric achiral trisubstituted ferrocenes (**11**–**14**; Scheme 3) from two different Cp salts: the process is efficient and complete in two simple steps.[42,43] With the view to additionally improve the performance of a ligand, we chose to electronically enrich one of the phosphorus atoms and to provide the ferrocenyl backbone with better flexibility by unblocked axial rotation. This strategy prompted us to design and synthesize ferrocenyl aryl/alkyl triphosphane **12**, 1,2-bis(diphenylphosphanyl)-1′-(diisopropylphosphanyl)-4-*tert*-butylferrocene (Scheme 12).



Scheme 12.

The X-ray structural characterization (Figure 5) and the solution NMR spectroscopic study revealed that,[42] as expected, the rotational flexibility of **12** was greater than that of the tetraphosphane parents; in the preferred conformation the three phosphorus atoms are not pointing in the same direction. The palladium coordination complexes were found to be preferentially 1,2-P bonded.

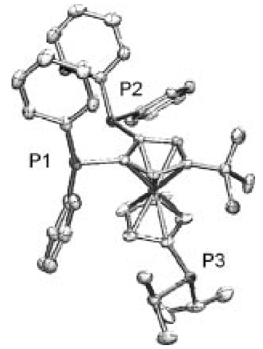
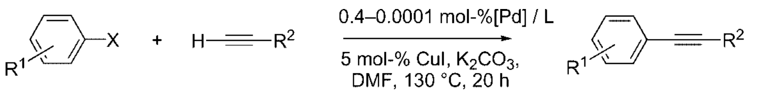


Figure 5. Molecular structure of **12** from X-ray diffraction studies.

Similar to its parent ligands, **12** is stored under air without any precaution and appeared insensitive to moisture and elevated temperatures in solution [the P(*i*Pr)$_2$ atom is not sensitive to oxidation].

Alkynylations with a Ferrocenyltriphosphane

The examination of Suzuki cross-coupling reactions with the use of **12** was not as promising as we expected. For instance, a TON of only 10000 was obtained in the coupling of electron-poor 4-bromoacetophenone with phenylboronic acid, whereas tetraphosphane **18** gave a TON of 77000 under similar conditions (Scheme 6). We then tested the performances of the triphosphane in the more demanding reaction of aryl alkynylation in the presence of palladium and copper (Sonogashira cross-coupling).[44] The scope and



X	R^1	R^2	mol-% cat.	Yield (%)	TONs
I	H	Ph	10^{-3}	95	95000
Br	4-COMe	Ph	10^{-4}	25	250000
			10^{-3}	94	94000
Br	4-CN	Ph	10^{-3}	46	46000
			10^{-2}	89	8900
Br	4-F	Ph	10^{-3}	20	20000
			10^{-2}	95	9500
Br	2-CF$_3$	Ph	10^{-2}	93	9300
9-bromoanthracene		Ph	10^{-1}	90	900
Br	4-OMe	Ph	10^{-1}	52	520
			4×10^{-1}	93	230
Cl	4-CN	Ph	10^{-1}	54	540*
			4×10^{-1}	86	215*
Cl	4-COMe	Ph	4×10^{-1}	82	205*

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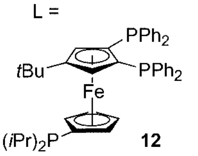


R^1	R^2	mol-% cat.	Yield (%)	TON
COMe	nC$_8$H$_{17}$	4×10^{-1}	62	620
COMe	CH$_2$OH	4×10^{-1}	46	460
COMe	CH$_2$OH	4×10^{-1}	92	230

(X = Br)

* Reactions performed without CuI (Heck conditions)

Scheme 13.

limitations of tridentate ferrocenylphosphane ligand **12** for the alkynylation of a variety of aryl bromides with alkynes is described in Scheme 13.

A very high TON of 95000 was obtained for the reaction of iodobenzene with phenylacetylene (yield 95%, 10^{-3} mol-% cat.).[44] In the presence of activating groups on the aryl bromide, high reaction rates were observed as well: the coupling of 4-bromoacetophenone, 4-bromobenzonitrile, and 4-fluorobromobenzene with phenylacetylene in the presence of 10^{-3} to 10^{-4} mol-% of [Pd/**12**] led to the coupling products in 94 to 20% yields (the highest TONs obtained were of 250000, 46000, and 20000, respectively). We determined the influence on the reaction of the presence of *ortho* substituents on the aryl bromide: with electronically activated 2-trifluoromethylbromobenzene: a good TON of 9300 was obtained with high conversion (yield 93%, 10^{-2} mol-% cat.). A lower TON of 900 was observed by using sterically congested 9-bromoanthracene (yield 90%, 10^{-1} mol-% cat.). The quantitative conversion of strongly deactivated 4-bromoanisole required a higher catalyst loading (0.4 mol-% cat.), consequently lower TONs of 230 to 520 were obtained. We also performed a few reactions with activated aryl chlorides such as 4-chlorobenzonitrile and 4-chloroacetophenone that were also converted in excellent yields with *less than 1 mol-%* of catalyst and in the absence of copper iodide (TONs of 540 and 205, respectively).[44] Finally, we extended the scope of the catalytic reaction to other alkynes such as dec-1-yne and but-1-yn-4-ol. With these alkynes, TONs of 620 and 460, respectively, were obtained with 4-bromoacetophenone. Consequently, this novel mixed ferrocenyl aryl/alkyl triphosphane was found thermally stable, insensitive to air and moisture, and its robustness allowed aryl alkynylation at 10^{-1} to 10^{-4} mol-% catalysts loading with iodides, bromides, and activated chlorides. Copper-free coupling with the use of phenylacetylene was also accessible in good yield. In the case of this ligand we must underline that no evidence of multidentarity (such as observed for **18**) was collected to date; nevertheless, only few multidentate ligands (tri-, tetradentate or more) have been tested for Sonogashira–Heck-type alkynylations. This is all the more surprising that, most of the time, threefold or more excess of monodentate ligands are used under the reported conditions. The emerging chemistry of multidentate ligands could be of high interest in the future development of catalyzed cross-coupling alkynylations.

Performances of a Bulky π-Acidic Ferrocenyldiphosphane in Sonogashira Alkynylation

To our surprise, the system based on diphosphane ligand **2** also efficiently catalyzed the arylation of phenylacetylene with activated and deactivated substrates.[41] By using 4-bromoacetophenone in the presence of 10^{-4} mol-% catalyst a TON of 920000 *among the highest reported* with bromides was obtained. 4-Bromoanisole was quantitatively converted with a lower TON of 1000, consistently with the results observed in Suzuki/Heck reactions.[41] We found in parallel that **2** could be also a useful ligand under mild reaction conditions in allylic amination reactions (see below).

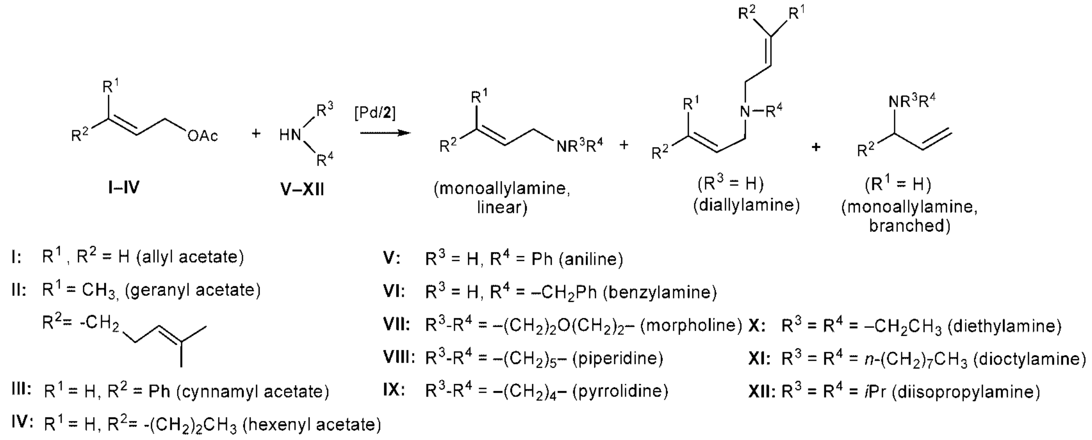
Performances of Ferrocenylphosphanes in Allylic Amination Reactions

Allylic Amination from Allylacetates with π-Acidic Ferrocenyldiphosphanes

Palladium-catalyzed amination of allyl acetates is recognized as being a powerful tool to form allylamine blocks. To test more efficient catalytic systems in terms of atom economy we employed the 1,1′-bis[bis(5-methyl-2-furyl)-phosphanyl]ferrocene (**2**) ligand in this reaction as well as related dissymmetric compound **3** (Scheme 10) and their coordination complexes.[45,46] Nucleophilic amination of allylic acetate was performed at r.t. with unprecedented turnover frequencies (Scheme 14, Table 2).

As seen in Table 2 (Entries 1–5): in the presence of 10^{-2} mol-% catalyst [Pd/**2**] the coupling of aniline to allyl acetate occurred at a high TOF of 10000 h^{-1} with complete conversion and 96% selectivity in monoallylamine; under identical conditions of temperature and concentration, 60% conversion was obtained after 40 h with the more electron-rich parent ligand 1,1′-bis[diphenylphosphanyl]ferrocene (150 h^{-1} TOF), the monophosphanes PPh_3 and PCy_3 were ineffective. Excellent conversions of 98 to 100% were achieved from the cyclic secondary amines pyrrolidine (TOF 4900 h^{-1}) and piperidine (TOF 5000 h^{-1}). Only a slightly decreased 85% conversion was obtained with less nucleophilic cyclic morpholine (TOF 4250 h^{-1}). The coupling of the primary amine benzylamine appeared more difficult and less selective (TOF 1825 h^{-1} for a 75% selectivity in monoallylation product). In addition to primary amines and cyclic secondary amines, more delicate aliphatic secondary amines were efficiently coupled (Table 2, Entries 6–8). Complete conversion of the sterically demanding diisopropylamine was obtained at 80 °C in the presence of 0.1 mol-% catalyst in 2 h (TOF 480 h^{-1}) and of the long alkyl chain bearing dioctylamine at r.t. after 20 h (best TOF 225 h^{-1}). These good results prompted us to investigate the allylic amination reaction employing a much more demanding substrate, the monoterpene derivative geranyl acetate (Table 2, Entries 9–11). At r.t., 75% conversion in geranylaniline was obtained after 20 h with total selectivity. Morpholine reacted with geranyl acetate in the presence of 1 mol-% catalyst to give a 60% conversion in 1 h at r.t. and 98% after 20 h. A TOF of 333 h^{-1} was obtained at 80 °C with 98% of geranylamine formed in 3 h.

This catalytic system was also found to be remarkably active and selective for the amination of substituted allylic acetates. The coupling reaction to amines of 3-phenylallyl acetate (Table 2, Entries 12–17) and (*E*)-hex-2-en-1-yl acetate (Table 2, Entries 18–22) was carried out at 0.1 and 0.01 mol-% [Pd/**2**]. 3-Phenylallyl acetate reacted with diethylamine, pyrrolidine, or morpholine to give complete con-



Scheme 14.

Table 2. Allylic amination from acetates with [Pd/**2**].

Entry	Acetate/Amine	mol-% of catalyst	Yield [%]	Selectivity [%][a]	TON	TOF [h^{-1}]
1	**I/V**	10^{-2}	100	96/4 (mono/di)	10000	10000
2	**I/IX**	10^{-2}	98	100	9800	4900
3	**I/VIII**	10^{-2}	100	100	10000	5000
4	**I/VII**	10^{-2}	85	100	8500	4250
5	**I/VI**	10^{-2}	73	75/25 (mono/di)	7300	1825
6	**I/XII**	10^{-1}	96	100	960	480
7	**I/XI**	10^{-1}	100	100	1000	50
8	**I/XI**	10^{-2}	45	100	4500	225
9	**II/V**	1	75	100	75	4
10	**II/VII**	1	60	100	60	60
11	**II/VII**	10^{-1}	100	98	1000	333
12	**III/X**	10^{-1}	100	94:6 (lin/brch)	1000	50
13	**III/X**	10^{-2}	76	94:6 (lin/brch)	7600	380
14	**III/IX**	10^{-1}	100	94:6 (lin/brch)	1000	50
15	**III/IX**	10^{-2}	26	94:6 (lin/brch)	2600	130
16	**III/VII**	10^{-1}	100	93:7 (lin/brch)	1000	50
17	**III/VII**	10^{-2}	48	93:7 (lin/brch)	4800	240
18	**IV/X**	4×10^{-1}	100	99:1 (lin/brch)	250	12
19	**IV/X**	10^{-1}	76	99:1 (lin/brch)	760	38
20	**IV/IX**	10^{-1}	100	94:6 (lin/brch)	1000	50
21	**IV/VII**	10^{-1}	98	94:6 (lin/brch)	980	49
22	**IV/XI**	4×10^{-1}	59	100	245	12

[a] Total selectivity is always in linear monoallylamine (mono = linear monoallylamine, di = diallylamine, lin = linear isomer, brch = branched isomer).

version with 0.1 mol-% catalyst. Lowering the catalyst loading to 0.01 mol-% resulted in TONs of 7600, 2600, and 4800, respectively. In each case, good regioselectivity was observed for the linear product (93–94%) The selectivity was found to be higher in linear monoallylamine for the coupling of $HNEt_2$ to (*E*)-hex-2-en-1-yl acetate (99%). Coupling reactions with cyclic secondary amines proceeded in more than 90% yield by employing 0.1 mol-% catalyst (94% selectivity in linear product). Only in the course of the addition of dioctylamine were lower TONs and TOFs observed because 0.4 mol-% catalyst was required to reach 60% conversion in 20 h at 50 °C. The results obtained are certainly due to an accelerating effect on the nucleophilic substitution induced by the electron-withdrawing furyl groups on the phosphorus atoms of the ligands; we have provided a more detailed discussion on this topic.[41] The performance of the [Pd/**3**] system was found to be similar or slightly inferior to that of [Pd/**2**].[45] Finally, we have recently shown that multidentate ferrocenylphosphanes can also be useful in allylic substitution reactions.[47]

Trends and Perspectives in Rationally Designed Ferrocenylpolyphosphane Ligands for Low Loading Catalysis

The ferrocenylphosphane species we developed present several features that are profitable to the rational design of a large number of new metalloligands. Figure 6 summarizes some of these useful points to produce adaptable systems of high-efficiency in catalytic reactions. We briefly discuss the expected effects on catalysis of the possible structural modifications (a more detailed discussion on ferrocenylpolyphosphane structural effects in catalysis was reported else-

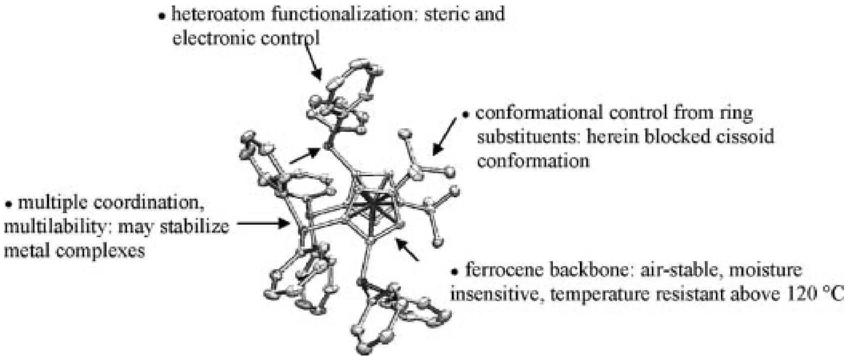


Figure 6. General features of adaptable ferrocenylphosphane ligands for high-performance catalytic reactions.

where[48]): (1) The first advantage in catalysis of these ferrocenylphosphane ligands is the robustness of the ferrocenyl backbone, which allows their handling and storage under air for years without any particular precaution. Non-glovebox conditions and temperatures above 120 °C can be used in long-term reactions without deactivation. (2) The advantage of having three or more phosphanyl groups on the ferrocene backbone is an important question. First from a practical point of view, a recent review of the use of dppf and derivatives showed that, up to now, no results matching the ultra-low loading catalysis presented herein were obtained with these diphosphanes.[48] Several reported studies from our group and others,[30–32,37,45] clearly established that classical ligands [such as PPh_3, dppe, dppb = 1,2-bis(diphenylphosphanyl)butane, or dppf] led to less stable catalytic systems under the conditions of low catalyst concentrations that we investigated. The ligand behavior of tetradentate phosphane **18** is expected to furnish to the Pd^0 species multiple coordination, as described above for Pd^{II}, which stabilizes the catalytic systems and therefore leads to efficient catalysis in the presence of only low loadings of the precious metal. More positions for substitution on phosphorus (or other donor atoms) are available on the ferrocenyl backbone. Therefore, polyphosphanes of higher-rank such as penta- or hexaphosphanes (or more) should be reachable. We believe that such a kind of "*enhanced multidentarity*" would permit one to pursue the effort for stabilizing catalytic systems, and promoting their longevity under ultra-low concentrations. (3) The substituents on the cyclopentadienyl rings allow the conformation of the ferrocene to be controlled, and therefore can induce a more-or-less important rigidity to the ligand as a function of their hindrance. Therefore, when a specific conformation is required, such as the orientation of several donor atoms in the same direction of space (this was shown with phosphorus atoms, but it could probably be extended to other donors, such as nitrogen atoms, etc.) very hindering substrates such as *tert*-butyl groups could be used. We envision the use of more hindered substituents (such as trityl groups, CPh_3) with the view to determine their influence on the conformation. Additionally, positive or negative electronic effects can be expected, as well, from the noncoordinating substituents on the Cp rings and should be worthy of further investigations. (4) We showed that the substituents on the phosphorus atoms can be modified to either more electron-donating (e.g. *i*Pr) or more electron-withdrawing groups (e.g. furyl), or to have increased bulkiness. This is a very important point as the use of modified ligands containing either electron-rich PCy_2 or $P\mathit{t}Bu_2$ moieties are well-known for having induced impressive results in cross-coupling reactions (by facilitating the oxidative addition step of the catalytic cycles, see first section).

Following these trends, a number of new ligands are currently being developed in our laboratory, that incorporate other substituents on the Cp ring and on phosphorus atoms, as well as unique conformations: their features and performances are under investigation and will be reported in due time.

Conclusions

Multidentate[49] ferrocenylphosphane ligands offer some of the highest TONs observed in Heck, Suzuki, and Sonogashira cross-coupling reactions. Demanding substrates such as aryl bromides and activated aryl chlorides were coupled with fairly good to excellent TONs from different ferrocenylpolyphosphane auxiliaries. In the achiral version of the palladium-catalyzed allylic acetate amination reaction, the modification of dppf with π-acidic furyl heterocycles provided ferrocenyldiphosphane catalysts for which high TONs were obtained together with several of the best TOFs reported to date. To obtain high TONs (>10000), relatively elevated reaction temperatures are often required for cross-coupling; under these conditions, the use of ferrocenylphosphane ligands certainly help to stabilize the catalytic species. In addition, these ligands with regard to their bulkiness would also have a positive influence as accelerators in the reductive elimination step of the cross-coupling catalytic cycle by inducing steric pressure on the active palladium center. Further mechanistic studies are absolutely necessary and in the future will certainly provide keys for the development of multidentate ligands resource-economic catalysts.

Acknowledgments

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[1] For instance, in Europe the COST program **2003–2006** "*Sustainable Chemical Processes: Stereoselective Transition Metal-Catalyzed Reaction"*, in the USA, the ACS-Green Chemistry Institute PRF programs, and since 2007, from the French Government, the ANR program "*Chemistry and Processes for Sustainable Development"*.

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[6] The palladium cost was stated at 350 USD/Oz (9500 €/kg) on the New York market SE, 03/19/2007.

[7] TON defined herein as the ratio [substrate on catalyst] multiplied by the yield of conversion in the desired product (i.e. 1 for a 100% yield), that corresponds to the value (mol product per mol catalyst).

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