Modular Functionalized Polyphosphines for Supported Materials: Previously Unobserved 31P-NMR « Through-Space » ABCD Spin Systems and Heterogeneous Palladium-Catalysed C–C and C–H Arylation

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Modular Functionalized Polyphosphines for Supported Materials: Previously Unobserved ^{31}P-NMR « Through-Space » ABCD Spin Systems and Heterogeneous Palladium-Catalysed C–C and C–H Arylation

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The modular design of polyphosphines, diversely functionalized for facile immobilization on virtually any kind
10 **of support is reported. Previously unobserved ABCD ^{31}P NMR spin-spin systems evidence the control exercised on the polyphosphines conformation. We illustrate the catalytic performance at low Pd loading of the recyclable immobilized polyphosphines in C–C bond formation reactions.**

15 The separation and recycling of molecular catalysts from reactions is a scientific challenge with environmental and economic implications.[1,2] In this respect, many techniques have been developed aimed at the immobilization of catalytic systems with the use of different solid supports,[3,4] and the development of
20 multiphasic reaction conditions.[5] Among the auxiliaries of easy access and industrial scale interest, supported phosphine ligands are currently used in transition-metal catalysis,[6] and some simple examples are commercially available, such as triphenylphosphine polystyrene (PS-PPh₃). Whatever the nature of the support, the
25 unavoidable high dispersion of the coordinating sites on the support associated to monophosphines renders it improbable for multiple remote donors to coordinate the same metal center. This is detrimental in terms of catalyst stability, an important parameter for industry. Polyphosphines form thermally and
30 kinetically more stable complexes with metal catalysts than monodentate ones, but they have been scarcely proposed for attachment to solid supports. Pioneering investigations have been limited to functionalization of the tripodal triphosphine 1,1,1-tris[(diphenylphosphino)methyl]ethane,[7-10] in spite of the wide
35 variety of linear, tripodal and other branched polydentate phosphines available.[11] Additionally, to the best of our knowledge no tetraphosphine has ever been immobilized on a support.

We provide herein a general synthetic pathway for assembling
40 a new class of branched tri- and tetraphosphine ligands having a controlled rigid conformation. These species are diversely functionalized for easy immobilization on any kind of support. As demonstrated by ^{31}P NMR and the strong « through-space » spin-spin [TS]J_{PP} coupling observed, these modified polyphosphines
45 induce, when immobilized on a support, a high local concentration of phosphorus donors spatially very close to each other. Accordingly, these functionalized ligands have been supported on polystyrene, providing easy access to either soluble or insoluble materials. These modular functionalized
50 polyphosphines were also used for the controlled implantation of donors onto commercial silica. We preliminary report on catalytic performance at 0.05-0.5 mol% palladium low loading of these unique supported polyphosphines and their recyclability. Heterogeneous direct C–H functionalization of heteroaromatics
55 with demanding chloroarene substrates was also successfully achieved at palladium low-loading, proving the high stability of the catalysts.

We recently disclosed that the ferrocene platform polyfunctionalized with three or four phosphorus atoms (Scheme
60 1) give access to molecular palladium homogeneous catalysts with excellent performance in topical direct C–H functionalization,[12] as well as C–C,[13] C–N,[14] and C–O[15] cross-couplings.
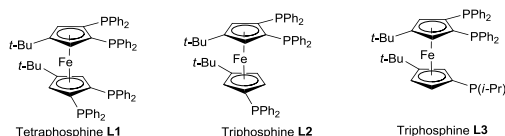
65 **Scheme 1** Ferrocenyl polyphosphines of controlled conformation.

The lack of supported polyphosphines reported in the literature may be attributed to the challenging requirements for the selective and efficient functionalization of the backbone of such sophisticated ligands. The introduction of phosphino groups at an
70 early stage of the design sequence renders subsequent modifications much more difficult. Protection and deprotection procedures for phosphorus donors may be necessary, and the loss of phosphine during the overall process may be considerable. We became interested in the challenge of providing a general access
75 to supported tri- and tetraphosphine ligands of controlled conformation inspired by **L1-L3** (Scheme 1). In order to achieve its anchorage on a solid support, the tetraphosphine ligand **L1** needs to be modified by the introduction of a reactive handle. This point of attachment should preferably be positioned far
80 enough away from the four phosphino groups to keep the active catalytic site uncluttered. The steric hindrance induced by the two bulky *tert*-butyl groups in **L1-L3** was essential to be reproduced to keep the specific cisoid conformation of P-atoms. Considering these prerequisites, we successfully devised a synthetic pathway
85 to generate the tetraphosphine derivative **1** (Scheme 2). Compound **1** possesses a carbonyl group that could be readily utilized and modified to achieve attachment of the tetraphosphine motif to a large variety of supports. Ketal-protected tetraphosphine **7** is indefinitely air-stable in solid-state and

solution.
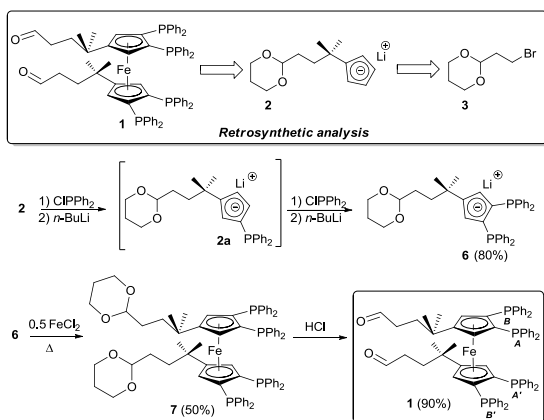
Scheme 2 Modular synthesis of reactive tetraphosphine **1**.

⁵ ³¹P solution NMR of the functionalized polyphosphines **7** and **1** confirmed the success of our strategy in achieving the desired cisoid conformation of ferrocenylphosphine by control with *gem*-dimethyl groups. Typical AA'BB' spin system signatures, which highlights the mutual proximity of the phosphorus atoms in **L1**,[16a] ¹⁰ was obtained for both functionalized polyphosphines. The existence of a strong « through-space » coupling $^{TS}J_{AA'}$ (64.3 Hz for **7**, 61.0 Hz for **1**) between internal heteroannular P-atoms arises from phosphorus lone pairs overlapping.[16] Such spin couplings dramatically depend on the spatial proximity of the ¹⁵ concerned atoms, and thus attest for the ligand conformation in solution. This was confirmed in the solid state by an X-ray diffraction structure of the acetal-functionalized polyphosphine **7** (see SI). Tetraphosphine **1** was then modified in single-step reactions to give the new functionalized polyphosphines **8-11** ²⁰ (Scheme 3). The carbonyl derivative **1** can be grafted directly on preformed Merrifield-type resins. Styrenyl moieties (**9**,**10**) allow for processing tetraphosphine immobilization by co-polymerization with styrene, and alkyltriethoxysilane (**11** from **8**) allow anchoring of the ligand on inorganic supports like silica.
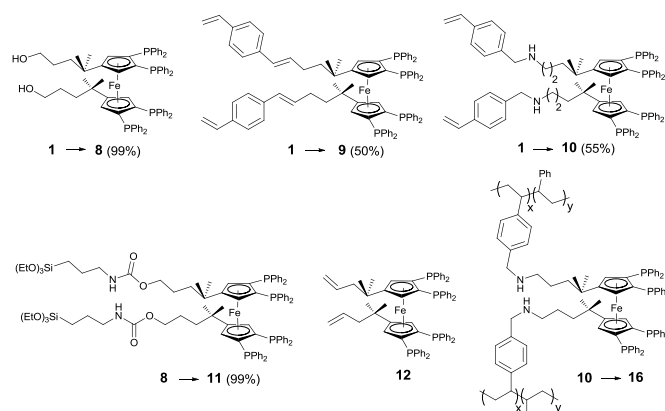
²⁵ **Scheme 3** Functionalized tetraphosphines accessible from **1**.

To further demonstrate the versatility of the method, following an analogous modular retrosynthetic approach by using 6,6-dimethylfulvene with allylmagnesium chloride, we synthesized ³⁰ vinyl-functionalized ferrocenyl tetraphosphine **12** (Scheme 3). In **12** the new vinyl functional group (FG) is in γ-position, closer to the Cp ring. An X-ray structure confirmed the conformation

control (see SI). Additionally, with the view to increase the flexibility of the anchoring upon immobilization the ³⁵ monofunctionalized analogues **13-15** (Scheme 4) of the difunctionalized tetraphosphines were also synthesized.
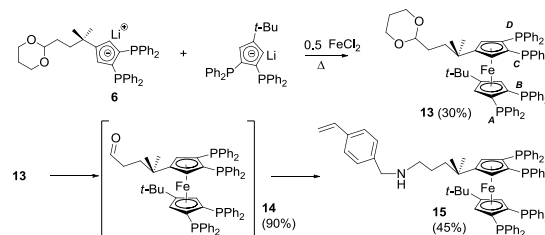
Scheme 4 Synthesis of the monofunctionalized tetraphosphines **13-15**.

⁴⁰ Again the ³¹P spin systems found for **13-15** support a cisoid conformation for the ferrocene backbone. However, they do not resemble the AA'BB' spin systems of tetraphosphines **1**, and **7-12**. Indeed, due to the dissymmetric nature of **13-15** the spin systems obtained show an additional complexity illustrated by ⁴⁵ unprecedented intricate ³¹P-NMR ABCD patterns (Scheme 5 top). The simulation of these second order spectrum allowed us to determine the ³¹P NMR chemical shifts and coupling constants, as is exemplified for **13** (Scheme 5, bottom). Thus, four different but proximate chemical shifts are obtained for the anisochronous ⁵⁰ phosphino groups. $^3J_{AB}$, $^3J_{CD}$ and $^{TS}J_{BC}$ were obtained which are consistent with the values obtained for $^{TS}J_{AA}$ and $^3J_{AB} = ^3J_{A'B'}$ in the symmetrical ferrocenylphosphine analogues;[16a] this ascertain the controlled conformation of the monofunctionalized tetraphosphines. The importance of such nonbonded spin-spin ⁵⁵ couplings for structural determination has been reviewed recently,[17] and these unedited examples supplement this fundamental topic.[18]
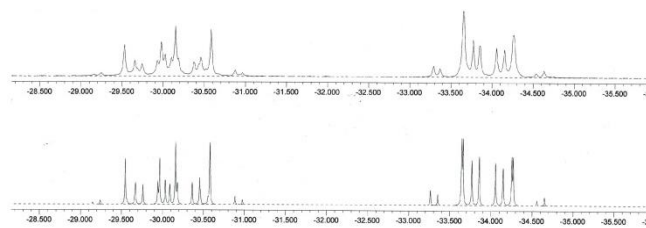

Scheme 5 ³¹P NMR of the ABCD spin system for tetraphosphine **13**: ⁶⁰ experimental (top) and simulated spectra (bottom); δ for **13** (ppm, ±0.1 ppm) and *J* constants (Hz, ±0.6 Hz): $\delta_A = -33.9$, $\delta_B = -29.9$, $\delta_C = -30.3$, $\delta_D = -34.0$, $J_{AB} = 73.3$, $J_{BC} = 61.6$, $J_{CD} = 74.2$ (see attribution in Scheme 4). All other *J* coupling constants involved in the ABCD ³¹P spin system have null values.

⁶⁵

Styrenyl tetraphosphine **10** formed with styrene either soluble or insoluble (cross-linked) supported polyphosphine. The radical polymerization of **10** with styrene and AIBN initiator in toluene at 85 °C for 48 h afforded, after removal of the solvent, ⁷⁰ compound **16** (Scheme 3) as the first non-cross linked polystyrene-supported tetraphosphine. This orange polymer is soluble in the most common organic solvents except for methanol and hexane. The elemental analysis of **16** indicated a phosphorus loading of 1.05% (0.34 mmol g⁻¹), and ³¹P NMR in CD_2Cl_2 ⁷⁵ showed two broad signals centered at –30.0 and –34.0 ppm. These chemical shifts are fully consistent with those of the non-supported parent ligand, attesting to the non-oxidized state of the phosphorus atoms. The presence of two signals evidenced in the supported ligand a differentiation between *internal* and ⁸⁰ *peripheral* phosphorus atoms. Gratifyingly, this confirmed the

expected conservation of the specific cisoid conformation of the tetraphosphine in the polymer. This controlled conformation for supported phosphines provides a localized high density of four proximate phosphorus atoms in the polymeric material designed.

Tetraphosphine **11** was immobilized on silica-gel (0.035-0.070 mm, 60 Å) to give brown-red beads powder (**11-SiO₂**, 0.84% P), which were found insoluble in all the solvents tested. The corresponding solid-state ^{31}P NMR CP-MAS spectrum indicated a broad singlet centered at –30 ppm. Our immobilization strategies were thus validated through these two examples.

We further proved our general solution for localized high density of phosphorus donors by using functionalized cyclopentadienyl **6** salt to design dissymmetric modified-triphosphines "ready for immobilization", in which the nature of the substituents on phosphino groups may differ (Scheme 6).
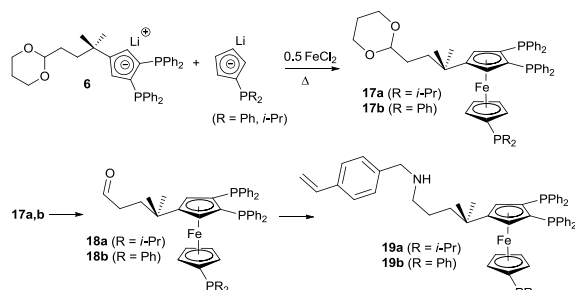
Scheme 6 Modular synthesis of functionalized triphosphines **17a,b-19a,b**.

The characterization of functionalized ligands **17**-**19** demonstrated the success of these syntheses, with typical chemical shift for the phosphorus atoms, as well as the signature of the FGs. Functionalized triphosphine **19a** was then immobilized by radical co-polymerization with styrene (60 equiv) and divinyl benzene (7 equiv) to give an insoluble resin **19a-PS** having a 1.05% content of phosphorus. The strategy we established is thus applicable to the entire class of triphosphine ligands we have developed in recent years.[12-14] Our protected cyclopentadienyl fragments (**2**, **2a**, **6**) may also be of synthetic utility to form other supported metallocenes such as titanocenes,[19] zirconocenes,[20,21] lanthanocenes,[22] *etc*.

We next conducted preliminary investigations of the performance of our set of immobilized polyphosphine ligands (**16**, **11-SiO₂**, **19a-Ps**) as catalytic materials, *in palladium-catalyzed reactions for which the homogeneous counterparts have been notably efficient at low catalyst loading* (Table 1).[12,13,23] The commercial immobilized phosphines (triphenylphosphine-polystyrene PS-PPh₃, and diphenylphosphinomethyl-polystyrene PS-CH₂PPh₂) *used at 0.05-0.5 mol%* with Pd for the reactions presented in Table 1 were totally inefficient – in agreement with the lack of reactivity observed for their homogeneous counterparts.[12,13]

The cross-coupling of phenylboronic acid with bromobenzenes was efficiently achieved by using [Pd/**16**] at 0.05-0.5 mol% (50-80%). The silica-supported system [Pd/**11-SiO₂**] achieved even better performance with yields above 80% for the coupling of unactivated 4-bromoanisole to phenyl boronic acid. While the high robustness of the polyphosphane-based heterogeneous catalysts and their stability was demonstrated, in general, efficient recycling of the catalysts after six runs has not been established, this is mainly due to accumulative loss of material during filtration. For the insoluble catalysts used at 0.5 mol%, ICP-AES analysis of the filtrate indicated no significant leaching (<10 ppm, less than 0.1 % of the initial Pd loading). Accordingly, the hot filtration test showed the termination of the cross-coupling

reactions by use of the filtrate recharged with reagents and bases. The resulting cumulative TONs (270-1700) of the catalysts compares favorably to their homogeneous counterparts.

The supported triphosphine **19a-PS** was investigated in the coupling of chloroarenes to furane, thiophene, and pyrrole substrates by direct *C2* C–H functionalization. These reactions were inspired by the performance of the ferrocenyltriphosphines reported in these relevant reactions that eliminate the need for pre-functionalization of substrates for coupling.[12]

Table 1 C–C bond formation from aryl halides and nucleophiles with immobilized polyphosphine catalysts.^{a}

Catalyst %	halide	nucleo-phile	product	yield % (run)	TONs
0.5 mol% [Pd/**16**]	PhBr	PhB(OH)₂		80(1) 77(2) 82(3) 75(4) 72(5) 68(6)	908
0.5 mol% [Pd/**16**]	OMe–Br	PhB(OH)₂	OMe	50(1) 49(2) 37(3)	272
0.05 mol% [Pd/**16**]	COMe–Br	PhB(OH)₂	COMe	65	1300
0.05 mol% [Pd/**11-SiO₂**]	COMe–Br	PhB(OH)₂	COMe	85	1700
0.5 mol% [Pd/**11-SiO₂**]	OMe–Br	PhB(OH)₂	OMe	85(1) 87(2) 83(3)	510
0.5 mol% [Pd/**19a-PS**]	CN–Cl	*n*-Bu furan	NC– *n*-Bu	68^b	136
0.5 mol% [Pd/**19a-PS**]	NO₂–Cl	*n*-Bu thiophene	O₂N– *n*-Bu	49^b	98
0.5 mol% [Pd/**19a-PS**]	CHO–Cl	Me-N pyrrole	Me	23^b	46

^{a} Conditions: [PdCl(η³-C₃H₅)]₂, 120 °C, DMF, 20 h. ^{b}Pd(OAc)₂, 150 °C for 40 h in *N,N*-dimethylacetamide, 2 equiv of tetra-*n*-butylammonium, GC and NMR yields are average value of two or more runs.

We were glad to observe that these direct arylation reactions of heteroaromatics, which are typically promoted by triphosphines under homogeneous conditions, were also achievable under heterogeneous conditions. The arylation of 2-*n*-butylfurane with 4-chlorobenzonitrile (68%) and the coupling of 2-*n*-butylthiophene to 4-chloronitrobenzene (49%) were achieved more efficiently than the C2 arylation of 1-methyl-2-formylpyrrole with 4-chlorobenzaldehyde (23%). All these coupling tolerate the functionalization of the chloroarene and heteroaromatic substrates, and represent promising results towards difficult C–H functionalization with demanding chloroarenes under "greener" heterogeneous conditions.

In summary, we have delivered a general strategy for synthesizing localized high density of donor atoms on a support. This may be additionally useful for organophosphorus catalysis,[24] and general surfaces modification.[25] Heterogeneous functional systems based on metal complexes with coordinating ligands have also been constructed for applications as photosensitizers

and for solar energy conversion.[4a] Accordingly, we introduced the conceptual novelty of controlling both *the implantation and conformational arrangement* of donors in immobilized catalysts,[26] which has not been achieved with other «classical ligands». The demonstration regarding the control of conformation is supported by high resolution ^{31}P-NMR in solution, for which the proximity of phosphino groups, and their interaction, is evidenced by intense nonbonded « through-space » spin-spin couplings. Additionally, this study provides proof-of-concept of supported catalytic materials built from modular polyphosphines for the formation of efficient and recyclable polydentate heterogeneous palladium catalysts.

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† Electronic Supplementary Information (ESI) available: Full experimental details, see DOI: 10.1039/b000000x/

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