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A soluble polyethyleneglycol-anchored phosphine as a highly active, reusable ligand for Pd-catalyzed couplings of aryl chlorides: comparison with cross and non-cross-linked polystyrene and silica supports

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Abstract—The so-called SPhos phosphine, an extremely active ligand in the amination and Suzuki coupling of sterically-hindered aryl chlorides, has been anchored on different supports such as non-soluble (cross-linked polystyrene) and soluble (non-cross-linked polystyrene and polyethyleneglycol) polymers, as well as high surface silica. SPhos anchored on polyethyleneglycol (PEG–SPhos) showed the best activity for both amination and Suzuki couplings. The PEG–SPhos ligand can be quantitatively recovered from the reaction mixture through precipitation with diethyl ether and recycled in four consecutive runs without loosing activity. ^{31}P NMR spectra of the reused anchored ligand showed that deactivation of the PEG–SPhos ligand comes from the progressive oxidation of the phosphine-to-phosphine oxide.

1. Introduction

Palladium-catalyzed cross-coupling reaction is one of the current hottest topics in chemistry.[1–14] A large number of research groups have expanded the scope of these transformations by designing and developing new ligands, including phosphines,[7,15–17] carbenes,[16,18,19] and other organic molecules.[20–26] Among the Pd-catalyzed cross-coupling reactions, the Buchwald–Hartwig amination[4,15,16,20,25,27–35] and the Suzuki–Miyaura cross-coupling[6,7,13,15,20,25,36,37] have shown to be powerful tools for the synthesis of new molecules, and there is a considerable number of examples in which this reaction has reached industrial application. The current challenge in these transformations consists of the coupling of electron-rich, hindered aryl chlorides.[7,15,27] Some bulky phosphine ligands such as adamantylphosphines[38] and *tert*-butylphosphines[39] are known to promote high activity in Pd-catalyzed reactions. Analogously, it has also been reported that 2-(2′,6′-dimethoxybiphenyl)-dicyclohexylphosphine (SPhos) and related structures exhibit high activity for the Suzuki–Miyaura cross-coupling and the Buchwald–Hartwig amination.[3,28,34,40] Some examples of this generation of sterically crowded, electron-rich biphenyl phosphines are shown in Chart 1. The catalysts derived from the complexation of the SPhos ligand with palladium acetate and other palladium salts allow the coupling of sterically congested aryl bromides and chlorides with hindered aryl boronic acids, alkenylboronic acids, and amines with less than 1 mol % of catalyst under very mild conditions,[15] even at room temperature.[27] These palladium complexes have been fully characterized by analytical and spectroscopic techniques, including structure determination by single-crystal X-ray diffraction.[27]

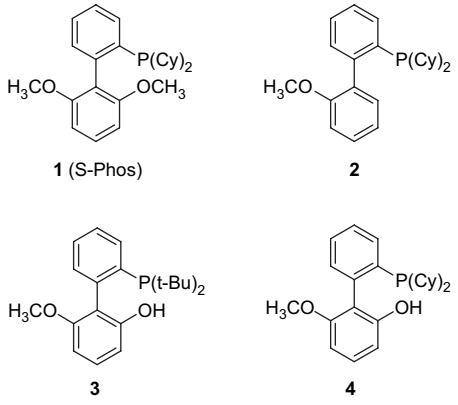

Chart 1. Sterically-hindered phosphines used as ligands for highly active Pd catalysts in coupling reactions.

In spite of the low percentages of palladium and phosphine needed to catalyze the coupling, the recovery of the highly valuable phosphine ligand is of considerable interest.[41,42]

Keywords: Green chemistry; Supported phosphine ligands; Soluble polymeric catalysts; Highly active recoverable palladium catalyst; Amination reaction; Suzuki reaction of aryl chlorides.
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On one hand, the ligand is a highly costly compound, whose preparation requires well-controlled conditions and hazardous starting materials.[15,27] On the other hand, the coupling product isolation makes necessary chromatographic purification to separate it from the phosphine ligand and palladium complex with the obvious consumption of solvents and time. Heterogeneous catalysis reduces wastes during the reaction work-up, contributing to the development of greener chemical systems and environmental friendly industrial processes.[43] One general methodology to transform a successful homogeneous catalyst into a heterogeneous system consists of anchoring a conveniently derivatized catalyst onto an insoluble support. Two types of insoluble solids are among the most widely used supports to anchor palladium complexes, namely silica[44–54] and polymers.[55–59] These two kinds of materials combine most of requirements for suitable supports including to be inert and easily available. Many different types of catalytic species including palladium nanoparticles and palladium salts have been incorporated onto organic polymers[60,61] and inorganic oxides.[62–64] Also, a wide range of ligands including heterocyclic carbenes have been anchored on these supports.

Apart from heterogeneous catalysts, the use of soluble but recoverable polymers as scaffolds for reagents and catalytic species has experienced an important growth in the last years.[65,66] These polymers have analogous chemical properties to their non-soluble counterparts but they are soluble in some organic solvents, and precipitating in others. In this way, a homogeneous but still recoverable and reusable catalytic system can be designed combining the high activity intrinsic of homogeneous catalysts with the ease of product separation characteristic of heterogeneous catalysts. In this context, polyethyleneglycol (PEG)[67,68] and non-cross-linked polystyrene (solPS)[69,70] have already been reported as supports for phosphine palladium complexes. These polymers are fully soluble in the usual reaction solvents for cross-coupling reactions such as toluene or tetrahydrofuran (THF), but precipitate quantitatively when either diethyl ether for PEG[71] or methanol for solPS is added to the reaction mixture. Thus, Janda and co-workers[72] have reported the successful use of triphenylphosphine bonded to PEG as stoichiometric soluble reagent in ozonide reduction and Wittig reactions. Plenio and co-workers have applied PEG-supported phosphines as palladium ligands for the Sonogashira[68] and Suzuki couplings[67,69] under biphasic DMSO–heptane conditions, including some Buchwald's biphenyl phosphines as the phosphines **3** and **4** for the last transformation. The results obtained showed that the Buchwald's type phosphines are twice more active than the diadamantyl benzylphosphine for the Suzuki coupling of 4-chloroacetophenone with phenylboronic acid, the catalytic data agreeing with the extremely high activity of this kind of biphenyl phosphines as ligands for the Suzuki reaction. However, the observed reusability of the PEG-anchored phosphines **3** and **4** for the Suzuki coupling of aryl chlorides was worst than that of the diadamantyl benzylphosphine, and only three cycles were achieved. The biphasic conditions employed by Plenio and co-workers have some resemblance to the use of perfluoroalkyl tagged phosphines in fluorous solvents,[73–77] in which case the phosphine remains in the fluorous phase and the products migrate to the conventional organic solvent.

SPhos (phosphine **1**) is, by far, the most active ligand for the Pd-catalyzed amination and Suzuki coupling. Beller and co-workers[18] have shown the superior activity of Buchwald's biphenyl phosphines with respect to heterocyclic carbenes as ligands for the Suzuki coupling of aryl chlorides. In previous work,[15,27] it has also been demonstrated the superior activity of SPhos as palladium ligand compared to the rest of biaryl and other substituted phosphines. In view of these precedents, the aim of this work is to anchor covalently an analogue SPhos to soluble and non-soluble polymers as well as to high surface area silica, with the intention of obtaining a highly active, reusable phosphine ligand for amination and Suzuki couplings. We want to disclose the influence of the support modulating the intrinsic activity of the complex on the catalytic activity.

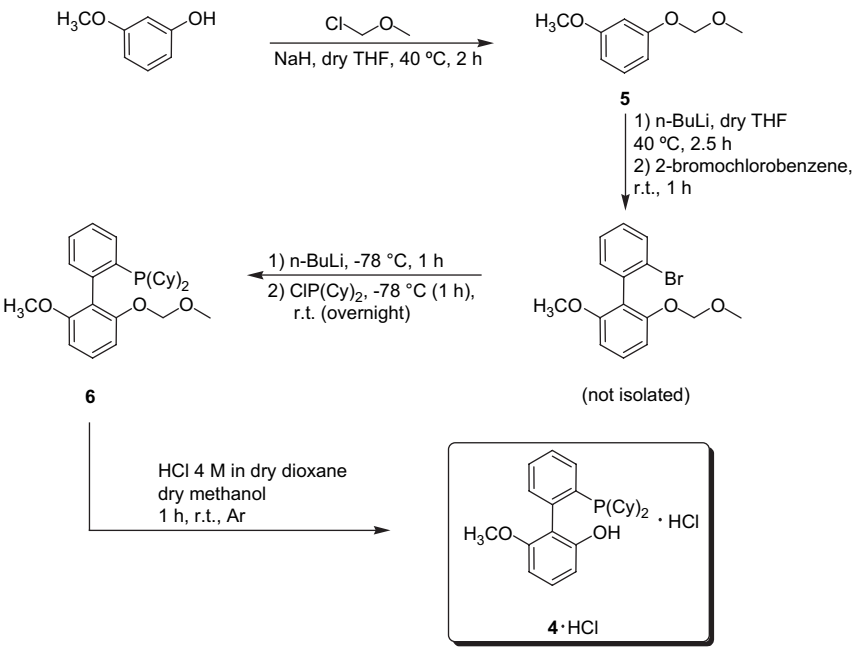
The strategy to synthesize the solid-supported SPhos phosphine analogue will consist of the preparation of an appropriate SPhos derivative able to readily react with the functional groups present in the supports. The final materials will have SPhos phosphines covalently anchored to the scaffold and will be used in the same way than the SPhos. The palladium–phosphine complex will be formed in situ in the appropriate solvent previous to the addition of reactants. The reactions will be performed under identical conditions to those previously reported for the underivatized SPhos. However, in our case, the supported SPhos will be recovered and used in consecutive runs.

2. Results and discussion

2.1. Synthesis of hydroxy derivative SPhos 4

Our strategy to anchor an SPhos analogue in soluble or insoluble scaffold is based on the preparation as key intermediate of an SPhos derivative having an aromatic hydroxyl group instead of one methoxy group. In this strategy the phenolic OH of the SPhos derivative **4** will act as nucleophile forming a covalent bond with the support conveniently functionalized with an appropriate leaving group (halogen or mesyl). According to this synthetic route to prepare SPhos ligand attached to polymeric or inorganic support, we proceeded in the first stage to prepare the biphenyl substituted phosphine **4**. Scheme 1 depicts the steps leading to the formation of compound **4**. Starting from resorcinol monomethyl ether, this synthetic sequence parallels the synthesis of SPhos reported by Buchwald,[15,27] in which the key reaction is the aromatic substitution of bromine by chlorodicyclohexylphosphine. We have proceeded to a previous protection of the OH group with chloromethyl methoxy methane. Subsequently, reaction with chlorodicyclohexylphosphine was carried out without isolating the methoxymethyl (MOM) protected brominated biphenyl and the final step was the deprotection of the MOM protecting group with dry HCl.

This MOM protecting group is stable under the harsh conditions required for phosphine formation[78,79] but then it can be selectively removed without altering the *meta* methoxy group under moderate acidic conditions.[78,79] The most salient spectroscopic data of compound **6** are the presence of a single peak in ^{31}P NMR at -8 ppm that appears at identical chemical shift as the signal of the P atom of SPhos. The



Scheme 1. Synthetic route followed to obtain the SPhos hydroxy derivative **4**.

rest of spectroscopic data are also compatible with the structure (see Section 4 for details), being remarkable the overall similarity of the IR spectra of **6** and SPhos. With respect to phosphine **4**, the most notable spectroscopic features are the presence of one OH band in IR spectroscopy at about 3400 cm^{-1} and the observation of a single peak at 19 ppm in ^{31}P NMR. The latter chemical shift clearly indicates that after the MOM deprotection the P atom becomes protonated. However, protonation increases the stability of the phosphine **4·HCl** in the presence of air, making easier the manipulation of the compound under ambient atmosphere.

2.2. Anchoring phosphine 4·HCl to the supports

Once the hydroxy SPhos was obtained (compound **4**), we proceed to anchor it on soluble and insoluble scaffolds. For the formation of the covalent bond we selected the nucleophilic substitution of leaving groups present in the supports by the phenolate formed from the phosphine **4·HCl**.

Preliminary controls were performed to follow the deprotonation of the phenolic OH group by ^{1}H (deprotonation causes the upfield shift of the hydrogens on the phenolate aromatic ring) and ^{31}P NMR spectroscopy with the aim to determine the stability toward air oxidation of the phosphine under our experimental procedure (lack of intense peak at 50 ppm due to PO phosphine oxide formation). According to this NMR study, the treatment of compound **4·HCl** with sodium hydride in DMF should give the phenoxide while the phosphine functionality was sufficiently stable versus oxidation to survive the nucleophilic substitution.

The scaffolds employed as supports were polyethyleneglycol (PEG), cross-linked (PS) and non-cross-linked polystyrene (solPS), and high surface area silica (SiO_2). The interest of comparing different supports comes from the fact that the nature of the support dramatically influences the catalytic activity of the final material.[80] Thus, it can be anticipated that SPhos ligand anchored to soluble polymers will give homogeneous catalysts with higher initial reaction rates than insoluble heterogeneous catalysts, in which phase transfer diffusion may control and limits the catalytic activity. But, in the other hand, reusability and separation from the reaction mixture should be easily accomplished using insoluble heterogeneous catalysts as compared to the soluble ones.[44,72] Except for the case of PS, for which a commercial Merrifield's chlorinated resin was employed, a previous functionalization of the rest of the supports was necessary to introduce the leaving group before proceeding to the covalent anchoring of SPhos derivative **4·HCl**. In the next paragraphs it is commented in detail the different protocols followed for each scaffold. In the reactions leading to the covalent anchoring of SPhos **4·HCl** to the supports, the degree of covalent anchoring was determined by integration of the corresponding peaks in solution ^{1}H NMR spectroscopy. The phosphine loading was also obtained for each SPhos bound-support by quantitative atomic absorption spectroscopy. The analytical data are summarized in Table 1.

2.2.1. Anchoring phosphine 4·HCl on polyethyleneglycol (PEG–SPhos). For the present study a soluble PEG polymer was used. Its average weight is sufficiently high to ensure the

Table 1. Analytical data of the SPhos anchored ligands prepared in this work

SPhos support	Leaving group exchange[a] (%)	P content[b] (mmol g^{-1})
PEG–SPhos	94	0.14
PS–SPhos	60	0.95
solPS–SPhos	75	1.00
SiO_2–SPhos	—	0.25

[a] Based on ratio of the ^{1}H NMR integrals corresponding to the peaks of –C**H**$_2$–O–SPhos (new signal) and –C**H**$_2$–X (X=OMes or Cl, functionalized support signal).

[b] Obtained by quantitative atomic absorption spectroscopy of the aqueous solutions after treating the solids with concentrated HCl (PEG), HBr (polystyrenes) or HF–HBr (silica) at 40 °C overnight.

quantitative precipitation from diethyl ether even in the presence of about 30% of other solvents such as toluene, while at the same time has a specific hydroxy group content of 0.3 mmol g^{-1}, that allows achieving a reasonably loading of SPhos.

The first step to prepare PEG–SPhos consisted of the chlorination of PEG. Almost quantitative chlorination of the terminal PEG hydroxy groups was easily obtained by reaction with thionyl chloride at 65 °C for 24 h. Unfortunately, the nucleophilic substitution of this chlorinated PEG by SPhos phenoxide was unsatisfactory due to the long reaction time required and the occurrence of concomitant P oxidation. Thus, PEG–SPhos oxide in which the P atom has become oxidized was obtained, due probably to the strong basic conditions employed for the nucleophilic substitution that favor P oxidation. In contrast to the results using chlorinated PEG, a mesyl-substituted PEG, easily synthesized at room temperature starting from PEG and mesyl chloride, renders excellent yields the expected PEG polymer having terminal SPhos ligands. Plenio and co-workers have reported analogous starting PEG derivative and reaction conditions to obtain other types of PEG-functionalized phosphines.[68] Scheme 2 shows the reagents and conditions followed for PEG mesylation and PEG–SPhos preparation.

Formation of mesylated PEG and its yield were determined by the appearance of new signals at 4.4 ppm (triplet) and 3.0 ppm (singlet) corresponding to the –C**H**$_2$–OMes and C**H**$_3$–SO_2– hydrogens, respectively. The methyl groups of $CH_3SO_2^-$ are also clearly observed in ^{13}C NMR spectroscopy as a new signal at 38 ppm.

After its synthesis, the PEG–SPhos was precipitated under nitrogen atmosphere with dry diethyl ether, washed, and redissolved in dry CH_2Cl_2. After solvent removal, PEG–SPhos was obtained as a light-brown solid. This experimental procedure avoids water extraction that could promote the phosphine oxidation. Even when PEG–SPhos is obtained and handled under the most careful conditions, trying to avoid phosphine oxidation, the corresponding ^{31}P NMR spectrum of as-synthesized PEG–SPhos showed the presence of significant amounts of phosphine oxide ($\delta \sim 50$ ppm, percentage 30%) accompanying the main peak corresponding to the phosphine P atom peaking at −8 ppm intensity (70%). For the sake of comparison, Figure 1 shows the ^{31}P NMR spectra of compound **4·HCl** (spectrum a) and those of the corresponding supported ligands, including PEG–SPhos (spectrum b).

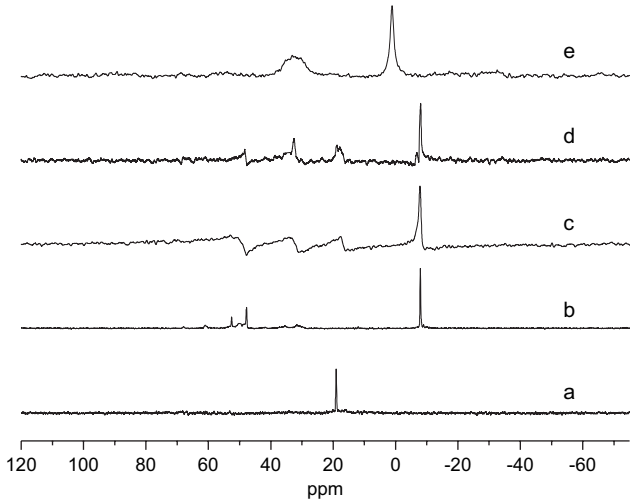
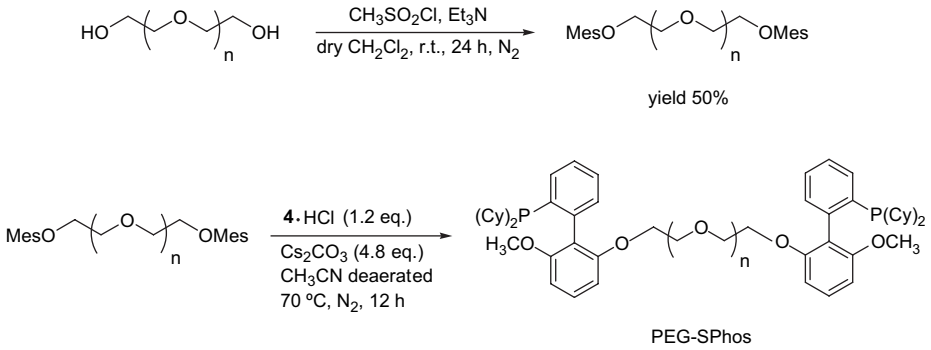


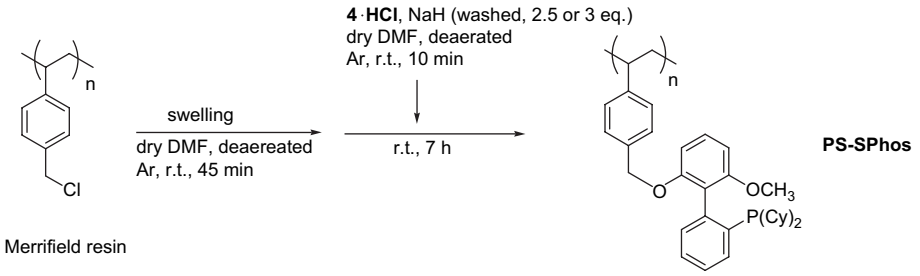
Figure 1. ^{31}P NMR spectra of (a) compound **4·HCl**, (b) PEG–SPhos in $CDCl_3$, (c) PS–SPhos as gel in $CDCl_3$, (d) solPS–SPhos in $CDCl_3$, and (e) SiO_2–SPhos (MAS CP ^{31}P NMR).

It is worth commenting that the protonated phosphine form has been described as equally active ligand as the non-protonated form,[67–69] probably because it occurs an initial deprotonation under the basic conditions necessary for the cross-coupling reactions. Handling protonated phosphine ligand before the reaction has the advantage of good air stability of the ligand since phosphine protonation prevents air oxidation. On the other hand, the ^{1}H NMR spectrum of the PEG–SPhos compared to PEG–OMes shows the disappearance of the peaks around 4.4 ppm (triplet) and 3.0 ppm (singlet) corresponding to the –C**H**$_2$–OMes and C**H**$_3$–SO_2 hydrogens, respectively, together with the appearance of a new triplet around 4.0 ppm, attributable to the new –C**H**$_2$–O–SPhos hydrogens.

2.2.2. Anchoring phosphine 4·HCl on Merrifield resin (PS–SPhos). The second solid employed for supporting SPhos was commercial, cross-linked, non-soluble polystyrene. Previously, the successful covalent anchoring of phosphine **2** (analogous to our phosphine compound **4**) to the same Merrifield resin has been reported by Buchwald.[59] Herein, we have followed the same synthetic strategy using



Scheme 2. Preparation route of PEG–SPhos.

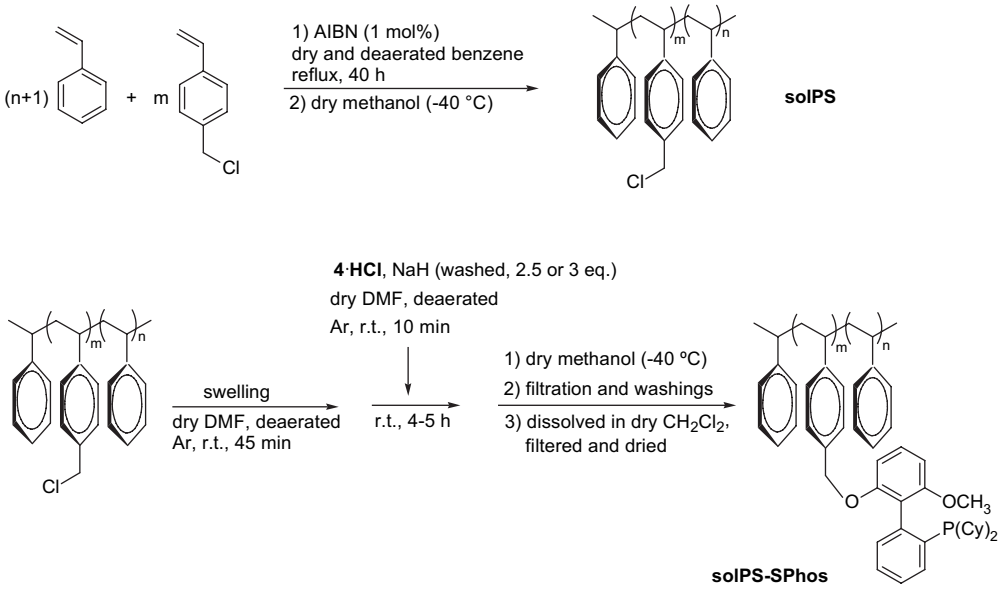


Scheme 3. Covalent anchoring of compound **4·HCl** onto the Merrifield resin.

phosphine **4** instead of phosphine **2**. The employed procedure is shown in Scheme 3.

As it can be seen in Scheme 3, after swelling the polymer, the previously formed phenoxide derivative of compound **4·HCl** was added to the polymer suspension and the heterogeneous mixture stirred at room temperature. The modified polymer containing PS–SPhos was obtained as a yellow solid by filtration, and it was exhaustively washed and vacuum dried overnight before characterization. The ^{1}H NMR of the PS–SPhos in gel phase[81] shows the decrease of the broad signal corresponding to the –C**H**$_2$–Cl hydrogens of the initial polymer together with the appearance of a new broad peak downfield shifted around 0.2 ppm. These spectral variations are in agreement with the formation of –C**H**$_2$–O–SPhos bonds. The degree of chlorine substitution by phenoxide groups calculated by ^{1}H NMR spectroscopy from the signal integrals is similar to the value estimated by chemical analysis from the corresponding phosphine loading (0.95 mmol g^{-1}). They correspond approximately to around 80% of the original 1.2 mmol g^{-1} of Cl present in the resin. The spectrum of the ^{31}P NMR in gel phase (Fig. 1, spectrum c) provides some information about the nature of the phosphorous functional groups present in the polymer. Thus, in addition to the expected dicyclohexylphosphine appearing at −8 ppm, we have observed the presence of other phosphorous peak corresponding to phosphine oxide (50 ppm, 10%), protonated phosphine (−19 ppm, 5%), and a fourth species attributable to quaternary phosphonium ion coming from the consecutive nucleophilic chlorine substitution of the Merrifield resin by already anchored SPhos acting as nucleophile (35 ppm, 5%). Nevertheless, it is convenient to note that the expected dicyclohexylphosphine (−8 ppm) is clearly observed as the predominant species in the ^{31}P NMR spectrum of PS–SPhos.

2.2.3. Anchoring phosphine 4·HCl on soluble polystyrene (solPS–SPhos). To encompass the broadest possible range of scaffolds to anchor SPhos, we proceeded to the synthesis of non-cross-linked soluble polystyrene properly functionalized with chloromethyl groups. Actually, we followed the procedure described by Enhlom et al. for the copolymerization of styrene and 4-chloromethyl styrene.[82] Since virtually all the co-monomers become part of the resulting polymer, this procedure allows an easy control on the amount of chlorine groups introduced on the polymer and assures a homogeneous incorporation of the chloromethyl styrene moieties into the polymeric network. For the sake of comparison with the insoluble PS polymer previously synthesized, we have prepared polystyrene having a Cl loading equal to the Merrifield's resin (1.2 mmol g^{-1}). Scheme 4 depicts the reaction conditions for the synthesis of solPS as well as the SPhos anchoring procedure. There are in the literature related precedents reporting the covalent anchoring of other phosphines on soluble polystyrene backbones,[69,70] but it was anticipated based on the relative



Scheme 4. Preparation of solPS–SPhos from **4·HCl**.

activity of the SPhos ligand in solution that our solPS–SPhos would be the most active. PS–Phos was soluble in many organic solvents, including toluene and CH_2Cl_2, but insoluble in alcohols and ethers. This solubility behavior will become useful for the recovery of the catalyst. The solubility of reagents and product in deuterated chloroform allows following conveniently the course of the anchoring reaction by solution ^1H and ^{31}P NMR spectroscopy. Thus, the peak corresponding to the –C**H**$_2$–Cl hydrogens of solPS in ^1H NMR at δ 4.5 ppm progressively disappears accompanied by a concomitant increase of a new peak at δ 4.9 ppm corresponding to the –C**H**$_2$–O–Ar hydrogens. ^{31}P NMR spectrum of solPS–SPhos shows the stability of phosphine P atom during the anchoring process except that, at long reaction times, progressive oxidation of phosphine starts to occur. After the synthesis, solPS–SPhos precipitated with cold, dry methanol from the reaction mixture. The resulting polymer was washed and freed from adventitious insoluble particles by dissolving solPS–SPhos in dry CH_2Cl_2, filtering off the solution, and removing the solvent to obtain yellow beads. As it can be seen in Figure 1, the ^{31}P NMR spectrum of solPS–SPhos is similar to that obtained for PS–SPhos, where the main peak of the expected phosphine is accompanied in minor proportion by the signals corresponding to the protonated form, the quaternary phosphonium, and the phosphine oxide.

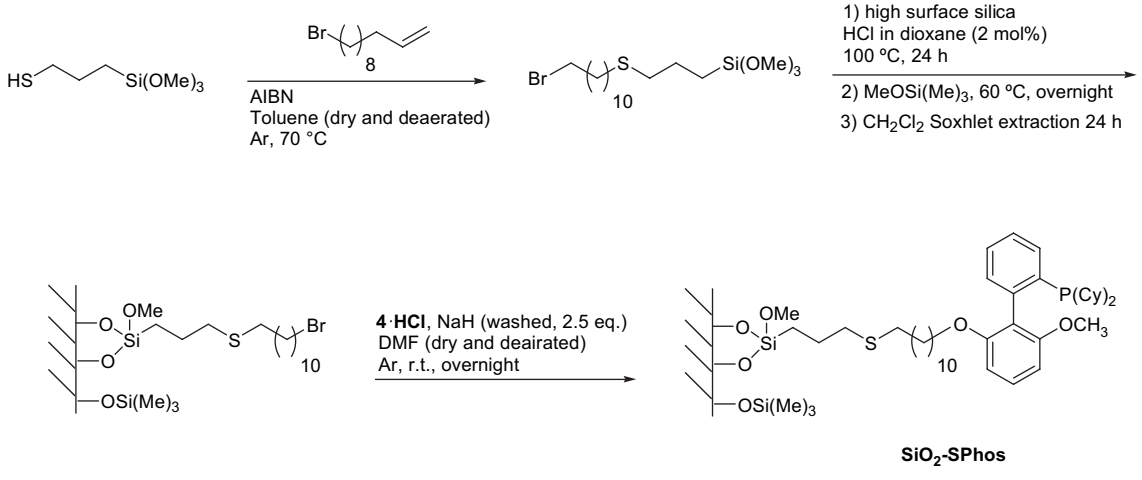
2.2.4. Anchoring phosphine 4·HCl on high surface area silica (SiO_2–SPhos). The last support in which we have anchored phosphine **4·HCl** was a silicon oxide having a large surface area (about 200 $m^2\,g^{-1}$). Silica has been one of the most widely used insoluble supports to anchor catalysts and, particularly, metallic complexes.[83] In our case, the methodology employed for the covalent anchoring of the compound **4** is shown in Scheme 5.

As it can be seen there, the first step consists of the formation of a trimethoxysilane derivative containing a long alkyl chain having terminal bromide leaving group connected through a thioether functional group. This compound was obtained quantitatively through an electrophilic addition of the silane mercapto group to the terminal double bond of the alkene promoted by catalytic amounts of azoisobutyronitrile (AIBN).[84] This radical coupling is effected very selectively under mild conditions, avoiding hydrolysis of the methoxysilyl groups. The formation of this compound was followed by ^1H NMR spectroscopy, observing the total disappearance of the signals corresponding to the protons of the C=C double bond together with the appearance of a triplet corresponding to the new –S–CH_2– bond (δ 2.5 ppm). This trimethoxysilane compound condenses easily with the silanol groups present on the silica surface leading to a bromide-functionalized silica. After silica functionalization with the desired loading of the brominated silyl groups, an excess of trimethylmethoxysilane was added to the reaction mixture to mask the remaining silanols of the silica surface. This exhaustive silanization of the silica surface has three benefits: (i) avoids interaction of the phosphine ligands with the silanol groups, (ii) allows the use of strong bases, and (iii) makes the material more hydrophobic. Although there is some bromide-functionalized silica commercially available, we purposely wanted to prepare a special bromide-functionalized silica with a long alkyl chain. This long alkyl chain acts as a spacer, allowing enough separation of the anchored active site from the silica surface and minimizing steric hindrance to the interaction with the substrates. The resulting bromide-functionalized, high surface area silica can undergo room temperature nucleophilic substitution by compound **4·HCl**. These reaction conditions minimize the oxidation of the phosphine ligand, which is an undesirable side reaction previously observed in the case of polymers. As a result of the mild reaction conditions, only two signals are recorded in the cross-polarization magic angle spinning solid-state ^{31}P NMR spectrum of SiO_2–SPhos, corresponding to the free and protonated phosphines.

2.3. Catalytic tests

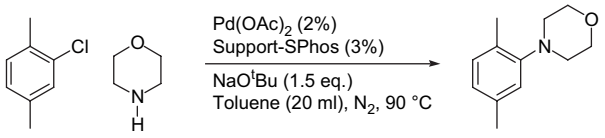
2.3.1. Amination reactions. With the series of recoverable ligands previously prepared, we proceeded to perform several Pd-catalyzed coupling reactions with the final goal to determine the relative activity and reusability of the anchored SPhos.

The first reaction that we tested was the Buchwald–Hartwig amination of aryl halides with secondary amines. A previous point was to screen the adequate Pd-to-ligand molar ratio. This point was addressed by performing the amination of



Scheme 5. Functionalization of a high surface area silica with terminal bromide leaving groups and covalent anchoring of compound **4**.

Table 2. Results for the reaction of chloro-*p*-xylene (134 μl, 1 mmol), morpholine (109 μl, 1.25 mmol), and sodium *tert*-butoxide (144.2 mg, 1.5 mmol) in anhydrous toluene (20 ml) at 90 °C, in the presence of $Pd(OAc)_2$ and the corresponding supported SPhos



1 mmol 1.25 eq.

Entry	Ligand	Pd (mol %)	SPhos (equiv to Pd)	Time (h)	Yield (%)
1	solPS–SPhos	0.2	7	0.5	9
2		0.2	7	24	30
3		1	7	0.5	>99
4		2	1.5	0.5	5
5		2	1.5	24	23
6	Reuse of entry 3[a]	—	—	0.5	3
7	PEG–SPhos	2	1.5	6	97
8	Reuse of entry 7[b]	2	—	16	5
9	PS–SPhos	0.5	1.1	4	5
10		1	7	24	95
11		2	1.5	24	20
12	SiO_2–SPhos	2	1.5	24	0.1

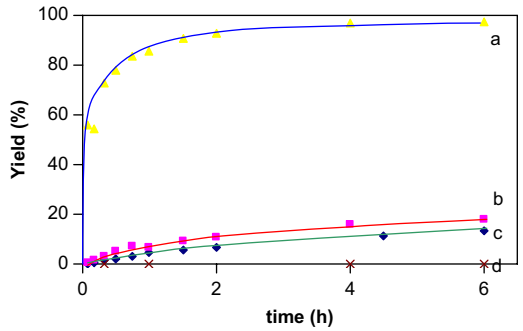
[a] No $Pd(OAc)_2$ was added.
[b] 2 mol % of $Pd(OAc)_2$ was added.

chloro-*p*-xylene with morpholine in the presence of palladium acetate and the supported SPhos ligands at different Pd–SPhos ratios (Table 2). From the results obtained it can be concluded that a large excess of SPhos ligand is beneficial for the catalytic activity of Pd, in agreement with previous reports in the literature.[40] Comparing the catalytic activity employing the different supported SPhos ligands, a large influence of the nature of the support was found. As it can be seen in Table 2, when SPhos is bonded to a polymeric scaffold and used in a high excess with respect to Pd, essentially complete formation of the expected aromatic amine was observed at sufficiently long reaction times. Moreover, there is a remarkable influence of the nature of the polymer; soluble ligands performing in homogeneous phase are more active than insoluble supports acting heterogeneously. The activity of PEG–SPhos was particularly remarkable. Based on related precedents, the high activity of PEG–SPhos could be attributed to the positive influence of the coordinating ability of the ethylene oxide units, complexing metal cations, rendering the anions more basic. In this regard, it can be proposed that NaO^{t}Bu in toluene enhances its strength as base when the sodium cation is complexed with the PEG backbone. On the other extreme, it is remarkable the low activity of SPhos bonded to silica. The low activity of SiO_2–SPhos could be due to the presence of residual, unprotected silanol groups playing a negative influence, neutralizing the base alcoxide and complexing Pd. These silanol groups can be located in nests and micropores that are difficult to be protected by TMS silanization. Figure 2 provides a time conversion plot for the amination of chloro-*p*-xylene in which the relative activity of the series of anchored SPhos can be clearly seen.

Reusability of covalently attached SPhos ligand after one reaction run was attempted by recovering the material from the reaction mixture either by precipitation in the case of soluble SPhos ligand or by filtration. Using chloro-*p*-xylene as substrate, the anchored ligands became severely deactivated, exhibiting only a very low residual activity. This almost complete decay in catalytic activity can be rationalized based on ^{31}P NMR spectra of used supported SPhos ligands, showing that P oxidation was occurring in a considerable extent.

It is known that aryl halides having electron deficient substituents are more reactive in Pd-catalyzed coupling reactions. This higher reactivity is manifested in two different ways. On one hand the reaction times required for complete conversion are considerably shorter. On the other hand, Pd catalyst does not require highly active phosphine ligands. In view of this, it may happen that a catalytic system that becomes deactivated for a highly demanding reaction is, however, reusable with gradual decay for other less-demanding reagents. According to this, we also studied the reusability of PEG–SPhos for the reaction of *p*-chloroacetophenone with morpholine. The results are shown in Table 3.

The higher reactivity of this activated chloroaromatic allows reusing the PEG–SPhos for eight runs. It was observed, however, that the initial reaction rate and even the final conversion decrease significantly upon reuse, this being compatible with the gradual oxidation of phosphine. This decay in activity is remarkably abrupt going from the seventh to the eighth reuse. ^{31}P NMR spectroscopy revealed again that PEG–SPhos deactivation is due to the formation of phosphine oxide.

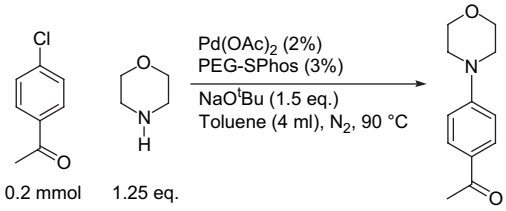


	TOF[a]
PEG-SPhos	672.3
SOLPS-SPhos	9.7
PS-SPhos	4.7
SiO_2-SPhos	0.1

[a] TurnOver Frequency: mmol aryl chloride/(mmol Pd x h^{-1})

Figure 2. Time conversion plot for the amination of chloro-*p*-xylene (134 μl, 1 mmol) by morpholine (109 μl, 1.25 mmol) and sodium *tert*-butoxide (144.2 mg, 1.5 mmol) in anhydrous toluene (20 ml) at 90 °C, in the presence of $Pd(OAc)_2$ (2 mol %) and the corresponding supported SPhos (3 mol%): (a) PEG–SPhos, (b) solPS–SPhos, (c) PS–SPhos, and (d) SiO_2–SPhos.

Table 3. Reusability of PEG–SPhos (3 mol %) for the reaction of 4-chloroacetophenone (26 μl, 0.2 mmol), morpholine (22 μl, 0.25 mmol, 1.25 equiv), and sodium *tert*-butoxide (28.8 mg, 0.3 mmol, 1.5 equiv) in anhydrous toluene (4 ml) at 90 °C, in the presence of $Pd(OAc)_2$ (2 mol %)



0.2 mmol 1.25 eq.

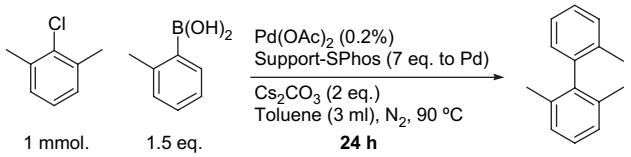
Use	Yield[a] (%)		
	1 h	2 h	4 h
1	66	95	—
2	68	>99	—
3	70	>99	—
4	50	—	>99
5	32	—	93
6[b]	14	—	39
7	10	—	70
8	2	—	28[c]

[a] Analyzed by GC using nitrobenzene as an external standard. Final yield corresponds to isolated product.
[b] No $Pd(OAc)_2$ was added.
[c] At 8 h.

2.3.2. Suzuki reactions. The series of supported SPhos ligands was also tested for the Suzuki cross-coupling of 2-chloro-*m*-xylene and *o*-tolylboronic acid. This Suzuki reaction employing *o*-substituted reagents is considered as a benchmark test to assess the catalytic activity of different Pd species. In our case, we use 0.2 mol % of Pd with an excess of supported SPhos. The results are shown in Table 4. As in the previous amination reactions, we observed complete conversions and high selectivity to the expected trimethylbiphenyl for the two SPhos ligands anchored on soluble supports. Again, SPhos anchored on silica was completely inactive for the coupling. The relative catalytic activity depending on the nature of the support can also clearly be seen in the time conversion plot shown in Figure 3.

None of the catalytic systems based on recoverable ligands showed, however, activity upon reuse, reflecting again the easiness of SPhos to undergo P oxidation. Reusability of PEG–SPhos was, however, possible for the less demanding coupling of 4-chloroacetophenone and *o*-tolylboronic acid, although a clear decrease in activity is also observed upon reuse. The results for 4-chloroacetophenone are shown in Table 5.

Table 4. Results for the Suzuki reaction of 2-chloro-*m*-xylene (132.5 μl, 1 mmol), *o*-tolylboronic acid (203.8 mg, 1.5 mmol), and Cs_2CO_3 (651.6 mg, 2 mmol) in anhydrous toluene (3 ml) at 90 °C for 24 h, in the presence of $Pd(OAc)_2$ (0.2 mol %) and the corresponding supported SPhos (1.4 mol %)



1 mmol. 1.5 eq.

	Yield[a] (%)
PEG–SPhos	>99
PS–SPhos	79
solPS–SPhos	95
SiO_2–SPhos	0.2

[a] Homocoupling of tolylboronic acid (1–3%) was also found.

2.4. Attempted regeneration of the catalyst

As commented earlier, SPhos anchored on polymeric supports exhibits a high activity that is lost while phosphine becomes oxidized even working under careful experimental conditions avoiding the presence of oxygen. This deactivation pathway has also been frequently reported in the literature for highly active phosphine ligands.[72,73,76] Reactivation has been possible in some cases using different phosphine oxide reducing reagents including: (i) trichlorosilane $SiHCl_3$,[72,73,76,85] in combination with or without triethylamine, (ii) $LiAlH_4$[17] or its derivative, alane AlH_3 formed in situ,[72,86,87] and (iii) polymethylhydrosiloxane in combination with titanium(IV) species as catalysts.[88] Apparently, $SiHCl_3$ is highly effective to perform phosphine reduction but when used in PEG it leads to the rupture of the C–O-aryl bonds.[72] For this reason, in the case of PEG-supported phosphines other alternatives have been employed. In particular, Janda[72] has reported complete reduction of a PEG-supported phosphine oxide using alane that is generated 'in situ' from $LiAlH_4$ and H_2SO_4. Based on these related precedents, we anticipated that in our case alane could also be the most suitable reducing agent to perform the reactivation of our PEG–SPhos ligand. However, in our case ^{31}P NMR spectroscopy clearly establishes that alane treatment does not effect any noticeable P reduction of PEG–SPhos oxide. This failure indicates the higher tendency of SPhos to undergo P oxidation as compared to triphenylphosphine. Spencer[89] has reported the quantitative reduction of aryl phosphine oxides by using $SiHCl_3$ as reducing agent in combination with triphenylphosphine as oxygen acceptor. The addition of triphenylphosphine allows to perform the reduction under considerably milder conditions, that prevents the rupture of the C–O-aryl bonds. In our case, some reduction of the phosphine oxide (20%, calculated from the integrated signals in ^{31}P NMR spectroscopy) in completely deactivated PEG–SPhos oxide could be achieved using $SiHCl_3$ in combination with triphenylphosphine under mild conditions. In addition, P chemical analysis showed that no detachment of the phosphine from the polymer occurs under these reduction conditions. However, when we attempted to drive the phosphine reduction to completion by using larger excess of $SiHCl_3$, complete detachment of SPhos from PEG was observed. Thus, a more efficient reactivation procedure to reduce PEG–SPhos oxide without attacking the covalent bond to the polymer is still to be performed.

3. Conclusions

SPhos anchored to organic polymers either soluble or insoluble at proportions lower than 3 mol % is a suitable ligand for highly demanding Pd-catalyzed reactions, including amination of aryl chlorides with electron donor substituents and the Suzuki reaction of highly encumbered substrates. The supported ligands undergo, however, deactivation by transformation of the phosphine into the corresponding

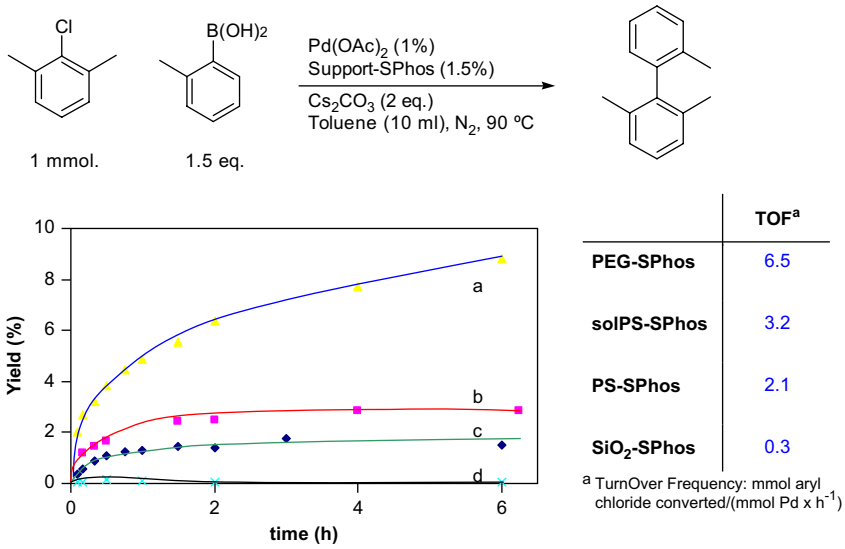
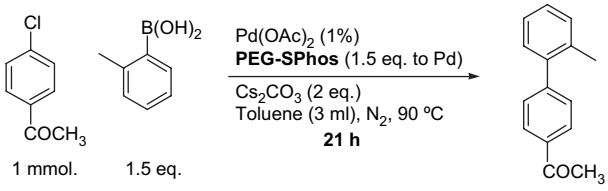


Figure 3. Time conversion plot for the Suzuki reaction of 2-chloro-*m*-xylene (132.5 μl, 1 mmol), *o*-tolylboronic acid (203.8 mg, 1.5 mmol), and Cs_2CO_3 (651.6 mg, 2 mmol) in anhydrous toluene (10 ml) at 90 °C, in the presence of $Pd(OAc)_2$ (1 mol %) and the corresponding supported SPhos (1.5 mol%): (a) PEG–SPhos, (b) solPS–SPhos, (c) PS–SPhos, and (d) SiO_2–SPhos. The turnover frequency values (TOF) have been estimated from the slope of the time conversion plot at 0 time.

Table 5. Reusability of PEG–SPhos (1.5 mol %) for the reaction of 4-chloroacetophenone (130 μl, 1 mmol), *o*-tolylboronic acid (203.8 mg, 1.5 mmol), and Cs_2CO_3 (651.6 mg, 2 mmol) in anhydrous toluene (3 ml) at 90 °C for 21 h, in the presence of $Pd(OAc)_2$ (1 mol %)



Use	Yield (%)
1	>99
2	93
3	67
4	13

oxide. Partial reduction was achieved using trichlorosilane in combination with triphenylphosphine, but more drastic treatments lead to extensive detachment of the phosphine to the polymer. Thus, the reusability could only be achieved for less-demanding substrates such as *p*-chloroacetophenone, although phosphine deactivation also takes place with these reactive substrates at certain moment. In the case of the amination coupling, PEG–SPhos (3 mol %) was reused up to eight times.

4. Experimental section

4.1. General

The reagents and solvents were obtained from commercial sources and were used without further purification. Degussa high surface area silica (ca. 200 $m^2\,g^{-1}$), Merrifield resin having a Cl loading of 1.2 mmol g^{-1}, and polyethyleneglycol (Acros, M_w ca. 6000 Da) were used as commercially available supports. A stock solution of $Pd(OAc)_2$ in anhydrous toluene (0.01 M, 2.25 mg/ml) was prepared and stored under nitrogen atmosphere into a previously dehydrated double-necked round-bottomed flask. This toluene $Pd(OAc)_2$ solution was sonicated for 5 min before being used. Gas chromatographic analyses were performed on a HP 5890 instrument equipped with a 25 m capillary column of 5% cross-linked phenylmethylsilicone. GC–MS analyses were performed on an Agilent 5973N spectrometer equipped with the same column and operated in the same conditions as the GC. ^1H and ^{13}C NMR spectra were recorded in a 300 MHz Bruker Avance instrument using $CDCl_3$ as solvent and TMS as an internal standard. ^{31}P NMR spectroscopy was performed in a Bruker AV-400, using a 4 mm Bruker probe for P. The C and H content of the solids were determined by combustion chemical analysis using a Fisons CHNSO analyzer. The P content for polyethyleneglycol support was determined by dissolving the solid (50 mg) in neat water (3 ml) and adding concentrated HCl (2 ml), diluting the solution in water (60 ml), and measuring by quantitative atomic absorption spectroscopy (Varian SpectrAA 10 plus). The P content for polystyrene supports was determined by treating the solid catalyst with concentrated HBr (5 mg of solid in ca. 3 ml) at 60 °C for 24 h, diluting the solution in water (60 ml), and measuring by quantitative atomic absorption spectroscopy. The P content for silica support was determined by dissolving the solid in a mixture of HF–HBr concn (40 mg of solid in ca. 2:2 ml), diluting the solution in water (30 ml), and measuring by quantitative atomic absorption spectroscopy. Quantification was achieved by comparing the response with a calibration plot.

4.1.1. Protection of 3-methoxyphenol with chloromethyl methyl ether (5). A 60 wt % dispersion of NaH (2.4 g, 60 mmol, 1.2 equiv) in heavy alkanes was placed in a previously dehydrated 250 ml three-necked round-bottomed flask under argon atmosphere. The solid was washed four times with 50 ml of pentane and dried under vacuum. Then, dry THF (125 ml) and 3-methoxyphenol (6.21 g, 5.49 ml,

50 mmol) are added and the suspension is magnetically stirred in a pre-heated oil bath at 50 °C for 15 min. Then, chloromethyl methyl ether (5.23 g, 4.94 ml, 65 mmol, 1.3 equiv) is slowly added dropwise under nitrogen atmosphere with vigorous magnetic stirring, observing the change in the color of the solution from red to yellow and the appearance of a white solid precipitate. The dispersion was left to react overnight. The complete conversion of the phenol is checked by taking aliquots from the reaction mixture and analyzing them by GC and GC–MS. The mixture is filtered and the solvent is slowly removed at moderate temperature under reduced pressure (the temperature has to be lower as possible in order to avoid some undesirable reactions with the excess of chloromethyl methyl ether or acids generated in the course of the reaction). The crude is dissolved in diethyl ether (400 ml) and extracted with NaOH (5 wt %, 800 ml). The aqueous phase is extracted with diethyl ether (200 ml, two times) and the organic phases are combined. The ether phases were extracted with NaOH again (800 ml, one time), distilled water (800 ml, three times, final pH=6–7), and brine (800 ml, two times). The solution was dried and filtered and the solvent removed under reduced pressure, obtaining 1-methoxy-3-methoxymethoxybenzene as yellow oil (4.47 g, 26.6 mmol, 53%). The product is stable more than one week. IR (neat, cm^{-1}): 2999, 2957, 2938, 2904, 2836, 1605, 1592, 1493, 1468, 1458, 1441, 1284, 1264, 1217, 1193, 1146, 1114, 1077, 1042, 991, 924. ^1H NMR δ_H (ppm, 300 MHz, $CDCl_3$): 7.20 (1H, dt, J=8.1, 0.5 Hz), 6.66 (1H, ddd, J=8.0, 2.3, 0.8 Hz), 6.63 (1H, td, J=2.4, 0.5 Hz), 6.58 (1H, ddd, 8.2, 2.4, 0.9 Hz), 5.19 (2H, s), 3.80 (3H, s), 3.50 (3H, s). ^{13}C NMR δ_C (ppm, 300 MHz, $CDCl_3$): 160.9, 158.6, 130.1, 108.5, 107.6, 102.7, 94.6, 56.2, 55.6. MS (*m/z*): 168 (M^+, 100%), 138, 107, 92, 77, 63, 52. Anal. Calcd for $C_9H_{12}O_3$ (168.19) (%): C 64.27; H 7.19. Found: C 63.60; H 7.37.

4.1.2. Synthesis of mono-MOM-protected SPhos (6). A solution of 1-methoxy-3-methoxymethoxybenzene (1.68 g, 10 mmol) in dry THF (30 ml) is magnetically stirred in a pre-heated oil bath at 40 °C under argon. Then, a solution of *n*-BuLi in hexane (6.88 ml, 11 mmol, 1.1 equiv) is added dropwise under argon atmosphere with vigorous magnetic stirring. The solution is left to react for 2 h 30 min. After this time, the solution is cooled to room temperature and 1-bromo-2-chlorobenzene (2.1 g, 1.29 ml, 11 mmol, 1.1 equiv) was slowly added dropwise and the reaction was stirred for additional 60 min. At this time, an aliquot from the reaction was taken and analyzed by GC and GC–MS, showing the complete conversion of 1-bromo-2-chlorobenzene (the isolation of the intermediate compound 2′-bromo-2-methoxy-6-methoxymethoxybiphenyl is described below). Then, the reaction was cooled to −78 °C (acetone–dry ice) and a solution of *n*-BuLi in hexane (6.88 ml, 11 mmol, 1.1 equiv) is added dropwise under argon atmosphere. The mixture is magnetically stirred at −78 °C under argon for 1 h and previously distilled chlorodicyclohexylphosphine (2.21 ml, 10 mmol) is added. The mixture was magnetically stirred at −78 °C under argon for 1 h and the cold bath was removed to stir the solution at room temperature overnight. Then, methanol was added to quench the excess of *n*-BuLi and the solution concentrated under reduced pressure. The crude was redissolved in the minimum amount of diethyl ether and filtered through flash silica gel topped with a layer of Celite, eluting with hexane (600 ml) and dry diethyl ether (300 ml). The ether phase was concentrated and left into the fridge at −10 °C for 3 days. After filtration under vacuum, dicyclohexyl-(2′-methoxy-6′-methoxymethoxybiphenyl-2-yl)-phosphane was obtained as a crystalline white solid (1.6 g, 36%). IR (neat, cm^{-1}): 2927, 2850, 1599, 1592, 1471, 1449, 1438, 1272, 1247, 1177, 1155, 1106, 1073, 1019, 1000, 924, 784, 762, 734. ^1H NMR δ_H (ppm, benzene-d_6): 7.57 (1H, dd, J=8.1, 1.2 Hz), 7.35 (1H, ddd, J=8.0, 3.7, 2.3 Hz), 7.23 (1H, dd, J=7.6, 1.7 Hz), 7.17 (1H, t, J=9.0 Hz), 7.0 (1H, dt, J=7.0, 1.2 Hz), 6.92 (1H, dd, J=6.3, 0.9 Hz), 6.40 (1H, dd, J=8.1, 0.9 Hz), 5.04 (1H, d, J=7.3 Hz), 4.81 (1H, d, J=7.3 Hz), 3.30 (3H, s), 3.11 (3H, s), 1.84 (6H, br m), 1.70 (6H, br m), 1.22 (10H, br m). ^{13}C NMR δ_C (ppm, $CDCl_3$): 157.6, 155.7, 143.0, 136.5, 132.5, 131.2, 129.1, 128.3, 126.4, 121.1, 107.2, 104.0, 94.9, 56.0, 55.4, 34.3, 34.1, 30.4, 30.2, 30.0, 29.7, 29.5, 29.1, 27.7, 27.6, 27.5, 26.7. ^{31}P NMR δ_P (ppm, $CDCl_3$): −8.3. Anal. Calcd for $C_{27}H_{37}O_3P$ (440.55) (%): C 73.61; H 8.47. Found: C 73.64; H 8.58.

4.1.3. Isolation of the intermediate 2′-bromo-2-methoxy-6-methoxymethoxybiphenyl. To check the formation of the biphenyl derivative through the chloro-substituted position of the 1-bromo-2-chloro-benzene, an aliquot was taken from the reaction mixture between this compound and 1-methoxy-3-methoxymethoxybenzene before the addition of the second amount of *n*-BuLi in the above synthesis. The reaction was quenched with methanol and the resulting mixture concentrated under reduced pressure. The crude was redissolved in the minimum amount of diethyl ether and was filtered through flash silica gel topped with a layer of Celite, eluting with ethyl acetate (300 ml). The organic phase was washed with water and brine, dried, and the solvent removed under reduced pressure. 2′-Bromo-2-methoxy-6-methoxymethoxybiphenyl was obtained as a white powder. IR (neat, cm^{-1}): 3054, 2999, 2958, 2936, 2905, 2834, 1601, 1588, 1471, 1436, 1276, 1249, 1154, 1120, 1106, 1072, 1015, 999, 923, 785, 758, 734. ^1H NMR δ_H (ppm, $CDCl_3$): 7.69 (1H, dd, J=7.9, 1.2 Hz), 7.39 (1H, td, J=7.9, 1.3 Hz), 7.35 (1H, t, 8.5 Hz), 7.27 (1H, td, J=7.9, 1.8 Hz), 7.22 (1H, dd, J=7.6, 1.8 Hz), 6.84 (1H, dd, J=8.5, 1.8 Hz), 6.67 (1H, dd, J=8.5, 0.9 Hz), 5.05 (1H, d, J=6.7 Hz), 5.02 (1H, d, J=7.0 Hz), 3.71 (3H, s), 3.31 (3H, s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 157.9, 155.3, 136.3, 132.4, 132.3, 129.6, 128.8, 127.0, 125.3, 120.2, 107.7, 105.1, 94.8, 56.1 (2×). MS (*m/z*): 324–322 (M^+, isotopic pattern of Br), 211 (more intense), 198, 183, 155, 139, 127. Anal. Calcd for $C_{15}H_{15}O_3Br$ (323.18) (%): C 55.75; H 4.68. Found: C 56.02; H 4.71.

4.1.4. Deprotection of the MOM group (4·HCl). A solution of MOM-protected SPhos (88 mg, 0.2 mmol) and dry methanol (53 μl) in a 4 M HCl solution in 1,4-dioxane (0.6 ml) was magnetically stirred at room temperature under argon for 1 h. Then, dry CH_2Cl_2 (4 ml) was added and the solution transferred via syringe to a previously dehydrated round-bottomed flask containing a 60 wt % dispersion of NaH (96 mg, washed three times with 5 ml of CH_2Cl_2) in CH_2Cl_2 (10 ml) under argon atmosphere. The mixture was magnetically stirred at room temperature under argon for 10 min and filtered through a PTFE filter (pore diameter

0.2 μm). The solvent and volatile compounds were removed under reduced pressure at 80 °C for 30 min, and 2′-dicyclohexylphosphanyl-6-methoxy-biphenyl-2-ol hydrochloride salt was obtained as a white powder (68 mg, 78%). IR (neat, cm^{-1}): 3054, 3005, 2936, 2859, 2194, 1601, 1594, 1466, 1450, 1438, 1254, 1088, 925, 788, 732. ^1H NMR δ_H (ppm, $CDCl_3$): 7.71 (1H, t, J=8.5 Hz), 7.63 (1H, t, J=8.0 Hz), 7.48 (1H, dd, J=7.7, 4.4 Hz), 7.42 (1H, dd, J=8.5, 4.7 Hz), 7.28 (1H, d, J=8.0 Hz), 7.23 (1H, d, J=8.3 Hz), 6.50 (1H, dd, J=6.9, 2.2 Hz), 5.78 (1H, d, J=6.6 Hz), 3.68 (3H, s), 1.92 (4H, br m), 1.80 (4H, br m), 1.68 (4H, br m), 1.20 (10H, br m). ^{13}C NMR δ_C (ppm, $CDCl_3$): 157.3, 154.9, 141.9, 134.0, 133.0, 132.9, 131.0, 128.0, 127.8, 113.7, 111.1, 102.1, 55.5, 29.9, 29.3, 29.0, 28.5, 27.3, 27.2, 26.8, 26.0, 25.8, 25.6, 25.0, 24.9. ^{31}P NMR δ_P (ppm, $CDCl_3$): 19.0 (minor peaks at 15.2 and 10.6). Anal. Calcd for $C_{25}H_{34}ClO_2P$ (432.96) (%): C 69.35; H 7.92; Cl 8.19. Found: C 66.98; H 8.31; Cl 10.72.

4.1.5. Formation of the phenoxide. To check phosphorus deprotonation, the hydrochloride form obtained above (44 mg, 0.1 mmol) was dissolved in dry THF under argon (0.5 ml) and added via syringe to a previously dehydrated round-bottomed flask containing a 60 wt % dispersion of NaH (9.6 mg, 2.4 equiv) in anhydrous THF–DMF (1:0.5 ml) under argon atmosphere and vigorous magnetical stirring. Strong bubbling and a progressive change in the color of the solution from pale yellow to orange were observed. After the bubbling stopped, dry THF (1.5 ml) was added and the mixture filtered through a PTFE filter (pore diameter 0.2 μm). The solvents were removed under reduced pressure. ^1H NMR δ_H (ppm, $CDCl_3$): 7.63 (1H, dt, J=6.6, 1.8 Hz), 7.52 (1H, tt, J=7.8, 1.8 Hz), 7.44 (1H, ddd, J=6.6, 1.8, 0.6 Hz), 7.40 (1H, dd, J=7.5, 1.8 Hz), 7.23 (1H, dd, J=8.4, 5.4 Hz), 6.63 (1H, dd, J=8.4, 0.9 Hz), 6.51 (1H, dd, J=8.1, 0.9 Hz), 3.68 (3H, s), 1.65 (12H, br m), 1.20 (10H, br m). ^{31}P NMR δ_P (ppm, $CDCl_3$): −7.6 (less intense peak at 51.9).

4.1.6. Synthesis of PEG–OMes. Following the procedure reported by Plenio and co-workers,[68] a solution of PEG (M_n ca. 6000, 10 g, 3.33 mmol) and methanesulfonyl chloride (MsCl, 386.6 μl, 572.2 mg, 4.99 mmol, 1.5 equiv) in dry CH_2Cl_2 (25 ml) was placed in a previously dehydrated two-necked round-bottomed flask under nitrogen. Triethylamine (936.6 μl, 680 mg, 6.66 mmol, 2 equiv) was added and the appearance of gas and a white solid is observed. The solid is redissolved after the addition of dry CH_2Cl_2 (25 ml) and the mixture is magnetically stirred at room temperature under nitrogen for 24 h. At this time, the solution is diluted with CH_2Cl_2 (350 ml) and extracted with water (50 ml, two times) and brine (50 ml, one time). The solvent was removed under reduced pressure and diethyl ether (100 ml) was added to the crude and stirred for 90 min. The solid was filtered and washed with additional diethyl ether (100 ml) and dried under vacuum for 2 h (9.45 g, 94%, degree of mesylation ca. 50%). IR (neat, cm^{-1}): 2947, 2883, 2860, 2806, 2740, 2695, 1590, 1466, 1358, 1342, 1280, 1242, 1174, 1147, 1109, 1061, 962, 945, 843. ^1H NMR δ_H (ppm, $CDCl_3$): 4.40 (2H, t), 3.90 (2H, t), 3.6 (ca. 260H, br s), 3.05 (3H, s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 70.9, 69.6, 69.4, 38.1. Anal. Found (%): C 53.55; H 9.04; S 0.47.

4.1.7. Anchoring of phosphine-supported PEG–SPhos. Following the procedure described,[68] a dispersion of PEG–OMes (300 mg), 2′-(dicyclohexylphosphanyl)phenyl-3-methoxybenzenol hydrochloride salt (43 mg, 0.1 mmol, 1.2 equiv), and Cs_2CO_3 (78 mg, 4.8 equiv) in previously deaerated CH_3CN (6 ml) is magnetically stirred at 70 °C under nitrogen for 12 h. The mixture was cooled, filtered under a nitrogen stream, and the solvent removed under reduced pressure. To the resulting crude diethyl ether was added and the mixture magnetically stirred at room temperature under nitrogen for 30 min (two times). The pale brown solid was filtered and dried under vacuum (299 mg, >99%). IR (neat, cm^{-1}): 3482, 2883, 2742, 2649, 1643, 1592, 1466, 1450, 1360, 1343, 1280, 1242, 1147, 1113, 1063, 1041, 964, 946, 843. (Major peaks for SPhos: 2922, 2850, 1589, 1471, 1459, 1448, 1431, 1248, 1110). ^1H NMR δ_H (ppm, $CDCl_3$): 7.90 (1H, t, J=8.5 Hz), 7.60 (1H, t, J=8.0 Hz), 7.45 (1H, dd, J=7.7, 4.4 Hz), 7.35 (1H, dd, J=8.5, 4.7 Hz), 7.30 (1H, d, J=8.0 Hz), 7.15 (1H, d, J=8.3 Hz), 4.05 (2H, t), 3.6 (br s), 3.50 (3H, s), 2.3 (8H, br m), 1.70 (2H, br m), 1.75 (6H, br m), 1.20 (6H, br m). ^{31}P NMR δ_P (ppm, $CDCl_3$): −8.9, 47.2. Anal. Found (%): C 52.85; H 8.38; S 0.36. P content (mmol g^{-1}) 0.058.

4.1.8. Synthesis of non-cross-linked polystyrene (solPS). Following the procedure described by Enholm, a solution of 4-vinylbenzyl chloride (1.17 g, 1.08 ml, 7.69 mmol, 1 equiv) and styrene (5.2 g, 5.71 ml, 50 mmol, 6.5 equiv) in anhydrous benzene (18 ml) is deaerated with argon for 45 min and is magnetically stirred in a pre-heated oil bath at reflux temperature under argon for 40 h in the presence of azobis(isobutyronitrile) (AIBN, 82.1 mg, 0.5 mmol, 1 mol %) as radical initiator, to obtain a chlorobenzyl–benzene molar ratio ca. 1:7. After this time, the mixture was slowly poured into cold (−40 °C) deaerated dry methanol, left to cool for 2 min, and the solid obtained was filtered and dried (2.98 g, 47%). IR (neat, cm^{-1}): 3084, 3059, 3026, 3002, 2927, 1602, 1493, 1452, 1266, 1029, 908, 843, 826, 760, 700, 681, 540. ^1H NMR δ_H (ppm, $CDCl_3$): 7.1 (br s), 6.6 (br s), 6.5 (br s), 4.5 (br s), 2.1 (br s), 1.8 (br s), 1.4 (br s), 1.1 (d), 1.0 (t). ^{13}C NMR δ_C (ppm, $CDCl_3$): 145.8, 145.3, 128.5, 128.2, 127.9, 126.4, 125.9, 46.6, 40.4. Anal. Calcd for $C_{73}H_{65}Cl$ (ca. 976) (%): C 89.7; H 6.6. Found: C 86.42; H 7.48.

4.1.9. Synthesis of phosphine-supported solPS–SPhos. A solution of 2′-(dicyclohexylphosphanyl)phenyl-3-methoxybenzenol hydrochloride salt (216.5 mg, 0.5 mmol) in anhydrous deaerated DMF (1 ml) was slowly added to a 60 wt % dispersion of NaH (previously washed with 0.25 ml of anhydrous DMF, 49.2 mg, 2.5 equiv) in anhydrous deaerated DMF (0.75 ml) under argon atmosphere and vigorous magnetic stirring. The dark red solution was left to react for 10 min. After this time, a solution of non-cross-linked polystyrene (240 mg, chloromethylphenyl sites: 0.3 mmol) in anhydrous deaerated DMF (1 ml) was added and the mixture was magnetically stirred at room temperature under argon. Aliquots from the reaction mixture were periodically taken, following the course of the reaction by ^1H NMR spectroscopy by monitoring the decrease in the peak corresponding to $–CH_2–Cl$ (4.5 ppm) and the increase of the peak corresponding to $–CH_2–O–$phosphine (4.8 ppm). When no further conversion was observed (typically 4–5 h),

the mixture was slowly poured into cold (−20 °C) deaerated dry methanol, left to cool for 2 min and the solid obtained was filtered, washed with cold dry methanol (100 ml), water (50 ml), 1 M HCl (50 ml), water (100 ml), and dry methanol (200 ml), and dried under vacuum overnight (290 mg, 92%). IR (neat, cm^{-1}): 3083, 3062, 3028, 3003, 2930, 2853, 2247, 2190, 1661, 1494, 1463, 1451, 1254, 1101, 911, 762, 733, 699. ^1H NMR δ_H (ppm, $CDCl_3$): 7.1 (br s), 6.6 (br s), 6.5 (br s), 4.8 (br s), 3.7 (s), 1.8 (br s), 1.7 (br s), 1.4 (br s), 1.1 (d), 1.0 (t). ^{13}C NMR δ_C (ppm, $CDCl_3$): 145.4, 134.1–130.5 (several peaks), 128.2, 127.1, 125.8, 67.2, 55.8, 53.6, 46.5–43.6 (several peaks), 40.4, 28.1–25-0 (several peaks). ^{31}P NMR δ_P (ppm, $CDCl_3$): −7.9 (other less intense peaks at 18.8, 32.3, 34.0, 48.1). Anal. Found (%): C 79.77; H 7.43. P content (mmol g^{-1}) 1.2.

4.1.10. Synthesis of PS–SPhos. A solution of 2′-(dicyclohexylphosphanyl)phenyl-3-methoxybenzenol hydrochloride salt (164.5 mg, 0.38 mmol, 1.6 equiv) in deaerated anhydrous DMF (0.8 ml) was slowly added to a 60 wt % dispersion of NaH (previously washed with 0.25 ml of anhydrous DMF, 38 mg, 2.5 equiv) in anhydrous deaerated DMF (0.4 ml) under argon atmosphere and vigorous magnetic stirring. The dark red solution was left to react for 5 min. After this time, the solution was added via syringe to a dispersion of swollen (under argon for 1 h) cross-linked polystyrene Merrifield's resin (200 mg, chloromethylphenyl sites: 0.24 mmol) in anhydrous deaerated DMF (1 ml) and the mixture was magnetically stirred at room temperature under argon for 5 h. Then the solid was filtered (collected with 5 ml of DMF), washed with 1 N HCl (5 ml, two times), water (10 ml, two times), dry methanol (10 ml, two times), and dry CH_2Cl_2 (20 ml, four times), and dried under vacuum overnight (265 mg, >99%). IR (neat, cm^{-1}): 1489, 1616, 1639, 2850, 3232, 3411, 3477, 3558. ^1H gel phase NMR δ_H (ppm, $CDCl_3$): 7.1 (br s), 6.9 (br s), 6.5 (br s), 5.2 (s), 5.1 (s), 3.6 (br s), 3.4 (br s), 2.2 (br s), 1.5 (br s), 1.4 (br s), 1.1 (br s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 160.0, 147.6, 146.1, 135.8–124.3 (several peaks), 42.0–40.0 (several peaks), 28.6–25-0 (several peaks). ^{31}P NMR δ_P (ppm, $CDCl_3$): −8.1 (other less intense peaks at 17.0, 32.4, 31.7, 48.2). Anal. Found (%): C 83.19; H 7.67. P content (mmol g^{-1}) 1.2.

4.1.11. Procedure for the preparation of silica functionalized with bromo-terminated alkyl chains. A solution of 11-bromo-1-undecene (548.4 μl, 583.0 mg, 2.5 mmol) and 3-mercaptopropyltrimethoxysilane (472.4 μl, 2.5 mmol) in previously deaerated anhydrous toluene (2 ml) is magnetically stirred in a pre-heated oil bath at 70 °C under argon in the presence of azobis(isobutyronitrile) (AIBN, 123.2 mg, 0.75 mmol) as radical initiator. Aliquots from the reaction mixture were periodically taken to follow the course of the reaction by ^1H NMR spectroscopy by monitoring the disappearance of the peaks corresponding to terminal C═C double bond and the increase of the peaks corresponding to $–CH_2–S–$. When complete absence of the peaks corresponding to the double bond was observed (typically 5 h) and the only product in solution characterized as [3-(11-bromoundecylsulfanyl)propyl]-trietoxysilane. ^1H NMR δ_H (ppm, $CDCl_3$): 3.55 (9H, s), 3.41 (2H, t), 2.54 (2H, t), 2.49 (2H, t), 1.86 (2H, quint), 1.70 (2H, quint), 1.60 (2H, quint), 1.25 (12H, mult), 0.88 (2H, t), 0.75 (2H, t). Previously dehydrated high surface silica (500 mg treated at 150 °C for 1 week) and dry toluene (8 ml) were added to a solution of the ω-bromoundecyl silane in toluene (5 ml) and the suspension stirred at 100 °C under argon atmosphere for 24 h. After this time, methoxytrimethylsilane (689.3 μl, 521.1 mg, 5 mmol) and 4 M HCl in dry dioxane (12.5 μl, 0.05 mmol, 2%) were added and the mixture stirred at 60 °C under argon atmosphere overnight. The solid was filtered, Soxhlet extracted with dichloromethane for 24 h, and dried under vacuum for 3 h (422 mg, 80%). Elemental analysis (%): C: 5.57; H 1.55; S 0.82. Loading of Br groups (based on S analysis): 0.26 mmol g^{-1}. Loading of trimethyl silylating groups (from the total C analysis subtracting the bromo-terminated alkyl chains): 0.35 mmol g^{-1}.

4.1.12. Synthesis of silica-supported SiO_2–SPhos. A solution of 2′-(dicyclohexylphosphanyl)phenyl-3-methoxybenzenol hydrochloride salt (70 mg, 0.16 mmol, 1.6 equiv) in deaerated anhydrous DMF (0.8 ml) was slowly added to a 60 wt % dispersion of NaH (previously washed with 0.25 ml of anhydrous DMF, 16 mg, 2.5 equiv) in anhydrous deaerated DMF (0.4 ml) under argon atmosphere and vigorous magnetic stirring. The dark red solution was left to react for 5 min and the bromo-functionalized silica (400 mg, active sites ca. 0.1 mmol) and additional deaerated anhydrous DMF (0.8 ml, total volume: 2 ml) were added. The mixture was magnetically stirred at room temperature under nitrogen for 90 min. After this time, the solid was filtered, washed under nitrogen atmosphere with DMF (10 ml), ethanol (5 ml), water (10 ml), ethanol (20 ml), and CH_2Cl_2 (20 ml), and Soxhlet extracted with CH_2Cl_2 under nitrogen atmosphere for 24 h. The solid was dried under vacuum for 90 min. IR (neat, cm^{-1}): 810, 1100, 1460, 1562, 1618, 1637, 1749, 2856, 2929, 3240, 3454. ^{31}P CP solid-state NMR δ_P (ppm, $CDCl_3$): 1.1 (together with a less intense peak at 33.0). Elemental analysis (%): C 5.38; H 1.09; S 0.28. P content (mmol g^{-1}) 0.52.

4.1.13. Typical procedure for amination reactions. A recently sonicated 0.01 M solution of $Pd(OAc)_2$ in anhydrous toluene (2 ml, 0.02 mmol Pd, 2%) was placed via syringe in a previously dehydrated double-necked round-bottomed flask under nitrogen and the corresponding SPhos-containing solid (1.5 equiv SPhos) was added. The resulting solution or suspension was magnetically stirred under nitrogen in a pre-heated oil bath at 30–40 °C for 20–30 min, observing the change in the colour of the solution from brown to yellow. Then, chloro-*p*-xylene (134 μl, 1 mmol), morpholine (109 μl, 1.25 mmol, 1.25 equiv), sodium *tert*-butoxide (144.2 mg, 1.5 mmol, 1.5 equiv), and additional anhydrous toluene (18 ml) were added and the mixture was magnetically stirred in a pre-heated oil bath at 90 °C. The course of the reaction was periodically followed by taking aliquots (0.1 ml), cooling them in an ice bath, and analyzing them immediately by GC, using nitrobenzene as an external standard. At the final time, the SPhos support and the base were removed by filtration under vacuum (PS and silica) or by precipitation with diethyl ether (20 ml) in an ice bath (solPS and PEG). In the cases where the recovered SPhos-catalyst was used in a new run, the solid was washed with additional 20 ml of diethyl ether (stirring, 30 min, room temperature), dried under vacuum, and used without additional washings. The organic phase was extracted with water (100 ml, two

times) and brine (50 ml, two times), dried, and analyzed by GC–MS, IR, ^{1}H and ^{13}C NMR, and DEPT. Spectroscopic data for *N*-(2,4-xylyl)morpholine: IR (neat, cm^{-1}): 3369, 2960, 2924, 2854, 2816, 2750, 2730, 2681, 1726, 1681, 1664, 1610, 1577, 1504, 1452, 1415, 1374, 1259, 1117, 1095, 1026, 874, 806, 700. ^{1}H NMR δ_H (ppm, $CDCl_3$): 6.98 (1H, d, J=7.5 Hz), 6.75 (1H, s), 6.73 (1H, d, J=7.5 Hz), 3.78 (4H, t, J=4.9 Hz), 2.82 (4H, d, J=4.9 Hz), 2.25 (3H, s), 2.18 (3H, s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 149.7, 134.8, 129.6, 127.9, 122.6, 118.3, 66.1, 50.9, 19.8, 16.0.

4.1.14. Reuses for the amination reaction using PEG–SPhos as ligand. After a first run (see above) using a 1 mM solution of $Pd(OAc)_2$ in anhydrous toluene (4 ml, 0.004 mmol Pd, 2%), 4-chloroacetophenone (26 μl, 0.2 mmol), morpholine (22 μl, 0.25 mmol, 1.25 equiv), and sodium *tert*-butoxide (28.8 mg, 0.3 mmol, 1.5 equiv), PEG–SPhos (1.5 equiv) was precipitated with cold dry diethyl ether (20 ml) in an ice bath under nitrogen atmosphere and stirring for 15–30 min. The ethereal supernatant was extracted with a pipette under nitrogen atmosphere and the solid remaining was washed twice with additional 20 ml of diethyl ether (stirring for 15 min, room temperature) and dried under vacuum. The organic phases were put together and ether was removed under reduced pressure. The toluene solution was analyzed by GC–MS. The toluene was removed under vacuum and the product was analyzed by ^{1}H and ^{13}C NMR and DEPT. Spectroscopic data for *N*-(4-acetylphenyl)-morpholine: ^{1}H NMR δ_H (ppm, $CDCl_3$): 7.80 (2H, dd, J=9.7, 1.3 Hz), 6.78 (2H, dd, J=9.7, 1.3 Hz), 3.65 (4H, t, J=6.0 Hz), 3.22 (4H, t, J=6.0 Hz), 2.44 (3H, s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 196.8, 154.6, 138.2, 130.7, 113.6, 66.9, 47.9, 26.5. The polymer was placed in a round-bottomed flask, vacuum-nitrogen purged (three times), and fresh 1 mM solution of $Pd(OAc)_2$ in anhydrous toluene (4 ml, 0.004 mmol Pd, 2%) was charged via syringe. The suspension was magnetically stirred under nitrogen in a pre-heated oil bath at 30–40 °C for 20–30 min. Then, fresh reagents and base were added and the mixture was magnetically stirred in a pre-heated oil bath at 90 °C for the time indicated. The process was repeated for consecutive runs.

4.1.15. Typical procedure for Suzuki reactions. A recently sonicated 0.01 M solution of $Pd(OAc)_2$ in anhydrous toluene (1 ml, 0.01 mmol Pd, 1%) was placed via syringe in a previously dehydrated double-necked round-bottomed flask under nitrogen and the corresponding SPhos-containing solid (1.5 equiv SPhos) was added. The suspension was magnetically stirred under nitrogen in a pre-heated oil bath at 30–40 °C for 20–30 min, observing the change in the colour of the solution from brown to yellow. Then, 2-chloro-*m*-xylene (132.5 μl, 1 mmol), *o*-tolylboronic acid (203.8 mg, 1.5 mmol, 1.5 equiv), Cs_2CO_3 (651.6 mg, 2 mmol, 2 equiv), and additional anhydrous toluene (9 ml) were added and the mixture was magnetically stirred in a pre-heated oil bath at 90 °C (solPS and PEG). The course of the reaction was followed periodically by taking aliquots (0.1 ml), cooling them in an ice bath, and analyzing them by GC, using nitrobenzene as an external standard. At the final time, the SPhos support and the base were removed by filtration under vacuum (PS and silica) or by precipitation with diethyl ether (20 ml) in an ice bath. In the cases where the recovered SPhos-catalyst was used in a new run, the solid was washed with additional 20 ml of diethyl ether (stirring for 30 min, room temperature), dried under vacuum, and used without additional washings. The organic phase was extracted with water (100 ml, two times) and brine (50 ml, two times), dried, and analyzed by GC–MS, ^{1}H and ^{13}C NMR.[27]

4.1.16. Reuses for the Suzuki reaction using PEG–SPhos as ligand. After a first run (see above) using 4-chloroacetophenone as substrate (130 μl, 1 mmol), the SPhos–PEG was precipitated with cold dry diethyl ether (20 ml) in an ice bath under nitrogen atmosphere and stirring for 15–30 min. The ethereal supernatant was extracted with a pipette under nitrogen atmosphere and the solid remaining was washed twice with additional 20 ml of diethyl ether (stirring for 15 min, room temperature) and dried under vacuum. The organic phases were put together and extracted with water (100 ml, two times) and brine (50 ml, two times), dried, and analyzed by GC–MS, ^{1}H and ^{13}C NMR, and DEPT. Spectroscopic data for 4-acetyl-2′-methylbiphenyl: ^{1}H NMR δ_H (ppm, $CDCl_3$): 7.92 (2H, dd, J=8.3, 1.2 Hz), 7.38 (2H, dd, J=8.3, 1.2 Hz), 7.22 (1H, mult), 7.20 (1H, dd, J=3.0, 1.8 Hz), 7.18 (1H, mult), 7.16 (1H, dd, J=3.0, 1.8 Hz), 2.55 (3H, s), 2.20 (3H, s). ^{13}C NMR δ_C (ppm, $CDCl_3$): 196.8, 145.9, 139.7, 134.6, 134.1, 128.7, 128.0, 127.7, 127.2, 126.9, 125.9, 14.5, 13.0. The round-bottomed flask containing the polymer was cycled three times with vacuum followed by nitrogen purging and afterward fresh 0.01 M solution of $Pd(OAc)_2$ in anhydrous toluene (1 ml, 0.01 mmol Pd, 1%) was placed via syringe. The suspension was magnetically stirred under nitrogen in a pre-heated oil bath at 30–40 °C for 20–30 min. Then, fresh reagents and base were added and the mixture was magnetically stirred in a pre-heated oil bath at 90 °C for typically 20 h. The process was repeated for consecutive runs.

4.1.17. Reduction of PEG–SPhos oxide. The PEG–SPhos ligand (50 mg, ca. 0.007 mmol phosphine oxide) recovered by ether precipitation after several reuses (completely oxidized as assessed by ^{31}P NMR) was placed in a previously dehydrated double-necked round-bottomed flask under nitrogen atmosphere. Then, triphenylphosphine (9 mg, 0.035 mmol, 5 equiv) and dry and deaerated toluene–THF (0.5:0.5) were added and the mixture was magnetically stirred under nitrogen for 5 min. Then, $SiHCl_3$ (28 μl, 0.28 mmol, 40 equiv from Aldrich) was added and the solution was magnetically stirred in a pre-heated oil bath at 60 °C under nitrogen for 2 h. In an alternative experiment using more drastic conditions, 100 equiv of $SiHCl_3$ and 10 equiv of triphenylphosphine were employed, rising the temperature to 80° C. At the final time, the SPhos–PEG was precipitated with cold dry diethyl ether (20 ml) in an ice bath under nitrogen atmosphere and stirring for 15–30 min. The ethereal supernatant was extracted with a pipette under nitrogen atmosphere and the solid remaining was washed twice with additional 20 ml of diethyl ether (stirring for 15 min, room temperature) and dried under vacuum. The ^{31}P NMR spectrum showed the peaks corresponding to the protonated SPhos (δ 22 ppm) together with the SPhos oxide (δ 52 ppm) and remaining triphenylphosphine oxide (δ 29 ppm).

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