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ORIGINAL PAPER

Phosphine functionalized polyphosphazenes: soluble and re-usable polymeric reagents for highly efficient halogenations under Appel conditions

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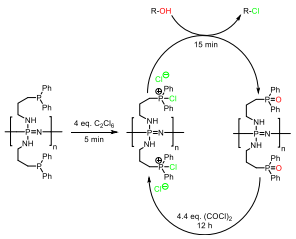
Abstract In this paper we present the preparation and application of a novel soluble phosphine functionalized polyphosphazene (poly[3-(diphenylphosphino)propylamino]phosphazene) and investigate its application as a polymeric reagent. Upon chlorination of the pendant phosphine groups, the polymer was found to facilitate the rapid and efficient transformation of alcohols to the corresponding chlorides and bromides under Appel-type conditions. Reaction times followed by ^{31}P NMR spectroscopy are shown to be rapid (several minutes) and the yields for the transformation of alcohols to the corresponding halides are in the range 80–99 %. The facile recovery of the oxidized polymeric agent by precipitation is also described, offering a significant advantage over notoriously difficult to remove small molecule phosphine oxide by-products. Furthermore the regeneration of the reactive phosphine chloride pendant groups is demonstrated, which could be efficiently re-used in a further chlorination reaction.

Graphical abstract



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Keywords Polyphosphazenes · Inorganic polymers · Polymeric reagents · Chlorination · Phosphorus compounds · Phosphine reagents

Introduction

Phosphines play an important role in today's synthetic organic chemistry [1]. They are employed as reagents [2–4], as complex-ligands for transition-metal catalysts or act as organo-catalysts [5–7]. The use of phosphines as reagents, in particular triphenylphosphine, enables a vast number of synthetic transformations including Appel-type halogenations [8], Staudinger [9], Mitsunobu [10–12], and Wittig reactions [13, 14], as well as amidations [15] and the reduction of sulfonyl chlorides and sulfoxides to thiols and sulfides [16, 17]. Although this wide variety of possible applications make phosphine reagents a valuable tool for the synthetic organic chemist, all of these examples suffer from two major drawbacks. Firstly, the formation of the corresponding phosphine oxide by-products which are often difficult to remove, even by chromatographic methods. This latter issue has been addressed by various groups using modified phosphines which either give water-soluble phosphine oxides after reaction for removal via aqueous extraction [18], or by polymer-supported phosphines [19–21] which can be more easily removed by filtration. Secondly, atom efficiency has also been a concern, and improvements in this regard have recently gained increasing attention. The two basic approaches here are the recovery of the initial phosphine by reductive methods [22], which often requires hazardous reagents and is not always efficient or the direct re-use of the phosphine oxides as reagents or catalysts [23–27].

Polyphosphazenes are an attractive class macromolecular carriers of reactive functionalities as they display a number of inherent features such as high functionality, with two functional groups per repeat unit, and the possibility of facile and variable post-polymerization chemical functionalization. The unusually high flexibility of the chemical backbone [28] and thus conformational flexibility further makes them ideally suited as solution state polymeric reagents in organic synthesis. Furthermore, the potential for chirality [29–31] renders them highly interesting as polymer supports [32–35].

Polyphosphazene supported phosphines have been synthesized and used as macromolecular ligands for transition-metal catalysts over recent decades [36–38] but, to the best of the authors knowledge, the use of pendant phosphines themselves as macromolecular reagents has not been investigated previously. Herein, we present the synthesis of a novel soluble phosphine functionalized polyphosphazene and investigate its use in the transformation of a series of alcohols to the corresponding chlorides and bromides, followed by recovery of the polymeric reagent by simple precipitation. Furthermore, the regeneration of the oxidized polymer and its re-application in such Appel-type reactions is investigated.

Results and discussion

The polymeric reagent poly[3-(diphenylphosphino)propylamino]phosphazene (**3**) was synthesized by macromolecular substitution of poly(dichloro)phosphazene $[PNCl_2]_n$ (**2**) [39, 40] with 3-(diphenylphosphino)propylamine. The precursor $[PNCl_2]_n$ was prepared via living cationic polymerization of trichlorophosphoranimine with triphenylchlorophosphonium chloride as initiator, previously prepared in situ by the reaction of triphenylphosphine with hexachloroethane [41]. The resulting $[PNCl_2]_n$ was converted to the polymeric phosphine reagent **3** by macromolecular substitution with 3-(diphenylphosphino)propylamine (Scheme 1), to give a soluble polymer with two-phosphine groups per repeat unit. $^{31}P\{^1H\}$-NMR spectroscopy was used to follow progress of the macromolecular substitution of $[NPCl_2]_n$ with 3-(diphenylphosphino)propylamine to give the fully substituted product **3** $[NPR_2]_n$ (details of this reaction and full spectra are given in the supplementary material, Fig. S2).

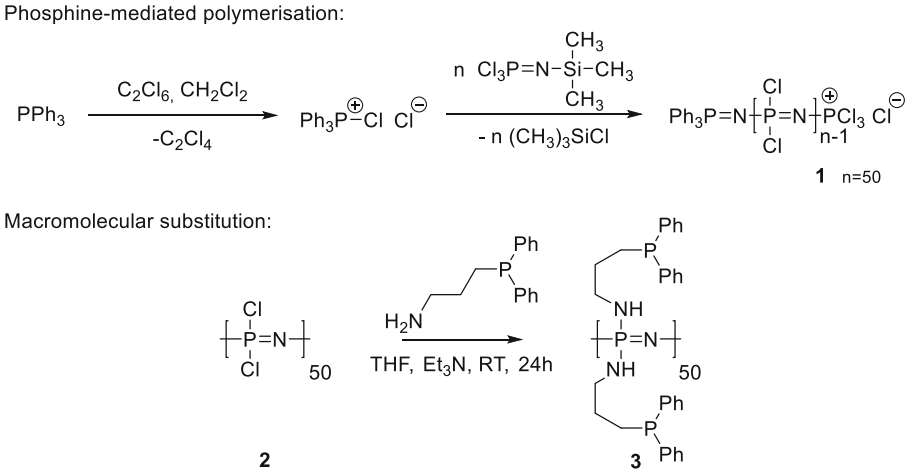
After purification, polymer **3** then underwent chlorination of the pendant phosphine ligands to give the chlorophosphonium chloride salt (polymer **4**, Scheme 2). The chlorination of the polymer-bound phosphine is rapid, as observed in $^{31}P\{^1H\}$ NMR measurements. Upon reaction with four equivalents of hexachloroethane in CD_2Cl_2, the initial phosphine is consumed within 5 min indicated by the loss of the NMR signal at −16 ppm and the appearance of a new signal at 79 ppm corresponding to the chlorophosphonium chloride salt [42] (Fig. 1).

Upon addition of one equivalent of 3,5-dimethoxybenzyl alcohol, and stirring for 10 min, a complete shift in the $^{31}P\{^1H\}$ NMR spectrum was observed. ^{31}P NMR signal of the reaction mixture to 34 ppm is observed, corresponding to complete formation of the phosphine oxide polymer **5**. These high reaction rates achieved in comparison to other polymer-supported alkyl diphenyl phosphines [43] can be explained by the polyphosphazenes exhibiting very open conformations in solution (assisted by the chain flexibility) that facilitate the accessibility of the reactive site groups. After completion of the reaction, the two products, phosphine oxide polymer and benzyl chloride were separated by precipitating a concentrated chloroform solution of the crude reaction mixture into cyclohexane. Excess hexachloroethane and the by-product, tetrachloroethylene were removed by a co-evaporation step with chloroform and drying under high vacuum. The oxidized polymer **5** was recovered in a 96 % yield (calculated from **3**) after filtration and washing with cyclohexane, while the product benzyl chloride was obtained in 80 % yield from the combined filtrates via simple evaporation.

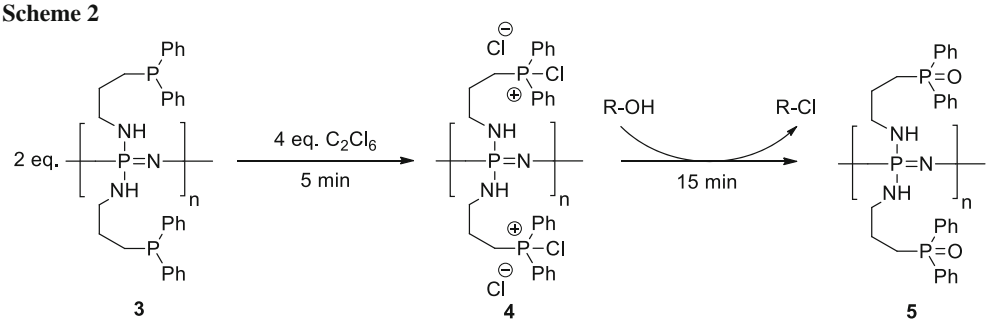
To evaluate the scope of the reaction, a series of alcohols, chosen to represent alcohols with widely differing properties, were reacted under similar conditions (Table 1). Among these examples were the electron-poor 4-nitrobenzyl alcohol, the highly electron-rich 2,4-dimethoxybenzyl alcohol, a secondary 4,4′-dichlorobenzhydrol as well as the aliphatic 1-hexadecanol and 2-hexadecanol. These alcohols were transformed into the corresponding chlorides within 15 min in good to very high yields (80–99 %), thus demonstrating the applicability of the polymeric reagents for a range of primary and secondary substrates. However, the reaction with 4-phenyl-2-methyl-2-butanol (**11a**) did not yield the desired product, instead the starting alcohol was quantitatively recovered. Further expansion of the scope to more polar products which are insoluble in hydrocarbons could be possible due to the fact that the polymer also precipitates efficiently from toluene and diethyl ether.

Since the polymer proved to be successful for use in chlorination reactions, the bromination of alcohols was also investigated. For this purpose, eight equivalents of CBr_4 were reacted with a solution of the polymer in CH_2Cl_2. The work-up of the reaction was performed in the same fashion as for the chlorination. However, the bromination reaction resulted in a mixture of substances as indicated by ^1H NMR spectroscopy. The major product with 70 % was the anticipated benzyl bromide but the mixture also contained some unreacted alcohol (25 %) and curiously also 5 % of the benzyl chloride (Fig. 2c). To clarify this, we repeated

Scheme 1



Scheme 2



the reaction in CD_2Cl_2 as a solvent and measured $^{31}P\{^1H\}$ NMR spectra at the various reaction stages. First, a shift in the $^{31}P\{^1H\}$ NMR spectrum from −16 to 32 ppm was observed confirming the reaction of the phosphine to the bromophosphonium salt. Interestingly, a minor signal at 79 ppm could also be observed, which is identical to the signal for the chlorophosphonium chloride in the chlorination reaction described above. Upon addition of one equivalent of 3,5-dimethoxybenzyl alcohol, both signals disappeared within 10 min and a new signal at 34 ppm representing the phosphine oxide could be observed. To rule out the participation of a possible C_2Cl_6 impurity we also prepared the reagent from commercially available triphenyl-chlorophosphonium chloride and compared the bromination reaction of 3,5-dimethoxybenzyl alcohol with both polymers, however, no influence of the polymer synthesis route on the composition of the crude bromination product was observed. Another suspected source for the chloride impurity was a non-innocent behavior of the solvent CH_2Cl_2. Therefore, we also performed the reaction in MeCN as this solvent and avoiding chlorinated solvents in the work-up and characterisation. MeCN is known to have a similar stabilizing effect as dichloromethane on the salt-like structure of R_3PX_2 -type compounds [42, 44] a prerequisite for the rapid transformation of alcohols to halides. Acetonitrile proved to be a more effective reagent for the bromination reagent giving 99 % yield of a mixture containing 75 % of the corresponding benzyl bromide and 25 % of unreacted alcohol (Fig. 2d).

Although the chlorination reactions described above are very rapid and highly efficient, they still suffer from the low atom economy that is distinct for non-catalytic phosphine mediated reactions. To address this issue, we also experimented with the re-use of the phosphine oxide polymer **5** of the chlorination reactions. Chlorination reactions with both small molecule, and polymer-supported phosphine oxides, were recently reported by the group of Denton [23–26]. In a similar approach, we reacted the phosphine oxide polymer **5** with 4.4 equivalents of oxalyl chloride in CH_2Cl_2 under an argon atmosphere for 12 h

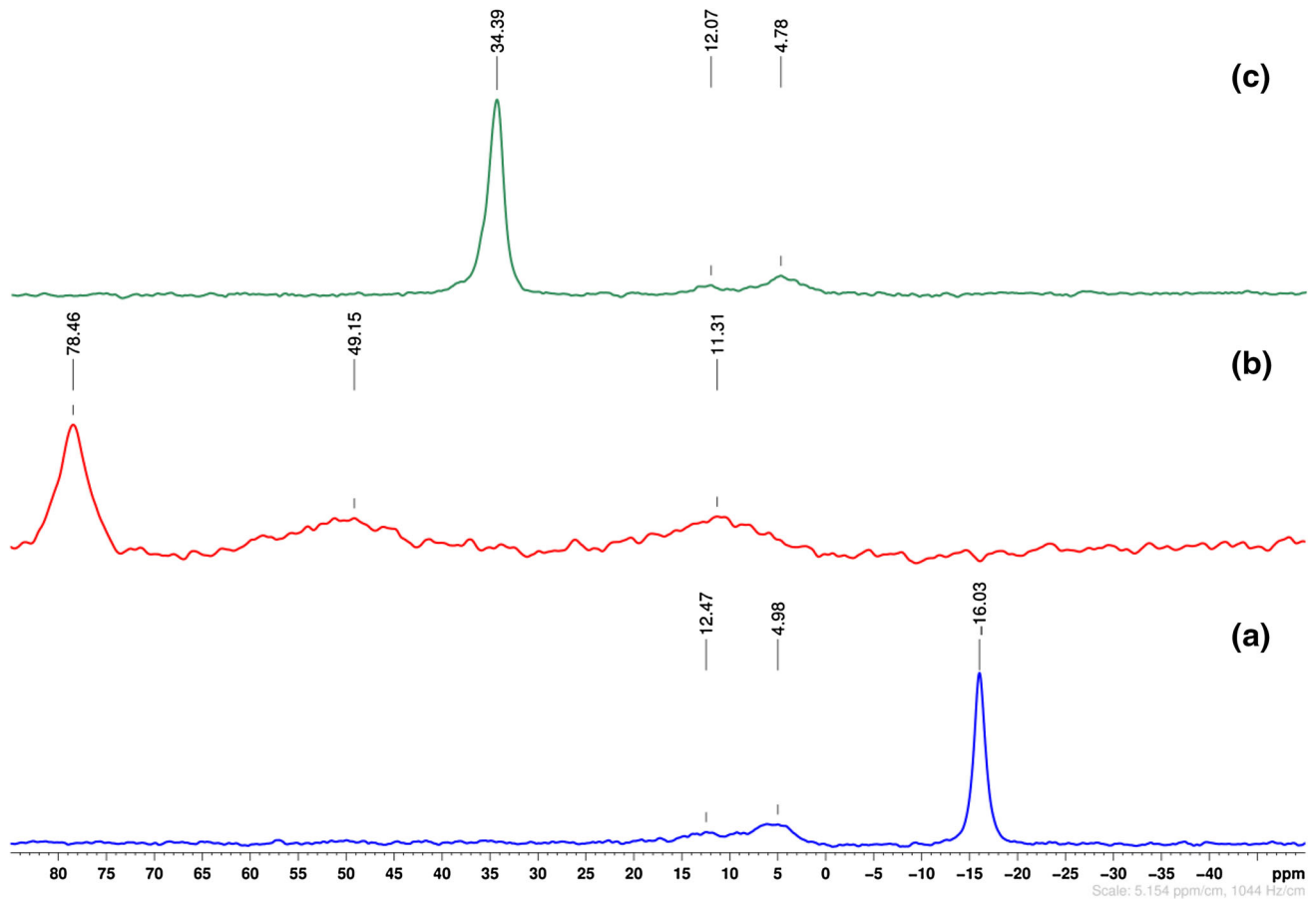


Fig. 1 $^{31}P\{^{1}H\}$ NMR spectra in CD_2Cl_2 of the polymeric reagent over the course of the reaction **a** free phosphine polymer (**3**) (−16.0 ppm); **b** polymer after chlorination (**4**) (78.5 ppm); **c** phosphine oxide polymer (**5**) after reaction (34.4 ppm). The signals at around 5 and 12 ppm correspond to the phosphorus nuclei in the backbone and the end groups, respectively (see supplementary material)

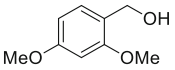
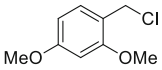
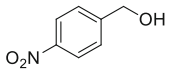
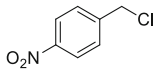
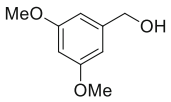
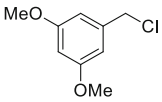
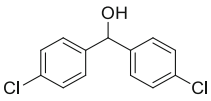
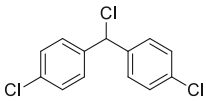
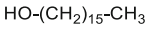
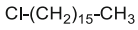
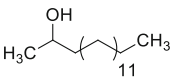
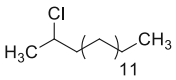
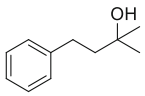
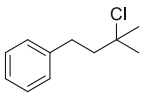
(Scheme 3). The successful conversion of the phosphine oxide to the chlorophosphonium chloride (**4**) was confirmed by the shift of the $^{31}P\{^{1}H\}$ NMR signal from 35 to 77 ppm. After removal of the solvent and excess oxalyl chloride in vacuo, the regenerated polymer **4** could be directly employed in the chlorination of alcohols under inert conditions. In an example reaction, 4-nitrobenzyl chloride (**6b**) could be obtained in excellent 97 % yield in 1 h reaction time.

The longer reaction time necessary for the full conversion of the alcohol is due to the film morphology of the re-chlorinated polymer which requires longer to fully dissolve. The solution only becomes clear as the reaction proceeds and the chlorophosphonium salt is consumed. A re-precipitation of the polymer film to regain a powdered form would be highly inconvenient due to the moisture sensitivity of the intermediate. Repeated re-use (2–3 cycles) showed decreased activity (see supplementary material Table S1 and Fig. S3).

Conclusion

The successful synthesis of a novel polyphosphazene-based phosphine reagent is reported and its employment as a polymeric reagent in the Appel-type chlorination of alcohols demonstrated on a range of alcohol substrates with broad spectrum of properties. The reactions were observed to be high yielding and fast for every example tested, with yields in the range of 80–99 % within 15 min reaction time. The polymeric reagent also proved to be convenient to handle, since it can be easily removed from the reaction mixture by simple precipitation in >95 % recovery. Furthermore, it is demonstrated that the phosphine-based polymer could be regenerated and re-used with similar efficiency a further reaction, although this activity was diminished upon further cycles. The polymeric reagent could also be used in the transformation of alcohols to the corresponding bromides, although this reaction proved to have inferior efficiency compared to the chlorination

Table 1 Scope of the chlorination reaction

Entry	Starting material	Product[a]	Yield[b]/%	Ref.
1	 **5a**	 **5b**	99	[45]
2	 **6a**	 **6b**	99	[46]
3	 **7a**	 **7b**	80	[47]
4	 **8a**	 **8b**	96	[48]
5	 **9a**	 **9b**	99	[49]
6	 **10a**	 **10b**	98	[c]
7	 **11a**	 **11b**	-	

Complementary characterization of all products is provided in the supplementary material

[a] Conditions: 2 eq. of **3**, 4 eq. C_2Cl_6, r.t., 15 min

[b] Isolated yield. Product purity exceeded 95 % in every case according to ^{1}H NMR spectroscopy

[c] No literature NMR spectra found for this compound

reactions. Overall, this polymer represents an interesting new polymeric reagent, due to its excellent reactivity combined with its simple recovery and efficient re-usability.

Experimental

3-(Diphenylphosphino)propylamine was purchased from ABCR Chemicals, other chemical from Sigma Aldrich, or TCI Chemicals. Anhydrous solvents were purchased from Alfa Aesar and stored under Argon, all other solvents were from VWR and used without further purification unless otherwise noted. The polymer synthesis and halogenation reactions were carried out in a glove box (MBRAUN) under argon. Proton (^{1}H NMR) and carbon (^{13}C NMR) spectra were recorded on a Bruker Ultra Shield 300 device at 300 and 75 MHz, respectively. Chemical shifts are given as parts per million (ppm) on the delta (δ) scale and referenced to the "solvent residual signal" at 7.26 and 77.16 ppm for $CDCl_3$ [37]. Phosphorus (^{31}P{^{1}H} NMR) were recorded on a Bruker Ultra Shield 300 device at

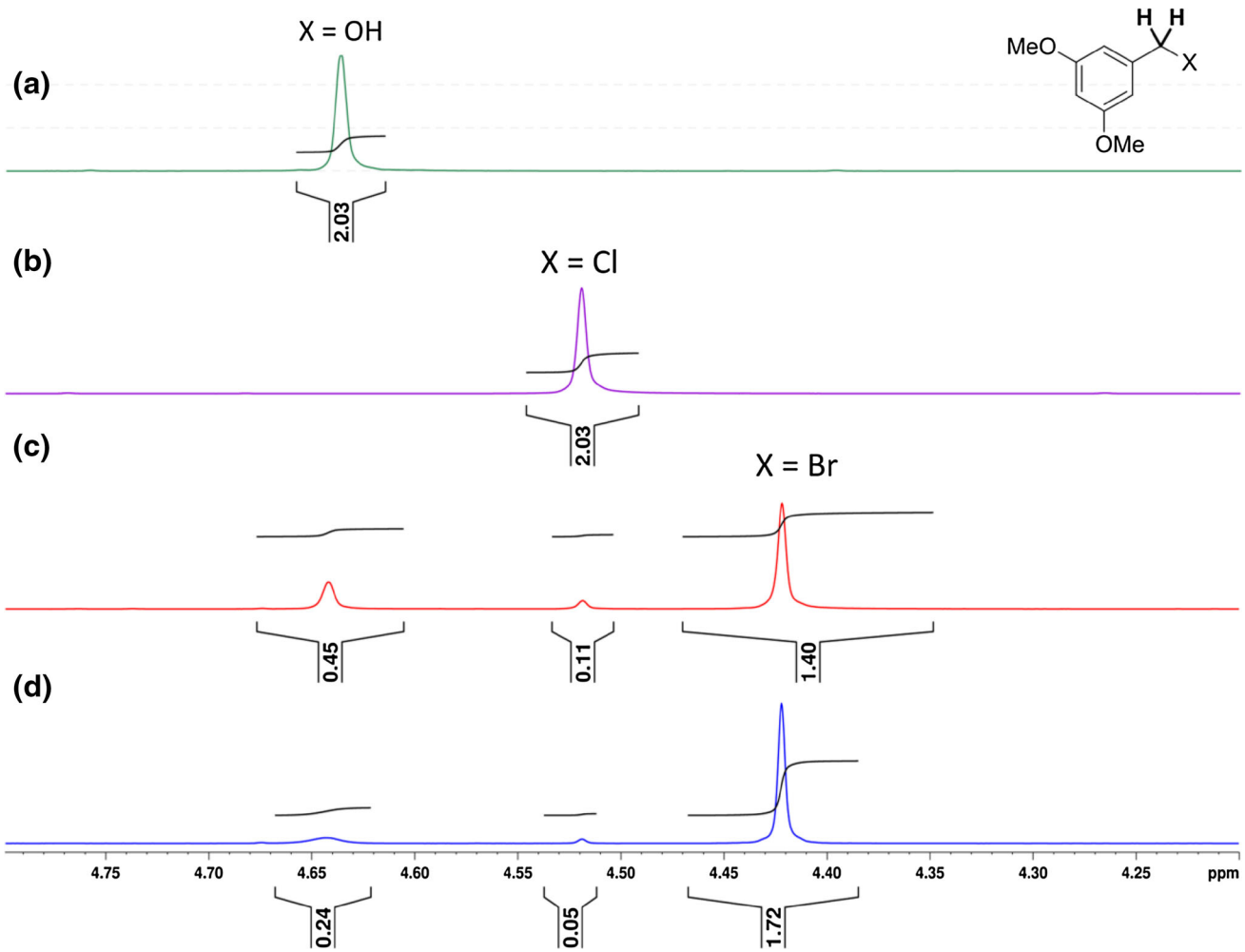
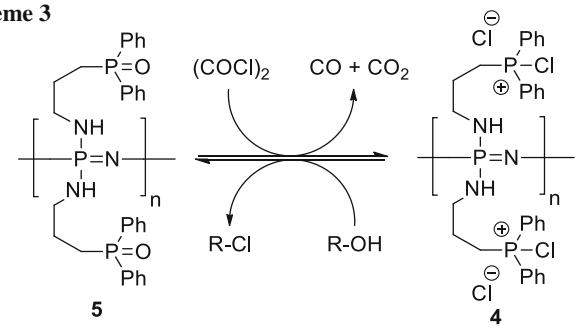


Fig. 2 ^{1}H NMR ($CDCl_3$) spectra of the benzylic CH_2 group **a** alcohol; **b** after chlorination; **c** after bromination in CH_2Cl_2, and **d** after bromination in MeCN

Scheme 3



121.4 MHz or on a Bruker DRX 500 device at 202.4 MHz, using 85 % phosphoric acid as an external standard. ATR-IR-spectra were recorded on a PerkinElmer Spectrum 100 Series. Gel permeation chromatography (GPC) was measured with a Viscothek GPCmax instrument equipped with a PFG column from PSS (Mainz, Germany; 300 mm × 8 mm, 5 µm particle size). The samples were eluted with DMF containing 10 mM LiBr at a flow rate of 0.75 cm^3/min at 60 °C. The molecular weight was estimated by multi-detector calibration (refractive index, right angle light scattering, low angle light scattering and viscosity detector) using a linear polystyrene standard.

Polyphosphazene reagent synthesis

Triphenylphosphine (7.5 mg, 28.6 µmol) was reacted with 7.4 mg C_2Cl_6 (31.5 µmol) in 1 cm^3 CH_2Cl_2 for 24 h at room temperature to yield dichlorotriphenylphosphorane. Then 320.9 mg *N*-(trimethylsilyl)-trichlorophosphoranimine (1.43 mmol) was added and stirred over night at room temperature to yield poly(dichloro)phosphazene. For macromolecular substitution 869.6 mg 3-(diphenylphosphino)propylamine (3.57 mmol) and 0.5 cm^3 Et_3N (361.7 mg, 3.57 mmol) were dissolved in 5 cm^3 anhydrous THF and added to the reaction mixture. The reaction was stirred for 16 h at room temperature. After filtration, the solvent was concentrated and the polymer precipitated

three times in heptane and three times in methanol to yield 490 mg of the product as colourless solid in 64 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (br, 3H, N<u>H</u> and –C<u>H</u>$_2$-PPh_2), 1.83 (br, 2H, –CH_2–C<u>H</u>$_2$–CH_2–), 2.81 (br, 2H, –NH–C<u>H</u>$_2$–), 7.75–6.99 (m, 10H, Ph-<u>H</u>) ppm; ^{13}C NMR (75.432 MHz, $CDCl_3$): $\delta = 138.8$, 132.7, 130.9, 128.4, 42.3, 28.3, 20.1 ppm; ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): $\delta = -17.13$ (–PPh_2), 3.49 ([NPR]$_2$), 10.43 (α-end group) ppm; SEC (multidetector calibration): $M_n = 35{,}000$ - g mol^{-1}, Đ: 1.1.

General procedure for the chlorination of alcohols

In a 10 cm^3 flask, 50 mg of phosphine-polyphosphazene (0.094 mmol) was dissolved in 3 cm^3 anhydrous CH_2Cl_2 under an argon atmosphere. The resulting solution was cooled to 0 °C and a solution of 0.384 mmol C_2Cl_6 in 1 cm^3 anhydrous CH_2Cl_2 was added followed by 0.094 mmol of the alcohol after 5 min. After further stirring for 15 min the solvent was removed, the residue was taken up in a minimum amount of $CHCl_3$ and the oxidized polymer was precipitated in an appropriate solvent. The polymer was removed by filtration, and washed with the precipitation solvent. The combined filtrates were evaporated to dryness and dried under high vacuum to yield the corresponding alkyl or benzyl chlorides.

General procedure for the re-use of the oxidized polymer

In a 25 cm^3 two-neck round bottom flask equipped with an argon inlet and a magnetic stirring bar were placed 56 mg of the phosphine oxide polymer (0.1 mmol) and dissolved in 4 cm^3 dry CH_2Cl_2 under an Argon atmosphere. After cooling the solution to 0 °C in an ice-bath 37 mm^3 oxalyl chloride (0.44 mmol) were added. After gas evolution (!care CO formation!) had ceased, the ice-bath was removed and the mixture stirred at room temperature for 12 h after which the solvent and excess reagent were removed in vacuo. The resulting residue was re-dissolved in 3 cm^3 dry CH_2Cl_2 and a solution of 0.1 mmol alcohol in 1 cm^3 CH_2Cl_2 was added. The reaction was stirred for 1 h, the solvent was removed, the residue was taken up in a minimum amount of $CHCl_3$ and the oxidized polymer was precipitated in an appropriate solvent. The polymer was removed by filtration, and washed with the precipitation solvent. The combined filtrates were evaporated to dryness and dried under high vacuum to yield the corresponding alkyl or benzyl chlorides. It is important to maintain inert conditions throughout the full regeneration and re-use procedure, as contact with moisture in the air instantaneously converts the polymer back to the phosphine oxide.

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