COMMUNICATION

# Synthesis and characterisation of β-aminophosphine ligands on a solid support †

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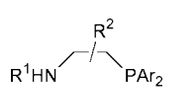
**A highly efficient and expeditious synthesis of mono-*N*-substituted β-aminophosphine ligands on a polystyrene support accompanied by thorough characterisation, utilising a combination of NMR techniques, was demonstrated for the first time.**

Polymer-immobilised catalysts combine useful properties of both homogeneous and heterogeneous systems. As such, they continue to be the focus of the research efforts and interest of catalytic chemists.[1] Catalysis based on solid matrix-bound structures represents a potentially fruitful field for the combinatorial approach and high throughput screening techniques.[2] One possible way toward a successful preparation of a polymer-immobilised catalytic library proceeds through an efficient and expeditious assembly of ligands on a solid support. While an attachment of phosphine ligands presynthesised in solution to a reactive polymer through a remote functionality is well known,[1d–f] a multistep assembly of such ligands *on resin* utilising a number of building blocks has hardly been investigated at all.[3]

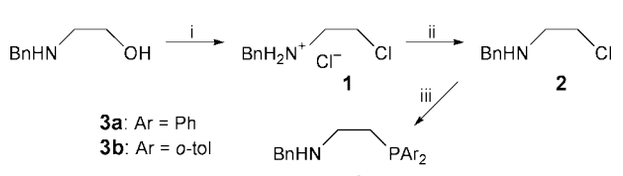
Due to our interest in catalytic systems with hemilabile ligands, we recently launched a research project aimed at the solid-phase synthesis of phosphorus–nitrogen ligands of type **I**.[4]




**I**

For the synthesis of ligands **I** on a support, the approach based on anchoring through the nitrogen substituent was chosen due to its synthetic simplicity as well as the diversity of the available building blocks. Our solid-phase synthesis of ligands **I** was preceded by an examination of the synthetic scheme in solution for a model compound. Remarkably, while the solution synthesis is characterised by a medium yield and a low reproducibility, an excellent, high yielding synthesis on a solid support was observed.

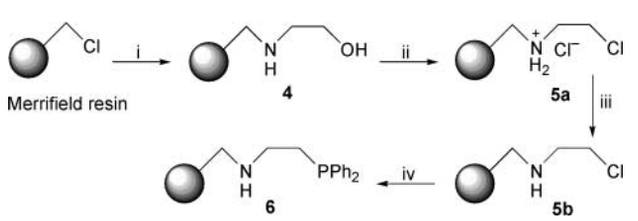
The synthesis in solution was based on a literature procedure.[5] Although the modified synthesis (Scheme 1) formed the model ligand **3a**, the overall yield never exceeded 45%, significantly lower than the reported one.[6] The substitution of the OH group by chloro afforded highly variable yields (30–60%) of colourless salt **1**. This rather disappointing result was attributed to side reactions forming di- and oligo-mers of the $C_2$ unit.[7] It was presumed that the observed side reactions would not affect the solid-phase synthesis due to the pseudodilution principle.[8] Deprotonation of **1** to give **2** proceeded smoothly. However, some difficulties were encountered while attempting to perform the phosphination of **2** with diphenylphosphide. While there is no doubt that the reaction of $HPPh_2$ with NaH or with $^t$BuLi formed *in situ* the required metal diphenylphosphides, both phosphides were completely unreactive towards **2**. Finally, the phosphination was successfully performed utilising $LiPPh_2$, generated *in situ* from $Ph_3P$ and Li.[9] Interestingly, while such an approach usually requires quenching of the byproduct PhLi with $^t$BuCl, omission of the quenching had no detrimental effect on the reaction outcome. Similar results regarding the nucleophilic reactivity of the *in situ* generated phosphides, as well as the tolerance of PhLi in the reaction mixture, were recently observed.[10] The phosphination step exhibited very high sensitivity to oxygen and therefore requires rigorous anaerobic conditions.




**Scheme 1** *Reagents and conditions*: i, $SOCl_2$, $CHCl_3$, 60 °C, 2 h, 35%; ii, NaOH, $H_2O$, 70%; iii, $LiPAr_2$, THF, r.t., 18 h, quant.

The success of the synthesis was confirmed by NMR measurements and comparison of product **3a** with an authentic sample obtained by an alternative method.[11]

After the model study in solution was completed, the synthesis on a solid support was targeted. Since the goal is a set of resin-bound ligands, a compatible cleavage procedure at the end of the synthetic sequence is not compulsory. Thus, the Merrifield resin, as one of the most robust supports for organic synthesis, was utilised. A synthetic scheme similar to the one established for the solution chemistry was exercised (Scheme 2).




**Scheme 2** *Reagents and conditions*: i, ethanolamine, DMF, 50 °C, 17 h; ii, $SOCl_2$, $CHCl_3$, 60 °C, 2 h; iii, $^iPr_2EtN$, THF; iv, $LiPPh_2$, THF, r.t., 24 h, 91% (4 steps).

According to the scheme, ethanolamine (2-aminoethanol) immobilisation on the Merrifield resin was followed by chlorodehydroxylation with $SOCl_2$ (to give resin **5a**). Deprotonation of the (chloroethyl)ammonium salt **5a** was followed by phosphination using the earlier established procedure to yield a pale yellow target resin **6**.‡ While the chlorodehydroxylation and phosphination steps closely followed the procedures in solution, an organic base ($^iPr_2EtN$) rather than hydroxide was used for the deprotonation step in order to better suit the solid-phase synthesis.

Major emphasis was placed on the determination of the purity and the yields of the product and the intermediates along

† Electronic supplementary information (ESI) available: details of the preparation of compounds **1**–**3**, **7**–**10**. http://www.rsc.org/suppdata/p1/b0/b009640g/

 DOI: 10.1039/b009640g

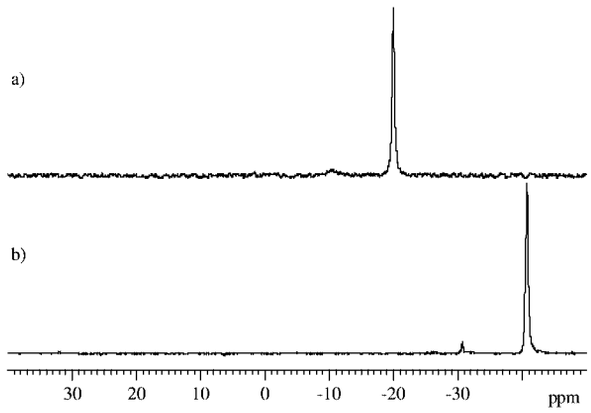
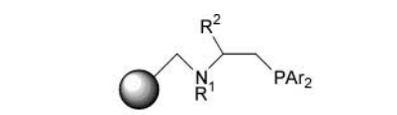



**Fig. 1** Gel-phase $^{31}$P NMR of **6** (a) and **10** (b).

the synthetic pathway. The efficiency and integrity of the synthesis were established by a combination of complementary techniques.

As expected, direct assessment of yields and selectivities through cleavage of the derivatised amine from resin **6** was not possible. Thus, a series of direct measurements of resin-bound compounds was undertaken. First, *gel-phase* $^{31}$P and $^{13}$C NMR were applied to the model resin **6** as well as to resins **7**–**10** prepared by analogous procedures.



**7**: Merrifield resin, $R^1$ = Bn, $R^2$ = H, Ar = Ph
**8**: Merrifield resin, $R^1$ = H, $R^2$ = $^i$Pr, Ar = Ph
**9**: Wang bromo resin, $R^1$ = H, $R^2$ = H, Ar = Ph
**10**: Merrifield resin, $R^1$ = H, $R^2$ = H, Ar = *o*-Tol

**11**: Merrifield resin, Ar = Ph

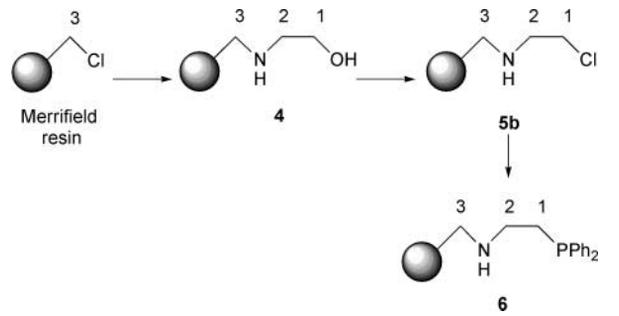
The $^{31}$P NMR of resins **6**–**9** exhibited clean spectra with a broad peak at *ca.* −20 ppm (Fig. 1(a)).§ In most cases, a very small broad peak (2–5% of the total) was observed at *ca.* −10 ppm. The main signal belongs to the target ligands (as evidenced by comparison to their soluble analogue **3a**). The smaller signal is attributed to the product of the diphenylphosphide reaction with unsubstituted chlorobenzyl sites on the resin. This assignment was confirmed by the direct reaction of $Ph_2PLi$ with Merrifield resin, forming resin **11**, which exhibited a single broad peak at −10.6 ppm.

The formation of **11** as a very minor byproduct could be explained by incomplete substitution of the chloromethyl sites of the Merrifield resin by ethanolamines in the first step of the sequence. An alternative explanation is a minor degree of cleavage of the resin-bound ethanolamine during the $SOCl_2$-induced substitution step.

For resin **10**, a similar spectrum was observed: a major peak at −41 ppm and a minor peak (~4%) at −30 ppm (Fig. 1(b)). The $^{31}$P NMR clearly showed that the product resins do not contain more than 5% of phosphorus-containing impurities.

The absence of impurities that do not contain phosphorus was proven by gel-phase $^{13}$C NMR of resins **6** and **10**.[12] For example, the gel-phase $^{13}$C NMR of **10** was compared to the $^{13}$C NMR of its soluble analogue **3b** (Fig. 2). Four aliphatic signals only were observed for **10** (as expected). These signals closely resemble the analogous peaks in the spectrum of **3b**. (Slight differences of up to 4 ppm are attributed to the differences in the environment polarity and steric crowding.) Although the polymer obscures some of the aromatic signals of **10**, broad signals near the polymer peak are clearly visible, disclosing the

**Table 1** $^{13}$C NMR chemical shifts of the aliphatic carbons for resins **4**, **5b** and **6** (from monitoring resin **6** synthesis)




| | 1 | 2 | 3 |
|---|---|---|---|
| Merrifield resin | — | — | 46.1 |
| **4** | 60.9 | 50.9 | 53.4 |
| **5b** | 44.7 | 50.4 | 52.9 |
| **6** | 29.7 | 53.6 | 57.7 |

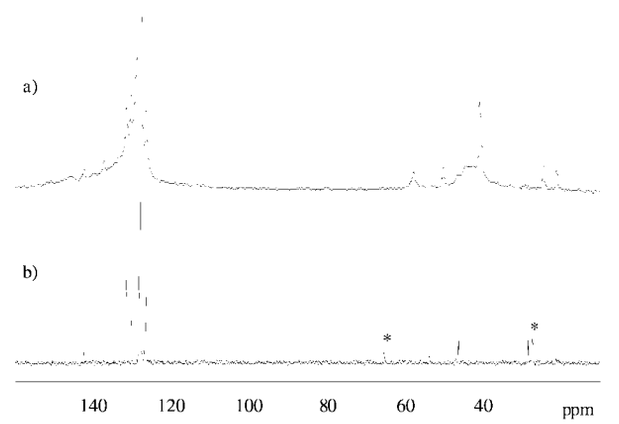



**Fig. 2** Comparison between gel-phase $^{13}$C NMR of **10** (a) and $^{13}$C NMR of **3b** (b). * denotes signals of an impurity in solution.

existence of a resin-bound diarylphosphine moiety. These observations, as well as similar data obtained for resin **6**, demonstrate with a high degree of confidence that the target compounds are cleanly formed on the support.

A continuous step-by-step monitoring of the synthesis of resin **6** followed the on-resin characterisation of the product ligands. The chemical shifts of the three aliphatic carbons are summarised in Table 1. The shifts are in full agreement with those of the soluble analogues of compounds **4**, **5b** and **6**. Moreover, each transformation results, according to the monitoring, in clean and practically quantitative conversion of the starting material into product. No byproducts or remaining starting materials were detected for any step. This observation is supported by the elemental analysis data.‡

Finally, a $^{31}$P NMR-based quantification experiment was performed with resins **6** and **10**. Each resin was mixed with a commercial polystyrene-immobilised triphenylphosphine reference resin.¶ After recording of the $^{31}$P gel-phase NMR spectra, the yields of resins **6** and **10** were determined using the mixing ratio, the integral ratio and the known reference loading. Yields of 91% and 95% were determined for resins **6** and **10** respectively.

The comparison of the solid-phase synthesis to that in solution reveals that all the three common steps proceed in a much more satisfactory fashion on a solid support. In contrast to solution chemistry, the dehydroxychlorination is practically quantitative. The absence of di- or oligo-merisation due to the pseudodilution principle is clearly responsible for this difference. The deprotonation step proceeds better on a solid support as well, probably because of milder conditions and a simpler purification technique. Finally, the significantly lower susceptibility to oxidation of the resin-bound phosphines, as compared

to soluble analogues, contributes markedly to the higher yield of phosphination on a solid support.

In conclusion, an expeditious and efficient method for the synthesis of β-aminophosphines on a solid support was established. This is a remarkable achievement, since the analogous synthesis in solution is far from satisfactory. An assessment strategy combining complementary on-resin characterisation techniques demonstrated the excellent yield and purity of the support-bound ligands. The combination of the applied synthetic and analytical methods represents an innovative and general approach to the solid-phase synthesis of phosphorus ligands.

## Acknowledgements

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## Notes and references

‡ Typical procedures. **4**: Ethanolamine (3.6 mmol, 10 eq.) was added to a suspension of the Merrifield resin (0.5 g, 0.36 mmol) in a minimal volume of dry DMF. The suspension was stirred for 17 h at 50 °C, filtered, the resin washed with ethanol (×2) and DCM (×2) and dried *in vacuo*. Yield 95% to quantitative. Partial gel-phase $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$ 60.9, 53.4, 50.9. IR (KBr): 3366, 3020, 2905, 1600, 1493, 1451, 1027 cm$^{-1}$. Anal. calcd. (for loading of 0.71 mmol g$^{-1}$ of $C_3H_8NO$ on PS-DVB, prepared from Merrifield resin with a loading of 0.72 mmol g$^{-1}$) C 89.96, H 7.90, N 0.99. Found C 89.20, H 7.86, N 0.96%.

**5b**: Thionyl chloride (0.37 ml, 5.04 mmol, 16 eq.) was added dropwise to a suspension of **4** (*ca*. 0.32 mmol) in a minimal amount of chloroform at 0 °C. After 30 min of stirring, the temperature was raised to 60 °C and the suspension stirred for 2 hours. After cooling, the resin was filtered, washed with DCM (×3), ethanol, DCM and dried *in vacuo* (**5a**). The deprotonation was performed by stirring the resin in a solution of 20 eq. of $^{i}Pr_2EtN$ in a minimal amount of THF for one hour, filtering the resin and resuming the stirring with the base for another hour. Finally, the resin was filtered, washed with THF (×3) and dried *in vacuo*. Yield 95% to quantitative. Partial gel-phase $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$ 52.9, 50.4, 44.7. IR (KBr): 3410, 3020, 2926, 1600, 1493, 1453, 1026 cm$^{-1}$. Anal. calcd. (for loading of 0.61 mmol g$^{-1}$ of $C_3H_7ClN$ on PS-DVB, prepared from Merrifield resin with a loading of 0.63 mmol g$^{-1}$) C 89.22, H 7.73, N 0.86, Cl 2.18. Found C 88.67, H 7.67, N 0.65, Cl 1.88%.

**6**: Under argon. Freshly cut Li wire (0.11 g, 15.3 mmol, 48 eq.) was added to a solution of triphenylphosphine (0.84 g, 3.2 mmol, 10 eq.) in 8 ml of THF. After stirring for 3 h, the residual lithium was filtered off and the filtrate was added to a suspension of resin **5b** (*ca*. 0.32 mmol) in a minimal volume of THF. The suspension was stirred for 24 h. The resin was filtered off and washed with water, acetone, chloroform, benzene and ether and dried *in vacuo.* Quantitative yield. Gel-phase $^{31}$P NMR (202 MHz, $C_6D_6$): $\delta$ −19.9(s). Partial gel-phase $^{13}$C NMR (125 MHz, $C_6D_6$): $\delta$ 133.0, 57.7, 53.6, 29.7. IR (KBr): 3417, 3022, 2922, 1668, 1599, 1488, 1445, 1180, 1025 cm$^{-1}$. Anal. calcd. (for loading of 0.56 mmol g$^{-1}$ of $C_{15}H_{17}NP$ on PS-DVB, prepared from Merrifield resin with a loading of 0.63 mmol g$^{-1}$) C 86.70, H 7.39, N 0.79. Found C 87.59, H 7.47, N 0.90%.

§ The $^{31}$P NMR chemical shifts are reported with reference to an external 85% $H_3PO_4$ standard.

¶ Purchased from Fluka, crosslinked with 1% divinylbenzene, particle size 100–200 mesh, 1.6 mmol g$^{-1}$.

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3 (*a*) W. Dumont, J.-C. Poulin, T.-P. Dang and H. B. Kagan, *J. Am. Chem. Soc.*, 1973, **95**, 8295; (*b*) J. M. Brown and H. Molinari, *Tetrahedron Lett.*, 1979, **31**, 2933; (*c*) phosphine-containing peptides were assembled on a solid support using a phosphine-containing amino acid: S. R. Gilbertson and X. Wang, *Tetrahedron Lett.*, 1996, **37**, 6475.

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5 M. M. T. Khan and A. P. Reddy, *Polyhedron*, 1987, **6**, 2009.

6 A possible explanation may be connected to an apprehension expressed in ref. 11 which states that in ref. 5 a dibenzylated ethanolamine, rather than the monobenzylated one, was utilised.

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12 For gel-phase $^{13}$C measurement, conditions reported by F. Lorge, A. Wagner and C. Mioskowski, *J. Comb. Chem.*, 1999, **1**, 25 were slightly altered (P1 = 10 μs, D1 = 175 ms). From numerous gel-phase $^{13}$C NMR measurements we assume that the upper limit for undetected impurities is 10%.