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Rapid assembly and synthetic applications of a supported poly-α-amino acid containing phosphine groups

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Abstract

A simple method for the rapid multiplication of the number of available amine sites on a polymer bead, using lysine *N*-carboxyanhydride, is described. The product may be functionalised with a phosphine and employed in a catalytic reaction.

There is currently a high level of interest in the development and use of funtionalised polymers as reagents in synthesis.[1] Polymers bearing phosphine groups, for example, may be employed for numerous catalytic reactions, yet also benefit from improved practicality in terms of recovery and reuse. Supported phosphine ligands of this type have been synthesised based on both a polyethyleneglycol–polystyrene (PEG/PS) graft copolymer (Tentagel®)[2] and soluble acrylamide polymers.[3] The PEG/PS supported reagents, formed by coupling the polymer to *p*-(diphenylphosphine)benzoic acid, have been employed in palladium-catalysed allylic substitution and Suzuki coupling reactions.[2] Water-soluble acrylate polymers containing phosphine groups have been used in a number of applications including the coupling of aryl halides with alkynes.[3]

The trifunctional structures of amino acids such as lysine may be employed in the synthesis of hyperbranched dendritic poly(amines).[4] Methods for the construction of such polymers, whilst effective, often require several cycles of multistep processes. One of the significant attractions of the method, however, is the capacity for the preparation of copolymers that serve to moderate the solubility properties to the advantage of the user. Homopolymers of a single amino acid often exhibit unfavourable solubility properties compared to copolymers, which may be a result of increased crystallinity imposed by the regular structure.[5]

In this paper we describe a simple and effective method for the multiplication of the level of functionalisation on an amine-loaded solid support through the use of *N*-carboxyanhydride

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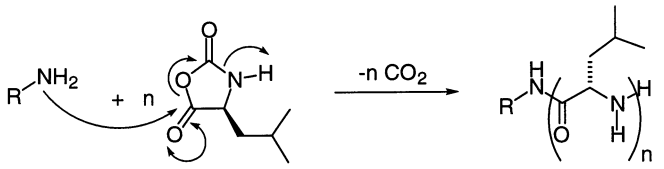
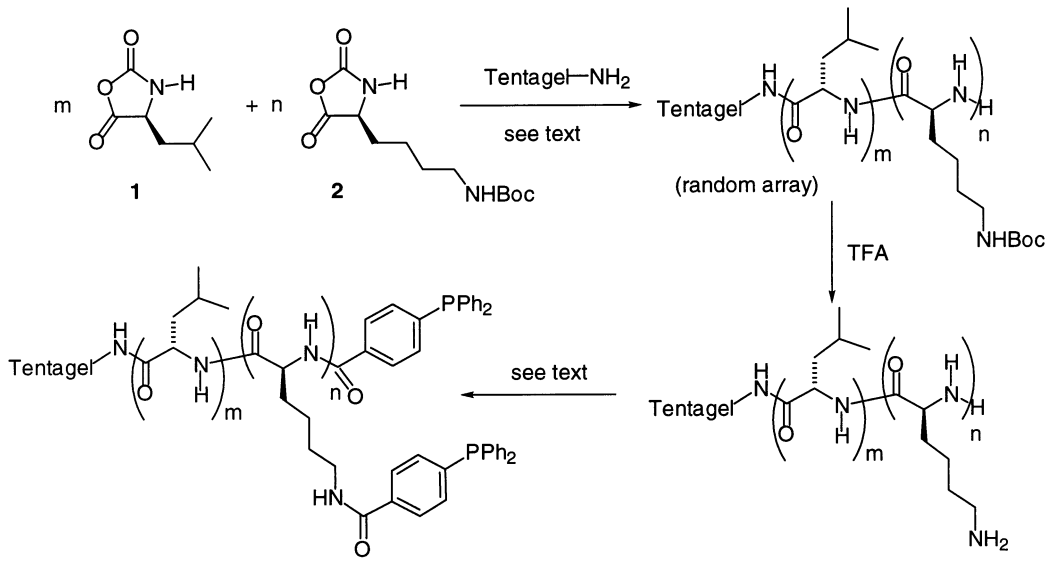
(NCA) derivatives of amino acids. The practical value of these materials is demonstrated through their functionalisation with catalytically active phosphine donor groups and application to a palladium-catalysed substitution reaction.

Our starting point was the well established reaction of amino acid *N*-carboxyanhydride (NCA) derivatives with amine initiators, a process which leads to the stepwise growth of a peptide chain accompanied by the loss of a carbon dioxide molecule with the addition of each residue (Scheme 1).[5] When the amine initiator is a part of a resin bead such as Merrifield resin or Tentagel®, this process results in the one-pot formation of a peptide-functionalised derivative. The use of this methodology to prepare resin-supported polyleucine, first reported by Itsuno,[6] has been exemplified and extended by Roberts, who has used the product as an asymmetric catalyst for the epoxidation of electron poor alkenes under non-aqueous conditions.[7]

We first prepared samples of pure crystalline leucine–NCA **1** and ε-*t*Boc protected lysine–NCA **2** in yields of 50–60%, depending on scale, using the established reaction of triphosgene with each precursor amino acid. These two reagents were then combined with commercially available Tentagel® to form peptide-functionalised derivatives (Scheme 2). Pure leucine and ε-*t*Boc protected polylysine derivatives were also prepared by the same means. A related NCA polymerisation method has been used for the synthesis of branched copolymers of lysine with other amino acids.[4b]



Scheme 1.



Scheme 2. Synthesis of supported phosphines

In the case of the resin-supported polypeptide, it is not possible to determine the degree of polymerisation with a high degree of accuracy, however we were able to measure increases in the mass of the polymer beads which corresponded well with those expected based on the quantities of NCAs used in each case.[†]

Infrared spectroscopy also proved to be a valuable analytical tool, and allowed the identification of both new amide and carbamate carbonyl functionality in the polymers. Given this information and the results of ^{31}P NMR (see below) of later derivatives, we have assumed that the mass increase of the polymer bead was in each case due to amino acid residues and, in the case of a copolymer, statistically distributed in a ratio corresponding to that of the NCAs used.

The resins were then deprotected, with quantitative mass recovery, using TFA to reveal the amine functionality (Scheme 2). At this point the reaction was followed by IR spectroscopy to monitor the loss of carbamate, and with the use of a Kaiser test to establish the presence of amines.

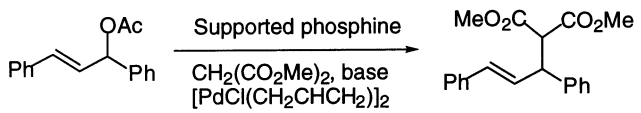
Functionalisation of the newly-revealed amino groups was attempted with both *o*- and *p*-diphenylphosphinobenzoic acid using EDC/HOBt/DMF. Before using our functionalised polymer beads we first examined the reaction of amino-functionalised Tentagel® alone in order to produce a 'baseline' polymer for comparison. In the case of the *o*-diphenylphosphinobenzoic acid the yields of coupling products were consistently poor, almost certainly due to steric hindrance. Rather better results were obtained using the *p*-diphenylphosphinobenzoic acid, for which Kaiser tests and ^{31}P NMR were used to determine the level of functionalisation. In all cases the mass recovery was almost quantitative. In the case of the supported polyleucine, only a weak ^{31}P NMR signal could be detected, as would be expected in the case where only the terminal nitrogen is available for amide formation. A strong but broad ^{31}P NMR signal was obtained for the phosphine-loaded leucine/lysine copolymer and the Kaiser test was negative, suggesting essentially complete functionalisation. In the case of the homolysine the ^{31}P NMR signal was strong but a positive Kaiser test indicated that many amine sites remained unfunctionalised, possibly due to inaccessibility or steric hindrance. Isolation at each step was achieved by a simple process of filtration and washing, followed by drying in a vacuum.

Having prepared the supported phosphines, we selected the palladium-catalysed reaction of a malonate anion with an allylic acetate to evaluate the potential use of the materials (Scheme 3, Table 1). In all cases the supported reagents were able to catalyse the substitution. Since the lack of solubility meant that the level of phosphine loading was difficult to establish with certainty, we used a relative mass of supported reagent to substrate.[‡] Although the lysine/leucine

[†] In a typical example 1.30 g of Tentagel® (0.4 mmol assuming amine loading 0.3 mMol/g) was combined with leucine–NCA (3.48 g, 22.2mmol) and lysine–NCA (1.91 g, 7.0 mmol) in toluene to give 4.97 g of resin-bound copolymer. Assuming full reaction of the NCAs, the theoretical mass of the functionalised material would be 5.33 g. The original Tentagel® will account for 1.30 g of this material, hence 4.67 g of amino acid was added, corresponding to ca. 90% of the theoretical value. The maximum loading of amino groups will therefore be: 0.4 (original amino groups on Tentagel®)+6.3 (90% of lysine–NCA)/4.97 = 1.34 mmol amine/g which is some 4-fold higher than the original material. In this case, removal of solvents from the filtrate gave 0.14 g of a mixture of unreacted leucine and lysine–NCAs. Notably the pure leucine and lysine homopolymers were not formed with such high efficiency (typically 40–60% of theoretical mass recovery).

[‡] As an example of a calculation, the previously described leucine/lysine copolymer of 1.34 mmol/g functionality, following a correction for the mass increase upon substitution of the *t*Boc by the diphenylphosphinobenzoate group, would give a supported reagent containing ca. 1.30 mmol phosphine/g. In a typical reaction 100 mg of this polymer would contain 0.13 mmol phosphine, and twice the mass (200 mg) of allylic acetate would consist of 0.78 mmol of material. In the same reaction we would use 1.30 mmol of palladium atoms, in the form of $[PdCl(allyl)]_2$. Whilst this appears to be a high loading at ca. 16%, it is likely that the heterogeneous nature of the catalyst will prevent all the phosphine sites from being available for reaction.

copolymer worked well, the highest yields and shortest reaction times were achieved with the homolysine polymer. Both polyamino acid systems were better than the functionalised Tentagel®. At the end of the reaction, which was followed by TLC, the ligand was removed by a simple process of filtration. Most notably, provided anaerobic conditions were used, the recovered resin could be reused with only a marginal loss of activity and without the need to add further palladium, suggesting that the palladium is retained by the resin.



Scheme 3. Use of supported phosphines in allylic substitution reactions

Table 1

Supported reagent	Catalyst:substrate weight:weight[a]	Reaction time (h)	Yield (%)
Tentagel–$NHCOC_6H_4PPh_2$[b]	1:1	48	19
Tentagel–$NHCOC_6H_4PPh_2$	1:1	48	48
Copolymer–$NHCOC_6H_4PPh_2$	1:1	15	89
Copolymer–$NHCOC_6H_4PPh_2$	1:2	48	78
Copolymer–$NHCOC_6H_4PPh_2$	1:2	48	85
Polylysine–$NHCOC_6H_4PPh_2$	1:2	15	89
Polylysine–$NHCOC_6H_4PPh_2$	1:2	24	84

[a] 100 mg (0.4 mmol) of allylic acetate and 200 mg (0.02 mmol) of palladium dimer were used in each case. For the copolymer, a 1:2 ratio corresponds to ca. 16 mol% phosphine. For the pure lysine polymer, a 1:2 ratio corresponds to 32 mol% phosphine assuming 50% amine functionalisation. The copolymer contains a 3:1 mixture of leucine and lysine residues.

[b] Carried out under dilute conditions; 100 mg/20 mL, all others were at 100 mg/2 mL.

Since it is known that the incorporation of phosphines into an enantiomerically pure peptide chain is capable of generating a reagent with the capacity to control absolute stereochemistry in certain reactions,[8] we considered it appropriate to examine the products of the substitution reaction for signs of asymmetric induction. In all cases, hovever, no enantiomeric excess could be measured. Presumably the phosphine-functionalised side-chains in our polymers are too distant from the chiral centres in the chain to be capable of transferring chiral information from the backbone to the products.

A further application of the polymer-supported polyamines which we have described may be as supports for combinatorial chemistry. The PAMAM family of dendritic hyperbranched polyamines are well-established and versatile materials with numerous synthetic applications.[9] The use of a rapid synthetic approach to such materials, using methods described in this paper, may be relevant to this methodology.

A more controlled polymerisation process would be of great value in the optimisation of polyamine-functionalised peptides. Recent reports of the use of organometallic species to very precisely control the level of NCA polymerisation suggest that this may be possible to achieve using certain nickel complexes.[10] We are currently examining the new possibilities which such a modification may make available to us.

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