Efficient Solid-Phase Synthesis of Peptide-Based Phosphine Ligands: Towards Combinatorial Libraries of Selective Transition Metal Catalysts

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Abstract: A new methodology for the solid-phase synthesis of peptide-based phosphine ligands has been developed. Solid supported peptide scaffolds possessing either primary or secondary amines were synthesised using commercially available Fmoc-protected amino acids and readily available Fmoc-protected amino aldehydes for reductive alkylation, in standard solid-phase peptide synthesis (SPPS). Phosphine moieties were introduced by phosphinomethylation of the free amines as the final solid-phase synthetic step, immediately prior to complexation with palladium(II), thus avoiding tedious protection/deprotection of the phosphine moieties during the synthesis of the ligands. The extensive use of commercial building blocks and standard SPPS makes this methodology well suited for the generation of solid-phase combinatorial libraries of novel ligands. Furthermore, it is possible to generate several different phosphine ligand libraries for every peptide scaffold library synthesised, by functionalising the scaffold libraries with different phosphine moieties. The synthesised ligands were characterised on solid support by conventional ^{31}P NMR spectroscopy and, cleaved from the support, as their phosphine oxides by HPLC, ^{1}H NMR, ^{31}P NMR and high resolution ESMS. Palladium(II) allyl complexes were generated from the resin bound ligands and to demonstrate their catalytic properties, palladium catalysed asymmetric allylic substitution reactions were performed. Good yields and moderate enantioselectivity was obtained for the selected combination of catalysts and substrate, but most importantly the concept of this new methodology was proven. Screening of ligand libraries should afford more selective catalysts.

Keywords: asymmetric catalysis · allylic compounds · peptides · phosphine ligands · solid-phase synthesis

Introduction

In Nature enzymes achieve their excellent efficiency and selectivity in the catalysis of biological processes through a combination of binding affinity and a delicate catalytic machinery. Hence, it is obvious to mimic Nature by designing peptidic catalysts for asymmetric synthesis.[1,2] This strategy has been explored by several groups. Peptides have been applied for asymmetric azidation and for regioselective functionalisation of carbohydrates by Miller and co-workers.[3,4] Functionalised peptides complexing transition metals, have been utilised for a number of asymmetric addition and substitution reactions in the group of Hoveyda,[5–12] and peptidic catalysts for the Strecker reaction have been developed by Jacobsen and co-workers.[13–15]

However, because of the expected high chemo-, regio- and stereoselectivity of peptide-based catalysts, there is a need for the development of a method for the identification of the most efficient catalyst for any specific reaction. The solution to this problem could be high-throughput screening of combinatorial libraries of potential catalysts, thereby, for each new reaction/synthetic challenge, being able to rapidly pick the best catalyst.[16–19] Immobilisation of library members on individual beads would greatly facilitate this screening. Thus it is important to be able to synthesise combinatorial libraries of peptide-based catalysts, preferentially on solid support.

Resin bound catalysts based upon phosphine functionalised peptides combines the excellent catalytic properties known from phosphine transition metal complexes with the selectivity and possibly increased reactivity imposed by a folded peptide scaffold, due to binding of the substrate. In this context it is important for the phosphines to be situated near the peptide backbone, so as to most efficiently transfer

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the chiral information to the transition metal.[20] Two types of catalysts can be envisaged (Figure 1). For type I the chelating phosphines are attached to the chiral peptide backbone via substitution on a single side chain, which not necessarily guaranties the transition metal to be embedded in a chiral environment. On the other hand, when the chelating phosphines are positioned at two different sites of the peptide chain (type II), complexation can assist the folding of the peptide, increasing the possibility for the active site to be surrounded by a chiral architecture.

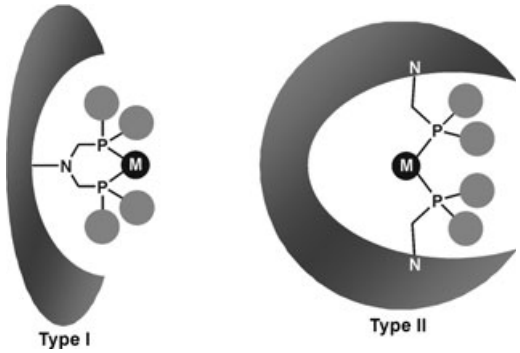


Figure 1. Peptide-based phosphine-transition metal catalysts of type I and II. In type II the folding of the peptide is assisted by the complexation. M = transition metal.

Recently Landis et al.[21] reported the incorporation of a 3,4-diazaphospholane moiety into a tetrapeptide, furnishing a monodentate solid supported phosphine ligand, which was applied in palladium catalysed allylic substitution. However, the pioneering work of Gilbertson and co-workers,[22–31] reported over the last ten years, constitutes the most important examples of resin bound peptide-based phosphine transition metal catalysts. Gilbertson's diphenyl- and dicyclohexylphosphinoserine building blocks contain an Fmoc-protected amine and a sulfide-protected phosphine.[22,23] They have been used for the parallel synthesis of small libraries of resin bound peptides containing sulfide-protected phosphine moieties. Subsequent reduction[24] of the phosphine sulfides and complexation with transition metals such as palladium and rhodium afforded resin bound catalysts of type II (Figure 1). Some of these catalysts were found to show good selectivity in transformations such as hydrogenations,[25,26] allylic substitutions[27,28] and desymmetrisation of *meso*-diols.[29] However, although the synthesis of the diphenyl- and dicyclohexylphosphinoserine building blocks was recently improved,[30] resulting also in a series of new aryl phosphinoserine building blocks,[28,31] it still involves several steps and protection of the phosphine moiety. Furthermore, incorporation of different phosphinoserine residues in the peptide sequence, requires new building block synthesis for each type of phosphine moiety.

Alternatively, if a peptide scaffold could be synthesised on solid support and, as the final synthetic step, immediately prior to complexation with transition metals, be functionalised with phosphine moieties, several advantages could be obtained. There would be no tedious protection/deprotection of the phosphine moieties and by using different phosphine reagents for functionalisation, several different ligands and complexes thereof could be obtained from the same peptide scaffold. Ideally, it should be possible to synthesise such a scaffold from mainly commercially available building blocks, combined with building blocks requiring a minimum amount of simple solution-phase synthesis. Importantly, the phosphine functionalisation of the peptide scaffolds should position the phosphine moieties close to the chiral peptide backbone and preferentially afford type II catalysts.

The new methodology presented is based upon this strategy, with the ultimate goal of synthesising combinatorial libraries of resin bound highly selective catalysts. The methodology is demonstrated by solid-phase synthesis of four different peptide-based phosphine ligands, the formation of palladium(II) allyl complexes on solid support and the screening of these complexes in the palladium catalysed asymmetric allylic substitution reaction.

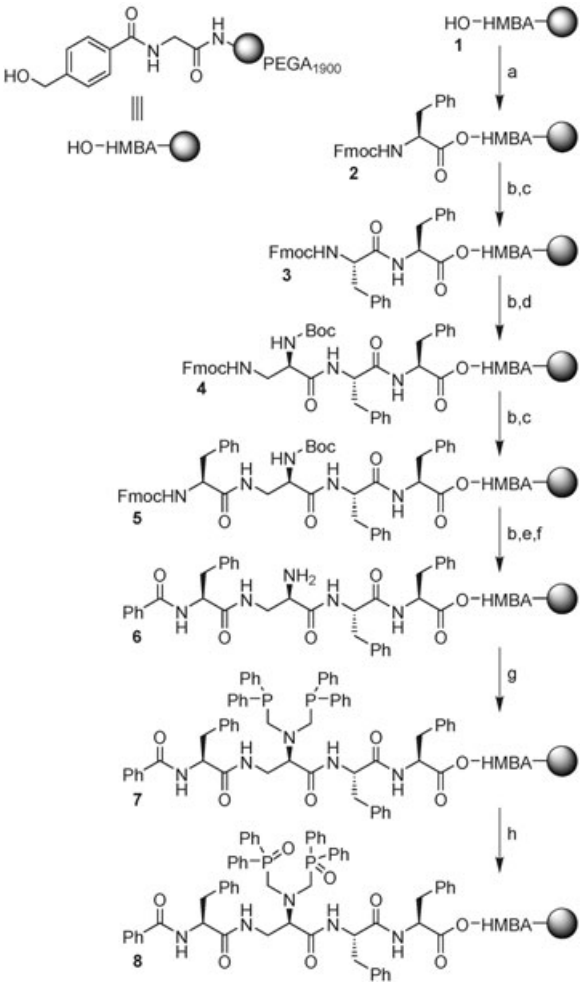
Results and Discussion

Solid-phase synthesis of peptide-based bidentate phosphine ligands: Initially, a reagent suitable for functionalising a solid supported peptide scaffold with phosphine moieties was investigated. Hydroxymethylphosphines can be easily obtained in situ, by heating a neat mixture of paraformaldehyde and a secondary phosphine,[32] and have been shown to react efficiently with both primary and secondary amines, affording the phosphinomethylated species in a Mannich type condensation. Furthermore, these very mild conditions allows for the presence of several unprotected functional groups like carboxylic acids, alcohols, phenols, esters and alkenes.[33] The most commonly used hydroxymethylphosphine reagent has been the diphenyl derivative. In solution it has been applied in the synthesis of spectacular dendritic structures,[34–37] as well as of more simple phosphine ligands made from amino acids[38,39] and aminopyridines.[40,41] By phosphinomethylation of primary amines, Alper, Arya and co-workers[42–46] have illustrated the use of hydroxymethyldiphenylphosphine as a reagent also suitable for solid-phase synthesis. In this manner, dendrimers have been functionalised with phosphine moieties and the derived palladium and rhodium complexes used for carbonylation reactions and selective hydroformylation, respectively. Two examples of non-selective solid supported catalysts, made using hydroxymethyldiphenylphosphine, were reported during the course of this work.[47,48] These catalysts did not posses a peptide structure rather the primary amines of amino-resins were phosphinomethylated directly.

Initially the diphenyl derivative was selected as the hydroxymethylphosphine reagent which should be used for the phosphinomethylation of solid supported amino-functionalised peptide scaffolds, well aware that the use of other commercially available secondary phosphines could be a source

for randomisation in a future library synthesis. Reaction of a primary amine with two equivalents or an excess of a hydroxymethylphosphine derivative affords a bidentate phosphine ligand, which upon complexation with a transition metal furnishes a favoured six-membered chelate. Thus solid-phase synthesis of peptide **6** (Scheme 1), possessing a primary amine as a side-chain, provides a resin bound scaffold suitable for the subsequent synthesis of peptide-based bidentate phosphine ligands. Accordingly, complexation with transition metals affords catalysts of type I (Figure 1).

As solid support, the $PEGA_{1900}$ resin was selected due to excellent swelling in organic solvents (acetonitrile, dichloromethane, *N*,*N*-dimethylformamide, dioxane, tetrahydrofuran and toluene) as well as in water.[49] This would allow the use of standard organic transformations during the synthesis of the ligands and later the screening of the catalysts to be performed in a range of solvents, including water, which is timely in the light of the development of green chemistry.



Scheme 1. Solid-phase synthesis and oxidation of peptide-based bidentate phosphine ligand **7**. a) Fmoc-Phe-OH, MSNT, methylimidazole, CH_2Cl_2; b) piperidine/DMF 2:8; c) Fmoc-Phe-OH, TBTU, NEM, DMF; d) Boc-Dap(Fmoc)-OH, TBTU, NEM, DMF; e) benzoic acid, TBTU, NEM, DMF; f) TFA/CH_2Cl_2 1:1; g) Ph_2PCH_2OH, MeCN; h) 3% aqueous H_2O_2.

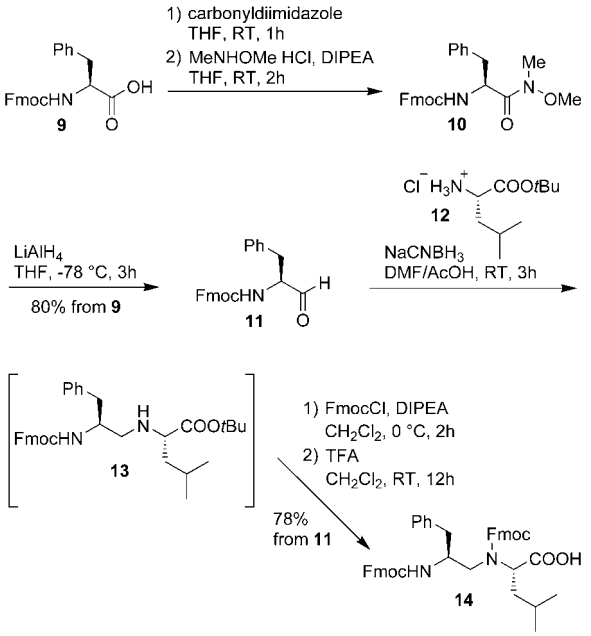
The free primary amines of the $PEGA_{1900}$ resin were functionalised with Fmoc-glycine by *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU) activation in *N*,*N*-dimethylformamide. Deprotection using 20% (*v*/*v*) piperidine in *N*,*N*-dimethylformamide and subsequent TBTU coupling of the hydroxymethylbenzoic acid (HMBA) linker furnished the functionalised solid support **1** (Scheme 1), which was used for the synthesis of all the ligands included in this work. The HMBA linker is efficiently cleaved under mild basic conditions and has proven to be ideal for the analysis of split/mix combinatorial libraries.[50] Also the HMBA linker is suitable for on-bead NMR analysis, since it possesses no stereocenter. In contrast, most chiral linkers (e.g. the Rink linker) are only commercially available as racemic mixtures, which would give rise to two sets of resonances in the NMR spectrum.

Ligand precursor peptide **6** was synthesised following the Fmoc protocol,[51] using commercially available Fmoc-amino acid derivatives. Phenylalanine was selected as the main residue, to increase the steric bulk around the primary amine side chain, which in turn should increase the selectivity of the derived catalyst. The first Fmoc-phenylalanine was attached to the HMBA linker by 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) activation in dichloromethane. Removal of the Fmoc group and TBTU coupling of a second Fmoc-phenylalanine yielded resin **3**. To position the primary amine and hence the reactive site of the catalyst as close as possible to the chiral backbone of the peptide, α,β-diaminopropionic acid (Dap) was incorporated as the β-aminopropionic acid, affording a primary amine side chain. Thus Boc-Dap(Fmoc)-OH was coupled using TBTU to give resin **4** and elongation by another Fmoc-phenylalanine afforded resin **5**, which was Fmoc deprotected and capped by TBTU coupling of benzoic acid. Subsequently, the Boc protecting group of the side chain primary amine was removed by trifluoroacetic acid (TFA) treatment, which yielded peptide scaffold **6** in high purity.[52] The resin bound bidentate phosphine ligand **7** was furnished by overnight treatment of **6** with a solution of hydroxymethyldiphenylphosphine. The formation of **7** was indicated by the presence of only a single resonance at −29.7 ppm in the ^{31}P NMR spectrum of the resin bound ligand. However, to investigate the purity of the cleaved product in solution, the phosphines were oxidised to their phosphine oxides before cleavage and HPLC analysis. In this manner partial oxidation of the ligand during analysis was avoided. The HPLC showed only a single peak, proving a clean and quantitative conversion of the amine **6**, and the structure of the oxidised ligand **8** was confirmed by HRMS and NMR spectroscopy.[52] Thus hydroxymethyldiphenylphosphine proved to be a reagent compatible with both peptide scaffolds and the PEGA resin. Furthermore, excess hydroxymethyldiphenylphosphine was easily washed out of the resin. This is a very important feature, since excess reagent trapped in the resin could otherwise compete for catalysis of reactions and thus reduce the selectivity of the immobilised peptide-based catalyst.

With the methodology for the synthesis and analysis of bidentate ligands such as resin **7** in hand, the more challenging peptide scaffolds **18a–c** could be pursued (Schemes 3 and 4). Scaffolds **18a–c** contain two reduced amide bonds and the secondary amines are able to accommodate one phosphinomethyl moiety each, upon reaction with hydroxymethyldiphenylphosphine. Thus, not only do scaffolds **18a–c** bring the phosphine moieties closer to the chiral peptide backbone, they also provide catalysts of the desired type II.

To prepare peptide scaffold **18a**, a reduced bond dipeptide building block **14**, which could be used in standard Fmoc-based solid-phase peptide synthesis, was synthesised in solution (Scheme 2). It was known that reduced peptide bonds could be made by reductive alkylation of an amino acid employing a Fmoc-protected amino aldehyde.[53] Thus Fmoc-protected phenylalaninal **11** was synthesised from the corresponding Fmoc-protected amino acid **9** via the Weinreb amide[54] **10**. The Weinreb amide was reduced to the aldehyde **11** using lithium aluminumhydride, following the procedure of Wen and Crews.[55] However, in our hands the near quantitative yields could only be reproduced by paying special attention to the quenching of the reaction.[56] The reaction mixture was poured onto a large volume of stirred ice water, to quickly dilute the generated base and in this way prevent cleavage of the Fmoc group, a problem also described by other groups[57] following the Wen and Crews procedure. The *tert*-butyl ester of leucine **12** was alkylated, generating a sterically hindered secondary amine **13** possessing two stereocenters. To avoid dialkylation, the reductive alkylation was carried out by slow addition of the aldehyde to a small excess of the amine, in the presence of sodium cyanoborohydride and acetic acid. The amine **13** was purified by column chromatography, however, evaporation to complete dryness of the fractions containing pure **13** was avoided, since this caused self-cleavage of the Fmoc protecting group by the free secondary amine. Instead the secondary amine of **13** was immediately protected using Fmoc-chloride in the presence of diisopropylethylamine, followed by deprotection of the *tert*-butyl ester using TFA. This afforded building block **14** in good yield after column chromatography.

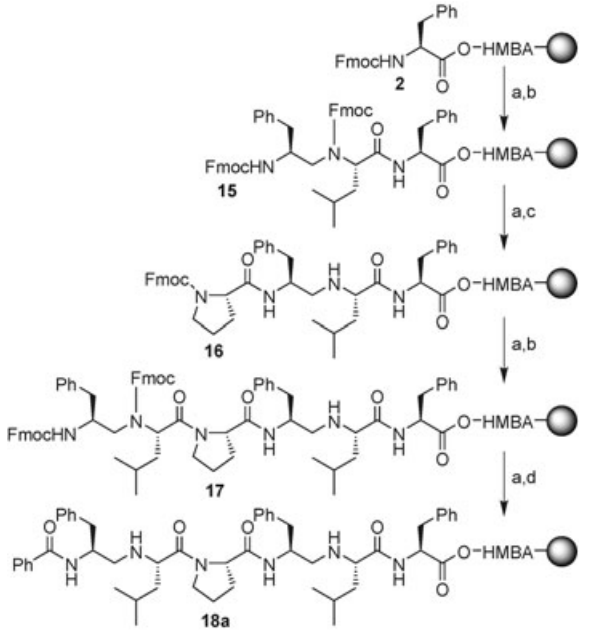
For the solid-phase peptide synthesis of the diamine peptide scaffold **18a** (Scheme 3), the HMBA functionalised $PEGA_{1900}$ resin **1** was utilised, and again the first amino acid in the sequence was phenylalanine. Building block **14** was coupled to the free amine of resin **2** using TBTU activation, and after 3 h a Kaiser test[58] showed complete reaction. The subsequent Fmoc deprotection also liberated the secondary amine of **15**, however, as expected, due to its sterically hindered nature, the secondary amine did not react in the following coupling reactions. Before the second incorporation of building block **14** into the peptide sequence, a proline was introduced to give **16**. A proline between the two reduced bonds in the scaffold was expected to induce a turn that together with the flexibility of the reduced bonds would facilitate chelation of the metal. After coupling of the second building block **14**, the peptide **17** was deprotected



Scheme 2. Synthesis of dipeptide building block **14** possessing a reduced amide bond.

and capped with benzoic acid to give **18a** in high purity, according to HPLC.[52] Benzoic acid proved to be an appropriate capping reagent, since it did not react with the secondary amines of **18a**.

In a more direct approach the reductive alkylation was performed on solid support, as previously reported for the synthesis of mouse melanocortin receptor agonists.[59] However, in that work racemisation of the aldehydes during the



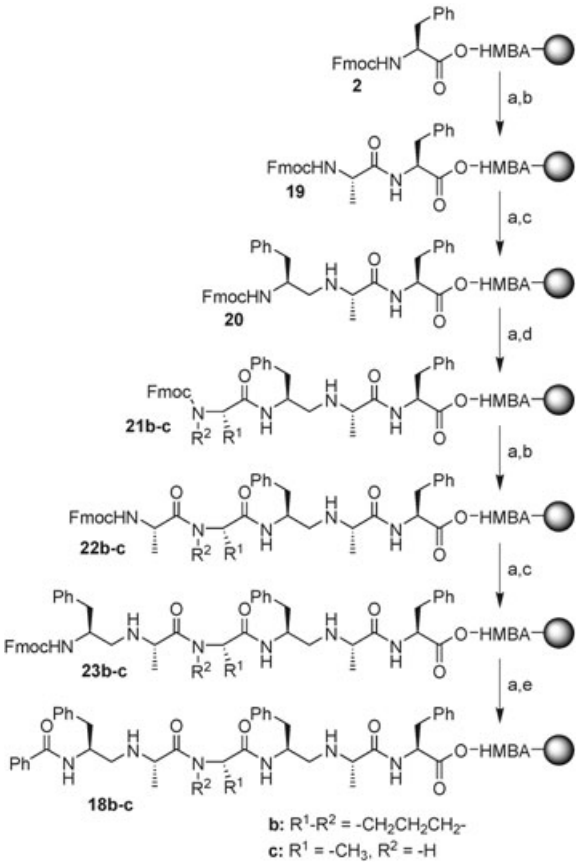
Scheme 3. Solid-phase synthesis of diamine **18a** using building block **14**. a) Piperidine/DMF 2:8; b) **14**, TBTU, NEM, DMF; c) Fmoc-Pro-OPfp, DhbtOH, DMF; d) benzoic acid, TBTU, NEM, DMF.

synthesis resulted in some formation of diastereomers, which could only be separated after cleavage from the support. This is detrimental to the synthesis of the phosphine ligands, since they should remain bound to the solid support. Thus the problem of racemisation was investigated.

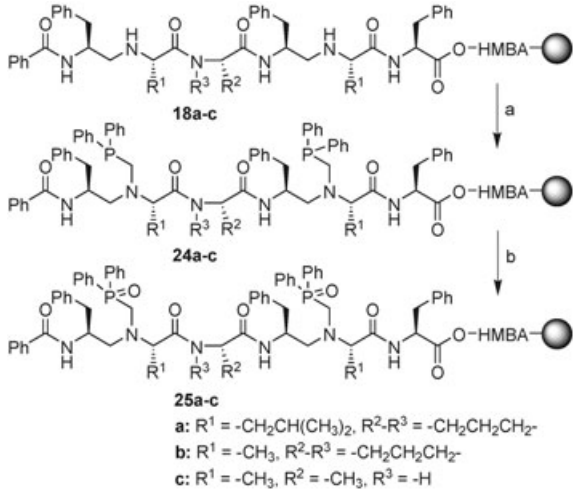
It was already known from the literature that silica gel chromatography caused racemisation of α-amino aldehydes.[60] However, for the synthesis of building block **14** the aldehydes could be obtained in an optically pure form and be used for further reaction without chromatography. The other critical factor for racemisation was the actual reductive alkylation. It was found that prolonged reaction times, sometimes needed to complete the reductive alkylations on solid support, but not in solution, lead to increased racemisation. If however the reaction time was restricted to 3 h, only negligible (<5% by HPLC) racemisation was observed, even when Fmoc-phenylalaninal, prone to racemisation, was used. To drive the reductive alkylation to completion within 3 h, the number of equivalents of Fmoc-amino aldehyde was increased (typically from three to six equivalents).

The synthesis of the two peptide scaffolds **18b** and **18c** was carried out starting from resin **2** (Scheme 4). Fmoc-alanine was coupled to the phenylalanine residue of **2** by TBTU activation to give **19**. Subsequent reductive alkylation using aldehyde **11** afforded compound **20** possessing the first of the two reduced amide bonds. The variation was introduced before the next reductive alkylation. For series **b** and **c** a proline and an alanine was incorporated, respectively, to investigate the effect of the proline for catalyst stability and selectivity. Coupling of another Fmoc-alanine to give **22b,c**, this time using the pentafluorophenyl (Pfp) ester with 1 equivalent of 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (DhbtOH), followed by reductive alkylation to give **23b,c**, and capping with benzoic acid, afforded the two diamine peptide scaffolds **18b,c** in high purity. Only a single peak was observed in HPLC and from the ^{1}H NMR spectrum it was clear that racemisation during the reductive alkylations had not been a problem with a reaction time less than 3 h.[52]

Batches of resin bound diamines **18a–c** were treated overnight with hydroxymethyldiphenylphosphine, followed by hydrogen peroxide oxidation to give the oxidised phosphine ligands **25a–c** (Scheme 5).[52] HPLC showed full and clean conversion of the diamines **18a–c**, in spite of their limited reactivity in peptide couplings, due to steric hindrance. Again ^{31}P NMR spectra of batches of resin bound ligands **24a–c**, recorded prior to oxidation, showed that no oxidation of the phosphines took place during the synthesis, as evidenced by only two resonances in the range −26 to −29 ppm, typical for phosphines (Figure 2a). For comparison, the solution ^{31}P NMR spectra of the oxidised ligands **25a–c** showed resonances in the range from 32 ppm to 35 ppm (Figure 2b).



Scheme 4. Synthesis of diamines **18b,c** by reductive alkylation on solid support. a) Piperidine/DMF 2:8; b) Fmoc-Ala-OPfp, DhbtOH, DMF; c) **11**, $NaCNBH_3$, AcOH, DMF; d) Fmoc-Pro-OPfp (for **18b**) or Fmoc-Ala-OPfp (for **18c**), DhbtOH, DMF; e) benzoic acid, TBTU, NEM, DMF.



Scheme 5. Phosphinomethylation and oxidation of the diamines **18a–c** on solid support. a) Ph_2PCH_2OH, MeCN; b) 3% aqueous H_2O_2.

Formation of resin bound palladium(II) complexes and their application in asymmetric synthesis: To investigate the ability of the peptide-based phosphine ligands **7** and **24a–c** to form complexes with transition metals for asymmetric synthesis, palladium(II) complexes were synthesised on solid

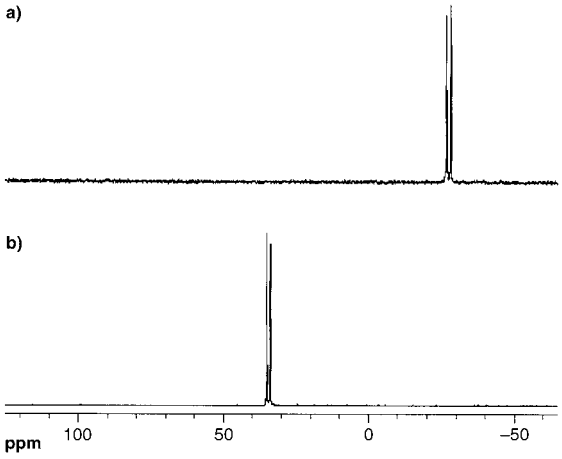
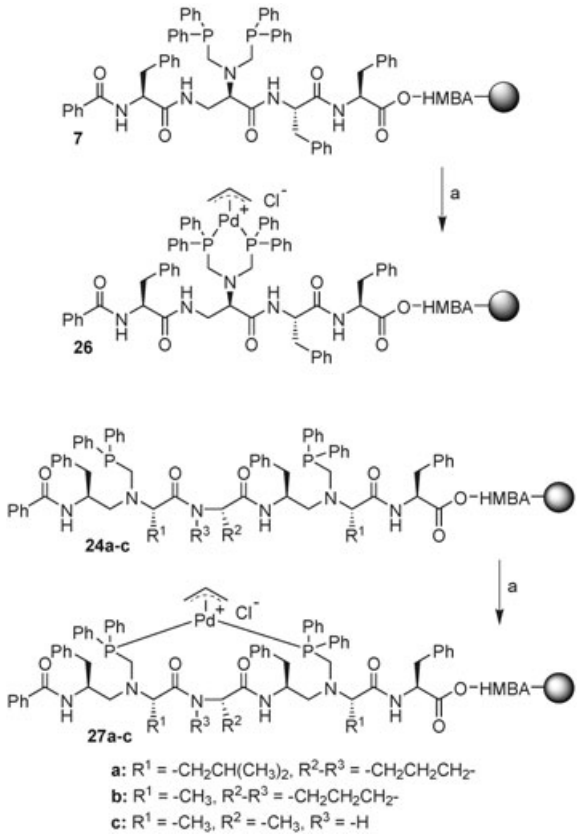


Figure 2. ^{31}P NMR of a) resin bound ligand **24a** in $CDCl_3$ and b) cleaved oxidised ligand **25a** in [D_6]DMSO. The spectra were referenced against H_3PO_4.

support. Batches of the phosphine ligands were freshly prepared and immediately after removal of excess hydroxymethyldiphenylphosphine, a degassed solution of allyl palladium chloride dimer (1 equivalent palladium) was added (Scheme 6). Within minutes the resin batches attained yellow to reddish-brown colours, and after 3 h the resins were drained and washed, affording resin bound allyl palladium(II) complexes **26**–**27a**–**c**.



Scheme 6. Formation of palladium(II) allyl complexes on solid support. a) [$PdCl(\eta^3$-$C_3H_5)]_2$, MeCN.

In Figure 3 molecular dynamics modelling of complex **26** and complex **27c** are presented. It is clear that the active metal in type II catalyst **27c** is much closer to and more embedded in the chiral environment of the peptide backbone than that of type I catalyst **26**. However, it was not confirmed by spectroscopy that all the ligand molecules in the resin form the complex represented by the model, but the low loading and the excellent swelling properties of the $PEGA_{1900}$ resin favour 1:1 complexes rather than larger cross linked aggregates of ligands and palladium ions.

To study the catalytic properties of the resin bound complexes, the palladium catalysed asymmetric allylic substitution reaction[61] was performed. Not only is this a common model reaction for evaluation of new ligands for palladium catalysed asymmetric synthesis, also used to assay the peptide-based phosphine catalysts synthesised by Gilbertson and co-workers,[27,28,31] it has also found widespread use in the synthesis of a vast array of bioactive targets.[62] Thus supported catalysts **26** and **27a**–**c** were used in 5 mol% (relative to the initial resin loading) for the reaction of 1,3-diphenylpropenyl acetate **28** with dimethylmalonate **29** under basic conditions[63] (Scheme 7). After 3 h the reactions were worked up and **30** isolated as a mixture of enantiomers. The enantiomeric excess was determined by ^1H NMR, using the chiral shift reagent [$Eu(hfc)_3$].[64] Isolated yields after column chromatography, and *ee* values are listed in Table 1.

Type I catalyst **26** afforded **30** in excellent yield, which could be expected due to its stable six-membered chelate. The enantioselectivity was modest, affording the *S* enantiomer in 15% excess, which could be a consequence of the metal being only partially embedded in a chiral environment in the open type I structure. Type II catalysts **27a** and **27b**, both possessing a proline residue between the phosphine moieties, showed a disappointingly low selectivity, yielding the *S* enantiomer in 9 and 8% *ee*, respectively. Furthermore, the sterically hindered leucine containing catalyst **27a** only converted 22% of substrate **28** compared to a conversion of 73% for the less hindered **27b**. Presumably this is due to steric congestion around the metal, preventing a geometry appropriate for the formation of a stable palladium(II) complex. The exchange of proline for alanine in **27c** did not seem to lower the stability compared to **27b**, in fact **27c** converted the substrate quantitatively within 3 h. Furthermore, the selectivity was better, unexpectedly affording the *S* enantiomer in 21% *ee*. Thus, prediction of the most selective catalyst was not possible, and even the relative stability of the complexes **26** and **27a**–**c** was not clear prior to synthesis, in spite of computer modelling, which underlines the importance of being able to synthesise the ligands in a combinatorial manner. Only screening of combinatorial catalyst libraries will allow for the selection of both stable and highly selective catalysts. This is in agreement with the unpredictable observations made by Gilbertson and co-workers[28] for their peptide-based phosphine palladium catalysts. Com-

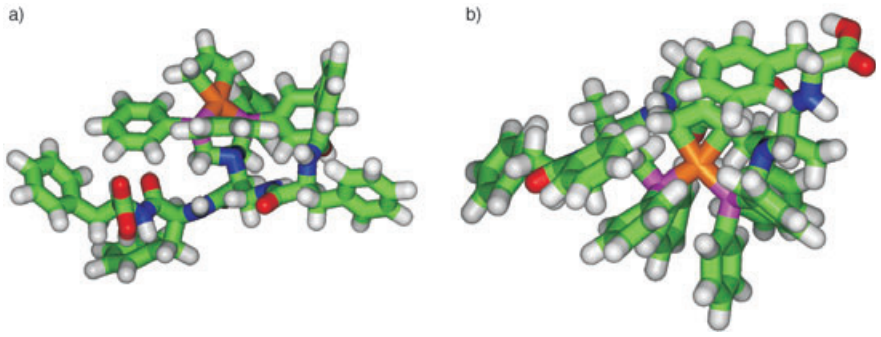
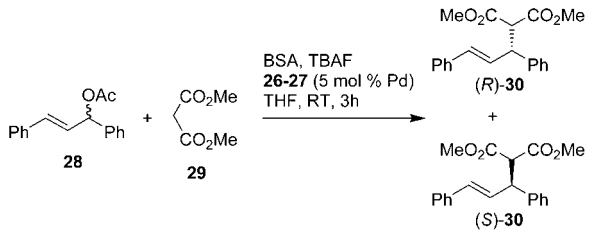
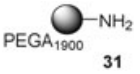
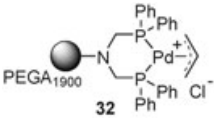


Figure 3. Molecular dynamics modelling of a) palladium(II) complex **26** and b) palladium(II) complex **27c**, generated using the Insight-Discover package from MSI. The chloride counter ions have been omitted for clarity. The structures were constructed and subjected to several rounds of MD-calculation at 650 and 350 K using CVFF forcefield and 1 fs steps to finally yield a structure that was stable for 100000 steps.



Scheme 7. Application of the complexes **26** and **27a–c** in palladium catalysed asymmetric allylic substitution.

Table 1. Palladium catalysed asymmetric allylic substitution.[a]

Entry	Catalyst	Solvent	Yield **30** [%][b]	*ee* **30** [%][c]
1	**26**	THF	93	15 (*S*)
2	**27a**	THF	22	9 (*S*)
3	**27b**	THF	73	8 (*S*)
4	**27c**	THF	97	21 (*S*)
5	**27b**	MeCN	95	10 (*S*)
6	**27c**	MeCN	90	18 (*S*)
7	 **31**	THF	0	-
8	 **32**	THF	96	0

[a] All reactions were performed at room temperature using 5 mol% Pd, relative to the initial resin loading. [b] Isolated yield. [c] Determined by ^{1}H NMR using a chiral shift reagent.

plexes based upon β-turn motifs catalysed the allylic substitution of cyclic allyl acetates with high selectivity, but could not catalyse substitution of linear substrates such as **28** at all. Furthermore, in the desymmetrisation of meso diols the selectivities of the β-turn based catalysts were inferior to catalysts possessing no particular secondary structure, illustrating the need for a catalyst screening for every new substrate or type of reaction considered.[29]

The effect of the solvent was investigated by performing the catalytic allylic substitution of **28** in acetonitrile, using the two most effective type II catalysts **27b** and **27c** (entries 5 and 6). However, changing the solvent did not affect the yields, nor did it alter the enantioselectivity significantly. Two control experiments were also performed. Unsubstituted $PEGA_{1900}$ resin **31** was treated with allyl palladium chloride dimer and used in catalysis under the same conditions as for the catalysts **26–27a–c**. As expected no background reaction was observed. Palladium(II) complex **32**, made from $PEGA_{1900}$ functionalised directly with phosphinomethyl moieties, was used for the second control experiment. Again the stable six-membered chelate afforded **30** in near quantitative yield, but this time as a racemic mixture, due to lack of ligand chirality.

Conclusion

This work paves the way for the synthesis of peptide-based phosphine transition metal catalyst libraries. An efficient and direct route from commercially available Fmoc-protected amino acids to elaborate peptide-based phosphine ligands has been developed. Solution-phase synthesis is limited to that of Fmoc-protected amino aldehydes needed for formation of backbone secondary amines as attachment points for phosphine moieties. In that context the choice of different phosphinomethylation reagents, made from different commercially available secondary phosphines, can afford sublibraries of phosphine ligands from the same library of ligand precursor scaffolds. Furthermore, protection/deprotection of phosphine moieties can be completely avoided. The building block approach (Schemes 2 and 3) may be considered for large-scale synthesis of identified catalysts, particularly when bulky amino acids more prone to racemisation are used in the reductive alkylation.

It was shown that ligands **7** and **24b,c** could form palladium(II) allyl complexes suitable for the palladium catalysed asymmetric allylic substitution reaction, whereas ligand **24a** seemed too sterically hindered. Although the enantioselectivities obtained using substrate **28** were only moderate, the concept of this new methodology was successfully proven. It is expected that screening of catalyst libraries will afford more selective catalysts. Furthermore, screening of other substrates could reveal catalysts **26–27a–c** to be more selective. New high-throughput screening methods are currently being developed for the screening of single-bead split/mix catalyst libraries, with the aim of discovering highly selective catalysts for several different reactions.

Experimental Section

General methods: ESMS spectra were recorded on a Micromass QTOF Global Ultima instrument and high-resolution MS determined using an appropriate internal reference. ^{1}H NMR and ^{31}P NMR spectra were recorded on a Bruker DRX250 250 MHz instrument. Chemical shifts for ^{1}H spectra are reported in ppm relative to the internal solvent peak (2.50 ppm for [D$_6$]DMSO and 7.26 for $CDCl_3$) and for ^{31}P spectra referenced against H_3PO_4. NMR spectra of reduced bond ligand precursors **18a–c** were recorded under acidic conditions to allow full protonation. Solid-phase reactions were performed in flat-bottomed polyethylene syringes equipped with sintered Teflon filters (50 μm pores), Teflon tubing, Teflon valves for flow control, and suction to drain the syringes from below. For solid-phase reactions carried out under argon, the syringes were equipped with a rubber septum and an argon inlet. TLC plates used were Merck silica gel 60 F_{254} on aluminium. Column chromatography was performed on silica gel 60H (230–400 mesh). Analytical reverse-phase HPLC was performed on a Waters system (490E detector at 215 nm, two 510 pumps with gradient controller and a Zorbax RP-18 column, 300 Å, 0.45×50 mm) with a flow rate of 1 mL min^{-1}. Eluents A (0.1% TFA in water) and B (0.1% TFA in acetonitrile/water 9:1 *v*/*v*) were used in a linear gradient (0% B → 100% B in 25 min) and retention times refer to this solvent system. PEGA$_{1900}$ was purchased from VersaMatrix. All solvents were HPLC grade. Anhydrous solvents were obtained by storing over 3 Å activated molecular sieves. Degassed solutions were obtained by bubbling with argon for 30 min. All other starting materials were purchased from commercial suppliers and used without further purification.

General procedure for cleavage of resin supported peptides: Cleavage of peptides was achieved with 0.1 M aqueous NaOH for 2 h followed by neutralisation with 0.1 M aqueous HCl.

General procedures for peptide couplings: TBTU couplings were performed by dissolving the acid (3 equiv) in *N*,*N*-dimethylformamide with NEM (4 equiv), followed by addition of TBTU (2.9 equiv). The resulting solution was left for preactivation for 5 min before being added to the resin (reaction time 2–3 h). Coupling of Pfp esters were performed by dissolving the Pfp ester (3 equiv) and DhbtOH (1 equiv) in *N*,*N*-dimethylformamide, whereupon the solution was added to the resin (reaction time 3 h). Peptide couplings were generally run in an amount of solvent just enough to cover the resin. After reaction, the resin was washed with *N*,*N*-dimethylformamide (×6) and methanol (×2) and finally checked using the Kaiser test.[58]

General procedure for Fmoc deprotection: Fmoc deprotection was achieved with 20% piperidine in *N*,*N*-dimethylformamide (*v*/*v*) for 2 + 18 min, followed by washing of the resin with *N*,*N*-dimethylformamide (×6) and methanol (×2). The cleavage was checked using the Kaiser test.[58]

General procedure for reductive alkylation: Two solutions of the same volume were prepared, so that the total volume was just enough to cover the resin. Solution 1: Sodium cyanoborohydride (10 equiv) and 2% (*v*/*v*) glacial acetic acid were dissolved in *N*,*N*-dimethylformamide. Solution 2: Fmoc-phenylalaninal (3–6 equiv) were dissolved in *N*,*N*-dimethylformamide. Solution 1 was added to the resin bound free amine, swollen in *N*,*N*-dimethylformamide. The resin was stirred for 1 min, whereupon solution 2 was added whilst stirring. The resin was left to react for 3 h, drained, and washed with *N*,*N*-dimethylformamide (×6) and methanol (×2). The reaction was checked using the Kaiser test.[58]

General procedure for phosphinomethylation: Neat paraformaldehyde (1 equiv) and diphenylphosphine (1 equiv) were heated at 110 °C for 1.5 h under argon, affording hydroxymethyldiphenylphosphine. The resin was dried in vacuo overnight and flushed with argon. To the resin was added a 0.15 M solution of hydroxymethyldiphenylphosphine in degassed acetonitrile (two times the volume needed to swell the resin, ca. 20 equiv). The resin was left to react under argon for 12 h at room temperature, drained and washed with degassed acetonitrile (×3) under argon.

General procedure for preparation of oxidised phosphine ligands: The freshly prepared resin bound phosphine ligand was washed with a 3% aqueous solution of hydrogen peroxide (×1), whereupon the hydrogen peroxide solution was added to cover the resin for 1 h. The resin was washed with methanol (×2), *N*,*N*-dimethylformamide (×6), methanol (×2) and with dichloromethane (×2), whereupon it was dried in vacuo.

General procedure for recording ^{31}P NMR spectre of resin bound ligands: The freshly prepared resin bound ligand was washed with degassed dichloromethane (×3) and with degassed 1% diisopropylethylamine in $CDCl_3$ (×1) under argon. The resin was swollen in a second volume of degassed 1% diisopropylethylamine in $CDCl_3$ and transferred to a standard 5 mm NMR tube under argon, whereupon the spectrum was recorded.

Procedure for determining enantioselectivity: The chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III) (0.4 equiv) was added to the NMR sample of **30** and the spectrum recorded. The two CO_2Me singlets at about 4 ppm were now split into two singlets for each of the two antipodes (see Supporting Information). One CO_2Me singlet was well-resolved into the *R*- and *S*-singlet, whereas the other was seen as an unresolved doublet. Using the D-antipode of the shift reagent, the singlet with the highest ppm value corresponds to the *R*-enantiomer.[64]

Preparation of functionalised resin 1: PEGA$_{1900}$[49] (2.00 g, loading 0.23 mmol g^{-1}, 0.46 mmol) was washed with *N*,*N*-dimethylformamide (×6), methanol (x 6) and dichloromethane (x 2) and dried in vacuo. Coupling of Fmoc-Gly-OH using TBTU activation according to the general procedure was performed twice, whereupon the Fmoc groups were removed. The HMBA linker was attached by TBTU coupling.

Ligand precursor 6: Resin **1** (0.50 g, 0.11 mmol) was dried in vacuo in the presence of phosphorous pentaoxide overnight. A solution of Fmoc-Phe-OH (3 equiv) and methylimidazole (2.25 equiv) in dry dichloromethane was added to MSNT (3 equiv), and the resulting solution was added to the dry resin and reacted for 1 h. The resin was washed with dry dichloromethane (×3) and the MSNT coupling repeated to give **2**. Resin **2** was washed with dichloromethane (×6) and *N*,*N*-dimethylformamide (×6), whereupon the Fmoc groups were removed. Fmoc-Phe-OH, Boc-Dap-(Fmoc)-OH and Fmoc-Phe-OH were coupled successively to the resin by using TBTU activation followed by Fmoc cleavage, to obtain resin bound peptide **5**. The Fmoc groups were removed and benzoic acid was coupled by TBTU activation. The resin was washed with *N*,*N*-dimethylformamide (×6) and dichloromethane (×6) and the Boc group was removed by treating the resin with TFA-dichloromethane 1:1 (*v*/*v*) for 15 min, which yielded ligand precursor **6**. The resin was washed with dichloromethane (×6), *N*,*N*-dimethylformamide (×6), methanol (×2) and dichloromethane (×2), whereupon it was dried in vacuo overnight. A sample of **6** (100 mg resin, 0.019 mmol) was cleaved for analysis, affording an amorphous colourless solid (11 mg, 89%). Analytical HPLC: t_R = 14.7 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 8.76 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.51 (brs, 1H; amide), 8.26 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.20 (d, ^3J(H,H) = 9 Hz, 1H; amide), 7.84 (d, ^3J(H,H) = 7 Hz, 2H; arom. H), 7.55–7.12 (m, 18H; arom. H), 4.70 (brs, 3H; NH_3^+), 4.69–4.60 (m, 1H; CH$^\alpha$), 4.56–4.48 (m, 1H; CH$^\alpha$), 4.45–4.36 (m, 1H; CH$^\alpha$), 3.44–3.38 (m, 1H; CH$^\alpha$), 3.22–2.76 (m, 8H; PhCH$_2$, Dap CH$_2$); HRMS (ES): *m*/*z*: calcd for $C_{37}H_{40}N_5O_6$: 650.2973, found: 650.2947 $[M+H]^+$.

Phosphine ligand 7: Phosphinomethylation of resin **6** was carried out according to the general procedure, to give resin bound phosphine ligand **7**. ^{31}P NMR ($CDCl_3$): δ = −29.7.

Oxidised phosphine ligand 8: Freshly prepared resin **7** was oxidised following the general procedure to give the resin bound oxidised ligand **8**. Oxidised ligand **8** (100 mg resin, 0.018 mmol) was cleaved, affording an amorphous colourless solid (17 mg, 88%). Analytical HPLC: t_R = 19.5 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 8.61 (d, ^3J(H,H) = 9 Hz, 1H; amide), 8.50 (d, ^3J(H,H) = 9 Hz, 1H; amide), 8.42 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.07 (brs, 1H; amide), 7.84 (d, ^3J(H,H) = 7 Hz, 2H; arom. H), 7.65–6.86 (m, 38H; arom. H), 4.82–4.73 (m, 1H; CH$^\alpha$), 4.53–4.40 (m, 2H; CH$^\alpha$), 3.90–3.71 (m, 3H; CH$^\alpha$, CH$_2$P), 3.49–3.19 (m, 2H; Dap CH$_2$), 3.12–2.62 (m, 8H; CH$_2$P, PhCH$_2$); ^{31}P NMR ([D$_6$]DMSO): δ = 32.8; HRMS (ES): *m*/*z*: calcd for $C_{63}H_{62}N_5O_8P_2$: 1078.4068, found: 1078.4037 $[M+H]^+$.

Fmoc-Phe-ψ[CH$_2$N]-Leu-O*t*Bu (13): The hydrochloride salt of the *tert*-butylester of leucine **12** (839 mg, 3.75 mmol) and sodium cyanoborohy-

dride (471 mg, 7.50 mmol) were dissolved in dry *N*,*N*-dimethylformamide (10 mL) and glacial acetic acid (200 μL) was added. The reaction mixture was stirred at room temperature whilst a solution of Fmoc-phenylalaninal[55,56] **11** (929 mg, 2.50 mmol) in *N*,*N*-dimethylformamide (10 mL) was added drop-wise over 1 h. Stirring was continued for 2 h, whereupon the reaction mixture was poured onto water. The mixture was extracted with dichloromethane (×3) and the combined organic phases washed with water (×2) and brine (×1), dried ($MgSO_4$) and concentrated to a pale yellow oil. The oil was purified by column chromatography (silica gel, acetone/dichloromethane 5:95) and the fractions containing pure **13** were combined and concentrated to a viscous colourless oil, but not to complete dryness. Since loss of Fmoc by self-cleavage was observed upon concentration and storage, **13** was not characterised any further, but used immediately in the next reaction.

Building block 14: Amine **13** (from 929 mg, 2.50 mmol **11**) was dissolved in dichloromethane (20 mL) and diisopropylethylamine (642 μL, 3.75 mmol) was added. The solution was cooled to 0 °C and stirred under argon. Fmoc-chloride (745 mg, 2.88 mmol) was added as a solid in one portion and the reaction mixture was left to stir for 2 h, whereupon it was allowed to attain room temperature. The reaction mixture was poured onto water and extracted with dichloromethane (×3). The combined organic phases were washed with water (×3), dried ($MgSO_4$) and concentrated. The resulting oil was redissolved in a 1:1 (*v*/*v*) mixture of TFA and dichloromethane (10 mL) and left to stir at room temperature for 12 h. Toluene (10 mL) was added and the reaction was concentrated to a viscous oil in vacuo. Purification by column chromatography (silica gel, methanol/dichloromethane 5:95) afforded **14** as an amorphous colourless solid (1.38 g, 78% from **11**). Analytical HPLC: t_R = 23.0 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 7.85 (d, ^3J(H,H) = 7 Hz, 4H; arom. H), 7.63–7.55 (m, 4H; arom. H), 7.38–7.17 (m, 14H; arom. H, NH), 4.41–4.10 (m, 7H; Fmoc CH_2CH, CH^α), 3.89–3.85 (m, 1H; CH^α), 3.43–3.06 (m, 2H; NCH_2), 2.87–2.59 (m, 2H; $PhCH_2$), 1.78–1.46 (m, 3H; Leu $CHCH_2$), 0.82 (brs, 6H; Leu CH_3); ^{13}C NMR ([D$_6$]DMSO): δ = 173.9, 156.8, 155.8, 155.5, 143.71, 143.68, 140.67, 140.57, 139.0, 138.8, 129.0, 127.9, 127.5, 126.9, 125.8, 125.1, 124.9, 120.0, 66.7, 66.5, 65.2, 59.3, 58.5, 52.3, 52.1, 50.1, 49.4, 46.65, 46.58, 38.2, 37.7, 24.7, 24.6, 22.9, 22.7, 21.73, 21.67;[65] HRMS (ES): *m*/*z*: calcd for $C_{45}H_{45}N_2O_6$: 709.3272, found: 709.3253 $[M+H]^+$.

Ligand precursor 18a: Fmoc-Phe-OH was attached to the HMBA linker of resin **1** (0.50 g, 0.11 mmol) to give resin **2**, in a MSNT coupling performed as described in the procedure for the synthesis of **6**. The Fmoc groups of **2** were removed and the resin reacted with building block **14** using TBTU activation, to give **15**. The Fmoc groups of **15** were removed before elongation by reaction with Fmoc-Pro-OPfp affording **16**. Removal of Fmoc groups and successive TBTU couplings of building block **14** and benzoic acid afforded ligand precursor **18a**. A sample of **18a** (100 mg resin, 0.019 mmol) was cleaved for analysis, yielding an amorphous colourless solid (14 mg, 86%). Analytical HPLC: t_R = 15.6 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 9.03 (brs, 4H; $R_2NH_2^+$), 9.01 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.46 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.23 (d, ^3J(H,H) = 7 Hz, 1H; amide), 7.77 (d, ^3J(H,H) = 7 Hz, 2H; arom. H), 7.55–7.41 (m, 3H; arom. H), 7.30–7.16 (m, 15H; arom. H), 4.63–4.46 (m, 2H; CH^α), 4.35–4.19 (m, 2H; CH^α), 4.10–3.99 (m, 1H; CH^α), 3.83–3.64 (m, 2H; CH^α, Pro CH_2N), 3.42–2.54 (m, 11H; $PhCH_2$, NCH_2C^α, Pro CH_2N), 2.06–1.49 (m, 10H; Pro $C^\alpha CH_2CH_2$, Leu $C^\alpha CH_2CH$), 0.94–0.81 (m, 12H; Leu CH_3); HRMS (ES): *m*/*z*: calcd for $C_{51}H_{67}N_6O_6$: 859.5117, found: 859.5119 $[M+H]^+$.

Ligand precursor 18b: Fmoc-Phe-OH was attached to the HMBA linker of resin **1** (0.50 g, 0.11 mmol) to give resin **2**, in a MSNT coupling performed as described in the procedure for the synthesis of **6**. The Fmoc groups of **2** were removed and the resin reacted with Fmoc-Ala-OPfp to give **19**. Cleavage of the Fmoc groups followed by reductive alkylation using Fmoc-phenylalaninal[55,56] **11** (6 equiv) afforded **20**. Removal of the Fmoc groups of **20** and coupling with Fmoc-Pro-OPfp and Fmoc-Ala-OPfp successively, afforded **22b**. The Fmoc groups of **22b** were removed and reductive alkylation using Fmoc-phenylalaninal[55,56] **11** (3 equiv) afforded **23b**. Cleavage of the Fmoc groups of **23b** followed by TBTU coupling of benzoic acid, afforded **18b**. A sample of **18b** (100 mg resin, 0.019 mmol) was cleaved from the resin to give an amorphous colourless solid (12 mg, 82%). Analytical HPLC: t_R = 13.6 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 9.15 (brs, 2H; $R_2NH_2^+$), 8.98 (brs, 2H; $R_2NH_2^+$), 8.87 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.43 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.30 (d, ^3J(H,H) = 8 Hz, 1H; amide), 7.78 (d, ^3J(H,H) = 8 Hz, 2H; arom. H), 7.55–7.41 (m, 3H; arom. H), 7.32–7.15 (m, 15H; arom. H), 4.57–4.46 (m, 2H; CH^α), 4.33–4.05 (m, 3H; CH^α), 3.91–3.77 (m, 1H; CH^α), 3.66–2.64 (m, 12H; $PhCH_2$, NCH_2C^α, Pro CH_2N), 2.04–1.76 (m, 4H; Pro $C^\alpha CH_2CH_2$), 1.40 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3), 1.36 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3); HRMS (ES): *m*/*z*: calcd for $C_{45}H_{55}N_6O_6$: 775.4178, found: 775.4182 $[M+H]^+$.

Ligand precursor 18c: The synthesis of **18c** from resin **1** (0.50 g, 0.11 mmol) was similar to the synthesis of **18b**, except that resin **20** was Fmoc deprotected and reacted with Fmoc-Ala-OPfp to give **21c**, instead of reaction with Fmoc-Pro-OPfp to give series **b**. A sample of **18c** (100 mg resin, 0.019 mmol) was cleaved from the resin, affording an amorphous colourless solid (13 mg, 91%). Analytical HPLC: t_R = 13.4 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 8.94 (brs, 4H; $R_2NH_2^+$), 8.87 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.66 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.42 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.09 (d, ^3J(H,H) = 8 Hz, 1H; amide), 7.80 (d, ^3J(H,H) = 8 Hz, 2H; arom. H), 7.55–7.41 (m, 3H; arom. H), 7.31–7.14 (m, 15H; arom. H), 4.57–4.47 (m, 2H; CH^α), 4.25–4.07 (m, 2H; CH^α), 3.94–3.80 (m, 2H; CH^α), 3.17–2.63 (m, 10H; $PhCH_2$, NCH_2), 1.37 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3), 1.33 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3), 1.17 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3); HRMS (ES): *m*/*z*: calcd for $C_{43}H_{53}N_6O_6$: 749.4021, found: 749.4069 $[M+H]^+$.

Phosphine ligands 24a–c: Phosphinomethylation of resins **18a–c** was carried out according to the general procedure, to give resin bound phosphine ligands **24a–c**.

Compound 24a: ^{31}P NMR ($CDCl_3$): δ = −27.2, −28.7.

Compound 24b: ^{31}P NMR ($CDCl_3$): δ = −27.2, −28.9.

Compound 24c: ^{31}P NMR ($CDCl_3$): δ = −26.8, −28.2.

Oxidised phosphine ligands 25a–c: Freshly prepared resins **24a–c** were oxidised following the general procedure to give the resin bound oxidised ligands **25a–c**. The oxidised ligands **25a–c** (100 mg resin, 0.017 mmol) were cleaved to give amorphous colourless solids.

Compound 25a: (19 mg, 87%). Analytical HPLC: t_R = 22.5 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 9.25 (d, ^3J(H,H) = 5 Hz, 1H; amide), 8.03 (brs, 1H; amide), 7.94–7.71 (m, 6H; amide, arom. H), 7.66–6.91 (m, 35H; arom. H), 4.54–4.43 (m, 1H; CH^α), 4.21–4.08 (m, 1H; CH^α), 3.95–3.83 (m, 1H; CH^α), 3.70–2.33 (m, 18H; CH^α, $PhCH_2$, PCH_2NCH_2, Pro CH_2N), 1.93–1.69 (m, 2H; Pro CH_2), 1.38–0.25 (m, 9H; Pro CH_2, Leu $C^\alpha CH_2CH$), 0.65 (d, ^3J(H,H) = 6 Hz, 3H; Leu CH_3), 0.54 (d, ^3J(H,H) = 6 Hz, 3H; Leu CH_3), 0.52 (d, ^3J(H,H) = 6 Hz, 3H; Leu CH_3), 0.42 (d, ^3J(H,H) = 6 Hz, 3H; Leu CH_3); ^{31}P NMR ([D$_6$]DMSO): δ = 35.0, 33.8; HRMS (ES): *m*/*z*: calcd for $C_{77}H_{90}N_6O_8P_2$: 644.3142, found: 644.3143 $[M+2H]^{2+}$.

Compound 25b: (17 mg, 83%). Analytical HPLC: t_R = 19.7 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 9.18 (d, ^3J(H,H) = 6 Hz, 1H; amide), 8.09 (d, ^3J(H,H) = 8 Hz, 1H; amide), 7.92–6.99 (m, 41H; arom. H, amide), 4.54–4.45 (m, 1H; CH^α), 4.24–4.11 (m, 1H; CH^α), 3.93–3.80 (m, 1H; CH^α), 3.67–2.13 (m, 19H; CH^α, $PhCH_2$, PCH_2NCH_2, Pro CH_2N), 1.08–0.44 (m, 4H; Pro $C^\alpha CH_2CH_2$), 0.87 (d, ^3J(H,H) = 6 Hz, 3H; Ala CH_3), 0.81 (d, ^3J(H,H) = 6 Hz, 3H; Ala CH_3); ^{31}P NMR ([D$_6$]DMSO): δ = 34.9, 33.2; HRMS (ES): *m*/*z*: calcd for $C_{71}H_{77}N_6O_8P_2$: 1203.5278, found: 1203.5186 $[M+H]^+$.

Compound 25c: (16 mg, 80%). Analytical HPLC: t_R = 19.7 min, >95% purity; ^{1}H NMR ([D$_6$]DMSO): δ = 8.49 (d, ^3J(H,H) = 8 Hz, 1H; amide), 8.14 (d, ^3J(H,H) = 8 Hz, 1H; amide), 7.86–7.02 (m, 42H; arom. H, amide), 4.57–4.48 (m, 1H; CH^α), 4.34–4.26 (m, 1H; CH^α), 3.99–3.83 (m, 2H; CH^α), 3.74–2.18 (m, 16H; CH^α, $PhCH_2$, PCH_2NCH_2), 0.98 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3), 0.83 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3), 0.75 (d, ^3J(H,H) = 7 Hz, 3H; Ala CH_3); ^{31}P NMR ([D$_6$]DMSO): δ = 33.9, 33.2; HRMS (ES): *m*/*z*: calcd for $C_{69}H_{75}N_6O_8P_2$: 1177.5122, found: 1177.5029 $[M+H]^+$.

General procedure for formation of resin bound palladium(II) allyl complexes: The freshly prepared resin bound phosphine ligand, still under argon and swollen in acetonitrile, was washed further with dry degassed acetonitrile (×3). To the drained resin was added a solution of allyl palladium chloride dimer (1 equiv) in dry degassed acetonitrile, whereupon it was left under argon for 3 h, in which time the resin attained a yellow (for **26**) or reddish-brown (for **27a–c**) colour. The resin was drained, washed with dry degassed acetonitrile (×3) and dried in vacuo overnight. The dry resin was used immediately for palladium catalysed asymmetric allylic substitution.

General procedure for palladium catalysed asymmetric allylic substitution—Synthesis of 30: Dimethyl malonate **29** (3 equiv) was dissolved in dry degassed tetrahydrofuran (4.0 mL mmol^{-1}) under argon. To the solution was added tetrabutylammonium fluoride (3 equiv of a 1.0 M solution in tetrahydrofuran) and *N,O*-bis(trimethylsilyl)acetamide (3 equiv) whereupon the solution was stirred for 15 min at room temperature. To the freshly prepared dry catalyst resin **26** or **27a–c** (5 mol% Pd, relative to the initial resin loading), now under argon, was added 1,3-diphenylpropenyl acetate **28** (1 equiv, typically 38 mg, 0.15 mmol) and then the malonate solution. The resin mixture was shaken under argon for 3 h, whereupon it was drained and washed with ethyl acetate (×3). The combined organic phases were concentrated in vacuo and purified by column chromatography (silica gel, pentane/diethyl ether 3:1) affording compound **30** as a colourless oil which solidified upon standing. ^{1}H NMR ($CDCl_3$): $\delta =$ 7.17–7.33 (m, 10H; Ph), 6.46 (d, ^3J(H,H) = 16 Hz, 1H; C_1 CH), 6.31 (dd, ^3J(H,H) = 16 Hz, ^3J(H,H) = 8 Hz, 1H; C_2 CH), 4.25 (dd, ^3J(H,H) = 11 Hz, ^3J(H,H) = 8 Hz, 1H; C_3 CH), 3.93 (d, ^3J(H,H) = 11 Hz, 1H; C_4 CH), 3.69 (s, 3H; CO_2CH_3), 3.50 (s, 3H; CO_2CH_3). The ^{1}H NMR spectrum was identical to that described in the literature.[64]

For catalyst 26: Using **28** (43 mg, 0.17 mmol) and **26** (0.0085 mmol Pd), compound **30** was isolated in 93% yield, 51 mg, and 15% *ee* (*S*).

For catalyst 27a: Using **28** (43 mg, 0.17 mmol) and **27a** (0.0085 mmol Pd), compound **30** was isolated in 22% yield, 12 mg, and 9% *ee* (*S*).

For catalyst 27b: Using **28** (43 mg, 0.17 mmol) and **27b** (0.0085 mmol Pd), compound **30** was isolated in 73% yield, 40 mg, and 8% *ee* (*S*).

For catalyst 27c: Using **28** (48 mg, 0.19 mmol) and **27c** (0.0076 mmol Pd), compound **30** was isolated in 97% yield, 60 mg, and 21% *ee* (*S*).

For catalyst 27b (acetonitrile as solvent): Using **28** (33 mg, 0.13 mmol) and **27b** (0.0065 mmol Pd), compound **30** was isolated in 95% yield, 40 mg, and 10% *ee* (*S*).

For catalyst 27c (acetonitrile as solvent): Using **28** (33 mg, 0.13 mmol) and **27c** (0.0065 mmol Pd), compound **30** was isolated in 90% yield, 38 mg, and 18% *ee* (*S*).

For catalyst 32: Using **28** (44 mg, 0.175 mmol) and **32** (0.0088 mmol Pd), compound **30** was isolated in 96% yield, 55 mg, and 0% *ee*.

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