Design, synthesis and preliminary studies on a novel class of chiral receptor for the recognition of amino acid derivatives[1]

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The design and synthesis of a novel class of chiral receptor for the recognition of amino acid derivatives is described. Moderate enantioselectivity is observed in binding experiments.

Introduction

The field of molecular recognition has its roots deep in the study of biological systems. The tertiary structure and function of complex molecules such as DNA and enzymes rely strongly on specific, non-covalent, inter- and intra-molecular interactions such as hydrogen bonding, ion pairing and charge transfer processes. In recent years the translation of these concepts to the synthetic arena has been achieved with increasing success.

The binding interaction between substrate and receptor will be significantly enhanced if the receptor topography is inherently complimentary to that of the substrate. Complimentarity is achieved when the desired interactions (such as hydrogen bonds) can be achieved without adverse clashing interactions and cavities occurring upon complexation. The concept of preorganisation is more complex and stems from an understanding of the thermodynamic aspects involved upon receptor–substrate interaction. Designing complimentary receptors will largely serve to control the favourable binding interactions, the conformational strain and the van der Waals terms. Preorganisation enables minimisation of entropy losses resulting in a reduction in internal rotational degrees of freedom.

Design of chiral cleft receptors for the recognition of amino acid derivatives

The goal of the project was to design and synthesise an enantioselective cleft receptor for chiral amino acid N-carbamates (see Fig. 1).[2] The concave nature of the cleft also reduces the probability of self complexation. A variety of cleft receptors have been used to bind amino acid derivatives and other small molecules.[3–5] It was envisaged that an additional cooperative effect could be achieved if a *cis* amide or *cis* carbamate were employed as the complimentary group to the acid. Owing to the inherent propensity of amides and carbamates to exist as the *trans* isomer such a *cis* conformation would have to be achieved by placing the amide or carbamate in a ring. The final hydrogen bond could be achieved using either a *trans* amide or a phosphonamide to coordinate to the carbamate N–H on the amino acid derivative. Rebek *et al*. have reported a cleft receptor which was employed as a chiral solvating agent for phenylalanine derivatives and Moran *et al*. have synthesised a cleft capable of binding Cbz-protected amino acids with enantioselectivities of up to 20%.[6–8]

The amino acid receptor designed by Moran *et al*. was unable to bind amino acids entirely within the cleft due to the narrow bite angle provided by the aromatic spacer.[8] The cleft size could be increased by using a rigid spacer with a wider bite angle, such as dibenzothiophene/dibenzofuran, which would force the substituents at the 4- and 6-positions to be further apart in space (Fig. 2).[9] Enantioselective binding could in theory be achieved

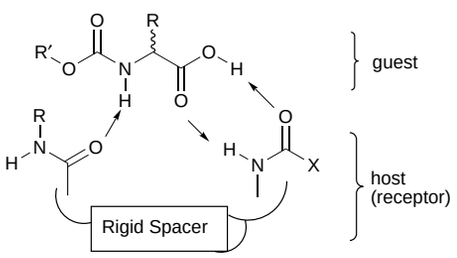


Fig. 1 Cleft receptor design

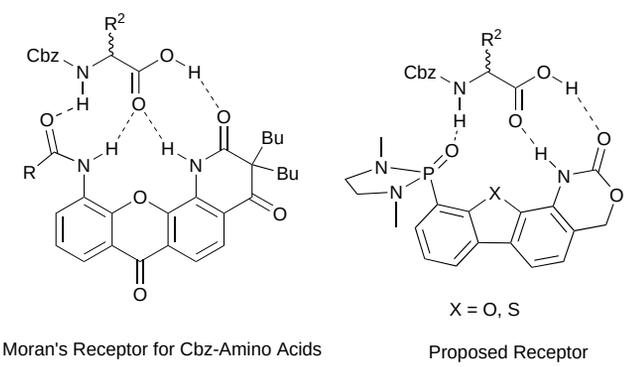


Fig. 2 Proposed receptor design

by employing a chiral diazaphospholidine oxide. If the diazaphospholidine oxide were derived from a C_2-symmetric diamine then the direction of rotation of the P=O group out of the aromatic plane could be controlled by the chiral backbone and thus axial chirality in the receptor would be induced. This control over the binding conformation of the receptor should then provide a means for enantioselective binding as discussed above.

We propose to use ^{1}H NMR spectroscopy to assess the strength of binding. The use of this technique to determine binding constants (K) and binding free energies (ΔG) has been described in detail.[10] Our strategy will be to firstly establish the critical association constant of the receptors in order that binding studies can be carried out at concentrations below this value.

General strategy for the synthesis of cleft receptors

It was envisaged that the proposed cleft receptors could be synthesised using a sequence of *ortho* lithiation reactions as outlined in a previous paper.[1] This methodology would then allow for the introduction of chirality into the clefts at a late stage in the synthesis, by incorporation of a chiral phosphonamide unit.

The first lithiation in the sequence relies on the *ortho* directing ability of the central heteroatom (X = O, S) to generate a 4-lithiated species which can be quenched by an electrophile. In the case of dibenzothiophene lithiation at the 4-position was first achieved by Gilman and co-workers in 1958 and has since been carried out using a variety of methods.[11,12] The most common method for mono lithiation of dibenzothiophene is that reported by Katritzky where treatment with two equivalents of Bu^{n}Li in THF at room temperature gives a good yield of 4-lithiodibenzothiophene after approximately five hours.[11d] In contrast the 4-lithiation of dibenzofuran, which was also first studied by Gilman and co-workers is best achieved using one equivalent of Bu^{n}Li in THF at room temperature.[11a,12]

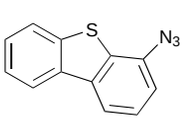
It was envisaged that the 4-lithiated species generated from either dibenzothiophene or dibenzofuran could be quenched with tosyl azide to give the 4-azido derivative which could then be reduced to the corresponding amine and protected as an *N*-Boc carbamate.[13] This resultant carbamate could then serve as the *ortho* directing group for the second lithiation reaction. Owing to the propensity of the *N*-Boc carbamate group to react with the more nucleophilic bases such as Bu^{n}Li the use of Bu^{t}Li was considered to be a prerequisite for this lithiation reaction.[14]

Existing literature precedents suggested that the desired cyclic urethane moiety could be generated using a base mediated ring closure of an alcohol onto the *N*-Boc carbamate group. Huwe and Blechert have reported the cyclisation of β-hydroxy carbamates to form the corresponding five-membered oxazolidinones using sodium hydride as base.[15] Once the cyclic urethane had been put in place it was envisaged that the final lithiation could be achieved by employing the *ortho* directing ability of X, in a similar manner to the first lithiation, to give a 6-lithiated species.[16]

The chiral phosphonamide group would be introduced by employing the corresponding chloro phosphonamide derivatives as electrophiles in the final lithiation reaction. The reaction of similar chloro phosphonamides and chloro phosphites with alkyllithiums and Grignard reagents has been demonstrated in the literature and would hopefully provide a precedent for the formation of the desired chiral phosphonamide derived receptors.[17]

Results and discussion

Lithiation of dibenzothiophene was achieved by using two equivalents of Bu^{n}Li in THF, at room temperature for 5 h.[11d] Quenching of the resultant 4-lithiodibenzothiophene with tosyl azide[13a] gave a triazene salt which was decomposed to the azide **1** in 74% yield by stirring with aqueous sodium pyrophosphate. After purification on a Florisil column the azide was reduced to the amine **2** in 42% yield,[18] using tin(II) chloride in aqueous dioxane solution.[19] Protection of the amine proved to be very difficult under standard conditions; use of Boc-anhydride and triethylamine in DCM with a catalytic amount of DMAP gave only a 16% yield of the carbamate **3a**. Use of refluxing methanol as solvent gave a similarly poor yield of 17%.[13d]



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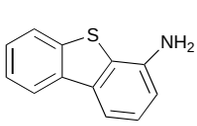
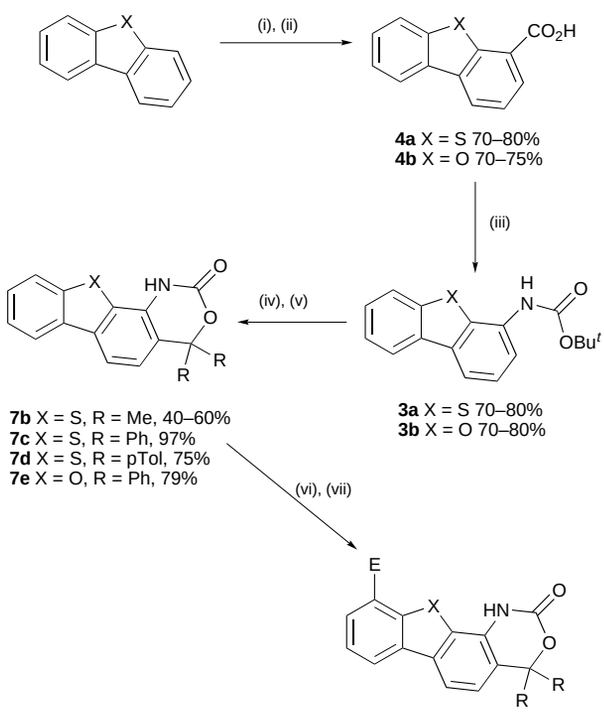


2

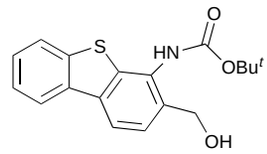
According to literature precedent the Boc-carbamate could potentially be synthesised by a one pot modification of the Curtius rearrangement from the corresponding carboxylic acid.[20] Lithiation of dibenzothiophene, using two equivalents of Bu^{n}Li and quenching of the 4-lithiodibenzothiophene with solid carbon dioxide gave the desired acid **4a** in 70–80% yield.

In the case of dibenzofuran a similar lithiation procedure could be employed but only one equivalent of Bu^{n}Li was required. Use of two equivalents of Bu^{n}Li resulted in complete bis-lithiation and gave only the diacid product. Quenching of the 4-lithiodibenzofuran with solid CO_2 gave the acid **4b** in 70–75% yield.[11a] Rapid reaction of the acid with five equivalents of diphenylphosphoryl azide (DPPA) under basic conditions (five equivalents of triethylamine) in a 1 : 1 toluene–Bu^{t}OH mixture gave the intermediate acyl azide, which rearranged to an isocyanate upon heating to reflux. The isocyanate was trapped *in situ* by the Bu^{t}OH to give the Boc-carbamates **3** directly. After some experimentation with conditions it was found that meticulous drying of solvents and purification of all starting materials enabled isolation of the carbamates **3**, as crystalline solids, in reproducible yields of 75–80% yields in both cases.

Lithiation of carbamate **3a** was achieved using a modification of the procedure recommended by Stanetty *et al.*[14b] After some experimentation it was discovered that reaction with Bu^{n}Li in diethyl ether at 0 °C for 2 h gave the bis anion in essentially quantitative yield. This could then be successfully quenched by a variety of electrophiles (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) Bu^{n}Li, THF; (ii) CO_2; (iii) DPPA, Bu^{t}OH, Et_3N, toluene, 100 °C, 5 h; (iv) 2.5 equiv. Bu^{t}Li, Et_2O, −78 °C, 2 h; (iv) for **7b**–**7d**; R_2CO, Et_2O, −78–20 °C; for **7e**; R_2CO, Et_2O; −78–20 °C then add 2 equiv. NaH, Et_2O, 2 h, rt (vi) 3 equiv. Bu^{s}Li–TMEDA, Et_2O, −78–20 °C, 3 h; (vii) E^+, Et_2O (see Table 1)



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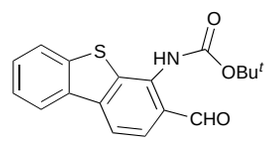

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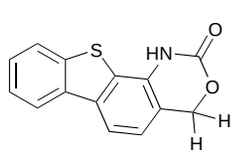
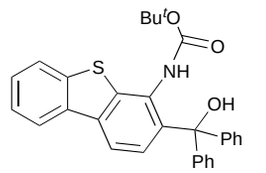


7a



7f

Since the simplest conceivable urethane was that derived from 3-methyl alcohol **5**, DMF was used as the electrophile in the lithiation step to give the aldehyde **6** in 72% yield. Reduction of this aldehyde using sodium borohydride and cyclisation of the intermediate alcohol **5**, using two equivalents of sodium hydride in ether at room temperature, gave the urethane **7a** in 93% yield.[15,21] Unfortunately this urethane exhibited very poor solubility in most solvents.

The use of symmetrical ketones as electrophiles in the lithiation reaction was expected to give rise to alcohol intermediates which could then be cyclised to give urethanes. This type of reaction, using ketones and aldehydes as electrophiles, had been reported by Muchowski and Venuti.[14a] In their example, the major product observed was the alcohol and only a small amount of cyclic urethane was isolated when overnight stirring at room temperature was allowed. However in the case of **7b–d** complete cyclisation to give urethanes was observed when analogous reaction conditions were employed (Scheme 1). However, the reaction with acetone proved to be unreproducible with variable amounts of self-aldol condensation side products being formed. The use of non-enolisable ketones such as benzophenone and 4,4′dimethylbenzophenone was thus preferred.

When this lithiation–cyclisation methodology was applied to the *tert*-butyl *N*-(dibenzofuran-4-yl)carbamate **3b** a rather disappointing result was obtained. A yield of only 62% of the desired urethane **7e** could be achieved after stirring at room temperature for 4 days. It appeared that, in this case, the cyclisation reaction was very much slower. Interestingly the remaining uncyclised alcohol **7f**, isolated from this reaction, could be cyclised rapidly to the urethane using the previously described method with two equivalents of sodium hydride, giving **7e** in an overall yield of 79% from **3b**. The sodium cation presumably enabled the formation of a 'naked' anion which was then able to participate in the cyclisation reaction more effectively.

According to literature there are three possible mechanisms by which a carbamate can react with a nucleophile.[22] The first is an E_1CB mechanism whereby loss of an alkoxide produces an intermediate isocyanate which reacts with a nucleophile in a rate limiting step. The second is reaction of the nucleophile to give a tetrahedral intermediate which collapses with expulsion of an alkoxide in a rate limiting step. The final possibility is a less precedented direct displacement of alkoxide by the nucleophile without formation of a tetrahedral intermediate.

In this case we believe that since an oxygen nucleophile is involved in the cyclisation that the 'tetrahedral intermediate' mechanism is operating. It seems possible that breakdown of the tetrahedral intermediate would be assisted by coordination of the ring heteroatom to the lithium on the carbamate nitrogen resulting in a weakening of the lithium–nitrogen bond. Given the differing geometries of the oxygen (sp^2 hydridised) and sulfur (sp^3 hydridised) lone pairs it is likely that the sulfur could participate in an interaction with the tetrahedrally disposed lithium, whereas oxygen could not.[11c,23] This would not only explain the enhanced reactivity of dibenzothiophene derived systems in the cyclisation reaction, but also the reason why cyclisation was observed to be slow in Muchowski and Venuti's case where no heteroatom was available for such a coordination.

Lithiation of the cyclic urethane **7c** at the 6-position, *ortho* to sulfur, proved to be very problematic. The use of Bu″Li in THF resulted in the formation of a complex mixture of products thought to be the result of direct attack by Bu″Li on the urethane moiety.[14b] In order to avoid such problems of nucleophilic attack the lithiation was attempted using a more hindered base. Use of Bu′Li resulted in decomposition and no product could be isolated.

According to a study by Cram and co-workers the bislithiation of dibenzofurans can be achieved by use of Bu^{s}Li–TMEDA.[24] This combination is considered to be non-

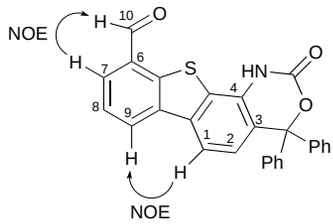


Fig. 3 NOE patterns in **8a**

nucleophilic and can be used in diethyl ether rather than THF because of the coordinative activation afforded by the TMEDA. The possibility of using diethyl ether as solvent also meant that the lithiation could be carried out at room temperature.[14b] Application of the Bu^{s}Li–TMEDA system in this lithiation reaction, after considerable experimentation with conditions, gave a good degree of the desired 6-lithiated urethane. The best conditions were found to be three equivalents of 1 : 1 Bu^{s}Li–TMEDA in diethyl ether, stirring at room temperature for 3 h. The use of less than three equivalents of base gave no lithiation. Presumably the first equivalent of base was required for removal of the urethane N–H, the second coordinated to the heterocyclic sulfur (*cf*. the lithiation of dibenzothiophene), and thus the third equivalent performed the desired deprotonation.

Quenching of the 6-lithiated urethane species with DMF as electrophile gave aldehyde **8a** in 54% yield, the remaining material being recovered starting material which could be recovered and recycled (Scheme 1).

A report by Haenel *et al*. highlighted the possibility of forming 9-substituted products in a similar lithiation of dibenzothiophene using refluxing diethyl ether as solvent. Under such forcing conditions it was clearly possible for lithio-migration from the 6- to the 9-position to occur.[25] It was therefore considered important to determine the regiochemical outcome of the dibenzothiophene diphenyl urethane lithiation in order to verify that the desired 6- rather than 9-lithiation had occurred. The regiochemistry of **8a** was verified using a combination of COSY and NOESY NMR techniques. Careful analysis of the COSY spectrum enabled a full assignment of all the signals to individual protons present in **8a**. Subsequently the NOESY data obtained clearly demonstrated that the 6-substituted product **8a** was the exclusive product of this lithiation reaction; showing an NOE between ring protons 1 and 9 and between aldehyde proton 10 and ring proton 7 (Fig. 3). Once optimised this final lithiation procedure could be applied to a variety of electrophiles. Since the proposed dibenzothiophene derived hosts required an amide functionality at the 6-position a direct route to these compounds was sought. Some precedent for the use of isocyanates as electrophiles in lithiation reactions had been demonstrated in the literature and their use was envisaged to enable direct access to the desired amides in one step without the need for an oxidation procedure.[16] (This was considered very important due to the oxidation sensitivity of the heterocyclic sulfur atom.) Reaction of urethane **7c** with phenyl isocyanate under the described conditions gave phenyl amide **8b** in an acceptable 50% yield. Use of benzyl isocyanate yielded 52% of the desired benzylamide **8c**. Both of the amides were highly crystalline materials which aided purification.

In order to test the applicability of phosphorus based electrophiles in this final lithiation both **7c** and **7e** were lithiated and reacted with diphenylphosphoryl chloride to give the corresponding phosphine oxides **8d** and **8e** in 56 and 49% yield respectively (Scheme 1, Table 1).

The proposed diazaphospholidine oxide cleft receptors could in principle be derived from either the dibenzothiophene urethane **7c** or the dibenzofuran urethane **7e**. Lithiation of urethane **7e** using the same conditions as for **7c** gave a good degree of lithiation at the 6-position. It was however a little

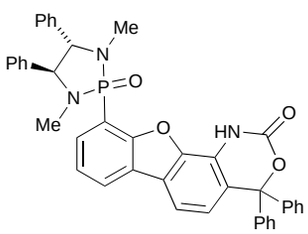
Table 1

Product[a]	X	E^+	E	Yield (%)
8a	S	DMF	CHO	54
8b	S	PhNCO	CONHPh	50
8c	S	BnNCO	CONHBn	52
8d	S	$Ph_2P(O)Cl$	$P(O)Ph_2$	56
8e	O	$Ph_2P(O)Cl$	$P(O)Ph_2$	49
8f	O	**9**	See diagram	33
8g	O	**10**	See diagram	63

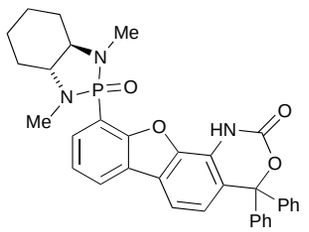
[a] R = Ph.

surprising that three equivalents of base were still required in order to effect lithiation instead of the expected two equivalents. This was clearly contrary to the case for dibenzofuran lithiation where only one equivalent of base was required compared to the two required by dibenzothiophene.

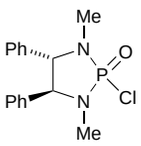
Treatment of the appropriate methylated diamines[26] with phosphorus oxychloride in a DCM solution, containing excess triethylamine as an HCl scavenger, gave the chlorodiazaphospholidine oxides **9** and **10**, as waxy solids, in 87 and 95% yields respectively.



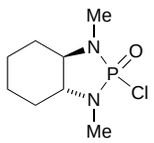
(*S*,*S*)-**8f**



(*R*,*R*)-**8g**



(*S*,*S*)-**9**



(*R*,*R*)-**10**

Synthesis of diazaphospholidine oxide derivatised cleft receptors **8f** and **8g** was achieved by the lithiation of urethane **7e**, using three equivalents of Bu^{t}Li–TMEDA in diethyl ether at room temperature for 3 h, as described previously, and quenching with the chlorodiazaphospholidine oxide electrophiles **9** and **10**.

Only the dibenzofuran derived urethane **7e** was derivatised in this manner because, in general, reactions of the dibenzofuran derived compound were more reproducible than those for the dibenzothiophene analogues and gave more soluble products which were easier to purify. Careful purification, by rapid suction flash chromatography, of electrophiles **9** and **10** was required to ensure that no phosphinic acids were present, as any trace of these appeared to interfere in the derivatisation and dramatically lower the yield. When very pure materials were used the receptors **8f** and **8g** were formed in 33 and 63% yield respectively (Scheme 1). Again the mass balance for these reactions was accounted for by recovery of the urethane **7e**.

Assessment of cleft receptors as amino acid binders—preliminary studies

Since the binding interactions between receptor and amino acid were expected to be hydrogen bonding in nature NMR analysis was considered to be a good means of assessing the strength of the interactions. The stronger the hydrogen bond the more deshielded the proton and hence the greater the downfield shift of the signal. In the case of the diazaphospholidine receptors it was envisaged that both ^{1}H and ^{31}P NMR could be employed, since hydrogen bonding interactions involving both the carbamate N–H and the P=O unit were expected to occur. ^{31}P NMR was particularly favoured due to the presence of only one signal in the spectrum, hence avoiding any problems of signal overlap.

Attempts to assess the binding properties of the dibenzothiophene amide receptors **8b** and **8c** failed due to the very poor solubility of these compounds in $CDCl_3$, (use of $CDCl_3$ was essential due to its low hydrogen bonding capacity compared to solvents such as [$^2H_6$]DMSO or [$^2H_4$]methanol), thus binding studies concentrated on the diazaphospholidines **8f** and **8g**. Here too problems were encountered due to the high affinity of these clefts for water (as seen in the X-ray structure). If any water was present in the NMR sample this bound very strongly to the cleft and precluded any amino acid binding. This problem was circumvented by meticulous drying of the cleft receptor, amino acid, $CDCl_3$ and NMR tubes before making the samples up under an atmosphere of dry nitrogen.

The first task was to determine a value of the critical association constant (CAC) for the diazaphospholidine clefts so that binding studies could be carried out at a cleft concentration where no appreciable self complexation of the clefts was occurring. A ^{1}H NMR dilution study of **8f** was carried out in $CDCl_3$ and the CAC determined to be at 1.85×10^{-3} M from the point of inflexion on the graph. Binding of **8g** to *N*-Boc-glycine was then investigated at a concentration (1.48×10^{-3} M) below that of the CAC. On addition of increasing amounts of amino acid an appreciable downfield shift in both the urethane N–H and P=O signals was observed. From the data obtained in the ^{1}H and ^{31}P NMR experiments an average value for the association constant K_{av} was calculated as 560 M^{-1}.

For a comparison of the binding abilities of clefts **8f** and **8g**, the binding of cleft **8g** to *N*-Boc-glycine was also assessed by ^{1}H and ^{31}P NMR spectroscopy. Working at a concentration of 1.74×10^{-3} M, from the NH data half complexation was found to be at 1.06 equiv. of guest, giving $K = 1030$ M^{-1}. For the ^{31}P data half complexation was found at 1.2 equiv. of guest, giving $K = 820$ M^{-1}. Thus an average value of $K_{av} = 930$ M^{-1} was determined in this case. The higher the value of K the more the binding equilibrium is shifted over towards complexation, indicating a stronger binding interaction. Clearly cleft **8g** was the stronger binder and thus further studies on binding of this cleft to chiral amino acid derivatives were then undertaken.

Using ^{31}P NMR analysis the binding of cleft **8g** to *N*-Boc-D- and L-alanine was investigated. In the case of *N*-Boc-D-alanine, a host concentration of 1.74×10^{-3} M was used. For the ^{31}P data half complexation was found at 1.06 equiv. of guest, giving $K = 1030$ M^{-1}. Using *N*-Boc-L-alanine (working at a host concentration of 1.74×10^{-3} M), from the ^{31}P data half complexation was found at 1.8 equiv. of guest, giving $K = 440$ M^{-1} under identical conditions. This difference in binding constants amounted to an enantiomeric excess of binding in the region of 40% in favour of *N*-Boc-D-alanine.

As discussed earlier it is possible that the orientation of the P=O bond could be controlled, in the solution phase, by the orientation of the N–Me groups on the diazaphospholidine oxide. If this is considered to be the case then upon binding of receptor **8g** to *N*-Boc-D- or L-alanine diastereomeric complexes would form as a result of the axial chirality of the receptor. It would be expected that the two diastereomeric complexes would differ in stability and hence one should form preferentially; this would be reflected by a difference in binding constants which is indeed the case.

Conclusions

This part of the project resulted in the successful synthesis of two chiral diazaphospholidine oxide derived cleft receptors **8f** and **8g**. It was demonstrated that both of these receptors are capable of binding to *N*-Boc protected amino acids with binding constants in the region of 10^{-3} M^{-1}. Furthermore receptor **8g** was capable of enantioselective binding to alanine deriva-

tives with an ee of 40%. Further detailed studies are presently being undertaken on the receptors described in this proposal and the results of this work will be reported in due course.

Experimental

THF and diethyl ether (referred to as ether) were distilled from their corresponding sodium benzophenone ketals. Toluene was distilled from sodium. DCM was distilled from calcium hydride. Methanol was distilled from activated magnesium sulfate. DMF was distilled under reduced pressure (water aspirator) from anhydrous magnesium sulfate and stored over 4 Å molecular sieves. All other solvents were used as supplied unless otherwise stated. Petrol refers to light petroleum with a boiling range of 60–80 °C. All air and moisture sensitive reactions were carried out in flame or oven dried Schlenck apparatus and under a dry nitrogen or argon atmosphere. All reactions were monitored using 0.25 mm silica gel plates (Merck). Flash column chromatography was carried out using 60 Å silica gel (Merck) unless otherwise stated.

All butyllithium reagents were stored below 0 °C in sealed, water-tight containers. Titration of the solutions against 4-biphenylmethanol in THF at 0 °C under inert atmosphere provided an accurate measure of their concentration. Most compounds were used as supplied by Aldrich, Fluka or Lancaster. Triethylamine and TMEDA were distilled from calcium hydride and stored over potassium hydroxide pellets under a nitrogen atmosphere. *tert*-Butyl alcohol was dried over activated calcium sulfate and distilled under nitrogen before use. Infra-red spectra were recorded as Nujol mulls or chloroform films between sodium chloride plates using a Perkin-Elmer 1310 FTIR spectrophotometer. NMR spectra were recorded for $CDCl_3$ or [$^2H_6$]DMSO solutions using a JEOL 270 270 MHz or JEOL 400 400 MHz spectrometer. All chemical shifts (δ) are measured in ppm down field of tetramethylsilane as internal reference. Coupling constants (J) are measured in Hz. DEPT techniques were commonly used to aid interpretation of ^{13}C spectra. ^{31}P spectra were usually fully proton-decoupled for simplicity. Mass spectra were recorded on a 7070E VG mass spectrometer for all EI and CI spectra. FAB and HRMS spectra were recorded by the EPSRC Mass Spectrometry service at Swansea. Microanalysis was performed using a Carlo Erba elemental analyser (MOD 1106). Specific rotations were recorded using a Perkin-Elmer polarimeter (sodium D line) and a 1 cm rotation cell, values of $[a]_D$ are given in 10^{-1} deg cm^2 g^{-1} at the specified temperature.

4-Azidodibenzothiophene 1

Dibenzothiophene (200 mg, 1.09 mmol) was dissolved in THF (3.0 ml) and cooled to −78 °C with stirring. Bu^{n}Li (0.87 ml, 2.18 mmol of a 2.5 M solution in hexanes) was added dropwise to give a pale orange solution. The mixture was allowed to warm to room temperature and stirred for 5 h, during which time the solution became dark red. The solution was recooled to −78 °C and a solution of tosyl azide (425 mg, 2.18 mmol) in THF (2.0 ml) was added dropwise. After 2 h the mixture was allowed to warm to −10 °C and stirred for 3 h. An aqueous solution of sodium pyrophosphate (960 mg, 2.16 mmol) in water (10 ml) was added and the mixture stirred at room temperature overnight. The separated aqueous phase was extracted with ether (3 × 10 ml), the combined organics were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting orange solid was purified by flash chromatography on Florisil (100–200 mesh) eluted with petrol to give the azide **1** as a yellow solid (180 mg, 74%), ν_{max}($CHCl_3$ film)/cm^{-1} 2115 (N_3); δ_H(270 MHz; $CDCl_3$) 8.16–8.13 (1H, m), 7.94 (1H, dd, *J* 7.8, 0.9), 7.89–7.86 (1H, m), 7.53–7.44 (3H, m), 7.25 (1H, dd, *J* 7.7, 0.9). Due to the instability of this compound the material was carried through to the next stage without further purification.

4-Aminodibenzothiophene 2[18]

A solution of $SnCl_2{\cdot}2H_2O$ (270 mg, 1.20 mmol) in water (2.0 ml) and 1,4-dioxane (4.0 ml) was stirred at 0 °C. 4-Azidodibenzothiophene **1** (90 mg, 0.40 mmol) in 1,4-dioxane (2.0 ml) was added dropwise and the mixture stirred at 0 °C for 1 h before allowing to warm to room temperature with stirring overnight. The mixture was extracted with ethyl acetate (3 × 10 ml) and the combined organics dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The brown residue was purified by flash chromatography on silica eluted with a gradient of 10–20% ethyl acetate–petrol to give amine **2** as an off-white solid (33 mg, 42%), ν_{max}(Nujol)/cm^{-1} 3422, 3313 and 3216 (NH); δ_H(270 MHz; [$^2H_6$]DMSO) 8.24–8.21 (1H, m), 8.01–7.98 (1H, m), 7.57 (1H, d, *J* 7.9), 7.48–7.44 (2H, m), 7.23 (1H, t, *J* 7.7), 6.75 (1H, d, *J* 7.7), 5.48 (2H, s, NH_2); δ_C(100 MHz; [$^2H_6$]DMSO) 143.2 (C*i*), 138.2 (C*i*), 136.0 (C*i*), 135.9 (C*i*), 126.5 (CH), 125.8 (CH), 124.4 (CH), 123.4 (C*i*), 123.0 (CH), 121.9 (CH), 110.9 (CH), 110.0 (CH); *m*/*z* (EI) 199 (M^+, 100%) (Found: M^+, 199.0465. $C_{12}H_9NS$ requires *M*, 199.0455).

***tert*-Butyl *N*-(dibenzothiophene-4-yl)carbamate 3a**

4-Aminodibenzothiophene **2** (100 mg, 0.50 mmol) was dissolved in THF (5.0 ml) and cooled to 0 °C with stirring. Sodium hydride (20 mg, 0.50 mmol of a 60% slurry in mineral oil) was added with stirring. After 10 min, when the effervescence had stopped, $(Boc)_2O$ (120 mg, 0.55 mmol) was added and stirred for 30 min before being allowed to warm to room temperature and stirred further overnight. The solvent was evaporated and the residue purified by flash chromatography on silica eluted with a gradient of 1–10% ethyl acetate–petrol to give carbamate **3a** as a white solid (52 mg, 35%) (see improved route for data).

Dibenzothiophene-4-carboxylic acid 4a[11b]

Dibenzothiophene (200 mg, 1.09 mmol) was dissolved in THF (3.0 ml) and cooled to −78 °C with stirring. Bu^{n}Li (0.87 ml, 2.18 mmol of a 2.5 M solution in hexanes) was added dropwise to give a pale orange solution. The mixture was allowed to warm to room temperature and stirred for 5 h, during which time the solution became dark red. The solution was then poured onto a slurry of solid CO_2 in ether (10 ml). The excess CO_2 was allowed to evaporate. The resultant yellow precipitate was diluted with ether and 2 M NaOH. The aqueous phase was washed with ether and then acidified with 2 M HCl until pH 3. The resultant creamy precipitate was extracted into ethyl acetate and the organics dried over sodium sulfate, filtered and solvent removed under reduced pressure. The orange–yellow solid was recrystallised from hot ethanol to give acid **4a** as fine, white crystals (186 mg, 75%) (Found: C, 68.5; H, 3.4. $C_{13}H_8O_2S$ requires C, 68.4; H, 3.5%); ν_{max}(Nujol)/cm^{-1} 1667 (C=O); δ_H(270 MHz; [$^2H_6$]DMSO) 8.66 (1H, d, *J* 7.7), 8.44–8.41 (1H, m), 8.17 (1H, dd, *J* 7.5, 1.1), 8.08–8.04 (1H, m), 7.66 (1H, t, *J* 7.7), 7.58–7.53 (2H, m); δ_C(100 MHz; [$^2H_6$]DMSO) 167.2 (CO_2H), 140.5 (C*i*), 139.9 (C*i*), 136.6 (C*i*), 134.0 (2C*i*), 129.0 (CH), 127.5 (CH), 126.4 (CH), 124.9 (CH), 122.8 (CH), 122.1 (CH); *m*/*z* (EI) 228 (M^+, 100%), 183 ($M^+ - CO_2H$, 35).

Dibenzofuran-4-carboxylic acid 4b[11a]

Dibenzofuran (5.0 g, 29.7 mmol) was dissolved in THF (25.0 ml) and cooled to −78 °C with stirring. Bu^{n}Li (12.0 ml, 29.76 mmol of a 2.48 M solution in hexanes) was added dropwise with stirring to give an orange–yellow precipitate. After complete addition the mixture was allowed to warm to room temperature and stirred for 3 h. The orange–brown solution was then cooled to −78 °C and poured onto excess CO_2(s) covered with anhydrous ether. The resulting white precipitate was allowed to stand at room temperature for 1 h. The product was extracted into 2 M NaOH and the resulting aqueous phase re-acidified with conc. HCl before extracting into ethyl acetate. This organic phase was then dried over sodium sulfate, filtered and the

solvent evaporated under reduced pressure to give acid **4b** as a white solid (4.67 g, 75%), mp 210–212 °C (from EtOH–water) [lit.,[11a] mp 213–214 °C (from EtOH–water)]; δ_H(270 MHz; [$^2H_6$]DMSO) 13.5 (1H, br s, CO_2H), 8.40 (1H, dd, *J* 7.7, 1.1), 8.20 (1H, d, *J* 7.7), 8.0 (1H, dd, *J* 7.7, 1.1), 7.80 (1H, d, *J* 8.1), 7.62–7.43 (3H, m).

***tert*-Butyl *N*-(dibenzothiophen-4-yl)carbamate 3a (improved route)**

Dibenzothiophen-4-carboxylic acid **4a** (1.88 g, 8.24 mmol) was suspended in Bu^{t}OH (25.0 ml) and toluene (25.0 ml) and Et_3N (5.7 ml, 41.2 mmol) were added with stirring at room temperature, to the resultant solution was added DPPA (8.92 ml, 41.2 mmol) and the mixture stirred at room temperature for 30 min before warming to 100 °C and stirring for a further 5 h. The mixture was then allowed to cool and diluted with ethyl acetate, washed with brine and the aqueous phase extracted with ethyl acetate (3 × 10 ml). The organics were then dried over sodium sulfate, filtered and the solvent evaporated. The orange oil was then purified by flash chromatography on silica eluted with a gradient of 0–5% ethyl acetate–petrol to give carbamate **3a** as a white solid (1.889 g, 77%) (Found: C, 67.7; H, 5.72; N, 4.67. $C_{17}H_{17}NO_2S$ requires C, 68.22; H, 5.68; N, 4.68%); ν_{max}(Nujol)/cm^{-1} 3335 (NH), 1697 (C=O); δ_H(270 MHz; $CDCl_3$) 8.15–8.11 (1H, m), 7.94–7.84 (3H, m), 7.49–7.42 (3H, m), 6.42 (1H, s, NH), 1.57 (9H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 153.6 (C*i*), 139.1 (C*i*), 137.5 (C*i*), 137.0 (C*i*), 133.8 (C*i*), 127.8 (CH), 126.4 (CH), 125.3 (CH), 123.7 (CH), 122.8 (CH), 119.2 (CH), 118.0 (CH), 32.1 (C*i*), 29.2 (3 CH_3); *m*/*z* (EI) 299 (M^+, 80%).

***tert*-Butyl *N*-(dibenzofuran-4-yl)carbamate 3b**

Dibenzofuran-4-carboxylic acid **4b** (2.50 g, 11.8 mmol) was suspended in a 1:1 mixture of toluene and Bu^{t}OH (50.0 ml) at room temperature to this was added Et_3N (4.9 ml, 35.4 mmol) followed by DPPA (7.6 ml, 35.4 mmol). The solution was stirred at room temperature for 1 h (complete conversion the acyl azide by TLC) and then heated to reflux at 100 °C for 3 h after which time there was no acyl azide remaining by TLC. The mixture was allowed to cool to room temperature before washing with brine (3 × 50 ml), drying over sodium sulfate, filtering and removal of solvent under reduced pressure. The oily residue was then dissolved in THF and added dropwise to an ice-cold suspension of excess $SnCl_2$ in water. The mixture was then allowed to warm to room temperature and stirred for 30 min until no excess DPPA remained by TLC. The reaction mixture was extracted with ethyl acetate (3 × 100 ml), the organics were dried over sodium sulfate, filtered and solvent removed under reduced pressure. The resulting creamy solid was then purified by flash chromatography on silica eluted with 5–30% ethyl acetate–petrol, recrystallisation from ethyl acetate then gave carbamate **3b** as a white crystalline solid (3.65 g, 73%) (Found: C, 71.80; H, 6.03; N, 4.86. $C_{17}H_{17}NO_3$ requires C, 72.08; H, 6.00; N, 4.94%); ν_{max}(Nujol)/cm^{-1} 3267 (NH), 1694 (C=O); δ_H(270 MHz; $CDCl_3$) 8.10 (1H, br d, *J* 7.5), 7.93 (1H, m), 7.57 (2H, td, *J* 7.9, 1.1), 7.45 (1H, td, *J* 7.2, 1.3), 7.38–7.22 (2H, m), 7.11 (1H, br s, NH), 1.57 (9H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 155.6 (C*i*), 152.5 (C*i*), 145.7 (C*i*), 127.0 (CH), 124.5 (C*i*) 124.1 (2C*i*), 123.3 (CH), 122.9 (CH), 120.8 (CH), 116.1 (CH), 114.3 (CH), 111.5 (CH), 80.9 (C*i*), 28.2 (CH_3); *m*/*z* (FAB) 283 (M^+, 21%), 284 (MH^+, 8).

***tert*-Butyl *N*-(3-formyldibenzothiophen-4-yl)carbamate 6**

tert-Butyl *N*-(dibenzothiophen-4-yl)carbamate **3a** (100 mg, 0.34 mmol) was dissolved in ether (2.5 ml) at room temperature with stirring. The mixture was cooled to −78 °C and Bu^{t}Li (0.80 ml, 1.02 mmol of a 1.27 M solution in hexane) was added dropwise. After stirring at −78 °C for 1 h the mixture was allowed to warm to 0 °C and stirred for a further 2 h, resulting in a pale orange solution. The mixture was recooled to −78 °C and DMF (0.03 ml, 0.37 mmol) was added resulting in formation of a pale cream precipitate. The mixture was allowed to warm to room temperature and stirred for 1 h before quenching with saturated aqueous ammonium chloride (10 ml). The separated aqueous layer was extracted with ether (3 × 10 ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. The crude solid was purified by flash chromatography on silica eluted with 5–10% ethyl acetate–petrol to give the aldehyde **6** as a pale yellow solid (81 mg, 72%), ν_{max}($CHCl_3$)/cm^{-1} 3011 (NH), 1724 (C=O urethane), 1607 (C=O aldehyde), 1597 (amide); δ_H(270 MHz; $CDCl_3$) 10.05 (1H, s, CHO), 9.54 (1H, br s, NH), 8.13 (1H, d, *J* 7.2), 8.01 (1H, d, *J* 8.1), 7.85 (1H, d, *J* 7.3), 7.70 (1H, d, 8.3), 7.55–7.42 (2H, m), 1.59 (9H, s, Bu^t); δ_C(100 MHz; $CDCl_3$) 193.3 (CHO), 152.5 (C=O), 142.0 (C*i*), 141.9 (C*i*), 135.7 (C*i*), 133.9 (C*i*), 133.2 (C*i*), 129.9 (CH), 128.4 (CH), 124.4 (CH), 123.3 (C*i*), 122.5 (CH), 122.4 (CH), 117.2 (CH), 81.6 (C*i* Bu^t), 28.1 (CH_3 Bu^t); *m*/*z* (EI) 327 (M^+, 75%).

***tert*-Butyl *N*-(3-hydroxymethyldibenzothiophen-4-yl)carbamate 5**

tert-Butyl *N*-(3-formyldibenzothiophen-4-yl)carbamate **6** (58 mg, 0.18 mmol) was dissolved in ethanol (5.0 ml) and $NaBH_4$ (8 mg, 0.20 mmol) was added with stirring at room temperature. After 20 min the reaction was quenched with water (10 ml) and the separated aqueous phase extracted with DCM (3 × 10 ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated to give the alcohol **5** as a white solid (51 mg, 86%), ν_{max}($CHCl_3$)/cm^{-1} 3389 (OH), 3013 (NH), 1707 (C=O); δ_H(270 MHz; $CDCl_3$) 8.13–8.10 (1H, m), 8.03 (1H, d, *J* 8.1), 7.89–7.82 (1H, m), 7.52 (1H, d, *J* 7.9), 7.48–7.44 (2H, m), 6.67 (1H, NH), 4.75 (2H, d, *J* 5.5, CH_2), 3.2 (1H, br s, OH), 1.55 (9H, s, Bu^t); *m*/*z* (EI) 329 (M^+, 55%). This compound was carried through directly to the next step without purification.

2,4-Dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*][1,3]oxazin-2-one 7a

tert-Butyl *N*-(3-hydroxymethyldibenzothiophen-4-yl)carbamate **5** (145 mg, 0.44 mmol) was dissolved in THF (1.0 ml) and cooled to 0 °C with stirring. NaH (19 mg, 0.48 mmol of a 60% slurry in mineral oil) was added all at once. After the initial effervescence had subsided the mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (1 ml) and the separated aqueous phase extracted with DCM (3 × 10 ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated to give the urethane **7a** as a white solid (104 mg, 93%), ν_{max}(Nujol)/cm^{-1} 1707 (C=O); δ_H(270 MHz; [$^2H_6$]DMSO) 8.76 (1H, d, *J* 5.9), 8.48–8.44 (2H, m), 7.96–7.93 (2H, m), 7.78 (1H, d, *J* 7.7), 5.88 (2H, s, CH_2), 3.80 (1H, s, NH); δ_C(100 MHz; [$^2H_6$]DMSO) 152.0 (C*i*), 138.8 (C*i*), 136.7 (C*i*), 135.1 (C*i*), 131.5 (C*i*), 127.6 (CH), 125.1 (CH), 123.9 (C*i*), 123.4 (CH), 122.4 (CH), 121.6 (CH), 117.0 (C*i*), 116.3 (CH), 67.9 (CH_2); *m*/*z* (CI) 256 (MH^+, 100%), 211 ($MH^+ - 44$, 10) (Found: M^+, 255.035297. $C_{14}H_9O_2NS$ requires *M*, 255.035400).

4,4-Dimethyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*]-[1,3]oxazin-2-one 7b

tert-Butyl *N*-(dibenzothiophen-4-yl)carbamate **3a** (100 mg, 0.34 mmol) was dissolved in ether (2.5 ml) at room temperature with stirring. The mixture was cooled to −78 °C and Bu^{t}Li (0.80 ml, 0.99 mmol of a 1.27 M solution in hexane) was added dropwise. After stirring at −78 °C for 1 h the mixture was allowed to warm to 0 °C and stirred for a further 2 h, resulting in the formation of a pale orange solution. The mixture was recooled to −78 °C and acetone (0.05 ml, 0.66 mmol) was added dropwise, the mixture was allowed to warm to room temperature and stirred for 3.5 h resulting in a pale cream precipitate. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 ml) and the separated aqueous phase

extracted with ethyl acetate (3 × 10 ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 5–30% ethyl acetate–petrol gave the dimethyl urethane **7b** as a white solid (62 mg, 67%) (Found: C, 67.76; H, 4.50; N, 4.82. $C_{16}H_{13}NO_2S$ requires C, 67.84; H, 4.59; N, 4.95%); ν_{max}(Nujol)/cm^{-1} 1720 (C=O); δ_H(270 MHz; $CDCl_3$) 8.43 (1H, s, NH), 8.16–8.13 (1H, m), 7.92–7.89 (1H, m), 7.87 (1H, d, *J* 8.1), 7.51–7.48 (2H, m), 7.27 (1H, d, *J* 7.1), 1.84 (6H, s, Me); δ_C(100 MHz; [$^2H_6$]DMSO) 150.5 (C*i*), 138.6 (C*i*), 136.2 (C*i*), 134.7 (C*i*), 129.5 (C*i*), 127.3 (CH), 124.8 (CH), 124.3 (C*i*), 124.0 (C*i*), 123.0 (CH), 122.0 (CH), 120.5 (CH), 116.3 (CH), 81.6 (C*i*), 27.7 (CH_3); *m*/*z* (EI) 283 (M^+, 100%).

4,4-Diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*]-[1,3]oxazin-2-one 7c

tert-Butyl *N*-(dibenzothiophen-4-yl)carbamate **3a** (100 mg, 0.34 mmol), Bu^{t}Li (0.61 ml, 0.84 mmol of a 1.38 M solution in hexane) and benzophenone (122 mg, 0.67 mmol) in ether (1.0 ml) were combined in the same way as for **7b** above. Purification by flash chromatography on silica eluted with 10–30% ethyl acetate–petrol gave the diphenyl urethane **7c** as a white solid (132 mg, 97%) (Found: C, 76.5; H, 4.02; N, 3.42. $C_{26}H_{17}NO_2S$ requires C, 76.6; H, 4.17; N, 3.44%); ν_{max}(Nujol)/cm^{-1} 1713 (C=O); δ_H(270 MHz; $CDCl_3$) 8.45 (1H, s, NH), 8.15–8.12 (1H, m), 7.92–7.88 (1H, m), 7.81 (1H, d, *J* 8.1), 7.54–7.46 (2H, m), 7.36–7.29 (6H, m), 7.28–7.24 (4H, m), 6.82 (1H, d, *J* 8.1); δ_C(100 MHz; $CDCl_3$) 151.7 (C*i*), 141.3 (C*i*), 139.0 (C*i*), 137.5 (C*i*), 135.2 (C*i*), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 125.0 (CH), 124.4 (CH), 123.2 (CH), 122.9 (C*i*), 122.0 (CH), 115.0 (CH); *m*/*z* (CI) 408 (MH^+, 25%).

4,4-Di-*p*-tolyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*]-[1,3]oxazin-2-one 7d

tert-Butyl *N*-(dibenzothiophen-4-yl)carbamate **3a** (200 mg, 0.67 mmol), Bu^{t}Li (1.2 ml, 0.84 mmol of a 1.38 M solution in hexane) and 4,4′-dimethylbenzophenone (280 mg, 1.34 mmol) were combined as described for **7b** above. Purification by flash chromatography on silica eluted with 10–100% ethyl acetate–petrol gave the di-*p*-tolyl urethane **7d** as a white solid (218 mg, 75%), ν_{max}(Nujol)/cm^{-1} 1719 (C=O); δ_H(270 MHz; $CDCl_3$), 8.15–8.12 (1H, m), 7.91–7.88 (1H, m), 7.83 (1H, s, NH), 7.79 (1H, d, *J* 8.3), 7.54–7.46 (2H, m), 7.14 (8H, m), 6.83 (1H, d, *J* 8.2), 2.35 (6H, s, Me); δ_C(100 MHz; $CDCl_3$) 150.7 (C*i*), 138.8 (C*i*), 138.6 (C*i*), 137.9 (C*i*), 136.9 (C*i*), 134.6 (C*i*), 130.9 (C*i*), 128.7 (CH), 127.4 (CH), 124.9 (CH), 124.6 (C*i*), 123.9 (CH), 123.3 (C*i*), 123.1 (CH), 122.1 (CH), 115.6 (CH), 88.2 (CH), 20.57 (CH_3); *m*/*z* (FAB) 436 (MH^+, 100%), 458 (MNa^+, 21) (Found: MH^+, 436.1370. $C_{28}H_{21}NO_2S$ requires *M*H, 436.1371).

4,4-Diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzofuro[7,6-*d*]-[1,3]oxazin-2-one 7e

tert-Butyl *N*-(dibenzofuran-4-yl)carbamate **3b** (1.0 g, 3.53 mmol) was dissolved in ether (5.0 ml) and cooled −78 °C with stirring. To this was added Bu^{t}Li (4.54 ml, 7.4 mmol of a 1.63 M solution in hexane) and the egg yellow suspension stirred at this temperature for 30 min. The mixture was then allowed to warm to 0 °C and stirred for a further 2 h to give a pale yellow suspension. The mixture was then recooled to −78 °C and benzophenone (1.28 g, 7.06 mmol) in ether (5.0 ml) was added dropwise. After complete addition the mixture was allowed to warm to room temperature and stirred for 4 days. After this time cyclisation was observed to be incomplete but the reaction was quenched by the addition of saturated aqueous ammonium chloride (20 ml) and the products extracted into DCM (3 × 50 ml), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The products were separated by flash chromatography on silica eluted with 30% ethyl acetate–petrol followed by 5% ethyl acetate–DCM to give **7e** as a white solid (1.7 g, 62%) and (0.664 g, 20%) of the uncyclised material **7f** as a white solid. This uncyclised product **7f** was redissolved in ether (10.0 ml) and NaH (0.122 g, 3.06 mmol of a 60% suspension in mineral oil) was added with stirring. After 2 h at room temperature full cyclisation was achieved and the reaction was worked up as described above. The crude product was recrystallised from ethyl acetate to give **7e** (0.474 g, 17% with respect to the starting carbamate, 79% overall yield), mp 180–182 °C (from ethyl acetate); ν_{max}(Nujol)/cm^{-1} 3743 (NH), 1710 (C=O); δ_H(270 MHz; $CDCl_3$), 7.94 (1H, d, *J* 7.7), 7.78 (1H, br s, NH), 7.61–7.47 (3H, m), 7.41–7.32 (7H, m), 7.26–7.22 (4H, m), 6.70 (1H, d, *J* 8.1); δ_C(100 MHz; [$^2H_6$]DMSO) 156.0 (C*i*), 150.3 (C*i*), 142.2 (C*i*), 141.6 (C*i*), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 125.1 (C*i*), 124.2 (C*i*), 123.6 (CH), 123.4 (C*i*), 121.9 (CH), 121.6 (CH), 121.5 (C*i*), 114.1 (CH), 111.8 (CH), 88.6 (C*i*); *m*/*z* (FAB) 392 (MH^+, 100%) (Found: MH^+, 392.128 932. $C_{26}H_{17}NO_3$ requires MH^+, 392.128 669).

tert-Butyl *N*-{3-[hydroxy(diphenyl)methyl]dibenzofuran-4-yl}-carbamate 7f

tert-Butyl *N*-(dibenzofuran-4-yl)carbamate **3b** (6.14 g, 21.7 mmol) was suspended in ether (40.0 ml) and cooled to −78 °C. Bu^{t}Li (27 ml, 45.6 mmol of a 1.7 M solution in hexane) was added slowly, dropwise. The yellow suspension was stirred at −78 °C for 30 min and then allowed to warm to 0 °C and stirred for a further 2.5 h. The pale cream suspension was recooled to −78 °C and benzophenone (4.7 g, 26 mmol) was added as a solution in ether (20.0 ml). After stirring for 15 min at −78 °C the mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (20 ml) and the aqueous phase extracted with DCM (3 × 100 ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated to give a pale yellow foam. Purification by flash chromatography on silica eluted with 0–10% ethyl acetate–DCM gave alcohol **7f** as a white solid (6.69 g, 67%) (Found: C, 77.03; H, 5.95; N, 2.88. $C_{30}H_{27}NO_4$ requires C, 77.42; H, 5.81; N, 3.01%); ν_{max}(Nujol)/cm^{-1} 3323 (OH), 1705 (C=O); δ_H(400 MHz; $CDCl_3$) 7.89 (1H, d, *J* 7.6), 7.58 (1H, d, *J* 8.2), 7.55 (1H, d, *J* 8.2), 7.43 (1H, t, *J* 7.9), 7.36–7.25 (11H, m), 7.20 (1H, br s, NH), 6.66 (1H, d, *J* 8.2), 3.79 (1H, br s, OH), 1.25 (9H, s); δ_C(100 MHz; $CDCl_3$) 156.8 (C*i*), 152.8 (C*i*), 152.1 (C*i*), 145.8 (C*i*), 138.9 (C*i*), 128.2 (CH), 27.6 (CH), 127.5 (CH), 125.7 (C*i*), 124.3 (CH), 124.0 (C*i*), 122.9 (C*i*), 122.7 (CH), 120.7 (CH), 116.2 (CH), 112.0 (CH), 83.0 (C*i*), 80.0 (C*i*), 28.1 (CH_3); *m*/*z* (thermospray +ve) 392 ($MH - Bu^tOH^+$, 100%).

2-Oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno-[7,6-*d*][1,3]oxazine-10-carbaldehyde 8a

Diphenyl urethane **7c** (300 mg, 0.74 mmol) was suspended in ether (3.0 ml) and TMEDA (0.33 ml, 2.22 mmol) was added with stirring at room temperature. The mixture was cooled to −78 °C and Bu^{s}Li (1.70 ml, 2.22 mmol of a 1.3 M solution in cyclohexane) was added dropwise. The reaction was warmed to room temperature and stirred for 3 h to give a dark red solution. The reaction was recooled to −78 °C and DMF (0.11 ml, 1.48 mmol) in ether (3.0 ml) was added dropwise and the mixture allowed to warm to room temperature. After 1 h the reaction was quenched by addition of saturated aqueous ammonium chloride (10 ml) and the separated aqueous phase extracted with DCM (3 × 10 ml). The organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 0–5% MeOH–DCM gave the aldehyde **8a** as a pale yellow solid (173 mg, 54%), ν_{max}($CHCl_3$)/cm^{-1} 3180 (NH), 1733 (C=O urethane), 1656 (C=O aldehyde); δ_H(270 MHz; [$^2H_6$]DMSO) 10.97 (1H, s, NH), 10.31 (1H, s, CHO), 8.72 (1H, d, *J* 8.1), 8.32 (1H, d, *J* 7.3), 8.17 (1H, d, *J* 8.1), 7.84 (1H, t, *J* 8.1), 7.43–7.41 (6H, m), 7.17–7.14 (4H, m), 6.79 (1H, d, *J* 8.1) (^{1}H–^{1}H COSY and NOESY data allow full assignment); δ_C(100 MHz; [$^2H_6$]DMSO) 192.0 (C*i*), 150.0 (C*i*), 141.0 (C*i*), 136.3 (C*i*), 136.2 (C*i*), 135.3 (C*i*), 131.1

(C*i*), 130.2 (C*i*), 128.5 (CH), 128.3 (2 × CH), 127.7 (CH), 127.5 (2 × CH) 127.0 (C*i*), 125.4 (CH), 124.3 (CH), 123.6 (C*i*); *m*/*z* (FAB) 436 (MH^+, 30%) (Found: MH^+, 436.0990. $C_{27}H_{18}NO_3S$ requires *M*H, 436.1007).

2-Oxo-*N*,4,4-triphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*][1,3]oxazine-10-carboxamide 8b

Diphenyl urethane **7c** (200 mg, 0.49 mmol), TMEDA (0.22 ml, 1.47 mmol), Bu^{s}Li (1.30 ml, 1.47 mmol of a 1.3 M solution in cyclohexane) and phenyl isocyanate (0.21 ml, 1.96 mmol) in ether (2 ml) were combined as for **8a** above. Purification by flash chromatography on silica eluted with 10–50% ethyl acetate–petrol and then 0–5% ether–DCM gave the amide **8b** as a white solid (129 mg, 50%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3401 and 3354 (NH), 1713 and 1660 (C=O); δ_H(270 MHz; $CDCl_3$) 8.35 (1H, d, *J* 8.1), 8.12 (1H, s, NH), 7.94 (1H, d, *J* 7.5), 7.84 (1H, d, *J* 8.2), 7.74–7.71 (2H, m), 7.64 (1H, t, *J* 7.7), 7.46 (1 H, t, *J* 7.7), 7.37–7.35 (6H, m), 7.24–7.20 (7H, m), 6.86 (1H, d, *J* 8.1); δ_C(67 MHz; [$^2H_6$]DMSO) 165 (C=O amide), 151 (C=O urethane), 149 (CH), 141.6 (C*i*), 139 (C*i*), 135 (C*i*), 134.8 (CH), 131 (C*i*), 129 (6 CH), 128.4 (CH), 127.7 (CH), 127 (C*i*), 126 (C*i*), 125 (C*i*), 124 (C*i*), 123 (C*i*), 120.7 (CH), 117 (C*i*); *m*/*z* (FAB) 527 (MH^+, 100%) (Found: MH^+, 527.1449. $C_{33}H_{22}N_2O_3S$ requires *M*H, 527.1429).

***N*-Benzyl-2-oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno[7,6-*d*][1,3]oxazine-10-carboxamide 8c**

Diphenyl urethane **7c** (200 mg, 0.49 mmol), TMEDA (0.22 ml, 1.47 mmol), Bu^{s}Li (1.30 ml, 1.47 mmol of a 1.3 M solution in cyclohexane) and benzyl isocyanate (0.24 ml, 1.96 mmol) in ether (2.0 ml) were combined as described for **8a** above. Purification by flash chromatography on silica eluted with 0–5% ether–DCM gave amide **8c** as a white solid (137 mg, 52%), ν_{max}(Nujol)/cm^{-1} 3248 and 3166 (NH), 1727 (C=O); δ_H(270 MHz; [$^2H_6$]DMSO) 9.46 (1H, br s, NH), 8.54 (1H, d, *J* 7.7), 8.23 (1H, d, *J* 7.7), 8.07 (1H, d, *J* 8.2), 7.67 (1H, t, *J* 7.7), 7.42–7.14 (15H, m), 6.72 (1H, d, *J* 8.1), 4.58 (2H, d, *J* 5.5, CH_2) (NH seen as inverse peak off scale); δ_C(67 MHz; [$^2H_6$]DMSO) 165.6 (C=O amide), 150.7 (C=O urethane), 141.6, 139.5, 139.1, 136.3, 130.9, 128.7, 128.4, 127.6, 127.4, 126.9, 125.9, 125.3, 125.0, 123.8, 123.5, 115.9, 88.3, 42.9 (CH_2); *m*/*z* (FAB) 541 (MH^+, 52%) (Found: MH^+, 541.1587. $C_{34}H_{24}N_2O_3S$ requires MH^+, 541.1585).

(2-Oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno-[7,6-*d*][1,3]oxazin-10-yl)(diphenyl)phosphine oxide 8d

Diphenyl urethane **7c** (100 mg, 0.24 mmol), TMEDA (0.11 ml, 0.72 mmol), Bu^{s}Li (0.56 ml, 0.72 mmol of a 1.3 M solution in cyclohexane) and diphenylphosphoryl chloride (0.11 ml, 0.6 mmol) in ether (1.0 ml) were combined as for **8a** above. The product was purified by flash chromatography on silica eluted with 60% ethyl acetate–petrol and then recrystallised from DCM–hexane to give **8d** as a white solid (81 mg, 56%), ν_{max}(Nujol mull)/cm^{-1} 1734 (C=O), 1172 (P=O); δ_H(270 MHz; $CDCl_3$) 8.32–8.28 (1H, m), 7.85–7.62 (5H, m), 7.59–7.41 (9H, m), 7.34–7.18 (10H, m), 6.83 (1H, d, *J* 8.2); δ_C(100 MHz; $CDCl_3$) 150.8 (C*i*), 142.3 (C*i*, d, $J_{C\text{-}P}$ 6), 141.28 (C*i*), 136.6 (C*i*, d, $J_{C\text{-}P}$ 9), 135.9 (C*i*), 132.4 (CH), 132.2 (CH, d, $J_{C\text{-}P}$ 11), 132.0 (CH, d, $J_{C\text{-}P}$ 11), 131.4 (C*i*), 130.3 (C*i*, d, $J_{C\text{-}P}$ 4), 128.7 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (C*i*), 126.4 (C*i*, d, $J_{C\text{-}P}$ 33), 125.4 (CH), 124.5 (CH, d, $J_{C\text{-}P}$ 13), 124.4 (CH), 123.4 (C*i*), 115.6 (CH), 89.9 (C*i*); δ_P(160 MHz; $CDCl_3$) 29.84 (s); *m*/*z* (FAB) 608 (MH^+, 100%) (Found: MH^+, 608.147 771. $C_{38}H_{26}NO_3PS$ requires MH, 608.144 929).

(2-Oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzothieno-[7,6-*d*][1,3]oxazin-10-yl)(diphenyl)phosphine oxide 8e

Diphenyl urethane **7e** (200 mg, 0.512 mmol) was suspended in ether (1.0 ml) and TMEDA (0.23 ml, 1.53 mmol) added with stirring at room temperature. The suspension was cooled to −78 °C and Bu^{s}Li (1.18 ml, 1.53 mmol of a 1.3 M solution in cyclohexane) was added dropwise. The mixture was then allowed to warm to room temperature resulting in a dark, wine red suspension. After 3 h at room temperature the suspension was recooled to −78 °C and diphenylphosphoryl chloride (0.29 ml, 1.53 mmol) in ether (2.0 ml) was added dropwise. After complete addition the mixture was allowed to warm to room temperature and stirred for 1 h before quenching with aqueous ammonium chloride (1 ml). The aqueous phase was extracted with DCM (3 × 10 ml), the organics were then dried over sodium sulfate, filtered and the solvent evaporated to give a yellow oil. Purification by flash column chromatography on silica eluted with 40% ethyl acetate–petrol gave **8e** as a white solid (147 mg, 49%), $\nu_{max}(CHCl_3$ film)/cm^{-1} 1732 (C=O), 1214 (P=O); δ_H(270 MHz; $CDCl_3$) 9.76 (1H, s, NH), 8.15–8.13 (1H, m), 7.73–7.44 (11H, m), 7.43–7.17 (12H, m), 6.72 (1H, d, *J* 8.1); δ_C(100 MHz; $CDCl_3$) 157.6 (C*i*), 151.0 (C*i*), 142.8 (C*i*), 141.4 (C*i*), 132.5 (CH), 131.9 (CH), 131.7 (CH, d, $J_{C\text{-}P}$ 11), 130.6 (C*i*), 128.7 (CH, d, $J_{C\text{-}P}$ 13), 128.5 (CH), 128.1 (CH, d, $J_{C\text{-}P}$ 6), 125.4 (CH), 125.0 (C*i*, d, $J_{C\text{-}P}$ 7), 124.3 (C*i*, d, $J_{C\text{-}P}$ 48), 123.2 (CH, d, $J_{C\text{-}P}$ 11), 122.6 (CH), 122.0 (C*i*), 116.9 (C*i*), 115.8 (C*i*), 113.5 (CH), 89.7 (C*i*); δ_P(160 MHz; $CDCl_3$) 28.14 (s); *m*/*z* (electrospray) 592 (MH^+, 100%) (Found: MH^+, 592.167 84. $C_{38}H_{26}NO_4P$ requires *M*H, 592.167 72).

(3a*R*,7a*R*)-1,3-dimethyl-2-chloro-2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxide 10[26]

(*R*,*R*)-*N*,*N*′-Dimethyl-1,2-diaminocyclohexane (450 mg, 3.19 mmol) was dissolved in DCM (60.0 ml) and triethylamine (1.33 ml, 9.57 mmol) was added with stirring. The mixture was cooled to 0 °C and $P(O)Cl_3$ (0.3 ml, 3.19 mmol) was added slowly dropwise. The mixture was gradually allowed to warm to room temperature overnight. The reaction was quenched by the addition of water (60 ml) and the separated organics dried over sodium sulfate, filtered and solvent evaporated. Purification by suction flash chromatography on silica eluted with 50% ethyl acetate–cyclohexane gave **10** as a white solid (673 mg, 95%), $[a]_D^{20}$ −54.09 (*c* 1.0, CH_2Cl_2) [lit.,[26] $[a]_D^{20}$ −57.7 (*c* 5.7, CH_2Cl_2)]; δ_H(250 MHz; $CDCl_3$) 2.90–2.81 (1H, m), 2.67 (3H, d, *J* 11.9), 2.64–2.53 (1H, m), 2.55 (3H, d, *J* 15.9), 2.04–2.00 (2H, m), 1.87 (2H, m), 1.36–1.18 (4H, m).

(4*S*,5*S*)-2-Chloro-1,3-dimethyl-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide 9[26]

Prepared as described for **10** in 87% yield, δ_H(270 MHz; $CDCl_3$) 7.36–7.31 (6H, m), 7.15–7.12 (2H, m), 7.08–7.05 (2H, m), 4.17–4.10 (1H, m), 3.84 (1H, d, *J* 8.6), 2.60 (3H, d, *J* 10.4), 2.45 (3H, d, *J* 14.5).

(4*S*,5*S*)-1,3-dimethyl-2-(2-oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzofuro[7,6-*d*][1,3]oxazin-10-yl)-4,5-diphenyl-1,3,2-diazaphospholidine 2-oxide 8f

Diphenyl urethane **7e** (170 mg, 0.4 mmol) was suspended in ether (0.5 ml) and TMEDA (0.2 ml, 1.31 mmol) was added. The mixture was cooled to −78 °C and Bu^{s}Li (1.0 ml, 1.31 mmol of a 1.3 M solution in cyclohexane) was added dropwise. After 15 min the mixture was allowed to warm to room temperature and stirred for 3 h. The resulting dark red suspension was recooled to −78 °C and the chlorodiazaphospholidine oxide **9** (278 mg, 0.87 mmol) in THF (2.0 ml) was added slowly. The resulting orange suspension was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by the addition of water and the aqueous phase extracted with ether (3 × 10 ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 60–70% ethyl acetate–petrol followed by recrystallisation from ethyl acetate–petrol gave **8f** (96 mg, 33%), $[a]_D^{20}$ −96.5 (*c* 1.0, $CHCl_3$); ν_{max}(Nujol mull)/cm^{-1} 3743, 3485 (NH), 1738 (C=O), 1245 (P=O); δ_H(270 MHz; $CDCl_3$) 9.65 (1H, s, NH), 8.18 (1H, d, *J* 7.7), 8.06–7.98

(1H, m), 7.60–7.54 (2H, m), 7.38–7.21 (18H, m), 7.13–7.11 (2H, m), 6.76 (1H, d, *J* 8.1), 4.37–4.25 (2H, AB overlapping *J* 8.4), 2.55 (3H, d, *J* 10.4), 2.32 (3H, d, *J* 10.3); δ_C(100 MHz; $CDCl_3$) 157.8 (C*i*), 150.8 (C*i*), 142.6 (C*i*), 141.5 (C*i*, d, $J_{C\text{-}P}$ 18.4), 137.9 (C*i*), 136.8 (C*i*), 132.6 (CH), 128.8–128.1 (CH), 127.3 (CH), 125.1 (C*i*), 125.0 (CH), 124.8 (C*i*, d, $J_{C\text{-}P}$ 20.3), 123.5 (C*i*, d, $J_{C\text{-}P}$ 11.1), 122.6 (CH), 121.9 (C*i*), 113.6 (CH), 89.8 (C*i*), 72.9–72.1 (CH_2), 30.3 (CH_3), 29.4 (CH_3); δ_P(160 MHz; $CDCl_3$) 28.395 (s); *m*/*z* (FAB) 676 (MH^+, 100%), 632 ($MH - CO_2^+$, 87) (Found: MH^+, 676.235 791. $C_{42}H_{34}N_3O_4P$ requires *M*H, 676.236 520).

(3a*R*,7a*R*)-1,3-Dimethyl-2-(2-oxo-4,4-diphenyl-2,4-dihydro-1*H*-benzo[2,3][1]benzofuro[7,6-*d*][1,3]-oxazin-10-yl)-2,3,3a,4,5,6,7,7a-octahydro-1*H*-1,3,2-benzodiazaphosphole 2-oxide 8g

Diphenyl urethane **7e** (1.0 g, 2.56 mmol) was suspended in ether (20.0 ml) and TMEDA (1.16 ml, 7.68 mmol) added with stirring. The mixture was cooled to −78 °C and Bu^{s}Li (6.15 ml, 7.68 mmol of a 1.25 M solution in cyclohexane) was added slowly dropwise. After stirring for 30 min the dark red suspension was allowed to warm to room temperature and the mixture stirred for a further 3 h. The suspension was then cooled to −78 °C and the chlorodiazaphospholidine oxide **10** (681 mg, 3.07 mmol) in THF (15.0 ml) was added dropwise. After 45 min the mixture was allowed to warm to room temperature and stirred for a further 16 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (10 ml) and the aqueous phase extracted with DCM (3 × 20 ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by flash chromatography on silica eluted with 0.5–5% MeOH–DCM followed by crystallisation from hot ethyl acetate gave **8g** (928 mg, 63%), mp 175–177 °C (ethyl acetate); $[a]_D^{20}$ +32.4 (*c* 1, $CHCl_3$) (Found: C, 68.47; H, 5.83; N, 6.90. $C_{34}H_{32}N_3O_4P{\cdot}H_2O$ requires C, 68.57; H, 5.71; N, 7.07%); ν_{max}($CHCl_3$ film)/cm^{-1} 3382 (NH), 1731 (C=O); δ_H(400 MHz; $CDCl_3$) 10.59 (1H, br s, NH), 8.10 (1H, d, *J* 7.6), 7.64 (1H, dd, *J* 13.7, 7.3), 7.53 (1H, d, *J* 7.9), 7.43 (1H, td, *J* 7.3, 2.1), 7.35–7.20 (10H, m), 6.73 (1H, d, *J* 7.9), 3.00 (1H, m), 2.64 (4H, d, *J* 11.6), 2.38 (3H, d, *J* 11.9), 2.19 (1H, br d, *J* 11.6), 2.04–1.91 (3H, m), 1.45–1.24 (4H, m); δ_C(100 MHz; $CDCl_3$) 158.3 (C*i*), 151.3 (C*i*), 142.9 (C*i*), 141.8 (C*i*), 131.6 (CH, d, $J_{C\text{-}P}$ 5.5), 128.5 (CH, d, $J_{C\text{-}P}$ 11.0), 128.2 (CH, d, $J_{C\text{-}P}$ 5.5), 128.1 (CH), 124.8 (CH, d, $J_{C\text{-}P}$ 9.2), 124.5 (C*i*), 123.2 (CH, d, $J_{C\text{-}P}$ 11.0), 122.5 (CH), 122.3 (C*i*), 115.2 (C*i*), 113.7 (C*i*), 113.4 (CH), 89.8 (C*i*), 64.6 (CH, d, $J_{C\text{-}P}$ 7.3), 64.0 (CH, d, $J_{C\text{-}P}$ 5.5), 28.8 (CH_3), 28.7 (CH_2), 28.3 (CH_2), 28.2 (CH_3), 27.9 (CH_2), 24.3 (CH_2); δ_P(160 MHz; $CDCl_3$) 31.54 (s); *m*/*z* (thermospray) 578 (MH^+, 100%), 534 ($MH - CO_2^+$, 20).

General procedure for the determination of critical association constant for hosts in $CDCl_3$ solution

A 1.48×10^{-2} M solution of **8f** (azeotrope dried from $CHCl_3$) in dry $CDCl_3$ was taken as a starting concentration. A 1 ml sample of this was subjected to ^{1}H NMR analysis (400 MHz; 21–22 °C) and the chemical shift of the carbamate NH noted. This sample was then diluted to half concentration and a 1 ml sample analysed. This process was repeated until a constant, minimum value for the NH chemical shift was found. In this case the CAC was found to be at 1.85×10^{-3} M.

General procedure for the NMR titration of host–guest systems in $CDCl_3$ solution

Stock solutions of **8g** (azeotrope dried from $CHCl_3$) and *N*-Boc-glycine were made in dry $CDCl_3$ under a nitrogen atmosphere. 1 ml NMR samples were made up, under an atmosphere of nitrogen, such that the sample concentration remained at a constant value of 1.74×10^{-4} M throughout. The ratio of guest (*N*-Boc-glycine) to host was gradually increased across the sample range keeping the concentration of host at a constant. ^{1}H NMR analysis (400 MHz; 21 °C), following the chemical shift of the carbamate NH in the host, across the sample range was then carried out. ^{31}P NMR analysis (160 MHz; 21 °C) of the same set of samples was also carried out. The change in chemical shift was plotted against host–guest ratio and a value of the binding constant (K/M^{-1}) calculated. In this case ^{1}H NMR gave K 1031 M^{-1} and ^{31}P NMR gave K 819 M^{-1} giving an average value of K 930 M^{-1}. This process was repeated in the cases of *N*-Boc-L- and -D-alanine for which the results are given in the main text.

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