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Synthesis and electrospray mass spectrometric studies on a chiral, non-racemic, phosphoramide receptor molecule

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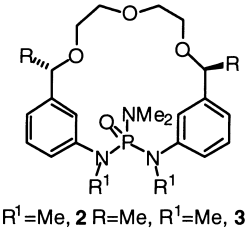
Abstract

The synthesis of a class of macrocyclic receptors containing a phosphoramide is described. The preliminary evaluation of this new receptor for interactions with several homochiral amines using electrospray ionisation mass spectrometry is also described.

The synthesis, and guest complexing properties, of a number of phosphorus-containing macrocycles such as **1**–**3** have been reported in the recent literature.[1] Macrocycles of this type, which contain a phosphoramide group within a ring composed otherwise of ether linkages, may complex a charged guest such as a Group 1 or 2 metal cation or a protonated primary amine in one of two modes. In the first mode, the oxygen atom of the phosphoramide participates,[2] whilst in the second mode it does not.[3] The energetic balance between each mode is low, hence there is potential for the use of these systems as 'molecular switches'.



1 R=H, R^1=Me, **2** R=Me, R^1=Me, **3** R=H, R^1=H

Having gained experience in the synthesis of phosphoramides and related systems in the course of our programme of research into asymmetric ketone reduction,[4] we were attracted by the synthetic potential of phosphorus-containing macrocycles. In addition to the complexing properties described above, we wished to test the materials as catalysts for the asymmetric catalysis of the reduction of ketones

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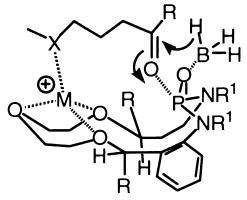
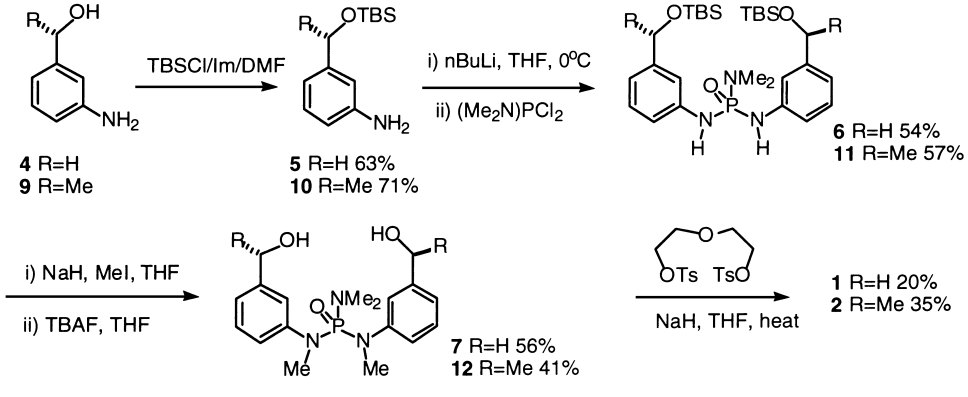


Figure 1. NMe_2 on P omitted for clarity

by borane. In particular we were intrigued by the potential of the heterocycles to act as 'substrate-selective' catalysts. This could be achieved through an interaction of a co-ordinating group within the substrate to a complexed cation, thus delivering the adjacent ketone to the reactive phosphoramide centre (Fig. 1). Should this mechanism operate, then the rate of reduction of ketones bearing the nearby co-ordinating group should be somewhat faster than the reduction of unfunctionalised ketones, which lack such a directing group. In this paper we report the synthesis of macrocycles **1**–**3** and the results of our preliminary studies into their behaviour as asymmetric reduction catalysts and receptors for small molecules.

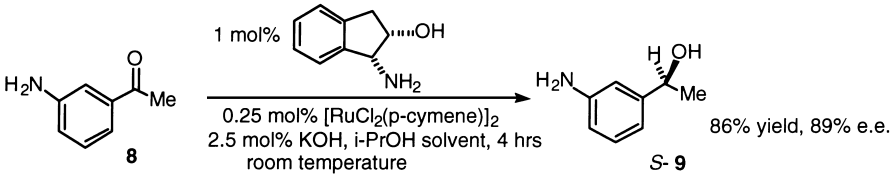
Our synthetic route to the target molecules is shown in Scheme 1. In designing our approach we first considered using the method employed by Dutasta et al., for the synthesis of closely related compounds.[5] This process involves the completion of the macrocyclisation through formation of the 'NPN' unit as the final step. In our hands, however, the product of the ring-closure was consistently contaminated with oligomeric side products. As a result of this we changed the order of bond formation. In the approach to the non-chiral receptor **1** we first protected the alcohol group in 3-amino benzylalcohol **4** to give **5**, which was then converted to the phosphorus-bridged dimer **6** in good yield. Completion of the synthesis of **3** was achieved through deprotection of **6** followed by reaction with diethyleneglycol ditosylate/sodium hydride (9% over two steps). The yield of deprotected **6** was rather low, probably due to losses in workup and purification of the insoluble diol. This situation was much improved through *N*-methylation of **6** prior to desilylation, yielding **7** in a 56% overall yield for two steps.[6] Completion of the synthesis of **1** was then achieved by heating overnight with diethyleneglycol ditosylate/sodium hydride.



Scheme 1.

Before proceeding with the synthesis of a chiral, non-racemic phosphoramide macrocycle, the potential use of these compounds as catalysts in reduction reactions was examined. The reduction of acetophenone by borane represents a convenient prototype reaction for the assessment of new catalysts and in our preliminary studies[4] the use of 10 mol% of **1** resulted in a small acceleration of some 2–3 fold over the background rate.[7] This represents a lower rate increase than with certain phosphinamide catalysts which may be the result of steric hindrance in the macrocycle.

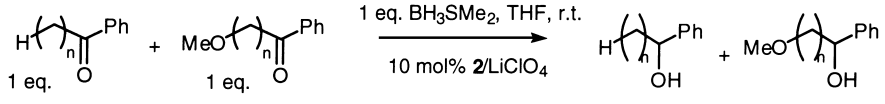
Having demonstrated a synthetic route to the macrocyclic structures we next prepared the C_2-symmetric chiral, non-racemic variant **2**. Crucial to the success of this synthesis was the asymmetric reduction of 3-aminoacetophenone **8** using transfer hydrogenation with a ruthenium(II)/*cis*-aminoindanol procedure which we have reported previously (Scheme 2).[8] Ketone **8** proved to be an excellent substrate, furnishing the corresponding alcohol **9** in 86% yield and 89% e.e., assigned as *S*-configuration on the basis of previous trends in this class of reduction.[9] Alcohol **9** was purified to >98% e.e. by recrystallisation.



Scheme 2.

Completion of the synthesis of **2** followed the route described for **1** (Scheme 1) and worked in good yield at each step except the final macrolactonisation, which was achieved in 35% yield and is as yet unoptimised. The ^{1}H, ^{13}C and ^{31}P NMR spectra of (*SS*)-**1** showed only one diastereoisomer of the macrocycle to be present, which was in contrast to the mixture of three products formed from the same set of transformations on racemic **9**, which was also prepared as a reference standard.[10]

With **2** in hand we then wished to investigate its molecular recognition properties. In the first study we examined the competitive reductions of a short series of ketones. The objective of this study was to compare the extent to which the macrocycle was able to discriminate between substrates containing proximal co-ordinating groups and those which did not (Scheme 3, Table 1). In each case a 1:1 mixture of two ketones of equal chain length was employed in a competitive reaction with 1 equivalent of borane–dimethylsulphide complex, 10 mol% macrocycle and 10 mol% lithium perchlorate. Substrate mixtures containing no macrocycle or lithium perchlorate were also reduced under the same conditions in order to provide a correction for the relative reactivity of each ketone. The results given in Table 1 reveal that in the case of α-methoxyacetophenone there was a change in the ratio of its reduction relative to acetophenone compared to the unmodified reaction, which indicates that the macrocycle was in some way influencing the reaction. The fact that the methoxy-substituted ketone is reduced to a lesser extent in the presence of the macrocycle suggests that there is a binding event which may be protecting the ketone from reduction, rather than activating it, as we had originally speculated. We are presently investigating this effect. The relative reduction rates for the other two pairs of ketones were unchanged and no asymmetric induction was observed in any of the products.



Scheme 3.

We also took the opportunity to examine the binding of our novel heterocycles to chiral amines using methods described previously.[11] In order to assess any enantioselectivity which might be achieved we chose to use electrospray MS.[12] In a series of experiments we combined a quantity of **2** with a known excess of both benzylamine and one enantiomer of an enantiomerically pure amine (both guest amines at an equimolar concentration). The mixtures were examined by electrospray mass spectrometry for selective binding of the enantiomerically pure amine relative to benzylamine, which acted as a standard for comparison. The ESI mass spectra showed strong ion signals of the host–guest complexes for all amines studied. The binding properties of the host **3** were evaluated with a range of amines: each

Table 1

n	Macrocycle **2**/ $LiClO_4$ added	combined yield alcohols/%	ratio reduction products MeO:H
1	No	60	1.35
1	yes	47	0.97
2	no	58	0.54
2	yes	42	0.59
3	no	72	0.81
3	yes	54	0.81

enantiomer of the amines α-methylbenzylamine, *cis*-amino indanol and all four isomers of ephedrine.[13] These preliminary studies reveal that our novel heterocycle host in general binds strongly with the amines examined. However, no chiral selectivity could be revealed from the ESI mass spectra for the whole range of studied amines. The full results of these and other studies will be published in due course.

Acknowledgements

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2. Delangle, P.; Dutasta, J.-P.; Oostenryck, L. V.; Tinant, B.; Declercq, J.-P. *J. Org. Chem.* **1996**, *61*, 8904.
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6. All new compounds gave satisfactory physical and spectroscopic data, and were fully characterised.
7. We used reverse phase HPLC to follow the reaction, correcting for the relative extinction coefficients of ketone and alcohol. See: Burns, B.; Studley, J. R.; Wills, M. *Tetrahedron Lett*. **1993**, *34*, 7105.
8. Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.
9. The reduction gave a product of 89% e.e. as measured using chiral HPLC. The absolute configuration of the novel compound was assigned as *S* on the basis of its structural similarity to 1-phenethanol. Reduction with borane using a chiral phosphinamide catalyst known to give the enantioselectivity to (1*R*,2*S*)-(+)-*cis*-aminoindanol (see Ref. 4) gave the opposite enantiomer of **10** in 56% yield and 69% e.e.
10. The ^{1}H, ^{13}C and ^{31}P NMR spectra of compound **2** displayed a distinctive set of signals corresponding to a single diastereomer. This was in contrast to the spectra of **2** prepared from racemic **8**, which appeared as a mixture of three diastereoisomers in a predicted 1:2:1 ratio. All the spectroscopic details will be described in a full paper in due course.
11. Jorgensen, T. J. D.; Roepstorff, P.; Heck, A. J. R. *Anal. Chem*. **1998**, *70*, 4427.
12. For an example of the use of electrospray MS in chiral recognition studies of related heterocycles, see: Deardon, D. V.; Dejsupa, C.; Liang, Y.; Bradshaw, J. S.; Izatt, R. M. *J. Am. Chem. Soc*. **1997**, *119*, 353, and references cited therein.
13. In a typical experiment we mixed a 1 mM solution of **2** (20 μL) with a 1 mM solution of a pure enantiomer of, for instance, *cis*-aminoindanol (40 μL) and a 1 mM solution of benzylamine (40 μL), all in MeCN. The final solution was made up to a total volume of 1 mL using either MeCN or an ammonium acetate buffer (5 mM, pH 5.05). The final concentration of host **2** was, therefore, typically 20 μM, whereas the equimolar guest concentrations were 40 μM. The mixture was analysed immediately by electrospray mass spectrometry using a Thermoquest LC-Q ion trap mass spectrometer. Approximately 2 μL of the final solutions was placed into a gold coated nanospray needle and used for analysis. Typical ion source conditions were: electrospray voltage 700 V, cone voltage 10 V, capillary temperature 120°C. Spectra were acquired in the positive ion mode. Host–guest complexes were detected as $[Host+Guest+H]^{+}$ ions. A table of ESI host–guest mass spectra data is given below: under the conditions employed, with an excess of guest competing for binding with the host, only the

relative abundances of the host and host–guest complexes were measured. Solutions were comprised of pre-equilibrium concentrations of: host 20 mM, guest 40 mM, benzylamine 40 mM in acetonitrile or, if stated, in ammonium acetate buffer (pH 5.05).

Amine	**% host**	**% host-guest**	**% host-benzylamine**
(*R*)-α-methylbenzylamine	68	100	89
(*S*)-α-methylbenzylamine	88	100	59
(1R, 2S) aminoindanol	42	23	100
(1S, 2R) aminoindanol	40	45	100
(1R, 2S) aminoindanol*	86	12	24
(1S, 2R) aminoindanol*	85	12	25
(+)-pseudoephedrine*	89	9	34
(-)-pseudoephedrine*	54	54	98
(+)-ephedrine*	95	5	12
(-)-ephedrine*	95	7	20

* in buffer solution, host/ammonium cation is 100% relative abundance