In summary, our experiments support a scheme whereby **1** and **2** are transformed upon treatment with various chemical agents to the intermediate **3** and then to the biradical **4**. The latter cyclization is rapid at 10 °C and is calculated to have a half-life of ~2 min at 37 °C.[15]

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

(14) Mechanisms that do not involve **1** as an intermediate in the formation of **11** and **12** from **2** can also be invoked.

(15) This calculation is based on an assumed $\Delta S^{\ddagger}$ of -11.6 ± 1.5 eu (ref 5).

Concave Functionality: Intracavity Phosphine Oxide as a Locus of Complexation

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The design of host molecules capable of binding neutral organic guests is an area of considerable current interest.[1] Our interest in macrocycles containing cavities bearing concave functionalities[2] led to our preparation of cages **2–5**. Since phosphine oxides have been demonstrated to serve as strong hydrogen-bond acceptors,[3] we chose to incorporate this functionality in the construction of macrocycles. We report the synthesis and preliminary binding studies of two exo–exo (**2** and **4**) and two endo–exo (**3** and **5**) bifunctional cages confirming that **3** and **5** exhibit intracavity complexation.

Synthesis. Reaction of tris(4-hydroxyphenyl)phosphine oxide[4] with propargyl bromide and K_2CO_3 in acetone afforded tris(4-propargyloxyphenyl)phosphine oxide (**1**). Treatment of **1** in pyridine at 60 °C with $Cu(OAc)_2 \cdot H_2O$ for 2 h provided 14% and 7% yields of **2** and **3**, respectively, after isolation (Scheme I). Monoclinic crystals of **2** from chloroform were suitable for an X-ray structure determination. The space-filling representation (Figure 1), excluding solvent, confirms the exo orientation of both phosphine oxides, and a P–P distance of 10.85 Å was observed.

Hydrogenation of **2** afforded **4** in 47% yield, while hydrogenation of **3** provided **5** in 53% yield. The ^1H NMR spectra of **3** and **5** indicated four types of aromatic protons while **2** and **4** showed only two. Lanthanide shift reagents confirmed that the most downfield of the aromatic protons (**3**, 8.06 ppm; **5**, 7.86 ppm) in the two endo–exo hosts were those ortho to the exo phosphine oxide. The X-ray structure of **5** (Figure 2) obtained from triclinic crystals grown from wet ethyl acetate verifies the presence of the endo phosphine oxide. The water in the crystal structure was observed to exist in either of two locations: both showed hydrogen bonding to the exo phosphine oxide. The reduced intracavity space of **5** relative to **2** is apparent.

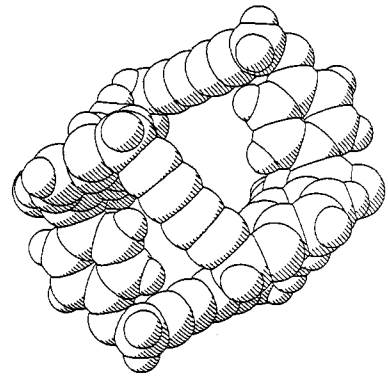

Figure 1. Space-filling representation of **2** generated by SHELXTL PLUS, based on X-ray data collected at −150 °C. Solvent molecules are excluded from the structure. The final R value after refinement was 0.108. The P–P distance is 10.85 Å.

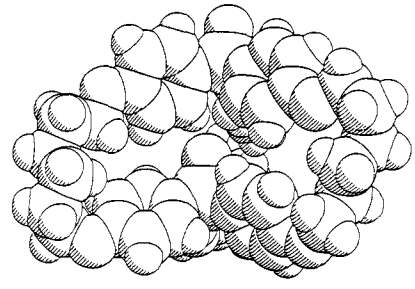

Figure 2. Space-filling representation of **5** generated by SHELXTL PLUS, based on X-ray data collected at −100 °C. Ethyl acetate and water molecules are excluded from the structure. The final R value after refinement was 0.0602.

Complexation. Titration of **3** or **5** with *p*-nitrophenol (PNP) in $CDCl_3$ results in a dramatic upfield shift of the protons ortho to the exo phosphoryl sites (**3**, 8.06 ppm; **5**, 7.86 ppm) in the ^1H NMR spectra. Similar treatment of **2** or **4** results in no substantial movement of host protons.[5] However, competition studies with **3** confirm the nonshifting exo complexation of PNP by **2** and **4**. The exo phosphoryl sites in **3** and **5** are proposed to bind similarly with an induced shift of host protons resulting only from endo complexation. The large shift of host protons ortho to the exo phosphine oxides upon endo complexation is attributed to the proximity of the guest's aromatic ring to these protons. Figures 3 and 4 illustrate the observed chemical shifts for the protons studied on **3** and **5** at various concentrations of PNP in addition to the curve fitted by Simplex.[6,7]

The two different phosphoryl sites on **3** and **5** indicate that initial complexation may occur at either the exo or the endo phosphoryl in 1:2 complex formation. Figure 3 is consistent with initial binding at the endo site, since the chemical shift of the 1:1 complex (7.42 ppm) derived from Simplex is substantially different from that of the free host, but identical with the derived shift of the 1:2 complex (7.42 ppm). The $^{endo}K_{assoc}$ is 354 M^{-1}, and the $^{exo}K_{assoc}$

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(5) No substantial movement indicates that less than 0.05 ppm shifting of any host proton occurred in the proton NMR on addition of 4 equiv of guest.

(6) A nonlinear-least-squares program was written by using the Simplex algorithm. It handles several complexation cases and has an attached PostScript and graphical user interface. The source (Turbo C) is available from the authors upon request.

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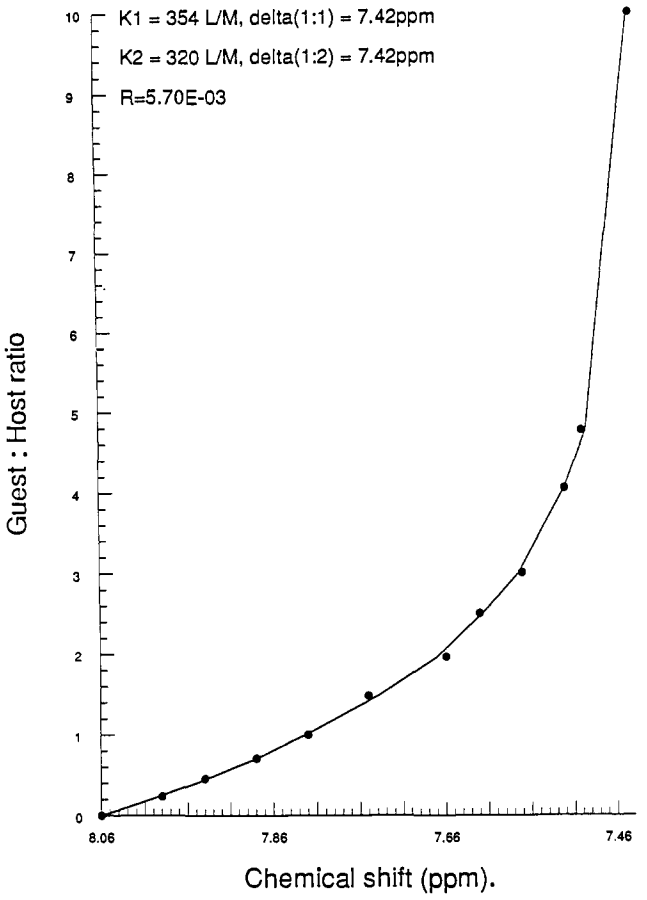


Figure 3. Plot of the chemical shift of the protons ortho to the exo phosphine oxide on **3** versus the equivalents of *p*-nitrophenol added at 25 °C. The points are the observed chemical shifts, and the curve is computer generated by Simplex using the association constants and chemical shifts shown.

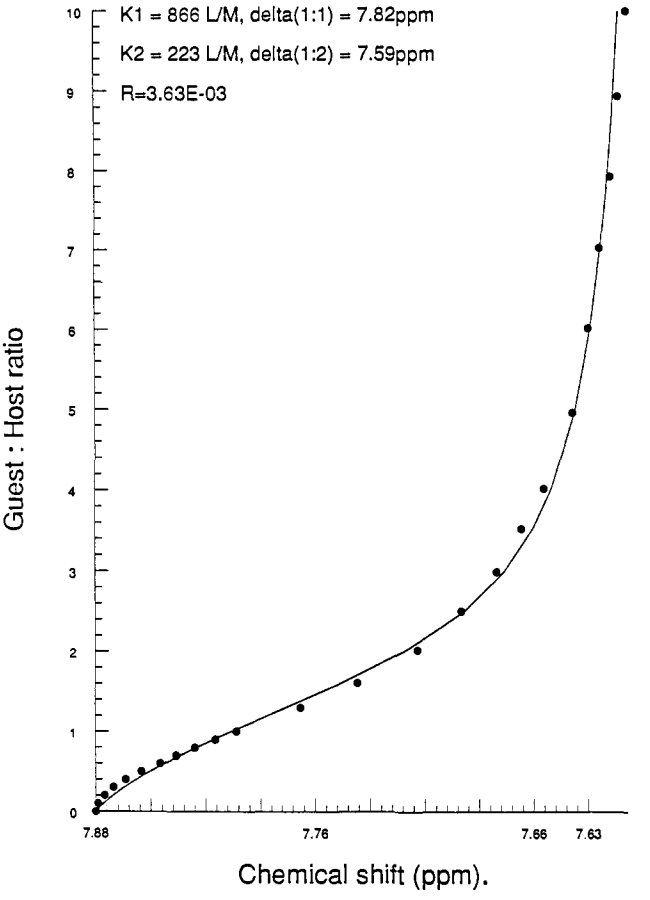
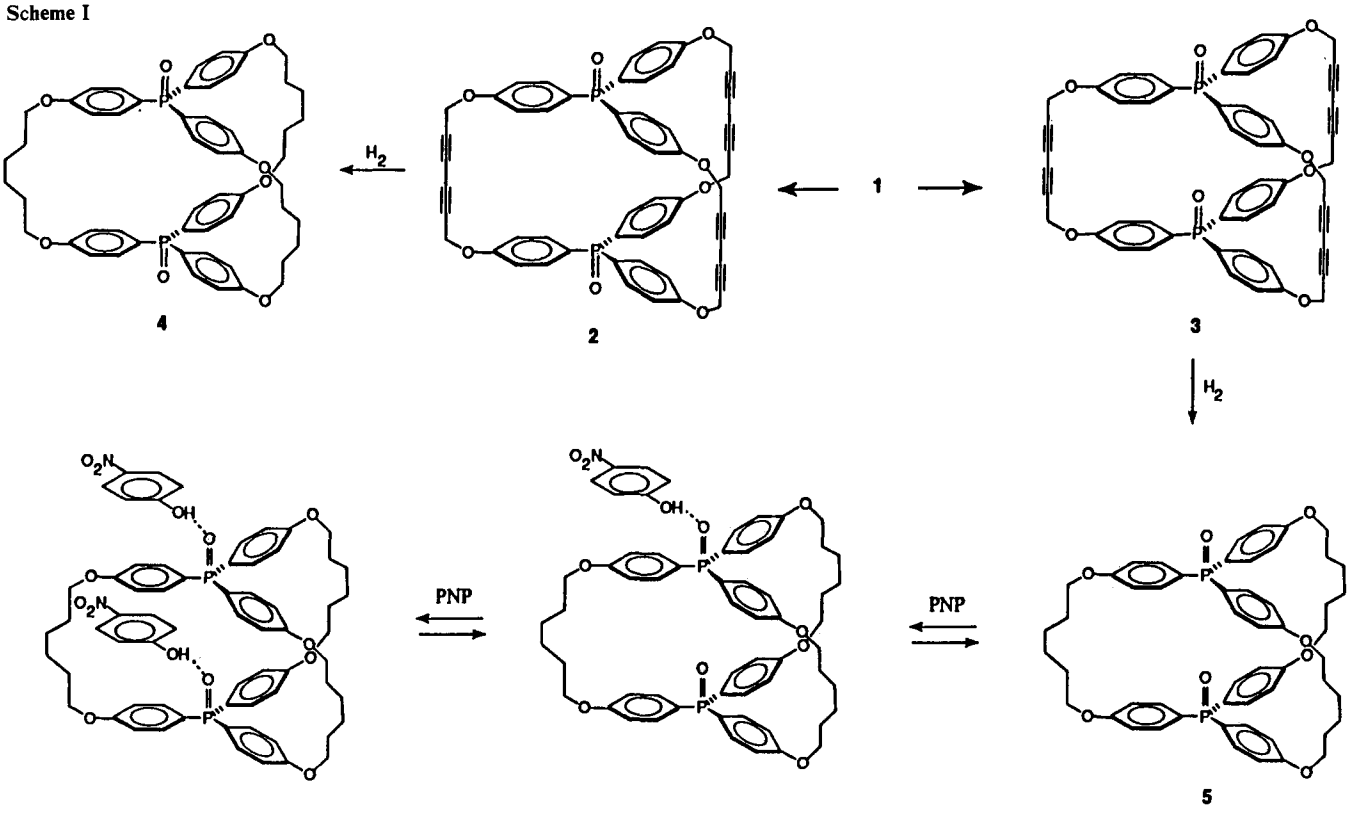


Figure 4. Plot fo the chemical shift of the protons ortho to the exo phosphine oxide on **5** versus the equivalents of *p*-nitrophenol added at 25 °C. The points are the observed chemical shifts, and the curve is computer generated by Simplex using the association constants and chemical shifts shown.

Scheme I



is 320 M^{-1}, indicating that only a slightly tighter complex is formed within the cavity. The sigmoidal curve in Figure 4 is consistent with initial binding at the exo phosphoryl presumably due to steric interactions since the derived chemical shift of the 1:1 complex (7.82 ppm) is close to that of the free host, but significantly different from that of the 1:2 complex (7.59 ppm). The $^{exo}K_{assoc}$ is 866 M^{-1}, and the $^{endo}K_{assoc}$ is 223 M^{-1}. The larger $^{exo}K_{assoc}$ of **5** relative to **3** is under investigation. Scheme I displays the proposed mechanism for 1:2 complex formation of **5** with PNP.

In conclusion, we have shown that phosphine oxide bifunctional macrocycles (**2**–**5**) form 1:2 complexes with PNP. While exo–exo hosts (**2** and **4**) form only extracavity complexes, the endo–exo hosts (**2** and **5**) also exhibit intracavity complexation. The diyne (**3**) initially complexes at the endo site, while the saturated bridge host (**5**) initially complexes at the exo phosphoryl due to the reduction of intracavity space present in **5**. The specificity of complexation is under current investigation.

Acknowledgment. We gratefully acknowledge D. R. Powell for assistance with the X-ray crystallographic analyses. Acknowledgement is made for partial support of this work by the National Science Foundation and the Office of Naval Research.

Supplementary Material Available: X-ray data for **2** and **5** including space-filling representations, SHELXTL PLUS drawings, crystal data, solution and refinement data, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen atom coordinates and isotropic displacement parameters (27 pages). Ordering information is given on any current masthead page.

Stereoselective Hydrogenation via Dynamic Kinetic Resolution

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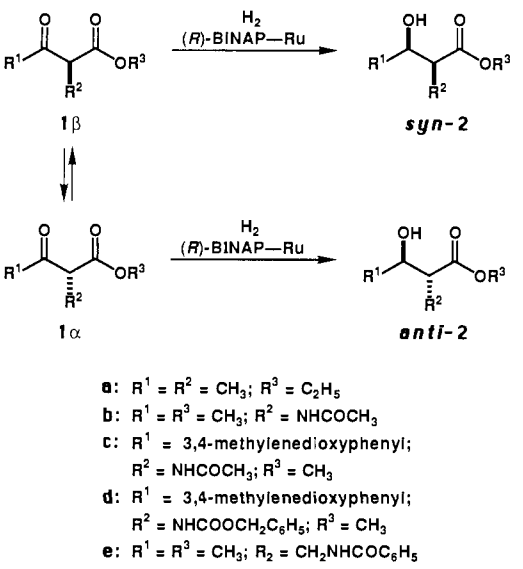
Although kinetic resolution of racemic compounds is increasing in synthetic significance,[1] most reactions suffer from the disadvantage that the yield of the desired chiral product does not exceed 50%. The chiral lability of 2-substituted 3-oxo carboxylic esters, coupled with the high chiral recognition ability of the BINAP–Ru(II) complexes,[2-5] has prompted us to investigate the possibility of stereoselective hydrogenation utilizing dynamic stereomutation as outlined in Scheme I. If the racemization of the enantiomers **1**α and **1**β could be rapid enough with respect to the hydrogenation giving **2**, then when rates of the reaction of **1**α and **1**β are substantially different, the hydrogenation would form one isomer selectively among the four possible stereoisomeric hydroxy esters. This second-order stereoselective transformation, if feasible, constitutes an ideal asymmetric catalysis which, in theory, is capable of converting a racemic starting material in 100% yield to a single chiral product possessing stereodefined vicinal asymmetric centers. We here disclose examples of both syn- and anti-selective hydrogenation based on this principle.

Scheme I



a: $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$
b: $R^1 = R^3 = CH_3$; $R^2 = NHCOCH_3$
c: R^1 = 3,4-methylenedioxyphenyl; $R^2 = NHCOCH_3$; $R^3 = CH_3$
d: R^1 = 3,4-methylenedioxyphenyl; $R^2 = NHCOOCH_2C_6H_5$; $R^3 = CH_3$
e: $R^1 = R^3 = CH_3$; $R_2 = CH_2NHCOC_6H_5$

The efficiency and sense of the enantio- and diastereoselective synthesis of **2** is highly influenced by substrate structures and reaction conditions. The BINAP–Ru catalyzed hydrogenation of simple 2-alkylated substrate **1a** proceeds with high stereoselectivity with respect to the C-3 position, but no appreciable resolution is seen, resulting in an equimolar mixture of *syn*-**2** and *anti*-**2**.[2a,6,7] However, appropriate skeletal or functional perturbation of substrates leads to clear differentiation of syn and anti transition states, as illustrated in Table I. In dichloromethane containing an (*R*)-BINAP–Ru complex, racemic *cyclic* ketone **3** was hydrogenated with high anti diastereoselectivity, to give a 99:1 mixture of the *trans*-hydroxy ester **4** (92% ee) and its C-2 epimer **5** (93% ee) quantitatively.[8] The reaction in methanol decreased diastereoselectivity (82:18). By contrast, an amide or carbamate group present in certain *acyclic* substrates exhibited remarkable syn directivity, leading to threonine type products in excellent ee's and in high yields. For instance, hydrogenation of 2-acetamido derivative **1b** in dichloromethane gave a protected L-threonine, *syn*-**2b** (98% ee), and allothreonine, *anti*-**2b**, with 99:1 selectivity.[7,9] Use of methanol as solvent lowered the diaster-

[†] Nagoya University.
[‡] Kyoto University.
[§] Takasago Research Institute.

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(3) Note: A limited, small quantity of $Ru(OCOCH_3)_2$[(*R*)- or (*S*)-BINAP][4] is available. Please contact R. Noyori at Nagoya University, indicating chirality of the complex and type of substrates.
(4) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566. RuX_2(BINAP) (X = Cl or Br, empirical formula) complexes were prepared by mixing $Ru(OCOCH_3)_2$(BINAP) and HX in a 1:2 ratio.[2] Use of the freshly prepared complex is recommended for reaction in dichloromethane. Since these polymeric complexes behave similarly to the well-defined monomeric complex $[RuCl(C_6H_6)(BINAP)]Cl$, the active catalyst precursor may be represented as $RuX_2(BINAP)(solvent)_2$.
(5) Resolution of secondary allylic alcohols: Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.
(6) Hydrogenation of methyl 2-methyl-3-oxobutanoate catalyzed by Raney nickel modified by (*R*,*R*)-tartaric acid gave methyl (2*S*,3*R*)-3-hydroxy-2-methylbutanoate (56.7% ee) and the 2*R*,3*R* isomer (64.4% ee) in a 3.6:1 ratio. See: Tai, A.; Watanabe, H.; Harada, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1468.
(7) The syn and anti isomers are not interconvertible under the reaction conditions.
(8) For biological methods, see: Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631. Buisson, D.; Sanner, C.; Larcheveque, M.; Azerad, R. *Ibid.* **1987**, *28*, 3939. Nakamura, K.; Miyai, T.; Nozaki, K.; Ushio, K.; Oka, S.; Ohno, A. *Ibid.* **1986**, *27*, 3155.

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