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Sterically congested macrobicycles with heteroatomic bridgehead functionality

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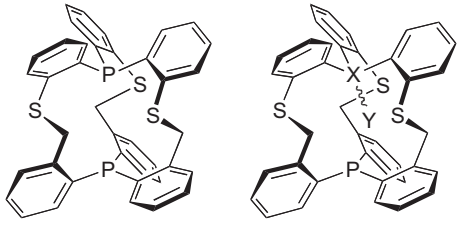
ABSTRACT

A series of cyclophanes composed of two triarylelement caps linked by two-atom bridges has been synthesized. The bridgehead functional groups include phosphines in combination with amines, hydrosilanes, methylsilanes, and ethoxysilanes. Computational studies accurately predicted that when the bridgehead substituents are small (lone pairs or protons), an *in*,*in* bridgehead stereochemistry is strongly favored, but larger bridgehead substituents favor the formations of *in*,*out* stereoisomers. The X-ray structures, spectra, and reactivity of these compounds are discussed, as well as the resolution of one of the cyclophanes into pure enantiomers.

1. Introduction

We recently reported the synthesis of the macrobicyclic *in*,*in*-bisphosphine **1**, a molecule with two interacting bridgehead phosphines that show strong spin–spin coupling and resist reaction with reagents larger than protons.[1] The *in*,*in* stereochemistry of compound **1** was hardly unexpected, based on the conformational restrictions imposed by the six aryl rings and the previously observed conformational preferences of other sterically congested *in*-cyclophanes,[2] but the incorporation of larger bridgehead functionality must eventually lead to the formation of *in*,*out* or even *out*,*out* stereoisomers.[3] Indeed, while the preparation of **1** was a logical extension of our studies of triarylphosphine-containing cyclophanes,[4–8] we have also made cyclophanes capped with triarylamines,[9] triarylhydrosilanes,[5] and triarylmethylsilanes;[7] thus macrobicycles containing mixed bridgehead heteroatoms might be prepared from precursors already in hand.

We have long been interested in the effects of strain and congestion on the spectra and reactivity of various functional groups in cyclophane structures, and we now report the synthesis and characterization of four new macrobicycles (Scheme 1, compounds **2**–**5**), each containing mixed bridgehead functionality, which display both *in*,*in* and *in*,*out* geometries, and which possess unusual structures, spectra, and reactivity.



1

2 X = N, Y = lp
3 X = Si, Y = H
4 X = Si, Y = Me
5 X = Si, Y = OEt

Scheme 1.

2. Results and discussion

2.1. Computational evaluation of possible macrobicyclic *in*/*out* isomers

Diphosphine **1** contains two strongly pyramidalized bridgehead atoms, and B3PW91/6-31G(d) calculations[10,11] indicate that an *in*,*in* geometry is favored by more than 18 kcal/mol[1] over either of the possible *in*,*out*-isomers, with the *out*,*out*-isomer even more unfavorable (see Table 1). The first question we ask is: would the *in*,*in* geometric preference be affected by substitution of a trigonal planar nitrogen (as it is in triphenylamine) for a pyramidal phosphorus? It seems not. Although the calculated degree of inward pyramidalization of the bridgehead nitrogen of the

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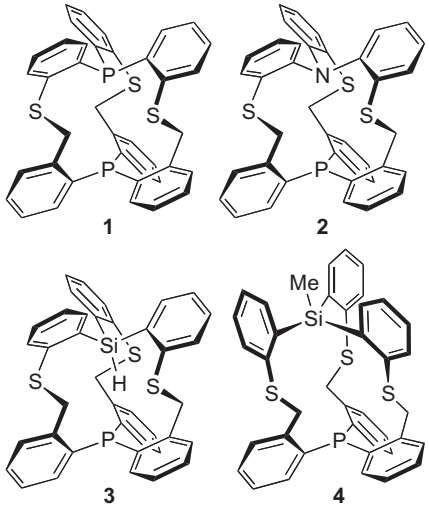
Table 1
Calculated relative energies of *in*/*out* isomers of bis(triarylelement) cyclophanes



Compound	E+ZPE (au)[a]	ΔE (kcal/mol)
in,*in*-P,P (**1**)	−3380.091662[b]	0.0
in,*out*-P,P-A	−3380.062618[b]	+18.2
in,*out*-P,P-B	−3380.061870[b]	+18.7
out,*out*-P,P	−3380.043331[b]	+30.3
in,*in*-N,P (**2**)	−3093.505473	0.0
in,*out*-N,P	−3093.481031	+15.3
out,*in*-N,P	Not a potential minimum	
out,*out*-N,P	Not a potential minimum	
in,*in*-HSi,P (**3**)	−3328.848381	0.0
in,*out*-HSi,P	−3328.817926	+19.1
out,*in*-HSi,P	−3328.832399	+10.0
out,*out*-HSi,P	−3328.813156	+22.1
in,*in*-MeSi,P	−3368.054971	+35.7
in,*out*-MeSi,P	−3368.056685	+34.6
out,*in*-MeSi,P (**4**)	−3368.111798	0.0
out,*out*-MeSi,P	−3368.092861	+11.9

[a] All calculations were performed at the B3PW91/6-31G(d) level; all compounds possess C_3 symmetry and display zero imaginary frequencies.
[b] Ref. 1.

aminophosphine **2** is much less than that of phosphorus, the *in*,*in*-isomer (*in*,*in*-N,P[12]) is still favored by 15 kcal/mol over the sole *in*,*out*-isomer (*in*,*out*-N,P[12]). Interestingly, the triarylamine can adopt only an *in*-conformation in this system; no computational minimum was found for *out*,*in*-N,P or *out*,*out*-N,P.[12]

A second, more interesting question is: how large a functional group may be contained within the macrobicycle? Compounds **1** and **2** possess only lone pair electrons. A proton can surely fit, because the hydrochloride salt of **1** is *in*-protonated in its X-ray structure.[1] Replacement of one phosphine with a hydrosilane again yields (at least computationally) a preference for an *in*,*in*-isomer (*in*,*in*-HSi,P), but it is notable that *out*,*in*-HSi,P, with the proton outside, is only 10 kcal/mol higher in energy. However, when the phosphine is replaced by a methylsilane, the *in*,*in*-isomer (*in*,*in*-MeSi,P) is very strongly disfavored, by almost 36 kcal/mol, with respect to *out*,*in*-MeSi,P. Furthermore, flipping the phosphine *out*, in order to provide more room for an *in*-methyl group, is not effective; *in*,*out*-MeSi,P is 35 kcal/mol less stable than the *out*,*in*-isomer.

These computational predictions were tested by synthesis.

2.2. Synthesis of macrobicycles with mixed bridgehead functionality

The syntheses of all of the target cyclophanes employed the same general method used to make diphosphine **1**.[1] Thus, tris[2-(chloromethyl)phenyl]phosphine[13] (**6**) was condensed with each of the appropriate tris(mercaptophenyl)element caps (**7**–**9**) by treatment with KOH at high dilution in refluxing benzene and ethanol (Scheme 2). The yields were variable and always low.

The most favorable reaction was the condensation of **6** and tris(2-mercaptophenyl)amine[9] (**7**) to give a 15% yield of aminophosphine **2**, which was easily isolated. The silane-capped phanes were more highly problematic. The reaction of tris(2-mercaptophenyl)silane[5] (**8**) gave only a 0.7% yield of the desired *in*,*in*-hydrosilane **3**, but other macrocyclic products were also present. The best characterized of these is the *out*,*in*-ethoxysilane **5** (1.6%) presumably formed via the reaction of ethoxide with precursor **8** prior to cyclization. An *out*,*in*-hydroxysilane also appeared to be present, but was not fully characterized. It should be noted that even before the X-ray structures of these compounds were obtained (see below), their bridgehead configurations were suggested by their ^{1}H NMR spectra, which are quite characteristic. Attempts to improve the yield of **3** by carrying out the synthesis in THF with hindered bases, in order to avoid the solvolysis of the hydrosilane, were not successful. In contrast to the hydrosilane cap **8**, tris(mercaptophenyl)methylsilane (**9**) is not vulnerable to substitution at silicon by alkoxides; nevertheless, condensation of **9** with phosphine **6** still gave only a low 2.2% yield of the expected *out*,*in*-methylsilane **4**. Despite the predicted high energy of *in*,*in*-MeSi,P, the reaction mixture was carefully searched for such a product, but without success.

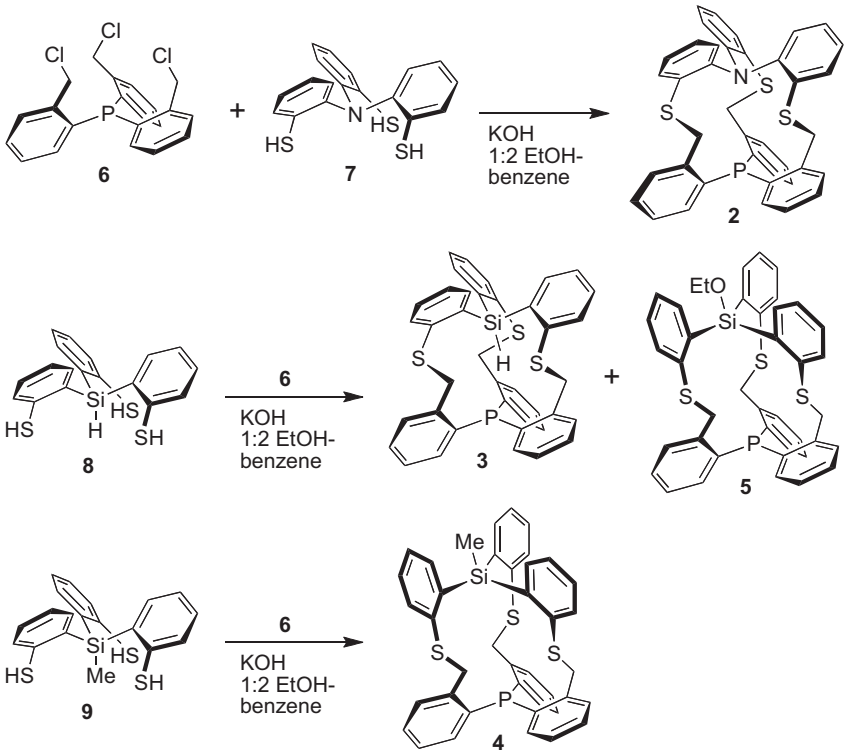
The NMR spectra of all of these compounds show diastereotopic methylene resonances, indicating that the enantiomerization of these molecules is slow on the NMR time scale. In addition, all of them show numerous doublets in their ^{13}C NMR spectra, but the ^{31}P–^{13}C coupling is perhaps more confusing than useful, because it is not always easy to determine, which lines are paired in the aromatic regions of the ^{13}C NMR spectra! However, the observed spin–spin coupling among the central atoms (P, H, and Si) in compound **3** is more informative. In the ^{1}H NMR spectrum of **3**, the central proton resonance is a doublet (δ 9.31, J_{PH}=25 Hz) due to coupling with the phosphorus, but in addition there exist easily visible ^{29}Si side bands that yield J_{SiH}=248 Hz (see the Supplementary data). Most interesting is the proton-decoupled ^{29}Si NMR spectrum of **3**, consisting of a lone doublet with strong coupling to phosphorus (J_{SiP}=76 Hz).

2.3. X-ray structures of macrobicycles with mixed bridgehead functionality

Generally speaking, the bis(triarylelement)-capped phanes crystallize easily, and satisfactory X-ray structures were obtained for compounds **2**, **3**, **4**, and **5**. The structures of the two *in*,*in*-macrobicycles (**2** and **3**) are illustrated in Fig. 1, and the *in*,*out*-macrobicycles (**4** and **5**) are illustrated in Fig. 2. Of the cyclophanes reported here, **2**, **3**, and **4** possess C_3 symmetry in gas phase calculations, and they have at least approximate C_3 symmetry in the solid state. Of these three, however, only compound **3** crystallized on a special position (in space group $P\bar{3}$) and thus its X-ray structure exhibits exact, crystallographic C_3 symmetry.

All of the *in*,*in*- and *in*,*out*-macrobicycles have both of the triarylelement propellers in same configuration; that is, the racemic mixture of each cyclophane contains molecules with (*P*,*P*) and (*M*,*M*) propeller configurations. As it happens, compound **5** crystallized in the chiral space group *P*1, but instead of providing easy access to pure enantiomers by selection of individual crystals, the asymmetric unit of this structure contains two independent molecules of **5** that by chance have opposite configurations; thus it too is a racemate.

The aminophosphine **2** adopts an *in*,*in*-conformation with approximate C_3 symmetry, although, as expected, the amine is more



Scheme 2.

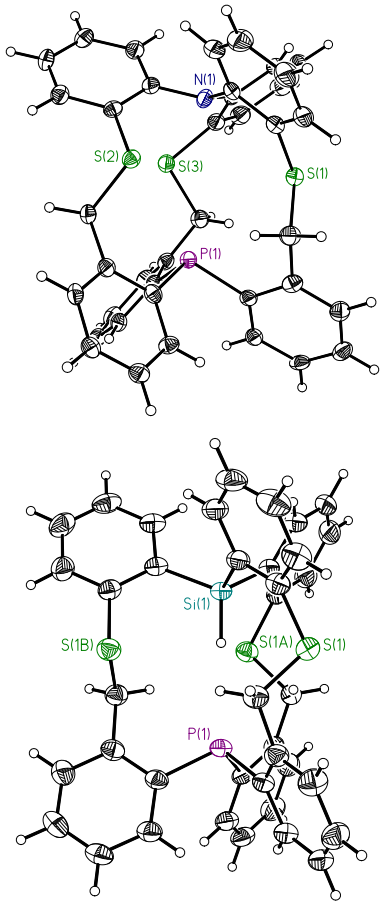


Fig. 1. Molecular structures of compounds **2** (top) and **3** (bottom); thermal ellipsoids have been drawn at the 50% probability level.

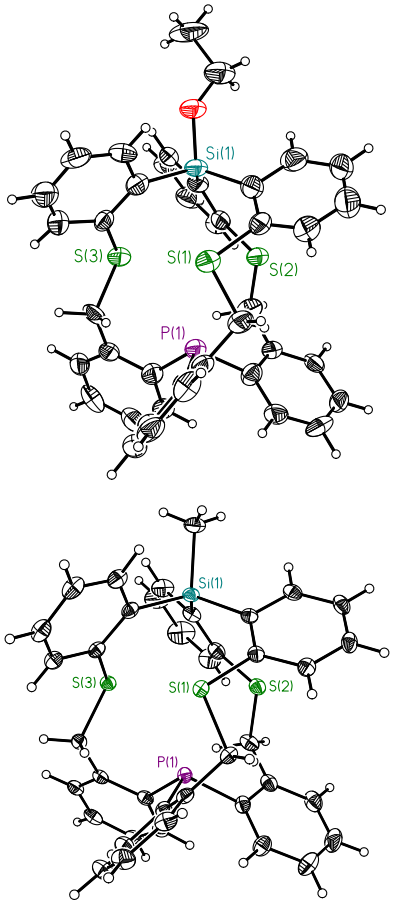


Fig. 2. Molecular structures of compounds **5** (top) and **4** (bottom); thermal ellipsoids have been drawn at the 50% probability level.

nearly planar than the highly pyramidalized phosphine (Fig. 1). The N–P contact distance is 4.17 Å, substantially longer than the 3.58 Å and 3.72 Å P–P contacts observed in the structures of diphosphine **1**.[1] The molecular structure of **3** strongly resembles that of the hydrochloride salt of diphosphine **1** (**1**·HCl).[1] The P–Si distance in **3** is, at 4.08 Å, slightly longer than the P–P distance in **1**·HCl, 3.88 Å, no doubt because Si–H bonds are slightly longer than P–H bonds, and the P^{+}–H···P interaction in **1**·HCl is attractive—a hydrogen bond—but the Si–H···P interaction in **3** is essentially repulsive.

The molecular structures of the *in*,*out*-macrobicycles **4** and **5** (Fig. 2) are extremely similar. One must expect the internal cavity to be larger than those in the *in*,*in*-phanes, but the effect is not particularly dramatic; the visual impression of the structures is that the *in*,*out*-macrobicycles are 'screwed together' more tightly than the *in*,*in*-isomers. Thus, the P–Si separation in **4** is 4.90 Å, and in the two independent molecules of **5** it is 5.05 Å and 5.06 Å, but the internal cavity is too narrow to accommodate functionality even as large as an *in*-methyl group. As noted previously, *in*,*in*-MeSi,P and *in*,*out*-MeSi,P are both (computationally) about 35 kcal/mol less stable than the observed *out*,*in*-MeSi,P (**4**).

2.4. Protonation of compounds 2, 3, and 4

When compound **1** was treated with HCl gas in chloroform solution at room temperature, protonation was slow; the reaction was first order with $t_{1/2}$=26 min, and the X-ray structure of the product showed that the proton was on the more basic, sulfur-substituted triarylphosphine.[1] We naturally wondered how the new macrobicycles would behave. Protonation of **2** under the same conditions proceeded almost identically: the reaction was first order with $t_{1/2}$=26 min, and it gave a single product that was characterized by ^{1}H NMR, ^{13}C NMR, and HRMS data. Thus the slightly larger cavity of **2** does not permit an increased rate of protonation relative to that of **1**. The new doublet at δ 9.31 in the product's ^{1}H NMR spectrum exhibited a coupling constant of 532 Hz, clearly indicating that protonation had occurred on phosphorus. Although glistening crystals of **2**·HCl were obtained upon evaporation of the solvent, they only poorly diffracted in X-ray experiments.

In contrast to the smooth, simple reaction observed with compound **2**, protonation experiments with silanes **3** and **4** were more highly problematic. Both compounds did undergo protonation, but somewhat more slowly than compounds **1** and **2**. Unfortunately, the rates of these reactions were inconsistent, and there was evidence of partial decomposition in both cases. In the case of compound **3**, there appeared to be more than one product formed by NMR analysis, but when the solvent was evaporated to leave some large, single crystals, X-ray analysis showed them to be only starting material. Thus, compound **3** had must have reacted, but later lost the added proton upon slow evaporation of chloroform and HCl. In the case of compound **4**, whose single methyl is an excellent reporter group for NMR spectroscopy, protonation yielded spectra with at least three new methyl resonances, with perhaps traces of four more. No good-quality crystals were obtained from this mixture, and the characterization of these products, which must result in part from ring fragmentation at silicon, was not pursued.

2.5. Resolution of compound 2

Cyclophane **2** proved to be easily resolved by supercritical fluid chromatography (SFC) on Chiralpak 1A (mobile phase: 40% EtOH/CO_2) (see Supplementary data). Ultimately, 25 mg of **2** were resolved into pure enantiomers, and these samples yielded specific rotations ($[\alpha]_D^{25}$) of +132 and −122 for the faster and slower eluting components, respectively.

We have previously reported the chromatographic resolution of diphosphine **1**, but it racemized quickly on the laboratory time scale.[1] This proved not to be the case for compound **2**. Indeed no racemization of enantiomerically pure (−)-**2** was observed upon heating for 24 h at 100 °C in toluene, and complete decomposition to unknown products was observed upon heating for 24 h at 180 °C in DMSO. The 100 °C experiment implies a $\Delta G^{\ddagger}_{rac}$ >31 kcal/mol for compound **2**, much greater than the 20.7 kcal/mol barrier estimated for compound **1**.[1] The reason for this difference is not at all obvious, and we have thus far failed to define computationally the racemization pathway for either molecule, despite numerous attempts and the expenditure of an enormous amount of computer time.

The resolution of compounds **3**, **4**, and **5** was not pursued because of the very limited amounts of material available.

3. Conclusion

Three cyclization reactions, between triarylelement precursors containing phosphorus, nitrogen or silicon as the central atoms, gave four macrobicyclic, bis(triarylelement)-containing cyclophanes, each bearing two different bridgehead heteroatoms. In every case the observed product was the thermodynamically favored *in*/*out* isomer as judged by DFT calculations. Since cyclizations based on S_N2 displacements of halides by thiolates are essentially irreversible and therefore under kinetic control, the much greater stability of the observed products is clearly reflected in the transition states for the cyclizations. Both computational studies and the results of the syntheses indicate that only lone pairs or protons as bridgehead substituents are small enough to form *in*,*in*-isomers in this series of molecules, and substitution of even a single methyl group forces the formation of an *in*,*out*-isomer. It seems that, in order to place a methyl or some larger functional group in so small a macrobicyclic cage, an entirely different synthetic strategy must be developed.

4. Experimental

4.1. General

Tris[2-(chloromethyl)phenyl]phosphine,[13] tris(2-mercaptophenyl)amine,[9] and tris(2-mercaptophenyl)silane[5] were prepared as described previously. All other solvents and reagents were commercial, reagent grade materials, and they were used without further purification. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Unity INOVA spectrometer; samples were dissolved in $CDCl_3$. ^{13}C NMR spectra were recorded on the same instrument at 101 MHz. ^{31}P and ^{29}Si NMR spectra were recorded on a Bruker AVANCE 300 spectrometer at 121 MHz and 60 MHz, respectively. GC–MS analyses were performed on coupled Varian 450-GC and Varian 300-MS instruments. High-resolution ESI-TOF mass spectra were recorded on an Agilent 6220 spectrometer.

4.2. Data for compounds

*4.2.1. in,in-N,P (**2**).* Tris[2-(chloromethyl)phenyl]phosphine[13] (561 mg, 1.38 mmol) and tris(2-mercaptophenyl)amine[9] (470 mg, 1.38 mmol) were mixed in 2:1 benzene–ethanol (1.2 L), and the solution was heated to reflux. An argon-saturated solution of KOH (372 mg, 6.62 mmol) in ethanol (55 mL) was added slowly over 5.5 h. After 17 h, the mixture was cooled, and the solvent was evaporated under reduced pressure to leave a white precipitate. The precipitate was extracted twice with chloroform. The combined extracts were concentrated and the resulting light yellow liquid was chromatographed on silica gel (solvent, 2:1 hexanes–benzene) and the fractions containing compound **2** were

combined and further purified by preparative TLC (silica gel, 1:1 hexanes–benzene) to give cyclophane **2** as a white solid (136.8 mg, 0.214 mmol, 15.5%). ^{1}H NMR ($CDCl_3$) δ 4.14 (dd, J=10 Hz, 2 Hz, 3H), 4.23 (dd, J=10 Hz, 1 Hz, 3H), 6.73 (dd, J=8 Hz, 1 Hz, 3H), 6.76 (dd, J=8 Hz, 2 Hz, 3H), 7.00 (td, J=8 Hz, 1 Hz, 3H), 7.12 (m, 6H), 7.24 (td, J=8 Hz, 1 Hz, 3H), 7.30 (m, 3H), 7.64 (dd, J=8 Hz, 2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 42.3 (d, J_{PC}=25 Hz), 124.0, 124.4, 128.4, 128.7, 129.3, 130.7 (d, J_{PC}=5 Hz), 131.8, 134.4, 136.9, 137.0 (d, J_{PC}=28 Hz), 140.8 (d, J_{PC}=29 Hz), 151.9 (13 of 13 expected resonances); HRMS (ESI) m/z 640.1350 (M+H), calcd for $C_{39}H_{31}NPS_3$ 640.1351. Single crystals, suitable for X-ray analysis, were obtained from $CHCl_3$–MeOH.

A portion of this material was resolved by preparative supercritical fluid chromatography (SFC) on a chiral support (Chiralpak IA; 40% EtOH/CO_2 at 100 bar). The faster eluting component had $[\alpha]_D^{25}$ +132±5 (c 0.00031, EtOH), the slower $[\alpha]_D^{25}$ −122±5 (c 0.00020, EtOH). The resolved enantiomers had chemical and optical purity in excess of 99%, as judged by analytical chiral SFC.

*4.2.2. in,in-N,P hydrochloride (**2**·HCl).* A stream of HCl gas was bubbled into an NMR tube containing a $CDCl_3$ solution of cyclophane **2** for 5 s, and then ^{1}H NMR spectra were recorded at intervals. Protonation was a slow process ($t_{1/2}$=26 min), but it was essentially complete in 6 h. ^{1}H NMR ($CDCl_3$) δ 3.91 (d, J=10 Hz, 3H), 4.52 (br d, J=10 Hz, 3H), 6.73 (br d, J=7 Hz, 3H), 7.18 (m, 9H), 7.65 (br d, J=7 Hz, 6H), 7.73 (br s, 3H), 7.84 (br s, 3H), 11.99 (d, J=532 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.4 (d, J_{PC}=8 Hz), 114.9 (d, J_{PC}=84 Hz), 125.0, 125.6, 129.7, 129.8, 131.2 (d, J=13 Hz), 133.5 (d, J=10 Hz), 135.4, 136.6 (d, J=10 Hz), 137.1, 140.3 (d, J=9 Hz), 150.7 (13 of 13 expected resonances); HRMS (ESI) m/z 640.1352 (M−Cl), calcd for $C_{39}H_{31}NPS_3$ 640.1351.

*4.2.3. in,in-HSi,P (**3**) and out,in-EtOSi,P (**5**).* Tris[2-(chloromethyl) phenyl]phosphine (563 mg, 1.38 mmol) and tris(2-mercaptophenyl)silane[5] (493 mg, 1.38 mmol) were mixed in 2:1 benzene–ethanol (1.2 L), and the solution was heated to reflux. An argon-saturated solution of KOH (376 mg, 6.70 mmol) in ethanol (55 mL) was added slowly over 6 h. After 18 h, the mixture was cooled, and the solvent was evaporated under reduced pressure to leave a white precipitate. The precipitate was extracted twice with chloroform. The combined extracts were concentrated and the resulting light yellow liquid was chromatographed on silica gel (solvent, 1:1 hexanes–benzene) and the fractions containing compound **3** were combined and further purified by preparative TLC (silica gel, 1:1 hexanes–benzene) to give cyclophane **3** as a white solid. This material exhibited a single component by TLC, but the ^{1}H NMR spectrum clearly indicated the presence of significant impurities. Further chromatographic purification was unsuccessful, but careful crystallization from $CHCl_3$–CH_2Cl_2–MeOH gave cyclophane **3** (6 mg, 9 μmol, 0.7%) as crystals suitable for X-ray analysis. ^{1}H NMR ($CDCl_3$) δ 4.04 (dd, J=10 Hz, 3 Hz, 3H), 5.09 (dd, J=10 Hz, 5 Hz, 3H), 7.06 (dd, J=8 Hz, 3 Hz, 3H), 7.19 (m, 6H), 7.29 (m, 6H), 7.39 (m, 3H), 7.51 (m, 3H), 7.82 (d, J=8 Hz, 3H), 9.31 (d, J=25 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.7 (d, J_{PC}=29 Hz), 128.0, 128.6, 129.6, 130.6, 131.7 (d, J_{PC}=6 Hz), 135.36, 135.40 (d, J_{PC}=17 Hz), 137.4, 137.6, 141.7 (d, J_{PC}=34 Hz), 141.8, 143.6 (d, J_{PC}=2 Hz) (13 of 13 expected resonances); ^{31}P NMR ($CDCl_3$) δ −48.9; ^{29}Si NMR ($CDCl_3$) δ −35.8 (d, J_{PSi}=76 Hz); HRMS (ESI) m/z 655.1173 (M+H), calcd for $C_{39}H_{32}PS_3Si$ 655.1168.

A second component proved to be the *out,in* compound **5** (15 mg, 21 μmol, 1.6%), which was obtained as crystals suitable for X-ray analysis from $CHCl_3$–CH_2Cl_2–MeOH. ^{1}H NMR ($CDCl_3$) δ 1.21 (t, J=7 Hz, 3H), 3.65 (d, J=11 Hz, 3H), 3.84 (dq, J=10 Hz, 7 Hz, 1H), 3.93 (dq, J=10 Hz, 7 Hz, 1H), 4.20 (d, J=11 Hz, 3H), 6.68 (dd, J=7 Hz, 2.5 Hz, 3H), 7.11 (td, J=7 Hz, 2 Hz, 3H), 7.16 (td, J=7 Hz, 2 Hz, 3H), 7.25 (m, 12H), 7.65 (dd, J=7.5 Hz, 1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.8 (s), 41.6 (d, J_{PC}=18 Hz), 60.3, 125.2, 128.6, 129.1, 130.4, 130.6, 130.9 (d, J_{PC}=6 Hz), 133.2, 135.9, 136.9 (d, J_{PC}=26 Hz), 139.7, 140.2 (d, J_{PC}=27 Hz), 145.5 (15 of 15 expected resonances); HRMS (ESI) m/z 699.1430 (M+H), calcd for $C_{41}H_{36}OPS_3Si$ 699.1435.

*4.2.4. Tris(2-mercaptophenyl)methylsilane (**9**).* Thiophenol (5.0 mL, 49 mmol) in cyclohexane (20 mL) was added to flask containing cyclohexane (110 mL), TMEDA (15.7 mL) and n-BuLi (2.5 M in hexane, 40.7 mL, 101.8 mmol) at 0 °C. The reaction was permitted to warm to room temperature and left for two days; a white precipitate formed. The cyclohexane was siphoned away, and the precipitate was washed with cyclohexane. After the precipitate settled again, the cyclohexane was removed, and THF (55 mL) was added. The solution was cooled to −78 °C, and $MeSiCl_3$ (1.35 mL) in THF (15 mL) were added dropwise. The mixture was permitted to warm to room temperature, and after 20 h it was acidified with 10% sulfuric acid (100 mL). The mixture was concentrated in vacuo to remove THF and the resulting aqueous mixture was extracted three times with $CHCl_3$. The combined organics were dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil. This material was purified by column chromatography on silica gel (3:1, then 1:1, hexanes–benzene) to give compound **9** as a thick yellow oil (0.39 g, 1.1 mmol, 6.7%). ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 3.48 (s, 3H), 7.15 (t, J=8 Hz, 3H), 7.29 (m, 6H), 7.40 (d, J=8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 0.68, 125.9, 130.7, 132.3, 135.5, 138.1, 138.5 (7 of 7 expected resonances); MS (EI) m/z 336 (M−H_2S, 24), 321 (M−H_2S−CH_3, 12), 227 (M−H_2S−C_6H_4SH, 100).

*4.2.5. out,in-MeSi,P (**4**).* Tris[2-(chloromethyl)phenyl]phosphine (413 mg, 1.01 mmol) and tris(2-mercaptophenyl)methylsilane (**9**, 376 mg, 1.01 mmol) were mixed in 2:1 benzene–ethanol (900 mL), and the solution was heated to reflux. An argon-saturated solution of KOH (280 mg, 4.99 mmol) in ethanol (100 mL) was added slowly over 9 h. After another 15 h, the mixture was cooled, and the solvent was evaporated under reduced pressure to leave a white precipitate. This material was extracted twice with chloroform. The combined extracts were concentrated, and the resulting light yellow liquid was chromatographed on silica gel (solvent, 1:1 hexanes–benzene). The fractions containing compound **4** were combined and further purified by preparative TLC (silica gel, 1:1 hexanes–benzene) to give cyclophane **4** as a white solid (15 mg, 0.022 mmol, 2.2%). ^{1}H NMR ($CDCl_3$) δ 0.77 (s, 3H), 3.66 (d, J=10 Hz, 3H), 4.22 (d, J=10 Hz, 3H), 6.70 (dd, J=8 Hz, 2 Hz, 3H), 7.12 (m, 6H), 7.24 (m, 12H), 7.47 (d, J=8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 5.3, 41.5 (d, J_{PC}=18 Hz), 125.1, 128.6, 129.0, 130.0, 130.1, 130.9 (d, J_{PC}=5 Hz), 133.1, 135.7, 136.9 (d, J_{PC}=26 Hz), 140.2 (d, J_{PC}=27 Hz), 140.5, 146.4 (14 of 14 expected resonances). HRMS (ESI) m/z 669.1324 (M+H), calcd for $C_{40}H_{34}PS_3Si$ 669.1324. Single crystals, suitable for X-ray analysis, were obtained from benzene–$CHCl_3$–MeOH.

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Supplementary data

(1) ^{1}H and ^{13}C NMR spectra of compounds **2**, **2**·HCl, **3**, **4**, **5**, and **9**; kinetics of protonation of **2**, and chiral SFC chromatograms for **2**. (2) An ASCII text file containing the atomic coordinates and energies of the calculated structures in Table 1. (3) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 955764–955767. Copies of the data can be obtained, free of charge, on application to CCDC,

12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.10.018.

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