Articles

Synthesis of a New Ligand for Metal Assembly to a Selective Receptor

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Diarylphosphinic acid **2**, bearing two ethylenediamine groups, was designed with the aim of assembly to form a hydrophobic cavity upon binding to metals. The new ligand was prepared in optically active form from phenylalanine by an efficient sequence which required chromatography only for the P−C bond forming steps. Versatile intermediates in the synthesis are described. Complexes of this ligand with Zn^{2+} were shown to bind closely related aromatic guests bearing anionic tethered groups with 1000-fold discrimination.

Introduction

Binding selectivity is the distinctive feature of biological receptors and catalysts that provides their most valued properties.[2] High selectivity results from the cooperation of multiple binding interactions.[3] The study of simple synthetic binding sites has led to useful materials[4] and to improvements in our understanding of noncovalent binding events.[5] These synthetic host molecules are generally less selective in binding to multifunctional organic guests than are antibodies, because of current limitations in design and preparation of large concave molecules with appropriately oriented interacting groups. Self-assembly, the formation at equilibrium of a well-defined ordered structure, provides an effective route to large structures.[6] Self-assembled structures capable of binding a substrate are of particular interest.[7−10]

We have reported the synthesis of a bis amino acid which self-assembles in the presence of Co^{2+} to form complex **1** (Figure 1), forming a cavity that binds hydrophobic guests.[9] Guest molecules that bear tethered carboxylate anions bind less strongly than their neutral analogues to the anionic complex, except for certain guests that bind more strongly.[10,11] These guests are able to bind such that the carboxylate can ligate the metal. The cooperation of the hydrophobic and polar binding interactions leads to significant selectivity for those guests that fit well. Our analysis suggests that this receptor very effectively juxtaposes the two types of binding sites.[10,11] Its limitations derive from the extremely weak binding of carboxylate to metal.

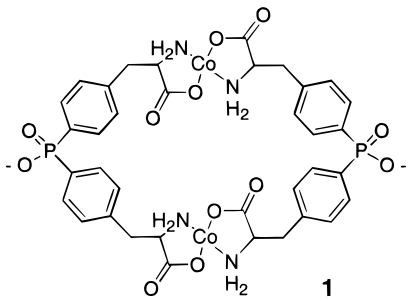

Figure 1.

Therefore, we decided to prepare a new ligand with a modified structure to allow a more positive metal center. Compound **2** retains the diarylphosphinate hydrophobic concavity appropriate for binding aromatic compounds from water, with its hydrophilic convex surface to prevent aggregation. Ethylenediamine groups, rather than amino acids of **13**, ligate metal without neutralizing the positive charge. The more positive metal center and overall complex should better bind an anionic ligand. In this

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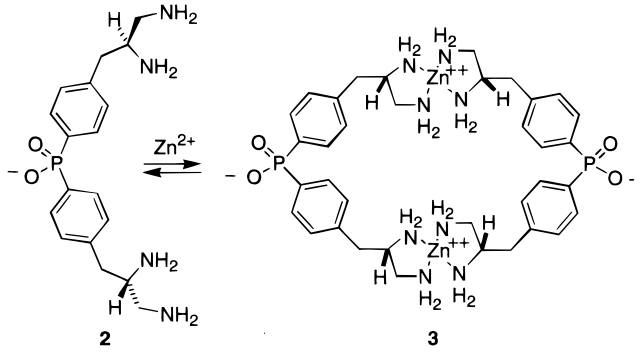
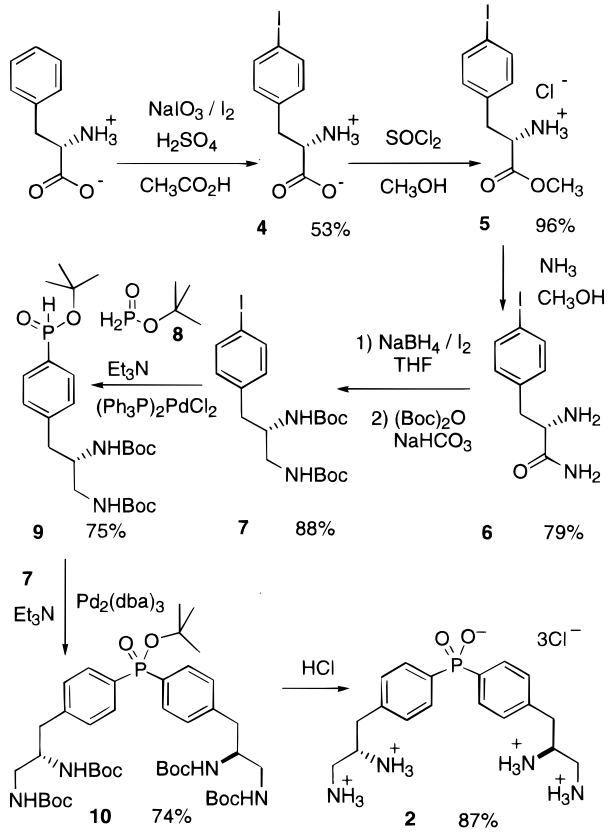


Figure 2. Self-assembly of **2** to form host **3**.

Scheme 1. Synthesis of Ligand 2



paper we describe the preparation of **2** (Figure 2) and demonstrate that its metal complexes bind organic guests.

Results and Discussion

Synthesis of Ligand 2. The synthesis of ligand **2** is outlined in Scheme 1. Iodination of phenylalanine, followed by esterification with $SOCl_2$ in methanol, was carried out as we have described,[12] with minor improvements. Compounds **4** and **5** are difficult to separate from contaminating diiodophenyl derivatives, sometimes produced by overiodination. Ester **5** was converted to amide **6** by treatment with ammonia in methanol. Amide **6** is easily crystallized, so that samples of iodophenylalanine that have been overiodinated will produce pure **6**.

The enantiomeric purity of **6** was confirmed by HPLC. Less than <0.5% epimerization was observed in a sample

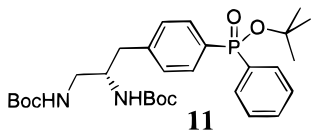


Figure 3.

of **6** allowed to stand in the presence of ammonia in methanol for 20 times the usual reaction time, followed by acylation of the crude mixture with Boc-L-alanine.

Amide **6** was reduced using borane THF complex, conveniently prepared by treating sodium borohydride with iodine in THF.[13] At reflux in THF, amide reduction is frequently accompanied by partial cleavage of iodine from the aryl group. This iodine cleavage is not simply a function of temperature: at reflux even in toluene/THF, sometimes amide reduction went without iodine cleavage. Chloroform solvent showed no advantages over THF, and amide reduction did not proceed in dichloromethane. Iodine cleavage was neither caused nor consistently prevented by intentional addition or careful exclusion of air or light, control of heating or quench rate, or washing of glassware with aqua regia to remove transition-metal contaminants. Though high temperature did not consistently cause iodine cleavage, lower temperature did consistently prevent it; at room temperature the reaction proceeded slowly but gave amine free of detectable iodine cleavage product. Diamine was isolated as Boc-protected derivative **7**, crystallized in 88% yield. This sequence readily yields decagram amounts of analytically pure **7** from phenylalanine with no chromatography.

Protected diamine **7** was coupled to *tert*-Butyl phosphinate **8** by the Pd-catalyzed procedure we have described.[14] *tert*-Butyl phosphinate rather than methyl phosphinate was used because the methyl analogue of **9** is difficult to separate from minor side products and the *tert*-butyl protecting group is more conveniently removed at the end of the sequence. *tert*-Butyl phosphinate is more stable than methyl phosphinate but reacts substantially more slowly. Thus *tert*-butyl phosphinate must be free of methyl phosphinate from which it is prepared.[14]

It is most effective to couple iodide **7** with an excess of *tert*-butyl phosphinate in the presence of $Pd(PPh_3)_2Cl_2$, cleanly producing monoarylphosphinate **9** because phosphinate decomposition products couple more slowly than does **8**. Compound **9** is freed of excess **8** and converted to diarylphosphinate **10** by reaction with iodide **7**, again under palladium catalysis.

A different catalyst is preferred for this second coupling step. When triphenylphosphine is used as the ligand for palladium, a side product is formed which was tentatively assigned structure **11** on the basis of ^{1}H NMR, ^{31}P NMR, and MS data (Figure 3). Presumably the unsubstituted phenyl group is derived from triphenylphosphine. Exchange of aryl groups on Pd with those of a phosphine ligand is known.[15] However, in other cross-coupling reactions of aryl iodide with methyl phosphinate or methyl arylphosphinate, we have not previously observed

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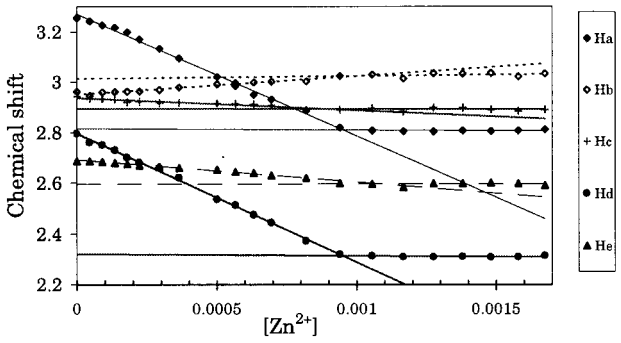

Figure 4. Titration of 9.1×10^{-4} M **2** with Zn^{2+} in 100 mM pD 9 borate in D_2O. This is well above the K_d. A linear change in chemical shift with added Zn^{2+} is seen in all signals (including the aromatic signals off scale of this graph) leveling off upon reaching a 1:1 ratio. Assignments based on COSY and NOESY spectra: $ArCH_bH_eCH_a(NH_2)CH_cH_dNH_2$.

such side products.[10,12,14,16] *tert*-Butyl ester **9**, while desirable in many ways, couples slowly enough that phenyl exchange is a problem. $(p\text{-}Me_2NC_6H_4)_3P$ as a ligand for palladium catalyst allows clean formation of **10**, uncontaminated by **11**. Presumably this is because oxidative addition of Pd^0 into the Ar−P bond is slower with the more electron-rich aryl group.

We have also defined conditions where these substrates efficiently react in the absence of triarylphosphine. The phosphine-free catalyst works well in this specific instance, but in general is less effective for P−H aryl halide cross-coupling reactions.[17] For example, in the absence of Ph_3P, conversion of **7** to **8** proceeds to only about 10% conversion.

Deprotection of **10** with aqueous HCl gave **2**, isolated as a trihydrochloride salt.

Binding Studies

Ligand **2** self-assembles in the presence of Zn^{2+} in 100 mM pH 9 borate buffer. Formation of complex is evident by the shift in the ^1H NMR resonances of **2**. Figure 4 shows that titration of a solution of **2** in pH 9 borate with Zn^{2+} causes a shift that is linear with increasing metal concentration and then levels off after 1 equiv of metal has been reached. This is strong evidence for a 1:1 stoichiometry, consistent with the desired 2:2 complex. The shift demonstrates rapid exchange on an NMR time scale between **2** and its Zn^{2+} complex, presumably **3**, and the linearity indicates a K_d for Zn^{2+} well below [**2**], as anticipated for ethylenediamines.[18] Organic guest binding studies were carried out with a slight excess of **2** over Zn^{2+}, and [Host] is specified as $[Zn^{2+}]/2$ in order to avoid any complications in analysis due to free Zn^{2+}. The large shift in aliphatic signals of **2** upon association with Zn^{2+}, without a substantial change in the aromatic spectral region, is consistent with the expected metal coordination to the ethylenediamines without coordination to the phosphinate oxygens. The complex of Zn^{2+} with **2** is presumed to be of 2:2 stoichiometry and is represented as **3** without direct evidence. It appears to have largely one composition over the concentration range investigated here: NMR and CD spectra of **3** change only in intensity between 10^{-3} and 10^{-5} M. Structural characterization of the metal complex was deferred in favor of binding characterization.

Table 1. Dissociation Constants of 1- and 2-Substituted Naphthalene Guests from Hosts 1 and 3

guest		K_D (M^{-1})	
	naphthyl substituent	host **1**	host **3**[b]
14-	$1\text{-}OCH_2CO_2^-$	$(1.65 \pm 0.52) \times 10^{-4}$ [a]	$(2.01 \pm 0.50) \times 10^{-3}$
15-	$2\text{-}OCH_2CO_2^-$	$(1.1 \pm 0.20) \times 10^{-2}$ [a]	$(6.1 \pm 3.0) \times 10^{-3}$
16-	$1\text{-}CH_2CO_2^-$	$(1.02 \pm 0.13) \times 10^{-3}$ [a]	$(1.05 \pm 0.33) \times 10^{-2}$
17-	$2\text{-}CH_2CO_2^-$	$(2.85 \pm 0.70) \times 10^{-3}$ [a]	$(8.58 \pm 2.13) \times 10^{-3}$
18-	$1\text{-}OPO_3^{2-}$	$(7.4 \pm 2.2) \times 10^{-3}$ [b]	$<1 \times 10^{-5}$
19-	$2\text{-}OPO_3^{2-}$	$(3.9 \pm 3.0) \times 10^{-3}$ [b]	$(2.52 \pm 0.68) \times 10^{-4}$

[a] From ref 10. [b] Present work.

All shifts were simultaneously fit by multidimensional nonlinear least squares to obtain dissociation constants shown in Table 1.

Titrations to determine affinity were carried out at host concentrations below the K_d. In the case of 1-naphthyl phosphate, binding is sufficiently strong that only an upper limit for the K_d can be determined, since solutions dilute enough to cause dissociation are not easily studied. However, titrations of **3** with 1-naphthyl phosphate clearly indicate a strong binding in a 1:1 ratio. The complexation-induced shifts are consistent with the proposed binding orientation.

Self-assembled dicationic host **3** has a different substrate binding selectivity than does dianionic host **1**. Charge is not the dominant factor: anions **14** and **15** are not bound better by the cationic host **3** than by anionic host **1**. However host **1** shows a 67-fold preference for 1-substituted **14** over 2-substituted **15**, while host **3** binds **14** only three times more strongly than **15**. Substrates **16** and **17**, with a shorter tether between carboxylate and naphthalene, are each bound similarly by the two host complexes. Dianionic 1-naphthyl phosphate **18** binds 7 times less strongly to **1** than does 1-naphthyl acetate **16** of the same tether length. The 2-substituted derivatives **17** and **19** bind to **1** with the same affinity.

In dramatic contrast, host **3** binds to 1-naphthyl phosphate **18** at least 1000-fold more strongly than to **16** of the same tether length. This factor of 1000 is a lower limit, since the binding of 1-naphthyl phosphate **18** is too strong to measure accurately by NMR. The 2-substituted **17** and **19** differ in their affinities for **1** by a much smaller but still substantial factor of 34. This preference for the dianionic substrate over the monoanionic one is reasonable for the cationic host, but the range of values for the preference demonstrates that charge is not the only factor of importance.

Differences in selectivity of binding are due to overall charge, shape-complementarity of the hydrophobic cavity for aromatic guest substituent, affinity of metal for polar guest substitutent, and the position of metal relative to bound guest. This last factor we believe to be of utmost

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importance to the creation of highly selective binding sites. All of these are affected by the nature of the metal center. Deciphering the contributions of these factors will require further studies. This simple approach to binding sites with multiple points of interaction clearly provides receptors capable of subtle discrimination between guests.

Conclusions

We have presented an effective synthesis of the new ligand **2**. The synthesis proceeds via **7**, readily prepared in large quantities without chromatography. The diamagnetic Zn^{2+} complex of **2** is capable of binding to naphthalene guests with substantial discrimination. Binding selectivity contrasts with that of previous self-assembled host complexes and is of sufficient interest to warrant further scrutiny, the results of which will be reported in due course.

Experimental Section

General Procedures. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield of TMS in organic solvents or DSS in D_2O. ^{13}C NMR spectra are ^{1}H decoupled, and phosphorus couplings are given; ^{31}P chemical shifts are reported versus external 85% H_3PO_4. Thin-layer chromatography (TLC) was performed on 0.25 mm Merck silica gel 60-F, and flash chromatography was on 230−400 mesh Merck Kieselgel 60 as described.[19] All chemicals were used as obtained from commercial suppliers unless otherwise specified. Crystalline anhydrous phosphinic acid was prepared by overnight rotary evaporation at room temperature of 50% aqueous phosphinic acid, evacuation at <0.05 Torr, and crystallization at 4 °C. *p*-Iodophenylalanine was prepared as described.[12] Substituted naphthalenes used as binding substrates were purchased or prepared by literature procedures and used after purity check by TLC and ^{1}H NMR with recrystallization if necessary. Acetonitrile was freshly distilled from P_4O_{10}. THF, CH_2Cl_2, toluene, and triethylamine were freshly distilled from CaH_2. DMF and *tert*-butyl alcohol were dried over activated 4A molecular sieves.

***p*-Iodo-L-Phenylalanine Methyl Ester Hydrochloride (5).** $SOCl_2$ (50 mL, 0.62 mol) was added over 20 min to 450 mL of CH_3OH with stirring on an ice bath. (S)-*p*-Iodophenylalanine acetic acid solvate (100 g, 0.285 mol) was added, the flask was stoppered, and ice bath was removed. After 18 h the solvents were removed by rotary evaporation, the residue was redissolved in 400 mL of CH_3OH, and the solvent was again evaporated. Recrystallization from 250 mL of CH_3OH and 1000 mL of diethyl ether gave 93.0 g (95.8%) of **5** in two crops having spectral properties identical to an authentic standard.[12]

^{1}H NMR (CD_3OD): δ 7.73 (d, J = 6.0 Hz, 2H), 7.05 (d, J = 6.0 Hz, 2H), 4.31 (t, J = 6.9 Hz, 1H), 3.81 (s, 3H), 3.22 (dd, J = 15.0, 6.0 Hz, 1H), 3.12 (dd, J = 15.0, 7.5 Hz, 1H). $[\alpha]_D^{30}$ = +9.64 (CH_3OH, *c* 2.16).

(*S*)-2-Amino-3-(4-iodophenyl)propionamide (6). *p*-Iodophenylalanine methyl ester hydrochloride (23.3 g, 68.4 mmol) in 320 mL of CH_3OH was stirred on an ice bath as ~100 g of NH_3 was added by 90 min bubbling. The flask, sealed with a clamped septum, was allowed to warm to 23 °C over 21 h. After careful venting, TLC (methyl ethyl ketone:acetic acid:water 12:3:1, R_f = 0.66) indicated completion. The residue from careful rotary evaporation (caution: NH_3 corrodes brass aspirators) was partitioned between 350 mL of 70% saturated $NaHCO_3$ and 1.75 L of EtOAc and separated, and the aqueous layer was extracted three times with 500 mL of EtOAc. Combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were removed by rotary evaporation and then high vacuum to give 19.0 g (95.7%) of crude **6**, pure by ^{1}H NMR. Recrystallization from 1 L of EtOAc gave 15.7 g (79%) of **6**, mp = 168.0−169.5 °C.

^{1}H NMR (250 MHz, CD_3OD): δ 7.65 (d, J = 8.1 Hz, 2H), 7.08 (br s, 1H), 6.99 (d, J = 8.1 Hz, 2H), 5.46 (br s, 1H), 3.59 (dd, J = 4.1, 9.1 Hz, 1H), 3.19 (dd, J = 4.1, 13.7 Hz, 1H), 2.72 (dd, J = 9.1, 13.8 Hz, 1H), 1.33 (br s, 1H). ^{13}C NMR (DMSO-d_6, 62.9 MHz): δ 176.21, 138.70, 138.52, 131.61, 91.39, 55.70, 40.42; IR (KBr) 3358, 3266; 3033, 1687, 1593. MS (FAB, Cs, glycerol): *m*/*z* 291 (M + 1; 100%). $[\alpha]_D^{30}$ = +9.84 (CH_3OH, *c* 1.59). Anal. Calcd for $C_9H_{11}IN_2O$: C, 37.26; H, 3.82; N, 9.66. Found: C, 37.57; H, 3.93; N, 9.28.

HPLC (Beckman ultrasphere 4.5 × 150 mm C-18, 1.0 mL/min, 30 min gradient 40 to 72% CH_3OH in H_2O, LL 19.19 min, LD 19.95 min) showed <0.5% LD isomer.

(*S*)-*N*,*N*′-Di(*tert*-butoxycarbonyl)-1,2-diamino-3-(4-iodophenyl)propane (7). A solution of I_2 (40.0 g, 315 mmol) in 100 mL of dry THF under N_2 was added over 30 min to a suspension of $NaBH_4$ (15.0 g, 396 mmol) and amide **6** (15.0 g, 51.7 mmol) in 200 mL of THF with stirring on an ice bath in the dark. The mixture was allowed to warm to room temperature, sealed with a wired on septum, and stirred for 52 h behind a blast shield. The mixture was cooled to 0 °C and quenched by careful addition of 200 mL of CH_3OH. The solvents were removed by rotary evaporation, and the residue was dissolved in 200 mL of CH_3OH and reevaporated. Concentrated HCl (75 mL) was added, the resulting solution was stirred, and after 1 h the solvent was removed by rotary evaporation. To the solid residue was added 36 g of $NaHCO_3$, 200 mL of H_2O, 800 mL of CH_3OH, and di-*tert*-butyl dicarbonate (27.0 g, 124 mmol). After 8 h of stirring at room temperature, the mixture was filtered and concentrated by rotary evaporation to 150 mL. Filtered solid and filtrate residue were partitioned between 850 mL of EtOAc and 400 mL of H_2O. Layers were separated, and aqueous layer was extracted three times with 200 mL of EtOAc. The combined organic layers were dried over Na_2SO_4 and filtered, and solvent was removed by rotary evaporation and oil pump to yield 27.0 g of crude **7** which was crystallized from 500 mL of CH_3CN to yield 21.7 g (88%) of **7** as a white solid, mp = 178−181 °C. Chromatography (3:1 $CHCl_3$/EtOAc) allowed isolation of 1.52 g (7.5%) of *t*-Boc-protected starting material.

^{1}H NMR (250 MHz, CD_3OD): δ 7.59 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 3.77 (m, 1H), 3.14 (dd, J = 5.4, 13.7 Hz, 1H), 3.04 (dd, J = 7.8, 13.6 Hz, 1H), 2.74 (dd, J = 5.2, 13.8 Hz, 1H), 2.67 (dd, J = 8.7, 13.7 Hz, 1H), 1.42 (s, 9H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 156.6, 155.8, 137.6, 137.4, 131.4, 91.8, 79.7, 79.6, 52.8, 44.0, 38.7, 28.4. FTIR (KBr): 3363, 2978, 1689, 1529. MS (FAB, Cs, glycerol): *m*/*z* 351 (M − I; 26%), 321, 295, 195 (100%), 251, 239, 195. $[\alpha]_D^{30}$ = −5.00 (CH_3OH, *c* 1.94). Anal. Calcd for $C_{19}H_{29}IN_2O_4$: C, 37.26; H, 6.14; N, 5.88. Found: C, 48.16; H, 6.36; N, 5.88.

***tert*-Butyl Phosphinate as a Toluene Solution (8).**[14] Anhydrous phosphinic acid (0.415 g, 6.3 mmol) in dry *t*-BuOH (3.00 mL, 31.8 mmol) was treated under N_2 at room temperature with trimethyl orthoformate (2.70 mL, 24.0 mmol). After 3 h, the ^{31}P NMR of reaction mixture diluted in $CDCl_3$ showed a 1.1:1 mixture of $H_2PO_2CH_3$:$H_2PO_2C(CH_3)_3$, with no significant side products. Et_3N (0.4 mL) was added, and volatiles were removed in vacuo. Two cycles followed the addition of *t*-BuOH (3.4 mL) and the removal of volatiles in vacuo after 90 min. The residue was then dissolved in 2 mL of toluene with 0.2 mL of Et_3N and filtered through a 5 × 0.4 cm column of basic alumina, followed by 1 mL of toluene, to yield 3.0 mL of 0.82 M solution of **8** (37%), free of phosphorus-containing side products by ^{31}P NMR. The concentration of **8** was determined by ^{1}H NMR integration versus 1,3,5-trimethoxybenzene standard. The solution was used directly in Pd-catalyzed coupling reactions with aryl iodides.

^{1}H NMR (6:1 $CDCl_3$/toluene): δ 7.10 (d, J = 559.7 Hz, 2H), 1.47 (s, 9H); toluene and *tert*-BuOH resonances are also present. ^{31}P NMR (6:1 $CDCl_3$/toluene): δ 4.03.

***tert*-Butyl (4-((2*S*)-2,3-di(*tert*-butoxycarbonylamino)-propyl)phenyl)phosphinate (9).** A suspension of iodoaryl **7** (190 mg, 4.00×10^{-4} mol), $(Ph_3P)_2PdCl_2$ (14.0 mg, 2.0×10^{-5}

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

mol) in CH_3CN (1.0 mL) and Et_3N (0.031 mL, 2.2×10^{-4} mol) was treated with a solution of *tert*-butyl phosphinate (8.2×10^{-4} mol, added as 1.00 mL of a 0.82 M toluene solution also 0.58 M in Et_3N). The reaction mixture was capped under N_2 and heated in a 90 °C oil bath for 100 min. After the solvent was removed by rotary evaporation, product was isolated by flash chromatography (silica, 19:1 EtOAc/Et_3N) as a white solid, mp = 56−60 °C (yield 0.142 g, 75%).

^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 551 Hz, 1H), 7.69 (dd, J = 13.8, 7.8 Hz, 2H), 7.33 (dd, J = 8.0, 3.1 Hz, 2H), 4.95 (br, 1H) 4.87 (br, 1H), 3.88 (br, 1H), 3.18 (br m, 2H), 2.88 (br m, 1H), 2.81 (dd, J = 13.2, 6.8 Hz, 1H), 1.57 (s, 9H), 1.44 (s, 9H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 156.7, 155.9, 142.8, 131.7 (d, J = 11.9 Hz), 129.6 (d, J = 139.3 Hz), 129.6 (d, J = 14.3 Hz), 83.1 (d, J = 11.0 Hz), 79.7, 79.5, 52.6, 43.7, 39.2, 30.4 (d, J = 4.5 Hz), 28.3 (two coincident resonances, demonstrated by HETCOR cross-peaks to 1.44 and 1.39 ^{1}H resonances). ^{31}P NMR ($CDCl_3$): diastereomers δ 15.66 and 15.70 (^{1}H-coupled, each dt, J = 552, 12.3 Hz). IR (neat): 3328 (Br), 2978, 2931, 1710, 1521, 1252, 1170, 980 cm^{-1}. MS (electrospray) (MeOH, positive ion): m/z calcd for M^+Na^+ 493.2, found 493.1 (62%), calcd for ($M + K^+$) 509.2, found: 509.1 (62%). The diastereomeric mixture crystallized in low yield from ether, mp = 76−82 °C. $[\alpha]_D^{29} = -1.29$ (CH_3OH, c 1.76). Anal. Calcd for $C_{23}H_{39}N_2O_6P$: C, 58.71; H, 8.35; N, 5.95. Found: C, 57.93; H, 8.73; N, 6.06.

(*S*,*S*)-*tert*-Butyl Bis(4-[2,3-Di(*tert*-butoxycarbonylamino)propyl]phenyl)phosphinate (10). *tert*-Butyl monoarylphosphinate **9** (679 mg, 1.44 mmol), aryl iodide **7** (1.37 g, 2.87 mmol), Pd_2(dibenzylideneacetone)$_3$ (71 mg, 0.076 mmol, 0.153 mmol Pd), and 10 mL of CH_3CN were mixed, and then Et_3N (2.00 mL, 14.3 mmol) was added. The reaction mixture was sealed with a wired-on septum and heated in a 90 °C oil bath for 14 h, and the solvent was removed by rotary evaporation. Flash chromatography in 4:1 hexanes/EtOAc gave unreacted **7**. Elution with EtOAc and crystallization from acetonitrile gave **10** (0.87 g, 74%), mp = 179−181 °C.

^{1}H NMR ($CDCl_3$): δ 7.69 (dd, J = 12.0, 7.8 Hz, 4H), 7.24 (dd, J = 7.8, 2.7 Hz, 4H), 4.93 (br m, 2H), d 4.86 (br m, 2 H), 3.86 (br m, 2 H), 3.15 (br m, 4H), 2.84 (br m, 2H), 2.75 (dd, J = 13.5 Hz, 6.9 Hz, 2H), 1.48 (s, 9H), 1.42 (s, 18H), 1.37 (s, 18H). ^{13}C NMR ($CDCl_3$): δ 156.7, 155.8, 141.6, 132.8 (d, J = 186.1 Hz), 131.8 (d, J = 13.8 Hz), 129.3 (d, J = 17.8 Hz), 83.6 (d, J = 10.9 Hz), 79.5, 79.4, 52.6 43.7, 39.0, 30.9 (d, J = 5.2 Hz) 28.4. ^{31}P NMR ($CDCl_3$): δ 26.51 (^{1}H-coupled, quintet, J = 11.7 Hz). IR (neat): 3335 (Br), 3054, 2977, 2932, 2872, 1716, 1539, 1271, 1251,1228, 1040 cm^{-1}. MS (electrospray) (MeOH): calcd for $M + Na^+ = C_{42}H_{67}N_4O_{10}P_1Na_1$ 841.4, found 840.7 (100%). $[\alpha]_D^{30} = -4.64$ (CH_3OH, c 0.517). Anal. Calcd for $C_{42}H_{67}N_4O_{10}P$: C, 61.60; H, 8.25; N, 6.48. Found: C, 61.22; H, 8.27; N, 6.68.

When Ph_3P is used in this process, an impurity tentatively assigned as **11** is formed.

^{1}H NMR ($CDCl_3$): δ 7.78 (dd, J = 13, 8 Hz, 2H), 7.70 (dd, J = 12, 8 Hz, 2H), 7.46 (m, 3H), d 7.25 (dd, J = 9, 3 Hz, 2H), 1.50 (s, 9H), 1.42 (s, 9H), 1.36 (s, 9H). ^{31}P NMR ($CDCl_3$): δ 26.65: MS (electrospray) (MeOH): calcd for $M + Na^+ = C_{29}H_{43}N_4O_6P_1Na_1$ 569.3, found 569.0 (100%).

Bis[4-(2*S*)-2,3-diaminopropyl)phenyl]phosphinic Acid Trihydrochloride Tetrahydrate (2). *tert*-Butyl diarylphosphinate **10** (513 mg, 0.626 mmol) suspended in 8.7 mL of 9 M HCl was stirred for 30 min at 80 °C, and then the solvents were removed by rotary evaporation. The residue in 4 mL of H_2O was decolorized with 90 mg of charcoal, filtered through Celite, evaporated to dryness, and crystallized from 2.0 mL of H_2O and 20 mL of EtOH to give **2**, pure by NMR and HPLC (85:15 H_2O/CH_3CN, 0.043% TFA, 4.3 mM sodium hexanesulfonate; 3 μm C-18 4.6 × 100 mm, 0.5 mL/min, 230 nm, R_f = 4.7 min (100%)) except for EtOH of crystallization. Dissolution in H_2O and lyophilization gave analytically pure **2** (0.317 g, 87%) free of EtOH.

^{1}H NMR (D_2O): δ 7.72 (dd, J = 11.7, 8.1 Hz, 4H), 7.42 (dd, J = 8.1, 2.4 Hz, 4H), 3.78 (dq, J = 8.7, 6.3 Hz, 2H), 3.40 (dd, J = 16.7, 6.3, 1H), 3.35 (dd, J = 16.7, 6.8, 1H), 3.23 (dd, J = 14.4, 6.3, 1H), 3.04 (dd, J = 14.4, 8.7, 1H). ^{13}C NMR (D_2O): δ 139.9, 138.6 (d, J = 177.2 Hz), 134.4 (d, J = 13.5 Hz), 132.2 (d, J = 16.7 Hz), 55.2, 43.4, 38.8, 7.0. ^{31}P NMR (D_2O): δ 25.55. IR (KBr): 3430, 2972 (br), 1606, 1508, 1403, 1205, 1044, 741 cm^{-1}. UV (0.1 M aqueous HCl): $\epsilon_{230} = (2.51 \pm 0.02 \times 10^4)$ M^{-1} cm^{-1}. $[\alpha]_D^{30} = -34.4$ (H_2O, c 1.84). MS (electrospray) (H_2O/MeOH, positive ions): $M = C_{18}H_{27}N_4O_2P$ calcd for [$M + H^+$, ($M + 2H^+$)/2, ($M + H^+ + Na^+$)/2] 363.2, 182.6, 193.6, found 362.8 (30%), 181.8 (100%), 192.5 (43%). Negative ions: calcd for [$M - H^+$, $2M - H^+$] 361.2, 723.4, found 361.0 (16%), 723.6 (8%). MS (electrospray) (H_2O/MeOH/NaOH, pH 9: positive ions): calcd for [$M + H^+$, ($M + Na^+$), ($M - H^+ + 2Na^+$)] 363.2, 385.4, 407.2, found 363.4 (20%), 385.3 (25%), 406.8 (100%). Negative ions: calcd for [$M - H^+$] 361.2, found 361.8 (100%). Anal. Calcd for $C_{18}H_{27}N_4O_2P_1 \cdot (HCl)_3 \cdot (H_2O)_4$: C, 39.75 H, 7.04; N, 10.30. Found: C, 39.52; H, 7.08; N, 10.07.

Zn Complex of Bis[4-(2*S*)-2,3-diaminopropyl)phenyl]-phosphinic Acid (3). A stock solution of (2.7 mM) complex **3** was prepared by adding 0.9 equiv of anhydrous $ZnSO_4$ in D_2O to **2** in 100 mM sodium borate in D_2O. Nominal [**3**] = [Zn^{2+}]/2.

^{1}H NMR (0.1 M borate in D_2O): δ 7.662 (dd, J = 11.0, 8.2 Hz, 8H), 7.28 (d, J = 7.2 Hz, 8H), 3.02 (d, J = 10.4 Hz, 4H), 2.86 (d, J = 12.8 Hz, 8H), 2.60 (dd, J = 12.8, 8.4 Hz, 4H) 2.31 (br, 4H).

NMR Titration Procedure. ^{1}H NMR titrations were performed at 20.0 ± 0.5 °C in 0.2 M borate buffer in D_2O at constant host concentration of ca. 10^{-4} M. Host was titrated with a solution of host and guest, and all distinguishable resonances of host and guest were fit to yield a single K_D, using multidimensional nonlinear least squares using Scientist (MicroMath) version 2.01. Error limits are 95% confidence (s plane).

Host resonances were fit using the following equation

$$\delta_i = \delta_{0i} + \frac{\Delta\delta_{\max i}}{H_0}\left(S - \sqrt{S^2 - 4H_0G_0}\right)$$

and guest resonances were fit using the following equation

$$\delta_j = \delta_{0j} + \frac{\Delta\delta_{\max j}}{G_0}\left(S - \sqrt{S^2 - 4H_0G_0}\right)$$

where K_D = dissociation constant, H_0 = total host added, and G_0 = total guest added, and $S = H_0 + G_0 + K_D$, all in molarity.

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Supporting Information Available: ^{1}H NMR spectra of **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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