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Bridging of Bipyridine Units by Phenylphosphine Links: Linear and Cyclic Oligomers and Some Acid Derivatives

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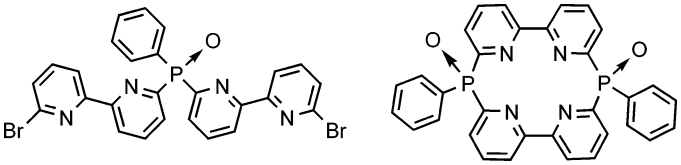

Reaction of 6,6′-dibromo-2,2′-bipyridine with phenylphosphine under palladium-promoted cross-coupling conditions provides a variety of linear oligomers bearing two reactive bromo substituents as well as a cyclic dimer, characterized by X-ray crystallography, in which the bipyridine units are constrained to a cis configuration by two phenylphosphine oxide bridges. Derivatives of the linear species containing both carboxylate and phosphonate substituents are readily obtained.

Introduction

Segmented multidentate ligands capable of producing linear chains or more complex arrays of metal centers are of considerable interest, both topologically and from the point of view of possible applications in the fields of molecular recognition and catalysis.[1,2] One of their characteristics is the formation of metallamacrocycles, some of which can bind selectively to further metal ions and which commonly show strong electronic absorption and photoluminescence.[3] An avenue to the synthesis of polynucleating ligands is the combination of phosphino units with a chelating framework based on nitrogen donor groups.[4] Phosphine oxide based ligands are efficient for the complexation and extraction of lanthanide cations in nuclear waste management.[5] When associated to chromophoric bipyridyl units, they ensure both strong coordination to the metal cations and good ability to generate highly luminescent complexes with ionophoric properties.[6] Furthermore, polymeric phosphine oxide have demonstrated attracting water solubilizing capabilities for hydrophobic CdSe semiconducting nanocrystals and Pd or Au nanoparticles.[7] Recently, the use of polymerizable functionalized phosphine oxide precursors, in particular those possessing activable C−Br functions, were adequately used to prevent aggregation of nanoparticles by the formation of polymer-nanoparticle composites ensuring a better dispersion of the nanoparticles in solid-state devices.[8] The synthesis of such oligomers combining coordinating phosphine oxide moieties associated to chromophoric bipyridyl units are very promising targets as capping layers for the photosensitization of lanthanide-based nanoparticles.[9] The definitive request for oligomeric bipyridine-based phosphine oxides prompted us to consider sustainable methods for large-scale production of such derivatives.

The synthetic value of P−C coupling reactions has been widely demonstrated with aryliodides,[10] alkenyl or aryl triflates,[11] 1,3-dienes,[12] vinyl bromide[13] or triflates,[14]

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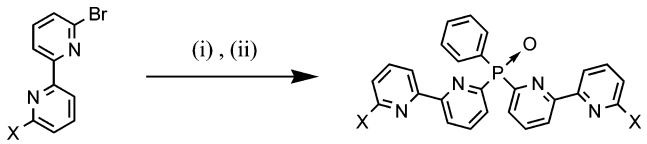
SCHEME 1[a]



1 ; X = CH_3
2 ; X = Br

3 ; X = CH_3
4 ; X = Br, oligomers

[a] Key: (i) $PhPH_2$ (0.5 equiv), $[Pd(PPh_3)_4]$ (10 mol %), $^iPr_2EtN$, CH_3CN, reflux; (ii) CH_2Cl_2, H_2O, $NaIO_4$, rt.

dinucleosides,[15] and tyrosine-containing peptides.[16] These preparations are commonly based on the use of trimethylstannyl- or trimethylsilyl-diphenylphosphine[17] or, more conveniently, primary or secondary phosphines.[18] The synthesis of 2-pyridylphosphane is achieved by metalation of pyridine at low temperature followed by reaction with chlorophosphane or dichlorophosphane. The recent use of pyridine-halogeno derivatives in metal catalyzed P−C cross-coupling reaction has enabled the preparation of mono-,[19] di-,[20] and tripyridinephosphane ligands.[21] In contrast, few examples of the P functionalization of bipyridine[22,23] or terpyridine[24] skeletons are known. By extension of our interest in the preparation and sensing properties of lanthanide-based compounds built from a bipyridine-based phosphine oxide,[6] we have turned our attention to the use of a palladium-promoted P−C cross-coupling reaction using phenylphosphine.

Results and Discussion

To the best of our knowledge, the use of dihalogeno-substituted bipyridine synthons has not yet been applied in reactions with arylphosphanes to produce oligomers or macrocycles. Inspired by the protocol described by Stelzer and co-workers for the one-step preparation of water soluble phosphines,[25] we found that reacting 6-bromo-6′-methyl-2,2′-bipyridine **1**[26] with $PhPH_2$, followed by subsequent phase transfer oxidation with sodium periodate, afforded **3** in 75% yield (Scheme 1). The phosphorus chemical shift (δ = 18.4 ppm) and the X-ray structure (Figure 2a) confirm the presence of the PO fragment.

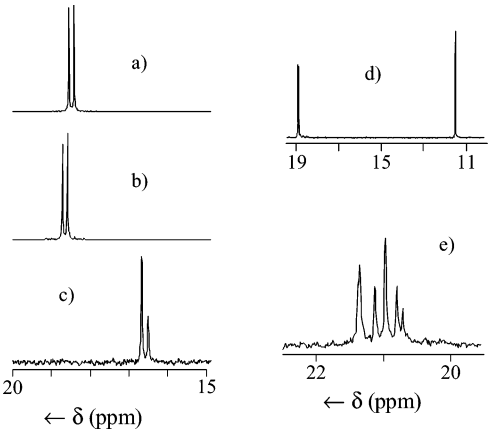


FIGURE 1. ^{31}P NMR at 162 MHz spectra for compounds: (a) **6** (in $CDCl_3$); (b) **7** (in $CDCl_3$); (c) **8** (in d_6-DMSO); (d) **9** (in $CDCl_3$); and (e) **13** (in CD_3OD).

After some experimentation, it was found that, when 6,6′-dibromo-2,2′-bipyridine **2**[27] was allowed to react under similar conditions with half an equivalent of $PhPH_2$, the monomer **4** was isolated in 47% yield. The phosphorus chemical shift (δ = 18.9 ppm) is in keeping with structure **3**. As would be expected by the presence of two reactive bromine functions in **2**, the macrocycle **5**, the dimer **6**, the trimer **11**, the tetramer **14**, and the pentamer **15** could be isolated, and these were purified by careful chromatography and crystallization procedures (Chart 1).

As a result of the presence of chiral tetrahedral phosphorus atoms, the ^{31}P NMR spectra of compounds became increasingly complicated along the series. The spectra of the dimers are particularly informative regarding the number of isomers and their relative proportions. For the bromo derivative **6**, ethylcarboxylic ester **7**, and diethylphosphonic ester **9**, two distinct peaks of nearly equal intensity around 19 ppm are assigned to the bridging phenylphosphine oxide phosphorus atoms (Figure 1), the phosphonic ester phosphorus in **9** giving rise to a singlet at 11.4 ppm (Figure 1d). Surprisingly, for the diacid **8**, the diastereomer ratio was found to be 70:30, possibly reflecting the stabilization of one diasteromer by hydrogen bonding interactions (Figure 1c). Further increase in the number of bipyridyl-phenylphosphine oxide units led to more complicated spectra. For the trimeric diacid **13**, where three diastereomers are possible and seven separate ^{31}P resonances should be observed, five signals can in fact be resolved (Figure 1e). The cyclic dimer **5** was also isolated in low yield in its cis form and unambiguously characterized by an X-ray structure determination (Figure 3). Attempts to develop methodologies for a chemioselective synthesis of the macrocyclic dimer failed up to now, despite the use of templating matrixes and high dilution environment. Interestingly, a single peak, strongly upfield shifted, was observed in the ^{31}P NMR spectrum at δ = 10.2 ppm, pointing to a single isomer. As previously observed for

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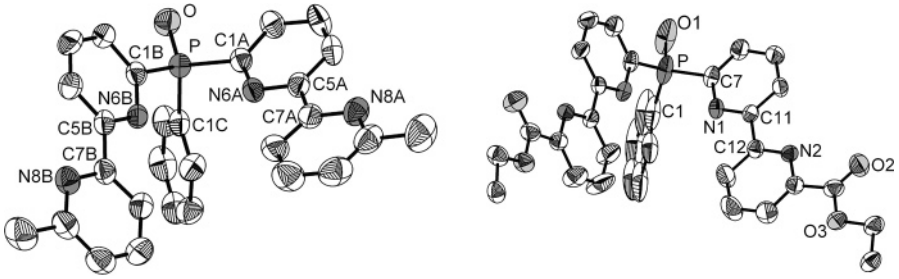
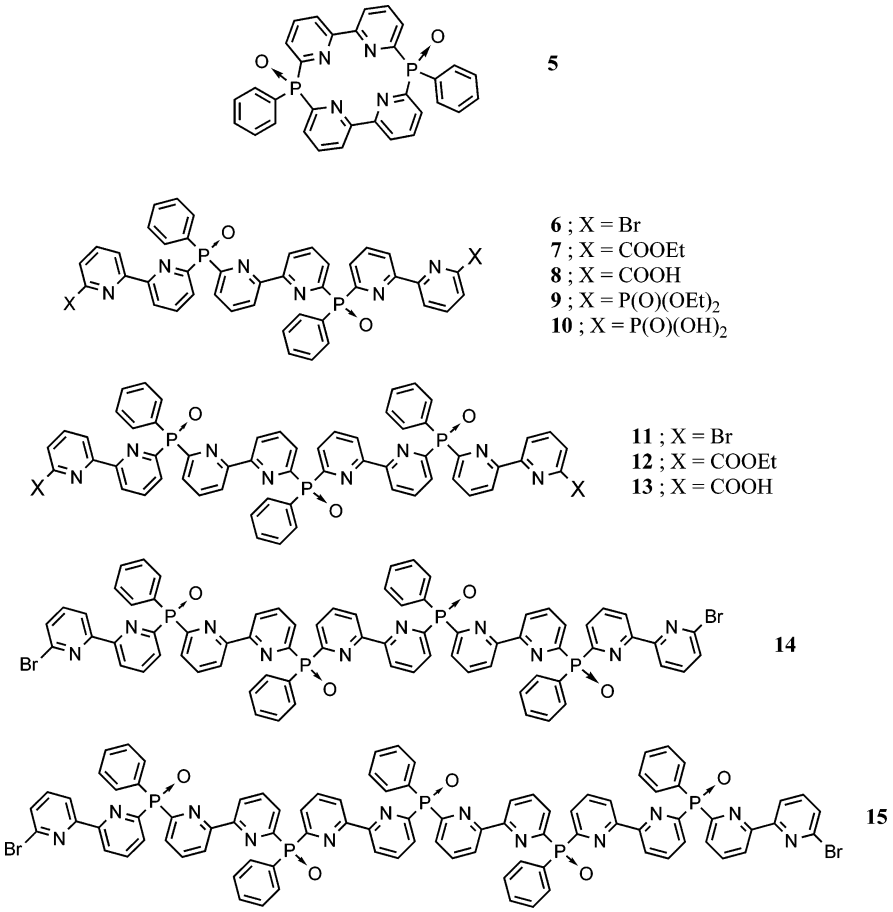


FIGURE 2. ORTEP drawing of the molecular unit of the lattice of compound **3** (left) and **19** (right) showing the principal numbering scheme (thermal ellipsoids drawn at 50% probability level).

CHART 1



related compounds,[28] the enforced cis configuration of the bipyridine fragments observed in the structure (vide infra) is mainly responsible for such an upfield shift.

We and others have previously shown that modifying chelating frameworks with deprotonatable functions such −COOH,[29] P(O)(OEt)(OH),[30] and P(O)(OH)$_2$[28] can provide various highly luminescent complexes of great promise in the fields of sensors and biomaterial labeling. To test this option here, we decided to transform the dibromo compound **2** to the diethylphosphonate **16** with diethyl phosphite in the presence of the Hünig base and catalytic amounts of tetrakis[triphenylphoshine]palladium.[18] This cross-coupling reaction is efficient (73% isolated yield for **16**) when excess triphenylphosphine is present. Selective hydrolysis is feasible with aqueous sodium hydroxide, providing **17** in 97% yield. The phosphonic ester group in **17** was converted into its acid form under mild conditions using excess bromotrimethylsilane.[31] Direct and quantitative conversion of **16** to **18** was also possible by the use of HCl (12 N) at reflux. Transformation of derivative **2** to the corresponding carboxylic esters and carboxylic acids was made possible by the use of a carboalkoxylation reaction promoted by Pd(0),[32] followed by a saponification of the ester.With these convenient

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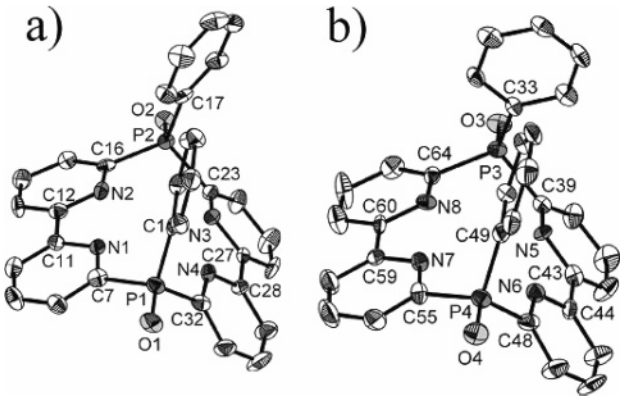
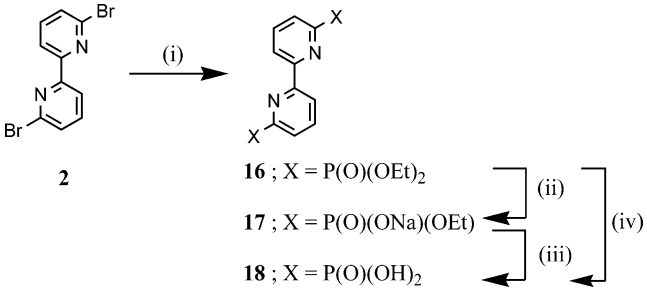


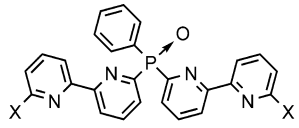
FIGURE 3. ORTEP representations of the two nonequivalent molecules of **5** present in the unit cell.

SCHEME 2[a]



[a] Key: (i) $HP(O)(OEt)_2$ (2 equiv), $[Pd(PPh_3)_4]$ (10 mol %), PPh_3 (1 equiv), $^iPr_2EtN$, toluene, reflux; (ii) CH_3OH, H_2O, NaOH (2 equiv), reflux; (iii) TMSBr, CH_2Cl_2, rt; (iv) HCl (concentrated) at reflux.

CHART 2



4 ; X = Br
19 ; X = COOEt
20 ; X = COOH
21 ; X = $P(O)(OEt)_2$
22 ; X = P(O)(ONa)(OEt)
23 ; X = $P(O)(OH)_2$

protocols in hand, it was then possible to transform the monomer **4**, dimer **6**, and trimer **11** to their corresponding acids. We first chose to transform derivative **4** to the biscarboxylic acid by a two-step procedure using a carboethoxylation reaction, leading to **19** in 91% yield, followed by saponification, leading to **20** in 78% isolated yield. This protocol has been extended to compounds **6** and **11**, giving rise to the diesters **7** (95%) and **12** (80%), respectively, and the carboxylic diacids **8** (83%) and **13** (91%) after hydrolysis (Chart 1).Phosphorylation of **4** is straightforward using $HP(O)(OEt)_2$, $^iPr_2EtN$, and $[Pd^0(PPh_3)_4]$ as mediator and leads to **21** in 91% yield. Hydrolysis with aqueous HCl (12 N) converts **21** to **23** in 81% yield and base hydrolysis provides **22** in 74% yield. Similar procedures can be used to convert **6** to **9** in 76% yield, and hydrolysis of **9** in HCl gives **10** (66%).

The X-ray crystal structure of compounds **3** and **19** unambiguously confirmed the grafting of the two bipyridine fragments on the phenylphosphine center (Figure 2). The phosphorus atom has a distorted tetrahedral geometry, evidenced in small deviations of the bond angles from the tetrahedral ideal (109° 28′). Whereas the O−P−C angles are all larger than this value (Table S1), the corresponding C−P−C angles are all smaller. The bipyridine fragments adopt a planar, transoid conformation, with dihedral angles of 177.8(3)° and 171.0(3)°. Repulsions between the lone pairs on O and N are presumably the reason for the trans conformation of both O−P−C−N moieties. For **19**, a symmetry plane containing the phenyl ring and the phosphorus atom bisects the molecule (Figure 2). The bipyridines are almost planar in a transoid conformation (N1−C11−C12−N2 = 179.8-(1)°). Detailed description of the crystal packing (Figure S1 and S2) is given as Supporting Information.

The molecular structure of the macrocycle **5** is shown in Figure 3. The asymmetric unit contains two molecules of **5**, only differing one from the other by a rotation of one of the phenyl rings. The macrocycle has the cis configuration, with the two almost planar bipyridine entities in a cisoid conformation (dihedral angles of 0.4 and 2.7° between the pyridine groups), linked by the phosphorus atoms, the oxygen atoms diverging from the macrocyclic void. Interestingly, the macrocyclic architecture appears to perturb slightly the pseudotetrahedral environment around the P atoms (Table S1) when compared to those in **3** and **19**. Notice that the oxygen atoms diverge from the macrocyclic void. The complete description of the crystal structure of compound **5** and its crystal packing (Figure S3) are provided in the Supporting Information.

In summary, an efficient synthesis of bis[6-bromo-2,2′-bipyridyl-6-yl]phenylphosphine oxide under mild conditions has been developed. This methodology produces interesting side products, including a macrocyclic dimer, and linear trimer, tetramer, and pentamer species. The resulting bromo-containing products can be readily elaborated to carboxylic esters, carboxylic acids, phosphonic esters, and phosphonic acids by using known organopalladium coupling chemistry. The monomeric methyl, carboxylic ester, and macrocyclic dimer were characterized by X-ray diffraction, revealing interesting features in the conformation of these molecules in the solid state. These oligomeric species are now currently used as photoactive capping layer in lanthanide based nanocrystals, and particular attention is given to the bromo derivatives as starting material in the synthesis of poly(paraphenylene-vinylene) quantum dots composite materials.

Experimental Part

Typical Procedure for the P−C Coupling Reactions. In a Schlenk tube under Ar, the bromo-bipyridine derivatives (1 equiv), phenylphosphine (0.5 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), and diisopropylethylamine were dissolved in dry acetonitrile and heated at 80 °C for 19 h. The solvent was removed under reduced pressure, and the resulting yellowish solid was partitioned between water (30 mL) and CH_2Cl_2 (80 mL), and $NaIO_4$ (excess) was added. After it was stirred for 20 h, the aqueous layer was extracted three times with 90 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness, and the resulting solid was purified by column chromatography.

Bis-[6′-bromo-2,2′-bipyridine-6-yl]phenylphosphine oxide (4). Phenylphosphine (2 g, 18.2 mmol), anhydrous diisopropylethylamine (6.6 mL, 38 mmol), **2** (11.4 g, 36.3 mmol), and $Pd(PPh_3)_4$ (2.1 g, 1.82 mmol) in CH_3CN (150 mL). Chromatography (Al_2O_3; CH_2Cl_2) gave compound **4** (5.01 g, 47%) as a white crystalline powder: $R_f = 0.50$, Al_2O_3, CH_2Cl_2/

MeOH = 99/1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, ^3J = 8.0 Hz), 7.48−7.64 (m, 5H), 7.94 (td, 2H, ^3J = 8.0 Hz, ^4J = 4.0 Hz), 8.10−8.13 (m, 4H), 8.19 (dd, 2H, ^3J = 8.5 Hz, ^4J = 1.0 Hz), 8.50 (d, br, 2H, ^3J = 8.0 Hz). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 120.1, 123.1 (d, J_{CP} = 3 Hz), 128.2, 128.3, 128.4, 128.5, 128.7, 130.3 (d, J_{CP} = 103 Hz), 132.3, 132.8 (d, J_{CP} = 9 Hz), 137.3 (d, J_{CP} = 10 Hz), 139.3, 154.7, 154.9, 155.1, 156.4, 156.6. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.90. IR (CH_2Cl_2; cm^{-1}): 2917 (w, ν_{CH}), 1600, 1575, 1545 (s, $\nu_{C=C}$, $\nu_{C=N}$), 1414 (s), 1207 (m, $\nu_{P=O}$), 1119 (s), 785 (s, $\nu_{C=C}$). MS (FAB$^+$): *m/z* = 357.2 ([M−$C_{10}H_6N_2Br$]$^\bullet$, 25%), 359.2 ([M−$C_{10}H_6N_2Br$]$^\bullet$, 25%), 593.2 ([M + H]$^+$, 100%). Anal. Calcd for $C_{26}H_{17}N_4Br_2PO$: C 52.73, H 2.89, N 9.46. Found: C 52.54, H 2.71, N 9.14%.

Compound 5 was obtained as a byproduct in the purification of **4**: (40 mg, 0.4%) as a white crystalline powder. R_f = 0.52, Al_2O_3, CH_2Cl_2/MeOH = 97/3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (dt, 4H, ^3J = 7.5 Hz, J_{PH} = 3.5 Hz), 7.46 (t, 2H, ^3J = 7.5 Hz), 7.85−7.91 (m, 8H), 8.36−8.40 (t, br, 4H), 8.51 (dd, 4H, ^3J = 8.1 Hz, J_{PH} = 11 Hz). ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 122.7 (J_{PC} = 3 Hz), 127.3 (J_{PC} = 21 Hz), 128.3 (J_{PC} = 12 Hz), 131.5, 132.3 (J_{PC} = 101 Hz), 132.5 (J_{PC} = 9 Hz), 136.6 (J_{PC} = 10 Hz), 155.65, 155.70, 156.0, 157.4. ^{31}P NMR (162 MHz, $CDCl_3$): δ 10.19; IR (CH_2Cl_2, cm^{-1}): 2928 (w), 1573 (m), 1552 (m), 1432 (m), 1412 (m), 1184 (s), 1158 (s), 1142 (m), 1105 (m), 799 (m), 763 (m), 746 (s). MS (FAB$^+$): *m/z* = 557.2 ([M + H]$^+$, 100%). Anal. Calcd for $C_{32}H_{22}N_4P_2O_2$: C 69.07, H 3.98, N 10.07. Found: C 68.81, H 3.64, N 9.76%.

Typical Procedure for the Carboethoxylation Reaction and Hydrolysis Step. A solution of the bromobipyridine (1 equiv) and [Pd(PPh_3)$_2$$Cl_2$] (0.1 equiv) in a 1/1 mixture of EtOH and Et_3N was heated at 70 °C for 20 h under a continuous flow of CO. The solvent was evaporated to dryness, and the residue was dissolved in CH_2Cl_2, filtered, and washed with water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was finally purified by column chromatography. The resulting ester were dissolved in a mixture of EtOH and NaOH in water and heated at 70 °C during 14 h. After the mixture had cooled to room temperature, the solvents were evaporated under reduced pressure. The solid was dissolved in H_2O, precipitated with aqueous HCl (2 N) and centrifuged.

Bis-[6′-carboethoxy-2,2′-bipyridine-6-yl]phenylphosphine oxide (19). A solution of **4** (77 mg, 0.13 mmol) and [Pd(PPh_3)$_2$$Cl_2$] (9.1 mg, 0.013 mmol) in a mixture of EtOH (20 mL) and Et_3N (20 mL) was heated at 70 °C for 20 h under a CO atmosphere. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (15 mL), filtered, and washed with water (5 mL). After the aqueous layer was washed with CH_2Cl_2 (10 mL), the combined organic layers were dried ($MgSO_4$), filtrated, and evaporated to dryness. The yellowish residue was purified by column chromatography (Al_2O_3 previously deactivated with 10% H_2O; CH_2Cl_2) to give compound **19** (69 mg, 91%) as a white crystalline solid. R_f = 0.29, Al_2O_3, CH_2Cl_2/MeOH = 99/1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, 6H, ^3J = 7.0 Hz), 4.47 (q, 4H, ^3J = 7.0 Hz), 7.49−7.59 (m, 3H), 7.78 (t, 2H, ^3J = 8.0 Hz), 7.97 (td, 2H,^3J = 8.0 Hz, $^4J_{PH}$ = 4.0 Hz), 8.07 (d, 2H, ^3J = 8.0 Hz), 8.13 (dd, 2H, ^3J = 7.5 Hz, $^3J_{PH}$ = 5.5 Hz), 8.21 (dd, br, 2H), 8.34 (d, 2H, ^3J = 8.0 Hz), 8.67 (d, br, 2H, ^3J = 8.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.4, 62.0, 123.3 (J_{PC} = 3 Hz), 124.3, 125.3, 128.2, 128.3, 128.4, 128.6, 130.5 ($^2J_{PC}$ = 103 Hz), 132.3 (J_{PC} = 3 Hz), 132.8 (J_{PC} = 9 Hz), 137.3 (J_{PC} = 10 Hz), 137.9, 148.0, 155.5, 155.6, 155.7, 156.3, 165.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.14. IR (CH_2Cl_2; cm^{-1}): 2918 (w, ν_{CH}), 1719 (m, ν_{CO}), 1594 (s, $\nu_{C=C}$,$\nu_{C=N}$), 1429 (m), 1384 (m), 1241 (m, $\nu_{P=O}$), 1133 (s), 1046 (m), 767 (m). MS (FAB$^+$): *m/z* = 578.1 ([M + H]$^+$, 100%). Anal. Calcd for $C_{32}H_{27}N_4O_5P$: C 66.43, H 4.70, N 9.68. Found: C 66.32, H 4.59, N 9.50%.

Bis-[6′-carboxy-2,2′-bipyridine-6-yl]phenylphosphine oxide (20). Compound **19** (180 mg, 0.30 mmol), NaOH (50 mg, 1.25 mmol), EtOH (15 mL), and H_2O (10 mL) are heated at 72 °C for 14 h to give **20**·2HCl·H_2O (147 mg, 78%) as a yellow crystalline solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.59−7.70 (m, 3H), 7.97 (t, 2H, ^3J = 8.0 Hz), 8.13−8.21 (m, 8H), 8.42 (d, 2H, ^3J = 8.0 Hz), 8.79−8.83 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, CD_3OD): δ 124.9, 125.5, 126.6, 129.5 (d, J_{PC} = 11 Hz), 129.8, 130.7 (d, J_{PC} = 104 Hz), 133.6 (J_{PC} = 9 Hz), 134.0, 139.1 (d, J_{PC} = 9 Hz), 139.8, 149.1, 156.4, 156.7, 156.8, 157.1, 167.9. ^{31}P NMR (CD_3OD): δ 21.45. IR (KBr, cm^{-1}): 2922 (w), 1763 (w), 1717 (s, ν_{CO}), 1577 (m, $\nu_{C=C}$,$\nu_{C=N}$), 1557 (w), 1430 (s, $\nu_{C=C}$), 1379 (m), 1353 (m), 1238 (m, $\nu_{P=O}$), 1135 (m), 1103 (m), 1077 (s), 766 (s). MS (FAB$^+$): *m/z* 523.3 ([M + H]$^+$, 100%). Anal. Calcd for $C_{28}H_{19}N_4PO_5$·2HCl·H_2O: C 54.83, H 3.78, N 9.13. Found: C 54.64, H 3.65, N 8.96%.

Typical Procedure for the Phosphorylation Reactions, Monohydrolysis, and Complete Hydrolysis. In a Schlenk tube under Ar, the bromo-bipyridine derivatives (1 equiv), diethyl phosphite (varying amount), [Pd(PPh_3)$_4$] (0.1 equiv), PPh_3 (1 equiv), and diisopropylethylamine were dissolved in dry toluene and heated at 110 °C for 12−20h. Toluene was removed under reduced pressure, and the resulting residue was oxidized by phase transfer using an aqueous solution of $NaIO_4$ (5 equiv) during one night. After extraction with dichloromethane and evaporation to dryness the residue was purified by column chromatography.

Monohydrolysis was performed with aqueous NaOH (1 equiv), H_2O (10 mL), and MeOH (15 mL) heated at 80 °C for 15 h. After the mixture had cooled to rt, the solvents were evaporated under reduced pressure. The solid was dissolved in H_2O/MeOH and precipitated with Et_2O. Conversion of this salt to the bisphosphonic acid is achieved using TMSBr in anhydrous dichloromethane at rt.

Dihydrolysis for the bisphosphonate was performed with concentrated aqueous HCl (12 mL) by heated at 75 °C for 35 h. After the mixture had cooled to rt, the solvent was evaporated under reduced pressure. The solid was recrystallized with MeOH−Et_2O to provide the phosphonic acid as a beige solid.

Bis-[6′-diethylphosphonate-2,2′-bipyridine-6-yl]phenylphosphine Oxide (21). Starting from **4** (100 mg, 0.17 mmol) and diethyl phosphite (50 μL, 0.39 mmol) gave compound **21** (109 mg, 91%) as a milky oil: R_f = 0.44, Al_2O_3, CH_2Cl_2/ MeOH = 97/3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, 12H, ^3J = 7 Hz), 4.14−4.32 (m, 8H), 7.44−7.56 (m, 3H), 7.74 (td, 2H, ^3J = 8.0 Hz, $^4J_{PH}$ = 5.5 Hz), 7.88 (ddd, 2H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, $^3J_{PH}$ = 6.4 Hz), 7.93 (td, 2H, ^3J = 8.0 Hz, $^4J_{PH}$ = 4.0 Hz), 8.11 (ddd, 2H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, $^3J_{CH}$ = 5.5 Hz), 8.12−8.23 (m, 2H), 8.30 (ddd, 2H, ^3J = 8.0 Hz, ^4J = 1.0 Hz, J_{PH} = 2.0 Hz), 8.57 (ddd, 2H, ^3J = 7.5 Hz, ^4J = 1.0 Hz, J_{PH} = 2.0 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.4, 16.5, 63.09, 63.12, 63.16, 63.18, 123.0 (d, J_{PC} = 2.5 Hz), 123.4 (d, J_{PC} = 3.5 Hz), 128.1 (d, J_{PC} = 9.0 Hz), 128.2 (d, J_{PC} = 3.5 Hz), 128.4 (d, J_{PC} = 21 Hz), 129.7 (d, J_{PC} = 103 Hz), 132.2 (d, J_{PC} = 2.5 Hz), 132.7 (d, J_{PC} = 8.5 Hz), 137.0 (d, J_{PC} = 12.5 Hz), 137.2 (d, J_{PC} = 9.0 Hz), 150.5, 152.7, 154.9, 155.3, 155.5, 155.8, 156.0, 156.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ 11.35, 18.67. IR (CH_2Cl_2, cm^{-1}): 2981 (m, ν_{CH}), 2927 (m, ν_{CH}), 1571 (m, $\nu_{C=C}$,$\nu_{C=N}$), 1428 (s), 1257 (s, $\nu_{P=O}$), 1203 (m, $\nu_{P=O}$), 1050 (s, $\nu_{CH2,CH3}$), 1025 (s, $\nu_{CH2,CH3}$), 971 (m, ν_{P-O}), 797 (s, $\nu_{C=C}$). MS (FAB$^+$): *m/z* = 662.3 ([M−EtO + H]$^+$, 28%), 707.2 ([M + H]$^+$, 100%). Anal. Calcd for $C_{34}H_{37}N_4O_7P_3$: C 57.79, H 5.28, N 7.93. Found: C 57.55, H 5.04, N 7.74%.

Bis-[6′-ethylphosphonate-2,2′-bipyridine-6-yl]phenylphosphine Oxide Sodium Salt (22). Compound **21** (104 mg, 147 μmol), NaOH (28 mg, 0.70 mmol), MeOH (15 mL), and H_2O (10 mL) were heated at 76 °C for 15 h to give **22** (78 mg, 74%) as a beige crystalline solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.24 (t, 6H, ^3J = 7.0 Hz), 4.09 (qt, 4H, ^3J = 7.0 Hz), 7.59−7.70 (m, 3H), 7.82−7.91 (m, 4H), 8.11−8.20 (m, 6H), 8.27 (d, br, 2H, ^3J = 8.0 Hz), 8.75−8.78 (m, 2H). ^{13}C{^{1}H} NMR (100

MHz, CD_3OD): δ 16.95, 17.01, 62.8, 62.9, 123.1 (br), 124.8 (br), 128.4 (J_{PC} = 22 Hz), 129.4 (J_{PC} = 21 Hz), 129.7 (J_{PC} = 12 Hz), 130.9 (J_{PC} = 104 Hz), 133.6 (J_{PC} = 9 Hz), 133.9, 138.2 (J_{PC} = 11 Hz), 138.9 (J_{PC} = 9 Hz), 155.0, 156.0, 156.2, 156.3, 157.1, 157.5, 157.7, 159.3. ^{31}P NMR (162 MHz, CD_3OD): δ 8.87, 21.27. IR (KBr, cm^{-1}): 3055 (w, ν_{CHali}), 2977 (w, ν_{CHaro}), 1567 (m, $\nu_{C=C}$,$\nu_{C=N}$), 1438 (m), 1227 (s, br, $\nu_{P=O}$), 1202 (m, $\nu_{P=O}$), 1071 (s, ν_{CH_2,CH_3}), 1046 (s, ν_{CH_2,CH_3}), 941 (m, ν_{P-O}), 749 (m). MS (FAB^-): *m/z* = 324.3 ($[M-2Na]^{2-}$, 25%), 625.1 ($[M-Na]^-$, 100%). Anal. Calcd for $C_{30}H_{27}N_4Na_2O_7P_3 \cdot H_2O$: C 50.57, H 4.10, N 7.86. Found: C 50.35, H 3.81, N 7.49%.

Bis-[6′-phosphonic acid-2,2′-bipyridine-6-yl]phenylphosphine Oxide (23). Compound **21** (107 mg, 150 μmol), concentrated HCl (12 mL) were heated at 75 °C for 35 h to give **23** (83 mg, 81%) as a beige solid. ^{1}H NMR (300 MHz, CD_3OD): δ 7.65 (s, br, 3H), 8.0−8.10 (m, 3H), 8.10−8.32 (m, 5H), 8.40−8.55 (m, 3H), 8.60−8.80 (m, 3H); $^{13}C\{^1H\}$-NMR (75 MHz, CD_3OD): δ 124.0, 124.9, 128.0, 128.3, 129.6, 129.8, 133.6, 134.0, 139.2, 154.1, 154.9, 156.1, 156.7, 157.0. ^{31}P NMR (162 MHz, CD_3OD): δ 11.90, 23.72. IR (KBr, cm^{-1}): 2923 (w, ν_{CHaro}), 1571 (m, $\nu_{C=C}$,$\nu_{C=N}$), 1429 (s), 1259 (m, br, $\nu_{P=O}$), 1142 (m), 988 (s), 935 (m, ν_{P-O}), 800 (m), 741 (s). MS (FAB^+): *m/z* = 595.2 ($[M+H]^+$, 100%). Anal. Calcd for $C_{26}H_{21}N_4O_7P_3.2HCl \cdot 2.5H_2O$: C 43.84, H 3.97, N 7.87. Found: C 43.85, H 4.37, N 7.71%.

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Supporting Information Available: Detailed X-ray crystal structure determination of compounds **3**, **19**, and **5** with their crystal packing (Figures S1−S3, pages S1−S6). Geometrical parameters observed by X-ray crystal structure for **3**, **19**, and **5** (Table S1, page S7). Experimental details and complete characterization of compounds **3** and **6**−**18** (pages S7−S16). This material is available free of charge via the Internet at http://pubs.acs.org.

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