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

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Supporting Information (16 pages)

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X-Ray crystal structure of compound 3 : Colorless prismatic crystals of compound **3** suitable for x-ray analysis were obtained as pure single phase by slow evaporation from a CH_2Cl_2/Cyclohexane mixture at room temperature. The crystal structure was investigated by single crystal X-ray diffraction at 293 K. Compound **3** crystallize in the $P2_1$ monoclinic space group (a = 8.403(3) Å; b = 14.622(6) Å; c = 9.752(4) Å; β = 91.29(3)°; V= 1197.91(80) $Å^3$, Z = 2) and the asymmetric unit is constituted by one molecule of **3** in general position. An Ortep view of the molecule with the main labeling scheme is represented in Figure 2 (main text). The geometry around the phosphorus atom carrying the two bipyridine fragments, the phenyl group and one oxygen atom is pseudo tetrahedral (P-C1A, 1.816(9) Å; P-C1B, 1.825(10) Å; P-C1C, 1.805(10) Å; P-O, 1.477(3) Å; C1A-P-O, 111.30(12) °; C1B-P-O, 111.36(10) °; C1B-P-O, 111.36(10) °; C1A-P-C1B, 111.36(10) °; C1A-P-C1C, 106.47(11) °; C1B-P-C1C, 106.15(11). The bipyridine fragments adopt a trans conformation and the pyridyl fragments are slightly twisted around the central carbon-carbon bond (dihedral angles N6A-C5A-C7A-N8A = 177.83(23) ° and N6B-C5B-C7B-N8B = 170.98(22) °). The two nitrogen atoms N6A and N6B on the pyridine fragments directly connected to the phosphorus atom point to the center of the molecule and force the oxygen atom to swing out by electrostatic repulsion (Distance N6A-N6B = 3.232 Å). The trans conformation of the bipyridine fragments orients the methyl groups to the exterior of the molecule. The whole molecule can be regarded as a Y-shaped molecule with the oxygen atom and the phenyl group in the same plane. It should be noted that this Y-shaped geometry is not perfect since one bipyridine fragment point above the P-O axis and the other below. The angle between the two bipyridine fragments is 59.59 °.

Different views of the crystal packing in the crystal are presented in Figure S1. The crystal structure can be described as made of stacks of molecules **3**, running along the *a* axis. These stacks form a 2-D array in the *bc* plane via C-C contacts between the pyridine fragments and the methyl groups with distances ranging from 3.9 to 4.8 Å.

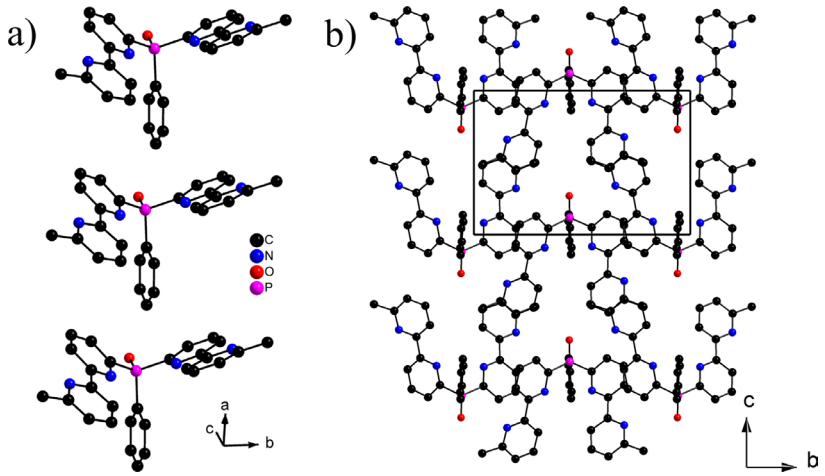

Figure S1: Crystal packing and molecular arrangement of molecule **3**: a) One stack of molecules along the *a* axis; b) Projection along the *a* axis showing the 2-D array through C-C contacts between the bipyridine fragments.

X-Ray crystal structure of compound 19 : The crystal structure of compound **19** was investigated by single crystal X-ray diffraction at 293 K on colorless prismatic crystals obtained as pure single phase by slow evaporation from a CH_2Cl_2/Cyclohexane mixture at room temperature. This compound crystallize in the monoclinic space group $P2_1/m$ with the lattice parameters: a = 8.1180(3) Å; b = 20.8664(8) Å; c = 8.9972(3) Å; β = 108.976(5)°, V= 1441.24(9) $Å^3$ and z = 2. One molecule is located on a mirror plane containing the phenyl group and the phosphorous atom and the whole molecule also adopt a perfect Y-shape like geometry by symmetry (Figure 2 main text). The angle between the two bipyridine fragments is 68.57 °. The angles between the bipyridine fragments and the phenyl group is 107.94(14)° (C1-P-C7) and the angle between the two bipyridine fragments is 105.62(19) (C7-P-C7). The geometry around the phosphorus atom carrying the two bipyridine fragments, the phenyl group and one oxygen atom is pseudo tetrahedral (P-C1, 1.754(10) Å; P-O1, 1.485(6) Å; P-C7, 1.820(4) Å; C7-P-O1, 110.94(13) °; O-P-C1, 113.11(36) °). Figure 2 (main text) shows

the atomic numbering and the main labeling scheme. The bipyridine fragments are planar and adopt a trans conformation (dihedral angle N1-C11-C12-N2 = 179.76(35) °). The oxygen atom also swings out from the center of the molecule **19** by electrostatic repulsion with the two nitrogen atoms N1 close to the phosphorus atoms (Distance N1-N1 = 3.330 Å).

The crystal structure can be described as made of ondulated layers parallel to the (110) plane lattice. These layers are constituted of stacks of Y-shaped molecules **19** running along the *a* axis which are interdigitated in the [010] direction (Figure S2). The stack overlap occurs between the ester group and half of the bipyridine fragment. Since no strong directing interactions such π-π stacking or hydrogen bonding are present, the crystal packing, which is mainly controlled by steric constraints, is maintained by van der Waals interactions.

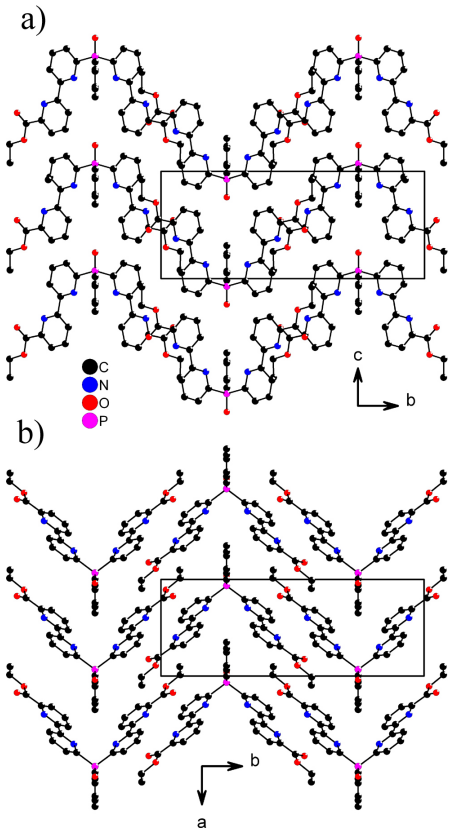

Figure S2. Crystal packing and molecular arrangement of molecule **19**: a) Projection along *a* showing the arrangement of the ondulated layers*;* b) Projection along the [001] direction of the layer of stacks.

Introduction of an ester group in place of the methyl group induce an elongation in the [010] direction and prevents C-C contacts between the bipyridine fragments which lead to a decrease of the dimensionality in the *bc* plane.

X-Ray crystal structure of compound 5 : Crystals of molecule **5** suitable for X-ray analysis were obtained as colorless prism by slow evaporation from a CH_2Cl_2/Cyclohexane mixture at room temperature. The X-ray data were collected at 293 K from a single crystal and this compound crystallize in the $P2_1$ monoclinic space group (*a* = 8.4707(2) Å; *b* = 14.1600(3) Å; *c* = 23.7508(7) Å; β = 97.370(5) °; V= 2825.3(1) $Å^3$, Z = 1). The asymmetric unit contains two molecules **5** as well as one molecule of methanol molecule and half of a dichloromethane molecule in general positions. The molecular structures of the two independent molecules **5** are presented in Figure 3 (main text). On the two molecules, the phosphorus atoms have a pseudo tetrahedral geometry with C-C distances ranging from 1.78 – 1.85 Å, P=O distances at 1.49 Å and C-P-C and C-P-O angles ranging from 106.0-113.5 °. It should be noted that the phenyl groups on both molecules are on the same side of the molecular cycle. This shape also force the oxygen atoms to point to the exterior of the molecule. The main difference between the two molecules come from the orientation of the phenyl fragments on the phosphorus atoms to the molecular cycle. On the two molecules, one phenyl ring is parallel to the plane containing of the P-O axes, whereas the second phenyl ring is rotated by 35.57 ° and 85.90 ° on the first and the second molecule respectively. Unlike molecules **3** and **19**, the cyclization of the molecule forces the bipyridine fragments to adopt a planar cis conformation and the nitrogen atoms form a molecular pocket (dihedral angles N1-C11-C12-N2 = 0.42 °; N3-C27-C28-N4 = 2.74 °; N5-C43-C44-N6 = 0.60 °; N7-C59-C60-N8 = 2.56 °). In the first molecule (Figure 3a), the distances between the nitrogen atoms N1-N4 and N2-N3 are 3.111 and 3.121 Å respectively and the P1-P2 distance is 6.984 Å . In the

second molecule (Figure 3b), the distance between the phosphorus atoms P3-P4 is 6.854 Å and the distances between the nitrogen atoms are N5-N8 = 3.086 Å and N6-N7 = 3.070 Å.

The molecular structure can be described as made of two different layers parallel to the (110) lattice plane alternating along the [001] direction (Figure S3). These Layers are isolated by dichloromethane and methanol solvent molecules. Each layers are constituted by stacks, of one type of molecule, along the *a* axis (Figure S3b and S3c). C-C contacts can be observed between the pyridyl fragments inside the layers (3.7 Å).

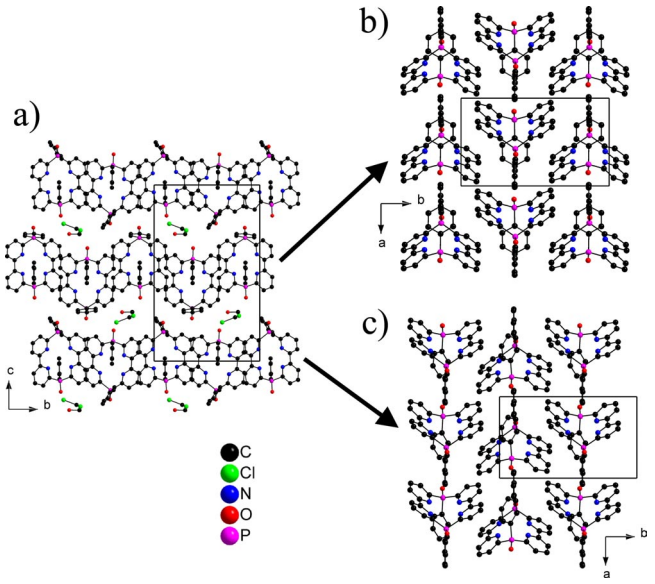

Figure S3. Crystal packing and molecular arrangement of molecule **5**: a) Projection along *a* showing the alternation of the two different layers in the [001] direction*;* b) and c) The two different types of layers made of stacks of molecules **5** having distinct conformations.

Table S1: Geometrical parameters around the P atoms observed in the X-ray crystal structures of compounds **3**, **19** and **5**.

	3	**19**	**5** [a]
Distances (Å)			
P-O	1.477(3)	1.485(6)	1.489(2)
P-C_{Phe}	1.805(10)	1.754(10)	1.796(8)
P-C_{pyr1}	1.816(9)	1.820(4)	1.831(10)
P-C_{pyr2}	1.825(10)	1.820(4)	1.811(13)
Angles (°)			
O-P-C_{Phe}	113.7(1)	113.1(4)	112.50
O-P-C_{pyr1}	111.3(1)	110.9(2)	110.8(4)
O-P-C_{pyr2}	111.4(1)	110.9(2)	111.9(4)
C_{Phe}-P-C_{pyr1}	106.5(1)	107.9(2)	107.4(3)
C_{Phe}-P-C_{pyr2}	106.2(1)	107.9(2)	107.2(13)
C_{Pyr1}-P-C_{pyr2}	107.4(1)	105.6(2)	106.7(8)

a) Values collected for **5** are averaged from the four crystallographically independent phosphorous atoms with the mean displacement around this values in parenthesis.

Experimental part

General Methods. The 200.1, 300.1, 400.1 (^{1}H) ; 50.3, 100.6 (^{13}C) and 162.0 MHz (^{31}P) NMR spectra were recorded at room temperature using perdeuterated solvents as internal reference (^{1}H and ^{13}C) or the internal reference of the spectrometer (^{31}P). When unambiguous, J_{PC} values are given. FT-IR spectra were recorded as KBr pellets or in solution otherwise stated. Fast-atom bombardment (FAB, positive mode) mass spectra were obtained using *m*-nitrobenzyl alcohol (*m*-NBA) as matrix. Chromatographic purification was conducted using 40-63/63-200 μm silica gel or neutral aluminium oxide deactivated with 6% water prior to use. TLC was performed on silica gel or aluminium oxide coated plates with fluorescent indicator. All mixtures of solvents are given in v/v ratio.

Materials. Phenylphosphine, $NaIO_4$, diethylphosphite, and EtOH were used as purchased. Toluene and diisopropymethylamine were distillated on CaH_2 and NaOH, respectively, prior to use. $[Pd(PPh_3)_4]$,[S1] $[Pd(PPh_3)_4]$,[S2] 6-bromo-6'-methyl-2,2'-bipyridine **1**,[S3] and 6,6'-dibromo-2,2'-bipyridine **2**,[S4] were obtained according to literature procedure.

Bis-[6'-methyl-2,2'-bipyridine-6-yl]phenylphosphine oxide (3): Phenylphosphine (155 μl, 1.41 mmol) was added in a Schlenk tube under Ar to a stirred solution of anhydrous di(isopropyl)ethylamine (506 μl, 2.90 mmol), **1** (700 mg, 2.81 mmol) and $Pd(PPh_3)_4$ (155 mg, 0.14 mmol) in dry CH_3CN (30 mL). The resulting mixture was heated at 80 °C for 19 h. The CH_3CN was removed under reduced pressure. The resulting yellowish solid was partitioned between water (20 mL) and CH_2Cl_2 (60 mL), and $NaIO_4$ (1.2 g, 5.62 mmol) was added. After stirring for 4 h, the aqueous layer was extracted three times with CH_2Cl_2 (45 mL). The combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness and the resulting solid was purified by column chromatography (Al_2O_3 previously deactivated with 10 % H_2O;

CH_2Cl_2) to give compound **3** (488 mg, 75 %) as a white crystalline powder : R_f = 0.31, Al_2O_3, CH_2Cl_2/MeOH: 99/1; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 6H), 7.13 (d, 2H, ^3J = 8.0 Hz), 7.47-7.57 (m, 5H), 7.91 (td, 2H, ^3J = 8.0 Hz, ^4J = 4.0 Hz), 8.04 (d, 2H, ^3J = 8.0 Hz), 8.11 (td, 2H, ^3J = 7.0 Hz, ^4J = 1.0 Hz), 8.26-8.32 (m, 2H), 8.54 (d, br, 2H, ^3J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 24.7, 118.5, 122.6 (d, J_{CP} = 3 Hz), 123.7, 127.8 (d, J_{CP} = 21 Hz), 128.1 (d, J_{CP} = 12 Hz), 130.1 (d, J_{CP} = 103 Hz), 132.0 (d, J_{CP} = 3 Hz), 133.0 (d, J_{CP} = 8 Hz), 136.9, 137.1 (d, J_{CP} = 10 Hz), 137.3, 154.9, 156.5 (d, J_{CP} = 51 Hz), 156.6, 158.0; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.37; IR (CH_2Cl_2; cm^{-1}): 2918 (w, ν_{CH}), 1594 and 1575 (s, $\nu_{C=C}$,$\nu_{C=N}$), 1433 (s), 1199 (m, $\nu_{P=O}$), 1109 (m), 789 (m, $\nu_{C=C}$); MS (FAB^+): *m/z* = 294.2 ($[M–C_{11}H_9N_2+H]^{+\cdot}$, 15 %), 463.1 ($[M + H]^{+\cdot}$, 100 %). Anal. Calcd for $C_{28}H_{23}N_4PO$: C 72.72, H 5.01, N 12.11. Found: C 72.43, H 4.70, N 11.82 %.

Compounds **6**, **11**, **14** and **15** were obtained as byproducts in the purification of **4**.

Compound 6: (0.4 g, 2.5 %) white crystalline powder. R_f = 0.74, Al_2O_3, CH_2Cl_2/MeOH: 97/3; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.61 (m, 10H), 7.80 (tdd, 2H, ^3J = 8.0 Hz, ^4J = 4.0 Hz, J = 1.0 Hz), 7.94 (td, 2H, ^3J = 8.0 Hz, J = 4.0 Hz), 8.06-8.32 (m, 12H), 8.48 (d, br, 2H, ^3J = 8.0 Hz); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 120.0 (d, J = 1 Hz), 122.9 (d, J = 3 Hz), 123.1 (br), 128.2, 128.27, 128.30, 128.4, 128.5, 128.58, 128.63, 129.6 (br), 131.0 (br), 132.3 (d, J = 2 Hz), 132.8 (d, J = 8 Hz), 137.1, 137.2, 137.4, 139.2 (d, J = 5 Hz), 141.7, 154.7 (br), 154.8 (br), 154.9 (br), 155.5, 155.7, 156.5 (br); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.45, 18.59; IR (CH_2Cl_2, cm^{-1}): 2918 (w), 1572 (s), 1547 (s), 1417 (s), 1203 (m), 1124 (m), 1107 (m), 1075 (m), 791(m), 742 (m); MS (FAB^+): *m/z* = 871.2 ($[M + H]^+$, 100 %); Anal. Calcd for $C_{42}H_{28}N_6Br_2P_2O_2$: C 57.95, H 3.24, N 9.65. Found: C 57.74, H 2.96, N 9.45 %.

Compound 11: (0.20 g, 0.9 %) pale yellow solid. R_f = 0.54, Al_2O_3, CH_2Cl_2/MeOH: 97/3; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.58 (m, 13H), 7.72 (td, 2H, ^3J = 8.0 Hz, J = 4.0 Hz), 7.79 (td, 2H, ^3J = 8.0 Hz, ^4J = 4.0 Hz), 7.93 (td, 2H, ^3J = 8.0 Hz, ^4J = 4.0 Hz), 8.04-8.14 (m, 8H),

8.17-8.28 (m, 9H), 8.45-8.50 (m, 2H); $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ 120.0, 122.9 (br), 123.0, 123.2, 128.2, 128.3, 128.5, 128.6, 128.7, 129.8, 130.8, 132.3, 132.75 (br), 132.84 (br), 137.06, 137.12, 137.16, 137.22, 137.28, 137.4, 139.2 (br), 141.7, 149.3, 154.7 (br), 154.9 (br), 155.1, 155.47 (br), 155.53, 155.6, 155.7 (br), 156.3, 156.4, 156.6; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.21, 18.24, 18.39, 18.42, 18.53, 18.55; IR (CH_2Cl_2, cm^{-1}): 2919 (m), 2850 (m), 1572 (s), 1548 (m), 1424 (s), 1201 (m), 1152 (m), 1124 (m), 1107 (m), 1076 (m), 793 (m), 743 (m), 694 (m); MS (FAB^+): *m/z* = 1149.2 ($[M]^+$, 100 %); Anal. Calcd for $C_{58}H_{39}N_8Br_2P_3O_3$: C 60.64, H 3.42, N 9.75. Found: C 60.42, H 3.13, N 9.54 %.

Compound 14: (0.10g, 0.4 %) white powder. R_f = 0.46, Al_2O_3, CH_2Cl_2/MeOH: 97/3; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.38-7.58 (m, 16H), 7.66-7.88 (m, 6H), 7.88-7.95 (m, 2H), 7.95-8.33 (m, 26H), 8.40-8.49 (m, 2H); $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$): δ 120.0, 122.9 (br), 123.16, 128.23, 128.4, 128.45, 128.54, 128.7, 130.0, 131.1, 132.3, 132.77, 132.84, 137.1, 137.2, 139.2 (br), 141.8, 155.0 (br), 155.5, 155.7, 156.3, 156.6; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.14, 18.21, 18.28, 18.34, 18.48;. IR (CH_2Cl_2, cm^{-1}): 2920 (m), 1571 (s), 1548 (m), 1426 (s), 1200 (s), 1153 (m), 1107 (m), 797 (m), 742 (s), 694 (w); MS (FAB^+): *m/z* = 1427.1 ($[M + H]^+$, 100 %); Anal. Calcd for $C_{74}H_{50}Br_2N_{10}O_4P_4$: C 62.29, H 3.53, N 9.82. Found: C 62.01, H 3.23, N 9.65 %.

Compound 15: (0.05 g, 0.16 %) yellow powder. R_f = 0.41, Al_2O_3, CH_2Cl_2/MeOH: 97/3; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.33-7.59 (m, 19H) , 7.64-7.84 (m, 6H) , 7.86-7.95 (m, 2H), 7.98-8.33 (m, 32H), 8.41-8.51 (m, 2H); $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$): δ 119.9, 122.7, 123.0, 128.1, 128.2, 128.4, 128.5, 130.0, 130.9, 132.2 (br), 132.58, 132.65, 132.70, 137.0, 137.1, 139.06, 139.11, 141.6, 154.6, 155.3, 155.5, 156.4; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.15, 18.17, 18.23, 18.26, 18.30, 18.33, 18.37, 18.52; IR (CH_2Cl_2, cm^{-1}): 3056 (m), 2926 (w), 1571 (s), 1548 (s), 1426 (s), 1368 (m), 1199 (s), 1153 (m), 1124 (m), 1107 (m), 1076 (m), 987 (m),

798 (s), 742 (s), 694 (m); MS (FAB^+): *m/z* = 1706.2 ($[M + H]^+$, 100 %); Anal. Calcd for $C_{90}H_{61}Br_2N_{12}O_5P_5$: C 63.39, H 3.61, N 9.86. Found: C 63.14, H 3.44, N 9.63 %.

Procedure for the phosphorylation of bromobipyridines: In a Schlenk tube under Ar , the bromobipyridine (1 equiv.), diethylphosphite (varying amount), $[Pd(PPh_3)_4]$ (0.1 equiv.), PPh_3 (1 equiv.), and N,N-diisopropylethylamine were dissolved in dry toluene and heated at 110 °C for 12 to 20h. Toluene was removed under reduced pressure and the resulting residue was purified by column chromatography.

6,6'-bis(diethylphosphonate)-2,2'-bipyridine (16): from 0.355 g (1.13 mmol) of **2** and 0.362 g (2.62 mmol) of $HPO(OEt)_2$ to give **16** (0.355 g, 73 %) as a white solid; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 12H, ^3J = 7Hz), 4.18-4.32 (m, 8H), 7.89-8.03 (m, 6H), 8.63 (d, 2H, br, ^3J = 7Hz); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 16.8, 16.9, 63.5, 63.6, 124.0 (d, J_{PC} = 4Hz), 128.7 (d, J_{PC} = 25 Hz), 137.5 (d, J_{PC} = 12 Hz), 152.0 (d, J_{PC} = 226 Hz), 156.1 (d, J_{PC} = 22 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 11.49; IR (CH_2Cl_2; cm^{-1}): 2930 (m), 1632 (m), 1575 (m), 1543 (m), 1429 (s), 1262 (m, br), 1200 (m), 1187 (m), 1156 (m), 1026 (s), 745 (m); MS (FAB^+): *m/z* 429.2 ($[M+H]^{+\cdot}$, 100 %), 399.2 ([M-OEt], 30 %), Anal. Calcd for $C_{18}H_{26}N_2O_6P_2$: C 50.46, H 6.13, N 6.54. Found: C 50.27, H 5.89, N 6.36 %.

Compound 9: Starting from **6** (250 mg, 0.29 mmol) and diethylphosphite (85 µL, 0.66 mmol) gave compound **9** (214 mg, 76 %) as white solid. R_f = 0.45, SiO_2, CH_2Cl_2/MeOH: 90/10; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, 12H, ^3J = 7.0 Hz), 4.17-4.36 (m, 8H), 7.45-7.60 (m, 6H), 7.60-7.78 (m, 4H), 7.79-7.93 (m, 4H), 8.00-8.29 (m, 12H), 8.58 (d, br, 2H, ^3J = 8 Hz). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 16.5, 16.6, 63.2, 63.3, 122.9 (br), 123.1, 123.2, 123.4, 123.5, 128.10, 128.12, 128.2 (br), 128.3 (br), 128.5 (br), 128.6 (br), 128.7 (br), 130.4 (J_{PC} = 103 Hz), 132.30, 132.32, 132.73, 132.75, 132.82, 132.84, 137.0, 137.1 (br), 137.2, 137.3 (br), 150.67, 150.69, 152.93, 152.95, 154.9 (br), 155.1 (br), 155.4, 155.5, 155.6, 155.7, 155.9,

156.1, 156.2, 156.4. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 11.35, 18.46, 18.50. IR (CH_2Cl_2, cm^{-1}): 2925 (m), 1571 (m), 1428 (s), 1256 (m, br), 1200 (m), 1156 (m), 1106 (w), 1024 (s), 800 (w), 745 (m); MS (FAB^+): *m/z* = 939.2 ($[M - OEt]^+$, 50 %), 985.2 ($[M]^+$, 100 %); Anal. Calcd for $C_{50}H_{48}N_6O_8P_4$: C 60.98, H 4.91, N 8.53. Found: C 60.80, H 4.75, N 8.40 %.

Typical procedure for the monohydrolysis and complete hydrolysis: Mono-hydrolysis 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 r.t., the solvents were evaporated under reduced pressure. The solid was dissolved in H_2O/MeOH and precipitated with Et_2O. Conversion of compound **17** to the bis-phosphonic acid is achieved using TMSBr in anhydrous dichloromethane at r.t..

Dihydrolysis for the bis-phosphonate was performed with conc. HCl (12 mL) by heated at 75 °C for 35 h. After the mixture had cooled to r.t., the solvent was evaporated under reduced pressure. The solid was recrystallized with MeOH-Et_2O to povide the phosphonic acid as a beige solid.

6,6'-di(monoethylphosphonate)-2,2'-bipyridine disodium salt (17): ^{1}H-NMR (200 MHz, DCl/D_2O/tBuOH): δ 1.23 (t, 6H, ^3J = 7 Hz), 3.92-4.07 (m, 4H), 7.83-8.02 (m, 2H), 815-8.22 (m, 2H), 8.33-8.50 (m, 2H); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 16.8, 63.5, 122.4 (d, J_{PC} = 4Hz), 122.7 (d, J_{PC} = 4Hz), 128.2 (d, J_{PC} = 24 Hz), 128.3 (d, J_{PC} = 25 Hz), 137.3 (d, J_{PC} = 11 Hz), 137.5 (d, J_{PC} = 12 Hz), 151.7 (d, J_{PC} = 226 Hz), 152.0 (d, J_{PC} = 223 Hz), 155.9 (d, J_{PC} = 20 Hz), 156.1 (d, J_{PC} = 22 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 10.87; IR (CH_2Cl_2; cm^{-1}): 2935 (m), 2925 (m), 1630 (m), 1577 (m), 1574 (m), 1543 (m), 1532 (m), 1432 (s), 1265 (m), 1187 (m), 1193 (m), 1154 (m), 1028 (s), 753 (m); MS (FAB^-): *m/z* 370.2 ($[M-Na]^+$, 100 %), 341.1 ([M-Na-OEt], 20 %), Anal. Calcd for $C_{14}H_{16}N_2O_6P_2Na_2$: C 40.40, H 3.87, N 6.73. Found: C 40.12, H 3.96, N 6.39 %.

6,6'-bisphosphonic-2,2'-bipyridineacid (18): ^{1}H-NMR (300 MHz, d_6-DMSO): δ 7.77 (t, 2H, br, ^{3}J = 7 Hz), 8.13-8.23 (m, 2H), 8.55 (d, 2H, ^{3}J = 8 Hz); ^{13}C{^{1}H}-NMR (100 MHz, d_6-DMSO): δ 122.5, 126.3 (d, J_{PC} = 21 Hz), 138.7 (d, J_{PC} = 10 Hz), 152.5 (d, J_{PC} = 19 Hz), 158.2 (d, J_{PC} = 206 Hz); ^{31}P-NMR (162 MHz, d_6-DMSO): δ 10.44; IR (CH_2Cl_2; cm^{-1}): 1588 (w), 1568 (w), 1443 (w), 1416 (w), 1172 (s), 1066 (s), 916 (s), 798 (m) ; MS (FAB^+): *m/z* 317.2 ($[M+H]^+$, 100 %). Anal. Calcd for $C_{10}H_{10}N_2O_6P_2$: C 37.99, H 3.19, N 8.86. Found: C 37.78, H 2.96, N 8.56 %.

Compound 10 : Compound **9** (144 mg, 146 μmol) was dissolved in conc. HCl (10 mL) and heated at 80 °C for 40 h. After the mixture had cooled to r.t., the solvent was evaporated under reduced pressure. The solid was recrystallized with MeOH-Et_2O to give **10** (93 mg, 66 %) as white solid. ^{1}H NMR (d_6-DMSO): δ = 7.47-7.67 (m, 6H), 7.80-7.99 (m, 6H), 8.04-8.27 (m, 10 H), 8.35-8.61 (m, 4H), 8.71 (d, 2H, ^{3}J = 8.0Hz). ^{13}C NMR (d_6-DMSO): 120.5, 121.5, 122.5, 122.7, 124.7, 124.8, 126.4, 126.7, 128.2, 128.28, 128.34, 128.4, 131.6, 131.7, 131.8, 132.16, 132.24, 133.9, 137.4, 137.5, 137.6, 137.7, 137.8, 137.85, 137.92, 138.0, 138.1, 138.2, 138.3, 138.6, 138.8, 141.2, 148.9, 149.4, 149.7, 154.4 154.5, 154.6, 154.75, 154.84, 155.0, 155.2, 155.3, 156.0, 156.06, 156.14, 156.3, 157.1 157.3, 157.9. ^{31}P NMR (d_6-DMSO): δ = 7.36, 16.84, 20.03. IR (KBr, cm^{-1}): 1610 (m), 1569 (m), 1428 (m), 1182 (m), 1141 (s, br), 988 (m), 935 (s), 800 (m), 741 (s); MS (FAB^+): *m/z* 873.2 ($[M+H]^+$, 100 %). 791.2 ($[M-H_2PO_3]^+$, 10 %); Anal. Calcd for $C_{42}H_{32}N_6O_8P_4.2HCl$: C 53.35, H 3.62, N 8.89. Found: C 53.25, H 3.63, N 8.46 %.

Typical procedure for the carboethoxylation reaction and hydrolysis step: A solution of the bromobipyridine (1 equiv.) and $[Pd(PPh_3)_2Cl_2]$ (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, 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 finely 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 r.t., the solvents were evaporated under reduced pressure. The solid was dissolved in H_2O, precipitated with diluted aqueous HCl (2 N) and centrifuged.

Compound 7 : Starting from compound **6** (400 mg, 0.46 mmol) gave **7** (374 mg, 95 %) as a white crystalline solid. R_f = 0.48, SiO_2, CH_2Cl_2/MeOH: 90/10; ^{1}H-NMR. (300 MHz, $CDCl_3$): δ 1.44 (t, 6H, ^{3}J =7.1 Hz), 4.46 (q, 4H, ^{3}J = 7.2 Hz), 7.45-7.59 (m, 6H), 7.68-7.81 (m, 4H), 7.95 (dt, 2H, J = 7.9Hz, J = 4.1Hz), 8.01-8.15 (m, 6H), 8.16-8.29 (m, 6H), 8.33 (d, br, 2H, ^{3}J = 6.8 Hz), 8.65 (d, br, 2H, ^{3}J = 7.9 Hz); ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ 14.4, 62.0, 122.9 (br), 123,4 (br), 124,3, 125.3, 128.2, 128.3 (br), 128.5 (br), 128.6, 130.4 (J=104Hz), 132.24, 132.28, 132.72, 132.84, 137.1, 137.2, 137.3, 137.83, 137.87, 148.0, 154.6, 154.8, 155.4, 155.6, 155.7, 156.4, 156.6, 165.2 (br); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 18.64, 18.76; IR (CH_2Cl_2, cm^{-1}): 2980 (w), 1740 (m), 1718 (s), 1576 (m), 1552 (m), 1429 (s), 1242 (m), 1199 (m), 1142 (s), 1107 (m), 1023 (m), 768 (m); MS (FAB$^+$): *m/z* = 857.2 ([M + H]$^+$, 100 %), 783.2 ([M - CO_2Et]$^+$, 35 %); Anal. Calcd for $C_{48}H_{38}N_6O_6P_2$: C 67.29, H 4.47, N 9.81. Found: C 66.94, H 4.18, N 9.79 %.

Compound 12 : A solution of **11** (170 mg, 148 μmol) and [$Pd(PPh_3)_2Cl_2$] (10.4 mg, 14.8 μmol) in a mixture of EtOH (15 mL) and Et_3N (15 mL) was heated at 70 °C for 22 h under a CO atmosphere. The resulting solution was evaporated to dryness, dissolved in CH_2Cl_2 (30 mL), filtered and washed with water (5 mL). After washing the aqueous layer with CH_2Cl_2 (15 mL), drying the combined organic layers ($MgSO_4$), filtration and evaporation to dryness, an orange residue is obtained which, after purification by column chromatography (Al_2O_3; CH_2Cl_2/MeOH : 100/0 to 98/2), gave **12** (136 mg, 80%) as an orange powder. R_f = 0.54,

Al_2O_3, CH_2Cl_2/MeOH: 97/3; ^{1}H-NMR. (300 MHz, $CDCl_3$): δ 1.45 (t, 6H, ^3J = 7.0 Hz), 4.47 (qd, 4H, ^3J = 7.0 Hz), 7.42-7.60 (m, 9H), 7.68-7.81 (m, 6H), 7.90-8.02 (m, 2H), 8.04-8.87 (m,18H), 8.65 (d, br, ^3J = 8.0Hz); $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ 14.7, 62.3, 123.1, 123.2, 123.7, 124.6, 125.6, 128.5, 128.6, 128.7, 128.8, 128.9, 130.7 (d, J_{PC} = 101 Hz), 132.6 (br), 133.0, 133.1, 137.35, 137.44, 137.6, 138.2, 148.3, 155.2, 155.7, 155.8, 155.9, 156.0, 156.4, 156.5,156.7, 165.5; ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 18.37, 18.43, 18.60, 18.68; IR (CH_2Cl_2, cm^{-1}): 2925 (s), 2853 (m), 1739 (s), 1720 (s), 1575 (s), 1428 (s), 1242 (m), 1201 (s), 1142 (s), 1107 (m), 743 (m); MS (FAB^+): *m/z* = 1135.2 ($[M + H]^+$, 100 %); Anal. Calcd for $C_{64}H_{49}N_8O_7P_3$: C 67.71, H 4.36, N 9.87. Found: C 67.68, H 4.25, N 9.73 %.

Compound 8: Compound **7** (44 mg, 0.051 mmol) in conc. HCl (6 mL) was heated at 75 °C for 20 h. After the mixture had cooled to r.t., the solvent was evaporated under reduced pressure. The solid was then dissolved in MeOH, precipitated with Et_2O and centrifugated to give **8** (38 mg, 83 %) as a dihydrochloride salt. ^{1}H-NMR (d_6-DMSO): δ 7.51-7.68 (m, 6H), 7.90-8.23 (m, 16H), 8.25-8.33 (m, 4H), 8.66 (d, 2H, br, ^3J = 8. 7Hz). ^{31}P NMR (162 MHz, d_6-DMSO): δ = 16.60, 16.76; IR (KBr, cm^{-1}): 3061 (w), 1719 (s, br), 1575 (m), 1553 (m), 1428 (s), 1352 (m), 1244 (m, br), 1186 (m), 1139 (s), 1106 (s), 1075 (m), 988 (w), 767 (m), 691 (s); MS (FAB^+): *m/z* = 801.2 ($[M + H]^+$, 100 %); Anal. Calcd for $C_{44}H_{30}N_6O_6P_2.2HCl.H_2O$: C 59.27, H 3.84, N 9.43 . Found: C 58.92, H 3.61, N 9.11 %.

Compound 13. A solution of compound **12** (60 mg, 52 μmol) and NaOH (9 mg, 0.22 mmol) in a mixture of EtOH (20 mL) and H_2O (10 mL) was heated at 80 °C for 39 h. After the mixture had cooled to r.t., the solvents were evaporated under reduced pressure. The solid was then dissolved in H_2O, precipitated with 2N HCl and centrifugated. The solid was then dissolved in MeOH and precipitated with Et_2O to give **13** (54 mg, 91%) as a pale yellow monohydrochloride salt. ^{1}H-NMR (400 MHz, CD_3OD): δ 7.40-7.75 (m, br, 10H), 7.75-8.45 (m, br, 25H), 8.46-8.85 (m, br, 3H); $^{13}C\{^1H\}$-NMR (100 MHz, CD_3OD): δ 124.3, 124.8 (br),

125.35, 125.42, 126.4 (br), 129.46, 129.54, 129.6, 129.8, 131.1 (br), 133.0, 133.1, 133.5, 133.6, 134.0, 138.9, 139.1 (br), 139.2, 139.5, 139.6, 139.7, 139.8, 148.8, 148.9 (br), 155.1 (br), 155.3 (br), 156.1 (br), 156.4, 156.6 (br), 156.7 (br), 156.9, 167.6, 167.7; ^{31}P-NMR (162 MHz, CD_3OD): δ 20.69, 20.78, 20.96, 21.12, 21.34; IR (KBr, cm^{-1}): 2920 (w), 1719 (s), 1575 (s), 1428 (s), 1249 (m), 1189 (s), 1141 (s), 1106 (s), 1078 (m), 988 (m), 769 (m), 742 (s), 693 (m); MS (FAB^+): *m/z* = 1079.2 ($[M]^+$, 50 %); Anal. Calcd for $C_{60}H_{41}N_8O_7P_3.HCl.H_2O$: C 63.58, H 3.91, N 9.89. Found: C 63.40, H 3.65, N 9.71 %.

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