Facile Ring-Opening Reactions of Phthalimides as a New Strategy to Synthesize Amide-Functionalized Phosphonates, Primary Phosphines, and Bisphosphines

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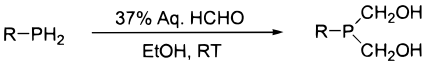
The nucleophile-assisted ring-opening reaction of phthalimides **1** has been studied. The reaction of phthalimides **1** with 0.5 equiv of hydrazine produced the novel bisphosphonates **2** in near quantitative yields whereas with 10-fold excess of hydrazine, diethyl aminoalkylphosphonates **3** was formed in 75% yields. The reaction of phthalimide **1b** with 3-(aminopropyl)phosphine resulted in a novel compound **4a** containing a P^{III} hydride and a P^{V} phosphonate within the same molecule. In addition, the reaction of **1b** with 2-aminoethanol and 2-aminoethanethiol resulted in the formation of new phosphonates **4b**,**c**. The reaction of bisphosphonates **2** with $LiAlH_4$ in THF at 0 °C selectively reduced the phosphonate groups producing corresponding air-stable primary bisphosphines **6** in 80% yields. Further, the formylation of bisphosphines **6** under very mild conditions using 37% aqueous formaldehyde produced the corresponding novel water-soluble bisphosphine chelating agents **7** in near quantitative yields. All the new compounds have been characterized by ^{1}H, ^{13}C, ^{31}P NMR, IR spectroscopy and mass spectrometry.

Introduction

Ligand design has gained considerable prominence in recent years. In particular, research in the design and development of ligands that produce water-soluble transition metal/organometallic compounds continues to attract considerable attention because of their potential applications in the fields of catalysis and biomedicine.[1−7] Of the various ligands available to produce aqueous soluble coordination compounds, functionalized phosphines are the most attractive class of ligands because of their versatile coordination chemistry.[3,8−10] The σ and π back-bonding interactions of phosphines with transition metals reinforce one another to produce strong metal−phosphorus bonds which are often stable even under the most stringent conditions. The water-soluble mono-, di-, or trisulfonated arylphosphines, such as P(*m*-$C_6H_4SO_3Na)_3$, have largely been employed in the development of highly active water-soluble transition metal catalysts.[2] However, hydrophilic alkyl phosphines are being highly sought after in order to gain specific structure−activity advantages both in catalytic and biomedical applications. In this context, the formylation reactions of P−H bonds, that produce hydroxymethyl-functionalized water-soluble phosphines, have been used as effective synthetic strategies for the development of water-soluble phosphine frameworks (Scheme 1).[3]

Scheme 1



Primary phosphines (RPH_2), especially alkyl phosphines, are, in general, air-sensitive compounds. Therefore, their backbone modification to afford new classes of alkyl-substituted phosphines are often challenging. Despite synthetic difficulties, primary phosphines are excellent precursors for reactions with many unsaturated systems. They undergo reactions with carbonyl groups, Michael acceptors, acid halides, alkyl halides, halogens, alkali metals, and Lewis acids (e.g., borane) to produce a variety of functionalized phosphines including chiral phosphines (as depicted in Scheme 2).[11−21] Therefore, new developments in organic chemistry leading to efficient

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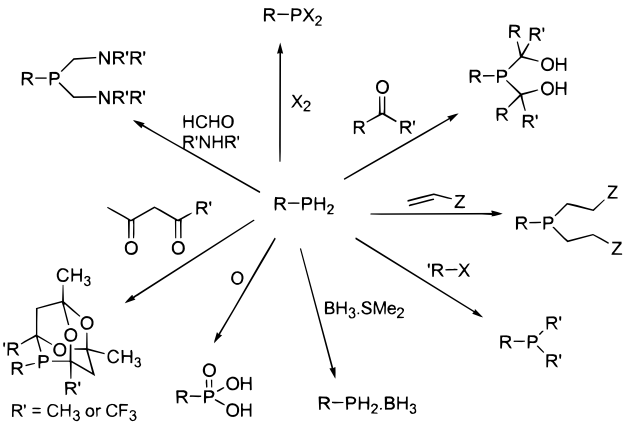
Scheme 2



synthetic strategies for producing alkyl primary phosphines using mild conditions will be of greater practical importance. We now report a facile synthetic strategy that utilizes the nucleophile-assisted ring-opening of phthalimides (Scheme 3). This methodology has resulted in the synthesis of novel chelating agents containing air-stable alkyl primary phosphines, bis-amido-functionalized phosphonates, and mixed phosphine−phosphonates in good yields (Scheme 3). In addition, a formylation reaction of new primary phosphines to produce functionalized water-soluble phosphine ligands is also described.

Results and Discussion

Commercially available *N*-(bromoalkyl)phthalimides were converted to phthalimides **1** in near quantitative yields utilizing the well-known Michaelis−Arbuzov reaction by refluxing with 5-fold excess of triethyl phosphite for 12 h (Scheme 3).[22] Treatment of phthalimides **1** with 0.5 equiv of hydrazine in ethanol at room temperature for 12 h produced ring-opened bisphosphonates **2,** in near quantitative yields. Whereas, the treatment of **1** with 10-fold excess of hydrazine resulted in diethyl aminoalkylphosphonates **3** exclusively, via the well-known Gabriel synthetic pathway,[23] in 75% yields (Scheme 3). The former products **2** were formed as a result of ring-opening of phthalimide by in situ generated nucleophiles **3**. When phthalimide **1** was treated with 0.5 equiv of hydrazine, only 50% of **1** reacted to produce **3**, and in turn, **3** further reacted with the remaining 50% of **1** to produce the novel ring-opened product **2**. To confirm the mechanism involved in the formation of bisphosphonate **2**, the stoichiometric reaction of compounds **1** with **3** under similar experimental conditions produced bisphosphonates **2** in near quantitative yields. Similar nucleophilic ring-opening reaction of *N*-methylphthalimide with ethylenediamine, to produce an adduct containing two units of *N*-methylphthalimide and one unit of ethylenediamine (*N*,*N*′-(*N*,*N*′-dimethyl)-diphthalamidoethane), was reported by Wolfe and co-workers.[24] However, to date, there is no literature precedence of similar reactions for the synthesis of phosphorus-containing ligands.

The generality of the nucleophile-assisted ring-opening reaction of phthalimide **1b** was tested by subjecting it to interact with 2-aminoethanol and 2-aminoethanethiol (Scheme 3). These reactions produced the corresponding phosphonates **4b**,**c** in near quantitative yields. The scope of this nucleophile-assisted ring opening was further tested by interacting (3-aminopropyl)phosphine with **1b**. This reaction produced the first example of phosphine-containing phosphonate **4a**, in 88% yield. It may be noted that compounds with combination of P^V phosphonates and P^{III} tertiary phosphines have been reported in the literature.[25−28] The proton-coupled phosphorus NMR of **4a** (Supporting Information) clearly shows the presence of a P^{III} center (−135.1 ppm, J_{P-H} = 196 Hz) and P^V center (+34.3 ppm) within the same molecule. Compound **4a** exemplifies the importance of "s" character of phosphorus center on the magnitude of phosphorus−carbon coupling constant across one bond. For example, the primary phosphine is expected to exhibit lower s character as compared to the phosphonate P^V in **4a**. Therefore, in the ^{13}C NMR spectrum of compound **4a**, P−C coupling was not observed for α-C to PH_2. However, α-C to $P(O)(OEt)_2$ showed a P−C coupling of 140.6 Hz. Compound **4a** is unique in that it provides an example of organophosphorus compound wherein P^{III} hydride and P^V phosphonate functionalities coexist within the same molecule. Compounds that contain disparate three and five oxidation state phosphorus centers are difficult to synthesize using traditional synthetic methods. In this context, the ease with which **4a** is produced, via the reaction summarized in Scheme 3, provides a novel pathway for the development of hetero oxidation state organophosphorus compounds. All new compounds were characterized by ^1H, ^{13}C, ^{31}P NMR spectroscopy and mass spectrometric methods.

It is interesting to note that reduction of bisphosphonates **2** with $LiAlH_4$ in dry THF at 0 °C (Scheme 4) was selective in terms of reducing only phosphonates, although amide groups are susceptible for reduction under these conditions. The novel bisphosphines **6** were obtained in 80% yield, as air-stable, pale yellow solids. The formation of bisphosphines **6** was confirmed by ^1H, ^{13}C, ^{31}P NMR and IR spectroscopic and high-resolution mass spectrometric methods. The characteristic triplet splitting of the peak at −146.7 ppm (with J_{P-H} = 195.6 Hz) in the proton-coupled ^{31}P NMR spectrum of **6a** indicates the presence of two protons attached to the phosphorus center (Supporting Information). It is inter-

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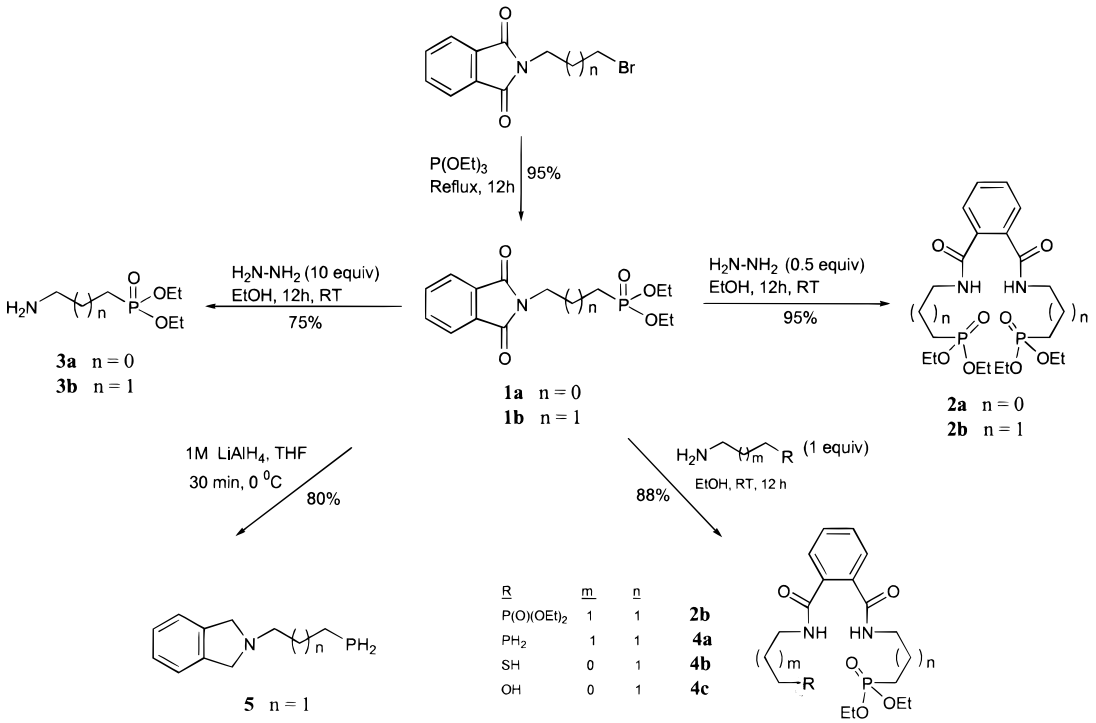
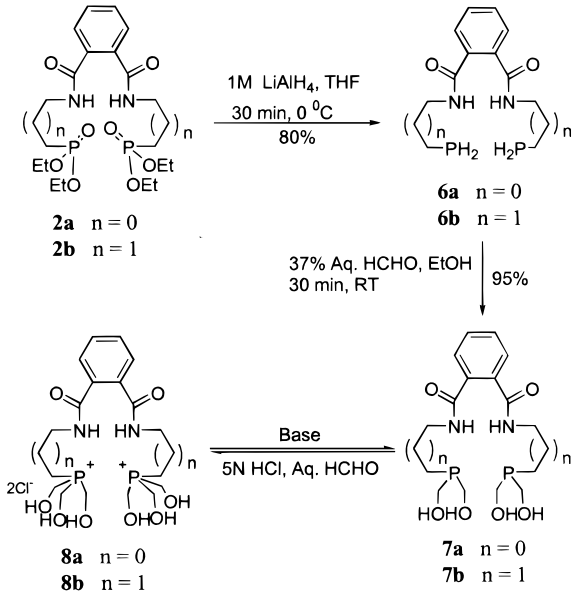
Scheme 3



esting to note that ^{31}P NMR parameters of **6a** are comparable with that of a simple primary phosphine compound $H_2P-CH_2-CO-NH-Ph$ (−144.5 ppm, J_{P-H} = 198 Hz) reported by Issleib and co-workers.[29] It is also important to recognize that the amide function in **6a** is four bonds away from PH_2 whereas it is disposed across two bonds in $H_2P-CH_2-CO-NH-Ph$. The presence of $-PH_2$ groups in **6** was further confirmed by the observation of characteristic band at 2282 cm^{-1} attributed to the P−H stretch in the IR spectra. The peak at 169.1 ppm in the ^{13}C NMR spectrum of **6a** (and a band at 1632 cm^{-1} in the IR spectrum) clearly indicated the presence of amide C═O group. The ^{13}C NMR resonance due to α-C (to PH_2) in **6a** was observed at 14.6 ppm (J_{P-C} = 10.5 Hz) and is comparable with the reported spectral data by Issleib and co-workers for a series of *N*-substituted (2-aminoethyl)phosphines.[30] It may be noted that in the propyl analogue, **6b**, P−C coupling was not observed for α-C to PH_2. Compounds **6** represent rare examples of primary alkyl phosphines with unusual stability toward air-oxidation.[3c,7,31] Recently Goodwin et al. and Brynda et al. have also reported high oxidative stability to primary phosphines functionalized with bulky substituents.[32−34]

The reduction reaction of compound **1b** with $LiAlH_4$ under similar experimental conditions produced the primary phosphine **5**, in which both imide and phosphonate groups were reduced (Scheme 3). The primary phosphine **5** is an air-stable white crystalline solid, which was

Scheme 4



purified on a silica gel column. The triplet splitting in proton-coupled ^{31}P NMR spectrum (134.8 ppm, J_{P-H} = 192.4 Hz) of **5** was found to be in accordance with that of [3-(*N*,*N*′-dimethylamino)propyl]phosphine (−138.9 ppm, J_{P-H} = 193.7 Hz) reported by Stelzer et al.[35] The reduction of the imide groups in **5** is, presumably, due to the general tendency of imides to be more susceptible for reduction than amides.

Furthermore, bisphosphines **6** were formylated by using 37% aqueous formaldehyde in ethanol at room temperature to produce the novel water-soluble hydroxymethyl-functionalized bisphosphines **7** in almost quantitative yields. The bisphosphines **7** were found to

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be oxidatively stable in aqueous solutions. These water-soluble phosphines can be conveniently stored over prolonged periods by conversion to stable phosphonium salts **8** via treatment with excess of formaldehyde and hydrochloric acid (Scheme 4). Phosphonium salts **8** can be easily converted back into (hydroxymethyl)phosphines **7** by titration with equivalent amounts of base such as sodium bicarbonate buffer (Scheme 4).

In summary, the results outlined in this report demonstrate the synthetic utility of the nucleophile-mediated ring-opening of phthalimides **1**. The methodology described, herein, can be used in the design and development of hitherto unknown amide-functionalized novel phosphonates and phosphines.

Experimental Section

All chemicals were purchased either from Aldrich Chemical Co. or Fisher Scientifics and used as received except tetrahydrofuran, which was distilled over sodium and benzophenone prior to use. 3-Aminopropylphosphine was prepared by a procedure reported in the literature.[36] Mass spectral analyses were performed by the Washington University Resource for Biomedical and Bio-Organic Mass Spectometry, St. Louis, MO.

[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)ethyl]phosphonic Acid Diethyl Ester (1a). *N*-(2-Bromoethyl)phthalimide (20.0 g, 79.05 mmol) was added to triethyl phosphite (65.6 g, 395.25 mmol) slowly at room temperature. The reaction mixture was refluxed for 12 h. The volatile compounds were distilled out under reduced pressure (3 mmHg) at 60 °C. The crude product was dissolved in 50% aqueous ethanol and the precipitate, unreacted *N*-(2-bromoethyl)phthalimide, was filtered. The removal of solvents from the filtrate gave pure phosphonate **1a** (15.5 g, 63%) as a pale yellow viscous oil. The ^{1}H NMR spectrum matched the published spectrum.[37] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84−7.68 (m, 4H), 4.13−4.03 (m, 4H), 3.98−3.89 (m, 2H), 2.24−2.13 (m, 2H), 1.29−1.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 133.3, 131.1, 122.4, 61.0, 31.3, 24.0 (d, J_{P-C} = 139.3 Hz), 15.5; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 28.9; LRFABMS *m*/*z* 312 (M^+ + 1). Anal. Calcd for $C_{14}H_{18}NO_5P$: C, 54.02; H, 5.83; N, 4.50. Found: C, 54.16; H, 5.89; N, 4.52.

[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)propyl]phosphonic Acid Diethyl Ester (1b). *N*-(3-Bromopropyl)phthalimide (10 g, 37.45 mmol) was added to triethyl phosphite (31 g, 187.26 mmol) slowly at room temperature. The reaction mixture was refluxed for 12 h, and then excess triethyl phosphite and other volatile compounds were distilled out under reduced pressure (3 mmHg) at 60 °C. The pure phosphonate **1b** (11.6 g, 95%) was obtained as a pale yellow viscous oil. The ^{1}H NMR spectrum matched the published spectrum.[37] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 2.21 Hz, 2H), 7.51 (d, J = 3.11 Hz, 2H), 3.85 (q, J = 5.60 Hz, 4H), 3.51 (t, J = 6.65 Hz, 2H), 1.77−1.62 (m, 2H), 1.59−1.51 (m, 2H), 1.08 (t, J = 6.96 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 133.5, 131.4, 122.6, 61.0, 37.6 (d, J_{P-C} = 19.4 Hz), 22.8 (d, J_{P-C} = 142.0 Hz), 21.4, 15.9; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 33.2; LRFABMS *m*/*z* 326 (M^+ + 1). Anal. Calcd for $C_{15}H_{20}NO_5P$: C, 55.38; H, 6.20; N, 4.31. Found: C, 55.31; H, 6.32; N, 4.43.

(2-{2-[2-(Diethoxyphosphoryl)ethylcarbamoyl]benzoylamino}ethyl)phosphonic Acid Diethyl Ester (2a). Anhydrous hydrazine (530 mg, 16.5 mmol) was added dropwise to a solution of phthalimide **1a** (10.03 g, 32.15 mmol) in ethanol (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The precipitated phthalyl hydrazide was filtered, and the solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column using a gradient of chloroform/methanol. The pure product was obtained by elution with a solvent system consisting of 10% methanol in chloroform. Evaporation of the solvent produced bisphosphonate **2a** (7.5 g, 95%) as a yellow viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.42 (m, 4H), 4.17−4.06 (m, 8H), 3.71−3.59 (m, 4H), 2.13−2.02 (m, 4H), 1.34 (t, J = 7.06 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 134.8, 129.7, 127.8, 61.4, 33.8, 25.1 (d, J_{P-C} = 137.9 Hz), 16.1; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 30.4; HRFABMS calcd for $C_{20}H_{34}N_2O_8P_2$ = 493.2425, found = 493.2422 (M^+ + 1). Anal. Calcd for $C_{20}H_{34}N_2O_8P_2$: C, 48.78; H, 6.96; N, 5.69. Found C, 48.87; H, 7.12; N, 6.86.

(3-{2-[3-(Diethoxyphosphoryl)propylcarbamoyl]benzoylamino}propyl)phosphonic acid diethyl ester (2b): pale yellow oil; yield 94%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91−7.87 (m, 2H), 7.38−7.36 (m, 2H), 3.94−3.84 (m, 8H), 3.26−3.19 (m, 4H), 1.65−1.42 (m, 8H), 1.16 (t, J = 7.04 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 134.6, 129.4, 128.0, 61.2, 39.8 (d, J_{P-C} = 17.9 Hz), 22.7 (d, J_{P-C} = 140.9 Hz), 22.1, 16.0; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 33.0; HRFABMS calcd for $C_{22}H_{38}N_2O_8P_2$ = 521.2182, found = 521.2178 (M^+ + 1). Anal. Calcd for $C_{22}H_{38}N_2O_8P_2$: C, 50.77; H, 7.36; N, 5.38. Found C, 50.93; H, 7.55; N, 5.53.

(2-Aminoethyl)phosphonic Acid Diethyl Ester (3a). Anhydrous hydrazine (10.24 g, 320 mmol) was added dropwise to a solution of phthalimide **1a** (9.98 g, 32 mmol) in ethanol (500 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The precipitated phthalyl hydrazide solid was filtered, and the solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column under nitrogen using a gradient of $CHCl_3$/MeOH (9:1). Evaporation of the solvent produced **3a** (4.3 g, 75%) as a pale-yellow liquid. The spectral data matched with the literature data.[38] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.12 (bs, 2H), 4.18−4.06 (m, 4H), 3.06−2.96 (m, 2H), 2.03−1.88 (m, 2H), 1.33 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.0, 35.5, 29.0 (d, J_{P-C} = 137.0 Hz), 15.8; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 32.2; Electronspray-MS *m*/*z* 182.2 (M^+ + 1).

(3-Aminopropyl)phosphonic Acid Diethyl Ester (3b). The spectral data matched with the literature data:[38] pale yellow liquid; yield 76%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.15−4.06 (m, 4H), 3.52 (bs, 2H), 2.86 (t, J = 6.0 Hz, 2H), 1.85−1.79 (m, 4H), 1.33 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) 60.6 (d, J_{P-C} = 5.4 Hz), 41.7 (d, J_{P-C} = 17.2 Hz), 25.6 (d, J_{P-C} = 4.2 Hz), 22.1 (d, J_{P-C} = 140.7 Hz), 15.7 (d, J_{P-C} = 5.3 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 34.0; Electronspray-MS *m*/*z* 196.1 (M^+ + 1).

{3-[2-(3-Phosphanylpropylcarbamoyl)benzoylamino]propyl}phosphonic Acid Diethyl Ester (4a). A solution of (3-aminopropyl)phosphine (280 mg, 3.0 mmol) in ethanol (5 mL) was added dropwise to a solution of compound **1b** (975 mg, 3.0 mmol) in ethanol (10 mL) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 12 h, and then solvent was removed under reduced pressure. The crude product **4a** was chromatographed on a silica gel column under nitrogen using a gradient of chloroform/methanol (19:5) to afford the pure product **4a** (1.1 g, 88%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57−7.28 (m, 4H), 4.04 (m, 4H), 3.43 (t, J = 6.24, 4H), 2.72 (dt, J_{P-H} = 194.75 Hz, J_{H-H} = 7.33 Hz, 2H), 1.90−1.69 (m, 6H), 1.65−1.50 (m, 2H), 1.29 (t, J = 7.00 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 168.6, 134.4, 129.0, 127.6, 127.4, 61.0, 39.6 (singlet merged with doublet, $^3J_{P-C}$ = 21.27 Hz), 32.0, 22.3 (d, $^1J_{P-C}$ = 140.6 Hz), 21.8, 15.9, 10.6; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 34.3, −135.1; Proton-coupled ^{31}P NMR ($CDCl_3$, 121 MHz) δ 34.3, −135.1 (t, J_{P-H} = 196.02 Hz); HRFABMS calcd for $C_{18}H_{30}N_2O_5P_2$ 417.1708, found 417.1719 $(M + 1)^+$.

{3-[2-(2-Mercaptoethylcarbamoyl)benzoylamino]propyl}phosphonic acid diethyl ester (4b): colorless solid; yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.26 (m, 4H), 3.98−3.86 (m, 4H), 3.58−3.48 (m, 2H), 3.27−3.18 (m, 2H), 2.80 (t, J = 6.42 Hz, 2H), 1.73−1.58 (m, 4H), 1.19 (t, J = 7.06); ^{13}C

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NMR ($CDCl_3$, 75 MHz) δ 168.2, 134.8, 134.4, 129.5, 127.8, 61.3, 39.83 (d, $J_{P-C} = 17.6$ Hz), 38.7, 37.2, 22.4 (d, $J_{P-C} = 140.9$ Hz), 21.9, 16.1; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 34.4; HRFABMS calcd for $C_{17}H_{27}N_2O_5PS$ 403.1456, found 403.1459 $(M + 1)^+$.

{**3-[2-(2-Hydroxyethylcarbamoyl)benzoylamino]-propyl}phosphonic acid diethyl ester (4c):** colorless solid; yield 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68−7.41 (m, 4H), 4.15−4.03 (m, 4H), 3.79−3.68 (m, 2H), 3.59−3.38 (m, 4H), 1.92−1.72 (m, 4H), 1.31 (t, $J = 7.03$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 169.2, 135.5, 134.8, 129.9, 129.6, 127.9, 127.8, 61.6, 60.7, 42.8, 39.8 (d, $J_{P-C} = 7.6$ Hz), 22.7 (d, $J_{P-C} = 139.9$ Hz), 22.2, 16.2; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 34.4; HRFABMS calcd for $C_{17}H_{27}N_2O_6P$ 387.1685, found 387.1692 $(M + 1)^+$.

2-(3-Phosphanylpropyl)-2,3-dihydro-1*H*-isoindole (5). Phthalimide **1b** (5 g, 15.38 mmol) was dissolved in dry THF (100 mL) and cooled to 0 °C, and 1 M $LiAlH_4$ in THF (46 mL, 46 mmol) was added dropwise. After stirring at 0 °C for 30 min, the reaction mixture was diluted with THF (200 mL) and quenched with a saturated solution of Na_2SO_4 (5 mL). The organic layer was passed through a pad of silica gel, and the solvent was removed under reduced pressure to give the phosphine **5**. The crude product was chromatographed on a silica gel column under nitrogen using a gradient of hexane/ethyl acetate (3:2). The pure product was obtained as a white solid (2.4 g, 81%) by elution with a solvent system consisting of 40% ethyl acetate in hexane. IR (KBr): $\nu = 2283$ (P−H) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.21 (s, 4H), 3.99 (s, 4H), 2.82 (t, $J_{H-H} = 7.4$ Hz, 2H) 2.76 (dt, $J_{P-H} = 194.8$ Hz, $J_{H-H} = 7.4$ Hz, 2H), 1.85−1.80 (m, 2H), 1.65−1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.7, 126.7, 121.7, 58.3, 55.6, 31.0, 10.9; ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ −134.8 (s); ^{31}P NMR (proton coupled, $CDCl_3$, 121.5 MHz) δ −134.8 (t, $J_{P-H} = 192.4$ Hz). HRFABMS calcd for $C_{11}H_{16}NP$ calcd for 194.1281, found 194.1286 $(M^+ + 1)$.

***N,N′*-Bis(2-phosphanylethyl)phthalamide (6a).** Bisphosphonate **2a** (4.92 g, 10 mmol) was dissolved in dry tetrahydrofuran (100 mL) and cooled to 0 °C. A solution of 1 M $LiAlH_4$ in THF (30 mL, 30 mmol) was added dropwise via a syringe under N_2. After stirring at 0 °C for 30 min, the reaction mixture was diluted with THF (200 mL). Then, a saturated solution of Na_2SO_4 (5 mL) was added at 0 °C to quench the excess $LiAlH_4$. The organic layer was passed through a pad of silica gel and the THF removed under reduced pressure at room temperature to give the pure diphosphine **6a** (2.3 g, 80%) as a pale yellow powder, which was used without any further purification. IR (KBr): $\nu = 2282$ (P−H), 1632 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.53−7.20 (m, 4H), 3.54−3.46 (m, 4H), 2.68 (dt, $J_{P-H} = 195.4$ Hz, $J_{H-H} = 7.8$ Hz, 4H), 1.80−1.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 169.1, 134.3, 130.2, 128.3, 42.9, 14.6 (d, $J_{P-C} = 10.5$ Hz); ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ −146.7; ^{31}P NMR (proton coupled, $CDCl_3$, 121.5 MHz) δ −146.7 (t, $J_{P-H} = 195.6$ Hz); HRFABMS calcd for $C_{12}H_{18}N_2O_2P_2$ 285.2337, found 285.2339 $(M^+ + 1)$.

***N,N′*-Bis(3-phosphanylpropyl)phthalamide (6b):** pale yellow powder; yield 81%; IR (KBr): $\nu = 2280$ (P−H), 1634 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.54−7.18 (m, 4H), 3.61−3.49 (m, 4H), 2.69 (dt, $J_{P-H} = 193.4$ Hz, $J_{H-H} = 7.7$ Hz, 4H), 2.01−1.69 (m, 8H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 169.4, 134.4, 129.63, 127.7, 40.1, 32.2, 10.9; ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ −135.64; ^{31}P NMR (proton coupled, $CDCl_3$, 121.5 MHz) δ −135.64 (t, $J_{P-H} = 193.3$ Hz); HRFABMS calcd for $C_{14}H_{22}N_2O_2P_2$ 313.2874, found 313.2871 $(M^+ + 1)$.

***N,N′*-Bis-[2-(bis(hydroxymethyl)phosphanyl)ethyl]-phthalamide (7a)**. The bisphosphine **5a** (2.28 g, 8.0 mmol) was dissolved in degassed ethanol (15 mL). A solution of 37% aqueous formaldehyde (2.6 mL, 32.0 mmol) was added, and the mixture was stirred for 30 min under N_2 at room temperature. The solvent was removed under reduced pressure to give the pure (hydroxymethyl)phosphine **7a**. ^{31}P NMR ($CDCl_3$): $\delta = -23.3$. For characterization purposes, the (hydroxymethyl)-phosphine **7a** was converted to (hydroxymethyl)phosphonium salt **8a** by adding excess of aqueous formaldehyde and 5 N hydrochloric acid in ethanol. After removing the solvent, the product was purified on a reverse phase Sep-Pak C-18 column using water−methanol gradient (1:1). Removal of the solvent in vacuo afforded pure phosphonium salt **8a** (4.08 g, 95%) as a colorless viscous oil. ^{1}H NMR (D_2O, 300.1 MHz) δ 7.52−7.47 (m, 4H), 4.67−4.57 (m, 12H), 4.81−4.65(m, 4H), 2.82−2.58 (m, 4H); ^{13}C NMR (D_2O, 75.5 MHz) δ: 171.3, 133.9, 131.3, 127.9, 50.3 (d, $J = 53.5$ Hz), 32.8, 14.4 (d, $J = 36.8$ Hz); ^{31}P NMR (D_2O, 121.5 MHz) δ 29.3; HRFABMS calcd for $C_{18}H_{32}N_2O_8P_2$ 233.2176, found 233.2167 (M^{2+}).

***N,N′*-Bis[3-(bis(hydroxymethyl)phosphanyl)propyl]-phthalamide (7b).** For characterization purposes, the (hydroxymethyl)phosphine **7b** was converted to (hydroxymethyl)-phosphonium salt **8b**: colorless oil; yield 94%; ^{1}H NMR (D_2O, 300.1 MHz) δ 7.54−7.48 (m, 4H), 4.52−4.48 (m, 12H), 4.81−4.65(m, 4H), 2.97−2.49 (m, 8H); ^{13}C NMR (D_2O, 75.5 MHz) δ 171.7, 134.3, 131.3, 127.1, 50.4 (d, $J = 53.2$ Hz), 40.4 (d, $J = 15.8$ Hz), 30.0, 11.6 (d, $J = 36.8$ Hz); ^{31}P NMR (D_2O, 121.5 MHz) δ 29.9; HRFABMS calcd for $C_{20}H_{36}N_2O_8P_2$ 247.2285, found 247.2291 (M^{2+}).

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Supporting Information Available: ^{13}C and ^{31}P NMR spectra of compounds **2**−**6** and **8**, proton-coupled ^{31}P NMR spectra of compounds **4a**, **5**, and **6a**, and the IR spectrum of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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