Synthesis of Bispyrrolidines by Radical Cyclisation of Diallylamines Using Phosphorus Hydrides

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Dedicated to Professor Sir Jack Baldwin F. R. S. on the occasion of his 70th birthday

Abstract: Sequential radical addition–cyclisation reactions of diallylamines using either hypophosphorous acid or a bisphosphinothioate are shown to afford bispyrrolidines in good to excellent yields.

Key words: addition reactions, cyclisations, phosphorus, radical reactions

Bispyrrolidines are an interesting family of compounds and their synthesis has attracted considerable interest. A small number of natural alkaloids are bispyrrolidines,[1] whereas synthetic bispyrrolidines have been investigated as potential anticancer agents,[2] antiarrhythmic agents,[3] complexing agents for metals[4] and as ligands, such as bisphosphoramide **1**, for use in synthesis (Figure 1).[5]

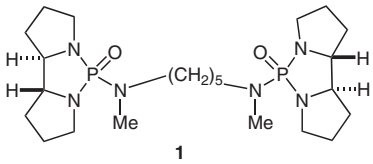
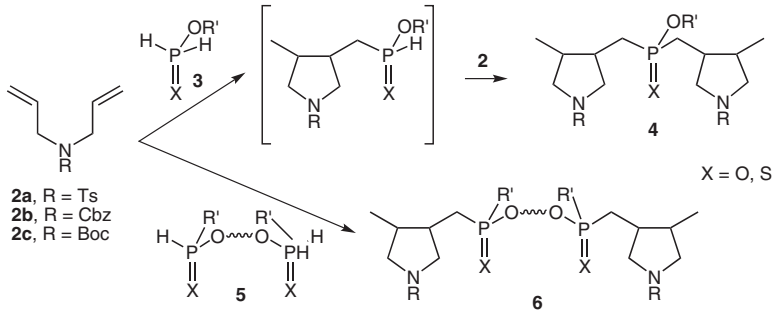


Figure 1

With the aim of developing a new, concise, general and mild synthetic route to bispyrrolidines, with phosphorus-containing groups linking the two rings, the radical cyclisation of diallylamines was investigated using various phosphorus hydrides (Scheme 1).[6] Previous studies in our group have shown, for example, that N-benzoylated diallylamines are efficiently cyclised to give pyrrolidines on reaction with $(EtO)_2P(O)H$, $(EtO)_2P(S)H$ or $Ph_2P(O)H$, and a radical initiator.[6b] To apply the radical cyclisation of diallylamines **2** to the synthesis of bispyrrolidines of type **4** and **6**, we report herein novel radical cyclisation reactions using compounds containing two P–H bonds; either a hypophosphorous acid derivative of type **3** or a bisphosphorus hydride of type **5**.

Preliminary studies concentrated on the reaction of 1 equivalent of hypophosphorous acid, H_3PO_2, with 2.3 equivalents of diallylamine **2a** or **2b** using AIBN as the initiator (Scheme 2). Pleasingly, both reactions gave the desired bispyrrolidine phosphinic acids, either **8a** or **8b**, which, following column chromatography, were isolated in excellent yields as mixtures of inseparable isomers (the ratio of pyrrolidine rings with *cis* vs. *trans* stereochemistry was calculated from the ^1H NMR spectra).[7,8] Similar yields of **8a** and **8b** were obtained when the reactions were carried out at room temperature, in the absence of THF, using Et_3B and O_2 as the initiator.

Previous work on the double radical addition of H_3PO_2 or sodium hypophosphite (H_2PO_2Na) to C=C bonds has shown how the ratio of reactants can influence the yields of products formed from mono- or diaddition.[9] As predicted from this work, increasing the number of equivalents of H_3PO_2 to the diallylamine resulted in the isolation of the intermediate phosphinic acid (**7a**,**b**). For example, heating ten equivalents of H_3PO_2 with one equivalent of diallyl-



Scheme 1

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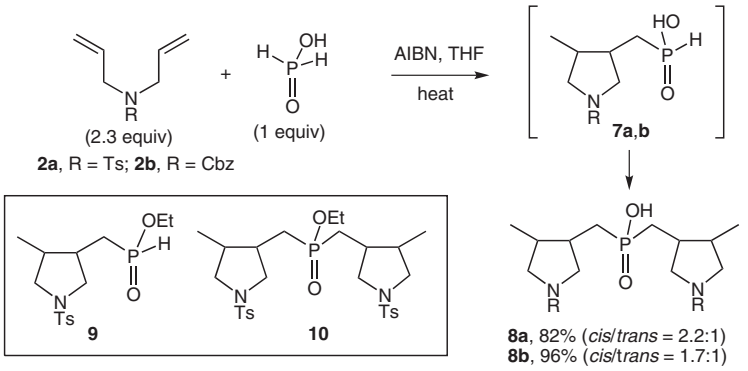


Scheme 2

amine **2a** and AIBN in THF, followed by esterification of the phosphinic acids (to aid product isolation/purification) using EtOCOCl and Et_3N,[10] gave monosubstituted phosphinate **9** in 31% yield (*cis*/*trans* = 3.2:1) and disubstituted phosphinate **10** in only 14% yield (*cis*/*trans* = 1.7:1) after chromatography. Similarly, when ten equivalents of H_3PO_2 were treated with one equivalent of diallylamine **2a** and Et_3B[11] at room temperature (in the absence of a solvent), followed by reaction with EtOCOCl and Et_3N, phosphinate **9** was isolated in 41% yield (*cis*/*trans* = 2.8:1) and phosphinate **10** in only 6% yield (*cis*/*trans* = 1.4:1).

An alternative one-pot synthesis of phosphinates **9** and **10** was also developed whereby esterification of H_3PO_2, followed by radical cyclisation, was combined in the same reaction pot. Hence, H_3PO_2 (10 equiv) was heated with diethoxy dimethylsilane, $(EtO)_2SiMe_2$ (15 equiv),[12] in THF. After heating for two hours, the crude solution of ethyl phosphinate, $H_2PO(OEt)$, was cooled to room temperature and diallylamine **2a** (1 equiv) and Et_3B added. Following workup and chromatography, phosphinate **9** was isolated in 43% yield (*cis*/*trans* = 1.6:1) and disubstituted phosphinate **10** in 22% yield (*cis*/*trans* = 3.2:1). It is noted that the reaction of phosphinates, such as $H_2PO(OEt)$, with two C=C bonds, to form disubstituted products, has been described as being generally inefficient and low-yielding.[6l]

In a related one-pot approach, reaction of H_3PO_2 (1 equiv) with triethyl orthoformate, $(EtO)_3CH$ (2 equiv), in THF–toluene at room temperature for two hours,[13] was used to form $H_2PO(OEt)$, which was immediately reacted with diallylamine **2a** (4 equiv) and Et_3B. Following workup and chromatography, disubstituted phosphinate **10** was isolated in 18% yield (*cis*/*trans* = 4.3:1) – the only other product isolated was phosphinate **11a** in 22% yield (*cis*/*trans* = 1.6:1; Figure 2). Similar results were obtained using diallylamines containing *N*-Cbz (**2b**) or *N*-Boc (**2c**) protecting groups.

The formation of phosphinate **11a** is presumably explained by the formation and subsequent radical addition reaction of ethyl (diethoxymethyl)phosphinate (**12a**). Indeed, esterification of H_3PO_2 using $(EtO)_3CH$ in the presence of PTSA at room temperature, under conditions

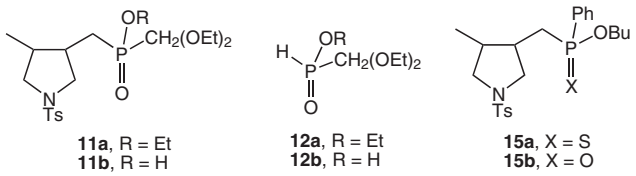
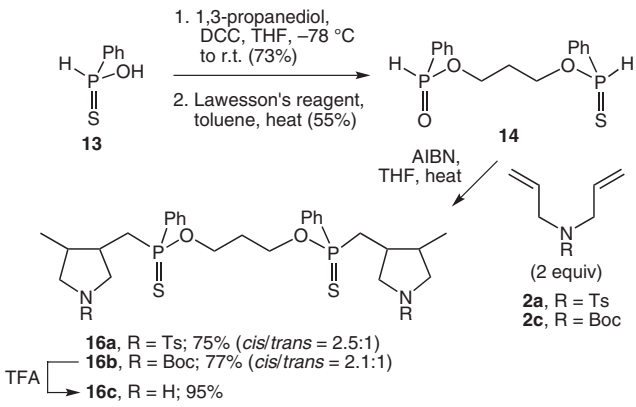


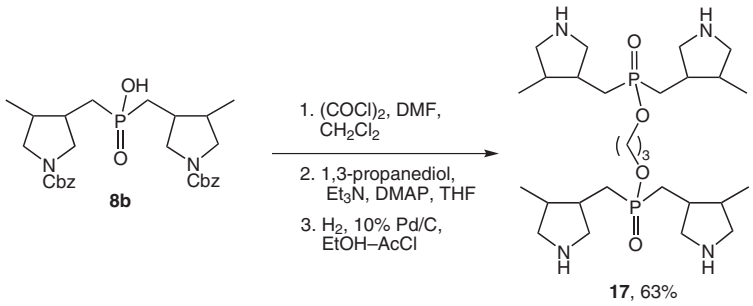
Figure 2



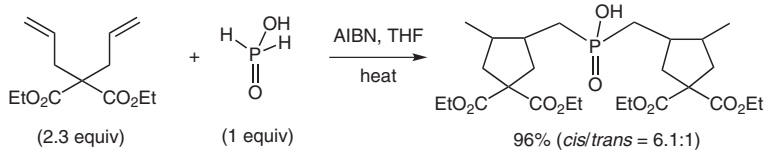
Scheme 3

known to efficiently form **12a** (10 equiv),[14] followed by addition of diallylamine **2a** (1 equiv) and Et_3B gave phosphinate **11a** in an excellent 90% yield (*cis*/*trans* = 5.3:1). Similarly, reaction of **2a** (1 equiv) with phosphinic acid **12b** (1.5 equiv) and Et_3B in THF gave **11b** in an excellent 91% yield (*cis*/*trans* = 4.6:1).

Our attention then moved to the preparation and radical reactions of bisphosphorus hydrides of type **5** (Scheme 1). Hence, novel racemic bisphosphorus hydride **14** was formed using a DCC-promoted coupling between phenylphosphinic acid **13** (2.1 equiv) and 1,3-propanediol (2 equiv) followed by thionation using Lawesson's reagent (Scheme 3). Conversion of the P=O bonds to P=S bonds was expected to weaken the adjacent P–H bonds,[6a,15] thereby producing a more efficient hydrogen-atom donor, that would react more effectively with a diallylamine. This proposed change in reactivity was supported by the results from a model study. When *O*-butyl phenylphosphinothioate, Ph(BuO)P(S)H (1.3 equiv), was heated with **2a** (1 equiv) and AIBN in THF this gave phosphinothioate



Scheme 4



Scheme 5

15a in an excellent 83% yield (*cis*/*trans* = 3:1; Figure 2). In comparison, when butyl phenylphosphinate, Ph(BuO)P(O)H, (1.3 equiv) was treated with **2a** under the same conditions, phosphinate **15b** was isolated in only 47% yield (*cis*/*trans* = 3.5:1). Even when using five equivalents of Ph(BuO)P(O)H to one equivalent of **2a** (under the same conditions), phosphinate **15b** was only isolated in 72% yield.

Gratifyingly, heating bisphosphinothioate **14** (1 equiv) with **2a** (2 equiv) and AIBN in THF gave bispyrrolidine **16a** in 75% yield, as a mixture of diastereomers (*cis*/*trans* = 2.5:1) after chromatography (Scheme 3).[16] Similarly, reaction of **14** (1 equiv) with **2c** (2 equiv) and AIBN, under the same reaction conditions, gave **16b** in 77% yield (*cis*/*trans* = 2.1:1). Surprisingly, no monopyrrolidine adduct could be detected from either of the radical reactions. Biscarbamate **16b** was subsequently deprotected using TFA in CH_2Cl_2 (0 °C to r.t.), to afford the corresponding bispyrrolidine **16c**, in 95% yield.

The bispyrrolidines prepared in this work are useful building blocks for the synthesis of oligopyrrolidines, which are of interest as RNA-binding agents and also, as subunits in artificial anion channels.[17] For example, reaction of **8b** with oxalyl chloride forms an intermediate phosphinyl chloride, which on treatment with 1,3-propanediol followed by N-deprotection gives tetrapyrrolidine **17** (Scheme 4).

In summary, we have developed new and efficient approaches to bispyrrolidines of type **4** and **6**, using radical addition–cyclisations of diallylamines promoted by hypophosphorous acid or a bisphosphinothioate. Using phosphorus hydrides in radical cyclisations of dienes offers an attractive alternative to traditional approaches (e.g., using toxic metal hydrides, such as Bu_3SnH) and the use of sequential cyclisations may find application in the preparation of target molecules with alternative ring systems, as illustrated in Scheme 5.

Acknowledgment

We thank Dr. Alastair Marrion for his time, expertise, and the helpful discussions during the course of the project. We thank the University of York for funding.

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(7) All new compounds gave spectroscopic data and high-resolution mass spectrometric data consistent with their assigned structure.

(8) **Bis({4-methyl-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinyl}methyl)phosphinic Acid (8a)**
A boiling solution of *N*,*N*-diallyl-4-methylbenzenesulfonamide (**2a**, 0.613 g, 2.439 mmol) and hypophosphorous acid (0.070 g, 1.061 mmol), in anhyd THF (5 mL) was treated with AIBN (4 × 0.087 g, 4 × 0.531 mmol) over 36 h. After cooling to r.t., brine (20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined layers were dried ($MgSO_4$), concentrated (under reduced pressure), and column chromatography [SiO_2, PE–EtOAc (4:6) to EtOAc–MeOH (1:1)] gave phosphinic acid **8a** (0.495 g, 82%) as an inseparable mixture of isomers, with a *cis*/*trans* ratio of 2.2:1 (from the ^{1}H NMR spectrum); white solid; mp 118–127 °C. IR (CH_2Cl_2): ν_{max} = 3541, 3058, 2964, 2882, 1598, 1479, 1454, 1406, 1384, 1337, 1160, 1093, 1044, 955 cm^{-1}.
cis-Diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 4 H, 4 × SCC*H*, arom), 7.43–7.38 (m, 4 H, 4 × C*H*CCH$_3$, arom), 3.52 (dd, *J* = 9.5, 7.5 Hz, 2 H, 2 × C*H*$_a$H$_b$CHCH$_2$P), 3.36–3.26 (m, 2 H, 2 × CH$_3$CHC*H*$_a$H$_b$), 3.08–2.95 (m, 4 H, 2 × CH$_a$*H*$_b$NCH$_a$*H*$_b$CHCH$_2$P), 2.50–2.30 (m, 2 H, 2 × C*H*CH$_2$P), 2.43, 2.42 (2 × br s, 6 H, 2 × ArC*H*$_3$), 2.30–2.11 (m, 2 H, 2 × CH$_3$C*H*), 1.47 (dq, *J* = 15.0, 4.5 Hz, 2 H, 2 × C*H*$_a$H$_b$P), 1.37–1.10 (m, 2 H, 2 × CH$_a$*H*$_b$P), 0.68, 0.65 (d and dd, *J* = 7.0 Hz and 7.0, 2.5 Hz, 6 H, 2 × C*H*$_3$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 144.9 (2 × S*C*CH, arom), 135.2, 135.1 (2 × CH*C*CH$_3$, arom), 130.8 (4 × *C*HCCH$_3$), 128.7, 128.6 (4 × SC*C*H, arom), 55.6 (2 × CH$_3$CH*C*H$_2$), 53.0, 52.7 (br s and d, $^3J_{CP}$ = 5.5 Hz, 2 × *C*H$_2$CHCH$_2$P), 37.9–37.4 (m, 2 × *C*HCH$_2$P), 37.7, 37.2 (2 × d, $^3J_{CP}$ = 12.0, 10.5 Hz, 2 × CH$_3$*C*H), 30.3 (br d, $^1J_{CP}$ = 89.5 Hz, 2 × *C*H$_2$P), 21.5 (2 × Ar*C*H$_3$), 13.7, 13.6 (2 × *C*H$_3$CH).
trans-Diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81–3.70 (m, 2 H, 2 × C*H*$_a$H$_b$CHCH$_2$P), 3.52–3.43 (m, 2 H, 2 × CH$_3$CHC*H*$_a$H$_b$), 3.08–2.90 (m, 2 H, 2 × CH$_a$*H*$_b$CHCH$_2$P), 2.73 (br t, *J* = 9.5 Hz, 2 H, 2 × CH$_3$CHCH$_a$*H*$_b$), 1.72–1.05 (m, 8 H, 2 × C*H*C*H*CH$_2$P), 0.91, 0.87 (d and dd, *J* = 6.5 Hz and 8.0, 6.5 Hz, 6 H, 2 × C*H*$_3$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7–55.2 (m, 2 × CH$_3$CH*C*H$_2$), 55.3–54.9 (2 × *C*H$_2$CHCH$_2$P), 41.9–41.3 (m, 2 × CH$_3$*C*H*C*H), 31.7 (br d, $^1J_{CP}$ = 90.5 Hz, 2 × *C*H$_2$P), 15.9, 15.8 (2 × *C*H$_3$CH). ^{31}P NMR (162 MHz; $CDCl_3$): δ = 39.6. ESI-MS: *m/z* (%) = 316 (100), 567 (92) [M – H$^+$]. ESI-HRMS: *m/z* calcd for $C_{26}H_{37}N_2O_6PS_2$: 567.1758; found: 567.1752.

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(11) In the absence of AIBN or Et_3B, pyrrolidine products were formed in low yields after extended reaction times. For example, heating **2a** (1 equiv) with H_3PO_2 (4.3 equiv) in degassed dioxane for 3 d, followed by esterification, gave a 4.7:1 mixture of **9** and **10**, respectively, in a combined yield of only 34%.

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(15) Bond-dissociation energies based on DFT calculations (B3LYP functional, 6-13G(d,p) basis set, calculations performed using Gaussian03) for PhP(S)(OEt)H and PhP(O)(OEt)H are around 316 and 345 kJ mol^{-1}, respectively. McGrady, J. E.; Pantazis, D. *unpublished results*.

(16) ***O*-(3-{[({4-Methyl-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinyl}methyl)(phenyl)phosphorothioyl]oxy}propyl){4-methyl-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinyl}methyl(phenyl)phosphinothioate (16a)**
A boiling solution of *N*,*N*-diallyl-4-methylbenzene sulfonamide (**2a**, 0.372 g, 1.479 mmol) and *O*-(3-{[phenyl(thioxo)phosphoranyl]oxy}propyl)phenylphosphinothioate (**14**, 0.264 g, 0.741 mmol) in anhyd THF (15 mL) was treated portionwise with AIBN (4 × 0.024 g, 4 × 0.148 mmol) over 36 h. After cooling to r.t., 1 M aq NaOH (20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), concentrated (under reduced pressure), and column chromatography [SiO_2, CH_2Cl_2–EtOAc (97:3)] gave bispyrrolidine **16a** (0.477 g, 75%) as an inseparable mixture of isomers, with a *cis*/*trans* ratio of 2.5:1 (from the ^{1}H NMR spectrum); white solid; mp 61–66 °C. IR ($CHCl_3$): ν_{max} = 3022, 2967, 2892, 2433, 2401, 2255, 1965, 1919, 1822, 1598, 1479, 1437, 1400, 1385, 1342, 1305, 1289, 1216, 1160, 1109, 1095, 1041, 1017, 968 cm^{-1}.
cis-Diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.75 (m, 4 H, 4 × PCC*H*, arom), 7.72–7.66 and 7.62–7.56 (2 × m, 4 H, 4 × SCC*H*, arom), 7.59–7.51 (m, 2 H, 2 × PCCHCHC*H*, arom), 7.55–7.41 (m, 4 H, 2 × PCCHC*H*, arom), 7.35–7.26 (m, 4 H, 4 × SCCHC*H*, arom), 4.20–4.04 and 3.75–3.58 (2 × m, 4 H, POC*H*$_2$CH$_2$C*H*$_2$), 3.25 (dd, *J* = 9.5, 6.5 Hz, 2 H, 2 × CH$_3$CHC*H*$_a$H$_b$N), 3.17 (br t, *J* = 9.0 Hz, 2 H, 2 × NC*H*$_a$H$_b$CHCH$_2$P), 3.04–2.94 (m, 2 H, 2 × CH$_3$CHCH$_a$*H*$_b$N), 2.80–2.67 (m, 2 H, NCH$_a$*H*$_b$CHCH$_2$P), 2.56–2.35 (m, 2 H, 2 × C*H*CH$_2$P), 2.44, 2.42 (2 × s, 6 H, 2 × ArC*H*$_3$), 2.30–1.96 (m, 2 H, 2 × CH$_3$C*H*), 2.05–1.65 (m, 4 H, 2 × C*H*$_2$P), 1.97–1.78 (m, 2 H, POCH$_2$C*H*$_2$), 0.74, 0.70 (2 × d, *J* = 7.0, 7.0 Hz) and 0.65–

0.59 (m, 6 H, 2 × C*H*$_3$CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2 (2 × SC*C*H, arom), 133.8–131.6 (m, 2 × P*C*CH, 2 × SCCHCH*C*CH$_3$, arom), 132.5–132.2 (m, 2 × PCCHCH*C*H, arom), 131.3–129.0 (m, 4 × PC*C*H, arom), 129.6, 129.5 (4 × SCCH*C*H, arom), 128.8–128.4 (4 × PCCH*C*H, arom), 127.3, 127.2 (4 × SC*C*H, arom), 60.9–60.2 (m, 2 × POCH$_2$), 54.1, 53.9 (2 × CH$_3$CH*C*H$_2$N), 51.2, 50.9 (2 × d, $^3J_{CP}$ = 5.5, 8.5 Hz, 2 × *C*H$_2$CHCH$_2$P), 36.3 (s) and 36.0–35.8 (m) (2 × *C*HCH$_2$P), 35.7, 35.6 (2 × d, $^3J_{CP}$ = 10.5, 10.5 Hz, 2 × CH$_3$*C*H), 34.5, 34.3 (2 × d, $^1J_{CP}$ = 79.5, 80.0 Hz, 2 × *C*H$_2$P), 31.1–30.7 (m, POCH$_2$*C*H$_2$), 21.4, 21.4 (2 × Ar*C*H$_3$), 13.2, 13.1 (2 × *C*H$_3$CH).

trans-Diastereomers: ^{1}H NMR (400 MHz; $CDCl_3$): δ = 3.82–3.68 (m, 2 H, 2 × NC*H*$_a$H$_b$CHCH$_2$P), 3.56–3.35 (m, 4 H, 2 × CH$_3$C*H*$_a$H$_b$NCH$_a$*H*$_b$CHCH$_2$P), 0.91–0.85 and 0.81–0.76 (2 × m, 6 H, 2 × *C*H$_3$CH). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 53.6–53.3 (m, 2 × CH$_3$CH*C*H$_2$), 53.4–53.0 (m, 2 × *C*H$_2$CHCH$_2$P), 40.3–40.1 and 40.0–39.8 (2 × m, 2 × *C*HCH$_2$P), 40.0–39.6 (m, 2 × CH$_3$*C*H), 38.9–37.5 (m, 2 × *C*H$_2$P), 15.6, 15.3 (2 × *C*H$_3$CH). HRMS–FAB: *m/z* calcd for $C_{41}H_{52}N_2O_6P_2S_4$: 859.2256; found: 859.2264.

(17) Arndt, H.-D.; Welz, R.; Müller, S.; Ziemer, B.; Koert, U. *Chem. Eur. J.* **2004**, *10*, 3945.