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# Pseudo-halogen behavior of thiophosphoryl azides as a tool for the functionalization of phosphorus macrocycles

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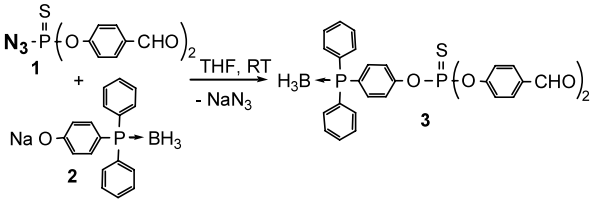
**Abstract**—Phosphoryl azides are known as azide-transfer agents in organic chemistry; such behavior denotes the pseudo-halogen character of the azide group when linked to a tetracoordinated phosphorus atom, but it was considered up to now only for the functionalization of organic substrates by $N_3$. We show in this paper that the azide can also be considered as a good leaving group, which facilitates the functionalization of the phosphorus atom which bore it. This reaction is first demonstrated on a small thiophosphoryl azide, then applied to the functionalization of more complex macromolecules, i.e. macrocycles incorporating in their structure thiophosphoryl azido groups.


Covalent azides are known for a wide range of elements over the periodic classification, but their chemical properties vary considerably, mainly depending on the elements to which the azide group is linked. Considering for instance main group elements, the reactivity of aluminum, tin, lead and antimony azides generally induces the lost of the three nitrogen atoms, whereas for boron, silicon, phosphorus, germanium and arsenic, one nitrogen remains often linked to the element.[1] Tetracoordinated phosphorus azides are well studied main group element azides; their reactivity mainly pertains to two types of reactions: Staudinger reactions[2] and Curtius rearrangements. Staudinger reactions with phosphines occur with elimination of $N_2$, thus without cleavage of the P–N bond;[3] Curtius type rearrangements lead to a variety of structures, depending at which step the rearrangement occurs. If it occurs on the phosphorus derivative, the P–N bond is preserved.[4] However, the rearrangement often happens on an organic substrate, after the cleavage of the P–N bond. Indeed, phosphorus azides, and more precisely diphenylphosphonic azide ($(PhO)_2P(O)N_3$), are considered as azide-transfer agents in organic chemistry; examples are known in which the azide group is entirely preserved in the final product,[5] or is further transformed.[6] In both cases, the azide behaves like a pseudo-halogen; such behavior is not surprising in view of the comparison between the absolute electronegativity according to Mulliken for Cl (8.3 eV), Br (7.5 eV) and $N_3$ (7.7 eV).[7] However, to the best of our knowledge, this fact was considered up to now only from the point of view of the functionalization of the organic substrate by $N_3$, and not as a way to functionalize the phosphorus derivative which bore the azide. Nevertheless, considering the $N_3$ function as a leaving group should allow carrying out nucleophilic substitutions on the phosphorus. Of course, P–Cl functions, which are often more easily available than P–$N_3$ functions, are widely used for nucleophilic substitutions, including for the synthesis of P–$N_3$ derivatives with $NaN_3$. However, for practical synthetic purposes, it may be useful to have diversified leaving groups. We will illustrate this fact, first on a small compound, then on various complex macrocyclic structures.

In the course of our researches about phosphorus-containing macromolecular structures such as macrocycles[8]




**Scheme 1.**

*Keywords*: azide; pseudo-halogen; phosphorus; substitution; macrocycle; leaving group.

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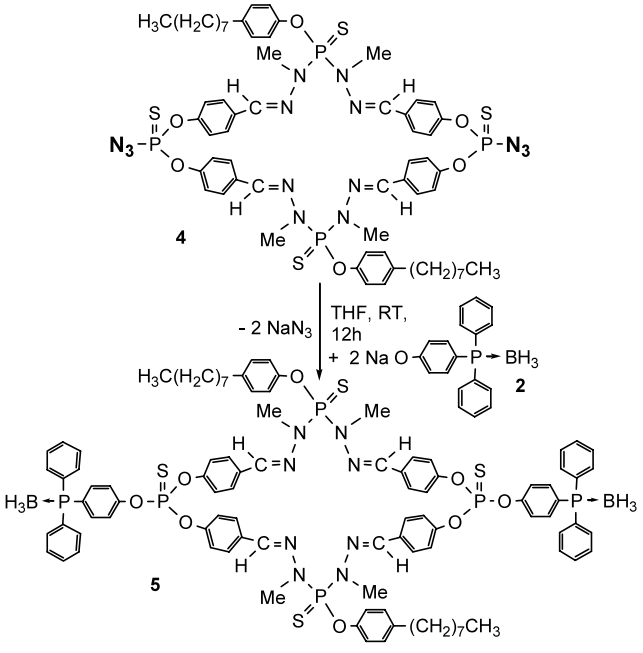
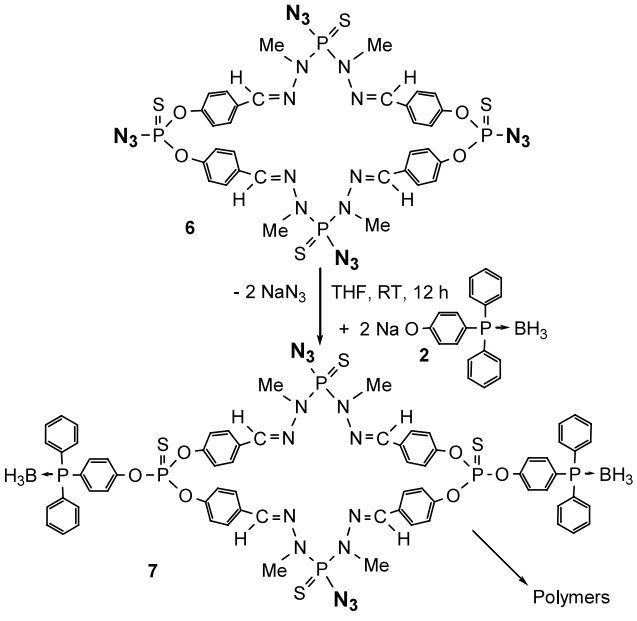
and dendrimers,[9] we were interested in synthesizing compounds possessing several types of functional groups, often of type $AB_2$, such as the trifunctional derivative **3** [$(OHCC_6H_4O)_2P(S)(OC_6H_4PPh_2BH_3)$]. The most obvious way to synthesize such compounds should consist in reacting $NaOC_6H_4PPh_2BH_3$ **2**[10] with $(OHCC_6H_4O)_2P(S)Cl$. However, this latter compound is often difficult to obtain in a pure form, and is too sensitive to be purified by chromatography on silicagel. Nevertheless, we attempted the above-mentioned reaction with crude $(OHCC_6H_4O)_2P(S)Cl$. The expected product **3** was obtained in the mixture, but attempts to purify it were unsuccessful. On the other hand, the azide **1** $(OHCC_6H_4O)_2P(S)N_3$ is obtained in a pure form after column chromatography,[11] by reaction of $NaN_3$ with crude $(OHCC_6H_4O)_2P(S)Cl$. Thus, we tried to obtain the trifunctional phosphorus derivative **3** starting from **1** and **2** (Scheme 1). The substitution reaction occurred within 2 h at room temperature, in the way expected, with elimination of $NaN_3$. The completion of the reaction was shown by $^{31}P$ NMR, which displays a shielding of the signal corresponding to the thiophosphoryl group from $\delta = 57.7$ ppm for **1** to $\delta =$ 50.1 ppm for **3**. Even if a few impurities due to side-reactions were also observed, compound **3** was isolated in pure form after column chromatography (eluent: AcOEt/hexane: 3/7).[12]

This very simple reaction could be particularly useful for the functionalization of more complex structures, such as macrocycles. We tested first the reaction on the diazide macrocycle **4**, which was obtained by cyclocondensation reaction of the dialdehyde **1** with the phosphorhydrazide $(H_2NNMe)_2P(S)(OC_6H_4(CH_2)_7CH_3)$. This cyclization reaction occurs selectively between two molecules of each reagent, as we have already shown in many cases,[8,13,14] and affords the macrocycle **4** in nearly quantitative yield. For the reason mentioned previously concerning the purification of the P–Cl dialdehyde, the bisazide macrocycle **4** is more easily obtained than the one having Cl functions in place of the $N_3$ groups. The macrocycle **4** undergoes very cleanly the expected substitution reaction within 12 h when reacted with the sodium salt **2**; no side reaction was observed in this case (Scheme 2). As already indicated for the synthesis of **3**, the substitution reaction induces the shielding of the signal corresponding to the phosphorus atoms which undergo the reaction, from $\delta = 59.3$ ppm for **4** to $\delta =$ 52.0 ppm for **5**, whereas no modification is observed for the other phosphorus atoms included in the macrocyclic chain ($\delta = 68.3$ ppm for **4** and **5**).[15] The occurrence of the expected reaction is also shown by IR spectroscopy, with the disappearance of the signal corresponding to the azide groups at 2161 $cm^{-1}$ for **4**.

In the literature, the use of phosphorus azides as azide-transfer agents is practically limited to $(PhO)_2P(O)N_3$; the pseudo-halogen behavior of our thiophosphoryl derivatives show that changing P(O) for P(S) has no influence on the type of reactivity, but what could happen when changing ArO by nitrogen derivatives? To answer this question, we synthesized macrocycle **6**, which possesses two types of phosphorus azides, $(ArO)_2P(S)N_3$ and $(>N)_2P(S)N_3$. In spite of the presence of 4 $N_3$ groups, the substitution was attempted with only two equivalents of **2**, in order to check a possible selectivity (Scheme 3). The reaction is monitored by $^{31}P$ NMR, which indicates that the substitution reaction occurs cleanly on only one type of phosphorus azide. Indeed, macrocycle **6** displays two singlets on the $^{31}P$ NMR spectrum at $\delta = 59.1$ ppm for $(ArO)_2P(S)N_3$ and $\delta = 67.2$ ppm for $(>N)_2P(S)N_3$. The macrocycle resulting from the substitution also displays two singlets at $\delta = 51.8$ ppm and $\delta = 67.2$ ppm. These data show without any ambiguity that only the azides linked to $(ArO)_2P(S)N_3$ were substituted, leading to macrocycle




**Scheme 2.**



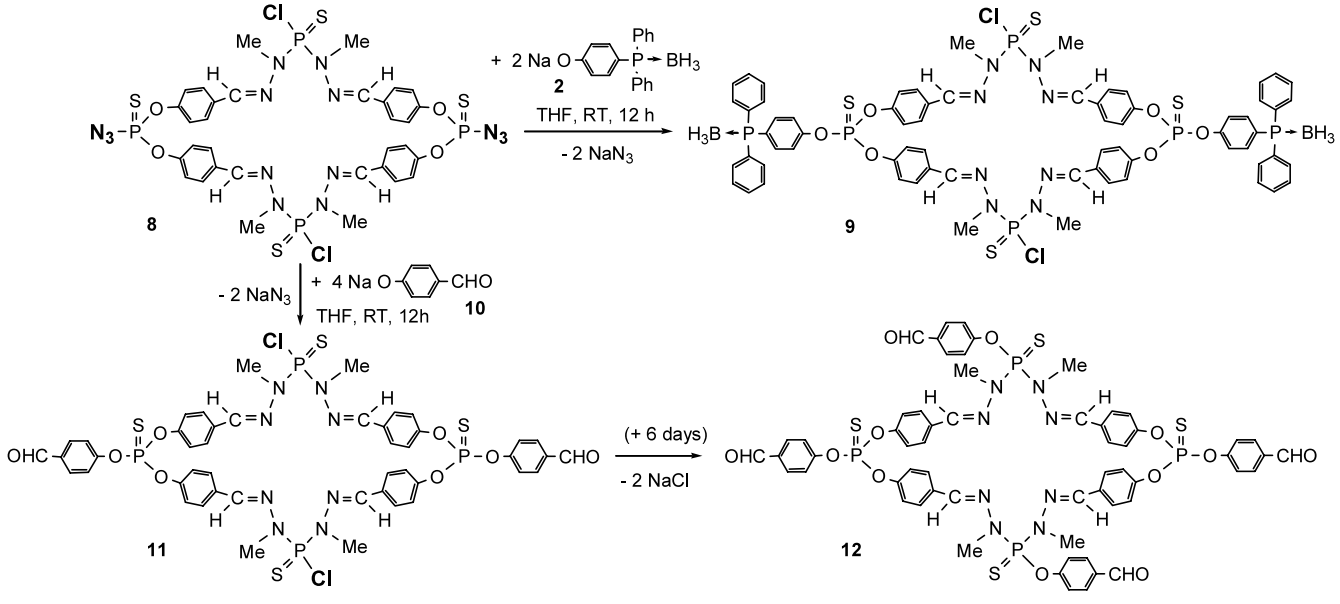

**Scheme 3.**

**7**. Thus, the substitution appears very clean on the crude product, but our attempts to isolated compound **7** failed. Indeed, the simple evaporation of THF gives a white powder impossible to dissolve again in any solvent. Even if no signal corresponding to free phosphines or to P=N–P linkages was observed in solution by $^{31}$P NMR, we believe that some $BH_3$ groups are transferred from phosphorus to the nitrogen atoms of the macrocycle, giving free phosphines, which react immediately with the azide of another macrocycle by a Staudinger reaction. Such reaction should give polymers by creating P=N–P links; this could explain the insolubility observed during the work-up of macrocycle **7**.

In order to avoid such problem, and to check a possible selectivity between P–Cl and P–$N_3$ groups in nucleophilic substitutions, we synthesized macrocycle **8**, which possesses two $(ArO)_2P(S)N_3$ and two $(>N)_2P(S)Cl$ groups. In this case also, only 2 equiv. of the sodium salt **2** were used. Monitoring the reaction by $^{31}$P NMR allows to show that the substitution occurs cleanly within 12 h at room temperature on the $(ArO)_2P(S)N_3$ groups, whose chemical shift varies from $\delta = 59.1$ ppm for **8** to $\delta = 51.9$ ppm for **9**, whereas no change is observed for the $(>N)_2P(S)Cl$ groups ($\delta = 74.8$ ppm for both compounds). In this case, the macrocycle **9** is isolated in very good yield, and fully characterized without any problem (Scheme 4).[15]

We should have tried to substitute the chlorine using more drastic conditions, but in view of relative instability of the P→$BH_3$ bond shown by the polymerization of **7**, we preferred to carry on the comparative test in the absence of such function. Thus, we used again macrocycle **8** as the starting compound, to be reacted with the sodium salt of hydroxybenzaldehyde **10**. Our aim in this case, as in the previous case, was to graft on the macrocycle functional groups usable for further functionalizations. Four equivalents of **10** were used, in order to try to substitute both the $N_3$ and the Cl functions. After 12 h, $^{31}$P NMR displays only two singlets at $\delta = 52.1$ and 74.8 ppm, indicating the presence of a single type of macrocycle. In view of the values of these chemical shifts, we can conclude again that only the phosphorus bearing the $N_3$ groups have reacted, leading to macrocycle **11**. We did not attempted to isolate compound **11**, and we left it several days in the presence of unreacted sodium salt **10**. Signals corresponding to a new macrocycle progressively appear on the $^{31}$P NMR spectra. The reaction went to completion after one week. The substitution of Cl by **10** induces the shielding of the signal corresponding to the $(>N)_2P(S)Cl$ groups, from $\delta = 74.8$ ppm for **8** and **11** to $\delta = 67.6$ ppm for **12**. Macrocycle **12**, possessing four aldehyde groups, was easily isolated in very good yield.[15] All these new compounds are characterized by multinucleus NMR ($^{31}$P, $^{1}$H, and $^{13}$C) and gave satisfactory elemental analyses. Mass spectrometry (CI, FAB, electrospray) was found unsuitable to check the purity of these compounds: even if the molecular ion is generally observed, it has a weak intensity, since it is accompanied with a lot of fragmentations.

In conclusion, we have shown that the azide group can be considered as a good leaving group for functionalizing tetracoordinated phosphorus derivatives by nucleophilic substitutions. Its reactivity is very similar to that of chlorine, and it constitutes an alternative when the corresponding Cl derivatives are difficult to isolate. This reaction is particularly suitable for the regioselective functionalization of macromolecular structures such as macrocycles. Obviously, other types of functionalized phenols can be used and presumably also other types of nucleophiles in such reactions. Work is in progress to apply this new tool for the selective functionalization of other macromolecules possessing complex architectures, such as dendrimeric species.




**Scheme 4.**

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11. **Caution**: in our hands, the $N_3$ derivatives appear more stable than the Cl derivatives (less sensitive to hydrolysis for instance). However, many azides are explosives, thus maximum care must be taken.
12. Spectroscopic data for compound **3** (isolated in 60% yield) in $CDCl_3$. $^{31}P$ $\{^1H\}$ NMR: $\delta = 20.5$ (brs, $PBH_3$), 50.1 (s, P=S). $^1H$ NMR: $\delta = 1.68$ (brs, 3H, $BH_3$), 7.20–7.65 (m, 18H, Har), 7.94 (d, $^3J_{HH} = 8.2$ Hz, 4H, Har), 9.99 (s, 2H, CHO). $^{13}C$ $\{^1H\}$ NMR: $\delta = 121.8$ (dd, $^3J_{CP} = 5.5$ Hz, $^3J_{CP} = 10.8$ Hz, *m*-$PC_6H_4$), 122.2 (d, $^3J_{CP} = 5.2$ Hz, *m*-$CHOC_6H_4$), 127.7 (d, $^1J_{CP} = 58.1$ Hz, $^5J_{CP} = 1.2$ Hz, *i*-$PC_6H_4$), 129.0 (d, $^1J_{CP} = 58.2$ Hz, *i*-Ph), 129.4 (d, $^3J_{CP} = 10.3$ Hz, *m*-Ph), 132.0 (d, $^4J_{CP} = 2.4$ Hz, *p*-Ph), 132.1 (s, *o*-$CHOC_6H_4$), 133.5 (d, $^2J_{CP} = 9.8$ Hz, *o*-Ph), 134.6 (d, $^5J_{CP} = 1.4$ Hz, *i*-$CHOC_6H_4$), 135.6 (d, $^2J_{CP} = 10.8$ Hz, *o*-$PC_6H_4$), 150.9 (d, $^2J_{CP} = 7.9$ Hz, *p*-$CHOC_6H_4$), 152.9 (dd, $^2J_{CP} = 7.6$ Hz, $^4J_{CP} = 2.4$ Hz, *p*-$PC_6H_4$), 191.0 (s, CHO). IR (KBr): 1700 ($\nu_{C=O}$) $cm^{-1}$. Anal. calcd for $C_{32}H_{27}BO_5P_2S$ (596.4): C, 64.45; H, 4.56. Found: C, 64.51; H, 4.64.
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15. Spectroscopic data for macrocycles in $CDCl_3$ ($\delta$ in ppm). **5** (isolated in 98% yield): $^{31}P$ $\{^1H\}$ NMR: 20.4 (brs, $PBH_3$), 52.0 (s, P–O), 68.3 (s, P–N). $^1H$ NMR: 0.86 (t, $^3J_{HH} = 6.7$ Hz, 6H, $CH_3C$), 1.25 (brs, 26H, $CH_2$, $BH_3$), 1.55 (tt, $^3J_{HH} = 7.1$ Hz, 4H, $CH_2$), 2.54 (t, $^3J_{HH} = 7.2$ Hz, 4H, $CH_2$), 3.37 (d, $^3J_{HP} = 9.2$ Hz, 12H, $CH_3N$), 7.10 (brs, 8H, Har), 7.17 (brd, $^3J_{HH} = 7.5$ Hz, 8H, Har), 7.24–7.67 (m, 40H, Har, CH=N). $^{13}C$ $\{^1H\}$ NMR: 14.2 (s, $CH_3C$), 22.7 (s, $CH_2$), 29.2 (s, 2 $CH_2$), 29.5 (s, $CH_2$), 31.4 (s, $CH_2$), 31.9 (s, $CH_2$), 33.1 (d, $^2J_{CP} = 9.2$ Hz, $CH_3N$), 35.3 (s, $CH_2$), 121.3 (brd, $^3J_{CP} = 3.7$ Hz, *m*-$CHNC_6H_4$, *m*-$CH_2C_6H_4$), 121.5 (dd, $^3J_{CP} = 5.4$ Hz, $^3J_{CP} = 10.5$ Hz, *m*-$PC_6H_4$), 126.8 (d, $^1J_{CP} = 58.8$ Hz, *i*-$PC_6H_4$), 128.1 (s, *o*-$CHNC_6H_4$), 128.7 (d, $^1J_{CP} = 59.3$ Hz, *i*-Ph), 128.9 (d, $^3J_{CP} = 9.8$ Hz, *m*-Ph), 129.3 (s, *o*-$CH_2C_6H_4$), 131.5 (s, *p*-Ph), 133.1 (d, $^2J_{CP} = 9.8$ Hz, *o*-Ph), 133.3 (s, *i*-$CHNC_6H_4$), 135.0 (d, $^2J_{CP} = 10.9$ Hz, *o*-$PC_6H_4$), 137.0 (d, $^3J_{CP} = 15.5$ Hz, CH=N), 140.0 (s, *i*-$CH_2C_6H_4$), 148.3 (d, $^2J_{CP} = 6.3$ Hz, *p*-$CH_2C_6H_4$), 150.6 (d, $^2J_{CP} = 8.3$ Hz, *p*-$CHNC_6H_4$), 152.8 (brd, $^2J_{CP} = 7.5$ Hz, *p*-$PC_6H_4$). Anal. calcd for $C_{96}H_{108}B_2N_8O_8P_6S_4$ (1837.7): C 62.75; H 5.93; N 6.10. Found: C 62.86, H 6.01, N 6.05. **7**: $^{31}P$ $\{^1H\}$ NMR: 20.3 (brs, $PBH_3$), 51.8 (s, P-O), 67.2 (s, P-N). **9** (isolated in 93% yield): $^{31}P$ $\{^1H\}$ NMR: 20.3 (brs, $PBH_3$), 51.9 (s, P–O), 74.8 (s, P–N). $^1H$ NMR: 1.30 (brs, 6H, $BH_3$), 3.32 (d, $^3J_{HP} = 11.2$ Hz, 12H, $CH_3N$), 7.11 (brd, $^3J_{HH} = 8.1$ Hz, 12H, Har), 7.40–7.65 (m, 36H, Har, CH=N). $^{13}C$ $\{^1H\}$ NMR: 32.4 (d, $^2J_{CP} = 10.4$ Hz, $CH_3N$), 121.4 (d, $^3J_{CP} = 5.0$ Hz, *m*-$CHNC_6H_4$), 121.5 (dd, $^3J_{CP} = 5.0$ Hz, $^3J_{CP} = 10.9$ Hz, *m*-$PC_6H_4$), 126.8 (d, $^1J_{CP} = 58.5$ Hz, *i*-$PC_6H_4$), 128.3 (d, $^1J_{CP} = 58.0$ Hz, *i*-Ph), 128.4 (s, *o*-$CHNC_6H_4$), 129.1 (d, $^3J_{CP} = 9.9$ Hz, *m*-Ph), 131.5 (s, *p*-Ph), 132.8 (s, *i*-$CHNC_6H_4$), 133.1 (d, $^2J_{CP} = 9.8$ Hz, *o*-Ph), 135.0 (d, $^2J_{CP} = 11.1$ Hz, *o*-$PC_6H_4$), 138.2 (d, $^3J_{CP} = 16.5$ Hz, CH=N), 150.9 (d, $^2J_{CP} = 7.9$ Hz, *p*-$CHNC_6H_4$), 152.7 (brd, $^2J_{CP} = 8.6$ Hz, *p*-$PC_6H_4$). Anal. calcd for $C_{68}H_{66}B_2Cl_2N_8O_6P_6S_4$ (1497.9): C, 54.52; H, 4.44; N, 7.48. Found: C, 54.71, H, 4.51, N, 7.41. **11**: $^{31}P$ $\{^1H\}$ NMR: 52.1 (s, P–O), 74.8 (s, P–N). **12** (isolated in 90% yield): $^{31}P$ $\{^1H\}$ NMR: 52.1 (s, P–O), 67.6 (s, P–N). $^1H$ NMR: 3.38 (brs, 12H, $CH_3N$), 7.17 (brs, 8H, Har), 7.38 (brs, 8H, Har), 7.62 (brs, 12H, CH=N, Har), 7.86 (brs, 8H, Har), 9.93 (brs, 4H, CHO). $^{13}C$ $\{^1H\}$ NMR: 33.3 (d, $^2J_{CP} = 9.6$ Hz, $CH_3N$), 121.8 (brs, *m*-$CHNC_6H_4$), 122.2–122.6 (2d, $^3J_{CP} = 4.8$ Hz, $^3J_{CP} = 4.6$ Hz, *m*-$CHOC_6H_4$), 128.6 (s, *o*-$CHNC_6H_4$), 131.8–132.0 (2s, *o*-$CHOC_6H_4$), 133.6 (s, *i*-$CHNC_6H_4$), 133.8–134.3 (2s, *i*-$CHOC_6H_4$), 138.0 (d, $^3J_{CP} = 15.0$ Hz, CH=N), 151.1 (d, $^2J_{CP} = 8.0$ Hz, *p*-$CHNC_6H_4$), 155.2–155.9 (2d, $^3J_{CP} = 7.5$ Hz, $^3J_{CP} = 6.8$ Hz, *p*-$CHOC_6H_4$), 191.1–191.3 (2s, CHO). IR (KBr): 1700 ($\nu_{C=O}$) $cm^{-1}$. Anal. calcd for $C_{60}H_{52}N_8O_{12}P_4S_4$ (1329.3): C, 54.22; H, 3.94; N, 8.43. Found: C, 54.43, H, 4.02, N, 8.34.