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Selective Synthesis of (*Z*)-Diazadiphosphafulvalene from 2,2′-bis-Azaphosphindole

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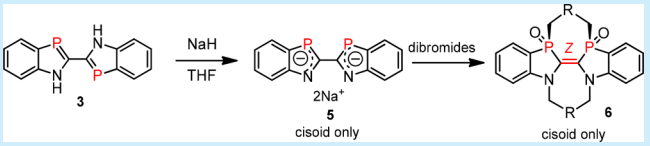
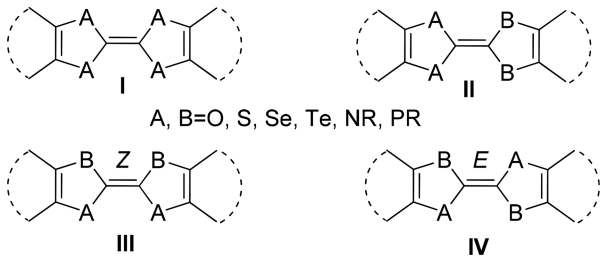
Supporting Information

ABSTRACT: The unprecedented 2,2′-bis(azaphosphindole) has been synthesized via a new route. Reaction with NaH afforded a dianion derivative **5**, which is easily transformed to alkylated bis(azaphosphindole) or (*Z*)-*P,P,N,N-cisoid* diazadiphosphafulvalene. The reaction features good regioselectivity and high steroselectivity. Relatively strong fluorescence is observed with diazadiphosphafulvalenes. The X-ray crystal structure analysis showed that dianion ligand **5** is bonded to two Na atoms in a bridging *cis*-fashion, which allows the synthesis of diazadiphosphafulvalene in a highly stereoselective approach.



Since the discovery of the first tetrathiafulvalene (TTF),[1] many new heterofulvalenes[2] have been discovered and developed for electronic, magnetic, and optical applications.[3−6] Thanks to continuous and extensive studies, the synthetic innovations provide not only symmetric **I** but also dissymmetric **II** heterofulvalenes. Unfortunately, the selective synthesis of heterofulvalenes *Z*-**III** and *E*-**IV** still remains challenging. Here, we report a selective synthesis of diazadiphosphafulvalene (*Z*-**III**, A = NR, B = PR) (see Scheme 1) from 2,2′-bis-azaphosphindole.

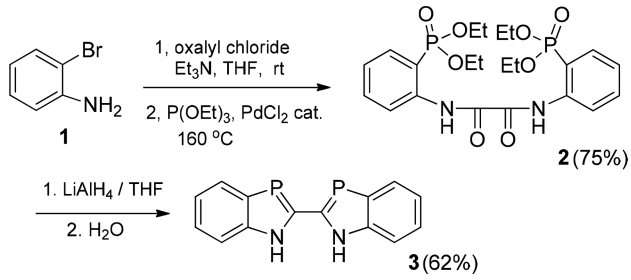
Scheme 1. Heterofulvalenes



1,4-Diazadienes and 2,2′-bipyridines are among the most useful ligands of transition-metal chemistry,[7] because of their ability to stabilize a wide range of oxidation states for a single element. The phosphorus analogues are not so well-known, as a result of the ready cyclization of 1,4-diphosphadienes into 1,2-dihydro-1,2-diphosphetes. In practice, only 2,2′-biphosphinines[8] and 3,4-bis(phosphinidene)cyclobutenes[9] have been studied to a certain extent. At the beginning, we wished to develop a new class of 1,4-diphosphadienes based on the 1,3-azaphosphindole monomeric unit.

The classical one-pot condensation method for the synthesis of azaphosphindoles[10] did not provide the desired species. A modified stepwise route was developed to synthesize this unknown compound **3** (Scheme 2). Reaction of 2-bromoaniline with oxalyl chloride, followed by a Pd-catalyzed phosphonylation with triethyl phosphite, gave **2**, and subsequent reduction with $LiAlH_4$ provided **3** in good yield.

Scheme 2. Synthesis of 2,2′-bis-Azaphosphindole



This new 2,2′-bis-azaphosphindole is quite stable in the solid state, and it could be stored without precaution in air and moisture for several days. Compound **3** was characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopies and by X-ray crystal analysis. The ^{31}P NMR resonance frequency for **3** (75.1 ppm) is in the same range as those of 1,3-azaphosphindoles.[10,11] The structure of **3** (depicted in Figure 4 on page s9 in the Supporting Information (SI)) shows that the two azaphosphindolyl rings adopt a coplanar trans conformation (torsion angle ∠P1−C1−C1′−N2′ = 0.78°). The P═C bond length is 1.731 Å, which is within the range of P═C bonds in

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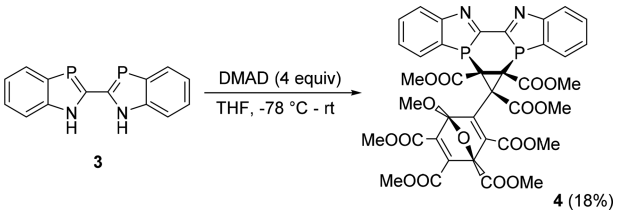
azaphospholes.[10−12] The length of the C1−C1′ bond that links the two five-membered rings is 1.445 Å, which is quite close to the bridge bond length of 2,2′-biphosphinine.[8] This coplanarity and shortening of the C1−C1′ bond indicate a conjugative interaction between the two azaphosphindole rings.

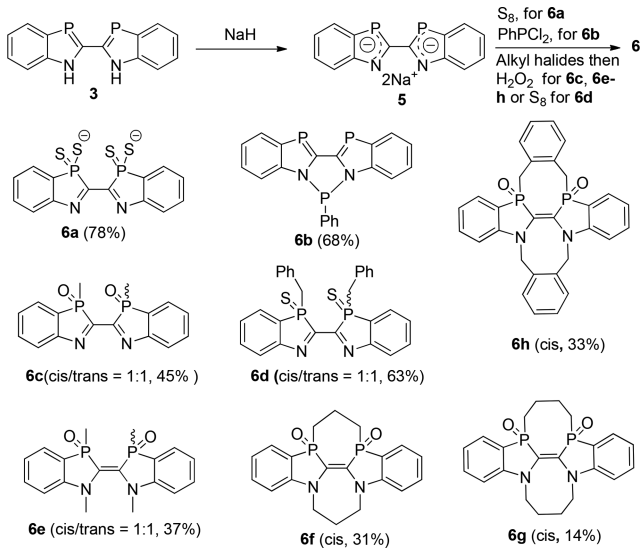
To understand the reactivity of **3**, we first investigated its nucleophilicity via the reaction with DMAD (dimethyl acetylenedicarboxylate). The reaction was monitored by ^{31}P NMR spectroscopy. We observed the disappearance of compound **3** and a new phosphorus species **4** appeared as an AB system at 4.1 and 6.6 ppm (J_{P-P} = 138.8 Hz). Some unidentified deposits also formed. The structure of **4** was resolved by X-ray crystal analysis (see Figure 5 on page s10 in the SI). To our surprise, two protons were removed and four molecules of DMAD were incorporated into the final product. The mechanism of the formation of **4** is unclear yet. We propose that the reaction is initiated by the nucleophilic attack of the phosphorus center onto DMAD, followed by domino additions between DMAD units. However, we cannot explain the dehydrogenation at the moment (see Scheme 3). Further experiments, with regard to reaction optimization, mechanism, and synthesis utility, are in progress.

Scheme 3. Reaction of 3 with Dimethylacetylenedicarboxylate



Then, we investigated the deprotonation reaction of **3**.[13] The reaction of **3** with NaH in THF proceeded smoothly to afford cleanly the sodium salt **5** (Scheme 4). The ^{31}P NMR spectrum of **5** showed one upfield singlet at δ = 61 ppm, which is quite close to those observed in the imidazolium 1,3-benzazaphospholide ion pairs (~64 ppm), suggesting an increased localization of electron density at the P atom in **5**. Then, the

Scheme 4. Reaction of Dianion 5 with Various Electrophiles



azaphospholide was trapped with various electrophiles. The direct reaction with sulfur gave bis-azaphosphindole sulfide **6a**. The reaction between **5** and $PhPCl_2$ proceeded selectively at nitrogen to give **6b**.[14] The structure of **6b** was confirmed by X-ray analysis (see Figure 7 on page s16 in the SI). The crystal structure of **6b** exhibits a relative planarity. The dihedral angle between the two terminal benzo planes is 7.61°.

Interesting observations were made when investigating the reactions between **5** and alkyl halides. The reactions with 2 equiv of methyl iodide or benzyl bromide selectively provided P-alkylated products. This selectivity was established by NMR spectroscopic analysis of their stable oxidized derivatives **6c** and **6d**, respectively. Note that the two cis/trans isomers of **6c** and **6d** can be separated by simple silica gel chromatography. The structure of *trans*-**6d** was definitively confirmed by X-ray diffraction (XRD) analysis (see Figure 8 on page s18 in the SI). The structure of *trans*-**6d** shows that the two azaphosphindole rings adopt a coplanar *trans* conformation (torsion angle ∠P2−C8−C7−N1 = 2.04°).

When the amount of alkyl halide was doubled (4 equiv), a new tetramethylated product **6e** was obtained as a mixture of *cis*/*trans*-isomers after oxidation. It is striking to find that the (*Z*)-*P*,*P*,*N*,*N*-fulvalene compound was obtained exclusively. The single-crystal XRD analysis (Figure 1) shows that the length of

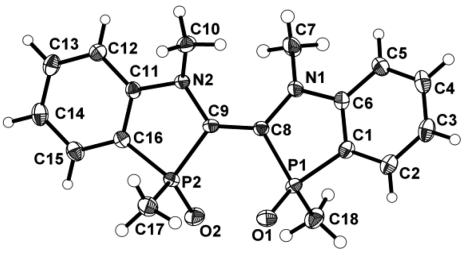


Figure 1. X-ray crystal structure analysis of compound *trans*-**6e** that was obtained from the mixture of *cis* and *trans* isomers. Main bond lengths: C8−C9, 1.347(3) Å; P1−C1, 1.797(3) Å; P1−C8, 1.831(2) Å; N1−C6, 1.403(3) Å; and N1−C8, 1.400(3) Å. Main bond angles: ∠C1−P1−C8, 90.35(11)°; ∠C6−N1−C8, 114.1(2)°; and ∠C9−N2−C11, 112.52(19)°.

the C8−C9 bond that links the two five-membered rings is reduced to 1.347 Å, which falls into the normal range of C=C double bonds. To the best of knowledge, this is the first example of diazadiphosphafulvalene.

Compound **6e** is a mixture of two diastereomers that result from the different relative orientations of the P=O bonds. However, this problem could be overcome by using dibromides; when 1,3-dibromopropane, 1,4-dibromobutane, and *o*-xylylene dibromide were used, and **6f**, **6g**, and **6h** were obtained as cis-isomer exclusively, as shown clearly from the crystal structures of **6g** (see Figure 10 on page s23 in the SI) and **6h** (see Figure 2).

In order to gain deeper insights into the origin of observed stereoselectivity, we prepared *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) complex of **5**. Fortunately, crystal of [**5**-TMEDA] was obtained through recrystallization from THF at room temperature. The single-crystal X-ray structure of [**5**-TMEDA] (Figure 3) clearly shows that (1) the two P atoms, being coordinated with one Na^+ each, are located on the same side of the ring skeleton; (2) each Na atom adopts a bridged coordination, and two Na atoms in a bisazaphospholide unit form a double-bridged disodium structure and give a polymeric

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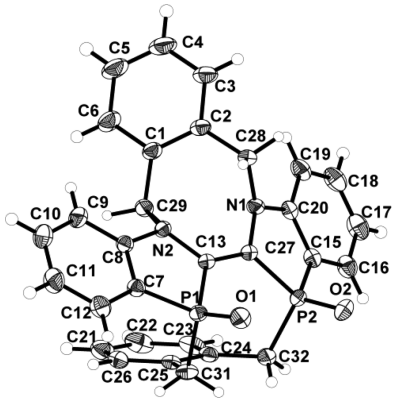

Figure 2. X-ray crystal structure analysis of compound **6h**. Main bond lengths: C13−C27, 1.341(3) Å; P1−C13, 1.826(2) Å; P1−C7, 1.786(3) Å; C27−N1, 1.408(3) Å; and C20−N1, 1.394(3) Å. Main bond angles: ∠N2−C13−P1, 110.52(16)°; ∠C7−P1−C13, 90.43(11)°.

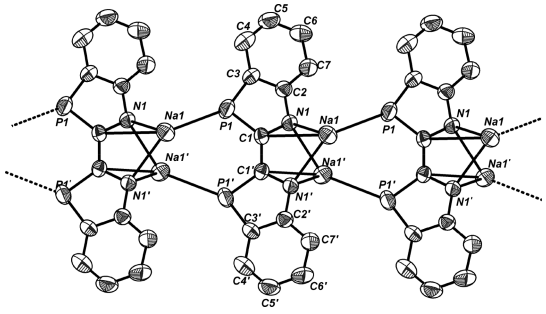

Figure 3. X-ray crystal structure analysis of compound **5**. H atoms and TMEDA are omitted for clarity. Main bond lengths: P1−Na1, 3.056(2) Å; N1−Na1, 2.547(4) Å; C1−Na1, 2.973(4) Å; P1−C1, 1.739(4) Å; P1−C3, 1.758(5) Å; N1−C1, 1.344(5) Å; N1−C2, 1.374(5) Å; and C1−C1′, 1.460(8) Å. Main bond angles: C1−P1−Na1, 119.68(14)°; C1−P1−C3, 88.19(19)°; N1−C1−P1, 117.0(3)°; and N1−C1−C1′, 119.4(2)°.

structure of [**5**-TMEDA]$_n$; (3) each Na atom is coordinated by two bisazaphospholide moieties in two different ways, through η^1-coordination by one P atom and η^2-coordination by a N═C−C═N moiety of the second bisazaphospholide unit. This η^2-coordination of Na with N═C−C═N moiety is crucial to the selective formation of (*Z*)-*P*,*P*,*N*,*N*-diazadiphosphafulvalene.

Measurements were performed in CH_2Cl_2. λ_{max} represents the wavelength of maximum UV absorption, $\lambda_{F,max}$ represents the wavelength of fluorescence maximum absorption, and φ is the fluorescence quantum yield.

Table 1 shows the UV-vis absorption and fluorescence spectra of **6f**−**6h** in CH_2Cl_2. **6g** (4817 cm^{-1}) and **6h** (4788 cm^{-1}) have larger Stokes shifts than that of **6f** (1527 cm^{-1}). All these bridged diazadiphosphafulvalenes exhibit intense emissions with high fluorescence quantum yields. Next, we

Table 1. Luminescent Properties of Diazadiphosphafulvalenes

compound	λ_{max} (nm)	$\lambda_{F,max}$ (nm)	φ
6f	442	474	0.53
6g	426	536	0.58
6h	424	532	0.70

examined the utility of **6h** ($\varepsilon_{524\ nm}$ = 7223.8 L mol^{-1} cm^{-1}) in live-cell imaging. Figure 4 clearly shows the penetration of **6h**

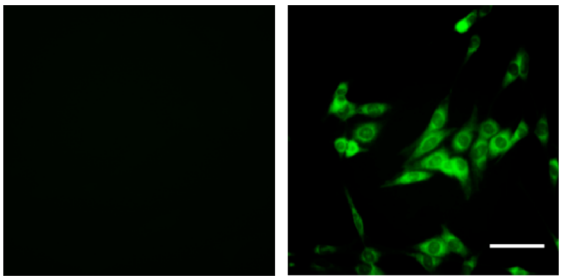

Figure 4. Fluorescence microscopic images of living PC12 cells. Cells stained without **6h** (left) and with **6h** (4 μM, right). Scale bar = 50 μm.

across the membrane and lighting up of the cytoplasm of rat pheochromocytoma cells (PC12). Finally, we determined the cytotoxicity of **6h** using a CCK8 assay and found that, at a concentration of 4 μM, the cells were completely viable (see Figures 1 and 2 on pages s8 and s9 in the SI).

In summary, a straightforward access to a range of new diazadiphosphafulvalenes as their P-oxides or P-sulfide has been described. By themselves or as their reduced P(III) derivatives, they open numerous possibilities in coordination chemistry that we are currently exploring. Their most specific feature is the coexistence inside a single conjugated backbone of donor nitrogen and strongly acceptor phosphoryl sites, suggesting interesting dipolar properties. Additional research is currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03971.

Experimental procedure and characterization of all new compounds (PDF)

Accession Codes

CCDC 1515639 (**3**), 1524758 (**4**), 1539284 (**5**), 1546555 (**6b**),1546556 (*trans*-**6d**), 1562501 (*trans*-**6e**), 1569257 (**6g**), and 1571295 (**6h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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