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Reaction of Phosphines with 1-Azido-(2-halogenomethyl)benzene Giving Aminophosphonium-Substituted Indazoles

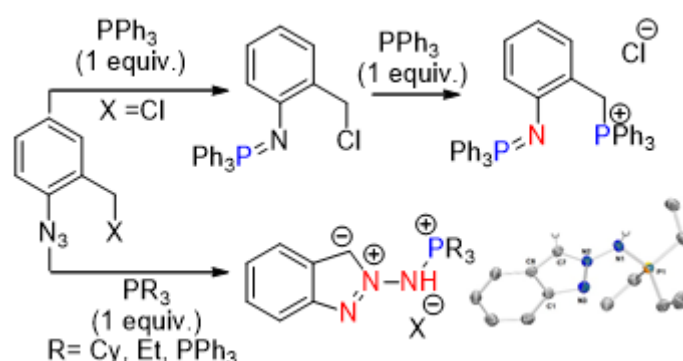
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Abstract: The reaction between a 1-azido-(2-halogenomethyl)benzene and a phosphine gives different products depending on the nature of the halogen, the phosphine itself and the solvent employed. While PPh_3 (2 equiv.) reacts with the chloro reagent in toluene to give the expected iminophosphorane-phosphonium adduct, trialkylphosphines (PCy_3 and PEt_3) surprisingly furnish an aminophosphonium substituted by a zwitterionic indazole. The bicyclic product can also form from PPh_3 using the bromo reagent in acetonitrile. A mechanism is proposed for this cyclization based on DFT calculations.

In a seminal paper dating back to 1919, J. Meyer and H. Staudinger reported that the reaction between a phosphine and an azide delivers a phosphinimine (or iminophosphorane) derivative featuring a $\text{P}=\text{N}$ bond, after release of N_2 gas.¹ This transformation has found numerous applications in organic synthesis² and also in chemical biology with the preparation of bioconjugates by the so-called Staudinger ligation.³ The involvement of phosphazides (Figure 1), initially postulated by Meyer and Staudinger, has been proved and its decomposition with loss of N_2 has been investigated.⁴ While they were first described as transient species, it has been demonstrated that they can be stabilized via the proper choice of the phosphorus substituents or by coordination to metals or main group

elements.⁵ Moreover, their trapping with a variety of C-sp^2 electrophiles leading to nitrogen heterocycles has also been explored.⁶ Of note, the Staudinger reaction has also been largely employed by chemists interested in the development of iminophosphorane based ligands.⁷

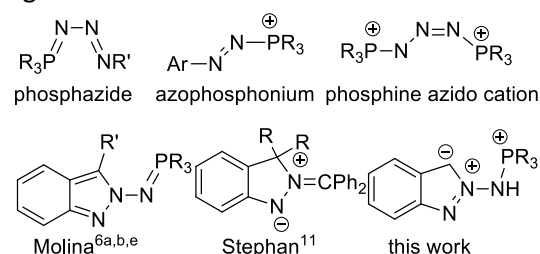
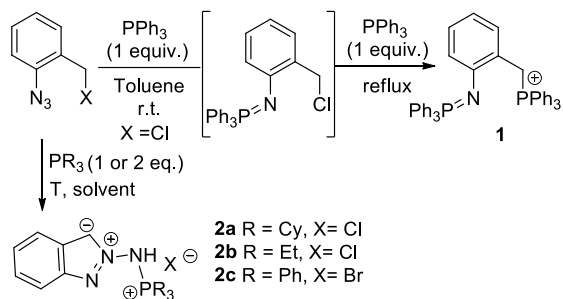


Figure 1 Examples of azo or azido containing compounds

In this report we describe our study of the reaction of a phosphine with a 1-azido-(2-halogenomethyl)benzene which, depending on

the nature of the phosphine, the halide, and the solvent, yields either the expected iminophosphorane **1** or, surprisingly, the aminophosphonium substituted indazole **2** (Scheme 1).



Scheme 1: Reaction of 1-azido-(2-methylhalogeno)benzene with phosphines

The latter belongs to the small family of organic molecules combining azo or azido fragments with phosphorus atoms (Figure 1). The deprotonation of the aminophosphonium derivatives **2** to give the corresponding iminosphosphoranes **3** is also described. A mechanism is proposed, based on DFT calculations, to explain the formation of the cyclic products **2**.

Addition of triphenylphosphine (1 equiv.) to a toluene solution of 1-azido-(2-chloromethyl)benzene at room temperature induced a strong nitrogen evolution (Scheme 1). After overnight stirring, the $^{31}\text{P}\{^1\text{H}\}$ NMR monitoring of the supernatant evidenced the formation of the iminophosphorane ($\delta=0.3$ ppm) and some unreacted PPh_3 in a ratio close to 95:5. A white precipitate also appeared indicating that the bifunctional iminophosphorane phosphonium derivative **1** started to form. To isolate **1**, a second equivalent of triphenylphosphine was added and the reaction mixture was heated to reflux for 24 h to favor the substitution of the chloride by PPh_3 . Thus, the iminophosphorane is formed prior to the chlorine substitution. Alternatively, the reaction can also be performed by adding directly 2 equiv. of PPh_3 and compound **1** precipitates out of the reaction mixture. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of this compound in CD_2Cl_2 shows two singlets at 7.6 and 20.4 ppm

corresponding respectively to the $\text{R}_3\text{P}=\text{N}$ and the phosphonium groups. Aside from several aromatic resonances, the ^1H NMR spectrum exhibits a doublet at 5.14 ppm ($^2J_{\text{P,H}} = 13.5$ Hz) corresponding to the two benzylic protons, which is in the range of data reported for benzyltriphenylphosphonium derivatives.⁸

The structure of **1** was confirmed by X-ray diffraction (Figure S1). The iminophosphorane and the phosphonium moieties exhibit bond lengths and angles which are typical for such functional groups. Of note, no interaction between the electron-rich nitrogen and the electron-deficient phosphonium group was observed in the solid state. On the contrary, the methylene-phosphonium group is almost orthogonal to the mean plan containing the aromatic ring and the iminophosphorane moiety (dihedral angle: 84.99° , see Figure S1).

A large amount of precipitate formed when the reaction was conducted with tricyclohexylphosphine (1 or 2 equiv.) at room temperature. $^{31}\text{P}\{^1\text{H}\}$ NMR monitoring of the supernatant did not show the formation of the expected iminophosphorane. Instead, only traces of Cy_3PO could be observed, as well as remaining PCy_3 when 2 equivalents were used. In that latter case, heating the reaction mixture to favor the consumption of the phosphine did not change the composition of the supernatant. The formed solid was isolated and analyzed by multinuclear NMR. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showed only a deshielded singlet at 58.0 ppm in CD_2Cl_2 and the ^1H NMR spectrum did not evidence any benzylic type proton. Instead, only aromatic and cyclohexyl resonances were observed, as well as a highly deshielded broad singlet at 8.41 ppm. The latter correlates with an aromatic resonance at 7.69 ppm in the COSY ^1H - ^1H spectrum, and the phosphorus signal in the heterocopy ^{31}P - ^1H . The elemental composition of the molecular ion (m/z 412.2875) obtained from HR-MS analysis is $\text{C}_{25}\text{H}_{39}\text{N}_3\text{P}$, giving a yield of 78 % for **2a**. Moreover, this ion loses N_2 to give an ion at m/z 384.2822 in Collision-Induced Dissociation (CID) experiments. This evidences that the N_3

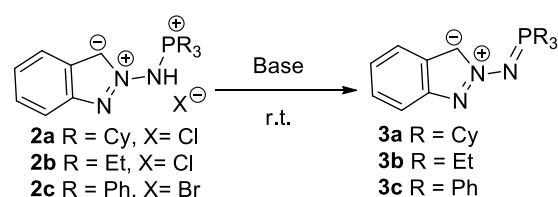
motif is kept during the reaction. Definitive evidence regarding the structure of **2a** came from X-ray analysis (Figure S2). It can be described as an aminophosphonium-substituted indazole (Scheme 1). Although the charges are localized in Scheme 1 for clarity, the planarity of the molecule (Figure S2, torsion angle C6C7N2N3: 0.74°) and the intermediate bond lengths measured within the bicycle (Table S3) reveal that the electron density is delocalized. We did not find any comparable P-NH-N-N motif in the CCDC database, nor a tricyclohexyl aminophosphonium to compare with. Nevertheless, the P-N bond in **2a** (1.6502(16) Å) is in the upper range of those reported for aminophosphonium derivatives. The endocyclic N2N3 bond, measured at 1.341(2) Å, is also rather long for a N=N bond. It is indeed longer than the average length measured for azophosphoniums⁹ (1.272 Å on average), non-metallated phosphazides (1.277 Å on average) or phosphine azido cations¹⁰ (1.277 Å on average) available in the CCDC database (Figure 1). Such a bond length is reminiscent of the N-N bond reported by Stephan's group in 2018 when deprotonating a cyclic (amino)(aryl)nitrenium cation α to the nitrogen (Figure 1) for which the N-N bond length is 1.3584(14) Å.¹¹ It should be noted that such a cyclic product was never observed when reacting PCy₃ with 2-(azidomethyl)-6-(chloromethyl)pyridine.^{7m} Here, the cyclization is probably driven by the stability of the indazole structure and the electron delocalization within the molecule. Indeed, **2a** can be stored in vials on the bench and the ³¹P{¹H} of its solution in chloroform or dichloromethane does not change within 1 or 2 days.

In order to determine whether the indazole could form with a less sterically hindered phosphine, the same reaction was conducted with PEt₃. ³¹P{¹H} NMR analysis of the supernatant of the crude reaction mixture obtained from toluene with 1 equiv. of PEt₃ showed several resonances. Nevertheless, NMR analysis of the precipitate evidenced 3

products, among which the major one exhibits a singlet ³¹P{¹H} resonance at 68.9 ppm, which fits with the ³¹P chemical shift reported for aminotriethylphosphonium.¹² Reasoning that the substitution reaction should be easier in more polar solvent, the reaction was repeated in acetonitrile, leading to less side products. The major compound labelled **2b** could be isolated in 65 % yield by precipitation in toluene and its characterization by multinuclear NMR pointed to a structure similar to **2a**. The structure of **2b** was also confirmed by X-ray diffraction analysis (see Figure S3). The bond lengths and angles are very similar to those of **2a** (Table S3).

The formation of the indazole from PPh₃ was also attempted with the seemingly more electrophilic 1-azido-(2-bromomethyl)benzene. When the reaction was conducted in toluene at room temperature, a mixture of at least 4 different products was obtained, but its analysis by HR-MS spectrometry evidenced the presence a compound of type **2**. The aminophosphonium substituted indazole **2c** could finally be isolated in 73% yield by reacting PPh₃ and 1-azido-(2-methylbromo)benzene in acetonitrile, from which the product precipitated out. **2c** was characterized by multinuclear NMR, HR-MS measurement and X-ray crystallography (Figure S4). The bond lengths and angles are similar to those of **2a** and **2b** except the NNP angle, which is more acute than that previously observed (116.25 ° vs 119.78 ° on average).

Other phosphines were tested without success: PMe₃ gave a mixture of inseparable products whatever the solvent used, and PMe₃ remained unreactive even towards the bromide electrophile in refluxing acetonitrile.

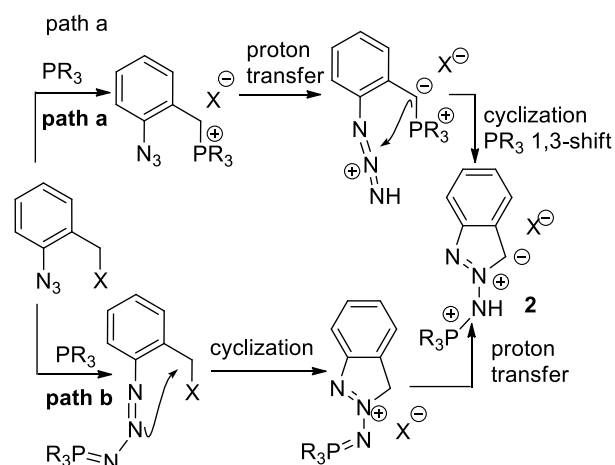


Scheme 2: Preparation of iminophosphorane **3a-c**

Iminophosphorane derivatives **3a-c** were prepared by deprotonation of aminophosphoniums **2a-c** (Scheme 2). These compounds resemble the nitrogen heterocycles described by Molina and coworkers^{6a, 6b, 6e} (Figure 1), except the absence of substituent at the benzylic carbon. Depending on the solubility of the formed iminophosphorane in organic solvents, the reaction was performed either with a stoichiometric amount of KHMDS in THF or with BuLi in Et₂O. Some compound was lost during workup, explaining the modest yield obtained for **3a** and **3c** (40% and 57% respectively). In ³¹P{¹H} NMR spectra, the deprotonation induces a large shielding of the phosphorus nucleus with ³¹P{¹H} resonances at 34.4, 37.1, and 11.3 ppm for **3a-c** respectively. On the contrary, the ¹H resonance of the benzylic hydrogen is only slightly shielded ($\Delta\delta$ between -0.1 and -0.4 ppm) as is the corresponding ¹³C{¹H} resonance, but a large increase of the *J*_{P,C} coupling constant from 3.0 Hz in **2** to 13.5-14.5 Hz in **3** was observed. The structures of **3a** and **3c** were analyzed by X-ray diffraction. They are very similar to those of **2a** (Figures S5, S6, and Table S3). The deprotonation is accompanied by an expected shortening of the PN bonds (1.6130(6) and 1.6002(14) Å in **3a** and **3c** respectively), which falls in the range of those commonly observed for iminophosphoranes. Otherwise, bonds and angles measured are similar to those of the corresponding aminophosphonium, except a slight shortening of the exocyclic NN bond (1.372(3) vs 1.388(2) Å) observed in **3a**.

In order to shed light on the mechanism of formation of **2**, DFT calculations were conducted at the M06-2X/6-311++G(2d,p)//M06-2X/6-31(d) level of theory (see the Supporting Information for details). Two different mechanisms can be proposed. The first one consists in an initial substitution of the halide by the phosphine followed by a proton transfer, a nucleophilic attack of the benzylic carbon on the central nitrogen, and a

1,3 carbon to nitrogen shift of the PR₃ fragment (Scheme 3, path a).



Scheme 3: Mechanistic pathways to form **2**

The second pathway involves the nucleophilic attack of the central N atom of the intermediate phosphazide onto the benzylic carbon followed by a proton transfer (Scheme 3, path b). These two mechanistic options were investigated with two model phosphines (PMe₃ and PPh₃) and two electrophiles (X = Cl, Br, see the Supporting Information). For path a, the substitution of the halide could be computed with activation barrier of 23.5 (PMe₃) and 26.5 kcal mol⁻¹ (PPh₃) for the chloride, and 17.3/20.3 kcal mol⁻¹ for the bromide substitution (Scheme S2, **Int1** to **Int6**). Nevertheless, the subsequent proton transfer could not be calculated. The formation of the final products from the azido-ylides could be calculated in 3 steps (Scheme S3, **Int7** to **Int13**) but the 1,3 transfer of the phosphine group faces an unsurmountable barrier ($\Delta G_{298} \geq 40$ kcal mol⁻¹), which is typical of a symmetry-forbidden 1,3-shift. The second option for the formation of the experimentally observed products (Scheme 3, path b) starts with the addition of the phosphine to the terminal nitrogen of the N₃ framework to give the corresponding azidophosphoniums **Int14-17** (Figure 2). In the chlorine series, the transition states lie at lower energies than those of the S_N2 pathway (21.6 vs 23.5, 24.4 vs 26.5 kcal mol⁻¹). On the other hand, the direct substitution of the bromine by the phosphine remains a faster process (21.7 vs 17.3, 23.9 vs 20.4 kcal mol⁻¹). Compounds **Int14-17** are

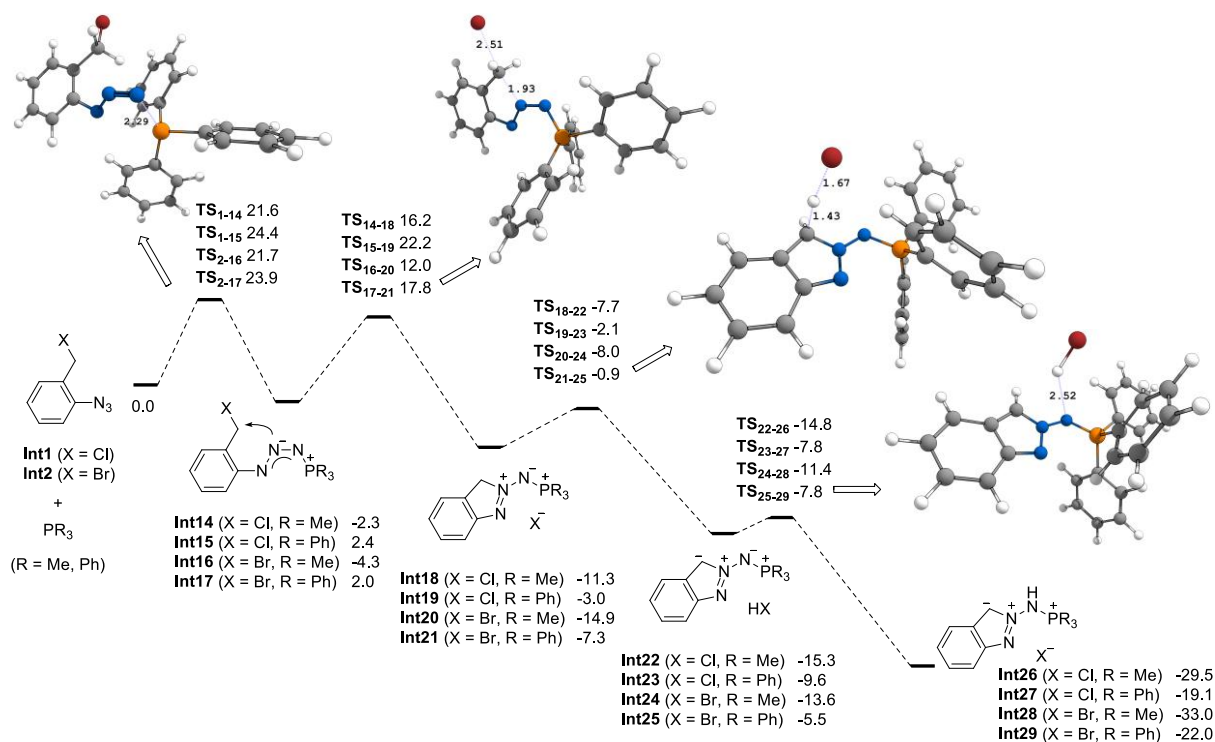


Figure 2: Free energy profile of the formation of the final products **Int26-29** from azidophosphoniums (ΔG_{298} , kcal mol⁻¹; selected distances in Å)

obtained in a *s-cis* configuration, which is more stable than the *s-trans* one by ~3-4 kcal mol⁻¹.¹³ These adducts are slightly more stable than the reactants with PMe₃ and slightly less with PPh₃. Substitution of the halide by the central nitrogen proceeds through transition states that are all more stable than those computed in the S_N2 case (Figure 2 and Scheme S3). As one could expect, displacement of the bromine is easier than that of the chlorine. This step is faster and more exergonic with the alkylphosphine PMe₃ than PPh₃. The proton transfer was modeled as a two-step downhill process using the halide as a base. Deprotonation of **Int18-21** is straightforward with barrier ranging from 1 to 7 kcal mol⁻¹. The protonation of the terminal nitrogen is also achieved at a low free energy cost of ~1-2 kcal mol⁻¹. The overall exergonicities are higher with PMe₃ (-29.5/-33.0 kcal mol⁻¹) than with PPh₃ (-19.1/-22.0 kcal mol⁻¹). Thus, path b in Scheme 3 better explains the formation of the final products. On both kinetic and thermodynamic grounds, an alkylphosphine such as PMe₃ is more likely to follow this pathway than a less electron-rich phosphine such as PPh₃.

In conclusion, we evidenced that the reaction of a phosphine with 1-azido-(2-halogenomethyl)benzene depends on the substituents of the P atom, the nature of the halide and the operating conditions. While iminophosphorane can be obtained from triphenylphosphine and 1-azido-(2-chloromethyl)benzene in toluene, allowing to isolate an iminophosphorane-phosphonium derivative using 2 equiv. of PPh₃, PCy₃ and PEt₃ do not give the iminophosphorane linkage. Instead, a bicyclic compound **2** is obtained. Such a compound can also be isolated from PPh₃ using a better leaving group on the carbon and a more polar solvent. The mechanism of this cyclization was investigated by DFT calculations; the nucleophilic attack of the phosphazide onto the electrophilic carbon appearing as the more favorable pathway. Iminophosphoranes **3** were then obtained by deprotonation of aminophosphonium **2**. These derivatives exhibit two electron rich atoms: the nitrogen of the P=N and the benzylic carbon. It would therefore be interesting to study their reactivity towards organometallic or organic electrophiles and Lewis acids. Remarkably,

more than a century after its discovery, Staudinger type reaction can still open access to unprecedented chemical structures.

Experimental section

General considerations. All reactions were conducted under an atmosphere of dry nitrogen, or argon, using standard Schlenk and glovebox techniques. Solvents and reagents were obtained from commercial sources. Solvents were dried with a M-Braun MB-SPS 800 solvent purification system. Deuterated solvents were used as received and stored over molecular sieves. All other reagents and chemicals were obtained commercially and used without further purification. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 300 spectrometer operating at 300 MHz for ^1H , 75.5 MHz for ^{13}C and 121.5 MHz for ^{31}P . Solvent peaks were used as internal references for ^1H and $^{13}\text{C}\{^1\text{H}\}$ chemical shifts (ppm). $^{31}\text{P}\{^1\text{H}\}$ NMR spectra are relative to a 85% H_3PO_4 external reference. Unless otherwise mentioned, NMR spectra were recorded at 300 K. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Coupling constant are expressed in hertz. The following abbreviations are used: br, broad; s, singlet; d, doublet; q, quadruplet; t, triplet; m, multiplet; v, virtual. The spectra were analyzed with MestReNova software. IR spectra were recorded on a IR-TF Thermo Scientific Nicolet iS5 spectrometer. Mass spectrometry experiments were recorded on tims-TOF mass spectrometer (Bruker, France). Samples are prepared in CH_3CN and introduced at $5 \mu\text{L} \cdot \text{min}^{-1}$ flow rate into the electrospray ion (ESI) source in positive mode. Both full scan (MS) and collision induced dissociation (CID) mass spectra have been carried for the compound characterization. In MS/MS experiment, the precursor ion was selected with an isolation window of 2 Da and the collision induced dissociation was performed using 20 eV as collision energy. Tuning mix (Agilent, France) was used for calibration. Accurate masses and elemental compositions were obtained using the DataAnalysis software. The elemental compositions were obtained with a tolerance below 5 ppm.

Preparation of 1: To a solution of 1-azido-2-(chloromethyl)benzene¹⁴ (341.8 mg, 2.04 mmol) in toluene (20 mL) was added triphenylphosphine (1.07 g, 4.08 mmol). After stirring the reaction mixture at room temperature under nitrogen stream overnight, the in situ $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of slight suspension evidences the formation of the iminophosphorane function ($\delta = 0.4$ ppm) and remaining triphenylphosphine. The reaction mixture was then heated at reflux with an oil bath, reinforcing the precipitation of a white solid. The reaction was stopped when only traces of triphenylphosphine are observed by in situ $^{31}\text{P}\{^1\text{H}\}$ NMR. The white solid was isolated by filtration, washed with toluene (20 mL) and dried to give compound **1** (1.2 g, 90 %). Single crystals of **1** were obtained by slow diffusion of pentane into a concentrated dichloromethane solution of the compound. ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 7.6 (s, N=P), 20.4 (s, P^{III}). ^1H NMR (300 MHz, CD_2Cl_2): δ 7.79 (br. t, $J_{\text{H,H}} = 7.5$ Hz, $J_{\text{P,H}} = 7.0$ Hz, 3H, CH(PPh₃)), 7.70-7.40 (m, 24 H, CH(PPh₃)), 6.87 (br. d, $J_{\text{H,H}} = 7.5$ Hz, 1H, CH(Ar)), 6.82 (br. d, $J_{\text{H,H}} = 8.5$ Hz, 1H, CH(Ar)), 6.49 (vt, $J_{\text{H,H}} = J_{\text{P,H}} = 7.5$ Hz, 1H, CH(Ar)), 6.33 (d, $J_{\text{H,H}} = 8$ Hz, 1H, CH(Ar)), 5.14 (d, $J_{\text{P,H}} = 13.5$ Hz, CH₂). $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, CD_2Cl_2): δ 151.2 (d, $J_{\text{P,C}} = 5$ Hz, C^{IV}-N), 134.9 (d, $J_{\text{P,C}} = 3.0$ Hz, CH(PPh₃)), 134.1 (d, $J_{\text{P,C}} = 9.5$ Hz, CH(PPh₃)), 132.4 (d, $J_{\text{P,C}} = 10.0$ Hz, CH(PPh₃)), 132.2 (d, $J_{\text{P,C}} = 3.0$ Hz, CH(PPh₃)), 130.3 (d, $J_{\text{P,C}} = 5.5$ Hz, CH(Ar)), 130.0 (d, $J_{\text{P,C}} = 12.5$ Hz, CH(PPh₃)), 129.7 (d, $J_{\text{P,C}} = 100.0$ Hz, C^{IV}(PPh₃)), 129.1 (d, $J_{\text{P,C}} = 4.0$ Hz, CH(Ar)), 128.8 (d, $J_{\text{P,C}} = 12.0$ Hz, CH(PPh₃)), 121.4 (d, $J_{\text{P,C}} = 10.5$ Hz, CH(Ar)), 129.7 (obs. by 2D NMR, C^{IV}(Ar)), 118.7 (dd, $J_{\text{P,C}} = 85.0$ Hz, C^{IV}(PPh₃)), 117.3 (d, $J_{\text{P,C}} = 3.5$ Hz, CH(Ar)), 26.9 (d, $J_{\text{P,C}} = 49.0$ Hz, CH₂). IR (neat, cm^{-1}): 2360, 1588, 1479, 1347 (N=P), 1111. HRMS (ESI⁺/Q-TOF) m/z : [**1**-Cl]⁺ Calcd for $\text{C}_{43}\text{H}_{36}\text{NP}_2^+$ 628.2318; Found 628.2319.

Preparation of 2a. A solution of PCy₃ (560 mg, 2.0 mmol) in toluene (3 mL) was added to a solution of 1-azido-2-(chloromethyl)benzene (335 mg, 2.0 mmol) in toluene (15 mL). The

reaction mixture was stirred overnight at room temperature and then heated to reflux for 1 h with an oil bath to complete the reaction. The precipitate was filtered and washed with toluene (5 x 5 mL) to deliver **2a** as an off-white colored solid (649 mg, 1.55 mmol, 78%). Single crystals of **2a** were obtained by slow diffusion of pentane into a concentrated dichloromethane solution of the compound. ³¹P NMR (121.5 MHz, CD₂Cl₂): δ 58.0 (s). ¹H NMR (300 MHz, CD₂Cl₂): δ 8.37 (br. s, 1H, CH-N), 7.61 (br. t, *J*_{H,H} = 9.0 Hz, 2H, CH(Ar)), 7.28 (br. t, *J*_{H,H} = 7.5 Hz, 1H, CH(Ar)), 7.09 (br. t, *J*_{H,H} = 7.5 Hz, 1H, CH(Ar)), 2.80 (vq, *J*_{H,H} = *J*_{P,H} = 12.5 Hz, *J*_{H,H} = 2.5 Hz, 3H, CH(Cy)), 2.11-1.26 (m, 30 H, CH₂(Cy)). ¹³C{¹H} NMR (75.5 MHz, CD₂Cl₂): δ 145.5 (s, C^{IV}-N), 125.9 (s, CH(Ar)), 121.9 (s, CH(Ar)), 120.7 (d, *J*_{P,C} = 3.0 Hz, CH-N), 120.8 (s, C^{IV}-C), 119.9 (s, CH(Ar)), 116.7 (s, CH(Ar)), 33.1 (d, *J*_{P,C} = 47.0 Hz, CH(Cy)), 26.7 (d, *J*_{P,C} = 13.0 Hz, CH(Cy)), 26.5 (d, *J*_{P,C} = 3.0 Hz, CH(Cy)), 25.5 (s, CH(Cy)). IR (neat, cm⁻¹): 2928, 2852, 2361, 2342, 1444, 1006. HRMS (ESI⁺/Q-TOF) *m/z*: [**2a**-Cl]⁺ Calcd for C₂₅H₃₉N₃P⁺ 412.2876; Found 412.2885.

Preparation of 2b. A solution of PEt₃ (237.7 mg, 2.01 mmol) in CH₃CN (3 mL) was added to a solution of 1-azido-2-(chloromethyl)benzene (337.2 mg, 2.01 mmol) in CH₃CN (7 mL). The reaction mixture was stirred overnight at room temperature. The solvent was then evaporated and the residue was washed with toluene (2x10 mL), THF (2x10 mL) to deliver **2b** as an off-white solid (372 mg, 1.30 mmol, 65%). Single crystals of **2b** were obtained by slow diffusion of pentane into a concentrated dichloromethane solution of the compound. ³¹P NMR (121.5 MHz, CD₂Cl₂): δ 68.9 (s). ¹H NMR (300 MHz, CD₂Cl₂): δ 8.20 (br. s, 1H, CH-N), 7.64 (dd, *J*_{H,H} = 8.5 Hz, *J*_{H,H} = 1.0 Hz, 1H, CH(Ar)), 7.60 (dd, *J*_{H,H} = 8.5 Hz, *J*_{H,H} = 1.0 Hz, 1H, CH(Ar)), 7.31 (ddd, *J*_{H,H} = 8.5 and 7.0 Hz, *J*_{H,H} = 1.0 Hz, 1H, CH(Ar)), 7.11 (ddd, *J*_{H,H} = 8.5 and 7.0 Hz, *J*_{H,H} = 1.0 Hz, 1H, CH(Ar)), 2.49 (dq, *J*_{H,H} = 7.5 Hz, *J*_{P,H} = 15.5 Hz, 6 H, CH₂), 1.30 (dt, *J*_{H,H} = 7.5 Hz, *J*_{P,H} = 19.5 Hz, 9 H, CH₃). ¹³C{¹H} NMR (75.5 MHz, CD₂Cl₂): δ 146.1 (s, C^{IV}-N), 126.4 (s, CH(Ar)), 122.3 (s, CH(Ar)), 121.5 (d, *J*_{P,C} = 3.0 Hz, CH-N), 120.7 (s,

C^{IV}-C), 120.0 (s, CH(Ar)), 116.8 (s, CH(Ar)), 14.7 (d, *J*_{P,C} = 56.0 Hz, PCH₂), 5.28 (d, *J*_{P,C} = 5.0 Hz, CH₃). IR (neat, cm⁻¹): 3387, 2900, 2541, 2361, 1454, 1050. HRMS (ESI⁺/Q-TOF) *m/z*: [**2b**-Cl]⁺ Calcd for C₁₃H₂₁N₃P⁺ 250.1468; Found 250.1467.

Preparation of 2c: Triphenylphosphine (266 mg, 1.05 mmol) was added to a solution of 1-azido-2-(bromomethyl)benzene (221 mg, 1.04 mmol) in acetonitrile (3 mL). After stirring 20 min., a white precipitate formed, and the solution was left to stir overnight at room temperature. The completion of the reaction was checked by ³¹P NMR, showing no triphenylphosphine left. The solid was filtered and washed with toluene (2 x 3 mL) to give the product as a white solid (361 mg, 73%). Single crystals of **2c** were obtained by slow diffusion of pentane into a concentrated dichloromethane solution of the compound. ³¹P NMR (121.5 MHz, CDCl₃): 41.5. ¹H NMR (300 MHz, CDCl₃): 7.98 (br. s, 1H, CH-N), 7.82 (td, *J*_{H,H} = 7.5, *J*_{P,H} = 13.5 Hz, 6H, CH(PPh₃)), 7.73 (td, *J*_{H,H} = 7.5, *J*_{P,H} = 1.5 Hz, 3H, CH(PPh₃)), 7.56 (td, *J*_{H,H} = 7.5, *J*_{P,H} = 4.0 Hz, 6H, CH(PPh₃)), 7.41 (t, *J*_{H,H} = 7.5, 2H, CH(Ar)), 7.15 (m, 1H, CH(Ar)), 6.97 (m, 1H, CH(Ar)). ¹³C{¹H} NMR (75.5 MHz, CDCl₃): 145.9 (s, C^{IV}-N), 135.4 (d, *J*_{P,C} = 3.0 Hz, CH(PPh₃)), 134.3 (d, *J*_{P,C} = 11.5 Hz, CH(PPh₃)), 129.8 (d, *J*_{P,C} = 14.50 Hz, CH(PPh₃)), 126.4 (s, CH(Ar)), 123.6 (d, *J*_{P,C} = 2.5 Hz, CH-N), 122.3 (s, CH(Ar)), 120.7 (s, C^{IV}-C), 120.0 (s, CH(Ar)), 118.9 (d, ¹*J*_{P,C} = 102.0 Hz, C^{IV}-P), 117.3 (CH(Ar)). IR (neat, cm⁻¹): 3075, 2563, 1628, 1586, 1483, 1438, 1403, 1377, 1323, 1111. HRMS (ESI⁺/Q-TOF) *m/z*: [**2c**-Br]⁺ Calcd for C₂₅H₂₁N₃P⁺ 394.1468; Found 394.1477.

Preparation of 3a (R = Cy): KHMDs (60 mg, 0.3 mmol) was added to a solution of **2a** (148 mg, 0.3 mmol) in THF (4 mL). The solution became slightly yellow after 1 h stirring. The reaction mixture was then centrifugated. The solid was discarded and the solution was evaporated to dryness. The residue was washed with pentane (2 x 5 mL) and dried to deliver **3a** as an off-white solid (49 mg, 40%). Single crystals of **3a** were obtained by slow evaporation of pentane

solution of the compound. ^{31}P NMR (121.5 MHz, C_6D_6): 34.4. ^1H NMR (300 MHz, C_6D_6): 8.03 (br. s, 1H, CH-N), 7.83 (d, $J_{\text{H,H}} = 8.5$, 1 H, CH(Ar)), 7.51 (d, $J_{\text{H,H}} = 8.0$, 1 H, CH(Ar)), 7.22 (m, 1 H, CH(Ar)), 7.03 (t, $J_{\text{H,H}} = 8.0$ Hz, 1 H, CH(Ar)), 2.32 (vq, $J_{\text{H,H}} = J_{\text{P,H}} = 12.0$ Hz, 3 H, $\text{CH}_2(\text{Cy})$), 1.91 (d, $J_{\text{H,H}} = 12.0$ Hz, 6 H, CH(Cy)), 1.75-1.35 (m, 16 H, CH(Cy)), 1.3-0.8 (m, 8 H, CH(Cy)). $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, C_6D_6): 145.3 ($\text{C}^{\text{IV}}\text{-N}$), 122.8 (s, CH(Ar)), 122.5 (s, $\text{C}^{\text{IV}}\text{-C}$), 119.6 (s, s, CH(Ar)), 118.2 (s, CH(Ar)), 115.1 (d, $J_{\text{P,C}} = 13.5$ Hz, CH-N), 114.5 (s, CH(Ar)), 35.7 (d, $J_{\text{P,C}} = 54.5$ Hz, $\text{CH}_2(\text{Cy})$), 27.3 (d, $J_{\text{P,C}} = 4.0$ Hz, CH(Cy)), 27.0 (s, CH(Cy)), 26.0 (s, CH(Cy)). IR (neat, cm^{-1}): 2927, 2851, 1448, 1430, 1378, 1259, 1169, 1019. HRMS (ESI⁺/Q-TOF) m/z: [**3a**+H]⁺ Calcd for $\text{C}_{25}\text{H}_{39}\text{N}_3\text{P}^+$ 412.2876; Found 412.2888.

Preparation of **3b** (R = Et): *n*-BuLi in hexanes (1.6 M, 0.92 mmol, 0.57 mL) was added to a suspension of **2b** (265 mg, 0.92 mmol) in Et_2O (4 mL) at -78 °C. The reaction mixture was allowed to slowly warm to room temperature and stirred overnight. The mixture was filtered to remove LiCl and the filtrate was evaporated to give a yellow oil (174 mg, 75 %). ^{31}P NMR (121.5 MHz, THF- d_8): 37.3. ^1H NMR (300 MHz, THF- d_8): 7.63 (br. s, 1H, CH-N), 7.40 (d, $J_{\text{H,H}} = 8.0$ Hz, 1 H, CH(Ar)), 7.33 (d, $J_{\text{H,H}} = 8.0$ Hz, 1 H, CH(Ar)), 6.99 (t, $J_{\text{H,H}} = 8.0$ Hz, 1 H, CH(Ar)), 6.83 (t, $J_{\text{H,H}} = 7.5$ Hz, 1 H, CH(Ar)), 2.07 (dq, $J_{\text{H,H}} = 7.5$ Hz, $J_{\text{P,H}} = 12.5$ Hz, 3 H, CH_2), 1.16 (dt, $J_{\text{H,H}} = 7.5$ Hz, $J_{\text{P,H}} = 15.5$ Hz, 9 H, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, THF- d_8): 146.2 ($\text{C}^{\text{IV}}\text{-N}$), 123.0 (s, CH(Ar)), 122.8 (s, $\text{C}^{\text{IV}}\text{-C}$), 119.8 (s, CH(Ar)), 118.6 (s, CH(Ar)), 115.9 (d, $J_{\text{P,C}} = 14.0$ Hz, CH-N), 115.3 (s, CH(Ar)), 18.2 (d, $J_{\text{P,C}} = 61.5$ Hz, CH_2), 6.54 (s, CH_3). IR (neat, cm^{-1}): 2969, 2937, 2878, 1502, 1452, 1430, 1377, 1258, 1168, 1040, 1015. HRMS (ESI⁺/Q-TOF) m/z: [**3b**+H]⁺ Calcd for $\text{C}_{13}\text{H}_{21}\text{N}_3\text{P}^+$ 250.1468; Found 250.1469.

Preparation of **3c** (R=Ph): KHMDS (66 mg, 0.33 mmol) was added to a solution of **2c** (169 mg, 0.33 mmol) in THF (2 mL). The solution became brown upon addition of KHMDS. After overnight stirring at room temperature, the reaction mixture was centrifugated. The solid was discarded and the solution evaporated to

give a yellow oil. The oil was washed with pentane (4 mL) and dried to deliver **3c** as a yellow solid (74 mg, 57%). Single crystals of **3c** were obtained by slow diffusion of pentane into a concentrated THF solution of the compound at -35 °C. ^{31}P NMR (121.5 MHz, THF- d_8): 11.3 ppm. ^1H NMR (300 MHz, THF- d_8): 7.89 (dd, $J_{\text{P,H}} = 12.0$ Hz, $J_{\text{H,H}} = 7.0$ Hz, 6H, CH(PPh_3)), 7.83 (br. s, 1H, CH-N), 7.51 (dt, $J_{\text{H,H}} = 7.5$ Hz, $J_{\text{P,H}} = 1.5$ Hz, 3H, CH(PPh_3)), 7.42 (qd, $J_{\text{H,H}} = 7.5$ Hz, $J_{\text{P,H}} = 4.0$ Hz, 6H), 7.39 (d, $J_{\text{H,H}} = 7.0$ Hz, 1H, CH(Ar)), 7.17 (d, $J_{\text{H,H}} = 8.5$ Hz, 1H, CH(Ar)), 6.90 (ddd, $J_{\text{H-H}} = 8.5$, 7.5 and 1.0 Hz, Hz, 1H, CH(Ar)), 6.79 (t, $J_{\text{H,H}} = 7.5$ Hz, 1H, CH(Ar)). $^{13}\text{C}\{^1\text{H}\}$ NMR (75.5 MHz, THF- d_8): 144.5 (s, $\text{C}^{\text{IV}}\text{-N}$), 133.3 (d, $J_{\text{P,C}} = 9.5$ Hz, CH (PPh_3)), 131.7 (d, $J_{\text{P,C}} = 3.0$ Hz, CH (PPh_3)), 129.7 (d, $J_{\text{P,C}} = 99.5$ Hz, $\text{C}^{\text{IV}}\text{-P}$), 128.1 (d, $J_{\text{P,C}} = 12.0$ Hz, CH (PPh_3)), 122.0 (s, CH(Ar)), 121.8 (d, $J_{\text{P,C}} = 12.0$ Hz, $\text{C}^{\text{IV}}\text{-C}$), 118.9 (s, CH (Ar)), 117.6 (s, CH (Ar)), 115.5 (d, $J_{\text{P,C}} = 14.5$ Hz, CH-N), 114.7 (s, CH (Ar)). IR (neat, cm^{-1}): 3075, 1431, 1371, 1264, 1223, 1015. HRMS (ESI⁺/Q-TOF) m/z: [**3c**+H]⁺ Calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{P}^+$ 394.1468; Found 394.1479.

X-ray crystallography: Data were collected at 150 K on a Bruker Kappa APEX II diffractometer using a Mo- κ ($\lambda=0.71069\text{\AA}$) X-ray source and a graphite monochromator. The crystal structures were solved using Shelxt¹⁵ or oleix¹⁶ and refined using Shelxl-97 or Shelxl-2014.¹⁷ ORTEP drawings were made using ORTEP III¹⁸ for Windows or Mercury. Details of crystal data and structure refinements are summarized in Table S1 and S2.

Computational details. The computations were performed using the Gaussian 09 software package.¹⁹ Following a recent report,²⁰ the geometry of all compounds and transition states was optimized with the M06-2X functional²¹ and the 6-31G(d) basis set. Frequency calculations furnished the thermal correction to the Gibbs free Energy G_{corr} . Using the gas phase geometry, single point calculations at the M06-2X/6-311++G(2d,p) level were carried out to obtain the energies in solution E_{SCRF} (IEF-PCM method with Bondi radii).²² The free energy in solution at 298 K was obtained by adding the single point energy to the thermal correction to the Gibbs free energy

($G = E_{\text{SCRF}} + G_{\text{corr}}$). The discussed free energies are ΔG_{298} in kcal/mol in toluene.

Supporting Information

X-ray structures and the corresponding data, HR-mass and CID data, coordinates, energies and imaginary Frequencies of the computed species, as well as NMR spectra.

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