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1-Phospha-2-azanorbornenes by Phospha-aza-Diels–Alder Reaction

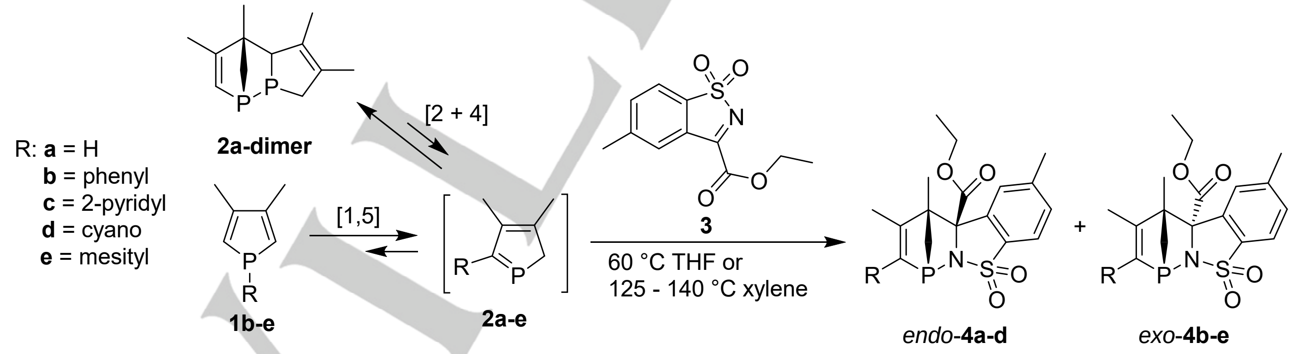
Peter Wonneberger, Nils König, Fabian B. Kraft, Menyhárt B. Sárosi, and Evamarie Hey-Hawkins*[a]

Abstract: The unprecedented phospha-aza-Diels–Alder reaction between an activated electron-poor imine and 2*H*-phospholes yields 1-phospha-2-azanorbornenes in a highly chemoselective and moderately diastereoselective reaction. The intermediate 2*H*-phospholes, which act as dienes, are formed in situ from the corresponding 1*H*-phospholes. Theoretical calculations confirm that the phospha-aza-Diels–Alder reaction is of normal electron demand. The reactive P–N bond in 1-phospha-2-azanorbornenes can be cleaved by nucleophiles with formation of 2,3-dihydrophospholes.

Hetero-Diels–Alder reactions, especially aza-Diels–Alder reactions, are a powerful and valuable way for obtaining heterocycles and are often a key step in natural product synthesis.[1] A large variety of functional groups and unsaturated nitrogen compounds can be used as dienophiles and/or dienes in aza-Diels–Alder reactions,[2] of which reactions involving activated imines as dienophiles are the most important.[2a] In contrast to their aza analogues, phospha-Diels–Alder-reactions have been investigated to a much lesser extent.[3] Beside phosphaalkenes,[4] phosphabutadienes,[5] various heterophospholes,[6] and phosphinines,[7] 2*H*-phospholes are versatile reactants for [2+4] and [4+2] cycloadditions.[8] However, combinations of both types of hetero Diels–Alder-reactions are rare. Bansal et al. described a phospha-aza-Diels–Alder reaction between a heterophosphole and an α,β-unsaturated imine.[9] Attempted Lewis acid-catalyzed phospha-aza-Diels–Alder reactions between 2*H*-phospholes and aldimines by Mathey et al. failed, but unexpectedly led to α-C_2-bridged diphospholes.[10]

Herein, we describe the first phospha-aza-Diels–Alder reaction between 2*H*-phospholes **2a**–**e** and an electron-poor imine, namely, *N*-sulfonyl α-imino ester **3**, resulting in unprecedented 1-phospha-2-azanorbornenes. In a highly chemo- and regioselective reaction, only the diastereomeric 1-phospha-2-azanorbornenes *endo*-**4a**–**d** and *exo*-**4b**–**e** are formed as racemic mixtures (Scheme 1, Table 1). Equimolar mixtures of the corresponding 1*H*-phospholes **1b**–**e** and **3** in xylene were heated to 125 or 140 °C. 3,4-Dimethyl-1-mesitylphosphole (**1e**) has not been reported up to now and was prepared from **1d** and mesityllithium according to the general procedure published by Mathey et al. (X-ray structure in Supporting Information).[11] Due to the bulky mesityl substituent, the sum of bond angles at the P atom (313.1(3)°) is, as expected, relatively large.[12] For **4a**, the dimer of **2a** was used as 2*H*-phosphole source.

The first and rate-determining step is the formation of the highly reactive 2*H*-phospholes **2** by a [1,5]-sigmatropic shift reaction (**1b–e**) or retro Diels–Alder reaction (**2a**).[8] Once formed, **2a**–**e** react immediately with dienophile **3**. At the temperatures employed (Table 1), no 2*H*-phosphole dimers (for **2b**–**e**) or other intermediates are detectable in the reaction mixture by $^{31}P\{^1H\}$ inverse gated decoupling NMR spectroscopy. Time-dependent NMR investigations of the phospha-aza-Diels–Alder reaction showed that the *exo* isomers are the kinetic and the *endo* isomers the thermodynamic products (shown for the reaction of **1b** and **3** in Figure 1). There is a strong correlation between the steric bulk of the substituent R in the corresponding 2*H*-phospholes **2** and the *endo*/*exo* ratio. A bulky substituent leads to *exo*-enriched 1-phospha-2-azanorbornenes. Thus, no *exo* isomer is observed for **4a**, and for **4e** no *endo* isomer was found in the reaction mixtures. The *endo*/*exo* ratios are only slightly



Scheme 1. The in-situ-formed 2*H*-phospholes **2a–e** react with imine **3** in a Diels–Alder reaction to form 1-phospha-2-azanorbornenes *endo*-**4a–d** and *exo*-**4b–e**. Only one enantiomer of each diastereomer is shown for clarity.

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Supporting information and detailed crystal structure information for this article is given via a link at the end of the document.

influenced by the reaction temperature (see Supporting Information). The reactivity of the phospholes decreases in the order **2a** > **1 c** > **1d** > **1b** > **1e** and reflects the dependence of the [1,5]-sigmatropic shift reactions on the substituent at phosphorus.[8a] The Diels–Alder reaction is fully reversible. Heating the pure diastereomers *endo*-**4b,c** and *exo*-**4b** in xylene for 24 h results in formation of the other isomers, *exo*-**4b,c** and *endo*-**4b**, in a thermodynamic equilibrium. The very high regioselectivity can be understood by considering the frontier molecular orbitals (Figure 2 for **2b** and **3**).

Table 1. Diels–Alder reaction between **2a** dimer, **1b–e**, and **3**. Reaction conditions and isolated products.

Phosphole	Reaction time and temperature	Ratio *endo*:*exo*	Yield[a] *endo*-**4**	Yield[a] *exo*-**4**
2a dimer	24 h, 60 °C	1:0	64%	-
1b	17 h, 140 °C	4:1	69%	7%
1c	90 min, 140 °C	5.5:1	42%	-
1d	3 h 45 min, 125 °C	9:1	73%	-
1e	11 h, 140 °C	0:1	-	63%

[a] Yield of isolated product.

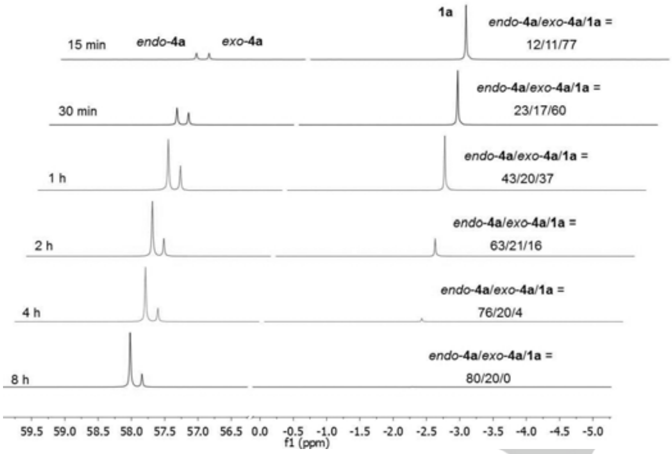
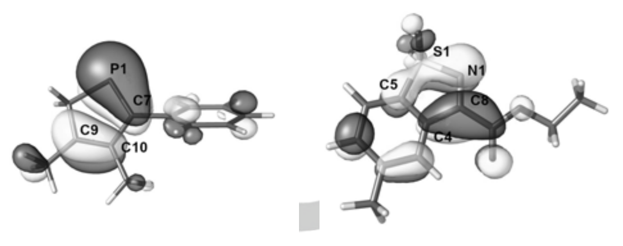


Figure 1. Time-dependent reaction of **1b** and **3** monitored by $^{31}P\{^1H\}$ inverse gated decoupled NMR spectroscopy.

Theoretical calculations (RI-B2PLYP-D3BJ/def2-TZVP,[13,14] gas phase) of the reaction between **2b** and **3** indicate clearly that this Diels–Alder reaction is of normal electron demand ($\Delta E_1 < \Delta E_2$).[15] During the Diels–Alder reaction, electron density is transferred from the HOMO of diene **2b** into the LUMO of dienophile **3**. The HOMO of **2b** has π(P1-C7) and π(C9-C10) character with the largest contributions coming from the P1 and C9 atomic orbitals. The LUMO of **3** has π*(N1-C8) character with the largest contributions coming from the atomic orbitals at N1 and C8. The greatest orbital overlap is observed between P1 in the LUMO of **2b** and N1 in the HOMO of **3**, and the second largest overlap is between C9 in the LUMO of **2b** and C8 in the HOMO of **3**. Thus, the electronic structures of **2b** and **3** favor the formation of a P–N bond.

$\Delta E_1 = E_{\mathrm{LUMO(dienophile)}} - E_{\mathrm{HOMO(diene)}} = 4.73$ eV
$\Delta E_2 = E_{\mathrm{LUMO(diene)}} - E_{\mathrm{HOMO(dienophile)}} = 8.19$ eV

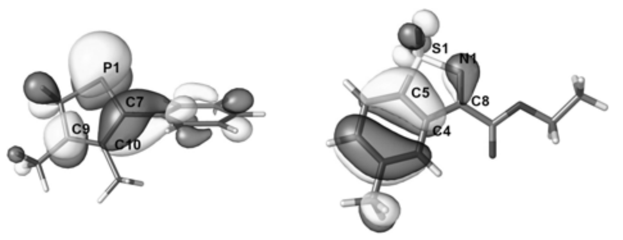
HOMO diene **2b**: LUMO dienophile **3**:



P1: 29.5% p_z; C7: 8.4% p_z
C9: 13.1% p_z; C10: 5.8% p_z

N1: 9.1% p_x; C8: 8.5% p_x
C5: 2.4% p_x; C4: 1.5% p_x

LUMO diene **2b**: HOMO dienophile **3**:



P1: 25.0% p_z; C7: 13.2% p_z
C9: 7.6% p_z; C10: 0.9% p_z

N1: 2.6% p_x; C8: 0.2% p_x
C5: 10.5% p_x; C4: 3.7% p_x

Figure 2. Frontier molecular orbitals of diene **2b** and dienophile **3**.

The pure diastereomers *endo*-**4b-d** and *exo*-**4b**,**e** were isolated by fractional crystallization from boiling toluene or toluene/hexane (or *n*-octane); *endo*-**4a** was obtained by crystallization from THF/toluene. Column chromatography was not suitable due to high moisture and oxygen sensitivity. The *exo* isomer of **4c,d** could not be isolated due to its very low concentration [*endo*/*exo* 5.5:1 (**4c**), 9:1 (**4d**)]; furthermore, on recrystallization of the *exo* isomer from boiling toluene, an *exo*/*endo* mixture is formed by *exo*–*endo* interconversion, which is faster for **4c** and **d** than for **4b**.

Structures of all isolated 1-phospha-2-azanorbornenes (*endo*-**4a–d** and *exo*-**4b,e**) were determined by 2D NMR experiments and X-ray structure analysis (Figures 3, 4 and Supporting Information); the isomers *exo*-**4c,d** were only verified by ^{1}H NMR and ^{31}P NMR spectroscopy in the reaction mixtures. The ^{31}P NMR chemical shifts (in $CDCl_3$) of the 1-phospha-2-azanorbornenes are in the range of 48.4 to 59.0 ppm. In the *endo* isomers (*endo*-**4a–d**), one of the diastereotopic hydrogen atoms at C18 (Figures 3 and 4) exhibits a strong anisotropic effect, which is not observed in *exo*-**4b**,**e**. For example, in *endo*-**4b**, the chemical shifts of the hydrogen atoms at C18 are 2.67 (dd, *J* = 11.5, 6.4 Hz) and 1.83 – 1.74 ppm (m), and those of *exo*-**4b** are 1.67–1.58 (m) and 1.52–1.44 ppm (m). The coordination geometry of phosphorus is distorted trigonal pyramidal. The P-N bond lengths in *endo*-**4a-d** and *exo*-**4b,e** (176.8 to 179.4 pm) correspond to a P-N single bond.[16] The P-C bonds have similar lengths. This is a clear difference to 1-phosphanorbornenes, in which the bond between P and the sp^2-hybridized C atom is shorter than the other P-C bonds.[17]

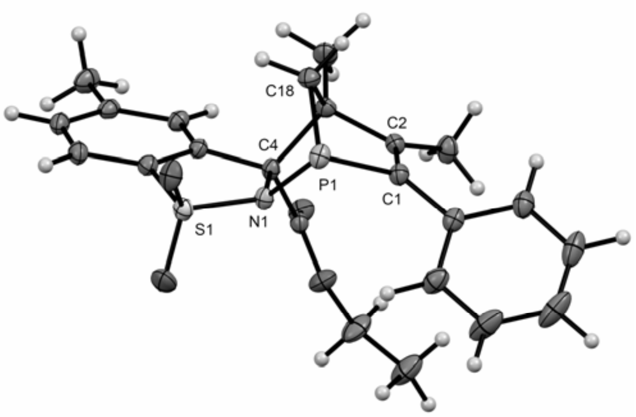


Figure 3. Molecular structure of *exo*-**4b**. Ellipsoids at 50% probability. Selected bond lengths [pm] and angles [°]:P1-N1 177.9(1), P1-C18 183.3(1), P1-C1 183.6(1), C1-C2 134.6(2), N1-C4 149.2(1); N1-P1-C1 94.95(5), N1-P1-C18 88.13(5), C1-P1-C18 88.49(6), S1-N1-P1 117.23(6).

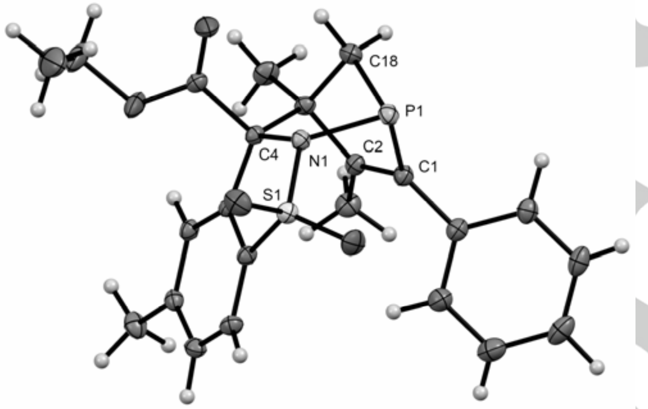
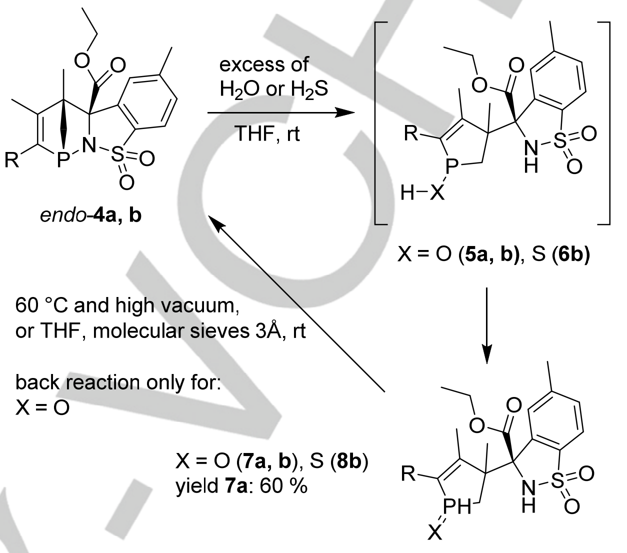


Figure 4. Molecular structure of *endo*-**4b**. Ellipsoids at 50% probability. Selected bond lengths [pm] and angles [°]: P1-N1 179.4(2), P1-C18 183.2(2), P1-C1 184.1(2), C1-C2 135.1(2), N1-C4 149.8(2); N1-P1-C1 96.39(7), N1-P1-C5 85.96(7), C1-P1-C18 88.43(8) S1-N1-P1 118.58(7).

The basicity of the *endo* isomers of 1-phospha-2-azanorbornenes was probed by treating solutions of *endo*-**4b** and *endo*-**4c** in toluene with an excess of gray selenium at 60 °C (*endo*-**4c**) or 80 °C (*endo*-**4b**). The very large ^{31}P-^{77}Se coupling constants of the resulting phosphine selenides (*endo*-**4b-Se**: 918.0 Hz; *endo*-**4c-Se**: 919.1 Hz)[18] indicate that 1-phospha-2-azanorbornenes are only weak bases. Reaction of *endo*-**4a** with tungsten pentacarbonyl complex [W(CO)$_5$(THF)] proceeded smoothly at room temperature with formation of **10a** [^{31}P{^{1}H} NMR: 66.2 ppm (s with ^{183}W satellites, $^1J_{P\text{-}W}$ 282.4 Hz)].

The reactivity of the P-N bond in 1-phospha-2-azanorbornenes towards nucleophiles gives access to novel dihydrophospholes, such as **7a,b** and **8b**. Selected reactions were conducted only with *endo*-**4a** and *endo*-**4b**, because the starting materials, phospholes **1b** and **2a** dimer, are much more easily obtained on a larger scale than phospholes **1c–e**. Reactions with water and hydrogen sulfide lead to 2,3-dihydrophospholes **7a,b** and **8b**; the postulated initially formed intermediates **5a,b** and **6b** were not observed (Scheme 2; molecular structure of **7b** in Figure 5).



Scheme 2. Cleavage of the P-N bond in *endo*-**4a,b** by water and hydrogen sulfide. The reactions are quantitative and highly selective. Back reaction takes place only for **7a,b**.

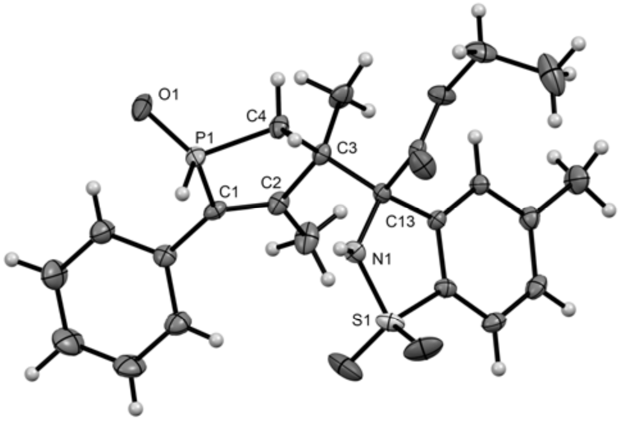
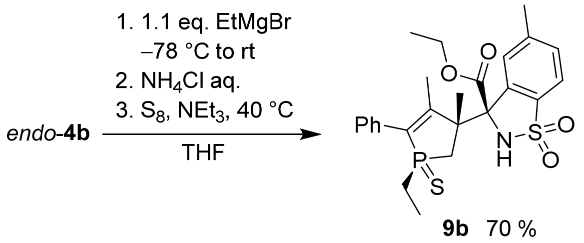


Figure 5. Molecular structure of **7b**. Ellipsoids at 50% probability. Selected bond lengths [pm] and angles [°]: P1-C1 178.0(2), P1-C4 179.5(3), P1-O1 149.1(2) C1-C2 134.1(3), N1-C13 146.1(3); C1-P1-C4 95.1(1), C1-P1-O1 115.6(1), C4-P1-O1118.2(1).

The hydrolysis reaction was quantitative and only **7a,b** were formed. The reaction is reversible; water is eliminated with formation of *endo*-**4a,b** in high vacuum at 60 °C or by adding molecular sieves (3 Å) to a THF solution. With hydrogen sulfide, a small amount of an unspecified byproduct [^{31}P{^{1}H} NMR: 27.5 ppm (s)] was observed besides the main product **8a**. For **7b** and **8b**, yields could not be determined, as the products contain residual THF, which was difficult to remove. In the ^{31}P NMR spectra of **7a,b** and **8b**, doublets (**7a**: 38.1, **7b**: 41.2, **8b**: 33.9 ppm) with large ^{31}P-^{1}H coupling constants are observed (**7a:** $^{1}J_{\text{P-H}}$ = 493.6 Hz; **7b**: $^{1}J_{\text{P-H}}$ = 497.5 Hz; **8b**: $^{1}J_{\text{P-H}}$ = 475.5 Hz). D$_2$O reacts with *endo*-**4b** to form the corresponding deuterated product characterized by a triplet at 40.7 ppm ($^{1}J_{\text{P-D}}$ = 76.3 Hz) in the ^{31}P{^{1}H} NMR spectrum.

Using a Grignard reagent, namely, ethylmagnesium bromide, as nucleophile in the reaction with *endo*-**4b** also leads to P-N bond cleavage. Hydrolytic workup followed by sulfur protection and recrystallization from boiling propan-2-ol gave **9b** in 70 % yield (Scheme 3, Figure 6).



Scheme 3. Alkylation of *endo*-**4b** with a Grignard reagent.

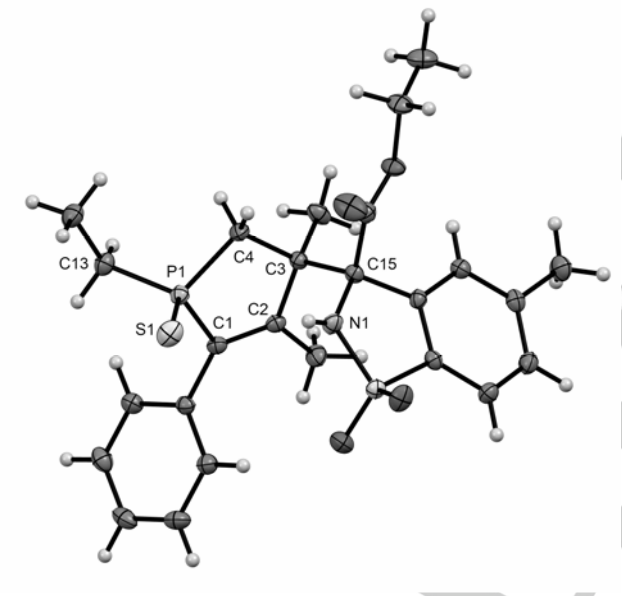


Figure 6. Molecular structure of **9b**. Ellipsoid level at 50%. Selected bond lengths [pm] and angles [°]: P1-C1 179.2(2), P1-C4 181.5(2), P1-C13 180.4(2), P1-S1 195.82(7), C1-C2 134.5(2), N1-C15 146.1(2); C1-P1-C13 109.80(8), C1-P1-C4 93.17(8), C4-P1-C13 107.22(9), S1-P1-C13 112.27(7).

In conclusion, the phospha-aza-Diels–Alder reaction between 2*H*-phospholes and electron-poor imine **3** are an innovative and efficient route to the new compound class of 1-phospha-2-azanorbornenes. The Diels–Alder reaction itself is of normal electron demand, highly chemoselective, and moderately *endo* selective. The isolated 1-phospha-2-azanorbornenes were characterized by the common analytical methods, including X-ray structure analysis. The formed P-N bond is highly reactive and can be cleaved by nucleophiles with formation of 2,3-dihydrophospholes, which are potential starting materials for a new type of P,N ligands. Further investigations in this area are underway.

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Keywords: cycloaddition • imines • nitrogen heterocycles• phospholes • phosphorus heterocycles

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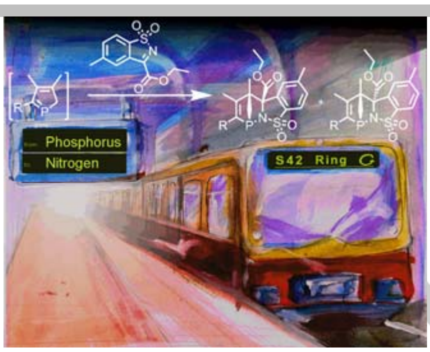
Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

2*H*-phospholes react in a highly chemoselective phospha-aza-Diels–Alder reaction with an activated, electron-poor imine to give a new class of compounds, namely, 1-phospha-2-azanorbornenes.



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1-Phospha-2-azanorbornenes by Phospha-aza-Diels–Alder Reaction