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Review

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The synthesis of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines

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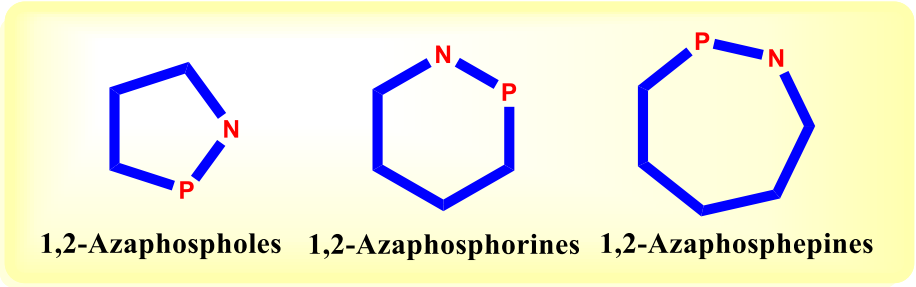
Abstract

1,2-Azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are prominent phosphorus heterocycles and are of interest due to their potent pharmacological activities. In this review, we provide the available literature data on the synthesis of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines.



Keywords: 1,2-azaphospholes, 1,2-azaphosphorines, 1,2-azaphosphepines, phosphorus heterocycles

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1. Introduction

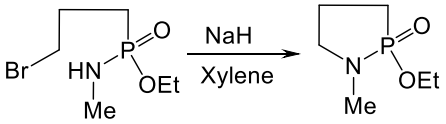
Organophosphorus compounds are important intermediates in organic synthesis and have been widely used as pharmaceutical,[1–9] agricultural,[10] and chemical agents.[11–15] Recently, phosphorus heterocycles[16,17] have

received considerable interest because of their unique biological activities as antimicrobial[18] and their anticancer effects.[19–22] Ifosfamide and cyclophosphamide are two important examples of phosphorus heterocycles that were launched on the market more than 30 years ago and are still used in treatment of cancer.[23,24] Much attention has been directed to the synthesis of phosphorus heterocycles due to their wide-ranging utilities as synthetic intermediates in organic syntheses.[25–31] Among these phosphorus heterocycles, 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines are of interest in several laboratories due to their potent pharmacological activities such as antitumor,[32] complexing agents,[33,34] and inhibitor of mammalian dihydroorotase.[35] The present review is focused on the most methodologies for the construction of 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines up to the end of 2019 and to supplement the information available in literature. In addition, there is discussion of mechanisms.

2. Synthetic Methods for Functionalized 1,2-Azaphosphole Derivatives

2.1 Cyclization of ethyl *N*-methyl-3-bromopropylphosphonamidate with NaH

Cyclization of ethyl *N*-methyl-3-bromopropylphosphonamidate (**1**) with sodium hydride in xylene at 120-125 ^{o}C gave 2-ethoxy-1-methyl-2-oxido-l,2-azaphospholidine (**2**) (Scheme 1).[36]

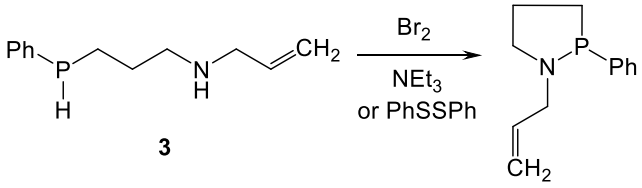


1 **2** (44%)

Scheme 1

2.2 Cyclization of γ-aminophosphorus compounds with bases

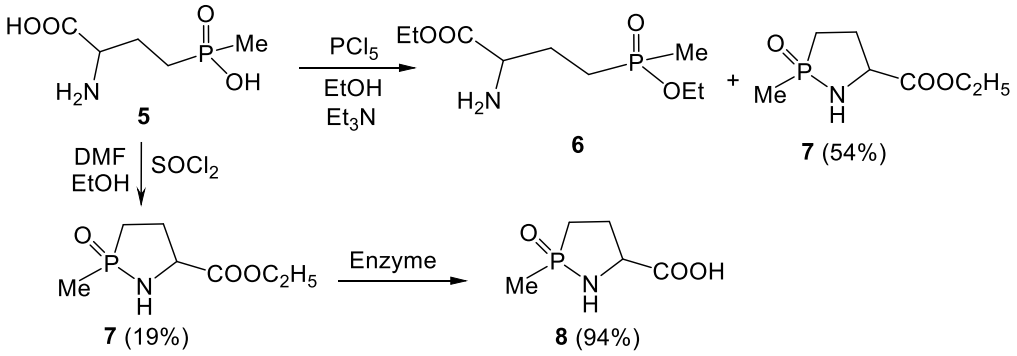
Ring closure of N-[3-(phenylphosphanyl)propyl]prop-2-en-1-amine (3) by using bromine in the presence of triethylamine or 1,2-diphenyldisulfane at 50-60 ^{o}C led to 1-allyl-2-phenyl-1,2-azaphospholidine (4) (Scheme 2).[36]



3 **4** (31%)

Scheme 2

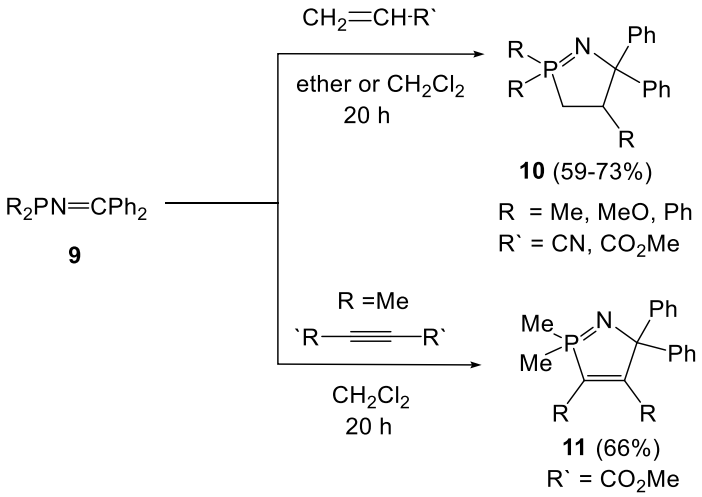
Treatment of 2-amino-4-[hydroxy(methyl)phosphoryl]butanoic acid (**5**) with phosphorus pentachloride in the presence of triethylamine as a catalyst and ethanol at 45-50 ^{o}C furnished ethyl 2-amino-4-[ethoxy(methyl) phosphoryl] butanoate (**6**) and ethyl 2-methyl-2-oxido-1,2-azaphospholidine-5-carboxylate (**7**) (Scheme 3). The product **7** was also formed by treatment of acid **5** with thionyl chloride and a catalytic amount of DMF at 100-110 ^{o}C, followed by addition of absolute ethanol. Enzyme catalyzed hydrolysis of product **7** to afford the corresponding free acid **8** (Scheme 3).[37]



Scheme 3

2.3 Reaction of methyleneaminophosphanes with activated alkenes and alkynes

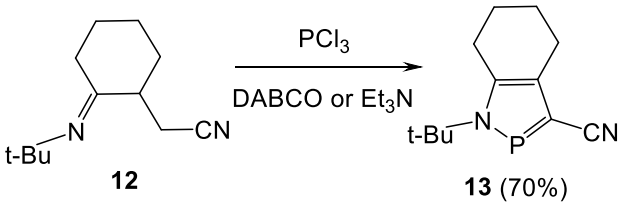
Methyleneaminophosphanes **9** reacted with activated alkenes such as acrylonitrile and methyl acrylate at room temperature to give the corresponding 5,5-diphenyl-4,5-dihydro-3*H*-1,2λ^5-azaphospholes **10** (Scheme 4), while its reaction with dimethyl acetylenedicarboxylate furnished dimethyl 2,2-dimethyl-5,5-diphenyl-5*H*-1,2λ^5-azaphosphole-3,4-dicarboxylate (**11**) (Scheme 4).[38]



Scheme 4

2.4 Cyclization of 2-[2-(*t*-butylimino)cyclohexyl]acetonitrile with PCl_3

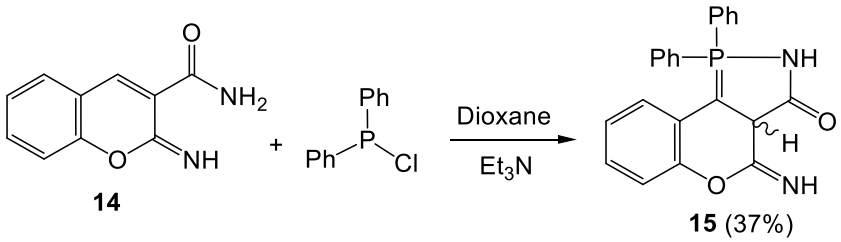
1-t-Butyl-4,5,6,7-tetrahydro-1*H*-1,2-benzazaphosphole-3-carbonitrile (**13**) was prepared by condensation of 2-[2-(t-butylimino)cyclohexyl]acetonitrile (**12**) with PCl_3 at 50-55 ^oC in the presence of triethylamine as a base. The yield was improved when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used in place of triethylamine (Scheme 5).[39]



Scheme 5

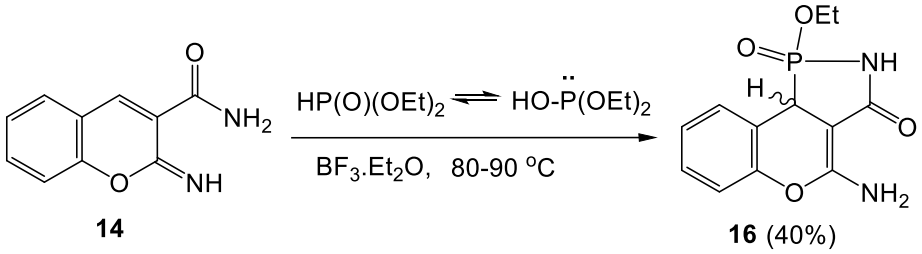
2.5 Cyclization of 2-imino-2*H*-chromene-3-carboxamide with chlorodiphenylphosphine and diethyl phosphite

2-Imino-2*H*-chromene-3-carboxamide (**14**) reacted with chlorodiphenylphosphine in dry dioxane containing a few drops of triethylamine at 90-95 °C to yield 1,1-diphenyl-4-imino-3a,4-dihydro-15-chromeno[4,3-*c*][1,2] azaphosphol-3(2*H*)-one (**15**) (Scheme 6).[40]



Scheme 6

4-Amino-1-ethoxy-1-oxido-1,9b-dihydrochromeno[4,3-*c*][1,2]azaphosphole-3(2*H*)-one (**16**) was obtained by treatment of the carboxamide **14** with diethyl phosphite in the presence of $BF_3.Et_2O$ as a catalyst at 80-90 °C (Scheme 7).[41]

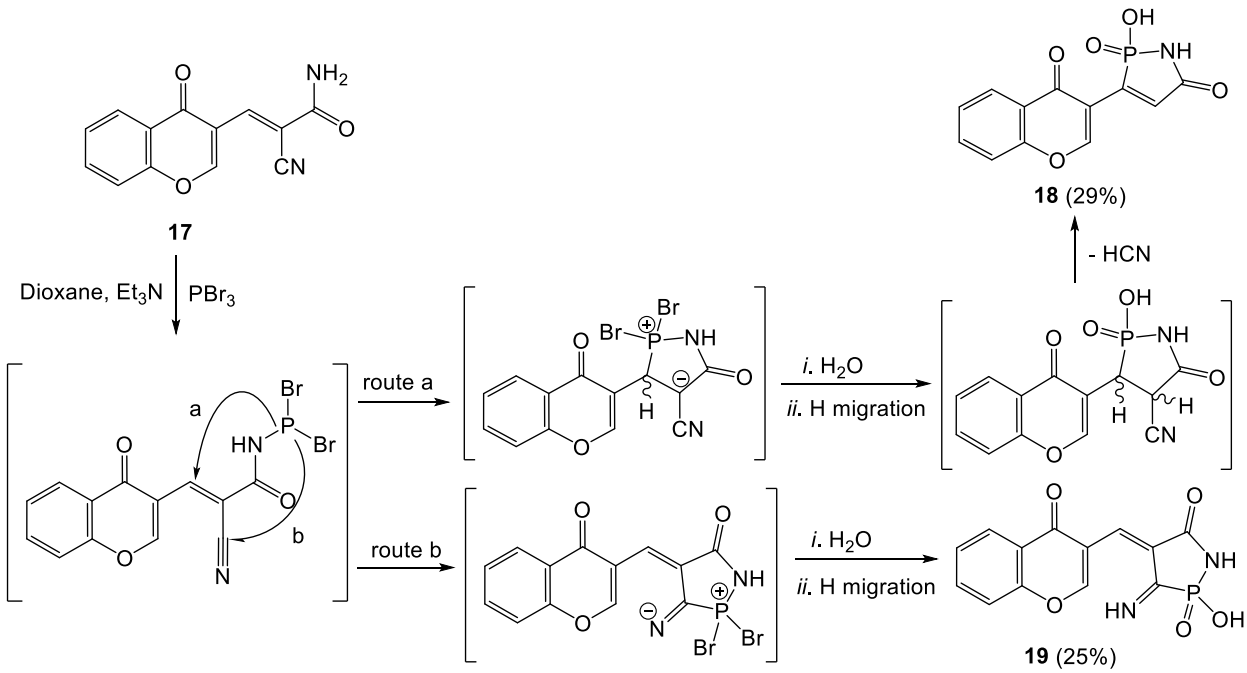


Scheme 7

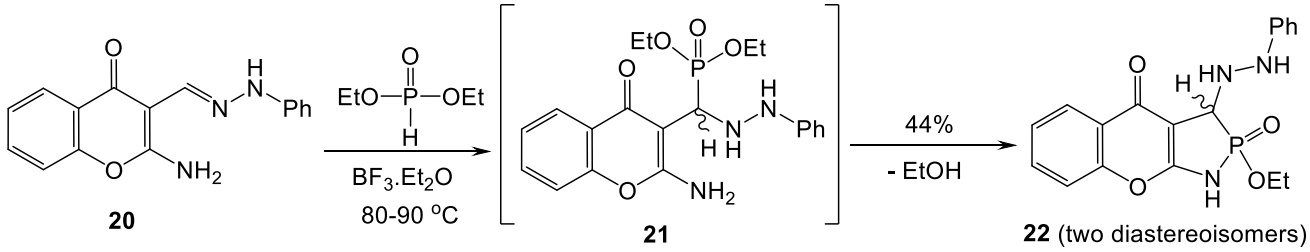
2.6 Cyclization of chromonyl arylidenes and hydrazones with phosphorus tribromide and diethyl phosphite

2-Cyano-3-(4-oxo-4*H*-chromen-3-yl)prop-2-enamide (**17**) reacted with phosphorus tribromide in dry dioxane containing a catalytic quantity of triethylamine 90-95 °C to give two isomeric chromonyl-1,2-azaphospholes **18** and **19** (Scheme 8).[42]

Fusion of the chromonyl phenylhydrazone **20** with diethyl phosphite at 80-90 °C in the presence of $BF_3.Et_2O$ as a catalyst under Pudovik reaction conditions resulted in the nonisolable diethyl hydrazino-phosphonate **21** (Scheme 9). The latter intermediate underwent spontaneous cyclization by elimination of ethanol to provide the chromeno[3,2-*d*][1,2]azaphosphole **22** as two diastereoisomers (Scheme 9).[32]



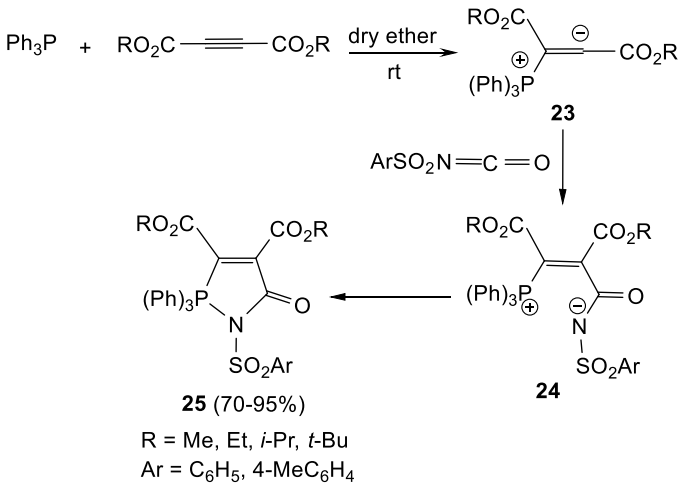
Scheme 8



Scheme 9

2.7 Reaction of dialkyl acetylenedicarboxylate with isocyanates and triphenylphosphine

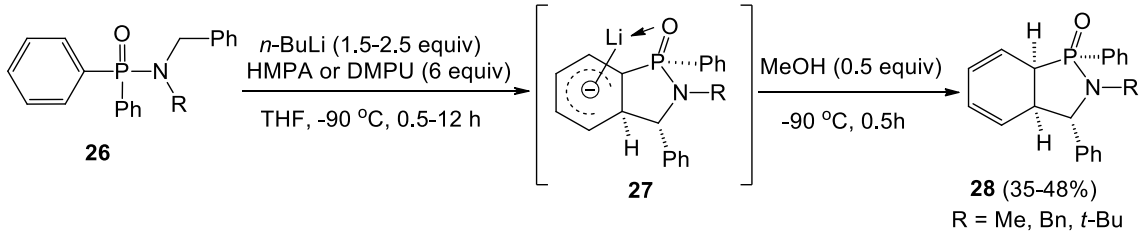
Dialkyl 2,5-dihydro-5-oxo-1,2-azaphosphole-3,4-dicarboxylates (**25**) resulted from a three-component reaction between triphenylphosphine, dialkyl acetylenedicarboxylate and arylsulfonyl isocyanates (Scheme 10). The product **25** was a result of the initial addition of triphenylphosphine to the acetylenic diester and subsequent attack of the resulting anion **23** to the carbonyl carbon atom of the arylsulfonyl isocyanate to yield the betaine **24**. The latter betaine underwent spontaneous cyclization to produce the 1,2-azaphosphole **25** (Scheme 10).[43]



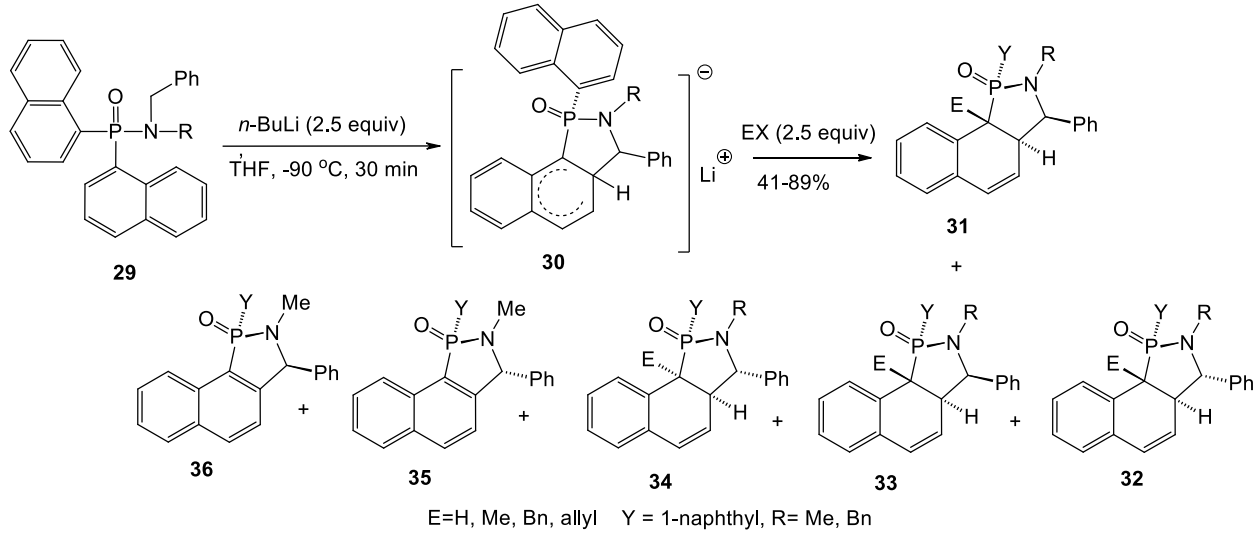
Scheme 10

2.8 Dearomatizing anionic cyclization of *N*-alkyl-*N*-benzyl-diarylphosphinamides

Treatment of *N*-alkyl-*N*-benzyl-diphenylphosphinamides (**26**) at low temperature with n-BuLi in THF in the presence of HMPA or DMPU gave the anions **27**. The developed anions **27** underwent anionic cyclization by Michael addition to the *ortho* position of the *P*-phenyl ring, which resulted in tetrahydro-2,1-benzazaphospholes **28** as a dearomatized species trapped with methanol with high regio- and stereo-control (Scheme 11).[44] Similarly, the cyclization of *N*-alkyl-*N*-benzyl-dinaphthylphosphinamides **29** by using n-BuLi in THF and subsequent trapping with a series of alkyl halides afforded a series of tetrahydro-1*H*-naphtho[1,2-*c*]-[1,2]azaphospholes **31-36** (Scheme 12).[44]

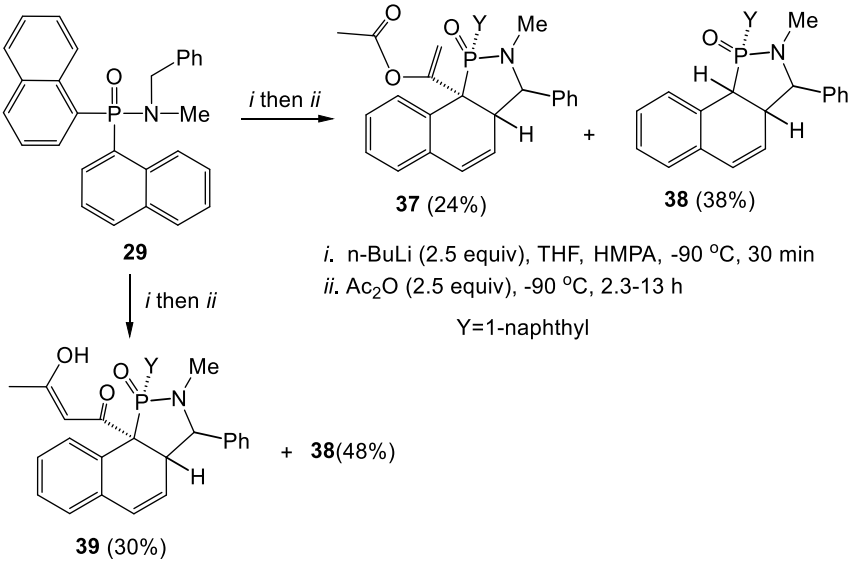


Scheme 11



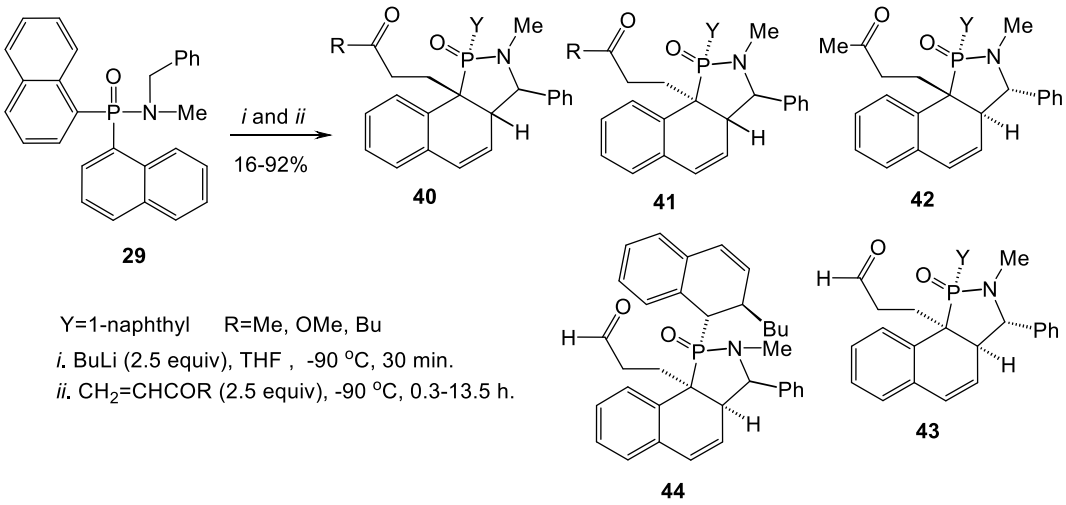
Scheme 12

N-Benzyl-*N*-methyl-dinaphthylphosphinamide (**29**) underwent cyclization by using n-BuLi in THF then adding acetic anhydride to isolate the azaphosphole **38** as the major product in the presence or absence of the *co*-solvent HMPA (Scheme 13). The acylation then deprotonation of the methyl group of the CH_3CO moiety and trapping gave the product of *O*-acetylation **37**, or *C*-acetylation **39** with low yields (Scheme 13).[45]



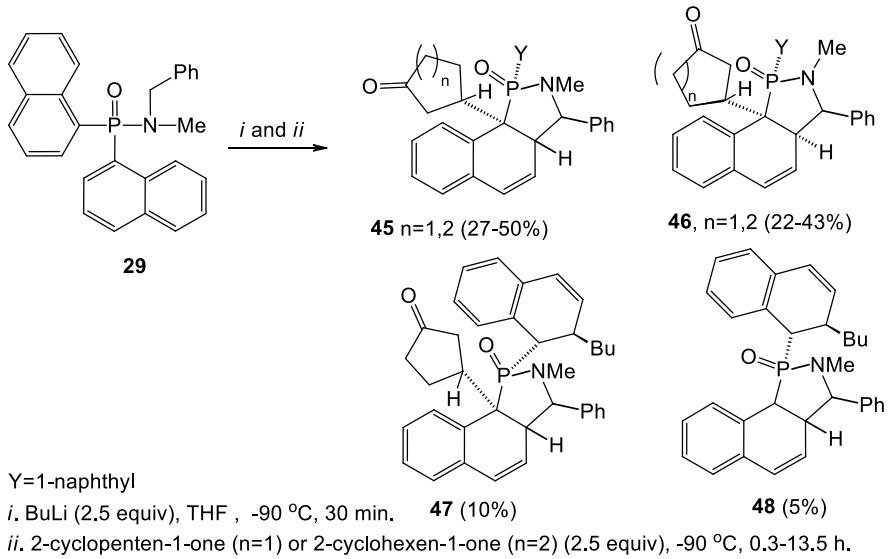
Scheme 13

In the same way, the reaction of compound **29** with n-BuLi in THF then acyclic α,β-unsaturated aldehydes and ketones afforded the functionalized tricyclic 1,2-azaphospholes **40**-**44** (Scheme 14).[45]



Scheme 14

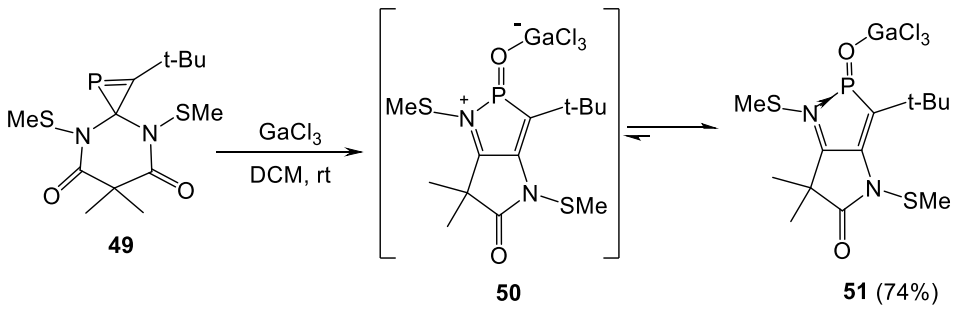
The reaction of starting material **29** with *n*-BuLi in THF followed by addition of 2-cyclopenten-1-one or 2-cyclohexen-1-one took place with good yield and low selectivity to form a mixture of tricyclic 1,2-azaphospholes **45** and **46** with a *cis*-junction in a ratio of 1:1.6 (Scheme 15). Other products (**47** and **48**) were also formed due to the dearomatization of the two naphthalene rings (Scheme 15).[45]



Scheme 15

2.9 Rearrangement of 4,8-diaza-1-phosphaspiro[2.5]oct-1-ene with $GaCl_3$

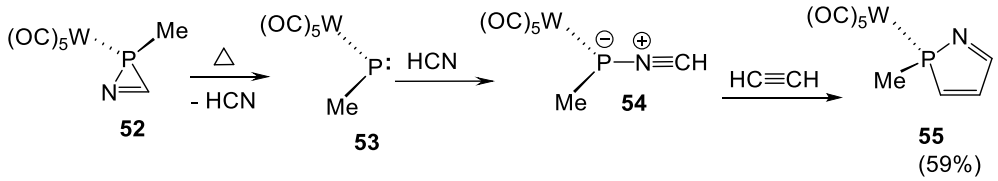
Reaction of 2-t-butyl-6,6-dimethyl-4,8-bis(methylthio)-4,8-diaza-1-phosphaspiro[2.5]oct-1-ene-5,7-dione (**49**) with $GaCl_3$ induced an unexpected rearrangement leading to the formation of the complex **50** which stabilized into 1,2-azaphosphole form **51** (Scheme 16).[46]



Scheme 16

2.10 Thermal ring opening of 2*H*-azaphosphirene complexes

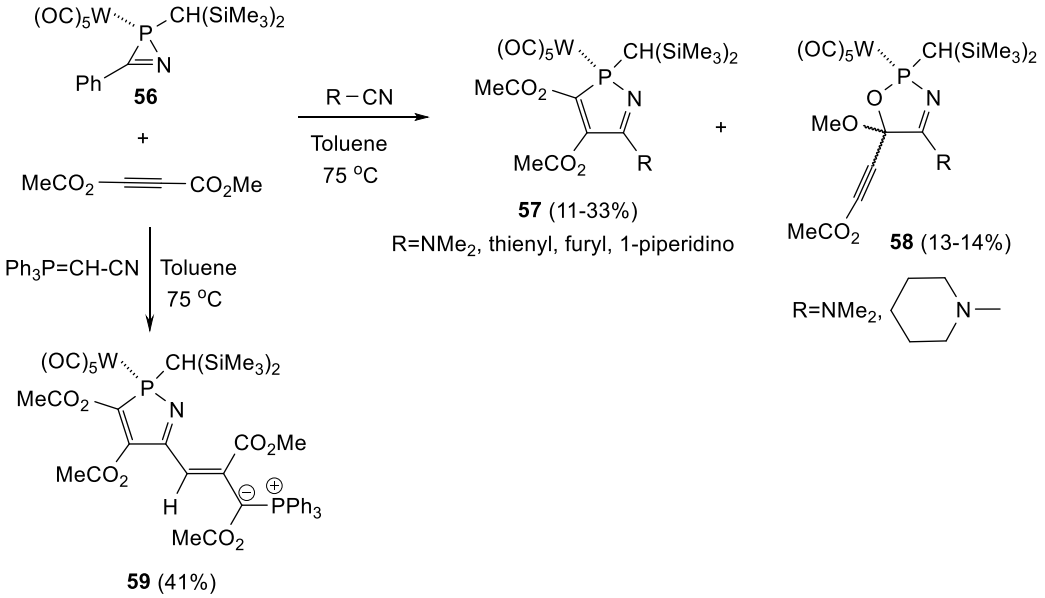
The thermolysis of the (2*H*-azaphosphirene)tungsten carbonyl complex **52** at 60 °C gave the nitrilium phosphanylide complex **54**, which reacted with acetylene to yield the 1,2-azaphosphole complex **55** (Scheme 17).[47]



Scheme 17

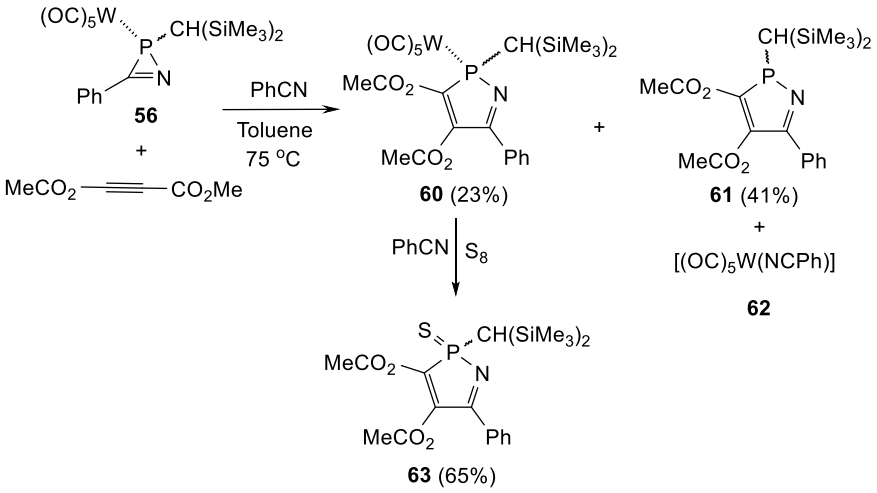
Thermal ring opening of the (2*H*-1,2-azaphosphirene)tungsten complex **56** with dimethyl acetylene-dicarboxylate and nitriles yielded the corresponding 1,2-azaphosphole complexes **57** (Scheme 18). When 1-piperidinocarbonitrile or dimethyl cyanamide was used, 1,3,2-oxazaphospholene complexes **58** (*meso* and

racemic in ratio of 1:1) was also obtained beside the desired product **57** (Scheme 18). Furthermore, the reaction of complex **56** with 2-(triphenyl-λ^5-phosphanyl)acetonitrile led to the formation of 1,2-azaphosphole **59** (Scheme 18).[33,48-50]



Scheme 18

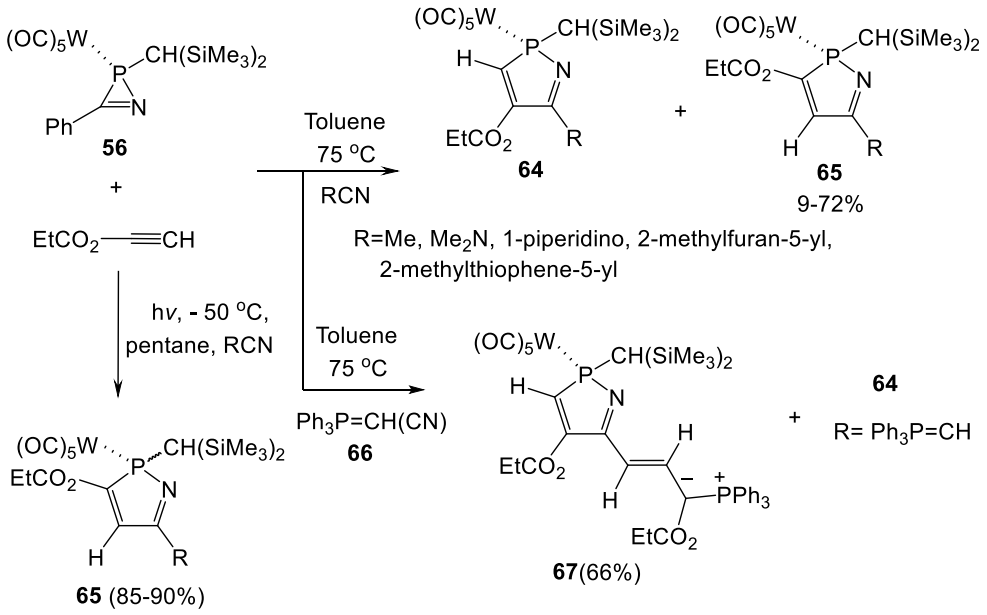
Also, ring opening reaction of 1,2-azaphosphirene complex **56** with dimethyl acetylenedicarboxylate and benzonitrile in toluene furnished a mixture of 2*H*-1,2-azaphosphole complexes **60** and **61** (Scheme 19). The yield of complex **60** was significantly improved to 90% when the reaction was carried out photochemically in pentane at -50 °C. Heating of complex **60** in benzonitrile with sulfur gave the 2-sulfido-2*H*-1,2-azaphosphole **63** (Scheme 19).[33,51-53]



Scheme 19

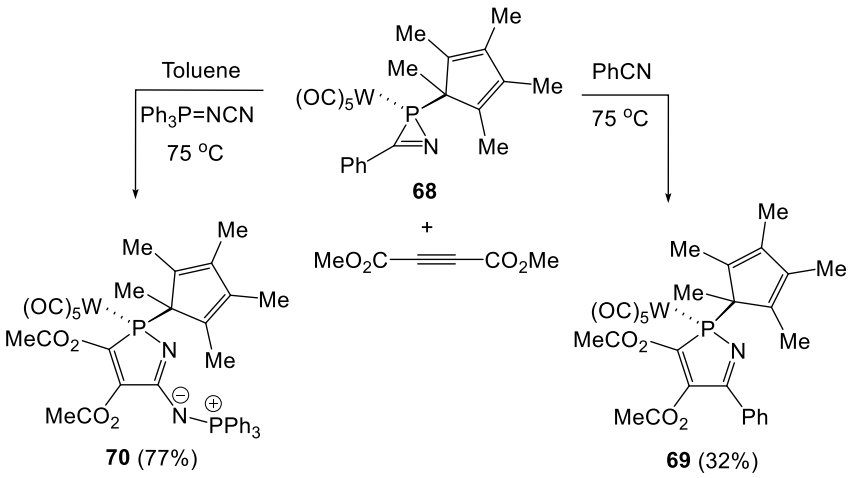
On the other hand, the three component reactions of 2*H*-azaphosphirene complex **56**, ethyl propiolate and nitriles led to the formation of the regioisomeric 2*H*-1,2-azaphosphole complexes **64** and **65** (Scheme 20). In case of using Ph_3P=CH(CN) (**66**), a mixture of 1,2-azaphosphole complexes **64** and **67** were formed. Also,

reaction of complex **56** with ethyl propiolate and different nitriles in pentane gave 1,2-azaphospholes **65** in high yield (Scheme 20).[49,50,52,54]



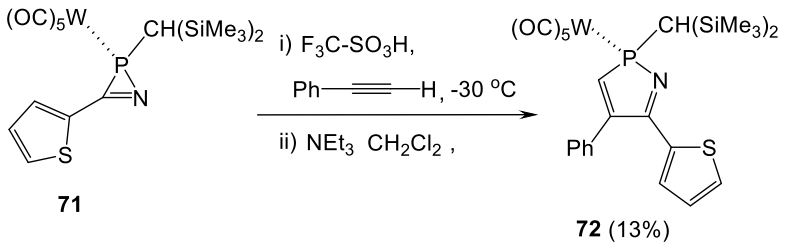
Scheme 20

Similarly, the ring-opening of the 1,2-azaphosphirene complex **68** in benzonitrile in the presence of dimethyl acetylenedicarboxylate as a trapping reagent afforded the 1,2-azaphosphole complex **69**. When the reaction was performed with Ph_3P=NCN in dry toluene, the 1,2-azaphosphole complex 7**0** was formed in high yield (Scheme 21).[33,55]



Scheme 21

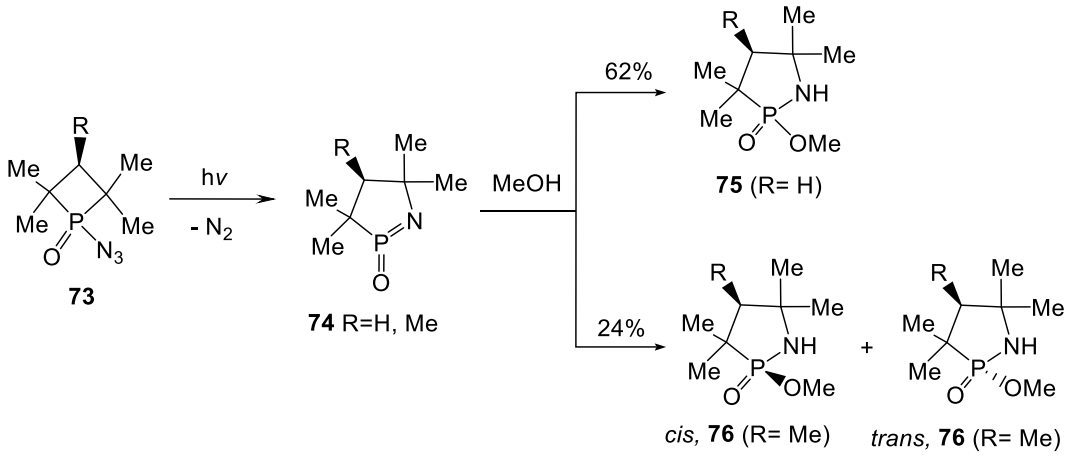
Reaction of the (2*H*-azaphosphirene)tungsten complex **71** with trifluoromethanesulfonic acid, phenylacetylene and triethylamine in CH_2Cl_2 proceeded through P–C bond ring enlargement to afford 2*H*-1,2-azaphosphole complex **72** in low yield (Scheme 22).[56]



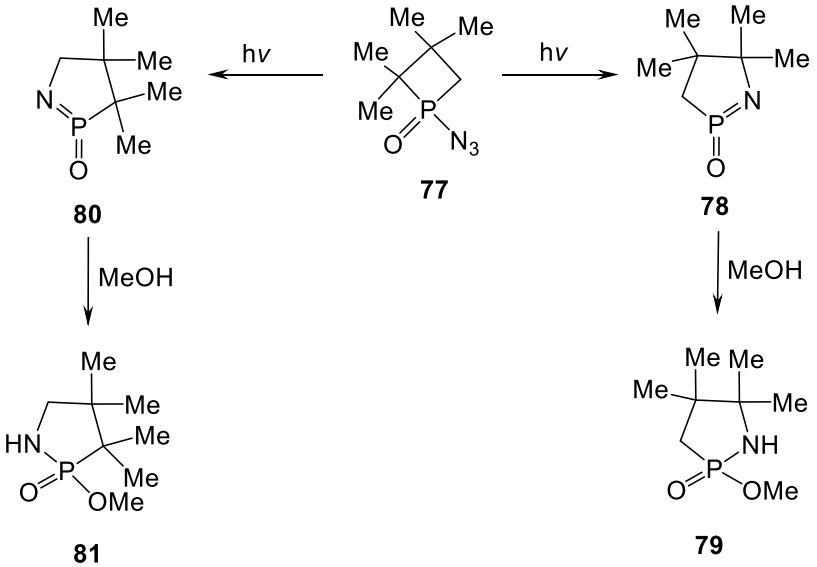
Scheme 22

2.11 Photolysis of azidophosphetanes

Photolysis of 1-azido-2,2,4,4-tetramethylphosphetane 1-oxide **73** (R=H) afforded the cyclic 1,2-aza-phospholidine **75** by elimination of N_2 and addition of methanol (Scheme 23). Likewise, photolysis of azide **73** (R = Me) gave a mixture of *cis*- and *trans*-1,2-azaphospholidines **76** (Scheme 23).[57]



Scheme 23

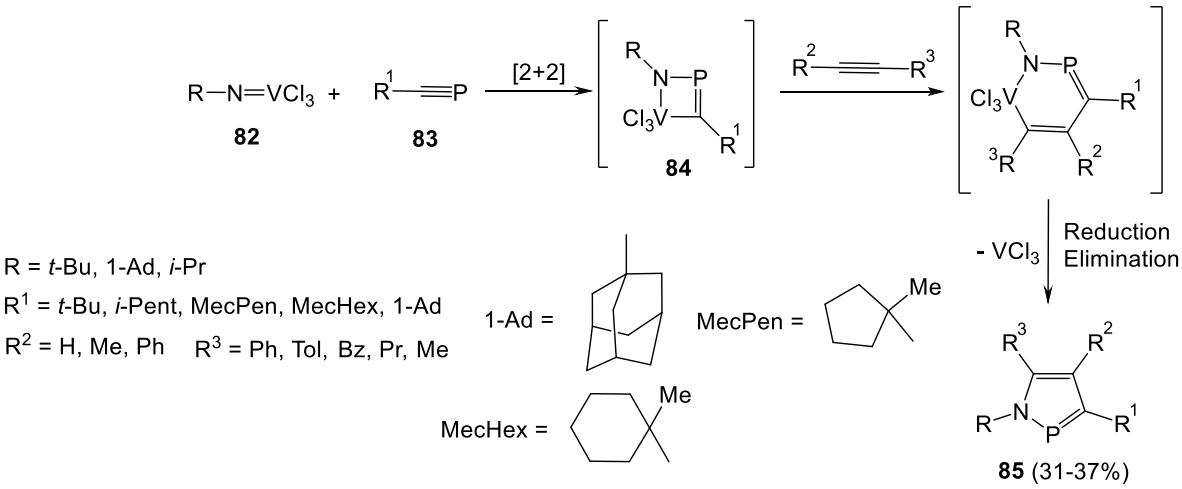


Scheme 24

Unlike **73**, the azide **77** lacks symmetry and has two possible modes of ring expansion. Thus, its photolysis in methanol yielded an approximately equimolar mixture (40% total) of the isomeric 1,2-azaphospholidines **79** and **81** (Scheme 24).[57]

2.12 Reaction of adduct of phosphaalkynes and imidovanadium with acetylenes

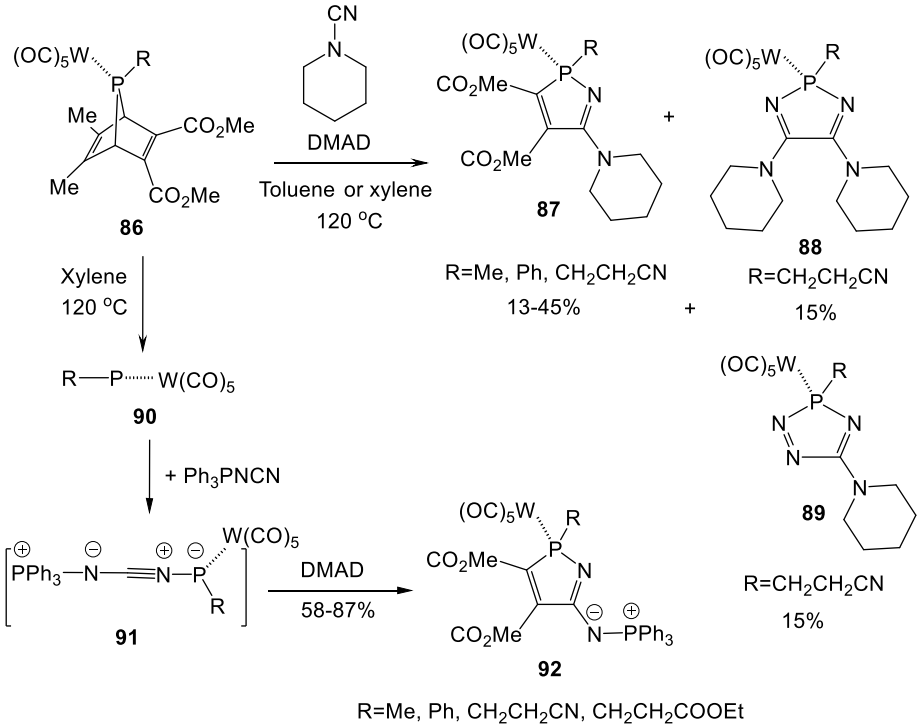
The cycloadduct **84** was generated in *situ* by addition of an equimolar amount of a phosphaalkynes **83** to the imidovanadium complexes **82** (Scheme 25). The cycloadduct **84** was treated with an excess of disubstituted acetylenes in toluene at -78 °C to form the tetrasubstituted 1,2-azaphospholes **85** in 31-71% yields (Scheme 25).[58]



Scheme 25

2.13 Thermal decomposition of 7-phosphanorbornadiene complex

In the presence of piperidine-1-carbonitrile and dimethyl acetylenedicarboxylate, 7-phosphanorbornadiene complex **86** underwent thermal decomposition in xylene at 120 °C to afford the 1,2-azaphosphole complex **87**

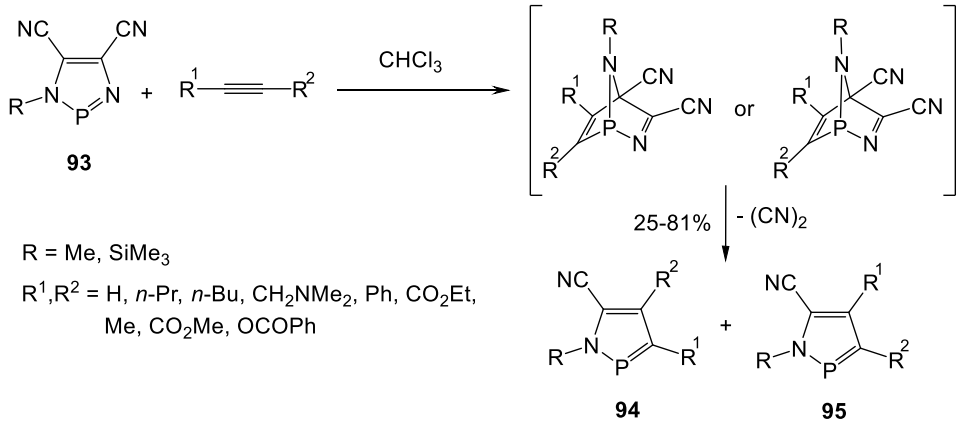


Scheme 26

beside a complicated mixture of the regioisomeric complexes **88** and **89** (Scheme 26). When the reaction was performed in dry toluene, the product 2*H*-1,2-azaphosphole complex **87** only was isolated. When another carbonitrile derivative such as Ph_3P=NCN was used, the thermal decomposition of complex **86** in xylene furnished the 2*H*-1,2-azaphosphole complex **92** through [3+2] cycloaddition reaction of nitrilium phosphane ylide complexes **91** formed with dimethyl acetylenedicarboxylate (Scheme 26).[59-61]

2.14 Reaction of l,3,2-diazaphosphole-4,5-dicarbonitriles with alkynes

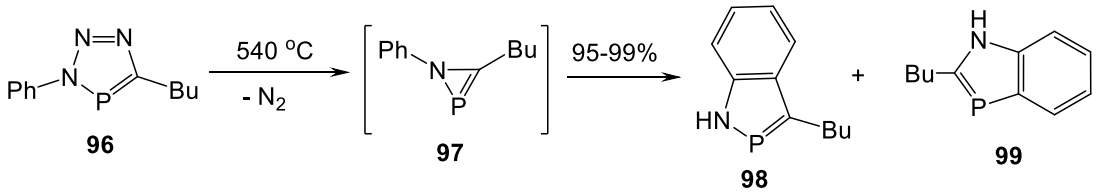
The regioselective cyclization of l,3,2-diazaphosphole-4,5-dicarbonitriles **93** with symmetrical and non-symmetrical alkynes in chloroform at room temperature yielded the l,2-azaphosphole-5-carbonitriles **94** (Scheme 27). In some cases of non-symmetrical alkynes, the other isomers **95** were also formed (Scheme 27).[62]



Scheme 27

2.15 Flash vacuum pyrolysis of 5-butyl-3-phenyl-l,2,3,4-triazaphosphole

Dinitrogen was split off from 5-butyl-3-phenyl-l,2,3,4-triazaphosphole (**96**) on flash vacuum pyrolysis to give the azaphosphirene intermediate **97**. This intermediate underwent 1,5-electrocyclization followed by proton migration to form the annulated 3-butyl-1*H*-[1,2]benzazaphosphole (**98**) and 2-butyl-1*H*-[1,3]benzazaphosphole (**99**) in a ratio of 4:1 (Scheme 28).[39]

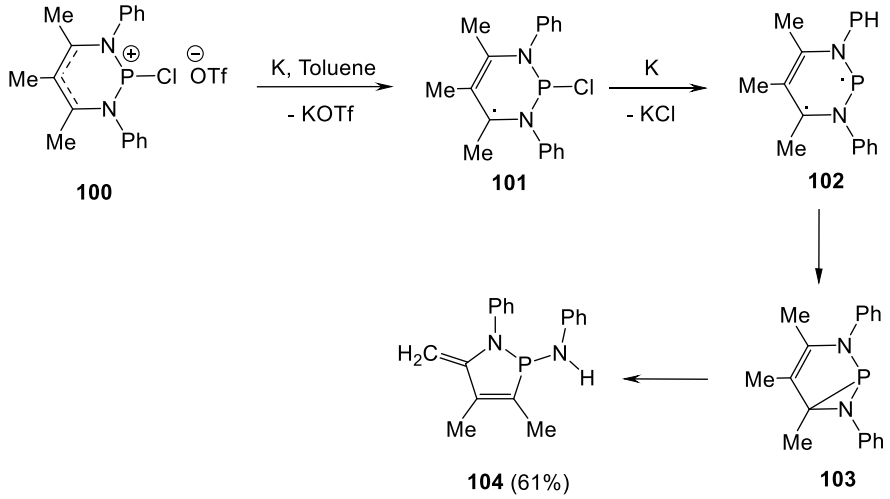


Scheme 28

2.16 Reaction of chlorophosphenium triflate with potassium metal

Treatment of chlorophosphenium triflate **100** with potassium metal in toluene at 25 °C resulted in a pale yellow crystalline 1,2-azaphospholidine **104** (Scheme 29). It was assumed that the two-electron reduction of the idealized chlorophosphenium ion **100** proceeded in two steps; addition of the first electron would generate the monoradical **101**. Addition of the second electron would then generate the triplet diradical phosphinidene **102**. The conversion of **102** to **103** took place by an intramolecular P–C bond formation to afford the derivative **103**. Finally, the latter **103** underwent N–C bond cleavage and hydrogen transferred from

β-methyl group to the nascent imido nitrogen center forming the isolated 1,2-azaphospholidine isomer **104** (Scheme 29).[63]

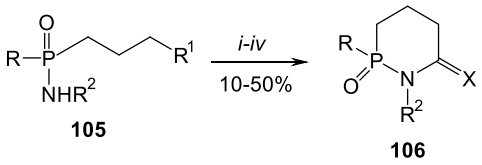


Scheme 29

3. Synthetic Methods for Functionalized 1,2-Azaphosphorine Derivatives

3.1 Cyclization of phosphinamides using various bases

Cyclization of different phosphinamides **105** using various bases at the boiling point of the used solvent furnished 2-oxido-1,2-azaphosphinanes **106** in different yields through removal of ethanol or hydrogen halide (Scheme 30).[64,65]

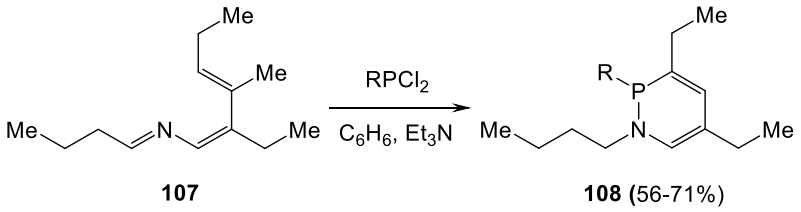


i, NaH, Xylene (X=H_2)
R = OEt, Ph, R^1 = CH_2Br, R^2 = H, CH_2Ph
ii, t-BuOK, BuOH (X=O)
R = OEt, R^1= CO_2Et, R^2 = CH_2Ph, Me, $CH_2CH=CH_2$
iii, NaH, C_6H_6 (X=O)
R = OEt, R^1 = CO_2Et, R^2 = H, Me
iv, Et_3N, THF, (X=O)
R = OEt, R^1 = COCl, R^2 = CH_2Ph

Scheme 30

3.2 Cyclization of *N*-[2-ethyl-3-methylhexa-1,3-dien-1-yl]butan-1-imine with $RPCl_2$

Cyclocondensation of *N*-[2-ethyl-3-methylhexa-1,3-dien-1-yl]butan-1-imine (**107**) with dichlorophosphine derivatives in dry benzene at 50 °C containing Et_3N afforded 1-butyl-3,5-diethyl-1,2-dihydro-1,2-aza-phosphorines (**108**) (Scheme 31).[66]



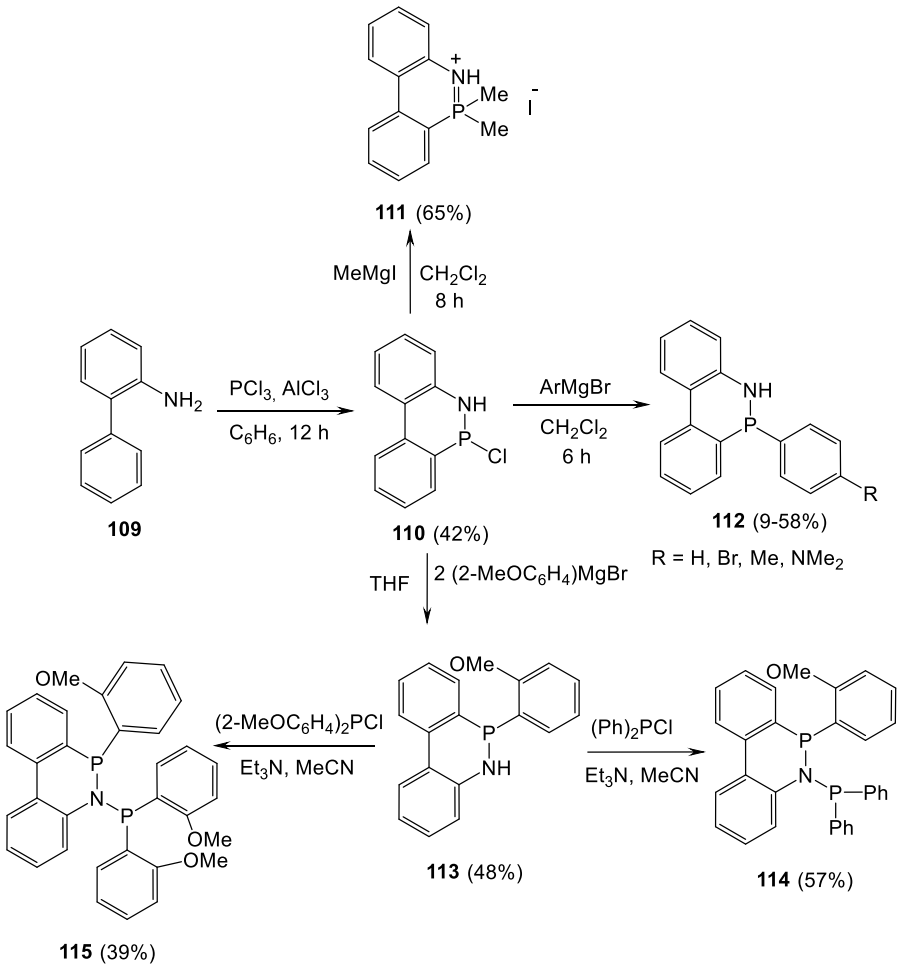
107 **108** (56-71%)

R = Cl, Et

Scheme 31

3.3 Cyclization of 2-aminobiphenyl with PCl_3

Reaction of 2-aminobiphenyl (**109**) with phosphorus trichloride in boiling benzene at 65 ^{o}C containing a catalytic amount of $AlCl_3$ afforded 10-chloro-9,10-dihydro-9,10-azaphosphaphenanthrene (**110**). Compound **110** has an active chlorine atom which can be substituted by a wide range of nucleophiles. Thus, treatment of the product **110** with methyl magnesium iodide in CH_2Cl_2 gave 10-methyl-9,10-dihydro-9,10-azaphosphaphenanthrene 10-methiodide (**111**) while its reaction with aryl magnesium bromide in dry CH_2Cl_2 at room temperature formed 10-aryl-9,10-dihydro-9,10-azaphosphaphenanthrenes **112** (Scheme 32). Also, reaction of compound **110** with (2-methoxyphenyl) magnesium bromide in THF at 60 ^{o}C gave 10-(2-methoxyphenyl)-9,10-dihydro-9,10-azaphosphaphenanthrene (**113**) which was phosphorylated with chlorodiarylphosphine in acetonitrile at room temperature to give 5-(diarylphosphanyl)-6-(2-methoxyphenyl)-5,6-dihydrodibenzo[*c*,*e*][1,2]azaphosphinines **114** and **115** (Scheme 32).[67-69]



109 **110** (42%) **112** (9-58%)

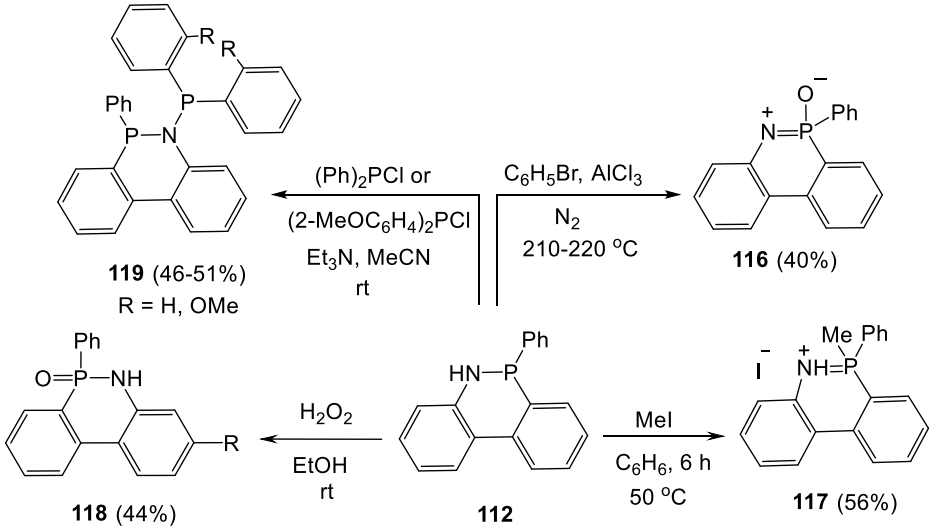
R = H, Br, Me, NMe_2

111 (65%)

113 (48%) **114** (57%) **115** (39%)

Scheme 32

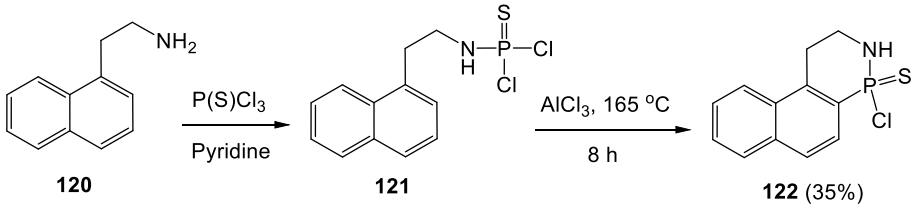
Compound **112** (R = H) acts as a substrate for the preparation of a series of functionalized 1,2-azaphospha-phenanthrenes. Thus, its reaction with bromobenzene in the presence of anhydrous $AlCl_3$ in current of nitrogen gas furnished 10-pheny1-9,10-dihydro-9,10-azaphosphaphenanthrene 10-oxide (**116**) (Scheme 33). Moreover, its reaction with methyl iodide in dry benzene gave 10-phenoxy-9,10-dihydro-9,10-azaphospha-phenanthrene methiodide **117** (Scheme 33)**.** Oxidation of compound **112** by hydrogen peroxide in ethanol at room temperature afforded the corresponding oxide **118**. Furthermore, reaction of compound **112** with chlorodiphenylphosphine or bis(2-methoxyphenyl)chlorophosphine in acetonitrile in the presence of triethylamine gave 5-(diarylphosphanyl)-6-phenyl-5,6-dihydrodibenzo[*c*,*e*][1,2]azaphosphinines (**119**) (Scheme 33).[67-69]



Scheme 33

3.4 Cyclization of naphthylethylamine with thiophosphoryl chloride

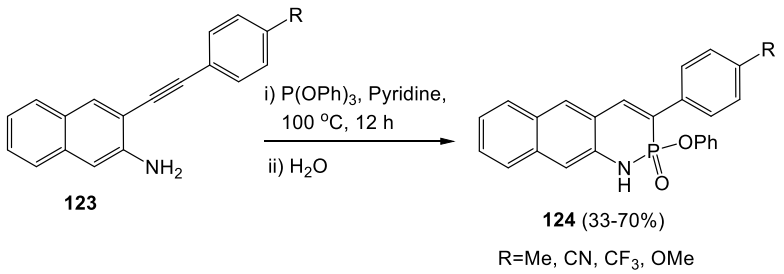
Treatment of naphthylethylamine **120** with thiophosphoryl chloride in dry pyridine at 100 °C gave 2-[(naphthalene-1-yl)ethyl]phosphoramidothioic dichloride (**121**), which with $AlCl_3$ at 165 °C for 8 h gave 4-chloro-1,2,3,4-tetrahydronaphtho[2,1-*c*][1,2]azaphosphinine 4-sulfide (**122**) (Scheme 34).[70]



Scheme 34

3.5 Cyclization of 2-amino-3-ethynylnaphthalenes with triphenoxyphosphine

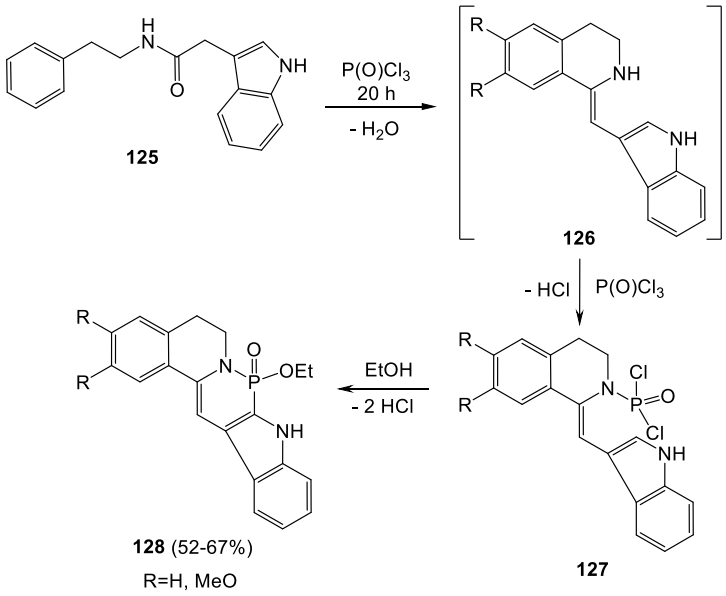
Cyclization of 2-amino-3-ethynylnaphthalenes (**123**) with triphenoxyphosphine in dry pyridine for 12 h furnished naphtho[2,3-*e*][1,2]azaphosphorines (**124**) in moderate yields (Scheme 35).[71]



Scheme 35

3.6 Cyclization of 2-(1*H*-indol-3-yl)-*N*-phenethylacetamides with phosphorus oxychloride

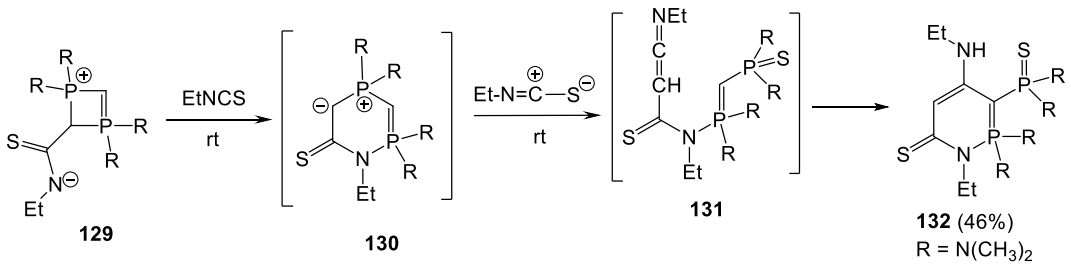
2-(1*H*-indol-3-yl)-*N*-phenethylacetamides (**125**) underwent double condensation using excess of phosphorus oxychloride at 175 °C to form the phosphoramide derivatives **127** (Scheme 36). Compounds **127** underwent another cyclocondensation reaction through the α-position of the indole nucleus followed by treatment with ethanol at room temperature to yield 8-ethoxy-5,6-dihydro-2,3-disubstituted-9*H*-indolo[2,3-*c*]isoquino[1,2-*f*][1,2]azaphosphorine 8-oxides **128** (Scheme 36).[72,73]



Scheme 36

3.7 Reaction of a 1λ^5,3λ^5-diphosphete adduct with ethyl isothiocyanate

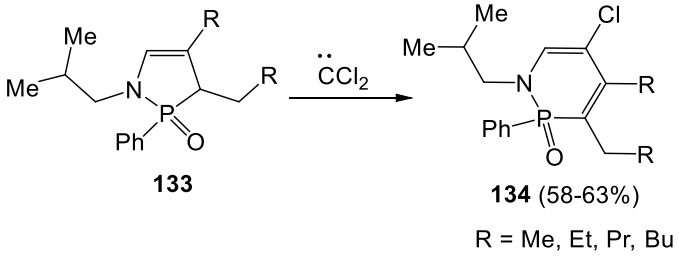
Reaction of 1,2-dihydro-1λ^5,3λ^5-diphosphete-2-carbothioamide adduct **129** with ethyl isothiocyanate gave the 1,2,4-azadiphosphinine intermediate **130**, which reacted with a second molecule of ethyl isothiocyanate to give the acyclic ketenimine **131** (Scheme 37). This easily underwent cyclization to afford the isolated 1,2-azaphosphinine **132** (Scheme 37).[74]



Scheme 37

3.8. Ring expansion of 2,3-dihydro-1,2-azaphospholes by dichlorocarbene

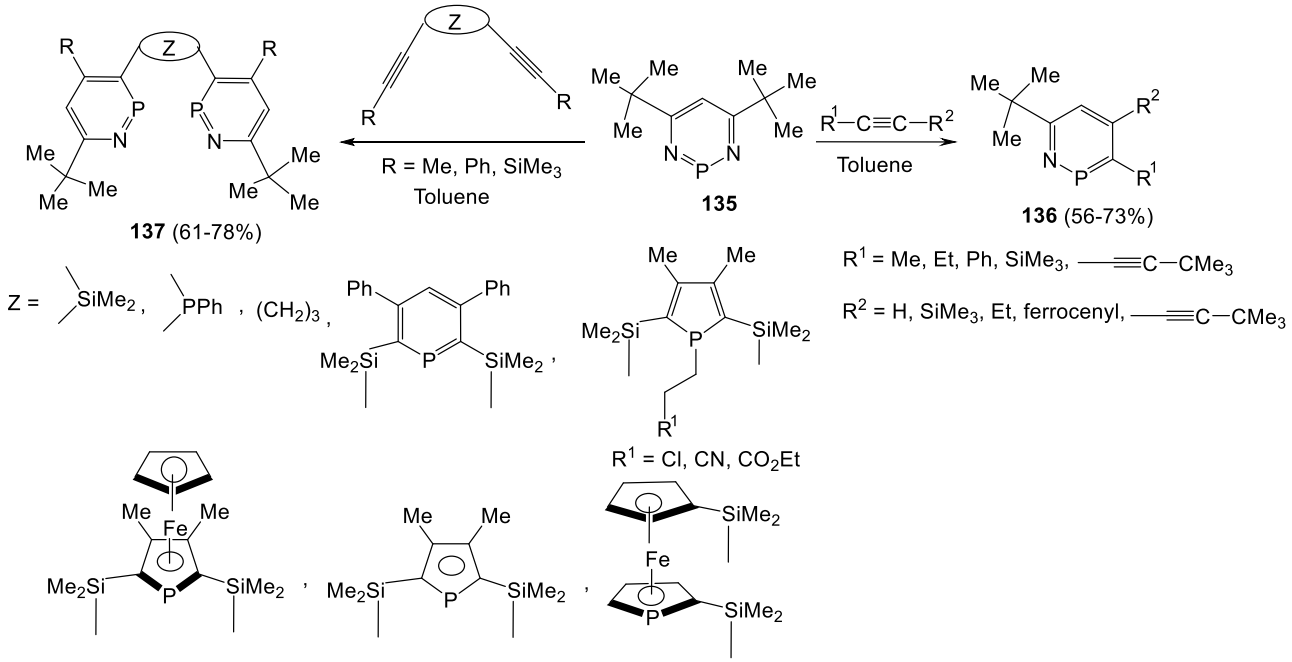
Reaction of 2,3-dihydro-1*H*-1,2-azaphosphole oxides (**133**) with dichlorocarbene at -25 °C gave the corresponding 1,2-azaphosphinine oxides **134** through Ciamician-Dennsted rearrangement (Scheme 38).[75]



Scheme 38

3.9. Reaction of 1,3,2-diazaphosphinines with alkynes

Reaction of 4,6-di-*t*-butyl-1,3,2-diazaphosphinine (**135**) with different alkynes in toluene 100 °C afforded the corresponding substituted 1,2-azaphosphinines **136** through [4+2] cycloaddition, while its reaction with *bis*-alkynes furnished the 1,2-azaphosphinine-based bidentate ligands **137** (Scheme 39).[76,77]

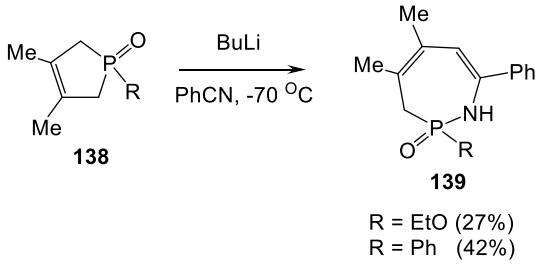


Scheme 39

4. Synthetic Methods for Functionalized 1,2-Azaphosphepine Derivatives

4.1 Ring expansion of phospholenes with benzonitrile

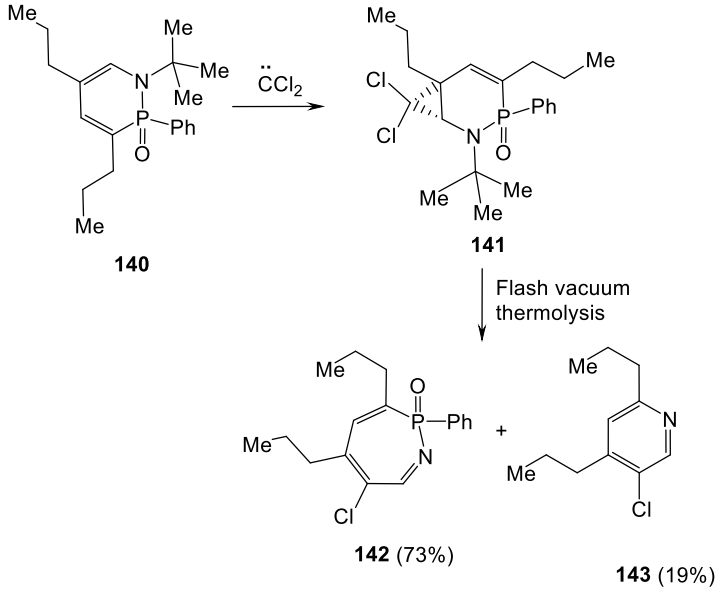
Treatment of 1-oxo-3,4-dimethyl-3-phospholenes (**138**) with *n*-BuLi in benzonitrile at -70 °C followed by hydrolysis formed the corresponding 1,2-azaphosphepine oxides **139** (Scheme 40).[78]



Scheme 40

4.2 Ring expansion of 1,2-azaphosphinines with dichlorocarbene

Reaction of 1-*t*-butyl-2-phenyl-3,5-dipropyl-1*H*-1,2-azaphosphinine (**140**) with dichlorocarbene by regioselective addition to the C_5-C_6 double bond at -25 °C yielded the 3-oxo-2-aza-3-phosphabicycloheptene **141** (Scheme 41). Flash vacuum thermolysis of **141** gave 6-chloro-3,4-dipropyl-2-phenyl-2-oxo-2*H*-1,2-azaphosphepine (**142**) and substituted 3-chloropyridines **143** (Scheme 41).[79]



Scheme 41

5. Conclusions

In conclusion, this survey has presented the synthetic methods for 1,2-azaphospholes, 1,2-azaphosphorines and 1,2-azaphosphepines. Most of these synthetic methods require special reaction conditions and specific starting materials that are not available in some laboratories. However, cyclization of amino- and hydrazino compounds with phosphorus reagents or cyclization of aminophosphorus compounds with simple

electrophiles are convenient and easy to perform. We hope that this review may encourage scientists to create new routes towards these ring systems with important biological activity.

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