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The aza-Wittig reaction: an efficient tool for the construction of carbon–nitrogen double bonds

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Abstract—Recent advances in the aza-Wittig reaction of phosphazene derivatives with several carbonyl compounds are reviewed. Phosphazenes afford inter- and intramolecular aza-Wittig reactions with different compounds such as aldehydes, ketones, esters, thioesters, amides, anhydrides and sulfimides. One of the most important applications of this reaction is the synthesis of a wide range of acyclic and heterocyclic compounds, ranging from simple monocyclic compounds to complex polycyclic and macrocyclic systems.

Contents

Abbreviations: AW-IC, aza-Wittig/intramolecular cyclization; AW-IEC, aza-Wittig/intramolecular electrocyclic ring closure; AW-IHA, aza-Wittig/intramolecular heterocumulene-mediated annelation; AW-IMADA, aza-Wittig/intramolecular aza-Diels–Alder; AW-NA-IC, aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BSM, bis(trimethylsilyl)-methylene; Cbz, benzyloxycarbonyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; KHMDS, potassium bis(trimethylsilyl)amide; MDR, multidrug resistance; MWI, microwave irradiation; Ns, nitrobenzenesulfonyl; pfp, pentafluorophenyl; PMB, *p*-methoxybenzyl; SAWU-3CR, Staudinger/intramolecular aza-Wittig/Ugi three-component reaction; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TMS, trimethylsilyl.

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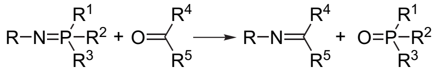
1. Introduction

In 1919, Staudinger and Meyer prepared PhN=PPh$_3$, the nitrogen analogue of a Wittig reagent (Scheme 1), the first example of an aza-Wittig reagent.[1] These phosphorus reagents are named λ^5-phosphazenes, iminophosphoranes or phosphine imines although, in this account, we will use the general term, phosphazenes. Phosphazenes were first prepared at the beginning of the last century, but it was not until Wittig's work, more than 30 years later, that the aza-Wittig reaction became accepted practise.



$$R-N=PR^1R^2R^3 + O=CR^4R^5 \longrightarrow R-N=CR^4R^5 + O=PR^1R^2R^3$$

Scheme 1.

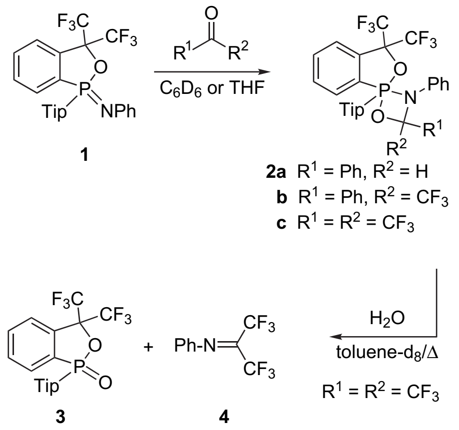
Since then, the Wittig and aza-Wittig reactions have undergone tremendous development and have become a powerful tool in organic synthetic strategies directed towards the construction of acyclic and cyclic compounds, mainly because the reaction is conducted in neutral solvents in the absence of catalysts, generally at mild temperatures, and usually proceeds in high yield.

The synthetic versatility of the phosphazenes has not been fully explored due, in part, to the poor variation of substituents on the nitrogen atom of the phosphazenes. Furthermore, the most commonly used substituted phosphorus group, triphenylphosphoranylidene, maybe replaced by other trisubstituted phosphoranylidene groups with a consequent increase or decrease in the nucleophilicity of the phosphazene moiety and/or other desired effects affecting the reaction rates. In an analogous manner to phosphorus ylides in the Wittig reaction, phosphazenes can also react with carbonyl compounds to afford an excellent method for the construction of C=N double bonds, first reported in the reaction of *N*-phenyltriphenylphosphazene with diphenyl ketene and carbon dioxide,[1] and latter expanded to the reactions with aldehydes, ketones, carbon disulfide and isocyanates.[2]

Numerous research papers and several reviews[3] have appeared describing the general use of phosphazenes as reagents and intermediates in organic synthesis. This account describes the mechanism of the aza-Wittig reaction, as well as reactions carried out in this area over the past decades, highlighting the major developments and dividing them into two parts, namely intermolecular and intramolecular aza-Wittig-type reactions.

2. Mechanism of the aza-Wittig reaction

Very little information has been described on the mechanism of the aza-Wittig reaction, although its similarity with the Wittig reaction has been reported.[4] For the elucidation of the mechanism of aza-Wittig reactions, it is important to isolate their intermediates, although these isolations are ordinarily difficult because of their instability. Kawashima et al. have, however, reported the synthesis, crystal structure and reactivity of *N*-apical 1,2-λ^5-azaphosphetidines **1** (with pentacoordinate *P* centres),[5] to give 1,3,2-λ^5-oxaazaphosphetidines **2a–c** (bearing the Martin ligand as a bulky substituent)[6] (Scheme 2). Thermolysis of the four-membered



Scheme 2.

ring compound **2c** ($R^1=R^2=CF_3$) revealed that the isolated compound can be regarded as an aza-Wittig reaction intermediate, due to the formation of the corresponding phosphanoxide **3** and iminic compound **4**.[7]

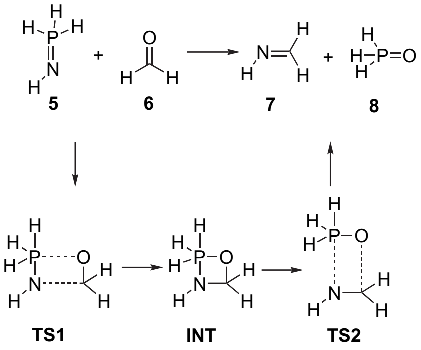
In 1997, Koketsu et al.[8] studied first the aza-Wittig reaction of iminopnictoranes with formaldehyde by ab initio calculations at the MP2/DZ-d level. The simplest models for iminopnictoranes (H_3MNH, i.e., M=P) and carbonyl compounds (CH_2O) were chosen, replacing all of the substituents on the heavy atoms by hydrogen atoms. These workers concluded that the aza-Wittig reaction is a two-step process and that there are four-membered cyclic intermediates with hypervalent pnictogens and the imine finally dissociates from the cyclic intermediates.

Lu et al. have developed a theoretical study of the aza-Wittig reaction of $X_3P{=}NH$ (X=Cl, H, or Me) with $O{=}CHCO_2H$ by means of ab initio calculations using HF/6-31G** structures at single-point energy calculations at the MP2/6-31G** level.[9] They obtained two similar intermediates for X=H and Cl (for X=Me, there is only one intermediate) at the HF/6-31G** level and proved that these two intermediates became accurately one minimum when the MP2/6-31G** method was used in the structure optimization. Moreover, to obtain better comprehensive information about the aza-Wittig route and also about four competitive reactions against the aza-Wittig method, these authors have performed theoretical studies with the second-order Møller–Plesset perturbation theory by use of a split valence plus polarization 6-31G** basis set.[10] Their calculations showed that other competitive reactions against the aza-Wittig route are less favourable.

The calculated results show that the aza-Wittig reaction is a two-step reaction via the first transition state (TS1a), a four-membered-ring intermediate (IS), and then via the second transition state (TS1b) (Fig. 1). It was observed that the aza-Wittig reaction surface calculated at the MP2/6-31G** level is somewhat different from that obtained at the MP2/DZ-d level,[8] and that only two of the three transition states at MP2/DZ-d can exist adequately at MP2/6-31G**.

Xue et al.[11] have performed ab initio calculations at the MP2/6-31G** level of theory and Monte Carlo simulation for the aza-Wittig reactions of $X_3P{=}NH$ with H_2CO (X=H, Cl, or Me) to obtain more information about these reactions in gas phase. The results show that this reaction is a stepwise process, with the first step being rate determining in the gas phase, that the four-membered cyclic compound is the only intermediate and that the aza-Wittig reaction can proceed more favourably when X=H, or Me than when X=Cl.

We have also carried out a theoretical–computational study at the B3LYP/6-31G level accompanied by an experimental analysis of several model transformations.[12] In our work, we have found that the aza-Wittig reaction between phosphazene **5** and aldehyde **6** takes place via a tandem [2+2] cycloaddition–cycloreversion through a thermally allowed supra–supra mechanism, with **INT** (Scheme 3) as a quite stable reaction intermediate, the bond distances of which agree with the X-ray data reported for the 1,3,2-λ^5-oxaazaphosphetidine intermediate isolated by Kawashima et al.[6,7] (vide supra). The stereochemical outcome of the whole reaction depends only upon the second step, because conformational changes in the intermediate 1,3,2-λ^5-oxaazaphosphazetidines have a much lower activation energy than the second [2+2] cycloreversion reaction with preferential or exclusive formation of the corresponding *E*-imine **7**.



Scheme 3.

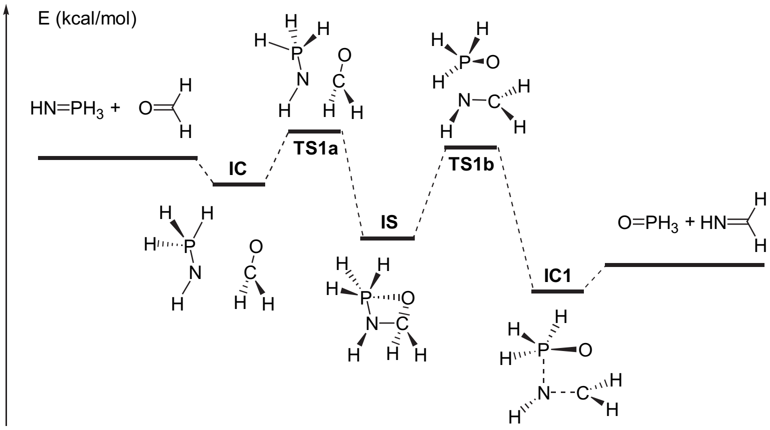
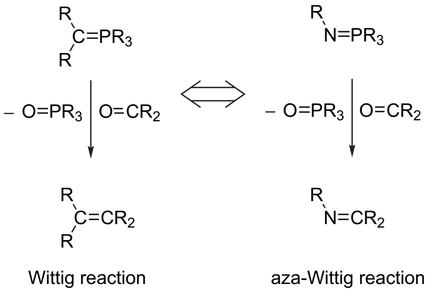


Figure 1. Schematic energy diagram, and MP2/6-31G** optimized geometries of the complexes (IC and IC1), the transition states (TS1a and TS1b) and the intermediate (IS) for the aza-Wittig reaction.

3. Intermolecular aza-Wittig reaction of phosphazenes with aldehydes and ketones: synthesis of iminic compounds

The Wittig reaction involving the reaction of phosphorus ylides with carbonyl compounds is an excellent tool for the formation of carbon–carbon double bonds, and simple phosphazenes, nitrogen isosteres of phosphorus ylides, are the starting materials widely used for the construction of imine (C=N) compounds through the aza-Wittig process (Scheme 4). This reaction seems to be one of the most efficient methods for the creation of the imine group in mild reaction conditions. The process is very general, and the reactions of simple (*N*-alkyl or *N*-aryl) and conjugated (*N*-vinylic) phosphazenes will now be described.



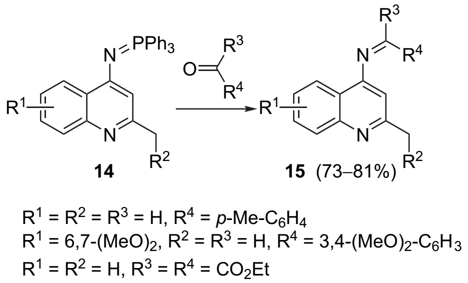
Scheme 4.

3.1. Simple phosphazenes

3.1.1. Synthesis of imines. The outstanding property of phosphazenes is their nucleophilicity, but the most interesting properties are those that depend upon a combination of a nucleophilic reaction and an elimination of the phosphorus group in an oxidized state. As mentioned before, the aza-Wittig reaction (see Scheme 4) is one of the most widespread methods for the conversion of P=N into C=N bonds in very mild reaction conditions.

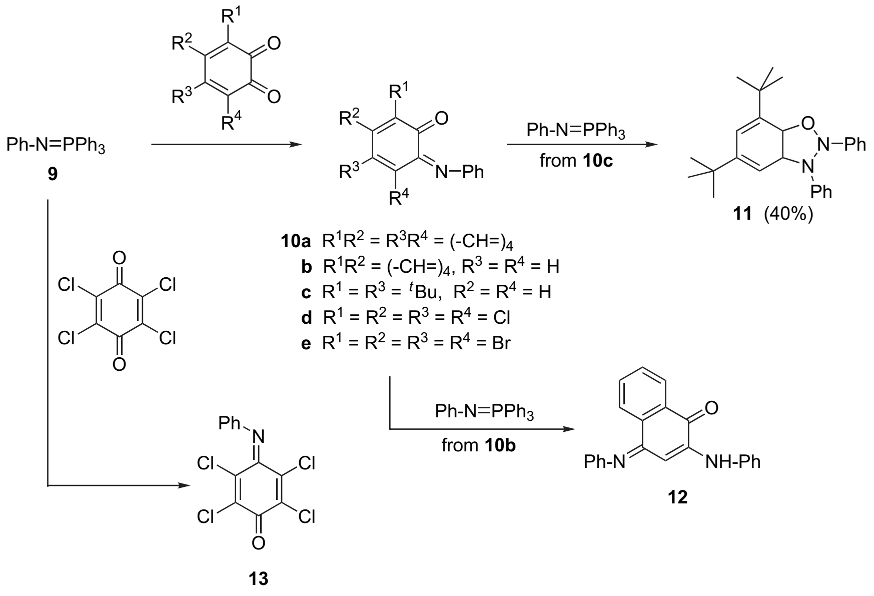
The reaction of *N*-phenyltriphenylphosphazene **9** with *ortho*- and *para*-quinones leads to different products, depending upon the substituent on the quinone, as well as the stability of the reaction product (Scheme 5).[13] The significance of these findings is not only the discovery of a new pattern for phosphazene, but also the establishment of facile methods for preparing the new benzoxadiazole **11**, as well as the phenylimino derivatives **10a–e**, **12** and **13**.

The reaction of phosphazenes **14** derived from quinolines[14] with carbonyl derivatives such as *p*-tolualdehyde (R^3=H, R^4=*p*-Me–C_6H_4), veratraldehyde [R^3=H, R^4=3,4-$(MeO)_2$–C_6H_3] and diethyl ketomalonate (R^3=R^4=CO_2Et) represents a simple strategy for the preparation of imino compounds **15** derived from 4-aminoquinolines (Scheme 6). In an analogous manner, the regiospecific preparation of 2-imino-benzothieno derivatives based on the aza-Wittig reaction of the *N*-benzothiophene-phosphazene with a variety of unsaturated heteroaromatic and aromatic aldehydes has been reported.[15]

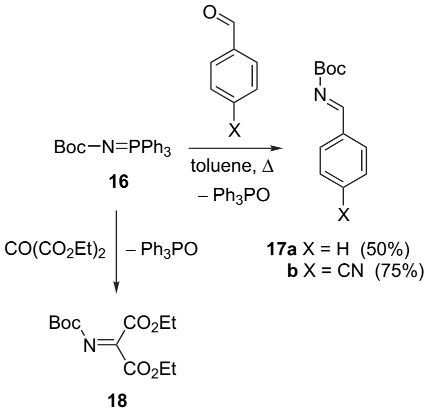


Scheme 6.

In this way, the *N*-Boc protected imine derivatives **17a**,**b** and **18** are easily obtained by an aza-Wittig reaction of the phosphazene **16** with benzaldehyde derivatives[16] or with diethyl ketomalonate,[17] respectively (Scheme 7).

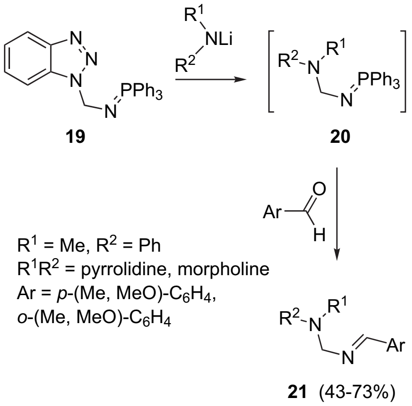


Scheme 5.



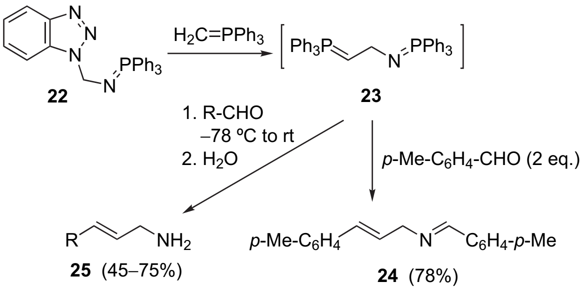
Scheme 7.

3.1.2. Synthesis of functionalized imines. The aza-Wittig reaction can be considered as a new route to α-(arylideneamino)alkylamines **21** (Scheme 8). Nucleophilic displacement of the benzotriazole moiety from **19** with lithium amides, and condensation of the resulting phosphazene intermediates **20** with aryl aldehydes, gave the corresponding amino-functionalized imines **21** in a moderate yield.[18]



Scheme 8.

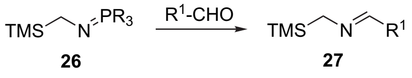
In order to compare the reactivity of phosphazenes and phosphorus ylides, Katritzky and Jiang[19] studied the behaviour of monoazabisphosphorus ylides such as **23** with aldehydes. Treatment of compound **23** (prepared from **22**) with 2 equiv of *p*-tolualdehyde gave the imine **24** (Scheme 9). When a limited amount of aldehyde is used, however, only the more nucleophilic ylide group of **23** reacts, and the phosphazene acts as a protecting group for the primary amine functionality, which is released during the aqueous work-up, affording the corresponding allylamine **25**.



R = *p*-(Me, MeO)-C$_6$H$_4$, 1-ethylhexyl, 1-methyl-2-butenyl, 2-furanyl, 2-chloro-1-cyclohexenyl, *o*-MeO-C$_6$H$_4$, 2-pentenyl

Scheme 9.

We have also studied the synthesis of functionalized imines **27**[12] (Scheme 10), in order to develop an efficient new synthetic method for imines with a good leaving group such as the trimethylsilyl group (TMS). It is noteworthy that, when phosphazenes derived from trimethylphosphine **26** (R=Me) were used, imines **27** were obtained in milder reaction conditions, showing the difference in the reactivity of trimethylphosphine derivatives in comparison with their triphenyl counterparts.

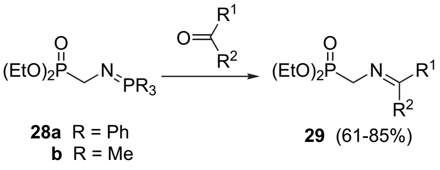


R = Ph, Me

R^1 = Me, Ph

Scheme 10.

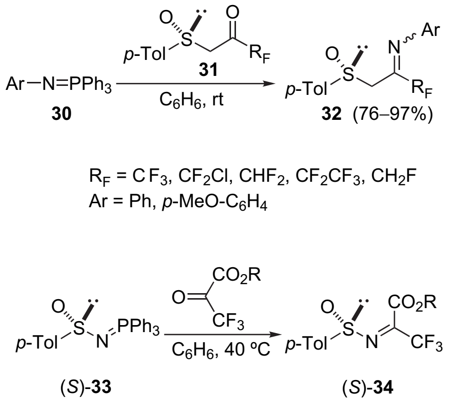
Functionalized imines **29** derived from aminophosphonates can be prepared by the aza-Wittig reaction of *N*-phosphorylalkyl phosphazenes **28** and carbonyl compounds.[20,21] The phosphazene **28a** was heated with aldehydes to give the *N*-phosphorylalkyl aldimines **29** (Scheme 11). The reaction was not limited to simple aldehydes, *N*-phosphorylalkyl phosphazene **28a** also reacting with pyruvonitrile (R^1=Me, R^2=CN) and ethyl cyanoformate (R^1=OEt, R^2=CN) to afford the corresponding functionalized imines **29**. The more reactive phosphazene derived from trimethylphosphine **28b** (R=Me) performs the process in milder reaction conditions when reacting with pyruvonitrile (R^1=Me, R^2=CN).



R^1 = H, Me, OEt
R^2 = *p*-(Me, NO$_2$, MeO)-C$_6$H$_4$,
o-CH$_2$=CHCH$_2$OC$_6$H$_4$, CN

Scheme 11.

This strategy turned out to be quite promising for the synthesis of biologically interesting chiral fluorinated and nitrogen-substituted molecules. Enantiomerically pure *N*-aryl (and *N*-alkyl) fluoroalkyl (arylsulfinyl)methylimines (*R*)-**32** (Scheme 12)[22,23] have been prepared by an aza-Wittig reaction between the semi-stabilized phosphazenes **30** and the (*R*)-γ-fluoro-β-ketosulfoxides **31**. When starting from the chiral sulfoxide-functionalized phosphazenes (*S*)-**33**, methyl or ethyl trifluoropyruvate (R=Me or Et) afforded non-racemic α-trifluoromethyl α-amino acid derivatives (*S*)-**34** (R=Me or Et).[24]

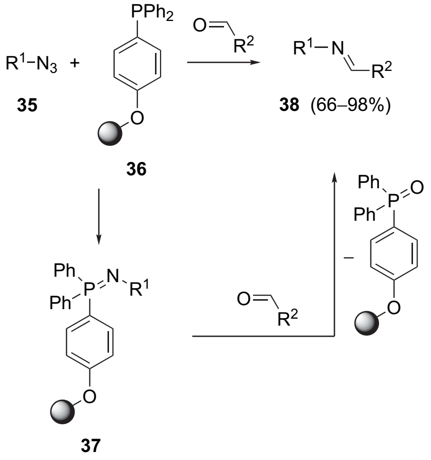


$R_F = CF_3, CF_2Cl, CHF_2, CF_2CF_3, CH_2F$
Ar = Ph, *p*-MeO-C_6H_4

R = Me, Et

Scheme 12.

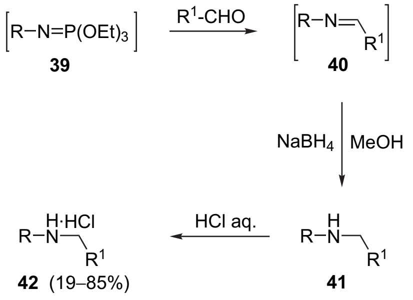
The aza-Wittig reaction has been used for the solid-phase organic synthesis of functionalized imines.[25,26] One of the biggest inconveniences of the aza-Wittig reaction is the isolation of the obtained imine derivatives from the phosphine oxide formed in the reaction. By using solid-phase methodology, however, imines **38**, prepared from aza-Wittig reaction of polymer-supported phosphazenes **37**, or secondary amines obtained from the in situ reduction of these imines **38** were obtained in a one-pot aza-Wittig reaction (Scheme 13). The rates of the reactions are comparable to those observed when triphenylphosphine is used as the reagent, indicating that the polymer-bound reagent **36** is comparable to free triphenylphosphine.



R^1 = TMS, Bn, Ph, *p*-MeO-C_6H_4, C_6H_{11},
3-pyridyl, Ph-CH=CH-CH_2
R^2 = Ph, *p*-(MeO, F)-C_6H_4, Ph-CH=CH, ^{t}Bu, Pr,
Me, Me(CH=CH_2)$_2$, Bn, phenethyl, *p*-anisyl

Scheme 13.

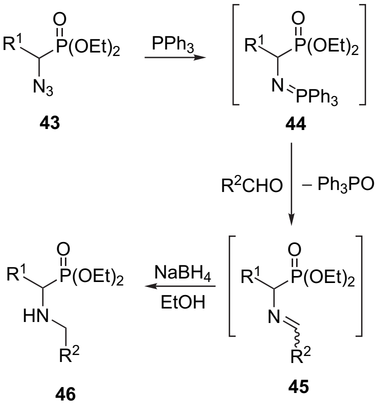
3.1.3. Synthesis of amines, amides and enamides. Through the imine intermediate, the aza-Wittig reaction could be considered as a useful route for the preparation of secondary amines in a convergent one-pot synthesis.[27] Phosphazenes **39** reacted easily with aliphatic and aromatic aldehydes to give the intermediate imines **40**, which were reduced with sodium borohydride in methanol to form the target secondary ammonium salts **42** via **41** (Scheme 14). The syntheses of α-(arylideneamino)alkylamines[18] have also been reported using this tool. *N*-Monomethylamines can be prepared through the same strategy of aza-Wittig reaction and in situ reduction of the formed imines.[28]



R = Ph-CH_2-CH_2, C_6H_{13}, CH_2=CH-CH_2, *sec*-Bu
R^1 = Ph, ^{i}Pr, Pr

Scheme 14.

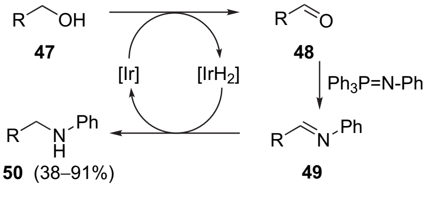
Aminoalkylphosphonates **46** can be prepared from the azidoalkylphosphonates **43**, which reacted with triphenylphosphine to give the phosphonate-substituted phosphazenes **44**. A subsequent aza-Wittig reaction with aldehydes and subsequent in situ reduction of the imine **45** yielded the corresponding aminoalkylphosphonates **46** (Scheme 15).[29]



R^1 = H, Me, ^{i}Pr, Ph
R^2 = ^{i}Pr, ^{t}Bu, Ph, Ph-CH=CH, ^{i}Bu

Scheme 15.

Activated alcohols **47** can be transformed into the amines **50**, via an aza-Wittig reaction between the aldehyde **48** and a phosphazene to give **49** (Scheme 16).[30] Therefore, by using

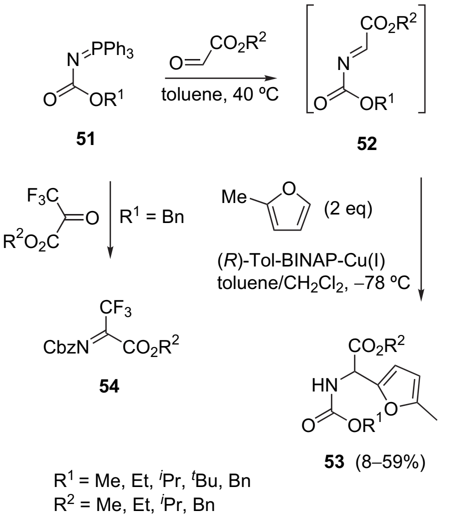


R = Ph, *p*-(NO_2, MeO)-C_6H_4, 2-furfuryl, Ph-$(CH_2)_2$

Scheme 16.

iridium catalyst, it is possible to convert alcohols into *N*-phenylamines via an indirect aza-Wittig reaction.

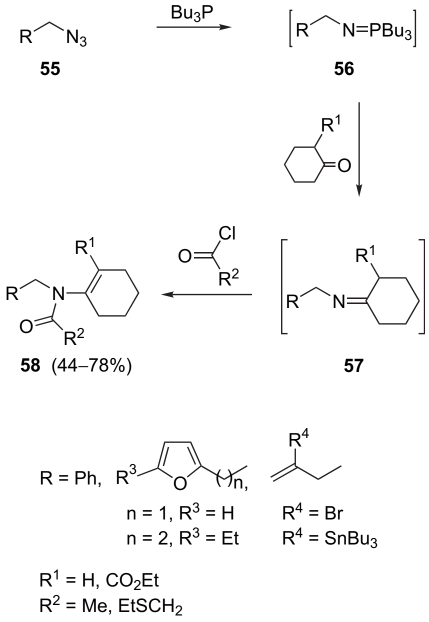
For the synthesis of non-natural aromatic and heteroaromatic α-amino acids **53**, the corresponding *N*-alkoxycarbonyl α-imino esters **52** were prepared via an aza-Wittig reaction of the *N*-carboalkoxyphosphazenes **51** and alkyl glyoxalates (Scheme 17).[31] Moreover, through an aza-Wittig reaction, the fluorinated imine derivatives could easily be obtained by the treatment of phosphazenes with fluorinated carbonyl compounds. Therefore, the reaction of phosphazenes **51** (R^1=Bn) with fluorinated carbonyl compounds has been used in the preparation of trifluoromethyl-imine derivatives **54** (Scheme 17). Trifluoromethyl-amino acid-containing peptides are a special class of peptide mimetics, which could markedly improve the pharmacodynamic and pharmacokinetic characteristics of the natural peptides.[32]



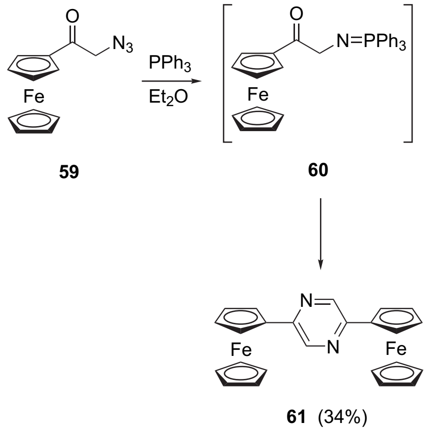
Scheme 17.

A variety of vinylogous amides can be prepared using an aza-Wittig reaction of phosphazenes **56**, derived from azides **55**, with cyclohexanone and subsequent condensation with carboxylic acid derivatives. The aza-Wittig-type reaction of phosphazenes **56** with ketones should generate the imines **57**, which were expected to furnish the desired vinylogous amide system **58** by reaction with acid chlorides (Scheme 18).[33] This optimized method was applied to a number of related condensation reactions where the precursor azides, ketones and acid chlorides were varied.

When α-ferrocenylazido ketone **59** was treated with PPh_3 at room temperature, the compound 2,5-bis(ferrocenyl)pyrazine **61** was obtained.[34] The formation of **61** was explained by the initial formation of the phosphazene **60**, which undergoes cyclocondensation through an intermolecular aza-Wittig reaction between two molecules of the same phosphazene **60** and, eventually, dehydrogenation of the resulting dihydropyrazine (Scheme 19).



Scheme 18.

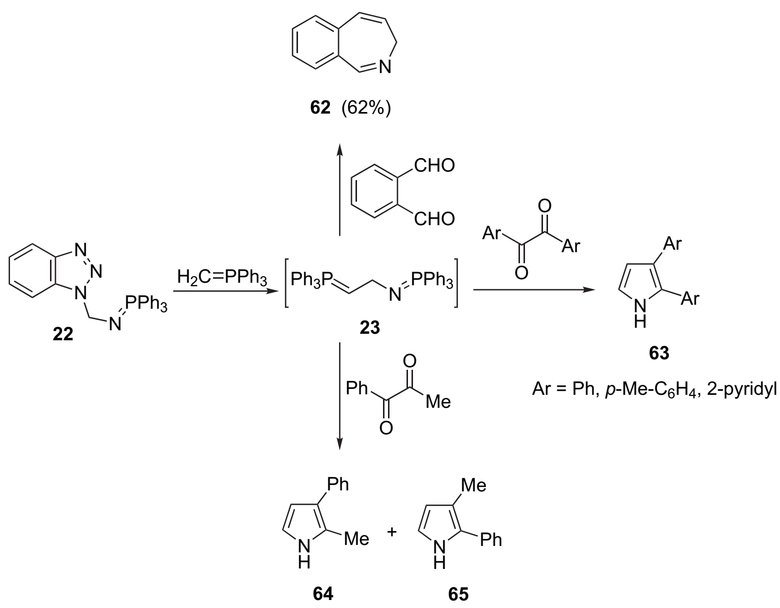


Scheme 19.

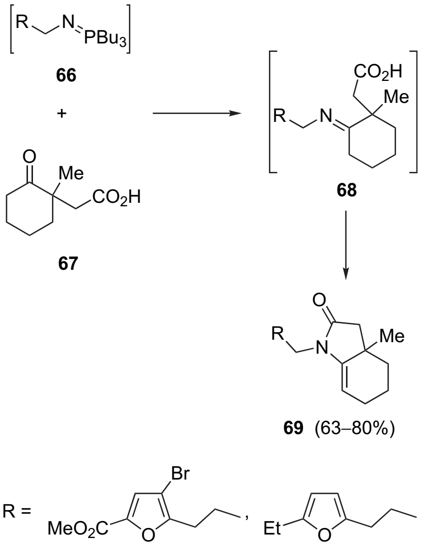
3.1.4. Heterocyclic synthesis: tandem aza-Wittig/intramolecular cyclization (AW-IC).

As has been demonstrated, the aza-Wittig reaction takes part in several strategies for heterocyclic synthesis. Although the reaction of tolualdehyde with monoazabisphosphorus ylides involves only the phosphorus ylide linkage (Wittig reaction, vide supra, Scheme 9), these functionalized phosphazenes containing a phosphorus ylide group react with dicarbonylic compounds (phthalic dicarboxaldehyde, 1,2-diketones) producing both the Wittig and the aza-Wittig products. The reactivity of both functional groups in **23** with carbonyl compounds and the simultaneous construction of carbon–carbon and carbon–nitrogen double bonds leads to the formation of benzazepine **62** or 2,3-disubstituted pyrroles **63–65** (Scheme 20).[19]

The hexahydroindolinone ring system can be prepared using an aza-Wittig reaction of phosphazenes derived from furanyl azides and 1-methyl-(2-oxo-cyclohexyl)acetic acid **67**.[33] An aza-Wittig-type reaction of phosphazenes **66** with the keto-acid **67** should generate the intermediate imine **68**, which was expected to rapidly cyclize and furnish the desired hexahydroindolinone system **69** (Scheme 21).



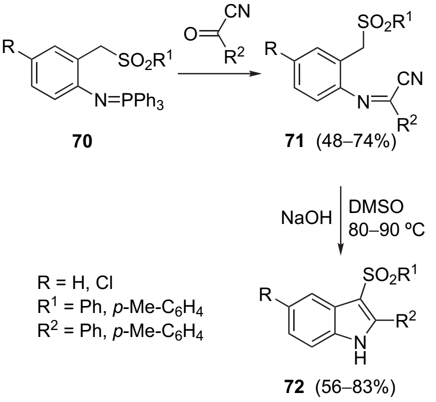
Scheme 20.



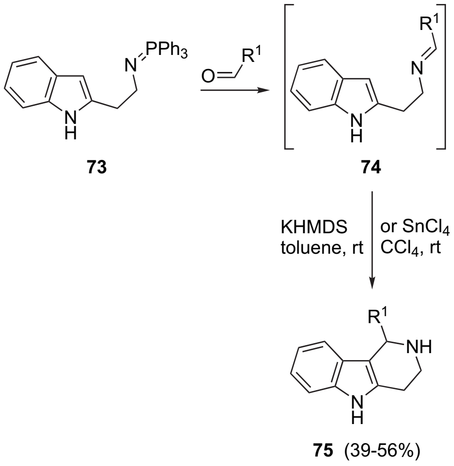
Scheme 21.

Starting from the phosphazenes **70**, which have an active methylene group adjacent to a sulfonyl group, and through aza-Wittig reaction with pyruvonitriles and subsequent intramolecular cyclization of imines **71**, 2-aryl-3-arylsulfonylindoles **72** can be obtained (Scheme 22).[35]

The tandem aza-Wittig/intramolecular cyclization (AW-IC) has been successfully utilized for the synthesis of heterocyclic systems and naturally occurring alkaloids, among which is lavendamycin.[36] Phosphazenes **73**, in which the indole ring is linked with a flexible alkyl chain containing two carbon atoms, reacted through an aza-Wittig reaction with aldehydes to afford the heterocyclic compounds **75** via **74** (Scheme 23).[37] In an analogous manner, the synthesis of heteroaromatic β-carboline-fused pentacycles has been reported.[38]



Scheme 22.



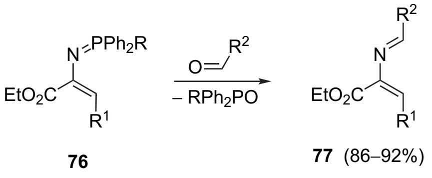
R^1 = Ph, Et, Ph-CH=CH, p-(Me, MeO)-C_6H_4, o-N_3-C_6H_4

Scheme 23.

3.2. *N*-Vinylic phosphazenes with carbonyl compounds

This section deals with selective 1,2-addition reactions (aza-Wittig reactions) of *N*-vinylic phosphazenes. The reaction of these compounds with carbonyl compounds has been used in the synthesis of functionalized iminic compounds such as 2-azadienes, excellent key intermediates in the preparation of heterocycles, through cycloaddition processes.[39,40]

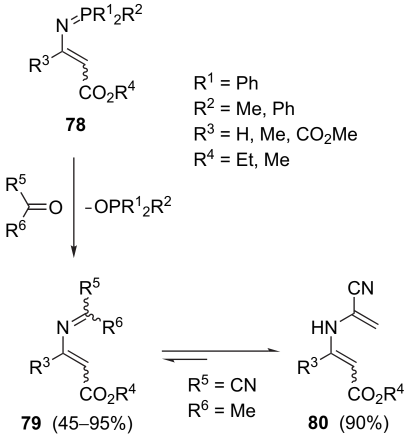
3.2.1. Reaction with simple carbonyl compounds: synthesis of 2-azadienes and derivatives. The aza-Wittig reaction of *N*-vinylic phosphazenes derived from α-amino acids with carbonyl compounds has been widely used in the synthesis of 2-azadiene systems. An aza-Wittig reaction of *N*-acrylic phosphazenes **76** with aldehydes gave the 3-ethoxycarbonyl-2-aza-1,3-butadienes **77** in very high yields (Scheme 24).[41]



R = Me, Ph
R^1 = Ph, Ph-CH=CH
R^2 = Ph, *p*-Cl-C$_6$H$_4$, Ph-CH=CH, 2-thienyl

Scheme 24.

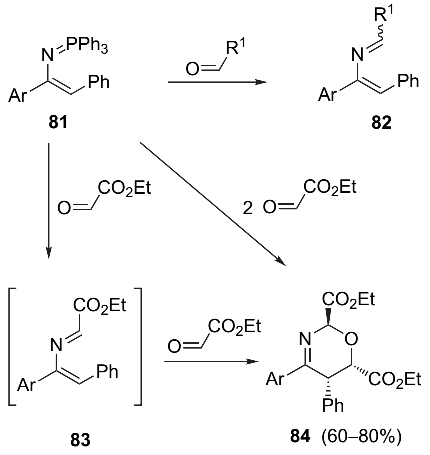
In a similar way, the reaction of *N*-vinylic phosphazenes **78**, derived from β-amino acids, with ethyl glyoxalate and diethyl ketomalonate gave the di-, tri- and tetrasubstituted 2-azadienes **79** (Scheme 25). These heterodienes derived from β-amino acids are suitable 4π-systems in [4+2] cycloaddition reactions.[39,42] Likewise, when pyruvonitrile was used as the carbonyl compound, the isolation of diene **79** (R^5=CN, R^6=Me) was not possible, but the tautomeric dienamine **80** was isolated instead, which confirmed the formation of the azadiene compound as the non-isolated intermediate.



R^1 = Ph
R^2 = Me, Ph
R^3 = H, Me, CO$_2$Me
R^4 = Et, Me

Scheme 25.

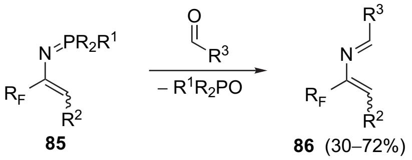
The aza-Wittig reaction of *N*-vinylic phosphazenes with carbonyl compounds represents a very efficient method for the preparation of 2-azadienes **82** (Scheme 26).[40] The reaction of ethyl glyoxalate with phosphazenes **81** was also explored and, surprisingly, the formation of the expected azadienes **83** was not observed, the six-membered heterocycles **84** being isolated instead in a regio- and a stereoselective fashion (Scheme 26). The formation of the heterocycles **84** can be explained by an aza-Wittig reaction of the phosphazenes **81** and aldehyde, followed by a [4+2] cycloaddition reaction of the heterodienes **83** with a second molecule of ethyl glyoxalate.



R^1 = Ph, 3-pyridyl,2-pyridyl, 1-indolyl, 2-thienyl,
5-Me-2-furyl, 2-pyrrolyl
Ar = Ph, 2-furyl, 2-pyridyl, 3-pyridyl, 2-thienyl

Scheme 26.

An aza-Wittig reaction of fluoroalkyl-substituted phosphazenes **85** afforded the fluoroalkyl-functionalized 2-azadienes **86** (Scheme 27).[43] These fluoroalkylated 2-aza-1,3-butadienes **86** maybe important synthons in organic synthesis and in the preparation of fluoroalkyl-substituted acyclic and heterocyclic compounds.

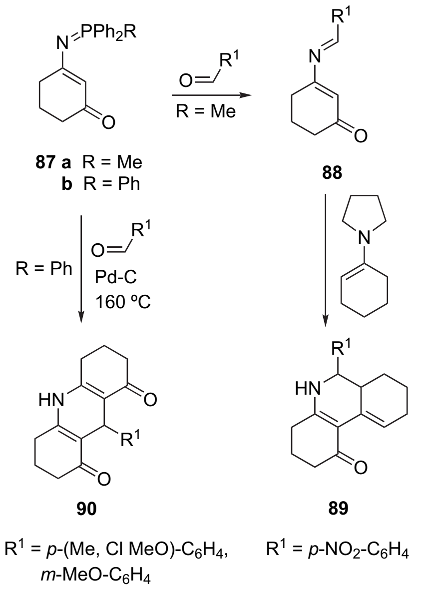


R$_F$ = CF$_3$, C$_2$F$_5$, C$_7$F$_{15}$
R = Ph, Me
R^1 = Ph, Me

R^2 = Ph, CO$_2$Me, CN
R^3 = Ph, 3-pyridyl,
p-NO$_2$-C$_6$H$_4$, CO$_2$Et,
2,4-(NO$_2$)-C$_6$H$_3$

Scheme 27.

Conjugated phosphazene **87a**, derived from cyclic ketones, reacts with aldehydes to give the aza-Wittig products **88**. The azadienes **88** were not isolated and were used in situ in a [4+2] cycloaddition reaction with pyrrolidine-cyclohexanone enamine, leading to the formation of the tricyclic phenanthridin-1-one derivatives **89**[42] (Scheme 28). When the phosphazene **87b**, derived from triphenylphosphine, was used, however, the 9-azaanthracene compounds **90** were obtained.[44] These findings are in contrast with the reported reaction of phosphazenes derived from methyldiphenylphosphine **87** (R=Me) with aldehydes, and can be rationalized in terms of an initial addition of the β-carbon atom of the phosphazene **87b** to the carbonyl carbon atom of the aldehyde to give an intermediate betaine. After regiospecific attack of a second molecule of the phosphazene **87b** on the betaine, with loss of two molecules of triphenylphosphine oxide, the compounds **90** were formed (Scheme 28).



87 a R = Me
b R = Ph

88

90

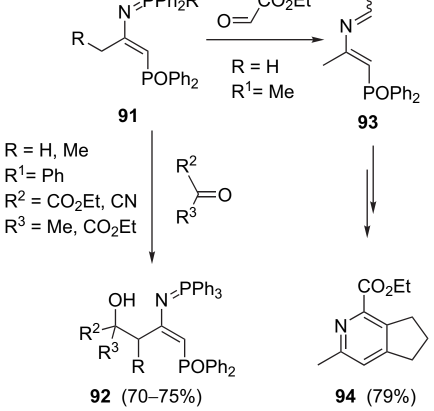
89

R^1 = *p*-(Me, Cl MeO)-C_6H_4, *m*-MeO-C_6H_4

R^1 = *p*-NO_2-C_6H_4

Scheme 28.

The presence of an electron-withdrawing group in the phosphazene, such as the phosphoryl group, seems to play an important role in the reactivity of the conjugated phosphazene.[45] Taking into account the high electron density on the C_γ atom of **91**, enhanced nucleophilicity of the vinyl moiety took place and, therefore, nucleophilic attack of the γ-carbon atom of *N*-vinylic phosphazenes **91** (R^1=Ph) on the carbonyl group of diethyl ketomalonate (R^3=CO_2R^2) and pyruvic ester (R^3=Me) was observed, with carbon–carbon simple bond construction, to afford the functionalized phosphazene compounds **92** (Scheme 29). The reaction with a more reactive phosphazene **91**, derived from methyldiphenylphosphine (R=H, R^1=Me), and ethyl glyoxalate, however, gave the corresponding aza-Wittig derivative **93**, which was trapped through a [4+2] cycloaddition reaction, giving the pyridine derivative **94**.



91

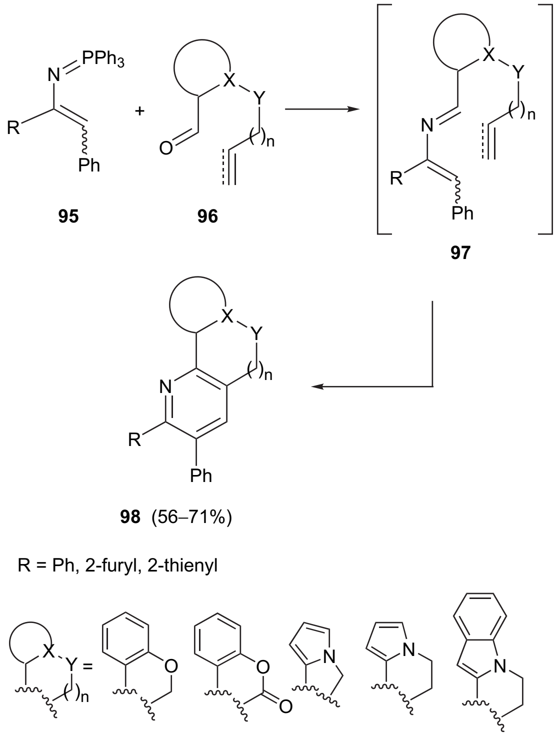
93

92 (70–75%)

94 (79%)

Scheme 29.

The tandem aza-Wittig/intramolecular aza-Diels–Alder (AW-IMADA) reactions of heteroaromatic-substituted *N*-vinylic phosphazenes **95** with functionalized aldehydes **96** provided a convenient route to a variety of tricyclic and tetracyclic condensed pyridines **98** via **97** (Scheme 30).[46]



95

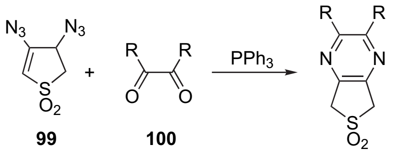
96

97

98 (56–71%)

Scheme 30.

Functionalized bisazides were used for the preparation of pyrazino-3-sulfolenes.[47] Aza-Wittig reaction of the phosphazenes, obtained from compound **99** containing an alkyl azide and a vinyl azide with α-dicarbonyl compounds **100** gave the corresponding pyrazino-3-sulfolenes **101** in moderate yields (Scheme 31).



99

100

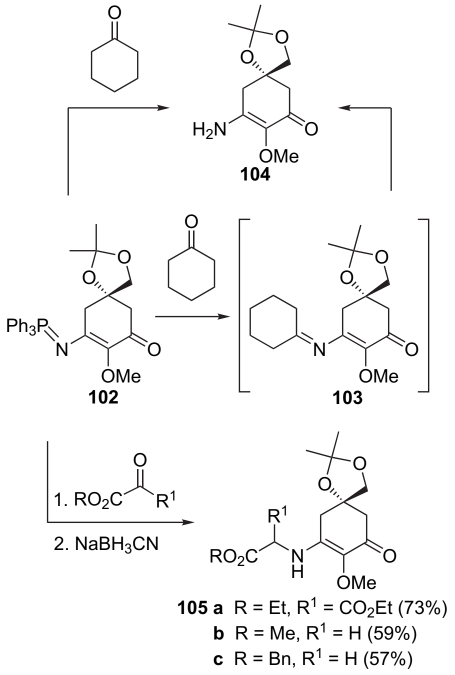
101 (28-47%)

R = H, Me
RR = –$(CH_2)_4$–

Scheme 31.

3.2.2. Synthesis of functionalized amides. Aza-Wittig reaction of the phosphazene **102** with cyclohexanone gave the enaminone **104**, rather than the expected imine **103**

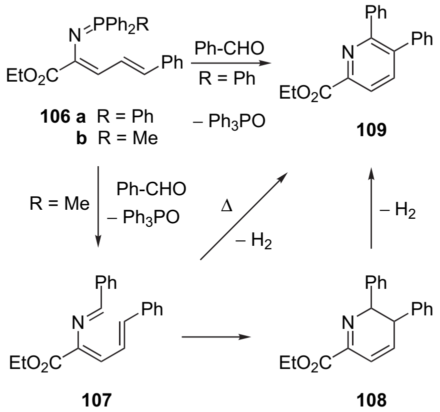
(Scheme 32). The imine **103** was initially formed, followed by hydrolysis under the reaction conditions to the primary enaminone **104**. Reaction with ketomalonate and in situ reduction of the resulting ketimine afforded the enaminone **105a** (R=Et, R^1=CO_2Et). This phosphazene does not condense with less reactive ketones, but an aza-Wittig reaction was observed when the phosphazene **102** was treated with methyl or benzyl glyoxalate, followed by in situ reduction of the intermediate aldimine with sodium cyanoborohydride, giving the cyclic enaminones **105b** or **105c**, which are the starting materials for the asymmetric synthesis of mycosporin I and mycosporingly.[48]



Scheme 32.

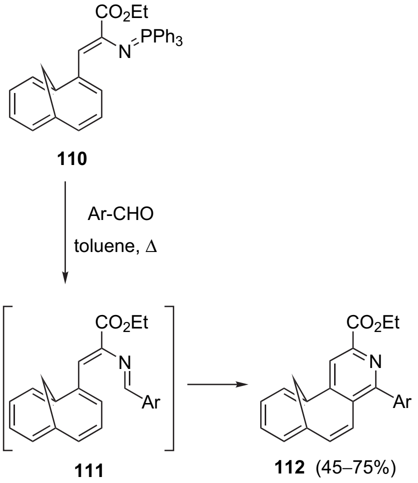
3.2.3. Heterocyclic synthesis: tandem aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC).

Many types of five- and six-membered *N*-heterocycles, including natural products and their analogous compounds, have been prepared by the tandem aza-Wittig/intramolecular electrocyclic ring closure strategy (AW-IEC), notably in the last decade. In this context, the aza-Wittig reaction of *N*-vinylic phosphazenes derived from α-amino acids has been used for the synthesis of heterocycles such as the pyridine derivative **109**. The dienyl phosphazene **106a** gave directly the pyridine **109** when this phosphazene **106a** reacted with benzaldehyde. Aza-Wittig reaction of the dienyl phosphazene **106b**, however, gave the 2-azahexa-1,3,5-triene **107**, and subsequent thermal 6π-electrocyclization of this compound **107** led to the formation of the pyridine **109** (Scheme 33).[49] The formation of this pyridine could be explained by cyclization and subsequent aromatization of the dihydropyridine **108**.



Scheme 33.

An important extension of the aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC) methodology has been used in the construction of fused pyridines such as thienopyridines[50] and alkaloids.[51,52] Similarly, tandem AW-IEC reactions have been explored for the synthesis of annulenopyridines. Thus, an aza-Wittig reaction of **110** with aldehydes afforded the non-isolated imines **111**, which after electrocyclization, gave a series of novel 1,6-methano[10]annuleno[3,2-*c*]pyridines **112** (Scheme 34).[53]

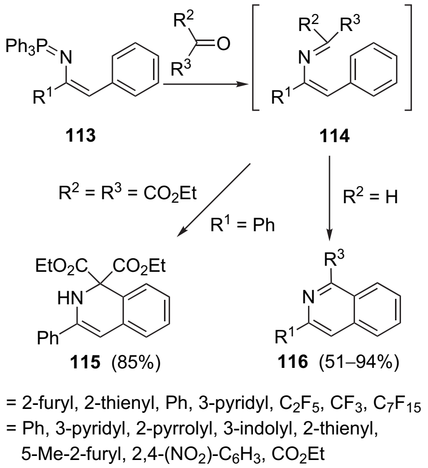


Ar = *p*-(Cl, CN, NO_2, MeO)-C_6H_4, *m*-NO_2-C_6H_4, *p*-NO_2-C_6H_4-CH=CH

Scheme 34.

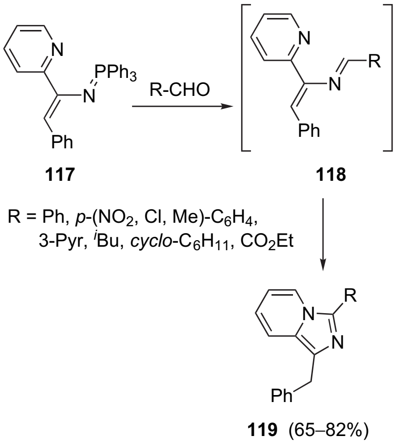
The isoquinoline derivatives **115** and **116** can alternatively be obtained in a one-pot procedure, when phosphazenes **113** and ketones or aldehydes, respectively, are directly heated in refluxing xylene (Scheme 35). Treatment of the phosphazene **113** with diethyl ketomalonate[40,54] gave the 3-pyridyldihydroisoquinoline derivative **115**, which suggests that the process involves an initial aza-Wittig reaction to give the unsaturated ketimine **114**, which subsequently undergoes 1,6-electrocyclic ring closure, leading to the formation of the bicyclic heterocycle **115**, or which is followed by complete aromatization to give the isoquinolines **116** when the process is carried out with aldehydes.[40,43a]

On the other hand, the tandem aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC) reaction has also been employed for the preparation of five-membered heterocyclic



Scheme 35.

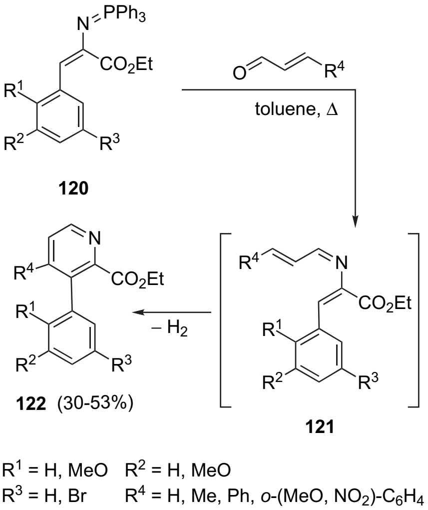
compounds. Likewise, an annelation of imino-functionalized pyridines **118**, generated in situ from the aza-Wittig reactions of phosphazene **117** with aliphatic, aromatic and heteroaromatic aldehydes, gave the imidazo[1,5-*a*]pyridines **119** (Scheme 36).[54]



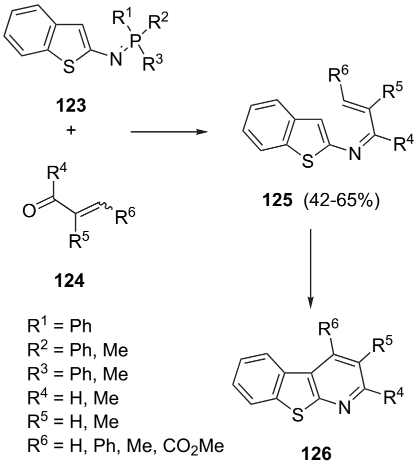
Scheme 36.

As pointed out previously, *N*-vinylic phosphazenes could react with α,β-unsaturated aldehydes through an aza-Wittig reaction (1,2-addition). In some cases, azatrienes, generated by means of an aza-Wittig reaction (1,2-addition) of *N*-vinylic phosphazenes with α,β-unsaturated aldehydes, could not be isolated, but they could be detected in the crude reaction mixtures.[55] 3-Arylpyridines **122** have been obtained when *N*-vinylic phosphazenes **120** were treated with α,β-unsaturated aldehydes (Scheme 37).[56] Electrocyclic ring closure of the intermediate azatrienes **121** and further dehydrogenation under suitable reaction conditions for the resulting dihydropyridine derivatives furnished the pyridines **122**. The reaction was extended to other *N*-vinylic phosphazenes bearing two ethoxycarbonyl groups at the two different positions of the vinylic chain,[44] or phosphazenes derived from α-amino acid intermediates in the synthesis of 4-arylpyridines.[57]

Imidazonaphthyridines are obtained by the reaction of *N*-benzoimidazoyl phosphazenes with α,β-unsaturated aldehydes.[58] A regiospecific preparation of benzo[*b*]thieno[2,3-*b*]pyridines **126** based on the aza-Wittig reaction of the phosphazenes **123** with a variety of α,β-unsaturated aldehydes **124** has been reported (Scheme 38).[15,59] When methyldiphenylphosphazene **123** (R^1=R^2=Ph, R^3=Me) was used, the α,β-unsaturated imine intermediates **125** could be isolated (42–65%). These iminic intermediates gave quantitatively, only after UV irradiation, the benzo[*b*]thieno[2,3-*b*]pyridines **126**. When dimethylphenylphosphazene **123** (R^1=R^2=Me, R^3=Ph) or triphenylphosphazene **123** (R^1=R^2=R^3=Ph) were used, however, the benzo[*b*]thieno[2,3-*b*]pyridines **126** were obtained directly. In a similar way, benzo[*b*]thieno[3,2-*b*]pyridines were prepared.[60]



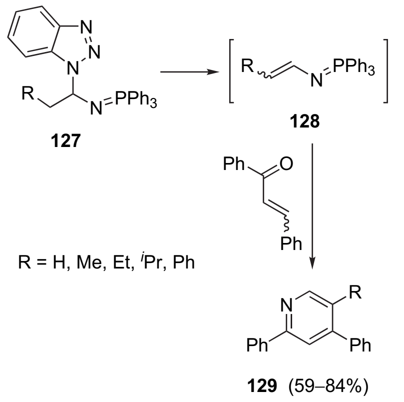
Scheme 37.



Scheme 38.

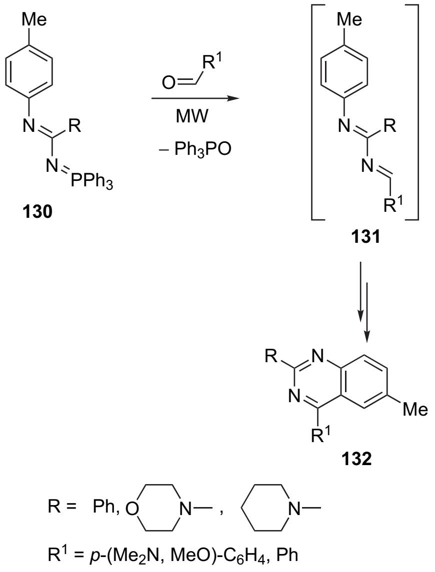
Katritzky et al.[61] reported the preparation of pyridines **129** from *N*-vinylic phosphazenes **128** (obtained from **127**) with α,β-unsaturated ketones (Scheme 39). The pathway followed by these compounds cannot be generalized, because the authors have observed experimentally that the Michael addition of *N*-vinylic phosphazenes to the β-carbon of the carbonyl compound seems to predominate when **128**

(R=Ph) was used, because little formation of triphenylphosphine oxide was observed. The aza-Wittig reaction between *N*-vinylic phosphazenes and α,β-unsaturated carbonyl compounds seemed to prevail, however, in the case of **128** (R=^{i}Pr), when triphenylphosphine oxide was readily formed at the beginning of the reaction.



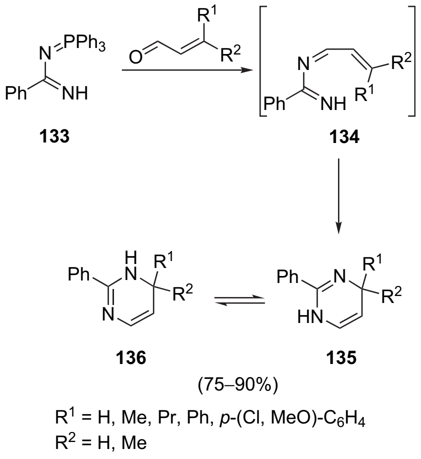
Scheme 39.

N-Imidoyl phosphazene is an aza-analogue of *N*-vinylic phosphazenes and showed a similar behaviour towards carbonyl derivatives. The exposure of a mixture of *N*-imidoyl phosphazenes **130** and aldehydes to microwave radiation resulted in excellent yields of the quinazolines **132** via **131** (Scheme 40).[62]



Scheme 40.

A tandem aza-Wittig reaction, followed by 6π-electrocyclic ring closure of the 1,3-diazatriene intermediate, can also explain the preparation of dihydropyrimidine derivatives **135** and **136** by a one-pot reaction of *N*-imidoyl phosphazene **133** with acyclic α,β-unsaturated aldehydes, ranging from unsubstituted to alkyl, aryl and substituted aryl aldehydes, via **134** (Scheme 41).[63]



Scheme 41.

4. Aza-Wittig reaction with CO_2 and CS_2: synthesis of isocyanate and isothiocyanate derivatives

The reaction of phosphazenes with carbon dioxide or carbon disulfide has been used extensively for the formation of isocyanates or isothiocyanates, respectively, which are appropriate substrates for the synthesis of different derivatives (Scheme 42).

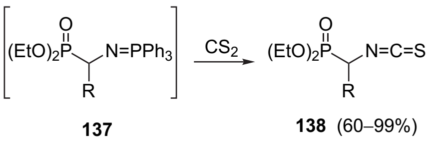
$$R{-}N{=}PPh_3 \xrightarrow[-PH_3PX]{X{=}C{=}X} R{-}N{=}C{=}X$$

$$X = O, S$$

Scheme 42.

4.1. Synthesis of isocyanates and isothiocyanates

An aza-Wittig reaction of appropriately functionalized phosphazenes **137** with carbon disulfide afforded the 1-(isothiocyanato)alkylphosphonates **138** with a range of aliphatic and aromatic substituents (Scheme 43).[64] The presence of more hindered alkyl substituents in phosphazene demanded prolonged heating with carbon disulfide.

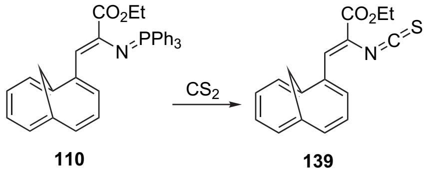


R = H, Me, Et, Pr, ^{i}Pr, Ph

Scheme 43.

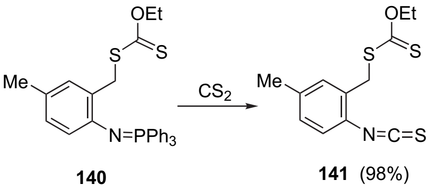
Suschitzky et al.[53] have been interested in the hetero-annelation of 1,6-methano[10]annulenes for the synthesis of annulenopyridines. When phosphazene **110** was treated with CS_2, however, a stable isothiocyanate **139** was obtained by an aza-Wittig reaction, and this could not be cyclized to give the desired annulenopyridines (Scheme 44).

An aza-Wittig reaction of aromatic substituted phosphazenes with CS_2 has been used to test the feasibility of the



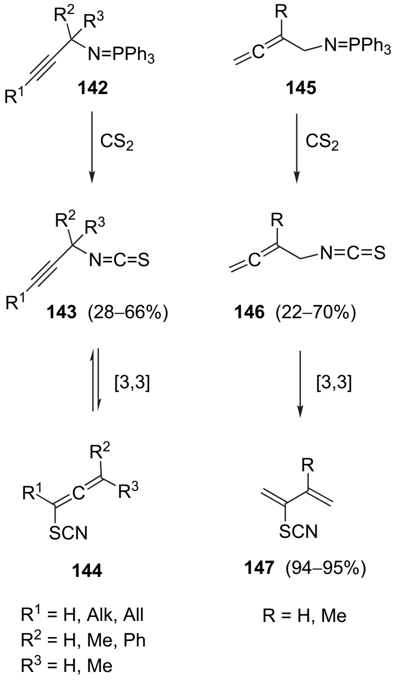
Scheme 44.

intramolecular addition of benzylic radicals onto carbodiimides.[65] Likewise, the required isocyanate **141** was easily obtained by the reaction of triphenylphosphazene **140** with carbon disulfide (Scheme 45).



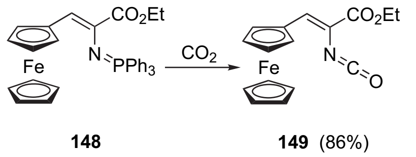
Scheme 45.

The isocyanates **143** or **146** have been synthesized by an aza-Wittig reaction of phosphazenes **142** or **145**, respectively, with CS_2 (Scheme 46).[66] In these cases, only after vacuum pyrolysis at 300 or 400 °C did the isothiocyanates **143** or **146** suffer a [3,3] sigmatropic rearrangement to give the vinyl thiocyanates **144** and **147**, respectively.



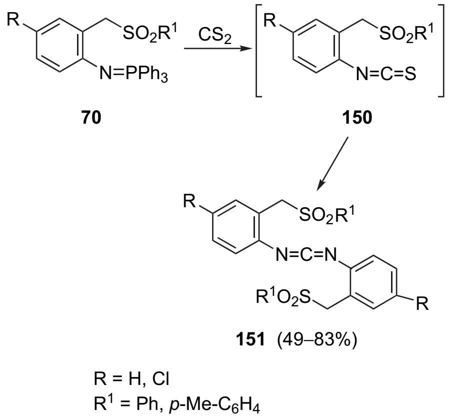
Scheme 46.

Novel ferrocene derivatives, bearing one or two ferrocene subunits such as β-ferrrocenylvinylheterocumulenes and ferrocene-containing imidazole rings, have been easily prepared from β-ferrocenylvinylphosphazene **148** by aza-Wittig reactions with carbon dioxide.[67,68] β-Ferrocenyl vinylheterocumulenes **149** are easily prepared by aza-Wittig reactions of the phosphazene **148**, derived from the β-ferrocenylvinyl azide, and carbon dioxide (Scheme 47).



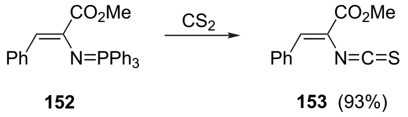
Scheme 47.

Takahashi and Suga have explained the preparation of 2,3-diarylsulfonylindoles **151**[35] by an aza-Wittig reaction of the sulfone phosphazene **70** with CS_2 and subsequent aza-Wittig reaction of the isothiocyanate derivative formed **150** with a second molecule of the starting phosphazene **70** (Scheme 48).



Scheme 48.

In a similar way, the reaction of the *N*-vinylic phosphazene **152**, derived from the α-amino ester, has been used for the preparation of the functionalized conjugated isothiocyanate **153**, used subsequently for the preparation of polysubstituted pyridines (Scheme 49).[69]



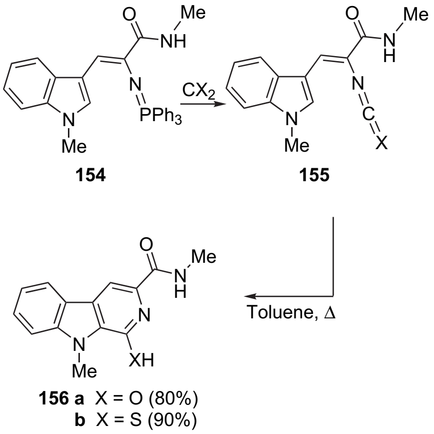
Scheme 49.

Isocyanates obtained by this strategy have been used for the synthesis of pseudoureido dipeptide esters or bisureas.[70] Aza-Wittig reactions of simple phosphazenes, obtained by the Appel procedure using primary amines or L-amino esters, with CO_2 and nucleophilic addition of a second equivalent of primary amines or L-amino esters gave the urea derivatives. In an analogous manner, the β-cyclodextrin azides[71] or bis-azides[72] can be used for the solid-phase synthesis of cyclodextrin ureas through an aza-Wittig reaction with CO_2 followed by nucleophilic addition of amines.

4.2. Heterocyclic synthesis

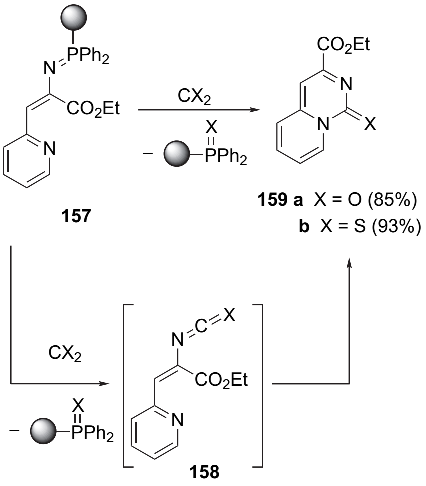
Isocyanates and isothiocyanates are very reactive heterocumulene derivatives and, therefore, this type of compounds can be subsequently used for the preparation of heterocyclic compounds by means of tandem or domino reactions.

4.2.1. Tandem reactions: aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC). Tandem aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC) has been used by Molina et al.[73] for the general synthesis of β-carbolines **156**. An aza-Wittig reaction of *N*-vinylic phosphazene **154** with carbon dioxide or carbon disulfide led to the formation of the heterocumulenes **155**, which after electrocyclic ring closure, generated the carbolines **156a**,**b** (Scheme 50).



Scheme 50.

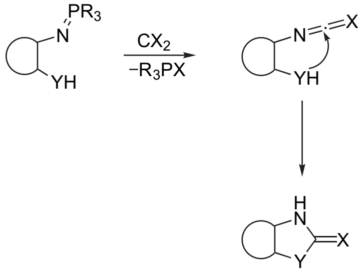
The utility of the aza-Wittig reaction of polymer-supported phosphazene **157** with carbon dioxide or carbon disulfide by using the solid-phase methodology to give bicyclic heterocyclic compounds **159a**,**b** via **158** has been reported (Scheme 51).[74]



Scheme 51.

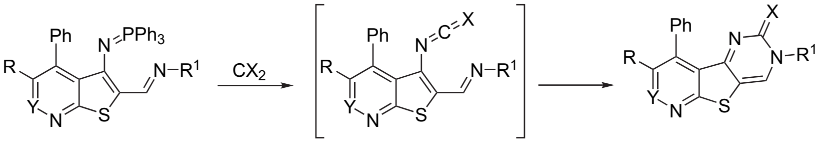
Pyrido- and pyrimido-thienopyridazine derivatives **162**[75,76] can be obtained by this methodology. Heating the functionalized phosphazenes **160** with carbon dioxide or carbon disulfide gave the corresponding isocyanate or isothiocyanate intermediates **161**, which can cyclize spontaneously to give **162** (Scheme 52). There are many available methods for synthesizing pyridothienopyrimidines, but this is the first example of the annelation of a pyrimidine ring to a pyridothieno system based on the aza-Wittig reaction of phosphazenes with heterocumulenes.

4.2.2. Tandem reactions: aza-Wittig/intramolecular cyclization (AW-IC). The strategy showed in Scheme 53 has been widely used for the preparation of the five- and six-membered skeleton of polycyclic heterocycles. The most common process involves the intramolecular nucleophilic cyclization of an amine or amide (Y=NH) to an iso(thio)cyanate (X=O, S) group. Moreover, the intramolecular addition of hydroxy (Y=O) and activated methylene (Y=CH) groups can also be performed.



Scheme 53.

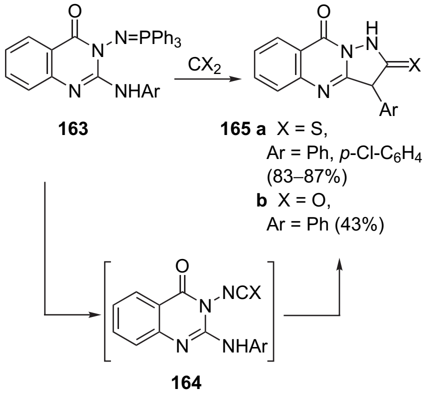
A new approach to the synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones by tandem aza-Wittig/intramolecular heterocumulene-mediated annelation (AW-IHA) of the easily accessible *N*-(2-arylamino-3*H*-quinazolin-4-on-3-yl)-triphenylphosphazenes with CS$_2$ or CO$_2$ has been described.[77] An initial aza-Wittig reaction between the phosphazenes **163** and CS$_2$ gave an intermediate isothiocyanate **164**, which undergoes cyclization to afford the 2-thioxo-1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones **165a** (Scheme 54). The 1,3-dihydro-1,2,4-triazolo[5,1-*b*]quinazolin-2,9-dione **165b** was obtained when the corresponding



R = CN, Ph
R^1 = Ph, *p*-(Me, MeO)-C$_6$H$_4$
X = O, S
Y = EtO-C, N

Scheme 52.

phosphazene **163** was allowed to react with CO_2. An aza-Wittig reaction between the phosphazene **163** and CO_2 afforded the intermediate isocyanate **164**, which undergoes cyclization to give **165b**.

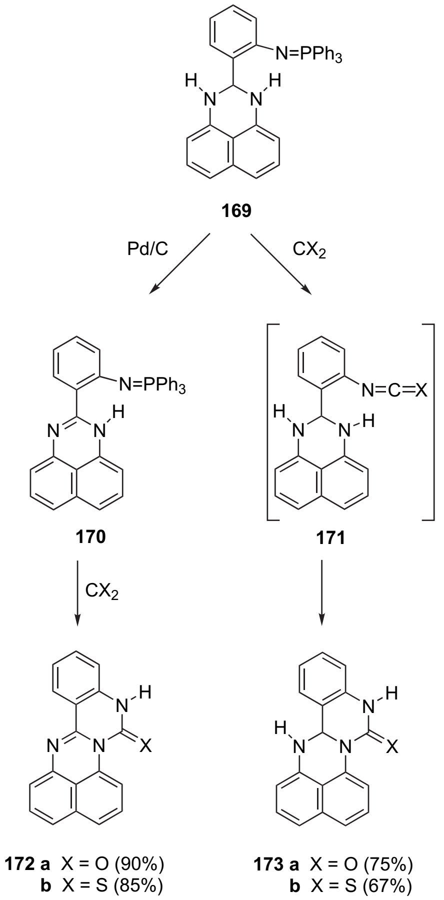


Scheme 54.

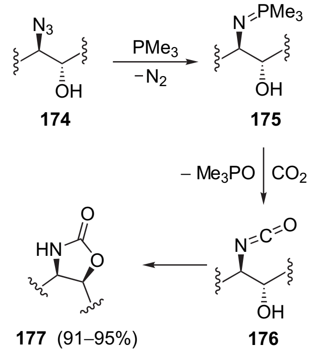
Aza-Wittig reactions of phosphazenes **166a**,**b** with carbon disulfide as the thiocarbonyl compound yielded 3-aryl-2-thioxoquinazolin-4(3*H*)-ones **167a**,**b** (Scheme 55). These arylthioxoquinazolinones were converted into quinconazole (**168a**) and fluquinconazole (**168b**) by subsequent treatment with sulfenyl chloride and 1,2,4-triazole sodium salt. The authors have also reported an approach to quinconazole and fluquinconazole inhibitors of fungal ergosterol biosynthesis in a solid-phase synthesis.[78]

Several heterocyclic compounds have been prepared via aza-Wittig reactions of phosphazenes and carbon disulfide or carbon dioxide, followed by electrocyclic ring closure, i.e., the synthesis of functionalized quinazolino[3,4-*a*]perimidines,[79] indole derivatives[37] and isoquinoline derivatives through a regiospecific electrocyclization of β-arylvinyl ketenimine intermediates[80] obtained from isocyanates and phosphorus ylides. Thus, an aza-Wittig-type reaction of the phosphazene **169** with carbon dioxide or carbon disulfide in a sealed tube at 100 °C provides the derivatives **173a** or **173b** via **171** in good yields (Scheme 56). On the other hand, phosphazene **169** reacts to give compounds **172a** or **172b** via **170** in excellent yields.

Oxazolidinones are obtained, instead of the Boc-amino alcohols, from vicinal azido alcohols **174** with trimethylphosphine and CO_2[81] via **175** by the use of DMAP and Boc_2O (Scheme 57). In this process, an intramolecular addition of the hydroxyl group to the isocyanate group in **176** explains the formation of the oxazolidinones **177**.

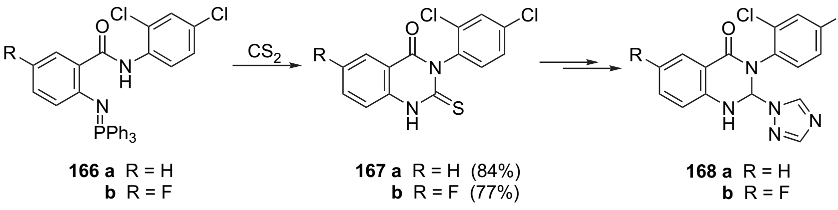


Scheme 56.



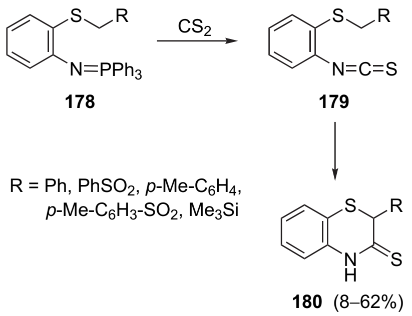
Scheme 57.

This tandem reaction can also be applied to the intramolecular methylene (CH_2) addition to the isothiocyanate group. Takahashi and Ohba prepared 2-substituted-2,3-dihydro-1,4-benzothiazine-3-thiones **180**[82] by an aza-Wittig reaction



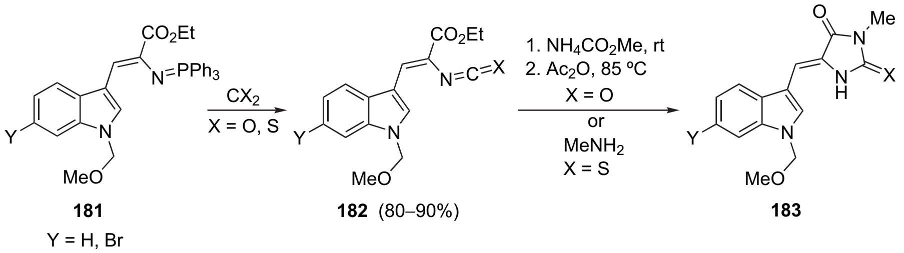
Scheme 55.

of thioarylphosphazenes **178** with CS_2, followed by an intramolecular methylene addition to the carbon atom of the isothiocyanate group of compounds **179** (Scheme 58).



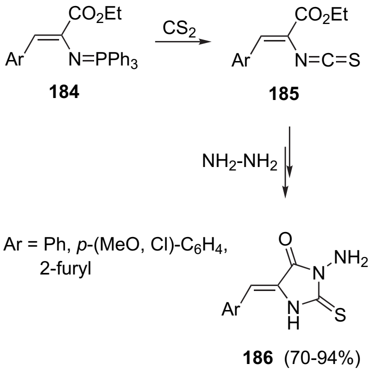
Scheme 58.

4.2.3. Domino reactions: aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW-NA-IC). Molina et al. reported a general entry to Aplysinopsin-type alkaloids **183**,[73a] bearing a nitrogen, oxygen or sulfur atom at position 3′ in the imidazole ring, through a tandem aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization, when amines are added to the isocyanate or isothiocyanate precursors **182** (obtained from **181**) (Scheme 59).



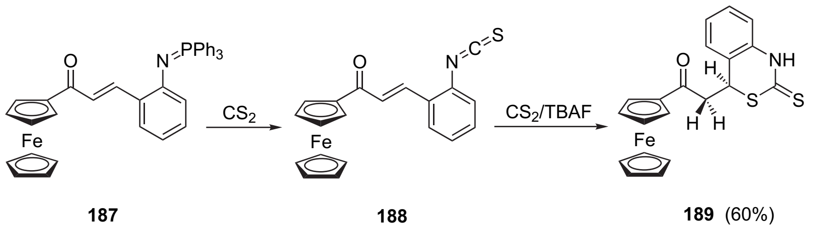
Scheme 59.

This domino strategy (aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization, AW-NA-IC) was also used for the synthesis of 3-amino-5-arylmethylene-2-thioxo-4-imidazolidinones **186** from the stable vinylphosphazenes **184** (Scheme 60). The phosphazenes **184** reacted with carbon disulfide to give the vinyl isothiocyanates **185**, precursors of the 3-amino-5-arylmethylene-2-thioxo-4-imidazolidinones **186**.[83]



Scheme 60.

Heterocycles derived from ferrocenes with sulfur atoms such as **189** were prepared in 60% yield by an aza-Wittig reaction of the phosphazene **187** with CS_2, followed by an intramolecular heteroconjugate addition of the isothiocyanate **188** to the CS_2/TBAF system (Scheme 61).[84]



Scheme 61.

5. Aza-Wittig reaction with isocyanates and isothiocyanates

From the range of general methods available for the construction of the carbodiimide functionality, the intermolecular aza-Wittig-type reaction of phosphazenes and isocyanates or isothiocyanates (Scheme 62) seems to be one of the most attractive, since it takes place under neutral conditions.

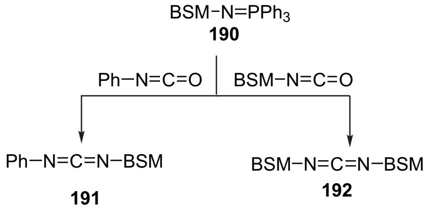
$$RN{=}PR_3 + X{=}C{=}N{-}R \longrightarrow R{-}N{=}C{=}NR + R_3P{=}X$$

$$X = O, S$$

Scheme 62.

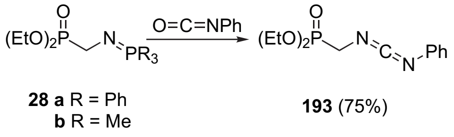
5.1. Synthesis of carbodiimides

Several studies have been directed towards the preparation of *N*-heterocumulenes **191** and **192** bearing the $(Me_3Si)_2CH$ substituent (BSM) from phosphazenes **190** (Scheme 63) and to investigate their reactivity and the development of new methodologies for the synthesis of heterocycles by exploring the synthetic potential of the BSM—N= function.[85]



Scheme 63.

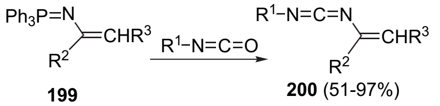
Functionalized carbodiimides such as **193** derived from aminophosphonates can be prepared by the aza-Wittig reaction of *N*-phosphoryl alkylphosphazenes **28** and isocyanates (Scheme 64).[21] This process has also been extended to mono-azabisphosphorus ylides (analogous reagents containing both a phosphazene and a phosphorus ylide) and a selective aza-Wittig reaction of the phosphazene linkage was observed.[19]



Scheme 64.

The aza-Wittig reaction of phosphazenes and heterocumulenes takes place under neutral conditions compatible with all common hydroxyl-protecting groups, which makes this methodology an appropriate tool for the chemistry of sugars and, therefore, for convergent strategies in the synthesis of unsymmetrical complex structures. Mono- and disaccharide glycosyl carbodiimides **196** have been prepared (Scheme 65) by two alternative synthetic pathways: (a) the reaction of glycosyl phosphazenes **194** with 6-deoxy-isothiocyanato sugars **195** and (b) the converse condensation of glycosyl isothiocyanates **197** and triphenylphosphoranylidene derivatives of 6-amino-6-deoxy aldohexoses **198**.[86,87] The corresponding carbodiimide-linked pseudooligosaccharides **196** appear to be very attractive synthetic intermediates, since the carbodiimide group plays a pivotal role in the preparation of ureas, thioureas and guanidines, among other functional groups, through standard transformations.

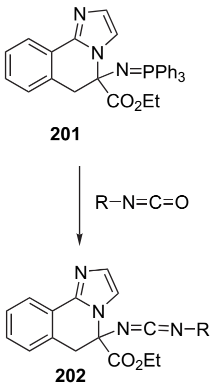
The formation of carbodiimides from *N*-vinylic phosphazenes offers a new entry to a variety of nitrogen-containing heterocyclic systems. In this way, the hetero-annelation of conjugated carbodiimides **200** (Scheme 66), prepared by the aza-Wittig reaction of *N*-vinylic phosphazenes **199** and isocyanates, was studied and the reactivity differences of conjugated carbodiimides in the cycloaddition were rationalized by computational treatment.[88] Similarly, the aza-Wittig reaction of *N*-vinylic phosphazenes with phenyl isocyanate could be used to give the carbodiimides **200** (R^1=Ph) as synthetic intermediates of several heterocyclic systems.[89]



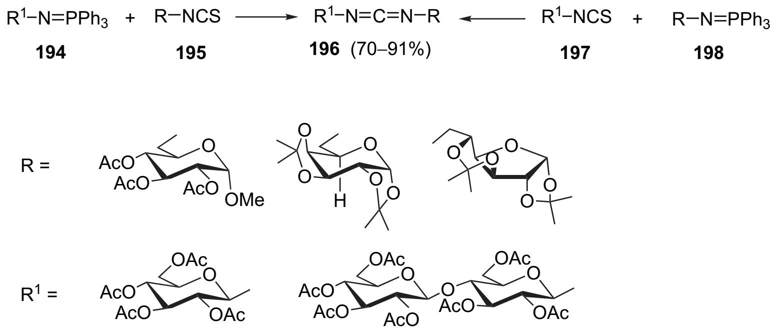
R^1 = Ph, *p*-(Me, MeO, Cl)-C_6H_4, *cyclo*-Hex, Me
R^2 = H, Ph, *p*-Me-C_6H_4
R^3 = H, Ph, *p*-Me-C_6H_4

Scheme 66.

In a similar way, the phosphazene **201** (Scheme 67) showed the characteristic behaviour in aza-Wittig-type reactions towards isocyanates, and the corresponding carbodiimides **202** were thus obtained.[90]

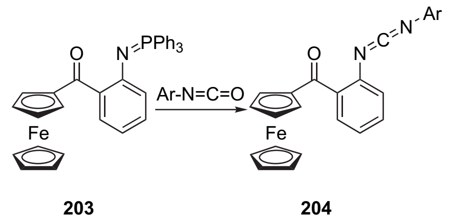


Scheme 67.



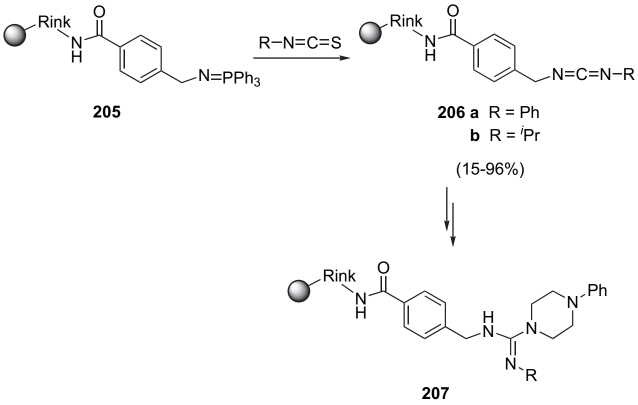
Scheme 65.

The aza-Wittig reaction of ferrocenylphosphazene **203** with aryl isocyanates[91] yielded the corresponding carbodiimides **204** (Scheme 68), which were used without further purification for the next step. All attempts to promote the thermal intramolecular cyclization of these carbodiimides failed.



Scheme 68.

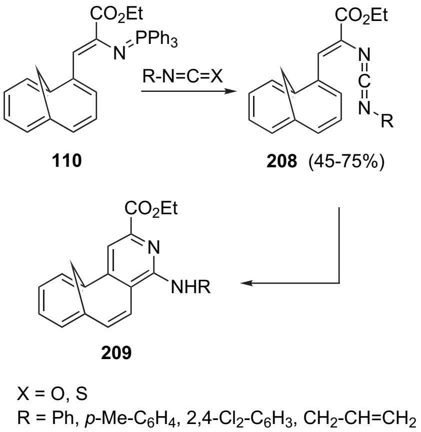
Although there are a number of reports detailing the application of the aza-Wittig/electrocyclization strategy of phosphazene derivatives with isocyanates to form carbodiimides and heterocyclic compounds, it was not until 1997 when a solid-phase approach for the synthesis of carbodiimides **206a**,**b** and trisubstituted guanidines **207**[92] by the reaction of phosphazenes such as **205** (Scheme 69) and isothiocyanates, was reported.



Scheme 69.

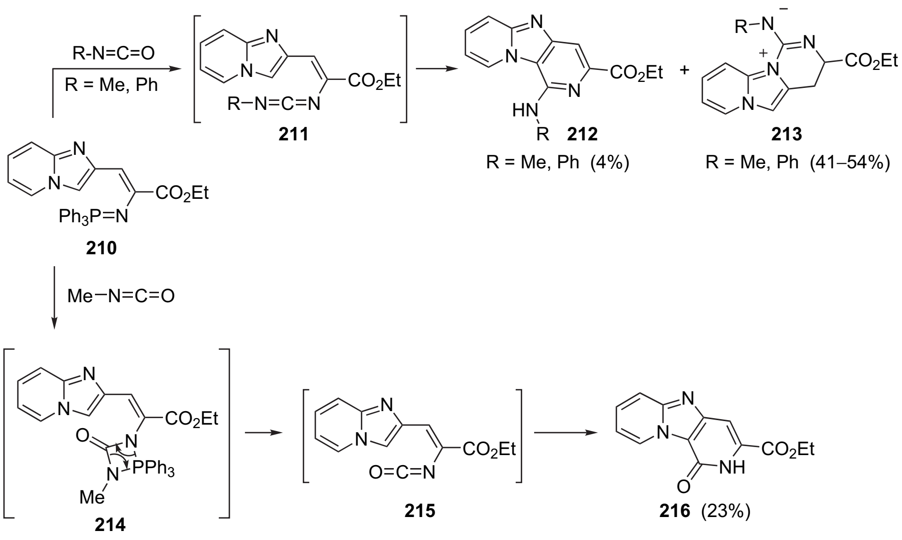
5.2. Tandem aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC)

The tandem aza-Wittig/intramolecular electrocyclic ring closure of phosphazenes with heterocumulenic compounds such isocyanates and isothiocyanates has been widely used for the synthesis of heterocyclic compounds. A series of annulenopyridines **209** have been prepared[53,93] from phosphazene **110** and the required isocyanates or isothiocyanates. The methano[10]annuleno derivatives **208** after electrocyclic ring closure afforded the corresponding annulenopyridines **209** (Scheme 70). Pyrrolo[2′,3′:4,5]furo[3,2-*c*]pyridines[94,95] were prepared by an aza-Wittig reaction of *N*-vinylic phosphazenes and phenyl isocyanates, followed by electrocyclic ring closure of the non-isolated carbodiimides.



Scheme 70.

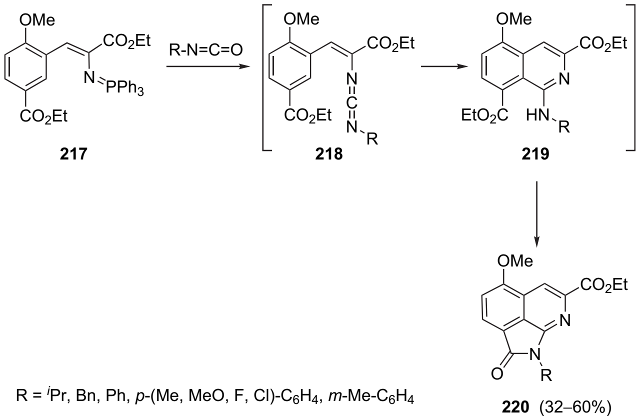
In the course of extensive studies on the reactivity of heterocycles with a bridgehead nitrogen atom, Teulade et al.[96] have prepared the azacarboline structures **212**, **213** and **216** (Scheme 71) by means of an aza-Wittig-type reaction of *N*-vinylic phosphazene **210** or aromatic phosphazenes[97] with isocyanates. The intermediate carbodiimides **211** or



Scheme 71.

isocyanate **215** spontaneously cyclize to give the condensed derivatives **212**, **213** or **216**. This provides information on the mechanism, as well as a useful method for the synthesis of azacarboline derivatives.

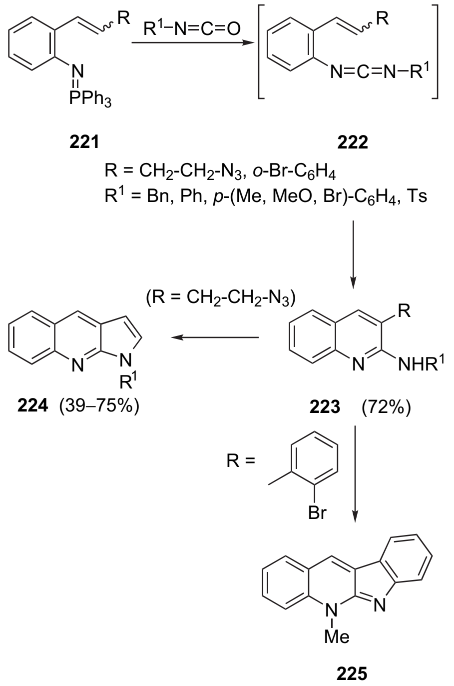
Treatment of *N*-vinylic phosphazenes bearing an aromatic substituent such as **217** (Scheme 72) with easily accessible isocyanates gave the pyrrolo[4,3,2-*ij*]isoquinoline derivatives **220**.[98] Formation of these heterocycles **220** could be explained through an aza-Wittig reaction of the *N*-vinylic phosphazene **217** with isocyanates to give the unsaturated carbodiimides **218**, which then undergo electrocyclic ring closure, followed by a 1,3-hydrogen shift and intramolecular acylation of **219**. By a similar procedure, when the carbodiimides obtained are indole-substituted, subsequent cyclization gave the indolopyridine derivatives.[73b]



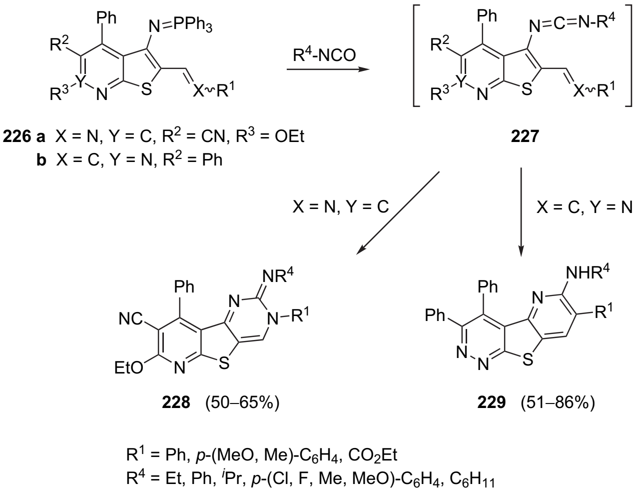
Scheme 72.

Aromatic phosphazenes have also been used in the synthesis of numerous heterocyclic systems following the strategy of aza-Wittig reactions and subsequent electrocyclic ring closure. Thus, the phosphazenes **221**, derived from anilines containing an unsaturated side chain at the *ortho*-position (Scheme 73), participate in an aza-Wittig/electrocyclic ring closure/nitrene-insertion process, allowing the preparation of pyrrolo[2,3-*b*]quinolines **224**[99] or indolo[2,3-*b*]quinolines **225**[100] through an intramolecular hetero Diels–Alder cycloaddition via **223**. In an analogous manner, ferrocenyl-aryl-phosphazenes react with aryl isocyanates to give the 2-arylamino-3-ferrocenecarbonylquinolines.[91]

Quintela et al. have studied the phosphazene-mediated synthesis of 2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **228**[75] (Scheme 74). Tandem aza-Wittig/heterocumulene-mediated annelation is a useful protocol for preparing fused polyheterocyclic systems including the pyrimidine moiety, this being one of the first examples of annelation to a pyrimidine ring. Similarly, the tandem aza-Wittig/intramolecular heterocumulene-mediated annelation (AW-IHA) strategy affords a general route to triheterocyclic systems bearing various substituents in the pyridine ring.[101] The reaction of *N*-heteroaryl phosphazenes **226b** with several aromatic and aliphatic isocyanates led directly to the pyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine derivatives **229** via **227**.[76]



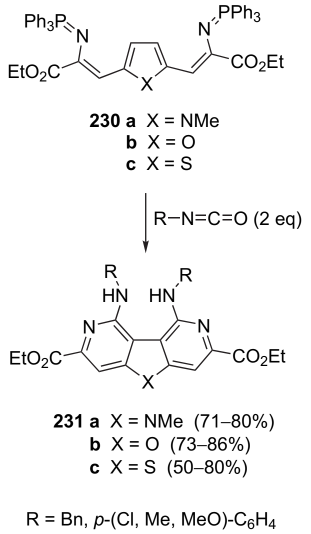
Scheme 73.



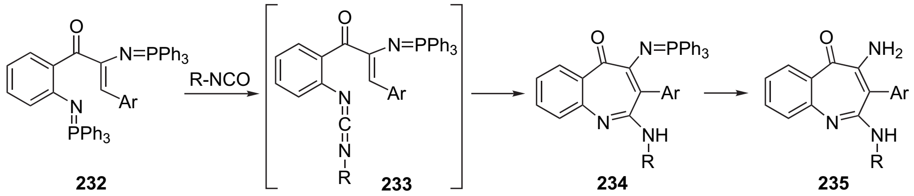
Scheme 74.

This approach has also been used for the preparation of polycyclic compounds by treating bisphosphazenes bearing an unsaturated group with easily accessible heterocumulenes such as isocyanates. Thus, bisphosphazenes **230a–c** reacted with 2 equiv of isocyanates to give the pyrrolodipyridines **231a**, furodipyridines **231b** or thienodipyridines **231c** (Scheme 75).[102]

Selective aza-Wittig reactions have been observed, depending upon the nature of the substituents bound to the nitrogen atom of the phosphazene, as in the *N*-aryl- (and *N*-vinyl-) bisphosphazenes **232** (Scheme 76). A selective aza-Wittig reaction between the more reactive *N*-aromatic phosphazene group of the compounds **232** with 1 equiv of aromatic isocyanate led to bicyclic compounds with a seven-membered-ring heterocycle **235** via **234**.[90] The formation of these compounds can be explained by the formation of the carbodiimides **233**, subsequent intramolecular cyclization and hydrolysis of the phosphazene group to give the heterocyclic compounds **235**.

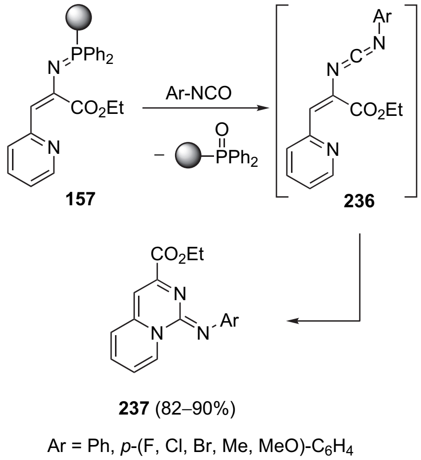


Scheme 75.



Scheme 76.

Polymer-supported phosphazenes such as **157** attached through the phosphorus atom could afford pyrido[1,2-*c*]pyrimidine derivatives **237**,[74] via carbodiimide intermediate **236**, based on an aza-Wittig/carbodiimide-mediated annelation process (Scheme 77).



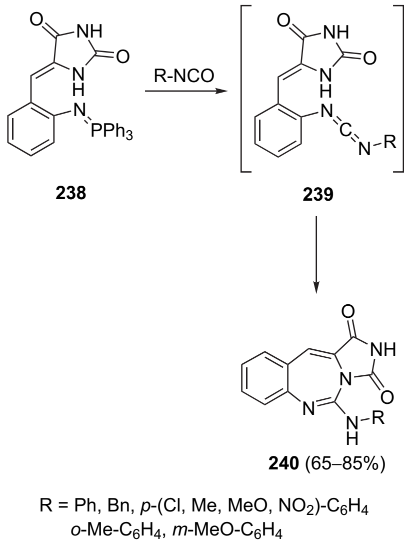
Scheme 77.

5.3. Tandem aza-Wittig/intramolecular cyclization (AW-IC)

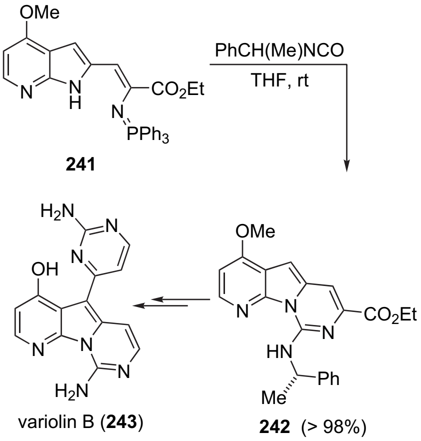
Several examples have been reported for the synthesis of numerous heterocyclic systems, based on the aza-Wittig reaction of phosphazenes with isocyanates and subsequent ring closure by nucleophilic addition of the amino group to the carbodiimide moiety.

Seven-membered heterocyclic compounds could be obtained, based on the construction of the seven-membered ring by nucleophilic attack of an NH group on the central carbon atom of a generated carbodiimide. By means of this strategy, an efficient and general method for the preparation of the tricyclic imidazo[1,3]benzodiazepine ring system[103] has been reported. The reaction of phosphazene **238** (Scheme 78) with a variety of aromatic isocyanates led directly to the imidazo[1,5-*c*][1,3]benzodiazepines **240** by nucleophilic attack of the NH group of the hydantoin ring on the central carbon atom of the carbodiimides **239**.

This methodology has also allowed the preparation of six-membered heterocyclic compounds yielding several alkaloids. The alkaloid, leucettamine B, of marine origin,[104] the 2-aminopyrimidine alkaloids, variolins and meridianins, of marine origin,[105] and a simple and general entry to the aplysinopsine-type alkaloids[73a] have been described following this methodology. A total synthesis of the potent antitumour marine alkaloid, variolin B **243**,[106] has also been completed in seven steps from the *N*-vinylic phosphazene **241** via **242** (Scheme 79).



Scheme 78.



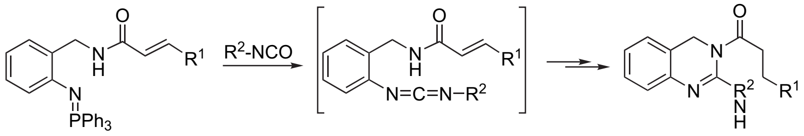
Scheme 79.

Taking advantage of the tandem aza-Wittig/intramolecular heteroconjugate addition/annelation strategy, the reaction of aromatic phosphazenes **244** with isocyanates led to a variety of pyrimidone-fused heterocycles, e.g., 2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones **246** via **245**, in which a guanidine moiety constitutes the fusion joint (Scheme 80).[107]

The aza-Wittig reaction of phosphazene **247** with aryl isocyanates gave 2-arylamino-3-(*o*-ferrocenecarbonyl)-phenyl-3*H*-quinazolin-4-ones **249**, by initial formation of the carbodiimides **248**, which under the reaction conditions, underwent cyclization by nucleophilic attack of the NH group of the amido function on the central sp-hybridized carbon atom of the carbodiimide moiety[91] (Scheme 81). Similarly, 6-arylamino-14,14a-dihydroquinazolino[3,4-*a*]perimidines and 6-alkyl(aryl)aminoquinazolino[3,4-*a*]perimidines[79] were prepared.

Construction of the five-membered ring of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones has been described by a tandem aza-Wittig/heterocumulene-mediated annelation of the easily accessible *N*-(2-arylamino-3*H*-quinazolin-4-on-3-yl)triphenylphosphazenes with isocyanates.[77] When solutions of the phosphazenes **163** (Scheme 82) were treated with aromatic isocyanates, the crystalline 2-arylamino-1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones **251** were obtained. The conversion of **163** into **251** involves an initial aza-Wittig reaction to give the carbodiimides **250**, as highly reactive intermediates, which easily undergo ring closure across the arylamino group.

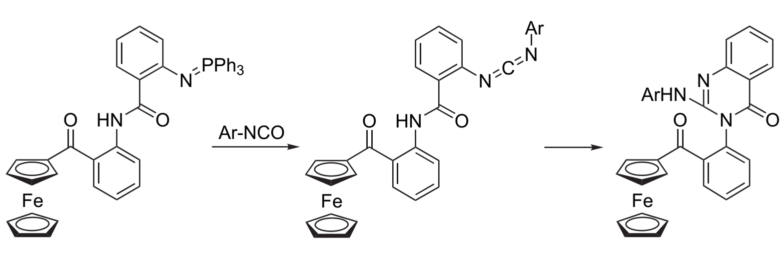
This strategy has also been developed using solid-phase methodology. Resin-bound phosphazenes **253**, prepared from the corresponding 2-aminobenzimidazoles **252**, reacted with alkyl and aryl isocyanates (Scheme 83). Alkyl isocyanates react at 100 °C, leading exclusively the normal aza-Wittig products **258**.[108] In contrast, using aryl



244 245 246

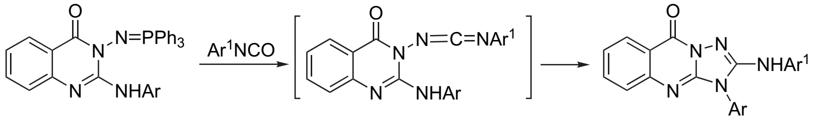
R^1 = H, Me, Ph
R^2 = Et, Ph, *p*-Me-C_6H_4, *cyclo*-Hex

Scheme 80.



247 248 **249** (40–49%)

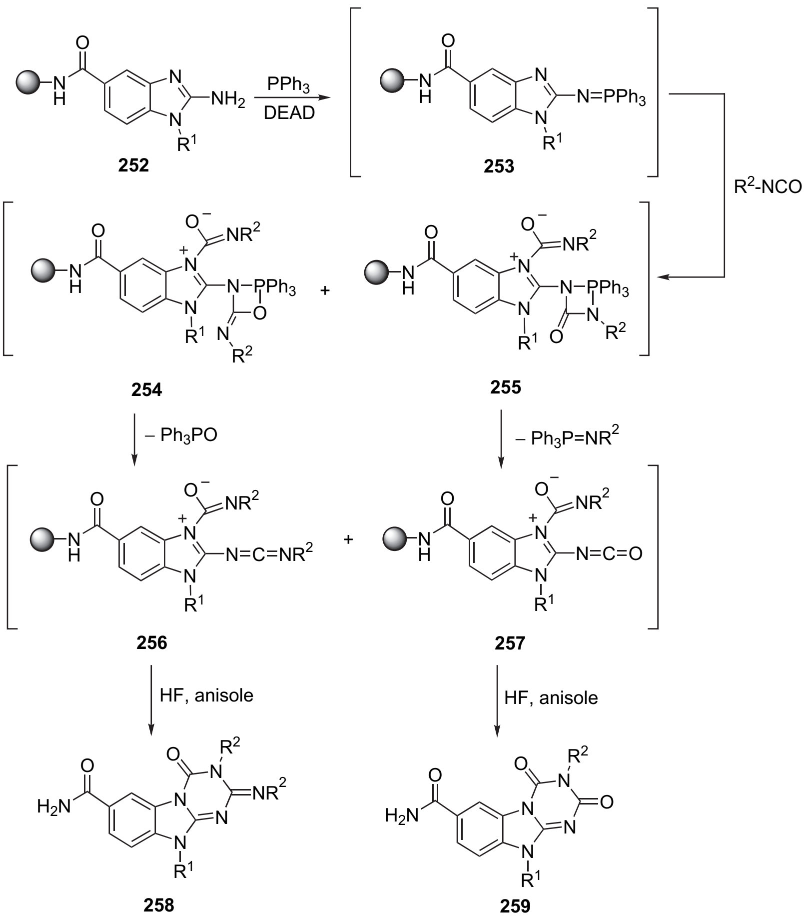
Scheme 81.



163 250 **251** (86–94%)

Ar = Ph, *p*-Cl-C_6H_4
Ar^1 = Ph, *p*-(Me, Cl)-C_6H_4, *m*-(Me, Cl)-C_6H_4

Scheme 82.

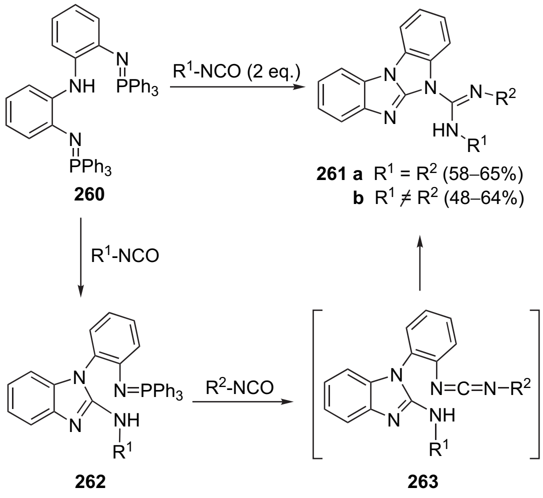


R^1 = Bu, Hexyl, C_6H_{11}, 1-ethylpropyl, 3-methoxypropyl
R^2 = Hexyl, Et, Bu, C_6H_{11}, Ph

Scheme 83.

isocyanates at 100 °C, significant amounts of the abnormal aza-Wittig products **259** were obtained, with the chemoselectivity depending upon the type of isocyanate employed. The authors suggest that electronic factors play a key role in the competition between the formation of the betaines **254** and **255**. Breakdown of **254** involving loss of triphenylphosphine oxide results in the carbodiimide intermediates **256** as the normal aza-Wittig products, which can undergo an intramolecular heterocyclization reaction, providing the compounds **258**. In contrast, betaines **255** can lead to the isocyanates **257** as the abnormal aza-Wittig products, involving the loss of triphenylphosphineimide. Subsequent heterocyclization reaction gave the compounds **259**.

When symmetrical bisphosphazenes were used with an excess of isocyanates, 11*H*-quinazolino[2,3-*b*]quinazoline-11,13-(5*H*)-diones, bearing two guanidine-type moieties[109] or tricyclic guanidines,[110] were obtained. Likewise, rigid bicyclic guanidines such as the benzimidazo[1,2-*a*]benzimidazole derivatives **261a** can also be obtained by the same procedure, but, in this case, two condensed five-membered heterocycles were formed.[111] Reaction of the symmetrical bisphosphazene **260** with 2 equiv of aromatic or aliphatic isocyanates afforded the compounds **261a** (Scheme 84). The same reaction with 1 equiv of isocyanate, however, afforded the phosphazenes **262**, which with another equivalent of a different isocyanate, formed the carbodiimides **263**, which underwent cyclization by nucleophilic attack of the secondary amino group on the central carbon atom of the carbodiimide moiety to give the heterocyclic compounds **261b**.

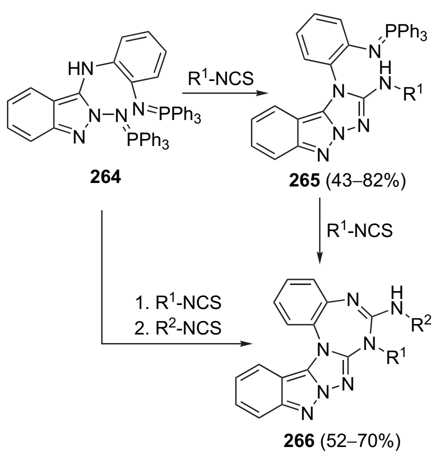


$R^1 = R^2$ = p-(Me, F)-C_6H_4, Bn, *cyclo*-Hex

$R^1 \neq R^2$ $\begin{cases} R^1 = p\text{-Me-}C_6H_4;\ R^2 = p\text{-OMe-}C_6H_4 \\ R^1 = {}^iPr;\ R^2 = Et \end{cases}$

Scheme 84.

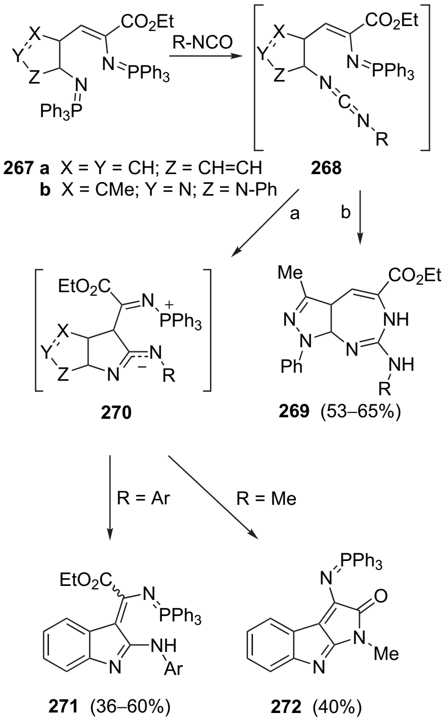
A wide variety of heterocyclic compounds such as 1,3,5-benzotriazepines and their derivatives have been described when asymmetrical bisphosphazenes were used.[112] From the results of this reaction, the authors conclude that *N*-heteroaryl phosphazenes are more reactive than *N*-aryl phosphazenes. Thus, the bisphosphazene **264** reacted with isothiocyanates to give the fused 1,3,5-benzotriazepines **266** through two consecutive aza-Wittig/cyclizations by nucleophilic attack of the secondary amino group on the central carbon atom of the carbodiimide moiety in **265** (Scheme 85). In a similar reaction, polymer-supported phosphazenes attached through the phosphorus atom could afford (bis)guanidines.[113]



R^1 = Et, Bn, *p*-(Me, OMe, F)-C_6H_4
R^2 = Et, *p*-(Me, OMe, F)-C_6H_4

Scheme 85.

Bisphosphazenes **267a**,**b** with an *N*-vinylic phosphazene group and an *N*-aryl or *N*-heteroaryl phosphazene group, react with 1 equiv of alkyl or aryl isocyanates through the *N*-aryl or *N*-heteroaryl phosphazene moiety to give the fused diazepines **269**,[114] and the indole derivatives **271** or **272**[112] (Scheme 86). The formation of these compounds can be explained through the carbodiimides **268**, formed by an initial aza-Wittig-type reaction between the *N*-aryl or *N*-heteroaryl phosphazene group in **267** and 1 equiv of the isocyanate derivative. Subsequent nucleophilic attack of the nitrogen atom of the *N*-vinylic phosphazene group onto the central carbon of the carbodiimide moiety in **268** gave the diazepines **269** (Scheme 86, path b). Nucleophilic attack of the β-carbon of the double bond onto the central carbon of the carbodiimide moiety in **268**, however, gave the zwitterionic compound **270**, which lead to the formation of the heterocyclic compounds **271** or **272** (Scheme 86, path a).



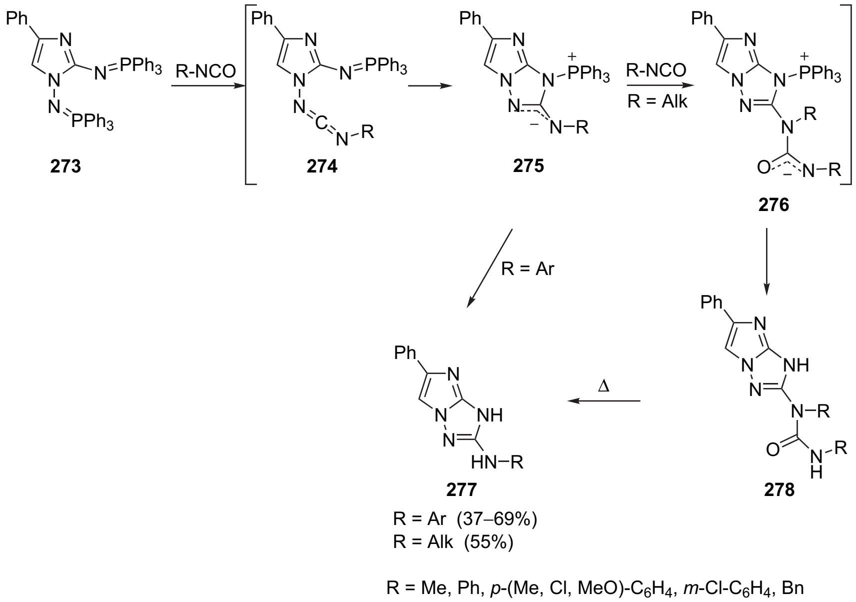
Scheme 86.

In a similar way, the asymmetrical bisphosphazene **273** (Scheme 87) reacted with aromatic isocyanates in the presence of triethylamine to afford the imidazo[1,2-*b*]-1,2,4-triazoles **277**.[115] The reaction with aliphatic isocyanates under the same conditions, however, provided the compounds **278**. The formation of these compounds can be explained by an initial aza-Wittig-type reaction between the *N*-phosphazene group and 1 equiv of the isocyanate. The carbodiimides **274** undergo cyclization by nucleophilic attack of the nitrogen atom of the phosphazene group onto the central carbon atom of the carbodiimide moiety to give the zwitterionic compound **275**, which undergoes hydrolytic cleavage to give **277** or reacts with a second equivalent of the aliphatic isocyanate across the negative nitrogen atom to give **276**, which by hydrolytic cleavage affords **278**.

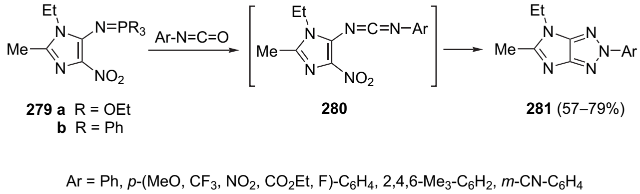
Intramolecular cyclization between the carbodiimide moiety and the nitro group, which is present in the five-membered heterocycles **280** has been investigated, and the formation of 2-aryl-imidazo[4,5-*d*][1,2,3]triazoles **281** was possible through the reaction of the 4-nitro-imidazol-5-yl phosphoramidate **279a**[116] or phosphazene **279b**[117] with aryl isocyanates (Scheme 88). An aza-Wittig reaction of the compounds **279** with isocyanates affords the 1-aryl-3-(4-nitro-1*H*-imidazol-5-yl)carbodiimides **280**, the thermal heterocyclization reaction of which gives access to the 2-aryl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazoles **281**.

Carbodiimides obtained in an aza-Wittig reaction can be attacked intramolecularly by the oxygen of the carbonyl or carboxyl moieties. Therefore, an aza-Wittig reaction of the *N*-vinylic phosphazenes **282** (Scheme 89) with aliphatic or aromatic isocyanates gave the corresponding carbodiimides **283**, which undergo ring closure across the ester functionality to give the azalactones **284**, followed by a spontaneous Dimroth lactone–lactam rearrangement to give the hydantoins **285**.[96,118]

When phosphazene quinones **286** (R=OMe or Me) reacted with aryl isocyanates, the heterocycles **289** and **290** were obtained, respectively.[119] In the aza-Wittig reaction, carbodiimides **287** are formed in the first step (Scheme 90). These intermediates cyclize through the enolic form of the quinonic carbonyl function giving the benzoxazoles **288**, which underwent hydrolytic cleavage to give the aminoquinone **289**. Carbodiimides **287** can also undergo a cyclization by



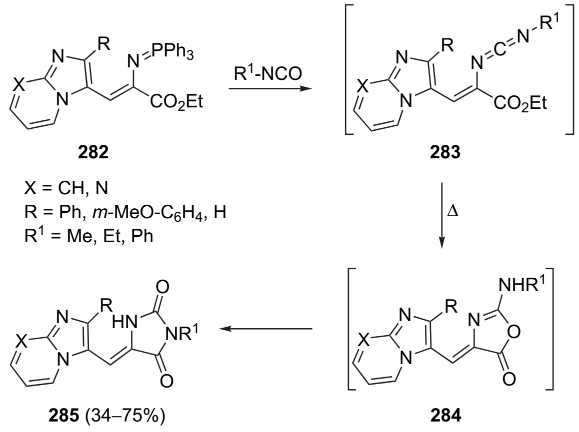
Scheme 87.



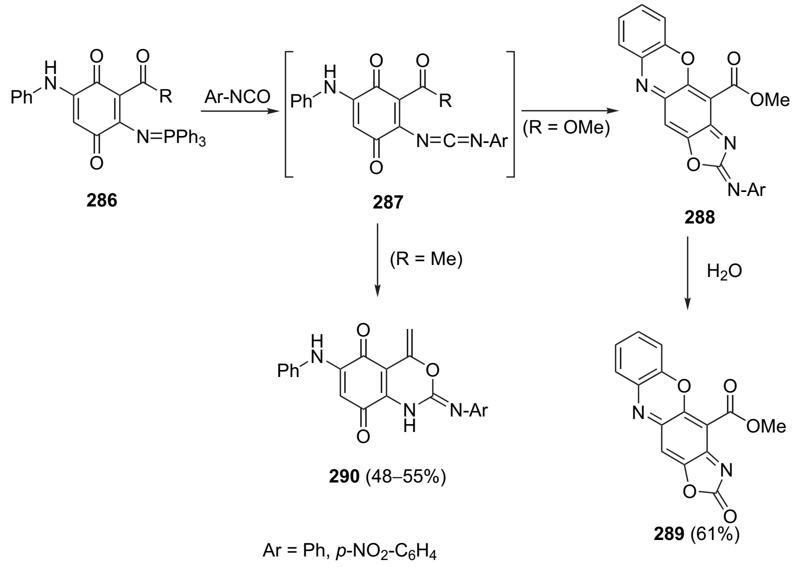
Scheme 88.

intramolecular nucleophilic attack of the ketone moiety, through its enol form, providing the oxazine ring of **290**.

Similarly, an aza-Wittig reaction of ketophosphazenes **291** (Scheme 91) with aryl isothiocyanates gave the 1,3-oxazoles **293** via **292**.[120] Heating the reaction mixture aids in the cyclization of the carbonyl group (or the enol form) across

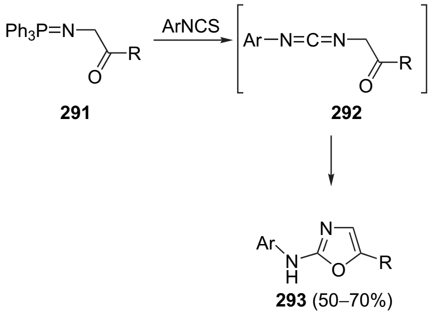


Scheme 89.

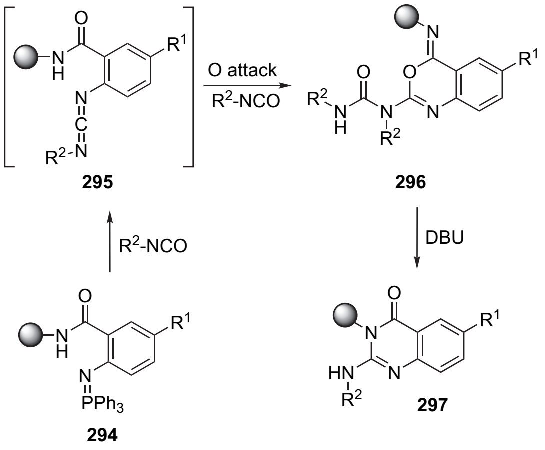


Scheme 90.

the carbodiimide. High-yielding syntheses of BMS-337197 have been achieved by employment of this methodology.



Scheme 91.



R^1 = 2,3-Me_2-C_6H_3O, ^{i}BuS, *cyclo*-$C_6H_{11}S$
R^2 = 2,3,4-Me_3-C_6H_2, Bn, *p*-Cl-C_6H_4, *m*-MeCO-C_6H_4

Scheme 92.

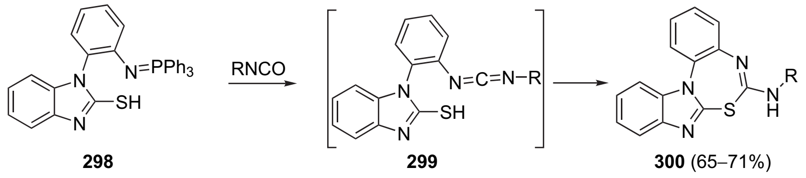
A broad array of different guanine mimetics **297** can be prepared by a solid-phase aza-Wittig reaction of phosphazenes **294** with isocyanates, followed by intramolecular nucleophilic addition of oxygen.[121] An aza-Wittig reaction of the polymer-supported phosphazenes **294** (Scheme 92) with isocyanates yielded the carbodiimides **295**, which reacted intramolecularly with the oxygen of the amide group to afford **297** via **296**.

On the other hand, the preparation of 1,3,6-benzothiadiazepino[3,2-*a*]benzimidazole derivatives **300** (Scheme 93) is possible by reaction of phosphazenes containing a thiol group such as **298** with isocyanates.[111] In this case, the carbodiimides **299** undergo cyclization by nucleophilic attack of the sulfur atom of thiol group on the central carbon of the carbodiimide moiety.

Functionalized carbodiimides obtained in the aza-Wittig reaction can react intramolecularly with a methylene carbon. In this way, Takahashi et al. have developed a useful methodology, based on an aza-Wittig reaction of phosphazenes **301** (Scheme 94) with isocyanates, for the synthesis of five-membered nitrogen and sulfur heterocycles. The formation of 2-aryl-3-aryl-sulfonylindoles **303**[35] or 2-substituted-2,3-dihydro-1,4-benzothiazine-3-thiones **304**[82] is possible by treatment of the intermediate carbodiimides **302** with base.

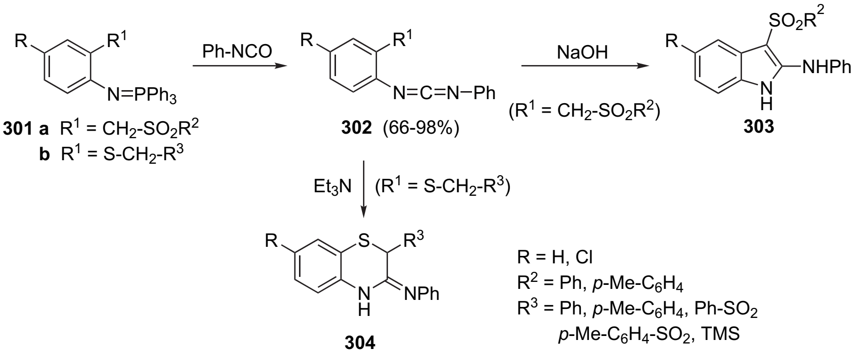
5.4. Tandem aza-Wittig/intramolecular [4+2] cycloaddition

N-Aromatic phosphazenes containing a triple bond reacted with heterocumulenes to give carbodiimides, which can give heteropolycyclic compounds through an intramolecular [4+2] cycloaddition reaction. Thus, initial aza-Wittig reaction of phosphazene **305a** (Scheme 95) with phenyl



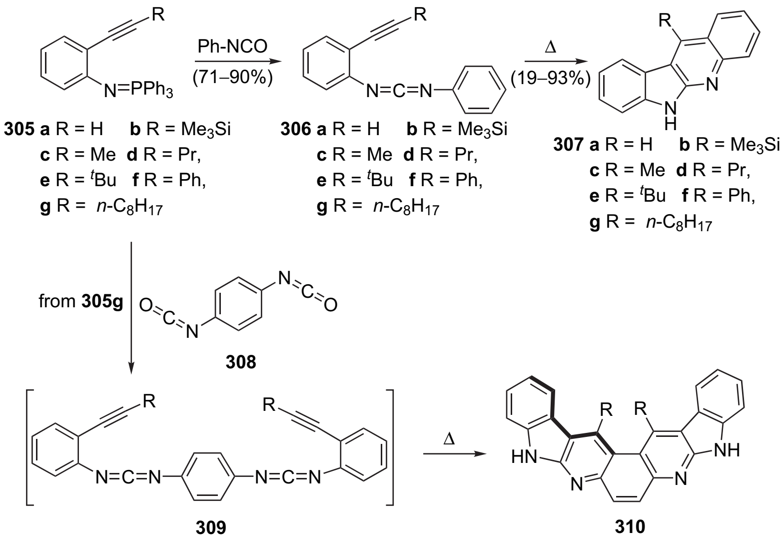
R = *p*-(Me, MeO)-C_6H_4

Scheme 93.

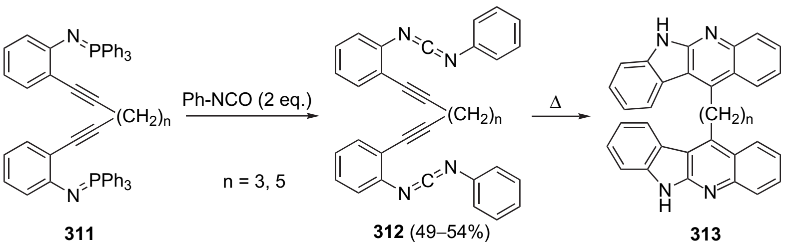


R = H, Cl
R^2 = Ph, *p*-Me-C_6H_4
R^3 = Ph, *p*-Me-C_6H_4, Ph-SO_2
p-Me-C_6H_4-SO_2, TMS

Scheme 94.



Scheme 95.



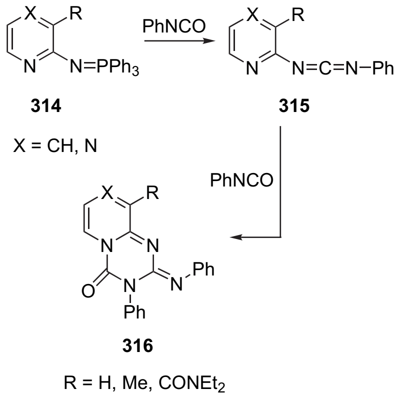
Scheme 96.

isocyanate and subsequent intramolecular cycloaddition of the formed carbodiimide **306a** gave the quinindoline **307a**.[122] Other indoloquinolines **307b–f** have been prepared[123] via **306b–f** by using *N*-aromatic phosphazenes containing a triple bond **305b–f** and phenyl isocyanate. Starting from 1,4-phenylene diisocyanate **308** and 2 equiv of phosphazene **305g** (Scheme 95) intermediate **309** was obtained, the subsequent thermolysis of which afforded heteropolycyclic compound **310** having two indoloquinoline units.[123]

Carbodiimides **306** (Scheme 95) can also be obtained by an aza-Wittig reaction of *N*-phenyl-*P*-triphenyl phosphazene and the corresponding 1-alkynyl-phenyl isocyanate. Moreover, these isocyanates can give an aza-Wittig reaction with phosphazenes derived from 2-, 3- and 4-aminopyridine[124] and 2-aminopyrazine or 2-aminopyrimidine[125] to give the carbodiimides containing a triple bond, which leads to indolonaphthyridines and other heterocyclic compounds by intramolecular [4+2] cycloaddition.

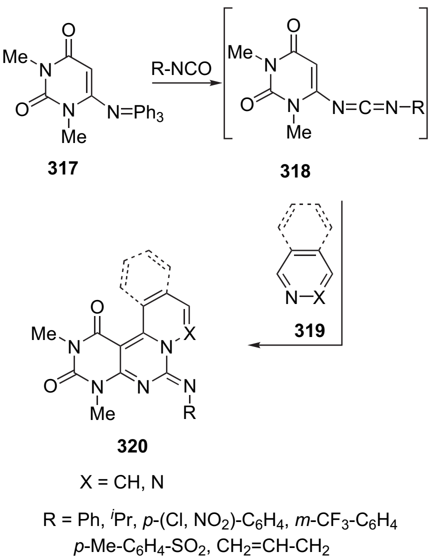
On the other hand, starting from symmetrical bisphosphazenes **311** containing two triple bonds, bis-carbodiimides **312** were prepared.[123] Intramolecular cycloaddition of compounds **312** led to compounds **313** with two connected units of indoloquinoline (Scheme 96).

N-Heterocyclic phosphazenes **314** (Scheme 97) derived from pyridine and its analogues can react through an aza-Wittig reaction with 2 equiv of isocyanates to give the carbodiimides **315**, which reacted with a second molecule of isocyanate by a [4+2] cycloaddition to give the pyridopyrimidine derivatives **316**.[126]



Scheme 97.

Wamhoff et al. studied a three-component reaction of (uracil-6-ylimino)phosphazene **317** (Scheme 98), isocyanate and heteroarenes **319**.[127,128] In a one-pot procedure, a variety of new polyheterocyclic compounds **320** were obtained via **318**, using heterodienophiles such as pyridine, isoquinoline, phthalazine and other heteroarenes (Scheme 98). The same procedure was applied to an aromatic pyrazole phosphazene and its derivatives.[129]



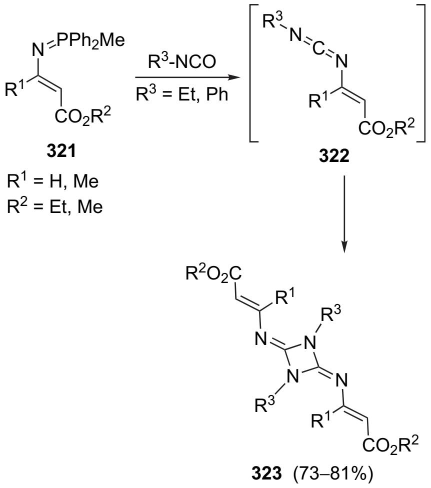
Scheme 98.

5.5. Tandem aza-Wittig/intramolecular [2+2] cycloaddition

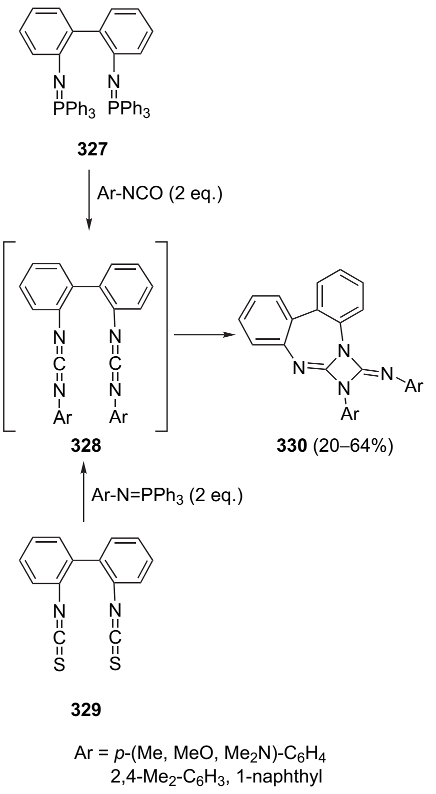
A few examples have been reported for the synthesis of four-membered heterocycles through an aza-Wittig reaction of phosphazenes and isocyanates, followed by a [2+2] cycloaddition process. Our group has developed a preparation of 1,3-diazetidines **323** by dimerization of the carbodiimide **322** when ethyl or phenyl isocyanate and *N*-vinylic phosphazenes **321** derived from β-amino acids were used (Scheme 99).[130]

Another example of four-membered heterocycle formation constitutes the preparation of fused 2,4-diimino-1,3-diazetidines **326** through an aza-Wittig/intramolecular [2+2] cycloaddition process.[114] When bisphosphazene **324** was treated with 2 equiv of aryl isocyanates, the fused heterocycles **326** were obtained in a tandem reaction by means of a [2+2] cycloaddition process of the intermediate bis-carbodiimides **325**, formed by an initial aza-Wittig reaction of **324** with isocyanates (Scheme 100).

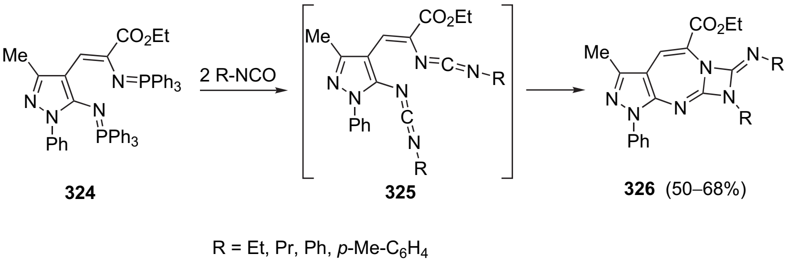
Bis-carbodiimides **328** were prepared by two independent aza-Wittig reactions (Scheme 101). Surprisingly, subsequent intramolecular [2+2] cycloaddition reaction of **328**, prepared via bisphosphazene **327** or bis-isothiocyanate **329**, could afford the tetracyclic compounds **330**, where seven- and four-membered heterocycles were concomitantly formed, in modest yields.[131]



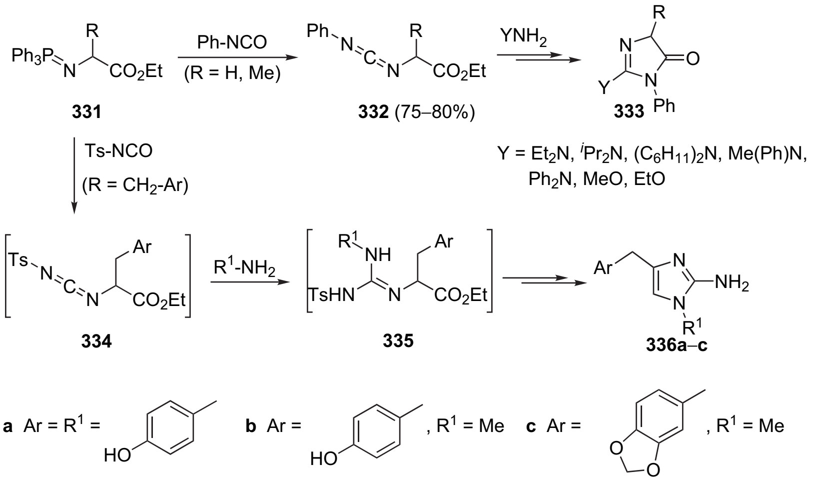
Scheme 99.



Scheme 101.



Scheme 100.

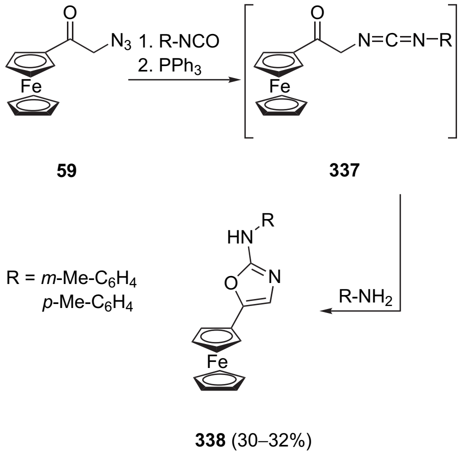


Scheme 102.

5.6. Domino aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW-NA-IC)

Usually, carbodiimides obtained by an aza-Wittig reaction of *N*-vinylic phosphazenes with isocyanates cannot be isolated, and the corresponding cyclic compounds were obtained, through an electrocyclic ring closure, as pointed out previously.[3f] Therefore, the very reactive carbodiimides can be used as synthetic intermediates of a wide variety of polyheterocycles by domino processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW-NA-IC).

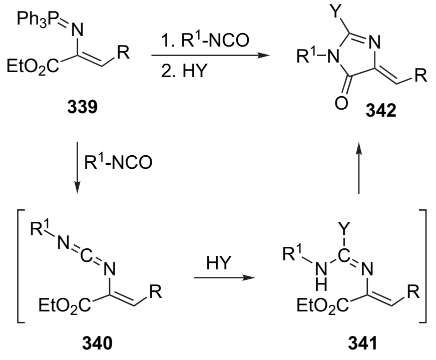
Five-membered heterocycles were obtained when amine nucleophiles reacted with carbodiimides. In this way, Liu et al. have prepared 2-amino-4*H*-imidazolin-4-one derivatives **333** with various substituents,[132] when carbodiimides **332** derived from α-amino acids (Scheme 102), prepared by aza-Wittig reactions of phosphazenes **331** with phenyl isocyanate, were treated with amines. Molina et al. have also used this methodology for the preparation of several alkaloids (Scheme 102). Syntheses of the marine alkaloids, isonaamine **336a**, dorimidazole **336b** and preclathridine **336c**,[133] have been described by aza-Wittig reactions of phosphazenes **331** (R=CH_2-Ar) with tosyl isocyanate, amine addition to the carbodiimide intermediate **334** and subsequent intramolecular cyclization of compound **335**. Similarly, 2-aminoimidazoles[134] and 4-methoxy-2-methylamino-5-methylthiocarbamoylimidazoles[135] have been prepared.



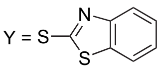
Scheme 103.

In order to avoid the dimerization of the phosphazene, generated between α-azido acetylferrocene **59** and phosphine, with formation of the pyrazine derivative,[34] the functionalized carbodiimide **337** was formed when the phosphazene formation was performed in the presence of aromatic isocyanates. This methodology allowed the one-flask preparation of 2-arylamino-5-ferrocenyl oxazoles **338** (Scheme 103).

Aza-Wittig reactions of *N*-vinylic phosphazenes **339** with aromatic isocyanates gave the carbodiimides **340** (Scheme 104).[49]



R = Ph, Y = NR^2R^3 (73–93%)
R = 2-furyl, Y = NR^2R^3 (51–87%)
R = Ph, Y = OR^4 (35–58%)
R = 2-furyl, *p*-Cl-C_6H_4, Ph,



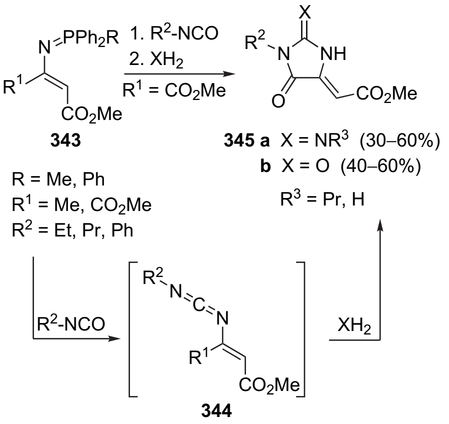
(34–56%)

R^1 = Ph, *p*-(Me, Cl)-C_6H_4, *m*-(Me, Cl)-C_6H_4
R^2 = Et, Pr, *sec*-Bu, ^{i}Pr, Bu, C_6H_{11}, Bn, $^nC_5H_{11}$, $^nC_6H_{13}$, ^{i}Bu
R^3 = Et, Pr, *sec*-Bu, ^{i}Pr, H, Bu, $^nC_5H_{11}$, $^nC_6H_{13}$, ^{i}Bu
R^2R^3 = –$(CH_2)_2$–, –$(CH_2)_2O(CH_2)_2$–
R^4 = Me, Et, Pr

Scheme 104.

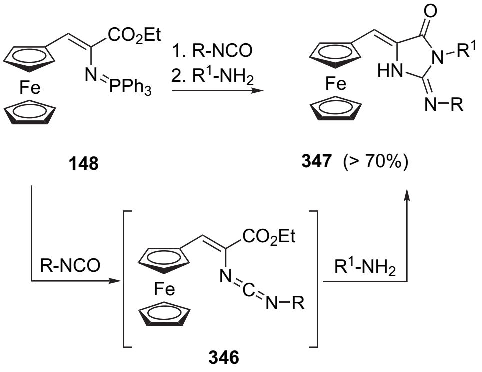
Subsequent reaction of **340** with amines,[136] alcohols[137] or thiols[138] led to the guanidine intermediates **341**, which cyclized to give the imidazolinones **342** (Scheme 104).

Likewise, conjugated carbodiimides **344** generated in situ by the reaction of *N*-vinylic phosphazenes **343**, derived from β-amino acids, with isocyanates (Scheme 105) were allowed to react with nitrogen nucleophiles to give the hydantoin derivatives **345a** or they suffered water addition during the column chromatography to give compounds **345b**.[130]



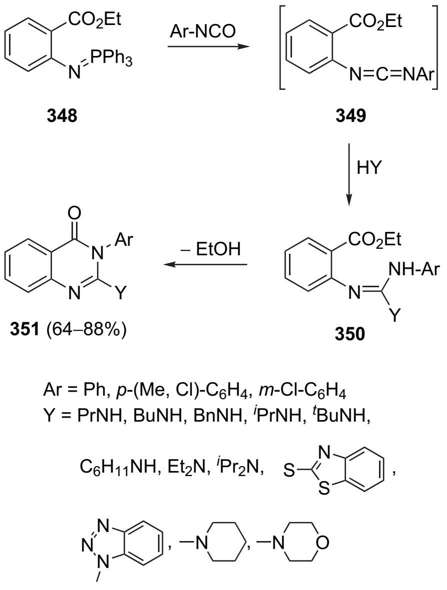
Scheme 105.

N-Vinylic ferrocenylphosphazene **148** was converted in a one-pot reaction into the corresponding highly functionalized ferrocenylimidazoles **347** by sequential treatment with isocyanates and then with primary amines.[67] This was a simple, but effective, new entry to ferrocene derivatives **347**, in which the ferrocene is conjugated to a heterocumulene fragment (Scheme 106). A similar route was used for the synthesis of a ferrocene attached to an imidazole ring by an ethylenic linkage, after hydrolysis of the corresponding β-ferrocenyl vinylheterocumulenes obtained by an aza-Wittig reaction.[68] Novel ferrocenylimidazolone derivatives of ferrocenylphosphazenes have also been prepared by the reaction of in situ synthesized heterocumulenes **346** with hydrazines.[139]



Scheme 106.

This strategy has been used for the preparation of quinazolinone-type heterocycles. Thus, phosphazene **348** reacted with aryl isocyanates (Scheme 107) at room temperature to give the carbodiimides **349**, which were allowed to react with nucleophilic reagents HY yielding quinazolinones **351** via cyclization of the guanidine-type intermediates **350**. This approach supplies an easily accessible route to 3*H*-quinazolin-4-ones **351** with various substituents.[77,138,140]

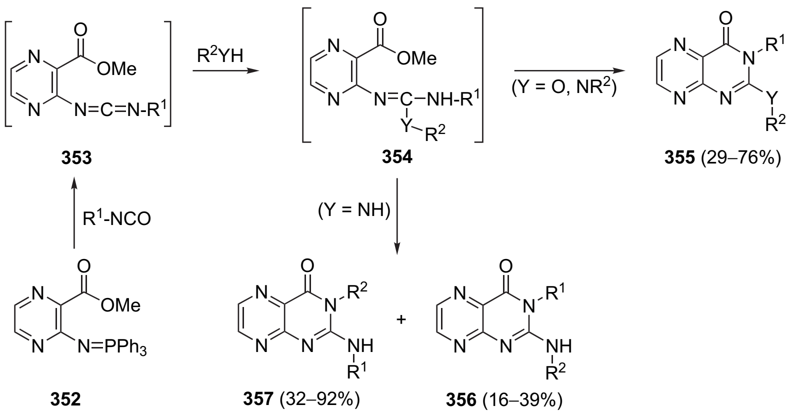


Scheme 107.

Eguchi et al.[141,142] described an elegant synthesis of 2,3-disubstituted ptheridin-4(3*H*)-ones **355–357** obtained through a one-pot reaction of aromatic phosphazene **352** with isocyanates to give **353**, addition of amines or alcohols and subsequent heterocyclization. In the guanidine-type intermediates **354** with two secondary amino groups (Y=NH), the nucleophilicity of both amines is similar, giving two possible isomeric compounds **356** and **357** (Scheme 108).

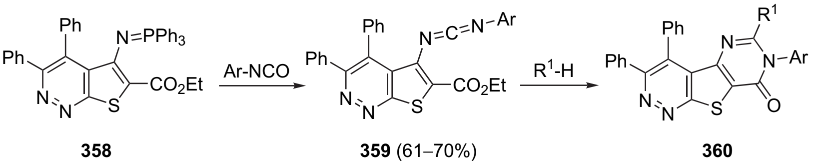
Whereas pyridine-annulated, sulfur-containing heterocycles have been extensively studied, comparatively little is known about aza-analogous systems in which an *S*-heterocycle is fused to a pyridazine nucleus. Thus, when the corresponding phosphazene **358** (Scheme 109)[143] derived from the heteroaromatic β-enamino ester was reacted with several isocyanates, the aza-Wittig reaction led to a pyrimidothieno system **359**, which was allowed to react with amines to give the pyrimido[4′,5′:4,5]-thieno[2,3-*c*]pyridazine derivatives **360**. In a similar way, an efficient synthesis of 2-substituted 5,6,7,8-tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones has been described.[144]

A new versatile solution-phase regioselective annelation process to synthesize novel 6-amino-3-alkylthio-1-phenyl-1,5-dihydro-pyrazolo[3,4-*d*]pyrimidin-4-one derivatives **363–365** has been reported (Scheme 110).[145] The phosphazenes **361** reacted with phenyl isocyanate to give the carbodiimides **362**, which were allowed to react with alkylamines.[146,147] A facile synthetic access to 6-alkoxyl(aroxyl)-3-methylthio-1,5-diphenyl-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one derivatives via the reaction of functionalized carbodiimides with alcohols has also been reported.[148]



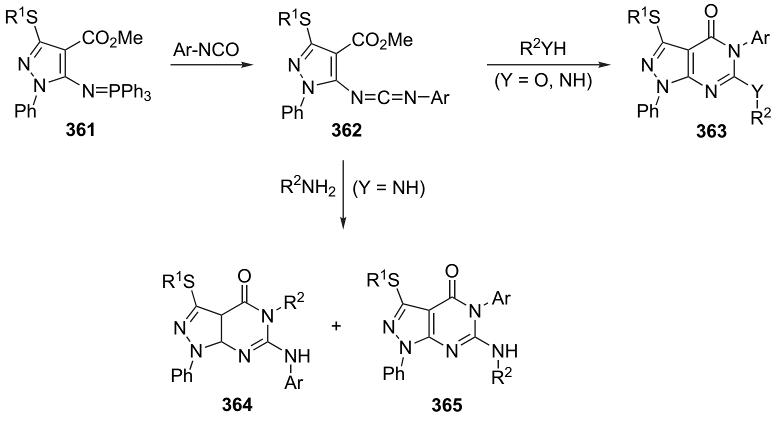
R^1 = Ph, p-(Me, MeO, Cl)-C_6H_4, m-Me-C_6H_4, o-Me-C_6H_4, 2-naphthyl
R^2 = Me, Et, Pr, ^{i}Pr

Scheme 108.



R^1 = Et_2N, piperidino, 3-Me-piperazino, morpholino, pyrrolidino, 4-Me-piperazino
Ar = p-(Cl, MeO, Me)-C_6H_4

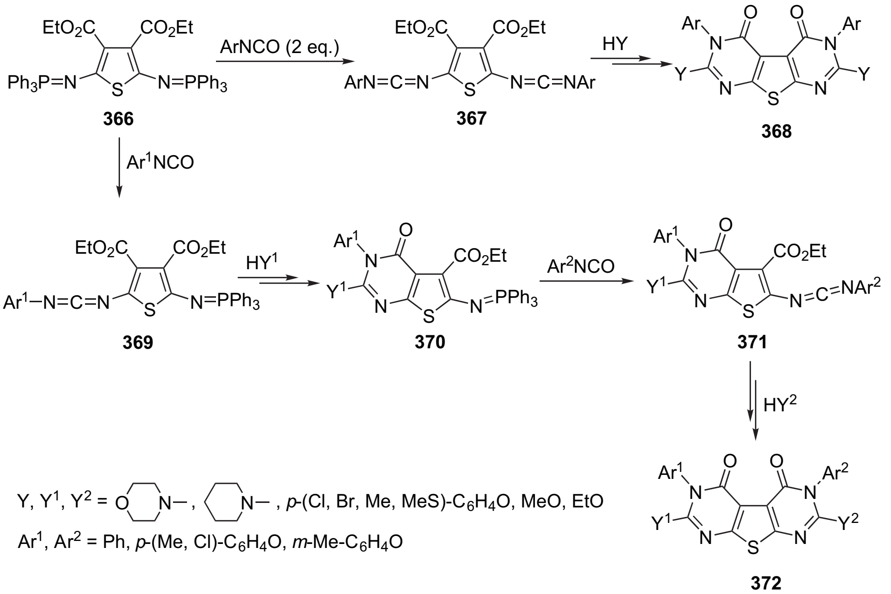
Scheme 109.



Ar = Ph, p-F-C_6H_4
R^1 = Me, Bn
R^2 = p-(Me, F)-C_6H_4-CH_2, 3-pyridinemethyl, 2-(1-ethylpyrrolidine)methyl,
2-thiophenemethyl, Pr, ^{i}Pr, H, Bu, ^{i}Bu

Scheme 110.

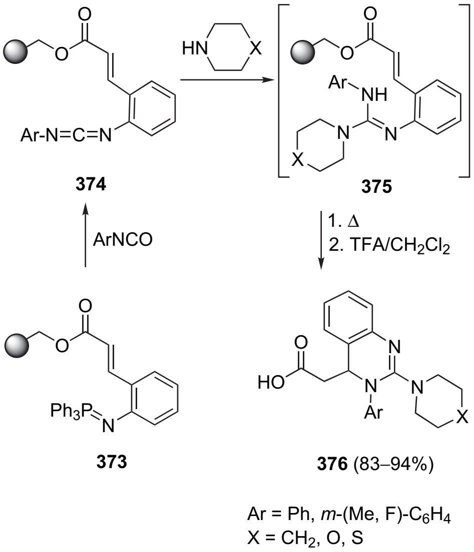
The synthesis of symmetrically and unsymmetrically substituted thieno[2,3-*d*:5,4-*d*′]dipyrimidine-4,5(3*H*,6*H*)-diones from the bis(phosphazene) **366** has been described (Scheme 111). The phosphazene **366** reacted with 2 equiv of aromatic isocyanates to give the bis-carbodiimides **367**, which were converted easily into symmetrically substituted 2,7-diaminothieno[2,3-*d*:5,4-*d*′]-dipyrimidine-4,5(3*H*,6*H*)-diones **368** by the addition of amines, alcohols or phenols to **367** and subsequent intramolecular cyclization. When an equimolar amount of aromatic isocyanate is used, only carbodiimides **369** are generated and monopyrimidinones **370** are obtained when the carbodiimides **369** are treated with amine under basic conditions, may be due to a lower reactivity of the second triphenylphosphoranylidenamino group of **369**, compared with bisphosphazene **366**. The phosphazene **370** reacted further with other aromatic isocyanates to give



Scheme 111.

the carbodiimides **371**, which provide unsymmetrically substituted 2,7-diaminothieno[2,3-*d*:5,4-*d′*]dipyrimidine-4,5(3*H*,6*H*)-diones **372**.[149]

Although there are a number of reports detailing the application of the domino process aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization (AW-NA-IC) of phosphazene derivatives with isocyanates to form heterocyclic compounds, not until 1997 was the use of phosphazenes in the solid-phase approach to the synthesis of 3,4-dihydroisoquinazolines **376**[150] reported. Phosphazenes **373** (Scheme 112), obtained via aza-Wittig reactions with aryl isocyanates, gave the carbodiimides **374**. Subsequent addition of a secondary amine to the carbodiimides **374**, followed by an intramolecular Michael addition of the amino group to the double bond of the α,β-unsaturated ester of the guanidine intermediates **375**, led to the desired heterocycles **376**.



Scheme 112.

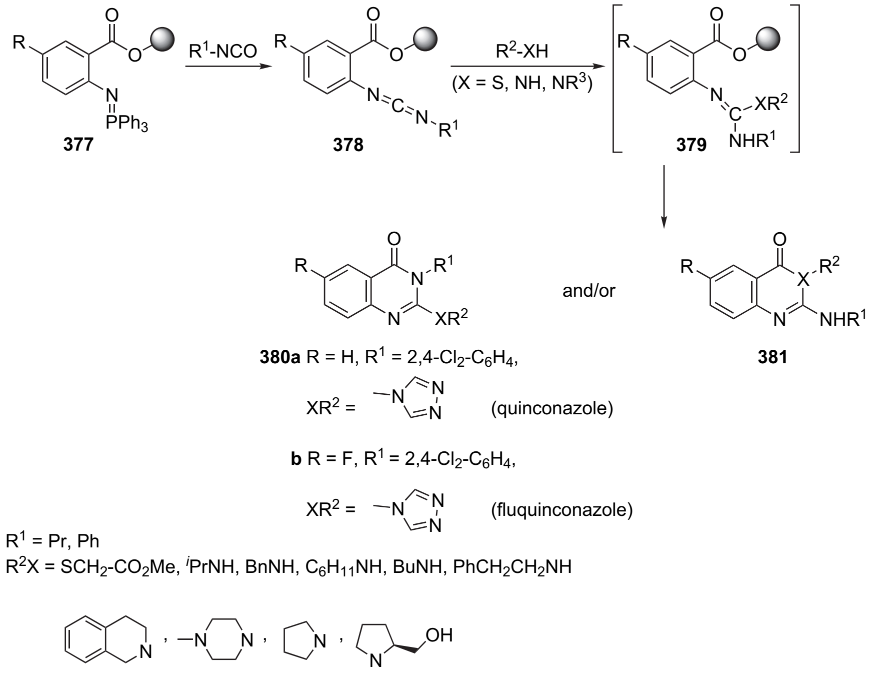
The mild reaction conditions and the selective multidirectional cyclization make the traceless linker strategy an attractive procedure towards the synthesis of highly functionalized quinazolinones and other heterocycles. Thus, a simple and efficient solid-phase methodology (Scheme 113) allowed a rapid synthesis of quinazoline libraries.[151] The aza-Wittig reaction of phosphazenes **377** with different isocyanates at room temperature smoothly formed the corresponding reactive carbodiimides **378**. Further treatment with different nucleophiles led via **379** to 3*H*-quinazolin-4-ones **380** and/or **381**. The syntheses of quinconazole **380a** and fluquinconazole **380b**, inhibitors of fungal ergosterol biosynthesis, have been accomplished by this procedure.[78]

6. Aza-Wittig reaction with ketenes: synthesis of heterocumulenes

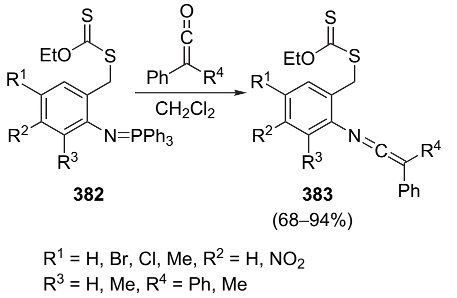
Owing to their high electron deficiency, heterocumulenes belong to the most reactive class of carbonyl and heterocarbonyl compounds, which make them especially suited for aza-Wittig reactions. Ketenes, which are even more reactive than isocyanates, react through an aza-Wittig process to afford ketenimines. In fact, one of the first reactions reported for phosphazenes by Staudinger and Meyer[1] was that with diphenyl ketene to produce triphenylketenimine, a typical aza-Wittig reaction.

Reaction of triphenylphosphazenes **382** with 1 equiv of methylphenyl ketene or diphenyl ketene, in dichloromethane at room temperature, gave isolable ketenimines **383** (Scheme 114).[152] Intramolecular addition of benzylic radicals onto the central carbon of these ketenimines **383** provides a novel radical-mediated synthesis of 2-alkylindoles.

Molina et al. have used the aza-Wittig reaction of phosphazenes and ketenes for the preparation of isoquinoline derivatives. Thus, conversion of azides **384** into heterocyclic compounds **387** involves an initial Staudinger reaction



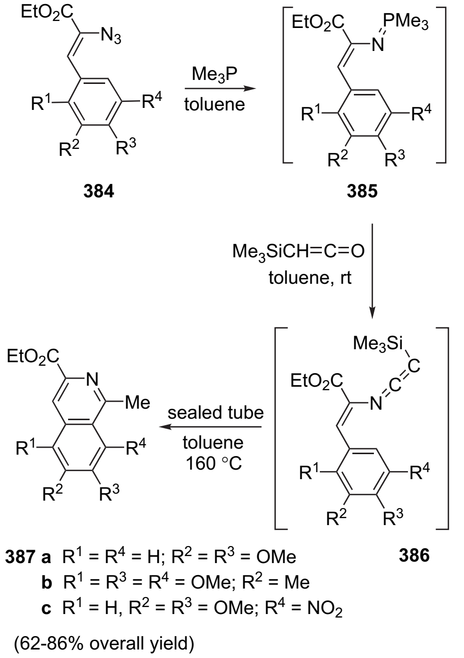
Scheme 113.



Scheme 114.

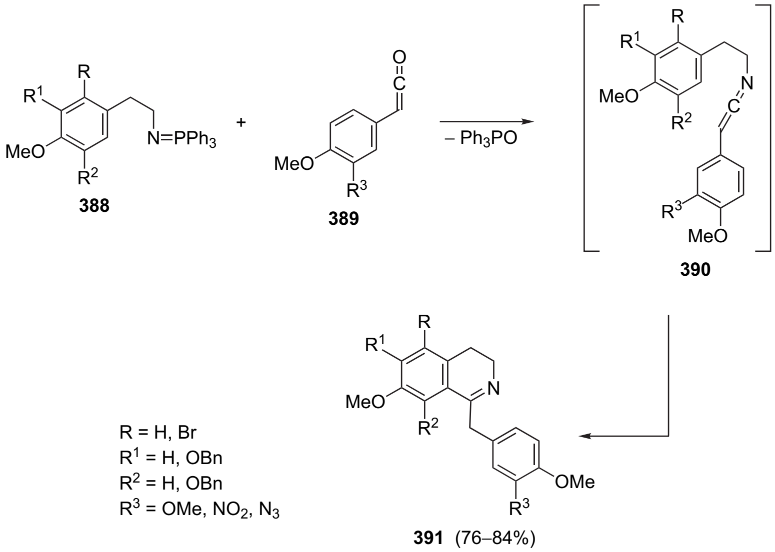
between the vinyl azides **384** and trimethylphosphine to give the phosphazenes **385** (Scheme 115). The aza-Wittig-type reaction of **385** with (trimethylsilyl)ethenone provides the ketenimines **386**, which underwent electrocyclic ring closure, followed by carbon–silicon bond cleavage, to give 1-methylisoquinolines **387a–c**, precursors in the synthesis of the marine alkaloids, aaptamine,[80] 5,8-dihydro-7-methoxy-1,6-dimethylisoquinoline-5,8-dione[153] and 3-ethoxycarbonylrenierol.[153]

The versatility of the aza-Wittig/intramolecular electrocyclic ring closure (AW-IEC) for the preparation of isoquinolines has been illustrated in the preparation of 1-benzyl-3,4-dihydroisoquinolines **391**,[154] which are necessary not only for the synthesis of (+)-cularine alkaloids, but also for isoquinoline alkaloids in general (Scheme 116). The aza-Wittig reaction of phosphazenes **388** and ketenes **389** led to the formation of non-isolable ketenimines **390**, which cyclized to give the compounds **391**.



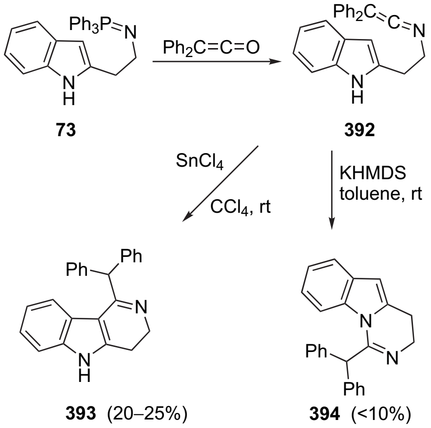
Scheme 115.

This strategy has been used not only for the preparation of isoquinoline derivatives, but also for the synthesis of dihydro-γ-carbolines or dihydropyrimido[3,4-*a*]indoles in a completely regiospecific fashion.[37] Phosphazene **73**, derived from indole, reacted with diphenyl ketene, providing the isolated ketenimine **392**, which was cyclized either by the action of $SnCl_4$, or by thermal treatment, to give dihydro-γ-carbolines **393**, although in low yield (Scheme 117). Treatment with potassium bis(trimethylsilyl)amide (KHMDS), however, afforded a complex mixture, from which only the dihydropyrimido[3,4-*a*]indole **394** could be isolated as an unstable compound in <10% yield.



R = H, Br
R^1 = H, OBn
R^2 = H, OBn
R^3 = OMe, NO_2, N_3

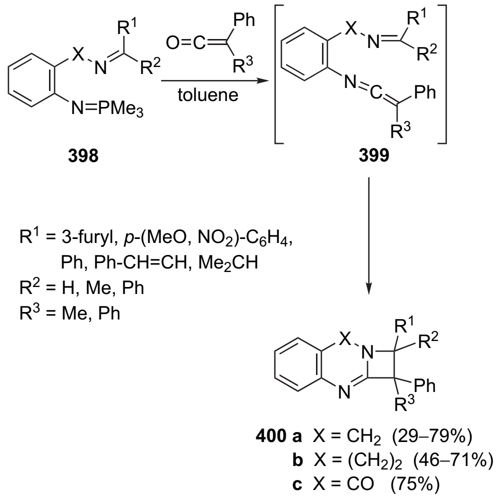
Scheme 116.



Scheme 117.

Other six-membered heterocycles can be formed by the tandem aza-Wittig/intramolecular electrocyclic ring closure. In this way, phosphazene **395** possessing a β-enamino-carbonyl site can undergo aza-Wittig-type reactions with diphenyl ketene (Scheme 118). The thieno[2,3-*d*]oxazinone ketenimine **396** that was formed, reacted with butylamine to afford a thieno[2,3-*d*]pyrimidinone **397** after cleavage of the oxazinone ring.[155]

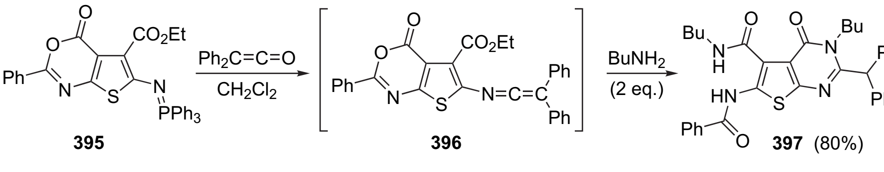
Alajarín et al.[156] reported the first intramolecular [2+2] cycloaddition reaction of ketenimines **399** (X=CH_2) (Scheme 119). Compounds **398** were easily converted into the corresponding ketenimines **399**, which would result from an aza-Wittig-type reaction, when the more reactive trimethylphosphazene **398** reacted with diphenyl ketene at room temperature. The ketenimines **399** were not isolated and, after purification, only the azeto[2,1-*b*]quinazolines **400a** (X=CH_2) were obtained in moderate yields. Intramolecular cycloaddition reactions have been performed by lengthening of the chain linking the reactive functions.[157] In fact, increasing by one methylene unit the aliphatic chain of intermediates **399** [X=–$(CH_2)_2$–] still allowed access to the corresponding cycloaddition products **400b** [X=–$(CH_2)_2$–], although this required a longer reaction time (Scheme 119). A further lengthening of the tether in **399** [X=–$(CH_2)_3$–], however, clearly prevented the intramolecular [2+2] cycloaddition reaction. Experimental and computational studies indicate that, in these reactions, high stereoselectivity can be achieved, in spite of the low stereocontrol of the step in which the new chiral centres are formed.[158]



R^1 = 3-furyl, *p*-(MeO, NO_2)-C_6H_4, Ph, Ph-CH=CH, Me_2CH
R^2 = H, Me, Ph
R^3 = Me, Ph

400 a X = CH_2 (29–79%)
b X = $(CH_2)_2$ (46–71%)
c X = CO (75%)

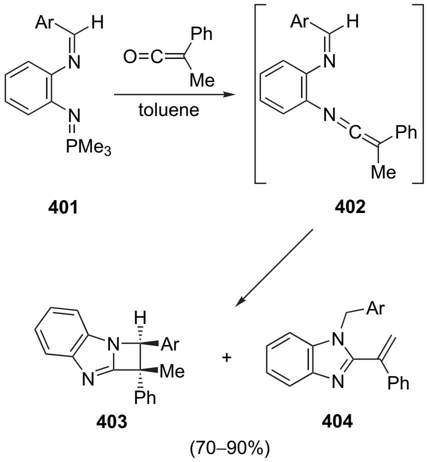
Scheme 119.



Scheme 118.

Efficient 1,4-asymmetric induction has been achieved in the highly stereocontrolled intramolecular [2+2] cycloaddition reaction of ketenimines and imines, leading to 1,2-dihydroazeto[2,1-*b*]quinazolines. The chiral methine carbon adjacent to the iminic nitrogen controls the exclusive formation of the cycloadducts with a relative trans-configuration at *C*-2 and *C*-8. Theoretical calculations fully support the stereochemical outcome of these cycloadditions.[159,160] More recently, the mode of selectivity in the intramolecular cyclization of ketenimines bearing *N*-acylimino units **399** (X=CO) has been studied by ab initio and DFT calculations.[161] Ab initio and DFT calculations predict that *N*-acylimino-ketenimines **399**, where the carbonyl carbon atom and the keteniminic nitrogen atom are linked either by a vinylic or by an *o*-phenylene tether, should easily undergo an intramolecular cyclization, leading to the corresponding [2+2] cycloadducts **400**, via a two-step process with the formation of cross-conjugated mesomeric betaines as intermediates. To check experimentally the results of the computational study, the requisite heterocumulenes **399** (X=CO) were prepared from an aza-Wittig reaction of the phosphazenes **398** with ketenes (Scheme 119). The formation of azetoquinazolinones **400c** (X=CO) was rationalized as occurring by a formal intramolecular [2+2] cycloaddition between the imine and the ketenimine functions of the putative imino-ketenimines **399**, thus confirming the predictions of the computational and kinetic analyses.

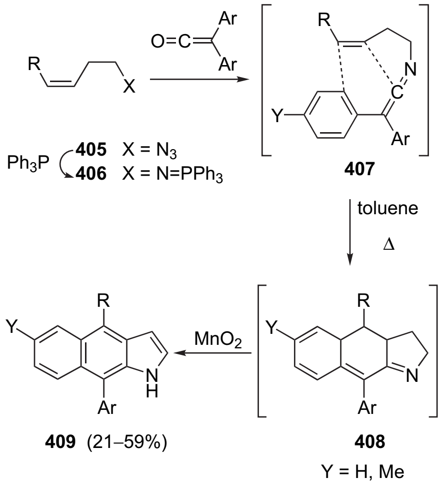
Imino-ketenimines **402**, obtained by treatment of phosphazenes **401** with ketenes, undergo intramolecular cyclization via two different reaction pathways, as shown in Scheme 120. A [2+2] cycloaddition yields the azeto[1,2-*a*]benzimidazoles **403**, but a rare imino-ene reaction afforded the 2-(α-styryl)benzimidazoles **404**. These results are interpreted in terms of a two-step mechanism involving two stereoisomeric conjugated betaines as intermediates.[162]



Ar = *p*-(MeO, Cl, CN, NO$_2$)-C$_6$H$_4$,
o-Me-C$_6$H$_4$, 3,4-Cl$_2$-C$_6$H$_3$, 2-Cl-5-NO$_2$-C$_6$H$_3$,
2,5-Cl$_2$-C$_6$H$_3$, 2,5-Me$_2$-C$_6$H$_3$

Scheme 120.

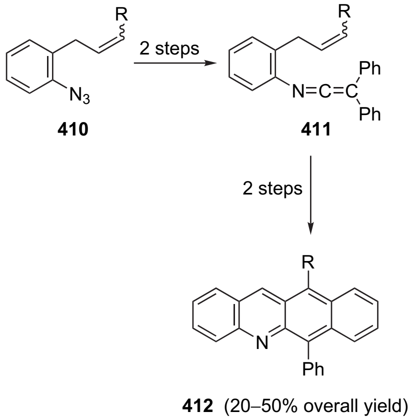
The synthesis of benz[*f*]indoles through a consecutive Staudinger reaction/aza-Wittig reaction/intramolecular Diels–Alder cycloaddition process of azido olefins **405** has been described by Molina et al.[163,164] The efficacy of the intramolecular cycloaddition of aryl ketenimines and styrene-like dienophiles that are linked with a flexible chain containing two carbon atoms **407** was found to be useful in the simultaneous formation of the pyrrole and phenyl rings in the synthesis of benz[*f*]indoles **409** (Scheme 121).



Ar = Ph, *p*-Me-C$_6$H$_4$,
R = Ph, *p*-(MeO, Cl, NO$_2$)-C$_6$H$_4$, Ph-CH=CH,
4-pyridyl, 3-thienyl, Et, CH$_2$=CH, 3-thienyl

Scheme 121.

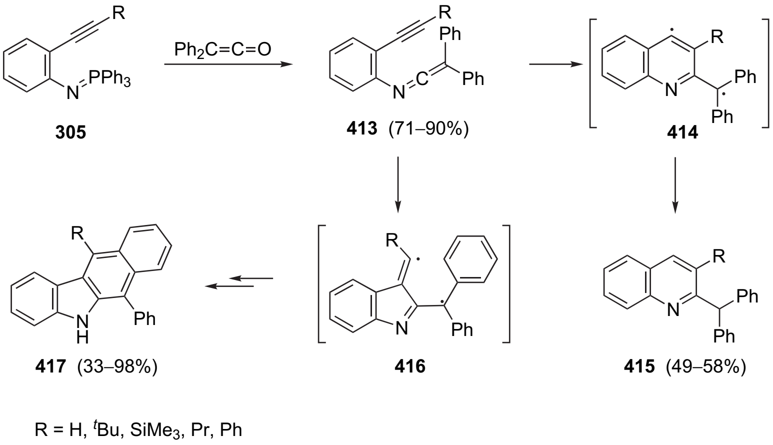
More recently, the consecutive Staudinger/aza-Wittig/intramolecular Diels–Alder cycloaddition process has been used for the preparation of benz[*b*]acridines[165] (Scheme 122). In this manner, Staudinger reaction of the azides **410**, followed by treatment of the resulting phosphazenes with diphenyl ketene, afforded the ketenimines **411**. These diphenyl ketenimines undergo a thermally induced intramolecular [4+2] cycloaddition to give the tetrahydrobenz[*b*]-acridines, which are converted into the fully aromatic benz[*b*]acridines **412** by oxidation with Pd/C.



R = H, *o*-(Br, NO$_2$)-C$_6$H$_4$,
p-(Br, Me, MeO, NO$_2$)-C$_6$H$_4$

Scheme 122.

Quinolines and 5*H*-benzo[*b*]carbazoles from *N*-[2-(1-alkynyl)phenyl] ketenimines were obtained by Wang et al.[123,166] by generation and subsequent trapping of biradicals. The

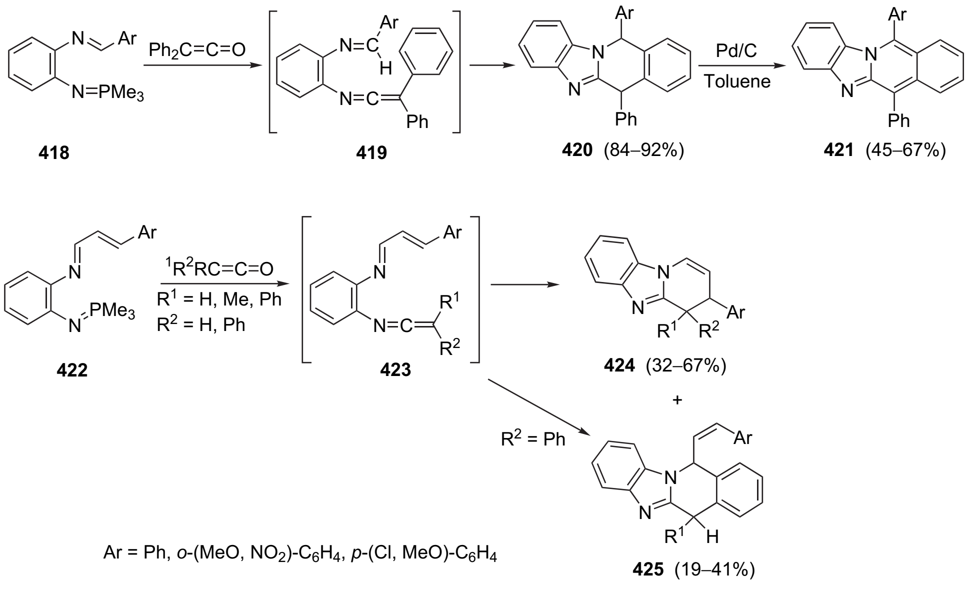


Scheme 123.

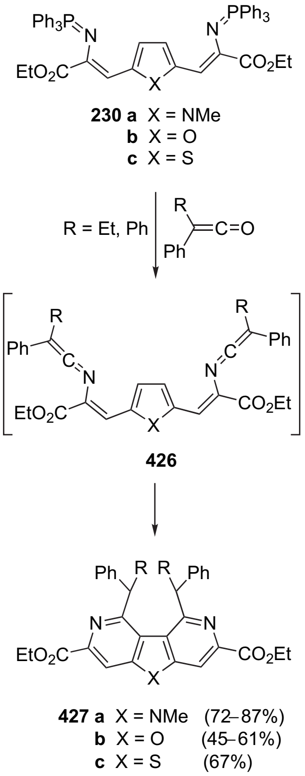
aza-Wittig reaction of phosphazenes **305** with ketenes, containing a large excess of 1,4-cyclohexadiene as a hydrogen-atom donor, furnished the quinolines **415** (Scheme 123). Apparently, the reaction proceeded through an initial formation of the ketenimines **413**, followed by cycloaromatization to produce biradicals **414** and, subsequently, heterocycles **415**. Similarly, thermolysis of some of the isolated synthesized ketenimines **413** in refluxing benzene gave the benzocarbazoles **417**. The cascade sequence outlined in Scheme 123 with an initial formation of a five-membered ring to produce biradical **416**, followed by an intramolecular radical–radical combination and a subsequent tautomerization, could account for the formation of **417**.

The synthesis of benzimidazo[1,2-*b*]isoquinolines **421**[167] and **425**[168] and pyrido[1,2-*a*]benzimidazoles **424**[168] has been reported by Alajarín et al. (Scheme 124). Although ketenimines **419** and **423** could neither be isolated nor be detected in the reaction mixture, they must be, reasonably, transient precursors of compounds **421**, **424** and **425**, resulting from the aza-Wittig reaction of ketenes with phosphazenes **418** and **422**. Thus, ketenimines **419** and **423** were converted into fused heterocycles **421**, **424** and **425** by [4+2] intramolecular cycloaddition of these ketenimines.

Bisphosphazenes **230a** (X=NMe) have been employed for the preparation of dipyrido[4,3-*b*:3,4-*d*]pyrroles **427a** (X=NMe) by a bispyrido annelation reaction onto a preformed five-membered heterocycle, achieved by the tandem aza-Wittig/electrocyclic ring closure methodology (Scheme 125).[102] Thus, bisphosphazenes **230a** reacted with 2 equiv of ketene at room temperature to afford the tricyclic heterocycles **427a** (X=NMe) in good yield via intermediate **426**. Extension of this methodology to the preparation of tricyclic compounds derived from furan and thiophene has been studied.[102] In this manner, reaction of bisphosphazenes **230b**,**c** (X=O, S) with ketenes gave the furodipyridines **427b** (X=O) or thienodipyridines **427c** (X=S).



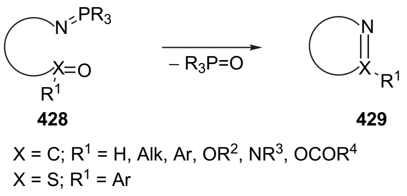
Scheme 124.



Scheme 125.

7. Intramolecular aza-Wittig reaction

Special interest has been focused on those aza-Wittig reactions of compounds **428** (Scheme 126) where both the phosphazene moiety and the carbon–oxygen double bond (C=O) (aldehydes, ketones, esters, amides, anhydrides…), or heteroatom-oxygen double bond (S=O) (sulfoxides…), are found within one molecule. This strategy involving intramolecular aza-Wittig reactions allows a method for the preparation of five- to higher-membered heterocyclic compounds **429** in very mild reaction conditions (Scheme 126).

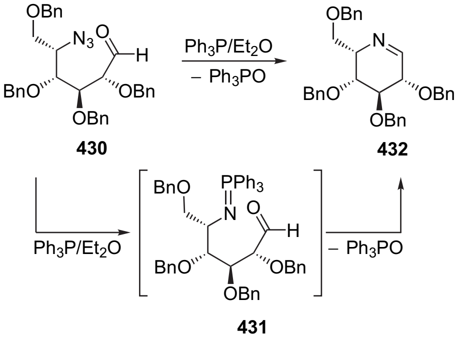


Scheme 126.

7.1. Phosphazenes derived from aldehydes

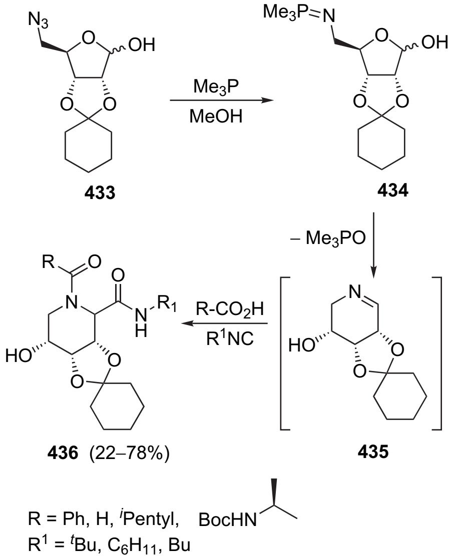
Functionalized phosphazenes containing an aldehyde group are excellent starting materials for the formation of the C=N double bond of heterocyclic systems.[3f]

The aza-Wittig reaction of phosphazenes has been successfully used for an elegant synthesis of six-membered nitrogen heterocycles with rigorous control of various asymmetric centres. As an example, piperidine systems **432**, precursors in the synthesis of polyhydroxylated nitrogen heterocycles such as (−)-adenophorine or 1-*epi*-adenophorine, as well as hydrophobically modified deoxynojirimycin (DNJ) variants, have been recently synthesized through the Staudinger/aza-Wittig sequence from compound **430**, as shown in Scheme 127.[169] A similar strategy has been used for the preparation of morpholine-based bisamides.



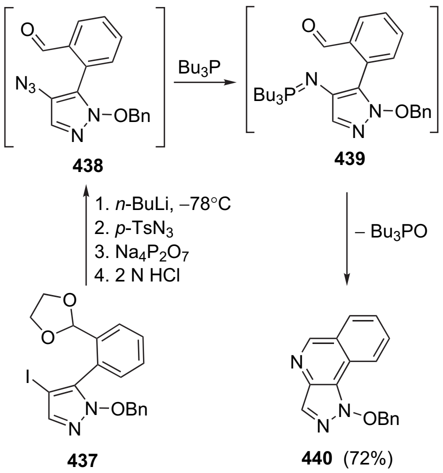
Scheme 127.

By combining a Staudinger/intramolecular aza-Wittig and an Ugi three-component reaction (SAWU-3CR), the construction of piperidine-based bisamides has been recently reported.[170] The preparation of these functionalized piperidine-based bisamides **436** starts with the reaction of trimethylphosphine with azido-aldehydes **433** to obtain the phosphazene **434**. At this stage, the intermediate imine **435** was brought to −78 °C, upon which the carboxylic acid or amino acid and alkyl isocyanide were added to afford the homogeneous SAWU-3CR product **436** as a single diastereoisomer (Scheme 128).



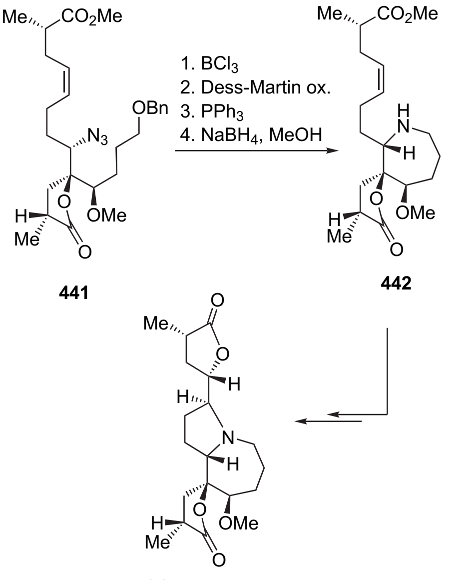
Scheme 128.

Functionalized phosphazenes derived from aldehydes can also be used for the preparation of a pyridine ring in polycyclic systems. 1-Hydroxypyrazolo[3,4-*c*]isoquinolines **440** have been prepared through the tandem Staudinger/intramolecular aza-Wittig reaction of 4-azido-5-aryl-substituted 1-benzyloxypyrazoles **438**, obtained from pyrazoles **437** (Scheme 129).[171] The pyridine ring of pyrazoloisoquinolines **440** was created via cyclization of a formyl group in a 2-formylphenyl substituent at *C*-5 with a phosphazene group installed at *C*-4 of 1-benzyloxypyrazole of **439** obtained from the Staudinger reaction of **438** with tributylphosphine.



Scheme 129.

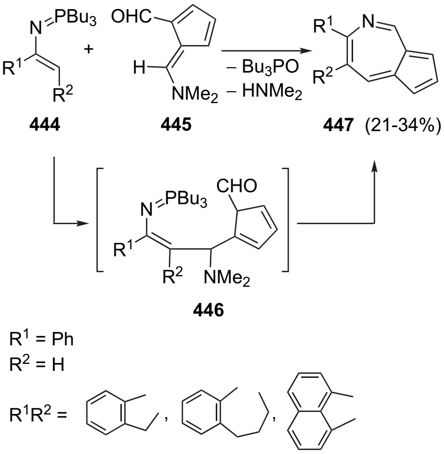
Synthetic applications of the aza-Wittig reaction of phosphazenes containing an aldehyde group are not restricted to the preparation of six-membered heterocycles and, for example, Yadav and Srinivas[172] have developed the synthesis of the optically active (3*S*,4*S*)-hexahydroazepine core of balanol and ophiocordin by ring expansion to the seven-membered azepine through an intramolecular aza-Wittig process. An intramolecular aza-Wittig reaction with an aldehyde function allowed the stereocontrolled total synthesis of the polycyclic stemona alkaloid, (−)-stemospironine **443**.[173] The required aldehyde was prepared from the starting azide **441** by cleavage of benzyl ether and Dess–Martin oxidation of the obtained primary alcohol (Scheme 130). Subsequent addition of triphenylphosphine and in situ reduction of the formed imine bond in the intramolecular aza-Wittig reaction gave a seven-membered ring precursor **442** of the expected alkaloid **443**. The intramolecular aza-Wittig reaction is also a valuable tool for the construction of seven-membered heterocyclic rings of polycyclic compounds, e.g., pyrazino-[2,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one derivatives.[174]



443 (−)-stemospironine

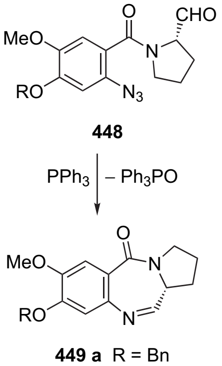
Scheme 130.

Similarly, this approach has been used for the synthesis of 5-azaazulene derivatives **447**[175] (Scheme 131). An initial nucleophilic reaction between phosphazenes **444** and aldehydes **445** could afford the intermediates **446**, which, after an intramolecular aza-Wittig reaction, gave the condensed bicyclic compounds **447**.



Scheme 131.

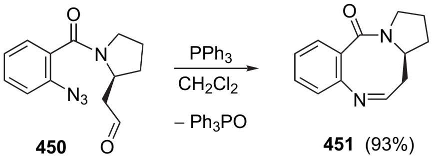
Likewise, the antibiotic DC-81 **449b** can be synthesized by using the same strategy.[176] Treatment of the azide **448** (R=Bn) with triphenylphosphine at room temperature afforded the intramolecular aza-Wittig compound **449a**, which, in turn, could be converted into DC-81 **449b** in a straightforward manner (Scheme 132). This strategy has been used for the preparation of the same antibiotic DC-81 **449b** by an intramolecular reductive cyclization with polymer-supported triphenylphosphine.[177]



449 a R = Bn
b R = H (92%)

Scheme 132.

O'Neil et al.[178] reported the synthesis of eight-membered heterocycles such as benzodiazocines **451** through a Staudinger/intramolecular cyclization process from **450** (Scheme 133). This, as far as we know, is the first example of the use of the Staudinger/aza-Wittig protocol for the construction of an eight-membered ring.

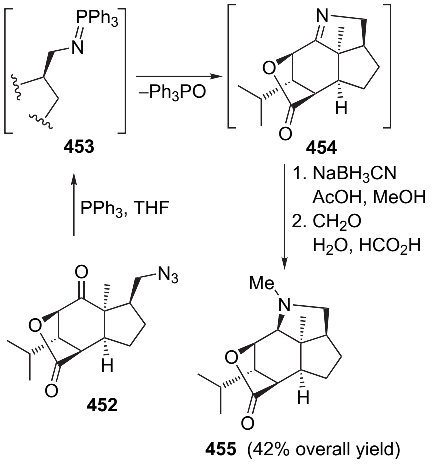


Scheme 133.

7.2. Phosphazenes derived from ketones

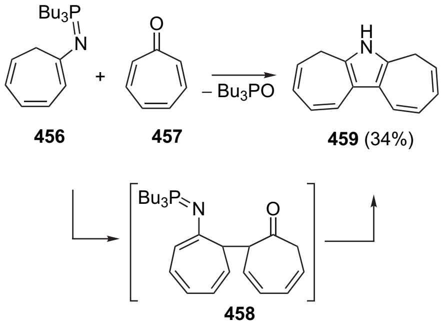
Phosphazenes having a ketone substitution cyclize by an intramolecular aza-Wittig reaction to give heterocyclic compounds. The first example was the formation of pyridine ring in the last step for the synthesis of the alkaloid, nigrifactine,[179] and the synthesis has been widely applied in the preparation of five-, six- and seven-membered heterocycles.[3f]

In the total synthesis of (−)-dendrobine **455**, the five-membered nitrogen heterocycle can be formed by an intramolecular aza-Wittig reaction of the azido ketone **452**.[180] Thus, treatment of **452** with triphenylphosphine gave polycyclic imine **454** via **453**. Reduction of the imine moiety with sodium cyanoborohydride from the less hindered α-face, followed by reductive methylation of the amine with paraformaldehyde and formic acid, afforded the enantiomerically pure (−)-dendrobine **455** (Scheme 134). In this synthesis, six stereogenic centres were induced, each in a stereoselective fashion, from a single chiral centre of the starting material.



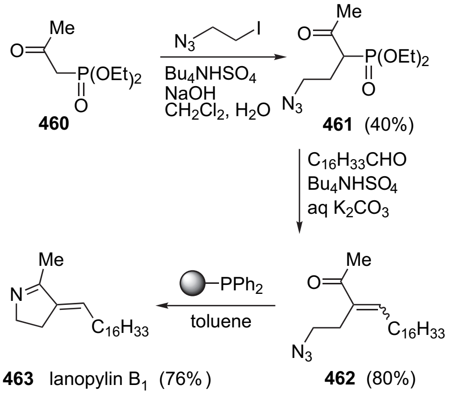
Scheme 134.

Nitta and Iino have reported an enamine-type alkylation of vinylic phosphazenes onto *C*-α of conjugated ketones for the preparation of fused nitrogen heterocycles.[181] Thus, a 5*H*-dicyclohepta[*b*,*d*]pyrrole ring system **459** can be obtained through an enamine-type alkylation of the phosphazene **456** onto *C*-α of the cyclic conjugated ketone **457** to give a keto-functionalized phosphazene **458** (Scheme 135). This intermediate **458** then undergoes an intramolecular aza-Wittig reaction, followed by hydrogen migration, to give the tricycle **459**. The same group has demonstrated the versatility of the enamine-type alkylation of vinylic phosphazenes/intramolecular aza-Wittig protocol for the preparation of other fused nitrogen heterocycles such as 11*H*-cyclohepta[*b*]indeno[2,1-*d*]pyrrole and acenaphtho[1,2-*b*]cyclohepta[*d*]pyrrole.[182] This methodology has also been used to construct phenyl-substituted and annulated 5-azaazulene (cyclopenta[*c*]azepine) derivatives.[183]



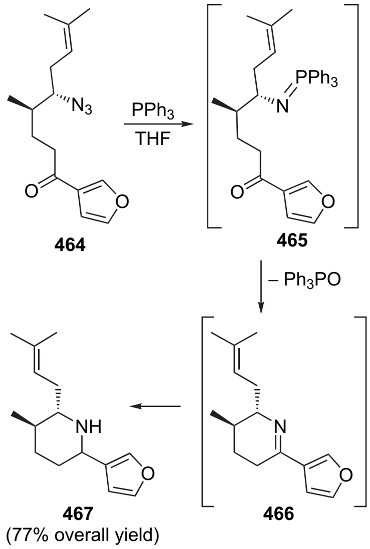
Scheme 135.

The formation of five-membered heterocycles through a Staudinger/intramolecular aza-Wittig reaction can also be performed by solid-phase synthesis and has been applied for the first synthesis of lanopylin B$_1$ **463**.[184] The total synthesis, which takes only four steps, starts with a phase-transfer alkylation of diethyl 2-oxopropylphosphonate **460** with a 2-iodoalkyl azide, affording the azido phosphonate **461**, which undergoes a phase-transfer Horner–Emmons–Wittig reaction with heptadecanal to provide the azido enone **462**. An intramolecular aza-Wittig reaction of the enone **462** with polymer-supported triphenylphosphine in toluene completed the first total synthesis of lanopylin B$_1$ **463** in 76% yield (Scheme 136). Substituted pyrrolines can be synthesized in a simple one-pot, microwave-assisted intramolecular aza-Wittig reaction of phosphazenes derived from γ-chlorobutyrophenone.[185]



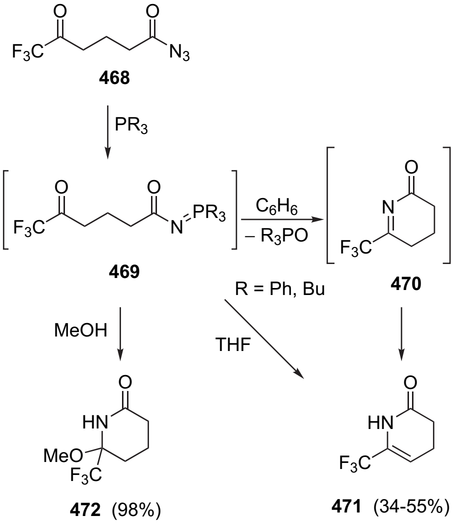
Scheme 136.

Intramolecular aza-Wittig reactions of phosphazenes with ketone substituents also afford an excellent method for the preparation of six-membered heterocycles. Since unsaturated esters can be easily converted into seleno azides, the aza-Wittig reaction appeared to be an easy route to tetrahydropyridines.[186] An optically active piperidine ring has been constructed by an intramolecular aza-Wittig reaction of the phosphazene **465**, obtained by a Staudinger reaction of azide **464** with triphenylphosphine, in refluxing THF. The non-isolated imine **466** was reduced with sodium borohydride in ethanol to give anhydronupharamine **467** stereoselectively (Scheme 137).[187]



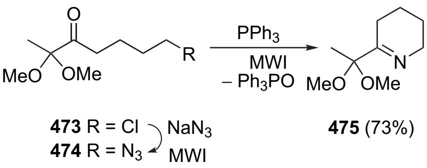
Scheme 137.

Eguchi et al.[188] reported the development of a new general route to pyridones, as well as indolizines and quinolizines, carrying a trifluoromethyl group on the bridgehead carbon of those skeletons. The strategy involves the intramolecular aza-Wittig reaction of the easily available acylphosphazenes **469** via acetylazida **468**, for the generation of 6-(trifluoromethyl)-4,5-dihydro-2(3*H*)-pyridones **471** or **472** (Scheme 138). These lactams have been applied to the synthesis of some fused-nitrogen heterocycles via radical cyclization of dihydropyridones.



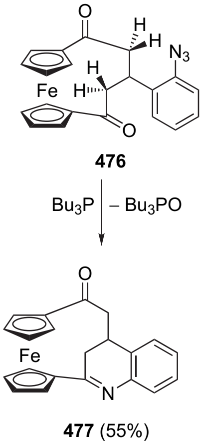
Scheme 138.

A microwave-assisted intramolecular aza-Wittig reaction was used by De Kimpe and Stevens[189] for the synthesis of the principal bread flavour component, 6-acetyl-1,2,3,4-tetrahydropyridine, among other acetal-protected such as **475** (Scheme 139). Azidation of the chloro compound **473** under classical conditions gave access to the azide **474**, which underwent a smooth intramolecular aza-Wittig reaction to afford the acetal **475**, derived from the bread flavour component, in 73% yield. The use of microwave irradiation (MWI)[185] seems to favour the intramolecular aza-Wittig reaction and shorter reaction times were necessary, while better yields were obtained. A similar strategy has been applied for the preparation of tetrahydropyridine precursors in the synthesis of (−)-adenophorine, 1-*epi*-adenophorine or deoxynojirimycin (DNJ) variants.[169]



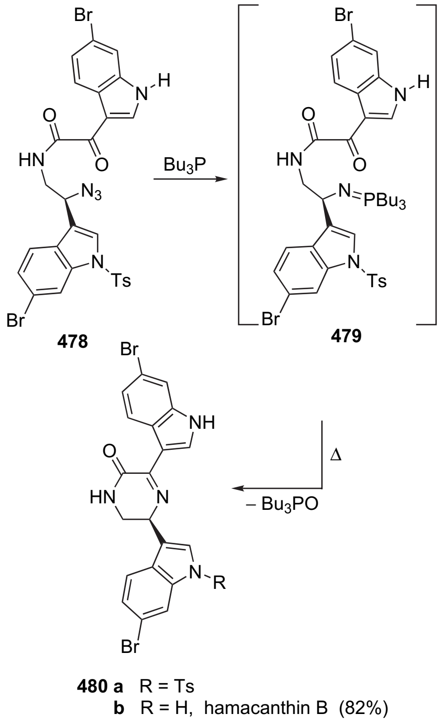
Scheme 139.

This methodology can also be used for the synthesis of polycycles containing a six-membered ring. A cryptand compound **477** has been prepared by an intramolecular aza-Wittig reaction of the ferrocenyl-substituted azido ketone **476**.[190] [5]-Ferrocenephane **476** underwent an intramolecular aza-Wittig reaction by treatment with tributylphosphine at room temperature to give the compound **477** bearing a 1,1′-disubstituted ferrocene bridge (Scheme 140). Likewise, six-membered nitrogen heterocycles have been formed by direct cyclization, via an intramolecular aza-Wittig reaction, to afford isoxazolo[4,3-*c*]quinolines.[191]



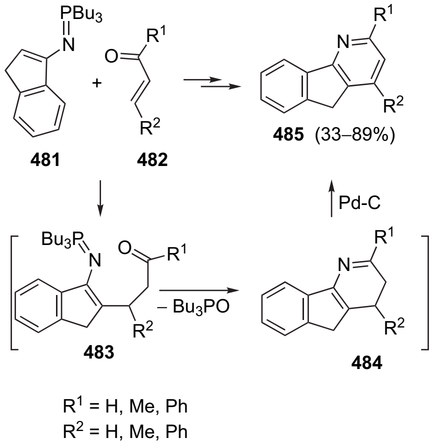
Scheme 140.

This approach has been also used as the key step for the enantioselective synthesis of the marine indole alkaloid, hamacanthin B **480b**[192] (Scheme 141) and the antipode of hamacanthin A.[193] The central pyrazinone ring was achieved by the reaction of azide **478** and tributylphosphine in toluene at room temperature, to afford phosphazene intermediate **479**, followed by heating, to provide the expected cyclized product **480a**. Deprotection of **480a** leads to the formation of hamacanthin B **480b** in 82% yield keeping the configuration of the *C*-α of the starting azide.



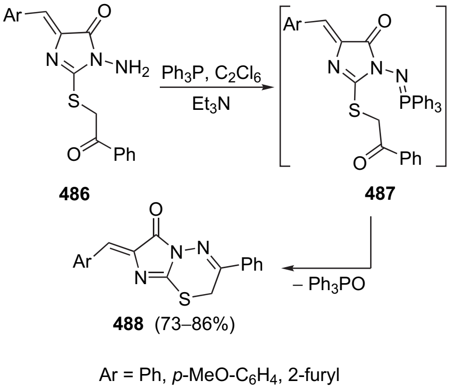
Scheme 141.

Reaction of *N*-vinylic phosphazenes such as (inden-3-ylimino) tributylphosphazene **481** with α,β-unsaturated aldehydes and ketones **482**, and 5 mol % Pd–C, gave 5*H*-indeno[1,2-*b*]pyridines **485** (Scheme 142).[194] Formation of the compounds **485** could be explained by an initial enamine-type alkylation (Michael addition) of substrate **481** onto the β-carbon atom of the enones **482**. An intramolecular aza-Wittig reaction of the keto-functionalized phosphazenes **483** gave the dihydropyridine intermediates **484**, which are dehydrogenated with Pd–C to give the compounds **485**. The same authors have described the preparation of 7,12-methanocyclodeca[*b*]pyridine ring systems[195] through the reaction of annulene phosphazenes with α,β-unsaturated ketones, in a similar way to that described before.



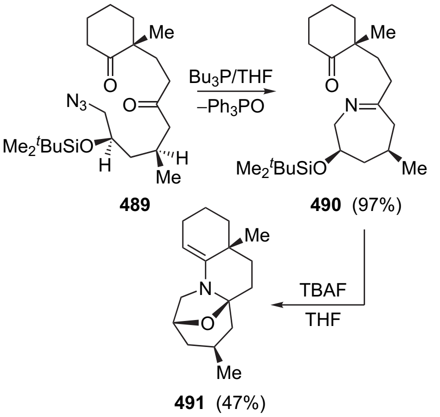
Scheme 142.

Intramolecular aza-Wittig reactions mainly involve phosphazenes generated by Staudinger reactions. Phosphazenes could, however, also be prepared by the Kirsanov reaction.[3f] In this context, a new efficient synthesis of thiadiazinones **488** has recently been reported by means of functionalized ketophosphazenes **487** (Scheme 143).[83] The synthesis implies treatment of 3-amino-4*H*-imidazol-4-ones **486** with triphenylphosphine, hexachloroethane and triethylamine to afford directly the 2*H*-imidazo[2,1-*b*]-1,3,4-thiadiazin-6(7*H*)-ones **488**. The conversion involves the initial transformation of **486** into phosphazenes **487** as reactive intermediates, which easily undergo intramolecular aza-Wittig reaction to give **488** (Scheme 143).



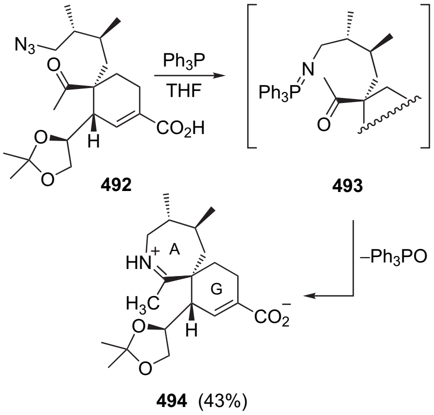
Scheme 143.

The synthesis of the enamine-aminal heterocyclic core **491** found in the zoanthamine alkaloids has been reported through an enantiocontrolled construction of the seven-membered heterocycle by an aza-Wittig process.[196] Direct intramolecular aza-Wittig condensation of **489** led to the isolation of the tetrahydroazepine **490** in excellent yield (Scheme 144). The hemi-aminal **491** was produced by desilylation of **490**, which resulted in ketalization, amination and dehydration to the tetracyclic core of the zoanthamine alkaloids.



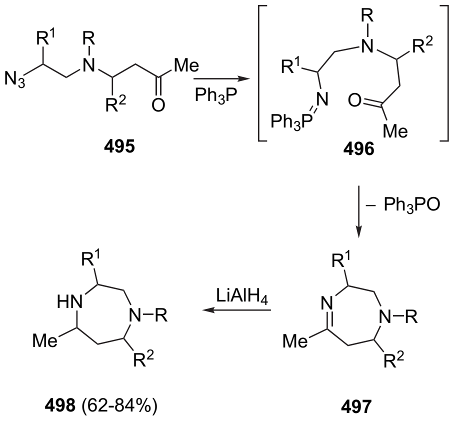
Scheme 144.

An efficient synthetic route to the spirally fused AG-ring model of pinnatoxin A has been devised using the intramolecular cyclization of an epoxy nitrile for the construction of the G-ring, followed by an aza-Wittig reaction to form the seven-membered cyclic imine[197] (Scheme 145). The cyclization of the A-ring took place when **492** was treated with triphenylphosphine and heated at 55 °C, to give **494** in 43% overall yield via **493**. A straightforward intramolecular aza-Wittig reaction of ω-azido-β-ketoesters for the preparation of heterocyclic secondary enamines has recently been developed by Wang et al.[198]



Scheme 145.

Intramolecular aza-Wittig reactions of phosphazenes **496** derived from amino azides with keto substituents **495** led to 2,3,6,7-tetrahydro-1*H*-1,4-diazepines **497**. Reduction of these compounds with lithium aluminium hydride afforded the corresponding saturated heterocycles **498** (Scheme 146).[199] In the same way, the intramolecular aza-Wittig reaction is a valuable tool for the construction of seven-membered heterocyclic compounds, e.g., benzodiazepines and benzothiadiazepines.[200]



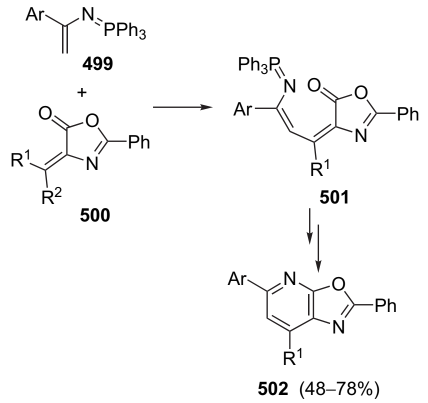
R = Me, Bn
R^1 = H, Me
R^2 = H, Me

Scheme 146.

7.3. Phosphazenes derived from esters

It is well known that the carbonyl group of esters is less reactive than that of aldehydes and ketones in an aza-Wittig reaction. Some examples have been reported for the preparation of five- and six-membered heterocycles[3f] and, in recent years, some reports of the intramolecular aza-Wittig reaction of phosphazenes containing ester derivatives in the molecule have appeared.

The preparation of oxazolo[5,4-*b*]pyridines **502**[201] was accomplished by using vinylic phosphazenes **499**. Thus, phosphazenes **499** and oxazolones **500** reacted smoothly in refluxing benzene or anisole, leading to the formation of the bicycles **502** (Scheme 147). Phosphazenes **499** with ambident nucleophilicity react, in this case, as carbon nucleophiles, rather than as nitrogen nucleophiles. Thus, the first step of the reaction can be envisaged as a conjugative addition (1,4-addition) of the phosphazenes to the exocyclic double bond of oxazolones **500** to give intermediates **501**, which after an intramolecular aza-Wittig reaction, afford the products **502** (Scheme 147).

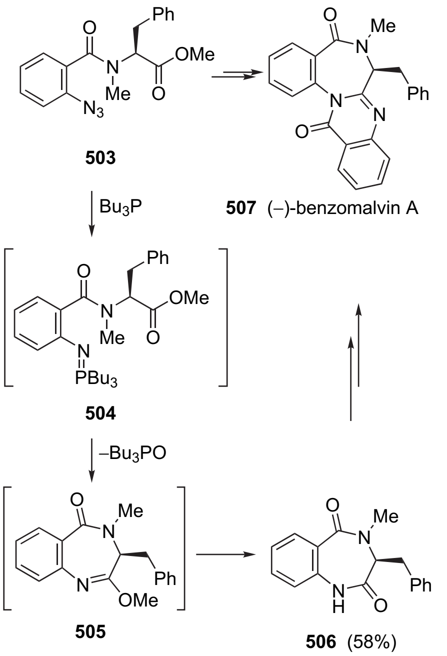


Ar = Ph, *p*-Me-C_6H_4
R^1 = H, Me, Ph, *p*-(Me, Cl)-C_6H_4
R^2 = H, OEt

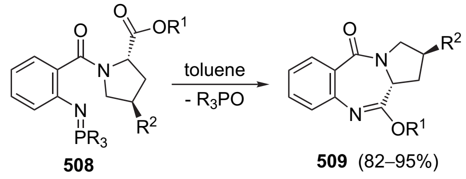
Scheme 147.

Methods for the preparation of seven-membered nitrogen-ring systems by the use of the intramolecular aza-Wittig reaction have increased in the last decade. In this way, benzodiazepines maybe prepared from *o*-azidobenzoyl-α-amino acid esters,[202–204] and this methodology has also been applied for the first total synthesis of (−)-benzomalvin A **507** (Scheme 148).[205,206] Reaction of the starting azide **503** with tributylphosphine leads to the formation of the phosphazene intermediate **504**, which under the reaction conditions affords the benzodiazepine **506** in 58% yield via compound **505**. Benzodiazepine **506** suffered subsequent transformations to obtain (−)-benzomalvin A **507**. Eguchi and Okawa have synthesized pyrazino[2,3-*e*][1,4]diazepin-5-one derivatives via the corresponding phosphazenes derived from 3-aminopyrazine-2-carboxylic acids and α-amino acid derivatives, by the intramolecular aza-Wittig methodology.[174,207] In an analogous manner, the process of the preparation of 1,3-benzoxazepines has been developed.[208]

This methodology can also be applied for the preparation of pyrrolo[1,4]benzodiazepines in their imine form and, in general, for the synthesis of [1,4]benzodiazepines fused to a saturated heterocyclic ring (Scheme 149).[176] Likewise, functionalized phosphazenes **508** were converted, by heating, to the polycyclic iminoethers **509**, in yields ranging from 82 to 95%. This intramolecular aza-Wittig reaction involving an ester functionality, as a key step for the preparation of pyrrolo[1,4]benzodiazepines **509**, was carried out in toluene in a sealed tube at 140 °C or at reflux (Scheme 149).



Scheme 148.

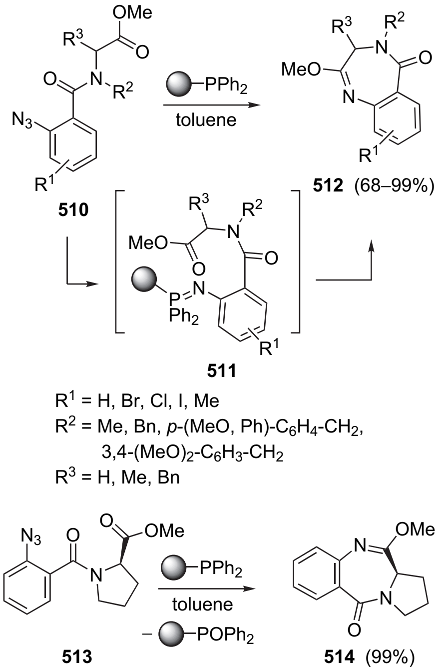


R = Ph, Bu
R^1 = Me, Et
R^2 = H, OH

Scheme 149.

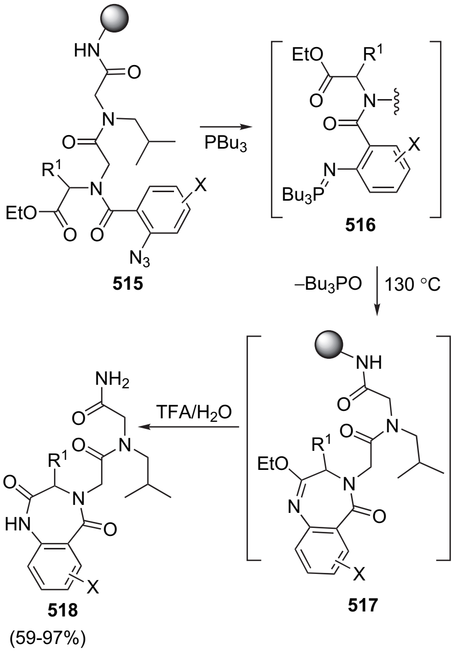
Highly functionalized 1,4-benzodiazepin-5-one derivatives have been synthesized by solid-phase methods.[209,177] Bicyclic compounds **512** and tricyclic heterocycles **514** were obtained by the cyclization of azides **510** and **513**, respectively, with polymer-supported triphenylphosphine, via the corresponding phosphazenes, e.g., **511**, at room temperature in toluene (Scheme 150). Subsequent heating at 100 °C in the same solvent without further purification steps produced the intramolecular aza-Wittig products **512** and **514**. The use of polymer-supported triphenylphosphine provides a more simplified purification procedure, relative to the corresponding solution-phase method.[202]

The synthesis of 1,4-benzodiapine-2,5-diones **518** from polymer-supported *o*-azidobenzamides **515** has been described by the split-resin method on solid-phase synthesis.[210] By using this approach and with the intramolecular aza-Wittig reaction of phosphazene **516** as the key step, diverse libraries of hybrid molecules combining a benzodiazepinedione nucleus with an appended *N*-substituted glycine side chain have been synthesized via **517** (Scheme 151).



R^1 = H, Br, Cl, I, Me
R^2 = Me, Bn, *p*-(MeO, Ph)-C$_6$H$_4$-CH$_2$, 3,4-(MeO)$_2$-C$_6$H$_3$-CH$_2$
R^3 = H, Me, Bn

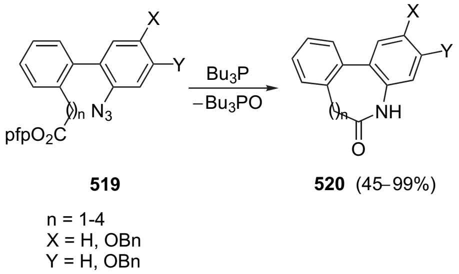
Scheme 150.



X = H, 10-Me, 9-Cl, 8-OTf, 8-NO$_2$
R^1 = H, Me, Bn, Ph, CH$_2$OH, ^{i}Pr, *p*-OH-C$_6$H$_4$-CH$_2$, CH$_2$-CO$_2$H, (CH$_2$)$_2$-CO$_2$H, (CH$_2$)$_4$-NH$_2$, (CH$_2$)$_3$-NH$_2$, CH(OH)Me

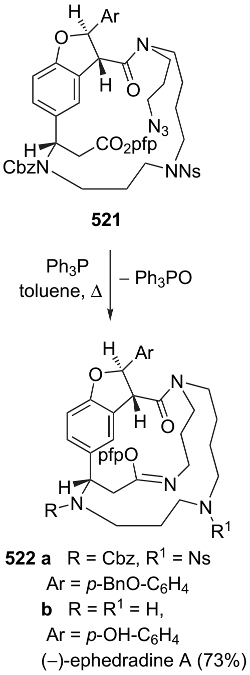
Scheme 151.

More recently, the Staudinger/intramolecular aza-Wittig reaction of ω-azido pentafluorophenyl (pfp) esters **519** has been successfully applied to the construction of seven- to 10-membered lactams **520**, demonstrating the generality and efficiency of the present tactic for the synthesis of medium-sized lactams (Scheme 152).[211] Cyclization of ω-azido pfp esters **519** proceeded smoothly at room temperature to give the corresponding seven- and eight-membered lactams **520**, when 5 equiv of Bu$_3$P as the reagent in high-dilution conditions were used. On the other hand, formation of the much challenging larger nine- and 10-membered lactams called for elevated temperature conditions to attain satisfactory yields.



Scheme 152.

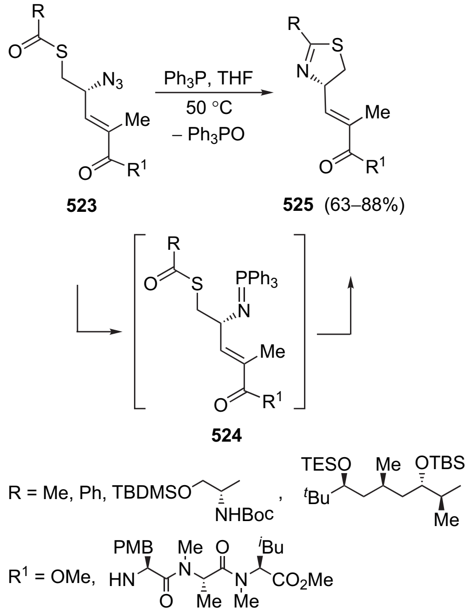
The formation of complex 13-membered macrocycles through a Staudinger/intramolecular aza-Wittig reaction has been applied to the total synthesis of (−)-ephedradine A (orantine) **522b**.[212,213] The formation of the 13-membered iminoether **522a** was successfully obtained by treatment of the azide **521** (Ar=*p*-BnO-C_6H_4) with Ph_3P in refluxing toluene under high-dilution conditions (Scheme 153). Subsequent hydrolysis, removal of the Ns group and simultaneous cleavage of the Cbz group and benzyl ether yielded (−)-ephedradine A **522b**.



Scheme 153.

7.4. Phosphazenes derived from thioesters

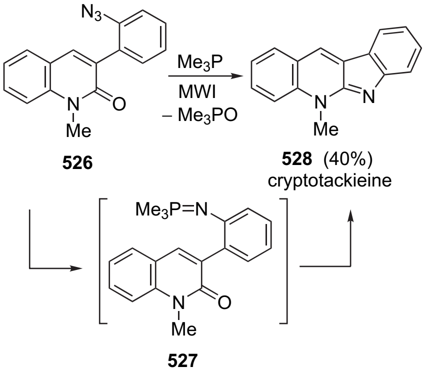
Recently, in developing a synthetic entry to the thiazoline-containing domain of the aprotoxin natural products, Forsyth and Chen[214,215] converted vicinal azido-thioesters **523** into 2,4-disubstituted thiazolines **525** via a sequential one-pot Staudinger reduction with the formation of intermediate **524** followed by intramolecular aza-Wittig reaction (Scheme 154). This method of thiazoline formation provides a mild and versatile process that is particularly well suited for acid-sensitive substrates, and results in good yields without any detectable epimerization of the 2-substituent α-stereogenic centres or at the 4-position of the thiazolines. Pyrrolo[1,4]benzodiazepines and, in general, [1,4]benzodiazepines have been prepared by using this methodology.[176]



Scheme 154.

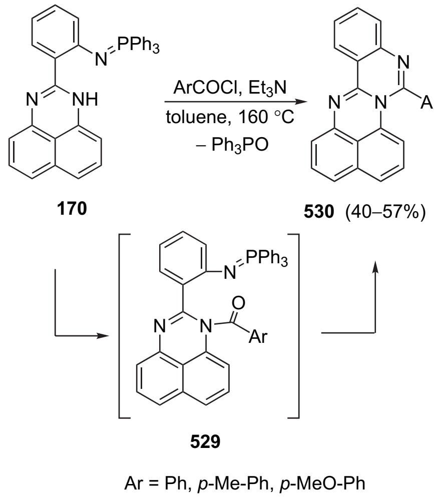
7.5. Phosphazenes derived from amides

Some examples of intramolecular aza-Wittig imination reactions involving less reactive amide carbonyl groups have been reported, usually suffering from low yields. One of them is a convenient combination of intramolecular aza-Wittig strategy and microwave technology for the preparation of the alkaloid, cryptotackieine.[216,217] Thus, treatment of 3-(*o*-azidophenyl)quinolin-2-one **526** with trimethylphosphine in nitrobenzene under microwave irradiation between 150 and 180 °C, after five-membered ring construction, afforded cryptotackieine **528** in 40% yield via **527** (Scheme 155).



Scheme 155.

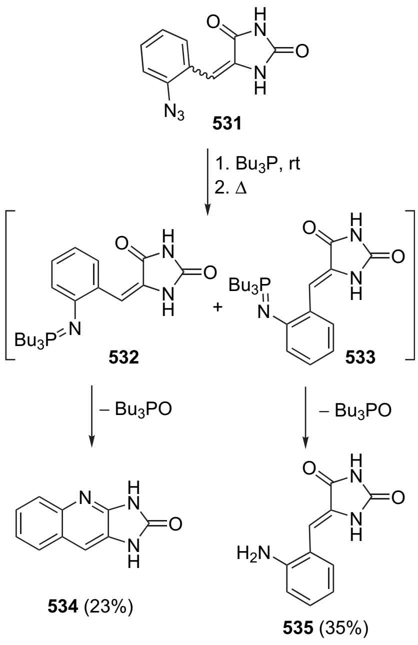
Six-membered heterocycles have also been prepared by using this approach. In this way, a general synthesis of functionalized quinazolino[3,4-*a*]perimidines, which is capable of modification to allow the introduction of a wide range of substituents, has been developed by Molina et al.[79] These perimidines **530** were obtained when phosphazenes **170** reacted with aroyl chlorides in the presence of triethylamine in a sealed tube at 160 °C (Scheme 156). These rigorous conditions suggest that the conversion of **170** into **530** involves initial acylation of the perimidine ring, instead of formation of an imidoyl chloride. An intramolecular aza-Wittig reaction between the carbonyl group of the amide moiety and the phosphazene group in **529** provides the cyclized products **530**. In a similar way, when bisphosphazenes have been employed in intramolecular aza-Wittig reactions, phosphazenes derived from the 2-(*o*-azidophenyl)-4(3*H*)-quinazolinone have been synthesized.[109]



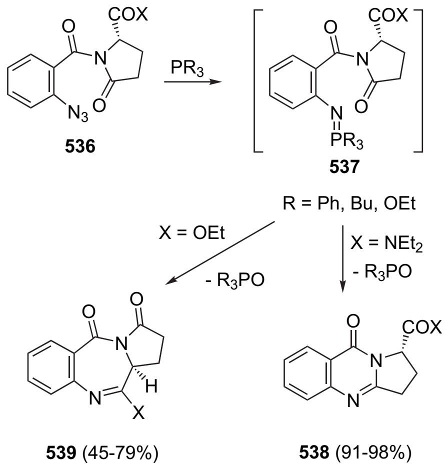
Scheme 156.

This methodology has also been used for the synthesis of the imidazo[4,5-*b*]quinolin-2-one ring.[103] When the *E*/*Z* azide **531** was treated with tributylphosphine at room temperature and the resulting phosphazenes **532** and **533** were heated at reflux, the 1,2-dihydroimidazo[4,5-*b*]quinolin-2-one **534** and the benzylidene hydantoin derivative **535** were isolated in 23 and 35% yield, respectively (Scheme 157). The formation of compound **534** can be explained by an intramolecular aza-Wittig reaction of the initially formed *E*-phosphazene **532**, which could not be isolated, whereas the *Z*-phosphazene **533** was hydrolyzed during the work-up to give **535**.

o-Azidobenzoyl-α-amino esters could also afford pyrrolo[2,1-*b*]quinazoline derivatives **538** or pyrrolo[2,1-*c*][1,4]benzodiazepine derivatives **539**. The formation ratio of the heterocyclic compounds (six-membered vs. seven-membered ring) was considerably dependant upon the carbonyl function (X=OMe, NEt$_2$) and the phosphorus reagents. Exclusive formation of the six-membered ring to give compound **538**, through an intramolecular aza-Wittig reaction with the cyclic amide, has been observed for exocyclic amide derivatives **537** (X=NEt$_2$) (obtained from **536**). A mixture of both compounds **538** and **539** was, however, obtained for the ester derivatives **537** (X=OMe), obtaining compound **539** as a major product when triethyl phosphite (R=OEt) was employed, which maybe due to a less hindered effect and mild reactivity (Scheme 158).[204]



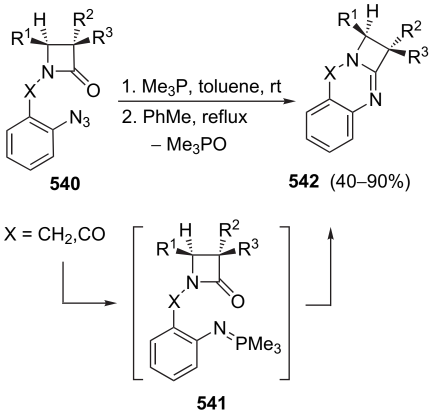
Scheme 157.



Scheme 158.

An intramolecular aza-Wittig reaction of a β-lactam carbonyl group has also been reported.[218] The intramolecular aza-Wittig reactions involving the amide carbonyl group were applicable for the preparation of azeto[2,1-*b*]quinazolines or quinazolin-8-ones **542** (Scheme 159). The method represents the first example of an aza-Wittig of the β-lactam carbonyl group and requires the intermediacy of a highly reactive *N*-aryl-trimethylphosphazene **541** obtained from the azido-compound **540**, and has only proved to be useful when it results in the formation of six-membered rings.

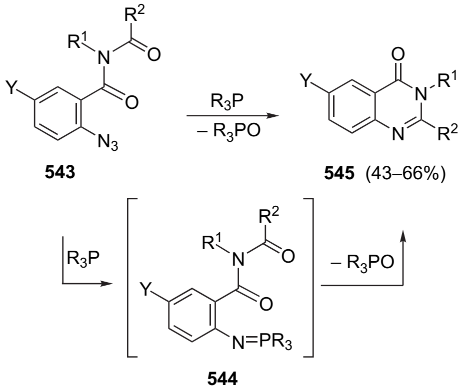
Simple quinazoline alkaloids and quinazoline alkaloids containing the indole skeleton such as rutecarpine, tryptanthrin[219] and the antitumour agent, Batracylin (NSC-320846),[220] have been constructed via intramolecular aza-Wittig reactions of amide derivatives (Scheme 160). The fused quinazoline ring could be synthesized efficiently in a one-pot procedure via the consecutive Staudinger/intramolecular aza-Wittig reaction of the corresponding azides **543** with phosphine to afford the heterocyclic compounds



R^1 = p-(Cl, Me, NO$_2$, MeO)-C$_6$H$_4$, H, Ph, MeCO$_2$, PhCO$_2$
R^2 = Ph, H, Me
R^3 = Ph, H

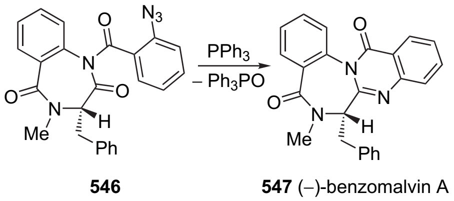
Scheme 159.

545 via intermediate **544**, under very mild reaction conditions. Likewise, heterocycles such as circundatin F, sclerotigenin and *ent*-funiquinazoline G have been prepared by the intramolecular aza-Wittig procedure.[221]



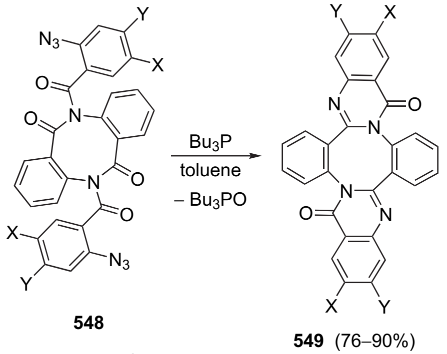
Scheme 160.

For the last step in the synthesis of benzomalvin A, the azide derivative **546** was treated with triphenylphosphine to generate the corresponding phosphazene, which reacted with the amide function to afford (−)-benzomalvin A **547** in 98% yield (Scheme 161).[206] The specific behaviour of (−)-benzomalvin A and comparison of the spectral and physical data with those reported for the natural product gave satisfactory matching results.



Scheme 161.

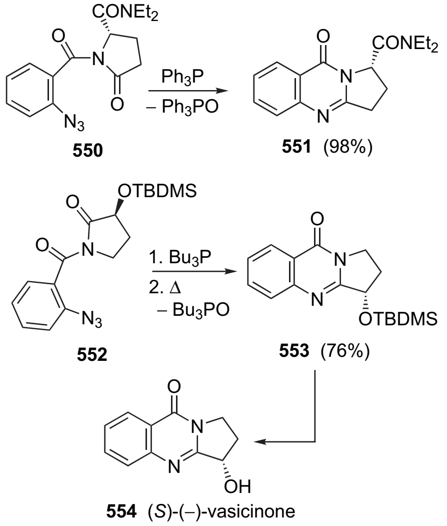
An intramolecular aza-Wittig reaction of an amide carbonyl group has also been used for the preparation of the six-membered ring of benzopolyazamacrocycles by Eguchi et al.[222] The quinazolinone annelation of lactams **548** provides compounds **549**. A further reductive ring-enlargement sequence provides a novel route to benzo-fused polyazamacrocycles (Scheme 162).



X = Y = H, OMe
X = Cl, Y = H

Scheme 162.

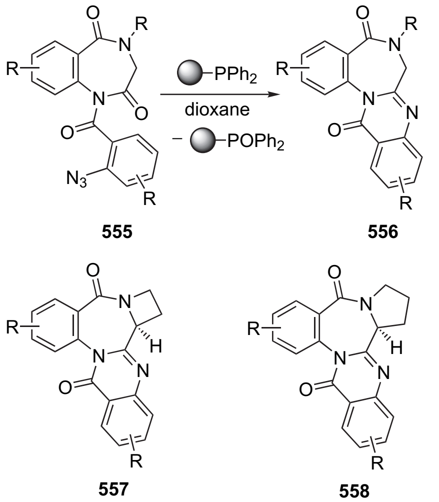
Similarly, the formation of six-membered heterocycles through a chemoselective intramolecular aza-Wittig reaction has been used for the preparation of 5-(1*H*)-pyrrolo[2,1-*b*]quinazolinone derivatives, e.g., **551** (Scheme 163).[223] This strategy has also been used for the synthesis of optically active (*S*)-(−)-vasicinone **554**.[224] After *O*-TBDMS protection, *o*-azidobenzoylation followed by treatment of compound **552** with tributylphosphine afforded (*S*)-(−)-vasicinone **554** via the tandem Staudinger/intramolecular aza-Wittig reaction followed by TBDMS deprotection of **553** (Scheme 163). Recently, deoxyvasicinone and related heterocycles have been synthesized through a solid-phase intramolecular aza-Wittig reaction employing a polymer-supported triphenylphosphine.[209] Synthetic approaches to 1-arylmethylenepyrazino[2,1-*b*]quinazoline-3,6-diones have been studied.[225] The same group has applied this approach to the synthesis of hexacyclic 7,10,16,16*a*-tetrahydro-11*H*-quinazolino[2′,3′:3,4]pyrazino[1,2-*b*]-β-carboline-5,8-diones, dihydro-*C*-homo analogs[226] and other analogues of



Scheme 163.

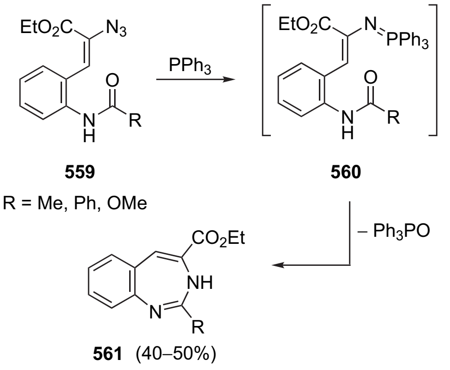
N-acetylardeemin,[227,228] inhibitors of multidrug resistance (MDR) to antitumour agents.

A concise building-block approach to a diverse multi-arrayed library of the circumdatin family of natural products has recently been reported.[229] This synthetic strategy relies on an efficient formation of the fused quinazolinone ring system using a polymer-supported phosphine in an intramolecular aza-Wittig reaction as a key step. In this manner, a diverse library of benzodiazepine–quinazolinone alkaloids (circumdatins) **556** has been prepared by treatment of the azides **555** with polymer-supported triphenylphosphine (Scheme 164). Following the same strategy, the libraries incorporating pentacyclic derivatives, such as derivatives **557** and **558**, were also prepared.



Scheme 164.

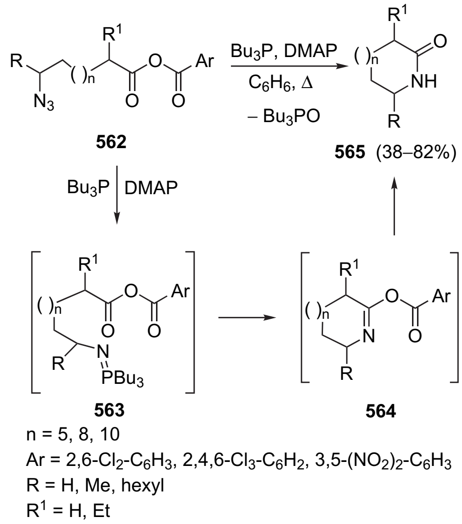
By means of an intramolecular aza-Wittig reaction between phosphazenes and the amide moiety of compounds **560** (prepared from azido compound **559**), seven-membered rings can also be constructed. In this case, however, higher temperatures are required for the synthesis of 1,3-benzodiazepines **561**, comparable with the temperatures required for the analogous phosphazenes, but with ester substitution (Scheme 165).[208]



Scheme 165.

7.6. Phosphazenes derived from anhydrides

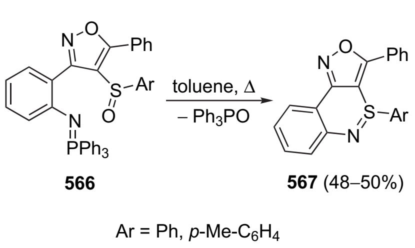
The carboxylic acid anhydride derivatives are able to form lactams by intramolecular aza-Wittig reaction; but, only one example has been reported showing this behaviour. ω-Azido acids, after activation of the carboxyl groups as mixed anhydrides **562**, can be converted via phosphazenes **563** to macrolactams **565**, in good yields by treatment with tributylphosphine (Scheme 166).[230] This procedure has been fruitfully applied for the synthesis of other difficult-to-cyclize ω-azido acids, via phosphazenes.



Scheme 166.

7.7. Phosphazenes derived from sulfimides

Finally, the use of phosphazenes in other intramolecular aza-Wittig-type reactions for the formation of hetero-bonds other than C=N is rare. In particular, there is only one example, recently reported, that details the synthesis of the N=S (sulfimide) bond involving the use of the S=O functionality. Thus, the synthesis of cyclic sulfimides **567** involving an intramolecular aza-Wittig-type ring closure process between a sulfoxide and a phosphazene moiety of compounds **566** has been reported.[231] Treatment of compounds **566** in anhydrous toluene at reflux gave triphenylphosphine oxide, together with the isoxazolo[4,3-*c*][2,1]benzothiazines **567** (Scheme 167).



Scheme 167.

8. Conclusions

In summary, this review has presented the recent progress in the synthesis of acyclic and heterocyclic compounds based on the intermolecular and intramolecular aza-Wittig reactions of phosphazenes with several carbonyl or analogous substituents. These results indicate the importance and utility of these phosphazenes as versatile building blocks, not only in the preparation of acyclic compounds, but also for heterocycle construction, ranging from simple monocyclic compounds to complex polycyclic and macrocyclic systems. In many cases, the synthesis is carried out stereoselectively and the resulting compounds are physiologically active or are potential intermediates in the synthesis of physiologically active compounds including analogues of natural products.

Acknowledgements

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Biographical sketch

Francisco Palacios was born in Vitoria, Spain (1951). He graduated in Chemistry in the University of Zaragoza and he received his Ph.D. degree in the University of Oviedo in 1977 under the supervision of Prof. José Barluenga. After two years (1979–1981) of postdoctoral work with Prof. Dr. Rolf Huisgen in the Organic Chemistry Institute of the Ludwig University (Munich, Germany) working on Cycloaddition Reactions, he came back to the University of Oviedo as Assistant Professor and became Associate Professor in 1983 in the same University. Since 1991 he has been full Professor of Organic Chemistry in the University of the Basque Country. He has held Visiting Professorships at the Ecole Nationale Superière de Chimie of Montpellier (France, 2003) and at the Department of Chemistry of the University of Coimbra (Portugal, 2005, 2006). His research interests are organic synthesis, organophosphorus chemistry (phosphazenes, phosphorus ylides, phosphine oxides, aminophosphonates), heterocyclic chemistry, cycloaddition reactions (azadienes and 1,3-dipoles) and solid-phase synthesis.

Domitilla Aparicio was born in Palencia, Spain, in 1945. She graduated in Chemistry in 1971 and she received her Ph.D. degree in Chemistry at the University of Valladolid in 1978 under the supervision of Prof. Angel Alberola and Prof. Felisa Alonso. She came to the University of Valladolid in Vitoria as Assistant Professor in 1972. Since 1988 she has been Titular Professor at the University of the Basque Country. Her current research interest is focused in organic synthesis, and the chemistry of nitrogen and phosphorus containing compounds for the preparation of acyclic and cyclic compounds.

Concepción Alonso was born in Vitoria-Gasteiz, Spain, in 1968. She had received her B.Sc. degree in Chemistry from the University of Valladolid in 1991, and Ph.D. degrees in Chemistry from the University of Basque Country in 1998, the latter under the supervision of Prof. Francisco Palacios. She stayed at the University of California at Davis as a postdoctoral fellow under the supervision of Prof. Mark J. Kurth during two years. After her return to Spain she has been working as a postdoctoral fellow and as research associate with Prof. Francisco Palacios at the University of Basque Country. Her current research interest is focused in the development of new reactions and methods for the synthesis of small organophosphorus molecules by solid-phase and combinatorial chemistry.

Gloria Rubiales was born in 1955 in Aranda de Duero (Burgos, Spain). She graduated in Chemistry from the University of Valladolid and she received her Ph.D. degree in Chemistry from the University of the Basque Country in 1991 under the supervision of Prof. Claudio Palomo and Prof. Fernando Cossío. She has worked at the University of the Basque Country as Assistant Professor since 1984 and she became Associate Professor in 1987. Since 1995 she was appointed as a Professor in Organic Chemistry at the same University. Her current research interest is focused in the development of new methodology in organic synthesis of phosphorus- and nitrogen-containing compounds for the preparation of heterocyclic compounds.

Jesús M. de los Santos was born in 1966 in Mondragón (Guipúzcoa, Spain). He graduated in Chemistry from the University of the Basque Country in 1990 and received his Ph.D. degree in 1996 under the supervision of Prof. F. Palacios. He held a Ph.D. extraordinary award for his dissertation on the chemistry of β-functionalized phosphorus compounds. He then stayed two years at the Penn State University at Pennsylvania (USA) with Prof. Steven M. Weinreb as a postdoctoral fellow working on the total synthesis of marine alkaloids. He returned to the University of the Basque Country as a Junior Scientist in 1997 and then, he was appointed as a Research Associate at the same University in 2003. His current research interest is focused in the development of new synthetic methodology in organic chemistry, which includes the chemistry of nitrogen- and phosphorus-containing compounds for the preparation of acyclic and cyclic compounds, as well as the solid-phase synthesis of small organic molecules.