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Wittig Reactions |*Hot Paper*|

Diazo Strategy for the Synthesis of Pyridazines: Pivotal Impact of the Configuration of the Diazo Precursor on the Process

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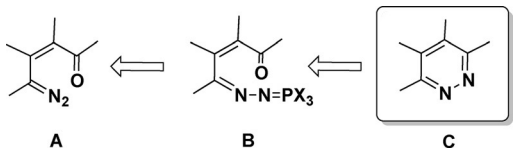
Abstract: Phosphazenes of vinyldiazocarbonyl compounds having *cis* stereochemistry of the functional groups on the vinyl bond readily produce pyridazines by a diaza-Wittig process, whereas their counterparts with *trans* configuration remain intact under similar reaction conditions. Upon UV irradiation *trans*-phosphazenes furnish pyridazines through a tandem *trans*-to-*cis* isomerization followed by intramolecular cyclization. At elevated temperatures *trans*-(triphenyl)-phosphazenes dissociate to give the initial vinyldiazo compounds, which produce pyrazoles in high yields. The first theoretical study on the mechanism of the diaza-Wittig process by DFT calculations at the M06-2X/6-31G(d) level of theory suggest that for the *cis*-phosphazenes a rapid tandem [2+2] cycloaddition/cycloelimination process with low energy barriers is preferred over *trans* isomers.

Introduction

Pyridazine derivatives are very attractive from the pharmaceutical point of view.[1] They have been reported to exhibit a variety of biological features ranging from anticancer and antituberculosis[2] to antibacterial, antimicrobial,[3] and various other kind of biological activities.[4] Some pyridazines are used in the treatment of Parkinson's, Alzheimer's, and other neurodegenerative diseases.[5] Moreover, pyridazine derivatives are currently considered as one of the most developable heterocyclic structures for small-molecule-based drug design.[6] Thus, elaboration of new methods for the preparation of pyridazines is a topical problem in synthetic organic chemistry.

One of the recent strategies adopted for the synthesis of pyridazine derivatives is based on reactions of diazo compounds with phosphines.[7–10] Thus, on reaction of a vinyldiazocarbonyl precursor **A** with a phosphine (PX_3) the corresponding phosphazene **B** is formed by a Staudinger reaction,[11] which proceeds easily and in many cases at room temperature[7b,9a,b,e] and gives rise to pyridazine **C** by intramolecular diaza-Wittig cyclization (Scheme 1).



Scheme 1. Diazo strategy for the synthesis of pyridazines.

In practice, only two types of diazo precursors have been tested thus far in these reactions, namely, vinyldiazocarbonyl compounds **D**[7,9,10a] and diazotricarbonyl compounds **E**[6b,8,10b] (Figure 1). However, it is evident that, in principle, the diazo strategy allows the employment of a range of different diazocarbonyl compounds for the synthesis of pyridazines and thus enables the preparation of a wide variety of pyridazine derivatives. Furthermore, the presence of functional groups in the structure of the resulting pyridazines provides a means for further modification of pyridazine scaffold in a site-selective way.[6b,10] In an effort to scope out the synthetic potential of the diazo approach for the synthesis of new pyridazine architectures, we explored the use of phosphazenes of fluoroalkyl-containing vinyldiazocarbonyl compounds and their nonfluori-

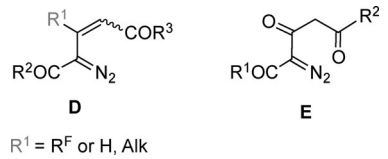


Figure 1. Two types of diazo precursors **D** and **E** used for the synthesis of pyridazines.

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nated counterparts **D** in this process (Figure 1; $R^1 = R^F$, H, alkyl (Alk), etc.).

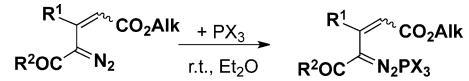
According to the early studies by Guillaume et al.[7b] and others,[9a,b,e] synthesis of 4-fluoroalkyl-substituted pyridazines can be readily accomplished from the appropriate vinyldiazocarbonyl compounds **D** (Figure 1; $R^1 = R^F$) through a tandem Staudinger/diaza-Wittig process. One would expect that, for the preparation of their nonfluorinated analogues in a similar way, the associated vinyldiazocarbonyl compounds **D** with $R^2 = H$, Alk, and so forth (Figure 1) can be simply used as a starting materials. However, synthesis of pyridazines from nonfluorinated vinyldiazocarbonyl compounds by the same scheme failed.[9e]

It was suggested that the main reason for the observed dissimilar reactivity of the fluoroalkyl-containing (**F**) and nonfluorinated (**H**) vinyldiazocarbonyl compounds and their phosphazenes was dictated by the different stereochemistry (*cis* or *trans*) of the functional groups ($AlkO_2C$, CN_2PX_3) around their vinylic double bonds.[9e] (Note that we use the *cis* and *trans* notation for the spatial arrangement of functional groups (CO_2Alk, CN_2) around the vinyl double bond, since application of *Z*,*E* nomenclature implies the same *Z* or *E* symbols for fluoroalkyl-containing and nonfluorinated vinyldiazo substrates with opposite configuration.) To the best of our knowledge, the effect of the stereochemistry of the vinyl double bond of phosphazenes on the outcome of their cyclization into pyridazines has not been considered thus far. In this connection the main goal of our current project was to carry out a detailed study on the reactions of phosphazenes derived from *cis*- and *trans*-vinyldiazocarbonyl compounds and to experimentally and theoretically ascertain the effect of the vinyl double-bond stereochemistry on the diaza-Wittig process.

Results and Discussion

The structures of the starting *trans*- and *cis*-phosphazenes **1** and **2** of vinyldiazo compounds involved in our current research are shown in Figure 2. They differ in the nature of substituents at the C-3 position of the phosphazene ($R^1 = H$, Me, CF_3, Ph) and the nucleophilicity of the phosphine component [PPh_3, $P(NMe_2)_3$] used. The majority of phosphazenes **1** and **2** were prepared by known protocols[9] from the corresponding vinyldiazocarbonyl compounds *trans*-**3** and *cis*-**4**[9a,b,e,12,13] by employing $P(NMe_2)_3$ and PPh_3 as phosphine components in yields of up to 92–94% (Table 1). Several of them (e.g., *cis*-**2f**,**g**,**g**′) were generated in the reaction mixture in the first stage of the process and subjected in situ to the intramolecular Diaza–Wittig reaction without isolation in their pure state.

Table 1. Synthesis of phosphazenes **1** and **2**.



3; *trans*-isomers, **4**; *cis*-isomers — **1**, **2**

Entry	Starting compound	R^1, R^2, Alk	X	Yield of **1** or **2** [%]
1	**3a**	H, OMe, Me	NMe_2	**1a**; 92
2	**3b**	Me, OMe, Me	NMe_2	**1b**; 84
3	**3c**	Me, OEt, Et	NMe_2	**1c**; 72
4	**3d**	Me, Me, Me	NMe_2	**1d**; 91
5	**3e**	CF_3, Me, Me	NMe_2	**1e**; 87
6	**3e**,**4e**[a]	CF_3, Me, Me	NMe_2	**1e**; 47 (94)[b]
7	**4e**	CF_3, Me, Me	NMe_2	**2e**; 71
8	**3a**	H, OMe, Me	Ph	**1a**′; 87
9	**3c**	Me, OEt, Et	Ph	**1c**′; 86
10	**3d**	Me, Me, Me	Ph	**1d**′; 74
11	**3e**	CF_3, Me, Me	Ph	**1e**′; 86
12	**3e**,**4e**[a]	CF_3, Me, Me	Ph	**1e**′; 40 (80)[b]

[a] Mixture of isomers **3e**:**4e** (1:1) used for Staudinger reaction. [b] Yields of **1e** and **1e**′ based on the initial **3e** are shown in parentheses.

In most of the cases, formation of phosphazenes **1a**–**e** (X = NMe_2 or Ph) from the *trans*-vinyldiazo compounds **3a**–**e** and reactions of *cis*-vinyldiazo compounds **4** with $P(NAlk_2)_3$ proceeded rapidly (about 10 min) and irreversibly. At the same time, reactions of *cis*-vinyldiazo compounds **4** with PPh_3 usually occurred at a far slower rate (from 3 to 21 h) than with *trans* isomers **3**. Moreover, the equilibrium in the reactions with triphenylphosphine was in many cases considerably displaced to the starting compounds (as established by ^1H NMR spectra), and this prevented isolation of the pure target phosphazenes **2**.

The structures of all phosphazenes **1** and **2** were confirmed by conventional physicochemical methods. The stereochemistry of the vinylic C=C bond in the structure of the nonfluorinated phosphazene **H-1c**′ and fluoroalkyl-containing phosphazene **F-1e**′ was ascertained by X-ray crystallographic analysis (Figures 3 and 4), and it was found to be the same as for the initial vinyldiazocarbonyl compounds **H-3c**[9e] and **F-3e**.[9a] By analogy with this stereochemical correlation, the configurations of the other phosphazenes **1** and **2** were also surmised to be the same as those of the parent *trans*- and *cis*-vinyldiazocarbonyl compounds **3** and **4**, respectively.[7b,9a,b,d,e,12,13]

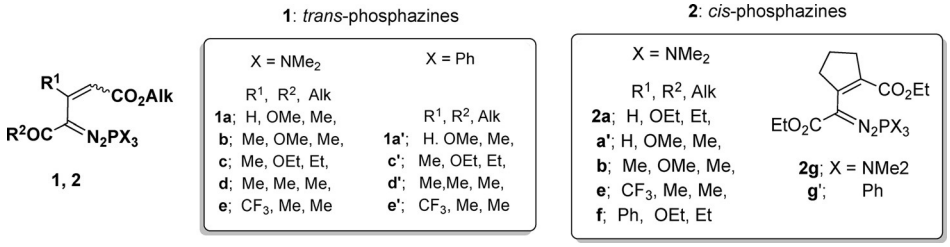


Figure 2. Structures of the initial *trans*- and *cis*-phosphazenes **1** and **2** used in the present work.

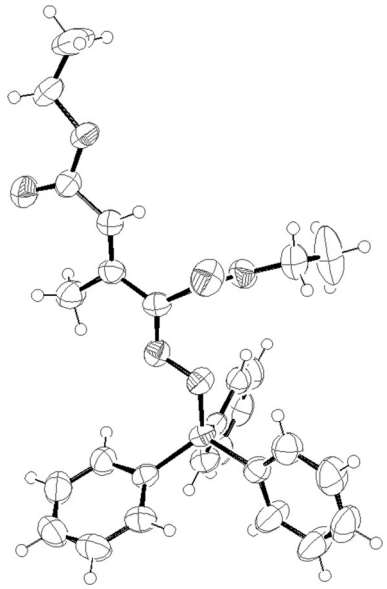


Figure 3. Molecular structure of *trans*-triphenylphosphazene **H-1 c′**. The ellipsoids denote 50% probability.[9e]

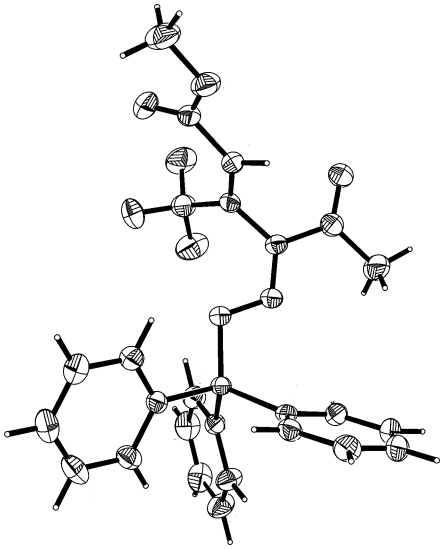


Figure 4. Molecular structure of *trans*-triphenylphosphazene **F-1 e′**. The ellipsoids denote 50% probability.

Thermal reactions of phosphazenes 1 and 2

On heating in benzene solution, *trans*-(triphenyl)phosphazenes **1 a′**,**c′**,**d′** did not give rise to the expected pyridazines **5** but instead produced the associated pyrazoles **6 a**,**c**,**d** in high yields (89–96%, Scheme 2). Evidently, under the reaction conditions studied, pyrazoles **6** were formed by way of dissociation of phosphazenes **1 a′**,**c′**,**d′** in solution to give PPh_3 and starting *trans*-vinyldiazo compounds **3 a**,**c**,**d**, followed by their intramolecular cyclization to pyrazoles **6 a**,**c**,**d** at elevated temperatures.[14a] Thermolysis of *trans*-phosphazene **F-1 e′**, unlike analogues **H-1 a′**,**c′**,**d′**, under the same reaction conditions resulted in the formation of a complex reaction mixture (similar to thermolysis of vinyldiazo ketone **F-3 e**[14b]).

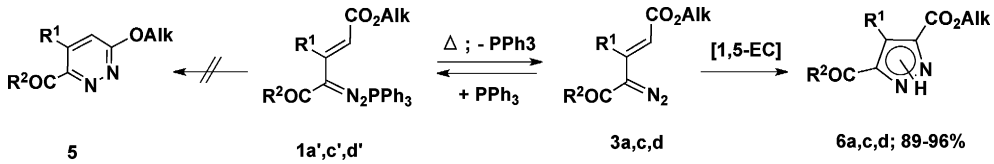
To avoid lability and dissociation of (triphenyl)phosphazenes in the reaction mixture, more stable tris(dimethylamino)phosphazines **1 a**–**d** were prepared by reaction of *trans*-vinyldiazo compounds **3 a**–**d** with more nucleophilic phosphine $P(NMe_2)_3$ instead of PPh_3. However, it turned out that the resulting phosphazenes **1 a**-**d** were extremely inert, and did not undergo the expected intramolecular diaza-Wittig reaction or any other changes even on heating to reflux in benzene solution for 2 d.

The reactions of nonfluorinated *cis*-vinyldiazo compounds **H-4 a**,**f**,**g** with tris(dimethylamino)phosphine or PPh_3 at room temperature or on heating in benzene solution produced directly the corresponding pyridazines **5 a**,**f**,**g** in good to excellent yields (Table 2, entries 1–5) instead of the anticipated phosphazenes **2**. In the case of diethyl *cis*-diazoglutaconate **H-4 a** (Table 2, entry 1) intermediate phosphazene **2 a** was also isolated from the reaction mixture (20%), and it was shown that under the reaction conditions it transforms into pyridazine **5 a** (Table 2, entries 1 and 2).

Interaction of 3-Ph-substituted *cis*-vinyldiazo ester **H-4 f** with $P(NMe_2)_3$ for 2 h furnished 88% of pyridazine **5 f** (Table 2, entry 3). Similar reactions of carbocyclic *cis*-vinyldiazo ester **4 g** with PPh_3 and $P(NMe_2)_3$ produced pyridazine **5 g** in moderate to high yields depending on the nature of phosphine component used (53–89%; Table 2, entries 4 and 5). In the reaction of **H-4 g** with PPh_3, in addition to pyridazine **5 g**, a small amount of the corresponding hydrazone **7 g**, the product of hydrolytic cleavage of the initial phosphazene **2 g′**, was also isolated (Table 2).[15]

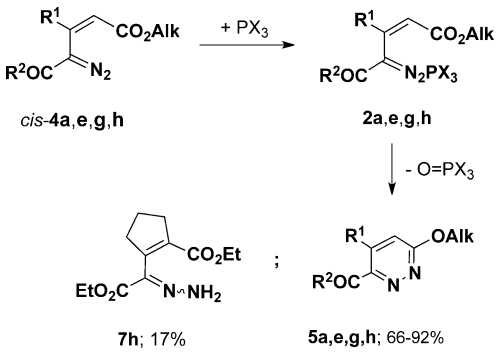
Fluorinated *cis*-vinyldiazo compound **F-4 e** on short-term interaction (for 10 min) with $P(NMe_2)_3$ in Et_2O followed by silica-gel separation of the reaction mixture gave rise to initially formed fluoroalkyl-containing *cis*-phosphazene **2 e** (71%). On storage or heating in benzene solution it produced 4-CF_3-substituted pyridazine **5 e** in good yield (Table 2, entry 6). It is remarkable that (triphenyl)phosphazene **2 e′** was very reactive in the subsequent diaza-Wittig process and underwent spontaneous cyclization to pyridazine **5 e** even at room temperature (Table 2, entry 7; see also Refs. [9a, b]).

To directly compare the reactivity of *trans*- and *cis*-phosphazenes under similar reaction conditions, a mixture of fluorinated *trans*- and *cis*-vinyldiazoketones **F-3 e**:**F-4 e** (1:1) was treated



Scheme 2. Thermolysis of *trans*-phosphazenes **1 a′**,**c′**,**d′** followed by cyclization to pyrazoles **6 a**,**c**,**d.**

Table 2. Reactions of *cis*-vinyldiazo compounds **4** and phosphazenes **2** to produce pyridazines **5**



Entry	Reagent; R^1, R^2, Alk	X	Conditions	Yield of **5** [%]
1	**4a**; H, OEt, Et	NMe_2	RT, 12 h, CH_2Cl_2	**5a**; 78[a]
2	**4a**; H, OEt, Et	NMe_2	80–81 °C, 2 h, CH_3CN	**5a**; 92
3	**4f**; Ph, OEt, Et	NMe_2	80–81 °C, 2 h, CH_3CN	**5f**; 88
4	**4g**; $(CH_2)_3$, OEt, Et	Ph	RT, 5 days, Et_2O	**5g**; 53
5	**4g**; $(CH_2)_3$, OEt, Et	NMe_2	RT, 36 h, CH_3CN	**5g**; 89
6	**2e**; CF_3, Me, Me	NMe_2	80–81 °C, 0.5 h, PhH	**5e**; 66[b]
7	**4e**; CF_3, Me, Me	Ph	RT, 19 h, Et_2O	**5e**; 88
8	**4e**+**3e**[c] -"-	Ph	RT, 19 h, Et_2O	**5e**; 41 (82)[d]
9	**4e**+**3e**[c] -"-	NMe_2	50–60 °C, 2 h, PhH	**5e**; 49[b](98)[d]

[a] Under these conditions (entry 1) phosphazene **2a** was also isolated in 20% yield. [b] Yield of two-stage process via **2e**. [c] Mixture of *cis*-**F-4e** and *trans*-**F-3e** (1:1) was used for this reaction. [d] Yield of **5e** based on the initial *cis*-**F-4e** is shown in parentheses.

with PPh_3 and $P(NMe_2)_3$ (Table 2, entries 8 and 9). In the case of PPh_3, pyridazine **5e** (41%) and *trans*-phosphazene **1e**′ (40%) were isolated after separation of the reaction mixture on silica gel (Table 2, entry 8)

The use of the more nucleophilic tris(dimethylamino)phosphine in this reaction at room temperature furnished a mixture of *trans* and *cis* stereoisomers of phosphazenes **F-1e**, **F-2e** in high overall yield and in the same ratio as the initial *trans*- and *cis*-vinyldiazoketones **F-3e**:**F-4e** (1:1). After subsequent heating of the reaction mixture in benzene solution, pyridazine **5e** and *trans*-phosphazene **1e** were isolated in 49 and 47% yield, respectively (Table 2, entry 9). Thus, under the conditions studied, *trans*-phosphazenes were unreactive in the diaza-Wittig process to produce pyridazines.

The structures of phosphazenes **1e**, **1e**′ and pyridazine **5e** were confirmed by their ^1H and ^{13}C NMR spectra, and the geometry of the *trans* stereoisomer of (triphenyl)phosphazene **1e**′ was also unambiguously established by X-ray crystallographic analysis (Figure 4).

Photochemical isomerization of *trans*-phosphazenes 1a,b,e to *cis* stereoisomers 2a,b,e

Photochemical isomerization of *trans*-phosphazenes **1a,b,e** to *cis* stereoisomers **2a,b,e** was performed to test the assumed stereocontrol of the reaction and to verify that *trans*-phosphazenes are fundamentally suitable for the synthesis of pyridazines by the diaza-Wittig approach.

On short-wavelength UV irradiation of *trans*-phosphazene **H-1a** ($\lambda > 210$ nm, room temperature, 20 h), followed by silica-gel chromatography of the reaction mixture, pyridazine **5a**′ (23%) and a mixture of unconverted phosphazenes *trans*-**1a** and *cis*-**2a**′ (R^2 = OMe, 76%, ≈1:1.6 by ^1H NMR spectroscopy) were isolated. Since at room temperature the second stage of the process (diaza-Wittig reaction) was apparently very slow, which left mostly unconsumed *cis*-phosphazene **2a**′ (R^2 = OMe), the photochemical experiment was repeated at 50–55 °C for 16 h, which resulted in the formation of pyridazine **5a**′ in 56% yield (Table 3, entry 1).

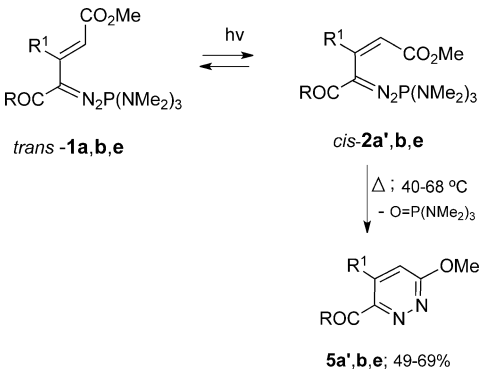
In the case of UV irradiation of *trans*-phosphazene **H-1b** at 254 nm in hexane followed by heating of the reaction mixture under reflux in $CHCl_3$ solution, pyridazine **5b** was isolated in 69% yield along with 29% of the recovered *trans*-phosphazene **1b** (Table 3, entry 2).

Fluoroalkyl-containing *trans*-phosphazene **F-1e** on long-wavelength irradiation (λ = 310–405 nm) also experienced slow isomerization to produce the corresponding *cis*-phosphazene **F-2e**. The initially formed **2e** at elevated temperature furnished 4-CF_3-subsituted pyridazine **5e**, which was isolated in a yield of 47% (Table 3, entries 3 and 4).

Hence, fluorinated and nonfluorinated *trans*-phosphazenes **1** under UV irradiation undergo photochemical isomerization to *cis* isomers **2** followed by thermal intramolecular diaza-Wittig cyclization to produce pyridazines **5**. This provides a means for employing *trans* isomers for the synthesis of pyridazines by the diaza-Wittig route.

The experimental results allow us to conclude that formation of pyridazines **5** from *cis*-vinyldiazocarbonyl compounds **4**

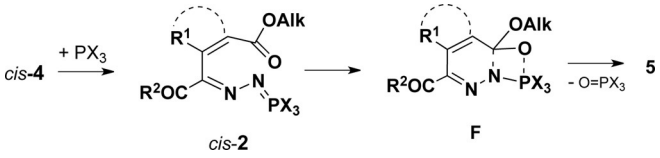
Table 3. Photochemical isomerization of *trans*-**1** to *cis*-**2** phosphazenes followed by diaza-Wittig reaction.



Entry	Phosphazene; R^1, R^2	Reaction conditions	Yield of **5** [%]
1	**1a**; H, OMe	$\lambda > 210$ nm, *t*BuOMe, 50–55 °C, 16 h	**5a**′; 56
2	**1b**; Me, OMe	λ = 254 nm, hexane, 72 h; $CHCl_3$, reflux	**5b**; 69 (97)[a]
3	**1e**; CF_3, Me	$\lambda > 310$ nm, Et_2O, reflux, 2 h	**5e**; 7 (15)[a]
4	**1e**; CF_3, Me	λ = 395–405 nm, benzene,40 °C, 70 h	**5e**; 47

[a] Yields of pyridazine **5** calculated with respect to the initial phosphazene are shown in brackets.

occurs as a tandem process, which involves the initial formation of *cis*-vinylphosphazenes **2** followed by intramolecular diaza-Wittig cyclization of these intermediates to produce pyridazines **5** and elimination of the corresponding phosphine oxide (Scheme 3). The facile nature of this process with vinyldiazocarbonyl compounds **4** is clearly related to and assisted by the *cis* configuration of the vinyldiazo compounds and the related phosphazenes **2**, since *cis* stereochemistry strongly favors the formation transition state **F** (Scheme 3), which is typical of the Wittig reaction.[16]



Scheme 3. General Scheme of diaza-Wittig reaction with *cis*-phosphazenes **2** to produce pyridazines **5**.

The high reactivity of the *cis*-vinylphosphazenes **2** towards intramolecular diaza-Wittig cyclization was rationalized by DFT calculations at the M06-2X/6-31G(d) level of theory,[17] and cyclization of **2a′** (Alk = Me) to give pyridazine **5a′** was initially selected as a model reaction (Figure 5).[18] Thus, stationary points corresponding to a tandem [2+2] cycloaddition/cycloelimination could be located and characterized. This mechanism is in close analogy with that of the aza-Wittig reaction between phosphazenes and aldehydes, which has been previously analyzed by DFT methods.[19]

According to our calculations, an initial [2+2] cycloaddition of the phosphazene moiety to the carbonyl group takes place, giving the cyclic oxazaphosphetane intermediate $\mathbf{INT}_{\mathbf{2a'\rightarrow 5a'}}$ (Figures 5 and 7). Then, a cycloelimination releases the phosphine oxide and the desired pyridazine **5a′** is formed. The process is highly exothermic (−42.4 kcal mol^{-1}). Furthermore, the relative energies of the transition states for the [2+2] cycloaddition and reversion are +10.4 and +10.5 kcal mol^{-1}, respectively (Figure 5). Notably, these relatively low energy barriers are in agreement with the experimental results, as they explain the rapid diaza-Wittig cyclization observed in most of the cases with *cis*-phosphazenes **2**.

Next we turned our attention to the *cis*-vinylphosphazene **2e′** (Alk = Me, R^2 = OMe), which contains a CF_3 group on the C-3 atom. We expected that the presence of such a strongly electron withdrawing group could have some influence on the calculated energy barriers or even on the properties of the calcu-

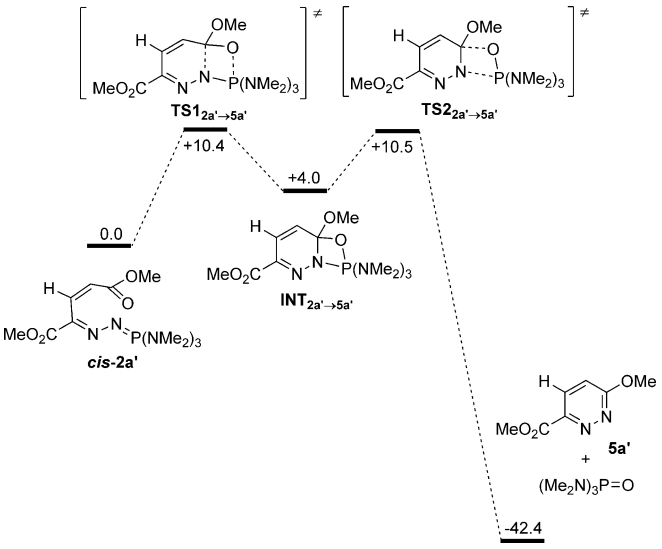


Figure 5. Energy profile [kcal mol^{-1}] for the diaza-Wittig cyclization of *cis*-**2a′** calculated at the M06-2X/6-31G(d) level of theory.

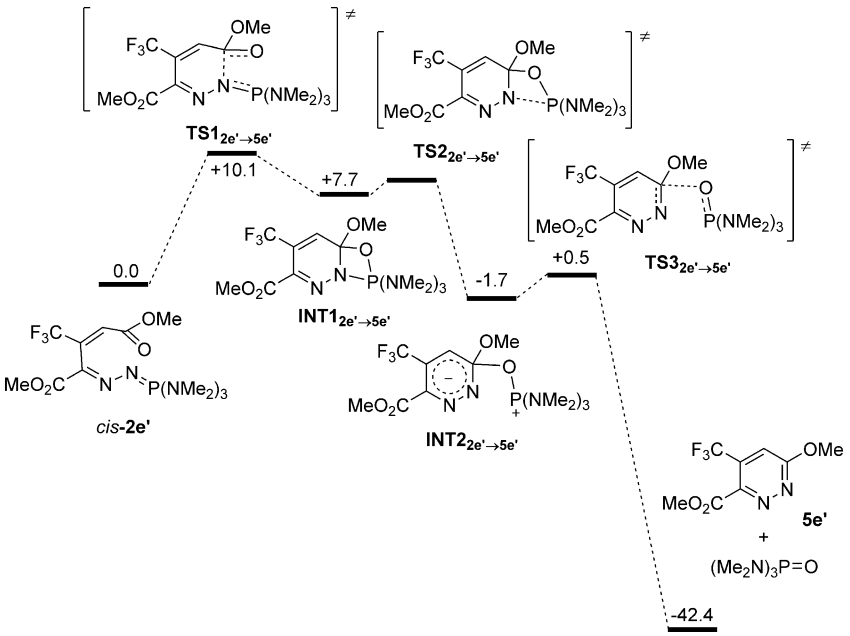


Figure 6. Energy profile [kcal mol^{-1}] for the diaza-Wittig cyclization of *cis*-**2e′**, calculated at the M06-2X/6-31G(d) level of theory.

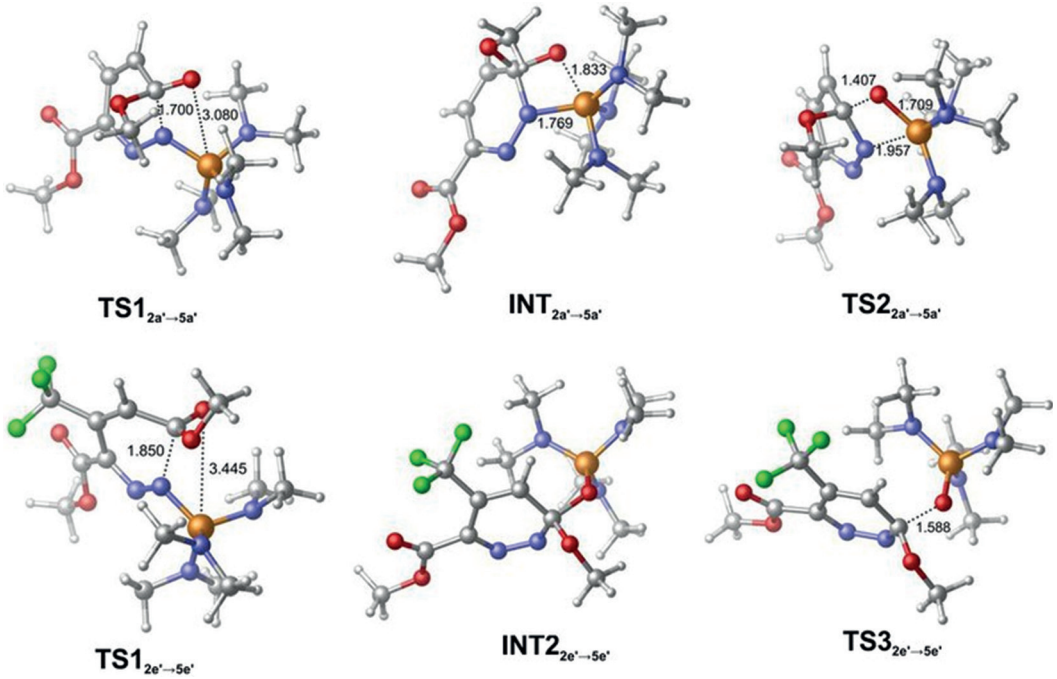


Figure 7. Key stationary points located for the diaza-Wittig cyclizations of *cis*-**H**-**2 a′** (top) and *cis*-**F**-**2 e′** (bottom).

lated stationary points. Surprisingly, the theoretical calculations revealed a different energy profile for this transformation (Figure 6). The initial transition state (**TS1**$_{2e'\rightarrow5e'}$) was found to be highly asynchronous, with a very long P–O distance of 3.44 Å (Figure 7). After the oxazaphosphetane **INT1**$_{2e'\rightarrow5e'}$ a new open intermediate was located (**INT2**$_{2e'\rightarrow5e'}$), in which the N–P bond is broken (see Figure 6 and Figure 7). In this step, 9.4 kcal mol^{-1} of energy is released, probably due to the ring strain in the oxazaphosphetane structure and stabilization of the negative charge on the ring by the electron-withdrawing CF_3 group. Unfortunately, the saddle point (**TS2**$_{2e'\rightarrow5e'}$) for this ring opening could not be located, and all attempts at geometry optimization led to the structure of **INT2**$_{2e'\rightarrow5e'}$.

We believe that this ring-opening process must have a very low or negligible energy barrier. Release of the phosphine oxide from **INT2**$_{2e'\rightarrow5e'}$ is very fast. In this case the corresponding transition structure could be located (**TS3**$_{2e'\rightarrow5e'}$), and the calculated barrier with respect to the intermediate was only +2.2 kcal mol^{-1} (Figure 6). The overall energy barrier for this process is +10.1 kcal mol^{-1}, and therefore analogous to that calculated for the Diaza–Wittig reaction of *cis*-**2 a**. Apparently the presence of the electron-withdrawing group does not affect significantly the reactivity of the starting *cis*-vinylphosphazene. However, according to the calculations, it does influence the actual mechanism of the reaction by stabilizing a new open intermediate **INT2**$_{2e'\rightarrow5e'}$. Although the mechanism of the aza-Wittig reaction of phosphazenes with aldehydes has been previously assessed by DFT calculations,[19] to the best of our knowledge this is the first theoretical study on the mechanism of the diaza-Wittig process.

In the case of *trans*-phosphazenes **1** derived from vinyldiazocarbonyl compounds **3**, *trans* alignment of the functional groups CO_2Alk with respect to CN_2PX_3 prevents the required approach of C=O and P=N groups involved in the ring-formation process. Therefore, formation of the transition state of type **F** becomes essentially impossible, and intramolecular diaza-Wittig cyclization with *trans*-phosphazenes **1** is not realized. Moreover, DFT calculations revealed that the thermal *trans*–*cis* isomerization of compounds **1** to **2** is not possible under the present experimental conditions. Compounds *trans*-**1 a** and *trans*-**1 e** were selected as models for this study. As expected, calculation of the transition states for the hypothetical thermal *trans*–*cis* isomerizations resulted in very high energy barriers (+52.3 and 48.9 kcal mol^{-1} for **1 a** and **1 e**, respectively), and this type of process can therefore be ruled out. Gratifyingly, UV irradiation of *trans*-phosphazenes resulted in photochemical isomerization of *trans*-to *cis*-hosphazenes, which are reactive and ultimately led to the conversion of *trans*-**1** compounds to the desired pyridazines **5**.

Conclusion

The observed difference in the reactivity of *cis*- and *trans*-phosphazenes towards diaza-Wittig reactions is caused by the different location of the functional groups ($AlkO_2C$, CN_2PX_3) around their vinylic C=C bonds: phosphazenes with *cis* configuration readily undergo the diaza-Wittig reaction producing the corresponding pyridazines, whereas their counterparts with *trans* stereochemistry remain intact under similar reaction conditions. Nevertheless, on UV irradiation of *trans*-phosphazenes, photochemical *trans*-to-*cis* isomerization occurs followed by intramolecular diaza-Wittig cyclization to form pyridazines. Hence, in principle, both vinyldiazocarbonyl stereoisomers can be used for the synthesis of 3,4,6-trisubstituted pyri-

dazines. DFT calculations at the M06-2X/6-31G(d) level of theory suggest a rapid tandem [2+2] cycloaddition/cycloelimination process for the *cis*-phosphazenes with low energy barriers. The presence of a strongly electron withdrawing group such as CF_3 on the C-3 atom of the starting phosphazene results in a more complex reaction pathway in which a stabilized ring-opened intermediate is possible. At the same time, when heated to 80 °C or above, *trans*-(triphenyl)substituted phosphazenes dissociate to give the initial *trans*-vinyldiazo compounds followed by their 1,5-electrocylization to pyrazoles.

Experimental Section

General methods

NMR spectra were recorded at 200, 300, and 600 MHz (^{1}H), 50, 75, and 150 MHz (^{13}C), 188 282 MHz (^{19}F), and 81 MHz (^{31}P) in $CDCl_3$ solution with TMS, $CHCl_3$, or H_3PO_4 as internal standard. A single crystal of **F-1e′** suitable for X-ray diffraction was selected from an analytically purified sample. Crystallographic measurements were made with an IPDS1 diffractometer [graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å)]. The structure was solved by direct methods by using the program SIR2002[20] and was refined by anisotropic approximation for the non-hydrogen atoms with SHELX-90 software.[21] All hydrogen atoms were calculated and refined in riding modus. CCDC 788805 (**F-1e′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

All reactions were carried out in carefully purified and dried solvents and were monitored by TLC with UV light and iodine as visualizing agents. Preparative column chromatography was carried out with neutral silica gel (70–230 mesh) and petroleum (40–70 °C) and diethyl ether as eluents in gradient regime. The yields determined by ^{1}H NMR spectroscopy are given in brackets; $(CHCl_2)_2$ was used as the internal standard. Starting vinyldiazocarbonyl compounds **3** and **4** were prepared by two known approaches:[12] 1) formation of the 2-vinylcarbonyl motif followed by diazo transfer to the methylene group of this compound (**3a–e**, **4f,g**; yields: 16–85%); 2) synthesis of a diazodicarbonyl compound accompanied by olefination of one of the carbonyl groups by the Wittig reaction or with the help of the other reaction manifolds (**3f**, **4a,e,f**; yields: 3–69%). Photochemical reactions were carried out by irradiation of phosphazenes **1a**,**b**,**e** at 40–68 °C with a medium-pressure mercury lamp (100–130 W) in a 25 mL reactor equipped with a quartz or Pyrex jacket ($\lambda > 210$ or 310 nm without any monochromatization; phosphazenes **H-1a**, **F-1e**), with monochromatic light ($\lambda = 254$ nm; phosphazene **H-1b**), or with a UV LED spotlight (395–405 nm; phosphazene **F-1e**).

Computational details

All calculations were carried out with the Gaussian 09 package.[22] The M06-2X density functional method[17] in conjunction with the 6-31G(d) basis set was selected for all the geometry optimizations and frequency analysis. The geometries were optimized with inclusion of solvation effects. For this purpose, the SMD solvation method[23] was employed. Photochemical isomerization of *trans*-phosphazene **1a** into the *cis* isomer **2a′** followed by cyclization was carried out in *t*BuOMe. Because this solvent is not internally stored in the Gaussian solvent list, diisopropyl ether was selected as solvent for all calculations because of their analogous properties. Frequency calculations at 298.15 K on all stationary points were carried out at the same level of theory as the geometry optimizations to ascertain the nature of the stationary points. Ground and transition states were characterized by none and one imaginary frequency, respectively. All of the presented relative energies are free energies at 298.15 K.

Synthesis of *trans*-phosphazenes 1a–d from vinyldiazo compounds 3a–d and $P(NMe_2)_3$

Tris(dimethylamino)phosphine (2.7 mmol) was added dropwise to a solution of diazo compound **3a–d** (2.7 mmol) in 10 mL of Et_2O, whereupon the reaction mixture took on a bright yellow color. The mixture was stirred for 10 min until the reaction was complete (by TLC), applied to 2.5 g of silica gel, transferred to a short column with 6 g of silica gel, and eluted with ethyl acetate (ca. 30 mL). The obtained eluate was dried with $MgSO_4$ and, after removing the solvents, the residue was recrystallized from Et_2O to provide phosphazenes **1a–d**.

Dimethyl ester of *trans*-4-[tris(dimethylamino)phosphoranylidene]azinopent-2-endioic acid (1a): Yield: 862 mg (92%), orange solid (Et_2O), m.p. 84–85 °C; $R_f = 0.34$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.73$ (d, $^3J(H,P) = 9.5$ Hz, 18H; CH_3), 3.74 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 7.34 (d, $^3J(H,H) = 16.0$ Hz, 1H; C^2H), 7.93 ppm (d, $^3J(H,H) = 16.0$ Hz, 1H; C^3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 37.7$ (6× CH_3), 51.6, 51.7 (2×$COOCH_3$), 118.0 (C^2), 130.2 (C^3), 137.1 (d, $^3J(C,P) = 43.8$ Hz; C=N), 167.3, 170.8 ppm (2×$COOCH_3$); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 234$ nm (3.17), 358 nm (3.39); UV (CH_3CN): λ^{max} ($\lg\varepsilon$) = 229 nm (3.41), 357 nm (3.37); elemental analysis calcd (%) for $C_{13}H_{26}N_5O_4P$: C 45.0, H 7.5, N 20.1; found: C 45.17, 45.12, H 7.61, 7.66, N 19.61, 19.62.

Dimethyl ester of *trans*-3-Me-[tris(dimethylamino)phosphoranylidene]azinopent-2-endioic acid (1b): Yield: 819 mg (84%), orange oil, $R_f = 0.35$ (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (d, $^4J(H,H) = 1.0$ Hz, 3H; CH_3), 2.67 (d, $^3J(H,P) = 9.0$ Hz, 18H; CH_3), 3.67 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 5.52 ppm (q, $^4J(H,H) = 1.0$ Hz, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (Me), 37.2 (d, $^2J(C,P) = 2.2$ Hz, NMe), 51.2, 50.6 (2×OMe), 112.5 (C^3), 147.6 (d, $^3J(C,P) = 47.1$ Hz, C=N), 150.9 (C^2), 167.8, 169.1 ppm (2×COOMe); ^{31}P NMR (160 MHz, $CDCl_3$): $\delta = 38.76$; IR (KBr): $\tilde{\nu} = 1726$, 1709 (CO), 1597 cm^{-1} (P=N); HRMS (ESI-LCQ) calcd for $C_{14}H_{29}N_5O_4P$ $[M+H]^+$: 362.1952; found: 362.1955.

Diethyl ester of *trans*-3-methyl-4-[tris(dimethylamino)phosphoranylidene]azinopent-2-endioic acid (1c): Yield: 757 mg (72%), orange oil, $R_f = 0.24$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 7.3$ Hz, 3H; CH_3), 1.33 (t, $J = 7.3$ Hz, 3H; CH_3), 2.39 (s, 3H; CH_3), 2.68 (d, $^3J(H,P) = 8.7$ Hz, 18H; CH_3), 4.13 (q, $J = 7.3$ Hz, 2H; CH_2), 4.32 (q, $J = 7.3$ Hz, 2H; CH_2), 5.56 ppm (s, 1H; CH=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 14.8 (CH_2CH_3), 37.7 (CH_3), 59.7, 60.6 (2× CH_2CH_3), 113.8 (CH=), 148.5 ($^3J(C,P) = 46.9$ Hz; C=N), 151.1 (C^3), 168.0, 169.1 ppm (CO_2Et); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 39.70$; IR (KBr): $\nu = 1597$ (CN), 1701 (CO), 1726 cm^{-1} (CO); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 336$ nm (4.30); MS (EI, 70 eV): *m/z*: 389.4 $[M^+]$; HRMS (ESI-LCQ) calcd for $C_{16}H_{32}N_5O_4P$ $[M+H]^+$: 389.2192; found: 389.2194.

Methyl ester of *trans*-3-methyl-5-oxo-4-[tris(dimethylamino)-phosphoranylidene]azinohex-2-enoic acid (1d): Yield: 850 mg (91%), yellow solid, m.p. 57–58 °C (Et_2O); $R_f = 0.11$ (EtOAc); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 212$ nm (4.01), 318 nm (4.24); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.29$ (d, $^4J(H,H) = 1.5$ Hz, 3H; CH_3), 2.33 (s, 3H; CH_3), 2.72 (d, $^3J(H,P) = 8.7$ Hz, 18H; CH_3), 3.67 (s, 3H; OCH_3), 5.68 ppm (d, $^3J(H,H) = 1.5$ Hz, 1H; C_2H=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.5$, 25.6 (2×CH_3), 37.7 (6×NCH_3), 51.1 ($COOCH_3$), 119.8 (C_2H=), 153.8 (C^3), 153.91 (d, $^3J(C,P) = 44.8$ Hz, C=N), 167.7 ($COOCH_3$), 192.6 ppm

($COCH_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 39.88$; IR (KBr): $\tilde{\nu} = 1626$ (CN), 1649 (CO), 1713 cm^{-1} (CO); elemental analysis calcd (%) for $C_{14}H_{28}N_5O_3P$: C 48.7, H 8.1, N 20.3; found: C 48.61, 48.54, H 8.03, 8.00, N 20.22, 20.19.

Synthesis of *trans*-phosphazenes 1 a′,c′,d′ by reactions of vinyldiazo compounds 3 a′,c′,d′ with PPh_3.

trans-Diazo compound **3 a**,**c**,**d** (1 mmol) was added to a solution of triphenylphosphine (1 mmol) in of Et_2O (≈3 mL) without immediate visible changes in the reaction mixture. After 3–21 h away from light and air at room temperature, a precipitate was separated by filtration, washed with benzene (2×1 mL), and dried under vacuum in a desiccator at 10–15 mm Hg to furnish phosphazenes **1 a′**,**c′**,**d′**. Phosphazenes **1 c′**,**d′** in $CDCl_3$ solution are slowly hydrolyzed (evidently by protic-acid catalysis), and in the ^1H NMR spectra of these compounds the signals of the hydrazone impurities appear with time (at room temperature in 2–3 d).

Dimethyl ester of *trans*-4-(triphenylphosphoranylidene)azinopent-2-endioic acid (1 a′): Yield: 388 mg (87%), yellow solid, m.p. 108–109 °C (Et_2O); $R_f = 0.16$ (petroleum ether/EtOAc 3:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.76$ (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 7.42–7.74 (m, 16H; 3×C_6H_5, C_2H=), 8.12 ppm (d, ^3J(H,H) = 16.0 Hz, 1H, C^3H=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 51.8$, 51.9 ($COOCH_3$), 119.9 (C^2), 127.1 (d, ^1J(C,P) = 93.8 Hz; *i*-C-arom.), 129.3 (d, ^3J(C,P) = 10.9 Hz; *m*-C-arom.), 130.1 (C^3), 133.2 (*p*-C-arom.), 134.1 (d, ^2J(C,P) = 8.9 Hz; *o*-C-arom.), 141.0 (d, ^3J(C,P) = 41.9 Hz; C=N), 166.7, 170.4 ppm ($COOCH_3$); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 219$ nm (3.53), 359 nm (3.33); UV (CH_3CN): $\lambda^{max}(\lg\varepsilon) = 223$ nm (3.90), 355 nm (3.73); elemental analysis calcd (%) for $C_{25}H_{23}N_2O_4P$: C 67.3, H 5.2, N 6.3; found: C 67.21, 67.37, H 5.11, 5.17, N 6.33, 6.61.

Diethyl ester of *trans*-3-methyl-4-(triphenylphosphoranylidene)azinopent-2-endioic acid (1 c′): Yield: 420 mg (86%), yellow solid, m.p. 145–146 °C (Et_2O); $R_f = 0.21$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.3$ Hz, 3H; CH_3), 1.34 (t, $J = 7.3$ Hz, 3H, CH_3), 2.31 (s, 3H; CH_3), 4.14 (q, $J = 7.3$ Hz, 2H; CH_2), 4.32 (q, $J = 7.3$ Hz, 2H; CH_3), 5.66 (s, 1H; CH=), 7.45–7.72 ppm (m, 15H; 3×C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (2×CH_3), 14.8, 14.9 (2×CH_2CH_3), 59.8, 60.9 (2×CH_2CH_3), 115.21 (C_2H=), 128.6 (d, ^1J(C,P) = 93.8 Hz; *i*-C-arom.), 129.0 (d, ^3J(C,P) = 12.0 Hz; *m*-C-arom.), 150.7 (C^3), 132.7 (*p*-C-arom.), 133.8 (d, ^2J(C,P) = 8.0 Hz; *o*-C-arom.), 151.7 (d, ^3J(C,P) = 45.9 Hz; C=N), 167.8, 168.8 ppm (2×CO_2Et); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 20.17$ ppm; IR (KBr): $\tilde{\nu} = 1606$ (CN), 1701 (CO), 1724 cm^{-1} (CO); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 209$ (4.08), 221 (4.05), 345 nm (3.97); elemental analysis calcd (%) for $C_{28}H_{29}N_2O_4P$: C 68.9, H 5.98, N 5.73; found: C 68.88, H 5.99, N 5.73.

Methyl ester of *trans*-3-methyl-5-oxo-4-(triphenylphosphoranylidene)azinohex-2-enoic acid (1 d′): Yield: 329 mg (74%), pale-yellow solid, m.p. 122 °C (Et_2O); $R_f = 0.17$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.19$ (s, 3H; CH_3), 2.34 (d, $J = 1.45$ Hz, 3H; CH_3), 3.71 (s, 3H; OMe), 5.81 (d, $J = 1.45$ Hz, 1H; CH=), 7.49–7.71 ppm (m, 15H; 3×C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$, 25.8 (2×CH_3), 51.2 ($COOCH_3$), 120.3 (CH=), 127.74 (d, ^1J(C,P) = 93.8 Hz; *i*-C-arom.), 129.2 (d, ^3J(C,P) = 12.0 Hz; *m*-C-arom.), 132.4 (d, ^2J(C,P) = 9.5 Hz; o-C-arom.), 133.1 (*p*-C-arom.), 153.7 (C^3), 156.6 (d, ^3J(C,P) = 42.0 Hz; C=N), 167.6 ($COOCH_3$), 196.7 ppm ($COCH_3$); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta = 21.32$ ppm; IR (KBr): $\tilde{\nu} = 1648$ (CO), 1714 cm^{-1} (CO); UV (EtOH): $\lambda^{max}(\lg\varepsilon) = 209$ (4.37), 220 (4.41), 223 (4.39), 274 (3.95), 326 nm (4.27); elemental analysis calcd (%) for $C_{26}H_{25}N_2O_3P$: C 70.27, H 5.6, N 6.3; found: C 70.23, 70.40, H 5.69, 5.78, N 6.34, 6.27.

Attempts to carry out diaza-Wittig cyclization with *trans*-phosphazenes 1 a′,c′,d′,e′, and 1 a–d

A solution of (triphenyl)phosphazene **1 a′**,**c′**,**d′**,**e′** (0.4 mmol) in absolute benzene (≈3 mL) was heated at 75–80 °C for 1–2 h until the initial phosphazene disappeared (by TLC). The precipitate formed after cooling was separated by filtration, washed with hexane, and dried in air to give pyrazole **7 a** (230 mg, 89%),[14a] **7 c** (266 mg, 96%),[14a] **7 d** (245 mg, 96%).[14a] *trans*-Phosphazene **F-1 e′**, on being heated under similar reaction conditions, gave a complex reaction mixture.[14b] Attempts to carry out the same reaction with tris(dimethylamino)phosphazenes **1 a**–**d** failed. After heating benzene solutions of these phosphazenes to reflux for 30 h, no changes in the reaction mixtures were observed (by TLC and ^1H NMR spectroscopy).

Tandem process for the synthesis of pyridazines 5 by reactions with $P(NMe_2)_3$

Tris(dimethylamino)phosphine (0.32 g, 2 mmol) was added dropwise to a solution of *cis*-vinyldiazoacetate **4 a**,**f**,**g** (2 mmol) in 5 mL of absolute CH_2Cl_2 (**4 a**), CH_3CN (**4 a**,**f**), or Et_2O (**4 g**). The addition was accompanied by exothermic process, and the reaction mixture was stirred at room temperature for 12 h (**4 a**), at 80–81 °C for 2 h (**4 a**,**f**), or 36 h (**4 g**) until the reaction was complete (monitoring by TLC and ^1H NMR or ^{31}P NMR spectra). After removal of the solvent the residue was subjected to flash chromatography (10 g of SiO_2, eluents: hexane and Et_2O in gradient regime) to furnish pyridazines **5 a**,**f**,**g**.

6-Ethoxy-3-ethoxycarbonylpyridazine (5 a): Yield (in CH_3CN): 361 mg (92%), colorless solid, m.p. 80–81 °C (hexane), $R_f = 0.49$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (t, $J = 7.4$ Hz, 3H; CH_3), 1.47 (t, $J = 7.0$ Hz, 3H; CH_3), 4.48 (q, $J = 7.4$ Hz, 2H; CH_2), 4.67 (q, $J = 7.0$ Hz, 2H; CH_2), 7.00 (d, ^3J(H,H) = 9.4 Hz, 1H; C^5H), 8.05 ppm (d, ^3J(H,H) = 9.4 Hz, 1H; C^4H); ^{13}C NMR (100 MHz, $CDCl_3$ $\delta = 14.2$, 14.4 (2×CH_2CH_3), 62.1, 64.2 (2×CH_2CH_3), 117.0 (C^5), 130.1 (C^4), 147.7 (C^3), 164.1 (C^6), 165.8 ppm (CO_2Et); IR (KBr): $\tilde{\nu} = 3065$ (CH δ), 1716 (CO), 1581, 1445 cm^{-1} (ring, γ); HRMS (ESI-GCT) calcd for $C_9H_{12}N_2O_3$ $[M+H]^+$: 197.0926; found: 197.0930.

6-Ethoxy-3-ethoxycarbonyl-4-phenylpyridazine (5 f): Yield: 480 mg (88%). Colorless solid, m.p. 67–69 °C (Et_2O), $R_f = 0.12$ (hexane/Et_2O 2:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.15$ (t, ^3J(H,H) = 7.3 Hz, 3H; OCH_2CH_3), 1.45 (t, ^3J(H,H) = 7.0 Hz, 3H; OCH_2CH_3), 4.25 (q, ^3J(H,H) = 7.3 Hz, 2H; OCH_2CH_3), 4.66 (q, ^3J(H,H) = 7.0 Hz, 2H; OCH_2CH_3), 6.91 (s, 1H; CH=), 7.34–7.31 (m, 2H; *o*-H-arom.), 7.43–7.42 ppm (m, 3H, *m*,*p*-H-arom.); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.3$, 14.0 (CH_2CH_3), 61.4, 63.5 (CH_2CH_3), 116.3 (CH=), 127.4 (*o*-C-arom.), 128.2 (*m*-C-arom.), 128.8 (*p*-C-arom.), 134.9 (*i*-C-arom.), 142.3 (C^3), 148.7 (C^6), 164.9 ppm (CO_2Et); IR (neat): $\tilde{\nu} = 1734$ (CO_2Et), 1590, 1497 cm^{-1} (Ph); HRMS (ESI-GCT) calcd for $C_{15}H_{16}N_2O_3$ $[M+H]^+$: 273.1239, found: 273.1239.

6-Ethoxy-3-ethoxycarbonyl-4,5-propanopyridazine (5 g): Yield: 420 mg (89%), colorless solid, m.p. 139–140 °C (Et_2O); $R_f = 0.33$ (hexane/EtOAc 1:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.45$ (t, $J = 7.3$ Hz, 3H; CH_3), 1.47 (t, $J = 6.5$ Hz, 3H; CH_3), 2.22–2.12 (m, 2H; CH_2), 2.93–2.88 (m, 2H; CH_2), 3.34–3.28 (m, 2H; CH_2), 4.46 (q, $J = 7.3$ Hz, 2H; CH_2), 4.69 ppm (q, $J = 6.5$ Hz, 2H; CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 14.3 (2×CH_2CH_3), 23.2, 28.6, 33.1 ($CH_2CH_2CH_2$), 61.3, 63.4 (2×CH_2CH_3), 133.5 (C=CCOEt), 145.2 (CCO_2Et), 149.0 (C=CCO_2Et), 163.6 (COEt), 164.9 ppm (CO_2Et); elemental analysis calcd (%) for $C_{12}H_{16}N_2O_3$: C 61.02, H 6.78, N 11.86; found: C 61.12, 61.03, H 6.83, 6.93, N 11.93, 11.93.

Tandem process for the synthesis of pyridazines 5 by reactions with PPh_3

PPh_3 (61 mg, 0.23 mmol) was added portionwise to a solution of *cis*-vinyldiazoketone **F-4e** (55 mg, 0.23 mmol) in Et_2O (7 mL). The solution was stirred for 19 h and then reaction mixture was separated by flash chromatography (7 g of SiO_2, eluent: petroleum ether/EtOAc, 2:1, 50 mL) to give 107 mg (88%) of pyridazine **5e**.

6-Methoxy-3-methylcarbonyl-4-(trifluoromethyl)pyridazine 5e: Yield: 62 mg (66%), colorless solid, m.p. 56–58°C.[9a]

Methyl ester of *cis*-5-oxo-4-[tris(dimethylamino)phosphoranylidene]azino-3-trifluoromethylhex-2-enoic acid (2e): Yield: 120 mg (71%), dark green oil, $R_f = 0.38$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H; CH_3), 2.71 (d, $^3J(H,P) = 9.3$ Hz, 18H; CH_3), 3.63 (s, 3H, OCH_3), 6.52 ppm (s, 1H; CH=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$ (CH_3), 37.5 (6×NCH_3), 51.8 ($COOCH_3$), 122.7 (q, $^1J(C,F) = 276.3$ Hz; CF_3), 126.1 (q, $^3J(C,F) = 5.0$ Hz; CH=), 142.3 (q, $^2J(C,F) = 32.9$ Hz; CCF_3), 143.1 (d, $^3J(C,P) = 46.9$ Hz; C=N), 164.7 (CO_2CH_3), 195.9 ppm ($COCH_3$); HRMS (ESI-GCT) calcd for $C_{14}H_{25}F_3N_5O_3P$ $[M+H]^+$: 400.1725, found: 400.1728.

A solution of diazoester **4g** (0.65 g, 2.6 mmol) in Et_2O (≈2 mL) was added to a solution of triphenylphosphine (0.68 g, 2.6 mmol) in absolute Et_2O (5 mL). After 5 d at room temperature away from light and air the reaction mixture was separated by flash chromatography (15 g of SiO_2, eluent: petroleum ether/*t*BuOMe in different ratios) to give pyridazine **5g** (317 mg) and hydrazone **7g** (111 mg).

Pyridazine 5g: Yield: 317 mg (53%).

Ethyl [2′-(ethoxycarbonyl)-cyclopent-1′-ene]-2-hydrozoneacetate (7g): Yield: 111 mg (17%), colorless solid, m.p. 68–69°C (Et_2O), R_f = 0.4 (petroleum ether/*t*BuOMe 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 6.5 Hz, 3H; CH_3), 1.22 (t, J = 6.5 Hz, 3H; CH_3), 1.96–1.86, 2.78–2.72 m (6H; $CH_2CH_2CH_2$), 4.10 (q, J = 6.5 Hz, 2H; CH_2), 4.15 (q, J = 6.5 Hz, 2H; CH_2), 8.17 ppm (brs, 2H; NH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 14.6 (2×CH_2CH_3), 21.9, 34.5, 38.0 ($CH_2CH_2CH_2$), 60.5, 60.7 (2×CH_2CH_3), 129.9 (C=N), 131.4 (*C*=CCO_2Et), 149.3 (C=*C*CO_2Et), 162.6, 166.1 ppm (2×CO_2Et); elemental analysis calcd (%) for $C_{12}H_{18}N_2O_4$: C 56.69, H 7.09, N 11.02; found: C 56.61, 56.63, H 7.38, 7.21, N 10.97, 10.97.

Two-stage synthesis of pyridazine 5e by reaction with $P(NMe_2)_3$

Tris(dimethylamino)phosphine (69 mg, 0.4 mmol) was added dropwise to a solution of *cis*-vinyldiazoketone **F-4e** (100 mg, 0.4 mmol) in 2 mL of Et_2O (slightly exothermic reaction, solution turned bright yellow). After 10 min the reaction mixture was separated by flash chromatography (**7g** of SiO_2, eluent: petroleum ether/EtOAc, 2:1, 50 mL) to give 120 mg of *cis*-phosphazene **2e**. A solution of the obtained phosphazene **2e** (120 mg, 0.3 mmol) in 2 mL of benzene was heated at 80–81°C for 30 min until the reaction was complete (by TLC), and after flash chromatography (7 g of SiO_2, eluent: petroleum ether/EtOAc, 2:1, 50 mL) followed by usual workup procedures, pyridazine 5e (62 mg) was isolated.

Interaction of the mixture of *trans*- and *cis*-vinyldiazoketones F-3e/F-4e with PPh_3

A mixture of *trans*- and *cis*-vinyldiazoketones **F-3e**/**F-4e** (250 mg, 1 mmol, 1:1) was added to a solution of triphenylphosphine (278 mg, 1 mmol) in Et_2O (3 mL). After 19 h at room temperature away from light and air a precipitate formed and was separated by filtration, washed with cold Et_2O (2×1 mL), and dried to give phosphazene **1e**′ (195 mg). The residue from the filtrate was separated by flash chromatography (7 g of SiO_2, eluent: petroleum ether/EtOAc 10:1 then 3:1) to give 95 mg of pyridazine **5e** and 15 mg of *trans*-phosphazene **1e**′ (total: 210 mg).

Pyridazine 5e: Yield: 95 mg (41%, 82% calculated on the basis of *cis*-**4e**), colorless solid, m.p. 56–58°C.[9a]

Methyl ester of *trans*-5-oxo-4-(triphenylphosphoranylidene)azino-3-trifluoromethyl-hex-2-enoic acid (1e′): Yield: 210 mg (40%), yellow solid, m.p. 140–140,5°C (decomp), (Et_2O); $R_f = 0.13$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.22$ (s, 3H; CH_3), 3.79 (s, 3H; OCH_3), 6.12 (s, 1H; CH), 7.45–7.72 ppm (m, 15H; 3×C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.4$ (Me), 52.6 (OMe), 120.4 (q, $^1J(C,F) = 276.2$ Hz; CF_3), 128.4 (d, $^2J(C,P) = 13.0$ Hz; *o*-C-arom.), 130.1 (q, $^2J(C,F) = 35.9$ Hz; CCF_3), 132.0 (*m*-C-arom.), 132.1 (*p*-C-arom.), 132.3 (d, $^1J(C,P) = 103.4$ Hz; *i*-C-arom.), 132.4 (q, $^3J(C,F) = 2.7$ Hz; CH=), 137.1 (C=N), 162.9 (CO_2Me), 195.4 ppm (COMe); IR (KBr): $\tilde{\nu}$ = 1656 (CO), 1739 cm^{-1} (CO); UV (EtOH): $\lambda^{max}(\lg \varepsilon) = 336$ nm (4.30); elemental analysis calcd (%) for $C_{26}H_{22}N_2O_3F_3P$: C 62.6, H 4.5, N 5.6; found: C 62.33, H 4.50, N 5.55.

Reaction of the mixture of *trans*- and *cis*-vinyldiazoketones F-3e/F-4e with $P(NMe_2)_3$

Tris(dimethylamino)phosphine (92 mg, 0.56 mmol) was added dropwise to a mixture of vinyldiazoketones **F-3e**/**F-4e** (120 mg, 0.56 mmol, 1:1) in 10 mL of Et_2O, whereby a slightly exothermic reaction was observed and the solution turned bright green. After 10 min at room temperature the reaction mixture was subjected to flash chromatography (6 g SiO_2, eluent: ethyl acetate, 30 mL) to give a mixture of stereoisomeric phosphazenes **1e**/**2e** [152 mg, ≈5:3; yield: 47% of **1e** (94% based on **F-3e**)] as a dark green, oily material. A solution of the obtained phosphazenes **1e**/**2e** in 3 mL of benzene was heated at 50–60°C for 2 h, whereupon the reaction mixture was separated by flash chromatography (10 g SiO_2, eluent: petroleum ether/ethyl acetate from 10:1 to 1:1) to give in order of elution from the column: pyridazine **5e** (55 mg) and *trans*-phosphazene **1e** (74 mg).

Pyridazine 5e: Yield: 55 mg (49%; 98% based on *cis*-**4e**), colorless solid, m.p. 56–58°C.[9a]

Methyl ester of *trans*-5-oxo-4-[tris(dimethylamino)phosphoranylidene]azino-3-trifluoromethyl-hex-2-enoic acid (1e): Yield: 74 mg (36%), dark green, oily material, $R_f = 0.38$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H; CH_3), 2.71 (d, $^3J(H,P) = 9.3$ Hz, 18H; CH_3), 3.76 (s, 3H; OCH_3), 6.01 ppm (s, 1H; CH=); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 25.3$ (CH_3), 37.5 (6×NCH_3), 52.0 ($COOCH_3$), 121.5 (q, $^1J(C,F) = 276.2$ Hz; CF_3), 128.4 (q, $^3J(C,F) = 3.50$ Hz; CH=), 142.3 (q, $^2J(C,F) = 32.9$ Hz; CCF_3), 143.1 (d, $^3J(C,P) = 46.9$ Hz; C=N), 164.0 (CO_2CH_3), 195.6 ppm ($COCH_3$); HRMS (ESI-GCT) calcd for $C_{14}H_{25}F_3N_5O_3P$ $[M+H]^+$: 400.1725, found: 400.1728.

Photochemical isomerization of *trans*-phosphazenes 1a,b,e to *cis* isomers 2a,b,e followed by cyclization to pyridazines 5a′,b,e

Pyridazine 5a′: Irradiation of phosphazene *trans*-**1a** (0.43 g, 1.24 mmol) in 20 mL of *t*BuOMe was carried out with UV light ($\lambda >$ 210 nm) at 50–55°C for 16 h, and the oily residue after removing the solvent was subjected to flash chromatography (7 g SiO_2, eluent: *t*BuOMe) to furnish 6-methoxy-3-(methoxycarbonyl)pyridazine (**5a′**). Yield: 117 mg (56%), colorless solid, m.p. 119–120°C (Et_2O), $R_f = 0.6$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.05$ (s, 3H; OCH_3), 4.24 (s, 3H; OCH_3), 7.07 (d, $^3J(H,H) = 9.0$ Hz, 1H; C^5H), 8.08 ppm (d, $^3J(H,H) = 9$ Hz, 1H; C^4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.40, 55.87 (2×OCH_3), 117.40 (HC^5=), 130.61 (HC^4=), 148.09

(CCO_2Me), 164.85 (CO_2CH_3), 166.45 ppm (COMe); HRMS (ESI-GCT) calcd for $C_7H_8N_2O_3$ $[M+H]^+$: 169.0613, found: 169.0615.

Pyridazine 5b: Irradiation of phosphazene *trans*-**1b** (0.85 g, 2.4 mmol) in 100 mL of hexane was performed with monochromatic UV light ($\lambda = 254$ nm) for 72 h (monitoring by ^{31}P NMR spectra) followed by flash chromatography of the reaction mixture (25 g SiO_2, eluent: hexane/EtOAc in gradient regime) to give pyridazine **5b** (170 mg, 39%) and a mixture of *trans*- and *cis*-phosphazenes **1b** and **2b**. The isolated mixture of phosphazenes **1b**/**2b** was heated in $CHCl_3$ solution at 60°C for 12 h followed by flash chromatography (25 g SiO_2, eluent: hexane/EtOAc in gradient regime) to give, after standard workup procedures, pyridazine **5b** (130 mg; totally 300 mg) and unconsumed *trans*-phosphazene **1b** (195 mg, 23%). 4-Methyl-6-methoxy-3-(methoxycarbonyl)pyridazine **5b**: Yield: 300 mg (69%), colorless solid, m.p. 119–120 °C (hexane), $R_f = 0.42$ (EtOAc); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (q, $^4J(H,H) = 1.0$ Hz, 1H; CH), 4.17 (s, 3H; OMe), 3.99 (s, 3H; OMe), 2.54 ppm (d, $^4J(H,H) = 1.0$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.4$ (CO_2Me), 165.0 (C^6), 148.1 (C^3), 142.1 (C^4), 117.8 (C^5), 54.9, 52.5 (2× OMe), 19.5 ppm (CH_3); IR (KBr): $\tilde{\nu} = 1734$ (CO), 1592, 1442 cm^{-1} (ring, γ); HRMS (ESI-GCT) calcd for $C_8H_{10}N_2O_3$ $[M+H]^+$: 183.0770, found: 183.0774.

Pyridazine 5e: Irradiation of phosphazene *trans*-**1e** (140 mg, 0.35 mmol) in 10 mL of Et_2O was carried out with UV light ($\lambda >$ 310 nm) at room temperature for 2 h, and the oily residue after removing the solvent was subjected to flash chromatography (7 g SiO_2, eluent: *t*BuOMe) to give 5.5 mg (7%) of pyridazine **5e**.

Irradiation of phosphazene *trans*-**1e** (140 mg, 0.35 mmol) in 5 mL of benzene was carried out with UV light ($\lambda = 395$–405 nm) at 40°C for 70 h, and the oily residue after removing the solvent was subjected to flash chromatography (7 g SiO_2, eluent: *t*BuOMe) to furnish pyridazine **5e**. Yield: 36 mg (47%), colorless solid, m.p. 56.5–58°C.[9a]

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