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Electrophilic Reactivities of 1,2-Diaza-1,3-dienes

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Abstract: The kinetics of the reactions of 1,2-diaza-1,3-dienes **1** with acceptor-substituted carbanions **2** have been studied at 20 °C. The reactions follow a second-order rate law, and can be described by the linear free energy relationship $\log k(20\,^{\circ}C) = s(N+E)$ [Eq. (1)]. With Equation (1) and the known nucleophile-specific parameters N and s for the carbanions, the electrophilicity parameters E of the 1,2-diaza-1,3-dienes **1** were determined. With E parameters in the range of −13.3 to −15.4, the electrophilic reactivities of **1a–d** are comparable to those of benzylidenemalononitriles, 2-benzylideneindan-1,3-diones, and benzylidenebarbituric acids. The experimental second-order rate constants for the reactions of **1a–d** with amines **3** and triarylphosphines **4** agreed with those calculated from E, N, and s, indicating the applicability of the linear free energy relationship [Eq. (1)] for predicting potential nucleophilic reaction partners of 1,2-diaza-1,3-dienes **1**. Enamines **5** react up to 10^2 to 10^3 times faster with compounds **1** than predicted by Equation (1), indicating a change of mechanism, which becomes obvious in the reactions of **1** with enol ethers.

Keywords: azo compounds · C–C bond formation · cycloaddition · kinetics · linear free energy relationships

Introduction

In recent years, 1,2-diaza-1,3-dienes **1** have become increasingly important as tools for the construction of a variety of heterocycles.[1] The electron-withdrawing effect of the azo group in the heterodiene system controls the regioselectivity of the nucleophilic attack at the terminal carbon. This regioselectivity is further enhanced by appropriate electron-withdrawing groups at the terminal carbon and/or nitrogen atom of the conjugated azo–ene system. As a consequence, typical reactions of conjugated azoalkenes with a variety of carbon, nitrogen, oxygen, phosphorus, sulfur, and selenium nucleophiles result in the formation of 1,4-hydrazonic adducts through Michael-type addition. From these intermediates, different intramolecular cyclizations lead to a variety of five- and six-membered heterocycles, for example, pyrroles, pyrazoles, imidazoles, thiazoles, selenazoles, 1,2,3-thiadiazoles, 1,2,3-selenadiazoles, 1,2,3-diazaphospholes, pyridazines, pyrazines, 1,4-thiazines, 1,2,4-triazines, and 1,2,4-oxadiazines. In many cases, the 1,4-additions of nucleophiles at 1,2-diaza-1,3-dienes are accompanied by spontaneous subsequent formations of heterocycles. Accordingly, heterocycles are frequently accessible by one-pot syntheses that do not require the use of anhydrous solvents or work under an inert atmosphere. Another advantage that makes compounds **1** attractive intermediates in organic chemistry is their good accessibility. Usually they are synthesized by the elimination of a leaving group X in the α position of a hydrazone. The leaving group X can either be present in the starting material, that is, a cyclic or acyclic carbonyl compound, or be introduced in the hydrazone derivative (Scheme 1).

In order to make the synthetic strategies that include the use of **1** more predictable and efficient, it was our goal to quantify the electrophilicity of different substituted 1,2-diaza-1,3-dienes **1**. We have, therefore, determined the reactivities of **1** towards nucleophiles in the first step of the complex, sequential transformations that lead to different products.

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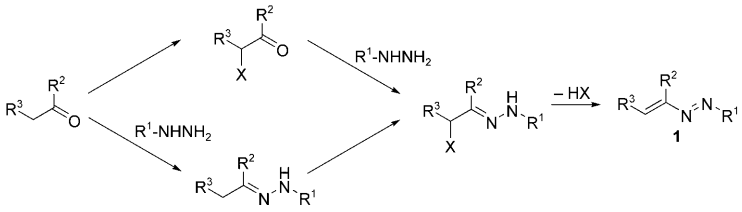
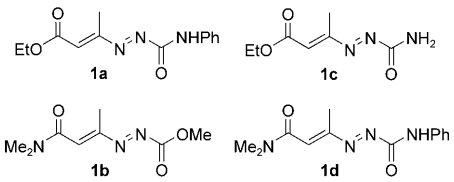


Scheme 1. Synthetic pathways to 1,2-diaza-1,3-dienes **1**.

Recently, the group of H. Mayr in München has shown that the reactions of carbocations and various electron-deficient alkenes with *n*-, π-, and σ-nucleophiles can be described by Equation (1), in which the nucleophiles are characterized by the parameters *N* and *s*, and the electrophiles are characterized by the parameter *E*.[2] In this way, it was possible to construct comprehensive nucleophilicity and electrophilicity scales.[3] Reactions of carbanions with typical Michael acceptors, such as benzylidenemalononitriles, benzylideneindandiones, benzylidene Meldrum's acids, and benzylidenemalonates, have been shown to follow Equation (1).[4]

$$\log k_2(20\,^{\circ}\mathrm{C}) = s(N+E) \qquad (1)$$

By assuming that the reactions of **1** with carbanions can also be described by Equation (1), we have determined the electrophilicities of four conjugated azoalkenes (1,2-diaza-1,3-dienes **1a–d**) with ester or amido substituents at positions 1 and 4 (Scheme 2).



Scheme 2. 1,2-Diaza-1,3-dienes **1a–d** used in this study.

For this purpose, we have investigated the rates of the reactions of **1a–d** with the carbanions **2a–e**, for which the *N* and *s* parameters are known (Table 1).[3b,5]

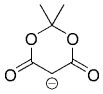
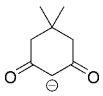
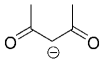
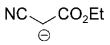
Results and Discussion

Reactions of 1,2-diaza-1,3-dienes 1 with carbanions 2

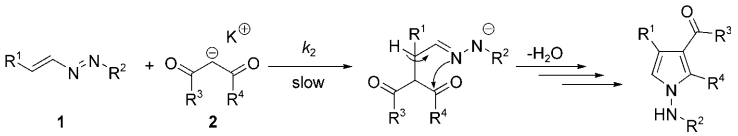
Product characterization: Many base-activated reactions of 1,2-diaza-1,3-dienes **1** with CH-acidic compounds, such as β-dicarbonyl compounds, have been reported to result in the formation of pyrroles (Scheme 3).[6]

In previous investigations,[1,6] the majority of the reactions between carbanions **2** and **1** were carried out in THF. As the structure of the resulting products was reported to depend on the solvent, we repeated some of the relevant reactions in those solvents used for the kinetic studies in this work, that is, DMSO or MeOH (Table 1, Scheme 4). The reactions of **1a** with the carbanions **2c** and **2e**, and of **1c** with carbanion **2e**, gave the expected pyrroles **2ca**, **2ea**, and **2ec**, whereas the reactions of **1a** with **2d** and of **1d** with carbanion **2c** yielded the acyclic 1,4-adducts **2da** and **2cd**, respectively. Because the products shown in Scheme 4 accordingly indicate initial attack of the carbanions at C4 of the diazadiene system, we have assumed that all other combinations of **1a–d** with **2** that were studied kinetically in this work proceed in an analogous manner.

Table 1. Reference carbanions **2** used in this study, and their nucleophilicity parameters *N* and *s*.

Carbanion[a]		*N* (*s*)[b]
	**2a**	13.91 (0.86) in DMSO
	**2b**	16.27 (0.77) in DMSO
	**2c**	17.64 (0.73) in DMSO
	**2d**	18.59 (0.65) in MeOH
	**2e**	19.36 (0.67) in DMSO

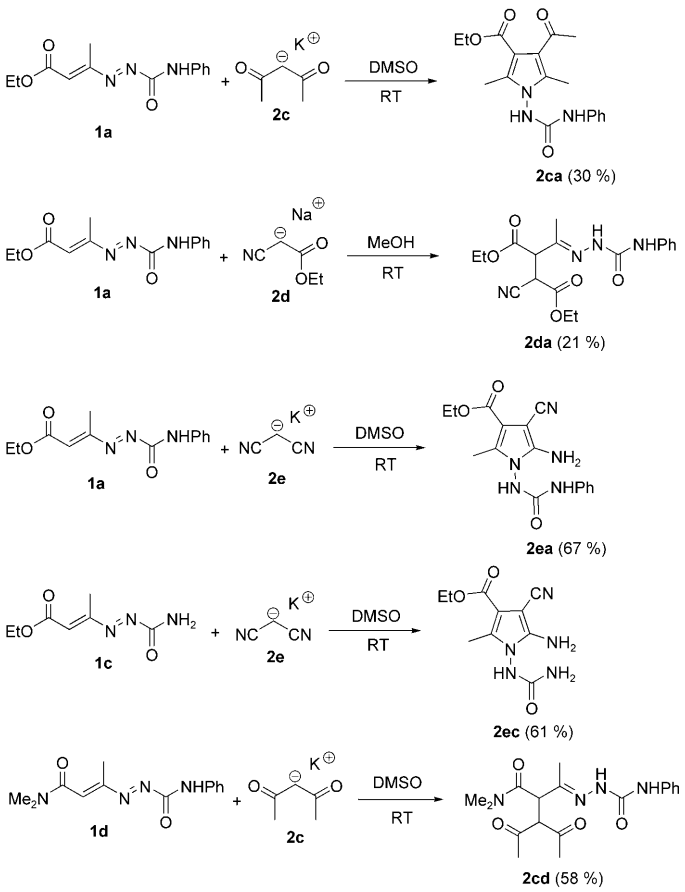
[a] Counterion for **2a**, **2b**, **2c**, and **2e**: K^+; counterion for **2d**: Na^+. [b] Refs. [3b] and [5].



Scheme 3. Michael addition of β-dicarbonyl compounds to 1,2-diaza-1,3-dienes **1** and subsequent cyclization.

Kinetic investigations: The rates of the reactions of **1** with the carbanions **2** were determined photometrically at 20 °C by using conventional or stopped-flow UV/Vis spectrometers. The carbanions **2** were used as preformed potassium salts, or were prepared in solution by deprotonation of the CH acids with 1.05 equiv of KO*t*Bu (or NaOMe in the case of **2d**). The reaction progress was monitored by the decrease of the absorbances of the electrophiles. By using the nucleophiles **2** in excess over the electrophiles **1**, first-order conditions were achieved. From the mono-exponential decays of the absorbances the first-order rate constants k_{obs} were obtained by a least-squares fit to $A = A_0 e^{-k_{obs}t} + C$. Details are given in the Supporting Information.

The reactions of **1** with the carbanion **2d** were performed in methanol, in which **2d** was generated by treatment of **2d**–H with sodium methanolate. Because ethyl cyanoacetate (**2d**–H) is only partially deprotonated by methoxide in



Scheme 4. Products of the reactions of **1a**, **1c**, and **1d** with carbanions **2** (isolated yields after column chromatography).

methanol, the evaluation of the kinetics of the reaction of **1** with **2d** has to consider the acid–base equilibrium (**2d**–Na + MeOH⇄**2d**–H + MeO$^-$Na$^+$) as well as the parallel reaction of **1** with MeO$^-$. The actual concentrations of **2d** and MeO$^-$ can be calculated by using the known equilibrium constant K_{2d}.[7] The independently determined second-order rate constants $k_{2,MeO}$ for the reactions of MeO$^-$ with the electrophiles **1** were then employed to subtract $k_{2,MeO}$[MeO$^-$] from k_{obs} to get to the pseudo-first-order rate constants for the reaction of **2d** with the 1,2-diaza-1,3-dienes **1** (for details see the Supporting Information and ref. [5]).

As exemplified in Figure 1 for the reaction of **1d** with **2b**, plots of k_{obs} (or $k_{obs}-k_{2,OMe}$[MeO$^-$] in the case of the reactions with **2d**) versus the carbanion concentrations were linear for all reactions of **1** with **2**. In these reactions, the attack of the carbanions at the electrophiles is rate limiting, and the slopes of the plots of k_{obs} versus [**2**] gave the second-order rate constants k_2 [Eq. (2)], which are listed in Table 2.

$$k_{obs} = k_2[\mathbf{2}] \qquad (2)$$

Figure 2 shows linear correlations of $(\log k_2)/s$ versus N with slopes of unity, as required by Equation (1). Consequently, the electrophilicity parameters E of **1a–d** could be derived from a least-squares fit of experimental and calculated rate constants by minimization of $\Delta^2 = \Sigma(\log k_2 - s(N+E))^2$. As discussed in previous reviews,[3] a special type of the linear free energy relationship in Equation (1) avoids long-ranging extrapolations because $E=-N$ for $(\log k_2)/s=0$, as shown graphically in Figure 2. Whereas in most cases the calculated (from E, N, s) and experimental rate constants agree within a factor of three (Table 2), **1c** reacts seven times faster with **2d** than calculated. Because this deviation is within the confidence limit of Equation (1), we abstain from an interpretation of this deviation.

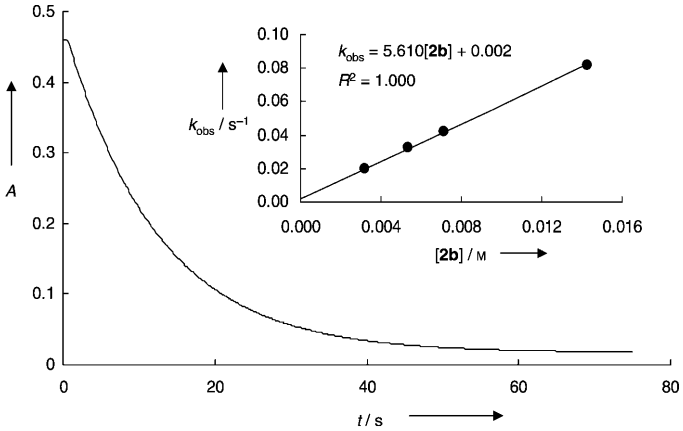


Figure 1. Exponential decay of the absorbance at 350 nm during the reaction of **1d** with the anion of dimedone in DMSO at 20 °C ([**2b**] = 1.43 × 10^{-2} M; k_{obs} = 8.21 × 10^{-2} s^{-1}, counterion: K$^+$). Insert: Determination of the second-order rate constant k_2 = 5.61 M^{-1} s^{-1} from the slope of the correlation of the first-order rate constants k_{obs} with the concentration of **2b**.

Table 2. Experimental and calculated second-order rate constants for the reactions of **1a–d** with carbanions **2a–e** at 20 °C in DMSO.

Electrophile (E)	Nucleophile	k_2^{exp} [M^{-1} s^{-1}]	k_2^{calcd} [M^{-1} s^{-1}][a]	k_2^{exp}/k_2^{calcd}
1a (−13.28)	**2a**	1.52	3.48	0.44
	2b	4.39×10^{2}	2.01×10^{2}	2.2
	2c	4.02×10^{3}	1.52×10^{3}	2.6
	2d	2.96×10^{3}[b]	2.83×10^{3}	1.0
	2e	4.44×10^{3}	1.18×10^{4}	0.37
1b (−13.90)	**2a**	5.15×10^{-1}	1.02	0.51
	2b	8.11×10^{1}	6.68×10^{1}	1.2
	2c	6.93×10^{2}	5.37×10^{2}	1.3
	2d	3.50×10^{3}[b]	1.12×10^{3}	3.1
	2e	2.21×10^{3}	4.55×10^{3}	0.49
1c (−14.91)	**2a**	7.98×10^{-2}	1.38×10^{-1}	0.58
	2b	1.88×10^{1}	1.11×10^{1}	1.7
	2c	3.86×10^{1}	9.84×10^{1}	0.39
	2d	1.64×10^{3}[b]	2.47×10^{2}	6.7
	2e	4.82×10^{2}	9.58×10^{2}	0.50
1d (−15.38)	**2a**	3.69×10^{-2}	5.41×10^{-2}	0.67
	2b	5.61	4.82	1.2
	2c	8.98×10^{1}	4.44×10^{1}	2.0
	2e	3.13×10^{2}	4.68×10^{2}	0.67

[a] Calculated by using Equation (1), N and s parameters from Table 1, and E from this table. [b] Solvent: MeOH.

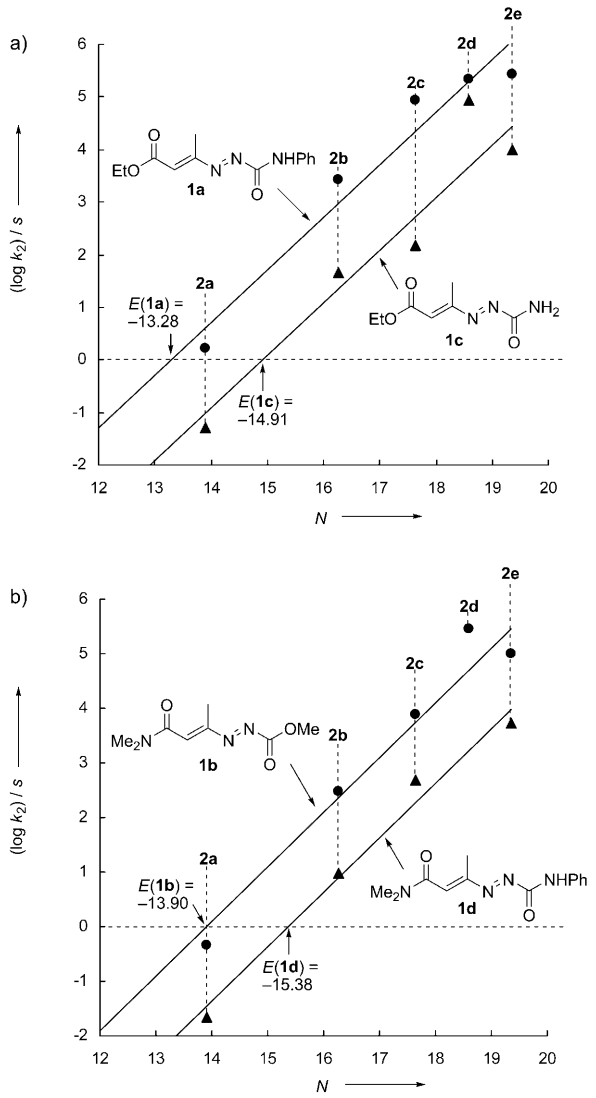


Figure 2. Plots of $(\log k_2)/s$ against the N parameters of the carbanions **2a**–**e** for the reactions of the 1,2-diaza-1,3-dienes **1a**, **1c** (a), **1b**, and **1d** (b) with **2a**–**e** in DMSO at 20 °C (the slopes are fixed to one as required by Equation (1); reactions of **2d** in methanol).

The electrophiles **1a**–**d** cover a reactivity range of two orders of magnitude and can be compared to benzylidenemalononitriles,[4a] benzylideneindandiones,[4b] benzylidenebarbituric acids,[4c] benzylidene Meldrum's acids,[4d] electron-deficient arenes,[8] and quinone methides[3g] (Figure 3). 1,2-Diaza-1,3-dienes are considerably more reactive than benzylidenemalonates ($E < -17.5$).[4e]

Reactions of the 1,2-diaza-1,3-dienes 1 with other nucleophiles: In order to examine whether the electrophilicity parameters of 1,2-diaza-1,3-dienes **1a**–**d** derived from the rates of their reactions with carbanions, which are listed in Figure 3, are suitable for the prediction of their reaction rates with other types of nucleophiles, we studied the kinetics of the reactions of **1a**–**d** with amines **3**, triarylphosphines **4**, and enamines **5** of known nucleophilicities.[3a,9]

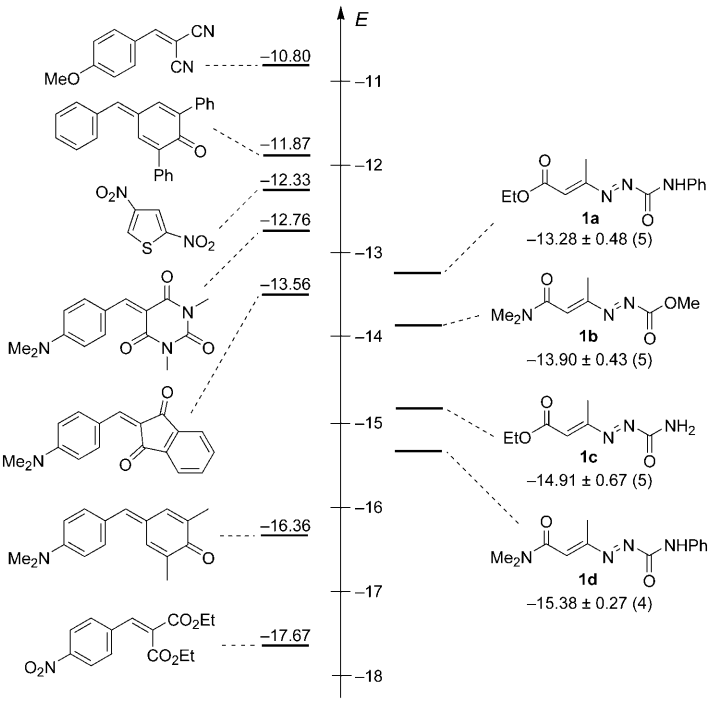


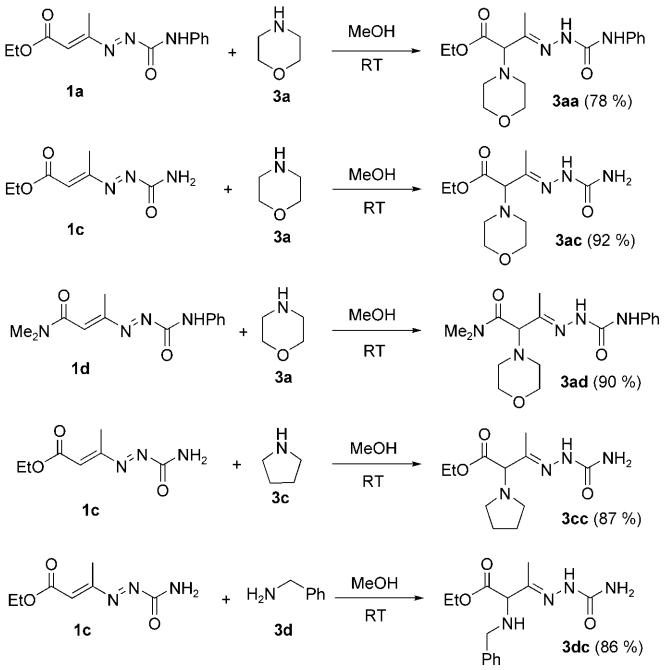
Figure 3. Comparison of the electrophilic reactivities of 1,2-diaza-1,3-dienes **1** with those of other classes of electrophiles (standard deviations are given for E(**1**) with the number of experiments in parentheses).

Product characterization

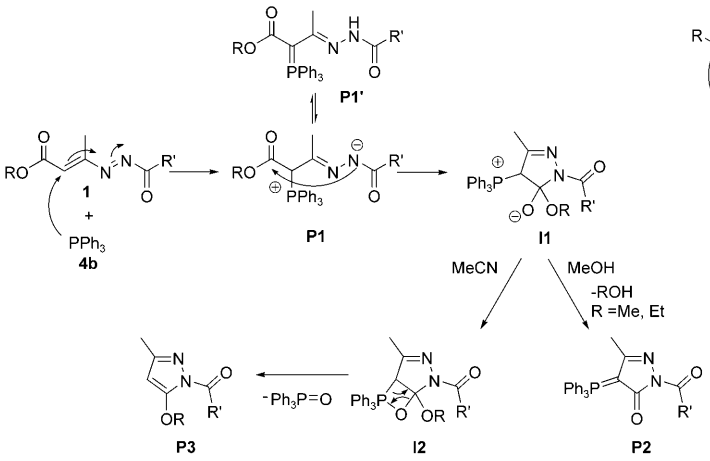
*Products of the reactions of **1** with amines **3***: The reactions of **1a**,**c**,**d** with the amines **3a**,**c**,**d** in MeOH furnished the expected[10] α-aminohydrazones **3aa**,**ac**,**ad**,**cc**,**dc** in high yield (Scheme 5).

*Products of the reactions of **1** with triarylphosphines **4***: Some of us[11] reported previously that the reactions of **1** with triphenylphosphine (**4b**) in ethyl acetate produced the 1,5-zwitterions **P1**, which precipitated from the solvent (Scheme 6). These intermediates undergo different heterocyclization reactions depending on the nature of the solvent used: in methanol the 1,4-adduct **P1** is transformed into a betaine intermediate **I1** by intramolecular attack of the nitrogen at the ester group. Subsequent loss of MeOH or EtOH yields 4-triphenylphosphoranylidene-4,5-dihydropyrazol-5-ones **P2**. Also in acetonitrile, the cyclic betaine intermediates **I1** are formed, which then cyclize to the oxaphosphetane intermediates **I2**. Finally, loss of triphenylphosphine oxide transforms **I2** into the corresponding pyrazoles **P3**.

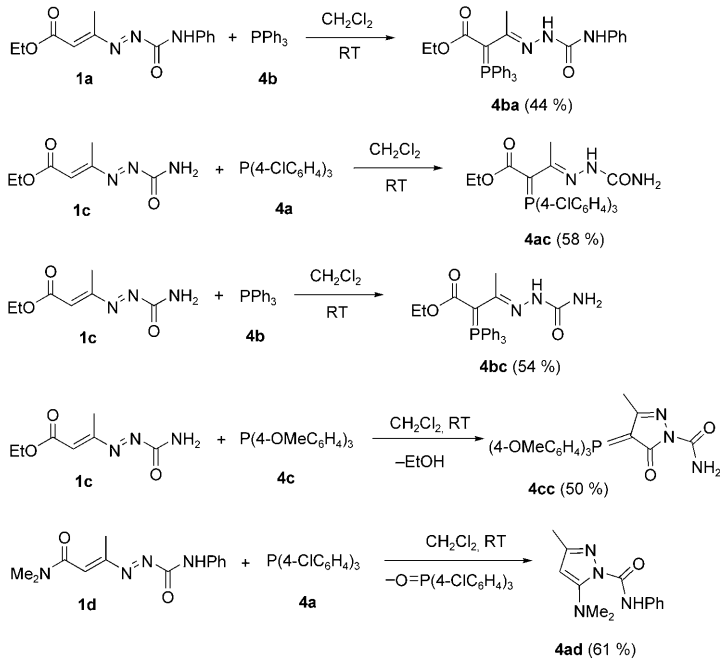
Because the kinetic experiments were performed in CH_2Cl_2, we also studied products of the reactions between **1a**,**c** and **4a**,**b** in this solvent. Scheme 7 shows the formation of the expected phosphorus ylides **4ba**, **4ac**, and **4bc**.[11a] In contrast, the reaction between **1c** and tris(4-methoxyphenyl)phosphine (**4c**) gave the 4-tris(4-methoxyphenyl)phosphoranylidene-4,5-dihydropyrazol-5-one (**4cc**),[11] and the reaction between **1d** and 4-tris(4-chlorophenyl)phosphine (**4a**) afforded the pyrazole **4ad**[11a] (Scheme 7).



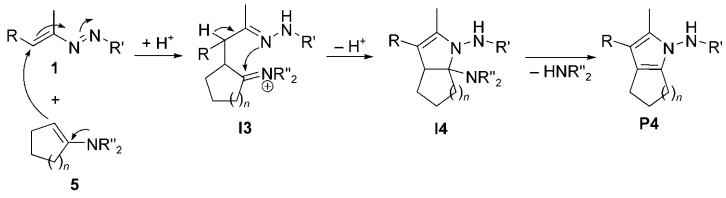
Scheme 5. Product studies of the reactions of **1** with amines **3** (isolated yields).



Scheme 6. Mechanism of the reactions of **1** with triphenylphosphine (**4b**).



Scheme 7. Products of the reactions of **1a**, **1c**, and **1d** with triarylphosphines (**4**; isolated yields after column chromatography).



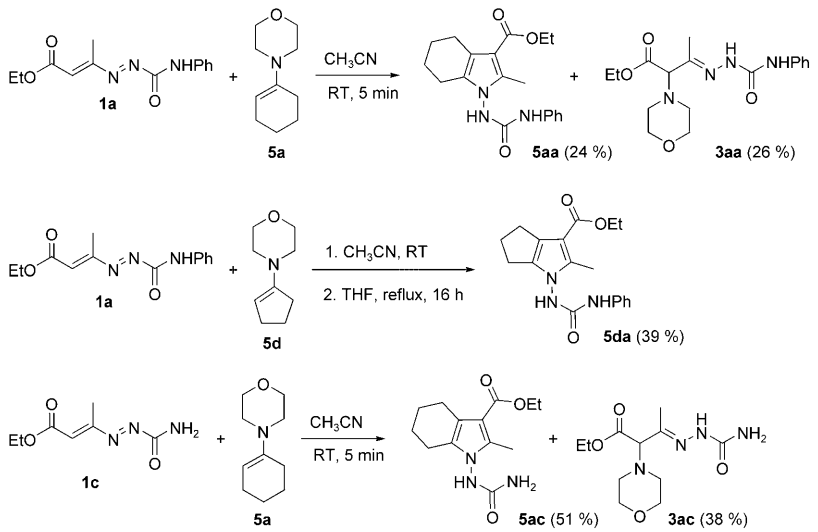
Scheme 8. Formation of 1-aminopyrroles **P4** from the reactions of **1** with enamines **5**.

*Products of the reactions of **1** with enamines **5***: Reactions of the conjugated azoalkenes **1** with α,β-disubstituted enamines **5** have been reported to yield 1-aminopyrroles **P4** in polar and apolar solvents. The initial attack of the nucleophilic carbon atom of the enamine **5** at the terminal carbon atom of the azo–ene system **1** produces hydrazonic intermediates **I3**, which undergo a [3+2] cyclization to furnish the 2-amino-substituted dihydropyrroles **I4**. The spontaneous subsequent loss of the secondary amine results in the formation of the 1-aminopyrrole derivatives **P4** (Scheme 8).[12]

For the product investigations, we have chosen the reactions between **1a**,**c** and the 1-morpholinocycloalkenes **5a**,**d** in acetonitrile. The reactions of **1a** and **1c** with morpholinocyclohexene (**5a**) delivered the 1-aminopyrroles **5aa** and **5ac**, respectively. The accompanying 1,4-adducts **3aa** and **3ac** are formed by addition of morpholine (a side product of the formation of the pyrroles, see Scheme 8) to the electrophiles **1a** and **1c**.[12a] In the reaction of **1a** with **5d**, the loss of morpholine did not occur spontaneously, therefore the reaction mixture in THF was heated to reflux until complete conversion into pyrrole **5da** was observed by TLC analysis (Scheme 9).

Kinetic studies: The kinetics of the reactions of **1** with amines **3**, triarylphosphines **4**, and enamines **5** were determined photometrically, as described above for the reactions of **1** with carbanions **2**.

*Reactions of **1** with amines **3***: The reactions of **1** with amines **3a–d** were studied in different solvents. Table 3 shows that the experimental rate constants for these reactions agree within a factor of seven with those calculated by Equation (1) from the electrophilicity parameters E of **1** (Table 2) and the N and s parameters of the amines **3a–c** previously determined from the rates of their reactions with benzhydrylium ions.[9b,d,e]



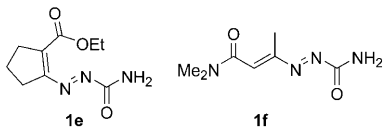
Scheme 9. Product studies of the reactions of **1a** and **1c** with enamines **5** (isolated yields after chromatographic workup).

Table 3. Experimental and calculated second-order rate constants for the reactions of 1,2-diaza-1,3-dienes **1** with amines **3** at 20 °C.

1	Amine 3	N/s[a]	k_2^{exp} [$M^{-1}s^{-1}$]	k_2^{calcd} [$M^{-1}s^{-1}$][b]	k_2^{exp}/k_2^{calcd}
1a	morpholine (**3a**) in MeOH	15.40/0.64	4.72	2.27×10^{1}	0.21
1a	morpholine (**3a**) in DMSO	16.96/0.67	4.12×10^{1}	2.92×10^{2}	0.14
1a	piperidine (**3b**) in MeOH	15.63/0.64	1.92×10^{1}	3.19×10^{1}	0.60
1a	piperidine (**3b**) in MeCN	17.35/0.68	2.22×10^{2}	5.86×10^{2}	0.38
1a	pyrrolidine (**3c**) in MeOH	15.97/0.63	3.18×10^{1}	4.95×10^{1}	0.64
1b	morpholine (**3a**) in MeOH	15.40/0.64	1.15×10^{1}	9.12	1.3
1b	morpholine (**3a**) in DMSO	16.96/0.67	1.45×10^{2}	1.12×10^{2}	1.3
1b	piperidine (**3b**) in MeOH	15.63/0.64	2.63×10^{1}	1.28×10^{1}	2.1
1c	morpholine (**3a**) in MeOH	15.40/0.64	2.17	2.06	1.1
1c	morpholine (**3a**) in DMSO	16.96/0.67	3.83	2.36×10^{1}	0.16
1c	piperidine (**3b**) in MeOH	15.63/0.64	9.81	3.11	3.2
1c	piperidine (**3b**) in MeCN	17.35/0.68	4.00×10^{1}	2.89×10^{1}	0.88
1c	pyrrolidine (**3c**) in MeOH	15.97/0.63	1.68×10^{1}	4.65	3.6
1c	benzylamine (**3d**) in MeOH	13.46/0.62	1.91×10^{-1}	1.26×10^{-1}	1.5
1d	morpholine (**3a**) in MeOH	15.40/0.64	1.69	1.03	1.6
1d	piperidine (**3b**) in MeOH	15.63/0.64	4.95	1.45	3.4
1e	morpholine (**3a**) in MeOH	15.40/0.64	1.19	–	–
1e	piperidine (**3b**) in MeOH	15.63/0.64	4.94	–	–
1f	morpholine (**3a**) in MeOH	15.40/0.64	8.04×10^{-1}	–	–
1f	piperidine (**3b**) in MeOH	15.63/0.64	2.35	–	–

[a] N and s parameters of amines from refs. [9b], [9d], and [9e]. [b] Calculated by using Equation (1).

The rate constants for the reactions of morpholine (**3a**) and piperidine (**3b**) with two additional 1,2-diaza-1,3-dienes **1e** and **1f** were studied in methanol. Tentative E parameters for **1e** and **1f** can be calculated by using Equation (1), from the known N and s parameters of **3a** and **3b** and the second-order rate constants listed in Table 3. The averaged values of the electrophilicity parameters E are −14.9 for **1e** and −15.3 for **1f**.



1,2-Diaza-1,3-dienes **1** with amido groups at the 1- and the 4-terminus are the least reactive (**1d** and **1f**). Their reactivity increases slightly when the amido substituents at the terminal carbon or the nitrogen atom are replaced by the stronger electron-withdrawing ester group (**1d** is less reactive than **1b** and **1a**). However, these substituent effects are small, and the electrophilicities of the 1,2-diaza-1,3-dienes studied in this work cover a very narrow reactivity range of only two orders of magnitude.

*Reactions of **1** with triarylphosphines **4***: The rates of the reactions of **1** with triarylphosphines **4a–c** were studied in CH_2Cl_2 by following the decay of the absorbance of the electrophiles. In analogy to the reactions of **1** with amines, the linearity of the k_{obs} versus [PR_3] plots proved that second-order rate laws were obeyed for all studied reactions. This fact allowed us to determine the second-order rate constants for the attack of PR_3 at the C=C double bond of **1**. Comparison of the experimentally obtained rate constants with those predicted by Equation (1) shows an excellent agreement of these values within a factor of 5 (Table 4).

*Reactions of **1** with enamines **5***: The reactions of **1** with the α,β-disubstituted enamines **5a–c** were studied in acetonitrile by following the decay of the absorbance of the electrophiles. The progress of the reaction of **1c** with morpholinocyclopentene (**5d**) can be monitored by the decrease of the absorbance of the electrophile and, additionally, by the increase of the absorbance of the reaction product. From the mono-exponential increases (as from the mono-exponential decays) the k_{obs} values were obtained by a least-squares fit to the function $A=(1-A_0\,e^{-k_{obs}t})+C$. The slope of the linear plot of k_{obs} versus [**5d**] yielded the second-order rate constants k_2. Figure 4 shows the reaction progress by the mono-exponential increase of the product and the mono-exponential decay of **1c** for the same reaction ($[\mathbf{1c}]_0=2.19\times10^{-4}$ M; $[\mathbf{5d}]_0=9.40\times10^{-4}$ M). The first-order rate constants

Table 4. Experimental and calculated second-order rate constants for the reactions of 1,2-diaza-1,3-dienes **1** with phosphines **4** in CH_2Cl_2 at 20 °C.

1	Phosphine (**4**)	N/s[a]	k_2^{exp} [$M^{-1}s^{-1}$]	k_2^{calcd} [$M^{-1}s^{-1}$][b]	k_2^{exp}/k_2^{calcd}
1a	$(4\text{-}ClC_6H_4)_3P$ (**4a**)	12.58/0.65	3.12×10^{-1}	3.51×10^{-1}	0.89
1a	Ph_3P (**4b**)	14.33/0.65	6.59	4.74	1.4
1a	$(4\text{-}OMeC_6H_4)_3P$ (**4c**)	16.17/0.62	1.02×10^{2}	6.19×10^{1}	1.6
1b	Ph_3P (**4b**)	14.33/0.65	9.63×10^{-1}	1.90	0.51
1c	$(4\text{-}ClC_6H_4)_3P$ (**4a**)	12.58/0.65	1.05×10^{-1}	3.06×10^{-2}	3.4
1c	Ph_3P (**4b**)	14.33/0.65	1.73	4.14×10^{-1}	4.2
1c	$(4\text{-}OMeC_6H_4)_3P$ (**4c**)	16.17/0.62	2.41×10^{1}	6.04	4.0

[a] N and s parameters of triarylphosphines **4a–c** from ref. [9c]. [b] Calculated by using Equation (1), N and s parameters from ref. [9c], and the E parameters from Table 2.

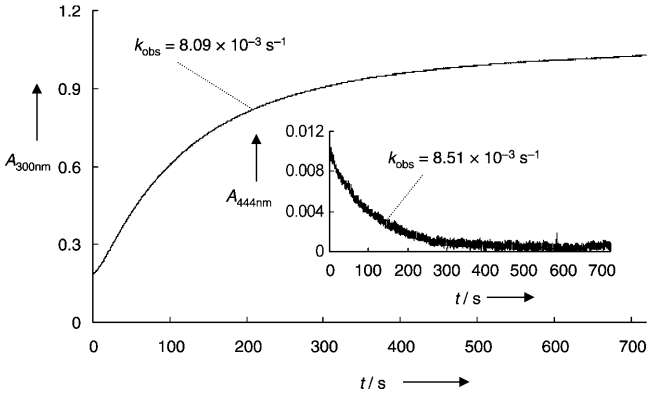
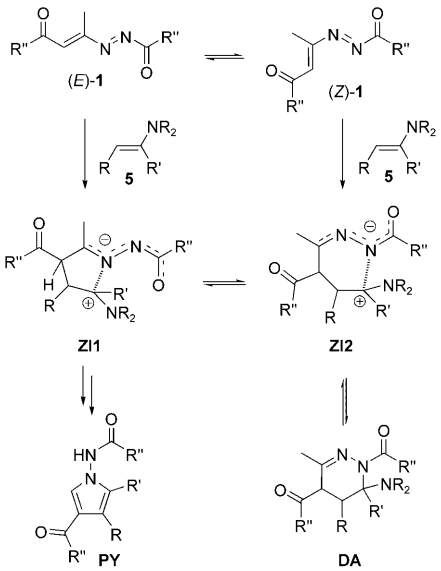


Figure 4. Exponential increase of the absorbance at 300 nm during the reaction of **1c** with morpholinocyclopentene (**5d**) ($[\mathbf{5d}]_0 = 9.40\times10^{-4}$ M). Insert: Exponential decay of the absorbance of **1c** at 444 nm during the reaction of **1c** with **5d**.

for the reactions of **1c** with **5d** obtained by the two different methods are in fair agreement. However, because of the high molar absorption coefficient of the product, the concentration of **1c** had to be kept small, which resulted in a very low absorption for **1c** and a less precise k_{obs} value determined from the decay of [**1c**].

Though some of the rate constants listed in Table 5 agree with the calculated ones within a factor of 10^2, all experimental rate constants are larger than calculated; most of the reactions are 10^2–10^3 times faster than derived from Equation (1), and the strongest deviation is found for the reactions of the least nucleophilic enamine **5a** with the least electrophilic azadienes **1c** and **1d**. Therefore, one can assume that these reactions experience a special acceleration. As shown in Scheme 10, **5** may react with the (*Z*,*E*) conformational isomers of the diazadienes **1** to give the zwitterions **ZI1** or **ZI2**. Stabilization of these intermediates and the preceding transition states by Coulombic



Scheme 10. Mechanism for the reactions of **1** with aldehyde- and ketone-derived enamines **5**.

attraction of the oppositely charged fragments may explain the increased reactivity of the enamines. The observation that the acceleration is highest for the slowest reactions may indicate that the transition state is even stabilized by partial formation of the second bond (hatched lines in **ZI1** and **ZI2**) leading to the heterocycles **DA** and **PY**, respectively.[13] In accord with this interpretation, aldehyde-derived enamines **5** (R' = H) have been reported to undergo [4+2] cycloadditions with 1,2-diaza-1,3-dienes.[12d]

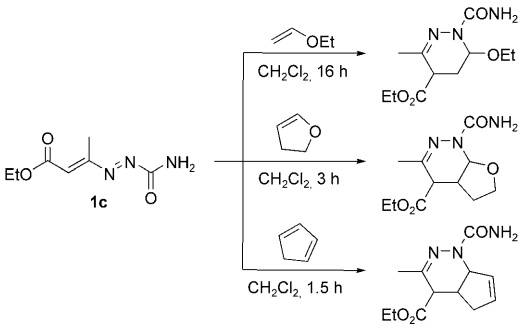
Table 5. Experimental and calculated second-order rate constants for the reactions of 1,2-diaza-1,3-dienes **1** with enamines **5** in acetonitrile at 20 °C.

1	Enamine **5**	N/s[a]	k_2^{exp} [$M^{-1}s^{-1}$]	k_2^{calcd} [$M^{-1}s^{-1}$][b]	k_2^{exp}/k_2^{calcd}
1a	morpholinocyclohexene (**5a**)	11.40/0.83	4.73	2.75×10^{-2}	172
1a	piperidinocyclopentene (**5b**)	15.06/0.82	1.23×10^{3}	2.88×10^{1}	43
1a	pyrrolidinocyclopentene (**5c**)	15.91/0.86	6.44×10^{3}	1.83×10^{2}	35
1b	morpholinocyclohexene (**5a**)	11.40/0.83	8.88×10^{-1}	8.41×10^{-3}	106
1b	piperidinocyclopentene (**5b**)	15.06/0.82	1.40×10^{2}	8.94	16
1b	pyrrolidinocyclopentene (**5c**)	15.91/0.86	1.07×10^{3}	5.35×10^{1}	20
1c	morpholinocyclohexene (**5a**)	11.40/0.83	8.05×10^{-1}	1.22×10^{-3}	660
1c	morpholinocyclopentene (**5d**)	13.41/0.82	7.59[c]	5.89×10^{-2}	128
1c	piperidinocyclopentene (**5b**)	15.06/0.82	1.96×10^{2}	1.33	148
1c	pyrrolidinocyclopentene (**5c**)	15.91/0.86	1.12×10^{3}	7.24	155
1d	morpholinocyclohexene (**5a**)	11.40/0.83	3.75×10^{-1}	4.97×10^{-4}	754
1d	morpholinocyclopentene (**5d**)	13.41/0.82	3.89	2.42×10^{-2}	160
1d	piperidinocyclopentene (**5b**)	15.06/0.82	6.47×10^{1}	5.47×10^{-1}	118

[a] N and s parameters from refs. [3a] and [9a]. [b] Calculated by using Equation (1). [c] k_{obs} values were obtained from the mono-exponential increases of the product.

Possibly analogous [4+2] cycloadditions also occur with the enamines **5a–d** studied in this work. However, when R'= alkyl, the zwitterion **ZI2** is sufficiently stabilized that it can be regenerated from the Diels–Alder adduct **DA**, and finally gives the pyrrole **PY** as indicated in Scheme 10.

From the nucleophilicity parameters N and s for ethyl vinyl ether ($N=3.92$, $s=0.90$), 2,3-dihydrofuran ($N=4.37$, $s=0.90$), and cyclopentadiene ($N=2.30$, $s=1.09$),[3c] one can derive that nucleophilic attack of these π systems at the 4-position of the 1,2-diaza-1,3-diene **1c** would occur with rate constants between 2×10^{-14} and 3×10^{-10} M^{-1}s^{-1}. From these calculated rate constants one can estimate that the Diels–Alder reactions with inverse electron demand depicted in Scheme 11 would require 10^2 to 10^6 years at 20 °C (half-reaction times for 1 M solutions) if they proceeded stepwise through a zwitterionic intermediate. The reported reaction times of 1.5 to 16 h at 15 °C are, therefore, clear evidence for the occurrence of concerted Diels–Alder reactions.[14]



Scheme 11. Diels–Alder reactions of **1c** with ethyl vinyl ether, 2,3-dihydrofuran, and cyclopentadiene (at 15 °C, from ref. [14]).

The considerably smaller deviations between calculated and experimental rate constants for the reactions of **1** with enamines **5** indicate that the potentially involved initial Diels–Alder reactions would profit much less from concertedness.

Conclusion

Figure 5 illustrates that the N and s parameters for carbanions **2**, amines **3**, and phosphines **4** derived from reactions with benzhydrylium ions also hold for their reactions with 1,2-diaza-1,3-dienes **1**. Though belonging to different classes of compounds, the deviations of these nucleophiles from the correlation line in Figure 5 are small. The positive deviations of enamines from this correlation line are indicative of a mechanistic change toward concerted [4+2] cycloadditions, which must be operating in the reactions of enol ethers with the dienes **1**, because the stepwise mechanism can be estimated to require more than 10^2 years.

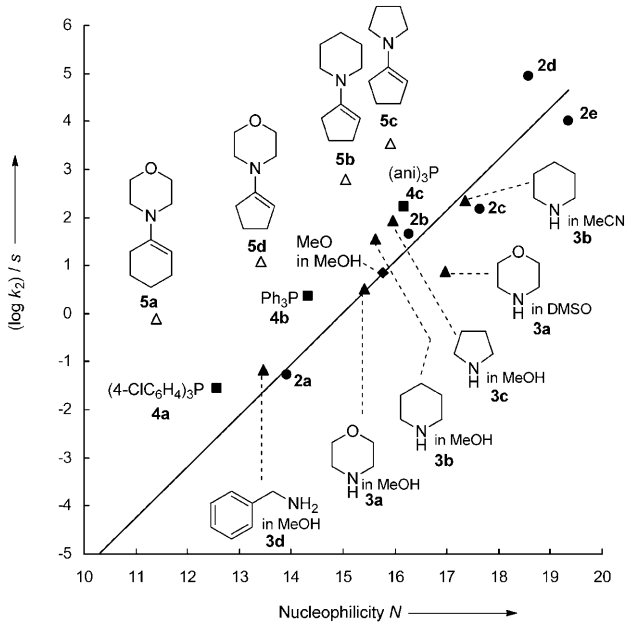


Figure 5. Plot of $(\log k_2)/s$ for the reactions of the 1,2-diaza-1,3-diene **1c** with **2**–**5** at 20 °C against the N parameters of the carbanions **2a–e** (●), the amines **3a–c** (▲), the phosphines **4a–c** (■, in CH_2Cl_2), the enamines **5a–c** (△, in MeCN), and methanolate (◆). The linear curve refers to the plot of $(\log k_2)/s$ against the N parameters of the carbanions **2a–e**, and the slope is fixed to unity as required by Equation (1). P(ani)$_3$ = tris(*p*-anisyl)phosphine **4c**.

Experimental Section

General methods and materials: 1,2-Diaza-1,3-dienes **1a–f**, the potassium salts of **2a–c** and **2e**, and the enamines **5a–d** were synthesized by following literature procedures.[1c,6b,15,16] Tris(4-chlorophenyl)phosphine (**4a**), triphenylphosphine (**4b**), and tris(4-methoxyphenyl)phosphine (**4c**) were purchased from ABCR (**4a**) and Aldrich (**4b** and **c**). Morpholine (**3a**), piperidine (**3b**), pyrrolidine (**3c**), and benzylamine (**3d**) were purchased and purified by distillation prior to use. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured on a Varian Inova 400 or Varian Mercury 400 NMR spectrometer. For details and characterization of the products see the Supporting Information.

Reactions of 1,2-diaza-1,3-dienes 1 with carbanions 2: 1,2-Diaza-1,3-dienes **1a**,**c**,**d** (1 equiv) were added to a mixture of nucleophiles **2c**,**e** (1 equiv) and KO*t*Bu (1.05 equiv) in DMSO at 20 °C, and the solution was stirred until the disappearance of the starting materials (monitored by TLC analysis), furnishing the products **2ca**, **2ea**, **2ec**, and **2cd**. Then the reactions were quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. The crude products were purified by column chromatography on silica gel. 1,2-Diaza-1,3-diene **1a** (1 equiv) was added to a stirred mixture of ethyl cyanoacetate **2d** (1 equiv) and NaOMe (1.05 equiv) in MeOH at 20 °C. The 1,4-hydrazonic adduct precipitated directly from the reaction medium. After filtration and washing with diethyl ether, **2da** was obtained in pure form.

Reactions of 1,2-diaza-1,3-dienes 1 with amines 3: 1,2-Diaza-1,3-dienes **1a**,**c**,**d** (1 equiv) were added to a solution of the amines **3a**,**c**,**d** (1 equiv) in MeOH at 20 °C, and the mixture was stirred until the disappearance of the starting materials (monitored by TLC analysis). The products **3aa**, **3ac**, **3ad**, and **3cc** precipitated directly from the reaction medium, and **3dc** was crystallized from diethyl ether/petroleum ether (40 to 60 °C) and collected by filtration.

Reactions of 1,2-diaza-1,3-dienes 1 with triarylphosphines 4: 1,2-Diaza-1,3-dienes **1a**,**c**,**d** (1 equiv) were added to a stirred solution of the triaryl-

phosphines **4a–c** (1 equiv) in CH_2Cl_2 at 20 °C. After the completion of the reaction, the solvent was evaporated at reduced pressure and the crude products **4ba**, **4ac**, **4bc**, **4cc**, and **4ad** were purified by column chromatography on silica gel.

Reactions of 1,2-diaza-1,3-dienes 1 with enamines 5: 1,2-Diaza-1,3-dienes **1a**,**c** (1 equiv) were added to a solution of the enamines **5a**,**d** (1 equiv) in acetonitrile at 20 °C. The solution was stirred until the disappearance of the starting materials (monitored by TLC analysis). In the case of the reactions of **1a** and **1c** with **5a**, the final products were the pyrroles **5aa** and **5ac** and the α-aminohydrazones **3aa** and **3ac**, respectively, which were isolated by column chromatography on silica gel. In the case of the reaction of **1a** with **5d**, after the disappearance of the starting materials, acetonitrile was evaporated at reduced pressure. The crude product mixture was dissolved in THF and then heated to reflux for 16 h, to obtain pyrrole **5da**, which was purified by column chromatography on silica gel.

Kinetics: The kinetics of the reactions of the conjugated azoalkenes **1** with the nucleophiles **2**–**5** were followed by UV/Vis spectroscopy by using working stations similar to those described previously.[3a,f,17] For slow reactions ($\tau_{1/2} > 10$ s) the UV/Vis spectra were collected at different times by using a J&M TIDAS diode array spectrophotometer connected to a Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) by fiber-optic cables with standard SMA connectors. All kinetic measurements were carried out in Schlenk glassware under exclusion of moisture. The temperature of the solutions during the kinetic studies was maintained to 20 ± 0.1 °C by using circulating bath cryostats monitored with thermo-couple probes that were inserted into the reaction mixture. Stopped-flow spectrophotometer systems (Applied Photophysics SX.18MV-R or Hi-Tech SF-61DX2) were used for the investigation of fast reactions of 1,2-diaza-1,3-dienes with nucleophiles ($\tau_{1/2} < 10$ s). The kinetic runs were initiated by mixing equal volumes of solutions of the 1,2-diaza-1,3-dienes and the nucleophiles. Concentrations and rate constants for the individual kinetic experiments are given in the Supporting Information.

The Supporting Information provides information on preparative procedures and product characterization, and details of the individual runs of the kinetic experiments are also available.

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[1] Reviews: a) O. A. Attanasi, *Org. Prep. Proced. Int.* **1986**, *18*, 299–327; b) O. A. Attanasi, P. Filippone, *Synlett* **1997**, 1128–1140; c) O. A. Attanasi, L. De Crescentini, P. Filippone, F. Mantellini, S. Santeusanio, *Arkivoc* **2002**, *XI*, 274–292; d) O. A. Attanasi, L. De Crescentini, G. Favi, P. Filippone, F. Mantellini, F. R. Perrulli, S. Santeusanio, *Eur. J. Org. Chem.* **2009**, 3109–3127.

[2] H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957.

[3] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512; b) R. Lucius, R. Loos, H. Mayr, *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95; c) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; d) H. Mayr, A. R. Ofial in *Carbocation Chemistry* (Eds.: G. A. Olah, G. K. S. Prakash), Wiley, New York, **2004**, Chapter 13, pp. 331–358; e) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; f) H. Mayr, A. R. Ofial, *J. Phys. Org. Chem.* **2008**, *21*, 584–595; g) D. Richter, N. Hampel, T. Singer, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2009**, 3203–3211.

[4] a) T. Lemek, H. Mayr, *J. Org. Chem.* **2003**, *68*, 6880–6886; b) S. T. A. Berger, F. H. Seeliger, F. Hofbauer, H. Mayr, *Org. Biomol. Chem.* **2007**, *5*, 3020–3026; c) F. Seeliger, S. T. A. Berger, G. Y. Remennikov, K. Polborn, H. Mayr, *J. Org. Chem.* **2007**, *72*, 9170–9180; d) O. Kaumanns, H. Mayr, *J. Org. Chem.* **2008**, *73*, 2738–2745; e) O. Kaumanns, R. Lucius, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 9675–9682.

[5] T. B. Phan, H. Mayr, *Eur. J. Org. Chem.* **2006**, 2530–2537.

[6] a) O. A. Attanasi, P. Bonifazi, E. Foresti, G. Pradella, *J. Org. Chem.* **1982**, *47*, 684–687; b) O. Attanasi, P. Filippone, A. Mei, S. Santeusanio, *Synthesis* **1984**, 671–672; c) O. A. Attanasi, P. Filippone, S. Santeusanio, F. Serra-Zanetti, *Synthesis* **1987**, 381–383; d) O. A. Attanasi, Z. Liao, A. McKillop, S. Santeusanio, F. Serra-Zanetti, *J. Chem. Soc. Perkin Trans. 1* **1993**, 315–320; e) A. Arcadi, O. A. Attanasi, L. De Crescentini, E. Rossi, F. Serra-Zanetti, *Tetrahedron* **1996**, *52*, 3997–4012.

[7] M. R. Crampton, J. A. Stevens, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1715–1720.

[8] F. Terrier, S. Lakhdar, T. Boubaker, R. Goumont, *J. Org. Chem.* **2005**, *70*, 6242–6253.

[9] a) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209–2218; b) S. Minegishi, H. Mayr, *J. Am. Chem. Soc.* **2003**, *125*, 286–295; c) B. Kempf, H. Mayr, *Chem. Eur. J.* **2005**, *11*, 917–927; d) T. B. Phan, M. Breugst, H. Mayr, *Angew. Chem.* **2006**, *118*, 3954–3959; *Angew. Chem. Int. Ed.* **2006**, *45*, 3869–3874; e) T. Kanzian, T. A. Nigst, A. Maier, S. Pichl, H. Mayr, *Eur. J. Org. Chem.* **2009**, 6379–6385.

[10] O. A. Attanasi, S. Berretta, L. De Crescentini, G. Favi, G. Giorgi, F. Mantellini, *Adv. Synth. Catal.* **2009**, *351*, 715–719.

[11] a) O. A. Attanasi, P. Filippone, A. Mei, *Tetrahedron* **1992**, *48*, 1707–1714; b) O. A. Attanasi, P. Filippone, D. Giovagnoli, *Org. Prep. Proced. Int.* **1994**, *26*, 321–326.

[12] a) S. Sommer, *Chem. Lett.* **1977**, 583–586; b) S. Sommer, *Angew. Chem.* **1979**, *91*, 756–757; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 695–696; c) A. G. Schultz, W. K. Hagmann, M. Shen, *Tetrahedron Lett.* **1979**, *20*, 2965–2968; d) E. Rossi, G. Abbiati, O. A. Attanasi, S. Rizzato, S. Santeusanio, *Tetrahedron* **2007**, *63*, 11055–11065.

[13] a) M. Hartnagel, K. Grimm, H. Mayr, *Liebigs Ann.* **1997**, 71–80; b) H. Mayr, J. Henninger, *Eur. J. Org. Chem.* **1998**, 1919–1922; c) H. Mayr, A. R. Ofial, J. Sauer, B. Schmied, *Eur. J. Org. Chem.* **2000**, 2013–2020; d) C. Fichtner, H. Mayr, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1441–1444.

[14] O. A. Attanasi, L. De Crescentini, P. Filippone, F. Fringuelli, F. Mantellini, M. Matteucci, O. Piermatti, F. Pizzo, *Helv. Chim. Acta* **2001**, *84*, 513–525.

[15] H. G. O. Becker, *Organikum*, 19th ed., Verlag der Wissenschaften, Berlin, **1993**.

[16] O. Attanasi, P. Filippone, A. Mei, S. Santeusanio, *Synthesis* **1984**, 873–874.

[17] H. Mayr, R. Schneider, C. Schade, J. Bartl, R. Bederke, *J. Am. Chem. Soc.* **1990**, *112*, 4446–4454.

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