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Quantification of the Electrophilicities of Diazoalkanes: Kinetics and Mechanism of Azo Couplings with Enamines and Sulfonium Ylides

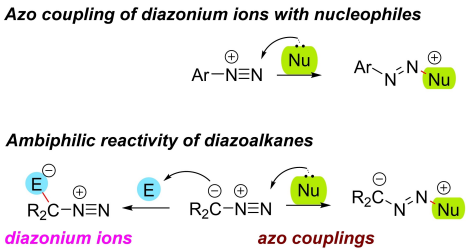
Le Li,[a] Robert J. Mayer,[b] David S. Stephenson,[a] Peter Mayer,[a] Armin R. Ofial,*[a] and Herbert Mayr*[a]

Dedicated to Professor Paul Knochel in recognition of his outstanding contributions to modern metalorganic chemistry.

Abstract: Kinetics and mechanism of the reactions of methyl diazoacetate, dimethyl diazomalonate, 4-nitrophenyldiazomethane, and diphenyldiazomethane with sulfonium ylides and enamines were investigated by UV-Vis and NMR spectroscopy. Ordinary alkenes undergo 1,3-dipolar cycloadditions with these diazo compounds. In contrast, sulfonium ylides and enamines attack at the terminal nitrogen of the diazo alkanes to give zwitterions, which undergo various subsequent reactions. As only one new bond is formed in the rate-determining step of these reactions, the correlation $\lg k_2(20\,^{\circ}C) = s_N(N+E)$ could be used to determine the one-bond electrophilicities E of the diazo compounds from the measured second-order rate constants and the known reactivity indices N and s_N of the sulfonium ylides and enamines. The resulting electrophilicity parameters ($-21 < E < -18$), which are 11–14 orders of magnitude smaller than that of the benzenediazonium ion, are used to define the scope of one-bond nucleophiles which may react with these diazoalkanes.

Introduction

Diazoalkanes are versatile reagents for organic synthesis. They are widely used 1,3-dipoles that react with dipolarophiles to give five-membered heterocycles (Huisgen reactions).[1] As ambiphilic reagents they have the ability to react with electrophiles as well as with nucleophiles (Scheme 1). While electrophiles attack at the carbon atom to yield diazonium ions, nucleophiles attack at the terminal nitrogen to yield azo compounds.[2] Mechanistically, the attack of a nucleophile at the terminal nitrogen of the diazoalkane parallels the well-known azo couplings of diazonium ions.[3]



Scheme 1. Reactions of diazoalkanes with electrophiles and nucleophiles and mechanistically analogous azo couplings with diazonium ions.

Kinetic investigations of the reactions of diazoalkanes with a series of benzhydrylium ions ($Aryl_2CH^+$) of known electrophilicity E have previously been performed to characterize the nucleophilicities of diazoalkanes, which are described by the parameters N and s_N in Equation (1).[4]

$$\lg k_{20\,^{\circ}C} = s_N(N+E) \quad (1)$$

In this way, diazoalkanes have been integrated in the currently most comprehensive nucleophilicity scales[5] showing that diazomethane has a nucleophilic reactivity comparable to enamines, whereas stabilized diazoalkanes, such as diazoacetates and diphenyldiazomethane, have nucleophilic reactivities similar to silylated enol ethers and allylsilanes (Figure 1). The least nucleophilic diazoalkanes characterized so far were diazomalonates with N parameters slightly lower than those of 1,1-dialkylethylenes and styrene. Based on these comparisons it

[a] L. Li, Dr. D. S. Stephenson, Dr. P. Mayer, Dr. A. R. Ofial, Prof. Dr. H. Mayr
Department Chemie
Ludwig-Maximilians-Universität München
Butenandtstr. 5–13, 81377 München (Germany)
E-mail: ofial@lmu.de
herbert.mayr@cup.uni-muenchen.de
Homepage: www.cup.uni-muenchen.de/oc/ofial/
www.cup.uni-muenchen.de/oc/mayr/

[b] Dr. R. J. Mayer
Institut des Science et d'Ingénierie Supramoléculaires (ISIS)
Université de Strasbourg & CNRS
8 Allée Gaspard Monge, 67000 Strasbourg (France)

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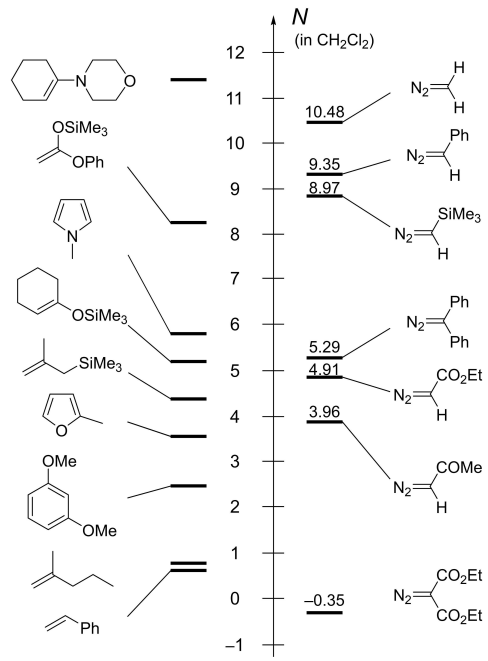


Figure 1. Comparison of the nucleophilicity parameters *N* of diazoalkanes (*N* in CH_2Cl_2 from Ref. [4a]) with those of other $\pi_{C=C}$-nucleophiles (*N* in CH_2Cl_2 from Ref. [5 f]).

was possible to derive a general ordering principle for the reactions of diazoalkanes with electrophiles.[4a]

We have now complemented this work by an analogous quantification of the electrophilicities *E* of the α-diazoesters **1 a** and **1 b**, *p*-nitrophenyldiazomethane (**1 c**), and diphenyldiazomethane (**1 d**) (Figure 2) by studying the rates of their reactions with the sulfonium ylides **2 a**–**b** and the enamines **3 a**–**e** as reference nucleophiles. The nucleophile-specific reactivity descriptors *N* and s_N of **2** and **3**, needed for these derivations by Equation (1), have previously been derived from the rates of

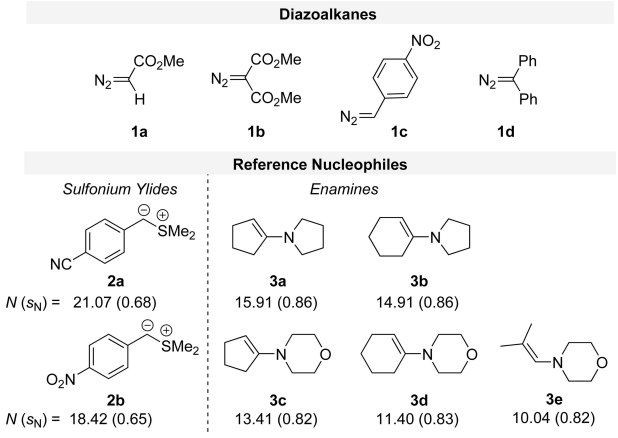


Figure 2. Diazoalkanes **1** and nucleophiles (N and s_N parameters of **2** in DMSO[6a] and of **3** in dichloromethane[5b,6b]) used in this work for determining the electrophilicities *E* of **1 a**–**d**.

their reactions with benzhydrylium ions and structurally related quinone methides (Figure 2).

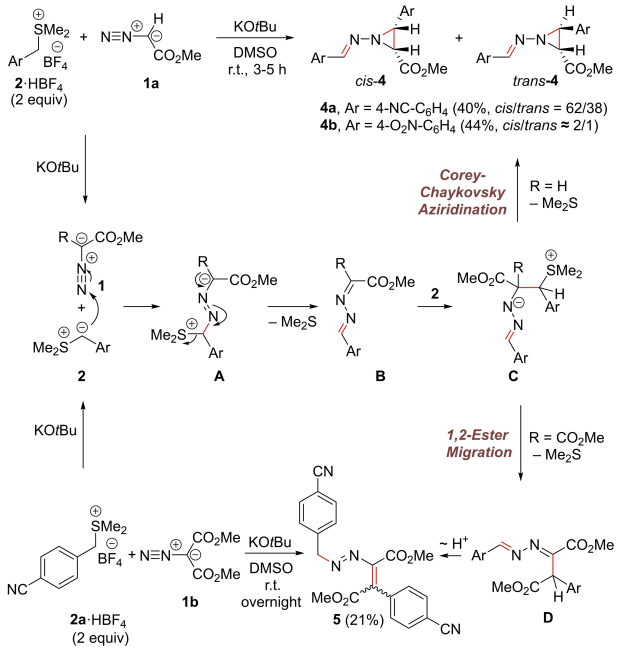
Prerequisite for the applicability of Equation (1) is a reaction mechanism, in which one, and only one, new σ-bond is generated in the rate-determining step.[5] Though earlier work had claimed concerted 1,3-dipolar cycloadditions of diazoacetate **1 a** and diazomalonate **1 b** with pyrrolidinocyclohexene **3 b**,[7a,c] we have recently demonstrated that these reactions proceed via rate-determining formation of azo coupling products, which undergo subsequent cyclizations.[8] Thus, the measured rate constants for these reactions reflect the one-bond electrophilicities of the diazoalkanes, as needed for our analysis.

Herein, we report on the reactions of the diazoalkanes **1** with sulfonium ylides **2** and enamines **3**. The second-order rate constants of these reactions are used for determining the one-bond electrophilicities *E* of diazoalkanes **1 a**–**d**. By demonstrating that the *E* values thus obtained allow one to rationalize previously reported azo couplings of diazoalkanes, it is shown that these parameters reflect the electrophilic potential of diazoalkanes and enable synthetic chemists to predict the scope of nucleophiles accessible for azo couplings with **1**.

Results and Discussion

Product analysis of the reactions of 1 a–b with the sulfonium ylides 2 a–b

Methyl diazoacetate **1 a** reacts with two equivalents of the sulfonium ylides **2 a** and **2 b** in DMSO to give mixtures of *cis*/*trans* aziridines **4** with a total yield of about 40 % (Scheme 2). Their formation can be explained by attack of **2** at the N



Scheme 2. Reactions of diazoalkanes **1** with sulfonium ylides **2**.

terminus of **1a** (→**A**) followed by elimination of Me_2S to give a 2,3-diazabuta-1,3-diene (**B**), which reacts with a second equivalent of **2** to yield **C**. An intramolecular nucleophilic substitution eventually furnishes the aziridines **4** (Scheme 2). An analogous Corey-Chaykovsky reaction of electrophilic 2,3-diazabutadienes affording aziridines has previously been reported.[9]

The formation of the azo compound **5** from **1b** with **2a** (Scheme 2) can analogously be explained by attack of a second equivalent of **2a** at the intermediate **B**. The resulting zwitterion **C** (R = CO_2Me) does not cyclize as in the case of R = H, but undergoes 1,2-ester migration concomitantly with or after Me_2S elimination to form **D** which gives **5** by a proton shift (Scheme 2). Related reactions of diazoalkanes with sulfonium ylides giving 2:1-products have recently been reported.[10]

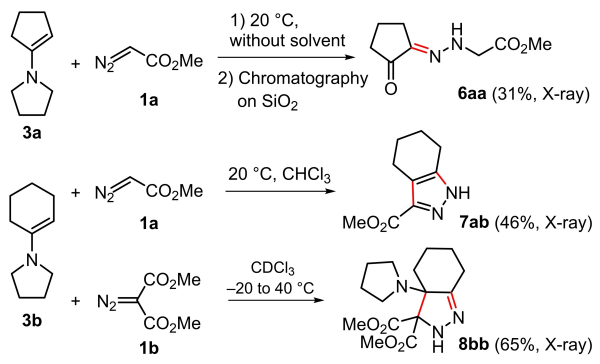
Products of the reactions of diazoalkanes with 1-(dialkylamino)cycloalkenes 3(a–d)

In recent work, we have confirmed the formation of **6aa**, **7ab** and **8bb** by the reactions of diazoacetate **1a** and diazomalonate **1b** with pyrrolidinocyclopentene **3a** and pyrrolidinocyclohexene **3b** (Scheme 3).[7,8]

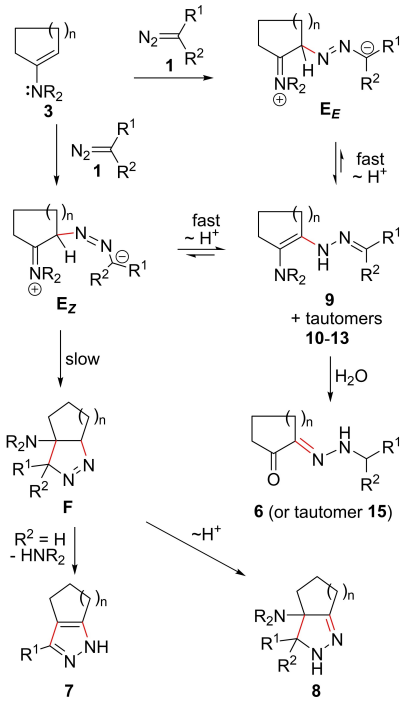
In contrast to earlier statements[7c] we found, however, that the heterocycles **7ab** and **8bb** are not formed via concerted 1,3-dipolar cycloadditions, but via azo couplings to give hydrazonoenamines **9** and other tautomers of the initially formed zwitterions $\mathbf{E}_E$ and $\mathbf{E}_Z$, which undergo subsequent cyclizations (Scheme 4). We now report that Scheme 4, which has been shown to rationalize the mechanisms of the formation of **6aa**, **7ab**, and **8bb** can also be used to explain the products and mechanisms of other combinations of the diazoalkanes **1a-d** with enamines **3a-e**.

Reactions of diazoalkanes 1 with the 1-(dialkylamino)cyclopentenes 3a and 3c

In line with an earlier report by Huisgen, Bihlmaier, and Reissig,[7b] combination of diazomalonate **1b** with pyrrolidinocyclopentene **3a** in Et_2O at 0 °C resulted in the precipitation of



Scheme 3. Products of the reactions of diazoacetate **1a** and diazomalonate **1b** with the enamines **3a** and **3b**.



Scheme 4. Mechanism for the reactions of diazoalkanes **1** with enamines **3**. Note: In designating specific reaction products, the first letter refers to the diazoalkane precursor, and the second letter specifies the enamine precursor; thus product **9ba** refers to structure **9** formed from diazoalkane **1b** and enamine **3a**.

brick-red needles (yield: 90%). The identity of the precipitated material was attributed by Huisgen et al. to the zwitterionic structure **Eba**.[7b] However, when we analyzed the precipitate by NMR and UV-Vis spectroscopy as well as by single crystal X-ray crystallography, we identified the red needles as the hydrazonoenamine **9ba** (Figure 3; UV-vis spectrum in Supporting Information: Figure S2a, black curve). From the electron densities calculated using X-ray diffraction data, a hydrogen bond from N2 to O4 (Figure 3a) was derived.

When isolated **9ba** was dissolved in $CDCl_3$ at −50 °C, only the signals of **9ba** were seen in the ^1H and ^{13}C NMR spectra (pp. S58-S59, Supporting Information). When this sample was warmed up to 20 °C, tautomerization led to a 2:3:5 mixture of **9ba**, **11ba**, and **12ba**, the ratio of which was derived from the ^1H NMR signals at δ = 2.77 (t, **9ba**), 5.25 (s, **11ba**), and 4.86 ppm (d, **12ba**). A signal of low intensity at δ = 4.26 ppm, which appeared during warming up at 0 °C and disappeared at 20 °C, was probably due to traces of **10ba** (Figure S3). As depicted in Figure S2a, the UV-vis spectrum of the red needles (**9ba**) measured at −50 °C in $CHCl_3$ showed an absorption maximum at λ = 491 nm which is close to that reported in Ref. [7b] (λ = 477 nm). The shape of the experimental spectrum is in agreement with the calculated spectrum for **9ba** (Supporting Information: Figure S2a, red curve). The originally suggested zwitterionic structure **Eba**[7b] for the red needles must, therefore, be revised. The decrease of the absorbance at 491 nm (**9ba**) during warming up (Figure S2b) is in line with the NMR-spectroscopically observed tautomerization of **9ba** (Figure S3).

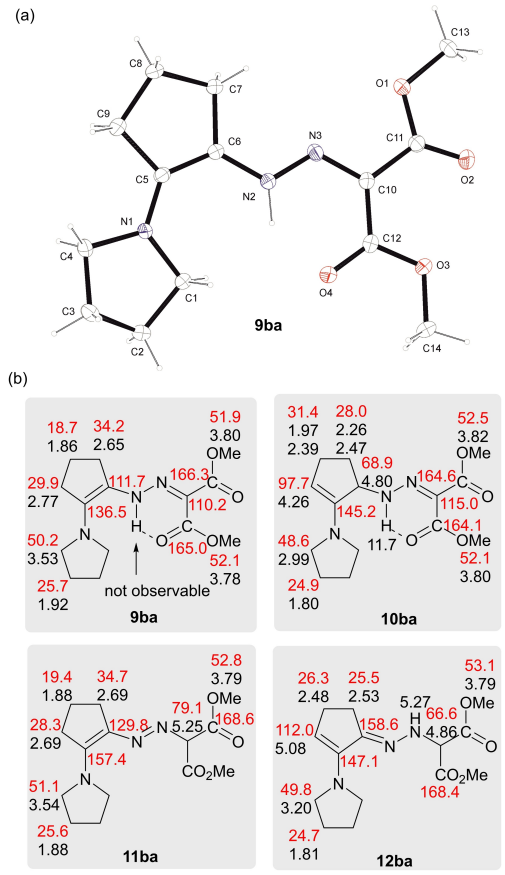
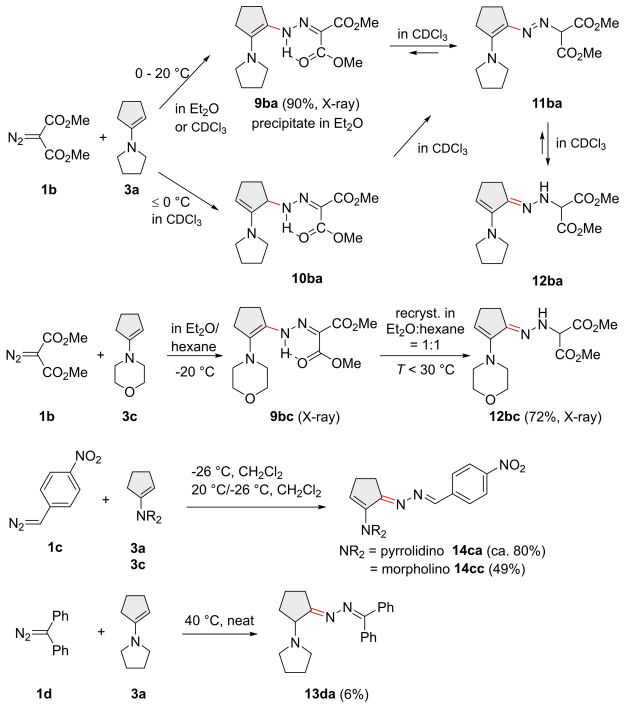


Figure 3. (a) Crystal structure of hydrazonoenamine **9ba**. (b) ^{1}H and ^{13}C NMR chemical shifts of the azo coupling products **9ba**, **10ba**, **11ba**, and **12ba**.



Scheme 5. Reactions of diazoalkanes **1b–d** with the cyclopentanone-derived enamines **3a** and **3c**.

When the reaction of **1b** with **3a** in $CDCl_3$ at −50 °C was followed by ^{1}H NMR spectroscopy, the simultaneous formation of **9ba**, **10ba** and **11ba** was observed (Figure S4). Whereas **9ba** and **10ba** are directly generated from zwitterion **Eba**, it is not clear whether **11ba** is directly formed from **Eba** or through tautomerization of **10ba**. NMR monitoring of the reaction at −30 °C showed that the concentration of **10ba** (Figure S4), originally formed from **Eba**, decreases at longer reaction times due to tautomerization, predominantly into **11ba**. At 20 °C, hydrazonoenamine **12ba** is the most stable tautomer. Of all the tautomers formed in the reaction of **1b** with **3a**, **12ba** is formed most slowly, which can be explained by the fact that in **12ba**, like in the tautomer **11ba**, a new C–H bond is generated, which has a higher intrinsic barrier than proton transfer to nitrogen.

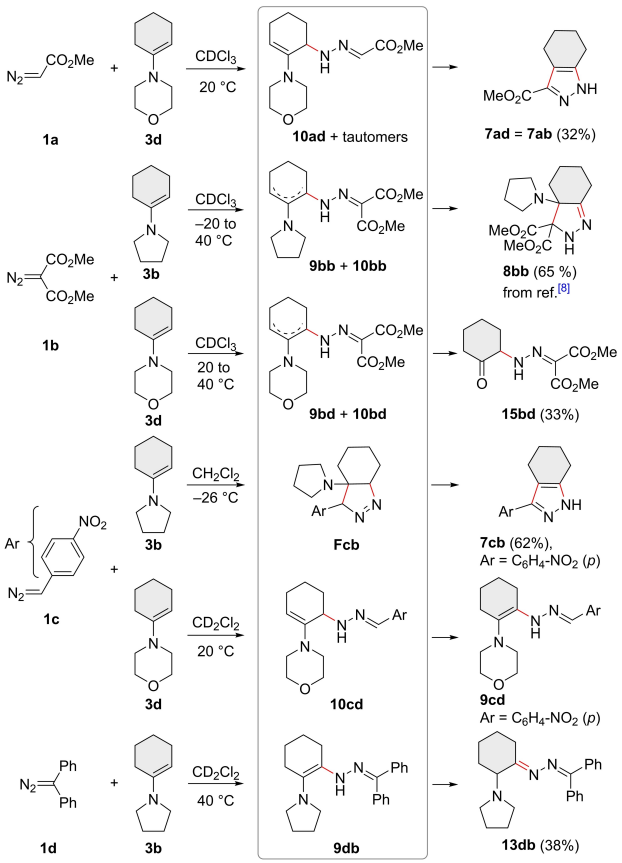
The reaction of diazomalonate **1b** with morpholinocyclopentene **3c** in Et_2O/hexane at −20 °C proceeded analogously (Scheme 5), and an orange needle formed in the reaction mixture was characterized as **9bc** by X-ray crystallography. Attempts to recrystallize **9bc** from Et_2O/hexane led to tautomerization and formation of **12bc** (72%), which was unequivocally identified by X-ray crystallography. In contrast to the equilibrium mixture of **12ba/11ba/9ba**, **12bc** appears to be the most stable tautomer, as it is the only species observed by NMR spectroscopy (pp. S79-S80, Supporting Information). Hydrazonoenamine **12bc** has previously been obtained from **1b** and **3c** in 66% yield in Et_2O at −30 °C,[7b] and the reported ^{13}C NMR spectra are in accord with our spectra. The close analogy of the ^{13}C NMR spectra of **12bc** and **12ba** (pp. S70-S74, Supporting Information) is another confirmation of the structure of **12ba**. When the reaction of **1b** with **3c** in $CDCl_3$ was followed by ^{1}H NMR spectroscopy at 20 to 40 °C, **12bc** was generally observed as the predominant species.

Combination of *p*-nitrophenyldiazomethane (**1c**) with the aminocyclopentenes **3a** and **3c** furnished compounds **14ca** and **14cc**, respectively. It is not clear, why neither **9ca**, **9cc**, nor any of their tautomers were detectable, and only the oxidized products **14ca** and **14cc** were observed.

Heating of diphenyldiazomethane (**1d**) with pyrrolidinocyclopentene **3a** without solvent for two days at 40 °C yielded **13da** in very poor yield (6%).

Reactions of diazoalkanes 1 with the 1-(dialkylamino)-cyclohexenes 3b and 3d

While cyclization products have not commonly been observed in the reactions of **1** with the cyclopentenyl amines **3a** and **3c** (Schemes 1 and 5),[11] pyrazole **7ad** (=**7ab**, Scheme 6) was the only product obtained in moderate yield from the reaction of methyl diazoacetate (**1a**) with pyrrolidinocyclohexene **3b** (Scheme 3) and morpholinocyclohexene **3d** (Scheme 6), in agreement with a previous report of Reissig and Huisgen who obtained 82% of **7ab** by the reaction of **1a** with **3b** in



Scheme 6. Reactions of diazoalkanes **1** with the cyclohexanone-derived enamines **3b** and **3d** (framed: intermediates detected by NMR spectroscopic monitoring).

chloroform at ambient temperature.[7c] ^{1}H NMR monitoring of this reaction in $CDCl_3$ showed the initial formation of the azo coupling product **10ad** (pp. S95-S98, Supporting Information), followed by the appearance of other tautomers and eventual cyclization with formation of **7ad** by elimination of morpholine and proton migration.

The initial formation of **10bd** followed by occurrence of **9bd** (pp. S101-S106, Supporting Information) was observed by ^{1}H NMR spectroscopy in the reaction of **1b** with morpholinocyclohexene **3d** at 20 to 40 °C, in analogy to the reaction of **1b** with **3b**, which initially gave a mixture of **9bb** and **10bb**. While the hydrazonoenamines **9bb** and **10bb** underwent ring closure and eventually gave **8bb**,[8] the hydrazonoenamines **9bd** and **10bd** did not cyclize, and the cyclohexanone derivative **15bd** was isolated in 33% yield after chromatography on silica gel.[12]

The ^{1}H NMR spectroscopic monitoring of the reaction of **1c** with **3b** at −10 °C allowed to identify the 1-pyrazoline **Fcb** (pp. S85–S88, Supporting Information) as an intermediate, before it underwent elimination of pyrrolidine and proton shift to give 62% of **7cb**.

The reaction of *p*-nitrophenyldiazomethane (**1c**) with morpholinocyclohexene **3d** yields enamine **10cd** initially (pp. S109–S110, Supporting Information), which also does not cyclize, but tautomerizes with formation of **9cd**. A plausible reason why only azo coupling products generated from cyclohexanone-derived enamines can undergo subsequent cyclization is given below.

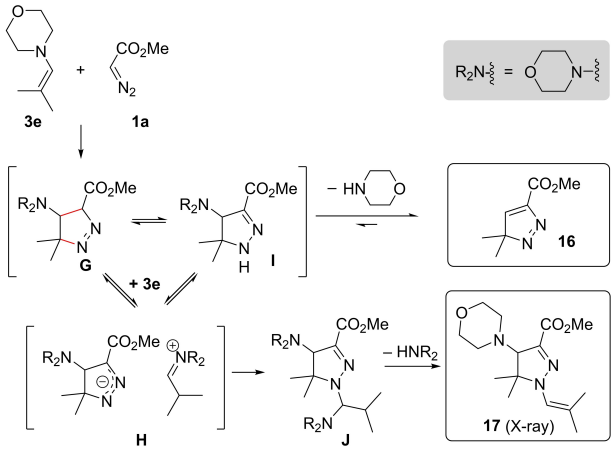
While mainly decomposition of pyrrolidinocyclopentene **3a** took place when treated with diphenyldiazomethane (**1d**, Scheme 5), we observed the formation of compound **9db** (pp. S91–S94, Supporting Information) in the reaction of **1d** with **3b**, as previously reported by Bettinetti and co-workers.[13] In repeating this reaction several times, we could not reproduce this result and instead isolated **13db**, a tautomer of **9db**.

Reactions of diazoalkane 1a with 1-morpholinoisobutene (3e)

The reaction of 1-morpholinoisobutene (**3e**) with **1a** in the dark (3 days at +50 °C)[14] furnished a mixture of the 1:1-product **16** and 2:1-product **17**, which was separated by column chromatography. In analogy to the reactions described in Scheme 4 we assume that the Δ^1-pyrazoline **G** is formed via stepwise Huisgen cycloaddition, followed by morpholine elimination, either directly or via tautomer **I**, to yield the isolated pyrazole **16**, which has previously been obtained by the reaction of **1a** with 1-pyrrolidinoisobutene.[7c] The 2:1 product **17**, whose structure was characterized by NMR spectroscopy and X-ray crystallography (Scheme 7), may be formed through proton transfer from **G** or **I** to enamine **3e** to give **H**, which may collapse with formation of **J**, the precursor of **17**. An alternative mechanism for the formation of **17** is suggested in Scheme S2. Both mechanisms are in line with the observed formation of **17** from isolated **16** and **3e** (Figure S6).

Kinetics of the reactions of 1 a–d with 2 and 3

The reactions of diazoalkanes **1** with sulfonium ylides **2** were studied photometrically by monitoring the decay of the UV-Vis absorbances of the sulfonium ylides in DMSO at 20 °C (Fig-



Scheme 7. Products and suggested mechanism for the reaction of **1a** with **3e**.

ure 4a). Due to the slow decomposition of the sulfonium ylides **2** (product formed by decomposition: p. S5, Supporting Information), they were generated in the flask used for the kinetic experiments by treating the solution of **2**(H)BF_4 in DMSO with KO*t*Bu (1.03-1.15 equiv) immediately before adding the diazoalkanes **1** (Figure 4b). In order to achieve pseudo-first-order kinetics, more than 9 equivalents of the diazoalkanes were used. The mono-exponential decays of the absorbances of the sulfonium ylides indicate that the reactions proceed with first-order in sulfonium ylides. The first-order in diazoalkanes **1** is indicated by the linear correlations of the pseudo-first-order rate constants k_{obs} with [**1**] (Figure 4c).

As previously reported,[8] the kinetics of the reactions of the diazoalkanes **1** with enamines **3** were investigated by time-resolved ^{1}H NMR spectroscopy, following the decrease of the vinylic hydrogens of the enamines **3** relative to an internal standard (mesitylene, dibromomethane, or 1,1,2,2-tetrachloroethane) in $CDCl_3$, CD_2Cl_2 or d_8-toluene/mesitylene (1 : 1) at various temperatures. Usually equimolar amounts of **1** and **3** were used, and the second-order rate constants k_2 were obtained as the slopes of plots of $1/[\mathbf{3}]_t$ versus time t according to $1/[\mathbf{3}]_t = k_2t + 1/[\mathbf{3}]_0$; in some cases 2 equivalents of **1** were used and evaluated as described on p S4 (Supporting Information).[15] Plots of $\ln(k_2/T)$ versus $(1/T)$ provided the Eyring activation parameters $\triangle H^{\neq}$ and $\triangle S^{\neq}$, from which the second-order rate constants k_2 at 20 °C were calculated (Table 1).

Kinetics of some of these reactions, which were measured by us between −50 to +50 °C in $CDCl_3$ had previously been studied by Reissig and Huisgen at +80.3 °C in toluene or at +110 °C in mesitylene.[7] In order to compare these data with our results, we used the Eyring activation parameters in Table 1 to calculate rate constants at the higher temperatures of the previous studies (Table S20). Due to the highly negative activation entropies and the small activation enthalpies, the rates of these reactions are not strongly affected by variation of temperature. Extrapolation of our previously reported rate constants for the reactions of methyl diazoacetate **1a** with **3a** and **3b** in $CDCl_3$ at −40 to −10 °C[8] by the Eyring equation gave values on average one order of magnitude greater than those reported at 80.3 °C in toluene.[7d] Analogous extrapolation of the rate constants in Table 1 ($CDCl_3$ and CD_2Cl_2, −50 to +50 °C) by the Eyring equation led to values, generally one order of magnitude higher, in the case of **1b** + **3a** 500 times higher than previously measured at +110 °C in mesitylene solution (Supporting Information).[7a,d] Solvent effects can only partially account for this discrepancy because our NMR studies showed that the reactions of **1b** with **3b** and **3c** are 3 and 6 times faster in $CDCl_3$ than in d_8-toluene/mesitylene = 1 : 1 (v/v) (Table S20).

Quantum chemical calculations

Quantum chemical calculations have been performed in order to examine our conclusion that zwitterions **E** are common intermediates of all reactions of the diazoalkanes **1a–d** with the enamines **3**, as depicted in Scheme 4. For that purpose, a conformational sampling was performed for all structures using the OPLS3 force field as implemented in Macromodel.[16] Subsequently, the geometries were optimized at the B3LYP–D3BJ/def2-SVP[17] level of theory considering solvation with the SMD model[18] for chloroform within the Gaussian set of codes.[19] For improved accuracy, the thermal corrections at this level were combined with single-point energies using the (SMD = $CHCl_3$)/MN15/def2-TZVPD method.[20] Eventually, the Gibbs energies of all conformers were Boltzmann weighted.

As previously reported for diazoacetate **1a**,[8] the lowest unoccupied orbital of the heteropropargyl system (ψ_3) does not correspond to LUMO of **1a**, but to LUMO + 1. Figure 5 shows that the situation is similar in **1b–1d**. In all cases, the previously neglected $\pi^*_{N=N}$ is significantly lower in energy than ψ_3 and generally corresponds to the LUMO. Only in 4-nitrophenyldiazomethane (**1c**), there is an even lower lying unoccupied molecular orbital which is largely localized at the nitro group. Since it is not relevant for the reactivity of **1c**, it is not depicted in Figure 5, but shown in Figure S10 (Supporting Information).

As reported for **1a**,[8] two separate trajectories have also been identified for the reactions of **1b–d** with enamines **3a** and

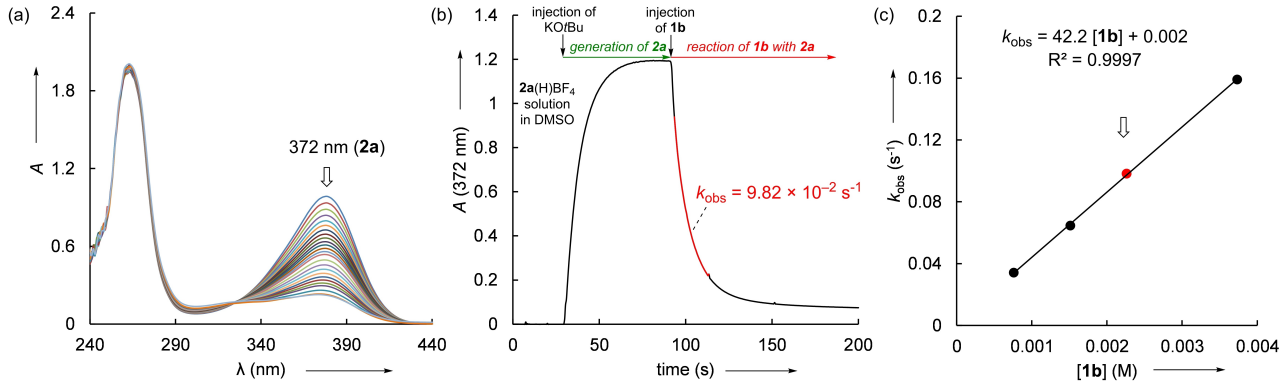


Figure 4. (a) UV-Vis spectroscopic monitoring of the reaction of **1b** (2.26×10^{-3} M) with **2a** (8.32×10^{-5} M) generated from a KO*t*Bu solution (1.14 equiv) and a **2a**(H)BF_4 solution in DMSO at 20 °C. (b) Mono-exponential decay of the absorbance A at 372 nm vs. time for the reaction of **1b** with **2a** in DMSO at 20 °C. (c) Linear correlation of k_{obs} with [**1b**] for determining the second-order rate constant $k_2 = 42.2\ M^{-1}s^{-1}$ at 20 °C.

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Table 1. Second-order rate constants k_2 and Eyring activation parameters $\triangle H^{\neq}$ and $\triangle S^{\neq}$ for the reactions of **1 a-d** with **2** and **3**.

Diazoalkanes	Nucleophiles (solvents)	T [°C]	k_2 [M^{-1} s^{-1}]	$\triangle H^{\neq}$ [kJ mol^{-1}]	$\triangle S^{\neq}$ [J mol^{-1} K^{-1}]
	Reactions with **1 a**				
1 a	**2 a** (DMSO)	+20	1.18×10^{2}		
1 a	**2 b** (DMSO)	+20	2.17		
1 a	**3 a** ($CDCl_3$)	+20	$(1.83\pm0.30)\times10^{-3}$ [a,b]	22.0 ± 2.1	−222 ± 9
1 a	**3 b** ($CDCl_3$)	+20	$(4.68\pm0.56)\times10^{-4}$ [a,b]	23.5 ± 1.8	−228 ± 7
1 a	**3 d** ($CDCl_3$)	+50	4.82×10^{-6}		
		+40	2.75×10^{-6}		
		+30	1.38×10^{-6}		
		+20	$(7.03\pm0.38)\times10^{-7}$ [a]	48.4 ± 2.1	−198 ± 7
1 a	**3 e** ($CDCl_3$)	+50	1.97×10^{-6}		
		+40	1.01×10^{-6}		
		+30	4.77×10^{-7}		
		+20	$(2.20\pm0.05)\times10^{-7}$ [a]	55.2 ± 0.9	−184 ± 3
	Reactions with **1 b**				
1 b	**2 a** (DMSO)	+20	4.22×10^{1}		
1 b	**3 a** ($CDCl_3$)	−50	6.96×10^{-4}		
		−40	1.40×10^{-3}		
		−30	2.38×10^{-3}		
		+20	$(2.59\pm0.42)\times10^{-2}$ [a]	25.8 ± 1.5	−187 ± 7
1 b	**3 b** ($CDCl_3$)	−50	8.98×10^{-5}		
		−40	1.40×10^{-4}		
		−30	1.84×10^{-4}		
		+20	$(7.59\pm1.50)\times10^{-4}$ [a]	14.3 ± 1.8	−256 ± 8
1 b	**3 c** ($CDCl_3$)	+40	1.92×10^{-4}		
		+30	1.47×10^{-4}		
		+20	9.71×10^{-5}		
		+20	$(9.91\pm0.37)\times10^{-5}$ [a]	23.6 ± 2.8	−241 ± 9
1 b	**3 d** ($CDCl_3$)	+40	7.25×10^{-6}		
		+30	6.19×10^{-6}		
		+20	4.74×10^{-6}		
		+20	$(4.81\pm0.13)\times10^{-6}$ [a]	13.7 ± 2.1	−300 ± 7
	Reactions with **1 c**				
1 c	**3 a** (CD_2Cl_2)	−40	1.03×10^{-3}		
		−30	1.47×10^{-3}		
		−20	2.18×10^{-3}		
		+20	$(7.20\pm0.59)\times10^{-3}$ [a]	16.4 ± 1.0	−230 ± 4
1 c	**3 b** (CD_2Cl_2)	−30	2.87×10^{-4}		
		−20	4.61×10^{-4}		
		−10	6.63×10^{-4}		
		+20	$(1.93\pm0.15)\times10^{-3}$ [a]	20.2 ± 1.2	−228 ± 5
1 c	**3 c** (CD_2Cl_2)	+20	7.59×10^{-5}		
1 c	**3 d** (CD_2Cl_2)	+20	1.80×10^{-6}		
	Reactions with **1 d**				
1 d	**3 b** (CD_2Cl_2)	+20	2.89×10^{-6}		

[a] Extrapolated from rate constants at other temperatures by using the Eyring equation; [b] Data from Ref. [8].

3 b. In all cases, the stepwise process, which involves rate-determining formation of the intermediate zwitterions $\mathbf{E}_E$ or $\mathbf{E}_Z$ by attack of the enamine at $\pi^*_{N=N}$, proceeds via considerably lower barriers than the concerted pathway (Table 2). For details of the non-occurring concerted pathway, which involves the

Table 2. Comparison of experimental and calculated activation Gibbs energies at 25 °C (in kJ mol^{-1}, at the (SMD = $CHCl_3$)/MN15/def2-TZVPD//(SMD = $CHCl_3$)/B3LYP–D3BJ/def2-SVP level of theory). - See text for the meaning of the color markings.

Entry		$\Delta G^{\neq}_{exp}$	$\Delta G^{\neq}_{E}$	$\Delta G^{\neq}_{Z}$	ΔG^0(**E**$_E$)	ΔG^0(**E**$_Z$)	ΔG^0(**F**)	ΔG^0(**9**)	ΔG^0(**10**)	ΔG^0(**11**)	ΔG^0(**12**)	$\Delta G^{\neq}_{cycl}$	$\Delta G^{\neq}_{conc}$
1 [a]	**1 a** + **3 a**	88.2	99.7	93.3	31.4	57.6	−24.2	−30.1	−27.0	−34.3	−45.0	83.5	135.3
2	**1 b** + **3 a**	81.6	93.0	109.6	42.6	79.1	1.5	−30.6	−17.4	−19.5	−31.8	– [b]	116.8
3	**1 c** + **3 a**	84.9 [c]	104.6	90.6	21.9	49.0	−26.9	−32.9	−33.7	−39.3	−43.5	72.9	– [b]
4	**1 d** + **3 a** [d]	–	108.6	124.3	42.0	102.1	2.0	−35.9	−35.5	−36.5	−43.5	– [b]	151.0
5 [a]	**1 a** + **3 b**	91.6	97.8	99.2	34.6	65.5	−24.6	−24.3	−25.6	−21.8	−28.9	75.6	144.5
6	**1 b** + **3 b**	90.5	91.6	116.6	48.2	83.2	2.4	−20.5	−19.7	−8.8	−15.2	– [b]	119.9
7	**1 c** + **3 b**	88.1 [c]	107.4	95.5	28.0	55.3	−32.9	−37.5	−34.1	−28.5	−28.9	67.6	145.4
8	**1 d** + **3 b**	104.0 [c,e]	105.6	126.5	51.2	110.7	3.3	−40.9	−35.3	−23.4	−27.0	– [b]	173.8

[a] From Ref. [8]. [b] TS could not be localized. [c] In CD_2Cl_2. [d] ΔG^0(**13 da**) = −37.3 kJ mol^{-1}. [e] Calculated from k_2(20 °C) with an estimated $\Delta S^{\neq}$ = −230 J mol^{-1} K^{-1}.

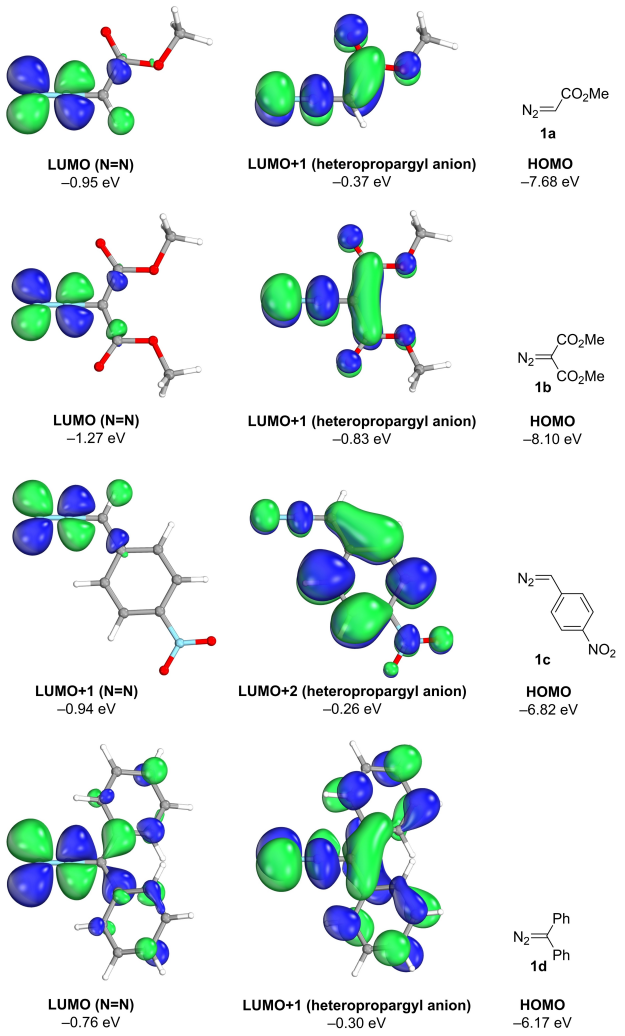


Figure 5. Lowest unoccupied molecular orbitals of **1a**–**d** and their energies at the (SMD = $CHCl_3$)/MN15/def2-TZVPD//(SMD = $CHCl_3$)/B3LYP-D3BJ/def2-SVP level of theory. Orbital energies of **1a** were reported in Ref. [8].

lowest unoccupied orbital of the propargyl system (ψ_3) see ref.[8] and Supporting Information (Figures S11 and S12).

All zwitterions $\mathbf{E}_E$ are more stable than $\mathbf{E}_Z$ (structures in Scheme 4), in line with the well-known higher stability of (*E*)-azo compounds relative to their (*Z*)-isomers.[3] The energy difference [$\Delta G^0(\mathbf{E}_Z)$ - $\Delta G^0(\mathbf{E}_E)$] increases with increasing steric effects and is largest for $R^1 = R^2 = Ph$ (≈60 kJ mol^{-1}, Table 2, entries 4 and 8) and smallest for $R^2 = H$, R^1 = aryl (≈27 kJ mol^{-1}, entries 3 and 7). However, the less-stable *cis*-isomers ($\mathbf{E}_Z$) are generally formed faster if one of the substituents (R^1 or R^2, Scheme 4) equals hydrogen (exception **1a** + **3b**). Coulomb interactions between the two termini, which give rise to the second bond in the corresponding 1,3-dipolar cycloadditions, may account for the faster formation of $\mathbf{E}_Z$ in these cases. If none of the substituents R^1 and R^2 is hydrogen, this stabilization of the transition state is overruled by steric effects, which account for the higher stability of the *trans* zwitterions $\mathbf{E}_E$ compared to $\mathbf{E}_Z$ (Table 2).

The barriers for cyclization of the zwitterions $\mathbf{E}_Z$ are calculated to be very low (reactions of **1a** and **1c**) or cannot be calculated at all, because attempts to localize transition states for the cyclizations of $\mathbf{E}_Z$ (reactions of **1b** and **1d**) led to collapse of the selected structures into the cycloadducts **F** (Figures 6 and S12). However, since in all reactions of the diazoalkanes **1** with the enamines **3**, tautomers of the zwitterions $\mathbf{E}_E$ and $\mathbf{E}_Z$ (i.e., **9**–**13**) were observed as intermediates or final products, proton shifts must generally be faster than cyclization. As discussed for the reactions of **1a** with **3a** and **3b**, the proton shifts in the zwitterions $\mathbf{E}_E/\mathbf{E}_Z$ proceed by intermolecular processes, which we could not describe computationally.[8]

Anyway, since the proton shifts are faster than the cyclizations, Figures 6, S11, and S12 imply that the formation of the zwitterions $\mathbf{E}_E$ or $\mathbf{E}_Z$ corresponds to the rate-determining step of all reactions. This conclusion is supported by the excellent agreement between the experimentally determined activation Gibbs energies $\Delta G^{\neq}_{exp}$ and the calculated barriers for the rate-determining step (smaller value of $\Delta G^{\neq}_E$ and $\Delta G^{\neq}_Z$ in Table 2). The green marked values in Table 2 show that the calculated barriers are generally 1–7 kJ mol^{-1} (11 kJ mol^{-1} for **1b** + **3a**) higher than the experimental values, whereas the calculated barriers $\Delta G^{\neq}_{conc}$ for the concerted processes (last column in Table 2) are 29 to 70 kJ mol^{-1} larger than the experimental numbers.

Figure 6 depicts the calculated Gibbs energy profiles for the reactions of **1b** with **3a** and **3b** (entries 2 and 6 of Table 2). Analogous illustrations for the reactions of enamines with **1a** (entries 1 and 5) are shown in Ref. [8], those for the reactions of enamines with **1c** and **1d** (entries 3, 4, 7, 8) in the Supporting Information (Figures S11 and S12).

In our recent analysis of the reaction of **1a** with the enamines **3a** and **3b**, we have discussed that cyclization of the initially formed azo coupling products proceeds via the (*Z*)-zwitterion $\mathbf{E}_Z$. The course of the reactions of **1b**–**1d** with **3a** and **3b** can now be rationalized analogously. Since the interconversions of the tautomers **9**, **10**, **11**, and **12** are faster than the cyclizations, the Curtin-Hammett principle applies, and the rate of cyclization depends on the difference of the Gibbs energies of the most stable of these tautomers (marked by yellow background in Table 2) and the Gibbs energy of the cyclization step ($\Delta G^{\neq}_{cycl}$ in Table 2). If a barrier between $\mathbf{E}_Z$ and the cycloadduct **F** could not be localized (as in the reactions with **1b**, Figure 6), $\Delta G^{\neq}_{cycl}$ can be replaced by $\Delta G^0(\mathbf{E}_Z)$. The barrier for cyclization can, therefore, be derived from the difference of the grey highlighted energies [$\Delta G^{\neq}_{cycl}$ or $\Delta G^0(\mathbf{E}_Z)$] in Table 2 and the yellow marked values (most stable tautomers). One can see that for all reactions with pyrrolidinocyclopentene **3a** (entries 1–4 in Table 2), as well as for the reaction of diphenyldiazomethane **1d** with **3b** (entry 8), these differences are greater than 110 kJ mol^{-1}, in accord with the observation that cyclized products are not commonly observed for these reactions. On the other hand, the corresponding energy differences are smaller than 105 kJ mol^{-1} in entries 5–7, in accord with the observation that in these reactions with pyrrolidinocyclohexene **3b**, formation of the pyrazolines has been observed. Because of

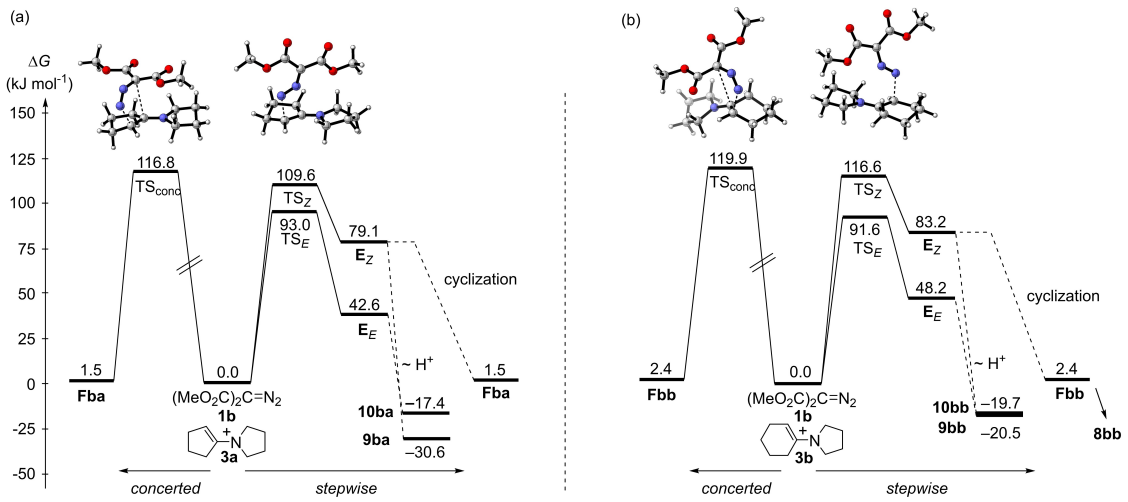


Figure 6. Gibbs energy profiles for the concerted and stepwise cycloadditions of **1 b** with (a) **3 a** and (b) **3 b** as computed at the (SMD = $CHCl_3$)/MN15/def2-TZVPD//(SMD = $CHCl_3$)/B3LYP-D3BJ/def2-SVP level of theory. Analogous illustrations for the reactions of enamines with **1 a** are shown in Ref. [8] and for **1 c** and **1 d** in Figures S11 and S12 (Supporting Information).

the error limits of these calculations, illustrated by the observation of **11 ba** in equilibrium with **9 ba** and **12 ba** (Scheme 5) despite its calculated 12 kJ/mol higher Gibbs energy (Table 2), this analysis should be considered as a plausible rationalization for the different behavior of **3 a** and **3 b**, but not as an unequivocal proof.

Table 2 (entries 1 & 2 and 5 & 6) shows that the calculated activation Gibbs energies for the reactions of both enamines **3 a** and **3 b** to give the (*E*)-zwitterions $\mathbf{E}_E$ ($\Delta G^{\neq}_E$) are only 6 kJ mol^{-1} lower for diazomalonate **1 b** than for diazoacetate **1 a**. Intuitively, one might explain this small difference by the fact that the additional ester group in **1 b** has little effect on $\pi^*_{N=N}$-(LUMO), because this orbital is not in conjugation with the π-system of the ester group. On the other hand, conjugation of the π-system of the ester group with ψ_3 of the heteropropargyl anion system (LUMO + 1) might account for the fact that the transition states for the concerted cycloadditions ($\Delta G^{\neq}_{conc}$) are lowered by 19 to 25 kJ mol^{-1} by the additional ester group in **1 b** (Table 2, entries 1 & 2 and 5 & 6).

This rationalization is not explicitly supported by the calculated orbital energies. Figure 5 shows that ψ_3 of the heteropropargyl anion system (LUMO + 1), which is in conjugation with the π-system of the ester group is only slightly more lowered in energy by the additional ester group in **1 b** (−0.46 eV) than $\pi^*_{N=N}$ (−0.32 eV). While we find a good agreement between calculated and experimental activation energies, the calculated orbital energies of the reactants correlate only poorly with the observed reactivity ordering of the diazo compounds.

Determination of the Electrophilicity Parameters *E* of the Diazoalkanes 1

Experimental studies and quantum chemical calculations thus agree that azo couplings as well as 1,3-dipolar cycloadditions of **1 a–1 d** with the enamines **3** proceed by rate-determining electrophilic attack of the diazoalkanes at the enamines yielding zwitterions **E** as short-lived intermediates (Scheme 4). These reactions thus fulfill the criteria for the applicability of Equation (1), in particular formation of one and only one new bond in the rate-determining step. Since solvent effects on rate constants are included in the nucleophile-specific parameters *N* and s_N in Equation (1), it is possible to use rate constants in different solvents for determining the solvent-independent electrophilicity parameters *E*.

Accordingly, Figure 7 shows linear correlations of (lg k_2)/s_N versus the 1-bond nucleophilicity parameters *N* of sulfonium ylides **2** and enamines **3** (Figure 2). The common nature of the rate-determining step in the reactions of diazoalkanes **1** with sulfonium ylides **2** and enamines **3** is thus confirmed. Least-squares analysis according to Equation (1), enforcing a slope of 1.00, yields the electrophilicity parameters *E* of **1 a–c**, which are given in Figure 7. Slopes between 0.93 and 1.04 are obtained when the correlations in Figure 7 are performed without restrictions of the slopes. Assuming that Equation (1) also holds for the reactions of diphenyldiazomethane **1 d** with enamines, *E*(**1 d**) = −21.4 is derived from the second-order rate constant k_2 for the reaction of **1 d** with **3 b**.

As shown in Figure 8, the electrophilicities of diazoalkanes **1 a–d** (*E* = −21.4 to −18.2) are much smaller than those of aryldiazonium ions (*E* = −10.4 to −2.5 in acetonitrile),[21] which can be rationalized by the electron-donating effect of the formal negative charge on the carbon adjacent to the N_2 group expressed by the ylide structures of **1 a–d** (Scheme 1). The similar electrophilicities of **1 a–c** as well as the three orders of

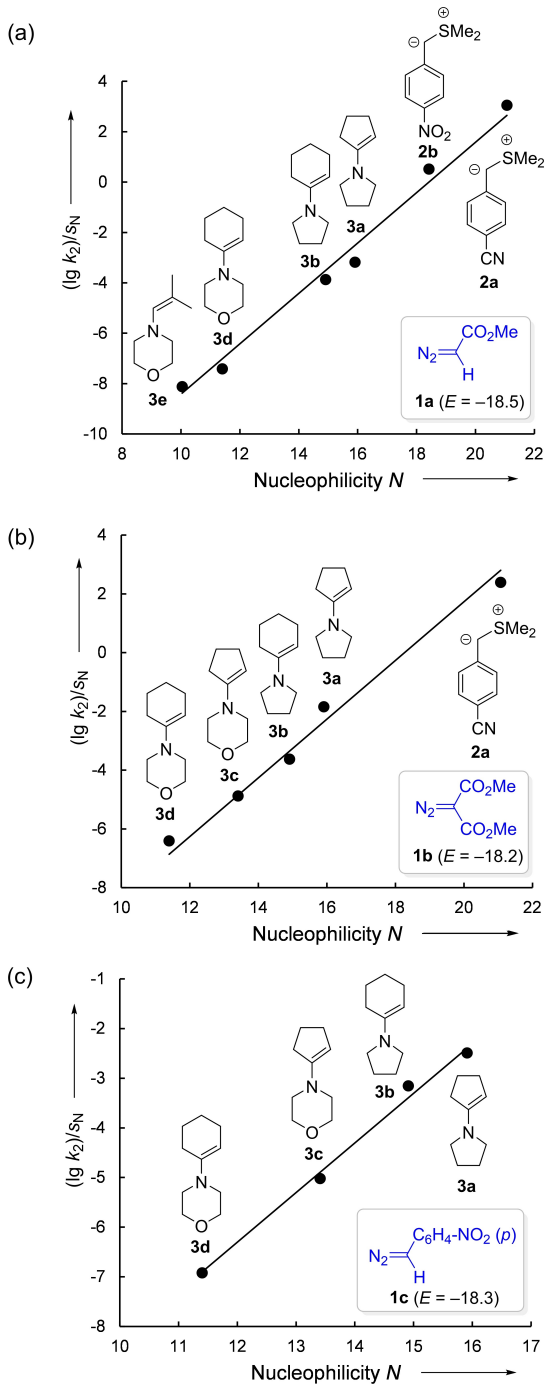


Figure 7. Plots of (lg k_2)/s_N vs. N for the reactions of (a) **1a** with **2a–b** (in DMSO) and **3a–e** (in $CDCl_3$), (b) **1b** with **2a** (in DMSO) and **3a–d** (in $CDCl_3$), and (c) **1c** with **3a–d** (in CD_2Cl_2); electrophilicity parameters E of **1a–1c** were calculated by the method of least-squares through iterative minimization of $\Delta^2 = \Sigma(\lg k_{2,i} - s_i(E + N_i))^2$, which implies enforcing a unity slope in the (lg k_2)/s_N vs N plots.

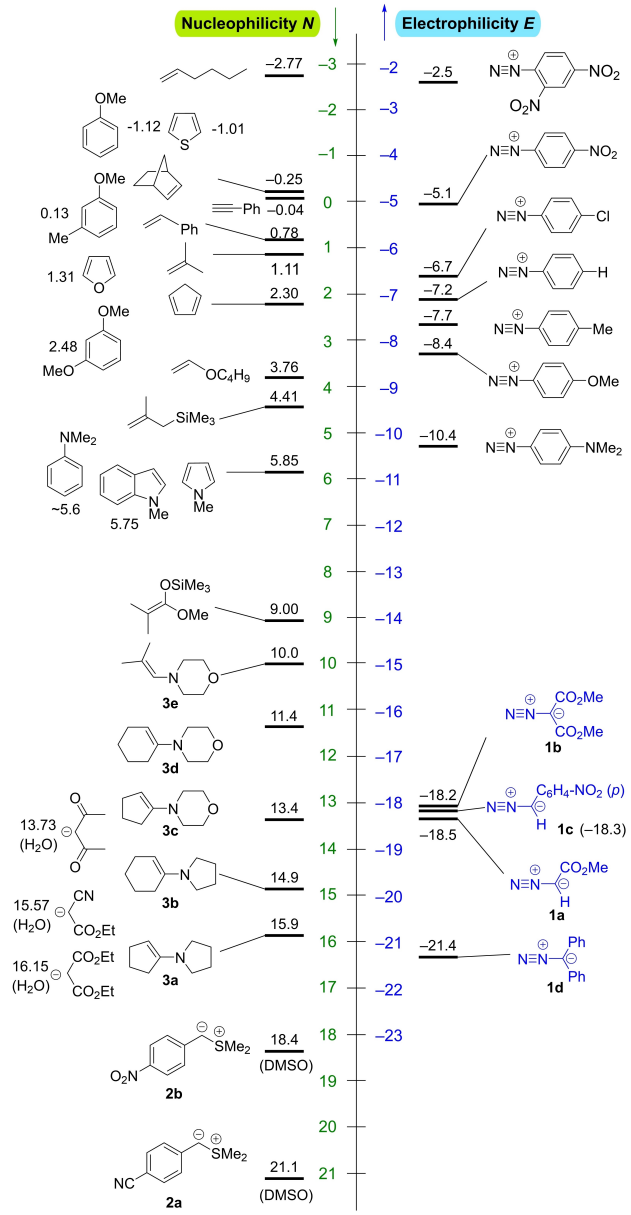


Figure 8. Potential nucleophilic reaction partners for diazoalkanes **1a–d** and diazonium ions. Note: E parameters for diazonium ions Ar-N_2^+ are from Ref. [21] and have not been parametrized through reactions with the usually used reference nucleophiles. Reactivity descriptors N for nucleophiles refer to CH_2Cl_2 (if not mentioned otherwise) and were taken from Ref. [5f].

magnitude lower electrophilicity of diphenyldiazomethane (**1d**) are in good agreement with the quantum chemically calculated Gibbs activation energies for their reactions with enamines, while a consistent rationalization by FMO analysis failed (see above).

In previous work we have reported that the reactivity parameters E and N can be used for a first guess whether certain reactions of electrophiles with nucleophiles can be expected to take place at room temperature. When electrophiles and nucleophiles are arranged as in Figure 8, where $E + N = -5$ for reactants on the same level, Equation (1) predicts lg $k_2(20\,^\circ C) = -5s_N$ for reactions of electrophiles with nearby nucleophiles. Since s_N is close to 1 for most $\pi_{C=C}$ nucleophiles,[5] one can expect that the diazonium ions and diazo compounds in Figure 8 will undergo azo couplings with substrates on the same horizontal level with second-order rate constants of

approximately 10^{-5} M^{-1} s^{-1} at 20 °C, corresponding to half-reaction times of about 1 day for 1 M solutions. As a consequence, azo couplings at ambient temperature can be expected with all nucleophiles, which are positioned below the corresponding electrophiles in Figure 8, but not with those nucleophiles located at significantly higher positions.

The suitability of this rule of thumb as an ordering principle for the reactions of diazonium ions with aromatic and aliphatic π-systems has already been demonstrated in refs.[21,22] Let us now consider literature reports on reactions of diazoalkanes with C-centered nucleophiles.

In Figure 8, arenes are positioned at significantly higher positions than the diazo compounds **1a–d**. Accordingly, azo couplings of the diazoalkanes **1a–d** with arenes have to our knowledge not been reported. While diazodimedone (**1e**) was found to react readily with phloroglucine under alkaline conditions (Scheme 8), an analogous reaction of diazoacetate was also mentioned in ref.[23] without giving details. Ciganek's report[24] that dicyanodiazomethane undergoes azo coupling with *N*,*N*-dimethylaniline indicates an electrophilicity level of this diazoalkane that is higher than that of **1a–d**.

In line with the relative position of **1a** and enamine **3e** in Figure 8, their combination required heating at 50 °C for 3 days (Scheme 7). Since enamines are among the strongest neutral C-nucleophiles, the electrophilic character of diazoalkanes has predominantly been observed in reactions with the more nucleophilic carbanions.[25]

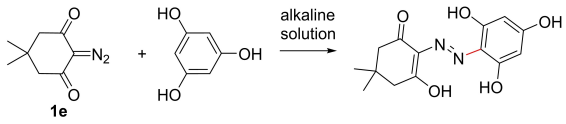
Klages reported the formation of a pyrazoline, when ethyl diazoacetate (**1f**) was combined with 1,3-diketones and aqueous NaOH, as depicted for the reaction with pentane-2,4-dione in Scheme 9.[26] Its formation can be rationalized by initial electrophilic attack of the diazoester **1f** at the anion of the diketone (in H_2O: $N = 13.73$), followed by cyclization and dehydration. Since the enolates derived from pentan-2,4-dione and diethyl malonate have nucleophilicities in water comparable to enamines, we consider the formation of the pyrazoles via concerted 1,3-dipolar cycloaddition across the C=C bond of the enolates unlikely.

An analogous reaction of ethyl diazoacetate (**1f**) with diethyl malonate catalyzed by sodium ethoxide has been reported by Bertho and Nüssel in 1927 (Scheme 10).[27a] In line with the relative position of **1a** and the anion of diethyl malonate (in H_2O: $N = 16.15$) in Figure 8, this reaction can again be rationalized by initial azo coupling of the diazo ester with the malonate anion, followed by cyclization.

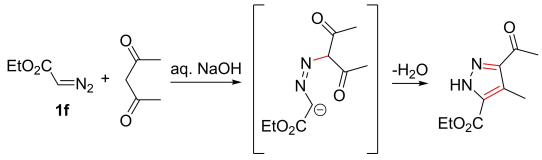
Assuming that structurally related diazoketones and diazoesters will also have similar electrophilicities as the diazoalkanes **1a–c**, one can analogously interpret the reactions of the diazo compounds **1e**,[27b] **1g**,[27c] and **1h**[27d] (Scheme 11) with CH acidic compounds by initial electrophilic attack of the diazo compounds at the corresponding carbanions, followed by proton shifts or cyclization. The most comprehensive studies in this field have been performed by Regitz and coworkes, as depicted in Scheme 12.[27b]

Azo couplings of CH acidic compounds have also been observed with the parent diazomethane under neutral conditions,[28] which has been suggested to proceed via protonation of diazomethane and attack of the resulting methyldiazonium ion at the simultaneously formed carbanion.[28b–d] Analogous reactions of diazonium ions are known as Japp-Klingemann reactions.[29]

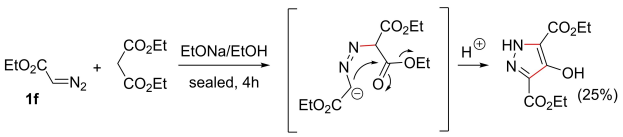
Alkyllithium and aryllithium, as well as the corresponding magnesium reagents are among the strongest C-centered nucleophiles. Though their nucleophilicities have so far not been quantified, they can be expected to be located at the very bottom of Figure 8, in line with the long-known reactions of organometallics with diazoalkanes.[2] Scheme 13 illustrates that the diazo esters **18** and **19** derived from α-amino acid esters react with PhLi at −68 °C, with PhMgBr at 0 °C, but not with PhZnI, even when raising the temperature.[30]



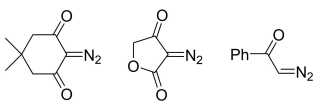
Scheme 8. Reaction of diazodimedone (**1e**) with phloroglucine.[23]



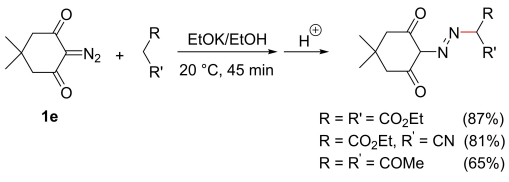
Scheme 9. Reaction of ethyl diazoacetate (**1f**) with pentane-2,4-dione.[26]



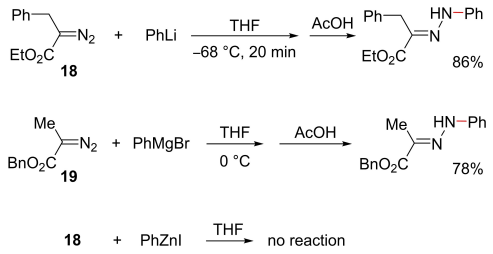
Scheme 10. Reaction of ethyl diazoacetate (**1f**) with diethyl malonate.[27a]



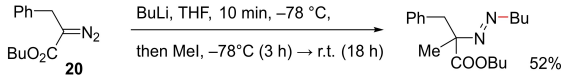
Scheme 11. Diazoketones and esters which have been reported to react with carbanions derived from CH-acidic compounds.



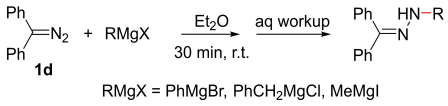
Scheme 12. Reactions of diazodimedone (**1e**) with C–H acids under catalysis of potassium ethoxide.[27b]



Scheme 13. Reactions of the α-diazo esters **18** and **19** with organometallic reagents.[30]



Scheme 14. Synthesis of an α-azo ester by sequential reaction of butyl lithium and methyl iodide with α-diazoester **20**.[31]



Scheme 15. Reactions of Grignard reagents with diphenyldiazomethane (**1 d**).[32]

Electrophilic amination of butyl lithium combined with subsequent trapping of the resulting azo-substituted carbanion by methyl iodide was used by Takamura and Yamada to introduce two different alkyl groups at both reactive sites of the diazoalkane functionality in the diazoester **20** (Scheme 14).[31]

The three orders of magnitude less electrophilic diphenyldiazomethane (**1 d**) reacted with Grignard reagents, such as phenylmagnesium bromide, benzyl magnesium chloride or methylmagnesium iodide within 30 min at room temperature to yield *N*-substituted hydrazones (Scheme 15).[32]

As mentioned at the beginning of this paragraph, **1 a**–**d** have not been reported to react with the arenes depicted in Figure 8. As expected, no reaction was observed when 1,3-dimethoxybenzene ($N = 2.48$) was heated with **1 b** for 2 days in $CDCl_3$ at 55 °C. The fact that ordinary alkenes, which have similar nucleophilic reactivity as 1,3-dimethoxybenzene, react with diazoalkanes indicates a change of mechanism (see below).

Conclusions

Nucleophilic attack of sulfonium ylides **2** and enamines **3** at the terminal nitrogen of the diazoalkanes **1 a**–**d** yields transient zwitterions, which undergo various subsequent reactions. NMR spectroscopic monitoring of the reactions with enamines showed that the pyrazoles **7** and pyrazolines **8** are formed by stepwise processes via intermediate hydrazonoenamines (Scheme 4) and not via concerted 1,3-dipolar cycloadditions, as previously postulated.[7c]

For all reactions of the diazoalkanes with enamines investigated in this work, the experimentally determined activation Gibbs energies agreed well with the quantum-chemically calculated values for the formation of the zwitterions, which arise from the interaction of the HOMO(enamine) with $\pi^*_{N=N}$(diazoalkane), i.e., LUMO(diazoalkane). The alternative concerted 1,3-dipolar cycloadditions, arising from the interaction of the HOMO(enamine) with ψ_3 of the heteropropargyl fragments of the diazoalkanes were calculated to have 29–70 kJ mol^{-1} higher Gibbs activation energies (Table 2) and did not occur.

Since only one new bond is formed in the first, rate-determining step of all reactions described in this article, Equation (1) applies and was used to calculate the electrophilicity parameters *E* of the diazoalkanes **1 a**–**d** from the measured second-order rate constants k_2 in Table 1 and the known nucleophile-specific parameters *N* and s_N of sulfonium ylides and enamines in Chart 1. Earlier studies[4a] have shown that the nucleophilicity of diethyl diazomalonate is five orders of magnitude lower than that of ethyl diazoacetate. Experimental investigations and quantum chemical calculations now concordantly show that the electrophilicities of **1 a**, **1 b**, and **1 c** are almost the same, while diphenyldiazomethane (**1 d**) has a three orders of magnitude lower electrophilicity. This observation can be rationalized by the fact that the π-acceptor orbitals of the substituents are in direct conjugation with the nucleophilic reaction center of diazoalkanes but perpendicular to $\pi^*_{N=N}$ which accounts for the electrophilic reactivity of diazoalkanes.

In accord with the *E* parameters of the diazoalkanes **1 a**–**d**, which are 8 to 19 orders of magnitude smaller than those of diazonium ions, azo couplings of diazoalkanes with arenes do usually not occur and have only been observed in rare cases. The well-known azo couplings of diazoalkanes with 1,3-diketones, 1,3-dicarboxylates, and related CH-acidic compounds under basic conditions can be rationalized by the high nucleophilicities of the corresponding enolates.

Figure 8 suggests that azo couplings of **1 a**–**d** with ordinary alkenes, styrene, or phenylacetylene cannot be expected to take place at room temperature. Equation (1) predicts reaction times of billions of years for these reactions. The fact that these reactions have actually been observed,[1] indicates a different mechanism. In a subsequent paper we will discuss the change from stepwise processes to concerted 1,3-dipolar cycloadditions when the enamines described in this article are replaced by less nucleophilic $\pi_{C=C}$ systems.

Experimental Section

For experimental details please see Supporting Information.

CCDC 2102953 (**9ba**, vv842), 2102954 (**9bc**, wv088), 2102955 (**12bc**, wv086), and 2102958 (**17**, yv006) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: diazoalkane · enamine · electrophilicity · kinetics · quantum chemical calculations

[1] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598; *Angew. Chem.* **1963**, *75*, 604–637; b) *1,3-Dipolar Cycloaddition Chemistry*, Vol. 1 and 2 (Ed.: A. Padwa), Wiley, New York, **1984**; c) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**; d) H. Suga, K. Itoh, *Methods and Applications of Cycloaddition Reactions in Organic Syntheses* (Ed.: N. Nishiwaki), Wiley, Hoboken, **2014**, p 175; e) M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293–12307; *Angew. Chem.* **2020**, *132*, 12389–12404; f) R. Jasinski, E. Dresler, *Organics* **2020**, *1*, 49–69.

[2] a) R. Huisgen, *Angew. Chem.* **1955**, *67*, 439–463; b) S. Patai, *The chemistry of diazonium and diazo groups*, Wiley, Chichester, **1978**; c) M. Regitz, *Diazoalkane*, Thieme, Stuttgart, **1977**; d) B. Eistert, M. Regitz, G. Heck, H. Schwall, *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed., Vol. 10/4, Georg Thieme Verlag Stuttgart, **1968**, pp. 589–710.

[3] H. Zollinger, *Diazo Chemistry I: Aromatic and Heteroaromatic Compounds*, VCH, Weinheim, **1994**.

[4] a) T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 4068–4076; b) M. Hartnagel, A. R. Ofial, H. Mayr, *Synthesis* **2022**, *54*, doi: 10.1055/s-0041-1737327..

[5] a) H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957; b) 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; c) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; d) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; e) H. Mayr, *Tetrahedron* **2015**, *71*, 5095–5111; f) For a database of nucleophilicity parameters (N/s_N) and electrophilicity parameters (E), check the link: https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank2/.

[6] a) R. Appel, N. Hartmann, H. Mayr, *J. Am. Chem. Soc.* **2010**, *132*, 17894–17900; b) B. Kempf, N. Hampel, A. R. Ofial, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 2209–2218.

[7] a) H.-U. Reissig, Dissertation, Ludwig-Maximilians-Universität München, **1978**; b) R. Huisgen, W. Bihlmaier, H.-U. Reissig, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 331–332; *Angew. Chem.* **1979**, *91*, 347–348; c) R. Huisgen, H.-U. Reissig, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 330–331; *Angew. Chem.* **1979**, *91*, 346–347; d) W. Bihlmaier, R. Huisgen, H.-U. Reissig, S. Voss, *Tetrahedron Lett.* **1979**, *20*, 2621–2624.

[8] L. Li, P. Mayer, D. S. Stephenson, A. R. Ofial, R. J. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* **2022**, *61*, e202117047; *Angew. Chem.* **2022**, *134*, e202117047.

[9] H. Metzger, K. Seelert, *Z. Naturforsch. B* **1963**, *18*, 336.

[10] D. Wu, Y. Wang, J. Zhou, Q. Sun, Y. Zhao, X. Xu, *Org. Lett.* **2019**, *21*, 8722–8725.

[11] For the formation of small quantities of cyclized products, see Ref. [7b].

[12] A structurally analogous azo coupling product was isolated when enamine **3 b** was combined with ethyl 2-diazo-3,3,3-trifluoropropanoate (80 °C, 5 days, work-up by column chromatography on silica gel and subsequent purification by HPLC): D. Gladow, S. Doniz-Kettenmann, H.-U. Reissig, *Helv. Chim. Acta* **2014**, *97*, 808–821.

[13] G. F. Bettinetti, A. Cogoli, A. O. Sale, *Ric. Sci.* **1968**, *38*, 806–809.

[14] Previous work reported photo decomposition of 3*H*-pyrazoles to give cyclopropanes, which underwent subsequent [2 + 2] cycloadditions with enamines a) M. Franck-Neumann, M. Miesch, H. Kempf, *Tetrahedron* **1988**, *44*, 2933–2942; b) M. Franck-Neumann, M. Miesch, H. Kempf, *Synthesis* **1989**, *11*, 820–824.

[15] P. W. Atkins, J. Paula in *Physical Chemistry*, Eighth Edition, W. H. Freeman and Co., New York, **2006**, p 802.

[16] a) E. Harder, W. Damm, J. Maple, C. Wu, M. Reboul, J. Y. Xiang, L. Wang, D. Lupyan, M. K. Dahlgren, J. L. Knight, J. W. Kaus, D. S. Cerutti, G. Krilov, W. L. Jorgensen, R. Abel, R. A. Friesner, *J. Chem. Theory Comput.* **2016**, *12*, 281–296; b) *Schrödinger Release 2019–4: MacroModel*, Schrödinger, LLC, New York, NY, **2019**.

[17] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456–1465; c) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

[18] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[19] *Gaussian 16, Revision A.03*, Gaussian, Inc., Wallingford CT, **2016**. For the full reference including all authors, see the Supporting Information.

[20] H. S. Yu, X. He, S. L. Li, D. G. Truhlar, *Chem. Sci.* **2016**, *7*, 5032–5051; 6278–6279.

[21] H. Mayr, M. Hartnagel, K. Grimm, *Liebigs Ann.* **1997**, 55–69.

[22] W. Gabsi, T. Boubaker, R. Goumont, *Int. J. Chem. Kinet.* **2016**, *48*, 266–273.

[23] T. Severin, *Angew. Chem.* **1958**, *70*, 745.

[24] E. Ciganek, *J. Org. Chem.* **1965**, *30*, 4198–4204.

[25] Since Equation (1) cannot be applied to the formation of heteroatom-heteroatom bonds, reactions of diazo compounds with phosphines, amines, hydride donors, thiolates or hydroxide ions (see Ref. [2]) are not considered here.

[26] a) A. Klages, *J. Prakt. Chem.* **1902**, *65*, 387–393; b) A. Klages, A. Rönneburg, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 1128–1132; c) W. Hampel, *J. Prakt. Chem.* **1969**, *311*, 1058–1064.

[27] a) A. Bertho, H. Nüssel, *Liebigs Ann. Chem.* **1927**, *457*, 278–307; b) M. Regitz, A. Liedhegener, D. Stadler, *Liebigs Ann. Chem.* **1968**, *713*, 101–112; c) L. Wolff, *Liebigs Ann. Chem.* **1902**, *325*, 129–195; d) D. G. Farnum, P. Yates, *Proc. Chem. Soc.* **1960**, *224*.

[28] a) R. Schmiechen, *Tetrahedron Lett.* **1969**, *10*, 4995–4996; b) S. Nesnow, R. Shapiro, *J. Org. Chem.* **1969**, *34*, 2011–2013; c) W. Uhde, K. Hartke, *Chem. Ber.* **1970**, *103*, 2675–2686; d) J. S. Pyrek, O. Achmatowicz, *Tetrahedron Lett.* **1970**, *11*, 2651–2652.

[29] a) F. R. Japp, F. Klingemann, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2942–2944; b) F. R. Japp, F. Klingemann, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3398–3401; c) R. R. Phillips, *The Japp-Klingemann Reaction*. In: *Organic Reactions*, Wiley, **2004**, doi: 10.1002/0471264180.or010.02.

[30] a) E. Yasui, M. Wada, N. Takamura, *Tetrahedron Lett.* **2006**, *47*, 743–746; b) E. Yasui, M. Wada, N. Takamura, *Tetrahedron* **2009**, *65*, 461–468.

[31] N. Takamura, S.-I. Yamada, *Chem. Pharm. Bull.* **1976**, *24*, 800–803.

[32] G. H. Coleman, H. Gilman, C. E. Adams, P. E. Pratt, *J. Org. Chem.* **1938**, *3*, 99–107.

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