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Steric Effects on the Regioselectivity in Two-Step Diels–Alder Reactions of 1,2,4,5-Tetrazines with 2-Cyclopropylidene-4,5-dihydro-1,3-dimethyl-imidazolidine

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—The regioselectivity of the two-step Diels–Alder reaction of unsymmetrically substituted tetrazines **4** with 2-cyclopropylidene-imidazolidine **6** is investigated. The first reversible step of the cycloaddition affording zwitterions **7** and **8** is controlled by steric effects, which are explained using a simple model. The overall regioselectivity, however, is determined in the second step of the cycloaddition or at an even later stage. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

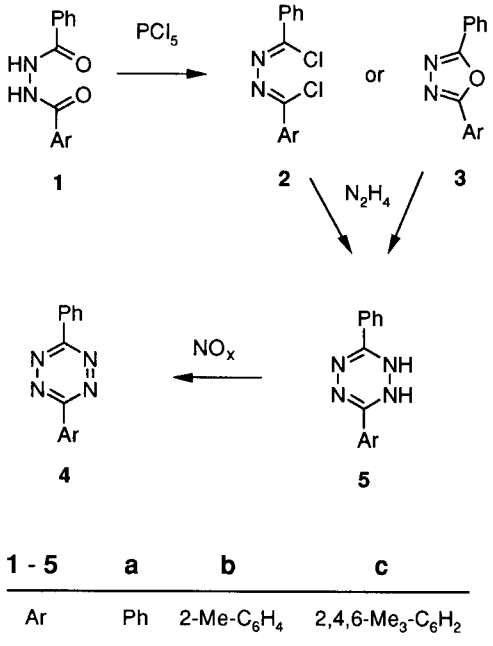
3,6-Diphenyl-1,2,4,5-tetrazine (**4a**) reacts rapidly at room temperature with 2-cyclopropylidene-1,3-dimethyl-imidazolidine (**6**) to give a dispiro adduct **11a** which is formed via [4+2]-cycloaddition and consecutive elimination of nitrogen in accordance with a generally accepted mechanism.[1,2] The high reactivity of the dienophile[3] in inverse electron demand Diels–Alder reactions[4] allows the addition to be performed at low temperatures and thus a zwitterion **7a** can be isolated as an intermediate. This seems to be an ideal system to investigate steric and electronic effects and to separate their implication on both steps of the [4+2]-cycloaddition. We report here on steric effects influencing the regioselectivity of two-step Diels–Alder reactions with unsymmetrically substituted 1,2,4,5-tetrazines.

Results

We selected diaryl substituted 1,2,4,5-tetrazines as dienophiles to get similar electronic influences and to avoid alkyl groups at the tetrazines, because the high basicity of **6**[5] is sufficient to deprotonate methyl groups in triazines and opens the route to competing reaction paths.[6] Thus the 2-methylphenyl- and the 2,4,6-trimethylphenyl-tetrazines **4b** and **4c** were prepared from diacylhydrazides **1** according to a procedure developed by Stollé.[7]

Activation of the hydrazides **1** with phosphorus pentachloride in refluxing tetrachloromethane afforded the hydrazidedioyl dichloride **2b** or the 1,3,4-oxadiazole **3c**. Both reacted smoothly with hydrazine hydrate to yield dihydrotetrazines **5**, which were oxidized by nitrous gases to the tetrazines **4** (Scheme 1).

On addition of 2-cyclopropylidene-imidazolidine **6** to the tolyl-tetrazine **4b** below −10°C in tetrahydrofuran the violet



Scheme 1.

Keywords: Diels–Alder reactions; ketene acetals; regiochemistry; zwitterions.

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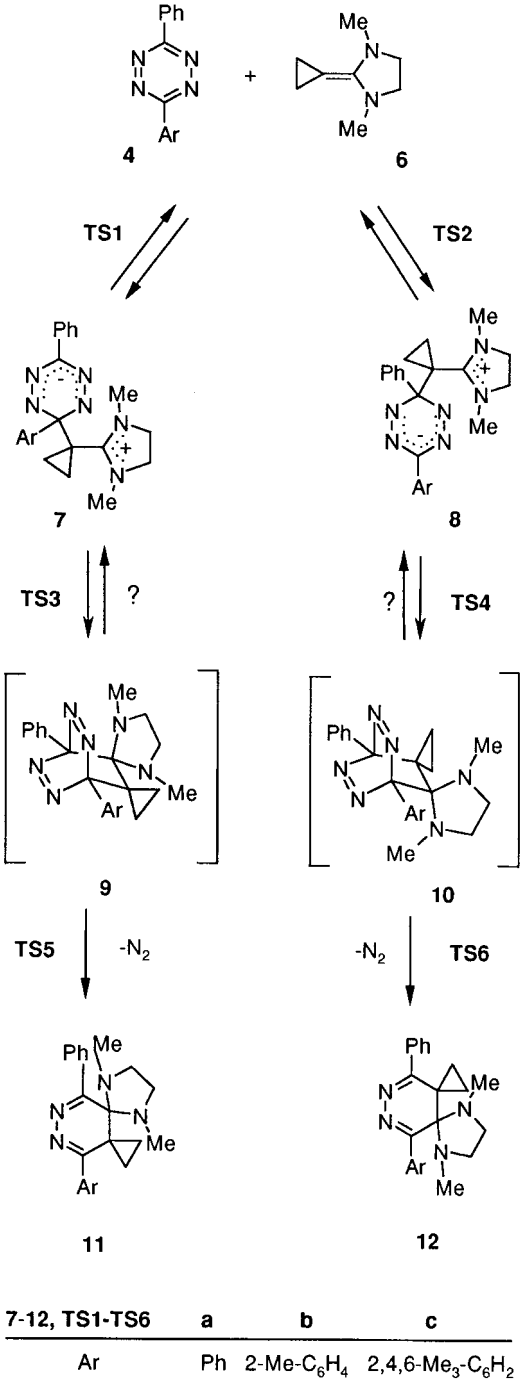
red color vanished after 1 h and an orange–yellow precipitate was formed. At −78°C this reaction was complete after 6 h. The precipitate was isolated below −20°C, dissolved in [D_2]dichloromethane and characterized as a mixture of zwitterions **7b** and **8b** (33:67). As **7b** and **8b** were far better soluble than the parent **7a** (=**8a**)[1] it was possible for the first time to get NMR data of such zwitterions. The structure assignment of the 2,3-dihydrotetrazinide[8] and 4,5-dihydroimidazolium moiety[1,5] is quite straightforward by comparison with literature data. However, the distinction between the two regioisomers was not quite trivial. A combination of high resolution ^{1}H, ^{13}C, HETCOR and COLOCS NMR spectra finally allowed the signals of all hydrogen and carbon atoms to be identified together with their connectivities and thus the structures of **7b** and **8b** were unambiguously assigned. Interestingly, the apparently more congested zwitterion **7b** shows separate signals for both the *N*-methyl and *N*-methylene groups. This might be caused by restricted rotation of the two single bonds connecting the imidazole and tetrazine rings.



Scheme 2.

When the solution of the zwitterions **7b** and **8b** (33:67) was allowed to warm slowly, gas evolution was monitored around 0°C. NMR spectra at intermediate times showed that the signals of **7b** decreased faster than those of **8b**. After reaching room temperature, both isomers had disappeared. But in the resulting mixture only dispiro adduct **11b** (56%) could be identified besides 44% of tetrazine **4b**. If the zwitterions **7b** and **8b** (33:67) were warmed up in tetrahydrofuran, nearly quantitative formation of **11b** was determined spectroscopically. Likewise, if the reaction of tetrazine **4b** with 2-cyclopropylidene-imidazolidine **6** was performed at room temperature in tetrahydrofuran, nitrogen evolution ceased after a few minutes and 84% of isomer **11b** could be isolated after recrystallization. The structure assignment again was based on intensive NMR studies such as above. In this case, however, the reliability of this method was proven by X-ray analysis[9] of **11b** (Scheme 2).

When 2-cyclopropylidene-imidazolidine **6** was added to the mesityl-tetrazine **4c** at temperatures below −10°C, again a yellow solid was formed. Isolation and NMR spectroscopic identification in [D_2]dichloromethane showed that only one regioisomeric zwitterion **8c** had been formed. Warming of this zwitterion to room temperature did not lead to a gas evolution, no traces of dispiro compounds **11c** or **12c** could be identified. After prolonged heating the zwitterion decomposed to the starting mesityl-tetrazine **4c** and reaction products of 2-cyclopropylidene-imidazolidine **6** with the solvent. The same behavior was observed in tetrahydrofuran and benzene.

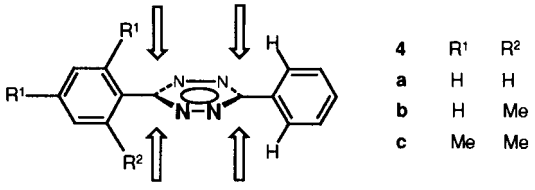


Figure 1.

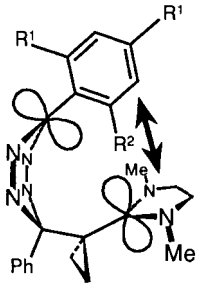


Figure 2.

Discussion

In principle four directions of attack at the 3- and 6-position of tetrazines **4** are possible (Fig. 1). In the diphenyl derivative **4a** the four additions should occur with the same probability leading to a 50:50 distribution of C-3 and C-6 attack which cannot be proven experimentally, as **7a** and **8a** are identical as well as **11a** and **12a**. A simple model may explain the selectivities found for the unsymmetrically substituted tetrazines **4b** and **4c**. The neighboring rings of the tetrazines **4** are probably not coplanar but rather perpendicular on the time average. This is corroborated by AM1 calculations.[10] The experimental results comply with the assumption, that a methyl group in 2- or 6-position of the aryl ring will completely prevent nucleophilic attack at the adjacent carbon from the same side of the tetrazine ring. Indeed the predicted ratios of 1:2 or 0:2 are exactly reproduced by the **7b**:**8b** (33:67) and **7c**:**8c** ratios (0:100), respectively. It is not necessary to consider the small electronic effect of the methyl group, because even strong donor-substituents such as dimethylamino or methoxy and/or acceptor-substituents in *para*- or *para*–*para′*-position of the phenyl rings in **4** did not influence the regioselectivity of zwitterions or cycloaddition products markedly.[11]

On heating, the minor tolyl zwitterion **7b** is converted to the dispiro adduct **11b**. However, the yield of **11b** was clearly higher in all cases than the maximum of 33% that could be expected from direct ring closure of **7b** and although the major regioisomeric zwitterion **8b** also disappeared from the reaction mixture, the expected regioisomeric dispiro adduct **12b** was not observed. Thus, **7b** and **8b** must both

Table 1. AM1 calculated relative energies (kcal mol^{-1}) for the intermediates and transition states of the cycloaddition reactions of **4** with **6**

	11	TS5	9	TS3	7	TS1	4+6	TS2	8	TS4	10	TS6	12
a	−40.2	44.7	23.0	27.2	17.6	28.7	0	28.7	17.6	27.2	23.0	44.7	−40.2
b	−40.6	46.7	25.6	35.4	21.1	34.8	0	33.2	18.6	35.3	29.0	51.2	−37.7
c	−38.7	55.5	31.8	39.9	27.4	43.6	0	39.8	19.4	46.7	38.6	65.8	−36.0

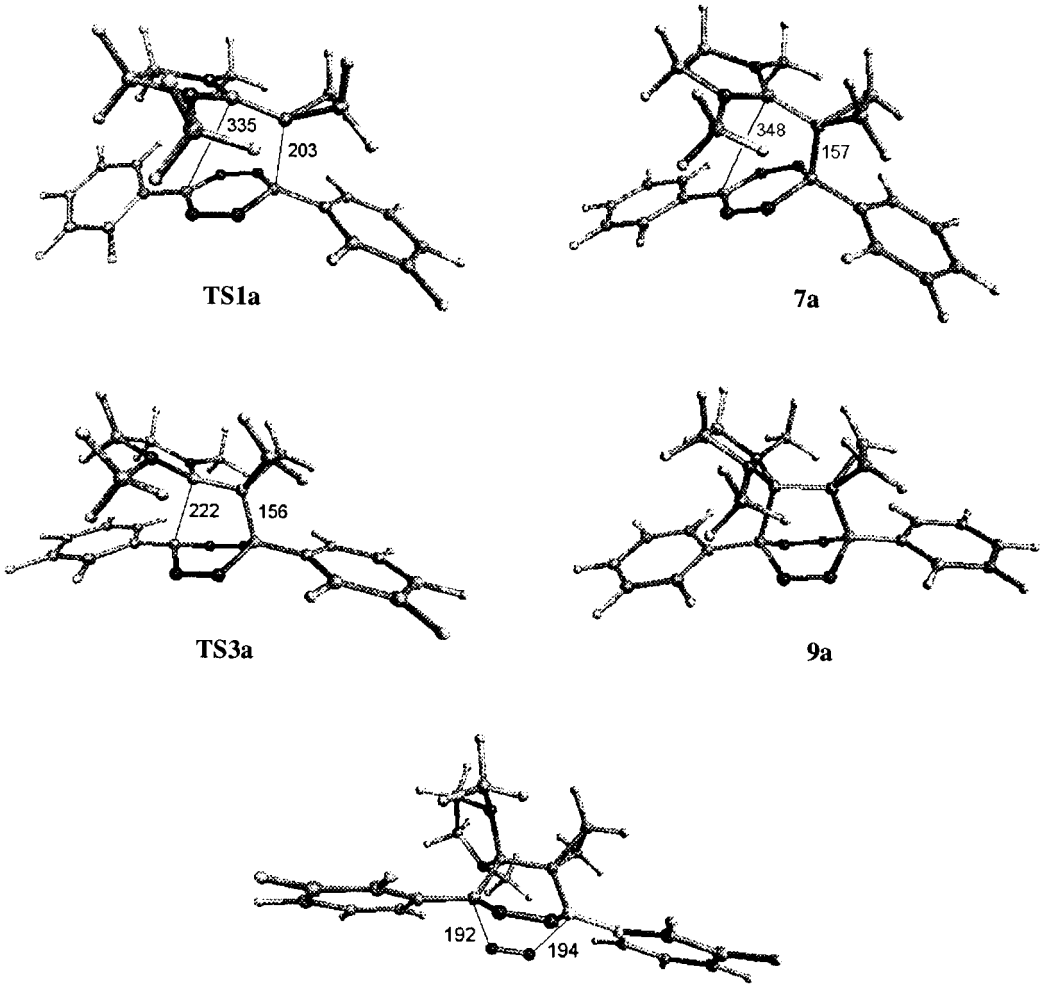


Figure 3. Structures of transition states and intermediates for the cycloaddition of **4a** and **6** with selected distances in pm, as calculated by AM1.

be precursors for **11b**. The only reasonable explanation demands that the zwitterion **8b** splits up to the starting materials **4b** and **6**, which recombine to give a mixture of **7b** and **8b** again. While **8b** is caught in a dead end equilibrium, **7b** is gradually converted to **11b** as the only product. The reason for this behavior again must clearly be a steric effect. To achieve ring closure, the imidazolium ring and the aryl or phenyl ring must be nearly coplanar. This is easily achieved with the phenyl ring in **7b**, while the methyl group in **8b** disfavors this conformation (Fig. 2).

The reactivity of **8c** is consistent with this picture. The mesityl ring prevents the ring closure to **12c**. **8c** Also splits up to the educts **4c** and **6** in equilibrium. In this case, however, nucleophilic attack to give the regioisomeric zwitterion **7c** and ring closure to **11c** is no feasible alternative and thus the highly reactive 2-cyclopropylidene-1,3-dimethyl-imidazolidine **6** slowly decomposes, e.g. by reaction with the solvent and the mesityl tetrazine **4c** accumulates.

But an alternative explanation for the regioselectivities of the overall reaction might be envisaged. The highest transition states on the way to the final products **11** or **12** do not necessarily have to be the ring closures. These could be reversible, low energy steps while the real obstacles are the [4+2]-cycloreversions with loss of nitrogen. There is no way to address this problem experimentally. Semiempirical calculations (AM1[10]) seem to support this second hypothesis (Table 1, Fig. 3). But these calculations are not very reliable, as they find the relative energies of the zwitterions too high by at least 20 kcal mol^{-1}, suggesting that they should not be isolable in these reactions at all. This weakness, which is probably due to the fact that the gas phase is much less favorable for zwitterions than a condensed phase, cannot be overcome by using solvent models.[12] But as it is probable that mainly the zwitterions and the surrounding transition states will be lowered in energy by solvation, the cycloreversion might really have the highest transition state in the whole reaction sequence. At any rate, the relative heights of the calculated barriers are compatible with the experimental selectivities for zwitterions (**TS1** vs. **TS2**) and final products (**TS3b** vs. **TS4b** or **TS5b** vs. **TS6b**).

Though we do not know what exactly the rate and product determining step is, it is absolutely clear that the final product ratios are not controlled by the preferred site of nucleophilic attack but rather in a later step. These results might help to understand other Diels–Alder reactions of ketene acetals with tetrazines and triazines,[2] where intermediates cannot be isolated, but may well be short-lived intermediates.

Experimental

General

All cycloaddition reactions were performed in oven-dried glassware with dry solvents under argon. NMR spectra: Varian VXR 400S or Bruker WP 80. UV spectra: Perkin–Elmer Lambda-3 and Zeiss PMQ II. MS spectra: Finnigan MAT 90. Semiempirical AM1 calculations were carried out by using the AMSOL[12] program package. Transition states were localized using the POWELL algorithm.[12]

***N*-Benzoyl-*N′*-(2,4,6-trimethylbenzoyl)hydrazide (1c).** 2,4,6-Trimethylbenzoyl chloride (5.88 g 32.2 mmol) was added dropwise to a solution of benzoyl hydrazide (4.39 g, 32.2 mmol) in 20.1 g pyridine. The mixture was stirred overnight and poured on 150 mL ice water. The precipitate was collected, washed with water and recrystallized from methanol/ethanol to yield 4.55 g (50%) colorless needles with mp 205°C. ^{1}H NMR (CD_3OD, 400 MHz): 2.23 (s, 4-Me); 2.40 (2/6-Me); 7.27 (3/5-H, Ar); 7.46 (3/5-H, 4-H, Ph); 7.89 (2/6-H, Ph). ^{13}C NMR (CD_3OD, 100 MHz): 19.4 (2/6-Me); 21.2 (4-Me); 128.7 (C-3/5, Ph); 129.1 (C-3/5, Ar); 129.6 (C-2/6, Ph); 133.2 (C-4, Ph); 133.7 (C-1, Ar); 133.9 (C-1, Ph); 136.3 (C-2/6, Ar); 140.3 (C-4, Ar); 169.2 (C═O, Ph); 172.5 (C═O , Ar). MS (220°C) *m/z*=282 M^+, 2%). Anal. Calcd for $C_{17}H_{18}N_2O_2$ (282.3): C, 72.32; H, 6.43; N, 9.92. Found: C, 72.07; H, 6.35; N, 10.09.

***N*-[1-Chloro-1-(2-methylphenyl)methylene]-*N′*-(1-chloro-1-phenylmethylene)-hydrazine (2b) 1b.**[13] (20.0 g, 78.7 mmol) and PCl_5 (87.6 g, 420 mmol) in 130 mL CCl_4 were heated to reflux until the gas evolution had stopped (2 h). The mixture was poured on ice water and extracted with ether (4×50 mL). The combined organic phases were washed with water, until it had pH 7, dried over $MgSO_4$ and evaporated. The resulting yellow oil (22.0 g, 96%) was used without further purification for the next step. ^{1}H NMR ($CDCl_3$, 80 MHz): 2.61 (s, Me); 7.0–7.5 (m, 3/5-H, 4-H, Ph; 3/5-H, 4-H, Ar); 7.67 (6-H, Ar); 8.00 (2/6-H, Ph). ^{13}C NMR ($CDCl_3$, 20.2 MHz): 21.4 (Me); 125.8 (C-5, Ar); 128.3 (C-2/6, Ph); 128.3 (C-3/5, Ph); 129.9 (C-3, Ar); 130.5 (C-6, Ar); 131.2 (C-4, Ar); 131.7 (C-4, Ph); 133.5 (C-1, Ph); 134.2 (C-1, Ar); 137.5 (C-2, Ar); 143.2 (CCl); 143.5 (CCl). UV (CCl_4): λ_{max}=272 (log ϵ=3.511). MS: *m/z* 294 (M^+, 4%).

2-Phenyl-5-(2,4,6-trimethylphenyl) 1,3,4-oxadiazole (3c) 1c. (12.5 g, 44.4 mmol) and PCl_5 (52.1 g, 250 mmol) in 70 mL CCl_4 were heated to reflux until the gas evolution had stopped (2 h). The mixture was poured on ice water and extracted with ether (4×30 mL). The combined organic phases were washed with water, until it had pH 7, dried over $MgSO_4$ and evaporated. The residue was recrystallized from CH_3CN to yield 6.44 g (55%) of a colorless solid with mp 91–92°C. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.31 (s, 2/6-Me); 2.34 (s, 4-Me); 6.97 (s, 3/5-H, Ar); 7.52 (3/5-H, 4-H, Ph); 8.10 (2/6-H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz): 20.5 (2/6-Me); 21.3 (4-Me); 121.1 (C-1, Ar); 124.1 (C-1, Ph); 128.9 (C-2/6, Ph); 128.9 (C-3/5, Ph); 128.9 (C-3/5, Ar); 131.7 (C-4, Ph); 138.8 (C-2/6, Ar); 141.0 (C-4, Ar); 163.9 (C-2); 164.8 (C-5). MS: *m/z* 264 (M^+, 100%). Anal. Calcd for $C_{17}H_{16}N_2O$ (264.3): C, 77.23; H, 6.10; N, 10.61. Found: C, 76.90; H, 6.10; N, 9.73.

1,2-Dihydro-3-(2-methylphenyl)-6-phenyltetrazine (5b). To a solution of dichloride **2b** (21.5 g, 73.8 mmol) in 350 ml acetonitrile absolute hydrazine hydrate (3.70 g, 74.0 mmol) was added dropwise and the mixture was stirred for 1 h at 40–50°C. The yellow precipitate was collected by filtration, washed with acetonitrile (3×20 mL) and degassed

water (20 mL). Drying in vacuo yielded 13.5 g (73%) of analytically clean **5b** as orange crystals with mp 204–205°C. ^{1}H NMR (CD_3OD, 400 MHz): 2.48 (s, Me); 7.25 (5-H, Ar); 7.27 (3-H, Ar); 7.35 (4-H, Ar); 7.45 (3/5-H, 4-H, Ph); 7.68 (2/6-H, Ph); 7.69 (6-H, Ar). ^{13}C NMR (CD_3OD, 100 MHz): 19.8 (Me); 126.1 (C-3/5, Ph); 126.2 (C-5, Ar); 128.9 (C-2/6, Ph); 128.9 (C-6, Ar); 130.1 (C-4, Ar); 130.2 (C-1, Ar); 130.7 (C-1, Ph); 130.7 (C-3, Ar); 131.0 (C-4, Ph); 137.0 (C-2, Ar); 148.6 (C-6); 149.9 (C-3). UV (CH_3CN): λ_{max}=335 (log ϵ=3.972). Anal. Calcd for $C_{15}H_{14}N_4$ (250.3): C, 71.98; H, 5.63; N, 22.38. Found: C, 72.05; H, 5.64; N, 22.18.

1,2-Dihydro-3-phenyl-6-(2,4,6-trimethylphenyl)tetrazine (5c). To a solution of oxadiazole **3c** (6.41 g, 24.3 mmol) in 125 ml acetonitrile absolute hydrazine hydrate (1.22 g, 24.4 mmol) was added dropwise and the mixture was stirred for 1 h at 40–50°C. The yellow precipitate was collected by filtration, washed with acetonitrile (3×20 mL) and degassed water (20 mL). Drying in vacuo yielded 4.33 g (64%) of analytically clean **5c** as orange crystals with mp 220°C. ^{1}H NMR (CD_3OD, 400 MHz): 2.30 (s, 4-Me); 2.32 (s, 2/6-Me); 6.90 (3/5-H, Ar); 7.44 (3/5-H, 4-H, Ph); 7.67 (2/6-H, Ph). ^{13}C NMR (CD_3OD, 100 MHz): 19.4 (2/6-Me); 21.2 (4-Me); 126.1 (C-3/5, Ph); 128.5 (C-3/5, Ar); 128.9 (C-2/6, Ph); 129.1 (C-1, Ar); 130.4 (C-1, Ph); 130.6 (C-4, Ph); 137.4 (C-2/6, Ar);139.5 (C-4, Ar); 148.4 (C-3); 149.4 (C-6). UV (CH_3CN): λ_{max}=340 (log ϵ=3.715). Anal. Calcd for $C_{17}H_{18}N_4$ (278.4): C, 73.35; H, 6.52; N, 20.13. Found: C, 73.10; H, 6.02; N, 20.06.

3-(2-Methylphenyl)-6-phenyltetrazine (4b). A 6 N solution of $NaNO_2$ in water (25 mL, 150 mmol) was added dropwise to 18 mL of conc. HCl (ca. 180 mmol). The resulting nitrous gases were bubbled through a suspension of **5b** (3.90 g, 15.4 mmol) in 15 mL of CH_2Cl_2 cooled to 0°C. After 0.5 h the solvent was evaporated and the residue recrystallized from methanol/ethanol to give 3.30 g (85%) of **4b** as violet–red needles with mp 93–94°C. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.70 (s, Me); 7.38–7.46 (m, 4/5-H, Ar), 7.50 (4-H, Ph); 7.58–7.67 (m, 3/5-H, Ph; 3-H, Ar); 8.17 (6-H, Ar); 8.67 (2/6-H, Ph). ^{13}C NMR ($CDCl_3$, 20.2 MHz): 21.6 (Me); 126.5 (C-5, Ar); 128.1 (C-3/5, Ph); 129.2 (C-2/6, Ph); 130.9 (C-3, Ar); 131.3 (C-1, Ph); 131.4 (C-6, Ar); 131.6 (C-1, Ar); 132.0 (C-4, Ar); 132.6 (C-4, Ph); 138.7 (C-4, Ar); 162.7 (C-6); 166.9 (C-3). UV/VIS ($CHCl_3$): λ_{max}=545 (log ϵ=3.073), 288 (3.683). Anal. Calcd for $C_{15}H_{12}N_4$ (248.3): C, 72.56; H, 4.87; N, 22.57. Found: C, 72.82; H, 4.93; N, 22.29.

3-Phenyl-6-(2,4,6-trimethylphenyl)tetrazine (4c). A 6 N solution of $NaNO_2$ in water (25 mL, 150 mmol) was added dropwise to 18 mL of conc. HCl (ca. 180 mmol). The resulting nitrous gases were bubbled through a suspension of **5c** (4.33 g, 15.6 mmol) in 15 mL of CH_2Cl_2 cooled to 0°C. After 20 min the solvent was evaporated and the residue recrystallized from methanol/ethanol to give 3.35 g (78%) of **4c** as violet–red needles with mp 98–99°C. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.17 (2/6-Me); 2.38 (4-Me); 7.00 (3/5-H, Ar); 7.58 (3/5-H, 4-H, Ph); 8.63 (2/6-H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz): 20.2 (2/6-Me); 21.3 (4-Me); 128.2 (C-3/5, Ph); 129.0 (C-3/5, Ar); 129.3 (C-2/6, Ph); 130.0 (C-1, Ph); 131.8 (C-1 Ar); 132.8 (C-4, Ph); 137.2 (C-2/6, Ar); 140.2 (C-4, Ar); 163.1 (C-3); 168.2 (C-6). UV/VIS ($CHCl_3$): λ_{max}=548 (log ϵ=3.919), 2.76 (3.539). Anal. Calcd for $C_{17}H_{16}N_4$ (276.3): C, 73.89; H, 5.79; N, 20.08. Found: C, 73.56; H, 5.77; N, 20.27.

2,3-Dihydro-3,6-diphenyl-3-[1-(4,5-dihydro-1,3-dimethyl-2-imidazolio)cyclopropyl]-1,2,4,5-tetrazinide (7a).[1] To a suspension of red tetrazine **4a** (550 mg, 2.35 mmol) in 20 mL toluene at −30°C **2** (400 mg, 2.89 mmol) was added dropwise. After 3 h at −15°C the color of the precipitate had changed to orange. The yellow solid was collected in a cooled glass filter, washed with toluene and dried for two days in vacuo at −20°C to yield 780 mg (86%) **7a**.

2,3-Dihydro-3-(2-methylphenyl)-6-phenyl-3-[1-(4,5-dihydro-1,3-dimethyl-2-imidazolio)cyclopropyl]-1,2,4,5-tetrazinide (7b) and 2,3-dihydro-6-(2-methylphenyl)-3-phenyl-3-[1-(4,5-dihydro-1,3-dimethyl-2-imidazolio)cyclopropyl]-1,2,4,5-tetrazinide (8b). To a solution of tetrazine **4b** (693 mg, 2.79 mmol) in 30 mL THF at −10°C a precooled solution of **6** (404 mg, 2.93 mmol) in 5 mL THF was added slowly. After the color had changed to orange, the yellow solid (1.02 g, 95%) was collected in a cooled glass filter, washed with pentane and dried in vacuo at −20°C. A solution of this solid in CD_2Cl_2 was prepared at −50°C and characterized by NMR spectroscopy as a mixture of **7b** and **8b** (33:67). ^{1}H NMR (CD_2Cl_2, 400 MHz, −50°C): **7b**: 0.92 (m_c, 2H, cPr); 1.32 (m_c, 2H, cPr); 2.44 (Me, Ar); 3.16 (s, N–Me); 3.26 (s, N–Me); 3.58 (m_c, N–CH_2); 3.74 (m_c, N–CH_2); 6.85 (5-H, Ar); 6.90 (3-H, Ar); 6.99 (4-H, Ar); 6.99 (4-H, Ph); 7.14 (3/5-H, Ph); 7.43 (6-H, Ar); 7.53 (2/6-H, Ph). 8b: 0.92 (m_c, 2H, cPr); 1.54 (m_c, 2H, cPr); 1.75 (Me, Ar); 3.14 (s, 2N–Me); 3.61 (m_c, 2N–CH_2); 6.94 (3-H, Ar); 6.94 (5-H, Ar); 7.04 (4-H, Ar); 7.09 (3/5-H, Ph); 7.13 (4-H, Ph); 7.35 (2/6-H, Ph); 7.88 (6-H, Ar). ^{13}C NMR (CD_2Cl_2, 100 MHz, −50°C): **7b**: 10.1 ($2CH_2$, cPr); 22.5 (cPr); 24.5 (Me, Ar); 35.4 (N–Me); 35.8 (N–Me); 49.60 (N–CH_2); 49.7 (N–CH_2); 87.0 (C-3, tetrazinide); 122.0 (C-2/6, Ph); 124.2 (C-3, Ar); 125.1 (C-4, Ph); 127.5 (C-4, Ar); 128.2 (C-3/5, Ph); 130.1 (C-6, Ar); 131.3 (C-3-Ar); 136.8 (C-1, Ar); 136.9 (C-1, Ph); 139.9 (C-2, Ar); 157.6 (C-6, tetrazinide); 168.4 (C-2, imidazolium). **8b**: 10.4 ($2CH_2$, cPr); 21.1 (Me, Ar); 23.4 (cPr); 35.3 (2N–Me); 49.61 (2N–CH_2); 84.5 (C-3, tetrazinide); 124.8 (C-6, Ar); 125.40 (C-5, Ar); 127.1 (C-3/5, Ph); 125.43 (C-4, Ar); 128.1 (C-4, Ph); 129.0 (C-2/6, Ph); 130.9 (C-3, Ar); 134.3 (C-2, Ar); 136.0 (C-1, Ar); 139.6 (C-1, Ph); 157.7 (C-6, tetrazinide); 168.8 (C-2, imidazolium).

2,3-Dihydro-3-phenyl-6-(2,4,6-trimethylphenyl)-3-[1-(4,5-dihydro-1,3-dimethyl-2-imidazolio)cyclopropyl]-1,2,4,5-tetrazinide (8c). To a solution of tetrazine **4c** (304 mg, 1.10 mmol) in 10 mL THF at −10°C a precooled solution of **6** (176 mg, 1.27 mmol) was added slowly. After the color had changed to orange, the solvent was evaporated and the remaining yellow solid (437 mg, 96%) dried in vacuo at −20°C. A solution of this solid in CD_2Cl_2 was prepared at −50°C and characterized by NMR spectroscopy as **8c**. ^{1}H NMR (CD_2Cl_2, 400 MHz, −50°C): 0.95 (m_c, 2H, cPr); 1.74 (m_c, 2H, cPr); 1.51 (2/6-Me, Ar); 2.20 (4-Me, Ar); 3.06 (s, 2N–Me); 3.70 (m_c, N–CH_2); 3.83 (m_c, N–CH_2); 6.71 (3/5-H, Ar); 7.10–7.22 (3/4/5-H, Ph); 7.44 (2/6-H, Ph). ^{13}C NMR

(CD_2Cl_2, 100 MHz, −50°C): 11.2 ($2CH_2$, cPr); 20.1 (2/6-Me, Ar); 21.1 (4-Me, Ar); 23.8 (cPr); 35.2 (2N-Me); 49.7 (2N-CH_2); 81.0 (C-3, tetrazine); 127.6 (C-3/5, Ph); 128.5 (C-4, Ph); 128.1 (C-3/5, Ar); 128.9 (C-2/6, Ph); 133.6 (C-4, Ar); 136.5 (C-1, Ar); 138.1 (C-2/6, Ar); 141.1 (C-1, Ph); 155.1 (C-6, tetrazinide); 168.5 (C-2, imidazolium).

5,8-Dimethyl-9,12-diphenyl-5,8,10,11-tetraazadispiro-[2.0.4.4]dodeca-9,11-diene (11a).[1] To **4a** (431 mg, 1.84 mmol) in 20 mL toluene **6** (307 mg, 2.22 mmol) was added at room temperature. The rapid gas evolution (44 mL, 1.96 mmol) ceased after a few minutes, the red color of the mixture had changed to yellow. The precipitate was collected by filtration, washed with toluene and recrystallized from ethanol/ethyl acetate to yield 515 mg (79%) yellow crystals with mp 186–187°C. UV ($CHCl_3$): λ_{max}=245 (log ϵ=4.113). MS: *m/z* 344 (M^+, 100%). Anal. Calcd for $C_{22}H_{24}N_4$ (358.5): C, 76.71; H, 7.02; N, 16.27. Found: C, 75.95; H, 6.98; N, 16.30.

5,8-Dimethyl-12-(2-methylphenyl)-9-phenyl-5,8,10,11-tetraazadispiro[2.0.4.4]dodeca-9,11-diene (11b). To a deep red solution of **4b** (816 mg, 3.29 mmol) in 3 mL THF, **6** (473 mg, 3.42 mmol) was added at room temperature. The rapid gas evolution (71 mL, 3.17 mmol) ceased after a few minutes, the red color had changed to yellow. The solvent was evaporated and the residue recrystallized from ethyl acetate to yield 991 mg (84%) yellow crystals with mp 172–173°C. ^{1}H NMR (CD_2Cl_2, 400 MHz): 1.25 (m_c, 4H, cPr); 2.00 (s, N–Me); 2.36 (s, Me, Ar); 2.60 (s, N–Me); 3.00 (m_c, 2N–CH_2); 7.25 (5-H, Ar); 7.27 (3-H, Ar); 7.30 (6-H, Ar); 7.33 (4-H, Ar); 7.39 (3/5-H, Ph); 7.42 (4-H, Ph); 7.88 (2/6-H, Ph). ^{13}C NMR (CD_2Cl_2, 100 MHz): 10.8 (C-1/2); 19.8 (Me, Ar); 22.5 (C-3); 36.5 (2N–Me); 52.5 (C-6/7); 75.8 (C-4); 125.2 (C-5, Ar); 127.9 (C-3/5, Ph); 128.7 (C-6, Ar); 129.1 (C-4, Ph); 129.7 (C-2/6, Ph); 130.0 (C-4, Ar); 130.9 (C-3, Ar); 134.8 (C-1, Ar); 136.8 (C-2, Ar); 140.8 (C-1, Ph); 160.9 (C-9); 169.2 (C-12). UV (CH_3CN): λ_{max}=295 (log ϵ=5.256). Anal. Calcd for $C_{23}H_{26}N_4$ (358.5): C, 77.06; H, 7.20; N, 15.63. Found: C, 77.07; H, 7.31; N, 15.77.

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