1,2,4,5-Tetrazine: Synthesis and Reactivity in [4+2] Cycloadditions☆

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Full details on the reactivity of the title compound as 4π component in inverse-type Diels–Alder reactions, including kinetic data, are reported. Donor-substituted alkynes, alkenes, donor-substituted and unsubstituted cycloalkenes, ketene acetals and aminals, as well as several cyclic enol ethers were used as dienophiles in these investigations. A number of 4-mono- and 4,5-disubstituted pyridazines can easily be obtained by this method.

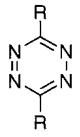
Introduction

1,2,4,5-Tetrazines such as **1** (Figure 1), with a large variety of substituents in the 3- and 6-positions of the heterocycle are easily accessible, and due to their potential role as 4-π components in inverse-type Diels−Alder reactions, members of this heterocyclic class have found widespread use in many fields of organic chemistry, ranging from mechanistic investigations to natural-product synthesis.[1]

However, as is also known for many other heterocycles, the preparation of the parent compound is often accompanied by various synthetic obstacles. Nevertheless the first preparation of 1,2,4,5-tetrazine (**2**) was reported as early as 1900 by Hantzsch and Lehmann.[2] Tetrazine **2** was obtained by thermal decarboxylation of 1,2,4,5-tetrazine-3,6-dicarboxylic acid. Unfortunately, this method is incovenient because this compound can only be obtained by a multistep procedure involving some low-yielding steps. These disadvantages prevented further intensive studies of the parent compound.

In our laboratory, the study of the parent compound 1,2,4,5-tetrazine (**2**) began in 1980, when this compound became readily available by a method developed by Sichert.[3] Further optimization of this procedure has made it possible to obtain **2** in 10-g quantities. Hence, we have carried out intensive investigations on the behaviour of this intriguing compound as 4-π component in Diels−Alder reactions. The results of our investigations concerning the [4+2] cycloadditions of **2** with a vast range of dienophiles, such as donor-substituted alkynes and cycloalkenes, ketene acetals and aminals, and styrenes, are discussed. Kinetic data are presented for the majority of these systems.

Figure 1. 1,2,4,5-Tetrazines (**1**): reactive electron-poor dienes



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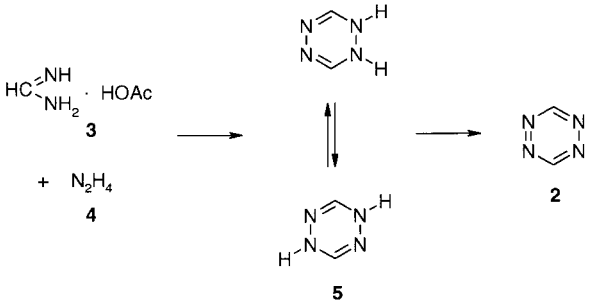
Results and Discussion

Synthesis of 1,2,4,5-Tetrazine (2)

1,2,4,5-Tetrazine (**2**) can be synthesized from the commercially available starting materials formamidine acetate and hydrazine hydrate (Scheme 1) in a one-pot procedure. This procedure was developed in our laboratory in 1980.[3] A similar procedure has been published in the meantime by van der Plas.[4] The formation of the 1,2,4,5-tetrazine ring system involves several condensation and elimination steps. No mechanistic investigations were undertaken, but the intermediate formation of dihydro-1,2,4,5-tetrazine (**5**) is beyond doubt. The dihydro compound, which is suspended in dichloromethane, can be oxidized to the fully conjugated ring system **2** by sodium nitrite in acetic acid or by externally generated nitrous fumes. Tetrazine **2** is very volatile due to the low molecular weight and tends to sublime rapidly, even at atmospheric pressure. Hence, the isolation and separation of residual solvent is lengthy and tedious. However, this optimized procedure allows the preparation of 10-g quantities of pure **2** with an acceptable overall yield of about 25%.

Scheme 1. Synthesis of 1,2,4,5-tetrazine (**2**)



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[4+2] Cycloaddition Reactions of 1,2,4,5-Tetrazine (2)

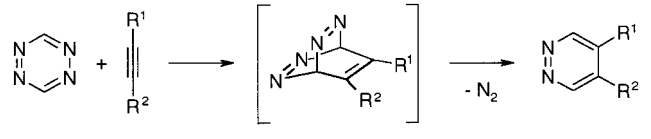
[4+2] Cycloadditions are by far the most important reactions of 1,2,4,5-tetrazines.[1] As early as 1959, Carboni and Lindsey reported the surprising result of successful cycloadditions of 1,2,4,5-tetrazines with simple alkenes and alkynes under mild thermal conditions to form 1:1 adducts, with the loss of nitrogen[5]. For electron-withdrawing substituents in the 3- or 6-positions, the reactivity is particularly high and 1,2,4,5-tetrazines were found to be the second case of Diels–Alder reactions with inverse electron demand, as proven by the kinetic measurements of Sauer et al.;[6] the first case was that of hexachlorocyclopentadiene.[7]

Therefore, [4+2] cycloadditions of alkynes to the now readily available parent compound **2** offer an elegant access to simple 4- or 4,5-substituted pyridazines. A basic requirement for successful reactions is that the electronic characters of the diene and the dienophile complement each other.[8] Electron-rich alkenes and alkynes are therefore the dienophiles of choice for the electron-deficient tetrazines. Apart from some previews,[1] our results have not yet been published.

Preparative Results

Cycloadditions with electron-rich alkynes afforded the expected donor-substituted pyridazines (Scheme 2). Conditions, yields, and supplementary kinetic data are shown in Table 1. All reactions proceed cleanly, side reactions are not observed and yields are generally high. The low yield for the reaction with acetylene (**6b**) can be attributed to unavoidable losses of the volatile diene when the gaseous dienophile is introduced into the solution of the diene. The reactivity of 2,2,5,5-tetramethyl-3-butyne (**10c**) is also low. Forcing conditions lead mainly to the formation of tar-like side products and a low yield of the desired cycloadduct. As expected, the different reaction conditions show large reactivity differences of the alkynes towards **2**. The rate constants span a range with a factor of 10^8 and will be discussed in the kinetic section of this paper. Sometimes, isolation of pure reaction products is difficult, because of the hygroscopic nature of some pyridazines. Nevertheless, correct elemental analyses were obtained for derivatives of these products. ^{1}H-NMR spectra show the typical AMX spin system of a monosubstituted pyridazine nucleus and additional resonance signals for the substituents.

Scheme 2. [4+2] Cycloadditions of 1,2,4,5-tetrazine (**2**) with alkynes



2 **6-11** **12-30**

The reactions with alkenes are somewhat more complicated, due to different subsequent reactions being possible.[1] These take place after formation of the bicyclic primary adduct and loss of nitrogen. The mode of these subsequent reactions depends on the structure of the dienophile, as well as on the substituents in the 3- and 6-positions of the 1,2,4,5-tetrazine. Aromatization occurs easily if an alcohol, thiol or amine can be eliminated. Therefore, the use of such donor-substituted cycloalkenes leads to bicyclic pyridazine derivatives by the discussed mechanistic steps (Scheme 3). Again, the dimethylamino group is by far the most activating substituent, but enamines do not give the best yields for all cases (Table 2). The spectroscopic data of the products isolated are in full agreement with the proposed structures. The ^{1}H-NMR resonances of the pyridazine protons of **12** and **35–37** appear as sharp singlets at $\delta = 8.80-9.08$.

For open-chain alkenes, the modes of subsequent reactions depend on the substituents of the alkene. For ethylene (**38**) as dienophile, the initially formed 4,5-dihydropyrid-

Table 1. Reactions of alkynes with 1,2,4,5-tetrazine (**2**); rate constants at 20°C in 1,4-dioxane

Nr.	Dienophile R^1	R^2	Reaction conditions	Product Nr.	Yield [%]	$\bar{k}_2 * 10^5$ [l mol^{-1} s^{-1}]
6a			0 °C / at once	**12**	84	2710000
6b	H	H	RT / 70h	**13**	27	2.91
7a	H	$C(CH_3)_3$	RT / 20d	**14**	90	0.169
7b	H	C_6H_5	90 °C / 13d	**15**	64	0.168
7c	H	C_6H_4-pOCH_3	90 °C / 22h	**16**	81	-
7d	H	C_6H_4-pNO_2	90 °C / 12h	**17**	72	-
8a	H	NMe_2	0 °C / at once	**18**	94	50200
8b	H	OMe	RT / 70h	**19**	93	0.687
8c	H	SMe	RT / 40h	**20**	96	1.47
9a	H	$SnBu_3$	RT / 12h	**21**	76	58.2
9b	H	$GeMe_3$	80 °C / 1.5h	**22**	80	19.0
9c	H	$SiMe_3$	80 °C / 2h	**23**	94	4.16
10a	MeS	NMe_2	RT / 5min	**24**	90	2170
10b	MeS	SMe	100 °C / 18h	**25**	89	0.018
10c	$(CH_3)_3C$	$C(CH_3)_3$	65 °C / 120h	**26**	12	-
11a	Me_3Sn	$SnMe_3$	RT / 2h	**27**	82	1242
11b	Bu_3Sn	$SnBu_3$	RT / 2h	**28**	71	366
11c	Me_3Ge	$GeMe_3$	RT / 120h	**29**	93	106
11d	Me_3Si	$SiMe_3$	80 °C / 12h	**30**	93	7.63

Scheme 3. [4+2] Cycloadditions of 1,2,4,5-tetrazine (**2**) with cyclic alkenes

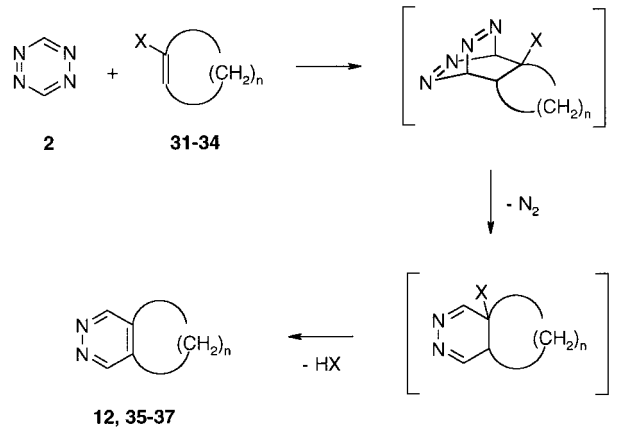
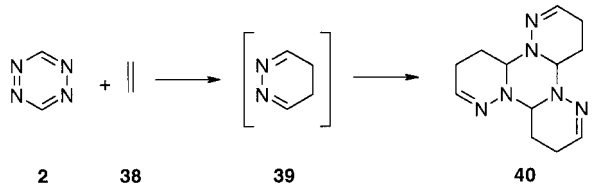


Table 2. Reactions of cyclic enamines and enol ethers with 1,2,4,5-tetrazine (**2**); rate constants at 20°C in 1,4-dioxane

Nr.	Dienophile X	n	Reaction conditions	Product Nr.	Yield [%]	$\bar{k}_2$*10^5 [l mol^{-1} s^{-1}]
31a	–NMe$_2$	3	RT / 15 min		68	1000000
31b	–OMe		80 °C / 50 h		89	3.44
31c	–OSiMe$_3$		70 °C / 68 h	**35**	51	2.44
32a	–NMe$_2$	4	100 °C / 80 min		63	21600
32b	–OMe		80 °C / 100 h		65	0.0168
32c	–OSiMe$_3$		80 °C / 36 h	**36**	92	0.0139
33a	–NMe$_2$	5	RT / 15 min		83	683000
33b	–OMe		80 °C / 14 h		86	11.9
33c	–OSiMe$_3$		60 °C / 20 h	**37**	51	12.2
34a	–NMe$_2$	6	RT / 15 min		67	2140000
34b	–OMe		80 °C / 8 h		92	12.6
34c	–OSiMe$_3$		60 °C / 110 h	**12**	72	5.13

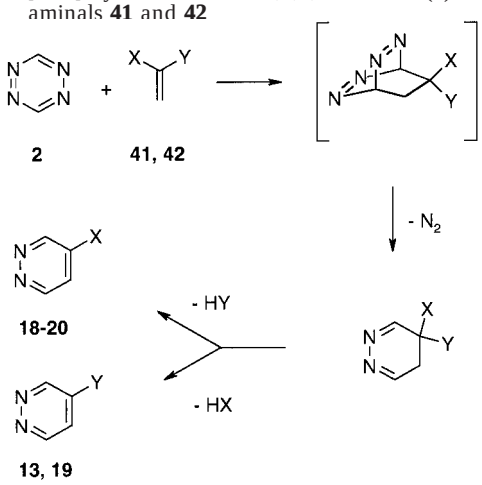
Scheme 4. [4+2] Cycloaddition of 1,2,4,5-tetrazine (**2**) with ethylene (**38**)



azine (**39**) undergoes immediate trimerization to a mixture of stereoisomers **40** with respect to the central 1,3,5-triazane ring system (Scheme 4). The peripheral ring systems can be attached to the central 1,3,5-triazane ring either in an axial or equatorial manner.

Enol ethers and enamines undergo cycloaddition to 1,2,4,5-tetrazine (**2**) in a normal manner, as described for their cyclic analogues. If ketene aminals or acetals are used, elimination of an alcohol, thiol or amine can, in principle, lead to a mixture of substituted pyridazines (Scheme 5). However, a mixture of pyridazines **18** and **19** was only obtained for for the N,O aminal **42b** and separated by means of column chromatography. For the N,S aminal **42d** only the elimination of the −SMe group was observed (Table 3). Again, yields are very good and reactivity differences cover a range with a factor > 10^6. Spectroscopic data of pyridazines **13** and **18**−**20** agree with authentic samples prepared by other means.

Scheme 5. [4+2] Cycloadditions of 1,2,4,5-tetrazine (**2**) with ketene aminals **41** and **42**



Substituted styrenes **43** are amongst the most frequently used dienophiles in inverse-type cycloadditions due to their high reactivity towards electron-deficient dienes. In most cases the 4,5-dihydropyridazine, originally formed after loss of nitrogen, undergoes a rapid [1,3] hydride-shift to form the more stable 1,4-dihydropyridazines **44**. Because tautomerization is always faster than cycloaddition, 1,4-dihydropyridazines are often obtained as the first isolated reaction products. Sometimes, isolation of these dihydropyridazines is difficult, because the oxidizing power of dioxygen is sufficient for their oxidative conversion into the stable, fully conjugated pyridazine derivatives.

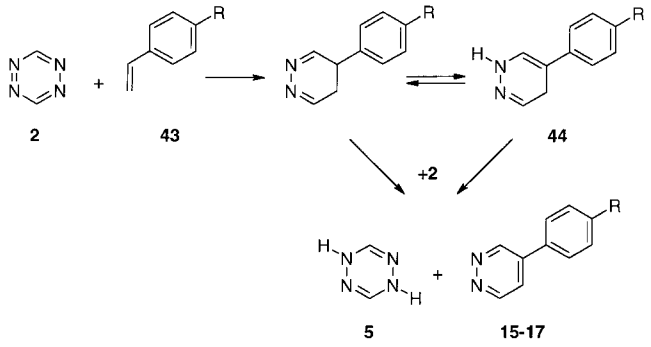
The styrenes **43** decolourized equimolar solutions of **2** in dioxane at room temperature within 50 h (R = *p*-MeO), 70 h (R = H), and 120 h (R = *p*-NO$_2$). In addition to the described tautomerization, the dihydropyridazines were also oxidized to aromatic pyridazines **15**−**17** by **2** (Scheme 6) under an inert atmosphere.

Our attempts to isolate the reaction products by flash column chromatography failed, because 1,4-dihydro-1,2,4,5-tetrazine (**5**) formed during the reaction was slowly reoxidized to 1,2,4,5-tetrazine (**2**) during chromatography. Since the R_f value of **5** is lower than those of the dihydropyridazines **44**, and the R_f value of **2** is larger, a quantitative separation on a preparative scale was not possible. Therefore, the contents of the individual compounds in the reaction mixture were determined by HPLC.

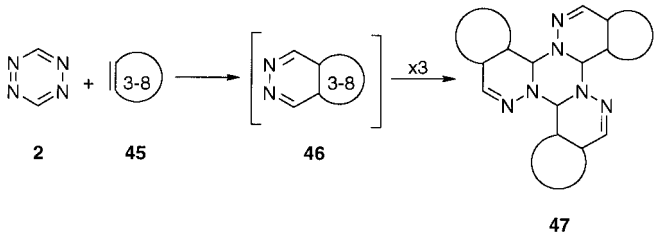
Table 3. Reactions of mono- and 1,1-donor-disubstituted ethylenes with 1,2,4,5-tetrazine (**2**); rate constants at 20°C in 1,4-dioxane

Nr.	X	Y	Reaction conditions	Product(s) X (yield [%])	Product(s) Y (yield [%])	$\bar{k}_2 * 10^5$ [l mol^{-1} s^{-1}]
41a	NMe_2	H	RT/5 min	–	**13** (61)	–
41b	OEt	H	80°C/30 min	–	**13** (78)	80.4
41c	SMe	H	100°C/2 h	–	**13** (76)	14.4
42a	NMe_2	OEt	RT/10 min	**18** (72)	–	1360000
42b	NMe_2	OMe	RT/15 min	**18** (73)	**19** (22)	–
42c	NMe_2	NMe_2	RT/10 min	**18** (96)	identical	681000
42d	NMe_2	SMe	RT/10 min	**18** (93)	0	61400
42e	OEt	OEt	RT/18 h	**19** (94)	identical	120
42f	SMe	SMe	70°C/90 h	**20** (87)	identical	0.247

Scheme 6. [4+2] Cycloadditions of 1,2,4,5-tetrazine (**2**) with styrenes **43**



Scheme 7. [4+2] Cycloadditions of 1,2,4,5-tetrazine (**2**) with cyclic alkenes **46**



Complications concerning the stereochemical identity of the trimeric products obtained arise when simple cyclic alkenes **45** are used as dienophiles. As already observed in the reaction with ethylene, the intermediately formed 4,5-dihydropyridazines **46** trimerize rapidly to yield **47** (Scheme 7). In addition to the stereochemical possibilities with respect to the central 1,3,5-triazane ring, there are now further possibilities concerning the configuration of the cyclic alkyl chains. Detailed investigations including HPLC separation of stereoisomers[9] and X-ray-crystallographic analyses are currently in progress, and will be reported in due course. However, these subsequent trimerization reactions are irrelevant for kinetic measurements, because the initial rate-determining step, the cycloaddition of the dienophile to the 1,2,4,5-tetrazine, is slow relative to all following steps. Therefore, kinetic data of these dienophiles showing the effect of angle strain on the reactivity as dienophile will be included in the kinetic section of this paper (Table 5).

The primary cycloadducts of 3,6-disubstituted 1,2,4,5-tetrazines and cyclic enol ethers, like 2,3-dihydrofuran or 1,3-dioxole, tend to undergo a number of successive reactions.[10] It is therefore not surprising that thin-layer chromatography revealed a number of reaction products, when 1,2,4,5-tetrazine was allowed to react with these dienophiles.[9] However, the rate-determining step is again the initial cycloaddition of 1,2,4,5-tetrazine to form the dihydropyridazine after nitrogen elimination, and for this reason kinetic data are reported in the following section of this paper.

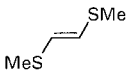
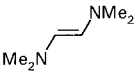
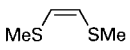
Kinetic Results

[4+2] Cycloadditions of 1,2,4,5-tetrazines are $LUMO_{diene}-HOMO_{phil}$-controlled reactions.[1] For a particular diene **2**, the reactivity change of the system parallels the HOMO energy of the dienophiles. Donor substituents raise the HOMO energy of the dienophiles and by decreasing the $LUMO_{diene}-HOMO_{phil}$ gap, increase the rate constants of the cycloaddition step. In principle, any exchange of hydrogen in the dienophile for a larger substituent has an impeding steric effect. So, as a net result, the substitution of hydrogen by a substituent in the dienophile component, depending on its electron-donating power, can lead to an increase or decrease of the dienophile's reactivity.

Table 4. Reactions of 1,2,4,5-tetrazine (**2**) with styrenes at 20°C in dioxane; product yields were determined by HPLC

Dienophile	Styrene (**43a**) Yield [%]	*p*-Methoxystyrene (**43b**) Yield [%]	*p*-Nitrostyrene (**43c**) Yield [%]
Dihydropyridazine (**44**)	72	44	59
Pyridazines **15**–**17**	10	16	18
Dihydrotetrazine (**5**)	11	16	22
Unchanged dienophile **43**	14	13	18

Table 5. Reactions of 1,2,4,5-tetrazine (**2**) with selected open-chain and cyclic dienophiles; rate constants at 20°C in 1,4-dioxane

	Dienophile	$\bar{k}_2 * 10^5$ [l mol^{-1} s^{-1}]		Dienophile	$\bar{k}_2 * 10^5$ [l mol^{-1} s^{-1}]
38		2150	**48a**		24.1
45a		3510	**48b**		437
45b		276	**48c**		73
45c		2.75	**48d**		1.75
45d		359	**48e**		0.097
45e		575			
49a		0.0167	**50**		3970
49b		0.0221	**51**		467

In the course of [4+2] cycloadditions of tetrazines, the colour of the diene component disappears. So it is quite easy to monitor the reactions by the disappearance of the typical n→π* absorption of tetrazine **2** at λ = 548 nm. All cycloadditions studied kinetically in this contribution cleanly follow a second-order rate law between less than 10% and mostly more than 90% conversion. The second-order rate constants [values for $10^5 \times k_2$ (L mol^{-1} s^{-1})] in Tables 1−5 span a range with a factor of 10^8−10^9 and illustrate the tremendous influence of structural variations in the dienophile component. As will be shown below, these substituent effects on the cycloaddition rate of **2** are typical for other tetrazine cycloadditions. Therefore, some "principal rules", also very important for preparative aspects, will be discussed briefly. Some kinetic data, already published by our group, are included in this discussion.[11−14]

1. Olefinic dienophiles exceed acetylenic dienophiles in reactivity. Ethylene is more reactive by a factor of 740 relative to acetylene (Table 5: **38**; Table 1: **6b**). The same effect is found when the rate constants of correspondingly substituted dienophile pairs are compared; for instance, the methoxy derivatives **41b** (Table 3) and **8b** (Table 1), the thioethers **41c** and **8c** or styrene (**43a**) and phenylacetylene (**7b**).

2. The strain relief when angle-strained dienophiles are used, may be responsible for tremendous rate differences. Cyclooctyne is the most reactive dienophile studied (Table 1: **6a**) and exceeds acetylene (**6b**) by a factor of about 930000 in rate. The same effect is certainly responsible for the rate sequence cyclobutene → cyclopentene → cyclohexene (Table 5: **45a**, **45b**, **45c**); the rate minimum for cyclohexene and the rate increase on going to the higher homologues cycloheptene and cyclooctene (Table 5: **45d**, **45e**) is well documented[1] and is observed in all cycloadditions studied. Further examples for this effect are found for cyclic enamines **31a**−**34a**, cyclic enol ethers **31b**−**34b** and TMSO-substituted cycloalkenes **31c**−**34c** (Table 2).

Table 6. Temperature dependance of rate constants for the reaction of 1,2,4,5-tetrazine (**2**) with styrenes and phenylacetylenes; rate constants at 20°C in 1,4-dioxane

	Dienophile	T [°C]	$k_2 * 10^5$ [l mol^{-1} s^{-1}]
43b	*p*-Methoxystyrene	30	225.9
43a	Styrene	30	119.6
43c	*p*-Nitrostyrene	30	42.3
43a	Styrene	20	70.4
43a	Styrene	40	204.1
7c	(*p*-Methoxyphenyl)acetylene	90	71.4
7b	Phenylacetylene	90	48.4
7d	(*p*-Nitrophenyl)acetylene	90	17.6
7b	Phenylacetylene	80	25.2
7b	Phenylacetylene	100	88.5

Table 7. Activation parameters for the reaction of 1,2,4,5-tetrazine (**2**) with styrene and phenylacetylene

Nr.	Dienophile	ΔH^{+} [kcal mol^{-1}]	ΔS^{+} [cal mol^{-1} K^{-1}]
43a	Styrene	9.1 ± 0.2	−42 ± 1
7b	Phenylacetylene	15.8 ± 0.2	−31 ± 0.2

3. As already mentioned, the electron-donating power of substituents can exert a tremendous effect on the cycloaddition rate. As is demonstrated by many examples in Tables 1−5, the dialkylamino group is a strongly activating substituent. Enamines and ynamines are highly active dienophiles (Table 1: **6b**/**8a**, **10a**). Ketene aminals, such as **42a**−**42d** (Table 3) also show high reactivity.

In contrast, the impeding steric substituent effect of MeO, EtO, TMSO and MeS is apparent in all alkenes and alkynes bearing these substituents, outweighing the mild electron-donating effect (Table 1: **6b**/**8b**/**8c**; Tables 2 and 5: **45b**/**31b**/**31c**, **45c**/**32b**/**32c**, **45d**/**33b**/**33c**, **45e**/**34b**/**34c**). Even the introduction of two SR or OR groups in an unsymmetrical 1,1-fashion shows no accelerating effect (Table 5: **38** versus Table 3: **42e**/**42f**).

The introduction of two substituents in a 1,2-fashion in ethylene exerts an even greater influence. The *cis*/*trans*-isomeric bis(methylthio)ethylenes **49a** and **49b** (Table 5) show comparable reactivity, but these dienophiles are far less reactive than ethylene itself, as indicated by a sharp drop of the rate constants by a factor of about 100000. Even *trans*-1,2-bis(dimethylamino)ethylene shows only comparable reactivity to ethylene, in spite of two strong donor-functional groups (Table 5: **50**/**38**). Nevertheless, the normal order of reactivity is still obeyed: The dimethylamino derivative **50** exceeds the corresponding thioether **49a** by a factor of 238000 in rate constants (Table 5).

4. An interestingly delicate interplay of substituent influence is observed for the series of cyclic dienophiles **45b** → **48a** → **48b** → **48c** and **45c** → **48d** → **48e** (Table 5).

Figure 2. Comparison of reactivity data (log k_2 + 7) for [4+2] cycloadditions of **1** (R = CO_2CH_3) and **2** with all dienophiles of Tables 1−5, 20°C, dioxane

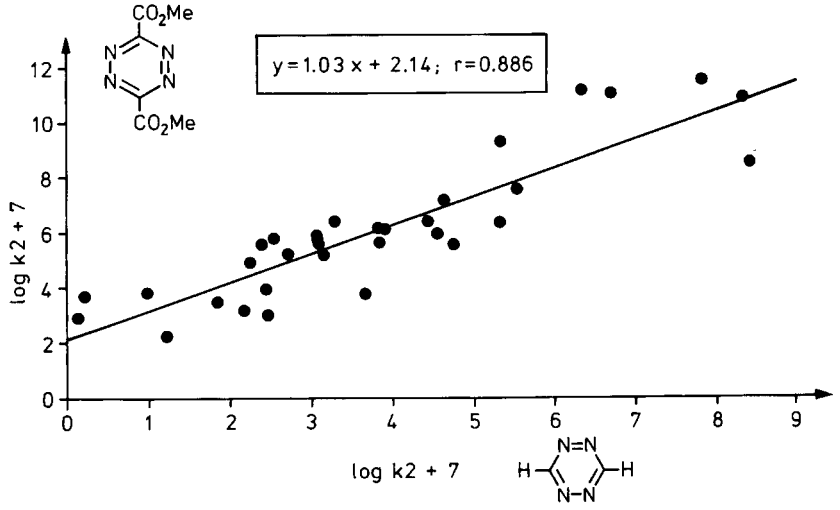
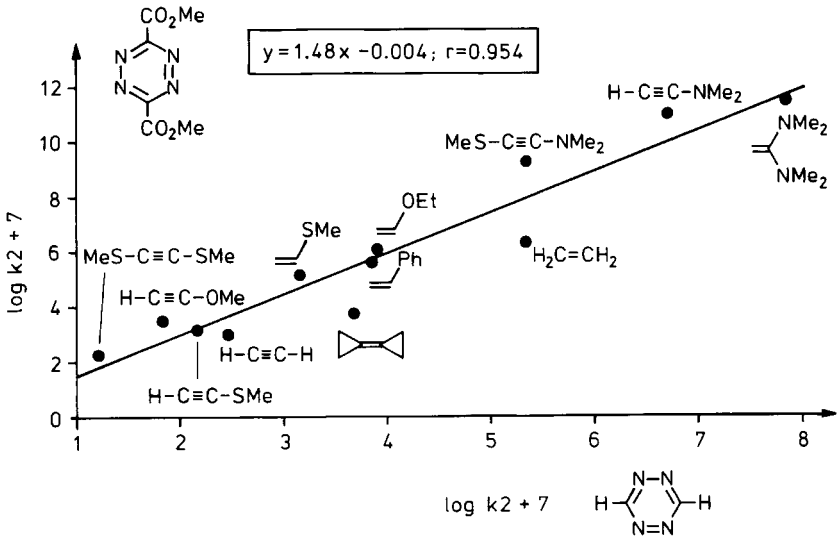


Figure 3. Comparison of reactivity data (log k_2 + 7) for [4+2] cycloadditions of **1** (R = CO_2CH_3) and **2** with open-chain alkenes and alkynes, 20°C, dioxane



5. Table 1 shows a series of rate constants for the cycloadditions of Me_3Si-, Me_3Ge-, Me_3Sn-, and Bu_3Sn-substituted acetylenes. The alkynylstannanes proved to be especially valuable intermediates for the preparation of pyridazine, pyridine and α-pyrone derivatives, otherwise not accessible by simple synthetic procedures.[15] As expected, when steric factors are kept constant, the reactivity increases on going from silanes to germanes and stannanes (Table 1: **9a**−**9c**, **11a**−**11d**).

6. Finally, as expected for concerted [4+2] cycloaddition reactions, the ρ values are small, when substituted styrenes and phenylacetylenes [Table 6: **43** (ρ = −0.67), **7** (ρ = −0.58)] are used as dienophiles. For styrene and phenylacetylene the highly negative values for the activation entropy $\Delta S^{\neq} = -42$ and $\Delta S^{+} = -31$ (cal mol^{-1} K^{-1}) are also in agreement with a highly ordered rate-determining transition state, a precondition for a concerted cycloaddition (Table 7).

As indicated above, the rate constants for the [4+2] cycloadditions of 1,2,4,5-tetrazine (**2**) with a large variety of electron-rich dienophiles are also representative for cycloadditions of other substituted 1,2,4,5-tetrazines **1**. This can be demonstrated briefly by four reactivity plots (Figures 2−5), in which the corresponding rate constants for [4+2] cycloadditions of **2** are compared with those of **1** (R = CO_2CH_3); the rate constants for angle-strained and electron-rich dienophiles cited in Tables 1−5 were plotted. As expected, dienophiles with different structures and steric demands have poorer correlation coefficients, while the comparison of dienophiles with similar steric properties leads to quite satisfying *r* values: (a) Figure 2 presents a comparison of all dienophiles included in this study for dimethyl

Figure 4. Comparison of reactivity data (log k_2 + 7) for [4+2] cycloadditions of **1** (R = CO_2CH_3) and **2** with cyclic alkenes, 20°C, dioxane

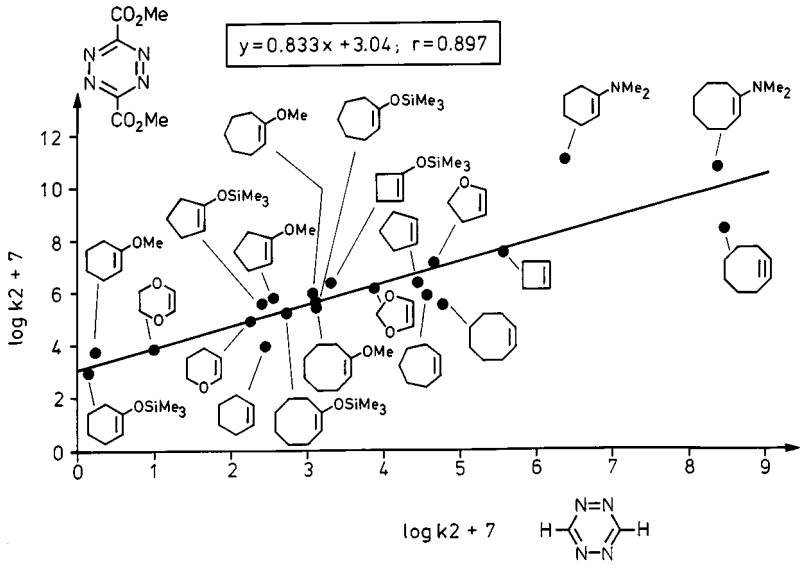
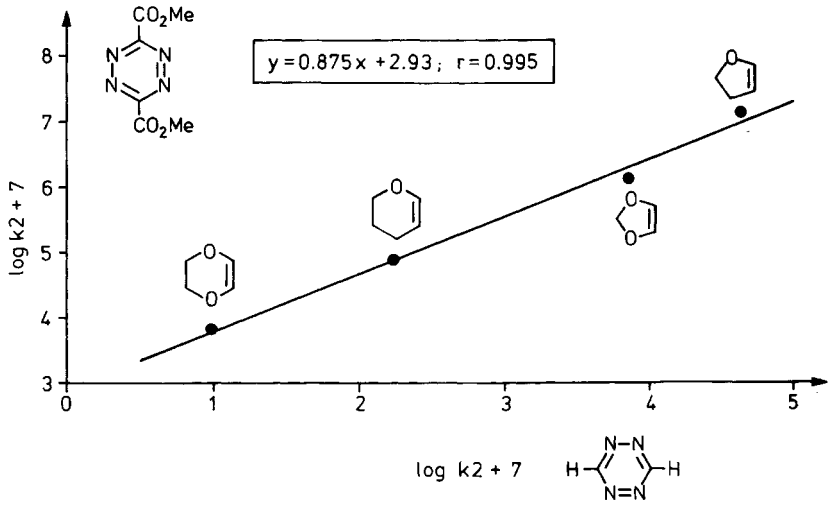


Figure 5. Comparison of reactivity data (log k_2 + 7) for [4+2] cycloadditions of **1** (R = CO_2CH_3) and **2** with selected cyclic enol ethers, 20°C, dioxane



1,2,4,5-tetrazine-3,6-dicarboxylate (**1**, R = CO_2CH_3) and 1,2,4,5-tetrazine (**2**). The rather poor correlation coefficient (r = 0.886) is not unexpected. (b) Selecting dienophile groups of greater steric similarity improves the correlation, as is demonstrated in Figure 3 for a number of open-chain dienophiles (alkenes and alkynes), and in Figure 4 for a large variety of cyclic dienophiles. Finally, when only cyclic dienophiles with similar steric effects are compared, the correlation is almost perfect (Figure 5, r = 0.995). (c) The slope of the reactivity plots as shown in Figures 2−5 indicate the relative selectivity of different tetrazines in [4+2] cycloadditions. A slope of approximately 1 for all dienophiles (Figure 2) implies equal selectivity for both tetrazines. Figures 3−5 show slightly different selectivities for open-chain and cyclic dienophiles. (d) The reactivity-selectivity comparison shown in Figures 2−5 can be extended to other 1,2,4,5-tetrazines (**1**, R = CF_3, C_6H_5) as shown by extensive kinetic studies[1,13,16]. Predictions can thus be made for the reactivity of systems not yet studied kinetically, which may be of interest for synthetic purposes.

Conclusion

As shown for a large number of open-chain and cyclic dienophiles, 1,2,4,5-tetrazine (**2**) can be used as an electron-poor diene in inverse-type Diels−Alder reactions to yield a great variety of pyridazine derivatives not easily accessible by other synthetic methods. The rate constants obtained by extensive kinetic measurements lead to quantitative rules for the influence of steric and electronic substituent effects in the dienophile. The results obtained using 1,2,4,5-tetrazine (**2**) as diene can, in principle, be applied to other tetrazines. Rate effects can hence be easily predicted for synthetic purposes in the tetrazine field.[1]

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Experimental Section

General Remarks: IR spectra: Beckmann Acculab 1. − UV/Vis spectra and kinetics: Zeiss Specord M 500, featuring an automatic changer for up to six 1-cm quartz cuvettes and a Colora MC15 thermostat. Stopped-flow kinetics: Durrum D110 instrument with a Nicolet oscilloscope and a Colora thermostat. UV/Vis and stopped-flow kinetic measurements: Separate solutions of pure tetrazine **2** and pure dienophiles (> 95−98% by ^{1}H-NMR and GC analysis or acid titration for enamines) were prepared in degassed dry 1,4-dioxane at 20.0°C. The stability of **2** in 1,4-dioxane was checked by monitoring its absorption maximum at λ = 548 nm. Solutions containing **2** [$(1.2-13.0) \times 10^{-3}$ mol L^{-1}] and a 40−800-fold excess of dienophiles were pipetted into quartz cuvettes for UV measurements and thoroughly mixed. The progress of the reactions was followed by monitoring the n→π* transition of the diene **2** at λ = 548 nm, usually covering 10−90% of the reaction. All kinetic runs were duplicated at least once, k_2 values differed less than ± 5% Further experimental details for kinetic runs can be found in the literature.[16] − NMR spectra: Bruker AC250 (250 MHz for ^{1}H and 63 MHz for ^{13}C), Bruker AW 80 (80 MHz, ^{1}H) or Varian T 60 (60 MHz, ^{1}H). Chemical shifts in $CDCl_3$ are reported in δ values in ppm relative to internal or external (Si-, Ge-containing compounds) tetramethylsilane (TMS, δ = 0.00). The degree of substitution of the C atoms was determined by the DEPT-135 method. − Mass spectra: Varian MAT 311A or CH5 instrument at an ionizing voltage of 70 eV by electron impact. − Melting points: Büchi melting point apparatus (uncorrected values). − Elemental analyses: Microanalytical laboratory of the Chemical Institute of the University of Regensburg, Heraeus Mikro U/E and CHN-Rapid instruments. − Analytical thin-layer chromatography (TLC) was performed on precoated plastic sheets (POLYGRAM SIL G/UV254, Macherey-Nagel), observed under UV light. Silica gel 60 (230−400 mesh, 0.040−0.063 mm, Merck) was used for flash column chromatography (FCC). − HPLC separations: Spectra-Physics SP 8700 controller, SP 8300 UV detector (λ = 254 nm), SP 4020 interface, SP 4060 integrator, processor SP 4000. − GC analyses: Hewlett Packard HP 5890 II equipped with a capillary column DB1 (60 m, 0.25 mm). − Reactions were carried out under nitrogen. − Compounds **3**,[17] **6a**,[18] **7a**,[19] **7c**,[20] **7d**,[21] **8a−8c**,[22] **9a**,[23] **9b**,[24] **9c**,[25] **10a**,[22b] **10b**,[22a] **10c**,[26] **11a**,[27] **11b**,[28] **11c**,[27] **11d**,[22a] **31−34a**,[29] **31−34b**,[30] **31−34c**,[31] **41a**,[32] **41c**,[22a] **42a−c**,[33] **42d**,[34] **42e**,[35] **42f**[36] **43b**,[37] **43c**,[38] **45a**[,39] **48c**,[40] **48e**,[41] **49a**,[42] **49b**,[43] **50**,[44] **51**[45] were prepared according to published procedures. **7b**, **41b**, **43a**, **45b−e**, **48a**,**b**,**d** are commercially available and were distilled under nitrogen prior to use.

1,2,4,5-Tetrazine (**2**): Formamidine acetate (**3**, 120.0 g, 1.15 mmol) and MeOH (200 ml) were placed in a 2-l flask equipped with a mechanical stirrer, pressure-equalizing dropping funnel, and a thermometer. At 0°C, hydrazine hydrate (**4**, 120.0 g, 2.40 mmol) was added with stirring. Glacial acetic acid (400 ml) was then added dropwise at 0−5°C over a period of 30 min. The reaction mixture was allowed to reach ambient temperature (30 min) and a clear solution was obtained. The mixture was cooled to 10°C and solid $NaNO_2$ (175.0 g, 2.58 mmol) was added. The resulting reaction mixture was stirred at 10°C for 60 min, then at ambient temperature for a further 60 min. $NaHCO_3$ (250.0 g) and H_2O (300 ml) were added and the resulting suspension was stirred for 30 min. Undissolved $NaHCO_3$ was filtered off with suction. The filtrate was extracted with CH_2Cl_2 (10 × 100 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (300 ml) and H_2O (300 ml) and dried with $CaCl_2$. The red solution was concentrated carefully at atmospheric pressure to a volume of about 50−100 ml using a Vigreux column (30 cm), purified by column chromatography (100 g, CH_2Cl_2) and concentrated again. The last 50 ml of the solvent was removed under reduced pressure (−40°C, 0.1 Torr). Sublimation (bath 10°C, cooling finger −50°C, 0.1 Torr) afforded **2** as bright red crystals (10.0−12.2 g, 21−26%), m.p. 94−95°C. − UV/Vis (dioxane): λ_{max} (lg ε) = 548 nm (2.66), 528 (2.85), 510 (2.78), 249 (3.45). − ^{1}H NMR (60 MHz, $CDCl_3$): δ = 10.36 (s, 2 H).

5,6,7,8,9,10-Hexahydrocycloocta[d]pyridazine (**12**). − *Method A:* Cyclooctyne (**6a**, 349 mg, 3.22 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of **2** (221.1 mg, 2.69 mmol) in CH_2Cl_2 (6 ml) at 0°C. The addition resulted in vigorous evolution of nitrogen and rapid decolourization of the red solution. The solvent was removed and recrystallization of the pale yellow residue from hexane gave **12** (366 mg, 84%), colourless crystals, m.p. 82−82.5°C. − *Method B:* 1-(Dimethylamino)cyclooctene (**34a**, 625 mg, 4.08 mmol) in dioxane (10 ml) was added dropwise over a period of 15 min to a stirred solution of **2** (269 mg, 3.28 mmol) in dioxane (10 ml) at ambient temperature. Removal of all volatiles in vacuo gave a crude, oily, brown product, which was recrystallized from hexane to give **12** (355 mg, 67%). − *Method C:* **2** (187 mg, 2.28 mmol) and 1-methoxycyclooctene (**34b**, 360 mg, 2.57 mmol) in dioxane (10 ml) were heated with stirring at 80°C until the red colour became decoloured to yellow-brown. Volatiles were removed in vacuo and the resulting red-brown solid recrystallized from hexane to afford **12** (340 mg, 92%). − *Method D:* **2** (344 mg, 4.19 mmol) and 1-(trimethylsiloxy)cyclooctene (**34c**, 932 mg, 4.70 mmol) in dioxane (10 ml) were heated with stirring at 60°C for 110 h to give a yellow-brown reaction mixture. Volatiles were removed in vacuo. Recrystallization of the brownish residue from hexane afforded **12** (488 mg, 72%). − IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 2920, 2860, 1560, 1460, 1430. − UV/Vis (dioxane): λ_{max} (lg ε) = 315 nm (2.64), 250 (2.98). − ^{1}H NMR (60 MHz, $CDCl_3$): δ = 1.1−2.1 (m, 8 H), 2.5−3.2 (m, 4 H), 8.85 (s, 2 H, 3-H, 6-H, pyridazine). − $C_{10}H_{14}N_2$ (162.2): calcd. C 74.04, H 8.70, N 17.27; found C 73.75, H 8.66, N 17.11.

Pyridazine (**13**). − *Method A:* Purified gaseous acetylene (**6b**) was introduced (1 bubble/5 s) into a solution of **2** in dioxane (10 ml) for 70 h. The solution decolourized during this period. Removal of the solvent afforded a pale brownish liquid which was purified by FCC (CH_2Cl_2/EtOH, 10:2) to afford **13** (62 mg, 27%), colourless liquid, which tends to darken rapidly. − *Method B:* **2** (225 mg, 2.74 mmol) in dioxane (10 ml) was added dropwise to a hot solution (80°C) of ethyl vinyl ether (**41b**, 2.25 g, 31.2 mmol) in dioxane (5 ml). The rate of addition was initially controlled by complete decolourization of the red tetrazine colour. A brown colour persisted at the end of the addition and total reaction time was about 30 min. Removal of the solvent in a rotary evaporator and FCC (CH_2Cl_2/EtOH, 15:1) afforded **13** (172 mg, 78%). − *Method C:* **2** (73.1 mg, 0.89 mmol) in dioxane (10 ml) was added dropwise to a hot solution (100°C) of methyl vinyl sulfide (**41c**, 1.55 g, 20.9 mmol) in dioxane (10 ml) The reaction required about 2 h. Removal of the solvent in a rotary evaporator and FCC (CH_2Cl_2/EtOH, 15:1) afforded **13** (54.0 mg, 76%). − *Method D:* A solution of *N,N*-dimethylvinylamine (**41a**, 372 mg, 5.24 mmol) in dioxane (5 ml) was added dropwise at ambient temperature to **2** (282 mg, 3.43 mmol) in dioxane (10 ml) over a period of 5 min. The red solution decolourized immediately to pale yellow with vigorous gas evolution. Removal of the solvent in a rotary evaporator and FCC (CH_2Cl_2/EtOH, 15:1) afforded **13** (168 mg, 61%). − IR (film): $\tilde{\nu}$ =

3070 cm^{-1}, 1570, 1450, 1420, 1290, 1070, 970, 765, 675. – UV/Vis (dioxane): λ_{max} (lg ε) = 328 nm (2.59), 239 (627, 2.80). – ^1H NMR (60 MHz, $CDCl_3$): δ = 7.47–7.60 (m, 2 H), 9.20–9.33 (m, 2 H).

4-tert-Butylpyridazine (**14**): A solution of **2** (242 mg, 2.95 mmol) and 3,3-dimethylbutyne (**7a**, 1.00 g, 12.2 mmol) was stirred in a closed flask for 20 d until decolourization of the red solution (the flask was opened carefully from time to time to release pressure). Volatiles were removed and the residue subjected to FCC (CH_2Cl_2/EtOH, 20:1). Pure **14** (360 mg, 90%) was obtained by kugelrohr distillation (120–140°C/17 Torr) as a colourless liquid. – IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2970, 2920, 2880, 1585, 1480, 1465, 1380, 1355, 1285, 1060, 985, 865, 740. – UV/Vis (dioxane): λ_{max} (lg ε) = 322 nm (2.58), 255 (3.00). – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.37 [s, 9 H, $C(CH_3)_3$], 7.41 (dd, ^3J = 5.5 Hz, ^4J = 2.5 Hz, 1 H, 5-H), 9.07 (dd, ^3J = 5.5 Hz, ^5J = 1.0 Hz, 1 H, 6-H), 9.26 (dd, ^4J = 2.5 Hz, ^5J = 1.0 Hz, 1 H, 3-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 29.96 (3 C, +), 33.59 (0), 122.56 (+), 149.72 (0), 150.35 (+), 150.89 (+). – MS (70 eV); *m/z* (%): 136 (100) [M^+], 121 (60) [$M^+ - CH_3$], 93 (49) [121 – N_2], 77 (30), 67 (15), 57 (25) [CMe_3^+], 51 (20), 41 (36) 30 (30). – $C_8H_{12}N_2$ (136.2): calcd. C 70.55, H 8.88, N 20.57; found C 70.35, H 8.88, N 20.87.

4-Phenylpyridazine (**15**): **2** (229 mg, 279 mmol) and ethynylbenzene (**7b**, 276 mg, 2.71 mmol) in dioxane (10 ml) were heated at 90°C for 13 d. The pale red solution was concentrated and the residue purified by FCC (EtOAc $\tilde{\nu}$ CH_2Cl_2/EtOH, 10:1). Recrystallization from petroleum ether 90/110 afforded **15** (270 mg, 64%), colourless crystals, m.p. 86–87°C. – UV/Vis (dioxane): λ_{max} (lg ε) = 327 (2.69), 258 (4.18). – Further spectral data agree with those reported in ref.[46]

4-(4-Methoxyphenyl)pyridazine (**16**): **2** (207 mg, 2.52 mmol) and (4-methoxyphenyl)acetylene (**7c**, 375 mg, 2.84 mmol) in dioxane (10 ml) were heated at 60°C for 120 h and at 90°C for further 20 h. The pale red solution was concentrated and the residue purified by FCC (CH_2Cl_2 → CH_2Cl_2/EtOH, 10:1). Recrystallization from hexane afforded **16** (380 mg, 81%), colourless needles, m.p. 81–82°C; m.p. 85°C.[47] – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1}, 2940, 2840, 1605, 1580, 1515. – UV/Vis (dioxane): λ_{max} (lg ε) = 327 (2.69), 258 (4.18). – ^1H NMR (250 MHz, $CDCl_3$): δ = 3.38 (s, 3 H, OCH_3), 7.00–7.70 (AA′BB′, 4 H, aromatic H), 7.60 (dd, ^3J = 5.5 Hz, ^4J = 2.5 Hz, 1 H, 5-H), 9.16 (dd, ^3J = 5.5 Hz, ^5J = 1.2 Hz, 1 H, 6-H), 9.44 (dd, ^4J = 2.5 Hz, ^5J = 1.2 Hz, 1 H, 3-H). – $C_{11}H_{10}N_2O$ (186.2): calcd. C 70.95, H 5.41, N 15.04; found C 70.89, H 5.60, N 15.01.

4-(4-Nitrophenyl)pyridazine (**17**): **2** (210 mg, 2.56 mmol) and (4-nitrophenyl)acetylene (**7d**, 374 mg, 2.54 mmol) in dioxane (10 ml) were heated at 90°C for 12 d. The pale red solution was concentrated and the residue purified by FCC (EtOAc → CH_2Cl_2:EtOAc 10:1). The crude product was dissolved in boiling toluene (50 ml), reprecipitated by the addition of petroleum ether 90/110 (10 ml) and cooling to –50°C, and filtered with suction to afford, after drying, **17** (370 mg, 72%), m.p. 178–180°C. – IR (KBr): $\tilde{\nu}$ = 3130 cm^{-1}, 3100, 1610, 1590, 1520. – UV/Vis (dioxane): λ_{max} (lg ε) = 340 nm (3.03), 281 (4.22). – ^1H NMR (250 MHz, $CDCl_3$): δ = 7.72 (dd, ^3J = 5.4 Hz, ^4J = 2.5 Hz, 1 H, 5-H), 7.85–8.50 (AA′BB′, 4 H, aromatic H), 9.35 (dd, ^3J = 5.4 Hz, ^5J = 1.2 Hz, 1 H, 6-H), 9.51 (dd, ^4J = 2.5 Hz, ^5J = 1.2 Hz, 1 H, 3-H). – ^{13}C NMR (63 MHz, $CDCl_3$): δ = 123.68 (+), 124.75 (2 C, +), 128.39 (2 C, +), 130.40 (0), 141.09 (0), 149.04 (0), 149.51 (+), 151.62 (+). – $C_{10}H_7N_3O_2$ (201.2): calcd. C 59.70, H 3.51, N 20.89; found C 59.52, H 3.47, N 20.95.

4-(Dimethylamino)pyridazine (**18**). – *Method A:* The solution of **2** (280 mg, 3.41 mmol) in CH_2Cl_2 (10 ml) was added dropwise to the ice–cold (0°C) solution of (dimethylamino)acetylene (**8a**, 400 mg, 5.79 mmol) in CH_2Cl_2 (5 ml). The tetrazine solution added decolourized at once with vigorous gas evolution. After removal of volatile contents under reduced pressure, the residue was subjected to kugelrohr distillation (100–120°C/0.05 Torr) to afford **18** (395 mg, 94%) as hygroscopic colourless crystals, m.p. 45°C.[48a] – *Method B:* A solution of **2** (342 mg, 4.17 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of 1,1-bis(dimethylamino)ethene (**42c**) over a period of 10 min. A clear, almost colourless solution was obtained. The CH_2Cl_2 was removed and the residue subjected to kugelrohr distillation (100–120°C/0.05 Torr) to afford **18** (495 mg, 96%). – *Method C:* A solution of **2** (607 mg, 7.40 mmol) in CH_2Cl_2 (15 ml) was added dropwise to the solution of 1-(dimethylamino)-1-methoxyethene (**42b**, 940 mg, 9.30 mmol) in CH_2Cl_2 (5 ml) over a period of 5 min. A pale red colour persisted for a further 2 h at ambient temperature. Separation of the reaction products **18** and **19** by FCC (CH_2Cl_2/EtOH, 5:1) and subsequent kugelrohr distillation (**19**: 80°C/0.05 Torr; **18**: 80°C–120°C/0.05 Torr) afforded **18** (663 mg, 73%) and **19** (180 mg, 22%). – *Method D:* A solution of **2** (259 mg, 3.15 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of 1-(dimethylamino)-1-(methylthio)-ethene (**42d**, 600 mg, 5.12 mmol) in CH_2Cl_2 (5 ml) over a period of 10 min. A colourless reaction mixture was obtained. Volatiles were removed under reduced pressure and the residue was subjected to kugelrohr distillation (140–170°C/16 Torr) to afford only **18** (360 mg, 93%). – Spectral data agree with those reported in ref.[48b] – Correct elemental analysis was obtained for the methiodide prepared by the reaction of **18** with iodomethane in nitromethane. $C_7H_{12}N_6I$ (265.1): calcd. C 31.72, H 4.56, N 15.85; found C 31.90, H 4.63, N 15.81.

4-Methoxypyridazine (**19**). – *Method A:* **2** (226 mg, 2.75 mmol) and methoxyacetylene (**8b**, 260 mg, 4.64 mmol) in CH_2Cl_2 (10 ml) were stirred in a closed flask at ambient temperature for 70 h (caution: pressure). The solvent was removed in a rotary evaporator and the brown residue subjected to a kugelrohr distillation (60–90°C/0.05 Torr) to give **19** (281 mg, 93%) as hygroscopic colourless crystals. – *Method B:* Compound **19** was obtained as by-product (22% yield) in a reaction described above (Method C for **18**). – *Method C:* Compound **2** (366 mg, 4.46 mmol) and 1,1-bis(ethoxy)ethene (**42e**, 600 mg, 5.16 mmol) in CH_2Cl_2 (20 ml) were stirred at ambient temperature for 18 h. The solvent was removed in a rotary evaporator and the residue purified by kugelrohr distillation (90–110°C/0.05 Torr) to afford **19** (522 mg, 94%). – Spectral data agree with those reported in ref.[48b,49] – Correct elemental analysis was obtained for the picrate prepared by the reaction of **19** with picric acid in ethanol, m.p. 141–142°C (ref.[49] m.p. 143–144°C). $C_{11}H_9N_5O_8$ (339.2): C 38.95, H 2.67, N 20.65; found C 39.27, H 2.85, N 20.77.

4-(Methylthio)pyridazine (**20**). – *Method A:* Compound **2** (465 mg, 5.67 mmol) and (methylthio)acetylene (**8c**, 980 mg, 13.6 mmol) in CH_2Cl_2 (5 ml) were stirred under argon at ambient temperature for 40 h. The solvent was removed in a rotary evaporator and the residue subjected to a kugelrohr distillation (80–100°C/0.05 Torr) to give **20** (690 mg, 96%) as weakly hygroscopic, colourless crystals, m.p. 44–45°C (ref.[50] m.p. 44–45°C). – *Method B:* **2** (281 mg, 3.46 mmol) and 1,1-bis(methylthio)ethene (**42f**, 509 mg, 4.23 mmol) in dioxane (5 ml) were heated at 70°C for 90 h. The colour of the reaction mixture changed from red to brown during this period. Removal of the solvent afforded a brown oil, which was purified by kugelrohr distillation (100–120°C/0.1 Torr) and recrystallized from diethyl ether to afford **20** (376 mg, 87%). – *Method C:* Compound **2** (157 mg, 1.92 mmol) and (*Z*)-1,2-bis(methylthio)ethene (**49b**) in dioxane (5 ml) were heated at 80°C for 60 h. The colour

of the reaction mixture changed from red to brown. After removal of the solvent, the residue was purified by FCC (CH_2Cl_2/EtOH, 15:1) and recrystallization from diethyl ether to afford **20** (169 mg, 70%). − *Method D:* **2** (291 mg, 3.54 mmol) and (*E*)-1,2-bis(methylthio)ethene (**49a**) in dioxane (5 ml) were heated at 80°C for 50 h. The orange-brown reaction mixture was concentrated to give a brown oil, which was purified by FCC (CH_2Cl_2/EtOH, 15:1) and subjected to kugelrohr distillation (70−80°C/0.02 Torr) to afford **20** (340 mg, 76%). − IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 2930, 1560, 1440, 1355. − UV/Vis (dioxane): λ_{max} (lg ε) = 315 nm (sh, 2.74), 279 (sh, 3.76), 262 (3.91). − ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, SC*H*$_3$), 7.25 (dd, ^3J = 5.5 Hz, ^4J = 2.8 Hz, 1 H, 5-H), 8.80−9.00 (m, 2 H, 3-H, 6-H). − $C_5H_6N_2S$ (126.2): calcd. C 47.59, H 4.79, N 22.20; found C 47.63, H 4.91, N 22.33.

4-(Tributylstannyl)pyridazine (**21**): Compound **2** (211 mg, 2.55 mmol) and tributyl(ethynyl)tin (**9a**, 0.8 ml, 2.65 mmol) were heated in toluene (6 ml) at 80°C for 5 h until complete decolourization. The solvent was removed under reduced pressure and the residue subjected to kugelrohr distillation (150−155°C/0.1 Torr) to afford **21** (701 mg, 76%) as pale yellow liquid. − IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2960, 2920, 2880, 2860, 1540, 1510, 1460, 1410, 1370, 1330, 1280, 1100, 1070, 1050, 870. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 9 H, CH_2CH_3), 1.13−1.19 (m, 6 H, $-CH_2-$), 1.26−1.41 (m, 6 H, $-CH_2-$), 1.48−1.58 (m, 6 H, $-CH_2-$), 7.54 (dd, ^3J = 4.8 Hz, ^4J = 1.6 Hz, 1 H, 5-H), 9.02 (dd, ^3J = 4.8 Hz, ^5J = 1.5 Hz, 1 H, 6-H), 9.17 (dd, ^5J = 1.5 Hz, ^4J = 1.6 Hz, 1 H, 3-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 9.76 (3 C, −), 13.50 (3 C, +), 27.18 (3 C, −), 28.86 (3 C, −), 135.06 (+), 142.94 (0), 150.62 (+), 157.79 (+). − Purity (GC): 97.5%. − $C_{16}H_{30}N_2Sn$ (369.1): calcd. C 52.06, H 8.19, N 7.59; found C 52.16, 51.03, H 8.14, 7.76, N 8.14, 7.77.

4-(Trimethylgermyl)pyridazine (**22**): **2** (82.0 mg, 1.00 mmol) and (ethynyl)trimethylgermane (**9b**, 300 mg, 1.80 mmol, contains about 20% THF) in acetonitrile were heated to reflux for 90 min. The pale yellow solution was concentrated in vacuo. The brown liquid was purified by FCC (diethyl ether) to afford **22** (158 mg, 80%) as colourless liquid, which turns yellow quite rapidly. − IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1}, 3040, 2980, 2910, 2860, 2810, 1550, 1520, 1410, 1325, 1280, 1240, 1120, 1050, 970, 825, 765. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.45 (s, 9 H, $GeCH_3$), 7.50 (dd, ^3J = 4.9 Hz, ^4J = 1.8 Hz, 1 H, 5-H), 9.06 (dd, ^3J = 4.9 Hz, ^5J = 1.4 Hz, 1 H, 6-H), 9.17 (dd, ^4J = 1.8 Hz, ^5J = 1.4 Hz, 1 H, 3-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = −2.43 (3 C, +), 131.29 (+), 142.43 (0), 150.64 (+),154.98 (+). − Purity (GC): 98.8%. − MS (70 eV); *m/z* (%): 198 (64) [M^+], 183 (100) [$M^+ - CH_3$], 155 (4) [183 − N_2], 129 (20) [$Me_2GeC{\equiv}CH^+$], 119 (70) [Me_3Ge^+], 89 (11) [$MeGe^+$]. − $C_7H_{12}N_2Ge$ (197.8): calcd. C 42.73, H 6.14, N 14.24; found C 43.24, H 6.17, N 14.03.

4-(Trimethylsilyl)pyridazine (**23**): **2** (165.0 mg, 2.00 mmol) and (ethynyl)trimethylsilane (**9c**, 1.0 ml, 7.22 mmol) in acetonitrile (5 ml) were heated to reflux for 2 h. The colourless solution was concentrated in vacuo. The resulting pale yellow liquid was purified by FCC (diethyl ether) and kugelrohr distillation (50−60°C, 0.05 Torr) to afford **23** (285 mg, 94%) as colourless liquid. − IR (KBr): $\tilde{\nu}$ = 3070 cm^{-1}, 3040, 2960, 2905, 1560, 1520, 1445, 1420, 1325, 1250, 1140, 1050, 970, 860, 760. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.31 (s, 9 H, $SiCH_3$), 7.49 (dd, ^3J = 4.9 Hz, ^4J = 1.9 Hz, 1 H, 5-H), 9.08 (dd, ^3J = 4.9 Hz, ^5J = 1.5 Hz, 1 H, 6-H), 9.17 (dd, ^4J = 1.9 Hz, ^5J = 1.5 Hz, 1 H, 3-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = −2.07 (3 C, +), 131.16 (+), 139.43 (0), 150.60 (+), 154.69 (+). − Purity (GC): 100%. − MS (70 eV); *m/z* (%): 152 (100) [M^+], 137 (60) [$M^+ - CH_3$], 109 (11) [137 − N_2], 83 (31) [109 − C_2H_2 = $Me_2SiC{\equiv}CH^+$], 73 (60) [$SiMe_3^+$], 45 (11), 43 (14). − $C_7H_{12}N_2Si$ (152.3): calcd. C 55.22, H 7.94, N 18.40; found C 54.72, H 7.73, N 18.85.

4-(Dimethylamino)-5-(methylthio)pyridazine (**24**): A solution of **2** (309 mg, 3.76 mmol) in CH_2Cl_2 (10 ml) was added dropwise to 1-(dimethylamino)-2-(methylthio)acetylene (**10a**, 350 mg, 3.91 mmol) in CH_2Cl_2 (5 ml). The reaction mixture decolourized within 5 min. Volatiles were removed in a rotary evaporator and the residue purified by kugelrohr distillation (140−160°C/0.05 Torr). The orange oil thus obtained was purified by FCC (CH_2Cl_2/EtOH, 10:1) and redistilled under identical conditions to afford **24** (575 mg, 90%) as colourless, hygroscopic crystals. − IR (film): $\tilde{\nu}$ = 3060 cm^{-1}, 2990, 2950, 2930, 2880, 2810, 1545, 1520, 1455, 1435, 1360, 1190, 1165, 1025, 955, 710. − ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, SCH_3), 2.95 [s, 6 H, $N(CH_3)_2$], 8.45 (s, 1 H, 3/6-H), 8.55 (s, 1 H, 6/3-H). − MS (70 eV); *m/z* (%): 169 (100) [M^+], 154 (16), 136 (28). HR MS: calcd. 169.06737, found 169.06742. − The picrate was prepared from **24** (330 mg, 1.85 mmol) and picric acid (450 mg, 1.96 mmol) in ethanol (15 ml) for elemental analysis. Yellow crystals (650 mg, 88%), m.p. 143−145°C. $C_{13}H_{14}N_6O_7S$ (398.4): calcd. C 39.20, H 3.54, N 21.10; found C 39.36, H 3.59, N 21.22.

4,5-Bis(methylthio)pyridazine (**25**): **2** (433 mg, 5.27 mmol) and bis(methylthio)acetylene (**10b**, 2.85 g, 24.1 mmol) in dioxane (5 ml) were heated at 100°C for 18 h under nitrogen. The colour of the reaction mixture changed from red to brown and a precipitate was formed. After cooling to ambient temperature, the precipitate was filtered and washed with dioxane (30 ml) and diethyl ether (20 ml) to give bright brown crystals (760 mg). Concentration of the filtrate under reduced pressure and FCC (CH_2Cl_2/EtOH, 10:1) afforded further crude **25** (120 mg). Both crops were sublimed (120−150°C/0.05 Torr) to afford **25** (805 mg, 89%), colourless crystals, m.p. 193−193.5°C. − IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3000, 2930, 1525, 1495, 1270, 780, 710. − UV/Vis (dioxane): λ_{max} (lg ε) = 292 nm (3.92), 253 (4.00). − ^{1}H NMR (60 MHz, $CDCl_3$): δ = 2.65 (s, 6 H, SCH_3), 8.80 (s, 2 H, 3-H, 6-H). − $C_6H_8N_2S_2$ (172.3): calcd. C 41.83, H 4.68, N 16.26; found C 41.90, H 4.71, N 16.23.

4,5-Bis(tert-butyl)pyridazine (**26**): **2** (35.0 mg, 0.43 mmol) and 2,2,5,5-tetramethyl-3-butyne (**10c**, 180 mg, 1.30 mmol) in $CDCl_3$ (2 ml) were heated in a closed flask (caution: pressure) at 80°C for 5 d. Brown tar-like products were formed during this period on the flask walls. ^{1}H-NMR analysis revealed a **2**/**26** ratio of about 1:1 in the red solution. **26** was separated from **2** by FCC (CH_2Cl_2 → EtOAc) and obtained as colourless crystals (9.9 mg, 12%), m.p. 105°C (ref.[51] m.p. 109°C). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $C(CH_3)_3$], 9.18 (s, 2 H, 3-H, 6-H). − The spectroscopic properties agree with those reported in the literature.[51]

4,5-Bis(trimethylstannyl)pyridazine (**27**): **2** (38 mg, 0.46 mmol) and bis(trimethylstannyl)acetylene (**11a**, 174 mg, 0.49 mmol) in CH_2Cl_2 (5 ml) were stirred at ambient temperature until complete decolourization (2 h). After removal of the solvent, the product was isolated by FCC (diethyl ether) to afford **27** (152 mg, 82%), pale yellow crystals, m.p. 79−80°C. − IR (KBr): $\tilde{\nu}$ = 3035 cm^{-1}, 2990, 2920, 1510, 1455, 1440, 1260, 1200, 1140, 1100, 765. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.40 [s, 9 H, $Sn(CH_3)_3$], 9.02 (s, 2 H, 3-H, 6-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = −7.67 (6 C, +), 152.89 (2 C, 0), 156.35 (2 C, +). − MS (70 eV); *m/z* (%): 408 (4) [M^+], 393 (10) [$M^+ - CH_3$], 258 (27), 165 (100) [Me_3Sn^+], 135 (33) [$MeSn^+$]. − $C_{10}H_{20}N_2Sn_2$ (405.7): calcd. C 29.61, H 4.97, N 6.91; found C 29.73, H 5.03, N 6.90.

4,5-Bis(tributylstannyl)pyridazine (**28**): **2** (164 mg, 2.00 mmol) and bis(tributylstannyl)acetylene (**11b**, 1.03 ml, 2.00 mmol) in

CH_2Cl_2 (6 ml) were stirred at ambient temperature under nitrogen (2 h). The colour of the reaction mixture changed from deep red to bright orange to brown. After removal of the solvent, the product was isolated by FCC (diethyl ether/petroleum ether 40/60, 4:1) to afford **28** (935 mg, 71%), yellow oil. − IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 2960, 2930, 2880, 2860, 1520, 1460, 1410, 1375, 1195, 1100, 1070, 960, 870. − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 9 H, $-CH_3$), 1.11−1.21 (m, 6 H, $-CH_2-$), 1.27−1.41 (m, 6 H, $-CH_2-$), 1.45−1.64 (m, 6 H, $-CH_2-$), 8.99 (s, 2 H, 3-H, 6-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.87 (6 C, −), 13.55 (6 C, +), 27.34 (6 C, −), 29.03 (6 C, −), 153.90 (2 C, 0), 157.10 (2 C, +). − $C_{28}H_{56}N_2Sn_2$ (658.2): calcd. C 51.10, H 8.58, N 4.26; found C 51.29, H 8.42, N 4.72.

4,5-Bis(trimethylgermyl)pyridazine (**29**): **2** (38.5 mg, 0.47 mmol) and bis(trimethylgermyl)acetylene (**11c**, 126 mg, 0.49 mmol) in dioxane (8 ml) were stirred at ambient temperature until the red tetrazine colour disappeared completely (5 d). After removal of the solvent, the crude crystals were recrystallized from petroleum ether 40/60 to afford **29** (137 mg, 93%), colourless crystals, m.p. 93−94°C. − IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 2980, 2920, 2820, 1530, 1485, 1410, 1245, 1210, 1155, 1120, 1085, 830, 760. − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.51 (s, 18 H, $-CH_3$), 8.99 (s, 2 H, 3-H, 6-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 0.32 (6 C, +), 153.90 (2 C, 0), 157.10 (2 C, +). − MS (70 eV); *m/z* (%): 314 (13) [M^+], 299 (13) [$M^+ - CH_3$], 212 (34) [$M^+ - GeMe_3$], 119 (100) [$GeMe_3^+$], 104 (11) [119 − CH_3], 89 (13) [104 − CH_3], 40 (13) [CN_2^+] − $C_{10}H_{20}N_2Ge_2$ (313.2): calcd. C 38.32, H 6.43, N 8.94; found C 38.21, H 6.34, N 8.65.

4,5-Bis(trimethylsilyl)pyridazine (**30**): **2** (175 mg, 2.13 mmol) and bis(trimethylsilyl)acetylene (**11d**, 375 mg, 2.20 mmol) in acetonitrile (5 ml) were heated to reflux under nitrogen until the red tetrazine colour disappeared completely (12 h). After removal of the solvent, the crude crystals were recrystallized from petroleum ether 40/60 to afford **30** (445 mg, 93%), colourless crystals, m.p. 94−95°C. − IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 2960, 2900, 1530, 1480, 1460, 1410, 1250, 1190, 1160, 1120, 1090, 840, 760. − ^1H NMR (250 MHz, $CDCl_3$): δ = 0.40 (s, 18 H, $-CH_3$), 9.18 (s, 2 H, 3-H, 6-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 0.64 (6 C, +), 144.81 (2 C, 0), 154.34 (2 C, +). − MS (70 eV); *m/z* (%): 224 (39) [M^+], 209 (19) [$M^+ - CH_3$], 193 (10), 83 (12), 73 (100) [Me_3Si^+], 45 (19).− $C_{10}H_{20}N_2Si_2$ (224.5): calcd. C 53.51, H 8.98, N 12.48; found C 53.54, H 9.10, N 12.35.

6,7-Dihydro-5H-cyclopenta[d]pyridazine (**35**). − *Method A:* 1-(Dimethylamino)cyclopentene (**31a**, 252 mg, 2.27 mmol) in dioxane (10 ml) was added dropwise to a stirred solution of **2** (145 mg, 1.76 mmol) in dioxane (5 ml). After removal of all volatiles in vacuo, the brown oily crude product was subjected to kugelrohr distillation (110−130°C/0.4 Torr). Recrystallization from diethyl ether afforded **35** (144 mg, 68%), colourless crystals, m.p. 83−84°C; m.p. 85−87°C[52a]. − *Method B:* **2** (219 mg, 2.66 mmol) and 1-methoxycyclopentene (**31b**, 312 mg, 3.18 mmol) in dioxane (10 ml) were heated with stirring at 80°C until the red colour became decoloured to yellow-brown. Volatiles were removed in vacuo and the crystalline residue was recrystallized from petroleum ether 40/60 to afford **35** (284 mg, 89%). − *Method C:* **2** (258 mg, 3.15 mmol) and 1-(trimethylsiloxy)cyclopentene (**31c**, 583 mg, 3.73 mmol) in dioxane (10 ml) were heated with stirring at 70°C for 70 h. Volatiles were removed in vacuo and the crystalline brown residue was recrystallized twice from petroleum ether 40/60 to afford **35** (193 mg, 51%). − IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3005, 2980, 2920, 2880, 2860, 1575, 1555. − ^1H NMR (60 MHz, $CDCl_3$): δ = 2.1−2.2 (m, 2 H), 2.93 (t, 4 H), 9.07 (s, 2 H, 3-H, 6-H). − The spectral data agree with those reported in the literature.[52b]

5,6,7,8-Tetrahydrophthalazine (**36**). − *Method A:* **2** (725 mg, 8.83 mmol) in dioxane (15 ml) was added dropwise to a hot stirred solution of 1-(dimethylamino)cyclohexene (**32a**, 252 mg, 2.27 mmol) in dioxane (10 ml) at 100°C. The reaction required about 80 min. Finally, a bright brown reaction mixture was obtained. Removal of all volatiles in vacuo afforded a brown crude product, which was recrystallized from hexane and diethyl ether to afford **36** (742 mg, 63%), colourless crystals, m.p. 88−88.5°C (ref.[52a] m.p. 88.5−89°C). − *Method B:* **2** (182 mg, 2.22 mmol) and 1-methoxycyclohexene (**32b**, 451 mg, 4.02 mmol) in dioxane (10 ml) were heated with stirring at 80°C until the red colour changed to yellow-brown. Volatiles were removed in vacuo and the resulting brown oil subjected to kugelrohr distillation (100−120°C/0.05 Torr) to provide a brown solid, which was recrystallized from petroleum ether 40/60 to afford **36** (193 mg, 65%). − *Method C:* **2** (250 mg, 3.05 mmol) and 1-(trimethylsiloxy)cyclohexene (**32c**, 2.59 g, 15.23 mmol) in dioxane (5 ml) were heated with stirring at 80°C for 36 h to give a brown reaction mixture. Volatiles were removed in vacuo and the oily brown residue which solidified upon addition of petroleum ether 40/60. Recrystallization from petroleum ether 40/60 afforded **36** (377 mg, 92%). − IR (KBr): $\tilde{\nu}$ = 3050 cm^{-1}, 2960, 2930, 2890, 2860, 1560, 1445, 1425, 1280, 1230, 975, 945. − ^1H NMR (80 MHz, $CDCl_3$): δ = 1.75−1.97 (m, 4 H), 2.56−2.80 (m, 4 H), 8.87 (s, 2 H, 3-H, 6-H).

6,7,8,9-Tetrahydro-5H-cyclohepta[d]pyridazine (**37**). − *Method A:* 1-(Dimethylamino)cycloheptene (**33a**, 658 mg, 4.72 mmol) in dioxane (10 ml) was added dropwise over a period of 15 min to a stirred solution of **2** (258 mg, 3.14 mmol) in dioxane (10 ml). The red colour changed to yellow-brown. Removal of all volatiles in vacuo gave a brown oily crude product, which was subjected to kugelrohr distillation (100−110°C/0.1 Torr). **35** (144 mg, 68%) was obtained as colourless crystals, m.p. 68.5−69°C. − *Method B:* **2** (196 mg, 2.39 mmol) and 1-methoxycycloheptene (**33b**, 348 mg, 2.75 mmol) in dioxane (10 ml) were heated with stirring at 80°C until the red colour became decolourized to yellow-brown. Volatiles were removed in vacuo and the resulting brown solid recrystallized from petroleum ether 40/60 to afford **37** (305 mg, 86%). − *Method C:* **2** (351 mg, 4.28 mmol) and 1-(trimethylsiloxy)cycloheptene (**33c**, 897 mg, 6.05 mmol) in dioxane (10 ml) were heated with stirring at 60°C for 20 h to give a yellow-brown reaction mixture. Volatiles were removed in vacuo. Recrystallization of the brownish residue from petroleum ether 40/60 afforded **37** (322 mg, 51%). − IR (KBr): $\tilde{\nu}$ = 3030 cm^{-1}, 2910, 2850, 1560, 1445, 1430, 1325, 1300, 1275, 995. − UV/Vis (dioxane): λ_{max} (lg ε) = 319 nm (2.65), 250 (3.01). − ^1H NMR (80 MHz, $CDCl_3$): δ = 1.50−2.07 (m, 6 H), 2.67−2.90 (m, 4 H), 8.87 (s, 2 H, 3-H, 6-H). − $C_9H_{12}N_2$ (148.2): calcd. C 72.94, H 8.16, N 18.90; found C 72.96, H 8.18, N 18.95.

Reaction of 2 with Ethylene (**38**): Gaseous ethylene (**38**) was introduced into a solution of **2** (119 mg, 84%) in dioxane (20 ml) until decolourization occurred (60 min). Removal of all volatiles in vacuo gave a colourless oily crude product, which was purified by FCC (CH_2Cl_2/diethyl ether, 10:1) and recrystallized from diethyl ether to give the trimer **40**, colourless crystals, m.p. 133−134°C. − IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 3005, 2960, 2920, 2860, 1625, 1305, 1125, 1100, 960, 915, 790. − ^1H NMR (80 MHz, $CDCl_3$): δ = 2.13−2.40 (m, 12 H), 3.57−3.73 (m, 3 H), 6.90 (m, 3 H, N=CH).

Reaction of **2** *with Styrenes:* The product mixture was analysed by means of HPLC using isocratic elution (methanol/water, 40:60) on an RP-18 (4 × 350 mm) column at a flow rate of 1 ml min^{-1}. Naphthalene was used as internal standard. The product distribution is described in the section Results and Discussion (Table 4).

Reaction of **2** *with Styrene* (**43a**): **2** (35.7 mg, 0.435 mmol) and styrene (**43a**, 45.3 mg, 0.435 mmol) in dioxane (5 ml) were stirred for 70 h at ambient temperature.

Reaction of **2** *with 4-Nitrostyrene* (**43c**): **2** (49.6 mg, 0.604 mmol) and 4-nitrostyrene (**43c**, 90.0 mg, 0.603 mmol) in dioxane (5 ml) were stirred for 120 h at ambient temperature.

Reaction of **2** *with 4-Methoxystyrene:* **2** (46.6 mg, 0.566 mmol) and 4-methoxystyrene (**43b**, 76.0 mg, 0.566 mmol) in dioxane (6 ml) were stirred for 50 h at ambient temperature.

☆ Dedicated to Professor *Wolfgang Steglich* on the occasion of his 65th birthday.

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