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Nucleophilic Attack on Nitrogen in Tetrazines by Silyl-Enol Ethers

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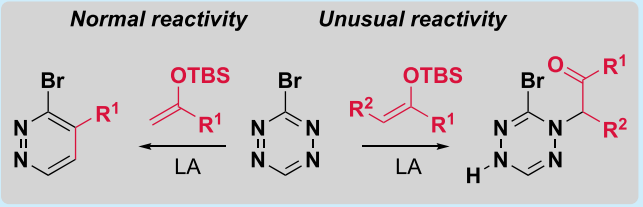
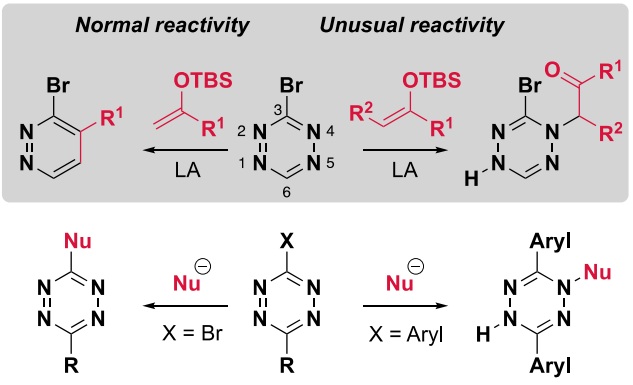
ABSTRACT: The nucleophilic addition of silyl-enol ethers to nitrogen in 3-monosubstituted s-tetrazines mediated by BF_3 is reported. The preference for this azaphilic addition over the usually observed inverse electron demand Diels–Alder reactions was evaluated theoretically and corroborated by experiments. The substrate dependency of this unusual reaction was rationalized by determination of the activation barriers and on the basis of the activation strain model by employing density functional theory.



s-Tetrazines have emerged as the heterocycles of choice for a wide range of applications, in particular with regard to bioorthogonal chemistry.[1,2] In such settings, the inverse electron demand [4 + 2] Diels–Alder (iEDDA) reaction of *s*-tetrazines with strained alkenes and alkynes enabled successful conjugation reactions, even at biologically relevant concentrations.[2,3] As pioneered by Sauer and co-workers,[4] olefins typically result in the corresponding aromatic pyridazines, a process that can also be accelerated by Lewis acids (Scheme 1 left).[5]

Scheme 1. Reactivity of *s*-Tetrazines and General Numbering of *s*-Tetrazines (LA: Lewis Acid)



In this letter, and in contrast to previous reports, we demonstrate an unusual *nucleophilic* attack on the *electrophilic nitrogen* atom in electron-deficient tetrazines in an Umpolung reaction (Scheme 1, bottom right). In addition, no elimination and no concomitant restoration of aromaticity are observed, as this reaction strikingly leads to the corresponding nonaromatic dihydro-derivatives.

In contrast to cycloaddition reactions, direct addition reactions of nucleophiles to *N*-containing aromatics have rarely been described in the literature and are generally limited to 1,2,3-benzotriazoles, 1,2,3-triazines, and 1,2,4,5-tetrazines.[6,7] To date, there is only a limited number of reports on the addition of hard organometallic reagents, such as RLi or RMgX, to the tetrazine core.[6,8,9] After this work was published on ChemRXiv,[9] Boger and co-workers reported the selective N1/N4-cycloaddition of *s*-tetrazine, which is likely to occur via an initial azaphilic attack of an enamine.[10a] In the context of our research on the chemistry of 3-monosubstituted *s*-tetrazines and specifically 3-bromotetrazine (3-Br-Tet) (**1**), a small *s*-tetrazine building block for the labeling of macromolecules previously reported by our group and others,[9,11] we investigated their reactivity with silyl-enol ethers. We observed that the reactivity of silyl-enol ethers can switch from a cycloaddition reaction to an unprecedented nucleophilic (azaphilic) addition depending on the steric demand of the group R^2 (Scheme 1).

Preliminary experiments revealed that a Lewis acid mediator was necessary in order to promote the reaction of silyl-enol ethers with 3-Br-Tet (**1**, Scheme 2). The reaction of 3-Br-Tet (**1**) with TBS-silyl-enol ether **2** cleanly produced 3-bromo-4-phenylpyridazine (**3**) in 82% yield in the presence of $BF_3{\cdot}OEt_2$, and the constitution was confirmed by a single crystal X-ray structure analysis. Remarkably, the reaction proved to be very fast (15 min, room temperature) and regioselective (single isomer observed). Interestingly, when the more highly substituted silyl-enol ethers **4** and **5** were employed, the outcome of the reaction changed drastically. When methyl-substituted silyl-enol ether **4** was reacted with 3-Br-Tet (**1**), the pyridazine **6** was only observed as the minor product of this

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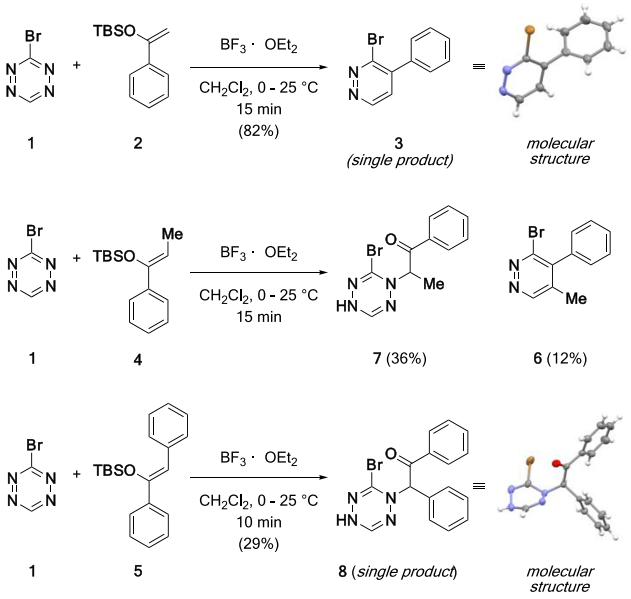
Scheme 2. Reactivity of Silyl-Enol Ethers with 3-Br-Tet (1)



transformation in low conversion (12%) together with a major unknown compound, as judged by ^{1}H NMR spectroscopy.

The major product was found to be the azaphilic addition product **7** by extensive NMR analysis. However, since an inseparable mixture of adduct and pyridazine was obtained, we employed the bulkier silyl-enol ether **5** in the hope of achieving exclusive selectivity and easy separation from impurities. In this case, a single product was obtained (as observed by UHPLC-MS and NMR analysis of the reaction mixture) and single-crystal X-ray structure analysis unambiguously confirmed the structure of **8** to correspond to the azaphilic addition product.

In order to gain insight into this unique and novel reactivity of silyl-enol ethers with 3-Br-Tet (**1**) and to understand the crucial role of the Lewis acid, we extensively studied theoretically the effect of the coordination of BF_3·OEt_2 to 3-Br-Tet (**1**) and the influence of substituents on the silyl-enol ether. We analyzed the frontier molecular orbitals (FMOs) of the tetrazine by means of condensed Fukui functions (electrophilic, f^-; nucleophilic, f^+) (see Supporting Information for a detailed description of the used computational methods and their validation). Based on our preliminary experimental observations and theoretical calculations on the relative stability of BF_3 adducts (Figure 1), we propose the coordination of a single Lewis acid moiety at N-1 of 3-Br-Tet (**1**) (see Table S8).

In order to rationalize the selectivity toward either the azaphilic addition for enol ethers **4** and **5** or the iEDDA reaction for enol ether **2**, we employed the active strain model (ASM).[12] The ability of the dienophiles used in this study to undergo an iEDDA-like reaction is clearly dependent on the steric demand imposed by the alkyl/aryl substituent. This can be seen from the distinctive difference in the deformation energy as a function of the C−C bond formation, which follows the expected trend E_{strain}: Ph > Me > H (see Figure 2).

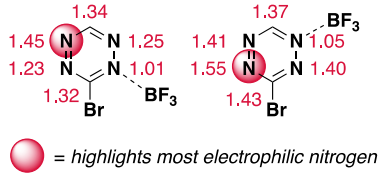


Figure 1. Relative local electrophilicity index of the BF_3 adducts relative to native 3-Br-Tet (**1**). This dimensionless quantity helps to rationalize the reactivity of tetrazine toward an azaphilic addition. The most electrophilic site (highlighted) corresponds to the nitrogen atom that is found to undergo the azaphilic addition reaction.

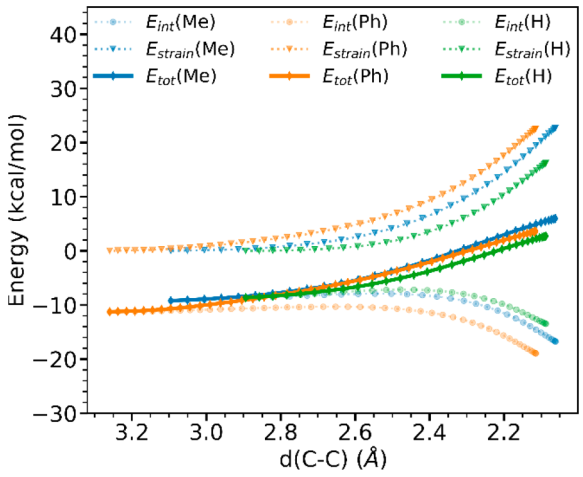


Figure 2. Plot of the total electronic energy (E_{tot}), distortion energy (E_{strain}), and interaction energy (E_{int}) versus the bond distance of the C−C bond that is to be formed between the dienophiles (H (**2**), Me (**4**), and Ph (**5**)) and 3-Br-Tet (**1**) without the aid of a Lewis acid. Note, the E_{strain} of the structures representing the associated reactant (AR) was set to zero for all derivatives. $E_{tot} = E_{int} + E_{strain}$.

The energetic stabilization due to the interaction of the two reactants (E_{int}) is only marginally different among the three derivatives and follows the same trend as E_{strain} with an opposite sign. On the other hand, the azaphilic addition is, as expected, only marginally affected by the nature of the substituents of the dienophile, as can be seen from E_{strain} and E_{int} energies that are almost identical for the three derivatives (see Figure S6).

The conclusions drawn from the ASM analysis are supported by the calculated activation barriers for all three silyl-enol ethers **2**, **4**, and **5** in the presence and absence of BF_3, respectively (see Tables S6 and S7). The experimentally observed preference for either the azaphilic addition or the iEDDA reaction can be rationalized by the calculated activation energies, which are 21 (nuc.) vs 26 kcal/mol (iEDDA) in the case of the phenyl derivative, 7 vs 11 kcal/mol in the case of the methyl derivative, and 15 vs 12 kcal/mol in the case of the nonsubstituted allyl (see Figure 3 and Tables S6 and S7).

Based on the experimental and theoretical insights observed, we studied the steric and electronic influence of the substituents of the trisubstituted silyl-enol ethers (Scheme 3A). In addition, the effect of aryl and alkyl substitution on the *s*-tetrazine core was probed experimentally (Scheme 3B). As expected, introducing an electron-donating group in the para-position of the aromatic ring increased the yield to as much as 59% (compounds **9** and **10**). In contrast, *para*-bromo or *para*-fluoro substituents apparently had no effect on the yield of the reaction and led to the isolation of the azaphilic addition products **11** and **12** in 31% and 28% yield, respectively. The introduction of a "push−pull" system slightly increased the yield compared with **8**; compound **13** was isolated in 40%

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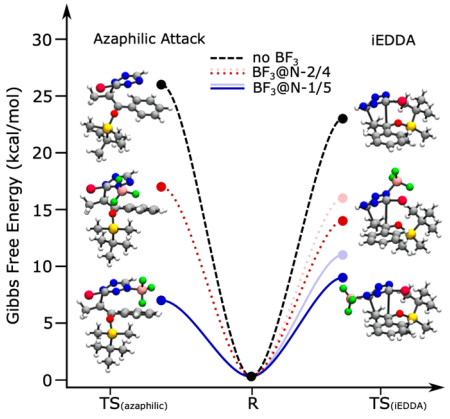
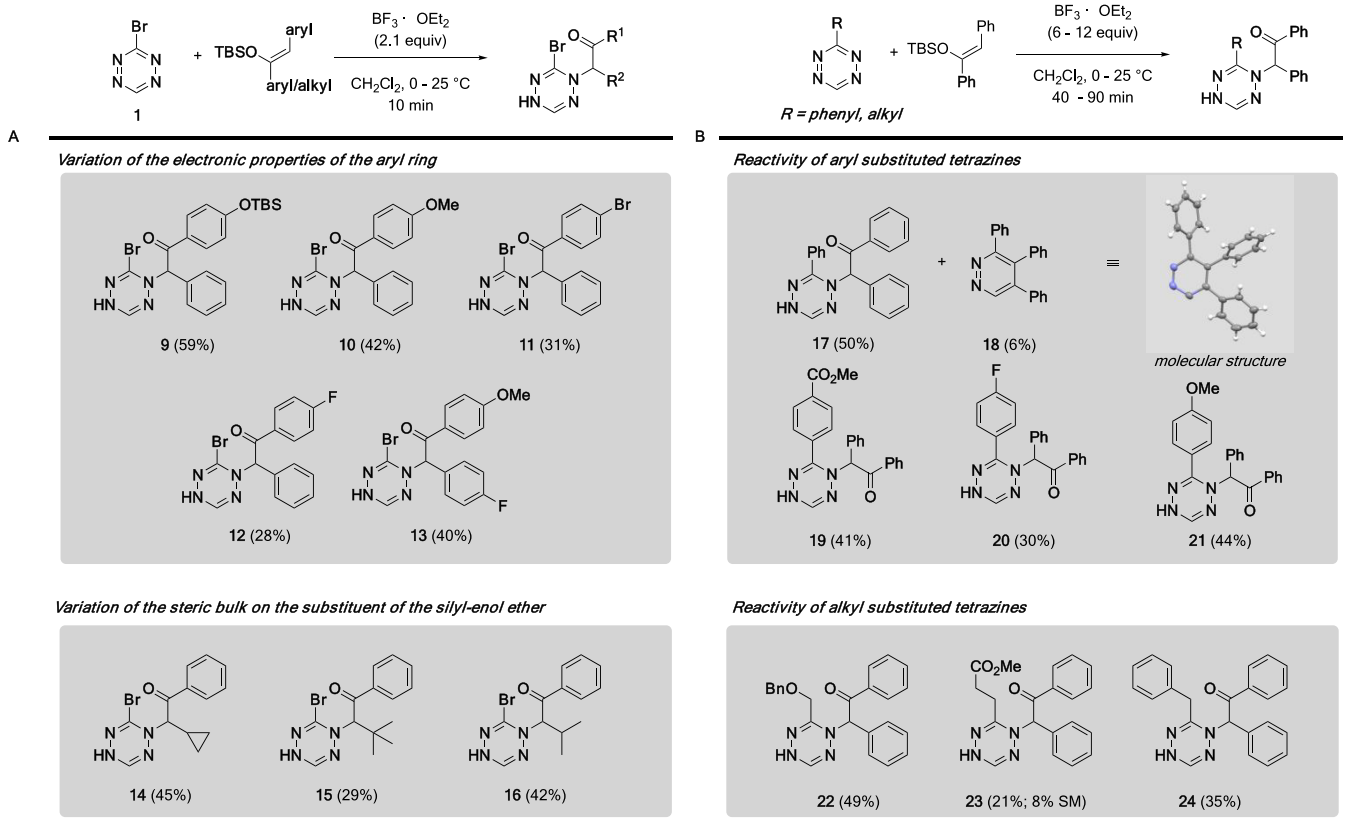


Figure 3. Gibbs free energy profile of the azaphilic attack and Diels–Alder like reaction for the methyl-derivative **4** with and without BF_3 adducts. In the case of the iEDDA reaction, only BF_3@N-1 and BF_3@N-2 are shown. Note that in the case of the azaphilic attack, only the nitrogen atoms in the *para* or *meta* position are expected to react.

yield. With these results in hand, we tried several alkyl residues in order to determine the minimum steric requirement for obtaining exclusively the azaphilic addition product, bearing in mind that a methyl substituent afforded a mixture. Interestingly, the pyridazine could only be observed with the respective cyclopropyl TBS-silyl enol ether; trace amounts of the corresponding product were detected by UHPLC-MS. The main product proved to be **14**, which was isolated in 45% yield. For a *tert*-butyl or isopropyl group, the azaphilic addition products **15** and **16** remained the only observed products of this transformation and could be isolated in 29% and 42% yield, respectively.

Having established the generality of the presented reaction with 3-Br-Tet (**1**), we were intrigued to see if this reactivity can be transferred directly to more electron-rich alkyl and aryl substituted tetrazines (Scheme 3B). Interestingly, a larger excess of $BF_3{\cdot}OEt_2$ was necessary to achieve synthetically useful conversions and yields. Possible reasons for this requirement could involve the stronger Lewis basicity of the corresponding reaction products binding multiple equivalents of BF_3. Along these lines, aryl substituted tetrazines required 6 equiv of Lewis acid and alkyl substituted tetrazines required 12 equiv of $BF_3{\cdot}OEt_2$, together with longer reaction times compared to azaphilic attack on 3-Br-Tet (**1**). The longer reaction time can be correlated with the higher electron density within the tetrazine ring resulting from the electron donating ability of the alkyl or aryl substituents. This effect of the substituent then leads to a less favorable azaphilic addition pathway. Nevertheless, also for alkyl and aryl substituents, the azaphilic addition pathway is favored over the inverse electron demand Diels–Alder reaction, and only in the case of compound **17** was the pyridazine **18** obtained in isolable amounts as a minor byproduct (6%) (Scheme 3B). Electron acceptors, as well as donors, on the tetrazine core were tolerated under these conditions and led to the formation of dihydrotetrazines **19**–**21** in moderate yields. Several alkyl substituted dihydrotetrazines **22**–**24** could also be isolated and were obtained in 21–49% yield and with exclusive regioselectivity. In order to gain further experimental insight into the transformation, we explored whether or not a phenyl

Scheme 3. Products and Yields from Azaphilic Addition to 3-Bromo, 3-Aryl, and 3-Alkyl Substituted *s*-Tetrazines



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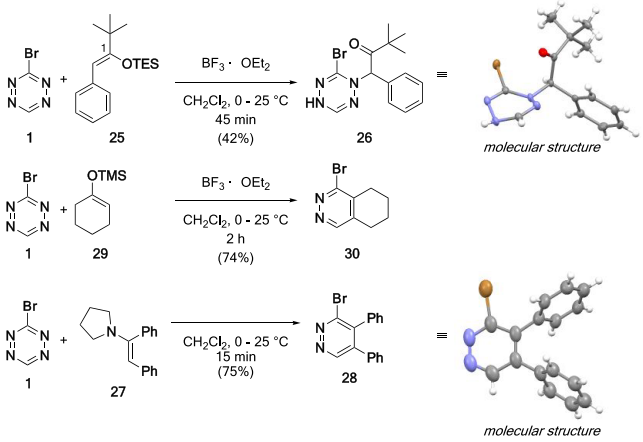
group at C1 in the silyl-enol ether is mandatory (Scheme 4), or if a bulky alkyl residue also promotes azaphilic addition.

Scheme 4. Reactivity of TES-Silyl-Enol Ethers, Enamines, and Cyclic Silyl-Enol Ethers



Along these lines, we synthesized TES-silyl-enol ether **25**; the corresponding TBS-silyl-enol ether remained synthetically inaccessible despite employing several enolization procedures. The respective TES-silyl-enol ether was subjected to the standard reaction conditions, which led to smooth and exclusive formation of dihydrotetrazine **26**; the adduct could be isolated in 42% yield. The structure was unambiguously verified via single-crystal X-ray structure analysis.

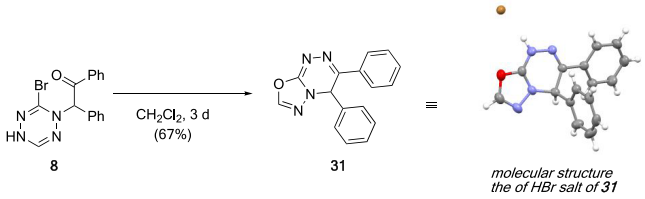
Additionally, we probed the result of the ASM study experimentally, by correlating the observed azaphilic addition reactivity with the double-bond geometry of the silyl-enol ethers being *Z*. In order to evaluate this hypothesis, the cyclic silyl-enol ether **29** (locked in an *E* configuration) was reacted under the conditions reported herein, and only the bicyclic pyridazine **30** was obtained; the corresponding azaphilic addition product remained elusive. TMS-enol ethers were used in this case, because higher yields were obtained than with the TBS analogs. This result thus provides experimental evidence for the importance of the double-bond geometry in the silyl-enol ethers, if azaphilic addition is the desired reaction pathway.

Additionally, we prepared enamine **27**,[13] which features an (*E*) configuration. Also, in this case, pyridazine **28** was the only observable product, being obtained in good yield (75%). Remarkably, this highly substituted pyridazine was obtained with exclusive selectivity without the use of a Lewis acid in short reaction times. Since the synthesis of highly substituted pyridazines with high regiocontrol still remains a challenge, this method potentially gives an easy entry to the synthesis of complex pyridazines bearing a Br-atom for further functionalization via cross-coupling reactions.[14]

Lastly, we investigated the decomposition of the adducts by using dihydrotetrazine **8** as a model substrate. After several attempts, we were able to obtain suitable crystals of the HBr salt of the rearranged product **31** for a single-crystal X-ray structure analysis (Scheme 5).[15] Studies on the mechanism of this unprecedented rearrangement are currently being conducted in our laboratory.

In conclusion, to the best of our knowledge, this is the first report of an azaphilic addition to *s*-tetrazines with mildly

Scheme 5. Rearrangement of Dihydrotetrazine 8 to Triazine Derivative 31



nucleophilic silyl-enol ether reagents. This reactivity opens a completely new and unprecedented reaction pathway, in addition to the expected iEDDA, for *s*-tetrazines with unsaturated compounds. In contrast, rare previous reports observed azaphilic additions only with strongly nucleophilic organometallic reagents (Grignard reagents, organolithium reagents),[16] whereas we could induce this reactivity by using a mild protocol with BF_3 as a Lewis acid mediator and a silyl-enol ether as a mild carbon nucleophile. The independent and parallel work of Boger and co-workers also suggests that other soft nucleophiles might be employed in similar reactions.[10] Along these lines, unprecedented dihydrotetrazine scaffolds with the structure of **8** were obtained. Experimental findings were supported by X-ray crystal-structure analyses, which unambiguously confirmed the structures of the adducts, as well as the exclusive regioselectivity. Theoretical calculations of the reaction provided additional valuable insights into the formation of the dearomatized dihydrotetrazines. Finally, a novel rearrangement of the dihydrotetrazine core to a triazine **31** derived bicyclic scaffold was recognized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04113.

Computational results (PDF)
Detailed experimental procedures and characterization data together with crystallographic data and the employed computational methods (PDF)

Accession Codes

CCDC 2036281−2036286 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/structures.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pinner, A. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2126−2135.
(2) Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. *Chem. Soc. Rev.* **2017**, *46*, 4895−4950.
(3) (a) Clavier, G.; Audebert, P. *Chem. Rev.* **2010**, *110*, 3299−3314. (b) Wu, H.; Devaraj, N. K. *Acc. Chem. Res.* **2018**, *51*, 1249−1259. (c) Miomandre, F.; Audebert, P. *J. Photochem. Photobiol., C* **2020**, *44*, 100372.
(4) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, *1998*, 2885−2896.
(5) Hong, L.; Ahles, S.; Strauss, M. A.; Logemann, C.; Wegner, H. A. *Org. Chem. Front.* **2017**, *4*, 871−875.
(6) Faragó, J.; Novák, Z.; Schlosser, G.; Csámpai, A.; Kotschy, A. *Tetrahedron* **2004**, *60*, 1991−1996.
(7) Katritzky, A. R.; Rachwal, S.; Offerman, R. J.; Najzarek, Z.; Yagoub, A. K.; Zhang, Y. *Chem. Ber.* **1990**, *123*, 1545−1552.
(8) (a) Hunter, D.; Neilson, D. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2779−2783. (b) Neugebauer, F. A.; Siegel, R. *Chem. Ber.* **1985**, *118*, 2157−2163. (c) Zhou, Q.; Audebert, P.; Clavier, G.; Miomandre, F.; Tang, J. *RSC Adv.* **2014**, *4*, 7193−195. (d) Lambert, W. D.; Fang, Y.; Mahapatra, S.; Huang, Z.; am Ende, C. W.; Fox, J. M. *J. Am. Chem. Soc.* **2019**, *141*, 17068−17074. (e) Xie, Y.; Fang, Y.; Huang, Z.; Tallon, A. M.; am Ende, C. W.; Fox, J. M. *Angew. Chem., Int. Ed.* **2020**, *59*, 16967−16973. (f) Suh, S.-E.; Chen, S.; Houk, K. N.; Chenoweth, D. M. *Chem. Sci.* **2018**, *9*, 7688−7693.
(9) Schnell, S. D.; Schilling, M.; Sklyaruk, J.; Linden, A.; Luber, S.; Gademann, K. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.13110533.v1.
(10) For recent publications on tetrazine synthesis and functionalizations, see: (a) Zhu, Z.; Glinkerman, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 20778−20787. (b) Mboyi, C. D.; Vivier, D.; Daher, A.; Fleurat-Lessard, P.; Cattey, H.; Devillers, C. H.; Bernhard, C.; Denat, F.; Roger, J.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2020**, *59*, 1149−1154. (c) Xiong, H.; Gu, Y.; Zhang, S.; Lu, F.; Ji, Q.; Liu, L.; Ma, P.; Yang, G.; Hou, W.; Xu, H. *Chem. Commun.* **2020**, *56*, 4692−4695. (d) Qu, Y.; Sauvage, F.-X.; Clavier, G.; Miomandre, F.; Audebert, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 12057−12061. (e) Bender, A. M.; Chopko, T. C.; Bridges, T. M.; Lindsley, C. W. *Org. Lett.* **2017**, *19*, 5693−5696. (f) Testa, C.; Gigot, E.; Genc, S.; Decréau, R.; Roger, J.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2016**, *55*, 5555−5559. (g) Wu, H.; Yang, J.; Seckute, J.; Devaraj, N. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 5805−5809.
(11) (a) Schnell, S. D.; Hoff, L. V.; Panchagnula, A.; Wurzenberger, M. H. H.; Klapötke, T. M.; Sieber, S.; Linden, A.; Gademann, K. *Chem. Sci.* **2020**, *11*, 3042−3047. (b) Ros, E.; Bellido, M.; Verdaguer, X.; Ribas de Pouplana, L.; Riera, A. *Bioconjugate Chem.* **2020**, *31*, 933−938. (c) Counotte-Potman, A.; Van der Plas, H. C.; Van Veldhuizen, B.; Landheer, C. A. *J. Org. Chem.* **1981**, *46*, 5102−5109.
(12) (a) Vermeeren, P.; van der Lubbe, S. C. C.; Fonseca Guerra, C.; Bickelhaupt, F. M.; Hamlin, T. A. *Nat. Protoc.* **2020**, *15*, 649−667. (b) Bickelhaupt, F. M.; Houk, K. N. *Angew. Chem., Int. Ed.* **2017**, *56*, 10070−10086. (c) Houk, K. N.; Liang, Y.; Liu, F. *Acc. Chem. Res.* **2017**, *50*, 539−543. (d) Wolters, L. P.; Bickelhaupt, F. M. *WIRES Comput. Mol. Sci.* **2015**, *5*, 324−343. (e) Fernández, I.; Bickelhaupt, F. M. *Chem. Soc. Rev.* **2014**, *43*, 4953−4967. (f) Bickelhaupt, F. M. *J. Comput. Chem.* **1999**, *20*, 114−128. (g) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646−10647.
(13) Timofeeva, D. S.; Mayer, R. J.; Mayer, P.; Ofial, A. R.; Mayr, H. *Chem. - Eur. J.* **2018**, *24*, 5901−5910.
(14) Balkenhohl, M.; Jangra, H.; Lenz, T.; Ebeling, M.; Zipse, H.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2019**, *58*, 9244−9247.
(15) Hetzheim, A.; Schneider, D. *Z. Chem.* **1975**, *15*, 219−220.
(16) Corral-Bautista, F.; Klier, L.; Knochel, P.; Mayr, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 12497−12500.