Article

Activating pyrimidines by pre-distortion for the general synthesis of 7-aza-indazoles from 2-hydrazonylpyrimidines via intramolecular Diels-Alder reactions

Vincent Le Fouler, Yu Chen, Vincent Gandon, Vincent Bizet, Christophe Salome, Thomas Fessard, Fang Liu, K. N. Houk, and Nicolas Blanchard

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 02 Sep 2019

Activating pyrimidines by pre-distortion for the general synthesis of 7-*aza*-indazoles from 2-hydrazonylpyrimidines via intramolecular Diels-Alder reactions

Vincent Le Fouler,[‖] Yu Chen,[⊤] Vincent Gandon,[≐] Vincent Bizet,[‖] Christophe Salomé,[ǂ] Thomas Fessard,[ǂ] Fang Liu,[Ⅱ*] K. N. Houk,[ǁ*] Nicolas Blanchard[‖*]

[‖] Université de Haute-Alsace, Université de Strasbourg, CNRS, LIMA, UMR 7042, 68000 Mulhouse, France

[⊤] State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China.

[≐] Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Université Paris-Sud, Université Paris-Saclay, Bâtiment 420, 91405 Orsay cedex, France and Laboratoire de Chimie Moléculaire, CNRS UMR 9168, Ecole Polytechnique, IP Paris, route de Saclay, 91128 Palaiseau cedex, France

[ǂ] SpiroChem AG Rosental Area, WRO-1047-3, Mattenstrasse 24, 4058 Basel, Switzerland

[Ⅱ] College of Sciences, Nanjing Agricultural University, Nanjing 210095, China

[ǁ] Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

Supporting Information Placeholder

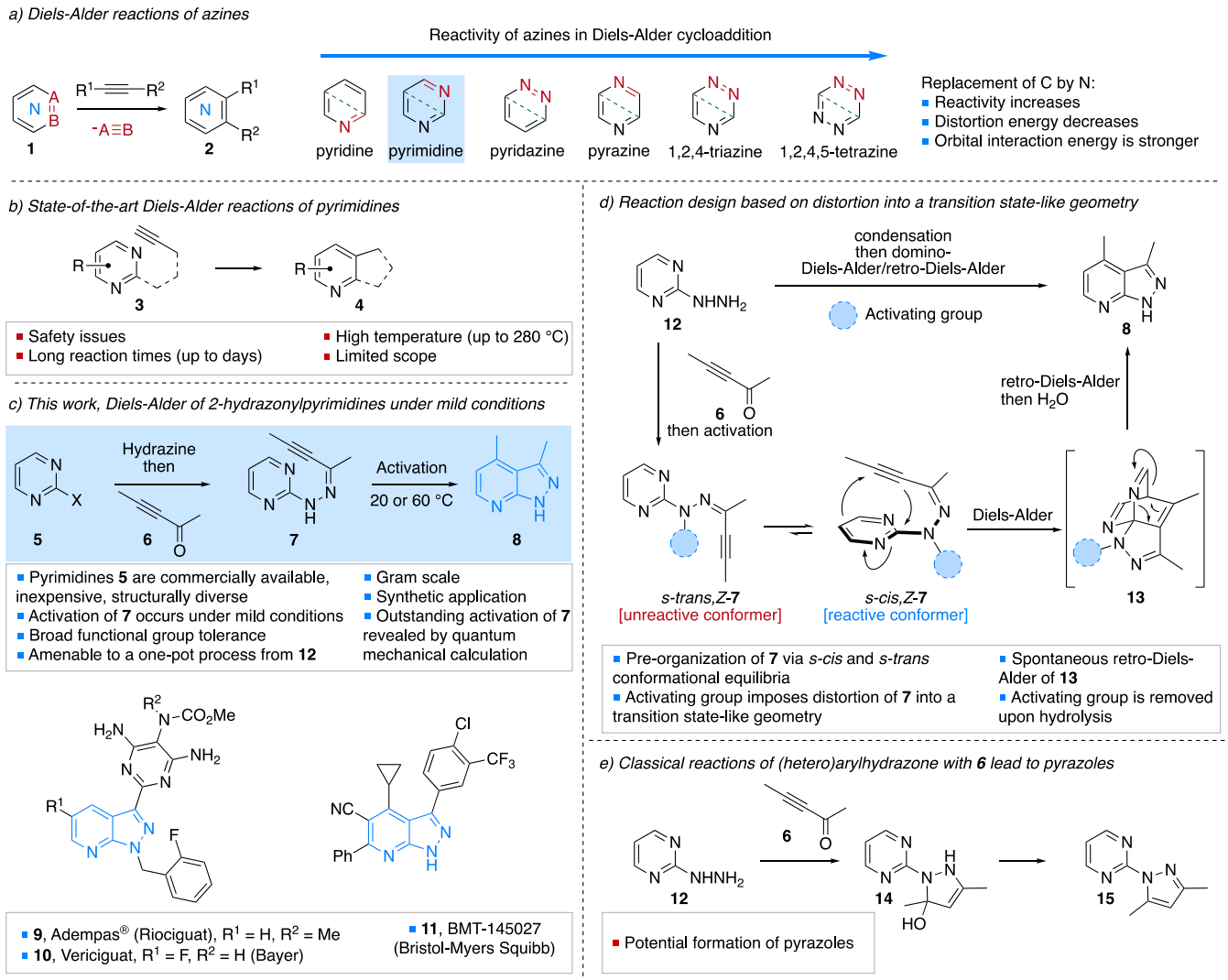
ABSTRACT: Pyrimidines are almost unreactive partners in Diels-Alder cycloadditions with alkenes and alkynes, and only reactions under drastic conditions have previously been reported. We describe how 2-hydrazonylpyrimidines, easily obtained in two steps from commercially available 2-halopyrimidines can be exceptionally activated by trifluoroacetylation. This allows a Diels-Alder cycloaddition under very mild reaction conditions, leading to a large diversity of *aza*-indazoles, a ubiquitous scaffold in medicinal chemistry. This reaction is general, scalable and has an excellent functional group tolerance. A straightforward synthesis of a key intermediate of Bayer's Vericiguat illustrates the potential of this cycloaddition strategy. Quantum mechanical calculations show how the simple *N*-trifluoromethylation of 2-hydrazonylpyrimidines distorts the substrate into a transition state-like geometry that readily undergoes the intramolecular Diels-Alder cycloaddition.

Introduction

Cycloaddition reactions are unique tools that enable the rapid elaboration of complex scaffolds with control over regio- and stereochemistry. Applications of these pericyclic reactions, and in particular the Diels-Alder cycloaddition, can be found in natural products synthesis and the preparation of pharmaceutically relevant molecules.[1,2] From a strategic standpoint, the inverse electron-demand Diels-Alder cycloaddition of azines **1**[3-5] is of great interest as it generates nitrogen-containing heterocycles **2**, a privileged scaffold in life-science research and industry (Scheme 1a).[6-8] High reactivity is generally observed with an increasing number of nitrogen atoms in the azine, which reduces the aromaticity of the 6π system and also favorably influences both distortion and interaction energies required to reach the transition state of the Diels-Alder cycloaddition.[9] The 1,2,4,5-tetrazines are prototypical example of highly reactive *aza*-diene that reacts with a diversity of dienophiles, especially electron-rich, under mild conditions.[5] This rapid Diels-Alder reaction is central to numerous chemical biology studies and drug activation chemistries.[10-12] Triazines can also be reactive as *aza*-dienes as demonstrated by studies by Boger,[13,14] and applications in chemical biology by Prescher.[15]

By contrast, near the other end of the azine spectrum, pyrimidines stand as unreactive 4π partners.[9,16,17] Seminal studies by Neunhoeffer[18] and van der Plas[19,20] demonstrated some decades ago that the lack of reactivity of pyrimidines **3** in inter- or intramolecular Diels-Alder cycloadditions has to be overcome by an exceptionally reactive dienophile (e.g. ynamines[18,21-23]) or harsh reaction conditions (up to 280 °C in batch[24] and 310 °C in continuous flow[25]) and long reaction times (up to several days) (Scheme 1b).[26] The scope of these early studies remained very limited, and only a handful of applications were reported.[26]

Scheme 1. Diels-Alder cycloadditions of 2-hydrazinyl-pyrimidines: an entry to relevant *N*-containing heterocycles.



Because of their low reactivity, the potential of the Diels-Alder cycloadditions of pyrimidines remains untapped. If the reactivity challenge posed by pyrimidines could be met, it would be of high significance in terms of heterocyclic chemistry and would constitute a fertile ground for theoretical explanation. Indeed, pyrimidines are small building blocks that possess key advantages; a large collection of structurally diverse pyrimidines is accessible at low price, which stands in sharp contrast with the triazines or tetrazines (see Supporting Information).

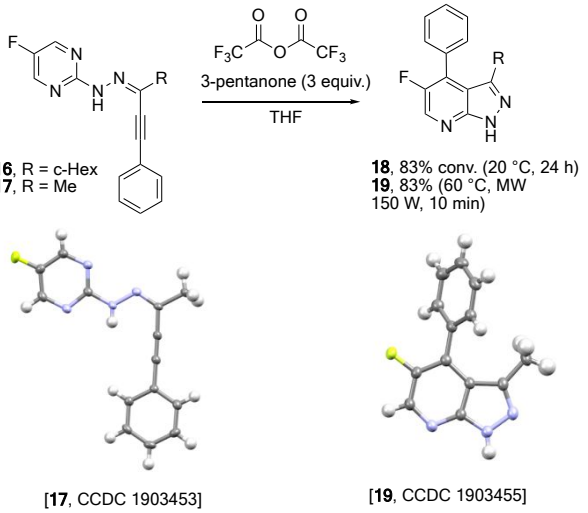
We have discovered that 2-hydrazonopyrimidines **7** can be activated towards Diels-Alder cycloaddition under mild conditions (20 or 60 °C, microwave irradiation or classical heating, Scheme 1c) in sharp contrast with previous observations about pyrimidine reactivity. The corresponding cycloadducts are *aza*-indazoles **8**, obtained in a straightforward three-step sequence from 2-halopyrimidines **5** that are commercially available, inexpensive and structurally diverse chemicals. 7-*Aza*-indazoles **8** are relevant nitrogen-containing heterocycles[27] that can be found in the marketed drug Adempas® (**9**, Bayer[28]), Vericiguat (**10**, Bayer and Merck & Co.[29]) actually in phase III clinical trials and BMT-145027 (**11**, Bristol-Myers Squibb[30]). This conceptually new synthetic approach of 7-*aza*-indazoles **8** has a very wide scope, is amenable to a one-pot procedure and could be performed on a gram scale. We also report quantum mechanical calculations of this Diels-Alder reaction that shed light on the exceptional activation of the 2-hydrazonopyrimidines **7**. Indeed, this phenomenon can be explained by the formation of an activated conformer ***s-cis,Z*-7** that is distorted into a transition state-like geometry (Scheme 1d). After Diels-Alder cycloaddition, a spontaneous retro-Diels-Alder and hydrolysis of the activating group delivers the desired 7-*aza*-indazole **8**. The nature of the activating group is thus central to prevent *N*-cyclization to the corresponding pyrazole **15**

(Scheme 1e),[31,32] to pre-organize the system through conformational equilibria and to dramatically increase the reactivity (and thus functional group tolerance) of the overall process.

Results and discussion

Unsubstituted pyrimidines are particularly challenging substrates; the intramolecular cycloaddition of *N*-(but-3-yn-1-yl)pyrimidin-2-amines into 7-*aza*-indolines at 210 °C was reported to only lead to decomposition.[33] The hydrazone **7** was found to undergo very slow and inefficient intramolecular Diels-Alder reactions. We thus screened activating groups that could be easily introduced on the hydrazone **7** to enhance reactivity.[34] Trifluoroacetic anhydride was identified as the optimal *N*-acylating agent, allowing a clean cycloaddition of model substrate **16** into 7-*aza*-indazole **18** at room temperature in THF in the presence of 3-pentanone as a formonitrile trap[25] (Scheme 2). This dramatic increase in reactivity of pyrimidines in Diels-Alder cycloaddition is unprecedented and opens new avenues in terms of synthetic applications. Further optimization of the reaction temperature and time with hydrazone **17** demonstrated that a complete conversion to **19** could be obtained in only 10 min at 60 °C under microwave irradiation. This latter set of conditions was selected for the exploration of the scope of this Diels-Alder/retro-Diels-Alder cycloaddition (Table 1).

Scheme 2. Diels-Alder cycloadditions of pyrimidines under mild conditions.



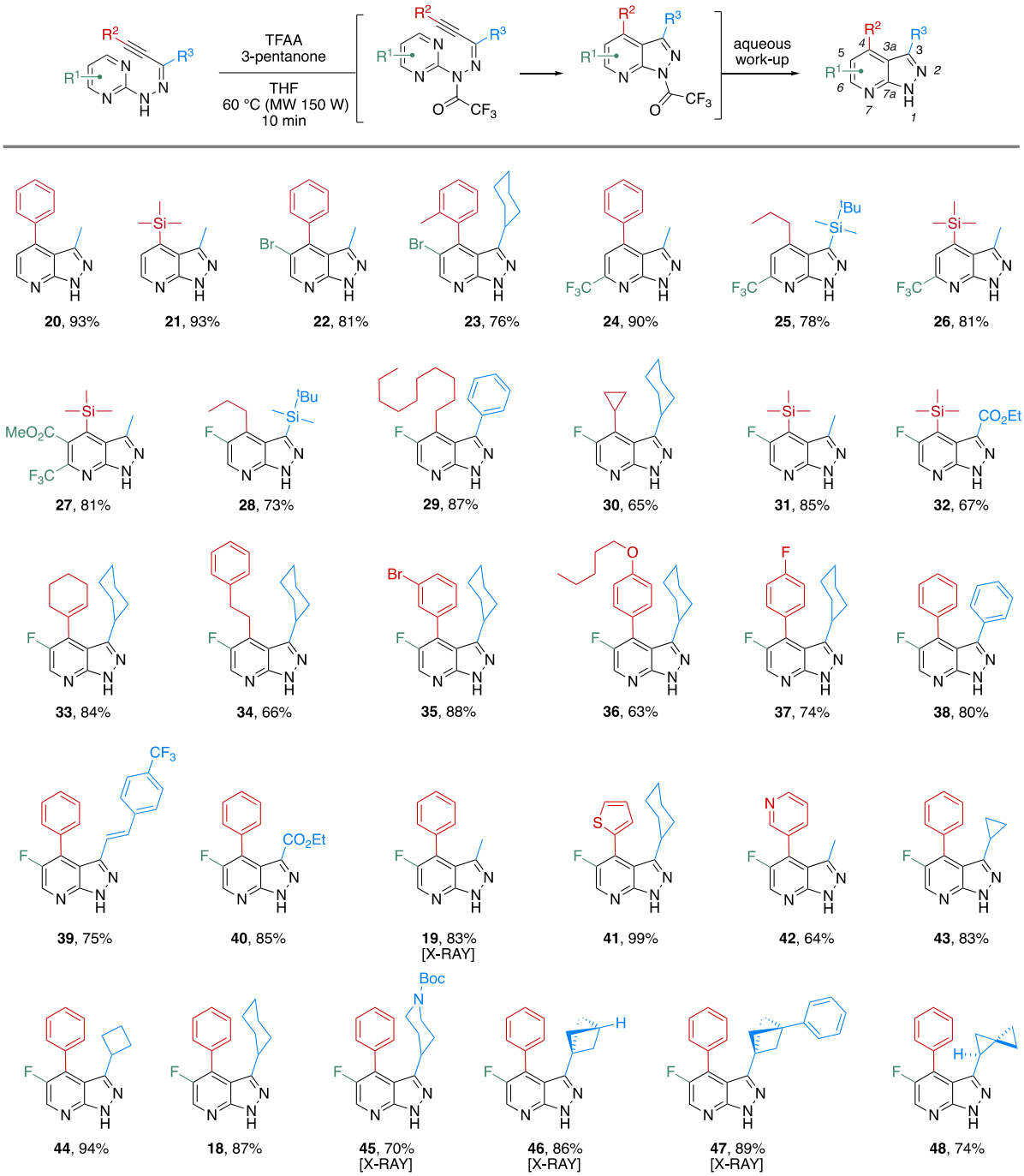
This new method efficiently converts unsubstituted pyrimidines into reactive *aza*-dienes upon treatment with TFAA, leading to 7-*aza*-indazoles **20** and **21** in 93% yield (Table 1). 5-Bromo pyrimidines are symmetrical pyrimidines that delivered 7-*aza*-indazoles **22** and **23** possessing an alkyl or cycloalkyl on the 3-position in 76-81% yield. With unsymmetrical *aza*-dienes such as 4-trifluoromethyl-pyrimidines, 7-*aza*-indazoles **24**-**27** were obtained in 78-90%. Although two pathways could be envisaged for the retro-Diels-Alder cycloaddition,[35,36] a single cycloadduct was observed in each case in the crude reaction mixture.

The largest number of examples involve substituted 5-fluoro-pyrimidines, leading to *aza*-indazoles **29**-**48** in good to excellent yields. Systematic variations of the electronic and steric natures of the R^1, R^2 and R^3 substituents of the cycloaddition precursor demonstrated that a broad range of motifs and functional groups are tolerated, leading to a unique collection of 7-*aza*-indazoles. Aromatic and heteroaromatic groups could be introduced on the 3 or 4-position of the cycloadduct, as in **29** (87%), **36** (63%), **41** (99%), and **42** (64%). Halo-substituted aromatics are also compatible with the process, as shown by **35** obtained in 88%. The latter is poised for metal-catalysed cross-coupling, leading to further chemical diversity. Esters can be present in the 3-position of the 7-*aza*-indazoles (**32** 67%, **40** 85%) as well as ^{n}alkyl (**19** 83%, **42** 64%), cycloalkyl (**30** 65%, **43** 83%, **44** 94%) or saturated *N*-heterocycles such as a piperidin-4-yl motif in **45** (70%).

To further expand the chemical space in these series, the synthesis of 7-*aza*-indazoles with two classes of substituents frequently used in drug design was studied. Cycloadducts **46** and **47** possessing a C3-bicyclo[1.1.1]pentane as a relevant mimic of *para*-disubstituted aromatic group[37,38] were obtained in good yields (86% and 89% respectively). Finally, we investigated spirocyclic substituents, as their reduced lipophilicity, their high sp^3/sp^2 carbon atoms ratio and their intrinsic positioning of bond vectors make them attractive rigid scaffolds for medicinal chemistry;[39] the 7-*aza*-indazole **48** was obtained in 70% as a single compound.

Density functional theory (DFT) calculations were carried out to understand the origin of the activation of pyrimidines. Gas phase geometry optimization was carried out at the M06-2X/6-31G(d) level of theory, followed by single point energy calculations using 6-311+G(d,p) basis set with a CPCM solvation model. Studies of the pyrimidine-alkyne cycloadditions revealed that the Diels-Alder reaction is the rate-determining step, while the following retro-Diels-Alder has a low activation barrier and is significantly exergonic with the release of formonitrile (Supporting Information).[36] Based on the broad scope of this reaction, we first studied the impact of *N*-trifluoroacetylation on the activation of three simplified pyrimidines, **49**, **59** and **51** (Scheme 3).

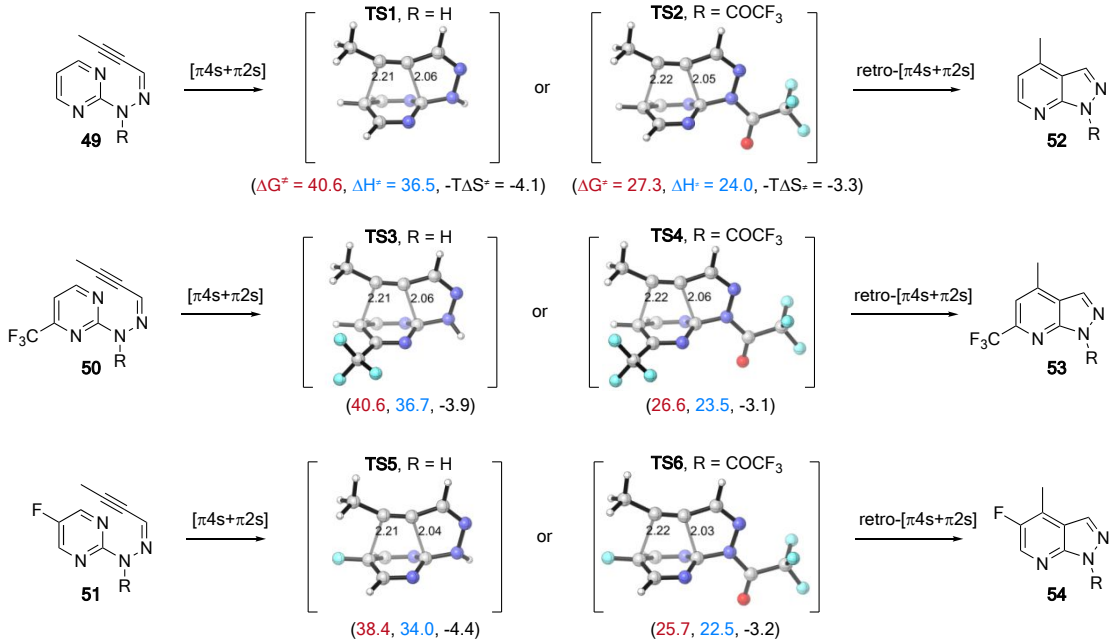
Table 1. Scope of the Diels-Alder cycloaddition.



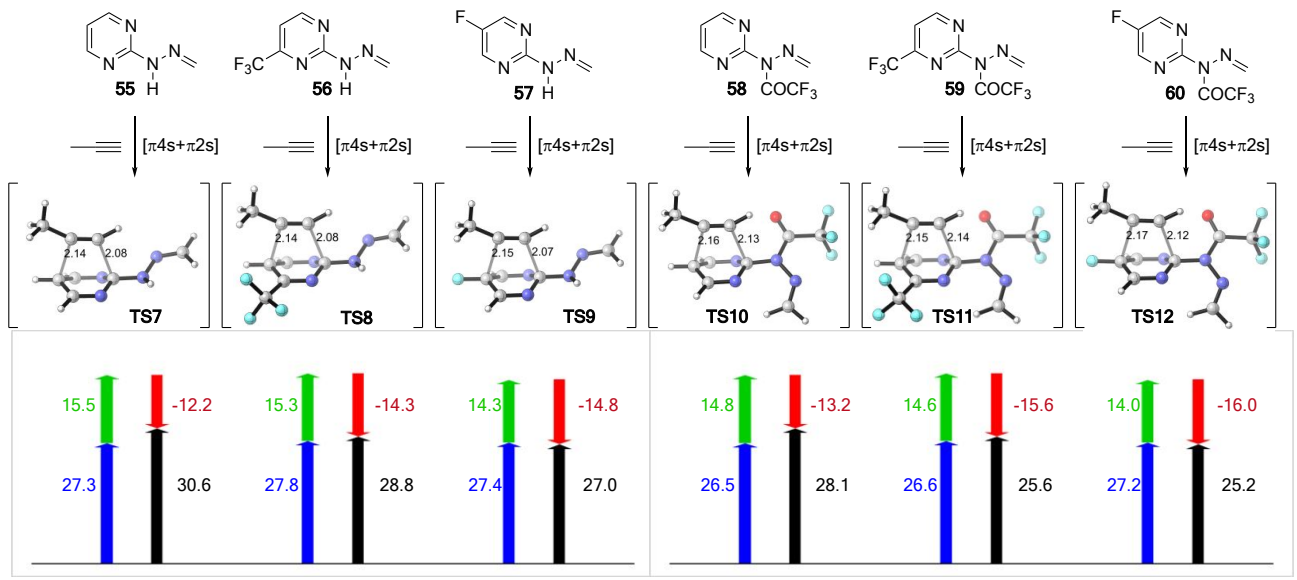
Reaction conditions: 2-hydrazonopyrimidine (1 equiv.), 3-pentanone (3 equiv.), TFAA (1.5 equiv) in THF ([0.2 M]) at 60 °C (microwave irradiation, 150 W, ramp time: 45 s) for 10 min. Yields were determined after chromatography on silica gel. X-ray crystallographic structures were obtained for **19**, **45**, **46** and **47**. Boc, *t*Butoxycarbonyl.

Scheme 3. Density functional theory calculations.

a) Transition state structures and computed activation energies for the non-activated (R = H) and for the activated (R = $COCF_3$) cases



b) Distortion/Interaction analysis on the intermolecular Diels-Alder cycloadditions reactions of substituted pyrimidines with propyne



a) $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, $-T\Delta S^{\ddagger}$ in red, blue, and black, respectively, in kcal/mol. b) The sum of distortion energy of pyrimidine (blue arrow), distortion energy of propyne (green arrow), and interaction energy (red arrow) gives the activation energies of the process (black arrow). Energies are in kcal/mol.

Scheme 3a shows the transition state structures involved in these reactions, with the forming bond lengths labeled (in Å) and the activation energies shown below (in kcal/mol). The 4-trifluoromethyl and 5-fluoro groups on the pyrimidine scaffold lower the activation energy slightly (0-2 kcal/mol, **TS3** and **TS5** vs. **TS1**). On the other hand, the *N*-trifluoroacetyl has an enormous impact, decreasing the reaction barriers by 12-14 kcal/mol (**TS2**, **TS4** and **TS6** vs. **TS1**, **TS3** and **TS5** respectively). To understand the *N*-trifluoroacetyl effect, we studied the corresponding intermolecular reactions and analyzed the results with the distortion/interaction model (Scheme 3b). The 3-trifluoromethyl group, 5-fluoro atom, and *N*-trifluoroacetyl group lower the activation barriers by 2-3 kcal/mol by improving interaction energies. Analysis of the molecular orbital energies (Supplementary Information) showed that the *N*-trifluoroacetyl group lowers the energy of the second lowest unoccupied molecular orbital which interacts with the HOMO of alkyne, increasing the stabilizing interaction energy due to charge transfer in this inverse-electron-demand Diels-Alder reaction. However, in the intermolecular cycloaddition case, the activation from trifluoroacetyl group is small (~2 kcal/mol), far less than in the intramolecular cycloaddition case.

To explain the origin of this powerful effect for the intramolecular reaction, we propose a two-phase model, dividing the intramolecular reaction into : pre-organization and cycloaddition phases (Scheme 4a). The pre-organization phase refers to the process in which the reactant undergoes conformational change from the ground state to a reactive state where the *aza*-diene and the dienophile (pyrimidine and alkyne in this case) are close in proximity in order to react. These conformational changes can be described through dihedral angle θ and the degree of pyramidalization φ of the N1-nitrogen atom (Scheme 4b). The cycloaddition phase refers to the actual bond forming/cleavage process.

As shown in Scheme 4c, the ground state structure of 2-hydrazonopyrimidine **51a** adopts a planar geometry (θ = 0°). This extended geometry is supported by X-ray crystallography of alkynyl-pyrimidine **17** (Scheme 2).

Bringing the triple bond closer to pyrimidine moiety costs 7.6 kcal/mol and even in the reactive state, the triple bond of **51a** orients away from the perfect perpendicular position (θ = 143° and φ = 144°). However, when a *N*-trifluoracetyl group is present as in **51b**, due to the steric repulsion between the pyrimidine N and carbonyl O, the triple bond is naturally positioned over the pyrimidine moiety, perfectly in position for the cycloaddition reaction (θ = 0° and φ = 180°). In this case, the ground state is also the reactive state. In addition, in the cycloaddition phase, the *N*-trifluoroacetyl group further lowers the activation barrier by 5.8 kcal/mol due to the larger interaction energy.

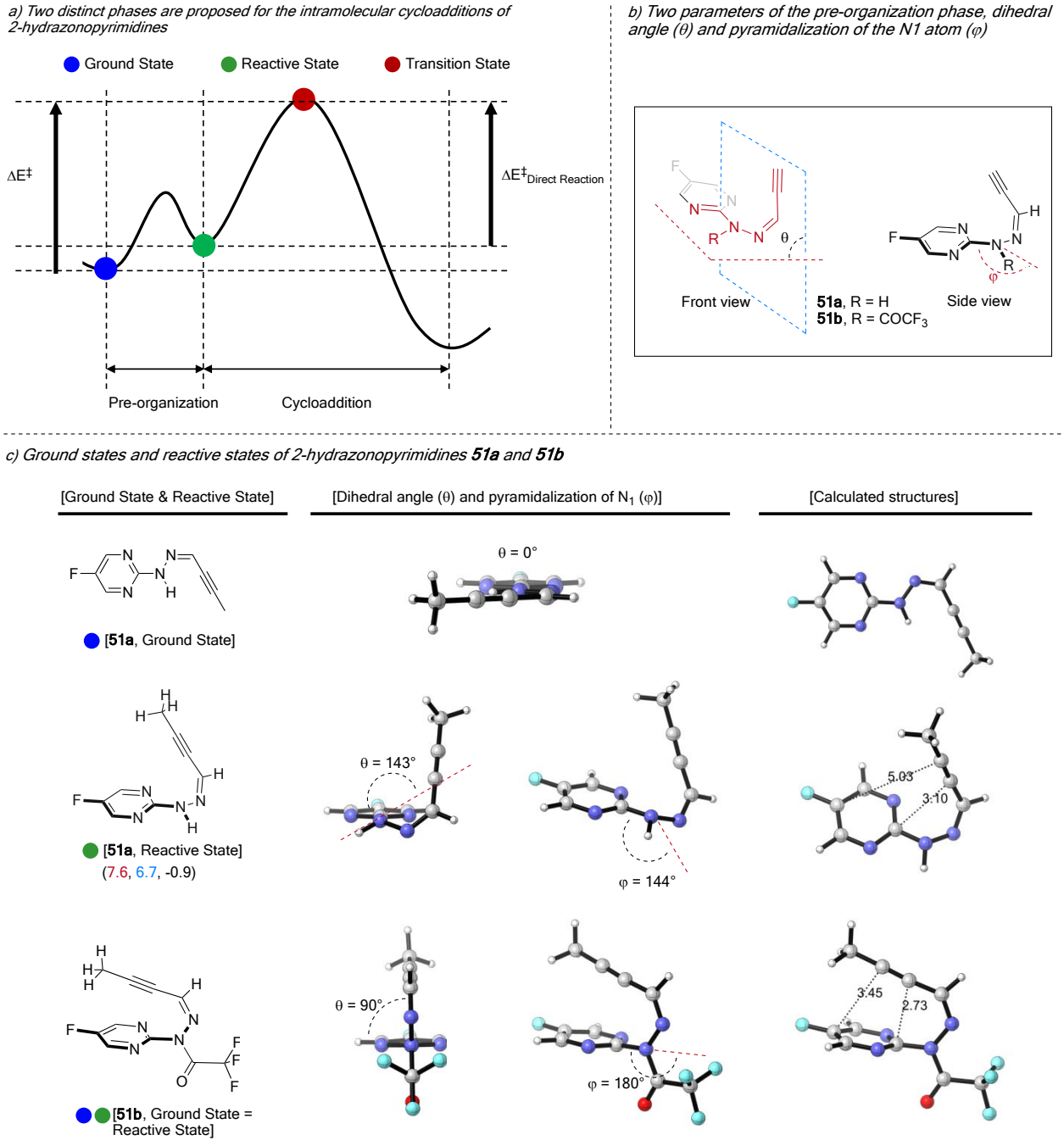
This DFT study shows that *N*-trifluoroacetyl group pre-organizes the triple bond, not only changing the s-*trans* hydrazone conformation to s-*cis*, but also rotating the Ar—N bond so that the hydrazone is perpendicular to the diazine, placing the alkyne in perfect position for cycloaddition. The activation by the *N*-trifluoroacetyl group is thus due to the electronic substituent effect, preorganization, and more favorable entropy.

To gain further insights into the reaction mechanism, the cycloaddition reaction of **16** was followed by ^{19}F NMR in THF at 20 °C for 24 h (Scheme 5a). A clean transformation of **16** into its trifluoroacetylated analog **61** was observed almost instantaneously, followed by the slow formation of **63** and its hydrolysed counterpart **18** due to traces of water. Tricyclic intermediate **62** was not observed, nor protonated **63** or **18**. The measured half-life is about 8 hours, which corresponds to an activation free energy of 23.3 kcal/mol, according to the Eyring equation and first order rate law. The computed activation free energy from DFT calculations is 24.2 kcal/mol, close to experimental data.

From a practical point of view, this Diels-Alder cycloaddition of 2-hydrazonopyrimidines is amenable to gram scale in a one-pot process, as demonstrated with the synthesis of **22** in 81% yield from commercially available compounds (Scheme 5b). 5-Bromo-2-chloropyrimidine **64** can be transformed into the corresponding 5-bromo-2-hydrazinopyrimidine **65** in quantitative yield using hydrazine monohydrate in ethanol at 60 °C for 40 min. Crude **65** could then be reacted with commercial ynone **66** using a catalytic amount of trifluoroacetic acid (5 mol%) in THF at 60 °C (classical heating) for 20 min. When the hydrazone formation is complete, trifluoroacetic anhydride and 3-pentanone are added. After 1 h at 60 °C, the 7-*aza*-indazole **22** is obtained as the only product in the crude reaction mixture; after purification by silica gel chromatography, 6.2 g of analytically pure **22** could be obtained.

The relevance of this extraordinary reactivity of 2-hydrazonopyrimidines in Diels-Alder reaction under mild conditions was further explored with the synthesis of an intermediate to Vericiguat (BAY 1021189 from Bayer), a soluble guanylate cyclase (sGC) stimulator for the chronic heart failure in Phase III clinical trials (Scheme 5c).[28] Vericiguat possesses a 7-*aza*-indazole scaffold substituted by a 2-fluorobenzyl on N1, a pyrimidine motif on C3 and a fluorine atom on C5; this compound could be obtained in 6 steps according to the Bayer medicinal chemistry route. In contrast, the latter was obtained in this work in only 4 steps (including a one-pot reaction) from commercially available compounds **67** and **68**.

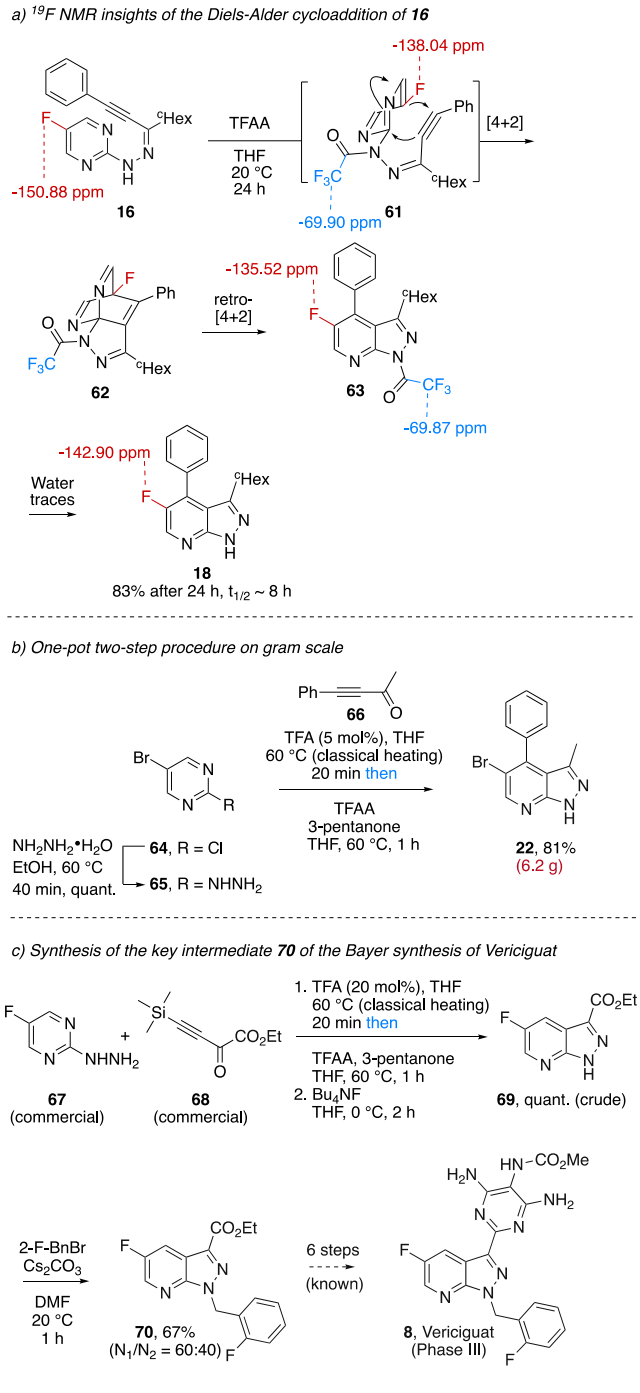
Scheme 4. Pre-organization phase and cycloaddition phase during the intramolecular Diels-Alder of pyrimidine.



Δ G‡, Δ H‡, -T Δ S‡ in red, blue, and black, respectively, in kcal/mol; calculated structures with distances in Å.

The one-pot condensation/domino Diels-Alder reactions proceeds smoothly at 60 °C (classical heating) and yields a single compound that is treated with tetrabutylammonium fluoride in THF at 0 °C. The disubstituted 7-*aza*-indazole **69** is finally converted to **70** using 2-fluorobenzyl bromide and cesium carbonate in DMF at room temperature in 67% (N1/N2 benzylation ratio = 60:40). This synthesis of **72** requires only a single chromatography at the very last step.

Scheme 5. NMR insights, gram scale one-pot reaction and synthetic applications



Conclusions

Pyrimidines are intrinsically unreactive *aza*-dienes in Diels-Alder cycloadditions, and this lack of reactivity under mild conditions has hampered the access to a diversity of original nitrogen-containing heterocycles from these simple, inexpensive and structurally diverse building blocks. We show that 2-hydrazonopyrimidines can be profoundly activated using a simple trifluoroacetyl group, leading to a domino Diels-Alder/retro-Diels-Alder cycloaddition even at room temperature. This reaction is general, presents an excellent functional group tolerance and can be scaled up on a gram-scale in a convenient one-pot process. A straightforward synthesis of a key intermediate of Bayer's Vericiguat, a soluble guanylate cyclase (sGC) stimulator for the chronic heart failure in Phase III clinical trials, illustrates the potential of this cycloaddition strategy. Central to this method is the impressive lowering of activation energy of the Diels-Alder reaction, that was analyzed by density functional theory calculations including an application of the distortion/interaction-activation strain model to intramolecular reactions. The trifluoroacetyl activating group preorganizes the cycloaddition precursor, electronically activates the *aza*-diene and confers a favorable entropy on the transition state of the Diels-Alder cycloaddition.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs....

Experimental procedures, characterization data, and copies of NMR spectra for all products; computed energy components, Cartesian coordinates, and vibrational frequencies of all of the DFT-optimized structures (PDF). Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1903453 (**17**, CIF), CCDC 1903455 (**19**, CIF), CCDC 1911671 (**45**, CIF), CCDC 1911386 (**46**, CIF) and CCDC 1911387 (**47**, CIF).

AUTHOR INFORMATION

Corresponding Authors

F. Liu: acialiu@njau.edu.cn
K. N. Houk: houk@chem.ucla.edu
N. Blanchard: n.blanchard@unistra.fr

ORCID:

Vincent Gandon: 0000-0003-1108-9410
Vincent Bizet: 0000-0002-0870-1747
Fang Liu: 0000-0002-0046-8434

K. N. Houk: 0000-0002-8387-5261
N. Blanchard: 0000-0002-3097-0548

Notes

CS and TF are Team Leader and CEO (respectively) of Spirochem, a Swiss CRO company selling the building blocks leading to compounds **45-48**.

ACKNOWLEDGMENT

The authors acknowledge funding from the Université de Haute-Alsace, the Université de Strasbourg and the CNRS (VLF, VB, NB), the Ecole Polytechnique (VG), Nanjing Agricultural University for setup package (FL) and the US National Science Foundation (CHE-1764328 to KNH).

REFERENCES

1. Ishihara, K.; Sakakura, A. in *Comprehensive Organic Synthesis II (Second Edition)* (ed Paul Knochel) 351-408 (Elsevier, 2014).
2. Ishihara, K.; Sakakura, A. in *Comprehensive Organic Synthesis II (Second Edition)* (ed Paul Knochel) 409-465 (Elsevier, 2014).
3. Boger, D. L. Diels-alder reactions of azadienes. *Tetrahedron* **1983**, *39*, 2869-2939.
4. Boger, D. L. Diels-Alder reactions of heterocyclic aza dienes. Scope and applications. *Chem. Rev.* **1986**, *86*, 781-793.
5. Foster, R. A. A.; Willis, M. C. Tandem inverse-electron-demand hetero-/retro-Diels-Alder reactions for aromatic nitrogen heterocycle synthesis. *Chem. Soc. Rev.* **2013**, *42*, 63-76.
6. Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, 57, 10257-10274.
7. Pennington, L. D.; Moustakas, D. T. The Necessary Nitrogen Atom: A Versatile High-Impact Design Element for Multiparameter Optimization. *J. Med. Chem.* **2017**, *60*, 3552-3579.
8. Cao, M.-H.; Green, N. J.; Xu, S.-Z. Application of the aza-Diels-Alder reaction in the synthesis of natural products. *Org. Biomol. Chem.* **2017**, *15*, 3105-3129.
9. Yang, Y.-F.; Liang, Y.; Liu, F.; Houk, K. N. Diels–Alder Reactivities of Benzene, Pyridine, and Di-, Tri-, and Tetrazines: The Roles of Geometrical Distortions and Orbital Interactions. *J. Am. Chem. Soc.* **2016**, *138*, 1660-1667.
10. Oliveira, B. L.; Guo, Z.; Bernardes, G. J. L. Inverse electron demand Diels–Alder reactions in chemical biology. *Chem. Soc. Rev.* **2017**, *46*, 4895-4950.
11. Oller-Salvia, B.; Kym, G.; Chin, J. W. Rapid and Efficient Generation of Stable Antibody–Drug Conjugates via an Encoded Cyclopropene and an Inverse-Electron-Demand Diels–Alder Reaction. *Angew. Chem. Int. Ed.* **2018**, *57*, 2831-2834.
12. Neumann, K.; Gambardella, A.; Bradley, M. The Emerging Role of Tetrazines in Drug-Activation Chemistries. *Chembiochem* **2019**, *20*, 872-876.
13. Glinkerman, C. M.; Boger, D. L. Catalysis of Heterocyclic Azadiene Cycloaddition Reactions by Solvent Hydrogen Bonding: Concise Total Synthesis of Methoxatin. *J. Am. Chem. Soc.* **2016**, *138*, 12408-12413.
14. a) Anderson, E. D.; Boger, D. L. Inverse Electron Demand Diels–Alder Reactions of 1,2,3-Triazines: Pronounced Substituent Effects on Reactivity and Cycloaddition Scope. *J. Am. Chem. Soc.* **2011**, *133*, 12285-12292. b) Zhang, J.; Shukla, V.; Boger, D. L., Inverse Electron Demand Diels–Alder Reactions of Heterocyclic Azadienes, 1-Aza-1,3-Butadienes, Cyclopropenone Ketals, and Related Systems. A Retrospective. *J. Org. Chem.* **2019,** *84*, 9397-9445.
15. Kamber, D. N.; Liang, Y.; Blizzard, R. J.; Liu, F.; Mehl, R. A.; Houk, K. N.; Prescher, J. A. 1,2,4-Triazines Are Versatile Bioorthogonal Reagents. *J. Am. Chem. Soc.* **2015**, *137*, 8388-8391.
16. Liu, F.; Liang, Y.; Houk, K. N. Bioorthogonal Cycloadditions: Computational Analysis with the Distortion/Interaction Model and Predictions of Reactivities. *Acc. Chem. Res.* **2017**, *50*, 2297-2308.
17. Matthias, B. F.; Houk, K. N. Analyzing Reaction Rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070-10086.
18. Neunhoeffer, H.; Werner, G. Cycloadditionen mit Azabenzolen, VII1) Reaktion von Pyrimidinen mit N,N-Diäthyl-1-propinylamin. *Liebigs Ann. Chem.* **1974**, 1190-1194.
19. van der Plas, H. C. in *Advances in Heterocyclic Chemistry* Vol. Volume 84 (ed R. Katritzky Alan) 31-70 (Academic Press, 2003).
20. van der Plas, H. C. Thirty years of pyrimidine chemistry in the laboratory of organic chemistry at the Wageningen Agricultural University, The Netherlands (review). *Chem. Heterocycl. Compd.* **1994**, *30*, 1427-1443.
21. Martin, J. C. Synthesis of pyridines from dicyanopyrimidines. A Diels-Alder approach to the C-ring of streptonigrin. *J. Heterocyclic Chem.* **1980**, *17*, 1111-1112.
22. Neunhoeffer, H.; Lehmann, B. Cycloadditionen mit Azabenzolen, VIII1) Reaktionen von Dimethylamino- und Methoxypyrimidinen mit Acetylendicarbonsäure-dimethylester. *Liebigs Ann. Chem.* **1975**, 1113-1119.
23. Marcelis, A. T. M.; van der Plas, H. C. Ring transformations of heterocycles with nucleophiles. 33. Cycloadditions of 5-nitropyrimidines with ynamines. Formation of 3-nitropyridines, N-5-pyrimidyl-alpha-carbamoylnitrones, and 2,2a-dihydroazeto[2,3-d]-3,5-diazocines. *J. Org. Chem.* **1986**, *51*, 67-71.
24. Shao, B. Synthesis of fused bicyclic pyridines with microwave-assisted intramolecular hetero-Diels–Alder cycloaddition of acetylenic pyrimidines. *Tetrahedron Lett.* **2005**, *46*, 3423-3427.
25. Martin, R. E.; Morawitz, F.; Kuratli, C.; Alker, A. M.; Alanine, A. I. Synthesis of Annulated Pyridines by Intramolecular Inverse-Electron-Demand Hetero-Diels–Alder Reaction under Superheated Continuous Flow Conditions. *Eur. J. Org. Chem.* **2012**, 47-52.
26. Duret, G.; Le Fouler, V.; Bisseret, P.; Bizet, V.; Blanchard, N. Diels–Alder and Formal Diels–Alder Cycloaddition Reactions of Ynamines and Ynamides. *Eur. J. Org. Chem.* **2017**, 6816-6830.
27. Aggarwal, R.; Kumar, S. 5-Aminopyrazole as precursor in design and synthesis of fused pyrazoloazines. *Beilstein J. Org. Chem.* **2018**, *14*, 203-242.
28. Follmann, M.; Griebenow, N.; Hahn, M. G.; Hartung, I.; Mais, F. J.; Mittendorf, J.; Schäfer, M.; Schirok, H.; Stasch, J. P.; Stoll, F.; Straub, A. The Chemistry and Biology of Soluble Guanylate Cyclase Stimulators and Activators. *Angew. Chem. Int. Ed.* **2013**, *52*, 9442-9462.
29. Follmann, M.; Ackerstaff, J.; Redlich, G.; Wunder, F.; Lang, D.; Kern, A.; Fey, P.; Griebenow, N.; Kroh, W.; Becker-Pelster, E.-M.; Kretschmer, A.; Geiss, V.; Li, V.; Straub, A.; Mittendorf, J.; Jautelat, R.; Schirok, H.; Schlemmer, K.-H.; Lustig, K.; Gerisch, M.; Knorr, A.; Tinel, H.; Mondritzki, T.; Trübel, H.; Sandner, P.; Stasch, J.-P. Discovery of the Soluble Guanylate Cyclase Stimulator Vericiguat (BAY

1021189) for the Treatment of Chronic Heart Failure. *J. Med. Chem.* **2017**, *60*, 5146-5161.
30. Hill, M. D.; Fang, H.; Brown, J. M.; Molski, T.; Easton, A.; Han, X.; Miller, R.; Hill-Drzewi, M.; Gallagher, L.; Matchett, M.; Gulianello, M.; Balakrishnan, A.; Bertekap, R. L.; Santone, K. S.; Whiterock, V. J.; Zhuo, X.; Bronson, J. J.; Macor, J. E.; Degnan, A. P. Development of 1H-Pyrazolo[3,4-b]pyridines as Metabotropic Glutamate Receptor 5 Positive Allosteric Modulators. *ACS Medicinal Chemistry Letters* **2016**, *7*, 1082-1086.
31. Bishop, B. C.; Brands, K. M. J.; Gibb, A. D.; Kennedy, D. J. Regioselective Synthesis of 1,3,5-Substituted Pyrazoles from Acetylenic Ketones and Hydrazines. *Synthesis* **2004**, 43-52.
32. Harigae, R.; Moriyama, K.; Togo, H. Preparation of 3,5-Disubstituted Pyrazoles and Isoxazoles from Terminal Alkynes, Aldehydes, Hydrazines, and Hydroxylamine. *J. Org. Chem.* **2014**, *79*, 2049-2058.
33. Frissen, A. E.; Marcelis, A. T. M.; van der Plas, H. C. Novel intramolecular Diels-Alder reactions of pyrimidines. Synthesis of heterocyclic annelated pyridines. *Tetrahedron Lett.* **1987**, *28*, 1589-1592.
34. Other activating groups were screened such as *p*-fluoro-benzoyl chloride, *p*-cyano-benzoyl chloride, *p*-nitro-benzoyl-chloride, *o*-nitro-benzoyl chloride, 2,4,6-trichloro-benzoyl chloride and 2,2,2-trichloro-1-ethoxyethanol but they all led to incomplete protection of the hydrazone and/or low yield of the domino cycloaddition. On the other hand, di-tert-butyldicarbonate was efficient and afforded the desired *N*-Boc-7-*aza*-indazoles in good yields.
35. Duret, G.; Quinlan, R.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N.. Inverse Electron-Demand [4 + 2]-Cycloadditions of Ynamides: Access to Novel Pyridine Scaffolds. *Org. Lett.* **2016**, *18*, 1610-1613.
36. Duret, G.; Quinlan, R.; Yin, B.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. Intramolecular Inverse Electron-Demand [4 + 2] Cycloadditions of Ynamides with Pyrimidines: Scope and Density Functional Theory Insights. *J. Org. Chem.* **2017**, *82*, 1726-1742.
37. Mykhailiuk, P. K. Saturated bioisosteres of benzene: where to go next? *Org. Biomol. Chem.* **2019**, *17*, 2839-2849.
38. Locke, G. M.; Bernhard, S. S. R.; Senge, M. O. Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. *Chem. Eur. J.* **2019**, *25*, 4590-4647.
39. Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257-8322.

Insert Table of Contents artwork here

Max: 8.5 cm x 4.75 cm