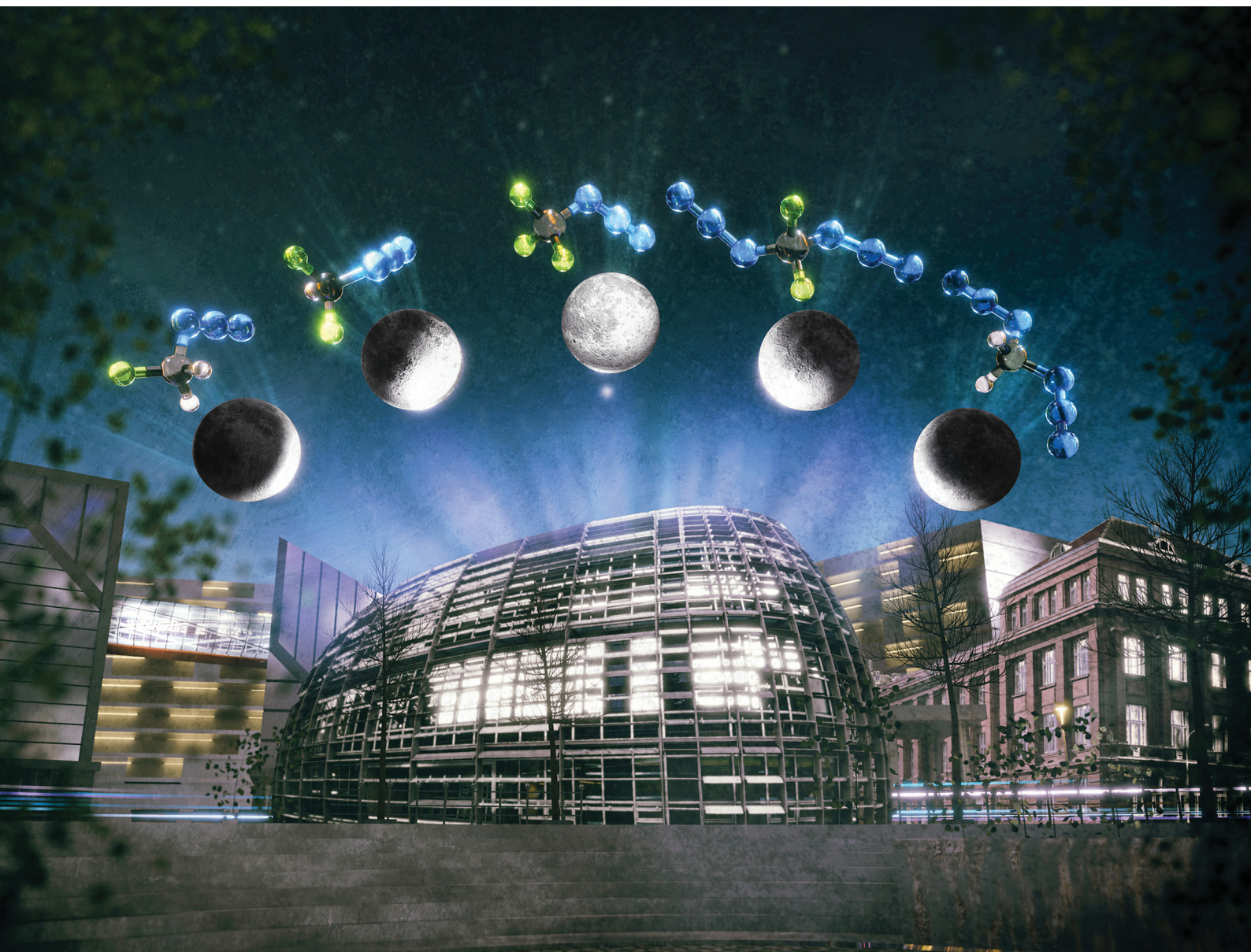


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# From boom to bloom: synthesis of diazodifluoromethane, its stability and applicability in the 'click' reaction†

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Diazodifluoromethane was prepared from dibromodifluoromethane, sodium azide and an alkanethiolate initiator. It represents the first example of a diazidomethane that is stable enough to be used in synthesis. The stability of (poly)azidomethanes was explored with *ab initio* calculations. Copper(i)-catalysed azide–alkyne cycloaddition of the title azide with alkynes afforded difluoromethylene-containing bis(1,2,3-triazoles) amenable to Rh(ii)-catalysed transannulation with nitriles to difluoromethylene bis(imidazoles).

In recent years,  $\alpha$ -fluorinated azidoalkanes have become the focus of considerable attention<sup>1,2</sup> as stable yet reactive precursors of trifluoromethyl diazonium amines,<sup>3</sup> trifluoromethylnitrene for *N*-trifluoromethylaziridines,<sup>4</sup> and *N*-fluoroalkylated 1,2,3-triazoles.<sup>5–8</sup> These unique triazoles have proven invaluable in the synthesis of a variety of *N*-fluoroalkylated nitrogen heterocycles *via* Rh(ii)-catalysed transannulation<sup>9–11</sup> or acid-mediated denitrogenation reactions leading to new *N*-alkenyl compounds, such as enamides,<sup>12</sup> imidoaldehydes,<sup>13</sup> and ketimines.<sup>14</sup>

Monofluoro-, difluoro- and trifluoroazidomethanes are known,<sup>1,2</sup> but diazodifluoromethane has not been reported before. Its non-fluorinated analogue diazidomethane is a highly sensitive compound that can be generated from dichloromethane or dibromomethane and nucleophilic azide salts or a polymeric azide reagent.<sup>15,16</sup> The intermediate azidochloromethane or azidobromomethane<sup>17</sup> could not be detected in these reactions,

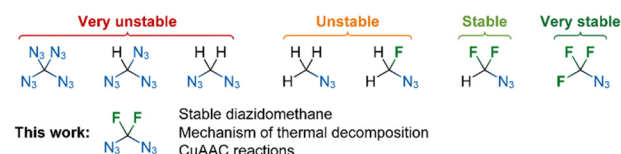


Fig. 1 Known and unknown fluorinated and non-fluorinated (poly)azidomethanes and their observed indicative stabilities/sensitivities. Very unstable – decomposes or explodes at rt. Unstable – slowly decomposes neat or in solution at rt. Stable – stable in solution for 1 h at <150 °C. Very stable – stable when heated to 150 °C neat or in solution.

even with substoichiometric amounts of azide salts, suggesting that the second halide displacement proceeds much faster than the first. Astonishingly, the whole family of azidomethanes from mono- to tetra-azidomethane is known; however, polyazidomethanes display explosive character (Fig. 1).<sup>18</sup>

Azidotrifluoromethane is a much more stable compound than azidomethane. Whereas azidomethane is a sensitive compound at room temperature, azidotrifluoromethane is safe to use in solution at temperatures below 150 °C.<sup>5</sup> It has been reported to decompose at 330 °C (ref. 19) (or above 1120 K in another report).<sup>20</sup> This is reflected in large differences between decomposition lifetimes ranging from a few hours (experimental value for CH<sub>3</sub>N<sub>3</sub>) to several years (calculated value for CF<sub>3</sub>N<sub>3</sub>) at 200 °C.<sup>21</sup> The reasons for this increased stability are not fully understood; nevertheless, activation barriers for the decomposition of azidomethanes into nitrenes are much higher for CF<sub>3</sub>N<sub>3</sub> than for CH<sub>3</sub>N<sub>3</sub>.

Taking these facts into account, we set out to synthesize diazodifluoromethane and investigate its stability and reactivity. The target compound is a new fluorinated one-carbon azide, potentially more stable and safer-to-use derivative of diazidomethane, which is unusable in synthesis.

At first, the synthetic strategy for obtaining diazodifluoromethane based on the nucleophilic displacement of a leaving group, for example, from commercial dibromodifluoromethane with azide salts, seemed unfeasible. Fully substituted

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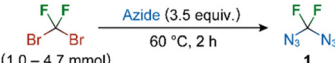
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† Electronic supplementary information (ESI) available. CCDC2382300 and 2382301. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4cc05128a>





**Table 1** Optimization of the preparation of diazodifluoromethane (**1**)<sup>a</sup>

				
Entry	Azide	Additive (10 mol%)	Solvent	Yield of <b>1</b> <sup>b</sup> (%)
1	NaN <sub>3</sub>	—	DMF	0
2	( <i>n</i> -Bu <sub>4</sub> N)N <sub>3</sub>	—	DMF	20
3	( <i>n</i> -Bu <sub>4</sub> N)N <sub>3</sub>	—	NMP	17
4	( <i>n</i> -Bu <sub>4</sub> N)N <sub>3</sub>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> SNa	DMF	39
5	[ <i>n</i> -Bu <sub>3</sub> P( <i>n</i> -C <sub>16</sub> H <sub>33</sub> )]N <sub>3</sub>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> SNa	DMF	27
6	NaN <sub>3</sub>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> SNa	NMP	15
7	NaN <sub>3</sub>	<i>n</i> -C <sub>12</sub> H <sub>25</sub> SNa	DMF	67 <sup>c</sup>

<sup>a</sup> See the ESI for more extensive optimization table. <sup>b</sup> <sup>19</sup>F NMR yield of **1** in the crude reaction mixture. <sup>c</sup> <sup>19</sup>F NMR yield of a solution of **1** obtained after the addition and distillation of THF (30 ml).

(per)fluoroalkyl halides do not undergo nucleophilic substitution. However, the azide anion is highly nucleophilic and sterically undemanding, and the substitution of the bromine atom in bromodifluoromethylated aromatics (ArCF<sub>2</sub>Br) with sodium azide to form ArCF<sub>2</sub>N<sub>3</sub> is known to proceed under mild conditions (50 °C in DMF), probably *via* an S<sub>RN</sub>1 mechanism rather than an S<sub>N</sub>2 or S<sub>N</sub>1 mechanism.<sup>22</sup>

The reaction of dibromodifluoromethane with an excess of sodium azide under elevated temperature in DMF did not lead to the target azide **1** (Table 1, entry 1). The same results were obtained when the reaction was performed in water, THF, MeCN or 1,2-dimethoxyethane solvents. When tetrabutylammonium azide was used instead of sodium azide in DMF or NMP, low product yields were observed (entries 2 and 3). A breakthrough was achieved when the additive sodium dodecylthiolate was used in a catalytic amount (entry 4). The addition of a low-boiling solvent (THF) followed by distillation afforded a solution of **1** in good yield. However, the product was contaminated with unreacted dibromodifluoromethane. The preparation of **1** was therefore scaled-up to 1 g (4.7 mmol) of the starting dibromodifluoromethane with the same efficiency. Pure, neat **1** was obtained by distillation of the reaction mixture without the addition of a low-boiling solvent.

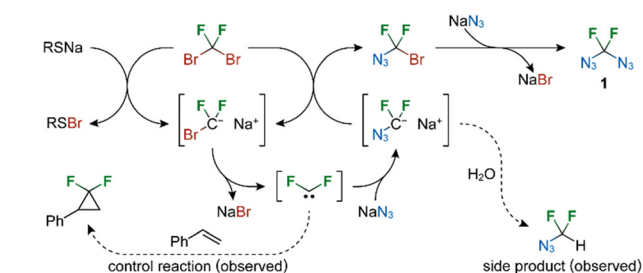
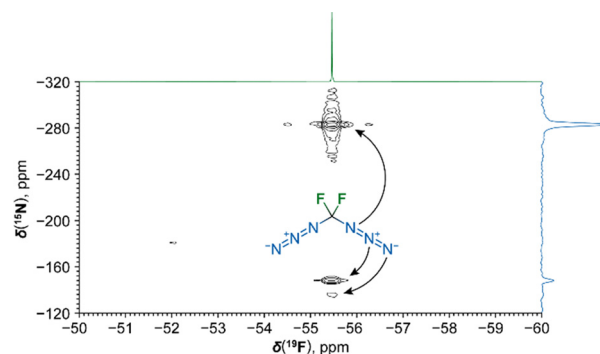
Considering the mechanism by which **1** is formed, the fact that the additive sodium dodecylthiolate was required for the efficient formation of **1** suggested the occurrence of bromophilic attack and that the reaction proceeds *via* difluorocarbene (Scheme 1). The presumed intermediate azidobromodifluoromethane was never identified, suggesting that the second

bromine substitution is a fast process. Radical intermediates are most probably not involved as control experiments with equimolar amounts of TEMPO or 1,1-diphenylethylene did not decrease the yield of **1** and did not show significant amounts of new fluorinated products. Further indirect support for the proposed reaction mechanism was provided by the <sup>1</sup>H and <sup>19</sup>F NMR observation of a small amount of N<sub>3</sub>CF<sub>2</sub>H as a side-product in a reaction conducted in wet DMF. This azide resulted from the protonation of unstable carbanion intermediate N<sub>3</sub>CF<sub>2</sub>Na. The addition of styrene led to the formation of a difluorocyclopropane product (detected by <sup>19</sup>F NMR), proving the formation of a difluorocarbene intermediate.

Compound **1** was characterized by <sup>19</sup>F, <sup>13</sup>C, <sup>15</sup>N NMR and infrared ( $\nu(\text{N}_3)$  2154 cm<sup>-1</sup>) spectroscopy and high-resolution mass spectrometry of [CF<sub>2</sub>N<sub>3</sub> + H]<sup>+</sup> and [CF<sub>2</sub>N]<sup>+</sup> fragments of **1** (no molecular signal was observed). An <sup>19</sup>F and <sup>15</sup>N gradient-enhanced HMBC NMR experiment revealed the topology of the diazidomethane molecule (Fig. 2).

The possible low stability and potentially explosive nature of **1** was of concern. However, we never observed any violent decomposition when handling any solution of **1**. A fall-hammer test (sensitivity to impact) at energy level of 50 J of a THF solution of **1** (0.1 M) turned out negative, which means that this solution can be considered not sensitive to impact according to UN and EU legislation. However, on one occasion a drop of neat **1** violently decomposed upon contact with a rough glass surface, so care should be taken even when handling a solution of **1**, similarly when handling a diazomethane solution. It can be expected that compound **1** is sensitive to excessive heat.

We calculated activation Gibbs free energies ( $\Delta G^\ddagger$ ), rate constants (*k*) and lifetimes for the decomposition of all possible fluorinated and non-fluorinated (poly)azidomethanes in the gas phase and in THF solution at 300 K and 473.15 K at the *ab initio* DLPNO-CCSD(T)/aug-cc-pVQZ level<sup>23,24</sup> with thermal corrections from PBE0/6-31+g\* calculations.<sup>25</sup> Geometries were optimized at the PBE0/6-31+g\* level. For each (poly)azidomethane, the  $\Delta G^\ddagger$  value includes all the transition states, corresponding to all the azide groups present (see the ESI† for details). The rate constants were evaluated using the Eyring–Polanyi equation. The data for the gas phase and solutions represented by a dielectric continuum were very similar. It was observed that starting from azidomethane, the formal substitution

**Scheme 1** Proposed mechanism of the formation of **1** (*R* = *n*-dodecyl).**Fig. 2** <sup>19</sup>F–<sup>15</sup>N gradient-enhanced HMBC NMR spectrum of **1**.

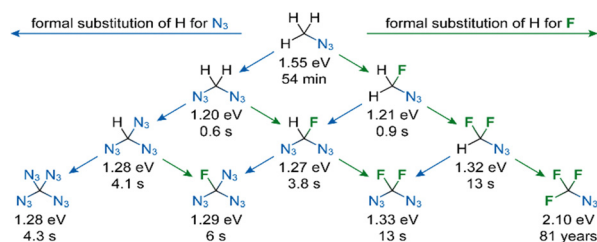


Fig. 3 Calculated activation Gibbs free energies ( $\Delta G^\ddagger$ ) in eV and lifetimes for the decomposition of (poly)azidomethanes in the gas phase at 200 °C.

of a hydrogen atom for an azido group or fluorine atom resulted in highly destabilized azides (Fig. 3, second row). Interestingly, further formal substitutions of hydrogens for  $N_3$  or F stabilized the azides, with  $CF_3N_3$  standing out as the most stable member of the family (Fig. 3, third and fourth rows). The indicative stabilities of known azides roughly correspond to these computed values. Furthermore, the calculations make it possible to predict that the unknown fluorinated polyazidomethanes  $CHF(N_3)_2$  and  $CF(N_3)_3$  are relatively unstable compounds, albeit more stable than  $CH_2(N_3)_2$ . Although the lifetime of **1** is predicted to be 13 s at 200 °C, it is actually about 400 years at room temperature.

The reaction mechanism of the decomposition of diazidodifluoromethane was revealed by *ab initio* computation in the gas phase using the same method. After losing a dinitrogen molecule the nitrene product  $N_3CF_2N$  undergoes a barrier-less decomposition forming difluorodiazirine,<sup>26</sup> a compound previously reported to be prepared by a multistep synthesis and known to quickly decompose into difluorocarbene, which can dimerize to form tetrafluoroethylene. Calculated activation Gibbs free energies and rate constants are presented in Fig. 4.

The prepared diazidodifluoromethane (**1**) was used in copper(i)-catalysed azide-alkyne cycloaddition (CuAAC) to afford bis(1,2,3-triazoles) **2** with a difluoromethylene linking unit (Table 2). The reaction proceeded with terminal alkynes and catalytic copper(i) 3-methylsalicylate (CuMeSal) as a THF-soluble catalyst at ambient temperature.

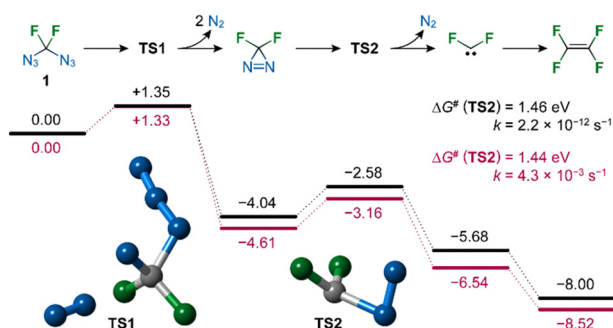


Fig. 4 Calculated activation Gibbs free energies ( $\Delta G^\ddagger$ ) and rate constants ( $k$ ) for the decomposition of diazidodifluoromethane in the gas phase at 300 K (black lines and values) and 473.15 K (red lines and values). The corresponding transition state structures are shown (colour codes: black – carbon, blue – nitrogen, green – fluorine). The lowest energy transition states are shown.

Table 2 Scope of the CuAAC reaction of diazidodifluoromethane (**1**)

$N_3CF_2N + R \equiv C \xrightarrow[THF, rt, 16 h]{CuMeSal (2 mol\%)} R-C_6H_4-N=N-CF_2-N=N-C_6H_4-R$	
<b>1</b> (1 mmol)	(2.1 equiv.)
<b>2a</b> , 89%	<b>2b</b> , 80%
<b>2c</b> , 70%	<b>2d</b> , 90%
<b>2e</b> , 64%	<b>2f</b> , 80%
<b>2g</b> , 67%	<b>2h</b> , 82%
<b>2i</b> , 71%	<b>2j</b> , 73%

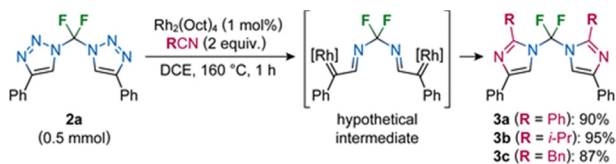
Aromatic acetylenes with electron-neutral, -withdrawing, or -donating groups participated efficiently in the reaction, as did *m*-pyridyl, alkyl and cycloalkyl acetylenes. Diverse functional groups, such as alkoxy, alkoxy carbonyl, halogen, trifluoromethyl and heterocyclic groups were well tolerated. The products (**2**) are stable solids.

The crystal structure of **2d** (CCDC 2382300†) confirmed the bis(triazole) structure and revealed the conformation in the solid state where the nitrogen atoms of the triazole rings point to the same side of the molecule.

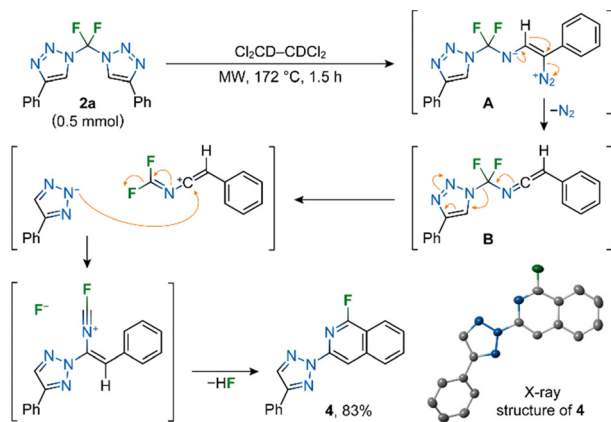
Using an excess of azide **1**, *N*-azidodifluoromethyl-containing triazole **2f'** was prepared and isolated from side-product bis(triazole) **2f**. A similar *N*-azidodifluoromethyl triazole was prepared by us in three steps from  $PhSO_2CF_2N_3$ .<sup>27</sup>

Differential scanning calorimetry measurement of **2a** revealed two endotherms, one at 157 °C and the other at 159 °C, that correspond to a mesophase transition and melting, respectively. A large exotherm with an onset at 163 °C and a maximum at 184 °C, corresponding to exothermic decomposition followed. We exploited this thermal decomposition behaviour by microwave heating of **2a** with benzonitrile, isobutyronitrile and phenylacetone in the presence of an Rh(II) catalyst in double transannulation reactions affording bis(imidazoles) **3a–3c** in excellent yields (Scheme 2).

On the other hand, microwave heating of **2a** in the absence of a catalyst or nitrile led to the formation of derivative 1-fluoroisoquinoline **4** in high yield (Scheme 3). The reaction most probably proceeds through the formation of vinyl diazonium **A** and ketenimine **B**, which undergoes a triazole ring shift



Scheme 2 Rh(II)-catalysed transannulation of bis(triazole) **2a** to bis(imidazoles) **3**.



Scheme 3 Thermal decomposition of bis(triazole) **2a**.

and  $S_EAr$  cyclization to **4**. Compound **4** (CCDC 2382301<sup>†</sup>) is the first example of a 1-fluoro-3-(2H-1,2,3-triazol-2-yl)isoquinoline structure.

In conclusion, a new diazidomethane  $CF_2(N_3)_2$  was prepared from dibromodifluoromethane by halogen substitution with nucleophilic azide salts in the presence of a thiolate additive which enables the reaction by acting as a bromophilic initiator. In contrast to other known polyazidomethanes, the new azide product is stable in solution. An *ab initio* study revealed trends in the stabilities of all possible fluorinated and non-fluorinated (poly)azidomethanes showing that diazidodifluoromethane is much more stable than diazidomethane. The computed reaction mechanism of the decomposition of the title azide suggests that it can proceed *via* difluorodiazirine and difluorocarbene intermediates. CuAAC of the title azide with terminal alkynes provided symmetrical difluorinated bis(1,2,3-triazoles) with high efficiency. The bis(triazoles) are amenable to Rh(II)-catalysed transannulation with nitriles to bis(imidazoles) or thermally decompose in an unprecedented way into a new 1-fluoroisoquinoline. This work demonstrates that diazidodifluoromethane can be obtained in a straightforward way and that it is stable enough to be used in synthesis to access new selectively fluorinated nitrogen heterocycles.

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## Data availability

The data supporting this article have been included as part of the ESI.<sup>†</sup>

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- O. Bakhanovich and P. Beier, *Chem. – Eur. J.*, 2020, **26**, 773.
- A. Markos, V. Matoušek and P. Beier, *Aldrichimica Acta*, 2022, **55**, 37.
- T. Saal, Z. E. Blastik, R. Haiges, A. Nirmalchandrar, A. F. Baxter, K. O. Christe, M. Vasiliu, D. A. Dixon, P. Beier and G. K. S. Prakash, *Angew. Chem., Int. Ed.*, 2020, **59**, 12520.
- N. Baris, M. Dračinský, J. Tarábek, J. Filgas, P. Slaviček, L. Ludvíková, S. Boháčová, T. Slanina, B. Klepetářová and P. Beier, *Angew. Chem., Int. Ed.*, 2024, **63**, e202315162.
- Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová and P. Beier, *Angew. Chem., Int. Ed.*, 2017, **56**, 346.
- Y. Cai, H. Jiang and C. Zhu, *Adv. Synth. Catal.*, 2023, **365**, 342.
- X. Wang, S. Liu, S. Xu, S. Wu, J. Wu and F. Wu, *Org. Chem. Front.*, 2024, **11**, 2054.
- C. Barrett, A. Alagaratnam, A. Knieb, C. J. Koch and G. K. S. Prakash, *Org. Lett.*, 2024, **26**, 6385.
- V. Motornov, A. Markos and P. Beier, *Chem. Commun.*, 2018, **54**, 3258.
- V. Motornov and P. Beier, *J. Org. Chem.*, 2018, **83**, 15195.
- O. Bakhanovich, B. Klepetářová and P. Beier, *Org. Biomol. Chem.*, 2023, **21**, 7924.
- A. Markos, S. Voltrová, V. Motornov, D. Tichý, B. Klepetářová and P. Beier, *Chem. – Eur. J.*, 2019, **25**, 7640.
- A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-Seara, B. Klepetářová and P. Beier, *Adv. Synth. Catal.*, 2021, **363**, 3258.
- A. Kubičková, A. Markos, S. Voltrová, A. Marková, J. Filgas, B. Klepetářová, P. Slaviček and P. Beier, *Org. Chem. Front.*, 2023, **10**, 3201.
- A. Hassner and M. Stern, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 478.
- A. Hassner, M. Stern, H. E. Gottlieb and F. J. Frolow, *J. Org. Chem.*, 1990, **55**, 2304.
- K. Banert, Y.-H. Joo, T. Rüffer, B. Walfort and H. Lang, *Tetrahedron Lett.*, 2010, **51**, 2880.
- K. Banert, Y.-H. Joo, T. Rüffer, B. Walfort and H. Lang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1168.
- S. P. Makarov, A. Y. Yakubovich, A. S. Filatov, M. A. Englin and T. Y. Nikiforova, *Zh. Obshch. Khim.*, 1968, **38**, 709.
- H. Bock, R. Dammel and D. D. Desmarteau, *Z. Naturforsch. B*, 1987, **42**, 308.
- S. Voltrová, J. Filgas, P. Slaviček and P. Beier, *Org. Chem. Front.*, 2020, **7**, 10.
- A. Haas, M. Spitzer and M. Lieb, *Chem. Ber.*, 1988, **121**, 1329.
- C. Riplinger and F. Neese, *J. Chem. Phys.*, 2013, **138**, 034106.
- F. Neese, F. Wennmohs, U. Becker and C. Riplinger, *J. Chem. Phys.*, 2020, **152**, 224108.
- C. Adamo, M. Cossi and V. Barone, *J. Mol. Struct.:THEOCHEM*, 1999, **493**, 145.
- R. A. Moss, L. Wang and K. Krogh-Jespersen, *J. Am. Chem. Soc.*, 2009, **131**, 2128.
- M. Ziabko, B. Klepetářová and P. Beier, *J. Org. Chem.*, 2023, **88**, 6939.

