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N-(Propargyl)diazenecarboxamides for 'click' conjugation and their 1,3-dipolar cycloadditions with azidoalkylamines in the presence of Cu(II)

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ABSTRACT

Propargyl functionalized diazenes **1** were prepared by two different approaches and were examined as alkyne click components in copper-catalyzed azide–alkyne cycloadditions (CuAAC) with 2-(azidomethyl)pyridine **5a** and four α-azido-ω-aminoalkanes C2–C5 (**5b–e**). Whereas the reactions with azidoalkylamines **5b–e** reached completion with copper(II) sulfate without the need of reducing agent typically in no more than few minutes, 2-(azidomethyl)pyridine **5a** required the addition of metallic copper and much longer reaction times (2–24 h). This difference in the reactivity was studied and addressed in terms of base effect and proximity effect to CuAAC.

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1. Introduction

We have developed diazenecarboxamides, subsequently referred to as diazenes (Fig. 1), as a new class of selective thiol-oxidizing agents.[1] In particular, we have been interested in the use of diazenes for the oxidation of glutathione (GSH), which constitutes one of the main cellular defenses against xenobiotics, an important issue in anticancer therapy. Tested on different tumor-cell lines, diazenes have been recognized as GSH-depleting agents, and cytotoxic activity for several tumor-cell lines and their drug-resistant sublines have been established.[2,3] In addition, recent studies indicated that GSH may not be the only cellular target of diazenes and their mode of action has yet to be elucidated.[2j]

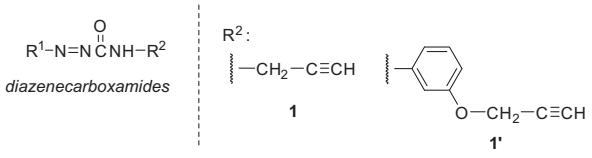

Figure 1. *N*-Alkyl (**1**) and *N*-aryl (**1′**) substituted diazenecarboxamides.

The oxidative efficiency and consequently the bio-activity of diazenes depend on the choice of the appropriate substituent R^1, while R^2 attached to the amide nitrogen only seems to have marginal influence.[1,2] This makes R^2 amenable for structural modifications, which can be achieved by introduction of a specific tag having desired electronic and steric characteristics, solubility, liphophilicity, etc. To prepare and subsequently test a library of thus modified diazenes, yet to avoid a redesign of the synthetic routes for any specific tag followed by time consuming preparative work, we recently reported an approach, which is based on the concept of a marked library, where each diazene library member carried propargyl group at R^2 (**1′**, Fig. 1).[4] The propargyl group has been selected because it can relatively easy be introduced into the parent molecule, it is stable in the course of diazene preparation, and it can readily be coupled with orthogonally reactive azides by copper-catalyzed azide–alkyne cycloaddition (CuAAC).[5,6] We have shown that tagged diazenes **1′** allow through CuAAC a convenient entry into a library of different ligand arm-functionalized analogs, a novel scaffold as ligands for platinum complexation. The propargyl group is a small biocompatible marker and its incorporation into the diazene library may also find other applications, such as diazene target identification process, etc.[7]

Our recent work has been focused on marked *N*-aryl substituted diazenes **1′**,[4] however, to gain a broader view on chemistry and biochemistry of marked diazenes, there is an urge for structurally related derivatives, such as *N*-alkyl analogs **1** (Fig. 1). In this paper, we describe the synthesis of *N*-(propargyl)diazenecarboxamides **1**, and their application in the synthesis of ligand arm-functionalized diazenes. The latter will be used for coordination to metal ions and subsequent bio-evaluation.

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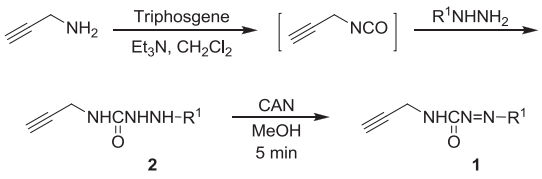
2. Results and discussion

2.1. Synthesis of diazenes 1

As diazenes are in general conveniently prepared by the addition of hydrazines to isocyanates,[8] with subsequent oxidation of the resulting semicarbazides,[1,9] this route initially seemed to be an attractive choice for the synthesis of **1** (Scheme 1, Table 1). Thus, propargylamine was transformed with triphosgene[10] into propargyl isocyanate in situ, which was then allowed to react with selected hydrazines. In contrast with our previous experiences in this field,[4,9] unsatisfactorily low overall yields of semicarbazides **2a–c** (Table 1, entries 1–3) were obtained. Furthermore, 4-methoxyphenylhydrazine and 2-hydrazinopyridine only afforded complex mixtures of products from which semicarbazides could not be isolated (Table 1, entries 6 and 7). These results could be accounted for by specific reactivity of propargylamine and its derivatives,[11] however, no attempts were made to analyze byproducts of the above reactions. The resulting semicarbazides **2a–e** were oxidized with cerium(IV) ammonium nitrate (CAN)[1,4,12] in methanol to diazenes **1a–e**. A simple extractive workup afforded the products in excellent yields with more than 95% purity, as determined by ^{1}H NMR.



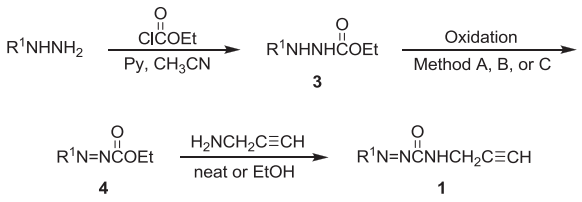
Scheme 1. Synthesis of semicarbazides **2** and diazenes **1**.

Table 1
Synthesis of diazenes **1** according to Scheme 1

Entry	R^1	**2**, Yield (%)[a]	**1**, Yield[a] (%)
1	C_6H_5–	**2a**, 25	**1a**, 99
2	4-CH_3–C_6H_4–	**2b**, 37	**1b**, 96
3	4-Cl–C_6H_4–	**2c**, 23	**1c**, 97
4	4-CF_3–C_6H_4–	**2d**, 88	**1d**, 100
5	C_6F_5–	**2e**, 81	**1e**, 100
6	4-CH_3O–C_6H_4–	—[b]	
7	2-Py	—[b]	

[a] Refers to yield of isolated pure product.
[b] Complex mixture of products was obtained.

Cumbersome isocyanate preparation, combined with disappointing yields of semicarbazides **2**, prompted us to seek for an alternative pathway to compounds **1**. Following the reaction sequence shown in Scheme 2, hydrazines were derivatized with ethyl chloroformate (ClCOOEt) into ethyl hydrazinecarboxylates **3a–i** (Table 2). Besides CAN, several other oxidants have been previously reported to selectively oxidize hydrazine derivatives, including nitric acid[13] and *N*-bromosuccinimide (NBS)/Py.[14] All these three oxidants were employed in our work for the oxidation of hydrazines **3** and provided the desired ethyl diazenecarboxylates **4a–i** in excellent yields, as shown in Table 2. Although slightly higher yields of compounds **4** were seen by employing NBS/Py, from an ecological and economical point of view, nitric acid proved to be superior when working on larger scales. In the last step of this preparative sequence, the ethoxy group in esters **4** was substituted with propargylamine as a nucleophile to afford diazenes **1** in quantitative isolated yields.



Scheme 2. Alternative approach to diazenes **1** via ethyl hydrazinecarboxylates **3** and ethyl diazenecarboxylates **4**.

Table 2
Synthesis of diazenes **1** according to Scheme 2[a]

Entry	R^1	**3**, Yield[b,c]	**4**, Yield[b] (Method[a])	**1**, Yield[b]
1	C_6H_5–	**3a**, 100	**4a**, 100 (A) **4a**, 100 (B) **4a**, 93 (C)	**1a**, 100
2	4-CH_3–C_6H_4–	**3b**, 96	**4b**, 72 (A) **4b**, 87 (B) **4b**, 86 (C)	**1b**, 100
3	4-Cl–C_6H_4–	**3c**, 96	**4c**, 84 (A) **4c**, 95 (B) **4c**, 98 (C)	**1c**, 100
4	4-CF_3–C_6H_4–	**3d**, 86	**4d**, 82 (A) **4d**, 92 (B) **4d**, 97 (C)	**1d**, 100
5	4-CH_3O–C_6H_4–	**3f**, 44	**4f**, 84 (A) **4f**, 88 (B) **4f**, 98 (C)	**1f**, 100
6	4-F–C_6H_4–	**3g**, 74	**4g**, 76 (A) **4g**, 91 (B) **4g**, 98 (C)	**1g**, 100
7	4-NO_2–C_6H_4–	**3h**, 92	**4h**, 67 (A) **4h**, 89 (B) **4h**, 100 (C)	**1h**, 100
8	2-Py	**3i**, 66	**4i**, 62 (A) **4i**, 83 (B) **4i**, 98 (C)	**1i**, 99

[a] Methods: A: **3** (1.0 mmol), CAN (2.2 mmol), MeOH (10 mL), room temperature, 5 min; B: **3** (30 mmol), $NaNO_2/H_2O$ (63 mmol/150 mL), 80% aq HOAc (150 mL), 0 °C then room temperature 1 h; C: **3** (1.0 mmol), NBS (1.1 mmol), pyridine (2.8 mmol), CH_2Cl_2 (7 mL), 30 min.
[b] Refers to percent yield of isolated pure product.
[c] Using modified literature procedures. See Experimental section.

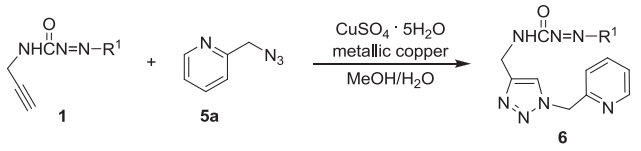
Although is seems that this substitution reaction at alkyl diazenecarboxylates could serve solely as a method for the preparation of differently tagged diazenes, several drawbacks associated with it are noteworthy. This substitution reaction only works well if conducted neat or at least in highly concentrated solutions and it is restricted to the aliphatic amines. Also inconveniently, alkyl diazenecarboxylates are moderately stable and should better be prepared just prior their use. Additionally, other nucleophilic sites potentially present at the amine partner would require suitable protective/deprotective work. On the other hand, *N*-(propargyl)diazenecarboxamides **1** are bench stable compounds and their conjugation by CuAAC is expected to render a desired functionalization quantitative even at low concentrations, and to be orthogonal with other chemistries.[6]

2.2. Cycloaddition reactions with diazenes 1

With diazenes **1** in hands, we tested CuAAC reaction to 2-(azidomethyl)pyridine (**5a**) and 1-azido-2-aminoethane (**5b**). We recently reported that owing to the specific chemical reactivity of propargyl marked diazenes **1′** (Fig. 1), including some solubility issues, typical Sharpless conditions for CuAAC failed.[4] Diazenes were not tolerated by sodium ascorbate, most commonly used for

the reduction of Cu^{II} into Cu^{I}, whereas the use of Cu^{I} salt such as $(CF_3SO_3Cu)_2 \cdot C_6H_6$, either without additives or in combination with Cu^{I}-stabilizing tris-(benzyltriazolylmethyl)amine (TBTA),[15] failed. Successfully overcoming these issues[4] by employing Cu^{II}/Cu^{0} couple for the in situ generation of catalytic Cu^{I} species stimulated us to apply this protocol also for diazenes (hereafter referred to as alkynes) **1**.

In the first part, CuAAC reaction between alkynes **1a–d,f–i** and azide **5a** was investigated, as shown in Scheme 3. After exposing the reactants to copper(II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) and metallic copper in wet methanol, clean conversion into the desired products **6a–d,f–g** was observed within 2 h (Table 3). Consistently, higher loading of $CuSO_4 \cdot 5H_2O$ resulted in shorter reaction times (compare entries 3 and 4). A longer reaction time in the case of **1h** (entry 8) was associated with its low solubility. Alkyne **1i**, immediately after being exposed to the copper catalyst, decomposed to a tarry material with no trace amounts of the desired product. The products **6a–d,f–h** were isolated in excellent yields by extractive workup with saturated aqueous ammonium chloride and dichloromethane. Consistent with our previous report,[4] the aqueous ammonium chloride workup was effective in extracting copper ions from the product.



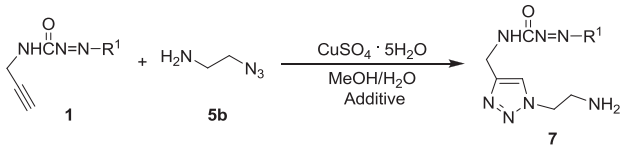
Scheme 3. Formation of triazole **6** by CuAAC between **1** and **5a**.

Table 3
Synthesis of triazole **6** (Scheme 3)[a]

Entry	1	R^1	Reaction time	**6**, Yield[b] (%)
1	**a**	C_6H_5–	2 h	**6a**, 99
2	**b**	4-CH_3–C_6H_4–	2 h	**6b**, 98
3	**c**	4-Cl–C_6H_4–	2 h	**6c**, 98
4	**c**	4-Cl–C_6H_4–	40 min[c]	**6c**, 95
5	**d**	4-CF_3–C_6H_4–	2 h	**6d**, 99
6	**f**	4-CH_3O–C_6H_4–	2 h	**6f**, 99
7	**g**	4-F–C_6H_4–	2 h	**6g**, 98
8	**h**	4-NO_2–C_6H_4–	24 h	**6h**, 93
9	**i**	2-Pyridyl		**6i**, 0

[a] Reaction conditions: **1**, **5a** (1.05 equiv), $CuSO_4 \cdot 5H_2O$ (2.5 mol %), granular copper (1.8 equiv), wet MeOH (80%, 4 mL/mmol of **1**), air, room temperature.
[b] Yield of isolated pure product.
[c] $CuSO_4 \cdot 5H_2O$ (5.0 mol %) was used.

Next, we examined 1-azido-2-aminoethane (**5b**) as a click component (Scheme 4). Unexpectedly, by mixing alkynes **1a–c** with azide **5b** under the identical reaction conditions as for **5a** resulted in almost instant formation of the desired products **7a–c** (entries 1, 3, and 5 in Table 4). The role of Cu^{0} is to reduce (i.e., comproportionate with) Cu^{II}. However, the rate of the formation of triazoles **7a–c** appeared too fast to be affected by presumably relatively slow dosing (due to the heterogeneity of the system) of Cu^{I} into the reaction mixture by comproportionation.[16] This assumption was verified by repeating the experiments from entries 1, 3, and 5 in the absence of metallic copper. Alkynes **1a–c** were exposed to azide **5b** and $CuSO_4 \cdot 5H_2O$ in wet methanol. As expected, prompt and quantitative cycloaddition into triazoles **7a–c** took place, as demonstrated in Table 4, entries 2, 4, and 6. Other alkynes **1d,f,h** tested, worked similarly. The reactions were conducted under aerobic conditions but the same outcome was seen by aerial oxygen exclusion. No reaction could be observed in the absence of $CuSO_4 \cdot 5H_2O$. In this case too, the cycloaddition of alkyne **1i** was unsuccessful, yielding tarry material (Table 4, entry 10).



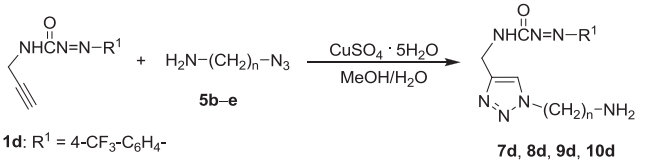
Scheme 4. Formation of triazole **7** by CuAAC between **1** and **5b**.

Table 4
Synthesis of triazole **7** (Scheme 4)[a]

Entry	1	R^1	Additive	Time (min)	**7**, Yield[b]
1	**a**	C_6H_5–	Copper[c]	5	**7a**, 80
2	**a**	C_6H_5–	—[d]	5	**7a**, 97
3	**b**	4-CH_3–C_6H_4–	Copper[c]	5	**7b**, 90
4	**b**	4-CH_3–C_6H_4–	—[d]	5	**7b**, 69
5	**c**	4-Cl–C_6H_4–	Copper[c]	5	**7c**, 96
6	**c**	4-Cl–C_6H_4–	—[d]	5	**7c**, 86
7	**d**	4-CF_3–C_6H_4–	—[d]	5	**7d**, 94
8	**f**	4-CH_3O–C_6H_4–	—[d]	10	**7f**, 65
9	**h**	4-NO_2–C_6H_4–	—[d]	10	**7h**, 74
10	**i**	2-Pyridyl	—[d]		—[e]

[a] Reaction conditions: **1**, **5b** (1.05 equiv), $CuSO_4 \cdot 5H_2O$ (2.5 mol %), wet MeOH (80%, 4 mL/mmol of **1**), air, room temperature.
[b] Refers to percent yield of isolated pure product.
[c] Granular copper (1.8 equiv relative to **1**) was added.
[d] Without additives.
[e] Complex reaction mixture was formed. See text.

Longer chain analogs of 1-azido-2-aminoethane, compounds **5c–e**, were also examined as click components in CuAAC with a selected alkyne, that of **1d** (Scheme 5, Table 5). Interestingly, in comparison with lower homologs C2–C4 (**5b–d**), the reaction of 1-azido-5-aminopentane (**5e**) was retarded (entry 3).



Scheme 5. α-Azido-ω-aminoalkanes **5b** (n=2), **5c** (n=3), **5d** (n=4), and **5e** (n=5) as click components.

Table 5
α-Azido-ω-aminoalkanes **5b–e** and **1d** as click components (Scheme 5)[a]

Entry	5	n	Reaction time (min)	Product, yield (%)[b]
1	**b**	2	5	**7d**, 72
2	**c**	3	5	**8d**, 77
3	**d**	4	5	**9d**, 91
4	**e**	5	30	**10d**, 99

[a] Reaction conditions: **1d**, **5** (1.5 equiv), $CuSO_4 \cdot 5H_2O$ (5 mol %), wet MeOH (50%, 10 mL/mmol of **1d**), argon, room temperature.
[b] Isolated pure product.

All CuAAC reactions under this investigation were regioselective, resulting in 1,4-disubstituted-1,2,3-triazoles. On selected examples, this was indicated by NOE between H-5 and the nearby protons of N-1 substituent of the triazole ring. Typical ^{1}H NMR chemical shift of the triazole H-5 proton, resonating at around δ 8.1 ppm, 7.7 ppm, and 8.45 ppm, for compounds **6**, **7–10**, and **11**, respectively, was seen.

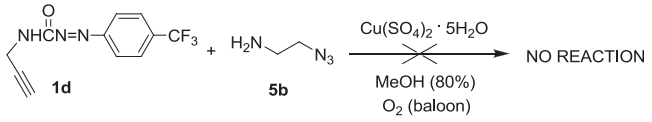
2.3. Mechanistic considerations of CuAAC between 1 and 5

The results from Tables 3 and 4 (as well as Table 5) reveal a striking azide-based difference in reactivity. In comparison with 2-(azidomethyl)pyridine (**5a**), unexpected rate enhancement is observed for cycloadditions with α-azido-ω-aminoalkanes (e.g., azide **5b**). The fact that in CuAAC reactions with the latter no

reducing agent was employed gains this difference even more pronounced. These observations raised several questions, including: (a) is Cu^{II} performing the cycloaddition of **5b**–**e**, and (b) what is the reason for high reactivity of **5b**–**e**, which will be addressed as follows.

2.3.1. Cu^{I} or Cu^{II}? Although there is a vast amount of evidence that Cu^{I} is the most likely species in CuAAC,[6] there are reports suggesting that Cu^{II} catalyzes the formation of triazole from alkyne and azide almost as effectively.[17] For these examples, however, it is also reasonable to assume an in situ reduction of Cu^{II} and stabilization of Cu^{I} by specific combinations of compounds present in the reaction mixtures. This alternative explanation should be considered because similar redox chemistry is precedented in copper catalysis.[18,19]

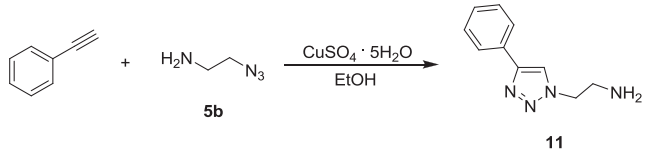
To gain some insight into the oxidation state of the catalytically active copper species in the CuAAC reactions with α-azido-ω-aminoalkanes shown in Schemes 4 and 5, we conducted the reaction between alkyne **1d** and 1-azido-2-aminoethane (**5b**) with $CuSO_4 \cdot 5H_2O$ in the presence of oxygen (Scheme 6).



Scheme 6.

Thus, $CuSO_4 \cdot 5H_2O$ was added into the mixture of **1d**, **5b**, and wet methanol, saturated with oxygen. A constant stream of oxygen gas through the resulting reaction mixture was maintained for 2 h, within which time no starting alkyne **1d** consumption and no triazole formation could be detected by TLC. The onset of the cycloaddition was seen after the oxygen gas was no longer introduced. These results indicate that Cu^{I} species are catalytically active in the reactions from Schemes 4 and 5 and must have been formed as indicated above.

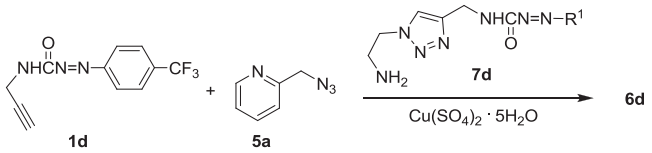
2.3.2. Substrate and ligand effect. The formation and stabilization of Cu^{I} in the reactions from Scheme 4 are associated with the presence of either azide **5b** or the triazole product **7** rather than the alkyne click component **1**. This was supported by the experiment in which $CuSO_4 \cdot 5H_2O$ (4 mol %) was added into the mixture of phenylacetylene (instead of **1**) and **5b** in wet methanol (Scheme 7). As judged by TLC analysis the reaction reached 100% completion in less than 10 min. Triazole **11** was isolated in 73% yield.



Scheme 7.

The ligand effect has been studied and it has been shown that some aliphatic amines and aromatic nitrogen containing compounds,[6k,20,21] including triazole-based[22] ligand TBTA,[15] greatly accelerate the rate of CuAAC reactions. A possibility that the reaction product **7** from Scheme 4 has similar effect on the reaction between **1** and **5b** (resulting in autocatalytic process) was tested by the experiment shown in Scheme 8 and the results are illustrated in Figure 2.

Incubating **5a**, **1d**, and $CuSO_4 \cdot 5H_2O$ in methanol at room temperature, the reaction reached approximately 10% completion in 4 h,



Scheme 8. CuAAC between alkyne **1d** and azide **5a** in the presence of triazole **7d** (R^1=4-CF_3–C_6H_4–). For results, see Figure 2.

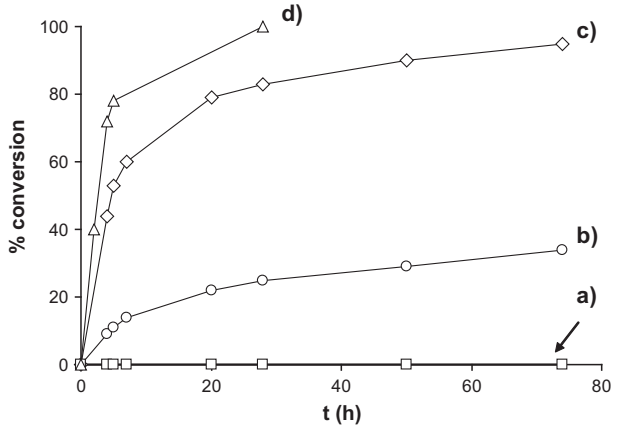
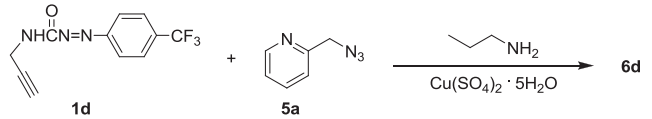


Figure 2. Formation of triazole **6d** (Scheme 8) in the reactions at 0.1 M in **1d** and **5a** in wet methanol (99%) at room temperature in the presence of: (a) without additives; (b) 10 mol % of $CuSO_4 \cdot 5H_2O$; (c) 10 mol % of $CuSO_4 \cdot 5H_2O$ and 10 mol % of **7d**; (d) 10 mol % of $CuSO_4 \cdot 5H_2O$ and 25 mol % of **7d**. The reaction was monitored by disappearance of **5a** by GC against an internal standard (PhBr). The clean conversion to triazole **6d** was confirmed by TLC. % Conversion refers to 100%−percent of unreacted **5a**.

whereas the use of 0.10 equiv or 0.25 equiv of ligand **7d** with respect to the substrates gave 45 and 75% completion, respectively, in the same time. No reaction occurred in the absence of $CuSO_4 \cdot 5H_2O$, excluding the possibility of uncatalyzed thermally driven process.

These results imply that the 1-(2-aminoethyl)-1,2,3-triazole moiety of **7** might be the CuAAC rate accelerator. However, an assumption that the mode of its action is associated with the chelation of catalytic Cu^{I} species with the aliphatic amine nitrogen and N-2 atom of the 1,2,3-triazole is against the recent reports that such chelates (known as inverse click chelates) are disfavored.[23,24]

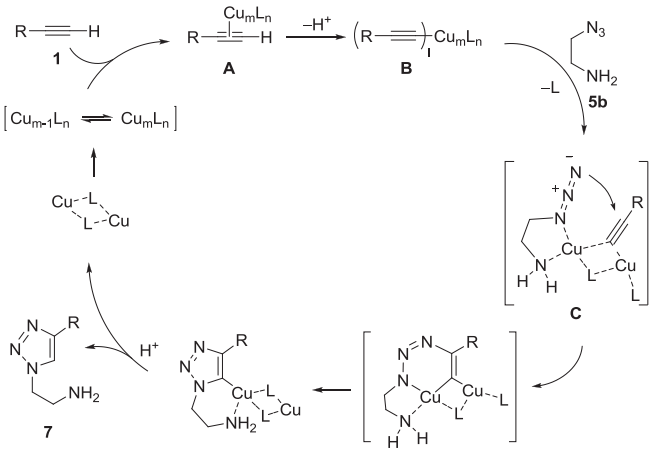
2.3.3. Basicity of additives. Basicity of additives is another important issue that should be considered. In general, more basic conditions promote CuAAC reaction by deprotonation of Cu^{I}/alkyne π-complex **A**, facilitating the formation of Cu-acetylide intermediate **B** (Scheme 10). In line with this, it has been reported that in comparison to pyridine-based ligands ($pK_{b\ (pyridine)}$ 8.75) aliphatic amine ligands ($pK_{b\ (alkylamines)}$ 3–5) facilitate CuAAC reactions more efficiently.[21] To examine the function of the alkylamine structural element present in **5b**–**e**, as well as their corresponding triazole products **7**–**10**, we conducted an experiment similar to that from Scheme 8 in which propylamine (pK_b 3.3) was used instead of **7d**. Thus, in the reaction at 0.1 M in **1d** and **5a** in wet methanol (99%) in the presence of 10 mol % of $CuSO_4 \cdot 5H_2O$ and 25 mol % of propylamine the formation of triazole **6d** was monitored by TLC (Scheme 9). The reaction reached completion in 25 min.



Scheme 9. CuAAC between alkyne **1d** and azide **5a** in the presence of propylamine.

Comparing the results of α-azido-ω-aminoalkanes **5b**–**e** (from Table 5) as click components with those from Scheme 9 it is seen

that propylamine assists CuAAC reaction as efficiently as 5-azido-1-aminopentane (**5e**), but less than **5b**. This result, as well as different reactivities of **5b–d** in comparison with **5e** could be explained in terms of proximity effect. An interpretation, consistent with the currently accepted mechanism for CuAAC (Scheme 10),[6c,k] is that the aliphatic amine group of the azide **5b–e** participates as a ligand to the catalytically active Cu^{I} species, delivering azido moiety to the Cu-acetylide **B**, and thus increasing the local concentration of the azide in the intermediate **C**. To gain some evidence in this direction we estimated the relative reactivities of **5b–e** by simple competitive experiment in which alkyne **1d** (0.04 M) was in wet methanol (80%) reacted with a mixture of five-fold excess of each of the azide **5b–e** (0.20 M in each azide) in the presence of 25 mol % of $CuSO_4 \cdot 5H_2O$. The relative ratio of products **7d–9d**, determined on the basis of ^1H NMR integral measurements, revealed **5c** as the most reactive in the series. The relative rates followed the order **5c** (4.6)>**5b** (1)≫**5d** (<0.1)≈**5e** (<0.1). The less effective performance of higher homologs **5d,e** may be accounted for by less efficient bidentate coordination to copper and/or entropic factors. It is noteworthy that a dinuclear Cu^{II} complex[25,26] with 1-azido-2-pyrazolyl-cyclohexane is featuring similar connectivity as proposed for Cu^{I} intermediate **C** in Scheme 10.



Scheme 10. A drawing of the CuAAC mechanism as adopted from the literature[6k] with our logic explaining proximity effect in the reaction with 1-azido-2-aminoethane (**5b**). Ligand (L) exchange with **5b** could also take place at intermediate **A**, which may (in contrast to the pyridine ligand in **5a**)[21] take a part in the stabilization of Cu^{I}/alkyne π-complex **A**.

Interestingly, although azides **5b**[24,27] and **c**[27b,28] have previously been employed as reaction partners in CuAAC, similar reactivity has not yet been documented. The facile CuAAC reactions involving **5a** have been recently reported by Zhu et al.[19]

3. Conclusions

Routes to diazenes tagged with a propargyl handle were developed. These compounds were employed as click components in copper-catalyzed azide–alkyne cycloadditions (CuAAC) with two types of azides having pyridine and alkylamine side-chain. Whereas the reactions with 2-(azidomethyl)pyridine behaved in accord with the expected pattern for CuAAC, this was not the case for azidoalkylamines. The latter formed the corresponding triazoles much faster and interestingly, in combination with copper(II) sulfate, did not require any addition of the reducing agent. This difference in the reactivity was studied and addressed in terms of base effect and proximity effect to CuAAC.

We believe this study will help in deeper understanding of the CuAAC mechanism. More detailed and systematic investigation of the above observations including the issue of copper speciation among Cu^{II} and Cu^{I} oxidation states is beyond the scope of this paper and will be performed at more appropriate model substrates, rather than *N*-(propargyl)diazenecarboxamides.[29]

4. Experimental section

4.1. General

Reagents and solvents were used as purchased (Fluka, Aldrich, Alfa Aesar) unless otherwise noted. Triethylamine was dried and stored over KOH pellets in Ar atmosphere. Dichloromethane used for the preparation of isocyanates was distilled from P_2O_5. All syntheses involving isocyanates were performed under argon atmosphere using dry glassware and solvents. The reactions were monitored by TLC on TLC-CARDS SILICA GEL, 220–440 mesh. NMR spectra were recorded at 302 K on a Bruker Avance DPX 300 spectrometer operating at 300 MHz, 75 MHz, and 282 MHz for ^1H, ^{13}C, and ^{19}F, respectively, and Varian Unity Inova 600 MHz spectrometer, operating at 600 MHz for ^1H. Proton and carbon spectra were referenced to TMS as the internal standard. Some ^{13}C chemical shifts were determined relative to the ^{13}C signal of the solvent: $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm). ^{19}F NMR spectra were referenced to CCl_3F as external standard at δ=0. Chemical shifts are given on the δ scale (ppm). Coupling constants (*J*) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broadened). Mass spectra and high-resolution mass spectra were obtained with a VG-Analytical AutospecQ instrument and Q-TOF Premier instrument. Data are reported as *m*/*z* (relative intensity). Infrared spectra were recorded on a BIO-RAD Excalibur Series spectrophotometer using samples in potassium bromide disks or salt plates. Elemental analyses (C, H, N) were performed with a Perkin–Elmer 2400 Series II CHNS/O Analyzer. Melting points were determined on a Kofler block and are uncorrected.

Azides[30] 2-(azidomethyl)pyridine (**5a**),[31] 1-azido-2-aminoethane (**5b**),[32] 1-azido-3-aminopropane (**5c**),[33] 1-azido-4-aminobutane (**5d**),[33] 1-azido-5-aminopentane (**5e**),[33] were prepared as reported in the literature. Spectra of **5c–e** are reported in Ref. 34.

4.2. Typical procedure for the synthesis of semicarbazides 2a–c from in situ generated propargyl isocyanate and hydrazine hydrochlorides (Scheme 1, Table 1)

In a round-bottomed flask equipped with a stirring bar triphosgene (545 mg, 1.84 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under Ar. The reaction mixture was flushed with argon gas and the flask was capped with a septum. Under stirring a mixture of propargylamine (98%, 350 μL, 5.36 mmol) and triethylamine (1.51 mL, 10.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe at room temperature. The reaction mixture was stirred for 30 min. Then an appropriate hydrazine hydrochloride (5.00 mmol) was added, followed by second portion of triethylamine (0.76 mL, 5.5 mmol). The stirring was continued for 10 min under Ar. The reaction mixture was diluted with aq HCl (10^{-5} M, 100 mL). The organic layer was separated, and water layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and the solvent was evaporated to dryness. The residue was triturated in diethyl ether, cooled to 0 °C, and the precipitate was filtered to afford semicarbazide **2**.

*4.2.1. 2-Phenyl-N-(prop-2-ynyl)hydrazinecarboxamide (**2a**).* Off-white solid, mp 128–129 °C, yield: 237 mg (1.25 mmol), 25% (relative to phenylhydrazine hydrochloride). Found: C, 63.43; H, 5.91; N, 22.33. $C_{10}H_{11}N_3O$ requires C, 63.48; H, 5.86; N, 22.21%. ν_{max} (KBr) 3373, 3310, 3256, 3081, 1663, 1549, 1260, 1125, 890, 755, 620, 502 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.20 (1H, t, *J* 2.7 Hz), 4.08 (2H, dd, *J*

5.4, 2.7 Hz), 5.65 (1H, br s), 6.01 (2H, br s), 6.86 (2H, d, *J* 7.5 Hz), 6.97 (1H, t, *J* 7.5 Hz), 7.29 (2H, t, *J* 7.5 Hz); δ_C (75 MHz, DMSO-d_6) 28.6, 72.0, 82.5, 112.3, 118.7, 128.7, 149.4, 158.8; *m*/*z* (EI) 189 (42, M^+), 108 (100), 92 (28), 77 (30%).

*4.2.2. N-(Prop-2-ynyl)-2-p-tolylhydrazinecarboxamide (**2b**).* Off-white solid, mp 131–132 °C, yield: 376 mg (1.85 mmol), 37% (relative to *p*-tolylhydrazine hydrochloride); ν_{max} (KBr) 3373, 3287, 3217, 3080, 1660, 1544, 1250, 820, 641 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.20 (1H, t, *J* 2.7 Hz), 2.29 (3H, s), 4.06 (2H, dd, *J* 5.4, 2.7 Hz), 5.57 (1H, br s), 6.00 (1H, br s), 6.07 (1H, br s), 6.76 (2H, d, *J* 8.4 Hz), 7.09 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, DMSO-d_6) 20.1, 28.6, 72.0, 82.5, 112.4, 127.4, 129.0, 147.0, 158.8; *m*/*z* (EI) 203 (62, M^+), 122 (100), 106 (40), 91 (22), 57 (20%); *m*/*z* (FAB) 204 (84, MH^+), 71 (92), 55 (100%); HRMS (EI): M^+, found 203.1069. $C_{11}H_{13}N_3O$ requires 203.1059.

*4.2.3. 2-(4-Chlorophenyl)-N-(prop-2-ynyl)hydrazinecarboxamide (**2c**).* Pale-yellow solid, mp 141–143 °C, yield: 257 mg (1.15 mmol), 23% (relative to 4-chlorophenylhydrazine hydrochloride). Found: C, 53.52; H, 4.58; N, 18.60. $C_{10}H_{10}ClN_3O$ requires C, 53.70; H, 4.51; N, 18.79%. ν_{max} (KBr) 3392, 3283, 3210, 3076, 1668, 1549, 1253, 1090, 826, 650 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.21 (1H, t, *J* 2.7 Hz), 4.06 (2H, dd, *J* 5.4, 2.7 Hz), 5.67 (1H, br s), 5.96 (1H, br s), 6.07 (1H, br s), 6.80 (2H, d, *J* 8.4 Hz), 7.23 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 29.3, 71.0, 80.8, 114.3, 124.8, 128.9, 147.2, 160.0; *m*/*z* (EI) 223 (41, M^+), 142 (100), 126 (38), 77 (23%).

4.3. Typical procedure for the synthesis of semicarbazides 2d,e from in situ generated propargyl isocyanate and hydrazines (Scheme 1, Table 1)

In a round-bottomed flask equipped with a stirring bar triphosgene (545 mg, 1.84 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under Ar. The reaction mixture was flushed with argon gas and the flask was capped with a septum. Under stirring a mixture of propargylamine (98%, 350 μL, 5.36 mmol) and triethylamine (1.51 mL, 10.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise via syringe at room temperature. The reaction mixture was stirred for 30 min. Then an appropriate hydrazine (5.0 mmol) was added and the stirring was continued for 10 min under Ar. The reaction mixture was diluted with aq HCl (10^{-5} M, 100 mL). The organic layer was separated, and water layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and the solvent was evaporated to dryness. The residue was triturated in diethyl ether, cooled to 0 °C, and the precipitate was filtered to afford semicarbazide **2**.

*4.3.1. N-(Prop-2-ynyl)-2-(4-(trifluoromethyl)phenyl)hydrazinecarboxamide (**2d**).* Off-white plates, mp 159–160 °C (ethyl acetate/hexanes), yield: 226 mg (4.40 mmol) 88% (relative to 4-(trifluoromethyl)phenylhydrazine); ν_{max} (KBr) 3332, 3312, 2127, 1660, 1632, 1574, 1333, 1108, 1069, 831 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.21 (1H, t, *J* 2.7 Hz), 4.06 (2H, dd, *J* 5.4, 2.7 Hz), 5.89 (1H, br s), 5.93 (1H, br s), 6.12 (1H, br s), 6.80 (2H, d, *J* 8.4 Hz), 7.53 (2H, d, *J* 8.4 Hz); δ_H (300 MHz, DMSO-d_6) 2.99 (1H, t, *J* 2.4 Hz), 3.78 (2H, dd, *J* 5.7, 2.4 Hz), 6.80 (2H, d, *J* 8.4 Hz), 6.91 (1H, t, *J* 5.7 Hz), 7.48 (2H, d, *J* 8.4 Hz), 8.11 (1H, br s), 8.19 (1H, br s); δ_C (75 MHz, DMSO-d_6) 29.8, 71.0, 80.9, 112.4 (q, *J* 32 Hz), 124.0 (q, *J* 273 Hz), 126.3, 126.6 (q, *J* 3.7 Hz), 152.7, 158.8; *m*/*z* (ESI^+) 288.1 (100, MNa^+), 258.1 (60, MH^+); HRMS (ESI^+): MH^+, found 258.0852. $C_{11}H_{11}F_3N_3O$ requires 258.0854.

*4.3.2. 2-(Perfluorophenyl)-N-(prop-2-ynyl)hydrazinecarboxamide (**2e**).* Brown solid, mp 113–114 °C (CH_2Cl_2), yield: 1.13 g (4.05 mmol), 81% (relative to pentafluorophenylhydrazine); ν_{max} (KBr) 3439, 3312, 3077, 1678, 1566, 1527, 1026, 978, 688 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.25 (1H, t, *J* 2.7 Hz), 4.08 (2H, dd, *J* 5.4, 2.7 Hz), 5.80 (2H, br s), 6.52 (1H, br s); δ_C (75 MHz, DMSO-d_6) 28.7, 72.3, 82.2, 125.1 (m), 131.8 (m), 135.0 (m), 135.6 (m), 138.9 (m), 158.1; ^{19}F NMR (282 MHz, DMSO-d_6) −158.5 (m), −165.8 (m), −171.2 (m); *m*/*z* (EI) 279 (18, M^+), 198 (100), 182 (46), 155 (22%); *m*/*z* (FAB) 280 (100, MH^+), 198 (24), 71 (25), 55 (31%); HRMS (EI): M^+, found 279.0439. $C_{10}H_6F_5N_3O$ requires 279.0431.

4.4. General procedure for the oxidation of semicarbazides 2a–e with CAN (Scheme 1, Table 1)

A solution of CAN (1.21 g, 2.21 mmol) in MeOH (2 mL) was dropwise, under stirring added into the solution of semicarbazide **2** (1.00 mmol) in MeOH (2 mL). The reaction mixture was stirred for 5 min, diluted with saturated aq $NaHCO_3$ (15 mL), and the product was extracted with CH_2Cl_2 (8×5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and evaporated to dryness to give pure diazene **1**. When necessary, the crude product was re-crystallized from an appropriate solvent, as indicated below.

*4.4.1. 2-Phenyl-N-(prop-2-ynyl)diazenecarboxamide (**1a**).* Red needles, mp 60 °C (light petroleum), yield: 185 mg (0.99 mmol), 99% (relative to **2a**). Found: C, 64.15; H, 4.93; N, 22.12. $C_{10}H_9N_3O$ requires C, 64.16; H, 4.85; N, 22.45%. ν_{max} (KBr) 3376, 3287, 3210, 1704, 1493, 1269, 1194, 1148, 1020, 785, 670 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.33 (1H, t, *J* 2.7 Hz), 4.30 (2H, dd, *J* 5.4, 2.7 Hz), 6.62 (1H, br s), 7.58 (3H, m), 7.96 (2H, m); δ_C (75 MHz, DMSO-d_6) 29.2, 73.7, 80.2, 122.8, 129.6, 133.3, 151.0, 162.7; *m*/*z* (EI) 188 (2, MH^+), 105 (73), 82 (97), 77 (100), 55 (43%); *m*/*z* (FAB) 188 (7, MH^+), 95 (33), 81 (44), 69 (74), 55 (100%).

*4.4.2. N-(Prop-2-ynyl)-2-p-tolyldiazenecarboxamide (**1b**).* Orange needles, mp 59 °C (light petroleum), yield: 193 mg (0.96 mmol), 96% (relative to **2b**). Found: C, 65.34; H, 5.62; N, 20.78. $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%. ν_{max} (KBr) 3279, 3043, 1690, 1506, 1258, 1152, 1030, 830, 670 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.32 (1H, t, *J* 2.7 Hz), 2.46 (3H, s), 4.28 (2H, dd, *J* 5.4, 2.7 Hz), 6.62 (1H, br s), 7.33 (2H, d, *J* 8.4 Hz), 7.87 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 21.7, 30.4, 72.4, 78.5, 124.2, 130.0, 145.2, 149.0, 160.0; *m*/*z* (FAB) 202 (100, MH^+), 119 (30), 91 (43), 69 (44), 55 (57%).

*4.4.3. 2-(4-Chlorophenyl)-N-(prop-2-ynyl)diazenecarboxamide (**1c**).* Red solid, mp 128–129 °C (light petroleum), yield: 215 mg (0.97 mmol), 97% (relative to **2c**). Found: C, 54.35; H, 3.71; N, 18.96. $C_{10}H_8ClN_3O$ requires C, 54.19; H, 3.64; N, 18.96%. ν_{max} (KBr) 3292, 1706, 1493, 1275, 1083, 1010, 840, 655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.33 (1H, t, *J* 2.7 Hz), 4.29 (2H, dd, *J* 5.4, 2.7 Hz), 6.58 (1H, br s), 7.52 (2H, d, *J* 8.4 Hz), 7.92 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, DMSO-d_6) 29.3, 73.8, 80.1, 124.6, 129.8, 138.0, 149.6, 162.4; *m*/*z* (EI) 222 (5, MH^+), 139 (57), 111 (71), 82 (100%).

*4.4.4. N-(Prop-2-ynyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**1d**).* Orange solid, mp 119 °C, yield: 255 mg (1.00 mmol), 100% (relative to **2d**). Found: C, 51.54; H, 3.28; N, 16.32. $C_{11}H_8F_3N_3O$ requires C, 51.77; H, 3.16; N, 16.47%. ν_{max} (KBr) 3310, 3202, 3019, 1707, 1546, 1327, 1168, 1113, 1067, 851, 655 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.35 (1H, t, *J* 2.7 Hz), 4.31 (2H, dd, *J* 5.4, 2.7 Hz), 6.59 (1H, br s), 7.82 (2H, d, *J* 8.4 Hz), 8.06 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, DMSO-d_6) 29.3, 73.9, 80.0, 123.4, 123.7 (q, *J* 273 Hz), 126.9 (q, *J* 3.7 Hz), 132.3 (q, *J* 32 Hz), 153.2, 162.3; ^{19}F NMR (282 MHz, DMSO-d_6) −61.8; *m*/*z* (FAB) 256 (100, MH^+), 71 (27), 55 (29%).

*4.4.5. 2-(Perfluorophenyl)-N-(prop-2-ynyl)diazenecarboxamide (**1e**).* Brown needles, mp 112–114 °C, yield: 277 mg (1.00 mmol), 100% (relative to **2e**). Found: C, 43.41; H, 1.57; N, 15.08. $C_{10}H_4F_5N_3O$

requires C, 43.34; H, 1.45; N, 15.16%. ν_{max} (KBr) 3250, 2120, 1715, 1518, 1500, 1258, 1138, 1026, 691, 559 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.36 (1H, t, *J* 2.7 Hz), 4.32 (2H, dd, *J* 5.4, 2.7 Hz), 6.56 (1H, br s); δ_C (75 MHz, DMSO-d_6) 29.5, 74.0, 79.8, 126.1 (m), 136.0 (m), 139.4 (m), 141.0 (m), 142.8 (m), 144.4 (m), 161.1; ^{19}F NMR (282 MHz, DMSO-d_6) −149.0 (m), −149.6 (m), −162.3 (m); *m*/*z* (FAB) 278 (100, MH^+), 197 (15), 71 (28), 55 (35%).

4.5. Typical procedure for the synthesis of ethyl hydrazinecarboxylates 3a–c,f,g from hydrazine hydrochlorides (Scheme 2, Table 2)

An appropriate hydrazine hydrochloride (50 mmol) was dissolved in CH_3CN (100 mL). Pyridine (8.54 mL, 106 mmol) was added. The solution was cooled to 0 °C and ethyl chloroformate (5.2 mL, 55 mmol) was added dropwise under stirring. The reaction mixture was stirred for 15 min at 0 °C and then for 1 h at room temperature. Water (100 mL) was added and the resulting mixture was acidified with HCl (6 M) to pH 4–6. The product was extracted with CH_2Cl_2 (5×50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, and the solvent was evaporated to dryness. When necessary, the crude product was for analysis re-crystallized from an appropriate solvent, as indicated below.

*4.5.1. Ethyl 2-phenylhydrazinecarboxylate (**3a**)*[35]. White needles, mp 71–72 °C, mp (lit.[35]) 71–72 °C, yield: 9.0 g (50 mmol), 100% (relative to phenylhydrazine hydrochloride); δ_H (300 MHz, $CDCl_3$) 1.26 (3H, m), 4.19 (2H, q, *J* 7.2 Hz), 5.75 (1H, br s), 6.50 (1H, br s), 6.83 (2H, d, *J* 7.9 Hz), 6.89 (1H, dd, *J* 7.4, 7.4 Hz), 7.20–7.28 (2H, m).

*4.5.2. Ethyl 2-p-tolylhydrazinecarboxylate (**3b**)*[36]. Pale-yellow cubes, mp 81–82 °C, mp (lit.[36]) 82–84 °C, yield: 9.3 g (48 mmol), 96% (relative to *p*-tolylhydrazine hydrochloride). Found: C, 62.21; H, 7.54; N, 14.07. $C_{10}H_{14}N_2O_2$ requires C, 61.84; H, 7.27; N, 14.42%. ν_{max} (KBr) 3362, 3271, 2982, 1703, 1514, 1284, 1238, 1184, 1038, 819 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz), 2.26 (3H, s), 4.18 (2H, q, *J* 7.1 Hz), 5.66 (1H, br s), 6.47 (1H, br s), 6.74 (2H, d, *J* 8.2 Hz), 7.04 (2H, d, *J* 8.2 Hz); δ_C (75 MHz, DMSO-d_6) δ 14.6, 20.1, 60.1, 112.0, 126.8, 129.1, 147.2, 157.0; *m*/*z* (EI) 194 (70, M^+), 121 (100), 91 (37%).

*4.5.3. Ethyl 2-(4-chlorophenyl)hydrazinecarboxylate (**3c**)*[37]. Pale-yellow cubes, mp 82–84 °C, mp (lit.[37]) 89–92 °C, yield: 10 g (48 mmol), 96% (relative to 4-chlorophenylhydrazine hydrochloride); δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz), 4.19 (2H, q, *J* 7.2 Hz), 5.76 (1H, br s), 6.48 (1H, br s), 6.76 (2H, d, *J* 8.9 Hz), 7.19 (2H, d, *J* 8.9 Hz).

*4.5.4. Ethyl 2-(4-methoxyphenyl)hydrazinecarboxylate (**3f**)*[38]. Brown needles, mp 78–81 °C, mp (lit.[38]) 99.5–100.5 °C, yield: 4.6 g (22 mmol), 44% (relative to 4-methoxyphenylhydrazine hydrochloride); δ_H (300 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.2 Hz), 3.76 (3H, s), 4.19 (2H, q, *J* 7.2 Hz), 5.60 (1H, br s), 6.48 (1H, br s), 6.81 (4H, s).

*4.5.5. Ethyl 2-(4-fluorophenyl)hydrazinecarboxylate (**3g**).* White needles, mp 86–87 °C, yield: 7.3 g (37 mmol), 74% (relative to 4-fluorophenylhydrazine hydrochloride). Found: C, 54.54; H, 5.66; N, 14.20. $C_9H_{11}FN_2O_2$ requires C, 54.54; H, 5.59; N, 14.13%. ν_{max} (KBr) 3354, 3275, 3039, 2986, 1708, 1506, 1217, 1044, 831 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz), 4.19 (2H, q, *J* 7.2 Hz), 5.70 (1H, br s), 6.50 (1H, br s), 6.78 (2H, m), 6.94 (2H, m); δ_C (75 MHz, DMSO-d_6) δ 14.5, 60.2, 112.8 (d, *J* 7.2 Hz); 115.1 (d, *J* 22.3 Hz); 146.0; 155.7 (d, *J* 233.0 Hz); 156.9; *m*/*z* (EI) 198 (57, M^+), 125 (100), 110 (31), 69 (34%).

*4.5.6. Ethyl 2-(4-(trifluoromethyl)phenyl)hydrazinecarboxylate (**3d**).* Into a solution of 4-(trifluoromethyl)phenylhydrazine (8.8 g, 50 mmol) in CH_3CN (50 mL), pyridine (4.5 mL, 55 mmol) was added. The solution was cooled to 0 °C and ethyl chloroformate (5.2 mL, 55 mmol) was added dropwise under stirring. The reaction mixture was stirred for 15 min at 0 °C and then for 1.5 h at room temperature. Water (100 mL) was added and the resulting mixture was acidified with HCl (6 M) to pH 4–6. The product was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, and the solvent was evaporated to dryness, to give pure **3d** (11 g, 43 mmol, 86% relative to 4-(trifluoromethyl)phenylhydrazine), as brown needles. Mp 131–132 °C; ν_{max} (KBr) 3329, 2993, 1689, 1619, 1332, 1256, 1097, 828 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz), 4.21 (2H, q, *J* 7.2 Hz), 5.98 (1H, br s), 6.52 (1H, br s), 6.87 (2H, d, *J* 8.4 Hz), 7.48 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, DMSO-d_6) δ 14.5, 60.5, 111.0, 118.1 (q, *J* 32.2 Hz), 125.0 (q, *J* 270.0 Hz), 126.2 (q, *J* 3.8 Hz), 152.5, 156.7; *m*/*z* (EI) 248 (46, M^+), 175 (100%); HRMS (ESI^+): MH^+, found 249.0855. $C_{10}H_{12}F_3N_2O_2$ requires 249.0851.

*4.5.7. Ethyl 2-(4-nitrophenyl)hydrazinecarboxylate (**3h**)*[39,13b]. Into a solution of 4-nitrophenylhydrazine (7.7 g, 50 mmol) in CH_3CN (100 mL), pyridine (4.5 mL, 55 mmol) was added. The solution was cooled to 0 °C and ethyl chloroformate (5.2 mL, 55 mmol) was added dropwise under stirring. The reaction mixture was stirred for 15 min at 0 °C and then for 3.5 h at room temperature. The volatiles were reduced by rotary evaporator to approximately 5 mL and the residue was triturated with water (100 mL). The precipitate was filtered and washed with water, to give **3h** (10 g, 46 mmol, 92% relative to 4-nitrophenylhydrazine) as brown needles. Mp 194–196 °C, mp (lit.[39]) 197 °C, mp (lit.[13b]) 195–196 °C; δ_H (300 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz), 4.23 (2H, q, *J* 7.2 Hz), 6.21 (1H, br s), 6.54 (1H, br s), 6.85 (2H, d, *J* 9.0 Hz), 8.15 (2H, d, *J* 9.0 Hz).

*4.5.8. Ethyl 2-(pyridin-2-yl)hydrazinecarboxylate (**3i**)*[35]. This compound was prepared as described in the literature[35] in 66% yield from 2-hydrazinopyridine. Pale-yellow cubes, mp 99–101 °C; δ_H (300 MHz, $CDCl_3$) 1.26 (3H, m), 4.20 (2H, q, *J* 6.9 Hz), 6.54 (1H, br s), 6.68–6.82 (2H, m), 6.86 (1H, br s), 7.54 (1H, m), 8.16 (1H, m).

4.6. General procedure for the oxidation of ethyl hydrazinecarboxylates 3a–d,f–i with CAN (Table 2, Method A)

A solution of CAN (1.21 g, 2.21 mmol) in MeOH (5 mL) was added dropwise under stirring into the solution of ethyl hydrazinecarboxylate **3** (1.0 mmol) in MeOH (5 mL). The reaction mixture was stirred for 5 min, diluted with water (30 mL), and the product was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (5 mL), brine (10 mL), dried over Na_2SO_4, and evaporated to dryness to give pure ethyl diazenecarboxylate **4**.

*4.6.1. Ethyl 2-phenyldiazenecarboxylate (**4a**)*[35]. Red oil, yield: 178 mg (1.00 mmol), 100% (relative to **3a**); δ_H (300 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.1 Hz), 4.52 (2H, q, *J* 7.1 Hz), 7.55 (3H, m), 7.93 (2H, m).

*4.6.2. Ethyl 2-p-tolyldiazenecarboxylate (**4b**).* Red oil, yield: 138 mg (0.720 mmol), 72% (relative to **3b**); ν_{max} (NaCl) 2985, 1755, 1601, 1508, 1245, 1197, 1148, 827 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz), 2.45 (3H, s), 4.51 (2H, q, *J* 7.2 Hz), 7.32 (2H, d, *J* 8.2 Hz), 7.84 (2H, d, *J* 8.2 Hz); δ_C (75 MHz, DMSO-d_6) 13.9, 21.1, 59.0, 64.1, 123.2, 130.2, 145.1, 149.1, 161.9; *m*/*z* (FAB) 193 (100% MH^+); HRMS (ESI^+): MNa^+, found 215.0794. $C_{10}H_{12}N_2O_2Na$ requires 215.0796.

*4.6.3. Ethyl 2-(4-chlorophenyl)diazenecarboxylate (**4c**).* Red oil, yield: 179 mg (0.840 mmol), 84% (relative to **3c**); ν_{max} (NaCl) 2985, 1759, 1499, 1246, 1148, 1087, 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1,47 (3H, t, *J* 7.2 Hz), 4.52 (2H, q, *J* 7.2 Hz), 7.51 (2H, d, *J* 8.9 Hz), 7.88 (2H,

d, *J* 8.9 Hz); δ_C (75 MHz, DMSO-d_6) 13.9, 64.5, 124.8, 129.9, 138.9, 149.4, 161.6; HRMS (ESI$^+$): MNa^+, found 235.0239. $C_9H_9{}^{35}ClN_2O_2Na$ requires 235.0234.

*4.6.4. Ethyl 2-(4-(trifluoromethyl)phenyl)diazenecarboxylate (**4d**).* Red oil, yield: 202 mg (0.820 mmol), 82% (relative to **3d**); ν_{max} (NaCl) 2989, 1763, 1324, 1248, 1133, 1066, 852, 745 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.2 Hz), 4.54 (2H, q, *J* 7.2 Hz), 7.81 (2H, d, *J* 8.4 Hz), 8.01 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, DMSO-d_6) 13.7, 64.6, 123.4 (q, *J* 272.6 Hz), 123.6, 126.8 (q, *J* 3.8 Hz), 133.1 (q, *J* 32.2 Hz), 152.8, 161.3; HRMS (ESI$^+$): MH^+, found 247.0689. $C_{10}H_{10}F_3N_2O_2$ requires 247.0694.

*4.6.5. Ethyl 2-(4-methoxyphenyl)diazenecarboxylate (**4f**).* Red oil, yield: 175 mg (0.840 mmol), 84% (relative to **3f**); ν_{max} (NaCl) 2982, 2842, 1751, 1601, 1504, 1248, 1200, 1138, 1027, 842 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz), 3.91 (3H, s), 4.51 (2H, q, *J* 7.2 Hz), 7.00 (2H, d, *J* 9.0 Hz), 7.96 (2H, d, *J* 9.0 Hz); δ_C (75 MHz, DMSO-d_6) 13.9, 55.8, 63.8, 114.9, 125.7, 145.3, 161.9, 164.3; *m*/*z* (EI) 209 (27, MH^+), 163 (40), 135 (100), 107 (71), 92 (40), 77 (48%); *m*/*z* (FAB) 209 (100, MH^+), 135 (74), 107 (37%); HRMS (ESI$^+$): MH^+, found 209.0919. $C_{10}H_{13}N_2O_3$ requires 209.0926.

*4.6.6. Ethyl 2-(4-fluorophenyl)diazenecarboxylate (**4g**).* Red oil, yield: 149 mg (0.760 mmol), 76% (relative to **3g**). Found: C, 55.01; H, 4.73; N, 14.56. $C_9H_9FN_2O_2$ requires C, 55.10; H, 4.62; N, 14.28%. ν_{max} (NaCl) 2986, 1760, 1595, 1508, 1250, 1225, 1136, 847 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz), 4.52 (2H, q, *J* 7.2 Hz), 7.21 (2H, m), 7.97 (2H, m); δ_C (75 MHz, DMSO-d_6) 13.8, 64.3, 116.8 (d, *J* 23.3 Hz), 125.9 (d, *J* 9.9 Hz), 147.7 (d, *J* 2.7 Hz), 161.6, 165.4 (d, *J* 254.0 Hz);

*4.6.7. Ethyl 2-(4-nitrophenyl)diazenecarboxylate (**4h**)*[12,39]. Brown needles, mp 62–63 °C, mp (lit.[39]) 73–74 °C, yield: 150 mg (0.670 mmol), 67% (relative to **3h**); δ_H (300 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.2 Hz), 4.55 (2H, q, *J* 7.2 Hz), 8.05 (2H, d, *J* 9.0 Hz), 8.40 (2H, d, *J* 9.0 Hz).

*4.6.8. Ethyl 2-(pyridin-2-yl)diazenecarboxylate (**4i**)*[35]. Red oil, yield: 111 mg (0.620 mmol), 62% (relative to **3i**); δ_H (300 MHz, $CDCl_3$) 1.46 (3H, t, *J* 6.9 Hz), 4.53 (2H, q, *J* 6.9 Hz), 7.51 (1H, m), 7.85 (1H, m), 7.96 (1H, m), 8.76 (1H, m).

4.7. General procedure for the oxidation of ethyl hydrazinecarboxylates 3a–d,f–i with $NaNO_2$ (Scheme 2, Table 2, Method B)

Ethyl hydrazinecarboxylate **3** (30 mmol) was dissolved in aq acetic acid (80%, 150 mL) and chilled to 0 °C. The mixture was kept at this temperature during the addition of $NaNO_2$ (4.4 g, 63 mmol) in water (150 mL) under vigorous stirring. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h, diluted with water (150 mL), and the product was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (50 mL), brine (30 mL), dried over Na_2SO_4, and evaporated to dryness to give pure ethyl diazenecarboxylate **4**. For the yields of products, see Table 2. Spectroscopic and analytical data of products **4a–d**,**f–i** were identical with those obtained by Method A and are given above.

4.8. General procedure for the oxidation of ethyl hydrazinecarboxylates 3a–d,f–i with NBS (Scheme 2, Table 2, Method C)

Ethyl hydrazinecarboxylate **3** (1.00 mmol) was dissolved in CH_2Cl_2 (7 mL). Pyridine (227 μL, 2.81 mmol) was added. Then NBS (196 g, 1.10 mmol) was added portionwise. The reaction mixture was stirred for 30 min and then washed with aq HCl (5%, 10 mL), aq sodium thiosulfate (1.5%, 5 mL), saturated aq $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated to dryness to give pure ethyl diazenecarboxylate **4**. For the yields of products, see Table 2. Spectroscopic and analytical data of products **4a–d**,**f–i** were identical with those obtained by Method A and are given above.

4.9. General procedure for the preparation of *N*-(propargyl)-diazenecarboxamides 1a–d,f–i from ethyl diazenecarboxylate 4a–d,f–i and propargylamine (Scheme 2, Table 2)

A round-bottomed flask equipped with a stirring bar was charged with ethyl diazenecarboxylate **4** (20 mmol). Propargylamine (98%, 1.4 mL, 21 mmol) was added dropwise under stirring. If product precipitated during the addition, abs. EtOH (~4 mL) was added. The reaction mixture was stirred for 1.5 h and volatiles were removed in vacuo to give pure *N*-(propargyl)diazenecarboxamide **1**. Spectroscopic and analytical data of products **1a–d** were identical with those obtained by oxidation of semicarbazides **2** (Table 1), and are given above. For the yields of **1a–d**, see Table 2. When necessary, the crude product was for analysis re-crystallized from an appropriate solvent, as indicated below.

*4.9.1. 2-(4-Methoxyphenyl)-N-(prop-2-ynyl)-diazenecarboxamide (**1f**).* Orange solid, mp 103–104 °C, yield: 4.3 g (20 mmol), 100% (relative to **4f**); ν_{max} (KBr) 3283, 1694, 1599, 1505, 1262, 1140, 1016, 839 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.32 (1H, t, *J* 2.4 Hz), 3.91 (3H, s), 4.28 (2H, dd, *J* 5.7, 2.4 Hz), 6.66 (1H, br s), 7.01 (2H, d, *J* 9.0 Hz), 7.97 (2H, d, *J* 9.0 Hz); δ_C (75 MHz, DMSO-d_6) 29.2, 55.8, 73.5, 80.4, 114.8, 125.3, 145.2, 162.6, 163.5; *m*/*z* (EI) 218 (50, MH^+), 107 (100), 92 (72), 77 (81); *m*/*z* (FAB) 218 (100, MH^+), 69 (80), 57 (84%); HRMS (ESI$^+$): MH^+, found 218.0941. $C_{11}H_{12}N_3O_2$ requires 218.0930.

*4.9.2. 2-(4-Fluorophenyl)-N-(prop-2-ynyl)diazenecarboxamide (**1g**).* Brown solid, mp 96–99 °C, yield: 4.1 g (20 mmol), 100% (relative to **4g**). Found: C, 58.19; H, 4.09; N, 20.26. $C_{10}H_8FN_3O$ requires C, 58.53; H, 3.93; N, 20.48%. ν_{max} (KBr) 3303, 3188, 3067, 1699, 1508, 1217, 1140, 845, 664, 511 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.33 (1H, t, *J* 2.6 Hz), 4.29 (2H, dd, *J* 5.5, 2.6 Hz), 6.63 (1H, br s), 7.22 (2H, m), 8.00 (2H, m); δ_C (75 MHz, DMSO-d_6) 29.3, 73.7, 80.1, 116.7 (d, *J* 23.2 Hz), 125.5 (d, *J* 9.7 Hz), 147.8, 162.4, 164.9 (d, *J* 252.4 Hz); *m*/*z* (FAB) 206 (41, MH^+), 75 (100), 57 (72%).

*4.9.3. 2-(4-Nitrophenyl)-N-(prop-2-ynyl)diazenecarboxamide (**1h**).* Brick-red solid, mp 172–173 °C, yield: 4.6 g (20 mmol), 100% (relative to **4h**); ν_{max} (KBr) 3267, 3102, 2118, 1708, 1522, 1347, 863, 710, 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.36 (1H, t, *J* 2.4 Hz), 4.33 (2H, dd, *J* 5.7, 2.4 Hz), 6.63 (1H, br s), 8.09 (2H, d, *J* 9.0 Hz), 8.41 (2H, d, *J* 9.0 Hz); δ_C (75 MHz, DMSO-d_6) δ 29.3, 73.9, 79.9, 123.8, 125.1, 149.6, 154.1, 162.1; *m*/*z* (FAB) 233 (10, MH^+), 107 (33), 71 (87), 55 (100%); HRMS (ESI$^+$): MNa^+, found 255.0492. $C_{10}H_8N_4O_3Na$ requires 255.0494.

*4.9.4. N-(Prop-2-ynyl)-2-(pyridin-2-yl)diazenecarboxamide (**1i**).* Brick-red solid, mp 116–117 °C, yield: 3.73 g (19.8 mmol), 99% (relative to **4i**); ν_{max} (KBr) 3256, 3181, 2992, 2118, 1726, 1512, 1244, 1000, 789, 718 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.32 (1H, t, *J* 2.4 Hz), 4.29 (2H, dd, *J* 5.4, 2.4 Hz), 6.82 (1H, br s), 7.54 (1H, m), 7.98 (2H, m), 8.77 (1H, m); δ_C (75 MHz, DMSO-d_6) 29.3, 73.8, 80.0, 114.8, 127.2, 139.3, 149.6, 161.7, 162.7; *m*/*z* (FAB) 189 (67, MH^+), 108 (100), 71 (60), 55 (73%); HRMS (ESI$^+$): MNa^+, found 211.0588. $C_9H_8N_4ONa$ requires 211.0596.

4.10. General procedure for the synthesis of triazoles 6a–d,f–h (Scheme 3, Table 3)

A mixture of an appropriate alkyne **1** (5.00 mmol), 2-(azidomethyl)pyridine **5a** (704 mg, 5.25 mmol), $CuSO_4 \cdot 5H_2O$ (31 mg,

0.12 mmol, 2.5 mol% relative to **1**), and granular copper (0.58 g, 9.1 mmol, 1.8 equiv relative to **1**) in wet MeOH (80%, 20 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with saturated aq NH_4Cl (50 mL), filtered, and extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with saturated aq NH_4Cl (2×50 mL) and brine (10 mL). Each time the product was back-extracted from the water layers with few milliliters of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and the solvent of the filtrate was removed in vacuo to give triazole **6**, >95% pure as determined by ^1H NMR. When necessary, the crude product was for analysis re-crystallized from an appropriate solvent, as indicated below.

*4.10.1. 2-Phenyl-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)-methyl)diazenecarboxamide (**6a**).* Orange needles, mp 129–131 °C (ethyl acetate), yield: 1.59 g (4.95 mmol), 99% (relative to **1a**). Found: C, 59.66; H, 4.65; N, 30.54. $C_{16}H_{15}N_7O$ requires C, 59.80; H, 4.71; N, 30.51%. ν_{max} (KBr) 3185, 3130, 2977, 1719, 1510, 1254, 1148, 766 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.53 (2H, d, *J* 5.8 Hz), 5.71 (2H, s), 7.30 (1H, d, *J* 7.8 Hz), 7.35 (1H, dd, *J* 7.1, 5.3 Hz), 7.55–7.70 (3H, m), 7.76–7.88 (3H, m), 8.13 (1H, s), 8.55 (1H, d, *J* 4.2 Hz), 9.10 (1H, br t, *J* 5.6 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.3, 122.2, 122.8, 123.2, 123.9, 129.6, 133.2, 137.3, 144.0, 149.4, 151.1, 155.0, 162.8; *m*/*z* (ESI^+) 344.1 (55, MNa^+), 322.1 (27, MH^+), 214.1 (88), 158.0 (100), 141.0 (89%).

*4.10.2. N-((1-(Pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-p-tolyldiazenecarboxamide (**6b**).* Orange solid, mp 90–91 °C (ethyl acetate), yield: 1.6 g (4.9 mmol), 98% (relative to **1b**). Found: C, 60.62; H, 4.98; N, 29.32. $C_{17}H_{17}N_7O$ requires C, 60.88; H, 5.11; N, 29.24%. ν_{max} (KBr) 3213, 1720, 1476, 1148, 765 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.41 (3H, s), 4.51 (2H, d, *J* 6.0 Hz), 5.71 (2H, s), 7.29 (1H, d, *J* 7.8 Hz), 7.35 (1H, dd, *J* 7.3, 5.0 Hz), 7.44 (2H, d, *J* 8.1 Hz), 7.75 (2H, d, *J* 8.1 Hz), 7.82 (1H, dd, *J* 7.7, 7.7 Hz), 8.11 (1H, s), 8.55 (1H, br d, *J* 4.5 Hz), 9.05 (1H, br t, *J* 5.6 Hz); δ_C (75 MHz, DMSO-d_6) 21.1, 35.4, 54.3, 122.2, 122.9, 123.2, 123.9, 130.1, 137.3, 143.8, 144.1, 149.2, 149.4, 155.0, 162.9; *m*/*z* (ESI^+) 358.1 (100, MNa^+), 336.2 (8, MH^+), 216.1 (33), 145.1 (39%).

*4.10.3. 2-(4-Chlorophenyl)-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)diazenecarboxamide (**6c**).* Orange solid, mp 114 °C (ethyl acetate), yield: 1.7 g (4.9 mmol), 98% (relative to **1c**). Found: C, 53.86; H, 3.85; N, 27.50. $C_{16}H_{14}ClN_7O$ requires C, 54.01; H, 3.97; N, 27.56%. ν_{max} (KBr) 3216, 1705, 1505, 1260, 1143 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.53 (2H, d, *J* 5.8 Hz), 5.71 (2H, s), 7.30 (1H, d, *J* 7.8 Hz), 7.35 (1H, dd, *J* 7.1, 5.2 Hz), 7.70 (2H, d, *J* 8.7 Hz), 7.78–7.89 (3H, m), 8.13 (1H, s), 8.55 (1H, d, *J* 4.4 Hz), 9.13 (1H, br t, *J* 5.6 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.3, 122.2, 123.2, 123.9, 124.5, 129.8, 137.3, 137.8, 143.9, 149.4, 149.6, 155.0, 162.6; *m*/*z* (ESI^+) 378.1 (100, MNa^+), 356.1 (50, MH^+), 129.1 (57%).

*4.10.4. N-((1-(Pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**6d**).* Yellow solid, mp 140–144 °C, yield: 1.93 g (4.95 mmol), 99% (relative to **1d**). Found: C, 52.12; H, 3.48; N, 25.02. $C_{17}H_{14}F_3N_7O$ requires C, 52.44; H, 3.62; N, 25.18%; ν_{max} (KBr) 3198, 3015, 1724, 1628, 1112, 1065, 858, 756 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.58 (2H, d, *J* 5.8 Hz), 5.73 (2H, s), 7.32 (1H, d, *J* 8.1 Hz), 7.35 (1H, dd, *J* 7.2, 5.0 Hz), 7.83 (1H, ddd, *J* 7.7, 7.7, 1.6 Hz), 7.96–8.06 (4H, m), 8.17 (1H, s), 8.56 (1H, d, *J* 4.2 Hz), 9.16 (1H, br t, *J* 5.6 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.4, 122.2, 123.2, 123.4, 123.7 (q, *J* 272.7 Hz), 124.0, 126.8 (q, *J* 3.8 Hz), 132.2 (q, *J* 32.1 Hz), 137.3, 143.8, 149.4, 153.2 (q, *J* 1.2 Hz), 155.0, 162.4; *m*/*z* (ESI^+) 214.1 (100, MNa^+), 390.1 (9, MH^+), 188.1 (23%).

*4.10.5. 2-(4-Methoxyphenyl)-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)diazenecarboxamide (**6f**).* Orange solid, mp 117–118 °C (ethyl acetate), yield: 1.74 g (4.95 mmol), 99% (relative to **1f**). Found: C, 58.00; H, 4.88; N, 28.12. $C_{17}H_{17}N_7O_2$ requires C, 58.11; H, 4.88; N, 27.90%; ν_{max} (KBr) 3220, 1705, 1503, 1260, 1143 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.88 (3H, s), 4.53 (2H, d, *J* 5.9 Hz), 5.72 (2H, s), 7.15 (2H, d, *J* 9.0 Hz), 7.28 (1H, d, *J* 7.8 Hz), 7.32 (1H, dd, *J* 7.3, 5.1 Hz), 7.78–7.90 (3H, m), 8.12 (1H, s), 8.55 (1H, d, *J* 4.5 Hz), 9.01 (1H, br t, *J* 5.8 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.3, 55.8, 114.7, 122.2, 123.2, 123.8, 125.2, 137.3, 144.2, 145.2, 149.4, 155.0, 162.8, 163.4; *m*/*z* (ESI^+) 374.1 (100, MNa^+), 352.2 (20, MH^+), 216.1 (35%).

*4.10.6. 2-(4-Fluorophenyl)-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)diazenecarboxamide (**6g**).* Orange needles, mp 116–117 °C (ethyl acetate/light petroleum), yield: 1.7 g (4.9 mmol), 98% (relative to **1g**). Found: C, 56.50; H, 4.12; N, 28.91. $C_{16}H_{14}FN_7O$ requires C, 56.63; H, 4.16; N, 28.89%; ν_{max} (KBr) 3261, 1721, 1503, 1223, 1136, 852, 762 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.54 (2H, d, *J* 5.8 Hz), 5.72 (2H, s), 7.30 (1H, d, *J* 7.8 Hz), 7.32 (1H, dd, *J* 7.2, 5.3 Hz), 7.42–7.51 (2H, m), 7.82 (1H, ddd, *J* 7.7, 7.7, 1.7 Hz) 7.88–7.98 (2H, m), 8.14 (1H, s), 8.55 (1H, d, *J* 4.4 Hz), 9.05 (1H, br t, *J* 5.7 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.3, 116.5, 116.8, 122.2, 123.2, 123.9, 125.4, 125.5, 137.3, 144.0, 147.8, 149.4, 155.0, 162.6, 163.1, 166.5; *m*/*z* (ESI^+) 362.1 (100, MNa^+), 340.1 (20, MH^+), 216.1 (30), 188.1 (24), 145.1 (29%).

*4.10.7. 2-(4-Nitrophenyl)-N-((1-(pyridin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)diazenecarboxamide (**6h**).* Brick-red needles, mp 166–168 °C (CH_2Cl_2/ethyl acetate), yield: 1.70 g (4.65 mmol), 93% (relative to **1h**). Found: C, 52.22; H, 3.78; N, 30.44. $C_{16}H_{14}N_8O_3$ requires C, 52.46; H, 3.85; N, 30.59%; ν_{max} (KBr) 3205, 1728, 1521, 1347 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 4.56 (2H, d, *J* 5.7 Hz), 5.72 (2H, s), 7.31 (1H, d, *J* 7.8 Hz), 7.33 (1H, dd, *J* 7.3, 5.4 Hz), 7.83 (1H, ddd, *J* 7.7, 7.7, 1.5 Hz), 8.03 (2H, d, *J* 8.9 Hz), 8.16 (1H, s), 8.45 (2H, d, *J* 8.9 Hz), 8.55 (1H, d, *J* 3.9 Hz), 9.27 (1H, br t, *J* 5.5 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 54.3, 122.2, 123.2, 123.7, 124.0, 125.1, 137.3, 143.7, 149.4, 149.5, 154.2, 155.0, 162.3; *m*/*z* (ESI^+) 389.1 (100, MNa^+), 367.1 (39, MH^+), 188.1 (29%).

4.11. General procedure for the synthesis of triazoles 7a–d,f,h (Scheme 4, Table 4)

An appropriate alkyne **1** (5.00 mmol), 1-azido-2-aminoethane **5b** (452 mg, 5.25 mmol), and $CuSO_4 \cdot 5H_2O$ (31 mg, 0.12 mmol, 2.5 mol% relative to **1**) were dissolved in wet MeOH (80%, 20 mL) (Table 4, entries 2, 4, and 6–9). Granular copper (0.58 g, 9.1 mmol, 1.8 equiv relative to **1**) was added when appropriate (Table 4, entries 1, 3, and 5). The reaction mixture was stirred at room temperature for 5 min, and when appropriate filtered to remove granular copper. Water (50 mL) and NH_4OH (25%, 1 mL) were added, and the product was extracted with CH_2Cl_2 (8×20 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and evaporated to dryness to give triazole **7**. When necessary, the crude product was for analysis re-crystallized from an appropriate solvent, as indicated below.

*4.11.1. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-phenyldiazenecarboxamide (**7a**).* Red solid, mp 114 °C, yield (with copper additive, entry 1): 1.09 g (3.99 mmol), 80% (relative to **1a**), yield (without additive, entry 2): 1.33 g (4.87 mmol), 97% (relative to **1a**). Found: C, 52.29; H, 5.70; N, 35.58. $C_{12}H_{15}N_7O$ requires C, 52.74; H, 5.53; N, 35.88%; ν_{max} (KBr) 3351, 3294, 3141, 2931, 1712, 1553, 1501, 1276, 1147, 1021, 939, 782, 682 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.52 (4H, br s), 4.32 (2H, br s), 4.77 (2H, d, *J* 6.0 Hz), 7.07 (1H, br s), 7.55 (3H, m), 7.76 (1H, s), 7.94 (2H, m); δ_C (75 MHz, DMSO-d_6) 35.4, 41.8, 52.6, 122.8, 123.4, 129.6, 133.2, 143.6, 151.1, 162.8; *m*/*z* (EI) 274 (6, MH^+), 210 (4), 168 (100), 77 (85), 68 (60%); *m*/*z* (FAB) 274 (100, MH^+), 168 (74), 91 (43), 71 (61), 55 (75%).

*4.11.2. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-p-tolyldiazenecarboxamide (**7b**).* Orange plates, mp 138–140 °C (light

petroleum), yield (with copper additive, entry 3): 1.29 g (4.49 mmol), 90% (relative to **1b**), yield (without additive, entry 4): 0.99 g (3.45 mmol), 69% (relative to **1b**). Found: C, 53.84; H, 6.10; N, 34.38. $C_{13}H_{17}N_7O$ requires C, 54.34; H, 5.96; N, 34.12%; ν_{max} (KBr) 3356, 3294, 3134, 2930, 1711, 1508, 1265, 1152, 1023, 828 cm^{-1}; δ_H (300 MHz, $CDCl_3$+DMSO-d_6) 2.44 (3H, s), 3.12 (4H, br s), 4.38 (2H, br s), 4.64 (2H, d, *J* 5.7 Hz), 7.34 (2H, d, *J* 8.4 Hz), 7.78 (2H, d, *J* 8.4 Hz), 7.89 (1H, s), 8.77 (1H, s); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 21.0, 35.5, 122.8, 122.9, 129.4, 143.5, 143.6, 148.9, 161.8; *m*/*z* (FAB) 288 (100, MH^+), 168 (87), 69 (66), 55 (87%).

*4.11.3. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-chlorophenyl)diazenecarboxamide (**7c**).* Orange solid, mp 124–126 °C (methanol/diethyl ether), yield (with copper additive, entry 5): 1.48 g (4.81 mmol), 96% (relative to **1c**), yield (without additive, entry 6): 1.32 g (4.29 mmol), 86% (relative to **1c**); ν_{max} (KBr) 3392, 3066, 2946, 1719, 1553, 1497, 1267, 1150, 1086, 1010, 844 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.45 (4H, br s), 4.40 (2H, br s), 4.76 (2H, d, *J* 5.7 Hz), 7.07 (1H, br s), 7.51 (2H, d, *J* 8.4 Hz), 7.75 (1H, s), 7.90 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 34.2, 121.9, 123.0, 128.0, 136.8, 142.2 148.1, 160.5; *m*/*z* (FAB) 308 (11, MH^+), 55 (100%). HRMS (ESI^+): MH^+, found 308.1034. $C_{12}H_{15}ClN_7O$ requires 308.1027.

*4.11.4. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**7d**).* Orange solid, mp 119–120 °C (dichloromethane/light petroleum), yield: 1.61 g (4.72 mmol), 94% (relative to **1d**). Found: C, 45.47; H, 4.22; N, 28.43. $C_{12}H_{14}F_3N_7O$ requires C, 45.75; H, 4.13; N, 28.73%; ν_{max} (KBr) 3381, 3137, 3068, 2930, 1721, 1487, 1329, 1175, 1130, 1065, 1014, 854 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.51 (4H, br s), 4.41 (2H, br s), 4.79 (2H, d, *J* 5.7 Hz), 7.33 (1H, br s), 7.80 (3H, m), 8.03 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 36.2, 47.7 (br s), 53.5 (br s), 123.5 (q, *J* 273 Hz), 123.7, 124.1, 126.6 (q, *J* 3.7 Hz), 134.7 (q, *J* 33 Hz), 143.5 (br s), 152.8, 160.1; ^{19}F NMR ($CDCl_3$) −63.4; *m*/*z* (FAB) 342 (50, MH^+), 69 (80), 55 (100%).

*4.11.5. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-methoxyphenyl)diazenecarboxamide (**7f**).* Orange solid, mp 114–115 °C (MeOH/^{t}BuOMe), yield: 0.99 g (3.26 mmol), 65% (relative to **1f**); ν_{max} (KBr) 3358, 1701, 1597, 1503, 1314, 1262, 1207, 1142, 1019, 908, 847 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 3.20 (4H, br s), 3.87 (3H, s), 4.34 (2H, br s), 4.50 (2H, d, *J* 5.6 Hz), 7.15 (2H, d, *J* 8.9 Hz), 7.86 (2H, d, *J* 8.9 Hz), 8.02 (1H, s), 8.98 (1H, br t, *J* 5.2 Hz); δ_C (75 MHz, DMSO-d_6) 35.5, 55.9, 114.9, 123.5, 125.4, 143.9, 145.3, 162.8, 163.5; *m*/*z* (ESI^+) 326.1 (22, MNa^+), 304.2 (100, MH^+); HRMS (ESI^+): MH^+, found 304.1516. $C_{13}H_{18}N_7O_2$ requires 304.1522.

*4.11.6. N-((1-(2-Aminoethyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-nitrophenyl)diazenecarboxamide (**7h**).* Brick-red solid, mp 127–130 °C (MeOH), yield: 1.18 g (3.71 mmol), 74% (relative to **1h**); ν_{max} (KBr) 3357, 3196, 1719, 1524, 1350, 1265, 865 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 1.73 (2H, br s), 2.95 (2H, br s), 4.31 (2H, t, *J* 6.2 Hz), 4.53 (2H, d, *J* 5.6 Hz), 8.03 (2H, d, *J* 8.9 Hz), 8.06 (1H, s), 8.45 (2H, d, *J* 8.9 Hz), 9.25 (1H, br t, *J* 5.4 Hz); δ_C (75 MHz, DMSO-d_6) 35.4, 41.8, 52.6, 123.5, 123.8, 125.2, 143.3, 149.5, 154.2, 162.2; *m*/*z* (ESI^+) 341.1 (20, MNa^+), 319.1 (100, MH^+); HRMS (ESI^+): MH^+, found 319.1277. $C_{12}H_{15}N_8O_3$ requires 319.1267.

4.12. General procedure for the synthesis of triazoles 7d, 8d, 9d, 10d (Scheme 5, Table 5)

A solution of alkyne **1d** (51 mg, 0.20 mmol), and an appropriate azide **5** (0.30 mmol, 1.5 equiv, Table 5) in MeOH (1 mL) was flushed with argon gas. An aqueous solution of $CuSO_4 \cdot 5H_2O$ (0.01 M, 1.0 mL, 5 mol % relative to **1d**) was added and the reaction mixture was stirred at room temperature for the time indicated in Table 5. Water (10 mL) and NH_4OH (25%, 0.5 mL) were added, and the product was extracted with CH_2Cl_2 (8×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness to give triazoles **7d**–**10d**. Spectral and analytical data for **7d** were identical to those of authentic sample and are given above (4.11.4).

*4.12.1. N-((1-(3-Aminopropyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**8d**).* Orange solid, mp 103 °C (CH_2Cl_2/light petroleum), yield: 55 mg (0.16 mmol), 77% (relative to **1d**). Found: C, 46.73; H, 4.55; N, 26.86. $C_{14}H_{16}F_3N_7O$ requires C, 47.32; H, 4.54; N, 27.59%; ν_{max} (KBr) 3374, 3290, 2930, 2100, 1719, 1326, 1173, 1065, 1013, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.56 (4H, br s), 2.05 (2H, br s), 4.50 (2H, br s), 4.77 (2H, d, *J* 5.7 Hz), 7.13 (1H, br s), 7.69 (1H, s), 7.80 (2H, d, *J* 8.4 Hz), 8.03 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 36.2, 47.9, 122.7, 123.5 (q, *J* 273 Hz), 124.1, 126.6 (q, *J* 3.7 Hz), 134.7 (q, *J* 33 Hz), 134.5, 152.8, 160.2; ^{19}F NMR (282 MHz, $CDCl_3$) −63.4; *m*/*z* (FAB) 356 (34, MH^+), 69 (87), 55 (100%).

*4.12.2. N-((1-(4-Aminobutyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**9d**).* Orange solid, mp 87–88 °C (CH_2Cl_2/light petroleum), yield: 67 mg (0.18 mmol), 91% (relative to **1d**). Found: C, 48.44; H, 4.95; N, 26.02. $C_{15}H_{18}F_3N_7O$ requires C, 48.78; H, 4.91; N, 26.55%; ν_{max} (KBr) 3368, 3303, 3135, 3068, 1706, 1331, 1173, 1104, 1067, 852 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.56 (6H, br s), 1.98 (2H, br s), 4.40 (2H, br s), 4.77 (2H, d, *J* 4.8 Hz), 7.13 (1H, br s), 7.67 (1H, s), 7.80 (2H, d, *J* 8.4 Hz), 8.03 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 29.7, 36.2, 50.4, 122.6, 123.5 (q, *J* 273 Hz), 124.1, 126.6 (q, *J* 3.7 Hz), 134.7 (q, *J* 33 Hz), 143.6, 152.8, 160.2; ^{19}F NMR (282 MHz, $CDCl_3$) −63.4; *m*/*z* (FAB) 370 (48, MH^+), 71 (63), 55 (100%).

*4.12.3. N-((1-(5-Aminopentyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(trifluoromethyl)phenyl)diazenecarboxamide (**10d**).* Orange solid, mp 71–73 °C (CH_2Cl_2/light petroleum), yield: 76 mg (0.20 mmol), 99% (relative to **1d**). Found: C, 49.73; H, 5.25; N, 25.37. $C_{16}H_{20}F_3N_7O$ requires C, 50.13; H, 5.26; N, 25.57%; ν_{max} (KBr) 3380, 3310, 2934, 2863, 2099, 1719, 1326, 1167, 1128, 1066, 1011, 853 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (8H, m), 1.95 (2H, br s), 4.37 (2H, t, *J* 6.6 Hz), 4.77 (2H, d, *J* 4.8 Hz), 6.91 (1H, br s), 7.66 (1H, s), 7.80 (2H, d, *J* 8.4 Hz), 8.03 (2H, d, *J* 8.4 Hz); δ_C (75 MHz, $CDCl_3$) 23.6 (br), 29.5 (br), 36.1 (br), 49.5 (br), 123.4 (q, *J* 273 Hz), 124.0, 126.5 (br), 134.5 (br), 143.6 (br), 152.8 (br), 160.4 (br); ^{19}F NMR (282 MHz, $CDCl_3$) −63.4; *m*/*z* (FAB) 384 (8, MH^+), 69 (85), 55 (100%).

4.13. 2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethanamine (11)

A solution of phenylacetylene (204 mg, 2.00 mmol), 1-azido-2-aminoethane (**5b**, 172 mg, 2.00 mmol), and $CuSO_4 \cdot 5H_2O$ (17 mg, 0.07 mmol, 4 mol %) in wet methanol (90%, 5 mL) was stirred at room temperature. After 10 min precipitate forms. The stirring was continued for an additional 1 h, then the reaction mixture was diluted with water (5 mL) and NH_4OH (0.5 mL) and the product was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered, and evaporated to dryness to give triazole **11** (274 mg, 1.46 mmol, 73% relative to phenylacetylene) as white needles. Mp 74–79 °C (EtOH/light petroleum); ν_{max} (KBr) 3130, 1463, 1220, 1076, 1040, 970, 762, 697 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 2.80–3.50 (4H, two br s), 4.36 (2H, d, *J* 6.0 Hz), 7.23 (1H, t, *J* 7.5 Hz), 7.45 (2H, dd, *J* 7.5, 7.5 Hz), 7.84 (2H, d, *J* 7.5 Hz), 8.54 (1H, s); δ_C (75 MHz, DMSO-d_6) 41.8 (br, CH_2NH_2), 53.0 (br, $CH_2CH_2NH_2$), 121.6 (C-5 of triazole), 125.1 (C-2, C-6 of Ph), 127.7 (C-4 of Ph), 128.8 (C-3, C-5 of Ph), 130.9 (C-1 of Ph), 146.1 (C-4 of triazole); *m*/*z* (ESI^+) 189.1 (100, MH^+); HRMS (ESI^+):

MH^+, found 189.1131. $C_{10}H_{13}N_4$ requires 189.1140. Salt **11** HCl has been reported in the literature.[24]

4.14. Competitive experiment—CuAAC reaction of alkyne 1d with a mixture of azides 5b–e

To the solution of alkyne **1d** (25.5 mg, 0.100 mmol) in MeOH (1.5 mL), $CuSO_4 \cdot 5H_2O$ (0.05 M, 0.5 mL, 0.025 mmol, 25 mol % relative to **1d**) was added and the resulting mixture was flushed with argon gas. Then a mixture of azides **5b** (43.1 mg, 0.500 mmol), **5c** (50.1 mg, 0.500 mmol), **5d** (57.1 mg, 0.500 mmol), **5e** (64.1 mg, 0.500 mmol) in MeOH (1.0 mL), flushed with argon gas, was introduced at room temperature and under stirring. The reaction mixture was stirred for 10 min (TLC indicated complete consumption of starting **1d**), diluted with water (6 mL), and the products were extracted with CH_2Cl_2 (6×5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvents were evaporated. The residue was dissolved in $CDCl_3$ and analyzed by ^1H NMR at 600 MHz NMR instrument, at 313 K. The relative ratio of products **7d** (1.0), **8d** (4.6), **9d** (<0.1), and **10d** (<0.1) was determined by integrating the corresponding baseline resolved triazole H-5 resonances (at δ 7.76 ppm, 7.68 ppm, 7.66 ppm, and 7.64 ppm, respectively) and (N-1)–C*H*$_2$– resonances (at δ 4.39 ppm, 4.47 ppm, 4.37 ppm, and 4.35 ppm, respectively).

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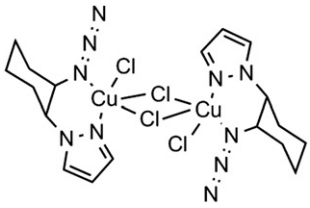

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