Synthesis of N-unsubstituted 1,2,3-triazoles via a cascade including propargyl azides, allenyl azides, and triazafulvenes

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Abstract

About thirty NH-1,2,3-triazoles with at least one additional functional group in a side chain at C-4 were prepared from propargyl substrates. These reactions included propargyl azides and their [3,3]-sigmatropic rearrangement to generate short-lived allenyl azides, which cyclized to form triazafulvenes that could be trapped by addition of N- or O-nucleophiles. In most cases, simple substrates and cheap sodium azide were utilized as starting compounds, and the syntheses were performed by using a one-pot procedure without isolation of any dangerous azides. This method to prepare NH-1,2,3-triazoles turned out to be compatible with quite different substitution patterns of the propargyl substrate.

Keywords: Electrocyclic ring closure, nitrogen heterocycles, nucleophilic addition, short-lived intermediates, sigmatropic rearrangement

Introduction

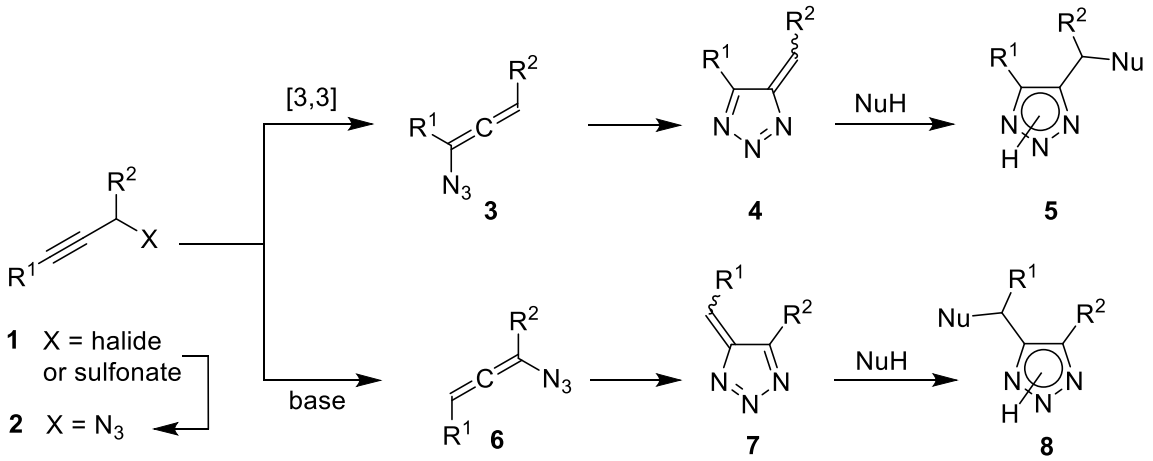
1,2,3-Triazoles are important heterocyclic compounds, which find numerous applications in industry, for example, as dyestuffs, fluorescent whiteners, photostabilizers of polymers, optical brightening agents, corrosion inhibitors, and as photographic photoreceptors.[1-5] Although up to now no natural products have been isolated containing 1,2,3-triazole moieties, such nitrogen heterocycles are successfully utilized in medicine and as agrochemicals owing to their extensive biological activities. The importance of 1,2,3-triazole compounds increased significantly after development of the copper-catalyzed 1,3-dipolar cycloaddition of organic azides at terminal alkynes under mild conditions.[6-7] This regioselective formation of 1,4-disubstituted 1*H*-1,2,3-

triazoles has proved to be the best example of click chemistry[8] and has found extensive applications in manifold domains of chemistry.[9-11]

However, N-unsubstituted, so-called NH-1,2,3-triazoles, cannot be prepared directly by means of a copper-catalyzed [3+2]-cycloaddition strategy. Thus, their synthesis requires special azides and a sequence involving cycloaddition and deprotection steps.[12-16] Alternatively, NH-1,2,3-triazoles are available by treating alkynes with electron-withdrawing substituents, such as propynals, with sodium azide.[17,18] Other routes include starting compounds, which are quite different to alkynes, for example, β-nitrostyrenes,[19-21] 1-bromo-1-alkenes,[22] 3-aryl-2,3-dibromopropanoic acids,[23,24] α-haloacrylates,[25] α-chloroacrylonitriles,[25] or 1-substituted 5-amino-1*H*-1,2,3-triazoles[26,27] (Dimroth rearrangement).

We earlier discovered a one-pot cascade to transform propargyl halides or sulfonates **1** into N-unsubstituted 1,2,3-triazoles **5** that bear at C-4 a side chain with the functional group Nu (Scheme 1).[28] This method includes nucleophilic substitution of **1** with the help of stoichiometric amounts of sodium azide. The resulting azide **2** is not isolated but slightly heated to undergo [3,3]-sigmatropic migration of the azido group with formation of allenyl azide **3**. Such intermediates can be detected by NMR spectroscopy or even isolated in special cases;[29] however, **3** tends to rapid ring closure to generate triazafulvene **4**, which is trapped by addition of the nucleophile NuH to yield the final product **5**. The intermediacy of very short-lived species **4** becomes plausible after treating optically active **3** with R^1 = H and R^2 = Me with the nucleophile MeOH to give completely racemic **5** via achiral **4**.[28]

In the presence of a Brønsted base, the one-pot cascade to prepare NH-1,2,3-triazoles can also transform the substrates **1** into products **8**.[30,31] Allenyl azide **6** is formed by prototropic rearrangement of **2** in this case, and subsequent ring closure followed by nucleophilic addition of NuH at the resulting intermediate **7** leads to the heterocyclic product **8**, which is an isomer of **5** (for $R^1 \neq R^2$). There is no need that the base for the step **2** → **6** is identical with the nucleophile NuH, which is necessary for the formation of **8**.



Scheme 1. One-pot cascades to transform the starting compounds **1** into the N-unsubstituted 1,2,3-triazoles **5** and **8**.

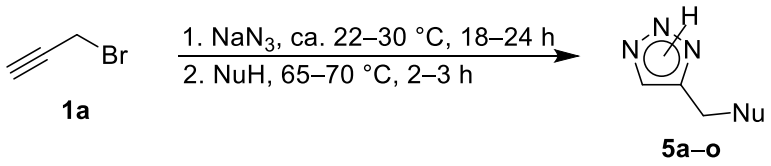
Both variants of the one-pot cascades start with easily accessible or even commercially available substrates **1** and cheap sodium azide. Furthermore, the isolation of any dangerous organic azide is avoided. Thus, the methods have already been applied to prepare some N-unsubstituted 1,2,3-triazoles.[32-45] Our previous studies were focused on the mechanisms to explain the formation of these heterocycles.[28-31]

Results and Discussion

In this article, we have investigated the scope of the methods in connection with the structure of the substrate **1** and the possible nucleophiles NuH. Moreover, we elaborated convenient procedures to isolate the NH-triazoles, which form salts in the presence of acids but also under alkaline conditions. Some of these N-unsubstituted triazoles are very polar and extremely water-soluble even as neutral compounds, and this hampers separation of reagents and by-products.

NH-1,2,3-triazoles from propargyl bromide, sodium azide, and different nucleophiles. First we tested different O- and N-nucleophiles NuH by utilizing the parent azide **2a** ($R^1 = R^2 = H$) as an intermediate, which is easily generated from propargyl tosylate[46] or more conveniently from commercially available bromide **1a** (Table 1). When substrate **1a** was treated at room temperature with an aqueous solution of sodium azide, a minimum amount of a non-nucleophilic organic solvent, such as 1,4-dioxane, dimethyl sulfoxide, acetonitrile, or the alcohol, which is used as nucleophile NuH in the final step (entries 2–6 and 8), should be added to avoid the separation of neat propargyl azide (**2a**). Thus, it was appropriate to apply a lower concentration (for example, 0.24 g/mL) instead of a saturated aqueous solution of sodium azide (0.408 g/mL, 20 °C) to get a homogenous reaction mixture more easily. The neat azide **2a** is dangerously explosive and should not be isolated in large quantity.[47] Furthermore, the undiluted compound tends to dimerization, which leads to a mixture of unwanted 1,4- and 1,5-disubstituted 1,2,3-triazoles via uncatalyzed 1,3-dipolar cycloaddition.[29] If an excess of sodium azide is used, this salt transforms not only **1a** into **2a**, but it acts also as a strong nucleophile to trap the triazafulvene intermediate of type **4**. Consequently, the final product **5o** was formed after heating the reaction mixture, and the yield of this one-pot sequence was determined to be 70% (entry 15). In most cases, we applied a small excess of bromide **1a** and observed complete conversion of sodium azide within 18–24 hours at ambient temperature. The course of this substitution reaction could be detected by measuring the decreasing pH. Protection from light can exclude any photochemical decomposition of azides.

Table 1. One-pot synthesis of NH-1,2,3-triazoles **5a**–**o** from propargyl bromide (**1a**).



Entry	Nu	Conditions (1. step)	Conditions (2. step)	Isolated yield (%)
1[a]	OH	DMSO	NaOH, H_2O	**5a**, 58
2	OMe	H_2O, MeOH	NaOH, MeOH	**5b**, 92
3	OEt	H_2O, EtOH	NaOH, EtOH	**5c**, 82
4	OPr	H_2O, PrOH	NaOH, PrOH	**5d**, 80
5	O*i*Pr	H_2O, *i*PrOH	NaOH, *i*PrOH	**5e**, 85
6	OCH_2CH_2OEt	H_2O, $MeOCH_2CH_2OH$	NaOH, $MeOCH_2CH_2OH$	**5f**, 44
7[b]	$OCH_2C{\equiv}CH$	H_2O, dioxane	NaOH, $HC{\equiv}CCH_2OH$	**5g**, 57
8[b]	$OCH_2CH{=}CH_2$	H_2O, $CH_2{=}CH{-}CH_2OH$	NaOH	**5h**, 59
9[c]	OPh	H_2O, MeCN	NaOH, PhOH, H_2O	**5i**, 50
10	OAc	H_2O, DME	NaOAc, H_2O	**5j**, 74
11[d]	NH_2	H_2O, dioxane	NH_3, H_2O	**5k**, 77
12[e]	NHMe	H_2O, dioxane	$MeNH_2$, H_2O	**5l**, 50
13[e]	NMe_2	H_2O, dioxane	Me_2NH, H_2O	**5m**, 15
14[f]	$N[(CH_2)_7Me]_2$	H_2O, dioxane	$HN[(CH_2)_7Me]_2$	**5n**, 62
15	N_3	H_2O, dioxane	NaN_3	**5o**, 70

[a]The reaction can also be performed with propargyl tosylate instead of **1a**. [b]Heated at 70 °C for 60 h in the second step. [c]Propargyl chloride instead of **1a** was utilized. [d]Recondensation of the reaction mixture after the first step, and heating at 50–60 °C for 3 days in the second step. [e]Heated at 50–55 °C for 24 h in the second step. [f]Heated at 60 °C for 10 days in the second step.

After the transformation **1a** → **2a**, the one-pot reaction sequence to prepare triazoles **5a–n** was finished by adding an excess of the O- or N-nucleophiles NuH and heating the homogeneous mixture for 2–3 hours at 65–70 °C. Addition of sodium hydroxide was necessary in the cases of weak nucleophiles, such as water or phenol, to form stronger nucleophilic species (entries 1 and 9). Otherwise, low yields of the desired products, for example **5a** and **5i**, were obtained. We assume that in the absence of efficiently competing reagents, the product of type **5** will function as nucleophile to trap the short-lived intermediate **4**. This would lead to unwanted oligomeric or polymeric products. Even when aliphatic alcohols with pK_a > 14 are used as nucleophiles NuH, addition of sodium hydroxide could be advantageous, although only small proportions of the more nucleophilic alcoholates are generated. In the presence of strong bases, the reaction cascade can

switch from **2** → **3** → **4** → **5** to the base-catalyzed sequence **2** → **6** → **7** → **8**. In the case of the parent compounds **1a** and **2a** (R^1 = R^2 = H), however, the products **5** and **8** are identical. Basic aqueous solutions, in which the NH-1,2,3-triazoles **5** form triazolide salts, can be utilized to remove any non-salt impurities by washing with an organic solvent like diethyl ether. Such a procedure will liberate the reaction mixture from any not consumed dangerous azide of type **2**. On the other hand, separation of the desired product **5** and inorganic salts is very difficult if **5** is present as triazolide or triazolium salt. Thus, pH adjustment of the reaction mixture is necessary to form the uncharged compound **5** before extraction with an organic solvent such as diethyl ether is started. An estimation of the pK_a is useful to reach the isoelectric point of the NH-1,2,3-triazole **5**. For example, pK_a = 8.6 was calculated as an average value of the three tautomers of 4-alkoxymethyl-1,2,3-triazoles depicted in Table 1.[48] In most one-pot sequences, the mixtures were neutralized to pH = 6–7, and even when pH adjustment is optimized, extractions of **5** with the help of Soxhlet apparatus or continuous extraction with perforator equipment were often necessary, since the desired NH-1,2,3-triazoles are highly polar compounds. Especially in the case of 4-aminomethyl-1,2,3-triazole (**5k**), water solubility is excellent and solubility in diethyl ether or chloroform proved to be very low (entry 11). Probably, the formation of internal salts, 4-(ammoniummethyl)-1,2,3-triazolides, is responsible for these properties of NH-1,2,3-triazoles bearing an aminomethyl group in the 4-position. Thus, extractive separation of inorganic salts and **5k** was impossible. Consequently, the reaction mixture was carefully recondensed under reduced pressure after treatment of **1a** with sodium azide. Thereafter, the condensate including a solution of **2a** was heated with aqueous ammonia, which enabled simple workup by evaporation and isolation of the pure product **5k** by recrystallization or sublimation.

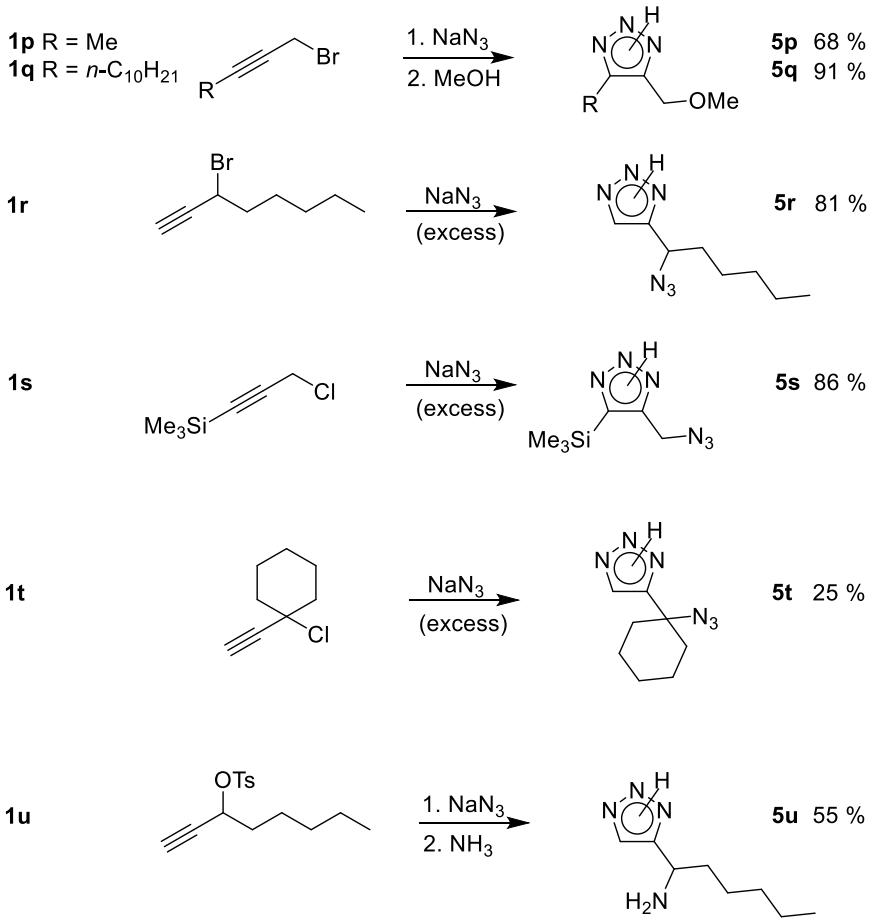
Best yields of the desired products **5a–o** were achieved when a large excess of the nucleophile NuH is utilized to trap the highly reactive intermediate of type **4**. This is no problem in the case of cheap alcohols (see entries 2–5 for example), which can be easily separated from **5** in the workup. However, a compromise is necessary for more expensive or less volatile nucleophiles. Fortunately, amines such as dioctylamine are stronger nucleophiles, and an excess of only 1.33 equivalents led to an acceptable yield of the desired product **5n** (entry 14). In the case of very volatile nucleophiles like ammonia, methylamine, or dimethylamine, the second step has to be performed in an autoclave to avoid early loss of NuH. Alternatively, lower temperatures (50–60 °C) and longer reaction times can be used (entries 11–13). When heated in the presence of organic azides, unsaturated compounds, such as allyl and propargyl alcohols, can undergo unwanted 1,3-dipolar cycloaddition to generate disubstituted 1*H*-1,2,3-triazoles. Obviously, this side reaction could not efficiently compete with the desired formation of **5g** and **5h** (entries 7 and 8), although the yields were somewhat lower than those of heterocycles **5b–e**, which resulted from saturated alcohols (entries 2–5).

It is well known that NH-1,2,3-triazoles exist as a mixture of three tautomers, and rapid equilibration of these species occurs "on the NMR time scale" at room temperature.[1-5,49-51] This leads to a single set of (broad) NMR signals for NH-1,2,3-triazoles and excludes the possibility to separate and isolate the tautomers at ambient temperature.[52,53] We also obtained a single set of

broad ^{13}C NMR signals for the carbon atoms C-4 and C-5 in each case of **5a–o** and did not receive any hint that separation of the tautomers can be achieved at room temperature. Nevertheless, isolation of such tautomers by liquid column chromatography at ambient temperature was recently claimed for several NH-1,2,3-triazoles, including **5a** and **5k**, without any comment on the usually (very) rapid equilibration and any citation of the corresponding previous investigations.[54]

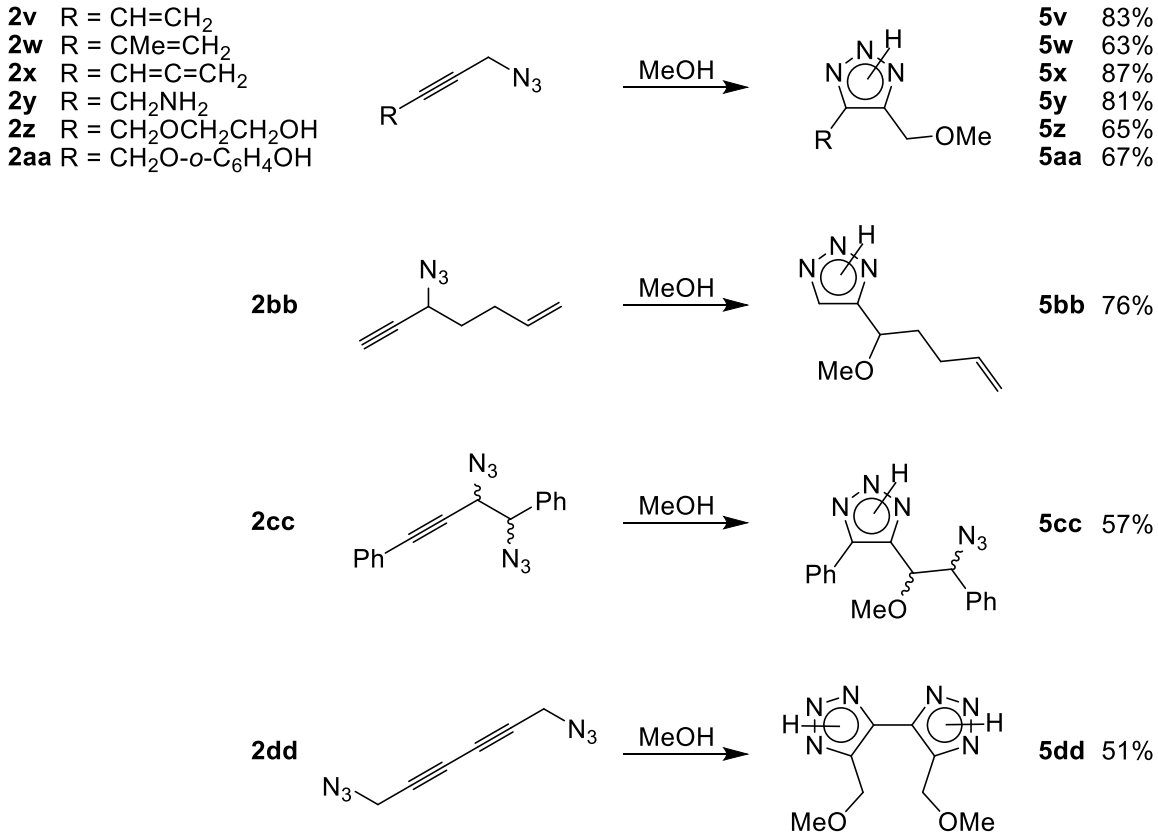
One-pot procedures to prepare NH-1,2,3-triazoles from substituted propargyl halides or sulfonates. By using similar conditions as described in Table 1, we were able to synthesize NH-1,2,3-triazoles **5p–u** (Scheme 2). Thus, propargyl bromides with substituents in 3- or 1-position as well as substituted propargyl chlorides and tosylates could be utilized as substrates. In the case of the tertiary substrate **1t**, the yield of the desired product **5t** was significantly lower. We assume that the transformation of **1t** into the corresponding tertiary propargyl azide of type **2** was hampered by a competing elimination reaction, which should produce an enyne.

The other substrates **1p–s,u** include an unsymmetrical substitution pattern and, in principle, can lead to distinguishable NH-1,2,3-triazoles **8** via prototropic rearrangement **2** → **6** followed by cyclization and trapping of intermediate **7**. Since strongly basic reaction conditions were avoided, heterocyclic products **5p–s,u**, instead of isomeric triazoles of type **8**, were formed through the [3,3]-sigmatropic step **2** → **3** and ring closure to give species **4**.



Scheme 2. Synthesis of NH-1,2,3-triazoles from substituted propargyl halides or sulfonates.

NH-1,2,3-triazoles from functionalized propargyl azides and methanol. In order to clarify whether the sequence **2** → **3** → **4** → **5** is affected or prevented by additional functional groups, for example, by an unwanted further [3,3]-sigmatropic rearrangement of intermediate **3**, we tested the substrates **2v–z,aa–dd** (Scheme 3). The starting compounds **2w,bb**,[55] and **2dd**[56] were described in literature and prepared by simple treatment of the corresponding bromides or mesylates with sodium azide. Similarly, the azide **2v** was available from the appropriate and known[57] mesylate, whereas **2x** was synthesized from hexa-4,5-dien-2-yn-1-ol[58] and phosphorus tribromide followed by the reaction of the resulting propargyl bromide with sodium azide.[59] The amine **2y** was accessible by treating 4-chlorobut-2-yn-1-ylamine hydrochloride[60] with an excess of sodium azide.[59] In the cases of **2z** and **2aa**, the propargyl chlorides, which were necessary to synthesize the azido compounds, were prepared by the reaction of 1,4-dichlorobut-2-yne with ethylene glycol or catechol in the presence of potassium hydroxide.[59] When 2-bromo-2-phenylacetaldehyde[61,62] was reacted with phenylethynylmagnesium bromide, the resulting bromohydrin was transformed into the azidohydrin on exposure to sodium azide followed by mesylation and a second nucleophilic substitution to produce diazide **2cc** as a mixture of *anti/syn* diastereomers.[59]

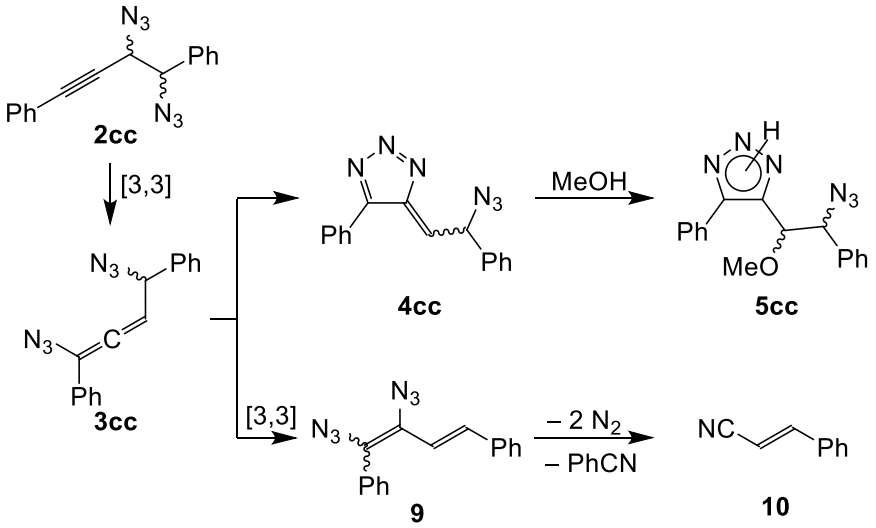


Scheme 3. Treatment of functionalized propargyl azides with methanol to produce 4-methoxymethyl-1,2,3-triazoles.

On gentle heating with an excess of methanol the propargyl azides **2v**, **2w**, and **2x** afforded in moderate to good isolated yields the NH-1,2,3-triazoles **5v**, **5w**, and **5x**, respectively. Obviously, unwanted side reactions of the intermediate allenyl azides **3v–x**, such as electrocyclization of the carbon scaffold or another [3,3]-sigmatropic migration of the azido group, did not hamper the desired ring closure to form **4v–x** and the interception products **5v–x**. On the other hand, it is known from previous experiments that short-lived azidoallenes **3w** and **3x** can be trapped by [4+2]-cycloaddition when solutions of the precursors **2w** or **2x** in tetrahydrofuran were heated in the presence of tetracyanoethene.[63] The allenyl azide **3bb** did not undergo an unwanted Cope rearrangement because of the mild conditions of its formation and subsequent ring closure. Thus, substrate **2bb** led to NH-1,2,3-triazole **5bb** via intermediates **3bb** and **4bb**. This is in contrast to the reported[64] isomerization of 5-thiocyanatohept-1-en-6-yne by flash vacuum pyrolysis at 260–400 °C. In this case, the [3,3]-sigmatropic migration of the thiocyanato group to generate an allenyl isothiocyanate was always accompanied by a succeeding Cope rearrangement.

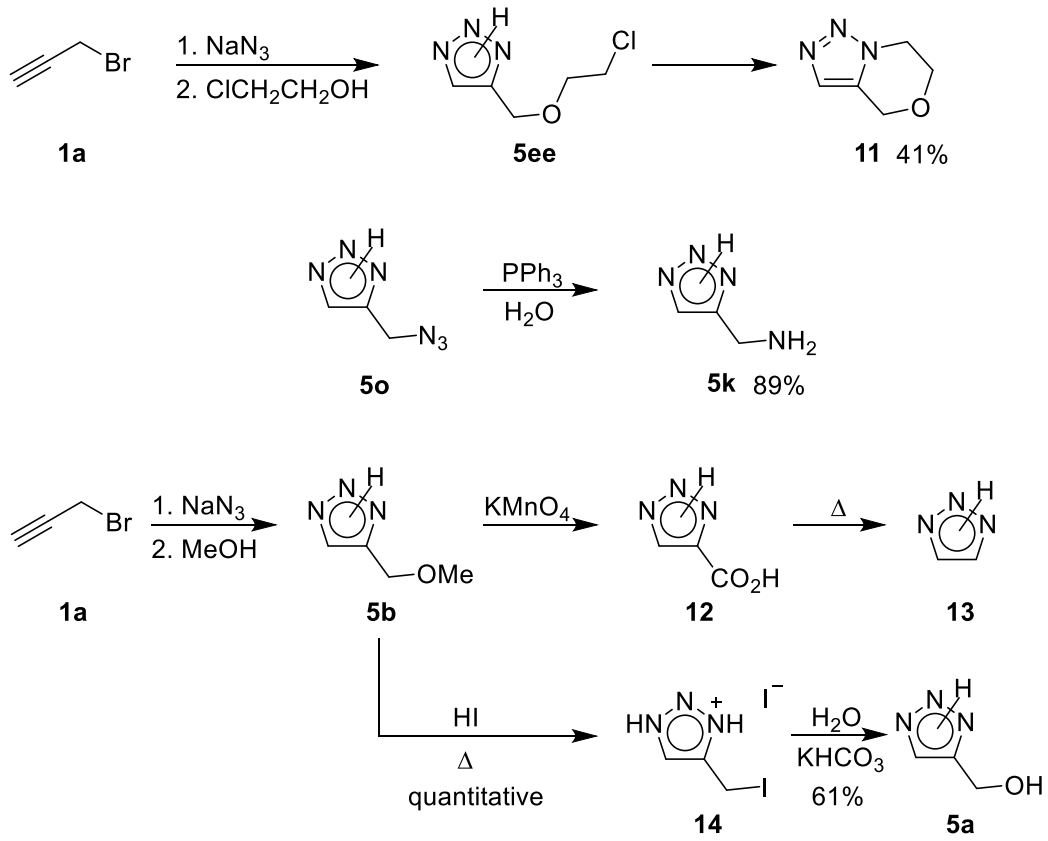
After heating a solution of diazide **2cc** (*anti/syn* ca. 1:1) in methanol, the NH-1,2,3-triazole **5cc** was isolated as a 6:1 mixture of diastereomers with 57% yield. Careful analyses of the crude reaction mixtures with the help of ^{1}H NMR spectroscopy showed that always 9% of cinnamonitrile (**10**) was formed besides 69–71% of the main product **5cc** when substrates *anti*-**2cc** or *syn*-**2cc** were treated with boiling methanol. We explain the generation of the side product **10** through a further [3,3]-sigmatropic shift of an azido group occurring in the intermediate **3cc**, which led to the unstable diazide **9** that liberated two molecules of dinitrogen with formation of **10** and benzonitrile (Scheme 4). The analogous decay of other open-chain 1,2-diazidoethenes to produce two cyano-substituted fragments via very short-lived 2-azido-2*H*-azirines was recently investigated.[65] The competing secondary reactions of **3cc**, electrocylic reaction to generate **4cc** and sigmatropic isomerization to form **9**, are similar to those of 3,4-diazidobuta-1,2-dienes, which were accessible as elusive intermediates by [3,3]-sigmatropic rearrangement of 1,4-diazidobut-2-ynes. In the latter cases, both electrocylization yielding NH-1,2,3-triazoles,[37] and alternatively a second sigmatropic shift to produce 2,3-diazidobuta-1,3-dienes[66-68] were previously reported. The diazide **2dd** did not lead to unwanted side products; however, longer reaction times were necessary to prepare the bi-1,2,3-triazol-4-yl derivative **5dd**.

On heating solutions of **2y**, **2z**, or **2aa** in methanol, the NH-1,2,3-triazole products did not include those of intramolecular trapping of the intermediates **4y**, **4z**, or **4aa**, namely pyrrole or 1,4-dioxocine compounds. Instead, the methanol interception products **5y**, **5z**, and **5aa** were isolated in moderate to good yields. Obviously, intramolecular trapping of the corresponding triazafulvene species **4** is highly disfavored, and even heating of **2y**, **2z**, or **2aa** in non-nucleophilic organic solvents like chloroform or toluene yielded at the most trace amounts (<1%) of such products. The NH-1,2,3-triazole **5y** was previously prepared by treating 4-methoxybut-2-yn-1-yl benzenesulfonate first with sodium azide and then with aqueous ammonia.[30]



Scheme 4. Competing reactions of intermediate diazide **3cc**.

Further reactions of NH-1,2,3-triazoles. When the one-pot synthesis of 1,2,3-triazoles was performed with the substrates **1a**, sodium azide, and 2-chloroethanol, a second ring closure occurred under the reaction conditions, and the final product **11** was isolated (Scheme 5). Obviously, this heterocyclic compound was generated via intermediate **5ee**. Attempts to prepare **11** by treatment of **5a** with 1,2-dibromoethane in the presence of sodium hydroxide only led to very low yields. The Staudinger reaction of azide **5o** with the help of triphenylphosphine and subsequent hydrolysis afforded the amino compound **5k**. In contrast to the phosphorus reagent and the byproduct, the desired product shows excellent water solubility, and thus separation and purification of **5k** was convenient. Oxidation of the methoxymethyl compound **5b** with aqueous potassium permanganate yielded the carboxylic acid **12**. When the one-pot synthesis of **5b** was combined with the oxidation of the crude 4-methoxymethyl-1,2,3-triazole and the known[69] decarboxylation of **12**, the parent 1,2,3-triazole (**13**) could be prepared in 33% yield based on the completely consumed sodium azide (first step). Treatment of **5b** with boiling aqueous hydrogen iodide induced ether cleavage and quantitatively furnished the salt **14**, which could be isolated as an air-sensitive solid. Hydrolysis of **14** led to 4-hydroxymethyl-1,2,3-triazole (**5a**) that confirmed the structure of **14**.



Scheme 5. Further reactions of NH-1,2,3-triazoles.

Conclusions

The one-pot cascade including propargyl azides, allenyl azides, and triazafulvenes turned out to be a convenient method to prepare NH-1,2,3-triazoles. Although this method includes several steps, the formation of the desired products is not hampered by additional functionalities in the propargyl substrates and is compatible with the installation of quite different N- or O-functional groups in the side chain at C-4 of the triazoles. Some of these functionalized NH-1,2,3-triazoles show excellent water solubility, which is a challenge for appropriate workup. On the other hand, such properties are highly welcome when NH-1,2,3-triazoles were synthesized as biologically active agents by the cascade method.[32-36,38-42,45]

Experimental Section

General. Alternative methods to prepare compounds **5b**,[70] **5i**,[70-72] **5o**,[37] and **5y**[30] were reported in the literature. Since we already described the synthesis of **5a**[30] and **5k**[28], these procedures are not

repeated here. Melting points were determined with a Pentakon Dresden Boetius apparatus, and are uncorrected. Refractive indices were measured with a refractometer from Carl Zeiss. FTIR spectra were recorded on a Bruker IFS 28 FTIR spectrophotometer. IR measurements were made on solutions in KBr cuvettes or as potassium bromide pellets. ^{1}H NMR spectra were recorded on Varian Gemini 2000 or Unity Inova 400 spectrometers operating at 300 and 400 MHz, respectively. Using the same spectrometers, ^{13}C NMR data were achieved at 75.4 and 100 MHz. NMR signals were referenced to TMS (δ = 0) or solvent signals and recalculated relative to TMS. The multiplicities of ^{13}C NMR signals were determined with the aid of DEPT135 experiments. MS spectra were measured on a MS9 spectrometer from AEI/Manchester. GC-MS spectra were acquired with Shimadzu quadrupole mass spectrometer. Ionization was performed by EI (70 eV). For the previous separation, a Shimadzu GC-17A gas chromatograph with thermal conductivity detector and DB-1 column (30 m) was used. HR-MS (ESI) spectra were recorded on Applied Biosystems Mariner 5229 mass spectrometer or Bruker micrOTOF-QII spectrometer. For elemental analyses, a Vario EL elemental analyzer from Elementar Analysensysteme GmbH Hanau or a Vario Micro Cube from Elementar were used. Elemental analyses of explosive azides could not be conducted. Flash column chromatography was performed on silica gel 60 (0.04–0.063 mm) from Machery–Nagel. Separations by HPLC were carried out with Knauer HPLC-pump 64 and UV-detector (λ 254 nm).

General procedure for the synthesis of 5b−i. In the first step, sodium azide (1.0 eq) was dissolved in water (15.0 eq); 3-halo-1-propyne (1.1 eq, X = Br, Cl) and defined organic solvent (10 eq, shown in Table 1) were added and stirred at about 30 °C for 18−24 h. In the second step, sodium hydroxide (10 eq) and corresponding alcohol/phenol (10 eq), if needed, were added and heated to 65−70 °C for 2−3 h.

Workup A. The solution was cooled to ambient temperature, neutralized with hydrochloric acid to pH 6−7, and solvents evaporated under vacuum. The residue was dissolved in water, extracted with diethyl ether, and dried over magnesium sulfate. Diethyl ether was evaporated and the crude products were purified by bulb tube distillation (**5b−f**) or by recrystallization (**5i**) to afford pure products.

Workup B. The solution was diluted with water and washed with diethyl ether at pH 12 to remove organic side products. It was neutralized with hydrochloric acid to pH 6−7 and extracted with diethyl ether. The organic layer was washed with water and dried over magnesium sulfate. The volatiles were removed under reduced pressure to afford pure products (**5g,h**).

4-Methoxymethyl-1,2,3-triazole (5b). Yield (92%); bp 95 °C/0.01 mbar; n_D^{20}: 1.4899. IR (film): $\tilde{\nu}$ 3180 (N-H), 2940 (C-H), 1100 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ3.41 (s, 3H, OC*H*$_3$), 4.66 (s, 2H, OC*H*$_2$), 7.78 (s, 1H, C*H*), NH signal could not be detected. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ57.92 (q, O*C*H$_3$), 64.89 (t, O*C*H$_2$), 129.04 (d, *C*H, Ar), 142.67 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 113 (18, M^+), 112 (52, $[M - H]^+$), 82 (82, $[M - OCH_3]^+$). Anal. calcd. for $C_4H_7N_3O$: C, 42.47; H, 6.23; N, 37.14. Found: C, 41.72; H, 6.32; N, 36.70.

4-Ethoxymethyl-1,2,3-triazole (5c). Yield (82%); bp 105 °C/0.01 mbar; n_D^{20}: 1.4769. IR (film): $\tilde{\nu}$ 3150 (N-H), 2980, 2880 (C-H), 1100 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, ^3J 7.0 Hz, 3H, C*H*$_3$), 3.60 (q, ^3J 7.0 Hz, 2H, OC*H*$_2$Me), 4.71 (s, 2H, OC*H*$_2$), 7.79 (s, 1H, C*H*), 13.98 (s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.65 (q, *C*H$_3$), 62.93 (t, O*C*H$_2$), 65.87 (t, O*C*H$_2$Me), 128.89 (d, *C*H, Ar), 142.89 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 126 (1, M^+), 82 (84, [M − OEt]$^+$). Anal. calcd. for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.04. Found: C, 47.04; H, 7.13; N, 33.10.

4-Propoxymethyl-1,2,3-triazole (5d). Yield (80%); bp 110 °C/0.01 mbar; n_D^{20}: 1.4806. IR (film): $\tilde{\nu}$ 3140 (N-H), 2970, 2940, 2880 (C-H), 1105 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, ^3J 7.45 Hz, 3H, C*H*$_3$), 1.63 (tq, 2H, C*H*$_2$Me), 3.49 (t, ^3J 6.80 Hz, 2H, OC*H*$_2$Et), 4.71 (s, 2H, OC*H*$_2$), 7.77 (s, 1H, C*H*), 13.10 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.82 (q, *C*H$_3$), 22.13 (t, *C*H$_2$Me), 62.85 (t, O*C*H$_2$), 71.90 (t, O*C*H$_2$Et), 128.34 (d, *C*H, Ar), 142.62 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 142 (5, [M + H]$^+$), 112 (55, [M − Et]$^+$), 98 (45, [M − C_3H_7]$^+$), 82 (80, [M − OC_3H_7]$^+$). HR-MS (ESI): *m*/*z* 142.0969 [$C_6H_{12}N_3O$, M + H$^+$, calc.: 142.0980], 164.0788 [$C_6H_{11}N_3NaO$, M + Na$^+$, calc.: 164.0799].

4-Isopropoxymethyl-1,2,3-triazole (5e). Yield (85%); bp 115 °C/0.01 mbar; n_D^{20}: 1.4773. IR (film): $\tilde{\nu}$ 3140 (N-H), 2980, 2880 (C-H), 1130, 1070 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, ^3J 6.1 Hz, 6H, C*H*$_3$), 3.75 (sept, ^3J 6.1 Hz, 1H, OC*H*), 4.70 (s, 2H, OC*H*$_2$), 7.75 (s, 1H, C*H*), 13.00 (s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.80 (q, 2 x *C*H$_3$), 60.82 (t, O*C*H$_2$), 71.58 (d, *C*HMe$_2$), 129.67 (d, *C*H, Ar), 143.80 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 142 (4, [M + H]$^+$), 126 (20, [M − CH$_3$]$^+$), 98 (8, [M − *i*Pr]$^+$), 82 (100, [M − O*i*Pr]$^+$). Anal. calcd. for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.76. Found: C, 51.17; H, 7.87; N, 29.68.

4-(2-Ethoxyethoxy)methyl-1,2,3-triazole (5f). Yield (44%); bp 137 °C/0.01 mbar. IR (film): $\tilde{\nu}$ 3200 (N-H), 2960, 2850 (C-H), 1100 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, ^3J 7.0 Hz, 3H, C*H*$_3$), 3.57 (q, ^3J 7.0 Hz, 2H, C*H*$_2$Me), 3.69 (m, 4H, O(C*H*$_2$)$_2$O), 4.72 (s, 2H, OC*H*$_2$), 7.67 (s, 1H, C*H*), NH signal could not be detected. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.92 (q, *C*H$_3$), 63.90 (t, O*C*H$_2$), 66.70 (t, O*C*H$_2$), 69.61 (t, O*C*H$_2$), 69.66 (t, O*C*H$_2$), 130.06 (d, *C*H, Ar), 142.77 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 171 (40, M^+), 142 (3, [M − Et]$^+$), 126 (10, [M – OEt]$^+$), 98 (99, [M − C_2H_4OEt]$^+$), 82 (100, [M − OC_2H_4OEt]$^+$). HR-MS (ESI): *m*/*z* 172.1074 [$C_7H_{14}N_3O_2$, M + H$^+$, calc.: 172.1086], 194.0894 [$C_7H_{13}N_3NaO_2$, M + Na$^+$, calc.: 194.0905].

4-(Prop-2-ynyloxy)methyl-1,2,3-triazole (5g). Yield (57%). IR (film): $\tilde{\nu}$ 3439 (N-H), 3302 (C≡CH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (t, ^4J 2.2 Hz, 1H, C≡C*H*), 4.20 (d, ^4J 2.2 Hz, 2H, OC*H*$_2$C≡CH), 4.77 (s, 2H, OC*H*$_2$), 7.74 (s, 1H, C*H*), 13.52 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.52 (t, O*C*H$_2$C≡CH), 62.26 (t, O*C*H$_2$), 75.28 (d, C≡*C*H), 78.98 (s, *C*≡CH), 130.79 (d, *C*H, Ar), 143.10 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 137 (6, [M + H]$^+$). HR-MS (ESI): *m*/*z* 138.0678 [$C_6H_8N_3O$, M + H$^+$, calc.: 138.0667], 160.0488 [$C_6H_7N_3NaO$, M + Na$^+$, calc.: 160.0487].

4-(Prop-2-en-1-yloxy)methyl-1,2,3-triazole (5h). Yield (59%). IR (film): $\tilde{\nu}$ 3442 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (d, ^3J 6.0 Hz, 2H, CH=C*H*$_2$), 4.65 (s, 2 H, OC*H*$_2$), 5.19 (d, $^3J_{cis}$ 10.2 Hz, 1H, CH=C*H*$_2$), 5.26 (d, $^3J_{trans}$ 17.4 Hz, 1H, C*H*$_2$CH), 5.88 (ddt, $^3J_{trans}$ 17.4 Hz, $^3J_{cis}$ 10.2 Hz, ^3J 6.0 Hz, 1H, C*H*=CH$_2$), 7.71 (s, 1H, C*H*), 8.30 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz,

$CDCl_3$): δ 62.64 (t, O*C*H_2), 71.31 (t, O*C*H_2CH=CH_2), 117.69 (t, CH=*C*H_2), 130.22 (d, *C*H, Ar), 133.79 (d, *C*H=CH_2), 143.36 (s, *C*, Ar). HR-MS (ESI): *m*/*z* 140.0873 [$C_6H_{10}N_3O$, M + H^+, calc.: 140.0824], 162.0691 [$C_6H_9N_3NaO$, M + Na^+, calc.: 162.0643].

4-Phenoxymethyl-1,2,3-triazole (5i). Yield (50%); mp 123.5 °C. IR (KBr): $\tilde{\nu}$ 3170 (N-H), 3040 (=CH), 2930 (C-H), 1600 (C=C), 1240, 1230 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (s, 2H, OC*H*$_2$), 6.96−7.02 (m, 3H, C*H*, Ph), 7.24−7.34 (m, 2H, C*H*, Ph), 7.81 (s, 1H, C*H*), 12.31 (s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 61.60 (t, *C*H_2), 114.90 (d, *C*H, Ph), 121.52 (d, *p*-*C*H, Ph), 129.62 (d, *C*H, Ph), 130.36 (d, *C*H, Ar), 143. 31 (s, *C*, Ar), 158.21 (s, *ipso*-*C*, Ph). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 175 (96, M^+), 146 (13, [$M - N_2 - H]^+$), 118 (37, [$M - CH_3N_3]^+$), 94 (100, PhOH), 82 (80, [$M - OC_5H_5]^+$). Anal. calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.74; H, 5.27; N, 23.96.

4-Acetoxymethyl-1,2,3-triazole (5j). In the first step, sodium azide (6.5 g, 0.1 mol) was dissolved in water (27 mL); 3-bromo-1-propyne (**1a**, 8.3 mL, 0.11 mol) and ethylene glycol dimethyl ether (80 mL) were added and stirred at 22 °C for 18 h. In the second step, a solution of sodium acetate (180.0 g, 2.19 mol) in acetic acid (8.6 mL, 0.15 mol), water (150 mL), and ethylene glycol dimethyl ether (900 mL), was added to the reaction mixture, which was then heated to 70 °C for 2.5 h. The workup was carried out as described at workup A of **5b−i**.

Yield (74%); bp 135 °C/0.01 mbar; n_D^{20}: 1.4907. IR (film): $\tilde{\nu}$ 3120 (N-H), 2920, 2820 (C-H), 1725 (C=O), 1220 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H, C*H*$_3$), 5.29 (s, 2H, OC*H*$_2$), 7.82 (s, 1H, C*H*), 14.00 (s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 20.30 (q, *C*H_3), 56.78 (t, O*C*H_2), 129.34 (d, *C*H, Ar), 141.25 (s, *C*, Ar), 170.97 (s, *C*O). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 141 (8, M^+), 98 (28, [M – Ac]$^+$), 82 (38, [M – OAc]$^+$), 82 (100, [M – O*i*Pr]$^+$). HR-MS (ESI): *m*/*z* 142.0605 [$C_5H_8N_3O_2$, M + H^+, calc.: 142.0611], 164.0428 [$C_5H_7N_3NaO_2$, M + Na^+, calc.: 164.0430].

General procedure for the synthesis of 5l−n. In the first step, sodium azide (1.0 eq) was dissolved in water (15.0 eq); 3-bromo-1-propyne (**1a**, 1.1 eq) and 1,4-dioxane (10 eq) were added and stirred at about 30 °C for 18−24 h. In the second step, an aqueous solution of amine (80 eq) or rather pure dioctyl amine (1.3 eq) were added and heated to 50−60 °C for 1−10 days.

Workup A. The solution was cooled to ambient temperature, and solvents were evaporated under vacuum. The residue was dissolved in water and extracted with diethyl ether. The volatiles were evaporated, and the crude products were purified by bulb tube distillation (**5l,m**).

Workup B. The solution was diluted with water and extracted with diethyl ether at pH 7. The organic layer was washed with water and dried over magnesium sulfate. The volatiles were removed under reduced pressure. Dioctyl amine was evaporated by short way distillation at 150 °C/0.01 mbar to afford pure product (**5n**).

4-(*N*-Methylamino)methyl-1,2,3-triazole (5l). Yield (50%); mp 139−142 °C; bp 155 °C/0.01 mbar. IR (KBr): $\tilde{\nu}$ 3600−2800 (N-H), 1660, 1630 (C=C), 1080 cm^{-1}. ^{1}H NMR (300 MHz, D_2O): δ 2.37 (s, 3H, C*H*$_3$), 3.96 (s, 2H, NC*H*$_2$), 7.42 (s, 1H, C*H*). ^{13}C NMR (75.4 MHz, D_2O): δ 32.68

(q, *C*H_3), 43.90 (t, N*C*H_2), 132.00 (d, *C*H, Ar), 137.10 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 112 (28, M^+), 111 (36, $[M - H]^+$), 97 (5, $[M - CH_3]^+$). HR-MS (ESI): *m*/*z* 113.0832 [$C_4H_9N_4$, M + H^+, calc.: 113.0822], 135.0638 [$C_4H_8N_4Na$, M + Na^+, calc.: 135.0641]. Anal. calcd. for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.96. Found: C, 42.14; H, 7.01; N, 49.88.

4-(*N*,*N*-Dimethylamino)methyl-1,2,3-triazole (5m). Yield (15%); mp 90 °C; bp 80−125 °C/0.01 mbar. IR (KBr): $\tilde{\nu}$ 3400−2800 (N-H), 1560 (C=C) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 6H, C*H*$_3$), 3.67 (s, 2H, NC*H*$_2$), 7.60 (s, 1H, C*H*), 12.19 (s, 1H, N*H*). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 44.37 (q, 2 x *C*H_3), 53.20 (t, *C*H_2), 130.86 (d, *C*H, Ar), 141.96 (s, *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 126 (68, M^+), 125 (44, $[M - H]^+$), 82 (34, $[M - NMe_2]^+$), 44 (100, NMe_2). HR-MS (ESI): *m*/*z* 127.0992 [$C_5H_{11}N_4$, M + H^+, calc.: 127.0978], 149.0800 [$C_5H_{10}N_4Na$, M + Na^+, calc.: 149.0798]. Anal. calcd. for $C_5H_{10}N_4$: C, 47.60; H, 7.98; N, 44.40. Found: C, 47.11; H, 7.70; N, 44.15.

4-(*N*,*N*-Dioctylamino)methyl-1,2,3-triazole (5n). Yellow oil; yield (62%). IR (film): $\tilde{\nu}$ 3444 (N-H) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, ^3J 7.0 Hz, 6H, C*H*$_3$), 1.26 (m, 20H), 1.48 (m, 4H, NCH$_2$C*H*$_2$), 2.44 (t, ^3J 8.0 Hz, 4H, NC*H*$_2$), 3.79 (s, 2H, OC*H*$_2$), 7.61 (s, 1H, C*H*), 9.80 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.07 (q, 2 x *C*H_3), 22.61 (t, 2 x *C*H_2), 26.50 (t, 2 x *C*H_2), 27.45 (t, 2 x *C*H_2), 29.24 (t, 2 x *C*H_2), 29.45 (t, 2 x *C*H_2), 31.77 (t, 2 x *C*H_2), 47.90 (t, N*C*H_2C), 53.68 (t, 2 x N*C*H_2CH$_2$), 131.96 (d, *C*H, Ar), 142.33 (s, *C*, Ar). Anal. calcd. for $C_{19}H_{38}N_4$: C, 70.75; H, 11.87. Found: C, 70.74; H, 11.66.

4-Azidomethyl-1,2,3-triazole (5o). Sodium azide (50.0 g, 0.77 mol) was dissolved in water (200 mL); 3-bromo-1-propyne (**1a**, 4.44 g, 0.126 mol) and dioxane (50 mL) were added over 3 h at 70 °C and stirred at the same temperature for 2 h. The workup was carried out as described at workup B of **5b−i**.

Light yellow oil; yield (70%). IR (film): $\tilde{\nu}$ 2103 (N_3) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55 (s, 2H, C*H*$_2$), 7.79 (s, 1H, C*H*), NH signal could not be detected. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.09 (t, *C*H_2), 129.65 (d, *C*H, Ar), 142.04 (s, *C*, Ar).

4-(Methoxymethyl)-5-methyl-1,2,3-triazole (5p). In the first step, sodium azide (4.7 g, 0.073 mol) was dissolved in water (16 mL); 1-bromo-2-butyne (**1p**, 11.0 g, 0.083 mol) and methanol (45 mL) were added and stirred at 22 °C for 18 h. In the second step, sodium hydroxide (29.2 g, 0.73 mol) in methanol (1 L) was added and heated to reflux for 2 h. The workup was carried out as described at workup A of **5b−i**.

Yield (68%); mp 27 °C; bp 125 °C/0.01 mbar. IR (film): $\tilde{\nu}$ 3160 (NH), 2940 (CH), 1605 (C=C), 1100 (C-O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, C*H*$_3$), 3.39 (s, 3H, OC*H*$_3$), 4.59 (s, 2H, OC*H*$_2$), 14.05 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 8.30 (q, *C*H_3), 57.45 (q, O*C*H_3), 64.01 (t, O*C*H_2), 139.53 (s, 2 x *C*, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 127 (48, M^+), 112 (12, $[M - CH_3]^+$), 97 (100, $[M - 2CH_3]^+$). Anal. calcd. for $C_5H_9N_3O$: C, 47.23; H, 7.14; N, 33.05. Found: C, 47.19; H, 7.10; N, 33.03.

4-Decyl-5-methoxymethyl-1,2,3-triazole (5q). In the first step, sodium azide (0.24 g, 3.7 mmol) was dissolved in methanol (10 mL) and water (3 mL); 1-bromo-2-tridecyne[73] (**1q**, 1.0 g, 3.9 mmol) and methanol (10 mL) were added and stirred at 30 °C for 24 h. In the second step, methanol (150 mL) was added, and the mixture was heated to 60 °C for 4 days. The solution was cooled to ambient temperature and methanol evaporated under vacuum. The residue was dissolved in water and extracted with methyl *tert*-butyl ether. The organic layer was washed with water and dried over magnesium sulfate. The volatiles were removed under reduced pressure to afford the pure product.
Yellow oil; yield (91%). IR (film): $\tilde{\nu}$ 3443 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, ^3J 7.0 Hz, 3H, C*H*$_3$), 1.25 (m, 14H, C*H*$_2$), 1.68 (m, 2H, CCH$_2$C*H*$_2$), 2.73 (t, ^3J 7.0 Hz, 2H, CC*H*$_2$), 3.37 (s, 3H, OC*H*$_3$), 4.58 (s, 2H, OC*H*$_2$), 15.05 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.87 (q, *C*H$_3$), 22.46 (t, *C*H$_2$), 22.45 (t, *C*H$_2$), 28.92 (t, *C*H$_2$), 29.13 (t, *C*H$_2$), 29.35 (t, *C*H$_2$), 29.38 (t, *C*H$_2$), 57.89 (q, O*C*H$_3$), 64.60 (t, O*C*H$_2$), 140.52 (s, *C*, Ar), 144.94 (s, *C*, Ar). Anal. calcd. for $C_{14}H_{27}N_3O$: C, 65.59; H, 10.61; N, 16.39. Found: C, 66.16; H, 10.65; N, 16.92.

General procedure for the synthesis of 5r−t. The 3-halo-1-propynes **1r**,[74] **1s**,[75] or **1t**[76] (1.0 eq) were dissolved in a solution of dioxane/water (3:1); sodium azide (6.0 eq) and ammonium chloride (3.0 eq) were added and stirred at 85 °C for 16−20 h. The workup was carried out as described at workup B of **5b−i**.
4-(1-Azidohexyl)-1,2,3-triazole (5r). Yellow oil; yield (81%). IR (film): $\tilde{\nu}$ 2102 (N_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 3H, C*H*$_3$), 1.30 (m, 6H, C*H*$_2$), 1.90 (m, 2H, C*H*$_2$), 4.66 (t, ^3J 7.2 Hz, 1H, C*H*N$_3$), 7.71 (s, 1H, C*H*, Ar), 8.40 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.94 (q, *C*H$_3$), 22.43 (t, *C*H$_2$), 25.57 (t, *C*H$_2$), 31.26 (t, *C*H$_2$), 34.30 (t, *C*H$_2$), 57.49 (d, *C*HN$_3$), 129.89 (d, *C*H, Ar), 146.83 (s, *C*, Ar). HR-MS (ESI): *m*/*z* 152.1185 [$C_8H_{14}N_3$, M – N_3^-, calc.: 152.1185], 167.1265 [$C_8H_{14}N_4$, M – N_2, calc.: 167.1297], 195.1354 [$C_8H_{15}N_6$, M + H^+, calc.: 195.1358], 217.1190 [$C_8H_{14}N_6Na$, M + Na^+, calc.: 217.1178].
4-Azidomethyl-5-trimethylsilyl-1,2,3-triazole (5s). White needles, yield (86%), mp 125−128 °C. IR (film): $\tilde{\nu}$ 3431 (NH), 2102 (N_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.40 (s, 9H, C*H*$_3$), 4.56 (s, 2H, C*H*$_2$), 12.00 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −1.22 (q, 3 x *C*H$_3$), 45.72 (t, *C*H$_2$), 135.27 (s, *C*, Ar), 147.11 (s, *C*, Ar). HR-MS (ESI): *m*/*z* 197.0972 [$C_6H_{13}N_6Si$, M + H^+, calc.: 197.0971], 219.0822 [$C_6H_{12}N_6Na$, M + Na^+, calc.: 219.0790].
4-(1-Azidocyclohexyl)-1,2,3-triazole (5t). Yellow oil, yield (25%). IR (film): $\tilde{\nu}$ 3440 (NH), 2104 (N_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38−2.12 (m, 10H, C*H*$_2$), 7.70 (s, 1H, C*H*, Ar), NH signal could not be detected. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.93 (t, 2 x *C*H$_2$), 24.95 (t, *C*H$_2$), 35.09 (t, 2 x *C*H$_2$), 61.39 (s, *C*N$_3$), 128.82 (d, *C*H, Ar), 150.54 (s, *C*, Ar). HR-MS (ESI): *m*/*z* 122.0965 [$C_8H_{12}N$, M – N_2 − N_3^-, calc.: 122.0970], 150.1008 [$C_8H_{12}N_3$, M – N_3^-, calc.: 150.1031], 190.0932 [$C_8H_{10}N_6$, M − 2H^+, calc.: 190.0967], 193.1173 [$C_8H_{13}N_6$, M + H^+, calc.: 193.1202], 215.1001 [$C_8H_{12}N_6Na$, M + Na^+, calc.: 215.1021], 299.1977 [$C_{16}H_{23}N_6$, 2M – H^+ − N_3^-, calc.: 299.1984].

4-(1-Aminohexyl)-1,2,3-triazole (5u). In the first step, sodium azide (0.43 g, 6.6 mmol) was dissolved in methanol (10 mL) and water (3 mL); oct-1-in-3-ol *p*-toluenesulfonate[77] (**1u**, 1.53 g, 5.46 mmol) and methanol (10 mL) were added and stirred at 22 °C for 24 h. The solution was diluted with water and extracted with diethyl ether. The organic layer was washed with water and evaporated at low temperature. In the second step, ammonia (25% in water, 150 mL) was added and heated to 60 °C for 3 days. The volatiles were removed under reduced pressure (30 °C/0.001 mbar) to afford the pure product, which was purified by sublimation at 70 °C/0.001 mbar.
Colorless solid; yield (55%), mp 172 °C. IR (KBr): $\tilde{\nu}$ 3492 (NH/NH_2), 1658 (NH/NH_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, ^3J 6.0 Hz, 3H, CH_3), 1.28 (m, 6H, CH_2), 1.74 (m, 2H, CHCH_2), 4.08 (t, ^3J 7.0 Hz, 1H, C*H*NH_2), 7.56 (s, 1H, C*H*, Ar), NH and NH_2 signals could not be detected. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 12.37 (q, *C*H_3), 20.97 (t, *C*H_2), 24.13 (t, *C*H_2), 30.01 (t, *C*H_2), 36.33 (t, *C*H_2), 46.32 (d, *C*HNH_2), 127.52 (d, *C*H, Ar), 149.21 (s, *C*, Ar). Anal. calcd. for $C_8H_{16}N_4$: C, 57.11; H, 9.58; N, 33.30. Found: C, 57.21; H, 9.51; N, 32.74.

General procedure for the synthesis of 5v−dd. Propargyl azide **2v−z,aa−dd**[59] was dissolved in methanol and stirred at 60 °C for 1−17 days. The volatiles were removed under reduced pressure to afford the pure products **5v−z,bb**. In case of **5aa**, the crude product was suspended in chloroform to crystallize the pure product. The workup of **5cc** was carried out as described at workup B of **5b−i**. The residue of **5dd**, after evaporation of the solvents, was dissolved in a solution of methanol/water (3:1). This mixture was triturated with diethyl ether, thereby, resulting in the precipitation of a solid, which was washed with methanol to afford the pure product **5dd**.
4-Ethenyl-5-(methoxymethyl)-1,2,3-triazole (5v). Heated for 1 day, yellow oil; yield (83%). IR ($CDCl_3$): $\tilde{\nu}$ 3437 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2), 5.45 (d, $^3J_{cis}$ 11.0 Hz, 1H, CH=CH_2), 5.90 (d, $^3J_{trans}$ 17.0 Hz, 1H, CH=CH_2), 6.73 (dd, $^3J_{trans}$ 17.0 Hz, $^3J_{cis}$ 11.0 Hz, 1H, C*H*=CH_2), 10.30 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.89 (q, O*C*H_3), 64.63 (t, O*C*H_2), 118.40 (t, C=*C*H_2), 123.60 (d, *C*H=CH_2), 139.50 (s, *C*, Ar), 141.01 (s, *C*, Ar). GC-MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 139 (25, M^+). Anal. calcd. for $C_6H_9N_3O$: C, 51.79; H, 6.52. Found: C, 51.28; H, 6.79.
4-(Methoxymethyl)-5-(1-methylethenyl)-1,2,3-triazole (5w). Heated for 3 days, brown oil; yield (63%). IR ($CDCl_3$): $\tilde{\nu}$ 3440 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2), 5.26 (s, 1 H, C=CH_2), 5.45 (s, 1 H, C=CH_2), 11.05 (s, 1 H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.65 (q, *C*H_3), 57.94 (q, O*C*H_3), 65.46 (t, O*C*H_2), 116.48 (t, C=*C*H_2), 133.53 (s, *C*, Ar), 139.23 (s, *C*, Ar), 144.58 (s, *C*=CH_2). GC-MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 153 (23, M^+). Anal. calcd. for $C_7H_{11}N_3O$: C, 54.89; H, 7.24; N, 27.43. Found: C, 54.30; H, 6.87; N, 27.41.
4-(Methoxymethyl)-5-(propa-1,2-dienyl)-1,2,3-triazole (5x). Heated for 4 days, brown oil; yield (87%). IR ($CDCl_3$): $\tilde{\nu}$ 3437 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (s, 3H, OCH_3), 4.63 (s, 2H, OCH_2), 5.21 (d, ^4J 7.0 Hz, 2H, C=CH_2), 6.39 (t, ^4J 7.0 Hz, 1H, C=C*H*), 13.85 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 58.25 (q, O*C*H_3), 64.92 (t, O*C*H_2), 79.01 (t, C=*C*H_2), 82.85 (d,

C=*C*H), 137.92 (s, *C*, Ar), 140.16 (s, *C*, Ar), 210.76 (s, *C*=CH_2). GC-MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 151 (35, M^+). Anal. calcd. for $C_7H_9N_3O$: C, 55.62; H, 6.00. Found: C, 55.79; H, 5.58.

4-(2-Hydroxyethoxymethyl)-5-(methoxymethyl)-1,2,3-triazole (5z). Heated for 4 days, brown oil; yield (65%). IR ($CDCl_3$): $\tilde{\nu}$ 3438 (OH), 3130 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ3.34 (s, 3H, OC*H*$_3$), 3.64 (t, *J* 4.0 Hz, 2H, OC*H*$_2$), 3.75 (t, *J* 4.0 Hz, 2H, OC*H*$_2$), 4.57 (s, 2H, OC*H*$_2$), 4.69 (s, 2H, OC*H*$_2$), 14.30 (s, 1H, N*H*) (OH signal could not be detected). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ57.33 (q, O*C*H$_3$), 60.47 (t, O*C*H$_2$), 62.35 (t, O*C*H$_2$), 63.75 (t, O*C*H$_2$), 71.36 (t, O*C*H$_2$), 139.83 (s, 2 x *C*, Ar). HR-MS (ESI): *m*/*z* 188.1038 [$C_7H_{14}N_3O_3$, M + H^+, calc.: 188.1035], 210.0860 [$C_7H_{13}N_3NaO_3$, M + Na^+, calc.: 210.0855], 226.0594 [$C_7H_{13}KN_3O_3$, M + K^+, calc.: 226.0594].

4-(o-Hydroxyphenoxymethyl)-5-(methoxymethyl)-1,2,3-triazole (5aa). Heated for 3 days, colorless solid, yield (67%), mp 136 °C. IR (KBr): $\tilde{\nu}$ 3430 (OH/NH) cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ3.21 (s, 3H, OC*H*$_3$), 3.56 (s, 1H, O*H*), 4.42 (s, 2H, C*H*$_2$OMe), 5.12 (s, 2H, C*H*$_2$OAr), 6.71 (m, 1H, Ar), 6.78 (m, 2H, Ar), 7.00 (m, 1H, Ar), 8.96 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, d_6-DMSO): δ56.42 (q, O*C*H$_3$), 60.16 (t, *C*H$_2$), 62.58 (t, *C*H$_2$), 114.00 (d, *C*H, Ar), 114.90 (d, *C*H, Ar), 118.11 (d, *C*H, Ar), 120.80 (d, *C*H, Ar), 141.84 (s, *C*, triazole), 142.92 (s, *C*, triazole), 146.14 (s, *C*, Ar), 147.12 (s, *C*, Ar). GC-MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 151 (35, M^+). Anal. calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.90; H, 5.52; N, 17.65.

4-(1-Methoxypent-4-en-1-yl)-1,2,3-triazole (5bb). Heated for 3 days, brown oil; yield (76%). IR ($CDCl_3$): $\tilde{\nu}$ 3442 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ1.86 (m, 2H, CH(OMe)C*H*$_2$), 2.12 (m, 2H, CHC*H*$_2$), 3.28 (s, 3H, OC*H*$_3$), 4.50 (t, ^3J 7.1 Hz, 1H, C*H*OMe), 4.96 (d, $^3J_{cis}$ 10.0 Hz, 1H, CH=C*H*$_2$), 5.01 (d, $^3J_{trans}$ 17.4 Hz, 1H, CH=C*H*$_2$), 5.80 (ddt, $^3J_{trans}$ 17.4 Hz, $^3J_{cis}$ 10.0 Hz, ^3J 7.1 Hz, 1H, C*H*=CH_2), 7.27 (s, 1H, C*H*, Ar), 9.38 (s, 1H, N*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ29.42 (t, *C*H$_2$), 34.87 (t, *C*H$_2$), 56.72 (q, O*C*H$_3$), 74.86 (d, *C*HOMe), 115.10 (t, CH=*C*H$_2$), 128.67 (d, *C*H, Ar), 137.52 (d, *C*H=CH_2), 146.84 (s, *C*, Ar). HR-MS (ESI): *m*/*z* 168.1153 [$C_8H_{14}N_3O$, M + H^+, calc.: 168.1137].

5-(2-Azido-1-methoxy-2-phenylethyl)-4-phenyl-1,2,3-triazole (5cc). Heated for 40 h, brown-orange oil; yield (57%). IR ($CDCl_3$): $\tilde{\nu}$ 3433 (NH), 2108 (N_3) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ3.38 (s, 3H, OC*H*$_3$), 4.74 (d, ^3J 7.6 Hz, 1H, C*H*, minor isomer), 4.84 (d, ^3J 9.4 Hz, 1H, C*H*, main isomer), 4.98 (d, ^3J 9.4 Hz, 1H, C*H*, main isomer), 5.02 (d, ^3J 7.4 Hz, 1H, C*H*, minor isomer), 6.84−7.70 (m, 10H, C*H*, Ph), 13.58 (s, 1H, N*H*) (OH signal could not be detected). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ57.07 (q, O*C*H$_3$), 67.91 (d, *C*H), 79.40 (d, *C*H), 127.50 (d, *C*H, Ar), 128.40 (d, *C*H, Ar), 128.41 (d, *C*H, Ar), 128.74 (d, *C*H, Ar), 129.10 (d, *C*H, Ar), 131.31 (s, *C*, Ar), 132.25 (s, *C*, Ar), 135.62 (d, *C*H, Ar) 139.41 (s, *C*, triazole), 144.98 (s, *C*, triazole). HR-MS (ESI): *m*/*z* 343.1302 [$C_{17}H_{16}N_6NaO$, M + Na^+, calc.: 343.1283].

Thermolysis of 2cc. A solution of 3,4-diazido-1,4-diphenylbut-1-yne (***syn***- or ***anti***-**2cc**, 10.0 mg, 0.0347 mmol) in methanol (3 mL) was stirred at 60 °C for 3 days. The methanol was evaporated and the residue contained a mixture of **5cc** (69−71%), and cinnamonitrile (**10**, 9%), analyses by ^1H NMR including an internal standard.

5,5'-Bis(methoxymethyl)-[4,4']bi[1,2,3-triazolyl] (5dd). Heated for 17 days, light-brown solid, yield (51%), mp 199 °C. IR (KBr): $\tilde{\nu}$ 3163 (NH) cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO): δ 3.25 (s, 6H, OC*H*$_3$), 4.74 (s, 4H, OC*H*$_2$), 7.40 (s, 2H, N*H*). ^{13}C NMR (100.6 MHz, d_6-DMSO): δ 57.57 (q, O*C*H$_3$), 63.94 (t, O*C*H$_2$), 136.66 (s, *C*, Ar), 141.44 (s, *C*, Ar). Anal. calcd. for $C_8H_{12}N_6O_2$: C, 42.85; H, 5.39; N, 37.48. Found: C, 42.97; H, 5.01; N, 36.53.

6,7-Dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (11). Sodium azide (6.5 g, 0.1 mol) was dissolved in water (80 mL); 3-bromo-1-propyne (**1a**, 8.3 mL, 0.11 mol) in ethylene glycol dimethyl ether (400 mL) was added, and the mixture was stirred at 22 °C for 18 h. The reaction mixture was charged with 2-chloroethanol (1.0 L, 14.93 mol) and heated to 65−70 °C for 3 h. The volatiles were removed under reduced pressure. The residue was dissolved in water (1.5 L), potassium hydroxide (6.17 g, 0.11 mol) was added and heated under reflux for 18 h. Water was evaporated, the residue was suspended in chloroform (150 mL), and undissolved salts were removed by filtration. The solvents were evaporated under reduced pressure and the crude product was purified by bulb tube distillation at 140−150 °C/0.01 mbar to afford the pure product, which is sensitive to oxidation; thus, the ether functionality is easily transformed into a lactone (6,7-dihydro-[1,2,3]triazolo[5,1-c][1,4]oxazin-4-one).
Yield (41%); bp 145 °C/0.01 mbar; n_D^{20}: 1.5246. IR (film): $\tilde{\nu}$ 3130 (C-H), 2870 (C-H), 1085 (C-O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.12 (t, *J* 5.26 Hz, 2H, C*H*$_2$), 4.44 (t, *J* 5.26 Hz, 2H, C*H*$_2$), 4.93 (d, *J* 0.49 Hz, 2H, C*H*$_2$), 7.49 (s, 1H, C*H*, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 45.35 (t, *C*H$_2$), 62.20 (t, *C*H$_2$), 63.54 (t, *C*H$_2$), 128.06 (*C*=*C*H, Ar), 130.60 (*C*=*C*H, Ar). MS [*IP* 70 eV; *m*/*z* (% rel. int.)]: 125 (100, *M*), 111 (3, $[M - CH_2]^+$), 109 (2, $[M - O]^+$), 95 (10, $[M - CH_2O]^+$), 67 (100, $[M - CH_2OC_2H_4]^+$). HR-MS (ESI): *m*/*z* 126.0666 [$C_5H_8N_3O$, $M + H^+$, calc.: 126.0662], 148.0480 [$C_5H_7N_3NaO$, $M + Na^+$, calc.: 148.0481].

Staudinger reaction of 5o. 4-Azidomethyl-1,2,3-triazole (**5o**, 0.68 g, 5.5 mmol) was dissolved in dry diethyl ether (20 mL), charged with a solution of triphenylphosphine (1.57 g, 6.0 mmol) in dry diethyl ether (20 mL), and stirred at room temperature for 24 h. The diethyl ether was evaporated, the residue diluted with tetrahydrofuran (40 mL) and water (10 mL), and refluxed for 1.5 h. The volatiles were removed under reduced pressure, the residue was stirred in water (50 mL), and washed with organic solvent. The water was evaporated to afford the pure product **5k** (0.48 g, 4.9 mmol, 89%), which was identical with the previously synthesized[28] compound.

Oxidation of 5b followed by decarboxylation to form 13. 3-Bromo-1-propyne (**1a**, 23.8 g, 0.200 mol) was dissolved in methanol (100 mL), charged with sodium azide (11.8 g, 0.1815 mol) in water (50 mL), and stirred at room temperature for 14 h. The mixture was added to a solution of sodium hydroxide (36.3 g, 0.908 mol) in methanol (700 mL) and heated under reflux for 2 h. The methanol was evaporated and the residue diluted with water (400 mL). Potassium hydroxide (17.7 g, 0.315 mol) was added to the solution, which was charged in portions with potassium permanganate (41.1 g, 0.259 mol). The mixture was stirred for 12 h at room temperature and,

thereafter, heated at 70 °C for 3 h. The suspension was filtered and the clear filtrate dissolved in hydrochloric acid. During the evaporation of the volatiles, carboxylic acid **12**[69] crystallized in the cold solution. The solid was separated by filtration and heated at 300 °C in an open apparatus of recondensation to remove carbon dioxide. The triazole **13** (4.18 g, 60.5 mmol, 33%, based on sodium azide) was isolated by recondensation ($5\cdot10^{-3}$ mbar) at room temperature.

Synthesis of 14. 4-Methoxymethyl-1,2,3-triazole (**5b**, 12.0 g, 0.11 mol) and hydroiodic acid (24.0 g, 57% aqueous solution) were heated under reflux and methyl iodide and water removed by distillation for 3 h until yellow hydroiodic acid was noticed. The solution was cooled to ambient temperature and the volatiles were removed under reduced pressure ($5\cdot10^{-3}$ mbar) to afford the crude product (34.4 g, 0.10 mmol, 96%). The pure product was obtained by recrystallization (MeCN).

4-(Iodomethyl)-1,2,3-triazole hydroiodide (14). White solid, yield (96%), mp 159−163 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 4.61 (s, 2H, CH_2), 8.20 (s, 1H, C*H*, Ar). ^{1}H NMR (400 MHz, D_2O): δ 4.40 (s, 2H, CH_2), 7.95 (s, 1H, C*H*, Ar). ^{13}C NMR (100.6 MHz, CD_3OD): δ ca. −12.5 (s, 2H, CH_2), 128.32 (d, *C*H, Ar), 144.87 (s, *C*, Ar).

Hydrolysis of 14. 4-(Iodomethyl)-1,2,3-triazole hydroiodide (**14**, 3.4 g, 10.1 mmol) in acetonitrile (20 mL) was added dropwise to a solution of potassium bicarbonate (3.03 g, 30 mmol) in water (20 mL), and the mixture was stirred at room temperature for 24 h followed by heating at 50 °C for 6 h. After evaporation, the residue was dissolved in water, and sulfuric acid was added to generate a pH of 5−6. Water was removed under reduced pressure, and the crude product was extracted by Soxhlet extraction with diethyl ether for 2 days. The diethyl ether was evaporated and a distillation ($5\cdot10^{-3}$ mbar) afford the pure product **5a** (0.61 g, 6,2 mmol, 61%), which was identical with the previously prepared[30] compound.

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Supplementary Materials

Supplementary materials include synthesis and characterization of the azides **2v**, **2x**, **2y**, **2z**, **2aa**, and **2cc**.

References

1. Tomé, A. C. In *Science of Synthesis, Vol. 13*; Storr, R. C.; Gilchrist, T. L., Eds.; Thieme: Stuttgart, 2004; pp 415–601.
2. Fan, W.-Q., Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II, Vol. 4*; Katritzky, A. R., Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, 1996; pp 1–126.
3. Wamhoff, H. In *Comprehensive Heterocyclic Chemistry, Vol. 5, Part 4A*; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon: Oxford, 1984; pp 669–732.
4. Finley, K. T. In *The Chemistry of Heterocyclic Compounds, Vol. 39, Triazoles: 1,2,3*; Montgomery, J. A., Ed.; Wiley: New York, 1980.
5. Dehne, H. In *Houben–Weyl, Vol. E8d*; Schaumann, E., Ed.; Thieme: Stuttgart, 1994; pp 305–405.
6. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. http://dx.doi.org/10.1021/jo011148j
7. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. http://dx.doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
8. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021. http://dx.doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5
9. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952–3015. http://dx.doi.org/10.1021/cr0783479
10. Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. Eur. *J. Org. Chem.* **2006**, 51–68. http://dx.doi.org/10.1002/ejoc.200500483
11. Schilling, C.; Jung, N.; Bräse, S. In *Organic Azides: Syntheses and Applications*; Bräse, S.; Banert, K., Eds.; Wiley: Chichester, UK, 2010; pp 269–284.
12. Loren, J. C.; Krasiñski, A.; Fokin, V. V.; Sharpless, K. B. *Synlett* **2005**, 2847–2850. doi.org/10.1055/s-2005-918944
13. Thompson, R. L.; Damodaran, K.; Luebke, D.; Nulwala, H. *Synlett* **2013**, 24, 1093–1096. http://dx.doi.org/10.1055/s-0033-1338435
14. Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789–3791. http://dx.doi.org/10.1002/ejoc.200400442
15. Birkofer, L.; Ritter, A. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 417–429 http://dx.doi.org/10.1002/anie.196504171
16. Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786–7787. http://dx.doi.org/10.1021/ja034191s
17. Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117–9118. http://dx.doi.org/10.1016/S0040-4039(01)01923-2
18. Rasberger, M.; Zbiral, E. *Monatsh. Chem.* **1969**, *100*, 64–67. http://dx.doi.org/10.1007/BF00938237

19. Quiclet-Sire, B.; Zard, S. Z. *Synthesis* **2005**, 3319–3326. http://dx.doi.org/10.1055/s-2005-918463
20. Zefirov, N. S.; Chapovskaya, N. K.; Kolesnikov, V. V. *Chem. Commun.* **1971**, 1001–1002. http://dx.doi.org/10.1039/C29710001001
21. Wu, L.; Wang, X.; Chen, Y.; Huang, Q.; Lin, Q.; Wu, M. *Synlett* **2016**, *27*, 437–441. doi.org/10.1055/s-0035-1560528
22. Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 6893–6896. http://dx.doi.org/10.1002/anie.200601045
23. Jiang, Y.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 4256–4260. DOI: 10.1055/s-0030-1258312
24. Zhang, W.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 283–287. DOI: 10.1055/s-0029-1217097
25. Augustine, J. K.; Boodappa, C.; Venkatachaliah, S. *Org. Biomol. Chem.* **2014**, *12*, 2280–2288. http://dx.doi.org/10.1039/c3ob42276c
26. Ognyanov, V. I.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 899–903. http://dx.doi.org/10.1002/hlca.19910740421
27. Dimroth, O. *Justus Liebigs Ann. Chem.* **1909**, *364*, 183–226. http://dx.doi.org/10.1002/jlac.19093640204
28. Banert, K. *Chem. Ber.* **1989**, *122*, 911–918. http://dx.doi.org/10.1002/cber.19891220520
29. Banert, K.; Hagedorn, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1675–1676. http://dx.doi.org/10.1002/anie.198916751
30. Banert, K. *Chem. Ber.* **1989**, *122*, 1963–1967. http://dx.doi.org/10.1002/cber.19891221022
31. Banert, K. *Chem. Ber.* **1989**, *122*, 1175–1178. http://dx.doi.org/10.1002/cber.19891220624
32. Harrison, T.; Owens, A. P.; Williams, B. J.; Swain, C. J.; Williams, A.; Carlson, E. J.; Rycroft, W.; Tattersall, F. D.; Cascieri, M. A.; Chicchi, G. G.; Sadowski, S.; Rupniak, N. M. J.; Hargreaves, R. J. *J. Med. Chem.* **2001**, *44*, 4296–4299. http://dx.doi.org/10.1021/jm0109558
33. Owens, A. P. (Merck Sharp and Dohme Limited, UK), WO 9629317, 1996; *Chem. Abstr.* **1997**, *126*, 8122.
34. Baker, R.; Elliot, J.; Stevenson, G. I.; Swain, C. J. (Merck Sharp and Dohme Limited), WO 9701553, 1997; *Chem. Abstr.* **1997**, *126*, 171610.
35. Baker, R.; Elliot, J.; Stevenson, G. I.; Swain, C. J. (Merck Sharp and Dohme Limited), WO 9701554, 1997; *Chem. Abstr.* **1997**, *126*, 171611.
36. Moseley, J. D.; Swain, C. J.; Williams, B. J. (Merck Sharp and Dohme Limited, UK), GB 2302689, 1997; *Chem. Abstr.* **1997**, *126*, 277501.
37.

38. Loren, J. C.; Sharpless, K. B. *Synthesis* **2005**, 1514–1520. DOI: 10.1055/s-2005-869892
39. Blackaby, W. P.; Atack, J. R.; Bromidge, F.; Lewis, R.; Russell, M. G. N.; Smith, A.; Wafford, K.; McKernan, R. M.; Street, L. J.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2005**, 4998–5002. http://dx.doi.org/10.1016/j.bmcl.2005.08.006
40. Weide, T.; Saldanha, S. A.; Minond, D.; Spicer, T. P.; Fotsing, J. R.; Spaargaren, M.; Frère, J.-M.; Bebrone, C.; Sharpless, K. B.; Hodder, P. S.; Fokin, V. V. *ACS Med. Chem. Lett.* **2010**, *1*, 150–154. http://dx.doi.org/10.1021/ml900022q
41. Minond, D.; Saldanha, S. A.; Subramaniam, P.; Spaargaren, M.; Spicer, T.; Fotsing, J. R.; Weide, T.; Fokin, V. V.; Sharpless, K. B.; Galleni, M.; Bebrone, C.; Lassaux, P.; Hodder, P. *Bioorg. Med. Chem.* **2009**, *17*, 5027–5037. http://dx.doi.org/10.1016/j.bmc.2009.05.070
42. Seward, E. M.; Carlson, E.; Harrison, T.; Haworth, K. E.; Herbert, R.; Kelleher, F. J.; Kurtz, M. M.; Moseley, J.; Owen, S. N.; Owens, A. P.; Sadowski, S. J.; Swain, C. J.; Williams, B. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2515–2518. http://dx.doi.org/10.1016/S0960-894X(02)00506-1
43. Koszytkowska-Stawińska, M.; Sas, W. *Tetrahedron* **2013**, *69*, 2619–2627. http://dx.doi.org/10.1016/j.tet.2013.01.042
44. Wang, T.; Zhou, W.; Yin, H.; Ma, J.-A.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10823–10826. http://dx.doi.org/10.1002/anie.201205779
45. Fotsing, J. R.; Banert, K. Eur. *J. Org. Chem.* **2005**, 3704–3714. http://dx.doi.org/10.1002/ejoc.200500135
46. Willoughby, C.; Chapman, K. T. (Merck & Co., Inc.), WO2003065987, 2003; *Chem. Abstr.* **2003**, *139*, 164981.
47. Reppe, W. Liebigs *Ann. Chem.* **1955**, *596*, 1–224. http://dx.doi.org/10.1002/jlac.19555960102
48. Priebe, H. *Acta Chem. Scand.* **1984**, *B38*, 895–898. http://dx.doi.org/10.3891/acta.chem.scand.38b-0895
49. Estimation of pKa and isoelectric point were done by MarvinSketch 6.0.4 (by ChemAxon) or by chemicalize.org. The chemicalize.org website including all name to structure and structure based calculations and predictions by ChemAxon is licensed under a Creative Commons License.
50. Abboud, J.-L. M.; Foces-Foces, C.; Notario, R.; Trifonov, R. E.; Volovodenko, A. P.; Ostrovskii, V. A.; Alkorta, I.; Elguero, J. *Eur. J. Org. Chem.* **2001**, 3013–3024. http://dx.doi.org/10.1002/1099-0690(200108)2001:16<3013::AID-EJOC3013>3.0.CO;2-Y
51. Catalán, J.; Sánchez-Cabezudo, M.; de Paz, J. L. G.; Elguero, J.; Taft, R. W.; Anvia, F. *J. Comput. Chem.* **1989**, *10*, 426–433. http://dx.doi.org/10.1002/jcc.540100318

52. Albert, A.; Taylor, P. J. *J. Chem. Soc. Perkin Trans. II* **1989**, 1903–1905. http://dx.doi.org/10.1039/p29890001903
53. Begtrup, M. *J. Chem. Soc. Perkin Trans. II*, **1976**, 736–741. http://dx.doi.org/10.1039/P29760000736
54. Toppet, S.; Wouters, G.; Smets, G. *Org. Magn. Reson.* **1978**, *11*, 578–579. http://dx.doi.org/10.1002/mrc.1270111110
55. Molteni, G.; Buttero, P. D. *Tetrahedron* **2005**, *61*, 4983–4987. http://dx.doi.org/10.1016/j.tet.2005.03.049
56. Banert, K.; Hagedorn, M.; Müller, A. *Eur. J. Org. Chem.* **2001**, 1089–1103. http://dx.doi.org/10.1002/1099-0690(200103)2001:6<1089::AID-EJOC1089>3.0.CO;2-N
57. Priebe, H. *Acta Chem. Scand. B* **1984**, *38*, 623–626. http://dx.doi.org/10.3891/acta.chem.scand.38b-0623
58. Roberts, C.; Walton, J. C. *J. Chem. Soc. Perkin Trans. 2* **1981**, 553–560. http://dx.doi.org/10.1039/p29810000553
59. Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981, pp 194–195.
60. For details, see the supplementary materials.
61. Marszak-Fleury, A. *C. R. Acad. Sci. Paris* **1955**, *241*, 752–754.
62. Jacobs, T. L.; Scott Jr., W. R. *J. Am. Chem. Soc.* **1953**, *75*, 5500–5504. http://dx.doi.org/10.1021/ja01118a011
63. Benincasa, M.; Boni, M.; Ghelfi, F.; Pagnoni, U.M. *Synth. Commun.* **1995**, *25*, 1843–1848. http://dx.doi.org/10.1080/00397919508015429
64. Banert, K. In *Organic Azides: Syntheses and Applications*, Bräse, S.; Banert, K., Eds.; Wiley: Chichester, UK, 2010, pp 115–166.
65. Banert, K.; Fendel, W.; Schlott, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 3289–3292. http://dx.doi.org/10.1002/(SICI)1521-3773(19981217)37:23<3289::AID-ANIE3289>3.0.CO;2-K
66. Banert, K.; Fotsing, J. R.; Hagedorn, M.; Reisenauer, H. P.; Maier, G. *Tetrahedron* **2008**, *64*, 5645–5648. http://dx.doi.org/10.1016/j.tet.2008.04.037
67. Priebe, H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 736–738. http://dx.doi.org/10.1002/anie.198407361
68. Banert, K. *Tetrahedron Lett.* **1985**, *26*, 5261–5264. http://dx.doi.org/10.1016/S0040-4039(00)95010-X
69. Banert, K. *Chem. Ber.* **1987**, *120*, 1891–1896. http://dx.doi.org/10.1002/cber.19871201119
70. Baltzer, O.; von Pechmann, H. *Justus Liebigs Ann. Chem.* **1891**, *262*, 314–324. http://dx.doi.org/10.1002/jlac.18912620305
71. Farooq, T.; Sydnes, L. K.; Törnroos, K. W.; Haug, B. E. *Synthesis* **2012**, *44*, 2070–2078. http://dx.doi.org/10.1055/s-0031-1291160

72. Cohrt, A. E.; Jensen, J. F.; Nielsen, T. E. *Org. Lett.* **2010**, *12*, 5414–5417. http://dx.doi.org/10.1021/ol102209p
73. Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035–3038. http://dx.doi.org/10.1016/j.tetlet.2006.03.020
74. Christie, W. W.; Holman, R. T. *Chem. Phys. Lipids* **1967**, *1*, 407–423. http://dx.doi.org/10.1016/0009-3084(67)90019-9
75. Colas, Y.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 845–848. http://dx.doi.org/10.1016/S0040-4039(01)80043-5
76. Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981, p 66.
77. Brandsma, L. *Preparative Acetylenic Chemistry*, *Sec. Ed.*; Elsevier: Amsterdam, 1988, pp 253–254.
78. Baudouy, R.; Goré, J. *J. Chem. Res.* (S) **1981**, 278–279.

