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Synthetic Methods

Metal-Free Intermolecular Azide–Alkyne Cycloaddition Promoted by Glycerol

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Abstract: Metal-free intermolecular Huisgen cycloadditions using nonactivated internal alkynes have been successfully performed in neat glycerol, both under thermal and microwave dielectric heating. In sharp contrast, no reaction occurs in other protic solvents, such as water, ethanol, or diols. DFT calculations have shown that the BnN_3/glycerol adduct promotes a more important stabilization of the corresponding LUMO than that produced in the analogous BnN_3/alcohol adducts, favoring the reactivity with the alkyne in the first case. The presence of copper salts in the medium did not change the reaction pathway (Cu(I) acts as spectator), except for disubstituted silylalkynes, for which desilylation takes place in contrast to the metal-free system.

Introduction

Azide–alkyne cycloadditions (AAC) represent a powerful tool for the synthesis of 1,2,3-triazoles, valuable heterocycles involved in diverse fields, such as biochemistry, organic synthesis, or materials science.[1] Although this reaction was first reported in 1893 by Michael[2] and in particular developed by Huisgen in the 1960s,[3] it was not up to the beginning of the 21st century that the reaction found widespread practical interest after overcoming kinetic and regioselective concerns by transforming the thermally activated process into a catalytic reaction, mainly by using copper-based systems.[1,4] Since then, many catalytic systems have been described, also including metals other than copper (such as Ag,[5] Ru,[6] Ir,[7] or Ni[8]), which allow access to substituted-1,2,3-triazoles from organic azides and alkynes. The use of internal alkynes leading to the formation of 1,4,5-trisubstituted 1,2,3-triazoles generally requires harsher conditions, and activated alkynes (either substituted by electron-withdrawing groups or strained).

For biological and pharmacological applications, metal-free AAC methodologies (back to the origins) still remain attractive approaches.[9] Bertozzi and co-workers first used the strained-promoted strategy involving substituted cycloalkynes for bioconjugation purposes.[10] Another elegant method is through intramolecular AAC reactions by taking advantage of the favorable entropy effects.[11] However, to the best of our knowledge, intermolecular cycloadditions between organic azides and nonactivated internal alkynes under metal-free conditions remain an important challenge to be solved.

In the last years, with the purpose of using ecofriendly solvents, we have developed glycerol catalytic phases. They exhibit appealing properties mainly regarding the immobilization of the metal species, probably owing to the supramolecular arrangement shown by glycerol.[12] In particular, Cu_2O nanoparticles prepared in neat glycerol led to the synthesis of 1,4-disubstituted-1,2,3-triazoles, permitting an easy recycling of the catalytic phase.[13] With the assumption of glycerol having a noninnocent role in this process, we decided to investigate the metal-free AAC in glycerol for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Results and Discussion

As a benchmark reaction, the intermolecular azide–alkyne cycloaddition (AAC) between diphenylacetylene (**1**) and benzyl azide (**a**) in neat glycerol under microwave dielectric heating for 30 minutes was chosen, affording 1-benzyl-4,5-diphenyl-1,2,3-triazole (**1a**; Table 1).[14] The organic products were isolated by a biphasic liquid–liquid extraction after adding dichloromethane to the reaction mixture. The triazole **1a** was exclusively obtained in a high yield of 85% (Table 1, entry 1). With the aim of investigating the effect of copper in this reaction,[15] we carried out the synthesis in the presence of a copper salt (2.5 mol% of CuCl), obtaining **1a** in almost the same isolated

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yield (Table 1, entry 2). This evidences the spectator role of copper (see Table S1 in the Supporting Information).[16] A similar trend was observed under classical thermal-promoted conditions (Table 1, entries 3 and 4), albeit in lower yields (< 35%) after 20 h. In the absence of glycerol (i.e., under solvent-free conditions), the product was obtained in only 18% yield (Table 1, entry 5). No copper was detected by ICP-AES analysis of neat glycerol (< 3 ppm).

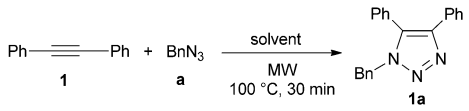
To better control the temperature (the reaction conditions were set at a targeted temperature, controlled by an external infrared temperature sensor),[17] we employed a MW instrument combining both internal optical fiber and external infrared temperature sensors (Figure S1 in the Supporting Information). We carried out the cycloaddition at different temperatures (100, 140, and 180 °C, according to the internal optical fiber sensor) and observed that the yield obtained at 180 °C was comparable to that obtained working with the instrument equipped only with an infrared sensor (Table S2 in the Supporting Information). Under classical heating conditions (oil bath), only 65% yield was achieved at 180 °C in the same reaction time, which is consistent with a less efficient heat transfer.

Then, we decided to study the influence of the solvent under metal-free conditions. Surprisingly, no reaction took place when using other alcohol-based solvents, including ethanol and diols, such as ethylene glycol, propane-1,2-diol, and propane-1,3-diol (Table 1, entry 6). Water gave a very low conversion of benzyl azide of 13% (Table 1, entry 7). Aprotic polar solvents, such as 1,4-dioxane and fluorobenzene, also disfavored the cycloaddition (Table 1, entries 8 and 9). The varying reactivity observed by using different protic solvents can be explained by the solvent interaction with an external electric field. Alcohols, in particular polyols, form extensive hydrogen bonds, which in turn correlate with long relaxation times (the time taken to achieve the random state after being submitted to an external electric field).[18] Therefore, water (9.2 ps), ethanol (170 s), ethylene glycol (170 ps), or propane-1,3-diol (340 ps) exhibit shorter relaxation times than glycerol (1,215 ps), making it more relevant than other protic solvents for synthetic purposes under microwave conditions, as illustrated here for the AAC reaction.

Under thermal conditions (Table S3 in the Supporting Information), the reactivity in the different solvents follows the same trend, except for ethylene glycol and water for which **1a** was obtained in 25 and 31% yield, respectively (33% yield in glycerol; Table 1, entry 3), after 20 h at 100 °C. This clearly contrasts with the lack of reactivity observed under microwave heating (Table 1, entries 6 and 7), despite the high internal temperature achieved under MW activation (see above).

With these results in hand, we decided to study the scope of the process by using other internal alkynes (Table 2). For the symmetrical disubstituted alkynes **2**–**5** (Table 2, entries 1–4), moderate to high yields were obtained (32–90%). No transesterification reaction between the alkyne **2** or the triazole **2a** and glycerol was observed, in contrast to the reaction in ethanol (see Tables S4 and S5 in the Supporting Information). It is important to note that the nonactivated 4-octyne reacted with BnN_3 to give 1-benzyl-4,5-dipropyl-1,2,3-triazole **5a** in 71% isolated yield (after 1 h under microwave irradiation; Table 2, entry 4).

Table 1. Azide–alkyne cycloaddition of diphenylacetylene and benzyl azide in neat glycerol.[a]



Entry	Solvent	Conversion [%][b][c]	Isolated yield [%][d]
1	glycerol	85	85 (85)
2[e]	glycerol	86	82 (80)
3[f]	glycerol	37	33 (33)
4[e][f]	glycerol	42	28 (27)
5	–	20	18[g]
6[h]	protic solvent	n.r.	–
7	H_2O	13	n.d.
8	1,4-dioxane	n.r.	–
9	fluorobenzene	n.r.	–

[a] Results from duplicate experiments. Reaction conditions: benzyl azide (0.4 mmol) and diphenylacetylene (0.6 mmol) in solvent (1 mL) under microwaves activation (250 W) at 100 °C for 30 minutes (temperature controlled by external infrared sensor). [b] Based on benzyl azide. [c] Determined by ^{1}H NMR spectroscopy using 2-methoxynaphthalene as an internal standard. [d] In brackets: yields determined by ^{1}H NMR spectroscopy using 2-methoxynaphthalene as an internal standard. [e] In the presence of 2.5 mol% of CuCl. [f] Reaction in a sealed tube under thermal activation at 100 °C for 20 h. [g] Determined by ^{1}H NMR spectroscopy using 2-methoxynaphthalene as an internal standard. [h] Results obtained with the following alcohols as solvents: ethanol, ethylene glycol, propane-1,2-diol, and propane-1,3-diol.

Unsymmetrically substituted alkynes **6** and **7** led to an almost equimolar mixture of both regioisomers (Table 2, entries 5 and 6). In view of synthetic applications and to explore the role of the silyl group as a directing group during the cycloaddition,[19] we carried out the synthesis of triazoles **8**–**10** from the corresponding alkynes containing silyl-based groups, such as $SiMe_3$ (alkynes **8** and **9**; Table 2, entries 7 and 8) and $Si(tBu)Me_2$ (**10**; Table 2, entry 9). As expected, the 4-silyl-substituted heterocycle was obtained as the major regioisomer[20] and as the sole product for the bulky *tert*-butyldimethylsilyl (TBDMS) derivative (Table 2, entry 9).

Phenyl (**b**) and *n*-octyl (**c**) azides also gave the expected triazoles; conversions and yields were lower than those obtained when using benzyl azide (Figure 1).[21] In contrast to benzyl and *n*-octyl azides, PhN_3 tends to decompose under the reaction conditions employed.[22]

We studied the effect of Cu(I) in the synthesis of silyl-based triazoles **8a**–**10a**. For the synthesis of **10a**, bearing a TBDMS group, the reactivity was similar to the one observed in the absence of Cu(I). However, for the TMS-substituted ones (**8a**, **9a**), a mixture of two triazoles was obtained: the expected **8a** or **9a** and the desilylated 1-benzyl-4*R*-1,2,3-triazole (R = Me (**11a**), Ph (**12a**)), which was obtained as a single regioisomer (Scheme 1). Under the classical thermal conditions, the same behavior was observed (Scheme S1 in the Supporting Information).

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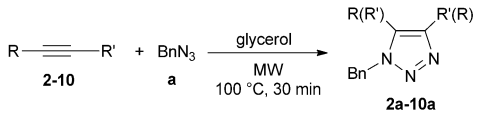
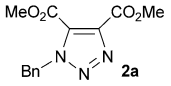
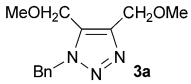
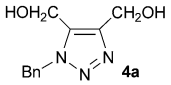
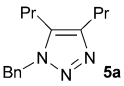
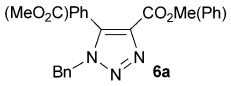
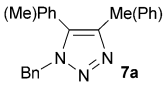
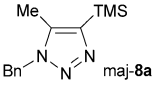
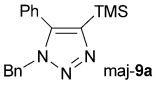
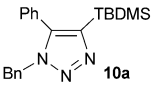
Table 2. Azide–alkyne cycloaddition of internal alkynes and benzyl azide in neat glycerol.[a]



Entry	Alkyne (R, R')	Product	Conv. [%][b][c]	Yield [%][c]
1[d]	**2** (CO_2Me)	 **2a**	100	78
2	**3** (CH_2OMe)	 **3a**	96	90
3	**4** (CH_2OH)	 **4a**	56	32
4[e]	**5** (Pr)	 **5a**	73	71
5	**6** (Ph, CO_2Me)	 **6a**	91	83[f]
6	**7** (Ph, Me)	 **7a**	49	49[f]
7	**8** (Me, TMS)	 maj-**8a**	65	62 (9:1)[g]
8	**9** (Ph, TMS)	 maj-**9a**	92	85 (9:1)[g]
9	**10** (Ph, TBDMS)	 **10a**	85	84[h]

[a] Results from duplicate experiments. Reaction conditions: benzyl azide (0.4 mmol) and the corresponding alkyne (0.6 mmol) in solvent (1 mL) under microwaves activation (250 W) at 100 °C for 30 min (temperature controlled by external infrared sensor). [b] Based on benzyl azide. [c] Determined by ^{1}H NMR spectroscopy using 2-methoxynaphthalene as an internal standard. [d] Reaction time: 15 min. [e] Reaction time: 60 min. [f] Regioisomer ratio: 1:1. [g] In brackets: regioisomer ratio (major isomer: 1-benzyl-4-trimethylsilyl-5*R*-1,2,3-triazole (for R = Me: maj-**8a**; for R = Ph: maj-**9a**); minor isomer: 1-benzyl-5-trimethylsilyl-4*R*-1,2,3-triazole (for R = Me: min-**8a**; for R = Ph: min-**9a**). [h] Only one isomer was obtained (1-benzyl-4-*tert*-butyldimethylsilyl-5-phenyl-1,2,3-triazole); see ref. [20].

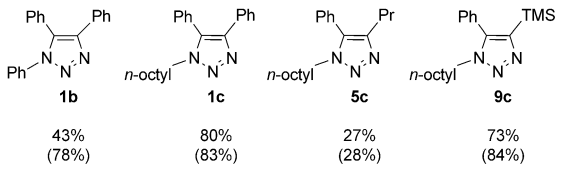
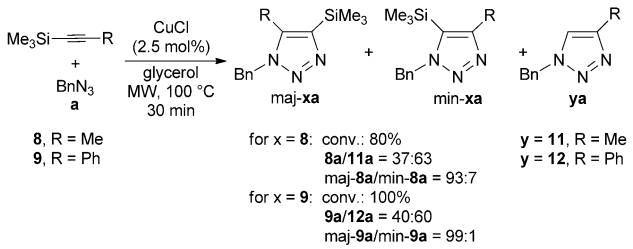
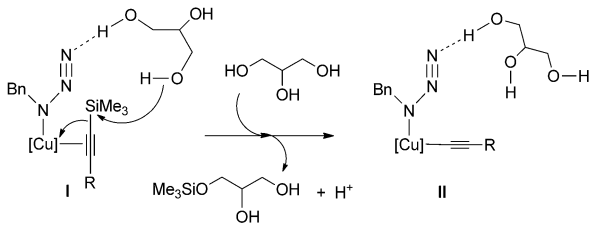


Figure 1. 1,4,5-Trisubstituted 1,2,3-triazoles from phenyl (**1b**) and *n*-octyl azides (**1c**, **5c**, **9c**). Isolated yields are given (conversions are given in brackets).



Scheme 1. Reactivity of silyl-based alkynes in the presence of CuCl under microwave activation. Data from NMR analysis.

Control experiments proved that the desilylation neither took place on the alkyne **8** or **9** nor on the triazole **8a** or **9a** (Scheme S2 in the Supporting Information). In addition, when the AAC reaction was carried out in dioxane, no corresponding desilylation occurred. Monitoring the reaction by GC-MS demonstrated that the formation of **9a** is faster than that corresponding to **12a** (after 5 min, the ratio **9a**/**12a** was approximately 3.4:1; after 15 min, the ratio was approximately 1.2:1, with full conversion of BnN_3). Once BnN_3 was consumed completely, desilylation of the alkyne **9** could be observed (Figure S4 in the Supporting Information). These facts led us to propose that the desilylation giving **12a** (and **11a**) occurs upon coordination of the alkyne to copper (intermediate **I** in Scheme 2), which is promoted by glycerol that is undoubtedly



Scheme 2. Plausible Cu-mediated desilylation of $SiMe_3$-based alkynes promoted by glycerol.

close to the coordination sphere owing to its interaction with BnN_3 through hydrogen bonds (see below). Intermediate **II** then evolves to give the favored regioisomer 1-benzyl-4*R*-1,2,3-triazole, according to the accepted Cu-catalyzed mechanisms.[4b,23] The formation of the corresponding silyl derivative of glycerol was proven by NMR spectroscopy (see Figures S5 and S6 in the Supporting Information).[24] Alkyne **10** did not give the corresponding desilylated triazole, probably as a consequence of the steric hindrance triggered by the TBDMS group around the metal center.

To rationalize the effect of glycerol in AAC reactions, we studied the interaction of glycerol with benzyl azide by theoretical calculations (DFT B3LYP, 6-31G*), taking into account the ability of glycerol to form hydrogen bonds.[25,26] For comparative purposes, we also analyzed this effect with ethanol and several diols (ethylene glycol, 1,2-, and 1,3-propanediol). The resulting BnN_3/alcohol adducts increase the dipolar character of BnN_3 in relation to neat benzyl azide (see calculated charges

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in Figure S7 in the Supporting Information). It is important to note that in the case of polyols (ethylene glycol, 1,2-propanediol, and glycerol) the intramolecular hydrogen bonds trigger an additional stabilization of the corresponding BnN_3/alcohol adduct (see Figure S8 in the Supporting Information). The analysis of the relative energies of frontier orbitals for the different BnN_3/alcohol adducts (see Figure S9 in the Supporting Information) showed that the BnN_3/glycerol LUMO, which overlaps with the dipolarophile HOMO (diphenylacetylene was chosen for the calculations), is more stable than the ones obtained for the other adducts (see Table S6 in the Supporting Information). In consequence, the reactivity should be enhanced, as observed in this work for a range of alkynes.

Conclusion

We have shown that glycerol acts as a noninnocent solvent for metal-free azide–alkyne cycloadditions, promoting the reaction between internal alkynes and organic azides in contrast to other protic solvents, both under classical and dielectric heating. Moreover, the reactivity in glycerol was particularly enhanced by microwave heating, probably owing to the long relaxation time of glycerol in comparison with other protic solvents, which is related to its supramolecular arrangement through intermolecular hydrogen bonds. At a molecular level, analysis of the frontier orbitals for the BnN_3/glycerol adduct pointed to a higher stabilization of the corresponding LUMO than that for comparable adducts involving ethanol and diols. This trend justifies the increase of the reaction rate according to a concerted pathway for the metal-free cycloaddition.

These results permit us to envisage the formation of fully substituted 1,2,3-triazoles by using a metal-free methodology, which is particularly interesting for the synthesis of drugs and natural products.

Experimental Section

General

All manipulations were performed by using standard Schlenk techniques under argon atmosphere. Unless stated otherwise, commercially available compounds were used without further purification. Glycerol was treated under vacuum at 80 °C overnight prior to use. NMR spectra were recorded on Bruker Avance 300, 400, and 500 spectrometers at 293 K. GC analyses were carried out on an Agilent GC6890 with a flame ionization detector using a SGE BPX5 column composed of 5% of phenylmethylsiloxane. Reactions under microwave activation were carried out on single-mode microwave CEM Explorer SP 48, 2.45 GHz, Max Power 300 W Synthesis System, CEM Focused MicrowaveTM Synthesis System Model Discover, and Anton Paar Monowave 300 instruments. Theoretical studies were carried out by using the following software: SPARTAN'14 for Windows and Linux, Wavefunction, InC. 18401 Von Karmaan Avenue, suite 307, Irvine, CA 92612, USA. Calculations were carried out with Density Functional B3LYP by using the basis set 6-31G*.

General AAC procedure in glycerol under microwave activation

A sealed tube equipped with a stirring bar was successively charged with the corresponding alkyne (0.6 mmol) and glycerol (1 mL); the mixture was stirred at room temperature for 5 min. Benzyl azide (0.4 mmol, 53.2 mg) was then added and the sealed tube was placed into the microwave reactor (100 °C, 250 W) for 30 min (or the appropriate time). It is important to note that at room temperature the reaction mixture gave a kind of emulsion but that at 100 °C a homogeneous solution was obtained (i.e., reagents and products were soluble in glycerol).[27] The organic products were extracted with dichloromethane (6×2 mL). The combined chlorinated organic layers were filtered through a Celite pad and the resulting filtrate was concentrated under reduced pressure. The products were purified by chromatography (silica short column, eluent: cyclohexane/ethyl acetate 1:1) to determine the isolated yields of the corresponding triazoles.

Compound maj-8a: Yellow oil; IR (neat): $\tilde{\nu}$ = 1606, 1497, 1416, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.35 (s, 9H), 2.22 (s, 3H), 5.51 (s, 2H), 7.15–7.20 (m, 2H), 7.27–7.39 ppm (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = −0.9, 9.3, 51.2, 127.2, 128.1, 128.9, 135.1, 138.1, 143.8 ppm; HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{20}N_3Si$: 246.1412; found: 246.1421; elemental analysis calcd (%) for $C_{13}H_{19}N_3Si$: C 63.63, H 7.80, N 17.11; found: C 63.22, H 7.88, N 16.94.

Compound 10a: Yellow oil; IR (neat): $\tilde{\nu}$ = 1606, 1497, 1456, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6H), 0.90 (s, 9H), 5.35 (s, 2H), 6.94–7.00 (m, 2H), 7.05–7.10 (m, 2H), 7.21–7.28 (m, 3H), 7.35–7.40 (m, 2H), 7.43–7.48 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ = 5.3, 26.6, 51.4, 127.6, 127.9, 128.2, 128.5, 128.8, 129.3, 130.4, 135.6, 142.8, 144.1, 173.4 ppm; HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{21}H_{28}N_3Si$: 350.2050; found: 350.2047; elemental analysis calcd (%) for $C_{21}H_{27}N_3Si$: C 72.16, H 7.79, N 12.02; found: C 72.24, H 8.27, N 11.87.

Compound 5c: Yellow oil; IR (neat): $\tilde{\nu}$ = 1611, 1570, 1544, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.20–1.40 (m, 10H), 1.53–1.62 (m, 2H), 1.68–1.77 (m, 2H), 1.83–1.96 (m, 2H), 2.55–2.61 (m, 4H), 4.16–4.20 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 13.85, 13.98, 14.05, 22.58, 22.60, 22.94, 24.49, 26.69, 27.23, 29.06, 29.70, 30.35, 31.71, 47.89, 132.44, 144.71 ppm; HRMS (ESI^+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{32}N_3$: 266.2591; found: 266.2594; elemental analysis calcd (%) for $C_{16}H_{31}N_3$: C 72.40, H 11.77, N 15.83; found: C 72.13, H 12.28, N 15.53.

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Keywords: azide–alkyne cycloaddition · density functional calculations · glycerol · metal-free reactions · microwave activation

[1] For some selected recent reviews, see: a) R. Berg, B. F. Straub, *Beilstein J. Org. Chem.* **2013**, *9*, 2715 – 2750; b) N. V. Sokolova, V. G. Nenajdenko,

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RSC Adv. **2013**, *3*, 16212 – 16242; c) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905 – 4979; d) P. L. Golas, K. Matyjaszewski, *Chem. Soc. Rev.* **2010**, *39*, 1338 – 1354; e) P. Wu, V. V. Fokin, *Aldrichimica Acta* **2007**, *40*, 7 – 17; f) C. G. S. Lima, A. Ali, S. van Berkel, B. Westermann, M. W. Paixão, *Chem. Commun* **2015**, *51*, 10784 – 10796.

[2] A. Michael, *J. Prakt. Chem.* **1893**, *48*, 94 – 95.

[3] a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565 – 598; *Angew. Chem.* **1963**, *75*, 604 – 637; b) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633 – 645; *Angew. Chem.* **1963**, *75*, 742 – 754.

[4] For the first Cu-catalyzed works, see: a) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599; *Angew. Chem.* **2002**, *114*, 2708 – 2711.

[5] J. McNulty, K. Keskar, R. Vemula, *Environ. Chem. Chem. Eur. J.* **2011**, *17*, 14727 – 14730.

[6] For the first report on Ru-catalyzed AAC reactions, see: a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998 – 15999; for a selected recent review, see: b) Y. Yamamoto, *Heterocycles* **2013**, *87*, 2459 – 2493.

[7] a) E. Rasolofonjatovo, S. Theeramunkong, A. Bouriaud, S. Kolodych, M. Chaumontet, F. Taran, *Org. Lett.* **2013**, *15*, 4698 – 4701; b) S. Ding, G. Jia, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 1877 – 1880; *Angew. Chem.* **2014**, *126*, 1908 – 1911.

[8] H. S. P. Rao, G. Chakibanda, *RSC Adv.* **2014**, *4*, 46040 – 46048.

[9] J. M. Baskin, C. R. Bertozzi, *Aldrichimica Acta* **2010**, *43*, 15 – 23.

[10] For a selected work, see: J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793 – 16797.

[11] For some representative examples, see: a) M. Sau, C. Rodríguez-Escrich, M. A. Pericàs, *Org. Lett.* **2011**, *13*, 5044 – 5047; b) R. A. Brawn, M. Welzel, J. T. Lowe, J. S. Panek, *Org. Lett.* **2010**, *12*, 336 – 339; c) V. Declerck, L. Toupet, J. Martinez, F. Lamaty, *J. Org. Chem.* **2009**, *74*, 2004 – 2007; d) A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 1617 – 1619.

[12] a) F. Chahdoura, S. Mallet-Ladeira, M. Gómez, *Org. Chem. Front.* **2015**, *2*, 312 – 318; b) F. Chahdoura, I. Favier, C. Pradel, S. Mallet-Ladeira, M. Gómez, *Catal. Commun.* **2015**, *63*, 47 – 51; c) F. Chahdoura, I. Favier, M. Gómez, *Chem. Eur. J.* **2014**, *20*, 10884 – 10893; d) F. Chahdoura, C. Pradel, M. Gómez, *Adv. Synth. Catal.* **2013**, *355*, 3648 – 3660.

[13] F. Chahdoura, C. Pradel, M. Gómez, *ChemCatChem* **2014**, *6*, 2929 – 2936.

[14] For a selected contribution on the microwave-assisted synthesis in glycerol, see: W.-J. Zhou, X.-Z. Zhang, X.-B. Sun, B. Wang, J.-X. Wang, L. Bai, *Russ. Chem. Bull. Int. Ed.* **2013**, *62*, 1244 – 1247.

[15] For the Cu-catalyzed synthesis of 1-benzyl-4,5-diphenyl-1,2,3-triazole by using preformed well-defined complexes (**15a**: 72% yield after 48 h at 80 °C; **15b**: 68% yield after 12 h at 120 °C in DMF) and heterogeneous catalyst (**15c**: 54% yield after 24 h at 80 °C), see: a) S. Hohloch, D. Scheiffele, B. Sarkar, *Eur. J. Inorg. Chem.* **2013**, 3956 – 3965; b) B.-H. Lee, C.-C. Wu, X. Fang, C. W. Liu, J.-L. Zhu, *Catal. Lett.* **2013**, *143*, 572 – 577; c) P. Li, L. Wang, Y. Zhang, *Tetrahedron* **2008**, *64*, 10825 – 10830.

[16] We tested different Cu(I) salts that gave similar results under the same catalytic conditions (see Table S1 in the Supplementary Information).

[17] a) M. A. Herrero, J. M. Kremsner, C. O. Kappe, *J. Org. Chem.* **2008**, *73*, 36 – 47; b) D. Obermayer, C. O. Kappe, *Org. Biomol. Chem.* **2010**, *8*, 114 – 121.

[18] C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213 – 223.

[19] For selected contributions, see: a) L. Li, T. Shang, X. Ma, H. Guo, A. Zhu, G. Zhang, *Synlett* **2015**, 695 – 699; b) S. J. Coats, J. S. Link, D. Gauthier, D. J. Hlasta, *Org. Lett.* **2005**, *7*, 1469 – 1472; c) D. J. Hlasta, J. H. Ackerman, *J. Org. Chem.* **1994**, *59*, 6184 – 6189; d) A. Padwa, M. W. Wannamaker, *Tetrahedron* **1990**, *46*, 1145 – 1162.

[20] For **8a**, the assignment of both regioisomers was carried out by NOESY NMR correlations (see Figure S2 in the Supporting Information). For **9a** and **10a**, desilylation reactions with tetrabutylammonium fluoride (TBAF) were carried out to unambiguously determine the major isomer (see Figure S3 in the Supporting Information).

[21] Reaction conditions: azide (0.4 mmol) and the corresponding alkyne (0.6 mmol) in solvent (1 mL) under microwave activation (250 W) at 100 °C for 1 h (**1c**), 2 h (**5c**), or 30 min (**9c**). For **1b**, similar conditions were used but with applying a power of 150 W for 1 h. Reactions involving PhN_3 were protected from light.

[22] 70 and 56% of PhN_3 were recovered from a glycerol solution of PhN_3 after 30 min under MW activation at 150 and 250 W, respectively. Under classical heating, 95% of PhN_3 was recovered after 20 h at 100 °C.

[23] B. T. Worrell, J. A. Malik, V. V. Fokin, *Science* **2013**, *340*, 457 – 460.

[24] A control experiment between glycerol and TMSCl was carried out to identify the major concomitant silylglycerol derivative observed (see Experimental part of the Supporting Information, Scheme S3 and Figures S5 and S6).

[25] T. Kusukawa, G. Niwa, T. Sasaki, R. Oosawa, W. Himeno, M. Kato, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 351 – 353.

[26] DOSY NMR experiments were inconclusive on the effect of different solvents on the interaction with reagents involved in azide – alkyne cycloadditions (see Table S7 in the Supporting Information).

[27] When using other solvents instead of glycerol (water, ethanol, ethylene glycol, propane-1,2-diol, propane-1,3-diol, dioxane, fluorobenzene), the reagents and products were soluble, even at room temperature for ethanol, dioxane and fluorobenzene.

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