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Regioselective $Zn(OAc)_2$-catalyzed azide–alkyne cycloaddition in water: the green click-chemistry†

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A new method of azide–alkyne cycloaddition (AAC) in the presence of $Zn(OAc)_2$ as an inexpensive and environmentally friendly catalyst in neat water has been developed. The proposed methodology has been applied for the synthesis of 1,4-disubstituted-1,2,3-triazoles from terminal alkynes and 1,4,5-trisubstituted-1,2,3-triazoles from internal alkynes. It has been found that Zn-catalyzed AAC is extremely sensitive to steric hindrance in acetylenes and a method of regioselective triazole ring formation has been proposed. Particularly important is the isolation and characterization of a relatively stable Zn-containing intermediate, which has been characterized by NMR and HRMS.

Introduction

Recently, the azide–alkyne cycloaddition (AAC), originally proposed by Huisgen, has become a powerful basis for the "click-reactions".[1] Since 2001, when the concept of "click-chemistry" was established by Sharpless and co-workers,[2] this reaction has been transformed into a unique tool for the design and synthesis of a wide range of products. The modern Cu-catalyzed azide–alkyne cycloaddition (CuAAC) was originally developed by Fokin and Sharpless.[3] This method is characterized by high regioselectivity, inexpensive catalytic system, and it can be realized in neat water or alcohols. The procedure has a wide synthetic applicability: the reaction proceeds smoothly with various terminal alkynes and azides which can be generated *in situ*.[4] The CuAAC has been applied in the synthesis of dendrimers,[5] rotaxanes and catenanes,[6] in the design of new drugs[7] and functional polymers,[8] and in materials science.[9]

In the last decade, numerous modifications have been suggested for the improvement of the AAC catalysts. Thus, it was found that the addition of nitrogen ligands results in a decreased reaction time and allows the use of a smaller amount of catalyst.[10] Furthermore, the development of new catalytic systems based on transition metals (MAAC) has become a new trend in click-chemistry.[4a,11] The utilization of new catalysts made it possible to decrease the reaction time, increase the yields of 1,2,3-triazoles, and change the reaction path from the formation of 1,4-disubstituted-1,2,3-triazoles to 1,5-disubstituted-1,2,3-triazoles. For example, the Ag_2O nanoparticles have been successfully applied in AgAAC reaction as well as the $AgN(CN)_2$/DIPEA system in aqueous ethylene glycol solution.[12] The Cu(111) or Au-assisted AAC has made it possible to carry out the on-surface covalent coupling and significantly improved the applicability of click-reactions in materials science.[13] Recently, the highly active catalytic systems based on nickel have been developed.[15] However, all catalytic systems listed above have a significant disadvantage: they are applicable only for the preparation of 1,4-disubstituted-1,2,3-triazoles from terminal alkynes.[14] The originally proposed Ru-catalyzed AAC based on a Cp*RuCl complex allowed the synthesis of 1,5-disubstituted-1,2,3-triazoles from terminal alkynes and 1,4,5-trisubstituted-1,2,3-triazoles from internal alkynes.[16] Later, the replacement of Cp*RuCl with $RuH_2(CO)(PPh_3)_3$ made it possible to change the reaction path to the regioselective formation of 1,4-disubstituted-1,2,3-triazoles.[16,17] Noteworthily, the procedure utilizing Ru-based catalytic systems is quite complicated and requires an inert

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atmosphere and Schlenk techniques, which significantly decreases the synthetic applicability of this method. Moreover, the Ru-based catalysts are relatively expensive.

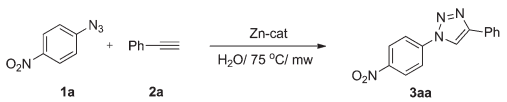
In 2010 Chen and co-workers have proposed the procedure for azide–alkyne cycloaddition catalyzed by zinc on charcoal.[18] This method has an excellent tolerance to functional groups: the cycloaddition readily proceeds with aryl or alkyl azides and alkynes with a broad range of substituents. This catalytic system can be easily recycled with a slight decrease of catalytic activity. The main advantage of ZnAAC is in the possibility of cycloaddition of di-substituted alkynes and appropriate azides with the formation of 1,4,5-trisubstituted-1,2,3-triazoles. However, the authors could not provide the mechanistic rationalization and explanation of the observed reactivity. This catalytic system does not allow the use of neat water; the authors have obtained satisfactory yields of the targeted 1,2,3-triazoles only in DMF. It should be noted that the steric hindrance has a strong effect on the product yields, and this method is not suitable for the synthesis of 1,2,3-triazoles from *o*-substituted aromatic azides. Later, Greaney and Smith have developed an alternative ZnAAC methodology *via* interactions of terminal alkynes with azides in the presence of an equimolecular amount of $ZnEt_2$.[19] The $ZnEt_2$-assisted AAC led to the formation of 1,5-disubstituted-1,2,3-triazoles or 1,4,5-trisubstituted-1,2,3-triazoles *via* the interaction of the intermediate triazolyl-zinc derivative with an electrophile. The authors proposed the generation of the corresponding zinc-acetylides *via* the direct interaction between $ZnEt_2$ and acetylenes. The regioselectivity of this reaction was explained by Lan through the computational studies of the transition states of the proposed Zn-intermediates.[20] Unfortunately, a clear explanation of the ZnAAC mechanism for the reactions of internal alkynes has not been presented yet. Moreover, the known procedures of ZnAAC are not in full agreement with the basic principles of "click" methodology. Therefore, there is a strong need for a mechanistic understanding of zinc-catalysed AAC for controlling the regioselectivity in the reactions of internal alkynes. Moreover, in comparison with Ru- and Cu-catalyzed AAC, whose mechanisms have been clearly explained,[16c,21] the ZnAAC mechanism remains a blind spot in the MetAAC chemistry.

Results and discussion

In this work, we present a new method for Zn-promoted AAC with substrate-controlled regioselectivity in neat water using $Zn(OAc)_2$ as an inexpensive and environmentally friendly catalyst. This procedure is applicable to the cycloaddition of alkyl or aryl azides with internal and terminal alkynes. Also, our procedure can be applied to the synthesis of aryl-substituted triazoles directly from aromatic amines. Moreover, we have isolated and characterized the key Zn-containing intermediate, which provides an insight into the mechanism of ZnAAC.

The optimization of Zn-catalyzed alkyne–azide cycloaddition was conducted using various Zn-containing catalytic systems in neat water and at various temperatures in the reaction between 4-azidonitrobenzene **1a** and phenylacetylene **2a** (Table 1). In agreement with the previous observation of Chen and co-workers, Zn on charcoal demonstrates low activity in neat water and the formation of the desired 1,2,3-triazoles is not observed (entry 1).[18] In contrast, the reaction in the presence of the water-soluble $Zn(OTf)_2$ affords 1,2,3-triazole **3aa** with quantitative yield (entry 2). Similar activity has been demonstrated by $Zn(OAc)_2$ with product **3aa** being isolated in excellent yield (entry 6). Increasing the temperature to 75 °C resulted in a significant reduction of the reaction time with slightly lower product yields (entries 3 and 7). Furthermore,

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst, mol%	T (°C)	t (h)	Yield[b] (%)
1	Zn/C, 10 mol%[c]	50	15	0
2	$Zn(OTf)_2$, 10 mol%	rt	320	95
3	$Zn(OTf)_2$, 10 mol%	75	30	90
4	$Zn(OTf)_2$, 10 mol%, ascorbic acid, 20 mol%	75	16	86
5[d]	$Zn(OTf)_2$, 10 mol%, ascorbic acid, 20 mol%	75	5.5	87
6	$Zn(OAc)_2$, 10 mol%	rt	320	96
7	$Zn(OAc)_2$, 10 mol%	75	28	88
8	$Zn(OAc)_2$, 10 mol%, ascorbic acid, 20 mol%	75	16	85
9[d]	$Zn(OAc)_2$, 10 mol%, ascorbic acid, 20 mol%	75	6	97
10[d]	$Zn(OAc)_2$, 5 mol%, ascorbic acid, 10 mol%	75	8	85
11[d]	$Zn(OAc)_2$, 20 mol%, ascorbic acid, 40 mol%	75	5	94
12[d]	$ZnCl_2$, 10 mol%, ascorbic acid, 20 mol%	75	6	50[e]
13[d]	$ZnSO_4$, 10 mol%, ascorbic acid, 20 mol%	75	6	48[e]

[a] Reactions conditions: **1a** (1 equiv.), **2a** (1 equiv.), water (10 ml). [b] Isolated yield. [c] Described previously.[18] [d] Reaction was carried out under microwave irradiation (75 °C, constant power 80 W). [e] Full conversion of the starting materials was not achieved.

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the addition of ascorbic acid allowed the achievement of full conversion of the starting materials in 16 hours with high product yields (entries 4 and 8).

Finally, we have found that the target 1,2,3-triazole **3aa** is formed in high yield at 75 °C in a microwave reactor. Surprisingly, the inexpensive and readily available $Zn(OAc)_2$ demonstrates slightly higher activity than $Zn(OTf)_2$ (entries 5 and 9). We have also tested $ZnCl_2$ and $ZnSO_4$, but the full conversion of the starting materials has not been achieved after 6 hours in a microwave reactor and product **3aa** was isolated only in 48–50% yield (entries 12 and 13).

In order to exclude the possible formation of triazoles under simple heating we carried out the experiment under similar conditions without the addition of the Zn catalyst (Scheme 1). The full conversion of **1a** and **2a** was not achieved. We observed the formation of both the isomers of the triazole (1,4- and 1,5-triazoles) with 37% total yield and an isomer ratio of 81 : 19. These results confirm the crucial role of $Zn(OAc)_2$ for the regioselectivity of the process.

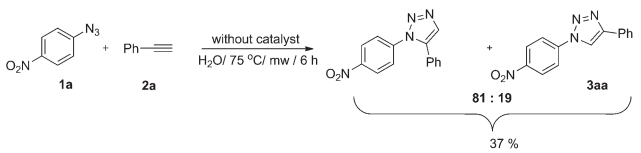
Using optimized reaction conditions, we have investigated the synthesis of 1,4-disubstituted-1,2,3-triazoles. The optimized catalytic system allowed the preparation of a wide range of 1,2,3-triazoles from aromatic and benzylic azides as well as aromatic and aliphatic acetylenes in good to excellent yields (Table 2).

In the case of 2-azidonitrobenzene, the desired 1,2,3-triazole was not obtained. We observed the formation of benzofuroxan (Scheme 2). According to a published procedure, the microwave heating of the 2-azidonitrobenzene derivatives led to the formation of appropriate benzofuroxans with good yields.[22] In order to exclude the influence of the Zn catalyst, we carried out the experiment without any additives of ascorbic acid or $Zn(OAc)_2$.

Simple heating of 2-azidonitrobenzene under microwave irradiation in neat water led to the formation of benzofuroxan in 79% yield.

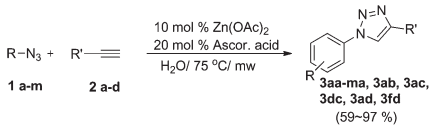
Previously, Chen and co-workers have demonstrated that Zn on charcoal allows the AAC reaction of tolane as an example of an internal alkyne.[18] In order to evaluate the reactivity of the $Zn(OAc)_2$–ascorbic acid catalytic system, we conducted experiments with a range of disubstituted acetylenes (Table 3).

In agreement with literature data, internal acetylenes exhibited lower reactivity than terminal acetylenes. In order to reduce the reaction time, all experiments were carried out at higher temperatures and under an increased power of the MW-source.



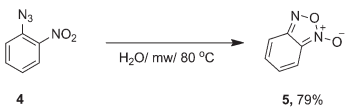
Scheme 1 AAC reaction of 1-azido-4-nitrobenzene **1a** and phenylacetylene **2a** without the catalyst.

Table 2 $Zn(OAc)_2$-catalyzed cycloaddition of organic azides and terminal acetylenes[a]



Entry	Azide, R =	Acetylene, R′ =	Triazole, yield[b] (%)	t (h)
1	**1a**, 4-$O_2NC_6H_4$	**2a**, Ph	**3aa**, 97	6
2	**1b**, 3-$O_2NC_6H_4$	**2a**, Ph	**3ba**, 94	7
3	**1c**, 4-NCC_6H_4	**2a**, Ph	**3ca**, 92	7
4	**1d**, 4-MeC_6H_4	**2a**, Ph	**3da**, 90	9
5	**1e**, 2-MeC_6H_4	**2a**, Ph	**3ea**, 61	7
6	**1f**, 4-$MeOC_6H_4$	**2a**, Ph	**3fa**, 92	5
7	**1g**, 2-$MeOC_6H_4$	**2a**, Ph	**3ga**, 59	7
8	**1h**, 2-(PhCO)-5-ClC_6H_3	**2a**, Ph	**3ha**, 70	9
9	**1i**, 2,4,6-$Br_3C_6H_2$	**2a**, Ph	**3ia**, 78	7
10	**1j**, 4-PhC_6H_4	**2a**, Ph	**3ja**, 75	8
11	**1k**, β-$C_{14}H_9$	**2a**, Ph	**3ka**, 71	6
12	**1l**, $C_6H_5CH_2$	**2a**, Ph	**3la**, 87	6
13	**1m**, C_4H_9	**2a**, Ph	**3ma**, 66	6
14	**1a**, 4-$O_2NC_6H_4$	**2b**, 4-$O_2NC_6H_4$	**3ab**, 77	5
15	**1a**, 4-$O_2NC_6H_4$	**2c**, pentyl	**3ac**, 92	6
16	**1d**, 4-MeC_6H_4	**2c**, pentyl	**3dc**, 80	5
17	**1a**, 4-$O_2NC_6H_4$	**2d**, $OHCH_2$	**3ad**, 93	6
18	**1f**, 4-$MeOC_6H_4$	**2d**, $OHCH_2$	**3fd**, 61	7

[a] Reaction conditions: azide (1 equiv.), acetylenes (1 equiv.), water (10 ml), microwave irradiation (75 °C, constant power 80 W). [b] Isolated yield.



Scheme 2 Formation of benzofuroxan from 2-azidonitrobenzene.

Cycloaddition of the highly reactive 4-azidonitrobenzene **1a** and tolane **2e** afforded 1,2,3-triazole **3ae** in almost quantitative yield (Table 3, entry 1). Arylazides **1g** and **1e** with electron-donating substituents showed significantly lower reactivity producing the corresponding 1,2,3-triazoles **3ge** and **3ee** in moderate yields even after using a double excess of the azide (entries 2 and 3). It should be noted that the Zn/C catalyst was completely unreactive in the reaction between *o*-substituted azides and tolane.[18] The high reactivity of our catalytic system is best demonstrated by the reaction of 4-azidonitrobenzene **1a** with the electron-poor acetylenedicarboxylic acid **2f**, which produced 1,2,3-triazole **3af** in 60% yield (entry 4).

The high reactivity of the $Zn(OAc)_2$ catalyst allowed us to develop a substrate-determined regioselective method for the synthesis of fully decorated 1,4,5-trisubstituted-1,2,3-triazoles (entries 5–10). We have found that the Zn-catalyzed AAC reaction is very sensitive to steric hindrance in the acetylene moiety. In particular, the reaction of aromatic azides **1a**, **1d**, and **1n** and TIPS-substituted phenylacetylene **2h** led to the formation of 1,5-diaryl derivatives of 1,2,3-triazoles **3ah**, **3dh**, and

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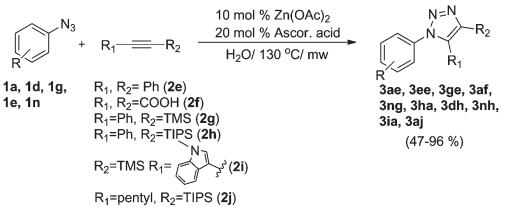
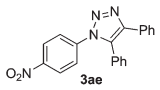
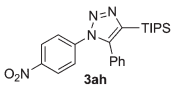
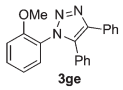
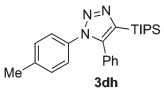
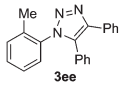
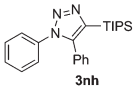
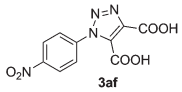
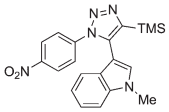
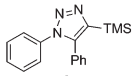
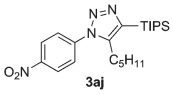
Table 3 The ZnAAC with disubstituted acetylenes[a]



Entry	1,2,3-Triazole	Yield[b] (%)	Entry	1,2,3-Triazole	Yield[b] (%)
1	 3ae	96	6	 3ah	80
2	 3ge	51[c]	7	 3dh	79
3	 3ee	47[c]	8	 3nh	70
4	 3af	60	9	 3ai	69[d]
5	 3ng	65	10	 3aj	69

[a] Reaction conditions: azide (1.1 equiv.), acetylenes (1 equiv.), water (10 ml), microwave irradiation (130 °C, constant power 150 W). [b] Isolated yield. [c] Reaction conditions: azide (2 equiv.), acetylenes (1 equiv.), water (10 ml), microwave irradiation (130 °C, constant power 150 W). [d] Reaction conditions: azide (2 equiv.), acetylenes (1 equiv.), water (10 ml), microwave irradiation (80 °C, constant power 90 W).

3nh (entries 6–8). The TIPS-derivative of 1-hexyne **2j** reacted in a similar way (entry 10). Similar regioselectivity was observed in the reactions of TMS-substituted acetylenes **2g** and **2i** (entries 5 and 9). The structures of triazoles **3ai**, **3aj** and **3dh** were established by X-ray analysis (Fig. 1; X-ray structures of **3aj** and **3dh** are provided in the ESI†).

The relatively high temperatures can cause the formation of desired triazoles without the Zn catalyst. In order to clarify this question, we carried out the reaction between 1-azido-4-nitrobenzene **1a** and the TIPS-derivative of phenylacetylene **2h** in the absence of $Zn(OAc)_2$. After 6 hours of microwave heating we observed the formation of black tar without any traces of desired triazole **3ah**.

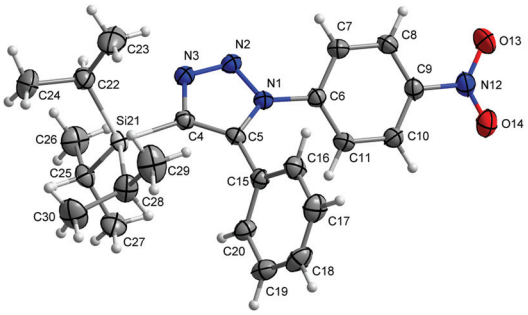


Fig. 1 The X-Ray structure of 1,2,3-triazole **3ah**.

The observed high regioselectivity of $Zn(OAc)_2$-catalyzed AAC requires a suitable mechanistic explanation. Two main approaches to the regioselective synthesis of 1,2,3-triazoles are currently known: the RuAAC with the formation of 1,5-disubstituted-1,2,3-triazoles[17] and the CuAAC for the preparation of 1,4-disubstituted-1,2,3-triazoles.[10e,23] The mechanisms of both reactions were thoroughly investigated by experimental and theoretical studies.[3,4a,5a,17] A substrate-determined regioselectivity has not been previously observed in the ZnAAC reactions. In fact, the previously published $ZnEt_2$-mediated cycloaddition is not applicable to the reactions of disubstituted alkynes because its mechanism involves the initial formation of Zn-acetylides from terminal alkynes.[19]

Chen and co-workers have proposed that Zn-catalyzed AAC can proceed through the intermediate formation of a Zn-containing six-membered cycle.[18] Based on this suggestion, we propose the mechanism of $Zn(OAc)_2$-catalyzed AAC shown in Scheme 3.

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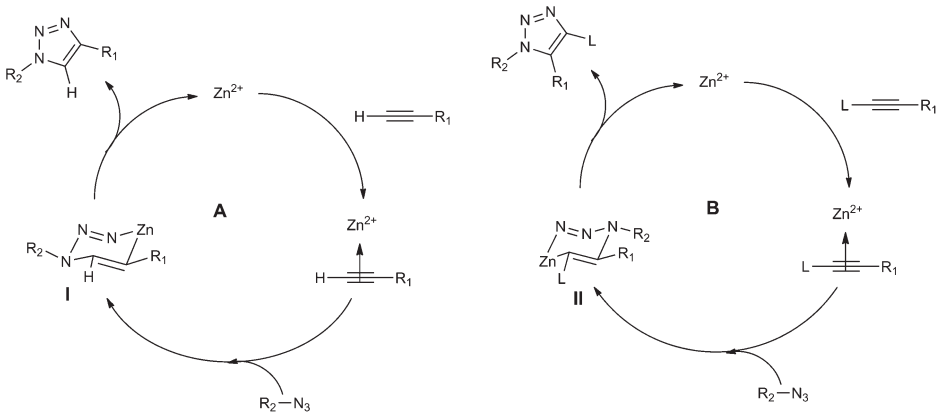


Scheme 3 The proposed mechanism for the Zn-catalyzed formation of (A) 1,4-disubstituted-1,2,3-triazoles and (B) 1,4,5-trisubstituted-1,2,3-triazoles.

We suggest that the initial step of ZnAAC is the formation of a π-complex between $Zn(OAc)_2$ and acetylene. In the next step, the resulting complex interacts with the azide giving the metallacycle **I**. In the final stage the Zn^{2+} is regenerated *via* extrusion from metallacycle **I**. We may speculate that the presence of ascorbic acid accelerates the reaction due to its participation in the redox processes involving zinc species, or due to the general acid catalysis.

We suggest that the regioselectivity of the formation of the intermediate is determined by the conformation of a six-membered metallacycle. In the case of a mono-substituted acetylene, the hydrogen does not restrict the formation of metallacycle **I**. Moreover, the R^1 group makes unfavorable the addition of the azide with opposite orientation.

Surprisingly, the alkyl-substituents in terminal acetylenes **2c** and **2d** also have a strong effect on regioselectivity. The formation of the regioisomeric 1,5-disubstituted-1,2,3-triazoles in the reaction of azides **1a**, **1d**, and **1f** with terminal acetylenes **2c** and **2d** was not observed (Table 2, entries 15–18). In contrast, the presence of a large (L) group such as TIPS or TMS makes entirely unfavorable the formation of intermediate **I**. Only one possible reaction path is possible through the generation of intermediate **II**.

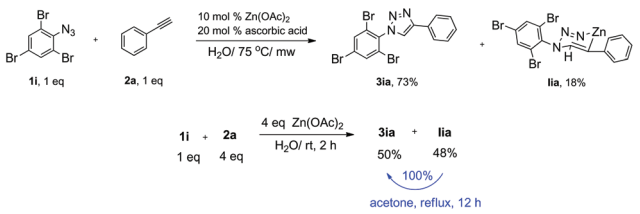
Obviously, the steric hindrance of the R^2-group affects the reaction conditions, and the AAC requires the increased temperature and microwave power and longer reaction time (Table 3). Even under these conditions we did not observe the formation of 1,4-diarylsubstituted-1,2,3-triazole derivatives in the reaction with TIPS-acetylenes.

In order to prove the formation of intermediate **I** we carried out a comprehensive study of the reaction between azide **1i** and acetylene **2a**. The GCMS analysis of the reaction mixture after full conversion of the starting materials showed that the reaction mixture contains a compound with retention time and mass-spectra different from product **3ia** (the chromatogram and mass-spectrum are presented in ESI Fig. S1†). Moreover, in the mass-spectra we observed the presence of a Zn-cation, which made possible the identification of the Zn-containing intermediate **IIa**. The HPLC analysis with qTOF detection confirmed the presence of intermediate **IIa** as a complex with MeCN (Fig. S2†). The isotopic pattern of the isolated intermediate **IIa** was in agreement with the presence of a tribromobenzene ring and Zn in the molecular ion. In particular, the peak with *m*/*z* 560 indicates the presence of ^{64}Zn. Moreover, the discrepancy in the intensity of typical bromine isotopes (*m*/*z* 562 and 564) can be explained by the appearance of two isotopes of Zn: ^{64}Zn and ^{66}Zn. It should be noted that intermediate **IIa** decomposes in the process of ionization with the formation of triazole **3ia**.

We succeeded in the isolation of the pure intermediate **IIa** in 18% yield after full conversion of the starting azide and acetylene (Scheme 4). In order to improve the yield of compound **IIa**, we carried out the reaction at room temperature using four equivalents of phenylacetylene and $Zn(OAc)_2$ (Scheme 4).

This procedure allows the isolation of intermediate **IIa** in 48% yield after 2 hours. Interestingly the addition of phenylacetylene to the reaction mixture significantly increased the yield of **IIa** (Scheme 4). It should be noted that simple heating of the isolated intermediate **IIa** in acetone affords 1,2,3-triazole **3ia** in quantitative yield after simple filtration of acetone solution through the silica pad for removing of the Zn-containing byproduct.

The NMR study of compound **IIa** demonstrated a significant difference of chemical shifts of azide **1i**, phenylacetylene



Scheme 4 The synthesis and reactivity of intermediate **IIa**.

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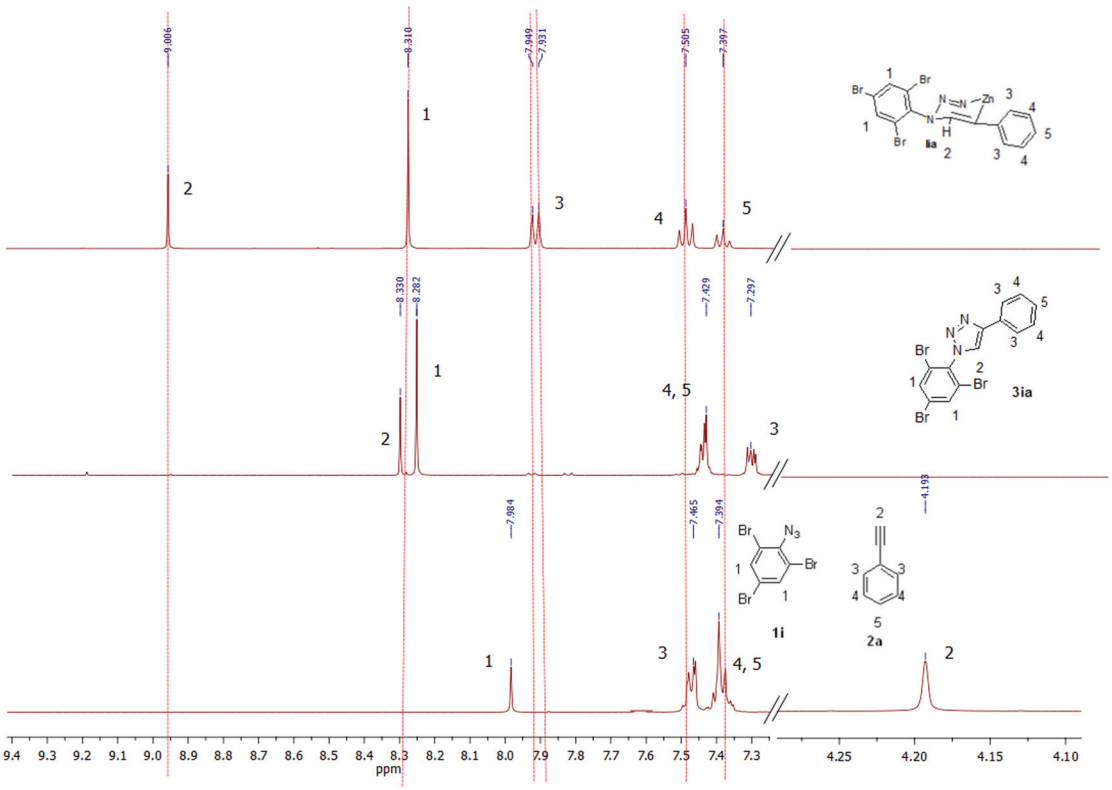

Fig. 2 The comparison of the ^{1}H NMR spectra of intermediate **Iia**, 1,2,3-triazole **3ia** and a mixture azide **1i** with alkyne **2a**.

2a, and isolated 1,2,3-triazole **3ia** (Fig. 2). The protons of the phenyl ring (H3–H5) shifted downfield in comparison with the starting phenylacetylene. The most pronounced effect was observed for *o*-protons (H3): from 7.46 to 7.95 ppm. A similar change was observed for the singlet of protons H1 (from 7.98 to 8.31 ppm).

The presence of a signal from proton H2 clearly indicates that the formation of intermediate **Iia** proceeds without the involvement of an acetylenic C–H bond. However, the signal of H-2 protons shifted downfield by 4.83 ppm (from 4.19 to 9.01 ppm). We explain this fact by the formation of a metallacycle (Fig. 2). It should be noted that HMBS data demonstrated a correlation between proton H2 and carbon C2 (Fig. S5†). The ^{13}C NMR spectra for intermediate **Iia** in a mixture with the starting materials were in agreement with these observations (Fig. S6†).

The signals of acetylenic carbons shifted from 80.7 ppm (β-carbon of the acetylenic bond) to 129.07 ppm and from 83.4 ppm (α-carbon of the acetylenic bond) to 123.4 ppm.

These shifts can be explained by the formation of intermediate **Iia** with the disappearance of the acetylenic C–C bond. In order to exclude the possible formation of 1,2,3-triazole **3ia**, we compared the NMR spectra of intermediate **Iia** with the spectra of product **3ia** (Fig. 2). The differences of chemical shifts were found for all characteristic protons and also carbons (Fig. S6†).

Thus, the mechanistic studies confirm the hypothesis about the formation of a six-membered metallacycle as the reaction intermediate. The regioselectivity of AAC is controlled by steric hindrance of the substituent in the structure of the internal acetylene.

Taking into account the availability of silyl acetylenes and the possibility of a straightforward desilylation, our method offers a good approach to the general synthesis of 1,4- and 1,5-disubstituted-1,2,3-triazoles. Moreover, compared to the Ru- or Ir-based systems, $Zn(OAc)_2$ in water represents a much cheaper and greener catalytic system.

Conclusions

In conclusion, we have developed a new method for the azide–alkyne cycloaddition reaction catalyzed by $Zn(OAc)_2$–ascorbic acid in neat water. The proposed method has a good tolerance to various functional groups and allows the preparation of 1,4-disubstituted-1,2,3-triazoles and 1,4,5-trisubstituted-1,2,3-triazoles from aromatic or aliphatic azides and terminal or internal acetylenes. Based on the developed ZnAAC, we have proposed a regioselective procedure for the synthesis of silylated triazole derivatives with controlled regioselectivity from available silyl-acetylenes. In order to prove the proposed mechanism of ZnAAC, we have isolated the reaction intermediate and identified its structure by HRMS and NMR studies.

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We believe that the developed method has great potential in organic synthesis.

Experimental

General procedure for the preparation 1,4-disubstituted-1,2,3-triazoles from azides (1a–m) and terminal alkynes (2a–d)

The mixture of azides (**1a–m**) (0.5 mmol) and alkynes (**2a–d**) in water (10 ml) was vigorously stirred for 2–3 minutes. After that, 10 mol% $Zn(OAc)_2$ (0.05 mmol, 0.011 g) and 20 mol% ascorbic acid (0.10 mmol, 0.017 g) were added to the reaction mixture. The reaction vessel was placed in a microwave reactor (t = 75 °C and power = 80 W) and heated until full conversion of the starting materials and intermediate (TLC, hexane : EtOAc = 7 : 3). After completion of the reaction, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water and brine and then dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the crude 1,4-disubstitituted-1,2,3-triazoles (**3aa–ma**, **3ab**, **3ac**, **3dc**, **3ad**, and **3fd**) which were purified by column chromatography (silica gel, eluent: hexane : EtOAc = 9 : 1).

4-Phenyl-1-(2,4,6-tribromophenyl)-1*H*-1,2,3-triazole (3ia). The reaction of 2-azido-1,3,5-tribromobenzene **1i** (0.5 mmol, 0.178 g) and phenylacetylene **2a** (0.5 mmol, 0.051 g, 55 μl) according to the general procedure for 7 hours afforded 4-phenyl-1-(2,4,6-tribromophenyl)-1*H*-1,2,3-triazole **3ia** 0.178 g (yield 78%) as a white solid, m.p. = 140–142 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.33 (s, 1H), 8.28 (s, 2H), 7.45–7.43 (m, 3H), 7.31–7.28 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 138.43, 135.35, 134.39, 132.53, 129.83, 129.30, 127.08, 125.65, 125.38, 124.03. HRMS (ESI-positive mode): calcd for $C_{14}H_8{}^{79}Br_3N_3$ ([M] + H$^+$) 457.8327; Found 457.8277; calcd for $C_{14}H_8{}^{81}Br_3N_3$ ([M] + H$^+$) 459.8305; Found 459.8271.

The crystal suitable for the X-ray study was obtained by slow evaporation of ether solution of **3ia**.

General procedure for the preparation 1,4,5-trisubstituted-1,2,3-triazoles from aromatic azides (1a, 1d, 1g, 1e, and 1n) and disubstituted acetylenes (2e–j)

The mixture of azides (**1a**, **1d**, **1g**, **1e**, and **1n**) (0.5 mmol) and disubstituted acetylenes (**2e–j**) in water (10 ml) was vigorously stirred for 2–3 minutes. After that, 10 mol% $Zn(OAc)_2$ (0.05 mmol, 0.011 g) and 20 mol% ascorbic acid (0.10 mmol, 0.017 g) were added to the reaction mixture. The reaction vessel was placed in a microwave reactor (t = 130 °C and power = 150 W) and heated until full conversion of the starting materials and intermediate (TLC, hexane : EtOAc = 7 : 3). After completion of the reaction, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), washed with water and brine and then dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give the crude 1,4,5-trisubstituted-1,2,3-triazoles (**3ae**, **3ee**, **3ge**, **3af**, **3ng**, **3ah**, **3dh**, **3nh**, **3ai**, and **3aj**) which were purified by column chromatography (silica gel, eluent: hexane : EtOAc = 9 : 1).

1-(4-Nitrophenyl)-5-phenyl-4-(triisopropylsilyl)-1*H*-1,2,3-triazole (3ah). The reaction of 1-azido-4-nitrobenzene **1a** (0.5 mmol, 0.082 g) and triisopropyl(phenylethynyl)silane **2h** (0.5 mmol, 0.142 g) according to the general procedure for 5.5 hours afforded 1-(4-nitrophenyl)-5-phenyl-4-(triisopropylsilyl)-1*H*-1,2,3-triazole **3ah** 0.169 g (yield 80%) as a slight yellow solid, m.p. = 84–85 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.25 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.46–7.39 (m, 3H), 7.36–7.34 (m, 2H), 1.23–1.14 (m, 3H), 0.98–0.96 (m, 18H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 147.08, 144.47, 140.99, 140.77, 130.35, 129.90, 128.55, 127.90, 126.29, 124.65, 18.54, 11.11; HRMS (ESI-positive mode): calcd for $C_{23}H_{31}N_4O_2Si$ ([M] + H$^+$) 423.2216, Found 423.2214.

The crystal suitable for the X-ray study was obtained by slow evaporation of ether solution of **3ah**.

The full characterization of all the prepared compounds, including the NMR-spectra, HRMS data and X-ray structures is provided in the ESI.†

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