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An efficient Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction in aqueous medium with a zwitterionic ligand, betaine†

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Cu-catalyzed azide–alkyne cycloaddition reaction in aqueous medium was dramatically accelerated by a simple zwitterionic additive, betaine, at ambient temperature. In the presence of betaine, 1,4-disubstituted-1,2,3-triazoles were obtained from azides and terminal alkynes in excellent yields under 2.5–200 ppm levels of $Cu^{(I)}$ in water. This method resulted in the remarkable reduction of the $Cu^{(I)}$ concentration down to ppm levels. The advantages of this protocol include the use of a conventional Cu catalytic system with commercially available betaine, which is generally non-toxic for biological application. Therefore, this efficient catalytic system should have broad applications in life science research and materials science.

Introduction

Azide–alkyne cycloaddition reaction, first discovered by Huisgen,[1] has received enormous attention as a powerful tool to form 1,4-disubstituted-1,2,3-triazoles, since Sharpless and Meldal developed the $Cu^{(I)}$-catalyzed azide–alkyne 1,3-cycloaddition (CuAAC) reaction.[2] The CuAAC reaction is easy, highly efficient, regioselective and compatible with various functional groups. Therefore, it has been extensively utilized in organic synthesis, biochemistry, medicinal chemistry, chemical biology and materials science.[3] For biological application, since it is desirable for the reaction to be compatible with living systems, especially in aqueous medium and live cells, highly efficient $Cu^{(I)}$ catalysts have been developed for the synthesis of triazoles to minimize the amount of $Cu^{(I)}$ catalyst used. To improve the activity of the catalysts, various ligands such as polysaccharide-supported nanoparticles,[4] polymer-embedded catalysts,[5] and particularly catalysts with nitrogen ligands such as *N*-heterocyclic carbenes,[6] polytriazoles,[7] and tri(aminoalkyl)amine derivatives[8] have been developed.

To further reduce the cellular toxicity of the catalysts, a dendritic nanoreactor containing intradendritic triazoles,[9] poly(*N*-isopropylacrylamide-*co*-*N*-vinylimidazole) polymers,[10] and tris(triazolyl)-polyethylene glycol[11] promoted CuAAC, which reduced the amount of $Cu^{(I)}$ catalyst for the reaction to the part per million (ppm) level. Even though these endeavours led to great advances in reducing the amount of Cu catalyst, they still have shortcomings.

The major limitation of the aqueous medium of biological systems is the mixing problem with organic materials including the ligands of CuAAC catalysts, and thus even the reactive ligands work less efficiently. To overcome this mixing problem in general, various surfactants and phase transfer catalysts have been employed.[12] Recently, Lipshutz reported a CuAAC reaction using TPGS-750-M as a non-ionic surfactant in water,[13] and Scarso also reported that organic bromide was reacted with sodium azide and a terminal alkyne in the presence of a surfactant to give 1,4-disubstituted-1,2,3-triazoles in water.[14] In the same context, we have successfully introduced β-cyclodextrin as the nanoreactor and the carrier of substrates to the aqueous phase to accelerate the CuAAC reaction.[15]

As a part of our continuing studies on the development of readily applicable methods for triazole synthesis in water, we tested the CuAAC reaction using different surfactants such as nonionic, cationic, anionic, and zwitterionic types, with anticipation of increasing the reaction efficiency through micellar effects[12a] and the on-water effect.[16] Herein we report a synthetic method for triazoles using ppm levels of a $Cu^{(I)}$ catalyst in the presence of betaine, which is a readily available and biocompatible zwitterionic surfactant. With amounts of 0.0003 mol% (2.5 ppm) to 0.025 mol% (200 ppm) of $Cu^{(I)}$, the CuAAC reaction was carried out at 30 °C, efficiently affording excellent yields of triazoles.

Results and discussion

Initially with anticipation of micellar effects, we carried out CuAAC reactions with various additives such as β-cyclodextrin (the phase transfer catalyst), SDS, aliquat 128, Triton X-100,

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and betaine (anionic, cationic, non-ionic, and zwitterionic surfactants, respectively) in water. The reaction of benzyl azide **1a** with phenyl acetylene **2a** in the presence of 200 ppm of $Cu^{(I)}$ and 5 mol% of surfactant in water at 30 °C gave the corresponding triazole **3aa**, and the results are listed in the Table 1. Interestingly, different reaction rates for triazole formation were observed depending on the surfactant type. Among them, in the case of using the zwitterionic surfactant betaine, the reaction showed a remarkable improvement in the reactivity to produce **3aa** in 98% conversion in 1 h (entry 6).

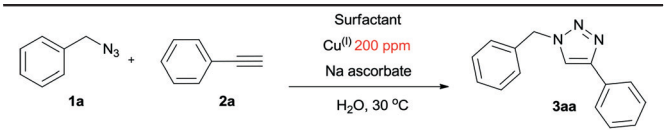
Through these experiments, we decided to investigate the betaine–Cu catalytic system in detail. To verify the effects of betaine, reactions were performed in various amounts of $Cu^{(I)}$ with 5 mol% of betaine (Table 2). No reaction occurred in the absence of $Cu^{(I)}$ regardless of the presence of betaine for 24 h (entry 1–2). Without betaine, the reaction also proceeded sluggishly using 100 ppm of $Cu^{(I)}$ (entry 3). On the other hand, in the presence of betaine, **3aa** was obtained in 97% conversion even with only 10 ppm of $Cu^{(I)}$ in 5 h (entry 4). Reduction of the $Cu^{(I)}$ concentration to 1 ppm resulted in 77% conversion, leading to TONs of up to 616 000 and TOFs of up to 123 200 h^{-1} (entry 5). Surprisingly, when the reaction temperature was increased to 40 °C, **1a** was converted to **3aa** in 24 h cleanly even at a 25 ppb level of $Cu^{(I)}$ (entry 6). Even though the best results were obtained at 40 °C, considering a wide range of applications including chemical biology and bioorthogonal chemistry, all the reactions were carried out at 30 °C. These results implied that both Cu and betaine play important roles in the CuAAC reaction in water.

Then, to gain insight into the role of betaine in the Cu catalytic mechanism, we tested other additives, such as choline chloride, sodium acetate, and sodium propionate, with respect to their potential to accelerate triazole formation (Table 3). In the case of choline chloride, which has only an ammonium part in the molecule, the reaction gave a moderate conversion of 66% in the presence of 200 ppm of $Cu^{(I)}$ for 1 h at 30 °C (entry 1). This result indicates that the ammonium part of choline chloride contributes to the catalytic system. Sodium acetate and sodium propionate, having a carboxylate group in their molecules, showed 46% (entry 2) and 74% (entry 3) conversions, respectively. Remarkably, betaine, which has both a positively charged quaternary ammonium group and a negatively charged carboxylate group, existing in the zwitterionic form, showed an excellent conversion under the same reaction conditions (entry 4). These results showed clearly that both the ammonium part and the anionic part play important roles in this catalytic system. It is well known that betaine coordinates easily with Cu to stabilize and/or activate it.[17] Therefore, we could speculate that betaine improves the solubility of the reactants and reagents in water, facilitates deprotonation of the terminal alkyne, and stabilizes the $Cu^{(I)}$ generated in the catalytic cycle.[18]

Next, the recycling of the CuAAC reaction between **1a** and **2a** in the presence of 200 ppm of $Cu^{(I)}$ and betaine (5 mol%) was performed; a longer reaction time was required to observe the complete conversion with successive reuse of the betaine–Cu system (1st cycle: 1 h, 2nd cycle: 3.5 h, 3rd cycle: 9 h). The decrease in catalytic activity was ascribed to the well anticipated loss of Cu in the aqueous medium during workup.

To find the minimum concentration of Cu, we carried out experiments to optimize the reaction conditions for the CuAAC reaction depending on various substrates. As shown in Table 4, **1a** was reacted with various alkynes **2a–2n** in the presence of 2.5–200 ppm of Cu at 30 °C, affording the desired triazoles **3aa–3an**. Although most reactions were completed within several hours, the reaction time was set to 24 h to maximize the conversion and to compare the results with the recently reported CuAAC reaction results using ppm levels of $Cu^{(I)}$.[9–11] In the case of phenyl acetylene (**2a**), the desired triazole **3aa** was obtained quantitatively with only 2.5 ppm of $Cu^{(I)}$ in water at 30 °C for 24 h. Moreover, a large-scale reaction (**1a**, **1g** scale) under these conditions was also successfully conducted to afford an excellent isolated yield (95%)

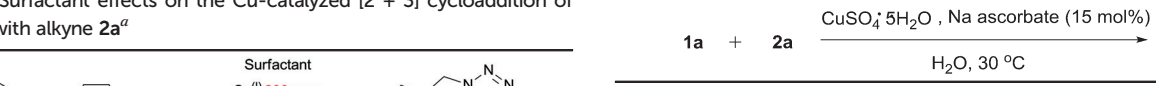
Table 1 Surfactant effects on the Cu-catalyzed [2 + 3] cycloaddition of azide **1a** with alkyne **2a**[a]



Entry	Surfactant	Type	Time	Conv. (%)
1	—	—	5 h	49
2[b]	β-CD	—	1 h	61
3	SDS	Anionic	1 h	68
4	Aliquat 128	Cationic	1 h	33
5	Triton X-100	Non-ionic	1 h	42
6	Betaine	Zwitterionic	1 h	98

[a] All the reactions were carried out with benzyl azide **1a** (0.75 mmol), phenyl acetylene **2a** (1.05 equiv.), $CuSO_4{\cdot}5H_2O$ (0.025 mol%, 200 ppm based on Cu), Na ascorbate (0.15 equiv.) and a surfactant (0.05 equiv.) in H_2O (1 mL) at 30 °C. [b] β-CD, the phase transfer catalyst.

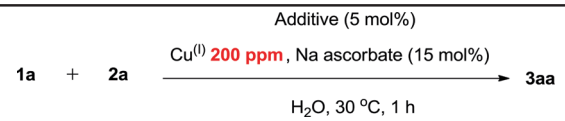
Table 2 CuAAC reaction between **1a** and **2a** using various concentrations of the Cu catalyst[a]

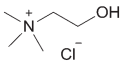
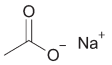
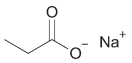
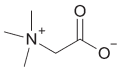


Entry	Cu[(I)]	Betaine (mol%)	Time (h)	Conv. (%)	TON	TOF (h^{-1})
1	—	—	24	<1	—	—
2	—	5	24	<1	—	—
3	100 ppm (0.0125 mol%)	—	5	48	3840	768
4	10 ppm	5	5	97	77 600	15 520
5	1 ppm	5	5	77	616 000	123 200
6[b]	25 ppb	5	24	100	32 000 000	1 333 333
7[b]	10 ppb	5	24	19	15 200 000	633 333

[a] All the reactions were carried out with **1a** (0.75 mmol), **2a** (1.05 equiv.), $CuSO_4{\cdot}5H_2O$ (25 ppb – 100 ppm based on Cu), Na ascorbate (0.15 equiv.) and betaine (0.05 equiv.) in H_2O (1 mL) at 30 °C. [b] The reaction was carried out at 40 °C.

Table 3 Comparative screening of other additives, similar types of betaine, for the CuAAC reactions[a]



Entry	Additive	Structure	Conv. (%)
1	Choline chloride		66
2	Sodium acetate		46
3	Sodium propionate		74
4	Betaine		98

[a] All the reactions were carried out with benzyl azide **1a** (0.75 mmol), phenyl acetylene **2a** (1.05 equiv.), $CuSO_4{\cdot}5H_2O$ (0.025 mol%, 200 ppm based on Cu), Na ascorbate (0.15 equiv.) and an additive (0.05 equiv.) in H_2O (1 mL) at 30 °C for 1 h.

close to the conversion yield.[19] For aryl alkynes containing electron-donating and electron-withdrawing groups, the reactions were completed in 24 h, with excellent isolated yields only at less than 25 ppm $Cu^{(I)}$ levels (**3ab**–**3ag**). Alkyne **3ah** bearing the sterically demanding adamantane group required a higher amount of the catalyst (100 ppm) to form the corresponding triazole. Also, for alkynes containing a hydroxyl group, more $Cu^{(I)}$ was required for the completion of the reaction (100 ppm for **3ai** and 200 ppm for **3aj**), probably due to the compromised hydrophobic effect of the ligand. Moreover, aliphatic alkynes **3ak**, **3al**, and **3am** efficiently reacted with only 75–100 ppm of $Cu^{(I)}$. Interestingly, ethynylferrocene (**2n**) also reacted with **2a** without any difficulty, with only 25 ppm of $Cu^{(I)}$, to produce the desired product **3an** in 94% isolated yield.

To further demonstrate the general applicability and versatility of this catalytic system, diverse azides **1b**–**1h** were also allowed to react with alkynes **2a**–**2l** in the presence of the betaine–Cu system (Table 5). Most aryl or aliphatic azides and alkynes afforded good yields of the corresponding triazoles using low $Cu^{(I)}$ levels of 25–75 ppm (**4ba**, **4bl**, **4ca**, **4da**, **4ee**, **4ea**, **4el**, **4fa**, **4fl**, and **4ga**). An azide containing a carboxyl group and alkynes containing a hydroxyl group required 125 and 150 ppm of $Cu^{(I)}$ to produce the desired products **4ha** and **4bi** in high yields, respectively.

Conclusions

A simple betaine–Cu catalytic system with remarkably small amounts of Cu, which provided facile and convenient access to triazoles, was developed. The use of this catalytic system in water at 30 °C efficiently produced a wide range of triazoles in good to excellent yields. Furthermore, workup was easy, requiring only simple suction filtration or solvent extraction. In addition, this method resulted in the remarkable reduction of the $Cu^{(I)}$ concentration down to ppm levels during the reaction, which demonstrates easy applicability since specially designed ligands were not required for the activation and stabilization of $Cu^{(I)}$. The advantages of this protocol include the use of a conventional Cu catalytic mixture that is easily generated from $CuSO_4$–Na ascorbate and betaine, which is an easily obtained, commercially available, biodegradable, and biocompatible surfactant. Therefore, this efficient catalytic system is believed to have broad applications in biological and materials sciences.

Experimental section

General information

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AVANCE 400 spectrometer. Chemical shifts are given with respect to residual $CHCl_3$ (7.28 ppm) in $CDCl_3$. IR spectra of all compounds were recorded on a Frontier FT-IR spectrometer, and HRMS analyses were carried out using a Bruker micrOTOF-Q instrument with electrospray ionization operating in positive mode. The melting temperature was determined with an IA 9200 melting point apparatus from Electrothermal Thermo Scientific. The mass fractions of residual Cu in the products were determined by inductively coupled plasma mass spectrometry (ICP-MS, Thermo Scientific Neptune Plus) with the external calibration method.

Typical procedure for CuAAC

In a vial fitted with a screw cap, to a solution of benzyl azide **1a** (100 mg, 0.75 mmol) and phenyl acetylene **2a** (83 mg, 1.05 equiv.) was added sodium ascorbate (23 mg, 0.15 equiv.), betaine (4.5 mg, 0.05 equiv.), and copper(II) sulfate pentahydrate in H_2O (1 mL of stock solution, 2.5 ppm based on Cu) at 30 °C. The reaction mixture was stirred for 24 h at 30 °C. The resulting product was extracted with CH_2Cl_2 (3 mL) three times. The combined organic layer was concentrated *in vacuo*. The crude compound was washed with pentane to give 172 mg of **3aa** (97%).

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3aa)

Ivory needles (97%); mp = 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.1 Hz, 2H), 7.67 (s, 1H), 7.44–7.33 (m, 7H), 5.60 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.1, 134.6, 130.5 (2C), 129.0 (2C), 128.7, 128.6, 128.0, 127.9 (2C), 125.6 (2C), 119.5, 54.1.

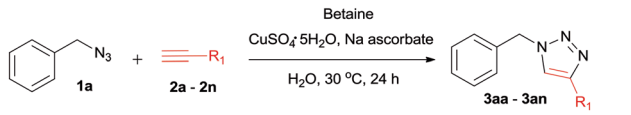
1-Benzyl-4-(*p*-tolyl)-1*H*-1,2,3-triazole (3ab)

White needles (91%); mp = 154–155 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.4 Hz, 2H), 7.64 (s, 1H), 7.42–7.38 (m, 3H), 7.35–7.31 (m, 2H), 7.23 (d, J = 7.6 Hz, 2H), 5.58 (s, 2H), 2.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.3, 138.0, 134.7, 129.4 (2C), 129.1 (2C), 128.7, 128.0, 127.7 (2C), 125.6 (2C), 119.1, 54.2, 21.2.

1-Benzyl-4-(3-fluorophenyl)-1*H*-1,2,3-triazole (3ac)

Ivory needles (100%); mp = 109–111 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.57–7.53 (m, 2H), 7.38–7.30 (m, 6H),

Table 4 Results of the CuAAC reaction between **1a** and various alkynes **2a–2n** using betaine in water[a]



Entry	Alkyne	Product	$Cu^{(I)}$ (ppm)	Isolated yield (%)
1	**2a**	**3aa**	2.5	97
2	**2b**	**3ab**	25	97
3	**2c**	**3ac**	25	88
4	**2d**	**3ad**[b]	25	98
5	**2e**	**3ae**	25	97
7	**2f**	**3af**	25	95
8	**2g**	**3ag**	25	96
9	**2h**	**3ah**	100	83
10	**2i**	**3ai**	100	98
11	**2j**	**3aj**	200	87
12	**2k**	**3ak**	100	93
13	**2l**	**3al**	75	97
14	**2m**	**3am**	100	76
15	**2n**	**3an**	25	94

[a] All reactions were performed with azide **1a** (0.75 mmol), alkynes **2a–2n** (1.05 equiv.), $CuSO_4{\cdot}5H_2O$ (2.5–200 ppm based on Cu), Na ascorbate (0.15 equiv.), and betaine (0.05 equiv.) in water (1 mL) for 24 h at 30 °C. The yields shown represent those obtained for isolated products. [b] The concentration of residual Cu in the product was 14 ppm.

7.00 (t, J = 8.4 Hz, 1H), 5.56 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J = 245.6 Hz), 147.0, 134.4, 132.6 (d, J = 8.6 Hz), 130.3 (d, J = 8.4 Hz), 129.1 (2C), 128.7, 127.9 (2C), 121.2 (d, J = 2.8 Hz), 119.9, 114.7 (d, J = 21.2 Hz), 112.4 (d, J = 23.0 Hz), 54.1.

1-Benzyl-4-(2,4-difluorophenyl)-1*H*-1,2,3-triazole (3ad)

Tan needles (98%); mp = 124–126 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, J = 15.3, 7.2 Hz, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.42–7.31 (m, 5H), 7.00 (t, J = 8.4 Hz, 1H), 6.87 (t, J = 10.8 Hz, 1H), 5.60 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J = 12.2 Hz), 160.8 (dd, J = 83.9, 11.9 Hz), 157.9 (d, J = 11.7 Hz), 140.9, 134.6, 129.1 (2C), 128.9–128.6 (m), 127.9 (2C), 122.1 (d, J = 12.2 Hz), 115.0 (dd, J = 13.2, 3.8 Hz), 111.9 (dd, J = 21.3, 3.4 Hz), 104.0 (t, J = 25.7 Hz), 54.2.

1-Benzyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (3ae)

White amorphous solid (97%); mp = 70 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.57–7.48 (m, 2H), 7.42–7.31 (m, 5H), 5.59 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.8, 134.4, 131.4, 131.4 (q, J = 32.4 Hz), 129.3, 129.2 (2C), 128.9, 128.8, 128.1 (2C), 124.7 (q, J = 3.7 Hz), 124.0 (d, J = 272.3 Hz), 122.4 (q, J = 3.9 Hz), 120.0, 54.3.

1-Benzyl-4-(3,5-dimethoxyphenyl)-1*H*-1,2,3-triazole (3af)

Tan needles (95%); mp = 119–121 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.37–7.29 (m, 5H), 6.99 (s, 2H), 6.44 (s, 1H), 5.55 (s, 2H), 3.82 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.1 (2C), 147.9, 134.6, 132.3, 129.0 (2C), 128.6, 127.9 (2C), 119.8, 103.5 (2C), 100.5, 55.3 (2C), 54.1; FT-IR (KBr, cm^{-1}) 3119 (m), 3089 (w), 2998 (w), 2961 (w), 2936 (w), 2837 (w), 1595 (vs), 1551 (w), 1497 (w), 1474 (m), 1453 (m), 1417 (m), 1359 (m), 1274 (w), 1229 (m), 1153 (s), 1179 (m), 1200 (vs), 1092 (m), 1065 (m), 1044 (m), 1001 (m), 925 (m), 849 (m), 833 (s), 716 (s); HRMS $[M + Na]^+$ calcd. For $C_{17}H_{17}N_3O_2Na$ 318.1218, found 318.1226.

3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)aniline (3ag)

Brown needles (96%); mp = 135–137 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.41–7.38 (m, 3H), 7.38–7.31 (m, 6H), 7.30–7.28 (m, 2H),7.25 (s, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7,12–7.11 (m, 1H), 6.66–6.64 (m, 1H), 5.57 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.3, 146.9, 134.7, 131.4, 129.7 (2C), 129.1, 128.7, 128.0 (2C), 119.5, 115.9, 114.9, 112.2, 54.1.

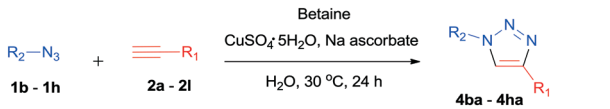
4-((Adamantan-1-ylmethoxy)methyl)-1-benzyl-1*H*-1,2,3-triazole (3ah)

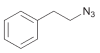
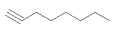
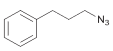
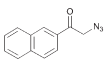
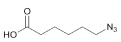
Yellow solid (94%); mp =125–127 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.40–7.37 (m, 2H), 7.30–7.28 (m, 3H), 5.55 (s, 2H), 4.60 (s, 2H), 3.07 (s, 2H), 1.95 (s, 3H), 1.66 (dd, J = 32.0, 12.2 Hz, 6H), 1.51–1.50 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.5, 134.7, 129.0 (2C), 128.7, 128.0 (2C), 122.1, 81.5, 65.1, 54.1, 39.7 (3C), 37.1 (3C), 34.0, 28.2 (3C); FT-IR (KBr, cm^{-1}) 3141 (w), 2901 (vs), 2847 (s), 1722 (w), 1638 (w), 1497 (w), 1454 (m), 1362 (w), 1344 (w), 1224 (m), 1156 (w), 1089 (m), 1048 (m), 812 (w), 723 (m), 695 (w); HRMS $[M + Na]^+$ calcd. For $C_{21}H_{27}N_3ONa$ 360.2052, found 360.2038.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (3ai)

Ivory needles (98%); mp = 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 4H), 7.27–7.25 (m, 2H), 5.47 (s, 2H), 2.92 (brs, 1H, OH), 1.93–1.25 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.0, 134.6, 128.9 (2C), 128.7, 128.1 (2C), 119.6, 69.4, 54.0, 37.9 (2C), 25.2, 21.8 (2C).

Table 5 Results of the CuAAC reaction of different azides **1b–1h** with alkynes **2a–2l** using betaine in water[a]



Entry	Azide	Alkyne	Product	Cu(I) (ppm)	Isolated yield (%)
1	 **2b**	 **2a**	**4ba**	25	95
2	**2b**	 **2l**	**4bl**[b]	75	96
3	**2b**	 **2i**	**4bi**	150	96
4	 **2c**	**2a**	**4ca**	25	100
5	 **2d**	**2a**	**4da**	25	94
6	 **2e**	 **2e**	**4ee**	25	94
7	**2e**	**2a**	**4ea**	75	92
8	**2e**	**2l**	**4el**	75	97
9	 **2f**	**2a**	**4fa**	25	92
10	**2f**	**2l**	**4fl**	75	92
11	 **2g**	**2a**	**4ga**	50	94
12	 **2h**	**2a**	**4ha**	125	90

[a] All reactions were performed with azides **1b–1h** (0.75 mmol), alkynes **2a–2l** (1.05 equiv.), $CuSO_4{\cdot}5H_2O$ (25–150 ppm based on Cu), Na ascorbate (0.15 equiv.), and betaine (0.05 equiv.) in water (1 mL) for 24 h at 30 °C. The yields shown represent those obtained for isolated products. [b] The concentration of residual Cu in the product was 16 ppm.

3-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-1-ol (3aj)

Yellow oil (87%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 3H), 7.28–7.25 (m, 3H), 5.50 (s, 2H), 3.70 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H), 2.70–2.60 (brs, 1H, OH), 1.92 (quintet, J = 6.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.0, 134.6, 128.8 (2C), 128.4, 127.7 (2C), 121.0, 61.1, 53.8, 31.8, 21.7.

1-Benzyl-4-butyl-1*H*-1,2,3-triazole (3ak)

Ivory amorphous solid (93%); mp = 60–62 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 3H), 7.28–7.26 (m, 2H), 7.19 (s, 1H), 5.51 (s, 2H), 2.71 (t, J = 7.6 Hz, 2H), 1.68–1.61 (m, 3H), 1.38 (sextet, J = 7.5 Hz, 2H), 0.93 (t, J = 7.6 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 149.0, 135.0, 129.0 (2C), 128.6, 127.9 (2C), 120.4, 54.0, 31.5, 25.4, 22.3, 13.8.

1-Benzyl-4-hexyl-1*H*-1,2,3-triazole (3al)

Ivory amorphous solid (97%); mp = 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 3H), 7.37–7.35 (m, 3H), 5.60 (s, 2H), 2.79 (t, J = 7.7 Hz, 2H), 1.77–1.71 (m, 2H), 1.46–1.39 (m, 6H), 0.98–0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.0, 129.0 (2C), 128.6, 127.9 (2C), 120.4, 54.0, 31.5, 29.3, 28.9, 25.7, 22.5, 14.0.

1,5-Bis(1-benzyl-1*H*-1,2,3-triazol-4-yl)pentane (3am)

Ivory amorphous solid (98%); mp = 125–127 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42–7.36 (m, 6H), 7.30–7.28 (m, 4H), 7.21 (s, 2H), 5.52 (s, 4H), 2.71 (t, J = 7.4 Hz, 4H), 1.74–1.67 (m, 4H), 1.46–1.40 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.6 (2C), 135.0 (2C), 129.0 (4C), 128.6 (2C), 127.9 (4C), 120.5 (2C), 54.0 (2C), 29.0 (2C), 28.6 (2C), 25.5.

1-Benzyl-4-ferrocenyl-1*H*-1,2,3-triazole (3an)

Red needles (94%); mp = 153–155 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (m, 4H), 7.29–7.28 (m, 2H), 5.54 (s, 2H), 4.71 (s, 2H), 4.23 (s, 2H), 4.07 (s, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.1, 134.8, 129.0 (2C), 128.6, 127.8 (2C), 118.7, 75.3, 69.4 (5C), 68.5 (2C), 66.5 (2C), 53.9.

1-Phenethyl-4-phenyl-1*H*-1,2,3-triazole (4ba)

White amorphous solid (95%); mp = 140 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 2H), 7.49 (s, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.36–7.26 (m, 2H), 7.17–7.15 (m, 4H), 4.66 (t, J = 7.0 Hz, 2H), 3.28 (t, J = 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.5, 137.1, 130.7, 128.8 (2C), 128.8 (2C) 128.7 (2C), 128.1, 127.1, 125.7 (2C), 119.9, 51.7, 36.8.

4-Hexyl-1-phenethyl-1*H*-1,2,3-triazole (4bl)

Yellow oil (96%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 3H), 7.11 (d, J = 7.2 Hz, 2H), 7.00 (s, 1H), 4.55 (t, J = 7.2 Hz, 2H), 3.20 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 1.64–1.59 (m, 2H), 1.33–1.29 (m, 6H), 0.91–0.88 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.1, 137.2, 128.7 (2C), 128.6 (2C), 126.9, 120.9, 51.4, 36.8, 31.5, 29.4, 28.8, 25.5, 22.5, 14.0.

1-(1-Phenethyl-1*H*-1,2,3-triazol-4-yl)cyclohexan-1-ol (4bi)

Ivory needles (96%); mp = 109 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.29–7.17 (m, 4H), 7.09 (d, J = 7.0 Hz, 2H), 4.55 (t, J = 7.0 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 2.77 (brs, 1H, OH), 1.96–1.70 (m, 6H), 1.59–1.32 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.1, 137.0, 128.7 (2C), 128.6 (2C), 127.0, 120.1, 69.3, 51.5, 38.0, 36.7, 25.3, 22.0.

4-Phenyl-1-(3-phenylpropyl)-1*H*-1,2,3-triazole (4ca)

Ivory amorphous solid (100%); mp = 81–82 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 2H), 7.74 (s, 1H), 7.45 (t, J

= 7.6 Hz, 2H), 7.38–7.32 (m, 3H), 7.27–7.21 (m, 3H), 4.43 (t, *J* = 7.0 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.33 (quintet, *J* = 7.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.8, 140.1, 130.7, 128.8, 128.6, 128.5, 128.1, 126.4, 125.7, 119.5, 49.6, 32.5, 31.7.

4-Phenyl-1-(8-phenyloctyl)-1*H*-1,2,3-triazole (4da)

White amorphous solid (94%); mp = 70–73 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.75 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38–7.34 (m, 1H), 7.32–7.26 (m, 2H), 7.20–7.18 (m, 3H), 4.41 (t, *J* = 7.1 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.00–1.93 (m, 2H), 1.63–1.60 (m, 2H), 1.38–1.34 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.7, 142.7, 130.7, 128.8 (2C), 128.4 (2C), 128.2 (2C), 128.1, 125.7(2C), 125.6, 119.3, 50.4, 35.9, 31.4, 30.3, 29.2, 29.1, 28.9, 26.5; FT-IR (KBr, cm^{-1}) 3081 (m), 3031 (w), 2917 (vs), 2849 (vs), 1609 (w), 1462 (m), 1384 (w), 1352 (w), 1222 (w), 1202 (w), 1180 (w), 1085 (w), 1051 (w), 1027 (w), 912 (w), 861 (w), 766 (s), 697 (s), 517 (w); HRMS [M + Na]$^+$ calcd. For $C_{22}H_{27}N_3Na$ 356.2103, found 356.2088.

1-Octyl-4-(3-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (4ee)

Yellow oil (94%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.87 (s, 1H), 7.58–7.50 (m, 2H), 4.40 (t, *J* = 7.1 Hz, 2H), 1.95 (s, 2H), 1.36–1.23 (m, 10H), 0.87 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 146.3, 131.6, 131.4 (q, *J* = 32.4 Hz), 129.2, 128.0, 124.5 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.3 Hz), 122.3 (q, *J* = 3.9 Hz), 119.9, 50.5, 31.6, 30.2, 28.9, 28,8, 26.4, 22.5, 13.9; FT-IR (KBr, cm^{-1}) 3132 (w), 3096 (w), 2930 (vs), 2858 (s), 1622 (w), 1596 (w), 1557 (w), 1490 (w), 1457 (m), 1420 (m), 1353 (m), 1323 (vs), 1228 (s), 1167 (vs), 1128 (s), 1096 (s), 988 (w), 911 (m), 804 (s), 710 (m), 698 (s); HRMS [M + Na]$^+$ calcd. For $C_{17}H_{22}F_3N_3Na$ 348.1664, found 348.1642.

1-Octyl-4-phenyl-1H-1,2,3-triazole (4ea)

White amorphous solid (92%); mp = 74–76 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.75 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36–7.33 (m, 1H), 4.41 (t, *J* = 7.2 Hz, 2H), 1.99–1.94 (m, 2H), 1.38–1.28 (m, 10H), 0.91–0.88 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 147.7, 130.8, 128.8 (2C), 128.0, 125.7 (2C), 119.3, 50.4, 31.7, 30.3, 29.0, 28.9, 26.5, 22.6, 14.0.

4-Hexyl-1-octyl-1*H*-1,2,3-triazole (4el)

White oil (97%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 4.30 (t, *J* = 7.1 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.89–1.85 (m, 2H), 1.68–1.64 (m, 2H), 1.35–1.25 (m, 16H), 0.87 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 148.1, 120.2, 49.9, 31.5, 31.4, 30.1, 29.3, 28.8, 28.8, 28.7, 26.3, 25.5, 22.4, 22.3, 13.8 (2C).

1-(3-Methoxyphenethyl)-4-phenyl-1*H*-1,2,3-triazole (4fa)

Ivory amorphous solid (92%); mp = 77–78 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.51 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H) 6.82 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.68 (s, 1H), 4.65 (t, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.25 (t, *J* = 7.1 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.9, 147.5, 138.6, 130.6, 129.9, 128.8 (2C), 128.1, 125.7 (2C), 121.0, 119.9, 114.3, 112.6, 55.2, 51.6, 36.8; FT-IR (KBr, cm^{-1}) 3120 (w), 3005 (w), 2951 (w), 2841 (w), 1602 (s), 1593 (w), 1494 (m), 1480 (m), 1466 (s), 1435 (w), 1358 (w), 1319 (m), 1276 (m), 1262 (s), 1225 (m), 1193 (w), 1169 (s), 1081 (m), 1041 (s), 1015 (m), 972 (w), 926 (w), 913 (w), 857 (m), 820 (m), 785 (m), 765 (vs), 721 (m), 691 (vs), 559 (w), 510 (w); HRMS [M + Na]$^+$ calcd. For $C_{17}H_{17}N_3ONa$ 302.1269, found 302.1260.

4-Hexyl-1-(3-methoxyphenethyl)-1*H*-1,2,3-triazole (4fl)

Yellow oil (92%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 7.4 Hz, 1H), 6.61 (s, 1H), 4.52 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 3.14 (t, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.4 Hz, 2H), 1.62–1.56 (m, 2H), 1.28 (s, 6H), 0.88–0.84 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 148.0, 138.7, 129.6, 120.9, 114.2, 112.3, 55.0, 51.3, 36.7, 31.4, 29.3, 28.7, 25.4, 22.4, 13.9; FT-IR (KBr, cm^{-1}) 3134 (w), 2930 (vs), 2857 (s), 1603 (s), 1586 (s), 1551 (w), 1492 (s), 1456 (s), 1437 (s), 1293 (m), 1263 (C–O, vs), 1216 (m), 1154 (m), 1127 (w), 1050 (C–O, s), 874 (m), 782 (m), 697 (m); HRMS [M + Na]$^+$ calcd. For $C_{17}H_{25}N_3ONa$ 310.1895, found 310.1879.

1-(Naphthalene-2-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-one (4ga)

Yellow amorphous solid (94%); mp = 183–185 °C; ^{1}H-NMR (400 MHz, $CDCl_3$); 8.60 (s, 1H), 8.08–7.90 (m, 7H), 7.72–7.64 (m, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 6.05 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.2, 148.3, 136.2, 132.4, 131.3, 130.5, 130.3, 129.8, 129.4, 129.3, 128.8, 128.2, 128.0, 127.4, 125.8, 123.3, 121.4, 55.5.

5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pentanoic acid (4ha)

Ivory amorphous solid (90%); mp = 130–131 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 4.40 (t, *J* = 6.7 Hz, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 1.93–1.83 (m, 2H), 1.52–1.45 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 174.6, 146.7, 131.3, 129.3 (2C), 128.2, 125.6 (2C), 121.8, 49.7, 33.4, 29.5, 21.9; FT-IR (KBr, cm^{-1}) 3121 (m), 2952 (w), 2869 (w), 2815 (w), 1709 (vs), 1694 (C═O, vs), 1464 (m), 1441 (w), 1332 (w), 1273 (w), 1215 (m), 1190 (w), 1132 (w), 1080 (m), 1052 (w), 977 (w), 839 (w), 763 (s), 696 (s), 629 (w), 526 (w); HRMS [M + Na]$^+$ calcd. For $C_{13}H_{15}N_3O_2Na$ 268.1062, found 268.1055.

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19 Procedure for a gram-scale synthesis of **3aa**: In a round bottom flask, to a solution of benzyl azide **1a** (1 g, 7.5 mmol) and **2a** (1.05 equiv.) was added sodium ascorbate (0.15 equiv.), betaine (0.05 equiv.), and copper(II) sulfate pentahydrate in H_2O (10 mL of stock solution, 2.5 ppm based on Cu). The reaction mixture was stirred for 24 h at 30 °C. The resulting mixture was filtered, washed several times with water, and dried. Product **3aa** was obtained (1.68 g) as a white solid in 95% isolated yields.