Copper on Iron: Catalyst and Scavenger for Azide–Alkyne Cycloaddition

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Abstract: Dipolar cycloaddition of terminal alkynes and azides catalyzed by the Cu/Fe bimetallic system is reported. In the presence of a readily accessible nanosized copper source, the cycloaddition reaction can be easily achieved at ambient temperature with high efficiency. The product obtained from the reaction catalyzed by Cu/Fe contains significantly lower copper contaminants compared to various active homogeneous copper complexes. Iron not only behaves as support for copper, but acts as a redox scavenger, and reduces the copper contamination of the organic product.

Key words: alkynes, azides, copper, iron, supported catalysis

Since its independent discovery by Sharpless and Meldal,[1] the copper-catalyzed azide–alkyne cycloaddition (CuAAC) has become a powerful tool for the rapid and regioselective formation of 1,2,3-triazoles.[2] The importance of this synthetic transformation[3] has been shown by several applications in organic synthesis,[4] material science,[5] polymer chemistry,[6] bioconjugation,[7] or fluorescence-based quantitative analytical determinations.[8] In general, Cu(I) is used as the catalyst for the transformation, which usually generated in situ by reduction of Cu(II) with reducing agents.[1b,2e] Beside these homogeneous copper sources,[9] there are several examples of CuAAC reactions catalyzed by heterogeneous copper catalysts[10] using charcoal,[10a,i] polymer,[10c] biopolymer,[10b] zeolite,[10f] silica gel[10k] and iron nanoparticles[10m] as the support. Copper nanoparticles either stabilized in solution[10g,11] or deposited on the surface of charcoal[10a,12] were also utilized as catalysts for the synthesis of triazoles. In general, with few exceptions for procedures utilizing Cu(0), relatively high temperatures are required to achieve the cycloaddition compared to the homogeneous or heterogeneous Cu(I)-catalyzed versions.

Based on the definition of ‘click chemistry’ by Sharpless et al.[3] most CuAAC procedures are designated as click reactions. Although, some click syntheses do not include chromatographic purifications to obtain the desired triazole products with acceptable ‘organic purity’, the question of copper impurities has rarely been examined. However, removal of trace impurities is a scavenger-, energy-, and time-consuming follow up procedure.

There are several methods for the removal of copper impurities from triazole products,[13] but the simplest, most convenient and elegant procedure was developed by Veinot et al.[14] Any metal ions with an appropriate reduction potential can be removed from organic products using Fe@Fe$_x$O$_y$. For example, copper contamination of the triazole product that originated from a copper(II) sulfate/ascorbate reaction could be reduced from 2026 ppm to 4.6 ppm with the aid of this iron sequester. Inspired by these excellent findings and our previous work, in which we developed and successfully applied a copper-on-iron (Cu/Fe) catalyst for the thiolation of aromatic halides,[15] we aimed to utilize the Cu/Fe bimetallic catalyst system in azide–alkyne cycloadditions.

Considering the reducing ability of iron, we supposed that our bimetallic catalyst could be highly active due to the presence of nanosized copper particles on the surface of the iron, and additionally, the presence of iron support can serve as a copper scavenger during the reaction to obtain triazoles with lower copper contamination. The synthesis of the Cu/Fe catalyst is very simple, it can be performed without the use of a glove box, and it requires only a nontoxic reducing agent, in contrast to other procedures developed for the preparation of nanosized copper catalysts.[10g,16]

Also, the unique structure and properties of the Cu/Fe bimetallic catalyst offer the possibility of easy separation from the reaction mixture by using an external magnetic field.

Phenylacetylene (**2a**) and benzyl azide (**1a**) were selected as the as reactants for the model reaction, first we examined the effect of temperature on the reaction in toluene in the presence of 5 mol% copper using 5 wt% Cu/Fe catalyst. We found that the catalysts worked excellently in the cycloaddition to give **3aa** at 50 °C (Table 1, entry 1). Moreover, we obtained complete reaction in 16 hours even at 30 °C (entry 2), which is relatively low temperature for the transformation in the presence of the Cu/Fe catalyst. However, the conversion of the reaction performed in toluene after five hours was only 31% (entry 3).

Next we carried out the reaction in various solvents, and we found that the cycloaddition took place to give **3aa** slowly in polar solvents such as *N*,*N*-dimethylformamide or ethanol. In these solvents only 5% and 8% conversion was measured respectively (entries 4 and 5); 80% conversion was observed when the reaction was conducted at 30 °C ‘on water’ and in acetonitrile after eight and five hours, respectively (entries 6 and 7).

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Further study of the reaction in dichloromethane at 30 °C revealed that the cycloaddition of benzyl azide (**1a**) and phenylacetylene (**2a**) was complete in five hours in the presence of 5 mol% Cu (5 wt% Cu/Fe) (entry 8). Decreasing the Cu catalyst loading to 1 mol% (5 wt % Cu/Fe), the reaction was also complete in five hours (entry 9). For complete conversion with 0.1 mol% Cu catalyst (5 wt% Cu/Fe) loading eight hours reaction time was necessary (entry 10); a similar result was observed when 5 mol% Cu (1 wt% Cu/Fe) was added (entry 11). Iron itself is not able to catalyze the cycloaddition as the result of our experiment showed (entry 12). Application of copper turnings and powder gave lower conversions (9%, 10%) after four hours, and with these catalysts the reaction did not reached complete conversion even after 24 hours reaction time (entries 13 and 14). However, freshly prepared microsized copper powder[17] showed comparable activity (entry 15) to the Cu/Fe systems, indicating the importance of the copper particle size in this transformation.

After proving the applicability of Cu/Fe as catalyst in the CuAAC reaction, we turned our attention to the copper

Biographical Sketches

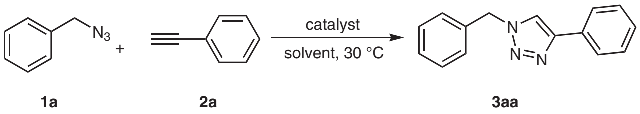
Szabolcs Kovács was born in 1985 in Hungary. He received his Master's degree in organic chemistry at the Budapest University of Technology and Economics in 2009. He started his Ph.D. research in 2009 at the Eötvös Loránd University under the guidance of Prof. Zoltán Novák. His scientific interest is mainly focused on metal-catalyzed reactions and aryne chemistry.

Katalin Zih-Perenyi studied chemistry at the Eötvös Loránd University of Sciences (Budapest, Hungary). She received her Ph.D. degree in analytical chemistry at the same university in 2001. Since 2004 she has been an Assistant Lecturer at the Chemical Institute of Eötvös Loránd University of Sciences (Budapest, Hungary).

Ádám Révész undertook his Master's degree in Physics (1996) at the Eötvös Loránd University in Budapest. He obtained his Ph.D. degree in materials physics under the supervision of Prof. J. Lendvai (2000) at the same institution. After postdoctoral studies at the Universitat Autonoma de Barcelona (2001–2002) and at the University of Maryland (2005–2006), he returned to his alma mater as an Assistant Professor. After gaining his habilitation in 2011, Ádám became an Associate Professor.

Zoltan Novak was born in 1974 in Budapest, Hungary. After completing his M.Sc. studies at the Eötvös Loránd University, Budapest with Prof. András Kotschy in 1999, he performed doctoral studies in the same research group and received his Ph.D. in 2004. In 2004–2005 he joined the group of Prof. Brian M. Stoltz at California Institute of Technology as a postdoctoral researcher. After returning to Hungary he continued his research at Eötvös Loránd University again in the group of Prof. Kotschy. From September 2007 he started his independent research career at the Department of Organic Chemistry, Institute of Chemistry at Eötvös Loránd University as an Assistant Professor.

Table 1 Solvent and Catalyst Effect on the Formation of **3aa**[a]



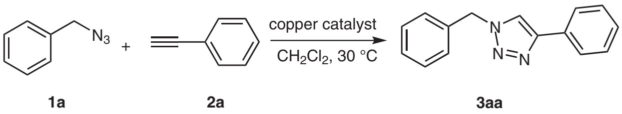
Entry	Catalyst	Cu (mol%)	Solvent	Time (h)	Conv.[b] (%)
1	Cu/Fe (5 wt%)	5	toluene	16	100[c]
2	Cu/Fe (5 wt%)	5	toluene	16	100
3	Cu/Fe (5 wt%)	5	toluene	5	31
4	Cu/Fe (5 wt%)	5	DMF	5	5
5	Cu/Fe (5 wt%)	5	EtOH	5	8
6	Cu/Fe (5 wt%)	5	H_2O	8	80
7	Cu/Fe (5 wt%)	5	MeCN	5	82
8	Cu/Fe (5 wt%)	5	CH_2Cl_2	5	100
9	Cu/Fe (5 wt%)	1	CH_2Cl_2	5	100
10	Cu/Fe (5 wt%)	0.1	CH_2Cl_2	8	100
11	Cu/Fe (1 wt%)	5	CH_2Cl_2	4	97
12	Fe powder	0	CH_2Cl_2	4	0
13	Cu turnings	5	CH_2Cl_2	4	10
14	Cu powder (~500 μm)	5	CH_2Cl_2	4	9
15	Cu powder (<100 μm)	5	CH_2Cl_2	4	82

[a] Reaction conditions: phenylacetylene (**2a**, 1.5 mmol, 1 equiv), BnN_3 (**1a**, 1.5 mmol, 1 equiv), catalyst, solvent (900 μL), stirring, 30 °C.
[b] Composition of the product determined by GC.
[c] At 50 °C.

impurities in the triazole product **3aa**. Regarding the copper impurities in the triazole, to the best of our knowledge, only one example of reported data[14] on the expected value of the copper content of triazoles produced in a homogeneous copper-catalyzed click reaction of azides and terminal acetylenes is available. Due to the good coordinating ability of the nitrogen heterocycles formed in this straightforward reaction, significant copper contamination of the triazoles produced in every homogeneously catalyzed transformation would be expected. We measured and compared the copper impurities of triazoles synthesized under the most frequently used reaction conditions and catalysts for the azide–alkyne cycloaddition, such as water–methanol mixture with 5 mol% copper(II) sulfate/ascorbate system, 5 mol% copper(I) iodide, 0.5–5 mol% homogeneous $Cu(PPh_3)_2NO_3$, and 5 mol% of our Cu/Fe catalyst in dichloromethane at 30 °C.

To demonstrate the copper contamination effect of traditional homogeneous copper-catalyzed reactions, we determined the copper content of triazoles with AAS after recrystallization and column chromatography, as the most frequently used purification methods of organic compound in the laboratory (Table 2). The results of the analytical measurements showed that the copper content of products varied from 175 ppm up to the high 2770 ppm level depending on the type of catalyst and its loading, while the product obtained from the reaction catalyzed by Cu/Fe was contaminated only with 51 ppm copper. Attempted removal of copper impurities with disodium tetraethylenediaminetetraacetic acid (Na_2EDTA) extraction from product prepared using the Cu(I)/tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) catalyzed reaction resulted one order of magnitude lower copper content in the triazole product (27 ppm down from 412 ppm, entry 6). After these traditional tools for the purification of organic compounds, we utilized the modified Veinot method for the removal of trace copper impurities. To achieve this we treated the purified triazole product derived from the 5 mol% $Cu(PPh_3)_2NO_3$ catalyzed reaction twice with iron powder in tetrahydrofuran–aqueous potassium hydroxide system. Comparative studies showed that the highly efficient copper–phosphine complexes are a significant contaminant of the cycloadduct product, and the copper content of the triazole could be reduced from 2770 ppm only to 119 ppm. Utilizing our Cu/Fe catalyst in CuAAC reaction lowers the copper content of the product by one order of magnitude (51 μg/g) relative to other methods.

Table 2 Copper Content and Catalytic Activity of Triazole **3aa** Synthesized in Different CuAAC Reactions[a]



Entry	Catalyst for triazole synthesis[a]	Copper content of the triazole[b] (μg/g)
1	5 mol% $Cu(PPh_3)_2NO_3$, CH_2Cl_2, 30 °C	2770 (119)[c]
2	1 mol% $Cu(PPh_3)_2NO_3$, CH_2Cl_2, 30 °C	284 ± 14
3	0.5 mol% $Cu(PPh_3)_2NO_3$, CH_2Cl_2, 30 °C	175 ± 8
4	5 mol% CuI, CH_2Cl_2, 30 °C	419
5	5 mol% $CuSO_4$, sodium ascorbate, MeOH–H_2O, 30 °C	1090
6	5 mol% $CuSO_4$, TBTA, sodium ascorbate, MeOH–H_2O, 30 °C	412 ± 14 (27 ± 3)[d]
7	5 mol% Cu/Fe, CH_2Cl_2, 30 °C	51.3 ± 1.3

[a] Catalysts and conditions for Cu-catalyzed reaction of BnN_3 (**1a**) and phenylacetylene (**2a**).
[b] After column chromatography and recrystallization; Cu content was determined by AAS measurement).
[c] In parentheses: Cu content after treatment (2 ×) with Fe powder using the purification method of Veinot.
[d] In parentheses: Cu content after extraction with Na_2EDTA solution.

On the basis of these results, we can conclude that the iron component of our Cu/Fe catalyst behaves as a scavenger for copper and significantly reduce the copper contamination of the triazole product. Moreover, iron serves as nontoxic support, and taking the mass balance into consideration it is not necessary to add large amount of ligands such as phosphines with high-molecular mass to the reaction mixture. These properties make the Cu/Fe catalyst advantageous compared to homogeneous copper catalysts especially to copper–phosphine complexes.

Next, we examined the possible of recycling the Cu/Fe catalyst using 5 mol% Cu/Fe catalyst to ensure rapid reaction and sufficient iron for redeposition of copper.[18]

The easy separation of organic materials from the bimetallic system can be achieved with the aid of an external magnetic field. After washing the catalyst with dichloromethane, the next reaction cycle can be performed in the same vessel with a new batch of reactants.

We repeated the recycling process 14 times and we did not observe a significant reduction in the rate of the reaction during the entire study. The cycloaddition of benzyl azide (**1a**) and phenylacetylene (**2a**) was completed in six hours even in the 15th run at 30 °C (not shown), and the time-conversion curve profiles (1–10 runs) showed no change of the reaction rate (Figure 1). These exhaustive studies show that the copper source can be used multiple times without a significant change in the reaction rate.[19]

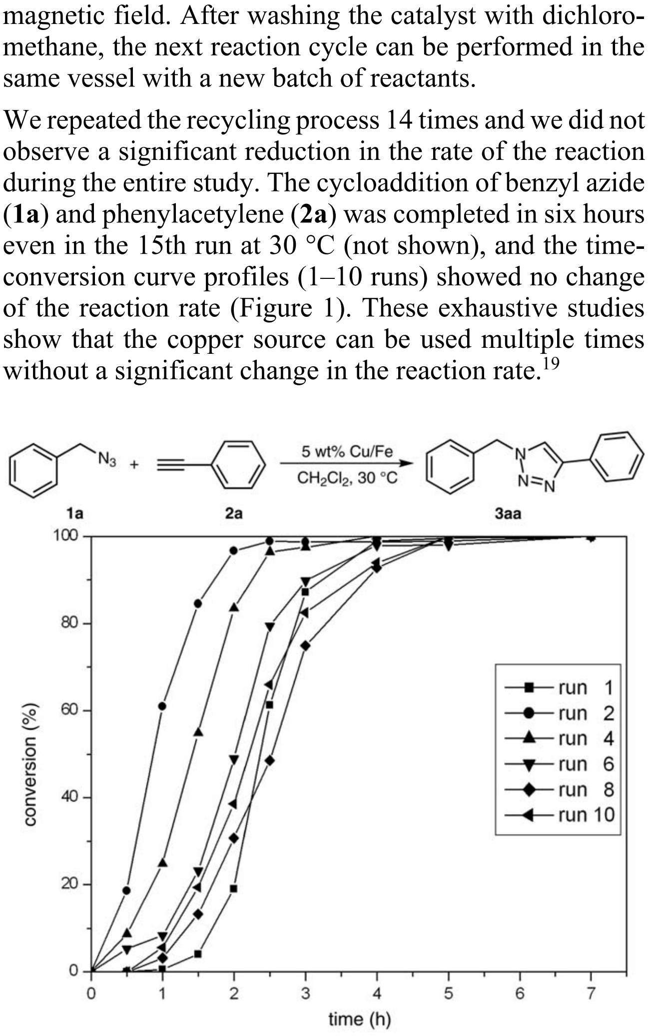


Figure 1 Catalyst recycling. *Reagents and conditions:* phenylacetylene (**2a**, 1.5 mmol, 1 equiv), BnN_3 (**1a**, 1.5 mmol, 1 equiv), Cu/Fe (5 mol%, 5 wt %; 96 mg, 0.075 mmol Cu), CH_2Cl_2 (900 μL), stirring, 30 °C.

The cycloaddition reaction has an induction period when the Cu/Fe catalyst was used in the transformation.[11] We supposed that, in our case this phenomenon could be explained with copper leaching and possible ligand acceleration by the triazole product, rather than the effect of catalyst surface area.[20]

Monitoring the reaction with GC analysis, we observed the formation of triazoles **3** only after 90 minutes when the conversion was 5%. However, in the next 180 minutes the reaction showed completion. These results confirm the presence of released copper and suggest the presence of catalytically active dissolved copper species in solution, which are responsible for the transformation.

In order to gather structural information on our Cu/Fe catalyst we examined the physical properties of the bimetallic material with XRD and SEM. The XRD analysis showed the presence of Cu(0), but after two runs the characteristic peak of elemental copper was not measurable by this method (see Supporting Information). The scanning electron microscope images (Figure 2) showed the presence of different types of microstructures in the catalyst. The major part of the Cu/Fe catalyst consist of iron spheres with the average size of 3–6 μm covered with copper layer (‘A’ type particle). The catalyst contains cloud-like particles (‘C’ type particle), which are significantly richer (ratio Cu/Fe 1:4) in copper than the spheres (ratio Cu/Fe 1:15). After the second use of the catalyst the same particle distribution was observed in the SEM images [Figure 2, (2)]. However, minor changes in the copper/iron ratio of each type of particles was observed. The copper content of the ‘A’ type spheres decreased but the B-type particle become richer in copper (ratio Cu/Fe 1:1). These findings correlate well with the results of the studies focusing to the catalytic activity and the homogeneity of the reaction. After eight uses the particle distribution become more homodisperse regarding the type of particles, and only the spheres and its distorted variants can be observed in various sizes on the SEM images.

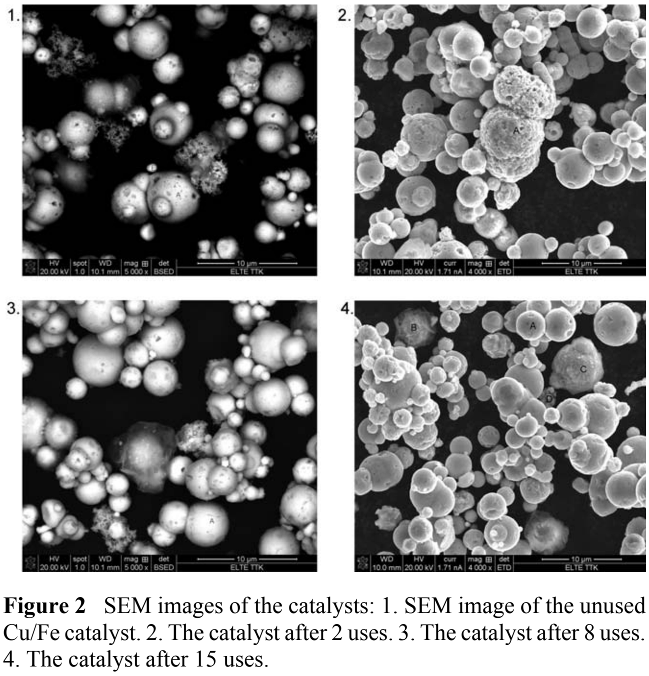
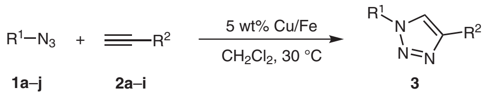


Figure 2 SEM images of the catalysts: 1. SEM image of the unused Cu/Fe catalyst. 2. The catalyst after 2 uses. 3. The catalyst after 8 uses. 4. The catalyst after 15 uses.

Demonstrating the applicability of the Cu/Fe catalyst under the developed conditions, we synthesized several triazoles **3** from diverse azides **1a**–**j** and terminal acetylenes **2a**–**i** in CuAAC reaction (Table 3). 1-Benzyl-4-phenyl-1,2,3-triazole (**3aa**) was synthesized and isolated in 98% yield. Substituted benzyl azides **1b**–**d** reacted smoothly with phenylacetylene (**2a**) and gave the appropriate triazole products **3ba**–**da** in high isolated yields. Reaction of bulky 1-adamantyl azide (**1e**) required a longer reaction time (24 hours), but the *N*-adamantyl triazole **3ea** was obtained in 79% yield. Isopropyl-substituted aryl azide **1f** also gave the appropriate heterocycle **3fa** with phenylacetylene (**2a**). The Cu/Fe catalyst was also applicable for the dipolar cycloaddition of alkyl azides **1g**–**j** with terminal acetylenes under our conditions. Expanding the scope of the reaction several terminal acetylene **2b**–**i** (aryl, hetaryl, alkyl, silyl) were successfully reacted with benzyl azide (**1a**) and in all cases the appropriate triazoles were isolated with good to excellent yields **3ab**–**ai**.

In conclusion, we successfully utilized the previously developed Cu/Fe catalyst in the copper-catalyzed azide–alkyne cycloaddition. The easily accessible nanosized copper pre-catalyst proved to be applicable for the construction of versatile 1,4-substituted triazoles in a simple procedure. The reaction conditions enable the easy preparation of the desired CuAAC product, and the composition of the catalysts ensures the straightforward separation of the bimetallic system after the reaction with the application of outer magnetic field. We demonstrated that the Cu/Fe catalyst serves as an excellent source of highly active homogeneous copper species for the cycloaddition reaction, and the Cu/Fe system is reusable in 15 consecutive reactions without a reduction in the reaction rate. Further advantages of our catalyst is that the copper contamina-

Table 3 Copper Content and Catalytic Activity of Triazoles Synthesized in Different CuAAC Reactions[a]



Entry	Azide	R^1	Acetylene	R^2	Time (h)	Product	Yield[b] (%)
1	**1a**	Bn	**2a**	Ph	8	**3aa**	98
2	**1b**	4-$IC_6H_4CH_2$	**2a**	Ph	8	**3ba**	94
3	**1c**	4-$BrC_6H_4CH_2$	**2a**	Ph	12	**3ca**	89
4	**1d**	4-$O_2NC_6H_4CH_2$	**2a**	Ph	12	**3da**	98
5	**1e**	1-adamantyl	**2a**	Ph	24	**3ea**	80
6	**1f**	4-*i*-PrC_6H_4	**2a**	Ph	8	**3fa**	98
7	**1g**	CH_2SPh	**2a**	Ph	8	**3ga**	98
8	**1h**	$CH_2CH(Me)CH_2Cl$	**2a**	Ph	12	**3ha**	80
9	**1i**	$(CH_2)_4CH=CH$	**2a**	Ph	12	**3ia**	92
10	**1j**	$(CH_2)_4CO_2Et$	**2a**	Ph	12	**3ja**	93
11	**1a**	Bn	**2b**	3-MeC_6H_4	8	**3ab**	98
12	**1j**	$(CH_2)_4CO_2Et$	**2c**	CH_2OAc	12	**3jc**	97
13	**1a**	Bn	**2d**	2-pyridyl	8	**3ad**	85
14	**1a**	Bn	**2e**	$(CH_2)_3CN$	12	**3ae**	95
15	**1a**	Bn	**2c**	CH_2OAc	12	**3ac**	93
16	**1a**	Bn	**2f**	Bu	16	**3af**	92
17	**1a**	Bn	**2g**	TMS	36	**3ag**	61
18	**1a**	Bn	**2h**	CH_2OH	12	**3ah**	95
19	**1a**	Bn	**2i**	CMe_2OH	24	**3ai**	96

[a] Reaction conditions: acetylene **2** (0.5 mmol, 1 equiv), azide **1** (0.5 mmol, 1 equiv), Cu/Fe (5 mol%, 5 w %) (32 mg, 0.025 mmol Cu), CH_2Cl_2 (300 μL), stirring, 30 °C.

[b] Isolated yields.

tion of the product is significantly lower than the triazoles synthesized under homogeneous conditions, showing that iron not only behaves as a support for copper, but acts as a redox scavenger, and reduces the copper contamination of the organic products. Additionally, we indicate the importance and necessary determination of copper impurities in triazole compounds prepared via CuAAC.

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purification. Analytical TLC was performed on Merck DC precoated TLC plates with 0.25-mm Kieselgel 60 F$_{254}$. Visualization was performed with a 254-nm UV lamp. ^{1} H and ^{13}C NMR spectra were recorded on a Bruker Avance-250 spectrometer in CDCl$_3$ with residual solvent protons as internal standards [δ = 7.26 (^{1}H), 77.0 (^{13}C)]. Combination GC and LR-MS was obtained on an Agilent 6890N gas chromatograph (30 m × 0.25 mm column with 0.25-μm HP-5MS coating, He carrier gas) and Agilent 5973 mass spectrometer (ion source: EI+, 70 eV, 230 °C; interface: 300 °C). IR spectra were obtained on a Bruker IFS55 spectrophotometer on a single-reflection diamond ATR unit. All melting points were measured on Büchi 501 apparatus and are uncorrected. HRMS were recorded on an Agilent Technologies 6210 TOFMS. Microstructure of the powders was examined by powder X-ray diffraction (XRD) on a Philips Xpert diffractometer using Cu-Kα radiation in the range of 30–130° with a step width of 0.02° in θ–2θ geometry. The instrumental pattern was measured on a NIST SRM660a LaB$_6$ peak profile standard material. Morphology studies were performed on a FEI Quanta dual-beam scanning electron microscope (SEM) in backscattered electron (BSE) mode. Compositional changes were quantitatively determined by energy dispersive X-ray (EDX) analysis with a relative accuracy of 3%.

Triazoles were recrystallized from EtOH. The copper contents were measured with AAS. The sample (ca. 10 mg) was dissolved in concd HNO$_3$ (0.5 mL) and diluted to 10 mL with MeOH/distilled H$_2$O (1:1). The soln was analyzed by FAAS and GFAAS using a Perkin Elmer AAnalyst 800 atomic absorption spectrometer. External calibration with matrix-matched standards were used. The recoveries were between 90–106%, the reproducibility of the sampling was below 5%.

Preparation of the Cu/Fe Catalyst

A round-bottom flask was charged with Fe powder (5 g, 89.5 mmol) and H$_2$O (deoxygenated with argon) (50 mL). The mixture was stirred vigorously with a mechanical stirrer and a soln of CuSO$_4$ (125.6 mg, 0.79 mmol) in H$_2$O (50 mL) was added dropwise under an argon atmosphere over 1 h, and stirring was continued for 3 h. The catalyst was separated with a magnet and washed with deoxygenated H$_2$O (5 × 20 mL) then acetone (3 × 20 mL) and dried under reduced pressure.

Cu/Fe Catalyzed CuAAC Reaction; General Procedure

A mixture of terminal acetylene (0.5 mmol, 1 equiv), azide (0.5 mmol, 1 equiv), Cu/Fe (5 mol%, 5 w/w%) (32 mg, 0.025 mmol Cu) and CH$_2$Cl$_2$ (200 μL) was heated for 8–24 h at 30 °C. After the appropriate time the mixture was diluted with CH$_2$Cl$_2$ (5 mL). The catalyst was separated with a magnet and washed with CH$_2$Cl$_2$ (4 × 5 mL). The organic phase was separated, dried (MgSO$_4$), and filtered, and the solvent was removed under vacuum. The residue was purified by chromatography (silica gel) to give desired triazole.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3aa)[10f]

Following the general procedure; time: 8 h; white solid; yield: 115 mg (0.49 mmol, 98%); mp 128–130 °C; R_f = 0.48 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.81 (d, J = 6.75 Hz, 2 H), 7.69 (s, 1 H), 7.42–7.27 (m, 8 H), 5.53 (s, 2 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 148.0, 134.6, 130.4, 128.9, 128.6, 128.5, 128.0, 127.8, 125.5, 119.5, 54.0.

MS (EI, 70 eV): m/z (%) = 235 (8, [M$^+$]), 206 (24), 180 (8), 130 (9), 116 (100), 104 (24), 91 (97), 65 (25).

1-(4-Iodobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3ba)[9a]

Following the general procedure; time: 8 h; white crystals; yield: 169 mg (0.47 mmol, 94%); mp 153–156 °C; R_f = 0.40 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.81–7.78 (m, 2 H), 7.72–7.67 (m, 3 H), 7.44–7.29 (m, 3 H), 7.04 (d, J = 8.21 Hz, 2 H), 5.51 (s, 2 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 146.6, 138.2, 134.3, 130.3, 129.7, 128.8, 128.2, 125.6, 119.4, 94.5, 52.4.

MS (EI, 70 eV): m/z (%) = 361 (5, [M$^+$]), 332 (5), 230 (4), 217 (9), 206 (12), 116 (100), 89 (43).

1-(4-Bromobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3ca)[10i]

Following the general procedure; time: 12 h; white crystals; yield: 140 mg (0.44 mmol, 89%); mp 150–152 °C; R_f = 0.35 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.80 (d, J = 7.1 Hz, 2 H), 7.69 (s, 1 H), 7.50 (d, J = 8.3 Hz, 2 H), 7.43–7.32 (m, 3 H), 7.16 (d, J = 8.2 Hz, 2 H), 5.51 (s, 2 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 133.6, 132.2, 129.6, 128.8, 128.2, 125.6, 122.8, 53.4.

MS (EI, 70 eV): m/z (%) = 315 (4, [M$^+$]), 286 (6), 284 (7), 206 (10), 169 (14), 171 (16), 116 (100), 89 (35).

1-(4-Nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole (3da)[21]

Following the general procedure; time: 12 h; white solid; yield: 138 mg (0.49 mmol, 98%); mp 151–153 °C; R_f = 0.59 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.21 (d, J = 8.5 Hz, 2 H), 7.81–7.77 (m, 2 H), 7.45–7.30 (m, 6 H), 5.68 (s, 2 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 141.7, 130.0, 128.9, 128.5, 128.4, 125.7, 124.3, 119.7, 53.1.

MS (EI, 70 eV): m/z (%) = 280 (4, [M$^+$]), 251 (4), 205 (4), 116 (100), 106 (10), 89 (31).

1-(1-Adamantyl)-4-phenyl-1*H*-1,2,3-triazole (3ea)[22]

Following the general procedure; time: 24 h; white solid; yield: 112 mg (0.40 mmol, 80%); mp 193–195 °C; R_f = 0.65 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.79–7.75 (m, 3 H), 7.37–7.20 (m, 3 H), 2.21 (br s, 9 H), 1.72 (br s, 6 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 146.7, 131.0, 128.7, 127.7, 125.5, 116.0, 59.5, 43.0, 35.8, 29.3.

MS (EI, 70 eV): m/z (%) = 279 (4, [M$^+$]), 223 (4), 181 (5), 135 (100), 116 (13), 107 (15), 93 (30), 79 (37), 67 (15).

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

Following the general procedure; time: 8 h; slightly yellow solid; yield: 130 mg (0.49 mmol, 98%); mp 53–55 °C; R_f = 0.75 (hexane–EtOAc, 3:1).

IR (ATR): 3121, 3052, 2973, 2860, 1519, 1455, 1229, 1039 cm^{-1}.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.18 (s, 1 H), 7.91 (d, J = 7.0 Hz, 2 H), 7.70 (d, J = 8.5 Hz, 2 H), 7.48–36 (m, 5 H), 2.99 (q, 1 H), 1.29 (d, J = 7.0 Hz, 6 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 149.7, 148.1, 134.9, 130.3, 128.8, 128.3, 127.6, 125.7, 120.5, 117.6, 33.8, 23.8.

MS (EI, 70 eV): m/z (%) = 263 (2, [M$^+$]), 235 (43), 220 (100), 204 (13), 193 (91), 165 (22), 110 (75), 103 (32), 89 (38), 77 (34).

HRMS: m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_3$: 264.1495; found: 264.1501.

4-Phenyl-1-[(phenylthio)methyl]-1*H*-1,2,3-triazole (3ga)[9a]

Following the general procedure; time: 8 h; white crystals; yield: 131 mg (0.49 mmol, 98%); mp 92–94 °C; R_f = 0.50 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.81–7.78 (m, 3 H), 7.45–7.30 (m, 8 H), 5.65 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 148.1, 132.2, 131.7, 130.2, 129.4, 128.8, 128.6, 128.2, 125.6, 119.0, 53.8.

MS (EI, 70 eV): m/z (%) = 267 (4, $[M^+]$), 238 (13), 130 (100), 123 (18), 116 (17), 103 (61), 77 (43), 51 (18).

1-(3-Chloro-2-methylpropyl)-4-phenyl-1*H*-1,2,3-triazole (3ha)[9a]

Following the general procedure; time: 12 h; white crystals; yield: 94 mg (0.40 mmol, 80%); mp 50–51 °C; R_f = 0.40 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.85–7.80 (m, 3 H), 7.45–7.29 (m, 3 H), 4.49–4.32 (m, 2 H), 3.45 (d, J = 5.1 Hz, 2 H), 2.63–2.51 (m, 1 H), 1.09 (2, J = 6.8 Hz, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 130.3, 128.8, 128.1, 125.6, 120.4, 52.4, 47.3, 36.1, 15.4.

MS (EI, 70 eV): m/z (%) = 235 (9, $[M^+]$), 172 (14), 158 (11), 145 (6), 130 (45), 117 (100), 103 (35), 89 (21), 77 (16), 63 (16), 55 (31).

1-(Hex-5-enyl)-4-phenyl-1*H*-1,2,3-triazole (3ia)[9a]

Following the general procedure; time: 12 h; white crystals; yield: 104 mg (0.46 mmol, 92%); mp 52–53 °C; R_f = 0.48 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.0 Hz, 2 H), 7.74 (s, 1 H), 7.44–7.31 (m, 3 H), 5.83–5.67 (m, 1 H), 5.04–4.95 (m, 2 H), 4.37 (t, J = 7.1 Hz, 2 H), 2.13–2.05 (m, 2 H), 2.00–1.88 (m, 2 H), 1.50–1.38 (m, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 137.6, 130.6, 128.7, 128.0, 125.4, 119.4, 115.2, 50.1, 32.9, 29.6, 25.5.

MS (EI, 70 eV): m/z (%) = 227 (18, $[M^+]$), 198 (26), 156 (32), 117 (100), 102 (35), 89 (42), 55 (69).

Ethyl 5-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pentanoate (3ja)[9a]

Following the general procedure; time: 12 h; white crystals; yield: 127 mg (0.46 mmol, 93%); mp 50–53 °C; R_f = 0.57 (hexane–EtOAc, 1:1).

^{1}H NMR (MHz, $CDCl_3$): δ = 7.78 (t, J = 8.2 Hz, 3 H), 7.41–7.29 (m, 3 H), 4.37 (t, J = 7.0 Hz, 2 H), 4.13–4.05 (m, 2 H), 2.32 (t, J = 7.1 Hz, 2 H), 2.02–1.91 (m, 2 H), 1.71–1.59 (m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.8, 130.5, 128.7, 128.0, 125.6, 119.5, 60.4, 49.9, 33.3, 29.5, 21.7, 14.1.

MS (EI, 70 eV): m/z (%) = 273 (9, $[M^+]$), 228 (4), 200 (43), 144 (30), 129 (57), 116 (60), 101 (73), 83 (50), 55 (100).

1-Benzyl-4-*m*-tolyl-1*H*-1,2,3-triazole (3ab)[9a]

Following the general procedure; time: 8 h; white crystals; yield: 122 mg (0.49 mmol, 98%); mp 147–149 °C; R_f = 0.45 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (s, 2 H), 7.58 (d, J = 7.5 Hz, 1 H), 7.38–7.25 (m, 6 H), 7.13 (d, J = 7.5 Hz, 1 H), 5.55 (s, 2 H), 2.38 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 148.2, 138.4, 134.6, 130.3, 129.0, 128.8, 128.63, 128.60, 127.9, 126.2, 122.7, 119.4, 54.1, 21.3.

MS (EI, 70 eV): m/z (%) = 249 (8, $[M^+]$), 220 (25), 179 (10), 130 (100), 103 (17), 91 (83), 77 (18).

Ethyl 5-[4-(Acetoxymethyl)-1*H*-1,2,3-triazol-1-yl]pentanoate (3jc)[9a]

Following the general procedure; time: 12 h; colorless oil; yield: 130 mg (0.48 mmol, 97%); R_f = 0.61 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 5.12 (s, 2 H), 4.31 (t, J = 7.1 Hz, 2 H), 4.05 (q, J = 7.1 Hz, 2 H), 2.27 (t, J = 7.1 Hz, 2 H), 2.00 (s, 3 H), 1.96–1.84 (m, 2 H), 1.64–1.52 (m, 2 H), 1.17 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.7, 170.7, 60.3, 57.4, 49.8, 33.2, 29.3, 21.5, 20.7, 14.0.

MS (EI, 70 eV): m/z (%) = 269 (2, $[M^+]$), 226 (10), 199 (12), 154 (20), 136 (20), 108 (30), 101 (48), 84 (69), 55 (100).

1-Benzyl-4-(2-pyridyl)-1*H*-1,2,3-triazole (3ad)[23]

Following the general procedure; time: 8 h; light brown crystals; yield: 100 mg (0.42 mmol, 85%); mp 113–115 °C; R_f = 0.32 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.51 (d, J = 4.6 Hz, 1 H), 8.15 (d, J = 7.9 Hz, 1 H), 8.03 (s, 1 H), 7.73 (td, J_1 = 7.8 Hz , J_2 = 1.8 Hz, 1 H), 7.36–7.29 (m, 5 H), 7.20–7.15 (m, 1 H), 5.55 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 150.2, 149.3, 148.6, 136.8, 134.3, 129.1, 128.7, 128.2, 122.7, 121.8, 120.1, 54.3.

MS (EI, 70 eV): m/z (%) = 236 (5, $[M^+]$), 207 (47), 180 (10), 117 (51), 91 (100), 65 (23).

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)butanenitrile (3ae)[9a]

Following the general procedure; time: 12 h; white solid; yield: 108 mg (0.48 mmol, 95%); mp 64–66 °C; R_f = 0.20 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.31–7.29 (m, 3 H), 7.22–7.18 (m, 3 H), 5.43 (s, 2 H), 2.77 (t, J = 7.0 Hz, 2 H), 2.34 (t, J = 7.25 Hz, 2 H), 1.98 (p, J = 7.0 Hz, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 145.9, 134.5, 129.0, 128.6, 127.9, 121.1, 119.3, 54.0, 24.7, 24.1, 16.4.

MS (EI, 70 eV): m/z (%) = 226 (3, $[M^+]$), 197 (4), 144 (4), 130 (4), 104 (4), 91 (100), 65 (12).

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl Acetate (3ac)[9a]

Following the general procedure; time: 12 h; slightly yellow crystals; yield: 108 mg (0.47 mmol, 93%); mp 55–56 °C; R_f = 0.50 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51 (s, 1 H), 7.32–7.21 (m, 5 H), 5.46 (s, 2 H), 5.11 (s, 2 H), 1.98 (s, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.6, 142.9, 134.2, 128.9, 128.6, 127.9, 123.5, 57.3, 53.9, 20.6.

MS (EI, 70 eV): m/z (%) = 231 (1, $[M^+]$), 188 (6), 161 (5), 91 (100), 65 (14).

1-Benzyl-4-butyl-1*H*-1,2,3-triazole (3af)[24]

Following the general procedure; time: 16 h; white crystals; yield: 99 mg (0.46 mmol, 92%); mp 57–59 °C; R_f = 0.35 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 3 H), 7.24–7.18 (m, 3 H), 5.46 (s, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.65–1.54 (m, 2 H), 1.40–1.25 (m, 2 H), 0.88 (t, J = 7.25 Hz, 3 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 134.9, 128.9, 128.4, 127.8, 53.8, 31.4, 25.3, 22.2, 13.7.

MS (EI, 70 eV): m/z (%) = 215 (1, $[M^+]$), 173 (5), 144 (3), 104 (5), 91 (100), 65 (10).

1-Benzyl-4-(trimethylsilyl)-1*H*-1,2,3-triazole (3ag)[25]

Following the general procedure; time: 36 h; white solid; yield: 71 mg (0.31 mmol, 61%); mp 53–55 °C; R_f = 0.43 (hexane–EtOAc, 3:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.43 (s, 1 H), 7.37–7.24 (m, 5 H), 5.54 (s, 2 H), 0.29 (s, 9 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = = 148.2, 136.1, 130.20, 130.15, 129.7, 129.2, 129.1, 54.5, 0.0.

MS (EI, 70 eV): *m/z* (%) = 216 (2, [M$^+$]), 173 (48), 144 (8), 104 (4), 91 (100), 65 (10), 58 (13).

1-Benzyl-1*H*-1,2,3-triazole-4-methanol (3ah)[25]
Following the general procedure; time: 12 h; white solid; yield: 89 mg (0.48 mmol, 95%); mp 52–53 °C; R_f = 0.09 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.38 (s, 1 H), 7.28–7.14 (m, 5 H), 5.38 (s, 2 H), 4.63 (s, 2 H), 4.10 (br s, 1 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 148.2, 134.4, 129.0, 128.6, 128.0, 121.8, 55.9, 54.0.

MS (EI, 70 eV): *m/z* (%) = 187 (2, [M$^+$]), 158 (30), 130 (23), 104 (8), 91 (100), 77 (8), 65 (21).

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (3ai)[21]
Following the general procedure; time: 24 h; white solid; yield: 104 mg (0.48 mmol, 96%); mp 78–80 °C; R_f = 0.18 (hexane–EtOAc, 1:1).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 7.36–7.23 (m, 6 H), 5.46 (s, 1 H), 3.13 (br s, 1 H), 1.58 (s, 6 H).

^{13}C NMR (62.5 MHz, CDCl$_3$): δ = 156.0, 134.5, 129.0, 128.6, 128.0, 119.0, 68.4, 54.0, 30.3.

MS (EI, 70 eV): *m/z* (%) = 217 (1, [M$^+$]), 202 (18), 170 (4), 104 (4), 91 (100), 65 (13).

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(18) Examination of heterogeneity showed some copper leaching from the surface of iron during the reaction, see the Supporting Information.

(19) During the recycling process some part of the copper was leached from the iron support (for AAS results, see ESI), but it does not contaminate the triazole product. When 1 w/w% Cu/Fe was recycled and reused, significant loss of activity was found in the second run. When we started from 5 wt% Cu/Fe catalyst we reached 0.8 wt% copper content after 8 runs, and interestingly the catalyst could be reused additional 7 times without loss of activity. We suppose that significant structural changes of the catalyst occur during the recycling, and more stable catalyst was formed.

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