

Azide–Alkyne Cycloaddition Catalyzed by Copper(I) Coordination Polymers in PPM Levels Using Deep Eutectic Solvents as Reusable Reaction Media: A Waste-Minimized Sustainable Approach

Subrat Sethi, Narayan Ch. Jana, Sourav Behera, Rakesh R. Behera, and Bidraha Bagh*

Cite This: *ACS Omega* 2023, 8, 868–878

Read Online

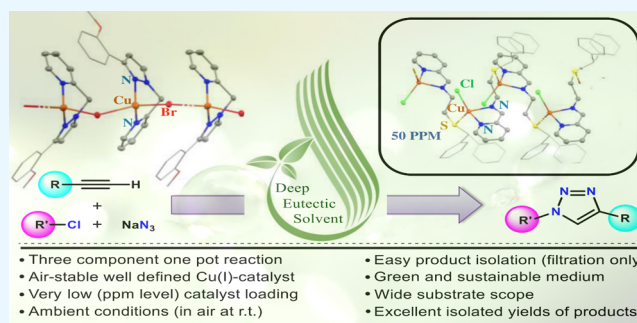
ACCESS |

Metrics & More

Article Recommendations

Supporting Information

ABSTRACT: Two air-stable copper(I)–halide coordination polymers **1** and **2** with NNS and NNO ligand frameworks were synthesized and successfully utilized as efficient catalysts in an important organic reaction, namely, copper-catalyzed azide–alkyne cycloaddition, which is generally conducted in a mixture of water and organic solvents. The azide–alkyne “click” reaction was successfully conducted in pure water at r.t. under aerobic conditions. Other green solvents, including ethanol and glycerol, were also effectively used. Finally, deep eutectic solvents as green and sustainable reaction media were successfully utilized. In deep eutectic solvents, complete conversion with excellent isolated yield was achieved in a short period of time (1 h) with low catalyst loading (1 mol %) at r.t. Full conversion could also be achieved within 24 h with ppm-level (50 ppm) catalyst loading at 70 °C. Optimized reaction conditions were used for the syntheses of a large number of 1,4-disubstituted 1,2,3-triazoles with various functionalities. Triazole products were easily isolated by simple filtration. The reaction media, such as water and deep eutectic solvents, were recovered and recycled in three consecutive runs. The limited waste production is reflected in a very low *E*-factor (0.3–2.8). Finally, the CHEM21 green metrics toolkit was employed to evaluate the sustainability credentials of different optimized protocols in various green solvents such as water, ethanol, glycerol, and deep eutectic solvents.



INTRODUCTION

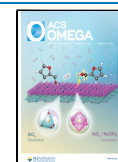
Sustainable chemical transformations for the syntheses of useful chemicals are highly essential in the present era, and the scientific community is keen to evaluate the environmental and green aspects of a chemical process led by “The 12 Principles of Green Chemistry”.^{1–5} These 12 principles involve catalysis as one of the strategic factors.^{6–8} At least one (often more) catalytic reaction step is involved in most of the significant chemical reactions for the production of valuable chemicals, and catalysts play crucial roles in most of the industrial processes impacting the economy significantly. However, a majority of these chemical processes are dominated by scarce, expensive, and mostly toxic noble metal catalysts. As the use of noble metal catalysts is not sustainable, earth-abundant and cheap (and often less toxic) base metals such as manganese, iron, cobalt, nickel, and copper can serve as indispensable alternatives. Employing copper complexes as catalysts instead of noble metals for the production of agrochemical and pharmaceutical commodities has indeed led to the discovery of new synthetic methodologies within the toolbox of organic synthetic chemistry.⁹ Copper has high potential in homogeneous catalysis because of the following reasons: (i) copper is earth-abundant and cheap; (ii) it has various stable oxidation states (0 to +3) with dynamic geometries (linear, trigonal

planar, square planar, tetrahedral, square pyramidal, trigonal bipyramidal, and octahedral); (iii) it accommodates both hard and soft ligands and forms both σ - and π -complexes; and (iv) it is a less toxic and sustainable base metal. Copper is usually considered as a “metal of choice” in organometallic chemistry and homogeneous catalysis due to its vast applications in a wide variety of organic transformations.^{10–23} One important example is the copper(I)-catalyzed 1,3-dipolar cycloaddition of organic azides and alkynes, commonly called CuAAC, which is one of the most versatile and reliable strategies for the synthesis of 1,4-disubstituted 1,2,3-triazole. This triazole (containing different functional groups) is a significant class of nitrogen-containing heterocycles that has found widespread applications in pharmaceutical,^{24,25} biological,^{26,27} and material sciences (dyes, corrosion inhibitors, photostabilizers, etc.).^{25,28–31} Moreover, they are used as ligands^{32,33} or precursors of an important class of NHCs^{34–38} for the

Received: September 27, 2022

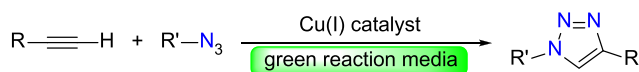
Accepted: November 25, 2022

Published: December 21, 2022



Scheme 1. CuAAC Reaction in Green Reaction Media and Sustainable Features of the Present Study

Previous work:



Vaccaro et al. (*Green Chem.*, 2016, **18**, 6380)

Catalyst: CuSO₄·5H₂O (2 mol%), Na-ascorbate (10 mol%), Imidazole ligand (20 mol%)

Reaction media: Furfuryl alcohol/water azeotrope

Temperature & time: 30 °C, 3 to 24 h

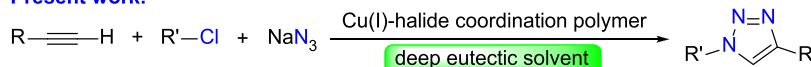
Vaccaro et al. (*Green Chem.*, 2018, **20**, 183)

Catalyst: CuSO₄·5H₂O (2 mol%), Na-ascorbate (10 mol%)

Reaction media: Polar clean/water (4:1)

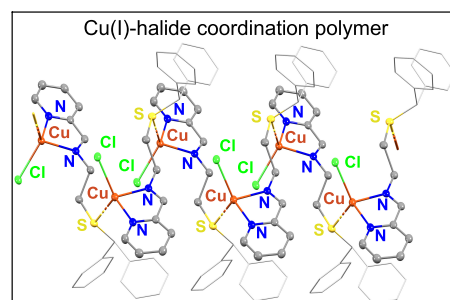
Temperature & time: 50 °C, 24 h

Present work:



Reaction condition A: Cu(I)-catalyst (1 mol%), deep eutectic solvent, r.t., 1 h

Reaction condition B: Cu(I)-catalyst (50 ppm), deep eutectic solvent, 70 °C, 24 h



- Three component one pot reaction
- Air-stable well defined Cu(I)-catalyst
- Very low (ppm level) catalyst loading
- Ambient conditions (in air at r.t.)
- Green and sustainable medium
- Easy product isolation (filtration only)
- Reaction media recycled 5 times
- Wide substrate scope
- Excellent isolated yields of products

synthesis of metal complexes. In CuAAC reactions, either Cu(I) species is generated in situ by reducing a Cu(II) salt (commonly by sodium ascorbate)^{39,40} or Cu(I) complexes with various ligand frameworks are directly utilized.^{19,41–55} These reactions are generally performed in a mixture of water and organic solvent, such as alcohols (*t*-BuOH, EtOH, and MeOH), dichloromethane, acetonitrile, and THF.^{41–55} The purification of triazole products often includes chromatographic separation, which also produces a lot of solvent waste.

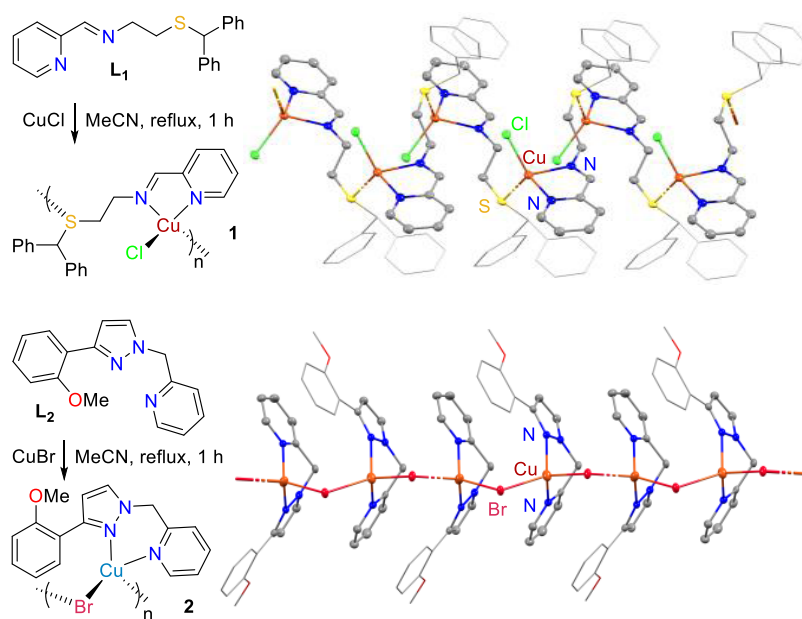
A key factor for the advancement of the green and sustainable process is the use of benign solvents.^{56–82} Solvents are commonly the major sources of waste generation in a vast majority of organic syntheses, and thus, currently, chemical industries are often concerned with selecting solvents. The use of bio-based solvents for metal-catalyzed organic transformation has attracted significant attention recently.^{63–69} The utilization of green and reusable solvents as reaction media for the CuAAC reaction is very important, and some important advancements in this regard have been reported by Vaccaro et al. (Scheme 1). They utilized an azeotropic mixture of water and biomass-derived furfuryl alcohol as an effective solvent.⁷⁰ In the recent past, Vaccaro et al. utilized a mixture of water and Polarclean as a safe, reusable, and sustainable reaction medium.⁷¹ To use green and sustainable reaction media, we searched for other potential alternatives for sustainable development in synthetic chemistry. We focused our attention on deep eutectic solvents (DESs), an emerging class of green media that can balance the major disadvantages of ionic liquids, such as high cost, complex synthesis and

purification, high toxicity, and nonbiodegradability.^{72–76} Although the use of DESs in organic synthesis is limited as compared with common organic solvents, current research interest has grown significantly.⁷⁷ DESs have found many applications in various fields of material chemistry such as solvents for electrochemically conducting polymers,⁷⁸ recognition of analytes (e.g., Li⁺, Na⁺) in analytical devices,⁷⁹ lubrication of metal contacts,⁸⁰ production of carbon electrodes for capacitors,⁸¹ electrolytes for dye-sensitized solar cells,^{81,82} and synthesis of drug solubilization vehicles.^{83,84} With our specific goal of exploring the potential applicability of DES as a sustainable reaction medium in important chemical transformations, we decided to investigate the CuAAC reaction using DESs as solvents.

Herein, we report readily accessible and air-stable copper(I)-halide coordination polymers with NNO and NNS ligand moieties as very efficient and sustainable catalysts for the CuAAC reaction in green solvents such as water, glycerol, and DESs (Scheme 1). The green and sustainable features of the optimized catalytic protocols are also evaluated utilizing the CHEM21 green metrics toolkit.⁵⁶

RESULTS AND DISCUSSION

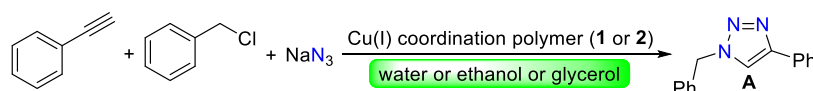
Generally, Cu(I)-halides (often CuI) are used for CuAAC reactions. However, the instability and insolubility of simple copper(I) salts in most of the reaction media (particularly organic) are the main setbacks. Alternatively, the active species are often generated in situ from a copper(II) salt in the presence of a reducing agent such as sodium ascorbate.

Scheme 2. Synthesis of Copper(I) Complexes 1 and 2 (the Molecular Structures Showing 30% Ellipsoids and Hydrogen Atoms are Omitted for Clarity)

However, such in situ-generated Cu(I) species are often unstable and have a tendency to disproportionate into Cu(0) and Cu(II) or may get oxidized to Cu(II) species under aerobic conditions. Hence, often a large amount of copper salt is required for the desired yield. However, the removal of copper from the product is a problem, particularly when triazoles find applications in electronics and pharmaceuticals.^{85–87} To avoid this situation, stable and highly active (very low catalyst loading) Cu(I) complexes with appropriate ligands are essential. Therefore, the synthetic catalysis community of the present day is expected to pay attention to designing new copper catalysts decorated with ancillary ligands for the CuAAC reaction in sustainable organic synthesis. Yamada and Uozumi et al. reported polymeric copper(II) catalysts with a poly-(imidazole-acrylamide) ligand framework as very active catalysts (0.25 mol %) for the CuAAC reaction in the presence of sodium ascorbate (10 mol %) in a *t*-BuOH/water mixture.⁸⁸ Zimmerman et al. used a copper-crosslinked single-chain metal–organic framework as a highly efficient Cu(II) catalyst (ppm level) for the same purpose in water in the presence of a reducing agent. Such bulky ligand frameworks not only protected the in situ-generated Cu(I) center from further oxidation but also significantly improved the catalytic activity (ppm level).⁸⁹ However, the above catalysts are heterogeneous in nature and the use of a reducing agent to reduce Cu(II) to active Cu(I) species is necessary. Furthermore, use of polymeric copper entities is limited due to its slow rate of dissociation to form active monomeric or dimeric Cu(I) species. In this regard, stable Cu(I) polymers equipped with ancillary ligands having pendant labile ligand arms are more beneficial. The labile arm can easily decoordinate the metal center, which helps substrate binding (alkyne coordination). Hence, careful attention to the development of a suitable ancillary ligand system is necessary to create a favorable coordination linkage around the metal center. In this regard, we have developed an NNS ligand (L_1) with a bulky, labile, and soft thioether arm (Scheme 2). We previously demonstrated the hemilabile nature of this type of NNS

ligands.⁹⁰ For a useful comparison, we also used an NNO ligand (L_2) with a harder ether arm (Scheme 2). The facile coordination of L_1 with CuCl resulted in the formation of complex 1 (Scheme 2). Similarly, the reaction of L_2 with CuBr yielded complex 2 (Scheme 2). Both 1 and 2 were characterized by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, and elemental analysis. NNS and NNO ligand frameworks were clearly visible in the ^1H NMR spectra of complexes 1 and 2, respectively. In the ^1H NMR spectra, the aromatic protons were observed as multiplets in the range of 8.74–7.18 ppm and 8.28–6.68 for complexes 1 and 2, respectively. Resonance for the benzylic proton in complex 1 was observed as a singlet at 5.27 ppm. The methylene moieties in complex 1 were observed as two triplets at 3.86 and 2.50 ppm, whereas a singlet was observed at 5.47 ppm for the methylene protons in complex 2. In the ^1H NMR spectrum of complex 2, the methoxy protons appeared as singlets at 3.70 ppm. In the IR spectrum of free ligand L_1 , a sharp band was observed at 1646 cm^{-1} , which is the characteristic peak for the azomethine stretching vibration. The azomethine stretching band is slightly shifted to 1651 cm^{-1} in complex 1. In the IR spectrum of free ligand L_2 , the pyrazole mixed stretching vibration of C=N and C=C bonds was observed at 1504 cm^{-1} , which is slightly shifted to 1517 cm^{-1} in complex 2. Medium-intensity bands in the range of $3000\text{--}2800\text{ cm}^{-1}$ were attributed to symmetric and asymmetric stretching vibrations of C(sp³)–H bonds, respectively, in both 1 and 2. The vibrational bands in the range of $1400\text{--}1610\text{ cm}^{-1}$ were assigned to pyridyl (C=N) and phenyl (C=C) stretching vibrations.

The identities of 1 and 2 were further confirmed by single-crystal X-ray diffractometry (XRD) (Scheme 2). XRD revealed that 1 crystallized in the monoclinic system with space group $P2_1/c$, whereas 2 crystallized in the triclinic system with space group $P1$. The asymmetric unit of 1 consists of a copper, a chloride, and an NNS ligand, whereas double units of copper, bromide, and NNO ligands are present in the asymmetric unit of 2. The geometry around the Cu(I) center in 1 and 2 can be

Table 1. Catalytic Performances of 1 and 2 for the Three-Component CuAAC Reaction in Pure Water, Ethanol, and Glycerol as Green Solvents^a

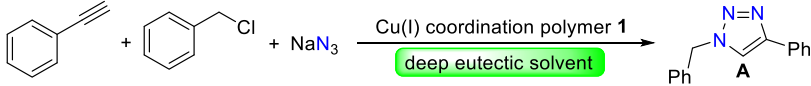
ent.	cat. (mol %)	solvent	temp. (°C)	time (h)	yield (%) ^b
1	1 (5)	water	r.t.	12, 8, 6	>99
2	2 (5)	water	r.t.	12, 8, 6	>99
3	1 (2)	water	r.t.	6	77
4	2 (2)	water	r.t.	6	48
3	1 (2)	water	r.t.	12	>99
4	2 (2)	water	r.t.	12	88
5	1 (2)	water	r.t.	10, 8	>99
6	1 (2)	water	70	6, 5	>99
7	1 (2)	water	70	4	80
8	1 (2)	water	100	5, 4	>99
9	1 (2)	water	100	3	85
10	1 (2)	ethanol	r.t.	8	30
11	1 (2)	ethanol	70	12, 8, 6	>99
12	1 (2)	ethanol	70	5	86
13	1 (2)	glycerol	r.t.	8, 6	>99
14	1 (2)	glycerol	r.t.	5	88

^aReactions conducted in a vial (10 mL) with 0.50 mmol of benzyl chloride, 0.50 mmol of phenyl acetylene, 1.25 mmol of sodium azide, 5:2 mol % of 1:2 in 2 mL of water/ethanol/glycerol at r.t.:70:100 °C. ^bIsolated yields of the triazole product.

described as distorted tetrahedral. Both **1** and **2** are one-dimensional (1D) coordination polymers with the general formula [Cu(L)X]_n (L: L₁/L₂; X: Cl/Br); however, they are very different from each other. In species **1**, the pendent thioether arm of the NNS ligand propagates the structure in the 1D chain. On the other hand, the bromide ion acts as the bridging unit in **2**; the ether arm of the NNO ligand remains uncoordinated and is located roughly opposite to the metal coordination environment. This is probably because the soft Cu(I) center is likely to bind the soft sulfur donor and avoid the harder oxygen donor. The intrachain Cu–Cu distances are 5.988 and 4.101 Å in **1** and **2**, respectively. The Cu–N bond lengths vary from 2.063(5) to 2.259(5) Å in **1** and **2**. The Cu–S (2.2440(13) Å), Cu–Cl (2.2786(13) Å), and Cu–Br (2.4352(11)–2.5276(10) Å) bond lengths are in the expected range consistent with tetrahedral Cu(I) complexes.^{91–93} Mostly, the C–H···π and π···π stacking interactions are responsible for the solid-state stability of **1** and **2**. It is worth mentioning that both coordination polymers **1** and **2** are air- and moisture-stable.

In homogeneous catalysis, significant attention is focused on the manipulation of the ligand environment (electronic and steric factors) for the development of better-performing catalysts. However, the selection of solvents for sustainable catalysis is often ignored. A major aspect of green chemistry is the selection of environmentally benign and sustainable solvents because solvents often produce the major amount of waste mass in a synthetic process.^{57–60} Various organic solvents often used in organic syntheses are considered to be problematic or even hazardous, such as acetonitrile, toluene, xylene, DMSO, THF, dichloromethane, chloroform, and benzene.⁵⁶ However, acetonitrile, dichloromethane, and THF are frequently used as solvents in CuAAC reactions catalyzed by well-defined organometallic Cu(I) complexes.^{44–46,50–55} Herein, we report the utilization of various green solvents for the CuAAC reaction catalyzed by the well-defined Cu(I) coordination polymers **1** and **2**.

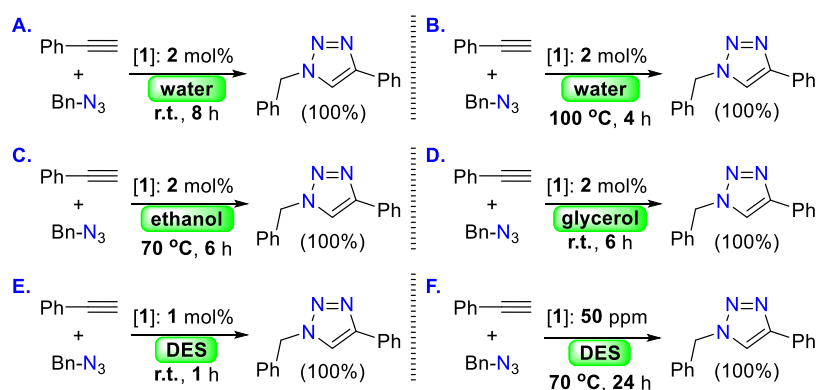
We started testing the catalytic activities of two Cu(I)-halide coordination polymers **1** and **2** using pure water as a green solvent (Table 1) under aerobic conditions at r.t. Using 5 mol % catalyst loading, both **1** and **2** achieved a quantitative yield of triazole product **A** in 6 h (entries 1 and 2). On reducing the catalyst loading to 2 mol %, **1** and **2** provided 77 (entry 3) and 48% (entry 4) yields of products, respectively. The Cu(I)-chloride coordination polymer with an NNS backbone (**1**) displayed better catalytic performance as compared with the Cu(I)-bromide coordination polymer with an NNO backbone (**2**). Species **1** with 2 mol % loading also achieved full conversion to the product in 8 h at r.t. (entry 5), which was considered as the optimized condition at r.t. (depicted in green in Table 1). Thereafter, we explored the performance of **1** at elevated temperatures. Using the same catalyst loading of 2 mol %, a quantitative yield of triazole **A** was obtained in 5 h at 70 °C (entry 6). On further increasing the reaction temperature to 100 °C, complete conversion to products was achieved in 4 h (entry 8). Therefore, the reaction time was reduced to half at 100 °C as compared with the reaction at r.t. Thereafter, we shifted our focus to ethanol. Ethanol is an attractive candidate in the context of sustainable chemistry as it is bio-abundant, cheap, and environmentally benign. We started with the previously optimized conditions for water (entry 5); however, 30% yield of product was noted with 2 mol % loading of **1** in 8 h at r.t. (entry 10). Hence, the reaction temperature was increased to 70 °C (below the boiling point of ethanol) to achieve a better yield of the product. The following conditions were accepted as the optimized conditions in ethanol: 2 mol % of **1**, 70 °C, 6 h (entry 11, depicted in green in Table 1). Thereafter, we utilized glycerol, a waste produced by the biodiesel industry, which is considered as a valuable green solvent. Again, we started with the previously optimized conditions for water (entry 5), and complete conversion to triazole product **A** was achieved in 8 h. The best conditions of the CuAAC reaction in glycerol are

Table 2. Catalytic Performance of **1** for the CuAAC Reaction in Deep Eutectic Solvents as Sustainable Reaction Media^a


ent	cat. 1 (mol %)	solvent mixture (ratio)	temp. (°C)	time (h)	yield (%) ^b
1	2	ChCl/glycerol (1:2)	r.t.	8:4:2	>99
2	1	ChCl/glycerol (1:2)	r.t.	2:1	>99
3	1	ChCl/glycerol (1:2)	r.t.	0.5	66
4	0.1	ChCl/glycerol (1:2)	r.t.	24	>99
5	0.1	ChCl/glycerol (1:2)	r.t.	18	87
6	0.05	ChCl/glycerol (1:2)	r.t.	24	75
7	0.05	ChCl/glycerol (1:2)	70	24	>99
8	0.05	ChCl/glycerol (1:2)	70	18	82

^aReactions conducted in a vial (10 mL) with 0.50 mmol of benzyl chloride, 0.50 mmol of phenyl acetylene, 1.25 mmol of sodium azide, 2–0.05 mol % **1** in 1 mL of ChCl/glycerol (1:2) at r.t. ^bIsolated yields of the triazole product. ChCl stands for choline chloride.

Scheme 3. CuAAC Reaction Using Different Optimized Reaction Conditions (Bn-N₃ was Synthesized In Situ by Reacting Bn-Cl and NaN₃)



the following: 2 mol % of **1**, r.t., 6 h (entry 13, depicted in green in Table 1).

Finally, we turned our attention to DESs as an emerging class of green reaction media. Although DESs are highly underexplored for organic transformations, they may have high potential applicability in the CuAAC reaction. Previously, few groups reported CuAAC reactions in DESs as reaction media,^{66,74,76,94,95} A mixture of choline chloride and glycerol (1:2) is a commonly used DES. It is a type-III DES that does not contain metal ions with probable toxicity.^{72–76} Therefore, we chose choline chloride and glycerol mixture (1:2) as the reaction media for the following CuAAC tests (Table 2). We started with the previously optimized conditions for water (entry 5 in Table 1). Using 2 mol % loading of complex **1**, a quantitative yield of triazole product **A** was obtained in 8 h at r.t. (entry 1 in Table 2). Complete conversion to product **A** was also achieved in 2 h (entry 1). Reducing the catalyst loading to 1 mol %, we observed a quantitative yield of the triazole product in just 1 h (entry 2), and this condition was considered as one of the optimized conditions using DESs as reaction media. Under identical reaction conditions, roughly 70% yield of the product was obtained in half an hour (entry 3). On further reduction of the catalyst loading to 0.1 mol %, full conversion of substrates to the desired triazole product **A** was noted in 24 h at r.t. (entry 4). Encouraged by this result, we further reduced the catalyst loading to the level of 50 ppm. However, complete conversion to the product (isolated yield 75%) could not be achieved in 24 h at r.t. (entry 6). Therefore, the reaction temperature was increased to 70 °C, and a

quantitative yield was achieved in 24 h with ppm-level catalyst loading (entry 7). Hence, the second optimized condition in the choline chloride and glycerol mixture (1:2) is as follows: 0.05 mol % of **1**, 70 °C, 24 h (entry 7, depicted in green in Table 2).

Developing a highly efficient catalyst for an organic transformation is important; however, more importance should be given to the development of a more sustainable catalytic process for that chemical transformation as green and sustainable protocols are essential in the present era. Hence, we feel the necessity to evaluate the drawbacks and benefits of our optimized catalytic protocol for the CuAAC reaction with the green credentials based on “The 12 Principles of Green Chemistry”.^{1,4–6,96–98} To begin with, we did not use a copper(II) salt and reducing agent to generate the Cu(I) active catalyst. The use of a well-defined and air-stable organometallic Cu(I) catalyst for the three-component CuAAC reaction (in situ-generated organic azides) is no doubt advantageous. We selected six previously optimized catalytic protocols for the CuAAC reaction and further examined the green and sustainable aspects of these processes in various green reaction media such as water (methods A and B), ethanol (method C), glycerol (method D), and DES (methods E and F) (Scheme 3).

The above six catalytic protocols (methods A, B, C, D, E, and F) for the CuAAC reaction were evaluated with the CHEM21 green metrics toolkit, which is a quantifiable extension of “The 12 Principles of Green Chemistry” (summarized in Table 3).⁵⁶ The CHEM21 green metrics

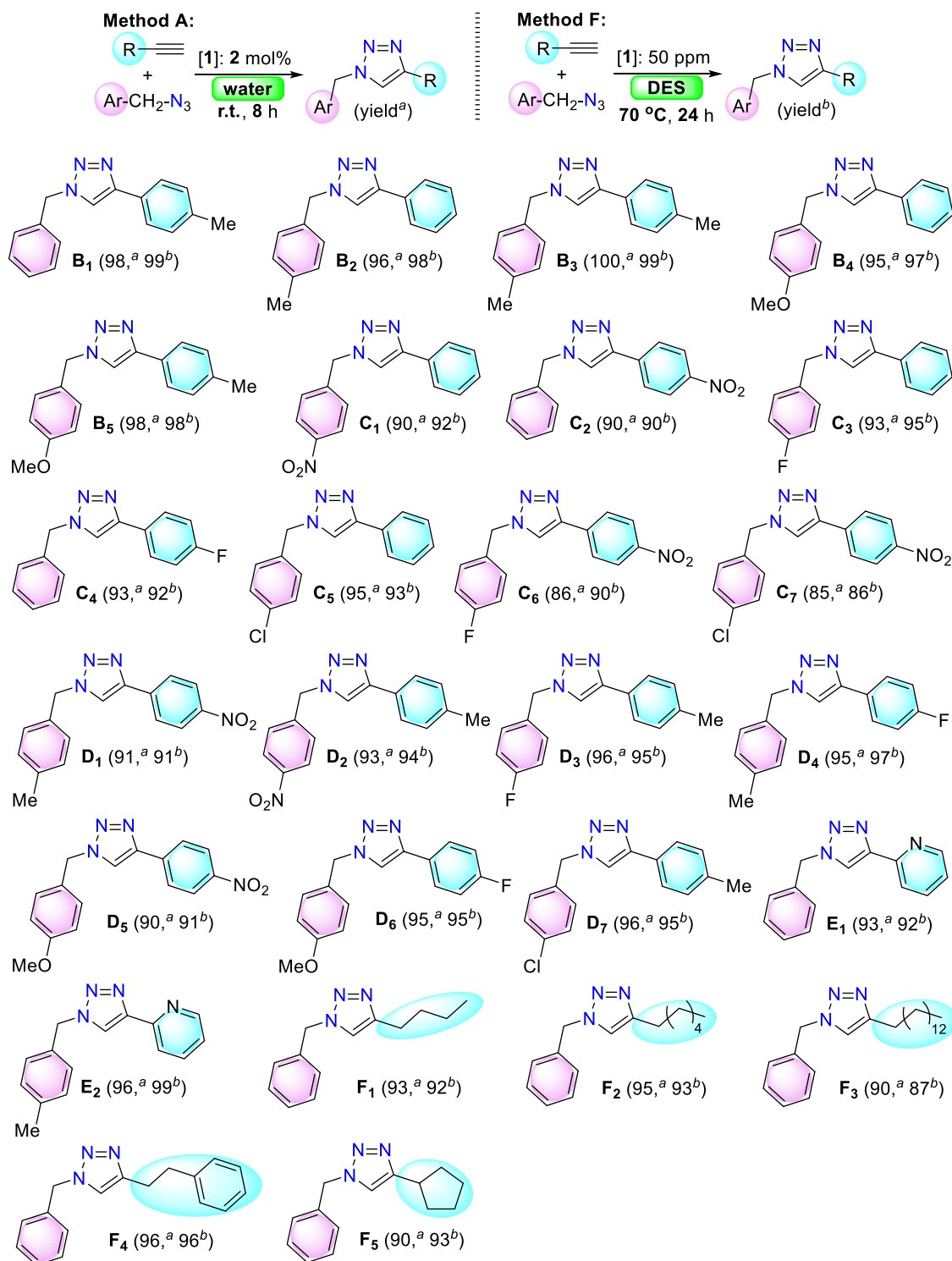
Table 3. Comparison of the Six Different Methods (Methods A–F) of the CuAAC Reaction

Metric	Method A	Method B	Method C	Method D	Method E	Method F
Yield	100	100	100	100	100	100
Conversion	100	100	100	100	100	100
Selectivity	100	100	100	100	100	100
Atom economy	80.1	80.1	80.1	80.1	80.1	80.1
Reaction mass efficiency	60.1	60.1	60.1	60.1	60.1	60.1
Optimum efficiency	75.1	75.1	75.1	75.1	75.1	75.1
Process mass intensity	18.7	18.7	16.1	15.6	15.3	15.2
Solvent	water	water	EtOH	gly	DES	DES
Catalyst	Yes	Yes	Yes	Yes	Yes	Yes
Catalyst recovery	No	No	No	No	No	No
Media recovery	Yes	Yes	No	Yes	Yes	Yes
Element	Cu	Cu	Cu	Cu	Cu	Cu
Reactor	Batch	Batch	Batch	Batch	Batch	Batch
Work up	Filter	Filter	Drying	Filter	Filter	Filter
Energy	r.t.	r.t.	70 °C	r.t.	r.t.	70 °C

toolkit was previously utilized to evaluate various catalytic organic transformations.^{36,91,99–103} Methods A–F were examined utilizing only the zero pass and first pass of the CHEM21 green metrics toolkit as the second pass and third pass are considered as industrial toolkits. Favorable and undesirable processes are flagged by green and red colors, respectively. An amber flag presents an acceptable process with concerns. Methods A–F were analyzed by various metrics, including yield, conversion, and selectivity. All six methods provided quantitative conversions and yields in specified times with excellent selectivity, and thus, all six protocols for the CuAAC reaction received green flags for their yield, conversion, and selectivity. The atom economy, reaction mass efficiency, and optimum efficiency for methods A–F are also good. Similar to most of the homogeneous catalytic processes, solvents constitute most of the mass intensity for all six methods, and hence, the solvent is a crucial metric for the measure of sustainability. Methods A–E all earned green flags as the solvents used for the six processes (water, ethanol, glycerol, and DES) are green solvents. Then, the following metrics were used one by one: catalyst, catalyst recovery, element, reactor, and work-up. All methods are catalytic protocols, and they receive green flags for the use of catalysts. Catalysts could not be recovered. In the CuAAC reaction, the triazole product binds with the copper center, and the catalyst is lost with the product. The reaction media were copper-free, and the copper

catalyst could not be recycled. Thus, using ppm-level catalyst loading (in method F) is very beneficial. All these methods earned red flags for catalyst recovery. However, the recovery of reaction media was performed very easily (just filtration of product) when water was used as the reaction medium (methods A and B). Similarly, reaction media were also recovered (dilution with water and filtration) in method D (glycerol) and methods E and F (DES). The recovered reaction media in methods A, B, D, E, and F were also reused. The reaction medium in method C was ethanol, in which the triazole product was soluble. The product was isolated by evaporating the reaction media, and thus, the reaction medium could not be recovered in method C. The copper catalyst was used in all methods from A to F, and hence, all methods received amber flags for the element. Copper is an earth-abundant and very cheap base metal (in the earth's crust and seawater). However, geopolitical issues often decide the availability of the metal worldwide. A continuous flow process is generally desirable and receives green flags. However, we performed all six CuAAC reactions in batches; therefore, amber flags were again assigned for reactors in methods A–F. Then, the work-up processes were considered. Methods A and B involved only filtration as a quick work-up process. Ethanol was just evaporated under vacuum in method C. Methods D, E, and F involve dilution of the reaction media with water followed by filtration. Therefore, we utilized very common and

Scheme 4. CuAAC Reactions of Various Alkynes with In Situ-Generated Organic Azides Using Methods A and F



easy work-up techniques such as filtration, evaporation, and dilution, and all six methods are assigned green flags. Thereafter, all six methods were analyzed using energy parameters. CuAAC reactions of methods A, D, and E were performed at ambient temperature (r.t.), and hence, they are favorable processes and receive green flags. Methods C and F were carried out at 70 °C. The acceptable temperature range for a favorable process is 0–70 °C. In addition, the reaction temperature of a desirable process should be 5 °C (or more)

below the boiling point of the used reaction medium. As boiling points of glycerol and the used DES were much higher than 70 °C, both methods C and F were assigned green flags (although the reactions were performed at elevated temperatures). Method B was performed at 100 °C, and it received a red flag indicative of an unfavorable process as the boiling point of water is also 100 °C. For methods A, B, C, and D, CuAAC reactions were performed in the presence of the same catalyst loading (2 mol %) either at ambient temperature or

elevated temperature (70 or 100 °C) in water, ethanol, and glycerol. Among these four methods, method A is the most sustainable due to the use of water at r.t. DES as a sustainable solvent was used in methods E and F. Although the CuAAC reaction in method F was performed at elevated temperatures, it is still in the acceptable temperature range. In addition, the ppm-level catalyst loading in method F is also attractive. Therefore, we considered methods A and F as the two most favorable processes. To establish the practical utility and robustness of these two catalytic protocols (methods A and F), gram-scale (10 mmol) reactions were successfully conducted. In addition, reaction media were successfully recovered and reused five times for methods A and F.

For the green and sustainable development, it is crucial to quantitatively evaluate the waste (leftover reactants, by-products, unrecovered catalysts and catalyst supports, solvent losses, etc.) generated in the process, and thus, the *E*-factor is an important parameter for sustainability.^{70,71,104,105} We calculated the *E*-factor of large-scale reactions for methods A (water as the solvent) and F (DES as the solvent) for a single run and also for three consecutive runs (see the [Supporting Information](#) for details). The *E*-factor for method A is in the range of 0.3–0.7. Method F involved a slightly higher *E*-factor (2.4–2.8) as water was used for washing and it was not recovered. The overall range of the *E*-factor for methods A and F is very low (0.3–2.8), lower than the previous reports by Vaccaro et al.^{70,71} However, Vaccaro et al. recovered the used catalyst, and we failed to do so. We could recover the reaction media only.

Encouraged by the high catalytic activity of complex **1**, we focused our attention on exploring various aromatic and aliphatic alkynes and organic azides (in situ generated by reacting sodium azide and the corresponding organic chlorides) to expand the substrate scope ([Scheme 4](#)). Organic azides and alkynes with various arene moieties containing electron-donating and electron-withdrawing functionalities were tested utilizing previously optimized protocols in methods A and F ([Scheme 4](#)). Substituted benzyl azides and aromatic alkynes with electron-donating groups such as methyl and methoxy groups were tested, and both methods (methods A and F) produced the corresponding triazoles (**B**₁, **B**₂, **B**₃, **B**₄, and **B**₅) in almost quantitative yields. Strong and weak electron-withdrawing groups such as nitro, fluoro, and chloro groups were also used, and we obtained excellent isolated yields of triazole products (**C**₁, **C**₂, **C**₃, **C**₄, **C**₅, **C**₆, and **C**₇). We also combined substituted benzyl azides and aromatic alkynes with either electron-donating or -withdrawing groups, and CuAAC reactions under both methods smoothly produced the expected triazoles (**D**₁, **D**₂, **D**₃, **D**₄, **D**₅, **D**₆, and **D**₇). We also successfully synthesized pyridyl 1,2,3-triazoles (**E**₁ and **E**₂) using 2-ethynylpyridine. Finally, several aliphatic alkynes such as 1-hexyne, 1-octyne, 1-hexadecyne, but-3-yn-1-ylbenzene, and ethynylcyclopentane were tested, and the corresponding triazole products (**F**₁, **F**₂, **F**₃, **F**₄, and **F**₅) were isolated in excellent yields. However, we did not explore the use of aryl azides due to their highly explosive nature. Therefore, various alkynes and azides smoothly reacted to yield the expected triazole products in excellent yields irrespective of the nature of substituents. Present catalytic protocols are not limited to phenyl acetylene and benzyl azide; various electron-donating and -withdrawing groups were tolerated. Synthesized triazoles may be directly used as monodentate or bidentate (such as triazoles **E**₁ and **E**₂ with a pyridyl arm) ligands or can serve as

precursors to NHCs (triazolylidenes) with electron-donating and -withdrawing substituents.

CONCLUSIONS

The facile coordination of the tridentate NNS (**L**₁) and NNO (**L**₂) ligands with copper(I) halide yielded coordination polymers **1** and **2**, respectively. The pendant ether arm of the NNO ligand in **2** remains uncoordinated, and bromide acts as the bridging unit. In contrast, the thioether arm of the NNS ligand in **1** propagates the 1D chain structure. Both **1** and **2** are air-stable and display efficient catalytic activities for CuAAC reactions. However, **1** displayed better catalytic activity. Using an air-stable and well-defined copper(I) complex is advantageous. The nature of solvents for the sustainable development of chemical syntheses is crucial as solvents commonly produce most of the waste. The CuAAC reactions were performed in various green and sustainable solvents such as water, ethanol, glycerol, and DESs. Several catalytic methods for the CuAAC reaction were optimized (methods A, B, C, D, E, and F). The CHEM21 green metrics toolkit was utilized to analyze the advantages and setbacks of the six optimized catalytic protocols (methods A, B, C, D, E, and F). One of the favored protocols (method A) involved the reaction in water at r.t. in the presence of 2 mol % catalyst loading. However, the DES proved to be a much better reaction medium. Only 1 mol % catalyst loading achieved complete conversion of substrates to the desired triazole product in 1 h at r.t. (method E). In addition, ppm-level catalyst loading (50 ppm) for complete conversion was achieved in the DES at 70 °C (method F). The present robust catalytic system (methods A and F) was successfully utilized for the gram-scale synthesis of triazoles. Finally, methods A and F were successfully used to expand the substrate scope (26 additional substrates with various functionalities). The catalyst could not be recovered, and the reaction media were highly recyclable. The calculated *E*-factor is very low (in the range of 0.3–2.8), and this reflects a process with very low waste generation. The present robust and air-stable catalytic system might be realistic for possible large-scale applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c06231>.

Experimental procedures for the synthesis of ligands **L**₁ and **L**₂ and the Cu(I) coordination polymers (**1** and **2**), characterization of **L**₁, **L**₂, **1**, and **2**; general experiments of CuAAC reactions in green solvents; gram-scale CuAAC reactions using methods A and F; copies of the NMR spectra of **L**₁, **L**₂, **1**, and **2**; and all products of CuAAC reactions ([PDF](#))

Crystal data of copper complexes **1** and **2**, and the summary of the zero pass and first pass for methods A, B, C, D, E, and F ([CIF](#))

X-ray data for **1** and **2** with accession codes CCDC 2196025 and 2196026, respectively ([CIF](#))

AUTHOR INFORMATION

Corresponding Author

Bidraha Bagh – School of Chemical Sciences, National Institute of Science Education and Research (NISER), An OCC of Homi Bhabha National Institute, Odisha 752050,

India; orcid.org/0000-0003-0489-3312;
Email: bidraha@niser.ac.in

Authors

Subrat Sethi – School of Chemical Sciences, National Institute of Science Education and Research (NISER), An OCC of Homi Bhabha National Institute, Odisha 752050, India

Narayan Ch. Jana – School of Chemical Sciences, National Institute of Science Education and Research (NISER), An OCC of Homi Bhabha National Institute, Odisha 752050, India; orcid.org/0000-0002-2849-5784

Sourav Behera – School of Chemical Sciences, National Institute of Science Education and Research (NISER), An OCC of Homi Bhabha National Institute, Odisha 752050, India; orcid.org/0000-0003-0501-6442

Rakesh R. Behera – School of Chemical Sciences, National Institute of Science Education and Research (NISER), An OCC of Homi Bhabha National Institute, Odisha 752050, India

Complete contact information is available at:
<https://pubs.acs.org/10.1021/acsomega.2c06231>

Author Contributions

This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

SERB New Delhi (ECR/2018/000003), DAE, and NISER.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank SERB New Delhi (ECR/2018/000003), DAE, and NISER for financial support. S.S. and N.C.J. acknowledge CSIR and NISER, respectively, for fellowships.

ABBREVIATIONS

IR, infrared; NMR, nuclear magnetic resonance; CuAAC, Cu-catalyzed azide–alkyne cycloaddition reaction; ChCl, choline chloride; DES, deep eutectic solvent; *E*-factor, environmental factor

REFERENCES

- (1) Anastas, P. T.; Warner, J. C. *Principles of Green Chemistry*. In *Green Chemistry: Theory and Practice*; Oxford University Press, 1998; pp 29–56.
- (2) Anastas, P. T.; Heine, L. G.; Williamson, T. C. *Green Chemical Syntheses and Processes*; American Chemical Society: Washington, DC, 2000.
- (3) Anastas, P. T.; Kirchhoff, M. M. Origins, Current Status, and Future Challenges of Green Chemistry. *Acc. Chem. Res.* **2002**, *35*, 686–694.
- (4) Anastas, P.; Eghbali, N. Green chemistry: Principles and practice. *Chem. Soc. Rev.* **2010**, *39*, 301–312.
- (5) Sheldon, R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.
- (6) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546–4551.
- (7) Rodríguez-Padrón, D.; Puente-Santiago, A. R.; Balu, A. M.; Muñoz-Batista, M. J.; Luque, R. Environmental Catalysis: Present and Future. *ChemCatChem* **2019**, *11*, 18–38.
- (8) Polshettiwar, V.; Varma, R. S. Green chemistry by nano-catalysis. *Green Chem.* **2010**, *12*, 743–754.
- (9) Anilkumar, G.; Saranya, S. *Copper Catalysis in Organic Synthesis*; John Wiley & Sons: Weinheim, Germany, 2020.
- (10) Evano, G.; Blanchard, N. *Copper-Mediated Cross-Coupling Reactions*; Wiley & Sons: New Jersey, USA, 2013.
- (11) Alexakis, A.; Krause, N.; Woodward, S. *Copper-Catalyzed Asymmetric Synthesis*; Wiley-VCH, 2014.
- (12) Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C–N, C–O, C–S, and C–C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136–16179.
- (13) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234–6458.
- (14) Chen, S.-J.; Golden, D. L.; Krska, S. W.; Stahl, S. S. Copper-Catalyzed Cross Coupling of Benzylic C–H Bonds and Azoles with Controlled N-Site Selectivity. *J. Am. Chem. Soc.* **2021**, *143*, 14438–14444.
- (15) Müller, D. S.; Marek, I. Copper mediated carbometalation reactions. *Chem. Soc. Rev.* **2016**, *45*, 4552–4566.
- (16) Tang, X.; Wu, W.; Zeng, W.; Jiang, H. Copper-Catalyzed Oxidative Carbon–Carbon and/or Carbon–Heteroatom Bond Formation with O₂ or Internal Oxidants. *Acc. Chem. Res.* **2018**, *51*, 1092–1105.
- (17) Guan, X.; Zhu, H.; Driver, T. Cu-Catalyzed crosscoupling of nitroarenes with aryl boronic acids to construct diarylamines. *ACS Catal.* **2021**, *11*, 12417–12422.
- (18) Meldal, M.; Tornøe, C. W. Cu-Catalyzed Azide–Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952–3015.
- (19) Wang, P.-Z.; Wu, X.; Cheng, Y.; Jiang, M.; Xiao, W.-J.; Chen, J.-R. Photoinduced Copper-Catalyzed Asymmetric Three-Component Coupling of 1,3-Dienes: An Alternative to Kharasch–Sosnovsky Reaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 22956–22962.
- (20) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229–1243.
- (21) Geng, H. Q.; Meyer, T.; Franke, R.; Wu, X. F. Copper-catalyzed hydroformylation and hydroxymethylation of styrenes. *Chem. Sci.* **2021**, *12*, 14937–14943.
- (22) Besalú-Sala, P.; Magallón, C.; Costas, M.; Company, A.; Luis, J. M. Mechanistic Insights into the *ortho*-Defluorination-Hydroxylation of 2-Halophenolates Promoted by a Bis(α -oxo)dicopper(III) Complex. *Inorg. Chem.* **2020**, *59*, 17018–17027.
- (23) Trammell, R.; Rajabimoghadam, K.; Garcia-Bosch, I. Copper Promoted Functionalization of Organic Molecules: from Biologically Relevant Cu/O₂ Model Systems to Organometallic Transformations. *Chem. Rev.* **2019**, *119*, 2954–3031.
- (24) Kolb, H. C.; Sharpless, K. B. The growing impact of click chemistry on drug discovery. *Drug Discovery Today* **2003**, *8*, 1128–1137.
- (25) Moses, J. E.; Moorhouse, A. D. The Growing Applications of Click Chemistry. *Chem. Soc. Rev.* **2007**, *36*, 1249–1262.
- (26) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. *Chem. Rev.* **2013**, *113*, 4905–4979.
- (27) Mamidyala, S. K.; Finn, M. G. In Situ Click Chemistry: Probing the Binding Landscapes of Biological Molecules. *Chem. Soc. Rev.* **2010**, *39*, 1252–1261.
- (28) Golas, P. L.; Matyjaszewski, K. Marrying Click Chemistry with Polymerization: Expanding the Scope of Polymeric Materials. *Chem. Soc. Rev.* **2010**, *39*, 1338–1354.
- (29) Qin, A.; Lamb, J. W. Y.; Tang, B. Z. Click Polymerization. *Chem. Soc. Rev.* **2010**, *39*, 2522–2544.
- (30) Nandivada, H.; Jiang, X.; Lahann, J. Click Chemistry: Versatility and Control in the Hands of Materials Scientists. *Adv. Mater.* **2007**, *19*, 2197–2208.
- (31) Aromí, G.; Barrios, L. A.; Roubeau, O.; Gamez, P. Triazoles and tetrazoles: prime ligands to generate remarkable coordination materials. *Coord. Chem. Rev.* **2011**, *255*, 485–546.
- (32) Crowley, J. D.; Gavey, E. L. Use of di-1,4-substituted-1,2,3-triazole “click” ligands to self-assemble dipalladium(II) coordinatively

- saturated, quadruply stranded helicate cages. *Dalton Trans.* **2010**, 39, 4035–4037.
- (33) Ghosh, R.; Jana, N. C.; Panda, S.; Bagh, B. Transfer Hydrogenation of Aldehydes and Ketones in Air with Methanol and Ethanol by an Air-Stable Ruthenium–Triazole Complex. *ACS Sustainable Chem. Eng.* **2021**, 9, 4903–4914.
- (34) Vivancos, Á.; Segarra, C.; Albrecht, M. Mesoionic and Related Less Heteroatom Stabilized N-Heterocyclic Carbene Complexes: Synthesis, Catalysis, and Other Applications. *Chem. Rev.* **2018**, 118, 9493–9586.
- (35) Maity, R.; Sarkar, B. Chemistry of Compounds Based on 1,2,3-Triazolylidene-Type Mesoionic Carbenes. *JACS Au* **2021**, 2, 22–57.
- (36) Bagh, B.; McKinty, A. M.; Lough, A. J.; Stephan, D. W. 1, 2, 3-Triazolylidene ruthenium (II) (η^6 -arene) complexes: synthesis, metallation and reactivity. *Dalton Trans.* **2014**, 43, 12842–12850.
- (37) Bagh, B.; McKinty, A. M.; Lough, A. J.; Stephan, D. W. 1,2,3-Triazolylidene Ruthenium(II)-Cyclometalated Complexes and Olefin Selective Hydrogenation Catalysis. *Dalton Trans.* **2015**, 44, 2712–2723.
- (38) Bagh, B.; Stephan, D. W. Half Sandwich ruthenium(II) Hydrides: Hydrogenation of Terminal, Internal, Cyclic and Functionalized Olefins. *Dalton Trans.* **2014**, 43, 15638–15645.
- (39) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective Ligation of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, 41, 2596–2599.
- (40) Khatua, M.; Goswami, B.; Kamal; Samanta, S. Azide–Alkyne “Click” Reaction in Water Using Parts-Per-Million Amine-Functionalized Azoaromatic Cu(I) Complex as Catalyst: Effect of the Amine Side Arm. *Inorg. Chem.* **2021**, 60, 17537–17554.
- (41) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, 40, 2004–2021.
- (42) Perez-Balderas, F.; Ortega-Munoz, M.; Morales-Sanfrutos, J.; Hernandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-García, J.; Santoyo-Gonzalez, F. *Org. Lett.* **2003**, 5, 1951–1954.
- (43) Lal, S.; Diez-Gonzalez, S. [CuBr(PPh₃)₃] for azide-alkyne cycloaddition reactions under strict click conditions. *J. Org. Chem.* **2011**, 76, 2367–2373.
- (44) Shao, C.; Wang, X.; Zhang, Q.; Luo, S.; Zhao, J.; Hu, Y. Acid-base jointly promoted copper(I)-catalyzed azide-alkyne cycloaddition. *J. Org. Chem.* **2011**, 76, 6832–6836.
- (45) Worrell, B. T.; Malik, J. A.; Fokin, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science* **2013**, 340, 457–460.
- (46) Venderbosch, B.; Oudsen, J.-P. H.; van der Vlugt, J. I.; Korstanje, T. J.; Tromp, M. Cationic Copper Iminophosphorane Complexes as CuAAC Catalysts: A Mechanistic Study. *Organometallics* **2020**, 39, 3480–3489.
- (47) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *J. Am. Chem. Soc.* **2005**, 127, 210–216.
- (48) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. Mechanism of the ligand-free Cu^I-catalyzed azidealkyne cycloaddition reaction. *Angew. Chem., Int. Ed.* **2005**, 44, 2210–2215.
- (49) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, 67, 3057–3064.
- (50) Alonso, F.; Moglie, Y.; Radivoy, G. Copper nanoparticles in click chemistry. *Acc. Chem. Res.* **2015**, 48, 2516–2528.
- (51) Patterson, M. R.; Dias, H. R. Tetranuclear and trinuclear copper (I) pyrazolates as catalysts in copper mediated azide–alkyne cycloadditions (CuAAC). *Dalton Trans.* **2021**, 51, 375–383.
- (52) Zhang, X. F.; Zhi, S. J.; Wang, W.; Liu, S.; Jasinski, J. P.; Zhang, W. A pot-economical and diastereoselective synthesis involving catalyst-free click reaction for fused-triazolobenzodiazepines. *Green Chem.* **2016**, 18, 2642–2646.
- (53) Chassaing, S.; Bénétou, V.; Pale, P. When CuAAC “Click Chemistry” Goes Heterogeneous. *Catal. Sci. Technol.* **2016**, 6, 923–957.
- (54) Haldón, E.; Nicasio, M. C.; Pérez, P. J. Copper-Catalyzed Azide–Alkyne Cycloadditions (CuAAC): An Update. *Org. Biomol. Chem.* **2015**, 13, 9528–9550.
- (55) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Click Chemistry beyond Metal-Catalyzed Cycloaddition. *Angew. Chem., Int. Ed.* **2009**, 48, 4900–4908.
- (56) McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J. H. Towards a Holistic Approach to Metrics for the 21st Century Pharmaceutical Industry. *Green Chem.* **2015**, 17, 3111–3121.
- (57) DeSimone, J. M. Practical Approaches to Green Solvents. *Science* **2002**, 297, 799–803.
- (58) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. So you think your process is green, how do you know?—Using principles of sustainability to determine what is green—a corporate perspective. *Green Chem.* **2001**, 3, 1–6.
- (59) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. Metrics to ‘green’ chemistry—which are the best? *Green Chem.* **2002**, 4, 521–527.
- (60) Sheldon, R. A. Green solvents for sustainable organic synthesis: state of the art. *Green Chem.* **2005**, 7, 267–278.
- (61) Dyson, P. J.; Jessop, P. G. Solvent Effects in Catalysis: Rational Improvements of Catalysts via Manipulation of Solvent Interactions. *Catal. Sci. Technol.* **2016**, 6, 3302–3316.
- (62) Winterton, N. The Green Solvent: A Critical Perspective. *Clean Technol. Environ. Policy* **2021**, 23, 2499–2522.
- (63) Gandeepan, P.; Kaplaneris, N.; Santoro, S.; Vaccaro, L.; Ackermann, L. Biomass-Derived Solvents for Sustainable Transition Metal-Catalyzed C–H Activation. *ACS Sustainable Chem. Eng.* **2019**, 7, 8023–8040.
- (64) Gu, Y.; Jérôme, F. Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. *Chem. Soc. Rev.* **2013**, 42, 9550–9570.
- (65) Tshibalonza, N. N.; Monbaliu, J.-C. M. The deoxydehydration (DODH) reaction: a versatile technology for accessing olefins from bio-based polyols. *Green Chem.* **2020**, 22, 4801–4848.
- (66) Vidal, C.; García-Álvarez, J. Glycerol: a biorenewable solvent for base-free Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes. Highly efficient transformations and catalyst recycling. *Green Chem.* **2014**, 16, 3515–3521.
- (67) Zhao, J.; Li, P.; Xu, Y.; Shi, Y.; Li, F. Nickel-Catalyzed Transformation of Diazoacetates to Alkyl Radicals Using Alcohol as a Hydrogen Source. *Org. Lett.* **2019**, 21, 9386–9390.
- (68) Xu, J.; Huang, W.; Bai, R.; Queneau, Y.; Jérôme, F.; Gu, Y. Utilization of bio-based glycolaldehyde aqueous solution in organic synthesis: application to the synthesis of 2,3-dihydrofurans. *Green Chem.* **2019**, 21, 2061–2069.
- (69) García, N.; García-García, P.; Fernández-Rodríguez, M. A.; García, D.; Pedrosa, M. R.; Arnáiz, F. J.; Sanz, R. An unprecedented use for glycerol: chemoselective reducing agent for sulfoxides. *Green Chem.* **2013**, 15, 999–1005.
- (70) Rasina, D.; Lombi, A.; Santoro, S.; Ferlin, F.; Vaccaro, L. Searching for novel reusable biomass-derived solvents: furfuryl alcohol/water azeotrope as a medium for waste-minimised coppercatalysed azide–alkyne cycloaddition. *Green Chem.* **2016**, 18, 6380–6386.
- (71) Luciani, L.; Goff, E.; Lanari, D.; Santoro, S.; Vaccaro, L. Waste minimised copper-catalysed azide–alkyne cycloaddition in Polarclean as a reusable and safe reaction medium. *Green Chem.* **2018**, 20, 183–187.
- (72) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. *Chem. Commun.* **2003**, 70–71.
- (73) Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep Eutectic Solvents (DESs) and Their Applications. *Chem. Rev.* **2014**, 114, 11060–11082.
- (74) Nebra, N.; García-Álvarez, J. Recent Progress of Cu-Catalyzed Azide-Alkyne Cycloaddition Reactions (CuAAC) in Sustainable

- Solvents: Glycerol, Deep Eutectic Solvents, and Aqueous Media. *Molecules* **2020**, *25*, 2015–2032.
- (75) Giofrè, S. V.; Tiecco, M.; Ferlazzo, A.; Romeo, R.; Ciancaleoni, G.; Germani, R.; Iannazzo, D. Base-Free Copper-Catalyzed Azide-Alkyne Click Cycloadditions (CuAAC) in Natural Deep Eutectic Solvents as Green and Catalytic Reaction Media. *Eur. J. Org. Chem.* **2021**, *2021*, 4777–4789.
- (76) Kafle, A.; Handy, S. T. A one-pot, copper-catalyzed azidation/click reaction of aryl and heteroaryl bromides in an environmentally friendly deep eutectic solvent. *Tetrahedron* **2017**, *73*, 7024–7029.
- (77) Hansen, B. B.; Spittle, S.; Chen, B.; Poe, D.; Zhang, Y.; Klein, J. M.; Horton, A.; Adhikari, L.; Zelovich, T.; Doherty, B. W.; Gurkan, B.; Maginn, E. J.; Ragauskas, A.; Dadmun, M.; Zawodzinski, T. A.; Baker, G. A.; Tuckerman, M. E.; Savinell, R. F.; Sangoro, J. R. Deep Eutectic Solvents: A Review of Fundamentals and Applications. *Chem. Rev.* **2021**, *121*, 1232–1285.
- (78) Skopek, M. A.; Mohamoud, M. A.; Ryder, K. S.; Hillman, A. R. Nanogravimetric observation of unexpected ion exchange characteristics for polypyrrole film p-doping in a deep eutectic ionic liquid. *Chem. Commun.* **2009**, 935–937.
- (79) Abbott, A. P.; Barker, G. W.; Walter, A. J.; Kocovsky, P. Electrochemical recognition of analytes using quaternary ammonium binaphthyl salts. *Analyst* **2003**, *128*, 245–248.
- (80) Lawes, S. D. A.; Hainsworth, S. V.; Blake, P.; Ryder, K. S.; Abbott, A. P. Lubrication of Steel/Steel Contacts by Choline Chloride Ionic Liquids. *Tribol. Lett.* **2010**, *37*, 103–110.
- (81) Gutiérrez, M. C.; Carriazo, D.; Tamayo, A.; Jiménez, R.; Picó, F.; Rojo, J. M.; Ferrer, M. L.; del Monte, F. Deep-Eutectic-Solvent-Assisted Synthesis of Hierarchical Carbon Electrodes Exhibiting Capacitance Retention at High Current Densities. *Chem. -Eur. J.* **2011**, *17*, 10533–10537.
- (82) Jhong, H. R.; Wong, S. H.; Wan, C. C.; Wang, Y. Y.; Wei, T. C. A novel deep eutectic solvent-based ionic liquid used as electrolyte for dye-sensitized solar cells. *Electrochem. Commun.* **2009**, *11*, 209–211.
- (83) Morrison, H. G.; Sun, C. C.; Neervannan, S. Characterization of thermal behavior of deep eutectic solvents and their potential as drug solubilization vehicles. *Int. J. Pharm.* **2009**, *378*, 136–139.
- (84) Serrano, M. C.; Gutiérrez, M. C.; Jiménez, R.; Ferrer, M. L.; Monte, F. Synthesis of Novel Lidocaine-Releasing Poly(Diol-CoCitrate) Elastomers by Using Deep Eutectic Solvents. *Chem. Commun.* **2012**, *48*, 579–581.
- (85) Deraedt, C.; Pinaud, N.; Astruc, D. Recyclable Catalytic Dendrimer Nanoreactor for Part-Per-Million Cu(I) Catalysis of "Click" Chemistry in Water. *J. Am. Chem. Soc.* **2014**, *136*, 12092–12098.
- (86) Díez-González, S.; Nolan, S. P. [(NHC)₂Cu]X Complexes as Efficient Catalysts for Azide-Alkyne Click Chemistry at Low Catalyst Loadings. *Angew. Chem., Int. Ed.* **2008**, *47*, 8881–8884.
- (87) Wang, C.; Wang, D.; Yu, S.; Cornilleau, T.; Ruiz, J.; Salmon, L.; Astruc, D. Design and applications of an efficient amphiphilic "click" CuI catalyst in water. *ACS Catal.* **2016**, *6*, 5424–5431.
- (88) Yamada, Y. M. A.; Sarkar, S. M.; Uozumi, Y. Amphiphilic Self Assembled Polymeric Copper Catalyst to Parts Per Million Levels: Click Chemistry. *J. Am. Chem. Soc.* **2012**, *134*, 9285–9290.
- (89) Bai, Y.; Feng, X.; Xing, H.; Xu, Y.; Kim, B. K.; Baig, N.; Zhou, T.; Gewirth, A. A.; Lu, Y.; Oldfield, E.; Zimmerman, S. C. A Highly Efficient Single-Chain Metal–Organic Nanoparticle Catalyst for Alkyne–Azide "Click" Reactions in Water and in Cells. *J. Am. Chem. Soc.* **2016**, *138*, 11077–11080.
- (90) Jana, N. C.; Sethi, S.; Saha, R.; Bagh, B. Aerobic oxidation of vanillyl alcohol to vanillin catalyzed by air-stable and recyclable copper complex and TEMPO under base-free conditions. *Green Chem.* **2022**, *24*, 2542–2556.
- (91) Troyano, J.; Zapata, E.; Perles, J.; Amo-Ochoa, P.; FernándezMoreira, V.; Martínez, J. I.; Zamora, F.; Delgado, S. Multifunctional Copper(I) Coordination Polymers with Aromatic Mono- and Ditopic Thioamides. *Inorg. Chem.* **2019**, *58*, 3290–3301.
- (92) Liang, X.-Q.; Gupta, R.-K.; Li, Y.-W.; Ma, H.-Y.; Gao, L.-N.; Tung, C.-H.; Sun, D. Structural Diversity of Copper(I) Cluster-Based Coordination Polymers with Pyrazine-2-thiol Ligand. *Inorg. Chem.* **2020**, *59*, 2680–2688.
- (93) Pathaw, L.; Maheshwaran, D.; Nagendraraj, T.; Khamrang, T.; Velusamy, M.; Mayilmurugan, R. Tetrahedral copper(I) complexes of novel N,N-bidentate ligands and photophysical properties. *Inorg. Chim. Acta* **2021**, *514*, 119999–120008.
- (94) Ilgen, F.; König, B. Organic reactions in low melting mixtures based on carbohydrates and L-carnitine—a comparison. *Green Chem.* **2009**, *11*, 848–854.
- (95) Xiong, X.; Yi, C.; Liao, X.; Lai, S. A practical multigram-scale method for the green synthesis of 5-substituted-1H-tetrazoles in deep eutectic solvent. *Tetrahedron Lett.* **2019**, *60*, 402–406.
- (96) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehadeh, S.; Dunn, P. J. CHEM21 Selection Guide of Classical and Less Classical-Solvents. *Green Chem.* **2016**, *18*, 288–296.
- (97) Allen, D. T.; Gathergood, N.; Licence, P.; Subramaniam, B. Expectations for Manuscripts Contributing to the Field of Solvents in ACS Sustainable Chemistry & Engineering. *ACS Sustainable Chem. Eng.* **2020**, *8*, 14627–14629.
- (98) Kuok Mimi Hii, K.; Moores, A.; Pradeep, T.; Sels, B.; Allen, D. T.; Licence, P.; Subramaniam, B. Expectations for Manuscripts on Catalysis in ACS Sustainable Chemistry & Engineering. *ACS Sustainable Chem. Eng.* **2020**, *8*, 4995–4996.
- (99) Allen, D. T.; Carrier, D. J.; Gong, J.; Hwang, B.-J.; Licence, P.; Moores, A.; Pradeep, T.; Sels, B.; Subramaniam, B.; Tam, M. K. C.; Zhang, L.; Williams, R. M. Advancing the Use of Sustainability Metrics in ACS Sustainable Chemistry & Engineering. *ACS Sustainable Chem. Eng.* **2018**, *6*, 1.
- (100) Drosesbeke, M. A.; Du Prez, F. E. Sustainable Synthesis of Renewable Terpenoid-Based (Meth)acrylates Using the CHEM21 Green Metrics Toolkit. *ACS Sustainable Chem. Eng.* **2019**, *7*, 11633–11639.
- (101) Prieschl, M.; García-Lacuna, J.; Munday, R.; Leslie, K.; O’Kearney-McMullan, A.; Hone, C. A.; Kappe, C. O. Optimization and sustainability assessment of a continuous flow Ru-catalyzed ester hydrogenation for an important precursor of a β 2-adrenergic receptor agonist. *Green Chem.* **2020**, *22*, 5762–5770.
- (102) Dalidovich, T.; Mishra, K. A.; Shalima, T.; Kudrjasova, M.; Kananovich, D. G.; Aav, R. Mechanochemical Synthesis of Amides with Uronium-Based Coupling Reagents: A Method for Hexaamidation of Biotin[6]juril. *ACS Sustainable Chem. Eng.* **2020**, *8*, 15703–15715.
- (103) Zhu, Z.; Wang, Z.; Jian, Y.; Sun, H.; Zhang, G.; Lynam, J. M.; McElroy, C. R.; Burden, T. J.; Inight, R. L.; Fairlamb, I. J. S.; Zhang, W.; Gao, Z. Pd-Catalyzed carbonylative Suzuki–Miyaura cross-couplings using Fe(CO)₅ under mild conditions: generation of a highly active, recyclable and scalable 'Pd–Fe' nanocatalyst. *Green Chem.* **2021**, *23*, 920–926.
- (104) Sheldon, R. A. The E Factor: Fifteen Years On. *Green Chem.* **2007**, *9*, 1273–1283.
- (105) Lam, C. H.; Escande, V.; Mellor, K. E.; Zimmerman, J. B.; Anastas, P. T. Teaching Atom Economy and E-Factor Concepts through a Green Laboratory Experiment: Aerobic Oxidative Cleavage of meso-Hydrobenzoin to Benzaldehyde Using a Heterogeneous Catalyst. *J. Chem. Educ.* **2019**, *96*, 761–765.