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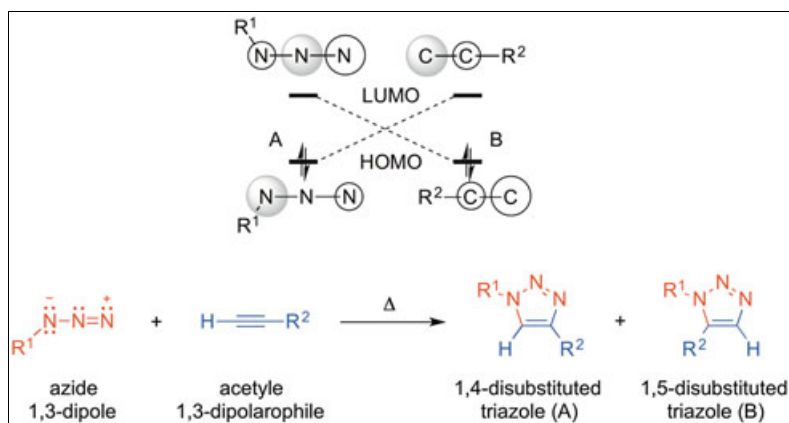
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The heterocyclic family of azoles have recently become one of the most widely used members of the *N*-heterocycles; the most prominent one being 1*H*-1,2,3-triazole and its derivatives. The sudden growth of interest in this structural motif was sparked by the advent of click chemistry, first described in the early 2000s. From the early days of click chemistry, when the accessibility of triazoles made them into one of the most versatile linkers, interest has slowly turned to the use of triazoles as functional building blocks. The presence of multiple *N*-coordination sites and a highly polarized carbon atom allows for metal coordination and the complexation of anions by both hydrogen and halogen bonding. Exploitation of these multiple binding sites makes it possible for triazoles to be used in various functional materials, such as metallic and anionic sensors. More recently, triazoles have also shown their potential in catalytic systems, thus increasing their impact far beyond the initial purpose of click chemistry. This report gives an overview of the structure, functionalities, and use of triazoles with a focus on their use in catalytic systems.

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INTRODUCTION

Over the time span of a single decade, the 1*H*-1,2,3-triazole group (hereafter referred to as triazole) has become one of the most synthesized heterocycles. Triazole formation was popularized by the so-called click reaction between an azide and an acetylene, two groups that are inert toward many functional groups and reaction conditions. Besides the copper-catalyzed mechanism, strain-promoted reactions have also been reported, and the reaction has impacted virtually any field of chemistry, materials science, and molecular biology. Although initially only the result of an orthogonal linking reaction, the triazole group later developed into a versatile functional group. Many excellent reviews have been published that cover certain aspects of triazole click chemistry, such as its mechanisms [1–4], (bio) conjugation applications [5,6], or functionality [7–13]. Here, we overview the recent developments of all

aspects, including synthetic strategies and major applications: as a linking group, for instance, in chemical biology and *in-vivo* studies, as a reporter in sensory materials, and as a ligand in catalysis.

The 1,3-dipolar cycloaddition reaction. In 1893, the first example of a 1,3-dipolar cycloaddition reaction was reported by Michael, who investigated the reaction between phenyl azide and dimethyl acetylenedicarboxylate [14]. This report, however, did not attract the interest of the synthetic community until approximately 70 years later when this class of reactions was thoroughly examined and described by Huisgen and his team [15–17]. They developed reactions that were efficient methods toward di- or trisubstituted triazoles (sometimes referred to as *v*-triazole for vicinal); however, high activation energies required the use of activated precursors and, in most cases, elevated temperatures for the reactions to proceed. The observed reaction rates and regioselectivity of the reaction were later explained by

Sustmann [18,19] and Houk [20], who applied frontier molecular orbital models to describe the reaction (Scheme 1a). In their models they assumed that the reaction between the 1,3-dipole (azide) and the 1,3-dipolarophile (acetylene) proceeded through an interaction of the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other reactant, with a reaction rate that depended on the corresponding energy gap. Furthermore, because of the very similar HOMO–LUMO energy-level differences in the 1,3-dipole and 1,3-dipolarophile, the cycloaddition reaction can proceed through a dipole–HOMO- (1,4-regioisomer; A, Scheme 1) or dipole–LUMO-controlled (1,5-regioisomer; B, Scheme 1) pathway [21].

By employing electron-donating or -withdrawing groups at the dipolarophile, the regioselectivity of this reaction can be adjusted to yield predominantly the 1,5- or 1,4-regioisomer, respectively. Only a handful of substituents provided the exclusive formation of one of the regioisomers [22].

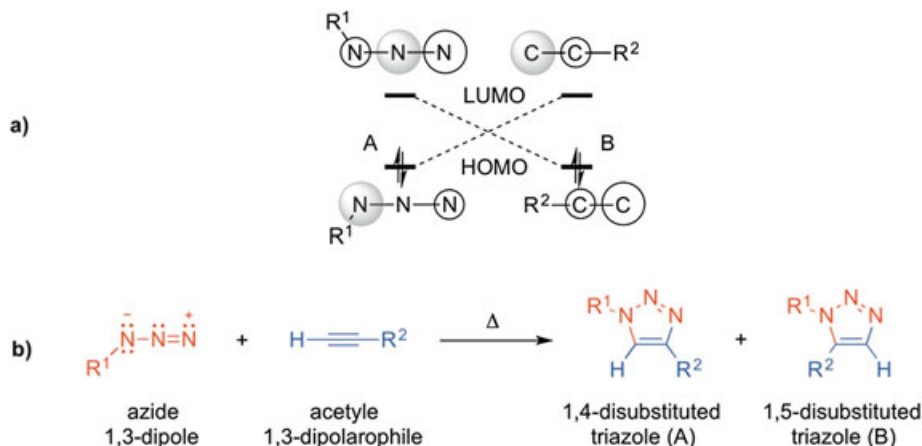
The copper(I)-catalyzed azide–alkyne cycloaddition. It was as recent as 2001 when the copper(I)-catalyzed azide–alkyne cycloaddition reaction (CuAAC) gained significant interest with the introduction of the concept of “click chemistry”. Click chemistry, although often synonymous with 1,3-dipolar cycloaddition to yield the triazole, is more accurately attributed to a set of powerful, highly reliable, selective and atom-efficient reactions for the facile synthesis of useful new compounds [23]. To be classified under the banner of click reactions, the route should employ simple reaction conditions and readily available starting materials and reagents. They should use no solvent or a solvent that is either aqueous (for biological applications) or easily removed from the reaction mixture. Finally, the product should be easily

isolated from any residual starting materials. A careful reader might argue that the Huisgen reaction does not comply with some of the aforementioned requirements, especially because of the potentially explosive decomposition route of many azides [24,25] and the harsh reaction conditions, often reaching temperatures in excess of the boiling point of many solvents, required for the dipolar cycloaddition to take place. It was soon after establishing the foundations of click chemistry when Meldal and Sharpless almost simultaneously reported the CuAAC reaction [26,27]. This reaction, involving Cu(I) as the catalyst, was described as highly reliable and exhibiting an unusually wide scope with respect to both starting components [3,28,29]. Furthermore, the use of Cu(I) significantly changes the reaction mechanism (Scheme 2), resulting in the exclusive formation of the triazole-1,4-diyl unit (Scheme 1).

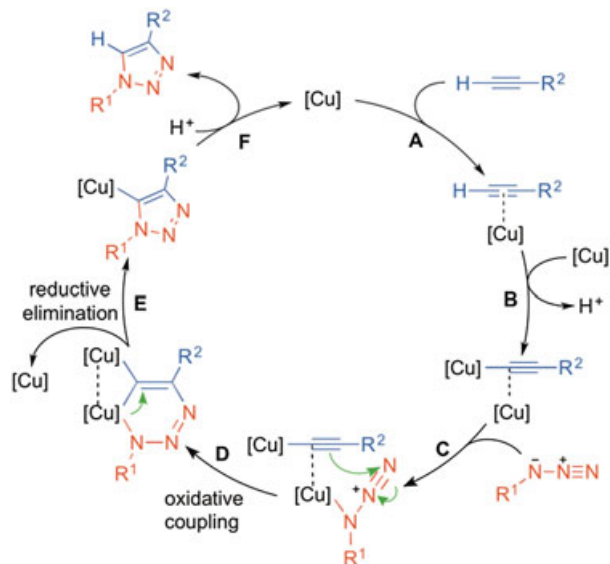
Many studies have been undertaken that focused on describing the catalytic cycle, both from an experimental and computational viewpoint. These studies revealed a stepwise mechanism, involving unprecedented metallacycle intermediates, which appeared to be common for a variety of dipoles [30].

In the proposed reaction mechanism (Scheme 2), the reaction proceeds as follows: The first step (A) is the π -coordination of the Cu(I) ion to the alkyne, which increases the pK_a of the alkyne and, thus, allows the subsequent deprotonation and formation of Cu(I) acetylide with a second Cu(I) ion (B). This is followed by the coordination of an azide at the π -coordinated Cu(I) (C). Coordination of the azide could occur either through the substituted or terminal nitrogen atom. Because the substituted nitrogen atom is more electron-rich, it is more likely that the azide coordinates to Cu(I) through this atom. Additionally, it increases the electron density on the metal center, which facilitates subsequent oxidative

Scheme 1. (a) Azide–alkyne frontier molecular orbital interactions. (b) Structure of the two possible products of the Huisgen 1,3-dipolar cycloaddition. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. Proposed mechanism of the CuAAC reaction [30–32]. [Cu] denotes a copper fragment that varies in the number of ligands and in the formal oxidation state. [Color figure can be viewed at wileyonlinelibrary.com]



coupling (D). The observed selectivity for the 1,4-regioisomer may be explained by the preference of the π -coordinated Cu(I) to form a bond with the terminal carbon atom of the acetylide, which directs the nucleophilic attack of the non-terminal carbon atom of the acetylide at the terminal nitrogen atom of the azide (D). As a result, a six-membered metallacycle is formed, which includes a μ -alkenylidene moiety. Finally, the reductive elimination of Cu(I) affords the Cu(I)-bound triazide in a highly exothermic process (E). In aqueous media, the Cu(I) triazide then readily undergoes protonolysis (F), providing the free triazole and allowing the Cu(I) species to participate again in the catalytic cycle.

The efficiency of this copper-mediated catalytic cycle, which results in virtually quantitative yields of the desired triazoles and a rate improvement of a factor of 10^7 (when compared with the thermal cycloaddition reaction), resulted in immediate focus on this reaction by many fields of synthetic chemistry. The resulting triazole unit is essentially chemically inert to many subsequent reaction conditions, such as oxidation, reduction, and hydrolysis, thus fulfilling all criteria outlined in the concepts of click chemistry. This robust, inert, versatile, and orthogonal reaction has found a number of applications over the past decade, for example, in biomolecular ligation [5], polymerization reactions [33], and synthesis of functional materials [34].

With ever-growing interest in using the triazole linker in bio-related applications, the means of eliminating the use of copper as a catalyst for this reaction were examined. Not only are the Cu(I) residues cytotoxic, they can also

bind to the active site of many enzymes, thereby blocking or reducing their biological activity [35,36]. Furthermore, Cu(I) is easily disproportionated in an aqueous environment, which reduces the rate of the reaction [37].

In 1961, Wittig and Krebs showed that cyclooctyne reacted quantitatively with phenyl azide (Scheme 3) to form a triazole unit [38].

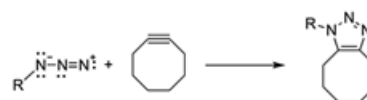
Recently, Bertozzi and co-workers developed this reaction as an attractive alternative to the copper-catalyzed click cycloaddition for use in living systems [36,39]. This strain-promoted azide–alkyne cycloaddition (SPAAC), in combination with the employment of electron-withdrawing groups next to the alkyne, was shown to greatly enhance the rate of the reaction (1, Fig. 1) [6,40,41].

Boons and co-workers reported the use of the highly reactive dibenzocyclooctynol for glycoprotein imaging (2, Fig. 1) [42]. Rutjes and co-workers introduced a nitrogen-containing cyclooctyne analogue (3, Fig. 1), in which the nitrogen atom allowed straightforward functionalization of the aniline moiety and modification of the system, for example, by sulfonation [43–45]. This system allowed for efficient coupling of various enzymes to poly(ethylene glycol) (PEG; termed PEGylation), as well as the construction of multi-functional enzyme complexes [46]. Recently, functionalized analogues of BCN (bicyclo[6.1.0]non-4-yne, Fig. 1) were prepared by the Rutjes group [47,48]. Besides a much easier preparation, the BCN derivatives were shown to be stable, relatively non-lipophilic, and symmetrical, which prevented the formation of regioisomers during cycloaddition. Beads appended with BCN were, for example, used as a so-called “azido-trap” for the selective enrichment of azide-functionalized (glyco)proteins [49].

TRIAZOLES AS LINKERS

The CuAAC reaction was shown to be high yielding, specific, regioselective, and tolerant to other functional groups present within the components. These reactions proceed in many different solvents, including aqueous media, without a loss of efficiency and with an easy work-up. The rigidity of the triazole ring prevents interactions between the linked components [2]. These favorable properties made the triazole unit a very useful linker for small molecules [50–52] and polymers [9,10,12], particularly in the synthesis of biohybrid

Scheme 3. Wittig–Krebs cyclooctyne cycloaddition.



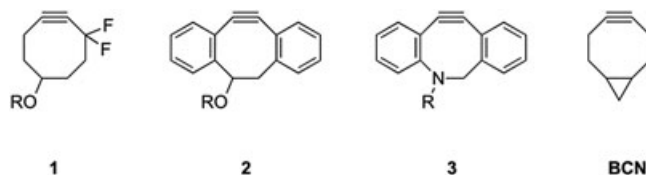


Figure 1. Strain-activated acetylenes.

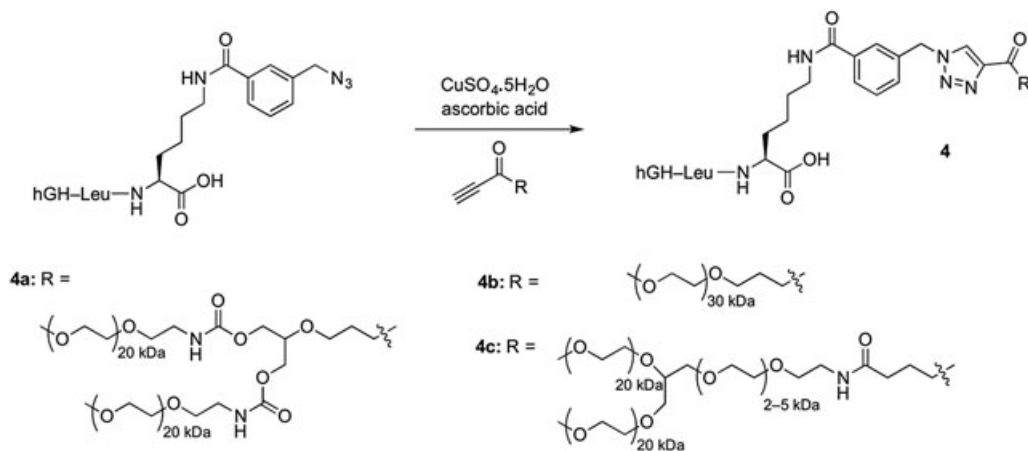
materials, which require methods that are selective and biocompatible to ensure that the properties of the building blocks are retained in the final structure [53,54]. Although this review is focused on the use of triazoles as a functional, rather than structural, element, some interesting examples of triazoles as linkers for bioconjugation are also presented. Several comprehensive reviews on this topic can be found in the literature [5,55–59].

Protein conjugates. The combination of synthetic polymers with biomacromolecules, such as proteins, is an attractive method for increasing the *in vivo* and *in vitro* applications of these compounds. The inclusion of the polymer alters the solubility and surface properties of the protein and, therefore, affects its stability, activity, and biocompatibility. The applications for these types of biohybrid compounds include the areas of bio-sensors, artificial enzymes, biometrics, light-harvesting systems, and photonics, as well as applications in nano-electronic devices [60].

The PEGylation of a protein often increases the stability and solubility of biomolecules and has therefore become a frequently employed technique in the field of bioconjugation. Peschke *et al.* elongated human growth hormone at its C terminus by the addition of a Leu–Ala motif [61]. The C-terminal amino acid could then be converted into an azide, which was then clicked with various molecular weight methoxypoly(ethylene glycol) moieties to give

PEGylated human growth hormone derivatives (Scheme 4). The *in vitro* biological activity of these bioconjugate molecules was governed by both the molecular weight and branching structure of the attached PEG group (**4a–c**, Scheme 4).

The group of Schultz demonstrated site-specific PEGylation by the incorporation of non-natural amino acids containing azide functionalities (e.g., azidohomoalanine, azidonorvaline, and azidonorleucine) into mutant proteins by genetic engineering [62,63]. Conjugation with alkyne-terminated PEGs of various lengths resulted in enzymes that showed activity similar to that of the native enzyme; a key enzyme in the processes that prevent the formation of reactive oxygen species in cells. The catalytic activity of enzymes has been vastly studied in bulk but only recently have their characteristics been studied at the single-molecule level [64]. The groups of Nolte and Rowan constructed a heterodimer enzyme–protein conjugate from *Thermomyces lanuginosa* lipase and BSA, in which the latter acted as a “protein foot” to stick the enzyme onto the surface [65]. BSA was functionalized with an azide moiety and clicked to the monoalkyne-appended lipase, constructed from the derivatization of the only accessible lysine residue (Lys46) with 4-pentynoic acid. The resulting dimer was found to not only have improved adsorption properties but also showed a two-fold increase in catalytic activity compared with that of the non-functionalized lipase.

Scheme 4. Synthesis of PEGylated proteins **4a–c**.

Glycoconjugates. In addition to the click modifications of peptides, click chemistry has also been applied in carbohydrate chemistry. Carbohydrates can polymerize in a branched or linear fashion at a number of linkage positions, because of the presence of polyvalent repeat units. This feature gives rise to many different geometries and therefore a high degree of complexity. This is evident when it comes to their *de novo* synthesis through gluconeogenesis in the human body, which, in contrast to peptides and nucleic acids, is far from trivial, as a result of the large variety of functional groups present and the need for control over bio- and stereochemical factors. In addition, carbohydrates are often attached to other biomolecules, such as lipids, proteins, and nucleic acids, highlighting the need for orthogonal coupling reactions that use mild conditions. Click glycochemistry has proven to be a valuable tool in the construction of glycosylated biohybrid materials and allows for the construction of materials that are otherwise unobtainable [66,67]. Riguera and co-workers used the click reaction with alkyne-appended unprotected sugars to decorate three generations of azido-terminated gallic acid-triethylene glycol dendrimers [68]. In a different approach, Lee and co-workers prepared glycoclusters from an alkyne-functionalized carbohydrate core unit [69]. Four individual alkyne groups were introduced onto a methyl β -D-galactopyranoside unit and were then functionalized with azido-linked lactose or *N*-acetyl lactosamine derivatives (**5**, Scheme 5). The resulting sugar-cored glycoclusters were found to be stronger inhibitors of RCA₁₂₀ lectin than that of monovalent lactose.

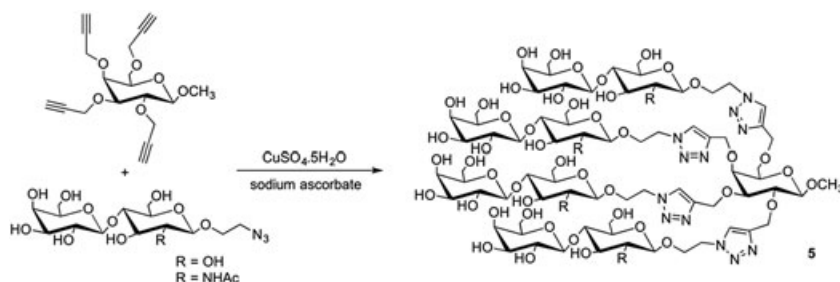
Glycopeptides. Another group of compounds commonly linked with click chemistry are the glycopeptides, which consist of an oligosaccharide linked

through an N or O atom to a protein [70]. This glycosyl-protein bond is intrinsically sensitive toward enzymatic hydrolysis, resulting in limited metabolic stability. The groups of Rutjes [71,72] and Dondoni [73] independently investigated the incorporation of triazole linkages as stable isosteres for native glycosidic linkages. To determine the synthetic viability of triazolyl glycoamino acids, Rutjes and co-workers performed the CuAAC reaction with a range of anomeric azidoglycosides with *N*-Boc-propargylglycine methyl ester (Boc = *tert* butoxycarbonyl) and isolated the triazole-linked products in good yields (**6**, Scheme 6) [71].

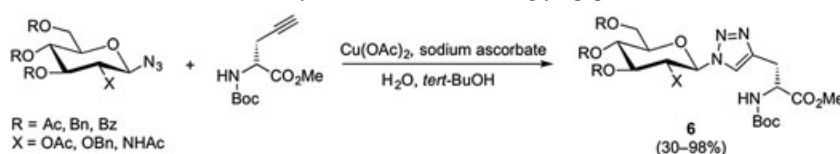
They also observed that triazole formation was successful when (i) using a disaccharide, (ii) varying the amino acid moiety, or (iii) swapping the azide and alkyne functionalities of the sugars and amino acids. To further evaluate the amido isosteric properties of the triazole moiety, Rutjes and co-workers synthesized side-chain glycosylated cyclic arginine-glycine-aspartate (cRGD) derivatives for biological comparison studies [74]. Such RGD peptide motifs are commonly found in proteins of the extracellular matrix, such as fibrinogen and laminin, and act as cellular adhesion sites for integrin binding.

Macromolecular and live cell labeling. In addition to the previously presented functional improvements of biomolecules by appending new structures [75] or new functional sites to (bio)polymers [11], a great deal of interest has also been focused on the visualization of such biomolecules [76]. A coumarin-based fluorescent marker, linked through a triazole unit, was, for example, used for the visualization of oligonucleotides [66,77]; similar coumarine- and perylene-based moieties functionalized with azides were successfully coupled to helical dipeptide polyisocyanides containing acetylene functionalities [78]. The potential of these scaffold types was further

Scheme 5. Synthesis of glycocluster **5** [69].



Scheme 6. Synthesis of triazole-linked glycopeptides **6**.



investigated with relation to their attachment to other molecules of biological relevance, such as antibodies, proteins, and peptides [79,80]. Carell and co-workers prepared alkyne-functionalized DNA strands, which were sequence-selectively appended with azido sugars or fluorescent labels under CuAAC conditions [81].

Utilizing the previously described and developed methods for click bioconjugation reactions, click chemistry was recently shown to be a very appealing method for the direct labeling of live cells [56,82,83], in which the orthogonality of the click reaction provided a means for the specific targeting of various parts of live cells, such as proteins [84], nucleic acids [82,85], or cell membranes [86]. Very often these approaches utilize the SPAAC reaction, as shown by Bertozzi and co-workers, who performed live-cell labeling of specific protein glycoforms, providing a useful platform for investigating the roles of protein-specific glycosylation in various cellular contexts [87]. Wnuk and co-workers demonstrated the labeling of nucleosides and showed the potential application of this method for dynamic measuring and tracking of signaling events inside single living cancer cells (Fig. 2) [88].

TRIAZOLES IN FUNCTIONAL MATERIALS AND SENSORS

Functional properties of triazoles. In addition to the extensive use of triazoles as linkers, their structure makes them ideal candidates for incorporation as a functional building block. The three nitrogen atoms of the triazole ring cause a strong polarization of the aromatic π system, resulting in a partial positive charge on the carbon atoms and the nitrogen atom in the 1-position; the 2- and 3-position nitrogen atoms show partial negative charges [89]. This model is supported by experimental [90] and computational data [91] and further confirmed by the relatively large dipole moment, of almost 5 Debye, calculated for the triazole moiety (Fig. 3) [92].

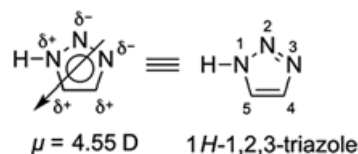


Figure 3. Partial charges and the numbered structure of the 1H-1,2,3-triazole.

The electronic structure of the triazole moiety, together with the lone electron pairs present on the nitrogen atoms, provides the triazole units with the ability to coordinate metals and serve as hydrogen-bond acceptors. The polarized hydrogen atom on the C5 carbon atom provides triazole with the ability to serve as a hydrogen-bond donor [4,93]. Several studies have emerged lately that exploit these favorable properties; a more detailed overview is presented below.

Triazoles as hydrogen-bond mediators. The ability of triazole to act as a hydrogen-bond donor stems from the lowered electronegativity of the C5 atom; this is caused by the electron-withdrawing properties of the three nitrogen atoms (Fig. 3), which result in an increased acidity of the C5 proton [94,95]. Flood and co-workers used the potential anion-binding properties of the triazole unit in the design and synthesis of triazolophane **7** (Fig. 4) [95–97].

Titration studies of **7** with halogen anions showed exceptionally high binding constants for chloride ($K_A = 11 \times 10^6 \text{ M}^{-1}$) and bromide ($K_A = 7.5 \times 10^6 \text{ M}^{-1}$) anions. Fluoride and iodide anions showed much lower binding constants ($K_A = 2.8 \times 10^5$ and $1.7 \times 10^4 \text{ M}^{-1}$, respectively) as a result of the size mismatch between the triazolophane receptor and respective halogen anion. In parallel, a very similar system of reconfigurable oligo (aryl-triazoles) was reported by Craig (**8**, Fig. 4) [98,99]. Because of the acyclic structure of these anion receptors, they showed approximately 100 times lower binding constants for halogen anions than that of **7**. A similar observation was described by Flood, who made a direct comparison between **7** and its open-ring analogue **9**.

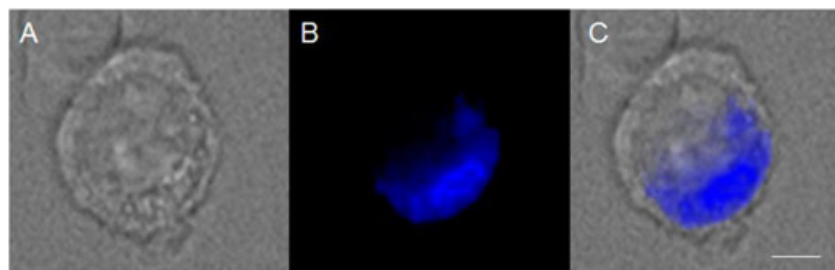


Figure 2. Fluorescence microscopy and phase images of live cells: (A) Phase image of MCF-7 cancer cells after the reaction of azide with cyclooctyne. (B) Fluorescence microscopy image of the same MCF-7 cell. (C) Merged images of panels A and B. Scale = 20 μm . (Reprinted with permission from Ref. [88]. Copyright 2015 American Chemical Society.). [Color figure can be viewed at wileyonlinelibrary.com]

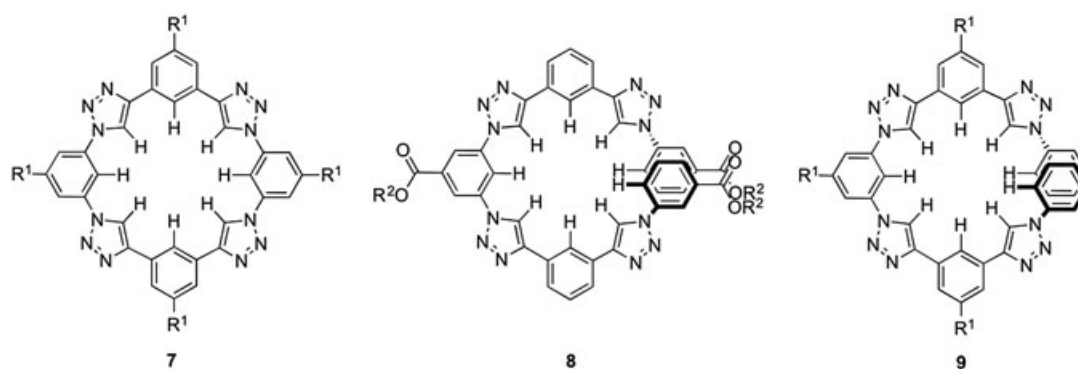


Figure 4. Structures of anion receptors 7–9.

The differences in the binding constants were ascribed to the need of pre-organization in case of **8** and **9**, which had to pay an energy penalty upon anion binding [100]. The strong anion binding of triazolophanes makes them ideal candidates for application as ionophores [101], whereas triazole oligomers, such as **8** and **9**, are potentially suitable for molecular switches, because of the anion-responsive folding behavior [99]. Recently, Shainaz and co-workers demonstrated a similar type of anion sensor composed of a simple 1,4-diaryltriazole unit containing a phenol moiety, which was selective for fluorine anions [102].

In a very recent report, Flood and co-workers prepared a cyclic triazolophane **tricarb** conveniently in one pot from the azide and alkyne-functionalized carbazole **10** (Scheme 7) [103].

The **tricarb** macrocycle was shown to bind anions that are generally considered too weak to be coordinated, such as PF_6^- , as well as the ability to assemble into ultrathin films of hierarchically ordered tubes on graphite surfaces, as observed by using scanning tunneling microscopy.

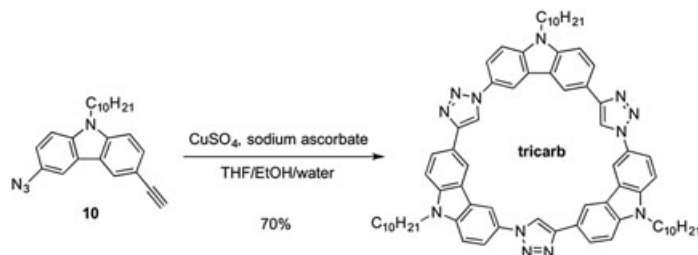
Hecht and co-workers took advantage of the hydrogen-bonding and metal-coordination abilities of the nitrogen atoms of the triazole units by preparing a variety of 2,6-bis(1*H*-1,2,3-triazol-4-yl)pyridine foldamers (**11**) as click analogues to the well-known 2,2':6',2''-terpyridine (**terpy**) ligands (Fig. 5) [104].

The free and coordinated forms of compound **11** were shown to be in a dynamic equilibrium, and the orientation of the triazoles, and hence the geometry of the whole system, was pre-organized through intramolecular hydrogen bonding or by coordination to metals [105]. Chiral oligomeric analogues of **11** have remarkable self-assembly properties upon anion complexation, forming macromolecular helices (Fig. 6a). Their helicity was shown to be tuneable and governed by the type of achiral anion [106,108]. The equilibration of the Fe^{2+} complexes of **11**, together with their tuneable stability and interesting magnetic properties, should enable the design of dynamic metallo-supramolecular materials [109].

Klumperman and co-workers designed and prepared much larger click foldamers that possessed a cavity of nearly 31 Å (Fig. 6b). This was achieved by decreasing the curvature of the triazole–aryl–triazole unit by using 1,4-substituted phenylene groups. Furthermore, by functionalizing the phenylene groups with chiral substituents, and by macromolecular templating of the clickamers using poly(γ -benzyl-L-glutamate), helical synthetic analogues of the tobacco mosaic virus were obtained [107,110].

Triazole–metal coordination. The presence of the electron lone pairs on the triazole N2 and N3 atoms, which are able to coordinate metal ions, introduces the possibility for triazoles to be used as metal sensors or stabilizing ligands (Fig. 7) [7,111–113]. The nitrogen

Scheme 7. Synthesis of cyclic triazolophane tricarb.



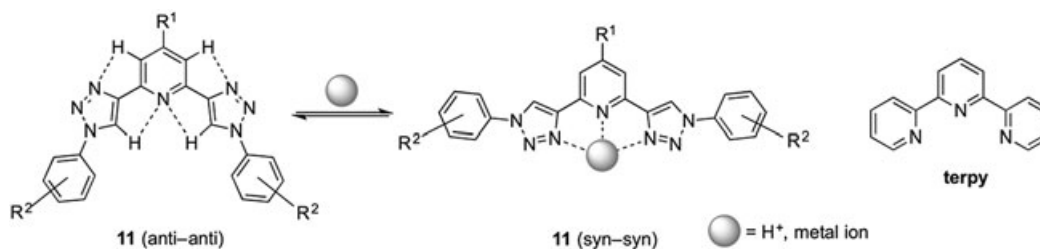


Figure 5. Free and coordinated forms of **11** and ligand **terpy**.

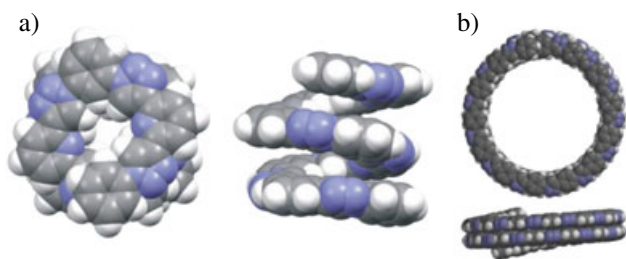


Figure 6. (a) Foldamers prepared by Hecht *et al.* (Reprinted with permission from Ref. [106]. Copyright 2008 Wiley-VCH). (b) Foldamers prepared by Klumperman *et al.* (Reprinted with permission from Ref. [107]. Copyright 2013 Wiley-VCH). [Color figure can be viewed at wileyonlinelibrary.com]

atoms can coordinate individually or simultaneously in a bridging fashion [114–116]. The increased electron density at N3, however, generally results in much more stable metal–N3 complexes, compared with metal–N2 complexes. This was supported by competitive binding studies with multi-dentate ligand **12** in which a direct comparison of these two coordination modes was conducted (Fig. 7) [117,118].

Cavitands functionalized with triazoles. Calixarenes are a class of macrocyclic molecules that are extensively used in supramolecular chemistry [119]. The parent calix[*n*]arenes (*n* = 4, 6, 8) are conveniently prepared through a condensation reaction of formaldehyde with phenol; their functionalization with triazole groups has been achieved, in most cases, by clicking alkynyl calixarenes to azide-bearing fluorophores (**13**, Fig. 8).

The nitrogen atoms from the triazole groups and the calixarene oxygen atoms form a binding pocket, which makes these calixarenes highly effective cationic sensors.

Chung and co-workers presented the first examples of such systems (**14**) by utilizing a crown ether binding site [120]. This design provided a chemosensor, which could be switched on and off by using K⁺ and Pb²⁺ ions as the triggers. The ¹H NMR spectroscopic studies indicated that Pb²⁺ bound to the triazole binding pocket, quenching the anthracene fluorescence. Addition of K⁺, which binds to the crown ether pocket, results in the renewal of the fluorescence signal by decomplexation of Pb²⁺, attributed to electrostatic repulsion. A similar switchable sensor was later reported by the group of Vicens (Fig. 8, **13a**) [121]. Compound **13a** was found to be selective for the binding of Zn²⁺ and Cd²⁺ ions to enhance the fluorescence signal, whereas Pb²⁺ had the effect of quenching the pyrene fluorescence. The quinoline analogue **13b** was reported to be a Hg²⁺ fluorescence quenching sensor [122]. Investigation into the binding mechanism of **13b** by ¹H NMR spectroscopy indicated the involvement of both the quinoline and triazole units in metal binding, whereas a single-armed analogue showed no fluorescent switching behavior, which pointed toward the favorable pre-organization of the binding site induced by the calixarene. In another example, a reversed orientation of the triazoles was achieved (C–H facing the inside of the cavity) by linking both triazole moieties in **13c** to a single anthracene unit [123]. This provided a cavitand selective for binding of bromide and iodide ions, suggesting their potential as anionic sensors.

Another group of molecules often used in binding studies and supramolecular chemistry is cyclodextrins (**15**, Fig. 9) [124]. These are generally obtained from the enzymatic degradation of starch and are therefore readily available. Like calixarenes, they belong to the family of cage molecules; that is, the core of their structure is

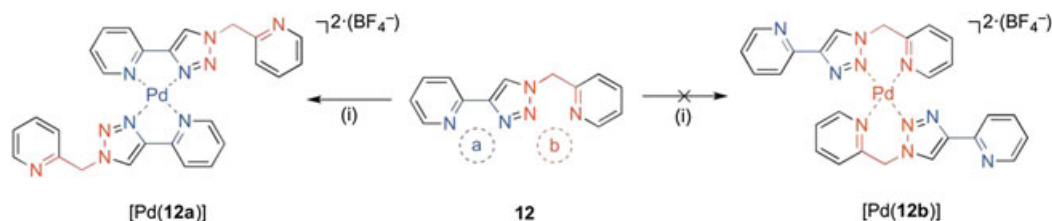


Figure 7. Competitive binding study to demonstrate stronger donation from N3 (the two possible binding sites, a and b, are denoted with dashed circles; (i) [Pd(CH₃CN)₄](BF₄)₂, CH₃CN, r.t., 1 h). [Color figure can be viewed at wileyonlinelibrary.com]

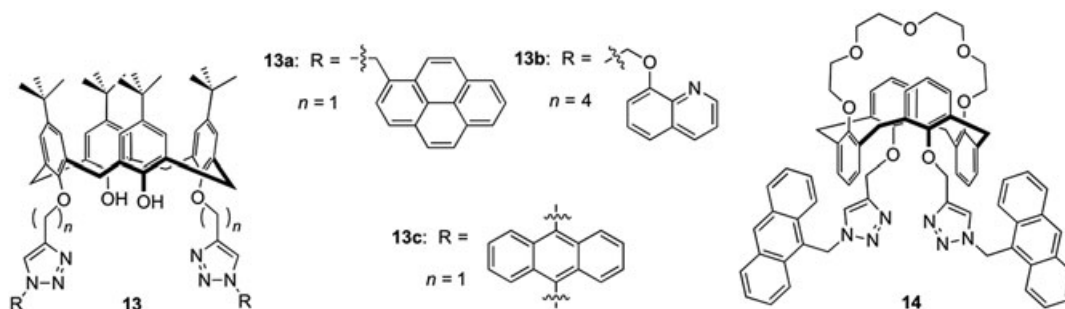


Figure 8. General structure of click calixarenes **13** and the dual sensor **14**.

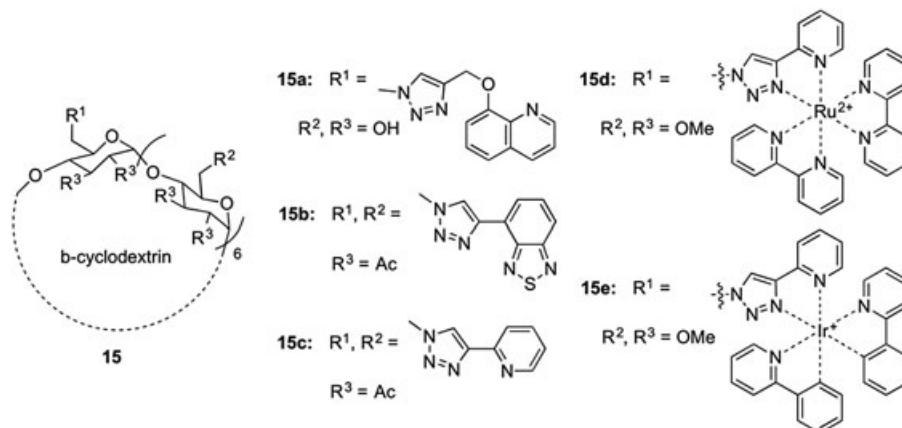


Figure 9. General structure of β -cyclodextrin **15** and the respective substituents.

composed of a cavity that can trap or encapsulate other molecules.

Similar to calixarenes, click chemistry has been used as a tool to attach fluorescent molecules to cyclodextrins. The resulting triazole nitrogen atoms on the functionalized cyclodextrins served as a binding site for metal ions. Liu and co-workers prepared a selective Cd^{2+} sensor **15a** [125], in which Cd^{2+} ions enhanced the fluorescence intensity of the hydroxyquinoline group. Other metal ions, such as Cu^{2+} , Fe^{3+} , and Ag^+ , caused fluorescence quenching. Benzathiodiazoyl triazole fluorophores have been used to create sensor **15b**. Selective fluorescence quenching was observed upon the addition of Ni^{2+} ions to a solution of the sensor. The addition of Zn^{2+} with **15c**, in a 1:1 stoichiometry, resulted in a complex with a sevenfold increase of fluorescence intensity [126]. Similar to **15c**, cyclodextrins **15d** and **e** were functionalized with the 2-pyridyl-triazole ligand; however, this time only on one of the amylose units. These were then used for the formation of Ir^{3+} and Ru^{2+} complexes. The Ir^{3+} complexes were found to be highly luminescent compounds with emission quantum yields ranging from 0.54 to 0.70. The presence of the cyclodextrin cavity led to highly luminescent species and reduction of the sensitivity of the Ir^{3+} complexes to dioxygen. This was

ascribed to the partial self-inclusion of the iridium complex into the primary site of the cyclodextrin cavity, which acted as an enantioselective second-coordination-sphere protective ligand.

Triazoles in conjugated and functional polymers. In an effort toward adding an additional function to the triazole linkers, Reek and co-workers [127], later followed by the group of Jin [128,129], incorporated triazole units into conjugated (co)polymers (Fig. 10) for potential use in organic solar cells.

Despite the heteroaromatic character of the triazole ring, the UV-vis and fluorescence spectra of triazole-containing polymers indicated that there was only poor electronic communication between the linked aromatic units. This was attributed to the fact that the N1 nitrogen atom acted as a conjugation barrier because its lone electron pair could not enter into effective conjugation with the aromatic substituent [50,130].

Polymeric systems offer a convenient way of amplifying the metal-binding abilities of a respective sensing unit, such as a triazole unit. The presence of the polymeric backbone was shown to greatly enhance the observed guest-induced changes in these receptors [131,132]. Cheng and co-workers used this approach for the synthesis of copolymer-based metal sensors **16a–c** (Fig. 11) [133–135].

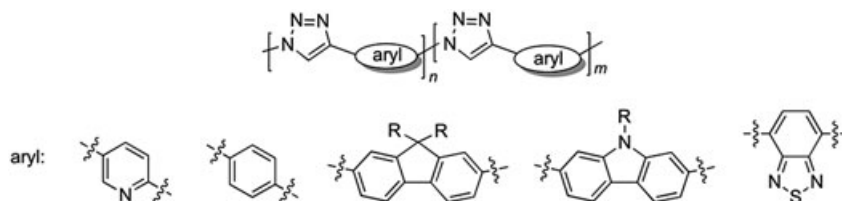


Figure 10. Aromatic triazole-linked (co)polymers.

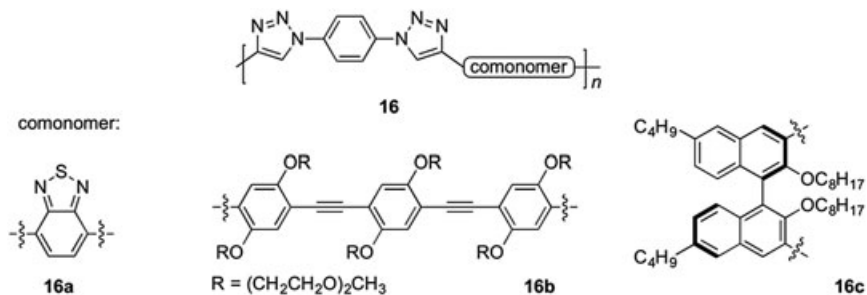


Figure 11. Structures of copolymers 16a–c.

Polymer **16a** was reported to be selective toward the addition of Ni^{2+} ions, and polymers **16b** and **16c** were reported to be very sensitive toward Hg^{2+} , resulting in strong fluorescence quenching of the polymers.

Triazoles in multivalent systems. The group of Tang reported the synthesis of hyperbranched polytriazoles by reacting multifunctional acetylene and azide compounds [33,136]. They demonstrated an elegant process to adjust the optical properties of the obtained polymeric films by the photolysis of the polymers; this offers methodology to tune the emission color of a polymer film simply by changing the regiostructure of the polytriazoles.

In the group of Sharpless, a similar type of multivalent molecule was shown to act, after polymerization, as a very efficient adhesive, showing comparable or superior adhesive strength to that of standard commercial glues (Fig. 12) [137].

These studies on multivalent molecules have paved the way for the use of click chemistry in dendrimeric synthesis [138,139]. The synthesis of these well-defined

macromolecules is highly dependent on the efficiency of the reactions used in the synthetic process because structural defects can be, statistically, very easily introduced into the dendritic structure [140–143].

The group of Sharpless demonstrated a highly efficient route to triazole-based dendrimers; they utilized Fréchet's convergent approach in their dendrimer synthesis [144–146]. This efficient strategy toward such dendrimers was subsequently used in the synthesis of multivalent bifunctional dendrimers (**17**, Fig. 13). By incorporating mannose units into the binding portion of the dendrimers, complemented by coumarin fluorescent units in the reporting part, highly efficient dual-purpose recognition/detection agents for the inhibition of hemagglutination were prepared [145]. The synergistic benefits provided by the multivalent dendritic array of these mannose receptor groups were demonstrated by a 240-fold greater potency of the prepared dendrimer toward detection of the protein concanavalin A [147] than that observed in monomeric mannose.

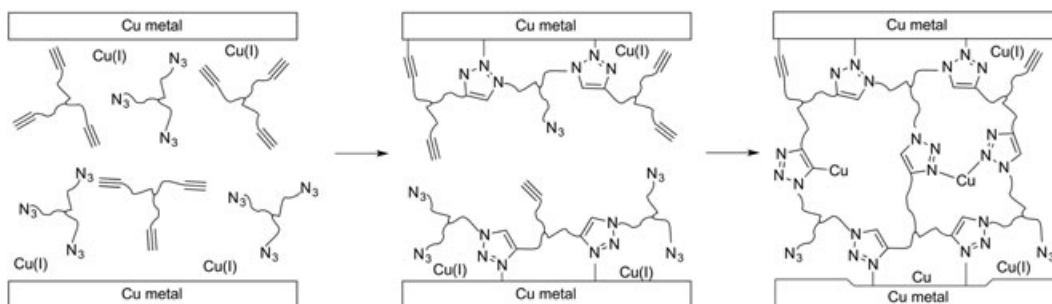


Figure 12. Copper adhesion by the formation of hyperbranched polymers [137].

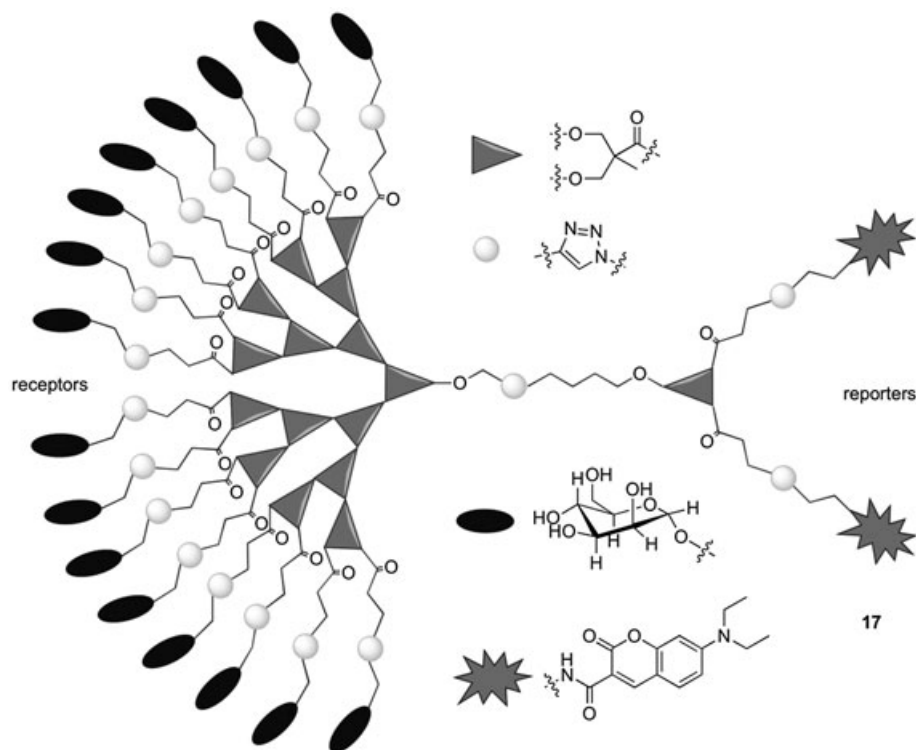


Figure 13. Structure of bifunctional dendrimer 17.

In the Astruc group, the synergistic effects of dendrimers were exploited even further by utilizing a divergent synthetic approach. In addition to the use of click chemistry as a tool for the decoration of the dendritic periphery with ferrocene moieties, they also exploited the coordination and supramolecular capabilities of the intradendritic triazole linkers (**18**, Fig. 14) [148]. The triazole linkers allowed for very efficient functionalization of platinum electrodes with these dendrimers; binding was strongest for the third-generation dendrimers possessing 243 triazole units (**18**, $n=9$). The presence of the ferrocene moieties allowed for electrochemical recognition of oxoanions H_2PO_4^- and ATP^{2-} , as well as Pd^{2+} cations [149].

The poly(triazole)ferrocene dendrimers were shown to be a convenient neutral ligand for the stabilization of functional gold nanoparticles in polar organic solvents, which find application in organic synthesis, sensing, and catalysis [150]. In addition, the ability of these dendrimers to efficiently bind metal cations, such as palladium, has turned them into very useful nanoreactors for the catalysis of a number of carbon–carbon bond-forming reactions (see the Triazoles as Ligands in Catalytic Reactions section for further details).

Triazoles in bidentate ligands. As previously outlined, a considerable amount of work involving triazole complexes has been focused on the coordination of the triazole unit as part of the 2-pyridyl-triazole ligand (Fig. 15). The reason

for this is that it closely resembles 2,2'-bipyridine (**bipy**), which is one of the most widely used bidentate nitrogen ligands [151].

Click chemistry provides a very convenient route for the synthesis of 2-pyridyltriazoles (**pyta**), and in comparison with **bipy**, it is relatively easy to vary the steric and electronic properties of the triazole ligands. In a pilot study, Schweinfurth and co-workers prepared the triazole-linked push–pull system **19**, as well as the **pyta** analogue **20a** and its regioisomers **20b** and **20c** (Fig. 16) [152]. Compounds **20a** and **c** had much better metallochromic properties than that of **20b**; this was ascribed to the more favorable relative position of the nitrogen atoms. When the pyridyl group was replaced by a phenyl group, the triazole unit in **19** was shown to function as a metal-ligating entity, but the metal-cation-induced changes in absorption were much smaller than those of **20**.

The initial examination of the metallochromic properties of **19** and **20** was followed up by a study focused on the synthesis of ligands **21a–d**, which resembled the structure of **20a**. Using these ligands, it was possible to prepare a library of Pt^{2+} and Pd^{2+} complexes, demonstrating their feasibility for use in coordination chemistry and catalysis [153]. Yano and co-workers used ligand **21c** for the synthesis of a Rh^+ complex [154]. This complex showed enhanced luminescence intensity and lifetime, which indicated a possible application of **pyta**–metal complexes as luminescence probes in time-gated imaging. Crowley

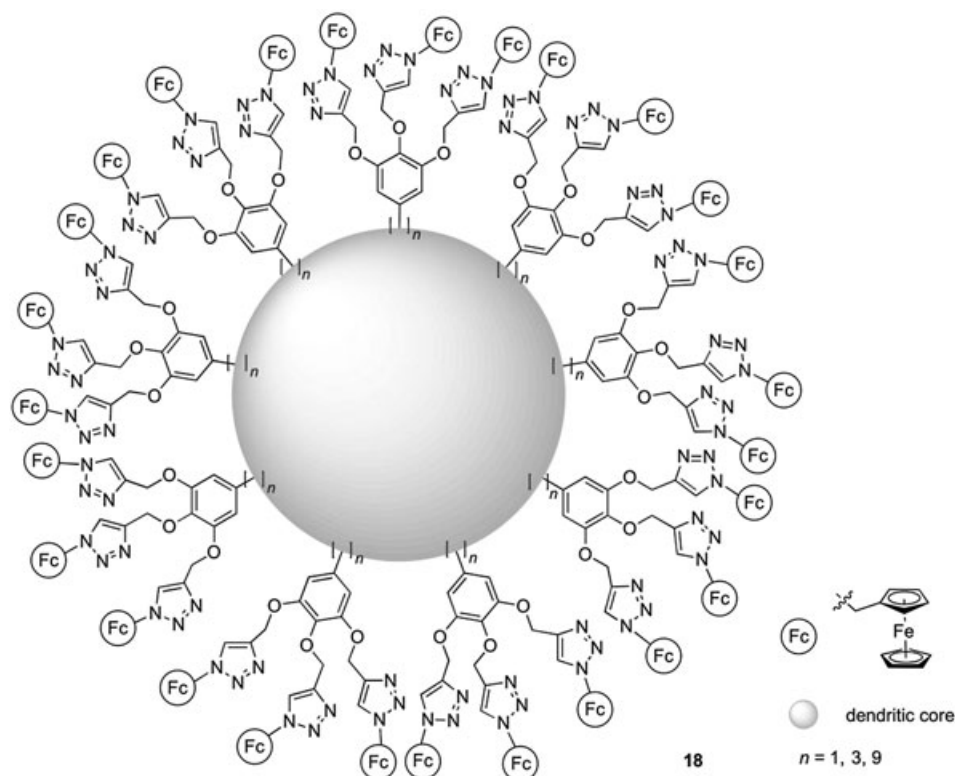
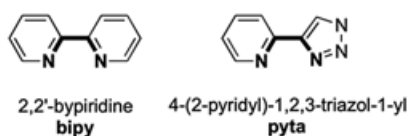
Figure 14. Structure of the polyferrocenyl dendrimers **18**.

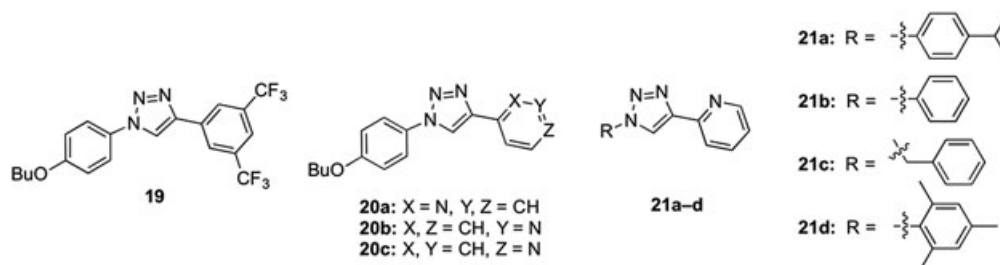
Figure 15. Structure of 2-pyridyl triazole and 2,2'-bipyridine.

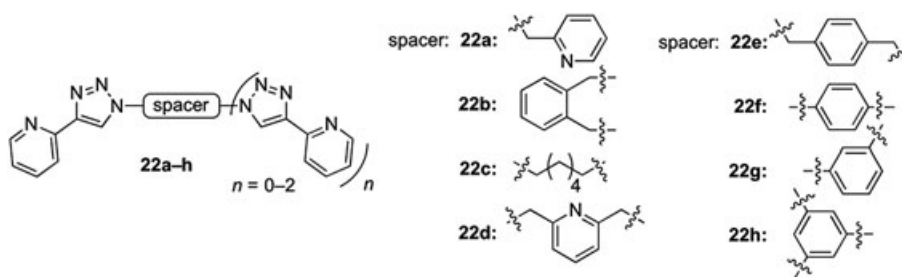
and co-workers prepared a library of multi-functional **pyta**-based ligands as building blocks for metallocsupramolecular architectures (Fig. 17). The presence of multiple binding sites that were able to coordinate Ag^+ ions allowed the formation of both discrete monomeric and supramolecular polymeric structures [155].

A study of the Pd^{2+} complexes of similar **pyta**-based ligands indicated that the formation and stability of the Pd^{2+} complexes was essentially unaffected by the

electronic and steric properties of the **pyta** peripheral substituents [117,156]. This provides the possibility of using this family of ligands to generate novel Pd^{2+} and Pt^{2+} complexes for use as catalysts.

In the Rowan group, a series of luminescent **pyta**- Ir^{3+} complexes were prepared, and their electronic properties were studied [157]. Only limited electronic interactions were observed between the Ir^{3+} centers of these multi-chromophoric systems. These observations confirmed that conjugation in the heteroaromatic backbone did not extend through the sp^3 -hybridized nitrogen atom of the triazole ring. The modular synthesis reported by Rowan and co-workers, together with the fact that each part of the system retained its individual optical properties, provided a convenient route toward covalently linked tuneable chromophoric systems.

Figure 16. Structures of the **pyta** ligands **19**–**21**.

Figure 17. Structures of **pyta** ligands **22a–h**.

A comparative study of **bipy**, **pyta**, and 1,1'-disubstituted 4,4'-bis(triazoles) (**bita**) as bidentate ligands for the formation of Ru^{2+} complexes was conducted by Fletcher and co-workers (**21b**, **23**, **24a–b**; Fig. 18) [158].

The **pyta** and **bita** ligands were shown to form stable Ru^{2+} coordination complexes, analogous to their **bipy** counterpart. The optoelectronic properties of these complexes appeared to be sensitive to the chelator identity, in which the HOMO–LUMO energy gap of the octahedral Ru^{2+} complexes increased as the number of triazole rings increased. The coordinatively symmetrical **bita** complexes were found to be largely optically transparent and non-fluorescent. In addition to the synthesis of similar Ru^{2+} complexes, Monkowius and co-workers used these synthetically available chelators for the preparation of Cu^+ and Re^+ complexes [159]. The formation of stable complexes was reported, and similarly to the Ru^{2+} complexes, they were found to be non-fluorescent, making them suitable for use as spectator ligands.

Multi-dentate triazole ligands. Two of the most widely used structural motifs in the design of multi-dentate triazole ligands are the tris(2-pyridylmethyl)amine (**tpa**) and **terpy** ligands (Fig. 19) [160].

Fokin and co-workers reported the first example of a click analogue of the **tpa** ligand [161]. During early mechanistic investigations of certain polyvalent CuAAC substrates, they serendipitously discovered that their reaction rates were unusually high and that these reactions appeared to be autocatalytic. The ligands appear to tightly bind to Cu^+ , thereby stabilizing this oxidation state of the metal, as confirmed by cyclic voltammetry. From the various ligands tested, a **tpa** analogue, tris (benzyltriazolylmethyl)amine (**tbta**), clearly stood apart. Its tetradentate binding cavity was able to completely envelope the Cu^+ center [162]. Recently, a *tert*-butyl analogue of **tbta** (**ttta**) displayed even better catalytic activity than that of **tbta** [32,163]. Because of the poor solubility of **tbta** in aqueous media, more polar analogues of this ligand were prepared (**thpta**, **25a**, and **25b**; Fig. 19) [136,164]. The catalytic applications of these will be discussed in more detail in the Triazoles as Ligands in Catalytic Reactions section.

Because of the outstanding chelating properties of the **tpa**-type ligands, they have found applications in various metal-sensing systems. Ingale and Seela reported pyrene-functionalized compound **26**, which displayed ratiometric selectivity for Zn^{2+} ions (**26**– Zn^{2+} 1:1) [165]. The

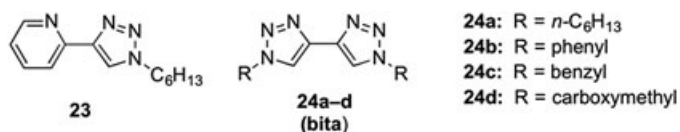
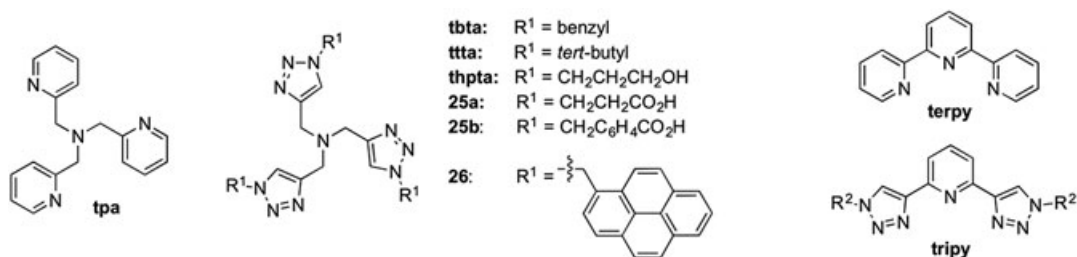
Figure 18. Structures of bidentate ligands **23** and **24a–d**.

Figure 19. Multi-dentate pyridine and triazole ligands.

observed 80-fold increase of fluorescence intensity upon the addition of 10 equivalents of Zn^{2+} was attributed to the spatial separation of the pyrene units; thus preventing the π - π stacking interactions necessary for excimer emission. Zhu and co-workers prepared compounds **27a** and **27b** functionalized with anthracene units (Fig. 20) [166]. These probes showed a fluorescent enhancement in response to Cd^{2+} and Zn^{2+} . Compound **27b**, without the methylene spacer between the triazole and anthracene unit, showed a greater fluorescent enhancement and a redshifted emission maximum compared with compound **27a**. The coumarine-functionalized analogue **27c** was prepared by Davidson and co-workers [167]. Similarly to **27a** and **27b**, a strong affinity toward Zn^{2+} was observed, and the complex was therefore used for the visualization of free Zn^{2+} ion distribution in live HeLa cells. The boron dipyrromethene (BODIPY) derivative **27d** was prepared by Lippard and Rosenthal [168]. The Cu^{2+} complex of **27d** was found to be a selective sensor for nitroxyl in aqueous solution. The sensor takes advantage of paramagnetic fluorescence quenching by Cu^{2+} . Upon exposure to an excess of nitroxyl, Cu^{2+} is reduced to Cu^+ , which is reflected by a fourfold increase in fluorescence intensity, whereas no response is recorded for various other reactive nitrogen and oxygen species. Compound **27d** was also shown to be cell permeable, allowing the sensing of nitroxyl in HeLa cells.

Ng and co-workers functionalized the BODIPY molecule with a pair of bis(triazolylmethyl)anilines to generate **28** (Fig. 20) [169]. Reaction of **28** with Cu^{2+} or Hg^{2+} ions resulted in 2:1 metal/fluorophore complexes. In these constructs, each bis(triazolylmethyl)aniline arm is presumed to bind one metal ion. Binding results in a color change of the solution, as well as fluorescence enhancement, each of which is unique, depending on the metal that is complexed. Similarly, Wu Vedamalai synthesized the functionalized BODIPY dyes **29** and **30**

[170,171]. In the presence of Hg^{2+} ions, these non-fluorescent probes become emissive and exhibit a color change. The fluorescence response is selective for Hg^{2+} ions (1:1 binding ratio) and is observed even in the presence of other metals, such as Cu^{2+} and Zn^{2+} ions. Compound **29** was also used to image Hg^{2+} ions in live cells.

The **terpy** analogue **tripy** (2,6-bis(1,2,3-triazol-4-yl)pyridine, Fig. 19) was shown to form stable transition-metal complexes with Fe^{2+} , Ru^{2+} , and Eu^{3+} ions [172]. For the Fe^{2+} and Ru^{2+} cations, a greater distortion from octahedral geometry was observed in the case of the less curved **tripy** ligands than that for complexes formed from the **terpy** ligands. Meudtner and co-workers utilized the formation of these Fe^{2+} and Eu^{3+} complexes in the synthesis of metal-responsive scaffolds based on **tripy**, which readily changed their conformation upon the addition of metal ions (see **11**, Fig. 5) [104]. Schubert and co-workers focused on the study of Ru^{2+} complexes using **tripy** derivatives as ligands for use in dye-sensitized solar cells. When compared with the analogous **terpy** ligand complexes, they showed lower extinction coefficients and longer excited-state lifetimes. The authors demonstrated ways to increase the extinction coefficients; this underlies the versatility of these ligands [173]. With the same aim, a series of photoredoxactive coordination polymers was prepared (Fig. 21) [174]. These have shown good solubility and film-forming properties, which, together with their optoelectronic properties, suggest their potential utilization in printable photovoltaic devices.

Govindaraju and Maity reported two Al^{3+} -selective fluorescent sensors, **31a** and **31b**, incorporating **terpy**-like binding sites and containing dansyl and coumarin fluorophores, respectively (Fig. 22) [175,176]. Both sensors showed a large increase in fluorescence emission upon exposure to Al^{3+} , accompanied with a significant

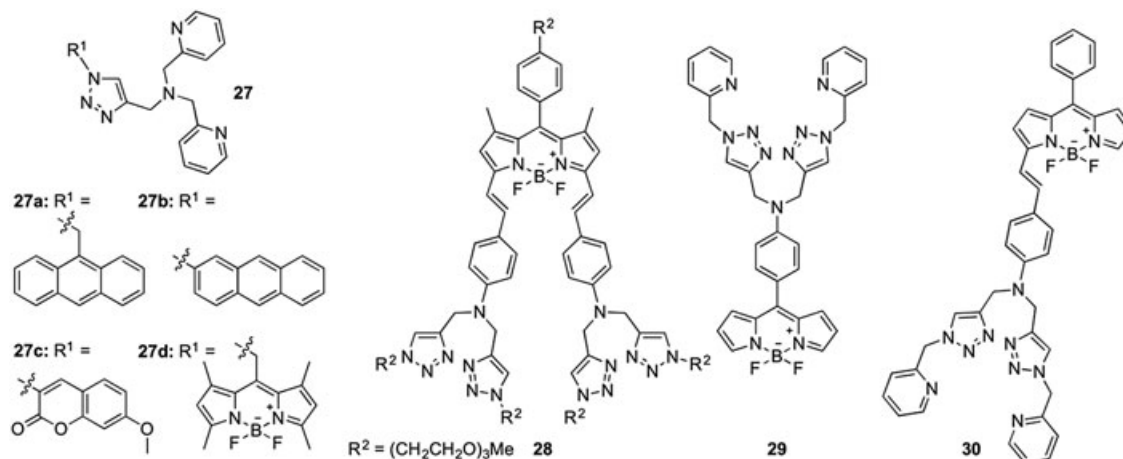


Figure 20. The **tpa**-like metal sensors.

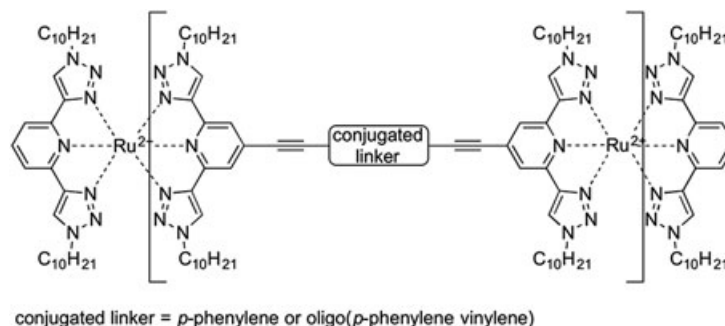
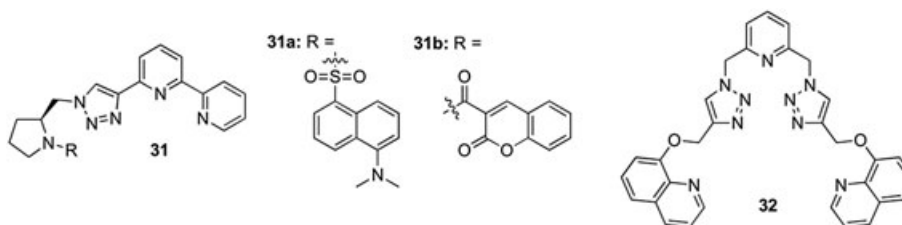


Figure 21. Structure of coordination metallopolymers.

Figure 22. Structures of **terpy**-like metal ligands and sensors.

blueshift in the case of **31a**. The fluorescent response is, however, completely quenched upon the addition of competing metal ions, such as Cu^{2+} and In^{3+} . These ions form non-fluorescent complexes in the presence of **31a** and **31b**. ^1H NMR spectroscopic experiments indicate that the pyridine, triazole, and fluorophore heteroatoms all contribute to Al^{3+} binding.

The tridentate fluorescent probe **32**, functionalized with hydroxyquinoline moieties, showed a response to several metal ions [177]. Fluorescence was enhanced by Cd^{2+} and, to a greater extent, Zn^{2+} ions, whereas it was quenched by Fe^{2+} , Cu^{2+} , Ni^{2+} , and Al^{3+} ions. A 1:2 binding stoichiometry of compound **32** to Zn^{2+} ions was observed. Moreover, the zinc-induced fluorescence enhancement persisted in the presence of other metals, underlining the selectivity of this sensor.

TRIAZOLES AS LIGANDS IN CATALYTIC REACTIONS

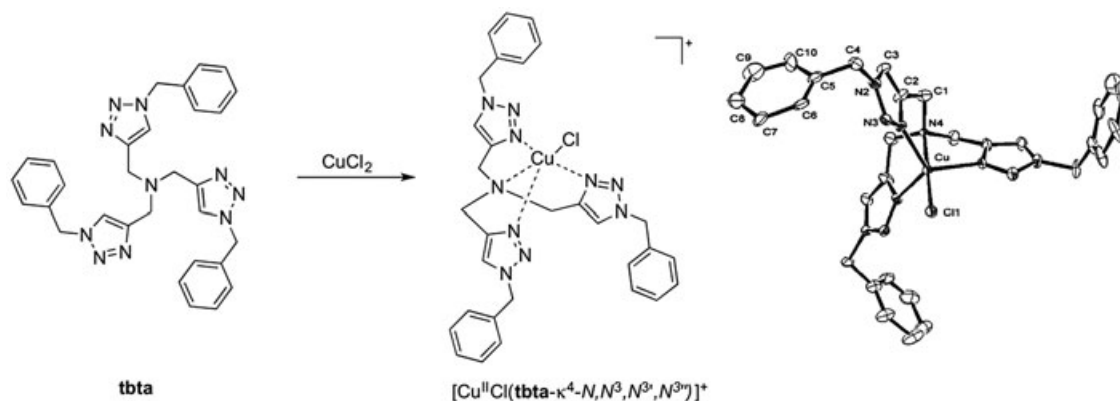
As suggested from the sensory and metal-binding studies summarized in the previous section, the triazole-derived chelators are a rather versatile ligand group [7,34] with the potential of being used as part of catalytically active metal complexes [13]. Their ease of functionalization allows for the synthesis of water-soluble complexes with predictable electronic properties and the potential to be built into functional supramolecular

architectures. The most interesting applications of triazole-based ligands in catalytic systems are discussed in the next section.

Triazoles as ligands in click reaction catalysts. The **tbta** ligands and their analogues (Fig. 19), described by Fokin and co-workers, were found to greatly enhance the rate of the copper-mediated click reaction [161] because of the formation of a protective capsule surrounding the copper species (Scheme 8) [114]. In the presence of a reducing agent, such as sodium ascorbate, the Cu^{2+} complex is converted into an active Cu^+ catalyst, with the central tertiary amine being permanently coordinated throughout the catalytic process. The pendant triazole groups transiently dissociate from the metal center to allow the formation of a Cu^+ -acetylide, which is crucial for the catalytic cycle. Because the copper center is enveloped by the nitrogen ligands, no free binding sites are available for potential destabilizing interactions, for example, with oxygen, making the **tbta** ligand suitable for bioconjugation click reactions [178].

As discussed in the Multi-dentate Triazole Ligands section, several **tbta** analogues have been reported recently that showed an increase in both their catalytic activity and solubility in polar solvents, such as water [32,136,164]. Nanoparticle-supported tris(triazolyl)- Cu^+ complexes were described by Astruc and co-workers [179]. They were reported to have outstanding catalytic properties and to be easily separable from the reaction mixtures and re-used without a significant loss of

Scheme 8. Formation of the Cu^{2+} complex of **tbta**. An ORTEP representation of the $[\text{Cu}^{\text{II}}\text{Cl}(\text{tbta-}\kappa^4\text{-}N,N^3,N^3',N^3'')^+]$ complex with ellipsoids at the 20% probability level. (Reprinted with permission from Ref. [114]. Copyright 2008 The Royal Society of Chemistry).



catalytic activity, owing to the solid-support character of these catalysts.

Triazoles as ligands in catalysts for cross-coupling reactions. The development of metal-catalyzed cross-coupling reactions over the past 30 years has revolutionized the way in which carbon–carbon bonds between sp - and sp^2 -hybridized carbon atoms are formed. These methods have profoundly changed the protocols for the construction of natural products, building blocks for supramolecular chemistry and self-assembly, organic materials and polymers, and lead compounds for use in medicinal chemistry [180]. The importance of this type of reaction was also recognized in 2010 by the Royal Swedish Academy of Sciences, who awarded the Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki “*for palladium-catalysed cross-couplings in organic synthesis*” [181]. The constant development and refinement of the catalysts used for these reactions are

ongoing. Lately, several examples of triazole derivatives serving as ligands in the catalysts for cross-coupling reactions have emerged.

As outlined in the Triazoles in Multivalent Systems section, Astruc and co-workers designed and prepared a series of polytriazole dendritic compounds [148,182,183]. These were found to effectively bind various metal ions within their dendritic structure. The sulfonated analogues of dendrimers, shown in Fig. 14, were applied in the stabilization of palladium nanoparticles (PdNPs) and used as catalysts for the Suzuki–Miyaura coupling reaction in aqueous media [184]. The dendrimer-stabilized palladium nanoparticles showed remarkably high turnover numbers (TONs) and turnover frequencies, giving nearly quantitative yields at minimal (0.01 mol%) catalyst loading (Scheme 9).

In a later modification, the same type of dendrimer (**33**) was functionalized with hydrophilic triethylene glycol (TEG) tails (Fig. 23) [185]. This new type of dendrimer

Scheme 9. Suzuki–Miyaura coupling catalyzed by PdNPs.

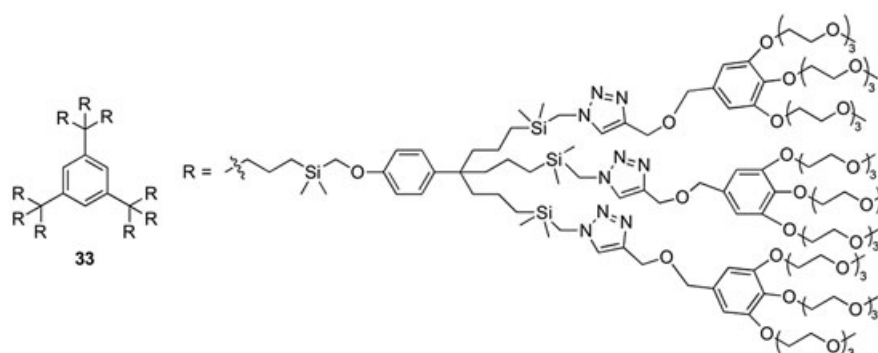
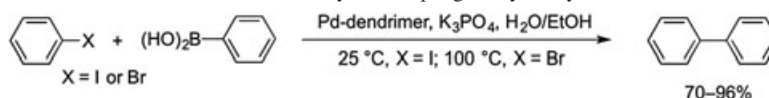


Figure 23. TEG-functionalized triazole dendrimer **33** for PdNP stabilization.

was also able to stabilize PdNPs, and the formed catalysts remained stable for several months. The catalytic activity of these PdNPs was reported to be exceptionally high with bromoarenes (>90% yield), reaching TONs that were equal to or larger than 10^6 . Such exceptional values were not reached with the PdNPs stabilized with ferrocene [186,187] or sulfonate groups reported earlier [184].

The positive synergic effect of the stabilizing triazoles and TEG groups was examined further using oligomers **34** and polymers **35**, which were both able to coordinate to palladium (Fig. 24) [188]. Interestingly, the TEG units in **34** led only to the formation of PdNP aggregates, and oligomers **34** were not a sufficiently efficient stabilizer to provide active PdNPs. This was not the case for polymer **35**, which was found to provide active PdNPs and could be attributed to the fact that several polymer molecules of **35** could envelop the PdNPs.

The prepared PdNPs were tested as catalysts for the Suzuki–Miyaura reaction. The combination of triazole rings and oligo(ethylene glycols) resulted in excellent activity in catalyzing the reaction of bromoarenes and aryl boronic acids in EtOH/H₂O (1:1) with a very low catalyst loading (0.001–0.1 mol%). A comparison between triazole-containing dendrimer **33** and polymer **35** showed that the polymer resulted in higher turnover frequency values because of freer access of the PdNP than that in the dendrimer, whereas the better-shielded

interior of the dendrimer offered higher TONs than those with the polymer because of better PdNP stabilization. In a later approach, the dendrimers used by Astruc's group were combined with the widely used **pyta** ligands (Fig. 15). By reacting palladium acetate with these ligands, various mono- and polymetallic palladium complexes were synthesized (**36**, Scheme 10) [189].

The solubility of the nona-**pyta** complexes decreased with an increasing number of complexed metal ions. The complexes at various stages of metal complexation ($n = 3, 4, 9$) could be separated, which allowed for the isolation of soluble tri-metallic, less soluble tetra-metallic, and insoluble nona-metallic complexes. This new group of palladium complexes was shown to be excellent as homo- or heterogeneous catalysts for the Suzuki–Miyaura, Sonogashira, and Heck reactions of haloarenes. The nona-metallic complex of **36** was an efficient heterogeneous catalyst that could be recycled at least 10 times without significant loss of its catalytic activity.

Verma and co-workers designed and prepared a robust *N,N*-type bidentate ligand based on benzotriazole (**37**) for the catalysis of various cross-coupling reactions, such as the Suzuki–Miyaura, Heck, Fujiwara–Moritani, and Sonogashira reactions (Scheme 11) [190].

The electron-donating ability of ligand **37** is enhanced relative to that of **pyta** because of the additional fused benzene ring. The ligand was found to be inexpensive, thermally stable, and easy to synthesize from easily

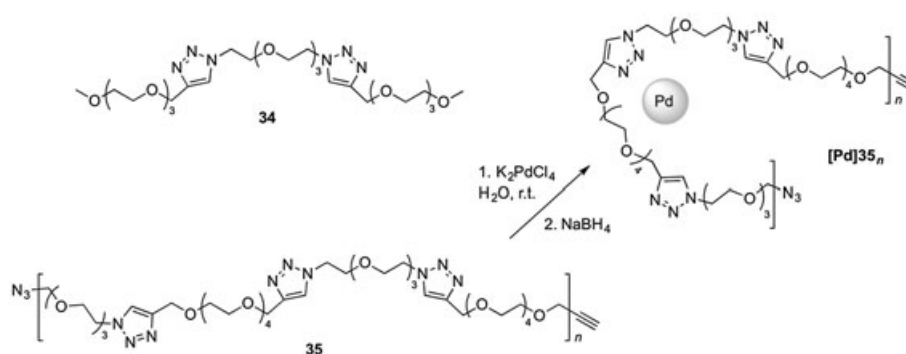
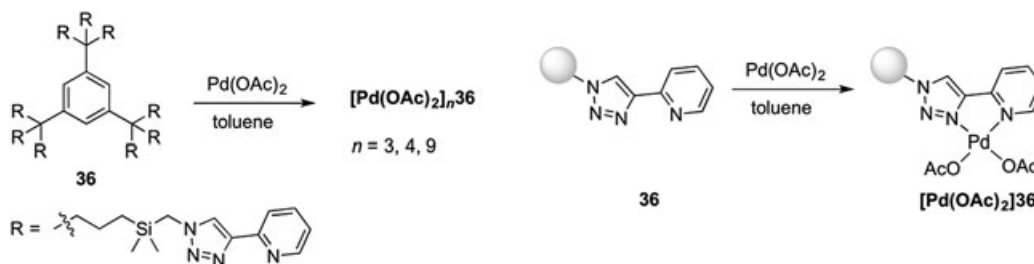
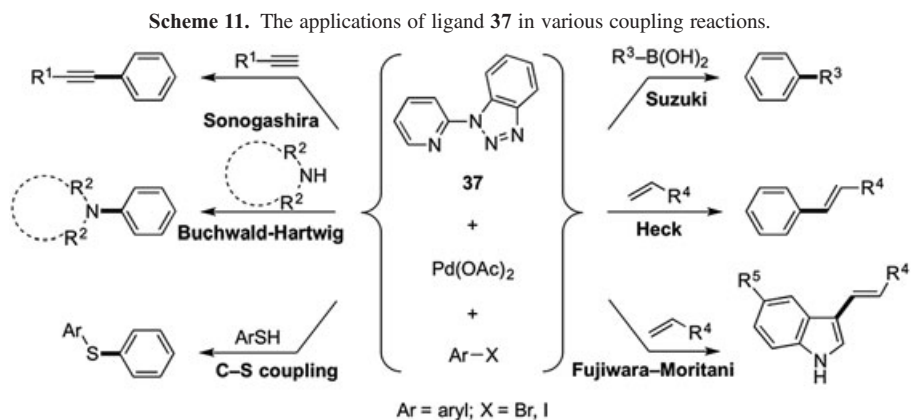


Figure 24. Polymer-stabilized PdNPs.

Scheme 10. Formation of the **pyta**-dendrimer catalysts.





accessible starting materials on a multi-gram scale and showed robustness in application. It was also found to be effective in a variety of coupling reactions.

Scrivanti and co-workers prepared and tested ligand **38**, which was designed in such a way that metal complexation could proceed only through the N2 nitrogen atom of triazole, which formed a weaker metal–nitrogen bond than that of the N3 nitrogen atom (Fig. 25) [191]. This feature was expected to have a positive effect on the attack of the boronic acid at the metal center during the transmetallation step of the Suzuki–Miyaura coupling. Preliminary results from the **38**–palladium complex as a catalyst for Suzuki–Miyaura coupling showed, however, only moderate yields with various aryl bromides.

Yi and co-workers prepared a fluoroalkylated triazole ligand **39** [192]. Upon complexation with Pd^{2+} , the ligand was used as a catalyst for the Suzuki–Miyaura reaction, providing very good yields when catalyzing reactions with aryl bromides (>82%) as well as aryl chlorides (46–89%). Moreover, owing to the perfluorinated alkyl substituent, it could be easily recovered by fluorous solid-phase extraction with excellent purity and reused with only a slight decrease in activity.

Zhang and co-workers reported an additional example of ligands used for catalysis of Suzuki–Miyaura reaction when they combined triazole moieties with phosphines [193,194]. They prepared a series of triazole-based monophosphine ligands (ClickPhos, **40**), for which the associated palladium complexes were demonstrated to be effective catalysts in the coupling reactions of inactivated aryl chlorides with high yields (86–99%).

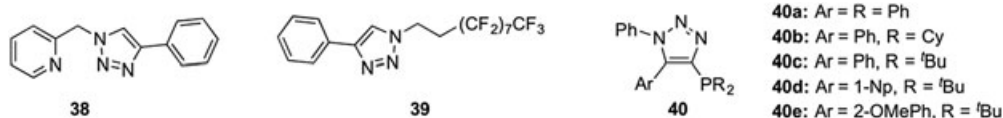


Figure 25. Various ligands used for palladium catalysis.

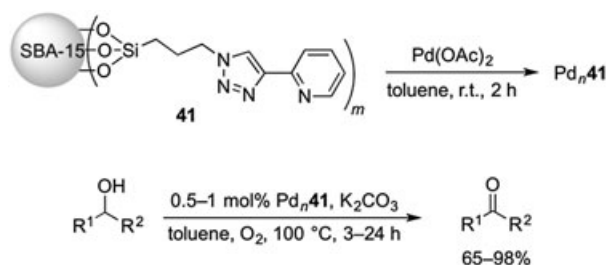
Triazole-based ligands for oxidation/reduction catalysis.

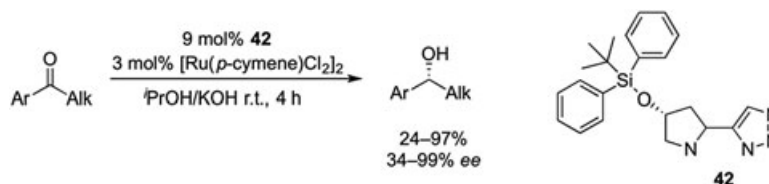
An important class of synthetic reactions are the oxidation and reduction reactions. They are widely used in the chemical and food industry, and triazole ligands provide a convenient route toward the synthesis of custom-made catalysts. Solid-support catalysts are especially desirable for heterogeneous catalysis because they allow for easy catalyst separation and recycling.

The SBA-15 (ordered mesoporous silica)-supported catalyst **41**, containing a triazole unit, was reported by Ding and co-workers (Scheme 12). The **pyta** unit acted as both a stable linker and a good chelator and was applied as a ligand in the palladium-catalyzed aerobic oxidation of benzyl alcohols.

Pericàs and Cambeiro reported the synthesis and use of proline-derived aminotriazole ligands, such as **42**, for homogenous ruthenium-catalyzed hydrogenation reactions (Scheme 13) [195]. From the ligands prepared, compound **42**, equipped with a bulky diphenyl *tert*-butyl siloxane substituent group, showed the best catalytic activity and enantioselectivity.

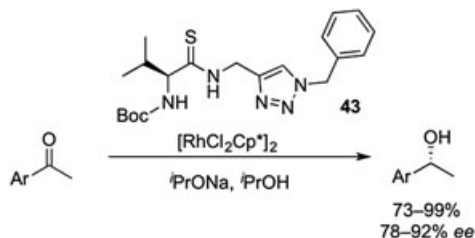
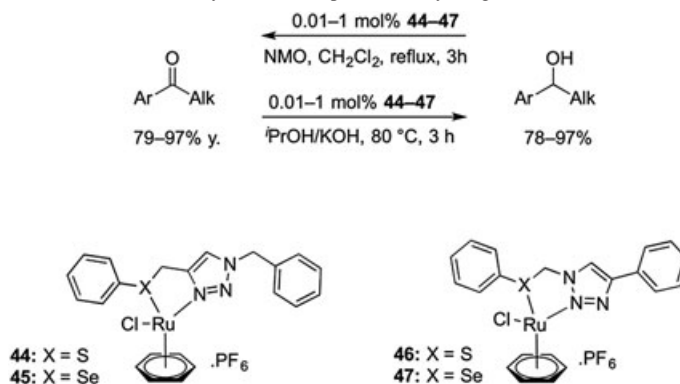
Scheme 12. Palladium-catalyzed oxidation of alcohols using ligand **41**.



Scheme 13. Catalyzed hydrogenation reaction using a Ru-complex with ligand **42**.

Similarly, Adolfsson and Tinnis prepared a series of amino acid derived ligands for the enantioselective reduction of ketones (**43**, Scheme 14) [196]. The catalytic activity and enantioselectivity of the *in situ* formed rhodium complexes was, in general, very good. Although the typical amount of catalyst used in hydrogenation reactions is 0.5–1 mol%, and going below this amount usually results in unproductive conversions, in some cases the required catalytic loading of **43** is only 0.1 mol%.

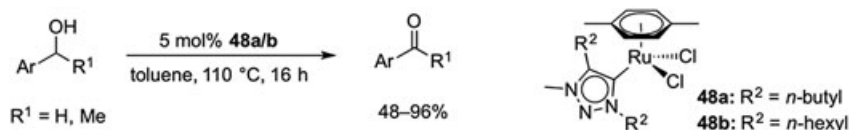
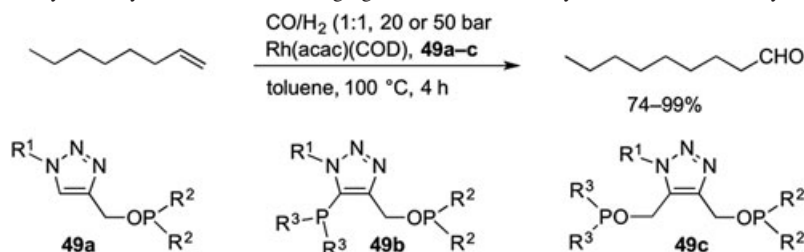
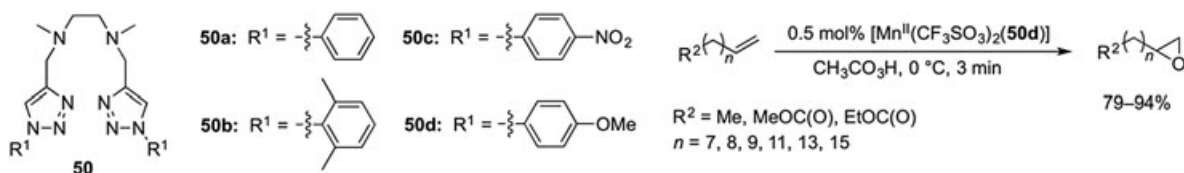
Singh and co-workers prepared a series of ruthenium catalysts (**44–47**), which they used for the oxidation of primary and secondary alcohols (in the presence of *N*-methylmorpholine *N*-oxide) and for the hydrogenation of ketones (Scheme 15) [197]. The catalysts, in which the N2 atom is bound to ruthenium (**46**, **47**), were shown to be more efficient than those involving N3–metal coordination. This could be attributed to the weaker N2–metal bond, compared with that in the N3-coordinated analogues.

Scheme 14. Reduction reaction using the thioamide–triazole ligand **43**.**Scheme 15.** Catalytic reactions performed by Singh and co-workers.

Albrecht and Canseco-Gonzalez reported the synthesis of ruthenium triazolydene complexes for base-free alcohol oxidation (Scheme 16) [198]. Catalysts **48a** and **48b** showed the best activity of those screened, and oxidation of various primary and secondary benzylic alcohols provided the corresponding aldehydes and ketones in good to excellent yields. Furthermore, omitting the base is very appealing from an atom-efficiency perspective and allows for wider functional-group tolerance. In the same group, similar triazolydene–iridium complexes were shown to be very efficient in the catalytic oxidation of water, producing O_2 [199].

The combination of phosphites and triazole ligands has received much attention in rhodium catalysis. Mono- and bidentate triazole-based phosphite ligands (**49a–c**) were prepared by Börner and co-workers and applied to the rhodium-catalyzed hydroformylation of 1-octene. The *in situ* formed catalyst provided high conversions and *n*-regioselectivities (Scheme 17) [200].

Wang and co-workers recently reported an efficient method for the synthesis of triazole-based tetradentate ligands (**50a–d**, Scheme 18) [201]. The triazole unit of these ligands offers an elegant alternative to pyridyl-based ligands and can easily be used for further functionalization. Their Mn^{2+} complexes were used in the epoxidation of various terminal aliphatic olefins with peracetic acid as an oxidant and showed short reaction times and good catalytic activities.

Scheme 16. Oxidation of alcohols catalyzed by **48a** and **b**.**Scheme 17.** Hydroformylation of 1-octene using ligands **49a–c**. acac, acetylacetonate; COD, 1,5-cyclooctadiene.**Scheme 18.** Structures of ligands **50a–d** and their use in catalytic oxidation reactions.

CONCLUSION

For more than a decade, the triazole moiety has become one of the most widely used structural elements in the toolbox of synthetic chemists. The broad scope and use of triazole-functionalized structures has also created the need for alternative methods toward its synthesis, such as the copper-free SPAAC reaction, which is especially useful in biologically relevant applications. Moreover, during the last few years, triazole has been shown to be more than just a structural element; it has presented itself as a versatile functional group with diverse binding properties for a range of sensing applications. The favorable metal-binding properties and variety of coordination modes have made it possible for triazoles to be employed as a coordination site in various catalytic systems. The similarity to and relationship with imidazole and imidazolium ligands provide a plethora of possibilities in catalysis by both transition-metal complexes and nanoparticles that will continue to grow at a fast rate in the future.

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