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Review

The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction and its applications. An overview

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ABSTRACT

A short overview of the copper(I)-catalyzed azide alkyne cycloaddition (CuAAC), the most used "click" reaction, is presented, including the introduction of the "click" concept, the conditions of copper(I) catalysis, the regioselectivity, the nature of the catalysts and ligands, mechanistic features, experimental conditions and applications to organic synthesis and organic materials.

1. Introduction

In 2001, Kolb, Finn and Sharpless defined the very useful and "green" concept of a "click" reaction, with the aim of binding two molecular building blocks together in a facile, selective, high-yield reaction under mild water-tolerant conditions with little or no by-products [1]. The most used "click" reaction that can fulfill these conditions is by far the Cu^{I}-catalyzed azide/alkyne cycloaddition (CuAAC). Other "click" reactions are the thiol-ene, oxime, Diels-Alder, Michael addition and pyridyl sulfide reactions [1,2]. In 2002, the research groups of Fokin and Sharpless [3] and of Meldal et al. [4] have independently reported the efficient Cu^{I} catalysis of the

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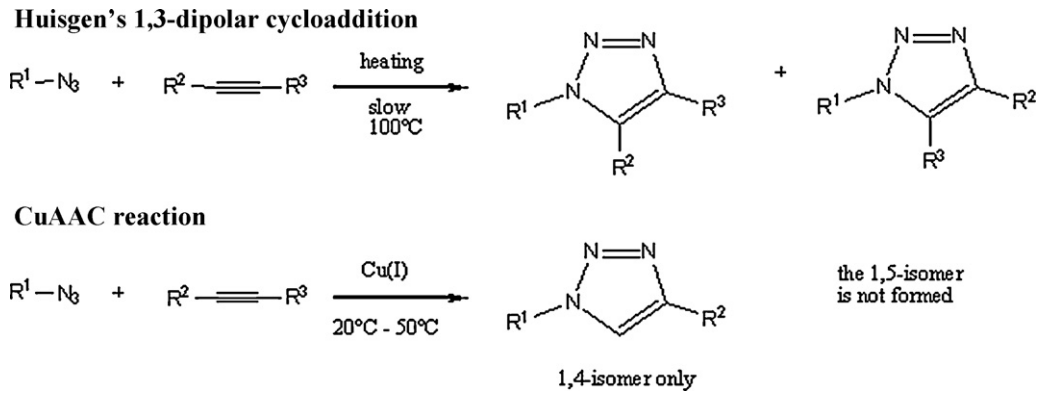


Scheme 1.

azide/alkyne cycloaddition. The non-catalyzed azide/alkyne reaction has been known since 1893 when A. Michael reported the first synthesis of 1,2,3-triazoles from diethyl acetylenedicarboxylate and phenyl azide. It is known as the Huisgen reaction following Huisgen's studies of the family of 1,3-dipolar cycloaddition reaction in the middle of the 20th century [5]. The Huisgen reaction produces a mixture of 1,4 and 1,5-disubstitution products; whereas, the CuAAC reaction of terminal alkynes is completely selective in the formation of the 1,4-disubstituted triazoles (Scheme 1) with a variety of Cu^{I} catalysts or precursors of Cu^{I} catalysts [3,4].

Thus, the CuAAC reaction has become very popular as a "click" reaction, and more than 1000 research articles including many reviews [6–24] have been published on CuAAC since the Meldal and Fokin–Sharpless publications of 2002. The reasons for its success are that this "click" reaction is so easy to carry out and widely applicable. Indeed, it is unaffected by a variety of functional groups and can be achieved with many sources of Cu^{I} catalysts and solvents, including aqueous. By completely changing the mechanism, the Cu^{I} catalysts easily overcome the activation barrier that is high in the non-catalyzed Huisgen reaction (for instance 105 kJ Mol^{-1} for the reaction between methylazide and propyne [25]). In 2005, the group of Fokin and Sharpless also reported the formation of the 1,5-disubstituted triazole isomer from azides and terminal alkynes upon catalysis by ruthenium cyclopentadienyl complexes (RuAAC reaction) [26]. Other less efficient catalysts include Ni^{2+} [27], Pd^{2+} [28], Pt^{2+} [28] and Au^{I} [29]. So far, applications in organic and materials' syntheses are essentially concerned with the CuAAC reaction that is briefly reviewed.

2. The Cu^{I} catalysts and pre-catalysts

A large variety of copper catalysts can be used for the CuAAC reaction provided that some Cu^{I} species is generated [3,4,6–9]. It is essential to keep the Cu^{I} concentration at its maximum in order to facilitate the reaction. The pre-catalyst can be a Cu^{II} salt (usually $CuSO_4$) together with a reducing agent (usually sodium ascorbate), a Cu^{I} compound (preferably CuBr or CuOAc), together with a base or amine ligand and a reducing agent (sodium ascorbate) in order to inhibit aerobic oxidation to Cu^{II}, or a Cu^{0} compound (wire, turnings, powder, or nanoparticles) [30,31], the surface of which forms the required Cu^{I} species. Some cupric salts or complexes such as $Cu(OAc)_2$ without added reductant also work as pre-catalysts, because they are strong oxidants that are reduced to catalytically active Cu^{I} species by alkynes, as for instance in the well-known Glaser coupling [5,7–10,33]. The solvent is very flexible from organic to aqueous, which is remarkable. The most common conditions are those reported by the Fokin and Sharpless group in 2002 using $CuSO_4$ and 10 equiv. sodium ascorbate in an aqueous solvent such as water + an alcohol (*t*-BuOH, MeOH or EtOH) in order to solubilize the substrate and retain the favorable aqueous medium (only 2 equiv. sodium ascorbate are generally used). These aqueous conditions are very useful for biochemical conjugations as well as for organic syntheses. The recent review by Meldal and Tornøe *inter alia* comprehensively lists the various catalysts and conditions used for the CuAAC reaction. Catalysis in water of the CuAAC reaction between the water-soluble substrates azidopropanol and propargyl alcohol using 8% Cu *per* substrates has very recently been shown to proceed with >95% conversion in 1–3 h using Cu^{I}/Cu^{0} loaded in polyamidoamine (PAMAM) dendrimers PAMAM-OH and PAMAM-NH_2 with Cu:ligand ratio of 1:1 and 30:1, respectively [34,36].

3. Accelerating polyligands

Although ligands are usually not necessary to carry out the CuAAC reaction, they can enhance the reaction rate [5–10]. Under ambient condition, for instance, the CuAAC reaction rate is low if the catalyst is not present in high concentration, which is a problem for bioconjugation. The most used ligands are polydentate nitrogen donors, but amine ligands provide faster reaction rates than pyridines [28]. Tris(triazolyl)methyl amine ligands with various substituents have been reported by the Fokin, Finn and Sharpless groups including water-soluble derivatives and proved useful in the case of bioconjugation (Chart 1) [37–42]. Matyajeswski's group has compared the accelerating effect of various polyamine ligands and found that tetradentates such as tren provided less acceleration (for instance, the rate constant is 50 times larger with CuBr in the presence of tren than with CuBr alone) compared to triamines (250 times) [10,28]. Saturation of the Cu^{I} coordination sphere may indeed be an obstacle, even if the ligands are somewhat labile, for the optimization of substrate coordination and activation. Other efficient ligands include PPh_3 and carboxylates. For instance, Lal and Gonzalez recently reported that commercial $[CuBr(PPh_3)_3]$ is active at room temperature with 5% Cu, yielding > 95% triazole from phenylacetylene and benzylazide in various solvents (water/*t*-BuOH, water or neat) in less than 2 h [43]. Care must be taken with PPh_3, however, because the Staudinger reaction of PPh_3 destroys the azide component by reduction of the azide to the amine; thus this catalyst should not be used in stoichiometric amounts. The group of Wang and Hu reported that benzoic acid was a valuable additive in 10-fold excess (0.1 equiv.) vs. $CuSO_4{\cdot}5H_2O$ (0.01 equiv) with sodium ascorbate (0.02 equiv.) in *t*-BuOH/H_2O yielding 98% product for the same reaction at room temperature after 4 min [44]. Cu_2O (0.1 equiv.) in water was found to catalyze the same reaction at room temperature in 15 min with 91% yield [45].

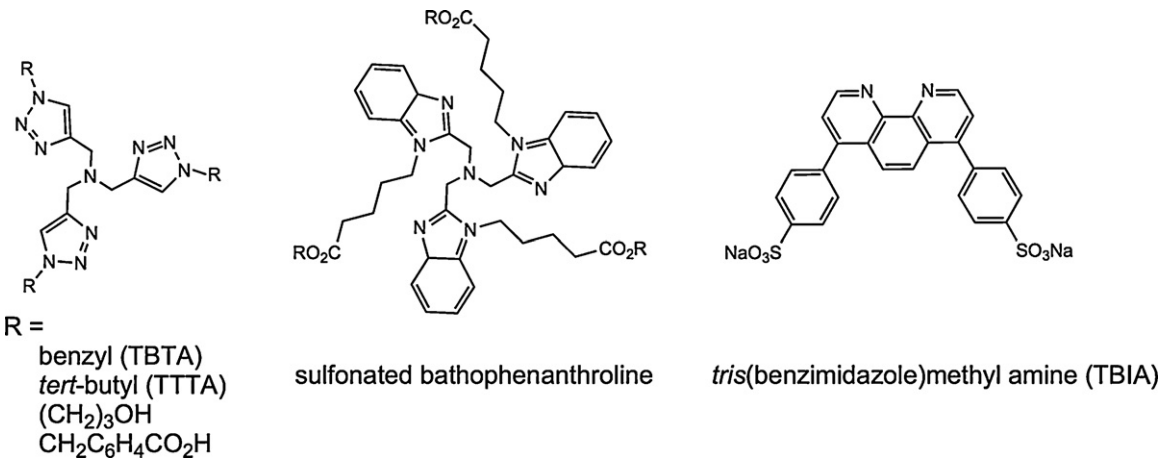


Chart 1. Most efficient polydentate nitrogen donors for the CuAAC reaction.

4. Mechanism

The Script group has investigated the mechanism of the CuAAC reaction using kinetic studies and DFT calculations [8,9,46,47]. Alkyne coordination was estimated to lower its pK_a by 9.8 pH units, which explained deprotonation of the π-alkyne-Cu^I intermediate by water itself in aqueous medium even in the absence of an additional base to form the σ-alkynyl-Cu^I species [47,48]. Kinetic studies indicated that the rate of the reaction was second order in Cu^I at low Cu^I concentration (even with the TBTA ligand) and formation of less reactive copper aggregates at higher concentrations. First a bimetallic mechanism was proposed (Scheme 2) in which the alkynyl was coordinated to one Cu center, whereas the azide attacked a second one [53]. In reinvestigation, another related mechanism was suggested in which the azide attacked the same Cu center bearing the alkynyl ligand (Scheme 3) [8].

A bimetallic structure was also involved in this mechanism, because a π-complexation of the σ-alkynyl-Cu^I species was invoked as enhancing the reactivity of the alkynyl ligand by decreasing electron density on the sp carbon atoms [8,9,47,48]. DFT calculation confirmed that the second Cu^I atom interacted with the Cu^I-acetylide [8,9,47,48]. The azide attack was followed by formation of a Cu^{III} vinylidene metallacycle [8,9]. According to Fokin, tris(triazolyl)methyl amine ligands are labile enough to be easily displaced by substrates and strong enough to avoid the formation of higher unreactive or less reactive Cu^I aggregates. In these conditions, the μ_2-liganded σ–π-alkynyl dicopper transition state, shown in Chart 2, is proposed [9].

5. Alkynes and azide substrates

It is important to note that low molecular-weight azides can be hazardous and dangerous to handle, especially those with several azide functionalities, and thus should never be separated from solvent. These derivatives are best generated in situ by S_N2 reactions from organic halides or arylsulfonates and sodium azide just before the click reaction [9].

Stereoelectronic effects on the substituents have significant influences on the reaction rates, but the CuAAC is fairly general with a broad range of alkynes and azides. Matyjaszewski' s group has examined the influence of the electronic and steric effects on the rate of the reaction and concluded that the fastest reactions were observed for azides with electron-withdrawing and less sterically congested azides [10]. Alkynes with α-carbonyl groups are more reactive than alkylalkynes for the Huisgen reaction. It was pointed out that the solubility of the substrates is a key factor for successful outcome [49]. Let us recall, however, that the non-catalyzed Huisgen reaction between azides and alkynes proceed "on" water even at room temperature with insoluble substrates in the case of simple electron-deficient alkynes such as carboxyethylacetylene, which was reacted with DNA-azide compounds [32,50].

When several azide groups are held in proximity, rate enhancement were disclosed [51,52] and studied mechanistically [53], but in contrast to when several alkynes are held in proximity [51].

Iodoalkynes (obtained from terminal alkynes and *N*-iodomorpholine in the presence of Cu^I) are stable and were recently found to be even more reactive than terminal alkynes in the CuAAC reaction catalyzed by Cu^I with a tris(pyrazolyl)methyl amine ligand, such as TBTA or TTTA, that appears to be essential [54]. In addition, the 5-iodo-1,2,3-triazoles products are amenable to further useful functionalization. Mechanistic proposals by Fokin in the case of the CuAAC reaction with iodoalkynes involve either direct attack of the coordinated azide onto the π-iodoalkyne ligand or Cu-alkynyl formation followed by attack of the coordinated azide and incorporation of the iodo substituent on the triazole product by means of a σ-bond metathesis with the iodoalkyne [5,54].

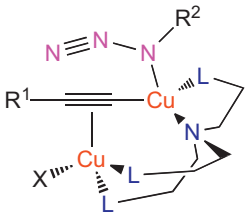
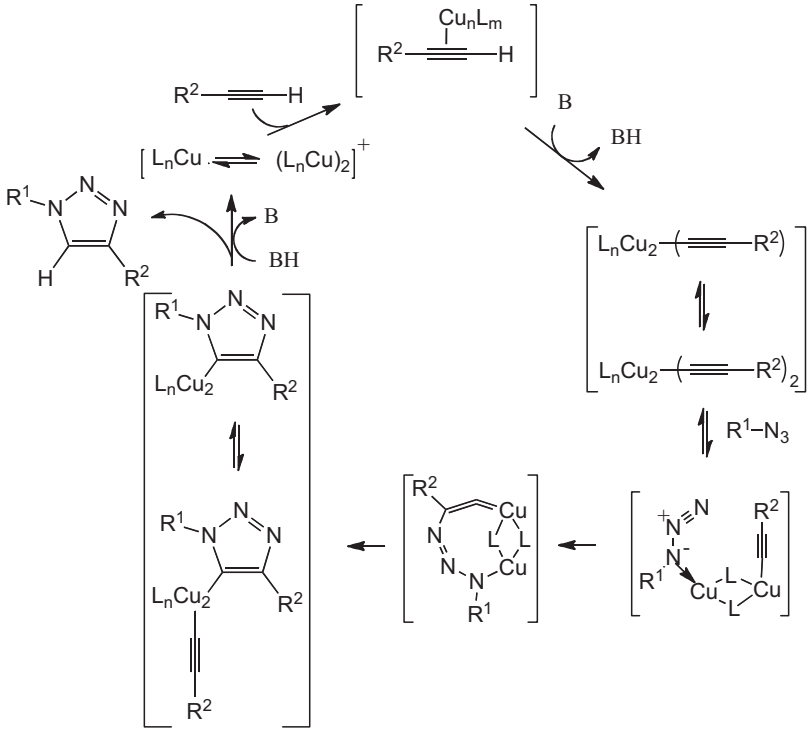


Chart 2. Alkyne-briged bimetallic species proposed by Fokin and Finn as the key active species for the CuAAC reaction with a [Cu^I{tris(triazolylmethyl)amine}] catalyst.

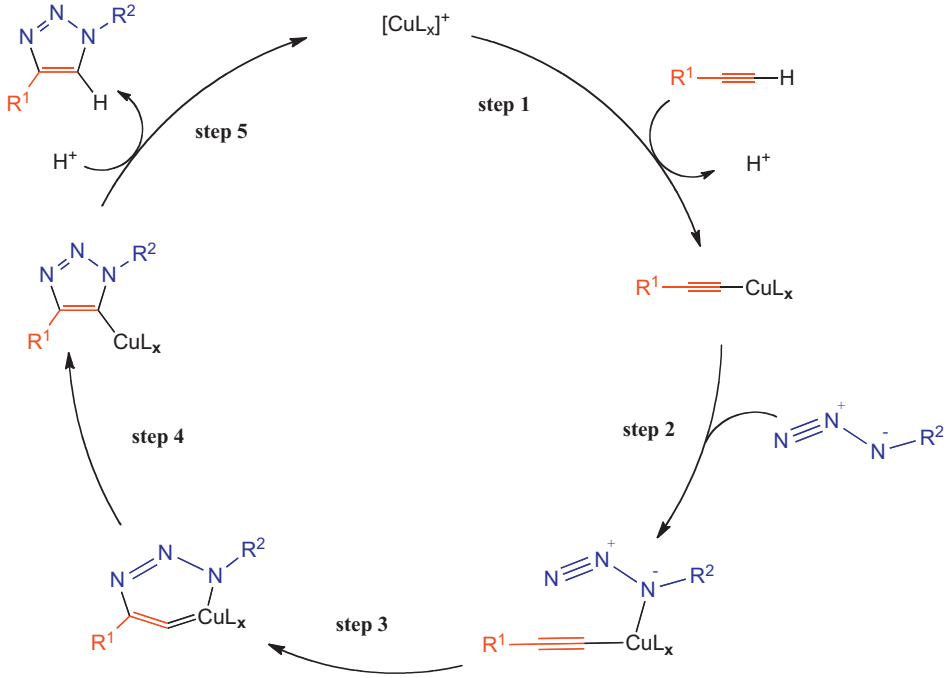
6. Solvents

The variety of solvents used in the CuAAC reaction, is one of the most remarkable features of this reaction. The numerous solvent conditions comprehensively listed in the review by Meldal and Tornøe [4] include non-coordinating solvents such as toluene, chloroform and dichloromethane, weakly coordinating solvents such as THF, pyridine, and dioxane, polar solvents such as acetone, MeCN, DMF, DMSO, alcohols, and aqueous solvents including mixtures of water with an alcohol, acetone, THF, MeCN, DMSO, dioxane, biphasic media mixing water with dichloromethane, and other mixtures of two or even three solvents. The $CuSO_4$ + sodium



Scheme 2. An outline of the proposed catalytic cycle involving a bimetallic mechanism in which an alkynyl ligand binds one metal and the azide to the other metal [53].

ascorbate catalyst and the Cu^0 catalysts were used with a variety of aqueous solvents, whereas Cu^I catalysts used a non-aqueous solvent most of the time. A key role of the solvent or solvent mixture is to solubilize the substrates and Cu^I catalyst in order to insure rapid reactions. Polar solvents favor the heterocycle bond-formation step and the solubility of the substrate and catalysts, but if the solvents are coordinating, they can inhibit or slow down the required metal–substrate coordination. Therefore, DMF is an optimal solvent for the CuBr catalyst without additional ligand. In the presence of polyamine ligands, toluene gives good results, because it provides solubilization of both catalyst and substrates without inhibiting substrate coordination. Along this line, pentane was also excellent with the catalyst $[Cu^I\{tren(C_{18}H_{37})_6\}][Br]$ [55]. Water alone has been used as a medium for click reactions "on" water [45,56]. For instance, dinuclear alkynyl-Cu^I complexes or copper-ladder polymers are catalysts at 0.1% Cu upon microwave



Scheme 3. Fokin and Finn's proposed catalytic cycle for the CuAAC reaction based on DFT calculations. Introduction of a second Cu^I atom favorably influences the energetic profile of the reaction for the key C–N bond-formation step 3 (see Chart 2) [9].

irradiation yielding 72% triazole from propargyl alcohol and benzyl azide [56].

7. Applications of the click CuAAC reaction

7.1. Organic synthesis

The CuAAC reaction has been widely used in organic syntheses including several types of macromolecules (see also Section 7.3). Organic chemists have extended the CuAAC reaction in tandem coupling with other major reactions, such as Pd^0-catalyzed allyl transfer [57], ruthenium-catalyzed olefin metathesis [58], intramolecular $Pd(OAc)_2$-catalyzed Heck reaction [59]. Multiple-sequence reactions were used for instance for the synthesis of large complex spiro compounds involving sequential aldol, Wittig, Knoevenagel, Michael addition, and Diels-Alder reactions followed by the CuAAC reaction [60]. Strategies sometimes involve masking the azide as an amine that is readily converted to the azide by diazo transfer [61]. Triazoles are also synthesized in solid phase. Repetitive solid-phase synthesis was alternated with peptide coupling [62]. In immobilization reactions, amino resins are converted to azido resins by diazo transfer followed by a CuAAC reaction. Alkyne-containing proteins have been immobilized by triazole formation [63]. The peptide functions have been modified with triazoles [64,65]. Triazoles are excellent mimetics of the peptide bonds which can provide efficient inhibitors of key mammalian, bacterial and viral proteases [66]. Natural products and drugs have been modified with triazoles in order to enhance the solubility or bioavailability, to attach a biolabel or a fluorophore, or to diversify the drug structure [7–10]. Although large macrocycles (from 8 to 14 atoms) are extremely difficult to achieve, the CuAAC reaction offers possibilities. The Cu^I transition-state cluster has the ability to coordinate a second alkyne residue, favoring an intramolecular reaction, which was first achieved with an hexapeptide [67]. Likewise, glycopeptides containing three sugar units and terminated by an alkyne and an azido group at their ends cyclize to give a bis-triazole hexa sugar mimicking cyclodextrins (Scheme 4) [68].

The triazole formation is a useful strategy to immobilize catalysts on a solid support [69], to introduce ^{18}F label peptides [70] and nucleic acids [71], and to modify DNA [7]. The triazole link allows to synthesize calixarenes functionalized with carbohydrates [72] and to conjugate tryptophanes for ^{129}Xe binding and NMR monitoring [73]. Triazole formation has been used to syntheses of rotaxanes [74–76]. Triazole formations have been numerous in carbohydrate chemistry. They can modify sugars with organic groups, form clustered entities, bind sugars to biomolecules and allow to mimic glycopeptides and oligosaccharides. Most frequently, the azide group is introduced in the 1-, 2-, or 6-position of the sugar, but propargyl glycoside is also used [7].

7.2. Dendrimers

7.2.1. Dendrimers convergent synthesis: click access to dendrons

The synthesis of dendrimers by CuAAC chemistry has appeared in the middle of last decade and has been reviewed including in reviews of click organic materials synthesis [7–19]. In 2004, Wu et al. reported the convergent synthesis of dendrimers with triazoles at branching points till the 4th generation using AB_2 dendrons containing two alkyne units and a chloride atom at the focal point. After click synthesis, the focal point was transformed into an azide upon reaction with NaN_3, and the next generation was synthesized by reaction with the AB_2 dendron (Scheme 5) [77].

Alternatively, the divergent strategy used an AB_2 monomer containing two hydroxymethyl functionalities and a propargyl ether focal point. After a click reaction with a bis-azide core, the hydroxymethyl groups were transformed into chloromethyl using $SOCl_2$, then azidomethyl before the next click reaction with the AB_2 dendron [78]. A double-stage strategy using $AB_2 + CD_2$ dendrons was a variant for rapid dendrimer construction [79]. Thus, building blocks for dendrimer synthesis by CuAAC are available [80]. Click chemistry was also simply used to click two dendrons via their focal points leading to Janus-type dendrimers with for instance two terminal functionalities [81–91], including with PAMAM dendrons [92,93] or Fréchet-type dendrons [94].

7.2.2. Principle of surface functionalization of dendrimers

The divergent construction can be used to either proceed to the next dendrimer generation by iteration of the reactions or to functionalize the dendrimers, as for instance in Scheme 6. Both reaction types are practically carried out by CuAAC reactions. The peripheral functionalization or "decoration" of dendrimers is extremely useful for applications to many fields [95]. They allow the molecule to carry a large number of molecular fragments of interest for their physical, catalytic or biomedical properties, and this broad area has recently been reviewed [96]. Click reactions are indeed one of the very best methods for this purpose [16,97–110]. A simple example of such click construction is illustrated in Scheme 5, including decoration in Chart 3 [111–113].

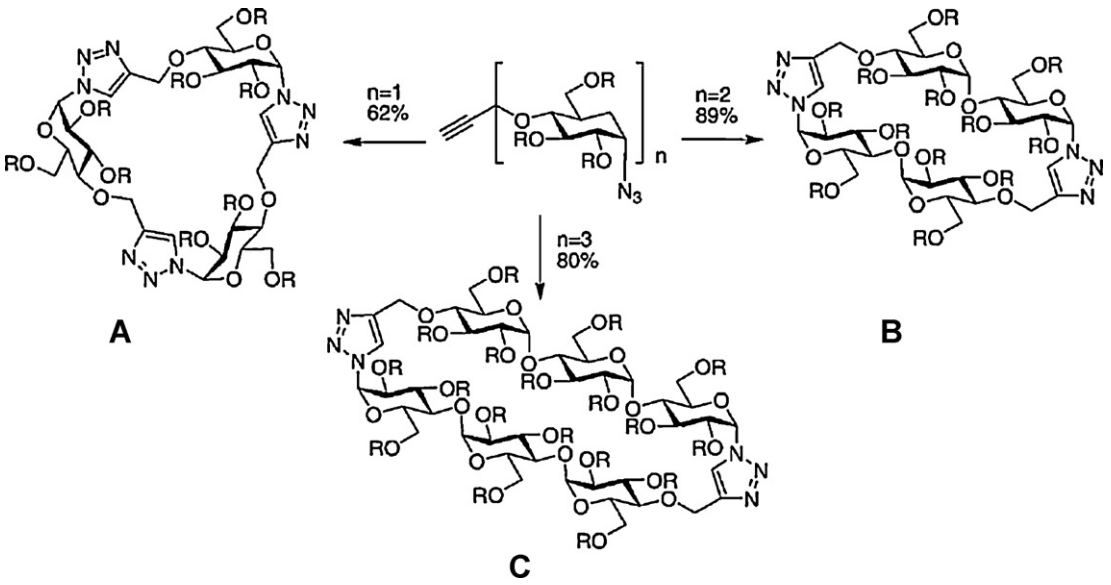
Malkoch et al. used peripheral click functionalization for access to a library of extremities arms and legs [95]. The introduction of biologically active moieties by click chemistry has been exemplified [114,115] including peptide dendrimers [116–120] and glycodendrimers [103,121–126] and examples of bioconjugation are developed in Section 7.3.2 (vide infra).

The introduction of catalysts by click chemistry at the dendrimer periphery has been examined in a few cases [17,95,128]. The Caminade-Majoral group grafted up to 48 alkyne-based azabis(oxazoline) ligands to dendrimer backbones containing azide moieties and showed that catalytic asymmetric benzoylation of a diol did not bind Cu^{II} [127]. Niu et al. used clicked dendrimers for asymmetric borane reduction of prochiral ketones with excellent yields and ee values [128].

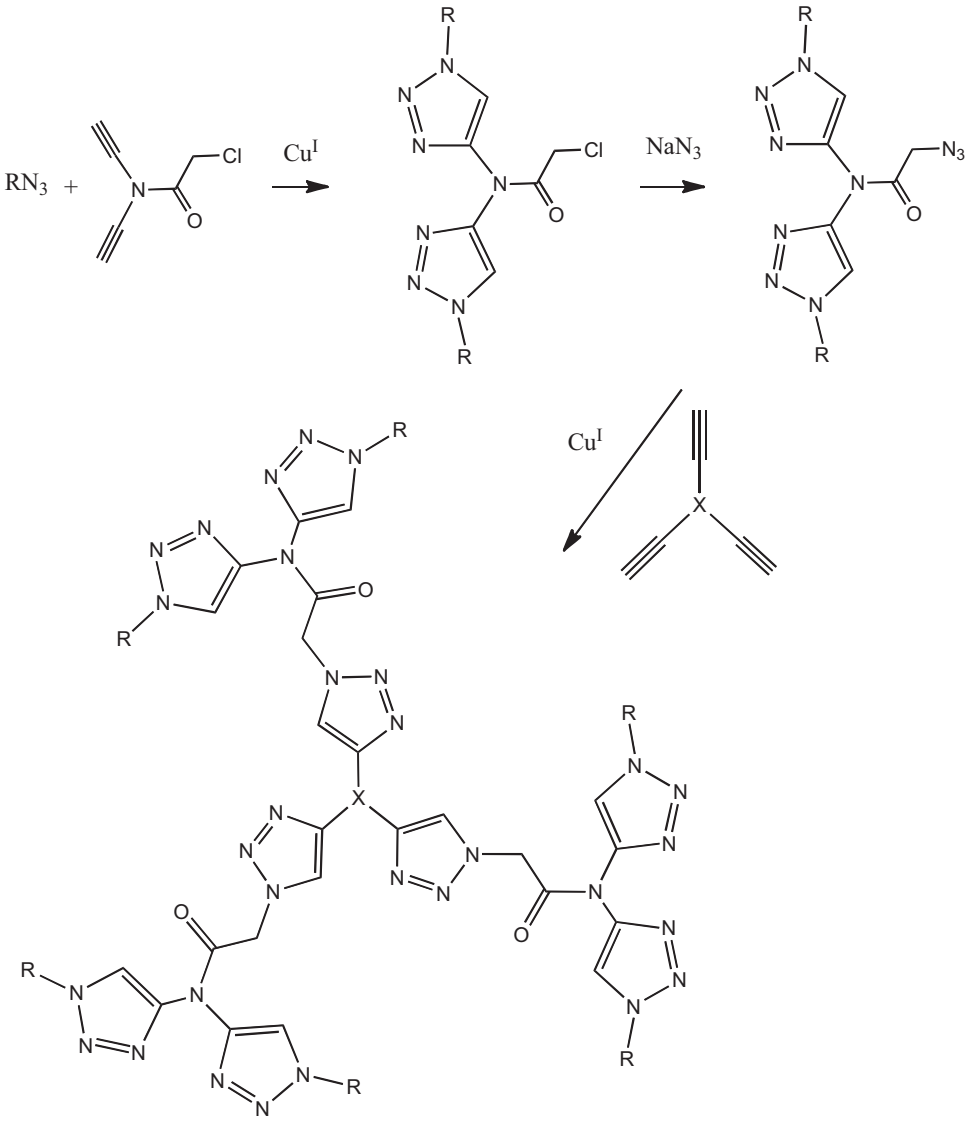
Clicked dendrimers have also been used to introduce a large number of carboranes, the high boron density in nanomaterials being useful for boron neutron cancer therapy (BNCT) [129]. Click chemistry has been used to introduce ferrocenes and cobaltocene capped with cyclodextrins [130]. A new solution processable dendrimer, with carbazole as a hole transporting unit, was efficiently synthesized based on convergent approach by alternation of Cu^I-catalyzed azide/alkyne cycloaddition (CuAAC) reaction and Williamson ether synthesis. The orthogonal chemistry completely avoided protection and activation of the focal points in the process of dendrimer synthesis [131]. A divergent dendrimer construction using CuAAC and furan–maleimide Diels–Alder in a layer-by-layer fashion yielded dendrimers that underwent thermal disassembly via a retro-Diels–Alder reaction [132]. Similarly, dendrimers with 8 and 16 hydroxy end-groups on the periphery have been synthesized using double click reactions involving CuAAC and Diels-Alder cycloaddition in a one-pot [133].

7.2.3. Click dendrimer chemistry for molecular recognition and nanoparticle catalysis

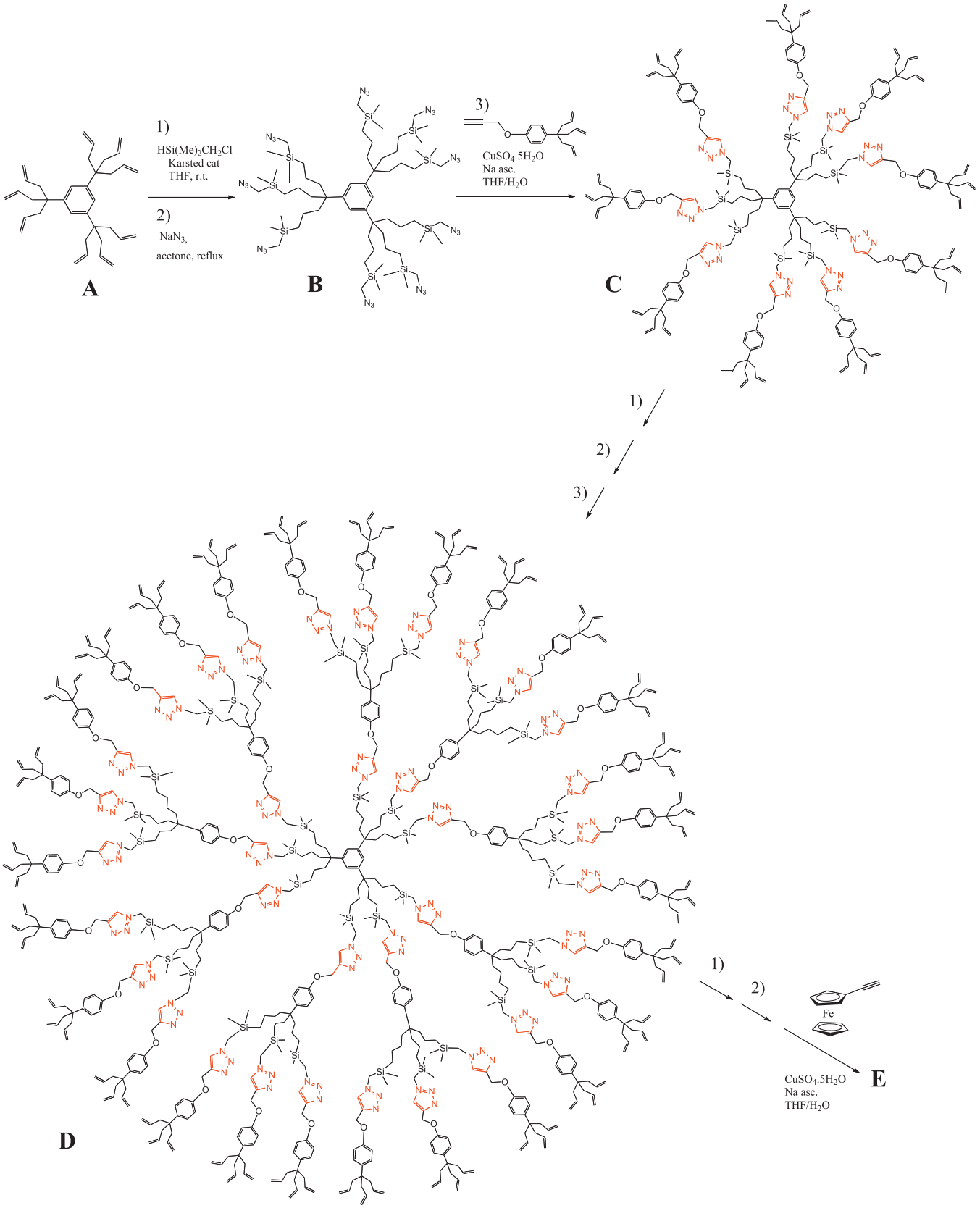
Divergent click dendrimer construction has been used to introduce triazolylferrocene and triazolylbiferrocene groups at the dendrimer periphery [111,134,135]. The ferrocenyl groups around the ferrocenyl-terminated dendrimers are equivalent and recognize late transition-metal cations and ATP^{2-} anion by selective shift of the ferrocenyl wave in cyclic voltammetry resulting from coordination or interaction with the triazolylferrocenyl groups (Fig. 1) [111,134–136].



Scheme 4. Macrocyclization of propargylated azido sugars may be achieved by CuAAC to mimic cyclodextrins. Reprinted with permission of the American Chemical Society (Ref. [7], Medal's group).



Scheme 5. First exploration of a convergent dendrimer synthesis. This strategy was extended to the syntheses of higher-generation dendrimers [77].



Scheme 6. Synthesis of the 27-allyl dendrimer C and 81-allyl dendrimer D by successive CuAAC reactions [111]. The nona-allyl arene precursor A was synthesized by $(\eta^5\text{-}C_5H_5)Fe^+$-induced nona-allylation of mesitylene with KOH and allylbromide [112,113]. See the structure of E in Chart 3 [112].

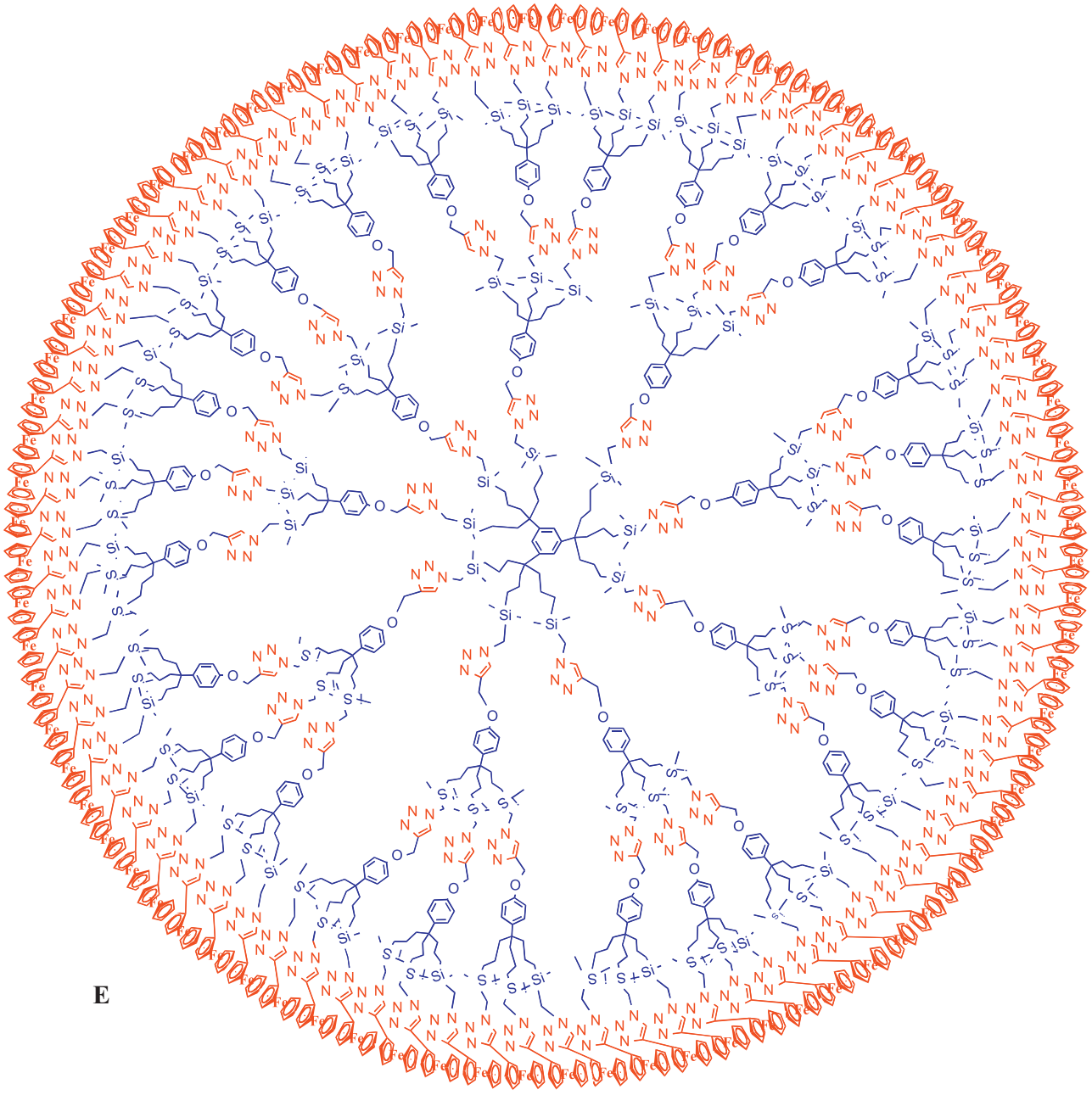


Chart 3. 81-triazolylferrocenyl dendrimer E synthesized by successive CuAAC reactions according to Scheme 5 [111].

Coordination of Pd^{II} to the triazolyl intradendritic ligands followed by reduction to Pd nanoparticles allowed encapsulation of these nanoparticles inside the dendrimer if the dendrimer was large enough or to stabilize the nanoparticles by several dendrimers if the dendrimer was too small (Fig. 2). These tailored nanoparticles have sizes determined by transmission electron microscopy that match the prediction as a function of the number of palladium atoms of the encapsulated nanoparticle. The catalytic activity was investigated for styrene hydrogenation and Miyaura-Suzuki reactions. The results indicated that the hydrogenation catalysis was easier as the nanoparticles were smaller as expected [136]. On the other hand, the results of the cross C–C coupling reaction (under ambient conditions) were approximately invariant with the size and mode of protection of the nanoparticles. In addition, the catalysis worked better as the nanoparticle concentration was lower (homeopathic mechanism). Thus the click dendrimer engineering ended up in a fine evaluation of the Pd-nanoparticle catalysis mechanism [137–139].

Triazolylbiferrocenyl dendrimers allowed differentiation of the outer ferrocenyl groups from the inner ones by cyclic voltammetry. The former was oxidized first to give the mixed-valence dendrimers, and they recognized ATP^{2-}, whereas the latter recognized Pd^{2+} cation due to coordination to the nearby triazolyl groups [134].

Clicked dendrimers decorated with polyethylene glycol termini were also able to stabilize gold nanoparticles of various sizes depending on the solvent and size of the dendrimers [140].

7.3. Polymers

7.3.1. General: click polymers

Since 2004, the polymer field has largely exploited the CuAAC reaction for click polymerizations as well as polymer modification

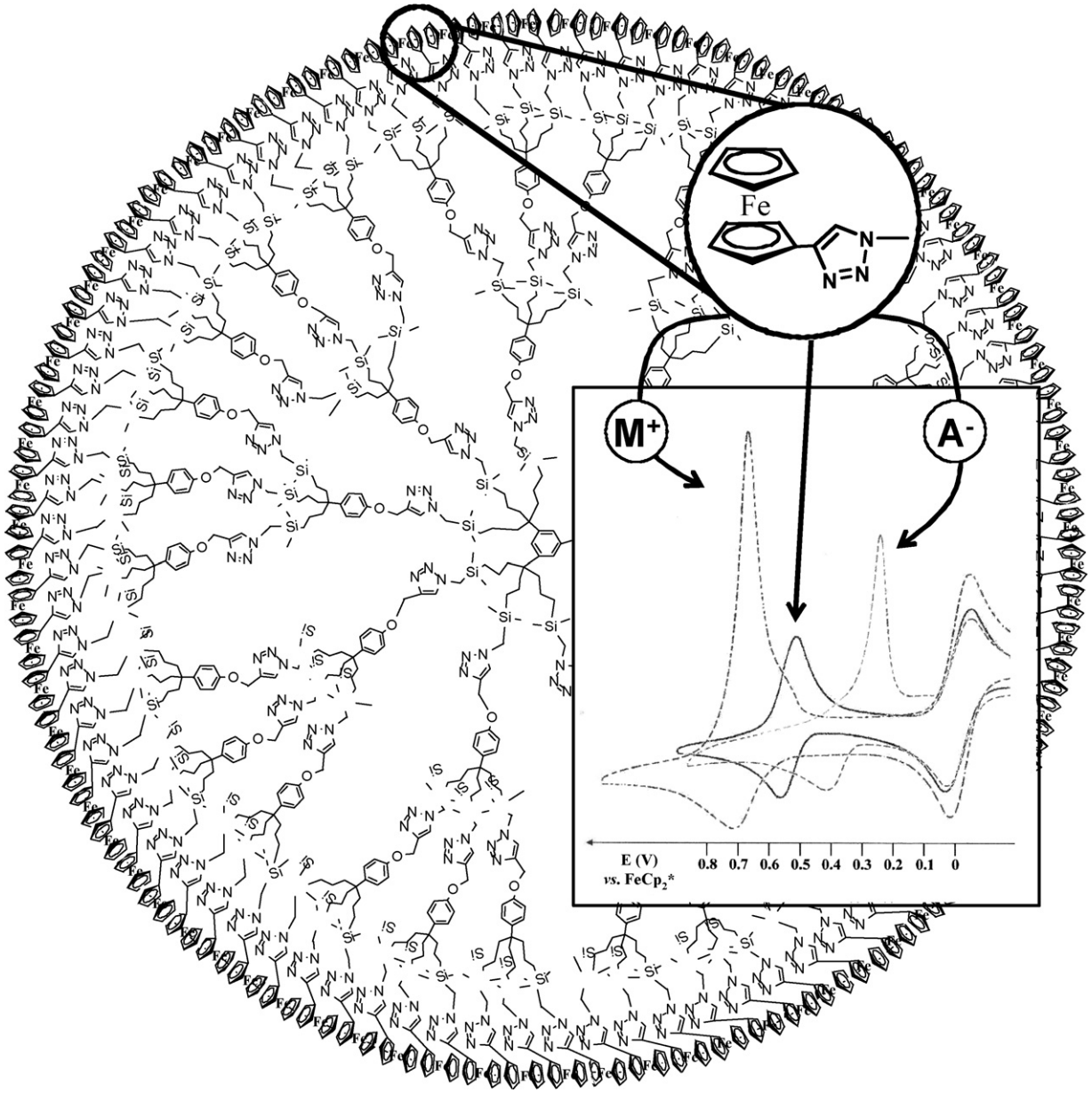


Fig. 1. Redox recognition of transition-metal cations (M^+) and oxo-anions (A^-) upon shift of the ferrocenyl cyclovoltammetry wave in the triazolylferrocenyl-terminated dendrimers.

[10]. Indeed, the CuAAC reaction is solving a number of problems in polymer science due to the ease of this click reaction, in particular, for graft-, star-, block copolymers. The reaction conditions being much more facile with the CuAAC reactions than in other conventional reactions, the materials that are obtained are cleaner and better defined, purification is easier, and incomplete reactions are less frequent. Engineering the functional groups of polymers is an essential issue for the development of soft materials in the fields of health and energy. In this respect, the applications of orthogonal chemistry for the synthesis of various polymer morphologies are increasing at a fast rate [2]. Indeed, linear polymers, including multiblock polymers, cross-linking, and star and graft polymers have been synthesized by CuAAC (Chart 3). Finally, in connecting with dendrimers, dendritic polymers including dendronized polymers and polymers including nanoparticles have greatly benefited from the CuAAC reaction, and these fields are expanding (Fig. 3). Many reviews are available [2,7–18].

7.3.2. Click reactions with dendrimers for bioconjugation in biomacromolecules

In Sections 7.1–7.2.2, the application of the CuAAC reaction to branching sugars, peptides, has been indicated. Bioconjugation of dendrimers using click chemistry is a very promising area that has already been the subject of several recent reviews [20–24,95]. Indeed, the triazole bridge is considered to be biologically stable [141]. Here recent examples of click strategy for such bioconjugation leading to biomacromolecules are provided [142,143].

Dendrimer-based drug delivery platforms were designed. For instance, a biologically active platform containing receptor mediated targeting and fluorescence imaging modules was synthesized by coupling a folic acid (FA) conjugated dendrimer with a fluorescein isothiocyanate (FITC) conjugated dendrimer. The two different dendrimer modules were coupled via CuAAC between an alkyne moiety on the surface of the first dendrimer and an azide moiety on the second dendrimer. Two simplified model systems were

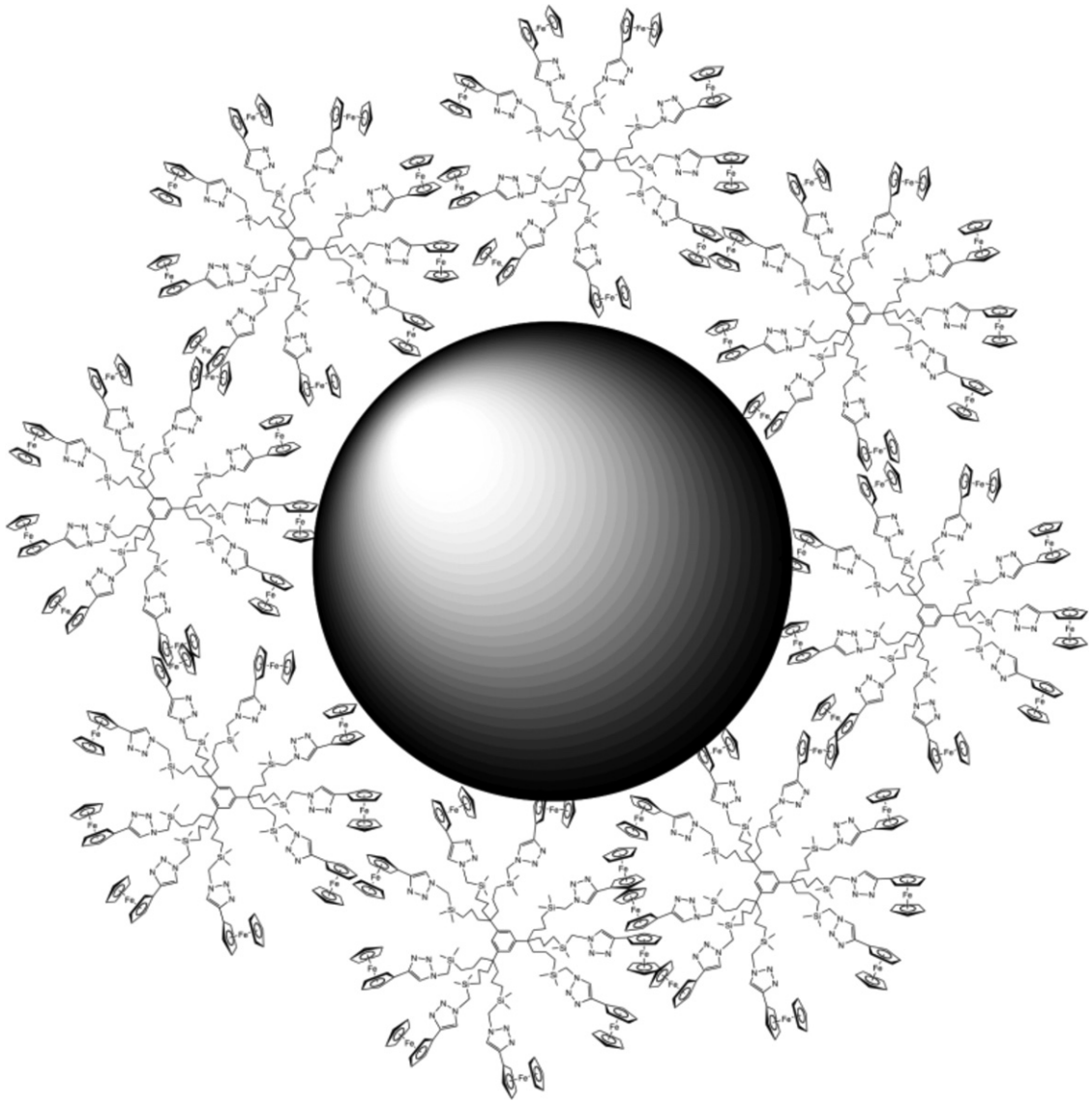


Fig. 2. Pd nanoparticle surrounded and stabilized by several small G_0 nona(triazolylferroce nyl) dendrimers.

also synthesized to develop appropriate CuAAC reaction conditions and aid in spectroscopic assignments. The FA-FITC modular platform was evaluated *in vitro* with a human epithelial cancer cell line (KB) and found to specifically target the overexpressed folic acid receptor [144].

The synthesis of multimodule platforms using both unfunctionalized PAMAM dendrons [145] and unfunctionalized Fréchet-type dendrons has been reported for each of the modules [146]. In these systems, the focal point of the dendron possessed either an azide or alkyne moiety. A 2,2-bis-(hydroxymethyl)propionic acid based asymmetric modular dendron with 16 mannose units and 2 coumarin chromophores has been developed, and binding in a hemagglutination assay has been demonstrated [94]. Poly(amine) dendrimers that possessed a single aldehyde or azide moiety on the dendrimer periphery capable of orthogonal functionalization by small molecule functional groups have been reported [147].

Cationic lipids and polycations including PAMAM dendrimers forming lipoplexes or polyplexes with negatively charged plasmid DNA (pDNA), antisense oligonucleotides (AONs), double stranded RNA (dsRNA) or small interfering RNA (siRNA) are known as non-viral gene vectors [148–153]. Therefore, site-specific conjugation of an epidermal growth factor (EGF)-polyethylene glycol (PEG) chain has been achieved by click chemistry onto a poly(amido amine) (PAMAM) dendron, as a key step toward defined multifunctional carriers for targeted gene delivery. Among the different oligoamine-modified dendrons, PAMAM-pentaethylenehexamine (PEHA) dendron polyplexes displayed the best gene transfer ability. Conjugation of PAMAM-PEHA dendron with PEG spacer was conducted via click reaction, which was performed before amidation with PEHA. The resultant PEG-PAMAM-PEHA copolymer was then coupled with EGF ligand. pDNA transfections in HuH-7 hepatocellular carcinoma cells showed a 10-fold higher efficiency with the polyplexes containing conjugated EGF as compared to the ligand-free ones, demonstrating the concept of ligand targeting [151]. For DNA-templated covalent coupling of PAMAM dendrimers, surface-functionalization with azides or alkynes and conjugation to one DNA strand were carried out. DNA-controlled self-assembly of alternating azide and alkyne dendrimers on a DNA template enabled the coupling of the dendrimers by the azide-alkyne "click" reaction to form covalently coupled dimers, trimers, tetramers and polymers including circular structures imaged by AFM [143,152]. Twenty-two triazolyl tryptoline derivatives were synthesized by linking tryptoline, a core structure of

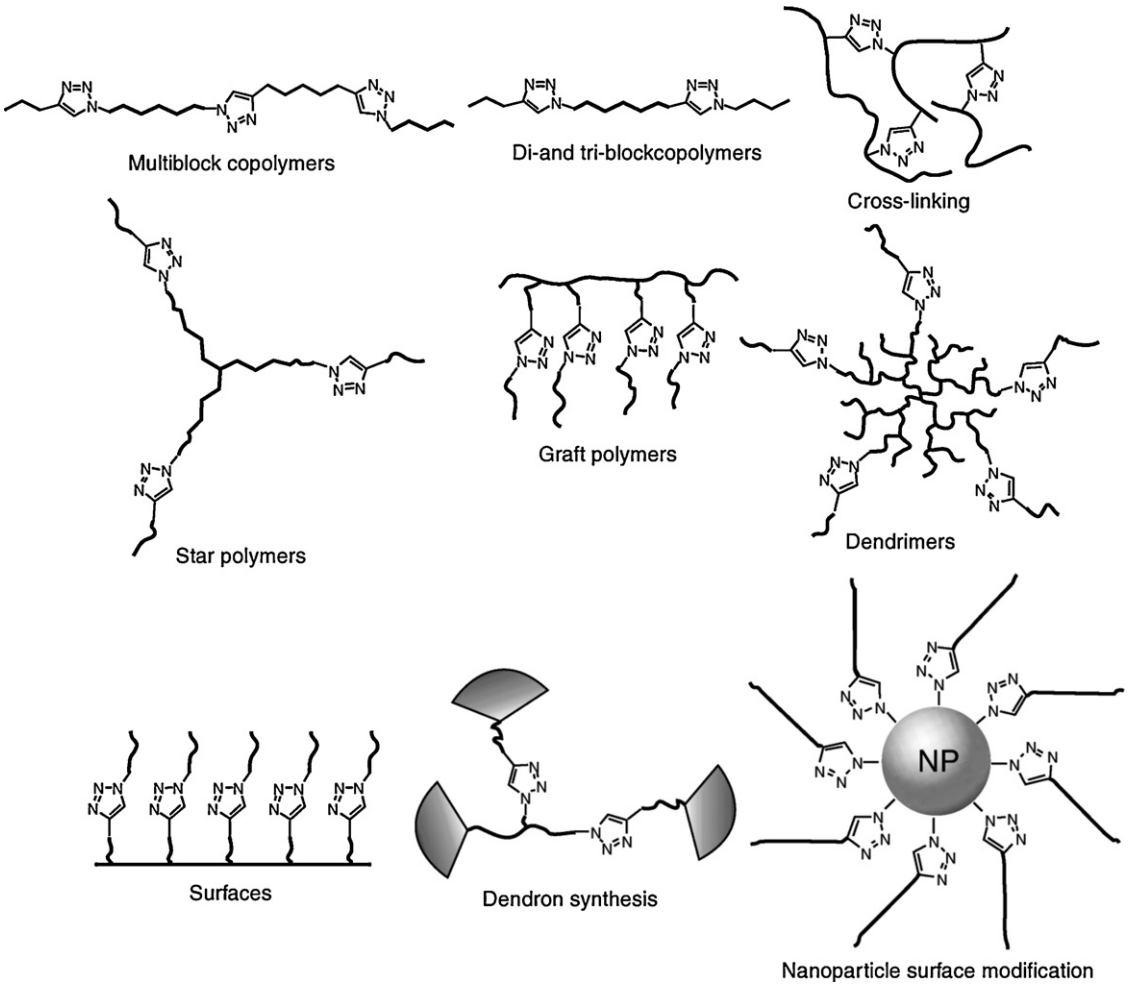


Fig. 3. Variety of macromolecular architectures accessible by CuAAC reactions.
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ochrolifuanine E, to side chains using the CuAAC reaction and screened for the inhibitory action against BACE1 [153].

7.3.3. Dendritic and dendronized click polymers

Dendritic star polymers [154,159–162] are the structural hybrids of the dendrimers and star polymers. They have the common features and properties of both and are the subject of an increasing attention due to their specific physical and chemical properties related to their branching structures and shapes. They show potential applications as stabilizers for colloids, DNA release, electrokinetic capillary chromatography, etc. They can be synthesized using either divergent or convergent methodologies [155,156]. In a divergent strategy, the polymer chains are simultaneously grown from a multifunctional initiator via living polymerization techniques. In the convergent approach, perfect polymer chains with an proper end-group functionality are coupled onto a preformed multifunctional core, but this strategy is marred by steric effect increase, resulting in shortcomings of incomplete grafting and low yields [154]. The combination of dendrons introduced by CuAAC reaction and high-temperature acrylate polymerization represents a viable route to form dendronized macromonomers [161]. A class of well-defined dendritic star polymers with poly(ε-caprolactone) (PCLs) on the periphery has been prepared via one-pot CuAAC and Diels-Alder [4 + 2] cycloaddition reactions [157,158].

Dendronized polymers are molecular cylinders, and they can be visualized by scanning force microscopy (SFM). They have also been patterned on surfaces by SFM [159–162]. There are three main pathways for synthesizing dendronized polymers. The first one is a "graft-to" approach whereby a preformed dendron is coupled to a polymer that contains pendant groups for attachment. This convergent route is marred by incomplete coverage of the backbone using high generation dendrons due to the bulk problem, but the CuAAC overcomes the problem [163].

The second route, the "graft-from" approach, proceeds via a step growth process from the polymer backbone. It provides a way to achieve the maximum degree of dendronization and has been favored [164].

The third route, a macromonomer approach, incorporates dendrons into the monomer. Advantages are that each repeat unit in the polymer has a perfect pendant dendron, and maximum dendronization has been achieved. The disadvantage is that macromonomers with high generation dendrons usually reach only low degrees of polymerization [165–168].

8. Conclusion

Many Cu^{I} sources selectively catalyze the CuAAC reaction, yielding 1,4-disubstituted 1,2,3-triazoles from azides and terminal alkynes under ambient or mild conditions. Although Cu^{I} complexes are clearly the catalytically active species, there are no ideal catalysts, but a large variety of catalytic conditions are suitable. The initial Fokin–Sharpless catalyst $CuSO_4$ + sodium ascorbate in an aqueous medium remains the most practical and most used

catalytic system, although many genuine Cu^{I} molecular catalysts are more reactive. The mechanism of the reaction involved the formation of Cu^{I} acetylide, then of a metallaheterocycle that is further protonated yielding the 1,2,3-triazoles. The reaction is easily carried out under ambient or mild conditions in organic or aqueous solvents and even in water. Applications are considerable and largely expanding in the fields of organic synthesis, polymers, dendrimers, dendritic, and dendronized polymers and biomacromolecules. The copper component may be a problem if traces remain under physiological conditions, but it can be overcome *inter alia* by copper-free strategies [35,169]. One should also be very careful to avoid isolated small azide molecules without solvent, but organic halides are readily converted to azides by reaction with NaN_3 that can react in situ in the CuAAC reactions. This click reaction is also combined with other click reactions or with classic reactions in sequences for sophisticated materials synthesis. The expansion of this area of inorganic, organic, biomaterials and polymer chemistry is considerable.

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