Click Dendrimers and Triazole-Related Aspects: Catalysts, Mechanism, Synthesis, and Functions. A Bridge between Dendritic Architectures and Nanomaterials

DIDIER ASTRUC,* LIYUAN LIANG, AMALIA RAPAKOUSIOU, AND JAIME RUIZ
Institut des Sciences Moléculaires, UMR CNRS No. 5255, Université Bordeaux 1, 33405 Talence Cedex, France
RECEIVED ON SEPTEMBER 9, 2011

CONSPECTUS

One of the primary recent improvements in molecular chemistry is the now decade-old concept of click chemistry. Typically performed as copper-catalyzed azide–alkyne (CuAAC) Huisgen-type 1,3-cycloadditions, this reaction has many applications in biomedicine and materials science. The application of this chemistry in dendrimer synthesis beyond the zeroth generation and in nanoparticle functionalization requires stoichiometric use of the most common click catalyst, CuSO₄·5H₂O with sodium ascorbate.

Efforts to develop milder reaction conditions for these substrates have led to the design of polydentate nitrogen ligands. Along these lines, we have described a new, efficient, practical, and easy-to-synthesize catalytic complex, [Cu I (hexabenzyltren)]Br, 1 [tren = tris(2-aminoethyl)amine], for the synthesis of relatively large dendrimers and functional gold nanoparticles (AuNPs).

This efficient catalyst can be used alone in 0.1% mol amounts for nondendritic click reactions or with the sodium-ascorbate additive, which inhibits aerobic catalyst oxidation. Alternatively, catalytic quantities of the air-stable compounds hexabenzyltren and CuBr added to the click reaction medium can provide analogously satisfactory results. Based on this catalyst as a core, we have also designed and synthesized analogous CuI-centered dendritic catalysts that are much less air-sensitive than 1 and are soluble in organic solvents or in water (depending on the nature of the terminal groups). These multivalent catalysts facilitate efficient click chemistry and exert positive dendritic effects that mimic enzyme activity. We propose a monometallic CuAAC click mechanism for this process.

Although the primary use of click chemistry with dendrimers has been to decorate dendrimers with a large number of molecules for medicinal or materials purposes, we are specifically interested in the formation of intradendritic [1,2,3]-triazole heterocycles that coordinate to transition-metal ions via their nitrogen atoms. We describe applications including molecular recognition of anions and cations and the stabilization of transition metal nanoparticles (AuNPs).

Introduction

The study of dendrimers1–21 is now a broad and crucial supramolecular research field8–11 that has applications inter alia in catalysis,11–14 materials science,11,15,16 and nanomedicine.17–21 Click dendrimers have evolved in 200422 subsequently to Sharpless’ concept of easy and practical
Click Dendrimers and Triazole-Related Aspects

Astruc et al.

assembly of molecular fragments.23 Among the various click reactions,23 the copper-catalyzed azide–alkyne cycloaddition (CuAAC)24 rapidly appeared as the most useful one and will be examined here (Scheme 1). There are indeed myriad ways to synthesize dendrimers,1 but the CuAAC click reaction has recently appeared as one of the most efficient and productive.29–32

Since our initial interest in iterative reactions33 on the way to dendrimers, we have developed dendrimer synthetic pathways that involve the Williamson reaction,34,35 cross olefin metathesis,36 and finally the CuAAC click reaction. The latter was used by either introducing the azido groups at the periphery and the ethynyl group at the focal point of incoming dendrons37 or the converse.38 We will first delineate here the specific problems encountered for the click synthesis of nanosystems that led us to disclose new efficient catalysts including dendritic ones. Then, whereas in the rich click literature the purpose was to assemble useful functional groups, our goal has also been to utilize the inorganic properties of the coordination and supramolecular interactions of the intradendritic [1,2,3]-triazole link. Designed applications are toward control of transition-metal nanoparticle growth and molecular recognition and will also be the subject of this Account.

CuAAC Click Synthesis in Nanoscience: A New, Efficient, and Easily Available Catalyst

The CuAAC click reaction is catalyzed by a large variety of CuI species that can be either generated in situ or directly introduced into the reaction medium.23–32 One of the most important properties of the Sharpless catalyst, CuSO4 + sodium ascorbate, is its simplicity and easy use including in aqueous solvents. Another key property, shared by all the CuI catalysts, is that it yields a single triazole isomer, the 1,4-substituted one, whereas the noncatalyzed Huisgen cycloaddition produces a mixture of 1,4- and 1,5-disubstituted triazoles (Scheme 1).

Finally, catalysis allows one to conduct the reactions under much milder conditions (20–60 °C) than the uncatalyzed reactions, which require temperatures above 100 °C, especially if the alkyne substituent is electron-rich. Indeed this catalyst presently is by far the most used CuAAC catalyst.24 Several research groups have synthesized click dendrimers using this catalyst.29,30 We have found, however, that catalytic amounts of this Sharpless catalyst probing in several solvents and under various temperatures could not lead to completion of the click reaction in the dendrimers.
and that a stoichiometric amount of catalyst was required to obtain a satisfactory result beyond the zeroth dendritic generation.\textsuperscript{37,38} The use of large quantities of toxic copper reagent is not compatible with green conditions required for biomedical use; thus improvements are needed. This problem in dendrimers and other branched nanosystems results from the coordination of the Cu\textsuperscript{1} species to two or several intradendritic triazoles formed in the reactions, blocking further catalysis. The dendrimer topology facilitates this entropy-favored interbranch chelation of Cu\textsuperscript{1} in dendrimers, a problem that is not encountered in nondendritic click syntheses. We also noticed that the click CuAAC functionalization of gold nanoparticles (AuNPs) that were reported in the literature had involved very low reaction yields.\textsuperscript{39} We could improve the click CuAAC functionalization of AuNPs with a variety of alkynes by carrying out the reaction under inert atmosphere, but again a stoichiometric amount of Sharpless catalyst\textsuperscript{40} or even more\textsuperscript{41} was required. Matyjaszewski’s group showed that the Me\textsubscript{6}tren [tren = tris(2-aminoethyl)amine] ligand accelerates the CuI click catalysis by a factor of 50 compared with CuBr.\textsuperscript{42} Subsequently, the pentane-soluble complex Cu[tren(CH\textsubscript{2}Ph)\textsubscript{6}]Br, \textsuperscript{2} was shown to catalyze the click functionalization of a zeroth-generation dendrimer bearing nine azido termini,\textsuperscript{43} but this catalyst was inefficient for the click synthesis of the corresponding first-generation dendrimer because of its bulk.\textsuperscript{44} On the other hand, the new toluene-soluble complex Cu[tren(CH\textsubscript{2}Ph)\textsubscript{6}]Br, \textsuperscript{1}, was an efficient catalyst for the CuAAC click reaction of the first-generation (G1) dendrimer \textsuperscript{3} containing 27 azido termini with a dendron \textsuperscript{4} functionalized at the focal point with a propargyl group, cleanly yielding dendrimer \textsuperscript{5} with 81 allyl termini (Scheme 2).\textsuperscript{44}
This complex was also an efficient catalyst in 10 mol % for the click functionalization of AuNPs. The complex 1 was synthesized by reaction of commercial tren with benzylbromide followed by heating hexabenzyltren with CuBr in dioxane (Scheme 3).

Although the medium is air-sensitive, the click reactions using this catalyst work well under air in the additional presence of sodium ascorbate. Alternatively, catalysis can be carried out as well if equal molar amounts of the air stable compound hexabenzyltren and CuBr are added together to the reaction medium in catalytic quantities. The catalytic use of 1 in click dendrimer synthesis and AuNP functionalization shows that the hexabenzyltren ligand of 1 resists full decoordination that would trap CuI stoichiometrically as in the case of the Sharpless CuI catalyst. This is also in favor of the monometallic mechanism shown in Scheme 2 for the series of CuI tren catalysts.

Reactions using the catalyst 1 or its above components are best conducted in toluene in which 1 is soluble, because the triazole reaction products are insoluble in this solvent and thus easily separated.44

**Positive Dendritic Effects in CuAAC Click Catalysis and Catalysis “on” Water**

Cu[tren(CH₂Ph)₆]Br-centered dendritic catalysts of zeroth and first generations, 6 and 7, have been synthesized by covalently attaching dendrons in the para position of the phenyl groups of 1,44 according to a 1 → 3 connectivity (Scheme 4).45–47 Aerobic CuI oxidation to μ-oxo-bridged dicopper species is sterically prevented in these CuI-centered dendrimers. These dendritic catalysts are consequently much less air-sensitive than the parent complex 1, due to the absence of possible inner-sphere oxidation pathways. Catalytic click reactions in toluene were also shown to proceed faster with 6 and 7 than with the parent catalyst 1. Some click reactions such as that of phenyl acetylene with benzylazide are even faster with the G1 catalyst 7 than with the G0 catalyst 6, indicating that intradendritic CuI–substrate supramolecular interactions are reminiscent of enzymatic catalysis. Thus for small substrates, the dendritic effect is positive. This also shows that a monometallic mechanism is efficient for the click reaction (Scheme 5), because the
Click Dendrimers and Triazole-Related Aspects  Astruc et al.

dendritic frame inhibits the approach of a second Cu\(^{1}\)-centered
dendrimer.

Following detailed kinetic studies, Fokin and Finn pointed
out the possibility of a \(\sigma,\pi\)-bimetallic Cu\(^{1}\) intermediate.\(^{28,49\text{–}51}\) Indeed, in the absence of bulky (dendritic) polydentate accel-
erating ligands, a bimetallic mechanism is favored, because the
\(\pi\)-Cu\(^{1}\) coordination of the \(\sigma\)-alkynyl ligand decreases the elec-
tronic density on this ligand, which facilitates the azide attack.

If the tridentate ligand is not bulky, partial decoordination
(even in the case of 1) can eventually also give rise to this
bimetallic mechanism. This was shown by the Scripps group
using very efficient click catalysts of the type Cu\(^{1}\)\{(tris-
(triazolylmethyl)amine\} and related catalysts.\(^{28,51}\)

Finally, a water-soluble Cu[tren(CH\(_2\)Ph)\(_6\)]\(^{1}\)-centered click
catalyst 8 was synthesized by CuAAC click reaction between
the Cu[tren(CH\(_2\)Ar)\(_6\)]Br core functionalized in the \(para\) aryl

SCHEME 8. Selective Oxidation of the Outer Ferrocenyl Groups of the Triazolylbiferrocenyl Dendrimer 10 Using Ferrocenium Hexafluorophosphate
Producing the Mixed-Valence Dendrimer 14
position with azido groups and a tri(ethylene glycol)-terminated dendron bearing a propargyl group at the focal point. The click synthesis of the dendritic tren ligand of the 81-biferrocenyl dendrimer in the redox recognition of ATP and PdCl_2. Cyclic voltammograms of the G2-81-biferrocenyl dendrimer (a) in CH_2Cl_2, [n-Bu_4N][PF_6] 0.1 M, (b) progressive adsorption upon scanning around the potential of the biferrocenyl potential area, (c) splitting of the outer-biferrocenyl CV wave upon addition of ATP, and (d) addition of Pd(OAc)_2 provoking the splitting of the inner ferrocenyl CV wave at 0.7 V.

**FIGURE 1.** Selective roles of the inner and outer ferrocenyl groups of the 81-biferrocenyl dendrimer in the redox recognition of ATP and PdCl_2. Cyclic voltammograms of the G2-81-biferrocenyl dendrimer (a) in CH_2Cl_2, [n-Bu_4N][PF_6] 0.1 M, (b) progressive adsorption upon scanning around the potential of the biferrocenyl potential area, (c) splitting of the outer-biferrocenyl CV wave upon addition of ATP, and (d) addition of Pd(OAc)_2 provoking the splitting of the inner ferrocenyl CV wave at 0.7 V.

Recognition of Transition-Metal Cations and Oxo-Anions Using the Coordination of Intradendritic [1,2,3]-Triazolyl Groups

Click dendrimer syntheses were designed not only as a very practical way to decorate dendrimers with useful organometallic groups, water-solubilizing sugars, and thermally robust carboranes (which advantageously bring a large number of such groups within a single molecular assembly) but also specifically in order to benefit from the intradendritic generation of [1,2,3]-triazolyl ligands for coordination to transition-metal ions. For instance, with PdCl_2(PhCN)_2, an X-ray crystal structure determination allowed the location of the [1,2,3]-triazole coordination site of PdCl_2 on the terminal N atom next to the substituent of the alkyne precursor of the triazole. Such a coordination allowed the recognition of Cu^2+, Cu^3+, Pd^0, and Pd^2+. The case of Pd^0, titration could indicate a 1:1 triazole/Pd^0 stoichiometry and predict the number of Pd^0 atoms, confirmed by transmission electron microscopy, in intradendritic PdNPs formed by reduction of these Pd^0 ions in large dendrimers. This strategy generated with precise PdNP catalytic studies was inspired by Crooks’ pioneering studies of the poly(amido amine) (PAMAM)-dendrimer encapsulated PdNP catalysts. Extremely efficient (“homeopathic”) PdNP catalysts were discovered in this way, including some that were very efficient in aqueous media. Along this line, note Yamamoto’s approach who also conducted dendrimer encapsulation of transition-metal species using intradendritic phenylazomethine ligands for catalysis and materials science purposes.

A recent remarkable use of triazole-containing dendrimers was achieved with biferrocenyl triazole dendrimers, which were synthesized by click reactions between five generations of azido-terminated dendrimers, constructed with 1 → 3 connectivity, and ethynylbiferrocene (Scheme 7). Biferrocenyl-containing nanomaterials have been extensively studied by Nishihara’s group and present unique mixed-valence properties. Mixed-valence biferrocenium triazole dendrimers such as were synthesized by oxidation of the neutral metalloidendrimers with ferricinium hexafluorophosphate (Scheme 8).

These polycationic dendrimers result from selective oxidation of the outer ferrocenyl groups (vide infra), because the inner ferrocenyl groups are more difficult to oxidize due to the presence of the nearby electron-withdrawing triazolyl group. The Mössbauer spectrum at zero field of the mixed-valence dendrimer with 27 biferrocenium termini showed a doublet for the ferrocenium groups and another one for the ferrocenyl groups indicating the localization of the mixed valence. The cyclic voltammograms (CVs) of these dendrimers showed two chemically and electrochemically reversible waves at 0.4 and 0.7 V vs the internal reference decamethylferrocene, although adsorption characterized by the decrease of the difference of potential between the anodic and cathodic waves decreased as the dendrimer generation increased (Figure 1). Addition of [Pd(MeCN)_2][PF_6] to a CH_2Cl_2 solution of the dendrimer containing 81 biferrocenyl triazole termini led to selective recognition by the second oxidation wave at 0.7 V, whereas addition of the oxo anion [n-Bu_4N][ATP] to the same solution of 11 led to selective recognition by the first oxidation wave at 0.4 V. This confirms that the inner ferrocenyl groups that are located near the triazole rings are more difficult to oxidize than the
Click Dendrimers and Triazole-Related Aspects

Astruc et al.

outer ones. The easier oxidation of the outer ferrocenes to ferricinium selectively creates positive charges at the dendrimer periphery that form ion pairing with the [ATP] anions just by setting the potential between 0.4 and 0.7 V (Figure 1).

Use and Role of the Intradendritic [1,2,3]-Triazolyl Groups in the Formation of Water-Soluble Dendrimer-Stabilized Gold Nanoparticles (AuNPs)

Initial work on click dendrimer-mediated stabilization of nanoparticles involved catalytically active PdNPs as mentioned above. We have recently been interested in click-dendrimer stabilization of water-soluble AuNPs because of the roles of AuNPs in catalysis (small AuNPs, in the range 1–3 nm) and nanomedicine (large AuNPs, in the range 3–50 nm giving rise to plasmonic absorptions that are useful for both diagnostics and therapy). Seminal work on PAMAM-dendrimer stabilization of AuNPs and other transition-metal NPs was carried out in the late 1990s, in particular by the Crooks group, and has been reviewed including catalytic properties.

In order to stabilize AuNPs in water, a variety of new dendrimers were synthesized from poly-azido-terminated...
Click Dendrimers and Triazole-Related Aspects

Astruc et al.

Dendrimers were compared with other structurally related dendrimers built using Williamson coupling instead of CuAAC click coupling, in order to investigate the influence of the intradendritic triazolyl motifs. The TEG termini provided ideal conditions for AuNP formation from HAuCl₄ either using NaBH₄ as the reductant or without external reductant. With NaBH₄, however, it was also indispensable to use click dendrimers terminated by Percec-type TEG dendrons in order to introduce AuIII inside the dendrimer by coordination to the triazole rings, which adequately modulated the nucleation. With the smallest dendrimer of the series that was terminated by only 27 TEGs, the AuNPs formed were larger (4.1 ± 0.5 nm) than the dendrimers and thus were stabilized by several dendrimers and showed a plasmon band at 540 nm. The larger dendrimers containing 81 (Figure 2) and 243 terminal TEGs (Figure 3) encapsulated AuNPs that were too small (1.9 ± 0.4 nm) to present a plasmon band. For comparison, when the dendrimer structure contained only TEG termini but no [1,2,3]-triazole or [1,2,3]-triazoles but no TEG-terminated dendrons, NaBH₄ reduction led to unstable AuNPs that precipitated after a few minutes. This was in contrast with PdNPs that were fully stabilized by such dendrimers and catalytically active in olefin hydrogenation and Suzuki–Miyaura reactions under ambient conditions. On the other hand, in the absence of external reductant, AuIII–triazole coordination slowed AuIII reduction in dendrimers terminated by TEG dendrons, because the distal Percec-type dendron itself was the reductant. The semicavitand effect of the three TEGs of the dendron was then crucial, as shown by the failure of AuIII reduction using a click dendrimer terminated by a linear tetra(ethylene glycol) instead of a Percec-type TEG dendron. Dendrimer-stabilized AuNPs were formed with the click as well as nonclick dendrimers from HAuCl₄ in this way in the absence of additional reductant. Then AuNPs had a 23–42 nm size depending on the generation. Choosing the AuCl₃/dendrimer stoichiometry also oriented the size of the AuNPs formed (Table 1).

Monoelectronic reductants such as ferrocene, ethynylferrocene, decamethylferrocene, and the electron-reservoir sandwich complex [Fe(η⁵-C₅H₅)(η⁶-C₆Me₆)], which has 19 valence electrons on the iron valence shell, have also been used for the first time for the reduction of HAuCl₄ to AuNPs (Figure 3). Their outer-sphere reduction mechanism implied a much slower reduction than that involving the inner-sphere reductant NaBH₄, and the size of the dendrimer-stabilized AuNPs formed (between 7 and 38 nm) was directly related to the standard oxidation potentials of the FeI and FeII reductants. This provided the possibility to finely tune the size of the AuNPs.

All these water-soluble dendrimer-stabilized PEGylated AuNPs were only weakly stabilized and are thus potentially useful for catalytic (small size) and biomedical applications (large size).

Conclusion and Prospects

The CuAAC click synthesis is a superb synthetic tool that has been usefully and successfully applied by the pioneers of this chemistry to the biological and biomedical field. Concerning the synthesis of relatively large dendrimers and click functionalized transition-metal nanoparticles the design of new liganded catalysts was required as illustrated here by the efficient, practical, and easily made complex Cu[tren-(CH₂Ph)₄]Br. Very efficient dendritic analogue catalysts showed that a mononuclear CuI catalysis is involved, and the positive dendritic effect recalls enzymatic catalysis. Even if the copper catalyst is not desired in green processes, it can be removed from the click reaction medium when these catalysts are used.
Alternatively, copper-free solutions are known either with electron-deficient alkyn substrates (the Huisgen cycloadditions are then possible in water under mild conditions) or using strain-promoted alkyn–azide cycloaddition. The synthesis of click dendrimers not only allows decoration of dendrimers with a large number of substrates of interest but also the introduction of the intradendritic [1,2,3]-triazoles to allow their use to coordinate transition-metal ions. Applications have been illustrated here in molecular recognition and for the fine-tuning of the formation of small catalytically active PdNPs as well as AuNPs of various sizes ranging from 1.8 to 42 nm. The difference of influence of the multiple structural and reactivity parameters on the stabilization and size of the NPs of these two metals is thus impressive. The intradendritic [1,2,3]-triazole ligands are also a key to redox recognition that is helpful for the control of the size of potentially useful, weakly liganded transition-metal nanoparticles.

In summary, CuAAC click chemistry plays a pivotal role in the interplay between dendritic architectures and nanoparticles, that is, between molecular nanoscience and nanomaterials, and this concept is clearly called for many further developments and applications.

Excellent contributions by the colleagues and students cited in the references and financial support from the Université Bordeaux 1, the Centre National de la Recherche Scientifique, and the Agence Nationale pour la Recherche (ANR project 07-CPD-05-01)) are gratefully acknowledged.

**FOOTNOTES**

*E-mail: d.astruc@igm.u-bordeaux1.fr.

**REFERENCES**

25. Tomae, C. W.; Christiansen, C.; Meldal, M. Peptido(1,2,3) Triazoles on Solid Support: [1,2,3]-Triazoles by Regiospecific Copper (I)-Catalyzed 1,3-Dipolar Cycloaddition of Terminal Alkynes to Azides. J. Org. Chem. 2002, 67, 3057–3064.
Click Dendrimers and Triazole-Related Aspects  Astruc et al.