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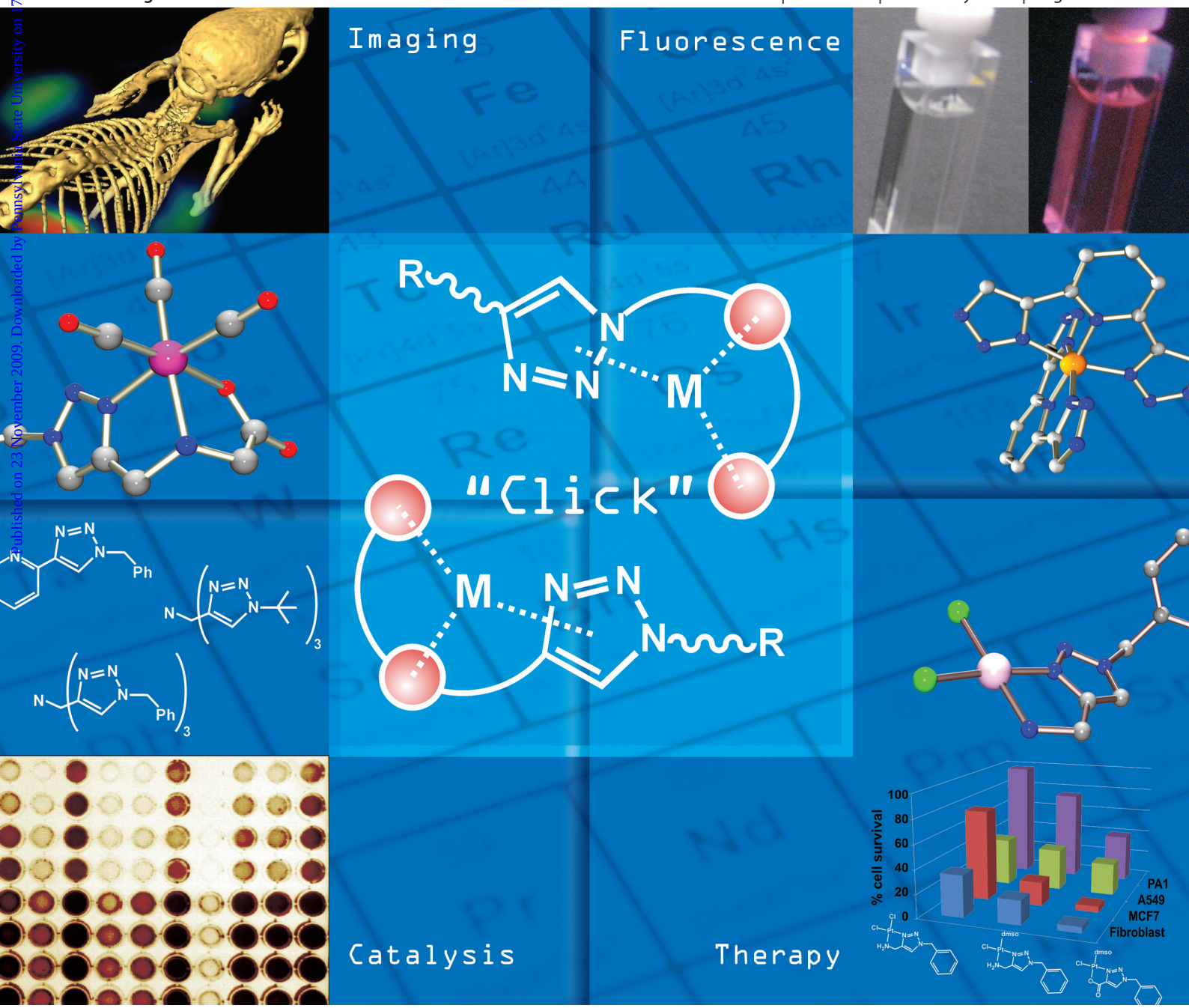

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Metal chelating systems synthesized using the copper(I) catalyzed azide-alkyne cycloaddition

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The copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) is the premier example of a click reaction. The reaction is modular, reliable and easy to perform, providing easy access to molecular diversity. The majority of reported applications of the reaction employ the 1,2,3-triazole as a stable linkage to connect two chemical/biological components, while the potential for metal coordination of the heterocycle itself has received much less attention. In fact, 1,4-functionalized 1,2,3-triazoles are versatile ligands offering several donor sites for metal coordination, including *N3*, *N2* and *C5*. In this article, we summarize the areas in which the CuAAC has been applied to the synthesis of novel triazole-containing ligands for transition metals.

Introduction

Transition metal complexes play crucial roles in many areas of catalysis, nanotechnology, materials, and life sciences, and will undoubtedly continue to do so in future. The design of ligand systems and chelators to provide metal complexes with optimal properties is fundamental in this respect. One challenge is to find novel strategies, which give access to large sets of potent metal chelators, while at the same time reducing the synthetic complexity of ligand preparation. Ideally such strategies would enable the rapid creation of diversity through the use of modular building blocks. In return this would accelerate the process of discovery and optimization of new metal chelating systems and metal complexes with novel properties or applications.

The term "click chemistry" was first introduced by Sharpless and co-workers in 2001.[1,2] It describes a modular approach to organic synthesis, rapidly creating molecular diversity using only a small number of near-perfect reactions. Click reactions are defined by a stringent set of criteria: they must be efficient and selective, but at the same time wide in scope, giving consistently high yields with a variety of starting materials. The reactions must be easy to perform, be insensitive to oxygen or water, and use only readily available or accessible reagents. Furthermore, reaction work-up and product isolation must be simple, ideally without requiring chromatographic purification.

The synthesis of 1,2,3-triazoles by the 1,3-dipolar cycloaddition of azides and alkynes is an example of a Huisgen cyclization (Scheme 1, route A).[3] Although this reaction was first reported

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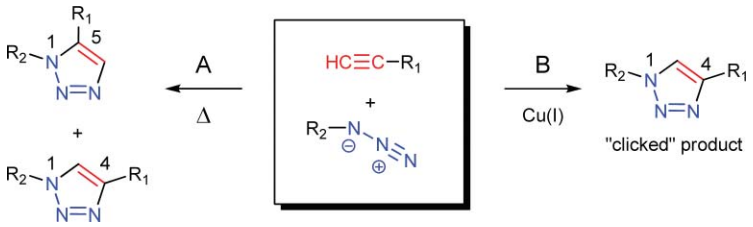

Scheme 1 Under thermal conditions the Huisgen cycloaddition of terminal alkynes and azides yields mixtures of isomers (A) whereas Cu(I)-catalysis results in exclusive formation of 1,4-disubstituted 1,2,3-triazoles (B). R_1 and R_2 represent two chemical/biochemical components to be connected by a stable triazole linker.

decades ago, it did not find widespread application due to the formation of mixtures of 1,4-substituted and 1,5-substituted isomers. In 2002, the Sharpless and Meldal groups independently reported the Cu(I)-catalyzed version of the cycloaddition, which leads to a dramatic improvement in both rate and regioselectivity, efficiently providing 1,4-disubstituted 1,2,3-triazoles under mild reaction conditions (route B).[4–6] As the premier example of a click reaction, the copper catalyzed azide-alkyne cycloaddition (CuAAC) is characterized by its efficiency, selectivity, the mild reaction conditions, the straightforward purification of the products and, as a result, its enormous scope. Additionally, alkynes and azides are usually easy to install and orthogonally reactive to most other common functional groups in organic chemistry, which eliminates the need for protecting group chemistry. The reaction proceeds as efficiently in water as in organic solvents and, with almost complete conversion and selectivity, the 1,2,3-triazole products can be readily isolated. The 1,2,3-triazole itself is also astonishingly stable and essentially inert to oxidation, reduction and hydrolysis. Not surprisingly, the reaction has found a multitude of wide-ranging applications in synthesis, medicinal chemistry, molecular biology, and materials science. Examples include the modification of natural products and drugs with property modifying groups or fluorophore or biotin tags, the synthesis of macrocyclic compounds, the modification of DNA and nucleotides, the synthesis of dendrimers and polymers, conjugation of carbohydrates and peptides, and the modification of surfaces and nanoparticles. The reaction in these contexts has been very recently comprehensively reviewed.[7]

The majority of reported applications of the CuAAC employ the 1,2,3-triazole as a stable linkage for the connection of two chemical/biological components. In contrast, the potential of the heterocycle itself has received much less attention. This is despite the fact that 1,4-disubsituted 1,2,3-triazoles are similar to amide bonds in terms of their molecular dimensions and planarity, and similar to substituted imidazoles in terms of their coordinative properties.[2,8,9] Similarly, while the CuAAC has been successfully employed for the attachment of ligand systems and metal complexes to various molecules and materials using a triazole linker ("pendant design"), 1,2,3-triazoles synthesized using the CuAAC and which are an integral part of a metal chelator ("integrated design") have been much less widely investigated (Fig. 1). In fact 1,4-functionalized 1,2,3-triazoles are potentially versatile ligands offering several donor sites for metal coordination.[10] In the majority of reports of triazole containing chelators, *N3* of the triazole is assumed to be coordinated to the metal centre. Nonetheless, metal complexes in which the triazole is coordinated through *N3*, *N2* and even *C5* have all been characterized, as will be discussed.

In this perspective article we will present an overview of transition metal complexes which incorporate 1,2,3-triazole-containing ligands that were synthesized using the CuAAC reaction. The discussion is limited to those complexes in which the 1,2,3-triazole forms an integral part of the metal chelating system, and has been organized according to the applications of the complexes. We have not included examples in which 1,2,3-triazoles are used to connect a metal-coordinating ligand or a complex to another biological/chemical component. There are, however, numerous reports where the triazole is used as a linker, for example, to conjugate 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA),[11], diethylene triamine pentaacetic acid (DTPA),[12] ferrocene,[13] or metallic nanoparticles.[14]

Ligand synthesis

The CuAAC is an extremely robust reaction, which works reliably under a wide range of different conditions.[7] First described by Sharpless and co-workers, the combination of $CuSO_4$ or $Cu(OAc)_2$ and sodium ascorbate as a reducing agent to generate the Cu(I) catalyst *in situ* has been widely used in aqueous systems.[4] Under these conditions copper(I)-stabilizing ligands have been shown

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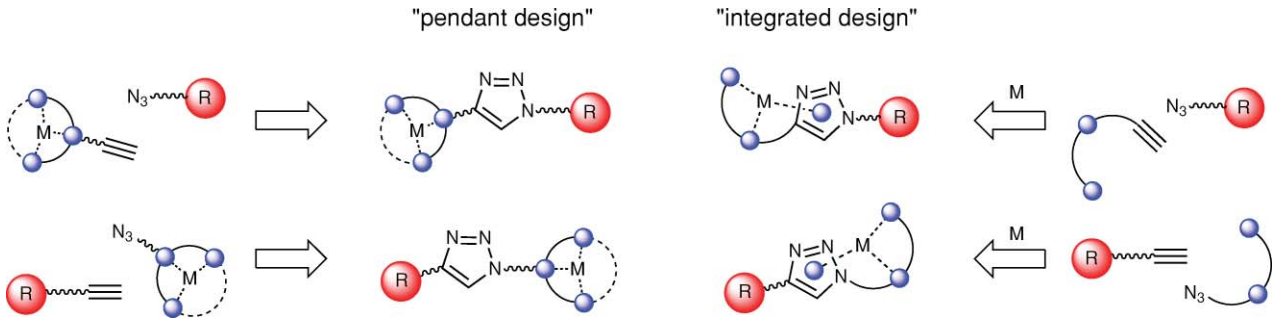


Fig. 1 Pendant *versus* integrated design of metal chelating systems using the CuAAC. **R** can be any chemical/biological component to be functionalized with a metal complex. The blue spheres represent metal coordinating groups.

to increase the rate of the copper-catalyzed reaction, but are by no means essential.[15,16] For reactions in organic solvents (*e.g.* DMF, THF, DMSO, CH_3CN), CuI has been the most frequently used copper(I) source due to its partial solubility in solvents of intermediate polarity.[5,7] CuI can be obtained in highly pure form and has proved applicable when special anhydrous conditions were required.[17] In the absence of water, however, a base (typically an amine base) is usually required in order to generate a sufficient concentration of acetylide anion.[18] Díez-González and Nolan have developed N-heterocyclic carbene copper complexes, which have proven to be particularly efficient catalysts for the cycloaddition reaction.[19] The compounds can be used in water, organic solvents or without solvent with a low catalyst loading and show remarkable activity in terms of rate and yield. Other sources of copper include metallic Cu(0),[20] copper catalysts immobilized on various solid supports[21] and Cu-nanoparticles[22] all of which aim to facilitate a more straightforward isolation of the triazole products. The CuAAC reaction has been most commonly performed at room temperature, with complete conversion of the click substrates usually achieved within several hours. However, increased reaction temperature or the use of microwave-assisted heating have been shown to provide the 1,2,3-triazole products at a considerably faster rate.[23] The concentration of the substrates appears to be a less crucial reaction parameter for triazole formation; successful examples employing the substrates in dilute concentrations as well as in neat form have both been reported.[7]

Using a copper catalyzed reaction to synthesize multidentate ligand systems, which are potentially also good chelators for copper, may challenge isolation of the uncomplexed ligand. As the examples discussed below illustrate, however, a variety of different chelating systems which combine the triazole and other coordinating groups have been successfully synthesized and isolated in high yields. The synthetic procedures vary, but in general common work-up procedures were employed for the separation of the copper catalyst from the products. For 1,2,3-triazole products insoluble in the reaction media, the most convenient means of separation was filtration.[9,15] For ligands soluble in organic solvents, extraction is a convenient method of purification. Washing with aqueous solutions of EDTA or ammonium salts has proven an effective way to remove the copper catalyst for both solution and solid phase syntheses.[5,24,25] Commercial metal scavenger resins can also be used to remove copper efficiently from the reaction mixture.[9]

Metal-stabilizing ligands for applications in catalysis

During the course of mechanistic studies of Cu(I)-catalyzed triazole formation, Fokin *et al.* found the reaction rates for the formation of certain polyvalent substrates to be unusually high, and that the reactions appeared to be autocatalytic.[15] They subsequently synthesized and tested a variety of polytriazole-containing compounds as stabilizing ligands for Cu(I) (Fig. 2) and investigated their effect on the yield of the Cu(I)-catalyzed cycloaddition. The best ligands were found to be oligotriazole derivatives derived from propargylamines, assumed to coordinate to copper by forming a five-membered chelate with the amine and *N3* of the triazole. *Tris*-(benzyltriazolylmethyl)amine (TBTA) was identified as being particularly efficient and has been widely used to accelerate the rate of the Cu(I)-catalyzed cycloaddition.[26] It has been suggested that the ligand is effective because the amine provides additional electron density for the metal centre while the labile triazole functionalities facilitate formation of the Cu(I)-acetylide/ligand complex thought to be involved in the Cu(I)-mediated reaction. Finn *et al.* compared the rate-accelerating ability of TBTA and other polytriazole ligands on the Cu(I)-catalyzed azide-alkyne cycloaddition with a large number of pyridine, benzimidazole and benzothiazole compounds, many of which also give substantial improvement in rates and yields.[16,27] They found in general that benzimidazoles were the most effective ligands for the Cu(I) catalyst, but that their effectiveness was often dependent on the reaction conditions.

Bergbreiter *et al.* used the Cu(I)-catalyzed cycloaddition to prepare a polyisobutylene-supported Cu(I) catalyst. The Cu(I)-catalyzed reaction between a polymer supported azide and a propargyl-triamine led to the polymer supported Cu(I) complex **1** in which copper was coordinated to the triazole, an amine and two pyridyl groups (Fig. 3).[28] The complex proved to be an effective catalyst for both the CuAAC and Cu(I)-catalyzed atom transfer radical polymerization, while the polyisobutylene support provided a convenient method to separate the catalyst from the reaction products.

Transition metal catalyzed cross-coupling reactions are widely used in organic synthesis and it is well documented that the ligands used to stabilize the transition metal can have a significant impact on the outcome of such reactions.[29,30] The CuAAC reaction has been used to synthesize a variety of ligands for potential applications in palladium and other transition metal catalyzed reactions. Triazole-containing analogues of phosphine

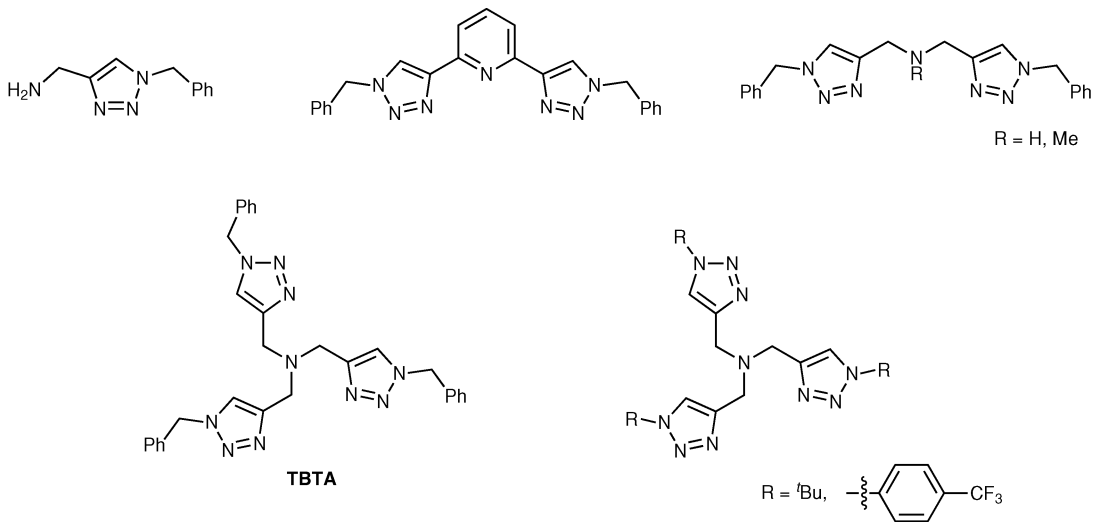


Fig. 2 Clicked ligands used to stabilize copper(I) catalysts.

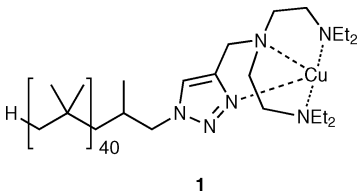


Fig. 3 Polymer supported copper(I) complex for Cu(I)-catalyzed reactions.

ligands,[31] bidentate *P*,*N*-chelates,[32] ferrocenyl bisphosphines,[33–35] pincer ligands[36] and abnormal carbenes[37] have all been reported (Fig. 4).

Zhang *et al.* used a non-catalyzed version of the azide-alkyne cycloaddition to synthesize a series of monophosphine-triazole compounds and could show that they were effective ligands for palladium complexes used in the cross-coupling reactions of aryl chlorides.[31,38] The triazole was not suspected in these cases to coordinate to the metal, but rather that the phosphine acted as a monodentate ligand. van Maarseveen *et al.* used the Cu(I)-catalyzed version of the cycloaddition to prepare potentially bidentate triazole-phosphine ligands for palladium (Scheme 2), and have shown that these complexes are effective catalysts for Suzuki coupling reactions.[32] Whether the catalyst exhibits monodentate (*P*-coordination only) or bidentate coordination (including *N3* of

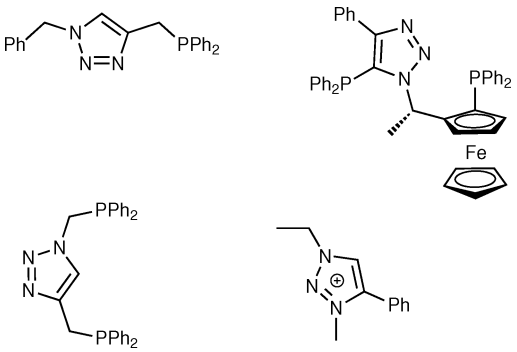
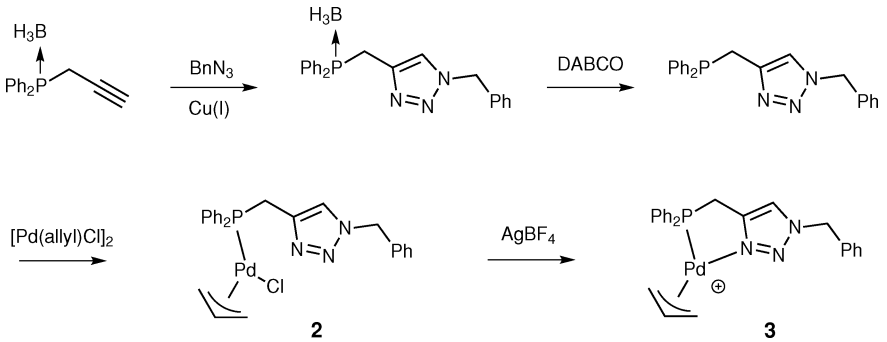


Fig. 4 Triazole-containing ligands for transition metal-catalyzed cross–coupling reactions.

the triazole) was not unambiguously determined. Crystal structure analysis revealed monodentate *P*-coordination (complex **2**) when the Pd complex was synthesized from $[Pd(allyl)Cl]_2$, although ^{1}H and ^{31}P NMR analyses suggested bidentate coordination of the ligand to the metal (complex **3**), after the monodentate complex **2** had been treated with $AgBF_4$. Mechanistic studies of palladium-catalyzed reactions have shown that it is monoligated complexes which are implicated in catalysis[30] and it is likely, therefore, that the monodentate complex **2** is the catalytically active complex. Kann *et al.* further demonstrated the scope of this approach and

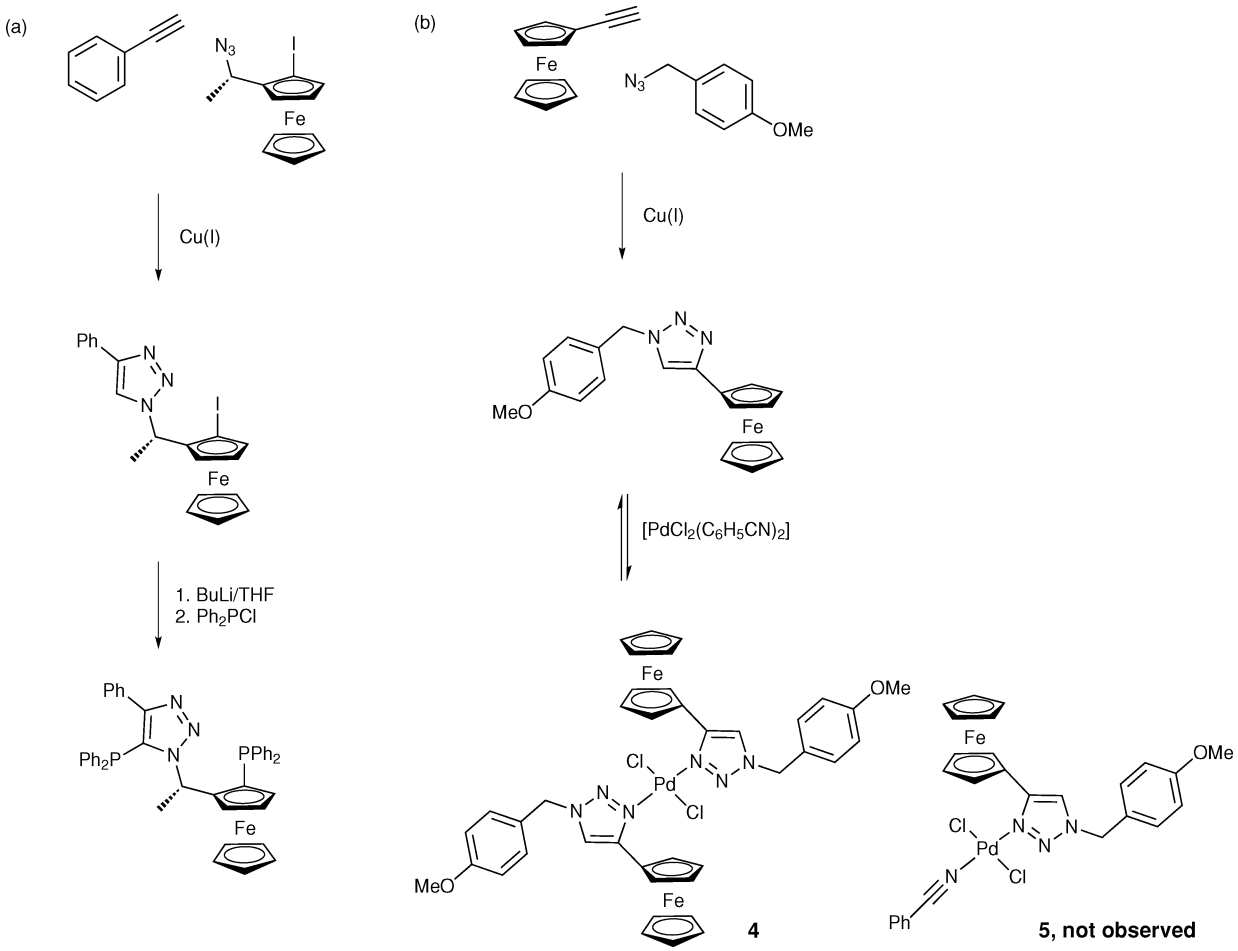


Scheme 2 Synthesis of phosphine/triazole-containing ligands for palladium.

the modular application of the CuAAC for the preparation of metal chelating ligands.[39] Using a library of suitable phosphine-containing azides and reacting them with various alkynes, a large number of potential *P*,*N*-ligands were synthesized, although the catalytic activity of their complexes was not evaluated.

Ferrocenyl bisphosphine ligands are also known to be effective ligands for a variety of metal-catalyzed reactions, most commonly in combination with palladium, rhodium, iridium and ruthenium.[40] In analogy to the work of Zhang *et al.*, Fukuzawa and co-workers used both the copper-catalyzed and Grignard-mediated azide-alkyne cycloaddition[41] to synthesize ferrocene-containing *P*,*P*- and *P*,*N*-ligands for rhodium and ruthenium,[33] and copper and silver,[34] starting from ferrocenyl azides (Scheme 3a). In the case of rhodium, only the *P*,*P*-chelate complexes were active as catalysts and asymmetric hydrogenation could not be achieved with the analogous complex of the potential *P*,*N*-ligand (triazole coordination). The Cu/*P*,*P*-chelates and Ag/*P*,*N*-chelates were envisaged as catalysts for the asymmetric 1,3-dipolar cycloaddition of azomethine and alkenes, however, only the copper complexes, which are not likely to involve coordination of the triazole, were found to be catalytically active. The catalytic activity of Cu(I) in combination with the *P*,*N*-chelate was not investigated. For the majority of triazole compounds which have been reported as stabilizing ligands for catalysts, the corresponding metal complexes have not been structurally characterized. More recently, however, the coordination chemistry of a palladium complex with a ferrocenyl-triazole ligand was investigated.[35] Three novel ferrocene-triazole ligands were synthesized using the Cu(I)-catalyzed reaction of ethynylferrocene and either azidomethylbenzene, diazidomethylbenzene or triazidomethylbenzene. Reaction of the monotriazole ligand with $[PdCl_2(PhCN)_2]$ led to the formation of complex **4** (Scheme 3b) which could be characterized by X-ray crystallography to show that *N3* of the triazole coordinates to the metal (Fig. 5). NMR-spectroscopic characterization of the complex revealed an equilibrium between the starting material and the disubstituted complex. The monosubstituted complex **5** was not observed, presumably as a result of the *trans* effect of the triazole ligand.

Pincer ligands are tridentate ligands with three coplanar donor groups. Many ligands of this type can be represented by the formula DCD, where D is a neutral two electron donor such as an amine, phosphine, ether or thioether, and C represents the anionic aryl carbon atom of a 2,6-disubstituted phenyl ring (Fig. 6a). Complexes of the platinum group metals with ligands of this type have found a wide range of applications in synthetic and supramolecular chemistry, as well as in nanoscience.[42] Much recent interest has been in the development of catalysts, for example, for Suzuki coupling and the Heck olefin arylation.[43] van Koten, Gebbink and co-workers investigated the use of



Scheme 3 Synthesis of ferrocenyl-1,2,3-triazolyl ligands derived from either a ferrocenyl-azide (a) or a ferrocenyl-alkyne (b).

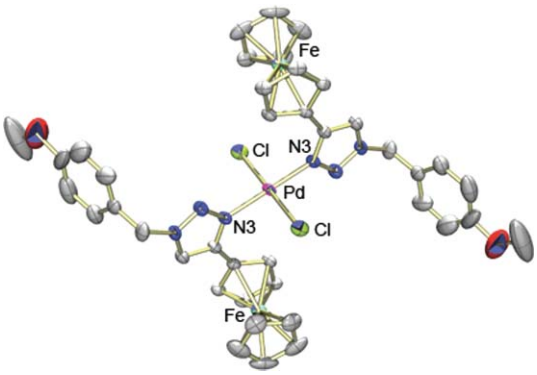


Fig. 5 X-ray crystal structure of **4**.

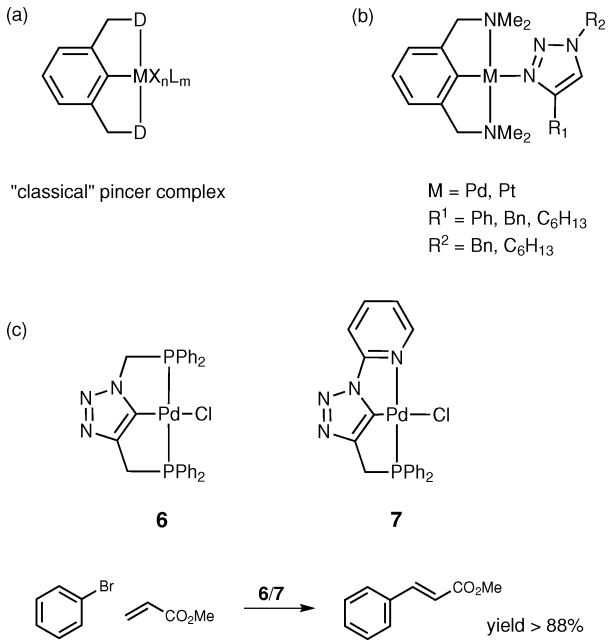


Fig. 6 (a) A "classical" pincer complex. (b) Pincer complexes with tuneable triazole ligands. (c) "Clicked" analogues of pincer complexes as novel catalysts for the Heck reaction.

1,4-disubstituted-1,2,3-triazoles as tunable monodentate ligands for the pincer complexes [M(2,6-($CH_2N(Me)_2$)$_2C_6H_3$)X] (M = Pd, Pt) (Fig. 6b).[44] Crystal structure analysis of one of the Pd complexes revealed that *N3* of the triazole coordinated to the metal. Variable temperature NMR experiments suggested that intermolecular triazole exchange was fast for the Pd complexes, whereas for the Pt complexes ligand exchange was much slower. Competitive ligand exchange experiments were performed between the triazole ligands and other commonly used Lewis bases and quantitatively assessed in terms of their relative association constants. It was shown that by varying the substituents at positions 1 and 4 of the triazole, the relative strength of the ligand could be altered. In an alternative approach, Gandelman *et al.* used click chemistry to design a series of pincer ligands in which the aryl part of the ligand was replaced by a 1,4-disubstituted triazole (Fig. 6c). The triazole based ligands contained two coordinating "arms" in the 1 and 4 positions, while the relatively acidic C–H bond of the heterocycle was suitable for insertion of a metal atom, providing an example of *C5* coordination.[36] From a library of suitable azide and alkyne functionalized building blocks, phosphorous-phosphorous, phosphorous-nitrogen and phosphorous-sulfur ligands were easily prepared, highlighting the advantage of this approach. Pd complexes with the ligands were prepared, and in the case of complex **6** crystal structure analysis confirmed the expected coordination of *C5* of the triazole and the donor groups at the *N1* and *C4* positions to the metal centre (Fig. 7). The complexes were all tested for their ability to catalyze the Heck reaction.[45] Two complexes (**6** and **7**) were identified as efficient catalysts for the model reaction investigated.

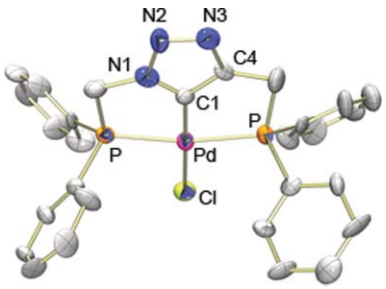


Fig. 7 X-ray crystal structure of **6**.

N-Heterocyclic carbenes have a wide range of applications in catalysis.[46] In a recent report, the CuAAC reaction was used to generate precursors for a new class of heterocyclic carbene ligands for late transition metals, the complexes of which may also have useful catalytic applications (Scheme 4).[37] Selective methylation of the *N3* nitrogen led to the formation of triazolium salts. Pd and Ag complexes were prepared by C–H bond activation, while transmetallation gave the corresponding Ru, Rh and Ir complexes. The dinuclear Pd complex **8**, and mononuclear Ir (**9**) and Rh (**10**) complexes were all characterized by X-ray structure analysis, to confirm the structure of the ligand and coordination of *C5* of the triazole ring to the metal (Fig. 8).

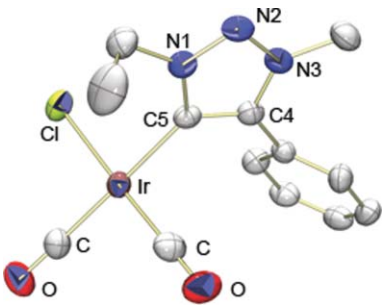
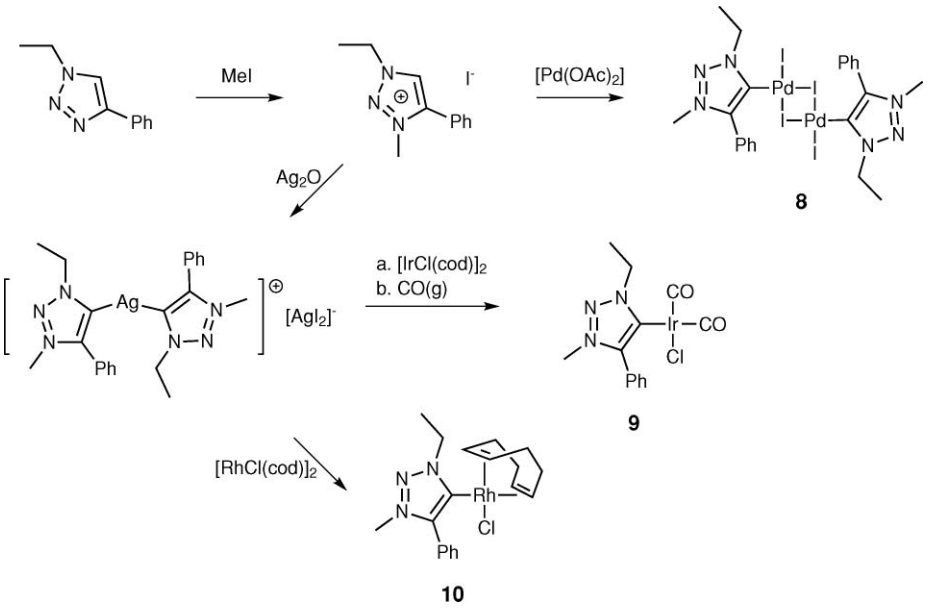
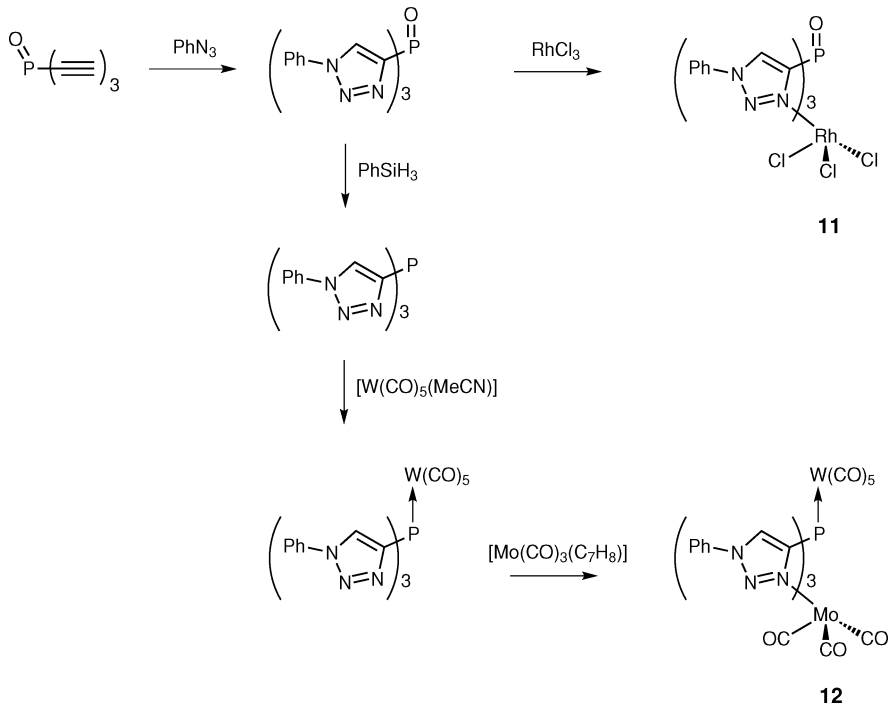


Fig. 8 X-ray crystal structure of **9**.

Lammertsma and co-workers produced an interesting series of scorpionate ligands using the reaction of phosphinoylethynes with one to three terminal acetylenes and phenyl azide (Scheme 5).[47] The [$RhCl_3$] complex **11** of the novel *tris*-(triazolyl)phosphine oxide was prepared. The ligand functions as a tripodal *N*,*N*,*N* ligand, thus coordinating in an analogous manner to *tris*-(pyrazolyl)phosphine oxides, which are known to coordinate to a range of transition metals.[48] Crystal structure analysis confirmed coordination of the *N3* nitrogen atoms of the three triazoles (Fig. 9). Reduction of the *tris*-(triazolyl)phosphine



Scheme 4 Using click chemistry to synthesize of a new class of heterocyclic carbenes.



Scheme 5 Synthesis of a phospha-scorpionate ligand and complexes.

oxide to the corresponding phosphine, gave a ligand capable of *P*-coordination and/or *N*-coordination. The reaction of this ligand with the tungsten precursor $[W(CO)_5(MeCN)]$ gave a stable W complex, although the ligand was shown by NMR and unequivocally by X-ray analysis to be coordinated to the $[W(CO)_5]$ core through phosphorous and not the triazoles. However, reaction of this complex with the precursor $[(C_7H_8)Mo(CO)_3]$ resulted in the bimetallic complex **12** in which the *N3* atoms of the three triazole rings were coordinated in a tridentate manner to the $[Mo(CO)_3]$ core, and which could also be characterized by X-ray crystallography (Fig. 9).

Click chemistry and in particular the Cu(I)-catalyzed cycloaddition has been widely used for the functionalization of polymers.[49] The reaction has proven particularly amenable to the attachment and immobilization of a variety of groups on to surfaces.[7] As a method to immobilize chiral ligands on to resins, click chemistry is attractive because it is more flexible with regard to ligand structure than, for example, nucleophilic substitution and allows a more diverse library of supported ligands to be prepared.[50] Reiser *et al.* compared two polymer supported aza(bisoxazolines), one linked using a benzyl spacer and the other using a triazole spacer, as ligands for the Cu(II)-catalyzed benzoylation of

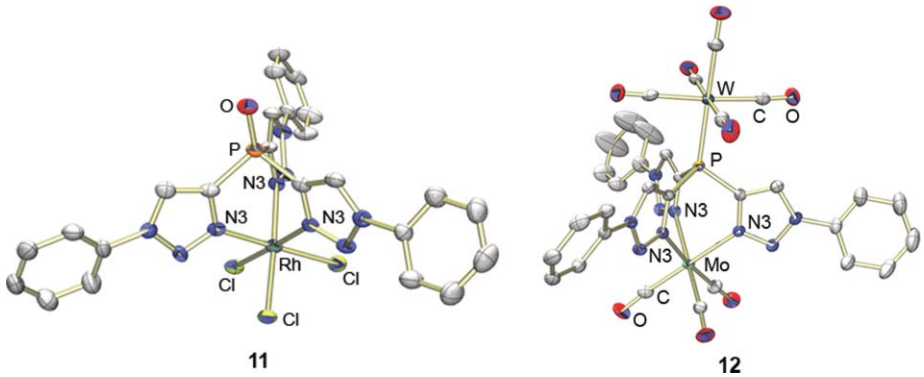


Fig. 9 X-ray crystal structures of **11** and **12**.

1,2-diols. Despite similar yields, much higher enantioselectivities were achieved when the 1,2,3-triazole was avoided as a linker.[51] Pericàs *et al.* investigated the use of 1,2,3-triazole linkers for the covalent immobilization of chiral ligands for the zinc-catalyzed enantioselective phenylation of aldehydes.[50] In agreement with the report on polymer supported aza(bisoxazolines), they found that the high levels of enantioselectivity achieved with the non-triazole linked ligands could not be reproduced using the triazole linked compounds. This observation held true even after optimization of the resin and ligand parameters, such as the length of the spacer between the triazole and the amino alcohol. This led to the suggestion that two catalytic processes were operating in parallel: one *via* an enantioselective pathway in which zinc is coordinated to the amino alcohol, and another *via* a non-enantioselective pathway, in which zinc is coordinated to the triazole (Fig. 10). Density functional theory (DFT) calculations were performed to gain insight into the complexation of zinc to the triazole linked amino alcohols. A series of hypothetical model complexes was used to demonstrate that interaction of dimethylzinc with the triazole ring leads to significant stabilization of the resulting complex (Fig. 11). The stabilization energies of triazole coordination were compared with those of coordination to a model amino alcohol, as well as *N*,*N*-coordination to an amine functionalized triazole. It is noteworthy that while coordination to the amino alcohol

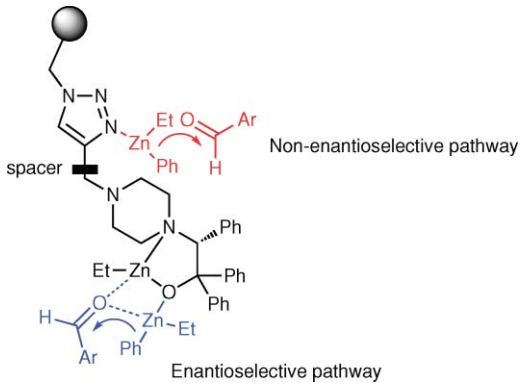


Fig. 10 Triazole amino alcohols linked to a solid support (sphere) with potential modes of zinc coordination leading to enantioselective and non-enantioselective catalysis.

appeared to represent the most favourable situation, the difference in comparison with the *N*,*N*-chelate was small. Furthermore *N*,*N*-chelate formation was only slightly more favourable than a simple monodentate interaction of zinc with the triazole ring, supporting their hypothesis that the two reaction pathways were able to compete.[50]

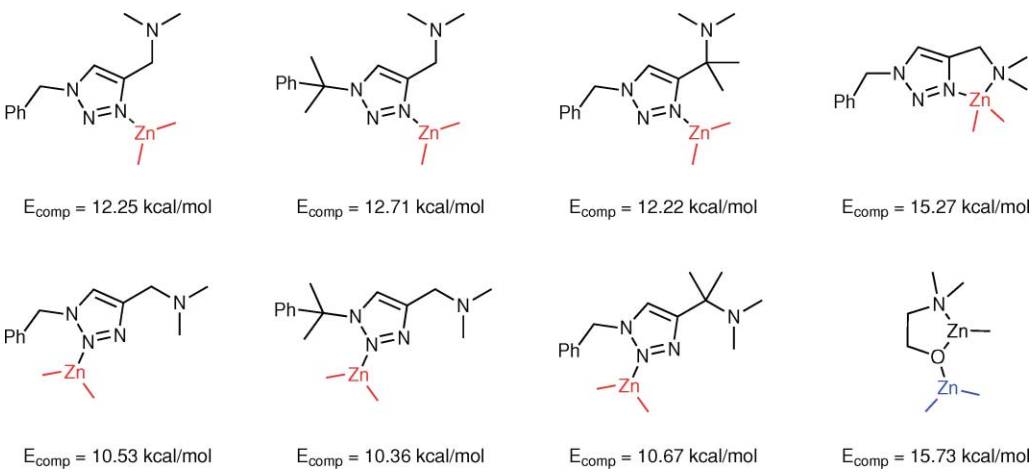


Fig. 11 Hypothetical interactions of dimethylzinc with 1,2,3-triazoles.

Bioconjugates and anticancer complexes

Radiopharmaceuticals

Single Photon Emission Computed Tomography (SPECT) and Position Emission Tomography (PET) are currently the most sensitive imaging modalities for the non-invasive detection of cancer *in vivo*.[52] The development of tumour-seeking molecules labelled with diagnostic radionuclides (γ-emitters for SPECT; β^+-emitters for PET) is therefore of paramount interest. At the same time, systemic delivery of molecules radiolabelled with particle emitting radionuclides such as α-emitters, β^--emitters and Auger-emitters may facilitate the destruction of disseminated tumours, which cannot be reached efficiently by other therapies.[53,54] Many isotopes with suitable decay properties for diagnostic applications, and the majority of isotopes with suitable decay properties for therapeutic applications are transition metal elements (Cu-64/67, Ga-67/68, Zr-89, Y-90, Tc-99m, Lu-177, Re-188, Bi-213 *etc.*).[54,55] To label targeting compounds with radiometals, the compounds first have to be functionalized with a bifunctional chelating agent (BFCA) capable of both stabilizing the metal centre and providing a means to conjugate the metal centre to the target molecule.[55] The preparation of such conjugates is often challenging due to the multi-functional character of both the metal chelating system and the targeting (bio)molecule. To avoid potential cross reactivity of the various functional groups present and obtain the desired conjugates in a selective and controllable manner, complex protection/deprotection strategies and long reaction sequences are often required. We have recently shown that the CuAAC reaction can help to overcome the problems encountered during the design and preparation of technetium-based radiopharmaceuticals.

Technetium-99m ($T_{1/2}$ = 6 h, 140 keV γ-radiation) is one of the most versatile radionuclides in nuclear medicine as a result of its low cost and ready availability from a $^{99}Mo/^{99m}Tc$ generator system.[56] A similar situation is encountered for rhenium-188 which is available as perrhenate ($Na[^{188}Re^{VII}O_4]$) from a $^{188}W/^{188}Re$ generator. Re-188 decays under emission of β^-- and γ-radiation ($E_\beta^{average}$ = 0.8 MeV, probability 70%; E_γ = 155 keV, probability 15%) with a half-life of 17 h. The chemical similarity of technetium and rhenium is an important feature of the use of their isotopes in radiopharmacy, in principle allowing the same radiolabelling methods to be used for both metals. While the γ-radiation of ^{99m}Tc is ideal for diagnostic applications, the β^--particle emission of ^{188}Re is suitable for radionuclide therapy, and at the same time the co-emitted γ-radiation allows *in vivo* tracking of radiolabelled biomolecules and dosimetry calculations.[57] A significant part of our research over the last 10 years has been dedicated to the development of the organometallic labelling precursors of Tc-99m and Re-188 with the general formulae $[M(H_2O)_3(CO)_3]^+$ (M = ^{99m}Tc, Re) and their incorporation into tumour-targeting biomolecules.[58] A large number of bifunctional chelating systems capable of tridentately coordinating to the metal centre while also providing a point for attachment to a biologically active molecule have been developed.[59] However, multi-step syntheses are a common feature of the preparation of such chelators and their incorporation into biomolecules often lacks efficiency and, as mentioned earlier, can be further complicated by cross-reactivity.

Using the CuAAC we prepared novel, polydentate metal chelators for the $M(CO)_3$-core (M = ^{99m}Tc, ^{nat}Re) starting from appropriate bidentate alkyne building blocks and reacting these with an azide-containing (bio)molecule (Fig. 12). The structures of the alkynes were varied in order to form complexes with different overall charges and varied hydrophilicity, since these factors can have a decisive impact on the targeting capacity as well as the pharmacokinetic profiles of radiopharmaceuticals.[60] By far the most elegant feature of this approach for the preparation of Tc-99m bioconjugates is that synthesis of the metal chelating system and functionalization of an azide-containing biomolecule can be achieved simultaneously, in one step, and without the use of protecting groups, which prompted us to call this approach "click-to-chelate". For characterization purposes, a series of model ligands were synthesized from the reactions of the bidentate alkynes with benzyl azide.[61] Non-radioactive rhenium complexes of all of the ligands were prepared and characterized. Representative neutral (**13**), cationic (**14**) and anionic (**15**) complexes were characterized by X-ray structure determination (Fig. 13) to confirm tridentate coordination to the tricarbonyl metal core.

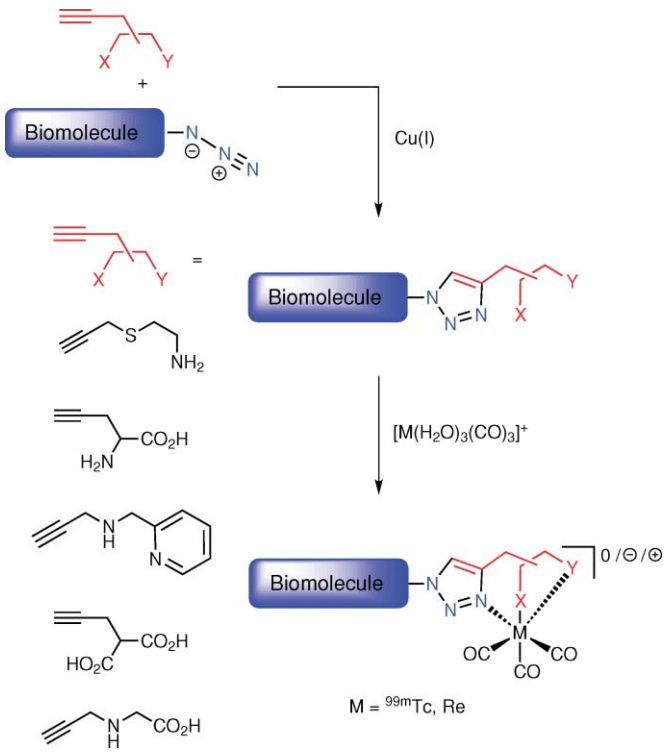


Fig. 12 Schematic drawing of the synthesis, incorporation into functionalized biomolecules, and radiolabelling of triazole-containing chelators ("click-to-chelate" approach).

Ligands derived from the reaction of an appropriate bidentate azide and an alkyne, which coordinate to the metal through *N2* of the triazole, were also investigated (Scheme 6). Rhenium complexes of these ligands were readily prepared and characterized. We found, however, that in the reaction with $[^{99m}Tc(CO)_3(H_2O)_3]^+$ to form $[^{99m}Tc(CO)_3\mathbf{L}]$, a higher ligand concentration was required to achieve quantitative radiolabelling (complete conversion of the metal precursor to the product) than for the ligands which coordinate through *N3*, suggesting *N3* coordination was more favourable.[9] This finding was supported by DFT calculations with simple 1,4-disubstituted 1,2,3-triazoles which revealed the

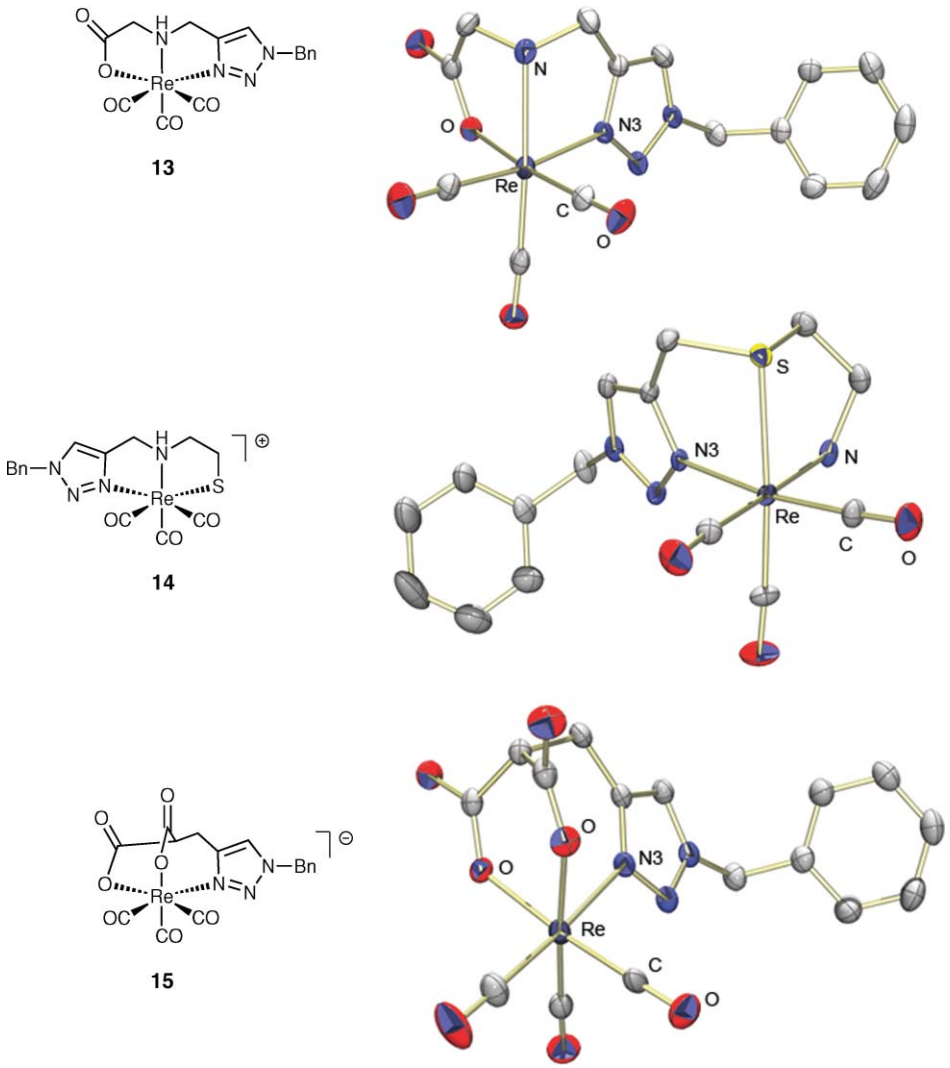
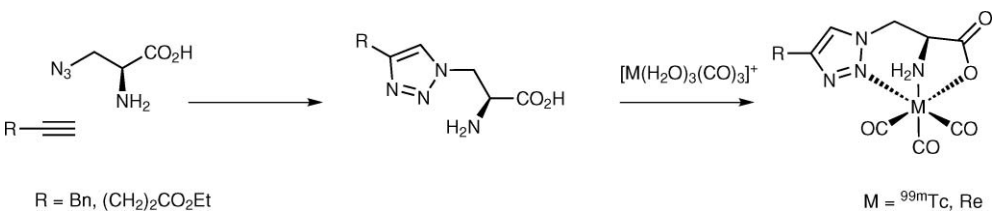


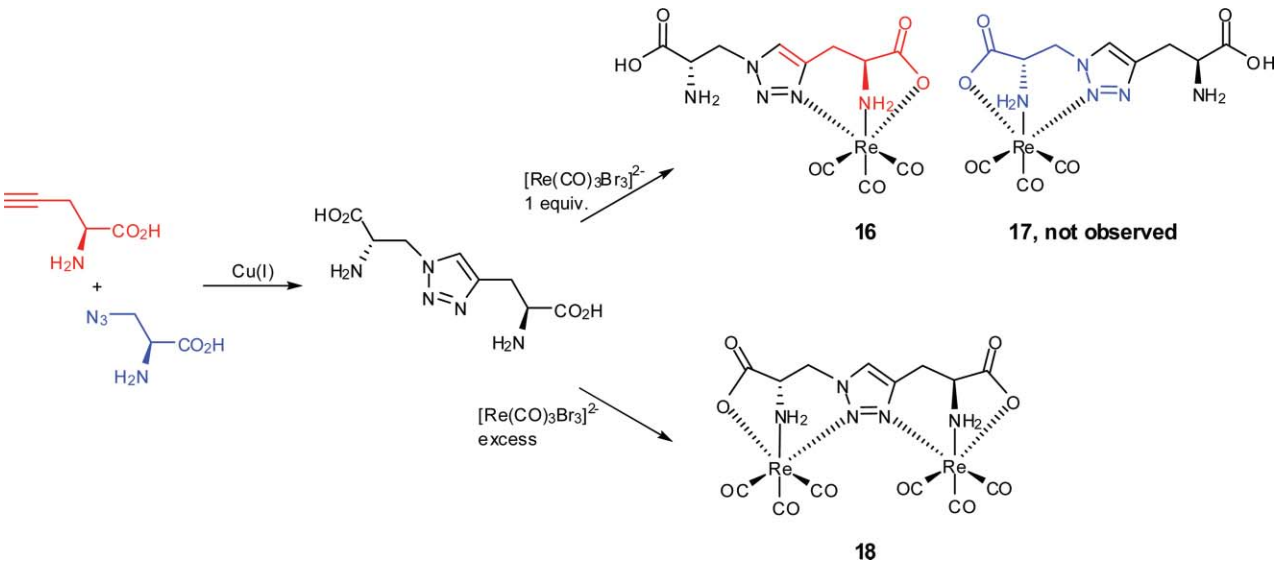
Fig. 13 X-Ray structure analysis of the model complexes **13** (neutral), **14** (cationic) and **15** (anionic).



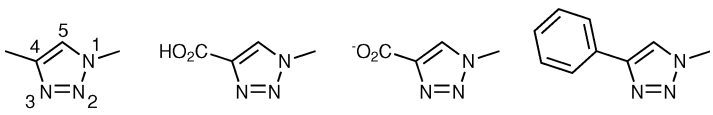
Scheme 6 Triazole-containing ligands which coordinate to the tricarbonyl core through *N2*.

highest electron density to be at *N3* of the triazole (Fig. 14).[9,62] To further investigate the preference for *N3* coordination, a ligand was prepared which offers two tridentate chelating systems within the same compound, one involving *N3* of the 1,2,3-triazole, and one involving *N2* of the 1,2,3-triazole (Scheme 7). Reaction of the ligand with one equivalent of $[ReBr_3(CO)_3][NEt_4]_2$ led to a single product (**16**), in which the metal was coordinated exclusively to the *N3*, *N*α-amine, carboxylate chelating system as revealed by NMR analysis. 1-D and 2-D NMR analyses showed clearly that the protons of the coordinated amine were coupled to the α-CH of the *C4* side chain. As further evidence for this mode of coordination, investigation of the reaction of the ligand with the technetium-99m precursor $[^{99m}Tc(CO)_3(H_2O)_3]^+$, revealed similar behaviour to other chelating systems which coordinate through *N3* in terms of the ligand concentration required to achieve quantitative radiolabelling. Coordination of the ligand *via* the *N2*, *N*α-amine, carboxylate chelating system to give the monometallic complex **17** was not observed. However, reaction of the ligand with excess $[ReBr_3(CO)_3][NEt_4]_2$ led to the formation of a bimetallic complex **18**.

The clicked triazole products from the reaction of a bidentate alkyne and an azide proved to be a class of extraordinarily good chelators for the $^{99m}Tc(CO)_3$ core. The alkyne and azide substrates, however, did not form well-defined complexes with the



Scheme 7 The triazole-containing ligand is capable of either *N2* or *N3* coordination.

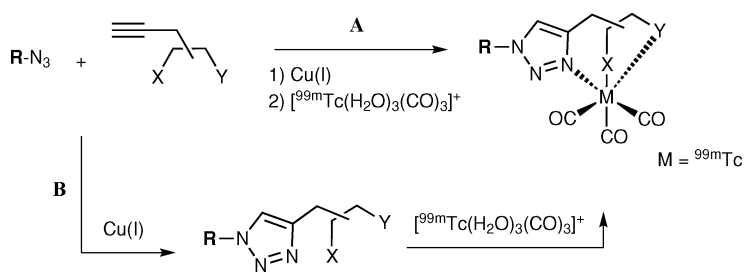


	A	B	C	D
N1	-0.198	-0.204	-0.236	-0.201
N2	-0.071	-0.067	-0.133	-0.071
N3	**-0.268**	**-0.216**	**-0.254**	**-0.264**
C4	-0.086	-0.042	0.012	0.078
C5	-0.060	0.014	-0.050	-0.041

Fig. 14 DFT calculated natural population analyses of compounds **A–D**.

$[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor. These circumstances facilitated a one-pot procedure in which clicked conjugates were prepared and labelled *in situ*. This circumvented isolation and/or purification of the triazole-containing ligands prior to the radiolabelling step.[9,61] We have shown that a variety of azides (including azide-functionalized biomolecules such as peptides, carbohydrates, phospholipids and nucleosides) can be reacted in aqueous solution with propargyl glycine or other alkynes in the presence of a Cu(I) catalyst and subsequently radiolabelled *in situ* (Scheme 8, path A). In all cases the products formed are identical to those obtained with pre-synthesized and purified ligands (path B). This procedure has the potential to provide an extremely efficient method for the preparation of ^{99m}Tc-based radiotracers.

The one-pot and the click-to-chelate concepts were combined to synthesize novel Tc-99m labelled thymidine derivatives (Fig. 15). An azide derivative of thymidine (dT-N_3) was reacted with a series of alkynes (see Fig. 12) to give conjugates with efficient triazole-containing chelating systems, which when labelled with the $M(CO)_3$ core gave complexes with different structures and overall charges.[61] In order to identify the structural and physicochemical parameters necessary to maintain activity towards the target enzyme human cytosolic thymidine kinase (hTK1), the thymidine-chelator conjugates were labelled with technetium. Technetium-labelled thymidine analogues have the potential to act as substrates for hTK1 and therefore as markers for cancer cell proliferation since hTK1 shows a higher than normal expression in a wide variety of cancer cells. Until recently, however, there were no reports of Tc/Re-labelled thymidine derivates with substrate activity towards hTK1.[63,64] Stock solutions of the different alkynes were reacted with dT-N_3, copper(II) acetate and sodium ascorbate in aqueous solution on a 100 μL scale (200 μg dT-N_3). After one hour at 60 °C, the reaction mixtures were labelled directly with the precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$. Investigation of the ability of the clicked, ^{99m}Tc-labelled thymidine analogues to act as substrates for hTK1 revealed that the overall charge and/or structure of the complexes are important parameters for recognition as a



Scheme 8 One-pot protocol (A) provides radiolabelled complexes identical to those obtained using purified triazole chelators (B).

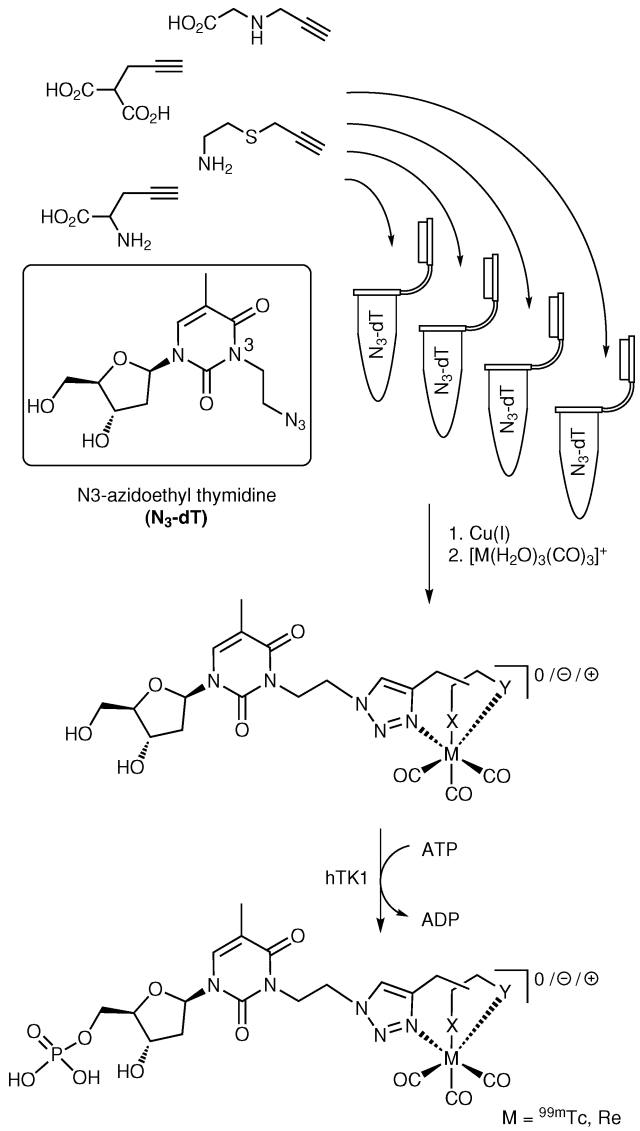


Fig. 15 One-pot synthesis and labelling of N3-functionalized thymidine derivatives, and their ATP-dependent phosphorylation by human thymidine kinase 1.

substrate. It could be shown that the complexes with a neutral overall charge were more readily phosphorylated than cationic thymidine complexes. Using this strategy, synthesis, radiolabelling and semi-quantitative structure–activity investigations could all be performed in a matter of hours; this is remarkable progress when compared with classical (radio)synthetic approaches.[64]

The 1,4-disubstituted 1,2,3-triazole products of the CuAAC reaction share structural, electronic, and coordinative properties with 1,4-disubstituted imidazoles, which are known to be very efficient ligand systems for $[M(H_2O)_3(CO)_3]^+$.[65] This suggested that the CuAAC could be used to prepare 1,2,3-triazole analogues of imidazole-containing chelating systems in which the heterocycle is replaced by a 1,2,3-triazole. To explore this hypothesis, we prepared and evaluated two structurally similar folate derivatives,[66] functionalized with a either a histidine-based chelating system or a triazole-based chelating system (Fig. 16a).[25,67] This comparative study proved the synthesis of the clicked, triazole variant to be considerably shorter and more efficient (approx. 80% overall yield) than the synthesis of the folate tracer with an N(τ)-His-chelating system (approx. 3% overall yield). However, the stability and biological affinity of the isostructural ^{99m}Tc-labelled derivatives *in vitro* were identical, as were their targeting capacities and pharmacological profiles *in vivo* (Fig. 16).[25]

Using appropriate dialkyne building blocks and reacting them with azide-containing compounds, novel ligand systems with two 1,2,3-triazole functionalities can be prepared.[68] Although chelating systems containing multiple triazole heterocycles have been reported,[15] only recently have chelators containing more than one coordinating triazole unit been applied to the functionalization of biomolecules.[24,68,69] With a view to radiopharmaceutical applications, our group has recently explored this approach in combination with the $[M(H_2O)_3(CO)_3]^+$ precursor (M= ^{99m}Tc, Re). The advantage of the dialkyne precursors is that they facilitate the relatively straightforward introduction of a secondary targeting structure, a pharmacokinetic modifier (PEG-tags *etc*), an affinity tag, a therapeutic agent, or a second imaging probe (*e.g.* an organic dye) that would give a multi-modal imaging agent. In the context of radiopharmaceutical development, the incorporation of secondary targeting structures and pharmacokinetic modifiers are of particular interest because off-target accumulation of radioactivity and/or poor uptake at the target are frequent problems. C(α)-bis-propargyl glycine, N(α)-bis-propargyl glycine and N(α)-bis-propargyl lysine were prepared and subsequently reacted with various azide building blocks (Scheme 9) to give tridentate chelators, all of which formed stable complexes with $[M(CO)_3(H_2O)_3]^+$ (M= ^{99m}Tc, Re). In the case of complex **19**, coordination of the two *N3* nitrogens of the triazole heterocycles to the metal core was confirmed by X-ray structure analysis (Fig. 17). We have shown that attached to a biomolecule (*e.g.* a fragment of the bombesin peptide) *via* the pendant carboxylate, the novel chelates are suitable for *in vivo* applications.[68] Furthermore, using two different azide derivatives and employing a sequential click strategy as reported by the Leigh and Hughes groups,[70] asymmetric bis-triazole compounds could be readily prepared. This procedure made use of a bis-propargyl compound in which one of the alkynes was protected with a trimethylsilyl group. After a first click reaction with the unprotected alkyne, the trimethylsilyl group was removed *in situ* and a second triazole-forming click reaction performed. In principle, this approach allows the incorporation of three different components into the final chelate.

The Benoist group used a similar approach to our own to prepare multidentate triazole-containing ligands for potential radiopharmaceutical or other bioanalytical applications, starting from a diazide precursor.[24] Their ligands contained two triazole units, each with an iminodiacetic acid or di(2-picolyl)amine side chain, and linked by either an ethyl or propyl spacer (Scheme 10). The aim was to provide a binding site for either a lanthanide or other transition metal cation, and at the same time incorporate a second functional group, in this case an amine, to allow conjugation to a biomolecule. The ligand with the di(2-picolyl)amine side chains was reacted with an $Re(CO)_3$ precursor, and as expected gave a complex with a metal-to-ligand ratio of 2 : 1. Coordination of the $Re(CO)_3$ core is reported to occur exclusively through the tridentate di(2-picolyl)amine side chains, without involvement of the 1,2,3-triazole. This is surprising, since our group has previously observed that a mixture of $Re(CO)_3$ complexes is formed when more than one potentially tridentate

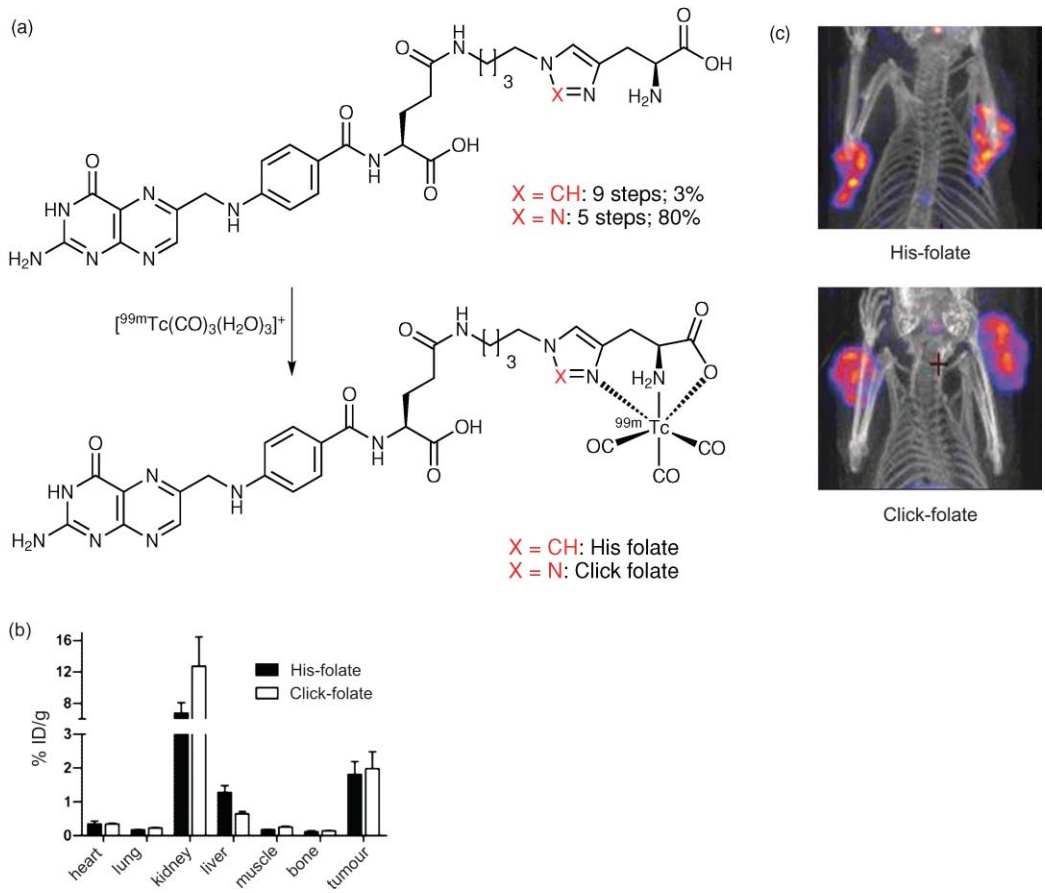


Fig. 16 Comparison of two isostructural folate derivatives: (a) Structure and synthetic yields of the His folate and click folate; (b) biodistributions of ^{99m}Tc-labelled folate tracers 24 h post injection; (c) combined small animal SPECT/CT of xenografted mice 24 h post injection of the radiotracer. Specific accumulation of both radiotracers was observed only in the tumour xenografts (coloured red) and in folic acid receptor positive organs such as the kidneys (not shown).

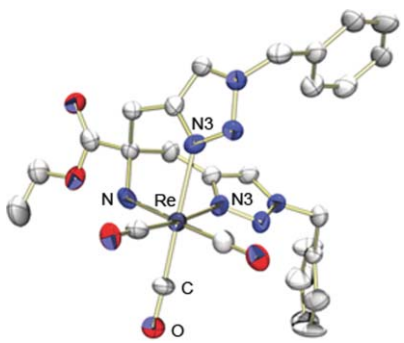


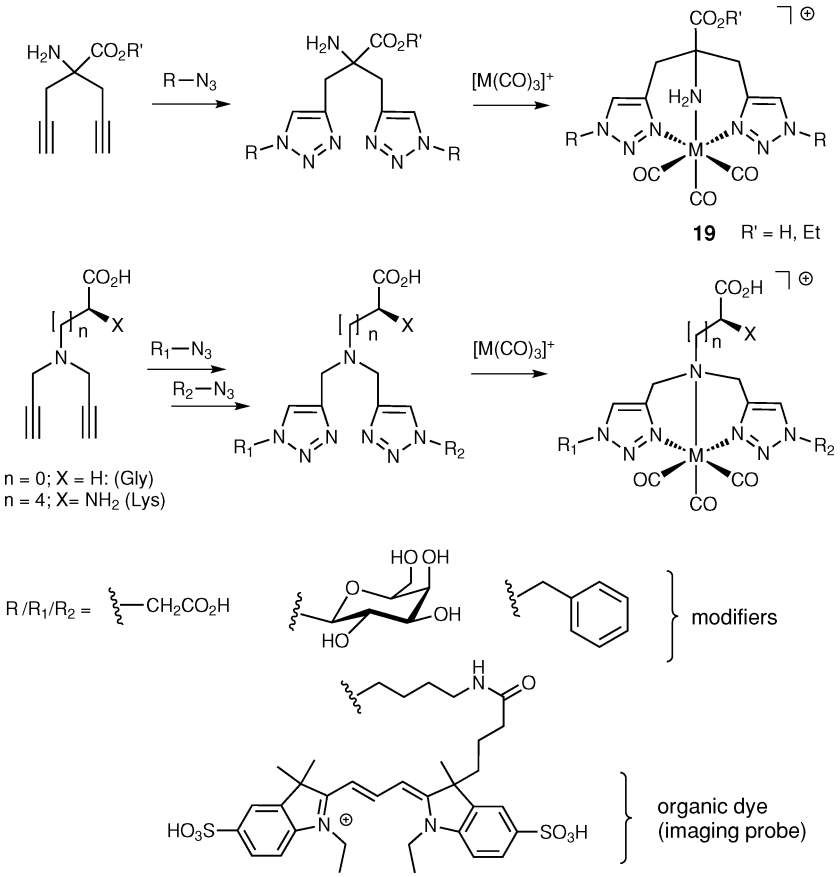
Fig. 17 X-ray structure analysis of the ethyl ester derivative of symmetrical complex **19** (R = Bn, R′ = Et).

(triazole-containing) chelating system is available in the same ligand system.[61]

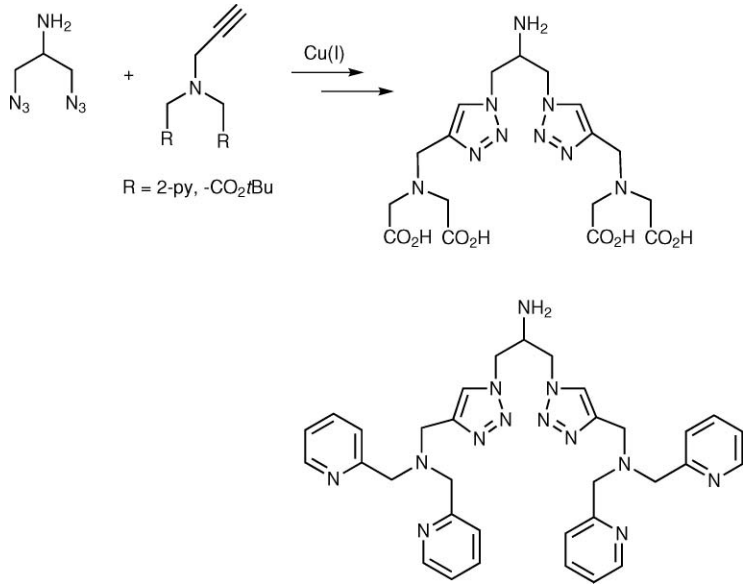
Other bioconjugates and potential chemotherapeutics

Many well-known platinum based anticancer compounds share the general formula *cis*-[$PtX_2(NR_3)_2$], where X is a leaving group such as chloride and R is an organic fragment.[71] Using the Cu(I)-catalyzed cycloaddition Gautier *et al.* prepared a series of potentially bidentate triazole-containing ligands and a number of Pt complexes. Several of the Pt complexes were screened against various cancer cell lines.[62] The first set of compounds was derived from an amine or carboxylic acid functionalized alkyne, so that *N3* of the triazole and the *C4* substituent coordinated to the metal centre to form a five-membered chelate (Fig. 18a). For the triazole-amine ligand, neutral (**20**) and cationic (**21**) *N*,*N3*-coordinated complexes were obtained depending on the platinum source used. Both complexes were characterized by NMR, and in the case of the neutral complex **20** by X-ray crystallography (Fig. 18b). The reaction of the analogous triazole-carboxylic acid ligand led to the formation of [PtL_2] and [PtX_2L] complexes, **22** and **23** respectively. The second series of potential ligands was derived from an amine or carboxylic acid functionalized azide, designed to coordinate to the metal *via N2* of the 1,2,3-triazole to form a six-membered chelate. However, neither of these ligands formed characterizable coordination complexes with platinum. Four of the novel Pt complexes were tested for their activity towards three cancer cell lines. In agreement with the known structure–activity relationships of platinum drugs,[71] only the *cis*-N_2PtCl_2 coordination complex **20** showed significant cytotoxicity.

Multidentate triazole-containing ligands for zinc have been attached to carbohydrates.[69] The aim was a flexible yet straightforward route to carbohydrate-metal complexes, which might be used to provide insight into carbohydrate-protein interactions.[72]



Scheme 9 Synthesis of double-click chelators for the $M(CO)_3$ core (M = ^{99m}Tc, Re).



Scheme 10 Multidentate triazole-containing ligands for potential complexation of (radio)lanthanide and transition metal cations.

Several potential ligand systems were synthesized, along with the corresponding Zn complexes of two of the compounds. The ligand systems were based on a bis-triazole motif, to coordinate to the metal through the two triazoles (*N3*) and two amides (*O*-coordination) (complex **24**) and in some cases also a pyridyl nitrogen (Fig. 19, **25**). It is reported that the first cycloaddition proceeds significantly faster than the second cycloaddition and so ligands with two different sugars can be prepared without having to use a mono-protected bis-alkyne substrate.[69] This is contrary to our own observations, however, where reactions of bis-alkynes with one equivalent of azide led to mixtures of products containing one or two triazoles.[68]

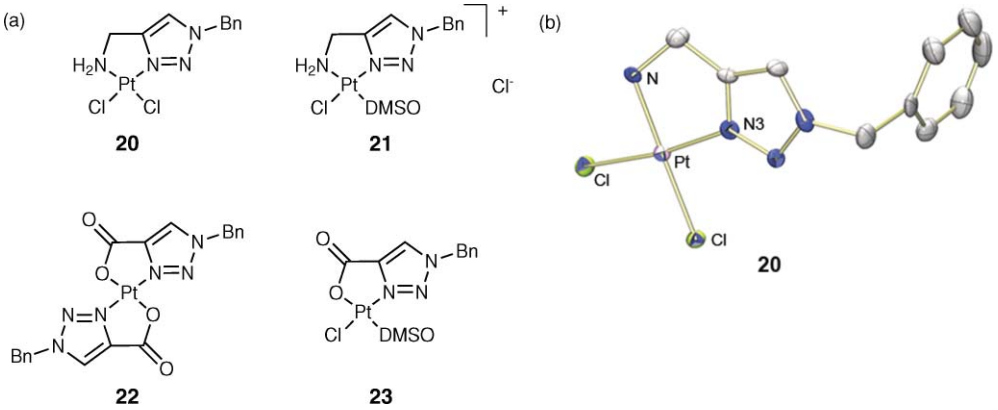


Fig. 18 (a) Pt complexes of triazole-containing ligands. Only **20** exhibited significant cytotoxicity. (b) X-Ray crystal structure of complex **20**.

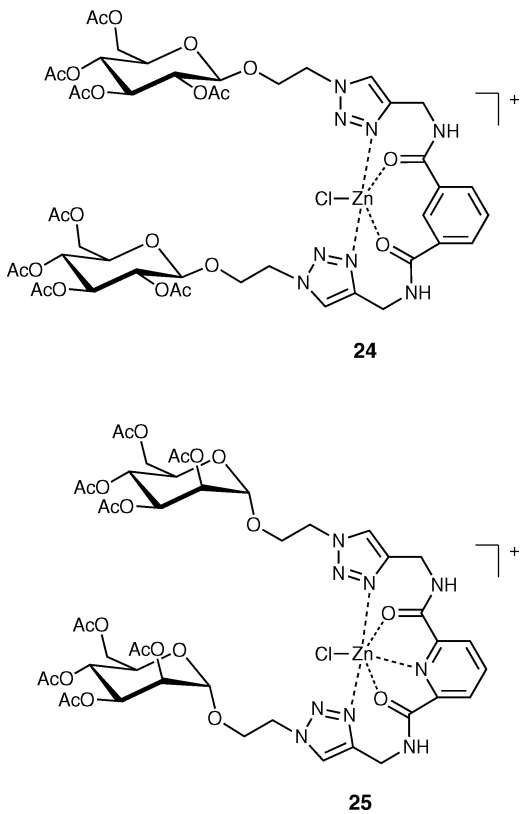
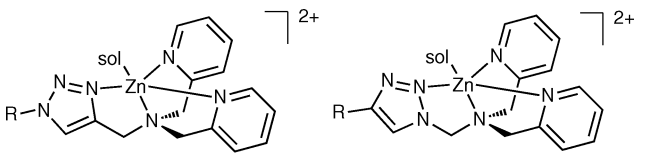


Fig. 19 Zinc complexes of bis-triazole functionalized carbohydrates.

Metal sensing chelators and complexes with interesting electrochemical and photophysical properties

Metal sensors

Chemical sensors for the recognition of environmentally and biologically important molecular and ionic species have been, and continue to be, widely investigated.[73] Several groups have used the CuAAC reaction for the synthesis of novel metal sensing compounds in which the triazole is likely to be involved in coordination to the metal. For example, Zhu *et al.* have identified nitrogen-rich polydentate ligands containing a triazole, tertiary amine, and two pyridine groups, which have the potential to be used as metal responsive fluorophores since the fluorescence increases dramatically on coordination of zinc.[74] Two of the zinc complexes in which *N3* of the triazole ligand coordinates to the metal were structurally characterized. Derivatives in which coordination of the ligand to the metal through *N3* of the triazole is sterically difficult, yet still show increased fluorescence on coordination of Zn^{2+} were also prepared (Fig. 20). In these cases it was suggested that coordination to the metal occurs through *N2* of the triazole. The Bunz group also synthesized small triazole-containing ligands, and investigated the changes in their fluorescence spectra on addition of divalent metal cations.[75] The ligands were prepared from either 2-, 3-, or 4-ethynyl pyridine and different azides. For comparative purposes a compound with only a triazole heterocycle and no pyridine was also investigated. This compound also showed increased fluorescence on addition of certain metal cations (Zn^{2+}, Mn^{2+}, Cu^{2+}), suggesting the triazole coordinated to the metal. However, in this case the changes in fluorescence were small relative to those induced with the pyridine-containing ligands. The ligand derived from 2-ethynyl pyridine was the only compound capable of bidentate coordination of metal cations, however, comparison with the metal response of the ligand derived from 4-ethynyl pyridine suggested that coordination is primarily to the pyridine unit.



26, *N3* coordination
R = anthracene

27, *N2* coordination
R = anisole

Fig. 20 Zinc complexes **26** and **27** showed increased fluorescence relative to the uncomplexed ligands.

Watkinson and Todd and co-workers have employed a different approach for the development of two novel chemical sensors. They used the CuAAC to synthesize scorpion-like ligands in which a triazole was attached to a macrocyclic compound to provide a weakly coordinating chelating ligand at the axial position (Fig. 21a). This type of ligand was first used to generate a selective zinc sensor by the reaction of an alkyne-functionalized cyclam with an azide-functionalized fluorophore.[76] Coordination of zinc (**28**) led to a significant enhancement of the fluorescence emission.

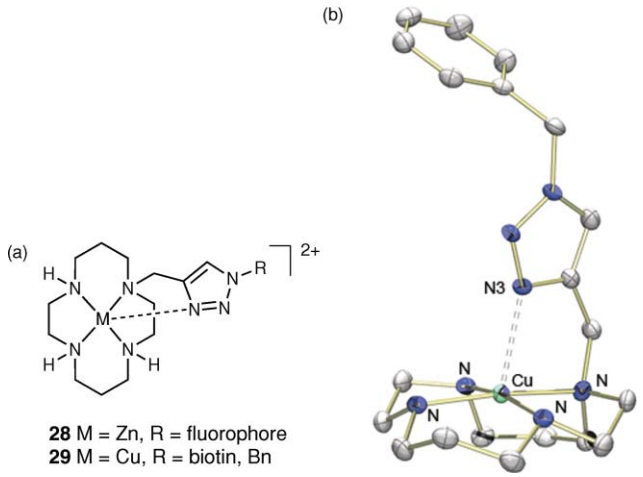


Fig. 21 (a) Scorpionate triazole complexes to detect zinc and copper. (b) X-Ray crystal structure of complex **29** (R = Bn).

Furthermore, zinc could be detected at concentrations significantly lower than the physiological Zn(II) level over a range of pHs, and the ligand proved selective for Zn(II) in competition with most other physiologically relevant metal ions. The same ligand motif was used to synthesize an "allosteric scorpionate", based on the weak axial coordination of the triazole to copper.[77] The cyclam-triazole ligand was coupled to biotin and its copper complex **29** was prepared. X-ray crystal analysis of a model compound confirmed the coordination of copper *via* the macrocyclic ligand and the triazole (Fig. 21b). For the biotin-coupled complex it could be elegantly shown by EPR that binding of the conjugate to avidin resulted in a change in the coordination sphere of copper, which was qualitatively consistent with labilisation of the scorpionate triazole ligand.

Reinaud and co-workers used click chemistry to provide a versatile strategy for the functionalization of calixarenes.[78] They were interested in calix[6]arenes functionalized on the small rim with metal coordinating groups such as *N*-methylimidazole, since incorporation of a metal centre rigidifies the cavity of the calixarene and provides a labile coordination site for host–guest recognition studies. Click chemistry was used to functionalize the large rim of an *N*-methylimidazole functionalized calix[6]arene, to give a compound with two potential *N*,*N*,*N* metal coordinating sites (Scheme 11). Addition of one equivalent of Zn^{2+} led exclusively to the coordination *via* the *N*-methylimidazole ligands (complex **30**), and addition of a second equivalent of Zn^{2+} gave the bimetallic complex **31** with coordination to the three triazole ligands.

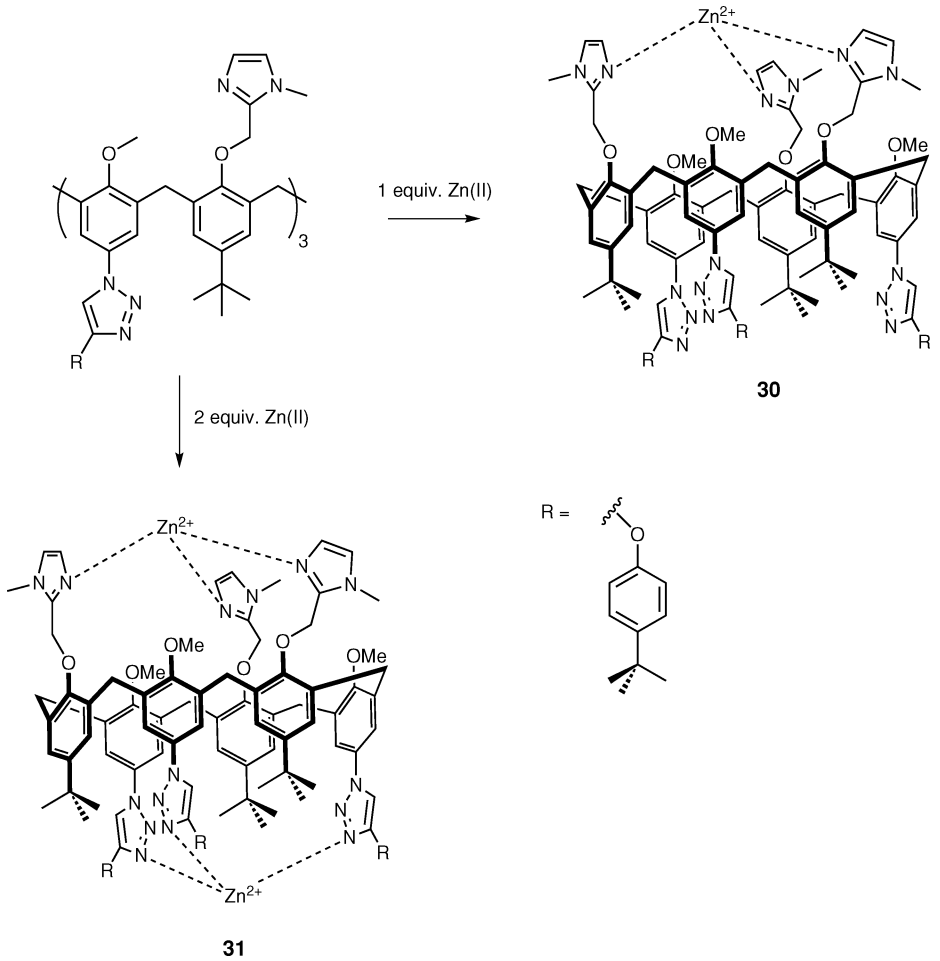
Several groups have investigated the selectivities of triazole-containing ligands towards a series of metal cations. Chung *et al.* used the CuAAC to couple potential bis-triazole chelators to pyrene, and examined the conditions required to quench the inherent fluorescence of the ligands.[79] Analysis of the effects of fifteen metal ions was indicative of two types of binding, suggesting the ligand can adopt two different conformations. Complexation of Cu^{2+}, Hg^{2+}, Cr^{2+}, Pb^{2+} and Ni^{2+} quenched both the monomer and excimer emissions, whereas complexation of Cd^{2+} and Zn^{2+} led to an increase in monomer emission, but quenched excimer emission (Fig. 22). Kim *et al.* and Yang *et al.* report similar effects when pyrene reporting units were fixed onto a rigid calix[4]arene support using two 1,2,3-triazoles as both spacers and cation-binding sites.[80] Coordination of Cd^{2+} and Zn^{2+} led to an enhanced monomer emission and decreased excimer emission. Using a similar strategy Xie *et al.* prepared two functionalized cyclodextrins as potentially metal responsive fluorophores (Fig. 23).[81] Their first compound, a C-6 triazole-pyridine functionalized cyclodextrin (**32**), showed increased fluorescence on complexation of Zn^{2} and Mg^{2+}, but the fluorescence was quenched completely by Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Ag^{+}. Model triazole derivatives confirmed that the fluorescence of the ligand originated from the conjugated triazole-pyridine system. With a similar compound, a C-6 triazole-benzothiadiazoyl functionalized cyclodextrin (**33**) no fluorescence enhancement was observed on addition of metal cations and instead the fluorescence emission was partially quenched by addition of a number of different first row transition metal cations, and completely quenched by addition of Ni^{2+}.

Complexes with pyridine-triazole ligands and analogues

Bipyridine (bpy) and terpyridine (tpy) ligand systems are among the most widely studied chelating ligands for transition metals as a result of the stability, electrochemical and photophysical properties of their complexes.[82] Complexes have found applications in opto-electronic devices, as redox and photo-catalysts, as building blocks for supramolecular structures and for medical and analytical purposes.[83] Functionalization of the ligand systems, is crucial for the optimization of the properties of the complexes, and it is therefore not surprising that triazole-containing analogues readily prepared by the CuAAC have begun to receive attention (Fig. 24). A number of analogues have been investigated, including bis-triazole (bta) compounds and their complexes with rhenium, ruthenium and copper;[84] pyridine-triazole (pyta) derivatives and their coordination behaviour with ruthenium[85,86] and rhenium;[87] and bis-triazole-pyridine (btpy) derivatives and their complexation with ruthenium, iron and europium.[88,89]

Monkowius and König and co-workers synthesized three symmetrical bis-triazole ligands from 1,3-butadiyne and different organic azides.[84] With all of the ligands, complexes of the general formula $[Ru(bta)_3]^{2+}$ were synthesized in good yield from $RuCl_3 4{\cdot}H_2O$, while with copper ($[Cu(bta)L]^{+}$) and rhenium ($[Re(CO)_3Cl(bta)]$) complexes with a metal-to-ligand ratio of 1 : 1 were prepared. For each metal, representative complexes were characterized by X-ray crystallography and confirmed the expected coordination of the bta ligands through the *N3* atoms of the triazoles to form five-membered chelate rings (Fig. 25). Despite the structural similarities of the bta complexes with their bpy analogues, the photophysical properties of the complexes were not comparable. The UV/vis spectra revealed two absorptions significantly higher in energy than for analogous complexes with bpy. Unlike bpy analogues, none of the complexes was an emitter in solution or the solid state. Since they did not form complexes with interesting properties in their own right, the bis-triazole ligands were therefore envisaged as easy to modify "innocent" ligands.

Monofunctionalized pyridine-triazole ligands can be readily prepared using click chemistry from 2-ethynyl pyridine and an azide, and form a five-membered chelate ring when coordinated to a metal. Schubert *et al.* investigated the reaction of ruthenium complexes with one, two and three equivalents of pyta ligand.[86] With three equivalents of the unsymmetrical ligand a statistical



Scheme 11 Functionalized calix[6]arene with two metal binding sites.

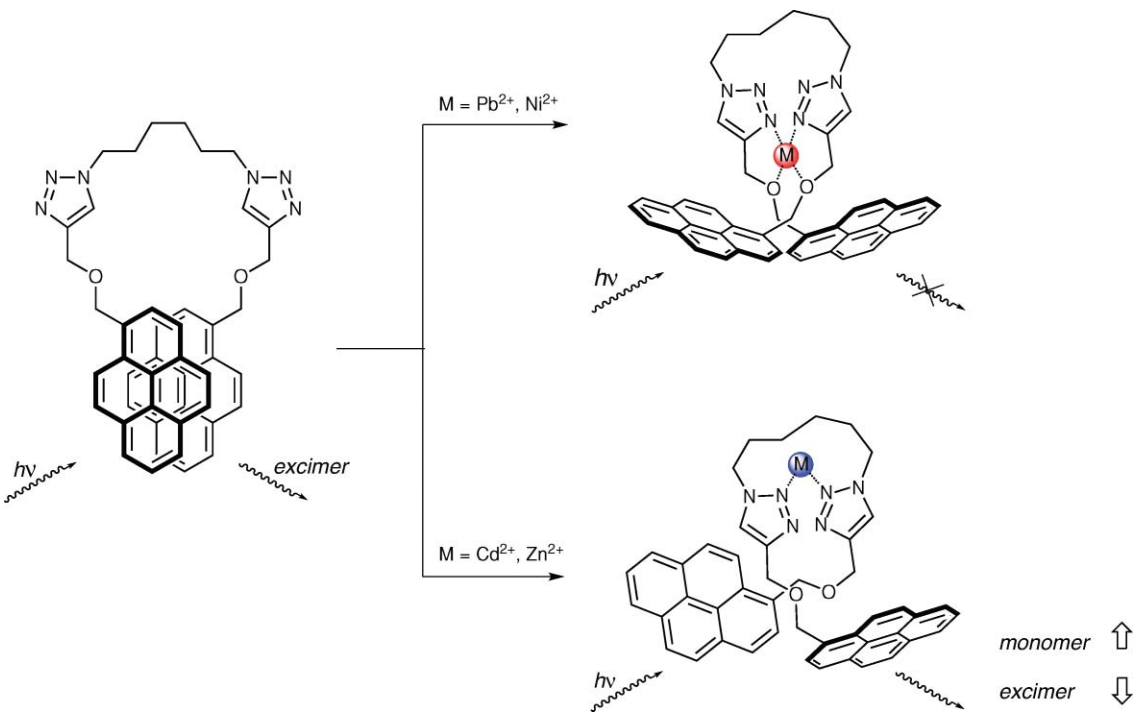
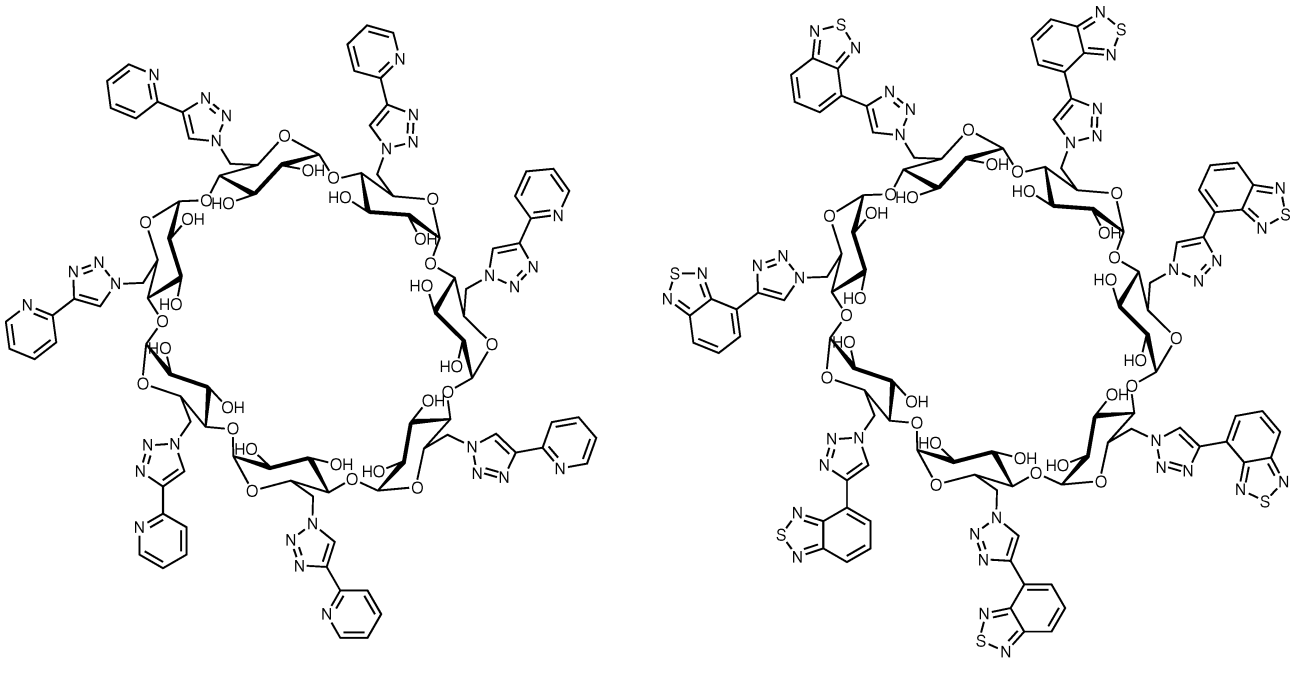


Fig. 22 Postulated binding modes of different metal cations with bis-triazole linked pyrenes.



32 **33**

Fig. 23 Functionalized cyclodextrins as metal responsive fluorophores. Only compound **32** showed increased fluorescence on addition of metal cations.

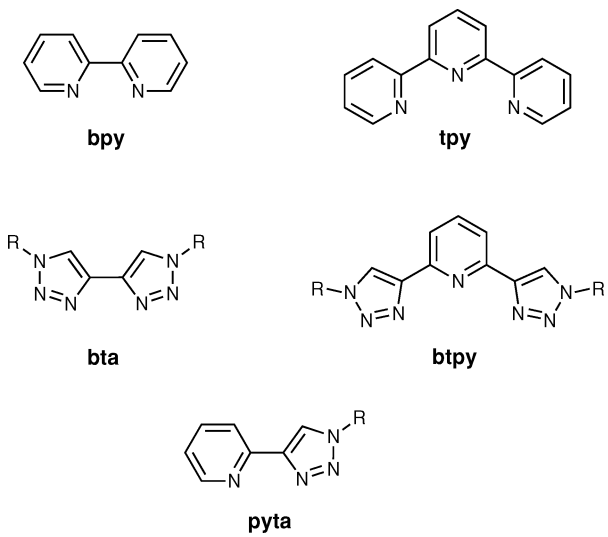
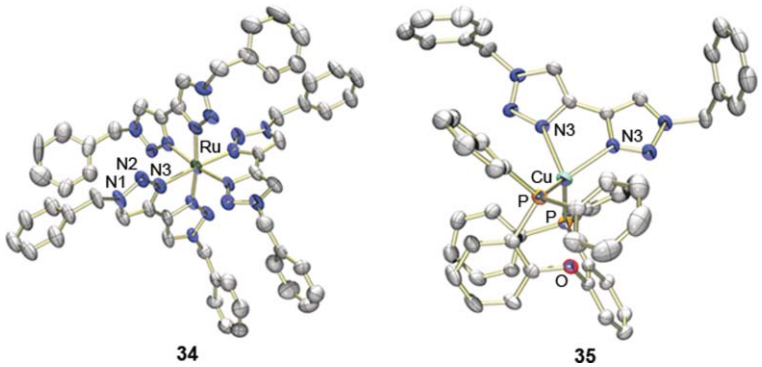


Fig. 24 Bipyridine (bpy), terpyridine (tpy) and "clicked" triazole analogues (bta, btpy, pyta).

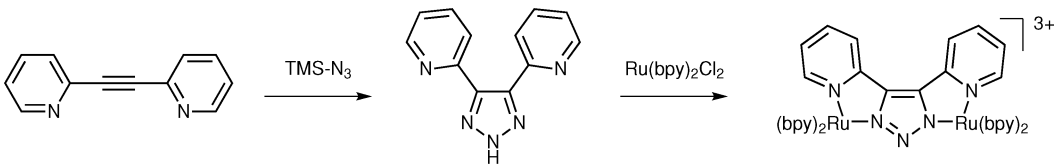
mixture of the *fac* and *mer* isomers of the complex $[Ru(pyta)_3]^{2+}$ was isolated, but only when a bulky substituent was included at position *N1* of the triazole heterocycle was it possible to separate the mixture of isomers of the corresponding complex. Analysis of photophysical and electrochemical properties of the complexes $[Ru(bpy)_{3-n}(pyta)_n]^{2+}$ revealed all had very similar properties. An increase in the number of pyta ligands led to a blue-shift of the MLCT band in the UV/vis spectra, a blue-shift of the photoluminescence spectra, and an increase in the energy band gap observed in the cyclic voltamograms. Yano *et al.* prepared $[Re(CO)_3Cl(pyta)]$ complexes and in contrast to the Re complexes with bta ligands, found that they exhibited similar photophysical properties to the $[Re(CO)_3Cl(bpy)]$ analogue.[87] Fletcher *et al.* compared the electrochemical properties of $[Ru(pyta)_3]^{2+}$ and $[Ru(bta)_3]^{2+}$ complexes.[85] They found that the replacement of the pyridine rings by triazoles resulted in significantly more negative reduction potentials, and also that the oxidation potentials were sensitive to the *N1* substituent of the triazole ring. Steel *et al.* describe a ligand system related to pyta synthesized using the copper-free cycloaddition of an internal alkyne and TMS-azide, and able to act as a bridging ligand between two metal centres.[90] The symmetrical, 4,5-difunctionalized ligand was synthesized from di(2-pyridyl)acetylene and azidotrimethylsilane (Scheme 12). Reaction with excess $[Ru(bpy)_2Cl_2]$ led to an approximately 1 : 1 ratio of the *meso* and *rac* isomers of the dinuclear complex $[(Ru(bpy)_2)_2L]$ (Fig. 26). Each of the stereoisomers showed two well-separated oxidation potentials, indicative of strong metal-metal interactions. The comproportionation constant provided a measure of the extent of the metal-metal interaction, and this was found to be stronger in the *rac* isomer.

Two groups have investigated triazole analogues of the commonly used tridentate terpy ligands. The triazole-containing ligands are synthesized from 2,6-diethynylpyridines and suitable azides. Flood *et al.* prepared btpy ligands from unsubstituted 2,6-diethynylpyridine and alkyl azides, and coordination compounds with iron, ruthenium and europium.[88] The btpy ligands were found to be less sterically demanding than their tpy analogues, as evident from the crystal structures of the complexes. For the Fe and Ru cations, a greater distortion from octahedral symmetry was accommodated than for analogous tpy complexes. The steric freedom when compared with tpy analogues was even more apparent in the tricapped trigonal prism structure of the $[Eu(btpy)_3]^{3+}$ cation. UV-vis spectra of the Fe and Ru complexes



34 35

Fig. 25 X-ray crystal structures of $[Ru(bta)_3]^{2+}$ (**34**) and $[Cu(bta)L]^{+}$ (**35**). L is a bridged bis(diphenylphosphine) ligand. Both bta ligands are derived from benzylazide (R = Bn; Fig. 23).



36

Scheme 12 Bis-triazole metal bridging ligand synthesized using click chemistry.

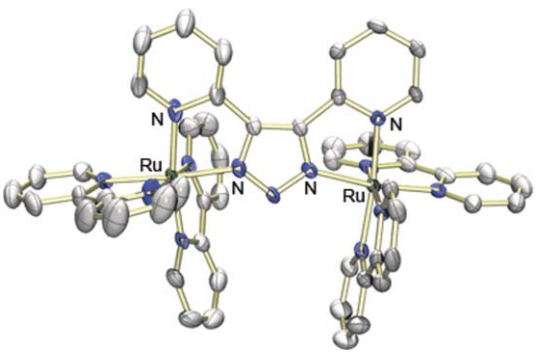
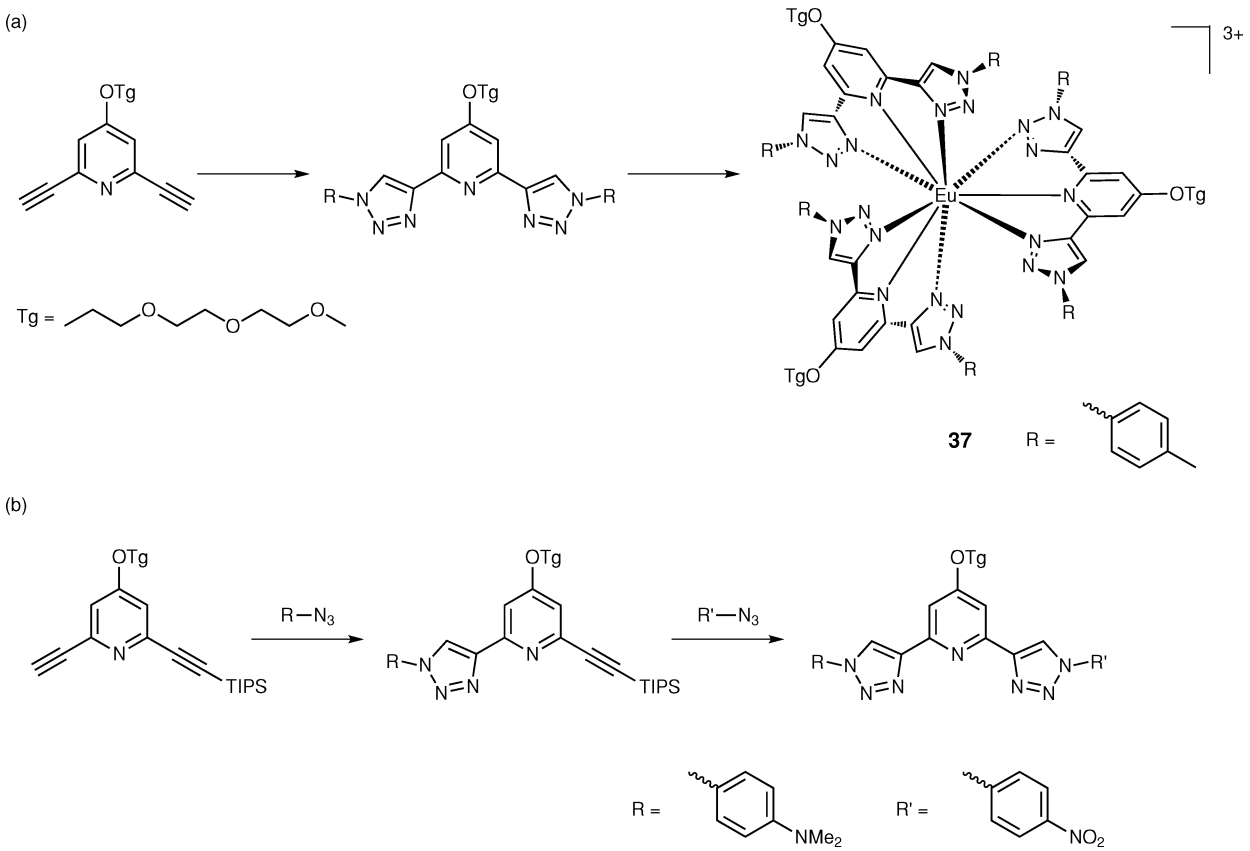


Fig. 26 X-Ray crystal structure of complex **36** (*rac* isomer).

were similar to analogous tpy complexes but blue-shifted, which is consistent with the LUMO of the ligand being at higher energy for the btpy ligand than for tpy. Hecht and Limberg and co-workers prepared btpy ligands with electron-donating and electron-withdrawing groups on the pyridine ring and a variety of substituents at the *N1* positions of the two triazoles (Scheme 13).[89] They synthesized both symmetrical and unsymmetrical ligands, using sequential click reactions. Preliminary investigations of the coordination chemistry were carried out with Fe and Eu. The $[Fe(btpy)_2]^{2+}$ complex prepared revealed unexpectedly short Fe–N bond lengths and ^{1}H NMR spectra which were consistent with a low-spin state. This suggests that the btpy ligand is more similar to tpy than bis(pyrazole)pyridine, since complexes with bis(pyrazole)pyridine ligands usually switch from low-spin ground states to high spin-states at temperatures significantly below room temperature. Structural characterization of a $[Eu(btpy)_3]^{3+}$ complex (**37**) revealed greater steric freedom than comparable complexes with tpy, which is in agreement with the results of Flood *et al.*[88]

Conclusions

The CuAAC has proven to be one of the most versatile ligation reactions available. The simplicity and robustness of the reaction have led to applications in many areas of chemistry and biochemistry. However, despite the fact that the 1,2,3-triazoles formed in the reaction are versatile ligands for a range of metals, capable of coordination *via* either *N2*, *N3* or *C5*, the scope and potential of the CuAAC in coordination chemistry are only just beginning to be appreciated. The overwhelming advantage of the CuAAC reaction in all its applications is the modular nature of the reaction and high functional group tolerance. These factors are particularly relevant in the synthesis of metal chelating systems, as they allow an unprecedented number of potential ligands to be readily prepared with high yields and minimal synthetic effort. Additional metal donor functionalities can be incorporated at the *N1* and *C4* positions of the 1,2,3-triazole, enabling the preparation of polydentate chelating systems in which the triazole is an integral part of the chelator. The modular nature of the reaction provides a unique and straightforward opportunity to systematically tune the electronic properties of the metal centre, the steric requirements of the ligand, hydrophilicity, charge and other physicochemical properties of the resulting complexes. The optimization of such properties is crucial in the preparation of metal complexes for use in catalysis, environmental and pharmaceutical applications. We have shown in the case of technetium-labelled radiopharmaceuticals, that the CuAAC reaction enables an incredibly efficient and straightforward method for the preparation of metal-labelled bioconjugates. In the case of technetium, the strategy provides a handle to label almost any azide-containing biomolecule with a diagnostically relevant radionuclide. This approach could easily be developed and applied to the synthesis of other (radio)metal conjugates for diagnostic or therapeutic applications. As the various other examples discussed have highlighted, the CuAAC



Scheme 13 (a) Synthesis of symmetrical triazole analogues of terpyridine. (b) Synthesis of unsymmetrical triazole analogues of terpyridine using a sequential click strategy.

reaction is beginning to be exploited for the preparation of ligands for a wide range of metals and applications. Given the ease with which novel chelators can be prepared and elaborated, we anticipate that the number and diversity of applications will continue to increase.

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