A metal-complex-tolerant CuAAC 'click' protocol exemplified through the preparation of homo- and mixed-metal-coordinated [2]rotaxanes†

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A series of mono- and *bis*-metallated [2]rotaxanes has been prepared using a CuAAC 'click' protocol that is compatible with metal-coordinated building blocks and ligands; the methodology provides a general means for appending a metal ion or complex to an organic scaffold *via* Cu(I)-catalysed 'click' chemistry, even when the molecule contains redox-active or kinetically labile metals or vacant ligand sites.

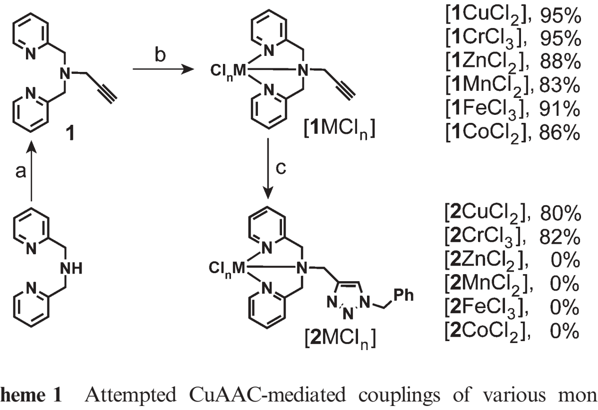
Since its discovery,[1] the Huisgen–Meldal–Fokin Cu(I)-catalyzed terminal alkyne–azide cycloaddition (the CuAAC[2] 'click'[3] reaction) has attracted great interest[4] because of its utility in chemically bonding functional molecular fragments in a precise, predictable and efficient fashion under a myriad of conditions and situations. Despite its exceptional versatility, however, to date there have been few reports on performing the CuAAC reaction in the presence of other redox-active metal ions or substrates containing multidentate binding sites capable of sequestering the copper catalyst.[5] The few examples of metal-coordinated alkynes or azides to have been successfully employed in the CuAAC reaction thus far include ethynylferrocene,[6] an organometallic iridium complex,[7] metalloporphyrins,[8] a lanthanide-bound cyclen derivative,[9] a ruthenium dimer functionalised with an alkyne[10] and Cu(I)-coordinated rotaxanes.[11] While some of these examples offer methods for attaching specific metals to particular molecular structures, most of the complexes are kinetically inert and none allow for the ready variation of the metal.

Here we present a strategy for the assembly of multiple (homo- and mixed-) metal-containing products using the CuAAC reaction by employing a simple alkyne functionalised tridentate ligand, **1**, capable of coordinating to a variety of transition metal ions (Scheme 1). Through this synthon, a series of homo- and mixed-metal-chelated [2]rotaxanes has been prepared (Schemes 2 and 3).

When attempting the CuAAC reaction in the presence of potentially ligating groups, the temptation is to use the Cu(I) salt in excess quantities to compensate for copper being sequestered by the ligand. The situation is further complicated if other transition metal ions are present as they may be displaced, either directly by Cu(I) or labilised by electron transfer to or from the redox-sensitive Cu(I). However, during studies to derivatise rotaxanes with metal-chelating groups,[12] we found that an alkyne-derivatised *bis*-pyridin-2-ylmethylamine (BPA) tridentate ligand **1** bound to either $CuCl_2$, [**1**$CuCl_2$], or the kinetically inert $CrCl_3$, [**1**$CrCl_3$], could be effectively employed in the CuAAC reaction using a catalytic amount (10 mol%) of Cu(I) to generate the metal-containing triazoles [**2**$CuCl_2$] and [**2**$CrCl_3$] in 80% and 82% yields, respectively (Scheme 1).

Attempts to extend this protocol to other first row transition metal complexes of **2**, including [**2**$ZnCl_2$], [**2**$MnCl_2$], [**2**$FeCl_3$] and [**2**$CoCl_2$], were unsuccessful, however. Although in some cases increasing the amount of the Cu(I) catalyst used to > 1 equivalent enabled the CuAAC reaction to proceed, this also resulted in displacement of the original metal from the BPA unit by oxidised Cu(II). In contrast, Cr(III) was not displaced during the formation or isolation of [**2**$CrCl_3$], nor did it participate in any electron transfer reactions. In fact, forcing conditions (1.5 equiv. of KCN, CH_3OH, reflux, 12 h, 80%) were necessary to liberate it from the derivatised BPA ligand.

These results led us to develop a method for coupling homo- and mixed-metal chelated fragments with the CuAAC reaction, exemplified through a series of [2]rotaxanes (Schemes 2 and 3). A functionalised [2]rotaxane, **3**, bearing two BPA chelating sites (one attached to the rotaxane macrocycle, one to the rotaxane thread) was synthesised using a hydrogen bond-templated clipping strategy (Scheme 2).[13] To a solution of thread **4**[12] and **5** (obtained from deprotection of **6**, Scheme 2, step a) in $CHCl_3$, was added 5-azidoisophthaloyl dichloride[14] to yield azido[2]rotaxane **7** (52%, Scheme 2, step b). Prior to reacting the azido[2]rotaxane with alkynes [**1**$CuCl_2$] and [**1**$CrCl_3$], the BPA tridentate binding site of the thread was protected by coordination to Cu(II), generating [**7**(*thread*-$CuCl_2$)] (Scheme 2, step c). Complexes



Scheme 1 Attempted CuAAC-mediated couplings of various mono-metallated alkyne substrates, [**1**MCl_n], with benzyl azide. a) Propargyl bromide, Et_3N, toluene, reflux, 12 h, 60%; b) MCl_n, CH_3OH, RT, 1 h; c) benzyl azide, 0.1 equiv. $Cu(CH_3CN)_4PF_6$, 1.1 equiv. *N*,*N*-diisopropylethylamine (DIPEA), CH_2Cl_2–CH_3OH (9 : 1), RT, 12 h.

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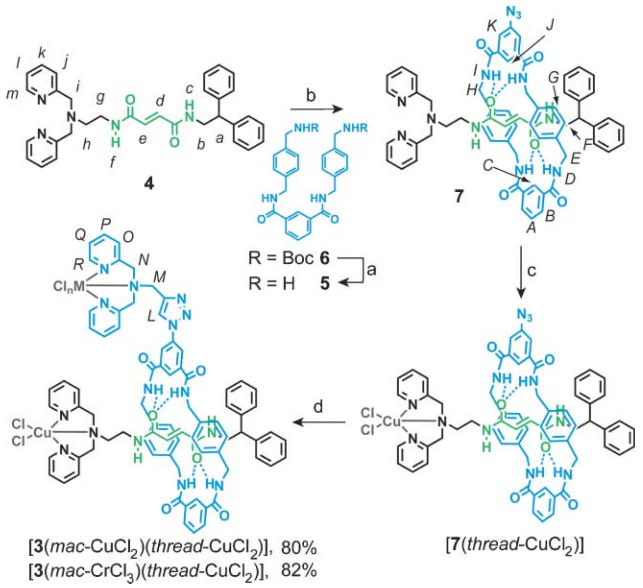
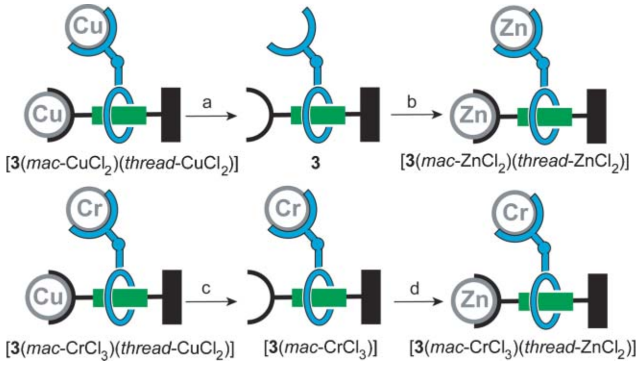


Scheme 2 Assembly of *bis*-metallated [2]rotaxanes *via* a CuAAC reaction. a) CF_3CO_2H, CH_2Cl_2, RT, 12 h; A-21 amberlyst, CH_2Cl_2–CH_3OH (1 : 1), RT, 1 h, quantitative; b) 5-azidoisophthaloyl dichloride, $CHCl_3$, Et_3N, RT, 12 h, 52%; c) $CuCl_2·2H_2O$, CH_3OH, RT, 1 h, 95%; d) [**1**$CuCl_2$] or [**1**$CrCl_3$], 0.1 equiv. $Cu(CH_3CN)_4PF_6$, DIPEA, CH_2Cl_2–CH_3OH (9 : 1), RT, 12 h.

[**3**(*mac*-$CuCl_2$)(*thread*-$CuCl_2$)] and [**3**(*mac*-$CrCl_3$)(*thread*-$CuCl_2$)] were then obtained in good yield using the standard CuAAC conditions.

The difference in lability of the metal ions allowed us to remove the Cu(II) and selectively coordinate other metal ions at the vacant BPA site(s). Compound [**3**(*mac*-$CuCl_2$)(*thread*-$CuCl_2$)] was fully demetallated by simple washing with a saturated aqueous solution of Na_4EDTA (tetrasodium ethylenediamine tetraacetate) to give the metal-free [2]rotaxane **3** (Scheme 3, step a). Addition of $ZnCl_2$ then afforded the *bis*-Zn(II)-metallated complex [**3**(*mac*-$ZnCl_2$)(*thread*-$ZnCl_2$)] (Scheme 3, step b). Alternatively, mixed-metal-chelated [2]rotaxanes could be prepared. Selective removal of the Cu(II) from [**3**(*mac*-$CrCl_3$)(*thread*-$CuCl_2$)] afforded the kinetically stable mono-metallated rotaxane [**3**(*mac*-$CrCl_3$)] (Scheme 3, step c). [**3**(*mac*-$CrCl_3$)] was then complexed with $ZnCl_2$ to produce the mixed-*bis*-metallated rotaxane complex [**3**(*mac*-$CrCl_3$)(*thread*-$ZnCl_2$)] (Scheme 3, step d). To the best of our knowledge, this is only the second example of a mixed-metal coordinated rotaxane.[15] The protection of the BPA ligand with Cu(II) or Cr(III) (which could subsequently be reduced to labile Cr(II) if it needed to be removed) makes it compatible with the CuAAC reaction and provides a general means of incorporating metal atoms or binding sites into organic structures *via* 'click' chemistry.



Scheme 3 Preparation of homo- and mixed-metallated [2]rotaxanes. a) 4 M Na_4EDTA (aq), RT, 72%; b) $ZnCl_2$, CH_3OH, RT, 1 h, 98%; c) 4 M EDTA (aq), RT, 71%; d) $ZnCl_2$, CH_3OH, RT, 1 h, 90%.

The diamagnetic complex [**3**(*mac*-$ZnCl_2$)(*thread*-$ZnCl_2$)] was amenable to structural investigation by ^1H NMR spectroscopy. The partial 400 MHz ^1H NMR spectra of the thread (**4**), demetallated rotaxane (**3**), and [**3**(*mac*-$ZnCl_2$)(*thread*-$ZnCl_2$)] in [D_7]-DMF are shown in Fig. 1. The upfield shifts of the coincident fumaramide olefin protons (H_d and H_e) in the rotaxane relative to those of the free thread **4** are typical of benzylic amide macrocycle-based rotaxanes,[13] resulting from shielding of the xylylene rings. In addition to the appearance of resonances from the second BPA binding site ($H_{M\text{-}R}$), the distinctive triazole proton (H_L) signal is evident (Fig. 1b and 1c). In the spectrum of compound [**3**(*mac*-$ZnCl_2$)(*thread*-$ZnCl_2$)] (Fig. 1c) the BPA aromatic protons are shifted downfield relative to those in **3** (Fig. 1b) due to metal coordination. Although the fumaramide olefin signals become separated as their inequivalence is emphasised by the zinc coordination to one end of the thread (Fig. 1c), the metal complexation does not appear to significantly change the conformation or co-conformation adopted by the mechanically interlocked fragments.

In conclusion, we have outlined a transition metal tolerant CuAAC protocol for the synthesis of mono- and *bis*-metallated [2]rotaxanes using a simple alkyne-functionalised tridentate ligand and its metal complexes. Indeed the methodology should prove a useful general way of appending a metal ion or complex to an organic scaffold, even when it contains redox-active or kinetically labile metals or vacant ligand sites. The ability to generate homo- and hetero-metallated [2]rotaxanes should allow for the exploration of non-covalent distance-dependent properties (*e.g.* electronic, magnetic and photochemical) between metal centres.

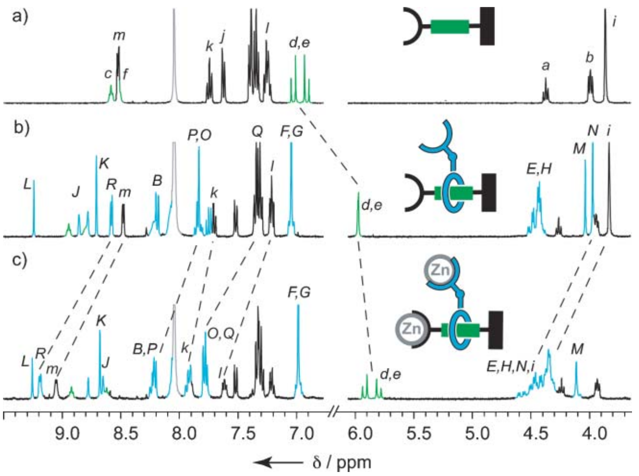


Fig. 1 Partial ^1H NMR spectra (400 MHz, [D_7]-DMF, 298 K) of a) thread **4**; b) metal-free [2]rotaxane **3**; c) [**3**(*mac*-$ZnCl_2$)(*thread*-$ZnCl_2$)]. Resonances are coloured and labelled as shown in Scheme 2. Peaks shown in light grey arise from residual nondeuterated solvent.

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